ORGANIC
LETTERS

2012
Vol. 14, No. 3
672–675

Visible Light Photoredox Catalysis: Generation and Addition of *N*-Aryltetrahydroisoquinoline-Derived α-Amino Radicals to Michael Acceptors

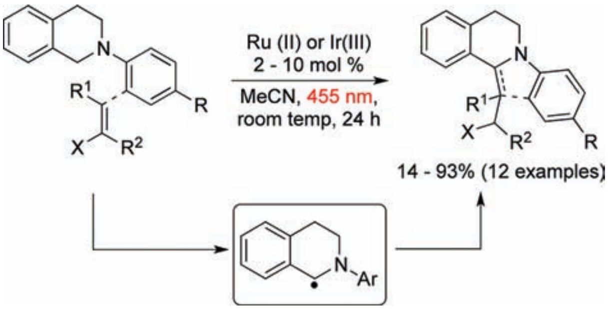
Paul Kohls,[†] Deepak Jadhav,[†,‡] Ganesh Pandey,[*,‡] and Oliver Reiser[*,†]

Institut für Organische Chemie, Universität Regensburg, Universitätsstrasse 31, 93053 Regensburg, Germany, and Division of Organic Chemistry, National Chemical Laboratory, Dr. Homi Bhabha Road, Pune-411 008, India

Oliver.Reiser@chemie.uni-regensburg.de; gp.pandey@ncl.res.in

Received October 23, 2011

ABSTRACT



The photoredox-catalyzed coupling of *N*-aryltetrahydroisoquinoline and Michael acceptors was achieved using Ru(bpy)$_3$Cl$_2$ or [Ir(ppy)$_2$-(dtb-bpy)]PF$_6$ in combination with irradiation at 455 nm generated by a blue LED, demonstrating the trapping of visible light generated α-amino radicals. While intermolecular reactions lead to products formed by a conjugate addition, in intramolecular variants further dehydrogenation occurs, leading directly to 5,6-dihydroindolo[2,1-*a*]tetrahydroisoquinolines, which are relevant as potential immunosuppressive agents.

In recent years, there has been increasing interest in the use of visible light to drive organic reactions because of its infinite availability, ease of handling, and promising application in industry.[1] Generally, photosensitizers or photocatalysts are required in such processes due to the inability of many organic molecules to absorb in the range between 400 and 800 nm.[2] Photoredoxcatalysts induce exchange of electrons with interacting substrates owing to their well-defined redox potential differences and hence generate potentially active ion radicals. The unique features of these photosensitized and photocatalyzed reactions are associated with the generation and subsequent facile cleavage of radical ions into radicals and ions, providing the basis for the development of many new and useful organic synthetic conversions.[3] In particular, one-electron oxidation of tertiary amines is known to produce planar radical cations, which in polar solvents

---

[†] Universität Regensburg.

[‡] National Chemical Laboratory.

(1) Leading reviews: (a) Narayanam, J. M. R.; Stephenson, C. R. J. *Chem. Soc. Rev.* **2011**, *40*, 102. (b) Yoon, T. P.; Ischay, M. A.; Du, J. N. *Nature Chem.* **2010**, *2*, 527. (c) Teplý, F. *Collect. Czech. Chem. Commun.* **2011**, *76*, 859. (d) Zeitler, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 9785.

(2) (a) Srinivasan, R. *J. Am. Chem. Soc.* **1963**, *85*, 3048. (b) Salomon, R. G.; Kochi, J. K. *J. Am. Chem. Soc.* **1974**, *96*, 1137. (c) Kochi, J. K. *Angew. Chem., Int. Ed.* **1988**, *27*, 1227.

(3) (a) DeLaive, P. J.; Lee, J. T.; Sprintschnik, H. W.; Abruna, H.; Meyer, T. J.; Whitten, D. G. *J. Am. Chem. Soc.* **1977**, *99*, 7094. (b) Nicewicz, D., A.; MacMillan, D. W. C. *Science* **2008**, *322*, 77. (c) Pham, P. V.; Nagib, D. A; MacMillan, D. W. C. *Angew. Chem., Int. Ed.* **2011**, *50*, 6119. (d) Ischay, M. A.; Anzovino, M. E.; Du, J.; Yoon, T. P. *J. Am. Chem. Soc.* **2008**, *130*, 12886. (e) Du, J.; Ruiz Espelt, L.; Guzei, I. A.; Yoon, T. P. *Chem. Sci.* **2011**, *2*, 2115. (f) Narayanam, J. M. R.; Tucker, J. W.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2009**, *131*, 8756. (g) Dai, C.; Narayanam, J. M. R.; Stephenson, C. R. J. *Nature Chem.* **2011**, *3*, 140. (h) Neumann, M.; Füldner, S.; König, B.; Zeitler, K. *Angew. Chem., Int. Ed.* **2010**, *123*, 981.

(4) (a) Lewis, F. D.; Ho, T.-I.; Simpson, J. T. *J. Org. Chem.* **1981**, *46*, 1077. (b) Lewis, F. D.; Ho, T.-I.; Simpson, J. T. *J. Am. Chem. Soc.* **1982**, *104*, 1924. (c) Lewis, F. D. *Acc. Chem. Res.* **1986**, *19*, 401. (d) Chow, Y. L.; Danen, W. C.; Nelsen, S. F.; Rosenblatt, D. H. *Chem. Rev.* **1978**, *78*, 243.

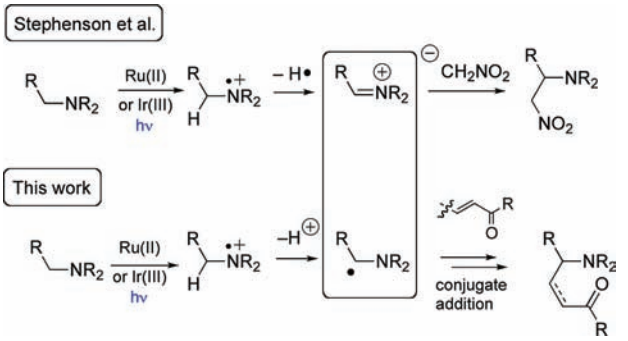
10.1021/ol202857t

undergo facile deprotonation, subject to kinetic acidity and stereoelectronic factors, to produce α-amino radicals (eq 1).[4]

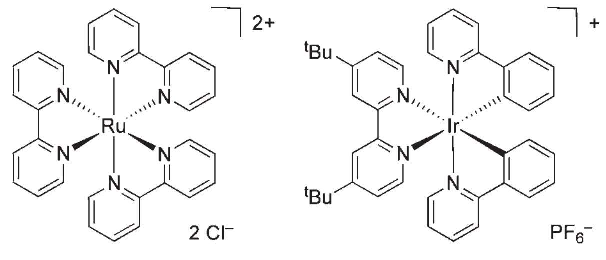
$$R_2NCHR'_2 \xrightarrow{-e^-} R_2\overset{\bullet +}{N}CHR'_2 \xrightarrow{-H^+} R_2N\overset{\bullet}{C}R'_2 \xrightarrow{-e^-} R_2\overset{+}{N}=CR'_2 \qquad (1)$$

Depending on the reaction conditions, the generated α-amino radicals could either react as a nucleophile with a suitable substrate or could undergo further one-electron oxidation due to their reduced ionization potential to form iminium cations, thus serving as an electrophile. Stephenson et al.[5a] have demonstrated the latter concept in combination with visible light photoredox catalysis by trapping the iminium cation of *N*-phenyltetrahydroisoquinoline with nitromethane (Scheme 1), which was subsequently demonstrated with other nucelophiles as well.[5b−e]

Scheme 1. Photocatalyzed α-Alkylation of Amines



Given our interest in photoredox processes[6] and α-functionalization of pyrrolidines and piperidines,[7] we were questioning if also the former process, i.e., the utilization of α-amino radicals as synthetically useful intermediates, can be realized by visible light driven photoredox catalysis (Figure 1).[8] We report here the successful realization of this concept with the coupling of teritiary amines and α,*β*-unsaturated carbonyl compounds in conjugate additions, contrasting copper(I) bromide catalyzed oxidative couplings of the same reaction partners reported by Bohle et al.[9]



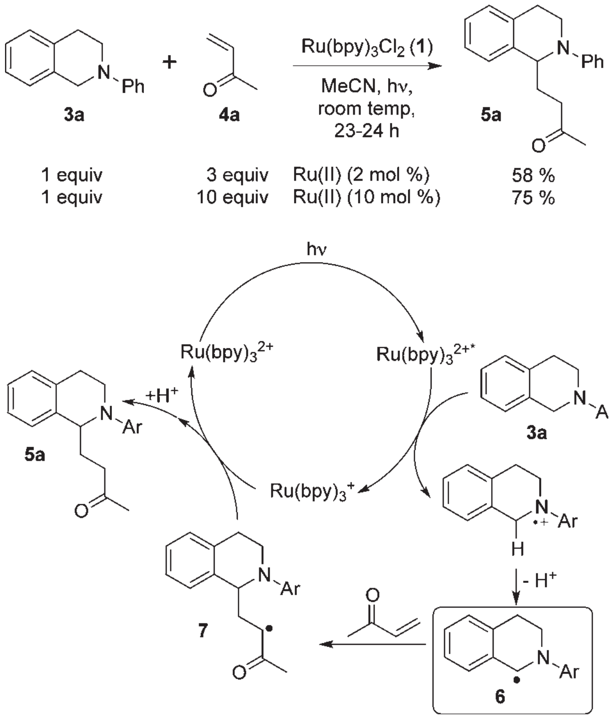
1 (Ru(bpy$_3$)Cl$_2$)   **2** ([Ir(ppy)$_2$(dtb-bpy)]PF$_6$)

Figure 1. Photoredoxcatalysts used in this work.

We began our investigation by irradiating a mixture of *N*-phenyltetrahydroisoquinoline (**3a**, 1 equiv) and methyl vinyl ketone (**4a**, 3 equiv) in the presence of catalytic amounts of Ru(bpy)$_3$Cl$_2$·6H$_2$O (**1**, 2 mol %) in degassed acetonitrile with a blue light emitting diode (LED; λ_{max} = 455 nm) gave rise to the conjugate addition product **5a** in 58% yield (Scheme 2). Increasing the amount of **4a** (10 equiv) and the ruthenium catalyst (10 mol %) resulted in an improvement of yield for **5a** (75%).

The formation of **5a** suggests α-amino radical **6** as a viable intermediate that subsequently undergoes conjugate addition to **7** followed by its reduction/protonation with concurrent regeneration of the ruthenium catalyst (Scheme 2).

Scheme 2. Photocatalyzed α-Functionalization of *N*-Phenylisoquinoline (**3**)



Further evidence for the occurrence of **6** was found by analyzing the crude product mixture by mass spectrometry

---

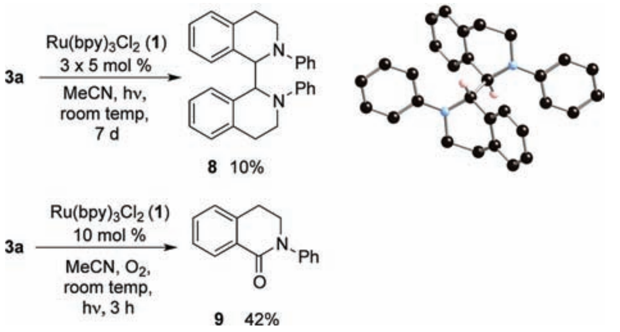
(5) (a) Condie, A. G.; Gonzalez-Gomez, J. C.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2010**, *132*, 1464. (b) Hari, D. P.; König, B. *Org. Lett.* **2011**, *13*, 3852. (c) Rueping, M.; Vila, C.; Koenigs, R. M.; Poscharny, K.; Fabry, D. C. *Chem. Commun.* **2011**, *47*, 2360. (d) Rueping, M.; Zhu, S.; Koenigs, R. M. *Chem. Commun.* **2011**, *47*, 8679. (e) Rueping, M.; Zhu, S.; Koenigs, R. M. *Chem. Commun.* **2011**, *47*, 12709.

(6) (a) Pandey, G. Photoinduced Redox Reactions in Organic Synthesis. In *Molecular and Supramolecular Photochemistry*; Ramamurthy, V., Ed.; Marcel-Dekker Inc.: New York, 1997; Vol. 1, p 245. (b) Pandey, G. Photoinduced Electron Transfer (PET) in Organic Synthesis. *Top. Curr. Chem.* **1993**, *168*, 175. (c) Pandey, G.; Rani, K. S.; Lakshmaiah, G. *Tetrahedron Lett.* **1992**, *33*, 5107. (d) Pandey, G. *Synlett* **1992**, 546. (e) Maji, T.; Karmakar, A.; Reiser, O. *J. Org. Chem.* **2011**, *76*, 736.

(7) (a) Heimgärtner, G.; Raatz, D.; Reiser, O. *Tetrahedron* **2005**, *61*, 643. (b) Bodmann, K.; Bug, T.; Steinbeisser, S.; Kreuder, R.; Reiser, O. *Tetrahedron Lett.* **2006**, *47*, 2061. (c) Gheorghe, A.; Schulte, M.; Reiser, O. *J. Org. Chem.* **2006**, *71*, 2173.

in which a prominent peak of 2-fold the mass of **6** was observed. Irradiation of **3a** under identical conditions in the absence of methyl vinyl ketone indeed results in the formation of **8** as a mixture of diastereomers. One of those was obtained in pure form allowing its structural assignment by X-ray analysis (Scheme 3).

Scheme 3. Photoredox-Catalyzed Reactions of *N*-Phenyltetrahydroisoquinoline (**3a**) in the Absence and Presence of Oxygen



Moreover, when the reaction solution was not deoxygenated, **9** was isolated instead, which can be explained by initial coupling of **6** with ground-state oxygen or by reaction with O_2^- generated through regeneration of $Ru(bpy)_3^{2+}$ via an electron transfer by $Ru(bpy)_3^+$ to dissolved air in the solvent (Scheme 3).[10]

These findings also support the intermediacy of **6** en route to its corresponding iminium cation, being so far the only species that could be trapped in a visible light photo redox process.[5] Very recently, compelling evidence for **6** was given by ESR measurements;[11] additionally, new studies have been reported that prove α-amino radicals as valuable synthetic intermediates in visible light photoredox processes.[12,13]

A representative spread of *N*-aryltetrahydroisoquinolines and acceptor-substituted alkenes was investigated (Figure 2) in this coupling reaction. In addition to $Ru(bpy)_3Cl_2$ (**1**), we also tested $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ (**2**) as photoredoxcatalyst, which proved to be superior in some but not all cases. Using 2−5 mol % catalyst and irradiation at 455 nm (blue LED), aldehydes and ketones gave the expected conjugate addition products with moderate to excellent yields (43−93%), while *exo*-methylene-γ-butyrolactone and acrylonitrile, most likely due to competing polymerization reactions, were less effective substrates (31−33% yield). *N*-Phenylpyrrolidine gave the coupling product **5j** with methyl vinyl ketone in low yields and only in the presence of iridium catalyst **2**, pointing to the necessity of an activating substituent on the α-position as also noted for the corresponding iminium cation chemistry.[5]

There seems to be quite a delicate balance with respect to electronic factors on both coupling partners, which also seem to interplay with the type of catalyst used in the process. While in all cases attack on the β-position of the α,β-unsaturated carbonyl compound is observed, pointing toward the nucleophilic nature[14] of **6**, increasing the donor character of the latter by switching the *N*-α-substituent from phenyl to *p*-methoxyphenyl resulted in a pronounced decrease in yield when iridium catalyst **2** was employed (**5a**/**5b** and **5d**/**5e**). On the other hand, switching from phenyl vinyl ketone to *p*-methoxyphenyl vinyl

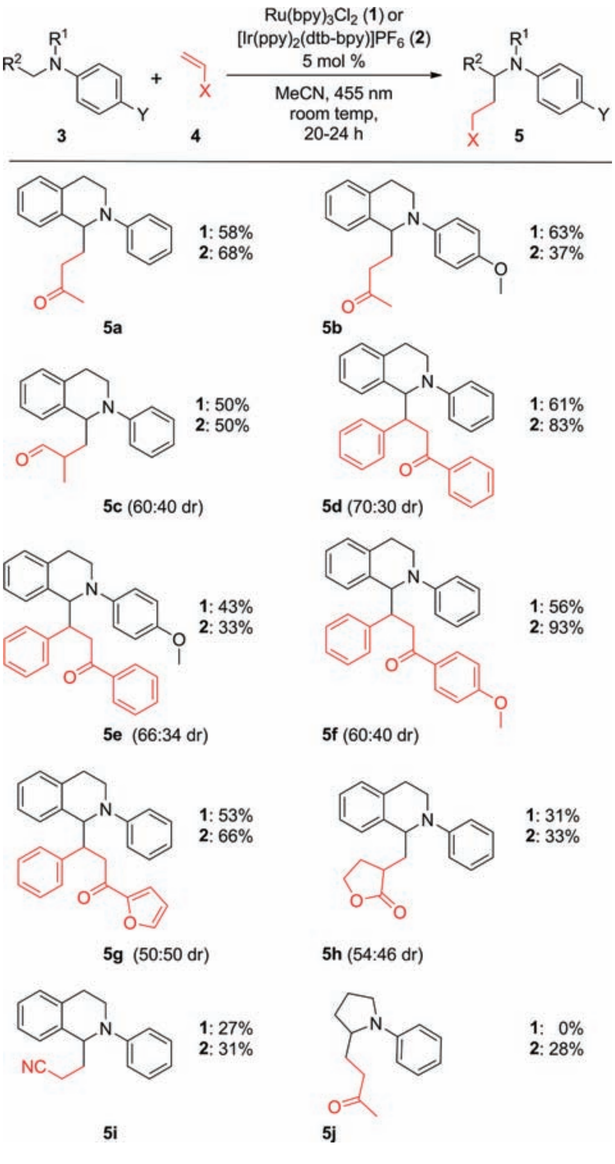


Figure 2. Photoredox-catalyzed coupling of *N*-arylamines (**3**) and Michael acceptors **4**.

---

(8) For pioneering work demonstrating the α-functionalization of tertiary amines under UV light irradiation, see: (a) Bertrand, S.; Glapski, C.; Hoffmann, N.; Pete, J.-P. *Tetrahedron Lett.* **1999**, *40*, 3169. (b) Bertrand, S.; Hoffmann, N.; Pete, J.-P. *Eur. J. Org. Chem.* **2000**, 2227. (c) Harakat, D.; Pesch, J.; Marinkovic, S.; Hoffmann, N *Org. Biomol. Chem.* **2006**, *4*, 1202. For the visible light generation and trapping of α-glucosyl radicals, see: (d) Andrews, R. S.; Becker, J. J.; Gagne, M. R. *Angew. Chem., Int. Ed.* **2010**, *49*, 7274. (e) Andrews, R. S.; Becker, J. J.; Gagne, M. R. *Org. Lett.* **2011**, *13*, 2406.

(9) Li, Z. P.; Bohle, D. S.; Li, C. J. *Proc. Nat. Acad. Sci. U.S.A.* **2006**, *103*, 8928.

(10) Anderson, C. P.; Salmon, D. J.; Meyer, T. J.; Young, R. C. *J. Am. Chem. Soc.* **1977**, *99*, 1980.

ketone, the latter being a weaker acceptor[14] than the former, resulted in an increase of yield when iridium catalyst **2** was used, resulting in almost quantitative product formation of **5f** (93%).

When applicable, the products were formed as diastereomeric mixtures: For **5d**–**i**, the relative configuration of the major diastereomer can be tentatively assigned on the basis of the X-ray-structure of (*R**,*S**)-**5d**, which was obtained diastereomerically pure by recrystallization (Figure 3).

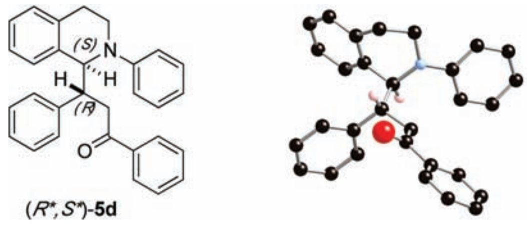
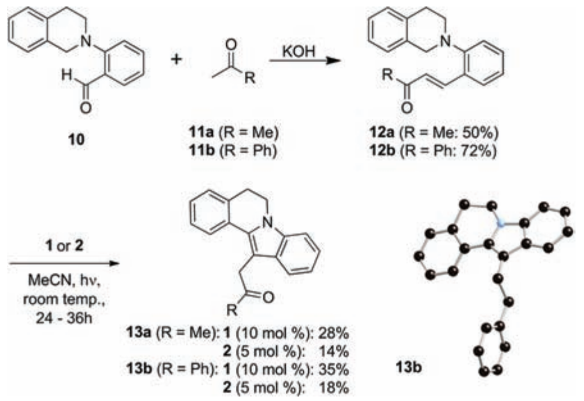


Figure 3. X-ray structure of (*R**,*S**)-**5d**.

Investigating the photocatalyzed coupling of **12**, being readily available from **10** and acetone (**11a**) or acetophenone (**11b**), respectively, as an example for substrates poised for undergoing intramolecular couplings, followed a different reaction pathway: We observed in addition to the expeceted cyclization also dehydrogenation, leading directly to the 5,6-dihydroindolo[2,1-*a*]-tetrahydroisoquinoline **13** (Scheme 4), a class of compounds that have been found to exhibit significant immunosuppresive activity against IL-2, IL-10, and IFN-γ.[15] However, the yields in which **13** is obtained are clearly not satisfactory, and it is surprising to note that the intermolecular process apparently proceeds more efficiently than the intramolecular variant.

Scheme 4. Synthesis of 5,6-Dihydroindolo[2,1-*a*]-tetrahydroisoquinolines **13**



In conclusion, we have developed a new visible light driven photocatalytic C–C-coupling between *N*-aryl-tetrahydroisoquinolines and Michael acceptors, suggesting α-amino radicals as key intermediates.

Acknowledgment. This work was supported by the DFG (Graduiertenkolleg 1626 Photocatalysis), Bayerische Graduietenförderung (fellowship PK) and the DAAD (Indigo). We are grateful to Dr. M. Zabel and S. Stempfhuber for carrying out X-ray structure analyses.

Supporting Information Available. Experimental procedures, characterization, ^{1}H and ^{13}C NMR spectra, and details on X-ray structures. This material is available free of charge via the Internet at http://pubs.acs.org.

---

(11) While this work was under review, the visible light mediated reaction of **3a** catalyzed by eosine was reported. By ESR-spectroscopy **6** could be characterized, which further broke down to its corresponding iminium cation being trapped by nitroalkanes: Liu, Q.; Li, Y-N; Zhang, H-H; Chen, B.; Tung, C-H; Wu, L-Z *Chem.—Eur. J.* **2012**, *18*, 620.

(12) While this work was under review, the visible light mediated trapment of α-amino radicals and 1,4-dicyanobenzene catalyzed by Ir(III) complexes was reported: McNally, A.; Proer, C. K.; MacMillan, D. W. C. *Science* **2011**, *334*, 1114.

(13) While this work was under review, the oxidation of **6** by $BrCCl_3$ as an efficent way to generate its corresponding iminium cation followed by trapping with nucelophiles was reported: Freemen, D. B.; Furst, L.; Condie, A. G.; Stephenson, C. R. J. *Org. Lett.* **2012**, *14*, 94.

(14) Cf. de Vleeschouwer, F.; van Speybroeck, V.; Waroquier, M.; Gerrlings, P.; de Proft, F. *Org. Lett.* **2007**, *9*, 2721.

(15) Kraus, G. A.; Gupta, V.; Kohut, M.; Singh, N. *Biorg. Med. Chem. Lett.* **2009**, *19*, 5539.