

## C-Glycosides

## Intermolecular Addition of Glycosyl Halides to Alkenes Mediated by Visible Light\*\*

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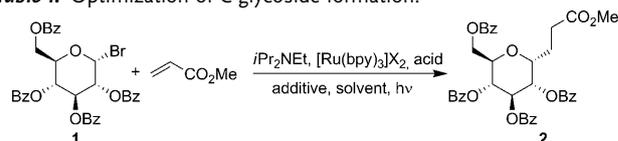
C-glycosides are an important class of bioactive compounds most notable for their resistance to metabolic processing and their prevalence in natural products.<sup>[1–3]</sup> Perhaps the most identifiable methodology for their synthesis is the  $\text{Bu}_3\text{SnH}$ -mediated radical addition of glycosyl bromides to activated alkenes.<sup>[4]</sup> Since its discovery, several variations of this reaction have been reported, including the utilization of transition metals<sup>[5]</sup> or UV light<sup>[6]</sup> to initiate the reaction. Our group recently developed a nickel-catalyzed reductive coupling of glycosyl bromides and alkenes, mechanistic studies on which suggested that the nickel catalyst was playing an electron-transfer (ET) role,<sup>[7]</sup> which implied that other compounds that are known to facilitate ET processes might behave even better (for example,  $[\text{Ru}(\text{bpy})_3]^{2+}$ ;  $\text{bpy} = 2,2'$ -bipyridyl).

The photoredox properties of  $[\text{Ru}(\text{bpy})_3]^{2+}$  and visible light has generated recent excitement as an environmentally benign method of promoting odd-electron organic reactions to drive complex bond constructions.<sup>[8]</sup> The initiating event in these reactions is the reduction of the photogenerated MLCT state,  $^*[\text{Ru}^{\text{III}}(\text{bpy})_2(\text{bpy}^-)]^{2+}$ , by amine to generate a potent ligand centered reducing equivalent (herein referred to as  $[\text{Ru}^{\text{II}}(\text{bpy})_3]^+$ ; Scheme 1). Stephenson recently demonstrated

that electrophilic radicals could be generated in this fashion and intramolecularly trapped in a cascade process.<sup>[8]</sup> We report herein that the combination of visible light and  $[\text{Ru}(\text{bpy})_3]^{2+}$  yields nucleophilic C1 sugar radicals<sup>[9]</sup> that react intermolecularly with electron-deficient alkenes to provide C-glycosides in yields approaching or exceeding previous bests and with outstanding C1 diastereoselectivities.

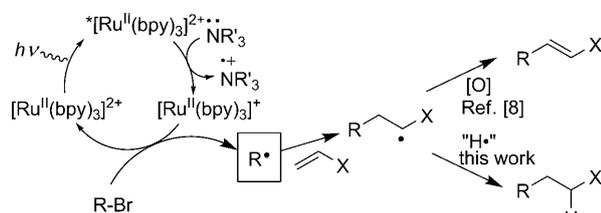
Guided by our previous nickel-based methodology,<sup>[7]</sup> we initiated our investigation on the reaction of  $\alpha$ -glycosyl bromide **1** and methyl acrylate with  $[\text{Ru}(\text{bpy})_3]X_2$  (5 mol%), a stoichiometric reductant, and an acid source to protonate a presumed enolate.<sup>[10]</sup> The best reductant proved to be *N,N*-diisopropylethylamine (**3**), as it provided promising yields of the  $\alpha$ -C-glycoside (**2**) and did not require highly polar solvents (Table 1, entries 2 and 7).<sup>[3–5]</sup>

Table 1: Optimization of C-glycoside formation.



Entry <sup>[a]</sup>	Acid	Additive	Solvent	X	Yield <sup>[a]</sup>
1	3-HBr	–	DMA	Cl	0
2	3-HBr	–	MeCN	Cl	26 <sup>[b]</sup>
3	3-HBF <sub>4</sub>	–	MeCN	Cl	44 <sup>[b]</sup>
4	3-HBF <sub>4</sub>	–	MeCN <sup>[c]</sup>	Cl	50 <sup>[b]</sup>
5	3-HBF <sub>4</sub>	–	MeCN <sup>[c]</sup>	BF <sub>4</sub>	61 <sup>[b]</sup>
6	3-HBF <sub>4</sub>	<b>5</b>	MeCN <sup>[c]</sup>	BF <sub>4</sub>	72 <sup>[b]</sup>
7	3-HBF <sub>4</sub>	<b>5</b>	CH <sub>2</sub> Cl <sub>2</sub> <sup>[c]</sup>	BF <sub>4</sub>	80 <sup>[d]</sup>
8	–	<b>5</b>	CH <sub>2</sub> Cl <sub>2</sub>	BF <sub>4</sub>	92 <sup>[d]</sup>

[a] DMA = *N,N*-dimethyl acetamide. Conditions: glycosyl bromide (0.12 mmol, 0.12 mM in solvent), methyl acrylate (0.24 mmol), reductant (0.36 mmol),  $[\text{Ru}(\text{bpy})_3]X_2$  (0.06 mmol), **5** (0.24 mmol) at room temperature with overnight irradiation with a 14W fluorescent bulb. [b] Yield of isolated product. [c] 0.06 M. [d] Yield determined by supercritical fluid chromatography.



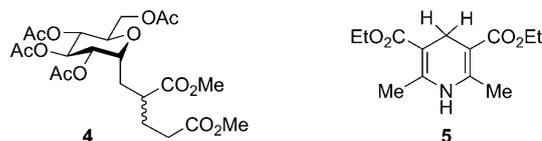
Scheme 1. Formation of alkyl radicals mediated by visible light. R = alkyl,  $\text{bpy} = 2,2'$ -bipyridyl.

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In these trials, the mass balance was dominated by over-conjugate addition (**4**), indicating that  $\alpha$ -radical reduction and its subsequent conjugate addition to additional acrylate were competitive. Stimulated by Stephenson's success with H• trapping of benzylic radicals, we found that Hantzsch ester (**5**)



successfully suppressed the oligomerization and led to improved yields, as did a switch to dichloromethane as solvent (suppressed hydrolysis). Final optimization showed the acid to be unnecessary and high reaction concentrations to be beneficial (Table 1, entry 8).<sup>[11]</sup>

The conditions arrived at in entry 8 were adopted to examine the scope of the coupling (Table 2). In general, alkenes known to rapidly react with alkyl radicals worked

**Table 2:** Scope of the C-alkylation with activated alkenes.<sup>[a]</sup>

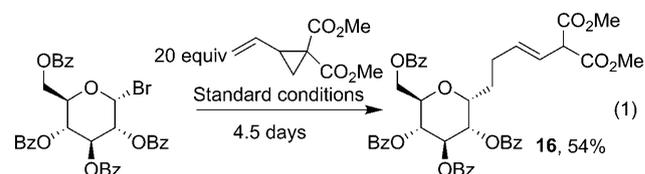
Entry	Product	Entry	Yield <sup>[b]</sup>
1		6	<b>6</b> , R = CO <sub>2</sub> Me: 94% <sup>[c]</sup> (75% <sup>[d]</sup> )
2		7	<b>7</b> , R = COMe: 86%
3		8	<b>8</b> , R = CHO: 85%
4		9	<b>9</b> , R = CN: 85%
5		10	<b>10</b> , 98%, d.r. = 1.5:1
6		11	<b>11</b> , 42% (63% <sup>[e]</sup> )
7		12	<b>12</b> , 51%
8		13	<b>13</b> , 98% (90% <sup>[d]</sup> ), d.r. = 1.8:1
9		14	<b>14</b> , 81% <sup>[c]</sup>
		15	<b>15</b> , 80%

[a] R' = Ac or Bz. [b] Yield of isolated product; conditions: glycosyl bromide (0.12 mmol, 0.12 mM in CH<sub>2</sub>Cl<sub>2</sub>), alkene (0.24 mmol), **3** (0.36 mmol), [Ru(bpy)<sub>3</sub>](BF<sub>4</sub>)<sub>2</sub> (0.06 mmol), **5** (0.24 mmol), irradiation overnight at room temperature with a 14W fluorescent bulb. [c] 0.134 mmol **5**. [d] 1.2 mmol glycosyl bromide. [e] 1.2 mmol alkene.

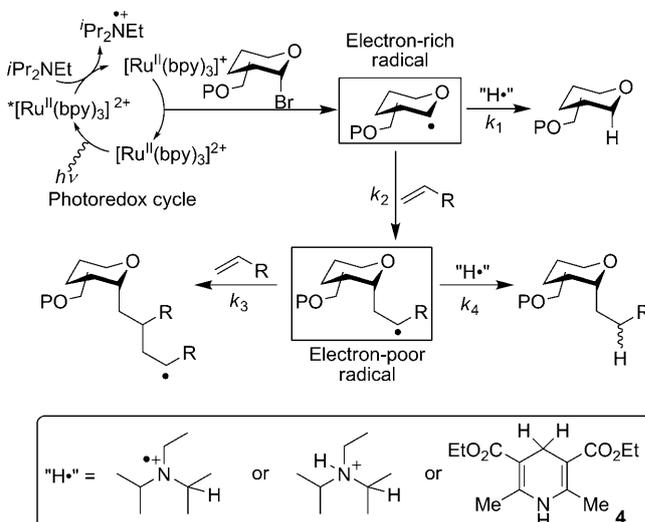
well,<sup>[12]</sup> though when they became too electron deficient, over-conjugate addition became problematic. Typical reaction times were about 15 h, though less electrophilic or bulkier substrates were slower. Higher alkene concentrations were helpful when over-conjugate addition was not rapid (Table 2, entry 6).<sup>[13]</sup> Mannosyl and galactosyl bromides were also well-behaved (entries 9 and 10), as were acetate and benzoate protecting groups (not pivaloate), and reactions could be successfully scaled to 1.2 mmol of substrate without complications (entry 1 and 6).<sup>[14]</sup> Although 1,1-disubstituted alkenes were tolerated, β-substituted enoates were not (e.g. methyl crotonate, methyl maleate).

Several control experiments helped to elucidate the role of the reaction components: 1) No products were formed in the absence of [Ru(bpy)<sub>3</sub>]<sup>2+</sup> or visible light, and when **3** was

omitted, **5** was quickly converted into the pyridine (< 2 h) accompanied by only a 25% consumption of **1** to **2**; 2) In the presence of an electrophilic hydrogen atom source (*t*BuSH), C1 reductive debromination was the major product accompanied by small amounts of the C-glycoside; 3) Consistent with a C1 radical intermediate was the cyclopropane ring-opening observed in **16** [Eq. (1)] and the detection of carbon-based radicals in time-resolved EPR measurements after pulsed irradiation of the reaction mixture.<sup>[9,15]</sup>



Based on these observations, we propose Scheme 2 as a plausible mechanism. ET from photogenerated [Ru<sup>II</sup>(bpy)<sub>3</sub>]<sup>+</sup> to glycosyl bromide generates the C1 radical, which can be



**Scheme 2.** A plausible mechanism for the reactions described herein.

reduced ( $k_1$ ) or added to the alkene ( $k_2$ ); for electron deficient alkenes  $k_2 > k_1$ . When  $k_1 \approx k_2$ , reductive debromination is competitive, though this can be partially compensated with an increase in the alkene concentration. Termination of the electron-deficient  $\alpha$  radical is subject to the relative rates of over-conjugate addition ( $k_3$ ) and reduction ( $k_4$ ), the latter being accelerated by Hantzsch ester.<sup>[16,17]</sup>

In summary, we have developed a reductive room-temperature visible-light-mediated conjugate addition of glycosyl halides into activated alkenes, which leads to fully saturated C-glycosides with exclusive  $\alpha$  selectivity. The procedure improves upon the classic Bu<sub>3</sub>Sn-H mediated methodologies pioneered by Giese and achieves near best results for each substrate class. Moreover, this procedure advances the growing role of photoredox catalysis in important C–C bond formations and generates an experimentally optimal proce-

cedure that reduces the amount of toxic byproducts (that is, tin-free). Efforts to observe and characterize the photogenerated radical intermediates by trapping or EPR measurements are underway.

## Experimental Section

General procedure: A flame-dried Schlenk tube equipped with a stir bar under argon was charged with [Ru(bpy)<sub>3</sub>](BF<sub>4</sub>)<sub>2</sub> (0.006 mmol, 5 mol %), Hantzsch ester **5** (0.268 mmol, 2.2 equiv), and glycosyl bromide (0.122 mmol, 1 equiv). The flask was evacuated and then backfilled with argon. Solvent (to a sugar concentration of 0.12 mM) was added, forming a bright orange heterogeneous solution, followed by *i*Pr<sub>2</sub>NEt (0.366 mmol, 3 equiv) and alkene (0.244 mmol, 2 equiv). The reaction tube was placed 6–10 cm from a 14 W fluorescent light bulb and stirred at room temperature until thin-layer chromatography showed consumption of starting material (12–72 h). The reaction was quenched by passing it through a plug of silica in Et<sub>2</sub>O (100 mL). Flash column chromatography provided the product as a white solid or a colorless oil after removal of solvents.

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