Photoredox Catalysis Hot Paper

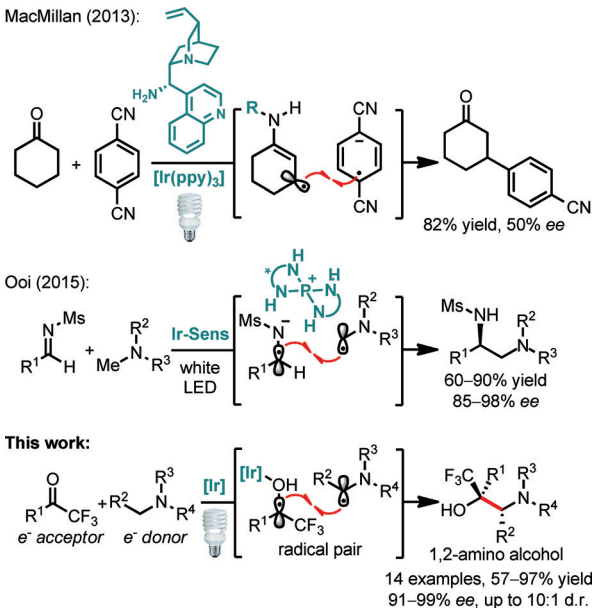
International Edition: DOI: 10.1002/anie.201509524
German Edition: DOI: 10.1002/ange.201509524

Asymmetric Radical–Radical Cross-Coupling through Visible-Light-Activated Iridium Catalysis

*Chuanyong Wang, Jie Qin, Xiaodong Shen, Radostan Riedel, Klaus Harms, and Eric Meggers**

Abstract: *Combining single electron transfer between a donor substrate and a catalyst-activated acceptor substrate with a stereocontrolled radical–radical recombination enables the visible-light-driven catalytic enantio- and diastereoselective synthesis of 1,2-amino alcohols from trifluoromethyl ketones and tertiary amines. With a chiral iridium complex acting as both a Lewis acid and a photoredox catalyst, enantioselectivities of up to 99% ee were achieved. A quantum yield of <1 supports the proposed catalytic cycle in which at least one photon is needed for each asymmetric C–C bond formation mediated by single electron transfer.*

Single electron transfer (SET) mediated reactions have recently attracted much attention owing to the useful reactivities of the intermediate radical ions or radicals, which expand the mechanistic repertoire for developing novel synthetic transformations.[1,2] In one mechanistic scenario, a direct photoinduced electron exchange between two involved substrates, one electron acceptor and one electron donor, creates two odd-electron species, which then generate a new σ-bond upon radical–radical recombination. For example, Mariano demonstrated the merit of this approach with the photoredox chemistry of iminium salts,[3] whereas MacMillan and co-workers introduced an elegant scheme based on single electron oxidation and subsequent deprotonation of intermediate enamines, followed by a radical–radical coupling.[4] However, for the photoredox-mediated β-hydroxyalkylation[4b] and β-aminoalkylation[4c] of cyclic ketones, only racemic products were reported, whereas for the β-arylation of cyclohexanone with a cinchona-derived aminocatalyst, a modest enantioselectivity of 50% *ee* was achieved (Scheme 1).[4a] Rendering such reactions catalytic and asymmetric is a formidable challenge owing to the intrinsic reactivity of the involved odd-electron species.[5] Herein, we report a catalytic asymmetric process that closely interlocks a visible-light-activated SET between two substrates with the stereocontrolled radical–radical cross-coupling of an intermediate radical pair, namely the catalytic enantio- and diastereoselective redox coupling of trifluoromethyl ketones with tertiary amines to 1,2-diamino alcohols.[6–9] A process relevant to this study was published after this manuscript had been submitted; Ooi and co-workers reported a visible-light-activated coupling of *N*-aryl aminomethanes with *N*-sulfonyl aldimines using an iridium photosensitizer in combination with a chiral arylaminophosphonium salt, a reaction that is proposed to proceed through a stereocontrolled radical anion–radical coupling.[10]



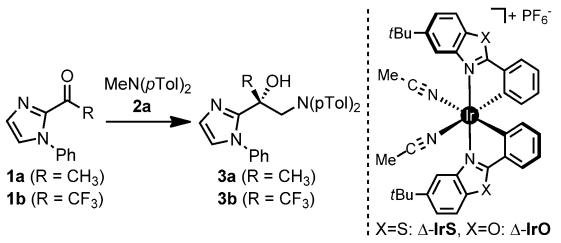
Scheme 1. Linking (photoinduced) single electron transfer between a donor substrate and an acceptor substrate to asymmetric radical–radical recombination. The shown stereochemistry of the 1,2-amino alcohol is based on an iridium catalyst with Λ configuration.

At the onset of our study, we envisioned that our previously developed dual-function chiral Lewis acid/ photoredox catalysts[11] would be capable of directing SET from an electron-rich substrate to a photoexcited catalyst-bound electron-deficient substrate, followed by enantioselective radical–radical cross-coupling controlled by the chiral environment of the propeller-type iridium complex. When 2-acetyl imidazole **1a** was reacted with amine **2a** in the presence of Δ-**IrO**[12] (3 mol%) under visible-light irradiation with a compact fluorescent lamp (CFL, 23 W), we were disappointed to not observe even traces of the desired product **3a** (Table 1, entry 1). However, using the more electron-deficient trifluoroacetyl imidazole **1b** instead provided the coupling product **3b** with 69% yield and 97% *ee* (entry 2). Replacing the solvent CH_2Cl_2 with $CHCl_3$ improved the yield to 75%, albeit with a slightly reduced enantioselectivity (entry 3). The

[*] C. Wang, J. Qin, X. Shen, R. Riedel, Dr. K. Harms, Prof. Dr. E. Meggers
Fachbereich Chemie, Philipps-Universität Marburg
Hans-Meerwein-Strasse 4, 35043 Marburg (Germany)
E-mail: meggers@chemie.uni-marburg.de
Prof. Dr. E. Meggers
College of Chemistry and Chemical Engineering
Xiamen University
Xiamen 361005 (P.R. China)

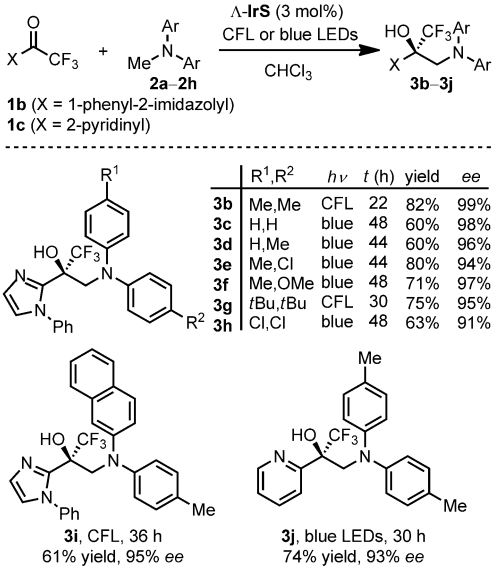
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201509524.

Table 1: Initial experiments and optimization of the visible-light-induced asymmetric C–C bond formation.[a]

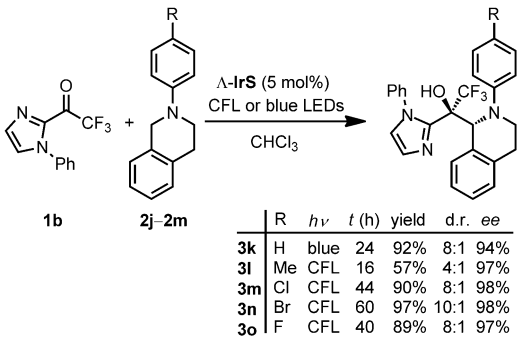


Entry	R	Catalyst	*hν*[b]	Solvent	Yield[c] [%]	*ee*[d] [%]
1	CH_3	Δ-**IrO**	CFL	CH_2Cl_2	0	n.d.
2	CF_3	Δ-**IrO**	CFL	CH_2Cl_2	69	97
3	CF_3	Δ-**IrO**	CFL	$CHCl_3$	75	95
4	CF_3	Δ-**IrO**	CFL	EtOAc	42	68
5	CF_3	Δ-**IrO**	CFL	toluene	30	11
6	CF_3	Δ-**IrO**	CFL	MeCN	0	n.d.
7	CF_3	Δ-**IrS**	CFL	CH_2Cl_2	72	98.9
8	CF_3	Δ-**IrS**	CFL	$CHCl_3$	82	98.6
9	CF_3	Δ-**IrS**	–	$CHCl_3$	0	n.d.
10	CF_3	–	CFL	$CHCl_3$	0	n.d.
11	CF_3	$[Ru(bpy)_3]Cl_2{\cdot}6H_2O$	CFL	$CHCl_3$	0	n.d.
12	CF_3	$[Ir(ppy)_2(dtbbpy)]PF_6$	CFL	$CHCl_3$	0	n.d.

[a] Reaction conditions: 2-Acyl imidazole **1a** or **1b** (0.2 mmol), aniline **2a** (0.6 mmol), and the catalyst (entries 1–9: 3.0 mol%, entry 11: 0.5 mol%, entry 12: 1.0 mol%) in the indicated solvent (0.4 mL) were photolyzed for 22 h under an atmosphere of nitrogen. [b] Light source: 23 W CFL at a distance of approximately 5 cm from the Schlenk tube. [c] Yields of isolated products. [d] Determined by HPLC analysis on a chiral stationary phase. bpy = 2,2′-bipyridine, dtbbpy = 4,4′-di-*tert*-butyl-2,2′-bipyridine, n.d. = not determined, ppy = 2-phenylpyridine.



Scheme 2. Substrate scope with respect to *N*-methyl diarylamines. Light source: 23 W CFL or 24 W blue LEDs. A crystal structure of **3h** was used to assign the absolute configuration of **3b–3j** as *S*.



Scheme 3. 2-Aryl 1,2,3,4-tetrahydroisoquinolines as amine substrates for enantio- and diastereoselective reactions. Light source: 23 W CFL or 24 W blue LEDs. Relative configurations were assigned based on a crystal structure of **3k**.

reaction is very sensitive to solvent effects, and other tested solvents did not provide satisfactory results (entries 4–6). With the catalyst Δ-**IrS**,[11a] the yields and enantioselectivities could be further enhanced (entries 7 and 8). With $CHCl_3$, 82% yield and excellent 98.6% *ee* were achieved. Control experiments in the absence of the catalyst or in the dark demonstrate that this reaction crucially depends on the presence of the iridium catalyst and light; otherwise no traces of product were observed (entries 9 and 10). It is also worth noting that the C–C coupling product is not formed when the common photoredox sensitizers $[Ru(bpy)_3]Cl_2{\cdot}6H_2O$ and $[Ir(ppy)_2(dtbbpy)]PF_6$ are used (entries 11 and 12).[2]

Next, we evaluated the scope of the visible-light-activated asymmetric aminoalkylation of trifluoromethyl ketones with catalyst Λ-**IrS**. The reaction between 2-trifluoroacetyl imidazole **1b** and various *N*-methyl diarylamines (**2a–2h**) provided the respective 1,2-amino alcohols (**3b–3i**) in satisfactory yields (60–82%) and with high enantioselectivity (91–99% *ee*, Scheme 2). The imidazole can also be replaced by a pyridyl moiety (**1c+2a→3j**), and *N*-aryl 1,2,3,4-tetrahydroisoquinolines (**2i–2m**) can be used as substrates, affording the corresponding products (**3k–3o**) with good diastereoselectivity (4.1 to 10:1 d.r.) and high enantioselectivity (94–98% *ee*; Scheme 3). It is noteworthy that we found empirically that certain reactions provided better results under white-light irradiation (CFL), whereas others preferred blue light (blue LEDs).

A plausible mechanism is shown in Figure 1a and starts with the photoactivation of the iridium-coordinated trifluoromethyl ketone (step 1), which induces a single electron transfer from a tertiary amine, thereby generating an amino radical cation[13,14] aside from a reduced iridium complex, which can be described as an iridium-coordinated ketyl radical (step 2). This is followed by a proton transfer (step 3) and a radical–radical cross-coupling between the electron-rich α-aminoalkyl radical and the electron-deficient ketyl radical (step 4), which is stereochemically controlled by the chiral iridium complex. Finally, the product is replaced by new substrate (step 5). Several mechanistic experiments support this mechanism. First, in the presence of oxygen, the C–C coupling product was not formed, which is consistent with the presence of intermediate radicals that react with oxygen

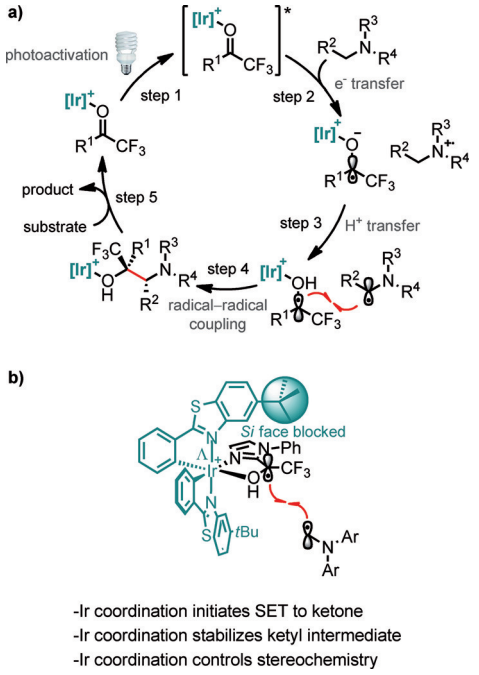


Figure 1. Putative mechanism for the visible-light-activated catalytic asymmetric process. a) Catalytic cycle. b) Model for the asymmetric induction in the course of the radical–radical recombination shown for selected substrates.

under diffusion control. Second, in the presence of dibenzyl azodicarboxylate, a hydrazone C–N coupling product was formed in high yield, which can be traced back to a reaction of the proposed intermediary (nucleophilic) α-aminoalkyl radical with the (electrophilic) N=N double bond, followed by reduction and protonation (see the Supporting Information for more details and additional reactions).[15] Third, we determined the quantum yield of the model reaction **1b**+**2a**→**3b** by ferrioxalate actinometry to be 0.09.[16] A quantum yield of ≤ 1 is in agreement with the expected closed catalytic cycle, as according to the proposed mechanism, no chain process is possible with one photon being required for each C–C bond formation event.[17–19] Finally, the observed absolute configuration of the C–C coupling product, with *S* configuration at the carbon atom next to the OH group when Λ-**IrS** is used, is consistent with this mechanistic picture in which the prochiral *Si* face of the iridium-coordinated ketyl radical is effectively shielded by one *tert*-butyl group of the propeller-type ligand sphere, providing excellent stereochemical control over the radical process (Figure 1 b).

In conclusion, we have introduced a unique catalytic asymmetric process in which a visible-light-driven single electron transfer reaction between a donor substrate and a catalyst-bound acceptor substrate is apparently followed by a stereocontrolled radical–radical recombination. With a chiral iridium complex as a dual Lewis acid/photoredox catalyst, 1,2-amino alcohols were synthesized from trifluoromethyl ketones and tertiary amines with high enantioselectivities of up to 99% *ee*. Such non-racemic trifluoromethyl-containing compounds might be useful building blocks for the synthesis of bioactive compounds.[20,21] It is also worth noting that this mild method follows the spirit of sustainable chemistry, not only because the activation energy is provided by visible light as an abundant light source, but also because in the course of the C–C bond formation with the implementation of one or two new stereocenters, no waste products are generated, thereby constituting perfect atom economy.

Acknowledgements

We are grateful to the German Research Foundation (ME 1805/11-1) and the University of Marburg for funding.

Keywords: asymmetric catalysis · electron transfer · photoredox catalysis · radicals

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 685–688
Angew. Chem. **2016**, *128*, 695–698

[1] For reactions involving single electron transfer, see: a) N. Zhang, S. R. Samanta, B. M. Rosen, V. Percec, *Chem. Rev.* **2014**, *114*, 5848–5958; b) A. Studer, D. P. Curran, *Nat. Chem.* **2014**, *6*, 765–773.

[2] For reviews on different aspects of photoredox catalysis, see: a) M. Fagnoni, D. Dondi, D. Ravelli, A. Albini, *Chem. Rev.* **2007**, *107*, 2725–2756; b) K. Zeitler, *Angew. Chem. Int. Ed.* **2009**, *48*, 9785–9789; *Angew. Chem.* **2009**, *121*, 9969–9974; c) T. P. Yoon, M. A. Ischay, J. Du, *Nat. Chem.* **2010**, *2*, 527–532; d) J. M. R. Narayanam, C. R. J. Stephenson, *Chem. Soc. Rev.* **2011**, *40*, 102–113; e) F. Teplý, *Collect. Czech. Chem. Commun.* **2011**, *76*, 859–917; f) J. Xuan, W.-J. Xiao, *Angew. Chem. Int. Ed.* **2012**, *51*, 6828–6838; *Angew. Chem.* **2012**, *124*, 6934–6944; g) L. Shi, W. Xia, *Chem. Soc. Rev.* **2012**, *41*, 7687–7697; h) D. Ravelli, M. Fagnoni, A. Albini, *Chem. Soc. Rev.* **2012**, *41*, 97–113; i) M. Reckenthäler, A. G. Griesbeck, *Adv. Synth. Catal.* **2013**, *355*, 2727–2744; j) C. K. Prier, D. A. Rankic, D. W. C. MacMillan, *Chem. Rev.* **2013**, *113*, 5322–5363; k) D. P. Hari, B. König, *Angew. Chem. Int. Ed.* **2013**, *52*, 4734–4743; *Angew. Chem.* **2013**, *125*, 4832–4842; l) M. N. Hopkinson, B. Sahoo, J.-L. Li, F. Glorius, *Chem. Eur. J.* **2014**, *20*, 3874–3886; m) D. M. Schultz, T. P. Yoon, *Science* **2014**, *343*, 1239176.

[3] P. S. Mariano, *Acc. Chem. Res.* **1983**, *16*, 130–137.

[4] a) M. T. Pirnot, D. A. Rankic, D. B. C. Martin, D. W. C. MacMillan, *Science* **2013**, *339*, 1593–1596; b) F. R. Petronijević, M. Nappi, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2013**, *135*, 18323–18326; c) J. L. Jeffrey, F. R. Petronijević, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2015**, *137*, 8404–8407.

[5] For an overview on enantioselective radical reactions, see: J. Zimmerman, M. P. Sibi, *Top. Curr. Chem.* **2006**, *263*, 107–162.

[6] The stable radical 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) has been used successfully for catalytic asymmetric radical–radical reactions; see, for example: a) M. P. Sibi, M. Hasegawa, *J. Am. Chem. Soc.* **2007**, *129*, 4124–4125; b) H.-S. Yoon, X.-H. Ho, J. Jang, H.-J. Lee, S.-J. Kim, H.-Y. Jang, *Org. Lett.* **2012**, *14*, 3272–3275.

[7] Melchiorre et al. recently proposed a mechanism in which a visible-light-absorbing charge-transfer complex leads to the formation and stereocontrolled reaction of two intermediate odd-electron species; see: E. Arceo, I. D. Jurberg, A. Álvarez-Fernández, P. Melchiorre, *Nat. Chem.* **2013**, *5*, 750–756.

[8] For recent reviews on asymmetric catalysis by visible-light activation, see: a) C. Wang, Z. Lu, *Org. Chem. Front.* **2015**, *2*, 179–190; b) E. Meggers, *Chem. Commun.* **2015**, *51*, 3290–3301; c) R. Brimioulle, D. Lenhart, M. M. Maturi, T. Bach, *Angew. Chem. Int. Ed.* **2015**, *54*, 3872–3890; *Angew. Chem.* **2015**, *127*,

3944 – 3963; d) M. Peña-López, A. Rosas-Hernández, M. Beller, *Angew. Chem. Int. Ed.* **2015**, *54*, 5006 – 5008; *Angew. Chem.* **2015**, *127*, 5090 – 5092.

[9] For selected examples of asymmetric catalysis by visible-light activation, see: a) D. A. Nicewicz, D. W. C. MacMillan, *Science* **2008**, *322*, 77 – 80; b) D. A. Nagib, M. E. Scott, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2009**, *131*, 10875 – 10877; c) M. Neumann, S. Füldner, B. König, K. Zeitler, *Angew. Chem. Int. Ed.* **2011**, *50*, 951 – 954; *Angew. Chem.* **2011**, *123*, 981 – 985; d) D. A. DiRocco, T. Rovis, *J. Am. Chem. Soc.* **2012**, *134*, 8094 – 8097; e) M. Cherevatskaya, M. Neumann, S. Füldner, C. Harlander, S. Kümmel, S. Dankesreiter, A. Pfitzner, K. Zeitler, B. König, *Angew. Chem. Int. Ed.* **2012**, *51*, 4062 – 4066; *Angew. Chem.* **2012**, *124*, 4138 – 4142; f) L. J. Rono, H. G. Yayla, D. Y. Wang, M. F. Armstrong, R. R. Knowles, *J. Am. Chem. Soc.* **2013**, *135*, 17735 – 17738; g) G. Cecere, C. M. König, J. L. Alleva, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2013**, *135*, 11521 – 11524; h) G. Bergonzini, C. S. Schindler, C.-J. Wallentin, E. N. Jacobsen, C. R. J. Stephenson, *Chem. Sci.* **2013**, *4*, 112 – 116; i) J. Du, K. L. Skubi, D. M. Schultz, T. P. Yoon, *Science* **2014**, *344*, 392 – 396; j) J. C. Tellis, D. N. Primer, G. A. Molander, *Science* **2014**, *345*, 433 – 436; k) Y. Zhu, L. Zhang, S. Luo, *J. Am. Chem. Soc.* **2014**, *136*, 14642 – 14645; l) O. Gutierrez, J. C. Tellis, D. N. Primer, G. A. Molander, M. C. Kozlowski, *J. Am. Chem. Soc.* **2015**, *137*, 4896 – 4899; m) Ł. Woźniak, J. J. Murphy, P. Melchiorre, *J. Am. Chem. Soc.* **2015**, *137*, 5678 – 5681; n) M. Silvi, E. Arceo, I. D. Jurberg, C. Cassani, P. Melchiorre, *J. Am. Chem. Soc.* **2015**, *137*, 6120 – 6123.

[10] D. Uraguchi, N. Kinoshita, T. Kizu, T. Ooi, *J. Am. Chem. Soc.* **2015**, *137*, 13768 – 13771.

[11] a) H. Huo, X. Shen, C. Wang, L. Zhang, P. Röse, L.-A. Chen, K. Harms, M. Marsch, G. Hilt, E. Meggers, *Nature* **2014**, *515*, 100 – 103; b) C. Wang, Y. Zheng, H. Huo, P. Röse, L. Zhang, K. Harms, G. Hilt, E. Meggers, *Chem. Eur. J.* **2015**, *21*, 7355 – 7359; c) H. Huo, C. Wang, K. Harms, E. Meggers, *J. Am. Chem. Soc.* **2015**, *137*, 9551 – 9554.

[12] H. Huo, C. Fu, K. Harms, E. Meggers, *J. Am. Chem. Soc.* **2014**, *136*, 2990 – 2993.

[13] For the visible-light-activated oxidation of amines to their α-aminoalkyl radicals and their follow-up radical reactions, see, for example: a) P. Kohls, D. Jadhav, G. Pandey, O. Reiser, *Org. Lett.* **2012**, *14*, 672 – 675; b) H. Zhou, P. Lu, X. Gu, P. Li, *Org. Lett.* **2013**, *15*, 5646 – 5649; c) L. Ruiz Espelt, I. S. McPherson, E. M. Wiensch, T. P. Yoon, *J. Am. Chem. Soc.* **2015**, *137*, 2452 – 2455.

[14] For a recent review on the chemistry of amine radical cations, see: J. Hu, J. Wang, T. H. Nguyen, N. Zheng, *Beilstein J. Org. Chem.* **2013**, *9*, 1977 – 2001.

[15] For an efficient reaction of α-aminoalkyl radicals with di-*tert*-butyl azodicarboxylate, see: Y. Miyake, K. Nakajima, Y. Nishibayashi, *Chem. Eur. J.* **2012**, *18*, 16473 – 16477.

[16] S. L. Murov, I. Carmichael, G. L. Hug, *Handbook of Photochemistry*, 2nd ed., M. Decker, New York, **1993**.

[17] The low quantum yield also demonstrates that this mechanism is different to that of previously reported reactions with this catalyst, for which quantum yields of >1 were determined; see Ref. [11c].

[18] For a recent discussion of closed catalytic cycles versus chain processes in photoredox reactions, see: a) M. D. Kärkäs, B. S. Matsuura, C. R. J. Stephenson, *Science* **2015**, *349*, 1285 – 1286; b) M. A. Cismesia, T. P. Yoon, *Chem. Sci.* **2015**, *6*, 5426 – 5434.

[19] Catalytic or stoichiometric amounts of single-electron oxidants cannot trigger this reaction. See the Supporting Information for more details.

[20] 2-Acyl imidazoles can be converted into a wide variety of carbonyl compounds; see: D. A. Evans, K. R. Fandrick, H.-J. Song, K. A. Scheidt, R. Xu, *J. Am. Chem. Soc.* **2007**, *129*, 10029 – 10041.

[21] For fluorine in pharmaceuticals, see, for example: K. Müller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881 – 1886.

Received: October 12, 2015
Published online: December 2, 2015

