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Indole Functionalization via Photoredox Gold Catalysis

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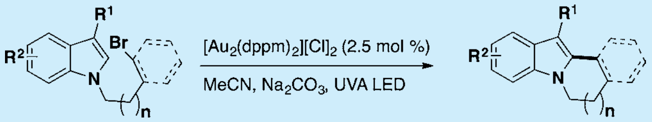
Supporting Information

ABSTRACT: The use of photoredox catalyst $[Au_2(dppm)_2]Cl_2$ to initiate free-radical cyclizations onto indoles is reported. Excitation of the dimeric Au(I) photocatalyst for the reduction of unactivated bromoalkanes and bromoarenes is used for the generation of carbon-centered radicals. Previous to this work, reduction processes leading to indole functionalization utilizing photoredox catalysts were limited to activated benzylic or α-carbonyl-positioned bromoalkanes. This method offers a mild and safe alternative to organostannanes and pyrophoric initiators for access to high energy radicals that were previously inaccessible through catalytic or stoichiometric means.

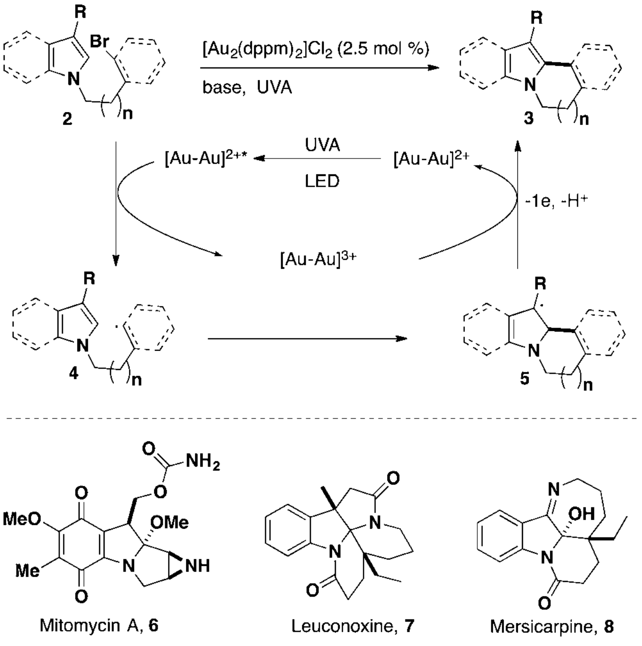


Radical chemistry has grown significantly in recent years, although its roots extend more than a century. Many advances have been made in understanding the reactivity of carbon-centered radicals and its application in synthesis.[1] Current methods to generate carbon-centered radicals from unactivated organohalides generally use potentially hazardous/toxic radical initiators (AIBN, peroxides, Et_3B/O_2) and hydrogen atom donors (organostannane).[2] With much interest being placed on sustainable chemistry, recent literature has shown movement toward the use of photoredox catalysis, which offers safe, efficient, and waste-minimizing methods to generate organic radicals.[3]

Inspired by biocomplexes that perform photosynthesis in nature, chemists have developed a variety of photoredox complexes for research in energy storage, water splitting, and photovoltaic devices.[4] Among these, polypyridine Ru(II)[5] and Ir(III) complexes such as $[Ru(bpy)_3Cl_2]$, $[Ir(ppy)_2(dtbbpy)]PF_6$, and *fac*-$Ir(ppy)_3$ possess high-energy, long-lived, and highly emissive excited states that are useful in organic synthesis. While these catalysts can generate carbon-centered radical intermediates via the reduction of carbon−halogen bonds, they suffer from low reduction potentials, limiting radical intermediates to those derived from activated carbon−halogen bonds. These include bromomalonates,[6] polyhalomethanes,[7] electron-deficient benzyl halides,[8] and iodoalkane[9] and iodoarenes. With these limitations in mind, it is important to develop new photoredox catalysts that offer the ability to reduce unactivated carbon−halogen bonds with higher reduction potentials, thus giving access to a wide range of organic free radicals.

In 2013, we reported the reductive scission of unactivated bromoalkanes/arene bonds using a catalytic amount of photoluminescent dimeric gold complex, $[Au_2(dppm)_2]Cl_2$ (**1**).[10] UVA irradiation of **1** generates a long-lived excited state, which can either undergo an oxidative or reductive quench cycle.[11,12] On the basis of these results, we were interested in the applicability of $[Au_2(dppm)_2]Cl_2$ (**1**) as a catalyst for the functionalization of indoles through a photoredox process **2** → **3**, which are common motifs in natural products and biologically active molecules (Scheme 1).

Scheme 1. Photoredox Transformation



In general, oxidative radical additions to indoles and pyrroles require the use of stoichiometric oxidants[13] such as $Mn(OAc)_3$[14,15] or activated carbon−halogen bonds using $[Ru(bpy)_3Cl_2]$ as photocatalyst.[16] We hypothesized that the C−Br reduction of **2** via an oxidative quenching cycle should produce the corresponding primary alkyl radical **4**, which upon cyclization would give the benzylic radical intermediate **5**.

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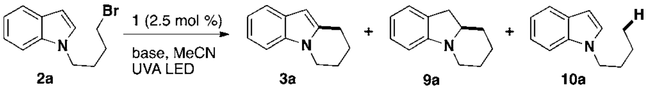
Concomitant oxidation of intermediate **5** and reduction of the $[Au-Au]^{3+}$ complex should provide the desired indole **3** and the dimeric gold photocatalyst (**1**) turnover.

To verify the hypothesis depicted in Scheme 1, bromoalkane **2a** was irradiated (UVA LED, 365 nm) in the presence of $[Au_2(dppm)_2]Cl_2$ (2.5 mol %) and DIPEA (5 equiv) in MeCN to produce an inseparable mixture of indole **3a** (42%), indoline **9a** (20%), and dehalogenated product **10a** (7%), along with some starting material (20%) (Table 1, entry 1). While amine bases act as sacrificial electron donors, one could envisage the diminution of the reduced side products **9a** and **10a** by using poor hydrogen donor amine bases. Irradiation in the presence of TMEDA, DABCO, or 1,2,2,6,6-pentamethylpiperidine (PMP) did not lead to any noticeable improvement (Table 1, entries 2–4). However, the replacement of the amine base by sodium carbonate led to the formation of **3a** in 41% yield (Table 1, entry 5). Although the reaction was not complete, no traces of reduced product **9a** and/or **10a** were observed in the crude reaction mixture. Finally, a complete conversion was reached after 12 h of irradiation (Table 1, entries 6 and 7). Indole **3a** was obtained as the sole product in 98% yield (Table 1, entry 7). Standard control experiments showed that in the absence of gold photocatalyst, UVA irradiation, or base a complete recovery of the starting material was obtained (Table 1, entries 8–10).

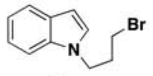
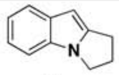
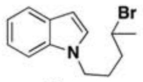
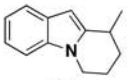
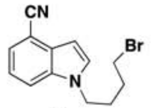
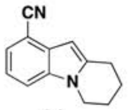
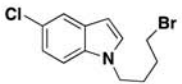
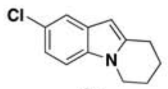
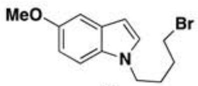
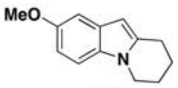
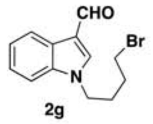
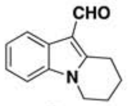
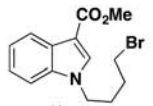
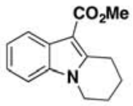
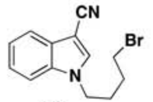
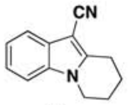
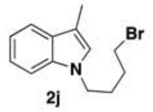
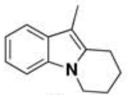
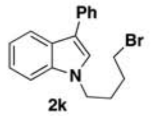
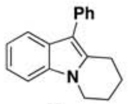
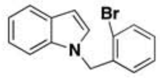
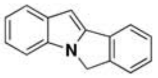
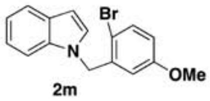
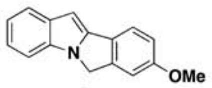
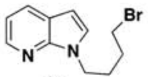
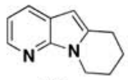
Table 1. Optimization of the Reaction Conditions[a]



			product (%)			
entry	base	time (h)	2a	3a	9a	10a
1	DIPEA[b]	1	20	42	20	7
2	TMEDA[b]	1	60	10	10	12
3	DABCO[b]	1	97			
4	PMP[b]	1	9	54	20	7
5	Na_2CO_3[c]	1	51	41		
6	Na_2CO_3[c]	6	15	78		
7	Na_2CO_3[c]	12		98		
8		12	>98			
9	Na_2CO_3[c,d]	12	>98			
10	Na_2CO_3[c,e]	12	>98			

[a] ^{1}H NMR yield with mesitylene as internal standard. [b] 5 equiv. [c] 2 equiv. [d] No catalyst. [e] No light.

Table 2. Scope of the Reaction[a]

entry	substrate	product	yield (%)[b]
1	 **2b**	 **3b**	88
2	 **2c**	 **3c**	98
3	 **2d**	 **3d**	90
4	 **2e**	 **3e**	95
5	 **2f**	 **3f**	98
6	 **2g**	 **3g**	95
7	 **2h**	 **3h**	92
8	 **2i**	 **3i**	95
9	 **2j**	 **3j**	86
10	 **2k**	 **3k**	98
11	 **2l**	 **3l**	72(24)[c]
12	 **2m**	 **3m**	48(48)[c]
13	 **2n**	 **3n**	s.m.

[a] $[Au_2(dppm)_2][Cl]_2$ (2.5 mol %) and Na_2CO_3 (5 equiv) in MeCN, UVA (365 nm), rt, 12 h. [b] Isolated yields and c = 0.2 M. [c] The yield in parentheses corresponds the dehalogenated products **10l** and **10m**.

With these optimized conditions in hand, we proceeded to examine the scope of the photoredox cyclization by using substituted *N*-alkylindole substrates (Table 2). Gold(I)-catalyzed photoredox cyclization of primary and secondary bromoalkanes **2b** and **2c** provided the desired indoles **3b** and **3c** in 88% and 98% yields respectively (Table 2, entries 1 and 2). The nature of the substitution on the indole ring has no detrimental effect on the photoredox transformation. The substrates having electron-withdrawing groups such as 4-cyano- and 5-chloroindoles **2d** and **2e** were easily converted to the corresponding cyclized products **3d** and **3e** in 90% and 95% yields, respectively (Table 2, entries 3 and 4). 5-Methoxyindole **2f** was converted to the tricyclic product **3f** in 98% yield (Table 2, entry 5). Although the addition of a primary radical at C2 is expected to be particularly favorable, apprehensions were raised regarding the photoredox cyclization of indoles **2g–i**. Assuming that the conversion of **5** to **3** does not proceed through a radical disproportionation, the concomitant oxidation/reduction manifold can be difficult when R = CO_2Me, CN, CHO due to the electrophilic nature of the radical intermediate **5** (Scheme 1).[15e,16a] Much to our delight, indoles **2g−i** were transformed to the desired products **3g−i** in yields ranging from 92% to 95% yields (Table 2, entries 6−8). From these results, one could imagine that the oxidation potential of the $[Au{-}Au]^{3+}$ is high enough to oxidize the radical intermediate **5** to the corresponding carbocation leading to indole **3**. As expected, C3 electron-rich indoles **2j** and **2k** were transformed into the desired products **3j** and **3k** in 86% and 98% yields, respectively (Table 2, entries 9 and 10). Radical cyclization of aryl bromides **2l** and **2m** afforded cyclized indoles **3l** (72%) and **3m** (48%) along with a significant amount of dehalogenated products **10l** (24%) and **10m** (48%). In an attempt to obtain 7-azaindole **3n**, only starting material **2n** was isolated, suggesting that pyridine moiety poisons the gold catalyst **1** (Table 2, entry 13).

In summary, we have described a light-mediated process for the generation of organic free radicals with unactivated bromoalkanes/arenes, resulting in the efficient functionalization of substituted indoles. This methodology allows for simple access of carbon-centered radicals not attained with previous photoredox catalysts, and without the use of toxic and/or harsh conditions. Further mechanistic studies along with its application in total synthesis of natural products will be reported in due course.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and ^1H and ^{13}C NMR spectra for all new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01260.

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Notes

The authors declare no competing financial interest.

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