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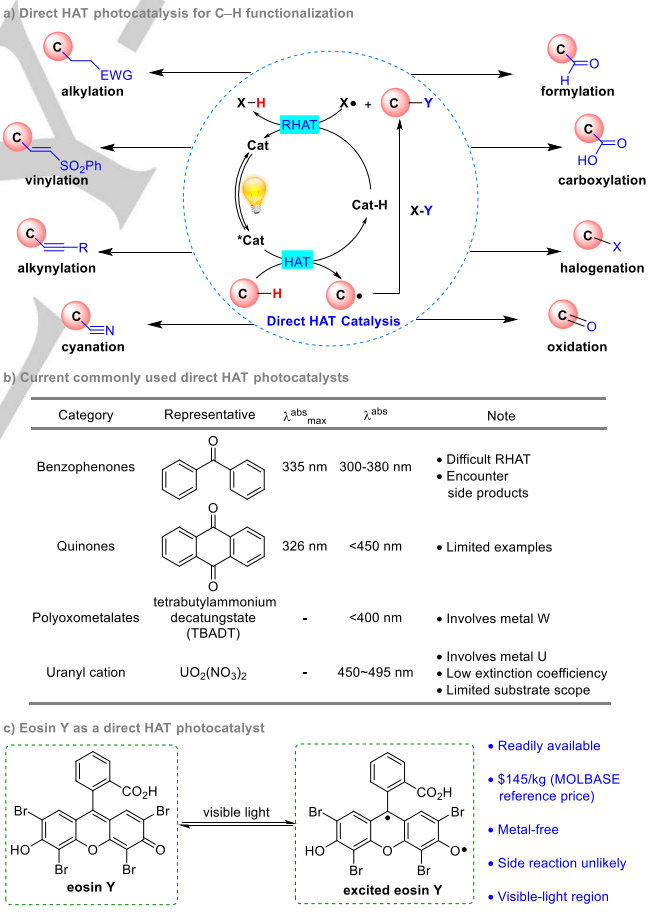
Eosin Y as a Direct Hydrogen Atom Transfer Photocatalyst for the Functionalization of C–H Bonds

Xuan-Zi Fan,[†] Jia-Wei Rong,[†] Hao-Lin Wu, Quan Zhou, Hong-Ping Deng, Jin Da Tan, Cheng-Wen Xue, Li-Zhu Wu, Hai-Rong Tao, and Jie Wu*

Abstract: *Eosin Y, a well-known economical alternative to metal catalysts in visible-light-driven single-electron transfer-based organic transformations, can behave as an effective direct hydrogen atom transfer catalyst for C–H activation. Using the alkylation of C–H bonds with electron-deficient alkenes as a model study revealed an extremely broad substrate scope, enabling easy access to a variety of important synthons. This eosin Y-based photocatalytic hydrogen atom transfer strategy is promising for diverse functionalization of a wide range of native C–H bonds in a green and sustainable manner.*

Dramatic developments in photocatalysis over the past decade have enabled previously inaccessible transformations.[1] In addition to single-electron transfer (SET) and energy transfer, hydrogen atom transfer (HAT) has been frequently involved in photocatalysis, which can activate substrates without the limitation of redox potentials, offering enormous opportunities for C–H activations.[2] Upon light absorption, HAT catalysis is normally achieved in three different ways.[2a] The first strategy is the direct HAT process, where the activated photocatalyst behaves as a HAT catalyst to abstract a H atom from a substrate. The catalytic cycle is subsequently turned over through a reverse hydrogen atom transfer (RHAT) to one of the generated intermediates.[3] The second mode is the indirect HAT process, where the excited photocatalyst activates another catalyst through SET or energy transfer, and the latter promotes the following HAT process.[4] The last route is the proton-coupled electron transfer (PCET) process, which involves a concerted transfer of an electron and a proton.[5] Among these three pathways, direct HAT catalysis represents the most reagent- and redox-economical method, as both the indirect HAT and PCET processes require other additives.

Photo-induced direct HAT catalysis has endowed with a large scope, allowing for the selective introduction of a plethora of functional groups in place of the original C–H bonds, e.g., via alkylation,[3d] vinylation,[3j] alkynylation,[3i] cyanation,[3m] formylation,[3b] carboxylation,[3f] halogenation,[3e,k,l] and oxidation[3h] (Scheme 1a). However, the major bottleneck to its wide application is the limited photocatalysts capable of performing direct HAT,[2a] being restricted to the families of benzophenones, quinones, polyoxometalates,[6] and a few others, such as the uranyl cation[3e] (Scheme 1b). Moreover, each of these catalysts has specific limitations. Activation of benzophenones and quinones normally requires ultraviolet (UV) light. Furthermore, a high catalyst loading of diaryl ketones is generally required as the ketyl radical intermediate formed in situ can undergo side reactions, such as self-dimerization.[1a] Both polyoxometalates and uranyl cation require the use of toxic transition metals. The former requires UV light,[6] and the latter suffers from a limited substrate scope.[3e] Therefore, it would be ideal to discover a direct HAT catalyst that is readily available, metal-free, activated by visible-light (*hv* 400-750 nm), and able to avoid side reactions.



Scheme 1. Direct HAT catalysis for C–H functionalization.

Xanthene dyes have been successfully used as catalysts for photoredox reactions. These dyes are typically inexpensive, easy to handle, completely absorb in the visible-light region, and possess excellent photocatalytic performance.[1a,7] Even though photochemical hydrogen abstraction properties of quinones

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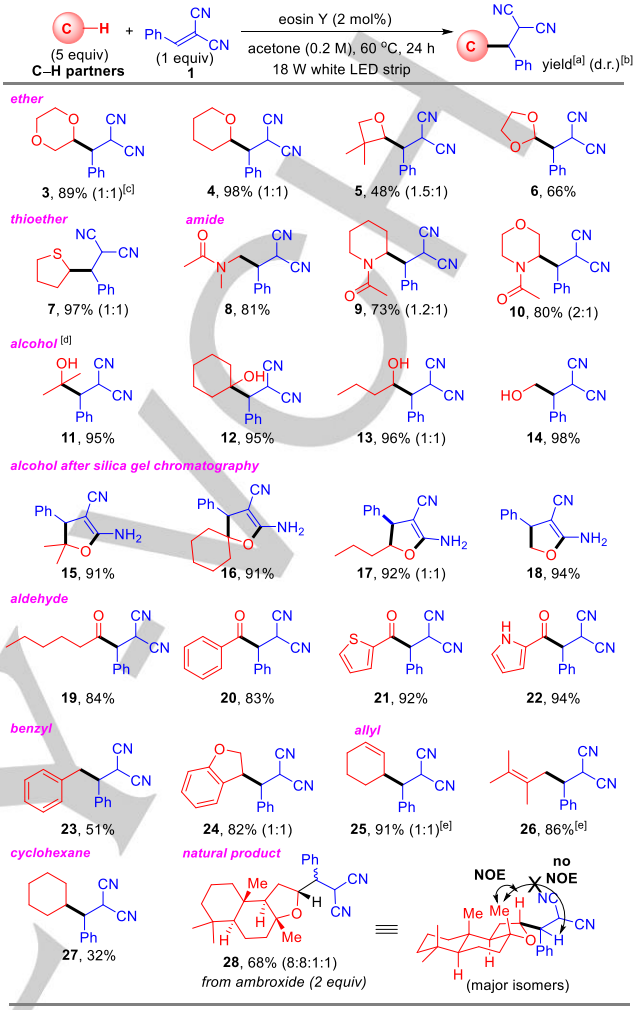
have long been known,[1a] xanthene dyes, possessing structural similarity with quinones, have never been utilized as direct HAT photocatalysts. We speculate that after absorbing a photon, the excited xanthene molecule may undergo HAT with a C–H bond to form a relatively stable radical intermediate due to both captodative[8] and steric effects, which is unlikely to participate in a side coupling reaction, thus enabling a more effective RHAT process (Scheme 1c).

To explore the possibility of using xanthene dyes as direct HAT catalysts, we selected the alkylation of C–H bonds via radical addition to electrophilic alkenes as a model reaction. This conceptually simplest transformation represents the most economically appealing process for C–C bond formation. However, current reported examples suffer from at least one drawback such as limited scope, requiring UV light, high catalyst loading, or poor reactivity/selectivity.[2]

We initiated the evaluation of various xanthene dyes by using tetrahydrofuran (THF) as the C–H partner and solvent in the presence of a dicyanide electron-deficient alkene **1** under white LED light (Table S1). A 50 °C water bath was applied to increase the reaction efficiency. To our delight, 2 mol% eosin Y could efficiently catalyze this transformation to deliver quantitative yield of alkylation product **2** in a three-hour reaction period. The heavy-atom effect contributing to effective intersystem crossing for a long-lived triplet excited state was essential, as fluorescein and rhodamine B gave very low product yields. Notably, employment of the dianionic form of eosin Y as the catalyst resulted in a significantly reduced reactivity. Moreover, the reaction using eosin Y was also effective in acetone or *t*BuOH as the solvent with 10 equiv of THF. Finally, no product formation was detected in the absence of either photocatalyst or light, demonstrating the need for these components.

We next investigated the scope of C–H bonds that can be activated by catalytic eosin Y under visible-light. The alkylation reactions were conducted with 5 equiv of C–H partners and electron-deficient olefin **1** (1 equiv) in the presence of 2 mol% eosin Y in acetone (0.2 M) under white LED irradiation in a 60 °C water bath. As shown in Scheme 2, ethers including 1,4-dioxane, tetrahydropyran, and 3,3-dimethyloxetane afforded the Giese adducts (**3** to **5**) in good yields. Only the 2-alkylation product **6**, which can be applied as an inexpensive formyl equivalent, was detected upon switching to 1,3-dioxolane as the C–H partner.[9] The reactions of thioethers or aliphatic amides proceeded smoothly to afford products **7**-**10** in very good yields, with alkylation exclusively at the carbon adjacent to the heteroatom. Alcohol substrates successfully produced the coupling products (**11** to **14**) in excellent yields. These products would undergo cyclization when treated with silica gel to give enamino-ketonitriles **15** to **18**, which are important synthons for constructing complex bioactive heterocycles.[10] Aldehydes can be applied as latent nucleophilic handles to achieve umpolung reactivity, accessing hydroacylation-type products (**19** to **22**) that can be further derivatized to 1,3-dicarbonyl compounds.[11] The direct alkylation of allylic or benzylic substrates proceeded smoothly (**23** to **26**). Notably, a simple unfunctionalized alkane, cyclohexane, could be direct alkylated using this method, although with a lower efficiency (**27**, 32%). Importantly, our method has shown the potential for site-selective C–H activation, as compounds **6**, **10**, and **24** were exclusively generated in the presence of at least one additional hydridic proton in the substrates. Furthermore, the value of this protocol is demonstrated by its applicability to the late-stage functionalization of natural products. The HAT acted regioselectively on the *α*-oxy carbon of ambroxide, delivering product **28** in good yield with the alkyl substituent installed at equatorial position in the major isomers.



Scheme 2. Scope of C–H partners. [a] Isolated yields. [b] D.r. based on the analysis of the ^{1}H NMR spectra of crude reaction mixtures. [c] C–H partners as the solvent. [d] Yields were determined from the crude ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard. [e] *t*BuOH as the solvent.

Experiments probing the scope of methylene-malononitriles revealed that sterically demanding tetra-substituted olefins smoothly delivered the desired products **29** and **30** in good yields. Further evaluation of the generality of the alkylation protocol with regard to the electron-deficient alkenes demonstrated an extremely broad substrate scope (Scheme 3a). Substrates including unsaturated aldehydes, ketones, esters, lactones, amides, imides, sulfones, and nitro compounds were all good candidates, delivering good yields of alkylation products (**31** to **39**). Vinylpyridines can also be utilized as building blocks for alkylation to introduce the biologically important pyridine moiety (**40**).[12] Substituents including electron-rich or electron-deficient aryl rings (**41**-**43**), heterocycles (**44**, **45**), and alkyl chains (**46**) were all tolerated. Diene Michael acceptors could be successfully applied to give 1,4-addition type products (**47**). Both the wide scopes of C–H partners and the electron-deficient alkenes were attributed to the HAT process which overcomes the redox limitation associated with the SET process.[11]

To demonstrate the synthetic applicability of this methodology, the alkylations were amenable to scale-up to gram quantities

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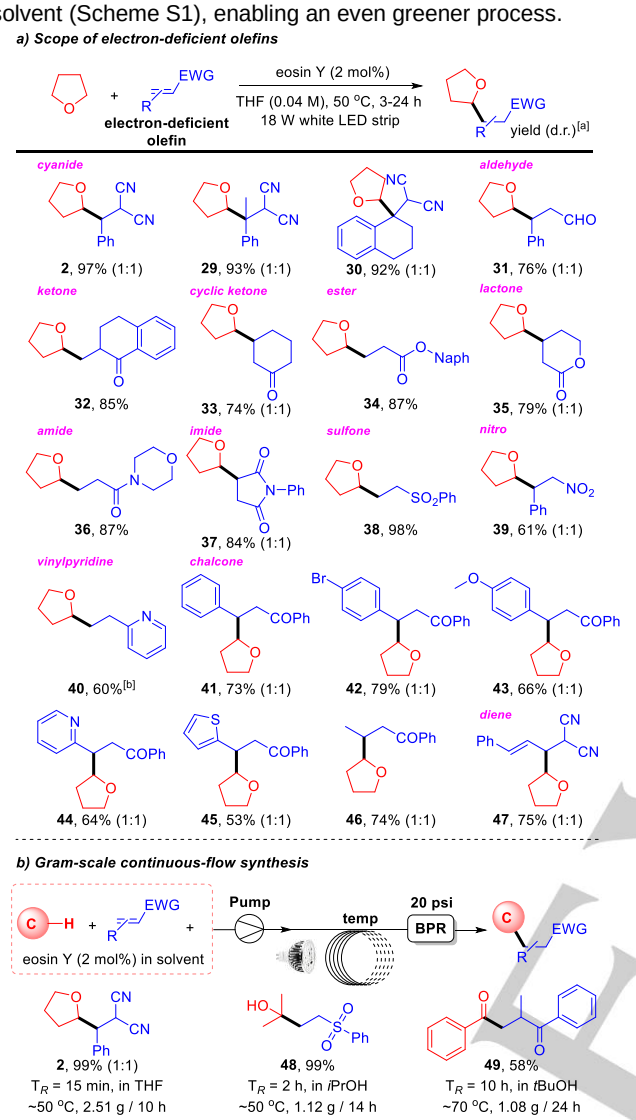
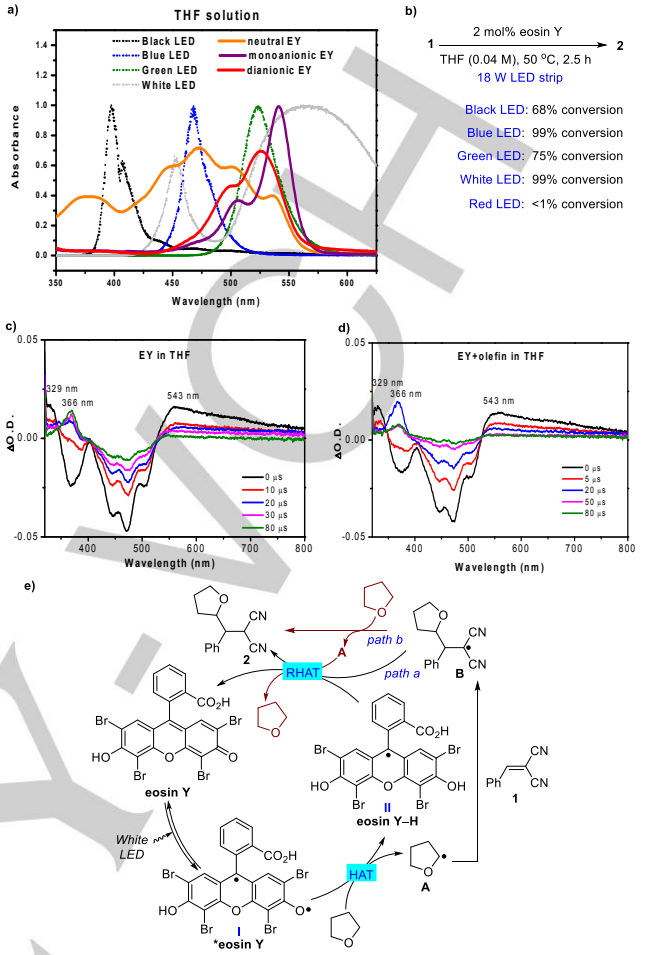
using continuous-flow reactors (Scheme 3b). Furthermore, the C–H alkylation could be effectively performed using water as solvent (Scheme S1), enabling an even greener process.



Scheme 3. Scope of electron-deficient olefins and continuous-flow synthesis. [a] Isolated yields. D.r. based on the analysis of ^{1}H NMR spectra of the reaction crude mixture. [b] *t*BuOH as the solvent with 10 equiv of THF.

Eosin Y can exist in four different structures in solution by acid-base equilibration: the spirocyclic form, the neutral form, the monoanionic form, and the dianionic form, exhibiting different absorption properties with visible-light (Scheme 4a, Figures S3, S4). It has been illustrated that the anionic forms of eosin Y were the active catalysts that promote SET-based redox catalytic cycles in majority of previous studies, where neutral eosin Y was considered inactive.[13] In order to elucidate the actual species of eosin Y in the HAT-based catalytic cycle, various control experiments were performed. C–H alkylation in THF was conducted under various light sources, and blue LED afforded the highest conversion (Scheme 4b), which coincided with the maximum absorption of neutral eosin Y (Scheme 4a). The same reaction in acetone under different light wavelengths (Table S3), catalyst-free reactions (Table S5), reaction monitoring by UV-Vis (Figure S5), and acid/base additive studies (Tables S7-S8, Figures S6-S7), indicated that the neutral eosin Y species was the active catalyst, which fundamentally differed from the SET process induced by anionic eosin Y.[14]

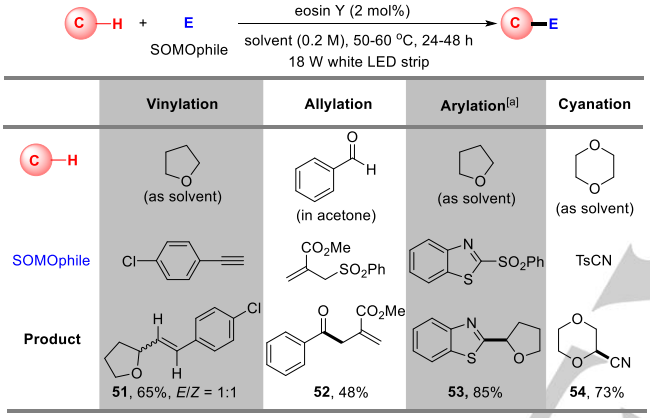


Scheme 4. Plausible mechanism with supporting evidence. a) Emission of light sources and UV-Vis of different forms of eosin Y in THF. b) C–H alkylation in THF under different light sources. c) Transient absorption spectra of eosin Y in THF and d) eosin Y + phenyl vinyl sulfone **50** in THF (degassed, excitation at 470 nm). e) Plausible mechanism.

Both the redox potential analysis and fluorescence quenching studies (Figure S11) indicated that the C–H activation was not induced by electron- or energy-transfer processes. Laser flash-photolysis was further employed to elucidate the transient intermediates during the reaction process. As shown in Scheme 4c, upon laser excitation at 470 nm, the THF solution of neutral eosin Y alone immediately exhibited a strong bleaching of the ground state from 350 nm to 520 nm, and two new absorption peaks at 329 nm and 543 nm decayed with very similar lifetimes (20.6 and 21.3 μs, Figures S9). We assigned them to the triplet state *eosin Y. Importantly, a new absorption peak emerged after 20 μs at 366 nm with an exceptional long lifetime (>4 ms), which we proposed to be the stable radical intermediate of eosin Y–H generated from HAT between *eosin Y and THF. The lifetime of 366 nm absorption decreased to 1.0 ms after adding alkene **50** into the mixture, which further supported our hypothesis that eosin Y–H would be consumed after adding the olefin substrate (Scheme 4d and Figure S9). Both light on/off experiments (Figure S13) and the calculated quantum yield (Φ = 0.40) suggested a nonchain pathway.[15] To gain further insight into the reaction mechanism, deuterium labeling study was

conducted by treating THF and d8-THF with alkene **50** in two different vessels or in one vessel under the optimized conditions, resulting in k_H/k_D 1.6 and 2.4 respectively. The KIE data indicated that the C–H cleavage was reversible and might occur before the rate-determining step.[16]

A plausible mechanistic pathway was proposed in light of all the experimental data (Scheme 4e). The formation of a carbon-centered radical was promoted by visible-light-activated *eosin Y through a HAT process. The derived carbon radical was subsequently trapped by an electron-deficient alkene to selectively form radical adduct **B**. The RHAT process between eosin Y-H **II** to radical **B** exhibited a high free energy barrier (32.3 kcal/mol) based on DFT calculation (path a).[17] Instead, another THF molecule and radical **B** might undergo a reversible HAT process (19.2 kcal/mol) to deliver the desired alkylation product, followed by RHAT between THF radical **A** and eosin Y-H **II** (19.9 kcal/mol) to regenerate ground state eosin Y catalyst (path b). However, we were unable to exclude the possibility of path a at current stage based on the deuterium labeling study (Scheme S2).[17]



Scheme 5. Eosin Y-based HAT for C–H functionalizations. [a] With 2.5 equiv of NaOAc as an additive.

The eosin Y-based direct HAT process provides an extremely convenient and green pathway for C–H activation, who's synthetic utility can be extended far beyond alkylation. Our very preliminary results illustrated that this visible-light-mediated C–H activation protocol can be extended to vinylation, allylation, arylation, and cyanation (Scheme 5).

In summary, we have developed a visible-light-mediated alkylation of C–H bonds with eosin Y as the catalyst. This transformation accommodates an extremely broad substrate scope, and is distinguished by its operational simplicity, green protocol, and amenability to large-scale synthesis via continuous-flow technology. A variety of synthons can be easily achieved by this method, which will likely find wide industrial application. Moreover, to the best of our knowledge, this study represents the first example of using xanthene dyes as direct HAT photocatalysts. Its metal-free, readily available, and low-costing nature, in addition to light absorption in the visible region and unlikely side reactions, makes eosin Y an ideal direct HAT photocatalyst, with great promise for C–H activation with a diverse range of functionalities. Unlike the well-established anionic eosin Y-based photoredox process, neutral eosin Y is the active catalyst to promote the photo-HAT transformation. Moreover, the easy structural modification of xanthenes provides a promising platform to tune the strength of HAT ability for site-selective and stereoselective C–H activation.

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Keywords: eosin Y • photocatalysis • organocatalysis • C–H functionalization • hydrogen atom transfer

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[14] Even though good conversions have been achieved with most substrates tested within 24 h using white LED, we expected that blue LED would afford more efficient transformations. See Table S4 for comparison studies.

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[17] See Supporting Information for detailed control experiment study, DFT calculation, and mechanistic analysis.

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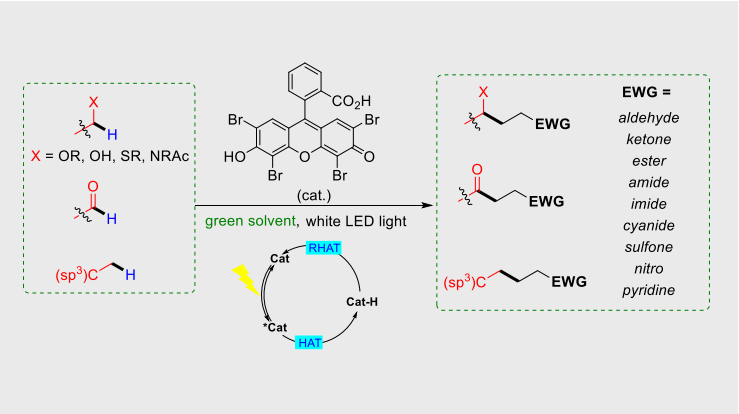

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Page No. – Page No.

Eosin Y as a Direct Hydrogen Atom Transfer Photocatalyst for the Functionalization of C–H Bonds

We discovered that neutral eosin Y could be employed as an effective direct hydrogen atom transfer photocatalyst to activate a wide range of native C–H bonds in a green and sustainable fashion.