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Published in:
Chemical Communications

DOI:
[10.1039/c7cc01416c](https://doi.org/10.1039/c7cc01416c)

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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2017

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Wan, I. C., Witte, M. D., & Minnaard, A. J. (2017). Site-selective carbon-carbon bond formation in unprotected monosaccharides using photoredox catalysis. *Chemical Communications*, 53(36), 4926-4929. <https://doi.org/10.1039/c7cc01416c>

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Cite this: *Chem. Commun.*, 2017, **53**, 4926

Received 22nd February 2017,
Accepted 11th April 2017

DOI: 10.1039/c7cc01416c

rsc.li/chemcomm

Site-selective carbon–carbon bond formation in unprotected monosaccharides using photoredox catalysis†

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Site-selective photoredox reactions with somophiles readily enable branching of the carbon skeleton of unprotected glucosides, allosides, and xylosides regioselectively at C3. These reactions open the possibility of selective C–C bond formation in monosaccharides without multi-step protection–deprotection strategies.

Site-selective catalysis is a rapidly developing area, pushed by the plethora of contemporary catalytic methods possessing high functional group compatibility and selectivity.^{1,2} This approach is of particular importance in late-stage modification of complex natural products.³ The number of methods to selectively functionalize carbohydrates is, however, still very limited and mainly focused on the anomeric hydroxyl group in reducing sugars and the primary hydroxyl group.⁴ This is not surprising as the secondary hydroxyl groups in, for example, glucose are very similar. Regioselective esterification and silylation in monosaccharides, mostly with the anomeric center and the primary hydroxyl group protected, have been reported using several catalysts and has been applied in natural product synthesis.^{5,6} These reaction types, while being very versatile, do not modify the structure of the carbohydrate itself. We have shown that catalytic regioselective oxidation of pyranoses, either mono-, di- or oligosaccharides,^{7,8} can be achieved with excellent selectivity. This provides an entry into carbohydrate interconversion, *e.g.* allose can be prepared from glucose,⁹ and to aminosugars. Still, also in these cases the carbon skeleton of the carbohydrate at hand remains unchanged, with the exception of an α -ketol rearrangement observed in a number of cases.⁹

Among the approaches in site-selective catalysis, the currently developing photo-catalytic Hydrogen Atom Transfer (HAT) strategies seem as such particularly suitable for application in the modification of unprotected carbohydrates, although this

has not been reported until now.¹⁰ Radical chemistry, unlike most polar chemistry, does not require protection of hydroxyl groups and is largely compatible with polar and protic solvents. The latter is an important requirement as carbohydrates have a limited solubility in most solvents other than water, and polar aprotic solvents like DMSO. A major stumble block in the application of HAT reactions to modify unprotected carbohydrates is, no different than for the other reactions, control over regioselectivity. If any selectivity would be expected, it would be at C1 as, in particular in the case of β -glycosides, the formed radical would be more stable.¹¹ The picture seemed bleak, until the group of MacMillan disclosed a study showing that HAT could be steered to a hydroxyl group in the presence of ethers and acetals.¹² By adding a hydrogen bond acceptor (dihydrogen-phosphate), the charge density on the oxygen of the hydroxyl group is increased compared to the present ether oxygens and HAT takes place with good selectivity on that α -carbon. The concept was demonstrated in, among other non-carbohydrate examples, a protected galactose derivative in which only the primary hydroxyl group at C6 remained (Scheme 1).

Taking this a step further, we reasoned that preferential hydrogen bond formation in compounds containing more than one hydroxyl group, *in casu* unprotected carbohydrates, might lead to site-selective HAT. It is known that carbohydrates form

Scheme 1 Photoredox activation of an α -hydroxy C–H bond as performed by MacMillan and coworkers.

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† Electronic supplementary information (ESI) available: Experimental procedures, and spectral characterization. See DOI: 10.1039/c7cc01416c

intramolecular hydrogen bonding networks that lead to subtle differences in the pK_a of the various secondary hydroxyl groups, a phenomenon that is used in site-selective acylation and silylation, and in liquid chromatography.^{13,14}

In order to study this hypothesis, methyl α -D-glucoside **1** was treated with methyl acrylate as the somophile using similar conditions as employed by MacMillan *et al.* As in contrast to the substrates reported, the reactivity of the various C–H bonds in tetraol **1** is expected to differ only slightly and the use of a large excess of somophile (10 equiv. in the aforementioned study) would likely lead to multiple HAT reactions. Therefore, only a slight excess of somophile (1.5 equiv.) was used when performing the reaction with **1**. Solvent selection initially proved to be problematic as well, as **1** has a limited solubility in acetonitrile and no reaction was observed in that solvent. While addition of water did improve solubility, it did not improve conversion. Finally, DMSO was selected to ensure acceptable solubility of **1**, and in the course of this study was shown to be compatible with photoredox catalysis conditions.¹⁵

Although after 18 h irradiation conversion was not complete, NMR analysis revealed to our delight that one main coupling product had formed. However, isolation and characterization of this ester product was severely complicated by regioisomeric lactone formation and the use of *tert*-butyl acrylate instead of methyl acrylate did not overcome this problem. By using phenyl vinyl sulfone as the somophile, lactone formation was avoided and near complete conversion (~ 80 – 90%) to a single product was observed, next to 10% oxidation at C3 (see ESI†). Tetrabutylammonium phosphate salts co-eluted with the product when the reaction mixture was subjected to silica gel column chromatography after removal of DMSO by lyophilization. Treating the crude reaction mixture with an ion-exchange resin (sodium form) prior to lyophilization effectively removed these salts and column chromatography provided **2** in 52% yield. ¹H-NMR and COSY analysis readily revealed that HAT had taken place at C3, because of the simplification of the splitting pattern of C2H and C4H and the disappearance of C3H. In addition, ¹³C-NMR (APT) showed that a tertiary alcohol had formed. NOE and NOESY studies unambiguously proved the stereochemistry of **2** to be as shown in Scheme 2. NOEs between C7H and C4H and C2H are observed which are typical for equatorial product **2**, while the expected NOE for the axial product is not detected. The stereoselectivity is most probably induced by shielding of the bottom face of the molecule by the axial anomeric methoxy group. According to ¹H-NMR analysis of the crude reaction mixture, with an estimated detection limit of 4%, HAT had taken place selectively at C3. This is an excellent result given the fact that all carbon atoms in the

Scheme 2 Determination of the stereochemistry at C3 by NOE.

substrate are involved in either an ether, an acetal or a hydroxyl functionality. The isolated yield is decreased compared to the crude yield clearly because of the high polarity of the product impeding effective isolation. Surprisingly, when the reaction was carried out without tetrabutylammonium dihydrogenphosphate, no reaction was observed, which is in contrast with the observation by MacMillan *et al.* in the reaction depicted in Scheme 1.¹²

Subsequently, we studied several somophiles using methyl α -D-glucoside **1** as the substrate. It turned out that the reaction works well with vinyl phosphonate providing again reaction at C3. The same was the case for cyclopentenone as the somophile, providing a 1:1 mixture of diastereomers. Methyl vinyl ketone afforded an intractable reaction mixture, probably due to polymerization of this somophile, whereas acrylamide and acrylonitrile afforded a single product, but with low conversion (Table 1).

Because of the difficult isolation of the products, the reaction of methyl α -D-glucoside **1** with phenyl vinyl sulfone was also carried out in DMF and the C6OH of product was silylated *in situ* with TBDMSCl/imidazole. This procedure led to a yield of 57% of **9** after work up and purification. Alternatively, using C6-TBDMS ether **3** for the HAT reaction in DMSO, the expected product **9** was obtained in 52% yield. The isolated yield could not be significantly increased by partial silylation of the starting material or the product. Although the use of a larger excess of somophile increased the conversion of **1**, the isolated yield of the product dropped as expected since more side products were formed, most likely due to HAT at various positions in the substrate.

Subsequently, the scope of the reaction was studied applying several methyl glycosides. With the results of **1** established, its C1 epimer (anomer) methyl β -D-glucoside **4** was studied. Also in this case the main product resulted from C3 alkylation, although in a lower yield compared to **1**. This is at least partly explained by a decreased stereoselectivity, as both faces of the ring are now accessible. Methyl α -D-xyloside **5** reacted similarly to **1**, providing the expected product **11** in 55% isolated yield. Methyl β -D-xyloside **6**, in turn, gave again a rather unselective reaction. Remarkably, methyl β -D-galactoside was unreactive confirmed by a competition experiment with glucoside **1**, while

Table 1 Somophiles in the HAT reaction of **1**

Entry	Somophile	Isolated yield ^a (%)
1		52
2		48
3		59 (1:1 mixture of diastereomers)

^a Adjusted for residual DMSO, if present.

methyl α -D-mannoside gave multiple products. Methyl α -D-N-acetyl glucosamine gave no conversion, but this is probably due to HAT at nitrogen.¹⁶ Why this does not lead to further reaction is not clear. Methyl α -D-alloside **7**, possessing an axial instead of an equatorial hydroxyl group at C3, reacted in an identical way as **1** producing **2** in 46% yield. Apparently, the stereochemistry at C3 is irrelevant for HAT.

Eager to get more insight into the role of the structure of the substrate in the observed regioselectivity, 1,2-propanediol **8** was subjected to the same reaction conditions. It turned out that the reaction shows a preference for HAT at the methine carbon but the selectivity is not outspoken, in contrast to the selectivity observed in the carbohydrates at hand. So, the intrinsic reactivity difference between the C–H bond of a primary alcohol and that of a secondary alcohol is clearly not enough to explain the selectivity observed in the carbohydrate substrates, let alone the observed preference for HAT at C3. A second difference is that **8** reacted also in the absence of dihydrogenphosphate, despite with low conversion, indicating that the hydroxyl groups in carbohydrates are deactivated compared to the hydroxyl groups in **8** (Table 2).

This study demonstrates that the “hydrogen bonding induced” selective HAT reaction as proposed by the MacMillan group is not only able to address a hydroxyl group in the presence of ethers and acetals but can also single out a particular hydroxyl group in a

polyol. This is a key observation, in particular for the regioselective functionalization of unprotected carbohydrates as shown here. The observed selectivity deserves further study, as it is not clear why in **1**, **5** and **7** reaction takes place selectively at C3, whereas methyl mannoside reacts unselectively and methyl galactoside is unreactive. This could be due to different hydrogen bonding networks in the substrates, influencing the pK_a of the C3OH. On the other hand, **7** reacts similar to **1**, whereas the hydrogen bonding network should be significantly different. Also the profound selectivity for the secondary hydroxyl group in the presence of a (sterically less hindered) primary hydroxyl group is remarkable. As the reaction does not take place in the absence of dihydrogen phosphate, its influence on the regioselectivity of the reaction is difficult to determine. The stereoselectivity of the reaction is better understood and probably due to steric shielding of the axial C1-OMe. This we deduce from the observation that β -configured substrates seem to react selectively at C3 as well, just like α -configured substrates, but with a low stereoselectivity.

Being able to modify, extend and branch the carbon skeleton of glucosides and related monosaccharides without multi-step protection–deprotection strategies is important.¹⁷ It expands the use of these readily available starting materials as pharmacophores and pharmaceutical building blocks. In chemical biology, the selective modification of carbohydrates is key to study the many cellular processes carbohydrates are involved in. For oligosaccharides, selective modification is currently hardly an option as protection strategies do not exist.⁸ The strategy reported here might contribute to this field, all the more so because seemingly disappointing results like the unreactivity of galactosides are welcomed in the modification of carbohydrates containing various different monosaccharides. Possibilities to expand the method to di- and oligosaccharides are therefore currently under investigation.

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Table 2 Carbohydrates in the HAT reaction with vinyl phenyl sulfone

Entry	Substrate	Product	Yield (%)
1			52 ^a
2			52
3			57
4			30 ^{a,b}
5			55
6			30 ^c
7			46 ^a
8			— ^d

^a Yield adjusted for residual DMSO. ^b Using 2 equiv. of substrate and 1 equiv. of somophile due to purification problems. ^c Substantial side product formation. ^d Product not isolated. Regioselectivity = ~2:1.

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