Photoredox Catalysis

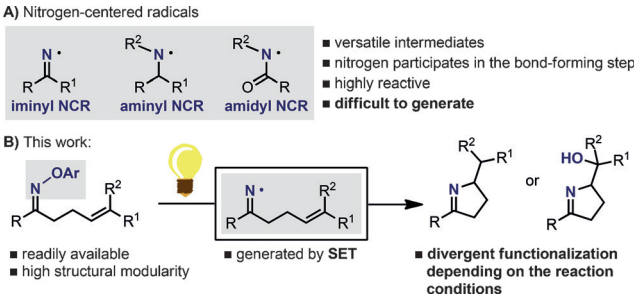
Deutsche Ausgabe: DOI: 10.1002/ange.201507641
Internationale Ausgabe: DOI: 10.1002/anie.201507641

Visible-Light-Mediated Generation of Nitrogen-Centered Radicals: Metal-Free Hydroimination and Iminohydroxylation Cyclization Reactions

*Jacob Davies, Samuel G. Booth, Stephanie Essafi, Robert A. W. Dryfe, and Daniele Leonori**

Abstract: *The formation and use of iminyl radicals in novel and divergent hydroimination and iminohydroxylation cyclization reactions has been accomplished through the design of a new class of reactive O-aryl oximes. Owing to their low reduction potentials, the inexpensive organic dye eosin Y could be used as the photocatalyst of the organocatalytic hydroimination reaction. Furthermore, reaction conditions for a unique iminohydroxylation were identified; visible-light-mediated electron transfer from novel electron donor–acceptor complexes of the oximes and Et_3N was proposed as a key step of this process.*

Nitrogen-centered radicals (NCRs) are a versatile class of intermediates that have wide applications in the synthesis of N-containing molecules (Scheme 1 A).[1] However, the difficulties associated with their generation have significantly thwarted their use in synthetic chemistry. In fact, established methods often rely on the homolysis of difficult-to-construct N–X bonds and require the use of toxic and hazardous reagents at elevated temperatures.[1a,2] The development of a mild, selective, and general method to catalytically generate NCRs from readily available precursors would enable the facile construction of many N-heterocycles, which are privileged motifs in natural products and therapeutic agents.[3]



Scheme 1. Nitrogen-centered radicals and divergent functionalization processes developed in this work.

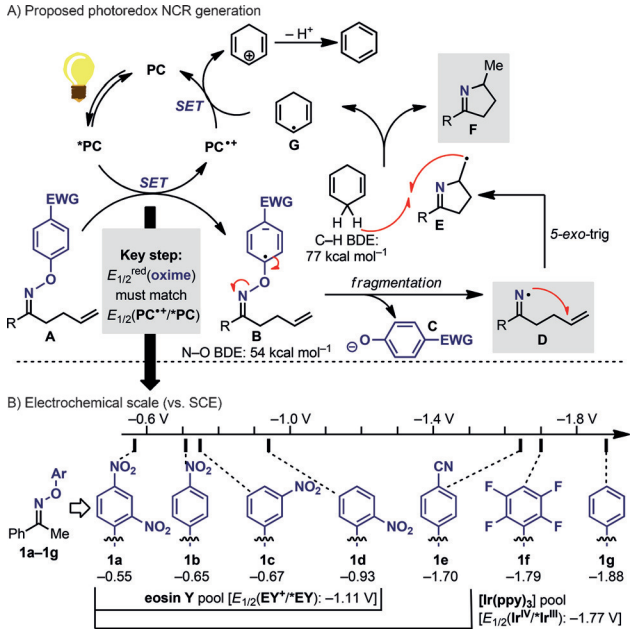
Photoredox catalysis has emerged as a powerful technique through which single electron transfer (SET) reactions can be performed under mild conditions.[4] MacMillan[5] and co-workers have developed an asymmetric visible-light-mediated amination of aldehydes by enamine catalysis, and the groups of Sanford,[6] Lee,[7] Yu,[8] and Luo[9] have reported the photoredox generation of phthalimidyl and saccharyl radicals and their use in Minisci-type reactions. The groups of Zheng[10] and Knowles[11] have developed a method for the photoredox generation of diaryl and aryl alkyl aminium radical cations and employed them in C–N bond-forming reactions.

Drawing inspiration from the work of Forrester,[12] Narasaka,[13] and Walton,[14] we speculated that appropriately functionalized *O*-aryl oximes could serve as general, bench-stable NCR precursors that could deliver iminyl radicals upon photoredox activation under mild conditions.[15] Such an approach would clearly benefit from the facile synthesis of aryl oximes, and we hoped that the high structural modularity of the *O*-aryl hydroxylamines would allow us to identify substrates that do not require the use of transition-metal-based photocatalysts.[16] Herein, we describe the successful implementation of this approach and the development of novel, transition-metal-free, visible-light-mediated hydroimination and iminohydroxylation cyclization reactions (Scheme 1 B).

The guiding principle of our photoredox NCR synthesis capitalized on the evidence that electron-poor aromatic compounds have reduction potentials compatible with SET reduction by visible-light-excited photocatalysts,[17] as shown by MacMillan and co-workers.[18] Our envisaged photoredox iminyl NCR generation was initiated by the visible-light-promoted excitation of a photocatalyst (PC→*PC)[19] followed by SET reduction of the aryl unit of oxime **A** to give radical anion **B** (Scheme 2 A). A fragmentation leading to phenoxide **C** and the desired NCR **D** was anticipated to occur next owing to the low bond dissociation energy of the N–O bond.[20] At this stage, we decided to test the viability of this activation mode by combining it with an intramolecular cyclization to synthesize valuable five-membered N-heterocycles.[21] After 5-*exo*-trig cyclization, the C-centered radical **E** was expected to abstract a H atom from 1,4-cyclohexadiene (CHD)[20b] to give the desired product **F** and radical **G**, which regenerates the photocatalyst by SET, closing the catalytic

[*] J. Davies, S. G. Booth, Prof. R. A. W. Dryfe, Dr. D. Leonori
School of Chemistry, University of Manchester
Oxford Road, Manchester, M13 9PL (UK)
E-mail: daniele.leonori@manchester.ac.uk
Dr. S. Essafi
School of Chemistry, University of Bristol
Cantock's Close, Bristol, BS8 1TS (UK)

Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under http://dx.doi.org/10.1002/anie.201507641.



Scheme 2. Proposed photoredox cycle and electrochemical studies. EY = eosin Y, ppy = 2-phenylpyridine.

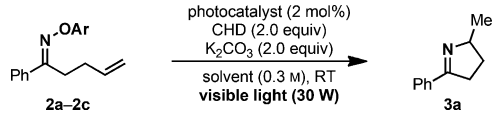
cycle. As *5-exo*-trig cyclizations occur rapidly ($k_c \approx 9 \times 10^3\ s^{-1}$ at RT),[22] we expected that the reaction yields would correlate with the efficiency of the photoredox system.

The SET between the visible-light-excited photocatalyst and the aryl oxime became a focal point. As the reduction potentials of many photocatalysts are known,[4a] we started our investigations by evaluating the redox profiles of various aryl oximes with the goal of identifying the most suitable/active substrates. Analysis of oximes **1a**–**1g** by cyclic voltammetry revealed irreversible reduction profiles that are in accordance with the expected fragmentation process. According to our electrochemical scale (Scheme 2B), almost all of the examined oximes are expected to undergo SET reduction by $*Ir^{III}$; whereas only the nitro-substituted substrates **1a**–**1d** have $E_{1/2}^{red}$ potentials suitable for SET with the excited state of the organic dye eosin Y.[23]

Based on these results, we selected oximes **2a**–**2c** as representative substrates for the evaluation of the proposed radical cyclization reaction (Table 1). To our delight, visible-light irradiation of **2a**–**2c** in the presence of $[Ir(ppy)_3]$, cyclohexadiene, and K_2CO_3 gave pyrroline **3a** in good to excellent yields (entries 2, 4, and 6). As predicted by the electrochemical studies, **2a** and **2b** furnished **3a** when eosin Y was used as the photocatalyst (entries 3 and 5), thus setting the stage for a fully organocatalytic photoredox hydroimination cyclization.

The substrate scope was evaluated with a focus on 2,4-dinitro-substituted aryl oximes owing to four favorable aspects: 1) The required hydroxylamine is commercially available, 2) these oximes are typically purified by crystallization, 3) their photoredox reactions do not require a transition-metal catalyst, and 4) the products can be purified by a simple acid–base wash (no chromatographic purification needed on the way from the ketone to the final product).

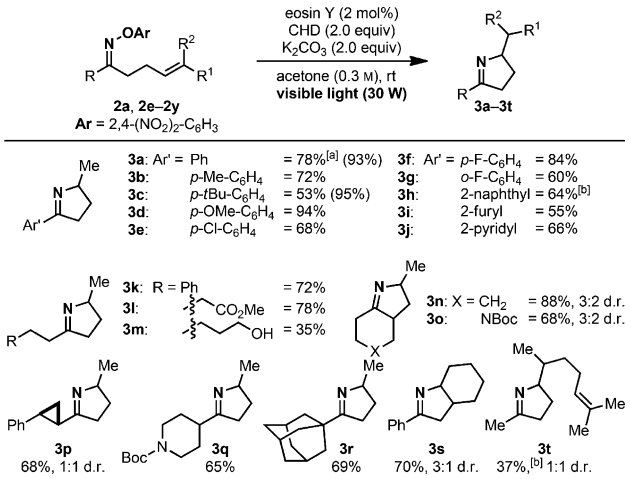
Table 1: Optimization of the hydroimination cyclization.



Entry	Substrate[a]	Photocatalyst	Solvent	Yield [%][b]
1	**2a**	$[Ir(ppy)_3]$	DMF	81
2	**2a**	eosin Y	DMF	68
3	**2a**	eosin Y	acetone	93[c]
4	**2b**	$[Ir(ppy)_3]$	DMF	53
5	**2b**	eosin Y	DMF	15
6	**2c**	$[Ir(ppy)_3]$	DMF	91
7	**2c**	eosin Y	DMF	7

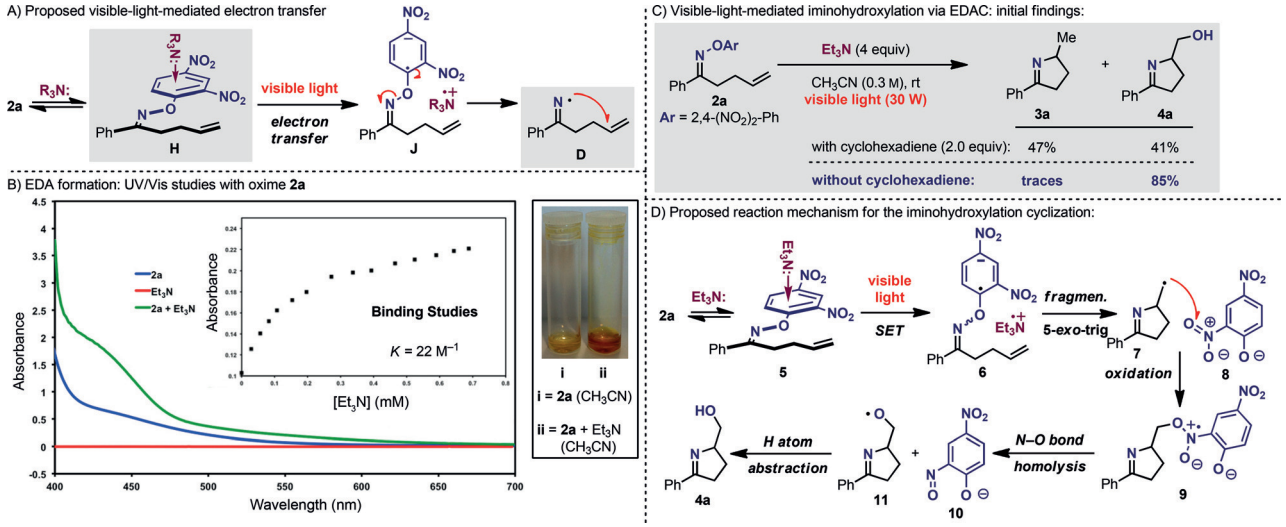
[a] **2a**: Ar = 2,4-$(NO_2)_2C_6H_3$; **2b**: Ar = 4-$(NO_2)C_6H_4$; **2a**: Ar = 4-$(CN)C_6H_4$. [b] Determined by ^1H NMR analysis; see the Supporting Information for control experiments. [c] 2,4-Dinitrophenol (**8**-H) was also isolated; see the Supporting Information.

A broad range of oximes with diverse electronic and steric properties participated efficiently in the visible-light-promoted process (Scheme 3). Bicyclic heterocycles were also obtained in good yields as well as products arising from the cyclization onto di- and trisubstituted olefins.



Scheme 3. Reaction scope. Yields of isolated products after acid–base wash are given. Yields determined by NMR spectroscopy are given in parentheses. [a] 1 mmol scale. [b] Reaction run in DMF. Boc = *tert*-butyloxycarbonyl.

Intrigued by the low reduction potential and LUMO energy[24] of the 2,4-dinitro-substituted aryl oxime **1a**, and inspired by the reports of Kochi,[25] Cossy,[26] and Melchiorre[27] on SET, we wondered whether a complementary activation mode could be exploited for the generation of NCRs by visible-light irradiation. As illustrated in Scheme 4A, we speculated that a simple tertiary amine would be able to reversibly interact with **2a** to give an electron donor–acceptor complex **H**.[28] Visible-light irradiation should then initiate a SET process to give the radical ion pair **J**.[29] Fragmentation to give **D**, *5-exo*-trig cyclization, and H atom



Scheme 4. A) Proposed visible-light-mediated electron transfer via an electron donor–acceptor complex for the hydroimination of *O*-aryl oximes. B) UV/Vis studies. C) Initial findings. D) Proposed reaction mechanism for the iminohydroxylation cyclization.

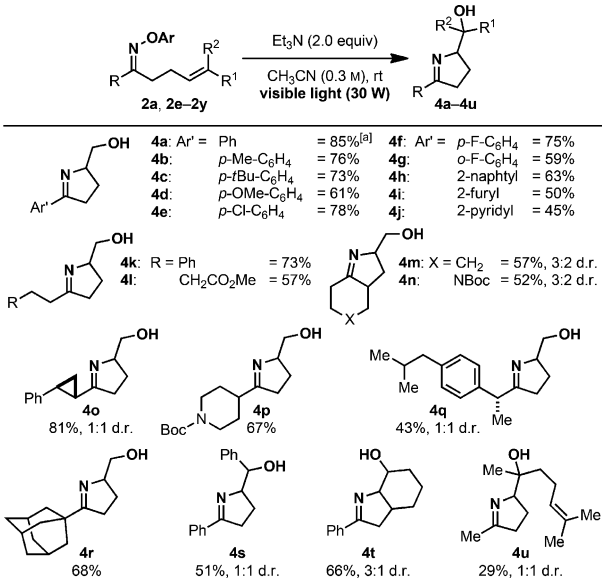
abstraction would deliver pyrroline **3a**. By using the Rehm–Weller equation for electron transfer [$\Delta G_{ET} = 0.24\,F(E_{1/2}^{Et_3N} - E_{1/2}^{2a}) - \Delta E_{excit} + \Delta E_{coul}$],[30] the process was calculated to be exergonic ($\Delta G \approx -30$ kcal mol^{-1}), which indicates a very favorable SET. UV/Vis spectroscopy data further corroborated this proposal. When a CH_3CN[31] solution of **2a** was treated with Et_3N, a bathochromic shift was observed, which indicates the formation of a donor–acceptor complex (Scheme 4B). The formation of such complexes has not been studied extensively, prompting us to evaluate the strength of this key interaction. By using Job's method, the **2a**/Et_3N stoichiometry in the complex was confirmed to be 1:1, and titration experiments gave an association constant of $K \approx 22\,M^{-1}$ (Scheme 4B). TD-DFT calculations [CAM-B3LYP/6-311++G(d,p) in CH_3CN] confirmed that absorption at approximately 440 nm is due to a transition from the nitrogen lone pair to the π^* orbital of the aromatic unit of the oxime.[24] Exposure of **2b** and **2c** to Et_3N (up to 10 equiv) did not lead to significant bathochromic shifts, which suggests that there is limited or no donor–acceptor complex formation.[24]

Encouraged by the UV/Vis studies, we decided to evaluate the ability of **2a** to undergo the proposed visible-light- and Et_3N-mediated SET process. Irradiation of a solution of **2a**, Et_3N, and cyclohexadiene in CH_3CN furnished the desired product **3a** (47%) together with iminoalcohol **4a** (41%; Scheme 4C). The unforeseen formation of **4a** opened the way to the development of the first visible-light-mediated iminohydroxylation cyclization reaction. By simply excluding cyclohexadiene from the reaction mixture, the yield of **4a** was increased to 85%. Other amines were evaluated, and they also selectively provided **4a**, albeit in lower yields. As suggested by the UV/Vis studies, substrate **2b** gave the desired product in low yield whereas **2c** did not react.[24]

The formation of **4a** raised additional questions about the underlying mechanism and the origin of the oxygen atom in the final product (Scheme 4D). The involvement of adventitious O_2 or H_2O was excluded by running the reaction under rigorously moisture- and oxygen-free conditions.[24] In contrast to the hydroimination cyclization, 2,4-dinitrophenol (**8**-H) was not formed, but we obtained 2-NO-4-NO_2-C_6H_3OH (**10**-H). This observation indicates a unique trifunctional role of the aromatic unit of the *O*-aryl oximes, which sequentially serves as a sensitizer, an electron acceptor, and an oxidant. Initial rate kinetics revealed the reaction to be first order in **2a** and to display saturation behavior in Et_3N (1st order at $0 < [Et_3N] < 1$ equiv and zero order at $[Et_3N] > 1$ equiv). Based on these findings, we propose the following mechanism: Fast and reversible binding of Et_3N and **2a** gives intermediate **5**, which undergoes SET upon visible-light excitation to give the dipolar species **6**. Fragmentation and 5-*exo*-trig cyclization give the C-centered radical **7** and the stable phenoxide **8** ($pK_a \approx 4$). Subsequent oxidation by attack of the radical onto the NO_2 group[32] leads to **9**, and successive N–O bond homolysis furnishes **10** and the O-centered radical **11**, which undergoes a fast hydrogen atom abstraction.[24]

With this very simple optimized procedure in hand, the scope of the iminohydroxylation was evaluated with the aryl oximes **2a** and **2e**–**2y**. All examined substrates reacted well and provided the desired iminoalcohols **4a**–**4u** in good to high yields (Scheme 5). Bicyclic products could be obtained, and substrates containing di- and trisubstituted olefins also reacted well, giving access to products containing up to three contiguous stereogenic centers.

In conclusion, we have developed a divergent strategy for the hydroimination and iminohydroxylation cyclization of unactivated olefins. Electrochemical studies facilitated the identification of a very reactive class of *O*-aryl oximes that obviate the need for a transition-metal photocatalyst and undergo organocatalytic hydroimination cyclizations. The unprecedented ability of the aryl unit to sequentially act as a sensitizer, electron acceptor, and oxidant enabled the development of a unique Et_3N- and visible-light-mediated iminohydroxylation cyclization. Future studies will focus on applying this method to other nitrogen-centered radicals and



Scheme 5. Scope of the iminohydroxylation cyclization reaction. [a] 2 mmol scale.

on developing asymmetric variants of the hydroimination and iminohydroxylation cyclizations.

Acknowledgements

We thank Dr. H. Burton (née Scott), Dr. X. Couso Cambeiro, Dr. M. De Poli, Dr. G. Gil-Ramirez, Dr. P. Harvey, Dr. T. Poisson, Dr. A. Pulis, and Dr. I. Vilotijevic for helpful discussions. D.L. thanks the European Union for a Marie Curie Career Integration Grant (PCIG13-GA-2013-631556) and the School of Chemistry at the University of Manchester for generous support.

Keywords: electron transfer · hydroimination · iminohydroxylation · photoredox catalysis · visible light

How to cite: *Angew. Chem. Int. Ed.* **2015**, *54*, 14017–14021
Angew. Chem. **2015**, *127*, 14223–14227

[1] For reviews, see: a) S. Z. Zard, *Chem. Soc. Rev.* **2008**, *37*, 1603; for selected examples of NCRs in synthesis, see: b) J. Cassayre, F. Gagosz, S. S. Zard, *Angew. Chem. Int. Ed.* **2002**, *41*, 1783; *Angew. Chem.* **2002**, *114*, 1861; c) L. Sharp, S. Z. Zard, *Org. Lett.* **2006**, *8*, 831.

[2] For selected recent examples, see: a) A. Faulkner, N. J. Race, J. S. Scott, J. F. Bower, *Chem. Sci.* **2014**, *5*, 2416; b) M. Bingham, C. Moutrille, S. S. Zard, *Heterocycles* **2014**, *88*, 953; c) M. Kitamura, Y. Shintaku, D. Kudo, T. Okauchi, *Tetrahedron Lett.* **2010**, *51*, 4890; d) M. Minozzi, D. Nanni, P. Spagnolo, *Chem. Eur. J.* **2009**, *15*, 7830; e) A. Beaume, C. Courillon, E. Derat, M. Malacria, *Chem. Eur. J.* **2008**, *14*, 1238; f) M. Noack, R. Göttlich, *Chem. Commun.* **2002**, 536; g) Y. Guindon, B. Guerin, S. R. Landry, *Org. Lett.* **2001**, *3*, 2293; h) X. Lin, G. D. Artman III, D. Stien, S. M. Weinreb, *Tetrahedron* **2001**, *57*, 8779.

[3] M. E. Welsch, S. A. Snyder, B. R. Stockwell, *Curr. Opin. Chem. Biol.* **2010**, *14*, 347.

[4] For reviews, see: a) C. K. Prier, D. A. Rankic, D. W. C. MacMillan, *Chem. Rev.* **2013**, *113*, 5322; b) Y. Xi, H. Yi, A. Lei, *Org. Biomol. Chem.* **2013**, *11*, 2387; c) M. N. Hopkinson, B. Sahoo, J.-L. Li, F. Glorius, *Chem. Eur. J.* **2014**, *20*, 3874; d) J. M. R. Narayanam, C. Stephenson, *Chem. Soc. Rev.* **2011**, *40*, 102.

[5] G. Cecere, C. M. König, J. L. Alleva, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2013**, *135*, 11521.

[6] L. J. Allen, P. J. Cabrera, M. Lee, M. S. Sanford, *J. Am. Chem. Soc.* **2014**, *136*, 5607.

[7] H. Kim, T. Kim, D. G. Lee, S. W. Roh, C. Lee, *Chem. Commun.* **2014**, *50*, 9273.

[8] Q. Qin, S. Yu, *Org. Lett.* **2014**, *16*, 3504.

[9] L. Song, L. Zhang, S. Luo, J.-P. Cheng, *Chem. Eur. J.* **2014**, *20*, 14231.

[10] a) S. Maity, N. Zheng, *Angew. Chem. Int. Ed.* **2012**, *51*, 9562; *Angew. Chem.* **2012**, *124*, 9700; b) J. Wang, N. Zheng, *Angew. Chem. Int. Ed.* **2015**, DOI: 10.1002/anie.201504076; *Angew. Chem.* **2015**, DOI: 10.1002/ange.201504076.

[11] A. J. Musacchio, L. Q. Nguyen, H. Beard, R. R. Knowles, *J. Am. Chem. Soc.* **2014**, *136*, 12217.

[12] a) S. Atmaram, A. R. Forrester, M. Gill, R. H. Thomson, *J. Chem. Soc. Perkin Trans. 1* **1981**, 1721; b) A. R. Forrester, M. Gill, J. S. Sadd, R. H. Thomson, *J. Chem. Soc. Perkin Trans. 1* **1979**, 612.

[13] a) K. N. T. Mikami, *Chem. Lett.* **2000**, 338; b) M. Kitamura, K. Narasaka, *Bull. Chem. Soc. Jpn.* **2008**, *81*, 539.

[14] a) R. T. McBurney, J. C. Walton, *J. Am. Chem. Soc.* **2013**, *135*, 7349; b) J. C. Walton, *Acc. Chem. Res.* **2014**, *47*, 1406.

[15] During the preparation of this manuscript, Zhang, Yu et al. reported the photoredox generation of iminyl radicals using $[Ir(ppy)_3]$ and *para*-trifluoromethylbenzoyl acyl oximes and their addition to aromatic compounds; see: H. Jiang, X. An, K. Tong, T. Zheng, Y. Zhang, S. Yu, *Angew. Chem. Int. Ed.* **2015**, *54*, 4055; *Angew. Chem.* **2015**, *127*, 4127.

[16] For reviews on photoorganocatalysis, see: a) D. Ravelli, M. Fagnoni, A. Albini, *Chem. Soc. Rev.* **2013**, *42*, 97; b) R. Brimioulle, D. Lenhart, M. M. Maturi, T. Bach, *Angew. Chem. Int. Ed.* **2015**, *54*, 3872; *Angew. Chem.* **2015**, *127*, 3944; for selected examples, see: c) D. J. Wilger, J.-M. M. Grandjean, T. R. Lammert, D. A. Nicewicz, *Nat. Chem.* **2014**, *6*, 720; d) D. P. Hari, P. Schroll, B. König, *J. Am. Chem. Soc.* **2012**, *134*, 2958; e) M. Neumann, S. Fuldner, B. König, K. Zeitler, *Angew. Chem. Int. Ed.* **2011**, *50*, 951; *Angew. Chem.* **2011**, *123*, 981; f) A. Bauer, F. Westkmäper, S. Grimme, T. Bach, *Nature* **2005**, *436*, 1139; g) R. Brimioulle, T. Bach, *Science* **2013**, *342*, 6160.

[17] M. Wakasa, Y. Sakaguchi, J. Nakamura, H. Hayashi, *J. Phys. Chem.* **1992**, *96*, 9651.

[18] For selected examples, see: a) J. A. Terrett, M. D. Clift, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2014**, *136*, 6858; b) Z. Zuo, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2014**, *136*, 5257; c) A. McNally, C. K. Prier, D. W. C. MacMillan, *Science* **2011**, *334*, 1114; d) M. T. Pirnot, D. A. Rankic, D. B. C. Martin, D. W. C. MacMillan, *Science* **2013**, *339*, 1593.

[19] A. Vogler, H. Kunkely, *Coord. Chem. Rev.* **2000**, *208*, 321.

[20] a) E. D. Lorance, W. H. Kramer, I. R. Gould, *J. Am. Chem. Soc.* **2002**, *124*, 15225; b) Y.-R. Luo, *Handbook of Bond Dissociation Energies in Organic Compounds*, CRC Press, Boca Raton, **2003**.

[21] J. B. Boivin, E. Fouquet, S. Z. Zard, *Tetrahedron* **1994**, *50*, 1745.

[22] F. Agabito, P. M. Nunes, B. J. Costa Cabral, R. M. Borges dos Santos, J. A. Martinho Simões, *J. Org. Chem.* **2007**, *72*, 8770.

[23] D. P. Hari, B. König, *Chem. Commun.* **2014**, *50*, 6688.

[24] See the Supporting Information for more information.

[25] a) S. V. Rosokha, J. K. Kochi, *Acc. Chem. Res.* **2008**, *41*, 641; b) R. Rathore, S. V. Lindeman, J. K. Kochi, *J. Am. Chem. Soc.* **1997**, *119*, 9393.

[26] J. Cossy, D. Belotti, *Tetrahedron* **2006**, *62*, 6459.

[27] a) S. R. Kandukuri, A. Bahamonde, I. Chatterjee, I. D. Jurberg, E. C. Escudero-Adan, P. Melchiorre, *Angew. Chem. Int. Ed.* **2015**, *54*, 1485; *Angew. Chem.* **2015**, *127*, 1505; b) E. Arceo, I. D. Jurberg, A. Alvarez-Fernadez, P. Melchiorre, *Nat. Chem.* **2013**, *5*, 750; c) M. Nappi, G. Bergonzini, P. Melchiorre, *Angew. Chem. Int. Ed.* **2014**, *53*, 4921; *Angew. Chem.* **2014**, *126*, 5021.

[28] For reviews, see: a) G. J. Kavarnos, N. J. Turro, *Chem. Rev.* **1986**, *86*, 401; b) J. Mattay, *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 825; *Angew. Chem.* **1987**, *99*, 849; for selected examples, see: c) G. Berionni, P.-A. Bertelle, J. Marrot, R. Goumont, *J. Am. Chem. Soc.* **2009**, *131*, 18224; d) S. Nad, H. Pal, *J. Phys. Chem. A* **2000**, *104*, 673.

[29] C. Costentin, M. Robert, J.-M. Saveant, *Chem. Phys.* **2006**, *324*, 40.

[30] S. Farid, J. P. Dinnocenzo, P. B. Merkel, R. H. Young, D. Shukla, G. Guirado, *J. Am. Chem. Soc.* **2011**, *133*, 11580.

[31] We have evaluated several solvents for the formation of the **2a**·Et_3N EDAC.[24] For a discussion of solvent effects on EDAC intermediates, see: a) N. J. Turro, R. Engel, *J. Am. Chem. Soc.* **1969**, *91*, 7113; b) T. Abe, A. Kawai, Y. Kaji, K. Shibuya, K. Obi, *J. Phys. Chem. A* **1999**, *103*, 1457.

[32] a) Y. Zhang, Y. Du, Z. Huang, J. Xu, X. Wu, Y. Wang, M. Wang, S. Yang, R. D. Webster, Y. R. Chi, *J. Am. Chem. Soc.* **2015**, *137*, 2416; b) N. A. White, T. Rovis, *J. Am. Chem. Soc.* **2014**, *136*, 14674.

Received: August 15, 2015
Published online: September 28, 2015

