

### Communication

# Realizing the Photo-Ene Reaction with alkenes under visible light irradiation and bypassing the favored [2+2]-photocycloaddition

Sapna Ahuja, Ramya Raghunathan, Elango Kumarasamy, Steffen Jockusch, and Jayaraman Sivaguru

J. Am. Chem. Soc., Just Accepted Manuscript • Publication Date (Web): 26 Sep 2018

Downloaded from http://pubs.acs.org on September 26, 2018

## **Just Accepted**

"Just Accepted" manuscripts have been peer-reviewed and accepted for publication. They are posted online prior to technical editing, formatting for publication and author proofing. The American Chemical Society provides "Just Accepted" as a service to the research community to expedite the dissemination of scientific material as soon as possible after acceptance. "Just Accepted" manuscripts appear in full in PDF format accompanied by an HTML abstract. "Just Accepted" manuscripts have been fully peer reviewed, but should not be considered the official version of record. They are citable by the Digital Object Identifier (DOI®). "Just Accepted" is an optional service offered to authors. Therefore, the "Just Accepted" Web site may not include all articles that will be published in the journal. After a manuscript is technically edited and formatted, it will be removed from the "Just Accepted" Web site and published as an ASAP article. Note that technical editing may introduce minor changes to the manuscript text and/or graphics which could affect content, and all legal disclaimers and ethical guidelines that apply to the journal pertain. ACS cannot be held responsible for errors or consequences arising from the use of information contained in these "Just Accepted" manuscripts.



is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Published by American Chemical Society. Copyright © American Chemical Society. However, no copyright claim is made to original U.S. Government works, or works produced by employees of any Commonwealth realm Crown government in the course of their duties.

7

8 9

10 11

12 13

14

15

16

17 18

19

20

21

22

23

24

25

26

27

28

29

30

31

32

33

34

35

36

37

38

39

40

41

42

43

44

45

46

47

48

49

50

51

52

53

54

55

56

57

58 59

60

# Realizing the Photo-Ene Reaction with alkenes under visible light irradiation and bypassing the favored [2+2]-photocycloaddition

Sapna Ahuja,<sup>§</sup> Ramya Raghunathan,<sup>†</sup> Elango Kumarasamy,<sup>†</sup> Steffen Jockusch,<sup>†</sup>

Jayaraman Sivaguru<sup>§,\*</sup>

<sup>§</sup> Center for Photochemical Sciences and Department of Chemistry, Bowling Green State University, Bowling Green, OH 43403, USA.

<sup>†</sup> Department of Chemistry Columbia University, New York, NY 10027, USA.

Supporting Information Placeholder

**ABSTRACT:** The text book photoreaction between two alkenes is the [2+2]-photocycloaddition resulting in functionalized cyclobutanes. Herein, we disclose an unusual reactivity of alkenes that favor photo-ene reaction over the [2+2]-photocycloaddition.

The synthetic utility of ene reaction lies in the fact that simple thermal reorganization affords C-C bond formation to access complex carbocycles and heterocycles. (Figure 1).<sup>1-4</sup> Thermally, different variants of ene reaction exist depending upon the nature of enophile such as alkene, alkyne, azo and carbonyl functionality.<sup>5-6</sup> Photochemical routes to access ene reactions are rare as photo-excited alkene undergo the preferred / photochemically-allowed [2+2]-photocycloaddition leading to cyclobutanes.<sup>7-9</sup> A well-known variant of photo-ene reaction is the formation of hydroperoxide upon reaction of alkene with singlet oxygen.<sup>10-14</sup> Weedon and coworkers have reported photo-ene reaction involving an alkene where the photo-ene adduct was observed as a minor side product (1-2% yield).<sup>15</sup> To the best of our knowledge, directing the photoreactivity of an excited alkene exclusively towards ene-reaction i.e., the photochemical equivalent of the thermal ene-reaction, is not reported in literature. In this report, we present our observation wherein the excited state reactivity of alkenes is exclusively directed towards photo-ene reaction and completely evading the preferred [2+2]-photocycloaddition (Figure 1-bottom). An important highlight of our finding is that the photo-ene reaction proceeds at ambient temperature with visible-light compared to thermal ene transformations that typically require elevated temperatures.

[2+2]-Photocycloaddition involving alkenes is a concerted process when it occurs from a  $\pi\pi^*$  singlet excited state.<sup>16</sup> Hence directing the excited state of the reactant to a different reaction pathway requires changing its characteristic and the associated dynamics which is quite challenging. However, [2+2]-photocycloaddition is also known to occur efficiently from a triplet  $\pi\pi^*$  excited state ( ${}^3\pi\pi^*$ ) in a stepwise mechanism. We believed this will present an opportunity to alter reactivity pathways. The stepwise pathway in a  ${}^3\pi\pi^*$  excited state typically



**Figure 1:** Preferred [2+2]-photocycloaddition of alkenes *vs.* photo-ene reaction.

Scheme 1: Photoreactivity of citraconicimide 1 with substituted alkenes 2a-d.



leads to biradicaloid intermediate(s), its excited state lifetime can be tuned by appropriately substituting the reactants. In this idealized scenario, a long-lived triplet biradical will likely open other competing pathways or at the very least make the other pathways competitive leading to new reactivity.<sup>16</sup> We have been successful in altering excited state pathways thereby uncovering new reactivity by employing restricted bond rotations in photoactive chromophores in unimolecular transformations.<sup>17-20</sup> To highlight the influence of restricted bond rotations in bimolecular photoreactions, we selected N-*tert*-butylphenyl citraconicimide **1** as model system and evaluated its reactivity with different alkenes **2a-d** (Scheme 1).<sup>20</sup> Citraconicimide **1** was synthesized using established literature procedures.<sup>20</sup> An added advantage of the

TABLE 1. Reaction optimization for photoreactivity of citraconicimide 1 with tetramethylethylene 2d.<sup>a</sup>

Entry	Irradiation conditions <sup>b</sup>	% Yield ( <b>5d</b> )
1	bb/Pyrex cutoff, Acetone, 2 h	21
2	bb/Pyrex cutoff, MeCN, 8 h	38
3	350 nm, X, MeCN, 2 h	16
4	420 nm, TX, MeCN, 2 h	65
5	420 nm, TX, DCM, 2 h	36
6	420 nm, TX, CHCl <sub>3</sub> , 2 h	25
7	420 nm, TX, MeOH, 2 h	6
8	420 nm, TX, EtOAc, 2 h	8

<sup>a</sup> [1]=3.3 mM at room temperature under N<sub>2</sub> atmosphere. 30 mol% xanthone (X) or thioxanthone, (TX) and 10 eq. of 2d. Yield based on <sup>1</sup>H-NMR spectroscopy using triphenylmethane as internal standard (error ±5%). <sup>b</sup> bb/Pyrex cutoff broadband irradiation using a medium pressure 450 W mercury lamp with Pyrex cutoff; <sup>c</sup> ~350 nm/~420 nm irradiations performed in a Rayonet reactor.

design is the restricted N-CArvi bond rotation which could be employed for atropselective transformations.<sup>17, 21-24</sup> Citraconicimide 1 exist as atropisomers and its energy barrier for N-C<sub>Arvl</sub> bond rotation was evaluated<sup>25</sup> through kinetics measurements of racemization at 70 °C in MeCN. As expected, 1 featured a high activation energy barrier of ~29.6 kcal/mol with a half-life for racemization  $(\tau_{1/2})$  of 8.3 days corresponding to the racemization rate constant  $(k_{rac})$  of 9.6x10<sup>-7</sup> s<sup>-1</sup>. Such high racemization barrier allows 1 to maintain its absolute configuration during reaction with alkene under ambient conditions. We evaluated the photochemical reactivity of 1 with various alkenes 2a-d. The reactions were performed under both direct and sensitized irradiation conditions (Tables 1-2). After the photoreaction, the reaction mixture was purified by column chromatography and analyzed by NMR spectroscopy and mass spectrometry. Unambiguous characterization of the photoproducts was established using single crystal XRD.<sup>26</sup> Table 1 displays the optimization of reaction conditions for reactivity of 1 with tetramethylethylene 2d.





<sup>a</sup> Irradiation with 30 mol% TX and 10 equiv of **2**. *ee* values from chiral stationary phase HPLC with A and B representing the order of eluting enantiomers; dr values from <sup>1</sup>H NMR spectroscopy (±3% error). Based on crude NMR (<5%) of side products (photo-ene product for **2b**; [2+2]-product for **2c**) were observed. In addition, there were also trace amounts of uncharacterized side products.

3

4

5

7

12

13

14

15

16

17

59

60



Figure 2: (A) Determination of bimolecular rate constant (k<sub>a</sub>) for quenching of xanthone and thioxanthone triplet states by 1 using laser flash photolysis ( $\lambda_{ex}$ =355 nm, 7 ns pulse width). Inverse xanthone and thioxanthone triplet lifetimes determined from triplet absorption decay traces monitored at 620 nm vs. varying concentration of 1 in argon saturated MeCN solutions. (B) Transient absorption spectrum of 1 monitored at the end of the laser pulse ( $\lambda_{ex}$ =308 nm, 20 ns pulse width) of argon saturated MeCN solutions. Inset: decay trace monitored at 350 nm. (C) Determination of  $k_q$  of <sup>3</sup>1\* by alkenes **2a-2d** using LFP ( $\lambda_{ex}$ =308 nm, 20 ns pulse width). Inverse triplet lifetime of 1 determined from triplet absorption decay traces monitored at 350 nm vs. varying concentration of 2 in argon saturated MeCN solutions.

18 Based on this observation, optimized reaction conditions 19 were developed (Table 2) to probe the reactivity of 1 with 20 various alkenes 2a-d. Irradiation was carried out at ~420 21 nm (Rayonet reactor) using thioxanthone as sensitizer. 22 Inspection of Table 2 reveals that [2+2]-photo-adducts 3 23 and 4 were observed as the major/isolated products up-24 on employing mono and di-substituted alkenes 2a-2b and 2e. However, photo-ene product 5 was observed as 25 the major product with tri- and tetrasubstituted 2c-2d. It 26 was interesting to observe that the chemoselectivity is 27 based on the substitution pattern on the alkene em-28 ployed. To further understand the chemoselectivity lead-29 ing to photo-ene reaction, we evaluated the photoreac-30 tivity of 1 with tetra-substituted alkene 2d under varying 31 reaction conditions. While the photo-ene product 5d was 32 observed under both direct and sensitized irradiations. 33 the reaction efficiency and the product yield was evidently much higher under triplet sensitized irradiation condi-34 tions (Table 1; compare entries 2 and 4). Based on this 35 observation, we believe that 1 reacts from the triplet ex-36 cited state and triplet sensitizer thioxanthone accelerates 37 the reaction by populating the triplet states of **1** through 38 energy transfer. Thus in the absence of sensitizer, the 39 reaction is less efficient due to poor intersystem crossing 40 rates of 1.20

41 Inspection of Table 2 shows that the alkene substitu-42 tion has a profound effect on the reaction outcome. Pho-43 toreaction of 1 (thioxanthone sensitization) with mono-44 substituted alkene 2a afforded the 1,2-substituted cyclo-45 butane **3a** and 1,3-substituted cyclobutane **4a** in 41% 46 and 23% isolated yields, respectively. We confirmed 47 these products unambiguously from the single crystal XRD of the major and minor regioisomers 3b and 4b 48 respectively. The absolute configurations were deter-49 mined to be (P,R,R)-3b, (M,S,S)-3b and (P,S,R)-4b, 50 (M,R,S) **4b**.<sup>26</sup> On the other hand, under identical condi-51 tions, photoreaction of 1 with tri-substituted alkene 2c 52 and tetra-substituted alkene 2d gave the respective pho-53 to-ene product 5c (45% isolated yield) and 5d respec-54 tively (41% isolated yield). When the reaction was car-55 ried out at -78 °C, the isolated yield of the photo-ene 56 adduct 5d increased to 83%. Unambiguous characteriza-57 tion of **5d** was established through single crystal XRD. 58

Based on our previous investigations on atropselective intramolecular photoreactions, we believed that the axial chirality would influence the stereochemical outcome of the reaction.<sup>17</sup> To establish the role of axial chirality, we performed photoreactions on enantiopure atropisomeric citraconicimide 1 with monosubstituted alkene 2a and analyzed the stereoselectivity in the product. Since alkene 2a is unsymmetric, two regioisomeric products 3a and 4a were isolated. The atropselectivity in the products were >97% suggesting that the axial chirality played a critical role by facially biasing the approach of the alkene leading to excellent stereoselectivity in the products. Inspection of the stereoselectivity and the crystal structure of photo-ene 5d shows that the enantiomer (M)-1 gave (M,S)-5d, while the opposite enantiomer (P)-1 gave the enantiomeric (P,R)-5d with atropselectivity >99%.<sup>26</sup> Irrespective of chemoselectivity in the reaction, the enantiomeric excess (atropselectivity) in the products is determined by the axial chirality of the citraconicimide 1.

To rationalize the above observations and to understand the mechanistic details for this chemoselectivity, we performed detailed photophysical experiments. As we have previously shown that maleimides feature only weak luminescence both at room temperature and at 77 K,<sup>20</sup> we turned to laser flash photolysis (LFP;  $\lambda_{ex}$  = 355 nm, 7 ns pulse width) to understand the excited state reactivity of 1 with alkenes 2. As the reaction occurred efficiently through triplet sensitization under both UV and visible light, we determined the bimolecular quenching rate constant  $k_q$  (Figure 2A) of excited sensitizers xanthone (X) and thioxanthone (TX) triplet states by 1. The excited sensitizers were efficiently quenched by 1 (for xanthone  $k_q^{X} = 6.6 \pm 0.1 \times 10^9 \text{ M}^{-1} \text{s}^{-1}$  and for thioxanthone  $k_{a}^{TX} = 4.6 \pm 0.1 \text{ x } 10^{9} \text{ M}^{-1} \text{s}^{-1}$ ). The high  $k_{a}$  indicated that the energy of the triplet state of 1 is below that of thioxanthone (~63 kcal/mol). Direct excitation of 1 with laser pulses at 308 nm (20 ns pulse width) generated a weak transient absorption spectrum which decayed with a lifetime of 8.7 µs (Figure 2B). The transient signal was assigned to the triplet state of 1 based on the high rate constant of quenching by molecular oxygen (~2 × 10<sup>9</sup> M<sup>-</sup> <sup>1</sup>s<sup>-1</sup>) and similarities with a previously reported triplet spectrum of maleimides.<sup>27</sup> This enabled us to determine

the quenching rate constants of <sup>3</sup>1<sup>\*</sup> by various alkenes **2a-2d** (Figure 2C). All the alkenes screened quenched <sup>3</sup>1<sup>\*</sup> efficiently with  $k_q$  ranging from 1 × 10<sup>8</sup> M<sup>-1</sup>s<sup>-1</sup> (for 2a) to 11 × 10<sup>8</sup> M<sup>-1</sup>s<sup>-1</sup> (for 2c). This shows that the nature of the alkene played a significant role in quenching the excited state of the citraconicimide. We believe the chemical quenching of the triplet excited state of 1 by alkenes results in the formation of the triplet biradicals (*vide infra*).

Scheme 2: Mechanistic rationale for the observed photoene reaction



To rationalize the formation of photo-ene product, we propose a mechanistic model from the excited state 1 that involves zwitterionic or radical pathway as detailed in Scheme 2. In radical pathway, we postulate that citraconicimide 1 react from the triplet excited state with alkene 2d to form triplet 1,4-biradical t-1,4-BR-2d. This t-1,4-BR-2d abstracts the allylic hydrogen of citraconicimide through a cyclic 6-memembered transition state to form triplet 1,2-biradical t-1,2-BR-2d. Subsequent intersystem crossing and recombination results in photoene product 5d. In ionic pathway, the triplet excited 1 could form an exciplex with the alkene which after addition leads to a zwitterionic intermediate ZW-2d. Hydride migration from this intermediate lead to the desired product 5d. Based on the oxidation potential of alkene (1.59 eV for 2c and 1.31 eV for 2d) and the reduction potential of **1** (1.66 eV),<sup>26</sup> we believe that the exciplex formation from the triplet excited state of 1 (estimated  $E_T$ ~ 62 kcal/mol)<sup>20</sup> and the ionic pathway is not very likely due to endergonic nature of electron transfer. Hence, in the present case, it is very likely that the reaction occurs through a radical mechanism. Based on the atropselective reaction of enantiopure 1 with 2d, the approach of the alkene towards the excited citraconicimide was dictated by the ortho-tert-butyl substituent on the N-aryl ring. In the case of triplet excited (M)-1 undergoing photo-ene reaction with 2d, the alkene approached the citraconicimide from the side opposite (Si-face) to that of

the ortho-tert-butyl substituent on the N-aryl ring leading to t-1,4-BR-2d. This fixed the stereochemistry of the point chiral stereocenter at the allylic position as the "S" configuration leading to the photo-ene (M,S)-2d. In mono- or di-substituted alkenes, the initially formed triplet 1,4-biradical is a primary radical center that will react at a faster rate leading to ring closure resulting in [2+2]photocycloaddition. In tri-and tetra- substituted alkene, the triplet biradical is relatively long lived enabling allylic hydrogen abstraction leading to photo-ene reaction. Thus, the nature of the biradical in the reaction pathway, its lifetime and stability that are dictated by the substituents on the alkenes determine the course of the photoreaction *i.e.*, [2+2]-cycloaddition vs. photo-ene reaction.

To conclude, our study has uncovered that by tuning the substitution on alkene, the photochemical reaction pathway between citraconicimide and alkenes can be entirely directed towards either [2+2]-photocycloaddition or photo-ene reaction. Additionally, irrespective of the chemoselectivity, the incorporation of axial chirality in the system leads to the stereo-enriched photoproduct where the steric handle in the axial chirality influence the approach of alkene towards the excited maleimide chromophore. Thus, our study has showcased the effectiveness of employing restricted bond rotations to open new avenues to perform light initiated reactions and uncover new reaction pathways. In the present case, our investigation has showcased the utility of light to promote one of the useful thermal transformations viz., ene-reaction at room temperature.

#### ASSOCIATED CONTENT

**Supporting Information**. Supporting Information is available free of charge on the ACS Publications website. Single-crystal XRD data (CIF), Experimental procedures, characterization data, analytical conditions, and photophysical studies (PDF).

#### **AUTHOR INFORMATION**

#### **Corresponding Author**

\* E-Mail: sivagj@bgsu.edu

#### ORCID

J. Sivaguru: 0000-0002-0446-6903 Steffen Jockusch: 0000-0002-4592-5280 Elango Kumarasamy: 0000-0002-7995-6894 Sapna Ahuja: 0000-0002-3060-9699

#### **Author Contributions**

Manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

#### **Funding Sources**

The authors thank the National Science Foundation for generous support for their research (CHE-1465075 and CHE-1811795).

#### Notes

Part of the work was conducted during SA, RR, EK and JS affiliation with North Dakota State University, Fargo, ND.

#### Acknowledgment

The authors thank Dr. Angel Ugrinov for solving the single crystal XRD structures.

1

2

3

4

5

6

7

8

9

10

11

12

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

60

#### REFERENCES

- 1. Alder, K.; Pascher, F.; Schmitz, A., *Ber. Dtsch. Chem.* Ges. **1943**, *76*, 27-53.
- 2. Hoffmann, H. M. R., Angew. Chem. Int. Ed. **1969**, *8*, 556-577.
- 3. Mikami, K.; Shimizu, M., Chem. Rev. 1992, 92, 1021-1050.
- 4. Oppolzer, W.; Snieckus, V., Angew. Chem. Int. Ed. 1978, 17, 476-486.
- Thaler, W. A.; Franzus, B., J. Org. Chem. 1964, 29, 2226-2235.
- Evans, D. A.; Tregay, S. W.; Burgey, C. S.; Paras, N. A.; Vojkovsky, T., *J. Am. Chem. Soc.* **2000**, *122*, 7936-7943.
  - Schuster, D. I.; Lem, G.; Kaprinidis, N. A., *Chem. Rev.* 1993, 93, 3-22.
    - Poplata, S.; Tröster, A.; Zou, Y.-Q.; Bach, T., *Chem. Rev.* 2016, *116*, 9748-9815.
  - 9. Ramamurthy, V.; Sivaguru, J., *Chem. Rev.* **2016**, *116*, 9914-9993.
  - 10. Foote, C. S., Acc. Chem. Res. 1968, 1, 104-110.
  - 11. Wasserman, H. H.; Murray, R. W., *Singlet Oxygen*. Academic: New York, 1979.
  - 12. Frimer, A. A., *Singlet Oxygen*. CRC: Boca Raton, 1985; Vol. 1-4.
  - 13. Turro, N. J., Tetrahedron 1985, 41, 2089-2098.
  - 14. Ghogare, A. A.; Greer, A., *Chem. Rev.* **2016**, *116*, 9994-10034.
- Andrew, D.; Hastings, D. J.; Oldroyd, D. L.; Rudolph, A.; Weedon, A. C.; Wong, D. F.; Zhang, B., *Pure Appl. Chem.* **1992**, 64, 1327-1334.

- Turro, N. J.; Ramamurthy, V.; Scaiano, J. C., Modern Molecular Photochemistry of Organic Molecules. University Science Books: Sausalito, CA, 2010; 705-799.
- Kumarasamy, E.; Ayitou, A. J.-L.; Vallavoju, N.; Raghunathan, R.; Iyer, A.; Clay, A.; Kandappa, S. K.; Sivaguru, J., *Acc. Chem. Res.* **2016**, *49*, 2713-2724.
- Kumarasamy, E.; Raghunathan, R.; Kandappa, S. K.; Sreenithya, A.; Jockusch, S.; Sunoj, R. B.; Sivaguru, J., J. Am. Chem. Soc. 2017, 139, 655-662.
- Kumarasamy, E.; Kandappa, S. K.; Raghunathan, R.; Jockusch, S.; Sivaguru, J., *Angew. Chem. Int. Ed.* **2017**, 56, 7056-7061.
- Kumarasamy, E.; Raghunathan, R.; Jockusch, S.; Ugrinov, A.; Sivaguru, J., *J. Am. Chem. Soc.* **2014**, *136*, 8729-8737.
- 21. Curran, D. P.; Qi, H.; Geib, S. J.; DeMello, N. C., *J. Am. Chem. Soc.* **1994**, *116*, 3131-3132.
- 22. Clayden, J., Angew. Chem. Int. Ed. 1997, 36, 949-951.
- Curran, D. P.; Hale, G. R.; Geib, S. J.; Balog, A.; Cass, Q. B.; Degani, A. L. G.; Hernandes, M. Z.; Freitas, L. C. G., *Tetrahedron: Asymmetry* **1997**, *8*, 3955-3975.
- 24. Clayden, J., Chem. Commun. 2004, 127-135.
- Wolf, C., Dynamic Stereochemistry of Chiral Compounds. Principles and Applications. RSC publishing: Cambridge, UK, 2008;
- 26. Refer to supporting information.
- 27. von Sonntag, J.; Knolle, W.; Naumov, S.; Mehnert, R., *Chem. Eur. J.* **2002**, *8*, 4199-4209.



