

Visible-Light Photoredox Catalysis: Aza-Henry Reactions via C–H Functionalization

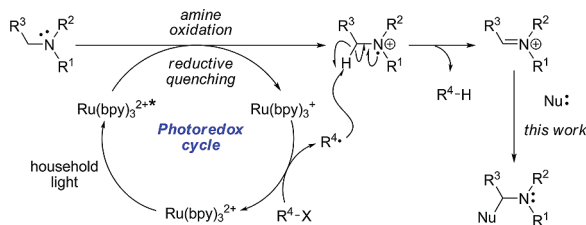
Allison G. Condie, José C. González-Gómez, and Corey R. J. Stephenson*

Department of Chemistry, Boston University, Boston, Massachusetts 02215

Received October 27, 2009; E-mail: crjsteph@bu.edu

The catalytic oxidation of sp^3 C–H bonds adjacent to nitrogen provides reactive imines or iminium ions and is a powerful method for amine functionalization.¹ Preliminary mechanistic investigations during our recent studies of photoredox catalysis for reductive dehalogenation reactions² suggested that iminium ions were likely byproducts in the reaction using tertiary amines as reductants (Scheme 1).^{3,4} In light of the mechanism presented in Scheme 1, we anticipated that with an appropriately chosen oxidant (R^4 –X functions as an oxidant in this reaction), the generated iminium ion could be trapped by a variety of nucleophiles under photoredox conditions. Indeed, radical cation intermediates generated under electrochemical,^{5a} metal-^{5b} or electron-transfer-mediated^{5c,d} oxidation conditions have been shown to undergo decomposition to give the corresponding imines.^{5e} In this communication, we describe the realization of the generation of iminium ions under photoredox conditions in the context of an oxidative aza-Henry reaction.⁶

Scheme 1. Iminium Ion Generation Using Photoredox Catalysis



Our initial studies focused on tetrahydroisoquinoline **1**, a substrate that is known to undergo oxidative C–H functionalization by Ru(III),⁷ Cu(I),⁸ and, as shown more recently, V(IV)⁹ or I(III).¹⁰ Using conditions closely related to those we used for reductive dehalogenation, we subjected **1** to oxidation using diethyl bromomalonate (**5**) as the stoichiometric oxidant.² After 2 h, **1** was converted into a more polar compound upon treatment with 2 mol % Ru(bpy)₃Cl₂ in *N,N*-dimethylformamide (DMF) in the presence of **5** (Table 1, entry 1), providing methoxyaminal **2** (X = OMe) in 73% yield. Use of CH₃OH as the solvent for the reaction also resulted in the complete conversion of **1** to the methoxyaminal (entry 2). We were surprised to find that the latter compound was formed even in the absence of **5**; however, the reaction was significantly slower (entry 3). From this surprising result, a change of solvent to nitromethane provided the oxidative Henry reaction product in 81% isolated yield after 20 h (entry 4). Degassing the reaction slowed the reaction (76% conversion after 20 h; entry 5), indicating that adventitious oxygen in the reaction may play a role in the mechanism but is not explicitly required. The use of a more reactive iridium catalyst,¹¹ Ir(ppy)₂(dtbbpy)PF₆, **4**,^{4d,12} significantly accelerated the reaction, and complete conversion was observed after 10 h (92% isolated yield; entry 6). Importantly, no conversion was observed when the reaction was conducted in the dark (entry 7), while a very slow background reaction (83% conversion after ~7.5 days) was observed in the absence of catalyst (entry 8).

Table 1. Oxidative Iminium Ion Generation and Trapping

entry	conditions ^a	conversion ^b (yield ^c)
1	3 (2 mol %), (EtO ₂ C) ₂ CHBr (5 , 1.5 equiv) DMF, 2 h; X = OCH ₃	100 (73) ^d
2	3 (1 mol %), 5 (1.5 equiv), CH ₃ OH, 2 h; X = OCH ₃	100
3	3 (1 mol %), no additive , CH ₃ OH, 16 h; X = OCH ₃	100
4	3 (1 mol %), CH ₃ NO ₂ , 20 h; X = CH ₂ NO ₂	100 (81)
5	3 (1 mol %), CH ₃ NO ₂ , 20 h; X = CH ₂ NO ₂ ; reaction was degassed	76
6	4 (1 mol %), CH ₃ NO ₂ , 10 h; X = CH ₂ NO ₂	100 (92)
7	4 (1 mol %), no light , CH ₃ NO ₂ , 48 h; X = CH ₂ NO ₂	0
8	no catalyst , CH ₃ NO ₂ , 180 h; X = CH ₂ NO ₂	83

^a With the exception of entry 5, the reactions were not rigorously degassed. ^b Calculated on the basis of crude ¹H NMR analysis. ^c Isolated yield after purification by chromatography on SiO₂. ^d Purified on SiO₂ using CH₃OH as a cosolvent.

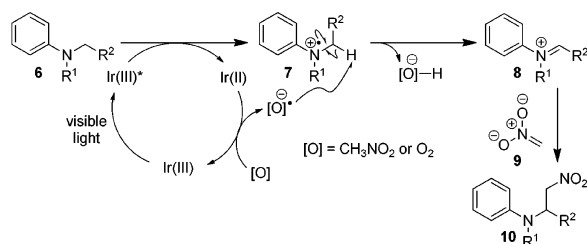
A variety of *N*-aryltetrahydroisoquinolines were subjected to the optimized conditions [**4** (1 mol %), RCH₂NO₂, r.t.] and uniformly afforded the desired coupling products in excellent yields (90–96%; Table 2, entries 1–8). Both nitromethane (entries 1, 3, and 5–9) and nitroethane (entries 2 and 4) provided the desired products. The reaction was generally insensitive to electronic effects on the aromatic rings (entries 3–8). Although the process was markedly slower, C–H oxidation of a nonbenzylic amine cleanly afforded the desired coupling product in moderate yield (40% conversion after 72 h; entry 9). These results compare favorably with the known oxidative aza-Henry reaction reported by Li and co-workers using Cu(I) and ^tBuOOH.^{6b,c} Although the Cu-mediated process is faster, the Ir-mediated process reported herein provides the desired products in higher yields, with the notable exception of the unactivated amine in entry 9.

Both light and catalyst are required for efficient conversion to the aza-Henry products (Table 1, entries 7 and 8). In addition, the exclusion of oxygen from the reaction results in a lower rate (Table 1, entry 5). Since nitrobenzene is a known oxidative quencher of Ru(bpy)₃^{2+*},¹³ we could not immediately rule out possible mechanisms involving this pathway. Accordingly, we conducted a series of fluorescence quenching experiments in which the fluorescence emission of a solution of **4** in CH₃NO₂ was found to be decreased by **1** in a concentration-dependent fashion, implicating the amine as a reductive quencher of the excited-state iridium complex.¹⁴ On the basis of this information, we propose the following mechanism for the C–H oxidation/aza-Henry reaction under photoredox catalysis (Scheme 2). Radical cation **7** is formed by reductive quenching of the excited state of **4** by **6**, forming the powerful reducing agent Ir²⁺ [Ir(III)/Ir(II) –1.51 V vs SCE]. Catalyst turnover may be accomplished by the reduction of nitromethane to its radical anion and/or adventitious

Table 2. Oxidative Aza-Henry Reaction

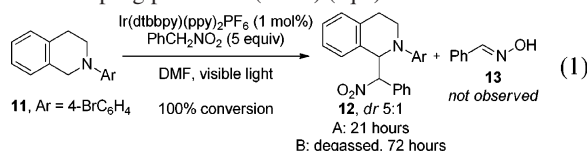
entry	substrate ^f	product	time (h)	yield (%) ^a
1			10	92 ^b
2			16	96 ^{b,c}
3			18	96 ^b
4			18	92 ^{b,d}
5			16	90 ^b
6			13	93 ^b
7			13	92 ^b
8			18	95 ^b
9			72	27 ^{b,e}

^a Isolated yield after purification on SiO₂. ^b Conditions: **4** (1.0 mol %), visible light, CH₃NO₂, rt. ^c dr = 2:1. ^d dr = 2.3:1. ^e Conversion = 40% as determined by crude ¹H NMR analysis. ^f See ref 15.

Scheme 2. Plausible Mechanism

oxygen.¹⁶ This radical anion may abstract a hydrogen atom from the trialkylammonium radical cation to form the desired iminium ion, **8**.² Addition of **9** to the iminium forms the observed product.

The product of nitromethane reduction is presumably nitrosomethane (or the oxime tautomer), neither of which were we able to observe in our reactions. We reasoned that the use of a less volatile nitro compound could provide evidence in favor of our proposed mechanism. Treatment of **11** with PhCH₂NO₂ (5 equiv) in DMF in the presence of Ir(dtbbpy)(ppy)₂PF₆ (1 mol %) and visible light resulted in full conversion to the desired oxidative coupling product **12** (5:1 dr) (eq 1).¹⁷



We did not observe the presence of **13** by ¹H NMR analysis of the crude reaction mixture, indicating that catalyst turnover may proceed via reaction with oxygen. However, rigorous degassing of the reaction in eq 1 also resulted in clean formation of **12**, albeit with an attenuated rate, suggesting that the nitroalkane may also play a role in catalyst turnover. Importantly, these experiments demonstrate that the reaction

of nitro compounds other than those conveniently used as the solvent also cleanly provide the desired product using DMF as solvent.

In summary, we have reported an operationally simple method for the oxidative coupling of nitroalkanes with tertiary *N*-arylamines using visible-light photoredox catalysis. Importantly, the reaction proceeds in high chemical yield using only 1 mol % Ir(III) catalyst and visible light without the need for an external oxidant. Further studies expanding upon the scope of this transformation as well as further mechanistic investigations are currently underway.

Acknowledgment. Boston University and the Department of Chemistry are gratefully acknowledged for financial support. Acknowledgment is made to the donors of the American Chemical Society Petroleum Research Fund (48479-G1) for partial support of this research. NMR (CHE-0619339) and MS (CHE-0443618) facilities at BU are supported by the NSF. The authors thank Professor John Porco (Boston University) and Professor Peter Wipf (University of Pittsburgh) for critical comments on this manuscript.

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

References

- (1) (a) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335. (b) Murahashi, S.-I.; Zhang, D. *Chem. Soc. Rev.* **2008**, *37*, 1490.
- (2) Narayanan, J. M. R.; Tucker, J. W.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2009**, *131*, 8756.
- (3) For reviews of 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.; Barigelletti, F.; Campagna, S.; Belser, P.; von Zelewsky, A. *Coord. Chem. Rev.* **1988**, *84*, 85.
- (4) (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) Nagib, D. A.; Scott, M. E.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2009**, *131*, 10875. (e) Du, J.; Yoon, T. P. *J. Am. Chem. Soc.* **2009**, *131*, 14604. (f) Tucker, J. W.; Narayanan, J. M. R.; Krabbe, S. W.; Stephenson, C. R. J. *Org. Lett.* **2010**, *12*, 368.
- (5) (a) Shono, T.; Matsumura, Y.; Tsubata, K. *J. Am. Chem. Soc.* **1981**, *103*, 1172. (b) Murahashi, S.-I. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2443. (c) Kalyanasundaram, K.; Kiwi, J.; Grätzel, M. *Helv. Chim. Acta* **1978**, *61*, 2720. (d) DeLaive, P. J.; Sullivan, B. P.; Meyer, T. J.; Whitten, D. G. *J. Am. Chem. Soc.* **1979**, *101*, 4007. (e) Nelson, S. F.; Ippoliti, T. J. *J. Am. Chem. Soc.* **1986**, *108*, 4879.
- (6) (a) Arrayás, R. G.; Carretero, J. C. *Chem. Soc. Rev.* **2009**, *38*, 1940. (b) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2005**, *127*, 3672. (c) Basle, O.; Li, C.-J. *Green Chem.* **2007**, *9*, 1047.
- (7) (a) Murahashi, S.-I.; Nakae, T.; Terai, H.; Komiya, N. *J. Am. Chem. Soc.* **2008**, *130*, 11005. (b) Murahashi, S.-I.; Komiya, N.; Terai, H. *Angew. Chem., Int. Ed.* **2005**, *44*, 6931. (c) Murahashi, S.-I.; Komiya, N.; Terai, H.; Nakae, T. *J. Am. Chem. Soc.* **2003**, *125*, 15312.
- (8) (a) Basle, O.; Li, C.-J. *Chem. Commun.* **2009**, 4124. (b) Li, Z.; Bohle, S.; Li, C.-J. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 9828.
- (9) Sud, A.; Sureshkumar, D.; Klusmann, M. *Chem. Commun.* **2009**, 3169.
- (10) Shu, X.-Z.; Xia, X.-F.; Yang, Y.-F.; Ji, K.-G.; Liu, X.-Y.; Liang, Y.-M. *J. Org. Chem.* **2009**, *74*, 7464.
- (11) For a review of photoactive iridium complexes, see: Flamigni, L.; Barbieri, A.; Sabatini, C.; Ventura, B.; Barigelletti, F. *Top. Curr. Chem.* **2007**, *281*, 143.
- (12) For the preparation of Ir(ppy)₂(dtbbpy)PF₆, see: Slinker, J. D.; Gorodetsky, A. A.; Lowry, M. S.; Wang, J.; Parker, S.; Rohl, R.; Bernhard, S.; Malliaras, G. G. *J. Am. Chem. Soc.* **2004**, *126*, 2763.
- (13) Bock, C. R.; Connor, J. A.; Gutierrez, A. R.; Meyer, T. J.; Whitten, D. G.; Sullivan, B. P.; Nagle, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 4815.
- (14) See the Supporting Information for details.
- (15) *N*-Aryltetrahydroisoquinolines were prepared via Buchwald–Hartwig coupling (see: Kwong, F. Y.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 581). For an alternative approach to *N*-arylation, see: Barker, T. J.; Jarvo, E. R. *J. Am. Chem. Soc.* **2009**, *131*, 15598.
- (16) An insightful reviewer suggested that this reaction may be mediated by singlet O₂ sensitization by **4** (see: Demas, J. N.; Harris, E. W.; McBride, R. P. *J. Am. Chem. Soc.* **1977**, *99*, 3547). Initial mechanistic investigations provided the following data for the known singlet O₂-mediated oxidation of dibenzylamine to the corresponding imine (see: Jiang, G.; Chen, J.; Huang, J.-S.; Che, C.-M. *Org. Lett.* **2009**, *11*, 4568): Using **4** under an oxygen atmosphere, we observed only 12% conversion of dibenzylamine to its imine after 12 h (cf. TPP, O₂, 10–14 h). In contrast, we found that TPP is capable of mediating the oxidative aza-Henry reaction of **1**, but the reaction required 72 h for complete conversion compared with only 10 h under our conditions using **4**. See the Supporting Information for further details.
- (17) Full conversion of **11** to **12** was observed by crude ¹H NMR analysis, but **12** was not stable under purification by chromatography.

JA909145Y