Photoredox Catalysis

International Edition: DOI: 10.1002/anie.201511235
German Edition: DOI: 10.1002/ange.201511235

Reductive Umpolung of Carbonyl Derivatives with Visible-Light Photoredox Catalysis: Direct Access to Vicinal Diamines and Amino Alcohols via α-Amino Radicals and Ketyl Radicals

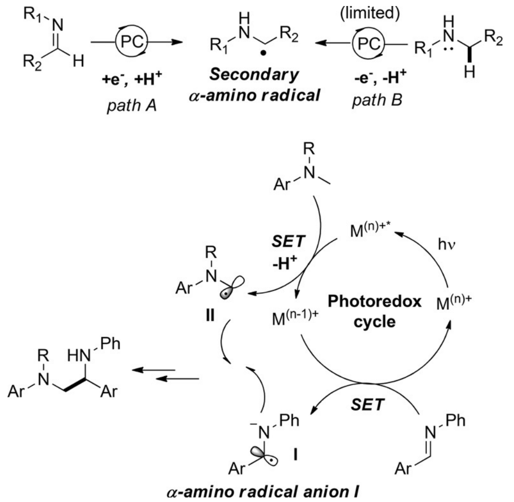
*Eleonora Fava, Anthony Millet, Masaki Nakajima, Sebastian Loescher, and Magnus Rueping**

Abstract: *Visible-light-mediated photoredox-catalyzed aldimine–aniline and aldehyde–aniline couplings have been realized. The reductive single electron transfer (SET) umpolung of various carbonyl derivatives enabled the generation of intermediary ketyl and α-amino radical anions, which were utilized for the synthesis of unsymmetrically substituted 1,2-diamines and amino alcohols.*

In the field of photochemistry, significant progress has been achieved over the past decades.[1] In particular, visible-light-mediated photoredox catalysis, which uses its ability to induce single electron transfer (SET) processes in organic molecules in a similar manner to conventional radical chemistry, has attracted increasing attention.[2] The circumvention of unstable radical initiators, simple practical implementation, and mild reaction conditions are undoubtedly attractive features. The strategic advantage of this concept lies in the chemical ambivalence of the catalyst, demonstrated by its flexibility to switch between oxidative, reductive, and energy-transfer processes according to the reaction conditions. Different reactive intermediates have been generated based on this strategy and successfully employed in carbon–carbon and carbon–heteroatom bond-forming reactions.

Recent advances in this field include the functionalization of carbonyl derivatives by reductive SET umpolung.[3,4] Our group recently reported the photoredox-catalyzed formation of ketyl radical intermediates by means of a proton-coupled electron transfer (PCET), which enabled the reductive dimerization of aldehydes, ketones, and aldimines.[5] The targeted use of persistent secondary α-amino radical anions derived from imines has also been described by the groups of MacMillan and Ooi.[6] The generation of such secondary α-amino radical anions through SET umpolung constitutes a complementary approach to the well-established SET oxidation of amines that are difficult to access by the latter pathway.[7]

As a continuation of our work, we wondered whether α-amino radical anions **I**, generated under catalytic photoredox conditions, would be able to undergo radical recombination with a second radical species **II**, which would be generated by SET oxidation of tertiary amines. Provided that the previously described dimerization of α-amino radical anions **I** and neutral α-amino radicals **II** can be suppressed, this strategy will enable the straightforward synthesis of unsymmetric 1,2-diamines,[8] a common motif found in many natural products with valuable biological properties that are difficult to synthesize otherwise (Scheme 1).



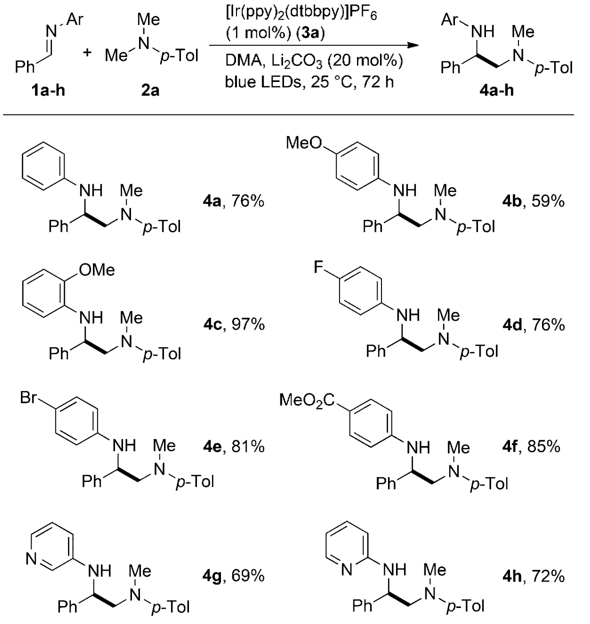
Scheme 1. Top: Complementary strategies for the generation of secondary α-amino radicals. Bottom: Proposed photoredox catalytic cycle for the synthesis of 1,2-diamines. PC = photocatalysis.

On the basis of the SET umpolung concept, we herein report a general method for the synthesis of vicinal diamines from easily accessible starting materials. Our initial investigations focused on the reaction between aldimine **1a** and *N*,*N*-dimethyl-4-methylaniline (**2a**) in combination with iridium polypyridyl complexes as the catalysts. Searching for suitable reaction conditions, we identified photocatalyst **3a** in dimethylacetamide (DMA) in combination with Li_2CO_3 as a crucial additive to be suitable for our transformation (see the Supporting Information for details; see Table S4 for solvent and additive effects).

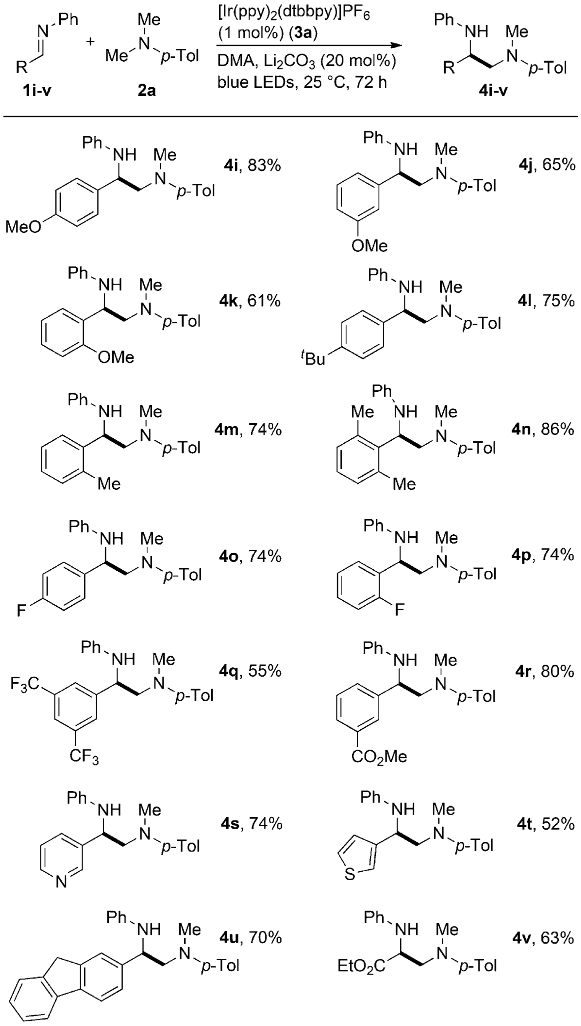
---

[*] Dr. E. Fava, Dr. A. Millet, Dr. M. Nakajima, B. Sc. S. Loescher, Prof. Dr. M. Rueping
Institute of Organic Chemistry, RWTH Aachen
Landoltweg 1, 52074 Aachen (Germany)
E-mail: Magnus.Rueping@rwth-aachen.de
Prof. Dr. M. Rueping
King Abdullah University of Science and Technology (KAUST)
KAUST Catalysis Center (KCC)
Thuwal, 23955-6900 (Saudi Arabia)

Supporting information for this article can be found under: http://dx.doi.org/10.1002/anie.201511235.



Scheme 2. Reaction conditions: **1** (0.3 mmol), **2a** (0.9 mmol), Li_2CO_3 (20 mol%), **3a** (1 mol%), degassed DMA (0.6 mL), room temperature, irradiation with blue LEDs (11 W, 450 nm), 72 h. Yields of isolated products are given. dtbbpy = 4,4′-di-*tert*-butyl-2,2′-bipyridine, ppy = 2-phenylpyridine.



Scheme 3. Reaction conditions: **1** (0.3 mmol), **2a** (0.9 mmol), Li_2CO_3 (20 mol%), **3a** (1 mol%), degassed DMA (0.6 mL), room temperature, irradiation with blue LEDs (11 W, 450 nm), 72 h. Yields of isolated products are given.

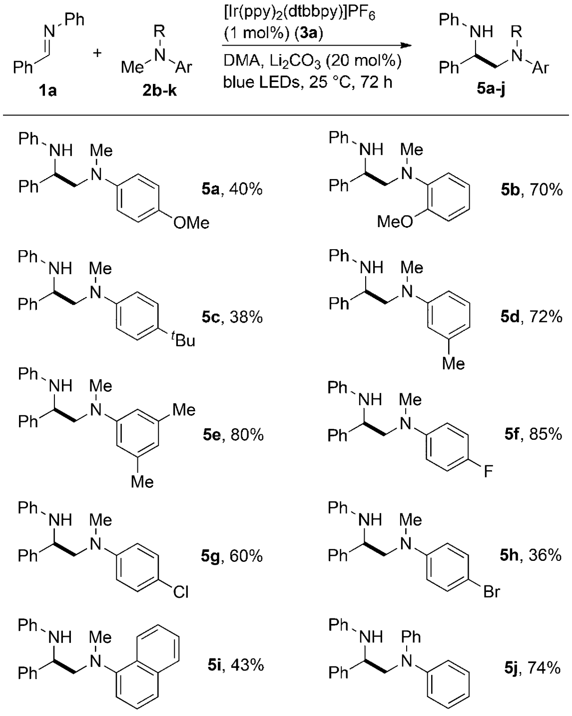
With the optimized reaction conditions in hand, we then examined the substrate scope and limitations of our radical–radical coupling reaction (Scheme 2). Regarding the N substitution of imines **1a–h**, both electron-poor and electron-rich (hetero)aromatic substrates with different substitution patterns were well-tolerated. Interestingly, even the reaction of *ortho*-substituted imine **1c** provided the corresponding product in nearly quantitative yield.

Next, we examined the imine scope with respect to variation of the aldehyde-derived R substituent. In all cases, good or excellent reactivity was observed in the presence of both electron-withdrawing and -donating groups on the aryl ring (Scheme 3). In particular, satisfactory reactivity was achieved with fluorine-containing aldimines (**1o–q**) and heterocyclic (**1s** and **1t**) and polycyclic imines (**1u**). Remarkably, our method is applicable to phenyliminoacetate **1v**, thus providing access to amino acid derivative **4v**.

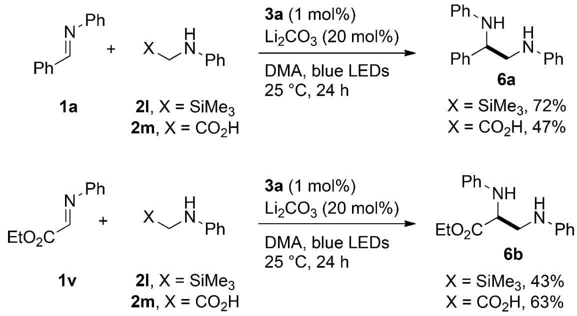
The scope was then extended by testing various anilines (Scheme 4), which could be coupled with our standard substrate **1a** in moderate to good yields. To our delight, *N*-methyldiphenylamine (**2k**) was converted into the corresponding product **5j** in 74% yield. Reduced yields were observed for substrates with electron-donating groups in the *para* position (**5a** and **5c**) or a bromine substituent (**5h**).

Intending to couple two secondary α-amino radical fragments, we next turned our attention to secondary anilines. Not surprisingly, our initial model substrate *N*-methylaniline turned out to be unreactive. However, the introduction of electrofugal groups, such as trimethylsilyl or carboxylic acid moieties, on the methylene moiety allowed us to obtain the desired products in satisfactory yields (Scheme 5). This approach was first developed by the groups of Mariano[9] and Pandey[10] for UV-mediated photochemistry in an attempt to suppress the formation of N-alkylation byproducts and was later applied to visible-light photoredox catalysis by the groups of Reiser and Nishibayashi.[11]

Encouraged by the promising results for the imine–aniline coupling, we took this idea further and tested carbonyl compounds as potential acceptor substrates (Scheme 6).[12] Surprisingly, whereas cyclic and aryl ketones were found to be generally inactive under these reaction conditions, benzaldehyde **7a** successfully provided the desired product **8a** in good yield. To the best of our knowledge, this reaction represents a rare example of a direct intermolecular ketyl radical coupling in the field of photoredox chemistry.[3c] Additional re-optimization revealed the beneficial effect of catalytic amounts of benzoic acid, which allowed us to carry out the amino alcohol synthesis at a catalyst loading of only 0.5 mol% and in significantly shorter reaction times (6 h). It should be noted that our reaction conditions are compatible with common functional groups, such as fluorine, chlorine, ester, ether, and acetamide moieties, as well as heterocycles.

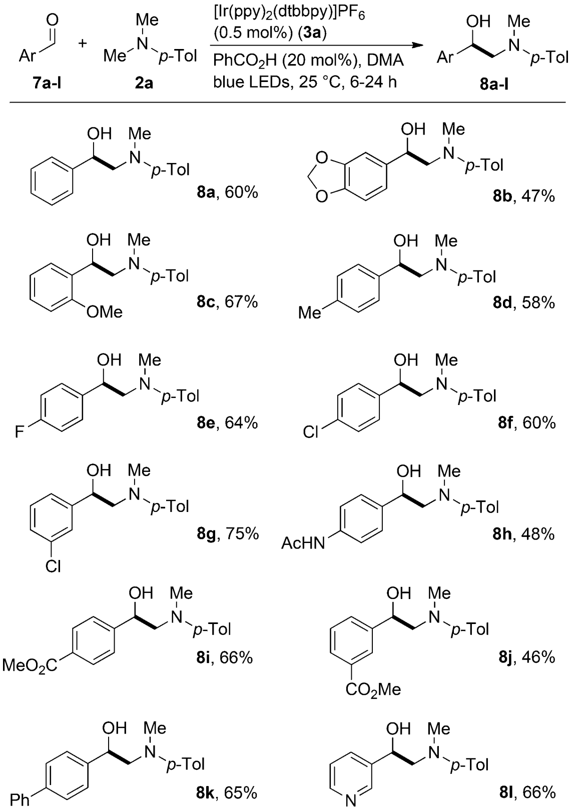


Scheme 4. Reaction conditions: **1a** (0.3 mmol), **2** (0.9 mmol), Li_2CO_3 (20 mol%), **3a** (1 mol%), degassed DMA (0.6 mL), room temperature, irradiation with blue LEDs (11 W, 450 nm), 72 h. Yields of isolated products are given.



Scheme 5. Reaction conditions: **1** (0.3 mmol), **2** (0.9 mmol), Li_2CO_3 (20 mol%), **3a** (1 mol%), degassed DMA (0.6 mL), room temperature, irradiation with blue LEDs (11 W, 450 nm), 24 h. Yields of isolated products are given.

In conclusion, we have developed a direct photocatalytic method for the synthesis of unsymmetric 1,2-diamines,[6d] with reductive SET umpolung of an aldimine as the key step. Moreover, we also applied the concept of reductive umpolung to aldehyde–aniline couplings. Ketyl radicals derived from aldehydes were thus coupled in an intermolecular fashion by photoredox catalysis for the first time. Biologically active amino alcohols and 1,2-diamines can thus be directly synthesized from simple starting materials in a straightforward library format. Remarkably, a wide range of functional groups as well as amino acids were tolerated under the mild conditions of our photoredox process.



Scheme 6. Reaction conditions: **7** (0.5 mmol), **2a** (1.5 mmol), $PhCO_2H$ (20 mol%), **3a** (0.5 mol%), degassed DMA (1 mL), room temperature, irradiation with blue LEDs (11 W, 450 nm), 6–24 h. Yields of isolated products are given.

Acknowledgments

The research leading to these results has received funding from the European Research Council under the European Union's Seventh Framework Programme (FP/2007-2013)/ ERC Grant Agreement No. 617044 (SunCatChem).

Keywords: amino alcohols · diamines · photocatalysis · redox chemistry · umpolung

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 6776–6779
Angew. Chem. **2016**, *128*, 6888–6891

---

[1] For selected reviews on photocatalysis, see: a) N. Hoffmann, *Chem. Rev.* **2008**, *108*, 1052; b) V. Balzani, A. Credi, M. Venturi, *ChemSusChem* **2008**, *1*, 26; c) M. Fagnoni, D. Dondi, D. Ravelli, A. Albini, *Chem. Rev.* **2007**, *107*, 2725; d) D. Ravelli, D. Dondi, M. Fagnoni, A. Albini, *Chem. Soc. Rev.* **2009**, *38*, 1999; e) *Handbook of Synthetic Photochemistry* (Eds.: A. Albini, M. Fagnoni), Wiley-VCH, Weinheim, **2010**; f) *CRC Handbook of Organic Photochemistry and Photobiology* (Eds.: A. Griesbeck, M. Oelgemöller, F. Ghetti), CRC, Boca Raton, **2012**; g) N. Hoffmann, *ChemSusChem* **2012**, *5*, 352; h) D. Ravelli, M. Fagnoni, A. Albini, *Chem. Soc. Rev.* **2013**, *42*, 97; i) *Chemical Photocatalysis* (Ed.: B. König), de Gruyter, Berlin, **2013**.

[2] For selected reviews on photoredox catalysis, see: a) K. Zeitler, *Angew. Chem. Int. Ed.* **2009**, *48*, 9785; *Angew. Chem.* **2009**, *121*, 9969; 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. Xuan, W. Xiao, *Angew. Chem. Int. Ed.* **2012**, *51*, 6828; *Angew. Chem.* **2012**, *124*, 6934; f) L. Shi, W.-J. Xia, *Chem. Soc. Rev.* **2012**, *41*, 7687; g) D. Ravelli, M. Fagnoni, *ChemCatChem* **2012**, *4*, 169; h) Y. Xi, H. Yi, A. Lei, *Org. Biomol. Chem.* **2013**, *11*, 2387; i) C. K. Prier, D. A. Rankic, D. W. C. MacMillan, *Chem. Rev.* **2013**, *113*, 5322.

[3] For the direct functionalization of ketyl radicals, see: a) P. Liu, R. R. Knowles, *J. Am. Chem. Soc.* **2013**, *135*, 10022; b) H. G. Yayla, D. Y. Wang, R. R. Knowles, *J. Am. Chem. Soc.* **2013**, *135*, 17735; c) F. R. Petronijević, M. Nappi, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2013**, *135*, 18323; examples of the photochemical generation of ketyl radicals are summarized in the following book: d) *Synthetic Organic Photochemistry*, *Vol. 12* of *Supramolecular and Molecular Photochemistry* (Eds.: A. G. Griesbeck, J. Mattay), Marcel Dekker, New York, **2005**.

[4] For the functionalization of ketyl radicals by conjugation, see: a) J. Du, T. P. Yoon, *J. Am. Chem. Soc.* **2009**, *131*, 14604; b) T. P. Yoon, *ACS Catal.* **2013**, *3*, 895; c) M. A. Ischay, M. E. Anzovino, J. Du, T. P. Yoon, *J. Am. Chem. Soc.* **2008**, *130*, 12886; d) Z. Lu, M. Shen, T. P. Yoon, *J. Am. Chem. Soc.* **2011**, *133*, 1162; e) E. L. Tyson, E. P. Farney, T. P. Yoon, *Org. Lett.* **2012**, *14*, 1110; f) M.-H. Larraufie, R. Pellet, L. Fensterbank, J.-P. Goddard, E. Lacôte, M. Malacria, C. Ollivier, *Angew. Chem. Int. Ed.* **2011**, *50*, 4463; *Angew. Chem.* **2011**, *123*, 4555; g) M. Neumann, K. Zeitler, *Chem. Eur. J.* **2013**, *19*, 6950; h) G. Pandey, S. Hajra, *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1169; *Angew. Chem.* **1994**, *106*, 1217; i) G. Pandey, S. Hajra, M. K. Ghorai, *Tetrahedron Lett.* **1994**, *35*, 7837; j) G. Pandey, S. Hajra, M. K. Ghorai, K. R. Kumar, *J. Am. Chem. Soc.* **1997**, *119*, 8777; for selected reviews, see: k) M. T. Crimmins, *Chem. Rev.* **1988**, *88*, 1453; l) D. I. Schuster, G. Lem, N. A. Kaprinidis, *Chem. Rev.* **1993**, *93*, 3; m) J. Streuff, *Synthesis* **2013**, *45*, 281; n) J. Streuff, A. Gansäuer, *Angew. Chem. Int. Ed.* **2015**, *54*, 14232; *Angew. Chem.* **2015**, *127*, 14438.

[5] M. Nakajima, E. Fava, S. Loescher, Z. Jiang, M. Rueping, *Angew. Chem. Int. Ed.* **2015**, *54*, 8828; *Angew. Chem.* **2015**, *127*, 8952.

[6] a) D. Hager, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2014**, *136*, 16986; b) J. Jeffrey, F. R. Petronijevic, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2015**, *137*, 8404; c) D. Uraguchi, N. Konoshita, T. Kizu, T. Ooi, *J. Am. Chem. Soc.* **2015**, *137*, 13768.

[7] For selected reviews on photoredox catalysis with amine substrates, see: a) Ref. [2f]; b) J. Hu, J. Wang, T. H. Nguyen, N. Zheng, *Beilstein J. Org. Chem.* **2013**, *9*, 1977; c) J. W. Beatty, C. R. J. Stephenson, *Acc. Chem. Res.* **2015**, *48*, 1474.

[8] For selected reports of the synthesis of 1,2-diamines, see: a) F. Cardona, A. Goti, *Nat. Chem.* **2009**, *1*, 269; b) H. Wu, X. Ji, H. Sun, G. An, J. Han, G. Li, Y. Pan, *Tetrahedron* **2010**, *66*, 4555; c) T. Kano, R. Sakamoto, M. Akakura, K. Maruoka, *J. Am. Chem. Soc.* **2012**, *134*, 7516; d) M. J. MacDonald, C. R. Hesp, D. J. Schipper, M. Pesant, A. M. Beauchemin, *Chem. Eur. J.* **2013**, *19*, 2597; e) K. Muñiz, C. Martínez, *J. Org. Chem.* **2013**, *78*, 2168; f) J. Agut, A. Vidal, S. Rodríguez, F. V. González, *J. Org. Chem.* **2013**, *78*, 5717; g) Q. Yang, J. Chang, J. Song, M.-T. Qian, J.-M. Yu, X. Sun, *Bioorg. Med. Chem. Lett.* **2013**, *23*, 4602; h) X. Liu, A. Gao, L. Ding, J. Xu, B. Zhao, *Org. Lett.* **2014**, *16*, 2118; i) D. E. Olson, J. Y. Su, D. A. Roberts, J. Du Bois, *J. Am. Chem. Soc.* **2014**, *136*, 13506.

[9] a) S.-K. Khim, E. Cederstrom, D. C. Ferri, P. S. Mariano, *Tetrahedron* **1996**, *52*, 3195; b) X. Zhang, S.-R. Yeh, S. Hong, M. Freccero, A. Albini, D. E. Falvey, P. S. Mariano, *J. Am. Chem. Soc.* **1994**, *116*, 4211; c) W. Xu, X.-M. Zhang, P. S. Mariano, *J. Am. Chem. Soc.* **1991**, *113*, 8863; d) Y. T. Jeon, C.-P. Lee, P. S. Mariano, *J. Am. Chem. Soc.* **1991**, *113*, 8847; e) X.-M. Zhang, P. S. Mariano, *J. Org. Chem.* **1991**, *56*, 1655; f) E. Hasegawa, W. Xu, P. S. Mariano, U.-C. Yoon, J.-U. Kim, *J. Am. Chem. Soc.* **1988**, *110*, 8099; g) U.-C. Yoon, J.-U. Kim, E. Hasegawa, P. S. Mariano, *J. Am. Chem. Soc.* **1987**, *109*, 4421.

[10] a) G. Pandey, G. D. Reddy, G. Kumaraswamy, *Tetrahedron* **1994**, *50*, 8185; b) G. Pandey, G. Kumaraswamy, U. T. Bhalerao, *Tetrahedron Lett.* **1989**, *30*, 6059.

[11] a) P. Kohls, D. Jadhav, G. Pandey, O. Reiser, *Org. Lett.* **2012**, *14*, 672; b) Y. Miyake, K. Nakajima, Y. Nishibayashi, *J. Am. Chem. Soc.* **2012**, *134*, 3338; c) Y. Miyake, K. Nakajima, Y. Nishibayashi, *Chem. Eur. J.* **2012**, *18*, 16473; d) S. Zhu, A. Das, L. Bui, H. Zhou, D. P. Curran, M. Rueping, *J. Am. Chem. Soc.* **2013**, *135*, 1823.

[12] For the photoredox-catalyzed umpolung of carbonyl derivatives with alcohols, see: a) A. G. Griesbeck, M. Reckenthäler, *Beilstein J. Org. Chem.* **2014**, *10*, 1143. During the revision of this manuscript, a photoredox-catalyzed ketone–amine coupling was reported; see: b) C. Wang, J. Qin, X. Shen, R. Riedel, K. Harms, E. Meggers, *Angew. Chem. Int. Ed.* **2016**, *55*, 685; *Angew. Chem.* **2016**, *128*, 695.

Received: December 3, 2015
Revised: February 7, 2016