

ChemComm

Accepted Manuscript



This article can be cited before page numbers have been issued, to do this please use: A. Iyer, S. Jockusch and J. Sivaguru, *Chem. Commun.*, 2017, DOI: 10.1039/C6CC09261F.



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 [author guidelines](#).

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, outlined in our [author and reviewer resource centre](#), 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.

Journal Name

COMMUNICATION

Photo-auxiliary approach - Enabling excited state classical phototransformations with metal free visible light irradiation

 Received 00th January 20xx,
 Accepted 00th January 20xx
Akila Iyer,^a Steffen Jockusch,^b and Jayaraman Sivaguru^{*a}

DOI: 10.1039/x0xx00000x

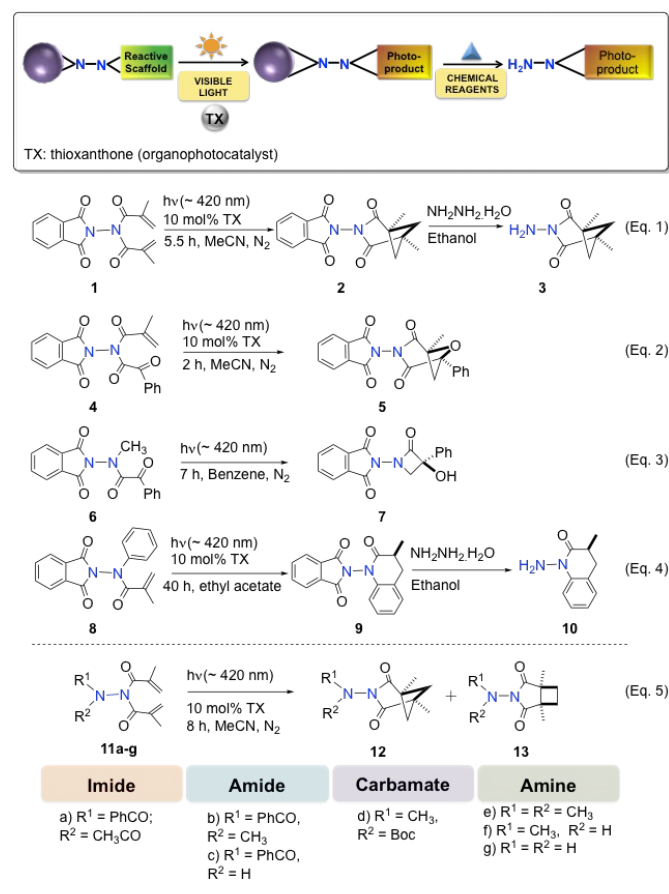
www.rsc.org/

Most traditional photoreactions require UV light to yield the desired product. To address this issue, photoreaction of hydrazide based chromophores were evaluated with visible light using a metal free photocatalyst to afford photoproducts in high yields. This hydrazide functionality itself may be removed/modified after the photoreaction highlighting its role as a “photo-auxiliary”. A preliminary mechanistic model based on photophysical experiments is provided to highlight the generality of the strategy.

Life-sustaining processes in nature have served as an inspiration to chemists for developing photoreactions that provide a pathway to synthesize complex structural scaffolds and build materials and molecular assemblies with unique architectures.¹ Recently, visible light initiated photo-redox chemistry has attracted the attention of chemists as it provides a user-friendly strategy for performing chemical reactions.² This methodology requires a judicious choice of a substrate(s) and a photo-catalyst/sensitizer to enable a single electron transfer (SET) that initiates the reaction.³ Further, only the photocatalyst reaches the excited state enabling an electron transfer to the substrate leading to a ground state radical cation or a radical anion intermediate(s) that subsequently is transformed to the product(s).^{3a, 3c} As the transformation of the substrate(s) to the product(s) takes place in the ground state, it can be applied to well-established transformations involving radical chemistry.⁴ However, this also places a limitation on the photoredox strategy as it cannot be employed for reactions that originate from the excited state(s) of the reactive substrate.⁵ Since most organic compounds are transparent to visible light irradiations and absorb only in the UV spectral region, developing a generalized methodology to initiate excited state reactions using visible

light for performing well-established photoreactions has presented significant challenges. In this report, we have addressed this long-standing issue by utilizing the features of hydrazides for performing excited state reactions (Scheme 1) viz., [2+2]-photocycloaddition (Eq. 1), Paternò-Büchi reaction (Eq. 2), Norrish-Yang cyclization (Eq. 3) and 6 π -photocyclization (Eq. 4). The N-N bond in hydrazides can be cleaved or subjected to functional group modifications, providing a handle for further manipulation.⁶

Scheme 1. Hydrazide chromophores for initiating excited state transformations.



^a Department of Chemistry and Biochemistry, North Dakota State University, Fargo, ND 58108-6050 Ph: 701-231-8923 / Fax: (+)01-701-21-8831
 E-mail: jayaraman.sivaguru@ndsu.edu
 Homepage: <http://sivaweb.chem.ndsu.nodak.edu>

^b Department of Chemistry, Columbia University, New York, NY 10025.

Electronic Supplementary Information (ESI) available: Experimental procedures for photoreactions, synthesis, characterization, and analysis conditions of the reactants and the photoproducts. Single crystal XRD structure of reactant and product (CCDC 1504566-1504568). See DOI: 10.1039/x0xx00000x

The use of hydrazides that feature an *N-N* bond has been explored in literature for accessing natural products and heterocycles.⁷ We envisioned that the presence of electron withdrawing carbonyl functionalities and the lone pair on the nitrogens in the hydrazides (Scheme 1) would impart unique excited state characteristics that may be utilized for photoreactions.⁸ To explore this possibility we built hydrazides **1**, **4**, **6** and **8** (Scheme 1) from the corresponding *N*-amino phthalimide derivatives in good yields, characterized by different analytical techniques and evaluated them for photoreactions (Table 1)⁹ under direct irradiation (UV light) and sensitized irradiation with visible light (with thioxanthone, TX as the sensitizer/photocatalyst).⁹

To establish the reaction conditions, we first evaluated hydrazides **1**, **4**, **6** and **8** towards [2+2]-photocycloaddition, Paternò-Büchi reaction, 6 π -photocyclization and Norrish-Yang reaction, respectively (Scheme 1). Inspection of Table 1 shows that employing 1-10 mol% of TX in acetonitrile led to effective transformation of the phthalimide based hydrazides to the corresponding photoproducts. Irradiation (~420 nm) of **1**¹⁰ with 10 mol% loading of TX led to the cyclobutane derivative **2** with quantitative conversions with 71% isolated yield (1 and 5 mol% TX gave 8% and 39% conversions, respectively). The phthalimide moiety acted as an auxiliary that facilitated the desired phototransformation and was easily removed by treating the photoproduct with hydrazine hydrate to yield the corresponding *N*-amino hydrazide derivative (**3** in the case of **2** and **10** in the case of **9**; Scheme 1). Irradiation of **1** at ~420 nm in the absence of TX did not result in any noticeable conversion with recovery of the reactant. We then evaluated the Paternò-Büchi reaction of **4** in the presence of 1, 5 and 10-mol% of TX (~420 nm irradiation) leading to oxetane **5** in 26, 100 and 100% conversions, respectively (Table 1). The isolated

yield was 88% with 10-mol% of TX. Irradiation of **4** with ~420 nm in the absence of TX led to **5** with 19% conversion. Similarly, 6 π -photocyclization of **8** in the presence of 1 and 10-mol% of TX at ~420 nm led to the corresponding 3,4-dihydroquinolin-2-one **9** in 88 and 90% conversions (62% isolated yield), respectively (Table 1). Direct irradiation of **8** at ~420 nm resulted in 7% conversion. In the case of Norrish-Yang cyclization, due to absorptivity of **6** in the visible region, direct irradiation was evaluated in MeCN that led to β -lactam **7** in 16% conversion (Table 1). In order to improve the yield of **7**, we evaluated the reaction of **6** in various solvents (Table 1). The photoreaction conversions were 80% and 55% in benzene and ethyl acetate, respectively. Similarly, the reaction of **1** in methanol gave quantitative conversion (similar to MeCN) of the cycloaddition product. Benzene and acetonitrile were found to be the optimal solvents for the Paternò-Büchi reaction of **4** leading to oxetane based photoproduct **5**. 6 π -Photocyclization of **8** was efficient in all the solvents that we had investigated showing moderate conversions in benzene and methylcyclohexane (MCH) and close to quantitative conversions in methanol, acetonitrile and ethyl acetate.

Having established the usefulness of the phthalimide based systems (Scheme 1) in promoting traditional photoreactions to work under visible light; we evaluated the features necessary for generalizing the chromophore responsible for reactivity. The acrylimide derivative **1** that underwent facile [2+2]-photocycloaddition (Scheme 1; Eq. 1) was chosen as the model system and its reactivity was compared with control substrates (Scheme 1; Eq. 5) that featured a di-methacryloyl functionality on one nitrogen and the 2nd nitrogen featuring one of the following functionalities viz., imide **11a**; 3^o amide **11b**; 2^o amide **11c**; carbamate **11d**; 3^o amine **11e**; 2^o amine **11f** and 1^o amine **11g**. Inspection of Table 1 reveals that the

Table 1. Photochemistry reactivity and physical parameters of *N-N* bond based compounds.

Entry	Compd ^[b]	Conversions (Isolated yield) ^[a]				Solvent effect ^[b,c]					E_{red} (eV) ^[d]	ΔG_{eT} (kcal/mol) ^[e]	E_{T} (kcal/mol) ^[f]	k_{q} (M ⁻¹ s ⁻¹) ^[g]
		0	1	5	10	MeOH	MeCN	EtOAc	C ₆ H ₆	MCH				
1	1 ^[h]	0	8	39	>98 (71)	>98	>98	<7	63	0	-1.25	1.2	64.5	1.2±0.1 × 10 ⁸
2	4	19	26	>98	>98 (88)	- ^[k]	>98	78	>98	71	-0.99	-4.8	62.0	9.8±0.2 × 10 ⁸
3	6 ^[i]					- ^[k]	16	55	80	- ^[j]	-1.28	1.8	62.4	6.7±0.1 × 10 ⁸
4	8	7	88	-	90 (62)	91	90	>98	60	71	-1.15	-1.2	62.4	3.1±1 × 10 ⁸
5	11a						56 (52)				-1.11	-2.1	75.8	6.0±0.1 × 10 ⁷
6	11b						- ^[j]				-0.76	-10.1	71.8	5.9±0.1 × 10 ⁷
7	11d						82 (29) ^[h]				-1.33	3.0	70.4	8.8±0.2 × 10 ⁷
8	11e						95 (40) ^[h, k]				-0.99	-4.8	70.7	7.2±0.2 × 10 ⁷
9	11f						>99 (40) ^[h, k]							

[a] ~420 nm irradiations under N₂ in a Rayonet reactor (minimum of 3 trials, ±5% error). % Conversions by ¹H NMR spectroscopy using triphenylmethane as an internal standard. Isolated yields in parenthesis. [b] Refer to ESI for concentrations and irradiation times. [c] 10 mol% TX. [d] vs. SEC, glassy carbon working electrode. MeCN Solvent. Concentrations provided in ESI. [e] ΔG_{eT} calculated from TX $E_{\text{ox}} = 1.7$ eV using Rehm-Weller equation (reference 10-11). We were unable to ascertain E_{ox} for the substrates under our experimental condition using cyclic voltammetry. [f] From phosphorescence spectra in 2-Me-THF at 77 K. [g] TX triplet quenching rate constants by laser flash photolysis in MeCN. [h] Minor amounts (< 10%) of straight photocycloaddition observed depending on the solvent (reference 9). [i] Direct irradiation of **6** without TX. [j] Decomposition observed. [k] Photoproduct ratio **12e**:**13e** = 70:30 and **12f**:**13f** = 80:20.

photoreaction of **11** in MeCN under visible light irradiation in the presence of 10-mol% of TX depends on the hydrazide functionality. Photoreaction of **11a** that features imide functionality resulted in 56% conversion with 52% isolated yield (Table 1; entry 5). Changing the functionality from an imide to an amide resulted in either decomposition (with 3° amide **11b**; Table 1; entry 6) or no observable product formation (with 2° amide **11c**). Changing the functionality to a carbamate based hydrazide **11d** resulted in 82% conversion with an isolated yield of 29% (Table 1; entry 7). We then changed the functionality to *N*-substituted amines **11e-g**. Tertiary and secondary amine derivatives **11e** and **11f** gave conversions of 95% (40% yield; **12e:13e**=70:30) and >99% (40% yield; **12f:13f**=80:20), respectively (Table 1; entries 8 and 9). There was no observable reaction with 1° amine derivative **11g**. To further probe the reactivity of amines, we selected **11e** to investigate the effect of solvents and TX loading levels.⁹ Changing the mol% of TX from 1, 5 to 10 resulted in 74%, 93% and 95% conversions, respectively.⁹ The reaction with 10-mol% of TX was also effective in ethyl acetate and in benzene with 55% and 52% conversions, respectively.

Traditional photochemical reactions promoted by hydrazide functionality under visible light irradiation with TX can happen either by energy transfer or electron transfer or a combination of both. To ascertain the feasibility of electron transfer, we measured the oxidation and reduction potentials of TX and *N-N* based derivatives **1**, **4**, **6**, **8**, **11a-b** and **11d-e** by cyclic voltammetry (Table 1).⁹ The free energy for electron transfer from excited TX to *N-N* based substrates was calculated using the Rehm-Weller equation.^{9,11} In all cases, the free energy for electron transfer (ΔG_{eT}) was either negative or close to zero, indicating that an electron transfer mechanism was indeed feasible in the system (Table 1).⁹ To evaluate the feasibility of energy transfer process in sensitized photoreactions we carried out detailed photophysical studies. As no appreciable luminescence was observed from phthalimides **1**, **4**, **6** and **8** at room temperature, steady-state luminescence was performed at 77 K in Me-THF glass.⁹ The luminescence was ascertained to be phosphorescence based on lifetime measurements and the triplet energies (E_{T}) were determined from the phosphorescence spectra (Table 1).⁹ Based on the triplet energy of TX ($E_{\text{T}} \approx 63$ kcal/mol),¹² triplet energy transfer from TX to the phthalimides was feasible. Photophysical studies on control substrates **11a-b** and **11d-e** revealed that their triplet energy was greater than of phthalimide based hydrazides **1**, **4**, **6** and **8** (Table 1; compare entries 5-8 with 1-4). In spite of the higher triplet energy, we observed photoreactivity of the control substrates with TX acting as a visible light absorbing catalyst/sensitizer. As the reaction was efficient with TX, we investigated its role in promoting the reaction using transient absorption spectroscopy. Laser excitation ($\lambda_{\text{ex}} = 355$ nm; 7 ns pulse width) of TX in the presence of varying concentrations of hydrazides in argon saturated MeCN solution was performed to ascertain the bimolecular quenching rate constant (k_{q} ; Figure 1; Table 1). In the case of hydrazide **4** in which both exergonic electron transfer and exothermic energy transfer are feasible from

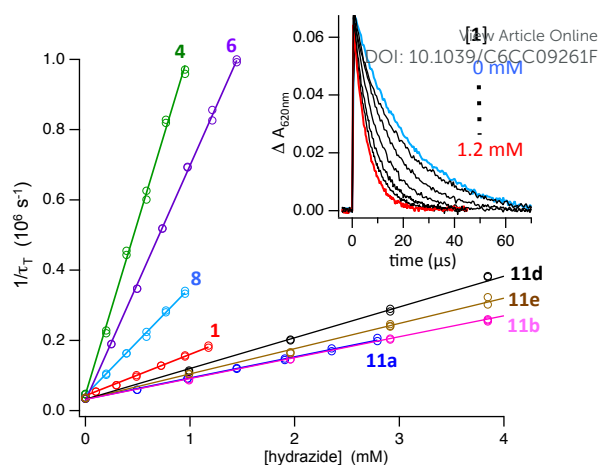


Figure 1. Inverse TX triplet lifetime determined from triplet absorption decay traces monitored at 620 nm vs. varying hydrazide concentrations in argon saturated MeCN solutions. Inset: Transient absorption decay traces of TX triplets measured at 620 nm at different concentrations of **1** using laser flash photolysis ($\lambda_{\text{ex}} = 355$ nm, 7 ns pulse width).

excited TX, the k_{q} was $9.8 \times 10^8 \text{ M}^{-1}\text{s}^{-1}$. Hydrazide **6** displayed a slightly positive ΔG_{eT} and downhill energy transfer from excited TX with k_{q} of $6.7 \times 10^8 \text{ M}^{-1}\text{s}^{-1}$. Hydrazide **8** with a slightly endergonic electron transfer (compared to **6**) and exothermic energy transfer from excited TX gave k_{q} of $3.1 \times 10^8 \text{ M}^{-1}\text{s}^{-1}$. Hydrazide **1** with a slightly endergonic electron transfer and endothermic energy transfer from excited TX gave k_{q} of $1.2 \times 10^8 \text{ M}^{-1}\text{s}^{-1}$. With **11a** as a control substrate, only endergonic electron transfer was feasible due to high triplet energy of the substrate that was correlated by the k_{q} of $6.0 \times 10^7 \text{ M}^{-1}\text{s}^{-1}$. For the hydrazides investigated in this study, the bimolecular quenching rate constants pointed to a complex scenario where the photoreaction was promoted either through electron transfer or energy transfer or a combination of both. This requires a comprehensive mechanistic model to explain the excited state reactivity of hydrazides.

To rationalize our experimental observations with substrate **1** and to decipher a plausible mechanistic reasoning for the observed chemical reactivity, we propose a mechanistic model as shown in Figure 2. Photoexcitation of TX leads to its triplet excited state. In the presence of the hydrazide substrates it forms an encounter complex.¹³ This encounter complex can lead to triplet energy transfer if the triplet energy level of the substrate is lower than TX. When a system has a favorable redox potential (e.g. in the case of **4**, **8**, **11a**, **11b** and **11e**), an electron transfer pathway is indeed feasible that will lead to a radical ion pair. The hydrazide radical anion thus formed can react efficiently forming the photoproduct radical anion. This product radical anion can then do a back electron transfer to regenerate TX. It should be emphasized that the mechanistic route via an electron transfer or energy transfer pathway leading to radical ion pair or diradicaloid intermediates, respectively, is dependent on the reactive substrate employed. For example, in the case of **11a** an electron transfer pathway is very likely due to favorable energetics and higher triplet state energies of the hydrazide.

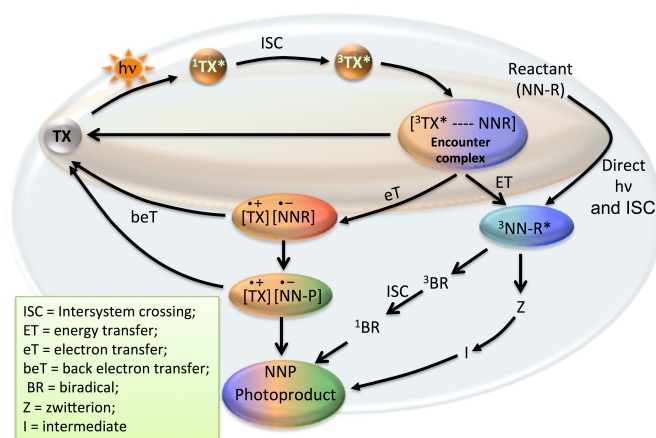


Figure 2. Mechanistic aspects - photochemical reaction of hydrazides.

On the other hand, in the case of the oxoamide based hydrazide **4**, the formation of a triplet excited state is likely (through direct excitation of the keto-amide).¹⁴ This triplet-excited state can react to form the photoproduct through a biradicaloid (³BR; Figure 2) species or through an intramolecular charge transfer pathway. This reactive triplet excited state of the reactant may also be accessed through direct irradiation (as in the case of hydrazide **6**). While the mechanistic details for a specific substrate presented in our system requires further scrutiny using photochemical and photophysical studies, our generalized approach where an excited state encounter complex initiates the reactivity is quite general for the investigated photochemical transformations. We propose that the substrates can adopt differing routes from the encounter complex (viz., electron vs. energy transfer pathway) depending on the oxidation and reduction potentials as well as on the triplet energy of the hydrazide derivative.

In summary, our study utilizes the features of a hydrazide chromophore for photoreactions with TX as the sensitizer. The study opens up avenues for chemists to utilize visible light to perform classical photoreactions that are useful for targeting complex structural scaffolds. Additionally, the hydrazide handle can be subjected to simple chemical modification, making the approach modular. Thus the hydrazide essentially acts as a “photo-auxiliary” enabling us to perform classical photoreactions with visible light sensitization. This novel strategy can enable chemists across disciplines to initiate photochemical reactions under metal free visible light irradiation conditions.

Notes and references

The authors thank the National Science Foundation for generous support for their research (CHE-1465075). Authors thank Dr. Angel Ugrinov for solving single crystal XRD structures, Prof. Guodong Liu for access to cyclic voltammetric instrumentation and Anthony Clay for intellectual discussions.

Single crystal XRD: **1:** C₁₆H₁₄N₂O₄ (298.29), monoclinic, P2(1)/c, a = 32.0290(13) Å, alpha = 90.00°; b = 11.6208(5) Å, beta = 103.875(2)°; c = 16.5874(7) Å, gamma = 90.00°. V = 5993.7(4)

Å³, Z = 16, T = 100(2) K, absorption coefficient = 0.803 mm⁻¹, reflections collected = 81097, unique = 10593 [R(int) = 0.0303], refinement by Full matrix least-squares on F₂, data/restraints/parameters = 10593/0/801, goodness-of-fit on F₂ = 1.041, final R indices [I > 2sigma(I)] R1 = 6.12%, wR2 = 17.26%; R indices (all data) R1 = 6.46%, wR2 = 17.68%, largest diff. peak and hole = 1.5 and -0.5 e Å⁻³, respectively.

2: C₁₆H₁₄N₂O₄ (298.29), monoclinic, P-1, a = 7.9596(2) Å, alpha = 107.407(2)°; b = 15.2341(4) Å, beta = 100.757(1)°; c = 16.7564(5) Å, gamma = 97.385(1)°. V = 1829.0(1) Å³, Z = 4, T = 100(2) K, absorption coefficient = 4.772 mm⁻¹, reflections collected = 29515, unique = 6332 [R(int) = 0.0345], refinement by Full matrix least-squares on F₂, data/restraints/parameters = 6332/0/473, goodness-of-fit on F₂ = 1.026, final R indices [I > 2sigma(I)] R1 = 2.96%, wR2 = 7.36%; R indices (all data) R1 = 3.22%, wR2 = 7.48%, largest diff. peak and hole = 0.3 and -0.3 e Å⁻³, respectively.

- a) M. D. E. Forbes, *ACS Central Science*, 2015, **1**, 354; b) M. D. Kärkäs, J. A. Porco and C. R. J. Stephenson, *Chem. Rev.*, 2016, **116**, 9683.
- a) M. Kozłowski and T. Yoon, *J. Org. Chem.*, 2016, **81**, 6895; b) C. K. Prier, D. A. Rankic and D. W. C. MacMillan, *Chem. Rev.*, 2013, **113**, 5322; c) J. Xuan and W.-J. Xiao, *Angew. Chem. Int. Ed.*, 2012, **51**, 6828; d) D. M. Schultz and T. P. Yoon, *Science*, 2014, **343**; e) J. D. Cuthbertson and D. W. C. MacMillan, *Nature*, 2015, **519**, 74; f) D. P. Hari, P. Schroll and B. König, *J. Am. Chem. Soc.*, 2012, **134**, 2958.
- a) C. R. Bock, J. A. Connor, A. R. Gutierrez, T. J. Meyer, D. G. Whitten, B. P. Sullivan and J. K. Nagle, *J. Am. Chem. Soc.*, 1979, **101**, 4815; b) D. G. Whitten and P. P. Zarnegar, *J. Am. Chem. Soc.*, 1971, **93**, 3776; c) D. G. Whitten, *Acc. Chem. Res.*, 1980, **13**, 83.
- C. R. J. Stephenson, A. Studer and D. P. Curran, *Beilstein J. Org. Chem.*, 2013, **9**, 2778.
- N. J. Turro, V. Ramamurthy and J. C. Scaiano, *Modern Molecular Photochemistry of Organic Molecules*, University Science Books, Sausalito, CA, 2010, 705-799.
- M. Zhu and N. Zheng, *Synthesis*, 2011, **2011**, 2223.
- a) P. Majumdar, A. Pati, M. Patra, R. K. Behera and A. K. Behera, *Chem. Rev.*, 2014, **114**, 2942; b) Z. Zheng, S. Ma, L. Tang, D. Zhang-Negrerie, Y. Du and K. Zhao, *J. Org. Chem.*, 2014, **79**, 4687; c) L. M. Blair and J. Sperry, *J. Nat. Prod.*, 2013, **76**, 794.
- a) A. C. Watterson and S. A. Shama, *J. Org. Chem.*, 1975, **40**, 19; b) C. W. Rees, T. L. Gilchrist and E. Stanton, *J. Chem. Soc. C*, 1971, 988; c) J. D. Coyle, G. L. Newport and A. Harriman, *J. Chem. Soc., Perkin Trans. 2*, 1978, 133; d) M. Oelgemoller, A. G. Griesbeck, J. Lex, A. Haeuseler, M. Schmittel, M. Niki, D. Heseck and Y. Inoue, *Org. Lett.*, 2001, **3**, 1593.
- Refer to supporting information.
- A. Iyer, S. Jockusch and J. Sivaguru, *J. Phys. Chem. A.*, 2014, **118**, 10596.
- D. Rehm and A. Weller, *Israel J. Chem.*, 1970, **8**, 259.
- S. Dadashi-Silab, C. Aydogan and Y. Yagci, *Polymer Chem.*, 2015, **6**, 6595.
- G. J. Kavarnos and N. J. Turro, *Chem. Rev.*, 1986, **86**, 401.
- C. A. Chesta and D. G. Whitten, *J. Am. Chem. Soc.*, 1992, **114**, 2188.