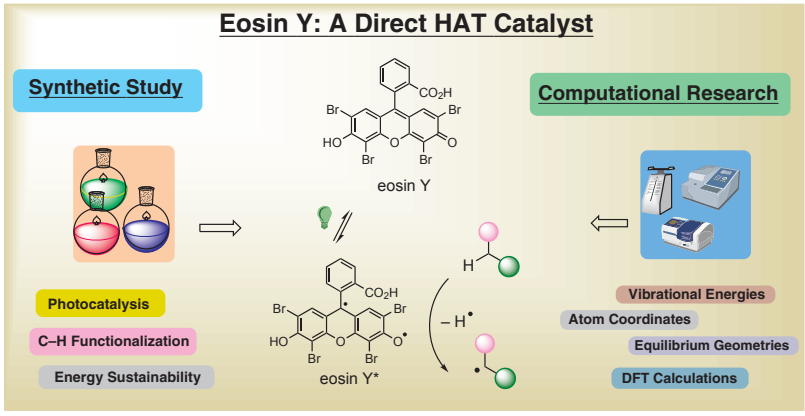
Synthesis J. Inoa et al. Short Review

Synthetic Applications and Computational Perspectives on Eosin Y Induced Direct HAT Process

Joan Inoa
Grecia Dominici
Reem Eldabagh
Jonathan J. Foley IV*
Yalan Xing*

Department of Chemistry, William Paterson University, Wayne, NJ, 07470, USA
xingy@wpunj.edu
foleyj10@wpunj.edu



Received: 01.12.2020
Accepted after revision: 08.02.2021
Published online: 08.02.2021
DOI: 10.1055/a-1385-9398; Art ID: ss-2020-m0616-sr

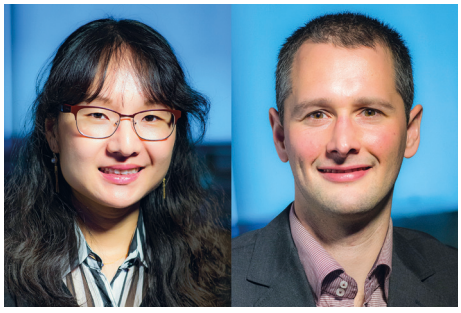
Abstract In recent years, advancements in photocatalysis have allowed for a plethora of chemical transformations under milder conditions. Many of these photochemical reactions utilize hydrogen atom transfer processes to obtain desired products. Hydrogen atom transfer processes can follow one of two unique pathways: the first, a direct path and the second, an indirect path. In this paper, we highlight the ability of eosin Y to act as a direct hydrogen atom transfer catalyst from both synthetic and computational chemistry perspectives.

Key words hydrogen atom transfer, Eosin Y, photocatalysis, visible light, computational study

Introduction

In recent years, visible-light photocatalysis has seen much advancement.[1] It offers a promising synthetic organic methodology that enables previously inaccessible transformations.[2] Compared to high-energy UV light, visible light is more sustainable, as it is cheaper to produce and easy to handle.[3] Since most organic compounds are not able to absorb visible light, photoredox catalysts (PC) such as polypyridyl metallic complexes of ruthenium or iridium[4] and metal-free catalysts[5] such as organic dyes like eosin Y,[6] are usually required to sensitize organic molecules.

Upon light irradiation, a photocatalyst (PC) can promote both direct and indirect hydrogen atom transfer (HAT) processes.[7] For a direct HAT pathway, the excited photocatalyst (PC*) abstracts a hydrogen atom from a substrate to generate the active radical species.[8] In indirect HAT processes, the excited photocatalyst is able to activate another additive or co-catalyst by a single electron transfer (SET) or energy transfer (ET) process, after which the additive/co-catalyst will promote the HAT process, which abstracts the hydrogen atom from the substrate.[9] Among these pathways, the direct HAT is the most attractive approach as it is the



Yalan Xing obtained her Ph.D. from West Virginia University in organic chemistry in 2011 and completed her postdoctoral training at Harvard University in 2014. Her graduate and postdoctoral research focused on synthetic studies on complex bioactive natural products. She became an Assistant Professor (2014) and Associate Professor (2020) at the Chemistry Department, William Paterson University. In 2018, Professor Xing received an ACS Petroleum Research Fund Undergraduate New Investigator Award. At William Paterson University, her research focuses on the development of green and sustainable novel organic synthetic methodologies for the synthesis of bio-active molecules.

Jonathan J. Foley IV is an Assistant Professor of Chemistry at William Paterson University. He received his PhD in physical chemistry in 2012 from the University of Chicago working on reduced density matrix mechanics. He was a postdoctoral fellow from 2012 to 2015 at the Center for Nanoscale Materials, Argonne National Laboratory, where he worked on theory and modeling of nanophotonics and plasmonics. He received the ACS Petroleum Research Fund Undergraduate New Investigator Award in 2018 and the Cottrell Scholar Award in 2019. Prof. Foley's research group develops and deploys multi-scale theoretical methods to study light–matter interactions.

most reagent- and redox-economical method, while other pathways require additional additives/co-catalysts.[10] However, the applications of direct HAT are limited by the fact that the number of available direct HAT photocatalysts is low.[11] Photocatalysts that are able to perform direct HAT processes under visible-light induced conditions are restricted to the families of benzophenones, quinones, and polyoxometalates.[11] Recently, evidence has been found that one of the most widely used organic dyes, eosin Y (Figure 1), can serve as a direct HAT photocatalyst for the functionalization of C–H bonds.[12]

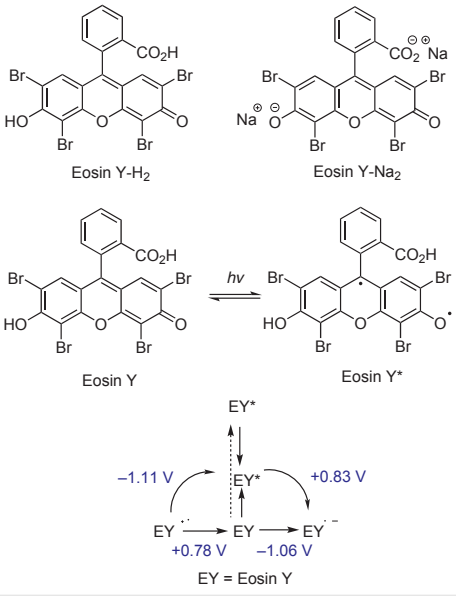
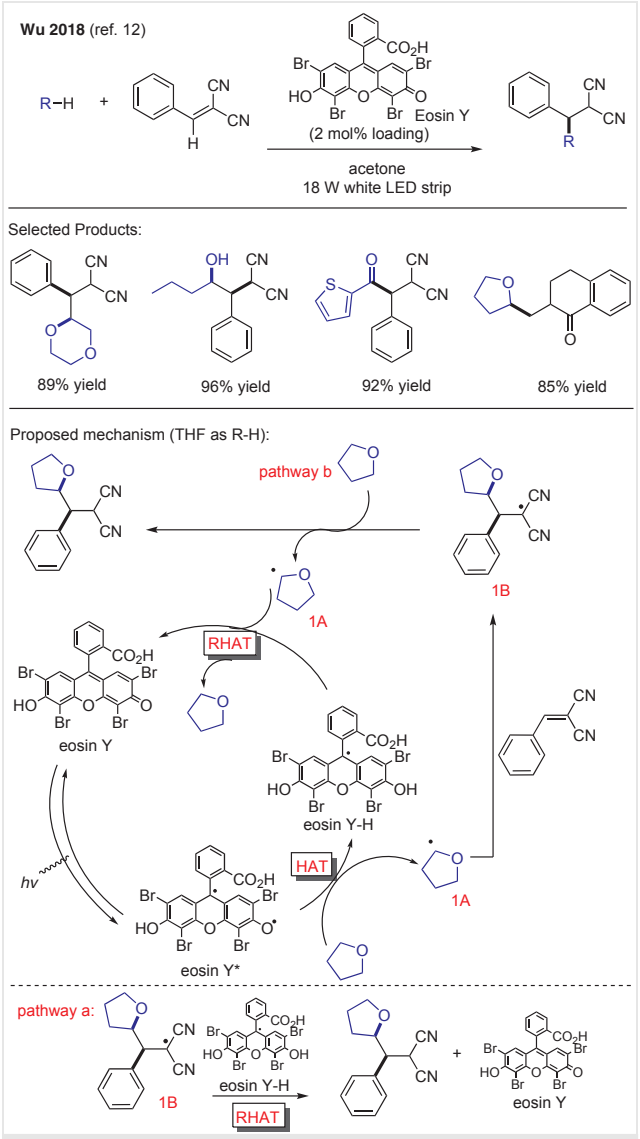


Figure 1 Eosin Y and its photoredox potentials

Eosin Y, a xanthene dye, is inexpensive and easy to handle, absorbs strongly in the visible spectrum, and exhibits excellent photocatalytic performance.[13] Eosin Y can exist in eosin Y-H_2 and eosin Y-Na_2 (disodium salt) forms (Figure 1). Estimated redox potentials of eosin Y in the excited state are shown in Figure 1.[14] Since Wu's first report of eosin Y as a direct HAT catalyst,[12,15] many studies have been published following this new mechanism. To illustrate the potential of eosin Y as a direct HAT agent, we have summarized various works that highlight the synthetic applications and mechanistic studies of eosin Y as a HAT catalyst.

Synthetic Applications of Eosin Y as Direct HAT Catalyst

In 2018, Wu and co-workers reported the alkylation of C–H bonds by use of eosin Y as a direct HAT catalyst (Scheme 1).[12] A variety of important synthons were successfully synthesized using this alkylation of C–H bonds with electron-deficient alkenes. In this study, tetrahydrofuran (THF) was used as both the C–H partner and solvent, along with electron-deficient alkenes which are irradiated with white LED light. Under these conditions, 2 mol% eosin Y was found to catalyze the transformation efficiently to give the products in quantitative yield. Fluorescein, rhodamine B, and the dianionic form of eosin Y as catalysts resulted in low product yield. The scope of C–H and olefin partners was expanded, demonstrating the broad substrate scope and excellent functional group compatibility of this transformation. To demonstrate the synthetic applicability of the method, Wu and co-workers carried out a scale-up reaction to gram quantities using flow chemistry; these reactions were further improved in this process with water being used as a viable solvent.



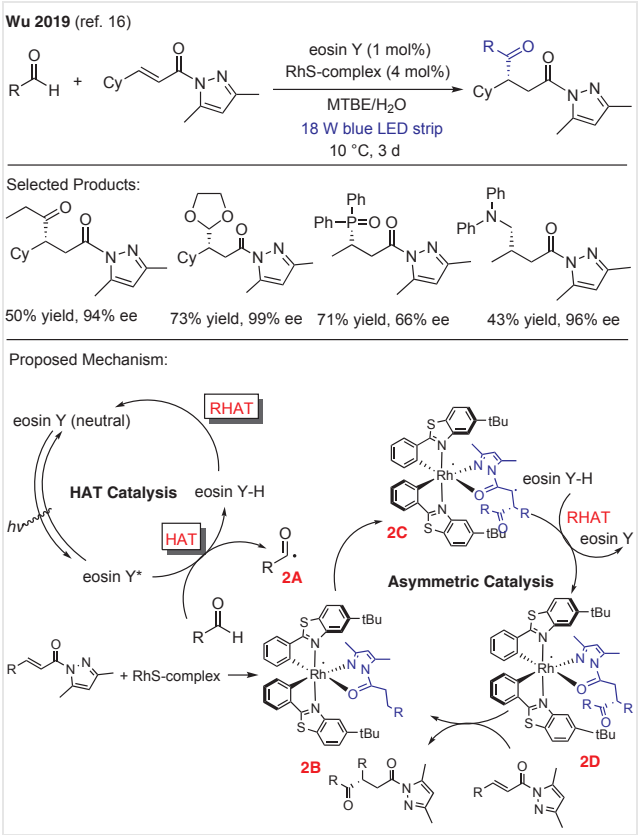
Scheme 1 Functionalization of C–H bonds catalyzed by eosin Y

A plausible mechanism was proposed based on a variety of mechanistic studies to elucidate the HAT mechanism (Scheme 1). The carbon-centered radical **1A** was generated by a HAT process with visible-light-activated eosin Y*. The resulting carbon radical **1A** was trapped by an electro-deficient alkene to form radical **1B**. The authors suggested two competing pathways (A and B) for the reverse hydrogen atom transfer (RHAT) process, which regenerates the photocatalyst eosin Y-H•. In the first mechanism (pathway a) the carbon radical eosin Y-H• reacts with **1B** to form the addition product plus the photocatalyst eosin Y. In the second mechanism (pathway b), **1B** abstracts a hydrogen from THF as part of a radical chain process to form the addition product and the radical **1A**. The radical chain process is then terminated and the photocatalyst is regenerated by the RHAT reaction between **1A** and eosin Y-H•. Wu's computational studies to elucidate this mechanism are discussed in a subsequent section. Wu's study represents the first suggestion of xanthene dyes acting as direct HAT photocatalysts.

In 2019, Wu and co-workers reported the asymmetric synthesis of 1,4-dicarbonyl compounds from aldehydes through HAT photocatalysis, using eosin Y and chiral Lewis acid (Scheme 2).[16] Enantioenriched 1,4-dicarbonyl compounds are highly versatile structural motifs in drug scaffolds and natural products.[17] Wu and co-workers discovered that acyl radicals can be generated from aldehydes catalyzed by eosin Y-induced HAT photocatalysis, which can be merged with chiral rhodium-based Lewis acid catalysis to deliver 1,4-dicarbonyl compounds in good yields and with high enantioselectivity. Additionally, the substrate scope of the reaction was extended to other types of C–H bonds such as THF, 1,3-dioxolane, acyclic and cyclic tertiary amines, sulfonic acid, and hydrophosphine oxide. A few of these substrates are shown in Scheme 2. Moreover, this method can be easily scaled up to gram-scale reactions and the product can be converted into a 2,3-disubstituted 1,4-dicarbonyl compound as a single isomer.

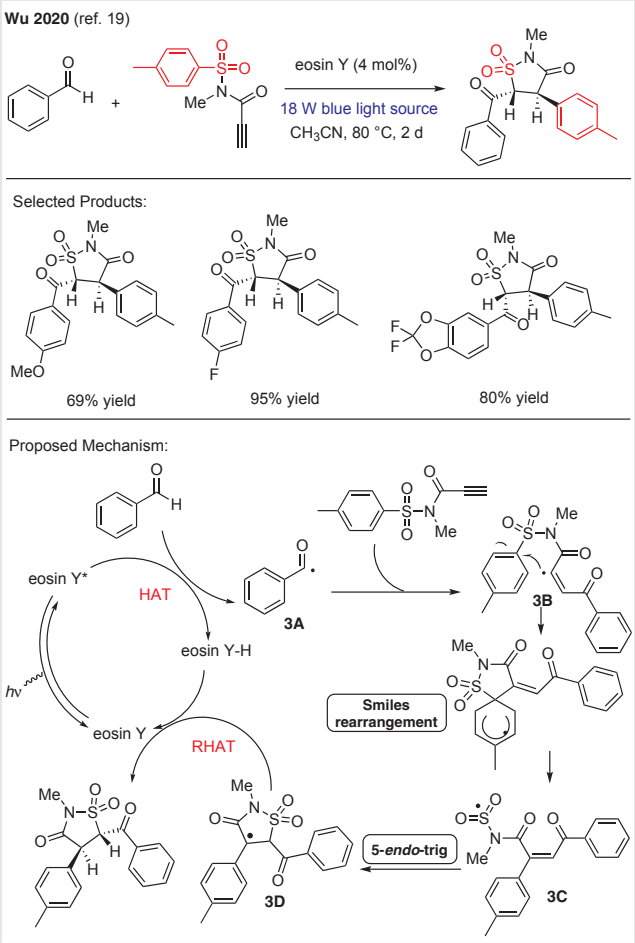
Wu and co-authors proposed a dual catalytic mechanism for this transformation (Scheme 2). Acyl radical **2A** is thought to be generated by a polarity-matched HAT[18] between photoactivated eosin Y and an aldehyde. Radical **2A** then adds to N,O-rhodium-coordinated *N*-acyl pyrazole substrate **2B** to generate the secondary radical intermediate **2C**. Reverse HAT of intermediate **2C** with eosin Y-H turns over the HAT catalytic cycle. In addition, ligand exchange between intermediate **2D** and the starting unsaturated amide delivers the chiral product and regenerates the active complex **2B**. This method is operationally simple, atom economic, and generates products in high yields (up to 99%) and with high enantioselectivity (up to 99% ee).

In 2020, Wu and co-workers expanded their C–H functionalization protocol using neutral eosin Y as a direct HAT photocatalyst on a cascade radical process for the preparation of functionalized isothiazolidin-3-one 1,1-dioxides with excellent diastereoselectivity (Scheme 3).[19] In fact, the



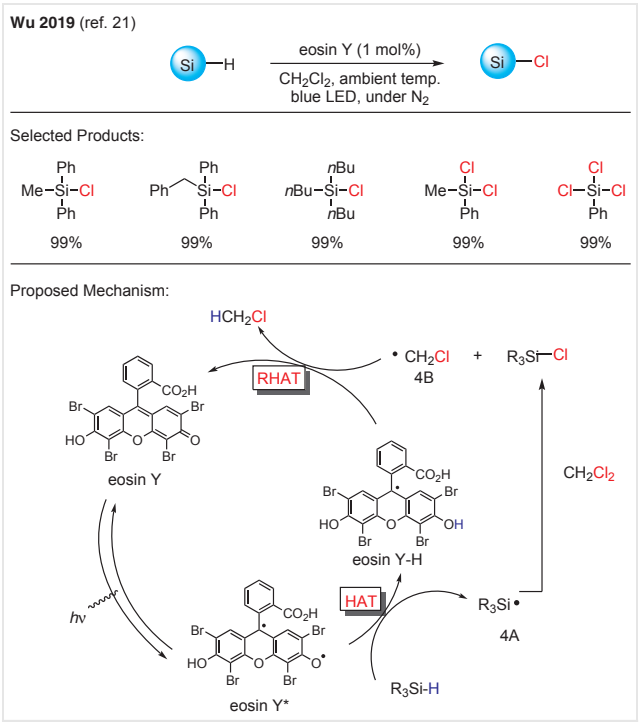
Scheme 2 Asymmetric synthesis of 1,4-dicarbonyl compounds catalyzed by eosin Y

cascade reaction involves various processes, which include: a visible-light-induced HAT, 1,4-addition, Smiles rearrangement, 5-*endo-trig* cyclization, and reverse HAT process to afford the final product. Furthermore, the isothiazolidin-3-one 1,1-dioxide moiety has been shown to exhibit potential anti-cancer activity.[20] As such, discovery of a facile method to synthesize these compounds would be highly beneficial. By subjecting aldehydes or phosphine oxides along with *N*-arylsulfonyl propiolamides to neutral eosin Y-based direct HAT photocatalytic conditions, a variety of unique functionalized isothiazolidin-3-one 1,1-dioxides were successfully synthesized with good yield, excellent functional group compatibility and diastereoselectivity. In addition, gram-scale cascade reactions were conducted to demonstrate the synthetic utility of the established protocol. A plausible mechanism was proposed based on the experimental results and on literature reports (Scheme 3). The excited eosin Y* undergoes a HAT with aldehyde to deliver an acyl radical **3A**, which participates in a 1,4-addition to *N*-arylsulfonyl propiolamides, Smiles rearrangement, and 5-*endo-trig* cyclization to form a benzylic radical **3D**. The benzylic radical **3D** regenerates eosin Y via a reverse HAT and forms the desired product.



Scheme 3 A radical Smiles rearrangement promoted by neutral eosin Y

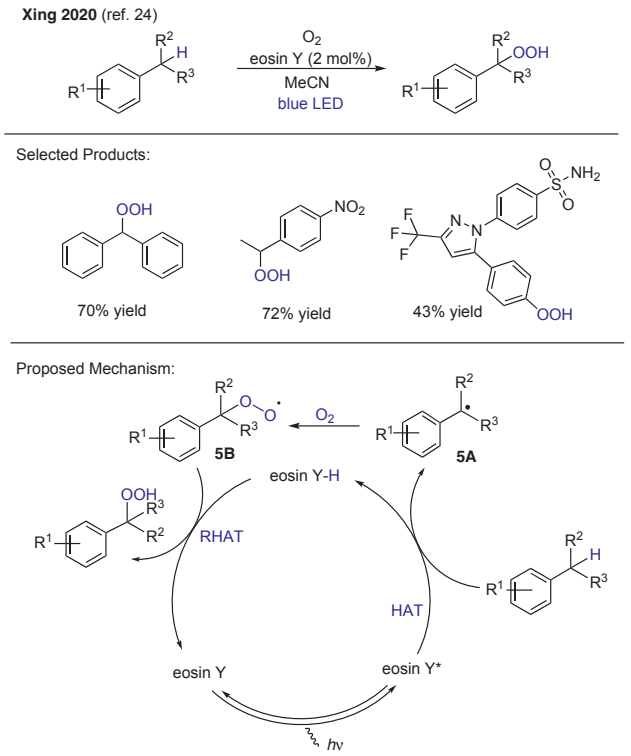
Wu and co-workers also developed a new approach to access silyl radials using photocatalytic Si–H activation promoted by eosin Y for the synthesis of valuable chlorosilanes in 2019 (Scheme 4).[21] Chlorosilanes are widely used reagents in organic chemistry and materials science.[22] However, Si–H activation as a method of synthesizing value-added silicon compounds by modern photocatalysis has not been extensively explored.[23] Wu's research group successfully applied their direct HAT photocatalysis strategies on Si–H bonds and accessed reactive silyl radicals for the synthesis of chlorosilanes. Their study showed that silane chlorination can be achieved by the use of blue LED light, 1 mol% of neutral eosin Y, and DCM as both a chlorinating agent and solvent under ambient temperature. This method also exhibits broad substrate scope with exclusive Si–H activation in the presence of activated C–H bonds such as benzylic C–H bonds. Moreover, selective di- and trihydrosilane chlorination were achieved by using continuous-flow micro-tubing reactors. Based on all the experimental data and on computational studies, a plausible mechanism was proposed (Scheme 4). The silyl radical **4A** was generated by the HAT from excited eosin Y* and hydrosilane. The resulting silyl radical **4A** then abstracted the chloride from DCM to produce the silyl chloride product and the chloromethyl radical **4B**. RHAT between **4B** and eosin Y-H regenerated ground-state eosin Y and chloromethane.



Scheme 4 Silane chlorination catalyzed by neutral eosin Y

In 2020, Xing and co-workers discovered a mild and efficient method of obtaining a wide array of benzylic hydroperoxides with the use of neutral eosin Y as a direct HAT photocatalyst in the presence of blue LED light and molecular oxygen (Scheme 5).[24] Peroxides, including hydro- and *endo*-peroxides, are present in many naturally occurring compounds and are known to possess antimalarial, antibacterial, cytotoxic, as well as other biological activities.[25] Primary, secondary, and tertiary hydroperoxides as well as silyl, benzyl, and acyl peroxides were successfully prepared with good yields and excellent functional group compatibility in this study. Compounds that contain more than one benzylic position were also investigated, with both mono- and di-hydroperoxides being formed. Furthermore, the reaction is thought to proceed through a direct HAT pathway in which neutral eosin Y serves as HAT photocatalyst. Initially, eosin Y enters the excited state upon light irradiation to form eosin Y*. Then, eosin Y* abstracts a hydrogen atom from a benzylic C–H bond to generate a benzylic radical **5A** and eosin Y-H. Molecular oxygen traps benzylic radical to produce a peroxy radical **5B**. A retro-HAT from eosin Y-H to the peroxy radical finally gives hydroperoxide product and regenerates eosin Y back into the catalytic cycle. Of course,

there is likely a completing radical chain mechanism in which the peroxy radical abstracts a benzylic hydrogen from the starting material to generate **5A**. This method provides a mild, sustainable, and metal-free approach for the synthesis of benzylic hydroperoxides and several *endo*-peroxides.

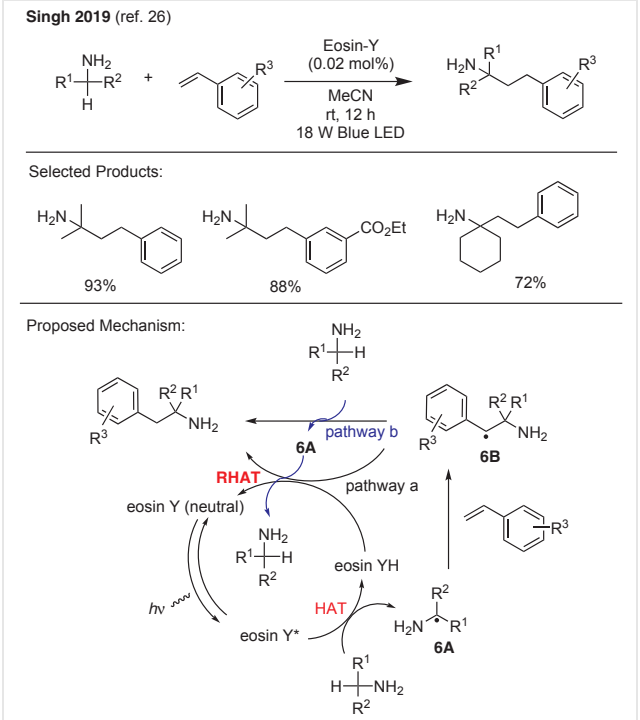


Scheme 5 Benzylic hydroperoxidation catalyzed by eosin Y

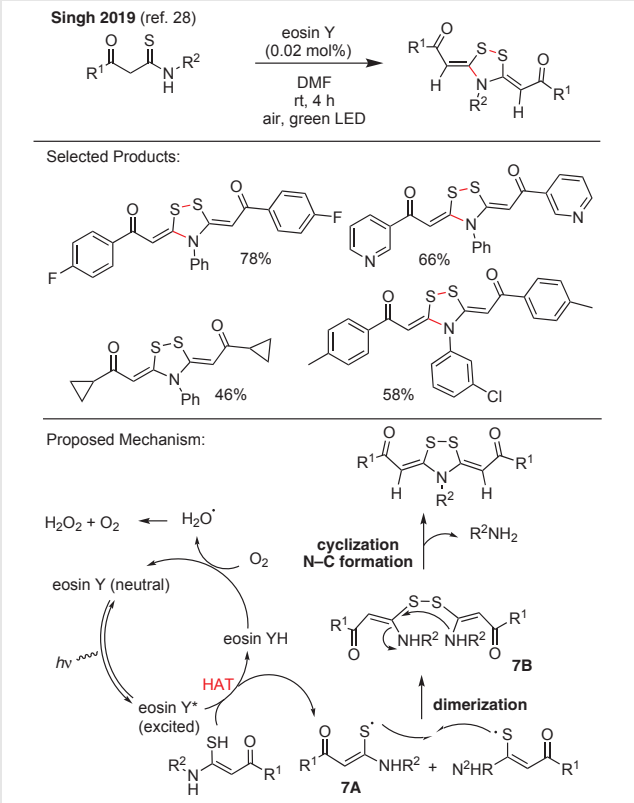
In 2019, Singh and co-workers reported a one-pot photocatalyzed eosin Y mediated C(sp^3)–H alkylation of amine substrates utilizing eosin Y as the catalyst through direct HAT (Scheme 6).[26] Amines are valuable substituents in various active biological compounds with a wide range of biological activities.[27] In fact, it was discovered that carbon-centered radicals, which are adjacent to nitrogen atoms of amines, can be generated via neutral eosin Y induced HAT photocatalysis. Sequential addition of the carbon-centered radical to functionalized styrene afforded the desired alkylation products in good yields and functional group compatibility. A plausible mechanism was proposed as follows: eosin Y is converted into its excited state eosin Y* via a visible-light-induced HAT process, forming the carbon-centered radical **6A**. An electron-deficient styrene trapped the carbon radical previously formed to create adduct **6B**. A RHAT process between eosin Y-H and radical **6B** produced the desired product and regenerated eosin Y (pathway a). A second pathway (b) involves another possible RHAT process between an amine molecule and radical **6B** to deliver the desired product, which is followed by a RHAT process between the amine radical **6A** and eosin Y-H to regenerate the ground-state eosin Y catalyst.

In 2019, Singh and co-workers reported a visible-light-mediated synthesis of 1,2,4-dithiazolidines from β-ketothioamides via a HAT photocatalytic approach of the catalyst, eosin Y (Scheme 7).[28] Derivatives of 1,2,4-dithizoles are important scaffolds that can be utilized in numerous ways in pharmaceutical sciences.[29] Thiyl radicals were generated in situ from β-ketothioamides via an eosin Y catalyzed HAT photocatalytic pathway under irradiation with green LED light. Dimerization/deaminative cyclization cascade of thiyl radicals enabled the reaction of dithiazolidine ring through successive formation of S–S and N–C bonds. Moreover, this method provides an efficient protocol to access highly functionalized 1,2,4-dithiazolidines exhibiting excellent functional group compatibility with electron-rich/electron-deficient arenes and heteroarenes. Three representative substrates are shown in Scheme 7.

A plausible mechanism was proposed as follows (Scheme 7): Eosin Y is converted into its excited state eosin Y* via visible-light irradiation, which extracts a hydrogen atom from β-ketothioamides, generating the thiyl radical **7A** and eosin Y-H. Radical **A** undergoes dimerization to produce disulfide-tethered enamine intermediate **7B**, which then proceeds through deaminative cyclization to produce the desired product 1,2,4-dithiazolidine. Eosin Y-H then goes through aerial oxidation to regenerate the ground-state eosin Y for the next catalytic cycle. Given the low concentration of the radical **7A**, we thought radical dimeriza-



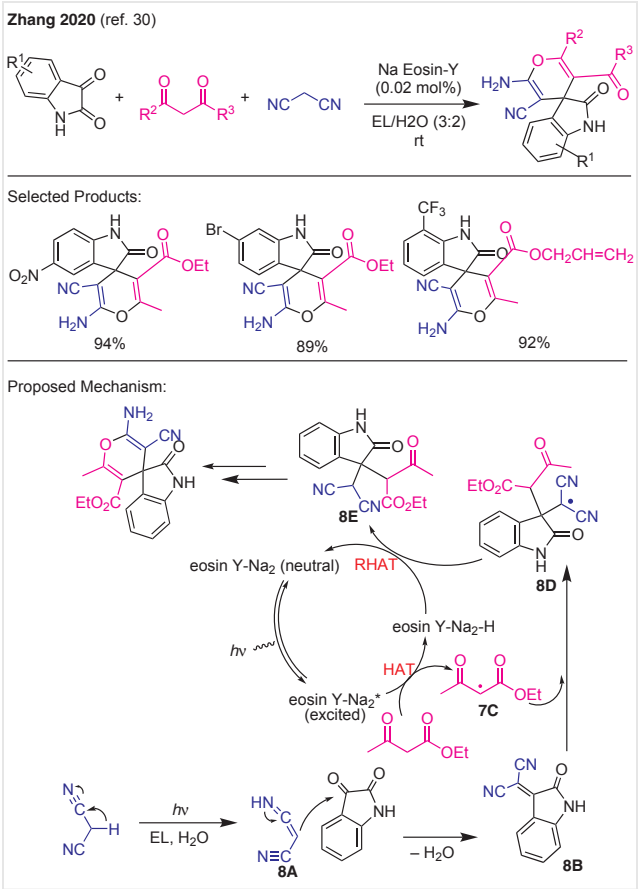
Scheme 6 C(sp^3)-H alkylation of amine substrates via direct HAT



Scheme 7 Synthesis of 1,2,4-dithiazolidines from β-ketothioamides

tion may not give sufficient yields of the reaction. Also, the sulfur-centered radical may easily be trapped by molecular oxygen.

In 2020, Zhang and co-workers published a one-pot synthesis of spiro[4*H*-pyran-oxindole] using eosin Y-Na_2 as a HAT photocatalyst (Scheme 8).[30] Spiro[4*H*-pyran-oxindole] derivatives present an assortment of biological activities which include anticancer, antifungal, antibacterial, antioxidant, spasmolytic, diuretic, and antianaphylactic properties.[31] Additionally, this three-component reaction of isatins, linear 1,3-dicarbonyl compounds and malononitriles generates a variety of spiro[4*H*-pyran-oxindole] derivatives in good yield and with excellent functional group compatibility. Zhang's report also included a proposed mechanism for the reaction (Scheme 8). First, malononitrile goes through a tautomerization in the presence of aqueous ethyl lactate (EL) producing **8A**, which undergoes a Knoevenagel condensation with isatin to produce intermediate **8B**. Following this, the α-carbonyl carbon-centered radical **8C** is generated by visible-light-activated eosin Y-Na_2* via a HAT process. Radical **8C** is then added onto electron-deficient 2-(2-oxoindolin-3-ylidene) **8B** to form radical **8D**. A RHAT process between eosin Y-Na_2-H and radical adduct **8D** regenerates the ground-state eosin Y-Na_2 and intermediate **8E**. Finally, intermediate **8E** undergoes an intramolecular cyclization to create the desired product. Alternatively, it is possible that these products are formed by an acid/base process that is initiated by a photochemically induced proton transfer. Ionic eosin Y could serve as a photoacid[15] and react with 1,3-dicarbonyl compound to generate a nucleophilic anion, which would then add to **8B**.



Scheme 8 Eosin Y catalyzed one-pot synthesis of spiro[4*H*-pyran-oxindole]

Advances in theoretical and computational methods have enabled the simulation of photochemical reactions with ever increasing levels of realism.[32] In the following section, we review computational elucidation of the light-induced HAT activity of eosin Y, and also describe state-of-the-art ab initio molecular dynamics methods that allow elucidation of the detailed dynamics of photochemical transformations that we believe may be brought to bear on light-induced HAT catalysis in the future.

Computational Elucidation of the HAT Activity of Eosin Y

Light-induced atom transfer is one of multiple mechanisms through which photocatalysts convert light into chemical energy for selective molecule activation. Eosin Y

has been found to facilitate a light-induced HAT mechanism in several C–H functionalization reactions. The HAT activity of eosin Y was first reported by Wu and co-workers in 2018.[15] In their report, eosin Y was found to be effective at C–H bond functionalization through direct HAT catalysis.

Wu and co-workers utilized electronic structure theory to investigate two possible light-induced HAT mechanisms in conjunction with their experimental work. In particular, they used density functional theory at the M06/cc-pVTZ level to identify critical structures associated with both reaction pathways and to compute Gibbs free energies for these critical structures, including reactant structures, product structures, and transition states.[15,30,33] A C-PCM model of acetone as solvent was used for both the geometry optimizations and Gibbs free energy calculations.[30,15] Furthermore, the M06-2X functional has been shown to compare favorably to coupled-cluster theory specifically for noncovalent interactions, which are crucial for elucidating the reaction paths for atom-transfer reactions where many of the critical structures involve bimolecular interactions.[34]

In these computationally investigated schemes, the initial HAT step involved **TS-A**, with an activation energy of 16.9 kcal/mol, followed by the addition of carbon-centered radical THF **A** to alkene **1** through **TS-B** (7.1 kcal/mol)[15] (see Figure 2). These steps, supported by computed energies, were also backed up by experimental data.

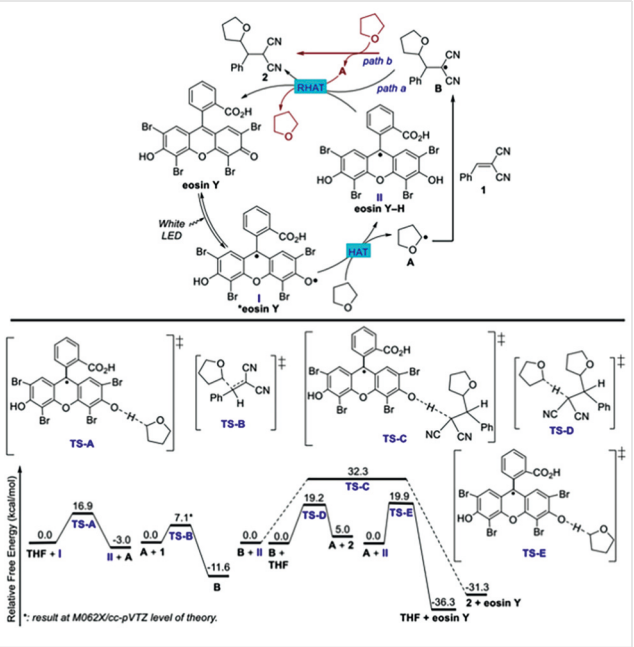


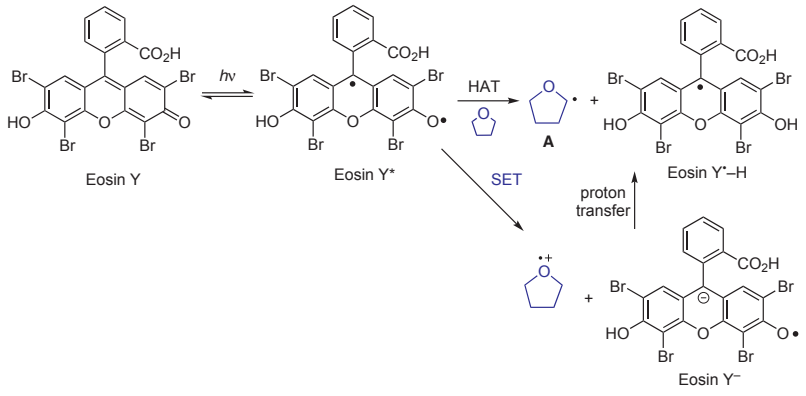
Figure 2 Illustration of critical structures and their relative Gibbs free energies (computed at the M06-2X/cc-pVTZ level of theory with a C-PCM solvation model) for several putative light-initiated HAT pathways of Eosin Y. Reproduced with permission from *Angew. Chem. Int. Ed.* **2018**, *57*, 8514. Copyright Wiley-VCH 2018.

Additionally, the reverse hydrogen atom transfer (RHAT) process had two plausible pathways – one through a single transition-state complex **TS-C** (herein referred to as pathway **a**) and a two-step pathway (herein referred to as pathway **b**) that proceeds through two transition-state complexes, **TS-D** and **TS-E** (Scheme 9). In pathway **a**, a direct, one-step RHAT occurs in which radical **B** directly abstracts a hydrogen atom back from eosin Y-H **II** to generate product **2** and regenerate eosin Y. Moreover, direct RHAT is associated with high activation energy of 32.3 kcal/mol, and hence involves a substantial energetic barrier. In pathway **b**, two steps are involved. First, radical **B** and THF form radical **A** and product **2** via **TS-D**. Then, through **TS-E**, eosin Y-H **II** and radical **A** regenerate eosin Y and THF. These two steps are both more energetically feasible (19.2 and 19.9 kcal/mol, respectively) than the single step of pathway **a** (32.3 kcal/mol) (Scheme 9).

It should be noted that there exists a competing mechanism to the proposed hydrogen atom transfer (HAT) reaction mechanism between the photoexcited state (eosin Y*) and substrate to form the radical A and EosinY•-H (Scheme 9). In this competing view, the direct hydrogen atom transfer to a photoexcited state like eosin Y* should not be kinetically competent due to the short half-life of the photoexcited state. That is to suggest that the HAT process should be slow compared to the relaxation of the excited state (eosin Y* back to eosin Y) and any competing single-electron transfer reaction (SET). In this alternative mechanism (Scheme 9), a much faster SET reaction could occur between the short-lived photoexcited state (eosin Y*) and the substrate (THF) to form a radical cation ($THF^{+\bullet}$) radical anion pair (eosin $Y^{-\bullet}$). A subsequent proton-transfer reaction between this ion pair would give the same HAT products (A + EosinY•-H). It is important to note that this issue with lifetimes only holds for the HAT reaction with the photoexcited state; the subsequent hydrogen-atom transfer reactions between ground state are well precedented.[14] While this mechanistic distinction might not appear significant, this difference is important for the selectivities in the C–H abstraction reaction. In this regard, Wu's deuterium labeling study show isotope effects that would be considered small for a direct HAT reaction in the selection steps.[12]

These different mechanistic proposals highlight the difficulty in unambiguously identifying photocatalytic mechanisms based on consideration of the energetics of critical structures only. A far richer picture of computational photochemistry is becoming possible; these new methods combine ab initio electronic structure theory with molecular dynamics, allowing for the success of previously unattainable computations.

Recent advances in the efficiency of high-accuracy electronic-structure methods have enabled the simulation of the dynamics of photochemical and photocatalytic transformations, which promise richer mechanistic insights than the static/structural studies. In such simulations, electron-



Scheme 9 HAT versus SET in the radical initiation step

ic-structure calculations are used to derive the internuclear forces arising from excited-state potential energy surfaces, and, typically, classical equations of motion are used to determine the motion of the nuclei.[35] Broadly speaking, these types of mixed quantum–classical simulations fall into two categories: adiabatic dynamics simulations, where the internuclear forces are derived from a single electronic potential energy surface (whether ground- or excited-state surface, see Hohenstein[36] for an example of the latter), or nonadiabatic dynamics simulations, where the impact of multiple electronic surfaces is accounted for.[15] One example that captures many of the salient features of light-initiated HAT was the study of the photoacidity of methylviologen using excited-state molecular dynamics simulation.[36] In this study, the internuclear forces on the S_1 state were computed using the Fractionally Occupied Molecular Orbital Complete Active Space Configuration Interaction (FOMO-CASCI) approach.[37] Furthermore, the electronic structure method provides a balanced description of ground- and excited-electronic states, which is critical for being able to compare the excited-state dynamics on the ground-potential energy surface. In this study, 100 water molecules were included in the explicit FOMO-CASCI computations, and a larger solvation shell was included using the transferable interatomic potential (TIP3P) model.[38] In addition, this study provided a real-time view of covalent bond formation between a solvent water molecule and methylviologen in its S_1 state, and then the subsequent proton abstraction by a second water molecule from the solvation shell, thus leading to a free hydronium and hydroxide covalently bound to methylviologen. Studies of this kind will no doubt have a transformative impact on the study of photochemical and photocatalytic mechanisms, since they provide dynamical information and also allow for the evolution of chemical species to be averaged over a suitable distribution of initial conditions rather than making inferences based on a small handful of static structures.

Conclusion

Visible-light photocatalysis has emerged as a powerful tool for organic synthetic transformations. The direct HAT pathway in photocatalysis is a highly attractive approach due to its reagent- and redox-economy.[10] Eosin Y, as a direct HAT catalyst, has received much attention because it is easy to handle, less expensive, environmentally friendly, nontoxic, and highly efficient. This review summarized several synthetic applications of important synthetic motifs and biologically active structures catalyzed by eosin Y induced direct HAT photocatalysis.

While the organic chemistry toolkit does not allow full investigation of proposed reaction mechanisms, it does provide support based on what may be deciphered from synthetic, analytical, and instrumental methods. Moreover, the coupling of organic chemistry toolkits with that of computational chemistry allows chemists to delve deeper into mechanistic details to obtain data on static/dynamic structures from calculations based on well-established theories. Thus, this combination of techniques allows for a better understanding of reaction mechanisms and helps fuel the discovery of new chemical reactivities. This review highlights the computational studies of the mechanisms using eosin Y as a HAT photocatalyst.

Conflict of Interest

The authors declare no conflict of interest.

Funding Information

Acknowledgment is made to the Donors of the American Chemical Society Petroleum Research Fund (PRF#58838-UNI1 and PRF#58853-UNI6) for support of this research. J.J.F. acknowledges the ART program at WPU for partial support of this work.

Acknowledgment

The authors would like to thank the Chemistry Department of William Paterson University of New Jersey.

References

(1) (a) Yoon, T. P.; Ischay, M. A.; Du, J. *Nat. Chem.* **2010**, *2*, 527. (b) Schultz, D. M.; Yoon, T. P. *Science* **2014**, *343*, 985. (c) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev.* **2013**, *113*, 5322. (d) Narayanam, J. M. R.; Stephenson, C. R. J. *Chem. Soc. Rev.* **2011**, *40*, 102. (e) Bian, C.; Singh, A. K.; Niu, L.; Yi, H.; Lei, A. *Asian J. Org. Chem.* **2017**, *6*, 386. (f) Shaw, M. H.; Twilton, J.; Macmillan, D. W. C. *J. Org. Chem.* **2016**, *81*, 6898.

(2) (a) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev.* **2013**, *113*, 5322. (b) Narayanam, J. M. R.; Stephenson, C. R. J. *Chem. Soc. Rev.* **2011**, *40*, 102. (c) Bian, C.; Singh, A. K.; Niu, L.; Yi, H.; Lei, A. *Asian J. Org. Chem.* **2017**, *6*, 386. (d) Stephenson, C. R. J.; Yoon, T. P.; MacMillan, D. W. C. *Visible Light Photocatalysis in Organic Chemistry*; Wiley: Weinheim, **2018**.

(3) Marzo, L.; Pagire, S. K.; Reiser, O.; König, B. *Angew. Chem. Int. Ed.* **2018**, *57*, 10034.

(4) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev.* **2013**, *113*, 5322.

(5) (a) Romero, N. A.; Nicewicz, D. A. *Chem. Rev.* **2016**, *116*, 10075. (b) Wei, G.; Basheer, C.; Tan, C.-H.; Jiang, Z. *Tetrahedron Lett.* **2016**, *57*, 3801.

(6) Ravelli, D.; Fagnoni, M.; Albini, A. *Chem. Soc. Rev.* **2013**, *42*, 97.

(7) Capaldo, L.; Ravelli, D. *Eur. J. Org. Chem.* **2017**, 2016.

(8) (a) Fagnoni, M.; Dondi, D.; Ravelli, D.; Albini, A. *Chem. Rev.* **2007**, *107*, 2725. (b) Ravelli, D.; Protti, S.; Fagnoni, M. *Acc. Chem. Res.* **2016**, *49*, 2232.

(9) Gentry, E. C.; Knowles, R. R. *Acc. Chem. Res.* **2016**, *49*, 1546.

(10) Ravelli, D.; Protti, S.; Fagnoni, M. *Chem. Rev.* **2016**, *116*, 9850.

(11) (a) Protti, S.; Fagnoni, M.; Ravelli, D. *ChemCatChem* **2015**, *7*, 1516. (b) Raviola, C.; Raveli, D. *Synlett* **2019**, *30*, 803.

(12) Fan, X.; Rong, J.; Wu, H.; Zhou, Q.; Deng, H.; Tan, J.; Xue, C.; Wu, L.; Tao, H.; Wu, J. *Angew. Chem. Int. Ed.* **2018**, *57*, 8514.

(13) (a) Romero, N. A.; Nicewicz, D. A. *Chem. Rev.* **2016**, *116*, 10075. (b) Hari, D. P.; König, B. *Chem. Commun.* **2014**, *50*, 6688.

(14) Srivastava, V.; Singh, P. *RSC Adv.* **2017**, *7*, 31377.

(15) Yan, D.; Chen, J.; Xiao, W. *Angew. Chem. Int. Ed.* **2019**, *58*, 378.

(16) Kuang, Y.; Wang, K.; Shi, X.; Huang, X.; Meggers, E.; Wu, J. *Angew. Chem. Int. Ed.* **2019**, *58*, 16859.

(17) DeMartino, M. P.; Chen, K.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 11546.

(18) Roth, H. G.; Romero, N. A.; Nicewicz, D. A. *Synlett* **2016**, *27*, 714.

(19) Yan, J.; Cheo, H. W.; Teo, W.; Shi, X.; Idres, S.; Deng, L.; Wu, J. *J. Am. Chem. Soc.* **2020**, *142*, 11357.

(20) (a) Combs, A. P.; Zhu, W.; Crawley, M. L.; Glass, B.; Polam, P.; Sparks, R. B.; Modi, D.; Takvorian, A.; McLaughlin, E.; Yue, E. W.; Wasserman, Z.; Bower, M.; Wei, M.; Rupar, M.; Ala, P. J.; Reid, B. M.; Ellis, D.; Gonneville, L.; Emm, T.; Taylor, N.; Yeleswaram, S.; Li, Y.; Wynn, R.; Burn, T. C.; Hollis, G.; Liu, P. C. C. *J. Med. Chem.* **2006**, *49*, 3774. (b) Maccari, R.; Ottanà, R. *J. Med. Chem.* **2012**, *55*, 2.

(21) Fan, X.; Xiao, P.; Jiao, Z.; Yang, T.; Dai, X.; Xu, W.; Tan, J.; Cui, G.; Su, H.; Fang, W.; Wu, J. *Angew. Chem. Int. Ed.* **2019**, *58*, 12580.

(22) Lalonde, M.; Chan, T. H. *Synthesis* **1985**, 817.

(23) (a) Savela, R.; Zawartka, W.; Leino, R. *Organometallics* **2012**, *31*, 3199. (b) Pongkittiphan, V.; Theodorakis, E. A.; Chavasiri, W. *Tetrahedron Lett.* **2009**, *50*, 5080. (c) Kusukawa, T.; Kabe, Y.; Nestler, B.; Ando, W. *Organometallics* **1995**, *14*, 2556. (d) Sommer, L. H.; Frye, C. L.; Parker, G. A.; Michael, K. W. *J. Am. Chem. Soc.* **1964**, *86*, 3271. (e) Curtice, J.; Gilman, H.; Hammond, G. S. *J. Am. Chem. Soc.* **1957**, *79*, 4754.

(24) Inoa, J.; Patel, M.; Dominici, G.; Eldabagh, R.; Patel, A.; Lee, J.; Xing, Y. *J. Org. Chem.* **2020**, *85*, 6181.

(25) (a) Terent'ev, A. O.; Borisov, D. A.; Vil, V. A.; Dembitsky, V. M. *Beilstein J. Org. Chem.* **2014**, *10*, 34. (b) Dembitsky, V. M. *J. Mol. Genet. Med.* **2015**, *9*, 1 DOI: 10.4172/1747-0862.1000163. (c) Norris, M. D.; Perkins, M. V. *Nat. Prod. Rep.* **2016**, *33*, 861.

(26) Srivastava, V.; Singh, P. K.; Singh, P. P. *Tetrahedron Lett.* **2019**, *60*, 1333.

(27) (a) Beatty, J. W.; Stephenson, C. R. J. *Acc. Chem. Res.* **2015**, *48*, 1474. (b) Froidevaux, V.; Negrell, C.; Caillol, S.; Pascault, J. P.; Boutevin, B. *Chem. Rev.* **2016**, *116*, 14181. (c) Dutcher, B.; Fan, M.; Russell, A. G. *ACS Appl. Mater. Interfaces* **2015**, *7*, 2137.

(28) Ansari, M. A.; Yadav, D.; Soni, S.; Srivastava, A.; Singh, M. S. *J. Org. Chem.* **2019**, *84*, 5404.

(29) (a) Jagodziński, T. S. *Chem. Rev.* **2003**, *103*, 197. (b) Ransborg, L. K.; Albrecht, Ł.; Weise, C. F.; Bak, J. R.; Jørgensen, K. A. *Org. Lett.* **2012**, *14*, 724. (c) Samai, S.; Chanda, T.; Ila, H.; Singh, M. S. *Eur. J. Org. Chem.* **2013**, 4026. (d) Wen, L.-R.; Men, L.-B.; He, T.; Ji, G.-J.; Li, M. *Chem. Eur. J.* **2014**, *20*, 5028. (e) Luo, X.; Ge, L.-S.; An, X.-L.; Jin, J.-H.; Wang, Y.; Sun, P.-P.; Deng, W.-P. *J. Org. Chem.* **2015**, *80*, 4611. (f) Li, M.; Kong, X.-J.; Wen, L.-R. *J. Org. Chem.* **2015**, *80*, 11999. (g) Li, C.-X.; Liu, R.-J.; Yin, K.; Wen, L.-R.; Li, M. *Org. Biomol. Chem.* **2017**, *15*, 5820. (h) Man, N.-N.; Wang, J.-Q.; Zhang, L.-M.; Wen, L.-R.; Li, M. *J. Org. Chem.* **2017**, *82*, 5566.

(30) Chen, M.; Di, J.; Li, J.; Mo, L.; Zhang, Z. *Tetrahedron* **2020**, *76*, 131059.

(31) (a) Han, C.; Zhang, T.; Zhang, A. Q.; Wang, D. D.; Shi, W. M.; Tao, J. C. *Synthesis* **2014**, *46*, 1389. (b) Yang, Y. T.; Zhu, J. F.; Liao, G. C.; Xu, H. J.; Yu, B. T. *Curr. Med. Chem.* **2018**, *25*, 2233.

(32) (a) Garavelli, M. *Theor. Chem. Acc.* **2006**, *116*, 87. (b) Schreiner, P. R. In *The Investigation of Organic Reactions and their Mechanisms, Chap. 7*; Maskill, H., Ed.; Blackwell Publishing Ltd: Oxford, **2006**.

(33) Tomasi, J.; Mennucci, B.; Cammi, R. *Chem. Rev.* **2005**, *105*, 2999.

(34) Hohenstein, E. G.; Chill, S. T.; Sherrill, C. D. *J. Chem. Theory Comput.* **2008**, *4*, 1996.

(35) (a) Tully, J. C. *J. Chem. Phys.* **1990**, *93*, 1061. (b) Subotnik, J. E.; Jain, A.; Landry, B.; Petit, A.; Outang, W.; Bellonzi, N. *Annu. Rev. Phys. Chem.* **2016**, *67*, 387. (c) Martinez, T. J.; Ben-Nun, M.; Levine, R. D. *J. Phys. Chem.* **1996**, *100*, 7884. (d) Curchod, B. F. E.; Martínez, T. J. *Chem. Rev.* **2018**, *118*, 3305.

(36) Hohestein, E. G. *J. Am. Chem. Soc.* **2016**, *138*, 1868.

(37) Slavíček, P.; Martínez, T. J. *J. Chem. Phys.* **2010**, *132*, 234102.

(38) Jorgensen, W. L.; Chandrasekhar, J.; Madura, J. *J. Chem. Phys.* **1983**, *79*, 926.