

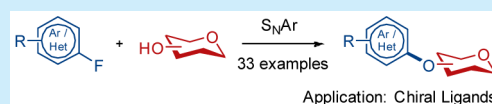
# Nucleophilic Aromatic Substitution ( $S_NAr$ ) as an Approach to Challenging Carbohydrate–Aryl Ethers

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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.

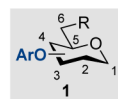


Aryl alkyl ethers are an important functional group in organic synthesis, and simple examples can be synthesized expediently using the classical Williamson etherification protocol.<sup>1</sup> However, the construction of more complex systems, such as those containing secondary alkyl groups, can be challenging.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

Although carbohydrate–aryl ethers **1** have been reported, most methodologies achieve arylation at C1–OH<sup>16,17</sup> or C6–OH.<sup>18</sup> 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.<sup>19,20</sup> 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).<sup>21</sup> 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.<sup>21</sup> Indeed, Wandless and co-workers have described the efficient synthesis of enantioenriched aryl-(3°)-alkyl ethers by  $S_NAr$  reaction of a

## Scheme 1

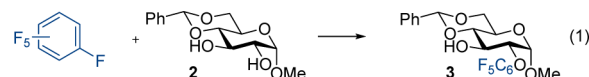
### (A) Carbohydrate–Aryl Ether Synthesis



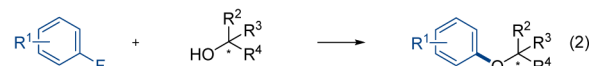
Methods:  
-O1: Glycosylation /  $S_NAr$   
-O6: Displacement of “O-Lg” via  $S_N2$   
-O2-4: Ring opening of anhydro-sugars

### (B) Previous Work:

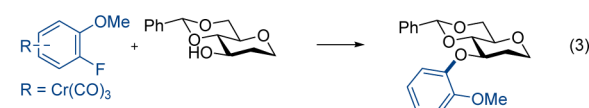
#### Haines and co-workers:



#### Wandless and co-workers ( $S_NAr$ with tertiary alcohols):



#### Shibasaki and co-workers ( $S_NAr$ at C3-OH):



### (C) This Work:



diverse set of fluorinated aromatics with sterically demanding tertiary alcohols (Scheme 1B, eq 2).<sup>8b</sup> 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).<sup>22</sup> 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,

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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<sup>a</sup>**

F-(het)aryl	product and yield <sup>b</sup>	F-(het)aryl	product and yield <sup>b</sup>
	<b>5a</b> 96% (THF)		<b>5b</b> 94% (THF)
	<b>5c</b> 79% (THF)		<b>5d</b> 89% (THF)
	<b>5e</b> 90% (THF)		<b>5f</b> 86% (DMF)
	<b>5g</b> 83% (DMF)		<b>5h</b> 93% (DMF)
	<b>5i</b> 95% (DMF)		<b>5j</b> 87% (DMF)
	<b>5k</b> 94% (DMF)		<b>5l</b> 87% (DMF)
	<b>5m</b> 89% (THF)		<b>5n</b> 87% (DMF)
	<b>5o</b> 59% (DMF)		<b>5p</b> 48% (DMF)

<sup>a</sup>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. <sup>b</sup>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).<sup>23,24</sup> Trifluorobenzenes<sup>25</sup> also reacted smoothly to give ethers **5f** and **5g**; the latter demonstrates that electron-deficient substituents are not necessarily required *ortho/para* to the C–F bond.<sup>26</sup> 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.<sup>3d</sup> 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

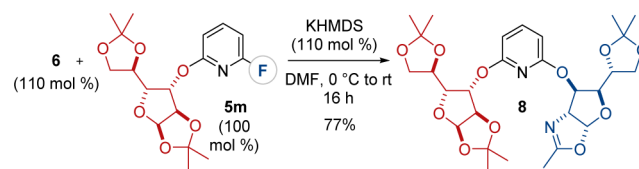
**Table 2. Bis-etherification via  $S_NAr$  between Furanosides **4** and **6** and Fluoro(hetero)aryl Partners<sup>a</sup>**

F-(het)aryl	product and yield <sup>b</sup>	F-(het)aryl	product and yield <sup>b</sup>
	<b>5d'</b> 76%		<b>5m'</b> 94%
	<b>5e'</b> 92%		<b>7m'</b> 48%

<sup>a</sup>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. <sup>b</sup>Isolated yields.

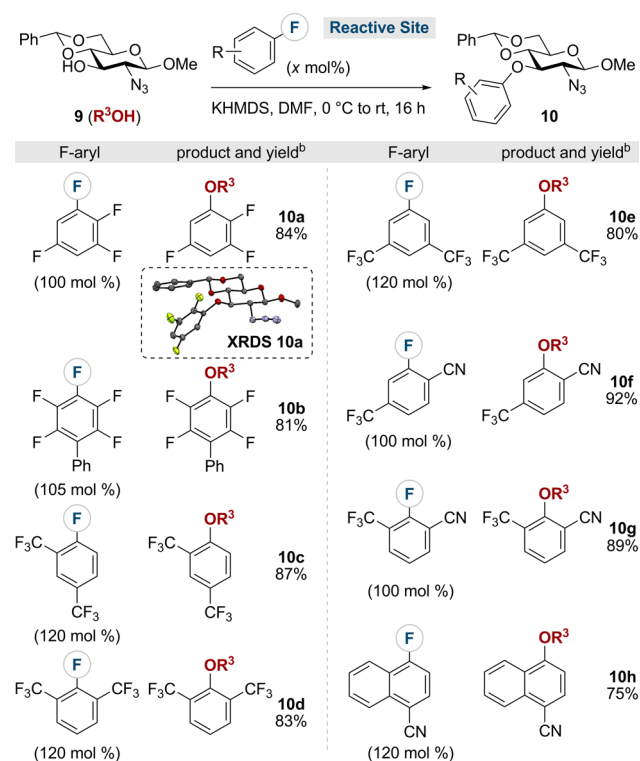
solvent, resulted in low yields for the conversion of **4** to bis-ether **5d'** ( $\leq 30\%$ ). However, by switching to DMF, a more polar solvent, bis-ethers **5d'**, **5e'**, and **5m'** were accessed in good yields (76–92%) and as single regioisomers.<sup>27</sup> Alcohol **6** was also amenable 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.<sup>28</sup> 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.<sup>29</sup>

**Scheme 2. Unsymmetrical Bis-aryl Ether Formation**



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-

**Table 3.**  $S_NAr$  between Representative Pyranoside **9** and Fluoroaryl Partners<sup>a</sup>



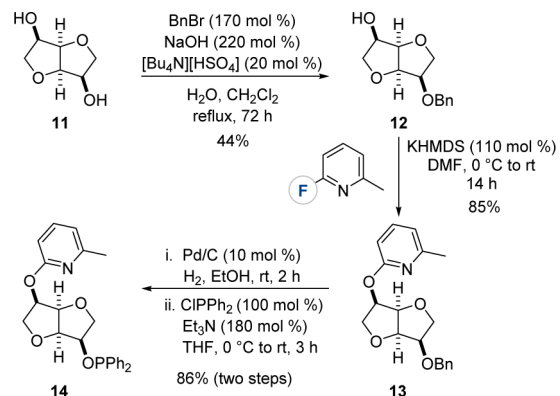
<sup>a</sup>Experimental details: **9** (1.0 equiv), F-aryl (1.0–1.2 equiv), KHMDS (1.5 equiv), DMF, 0 °C to rt, 16 h. <sup>b</sup>Isolated yields.

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.<sup>30</sup> 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-fluoronaphthalene 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,<sup>31</sup> as highlighted by their use in Ir-catalyzed enantioselective hydrogenations of unfunctionalized alkenes.<sup>32</sup> 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

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



and possesses a  $C_2$ -symmetric and rigid concave structure, rendering it an attractive scaffold for chiral auxiliary and phosphorus-based ligand syntheses.<sup>33</sup> 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.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: [10.1021/acs.orglett.5b02413](https://doi.org/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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- (24) Where applicable, product ether regioselectivity was assigned by <sup>13</sup>C NMR coupling constants. See: Pretsch, E.; Bühlmann, P.; Badertscher, M. *Structure Determination of Organic Compounds*, 4th ed.; Springer: New York, 2009.
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- (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.
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