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Nucleophilic Aromatic Substitution (S_NAr) as an Approach to Challenging Carbohydrate–Aryl Ethers

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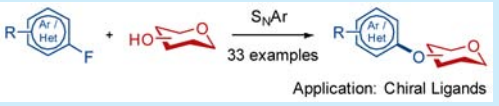
Supporting Information

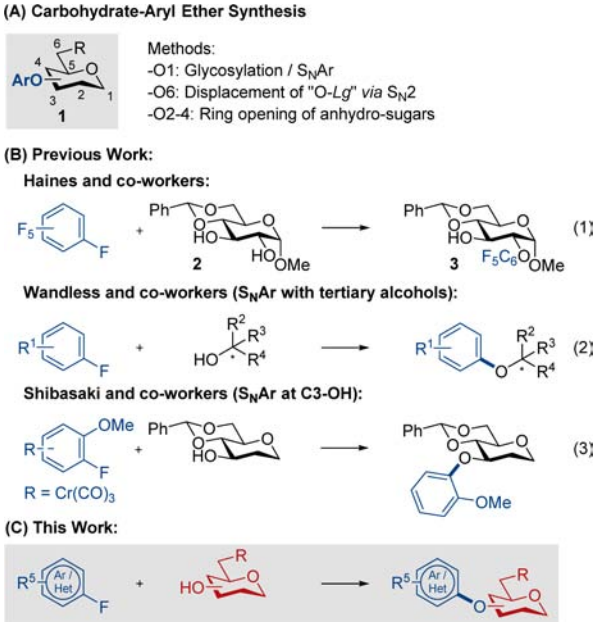
ABSTRACT: A general and practical route to carbohydrate–aryl ethers by nucleophilic aromatic substitution (S_NAr) is reported. Upon treatment with KHMDS, C–O bond formation occurs between carbohydrate alcohols and a diverse range of fluorinated (hetero)aromatics to provide the targets in good to excellent yields. Commercially available arylating agents, high atom economy, and high regioselectivity are notable features of the protocol. The aryl ether products have potential for wide-ranging applications as exemplified by the synthesis of a novel chiral P,N-ligand.



Aryl alkyl ethers are an important functional group in organic synthesis, and simple examples can be synthesized expediently using the classical Williamson etherification protocol.[1] However, the construction of more complex systems, such as those containing secondary alkyl groups, can be challenging.[2] Because of the potential importance of aryl alkyl ethers to chemical, biological, and materials applications,[2,3] a variety of C–O bond-forming methodologies have been reported, including *O*-arylations that employ transition-metal-catalyzed cross-coupling,[4,5] diaryliodonium salts,[6] benzynes,[7] or S_NAr reactions[8−10] and phenol alkylations using Mitsunobu chemistry.[11] Our interest in aryl alkyl ethers stems from a requirement to access novel carbohydrate–arene conjugates for use in chiral ligand synthesis,[12] carbohydrate chemistry, and glycobiology research; in these latter areas, the ability to install a chromophore or spectroscopic handle may be especially beneficial.[13] However, general methods that enable arylation of secondary carbohydrate hydroxyls are rare, revealing a surprising, yet significant, synthetic deficiency within carbohydrate chemistry.[14] Conceptually, the ideal process would "*click*" together the carbohydrate and aromatic components to provide diversity oriented access to ligand libraries or glyco–arene conjugates.[15]

Although carbohydrate–aryl ethers **1** have been reported, most methodologies achieve arylation at *C*1-OH[16,17] or *C*6-OH.[18] General strategies for achieving arylation of the C2–4 hydroxyls have not been described (Scheme 1A). Ring-opening of anhydro-sugars (oxiranes and oxetanes) with phenolates represents one of the few approaches to challenging C2–4 *O*-aryls. However, this results in inversion of stereochemistry, thus routinely generating unnatural carbohydrate stereoisomers.[19,20] We were intrigued by a solitary communication by Haines and co-workers, detailing the S_NAr reaction of furanosides and pyranosides (e.g., **2**) with hexafluorobenzene to yield C2-*O*-aryl ethers **3** (Scheme 1B, eq 1).[21] Although the scope of this process was limited (low yields of **3** were obtained and other substrates underwent polyarylation), its conceptual simplicity hinted at a general method for achieving challenging *O*-arylations.[21] Indeed, Wandless and co-workers have described the efficient synthesis of enantioenriched aryl-(3°)-alkyl ethers by S_NAr reaction of a diverse set of fluorinated aromatics with sterically demanding tertiary alcohols (Scheme 1B, eq 2).[8b] Additionally, Shibasaki and co-workers have arylated 3-hydroxyglucose derivatives using Cr-complexed fluoroarenes to deliver effective ligands for the enantioselective cyanosilylation of ketones (Scheme 1B, eq 3).[22] In this paper, we report mild and high-yielding conditions that enable S_NAr reactions between carbohydrate-based secondary alcohols and substituted fluoro(hetero)arene partners. The protocol tolerates common protecting groups and utilizes commercially available arylating agents to provide simple,

Scheme 1



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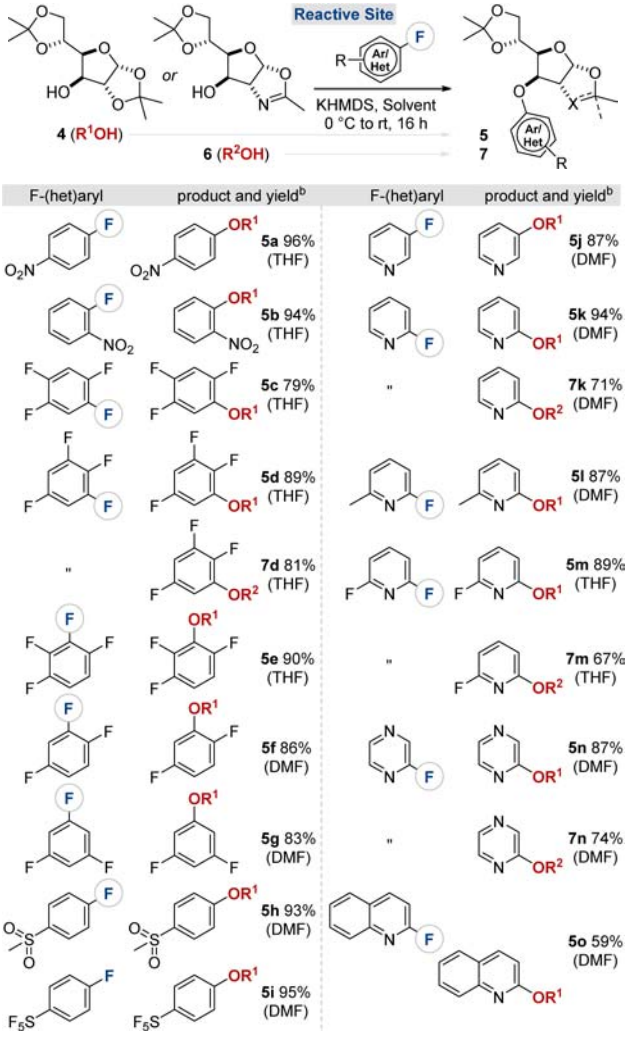
efficient, and regiocontrolled access to diverse glyco-arene that were previously inaccessible (Scheme 1C).

We began by exploring the reaction of furanosides **4** and **6** with a range of fluoro(hetero)aromatics under the action of KHMDS (Table 1). Initially, **4** was reacted with 1 equiv of 1-fluoro-4-

Table 1. Mono-etherification via S_NAr between Furanosides 4 and 6 and Fluoro(hetero)aryl Partners[a]



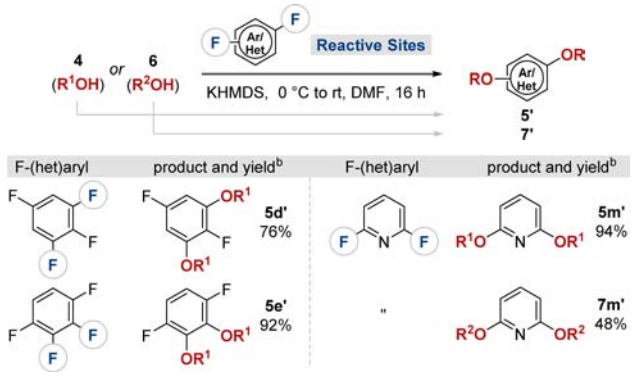
[a]Experimental details: **4** or **6** (1.1 equiv), F-(het)aryl (1.0 equiv), KHMDS (1.1 equiv), solvent, 0 °C to rt, 16 h. [b]Isolated yield.

nitrobenzene or 1-fluoro-2-nitrobenzene in THF, and in both cases, the product ethers (**5a**,**b**) were formed in near-quantitative yield. Encouraged by this initial result, we investigated if less activated fluoroaromatics, which do not embody a strongly electron-withdrawing nitro group *ortho*/*para* to the C−F bond, could be utilized. Pleasingly, tetrafluorobenzenes were successful S_NAr partners, and in THF, clean monoetherification was observed to afford products **5c**−**e** in excellent yields (79−90%) and, importantly, as single regioisomers (Table 1).[23,24] Trifluorobenzenes[25] also reacted smoothly to give ethers **5f** and **5g**; the latter demonstrates that electron-deficient substituents are not necessarily required *otho*/*para* to the C−F bond.[26] Other classes of activated fluoroaromatics, such as 4-fluorophenyl methyl sulfone and 4-fluorophenylsulfur pentafluoride, were effective coupling partners, affording ethers **5h** and **5i** in 93% and 95% yield, respectively.

To expand the scope of the reaction further, various fluorine-substituted heteroarenes (pyridines, pyrazines, and quinolines) were explored. All were suitable S_NAr partners for the arylation of furanoside **4**, and carbohydrate−heteroaryl ethers **5j**−**o** were generated in good to excellent yields (59−94%) (Table 1). Furanosyloxazoline **6** also underwent efficient *O*-arylation, and ethers **7d**, **7k**, **7m**, and **7n**, which each incorporate a different (hetero)aromatic, were isolated in 67−74% yield. Amino sugars are useful carbohydrate building blocks, whereas 6-ring heteroaromatic systems are of huge importance to medicinal chemistry.[3d] The present methodology offers a rapid and diversity-oriented entry to unusual derivatives of both classes.

We next aimed to establish if bis-etherification was possible by decreasing the fluoroarene stoichiometry from 1.0 to 0.5 equiv with respect to the sugar (Table 2). Initial studies, using THF as

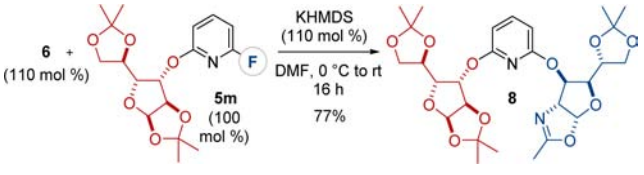
Table 2. Bis-etherification via S_NAr between Furanosides 4 and 6 and Fluoro(hetero)aryl Partners[a]



[a]Experimental details: **4** or **6** (1.1 equiv), F-(het)aryl (0.5 equiv), KHMDS (1.1 equiv), DMF, 0 °C to rt, 16 h. [b]Isolated yields.

solvent, resulted in low yields for the conversion of **4** to bis-ether **5d′** (≤30%). However, by switching to DMF, a more polar solvent, bis-ethers **5d′**, **5e′**, and **5m′** were accessed in good yields (76−92%) and as single regioisomers.[27] Alcohol **6** was also amenable to bis-etherification, and pyridine **7m′** was isolated in 48% yield. The observed solvent-dependent selectivity (THF for monoetherification vs DMF for bis-etherification) presumably reflects changes in the nucleophilicity of the in situ generated alkoxide.[28] By exploiting this, we envisaged a modular S_NAr approach to *nonsymmetrical* aryl linked carbohydrates. As already highlighted, 2,6-difluoropyridine was subjected to monoetherification with **4** in THF to afford selectively aryl ether **5m** (Table 1). Subsequent S_NAr reaction of **5m** with **6** in DMF furnished nonsymmetrical bis-aryl ether **8** in 77% yield (Scheme 2). It should be noted that, under acidic conditions, furanosides are readily transformed to the corresponding pyranoses, and this portends further potential applications for the chemistry described here.[29]

Scheme 2. Unsymmetrical Bis-aryl Ether Formation



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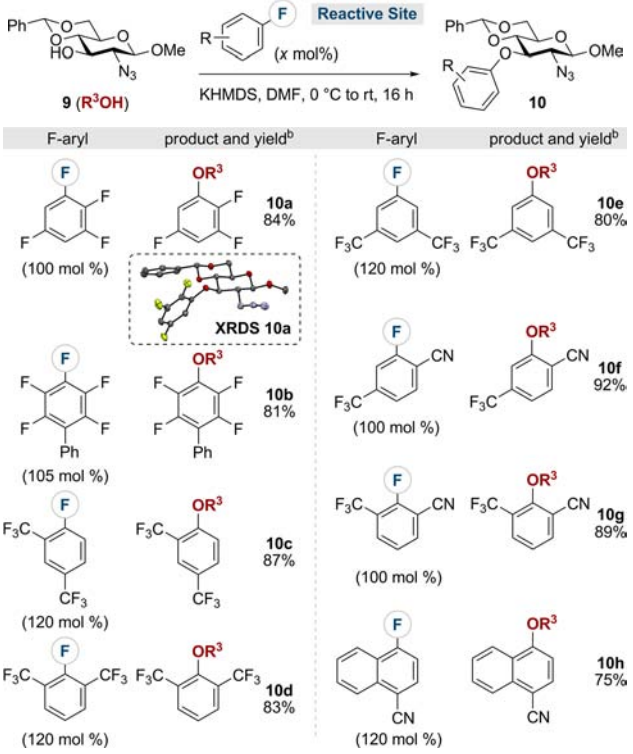
Direct *O*-arylation of pyranoside-based secondary alcohols is also possible. Differentially protected pyranoside substrate **9** was synthesized (see Supporting Information) and evaluated in *O*-arylations that included sterically demanding fluoroaromatics as coupling partners (Table 3). Initially, reaction of **9** with 1,2,3,5-tetrafluorobenzene, using previously optimized conditions (THF as solvent, see Table 1), yielded selectively the desired monoaryl ether product **10a** but only in modest yield (50%), thereby highlighting the difference in reactivity between the secondary alcohols of **4** and **9**. It is likely that the increased steric demands of alcohol **9** (vs **4**) are responsible for its diminished reactivity. However, by utilizing DMF as solvent **10a** was isolated in 84% yield; the regiochemistry of ether **10a** was confirmed by single-crystal X-ray diffraction. A pentafluorinated biaryl moiety coupled smoothly to give product **10b** as a single regioisomer. CF_3 groups also render the arene component sufficiently electrophilic for efficient S_NAr reactions, and ethers **10c–e** were obtained in excellent yields. Notably, double *ortho*-substitution can be tolerated on the aromatic partner, and this allowed efficient access to aryl ether **10d**. The facile incorporation of medicinally important CF_3 groups is a potentially useful aspect of the current methodology.[30] Cyano groups can also be used to activate the aromatic component, and *O*-arylation of **9** to afford **10f–g** occurred in excellent yield. Reaction of **9** with 1-fluoronapthalene was not successful; however, the 4-cyano-substituted derivative reacted smoothly to provide **10h** in high yield. The cyano moiety of **10f–h** is a useful handle for further manipulations.

Within the field of asymmetric transition-metal catalysis, chiral P,N-ligands have emerged as privileged systems for challenging transformations,[31] as highlighted by their use in Ir-catalyzed enantioselective hydrogenations of unfunctionalized alkenes.[32] To demonstrate the utility of the *O*-arylation methodology, we have applied it to the installation of the key pyridine moiety of novel P,N-ligand **14** (Scheme 3). Isomannide **11** is homochiral and possesses a C_2-symmetric and rigid concave structure, rendering it an attractive scaffold for chiral auxiliary and phosphorus-based ligand synthesizes.[33] Accordingly, selective *O*-benzylation of **11** afforded benzyl ether **12** in 44% yield. *O*-Arylation of the remaining free hydroxyl, with 2-fluoro-6-methylpyridine, proceeded smoothly under standard conditions to generate **13** in 85% yield. Hydrogenative *O*-debenzylation of **13** (Pd/C) in acidic ethanol furnished the corresponding alcohol, which was reacted directly with chlorodiphenylphosphine to provide target P,N-ligand **14** in 86% yield over the two steps.

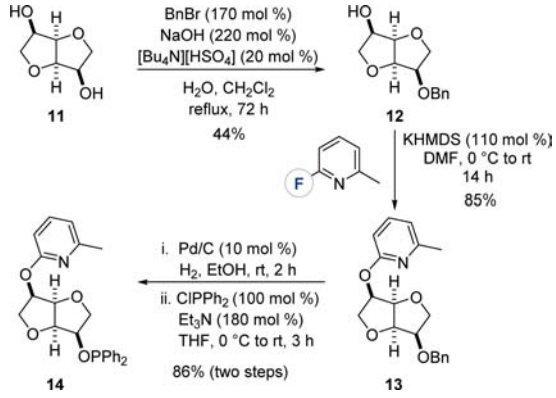
In conclusion, we demonstrate that S_NAr is a practical, general, and atom-economic methodology for arylating carbohydrate-based secondary alcohols. The resulting carbohydrate–arene conjugates are likely to be of interest for a wide range of synthetic and medicinal applications. A diverse variety of motifs can be introduced onto the carbohydrate core easily and in good yields. Critical to the success of the protocol is the selection of an appropriate solvent to facilitate either selective monoetherification or the coupling of sterically demanding components. The utility of the chemistry is exemplified by its application to a short and diversifiable synthesis of a novel P,N-ligand.

Table 3. S_NAr between Representative Pyranoside 9 and Fluoroaryl Partners[a]



[a]Experimental details: **9** (1.0 equiv), F-aryl (1.0–1.2 equiv), KHMDS (1.5 equiv), DMF, 0 °C to rt, 16 h. [b]Isolated yields.

Scheme 3. P,N-Ligand Synthesis via a S_NAr Approach



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02413.

Experimental procedures and characterization data (PDF)
Crystallographic information for **10a** (CIF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Williamson, A. *Justus Liebigs Ann. Chem.* **1851**, *77*, 37.
(2) (a) *The Chemistry of the Ether Linkage*; Patai, S., Ed.; John Wiley & Sons Ltd.: New York, 1967. (b) For a review on metal-catalyzed aryl ether synthesis, see: Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046.
(3) (a) Lovering, F.; Bikker, J.; Humblet, C. *J. Med. Chem.* **2009**, *52*, 6752. (b) Lednicer, D. *Strategies for Organic Drug Synthesis and Design*, 2nd ed.; John Wiley & Sons, Inc.: New York, 2008. (c) Roughley, S. D.; Jordan, A. M. *J. Med. Chem.* **2011**, *54*, 3451. (d) *Heterocyclic Chemistry in Drug Discovery*; Li, J. J., Ed.; Wiley-Blackwell: New York, 2013.
(4) Selected examples: (a) Maligres, P. E.; Li, J.; Krska, S. W.; Schreier, J. D.; Raheem, I. T. *Angew. Chem., Int. Ed.* **2012**, *51*, 9071. (b) Wu, X.; Fors, B. P.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2011**, *50*, 9943. (c) Torraca, K. E.; Huang, X.; Parrish, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 10770. (d) Terrett, J. A.; Cuthbertson, J. D.; Shurtleff, V. W.; MacMillan, D. W. C. *Nature* **2015**, *524*, 330.
(5) Selected reviews: (a) Hartwig, J. F. *Nature* **2008**, *455*, 314. (b) Monnier, F.; Taillefer, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 6954.
(6) (a) Merritt, E. A.; Olofsson, B. *Angew. Chem., Int. Ed.* **2009**, *48*, 9052. (b) Lindstedt, E.; Ghosh, R.; Olofsson, B. *Org. Lett.* **2013**, *15*, 6070. (c) Ghosh, R.; Lindstedt, E.; Jalalian, N.; Olofsson, B. *ChemistryOpen* **2014**, *3*, 54. (d) Sundalam, S. K.; Stuart, D. R. *J. Org. Chem.* **2015**, *80*, 6456.
(7) Selected example: Cano, R.; Ramón, D. J.; Yus, M. *J. Org. Chem.* **2011**, *76*, 654.
(8) Selected SNAr examples: (a) Raeppel, S.; Raeppel, F.; Suffert, J. *Synlett* **1998**, *1998*, 794. (b) Woiwode, T. F.; Rose, C.; Wandless, T. J. *J. Org. Chem.* **1998**, *63*, 9594. (c) Rodriguez, J. R.; Agejas, J.; Bueno, A. B. *Tetrahedron Lett.* **2006**, *47*, 5661. (d) Ouellet, S. G.; Bernardi, A.; Angelaud, R.; O'Shea, P. D. *Tetrahedron Lett.* **2009**, *50*, 3776.
(9) (a) Smith, M. B.; March. J. *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 6th ed.; John Wiley & Sons, Inc.: New York, 2007; pp 853. S_NAr reviews:. (b) Vlasov, V. M. *J. Fluorine Chem.* **1993**, *61*, 193. (c) Vlasov, V. M. *Russ. Chem. Rev.* **2003**, *72*, 681.
(10) Reviews on S_NAr with metal-complexed aromatics: (a) Rose-Munch, F.; Rose, E. *Eur. J. Inorg. Chem.* **2002**, *2002*, 1269. (b) Rosillo, M.; Domínguez, G.; Pérez-Castells, J. *Chem. Soc. Rev.* **2007**, *36*, 1589.
(11) Mitsunobu approach: (a) Manivel, P.; Rai, N. P.; Jayashankara, V. P.; Arunachalam, P. N. *Tetrahedron Lett.* **2007**, *48*, 2701. Other methods of activation have also been used: (b) Shintou, T.; Mukaiyama, T. *J. Am. Chem. Soc.* **2004**, *126*, 7359. (c) Sach, N. W.; Richter, D. T.; Cripps, S.; Tran-Dubé, M.; Zhu, H.; Huang, B.; Cui, J.; Sutton, S. C. *Org. Lett.* **2012**, *14*, 3886. (d) Shen, X.; Neumann, C. N.; Kleinlein, C.; Goldberg, N. W.; Ritter, T. *Angew. Chem., Int. Ed.* **2015**, *54*, 5662.
(12) Henderson, A. S.; Bower, J. F.; Galan, M. C. *Org. Biomol. Chem.* **2014**, *12*, 9180.
(13) Selected examples: (a) Galan, M. C.; Tran, A. T.; Bernard, C. *Chem. Commun.* **2010**, *46*, 8968. (b) Galan, M. C.; Benito-Alifonso, D.; Watt, G. M. *Org. Biomol. Chem.* **2011**, *9*, 3598. (c) Galan, M. C.; Tran, A. T.; Bromfield, K.; Rabbani, S.; Ernst, B. *Org. Biomol. Chem.* **2012**, *10*, 7091. (d) Benito-Alifonso, D.; Tremel, S.; Hou, B.; Lockyear, H.; Mantell, J.; Fermin, D. J.; Verkade, P.; Berry, M.; Galan, M. C. *Angew. Chem., Int. Ed.* **2014**, *53*, 810.
(14) Wuts, P. G. M.; Greene, T. W. *Greene's Protective Groups in Organic Synthesis*, 4th ed.; John Wiley & Sons, Inc.: New York, 2006.
(15) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004.
(16) Anomeric glycosylation with phenols is readily achieved via oxonium intermediates: Jacobsson, M.; Malmberg, J.; Ellervik, U. *Carbohydr. Res.* **2006**, *341*, 1266.
(17) Several reports outline S_NAr reactions of highly electron-deficient fluoroaromatics with anomeric hydroxyls to afford reactive glycosyl donors. For a review, see: Jensen, K. J. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2219.
(18) The primary C6-OH is amenable to conventional S_N2 chemistry to access C6-*O*-aryl ethers, typically with *p*-methoxyphenol under Mitsunobu conditions. For a representative example, see: Clausen, M. H.; Jørgensen, M. R.; Thorsen, J.; Madsen, R. *J. Chem. Soc., Perkin Trans. 1* **2001**, 543.
(19) Selected example: Shi, H.; Zhou, B.; Li, W.; Shi, Z.; Yu, B.; Wang, R. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 2855.
(20) Review: Černý, M. *Advances in Carbohydrate Chemistry and Biochemistry*; Horton, D., Ed.; Academic Press: New York, 2003; Vol. *58*, p 121.
(21) Haines, A. H.; Symes, K. C. *J. Chem. Soc., Perkin Trans. 1* **1973**, 53.
(22) (a) Hamashima, Y.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 7412. (b) Hamashima, Y.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2001**, *42*, 691.
(23) The reactions were generally fast (<3 h). However, prolonged reaction times were not detrimental to yield and were often used for convenience.
(24) Where applicable, product ether regioselectivity was assigned by ^{13}C NMR coupling constants. See: Pretsch, E.; Bühlmann, P.; Badertscher, M. *Structure Determination of Organic Compounds*, 4th ed.; Springer: New York, 2009.
(25) Reaction of 1,2,3-trifluorobenzene with **4** yielded separable regioisomeric products (see the Supporting Information).
(26) 1,4-Difluorobenzene was unreactive under the reaction conditions.
(27) The bis-etherified product resulting from reaction of 1,2,4,5-tetrafluorobenzene with **4** yielded nonseparable regioisomeric products.
(28) In DMF, reaction between equimolar quantities of **4** and 1,2,3,5-tetrafluorobenzene afforded a mixture (~2:1) of mono- and bis-etherification products.
(29) A representative example rearrangement of a furanoside to the corresponding pyranose is contained within the Supporting Information of ref 12. See also: Cai, Y.; Ling, C.-C.; Bundle, D. R. *Org. Lett.* **2005**, *7*, 4021.
(30) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320.
(31) *Privileged Chiral Ligands Catalysis*; Zhou, Q.-L., Ed.; Wiley-VCH: Weinheim, 2011.
(32) Woodmansee, D. H.; Pfaltz, A. *Top. Organomet. Chem.* **2011**, *34*, 31.
(33) Koert, U. Isomannide and Isosorbide. In *e-EROS Encyclopedia of Reagents for Organic Synthesis*, 2012. DOI: 10.1002/047084289X.rn01380.

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