Radical Reactions

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Photoredox Transformations with Dimeric Gold Complexes**

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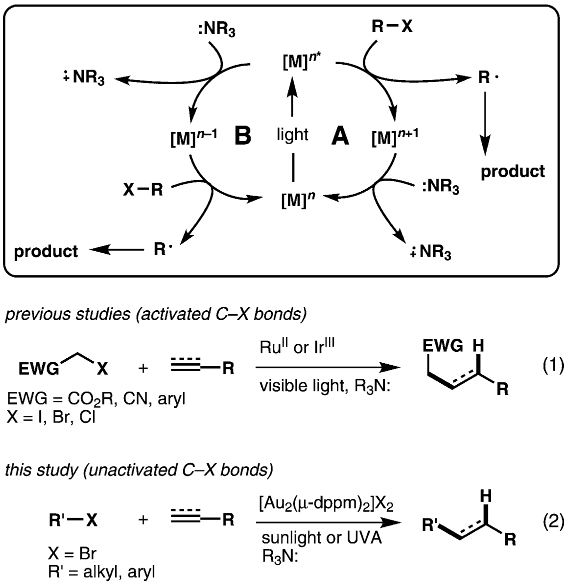
Dedicated to Professor Pierre Deslongchamps on the occasion of his 75th birthday

The conversion of solar energy into chemical energy in photosynthesis has enthralled scientists for decades. Sunlight could be used as an inexpensive, green, and sustainable source of energy to induce chemical reactions.[1,2] However, many organic compounds do not absorb sunlight or visible light, and the application of photochemistry in synthesis is therefore restricted. In response to this limitation, several light-absorbing photocatalysts have been developed in an effort to mimic the light-harvesting abilities of biocomplexes found in natural processes, such as photosynthesis.[3] The inorganic complex [Ru(bpy)$_3$Cl$_2$] (**1**) is one of the most used one-electron photoredox catalysts for research in energy storage, water splitting, and photovoltaic devices.[4,5] Increased attention is being placed on visible-light-mediated photoredox processes for the development of efficient and waste-minimizing processes of general applicability that should decrease our dependence on toxic chemical products.[6]

During the last decade, several metal complexes, such as [Ru(bpy)$_3$Cl$_2$] (**1**), [Ir(ppy)$_2$(dtbbpy)PF$_6$] (**2**), and *fac*-[Ir(ppy)$_3$] (**3**), have proven their potential in absorbing light and transforming it into electronic energy that can be used in organic synthesis to generate new C–C, C–N, and C–O bonds through a single-electron-transfer (SET) process.[6f] In general, the photoredox transformation can operate through two distinctive pathways, the oxidative quenching cycle (path A) or the reductive quenching cycle (path B; Scheme 1). In the former, the photoexcited metal complex transfers an electron to an oxidative quencher, such as an alkyl or aryl halide (R–X). The radical intermediate is converted into a product, whereas the oxidized metal returns to its original oxidation state by accepting an electron from a tertiary amine base (R$_3$N:). In the latter pathway, the photoexcited metal complex acts as an oxidant and accepts an electron from a sacrificial electron donor source (R$_3$N:) to generate a complex [M]$^{n-1}$ that may function as a reducing agent.



Scheme 1. General mechanism for metal-catalyzed photoredox reactions. EWG = electron-withdrawing group.

The reduction of carbon–halogen (C–X) bonds to produce carbon-centered radical intermediates is one of the most useful processes for accessing new reactivity and has broad scope for application in chemical synthesis.[7] Typically, methods to generate alkyl, vinyl, and aryl radicals from carbon–halogen bonds require the use of potentially hazardous and/or toxic chemical reagents, such as organostannane compounds and chemical initiators (AIBN, Et_3B/O_2, $K_2S_2O_8$).[8] The use of photoexcited Ru^{II} (path A) and Ir$^{II/III}$ polypyridine complexes **1**–**3** is an attractive alternative for efficient synthetic transformations involving the cleavage of carbon–halogen bonds (path A).[9–12] However, the reduction potential of these catalysts limits the range of possible radical intermediates to those derived from substrates with highly activated or weak carbon–halogen bonds, such as polyhalomethanes, bromomalonates, electron-deficient benzyl halides, and alkyl/aryl iodides [Eq. (1), Scheme 1].[11,12] Although important advances in photocatalysis have been made in the last decade, one might concede that efficient methods for the photocatalyzed reductive scission of unactivated carbon–halogen bonds have yet to be described.

In this context, the design of a photocatalytic system of broader applicability must fulfill specific criteria. Aside from an appropriate redox-potential window, the catalyst must possess a long-lived excited state to undergo productive oxidative quenching (path A) with alkyl, vinyl, and aryl halides. Furthermore, photoexcitation of the catalyst should occur within a readily accessible wavelength range and thus

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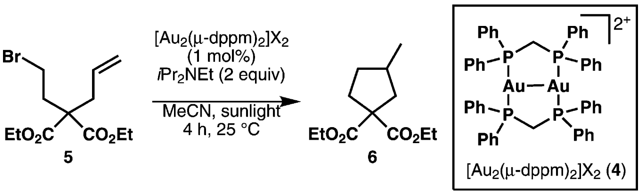
require no special equipment. On the basis of the rich photochemistry of dimeric gold complexes, we report herein a conceptually novel photocatalytic system for the efficient generation of carbon-centered radical intermediates from unactivated alkyl ($E^\circ_{\text{reduction}} = -1.90$ to -2.50 V versus the saturated calomel electrode (SCE)) and aryl bromides ($E^\circ_{\text{reduction}} = -2.05$ to -2.57 V versus SCE) under remarkably mild conditions [Eq. (2)].[13]

On the basis of studies by Che and co-workers, we considered the use of cationic $[Au_2(\mu\text{-dppm})_2]^{2+}$ (dppm = bis(diphenylphosphanyl)methane) species as potential photocatalysts.[14] These dimeric gold species absorb light in the UV region ($\lambda_{max} = 295$ nm) to produce an in situ high-energy and long-lived photoexcited state (quantum yield: 0.23) with a strong reduction potential $[E^\circ(Au_2^{3+} \rightarrow Au_2^{2+*}) = -1.6$ to $--1.7$ V versus SSCE (sodium-saturated calomel electrode)].[15] To demonstrate the applicability of dimeric gold complexes in synthesis, we selected the radical cyclization of bromoalkene **5** as the benchmark reaction. A survey of dimeric gold catalysts in conjunction with trialkyl amine bases as sacrificial electron and hydrogen donors revealed that the radical cyclization of alkyl bromide **5** to give **6** proceeded in excellent yield in the presence of diisopropylethylamine (iPr$_2$NEt) in acetonitrile (MeCN) with sunlight as the light source (Table 1, entry 2). Although the counteranion had little effect on the conversion of the radical cyclization, we found the gold catalyst **4e**[16] to be the most robust and photostable dimeric gold complex (Table 1, entries 3–6). UVA light (315–400 nm) proved to be a good surrogate for sunlight (Table 1, entry 7). Rigorous control experiments showed complete recovery of the starting material (0% conversion) when the reaction was carried out in the absence of a gold catalyst **4** or light (Table 1, entries 8 and 9). Similarly, no cyclization product **6** was observed when the visible-light photocatalysts **1–3** were used under standard conditions (with a 23 W compact fluorescent light (CFL) or white-light light-emitting diodes (LEDs); Table 1, entries 10–12).[11,12] These results confirm without ambiguity that 1) no background reactions took place in the absence of sunlight (UVA) or the gold(I) dimeric complex and 2) photoexcited [Ru(bpy)$_3$Cl$_2$] (**1**), [Ir(ppy)$_2$(dtbbpy)PF$_6$] (**2**), and *fac*-[Ir(ppy)$_3$] (**3**) cannot reduce unactivated alkyl carbon–bromide bonds by metal-to-ligand charge transfer (MLCT).

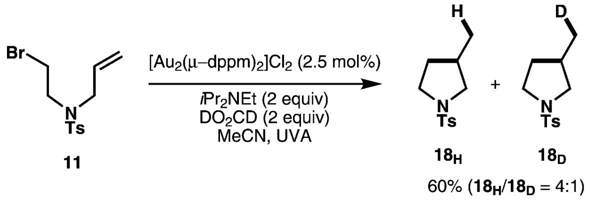
Table 1: Optimization of the photoredox reaction.[a]



Entry	Catalyst	Light source	Yield [%]
1[b]	[Au$_2$(μ-dppm)$_2$](OTf)$_2$ (**4a**)	sunlight	20
2	[Au$_2$(μ-dppm)$_2$](OTf)$_2$ (**4a**)	sunlight	94
3	[Au$_2$(μ-dppm)$_2$](NTf$_2$)$_2$ (**4b**)	sunlight	72
4	[Au$_2$(μ-dppm)$_2$](BF$_4$)$_2$ (**4c**)	sunlight	70
5	[Au$_2$(μ-dppm)$_2$](SbF$_6$)$_2$ (**4d**)	sunlight	90
6	[Au$_2$(μ-dppm)$_2$]Cl$_2$ (**4e**)	sunlight	86
7	[Au$_2$(μ-dppm)$_2$]Cl$_2$ (**4e**)	UVA (315–400 nm)	74
8[c]	–	sunlight/UVA	s.m.
9[d]	[Au$_2$(μ-dppm)$_2$]Cl$_2$ (**4e**)	–	s.m.
10[e]	[Ru(bpy)$_3$Cl$_2$] (**1**)	23 W CFL/LEDs	s.m.
11[e]	[Ir(ppy)$_2$(dtbbpy)]PF$_6$ (**2**)	23 W CFL/LEDs	s.m.
12[e]	*fac*-[Ir(ppy)$_3$] (**3**)	23 W CFL/LEDs	< 5

[a] All reactions were performed in degassed solvent with pyrex glassware. [b] Et$_3$N was used instead of *i*Pr$_2$NEt. [c] The reaction mixture was irradiated for 18 h. [d] The reaction mixture was heated at 60 °C for 24 h. [e] The reaction mixture was irradiated for 36 h. bpy = 2,2′-bipyridyl, dtbbpy = di-*tert*-butyl-2,2′-bipyridine, ppy = 2-phenylpyridinate, s.m. = starting material, Tf = trifluoromethanesulfonyl.

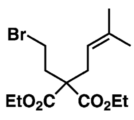
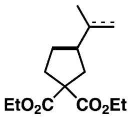
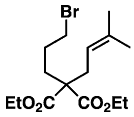
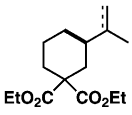
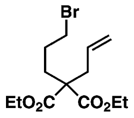
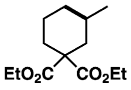
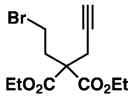
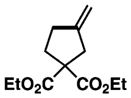
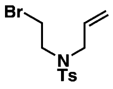
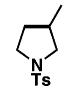
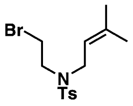
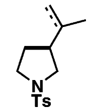
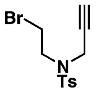
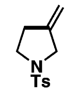
The scope of the reaction with respect to the alkyl or aryl bromide substrate was explored (Tables 2 and 3). The radical cyclization of alkyl bromides **7–10** with *i*Pr$_2$NEt (2 equiv; procedure A) in acetonitrile gave the corresponding cyclic products **14–17** in yields ranging from 58 to 93% (Table 2, entries 1–7). Irradiation with sunlight rather than UVA light led to a slight improvement in the reaction yield (Table 2, entries 2, 4, and 6). Surprisingly, complete conversion of the tosyl allylamine **11** into the corresponding pyrrolidine **18** required a prolonged irradiation time of 36 h (Table 2, entry 8). To decrease the reaction time, we examined various hydrogen donors. It was found that the addition of formic acid in the presence of *i*Pr$_2$NEt greatly enhanced the rate of the reaction.[17] Indeed, the conversion of **11** was completed after 1 h to produce **18** in 66% yield (Table 2, entry 9). As expected, the cyclization of bromides **12** and **13** gave the desired pyrrolidines **19** and **20** in 86 and 63% yield, respectively (Table 2, entries 10 and 11). Labeling experiments with DCO$_2$D (2 equiv) and *i*Pr$_2$NEt (2 equiv) indicated that *i*Pr$_2$NEt is the main hydrogen-atom source [Table 2, Eq. (3)].[18] Although superior reactivity was observed for photoredox reactions with formic acid, insufficient data are available at present to permit a detailed mechanistic discussion.[19]



(3)

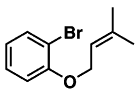
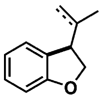
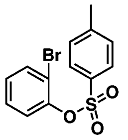
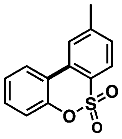
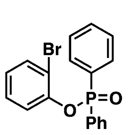
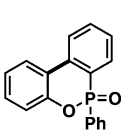
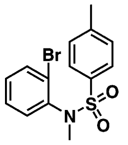
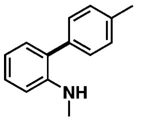
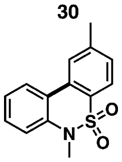
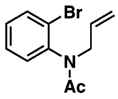
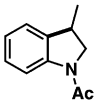
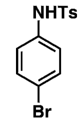
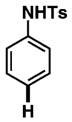
Having confirmed the applicability of the dimeric gold complexes in photoredox processes with alkyl bromides, we examined the reductive cleavage of aryl bromides (Table 3). The reductive radical cyclization of aryl bromide **21** afforded the cyclized product **27** as a mixture (71:29) of isopropyl- and isopropenyl-substituted compounds in 74% yield (Table 3, entry 1). Biaryl compounds **28** and **29** were formed in excellent yields (Table 3, entries 2–5), and the cyclization of sulfonamide **24** proceeded mainly by *ipso* substitution as anticipated to give the biaryl amine **30** as the major product along with tricycle **31** in 93% overall yield (Table 3, entry 6).[20] The reductive dehalogenation of aryl bromides **25** and **26** by procedure B led to the formation of indoline **32** and sulfonanilide **33** in 90 and 94% yield, respectively. As for the alkyl bromides series, control experiments confirmed that the SET reduction of aryl bromides did not operate in the absence of the dinuclear gold complex or with catalyst **2** or **3**.[21]

Table 2: Photoredox cyclization of alkyl bromides.

Entry	Substrate	Product	Procedure[a] (type of light)	Yield [%] (ratio)[b]
1 2	 **7**	 **14a,b**	A (UVA) A (sunlight)	81 (73:27) 92 (65:35)
3 4	 **8**	 **15a,b**	A (UVA) A (sunlight)	58 (84:16) 81 (86:14)
5 6	 **9**	 **16**	A (UVA) A (sunlight)	58 60
7	 **10**	 **17**	A (UVA)	93
8 9	 **11**	 **18**	A (UVA) B (UVA)	63 66[c]
10	 **12**	 **19a,b**	B (UVA)	86 (50:50)
11	 **13**	 **20**	B (UVA)	63

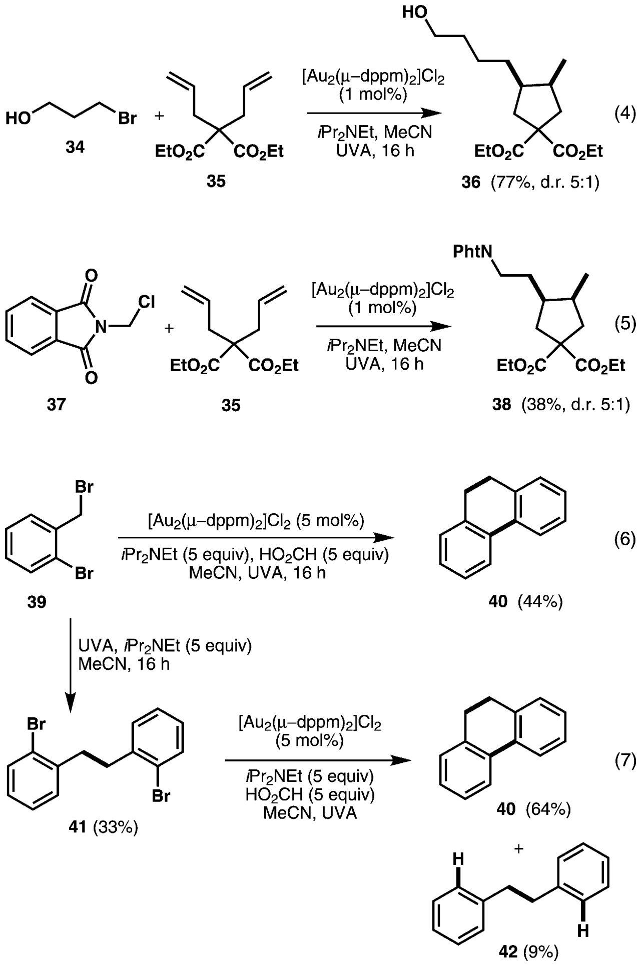
[a] Procedure A: $[Au_2(\mu\text{-dppm})_2]Cl_2$ (2.5 mol%), $i Pr_2NEt$ (2 equiv), MeCN, 2–8 h; procedure B: $[Au_2(\mu\text{-dppm})_2]Cl_2$ (2.5 mol%), $i Pr_2NEt$ (5 equiv), HCO_2H (2 equiv), MeCN, 1–4 h. [b] Ratio of the isopropyl- to the isopropenyl-substituted product. [c] The reaction was completed in 1 h.

Table 3: Photoredox cyclization and dehalogenation of aryl bromides.

Entry	Substrate	Product	Procedure[a] (type of light)	Yield [%] (ratio)
1	 **21**	 **27a,b**	A (sunlight)	74 (71:29)
2 3	 **22**	 **28**	A (UVA) A (sunlight)	75[b] 80
4 5	 **23**	 **29**	A (UVA) A (sunlight)	90[b] 91
6	 **24**	 **30**  **31**	A (UVA)	93[b] (63:37)
7	 **25**	 **32**	B (UVA)	90[b]
8	 **26**	 **33**	B (UVA)	94[b]

[a] Procedure A: $[Au_2(\mu\text{-dppm})_2]Cl_2$ (2.5 mol%), $i Pr_2NEt$ (2 equiv), MeCN, 2–8 h; procedure B: $[Au_2(\mu\text{-dppm})_2]Cl_2$ (2.5 mol%), $i Pr_2NEt$ (5 equiv), HCO_2H (2 equiv), MeCN, 1–4 h. [b] The reaction mixture was irradiated for 8–16 h; $[Au_2(\mu\text{-dppm})_2]Cl_2$ (5.0 mol%) was used.

We sought to further validate the gold-catalyzed photo-induced carbon–carbon bond-forming reaction by including intermolecular processes (Scheme 2). The radical addition of 1-bromopropanol (**34**) and *N*-chlorophthalidimide (**37**) to the diallylated malonate **35** produced the *cis*-substituted cyclopentanes **36** and **38** in 77 and 38% yield (d.r. 5:1), respectively [Eqs. (4) and (5), Scheme 2]. Notably, aryl bromide **39** was converted into dihydrophenanthrene **40** in the presence of formic acid (procedure B) in 44% yield [Eq. (6), Scheme 2]. To gain more insight into the reaction mechanism, we exposed aryl bromide **39** to UVA light for 16 h in the presence of $i Pr_2NEt$ and obtained the dibromodibenzyl product **41** in 33% yield. Irradiation of compound **41** according to procedure B produced dihydrophenanthrene **40** in 64% yield along with the dehalogenation product **42** in 9% yield [Eq. (7), Scheme 2]. These results suggest that the transformation most likely proceeds by an initial recombination of benzyl radicals.[22] The ring closure leading to compound **40** could then be explained by the subsequent generation of an aryl radical, which would attack the other aromatic ring in a formal *ipso* substitution of the bromine atom.



Scheme 2. Gold-catalyzed intermolecular radical cyclization reactions.

In summary, we have described a light-enabled reductive radical reaction of unactivated alkyl and aryl bromides in the presence of a dimeric phosphine–gold complex as the photocatalyst. It was demonstrated that the applicability of this photoredox process is not limited to intramolecular processes, but that intermolecular transformations are also possible. Although no clear mechanism has been established with respect to the use of formic acid, our results clearly demonstrate the uniqueness of this photoredox process and its high synthetic potential. We are currently exploring the application of this method in the context of synthesis and working toward a full understanding of the reaction mechanism.

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