α-C–H Photoalkylation of a Glucose Derivative in Continuous Flow

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Abstract
Site-selective photoalkylation is a powerful strategy to extend the carbon framework of carbohydrates, otherwise often attainable only through laborious syntheses. This work describes the adaptation and upscaling of the photoalkylation of a glucose derivative as a continuous flow process. The reported iridium catalyst is replaced by an organic sensitizer and the reaction has been carried out on 40-gram scale.

Key words
C–H functionalization, photoredox catalysis, carbohydrates, flow chemistry, hydrogen atom transfer, radicals

The natural abundance and diversity in stereochemistry of carbohydrates make them interesting starting materials for the development of novel pharmaceutical compounds and organic materials. The lion’s share of the literature on the modification of carbohydrates in this context is focused on reactions involving the hydroxyl groups, such as ether or ester formation.

As discrimination between these multiple hydroxy groups is difficult, protecting group strategies are commonly used. An alternative approach is direct carbon–carbon bond formation, but apart from reactions with the carbonyl group in carbohydrates (such as aldol and related reactions, and Strecker reactions) this approach is not often pursued. With the advent of synthetically attractive photoredox chemistry, site-selective photoalkylation has come into play as a powerful strategy to extend the carbon framework of carbohydrates. Carbohydrates are intrinsically attractive substrates for radical-based reactions involving the carbon skeleton, because the hydroxy groups themselves are not very reactive in such a setting. Nevertheless, the challenge of site-selectivity remains.

In 2015, the group of MacMillan made use of the fact that hydrogen bond formation between an acceptor and a hydroxy group weakens the α-C–H bond strength of that hydroxy group and this leads to preferential hydrogen atom transfer (HAT). The produced carbon-centered radical can subsequently react with an electron-deficient alkene, a ‘somophile’ (Scheme 1).

This activation is sufficiently large to discriminate between α-C–H bonds in ethers or acetals and a free hydroxyl group, and this was illustrated in the selective alkylation of a protected galactose derivative, possessing one hydroxy group (Scheme 2).

We subsequently showed that this photoredox alkylation reaction based on hydrogen bond based activation can also be applied on unprotected carbohydrates. The site-selectivity in these cases is substrate inherent and the hydrogen bond formation functions to increase the reactivity (or makes the reaction possible at all). In gluco- and allopypritinosides it was observed that alkylation occurs selectively at

Scheme 1
The addition of a hydrogen bond acceptor allows for α-C–H activation
**Biographical Sketches**

Marc Mouthaan obtained his B.Sc. and M.Sc. degrees in chemistry from the University of Groningen, working on the functionalization of carbohydrates with professor A. J. Minnaard. Upon completing his studies, he returned to the group of prof. Minnaard in late 2019 to pursue a Ph.D. in collaboration with industry partner Symeres. His current research is focused on employing carbohydrate derivatives as scaffolds for medicinal chemistry, as well as applying cheminformatics tools to assist organic synthesis.

Kees Pouwer received his PhD in 1995 in the group of professor Wynberg at the university of Groningen. He has worked at Symeres, formerly known as Syncom, since 1997. Currently he is director of Chemistry.

Mark Borst received his M.Sc. and Ph.D. studies at Vrije Universiteit Amsterdam, with professor Koop Lammertsma and obtained his Ph.D. in 2005. Right after, he joined Syncom (now part of Symeres) in Groningen, the Netherlands, since 2013 in the role of Project Leader, with a focus on scaffold design and parallel chemistry.

Martin D. Witte performed his Ph.D. studies at Leiden University, The Netherlands, under the supervision of Prof. Overkleeft and Prof. van der Marel and obtained his Ph.D. in 2009. In 2010, he joined the group of Prof. Ploegh at the Whitehead Institute for Biomedical Research, Cambridge, USA to do postdoctoral research. In 2013, he was appointed assistant professor in chemical biology at the University of Groningen, The Netherlands and in 2018 has been promoted to associate professor. His research focuses on the site selective modification of biomolecules and the development of new protein labeling tools.

Adriaan Minnaard obtained his PhD at Wageningen Agricultural University, The Netherlands. He is professor in Chemical Biology at the Stratingh Institute for Chemistry, University of Groningen, and has been director of this institute. His research interests are the synthesis and modification of complex natural products, including carbohydrates, and his group contributes as well to the development of new synthesis methods. His research on the lipidome of *M. tuberculosis* received the NWO-TEAM Science Award 2020.
the C3 carbon (Scheme 3). Furthermore, when the α-ano-
mers of the substrates were used, alkylation took place
from the top face, resulting in an
allo-configured product. This selectivity likely originates from the steric shielding by
the anomeric substituent. With
EWG−methyl glucosides, only
partial inversion was observed.

Next to hydrogen bond formation, several other
methods have been reported, with the common theme that the
electron density of the α-carbon is increased. Boron, tin and
silicon are less electronegative than hydrogen, so diaryl-
borinic acids, borinates, spirosilanes and organostan-
nanes have all been used successfully, and are instrumen-
tal to induce regioselectivity in the alkylation, with the lat-
ter being applied to rhamnopyranosides. Alkylation via 1,6-
HAT in a fructopyranoside has been reported as well.12

Also, the nature of the hydrogen atom transfer agent has
been studied, with quinuclidine being favored. Recently
however, quinuclidine,13 and DABCO-derived14 catalysts
have also proven useful for facilitating HAT. This type of
photocatalysis is not limited to alkylations: in more recent
reports, Wendlandt and co-workers have used the HAT re-
action for isomerization, providing access to rare monosac-
charides from commonly available monosaccharides,15,16
whilst the group of Taylor employed the system for oxida-
tions.17 Redox isomerization, a strategy that combines the
two, gives rise to ketodeoxysugars, with examples of both
furanosides18 and pyranosides19,20 having been investigated.
The photocatalytic system has also seen success in chiral
resolutions: with a chiral phosphate, racemic ureas could be
enantiomerically enriched.21

It is therefore clear that the versatility of these photore-
dox systems makes them very interesting candidates to ex-
plore otherwise challenging chemistry. Despite this prog-
ress however, the photoalkylation of carbohydrates has not
yet been used to prepare building blocks or scaffolds on a
preparative scale. In order to be synthetically useful, the
procedure needs to be scalable and cost-effective. In addi-
tion, the variety in somophiles is still rather limited, re-
stricting structural diversity. To improve upon this situa-
tion, we envisioned applying a continuous flow chemistry
approach. One of the key advantages of continuous flow
chemistry is the much larger surface area offered by the
tubing. This allows for more efficient irradiation compared
to a batch setup. In addition, the amount of product does
not depend on the scale of the reaction but on the overall
runtime.22

Since our primary goal was the upscaling of these
known alkylation reactions, use of the well-studied iridium
catalyst Ir(III)ppy3(dtb bpy)PF6 (Table 1) was not cost-
effective. Iridium prices have increased substantially in re-
cent times and producing multigram quantities of product
without being able to recycle the catalyst would be far too
costly. In 2020, Wendlandt and co-workers reported on the
selective epimerization of carbohydrates15 by photoredox
chemistry and in this study, the iridium catalyst was re-
placed by the organocatalyst 4-CzIPN. Given the similarity
of our reaction, as well as the range of redox potentials, we
hypothesized that 4-CzIPN might also be effective in our
alkylation reactions. In addition to being a metal-free alter-
native, 4-CzIPN is prepared in a single step from readily
available materials23 and has greater absorption in the visi-
ble light region, which better matches the used light source.
To facilitate workup and purification of the photoalkylated products, we chose methyl 4,6-O-benzylidene-α-D-glucopyranoside as the substrate. Although the photoalkylation reaction does not explicitly require the presence of the 4,6-O-benzylidene moiety, as we showed previously, 7 the starting material is readily prepared on large scale and soluble in acetonitrile. 26 In addition, the product is readily modified in subsequent transformations, a necessity for a building block to act as a scaffold. Acrylonitrile was chosen as the initial somophile due to its potential for subsequent derivatization.

To perform the flow reactions, we used an in-house constructed flow reactor, 27,28 equipped with 500 W input power of blue (460 nm) LEDs (Figure 1 and Figure 2). Perfluoroalkoxy (PFA) tubing is wound around a water-cooled copper core and provides an internal reactor volume of about 20 mL (ø 0.8 mm) along which the reaction mixture could be irradiated.

To prevent overheating and thermal side reactions, also the LEDs were water-cooled, maintaining a consistent temperature within the reactor. A continuous syringe pump offered precise flow control and pumps the reaction mixture through the PFA tubing at a constant rate. Behind the pump, a sample loop has been installed, which was used to inject small volume samples for conditions screening, bypassing the internal volume of the pump to prevent sample dilution.

The study commenced by translating the reaction system from our established batch conditions 7 to the continuous flow setup, after which several parameters were modified to optimize product yield.

Experiments to maximize the conversion were carried out varying several parameters. We observed that when the light output was reduced, the conversion dropped significantly, in an almost linear fashion. 30 Subsequently, the reaction was performed at different substrate concentrations. It was found that there was no significant change in conversion when the concentration of the substrate was either increased or decreased. We settled on a substrate concentration of 0.12 M, well below the maximum solubility in order to prevent precipitation.

Upon changing the iridium catalyst for 4-CzIPN in our batch flow system, similar conversions were observed albeit at a somewhat higher catalyst loading (Scheme 4). This is analogous to Wendlandt’s observations in the epimerization reaction. 15 Although no significant change in conversion was observed when the catalyst loading was varied between 2.5 mol% and 4 mol%, the latter was chosen for larger
scale reactions in order to have flexibility in the residence time. The apolar nature of 4-CzIPN allows it to be removed easily from the reaction mixture by chromatography.

Although we initially started with a 25 mol% loading of tetrabutylammonium dihydrogen phosphate (TBAP), reducing the loading of the TBAP cocatalyst to 15 mol% did not have a pronounced effect on the overall conversion and reduced the risk of precipitation. Increasing the equivalency of the somophile acrylonitrile above 1.5 did not have a positive result. Instead, unreacted or polymerized somophile was recovered after the reaction.

Purification of the reaction mixtures is rather straightforward. Dependent on the somophile used, the excess was evaporated under reduced atmosphere, together with the solvent. The TBAP and the quinuclidine were removed by aqueous wash, whilst the remaining 4-CzIPN and its decomposition products were removed by separation by column chromatography. With commercial equipment, it would be possible to carry out liquid–liquid extraction directly in-line, further simplifying purification.31

When subjected to these optimized conditions, with a residence time of $T_r = 20$ minutes, 1 could be alkylated on 1-gram scale in 55% isolated yield ($3a$). Increasing the residence time did not result in a significantly higher conversion. The impurity profile of the crude suggested that some decomposition of the benzylidene acetal took place, although a clear side product could not be isolated. It is not unlikely that the C–H bond of the acetal can also be activated in this reaction. The use of an alternative protecting group without such a hydrogen, for instance a di-tert-butyldimethylsilyl group, may avoid this problem, at the expense of increased cost.

In addition to acrylonitrile, several other somophiles were used in the alkylation reaction, with mixed results (Figure 3). Notably, the required residence time for these somophiles was significantly larger than that of acrylonitrile (0.25 mL/min vs 1 mL/min). Reactions with alkenes such as phenyl vinyl sulfone and diethyl vinyl phosphonate performed well, providing $3b$ and $3c$, respectively. In an attempt to increase the scope, we also studied styrene derivatives and vinylpyridine, although these were expected to be very weak somophiles. We were pleased to see that m-chlorostyrene and in particular 2-vinylpyridine do act as somophiles in this reaction, giving $3e$ and $3f$, respectively. Although the yields are somewhat unsatisfactory still, in particular for the preparation of pharmaceutical scaffolds this broadening of the scope is significant. Bromostyrenes were studied as well, but decomposed under these conditions.

To confirm the value of performing these reactions in flow, the alkylation of 1 with acrylonitrile was carried out on 40-gram scale. As increasing the residence time with this somophile had only negligible effect on product yield, a residence time $T_r = 20$ minutes was chosen. After purification, 45% (21.4 g) of $3a$ was isolated.

In summary, by performing the established photoalkylation in flow, it has been demonstrated that this reaction can be carried out on a multigram scale. The replacement of the iridium photocatalyst with an organo-photocatalyst al-
flows the reaction to be carried out cost-effectively, offering large-scale production potential. Reactions with several somophiles were carried out on gram scale and a representative example was scaled to 21 g of product. The set of applicable somophiles has been expanded with 3-chlorostyrene and 2-vinylpyridine, which makes the products more interesting from a pharmaceutical point of view. We are currently focused on the follow-up chemistry of these compounds. In the future, it would be interesting to investigate the reaction with the recently reported HAT agents, as well as different carbohydrate substrates.

All reagents were purchased from commercial sources. Somophiles were distilled prior to use, with exception of those that are heat-sensitive. Reaction mixtures were pumped through the flow reactor by means of a Syrris Asia syringe pump. NMR spectra were recorded on a Thermos Fisher Scientific FT-IR spectrometer. IR spectra were recorded on a Thermo Fisher Scientific LTQ Orbitrap XL (FTMS) instrument. IR: 3512, 3340, 2970, 2860, 1731, 1367, 1137, 1081, 1001 cm⁻¹ for 3a.

1H NMR (400 MHz, DMSO-d6): δ = 7.68 (d, J = 6.5, 2.3 Hz, 2 H), 7.34 (d, J = 7.4 Hz, 1 H), 4.79 (d, J = 5.0 Hz, 1 H), 4.61 (d, J = 9.4 Hz, 1 H), 1.96 (t, J = 8.0 Hz, 2 H), 1.28 (s, 1 H), 1.24 (s, 1 H), 1.19 (t, J = 8.0 Hz, 2 H), 0.99 (t, J = 6.9 Hz, 3 H).

13C NMR (100 MHz, CDCl3): δ = 129.99, 128.50, 126.19, 72.87, 71.32, 68.92, 58.72, 56.32, 51.84, 28.39, 16.41, 16.35.

HRMS (ESI): m/z [M + Na]^+ calcd for C_{20}H_{31}O_{9}P: 467.143; found: 467.143.

3b by Reaction of 1 with Phenyl Vinyl Phosphonate
Yellow solid; yield: 963 mg (61%); Rf = 0.35 (EtOAc/heptane, 40:60). IR: 3478, 2933, 1466, 1286, 1143, 1067, 1044, 998, 745, 688 cm⁻¹.

1H NMR (400 MHz, CDCl3): δ = 7.85–7.79 (m, 2 H), 7.61–7.56 (m, 1 H), 7.50–7.44 (m, 2 H), 7.39 (dd, J = 6.9, 3.0 Hz, 2 H), 7.36–7.30 (m, 3 H), 5.50 (s, 1 H), 4.61 (4.32 (d, J = 10.3, 5.0 Hz, 1 H), 1.93 (td, J = 9.9, 5.0 Hz, 1 H), 3.70 (td, J = 10.3 Hz, 1 H), 3.55–3.45 (m, 3 H), 3.44 (s, 3 H), 3.38 (s, J = 6.9 Hz, 1 H), 3.00 (s, 1 H), 2.56 (d, J = 11.9 Hz, 1 H), 2.31–2.13 (m, 2 H).

13C NMR (101 MHz, CDCl3): δ = 196.31, 184.04, 138.14, 134.23, 131.17, 129.26, 128.27, 126.30, 126.06, 125.04, 123.17, 121.75, 108.49, 108.24, 100.91, 100.60, 81.56, 72.87, 71.32, 69.02, 58.72, 56.32, 51.84, 28.40.

HRMS (ESI): m/z [M + Na]^+ calcd for C_{24}H_{24}O_{7}P: 473.124; found: 473.122.

3c by Reaction of 1 with Diethyl Vinyl Phosphonate
White solid; yield: 711 mg (55%); Rf = 0.2 (EtOAc/heptane, 50:50). IR: 3390, 2998, 2941, 2867, 2248, 1070, 1038, 1014, 997 cm⁻¹.

1H NMR (400 MHz, DMSO-d6): δ = 7.45 (d, J = 6.5, 2.3 Hz, 2 H), 7.42–7.35 (m, 3 H), 5.61 (s, 1 H), 4.86 (d, J = 9.4 Hz, 1 H), 4.62 (d, J = 4.0 Hz, 1 I), 4.25 (td, J = 10.1, 5.1 Hz, 1 H), 4.17 (td, J = 10.0, 5.1 Hz, 1 H), 3.94 (td, J = 10.3 Hz, 1 H), 3.50 (dt, J = 9.3, 2.1 Hz, 2 H), 3.33 (s, 3 H), 2.71–2.55 (m, 2 H), 1.98 (t, J = 8.0 Hz, 2 H).

13C NMR (101 MHz, DMSO-d6): δ = 138.26, 134.24, 133.34, 129.20, 128.27, 126.30, 126.06, 125.04, 124.12, 123.17, 121.75, 108.49, 108.24, 100.91, 100.60, 81.56, 72.87, 71.32, 69.02, 58.72, 56.32, 51.84, 28.40.

HRMS (ESI): m/z [M + Na]^+ calcd for C_{24}H_{24}O_{7}P: 473.124; found: 473.122.
HRMS (ESI): m/z [M + Na]+ calcd for C_{31}H_{23}O_{6}: 433.183; found: 433.182.

3e by Reaction of 1 with 3-Chlorostyrene
Yellow solid; yield: 412 mg (30%); R_f = 0.15 (DCM/MeOH, 98:2).

1^1H NMR (400 MHz, CDCl_3): δ = 7.55–7.50 (m, 2 H), 7.46–7.38 (m, 3 H), 7.26–7.17 (m, 3 H), 7.12 (dt, J = 7.2, 1.7 Hz, 1 H), 5.53 (s, 1 H), 4.83 (s, 1 H), 4.41 (dd, J = 10.3, 5.1 Hz, 1 H), 4.10 (dd, J = 9.9, 5.0 Hz, 1 H), 3.77 (t, J = 10.3 Hz, 1 H), 3.67 (dd, J = 12.0, 4.1 Hz, 1 H), 3.54 (s, 3 H), 3.49 (d, J = 9.6 Hz, 1 H), 2.96 (s, 1 H), 2.86–2.77 (m, 2 H), 2.68 (d, J = 12.1 Hz, 1 H), 2.20–2.08 (m, 2 H).

IR: 3478, 2942, 2844, 1071, 1016, 987, 697 cm–1.

Yellow solid; yield: 245 mg (16%); R_f = 0.4 (EtOAc/heptane, 50:50).

1^1C NMR (101 MHz, CDCl_3): δ = 144.06, 137.14, 134.15, 129.66, 128.52, 128.51, 128.31, 126.58, 126.16, 126.11, 101.78, 100.75, 79.86, 74.21, 69.68, 69.22, 58.71, 56.38, 35.21, 30.22.

HRMS (ESI): m/z [M + Na]+ calcd for C_{22}H_{25}ClO_{6}: 443.123; found: 443.122.

3f by Reaction of 1 with 2-Vinylpyridine
White solid; yield: 412 mg (30%); R_f = 0.6 (EtOAc/heptane, 50:50).

1^1H NMR (400 MHz, CDCl_3): δ = 7.26–7.17 (m, 3 H), 7.12 (dt, J = 7.2, 1.7 Hz, 1 H), 5.53 (s, 1 H), 4.83 (s, 1 H), 4.41 (dd, J = 10.3, 5.1 Hz, 1 H), 4.10 (dd, J = 9.9, 5.0 Hz, 1 H), 3.77 (t, J = 10.3 Hz, 1 H), 3.67 (dd, J = 12.0, 4.1 Hz, 1 H), 3.54 (s, 3 H), 3.49 (d, J = 9.6 Hz, 1 H), 2.96 (s, 1 H), 2.86–2.77 (m, 2 H), 2.68 (d, J = 12.1 Hz, 1 H), 2.20–2.08 (m, 2 H).

IR: 2931, 1068, 1044, 995, 748, 697 cm–1.

Supporting Information
Supporting information for this article is available online at https://doi.org/10.1055/a-1840-5483.

Conflict of Interest
The authors declare no conflict of interest.

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