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Charlotte S. Teschers, and Ryan Gilmour

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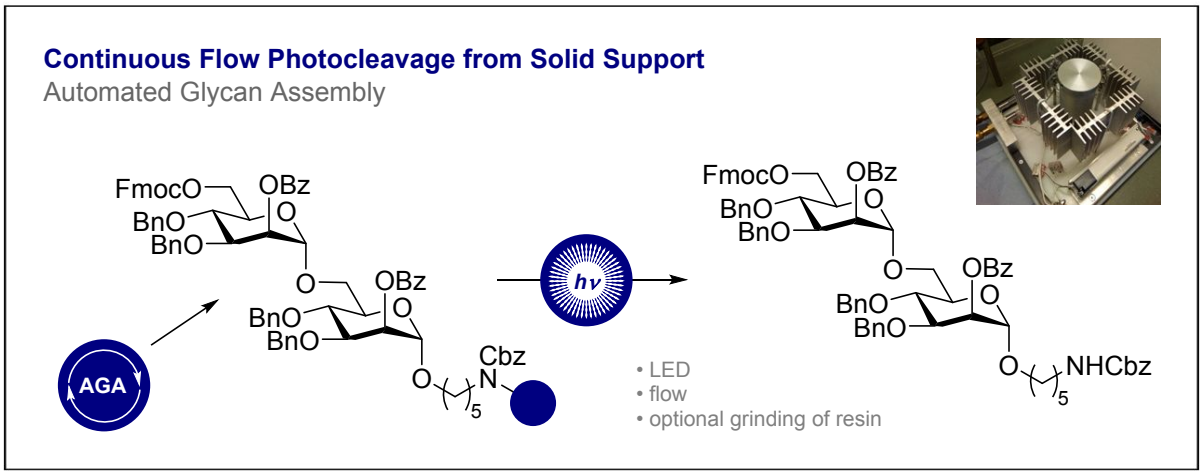
Flow Photocleavage for Automated Glycan Assembly (AGA)

AUTHORS *Charlotte S. Teschers, Ryan Gilmour**

AUTHOR ADDRESS Organisch-Chemisches Institut, Westfälische Wilhelms-Universität Münster, 48149 Münster, Germany



KEYWORDS Automated Glycan Assembly (AGA), flow chemistry, photochemistry, photocleavable linker.

ABSTRACT Automated glycan assembly (AGA) is contingent on the development of simple, efficient cleavage strategies to liberate complex, high value products from a solid support resin. Given the rapid advances in the structural complexity of carbohydrates that can be constructed via this enabling technology, effective cleavage is a persistent challenge. Photolabile linkers have a venerable history in AGA and mitigate potential complications arising from chemically-induced release protocols. However, photochemical cleavage strategies have traditionally relied upon mercury vapor lamps, which present challenges in establishing well-defined, reproducible, and non-hazardous conditions for this ultimate step of the AGA sequence. To complement the existing batch strategies, a safe and sustainable approach for the continuous flow photocleavage from solid support using LEDs has been developed. Employing a custom-built LED flow reactor, photocleavage yields of up to 80% were achieved in less than 1 h. Efficiency could be further improved by merging flow photochemistry with pre-grinding. Validation of this strategy is showcased in a proof of concept AGA synthesis of a model dimannoside.

INTRODUCTION

Automated glycan assembly (AGA) reconciles the demand for complex carbohydrates in biomedical research,[1-7] with the lack of biosynthesis blueprints that can be translated to a laboratory paradigm. Limited availability from natural sources renders the synthetic challenges associated with accessing well-defined oligosaccharides and glycoconjugates conspicuous, and this challenge is further amplified when diverse glycan libraries or non-natural glycans are required. This enabling strategy is predicated on a solid-phase synthesis (SPS) platform to facilitate purification, automation and recovery of excess reagents.[8,9]. However, the advantages conferred by solid state synthesis are tempered by the requirement for a linker motif that can be cleaved under conditions that are orthogonal to those employed in the glycan synthesis campaign.[10]

Investment in developing effective post-automation cleavage protocols are therefore essential to ensure uptake of this technology and circumvent this current bottleneck in AGA.[11] Photolabile linkers have proven to be ideally suited to this task. This is a consequence of their compatibility with conventional glycosylation conditions, their tolerance towards common protecting group manipulations, and potentially mild photochemical activation required for cleavage.[7,11,13-15] Despite the prominence of photo-linkers in AGA, inefficient photocleavage from solid support remains a pressing challenge and can significantly compromise the yield of complex, costly synthetic sequences.[11] A pre-condition of photocleavage is ensuring efficient penetration of light through the reaction medium through short irradiation distances and a homogeneous distribution in the reaction medium.[16] Continuous flow formats are ideally suited to this challenge and have the added advantage of enabling large scale, high throughput synthesis.[16-18] To date, mercury vapor lamps have been commonly employed as light sources for the photocleavage from solid support,[11-22] but safety concerns,[19,20] prohibitively high costs[20,21] and a potential lack of selectivity as a consequence of multiple and broad emission wavelengths[18] constitute persuasive arguments to explore less hazardous, inexpensive alternatives.[18] A recent batch study by Hurevich and co-workers has validated the potential of LEDs in AGA to achieve photocleavage. The study demonstrates the importance of grinding the resin to expose a larger surface area to the light.[22] To complement the works by Seeberger[15] and Hurevich, a customized LED-based flow setup was conceived as a platform for photocleavage from solid support (Figure 1).

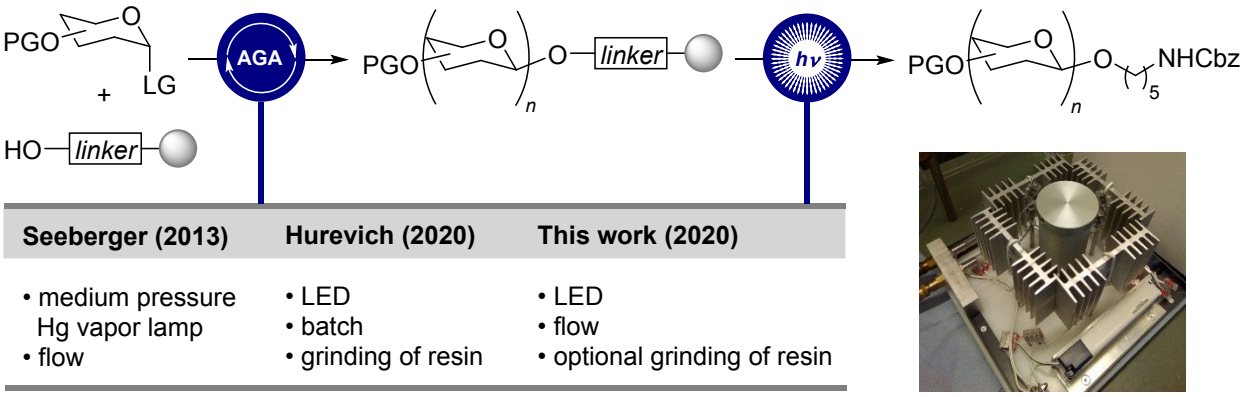
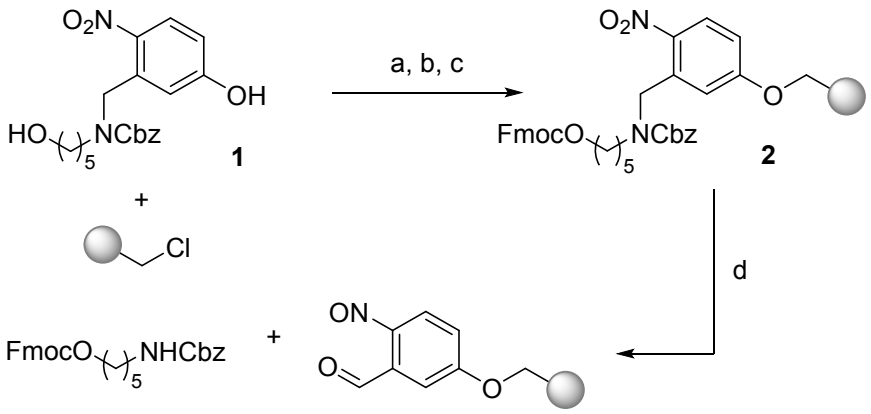


Figure 1. An overview of Automated Glycan Assembly (AGA) and strategies to enable photocleavage of the final glycan from the solid support.

RESULTS AND DISCUSSION

To explore this LED-based flow photocleavage platform for AGA, commercially available Merrifield resin was initially functionalized with the photolabile linker **1** according to established literature procedures (Scheme 1).[14] The photocleavable resin (PC-resin) was treated with Fmoc chloride and pyridine in CH_2Cl_2 to obtain the FPC-resin **2** as a probe to determine loading and photocleavage efficiency. Utilizing a protocol developed by White and co-workers for solid phase peptide synthesis[23] it was possible to establish the resin loading, whilst the photocleavage yield was determined by quantifying the amount of Fmoc remaining on the resin. This was referenced to non-irradiated FPC-resin of the same batch.



Scheme 1. Synthesis of Fmoc-protected photocleavable resin (FPC-resin) and photocleavage products. Reagents and conditions: a) CH_2Cl_2/DMF, Cs_2CO_3, TBAI, 60 °C, 200 mbar, 24 h; b) CH_2Cl_2/DMF, CsOAc, 60 °C, 200 mbar, 18 h; c) CH_2Cl_2, FmocCl, pyridine; d) CH_2Cl_2, $h\nu$ (365 nm).

Initial experiments to assess the feasibility of photocleavage with LEDs were performed with a low-power LED in batch. To that end, 25-30 mg of FPC-resin were irradiated at 365 nm with careful stirring. Characteristic browning of the resin was observed with time, and the cleavage efficiency was determined to be 75 and 81% after 8 and 16 h, respectively. These initial results, which are in line with the Hurevich study, encouraged us to design and fabricate a continuous flow LED photoreactor to address the final photocleavage phase of AGA. Cognizant of the importance of light distribution in photochemical processes,[21] LEDs with a wide beam angle (110°, total included angle 150°) were employed to irradiate a large area of the reaction coil. For this purpose, eight LEDs (each 2000-3800 mW radiant flux @ 750 mA) were installed around the reaction coil at a distance of 3 cm (Figure 2).

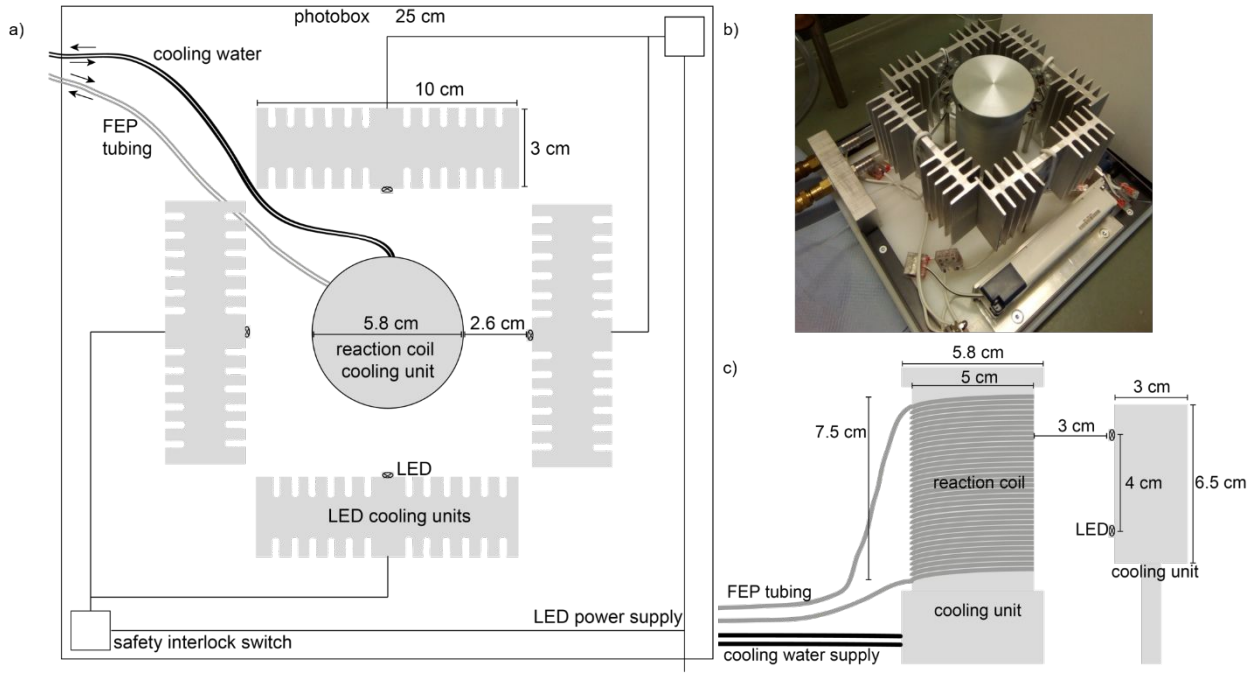


Figure 2. Schematic representation of this custom LED flow reactor. a) Top schematic of the photoreactor showing key dimensions. b) Photograph of the photoreactor without safety cover. c) Side schematic of the photoreactor displaying dimensions of reaction coil and LEDs with the respective cooling units. For the sake of clarity only one of the four LED units is shown. *Safety note*: *UV radiation can cause severe burns of skin and eyes. For safety reasons, the reactor is covered with a non-transparent lid to contain the UV radiation inside the photobox. A safety interlock switch shuts down the LED power supply if the reactor cover is opened during operation or not tightly closed. The electric fan is shielded by an additional plate inside the reactor cover to prevent the escape of light.*

Based on the promising results from the photocleavage in batch, we anticipated that the full power of the LEDs might not be required for this application. The LEDs were thus dimmed to 350 mA. One advantage of LEDs over mercury vapor lamps is the higher energy efficiency and concomitant lower residual heat which enables temperature control to be more easily achieved without

complex, highly-engineered cooling systems. The LEDs were mounted on aluminum cooling panels with a large surface area to enable high cooling efficiency by simple ventilation of the photoreactor with an electrical fan (Figure 2a). The temperature of the aluminum panels under continuous irradiation never exceeded 55 °C when ventilated. To enable the use of low boiling solvents such as CH_2Cl_2, including at low flow rates, an additional cooling unit for the reaction coil was installed. A thread matching the outer diameter of the fluorinated ethylene propylene (FEP) tubing used was cut into an aluminum cylinder to maximize the contact between reactor and cooling block, and the FEP tube was wrapped around it (Figure 2c). If necessary, this design allows for the aluminum cylinder to be cooled by water or lower-temperature cooling liquids.

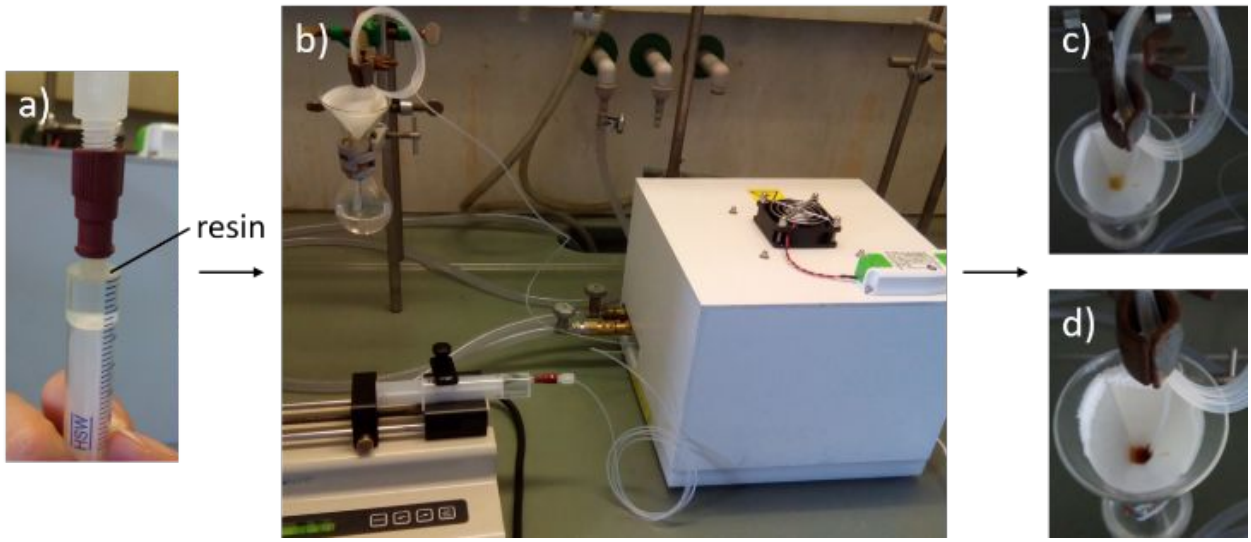


Figure 3. Workflow of the continuous flow photocleavage from solid support. a) Injection of the resin into the reactor tubing; b) photocleavage setup comprising syringe pump, LED-photoreactor and filtration/collection unit; c) collected resin is still yellow after the first irradiation cycle; d) characteristic brown resin after the second irradiation cycle.

With a view to allowing this strategy to be easily incorporated into pre-existing AGA setups, the procedure reported by Seeberger and co-workers using a medium pressure mercury vapor lamp flow reactor was followed.[15] To that end, the FPC-resin **2** was swollen in CH_2Cl_2, injected into the reactor and pushed through the FEP tubing with 15 mL of CH_2Cl_2 (Figure 3).

Using the same flow rate as reported by Seeberger and co-workers (18 mL/h),[15] a cleavage efficiency of 75% was achieved which is commensurate with the yields reported using mercury vapor lamps.[15] Since the volume of this flow reactor is much smaller than that previously reported, it was reasoned that a slower flow rate and longer irradiation time might increase the cleavage yield. Surprisingly, the yield did not increase when reducing the flow rate by a factor of two.

Next, we investigated if higher flow rates were tolerated to identify the minimum reaction time required for this transformation. Expectedly, the photocleavage efficiency decreased upon increasing the flow rate, with a loss of 10% efficiency at a flow rate of 50 mL/h (Figure 4).

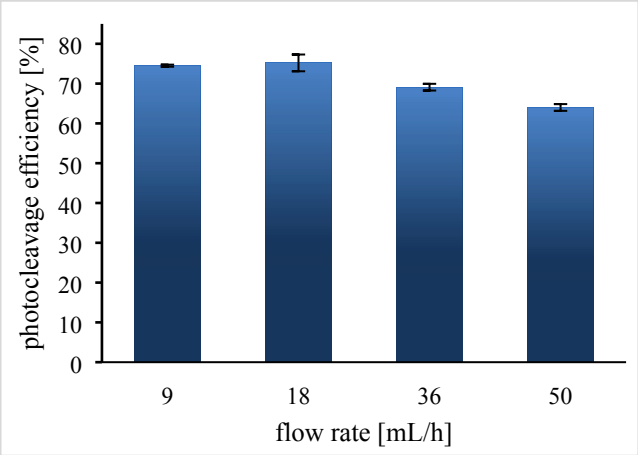


Figure 4. Effect of flow rate on the photocleavage efficiency determined by Fmoc quantification. Flow rates higher than 18 mL/h lead to a decrease in yield. Error bars indicate the standard error of the mean of two independent experiments for each flow rate.

Interestingly, the photocleavage appears to be tolerant towards changes of flow rate within the range of 9 to 36 mL/h, where the photocleavage yield only varies between 75 and 69%. For the purposes of further investigation, 18 mL/h was selected as the optimum flow rate.

Based on the observation that restricted mixing of polystyrene beads occurs in small-diameter FEP tubes which leads to inhomogeneous irradiation of the support,[15] the cleavage efficiency was expected to increase upon re-injection of the resin into the reactor. Despite a slight increase in yield for double-injection, about 20% of the Fmoc remained bound to the resin for both flow rates tested. It is interesting to note that significant browning of the resin was only observed after the resin left the photoreactor (see Figure 3). This late browning, which suggests that hydrolysis occurs after photocleavage, may contribute to the efficiency of the photocleavage observed in the first injection. This constitutes a clear advantage over batch processes, where the absorption by the nitrosobenzaldehyde may impact the efficiency of the photocleavage.[22, 24] In this flow protocol, this concern is mitigated and may only affect the second photocleavage cycle.

Table 1. Examining the efficiency of photocleavage from solid support using a continuous flow LED photoreactor: Varying number of cycles and flow rate.

Entry	Number of cycles	Flow rate [mL/h]	Yield [%][a]
1	1	18	75
2	1	9	74
3	2	18	79
4	2	9	78

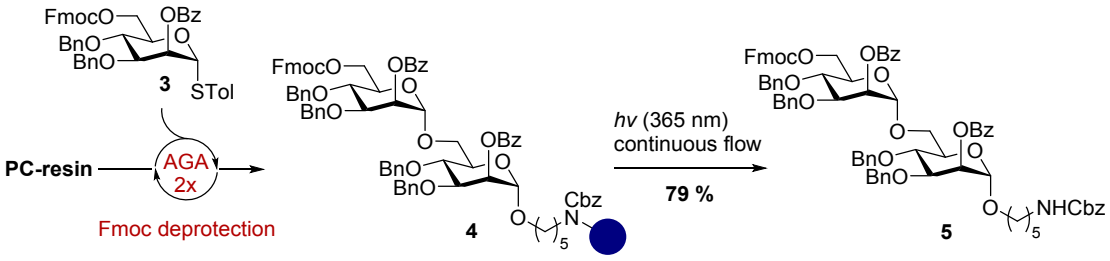
[a] *average yield of two experiments.*

In order to assess the reproducibility of the cleavage protocol, and to probe for possible incomplete removal of Fmoc chloride in the protection step or clogging of the resin in the reactor (leading to longer residence times and thus an overestimation of the cleavage efficiency), all experiments were conducted twice with two different batches of FPC-resin. The highest discrepancy in cleavage yields observed was 5%.

It is conceivable that the remaining Fmoc was most likely bound in the pores of the polystyrene beads. Due to the limited light-permeability of the beads, a quantitative cleavage could not be achieved for intact beads. This explanation is in line with the recent study by Hurevich and co-workers on the effect of grinding solid supports prior to irradiation on the photocleavage efficiency.[22] The authors elegantly demonstrated the dependency of cleavage efficiency on bead size and, by extension, on the particle surface which is exposed to light. Comparing these two approaches, batch photocleavage of ground resin versus photocleavage in flow, it is encouraging that these orthogonal approaches produce very similar yields.

Given that grinding is proven to substantially increase yield (40% for 1 h irradiation),[22] the FPC-resin **2** was ground and exposed to irradiation in flow. This resulted in 86% cleavage efficiency for a double injection (81% for single injection). Motivated by these findings, this protocol was applied to the AGA of a model disaccharide (Scheme 2). PC-resin was glycosylated with the mannose building block **3** (TfOH/NIS) using a Glyconeer 2.1 using standard AGA protocols. Fmoc deprotection followed by a second glycosylation sequence yielded the desired disaccharide-functionalized PC-resin **4**.

Gratifyingly, photocleavage (18 mL/h, 2 injections) under the optimized flow conditions liberated the desired disaccharide **5**. The Fmoc loading was calculated to be only 0.0525 mmol/g, corresponding to 79% photocleavage efficiency. The isolated yield of the crude disaccharide was 83%, which is in good agreement with the yield calculated from Fmoc loading.



Scheme 2. Synthesis of the model dimannoside **5** on a PC-resin via AGA, Fmoc deprotection and subsequent glycosylation. The functionalized resin was finally irradiated in the customized LED flow reactor under the optimized conditions.

EXPERIMENTAL SECTION

Photocleavage Setup. The photocleavage from solid support was performed in a custom-built 365 nm LED flow reactor. The photoreactor comprises eight LEDs (each 2000-3800 mW radiant flux @ 750 mA), which are dimmed to 350 mA. The reaction coil is located at a distance of 3 cm to the LEDs. The reaction coil consists of transparent FEP tubing (0.8 mm inner diameter) wrapped around a water-cooled aluminum cylinder. The total reactor volume is 6 mL (effective irradiation volume 4 mL). For details see the ESI.

General Procedure for Photocleavage in Flow. The reactor was equilibrated with CH_2Cl_2 (15 mL, 240 mL/h) before functionalized resin (25-30 mg), swollen in 1-1.5 mL of CH_2Cl_2, was

slowly injected from a 2 mL syringe into the reactor. The resin was pushed through the reactor with CH_2Cl_2 (15 mL) at the specified flow rate. To shrink out the remaining resin, the reactor was rinsed with CH_2Cl_2/MeOH (1/1 *v*/*v*, 7 mL, specified flow rate; then 6 mL, 240 mL/h) and MeOH (10 mL, 240 mL/h). Before the next injection, the reactor was re-equilibrated with CH_2Cl_2 (15 mL, 240 mL/h).

Determination of Fmoc loading.[23] The resin was incubated with a stock solution of 2% DBU in DMF (v/v, 2 mL) for 1 h. A 160 µL aliquot was transferred into a graduated 10 mL flask and diluted with acetonitrile and the UV absorption was measured. The absorbance at 294 and 304 nm were used to calculate the Fmoc loading according to equations (1) and (2). The average of both values is reported. The photocleavage yield was calculated relative to non-irradiated FCP-resin.

$$Loading_{294} = \frac{Abs_{294} * 14.2}{m_{resin}} \qquad (1)$$

$$Loading_{304} = \frac{Abs_{304} * 16.3}{m_{resin}} \qquad (2)$$

A blank solution was prepared in an analogous fashion without resin.

Synthesis of benzyl (5-hydroxy-2-nitrobenzyl) (6-hydroxyhexyl) carbamate (1). 5-Aminopentan-1-ol (1.540 g, 14.95 mmol, 1.0 eq.) was added to a suspension of 5-hydroxy-2-nitrobenzaldhyde (2.500 g, 14.95 mmol, 1.0 eq.) and $MgSO_4$ (2.340 g, 19.44 mmol, 1.3 eq.) in dry CH_2Cl_2 (65 mL) at room temperature under argon. The yellow suspension was stirred for 14 h, whereon the $MgSO_4$ was filtered off and washed thoroughly with CH_2Cl_2 and MeOH. The solvent was removed *in vacuo* to give an orange solid. The solid was dissolved in MeOH (100 mL) and $NaBH_4$ (566 mg, 15.0 mmol, 1.0 eq.) was added in small portions. The reaction mixture was stirred for 1 h, quenched with acetone and concentrated *in vacuo* to give a yellow foam. To a solution of the amine in MeOH (80 mL) NEt_3 (4.6 mL, 33 mmol, 2.2 eq.) and Cbz chloride (4.25 mL,

29.9 mmol, 2.0 eq.) were added. After stirring for 1 h at room temperature, K_2CO_3 (6.20 g, 44.9 mmol, 3.0 eq.) was added and stirring was continued for another hour. The mixture was filtered over celite®, concentrated *in vacuo* and the orange residue was partitioned between CH_2Cl_2 (250 mL) and water (50 mL). The organic layer was washed with 1M HCl and water (3 x 40 mL each), dried over $MgSO_4$ and concentrated *in vacuo*. The yellow syrup was purified by column chromatography (SiO_2, CyH/EtOAc 4/1 → 1/1) to yield **1** as a viscous yellow oil (2.302 g, 5.93 mmol, 40 %). The spectroscopic data are in good agreement with literature values:[14] ^{1}H NMR (300 MHz, $CDCl_3$, mixture of rotamers, resonances of major rotamer) δ 8.19 – 8.01 (m, 1H), 7.42 – 7.19 (m, 5H), 7.14 – 7.05 (m, 1H), 6.87 – 6.68 (m, 1H), 5.07 (m, 2H), 4.89 (s, 2H), 3.62 (m, 2H), 3.35 (t, J = 6.8 Hz, 2H), 1.63 – 1.32 (m, 6H) ppm.

Synthesis of FPC-resin. FPC-resin was synthesized according to literature procedures.[14] For details see ESI.

CONCLUSIONS

A new flow platform for the efficient cleavage of photolabile linkers on solid support has been disclosed, and demonstrated in the context of automated glycan assembly (AGA). Yields up to 80% were achieved employing a continuous flow LED system, which mitigates the need for hazardous mercury vapor lamps whilst retaining the efficiency and timeliness of the process. This strategy, in combination with grinding, enables the yield to be further enhanced. Gratifyingly, the performance of this flow LED setup was unaffected by aromatic protecting groups, enabling the fast and efficient photocleavage of a fully protected disaccharide from solid support. This LED-

based flow photocleavage platform can be easily integrated into existing AGA facilities, thereby mitigating cost and safety considerations in utilizing photolabile linkers in solid phase synthesis.

ASSOCIATED CONTENT

Supporting Information.

Details of experimental procedures and spectroscopic data (PDF)

AUTHOR INFORMATION

Corresponding Author

* Ryan Gilmour − Organisch-Chemisches Institut, Westfälische Wilhelms-Universität Münster, 48149 Münster, Germany; orcid.org/0000-0002-3153-6065; Email: ryan.gilmour@uni-muenster.de

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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Notes

The authors declare no competing financial interest.

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ABBREVIATIONS

AGA, automated glycan assembly; Cbz, benzyloxycarbonyl; CyH, cyclohexane; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DMF, *N,N*-dimethylformamide; FEP, fluorinated ethylene propylene; Fmoc, fluorenylmethoxycarbonyl; FPC-resin, fluorenylmethoxycarbonyl-protected photocleavable resin; LED, light-emitting diode; PC-resin, resin functionalized with photocleavable linker; SPS, solid-phase synthesis; TBAI, tetrabutylammonium iodide.

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