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Article

Flash Chemistry Approach to Organometallic *C*-Glycosylation for the Synthesis of Remdesivir

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ABSTRACT: In a rapidly changing environment, such as the current COVID-19 pandemic, continuous flow reactors bear the potential to increase the production of urgently needed active pharmaceutical ingredients (APIs) on demand. In the synthesis of remdesivir, the organometallic *C*-glycosylation step was identified as a limitation for the large-scale production, requiring long addition periods and cryogenic temperatures. Previous studies have focused on a Grignard-based protocol, but a flash chemistry approach, using organolithium reagents, has facilitated significant improvements. After gaining further understanding of the *C*-glycosylation, this step was successfully transferred to a five-stream continuous flow process, achieving 60% yield at a moderate temperature (−30 °C) in a total residence time of just 8 s. Stable processing was demonstrated for 2 h, providing an exceptionally high space−time yield of 10.4 kg L^{-1} h^{-1}, in a scalable flow reactor system.

KEYWORDS: *continuous flow chemistry, remdesivir, organometallics, lithium−halogen exchange, active pharmaceutical ingredients, flash chemistry*

INTRODUCTION

The rapid spread of the COVID-19 pandemic (SARS-CoV-2 virus) has resulted in over 94 million cases and 2 million deaths worldwide.[1] In a race to find effective treatments,[2] remdesivir (**4**) was the first drug approved by the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA).[3] Originally developed by Gilead Sciences as an Ebola treatment, $873m of sales of the drug, now marketed as Veklury, were reported in Q3 2020 alone.[4] The demand for this treatment has necessitated vastly increased production to meet the global demand.

The manufacture of remdesivir is complex, with initial batches reportedly taking more than 9 months to complete when taking starting material procurement into account.[5] Modern manufacturing technologies, such as continuous processing, may play an essential role in streamlining this process, as well as improving supply chain security.[6] Indeed, one synthetic step in this route has already been described in continuous flow, on plant scale,[7] providing improvements in safety, diastereoselectivity, process control, and space−time yield. It is envisaged that these advantages would be compounded, and others realized, by the translation of additional synthetic steps to continuous flow mode.

The synthetic sequence, as described in recent literature,[8,9] begins with the organometallic-mediated *C*-glycosylation of halogenated pyrrolotriazinamine **1**/**1a** with benzyl-protected D-ribono-1,4-lactone **2** to furnish key intermediate **3** (Scheme 1a). Five further synthetic steps are then required to furnish the API remdesivir (**4**).[8a] This initial organometallic step has been reported using both Grignard and organolithium reagents and identified as a step that could benefit from the implementation of continuous flow technology.

The Grignard chemistry has been most thoroughly investigated owing to its better temperature tolerance and reportedly improved reproducibility (Scheme 1a).[8b] The most recent iteration in the batch was performed on a 280 kg scale, achieving a 69% yield using stoichiometric $NdCl_3$ and tetrabutylammonium chloride additives to improve the selectivity for the nucleophilic attack on the lactone versus deprotonation.[7] This remains a lengthy process, which must be carried out at −20 °C with slow addition periods. In contrast, continuous flow technology has already been demonstrated to enable much faster and milder processing. We recently reported a Grignard procedure in flow, operating at room temperature, with a residence time of less than one minute. This provided the product with a synthetically useful 47% yield in the absence of additives.[10]

On the other hand, implementing an organolithium-based procedure permits the use of the cheaper and more mass-efficient heteroaryl bromide **1** as the organometallic precursor, in place of its iodide analogue.[11] A recent batch report details the use of 1,2-bis(chlorodimethylsilyl)ethane (BCDSE) as a bidentate silyl protecting group, coupled with *N*,*N*-diisopropylamine as an additive. Despite a low temperature (−78 °C) and long reaction time, this procedure has provided the highest yield for this process to date, at 74%.[11]

Arguably, the promise that microreactor technology and continuous processing holds is even more applicable to

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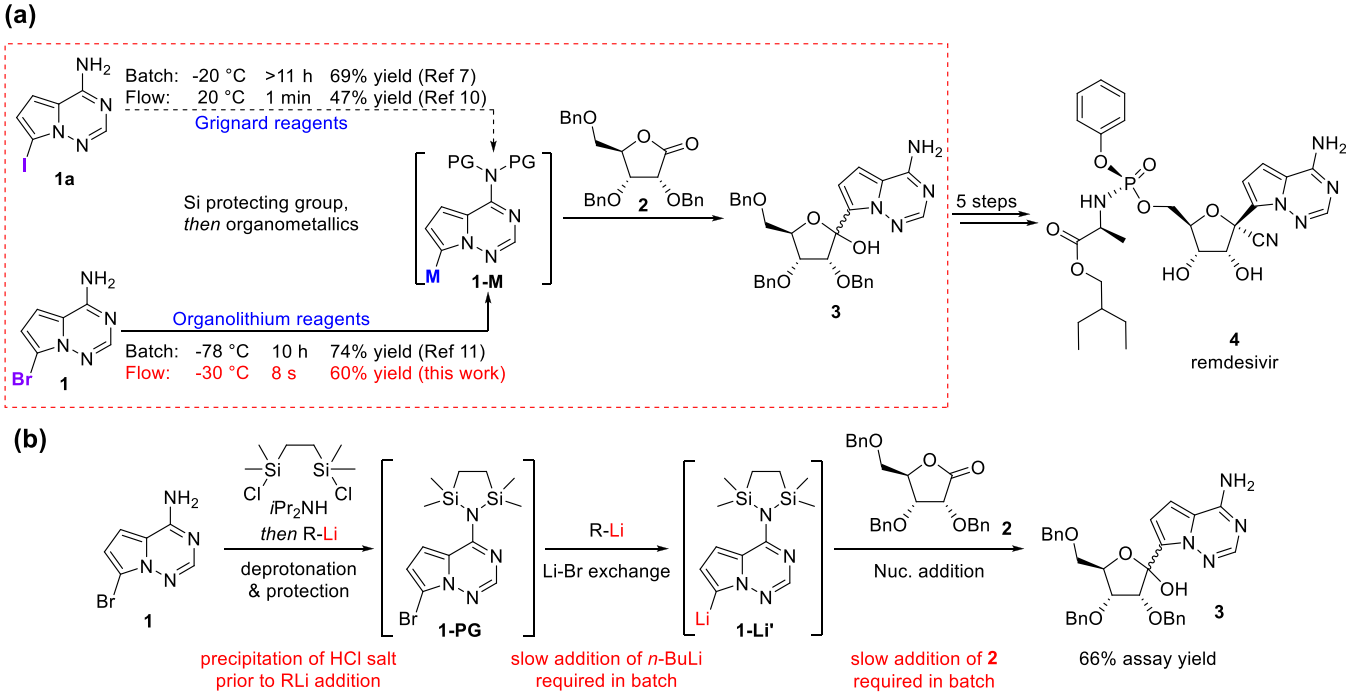
Scheme 1. Reported *C*-Glycosylation Processes toward the Synthesis of Remdesivir (4)[a,b]



[a]Scheme showing the C-glycosylation of pyrrolotriazinamine 1/1a with lactone 2 to furnish key intermediate 3 as part of the synthesis of remdesivir (4). The different literature approaches using Grignard or organolithium chemistry are highlighted. [b]Reproduction of published organolithium procedure,[11] focusing on the intermediates formed and any potential obstacles to developing a continuous flow process.

organolithium chemistries,[12] when compared to their milder Grignard counterparts. These highly reactive intermediates, and their corresponding exothermic reactions, benefit most from improved mass and heat transfer. This is encompassed within the field of flash chemistry,[13] which focuses on exceptionally fast reactions (up to a few seconds) in flow and has been demonstrated in many cases to enable chemistries that would otherwise be impossible or impractical. Of particular interest is the scalable manner in which flash chemistry can be achieved, which circumvents many significant scale-up issues faced during the development of manufacturing scale processes. Continuous processing has the potential to relieve the supply chain burden imposed by this challenging transformation at the beginning of the synthetic sequence.

Herein, we describe the development of a flash chemistry process in continuous flow, for the rapid synthesis of glycosylated pyrrolotriazinamine **3** using 7-bromopyrrolotriazinamine **1** as an organolithium precursor. By applying microreactor technology, the process temperature could be significantly raised from −78 to −30 °C. Furthermore, the reaction time could be drastically decreased to just 8 s for the entire transformation.

RESULTS AND DISCUSSION

Investigation of the *C*-Glycosylation Process. The *C*-glycosylation of 7-bromopyrrolotriazinamine **1** with 2,3,5-tri-*O*-benzyl-D-ribonolactone **2** consists of three consecutive steps (Scheme 1b). In the first step, the primary amine **1** is protected with a silyl protecting group (such as BCDSE), releasing HCl (2 equiv), which is neutralized by an organolithium base. A third equivalent of organolithium base is required to perform a Li−Br exchange and obtain heteroaryllithium **1-Li**. Finally, a nucleophilic attack on lactone **2** leads to the formation of the desired glycosylated pyrrolotriazinamine **3**.

Initially, the reported conditions[11] were reproduced in batch to examine the sensitivity of the process and observe any potential issues for translation to flow (Scheme 1b). To begin with, the published 0.2 M reaction concentration provided a slurry, so the concentration had to be halved to ensure the solubility of the starting material **1**. Another significant concern was the formation of solids following the addition of BCDSE, which could cause blockages within a flow reactor.[14] Previous characterization of the solids revealed that the protected amine itself was not responsible for the precipitation, as no signal at around 0 ppm (attributable to SiCH_3) was found in the ^{1}H NMR spectrum.[10] The precipitate was proposed to be the protonated form of heterocycle **1**, which can no longer undergo protection. The solid formation was observed to take ∼5 s at ambient temperature, leaving a short time window to introduce a base to scavenge HCl. It was envisaged that this short residence time could easily be achieved in a flow setup. A longer-term operation may be affected by the gradual solid formation but is expected to be manageable on a larger scale.

Utilizing a slow addition of *n*-BuLi was found to be vital to achieving a good yield of the glycosylated heterocycle **3** in batch. This is assumed to be because of poor heat transfer, resulting in localized hotspots in the vessel and poor mass transfer, resulting in local stoichiometric imbalances. Both of these effects could result in the decomposition of the lithiated intermediate and will be amplified as the reaction scale increases. However, performing the reaction in continuous flow enhances the heat and mass transfer and thus is expected to enable effective reaction in a scalable manner.[15]

The nucleophilic addition of heteroaryllithium **1-Li** to lactone **2** bears another key challenge. Past studies have shown that the

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lactone's α-proton is rapidly deprotonated by organometallics, resulting in quenching of the lithiated heterocycle **1-Li**. When using a Grignard reagent, it has been shown that Lewis acid additives can favor nucleophilic attack; however, the stoichiometric quantities of hygroscopic, insoluble, and rare metal species ($NdCl_3$ and tetrabutylammonium chloride) adds significant cost and complexity to the process.[7] The higher nucleophilicity of organolithium species may impart better selectivity for nucleophilic addition than its Grignard equivalent.

In our previously developed Grignard process, we observed the side products arising from a nucleophilic attack on an open-chain ketone intermediate of the ribonolactone adduct.[10] Interestingly, this reactivity was not observed in any significant quantities when using the organolithium approach. This may be due to the increased nucleophilicity of heteroaryllithium **1-Li**, which facilitates fast reaction with lactone **2**, rather than preferential reaction with the more electrophilic ketone intermediate. Alternatively, the Mg counterion may enable a higher proportion of the open-chain ketone form to be present in a solution.

To understand the relative rate of deprotonation versus Li−Br exchange, a batch experiment was carried out in which *n*-BuLi was added 1 equiv at a time. Surprisingly, after the addition of 1 equiv *n*-BuLi, 34% of the bromide had already exchanged and 62% after the addition of 2 equiv (Supporting Information, Table S1). This implies that there is no significant difference in the rate of the two reactions under these conditions. However, to avoid internal quenching of the formed heteroaryllithium, the two processes should be decoupled. Since *n*-BuLi is known to perform the Li−Br exchange rapidly, it was envisaged that the use of lithium *N*,*N*-diisopropylamide (LDA) would prevent salt formation while avoiding the Li−Br exchange.

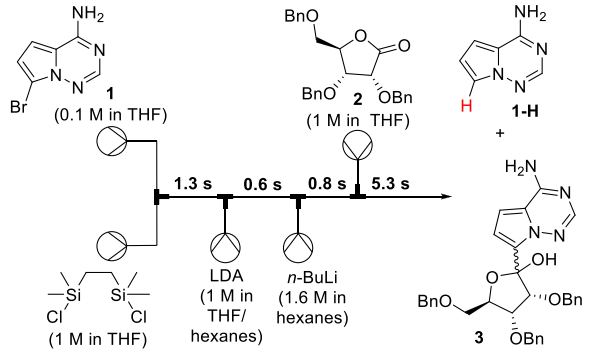
Initial Continuous Flow Process. Based on these observations in batch, a flow setup was devised (Table 1), ensuring a short reaction time between heterocycle **1** and BCDSE, before the addition of LDA (to prevent salt formation), followed by *n*-BuLi (to perform lithium−bromide exchange). We opted for a continuous flow microreactor (Ehrfeld, FlowPlate, Hastelloy C-22/sapphire)[16] equipped with a small-volume mixing plate (TG mixer,[17] internal volume 350 μL, channel width 0.2−0.5 mm, see the Supporting Information for further details), which facilitates rapid mixing and efficient heat transfer in a scalable system.[18]

During initial flow experiments, it was observed that the desired product underwent elimination in the aqueous quench solution to form an unsaturated carbonyl species (see the Supporting Information). In the absence of diisopropylamine, this did not occur and so was attributed to an amine-catalyzed mechanism. To avoid this degradation, the quench solution was simply neutralized using a small quantity of ammonium chloride.

The microreactor concept was successfully implemented by combining the heterocycle **1** (0.1 M in THF) with BCDSE (1.0 M in THF), followed by LDA (1.0 M in THF/hexanes) after 101 μL reactor volume. Then, *n*-BuLi (1.6 M in hexanes) was introduced to form the heteroaryllithium **1-Li**, which was quenched with lactone **2** to furnish the desired glycosylated pyrrolotriazinamine **3**. In the first instance, a 54% assay yield was achieved, alongside 21% of the protonated heterocycle side product **1-H**. Although no solid formation was observed, the heteroaryl bromide **1** proved to be far less soluble than its iodide analogue **1a**, necessitating its low concentration of 0.1 M.

Flow experiments were then performed to investigate reaction rates in this setup. A comparable yield was found when all flow rates were multiplied by a factor of 1.5 (total residence time = 5.3 s, entry 1 vs entry 2), implying that these residence times were sufficient for the complete reaction in each step. Conversely, halving the flow rates (total residence time = 16 s, entry 1 vs entry 3) resulted in a far poorer 31% yield of product **3**. This implies that the worse mixing and heat transfer at low flow rates significantly hamper the process.

Table 1. Initial Continuous Flow Results



entry	temp. [°C]	protonated heterocycle **1-H** [%][a]	desired product **3** [%][a]
1	−40	21	54
2[b]	−40	24	56
3[c]	−40	19	31
4[d]	−40	18	56
5[e]	−40	20	54
6	−50	21	56
7	−30	19	54
8	−20	24	50

[a]Experiments were performed in Ehrfeld FlowPlate using the following flow rates: **1** (4.11 mL/min, 1.0 equiv), BCDSE (0.452 mL/min 1.1 equiv), LDA (0.411 mL/min, 1.0 equiv), *n*-BuLi (0.848 mL/min 3.3 equiv), and **2** (0.822 mL/min, 2.0 equiv). HPLC yield versus biphenyl as an internal standard. [b]Flow rates ×1.5 compared to entry 1. [c]Flow rates ×0.5 compared to entry 1. [d]Additional capillary reactor (4 mL, −40 °C) after FlowPlate. [e]Additional capillary reactor (4 mL, 20 °C) after FlowPlate.

The nucleophilic addition of the heteroaryllithium **1-Li** on lactone **2** was expected to proceed slower compared to the lithiation step, which also led to a more detailed investigation of the residence time at this point. A capillary reactor was installed after the introduction of lactone **2**, providing an additional 38 s residence time (Supporting Information, Figure S8). When the capillary reactor was tempered to either −40 or 20 °C, the reaction output was consistent with the prior results, which indicated that the nucleophilic addition reached completion within the initial 5.3 s in the microreactor plate. Therefore, the additional capillary reactor proved to be unnecessary (Table 1, entries 4 and 5).

A critical improvement for organolithium reactions in the flow is often an improved temperature tolerance, versus their batch equivalent.[19] While the glycosylation process required cryogenic temperatures in batch (−78 °C), the flow process provided consistent results (54−56% yield) between −50 and −30 °C (Table 1, entries 6 and 7). Applying a further elevated temperature of −20 °C decreased the yield to 50% (entry 8), so the optimal reaction temperature of −30 °C was chosen for further experiments.

Further Optimization in Flow. During batch experiments, a combination of Grignard reagents (for deprotonation) and organolithium reagents (for Li−Br exchange) resulted in lower

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yields of **3** (36%, see the Supporting Information), presumably due to the Grignard formation by transmetalation of heteroaryllithium **1-Li** with Mg byproducts. Neither methyllithium nor its lithium−bromide complex (MeLi•LiBr) provided stable reaction conditions due to the evolution of gaseous methane. The use of phenyllithium caused precipitation, so its reaction performance could not be quantified.

As demonstrated in the initial experiments (Table 1), LDA acts as a strong base, whilst leaving the bromide completely intact (Figure 1a). Consequently, employing LDA for

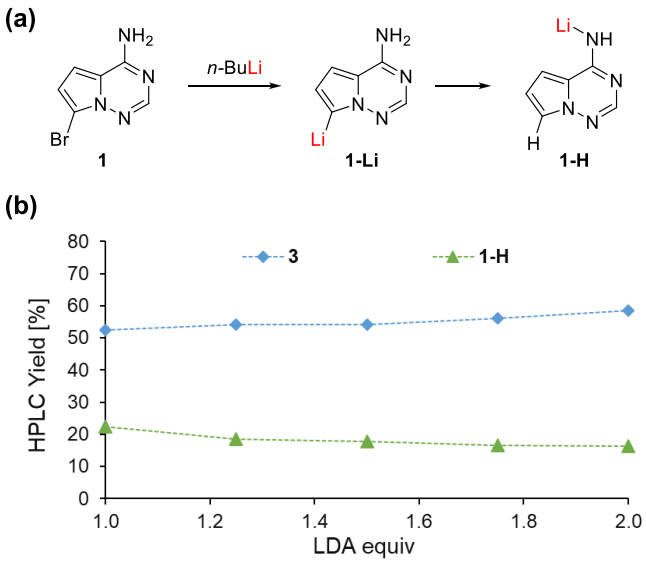

Figure 1. Internal quenching of heteroaryllithium and its prevention by varying LDA stoichiometry (a) Proposed mechanism of internal quenching to **1-H** arising from the rapid Li−Br exchange, which competes with deprotonation. (b) Results of experiments with varying LDA stoichiometry in an attempt to separate the deprotonation and lithium−halogen exchange steps.

deprotonation, followed by *n*-BuLi for Li−Br exchange was found to be the most suitable combination. The LDA stoichiometry was screened, between 1 and 2 equiv (Figure 1b). Increasing the amount of LDA increased the yield of the desired product **3** while simultaneously decreasing the amount of the protonated heterocycle **1-H**.

The other major side products formed during the glycosylation process were found to arise from the nucleophilic attack of the lithiated heterocycle **1-Li** on the silyl protecting group (Figure 2a). Intermediate **5** goes on to react again with an organolithium or to simply hydrolyze during the quench/HPLC analysis, forming side products **6**−**8**. It should be noted that the N−Si bonds (unlike the C−Si bonds) are unstable in the presence of water, so other undetectable intermediate species may also be present.

The presence of these side products implies the incomplete consumption of the BCDSE protecting group. In an attempt to eliminate them, the stoichiometry of BCDSE was gradually decreased from 1.0 to 0.5 equiv (Figure 2b). Surprisingly, the overall yield was not significantly affected. As the quantities of silyl-derived side products decreased, the protonated heterocycle **1-H** increased in their place. This implies a greater extent of internal quenching in place of lower silylated side products. For ease of purification (absence of silyl-derived side products) and reduction of cost, we decided to operate using 0.6 equiv.

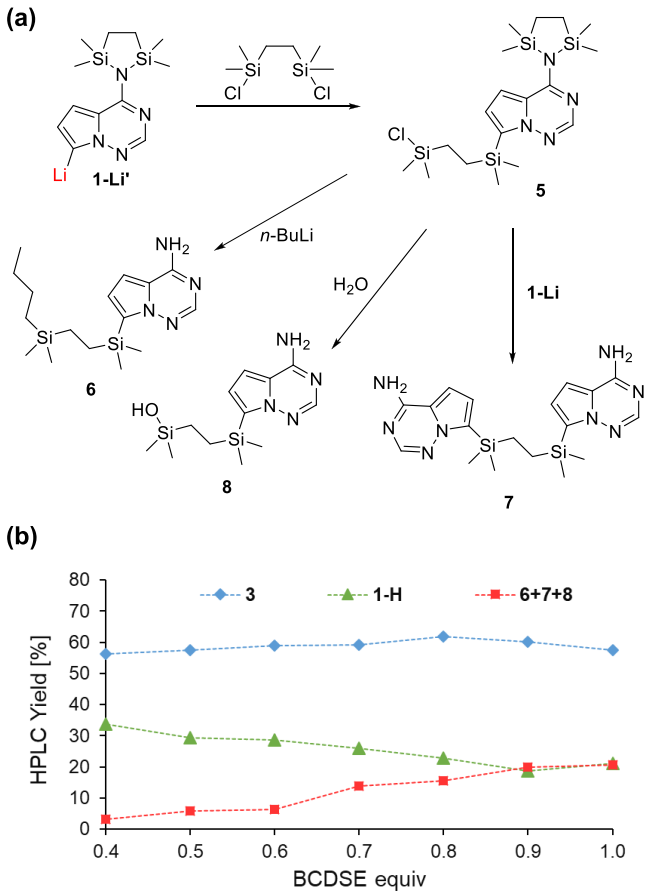

Figure 2. Side reaction of heteroaryllithium with silyl chloride (a) Observed side products arising from the reaction of heteroaryllithium with BCDSE. Structures are proposed based on LCMS analysis. (b) Results of experiments with varying BCDSE stoichiometry to minimize the formation of side products **6**−**8**. Yields of **3** and **1-H** are calibrated versus an internal standard, while the yield of **6** + **7** + **8** is based only on area%.

These unexpected results began to cast doubt upon the requirement for a bidentate protecting group. A comparison against the cheaper monodentate equivalent, trimethylsilyl chloride (TMSCl), was performed (Supporting Information, Figure S3). TMSCl was, indeed, found to provide a lower yield of **3** (~10% lower) at optimal stoichiometries. Previous results using benzyl protecting groups revealed weaknesses for monodentate protecting groups due to some selectivity for triazine ring protection.[10] Similar effects could also be at play in this instance; however, the overall reaction mechanism is undoubtedly complex and the precise species involved are not known.

Since a stable flow process was possible, even with substoichiometric BCDSE, an experiment was carried out in both batch and flow in the absence of any protecting group. To our surprise, the batch reaction yielded 20% and the flow reaction yielded 49% of the desired product **3** (see the Supporting Information). Unfortunately, the reaction of heterocycle **1** with *n*-BuLi in the absence of silyl protecting groups resulted in an almost instantaneous formation of solids, which renders this flow process impossible to run for longer than few minutes.

Similar to the previously developed batch process, it was found that excess of lactone **2** is required to achieve a good yield

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of the desired product. However, in this case, there was no significant difference between 1.8 and 2 equiv, so the lower of the two was selected (Supporting Information, Figure S5). Furthermore, *n*-BuLi stoichiometry showed a slight decrease in yield below 3 equiv (the theoretical minimum required), but no improvement with a slight increase to 3.3 equiv (Supporting Information, Figure S4).

Demonstration of Process Stability. Following this additional fine-tuning of reaction parameters, conditions achieving a 60% assay yield of **3**, with a total residence time of just 8 s, have been developed (Figure 3a). To demonstrate the stability of the process over a longer processing period, a long run was carried out for 2 h with sampling every 5 min (Figure 3b). The results depicted a very stable process, with assay yield varying by <2% across the entire operating period. During the course of this experiment, there was a slight increase in the pressure drop of the system, from 1.5 to 2.9 bar. This could be explained by a gradual formation of small amounts of solid (e.g., LiOH arising from trace water) but did not affect the yield and would likely be more easily manageable when performing experiments on a larger scale.

The reaction output was collected, providing 16.9 g (60% yield, taking into account 96% purity) of glycosylated product **3**. The material, in this instance, was purified by column chromatography, but larger-scale batches could make use of developed crystallization protocols.[7,11] This corresponds to a throughput of 8.5 g h^{-1}, or an exceptionally high space−time yield of 10.4 kg L^{-1} h^{-1}, when the small reactor volume of just 0.815 mL is taken into account. The high space−time yield clearly demonstrates the advantages of a flash chemistry approach to these transformations, whereby short reaction times enable high throughput, even in a small reactor. When combined with the opportunity of a facile scale-up, to larger versions of this proven reactor platform,[15,18] the potential savings in cost, time, and energy are dramatic.

In comparison with the reported Grignard batch procedure, using $NdCl_3$ and TBACl additives, this procedure is favorable in terms of the cost of the required additives. Although BCDSE appears a comparatively exotic silyl protecting group, this accounts for a cost of only €179 per mole of **1** processed.[20] On the other hand, the additives for the reported batch procedure cost €2091 per mole of **1a** processed.[21] Of course, it must be noted that these prices are taken from online catalogs and do not represent the manufacturing scale supply chains, but it is likely that the requirement for anhydrous $NdCl_3$ would add significant cost.

CONCLUSIONS

A study of the organolithium-based *C*-glycosylation toward the synthesis of remdesivir has enabled the transition to a continuous flow process. Through a careful analysis of the reaction mixture and addition sequence, the formation of solids within the microreactor could be avoided. Optimization of the reaction parameters, including the identity of silyl protecting groups and organometallic reagents, has led to minimized levels of side products in the transformation.

Precise tuning of the process parameters, in combination with superior heat and mass transfer bestowed by a microreactor environment, facilitated the highly exothermic *C*-glycosylation sequence in a total residence time of just 8 s. This was achievable at a significantly higher process temperature of −30 °C, which would lead to vast energy savings, compared to a batch process at −78 °C. The developed flow protocol has been established in a scalable reactor system, which has the potential to achieve more effective production of the key glycosylated intermediate and the corresponding API.

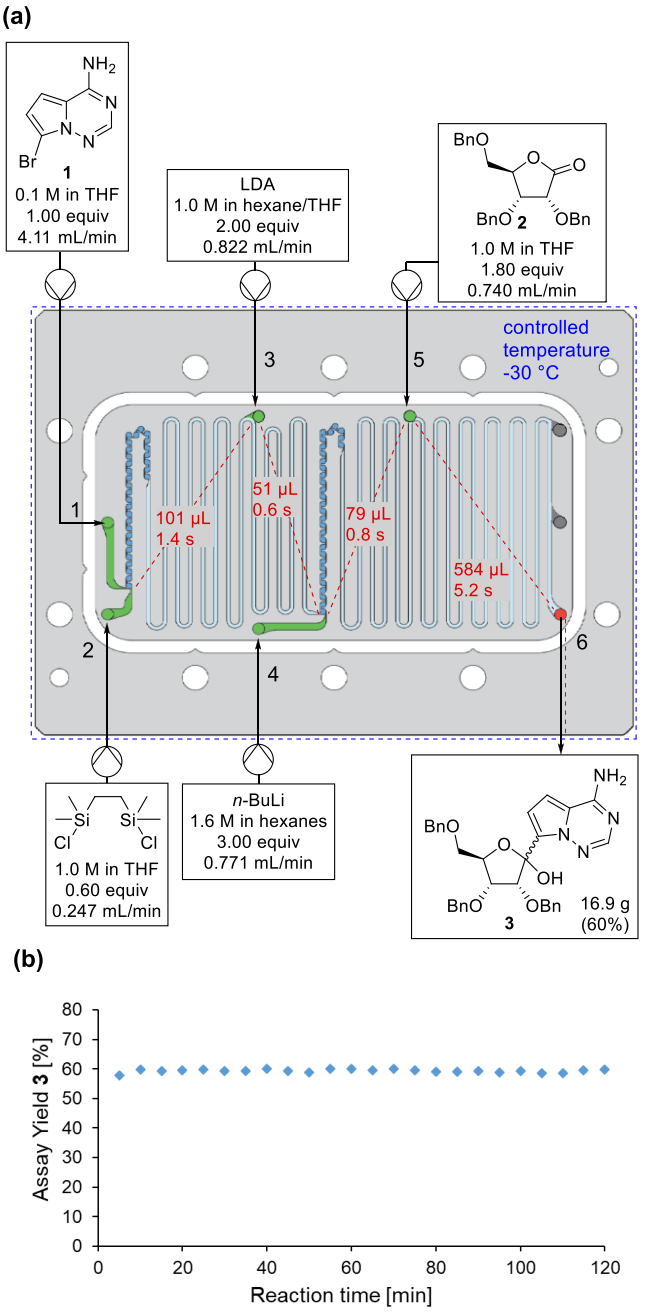

Figure 3. Schematic layout of the flow setup with optimized reaction conditions and long-run stability (a) Schematic layout of Ehrfeld FlowPlate (TG mixer), showing the optimized reaction conditions used for the long run. (b) Reaction performance over time during long-run operation. The yield was determined by HPLC analysis versus an internal standard.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.oprd.1c00024.

Further details of reaction setup, experimental results, and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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ABBREVIATIONS USED

API, active pharmaceutical ingredient; BCDSE, 1,2-bis-(chlorodimethylsilyl)ethane; TBACl, tetrabutylammonium chloride; TMS, trimethylsilyl

REFERENCES

(1) WHO Coronavirus Disease (COVID-19) Dashboard, World Health Organization, Jan 1, 2021, https://covid19.who.int/ (accessed 01-20-2010).

(2) (a) Liu, C.; Zhou, Q.; Li, Y.; Garner, L. V.; Watkins, S. P.; Carter, L. J.; Smoot, J.; Gregg, A. C.; Daniels, A. D.; Jervey, S.; Albaiu, D. Research and Development on Therapeutic Agents and Vaccines for COVID-19 and Related Human Coronavirus Diseases. *ACS Cent. Sci.* **2020**, *6*, 315−331. (b) De Savi, C.; Hughes, D. L.; Kvaerno, L. Quest for a COVID-19 Cure by Repurposing Small-Molecule Drugs: Mechanism of Action, Clinical Development, Synthesis at Scale, and Outlook for Supply. *Org. Process Res. Dev.* **2020**, *24*, 940−976.

(3) (a) First COVID-19 treatment recommended for EU authorisation, European Medicines Agency, June 25, 2020, https://www.ema.europa.eu/en/news/first-covid-19-treatment-recommended-eu-authorisation (accessed 01-20-2021). (b) European Commission secures EU access to Remdesivir for treatment of COVID-19. European Commission, July 29, 2020, https://ec.europa.eu/commission/presscorner/detail/en/ip_20_1416 (accessed 01-20-2021).

(4) Gilead's revenue rises 17% driven by sales of coronavirus treatment remdesivir, CNBC News, October 28, 2020, https://www.cnbc.com/2020/10/28/remdesivir-gileads-revenue-rises-17percent-on-sales-of-coronavirus-treatment.html (accessed 01-20-2021).

(5) (a) On the remdesivir manufacturing process: "The process is both resource- and time-intensive, with some individual manufacturing steps taking weeks to complete." See: Working to Supply Veklury for COVID-19. Gilead, October 22, 2020, https://www.gilead.com/purpose/advancing-global-health/covid-19/working-to-supply-veklury-for-covid-19 (accessed 01-20-2021). (b) Jarvis, L. M. Scaling up remdesivir amid the coronavirus crisis. Chem. Eng. News, April 20. 2020, https://cen.acs.org/biological-chemistry/infectious-disease/Scaling-remdesivir-amid-coronavirus-crisis/98/web/2020/04 (accessed 01-20-2021).

(6) (a) Hardy, M. A.; Wright, B. A.; Bachman, J. L.; Boit, T. B.; Haley, H. M. S.; Knapp, R. R.; Lusi, R. F.; Okada, T.; Tona, V.; Garg, N. K.; Sarpong, R. Treating a Global Health Crisis with a Dose of Synthetic Chemistry. *ACS Cent. Sci.* **2020**, *6*, 1017−1030. (b) Gutmann, B.; Cantillo, D.; Kappe, C. O. Continuous-Flow Technology - A Tool for the Safe Manufacturing of Active Pharmaceutical Ingredients. *Angew. Chem., Int. Ed.* **2015**, *54*, 6688−6728. (c) Baumann, M.; Baxendale, I. R. The Synthesis of Active Pharmaceutical Ingredients (APIs) Using Continuous Flow Chemistry. Beilstein. *J. Org. Chem.* **2015**, *11*, 1194−1219. (d) McWilliams, J. C.; Allian, A. D.; Opalka, S. M.; May, S. A.; Journet, M.; Braden, T. M. The Evolving State of Continuous Processing in Pharmaceutical API Manufacturing: A Survey of Pharmaceutical Companies and Contract Manufacturing Organizations. *Org. Process Res. Dev.* **2018**, *22*, 1143−1166. (e) Porta, R.; Benaglia, M.; Puglisi, A. Flow Chemistry: Recent Developments in the Synthesis of Pharmaceutical Products. *Org. Process Res. Dev.* **2016**, *20*, 2−25. (f) Lee, S. L.; O'Connor, T. F.; Yang, X.; Cruz, C. N.; Chatterjee, S.; Madurawe, R. D.; Moore, C. M. V.; Yu, L. X.; Woodcock, J. Modernizing Pharmaceutical Manufacturing: From Batch to Continuous Production. *J. Pharm. Innov.* **2015**, *10*, 191−199.

(7) Vieira, T.; Stevens, A. C.; Chtchemelinine, A.; Gao, D.; Badalov, P.; Heumann, L. Development of a Large-Scale Cyanation Process Using Continuous Flow Chemistry En Route to the Synthesis of Remdesivir. *Org. Process Res. Dev.* **2020**, *24*, 2113−2121.

(8) (a) Warren, T. K.; Jordan, R.; Lo, M. K.; Ray, A. S.; Mackman, R. L.; Soloveva, V.; Siegel, D.; Perron, M.; Bannister, R.; Hui, H. C.; et al. Therapeutic Efficacy of the Small Molecule GS-5734 against Ebola Virus in Rhesus Monkeys. *Nature* **2016**, *531*, 381−385. (b) Siegel, D.; Hui, H. C.; Doerffler, E.; Clarke, M. O.; Chun, K.; Zhang, L.; Neville, S.; Carra, E.; Lew, W.; Ross, B.; et al. Discovery and Synthesis of a Phosphoramidate Prodrug of a Pyrrolo[2,1-f][Triazin-4-Amino] Adenine C-Nucleoside (GS-5734) for the Treatment of Ebola and Emerging Viruses. *J. Med. Chem.* **2017**, *60*, 1648−1661. (c) Paymode, D. J.; Cardoso, F. S. P.; Agrawal, T.; Tomlin, J. W.; Cook, D. W.; Burns, J. M.; Stringham, R. W.; Sieber, J. D.; Gupton, B. F.; Snead, D. R. Expanding Access to Remdesivir via an Improved Pyrrolotriazine Synthesis: Supply Centered Synthesis. *Org. Lett.* **2020**, *22*, 7656−7661.

(9) See also examples from the patent literature: (a) Mackman, R. L.; Parrish, J. P.; Ray, A. S.; Theodore, D. A. Methods and Compounds for Treating Paramyxoviridae Virus Infections. U.S. Patent US20110451022011. (b) Butler, T.; Cho, A.; Kim, C. U.; Saunders, O. L.; Zhang, L. 1′-Substituted Carba-Nucleoside Analogs for Antiviral Treatment, U.S. Patent US20090414472009. (c) Mackman, R. L.; Parrish, J. P.; Ray, A.; Theodore, D. A. Methods and Compounds for Treating Paramyxoviridae Virus Infections. WO2012/012776A12012. (d) Chun, B. K.; Clarke, M. O. H.; Doerffler, E.; Hui, H. C.; Jordon, R.; Mackman, R. L.; Parrish, J. P.; Ray, A. S.; Siegel, D. Methods for Treating Filoviridae Virus Infections. WO2016/069826A12016. (e) Clarke, M. O. H.; Jordan, R.; Mackman, R. L.; Ray, A.; Siegel, D. Methods for Treating Filoviridae Virus Infections. WO2017/184668A12017. (f) Chun, B. K.; Clarke, M. O. H.; Doerffler, E.; Hui, H. C.; Jordon, R.; Mackman, R. L.; Parrish, J. P.; Ray, A. S.; Siegel, D. Methods for Treating Filoviridae Virus Infections. U.S. Patent US2019/0275063A12019.

(10) von Keutz, T.; Williams, J. D.; Kappe, C. O. Continuous Flow C-Glycosylation via Metal−Halogen Exchange: Process Understanding

and Improvements toward Efficient Manufacturing of Remdesivir. *Org. Process Res. Dev.* **2020**, *24*, 2362−2368.
(11) Xue, F.; Zhou, X.; Zhou, R.; Zhou, X.; Xiao, D.; Gu, E.; Guo, X.; Xiang, J.; Wang, K.; Yang, L.; Zhong, W.; Qin, Y. Improvement of the C-Glycosylation Step for the Synthesis of Remdesivir. *Org. Process Res. Dev.* **2020**, *24*, 1772−1777.
(12) For selected reviews and representative examples, see: (a) Plouffe, P.; Macchi, A.; Roberge, D. M. From Batch to Continuous Chemical Synthesis-a Toolbox Approach. *Org. Process Res. Dev.* **2014**, *18*, 1286−1294. (b) Hafner, A.; Filipponi, P.; Piccioni, L.; Meisenbach, M.; Schenkel, B.; Venturoni, F.; Sedelmeier, J. A Simple Scale-up Strategy for Organolithium Chemistry in Flow Mode: From Feasibility to Kilogram Quantities. *Org. Process Res. Dev.* **2016**, *20*, 1833−1837. (c) Colella, M.; Nagaki, A.; Luisi, R. Flow Technology for the Genesis and Use of (Highly) Reactive Organometallic Reagents. *Chem.−Eur. J.* **2020**, *26*, 19−32. (d) Power, M.; Alcock, E.; McGlacken, G. P. Organolithium Bases in Flow Chemistry: A Review. *Org. Process Res. Dev.* **2020**, *24*, 1814−1838.
(13) For selected reviews of flash chemistry, see: (a) Yoshida, J. I.; Nagaki, A.; Yamada, T. Flash Chemistry: Fast Chemical Synthesis by Using Microreactors. *Chem.-Eur. J.* **2008**, *14*, 7450−7459. (b) Yoshida, J.; Takahashi, Y.; Nagaki, A. Flash Chemistry: Flow Chemistry That Cannot Be Done in Batch. *Chem. Commun.* **2013**, *49*, 9896−9904. (c) Fanelli, F.; Parisi, G.; Degennaro, L.; Luisi, R. Contribution of Microreactor Technology and Flow Chemistry to the Development of Green and Sustainable Synthesis. Beilstein. *J. Org. Chem.* **2017**, *13*, 520−542. (d) Nagaki, A. Recent Topics of Functionalized Organolithiums Using Flow Microreactor Chemistry. *Tetrahedron Lett.* **2019**, *60*, No. 150923.
(14) Although handling solids in flow remains a challenge, commercial reactors do exist to achieve this purpose. For selected examples, see: (a) Bianchi, P.; Williams, J. D.; Kappe, C. O. Oscillatory Flow Reactors for Synthetic Chemistry Applications. *J. Flow Chem.* **2020**, *10*, 475−490. (b) Browne, D. L.; Deadman, B. J.; Ashe, R.; Baxendale, I. R.; Ley, S. V. Continuous Flow Processing of Slurries: Evaluation of an Agitated Cell Reactor. *Org. Process Res. Dev.* **2011**, *15*, 693−697. (c) Pomberger, A.; Mo, Y.; Nandiwale, K. Y.; Schultz, V. L.; Duvadie, R.; Robinson, R. I.; Altinoglu, E. I.; Jensen, K. F. A Continuous Stirred-Tank Reactor (CSTR) Cascade for Handling Solid-Containing Photochemical Reactions. *Org. Process Res. Dev.* **2019**, *23*, 2699−2706.
(15) (a) Kockmann, N.; Roberge, D. M. Scale-up Concept for Modular Microstructured Reactors Based on Mixing, Heat Transfer, and Reactor Safety. *Chem. Eng. Process.* **2011**, *50*, 1017−1026. (b) Plouffe, P.; Roberge, D. M.; Macchi, A. Liquid-Liquid Flow Regimes and Mass Transfer in Various Micro-Reactors. *Chem. Eng. J.* **2016**, *300*, 9−19.
(16) For selected examples of chemistry carried out in this reactor platform, see: (a) Sagmeister, P.; Williams, J. D.; Hone, C. A.; Kappe, C. O. Laboratory of the Future: A Modular Flow Platform with Multiple Integrated PAT Tools for Multistep Reactions. *React. Chem. Eng.* **2019**, *4*, 1571−1578. (b) Sagmeister, P.; Poms, J.; Williams, J. D.; Kappe, C. O. Multivariate Analysis of Inline Benchtop NMR Data Enables Rapid Optimization of a Complex Nitration in Flow. React. *Chem. Eng.* **2020**, *5*, 677−684. (c) von Keutz, T.; Cantillo, D.; Kappe, C. O. Continuous Flow Synthesis of Terminal Epoxides from Ketones Using in Situ Generated Bromomethyl Lithium. *Org. Lett.* **2019**, *21*, 10094−10098. (d) von Keutz, T.; Cantillo, D.; Kappe, C. O. Organomagnesium Based Flash Chemistry: Continuous Flow Generation and Utilization of Halomethylmagnesium Intermediates. *Org. Lett.* **2020**, *22*, 7537−7541. See also reference 10
(17) (a) Reckamp, J. M.; Bindels, A.; Duffield, S.; Liu, Y. C.; Bradford, E.; Ricci, E.; Susanne, F.; Rutter, A. Mixing Performance Evaluation for Commercially Available Micromixers Using Villermaux-Dushman Reaction Scheme with the Interaction by Exchange with the Mean Model. *Org. Process Res. Dev.* **2017**, *21*, 816−820. (b) Macchi, A.; Plouffe, P.; Patience, G. S.; Roberge, D. M. Experimental Methods in Chemical Engineering: Micro-Reactors. *Can. J. Chem. Eng.* **2019**, *97*, 2578−2587.
(18) Köckinger, M.; Wyler, B.; Aellig, C.; Roberge, D. M.; Hone, C. A.; Kappe, C. O. Optimization and Scale-Up of the Continuous Flow Acetylation and Nitration of 4-Fluoro-2-Methoxyaniline to Prepare a Key Building Block of Osimertinib. *Org. Process Res. Dev.* **2020**, *24*, 2217−2227.
(19) For selected examples of organometallic processes run at higher temperatures in continuous flow, see: (a) Hafner, A.; Mancino, V.; Meisenbach, M.; Schenkel, B.; Sedelmeier, J. Dichloromethyllithium: Synthesis and Application in Continuous Flow Mode. *Org. Lett.* **2017**, *19*, 786−789. (b) Murray, P. R. D.; Browne, D. L.; Pastre, J. C.; Butters, C.; Guthrie, D.; Ley, S. V. Continuous Flow-Processing of Organometallic Reagents Using an Advanced Peristaltic Pumping System and the Telescoped Flow Synthesis of (E/Z)-Tamoxifen. *Org. Process Res. Dev.* **2013**, *17*, 1192−1208. See also references 16 16c, and 16d
(20) Based on 0.6 equiv, at a price of £122 (~€139) per 100g, Fluorochem. http://www.fluorochem.co.uk/Products/Product?code=S01325 (accessed 02-04-2021).
(21) (a) NdCl3 (anhydrous) based on 1 equiv, at a price of €708 per 100 g, Alfa Aesar. https://www.alfa.com/de/catalog/018680/ (accessed 02-04-2021). (b) Tetrabutylammonium chloride based on 1 equiv, at a price of €113 per 100 g, Sigma Aldrich. https://www.sigmaaldrich.com/catalog/product/mm/814645 (accessed 02-04-2021).

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