Conjugate addition from the excited state

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Conjugate addition from the excited state†

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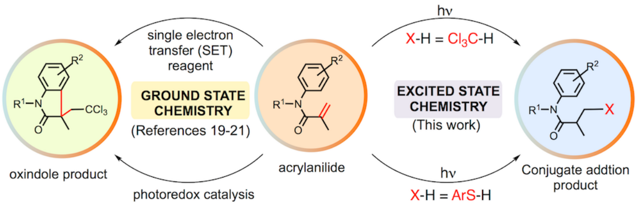
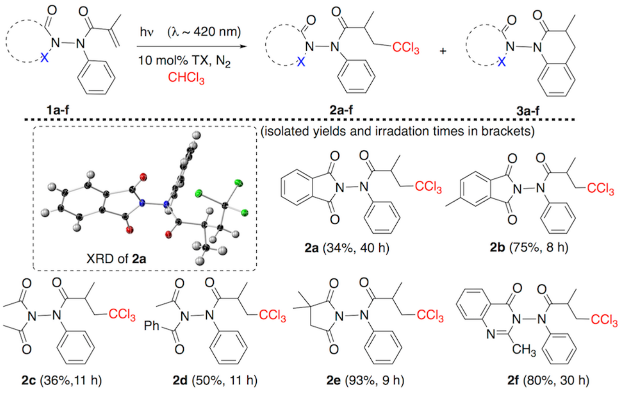
Conjugate addition occurs efficiently from excited hydrazide based acrylanilides under both UV and metal free visible light irradiations. The reaction proceeds via an excited state encounter complex, that bifurcates either via an electron or energy transfer pathway. The generality of excited state conjugate addition is demonstrated using chloromethylation and by thiol addition.

Conjugate addition is one of the well-known thermal transformations that has been exploited heavily to build complex structural skeletons.[1-4] In spite of this, the corresponding excited state analogue has not been explored. Herein we report the use of hydrazide based acrylanilides that can undergo excited state conjugate addition with excellent isolated yields. To demonstrate the uniqueness and feasibility of our strategy and to contrast excited state reactivity with well-known thermal conjugate addition (including photoredox mediated conjugate addition),[5] we have utilized chloromethylation[6, 7] and thiol addition[2, 8-11] as two model reactions. Recently, we reported the use of hydrazides as a photoauxiliary for enabling excited state reactivity with visible light.[12-18] To evaluate the reactivity of *N-N* bond and to expand the scope of the chromophore, we report the conjugate addition involving excited hydrazide based acrylanilides (Schemes 1 and 2). Chloromethylation of acrylanilides through single electron transfer (SET) process yields oxindole derivatives (Scheme 1 left).[19-21] The SET pathway in both traditional radical chemistry as well as in photoredox initiated pathway generates reactive intermediates (radical cations or radical anions) in the ground state, leading to cyclization resulting in oxindole derivatives. On the contrary, acrylanilides **1a-f** undergo conjugate addition (chloromethylation and thiol addition) from the excited-state (Scheme 1-right) clearly demonstrating that the difference in reactivity originating from the ground state and excited state surfaces.

Scheme 1: Contrasting excited state and ground state reactivities of acrylanilides.



Scheme 2: Excited state chloromethylation of acrylanilides.



Acrylanilides **1a-f** were synthesized from the corresponding hydrazides[16] and were evaluated for conjugate addition. We first evaluated the feasibility of chloromethylation (Scheme 2) leading to **2** under visible light illumination with 10-mol% of thioxanthone (TX) acting as a photocatalyst/sensitizer and chloroform acting as both a solvent and as a reagent. The isolated yields of the product **2** ranged from 34-93% (Scheme 2).[22] The products were characterized using ^{1}H and ^{13}C NMR spectroscopy and HRMS and single crystal XRD (for **2a,** Scheme 2; inset).[22] A closer inspection of the photoproduct reveals that the chloromethylation occurred at the β-carbon. To understand the features necessary for the chloromethylation reaction, we systematically varied the functionality around the hydrazide utilizing **1a** as our model system. We then

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Electronic Supplementary Information (ESI) available: Single-crystal XRD data (CIF; CCDC # 1850654-1850661), experimental procedures, characterization data, analytical conditions, and photophysical studies (PDF). See DOI: 10.1039/x0xx00000x synthesized imides **1b-d** that underwent chloromethylation to yield the corresponding chloromethylated products **2b-d** (isolated yields for **2b**=75%; **2c**=36% and **2d**=50%). Cyclic imide **1e** underwent chloromethylation efficiently resulting in 93% isolated yield. The quinazolinone derivate **1f** gave the corresponding chloromethylated product **2f** in 80% isolated yield.

Table 1. Solvent isotope effect on chloromethylation of **1a**. [a]

Entry	Solvent	% Yield [b]	**2a**:**3a** [c]
1	CCl_4	45 (**3a**)	1:99[d]
2	$CHCl_3$	79 (**2a**)	80:20[e]
3	$CDCl_3$	59 (**3a**)	20:80
4	CH_2Cl_2	78	25:75[f]
5	CD_2Cl_2	70	02:98

[a] [**1a**]=3.26 mM. λ≈420 nm, 10 mol% TX under N_2 atmosphere for 40 h. [b] NMR yield of **2a** (entry 4 **2a**+**3a**) calculated using $HCPh_3$ as internal standard (±5% error). [c] From crude ^{1}H-NMR. [d] trace amount of **2a**. [e] ratio at 12 h. [f] Corresponding dichloromethylated product.

Scheme 3: Control substrates for chloromethylation.

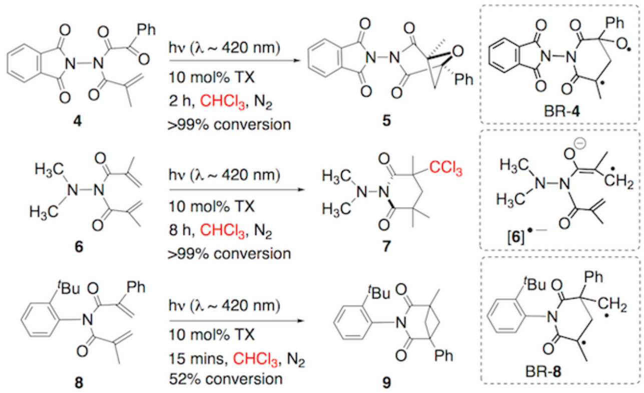


Table 2. Physical parameters of hydrazides.

Entry	Cmpd [a]	E_{red} [b] (V)	ΔG_{eT} [c] (kcal/mol)	E_T [d] (kcal/mol)	k_q [e] ($M^{-1}s^{-1}$)
1	**1a**	-1.15	-1.2	62.4	$3.1(\pm0.1)\times10^8$
2					$8.9(\pm0.1)\times10^7$ [f]
3	**1b**	-1.30	3.5	62.3	$9.7(\pm0.2)\times10^8$
4	**1c**	-1.14	-1.4	62.8	$2.1(\pm0.1)\times10^7$
5	**1e**	-1.26	1.4	62.7	$2.2(\pm0.1)\times10^7$
6	**6**	-0.99	-4.8	70.7	$7.2(\pm0.2)\times10^7$
7					$1.8(\pm0.1)\times10^7$ [f]

[a] [**1a**]=0.49 mM, [**1b**]=0.89 mM, [**1c**]=0.58 mM, [**1e**]=1.0 mM and [**6**]=0.76 mM; vs. SCE, glassy carbon working electrode in MeCN. [b] E_{ox}=1.7 eV for TX. E_{ox}=-1.11 eV for ^{3}TX*; E_T of TX from ref. 23 [c] From Rehm-Weller equation (ref. 24). [d] From phosphorescence in Me-THF at 77 K. [e] By laser flash photolysis in MeCN [f] or $CHCl_3$.

Keeping **1a** as the model system, we then varied the source of chloroalkane by changing the solvent from $CHCl_3$ to CCl_4 and CH_2Cl_2. Inspection of Table 1 shows that the type of solvent had a profound impact on the observed photoproduct. Use of CCl_4 as the solvent for the photoreaction (10 mol% TX under N_2 atmosphere) afforded the dihydroquinolinone **3a** exclusively (Table 1, entry 1). On the other hand, chloromethylated product **2a** was observed exclusively in $CHCl_3$ (Table 1; entry 2). Changing the solvent to CH_2Cl_2 resulted in both **2a** and **3a** in the ratio 1:3 (Table 1; entry 4). This indicated that the C-H hydrogen in the solvent played a crucial role in the chloromethylation reaction. To understand the mechanism, we evaluated the chloromethylation reaction in deuterated solvents viz., $CDCl_3$ and CD_2Cl_2. Chemoselective formation of chloromethylated product **2a** was observed in chloroform (Table 1; entry 2) whereas in chloroform-*d* **3a** was observed exclusively (Table 1; entry 3). Similarly, changing the solvent from CH_2Cl_2 to CD_2Cl_2 resulted in **3a** exclusively (Table 1; compare entries 4 and 5). Our observation with the solvent study indicated that the chloromethylation leading to **2** and 6π-photocyclization leading to **3** are competing excited state processes. To evaluate the nature of the excited state involved, we performed direct irradiation of **1a** in $CHCl_3$ at 300 nm (without TX) under both N_2 and O_2 atmospheres. Direct irradiation of **1a** under the optimized reaction conditions in oxygen-saturated atmosphere proceeded to yield the photoproduct **3a** with 17% conversion.[22] On the other hand, under N_2 atmosphere chloromethylation of **1a** leading to **2a** was observed exclusively (89% conversion). This implicates the likely involvement of triplet-excited states in acrylanilides **1**. To further understand the reactivity of hydrazides **1a-f** towards chloromethylation, we investigated control substrates **4**, **6** and **8** (Scheme 3). Irradiation of the oxoamide **4**, that features both phthalimide and hydrazide functionalities, resulted in the Paternò-Büchi reaction via BR-**4**. We envisioned trapping of similar intermediates if the intramolecular reactions can be side-stepped using chloromethylation. To achieve this, we employed acrylimide **6** where the intermediate (*vide infra*) was trapped intermolecularly leading to **7**. Irradiation of **8**, that features a restricted bond rotation around *N*-C_{Aryl} bond, under

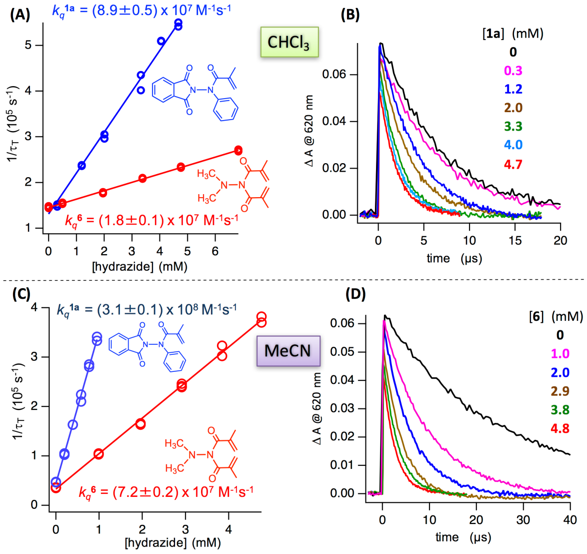
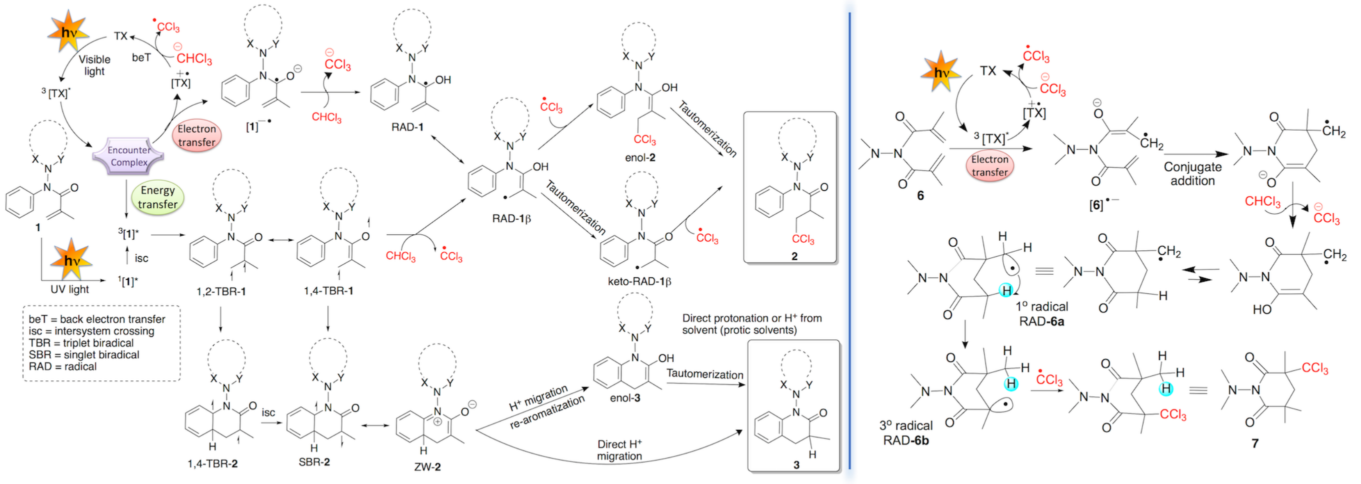


Figure 1. Left: Determination of the bimolecular quenching rate constants k_q for quenching of TX triplet states by acrylanilides using laser flash photolysis (λ_{ex} = 355 nm, 7 ns pulse width). Inverse TX triplet lifetime from triplet absorption decay traces monitored at 620 nm vs. varying hydrazide concentrations in argon saturated $CHCl_3$ (A) and MeCN (C) solutions. Right: Transient absorption decay traces of TX triplets different concentrations of **1a** and **6** in argon saturated $CHCl_3$ (B) and MeCN (D) solutions.

Scheme 4: Mechanistic pathway for chloromethylation of **1a-f**.

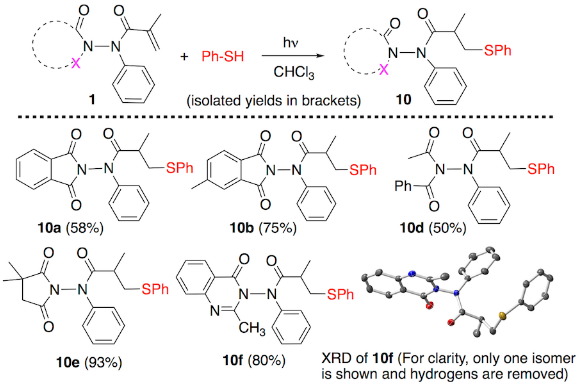


optimized conditions resulted in the expected cross [2+2]-photocycloadduct **9** through biradical BR-**8**.[25]

As the triplet excited state was likely implicated in the chloromethylation of **1a**, bimolecular quenching rate constants (k_q) were determined by quenching of TX triplet states by using laser flash photolysis (Figure 1; λ_{ex} = 355 nm, 7 ns pulse width). The triplet state of the TX sensitizer was quenched by model hydrazide **1a** and the control substrate **6** in $CHCl_3$ with a quenching rate constant of 8.9×10^7 $M^{-1}s^{-1}$ and 1.8×10^7 $M^{-1}s^{-1}$ respectively (Figure 1A). Similarly, in MeCN, the quenching rate constant of **1a** and **6** was 3.1×10^8 $M^{-1}s^{-1}$ and 7.2×10^7 $M^{-1}s^{-1}$ respectively (Figure 1C). The rate constants in chloroform (where chloromethylation leading to **2** was observed) and in acetonitrile (where cyclization leading to **3** was observed)[16] indicate that the initial quenching of TX triplet excited state depends on the nature of the quencher leading to energy and/or electron transfer. To further understand the system, the lowest excited triplet state energies of the substrates were ascertained from their phosphorescence spectra at 77 K in Me-THF glass (Table 2). Inspection of Table 2 shows that the triplet energies (E_T) of the *N-N* based substrates **1a-c** and **1e** were between 62-63 kcal/mol while for the control substrate **6** E_T was ~71 kcal/mol. Based on the lowest triplet excited state energy of TX (E_T = ~63 kcal/mol) we believe that an energy transfer pathway is likely for substrates with favorable triplet energies. We also calculated the feasibility of electron transfer from thioxanthone triplet excited state to imides **1** and **6**. Inspection of Table 2 shows that the free energy for electron transfer is exergonic for **1a** while it was endergonic for **1b**. As they feature the same chromophore with similar triplet energies, we postulate that the reaction can occur both via an electron transfer (if ΔG_{eT} is exergonic) and/or via energy transfer pathway (if the triplet energy is favorable as in the case of **1a** and **1c**). In the case of **1b** and **1e**, the energetics dictate that the reaction will likely proceed via triplet energy transfer due to the endergonic nature of electron transfer. In the case of substrate **6** that features a E_T of ~71 kcal/mol and an exergonic electron transfer, we believe an electron transfer pathway is likely leading to **7**. The involvement of the electron transfer pathway in addition to the energy transfer pathway was bolstered by our observation that the bimolecular quenching constant was higher in the more polar MeCN compared to $CHCl_3$ (Figure 1, Table 2).

To rationalize the above observations, we propose a mechanistic model for chloromethylation from the excited state as detailed in Scheme 4-left. Based on the triplet energy as well as the redox potential of thioxanthone and acrylanilides, an encounter complex[26] is postulated that leads to either an electron transfer or energy transfer pathways.[27] The encounter complex leads to a radical anion (e.g. in the case of **6**) of acrylanilides $\mathbf{1}^{\bullet-}$ and $TX^{\bullet+}$. This radical anion abstracts an acidic hydrogen from an appropriate solvent (e.g. $CHCl_3$) leading to a β-centered radical RAD-**1β** (can also be in resonance with RAD-**1**) The proton abstraction from chloroalkane is accompanied by the generation of corresponding haloalkyl anion that eventually gets reduced to the corresponding haloalkyl radical intermediate by SET to $TX^{\bullet+}$ thereby regenerating TX. This explains the requirement of catalytic amounts of TX for chloromethylation of acrylanilides. The β-centered radical RAD-**1β** (Scheme 4-left) generated by an electron transfer pathway is responsible for the formation of anilide-based product **2a-f** in contrast to oxindole product. The reaction could also be envisioned to occur via a triplet energy transfer (if the triplet energies are favorable as in the case of **1a**) from the encounter complex or by direct irradiation followed by intersystem crossing leading to triplet excited acrylanilide ^{3}[**1**]* that subsequently leads to a reactive triplet biradical (TBR-**1**). In deuterated solvents (e.g. $CDCl_3$), the triplet biradical subsequently cyclizes to 3,4-dihydroquinolinone product **3**. On the other hand, when the reaction is carried out in chlorinated solvents featuring abstractable hydrogen(s) (e.g. $CHCl_3$), the triplet biradical TBR-**1** abstracts the hydrogen from the solvent leading to β-centered radical RAD-**1β** and the corresponding haloalkyl radical. The radicals subsequently recombine to form **2**. Based on the above mechanism, the photoreactivity of **6** can be rationalized (Scheme 4-right). In the case of **6**, exergonic electron transfer from excited TX leads to a radical anion of **6**, that subsequently undergoes conjugate addition. The resulting enolate radical abstracts a proton from $CHCl_3$ to form the primary radical RAD-**6a** and $Cl_3C^{\ominus}$. The primary radical RAD-**6a** rearranges to a more stable tertiary radial RAD-**6b** that recombines with $Cl_3C^{\odot}$ (formed from $Cl_3C^{\ominus}$ through electron transfer to $TX^{\bullet+}$ regenerating TX) to form **7**. One aspect that we are not able to rationalize is the solvent isotope effect dependent chemoselectivity. Isotope dependent chemoselectivity is known in literature due to delicate balance of competing reaction rates,[28] a similar phenomenon can be envisioned in our system (cyclization vs H-abstraction). Efforts are underway in our lab to further understand this observation.

Scheme 5: Excited state conjugate addition of thiophenol to **1**.



To showcase the generality of our strategy, we employed conjugate addition involving thiols to *N-N* substituted acrylanilides. As shown in the Scheme 5, direct irradiation ($\lambda \approx 300$ nm) of **1** in 1:1 v/v of thiophenol/chloroform gave the expected 1,4 addition product **10** in 50-93% isolated yields. The thiol addition photoproduct was unambiguously identified by single crystal XRD (for **10f**). Control studies in the absence of light did not result in the conjugate addition product. While light initiated conjugate addition of thiols to hydrazide can be rationalized based on our proposed mechanism (Scheme 4-left), we cannot rule out the formation of ground state/excited state complex with thiols under our direct irradiation conditions. Further investigations are underway in our lab to showcase the utility of our findings and to understand the mechanism.

Conclusions

Our study has shown that the photochemistry of hydrazides offers new avenues to uncover photoreactivity due to their unique excited state properties. In the present case, acrylanilides that typically undergo 6π-photocyclization underwent conjugate addition (chloromethylation and thiol addition) from the excited state. The prospect of altering and uncovering new excited state reactivity will create new opportunities to develop novel and catalytic light initiated reactions.[29-32] Efforts along these lines are currently underway in our laboratory.

Conflicts of interest

There are no conflicts to declare.

Notes and references

1. B. E. Rossiter and N. M. Swingle, *Chem. Rev.*, 1992, **92**, 771-806.
2. M. P. Sibi and S. Manyem, *Tetrahedron*, 2000, **56**, 8033-8061.
3. S. R. Harutyunyan, T. den Hartog, K. Geurts, A. J. Minnaard and B. L. Feringa, *Chem. Rev.*, 2008, **108**, 2824-2852.
4. E. P. Farney, S. S. Feng, F. Schäfers and S. E. Reisman, *J. Am. Chem. Soc.*, 2018, **140**, 1267-1270.
5. A. Gualandi, E. Matteucci, F. Monti, A. Baschieri, N. Armaroli, L. Sambri and P. G. Cozzi, *Chem. Sci.*, 2017, **8**, 1613-1620.
6. A. T. Herrmann, L. L. Smith and A. Zakarian, *J. Am. Chem. Soc.*, 2012, **134**, 6976-6979.
7. H. Huo, C. Wang, K. Harms and E. Meggers, *J. Am. Chem. Soc.*, 2015, **137**, 9551-9554.
8. M. Saito, M. Nakajima and S. Hashimoto, *Tetrahedron*, 2000, **56**, 9589-9594.
9. G. L. Khatik, R. Kumar and A. K. Chakraborti, *Org. Lett.*, 2006, **8**, 2433-2436.
10. N. K. Rana, S. Selvakumar and V. K. Singh, *J. Org. Chem.*, 2010, **75**, 2089-2091.
11. N. Fu, L. Zhang, S. Luo and J.-P. Cheng, *Org. Lett.*, 2014, **16**, 4626-4629.
12. N. Vallavoju, S. Selvakumar, S. Jockusch, M. P. Sibi and J. Sivaguru, *Angew. Chem. Int. Ed.*, 2014, **53**, 5604-5608.
13. E. Kumarasamy, R. Raghunathan, S. Jockusch, A. Ugrinov and J. Sivaguru, *J. Am. Chem. Soc.*, 2014, **136**, 8729-8737.
14. N. Vallavoju, S. Selvakumar, B. C. Pemberton, S. Jockusch, M. P. Sibi and J. Sivaguru, *Angew. Chem. Int. Ed.*, 2016, **55**, 5446–5451.
15. E. Kumarasamy, A. J.-L. Ayitou, N. Vallavoju, R. Raghunathan, A. Iyer, A. Clay, S. K. Kandappa and J. Sivaguru, *Acc. Chem. Res.*, 2016, **49**, 2713-2724.
16. A. Iyer, S. Jockusch and J. Sivaguru, *Chem. Commun.*, 2017, **53**, 1692--1695.
17. E. Kumarasamy, R. Raghunathan, S. K. Kandappa, A. Sreenithya, S. Jockusch, R. B. Sunoj and J. Sivaguru, *J. Am. Chem. Soc.*, 2017, **139**, 655-662.
18. E. Kumarasamy, S. K. Kandappa, R. Raghunathan, S. Jockusch and J. Sivaguru, *Angew. Chem. Int. Ed.*, 2017, **56**, 7056-7061.
19. Y. Tian and Z.-Q. Liu, *RSC Advn.*, 2014, **4**, 64855-64859.
20. M.-Z. Lu and T.-P. Loh, *Org. Lett.*, 2014, **16**, 4698-4701.
21. M. Zhu and W. Fu, *Heterocyc. Comm.*, 2015, **21**, 387–390.
22. *Refer to supporting information*.
23. Q. Q. Zhu, W. Schnabel and P. Jacques, *J. Chem. Soc., Faraday Trans.*, 1991, **87**, 1531-1535.
24. D. Rehm and A. Weller, *Isreal J. Chem.*, 1970, **8**, 259-271.
25. A. Iyer, S. Jockusch and J. Sivaguru, *J. Phys. Chem. A.*, 2014, **118**, 10596-10602.
26. G. J. Kavarnos and N. J. Turro, *Chem. Rev.*, 1986, **86**, 401-449.
27. N. J. Turro, V. Ramamurthy and J. C. Scaiano, *Modern Molecular Photochemistry of Organic Molecules*, University Science Books, Sausalito, CA, 2010.
28. R. M. Gleixner, K. M. Joly, M. Tremayne, B. M. Kariuki, L. Male, D. M. Coe and L. R. Cox, *Chem. Eur. J.*, 2010, **16**, 5769-5777.
29. M. D. Kärkäs, J. A. Porco and C. R. J. Stephenson, *Chem. Rev.*, 2016, **116**, 9683-9747.
30. V. Ramamurthy and J. Sivaguru, *Chem. Rev.*, 2016, **116**, 9914-9993.
31. D. M. Schultz and T. P. Yoon, *Science*, 2014, **343**.
32. M. Kozlowski and T. Yoon, *J. Org. Chem.*, 2016, **81**, 6895-6897.

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