C–H Activation

DOI: 10.1002/anie.201210333

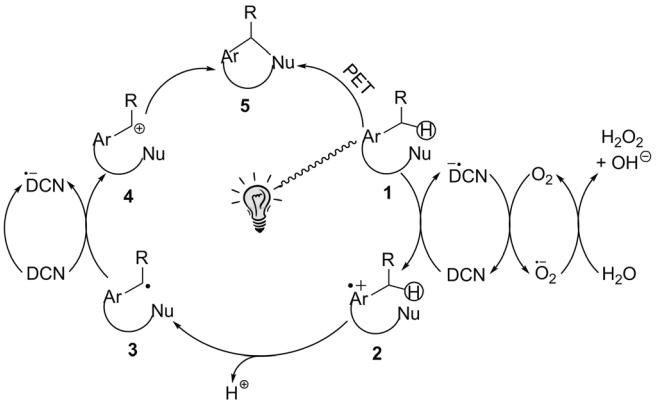
Direct Benzylic C–H Activation for C–O Bond Formation by Photoredox Catalysis**

Ganesh Pandey, Sujit Pal, and Ramkrishna Laha*

Dedicated to Professor Goverdhan Mehta on the occasion of his 70th birthday

A pressing demand of modern organic chemistry is to find a step-economic approach to build complex molecular structures through selective functionalization of a rather unreactive C–H bond.[1] The most fundamental difficulty in such endeavors lies with the selective C–H activation in a molecule which contains a diversity of C–H groups. Intense research activities by several research groups in this area have resulted in the development of some very useful protocols for regioselective C_{sp^2}–H activation through transition-metal catalysis,[2] however, the corresponding C_{sp^3}–H activation is still in its infancy.[3] The benzyl group is an important motif in organic syntheses and has relatively active C_{sp^3}–H bonds, because of the proximal aromatic ring, and have therefore been functionalized using either heteroatom-chelated transition-metal catalysts[4] or nondirected oxidative activations.[5,6] Nondirected oxidative activations have either required *tert*-butyl hydrogen peroxide (TBHP) in the presence of a metal catalyst,[5] or a chemical oxidant such as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in the cases where the benzyl group is flanked by an α-nitrogen/oxygen atom.[6] More recently, benzylic C–H activation of xanthenes as well as acridanes using molecular oxygen in the presence of a Brønsted acid was also reported.[7] In spite of impressive progress made in this area, the reported protocols are far from being environmentally benign as they either require moisture-sensitive and expensive metal catalysts or special structural requirements along with excessive use of chemical oxidants. Therefore, further research in this area is still warranted.

While exploring the new reactions of photoinduced electron-transfer (PET)-generated radical cations, our group had effected regioselective C_{sp^2}–H activation for C–C as well as C–Y (Y = O, N) bond-formation reactions.[8] The regioselectivity in such activations was explained on the basis of varying electron densities of the carbon atom in the arene radical cation.[9] In another related study, we had also reported a sequential electron-proton-electron (E-P-E) loss to generate an iminium ion from the PET oxidation of tertiary amines.[10] These two critical observations led us to envisage an unprecedented benzylic C–H bond-activation protocol by a photoredox cycle as shown in Scheme 1. We report herein



Scheme 1. Concept of benzylic C–H activation by photoredox catalysis.

the success of our concept for direct benzylic C–H activation for C–O bond formation and it requires neither a metal catalyst nor a chemical oxidant.

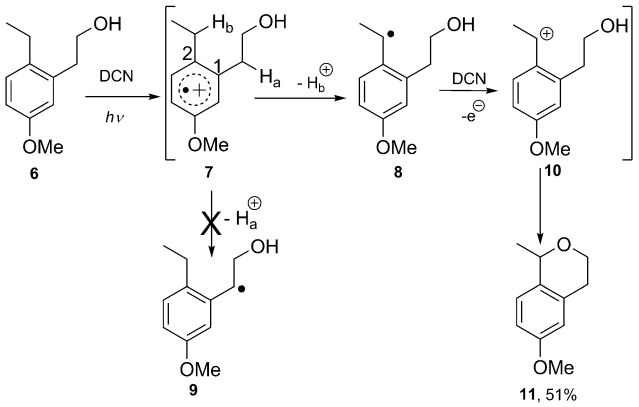
Initially, to test the feasibility of the proposed concept, a mixture of the alkylarene **6** (1 mmol) and 1,4-dicyanonaphthalene (DCN, 0.05 mmol) in acetonitrile was photolyzed using a 450-W Hanovia medium pressure lamp housed in a Pyrex glass immersion well (> 300 nm) for 4 hours (55% conversion, monitored by GC, all light absorbed by **6** only; Scheme 2). The usual work-up and purification of the reaction mixture produced 6-methoxy-1-methylisochroman (**11**) in 51% yield (calculated based on consumption of starting material). DCN and the unreacted **6** were recovered in 98 and 45%, respectively. A longer irradiation (> 5 h) produced a complex mixture of products. Control experiments involving the irradiation of **6** alone or a mixture of **6** and DCN, where all light was absorbed by DCN, did not yield any product.[11] Therefore, mechanistically, the present reaction is considered to be initiated by a single-electron transfer (SET) from the exicited state of **6** to the ground state of DCN, thus generating **7**, which produces **11** by the sequence as shown in Scheme 2.

The regioselective formation of **10** by H_b^+ loss from **7** is explained by natural bond orbital (NBO) analysis of the

[*] G. Pandey, S. Pal, R. Laha
Molecular Synthesis Laboratory,
Centre of Biomedical Research (CBMR),
Sanjay Gandhi Postgraduate Institute of Medical Science Campus
Raebareli Road, Lucknow-226014 (India)
E-mail: gp.pandey@cbmr.res.in

[**] Part of this work was carried out at the National Chemical Laboratory, Pune-411008, India. We thank the CSIR, New Delhi, India for Research Fellowships to S.P. and R.L. Financial support by the DST New Delhi through the J. C. Bose Fellowship is acknowledged. We also thank Nishamol Kuriakose (NCL, Pune) for theoretical calculations.

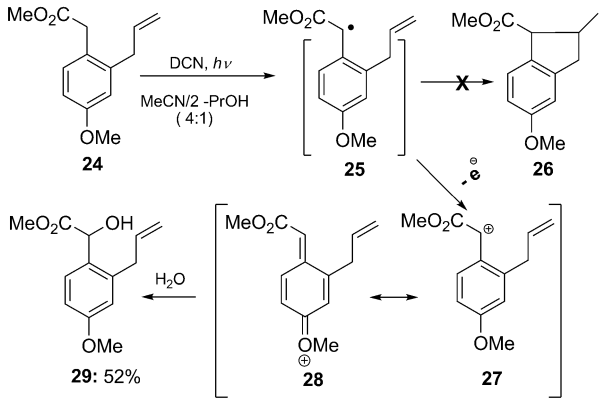
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201210333.



Scheme 2. Regioselective benzylic C–H activation for C–O bond formation.

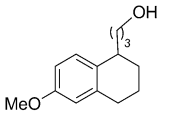
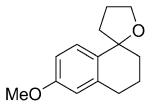
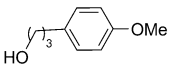
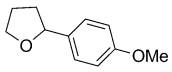
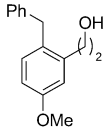
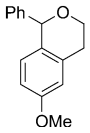
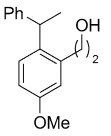
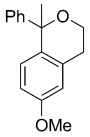
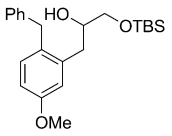
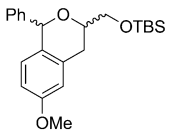
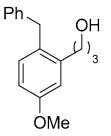
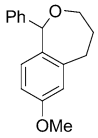
natural charge density on each carbon atom of **7** using DFT calculations in the Gaussian 09 suite of programs[12] where the B3LYP functional and 6-31 g* basis sets were used. The more positive charge residing on C2 (+ 0.2598) in comparison to C1 (+ 0.0593) plausibly makes H_b more acidic for accelerated deprotonation. Furthermore, the free energies of two optimized geometries of the radical intermediates **8** and **9** were calculated at the same level of theory and have shown that **8** is more stable than **9** by at least 1.07 kcal mol^{-1} (ΔG). Encouraged by this result, the alkylarenes **12** and **13** were activated in a manner identical to the one described for **6**, and produced the corresponding cyclic ethers **18** (62%) and **19** (51%). To broaden the substrate scope, we also studied the PET activation of **14**–**17** and the results of the formation of the corresponding cyclic ethers (**20**–**23**) are shown in Table 1.

Having successfully activated benzylic C–H bonds for cycloetherification reactions, we turned our attention to trapping the benzylic radical, which is the first intermediate formed in this reaction, by studying the PET activation of **24** with the hope that the stabilized radical **25** would be able to add to a tethered olefin to produce the corresponding indane derivative **26** (Scheme 3). However, it produced **29** (52%) possibly by the reaction of trace amounts of moisture, present in the solvent, with the intermediate **27**. This interesting and unprecedented reaction where a nucleophile has been added



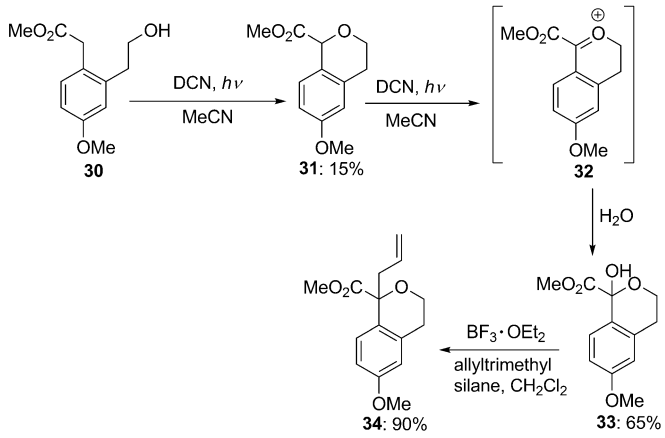
Scheme 3. Investigation of the benzyl radical cyclization reaction.

Table 1: Generality of the intramolecular cycloetherification reaction.[a]

Entry	Substrate	Product	t [h]	Yield [%][b]
1	 **12**	 **18**	5	62
2	 **13**	 **19**	3	51
3	 **14**	 **20**	3	72
4	 **15**	 **21**	4	64
5	 **16**	 **22**	4	61[c]
6	 **17**	 **23**	4	58

[a] Reaction conditions: DCN (5 mol%), acetonitrile, RT. [b] Yield of isolated product calculated based on consumption of starting material. [c] d.r. = 2:1. TBS = *tert*-butyldimethylsilyl.

α to an ester moiety is explained by implicating the intermediacy of the distonic carbocation **28**. The only parallel to this finding, to the best of our knowledge, may be made by the method of Ishihara and co-workers[13] for intramolecular oxylactonization of ketocarboxylic acid using hypervalent iodine as a catalyst in the presence of peroxides. However, this protocol suffers from the low chemoselectivity because of the competing Baeyer–Villiger oxidations.[13b] To trap the distonic cation of type **28** intramoleculary, we studied the activation of **30** and observed the formation of the unexpected cyclic hemiacetal **33** (65% yield, crystalline solid, m.p. = 255 °C–265 °C) along with the expected **31** (15% yield; Scheme 4). The structure of **33** was deduced on the basis of detailed ^{1}H and ^{13}C NMR spectroscopy, and mass spectrometry, and was further confirmed unambiguously by transformation of **33** into **34** (90% yield) by a BF_3.OEt_2-mediated allylation reaction. The formation of **33** obviously involved



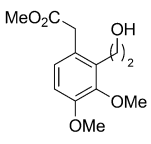
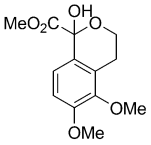
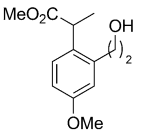
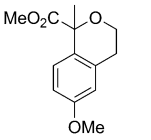
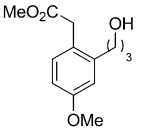
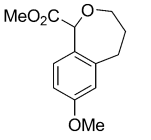
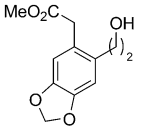
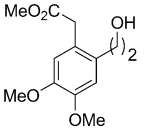
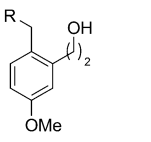
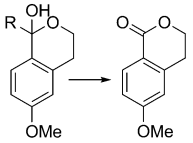
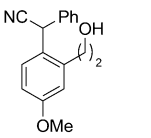
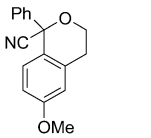
Scheme 4. Possible mechanism for cyclic hemiacetal formation.

facile formation of **32** by another E-P-E sequence from **31**, a result of enhanced kinetic acidity of the benzylic C–H bond. In an effort to generalize this reaction, we studied several substrates (**35**–**43**) and results are shown in Table 2. It was observed that **35** produced corresponding hemiacetals (**43**, 55% yield) as expected, whereas **37** gave **45** (44% yield) as the sole product, possibly because of an unfavorable cyclic seven-membered oxocarbenium ion geometry. Unfortunately, **38** and **39** produced an unidentified mixture of products possibly from the competing benzylic C–H activations. Furthermore, to broaden the scope of this reaction, we studied the activation of **40** and **41** and isolated, interestingly, same cyclic lactone **48** in each case, possibly from the decomposition of the unstable cyclic cyanohemiacetal **46** or the methoxy hemiacetal **47** intermediates, respectively. The involvement of **46** and **47** as intermediates for of **48** was suggested by the isolation of **49** from the activation of **42**.

After successful realization of benzylic C–H activation for intramolecular C–O bond formation, we enthusiastically turned our attention towards utilizing this protocol for direct transformation of arylalkyls into the corresponding aryl ketones as these are important compounds used in pharmaceuticals.[14] Although, arylalkyl ketones are synthesized by Friedel–Crafts acylation of arenes and by direct oxidation of arlyalkyls in the presence of hypervalent iodine,[15] metal catalysts[16] or organocatalysts,[17] regioselectivity, air and moisture sensitivity of the reagent, use of excess co-oxidants, limited substrate scope, and sometimes the formation of mixture of products puts severe limitations on the use of these protocols. Thus, we hypothesized that freely available water could be used as a source of oxygen for benzylic oxidation.

Initially, to substantiate our hypothesis, we activated **50** in an acetonitrile/water (4:1) mixture for 5 hours and isolated **52** in high yield (80%), and it presumably involved the benzylic alcohol **51** as an intermediate (for structures see Scheme 5). To prove the intermediacy of **51** in this reaction, an authentic sample of **51** was irradiated in an identical manner and **52** was obtained in quantitative yield. Furthermore, a control experiment in which **50** was irradiated only for 1 hour, afforded a mixture of **50** (42%) and **51** (20%), thus supporting the

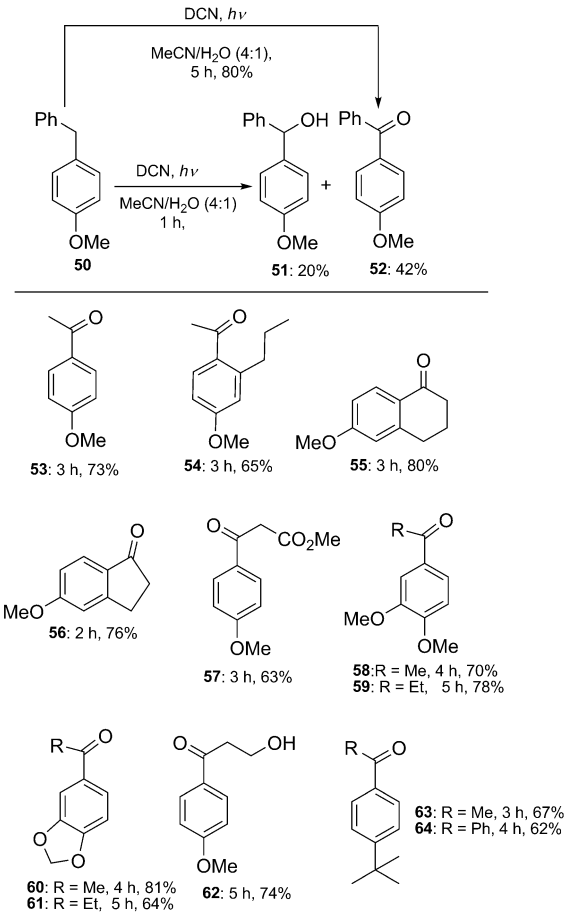
Table 2: Study of the substrate scope for cyclic hemiacetal formation.[a]

Entry	Substrate	Product	*t* [h]	Yield [%][b]
1	 **35**	 **43**	4	55
2[c]	 **36**	 **44**	5	52
3	 **37**	 **45**	4	44
4	 **38**	complex mixture		
5	 **39**	complex mixture		
6	 **40** (R = CN)	 **46** (R = CN) **48**	1	73 85
7	**41** (R = OMe)	**47** (R = OMe)		
8	 **42**	 **49**	3	74

[a] Reaction conditions: DCN (5 mol%), acetonitrile (except entry 2), RT. [b] Yield of the isolated product is based on the consumption of starting material. [c] Acetonitrile/water (4:1) was used as the medium.

mechanism of the direct transformation of **50** into **52**. To generalize the current protocol of arylalkyl oxidation, several arylalkyls were studied and the results (**53**-**64**) are shown in Scheme 5. Besides having established high regioselectivity (**54**–**56**) a unique chemoselectivity was also established by the PET activation of **62**.

In conclusion, we have successfully developed a new concept for benzylic C–H activation in intramolecular cyclo-



Scheme 5. Direct oxidation of arylalkyls to the corresponding ketones using water as an oxygen source.

etherification reactions as well direct oxidation to aryl ketones. Further studies on C–C as well as C–N bond-forming reactions are in progress and will be reported in due course.

Received: December 28, 2012
Revised: February 6, 2013
Published online: April 8, 2013

Keywords: arenes · C–H activation · heterocycles · photochemistry · reaction mechanisms

[1] a) R. G. Bergman, *Nature* **2007**, *446*, 391 – 393; b) K. Godula, D. Sames, *Science* **2006**, *312*, 67 – 72; c) J. A. Labinger, J. E. Bercaw, *Nature* **2002**, *417*, 507 – 514.

[2] a) N. Kuhl, M. N. Hopkinson, J. Wencel-Delord, F. Glorius, *Angew. Chem.* **2012**, *124*, 10382 – 10401; *Angew. Chem. Int. Ed.* **2012**, *51*, 10236 – 10254; b) L. Ackermann, *Chem. Rev.* **2011**, *111*, 1315 – 1345; c) O. Daugulis, H.-Q. Do, D. Shabashov, *Acc. Chem. Res.* **2009**, *42*, 1074 – 1086.

[3] a) O. Baudoin, *Chem. Soc. Rev.* **2011**, *40*, 4902 – 4911; b) S.-Y. Zhang, F.-M. Zhang, Y.-Q. Tu, *Chem. Soc. Rev.* **2011**, *40*, 1937 – 1949.

[4] a) Y. Xie, Y. Yang, L. Huang, X. Zhang, Y. Zhang, *Org. Lett.* **2012**, *14*, 1238 – 1241; b) N. Dastbaravardeh, *Org. Lett.* **2012**, *14*, 1930 – 1933; c) Y. Li, Z. Li, T. Xiong, Q. Zhang, X. Zhang, *Org. Lett.* **2012**, *14*, 3522 – 3525; d) T. Nanjo, C. Tsukano, Y. Takemoto, *Org. Lett.* **2012**, *14*, 4270 – 4273; e) P. Novák, A. Correa, J. Gallardo-Donaire, R. Martin, *Angew. Chem.* **2011**, *123*, 12444; *Angew. Chem. Int. Ed.* **2011**, *50*, 12236.

[5] a) C. J. Li, *Acc. Chem. Res.* **2009**, *42*, 335 – 344; b) P. Xie, Y. Xie, B. Qian, H. Zhou, C. Xia, H. Huang, *J. Am. Chem. Soc.* **2012**, *134*, 9902 – 9905; c) Z. Li, Li. Cao, C.-J. Li, *Angew. Chem.* **2007**, *119*, 6625 – 6627; *Angew. Chem. Int. Ed.* **2007**, *46*, 6505 – 6507; d) Z. Li, C. J. Li, *J. Am. Chem. Soc.* **2005**, *127*, 3672 – 3673.

[6] a) S. J. Park, J. R. Price, M. H. Todd, *J. Org. Chem.* **2012**, *77*, 949 – 955; b) L. Liu, P. E. Floreancig, *Angew. Chem.* **2010**, *122*, 6030 – 6033; *Angew. Chem. Int. Ed.* **2010**, *49*, 5894 – 5897; c) B. Yu, T. Jiang, Y. Su, X. Pan, X. She, *Org. Lett.* **2009**, *11*, 3442 – 3445; d) Y. Zhang, C. J. Li, *J. Am. Chem. Soc.* **2006**, *128*, 4242 – 4243.

[7] a) B. Zhang, S. K. Xiang, L. H. Zhang, Y. Cui, N. Jiao, *Org. Lett.* **2011**, *13*, 5212 – 5215; b) Á. Pintér, A. Sud, D. Sureshkumar, M. Klussmann, *Angew. Chem.* **2010**, *122*, 5124 – 5128; *Angew. Chem. Int. Ed.* **2010**, *49*, 5004 – 5007.

[8] a) G. Pandey, A. Murugan, M. Balakrishnan, *Chem. Commun.* **2002**, 624 – 625; b) G. Pandey, M. Karthikeyan, A. Murugan, *J. Org. Chem.* **1998**, *63*, 2867 – 2872; c) G. Pandey, A. Krishna, K. Girija, M. Karthikeyan, *Tetrahedron Lett.* **1993**, *34*, 6631 – 6634; d) G. Pandey, M. Sridhar, U. T. Bhalerao, *Tetrahedron Lett.* **1990**, *31*, 5373 – 5376; e) G. Pandey, *J. Org. Chem.* **1988**, *53*, 2364 – 2365.

[9] G. Pandey, A. Krishna, U. T. Bhalerao, *Tetrahedron Lett.* **1989**, *30*, 1867 – 1870.

[10] a) G. Pandey, *Synlett* **1992**, 546 – 552; b) G. Pandey, *Top. Curr. Chem.* **1993**, *168*, 175 – 221.

[11] "*Photoinduced SET initiated reactions: Generation and synthetic application of arene radical cations*": a) A. Krishna, Ph.D. Thesis entitled, submitted to Osmania University, Hyderabad, India, **1989**; b) C. Pac, A. Nakasone, H. Sakurai, *J. Am. Chem. Soc.* **1977**, *99*, 5806 – 5808.

[12] a) Gaussian 98 (Revision A.9): M. J. Frisch et al., see Supporting Information; b) A. E. Reed, R. B. Weinstock, F. Weinhold, *J. Chem. Phys.* **1985**, *83*, 735 – 746; c) D. B. Axel, *J. Chem. Phys.* **1993**, *98*, 5648 – 5652.

[13] a) M. Uyanik, H. Okamoto, T. Yasui, K. Ishihara, *Science* **2010**, *328*, 1376 – 1379; b) M. Uyanik, T. Yasui, K. Ishihara, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3848 – 3851.

[14] a) R. A. Sheldon, J. K. Kochi, *Metal Catalyzed Oxidations of Organic Compounds*, Academic Press, New York, **1981**; b) G. Cainelli, G. Cardillo, *Chromium Oxidations in Organic Chemistry*, Springer, Berlin, **1984**; c) M. Hudlicky, *Oxidion in Organic Chemistry*, American Chemical Society, Washington, DC, **1990**; d) M. Recupero, C. Punta, *Chem. Rev.* **2007**, *107*, 3800 – 3842.

[15] a) K. C. Nicolaou, P. S. Baran, Y-Li. Zhong, *J. Am. Chem. Soc.* **2001**, *123*, 3183 – 3185; b) Y. Xu, J. T. Hu, J. Yan, *Chin. Chem. Lett.* **2012**, *23*, 891 – 894.

[16] a) L. Zhang, G. Y. Ang, S. Chiba, *Org. Lett.* **2011**, *13*, 1622 – 1625; b) T. Nagano, S. Kobayashi, *Chem. Lett.* **2008**, *37*, 1042 – 1045; c) C. S. Yi, K. H. Kwon, D. W. Lee, *Org. Lett.* **2009**, *11*, 1567 – 1570; d) A. J. Catino, J. M. Nichols, H. Choi, S. Gottipamula, M. P. Doyle, *Org. Lett.* **2005**, *7*, 5167 – 5170; e) Y. Bonvin, E. Callens, I. Larrosa, D. A. Henderson, J. Oldham, A. J. Burton, A. G. M. Barrett, *Org. Lett.* **2005**, *7*, 4549 – 4552; f) N. H. Lee, C. S. Lee, D. S. Jung, *Tetrahedron Lett.* **1998**, *39*, 1385 – 1388.

[17] a) G. Yang, Q. Zhang, H. Miao, X. Tong, J. Xu, *Org. Lett.* **2005**, *7*, 263 – 266; b) K. Ohkubo, S. Fukuzumi, *Org. Lett.* **2000**, *2*, 3647 – 3650; c) R. Lechner, S. Kümmel, B. König, *Photochem. Photobiol. Sci.* **2010**, *9*, 1367 – 1377.

