

Triple-photoinduced electron transfer (tri-PET) catalysis for activation of super strong bonds

Amit Biswas¹, Simon Kolb², Sebastian Röttger², Arpan Das¹, Lukas J. Patalag², Swagata Sil¹, Subir Maji¹, Soumi Chakrabarty¹, Anup Bhunia³, Daniel B. Werz² & Swadhin K. Mandal¹

Abstract

Single electron redox processes allow the formation of highly reactive radicals – valuable intermediates that enable unique transformations in organic chemistry.^{1,2} An established concept to create radical intermediates is photoexcitation of a catalyst to a higher energy intermediate, subsequently leading to a photoinduced electron transfer (PET) with a reaction partner.^{3–7} The known concept of consecutive photoinduced electron transfer (con-PET) leads to catalytically active species even higher in energy by the uptake of two photons.⁸ This process has already been used widely for catalytic reductions; however, limitations towards strong bonds and electron-rich substrates remain.^{9,10} Generally speaking, increased photon uptake leads to a more potent reductant. Here, we introduce triple-photoinduced electron transfer catalysis, termed tri-PET, enabled by the three-photon uptake of a dye molecule leading to an excited dianionic super-reductant which is more potent than Li metal¹¹ – one of the strongest chemical reductants known. Irradiation of the metal-free catalyst by violet light enables the cleavage of strong carbon-fluoride bonds and reduction of other halides even in very electron-rich substrates. The resulting radicals are quenched by hydrogen atoms or engaged in carbon-carbon and carbon-phosphorus bond formations, highlighting the utility of tri-PET for organic chemistry. Thorough spectroscopic, chemical and computational investigations are presented to understand this novel mode of photoredox catalysis. The existence of the dianion which takes up a third photon when irradiated was proven by X-ray diffraction analysis.

The activation of strong bonds requires catalytically active species which are high enough in energy (or redox potential) and long-living enough to be engaged in reactions.¹² Previous endeavors to generate catalytically active species from photo-excitable molecules resulted in the consecutive uptake of up to two photons, enabling the reduction of various aryl halides and other functionalities (Fig. 1a and 1b).^{9,10} Seminal work on consecutive two-photon electron transfer (con-PET) catalysis was presented by König *et al.* who irradiated perylene diimides with blue LEDs (455 nm) to generate potent reductants.⁸ In recent studies, Nicewicz *et al.*¹³ utilized a mesityl-acridinium radical ($E_{1/2} = -3.36$ V vs. SCE) which was accessible by photoinduced reduction of the corresponding cation. Gilmour and coworkers applied con-PET catalysis to the reduction of Weinreb amides.¹⁴ Various other, similar strategies to generate super-reducing species have been developed.^{15–27} However, these systems are usually limited when challenging carbon-fluoride bonds, or if reduction of, very electron-rich substrates is desired. Overcoming those challenges should be possible by accessing more potent reductants, e.g. via three-photon uptake of a single molecule, leading to triple-photoinduced electron transfer (tri-PET) catalysis; a concept which to our knowledge has not yet been explored. However, triple photon uptake by a single molecule is known outside of catalysis.^{28–30} In a former work by Werz *et al.*,³¹ cyclic voltammetric studies of the recently designed dye molecule **1** (BOIMPY = borondifluoride-8-imidazodipyrromethene) revealed two reversible reduction waves which refer to the radical anion **2** ($E_{1/2}^1 = -0.40$ V) and the dianion **3** ($E_{1/2}^2 = -1.10$ V, both vs. Fc/Fc⁺, Fig. 1c), hence, in principle, allowing **1** to be a precatalyst in a tri-PET process. Chemical reduction of **1** using CoCp*₂ facilitated the challenging crystallization of the dianion **3** which was analyzed by X-ray diffraction (Fig. 1d). This gave evidence that the dianion **3** is indeed accessible upon two electron reduction and helped us to perform mechanistic

experiments on the tri-PET process (*vide infra*). Electroanalytic results revealed the super-reducing properties ($E_{1/2} = < -3.58$ V; cf. Li metal $E_{1/2} = -3.29$ V, both vs. SCE)¹¹ of the excited dianion **3*** which should allow single electron transfer (SET) reduction of aryl halides and benzene ($E_{1/2} = -2.24$ to -3.42 V vs. SCE, Fig. 1e)³²⁻³⁴. In addition, a long lifetime ($\tau = 9.21$ ns) for the excited dianion **3** was found, thus fulfilling both criteria crucial for catalytic strong bond activation. Herein, we introduce tri-PET catalysis which is enabled by irradiation of BOIMPY **1**, allowing the reduction of various very electron-rich halides and the engagement of the resulting radicals in hydrodehalogenations, carbon-carbon and carbon-phosphorus bond formations. In addition to a versatile scope and detailed mechanistic investigations for the tri-PET process, we performed similar experiments (computational, spectroscopic, kinetic and chemical investigations) for a con-PET process utilizing BOIMPY **1** under blue light irradiation (456 nm LEDs) – details can be found in the Supplementary Information.

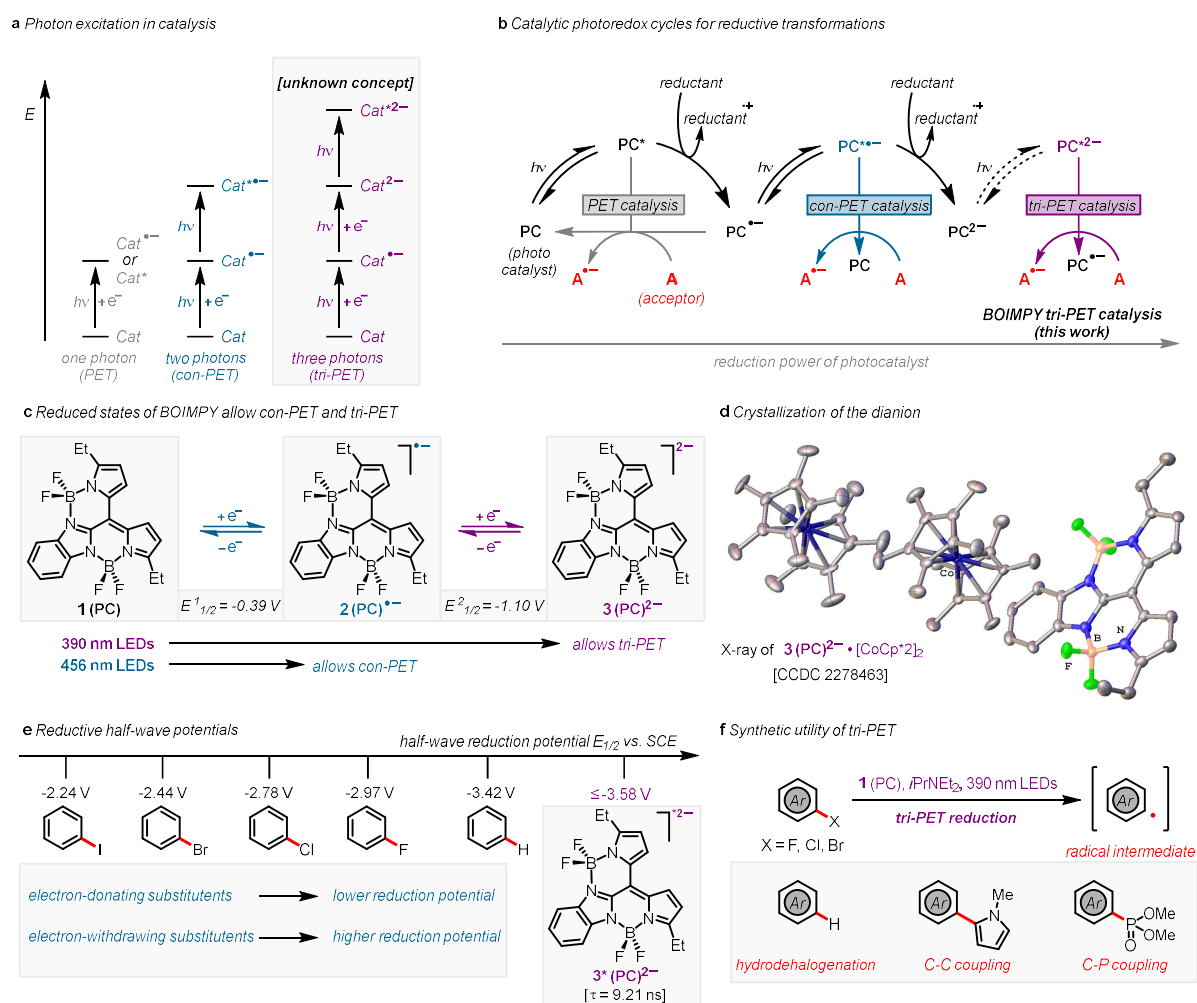


Fig.1 Photon excitation processes in catalysis. a, General catalytic concept on one photoinduced electron transfer (PET), consecutive two-photon PET (con-PET), and triple-photoinduced electron transfer (tri-PET). **b**, Catalytic cycles for PET, con-PET and tri-PET. **c**, Irradiation of BOIMPY **1** allows con-PET and tri-PET via dianion **3**. **d**, X-ray crystal structure of BOIMPY dianion **3(PC)**²⁻. H atoms are omitted for clarity. **e**, Reductive half-wave potentials of aryl halides, benzene and the excited species **3**. **f**, Synthetic utility of our process. SCE = saturated calomel electrode; $E_{1/2}$ = half-wave reduction potential.

To reach very deep reductions potentials ($E_{1/2}(\mathbf{3}^*) \leq -3.58$ V vs. SCE), we envisioned utilizing BOIMPY **1** for a tri-PET process by generating the doubly reduced species **3** photochemically and further exciting this dianion by uptake of a third photon. This was indeed feasible by irradiation of **1** with 390 nm LEDs in the presence of a mild reductant (*i*Pr₂NEt) in DMSO, hence allowing us to catalytically reduce strong bonds (Fig. 1f). With optimized conditions in hand, we started to explore the synthetic utility by simple dehydrohalogenations of a variety of aryl halides. Conversion of multi-aromatic fluorides **4** – **7** proceeded in up to 90% yield. Mono-, di- and trialkylated aryl fluorides were accepted by our protocol affording **8** – **10** (29 – 51%). Besides aryl fluorides, we also found less challenging chloride and bromide containing analogs to be reducible in comparable yields (**6**, **10**). Aryl fluorides and chlorides which contain electron-donating amine or multiple ether functions **11** – **15** were protodehalogenated smoothly when subjected to our established conditions. The F/H-exchange of only one fluoride was found when polyfluorinated structures **16** and **17** were used and only catalytic amounts of *i*Pr₂NEt were present. Next, we focused on pharmaceuticals and derivatives thereof. A variety of substrates that feature an aromatic chloride **18** – **25** were successfully converted (42 – 67%) which simultaneously shows wide functional group tolerance and the applicability of our method to different heterocycles. Fluorinated and chlorinated derivatives of vitamin E **26** and of steroidal structures **27** and **28** were found to be reactive. Besides aryl halides, we were able to protodehalogenate a tertiary alkyl chloride/bromide **29** as well as secondary **30** and primary alkyl chlorides **31** in mediocre yields.

Next, we tested our method's feasibility for use in metal-free carbon-carbon bond formation. Coupling of fluorobenzene and derivatives bearing electron-withdrawing groups **32** – **35** with a palette of pyrroles was found to proceed smoothly. Subjecting more challenging substrates **36** – **38** to our coupling protocol delivered the respective products in high yields. Coupling of highly electron-rich 2,4,6-trimethoxy substituted fluorobenzene **39** (63%) highlights the deep reduction potentials our catalytic system is able to reach. In addition to polyfluorinated structures **40** and **41** (coupling at three sites), dehalogenative coupling of pharmaceuticals **42** – **44** was achieved. With the aim to extend our protocol to carbon-phosphorus bond formations, we utilized phosphites as reaction partners which delivered the coupled phosphonates in excellent yields when electron-poor and electron-rich aryl fluorides (**45** – **48**: 73% – 89%) were used.

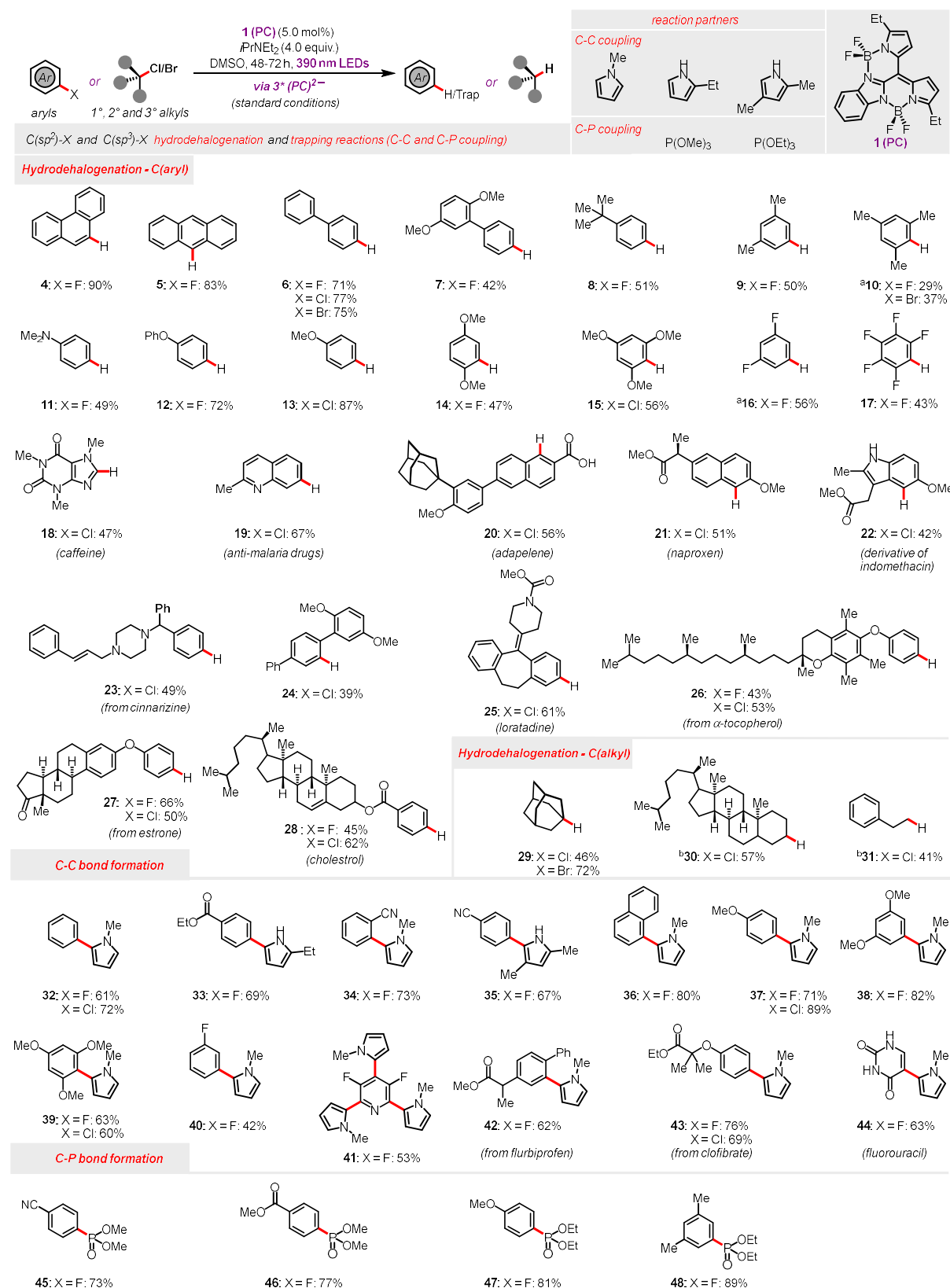


Fig. 2 Substrate scope of our tri-PET catalytic process using BOIMPY 1. All reactions were carried out with aryl halide (0.3 mmol), BOIMPY (0.015 mmol), *i*Pr₂NEt (1.2 mmol), and dry DMSO (2.0 mL) under irradiation with two 390 nm LEDs for 48 h. Yields are given as isolated yields. ^a GC yield. ^b Sodium dodecyl sulfate (SDS; 0.36 mmol) was added additionally; the reaction was run in DMSO/H₂O (1.2 mL/0.8 mL).

To prove that a tri-PET process is present, we undertook mechanistic and analytical investigations which started with the irradiation (390 nm LEDs) of a solution of BOIMPY **1** in DMSO under the presence of *i*Pr₂NEt and inert atmosphere (Fig. 3a). This resulted in a colored solution, different to the color observed when irradiation was performed with 456 nm LEDs (see Supplementary Information, Section 6 and 9), meaning that different species were formed dependent on the applied wavelength. No EPR signals were observed after the color change which indicates that a non-radical species such as the dianion **3** was formed. Irradiation of chemically generated radical anion **2** with 390 nm LEDs also led to the disappearance of EPR signals. Protodehalogenation of substrate **13-Cl** with crystallized dianion **3** instead of BOIMPY **1** being present, only proceeded when 390 nm light was applied to the reaction mixture (Fig. 3b). This gave evidence that the dianion **3** is not able to perform the reduction of **13-Cl** while the higher energy species **3*** is capable. Performance of an on/off experiment on the coupling between **13-Cl** and pyrrole **49** further showed that product **36** is only formed when the mixture is irradiated with 390 nm LEDs (Fig. 3c). UV-Vis spectroscopy of a solution of BOIMPY **1** and *i*Pr₂NEt in DMSO revealed an absorption maximum between 350 – 450 nm which fits the applied wavelength of 390 nm and is also in agreement with absorption maxima that have been observed when spectroelectrochemical investigations were carried out on BOIMPY **1**. (Fig. 3d and SI). Kinetic experiments were performed by applying standard conditions to 4-chloroanisole (**13**, Fig. 3e). Over the course of 10 h, a six-fold increase in the yield of **13** was found when the light intensity was doubled. con-PET processes are known to show a quadruple increase of yield;^{9,14} findings which are in accordance with our kinetic measurements when 456 nm LEDs are applied to our protocol (see Supplementary Information). This indicates that our process requires an uptake of more than two photons in order to occur and makes us comfortable postulating the following mechanism based on the presented analytical investigations (Fig. 3f). Irradiation of photocatalyst **1** (**PC**) with 390 nm LEDs and subsequent reduction of the excited species **1*** (**PC**) by *i*Pr₂NEt results in the formation of the radical anion **2** (**PC**)^{•-}. Iterative excitation and reductive quench of **2*** (**PC**)^{•-} delivers the dianion **3** (**PC**)²⁻ which can again be promoted to its excited state **3*** (**PC**)²⁻. The super-reductive species **3** (**PC***)²⁻ then transfers a single electron to the substrate to be reduced and restarts the catalytic cycle by generation of the radical anion **2** (**PC**)^{•-}.

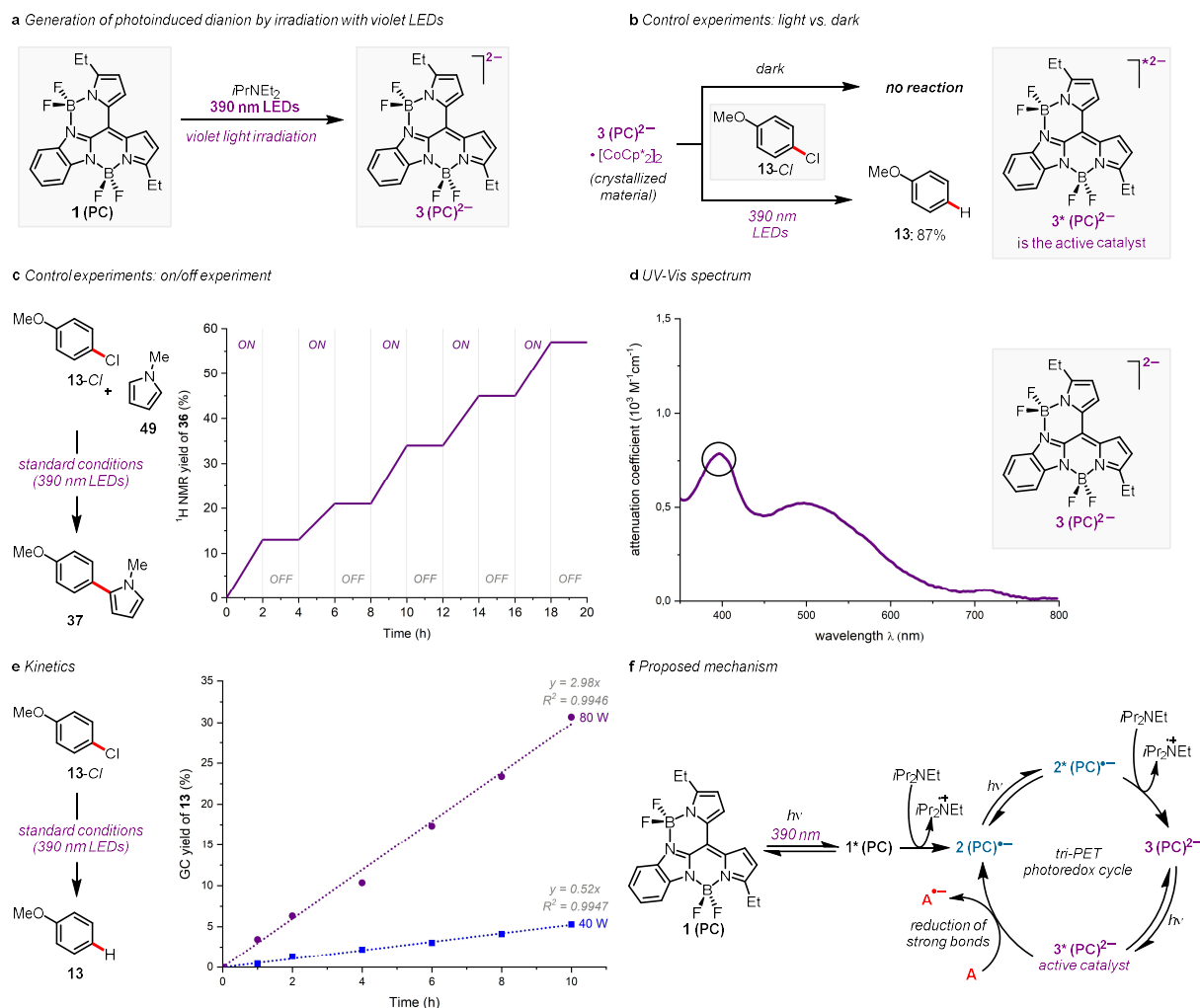


Fig. 3 Mechanistic investigation of triple-photon excited electron transfer process. **a**, Irradiation of BOIMPY **1** and $i\text{Pr}_2\text{NEt}$ with violet LEDs (390 nm) results in formation of dianion **3**. **b**, Crystallized material **3** only reacts with **13-Cl** under irradiation with 390 nm LEDs. **c**, On/off experiments. **d**, Control experiments with crystallized dianion of BOIMPY in the presence and absence of 390 nm light irradiation. **e**, Kinetic analysis by variation of the light intensity. **f**, Proposed mechanism for the tri-PET process using BOIMPY **1**.

In conclusion, for the first time consecutive triple-photon induced electron transfer (tri-PET) catalysis was realized by irradiation of BOIMPY **1** with 390 nm LEDs. The emerging super-reducing species **3*** ($E_{1/2} = < -3.58$ V vs. SEC) allows the catalytic reduction of strong bonds and electron-rich substrates (e.g. aryl fluorides and alkyl chlorides). The synthetic utility of this process was demonstrated by hydrodehalogenations, carbon-carbon and carbon-phosphorus bond formations. A broad variety of spectroscopic, kinetic and chemical investigations helped to understand the presented process. Experiments were made possible by successful crystallization of dianion **3** which formed the excited species **3*** upon irradiation. We are confident that more challenging transformations will be made feasible by utilizing tri-PET catalysis.

Keywords: tri-PET, con-PET, Photoredox, Radical Chemistry, Hydrodehalogenation, C-F Bond Activation, Super Reductants

Affiliation

¹ Department of Chemical Sciences, Indian Institute of Science Education and Research (IISER) Kolkata, Mohanpur Campus, Nadia, 741246, West Bengal, India. E-mail: swadhin.mandal@iiserkol.ac.in

² Albert-Ludwigs University Freiburg, Institute of Organic Chemistry, Albertstr. 21, 79104 Freiburg, Germany: E-mail: daniel.werz@chemie.uni-freiburg.de

³ Department of Chemical Sciences, Indian Institute of Science Education and Research (IISER) Kolkata, Mohanpur Campus, Nadia, 741246, West Bengal, India. E-mail: bhunia1988@iiserkol.ac.in

Data availability

The data supporting the findings of this study are available within the paper and its Supplementary Information.

Acknowledgements

Financial support from the Deutsche Forschungsgemeinschaft (DFG) – EXC-2193/1 (*livMatS* Cluster of Excellence). We thank Dr. Sukhendu Nath for helping to understand the spectroscopic techniques. A. Bhunia thanks DST SERB for the Ramanujan Fellowship Grant (RJF/2020/000099). A. Biswas thanks CSIR-New Delhi for a senior research fellowship. We are grateful for the generous financial support of the SERB, India (Grant No. CRG/2022/000471). We thank Gwyndaf A. Oliver (Uni of Freiburg) for proofreading the manuscript.

Author contributions

Conceived by D.B.W and S.K.M.

Conceptualization and presentation of the results were done by A. Biswas, S.K., A. Bhunia, D.B.W. and S.K.M.

Scope entries and reaction optimization was done by A. Biswas. Analytical investigation and data collection was carried out by A. Biswas, S.K., L.J.P, A. Bhunia.

BOIMPY synthesis was carried out by S.R. Data analysis was done by A. Biswas, S.K. and L.J.P.

The manuscript was written by A. Biswas., S.K., D.B.W. and S.K.M.

Overall supervision was carried out by A. Bhunia, D.B.W. and S.K.M.

References

1. Smith, J. M., Harwood, S. J. & Baran, P. S. Radical Retrosynthesis. *Acc. Chem. Res.* **51**, 1807–1817 (2018).
2. Parsaee, F. *et al.* Radical philicity and its role in selective organic transformations. *Nat. Rev. Chem.* **5**, 486–499 (2021).
3. Yoon, T. P., Ischay, M. A. & Du, J. Visible light photocatalysis as a greener approach to photochemical synthesis. *Nat. Chem.* **2**, 527–532 (2010).
4. Prier, C. K., Rankic, D. A. & MacMillan, D. W. C. Visible light photoredox catalysis with transition metal complexes: applications in organic synthesis. *Chem. Rev.* **113**, 5322–5363 (2013).
5. Schultz, D. M. & Yoon, T. P. Solar synthesis: prospects in visible light photocatalysis. *Science* **343**, 1239176 (2014).
6. Romero, N. A. & Nicewicz, D. A. Organic Photoredox Catalysis. *Chem. Rev.* **116**, 10075–10166 (2016).

7. McAtee, R. C., McClain, E. J. & Stephenson, C. R. J. Illuminating Photoredox Catalysis. *Trends Chem.* **1**, 111–125 (2019).
8. Ghosh, I., Ghosh, T., Bardagi, J. I. & König, B. Reduction of aryl halides by consecutive visible light-induced electron transfer processes. *Science* **346**, 725–728 (2014).
9. Glaser, F., Kerzig, C. & Wenger, O. S. Multi-Photon Excitation in Photoredox Catalysis: Concepts, Applications, Methods. *Angew. Chem. Int. Ed.* **59**, 10266–10284 (2020).
10. Schmalzbauer, M., Marcon, M. & König, B. Excited State Anions in Organic Transformations. *Angew. Chem. Int. Ed.* **60**, 6270–6292 (2021).
11. Scordilis-Kelley, C., Fuller, J., Carlin, R. T. & Wilkes, J. S. Alkali Metal Reduction Potentials Measured in Chloroaluminate Ambient-Temperature Molten Salts. *J. Electrochem. Soc.* **139**, 694–699 (1992).
12. Ochola, J. R. & Wolf, M. O. The effect of photocatalyst excited state lifetime on the rate of photoredox catalysis. *Org. Biomol. Chem.* **14**, 9088–9092 (2016).
13. MacKenzie, I. A. *et al.* Discovery and characterization of an acridine radical photoreductant. *Nature* **580**, 76–80 (2020).
14. Soika, J. *et al.* Organophotocatalytic N–O Bond Cleavage of Weinreb Amides: Mechanism-Guided Evolution of a PET to ConPET Platform. *ACS Catal.* **12**, 10047–10056 (2022).
15. Bardagi, J. I., Ghosh, I., Schmalzbauer, M., Ghosh, T. & König, B. Anthraquinones as Photoredox Catalysts for the Reductive Activation of Aryl Halides. *Eur. J. Org. Chem.* **2018**, 34–40 (2018).
16. Neumeier, M. *et al.* Dichromatic Photocatalytic Substitutions of Aryl Halides with a Small Organic Dye. *Chem. Eur. J.* **24**, 105–108 (2018).
17. Cowper, N. G. W., Chernowsky, C. P., Williams, O. P. & Wickens, Z. K. Potent Reductants via Electron-Primed Photoredox Catalysis: Unlocking Aryl Chlorides for Radical Coupling. *J. Am. Chem. Soc.* **142**, 2093–2099 (2020).
18. Graml, A., Nevesely, T., Jan Kutta, R., Cibulka, R. & König, B. Deazaflavin reductive photocatalysis involves excited semiquinone radicals. *Nat. Commun.* **11**, 3174 (2020).
19. Cole, J. P. *et al.* Organocatalyzed Birch Reduction Driven by Visible Light. *J. Am. Chem. Soc.* **142**, 13573–13581 (2020).
20. Kim, H., Kim, H., Lambert, T. H. & Lin, S. Reductive Electrophotocatalysis: Merging Electricity and Light To Achieve Extreme Reduction Potentials. *J. Am. Chem. Soc.* **142**, 2087–2092 (2020).
21. Rieth, A. J., Gonzalez, M. I., Kudisch, B., Nava, M. & Nocera, D. G. How Radical Are "Radical" Photocatalysts? A Closed-Shell Meisenheimer Complex Is Identified as a Super-Reducing Photoreagent. *J. Am. Chem. Soc.* **143**, 14352–14359 (2021).
22. Chmiel, A. F., Williams, O. P., Chernowsky, C. P., Yeung, C. S. & Wickens, Z. K. Non-innocent Radical Ion Intermediates in Photoredox Catalysis: Parallel Reduction Modes Enable Coupling of Diverse Aryl Chlorides. *J. Am. Chem. Soc.* **143**, 10882–10889 (2021).
23. Xu, J. *et al.* Unveiling Extreme Photoreduction Potentials of Donor-Acceptor Cyanoarenes to Access Aryl Radicals from Aryl Chlorides. *J. Am. Chem. Soc.* **143**, 13266–13273 (2021).
24. Halder, S., Mandal, S., Kundu, A., Mandal, B. & Adhikari, D. Super-Reducing Behavior of Benzobenzothiazine Anion Under Visible-Light Photoredox Condition. *J. Am. Chem. Soc.* **145**, 22403–22412 (2023).
25. Kang, W.-J. *et al.* Generation of Thioxanthone Hydrogen Anion by Double Photoreduction and Uses for Catalytic Photoreductions. *ACS Catal.*, 13588–13596 (2023).
26. Baek, Y. *et al.* Singly Reduced Iridium Chromophores: Synthesis, Characterization, and Photochemistry. *J. Am. Chem. Soc.* **145**, 12499–12508 (2023).
27. Singh, V., Singh, R., Hazari, A. S. & Adhikari, D. Unexplored Facet of Pincer Ligands: Super-Reductant Behavior Applied to Transition-Metal-Free Catalysis. *JACS Au* **3**, 1213–1220 (2023).

28. Singh, S. & Bradley, L. T. Three-Photon Absorption in Naphthalene Crystals by Laser Excitation. *Phys. Rev. Lett.* **12**, 612–614 (1964).
29. Mikhailov, I. A., Bondar, M. V., Belfield, K. D. & Masunov, A. E. Electronic Properties of a New Two-Photon Absorbing Fluorene Derivative: The Role of Hartree–Fock Exchange in the Density Functional Theory Design of Improved Nonlinear Chromophores. *J. Phys. Chem. C* **113**, 20719–20724 (2009).
30. Chołuj, M. *et al.* Much of a Muchness: On the Origins of Two- and Three-Photon Absorption Activity of Dipolar Y-Shaped Chromophores. *J. Phys. Chem. A* **126**, 752–759 (2022).
31. Patalag, L. J., Jones, P. G. & Werz, D. B. BOIMPYs: Rapid Access to a Family of Red-Emissive Fluorophores and NIR Dyes. *Angew. Chem. Int. Ed.* **55**, 13340–13344 (2016).
32. Andrieux, C. P., Blocman, C. & Savéant, J. M. Characterization of electrochemical reactions hidden in the background discharge the redox catalyzed reduction of fluorobenzene. *J. Electroanal. Chem.* **105**, 413–417 (1979).
33. Mortensen, J. & Heinze, J. The Electrochemical Reduction of Benzene—First Direct Determination of the Reduction Potential. *Angew. Chem. Int. Ed. Engl.* **23**, 84–85 (1984).
34. Pause, L., Robert, M. & Savéant, J.-M. Can Single-Electron Transfer Break an Aromatic Carbon–Heteroatom Bond in One Step? A Novel Example of Transition between Stepwise and Concerted Mechanisms in the Reduction of Aromatic Iodides. *J. Am. Chem. Soc.* **121**, 7158–7159 (1999).