ChemComm

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Journal:	*ChemComm*
Manuscript ID	CC-COM-01-2021-000496.R2
Article Type:	Communication

COMMUNICATION

Selective demethylation of *O*-aryl glycosides by iridium-catalyzed hydrosilylation

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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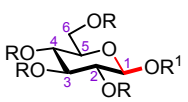
The cleavage of alkyl ethers by hydrosilylation is a powerful synthetic tool for the generation of silyl ethers. Previous attempts to apply this transformation to carbohydrate derivatives have been constrained by poor selectivity and preferential reduction of the anomeric position. *O*-aryl glycosides are found to be stable under iridium- and borane-catalyzed hydrosilylation conditions, allowing for alkyl ether cleavage without loss of anomeric functionality. A cationic bis(phosphine)iridium complex catalyzes the selective 3-demethylation of a variety of 2,3,4-tri-*O*-methyl pyranoses, offering a unique approach to 3-hydroxy or 3-acetyl 2,4-di-*O*-methylpyranoses.

The development of processes for the selective functionalization of carbohydrate derivatives is a challenging endeavor owing to their structural and stereochemical complexity and diversity.[1] Typical approaches to carbohydrate synthesis address this complexity by relying extensively on protecting groups to funnel reactivity away from other sites.[2] One of the simplest protecting groups is the methyl ether, which is commonly avoided in carbohydrate chemistry because of the forcing conditions required for its removal.[2-4]

A promising solution to alkyl ether cleavage is a class of catalytic reactions that involve catalyst-promoted silane heterolysis to give a silyloxonium ion which is then reduced *in situ*. The Gagné group and others have applied both electron-deficient borane and iridium catalysts which operate by this mechanism to the reduction of carbohydrate derivatives,[5-6] however in all cases the anomeric (C1) position is reduced in preference to C-O cleavage at other sites (Figure 1).[6-13] Such selectivity offers avenues for the synthesis of small molecule building blocks from carbohydrates, but has limited applications to the preparation of glycosides or polysaccharides where C1 reduction is undesired.



Catalysts

$B(C_6F_5)_3$ $B(Ar_{3,5\text{-}CF_3})_3$

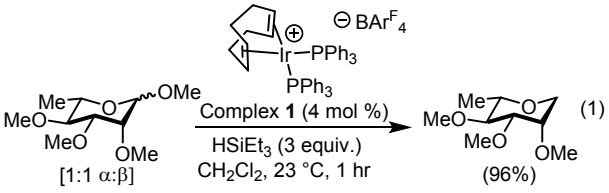
$(HO)B(C_6F_5)_2$

$[(POCOP)IrH(acetone)]B(C_6F_5)_4$

Figure 1. Preferential anomeric (C1) reduction in previous attempts at carbohydrate hydrosilylation.[6-11, 13]

Our group has been investigating simple bis(phosphine)iridium catalysts for the cleavage of alkyl ethers and have shown that they operate by an analogous mechanism to borane catalysts.[14] We recently demonstrated that modulation of the catalyst structure can influence the selectivity of ether cleavage in 6-membered carbocyclic ethers.[15] Our success in the selective cleavage of a single C-O bond in sterol derivatives inspired the examination of protected carbohydrate substrates. We now report a system for the selective 3-demethylation of 2,3,4-tri-*O*-methyl pyranoses with retention of anomeric functionality. This exquisitely selective method allows for the unmasking of the 3-hydroxy group in a variety of hexose derivatives.

When tetra-*O*-methyl-L-rhamnose is subjected to hydrosilylation with the iridium precatalyst **1**, C1 demethoxylation occurs in preference to reduction at other positions (eqn. 1). This preference for C1 reduction mirrors previous results obtained with borane catalysts and one previous iridium example.[6-13] Preferential reduction at C1 likely arises from the increased nucleophilicity of the acetal functionality relative to the methyl ethers at the 2, 3, and 4 positions, which promotes silyloxonium ion formation at this site. C-O cleavage likely occurs through elimination of the silyloxonium ion to give an oxocarbenium ion that is reduced *in situ*. In our case overreduction is not observed, unlike many previously examined catalysts.[7-8, 11-13, 16]



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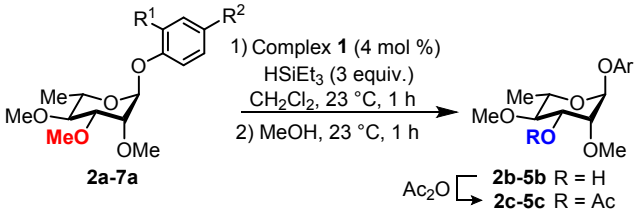
† Electronic Supplementary Information (ESI) available: Experimental procedures, compound characterization data, details of computational studies, and X-ray crystallographic analyses. See DOI: 10.1039/x0xx00000x

We hypothesized that *O*-aryl glycosides would show increased resistance to C1 reduction owing to the decreased nucleophilicity of the aryloxy group as well as the potential for steric protection of the acetal oxygen atoms. Indeed, attempts at reduction of a series of 1-aryloxy-2,3,4-tri-*O*-methyl-L-rhamnose derivatives show that suitably *ortho*-substituted aryloxy groups protect C1 under iridium-catalyzed hydrosilylation conditions. Comparison of the *o*-methyl, isopropyl, and t-butyl derivatives **2a**, **3a** and **4a** show progressively increasing yields of the 3-demethyl products with retention of the C1 aryloxy group. The parent phenol derivative **7a** and the *o*-methoxy derivative **6a** are both unsuitable. **7a** is reduced unselectively to numerous unidentified products, while **6a** undergoes exclusive C1 reduction to give 1-deoxy-2,3,4-tri-*O*-methyl-rhamnose. As part of this study, compounds **2a**, **3a**, **4a** and **5a** were characterized by X-ray crystallography, and the site of reduction was confirmed to be C3 by crystallization of **2c**, the product of **2a** reduction and acylation.

Table 1. Selective demethylation of *O*-aryl rhamnosides



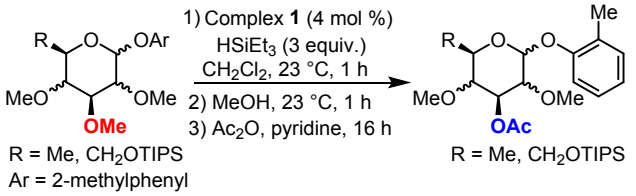
Entry	R^1	R^2	NMR Yield **2b-5b** (%)	Isolated Yield **2c-5c** (%)
2a	Me	H	74	70
3a	iPr	H	78	73
4a	tBu	H	97[a]	83[a]
5a	Cl	Cl	86	65
6a	OMe	H	0 (C1 red. obsv.)	-
7a	H	H	Unsel. reduction	-

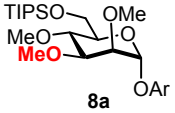
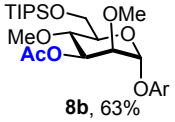
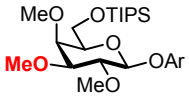
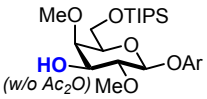
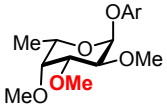
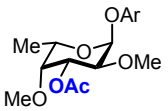
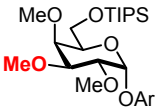
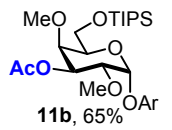
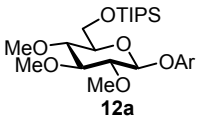
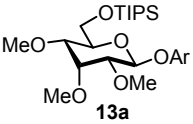
[a] 2 hr reaction time.

Although bulky ortho-substituted aryloxy groups serve as the best protecting groups of C1 in the rhamnose derivatives in Table 1, we found that *o*-cresol derivatives like **2a** were most convenient to prepare. Therefore we chose to explore the scope of selective C3-demethylation of *O*-aryl glycosides using the 2-methylphenyl-protected hexopyranoses shown in Table 2. *O*-aryl-α-mannose and β-galactose derivatives **8a** and **9a** both undergo selective C3-demethylation under our optimized conditions. The α-L-fucose derivative **10a** is also reduced via C3 demethylation. The catalytic reaction appears to be somewhat insensitive to the stereochemistry at C1, with α-galactose derivative **11a** undergoing C3 demethylation in comparable yield to the β anomer, though in this single case small amounts of C2 demethylation (**11c**) are also observed (see the supporting information). By comparison, the glucose derivative **12a** only undergoes slow C1 reduction. With the exception of 6-deoxy examples, we found it necessary to protect C6 as the corresponding triisopropylsilyl ether to prevent the formation of multiple products during catalysis.

The poor reactivity of glucose contrasts the relative success of rhamnose, mannose, galactose, and fucose derivatives to suggest a potential role for the relative stereochemistry of the 2 and 4 positions in controlling the reactivity of the 3-methoxy group.[17] In the successful examples in Tables 1 and 2, the 3-methoxy group is *cis* to one neighboring methoxy group and *trans* to the other, whereas the neighboring substituents are mutually *trans* in glucose derivative **12a**. Consistent with this hypothesis, the minor C2 demethylation product **11c** is only observed for the α anomer of galactose, in which C2 also possesses a *cis* and *trans* pair of neighboring groups.[18] When we examined allose derivative **13a** in which the 2, 3, and 4 methoxy groups are mutually *cis*, we found that C-O bond cleavage proceeds unselectively to give a complex mixture of products. A similar reactivity pattern has been observed recently in carbohydrate benzoylation.[17] More generally, the successful substrates possess a triad of mutually gauche alkoxy groups with the same directionality [g(+)/g(+) or g(-)/g(-)]. (Figure S1) Attempts to reduce pentose derivatives also gave complex mixtures. (Figure S2)

Table 2. Selective demethylation of *O*-aryl glycosides

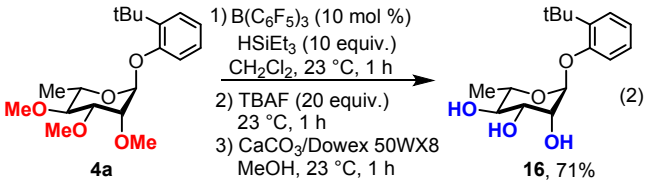


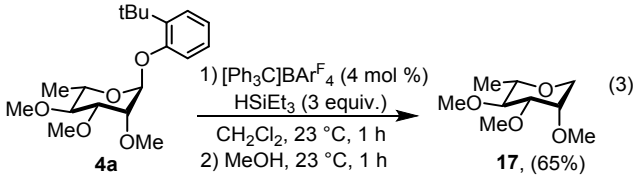
Derivative	Substrate	Product
α-D-mannose[a]	 **8a**	 **8b**, 63%
β-D-galactose[a]	 **9a**	 **9b**, 75%
L-fucose	 **10a** [10:1 α:β]	 **10b**, 67% [α]
α-D-galactose	 **11a**	 **11b**, 65% **11c**, 13% (C2)
β-D-glucose	 **12a**	recovered **12a** (63% *NMR*)
β-D-allose	 **13a**	complex mixture

[a] 2 hr reaction time.

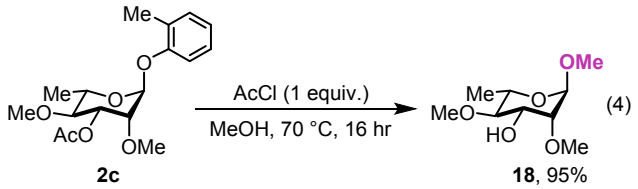
Thus, under optimized conditions, the use of iridium precatalyst **1** and a suitable aryloxy group allows for the selective 3-demethylation of 2,3,4-tri-*O*-methyl rhamnose, mannose, fucose, and galactose derivatives. A proposed mechanism for

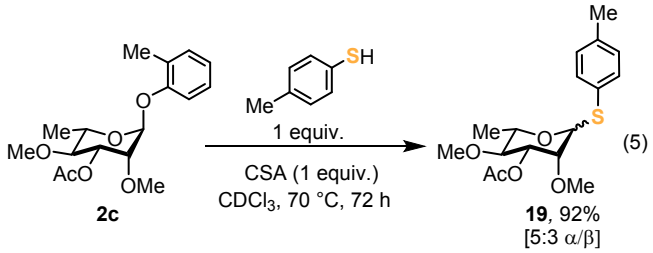
this transformation is given in Figure S3 and is based on previous work on related systems by ourselves and others.[14-15, 19-20] In the case of the reduction of **3a** by **1**, the catalyst resting state is observed to be a mixture of the known neutral tetrahydridosilyl complex $(PPh_3)_2IrH_4SiEt_3$ (**1a**)[15] and a species tentatively assigned as its cationic bis(σ-triethylsilane) precursor[21] $(PPh_3)_2IrH_2(HSiEt_3)_2^+$ (**1b**) (see Figure S4). Because silyloxonium ions are known to exchange silylium ion-equivalents with ethers,[19, 22] formation of **1a** via Ir-mediated silane heterolysis presumably gives a mixture of carbohydrate silyloxonium ions from which the major product of 3-demethylation is derived. A computational analysis of the relative energies of the **2a**-derrived silyloxonium ion isomers is consistent with some thermodynamic preference for silyloxonium ion formation at the C3 and C4 methyl ethers. Additional details are available in the supporting information (Figure S5).





In previous studies the Gagné group showed that the electron deficient borane $B(C_6F_5)_3$ is capable of extensive reduction of carbohydrate derivatives with the initial site of C-O cleavage being C1.[8-11] We have found that 1-aryloxy groups are also capable of protecting C1 against $B(C_6F_5)_3$-catalyzed hydrosilylation. The rhamnose derivative **4a** undergoes $B(C_6F_5)_3$-catalyzed reduction to give the tri-*O*-demethylated product **16** (eqn. 2). Lower molar equivalents of silane did not lead to selective reduction at C2, C3, or C4, but 10 equivalents is sufficient for complete demethylation without reduction of C1. Thus, 1-aryloxy groups appear to be applicable anomeric protecting groups beyond iridium-catalyzed hydrosilylative ether cleavage. The nature of the hydride equivalent is still an important factor however. When $[Ph_3C][BArF_4]$ is employed as the catalyst alone in the reduction of **4a**, C1 reduction is observed in preference to other sites of potential C-O cleavage (eqn. 3). In this case triethylsilane itself is presumed to act as the hydride source for reduction of the C1 silyloxonium or resulting oxocarbenium ion.[19, 23]





While the apparent stability of the 1-aryloxy group under hydrosilylative conditions is sufficient to protect the anomeric position, it can still be exchanged under suitable reaction conditions. Indeed, the hydrolytic lability of naturally-occurring *O*-aryl glycosides has been previously identified in studies of wine grapes exposed to wood smoke.[24] In our case, treatment of the product **2c** with a methanolic solution of hydrogen chloride (generated by addition of AcCl to methanol) gives the corresponding methyl glycoside **18** in high yield with liberation of free *o*-cresol and removal of the O3 acetyl protecting group (eqn. 4). The O-aryl glycoside **2c** can also be transformed into the corresponding thioglycoside **19** in high yield using camphorsulfonic acid (CSA). Thus the O-aryl glycoside products of this methodology are amenable to conversion into either glycosyl donors or acceptors in a single additional step.[25] The 3-position is a common site of glycosylation in carbohydrates, which further increases the value of this transformation.[26-28]

In summary, we report a catalytic system for the selective mono-3-demethylation of 2,3,4-tri-*O*-methyl carbohydrate derivatives. Substituted aryloxy groups are found to be suitable protecting groups for the anomeric position, enabling the first catalytic, hydrosilylative method for C-O bond cleavage in carbohydrate derivatives without anomeric reduction. 1-aryloxy protection of the anomeric position is similarly effective under borane catalysis, demonstrating the broad applicability of this approach. The success of rhamnose, galactose, mannose, and fucose derivatives appears correlated with the relative stereochemistry about the 3-position.

Notes and references

This material is based upon work supported by the National Science Foundation under grant no. CHE-1847813. Acknowledgment is made to the Donors of the American Chemical Society Petroleum Research Fund for partial support of this research.

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