

Investigating the Rate of Photoreductive Glucosyl Radical Generation

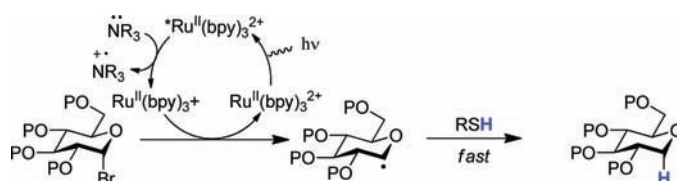
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Received March 10, 2011

ABSTRACT



The photoreduction of glucosyl halides to generate glucosyl radicals has been investigated to probe the nature of the photoredox cycle. Amine (the reductant) and catalyst concentration affect the reaction rate at low concentrations but exhibit saturation at higher concentrations. Water and hydrophobic catalysts were found to significantly increase the conversion efficiency.

Transition metal photocatalysts have generated significant interest as powerful single electron transfer (SET) reagents that operate under mild conditions.¹ Previously developed as a catalyst for the capture and conversion of solar energy,² Ru(bpy)₃²⁺ has been employed more

recently in a variety of synthetic reactions, including reductive dehalogenation,³ [2 + 2] cycloadditions,⁴ and radical additions into unsaturated bonds.⁵ The most promising aspect of this chemistry is the mild reaction conditions, generally requiring only a stoichiometric redox reagent and irradiation from household fluorescent bulbs, LEDs, or sunlight. Thus, photoredox catalysts have the exciting potential to convert sunlight, an abundant and cheap light source, into chemical energy for driving useful synthetic transformations.

The photophysical properties and reaction chemistry of Ru(bpy)₃²⁺ has been extensively studied.² Crudely speaking, absorption into a metal to ligand charge transfer (MLCT) band ($\lambda_{\text{max}} = 452 \text{ nm}$) generates an excited state complex (*Ru(bpy)₃²⁺) that can be chemically quenched to form the strong oxidant Ru(bpy)₃³⁺ or the strong reductant Ru(bpy)₃⁺. Despite the potential for providing unexplored venues for improving existing methods and discovering new ones, the applicability of these photophysical studies to synthetic protocols has not been established.

We recently reported the intermolecular coupling of electron deficient alkenes and glucose C1-radicals, the latter being generated by the reduction of α -glucosyl bromide by photogenerated Ru(bpy)₃⁺. While high yielding, this protocol was characterized by long irradiation times (18–48 h).^{5b} Since numerous researchers have

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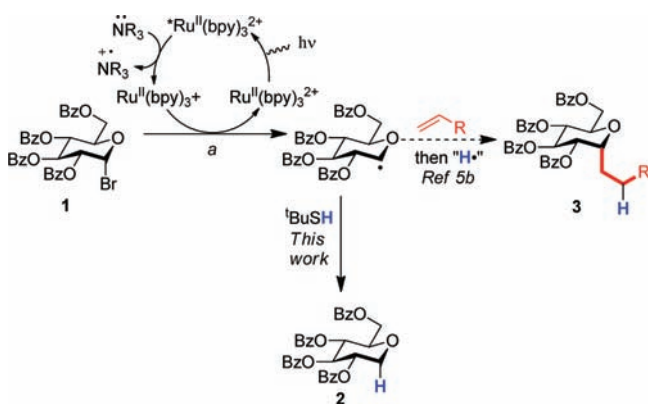
(3) (a) Narayanam, J. M. R.; Tucker, J. W.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2009**, *131*, 8756–8757. (b) Maji, T.; Karmakar, A.; Reiser, O. *J. Org. Chem.* **2011**, *76*, 736–739.

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demonstrated that photoexcitation and quenching of $\text{Ru}(\text{bpy})_3^{2+}$ is reversible and subject to energy-wasting back electron transfer (ET) processes,^{2,6} we considered the possibility that the source of our long reaction times was a nonproductive conversion of light into heat.

Scheme 1. Photoreduction of Glucosyl Radical



In the reaction mechanism in Scheme 1, we presumed that the reaction inefficiencies were localized in the photoredox cycle, as C1-radical trapping by methyl acrylate was expected to be fast and efficient. We therefore set out to probe the mechanism of the photoredox cycle and either support or refute our hypothesis. To simplify the overall transformation we utilized a reductive trap for the radical (i.e., $t\text{BuSH}$) in lieu of the alkene. Conditions similar to our previously described reactions (α -glucosyl bromide (**1**), $\text{Ru}(\text{bpy})_3^{2+}$, and N,N -diisopropylethylamine as stoichiometric reductant) were found to readily debrominate glucosyl bromide to **2** (Scheme 1).^{3a} Since these simple reactants and products were amenable to direct quantitation by ^1H NMR spectroscopy,⁷ the conversion efficiency of test reactions could be readily obtained from irradiations in NMR tubes.⁸ This procedure provided the means to readily compare reaction rates as a function of experimental conditions.

Importantly, control experiments indicated that reaction conversions were independent of thiol concentration,⁸ indicating that radical trapping was fast and that the conversions reflected the rate at which glucosyl radical was being generated. In contrast, the rate was dependent on $[\mathbf{1}]_{\text{ini}}$ (Figure 1), suggesting a turnover limiting SET from the reduced catalyst $\text{Ru}(\text{bpy})_3^+$ to **1** (step a, Scheme 1). Since the rate equation for this step would be dependent on both the concentration of **1** and $\text{Ru}(\text{bpy})_3^+$, our attention shifted toward designing experiments to probe how

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(7) Dispersion in the chemical shifts of **1** and **2** enabled independent quantitation through the H5 protons on the glucosides by comparison with 1,3,5-trimethoxybenzene as an internal standard.

(8) See Supporting Information for control experiments.

reaction conditions affected the steady state concentration of $\text{Ru}(\text{bpy})_3^+$.

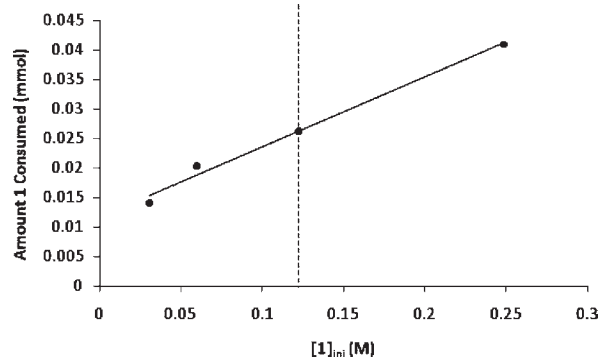


Figure 1. Amount of **1** consumed after 3 h of irradiation with a 14 W CFL source versus initial concentration of **1**. The dashed vertical line represents the approximate concentration for our radical addition reactions.^{5b} Reaction conditions: 6.0 mM $\text{Ru}(\text{bpy})_3^{2+}$, 0.37 M EtN^iPr_2 , 0.24 M $t\text{BuSH}$ in CD_3CN .

Varying the catalyst concentration revealed that under dilute conditions (< 4 mM) the rate of the reaction was proportional to $[\text{Ru}(\text{bpy})_3^{2+}]$ (Figure 2), though at concentrations > 4 mM the rate plateaued at a flux dependent efficiency. We rationalized this saturation to result from a photon limited scenario wherein the catalyst concentration was higher than the photon flux.

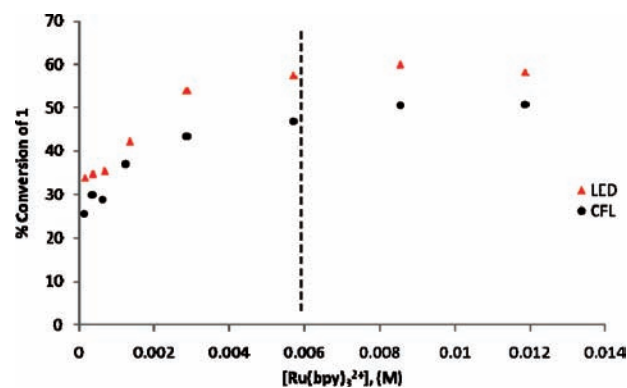


Figure 2. Conversion after 3 h of irradiation with increasing $[\text{Ru}(\text{bpy})_3^{2+}]$ for CFL and blue LED light sources. The dashed vertical line represents the catalyst concentration for our radical addition reactions.^{5b} Reaction conditions: 0.37 M EtN^iPr_2 , 0.24 M $t\text{BuSH}$, 0.12 M **1** in CD_3CN .

Consistent with this interpretation were the higher conversions of reactions using blue LED strips ($\lambda_{\text{emission}} = 435 \pm 15$ nm), which have been reported to create a higher flux at the MLCT absorption wavelength (Figure 2).⁹ Since the $\text{Ru}(\text{bpy})_3^+$ generation also requires a stoichiometric reductant to intercept the excited state, we varied the concentration of EtN^iPr_2 and similarly found that the reaction exhibited saturation behavior (Figure 3).

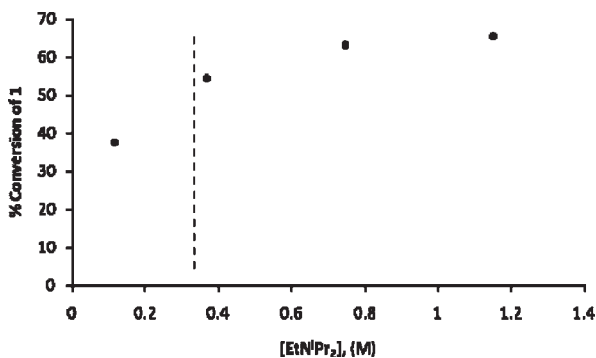
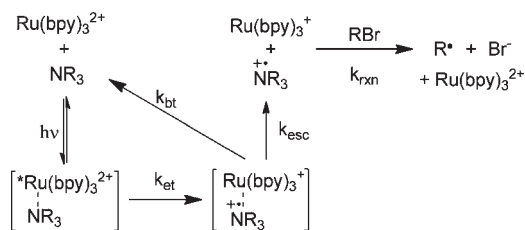


Figure 3. Conversions after 3 h of irradiation as a function of initial EtNⁱPr₂ concentration. The dashed vertical line represents the amine concentration for our radical addition reactions.^{5b} Reaction conditions: 5.9 mM Ru(bpy)₃²⁺, 0.24 M ^tBuSH, 0.12 M **1** in CD₃CN.

The observation that both catalyst and amine show saturation behavior near the experimental conditions suggested finely balanced rates for the elementary steps leading to Ru(bpy)₃⁺. In the search for approaches to improve the overall efficiency of Ru(bpy)₃⁺ generation, the bimolecular reductive quenching of *Ru(bpy)₃²⁺ was considered to be the most chemically manipulable as it has been previously described in typically Marcus terms, proceeding via an encounter complex (van der Waal) that precedes ET and successor complex resolution (Scheme 2).^{6,10}

Scheme 2. Resolution of Catalyst



Since the efficiency of the overall quenching is related to the competing rates of back ET (k_{bt}) and ion solvation (k_{esc}),^{6,10,11} and the latter process has been shown to be

(9) LED strips purchased from www.creativelightings.com. See also ref 5e.

(10) (a) Kitamura, N.; Kim, H. B.; Okano, S.; Tazuke, S. *J. Phys. Chem.* **1989**, *93*, 5750–5756. (b) Ballardini, R.; Varani, G.; Indelli, M. T.; Scandola, F.; Balzani, V. *J. Am. Chem. Soc.* **1978**, *100*, 7219–7223.

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highly sensitive to solvent effects, especially water, this appeared to be a logical place to look for increased efficiencies.^{5i,12}

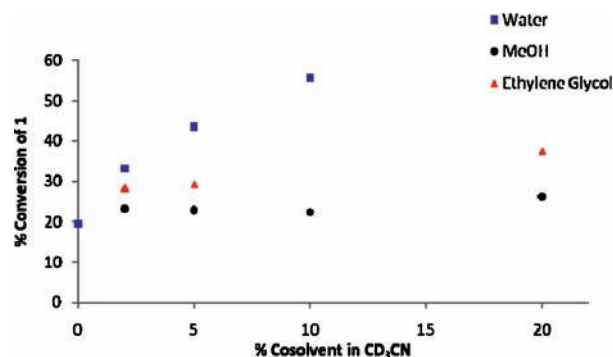


Figure 4. % conversion of **1** (20 min) after photolysis with blue LEDs versus cosolvent additive. Conditions: 5.9 mM Ru(bpy)₃²⁺, 0.37 M EtNⁱPr₂, 0.24 M ^tBuSH, and 0.12 M **1** in CD₃CN.

To determine if solvation effects were limiting our photoredox cycle, we investigated the effect of water, ethylene glycol, methanol, and DMF as cosolvents in acetonitrile. As shown in Figure 4, water dramatically enhanced this conversion efficiency (note that the time points are 20 min in Figure 4 compared to 3 h in Figures 1–3). Methanol and DMF (not shown) were ineffective while ethylene glycol was modestly effective.

Unexpectedly, the conversion dependence on catalyst concentration was markedly different from anhydrous conditions as [Ru(bpy)₃²⁺] < 1 mM led to strong linear increases with catalyst concentration, while this behavior inverted beyond this threshold (Figure 5).

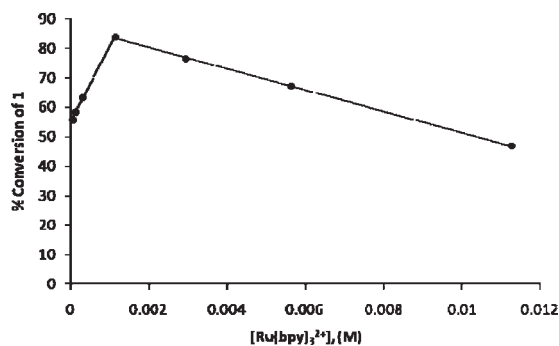


Figure 5. Conversion after 20 min of irradiation with blue LEDs with increasing [Ru(bpy)₃²⁺]. Reaction conditions: 0.33 M EtNⁱPr₂, 0.22 M ^tBuSH, 0.11 M **1** in 10:1 CD₃CN/H₂O.

Using a similar set of principles as Scheme 2, it has been shown that more hydrophobic photocatalysts will resolve more quickly after reductive quenching, which reduces the competitiveness of back-electron transfer (k_{bt}).¹³ To test this, Ru(dmb)₃²⁺ (dmb = 4,4'-dimethyl bpy) was

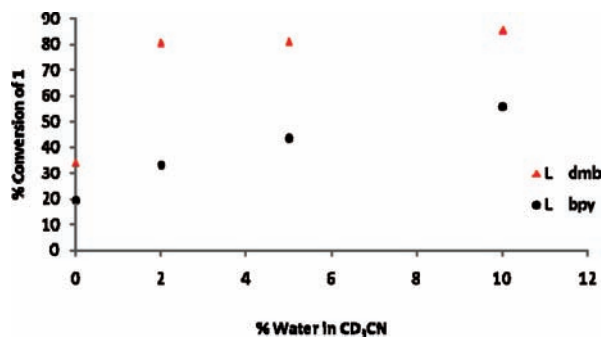


Figure 6. Conversion after 20 min of irradiation with blue LEDs for $\text{Ru}(\text{L})_3^{2+}$. Reaction conditions: 6.0 mM $\text{Ru}(\text{L})_3^{2+}$, 0.37 M EtN^iPr_2 , 0.24 M $t\text{BuSH}$, 0.12 M **1** in $\text{CD}_3\text{CN}/\text{H}_2\text{O}$.

used as the catalyst at varying concentrations of water. As shown in Figure 6 a significantly more effective transformation was observed that required only 2% water to achieve plateau behavior.

This more efficient catalyst was applied to the radical mediated coupling of **4** and methyl acrylate. As hoped for, a rate acceleration was observed for $\text{Ru}(\text{dmb})_3^{2+}$, which provided full conversion of **4** under anhydrous conditions in 6 h. In contrast, only 81% conversion was achieved with $\text{Ru}(\text{bpy})_3^{2+}$. While the $\text{Ru}(\text{dmb})_3^{2+}$ catalysts was indeed faster, the onset of substrate hydrolysis in acetonitrile reduced the yield, a phenomenon that was exacerbated with water cosolvent.^{14–16} Returning to conditions not promoting of hydrolysis (CD_2Cl_2), **4** was cleanly converted to **5** without hydrolysis, and $\text{Ru}(\text{dmb})_3^{2+}$ was faster than $\text{Ru}(\text{bpy})_3^{2+}$ (Scheme 3).^{17,18}

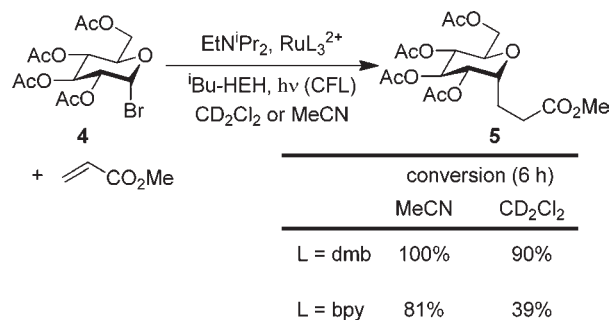
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(14) 75% yield for L = dmb; 54% yield for L = bpy (65% brsm).

(15) Full conversion was observed in 6.5 h for both **1** and **5** mol% $\text{Ru}(\text{dmb})_3^{2+}$ in 9:1 MeCN/ H_2O .

Scheme 3. Radical Mediated C–C Bond Formation



In summary, we have demonstrated that the rate of the photoredox cycle is dependent on several variables, including the hydrophobicity of the catalyst and the presence of polar cosolvents. Applying these observations to a known reaction demonstrated the applicability of these mechanistic studies to improving problems of synthetic relevance. Current work focuses on applying these concepts to a wider variety of photoredox reactions.

Acknowledgment. We thank Stephanie Kramer (UNC-CH) for her contribution to initial investigations. J.J.B. thanks the Army Research Office for Staff Research Funding, and M.R.G. thanks the Department of Energy (DE-FG02-05ER15630) for their support.

Supporting Information Available. Experimental procedures and results. This material is available free of charge via the Internet at <http://pubs.acs.org>.

(16) These same products have been accessed via metal catalyzed approaches that similarly proceed through glycosyl radicals. See: Gong, H.; Andrews, R. S.; Zuccarello, J. L.; Lee, S. J.; Gagné, M. R. *Org. Lett.* **2009**, *11*, 879–882.

(17) 84% yield for L = dmb (93% brsm); 38% yield for L = bpy (99% brsm).

(18) It is possible the increase in rate with L = dmb is due to an increased reduction potential ($E_{\text{red}} = -1.47$ V compared to -1.35 V vs SCE). Experiments with L = dtb-bpy (4,4'-di-*tert*-butyl-bpy, $E_{\text{red}} = -1.68$ V) resulted in a 94% conversion and 89% yield (95% brsm) in CD_2Cl_2 over 6 h of irradiation, similar to L = dmb.