Photochemistry

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A Photoflow Reactor for the Continuous Photoredox-Mediated Synthesis of *C*-Glycoamino Acids and *C*-Glycolipids**

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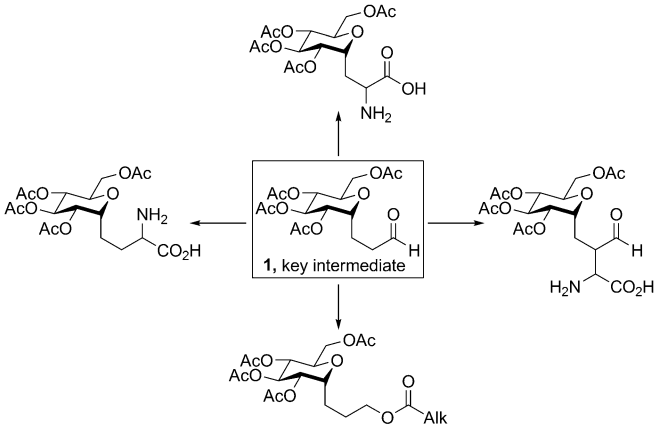
Glycoconjugates are essential biological compounds having various functions. For example, glycoproteins are involved in intercellular recognition events, such as immune response, and along with glycolipids they help to form mammalian cell surfaces.[1] These insights combined with their potential in vaccine therapeutics[2] continue to drive investigations to characterize the role of glycoconjugates in biological processes. A common feature of glycoconjugates is the metabolic instability of the *O*-glycosidic linkage,[3] which has stimulated the development of *C*-glycoside isosteres[4] to overcome this hydrolytic instability and thus extend bioavailability. Despite extensive efforts, improved methods of *C*-glycoside synthesis are still in demand.[5] To this end we have reported mild methods of *C*-glycoside synthesis through nickel-catalyzed[6,7] and photoredox processes.[8] The latter approach has received significant interest as a mild method of generating radicals using photochemical energy.[9] We report herein a high-yielding and scalable approach to *C*-glycopeptides and *C*-glycolipids which utilizes a continuous (flow) photoredox process.[10,11]

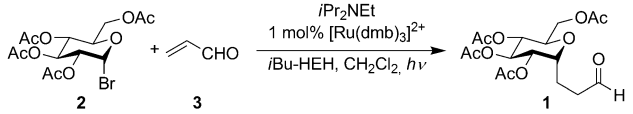
Previously reported syntheses of *C*-glycopeptides include the cross-metathesis of chiral alkenes,[12] Ramberg–Bäcklund olefination/hydrogenation seuqences,[13] addition of chiral carbon nucleophiles to glycosyl electrophiles,[14] and organocatalytic amidation of aldehydes.[15] While effective, these methods require multiple synthetic steps, use expensive or toxic reagents, harsh reaction conditions (strong acid or base), or the use of chiral starting materials (chiral auxiliaries or amino-acid-derived). As a more efficient alternative, we envisioned that aldehyde **1**, accessible in one step from commercial sources using our recently reported visible-light photoredox-mediated methodology,[8a] could function as a key intermediate for the divergent synthesis of *C*-glycoconjugate mimics (Scheme 1).

Recent advances in organocatalytic modification of aldehydes would enable the synthesis of a series of useful amino acid derivatives from a single intermediate to circumvent the disadvantages of previous approaches.[16,17] Aldehyde **1** can also enable the synthesis of *C*-linked glycosyl lipids by reduction and acylation. These goals therefore required a one-step scalable synthesis, and we envisioned that our photoredox methodology would provide the needed multigram quantities of **1**.



Scheme 1. Planned synthesis of *C*-glycoconjugates from common aldehyde intermediate.

Our efforts focused on the light-mediated conjugate addition of glycosyl radicals into acrolein (Scheme 2), which is high yielding in the presence of 1 mol% of $[Ru(dmb)_3]^{2+}$ (dmb = 4,4′-dimethyl-2,2′-bipyridine).[6d] Although scale-up experiments under standard reaction conditions in a 25 mL Schlenk flask proceeded smoothly, reactions on this scale required 24 hours of irradiation to reach 85% conversion, for a net turnover frequency (TOF) of 3.5 h^{-1}. A similar reaction in a 5 mm NMR tube afforded 73% conversion after only one hour of irradiation, thus corresponding to a TOF of 70 h^{-1}. Throughout our investigations of photoreductant-mediated reactions we have noted that reaction vessels having a thinner diameter generally result in faster reaction rates.



	t [h]	**2** mmol	Conv. [%]	TOF [h^{-1}]
25 mL flask	24	2.43	85	3.5
5 mm NMR tube	1	0.06	73	70

Scheme 2. Conversion and TOF based on vessel size.

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Since the molar extinction coefficient for $[RuL_3]^{2+}$ complexes are high ($17000\,M^{-1}cm^{-1}$ for $[Ru(dmb)_3]^{2+}$), we considered the possibility that the reaction was light-starved and the light source thus fails to irradiate the entire volume of the solution.[18] A simple analysis of the absorption profile of a theoretical vessel using the Beer–Lambert law at relevant concentrations of $[Ru(dmb)_3]^{2+}$ is shown in Figure 1. This

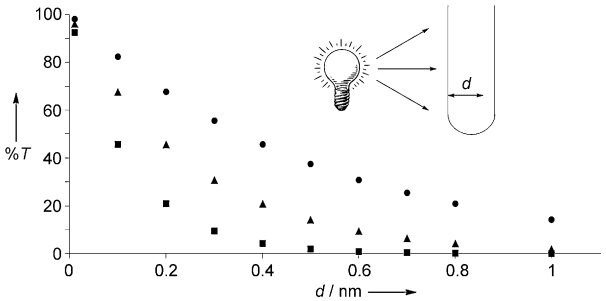


Figure 1. The percent transmittance versus distance from the wall (d) as calculated from the Beer–Lambert law. ● 0.5 mM $[Ru(dmb)_3]^{2+}$, ▲ 1 mM $[Ru(dmb)_3]^{2+}$, ■ 2 mM $[Ru(dmb)_3]^{2+}$.

analysis indicates that the vast majority of the reaction vessel receives negligible amounts of light. At a catalyst concentration of 1 mM, 98% of the incident light is absorbed within 1 mm of the vessel wall, while at 2 mM, this occurs within 0.5 mm. Since the light initiates the cascade of events that leads to free radical generation, the "active volume" is effectively determined by the surface area of the glass being irradiated; the remaining volume is not effectively irradiated.

This analysis suggests that decreasing the diameter of the reaction vessel should increase the flux of photons throughout the vessel and thereby increase the effective concentration of active catalyst and thus the rate of the reaction. The data in Figure 1 suggest that achieving reasonable irradiation of the entire reaction volume would require a vessel having a submillimeter diameter. Our solution to the problem of obtaining sufficiently thin diameters without sacrificing reactor volume was a photoflow reactor, which allows the continuous irradiation of a reaction mixture as it flows around a light source.

The basic design principle was initially demonstrated by Booker-Milburn,[11a] and several other examples of photoflow reactors for UV-light irradiation have since been reported.[10,11] As a result of the weak absorptivity of the reactants in these examples, these reactors are limited only by the flux of the light source and benefit from tubing with a thicker diameter and multiple layers of wrapping around the light source. In contrast, the above analysis suggested the optimal design would utilize tubing with a thin diameter and a single wrap around the light source.

As shown in Figure 2, our simple design utilizes clear fluorinated ethylene propylene (FEP)[19] tubing coiled once around a Liebigs condenser, three strips of blue LEDs placed inside the condenser, cool water passing through the condenser jacket for temperature control, and a flow rate that is controlled by the pump of a preparatory HPLC. The ends of the tubing are fitted to Swagelok connectors, which enable the

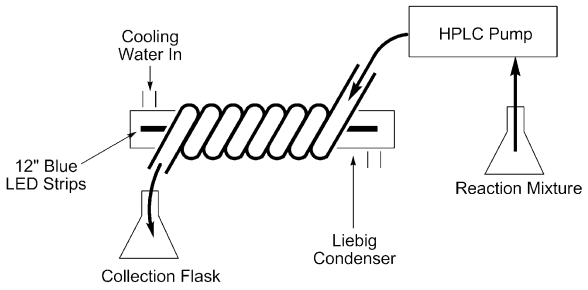


Figure 2. Diagram of the designed photoflow reactor.

modules to be connected in series to increase residence time without decreasing the flow rate.

By running the reaction depicted in Scheme 2, the efficiency of the photoflow reactor was examined for different concentrations of $[Ru(dmb)_3]^{2+}$ using two different tubing diameters (Figure 3). For tubing having a 1.6 mm interior diameter and 1.1 mM $[Ru(dmb)_3]^{2+}$ a TOF of $30\,h^{-1}$ was

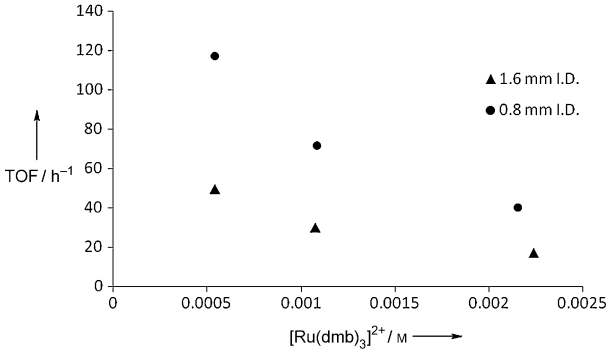


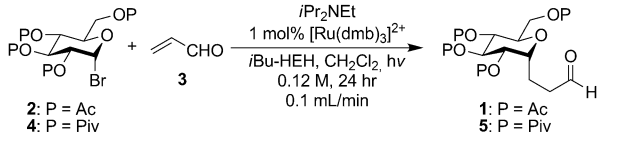
Figure 3. TOF versus $[Ru(dmb)_3]^{2+}$ for FEP tubing of two different inner diameters.

obtained with one module. At the same flow rate of $0.1\,mL\,min^{-1}$ and an increased $[Ru(dmb)_3]^{2+}$ concentration (2.2 mM) the rate of conversion was lower (TOF = $17\,h^{-1}$), whereas a lowered concentration increased the rate (TOF = $50\,h^{-1}$ at 0.5 mM). Consistent with the analysis in Figure 1, the reaction rate increased upon decreasing the inner diameter of the FEP tubing, that is, at 1.1 mM $[Ru(dmb)_3^{2+}]$ and with tubing having an inner diameter of 0.8 mm the TOF was $72\,h^{-1}$. Again, an inverse relationship between catalyst concentration and TOF was observed, with 0.5 mM $[Ru(dmb)_3]^{2+}$ giving the highest observed TOF ($120\,h^{-1}$). These flow reactions demonstrated higher TOFs than either the flask or batch reactor. More importantly, the TOFs increase significantly with decreasing tubing diameter, thus supporting the prediction provided from the data in Figure 1 of a photon-starved reaction. Decreasing the catalyst concentrations also led to an increase in the TOF, which is consistent with a previously photon-starved reaction which now enjoys an increase in photon flux throughout the diameter of the vessel.[20,21]

For our final reactor design, we chose a FEP tubing with a 1.6 mm inner diameter and a concentration of 1 mM

$[Ru(dmb)_3]^{2+}$ as these parameters provided the highest yields.[22] On a 18.2 mmol scale, this flow reactor, using two modules connected in series, was operated continuously (24 h) to obtain 4.5 g of **1** in 70% yield (entry 1, Table 1). The yield of **1** increased to 85% by increasing the concentration of acrolein, that is, 5.5 g of **1** after 24 h of irradiation. The pivaloate-protected substrate **4** was slower to react, thus resulting in only 75% conversion using two modules. However, full conversion of **4** was obtained by attaching a third module (entries 3 and 4, Table 1).

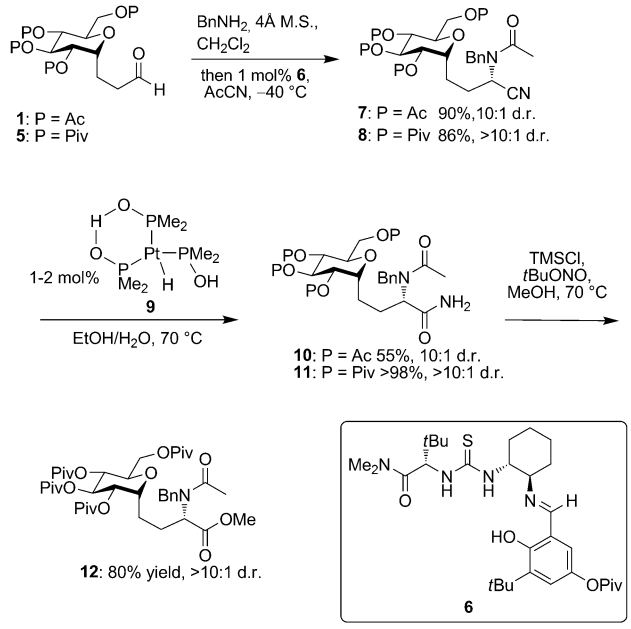
Table 1: Continuous flow reaction run for 24 hours for Ac- and Piv-protected sugars.



Entry	Substrate	**3** (equiv)	No. of modules	Product	Conv. [%][a]	Yield [%][a]
1	**2**	2	2	**1**	>97	70 (65)
2	**2**	4	2	**1**	>97	85 (77)
3	**4**	4	2	**5**	75	n.d.
4	**4**	4	3	**5**	>97	85 (46)

[a] Determined by ^{1}H NMR spectroscopy using *p*-dimethoxybenzene as internal standard. The yield of isolated product is given within the parentheses.

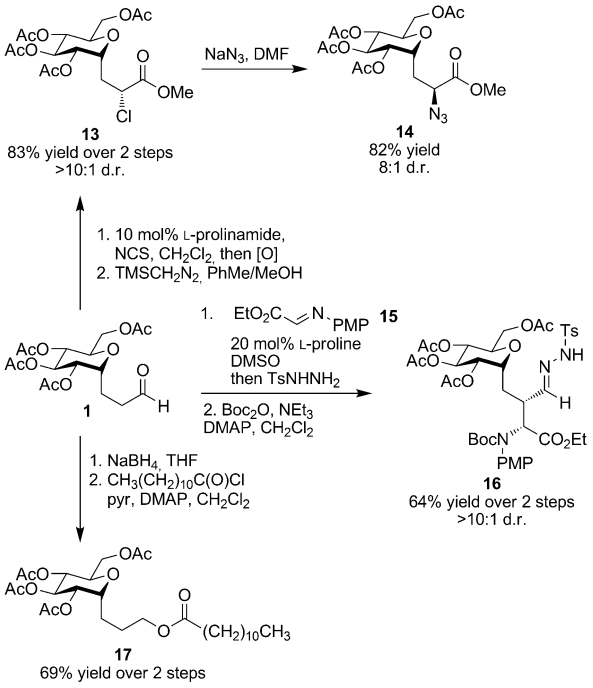
With the development of an efficient route to multigram quantities of **1**, we then focused on the synthesis of a *C*-serine glycoamino acid (Scheme 3). One-pot asymmetric Strecker cyanation leads to the aminonitrile in high yields and diastereoselectivity for both the acetate- (**7**) and pivaloate-protected (**8**) glycosides. While traditional reaction conditions



Scheme 3. Synthesis of *C*-linked isostere of glucosyl-serine. Bn = benzyl, M.S. = molecular sieves, TMS = trimethylsilyl.

for the hydrolysis (65% H_2SO_4) or alcoholysis (HCl in MeOH) of the nitrile failed to produce the desired product, hydration with Parkin's catalyst (**9**) provided the amide intermediate with no observable epimerization.[23] Alcoholysis of the primary amide provided protected *C*-serine aminoester **12** in excellent yields,[24] although these reaction conditions were problematic with acetate-protected sugars.

To further demonstrate the versatility of **1** as a launch pad for glycoconjugate synthesis, we performed a series of derivatizations of the aldehyde (Scheme 4). Selective α-chlorination with L-prolinamide and NCS and subsequent



Scheme 4. Synthesis of glycoconjugates from **1**. Boc = *tert*-butoxycarbonyl, DMAP = 4-dimethylaminopyridine, DMF = *N*,*N*-dimethylformamide, DMSO = dimethylsulfoxide, NCS = *N*-chlorosuccinimide, PMP = *para*-methoxyphenyl, pyr = pyridine, THF = tetrahydrofuran, Ts = 4-toluenesulfonyl.

oxidation provided the chloroester **13** as a single diastereomer.[25] Azide substitution led to the protected *C*-glucosyl alanine derivative as the azidoester in short order with a 51% overall yield from **2**. Proline-catalyzed addition of **1** into the iminoglyoxalate **15** and subsequent protection provided **16** as a single diastereomer.[26] Reduction of **1** and acylation with dodecanoyl chloride afforded the model *C*-glycolipid **17**.

In summary, a simple flow reactor provides an efficient solution to the problem of photon-starved large-scale photoredox reactions. Highly absorbing $[RuL_3]^{2+}$ catalysts create strong concentration gradients that localize photoactivated catalysts near the surface of the vessel, thus requiring thinner reaction vessels to maximize efficiencies. This efficiency was achieved through a flow apparatus using FEP tubing. The light-starved nature of the photoredox reaction was confirmed through assessing the relationship between tubing size and TOFs, which were considerably higher than those of typical batch reactions and independent of scale. This design

concept was applied to the synthesis of a key *C*-glycoside intermediate, which was subsequently converted into a series of *C*-linked glycoconujugates.

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