

Electron Transfer Photoredox Catalysis: Intramolecular Radical Addition to Indoles and Pyrroles

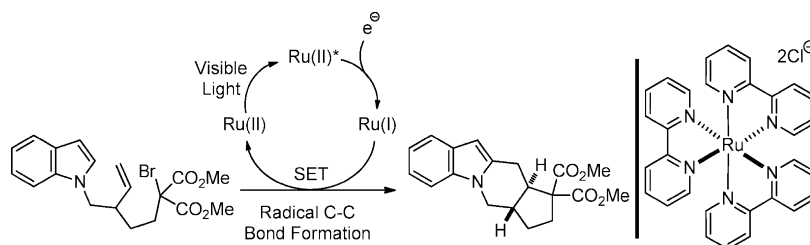
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ABSTRACT



The utilization of the photoredox catalyst, tris(2,2'-bipyridyl)ruthenium dichloride, and a household light bulb to effect radical cyclizations onto indoles and pyrroles at room temperature is reported. A reactive free radical intermediate is generated via the reduction of an activated C–Br bond by the single electron reductant, Ru(I), generated in a visible light induced photocatalytic cycle. This system represents an expansion of the application of photoredox catalysis in conventional free radical processes.

Concerted efforts over the past 40 years have established single-electron transfer (SET) and the formation of radicals as reliable processes to form new carbon–carbon bonds.^{1–3} Despite this prominence, there are still relatively few methods for the generation of radicals under benign conditions. For example, the stalwarts for radical formation have long been the highly toxic and persistent environmental pollutants, trialkyltin hydrides.⁴ Furthermore, these radical initiation systems often lack the necessary chemoselectivity and functional group tolerance for use with highly functionalized

substrates.⁵ In light of these issues, and cognizant of the broad chemical community's interest in the development of more environmentally benign chemical transformations,⁶ we have been exploring the application of photoredox catalysis as a new means of accessing free radical chemistry (Scheme 1).^{7,8} We have recently demonstrated the ability of the visible light activated photoredox catalyst, tris(2,2'-bipyridyl)ruthenium(II) chloride,⁹ to efficiently and chemoselectively act as a single electron reductant and afford the reductive de-

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(2) For recent reviews of photoelectron transfer chemistry in organic synthesis, see: (a) Hoffmann, N. J. *Photochem. Photobiol. C, Photochem. Rev.* **2008**, *9*, 43. (b) Cossy, J.; Belotti, D. *Tetrahedron* **2006**, *62*, 6459.

(3) For reviews on radical chemistry, see: (a) Curran, D. P. *Synthesis* **1988**, *6*, 417. (b) Ryu, I.; Sonoda, N.; Curran, D. P. *Chem. Rev.* **1996**, *96*, 177.

(4) For selected recent examples of tin-free radical reactions see: (a) Spiegel, D. A.; Wiberg, K. B.; Schacherer, L. N.; Medeiros, M. R.; Wood, J. L. *J. Am. Chem. Soc.* **2005**, *127*, 12513. (b) Hayashi, N.; Shibata, I.; Baba, A. *Org. Lett.* **2005**, *7*, 3093. (c) Gong, H.; Andrews, R. S.; Zuccarello, J. S.; Lee, S. J.; Gagné, M. R. *Org. Lett.* **2009**, *11*, 879.

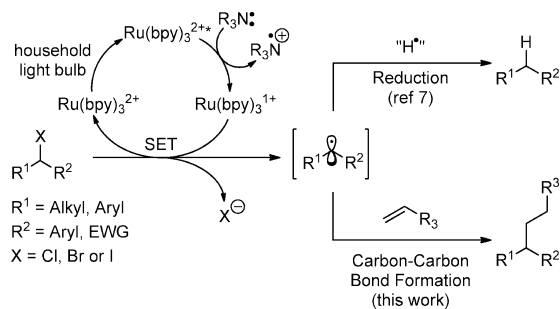
(5) For examples of functional group reactivity using other radical initiation systems, see: (a) Ferris, J. P.; Antonucci, F. R. *J. Am. Chem. Soc.* **1972**, *94*, 8091. (b) Molander, G. A. *Org. React.* **1994**, *46*, 211. (c) Bebbington, D.; Bentley, J.; Nilsson, P. A.; Parsons, A. F. *Tetrahedron Lett.* **2000**, *41*, 8941. (d) Bowman, W. R.; Bridge, C. F.; Brookes, P. *Tetrahedron Lett.* **2000**, *41*, 8989.

(6) For reviews on sustainable chemistry, see: (a) Albin, A.; Fagnoni, M. *Green Chem.* **2004**, *6*, 1. (b) Jenck, J. F.; Agterberg, F.; Droscher, M. J. *Green Chem.* **2004**, *6*, 544.

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(8) For the use of dihydroacridines as a hydrogen atom source for the reduction of α -haloacetophenones using Ru-mediated photoredox catalysis, see: Fukuzumi, S.; Mochizuki, S.; Tanaka, T. *J. Phys. Chem.* **1990**, *94*, 722.

Scheme 1. Generation of Radicals Using Photoredox Catalysis



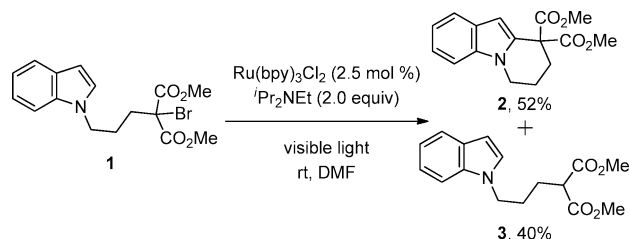
halogenation of compounds with activated carbon–halogen bonds via a reactive alkyl radical.^{10,11}

The functionalization of indoles and pyrroles, thanks to their abundance in biologically and medicinally active compounds, has received much attention to date.¹² We were inspired to investigate the utility of Ru–photoredox chemistry in the area of heterocycle functionalization by recent developments in Mn(III)-based malonyl radical cyclization reactions.^{13,14} In particular, Kerr and co-workers have recently demonstrated the utility of the oxidative generation of malonyl radicals with Mn(OAc)₃ for the intramolecular functionalization of indoles, indolines, and pyrroles.¹⁵ In this letter we report the application of photoredox catalysis to the intramolecular functionalization of substituted indoles and pyrroles.

Upon initial investigations of reaction conditions, we were encouraged to find that treatment of **1** with ⁱPr₂NEt (2 equiv) and Ru(bpy)₃Cl₂ (2.5 mol %) in DMF under

visible light irradiation yielded 52% of the desired cyclization product, **2**. The major byproduct, present to varying degrees in all subsequent cyclization reactions, is the corresponding reduced compound, **3**, obtained here in 40% yield (Scheme 2). In the absence of any of the

Scheme 2. Initial Cyclization Result



reaction components, Ru(bpy)₃Cl₂, light, and/or ⁱPr₂NEt, no reaction was observed.

Optimization of the reaction conditions involved the screening of amine bases to act as a sacrificial electron donor to reductively quench the photoinduced excited Ru(II)* species. To minimize the formation of the reductively dehalogenated product, bases that do not serve as good hydrogen atom donors were sought. Amines such as Ph₃N, Et₃N, DABCO, Me₃N, and (HOCH₂CH₂)₃N were all screened. Although DABCO, Me₃N, and (HOCH₂CH₂)₃N all proved to be effective hydrogen donors, they were poorly selective and provided product mixtures favoring **3**. Triethylamine provided the best balance of efficient reactivity and selectivity for the cyclization reaction over the competitive dehalogenation process. Of note, the most selective reaction involved the use of triphenylamine as an electron source resulting only in formation of the desired cyclization product, although even after prolonged reaction time (>48 h) only 60% conversion (34% isolated yield) was observed.

We next applied the optimized reaction conditions, consisting of the cyclization substrate in combination with Ru(bpy)₃Cl₂ (1.0 mol %) and Et₃N (2 equiv) in DMF under irradiation by a 14 W household light bulb, to a series of substituted indoles (Table 1). Both six- and five-membered fused rings are possible, although five-membered rings are more difficult to form and generally require a substituent at C-3 to stabilize the tertiary radical resulting from cyclization. The chemoselectivity of this photoredox system for the reduction of activated C–Br bonds over aryl C–Br bonds is demonstrated by entry 5. In addition, functional groups including esters, amides, and cyano groups are all well tolerated. Electron-rich indoles provided the desired cyclization product, and even electron-deficient indoles were modest substrates for this reaction, providing the corresponding cyclization product in 40% yield (entry 9).¹⁶ The reaction also works well for the preparation of linear tricyclic systems resulting from an endo cyclization of the malonyl radical (entry 10).

(16) The reduced compound is also observed in the crude ¹H NMR, present as an approximately 1:1 mixture with the cyclized product.

(9) For excellent reviews on the photochemistry and photophysics of Ru(bpy)₃²⁺ and related complexes, see: (a) Kalyanasundaram, K. *Coord. Chem. Rev.* **1982**, *46*, 159. (b) Juris, A.; Balzani, V.; Barigelli, F.; Campagna, S.; Belser, P.; von Zelewsky, A. *Coord. Chem. Rev.* **1988**, *84*, 85.

(10) For recent examples of photoredox catalysis, see: (a) Nicewicz, D. A.; MacMillan, D. W. C. *Science* **2008**, *322*, 77. (b) Ischay, M. A.; Anzovino, M. E.; Du, J.; Yoon, T. P. *J. Am. Chem. Soc.* **2008**, *130*, 12886. (c) Koike, T.; Akita, M. *Chem. Lett.* **2009**, *38*, 166. (d) Borak, J. B.; Falvey, D. E. *J. Org. Chem.* **2009**, *74*, 3894. (e) Du, J.; Yoon, T. P. *J. Am. Chem. Soc.* **2009**, *131*, 14604. (f) Nagib, D. A.; Scott, M. E.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2009**, *131*, 10875.

(11) For reviews on the photoactivation of metal complexes, see: (a) Salomon, R. G. *Tetrahedron* **1983**, *39*, 485. (b) Kutal, C. *Coord. Chem. Rev.* **1985**, *65*, 191. (c) Hennig, H. *Coord. Chem. Rev.* **1999**, *182*, 101. (d) Hoffmann, N. *Chem. Rev.* **2008**, *108*, 1052.

(12) For selected recent examples of the functionalization of indoles and pyrroles, see: (a) Baran, P. S.; Maimone, T. J.; Richter, J. M. *Nature* **2007**, *446*, 404. (b) Stuart, D. R.; Fagnou, K. *Science* **2007**, *316*, 1172. (c) Richter, J. M.; Whitefield, B. W.; Maimone, T. J.; Lin, D. W.; Castroviejo, M. P.; Baran, P. S. *J. Am. Chem. Soc.* **2007**, *129*, 12857. (d) Tanaka, M.; Ubukata, M.; Matsuo, T.; Yasue, K.; Matsumoto, K.; Kajimoto, Y.; Ogo, T.; Inaba, T. *Org. Lett.* **2007**, *9*, 3331. (e) Antos, J. M.; McFarland, J. M.; Iavarone, A. T.; Francis, M. B. *J. Am. Chem. Soc.* **2009**, *131*, 6301.

(13) For an excellent review on Mn(III) chemistry, see: Snider, B. B. *Chem. Rev.* **1996**, *96*, 339.

(14) For selected examples of radical initiated methods of indole/pyrrole functionalization, see: (a) Baciocchi, E.; Muragli, E. *J. Org. Chem.* **1993**, *58*, 7610. (b) Byers, J. H.; DeWitt, A.; Nasveschuk, C. G.; Swigor, J. E. *Tetrahedron Lett.* **2004**, *35*, 6587. (c) Guadarrama-Morales, O.; Méndez, F.; Mirana, L. D. *Tetrahedron Lett.* **2007**, *48*, 4515. (d) Lindsay, K. B.; Ferrando, F.; Christensen, K. L.; Overgaard, J.; Roca, T.; Benasar, M.; Skrydstrup, T. *J. Org. Chem.* **2007**, *72*, 4181.

(15) Magolan, J.; Kerr, M. A. *Org. Lett.* **2006**, *8*, 4561. Magolan, J.; Carson, C. A.; Kerr, M. A. *Org. Lett.* **2008**, *10*, 1437.

Table 1. Photoredox-Catalyzed Intramolecular Radical Functionalization of Indoles and Pyrroles*

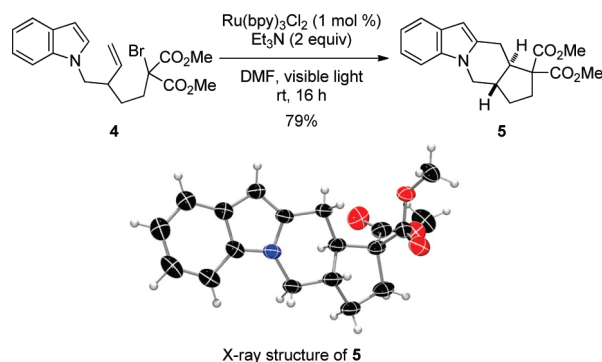
entry	substrate	product	yield ^a
1			60
2			73
3			55
4			60
5			55
6			61
7			59
8			60
9			40
10			62
11			80
12			95
13			79
14			53
15			82 ^b
16			89

* Reaction conditions: cyclization substrate (1.0 equiv), Et₃N (2.0 equiv), Ru(bpy)₃Cl₂ (1.0 mol %), visible light, DMF, rt, 12 h. ^a Isolated yield after purification by chromatography on SiO₂. ^b Combined yield of regioisomers (1:1).

We next broadened the scope of the radical functionalization of heteroaromatic compounds to a series of substituted

pyrrole substrates wherein the pyrrole substrates generally performed better than indoles.¹⁷ Again, good functional group tolerance was observed for the cyclization reaction onto pyrrole subunits. Furthermore, substitution at the C-2 and C-3 positions is well tolerated. Both electron-rich and -poor pyrroles fared well in the cyclization reaction; however, 3-phenylpyrrole, while providing the cyclization in an efficient yield of 82%, afforded an equal mixture of two regioisomeric cyclization products (entry 15). The α -bromooxazolidinone was also an excellent substrate, affording the cyclized product in 89% yield (entry 16). In general, the cyclization reactions proceed more quickly for the more electron-rich pyrroles, resulting in the formation of less of the corresponding reduction products.

To further expand upon this methodology, we wanted to examine the possibility of cascade radical cyclizations using photoredox-mediated reactions (Scheme 3). Treatment of **4**¹⁸

Scheme 3. Cascade Radical Cyclization

under the cyclization reaction conditions resulted in the formation of the double cyclization product **5** as a single diastereoisomer in 79% yield.¹⁹

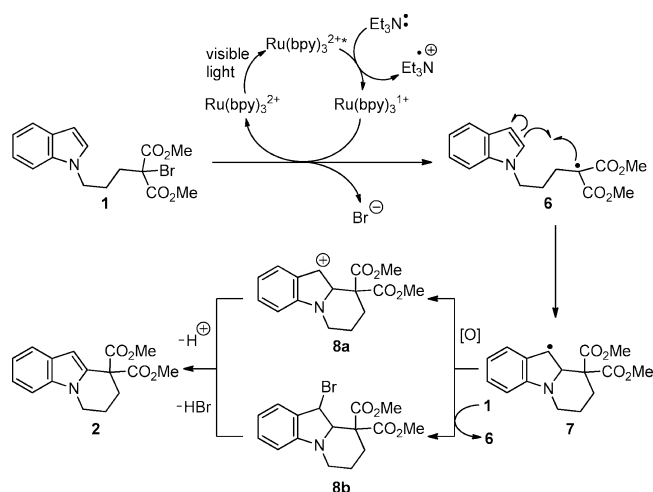
Given the observed reactivity, we propose the mechanism outlined in Scheme 4 to account for the formation of the observed cyclization product. Visible light irradiation generates the metal-to-ligand charge-transfer (MLCT) excited ruthenium(II)* species which is reductively quenched by Et₃N to generate the electron-rich ruthenium(I) complex and the triethylammonium radical cation. The reduced ruthenium species then acts as the single electron transfer agent and affords selective reduction of the activated carbon–bromine bond, generating the electron-deficient alkyl radical **6** and regenerating the catalyst, Ru(bpy)₃²⁺. The desired tricyclic product is produced via an initial intramolecular cyclization of the electron-rich aromatic species with the electrophilic

(17) For a discussion on the kinetic nucleophilicity of pyrroles, see: Nigst, T. A.; Westermaier, M.; Ofial, A. R.; Mayr, H. *Eur. J. Org. Chem.* **2008**, 2369. For a comparison of the rates of formylation of pyrroles and indoles, see: Cipiciani, A.; Clementi, S.; Linda, P.; Marino, G.; Savelli, G. *J. Chem. Soc., Perkin Trans. 2* **1977**, 1284.

(18) See the Supporting Information for the preparation of **4**.

(19) The relative configuration of the product was determined by X-ray crystallographic analysis. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre (CCDC 748503) via www.ccdc.cam.ac.uk/data_request/cif.

Scheme 4. Proposed Mechanism



radical to afford **7**. The resultant benzylic radical is then oxidized, possibly by the excited state Ru(II)^* species²⁰ or by bromomalonate **1**, to afford intermediate **8a** or **8b**, respectively. Elimination affords the aromatized product **2** along with triethylammonium hydrobromide.

(20) MacMillan and coworkers have previously postulated the oxidation of α -aminylradicals by the Ru(II)^* species²⁰ or by bromomalonate **1**, to afford intermediate **8a** or **8b**, respectively. Elimination affords the aromatized product **2** along with triethylammonium hydrobromide.

In conclusion, we report an efficient and operationally simple functionalization reaction of indoles and pyrroles via a single electron transfer process initiated by visible light irradiation. This methodology represents a potential means for accessing a variety of medicinally and biologically active natural products and provides an additional example of the utility of photoredox catalysis in the context of radical chemistry. Further studies into the application to the total synthesis of complex molecules as well as expanding upon the scope of photoredox catalysis in the realm of organic chemistry will further demonstrate its utility as a new avenue for free radical-mediated reactions.

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Supporting Information Available: Experimental procedures, ^1H and ^{13}C NMR spectra for all new compounds, and crystallographic data for **5**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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