

SUMMARY OF THE DISSERTATION DONE

BY

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**VISIBLE LIGHT PHOTOREDOX CATALYSIS WITH TRANSITION METAL COMPLEXES:
APPLICATIONS IN ORGANIC SYNTHESIS**

FROM

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1. INTRODUCTION

A fundamental aim in the field of catalysis is the development of new modes of small molecule activation. One approach toward the catalytic activation of organic molecules that has received much attention recently is visible light photoredox catalysis. In a general sense, this approach relies on the ability of metal complexes and organic dyes to engage in single-electron-transfer (SET) processes with organic substrates upon photoexcitation with visible light. Many of the most commonly employed visible light photocatalysts are polypyridyl complexes of ruthenium and iridium, and are typified by the complex tris(2,2'-bipyridine) ruthenium(II), or $\text{Ru}(\text{bpy})_3^{2+}$ (Figure 1). These complexes absorb light in the visible region of the electromagnetic spectrum to give stable, long-lived photoexcited states.^{1,2} The lifetime of the excited species is sufficiently long (1100 ns for $\text{Ru}(\text{bpy})_3^{2+}$) that it may engage in bimolecular electron-transfer reactions in competition with deactivation pathways.³ Although these species are poor single-electron oxidants and reductants in the ground state, excitation of an electron affords excited states that are very potent single-electron-transfer reagents. Importantly, the conversion of these bench stable, benign catalysts to redox-active species upon irradiation with simple household lightbulbs represents a remarkably chemoselective trigger to induce unique and valuable catalytic processes. The ability of $\text{Ru}(\text{bpy})_3^{2+}$ and related complexes to function as visible light photocatalysts has been recognized and extensively investigated for applications in inorganic and materials chemistry. In particular, photoredox catalysts have been utilized to accomplish the splitting of water into hydrogen and oxygen⁴ and the reduction of carbon dioxide to methane.⁵ $\text{Ru}(\text{bpy})_3^{2+}$ and its analogues have been used (i) as components of dye-sensitized solar cells⁶ and organic light-emitting diodes,⁷ (ii) to initiate polymerization reactions,⁸ and (iii) in photodynamic therapy.

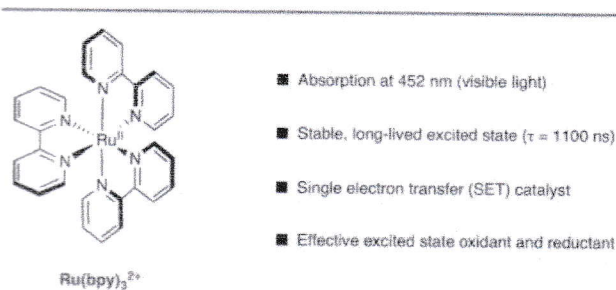


Figure 1. Ruthenium polypyridyl complexes: versatile visible light photocatalysts.

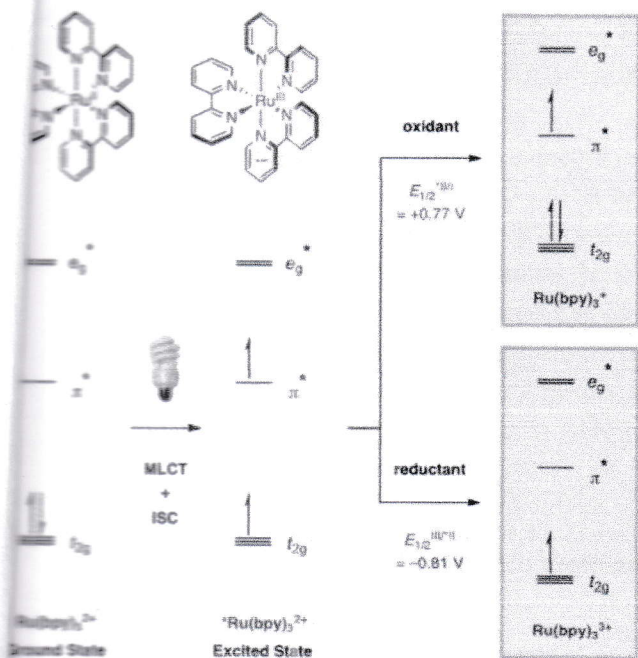
2. PHOTOCHEMISTRY OF $\text{Ru}(\text{bpy})_3^{2+}$

Before we discuss organic transformations enabled by photoredox catalysis, it is instructive to consider the photochemistry of the prototypical photoredox catalyst $\text{Ru}(\text{bpy})_3^{2+}$. Upon absorption of a photon in the visible region, an electron in one of the photocatalyst's metal-centered t_{2g} orbitals is excited to a ligand-centered π^* orbital (Scheme 1).^{1,19} This transition is thus termed a metal to ligand charge transfer (MLCT) and results in a species in which the metal has effectively been oxidized to a Ru(III) oxidation state and the ligand framework has undergone a single-electron reduction.²⁰ The initially occupied singlet MLCT state undergoes rapid

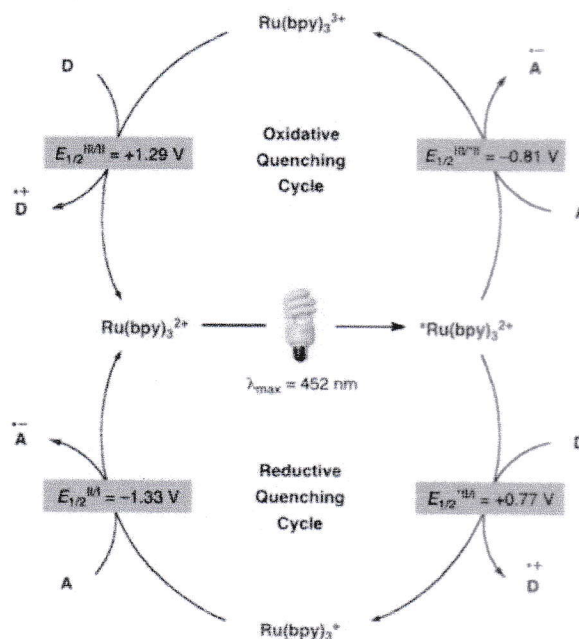
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intersystem crossing (ISC) to give the lowest-energy triplet MLCT state. This triplet state is the long-lived photoexcited species that engages in single-electron transfer; its long lifetime derives from the fact that decay to the singlet ground state is spin-forbidden.

Scheme 1. Simplified Molecular Orbital Depiction of $(\text{bpy})_3\text{Ru}^{2+}$ Photochemistry¹



Scheme 2. Oxidative and Reductive Quenching Cycle of $\text{Ru}(\text{bpy})_3^{2+}$



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3. NET REDUCTIVE REACTIONS

3.1. Reduction of Electron-Poor Olefins

The first reactions demonstrating the potential utility of visible light photoredox catalysis in organic synthesis were net reductive reactions, in which an electron donor is required to serve as the stoichiometric reductant.

Table 1. Redox Potentials and Selected Photophysical Properties of Commonly Utilized Visible Light Photocatalysts^a

entry	photocatalyst	$E_{1/2}$ (M^+/M^*)	$E_{1/2}$ (M^*/M^-)	$E_{1/2}$ (M^+/M)	$E_{1/2}$ (M/M^-)	excited-state lifetime, τ (ns)	excitation λ_{max} (nm)	emission λ_{max} (nm)	ref
1	$\text{Ru}(\text{bpm})_3^{2+}$	-0.21	+0.99	+1.69	-0.91	131 ^b	454	639 ^b	161
2	$\text{Ru}(\text{bpz})_3^{2+}$	-0.26	+1.45	+1.86	-0.80	740	443	591	55
3	$\text{Ru}(\text{bpy})_3^{2+}$	-0.81	+0.77	+1.29	-1.33	1100	452	615	1, 3
4	$\text{Ru}(\text{phen})_3^{2+}$	-0.87	+0.82	+1.26	-1.36	500	422	610 ^c	1, 129
5	$\text{Ir}\{\text{dF}(\text{CF}_3)\text{ppy}\}_2(\text{dtbbpy})^*$	-0.89	+1.21	+1.69	-1.37	2300	380	470	77
6	$\text{Ir}(\text{ppy})_2(\text{dtbbpy})^*$	-0.96	+0.66	+1.21	-1.51	557		581	58, 77
7	$\text{Cu}(\text{dap})_2^+$	-1.43		+0.62		270		670 ^d	33
8	<i>fac</i> - $\text{Ir}(\text{ppy})_3$	-1.73	+0.31	+0.77	-2.19	1900	375	494 ^e	38

^aAll potentials are given in volts versus the saturated calomel electrode (SCE). Measurements were performed in acetonitrile at room temperature unless otherwise noted. ^bDetermined in propylene carbonate. ^cDetermined in aqueous solution. ^dDetermined in dichloromethane. ^eDetermined in 1:1 ethanol/methanol glass at 77 K.

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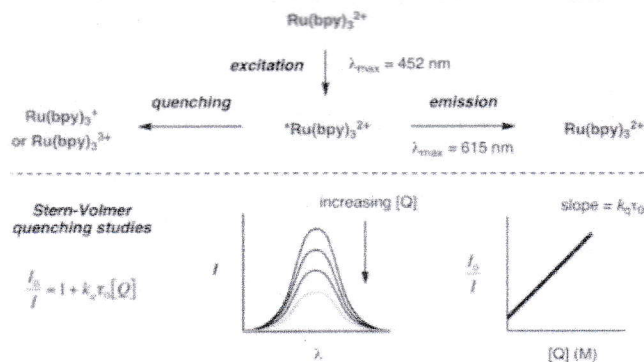
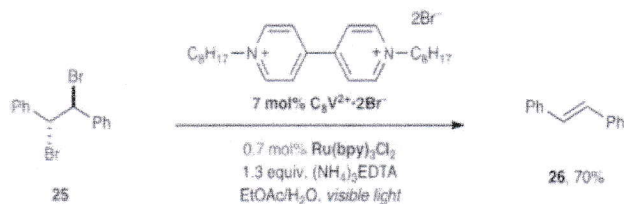


Figure 2. Fluorescence quenching (Stern–Volmer) studies.

3.2. Reductive Dehalogenation

Much early work was conducted in the area of reductive dehalogenation reactions, in which a C–X bond is reduced to a C–H bond. An early contribution from Fukuzumi in 1990 was the reduction of phenacyl bromides using visible light, Ru(bpy)₃ 2+ as a photocatalyst, and 9,10-dihydro-10-methylacridine as the stoichiometric reductant.²⁹ In the net transformation, the phenacyl bromide (9) is reduced by two electrons to give acetophenone (10), while the dihydroacridine 11 is oxidized by two electrons to give the acridinium byproduct 12 (Scheme 4). The reaction is initiated by single electron transfer from 9,10-dihydro-10-methylacridine (11, E1/2 red = +0.8 V vs SCE)³⁰ to *Ru(bpy)₃ 2+ to give the radical cation 13 and the reduced species Ru(bpy).

Scheme 10. Reduction of *vic*-Dibromides via Photoredox and Viologen Catalysis in a Biphasic System

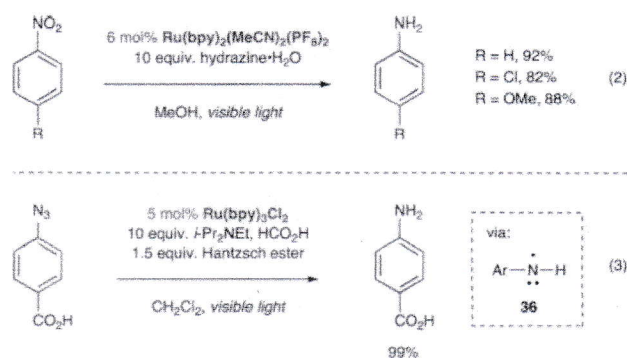


3.3. Nitrogen Functional Group Reductions

Photoredox catalysis has been employed in the reduction of numerous nitrogen-containing functional groups. Hirao and coworkers have reported the reduction of nitrobenzenes to anilines using either Ru(bpy)₃ 2+ or the related photocatalyst Ru(bpy)₂(MeCN)₂(PF₆)₂ (eq 2).⁵⁰ In these reactions, hydrazine is employed as the stoichiometric reductant, the source of the electrons that are ultimately transferred to the nitroarene. The reduction of nitrobenzenes to anilines has also been achieved using a resin loaded with the organic photocatalyst eosin Y.⁵¹ Additionally, the reduction of azides to amines has been accomplished by Liu using a catalytic system comprising Ru(bpy)₃ 2+, Hü nig's base, and Hantzsch ester (eq 3).⁵² The reaction is proposed to proceed first via reductive quenching of *Ru(bpy)₃ 2+ by the tertiary amine to give Ru(bpy)₃ +. Single-electron reduction of the azide by Ru(bpy)₃ + gives an azide radical anion, which upon expulsion of dinitrogen and protonation affords the aminyl radical 36. This intermediate may then abstract a hydrogen atom (from either Hantzsch ester or the radical cation of Hü nig's base) to furnish the primary amine product. Aryl as well as aliphatic azides may be reduced following this protocol. The reaction was also shown to be compatible with biomolecules, as demonstrated by the reduction of an azide tethered to a

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DNA oligonucleotide. Willner has also made use of a biphasic redox system similar to that discussed in section 3.2 to achieve the reduction of an azobenzene derivative.



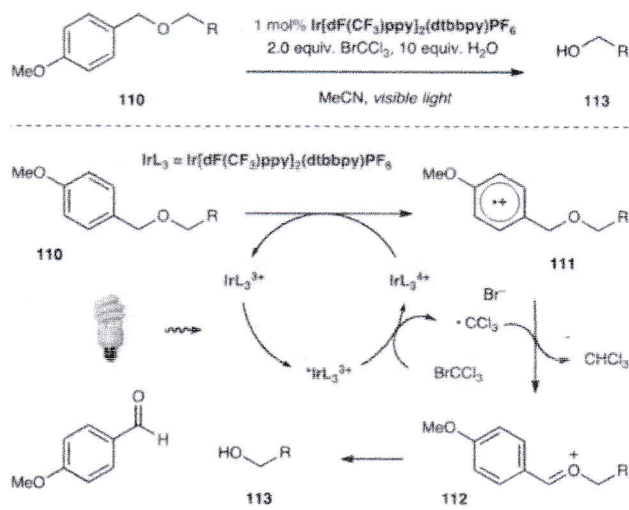
4. NET OXIDATIVE REACTIONS

Just as photoredox catalysis may be used to perform net reductive reactions when a stoichiometric electron donor is present, it may also be used to perform net oxidative reactions provided some species is present to function as a stoichiometric electron acceptor. Reactions in this category typically hinge on the single-electron oxidation of particularly electron-rich functional groups, such as electron-rich arenes and amines.

4.1. Oxidative Removal of the PMB Group

Just as photoredox catalysis has been applied to the cleavage of reduction-labile protecting groups, it has also been used to oxidatively cleave the common para-methoxybenzyl (PMB) protecting group. Stephenson and co-workers demonstrated that the iridium photocatalyst $\text{Ir}[\text{dF}(\text{CF}_3)\text{ppy}]_2(\text{dtbbpy})\text{PF}_6$ ($\text{dF}(\text{CF}_3)\text{ppy} = 2$ -(2,4-difluorophenyl)-5-trifluoromethylpyridine) is an effective catalyst for the deprotection of PMB ethers using bromotrichloromethane as the stoichiometric oxidant.⁷⁶ Photoexcitation of the heteroleptic iridium complex provides a species that is sufficiently reducing ($E_{1/2} \text{ IV}^*/\text{III} = -0.89 \text{ V vs SCE}$)⁷⁷ to transfer an electron to bromotrichloromethane ($E_{1/2} \text{ red} = -0.18 \text{ V vs SCE}$)⁷⁸ (Scheme 26).

Scheme 26. Oxidative Deprotection of *para*-Methoxybenzyl Ethers



4.2. Oxidative Biaryl Coupling

As has been illustrated thus far, photoredox protocols often do not generate new stereocenters, and those that do typically proceed in a racemic fashion; a significant challenge in this area is the development of strategies whereby reactive radical intermediates may be engaged in enantioselective transformations. As a way of addressing this challenge, Ohkubo and co-workers sought to determine if chiral photocatalysts could induce enantioselectivity in photoredox reactions. Octahedral metal complexes such as $\text{Ru}(\text{bpy})_3^{2+}$ are chiral, possessing a Δ and a Λ enantiomer, defined by whether the ligands form a right-handed (Δ) or left-handed helix (Λ) around the C_3 symmetry axis (Figure 3).

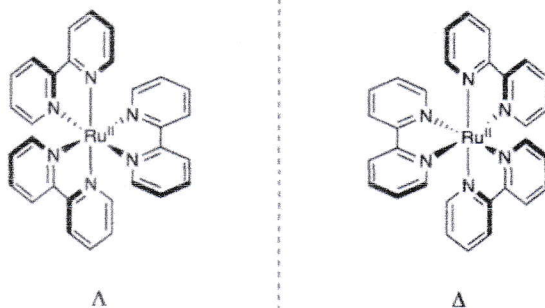


Figure 3. Enantiomeric forms of $\text{Ru}(\text{bpy})_3^{2+}$.

5. REDOX NEUTRAL REACTIONS

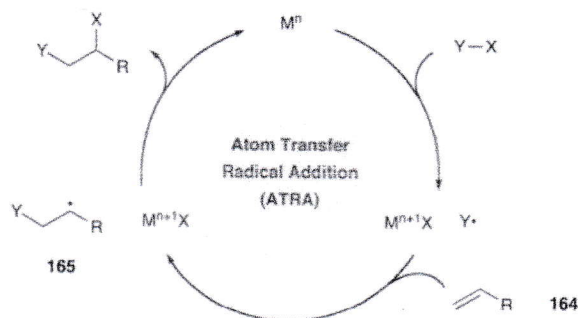
In the reactions described thus far, the overall reductive or oxidative nature of the transformation necessitates the use of a stoichiometric quantity of a molecule that can serve as a source or reservoir of electrons, respectively. In contrast to these reaction types, much recent work in photoredox catalysis has focused on redox neutral reactions. In these reactions, the substrate or substrates undergo both a single-electron oxidation and a single-electron reduction at disparate points in the reaction mechanism. As a result, there is no net oxidation state change between starting materials and products, and no stoichiometric external components are required to turn over the photocatalytic cycle.

5.1. Atom Transfer Radical Addition

The redox neutral approach is perhaps best exemplified by atom transfer radical addition (ATRA) reactions. In this generic reaction type, an atom transfer reagent formally undergoes σ bond cleavage and addition across a π bond of an alkene or alkyne, in the process forming two new σ bonds.¹⁰⁵ In practice, this transformation is commonly accomplished using haloalkanes as the atom transfer reagents and transition metals as catalysts: the metal first abstracts a halogen atom X from the haloalkane $Y-X$ (Scheme 36). This gives a radical $Y\cdot$, which adds to the unsaturated substrate 164. The resulting radical 165 then abstracts the halogen atom from the metal catalyst, completing the atom transfer reaction and regenerating the metal catalyst.

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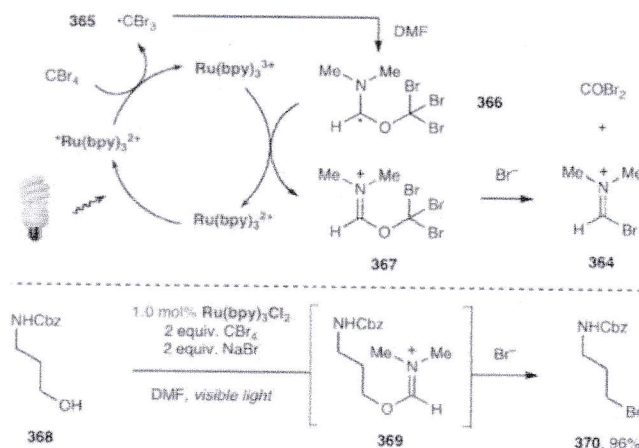
Scheme 36. Generic Atom Transfer Radical Addition (ATRA) Cycle



5.2. Generation of the Vilsmeier–Haack Reagent

A final application of redox-neutral photoredox catalysis is the generation of the Vilsmeier–Haack reagent (364), a species commonly used to perform formylation and nucleophilic displacement reactions. Stephenson and co-workers found that when tetrabromomethane was employed as a stoichiometric oxidant for Ru(bpy)₃²⁺ in N,N-dimethylformamide (DMF), alcohols are efficiently transformed into their corresponding bromides.¹⁸⁸ The reaction is believed to proceed first via single-electron reduction of tetrabromomethane to the tribromomethyl radical (365) (Scheme 79).

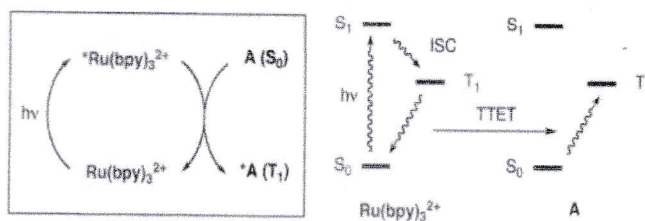
Scheme 79. Photoredox Generation of the Vilsmeier–Haack Reagent



6. ENERGY TRANSFER REACTIONS

The photoredox chemistry presented thus far relies on the ability of photoexcited catalysts (either organic or metal-based) to engage in electron transfer with organic molecules. A second, fundamental pathway for decay of photoexcited states, however, is energy transfer. Using Ru(bpy)₃²⁺ as an example, irradiation of this species excites the complex from its ground singlet state (S₀) to its lowest singlet excited state (S₁) (Scheme 80). Intersystem crossing (ISC) generates the long-lived lowest energy triplet state.

Scheme 80. Triplet–Triplet Energy Transfer from ^{*}Ru(bpy)₃²⁺ to Acceptor A



7. CONCLUSIONS

Although photoredox catalysis with transition metal complexes has only recently received widespread attention as a tool for synthetic organic chemists, it has already been applied to the development of a wide range of new carbon-carbon bondforming reactions. The utility of photoredox catalysis arises not from its ability to promote any one kind of bond formation, but rather from its ability to generate a diverse array of reactive intermediates via single-electron transfer. As we have shown, these species include electrophilic α -carbonyl radicals, trifluoromethyl radicals, arene radical cations, iminium ions, and enone radical anions, among others. These intermediates have been used to develop reactions as varied as atom transfer radical additions, arene C-H functionalizations, amine α -functionalizations, and [2 + 2] cycloadditions. Furthermore, photoredox catalysis has been merged with other modes of catalytic activation, such as enamine catalysis and N-heterocyclic carbene catalysis, to achieve enantioselective transformations, and has been merged with transition metal catalysis to achieve previously elusive bond constructions. Photoredox catalysis has also proven to be a valuable tool for the construction of complex molecules, as demonstrated by its application in the total syntheses of gliocladin C, heitziamide A, and aplyviolene, among others. In each of these syntheses, simple, typically inert functionalities in the starting materials are transformed into reactive intermediates upon single-electron oxidation or reduction. Particularly remarkable is the use of radical intermediates to forge congested quaternary carbon centers in the syntheses of gliocladin C and aplyviolene. Additionally, the challenges of performing photoredox catalysis efficiently on large scales have recently been addressed using continuous flow chemistry.²⁰⁰ The diverse applications of this chemistry, as well as the tremendous outpouring of work in the area that has appeared since 2008, demonstrate that visible light photoredox catalysis has emerged as a powerful tool for the development of new and valuable transformations of organic molecules.

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