Redox Chemistry

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Visible-Light-Promoted C–C Bond Cleavage: Photocatalytic Generation of Iminium Ions and Amino Radicals**

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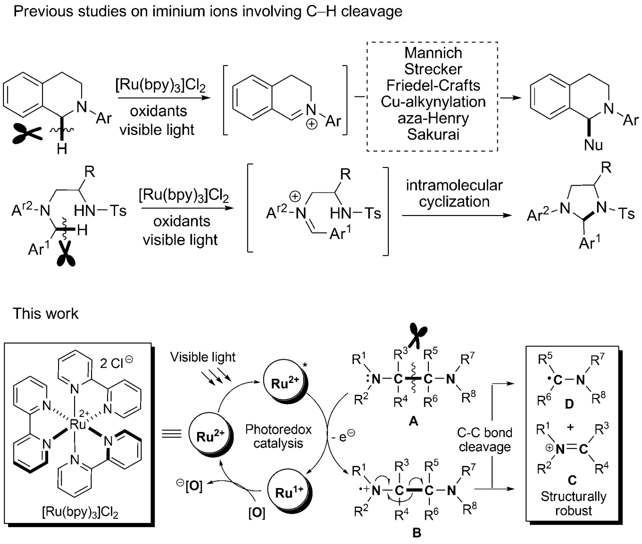
Although the use of photons as reagents has enjoyed an incredibly rich history,[1] the use of photons of red-shifted wavelengths, particularly those extending into what is known as the visible region (i.e., wavelengths ranging from 380 nm to 750 nm), in the context of promoting synthetically attractive organic transformations has attracted considerable attention only very recently.[2] Thanks to the pioneering work from the groups of MacMillan,[3] Yoon,[4] Stephenson,[5] and others,[6] this field has already demonstrated outstanding accomplishments and holds promise for uncovering new catalysis concepts and synthetic applications. Such efforts would most likely be fueled and accelerated in the future by the increasing demand for developing environmentally benign chemical processes with reduced energy consumption, as well as by the latest advancements in commercializing green light sources such as organic light-emitting diodes (OLEDs).[7] Not surprisingly, as organic compounds generally cannot absorb visible-light, the use of visible light as an effective means to initiate organic reactions must require a photosensitization strategy. Such sensitizers function as useful photocatalysts, the most widely employed example being a ruthenium(II)–polypyridine complex such as [Ru(bpy)$_3$Cl$_2$] (bpy = bipyridine).[8] As photocatalysts with suitable photoredox potentials and their commercial availabilities are both highly limited, it is thus readily recognizable that the success of unlocking the full potential of visible-light photocatalysis for synthetic reactions of broad utility lies in the identification of efficient methodologies for the convenient photocatalytic generation of some of the most versatile reactive species, but with the aid of only a few known sensitizers.

Among the synthetic chemists' arsenal, iminium ions[9] and radicals[10] clearly stand out as reactive intermediates of major significance. The goal that considerably motivates us is, thus, to devise and possibly implement new visible-light-promoted photocatalysis strategies which would allow facile production of structurally robust iminium ion or radical intermediates, and preferably, in a one-pot and controllable fashion. We believe that the ability of accessing such intermediates having variable substituents or structurally editable functionalities would ensure the "freedom-of-operation" to be conveniently practiced while merging them into intended catalysis cycles. In this context, it should be highlighted that the groups of Stephenson, Xiao, and Rueping have described significant examples of oxidative C–H functionalizations through in situ generation of iminium ions under visible-light photoredox conditions (Scheme 1).[5b,d,6]



Scheme 1. Design concept for visible-light-promoted photocatalytic C–C bond cleavage of the substituted the 1,2-diamine **A** which leads to simultaneous generation of the structurally variable iminium ion **C** and amino radical **D** as reactive intermediates. [O] denotes an oxidant, and * denotes a photoexcited state.

However, in nearly all of these reported cases, the reactivities appeared to be closely associated with *N*-aryl tetrahydroisoquinolines and their structurally related substrates. In the outlined mechanisms, the formation of putative iminium ions from these structures apparently benefited from the stabilization effects of the aryl substituents, in which the loss of a hydrogen atom from the corresponding amine radical cation precursor is significantly driven by charge delocalization along the *trans* aryl–C=N–aryl unit. In addition, MacMillan an co-workers[3a] and Reiser and co-workers[6j] had reported the generation of α-amino radicals from structurally related N-aryl substrates for reactions involving C–H arylations and cyclizations, respectively.

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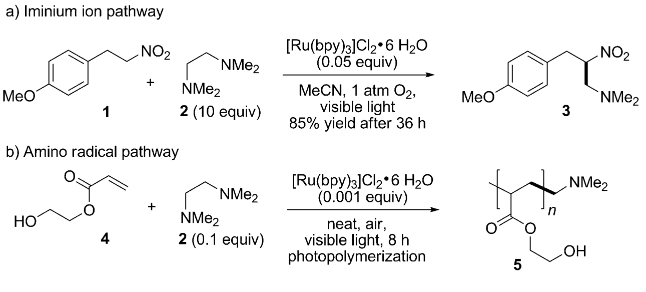
With the objective of discovering new and broadly applicable scenarios for efficient generation of structurally variable iminium ions (and other useful reactive intermediates) with visible-light photoredox catalysis, as shown in Scheme 1, we envisioned that a simple substituted 1,2-diamine such as **A** might constitute a reasonable starting point. The hypothesis is that in the presence of both visible light and an external oxidant, the $\{Ru^{2+}\text{-}[Ru^{2+}]^{*}\text{-}Ru^{1+}\}$ redox cycle would catalytically abstract an electron from the nitrogen lone pair in **A**, thus converting it into the radical cation species **B**. The presence of a β-nitrogen heteroatom in close proximity to the resultant N-centered radical cation would subsequently induce reorganization of electron densities in **B**, and lead to the cleavage of the central C−C bond as well as concomitant formation of both the iminium ion **C** and α-amino radical **D**. As a wide range of vicinal diamines **A** bearing multiple substitutions, that is, R^1 to R^8, are readily available, it could well be anticipated that this design concept, if successful, would provide a highly robust and visible-light-enabled entry to a plethora of new transformations associated with electrophilic or nucleophilic properties of the reactive species **C** and **D**.

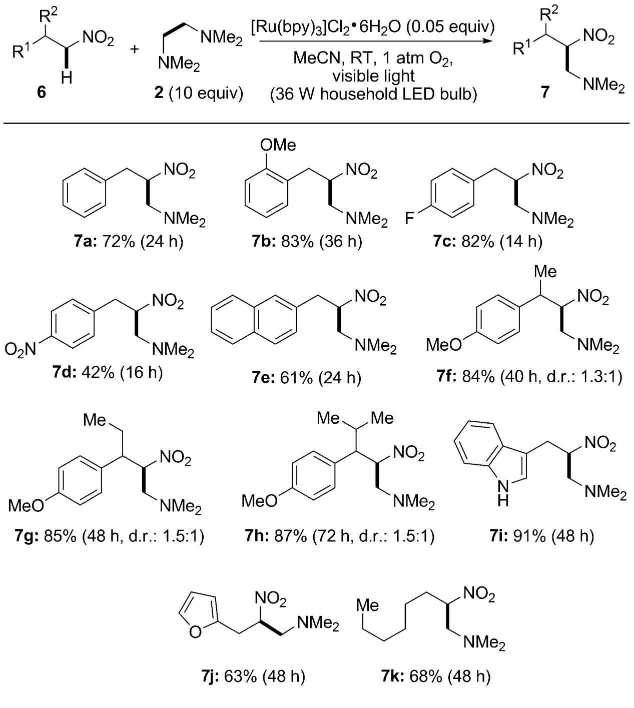
Fortunately, this design scenario was indeed found to be viable. As shown in Scheme 2, upon exposure to a household LED bulb (36 W), the NO_2-substituted substrate **1** reacted with tetramethylethanediamine (TMEDA; **2**) in the presence of a catalytic amount (5 mol %) of the photocatalyst $[Ru(bpy)_3]Cl_2\cdot 6H_2O$ under a balloon of oxygen to give the aza-Henry product **3**, after 48 hours at room temperature, in 27 % yield upon isolation. The product yield and reaction efficiency could be readily improved by employing the diamine **2** in excess, thus 85 % yield was obtained after 36 hours when 10 equivalents of **2** was used. The choice of solvent markedly influenced the reaction, and MeCN was found to be optimal in terms of achieving a high product yield. Other solvents examined, such as DMF, CH_2Cl_2, EtOH, and NMP, produced **3** in much lower yields (25–40 %) under otherwise identical reaction conditions, while no reaction and decomposition occurred when using 1,2-dichloroethane and trifluoroethanol, respectively. Control experiments conducted in the absence of either the photocatalyst or visible-light exposure showed no reaction, thereby confirming the operation of a photoredox catalysis cycle towards efficient iminium ion generation. Oxygen apparently functioned as the terminal oxidant as the formation of **3** was inhibited when the reaction was run under a nitrogen atmosphere.[11]



Scheme 2. Visible-light-promoted photocatalytic C−C bond cleavage of $Me_2NCH_2CH_2NMe_2$. a) Formation of an iminium ion for aza-Henry reaction. b) Formation of an amino radical for photopolymerization.

In addition, the amino radical pathway was directly detected by visible-light-induced free-radical photopolymerization of 2-hydroxyethylacrylate (HEA; **4**; Scheme 1) in the presence of 0.1 mol % of the photocatalyst and 10 mol % of TMEDA; a tube (20 mL) of the neat liquid monomer solidified to form polymer **5** after 8 hours of exposure to light. The dimethylamino radical attached to the polymer chains showed NMR resonances at approximately $\delta = 2.30$ ppm.[12] It is significant that, unlike many other free-radical polymerization systems which suffer severely from O_2 inhibition effects, the open-flask protocol described herein functioned effectively under an atmosphere of air. Photopolymerizations of olefinic monomers initiated by amino radicals serve as the cornerstone of what is known as the UV-curing industry,[13] thus a visible-light-enabled production of such reactive species offers significant energy-saving and environmental advantages over traditional methods which employ high-pressure Hg lamps or metal halide lamps.

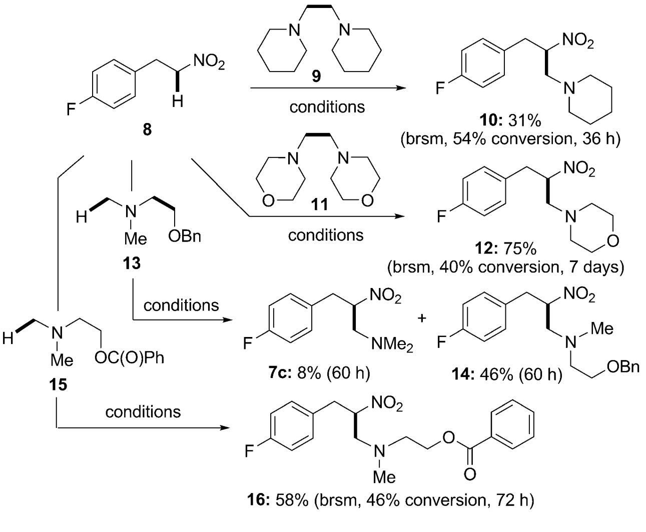
While the visible-light-promoted photopolymerization[14] clearly warrants further studies, we decided to focus on investigating the reactivities arising from iminium ion species. As summarized in Scheme 3, a range of nitro substrates (**6**) were found to undergo efficient electrophilic trapping by the $Me_2N{=}CH_2$ iminium ion that was photocatalytically generated in situ from TMEDA (10 equiv) to give the corresponding aza-Henry products **7** in good to excellent yields upon isolation. The reaction setup, employing a cold light source such as a household LED bulb at room temperature and



Scheme 3. Visible-light-promoted aza-Henry reactions by means of the photocatalytic C−C bond cleavage of $Me_2NCH_2CH_2NMe_2$. Yields are of the isolated product.

under neutral conditions, was both operationally simple and environmentally benign. Substrate aryl rings bearing an electron-donating substituent (**7b** and **7f–h**), electron-withdrawing substituent (**7c–d**), more conjugation (**7e**), or heteroatoms (**7i–j**) all gave the expected products with comparable yields (61–91%), except in the case of **7d** (42%) wherein the presence of a strongly electron-withdrawing NO_2 group appeared to impact negatively on the reaction efficiency. The purely aliphatic substrate **7k** also worked smoothly (68%). The increased steric size of the benzylic R^2 group in **7f–h** imposed little influence on the reaction diastereoselectivities (1.3:1 to 1.5:1), but did somewhat slow down the reactions as similar product yields (84–87%) were obtained with prolonged reaction times. Since the NO_2 group in **7** could be readily reduced to NH_2 or oxidized to a carbonyl group by conventional protocols,[15] the present discovery serves as a useful methodology for the facile preparation of functionalized vicinal diamines or α-amino ketones.

With **8** as a representative substrate, similar reactions proceeded with other iminium ion precursors such as **9** and **11** (5 equiv, Scheme 4), albeit with lower efficiency, thus generating the aza-Henry-type products **10** and **12**, respectively, in 31% and 75% yields upon isolation (based on the recovered starting materials). Notably, when an β-alkoxy amine precursor **13** was employed, the in situ formed photoexcited amine radical cation could apparently fragment competitively by C–H versus C–C bond-cleavage pathways, thus leading to the formation of both **14** (46%) and **7c** (8%). Furthermore, when the OBn substituent was replaced by an electron-withdrawing OC(O)Ph group, the C–C bond-cleavage pathway was found to be completely inhibited, and what was isolated was exclusively **16** (58%). These findings collectively hint at the exciting possibilities for fine-tuning of the reactivities, as well as selectivities of these synthetically attractive intermediates.



Scheme 4. Visible-light-promoted aza-Henry reactions by means of the photocatalytic C–C bond cleavage of other diamines and related iminium ion precursors. Reaction conditions: **8** (1 equiv), amine precursor **9**, **11**, **13**, or **15** (5 equiv), $[Ru(bpy)_3]Cl_2 \cdot 6H_2O$ (0.05 equiv), MeCN, O_2 balloon, RT, visible light (from 36 W household LED bulb). Yields are of the isolated product. brsm = based on recovered starting material.

In summary, by employing simple vicinal diamines as new precursors of photoexcited radical cations, we were able to record some fascinating examples of the visible-light-promoted photoredox catalytic cleavage of strong C^{α}–C^{β} bonds. The discovery enables structurally versatile and synthetically robust iminium ions and amino radical species to be simultaneously generated under exceptionally mild reaction conditions, thereby bringing about practically useful reactivities in such important contexts as aza-Henry condensations and radical photopolymerizations. Given the established significance of such reactive intermediates in modern synthetic transformations,[14] it could well be anticipated that such a visible-light-initiated photoredox catalysis approach would allow reactions of much broader scope to be tackled in a convergent and operationally simple manner.

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[1] a) N. J. Turro, *J. Org. Chem.* **2011**, *76*, 9863; b) G. Ciamician, *Science* **1912**, *36*, 385.

[2] For latest reviews on photoredox catalysis directed towards synthetic applications, see: a) K. Zeitler, *Angew. Chem.* **2009**, *121*, 9969; *Angew. Chem. Int. Ed.* **2009**, *48*, 9785; b) T. P. Yoon, M. A. Ischay, J. Du, *Nat. Chem.* **2010**, *2*, 527; c) J. M. R. Narayanam, C. R. J. Stephenson, *Chem. Soc. Rev.* **2011**, *40*, 102; d) F. Teplý, *Collect. Czech. Chem. Commun.* **2011**, *76*, 859; e) J. W. Tucker, C. R. J. Stephenson, *J. Org. Chem.* **2012**, *77*, 1617.

[3] a) A. McNally, C. K. Prier, D. W. C. MacMillan, *Science* **2011**, *334*, 1114; b) D. A. Nicewicz, D. W. C. MacMillan, *Science* **2008**, *322*, 77; c) D. A. Nagib, M. E. Scott, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2009**, *131*, 10875; d) H.-W. Shih, M. N. Vander Wal, R. L. Grange, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2010**, *132*, 13600; e) D. A. Nagib, D. W. C. MacMillan, *Nature* **2011**, *480*, 224; f) P. V. Pham, D. A. Nagib, D. W. C. MacMillan, *Angew. Chem.* **2011**, *123*, 6243; *Angew. Chem. Int. Ed.* **2011**, *50*, 6119.

[4] a) S. Lin, M. A. Ischay, C. G. Fry, T. P. Yoon, *J. Am. Chem. Soc.* **2011**, *133*, 19350; b) M. A. Ischay, Z. Lu, T. P. Yoon, *J. Am. Chem. Soc.* **2010**, *132*, 8572; c) M. A. Ischay, M. E. Anzovino, J. Du, T. P. Yoon, *J. Am. Chem. Soc.* **2008**, *130*, 12886; d) A. E. Hurtley, M. A. Cismesia, M. A. Ischay, T. P. Yoon, *Tetrahedron* **2011**, *67*, 4442; e) Z. Lu, M. Shen, T. P. Yoon, *J. Am. Chem. Soc.* **2011**, *133*, 1162; f) J. Du, L. R. Espelt, I. A. Guzei, T. P. Yoon, *Chem. Sci.* **2011**, *2*, 2115; g) J. Du, T. P. Yoon, *J. Am. Chem. Soc.* **2009**, *131*, 14604.

[5] a) C. Dai, J. M. R. Narayanam, C. R. J. Stephenson, *Nat. Chem.* **2011**, *3*, 140; b) A. G. Condie, J. C. González-Gómez, C. R. J. Stephenson, *J. Am. Chem. Soc.* **2010**, *132*, 1464; c) J. M. R. Narayanam, J. W. Tucker, C. R. J. Stephenson, *J. Am. Chem. Soc.* **2009**, *131*, 8756; d) D. B. Freeman, L. Furst, A. G. Condie, C. R. J. Stephenson, *Org. Lett.* **2012**, *14*, 94; e) J. W. Tucker, J. M. R. Narayanam, P. S. Shah, C. R. J. Stephenson, *Chem. Commun.* **2011**, *47*, 5040; f) J. W. Tucker, J. M. R. Narayanam, S. W. Krabbe, C. R. J. Stephenson, *Org. Lett.* **2010**, *12*, 368; g) L.

Furst, B. S. Matsuura, J. M. R. Narayanam, J. W. Tucker, C. R. J. Stephenson, *Org. Lett.* **2010**, *12*, 3104; h) J. W. Tucker, J. D. Nguyen, J. M. R. Narayanam, S. W. Krabbe, C. R. J. Stephenson, *Chem. Commun.* **2010**, *46*, 4985; i) J. W. Tucker, C. R. J. Stephenson, *Org. Lett.* **2011**, *13*, 5468; j) L. Furst, J. M. R. Narayanam, C. R. J. Stephenson, *Angew. Chem.* **2011**, *123*, 9829; *Angew. Chem. Int. Ed.* **2011**, *50*, 9655; k) J. D. Nguyen, J. W. Tucker, M. D. Konieczynska, C. R. J. Stephenson, *J. Am. Chem. Soc.* **2011**, *133*, 4160.

[6] a) D. Kalyani, K. B. McMurtrey, S. R. Neufeldt, M. S. Sanford, *J. Am. Chem. Soc.* **2011**, *133*, 18566; b) R. S. Andrews, J. J. Becker, M. R. Gagné, *Angew. Chem.* **2010**, *122*, 7432; *Angew. Chem. Int. Ed.* **2010**, *49*, 7274; c) R. S. Andrews, J. J. Becker, M. R. Gagné, *Org. Lett.* **2011**, *13*, 2406; d) M. Rueping, C. Vial, R. M. Koenigs, K. Poscharny, D. C. Fabry, *Chem. Commun.* **2011**, *47*, 2360; e) M. Rueping, S. Zhu, R. M. Koenigs, *Chem. Commun.* **2011**, *47*, 8679; f) M. Rueping, D. Leonori, T. Poisson, *Chem. Commun.* **2011**, *47*, 9615; g) J. Xuan, Y. Cheng, J. An, L.-Q. Lu, X.-X. Zhang, W.-J. Xiao, *Chem. Commun.* **2011**, *47*, 8337; h) Y.-Q. Zou, L.-Q. Lu, L. Fu, N.-J. Chang, J. Rong, J.-R. Chen, W.-J. Xiao, *Angew. Chem.* **2011**, *123*, 7309; *Angew. Chem. Int. Ed.* **2011**, *50*, 7171; i) G.-L. Zhao, C. Yang, L. Guo, H.-N. Sun, C. Chen, W.-J. Xia, *Chem. Commun.* **2012**, *48*, 2337; j) P. Kohls, D. Jadhav, G. Pandey, O. Reiser, *Org. Lett.* **2012**, *14*, 672; k) T. Maji, A. Karmakar, O. Reiser, *J. Org. Chem.* **2011**, *76*, 736; l) Y.-Q. Zou, J.-R. Chen, X.-P. Liu, L.-Q. Lu, R. L. Davis, K. A. Jorgensen, W.-J. Xiao, *Angew. Chem.* **2012**, *124*, 808; *Angew. Chem. Int. Ed.* **2012**, *51*, 784; m) X.-H. Ju, Y. Liang, P.-J. Jia, W.-F. Li, W. Yu, *Org. Biomol. Chem.* **2012**, *10*, 498; n) M. Rueping, R. M. Koenigs, K. Poscharny, D. C. Fabry, D. Leonori, C. Vila, *Chem. Eur. J.* **2012**, *18*, 5170.

[7] H. Sasabe, J. Kido, *Chem. Mater.* **2011**, *23*, 621.

[8] D. M. Hedstrand, W. H. Kruizinga, R. M. Kellogg, *Tetrahedron Lett.* **1978**, *19*, 1255.

[9] J. B. Brazier, N. C. O. Tomkinson, *Top. Curr. Chem.* **2010**, *291*, 281.

[10] G. J. Rowlands, *Tetrahedron* **2010**, *66*, 1593.

[11] It should be noted that, when the organic dye-type photocatalyst Eosin Y was used in place of $[Ru(bpy)_3]Cl_2\cdot 6H_2O$ in the same reaction under otherwise identical reaction conditions, **3** was formed in a lower yield (ca. 45%), thus demonstrating the feasibility of an organic-dye-catalyzed, visible-light-promoted C–C bond cleavage in such systems. For a pioneering study in this field, see: D. P. Hari, B. König, *Org. Lett.* **2011**, *13*, 3852.

[12] The amino radical intermediate generated in situ can also be intercepted and spectroscopically characterized; see the Supporting Information.

[13] K. Dietliker, T. Jung, J. Benkhoff, H. Kura, A. Matsumoto, H. Oka, D. Hristova, G. Gescheidt, G. Rist, *Macromol. Symp.* **2004**, *217*, 77.

[14] For visible-light-induced photopolymerizations, see: a) M.-A. Tehfe, J. Lalevée, F. Morlet-Savary, B. Graff, N. Blanchard, J.-P. Fouassier, *Macromolecules* **2012**, *45*, 1746; b) J. Lalevée, M. Peter, F. Dumur, D. Gigmes, N. Blanchard, M.-A. Tehfe, F. Morlet-Savary, J.-P. Fouassier, *Chem. Eur. J.* **2011**, *17*, 15027; c) M.-A. Tehfe, J. Lalevée, F. Morlet-Savary, B. Graff, N. Blanchard, J.-P. Fouassier, *ACS Macro. Lett.* **2012**, *1*, 198.

[15] R. C. Larock, *Comprehensive Organic Transformations: A Guide to Functional Group Preparations*, Wiley-VCH, 2nd ed., **1999**.