ACES
DOI: 10.1002/asia.201500497
CHEMISTRY
AN ASIAN JOURNAL
Communication

Photocatalysis

Remazol-Catalyzed Hydroperoxyarylation of Styrenes

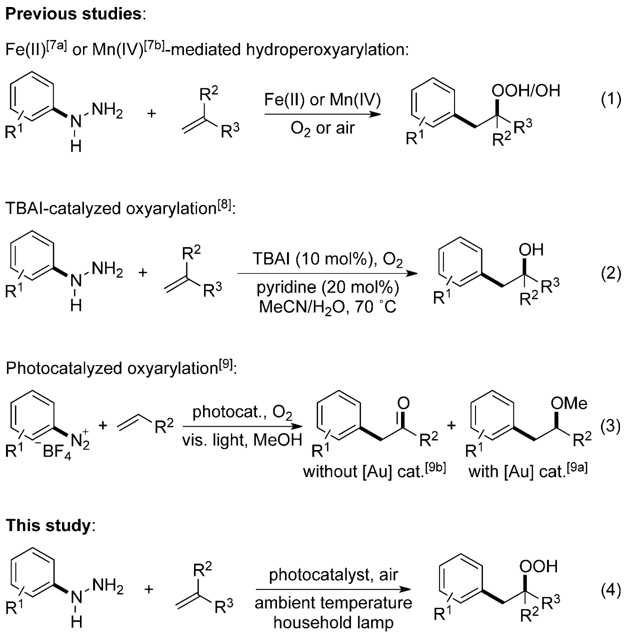
Ying-Ho Chen, Ming Lee, Yi-Zhen Lin, and Dasheng Leow*[a]

Abstract: A mild photocatalytic hydroperoxyarylation of styrenes has been developed, in which a novel photocatalyst, remazol brilliant blue R (RBBR), is employed at low catalytic loading (1 mol%). The operationally easy procedure uses air as the dioxygen source. Simple mono-substituted styrenes react with aryl hydrazines in moderate-to-good yields. RBBR is proposed to act as a photosensitizer for the generation of singlet oxygen.

The vicinal difunctionalization of olefins is an attractive method to access highly functionalized building blocks for organic synthesis. Two new functional groups are introduced within a single transformation, as exemplified by the classical Wacker process or Sharpless asymmetric dihydroxylation.[1] In recent years, the classical Meerwein arylation, which was discovered in 1939, has gained the attention of organic chemists.[2,3] Many new developments have already overcome the limitations of the original Meerwein arylation such as avoiding the use of toxic transition metals, wide substrate scope, and minimizing the formation of several side products.[4] Thus, this has become a viable route for selective radical alkene difunctionalization.

A highly valuable variant of the Meerwein coupling is the oxyarylation reaction, which results in both C–C and C–O bond formations, leading to highly functionalized products.[5] However, aryldiazonium salts are often unstable at room temperature, leading to rapid decomposition and resulting in the loss of nitrogen gas. One of the synthetic equivalents of aryldiazonium salts is the aryl hydrazine derivative, which is much more stable than the former one. Thus, aryl radicals can be easily generated from the oxidation of aryl hydrazines. In recent years, there has been significant advancement on new synthetic methods that generate aryl radicals from aryl hydrazine derivatives.[6]

The Meerwein oxyarylation variant provides the direct synthesis of highly functionalized alcohols from alkenes. In 2011, Taniguchi et al. reported the Fe^{II}-catalyzed hydroperoxyarylation of alkenes by aerobic oxidation of aryl hydrazines [Eq. (1)].[7a] In 2014, Heinrich's group reported that the same transformation could be achieved by using manganese dioxide as a co-oxidant [Eq. (1)].[7b] Jiao and co-workers discovered that by using different types of catalyst, the oxidation could be controlled at different levels for the direct synthesis of substituted alcohols, ketones, and diketones.[8] If a catalytic amount of tetrabutylammonium iodide (TBAI) was used, the reaction could be stopped at the alcohol stage [Eq. (2)]. The Meerwein oxyarylation could also be catalyzed by photoredox catalysis [Eq. (3)].[9] Glorius' group used gold catalysis in combination with photoredox catalysis to afford α-arylated ether products.[9a] Cai and co-workers observed the ketone product when using just photoredox catalysis alone.[9b]



Visible light photoredox catalysis is receiving renewed attention in recent years.[10] These reactions are usually highly selective and greener than the conventional radical chemistry. Many powerful organic transformations enabled by photoredox catalysis have been demonstrated by Bach, Macmillan, König, and other groups.[11] In particular, König et al. developed a series of robust photocatalytic Meerwein arylation reactions.[4]

Recently, we have made several contributions in the area of photocatalysis.[12] In particular, we observed that the visible light catalyzed the transfer hydrogenation of olefins with hydrazine.[12a] However, the research groups of Xiao and Chen recently accomplished the visible light photocatalytic generation of *N*-centered hydrazonyl radicals.[13a] Zhou and Mao et al. also

---

[a] *Y.-H. Chen, M. Lee, Y.-Z. Lin, Prof. D. Leow*
Department of Chemistry
National Tsing Hua University
101, Sec 2, Kuang-Fu Rd., Hsinchu 30013, Taiwan (R.O.C.)
E-mail: dsleow@mx.nthu.edu.tw

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/asia.201500497.

reported the photocatalytic cyclization of 2-isocyanobiphenyls with hydrazines.[13b]

With our continued interest in this direction, we envisage that aryl radicals can be generated from the photocatalytic oxidation of aryl hydrazine derivatives. Subsequently these aryl radicals can undergo hydroperoxyarylation reaction with olefins. Organic peroxides are useful functional groups in organic synthesis.[14,15] However, current hydroperoxyarylation methods require either an oxygen atmosphere[7a] or slow addition of the aryl hydrazine.[7b] The hydroperoxyarylation of mono-substituted olefins is problematic, which is often hampered by moderate yields. Herein we disclose the hydroperoxyarylation of styrene derivatives mediated by visible light photosensitizer using dioxygen from air [Eq. (4)].

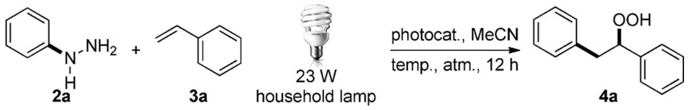
We selected the reaction between phenylhydrazine (**2a**) and mono-substituted styrene (**3a**) under 23 W compact fluorescent light (CFL) irradiation and an atmosphere of air for the optimization studies (Table 1). Among the common photocatalysts that were tested (Table 1, entries 1–4 and see Table S1 in the Supporting Information), moderate yields of the hydroperoxyarylated product were obtained. To our delight, the commercially available remazol brilliant blue R dye (RBBR, **1e**) gave a respectable yield of 74% (Table 1, entry 5). It performed better than some of the well-known photosensitizers such as TPP (**1c**)[11e] and methylene blue (**1g**). By increasing the amount of olefin **3a** to 1 mmol and lowering the catalytic loading to 1 mol% led us to an optimal yield of 87% (Table 1, entry 7).

Although the reaction yield dropped to 46% under an atmosphere of oxygen, the reaction stopped under an atmosphere of nitrogen (Table 1, entries 8 and 9). This indicated that oxygen was crucial for the reaction to occur. In the absence of photocatalyst, the reaction did not proceed any further (Table 1, entry 10). As the lamp warmed the reaction to 35 °C, we conducted the reaction at a controlled temperature of 25 °C and observed a drop in yield to 53% (Table 1, entry 11). We also tested the reaction at 35 °C with the exclusion of light. No product was also observed (Table 1, entry 12).

With the optimized reaction conditions in hand, the scope of styrene derivatives for the hydroperoxyarylation reaction was examined (Table 2). We found that these secondary or tertiary hydroperoxide derivatives **4** were stable after purification by column chromatography. Hydroperoxide **4a** was isolated in excellent yield of 83%. Both electron-withdrawing (**4b**–**d**) and electron-donating substituents (**4e**, **f**) were tolerated at the *para* position.

The yields decreased when the methyl group was at the *meta* and *ortho* positions but the presence of a fluoro group at the *ortho* position was more acceptable (**4g**–**i**). The phenyl group could be replaced by a naphthyl group with excellent yield (**4j**).

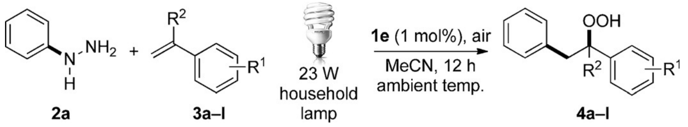
Table 1. Optimization of reaction conditions.[a]

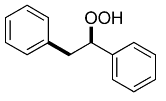


Entry	photocatalyst [mol%]	*T* [°C]	atm.	Yield [%][b]
1	**1a** $[Ru(bpy)_3]Cl_2$ [2]	ambient	air	47
2	**1b** eosin Y [2]	ambient	air	67
3	**1c** TPP [2]	ambient	air	69
4	**1d** $[Ir(ppy)_2(dtbbpy)]PF_6$ [2]	ambient	air	70
5	**1e** RBBR [2]	ambient	air	74
6[c]	**1e** RBBR [2]	ambient	air	84
7[c]	**1e** RBBR [1]	ambient	air	87
8	**1e** RBBR [2]	ambient	O_2	46
9	**1e** RBBR [2]	ambient	N_2	<5
10	none	ambient	air	<5
11[c]	**1e** RBBR [1]	25	air	53
12[c,d]	**1e** RBBR [1]	35	air	<5

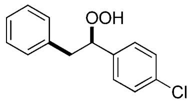
[a] Unless otherwise noted, the reaction conditions were as followed: Aryl hydrazine **2a** (0.10 mmol), photocatalyst **1e** (2 mol%), styrene **3a** (0.5 mmol), MeCN (1.0 mL), 12 h, ambient temperature, irradiated with a light source under a specific atmosphere. [b] Yield determined by ^1H NMR analysis of unpurified reaction mixture using $MeNO_2$ as internal standard. [c] Olefin **3a** (1 mmol) was used. [d] Reaction conducted in the dark. See the Supporting Information for details. Abbreviations: Me = methyl; bpy = 2,2′-bipyridyl; ppy = 2-phenylpyridinyl; dtbbpy = 4,4′-di-*tert*-butyl-2,2′-dipyridyl; TPP = 5,10,15,20-tetraphenyl-21*H*,23*H*-porphine; RBBR = remazol brilliant blue R.

Table 2. Scope of styrene derivatives.[a,b]

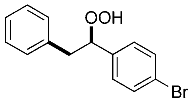




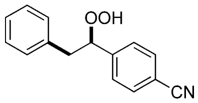
4a, 83%



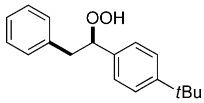
4b, 85%



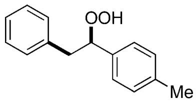
4c, 82%



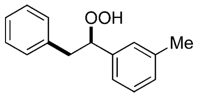
4d, 76%



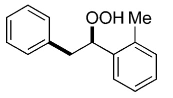
4e, 91%



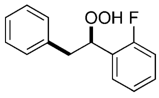
4f, 87%



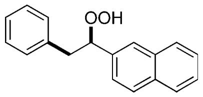
4g, 60%



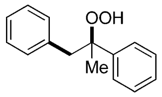
4h, 52%



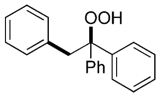
4i, 71%



4j, 81%



4k, 92%

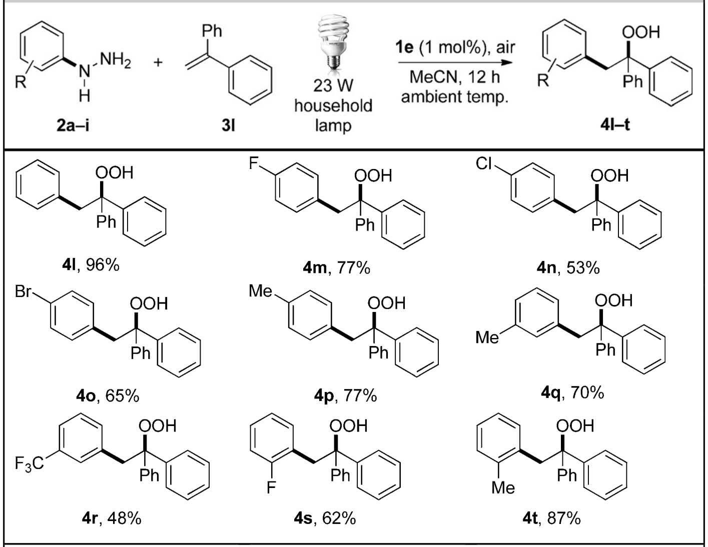


4l, 96%

[a] Unless otherwise noted, the reaction conditions were as followed: Aryl hydrazine **2a** (0.10 mmol), photocatalyst **1e** (1 mol%), olefin **3** (1 mmol), MeCN (1.0 mL), 23 W CFL, 12 h. [b] Yield of isolated product. See the Supporting Information for details.

Similar to previous observations by other groups, the yields further improved when 1,1-disubstituted styrene substrates were used (**4k**, **l**).[7] This is most likely due to the formation of a stable tertiary radical. In all examples, no corresponding alcohol side-product was detected and the reactions were highly selective. Olefins with heteroaromatic ring substitution

Table 3. Scope of aryl hydrazine derivatives.[a,b]

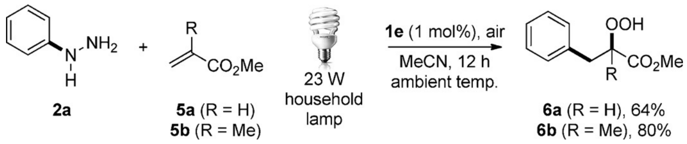


[a] Unless otherwise noted, the reaction conditions were as followed: Aryl hydrazine **2** (0.10 mmol), photocatalyst **1e** (1 mol%), olefin **3l** (1 mmol), MeCN (1.0 mL), 23 W CFL, 12 h. [b] Yield of isolated product. See the Supporting Information for details.

such as 4-vinylpyridine or 2-vinylthiophene failed to react. In addition, the reactivities of other electronically unbiased olefins such as β-pinene and 1,2-disubstituted styrene derivatives, turned out to be low.

Next, several aryl hydrazine derivatives **2a–i** reacted with olefin **3l** and the results are summarized (Table 3). Generally, the aryl hydrazines containing electron-donating and electron-withdrawing groups (**4m–p**) at the *para*-position gave lower yields than phenylhydrazine (**4l**). At the *meta*-position, the electron-donating substituent appeared to perform better than its electron-withdrawing counterpart (**4q**, **r**). This was also the similar case for the *ortho*-substituents (**4s**, **t**). All the aryl hydrazines used were in the base form. We attempted to use its hydrochloride salt form with K_2CO_3 but our efforts proved to be futile. The aryl hydrazines containing electron-withdrawing substituents were stable but the electron-donating substituents were freshly basified just before the reaction was carried out. We also experimented with alkyl hydrazines containing *tert*-butyl or 2-hydroxyethyl groups but these were unsuccessful. Scaling-up the model reaction (Table 1) to 0.3 mmol resulted in 55% yield. Further scaling-up led to diminishing yields.

We extended our method to methyl acrylate derivatives **5**, which contained an electron-withdrawing group (Scheme 1). We were pleased to find that the α-perhydroxylated ester product **6a** was formed in 64% yield when methyl acrylate **5a** was used. The yield even increased to 80% when methyl methacrylate **5b** was used. We also investigated other electron-withdrawing alkenes such as acrylonitrile, cinnamate ester, maleate ester, fumarate ester, and β-nitrostyrene. Unfortunately, all above examples were unsuitable, especially the 1,2-disubstituted ones. Hence this photocatalytic reaction was very sensitive to the steric environment at the aryl radical addition site.



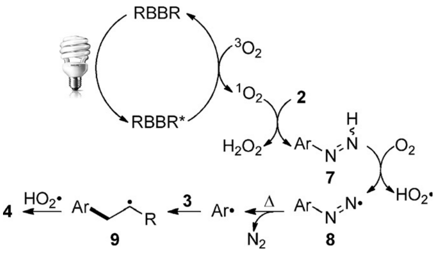
Scheme 1. Hydroperoxyarylation of acrylate derivatives.

The structure of the hydroperoxyarylated product was unambiguously determined by X-ray crystallography (see the Supporting Information). We also used one-dimensional selective NOESY NMR experiments to confirm the regioselectivity of hydroperoxyarylated product (see the Supporting Information). Last but not least, hydroperoxide **4o** was reduced to the corresponding alcohol in 97% yield by using 10% $Na_2S_2O_3$ solution and PPh_3 (1 equiv) as reductants [Supporting Information, Eq. (S1)].

Phenyldiazene was proposed to be a key intermediate in the reaction.[7a] Recently, Heinrich and co-workers showed the trapping of phenyldiazenes in cycloaddition reactions.[16] To understand the reaction mechanism, several experiments were performed. The hydroperoxyarylation of olefins was expected to proceed through a radical reaction. When phenylhydrazine **2a** was subjected to 2,2,6,6-tetramethylpiperidinoxyl (TEMPO), compound **S2** was obtained [Eq. (S2)], which was similar to previous observation with aryl diazonium salts.[4a] When TEMPO was added to the reaction under standard conditions, the TEMPO-trapped intermediate **S3** along with the hydroperoxyarylated product were obtained [Eq. (S3)]. This experimental evidence pointed towards a radical reaction pathway.

Hydrazine was oxidized into diimide during the transfer hydrogenation of olefins.[12a] We conducted the hydroperoxyarylation reaction in CD_3CN and did not observe any reduction of alkene to the saturated alkane using ^{1}H NMR spectroscopy [Eq. (S4)]. We conducted fluorescence quenching experiments with catalyst **1e** and hydrazine **2a** but no quenching effect was observed. As this reaction also did not proceed under dark conditions (Table 1, entry 12), catalyst **1e** was likely to be a singlet oxygen photosensitizer.[17] When aqueous H_2O_2 was added, the hydroperoxyarylation reaction proceeded sluggishly with 28% yield in the absence of catalyst and visible light at 35 °C [Eq. (S5)]. Then the same reaction was repeated but with added catalyst **1e**. This time, the yield went up to 64% [Eq. (S6)]. It was a well-established fact that diazenes decomposed under acidic or basic conditions (e.g. in the Wolff–Kishner reaction).[18] Therefore, basic catalyst **1e** might possibly be catalyzing the decomposition of aryldiazene **7**.

Based on the above-mentioned observations and precedent literature, we outlined a plausible mechanism (Scheme 2). Initially photocatalyst **1e** acted as a photosensitizer and generated singlet oxygen.[17] Then the resultant singlet oxygen oxidized aryl hydrazine **2** to aryl diazene **7**.[19] Next diazene **7** underwent further oxidation by dioxygen to form radical **8** and hydroperoxide radical. Then radical **8** decomposed thermally to give aryl radicals. Subsequently the aryl radicals were trapped by olefins to give radical intermediate **9**. Then radical **9** would be terminated by the hydroperoxide radical, which



Scheme 2. Plausible mechanism.

was generated previously, to give the desired hydroperoxide product **4**.

In summary, we report the synthesis of hydroperoxides through the carbooxygenation of styrenes using a novel photosensitizer, RBBR. Another major highlight of this reaction is the use of air to provide molecular oxygen. The reaction conditions are very mild, thus obviating the need for slow addition of the aryl hydrazine. The highly challenging mono-substituted styrenes are tolerated, thus forming a complementary method to existing ones. RBBR is proposed to act as a photosensitizer for the generation of singlet oxygen. We are currently developing a continuous flow process for large scale synthesis. Mechanistic studies are ongoing and will be reported in due course.

Experimental Section

General Procedure for the Remazol-Catalyzed Hydroperoxyarylation of Olefins

A Pyrex tube equipped with a magnetic stirrer bar was charged with phenylhydrazine **2a** (0.10 mmol, 1.0 equiv), photocatalyst **1e** (0.0010 mmol, 1 mol%), and olefin **3** or **5** (1 mmol). Then MeCN (1.0 mL) was added. The tube was placed approximately 2 cm from the light source (23 W 6500 K CFL). After stirring for 12 h, the crude reaction mixture was filtered through a short pad of silica gel. The filtrate was concentrated in vacuo, and the resulting residue was purified by flash chromatography.

Acknowledgements

We gratefully acknowledge National Tsing Hua University (NTHU) and the Ministry of Science and Technology (102-2113M-007-017-MY2) for financial support. We thank P.-L. Chen (NTHU Instrumentation Center) for X-ray analysis.

Keywords: carbooxygenation · hydrazines · photocatalysis · radicals · singlet oxygen

[1] For selected reviews, see: a) H. C. Kolb, M. S. VanNieuwenhze, K. B. Sharpless, *Chem. Rev.* **1994**, *94*, 2483; b) R. I. McDonald, G. Liu, S. S. Stahl, *Chem. Rev.* **2011**, *111*, 2981; c) F. Cardona, A. Goti, *Nat. Chem.* **2009**, *1*, 269; d) R. M. Romero, T. H. Wöste, K. Muñiz, *Chem. Asian J.* **2014**, *9*, 972.

[2] a) *Radicals in Organic Synthesis* (Eds.: P. Renaud, M. P. Sibi), Wiley-VCH, Weinheim, **2001**; b) G. Pratsch, M. R. Heinrich in *Topics in Current Chemistry* (Eds.: M. R. Heinrich, A. Gansäuer), Springer, Berlin, **2012**, pp. 33; c) S. Hammer, M. R. Heinrich in *Comprehensive Organic Synthesis, 2nd ed.* (Eds.: G. Molander, P. Knochel), Elsevier B. V., Amsterdam, **2014**.

[3] For recent reviews, see: a) C. Galli, *Chem. Rev.* **1988**, *88*, 765; b) M. R. Heinrich, *Chem. Eur. J.* **2009**, *15*, 820; c) F. Y. Mo, G. B. Dong, Y. Zhang, J. B. Wang, *Org. Biomol. Chem.* **2013**, *11*, 1582; d) D. P. Hari, B. König, *Angew. Chem. Int. Ed.* **2013**, *52*, 4734; *Angew. Chem.* **2013**, *125*, 4832; e) H. Bonin, M. Sauthier, F.-X. Felpin, *Adv. Synth. Catal.* **2014**, *356*, 645.

[4] For selected examples, see: a) D. P. Hari, P. Schroll, B. König, *J. Am. Chem. Soc.* **2012**, *134*, 2958; b) P. Schroll, D. P. Hari, B. König, *ChemistryOpen* **2012**, *1*, 130; c) T. Hering, D. P. Hari, B. König, *J. Org. Chem.* **2012**, *77*, 10347; d) D. P. Hari, T. Hering, B. König, *Angew. Chem. Int. Ed.* **2014**, *53*, 725; *Angew. Chem.* **2014**, *126*, 743.

[5] a) M. Hartmann, Y. Li, A. Studer, *J. Am. Chem. Soc.* **2012**, *134*, 16516; b) G. Fumagalli, S. Boyd, M. F. Greaney, *Org. Lett.* **2013**, *15*, 4398.

[6] For selected examples, see: a) T. Taniguchi, Y. Sugiura, H. Zaimoku, H. Ishibashi, *Angew. Chem. Int. Ed.* **2010**, *49*, 10154; *Angew. Chem.* **2010**, *122*, 10352; b) T. Taniguchi, A. Idota, H. Ishibashi, *Org. Biomol. Chem.* **2011**, *9*, 3151; c) H. Jasch, J. Scheumann, M. R. Heinrich, *J. Org. Chem.* **2012**, *77*, 10699; d) M.-K. Zhu, Y.-C. Chen, T.-P. Loh, *Chem. Eur. J.* **2013**, *19*, 5250; e) J. Hofmann, H. Jasch, M. R. Heinrich, *J. Org. Chem.* **2014**, *79*, 2314; f) T. Jiang, S.-Y. Chen, G.-Y. Zhang, R.-S. Zeng, J.-P. Zou, *Org. Biomol. Chem.* **2014**, *12*, 6922; g) S. Kindt, M. R. Heinrich, *Chem. Eur. J.* **2014**, *20*, 15344.

[7] a) T. Taniguchi, H. Zaimoku, H. Ishibashi, *Chem. Eur. J.* **2011**, *17*, 4307; b) S. Kindt, H. Jasch, M. R. Heinrich, *Chem. Eur. J.* **2014**, *20*, 6251.

[8] Y. Su, X. Sun, G. Wu, N. Jiao, *Angew. Chem. Int. Ed.* **2013**, *52*, 9808; *Angew. Chem.* **2013**, *125*, 9990.

[9] a) M. N. Hopkinson, B. Sahoo, F. Glorius, *Adv. Synth. Catal.* **2014**, *356*, 2794; b) M. Bu, T. F. Niu, C. Cai, *Catal. Sci. Technol.* **2015**, *5*, 830.

[10] For selected reviews, see: a) J. Svoboda, B. König, *Chem. Rev.* **2006**, *106*, 5413; b) T. Bach, J. P. Hehn, *Angew. Chem. Int. Ed.* **2011**, *50*, 1000; *Angew. Chem.* **2011**, *123*, 1032; c) C. K. Prier, D. A. Rankic, D. W. C. MacMillan, *Chem. Rev.* **2013**, *113*, 5322.

[11] For selected recent examples of photocatalysis, see: a) A. Bauer, F. Westkämper, S. Grimme, T. Bach, *Nature* **2005**, *436*, 1139; b) D. A. Nicewicz, D. W. C. MacMillan, *Science* **2008**, *322*, 77; c) M. A. Ischay, M. E. Anzovino, J. Du, T. P. Yoon, *J. Am. Chem. Soc.* **2008**, *130*, 12886; d) J. M. R. Narayanam, J. W. Tucker, C. R. J. Stephenson, *J. Am. Chem. Soc.* **2009**, *131*, 8756; e) G. Jiang, J. Chen, J.-S. Huang, C.-M. Che, *Org. Lett.* **2009**, *11*, 4568; f) H. Liu, W. Feng, C. W. Kee, Y. Zhao, D. Leow, Y. Pan, C.-H. Tan, *Green Chem.* **2010**, *12*, 953; g) M. Neumann, S. Füldner, B. König, K. Zeitler, *Angew. Chem. Int. Ed.* **2011**, *50*, 951; *Angew. Chem.* **2011**, *123*, 981; h) M. Rueping, C. Vila, R. M. Koenigs, K. Poscharny, D. C. Fabry, *Chem. Commun.* **2011**, *47*, 2360; i) D. P. Hari, B. König, *Org. Lett.* **2011**, *13*, 3852; j) Y. Zhao, C. Zhang, K. F. Chin, O. Pytela, G. Wei, H. Liu, F. Bureš, Z. Jiang, *RSC Adv.* **2014**, *4*, 30062.

[12] a) D. Leow, Y.-H. Chen, T.-H. Hung, Y. Su, Y.-Z. Lin, *Eur. J. Org. Chem.* **2014**, 7347; b) D. Leow, *Org. Lett.* **2014**, *16*, 5812.

[13] a) X.-Q. Hu, J.-R. Chen, Q. Wei, F.-L. Liu, Q.-H. Deng, A. M. Beauchemin, W.-J. Xiao, *Angew. Chem. Int. Ed.* **2014**, *53*, 12163; *Angew. Chem.* **2014**, *126*, 12359; b) T. Xiao, L. Li, G. Lin, Q. Wang, Z.-W. Mao, L. Zhou, *Green Chem.* **2014**, *16*, 2418.

[14] H. Klenk, P. H. Götz, R. Siegmeier, W. Mayr in *Organic Peroxy Compounds in Ullmann's Encyclopedia of Industrial Chemistry*, Wiley-VCH, Weinheim, **2002**.

[15] For selected examples on the synthesis of organic peroxides, see: a) J. D. Parrish, M. A. Ischay, Z. Lu, S. Guo, N. R. Peters, T. P. Yoon, *Org. Lett.* **2012**, *14*, 1640; b) Y. Yang, F. Moinodeen, W. Chin, T. Ma, Z. Jiang, C.-H. Tan, *Org. Lett.* **2012**, *14*, 4762; c) E. Watanabe, A. Kaiho, H. Kusama, N. Iwasawa, *J. Am. Chem. Soc.* **2013**, *135*, 11744.

[16] S. K. Fehler, G. Pratsch, M. R. Heinrich, *Angew. Chem. Int. Ed.* **2014**, *53*, 11361; *Angew. Chem.* **2014**, *126*, 11543.

[17] M. E. Dzhanashvili, V. M. Anisimov, O. N. Karpukhin, G. E. Krichevskii, *Russ. Chem. Bull.* **1979**, *28*, 1286.

[18] P.-K. C. Huang, E. M. Kosower, *J. Am. Chem. Soc.* **1968**, *90*, 2367.

[19] M. Zhu, N. Zheng, *Synthesis* **2011**, 2223.

Manuscript received: May 14, 2015
Final article published: June 17, 2015