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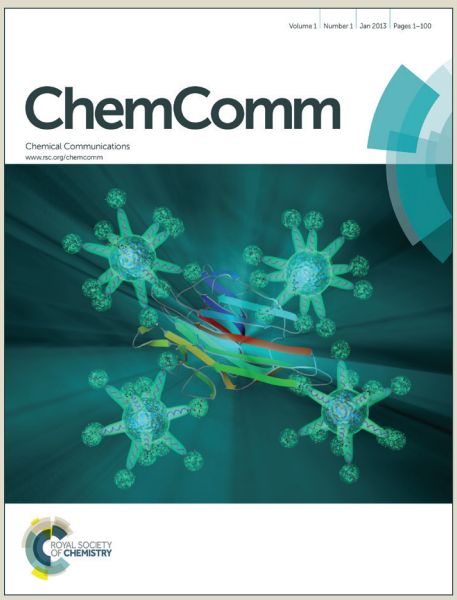

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ARTICLE TYPE

Synthetic Applications of Eosin Y in Photoredox Catalysis

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Eosin Y, a long known dye molecule, has recently been widely applied as a photoredox catalyst in organic synthesis. Low cost and good availability make eosin Y an attractive alternative to typical inorganic transition metal photocatalysts. We summarize the key photophysical properties of the dye and the recent synthetic applications in photoredox catalysis.

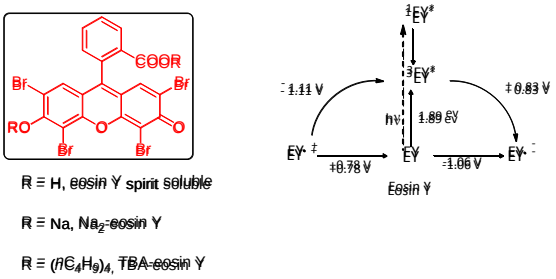
1. Introduction

Visible light photoredox processes have recently found many applications in organic synthesis,[1-13] but the general interest in the field started much earlier.[14] Unlike thermal reactions, photoredox processes occur under mild conditions and do not require radical initiators or stoichiometric chemical oxidants or reductants. Typical irradiation sources are LEDs or household lamps, which are cheaper and easier to apply than specialized UV reactors used in classical photochemistry. Ruthenium and iridium polypyridyl complexes are commonly employed visible light photocatalysts and their chemistry and application in organic synthesis has recently been summarized.[14, 15]

Despite the excellent photophysical properties of ruthenium and iridium polypyridyl complexes in visible light photocatalysis, the compounds are expensive and potential toxic, causing disadvantages on larger scale.[16] Organic dyes have been used as an attractive alternative to transition metal complexes in photoredox catalysis.[17-20] They are typically less expensive and less toxic, easy to handle and even outperform organometallic and inorganic catalysts in some cases.[16, 21-24] Particularly eosin Y was widely used as organo-photocatalyst in synthetic transformations. The classic dye is known for a long time and found use in cell staining,[25] as pH indicator,[26] as indicator in the analytical halide determination by Fajans[27, 28] and as dye pigment, e.g. in lip sticks.[29, 30] In this article, we discuss recent applications of eosin Y as visible light photocatalyst in organic synthesis.

2. Photochemistry of Eosin Y

The photochemistry of eosin Y is well investigated: upon excitation by visible light, eosin Y undergoes rapid intersystem crossing to the lowest energy triplet state, which has a life time of 24 µs.[31-33] Eosin Y absorbs green light; the UV-Vis spectrum shows a characteristic peak at 539 nm with a molar extinction coefficient ε = 60803 $M^{-1}cm^{-1}$. By excitation eosin Y becomes more reducing and more oxidizing compared to its ground state. The redox potentials of the excited state can be estimated from the standard redox potentials of the ground state, determined by cyclic voltammetry, and the triplet excited state energy. The measured ground state and the estimated excited state oxidation and reduction potentials are given in Scheme 1.[34, 35] In addition, the photo excited state of eosin Y may also undergo energy transfer.[36]



Scheme 1 Different forms of eosin Y and the redox potentials of eosin Y in CH_3CN/H_2O (1:1) in ground and corresponding excited states.

3. Reduction reactions

The first reaction demonstrating the use of eosin Y photocatalysis in organic synthesis was the photoreduction of sulfonium salts.

3.1 Reduction of phenacyl sulfonium salt

In 1978, Kellogg and coworkers reported the visible light induced reduction of phenacyl sulfonium salts by 1,4 dihydro-pyridines (Scheme 2).[37] Irradiation of a mixture of **1** and **2** in CD_3CN or CD_3COCD_3 without any photosensitizer provided the reduced product **3** in quantitative yield after 48 h using normal room light (neon fluorescent lamp at ca. 2 m distance) at 25°C. Addition of 1 mol% of Na_2-eosin Y accelerated the reaction resulting in complete conversion within 1 h of irradiation. The authors speculated that light induced single electron transfer (SET) steps are responsible for the formation of the reduced

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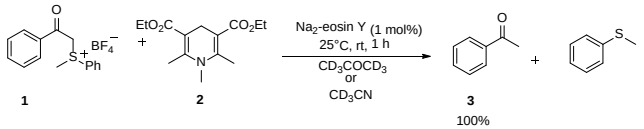
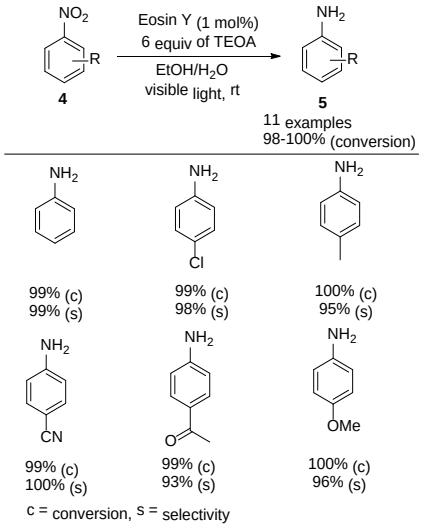
product and suggested an acceleration effect upon addition of the photocatalyst. However, the exact role of the photocatalyst in the reaction mechanism remains undisclosed.



Scheme 2 Visible light mediated reduction of phenacyl sulfonium salt.

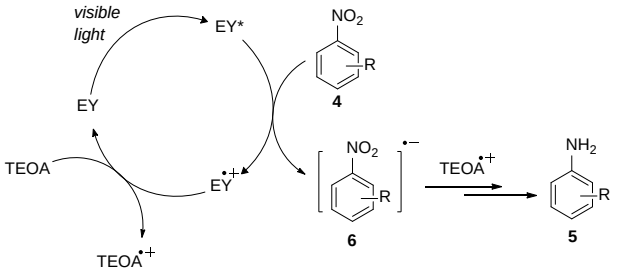
3.2. Reduction of nitrobenzene

Tung and coworkers utilized eosin Y as photocatalyst and triethanolamine (TEOA) as sacrificial reducing agent for the efficient photocatalytic reduction of nitrobenzene under green light irradiation (Scheme 3).[38] The reaction is chemoselective and tolerates the presence of other functional groups, such as carbonyls, halogen atoms, and nitriles. The nitro group is the better electron acceptor. Important factors to achieve the optimal reaction yield are the pH value of the reaction mixture in deoxygenated ethanol-water (3:2, v/v) mixture and the amount of added TEOA. Nitro groups of substrates bearing either electron donating or electron withdrawing substituents are smoothly reduced.



Scheme 3 Photoreduction of substituted nitrobenzenes to anilines.

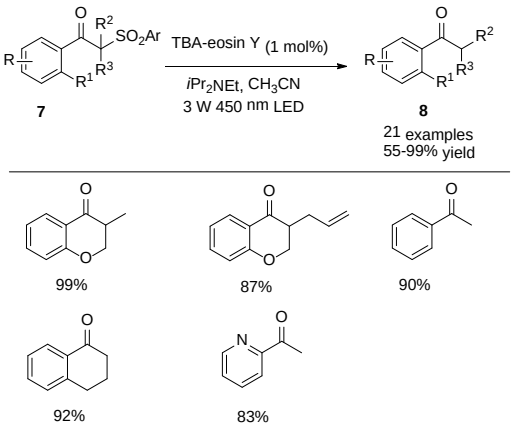
Based on quenching experiments and a flash photolysis study, the authors proposed a tentative mechanism for the photocatalytic reduction of nitrobenzene as shown in Scheme 4. A SET from eosin Y* to nitrobenzene generates **6** and the radical cation of eosin Y, which is reduced by TEOA to close the catalytic cycle and produce the radical cation of TEOA. The reaction of the radical anion **6** with the TEOA cation radical in the presence of water gives glycolaldehyde, diethanolamine and the further reduced intermediates, which are again reduced in a similar fashion to finally yield aniline.



Scheme 4 A plausible mechanism for the reduction of nitrobenzene to aniline via visible light photocatalysis.

3.3. Desulfonylation

The use of sulfones as auxiliary groups is an efficient synthetic strategy to generate a wide range of important products. Commonly the sulfone group is removed using metal containing reducing agents, such as Bu_3SnH, Al (Hg), or $Sm/HgCl_2$. Recently an environmental friendly desulfonylation reaction was reported by Wu and coworkers using eosin Y bis-tetrabutyl-ammonium salt (TBA-eosin Y) as photocatalyst and diiso-propylethylamine (iPr_2EtN) as a reducing agent (Scheme 5).[39]



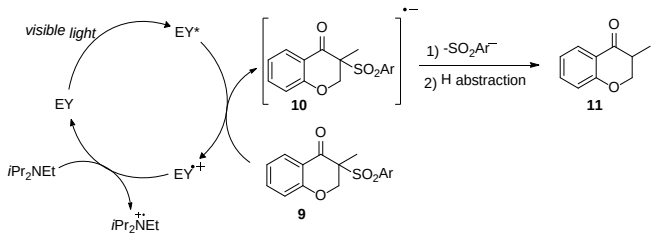
Scheme 5 Desulfonylation using TBA-eosin Y as a photocatalyst.

Durga Prasad Hari was born in Jarajapupeta, Nellimarla, Vizianagaram, A.P, India. He received his Bachelor degree from Silver Jubilee Degree College, Sri Krishnadevaraya University, Ananthpur, and then obtained his Master degree from IIT Madras. He is currently working under the supervision of Prof. Burkhard König for his PhD at the University of Regensburg. His research interests focus on the applications of visible light chemical photocatalysis towards organic synthesis.

Burkhard König was born in Wiesbaden, Germany. He obtained his PhD in 1991 from the university of Hamburg under the supervision of Prof. de Meijere. He pursued postdoctoral studies with Prof. M. A. Bennett, Research School of Chemistry, Australian National University, Canberra, and Prof. B. M. Trost, Stanford University. In 1996 he recieved his Habilitation at the University of Braunschweig. He became full professor of organic chemistry at the University of Regensburg from 1999. His current research interests include the development of synthetic receptors for the recognition of biological target structures and the application of visible light chemical photocatalysis towards organic synthesis.

Irradiation of a mixture of **7,** TBA-eosin Y and diisopropylethylamine under inert atmosphere using a 3 W blue LED in CH_3CN furnishes the desired product **8** in good yields. Sulfonylated aliphatic ketones give no reaction yield due to their very negative reduction potential of -1.94 V vs SCE not accessible by the excited state of TBA-eosin Y.

The mechanism for the desulfonylation reaction is proposed in Scheme 6. Irradiation of TBA-eosin Y generates its excited state, which is oxidatively quenched by β-arylketosulfones resulting in the formation of the cation radical of TBA-eosin Y and the radical anion of **9**. A SET from diisopropylethylamine to the radical cation of TBA-eosin Y regenerates the photocatalyst and closes the cycle. Finally, the radical anion **10** undergoes desulfonylation to produce a ketone radical which abstracts a hydrogen atom from the cation radical of diisopropylethylamine affording the desired ketone **11**. The radical cation of the TBA-eosin Y was identified in the presence of β-arylketosulfones by laser-flash photolysis. The observed absorption at 460 nm corresponds to the reported value for the eosin Y radical cation.



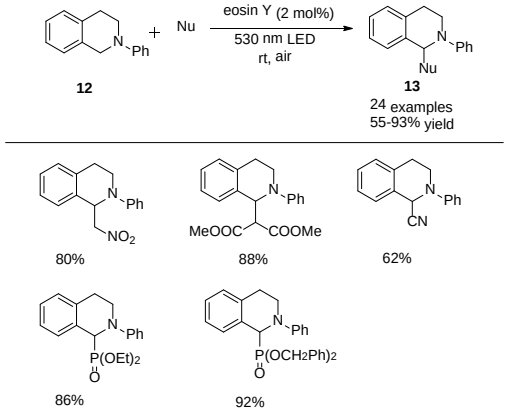
Scheme 6 Proposed mechanism for the photo-desulfonylation reaction.

4. Oxidation reactions

Eosin Y has been used to mediate photooxidation reactions in the presence of stochiometric amounts of electron acceptors. The reported reactions include the oxidation of amines, thioamides, and enol ethers.

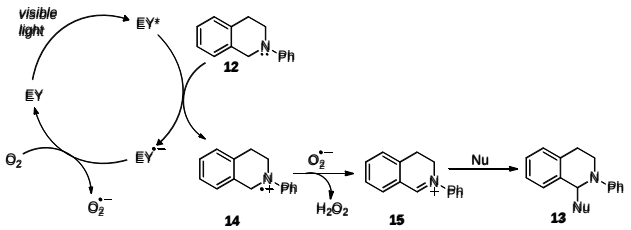
4.1. Oxidative iminium ion formation

The construction of C-C and C-P bonds by C-H activation is an emerging research area in organic synthesis.[40-48] Our group reported an efficient visible light mediated method for the formation of C-C and C-P bonds using eosin Y as photoredox catalyst in visible light (Scheme 7).[49] Nitroalkanes, dialkyl phosphonates, dialkyl malonates, and malononitrile were used as nucleophiles to trap the iminium ion leading to new bond formation at the α-position of tetrahydroisoquinolines. The reaction does not require the addition of stoichiometric oxidants and uses molecular oxygen from air as the terminal oxidant.



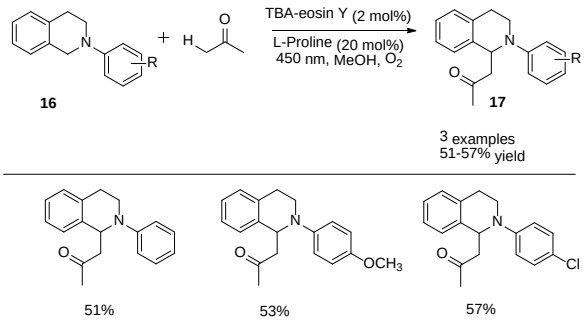
Scheme 7 Oxidative C-C and C-P bond formation.

The proposed mechanism of the reaction is depicted in Scheme 8. A single electron transfer from tetrahydroisoquinoline **12** to the excited state of eosin Y furnishes the aminyl radical cation **14** and the radical anion of eosin Y, which then transfers an electron to oxygen present in the reaction. The superoxide radical anion may abstract a hydrogen atom from **14** to generate the iminium ion **15**, which is finally trapped by a nucleophile resulting in the desired product **13.** H_2O_2 has been found as the by product.[17]



Scheme 8 Proposed mechanism for the photocatalytic oxidative coupling reaction of tetrahydroisoquinolines.

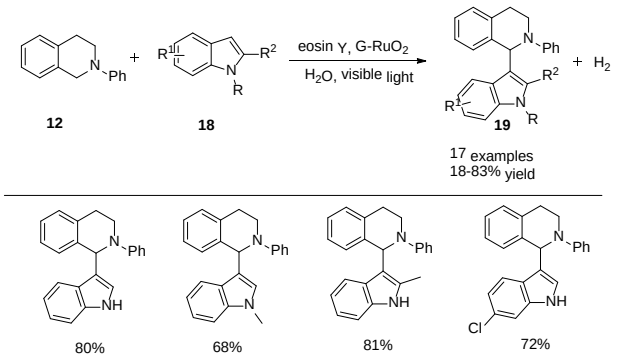
Later, Wu and coworkers reported the photocatalytic oxidative Mannich reaction under aerobic condition using molecular oxygen (Scheme 9).[50] Irradiation of TBA-eosin Y, L-proline, tetrahydroisoquinoline **16**, and acetone produce the synthetically important product **17** in moderate yields. The catalyst system consists only of organic compounds, which can be an advantage.



Scheme 9 The photocatalytic oxidative Mannich reaction.

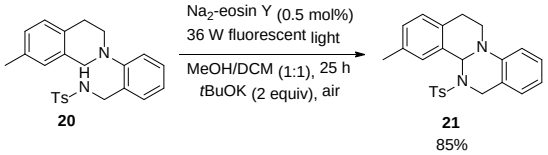
Wu and coworkers combined eosin Y as a photosenestizer with graphene-supported RuO_2 nanocomposites as catalyst for C-C bond formation without external oxidants. Hydrogen is generated in good to excellent yield as the only byproduct (Scheme 10).[51] Eosin Y initiates the coupling reaction of the tetrahydroisoquinoline with the nucleophile *via* visible light

photoredox catalysis and at the same time RuO_2 is used to capture the excess electron and proton from the C-H bonds of the substrates. Irradiation of eosin Y, grapheme-RuO2, tetrahydroisoquinoline **12**, and indole **18** at room temperature affords the desired cross coupling product **19** in good yield. The products containing halogen atoms may serve as important intermediates for further synthetic transformations. The cross coupling reaction occurs exclusively at the 3-position of indole **18** irrespective to the substitution on the indole moiety.



Scheme 10 Oxidative coupling between tetrahydroisoquinoline and indole with dihydrogen as second product.

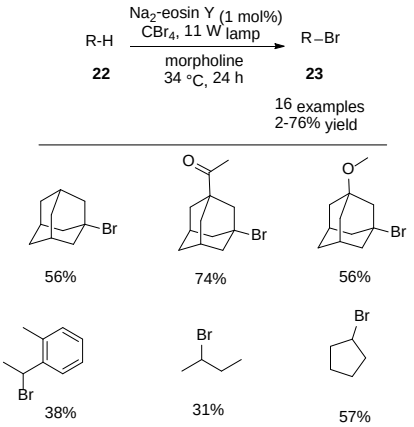
In the reactions described so far, the iminium ion and the nucleophile react intermolecularly. Recently, Xiao and coworkers reported the synthesis of isoquino[2,1-a]pyrimidine **21** *via* intramolecular trapping of the iminium ion with a pendant *N*-tosyl moiety using Na_2-eosin Y as photoredox catalyst (Scheme 11).[52] Irradiation of Na_2-eosin Y, *t*BuOK, 4-methyl-*N*-(2-(7-methyl-3,4-dihydroisoquinolin-2(1H)-yl)benzyl)benzene sulfonamide **20** in MeOH/dichloromethane affords 3-methyl-5-tosyl-4b,5,12,13-tetrahydro-6H-isoquinolino[2,1-a]quinazoline **21** in 85% yield after 25 h.



Scheme 11 Intramolecular trapping of a photogenerated iminium ion with an *N*-tosyl moiety.

4.2. Bromination

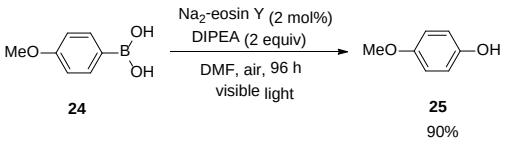
Selective bromination of C-H bonds under ambient conditions is an important synthetic method in organic synthesis. Recently, Tan and coworkers reported a selective method for the bromination of aliphatic and benzylic C-H bonds with visible light photoredox catalysis using eosin Y (Scheme 12).[53] The reaction was performed at mild conditions using CBr_4 as the bromine source and morpholine as reducing agent. The amount of water is essential for the reaction: a higher ratio of water to dichloromethane is important for the formation of the brominated product **23**. The authors conducted experimental and computational studies on the mechanism and suggest that an *N*-morpholino radical is responsible for the C-H activation step during the reaction. The reaction tolerates ester, ether, and ketone functional groups. Synthetic applications of the method are the selective bromination of (+)-sclareolide and of acetate protected estrone.



Scheme 12 Selective bromination of aliphatic and benzylic C-H bonds.

4.3. Hydroxylation

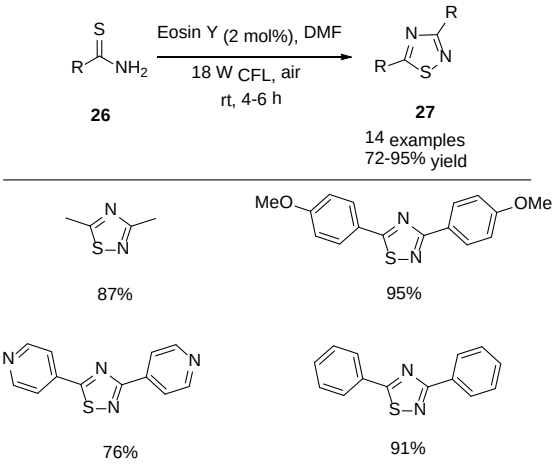
Xiao and coworkers reported a highly efficient method for the hydroxylation of arylboronic acids to aryl alcohols using visible light photoredox catalysis under aerobic oxidative conditions (Scheme 13).[54] Typical reaction conditions used transition metal photocatalysts, but in a single example Na_2-eosin Y was successfully adopted. Irradiation of a mixture of 2 mol% Na_2-eosin Y, arylboronic acid **24** (0.5 mmol), iPr_2NEt (2.0 equiv) in DMF provided the hydroxylated product **25** in 90% yield after 96 h. The superoxide radical anion, which is generated in the photoredox cycle, reacts with arylboronic acid **24**. Its Lewis acidity arises from the vacant boron p-orbital. A subsequent series of rearrangements and hydrolysis affords the desired aryl alcohol **25**.



Scheme 13 Hydroxylation of arylboronic acids *via* visible light catalysis using Na_2-eosin Y.

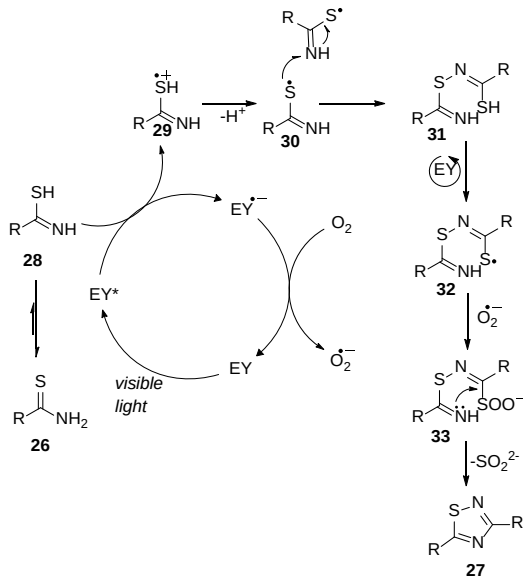
4.4. Cyclization of thioamides

1,2,4-Thiadiazoles have found applications in biology and pharmaceutical sciences. An example is the clinically used antibiotic cefozopram, which contains a 1,2,4-thiadiazole moiety. Elegant methods have been reported for synthesis of the privileged structure, but most of them require oxidizing agents. Yadav and coworkers reported recently a metal free synthesis of 1,2,4-thiadiazole avoiding stoichiometric oxidants and using instead visible light and molecular oxygen in the presence of eosin Y as a photoredox catalyst.[55] This reaction involves the oxidative cyclization of thioamides via the sequential formation of C-N and C-S bonds to afford the 1,2,4-thiadiazole in very good yields. Irradiation of benzothioamide **26** under aerobic conditions in the presence of 2 mol% eosin Y in DMF gave the desired product **27** in good yield (Scheme 14). A wide range of aliphatic, aromatic, and heteroaromatic primary amides underwent in this reaction smoothly.



Scheme 14 Photocyclization of thioamides giving 1,2,4-thiadiazoles.

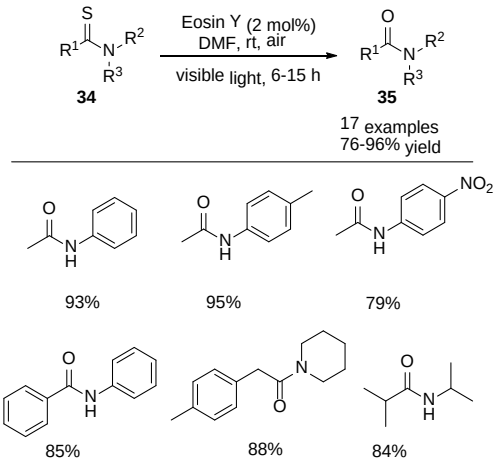
The suggested mechanism for the formation of 1,2,4-thiadiazole is depicted in Scheme 15. A single electron transfer from the thiolic form **28** to eosin Y* generates the radical anion of eosin Y and the radical cation **29**, which undergoes deprotonation to give a sulfur radical intermediate **30**. The cyclodesulfurization of intermediate **30** furnishes **31**, which gives another sulfur radical **32** by photooxidation as described before. The intermediate radical **32** is further oxidized by anion radical of O_2, which is produced in the photocatalytic cycle of eosin Y, to give peroxysulfenate **33**. Finally, an intermolecular nucleophilic attack of the imino nitrogen on the SO_2^- substituted carbon affords the desired product **27** with loss of SO_2^{2-}.[56]



Scheme 15 Proposed mechanism of the cyclization of thioamides.

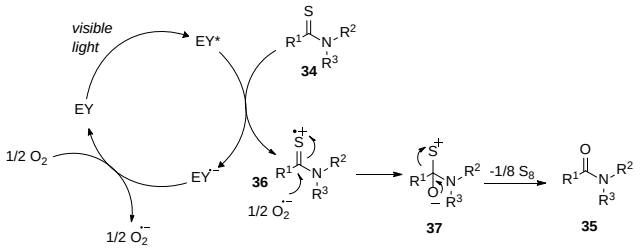
4.5. Desulfurization

Aerobic desulfurization of thioamides to amides has been achieved by Yadav and coworkers under visible light photoredox catalysis using eosin Y as a photocatalyst (Scheme 16).[57] Green light irradiation of 2 mol% eosin Y, thioamide **34** in DMF under air atmosphere affords the desired product **35** in very good yield. Control experiments demonstrated that there was no significant product formation in the absence of either light or eosin Y. The photoreaction tolerates a wide range of functional groups including nitro, bromo, and methoxy groups. Thioamides bearing electron donating groups on the aromatic ring reacted faster and gave higher yields in comparison to those bearing electron withdrawing groups. The reaction was not applicable to primary thioamides; which form dimers under identical reaction conditions.



Scheme 16 Desulfurization of thioamides using eosin Y photocatalysis.

The mechanism for the desulfurization of thioamides to amides is shown in Scheme 17. Initial SET from **34** to eosin Y* produces the radical anion of eosin Y and the radical cation **36**. This is oxidized to intermediate **37** which converts to the desired product **35** along with the formation of elemental sulfur as byproduct. The authors ruled out a singlet oxygen mechanism for this reaction by performing several control experiments. The use of O_2 (balloon) instead of open air did not increase the reaction yield and the reaction was not affected by singlet oxygen quenchers like 1,4-diazabicyclo[2.2.2]octane (DABCO) or 2,3 dimethyl-2-butene.

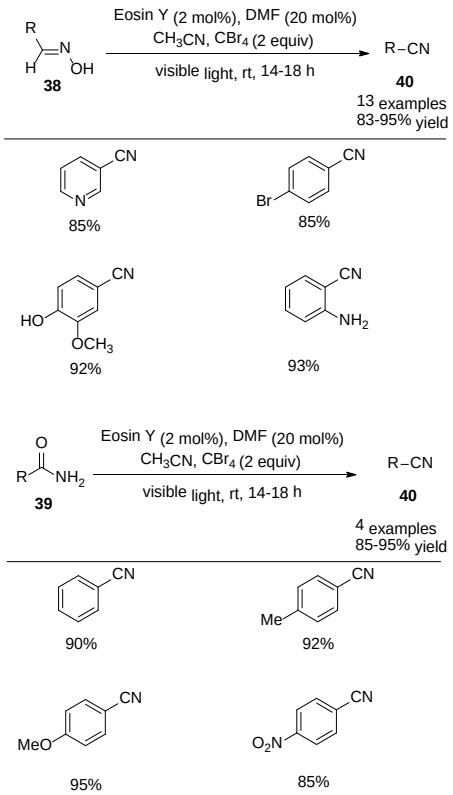


Scheme 17 Suggested mechanism for the desulfurization of thioamides into the amides.

4.6. Aldoximes and primary amides into nitriles

An efficient method for the transformation of aldoximes and primary amides into nitriles has been reported by Yadav and coworkers (Scheme 18).[58] The photoreaction involves the visible light initiated *in situ* generation of the Vilsmeier Haack reagent from DMF and CBr_4, which is the electrophilic reagent responsible for the conversion of primary amides and aldoximes into the corresponding nitriles. A mixture of aldoxime **38** (1 mmol), 2 mol% eosin Y, 2 equiv of CBr_4, and 20 mol% DMF was irradiated in CH_3CN for 14-18 h affording the desired product **40** in good yields. A wide range of aromatic, heteroaromatic, aliphatic aldoximes, and primary amides **39**

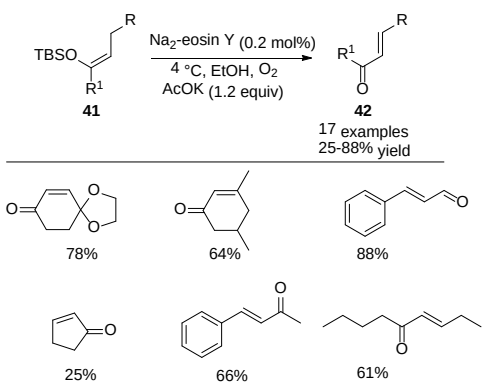
reacted smoothly under these conditions. The reaction yield was higher in the presence of electron donating groups in the aryl moiety of the oxime.



Scheme 18 Conversion of aldoximes and primary amides into nitriles.

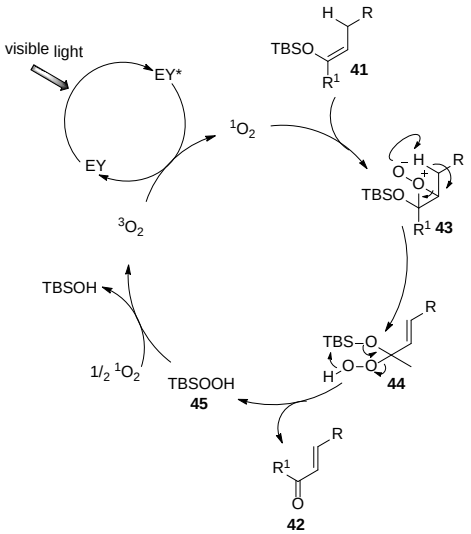
4.7. Oxidation of silyl enol ethers

α, β-Unsaturated carbonyl compounds are essential structural motifs for the construction of a variety of natural products. Elegant methods have been reported for their synthesis, but most of them require either metal catalysts or stoichiometric oxidants. Huang and coworkers utilized the photoredox chemistry of Na_2-eosin Y in visible light for the synthesis of α, β-unsaturated aldehydes and ketones from silyl enol ethers under aerobic oxidation conditions (Scheme 19).[36] Polar protic solvents like MeOH, EtOH as well as the polar aprotic solvent DMSO were identified as suitable for this reaction. The major side product of the reaction was the oxidative cleavage of the enol ether double bond.



Scheme 19 Preparation of α, β-unsaturated aldehydes and ketones from silyl enol ethers.

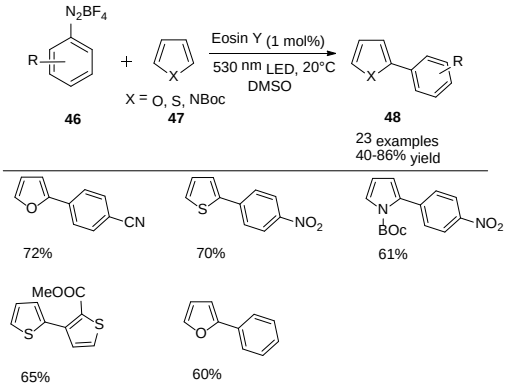
The authors proposed a singlet oxygen mechanism for this transformation based on radical clock experiments and literature reports (Scheme 20). First, singlet oxygen is generated from sensitization by Na_2-eosin Y*. An ene reaction between the silyl enol ether **41** and singlet oxygen produces the intermediate **43,** which is further converted in to a hydroperoxy silyl hemiacetal **44**. The intermediate **44** could undergoes an intramolecular silyl transfer to afford the desired product **42** along with hydroperoxysilane **45**, which further undergoes decomposition to give O_2 and silanol.



Scheme 20 Proposed reaction mechanism for the singlet oxygen mediated oxidation of silyl enol ethers

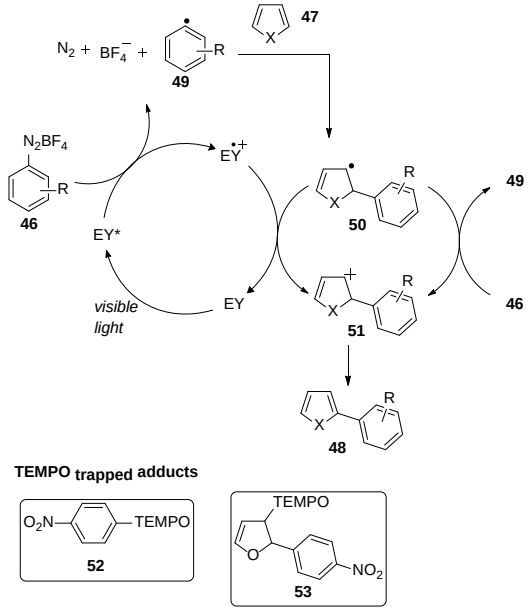
5. Arylation reactions

Aryl radicals can be generated from aryl diazonium salts *via* visible light photocatalysis. The method is an efficient alternative to reported procedures. We have used eosin Y as a photoredox catalyst for the direct arylation of heteroarenes with aryl diazonium salts in green light (Scheme 21).[59] The reaction tolerates a wide range of functional groups, such as nitro, ester, cyano, and hydroxyl groups and has a broad scope with respect to both aryl diazonium salts and the heteroarenes. In addition to aryl diazonium salt **46**, thienyl diazonium salts also reacts providing the corresponding products in good yields. External base decreased the reaction yield due to direct reaction between the aryl diazonium salt and the base. This metal free reaction represents an efficient alternative to transition metal catalyzed C-H arylation reactions and avoids the use of copper salts required in the classical Meerwein arylation protocol.



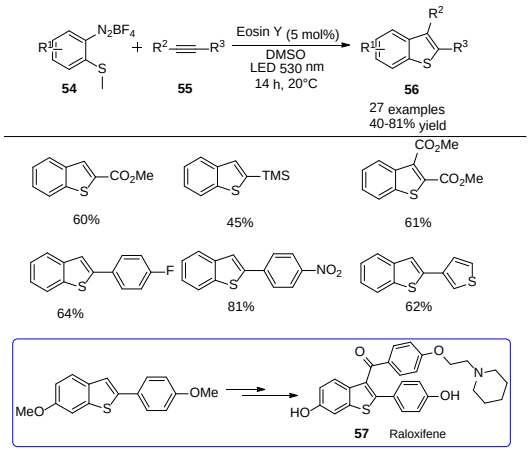
Scheme 21 Direct photocatalytic C-H arylation of heteroarenes.

The proposed mechanism of the photocatalytic direct C-H arylation reaction is shown in Scheme 22. Initial reduction of the aryl diazonium salt **46** by eosin Y* gives aryl radical **49** and the radical cation of eosin Y. The aryl radical **49** adds to heteroarene **47** yielding radical intermediate **50**, which is oxidized by the radical cation of eosin Y to carbenium ion **51** while regenerating the neutral form of the photocatalyst eosin Y. Finally, carbenium ion **51** is deprotonated to the desired product **48**. The oxidation of intermediate **50** is also possible by the aryl diazonium salt **46** directly *via* a radical chain mechanism. However, monitoring of the reaction progress after shutting off the irradiation indicates that the radical chains undergo only few turnovers. The radical intermediates **49** and **50** were trapped with (2,2,6,6-tetramethyl-piperidin-1-yl)oxyl (TEMPO) and the corresponding adducts **52** and **53** were confirmed by mass spectrometry.



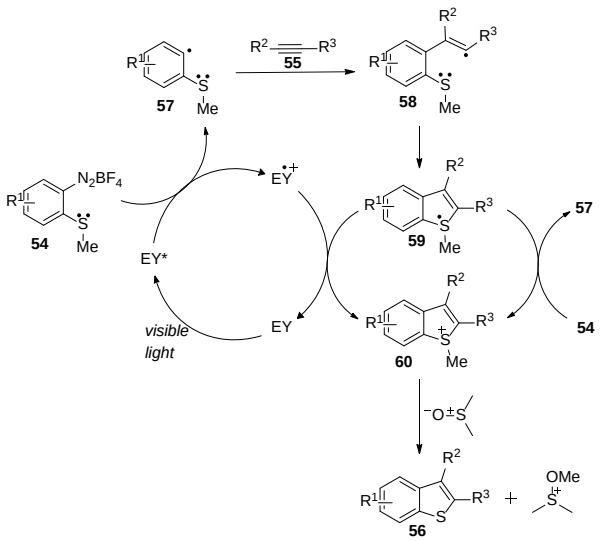
Scheme 22 Proposed mechanism for the direct photocatalytic C-H arylation of heteroarenes.

Substituted benzothiophenes find applications in biology, pharmaceutical and material science. We applied the direct C-H arylation method for the arylation of benzothiophenes, but unfortunately a mixture of regioisomers was obtained in low yields. To obtain a single regioisomer, we decided to explore a radical annulation for the synthesis of the benzothiophene moiety (Scheme 23).[60] Irradiation of a mixture of 5 mol% eosin Y, o-methylthio benzenediazonium salt **54** (0.25 mmol), and alkyne **55** (5 equiv) in DMSO afforded the desired product **56** in moderate to good yield after 14 h using a 530 nm LED. The scope of the reaction is wide and halogen substituted benzothiophenes are available by this route. We utilized the reaction for the synthesis of the drug intermediate Raloxifene **57**.



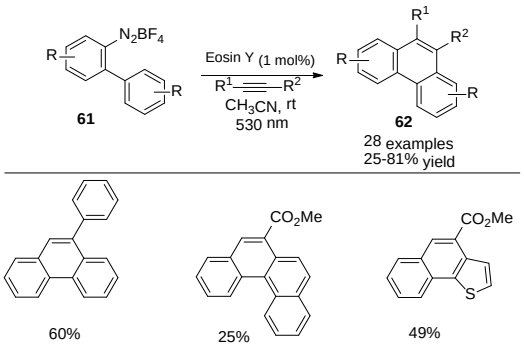
Scheme 23 Synthesis of substituted benzothiophenes via a photocatalytic radical annulation route.

The proposed mechanism of the radical annulation is shown in Scheme 24. Initially, eosin Y* is oxidatively quenched by the diazonium salt **54** to generate the reactive aryl radical **57** and the radical cation of eosin Y. Upon addition of the aryl radical **57** to alkyne **55** the radical intermediate **58** is obtained, which undergoes cyclization to give sulphuranyl radical **59**. Subsequent oxidation of **59** by the cation radical of eosin Y followed by transferring of the methyl group to nucleophiles present in the reaction, e.g. the solvent DMSO, yields the product **56**. The radical intermediate **59** may also be oxidized by the diazonium salt **54** in a radical chain transfer mechanism. TEMPO adducts of radical intermediates **57** and **58** were identified, which supports the proposed reaction mechanism.



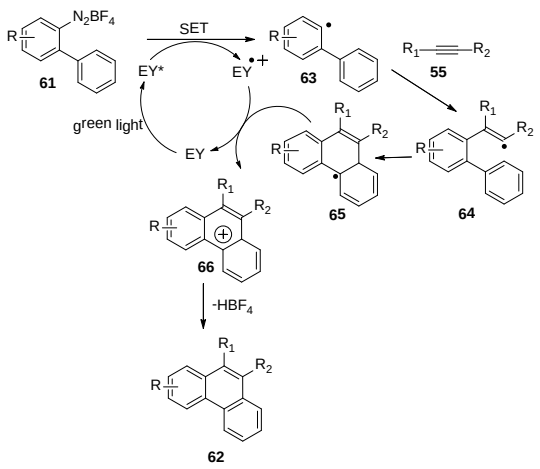
Scheme 24 Proposed mechanism of the photocatalytic radical annulation synthesis of benzothiophenes.

A visible light induced [4+2] benzannulation method for the synthesis of phenanthrenes was reported by Zhou et al. using eosin Y as photocatalyst under mild conditions (Scheme 25).[61] Eosin Y (1 mol%), biphenyldiazonium salt **61** (0.2 mmol), and an alkyne (3 equiv) were dissolved in CH_3CN and irradiated with a 24 W fluorescent bulb at room temperature giving the corresponding product **62** in very good yield. The reaction proceeds smoothly in polar solvents. In non-polar solvents the solubility of the diazonium salt **61** is poor. Additions of bases, such as *t*BuOLi or NEt_3 decrease the yield due to the direct reaction of the diazonium salt **61** and the base. The photoreaction tolerates many functional groups and has a broad scope of alkynes and biphenyldiazonium salts.



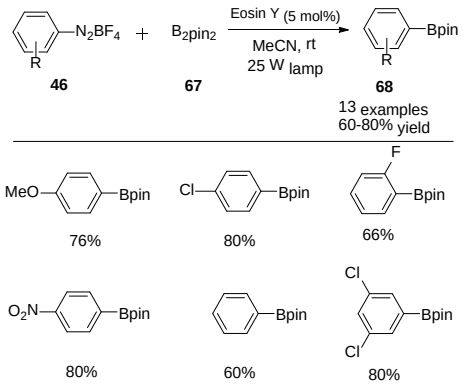
Scheme 25 Photocatalytic synthesis of phenanthrenes *via* a [4+2] benzannulation method.

The proposed reaction mechanism of the [4+2] photo-benzannulation is similar to the other diazonium salt reactions (Scheme 26). Initial SET from eosin Y* to biphenyl diazonium salt **61** generates the radical cation of eosin Y and biphenyl radical **63**, which upon addition to alkyne **55** furnishes vinyl radical **64**. Subsequent intramolecular radical cyclization affords the cyclized radical intermediate **65**. Oxidation of **65** by the eosin Y radical cation closes the catalytic cycle and produces the carbenium intermediate **66**. Finally, cation **66** is deprotonated to afford the desired phenanthrene **62**.



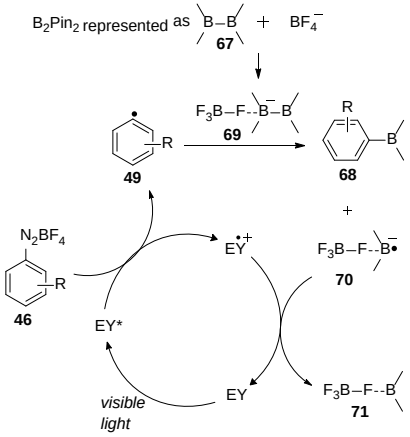
Scheme 26 Proposed mechanism for the synthesis of phenanthrenes.

Photoredox catalysis with eosin Y has been discussed so far, for the formation of C-C and C-P bonds. Recently, the Yan group utilized eosin Y for the borylation of aryl diazonium salts (Scheme 27).[62] Acetonitrile was found to be a suitable solvent to promote the reaction in good yields. Irradiation of a mixture of 5 mol% eosin Y, B_2Pin_2 **67** (0.3 mmol), and aryl diazonium salt **46** (1.5 equiv) in acetonitrile at room temperature affords the desired product **68** in good yields. Aryl diazonium salts bearing electron withdrawing groups showed higher reactivity than those bearing electron donating groups. The photoreaction tolerates a range of functional groups including acetyl, nitro, alkyl, halo, and alkoxy groups. Heteroaromatic diazonium salts are not suitable substrates for this reaction.



Scheme 27 Borylation of aryl diazonium salts.

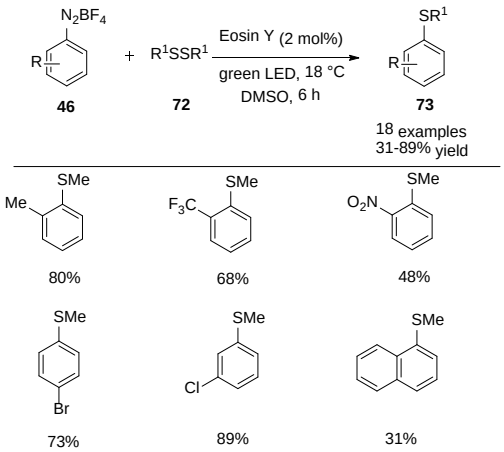
The proposed mechanism for the borylation of aryl diazonium salts is depicted in Scheme 28. Initially, a SET from eosin Y* to the aryl diazonium salt **46** gives the aryl radical **49** and the radical cation of eosin Y. Addition of the aryl radical **49** to the tetra-coordinated complex **69**, which was generated *in situ* from the interaction between B_2Pin_2 and the counter anion BF_4^-, affords the target borylated product **68** and the radical anion intermediate **70**. Finally, intermediate **70** was oxidized by the radical cation of eosin Y to complete the catalytic cycle.



Scheme 28 A plausible mechanism for the borylation of aryl diazonium salts.

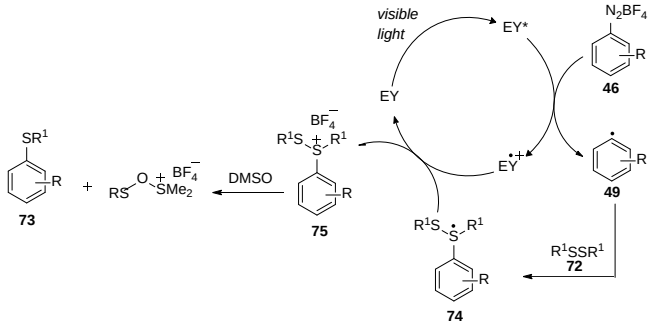
Arylsulfides are important structural motifs in synthetic and natural molecules and they are usually prepared by treatment of aryl diazonium salts with thiols under basic or neutral conditions. The intermediate diazosulfide, which is formed during the reaction, is a potent explosive. The recently reported method by Jacobi and coworkers avoids the risk by utilizing eosin Y as a

photoredox catalyst for the synthesis of arylsulfide **73** from aryl diazonium salt **46** and disulfide **72** under green light irradiation (Scheme 29).[63] DMSO was found to be a very good solvent for this reaction. Without eosin Y and without irradiation no product formation is observed, but irradiating the reaction mixture without eosin Y gave very low product yields. The observation is explained by a charge transfer complex between DMSO and the aryl diazonium salt, which absorbs in the visible range. In addition, the authors also prepared unsymmetrical diarylselenides from aryl diazonium salts and diphenyldiselenide.



Scheme 29 Synthesis of arylsulfides from diazonium salts and disulfides.

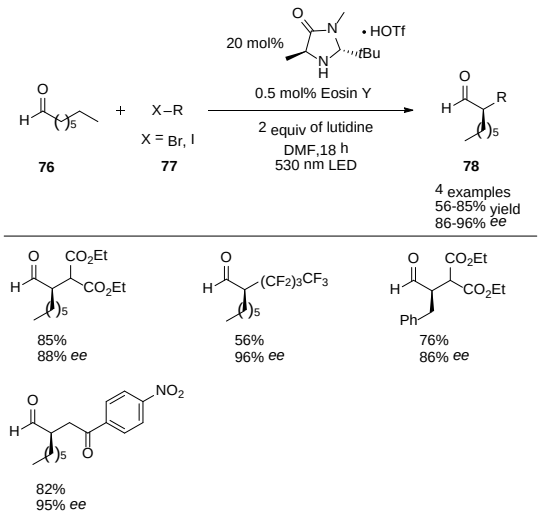
The suggested mechanism for the photocatalytic thiolation reaction is shown in Scheme 30. A SET reduction of aryl diazonium salt **46** by eosin Y* generates aryl radical **49** and the radical cation of eosin Y. The nucleophilic disulfide **72** attacks the aryl radical giving a trivalent sulfur radical **74**, which is stabilized by the adjacent aryl and sulfur groups. Oxidation of the intermediate **74** by the radical cation of eosin Y furnishes an electrophilic species **75** and completes the photocatalytic cycle. Finally, the cation intermediate **75** undergoes substitution with DMSO to give the desired product **73**.



Scheme 30 Suggested reaction mechanism for the photocatalytic thiolation reaction.

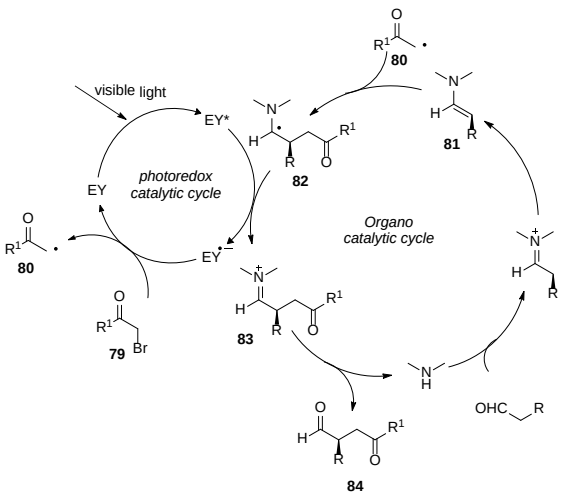
6. Cooperative catalysis

A dual catalytic combination of photocatalysis with organocatalysis was reported by Zeitler and coworkers for the enantioselective α-alkylation of aldehydes.[35] Eosin Y and imidazolidinone were found to be capable of alkylating aldehydes with electron deficient alkyl halides to provide the corresponding products in good yields with high enantiomeric excess (Scheme 31). Eosin Y catalyzed reactions require a little longer reaction times compared to the ruthenium-trisbipyridine catalyzed MacMillan reaction,[64] but did not give any product racemization. The photoreaction allows the stereospecific incorporation of fluorinated alkyl moieties, which are important structural units in drug to modulate their properties.



Scheme 31 Asymmetric α-alkylation of aldehydes.

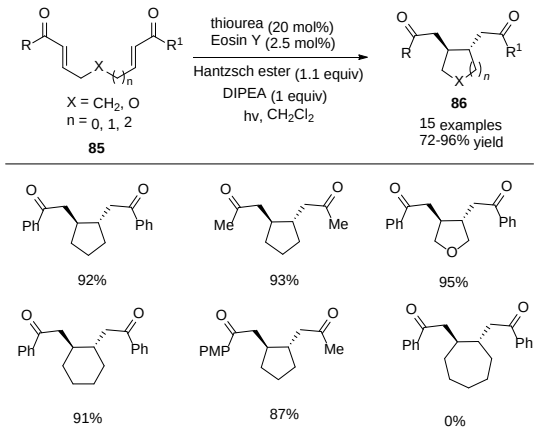
Following mainly the mechanism proposed by Mac Millan and coworkers,[64] the authors suggested a mechanism for the eosin Y reaction, which is shown in Scheme 32. Initially, a catalytic amount of enamine is oxidized by eosin Y* to generate the radical anion of eosin Y that reduces the halide **79** to give the electron deficient radical species **80**. Addition of radical **80** to the enamine **81** furnishes α-amino radical **82**. Subsequent oxidation of the amino radical **82** to the iminium ion **83** provides the electron for the reductive quenching of eosin Y*. Finally, iminium ion **83** undergoes hydrolysis to afford the desired alkylated product **84**.



Scheme 32 Mechanism for the asymmetric alkylation of aldehydes.

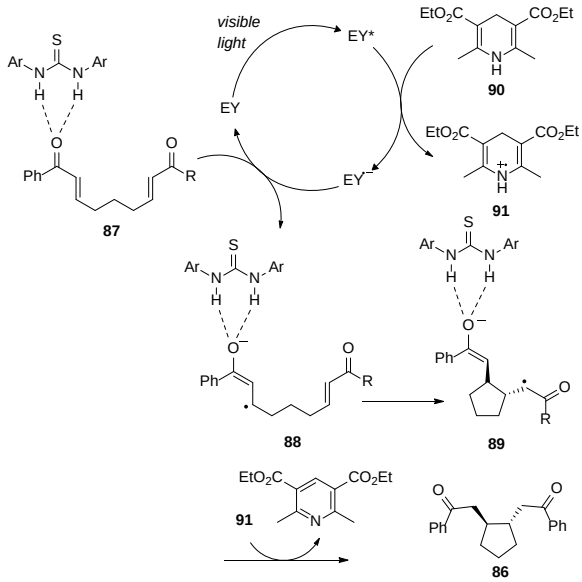
Another dual catalytic mode of hydrogen bond promoted organophotoredox catalysis was applied for highly diastereo-

selctive reductive enone cyclization by Zeitler et al.[65] These reactions proceed smoothly at ambient temperature using Na_2-eosin Y as a photocatalyst and thiourea or α,α,α',α'-tetraphenyl-1,3-di-oxolan-4,5-dimethanol (TADDOL) as organocatalysts (Scheme 33). The combination of Hantzsch ester and diisopropylethyl amine (DIPEA) was found to be a very good reductive quencher as well as hydrogen donor. Aryl bisenones bearing electron donating and electron withdrawing substituents undergo reductive enone cyclization to give the desired trans-cyclopentanes in good yields. However, aliphatic enones are not converted in this reaction due to their more negative potential compared to the eosin Y radical anion. In addition, heterocycles and cyclohexanes were also obtained in good yields, while cycloheptanes were not accessible.



Scheme 33 Reductive enone cyclization using eosin Y.

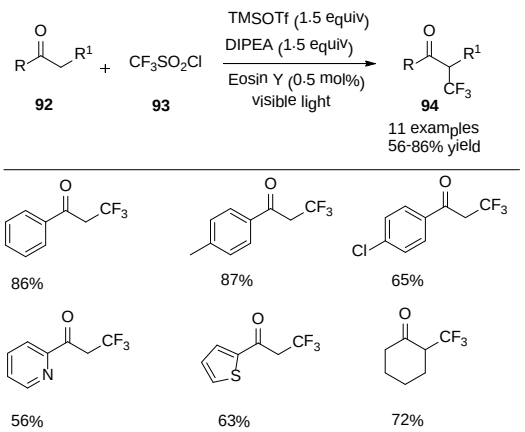
The proposed mechanism of the reaction starts with the reductive quenching of Na_2-eosin Y* by either the Hantzsch ester **90** or DIPEA to generate the radical anion of Na_2-eosin Y and **91** (Scheme 34). Subsequent reduction of **87** by the radical anion of Na_2-eosin Y closes the photocatalytic cycle and yields the 1,4-distonic radical anion **88**, which undergoes a 5-exo-trig cyclization to give α-carbonyl radical **89**. The radical abstracts a hydrogen atom from the radical cation **91** followed by a proton transfer to give the final product **92** and a pyridine derivative. An alternative mechanism is the oxidation of radical **89** followed by hydride transfer to give compound **92**.



Scheme 34 Suggested mechanism for the reductive enone cyclization.

7. Trifluoromethylation

α-Trifluoromethylation of ketones has been reported by Kappe and coworkers using a continuous flow visible light photoredox catalysis with eosin Y (Scheme 35).[24] The reaction proceeds in two steps: in the first step the ketones are converted into their respective silyl enol ethers by reaction with trimethylsilyl trifluoromethanesulfonat (TMSOTf) and DIPEA. The *in situ* formed silyl enol ethers are then converted in a visible light mediated trifluoromethylation process. The two step procedure is faster compared to reported reactions.[66] Several ketones including acetophenones, heteroaromatic ketones, and aliphatic ketones were successfully trifluoromethylated.



Scheme 35 α-Trifluoromethylation of ketones.

8. Conclusions

Visible light photoredox catalysis with metal complexes, such as $Ru(bipy)_3^{2+}$ or $Ir(ppy)_3$, has already received a lot of attention as tool for organic synthetic transformations. For several applications eosin Y serves as an attractive alternative to redox active metal complexes and even outperform them in some cases.[24] Eosin Y photocatalysis has been applied to generate

reactive intermediates including electrophilic α-carbonyl radicals, aryl radicals, iminium ions, trifluoromethyl radicals, and enone radical anions, which are utilized in arene C-H functionalization, [2+2] cyclo addition, amine α-functionalization, hydroxylation, reduction, and oxidation reactions.

In addition, eosin Y catalysis has been merged with other modes of catalysis, such as enamine catalysis and hydrogen bond promoted catalysis to achieve enantioselective reactions. The use of eosin Y photocatalysis in continuous flow technology has been described.[24, 67] Overall, the good availability, strong absorption in the visible part of the spectrum and suitable redox potential values for a variety of organic transformations make eosin Y an appealing and green photocatalyst for organic synthesis.

Acknowledgements

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