Acyl Glycosides through Stereospecific Glycosyl Cross-Coupling: Rapid Access to C(sp³)-Linked Glycomimetics

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ABSTRACT: Replacement of a glycosidic bond with hydrolytically stable C–C surrogates is an efficient strategy to access glycomimetics with improved physicochemical and pharmacological properties. We describe here a stereoretentive cross-coupling reaction of glycosyl stannanes with C(sp³)- and C(sp²)-thio(seleno)esters suitable for the preparation C-acyl glycosides as synthetic building blocks to obtain C(sp³)-linked and fluorinated glycomimetics. First, we identified a set of standardized conditions employing a Pd(0) precatalyst, CuCl additive, and phosphite ligand that provided access to C-acyl glycosides without deterioration of anomeric integrity and decarbonylation of the acyl donors (>40 examples). Second, we demonstrated that C(sp³)-glycomimetics could be introduced into the anomeric position via a direct conversion of C1 ketones. Specifically, the conversion of the carbonyl group into a CF₂ mimetic is an appealing method to access valuable fluorinated analogues. We also illustrate that the introduction of other carbonyl-based surrogates into the C1 position of mono- and oligosaccharides can be accomplished using the corresponding acyl donors. This protocol is amenable to late-stage glycodiversification and programmed mutation of the C–O bond into hydrolytically stable C–C bonds. Taken together, stereoretentive anomeric acylation represents a convenient method to prepare a diverse set of glycan mimetics with minimal synthetic manipulations and with absolute control of anomeric configuration.

INTRODUCTION

Oligosaccharides are one of the most abundant biopolymers characterized by a number of activities ranging from the storage of energy to the use as small-molecule drugs. The effective utilization of carbohydrates in the design of novel therapeutics, however, is restricted by a labile glycosidic bond—a linkage connecting two or more saccharides through the C1 carbon, which is easily cleaved under biological conditions. Some of the most successful approaches taken toward overcoming this lability focus on replacing the problematic C–O bond with more robust C–C surrogates. Given their enhanced resilience to enzymatic and hydrolytic cleavage, C-analogues to natural saccharides (C-glycosides) emerged as a privileged class of molecules with a diverse range of potential applications. Within this class, C-alkyl glycosides constitute the subset of oligosaccharides and glycoconjugates retaining a C(sp³) linkage at the anomeric carbon. Noteworthy representatives of this subclass are glycosides with a CH₂-linkage (e.g., 1, 2, 23) and, more recently, surrogates containing a CF₂ group (4). In comparison to the well-developed applications of organometallics in C(sp³) glycoside synthesis, the use of conventional, transition-metal catalyzed coupling methods to prepare C-alkyl glycosides is relatively rare. C–C bond formation at the C1 of C(sp³)-hybridized glycosyl halides with alkyl metal reagents suffers from a competing β-elimination pathway, which, in addition to difficulties with controlling anomeric stereoselectivity, make C-glycosylation one of the more challenging synthetic endeavors. Gagné and co-workers reported a Negishi cross-coupling approach of glycosyl halides to furnish C-alkyl glycosides in moderate yields and anomeric selectivities. While their work highlights an important achievement in this underdeveloped area, the narrow scope of saccharide substrates and poor functional group tolerance limits their method’s practical utilization in complex carbohydrate synthesis. On the basis of our previous studies on glycosyl cross-coupling, we decided to pursue an indirect approach to prepare C-alkyl glycosides. We envisaged that the stereocontrolled introduction of a C(sp³) anomer linkage could be accomplished through the installation of a handle that could be further elaborated to furnish the targeted product. C-glycosyl ketones (5) represent an ideal scaffold from which C(sp³)-glycomimetics can be accessed (Scheme 1B). Given the unique position of C-glycosyl ketones as versatile building blocks for target-specific C(sp³) glycodiversification through a reductive or deoxyfluorination method, and as interesting bioactive species in their own right (e.g., scleropentasides with antioxidant activities),
Scheme 1. (A) Selected Bioactive C(sp³)-Linked Glycosides and (B) Targeted Transformations of C-Acyl Glycosides

![Chemical Structures](image)

Our investigation centered around direct access to this class of key building blocks.

Several strategies for the anomeric acylation of carbohydrates are known, utilizing both direct and indirect approaches to access glycosyl ketones (Scheme 2). For example, anomeric acylation has been accomplished via a direct method using radical conditions with variable selectivities. Another direct acylation has been accomplished via a direct method using nickel-catalyzed reductive coupling of glycosyl bromides and carboxylic acids. (C) Synthesis of C(sp³)-glycomimetics using reductive coupling high selectivities.

**Scheme 2. Selected Methods for C1 Acylation of Saccharides**

![Chemical Structures](image)

**RESULTS AND DISCUSSION**

**Reaction Development.** On the basis of the previous studies on acylation of C(sp³) nucleophiles, we investigated a reaction of d-glucose 15 with various acyl donors (Table 1). From the outset of the catalyst identification studies, we aimed to achieve broad substrate compatibility. We hypothesized that the stereoretentive conditions established for the d-glucose β-anomer could be translated to the α anomer as well as other sugars. The key challenge of this process is controlling the competitive formation of d-glucal at either the stage of C1 stannane or other C1 organometallic intermediates.

First, we surveyed reactions with Pd(PPh₃)₄ (10 mol %) and CuCl (3 equiv). While aromatic solvents typically suppress glycal formation, in the case of anomeric acylation, PhMe resulted in a low yield of 17, likely due to the poor solubility of CuCl (entries 1–3). Changing the solvent to 1,4-dioxane resulted in an increase of the yield of 17 (56%, entry 3). Other copper counterions were screened (entries 4–6), but they only had detrimental effects on the formation of 17 and were thus excluded from further optimization studies. It is worth noting that replacement of CuCl with CuTc or CuOP(O)Ph₂ resulted in the formation of the hydrogenated side product in modest yields (entries 7 and 8). On the basis of the previous observations that phosphine ligands can control the rate of the β-elimination of the C2 groups, we tested a series of mono- and bidentate phosphines (entries 10–14), but these additives provided no beneficial impact on the yield.

At this point of the optimization studies, we focused on understanding the effect of the leaving group on the reaction efficiency (entries 15–19). By modulating the electronics of equivalent with an acyl donor, affording high selectivities but only for the substrates equipped with participating groups. These direct methods largely result in suboptimal dr and do not meet, in the current form, the stringent criteria of anomeric selectivities necessary for preparative carbohydrate chemistry. In terms of indirect approaches, a neighboring group that can direct the outcome of the acylation step, similar to O-glycosylation reactions, can provide high 1,2-trans selectivities.

This strategy was demonstrated in the addition reactions of a cyanide followed by reduction (Scheme 2B). These indirect protocols are plagued by a competitive glycal formation. Other methods toward C-acyl glycosides involve benzothiazole manipulations, vinylation and oxidative cleavage of the olefins, hydroacylation of glycals, and reactions involving C1 organolithium intermediates but require additional synthetic steps to afford glycosyl ketones. Despite these recent advancements, the absence of a general and predictable method for stereospecific anomeric acylation remains a major methodological gap preventing greater investigation into the biology and applications of these compounds as viable precursors to C(sp³)-glycosimetics.

Herein, we report a new methodology for the programmed synthesis of C-glycosyl ketones capitalizing on a stereospecific cross-coupling reaction of anomeric stannanes with thio- and selenoesters, resulting in exclusive control of the anomeric configuration for both anomers of various saccharides (Scheme 2D). We further demonstrate the utility of C-glycosyl ketones as important building blocks in the preparation of relevant C(sp³)-glycosimetics using reductive and deoxyfluorination methods to afford several examples of CH₂ and CF₂-linked glycosides.
the thiol leaving group, we aimed to gain better understanding of whether the electron-donating (ester B), electron-withdrawing (esters C and D), or aliphatic esters E could improve the yield. However, we found that only 4-fluorothiophenol ester C gave a yield comparable to phenyl ester (50%); other esters were significantly less efficient. A chelating 2-thiopyridine byproduct that can compete with the phosphine additives showed a diminished yield (21%). Anhydrides, reported to act as suitable acyl donors in reactions with C(sp2) boronic acids,53–57 were found ineffective (entry 19).

Acyl chlorides reportedly act as excellent acyl donors in cross-couplings with acyclic stannanes and boronic acids; however, they were found to be incompatible with per-benzylated C1 stannanes. It is interesting to note that a reaction of stannane 15 with benzoyl chloride and TiCl4 (1.0 equiv, 0 °C, CH2Cl2, 1 h) resulted in the formation of benzoyl D-glucose 17 in 8% and high β selectivity. The mechanism of this transformation likely involves activation of the acyl donor with a Lewis acid followed by a stereoretentive delivery of the nucleophile to the putative acylium intermediate. Given that the use of highly reactive Lewis acid additives with acyl chlorides is limited in scope, other methods for the stereoretentive synthesis of C-acyl glycosides were pursued. Taken together, we decided to continue our investigations using thioesters because of the ease of preparation, stability, and compatibility with a wide range of functional groups.

Other alterations to the reaction conditions were investigated to improve the yield. A simple increase in the amount of CuCl and stannane modestly improved the yield (entries 20 and 21). Addition of phosphite40 (entries 22−25) but not triaminophosphine (entry 26) ligands (40 mol %) increased the yield. Furthermore, P(OMe)3 exhibited the best reaction outcomes thus far and afforded C-acyl D-glucose 17 in 83% isolated yield (entry 23). The unique role of the phosphite ligand can be attributed to its ability to suppress the decarbonylation pathway40 and to prevent the formation of D-glucal. Finally, control experiments (entries 27 and 28) affirmed that both palladium precatalyst and copper(I) additives are necessary for the reaction to occur. From these results, we converged on the use of thioesters along with phosphite or bulky phosphine (JackiePhos) ligands in 1,4-dioxane using a Pd-catalyst in the presence of excess CuCl to investigate the reaction’s generality.

**Reaction Scope.** The scope of the anomeric acylation reaction was probed using various thioesters derived from C(sp2) and C(sp3) carboxylic acids, and D-glucose stannane 15.

Table 1. Optimization of Glycosyl Acylation Reaction

| Entry | Pd | Ligand | Cu | Acyl source | Solvent | Yield (%) |
|-------|----|--------|----|-------------|---------|-----------|
| 1     | 10% Pd(PPh3)4 |    | A  | PhMe        | 29      |
| 2     | 20% Pd(PPh3)4 |    | A  | PhMe        | 32      |
| 3     | 20% Pd(PPh3)4 |    | C  | 1,4-dioxane | 56      |
| 4     | 10% Pd(PPh3)4 |    | C  | 1,4-dioxane | 20      |
| 5     | 20% Pd(PPh3)4 |    | C  | 1,4-dioxane | <5      |
| 6     | 20% Pd(PPh3)4 |    | C  | 1,4-dioxane | <5      |
| 7     | 20% Pd(PPh3)4 |    | C  | 1,4-dioxane | <5      |
| 8     | 20% Pd(PPh3)4 |    | C  | 1,4-dioxane | <5      |
| 9     | 20% Pd(PPh3)4 |    | C  | 1,4-dioxane | 29      |
| 10    | 20% PdCl2 |    | C  | 1,4-dioxane | 50      |
| 11    | 20% PdCl2 |    | C  | 1,4-dioxane | 38      |
| 12    | 20% PdCl2 |    | C  | 1,4-dioxane | <5      |
| 13    | 20% PdCl2 |    | C  | 1,4-dioxane | 24      |
| 14    | 20% PdCl2 |    | C  | 1,4-dioxane | 24      |
| 15    | 20% PdCl2 |    | C  | 1,4-dioxane | 21      |
| 16    | 20% PdCl2 |    | C  | 1,4-dioxane | 10      |
| 17    | 20% PdCl2 |    | C  | 1,4-dioxane | <5      |
| 18    | 20% PdCl2 |    | C  | 1,4-dioxane | 72      |
| 19    | 20% PdCl2 |    | C  | 1,4-dioxane | 72      |
| 20    | 20% PdCl2 |    | C  | 1,4-dioxane | 81      |
| 21    | 15% PdCl2 |    | C  | 1,4-dioxane | 81      |
| 22    | 7.5% PdCl2 |    | C  | 1,4-dioxane | 81      |
| 23    | 7.5% PdCl2 | P(OMe)3 | C  | 1,4-dioxane | 83      |
| 24    | 7.5% PdCl2 | P(O-Pr) | C  | 1,4-dioxane | 77      |
| 25    | 7.5% PdCl2 | P(O-Ph) | C  | 1,4-dioxane | 77      |
| 26    | 7.5% PdCl2 | P(NEt) | C  | 1,4-dioxane | 77      |
| 27    | 7.5% PdCl2 | - | C  | 1,4-dioxane | 77      |
| 28    | 7.5% PdCl2 | P(OMe)3 | C  | 1,4-dioxane | 77      |

*Reaction conditions: thioester 16 (0.1 mmol), anomeric stannane 15 (2.0 equiv), Pd(PPh3)4 (20 mol %), CuCl (3 or 4 equiv), and anhy. 1,4-dioxane (2 mL) under N2, 110 °C, 48 h. Isolated yield. Thioester 16 (2 equiv), anomeric stannane 15 (1 equiv). Thioester 16 (3 equiv), 72 h. 96 h. 3 equiv of copper source. 4 equiv of copper source. CuTc = copper(1) thiophene-2-carboxylate; dcype = 1,2-bis(dicyclohexylphosphine)ethane; dba = dibenzylideneacetone.*
Under the optimized conditions, a wide range of C(sp$^2$)- and several examples of C(sp$^3$)-thioesters were readily converted to their corresponding glycosides in moderate to excellent yields (Scheme 3A,B). Aromatic thioesters containing electron-donating (19d–i) and electron-withdrawing (19c) groups on the aromatic ring as well as bicyclic (19a, b) systems are included in this group. Thioesters derived from furan and indole carboxylic acids also performed moderately well with our protocol (19j and 19k). Substrates with heteroaromatic moieties present a greater challenge for selective functionalization due to the system’s additional reactive sites which can coordinate with palladium and hinder catalytic efficiency. To our delight, we found that vinyl thioesters are also viable substrates as demonstrated by the smooth conversion of cinnamyl thioester into 19l in 50% yield. When we tested the reaction’s compatibility with thioesters of simple, C(sp$^3$)-carboxylic acids, we noticed that the yields for these transformations were about 15% higher than the reactions with simple aryl substrates (Scheme 2B). These results are especially interesting considering the likelihood of a decarboxylation of the thioester that can lead to a stabilized (e.g., benzylic) organopalladium intermediate (in a reaction leading to 19m).

To further investigate the versatility of the glycosyl cross-coupling method, we next applied the optimized acylation conditions to the glycodiversification of a series of...
commercially available pharmaceuticals and other biologically active molecules with d-glucose (Scheme 2C). Late-stage functionalization is advantageous for the preparation of new therapeutics, as acylated versions of pharmaceutical candidates can be rapidly accessed. Glycosyl ketones derived from indomethacin (19q), adapalene (19r), probenecid (19s), naproxen (19t), steroids (19u and 19v), and atorvastatin (19w) were prepared by simple conversion of the acids into the thioesters followed by cross-coupling with stannane 15. High chemoselectivity was observed in a reaction with halogen-containing substrates (19q), and even thioesters that were derived from benzyllic acids were converted into the products with no observed erosion of susceptible positions. For example, a reaction of a thioester that can lead to a stabilized benzyl intermediate after decarbonylation and a potential loss of optical purity was smoothly converted into the C1 ketone 19t in 50% yield. Substrates containing strong coordinating groups that compete with P(OMe)3 for coordination with the Pd catalyst can result in lower yields and a scrambling of stereochemistry. To overcome this obstacle, we found that conversion of probenecid thioester into 19s was achieved in 51% and high selectivity when a bulky ligand (JackiePhos, 30 mol %) was used. Interestingly, in the acylation manifold, 51% and high selectivity when a bulky ligand (JackiePhos, 30 mol %) was used. Interestingly, in the acylation manifold, 

In the case of transition metal-catalyzed C-S activation, a key step impacting the overall catalytic efficiency is activation of the bond formed between the transition metal-catalyst and the soft sulfur. 

We demonstrated the smooth conversions of 1,2-cis anomers of d-glucose 21a, d-galactose 21c, and d-glucosamine 21e into the corresponding ketones with retention of anomeric configuration in 53−85% isolated yields. Similar cross-coupling results were obtained for 1,2-trans isomers of monosaccharides resulting in the synthesis of 21b, 21d, 21h, 21i, and lactose 21j. 2-Deoxysugars, notorious for the difficulties they present to stereocontrolled anomeric derivatization, underwent smooth conversion into C1-acyl analogues 21f and 21g in excellent yields. C1 stannanes protected with benzylidene, a common protecting group in the preparative carbohydrate chemistry, are also well tolerated under the acylation conditions as illustrated by the synthesis of 21h in 73% isolated yield.

On the basis of the initial catalyst identification studies, thiophenol esters were found to be the optimal coupling partners. However, the yields of reactions with certain thiophenyl esters were suboptimal (e.g., 19p was formed in 32%). In the case of transition metal-catalyzed C-S activation, a key step impacting the overall catalytic efficiency is activation of the bond formed between the transition metal-catalyst and the soft sulfur. 

We surmised that low yields could be improved by using a more active acyl donor in the form of selenoesters. The C-Se bond is 24.9 kcal-mol−1 weaker than the C-S bond, which allows for the cleavage of the C-X (X = S or Se) bond to be accelerated. Additional considerations in switching to selenoesters involve the enhanced nucleofugality of the selenide which places a greater significance on the transmetallation step to ensure smooth reaction progress. This property of Se was extensively used in the generation of acyl radicals and in ortho-acylation of aryl halides. Thus, a reaction of 15 with phenylselenoester of the corresponding acid resulted in an improved yield of 19p (77%).

Noteworthy observations regarding the reactivity of the esters are reactions with 1,2-cis isomers (1) require high reaction temperatures (130 °C) for completion and (2) are prone to glycal formation. To this end, the use of JackiePhos is recommended to minimize the competing elimination pathway. It is also important to consider the potential obstacles encountered when employing substrates containing groups (e.g., 2-acetamide) capable of competing with P(OMe)3 for coordination with Pd catalyst. This problem can be addressed by replacing P(OMe)3 with JackiePhos, which furnishes the target products in good to excellent yields and high selectivities (21d,e). In terms of the scope of acyl donors that are compatible with C(sp2) nucleophiles, selenoesters are preferred for reactions involving 1,2-cis anomers (21a and 21c) and 2-deoxysugars (21f and 21g). Furthermore, analysis of the reaction mixtures revealed that the decarbonylation pathway plays only a minor role, and the potential C1-arylation products under the optimized conditions were formed in <5% yield.

The anomeric selectivity of the glycosyl cross-coupling reactions was determined by the analysis of 1H NMR of unpurified reaction mixtures. For all substrates presented in Scheme 3, formation of a single anomer was observed. The
configurations of the anomic carbon in compounds 19 and 21 were assigned based on the analysis of $^{1}J_{(HH)}$ coupling constants of the H1 proton signals. The diagnostic signals are typically located in the 3.81–5.25 ppm region (300 MHz, CDCl$_3$) and have $J$ values that fall in the 8.80–9.40 Hz and 4.20–6.20 Hz range for 1,2-trans and 1,2-cis isomers, respectively.

**Applications in the Synthesis of C-Disaccharides.** To further demonstrate the generality of the stereospecific anomic acylation reaction, we embarked on the synthesis of C-disaccharides (Scheme 5). Kishi demonstrated previously that CH$_2$-linked disaccharides (lactose) are viable surrogates of the natural oligosaccharides.$^{66-78}$ The predictable nature of our glycosyl cross-coupling method enables a programmed approach toward the stereospecific preparation of C-glycosides conferred by direct control of product configuration by the corresponding configuration of the substrate used. To this end, we demonstrated that phenylelensenoester of homoglucuronic acid 22 can be merged with both anomers of d-glucose and N-acetyl-d-glucosamine stannanes in high yields (50–88%) and with exclusive transfer of anomic configuration. The cross-coupling reaction using the phenylthioester derivative was also tested, but the corresponding yields were significantly lower (23% for 23a).

Access to both anomers of C(sp$^3$)-glycosides offers the unprecedented opportunity to synthesize complex oligosaccharide scaffolds in a programmed and predictable fashion by simple selection of the corresponding nucleophiles with a defined anomic configuration. The conformational studies provide the foundation for further explorations in this arena as the access to any desired configuration is feasible under a standardized protocol.

**Product Elaboration.** Acyl C-glycosides can be converted into C(sp$^3$)- and C(sp$^3$)-glycosides via a series of reactions depicted in Scheme 6. The carbonyl group in 17 was converted into alcohol 24 via reduction with NaBH$_4$ or by addition of MeMgBr forming tertiary alcohol 25 with $dr > 95:5$. The stereochemical outcome of this reaction can be rationalized using the Cram chelate model in which the endocyclic pyranosyl oxygen and the carbonyl group form a stable chelate with magnesium followed by addition of the nucleophile from the H1 face. The carbonyl moiety was also reduced into alkene 26 under catalytic hydrogenation with Pd/C and acetic acid (10 mol %) in 98%. These conditions removed all benzyl groups in a single step. The carbonyl group could be converted into an olefin, and this reaction sequence presents an indirect method for C(sp$^3$)-C(sp$^3$) cross coupling with a vinyl equivalent, which is otherwise inaccessible through standard palladium-catalyzed cross-coupling conditions. The Wittig (Ph$_2$PCH$_2$) or the Horner–Wadsworth–Emmons ((EtO)$_2$P(O)(CH$_2$)$_3$) protocols were ineffective in this case because of the competing elimination the C2 benzyloxy group. However, the Peterson olefination conditions (TMSCH$_2$MgBr followed by KHMDMS) were suitable for the installation of the vinyl group in 27 in 84%.

**Synthesis of Fluorinated Glycomimetics.** Unlike other classes of biopolymers such as nucleic acids and peptides, the replacement of selected functional groups in carbohydrates has largely been limited to hydroxyl groups around the saccharide core. Substitutions with fluorine are well-known—a premiere example being the isotopically labeled $^{18}$F d-glucose 28 which is used as a tracer for PET imaging. Replacement of the endocyclic oxygen atom with a CF$_2$ group has been reported (e.g., 29), and the fluorinated analogues showed improved stability as well as restored anomic effects which enabled the adoption of natural O-glycoside conformations in solution. Gem-difluoro glycosides, in which the exocyclic oxygen is replaced with a CF$_2$ surrogate, also constitute a promising class of glycomimetics because (a) the two fluorine atoms of the CF$_2$ group more accurately represent the electrostatic potential and H-bonding of the ethereal oxygen atom (30 vs 31) compared to CH$_3$ derivatives, and (b) CF$_2$-linked glycosides show conformational preferences similar to their natural cognates (Scheme 7). Additionally, fluorinated glycosides display unique physiochemical properties including increased lipophilic character and stability. The difluorinated surrogate of ganglioside GM4 (4) demonstrated inhibitory activity of lymphocyte proliferation similar to the natural GM4. Jiménez-Barbero and Vogel performed a series of NMR
and computational studies on a CF₂-linked β-galactoside and concluded that the conformational preferences of these unnatural saccharides mimic the natural counterparts, but subtle conformational differences have to be incorporated into the analysis to fully recapitulate the solution structures. These are reminiscent of earlier work by Kishi who systematically investigated the conformational behavior of CH₂-linked glycosides and demonstrated in a series of papers that CH₂-linked disaccharides display conformational preferences comparable with natural O-glycosides. Having access to both anomers of acyl glycosides, we next wondered if these compounds could serve as substrates for the preparation of fluorinated glycomimetics.

Prior to synthetic studies, we performed computational analyses of axial and equatorial isomers of tetrahydropyran derivatives summarized in Figure 1. First, we evaluated conformational preferences of O-glycosides calculated at the density functional theory (DFT) level of theory could be translated into the preference of CF₂ analogues for the axial and equatorial anomers (Figure 1A). In the model systems, the axial anomer of O-glycoside displays a single major conformer in which the substituent prefers the gauche conformation with the most stable conformer (dihedral angle, ψ = 50°). Similar preferences are also observed for CH₂ and CF₂ analogues with a global minimum located around ψ = 50° and ψ = 55°, respectively. However, the CH₂ analogue is more flexible than the fluorinated glycomimetics because the next lowest energy conformer is only 0.7 kcal·mol⁻¹ above the minimum (ψ = 61°) with the interconversion barrier of 2.0 kcal·mol⁻¹, whereas for the CF₂ glycomimetics the next lowest energy conformer is located 2.8 kcal·mol⁻¹ higher (ψ = 164°) with the rotational barrier of 2.5 kcal·mol⁻¹. For the equatorial isomers, all three analogues show similar minima around ψ ≈ 280–300°, but both CH₂ and CF₂ analogues have two other well-defined minima. For the equatorial CF₂-linked pyranose, the barriers of interconversion are much higher than for the CH₂-linked glycoside rendering these analogues less flexible.

Second, in silico studies were focused on the impact of the tetrahydropyran modification on the anomeric effect. Natural bond orbital (NBO) analysis allows for the evaluation of the energetic importance of orbital interactions by considering possible interactions between filled donors and empty acceptors using second-order perturbation theory. Figure 1B lists selected anomeric stabilization energies calculated for axial and equatorial conformers of substituted tetrahydropyran. For the thermodynamically most stable conformer, the acetal stabilization is a dominant contributor for the conformational preferences. The C(sp³) analogues show reduced “endo-anomeric” stabilizations as compared to O-glycoside, but they retain 64% of the oxygen anomeric stabilization for the CF₂ analogue and only 50% of the stabilization for the ethyl pyranose. In addition to the extra 1.85 kcal·mol⁻¹ of stabilization responsible for the increased conformational preferences of the axial anomer, the C1–CF₂ bond is also polarized, making the donor–acceptor interactions more favorable. The energetic gains resulting from nO(endo)→σ∗(C1–X) interactions are similar to the values calculated for gem-difluorocarbadisaccharides stabilized by the exo-anomeric effect. As expected, the stabilizing interactions are low for both equatorial C(sp³) surrogates.

Subsequent studies were aimed at establishing a synthetic route to CF₂-linked glycosides (Scheme 8). A conversion of the ketone functionality into a CF₂ group is well-documented for S(VI) reagents. Thus, DeoxoFluor was mixed with catalytic (10 mol %) amounts of MeOH to convert ketones into the gem-difluorides 32. Our initial concerns that the glycosidic bond might be unstable under these conditions were unwarranted—CF₂-linked disaccharide 32e was prepared with DeoxoFluor in 51% without cleavage of the methyl glycoside. The benzyl groups in CF₂-linked glycosides could be removed without concomitant defluorination demonstrated...
for 32f (98%). This synthesis presents an interesting example of a glycosidic bond mutated into a fluorinated isostere in a disaccharide system,95,106

Access to fluorinated glycosides with any desired anomeric configuration opens the opportunities to apply these surrogates as structural and functional probes.107−109 Similar to fluorinated peptides used to study protein−protein interactions, CF2-linked glycans can serve as probes to scrutinize glycan-lectin interactions by19F NMR.110

■ CONCLUSIONS

In summary, we have described a general and practical palladium-catalyzed stereospecific acylation reaction of anomeric nucleophiles with thio- and selenoesters. This newly developed method capitalizes on a stereoretentive transfer of anomeric configuration from configurationally stable C1 glycolyl stannanes without C2-directing groups to provide easy access to a wide range of C(sp3)- or C(sp2)-acyl glycosides under mild conditions. Given that these glycosides are easy to prepare and derivatize, this can serve as synthetic building blocks and amenable to this method provides an entry into C(sp3) glycomimetics that are notorious for their challenging preparation. We have been able to prepare via a series of straightforward manipulations a series of CF2-linked saccharides mimicking the natural saccharides. Taken together, the use of anomeric nucleophiles in the preparation of natural and designer saccharides presents an example of unprecedented scope and selectivity for the manipulation of the anomeric carbon in complex saccharide settings. The application of the glycosyl cross-coupling method in target-oriented synthesis and in glycodiversification is ongoing.

■ ASSOCIATED CONTENT

Supporting Information
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Detailed experimental procedures, copies of NMR spectra for all new compounds (PDF)

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The authors declare no competing financial interest.

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■ ABBREVIATIONS

4CzIPN, 2,4,5,6-tetra(9H-carbazol-9-yl)isophthalonitrile; LED, light-emitting diode

■ REFERENCES

(1) Varki, A.; Cummings, R. D.; Esko, J. D.; Freeze, H. H.; Stanley, P.; Bertozzi, C. R.; Hart, G. W.; Etzler, M. E. Essentials of Glycobiology; Cold Spring Harbor Laboratory Press: Cold Spring Harbor, NY, 2009.
(2) Wong, C. H. Carbohydrate-Based Drug Discovery; Weinheim: Wiley-VCH Verlag GmbH, 2005.
(3) Ernst, B.; Magnani, J. L. From carbohydrate leads to glycomimetic drugs. Nat. Rev. Drug Discovery 2009, 8, 661.
(4) Mamiyala, S. K.; Dutta, S.; Chrunyk, B. A.; Previle, C.; Wang, H.; Withka, J. M.; McColl, A.; Subashi, T. A.; Hawrylik, S. J.; Griffon, M. C.; Kim, S.; Pfefferkorn, J. A.; Price, D. A.; Menhaji-Klotz, E.; Mascitti, V.; Finn, M. G. Glycomimetic Ligands for the Human Asialoglycoprotein Receptor. J. Am. Chem. Soc. 2012, 134, 1978.
(5) Cecioni, S.; Imbert, A.; Vidal, S. Glycomimetics Versus Multivalent Glycoconjugates for the Design of High Affinity Lectin Ligands. Chem. Rev. 2015, 115, 525.
(6) Zhang, G.-L.; Ye, X.-S. Synthetic Glycans and Glycomimetics: A Promising Alternative to Natural Polysaccharides. Chem. - Eur. J. 2018, 24, 6696.
(7) Parker, K. A.; Roy, R. Glycomimetics: Modern Synthetic Methodologies; American Chemical Society: Washington, DC, 2005.
(8) Ko, K.-S.; Kruse, J.; Pohl, N. L. Synthesis of Isobutyl-C-galactoside (IBCG) as an Isopropylgalactoside (IPGT) Substitute for Increased Induction of Protein Expression. Org. Lett. 2003, 5, 1781.
(9) Liu, L.; Abdel Motaal, B.; Schmidt-Supprian, M.; Pohl, N. L. B. Multigram Synthesis of Isobutyl-β-C-galactoside as a Substitute of Isopropylgalactoside for Exogenous Gene Induction in Mammalian Cells. J. Org. Chem. 2012, 77, 1539.
(10) Yang, G.; Schmieg, J.; Tsuji, M.; Franck, R. W. The C-Glycoside Analogue of the Immunostimulant α-Galactosylceramide (KRN7000): Synthesis and Striking Enhancement of Activity. Angew. Chem. Int. Ed. 2004, 43, 3818.
(11) Mydock-McGrane, L.; Cusumano, Z.; Han, Z.; Binley, J.; Kostkioti, M.; Hannan, T.; Pinkner, J. S.; Klein, R.; Kalas, V.; Crowley, J.; Rath, N. P.; Hultgren, S. J.; Janetka, J. W. Antivirulence C-Mannosides as Antibiotic-Sparing, Oral Therapeutics for Urinary Tract Infections. J. Med. Chem. 2016, 59, 9390.
(12) Hirai, G.; Watanabe, T.; Yamaguchi, K.; Miyagi, T.; Sodeoka, M. Stereocontrolled and convergent entry to CF2-sialosides: synthesis of CF2-linked gangloside GM4. J. Am. Chem. Soc. 2007, 129, 15420.
(13) Poulin, F.; Serre, A. L.; Lalot, J.; Leclerc, E.; Quirion, J. C. Synthesis of α-CF2-mannosides and their conversion to fluorinated pseudoglycopeptides. J. Org. Chem. 2008, 73, 2435.
(14) Moreno, B.; Quehen, C.; Rose-Helene, M.; Leclerc, E.; Quirion, J. C. Addition of difluoromethyl radicals to glycals: a new route to α-CF2-glycosides. Org. Lett. 2007, 9, 2477.
(15) Sodeoka, M.; Hirai, G.; Watanabe, T.; Miyagi, T. A strategy for constructing C-sialosides based on Ireland–Claisen rearrangement and its application for synthesis of CF2-linked gangioside GM4 analog. Pure Appl. Chem. 2009, 81, 205.
(16) Karche, N. P.; Pierry, C.; Poulain, F.; Oulyadi, H.; Leclerc, E.; Pannecoque, X.; Quirion, J. C. Synthesis of β-CF2-d-mannopyranosides and β-CF2-d-galactopyranosides by Reformatsky addition onto S-ketohexoses. Synlett. 2007, 2007, 0123.
(17) Xu, B.; Unione, L.; Sardinha, J.; Wu, S.; Ethève-Quelquejeu, M.; Rauter, A. P.; Bleriot, Y.; Zhang, Y.; Martin-Santamaria, S.; Diaz, D.; Jiménez-Barbero, J.; Sollogoub, M. gem-Difluorocarbosaccharides: Restoring the exo-Anomeric Effect. Angew. Chem. Int. Ed. 2014, 53, 9597–9602.
(18) Gong, H.; Sinisi, R.; Gagné, M. R. A Room Temperature Negishi Cross-Coupling Approach to C-Alkyl Glycosides. J. Am. Chem. Soc. 2007, 129, 1908–1909.
(19) Gong, H.; Gagne, M. R. Diastereoselective Ni-catalyzed Negishi cross-coupling approach to saturated, fully oxygenated C-alkyl and C-aryl glycosides. J. Am. Chem. Soc. 2008, 130, 12177.
(20) Gong, H.; Andrews, R. S.; Zuccarello, J. L.; Lee, S. J.; Gagne, M. R. Sn-free Ni-catalyzed reductive coupling of glycosyl bromides with activated alkynes. *Org. Lett.*, 2009, 11, 879.

(21) Zhu, F.; Rodriguez, J.; Yang, T.; Kevlishvili, I.; Miller, E.; Yi, D.; O’Neill, S.; Rourke, M. J.; Liu, P.; Walczak, M. A. Glycosyl Cross-Coupling of Anomeric Nucleophiles: Scope, Mechanism, and Applications in the Synthesis of Aryl C-Glycosides. *J. Am. Chem. Soc.* 2017, 139, 17908−17922.

(22) Zhu, F.; Rourke, M. J.; Yang, T.; Rodriguez, J.; Walczak, M. A. Highly stereospecific cross-coupling reactions of anomeric stannanes for the synthesis of C-aryl glycosides. *J. Am. Chem. Soc.* 2016, 138, 12049−12052.

(23) Yi, D.; Zhu, F.; Walczak, M. A. Glycosyl Cross-Coupling with Diarylodonium Salts: Access to Aryl C-Glycosides of Biomedical Relevance. *Org. Lett.*, 2018, 20, 1936−1940.

(24) Disadee, W.; Mahidol, C.; Sahakitpichan, P.; Sithimoncha, S.; Ruchirawat, S.; Kancharanapoom, T. Unprecedented furan-2-carbonyl glycosides and phenolic diglycosides from Scleropyrum pentan-1-ol. *Phytochemistry* 2012, 74, 115−122.

(25) Badir, S. O.; Dumoulin, A.; Matsuji, K. J.; Molander, G. A. Synthesis of Reversed C-Acyl Glycosides through Ni/Photoredox Dual Catalysis. *Angew. Chem., Int. Ed.* 2018, 57, 6610−6613.

(26) Hung, S. C.; Wong, C. H. Samarium diiodide mediated coupling of glycosyl phosphates with carbon radical or anion acceptors-synthesis of C-glycosides. *Angew. Chem., Int. Ed. Engl.* 1996, 35, 2671.

(27) Jia, X.; Zhang, X.; Qian, Q.; Gong, H. Alkyl-aryl ketone synthesis via nickel-catalyzed reductive coupling of alkyl halides with aryl acids and anhydrides. *Chem. Commun.*, 2015, 51, 10302.

(28) Zhao, C.; Jia, X.; Wang, X.; Gong, H. Ni-catalyzed reductive coupling of alkyl acids with unactivated tertiary alkyl and glycosyl halides. *J. Am. Chem. Soc.* 2014, 136, 17645.

(29) Guisot, N. E. S.; Ella Obame, I.; Ireddy, P.; Nourry, A.; Saluzzo, C.; Duljardin, G.; Dubreuil, D.; Pipelier, M.; Guillaume, S. Reaction of Glyconitriles with Organometallic Reagents: Access to Acyl β-C-Glycosides. *J. Org. Chem.* 2016, 81, 2364.

(30) Dondoni, A.; Catozzi, N.; Marra, A. Concise and Practical Synthesis of C-Glycosyl Ketones from Sugar Benzothiazoles and Their Transformation into Chiral Tertiary Alcohols. *J. Org. Chem.* 2005, 70, 9257.

(31) Nicolau, K. C.; Cole, K. P.; Frederick, M. O.; Aversa, R. J.; Denton, R. M. Chemical Synthesis of the GHIJK Ring System and Further Experimental Support for the Originally Assigned Structure of Maitoxtin. *Angew. Chem., Int. Ed.* 2007, 46, 8875.

(32) Prades, A.; Fernández, M.; Pique, S. D.; Willis, M. C.; Weller, A. S. Well-Defined and Robust Rhodium Catalysts for the Hydroacylation of Terminal and Internal Alkenes. *Angew. Chem., Int. Ed.* 2015, 54, 8520.

(33) Westermann, B.; Walter, A.; Diedrichs, N. Diastereoselective Synthesis of C-Glycosylated Amino Acids with Lactams as Peptide Building Blocks. *Angew. Chem., Int. Ed.* 1999, 38, 3384.

(34) Frey, O.; Hoffmann, M.; Wittmann, V.; Kessler, H.; Ulhamann, P. V.; Valera, A. Preparation and transmetalation of a triphenylstannyl β-D-glycopyranoside: a highly stereoselective route to β-D-C-glycosides via glycosyl diansons. *Helv. Chim. Acta* 1994, 77, 2060.

(35) Zhu, F.; O’Neill, S.; Rodriguez, J.; Walczak, M. A. Stereoretentive Manipulations of Anomeric Nucleophiles: Applications in the Synthesis of Selenoglycosides. *Angew. Chem., Int. Ed.* 2018, 57, 7091.

(36) Zhu, F.; Yang, T.; Walczak, M. A. Glycosyl Stille Cross-Coupling with Anomeric Nucleophiles – A General Solution to a Long-Standing Problem of Stereoregulated Synthesis of C-Glycosides. *Synlett* 2017, 28, 1510.

(37) Yang, T.; Zhu, F.; Walczak, M. A. Stereoselective oxidative glycosylation of anomeric nucleophiles with alcohols and carboxyllic acids. *Nat. Commun.* 2018, 9, 3650.

(38) Zhu, F.; O’Neill, S.; Rodriguez, J.; Walczak, M. A. Rethinking Carbohydrate Synthesis - Stereoretentive Reactions of Anomeric Stannanes. *Chem. - Eur. J.* 2018, DOI: 10.1002/chem.201803082.
Development, Scope, and Computational Study. J. Am. Chem. Soc. 2009, 131, 16720.

(59) Fors, B. P.; Watson, D. A.; Biscoe, M. R.; Buchwald, S. L. A Highly Active Catalyst for Pd-Catalyzed Amination Reactions: Cross-Coupling Reactions Using Aryl Mesylates and the Highly Selective Monoarylation of Primary Amines Using Aryl Chlorides. J. Am. Chem. Soc. 2008, 130, 13552.

(60) Thubodeaux, C. J.; Melançon, C. E.; Liu, H.-W. Natural-Product Sugar Biosynthesis and Enzymatic Glycodiesulfur bond activation and transformations. Chem. Soc. Rev. 2013, 42, 599.

(61) Pan, F.; Shi, Z.-J. Recent Advances in Transition-Metal-Catalyzed C–S Activation: From Thioester to (Hetero)aryl Thioether. ACS Catal. 2014, 4, 280.

(62) Luo, Y. R. Comprehensive Handbook of Chemical Bond Energies; CRC Press: Boca Raton, FL, 2007.

(63) Goekjian, P. G.; Wu, T. C.; Kishi, Y. Preferred conformation of C-glycosides. 3. Preferred conformation of carbon analogs of 1,4-disaccharides. J. Org. Chem. 1987, 52, 4825.

(64) Miller, W. H.; Ryckman, D. M.; Goekjian, P. G.; Wang, Y.; Kishi, Y. Preferred conformation of C-glycosides. 5. Experimental support for the conformational similarity between C- and O-disaccharides. J. Org. Chem. 1988, 53, 5580.

(65) Haneda, T.; Goekjian, P. G.; Kim, S. H.; Kishi, Y. Preferred conformation of C-glycosides. 10. Synthesis and conformational analysis of carbon trisaccharides. J. Org. Chem. 1992, 57, 490.

(66) Wang, Y.; Babirad, S. A.; Kishi, Y. Preferred conformation of C-glycosides. 11. C-Sucrose: new practical synthesis, structural reassignment, and solid-state and solution conformation of its octacetate. J. Org. Chem. 1993, 58, 304.

(67) O'Leary, D. J.; Kishi, Y. Preferred conformation of C-glycosides. 13. A Comparison of the Conformational Behavior of Several C-, N-, and O-Furanosides. J. Org. Chem. 1994, 59, 6629.

(68) Tani, K.; Kishi, Y. Preferred conformation of C-glycosides. 12. Synthesis and conformational analysis of α,α'-, α,β'-, and β,β'-C-trehaloses. J. Org. Chem. 1994, 59, 88.

(69) Pasetto, P.; Franck, R. W. Synthesis of Both Possible Isomers of the Northwest Quadrant of Altromycin B. J. Org. Chem. 2003, 68, 8042.

(70) Surya Prakash, G. K.; Zibinsky, M.; Upton, T. G.; Kashemirov, B. A.; McKenna, C. E.; Oertell, K.; Goodman, M. F.; Batra, V. K.; Pedersen, L. C.; Beard, W. A.; Shock, D. D.; Wilson, S. H.; Olah, G. A. Synthesis and biological evaluation of fluorinated deoxynucleotide analogs based on bis-(difluoromethylene)triphosphoric acid. Proc. Natl. Acad. Sci. U. S. A. 2010, 107, 15693.

(71) Upton, T. G.; Kashemirov, B. A.; McKenna, C. E.; Goodman, M. F.; Prakash, G. K. S.; Kultseyhev, B.; Batra, V. K.; Shock, D. D.; Pedersen, L. C.; Beard, W. A.; Wilson, S. H. α,β'-Difluoromethylene Deoxynucleoside 5′-Triphosphates: A Convenient Synthesis of Useful Probes for DNA Polymerase β Structure and Function. Org. Lett. 2009, 11, 1883.

(72) Meanwell, N. A. Fluorine and Fluorinated Motifs in the Design and Application of Bioisosteres for Drug Design. J. Med. Chem. 2018, 61, 5822.

(73) Meng, H.; Kumar, K. Antimicrobial Activity and Protease Stability of Peptides Containing Fluorinated Amino Acids. J. Am. Chem. Soc. 2007, 129, 15615.

(74) Siddiqui, M. A.; Ambre, S.; Keay, S. K.; Bhyne, J. M.; Zhang, C.-O.; Barchu, J. J. Glycoaminoc Acid Analogues of the Thomsen–Friedenreich Tumor-Associated Carbohydrate Antigen: Synthesis and Evaluation of Novel Antiproliferative Factor Glycopeptides. ACS Omega 2017, 2, 5618.

(75) Card, P. J. Fluorinated carbohydrates. Use of DAST in the synthesis of fluorinated sugars. J. Org. Chem. 1983, 48, 393.

(76) van Straten, K. E.; Kuttitayveetil, J. R. A.; Sevrain, C. M.; Villaume, S. A.; Jiménez-Barbero, J.; Linclau, B.; Vincent, S. P.; Sanders, D. A. R. Structural Basis of Ligand Binding to UDP-Galactopyranose Mutase from Mycobacterium tuberculosis Using Substrate and Tetrafluorinated Substrate Analogue. J. Am. Chem. Soc. 2015, 137, 1230.

(77) Zhou, J.-S.; McCormick, N. E.; Timmons, S. C.; Jakeman, D. L. Synthesis of α-Dexoxyxymono and Difluorohexopyranosyl 1-Phosphates and Kinetic Evaluation with Thymidylyl- and Guanylyltransferases. J. Org. Chem. 2016, 81, 8816.

(78) Golten, S.; Fontenelle, C. Q.; Timofte, R. S.; Baille, L.; Light, M.; Sebben, M.; Oulyadi, H.; Linclau, B. Enanitoselective Synthesis of Dideoxy-tetrafluorinated Hexoses. J. Org. Chem. 2016, 81, 4434–4453.

(79) Lainé, D.; Denavit, V.; Giguère, D. Synthesis of Protected 3-Deoxy-3-fluoro and 4-Deoxy-4-fluoro-galactopyranosides from Levoglucosan. J. Org. Chem. 2017, 82, 4986.

(80) Beuthien-Baumann, B.; Hamacher, K.; Oberdorfer, F.; Steinbach, J. Preparation of fluorine-18 labelled sugars and derivatives and their application as tracer for positron-emission-tomography. Carbohydr. Res. 2000, 327, 107.

(81) Deleuze, A.; Menozzi, C.; Sollogoub, M.; Sinaj, P. Synthesis of gem-Difluorocarboc-D-glucose: A Step Further in Sugar Mimesis. Angew. Chem., Int. Ed. 2004, 43, 6680.

(82) Sardinha, J.; Guieu, S.; Deleuze, A.; Fernández-Alonso, M. C.; Rauter, A. P.; Sinaj, P.; Marrot, J.; Jiménez-Barbero, J.; Sollogoub, M. gem-Difluorocarbagusars, the cases of mannopyranose and galactopyranose. Carbohydr. Res. 2007, 342, 1689.

(83) Unione, L.; Xu, B.; Diaz, D.; Martín-Santamaría, S.; Poveda, A.; Sardinha, J.; Rauter, A. P.; Blériot, Y.; Zhang, Y.; Cañada, F. J.; Sollogoub, M.; Jiménez-Barbero, J. Conformational Plasticity in Glycomimetics: Fluorocarbamethyl-L-idopyranosides Mimic the Intrinsic Dynamic Behaviour of Natural Idose Rings. Chem. - Eur. J. 2015, 21, 10513.

(84) Leclerc, E.; Pannecoque, X.; Ethève-Quelquejeu, M.; Sollogoub, M. Fluoro-C-Glycosides and Fluoro-Carbagusars, Hydrolytically Stable and Synthetically Challenging Glycomimetics. Chem. Soc. Rev. 2013, 42, 4270.

(85) Calculated logP values for phenyl D-glucoside and the CF2 Omega analogue, are 0.33 and 0.46, respectively.

(86) van Straaten, K. E.; Kuttiyatveetil, J. R. A.; Sevrain, C. M.; Villaume, S. A.; Jiménez-Barbero, J.; Linclau, B.; Vincent, S. P.; Sanders, D. A. R. Structural Basis of Ligand Binding to UDP-Galactopyranose Mutase from Mycobacterium tuberculosis Using Substrate and Tetrafluorinated Substrate Analogue. J. Am. Chem. Soc. 2015, 137, 1230.

(87) Zhou, J.-S.; McCormick, N. E.; Timmons, S. C.; Jakeman, D. L. Synthesis of α-Dexoxyxymono and Difluorohexopyranosyl 1-Phosphates and Kinetic Evaluation with Thymidylyl- and Guanylyltransferases. J. Org. Chem. 2016, 81, 8816.

(88) Deleuze, A.; Menozzi, C.; Sollogoub, M.; Sinaj, P. Synthesis of gem-Difluorocarboc-D-glucose: A Step Further in Sugar Mimesis. Angew. Chem., Int. Ed. 2004, 43, 6680.

(89) Beuthien-Baumann, B.; Hamacher, K.; Oberdorfer, F.; Steinbach, J. Preparation of fluorine-18 labelled sugars and derivatives and their application as tracer for positron-emission-tomography. Carbohydr. Res. 2000, 327, 107.

(90) Deleuze, A.; Menozzi, C.; Sollogoub, M.; Sinaj, P. Synthesis of gem-Difluorocarboc-D-glucose: A Step Further in Sugar Mimesis. Angew. Chem., Int. Ed. 2004, 43, 6680.
(97) Kolympadi, M.; Fontanella, M.; Venturi, C.; Andre, S.; Gabius, H. J.; Jiménez-Barbero, J.; Vogel, P. Synthesis and conformational analysis of (α-d-galactosyl)phenylmethane and α-β-difluoromethane analogues: interactions with the plant lectin viscumin. *Chem. - Eur. J.* 2009, 15, 2861.

(98) Denton, R. W.; Tony, K. A.; Hernández-Gay, J. J.; Cañada, F. J.; Jiménez-Barbero, J.; Mootoo, D. R. Synthesis and conformational behavior of the difluoromethylene linked C-glycoside analog of β-galactopyranosyl-(1→1)-α-mannopyranoside. *Carbohydr. Res.* 2007, 342, 1624.

(99) Mo, Y. Computational evidence that hyperconjugative interactions are not responsible for the anomeric effect. *Nat. Chem.* 2010, 2, 666.

(100) Freitas, M. P. The anomeric effect on the basis of natural bond orbital analysis. *Org. Biomol. Chem.* 2013, 11, 2885.

(101) Reed, A. E.; Curtiss, L. A.; Weinhold, F. Intermolecular interactions from a natural bond orbital, donor-acceptor viewpoint. *Chem. Rev.* 1988, 88, 899.

(102) Hudlicky, M. Fluorination with diethylaminosulfur trifluoride and related aminofluorosulfuranes. *Org. React.* 1988, 35, 513.

(103) Umemoto, T.; Singh, R. P.; Xu, Y.; Saito, N. Discovery of 4-tert-Butyl-2,6-dimethylphenylsulfur Trifluoride as a Deoxofluorinating Agent with High Thermal Stability as Well as Unusual Resistance to Aqueous Hydrolysis, and Its Diverse Fluorination Capabilities Including Deoxofluoro-Arylsulfination with High Stereoselectivity. *J. Am. Chem. Soc.* 2010, 132, 18199.

(104) Singh, R. P.; Shreeve, J. n. M. Recent Advances in Nucleophilic Fluorination Reactions of Organic Compounds Using Deoxofluor and DAST. *Synthesis 2002*, 2002, 2561.

(105) Lal, G. S.; Pez, G. P.; Pesaresi, R. J.; Prozonic, F. M.; Cheng, H. Bis(2-methoxyethyl)aminosulfur Trifluoride: A New Broad-Spectrum Deoxofluorinating Agent with Enhanced Thermal Stability. *J. Org. Chem.* 1999, 64, 7048.

(106) Herpin, T. F.; Motherwell, W. B.; Tozer, M. J. The synthesis of difluoromethylene-linked C-glycosides and C-disaccharides. *Tetrahedron Asymmetry 1994*, 5, 2269.

(107) Colombel, S.; Van Hijfte, N.; Poisson, T.; Leclerc, E.; Pannecoque, X. Addition of electrophilic radicals to 2-benzoxylglycalcs: synthesis and functionalization of fluorinated α-C-glycosides and derivatives. *Chem. - Eur. J.* 2013, 19, 12778.

(108) Colombel, S.; Sanselme, M.; Leclerc, E.; Quirion, J.-C.; Pannecoque, X. Straightforward Preparation of Functionalized α-CF2-Galactosides through an Oxygen to Carbon Acyl Migration. *Chem. - Eur. J.* 2011, 17, 5238.

(109) Gouge-Ibert, V.; Pierry, C.; Poulain, F.; Serre, A. L.; Largeau, C.; Escriou, V.; Scherman, D.; Jubault, P.; Quirion, J. C.; Leclerc, E. Synthesis of fluorinated C-mannopeptides as sialyl Lewissy mimics for E- and P-selectin inhibition. *Bioorg. Med. Chem. Lett. 2010*, 20, 1957.

(110) Diercks, T.; Ribeiro, J. P.; Cañada, F. J.; André, S.; Jiménez-Barbero, J.; Gabius, H. J. Fluorinated Carbohydrates as Lectin Ligands: Versatile Sensors in 19F-Detected Saturation Transfer Difference NMR Spectroscopy. *Chem. - Eur. J.* 2009, 15, 5666.

(111) Matei, E.; André, S.; Glinschert, A.; Infantino, A. S.; Oscarson, S.; Gabius, H. J.; Gronenborn, A. M. Fluorinated Carbohydrates as Lectin Ligands: Dissecting Glycan–Cyanovirin Interactions by Using 19F NMR Spectroscopy. *Chem. - Eur. J.* 2013, 19, 5364.

(112) Ribeiro, P. J.; Diercks, T.; Jiménez-Barbero, J.; André, S.; Gabius, H. J.; Cañada, J. F. Fluorinated Carbohydrates as Lectin Ligands: 19F-Based Direct STD Monitoring for Detection of Anomeric Selectivity. *Biomolecules* 2015, 5, 3177.