

# ChemComm

Accepted Manuscript



This is an *Accepted Manuscript*, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

*Accepted Manuscripts* are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this *Accepted Manuscript* with the edited and formatted *Advance Article* as soon as it is available.

You can find more information about *Accepted Manuscripts* in the [Information for Authors](#).

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard [Terms & Conditions](#) and the [Ethical guidelines](#) still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this *Accepted Manuscript* or any consequences arising from the use of any information it contains.

## Protonation of Silylenol Ether *via* Excited State Proton Transfer Catalysis

Received 00th January 20xx,  
Accepted 00th January 20xx

Anjan Das,<sup>a</sup> Tanmay Banerjee<sup>a</sup> and Kenneth Hanson\*<sup>a</sup>

DOI: 10.1039/x0xx00000x

www.rsc.org/

We demonstrate the photocatalytic protonation of a silyl enol ether using 7-bromo-2-naphthol as an ESPT catalyst with phenol as the sacrificial proton source. Greater than 95% conversion is achieved with 1 mol % catalyst. The reaction cycle is dependent on the significantly increased acidity of the catalyst in the excited state as well as the long lifetime for the triplet excited state of 7-bromo-2-naphthol. The reaction does not occur in the absence of light (366 nm) and can readily be controlled by light intensity modulation. We also demonstrate that a 72% reaction yield can be obtained using unsubstituted naphthol as the catalyst by coupling triplet energy transfer via a visible light absorbing (445 nm) sensitizer into the catalytic cycle. These results open the door to an entirely new class of sensitized photocatalytic reactions that harness the excited state acidity of ESPT dyes.

Photocatalysis is an appealing strategy for chemical synthesis because it can proceed at room temperature under relatively gentle conditions and it uses light as a non-toxic reagent.<sup>1</sup> Current efforts in photocatalysis are primarily focused on redox chemistry with catalysts like ruthenium(II) tris-(2,2'-bipyridine)<sup>2</sup> that act as an excited state electron donor (or acceptor) to reduce (or oxidize) the substrate.<sup>3</sup> These photo-induced electron transfer reactions rely on changes in redox potentials of the catalyst upon photoexcitation.

For molecules that contain a proton donating group, an additional excited state perturbation can occur where the electron density shift associated with light absorption significantly increases the acidity of the molecule by upwards of 13 pK<sub>a</sub> units.<sup>4</sup> In the presence of base, excited state *intra-* or *intermolecular* proton transfer (ESIPT and ESPT respectively) can occur.<sup>5</sup> It has been shown that ESIPT can be used to facilitate organic transformations like deuterium exchange<sup>6</sup> or cycloaddition reactions<sup>7</sup> but the photoactive substrate is consumed during the transformation.

The transient and reversible nature of ESPT has been utilized for light controlled alcohol deprotection<sup>8a,b</sup> and enzyme activation/inhibition.<sup>8c,d</sup> However, to the best of our knowledge, ESPT catalysis that utilizes a weak sacrificial acid to regenerate the catalyst has not been demonstrated. Herein, we report the use of ESPT to photocatalytically protonate a silylenol ether with 7-bromo-2-naphthol (Br-NpOH) as the catalyst and phenol (PhOH) as the sacrificial proton source. The proposed catalytic cycle is in Figure 1a.

The relative pK<sub>a</sub> values and kinetic parameters associated with this catalytic cycle are depicted in Figure 1b. In this scheme the pK<sub>a</sub> of PhOH and the ground state Br-NpOH are higher than the substrate and thus the silyl enol ether is not protonated. Pivotal to the

reaction cycle is that upon excitation, the pK<sub>a</sub> of the catalyst significantly decreases ( $\Delta pK_a > 10$ )<sup>6a</sup> and becomes sufficiently acidic to transfer a proton to the substrate.

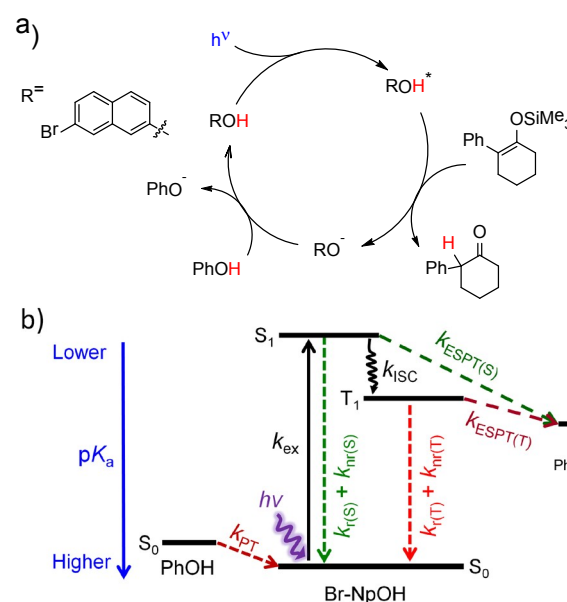


Figure 1. a) Proposed reaction cycle for the photocatalytic protonation of 1-phenyl-2-(trimethylsilyloxy)cyclohexene to generate 2-phenylcyclohexanone. b) Relative pK<sub>a</sub> values and kinetic parameters associated with the ESPT catalytic reaction cycle. (PT = proton transfer, ex = excitation, r = radiative decay, nr = non-radiative decay, ESPT = excited state proton transfer, S = singlet state, T = triplet state, ISC = intersystem crossing)

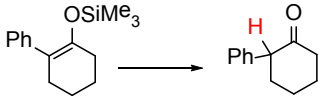
<sup>a</sup> Department of Chemistry and Biochemistry, Florida State University, Tallahassee, Florida, 32306, United States, Email: hanson@chem.fsu.edu

Electronic Supplementary Information (ESI) available: Experimental details, <sup>1</sup>H-NMR spectra, graph of intensity dependent study, table for sensitized ESPT catalysis. See DOI: 10.1039/x0xx00000x

Substituted naphthol was selected as the ESPT catalyst for this work because naphthol is one of the simplest organic chromophores and non-catalytic ESPT has previously been demonstrated with bromine substituted naphthol.<sup>8e,f</sup> One of the key features of this catalyst is that the heavy atom effect of bromine facilitates intersystem crossing into the long lived triplet excited state<sup>9</sup> which was found to be necessary for the protonation of the substrate (*vide infra*). The selection of substrate, 1-phenyl-2-(trimethylsiloxy)cyclohexene, was inspired by the work of H. Yamamoto and coworkers who have carried out the protonation of silylenol ether by using Lewis acid coordinated to binaphthol as a means of increasing its ground state acidity.<sup>10</sup>

Various conditions for the protonation of 1-phenyl-2-(trimethylsiloxy)cyclohexene were examined and the results are summarized in Table 1. The reaction was monitored by <sup>1</sup>H-NMR spectroscopy with the product yield calculated relative to an internal reference (triphenylmethane).

Table 1. Reaction conditions for the protonation of 1-phenyl-2-(trimethylsiloxy)cyclohexene in toluene-d<sub>8</sub>.<sup>a</sup>



Entry	Br-NpOH	PhOH	hν (nm)	Temp (°C)	Yield (%) <sup>b</sup>
1	0.025 M	-	-	65	0
2	-	5 M	-	65	0
3	0.025 M	5 M	-	65	0
4	-	5 M	367	22	0
5	0.025 M	-	367	22	1.8
6	0.025 M	5 M	367 <sup>c</sup>	22	0
7	0.025 M	5 M	367	22	84
8 <sup>d</sup>	0.025 M	5 M	sunlight	22	3.0
9 <sup>e</sup>	0.025 M	5 M	367	22	96

<sup>a</sup>Reactions were carried out for 20 h with 2.5 M of silylenol ether in 0.6 mL toluene-d<sub>8</sub> under atmosphere unless otherwise noted.

<sup>b</sup>Calculated by using <sup>1</sup>H-NMR with triphenylmethane as the internal reference. <sup>c</sup>Irradiation for 20 hours followed by addition of silylenol ether. <sup>d</sup>Reaction was carried out for 3 days. <sup>e</sup>Irradiated under a nitrogen atmosphere after bubble deaerating for 30 minutes.

Irradiation ( $\lambda=367$  nm, 8 mW/cm<sup>2</sup>) of a toluene-d<sub>8</sub> solution containing substrate, Br-NpOH (1 mol %) and PhOH (200 mol %) at room temperature produced 2-phenylcyclohexanone in 84% yield (entry 7 in Table 1). The wavelength of irradiation was chosen as to selectively excite the low energy absorption tail of Br-NpOH but not PhOH, substrate or product ( $\lambda_{\text{onset}} < 310$  nm; Figure S1 in supporting information). Assuming the mechanism proposed in Figure 1a, an 84% yield equates to 84 turnovers per catalyst. It is worth note that the reaction proceeds, albeit at a much slower rate, even under ambient sunlight with approximately 3% yield after 3 days of exposure (entry 8 in Table 1). Doubling the mole fraction of catalyst did not increase the reaction yield (85%) but a four-fold decrease in catalyst concentration significantly reduced the yield (54%). Therefore, all subsequent experiments were performed with 1 mol % of catalyst.

In the absence of light neither Br-NpOH nor PhOH alone, nor a mixture of the two, were sufficiently acidic to protonate the substrate and generate any observable 2-phenylcyclohexanone even at elevated temperatures (entries 1-3 in Table 1). Likewise,

irradiation of PhOH and substrate did not result in product formation (entry 4 in Table 1). Photoexcitation of Br-NpOH in the presence of substrate but without PhOH yielded 1.8% 2-phenylcyclohexanone indicating that Br-NpOH\* is sufficiently acidic to protonate 1-phenyl-2-(trimethylsiloxy)cyclohexene. However, in the absence of phenol as a sacrificial proton source the reaction yield is limited to approximately stoichiometric amounts of product. It is important to note that irradiation of Br-NpOH and PhOH followed by the addition of substrate in the dark did not yield product (entry 6 in Table 1). This control experiment demonstrates that the reaction is not driven by photo-induced decomposition of Br-NpOH to generate "free" acidic protons but is instead dependent on transient acidity of the excited state catalyst.

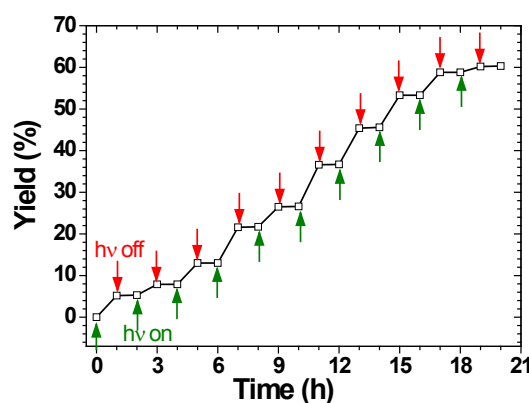


Figure 2. Percent yield of 2-phenylcyclohexanone with respect to time while modulating between light (green arrow) and dark (red arrow) conditions. (2.5 M substrate, 5 M PhOH and 0.025 M Br-NpOH in toluene-d<sub>8</sub>)

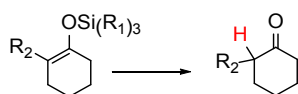
The reaction is light dependent as demonstrated by monitoring product formation while modulating between light and dark reaction conditions at 1 h intervals (Figure 2). Throughout the 20 h experiment the product yield increases during irradiation but remains constant in the dark. Additionally, the reaction yield/rate is directly dependent on the light intensity (Figure S2, in Supporting information) which corresponds with the rate of catalyst excitation ( $k_{\text{ex}}$  in Figure 1b). This light-modulated reaction mechanism provides an unprecedented degree of control as compared to traditional acid catalyzed reactions.

The above results support the proposed catalytic reaction cycle depicted in Figure 1a. Upon excitation, the ESPT catalyst protonates 1-phenyl-2-(trimethylsiloxy)cyclohexene to generate 2-phenylcyclohexanone and Br-NpOH\*. After relaxation, Br-NpOH\* is sufficiently basic to be protonated by PhOH to regenerate Br-NpOH which can then, upon excitation, undergo additional reaction cycles. Presumably, based on the results of Yamamoto and coworkers, the liberated TMS group is trapped by the excess PhOH/PhO<sup>-</sup> in solution to generate PhO-TMS.<sup>10</sup>

ESPT catalysis was effective with a range of silylenol ether substituted at the R<sub>1</sub> and R<sub>2</sub> positions as summarized in Table 2. The small decrease in reaction yield from entry 1 to 4 that can be attributed to the influence of the increased bulkiness of the R<sub>1</sub> substituent and +I effect that make the O-Si stronger and more difficult to cleave. Substitution at R<sub>2</sub> with electron donating or withdrawing groups had minimal influence on the reaction yield

(Entry 1 and 5-8, 75-90 %). Interestingly the highest reaction yield (94%) was achieved with 2-methyl-3-(trimethylsiloxy)indene (Entry 9, Table 2).

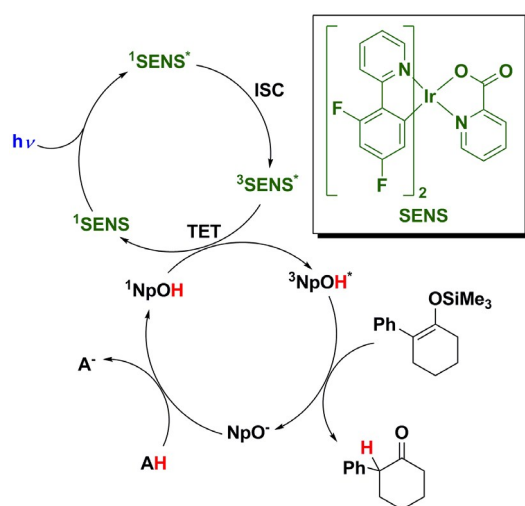
**Table 2.** Reaction yield for various silylenol ethers.<sup>a</sup>



Entry	R <sub>1</sub>	R <sub>2</sub>	Yield (%) <sup>b</sup>
1	CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	84
2	CH <sub>2</sub> CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	76
3	CH(CH <sub>3</sub> ) <sub>2</sub>	C <sub>6</sub> H <sub>5</sub>	68
4	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	64
5	CH <sub>3</sub>	(3-MeO) C <sub>6</sub> H <sub>4</sub>	90
6	CH <sub>3</sub>	Br	78
7	CH <sub>3</sub>	CH <sub>3</sub>	82
8	CH <sub>3</sub>	CH <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	75
9	2-methyl-3-(trimethylsiloxy)indene		94

<sup>a</sup> Reactions were carried out for 20 h with 2.5 M of silylenol ether, 5 M PhOH and 0.025 M Br-NpOH in 0.6 mL toluene-d<sub>8</sub>. <sup>b</sup> Calculated by using <sup>1</sup>H-NMR with triphenylmethane as the internal reference.

No product was generated when naphthol (NpOH) or 7-nitro-2-naphthol (NO<sub>2</sub>-NpOH) were used instead of Br-NpOH. Given the increased acidity of NO<sub>2</sub>-NpOH compared to Br-NpOH the lack of product generation is not due to the pK<sub>a</sub> of the excited catalyst. We attribute the effectiveness of Br-NpOH to the bromine atoms ability to facilitate intersystem crossing (*k*<sub>ISC</sub> in Figure 1b) to the triplet excited state.<sup>9b</sup> For NpOH and NO<sub>2</sub>-NpOH the radiative and non-radiative decay rate constants (*k*<sub>r(S)</sub> and *k*<sub>nr(S)</sub>; τ < 10 ns) from the singlet excited state are significantly faster than intersystem crossing (*k*<sub>ISC</sub>) or diffusion and ESPT (*k*<sub>ESPT(S)</sub>). On the other hand, fast ISC and slow, spin forbidden *k*<sub>r(T)</sub> and *k*<sub>nr(T)</sub> for the long lived triplet excited state of Br-NpOH (τ > 10 ms) likely allows sufficient time for a diffusion limited bimolecular reaction between the excited catalyst and substrate (*k*<sub>ESPT(T)</sub>).<sup>9</sup> It is worth noting that while the excited state pK<sub>a</sub> for the triplet state (~14.6 in MeCN) is higher than that of the singlet state (~13.7 in MeCN) it is still sufficiently acidic to protonate the substrate.<sup>8e</sup>



**Figure 3.** Proposed sensitized reaction cycle for the photocatalytic protonation of 1-phenyl-2-(trimethylsiloxy)cyclohexene. (NpOH = naphthol, SENS = Bis(4,6-difluorophenyl-

pyridine)(picolinate)iridium(III), AH = N-Hydroxysuccinimide, TET = triplet energy transfer, ISC = intersystem crossing)

Additional support for a triplet excited state reaction is that the yield decreases to 32% under an oxygen atmosphere and increases to 96% under nitrogen. The decreased yield in the presence of oxygen can be rationalized in terms of competitive quenching of the triplet excited state of Br-NpOH<sup>8b</sup> and an increased *k*<sub>nr(T)</sub> compared to *k*<sub>ESPT(T)</sub>.

Given that the reaction occurs from the triplet excited state of the ESPT dye we decided to explore the incorporation of a sensitizer and triplet energy transfer into the catalytic cycle as shown in Figure 3. The results of the sensitized catalytic reaction under various conditions are summarized in Table S1 (in supporting information).

We found that irradiating a solution of 1-phenyl-2-(trimethylsiloxy)cyclohexene, NpOH (50 mol %), SENS (2.5 mol %) and sacrificial acid (AH in excess) with 445 nm light gave product in 74% yield. This reaction yield corresponds to ~30 and ~30 turnovers for the sensitizer and ESPT dye, respectively. Emission quenching studies indicate relatively efficient (~65 %) SENS to NpOH energy transfer (Figure S4). No reaction occurred in the absence of NpOH or SENS. Without sacrificial acid only a substoichiometric amount of product was observed (35 %). N-Hydroxysuccinimide was selected as the sacrificial acid after initial attempts with phenol as the proton source resulted in formation of a precipitate. The decomposition occurs upon irradiation of SENS and phenol alone suggesting the photocatalytic decomposition via redox chemistry of PhOH is responsible for precipitate formation. Under the same conditions no decomposition of N-Hydroxysuccinimide was observed.

The sensitized photocatalytic reaction in Figure 3 has several advantages over the unsensitized cycle shown in Figure 1. The first is that unsubstituted naphthol, which is much more abundant, chemically robust and accessible than Br-NpOH, can be used as the ESPT catalyst because the triplet state is accessed through Dexter energy transfer and not direct excitation followed by ISC. The second advantage is that due to the small singlet-triplet gap of Bis(4,6-difluorophenyl-pyridine)(picolinate)iridium(III) we can shift the excitation to the visible region (445 nm) and still have sufficient excited state energy to sensitize <sup>3</sup>NpOH.

It is worth noting that although organic transformations *via* triplet sensitization are known<sup>11</sup> only few reports successfully use transition metal complexes as the sensitizer.<sup>11b-d</sup> Additionally, these reports involve the sensitization of the substrate which then undergoes a reaction. As far as we know this is the first example where a sensitizer is coupled to a photocatalyst that is then regenerated during the reaction cycle.

In summary we have demonstrated the photocatalytic generation of 2-phenylcyclohexanone from 1-phenyl-2-(trimethylsiloxy)cyclohexene by way of excited state proton transfer catalysis with phenol as the proton source. The reaction goes to near completion (96% yield) under a nitrogen atmosphere with only 1 mol % of Br-NpOH as the photocatalyst. Catalyst screening and the oxygen dependence indicate that proton transfer occurs from the triplet excited state of the ESPT catalyst. The reaction does not occur in the absence of light even at elevated temperature and thus the reaction progression can readily be controlled by light

modulation. Additionally by incorporating a sensitizer molecule into the cycle a 72% yield can be obtained under visible light excitation with naphthol as the catalyst. This is the first example of an organic transformation *via* direct and sensitized excited state proton transfer catalysts. These results open the door to an entirely new class of photocatalytic reactions that harness the acidity of excited state proton transfer dyes.

## Acknowledgements

This work is supported by a grant from the American Chemical Society Petroleum Research Fund (54435-DN14). We gratefully acknowledge Prof. Gregory B. Dudley for the helpful discussions.

## Notes and references

1. D. M. Schultz and T. P. Yoon, *Science*, 2014, **343**, 1239176.
2. (a) T. P. Yoon, M. A. Ischay and J. Du, *Nature Chemistry*, 2010, **2**, 527–532; (b) J. Du, K. L. Skubi, D. M. Schultz and T. P. Yoon, *Science*, 2014, **344**, 392–396; (c) L. R. Espelt, I. S. McPherson, E. M. Wiensch and T. P. Yoon, *J. Am. Chem. Soc.* 2015, **137**, 2452–2455; (d) E. L. Tyson, Z. L. Niemeyer and T. P. Yoon, *J. Org. Chem.* 2014, **79**, 1427–1436; (e) A. E. Hurtley, Z. Lu and T. P. Yoon, *Angew. Chem. Int. Ed.* 2014, **53**, 8991–8994; (f) Z. Lu, J. D. Parrish and T. P. Yoon, *Tetrahedron*, 2014, **70**, 4270–4278; (g) C. -J.; Yao, Q. Sun, N. Rastogi and B. König, *ACS Catal.* 2015, **5**, 2935–2938; (h) D. C. Fabry, J. Zoller, S. Raja and M. Rueping, *Angew. Chem. Int. Ed.* 2014, **53**, 10228–10231.
3. (a) D. J. Wilger, J. -M. M. Grandjean, T. R. Lammert and D. A. Nicewicz, *Nature Chem.* 2014, **6**, 720–726; (b) J. Zoller, D. C. Fabry, M. A. Ronge and M. Rueping, *Angew. Chem. Int. Ed.* 2014, **53**, 13264–13268.
4. (a) L. M. Tolbert and K. M. Solntsev, *Acc. Chem. Res.* 2002, **35**, 19–27; (b) W. Domcke and A. L. Sobolewski, *Science*, 2003, **302**, 1693; (c) A. P. Demchenko, K.-C. Tang and Pi-Tai.Chou, *Chem. Soc. Rev.*, 2013, **42**, 1379; (d) C.-C. Hsieh, Y.-M. Cheng, C.-J. Hsu, K.-Y. Chen and Pi-Tai. Chou, *J. Phys. Chem. A*, 2008, **112**, 8323–8332. (e) K. M. Solntsev and D. J. Huppert, *Phys. Chem. A* 1999, **103**, 6984–6997; (f) M. Barroso, L. G. Arnaut and S. J. Formosinho, *Journal of Photochemistry and Photobiology A: Chemistry*, 2002, **154**, 13–21; (g) A. Weller, *Prog. React. Kinet*, 1961, **1**, 187–214
5. (a) K. M. Solntsev, D. Huppert, N. Agmon and L. M. Tolbert, *J. Phys. Chem. A* 2000, **104**, 4658–4669; (b) C. Clower, K. M. Solntsev, J. Kowalik, L. M. Tolbert and D. Huppert, *J. Phys. Chem. A* 2002, **106**, 3114–3122; (c) O. F. Mohammed, D. Pines, J. Dreyer, E. Pines and E. T. J. Nibbering, *Science*, 2005, **310**, 83–86.
6. (a) M. Lukeman, M.-D. Burns and P. Wan, *Can. J. Chem.* 2011, **89**, 433–440; (b) Y.-H. Wang and P. Wan, *Photochem. Photobiol. Sci.*, 2013, **12**, 1571–1588; (c) N. Basarić, N. Doslić, J. Ivković, Y.-H. Wang, M. Malis̃ and P. Wan, *Chem. Eur. J.* 2012, **18**, 10617–10623.
7. (a) O. A. Mukhina, W. C. Cronk, N. N. B. Kumar, M. C. Sekhar, A. Samanta and A. G. Kutateladze, *J. Phys. Chem. A*, 2014, **118**, 10487–10496; (b) S. P. Roche, R. Cencic, J. Pelletier and J. A. Jr. Porco, *Angew. Chem.* 2010, **122**, 6683–6688; (c) B. Gerard, G. II. Jones and J. A. Jr. Porco, *J. Am. Chem. Soc.* 2004, **126**, 13620–13621.
8. (a) R. Iwata, K. Uda, D. Takahashi and K. Toshima, *Chem. Commun.*, 2014, **50**, 10695; (b) Y. Nishikubo, S. Kanzaki, S. Matsumura and K. Toshima, *Tetrahedron Letters*, 2006, **47**, 8125–8128; (c) H. Peretz-Soroka, A. Pevzner, G. Davidi, V. Naddaka, M. Kwiat, D. Huppert and F. Patolsky, *Nano Lett.* 2015, **15**, 4758–4768; (d) H. Peretz-Soroka, A. Pevzner, G. Davidi, V. Naddaka, R. Tirosh, E. Flaxer and F. Patolsky, *Nano Lett.* 2013, **13**, 3157–3168; (e) J. L. Dempsey, J. R. Winkler and H. B. Gray, *J. Am. Chem. Soc.*, 2010, **132**, 16774–16776; (f) L. Pretali, F. Doria, D. Verga, A. Profumo and M. Freccero, *J. Org. Chem.* 2009, **74**, 1034–1041.
9. (a) D. S. McClure, N. W. Blake and P. L. Hanst, *The Journal of Chemical Physics* 1954, **22**, 255–258; (b) D. S. McClure, *J. Chem. Phys.* 1949, **17**, 665.
10. (a) K. Ishihara, S. Nakamura, M. Kaneeda and H. Yamamoto, *J. Am. Chem. Soc.* 1996, **118**, 12854; (b) S. Nakamura, K. Ishihara and H. Yamamoto, *J. Am. Chem. Soc.* 2000, **122**, 8120.
11. (a) H. Ikezawa, C. Kutal, K. Yasufuku and H. Yamazaki, *J. Am. Chem. Soc.* 1986, **108**, 1589; (b) M. Wrighton and J. Markham, *J. Phys. Chem.* 1973, **77**, 3042; (c) R. R. Islang, J. M. Terry and F. N. Castellano, *Angew. Chem., Int. Ed.* 2006, **45**, 595–598; (d) Z. Lu and T. P. Yoon, *Angew. Chem., Int. Ed.* 2012, **51**, 10329.