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Visible Light Mediated Activation and *O*-Glycosylation of Thioglycosides

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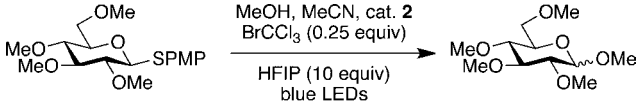
ABSTRACT



Visible light catalysis allows the efficient construction of single electron transfer (SET) redox cycles that result in minimal formation of byproducts and proceed under exogenous control of a removable light source. The *O*-glycosylation of thioglycosides *via* visible light photoredox chemistry is reported. Mechanistic studies show that the reaction is fully light responsive and support a mechanism involving decomposition of an oxidatively generated sulfur radical cation and propagation *via* reduction of the thiol side product.

Visible light catalysis is finding increasing application in organic synthesis.[1,2] Such efforts have been fed by the development of efficient catalysts for the oxidation of water to generate hydrogen. A significant appeal of visible light catalysis is that complementary odd-electron organic reactions can be joined to construct a viable catalytic cycle. Because the excited state metal complex is typically capable of giving or receiving an electron, catalytic cycles that are initiated by oxidation and reduction (termed oxidative or reductive quenching) have both been formulated (Figure 1A).[3] For example, Stephenson et al.[3] have recently reported the use of reductive quenching to convert alcohols to alkyl halides *via* intermediate formation of a Vilsmeier–Haack-type reagent, while multiple groups have employed oxidative quenching to generate and nucleophilically trap stabilized iminium ion intermediates.[3a,4]

Notably, although oxocarbenium ions have been invoked mechanistically in visible light reactions,[3c] they have not as yet been trapped in a manner similar to the iminium ions. Moreover, neither species, iminium nor oxocarbenium ions, when generated by visible light, has been reacted intermolecularly with a stoichiometric alcohol acceptor to yield the corresponding acetal or aminal linkage.[5] Glycosidic bond formation presents a specific example where such a reaction could be synthetically useful. Therefore, we initiated the efforts described herein, aimed at

[†] W.W. and M.A.C. contributed equally.

(1) Recent reviews: (a) Narayanam, J. M. R.; Stephenson, C. R. J. *Chem. Soc. Rev.* **2011**, *40*, 102. (b) Teply, F. *Collect. Czech. Chem. Commun.* **2011**, *76*, 859. (c) Inagaki, A.; Akita, M. *Coord. Chem. Rev.* **2010**, *254*, 1220. (d) Yoon, T. P.; Ischay, M. A.; Du, J. *Nat. Chem.* **2010**, *2*, 527. (e) Zeitler, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 9785.

(2) Representative examples: (a) Nagib, D. A.; MacMillan, D. W. C. *Nature* **2011**, *480*, 224. (b) Pham, P. V.; Nagib, D. A.; MacMillan, D. W. C. *Angew. Chem., Int. Ed.* **2011**, *50*, 6119. (c) Nicewicz, D. A.; MacMillan, D. W. C. *Science* **2008**, *322*, 77. (d) Lin, S.; Ischay, M. A.; Fry, C. G.; Yoon, T. P. *J. Am. Chem. Soc.* **2011**, *133*, 19350. (e) Du, J.; Espelt, L. R.; Guzei, I. A.; Yoon, T. P. *Chem. Sci.* **2011**, *2*, 2115. (f) Hurtley, A. E.; Cismesia, M. A.; Ischay, M. A.; Yoon, T. P. *Tetrahedron* **2011**, *67*, 4442. (g) Lu, Z.; Shen, M.; Yoon, T. P. *J. Am. Chem. Soc.* **2011**, *133*, 1162. (h) Du, J.; Yoon, T. P. *J. Am. Chem. Soc.* **2009**, *131*, 14604. (i) Furst, L.; Narayanam, J. M. R.; Stephenson, C. R. J. *Angew. Chem., Int. Ed.* **2011**, *50*, 9655. (j) Tucker, J. W.; Narayanam, J. M. R.; Shah, P. S.; Stephenson, C. R. J. *Chem. Commun.* **2011**, *47*, 5040. (k) Nguyen, J. D.; Tucker, J. W.; Konieczynska, M. D.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2011**, *133*, 4160. (l) Dai, C.; Narayanam, J. M. R.; Stephenson, C. R. J. *Nat. Chem.* **2011**, *3*, 140. (m) Tucker, J. W.; Nguyen, J. D.; Narayanam, J. M. R.; Krabbe, S. W.; Stephenson, C. R. J. *Chem. Commun.* **2010**, *46*, 4985.

(3) (a) Esswein, A. J.; Nocera, D. G. *Chem. Rev.* **2007**, *107*, 4022. (b) Kalyanasundaram, K. *Coord. Chem. Rev.* **1982**, *46*, 159. (c) Juris, A.; Balzani, V.; Barigelletti, F.; Campagna, S.; Belser, P.; von Zelewsky, A. *Coord. Chem. Rev.* **1988**, *84*, 85. (d) Balzani, V.; Bergamini, G.; Marchioni, F.; Ceroni, P. *Coord. Chem. Rev.* **2006**, *250*, 1254.

(4) Iminium ions have also been generated and trapped by alcohols intramolecularly or else with alcohol as cosolvent: (a) Courant, T.; Masson, G. *Chem.—Eur. J.* **2012**, *18*, 423. (b) Xuan, J.; Feng, Z.; Duan, S.-W.; Xiao, W.-J. *RSC Advances* **2012**, *2*, 4065.

(5) Visible light catalysis has recently been applied to a free radical mediated synthesis of C-glycosides from glycosyl bromides by Gagne et al.: (a) Andrews, R. S.; Becker, J. J.; Gagne, M. R. *Angew. Chem., Int. Ed.* **2010**, *49*, 7274–76. (b) Andrews, R. S.; Becker, J. J.; Gagne, M. R. *Org. Lett.* **2011**, *13*, 2406–09. (c) Andrews, R. S.; Becker, J. J.; Gagne, M. R. *Angew. Chem., Int. Ed.* **2012**, *51*, 4140–43.

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development of a visible light mediated *O*-glycosylation from thioglycoside donors.[5]

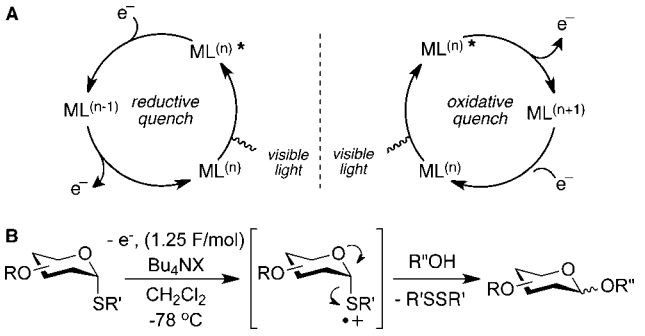


Figure 1. (A) General scheme of commonly employed visible light photoredox cycles and (B) electrochemical activation of thioglycosides.

We speculated that the metal−ligand charge complex generated by oxidative quenching of an excited state visible light catalyst, such as $Ru(bpy)_3Cl_2$ (**1**) or $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (**2**), would be strong enough to oxidize an electron-rich aryl thioglycoside, yielding a stabilized oxocarbenium ion intermediate *via* fragmentation of the radical cation.[6] Thioglycosides are stable, easily manipulable anomeric protecting groups that are widely employed in oligosaccharide synthesis.[7] Oxidation potentials of a number of thioglycoside donors are known and Yoshida et al. have demonstrated that these substrates can be cleanly oxidized in an electrochemical cell (Figure 1B).[8] Subsequent condensation with an alcohol acceptor would provide an *O*-glycosidic linkage with the byproduct formation of acid and the symmetric disulfide. Although photoinitiated glycosylations by UV irradiation of selenoglycosides are known, this would provide a unique example of a *visible light* mediated glycosylation from thioglycosides.[9]

We first sought to determine if oxidative quenching by commonly deployed co-oxidants, such as bromotrichloromethane or carbon tetrabromide, could be coupled to thioglycoside activation and alcohol trapping. We submitted *S*-phenyl- and *S*-(*p*-methoxy)phenyl-tetra-*O*-benzyl-thioglycosides (**3** and **4**, respectively) to visible light irradiation under the various conditions described in Table 1. As anticipated, based on the known oxidation potentials, neither **3** nor **4** was activated by $Ru(bpy)_3Cl_2$, and only **4** was activated by $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (**2**).[10] The oxidation potential of **3** has been measured at 1.31 eV (vs Ag/AgCl), and that of **4**, at 1.16 eV, just above and below the reported oxidation potential of **2** (1.21 eV), and well above that of **1**. In the event, a 96% yield of the methyl glycoside (**5**) was obtained in the presence of 2 equiv of bromotrichloromethane and 10 equiv of methanol (Table 1, entry 4). In addition, the symmetric bis(*p*-methoxyphenyl) disulfide could be isolated in near-quantitative yield. We further sought to reduce the number of equivalents of alcohol to make the reaction amenable to couplings with more precious alcohol acceptors. The efficiency of the reaction diminished appreciably, however, and only trace amounts of **5** could be obtained from our standard 6 h reaction time in the presence of 2 equiv of alcohol (Table 1, entry 5).

Table 1. Optimization of Glycosylation Conditions[a]

entry	MeOH (equiv)	Ar	cat.	co-oxidant	additive	yield
1	10	Ph (**3**)	Ru (**1**)	$BrCCl_3$ (2.0)	--	0
2	10	PMP (**4**)	Ru (**1**)	$BrCCl_3$ (2.0)	--	0
3	10	Ph (**3**)	Ir (**2**)	$BrCCl_3$ (2.0)	--	0
4	10	PMP (**4**)	Ir (**2**)	$BrCCl_3$ (2.0)	--	96
5	2	PMP (**4**)	Ir (**2**)	$BrCCl_3$ (2.0)	--	12
6	2	PMP (**4**)	Ir (**2**)	$BrCCl_3$ (2.0)	TFE (10)	37
7	2	PMP (**4**)	Ir (**2**)	$BrCCl_3$ (2.0)	HFIP (10)	51
8	2	PMP (**4**)	Ir (**2**)	CBr_4 (2.0)	HFIP (10)	58
9	2	PMP (**4**)	Ir (**2**)	CBr_4 (0.25)	HFIP (10)	65
10	2	PMP (**4**)	Ir (**2**)	$BrCCl_3$ (0.25)	HFIP (10)	61

[a] Reactions carried out at ~0.1 M thioglycoside in MeCN with 5 mol % catalyst, 10 equiv HFIP, 0.25 equiv X_3CBr, and irradiated for ~6 h with blue LEDs. PMP = *p*-methoxyphenyl. Yields are reported for isolated products as mixtures of anomers.

The importance of a protic solvent to aid solvation and disruption of the charge transfer complex has been well documented for visible light catalysts such as **1** and **2**.[5,11] Thus, we anticipated that by supplementing with a non-nucleophilic, protic solvent, we could effect glycosylation with ≤2 equiv of acceptor alcohol. After some testing, hexafluoroisopropanol (HFIP) proved an effective surrogate and a 51% yield of methyl glycoside could be

(6) To date, visible light photoredox chemistry of thiols has been limited to direct oxidation to sulfoxides: Zen, J. M.; Liou, S. L.; Kumar, A. S.; Hsia, M. S. *Angew. Chem., Int. Ed.* **2003**, *42*, 577–579. bUses as terminal reductants: Okada, K.; Okubo, K.; Morita, N.; Oda, M. *Tetrahedron Lett.* **1992**, *33*, 7377–7380.

(7) For example: (a) Crich, D.; Smith, M. *J. Am. Chem. Soc.* **2001**, *123*, 9015–16. (b) Yamago, S.; Yamada, T.; Maruyama, T.; Yoshida, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 2145 and references therein.

(8) (a) Amatore, C.; Jutand, A.; Mallet, J.-M.; Meyer, G.; Sinay, P. *Chem. Commun.* **1990**, 718. (b) Yamago, S.; Kokubo, K.; Hara, O.; Masuda, S.; Yoshida, J.-I. *J. Org. Chem.* **2002**, *67*, 8584–92. (c) Suzuki, S.; Matsumoto, K.; Kawamura, K.; Suga, S.; Yoshida, J.-I. *Org. Lett.* **2004**, *6*, 3755–58. (d) Nokami, T.; Shibuya, A.; Tsuyama, H.; Suga, S.; Bowers, A. A.; Crich, D.; Yoshida, J.-I. *J. Am. Chem. Soc.* **2007**, *129*, 10922–28. (e) Nokami, T.; Shibuya, A.; Yoshida, J.-i. *Trends Glycosci. Glycotechnol.* **2008**, *20*, 175–85. (f) Saito, K.; Ueoka, K.; Matsumoto, K.; Suga, S.; Nokami, T.; Yoshida, J.-i. *Angew. Chem., Int. Ed.* **2011**, *50*, 5153–56.

(9) (a) Furuta, T.; Takeuchi, K.; Iwamura, M. *Chem. Commun.* **1996**, 157. (b) Cumptsey, I.; Crich, D. *J. Carbohydr. Chem.* **2011**, *30*, 469. Although one example of UV (350 nm) activated glycosylation from thioglycosides has been reported [(c) Griffin, G. W.; Bandara, N. C.; Clarke, M. A.; Tsang, W.-S.; Garegg, P. J.; Oscarson, S.; Silwanis, B. A. *Heterocycles* **1990**, *30*, 939–47], reaction times are long (24–48 h) and substrate compatibility is poor (no protecting groups could be used and the only reported acceptor was methanol used as a cosolvent).

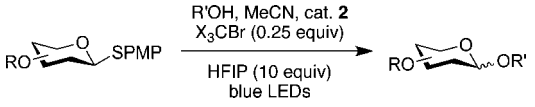
(10) (a) Lowry, M. S.; Goldsmith, J. I.; Slinker, J. D.; Rohl, R.; Pascal, R. A., Jr.; Malliaras, G. G.; Bernhard, S. *Chem. Mater.* **2005**, *17*, 5712. (b) Goldsmith, J. I.; Hudson, W. R.; Lowry, M. S.; Anderson, T. H.; Bernhard, S. *J. Am. Chem. Soc.* **2005**, *127*, 7502.

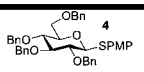
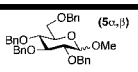
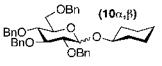
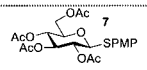
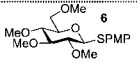
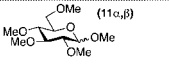
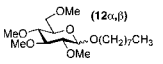
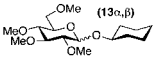
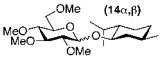
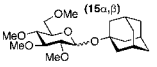
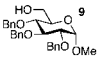
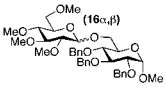
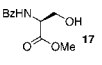
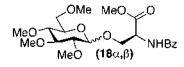
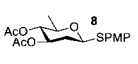
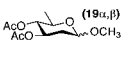
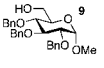
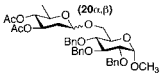
(11) (a) DeLaive, P. J.; Lee, J. T.; Sprintschnik, H. W.; Abruna, H.; Meyer, T. J.; Whitten, D. G. *J. Am. Chem. Soc.* **1977**, *99*, 7094. (b) DeLaive, P. J.; Foreman, T. K.; Giannotti, C.; Whitten, D. G. *J. Am. Chem. Soc.* **1980**, *102*, 5627.

obtained. Yields could be buffered by use of CBr_4 in place of $BrCCl_3$. However, a more significant increase in yield could be obtained when co-oxidant was employed in substoichiometric quantities. 0.25 equiv of either CBr_4 or $BrCCl_3$ provided good yields of methyl glycosides and reduced side products. The mass balance in this case was comprised of a complex mixture of decomposition products, which we presume to result from unchecked reactivity of a poorly stabilized oxacarbeniumion under the current conditions of reaction. The conditions from Table 1 (entries 9 and 10) were employed to further investigate substituent effects on this intermediate, as well as substrate compatibility for the visible light glycosylation.

Primary, secondary, and tertiary alcohols (Table 2) were all permissible nucleophiles and yielded *O*-glycosides as mixtures of anomers. Although the majority of exploratory work was carried out with tetramethyl donor **6**, tetrabenzyl variant **4** also afforded good yields. The tetra-acetyl thioglycoside (**7**) did not activate under the present conditions (entry 3), presumably due to the higher oxidation potential of this disarmed glycosyl donor. Acetates, however, are tolerated, as demonstrated by reactions employing the 2-deoxy-L-rhamnothioglycoside (**8**). Additionally, the reaction tolerates appreciable steric bulk (Table 2, entries 7−8), aryl functionalities (entries 9, 10, and 13), and an amide containing an enolizable stereocenter (entry 10). In the 2-deoxy series, yields with the tribenzyl-glucose-6-OH acceptor (**9**) were improved relative to the glucose series. We speculate that this is due to the heightened reactivity of an assumed glycosyl cation-like intermediate.

Table 2. Substrate Compatibility of Glycosylation[a]



entry	donor	R'OH (2 equiv)	product	% yield (α:β)
1		MeOH		65%[b] (0.9:1)
2				66%[b] (1:1.5)
3		MeOH	N/A	NR
4		MeOH		72%[b] (1.6:1)
5		$CH_3(CH_2)_7OH$		77%[b,d] (0.75:1)
6				87%[b] (1.6:1)
7				71%[c,e] (1.1:1)
8				71%[c,f] (1.6:1)
9				23%[c] (1.2:1)
10				61%[c,g] (1.6:1)
11		CH_3OH		82%[c] (1:4.1)
12				42%[c] (1:2.9)

[a] Reactions carried out at 0.1 M thioglycoside with 5 mol % catalyst and irradiated for 6 h with blue LEDs unless otherwise stated. Yields are reported for isolated products. [b] CBr_4 used. [c] $BrCCl_3$ used. [d] Irradiated for 23 h. [e] Irradiated for 18 h. [f] Irradiated for 9 h. [g] Irradiated for 10 h.

We next sought to interrogate the mechanism of thioglycoside activation. We systematically removed each of the individual components, light, alkyl halide, and catalyst, to demonstrate that all are necessary for conversion of the thioglycoside donor (Table 3, entries 1−3). In the absence of catalyst, no reaction is observed (Table 3, entry 2). However, without alkyl halide, the reaction still proceeds, albeit very slowly (entry 3). As expected, the reaction is completely responsive to light and shuts down in its absence. This was rigorously demonstrated in a time course experiment, in which the light source was varied on and off for 1 h intervals over a 6 h period and then allowed to remain on until the reaction had reached completion (see SI Figure 4A). At each time point, ^{1}H NMR of crude aliquots were examined and reaction progress was determined by integration of protons from the *S*-(*p*-methoxy)phenyl group of **6**, versus those of the disulfide byproduct. The reaction showed no progress during intervals when the light source was turned off.

Notably, in all instances, the final anomeric selectivity is inconsistent with a solvent "nitrile effect." The time course data show that there is in fact initial β-selectivity, presumably from a solvent effect, but that the selectivity erodes over the course of the reaction, particularly during instances of no light and, thus, no reaction (see SI Figure 4B).[12] This is presumably due to the combined acidity of HFIP and any other byproduct acid evolved during the reaction (pH ~4). Presumably an acid catalyzed background process is responsible for the diminished yields with acceptor **9**. Efforts to buffer the reaction with a non-nucleophilic base, such as DTBMP or TTBP, were unsuccessful.

^{19}F NMR of reaction mixtures before and after irradiation showed that HFIP is not consumed during the reaction. Similar experiments carried out for $BrCCl_3$ showed that it is only partially consumed when present at 1.0 equiv, reinforcing the need for only substoichiometric amounts (see SI).[13] In fact, the reaction proceeds, albeit slowly,

(12) (a) Sinay, P.; Pougny, J. R. *Tetrahedron. Lett.* **1976**, *17*, 4073. (b) Lemieux, R. U.; Ratcliffe, R. M. *Can. J. Chem.* **1979**, *57*, 1244. (c) Hashimoto, S.; Hayashi, M.; Noyori, R. *Tetrahedron. Lett.* **1984**, *25*, 1379. (d) Schmidt, R. R.; Behrendt, M.; Toepfer, A. *Synlett* **1990**, 694. (e) Satoh, H.; Hansen, H. S.; Manabe, S.; van Gunsteren, W. F.; Hünenberger, P. H. *J. Chem. Theory Comput.* **2010**, *6*, 1783.

(13) Likely alkyl halide byproducts, such as chloroform, hexachloroethylene, tetrachlorethane, and a number of possible products from reaction of a presumed trichlorocarbon radical, were absent from NMRs of reactions run in CD_3CN/CH_3CN and from GC/MS traces.

Table 3. Investigation of Glycosylation Mechanism

entry	cat.	X_3CBr[a]	HFIP	time	modifications	% conv
1	0.05	CBr_4	10	1 h (no light)	None	0%
				1 h (light)[b]		36%
2	--	CBr_4	10	6 h (light)	None	0%
3[c]	0.05	--	10	4 h (light)	None	21%
4	0.05	--	10	4 h (no light)	HBr (0.07 equiv.)	0%
				6 h (light)		78%
				10 h (light)		100%
5	0.05	--	10	4 h (no light)	TFA (2.0 equiv.)	trace
				4 h (light)[c]		59%
				6 h (light)		100%
6[d]	0.05	$BrCCl_3$	10	6 h (light	No oxygen	100%
7[d]	0.05	--	10	6 h (light)	No oxygen	17%

Reactions with donor **4** except where noted. [a] 0.25 equiv. [b] Negligible change after an additional 6 h of no light. [c] Negligible change (~3%) after an additional 2 h of no light. [d] Reaction was performed using tetra-OMe-*S*-PMP (**6**). Reactions carried out with 2.0 equiv of MeOH.

without any co-oxidant (Table 3, entry 3). The addition of acid, either substoichiometric HBr (entry 4) or 2 equiv of TFA (entry 5), enhances the $BrCCl_3$-independent mechanism. However, no conversion is observed in the absence of light, underscoring the fact that a strong acid itself does not catalyze activation of the thioglycoside. The reaction does not appear to be oxygen sensitive or dependent (Table 3, entries 6 and 7), and peroxide and halide tests were both negative under standard reaction conditions.

Based on these data we propose the mechanism illustrated in Figure 2, in which the catalytic cycle is initiated by the co-oxidant and propagated by reduction of a thiol radical generated from collapse of the thioglycoside radical cation. The latter thiol radical may be present as the naked radical or the thiol radical cation formed by combination with *in situ* generated acid. Isolation of the disulfide could then be explained by background oxidation of 2 equiv of this thiol, possibly with concomitant formation of molecular hydrogen.

Indeed, subjecting free thiol to our standard reaction conditions (no thioglycoside present) resulted in clean, rapid (< 4 h) formation of the disulfide. Disulfide formation occurred only in the presence of catalyst and light. Although necessary quantities of thioglycoside made it

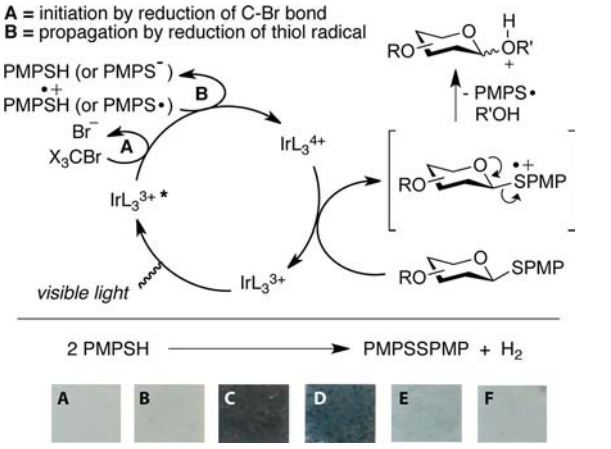


Figure 2. Proposed mechanism for visible light mediated *O*-glycosylation of thioglycosides and H-detection. A = untreated polymer, B = reaction with no light, C = polymer treated with H_2, D = reaction with light, E = reaction with light, no cat., F = reaction with HBr, no light.

difficult to assess hydrogen production in a glycosylation reaction, the disulfide formation could be run on a 200-fold scale in the presence of a H-detecting polymer (Figure 2).[14] Color change occurred only in the presence of light and a catalyst and was consistent with the formation of hydrogen. Typically, photocatalytic procedures for hydrogen production utilize both a photosensitizer, such as $Ru(bpy)_3Cl_2$ (**1**) or $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (**2**), and an electron relay catalyst, such as $Co(bpy)_3^{2+}$ or methyl viologen.[15] However, direct hydrogen production from aqueous solution, without the need for an electron relay, has been observed in the presence of strong acids such as HCl or HBr.[16,17]

In summary, we have developed a visible light mediated photoredox *O*-glycosylation reaction. The mechanism involves a unique visible light activated single-electron oxidation on sulfur, followed by collapse to an oxocarbenium ion. In its present iteration, this visible light glycosylation proceeds with limited stereoselectivity due to thermodynamic equilibration under the reaction conditions. However, recent advances in visible light catalysis in flow suggest a likely strategy for conducting the reaction under kinetic control.[18] Efforts to this end are ongoing in our laboratory.

Supporting Information Available. Procedures and data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.

(14) Molybdenum trioxide based polymers provided by Element One Inc. Chemistry are described at http://www.elem1.com/NHA2006final.pdf.

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