The Photoredox Catalyzed Meerwein Arylation

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Dedicated

To

Durgasri & my family

“Nothing is permanent in this wicked world, not even our troubles.”

— Charles Chaplin

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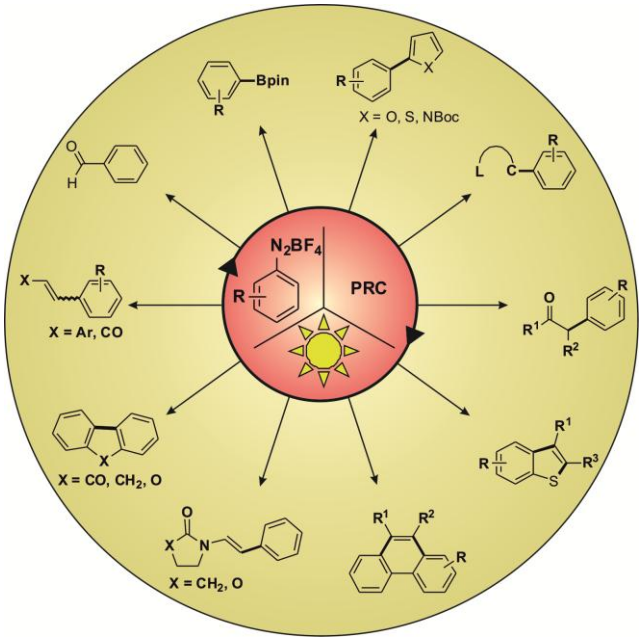
Chapter 1

1 The photocatalyzed Meerwein arylation: classic reaction of aryl diazonium salts in a new light



The use of diazonium salts for aryl radical generation and C-H arylation processes has been known since 1896 when Pschorr first used the reaction for intramolecular cyclizations. Meerwein developed it further in the early 1900s into a general arylation method. However, this reaction could not compete with the transition-metal-mediated formation of $C(sp^2)$-$C(sp^2)$ bonds. The replacement of the copper catalyst with iron and titanium compounds improved the situation, but the use of photocatalysis to induce the one-electron reduction and activation of the diazonium salts is even more advantageous. The first photocatalyzed Pschorr cyclization was published in 1984, and just last year a series of papers described applications of photocatalytic Meerwein arylations leading to aryl-alkene coupling products. In this chapter we summarize the origins of this reaction and its scope and applications.

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1.1 Introduction

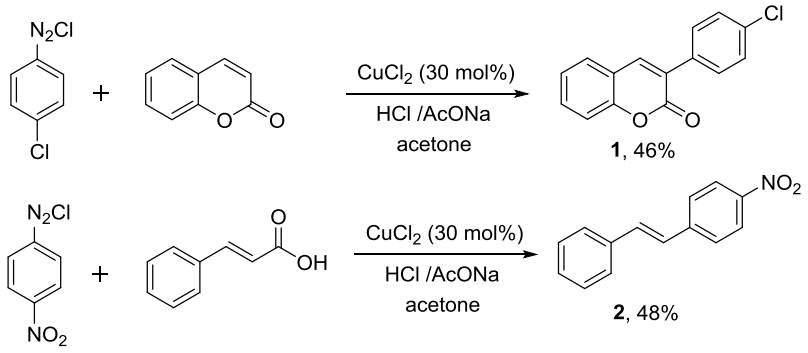
Aryl diazonium salts have, in addition to its classical applications as reagents in aromatic substitutions, always attracted chemists being an important source for aryl radicals[1] and an alternative to aryl halides and triflates in transition metal mediated coupling reactions.[1g,2] Aryl diazonium salts combine several advantages as starting materials in organic synthesis and have been therefore used extensively in preparative chemistry: 1) They are easily prepared in large quantities from aniline derivatives 2) their reactions take place at ambient conditions 3) the leaving group N_2 does not interfere with the reaction mixture and 4) the chemoselectivity of the coupling reactions can be high. Reactions of diazonium salts include either homolytic or heterolytic bond cleavage or the formation of aryne intermediates.[3] Aryl diazonium salts take up an electron from reducing reagents leading to aryl radicals and liberation of dinitrogen.[3a] This aryl radical chemistry is the basis for classic name reactions in organic chemistry: The Sandmeyer reaction, Pschorr cyclization, Gomberg and Bachmann reaction, and the Meerwein arylation.[1d,4] In 1896, Pschorr first reported the synthesis of phenanthrenes from the corresponding aryl diazonium salts and the extension of this reaction was reviewed by Leake and DeTar.[3a,5]

In 1939, Meerwein reported the arylation of olefins by aryl diazonium salts catalyzed by copper (II) salts.[6] The original arylation reaction was limited to alkenes with electron withdrawing groups such as in coumarin, cinnamic or acrylic acid, but its scope later expanded to electron rich olefins (Scheme 1a).[1f,7] An important application of the Meerwein arylation is the decarboxylative cross coupling, but the reaction has not been used frequently in organic synthesis.[8]

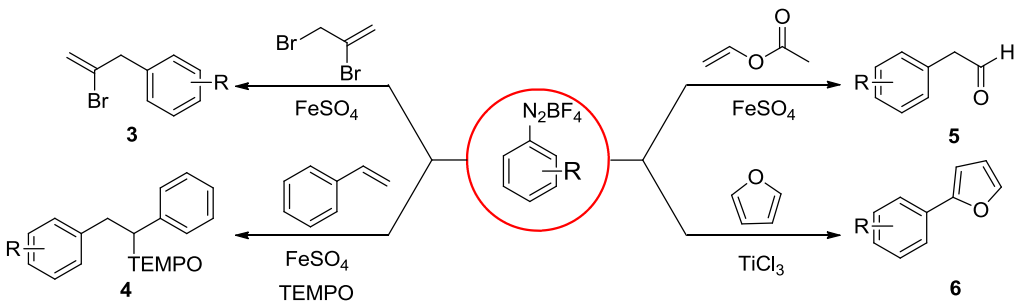
Even though the early Meerwein arylation has disadvantages such as limited substrate scope and many side products, examples giving aryl-alkene coupling serve as the foundation of sp^2-sp^2 cross coupling reactions. Several research groups contributed excellent new and improved variants for the Meerwein arylation and the Pschorr cyclization and their applications to the synthesis of privileged organic molecules. In 1985, Giuseppe Zanardi and his coworkers described the synthesis of benzothiophenes from corresponding *o*-methylthio arenediazonium salts with alkynes through a radical annulations process in the presence of freshly prepared copper powder or NaI or $FeSO_4$.[9] Recently, Heinrich et al. reported Meerwein type arylation reactions using stoichiometric amounts of $TiCl_3$ or $FeSO_4$ as reducing agents (Scheme 1b).[10] Shortly after, Schiesser et al. reported a synthesis of

benzoselenophene and benzothiophene analogues of eprosartan and milfasartan through a cyclization process involving the reaction of *o*-thioalkyl or *o*-selenoalkyl phenyl radicals with alkynes using iron (II) sulfate heptahydrate.[11]

(a) Classic Meerwein arylation reactions yielding aryl-alkene coupling products



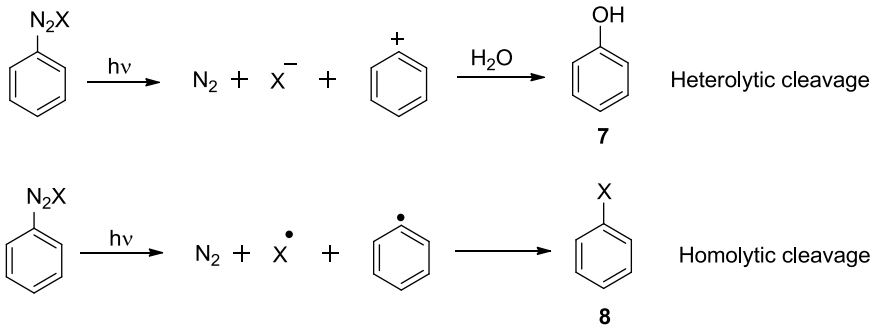
(b) Meerwein type arylation reactions using $TiCl_3$ and $FeSO_4$ as mediators for diazonium salt activation



Scheme 1. Meerwein type arylation cross coupling reactions and improved new variants.

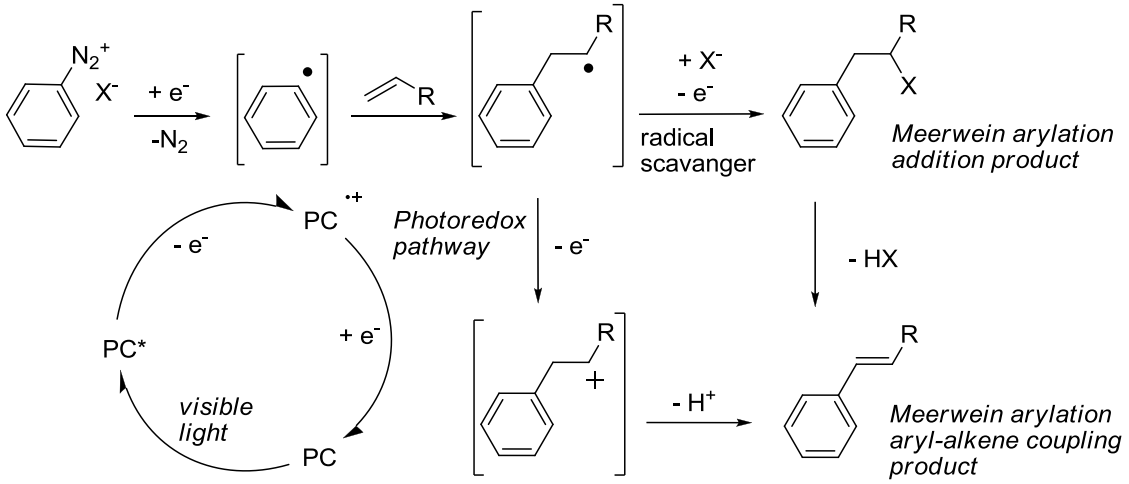
The generation of aryl radicals from diazonium salts requires in the classical protocols a catalytic or stoichiometric amount of a redox active transition metal salt. Visible light can provide the required redox energy as well and has been considered as an ideal reagent for organic synthesis because it is abundant, inexpensive, renewable and innocuous. The photochemistry of diazonium salts has already been studied from the early 19th century by noticing the change of the colour of benzenediazonium turning to red on exposure to sunlight.[12] The principle of photodecomposition of diazonium salts by loosing nitrogen on exposure to light has been utilized in industrial techniques such as processes for printing on silk or cotton, diazo copying, and photolithography, but photochemical reactions of diazonium salts and related systems have been explored only since 1959.[3a,12] Typical aryl diazonium salts ($ArN_2^+X^-$) absorb in the ultraviolet region of light. Direct photolysis of diazonium salts in aqueous solution leads to phenol **7** as the main product of a heterolytic

bond cleavage (Scheme 2). In addition to the photolytic hydro-dediazotization product the replacement of the diazo group by anions X^- is observed giving the homolytic Schiemann reaction product **8** (Scheme 2).[13] Solvents, counter ion, nucleophilic additives, and reducing agents are the important factors, which influence the cleavage of diazonium group either in homolytic or in heterolytic fashion.[3a,14]



Scheme 2. Direct photolysis of diazonium salts.

However, the inability of most aryl diazonium salts to absorb visible light has limited the number of photochemical applications of aryl diazonium salts to organic synthesis. Recently, many groups have utilized visible light absorbing photoredox catalysts to sensitize organic molecules by electron or energy transfer processes.[15] We will discuss in the following the photoredox chemistry of aryl diazonium salts using visible light and cover pioneering examples from the 20th century as well as the recent reports to summarize this fast developing area of research. So far, the photoredox versions of the Meerwein arylation led exclusively to the formation of cross coupling products and the valuable alkene addition products that can be obtained under classic Meerwein arylation conditions have not been reported.



Scheme 3. Reaction pathways of the Meerwein arylation addition and cross coupling and photoredox reactions.

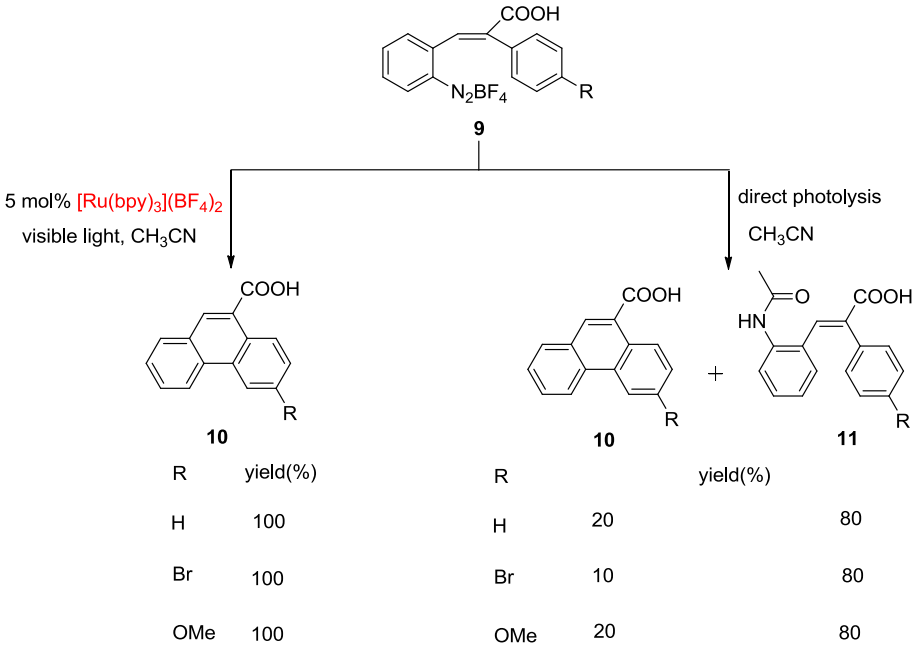
Scheme 3 summarises the different pathways: Electron transfer, either from the chemical reductant or the photocatalysts to the diazonium cation yields the aryl radical, which adds to a double bond. Scavenging of the alkyl radical give Meerwein alkene addition products that may eliminate HX yielding the unsaturated cross coupling products. Oxidation of the alkyl radical regenerating the photoredox catalyst yields a carbenium ion, which eliminates a proton giving the cross coupled compounds.

1.2 Aryl diazonium salts in visible light

In 1984, Cano-Yelo and Deronzier reported the photocatalyzed Pschorr reaction using $[Ru(bpy)_3]^{2+}$ as photoredox catalyst under irradiation with blue light.[16] The Pschorr reaction typically involves the reduction of diazonium salts followed by an intramolecular cyclization. The authors synthesized phenanthrene carboxylic acid **10** quantitatively from the corresponding stilbene diazonium salt **9** in acetonitrile under visible light irradiation (Scheme 4). Noteworthy, the direct photolysis ($\lambda > 360$ nm) of diazonium salts in the absence of the photocatalyst provided the corresponding acetamide **11** as the major product and phenanthrene only as minor product (Scheme 4a).

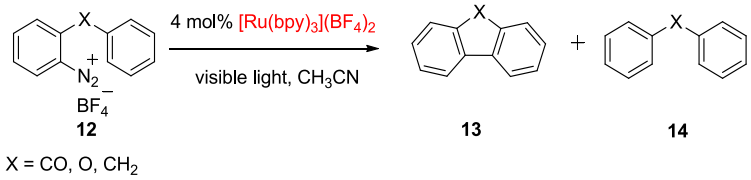
Following their success in photocatalytic Pschorr reaction, Cano-Yelo and Deronzier further extended their methodology to synthesize fluorenone, fluorene and dibenzofuran from the corresponding diazonium salts (Scheme 4b).[17] Visible light ($\lambda > 410$ nm) irradiation of $[Ru(bpy)_3]^{2+}$ and aryl diazonium salt **12** in dry CH_3CN gave mainly the non-cyclized product **14** (75-100%) and only small amounts of the cyclized product **13** (0-25%). The low reaction yield of cyclized product **13** in this reaction compare to the previously reported Pschorr reaction of stilbene diazonium salts was attributed by the authors to the less rigid structure of **12** and smaller gain in aromatic stabilization energy of compound **13** compared to compound **10**. To accelerate the slow photoreaction, 0.5 equivalents of 4-methoxy benzyl alcohol and collidine were added to the reaction mixture. The product distribution does not improve, but the reaction times are significantly shorter.

(a) Photocatalytic Pschorr reaction with $[Ru(bpy)_3]^{2+}$ and direct photolysis in absence of $[Ru(bpy)_3]^{2+}$



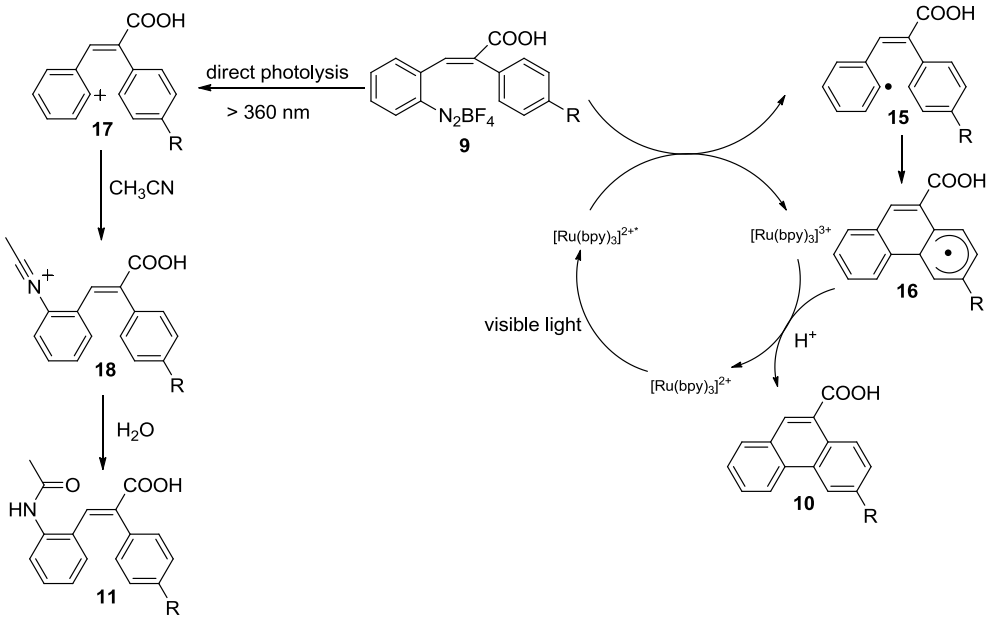
R	yield(%)	R	yield(%)	
H	100	H	20	80
Br	100	Br	10	80
OMe	100	OMe	20	80

(b) Photocatalytic Pschorr reaction for synthesis of fluorenone, fluorene and dibenzofuran



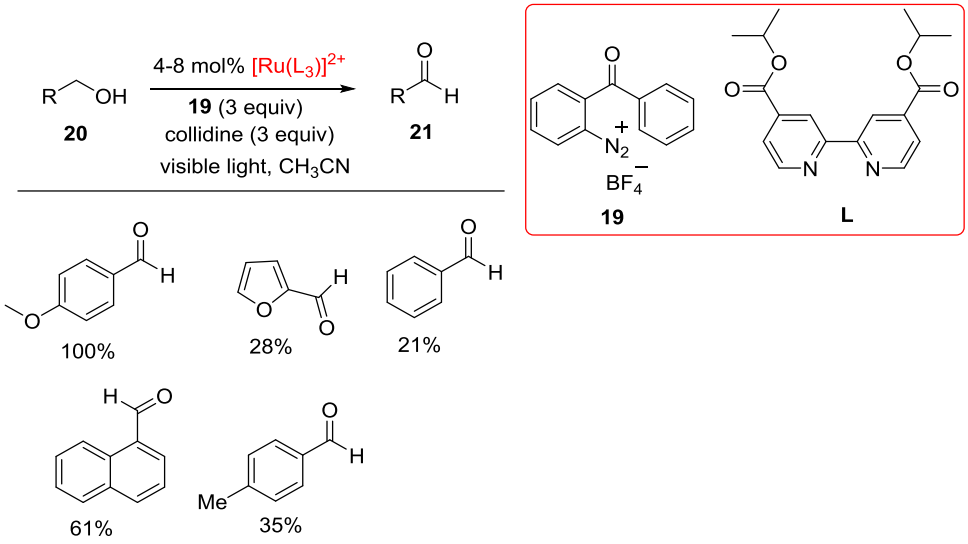
Scheme 4. Photocatalytic Pschorr reactions.

The proposed mechanism shown in Scheme 5 starts with the oxidative quenching of the excited state of $[Ru(bpy)_3]^{2+*}$ by the aryl diazonium salt **9** generating aryl radical **15** and the strong oxidant $[Ru(bpy)_3]^{3+}$. Intramolecular cyclization of **15** furnishes radical **16**, which is then oxidized by $[Ru(bpy)_3]^{3+}$ and undergoes subsequent deprotonation to give compound **10** and regenerate the photocatalyst. Direct photolysis of aryldiazonium salt **9** produces the corresponding aryl cation **17**, which further reacts with the solvent CH_3CN to give the aryl cation adduct **18**. The hydrolysis of the intermediate aryl cation **18** produces acetamide **11**. The authors also provided an indirect proof of the electron transfer mechanism by quenching experiments.[16,18] Irradiation of 4-bromobenzene diazonium salt and $[Ru(bpy)_3]^{2+}$ in dry CH_3CN generates $[Ru(bpy)_3]^{3+}$, which is verified by its characteristic absorption in the spectra evolving during photolysis. The back electron transfer from the diazonium salt to $[Ru(bpy)_3]^{3+}$ is suppressed by the fast, irreversible decomposition of diazonium salt.



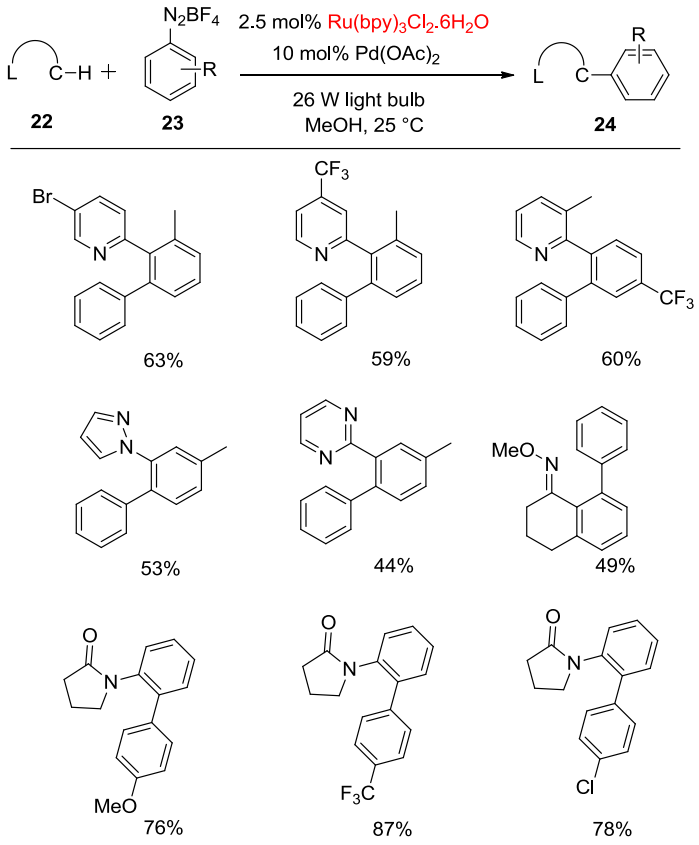
Scheme 5. Proposed mechanism for photocatalytic Pschorr reaction and direct photolysis.

Later, Cano-Yelo and Deronzier reported the oxidation of carbinols to aldehydes using aryl diazonium salts as oxidative quenchers.[19] Blue light irradiation of a mixture of carbinols **20**, the ruthenium complex, aryl diazonium salt **19**, and 2, 4, 6 trimethylpyridine (collidine) in dry CH_3CN provided the corresponding aldehyde **21** in moderate to good yields (Scheme 6). The aryl radical of **19** undergoes intramolecular cyclization to provide fluorenone (like in the Pschorr reaction) or the aryl radical of **19** abstracts a hydrogen atom from the benzylic position of the carbinol giving benzophenone. Benzophenone and fluorenone were observed as byproducts in the ratio of 3:1.The reaction yields were improved by adding a base in case of easily oxidizable carbinols, but lower yields were observed with less oxidizable carbinols. The lower yields with carbinols having higher oxidation potentials are explained by the oxidation of the base by the ruthenium complex. The same authors reported the oxidation of phenylated primary and secondary alcohols to the corresponding carbonyl derivatives in the presence of aryl diazonium salts and a basic agent in MeCN and compared the results with electrochemical redox catalysis.[20] They propose a mechanism involving the oxidative quenching of the excited state of $[Ru(L_3)]^{2+*}$ by the aryl diazonium salt leading to $[Ru(L_3)]^{3+}$. A single electron transfer from carbinols to $Ru(L_3)]^{3+}$ regenerates the catalytic cycle while producing the aldehyde. The photoreaction is significantly improved by adding collidine, because the oxidation of carbinols to the aldehyde requires two-electron and two-proton exchanges.



Scheme 6. Oxidation of carbinols to aldehydes by photoredox catalysis.

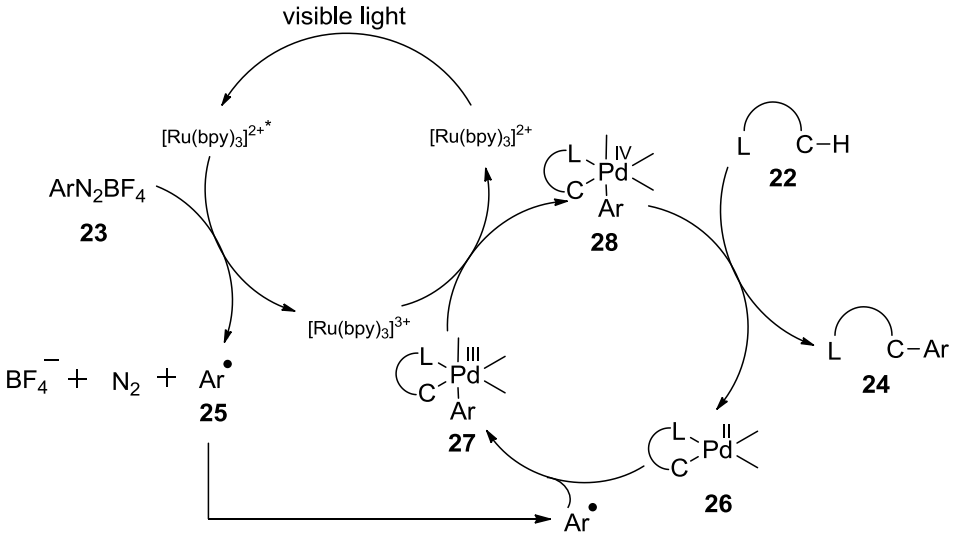
25 years after the first application of photoredox catalysis with diazonium salts from Cano-Yelo and Deronzier, Sanford and coworkers utilized the aryl radical for ligand-directed C-H arylation reactions with aryl diazonium salts by combining palladium catalysis with photoredox catalysis.[21]



Scheme 7. Ligand directed C-H arylation at room temperature by dual catalysis.

Blue light irradiation of diazonium salt **23**, substrate **22**, $Pd(OAc)_2$, and $Ru(bpy)_3Cl_2.6H_2O$ in MeOH at room temperature afforded the corresponding products in good to excellent yields (Scheme 7). Addition of the aryl radical to the Pd species is very fast, that is why MeOH can be used as the solvent. Advantages of this strategy are mild reaction conditions, broad scope of aryl diazonium salts, and tolerance to a wide range of functional groups. Amides, pyrazoles, pyrimidines, and oxime ethers are suitable directing groups for this photoreaction.

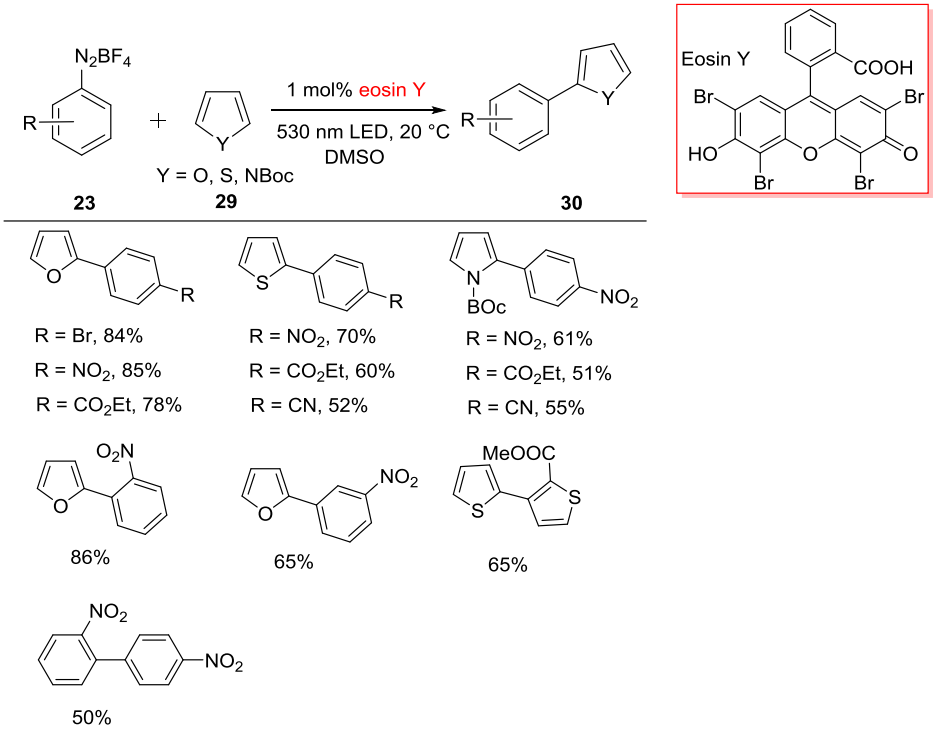
The proposed mechanism of the reaction starts with a single electron transfer to aryl diazonium salts **23** from the excited state of $[Ru(bpy)_3]^{2*}$, giving an aryl radical and $[Ru(bpy)_3]^{3+}$. Addition of the aryl radical **25** to the palladacycle **26**, which is generated by C-H activation of the substrate, affords the Pd^{III} intermediate **27**. A single electron oxidation of the Pd^{III} intermediate **27** by $[Ru(bpy)_3]^{3+}$ regenerates the photocatalyst while producing the Pd^{IV} intermediate **28**, which then undergoes reductive elimination to give the arylated product **24** and Pd^{II} catalyst **26** (Scheme 8).



Scheme 8. Proposed mechanism for the arylation by Pd/Ru catalysis.

Our group recently developed a method for the direct C-H arylation of heteroarenes with aryl diazonium salts using an organic dye eosin Y as photoredox catalyst in green light irradiation.[22] The reaction requires, compare to other C-H arylation methods, no metal catalyst, works at ambient temperature, and has a high functional group tolerance. Aryl diazonium salts bearing both electron-neutral or -withdrawing groups and a variety of heterocyclic compounds were shown to be efficient substrates for this photoreaction (Scheme 9). The methodology was applied to construct dithiophenes, which have found applications in material chemistry. Control experiments in the absence of catalyst or light confirmed the

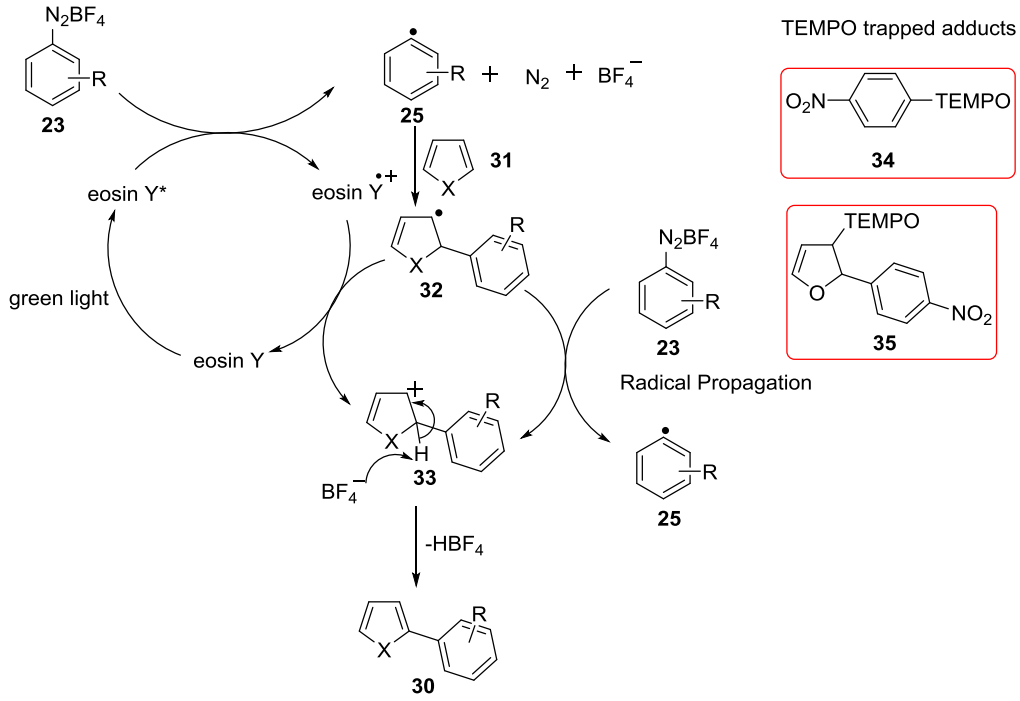
photocatalytic nature of the reaction. In addition to heteroarenes, nitrobenzene was subjected to the photoreaction conditions giving the expected cross coupling products in 50% yield.



Scheme 9. Direct C-H arylation of heteroarenes with eosin Y as the photoredox catalyst.

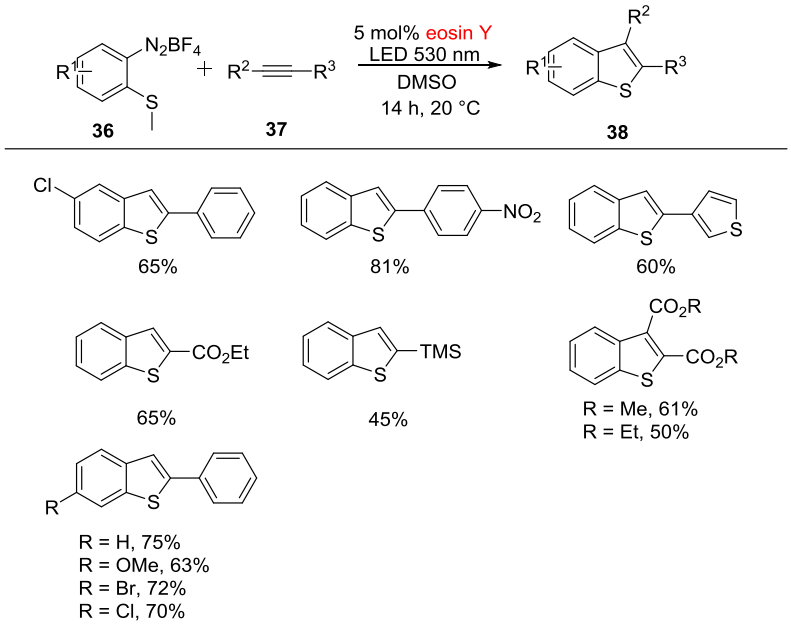
The suggested mechanism of the direct C-H arylation of heteroarenes is depicted in Scheme 10. First, green light irradiation of eosin Y initiates a single electron transfer to aryldiazonium salt **23** to produce aryl radical **25** and the cation radical of eosin Y. Then the aryl radical **25** adds to the heteroarene **31** to give the radical intermediate **32**, which then further oxidized either by the eosin Y cation radical to produce carbocation intermediate **33** and closing the catalytic cycle or it is oxidized by aryl diazonium salt **23** in a radical chain transfer mechanism. Finally, the carbocation intermediate **33** is deprotonated yielding product **30**. The authors were able to trap the radical intermediates **25** and **32** with TEMPO supporting the presence of radical intermediates during the photoreaction.

Next the photocatalyzed arylation reactions of heteroarenes were applied to synthesize privileged benzothiophene moieties, but unfortunately only poor yields and regioisomeric product mixtures were observed. The recently reported photocatalytic synthesis of benzothiophenes through a radical annulation process using eosin Y as photoredox catalyst in green light overcomes the problem.[23]



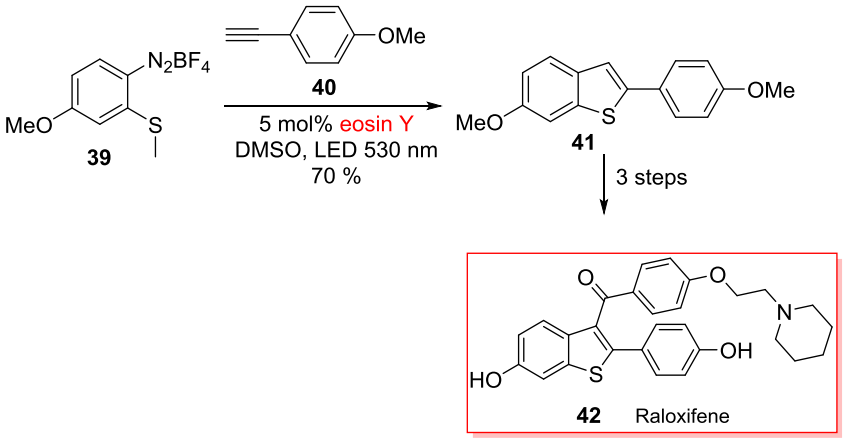
Scheme 10. Suggested mechanism for photocatalytic C-H arylation of heteroarenes.

A mixture of *o*-methylthio benzenediazonium salt **36**, alkyne **37** in dry DMSO is subjected to irradiation at 530 nm for 14 h providing only the required regioisomer in moderate to good yields (Scheme 11). Diazonium salts containing either electron donating or electron neutral substituents are compatible with this photoreaction. The annulations reaction proceeds well with different alkynes.

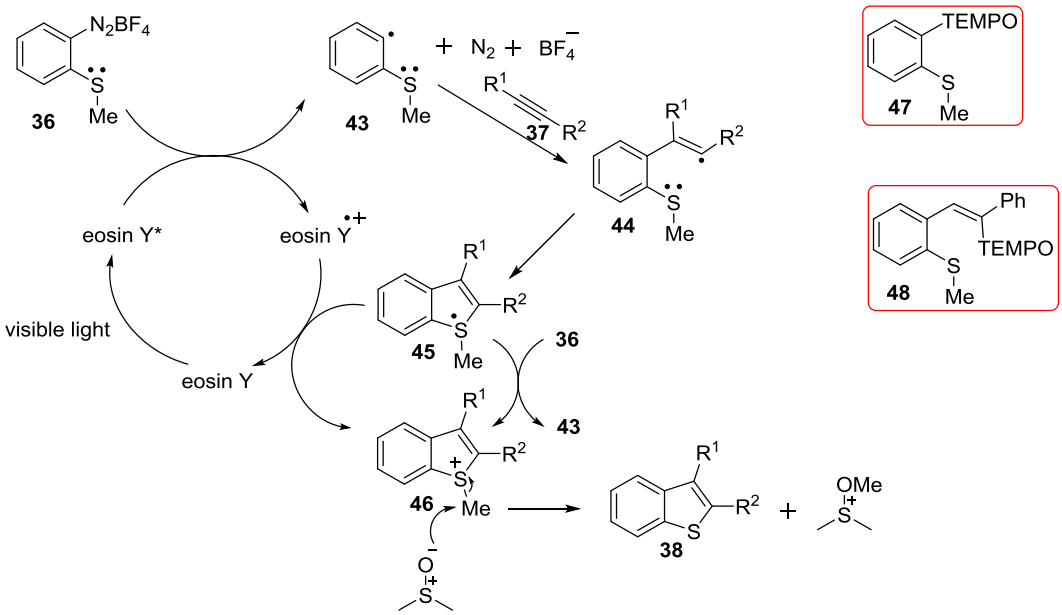


Scheme 11. Radical annulations for the synthesis of benzothiophenes by visible light photocatalysis using eosin Y.

The photoannulation reaction was used to prepare the key intermediate **41** in the synthesis of the commercialized drug Raloxifene **42**. A mixture of 4-methoxy-2-(methylthio)benzene-diazonium salt **39** and 1-ethynyl-4-methoxybenzene **40** in dry DMSO was subjected to the standard photoreaction conditions providing the Raloxifene intermediate **41** in 70% yield (Scheme 12).



Scheme 12. Visible light photocatalyzed preparation of a key intermediate of synthesis of the antiulcer drug Raloxifene.

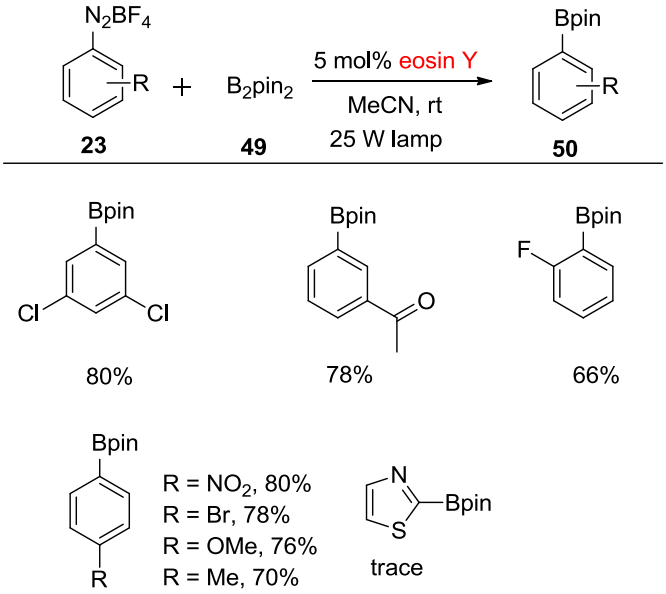


Scheme 13. Proposed mechanism for the photoannulation reaction.

The proposed mechanism of the photoannulation reaction starts with a single electron transfer (SET) from the excited state of eosin Y to *o*-methylthio benzenediazonium salt **36** to generate aryl radical **43** and the radical cation of eosin Y. The highly reactive aryl radical **43** adds to alkyne **37** to produce a vinyl radical intermediate **44**, which then undergoes homolytic

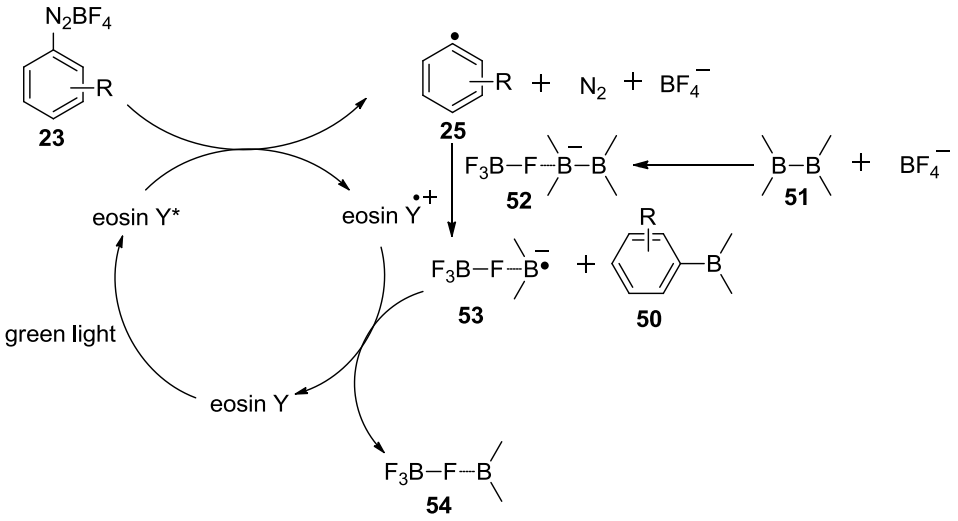
substitution at the sulfur atom to give the sulphuranyl radical intermediate **45**. Oxidation of intermediate **45** by the eosin Y cation radical regenerates the photocatalyst while affording the cation **46**. Noteworthy, oxidation of the intermediate **45** could also proceed with diazonium salts in a chain transfer mechanism. Finally, cation **46** transfers a methyl group to the solvent DMSO by an S_N2 process to afford product **38**. TEMPO trapped adducts **47** and **48** suggest the likely presence of radical intermediates in the reaction mechanism (Scheme 13).

All of the examples discussed so far address C-C bond forming reactions utilizing oxidative quenching of the photocatalysts. Very recently, Guobing Yan and coworkers reported C-B borylation reactions *via* photoredox catalysis under visible light irradiation with eosin Y.[24] The authors investigated the scope of the photoreaction by employing different diazonium salts. It was found that aryl diazonium salts bearing various electron-donating and withdrawing substituents smoothly gave the corresponding borylated products in moderate to good yields (Scheme 14). The borylation with heteroaromatic diazonium salts does not proceed as well compared to the aryl diazonium salts.



Scheme 14. Borylation of aryldiazonium salts via photoredox catalysis.

The authors proposed a reaction mechanism depicted in Scheme 15. After visible light excitation of eosin Y a single electron transfer to diazonium salt **23** gives aryl radical **25**. The aryl radical adds to complex **52,** which is formed *in situ* by the interaction between B_2pin_2 and the tetrafluoroborate anion, to afford the radical anion intermediate **53** and the borylated product **50**. Oxidation of the reaction intermediate **53** by the eosin Y cation radical closes the catalytic cycle.

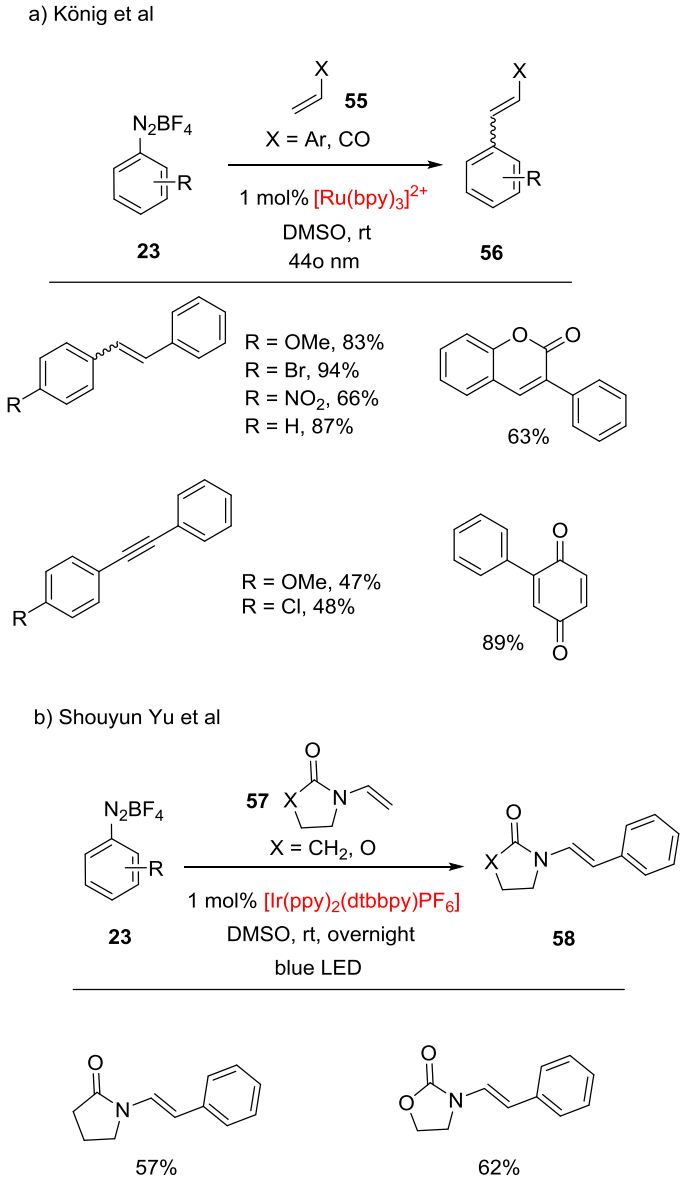


Scheme 15. Proposed mechanism for the borylation of aryl diazonium salts.

The Meerwein arylation protocol has been used to arylate various unsaturated compounds with metallic copper, iron (II), and iodine, but earlier reaction conditions suffered from low yields and side products. These drawbacks prevented the broader application of the Meerwein arylation reaction in organic synthesis. Improved reaction conditions, such as the use of chloride based ionic liquids as promoting agents allowed Meerwein arylations in satisfactory yields.[25] The recently reported photocatalytic version of the intermolecular Meerwein reaction for the arylation of alkenes, alkynes and enones with aryl diazonium salts using $[Ru(bpy)_3]^{2+}$ or eosin Y as photoredox catalysts further improves the process.[26] Photocatalyst and light were found to be essential for the useful conversion to the arylated products. A mixture of aryl diazonium salt **23**, unsaturated compound **55**, and the photocatalyst in dry DMSO was irradiated by blue light for 2 h yielding the corresponding coupling products in good to excellent yields. Halogen substituted diazonium salts have been employed in the photoreaction leaving the carbon-halogen bond intact and allowing further functionalization of the cross coupling products by transition metal catalyzed or organometallic transformations. However, the reaction is limited to activated unsaturated compounds including coumarins, styrenes, quinones, and phenyl acetylenes (Scheme 16a).

Shortly after, the Shouyun Yu group extended the photo Meerwein arylation to enamides and enecarbamates using aryl diazonium salts in blue light.[27] The photocatalysts $[Ir(ppy)_2(dtbbpy)PF_6]$ (1 mol%), aryl diazonium salt **23** and substrate **57** were irradiated overnight by visible light with a 3 W blue LED strip to afford the corresponding products in moderate to good yields (Scheme 16b). The mechanism of the photoreaction is initiated by oxidative quenching of photocatalyst by the aryl daizonium salt to form aryl radical. The

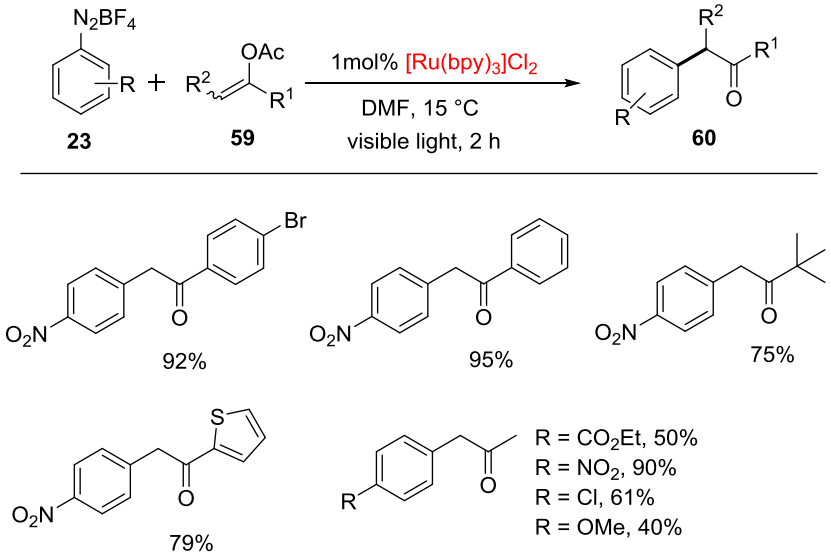
generated aryl radical adds to the unsaturated compound to give a radical intermediate, which then undergoes oxidation, followed by deprotonation yielding the desired product.



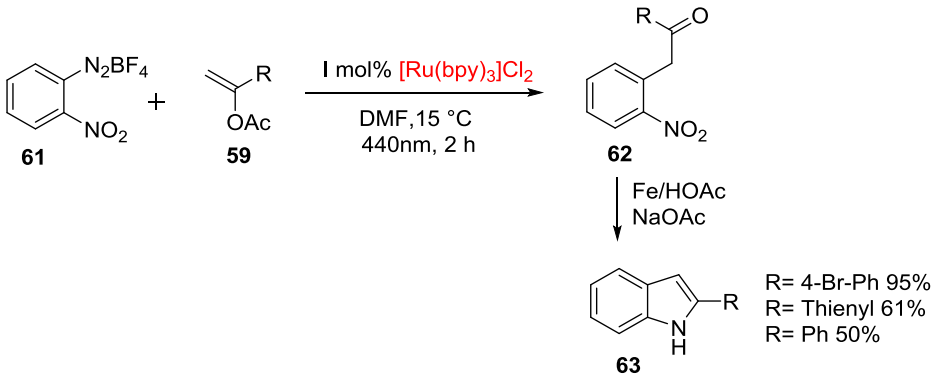
Scheme 16. Photo-Meerwein arylation of unsaturated compounds.

α-Aryl carbonyl compounds are important substructures of pharmaceutical and biological active molecules. Typical synthetic routes include transition metal and base catalyzed[28] steps, but an alternative approach is the use of photoredox catalysis utilizing aryl diazonium salts as radical source and enol acetates as coupling partners (Scheme 17).[29] Different photoredox catalysts and solvents were screened; the reaction proceeds best in DMF and DMSO with $[Ru(bpy)_2]Cl_2$ as the photocatalyst. The scope of the reaction was investigated for diazonium salts and enol acetates: Aryl diazonium salts containing electron withdrawing or, neutral groups and terminal enol acetates are suitable substrates. A synthetic application of the

photoredox catalysis was demonstrated, the preparation of compound **62**, which is reduced by iron to give the corresponding substituted indoles **63** in good to excellent yields without isolation of intermediates (Scheme 18).[30]

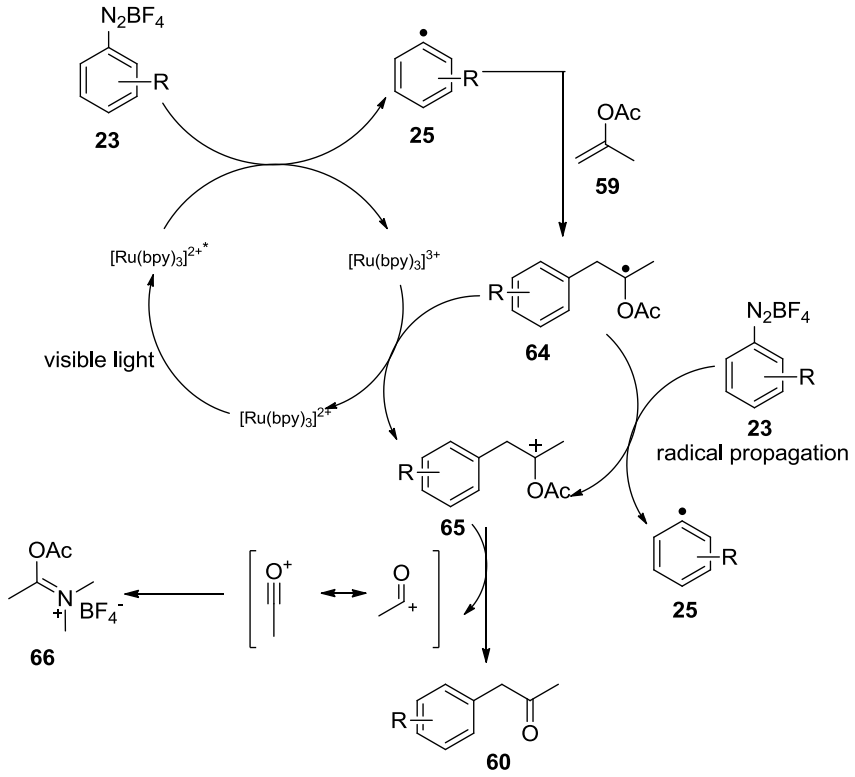


Scheme 17. α-Arylation of enol acetates by photoredox catalysis.



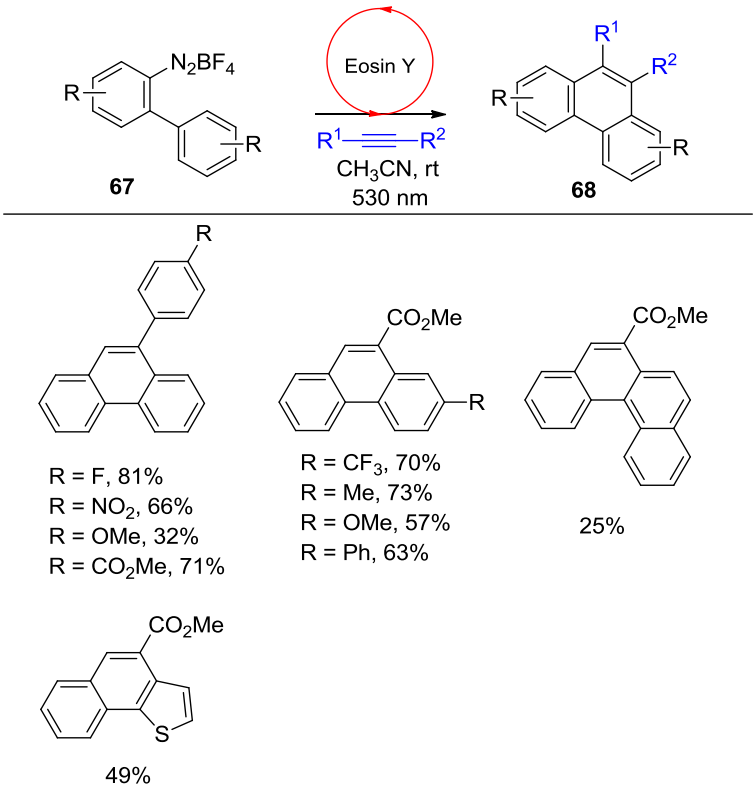
Scheme 18. Synthesis of substituted indols precursors by photoredox catalysis.

Similar to the previously discussed mechanisms the oxidative quenching of $[Ru(bpy)_3]^{2*}$ by aryl diazonium salt **23** gives aryl radical **25** and the strong oxidant $[Ru(bpy)_3]^{3+}$. An addition of the aryl radical to enol acetate **59** generates radical intermediate **64**. Re-oxidation of the intermediate **64** by the oxidant $[Ru(bpy)_3]^{3+}$ forms a carbocation intermediate **65** and regenerates the catalyst $[Ru(bpy)_3]^{2}$. The desired product **60** is obtained by transfer of an acyl cation from the intermediate carbocation **65** to a nucleophile present in the reaction mixture such as DMF giving the stable salt **66**, which is one of the likely intermediates in the first step of the Vilsmeier-Haack reaction. However, alternative pathways for the oxidation of the radical intermediate **64** by aryl diazonium salts cannot be excluded at this time (Scheme 19).



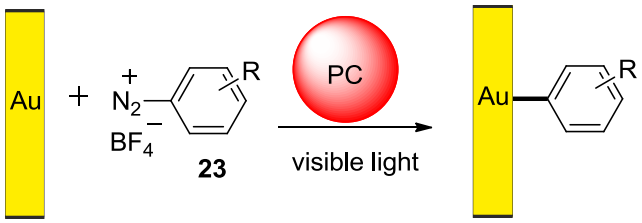
Scheme 19. Proposed mechanism for α-arylation of enol acetates with aryl diazonium salts in visible light.

A common synthetic approach to phenanthrenes is the photocyclization of stilbenes by UV light irradiation followed by oxidation. Lei Zhou and coworkers recently reported the synthesis of phenanthrenes from diazonium salts and alkynes using visible light and the organic dye eosin Y as photoredox catalyst.[31] Irradiation of mixtures of biphenyl diazonium salt **67**, 10 equiv of alkyne and 1 mol% eosin Y in CH_3CN under green light for 12 h afforded the corresponding products **68** in good to excellent yields (Scheme 20). It is important to note that the addition of base to the reaction mixture causes a decrease in the yield, presumably due to the direct reaction between the base and the diazonium salt. The photoreaction proceeds smoothly with a series of diazonium salts and alkynes. A range of functional groups including ketones, nitro, methoxy, halogen and ester groups do not interfere with this photoreaction. A SET from eosin Y* to the biaryl diazonium salt produces a biaryl radical. The generated radical adds to the alkyne to form a vinyl radical intermediate followed by intramolecular addition to the aromatic ring yielding the cyclic radical intermediate, which then further undergoes oxidation followed by deprotonation to give the final product.



Scheme 20. Visible light induced synthesis of phenanthrenes.

Functionalization of surfaces has found many applications from analytical and biochemical sensors to microelectronics and biomedical industrial applications. UV photochemical methods have been used for grafting of surfaces, but they are mainly restricted to alkenes and arylazides. Recently, Jean Pinson et al. described a photochemical method for gold surface modification with diazonium salts in visible light using either $[Ru(bpy)_3]^2$ or eosin Y as photo sensitizers (Scheme 21).[32]



Scheme 21. Functionalization of surface with diazonium salts via photoredox catalysis.

In addition to diazonium salts, aryl sulfonyl chlorides and aryl iodonium salts can also be used as aryl radical source in visible light catalysis. Recently, Li and co-workers reported the synthesis of functionalized indenes from aryl alkynes and arylsulfonyl chlorides through photoredox catalysis[33]. Sanford et al. developed a C-H arylation method with diaryliodonium reagents merging photoredox and transition metal catalysis.[34]

1.3 Conclusion

Visible-light photoredox catalysis utilizing diazonium salts as aryl radical source has become a powerful and efficient method in synthetic organic chemistry to form carbon-carbon and carbon-heteroatom bonds. The oxidative quenching of photocatalysts by diazonium salts allows for inter- and intramolecular cyclization reactions with regioselective formation of products and the method has already been applied to the synthesis of biologically active compounds and drug intermediates. Although the photocatalytic versions of the classic Meerwein arylation protocol gave so far only access to cross coupling and not to alkene addition products, the method significantly improves applications in organic synthesis. Despite excellent progress has been made in the area, many challenges and opportunities still remain.

Photocatalysis allows reactions at low temperatures, which may be beneficial for the development of stereoselective variants in particular if the scope is expanded to Meerwein alkene addition products. Aryl radical chemistry in combination with visible photocatalysis has not been broadly applied to carbonylation reactions, although two out of three industrial processes use aryldiazonium salts in carbonylation processes.[2b,35] While there is already good evidence for some of the radical intermediates, a more detailed mechanistic investigation is highly desirable to improve our understanding of the mechanisms and allow for a better design of new photocatalytic reactions of diazonium salts.

1.4 References

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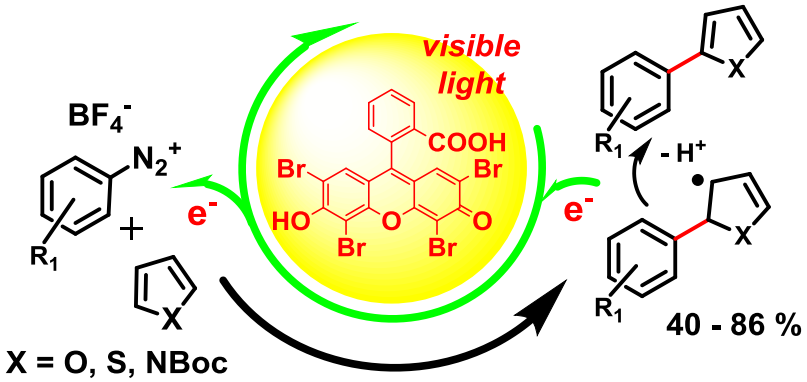
Chapter 2

2 Metal-Free, Visible-Light-Mediated Direct C–H Arylation of Heteroarenes with Aryl Diazonium Salts



Visible light and 1 mol% of eosin Y catalyzes the direct C-H bond arylation of heteroarenes with aryl diazonium salts by a photoredox process. We have investigated the scope of the reaction for several aryl diazonium salts and heteroarenes. The general and easy procedure provides a transition metal free alternative for the formation of aryl-heteroaryl bonds.

This chapter has been published:
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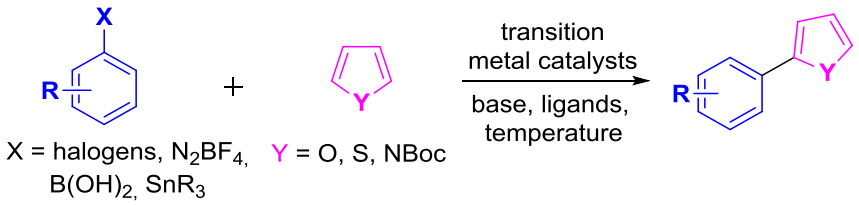
Author contributions:
DP carried out all the photoreactions and wrote the manuscript; PS prepared the diazonium salts in Table 2.

2.1 Introduction

Arylated heteroarenes are widely used in material science due to their interesting optical and electronic properties,[1] but they also find biomedical applications as peptide mimetic[2] or drugs.[3] The most efficient synthesis of aryl-aryl bonds is the direct arylation of heteroarenes by C-H bond activation. In contrast to the well-known cross-coupling reactions, such C-H activation methods do not require preactivation of the heteroarene and a variety of transition metal catalyzed processes using aryl halides, arylboronic acids, aryl tin reagents, and diazonium salts as coupling partners (Figure 1) have been developed.[4] However, photo-catalysis may provide a valuable alternative avoiding transition metals, ligands, base, or elevated temperatures. Recent reports have demonstrated the formation of C-C,[5] C-P,[5m,6] and C-N[7] bonds using visible light and ruthenium or iridium complexes or organic dyes as photoredox catalysts.

Metal-catalyzed direct C-H arylation of heteroarenes



Eosin Y catalyzed direct C-H arylation of heteroarenes (this work)

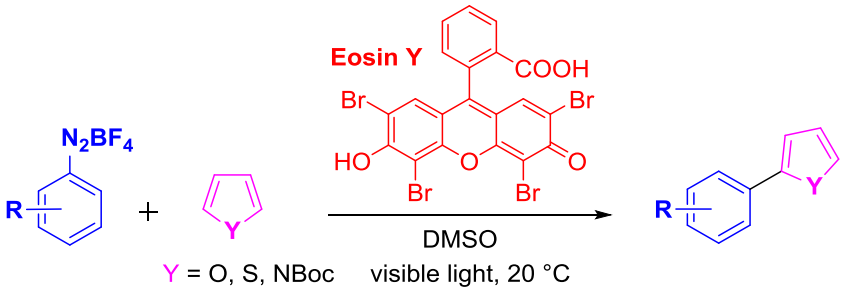


Figure 1. Metal-catalyzed and photocatalytic approaches for direct C-H arylation of heteroarenes.

Aryl diazonium salts are an excellent source of aryl radicals due to their relatively high reduction potential.[8] The long known Meerwein arylation uses this in a copper mediated redox process for the coupling of aryl diazonium salts to alkenes or heteroarenes. However, the reaction suffers from low yields typically in the range of 20-40%, high catalyst loadings

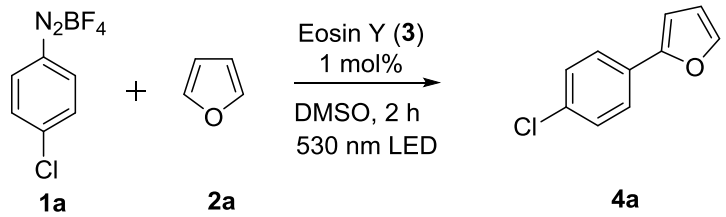
and restriction to aqueous reaction media. The Meerwein arylation has therefore not widely been used in synthesis.[9] Heinrich *et al*. reported the direct arylation of phenols, anilines, and furans with aryl diazonium salts using $TiCl_3$ catalysis; the reaction possibly proceeds through a radical mechanism.[10] Recently, Sanford *et al*. merged palladium catalysis with photocatalysis for C-H arylation.[11] Aryl diazonium salts are well known oxidative quenchers in photoredox chemistry,[5k,12] which was first applied by Cano-Yelo *et al*. in the visible light mediated Pschorr cyclization converting stilbene diazonium salts into the corresponding phenanthrene derivatives with $[Ru(bpy)_3]^{2+}$ as photoredox catalyst.[13] The same authors also used a ruthenium complex in an oxidative quenching cycle for the transformation of benzyl alcohol to aldehyde with aryl diazonium salts as oxidative quenchers.[14] We report now the photocatalyzed single electron transfer mediated direct C-H bond arylation of heteroarenes with aryl diazonium salts requiring only green light and the organic dye eosin Y as catalyst.

2.2 Results and Discussion

First, the reaction conditions were optimized for the direct arylation of furan **2a** with diazonium salt **1a,** 530 nm LED irradiation and 1 mol% eosin Y as photoredox catalyst. Various solvents, additives, and different equivalents of furan were examined at room temperature and the desired product was obtained in all cases. DMSO was found to be a good solvent for the photoreaction. The arylated product was obtained in good yield using an excess of 10 equivalents of furan (Table 1, entry 2). Excess of base decreased the product yields (Table 1, entries 10, 11, and 12), which was attributed to direct reaction of the base with **1a**. Control reactions confirmed that both light and eosin Y are required for a significant conversion to the product (Table 1, entries 13 and 14).

Having optimized the reaction conditions, we examined the scope of the reaction towards different aryl diazonium salts with furan. Among the aryl diazonium salts used for direct arylation of furan, electron-acceptor (Table 2, entries 2, 3, 4, 5, and 6) and neutral (Table 2, entries 1 and 7) substituted salts were found to be more efficient for product formation than donor substituted diazonium salts (Table 2, entries 8, 9, and 10). Moreover, a range of functional groups, such as nitro, ester, cyano, and hydroxyl groups were tolerated in this photoreaction. Notably, halogen-substituted aryl diazonium salts underwent successfully C-H bond arylation leaving the C-halogen bond intact, which is useful for further synthetic elaboration.

Table 1. Optimization of the reaction conditions**.**



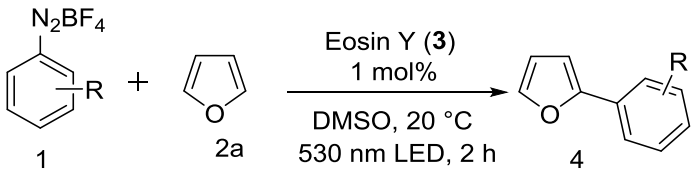
Entry	Conditions	Yield [%][a]
1	**2a** (5 equiv), DMSO	73
2	**2a** (10 equiv), DMSO	80
3	**2a** (15 equiv), DMSO	80
4	**2a** (10 equiv), DMF	48
5	**2a** (10 equiv), MeOH	55
6	**2a** (10 equiv), CH_3CN	12
7	**2a** (10 equiv), EtOAc	17
8	**2a** (10 equiv), THF	10
9	**2a** (10 equiv), DMSO/H_2O (3:1)	73
10	**2a** (10 equiv), DMSO, pyridine (2 equiv)	66
11	**2a** (10 equiv), DMSO, NaOAc (2 equiv)	54
12	**2a** (10 equiv), DMSO, ^{t}BuOK (2 equiv)	45
13	**2a** (10 equiv), DMSO, no light, 72 h	14
14	**2a** (10 equiv), DMSO, no catalyst, 72 h	19

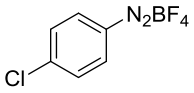
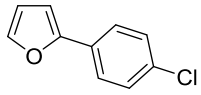
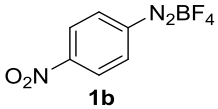
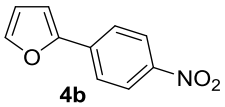
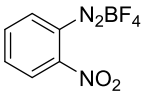
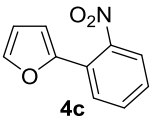
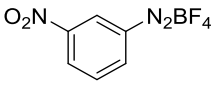
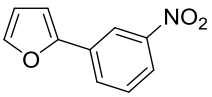
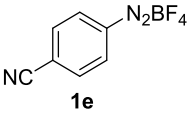
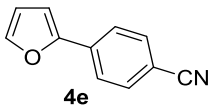
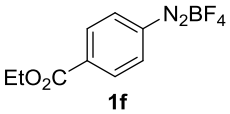
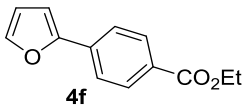
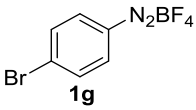
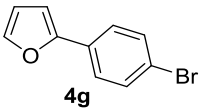
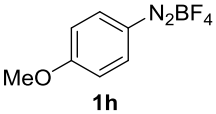
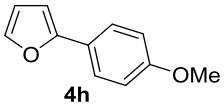
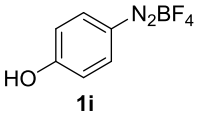
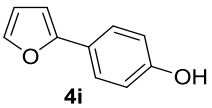
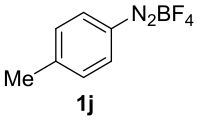
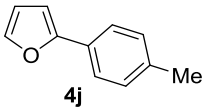
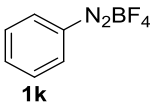
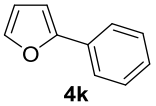
[a]Yieds were determined by 1H NMR.

The metal free, photocatalyzed C-H arylation was also effective for other heteroarenes, such as thiophene and pyrrole and the corresponding products were obtained in moderate to good yields (Table 3).

Thienyl diazonium salt **6** led to heterobiaryls **7** and **8**, which are typical structural motifs of organic semiconductors (Scheme 1a). In addition to heteroarenes, nitrobenzene is converted in 50% yield into compound **10** and other regioisomers (10%) after 20 h of irradiation by green light (Scheme 1b).

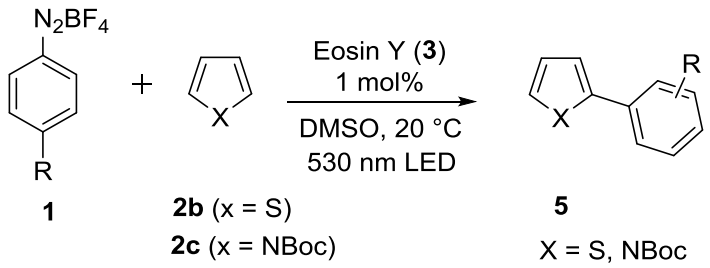
Table 2. Scope of aryl diazonium salts[a].

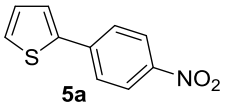
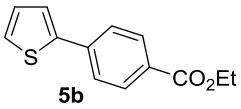
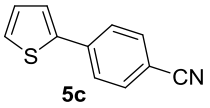
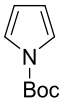
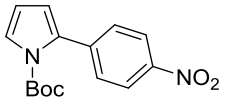
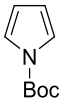
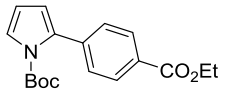
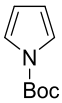
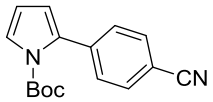
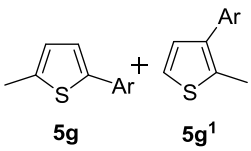
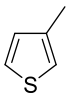
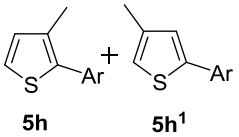


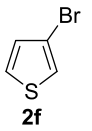
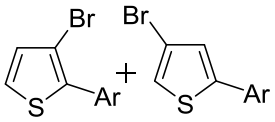
Entry	substrate	Product	Yield [%][b]
1	 **1a**	 **4a**	74
2	 **1b**	 **4b**	85
3	 **1c**	 **4c**	86
4	 **1d**	 **4d**	65
5	 **1e**	 **4e**	72
6	 **1f**	 **4f**	78
7	 **1g**	 **4g**	84
8	 **1h**	 **4h**	54
9	 **1i**	 **4i**	40
10	 **1j**	 **4j**	58
11	 **1k**	 **4k**	60

[a]The reaction was performed with **1** (0.23 mmol), furan (10 equiv) and eosin Y (0.01 equiv) in 1.0 mL of DMSO**.** [b]Isolated yield after purification on SiO_2.

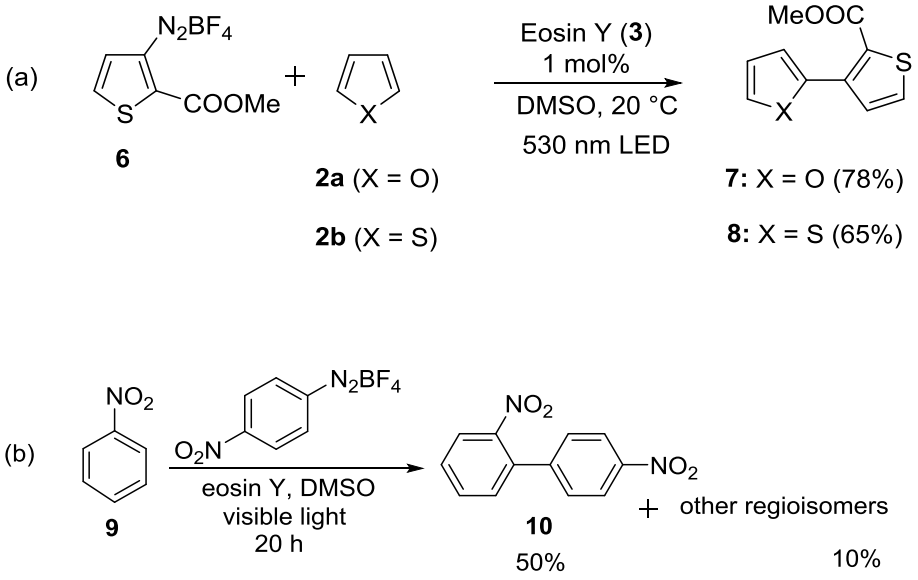
Table 3. Scope of heteroarenes[a].



Entry	R	X	t [h]	Product	Yield [%][b]
1	NO_2	 2b	4	 5a	70
2	CO_2Et	 2b	14	 5b	60
3	CN	 2b	16	 5c	52
4	NO_2	 2c	14	 5d	61
5	CO_2Et	 2c	18	 5e	51
6	CN	 2c	16	 5f	55
7	NO_2	 2d	16	 5g 5g[1] (5:1) Ar = 4-NO_2-C_6H_4	53
8	NO_2	 2e	24	 5h 5h[1] (5:1) Ar = 4-NO_2-C_6H_4	67

9	NO_2	 **2f**	24	 **5i** **5i[1]** (5:1) Ar = 4-NO_2-C_6H_4	60

[a]Reactions were carried out using **1** (0.23 mmol), heteroarene (5 equiv in case of thiophene derivatives, 2 equiv in case of pyrrole derivatives) and eosin Y (0.01 equiv) in 1.0 mL of DMSO**.** [b]Isolated yield after purification on SiO_2.



Scheme 1. Photo C-H arylation of (a) heteroarenes with thienyl diazonium salt. (b) nitrobenzene with aryl diazonium salts.

The C-H arylation of heteroarenes with aryl diazonium salts using eosin Y is expected to proceed through a radical mechanism and preliminary mechanistic investigation supported this assumption. When the reaction of aryl diazonium salts was conducted in absence of furan, but with added TEMPO compound **11** was obtained. Furthermore, addition of TEMPO to the reaction mixture of aryl diazonium salts, furan, and eosin Y stops the arylation process and the TEMPO-trapped intermediate **12** was detected. The identified compounds suggest that the photoreaction proceeds via a radical pathway (see experimental part for more details).

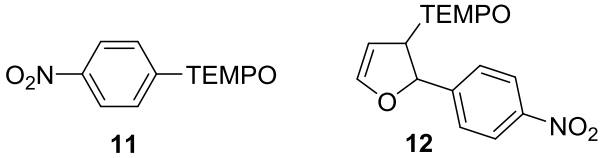
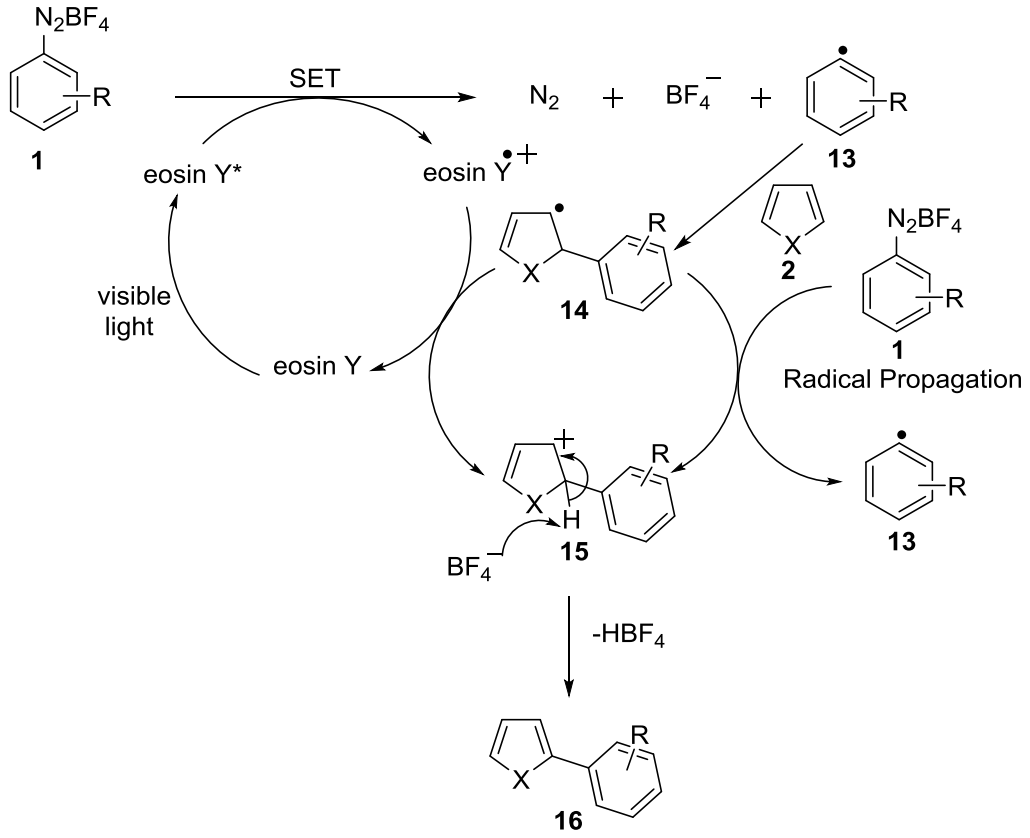


Figure 2. TEMPO-trapped reaction intermediates.

On the basis of the above observations and literature reports,[10,11,13,15] a plausible mechanism for this photoreaction is proposed (Scheme 2). Initially, aryl radical **13** is formed by SET from the excited state of eosin Y to aryl diazonium salt **1**. Addition of aryl radical **13** to heteroarene **2** gives radical intermediate **14**, which is further transformed to carbocation intermediate **15** by two possible pathways: (a) the oxidation of the radical intermediate **14** by the eosin Y radical cation giving **15**; (b) the oxidation of **14** by aryl diazonium salt **1** in a radical chain transfer mechanism. Finally, the intermediate **15** is deprotonated regenerating the aromatic system and leading to the desired coupling product **16**.



Scheme 2. Suggested mechanism for photocatalytic direct C-H arylation of heteroarenes.

2.3 Conclusion

In summary, we have reported a metal-free intermolecular direct C-H arylation of heteroarenes by photoredox catalysis with green light. The reaction proceeds smoothly at room temperature, does not require transition metal catalysts or bases and displays a broad scope towards diazonium salts and heterocycles with a wide range of functional group tolerance. This SET cross coupling represents an efficient alternative to the known transition metal catalyzed (Pd, Ru, Ir, Rh, and Ti) and ^{t}BuOK promoted strategies for C-H arylation and

it overcomes the significant drawbacks of the Meerwein arylation that prevented its broader application in organic synthesis. The induction of the reaction by visible light may find applications beyond synthesis, e.g. in the chemical patterning of surfaces. Further investigations on the mechanism of the reaction and its application are ongoing in our laboratory.

2.4 Experimental Part

General Information

Proton NMR spectra were recorded on a Bruker Avance 300 MHz spectrometer in $CDCl_3$ solution with internal solvent signal peak at 7.26 ppm. ^{13}C NMR were recorded at 75 MHz spectrometer in $CDCl_3$ solution and referenced to the internal solvent signal at 77.00 ppm. Proton NMR data are reported as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, dd = doublet of doublets, ddd = doublet of doublet of doublets, td = triplet of doublets, qd = quartet of doublets, m = multiplet, br. s. = broad singlet), and coupling constants (Hz). All reactions were monitored by thin-layer chromatography using Merck silica gel plates 60 F254; visualization was accomplished with short wave UV light (254 nm) and/or staining with appropriate stains (anisaldehyde orthophosphomolybdic acid). Standard flash chromatography was performed using silica gel of particle size 40−63 μm. Eosin Y (spirit soluble, 99% dye content) was purchased from Sigma Aldrich. All other commercially available reagents and solvents were used without further purification. The green light irradiation was performed using high-power LEDs Philips LUXEON® Rebel (1W, λ = 530±10 nm, 145 lm @700mA).

General Procedures

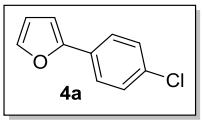
General procedure for the preparation of aryl diazonium tetrafluoroborates[16]

The appropriate aniline (10 mmol) was dissolved in a mixture of 4 mL of distilled water and 3.4 mL of 50% hydrofluoroboric acid. After cooling the reaction mixture to 0 °C using ice bath, a solution of sodium nitrite (0.69 g in 1.5 mL) was added dropwise in 5 min interval of time. The resulting mixture was stirred for 40 min and the precipitate was collected by filtration and re-dissolved in minimum amount of acetone. Diethyl ether was added until precipitation of diazonium tetrafluoroborate, which is filtered, washed several times with diethyl ether and dried under vacuum.

General procedure for the reaction of aryl diazonium tetrafluoroborates with furan

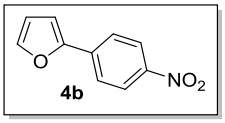
In a 5 mL snap vial equipped with magnetic stirring bar the Eosin Y (0.01 equiv), aryl diazonium tetrafluoroborate (1 equiv) and furan (10 equiv) were dissolved in dry DMSO (0.23 mmol/mL) and the resulting mixture was degassed by "pump-freeze-thaw" cycles (×2) via a syringe needle. The vial was irradiated through the vial's plane bottom side using green LEDs. After 2 h of irradiation the reaction mixture was transferred to separating funnel, diluted with diethyl ether and washed with 15 mL of water. The aqueous layer was washed three times with diethyl ether. The combined organic layers were dried over MgSO4, filtered and concentrated in vacuum. Purification of the crude product was achieved by flash column chromatography using petrol ether/ethyl acetate as eluent.

2-(4-Chloro-phenyl)-furan (4a)[17]



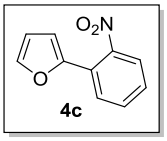
^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 7.60(d, *J* = 8.6 Hz, 2H), 7.47(d, *J* = 1.6 Hz, 1H), 7.35(d, *J* = 8.6 Hz, 2H), 6.64(d, *J* = 3.4 Hz, 1H), 6.48(dd, *J* = 3.4, 1.8 Hz, 1H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 152.9, 142.3, 132.9, 129.3, 128.8, 124.9, 111.7, 105.4

2-(4-Nitro-phenyl)-furan (4b)[17]



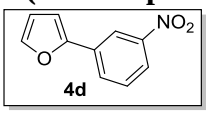
^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 8.24(d, *J* = 9.0 Hz, 2H), 7.78(d, *J* = 9.0 Hz, 2H), 7.57(d, *J* = 1.3 Hz, 1H), 6.87(d, *J* = 3.3 Hz, 1H), 6.55(dd, *J* = 3.4, 1.8 Hz, 1H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 151.6, 146.3, 144.1, 136.4, 124.3, 123.9, 112.4, 108.9

2-(2-Nitro-phenyl)-furan (4c)[20]



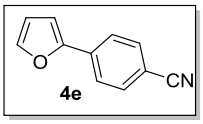
^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 7.72(dd, *J* = 7.9, 1.3 Hz, 1H), 7.68(dd, *J* = 8.1, 1.1 Hz, 1H), 7.57(dt, *J* = 7.7, 1.3 Hz, 1H), 7.51(d, *J* = 1.7 Hz, 1H), 7.41(dt, *J* = 7.8, 1.4 Hz, 1H), 6.67(dd, *J* = 3.5, 0.4 Hz, 1H), 6.50(dd, *J* = 3.5, 1.8 Hz, 1H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 148.3, 143.7, 131.8, 128.8, 128.2, 124.0, 123.8, 111.8, 109.7

2-(3-Nitro-phenyl)-furan (4d)[21]



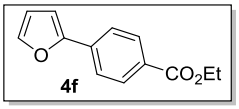
^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 8.49-8.48(m, 1H), 8.09(ddd, *J* = 8.2, 2.2, 0.8 Hz, 1H), 7..97-7.94(m, 1H), 7.57-7.51(m, 2H), 6.81(d, *J* = 3.4 Hz, 1H), 6.53(dd, *J* = 3.4, 1.8 Hz, 1H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 151.5, 148.6, 143.3, 132.3, 129.6, 129.2, 121.6, 118.5, 112.0, 107.2

2-(4-Cyano-phenyl)-furan (4e)[18]



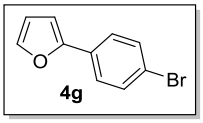
^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 7.74(d, *J* = 8.6 Hz, 2H), 7.65(d, *J* = 8.7 Hz, 2H), 7.54(d, *J* = 1.4 Hz, 1H), 6.81(d, *J* = 3.2 Hz, 1H), 6.53(dd, *J* = 3.5, 1.8 Hz, 1H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 151.9, 143.6, 134.6, 132.5, 123.9, 118.9, 112.2, 110.2, 108.1

2-(4-Ethoxycarbonyl-phenyl)-furan (4f)[18]



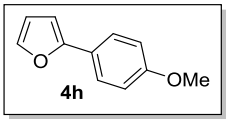
^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 8.06(d, *J* = 8.6 Hz, 2H), 7.72(d, *J* = 8.6 Hz, 2H), 7.52(d, *J* = 1.5 Hz, 1H), 6.79(d, *J* = 3.3 Hz, 1H), 6.51(dd, *J* = 3.4, 1.8 Hz, 1H), 4.38(q, *J* = 7.1 Hz, 2H), 1.40(t, *J* = 7.1 Hz, 3H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 166.3, 152.9, 143.0, 134.6, 130.0, 128.8, 123.3, 111.9, 107.1, 60.9, 14.3

2-(4-Bromo-phenyl)-furan (4g)[17]



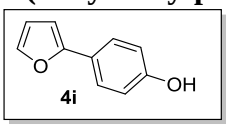
^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 7.58-7.47(m, 5H), 6.65(d, *J* = 3.0 Hz, 1H), 6.48(dd, *J* = 3.4, 1.8 Hz, 1H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 152.9, 142.3, 131.7, 129.7, 125.2, 121.0, 11.7, 105.5

2-(4-Methoxy-phenyl)-furan (4h)[17]



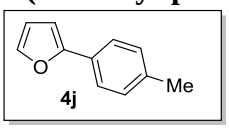
^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 7.61(d, *J* = 8.9 Hz, 2H), 7.43(d, *J* = 1.2 Hz, 1H), 6.93(d, *J* = 8.9 Hz, 2H), 6.52(d, *J* = 3.3 Hz, 1H), 6.45(dd, *J* = 3.3, 1.8 Hz, 1H), 3.83(s, 3H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 158.9, 154.0, 141.3, 125.2, 124.0, 114.0, 111.5, 103.3, 55.3

2-(4-Hydroxy-phenyl)-furan (4i)



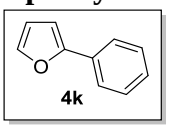
^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 7.56(d, *J* = 8.7 Hz, 2H), 7.43(d, *J* = 1.0 Hz, 1H), 6.86(d, *J* = 8.7 Hz, 2H), 6.51(d, *J* = 3.2 Hz, 1H), 6.45(dd, *J* = 3.2, 1.8 Hz, 1H), 4.86(br. s, 1H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 154.8, 153.9, 141.3, 125.4, 124.2, 115.5, 111.5, 103.3

2-(4-Methyl-phenyl)-furan (4j)[17]



^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 7.57(d, *J* = 8.2 Hz, 2H), 7.45(d, *J* = 1.8 Hz, 1H), 7.19(d, *J* = 8.0 Hz, 2H), 6.59(d, *J* = 3.3 Hz, 1H), 6.46(dd, *J* = 3.3, 1.8 Hz, 1H), 2.36(s, 3H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 154.2, 141.6, 137.1, 129.3, 128.2, 123.7, 111.5, 104.1, 21.2

2-phenyl-furan (4k)[17]

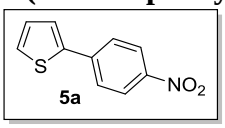


^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 7.69(d, *J* = 7.9 Hz, 2H), 7.48(d, *J* = 1.6 Hz, 1H), 7.39(t, *J* = 7.6 Hz, 2H), 7.29-7.24(m, 1H), 6.66(d, *J* = 3.4 Hz, 1H), 6.48(dd, *J* = 3.3, 1.8 Hz, 1H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 153.9, 142.0, 130.8, 128.6, 127.3, 123.7, 111.6, 104.9

General procedure for the reaction of aryl diazonium tetrafluoroborates with thiophene

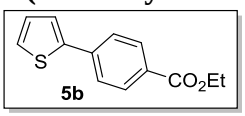
In a 5 mL snap vial equipped with magnetic stirring bar the Eosin Y (0.01 equiv), aryl diazonium tetrafluoroborate (1 equiv) and thiophene (5 equiv) were dissolved in dry DMSO (0.23 mmol/mL) and the resulting mixture was degassed by "pump-freeze-thaw" cycles (×2) via a syringe needle. The vial was irradiated through the vial's plane bottom side using green LEDs. After certain time of irradiation the reaction mixture was transferred to separating funnel, diluted with diethyl ether and washed with 15 mL of water. The aqueous layer was washed three times with diethyl ether. The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuum. Purification of the crude product was achieved by flash column chromatography using petrol ether/ethyl acetate as eluent.

2-(4-Nitro-phenyl)-thiophene (5a)[22]



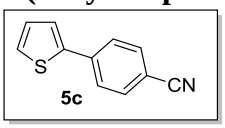
^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 8.23(d, *J* = 8.9 Hz, 2H), 7.74(d, *J* = 8.9 Hz, 2H), 7.48(dd, *J* = 3.7, 1.0 Hz, 1H), 7.44(dd, *J* = 5.1, 1.0 Hz, 1H), 7.15(dd, *J* = 5.1, 3.7Hz, 1H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 146.6, 141.6, 140.6, 128.7, 127.6, 126.0, 125.7, 124.4

2-(4-Ethoxycarbonyl-phenyl)-thiophene (5b)[18]



^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 8.05(d, *J* = 8.4 Hz, 2H), 7.67(d, *J* = 8.5 Hz, 2H), 7.42(dd, *J* = 3.7, 1.0 Hz, 1H), 7.36(dd, *J* = 5.1, 1.0 Hz, 1H), 7.11(dd, *J* = 5.1, 3.7Hz, 1H), 4.39(q, *J* = 7.1 Hz, 2H), 1.41(t, *J* = 7.1 Hz, 3H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 166.2, 143.1, 138.5, 130.2, 129.1, 128.2, 126.2, 125.4, 124.4, 60.1, 14.3

2-(4-Cyano-phenyl)-thiophene (5c)[19]

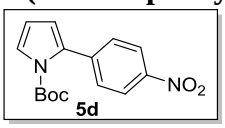


^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 7.70(d, *J* = 8.7 Hz, 2H), 7.65 (d, *J* = 8.7 Hz, 2H), 7.42(dd, *J* = 3.7, 1.1 Hz, 1H), 7.40(dd, *J* = 5.2, 1.1 Hz, 1H), 7.13(dd, *J* = 5.1, 3.7Hz, 1H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 142.0, 138.6, 132.7, 128.5, 127.0, 126.0, 125.0, 118.8, 110.5

General procedure for the reaction of aryl diazonium tetrafluoroborates with *N*-Boc pyrrole

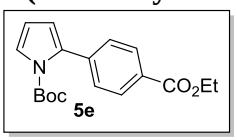
In a 5 mL snap vial equipped with magnetic stirring bar the Eosin Y (0.01 equiv), aryl diazonium tetrafluoroborate (1 equiv) and pyrrole (5 equiv) were dissolved in dry DMSO (0.23 mmol/mL) and the resulting mixture was degassed by "pump-freeze-thaw" cycles (×2) via a syringe needle. The vial was irradiated through the vial's plane bottom side using green LEDs. After certain time of irradiation the reaction mixture was transferred to separating funnel, diluted with diethyl ether and washed with 15 mL of water. The aqueous layer was washed three times with diethyl ether. The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuum. Purification of the crude product was achieved by flash column chromatography using petrol ether/ethyl acetate as eluent.

2-(4-Nitro-phenyl)-pyrrole-1-carboxylic acid *tert*-butyl ester (5d)[23]



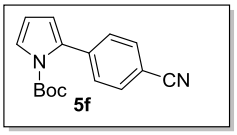
^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 8.22(d, *J* = 8.9 Hz, 2H), 7.51(d, *J* = 8.9 Hz, 2H), 7.41(dd, *J* = 3.3, 1.8 Hz, 1H), 6.33(dd, *J* = 3.4, 1.8 Hz, 1H), 6.27(t, *J* = 3.3Hz, 1H), 1.43(s, 9H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 148.8, 146.5, 140.6, 132.7, 129.5, 124.3, 122.9, 116.4, 111.1, 84.5, 27.7

2-(4- Ethoxycarbonyl -phenyl)-pyrrole-1-carboxylic acid *tert*-butyl ester (5e)[18]



^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 8.03(d, *J* = 8.4 Hz, 2H), 7.41(d, *J* = 8.4 Hz, 2H), 7.38(dd, *J* = 3.0, 2.1 Hz, 1H), 6.25-6.23(m, 2H), 4.39(q, *J* = 7.1 Hz, 2H), 1.41(t, *J* = 7.1 Hz, 3H), 1.38(s, 9H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 166.4, 149.1, 138.7, 134.0, 128.9, 128.8, 128.8, 123.4, 115.3, 110.8, 84.0, 60.9, 27.6, 14.3

2-(4-Cyano-phenyl)-pyrrole-1-carboxylic acid *tert*-butyl ester (5f)[19]

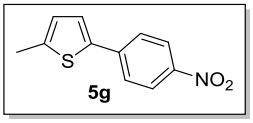


^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 7.63(d, *J* = 8.4 Hz, 2H), 7.45(d, *J* = 8.4 Hz, 2H), 7.39(dd, *J* = 3.1, 1.9 Hz, 1H), 6.28-6.24(m, 2H), 1.41(s, 9H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 148.9, 138.7, 133.0, 131.3, 129.5, 123.9, 118.9, 116.0, 111.0, 110.4, 84.3, 27.6

General procedure for the reaction of aryl diazonium tetrafluoroborates with thiophene derivatives

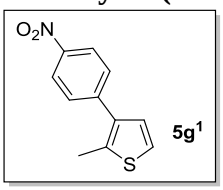
In a 5 mL snap vial equipped with magnetic stirring bar the Eosin Y (0.01 equiv), aryl diazonium tetrafluoroborate (1 equiv) and thiophene derivative (5 equiv) were dissolved in dry DMSO (0.23 mmol/mL) and the resulting mixture was degassed by "pump-freeze-thaw" cycles (×2) via a syringe needle. The vial was irradiated through the vial's plane bottom side using green LEDs. After certain time of irradiation the reaction mixture was transferred to separating funnel, diluted with diethyl ether and washed with 15 mL of water. The aqueous layer was washed three times with diethyl ether. The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuum. Purification of the crude product was achieved by flash column chromatography using petrol ether/ethyl acetate as eluent.

2-Methyl-5-(4-nitro-phenyl)-thiophene (5g)[4d]
Major regioisomer



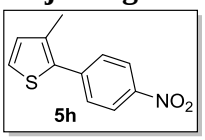
^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 8.20(d, *J* = 9.0 Hz, 2H), 7.65(d, *J* = 9.0 Hz, 2H), 7.28(d, *J* = 3.6 Hz, 1H), 6.80(dd, *J* = 3.6, 1.0 Hz, 1H), 2.54(s, 3H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 146.1, 142.9, 140.8, 139.0, 127.0, 125.7, 125.3, 124.3, 15.5

Minor regioisomer
2-Methyl-3-(4-nitro-phenyl)-thiophene (5g[1])



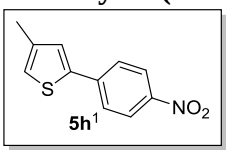
^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 8.27(d, *J* = 8.9 Hz, 2H), 7.55(d, *J* = 8.9 Hz, 2H), 7.17(d, *J* = 5.3 Hz, 1H), 7.07(d, *J* = 5.3 Hz, 1H), 2.54(s, 3H)

3-Methyl-2-(4-nitro-phenyl)-thiophene (5h)[4c]
Major regioisomer



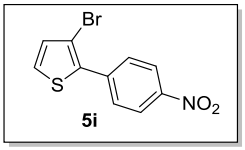
^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 8.26(d, *J* = 8.9 Hz, 2H), 7.62(d, *J* = 8.9 Hz, 2H), 7.33(d, *J* = 5.1 Hz, 1H), 6.98(d, *J* = 5.1 Hz, 1H), 2.38(s, 3H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 146.4, 141.5, 140.7, 139.3, 131.8, 129.1, 125.5, 123.8, 15.5

Minor regioisomer
4-Methyl-2-(4-nitro-phenyl)-thiophene (5h[1])



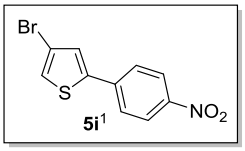
^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 8.22(d, *J* = 8.9 Hz, 2H), 7.70(d, *J* = 8.9 Hz, 2H), 7.29-7.28(m, 1H), 7.02-7.01(m, 1H), 2.31(s, 3H)

3-Bromo-2-(4-nitro-phenyl)-thiophene (5i)[4c]
Major regioisomer



^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 8.28(d, *J* = 8.9 Hz, 2H), 7.85(d, *J* = 8.9 Hz, 2H), 7.41(d, *J* = 5.3 Hz, 1H), 7.12(d, *J* = 5.3 Hz, 1H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 147.1, 139.3, 135.5, 132.4, 129.6, 126.9, 123.8, 109.5

Minor regioisomer
4-Bromo-2-(4-nitro-phenyl)-thiophene (5i[1])

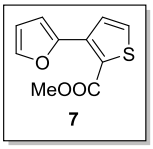


^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 8.20(d, *J* = 8.9 Hz, 2H), 7.65(d, *J* = 8.9 Hz, 2H), 7.32(d, *J* = 1.4 Hz, 1H), 7.28 (d, *J* = 1.3 Hz, 1H)

Procedure for synthesis of 3-furan-2-yl-thiophene-2-carboxylic acid methyl ester (7)

In a 5 mL snap vial equipped with magnetic stirring bar the Eosin Y (0.01 equiv), thienyl diazonium tetrafluoroborate (1 equiv) and furan (10 equiv) were dissolved in dry DMSO (0.23 mmol/mL) and the resulting mixture was degassed by "pump-freeze-thaw" cycles (×2) via a syringe needle. The vial was irradiated through the vial's plane bottom side using green LEDs. After 2 h of irradiation the reaction mixture was transferred to separating funnel, diluted with diethyl ether and washed with 15 mL of water. The aqueous layer was washed three times with diethyl ether. The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuum. Purification of the crude product was achieved by flash column chromatography using petrol ether/ethyl acetate as eluent.

3-Furan-2-yl-thiophene-2-carboxylic acid methyl ester (7)



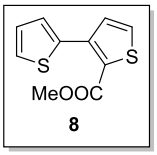
^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 7.55-7.53(m, 2H), 7.47-7.45(m, 2H), 6.52(dd, *J* = 3.5, 1.8 Hz, 1H), 3.89(s, 3H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 162.2, 148.9, 142.1, 136.6, 130.2, 128.7, 124.0, 112.7, 111.9, 52.0
HRMS:
Calculated: 208.0194

Found: 208.0191

Procedure for synthesis of [2,3']bis-thiophenyl-2'-carboxylic acid methyl ester (8)

In a 5 mL snap vial equipped with magnetic stirring bar the Eosin Y (0.01 equiv), thienyl diazonium tetrafluoroborate (1 equiv) and thiophene (10 equiv) were dissolved in dry DMSO (0.23 mmol/mL) and the resulting mixture was degassed by "pump-freeze-thaw" cycles (×2) via a syringe needle. The vial was irradiated through the vial's plane bottom side using green LEDs. After 14 h of irradiation the reaction mixture was transferred to separating funnel, diluted with diethyl ether and washed with 15 mL of water. The aqueous layer was washed three times with diethyl ether. The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuum. Purification of the crude product was achieved by flash column chromatography using petrol ether/ethyl acetate as eluent.

[2,3']Bis-thiophenyl-2'-carboxylic acid methyl ester (8)



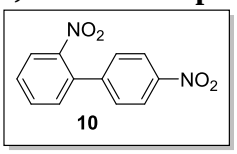
8

^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 7.59(dd, *J* = 3.6, 1.1 Hz, 1H), 7.48(d, *J* = 5.2 Hz, 1H), 7.38(dd, *J* = 5.1, 1.1 Hz, 1H), 7.25(d, *J* = 5.2 Hz, 1H), 7.10(dd, *J* = 5.1, 3.7Hz, 1H), 3.85(s, 3H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 162.3, 140.1, 136.2, 131.4, 130.1, 128.8,127.1, 126.5,124.4,52.0

Procedure for synthesis of 2,4'-dinitro-biphenyl (10)

In a 5 mL snap vial equipped with magnetic stirring bar the Eosin Y (0.01 equiv), aryl diazonium tetrafluoroborate (1 equiv) and nitrobenzene (5 equiv) were dissolved in dry DMSO (0.23 mmol/mL) and the resulting mixture was degassed by "pump-freeze-thaw" cycles (×2) via a syringe needle. The vial was irradiated through the vial's plane bottom side using green LEDs. After 24 h of irradiation the reaction mixture was transferred to separating funnel, diluted with diethyl ether and washed with 15 mL of water. The aqueous layer was washed three times with diethyl ether. The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuum. Purification of the crude product was achieved by flash column chromatography using petrol ether/ethyl acetate as eluent.

2,4'-Dinitro-biphenyl (10)[24]

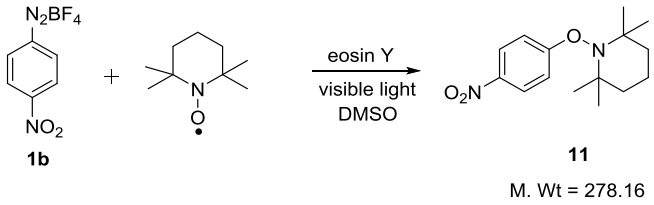


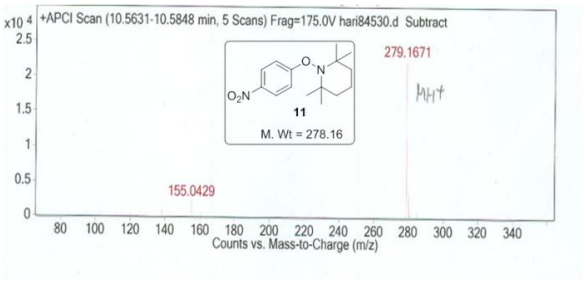
^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 8.30(d, *J* = 8.8 Hz, 2H), 8.01(dd, *J* = 8.1, 1.2 Hz, 1H)), 7.71(td, *J* = 7.5, 1.3 Hz, 1H) 7.60(td, *J* = 7.8, 1.5 Hz, 1H) 7.49(d, *J* = 8.8 Hz, 2H), 7.44(dd, J=7.6, 1.5 Hz, 1H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 148.5, 147.6, 144.3, 134.5, 132.9, 131.6, 129.5, 128.9, 124.7, 123.8

Radical Capturing Experiments

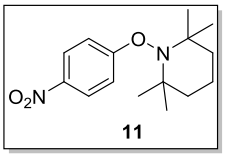
The experimental procedure for capturing radicals with TEMPO

1) In a 5 mL snap vial equipped with magnetic stirring bar the Eosin Y (0.2 equiv), aryl diazonium tetrafluoroborate (1 equiv) and TEMPO (2 equiv) were dissolved in dry DMSO (0.23 mmol/mL) and the resulting mixture was degassed by "pump-freeze-thaw" cycles (×2) via a syringe needle. The vial was irradiated through the vial's plane bottom side using green LEDs. After 2 h of irradiation, a TEMPO trapped compound **11** was detected by mass spectrometry.



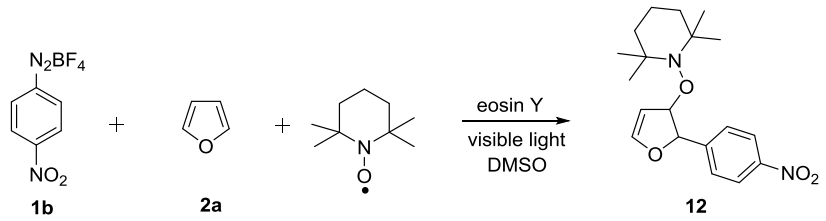


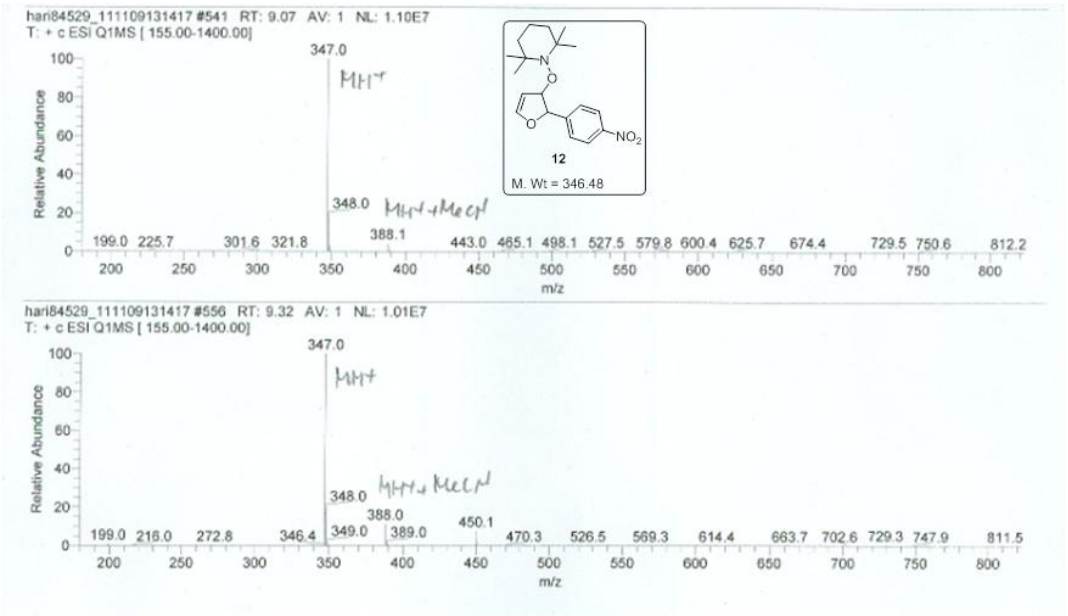
2,2,6,6-Tetramethyl-1-(4-nitrophenoxy)piperidine (11)



^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 8.14(d, *J* = 9.5 Hz, 2H), 7.4-7.1(m, 2H), 1.67-1.56(m, 5H), 1.46-1.42(m, 1H), 1.23(s, 6H), 0.98(s, 6H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 168.6, 141.0, 125.5, 114.1, 60.8, 39.6, 32.2, 20.4, 16.8

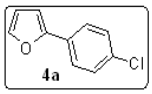
2) In a 5 mL snap vial equipped with magnetic stirring bar the Eosin Y (0.2 equiv), aryl diazonium tetrafluoroborate (1 equiv), furan (10 equiv) and TEMPO (2 equiv) were dissolved in dry DMSO (0.23 mmol/mL) and the resulting mixture was degassed by "pump-freeze-thaw" cycles (×2) via a syringe needle. The vial was irradiated through the vial's plane bottom side using green LEDs. After 2 h of irradiation, a TEMPO trapped compound **12** was detected by mass spectrometry.

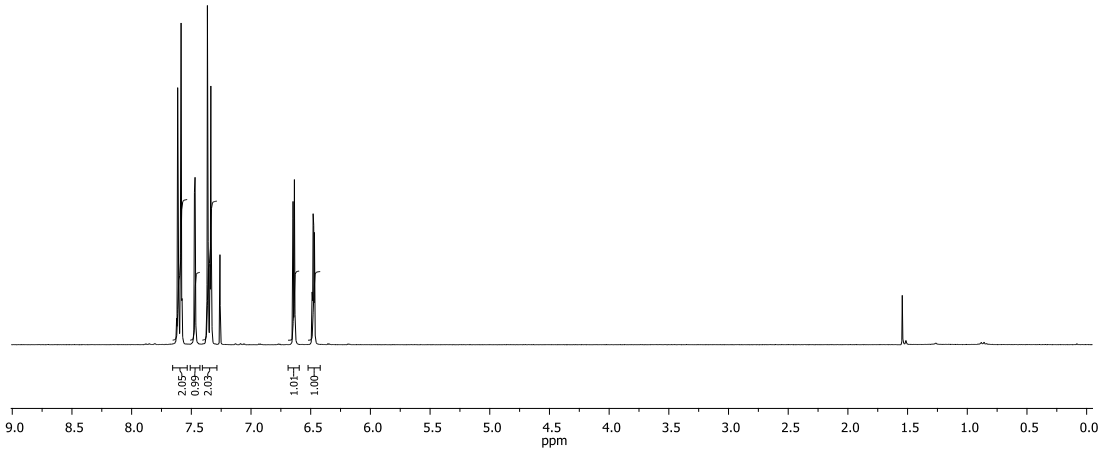




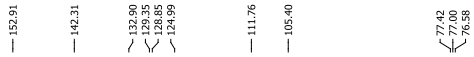
^{1}H and ^{13}C NMR spectra of selected compounds

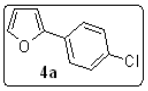
^{1}H NMR (300MHz, $CDCl_3$)

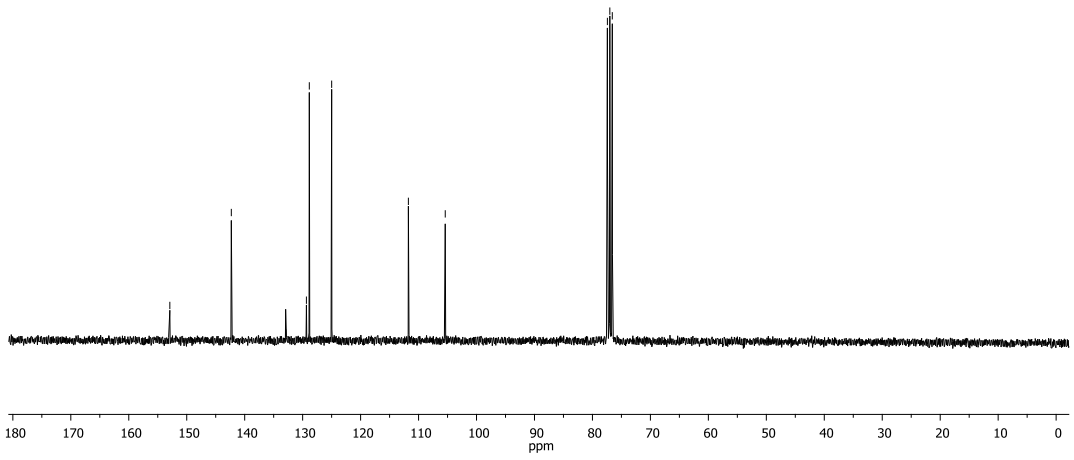




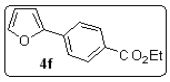
^{13}C NMR (75 MHz, $CDCl_3$)

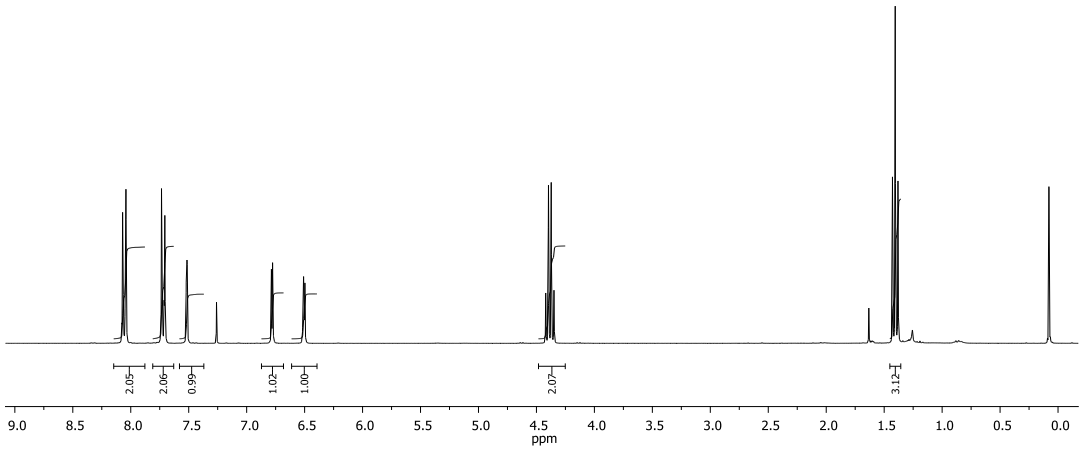




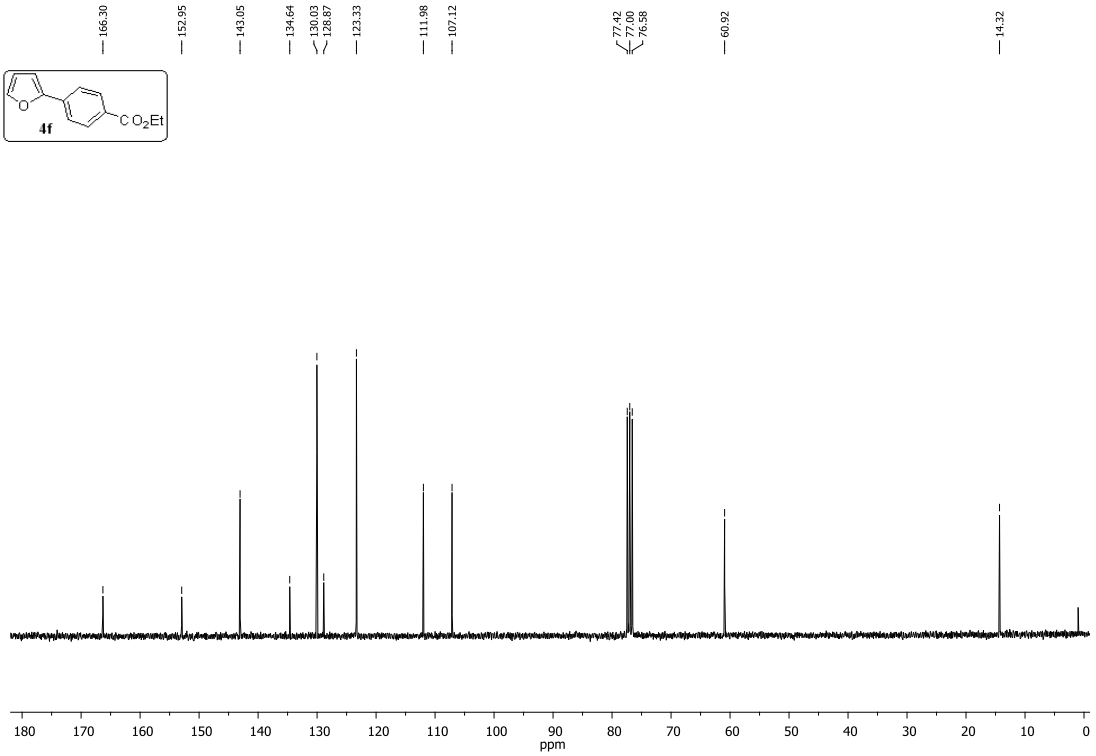


^{1}H NMR (300MHz, $CDCl_3$)





^{13}C NMR (75 MHz, $CDCl_3$)



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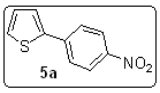
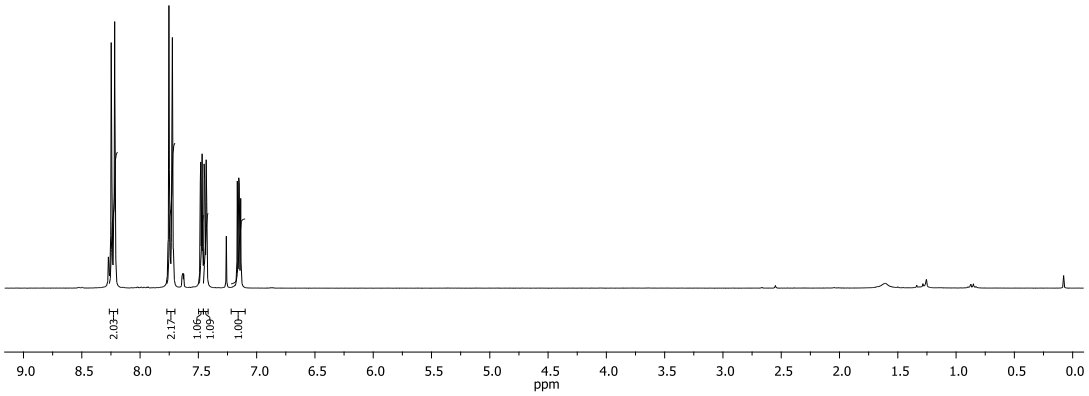
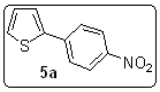




^{13}C NMR (75 MHz, $CDCl_3$)



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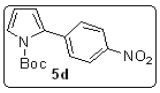
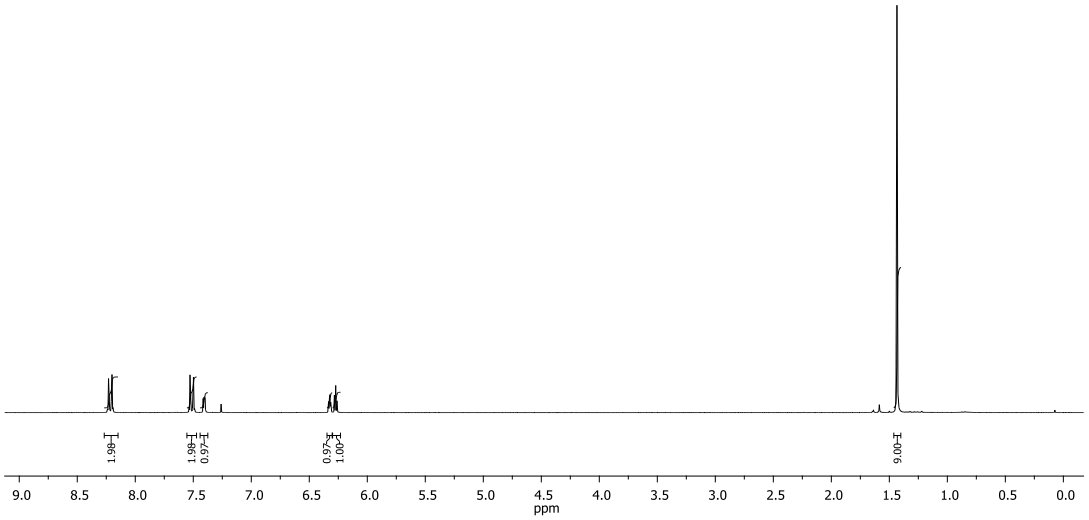
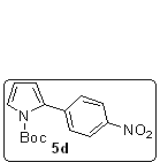
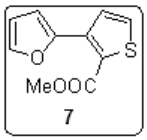


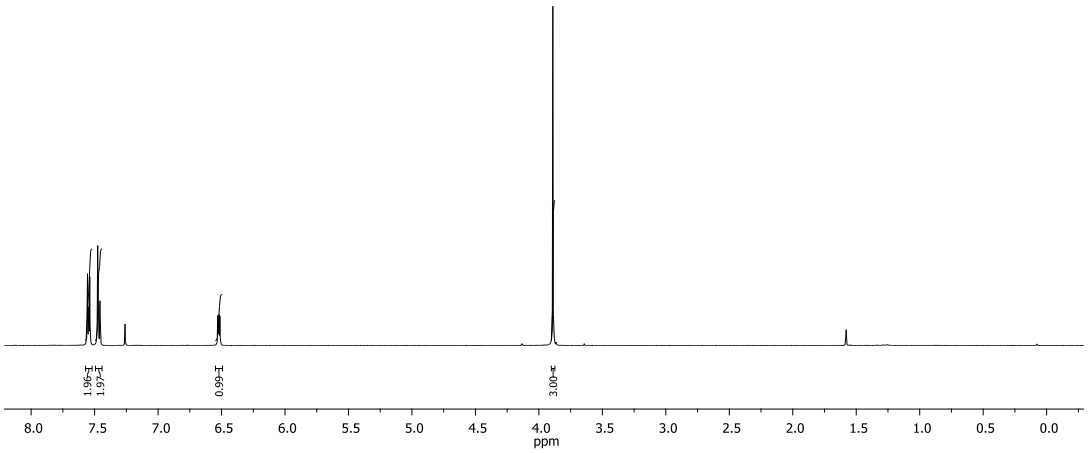


^{13}C NMR (75 MHz, $CDCl_3$)

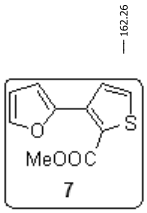


^{1}H NMR (300MHz, $CDCl_3$)





^{13}C NMR (75 MHz, $CDCl_3$)



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Photobiol. **2000**, *71*, 675. (c) Santhanalakshmi, J.; Venkatesan, P. *J. Nanopart. Res.* **2011**, *13*, 479. (d) Lazarides, T.; McCormick, T.; Du, P.; Luo, G.; Lindley, B.; Eisenberg, R. *J. Am. Chem. Soc.* **2009**, *131*, 9192. (e) Liu, H.; Feng, W.; Kee, C. W.; Zhao, Y.; Leow, D.; Pan, Y.; Tan, C.-H. *Green Chem.* **2010**, *12*, 953.

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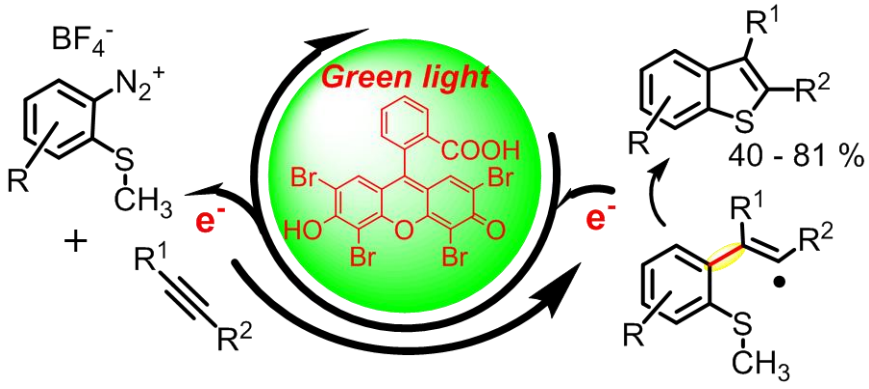
Chapter 3

3 Visible Light Photocatalytic Synthesis of Benzothiophenes



The photocatalytic reaction of *o*-methylthio-arenediazonium salts with alkynes yields substituted benzothiophenes regioselectively through a radical annulation process. Green light irradiation of eosin Y initiates the photoredox catalysis. The scope of the reaction was investigated by using various substituted diazonium salts and different alkynes.

This chapter has been published:
D. P. Hari, T. Hering, B. König, *Org. Lett.* **2012**, *14*, 5334-5337.
Author contributions:
DP carried out all the photoreactions and wrote the manuscript; TH prepared the diazonium salts in Table 2.

3.1 Introduction

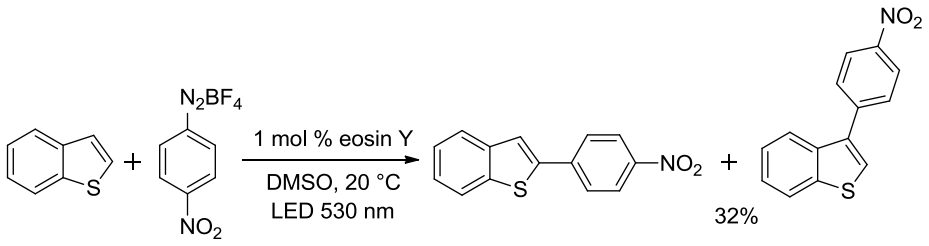
The synthesis of benzothiophene derivatives has attracted much attention in recent years due to their wide application in biology,[1] pharmacy,[2] catalysis,[3] and material science.[4] Several active drugs on the market contain the benzothiophene core: Zileuton is a potent and selective inhibitor of 5-lipoxygenase,[5] while raloxifene[6] and arzoxifene[7] are selective estrogen receptor modulators, and antitubulin agents.

Many elegant methods have been reported for the synthesis of substituted benzothiophenes.[8] Most of these methodologies rely on two approaches: (a) direct arylation of the benzothiophene moiety, (b) electrophilic cyclization and coupling cyclization reactions to construct the benzothiophene ring.[8a,9] Cyclization reactions are of more interest since they yield only the desired regioisomer. Typically, cyclization reactions are catalyzed by transition metals, such as palladium-catalyzed iodocyclizations,[10] copper-mediated halocyclizations,[11] and gold promoted annulation reactions.[12] Recently, we have reported a methodology for the arylation of heteroarenes using aryl diazonium salts in visible light photocatalysis.[13] We used the reaction for the synthesis of 2-substituted benzothiophenes, but unfortunately mixtures of regioisomers were obtained in rather low yields (Scheme 1a).

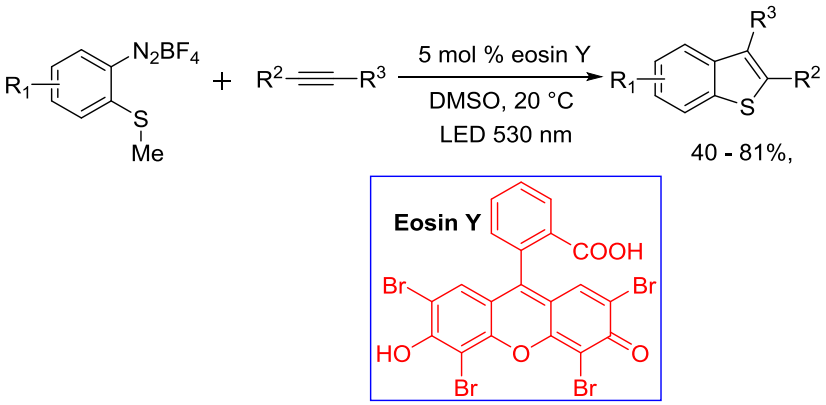
To overcome such disadvantages in the direct arylation of benzothiophene, we decided to explore an annulation method to construct the benzothiophene ring. Giuseppe Zanardi and his co-workers first reported the synthesis of benzothiophenes from the reaction of *o*-methyllthio-arenediazonium salts with alkynes using transition metals as catalysts.[14] In 2000, Larry G. Huffman, Jr *et al*. reported the synthesis of benzothiophenes from diazonium salts with stoichiometric amounts of $FeSO_4$ and $TiCl_3$.[15] Recently Carl H. Schiesser *et al*. prepared a potent AT_1 receptor antagonist through a cyclization process involving the addition of aryl radicals to alkynes, followed by intramolecular homolytic substitution at a sulfur or selenium heteroatom.[16]

All of these annulation reactions typically require stoichiometric amounts of transition metals and rather harsh reaction conditions. Visible light photocatalysis is emerging as powerful tool for mild and selective organic transformations.[17] We report here the visible light mediated synthesis of privileged benzothiophenes through a radical annulation process catalyzed by eosin Y at ambient conditions.

(a) Photocatalytic direct arylation of benzothiophene yields a mixture of regioisomers



(b) Photocatalytic cyclization gives the benzothiophene ring as single isomer in good yield (this work)

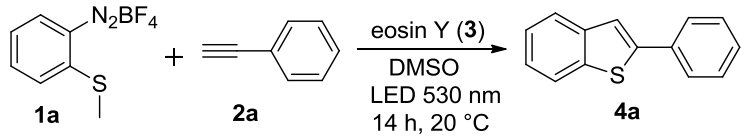


Scheme 1. Photocatalytic approaches to benzothiophenes.

3.2 Results and Discussion

Our initial studies focused on the reaction of the *o*-methylthio-benzenediazonium salt **1a** with phenyl acetylene using eosin Y (**3**) as photoredox catalyst by irradiating at 530 nm. We examined the amount of catalyst loading (Table 1, entries 2 and 5) and different equivalents of alkyne (Table 1, entries 4, 5, and 6) on this photoreaction. To our delight, when 5 mol % of eosin Y and 5 equiv of alkyne were used in DMSO, the desired product was obtained in good yield (Table 1, entry 5). We also examined rose bengal as photocatalyst, giving the expected product in 59% yield (Table 1, entry 7). To prove the essential role of photocatalysis for the annulation reaction, experiments without green light irradiation or without dye under irradiation were performed. As expected, we observed only 15 and 12% product yield, respectively, after 36 h at 20 °C (Table 1, entries 8 and 9).

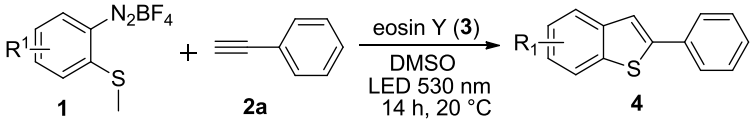
Table 1. Optimizing reaction conditions.



Entry	Conditions	Yield[a]
1	**3** (1 mol %), **2a** (2 equiv), DMSO	58
2	**3** (1 mol %), **2a** (5 equiv), DMSO	64
3	**3** (1 mol %), **2a** (5 equiv), DMF	56
4	**3** (5 mol %), **2a** (2 equiv), DMSO	68
5	**3** (5 mol %), **2a** (5 equiv), DMSO	75
6	**3** (5 mol %), **2a** (10 equiv), DMSO	75
7	rose bengal (5 mol %), **2a** (5 equiv), DMSO	59
8	**3** (5 mol %), **2a** (5 equiv), DMSO. no light	15[b]
9	no catalyst, **2a** (5 equiv), DMSO	12[b]

[a]Isolated yields after purification by flash column chromatography using silica gel. [b]36 h irradiation time.

Table 2. Photocatalyzed annulation of *o*-methylthio-arenediazonium salts with phenyl acetylene[a].



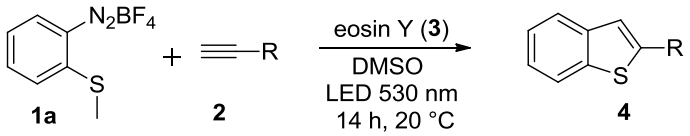
Entry	Substrate	R^1	Alkyne	Product	Yield[b]
1	**1a**	H	**2a**	**4a**	75
2	**1b**	4-Cl	**2a**	**4b**	70
3	**1c**	4-Me	**2a**	**4c**	72
4	**1d**	5-Cl	**2a**	**4d**	65
5	**1e**	4-OMe	**2a**	**4e**	63
6	**1f**	4-Br	**2a**	**4f**	72
7	**1g**	4-OEt	**2a**	**4g**	76
8	**1h**	4-F	**2a**	**4h**	62

[a]The reaction was performed with **1** (0.25 mmol), phenyl acetylene (5 equiv) and eosin Y (0.05 equiv) in 1.0 mL of DMSO. [b]Isolated yields after purification by flash column chromatography using silica gel.

Having optimized reaction conditions in hand, we investigated the reaction scope for *o*-methylthio-arenediazonium salts with phenyl acetylene for the photo annulation reaction. All diazonium salts were prepared according to literature described procedures.[15] *O*-methylthio-arenediazonium salts bearing electron donating substituents (Table 2, entries 3, 5 and 7) reacted well in the photoreaction to afford the corresponding benzothiophenes in good yields. Diazonium salts bearing halogen substituents (Table 2, entries 2, 4, 6 and 8) gave the corresponding benzothiophenes with intact carbon-halogen bond. Such molecules are difficult to synthesize using conventional methods and very useful for further synthetic elaborations.

Next we investigated the reaction scope of terminal alkynes in this photoreaction and the results are summarized in Table 3. Aromatic alkynes react smoothly and afford good yields (Table 3, entries 1-5). 3-Ethynylthiophene also reacted with **1a** to give the corresponding product in 62% yield (Table 3, entry 9). Molecules of this type find applications in the synthesis of optoelectronic materials. With ester, TMS, and *n*-butyl substituents on the alkynes good to moderate yields (Table 3, entries 6, 7, 8, and 10) were obtained.

Table 3. Photocatalyzed annulation of *o*-methylthio-benzenediazonium salt with terminal alkynes[a].

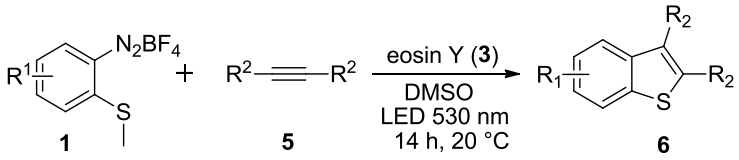


Entry	Substrate	Alkyne	R	Product	Yield[b]
1	**1a**	**2a**	Ph	**4a**	75
2	**1a**	**2b**	4-NO_2-C_6H_4	**4i**	81
3	**1a**	**2c**	4-OMe-C_6H_4	**4j**	72
4	**1a**	**2d**	3-CF_3-C_6H_4	**4k**	62
5	**1a**	**2e**	4-F-C_6H_4	**4l**	64
6	**1a**	**2f**	CO_2Me	**4m**	60
7	**1a**	**2g**	TMS	**4n**	45
8	**1a**	**2h**	CO_2Et	**4o**	65
9	**1a**	**2i**	3-C_6H_3S	**4p**	62
10	**1a**	**2j**	*n*-butyl	**4q**	30

[a]The reaction was performed with **1a** (0.25 mmol), terminal alkyne (5 equiv) and eosin Y (0.05 equiv) in 1.0 mL of DMSO. [b]Isolated yields after purification by flash column chromatography using silica gel.

Thionaphthene-2, 3-dialkyl esters are precursors for the synthesis of the corresponding cyclohydrazides of thionapthene, which are useful as indicators.[18] The synthesis of thionapthene-2, 3-dialkyl esters is largely unexplored compared to other benzothiophene derivatives and only a few literature reports exist including a recent paper by P. G. Jones *et al*. describing an approach using palladium chemistry.[19] We synthesized thionapthene 2, 3-dialkyl esters by simply reacting dialkyl but-2-ynedioate with *o*-methylthio-arenediazonium salts using eosin Y in visible light. The results are summarized in Table 4. Different diazonium salts were converted with dialkyl but-2-ynedioate affording thionapthene-2, 3-dialkyl esters in good to moderate yield.

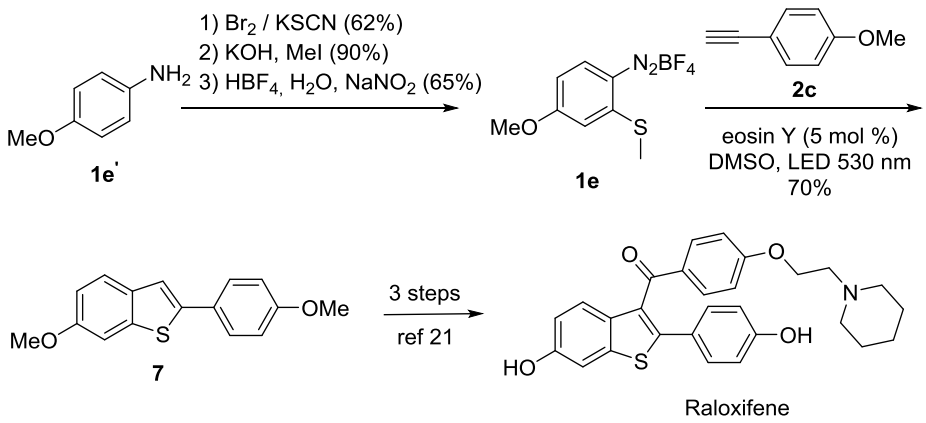
Table 4. Photocatalyzed annulation of *o*-methylthio-arenediazonium salts with dialkyl but-2-ynedioates[a]



Entry	Substrate	R^1	Alkyne	R^2	Product	Yield[b]
1	**1a**	H	**5a**	CO_2Me	**6a**	61
2	**1a**	H	**5b**	CO_2Et	**6b**	50
3	**1h**	4-F	**5a**	CO_2Me	**6c**	55
4	**1h**	4-F	**5b**	CO_2Et	**6d**	42
5	**1g**	4-OEt	**5a**	CO_2Me	**6e**	53
6	**1f**	4-Br	**5a**	CO_2Me	**6f**	55
7	**1f**	4-Br	**5b**	CO_2Et	**6g**	40
8	**1d**	5-Cl	**5a**	CO_2Me	**6h**	40
9	**1d**	5-Cl	**5b**	CO_2Et	**6i**	51

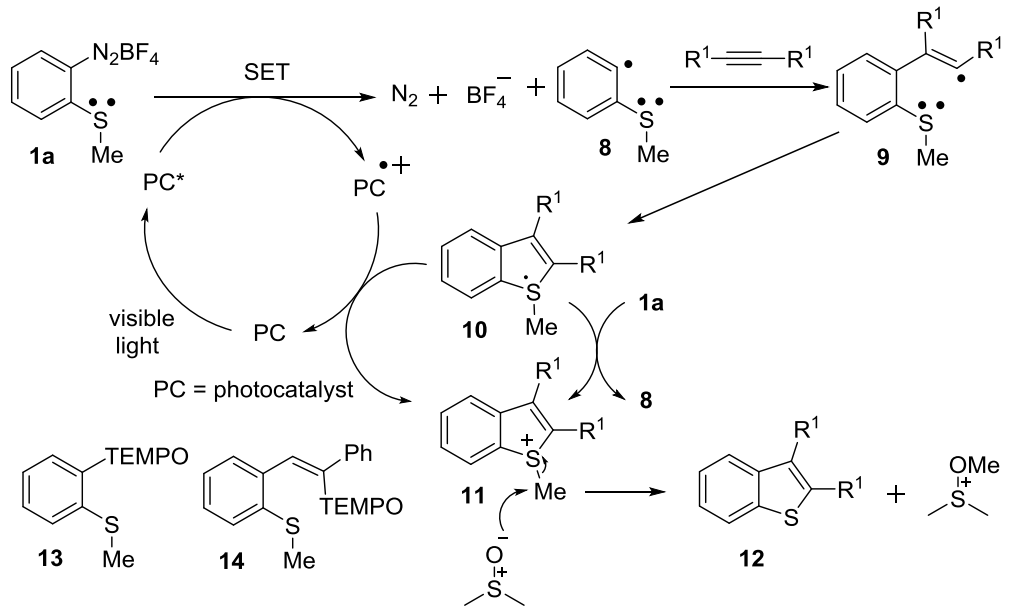
[a]The reaction was performed with **1** (0.25 mmol), internal alkyne (5 equiv) and eosin Y (0.05 equiv) in 1.0 mL of DMSO. [b]Isolated yields after purification by flash column chromatography using silica gel.

Finally, we employed our methodology to prepare the key intermediate **7** of the raloxifene synthesis by excluding metal catalysts.[15] We prepared **1e** from the corresponding amine and reacted it with **2c** using standard photocatalysis conditions to furnish **7** in 70% isolated yield (Scheme 2).



Scheme 2. Photocatalytic synthesis of the key intermediate **7** of Raloxifene.

To investigate the mechanism of the photoreaction, we performed radical trapping experiments. TEMPO adducts **13** and **14** were identified by mass spectrometry supporting the radical pathway. In accordance to literature reports[13-14,20] and the radical trapping experiments we propose a tentative mechanism in Scheme 3. Initially aryl radical **8** is formed by SET from the excited state of the photocatalyst to diazonium salt **1**. Addition of **8** to the alkyne yields the corresponding vinyl radical **9**, which then further cyclizes, to give sulphuranyl radical **10**. Radical **10** is oxidized to cation **11** that transfers a methyl group to nucleophiles present in the reaction mixture by an S_N2 process giving product **12**. Radical **10** is either oxidized by the cation radical of the photocatalyst to complete the electron transfer cycle or it is oxidized by the diazonium salt in a chain transfer mechanism. Investigations to elucidate the reaction mechanism in more detail are ongoing.



Scheme 3. Proposed reaction mechanism.

3.3 Conclusion

In conclusion, the first photocatalytic synthesis of benzothiophenes from diazonium salts has been accomplished. The method provides mild and efficient access to different types of benzothiophenes in a manner that avoids metal catalysts and high temperatures. Instead, only green light and a catalytic amount of organic dye as a catalyst are required. The substrate scope is large and many products have the potential for further synthetic transformations as demonstrated by the synthesis of the key intermediate of the drug raloxifene. Experiments to investigate the mechanism of the reaction, to expand the scope of the reaction and apply it to the synthesis of other biologically active molecules are ongoing in our laboratory.

3.4 Experimental Part

General Information

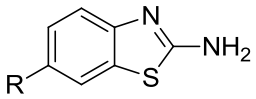
Proton NMR spectra were recorded on a Bruker Avance 300 MHz spectrometer in $CDCl_3$ solution with internal solvent signal peak at 7.26 ppm. Carbon NMR were recorded at 75 MHz spectrometer in $CDCl_3$ solution and referenced to the internal solvent signal at 77.00 ppm. Proton NMR data are reported as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, dd = doublet of doublets, ddd = doublet of doublet of doublets, td = triplet of doublets, qd = quartet of doublets, m = multiplet, br. s. = broad singlet), and coupling constants (Hz). All reactions were monitored by thin-layer chromatography using Merck silica gel plates 60 F254; visualization was accomplished with short wave UV light (254 nm) and/or staining with appropriate stains (anisaldehyde orthophosphomolybdic acid). Standard flash chromatography was performed using silica gel of particle size 40−63 μm. Eosin Y (spirit soluble, 99% dye content) was purchased from Sigma Aldrich. All other commercially available reagents and solvents were used without further purification. The green light irradiation was performed using high-power LEDs Philips LUXEON® Rebel (1W, λ = 530±10 nm, 145 lm @700mA).

General Procedures

Procedure for synthesis of 6-substituted-1, 3-benzothiazol-2-amine[22]

A mixture of aromatic aniline (0.01 mol) and KSCN (0.01 mol) in glacial acetic acid (10%) was stirred and cooled to 10 °C using ice cooled bath. To this stirred solution bromine (0.01 mol) was added drop wise at such a rate to keep the temperature about 10 °C. After the addition of bromine stirring was continued for an additional 3 h and then filtered, washed with

acetic acid and dried. The precipitate obtained was dissolved in hot water and neutralized with aqueous ammonia solution (25%) and then filtered, washed with water and dried, recrystallized with benzene to obtain 6-substituted-1, 3-benzothiazol-2-amine or purified by column chromatography using ethyl acetate/petrol ether (1:2) as eluent.



R = H, OMe, Me, Br, Cl, F, OEt

Procedure for synthesis of 2-Thiomethyl-4-substituted aniline[23]

To the stirred solution of KOH (6 g) in 24 mL of water, benzothioazole (3 mmol) was added and refluxed for 17 h. After cooling to room temperature, MeI (3 mmol) was added drop wise and stirring was continued for an additional 1 h. The resultant reaction mixture extracted with diethyl ether (3 x 25 mL) combined organic layers dried over $MgSO_4$, filtered and concentrated in vacuum. Purification of the crude product was achieved by flash column chromatography using petrol ether/ethyl acetate (15:1) as eluent.

Procedure for the preparation of *o*-methylthio-arenediazonium tetrafluoroborates[24]

The *o*-methylthio aniline (10 mmol) was dissolved in a mixture of 4 mL of distilled water and 3.4 mL of 50% hydrofluoroboric acid. The reaction mixture was cooled to 0 °C using ice-water bath, and then sodium nitrite solution (0.69 g in 1.5 mL) was added drop wise. The resulting mixture was stirred for 40 min at 0-5 °C and the precipitate was collected by filtration and re-dissolved in minimum amount of acetone. Diethyl ether was added until precipitation of diazonium tetrafluoroborate, which is filtered, washed several times with diethyl ether and dried under vacuum.

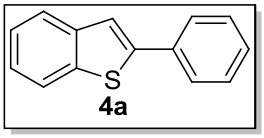
Photocatalytic reactions:

General procedure for the reaction of *o*-methylthio-arenediazonium tetrafluoroborates with terminal alkynes

In a 5 mL snap vial equipped with magnetic stirring bar the eosin Y (0.05 equiv), *o*-methylthio-arenediazonium tetrafluoroborate (1 equiv) and alkyne (5 equiv) were dissolved in dry DMSO (0.25 mmol/mL), and the resulting mixture was degassed by "pump-freeze-thaw" cycles (×3) via a syringe needle. The snap vial was irradiated through the vial's plane bottom side using 530 nm LEDs. After 14 h of irradiation, the reaction mixture was transferred to separating funnel, diluted with diethyl ether and washed with 15 mL of water. The aqueous

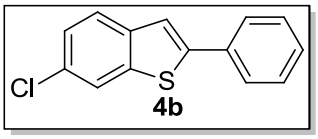
layer was washed three times (3 x 15 mL) with diethyl ether. The combined organic phases were dried over $MgSO_4$, filtered and concentrated in vacuum. Purification of the crude product was achieved by flash column chromatography using petrol ether/ethyl acetate as eluent.

2-Phenylbenzo[b]thiophene (4a)[9a]



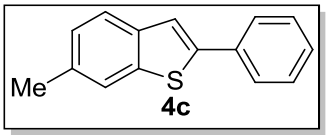
^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 7.84 (d, *J* = 7.4 Hz, 1H), 7.79 (dd, *J* = 7.0, 1.7 Hz, 1H), 7.73 (d, *J* = 7.2 Hz, 2H), 7.56 (s, 1H), 7.49 – 7.40 (m, 2H), 7.40 – 7.28 (m, 3H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 144.2, 140.6, 139.5, 134.3, 128.9, 128.2, 126.5, 124.5, 124.3, 123.5, 122.2, 119.4

6-Chloro-2-phenylbenzo[b]thiophene (4b)[9a]



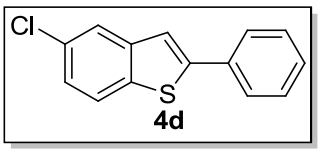
^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 7.81 (d, *J* = 1.8 Hz, 1H), 7.73 – 7.62 (m, 3H), 7.50 (s, 1H), 7.48 – 7.39 (m, 2H), 7.37 (dt, *J* = 5.2, 2.1 Hz, 1H), 7.32 (dd, *J* = 8.5, 1.9 Hz, 1H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 144.8, 140.4, 139.1, 133.8, 130.2, 129.0, 128.5, 126.4, 125.3, 124.3, 121.8, 118.9

6-Methyl-2-phenylbenzo[b]thiophene (4c)[9a]



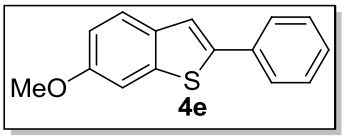
^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 7.68 (d, *J* = 7.1 Hz, 2H), 7.63 (d, *J* = 8.1 Hz, 1H), 7.60 (s, 1H), 7.48 (s, 1H), 7.44 - 7.35 (m, 2H), 7.34 – 7.25 (m, 1H), 7.15 (dd, *J* = 8.1, 1.0 Hz, 1H), 2.45 (s, 3H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 143.0, 139.8, 138.4, 134.4, 134.3, 128.9, 128.0, 126.3, 126.2, 123.2, 122.1, 119.2, 21.6

5-Chloro-2-phenylbenzo[b]thiophene (4d)



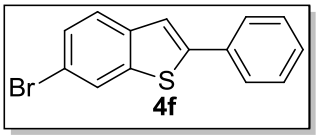
^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 7.81 – 7.63 (m, 4H), 7.50 – 7.33 (m, 4H), 7.30 – 7.25 (m, 1H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 146.3, 141.7, 137.5, 133.8, 130.7, 129.0, 128.9, 128.6, 126.5, 126.4, 124.7, 123.2, 123.0, 118.6

6-Methoxy-2-phenylbenzo[b]thiophene (4e)[25]



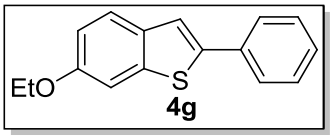
^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 7.74 – 7.62 (m, 3H), 7.47 (s, 1H), 7.46 – 7.38 (m, 2H), 7.37 – 7.27 (m, 2H), 6.99 (dd, *J* = 8.7, 2.4 Hz, 1H), 3.89 (s, 3H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 141.5, 140.9, 134.7, 134.4, 128.9, 127.8, 126.1, 124.2, 118.9, 114.5, 104.8, 55.5

6-Bromo-2-phenylbenzo[b]thiophene (4f)



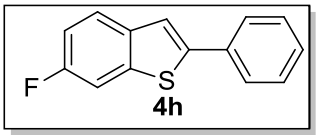
^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 7.96 (d, *J* = 1.6 Hz, 1H), 7.70 (d, *J* = 7.0 Hz, 2H), 7.62 (d, *J* = 8.5 Hz, 1H), 7.49 (s, 1H), 7.45 (dd, *J* = 12.7, 4.5 Hz, 3H), 7.40 – 7.32 (m, 1H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 144.9, 140.9, 139.4, 133.7, 129.0, 128.5, 127.9, 126.4, 124.7, 124.6, 118.9, 118.0
HRMS:
Calculated: 287.9608
Found: 287.9610

6-Ethoxy-2-phenylbenzo[b]thiophene (4g)



^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 7.78 – 7.54 (m, 3H), 7.46 (s, 1H), 7.45 – 7.38 (m, 2H), 7.36 – 7.27 (m, 2H), 6.99 (dd, *J* = 8.7, 2.3 Hz, 1H), 4.11 (q, *J* = 7.0 Hz, 2H), 1.47 (t, *J* = 7.0 Hz, 3H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 156.7, 141.4, 140.9, 134.6, 134.5, 128.9, 127.7, 126.1, 124.2, 119.0, 114.9, 105.5, 63.8, 14.8
HRMS:
Calculated: 254.0765
Found: 254.0769

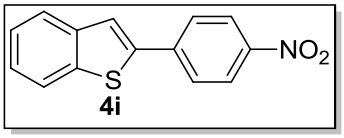
6-Fluoro-2-phenylbenzo[b]thiophene (4h)[9a]



^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 7.77 – 7.62 (m, 3H), 7.56 – 7.47 (m, 2H), 7.48 – 7.39 (m, 2H), 7.39 – 7.31 (m, 1H), 7.11 (td, *J* = 8.9, 2.4 Hz, 1H)

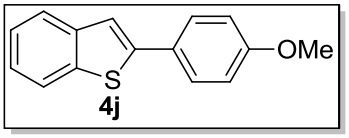
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 160.4 (d, *J* = 244.2 Hz), 143.9 (d, *J* = 4.1 Hz), 140.4 (d, *J* = 10.2 Hz), 137.1, 134.0, 129.0, 128.3, 126.3, 124.5 (d, *J* = 8.9 Hz), 118.8, 113.5 (d, *J* = 24.2 Hz), 108.4 (d, *J* = 25.6 Hz)

2-(4-Nitrophenyl)benzo[b]thiophene (4i)[26]



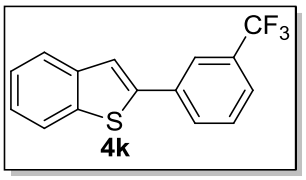
^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 8.23 (d, *J* = 8.9 Hz, 2H), 7.87 – 7.73 (m, 4H), 7.66 (s, 1H), 7.43 – 7.28 (m, 2H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 147.1, 141.1, 140.5, 140.2, 140.2, 126.7, 125.5, 125.0, 124.3, 124.2, 122.4. 122.4

2-(4-Methoxyphenyl)benzo[b]thiophene (4j)[26]



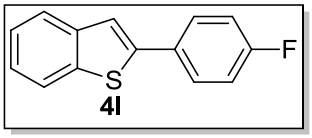
^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 7.81 (d, *J* = 7.8 Hz, 1H), 7.78 – 7.70 (m, 1H), 7.65 (d, *J* = 8.8 Hz, 2H), 7.43 (s, 1H), 7.39 – 7.26 (m, 2H), 6.96 (d, *J* = 8.8 Hz, 2H), 3.86 (s, 3H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 159.8, 144.0, 140.9, 139.2, 127.7, 127.0, 124.4, 123.9, 123.2, 122.2, 118.2, 114.3, 55.4

2-(3-(Trifluoromethyl)phenyl)benzo[b]thiophene (4k)[9a]



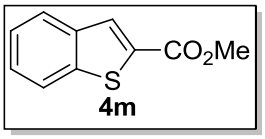
^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 7.96 (s, 1H), 7.91 – 7.83 (m, 2H), 7.81 (dd, *J* = 6.0, 2.1 Hz, 1H), 7.66 – 7.50 (m, 3H), 7.46 – 7.30 (m, 2H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 142.3, 140.5, 139.6, 135.1, 131.5(q, *J* = 32.5 Hz), 129.6, 129.5, 124.9, 124.8, 124.7 (q, *J* = 3.7 Hz), 123.9, 123.1 (q, *J* = 3.7 Hz), 122.3, 120.6

2-(4-Fluorophenyl)benzo[b]thiophene (4l)[27]



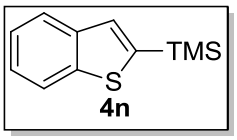
^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 7.83 (dd, *J* = 8.1, 0.9 Hz, 1H), 7.78 (dd, *J* = 6.9, 1.9 Hz, 1H), 7.73 – 7.60 (m, 2H), 7.47 (s, 1H), 7.35 (m, 2H), 7.13 (t, *J* = 8.7 Hz, 2H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 162.7 (d, *J* = 251.6 Hz), 143.0, 140.6, 139.4, 130.5 (d, *J* = 3.5 Hz), 128.1 (d, *J* = 8.1 Hz), 124.6, 124.4, 123.5, 122.2, 119.4 (d, *J* = 1.1 Hz), 115.9 (d, *J* = 21.9 Hz)

Methyl benzo[b]thiophene-2-carboxylate (4m)[28]



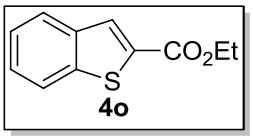
^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 8.07 (s, 1H), 7.87 (ddd, *J* = 7.8, 3.6, 1.6 Hz, 2H), 7.56 – 7.34 (m, 2H), 3.95 (s, 3H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 163.2, 142.2, 138.7, 133.3, 130.6, 126.9, 125.5, 124.9, 122.7, 52.5

Benzo[b]thiophen-2-yltrimethylsilane (4n)[29]



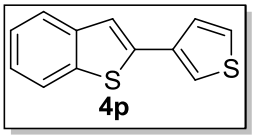
^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 7.89 (dd, *J* = 6.8, 2.1 Hz, 1H), 7.82 (dd, *J* = 6.5, 2.5 Hz, 1H), 7.48 (s, 1H), 7.39 – 7.27 (m, 2H), 0.39 (s, 9H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 143.5, 142.2, 141.0, 130.8, 124.1, 124.0, 123.4, 122.2, -0.3

Ethyl benzo[b]thiophene-2-carboxylate (4o)[30]



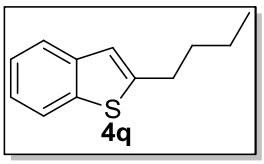
^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 8.06 (s, 1H), 7.94 – 7.80 (m, 2H), 7.56 – 7.34 (m, 2H), 4.41 (q, *J* = 7.1 Hz, 2H), 1.42 (t, *J* = 7.1 Hz, 3H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 162.8, 142.1, 138.7, 133.8, 130.3, 126.8, 125.5, 124.8, 122.7, 61.6, 14.3

2-(Thiophen-3-yl)benzo[b]thiophene (4p)[30]



^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 7.81 (d, *J* = 7.3 Hz, 1H), 7.76 (dd, *J* = 6.9, 1.8 Hz, 1H), 7.52 (dd, *J* = 2.8, 1.4 Hz, 1H), 7.42 (qd, *J* = 5.1, 2.2 Hz, 3H), 7.33 (tt, *J* = 8.7, 3.6 Hz, 2H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 140.4, 139.0, 138.9, 135.7, 126.5, 126.1, 124.5, 124.2, 123.4, 122.2, 121.3, 119.3

2-Butylbenzo[b]thiophene (4q)[31]

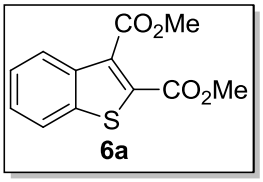


^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 7.76 (d, *J* = 9.0 Hz, 1H), 7.66 (d, *J* = 7.3 Hz, 1H), 7.33-7.22 (m, 1H), 7.27 – 7.21 (m, 1H), 7.00 (s, 1H), 2.91 (t, *J* = 8.0 Hz, 2H), 1.88 – 1.63 (m, 2H), 1.50-1.37 (dq, *J* = 14.5, 7.3 Hz, 2H), 0.96 (t, *J* = 7.3 Hz, 3H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 146.8, 140.2, 139.3, 124.0, 123.3, 122.6, 122.1, 120.4, 33.3, 30.5, 22.2, 13.8

General procedure for the reaction of *o*-methylthio-arenediazonium tetrafluoroborates with internal alkynes

In a 5 mL snap vial equipped with magnetic stirring bar the eosin Y (0.05 equiv), *o*-methylthio-arenediazonium tetrafluoroborate (1 equiv) and internal alkyne (5 equiv) were dissolved in dry DMSO (0.25 mmol/mL), and the resulting mixture was degassed by "pump-freeze-thaw" cycles (×3) via a syringe needle. The snap vial was irradiated through the vial's plane bottom side using 530 nm LEDs. After 14 h of irradiation, the reaction mixture was transferred to separating funnel, diluted with diethyl ether and washed with 15 mL of water. The aqueous layer was washed three times (3 x 15 mL) with diethyl ether. The combined organic phases were dried over $MgSO_4$, filtered and concentrated in vacuum. Purification of the crude product was achieved by flash column chromatography using petrol ether/ethyl acetate (30:1) as eluent.

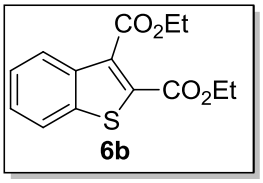
Dimethyl benzo[b]thiophene-2, 3-dicarboxylate (6a)[32]



6a

^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 7.93 (dd, *J* = 6.5, 2.4 Hz, 1H), 7.85 (dd, *J* = 6.7, 2.4 Hz, 1H), 7.56 – 7.40 (m, 2H), 4.03 (s, 3H), 3.95 (s, 3H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 164.9, 162.2, 140.3, 136.7, 133.2, 133.1, 127.4, 125.6, 124.5, 122.5, 52.9, 52.8
HRMS:
Calculated: 250.030
Found: 250.0299

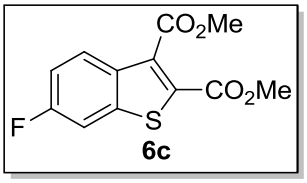
Diethyl benzo[b]thiophene-2, 3-dicarboxylate (6b)



6b

^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 7.98 – 7.89 (m, 1H), 7.89 – 7.79 (m, 1H), 7.54 – 7.38 (m, 2H), 4.50 (q, *J* = 7.2 Hz, 2H), 4.41 (q, *J* = 7.1 Hz, 2H), 1.44 (t, *J* = 5.7 Hz, 3H), 1.40 (t, *J* = 5.7 Hz, 3H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 164.53 , 161.8, 140.3, 136.8, 133.4, 133.2, 127.3, 125.5, 124.4, 122.5, 62.1, 61.9, 14.1
HRMS:
Calculated: 278.0613
Found: 278.0615

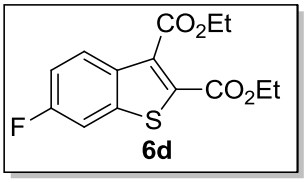
Dimethyl 6-fluorobenzo[b]thiophene-2, 3-dicarboxylate (6c)



6c

^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 7.90 (dd, *J* = 9.0, 5.1 Hz, 1H), 7.53 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.22 (td, *J* = 8.9, 2.4 Hz, 1H), 4.02 (s, 3H), 3.94 (s, 3H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 164.2 (d, *J* = 61.8 Hz), 161.1 (d, *J* = 98.5 Hz), 141.3 (d, *J* = 4.6 Hz), 133.3 (d, *J* = 1.4 Hz), 132.9 (d, *J* = 3.6 Hz), 132.7, 126.1 (d, *J* = 9.5 Hz), 115.4, 115.1, 108.5 (d, *J* = 25.7 Hz), 53.0, 52.9
HRMS:
Calculated: 268.0206
Found: 268.0203

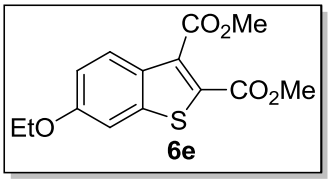
Diethyl 6-fluorobenzo[b]thiophene-2, 3-dicarboxylate (6d)



6d

^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 7.90 (dd, *J* = 9.0, 5.1 Hz, 1H), 7.52 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.21 (td, *J* = 8.9, 2.4 Hz, 1H), 4.49 (q, *J* = 7.2 Hz, 2H), 4.40 (q, *J* = 7.1 Hz, 2H), 1.43 (t, *J* = 5.5 Hz, 3H), 1.39 (t, *J* = 5.5 Hz, 3H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 164.0 (d, *J* = 39.1 Hz), 160.9 (d, *J* = 74.9 Hz), 141.4 (d, *J* = 10.6 Hz), 133.4 (d, *J* = 1.4 Hz), 133.3 (d, *J* = 4.3 Hz), 132.8, 126.0 (d, *J* = 9.5 Hz), 115.3, 115.0, 108.5 (d, *J* = 25.6 Hz), 62.2, 62.1, 14.1
HRMS:
Calculated: 296.0519
Found: 296.0517

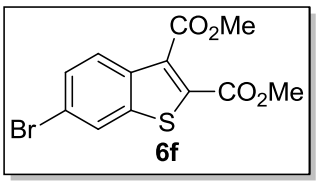
Dimethyl 6-ethoxybenzo[b]thiophene-2, 3-dicarboxylate (6e)



6e

^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 7.75 (d, *J* = 9.0 Hz, 1H), 7.23 (d, *J* = 2.3 Hz, 1H), 7.05 (dd, *J* = 9.0, 2.3 Hz, 1H), 4.09 (q, *J* = 7.0 Hz, 2H), 4.01 (s, 3H), 3.91 (s, 3H), 1.45 (t, *J* = 7.0 Hz, 3H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 165.2, 162.1, 159.1, 142.4, 133.4, 130.6, 129.5, 125.2, 116.9, 104.5, 63.9, 52.8, 52.7, 14.6
HRMS:
Calculated: 294.0562
Found: 294.0567

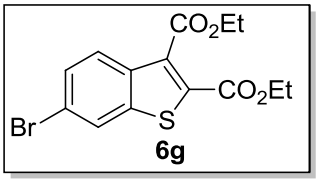
Dimethyl 6-bromobenzo[b]thiophene-2, 3-dicarboxylate (6f)



6f

^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 8.00 (d, *J* = 1.7 Hz, 1H), 7.80 (d, *J* = 8.7 Hz, 1H), 7.56 (dd, *J* = 8.7, 1.7 Hz, 1H), 4.01 (s, 3H), 3.95 (s, 3H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 164.3, 161.8, 141.4, 135.5, 133.8, 132.6, 129.3, 125.6, 125.0, 121.8, 53.1, 53.0
HRMS:
Calculated: 327.9405
Found: 327.9408

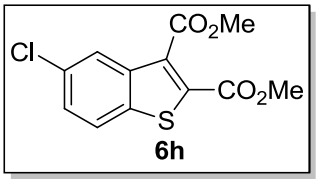
Diethyl 6-bromobenzo[b]thiophene-2, 3-dicarboxylate (6g)



6g

^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 8.00 (d, *J* = 1.7 Hz, 1H), 7.80 (d, *J* = 8.7 Hz, 1H), 7.56 (dd, *J* = 8.7, 1.7 Hz, 1H), 4.48 (q, *J* = 7.2 Hz, 2H), 4.40 (q, *J* = 7.1 Hz, 2H), 1.43 (t, *J* = 4.6 Hz, 3H), 1.39 (t, *J* = 4.6 Hz, 3H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 164.0, 161.4, 141.4, 135.6, 134.1, 132.7, 129.2, 125.6, 125.0, 121.6, 62.3, 62.1, 14.1
HRMS:
Calculated: 355.9718
Found: 355.9722

Dimethyl 5-chlorobenzo[b]thiophene-2, 3-dicarboxylate (6h)

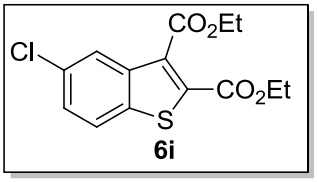


6h

^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 7.96 (d, *J* = 2.0 Hz, 1H), 7.77 (d, *J* = 8.6 Hz, 1H), 7.45 (dd, *J* = 8.7, 2.0 Hz, 1H), 4.02 (s, 3H), 3.95 (s, 3H)

^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 164.1, 161.8, 138.1, 137.7, 135.5, 132.2, 131.8, 128.0, 124.1, 123.6, 53.1, 52.9
HRMS:
Calculated: 283.9910
Found: 283.9914

Diethyl 5-chlorobenzo[b]thiophene-2, 3-dicarboxylate (6i)



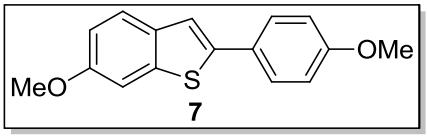
6i

^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 7.96 (d, *J* = 1.9 Hz, 1H), 7.76 (d, *J* = 8.7 Hz, 1H), 7.44 (dd, *J* = 8.7, 2.0 Hz, 1H), 4.49 (q, *J* = 7.1 Hz, 2H), 4.41 (q, *J* = 7.1 Hz, 2H), 1.44 (t, *J* = 5.5 Hz, 3H), 1.39 (t, *J* = 5.5 Hz, 3H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 163.8, 161.5, 138.1, 137.9, 135.9, 132.1, 131.9, 127.9, 124.1, 123.5, 62.4, 62.1, 14.1
HRMS:
Calculated: 312.0223
Found: 312.0222

Procedure for synthesis of core molecule for Raloxifene

In a 5 mL snap vial equipped with magnetic stirring bar the eosin Y (0.05 equiv), 4-methoxy-2-(methylthio)-benzenediazonium salt (1 equiv) and 1-ethynyl-4-methoxybenzene (5 equiv) were dissolved in dry DMSO (0.25 mmol/mL), and the resulting mixture was degassed by "pump-freeze-thaw" cycles (×3) via a syringe needle. The snap vial was irradiated through the vial's plane bottom side using 530 nm LEDs. After 14 h of irradiation, the reaction mixture was transferred to separating funnel, diluted with diethyl ether and washed with 15 mL of water. The aqueous layer was washed three times (3 x 15 mL) with diethyl ether. The combined organic phases were dried over $MgSO_4$, filtered and concentrated in vacuum. Purification of the crude product was achieved by flash column chromatography using petrol ether/ethyl acetate (80:1) as eluent.

6-Methoxy-2-(4-methoxyphenyl)benzo[b]thiophene (7)[15]



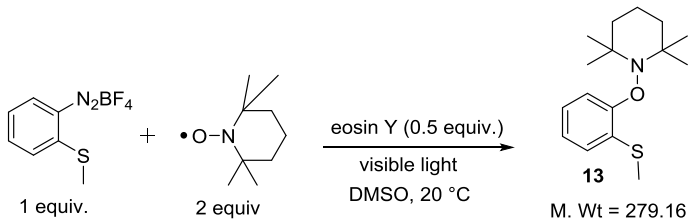
7

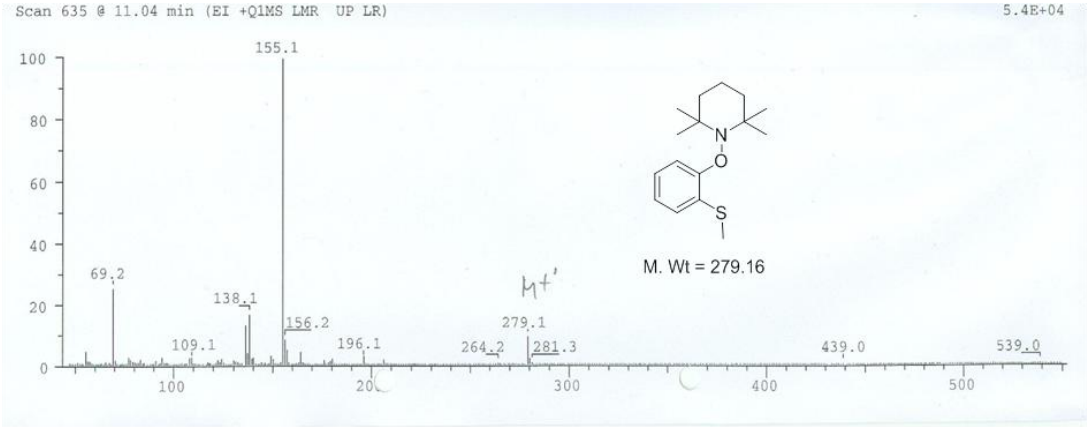
^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 7.67 – 7.52 (m, 3H), 7.34 (s, 1H), 7.29 (d, *J* = 2.3 Hz, 1H), 7.02 – 6.84 (m, 3H), 3.88 (s, 3H), 3.85 (s, 3H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 159.4, 157.2, 141.5, 140.6, 134.9, 127.4, 127.3, 123.9, 117.7, 114.3, 114.3, 104.9, 55.6, 55.4

Radical Capturing Experiments

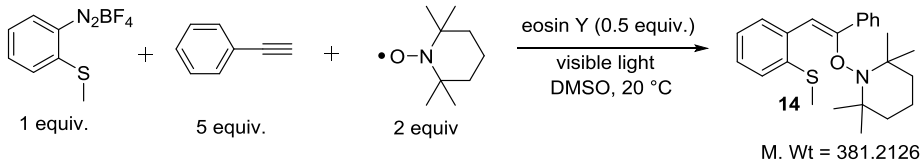
The experimental procedure for capturing radicals with TEMPO

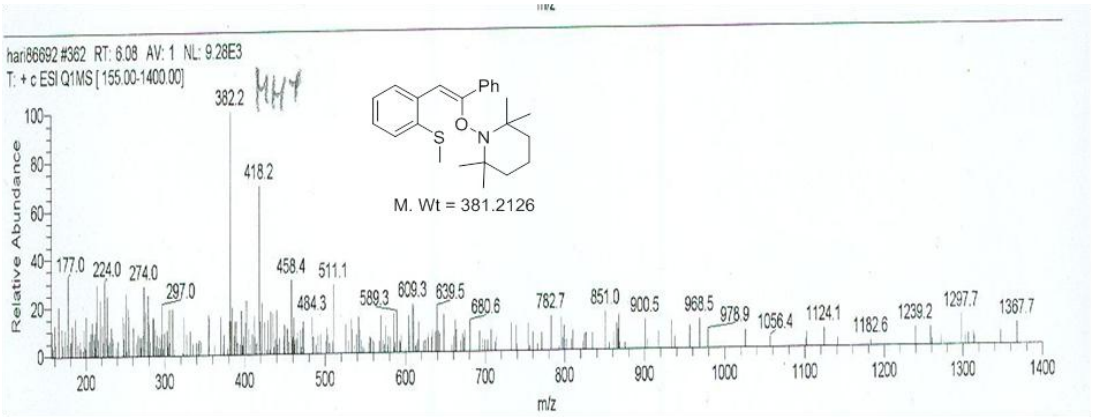
1) In a 5 mL snap vial equipped with magnetic stirring bar the eosin Y (0.5 equiv), *o*-methylthio-arenediazonium tetrafluoroborate (1 equiv) and TEMPO (2 equiv) were dissolved in dry DMSO (0.25 mmol/mL) and the resulting mixture was degassed by "pump-freeze-thaw" cycles (×2) via a syringe needle. The vial was irradiated through the vial's plane bottom side using green LEDs. After 4 h of irradiation, a TEMPO trapped compound **13** was detected by mass spectra.





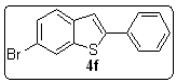
2) In a 5 mL snap vial equipped with magnetic stirring bar the eosin Y (0.5 equiv), *o*-methylthio-arenediazonium tetrafluoroborate (1 equiv), phenyl acetylene (5 equiv) and TEMPO (2 equiv) were dissolved in dry DMSO (0.25 mmol/mL) and the resulting mixture was degassed by "pump-freeze-thaw" cycles (×2) via a syringe needle. The vial was irradiated through the vial's plane bottom side using green LEDs. After 4 h of irradiation, a TEMPO trapped compound **14** was detected by mass spectra.

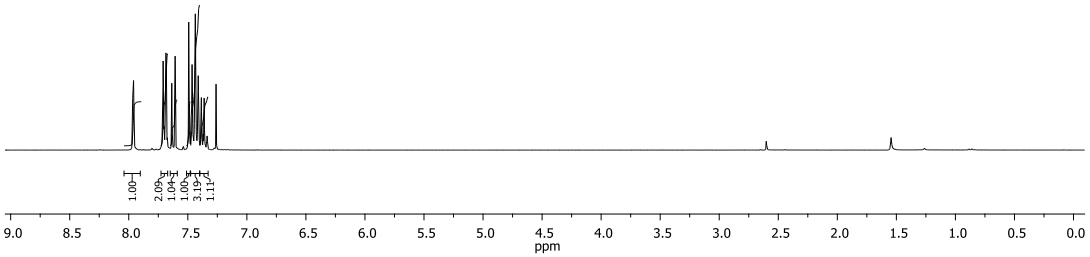



hari86692 #362 RT: 6.08 AV: 1 NL: 9.28E3
T: + c ESI Q1MS [155.00-1400.00]
382.2
MH+
418.2
Ph
O
N
S
M. Wt = 381.2126
Relative Abundance
177.0
224.0
274.0
297.0
458.4
511.1
484.3
589.3
609.3
639.5
680.6
782.7
851.0
900.5
968.5
978.9
1056.4
1124.1
1182.6
1239.2
1297.7
1367.7
m/z

^{1}H and ^{13}C NMR spectra of selected compounds

^{1}H NMR (300MHz, $CDCl_3$)





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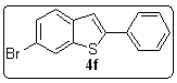

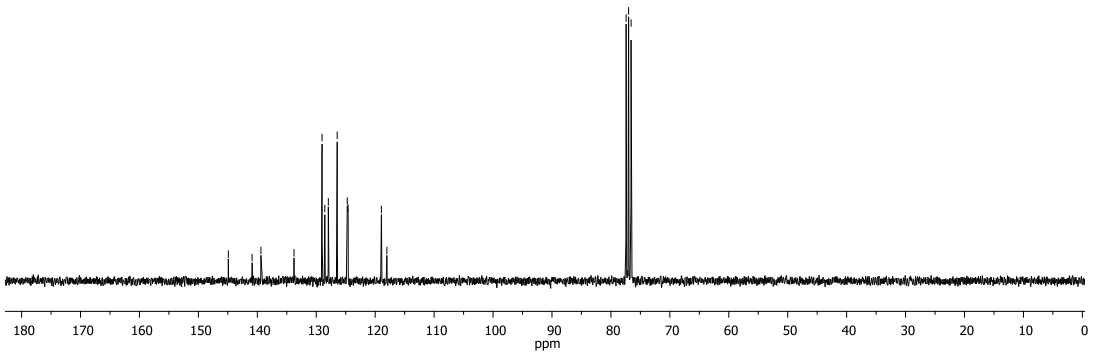

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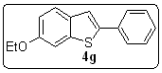

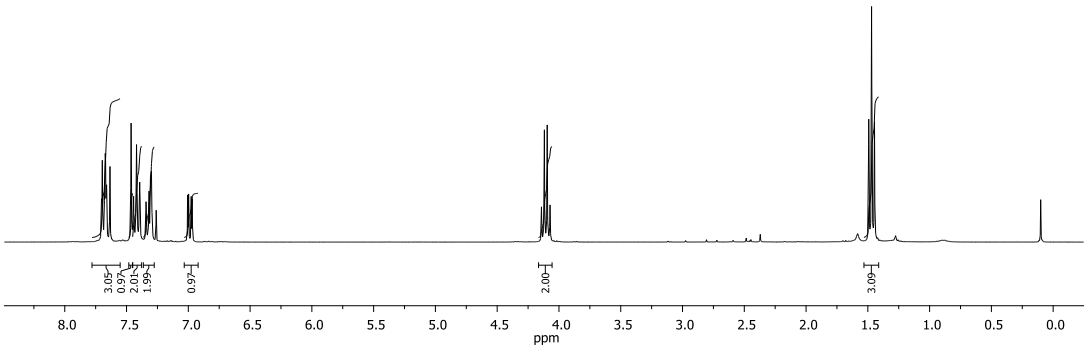

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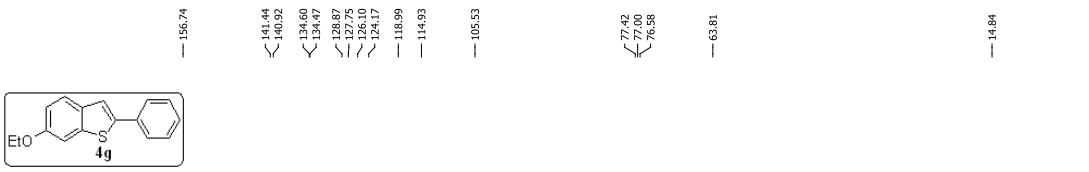

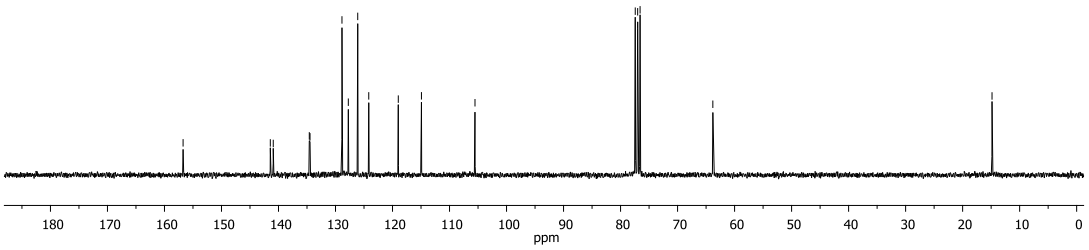

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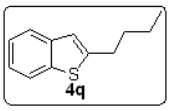

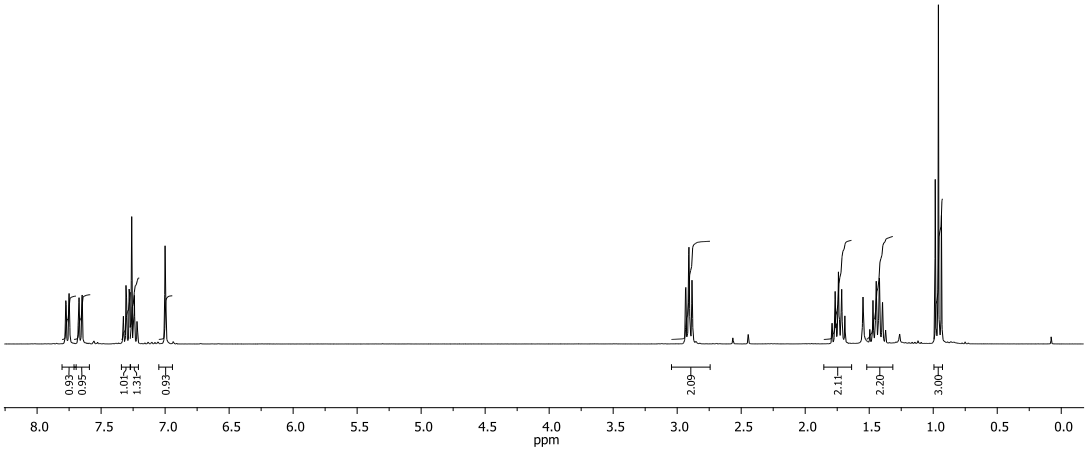

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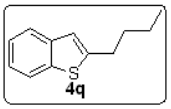

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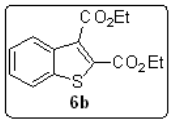

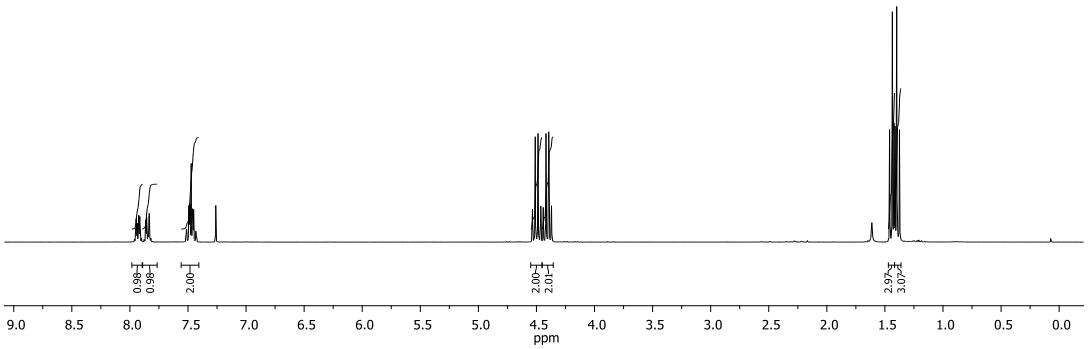

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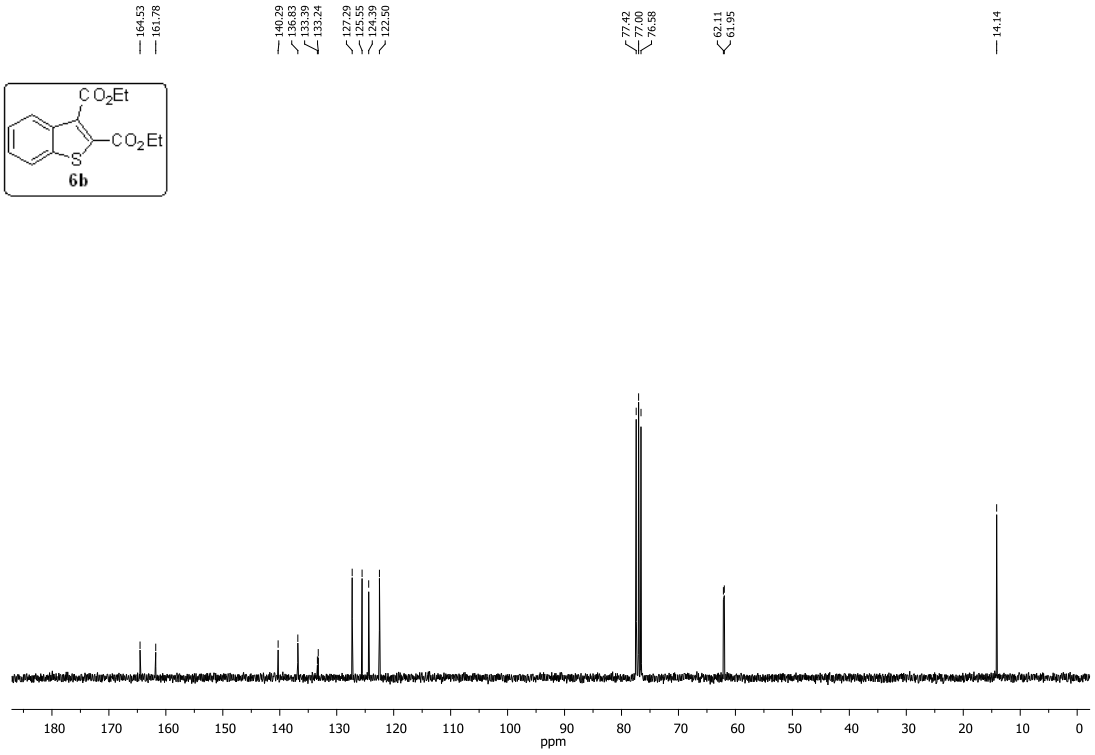

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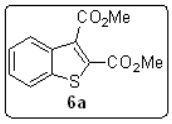

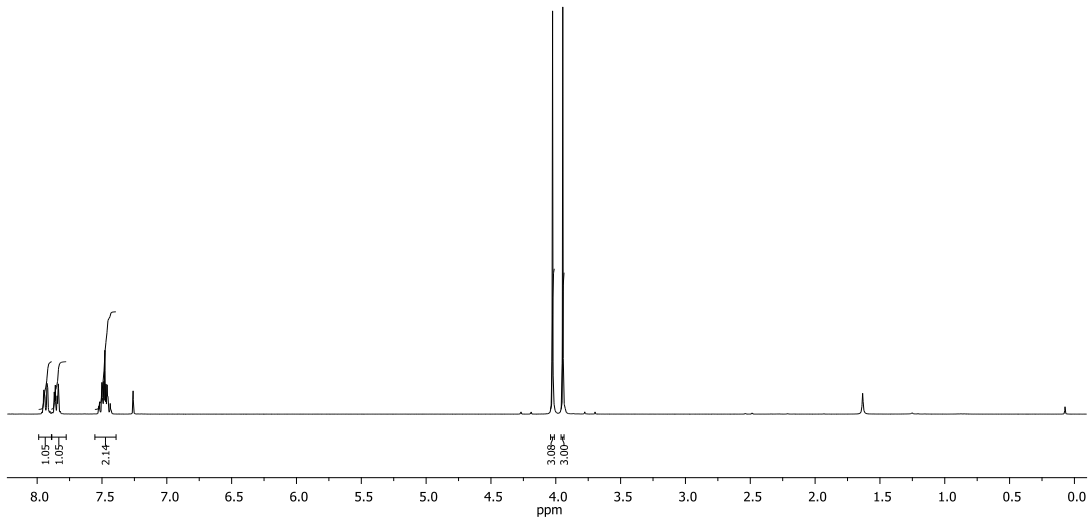

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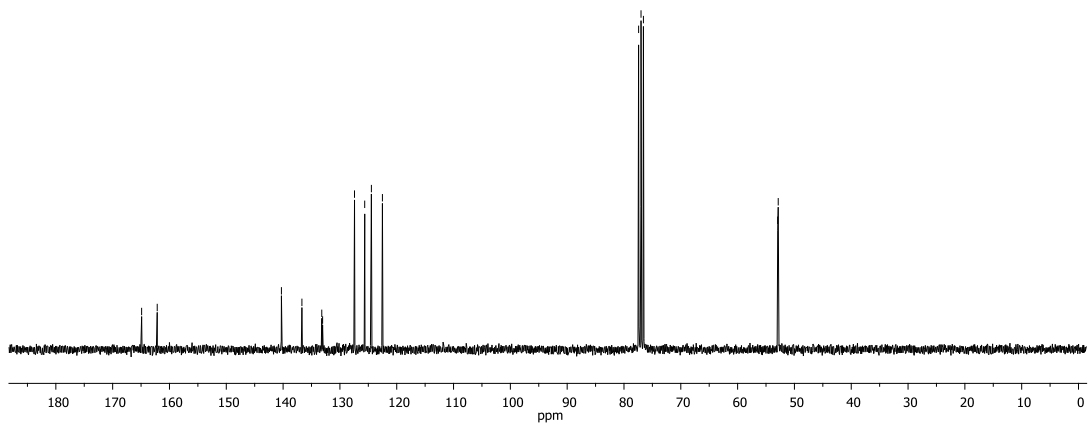

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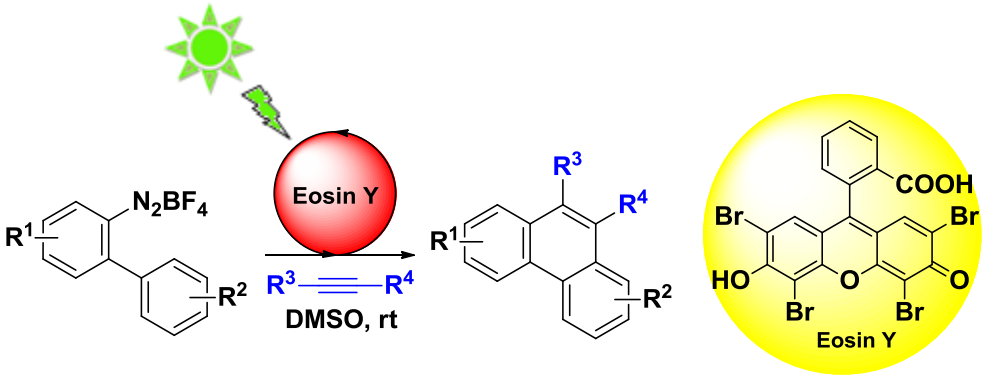
Chapter 4

4 Synthesis of Phenanthrene Derivatives by Visible Light Photocatalysis



Phenanthrenes have been synthesized from their corresponding biaryl diazonium salts and alkynes using 2 mol% eosin Y as photocatalyst under green light irradiation *via* a cascade radical addition and cyclization sequence. This reaction exhibits a wide range of functional group tolerance, broad substrate scope and is an attractive alternative to the transition metal mediated [4+2] benzannulation reaction.

Author contributions:
DP synthesized starting materials and carried out all the photochemical reactions.

4.1 Introduction

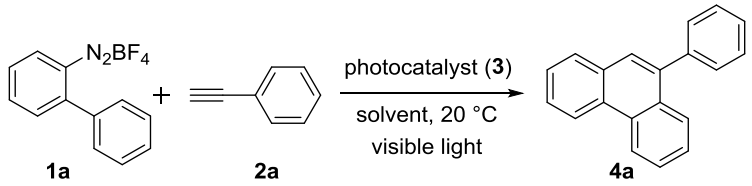
Phenanthrenes are important structural motifs in organic chemistry and they are found in natural products, in drugs and organic materials.[1] Many methods have been developed for the synthesis of phenanthrenes, which can be divided into three types: Carbocyclic ring expansion, intramolecular cycloaddition, and intermolecular cycloaddition.[2] A common synthetic approach to phenanthrenes is the photocyclization of stilbenes by UV light irradiation followed by oxidation.[3] The use of visible light to induce the reaction has advantages, such as easier available light sources and was demonstrated by several research groups.[4]

Cano-Yelo and Deronzier first reported the synthesis of phenanthrenes using an intramolecular Pschorr reaction.[5] Zanardi and co-workers synthesized phenanthrenes from the corresponding diazonum salts in pyridine at 0 °C.[6] Recently, Nakamura and co-workers reported the synthesis of phenanthrenes by an iron-catalysed [4+2] benzannulation reaction of alkynes with biaryl Grignard reagent.[7] However, all of these methods still require the use of transition metal catalyst to mediate the reaction. We report now the synthesis of phenanthrenes from biaryl diazonium salts and alkynes using visible light and the organic dye eosin Y as photoredox catalyst.[8]

4.2 Results and Discussion

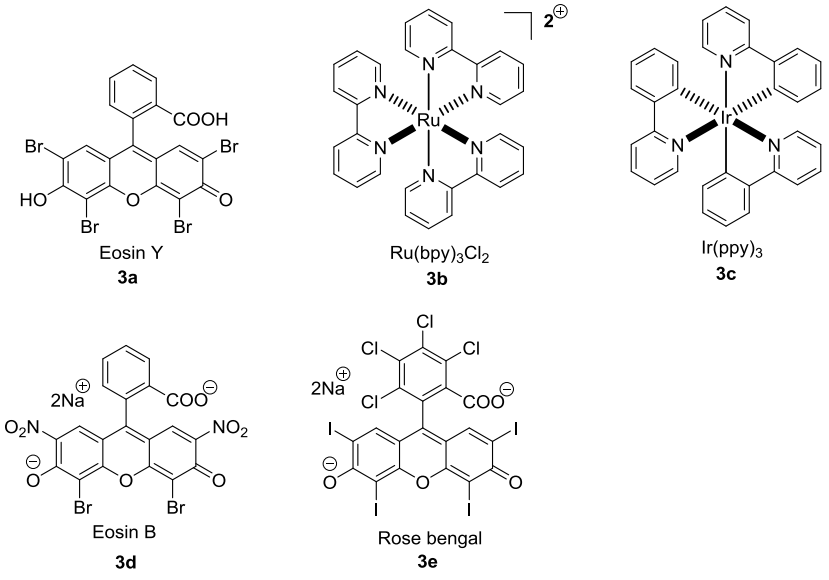
The reaction between diazonium salt **1a** and phenyl acetylene **2a** was conducted to optimize the reaction conditions, and the obtained results are summarized in Table 1. We examined a set of photoredox catalysts (Table 1, entries 1-5), different equivalents of phenyl acetylene (Table 1, entries 1, 6, and 7), and different solvents (Table 1, entries 7, 11, 12, and 13). Furthermore, we also varied the catalyst loading (Table 1, entries 1 and 8) and the reaction times (Table 1, entries 7 and 10). Finally, using 2 mol % of eosin Y, 10 equiv. of phenyl acetylene in DMSO gave optimal results after 2 h of green light irradiation. To show the significance of the photoreaction, we carried out control experiments without eosin Y and without green light. As expected, we observed 7 and 2 % of product yield, respectively (Table 1, entries 14 and 15).

Table 1. Optimisation of the reaction conditions.



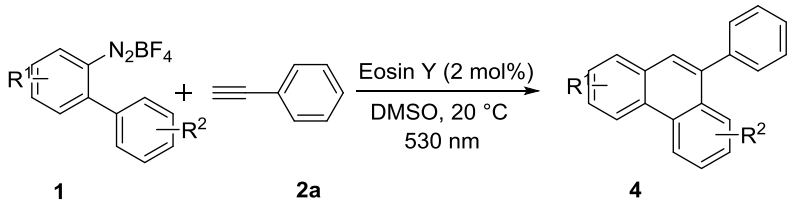
Entry	Conditions	Yield (%)[a]
1	**3a** (2 mol%), **2a** (5 equiv), DMSO, 2 h	73
2	**3b** (2 mol%), **2a** (5 equiv), DMSO, 2 h	73
3	**3c** (2 mol%), **2a** (5 equiv), DMSO, 2 h	73
4	**3d** (2 mol%), **2a** (5 equiv), DMSO, 2 h	71
5	**3e** (2 mol%), **2a** (5 equiv), DMSO, 2 h	71
6	**3a** (2 mol%), **2a** (2 equiv), DMSO, 2 h	55
7	**3a** (2 mol%), **2a** (10 equiv), DMSO, 2 h	82
8	**3a** (5 mol%), **2a** (5 equiv), DMSO, 2 h	73
9	**3a** (2 mol%), **2a** (5 equiv), DMSO, 4 h	71
10	**3a** (2 mol%), **2a** (10 equiv), DMSO, 4 h	82
11	**3a** (2 mol%), **2a** (10 equiv), DMF, 2 h	52
12	**3a** (2 mol%), **2a** (10 equiv), CH_3CN, 2 h	38
13	**3a** (2 mol%), **2a** (10 equiv), MeOH, 2 h	66
14	without **3a**, **2a** (10 equiv), DMSO, 2 h	7
15	**3a** (2 mol%), without light, **2a** (10 equiv), DMSO, 2 h	2

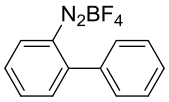
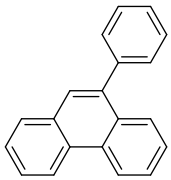
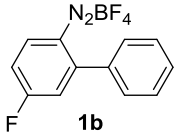
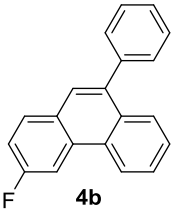
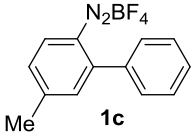
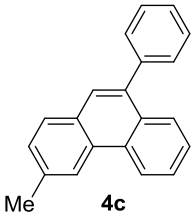
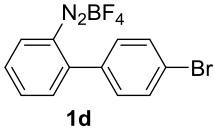
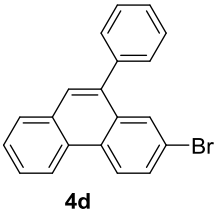
[a]GC yields.

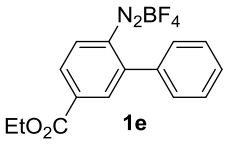
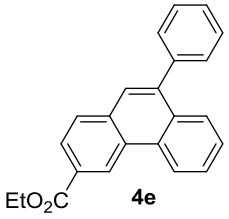
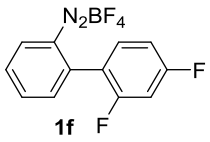
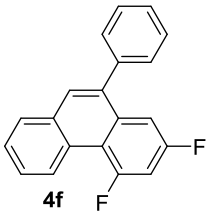
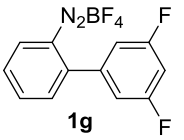
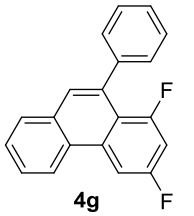
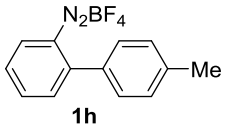
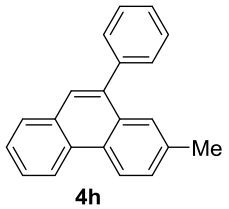
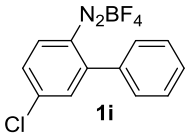
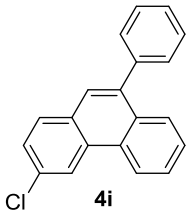


Having optimized reaction conditions in hand, the scope of the reaction towards biaryl diazonium salts was studied and the obtained results are summarized in Table 2. Biaryl diazonium salts bearing electron withdrawing and donating groups under went smoothly in this reaction to afford the corresponding products in good to excellent yields (Table 1, entries 3, 5, and 8). Notably, biaryl diazonium salts bearing chloro, bromo substitutents gave the corresponding phenanthrenes with an intact carbon-halogen bond (Table 1, entries 4 and 9). Such moieties are difficult to prepare using traditional methods and useful for further synthesis.[7]

Table 2. Scope of biaryl diazonium salts[a].



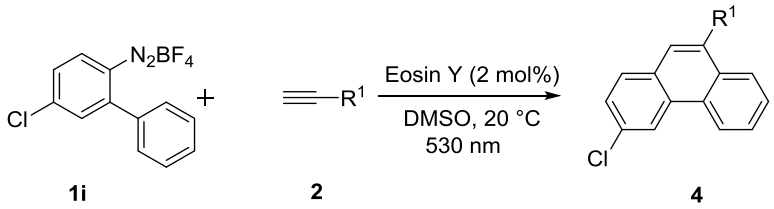
Entry	Substrate	Product	Yield (%)[b]
1	 1a	 4a	82
2	 1b	 4b	92
3	 1c	 4c	85
4	 1d	 4d	80

5			90
6			61
7			75
8			74
9			93

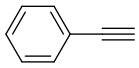
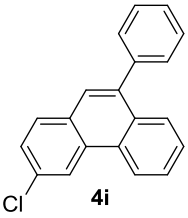
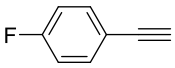
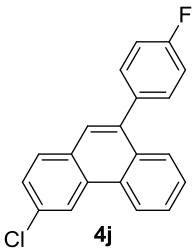
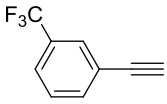
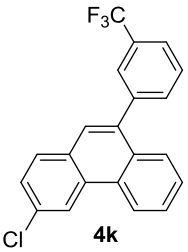
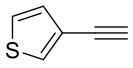
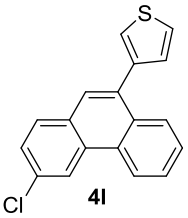
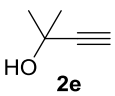
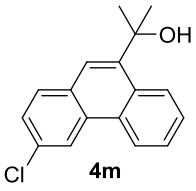
[a]The reaction was performed with **1** (0.25 mmol), phenyl acetylene **2a** (10 equiv), and eosin Y (0.02 equiv) in DMSO (0.25 M). [b]Isolated yields after purification by flash column chromatography using silica gel.

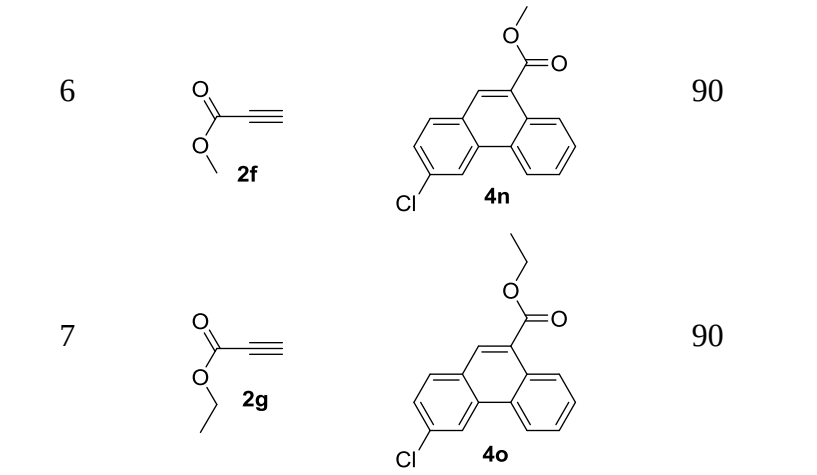
Next we investigated the scope of the reaction towards terminal alkynes in this photoreaction and the results are shown in Table 3. Aromatic alkynes bearing electron withdrawing and neutral groups are reacted well to afford the corresponding phenanthrenes in good to excellent yields (Table 3, entries 2 and 3). 3-Ethynylthiophene **2d** also reacted with **1i** to give the corresponding product **4l** in 82% yield (Table 3, entry 4). Such molecules find important applications in the synthesis of optoelectronic materials.[9] In addition to aromatic and hetero aromatic alkynes, aliphatic alkynes also reacted well in this reaction (Table 3, entries 5-7). Moreover, internal alkynes were converted successfully to give highly substituted phenanthrenes in moderate yields (Scheme 1).

Table 3. Scope of Terminal alkynes[a].

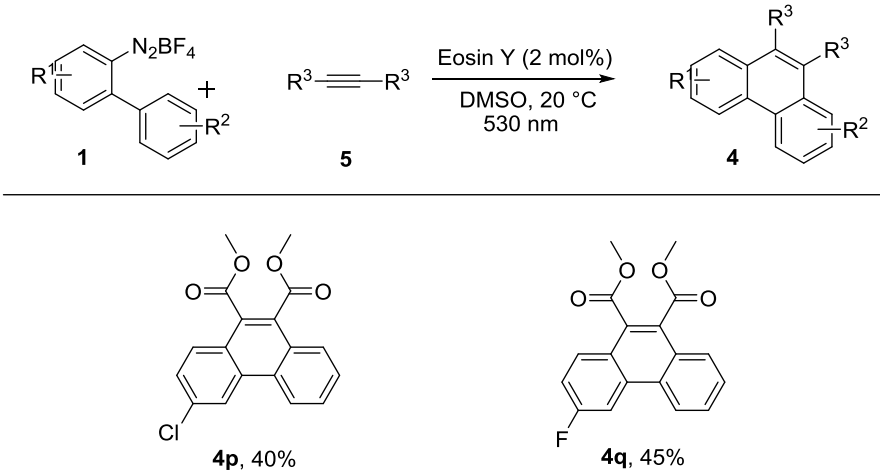


1i 2 4

Entry	Substrate	Product	Yield (%)[b]
1	 2a	 4i	93
2	 2b	 4j	90
3	 2c	 4k	87
4	 2d	 4l	82
5	 2e	 4m	85

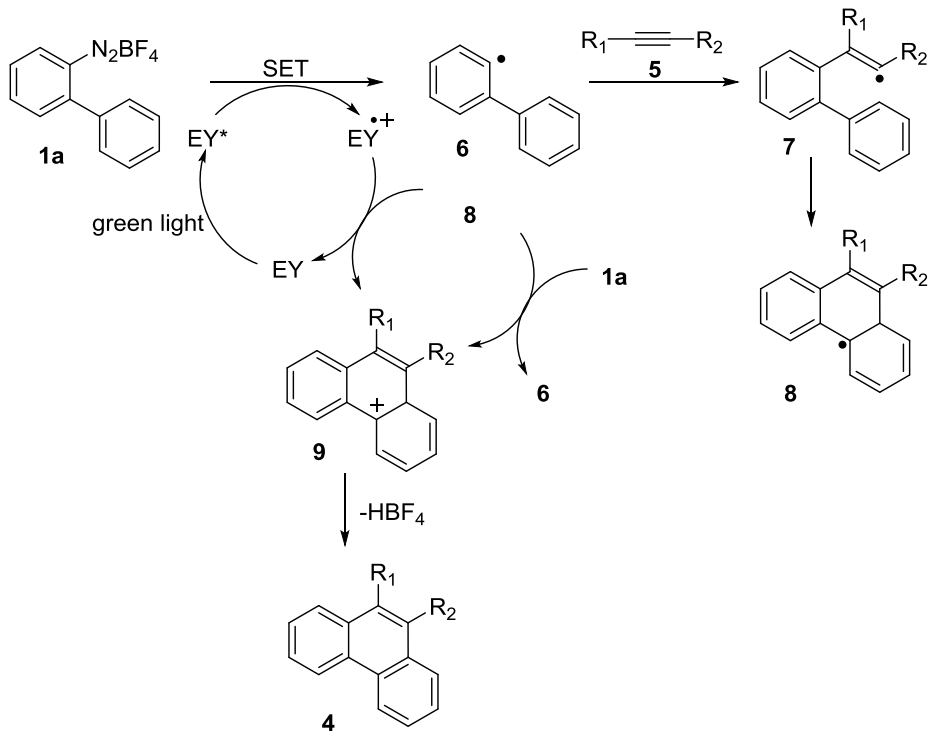


[a]The reaction was performed with **1i** (0.25 mmol), alkyne **2** (10 equiv), and eosin Y (0.02 equiv) in DMSO (0.25 M). [b]Isolated yields after purification by flash column chromatography using silica gel.



Scheme 1. Reaction of biaryl diazonium salts with internal alkynes.

The proposed mechanism of the reaction is depicted in Scheme 2. Initially, the excited state of eosin Y is oxidatively quenched by biaryl diazonium salt **1a** to generate the reactive biaryl radical **6** and the radical cation of eosin Y.[4a] An addition of radical **6** to alkyne **5** gives vinyl radical intermediate **7**, which undergoes intramolecular cyclization to give the cyclized radical intermediate **8.** Oxidation of **8** by the radical cation of eosin Y closes the catalytic cycle while generating the carbenium ion **9**. Finally, carbenium ion **9** undergoes deprotonation to afford the desired product **4**. Biaryl diazonium salt **1a** could also oxidize the intermediate **8** in a chain transfer mechanism.



Scheme 2. Proposed mechanism for the synthesis of phenanthrenes.

4.3 Conclusion

In summary, we have developed a metal free, visible light induced method for the synthesis of phenanthrenes *via* photoredox catalysis with green light. The method provides efficient access to a variety of phenanthrenes at ambient conditions and many products have potential for further synthetic elaboration. The present reaction displays a broad scope towards diazonium salts and alkynes with a wide range of functional group tolerance. The visible light mediated cascade radical addition and cyclization sequence represents an attractive alternative to known base - or transition metal catalyzed reactions.

4.4 Experimental Part

General Information

Proton NMR spectra were recorded on a Bruker Avance 300 MHz spectrometer in $CDCl_3$ with internal solvent signal peak at 7.26 ppm. Carbon NMR were recorded at 75 MHz spectrometer in $CDCl_3$ referenced to the internal solvent signal at 77.00 ppm. Proton NMR data are reported as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, dd = doublet of doublets, ddd = doublet of doublet of doublets, td = triplet of doublets, qd = quartet of doublets, m = multiplet, br. s. = broad

singlet), and coupling constants (Hz). All reactions were monitored by thin-layer chromatography using Merck silica gel plates 60 F254; visualization was accomplished with short wave UV light (254 nm). Flash chromatography was performed using silica gel of particle size 40−63 μm. All other commercially available solvents and reagents were used without any further purification.

General Procedures

Syntheses of 2-aminobiphenyls[10]

In a dry 100 mL round bottom flask, phenylboronic acid (768.16 mg, 6.3 mmol), K_2CO_3 (2.07 g, 15 mmol) and $Pd(OAc)_2$ (70 mg, 0.324 mmol) were added and dissolved in 14 mL of acetone and 17 mL of H_2O. To the reaction mixture, 2-bromoaniline (1.013 g, 5.96 mmol) was added and heated to 95 °C for 16 hours. After cooling, the reaction mixture was diluted with 100 mL of saturated aqueous NH_4Cl and 100 mL of CH_2Cl_2 and separated. The aqueous phase was extracted two times with DCM. The combined organic layers were washed with 100 mL of water and 100 mL of saturated aqueous $NaHCO_3$. The organic phase was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure and further purified by column chromatography using ethyl acetate and petrol ether.

Procedure for the preparation of biaryl diazonium tetrafluoroborates[11]

The appropriate 2-aminobiphenyl (10 mmol) was dissolved in a mixture of 3.4 mL of hydrofluoroboric acid (50%) and 4 mL of distilled water. The mixture was cooled down to 0 °C using an ice-water bath and then sodium nitrite ($NaNO_2$) solution (0.69 g in 1.5 mL) was added drop wise over 10 min. The resulting reaction mixture was stirred for 40 min at 0-5 °C and the obtained precipitate was collected by filtration, dried and re-dissolved in a minimum amount of acetone. Diethyl ether was added until precipitation of diazonium salt, which is filtered, washed several times with diethyl ether and dried under vacuum.

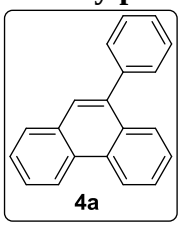
Photocatalytic reaction

General procedure for the reaction of biaryl diazonium tetrafluoroborates with alkynes

In a 5 mL snap vial equipped with magnetic stirring bar the catalyst eosin Y (0.02 equiv), biaryl diazonium tetrafluoroborate (1 equiv, 0.25 mmol), alkyne (10 equiv) dissolved in dry DMSO (0.25 M) and the resulting reaction mixture was degassed by 3x“pump-freeze-thaw” cycles *via* a syringe needle. The vial was irradiated through the vial’s plane bottom side using 530 nm green LEDs with cooling device maintaining a temperature around 20 °C. After 2 h of

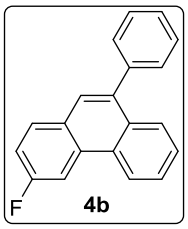
irradiation, the reaction mixture was transferred to a separating funnel, diluted with diethyl ether and washed with 15 mL of water. The aqueous layer was washed three times (3 x 15 mL) with diethyl ether. The combined organic phases were dried over Na_2SO_4, filtered and concentrated in vacuum. Purification of the crude product was achieved by flash column chromatography using petrol ether/ethyl acetate as eluent.

9-Phenylphenanthrene (4a)[12]



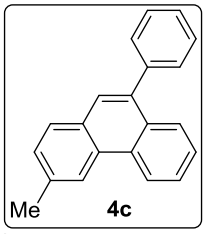
^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 8.79 (d, *J* = 8.3 Hz, 1H), 8.74 (d, *J* = 8.2 Hz, 1H), 7.91 (dd, *J* = 11.4, 4.9 Hz, 2H), 7.75 – 7.42 (m, 10H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 140.8, 138.7, 131.5, 131.1, 130.6, 130.0, 129.9, 128.6, 128.3, 127.5, 127.3, 126.9, 126.8, 126.6, 126.5, 126.4, 122.9, 122.5
HR: EI-MS [$M^{+\cdot}$]
Calculated: 254.1096
Found: 254.1095

3-Fluoro-9-phenylphenanthrene (4b)



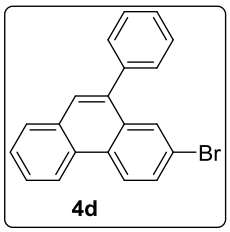
^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 8.64 (d, *J* = 8.1 Hz, 1H), 8.34 (dd, *J* = 11.2, 2.4 Hz, 1H), 7.94 (d, *J* = 8.2 Hz, 1H), 7.88 (dd, *J* = 8.8, 5.9 Hz, 1H), 7.74 – 7.64 (m, 2H), 7.63 – 7.43 (m, 6H), 7.38 (td, *J* = 8.5, 2.5 Hz, 1H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 161.6 (d, *J* = 245.3 Hz), 140.5, 138.0 (d, *J* = 2.7 Hz), 131.4 (d, *J* = 8.4 Hz), 131.3, 130.7 (d, *J* = 8.9 Hz), 130.0, 130.0, 128.3, 128.2 (d, *J* = 1.5 Hz), 127.4, 127.1, 127.0, 126.8, 126.5, 123.1, 115.9 (d, *J* = 23.9 Hz), 107.6 (d, *J* = 22.3 Hz)
HR: EI-MS [$M^{+\cdot}$]
Calculated: 272.1001
Found: 272.1003

3-Methyl-9-phenylphenanthrene (4c)[13]



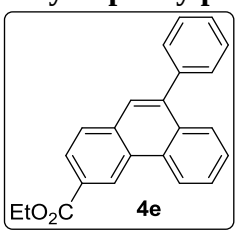
^{1}H NMR (300 MHz, $CDCl_3$):
δ 8.79 (d, *J* = 8.3 Hz, 1H), 8.54 (s, 1H), 7.93 (d, *J* = 8.3 Hz, 1H), 7.81 (d, *J* = 8.1 Hz, 1H), 7.73 – 7.62 (m, 2H), 7.63 – 7.40 (m, 7H), 2.67 (s, 3H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 140.9, 137.7, 136.3, 131.2, 130.3, 130.1, 130.0, 129.5, 128.6, 128.5, 128.2, 127.3, 127.2, 126.8, 126.3, 126.2, 122.8, 122.2, 22.2
HR: EI-MS [$M^{+\cdot}$]
Calculated: 268.1252
Found: 268.1246

2-Bromo-10-phenylphenanthrene (4d)



^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 8.64 (dd, *J* = 11.0, 8.4 Hz, 2H), 8.05 (d, *J* = 2.0 Hz, 1H), 7.90 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.79 – 7.60 (m, 4H), 7.58 – 7.45 (m, 5H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 140.0, 137.9, 132.6, 131.4, 129.9, 129.6, 129.5, 129.3, 129.1, 128.8, 128.7, 128.5, 127.7, 127.2, 127.0, 124.7, 122.4, 120.9
HR: EI-MS [$M^{+\cdot}$]
Calculated: 332.0201
Found: 332.0196

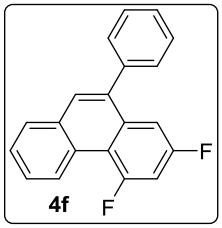
Ethyl 9-phenylphenanthrene-3-carboxylate (4e)



^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 9.48 (s, 1H), 8.89 (d, *J* = 8.2 Hz, 1H), 8.24 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.93 (t, *J* = 8.7 Hz, 2H), 7.81 – 7.66 (m, 2H), 7.67 – 7.41 (m, 6H), 4.52 (q, *J* = 7.1 Hz, 2H), 1.52 (t, *J* = 7.1 Hz, 3H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 166.9, 141.2, 140.3, 134.3, 131.2, 130.9, 129.9, 129.3, 128.6, 128.3, 128.0, 127.6, 127.1, 127.0, 127.0, 126.9, 126.7, 125.0, 123.1, 61.2, 14.4

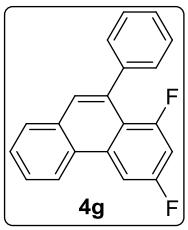
HR: EI-MS [$M^{+\cdot}$]
Calculated: 326.1307
Found: 326.1303

2,4-Difluoro-10-phenylphenanthrene (4f)[14]



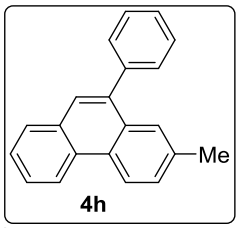
^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 9.08 (d, *J* = 8.0 Hz, 1H), 7.91 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.74 (s, 1H), 7.73 – 7.60 (m, 2H), 7.59 – 7.44 (m, 5H), 7.40 (ddd, *J* = 10.2, 2.6, 1.2 Hz, 1H), 7.19 (ddd, *J* = 13.9, 8.3, 2.7 Hz, 1H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 162.6 (dd, *J* = 161.4, 13.5 Hz), 159.3 (dd, *J* = 152.2, 13.5 Hz), 140.0, 137.7 – 137.6 (m), 134.6 (dd, *J* = 9.7, 5.9 Hz), 131.5, 130.0, 129.8, 128.7, 128.5, 127.8, 127.7, 127.5, 127.5, 127.1, 126.9, 126.9, 126.7, 116.8 (dd, *J* = 9.0, 2.9 Hz), 107.9 (dd, *J* = 21.8, 3.8 Hz), 103.2 (dd, *J* = 28.9, 27.2 Hz)
HR: EI-MS [$M^{+\cdot}$]
Calculated: 290.0907
Found: 290.0901

1,3-Difluoro-10-phenylphenanthrene (4g)[15]



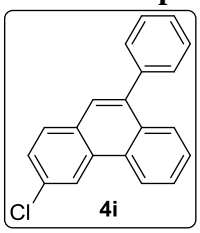
^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 8.55 (dd, *J* = 8.0, 5.0 Hz, 1H), 8.22 (ddd, *J* = 10.6, 2.3, 1.4 Hz, 1H), 7.94 – 7.81 (m, 1H), 7.74 – 7.63 (m, 2H), 7.57 (s, 1H), 7.53 – 7.37 (m, 5H), 7.02 (ddd, *J* = 12.1, 8.4, 2.5 Hz, 1H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 162.2 (dd, *J* = 23.3, 13.0 Hz), 158.8 (dd, *J* = 34.1, 13.0 Hz), 142.82 (d, *J* = 4.1 Hz), 134.8, 133.8 (dd, *J* = 9.7, 4.9 Hz), 131.7 (d, *J* = 0.5 Hz), 129.3 (d, *J* = 2.5 Hz), 128.7, 128.7, 128.6, 128.1, 127.5, 127.1, 126.9, 123.0, 117.4 (dd, *J* = 9.6, 2.6 Hz), 104.3 (dd, *J* = 21.8, 4.2 Hz), 103.1 (t, *J* = 26.9 Hz)
HR: EI-MS [$M^{+\cdot}$]
Calculated: 290.0907
Found: 290.0905

2-Methyl-10-phenylphenanthrene (4h)



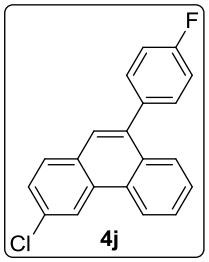
^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 8.70 (dd, *J* = 8.2, 5.0 Hz, 2H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.80 – 7.40 (m,10)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 140.9, 138.5, 136.3, 131.2, 131.1, 130.0, 130.0, 128.6, 128.4, 128.3, 128.2, 127.6, 127.3, 126.5, 126.4, 122.8, 122.3, 21.7
HR: EI-MS [$M^{+\cdot}$]
Calculated: 268.1252
Found: 268.1253

3-Chloro-9-phenylphenanthrene (4i)[6]



^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 8.79 – 8.58 (m, 1H), 7.94 (d, *J* = 8.2 Hz, 1H), 7.82 (d, *J* = 8.6 Hz, 1H), 7.73 – 7.62 (m, 1H), 7.61 – 7.43 (m, 1H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 140.4, 139.1, 132.5, 131.3, 131.0, 130.0, 129.9, 129.8, 129.6, 128.3, 127.5, 127.3, 127.1, 127.0, 126.7, 126.7, 122.9, 122.2
HR: EI-MS [$M^{+\cdot}$]
Calculated: 288.0706
Found: 288.0705

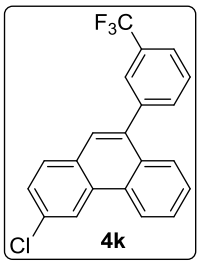
3-Chloro-9-(4-fluorophenyl)phenanthrene (4j)



^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 8.67 (t, *J* = 3.9 Hz, 2H), 7.84 (dd, *J* = 19.5, 8.3 Hz, 2H), 7.69 (t, *J* = 7.6 Hz, 1H), 7.64 – 7.53 (m, 3H), 7.49 (dd, *J* = 8.1, 5.6 Hz, 2H), 7.23 (dd, *J* = 14.8, 6.2 Hz, 2H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 162.4 (d, *J* = 246.5 Hz), 138.0, 136.3 (d, *J* = 3.4 Hz), 131.5 (d, *J* = 8.0 Hz), 131.3, 131.0, 130.0, 129.7, 129.6, 127.4, 127.2, 126.9, 126.8, 126.7, 123.0, 122.3, 115.30 (d, *J* = 21.4 Hz)

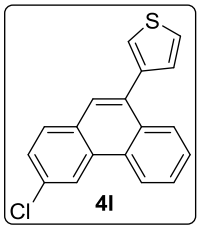
HR: EI-MS [$M^{+\cdot}$]
Calculated: 306.0612
Found: 306.0612

3-Chloro-9-(3-(trifluoromethyl)phenyl)phenanthrene (4k)



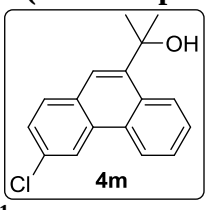
^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 8.74 – 8.66 (m, 2H), 7.87 – 7.77 (m, 3H), 7.77 – 7.54 (m, 7H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 141.2, 137.5, 133.3, 133.0, 131.2, 130.9, 130.1, 129.7, 129.6, 128.8, 127.6, 127.4, 127.2, 127.0, 126.7 (m), 126.5, 124.4 (m), 123.1, 122.3
HR: EI-MS [$M^{+\cdot}$]
Calculated: 356.0580
Found: 356.0577

3-(3-Chlorophenanthren-9-yl)thiophene (4l)



^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 8.66 (m, 2H), 8.06 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.80 (d, *J* = 8.5 Hz, 1H), 7.76 – 7.64 (m, 2H), 7.65 – 7.41 (m, 4H), 7.34 (dd, *J* = 4.8, 1.3 Hz, 1H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 140.7, 133.9, 132.6, 131.4, 131.0, 129.9, 129.8, 129.6, 129.5, 127.3, 127.2, 126.8, 126.8, 126.7, 125.5, 123.8, 122.9, 122.3
HR: EI-MS [$M^{+\cdot}$]
Calculated: 294.0270
Found: 294.0269

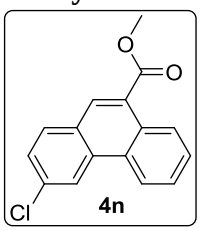
2-(3-Chlorophenanthren-9-yl)propan-2-ol (4m)[6]



^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 8.95 – 8.84 (m, 1H), 8.67 – 8.60 (m, 1H), 8.59 (d, *J* = 1.8 Hz, 1H), 7.81 – 7.73 (m, 2H), 7.69 – 7.59 (m, 2H), 7.52 (dd, *J* = 8.5, 2.0 Hz, 1H), 1.91 (s, 6H)

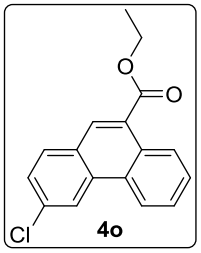
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 141.7, 132.7, 131.3, 130.6, 130.3, 130.2, 129.3, 128.2, 127.2, 126.5, 126.2, 123.3, 123.0, 122.0, 73.9, 31.5
HR: EI-MS [$M^{+\cdot}$]
Calculated: 270.0811
Found: 270.0810

Methyl 3-chlorophenanthrene-9-carboxylate (4n)



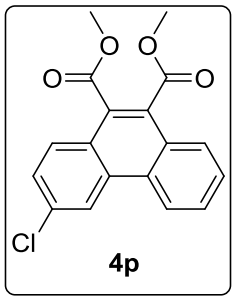
^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 8.97 – 8.84 (m, 1H), 8.64 – 8.51 (m, 2H), 8.38 (s, 1H), 7.84 (d, *J* = 8.5 Hz, 1H), 7.76 – 7.61 (m, 2H), 7.55 (dd, *J* = 8.5, 2.0 Hz, 1H), 4.04 (s, 3H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 167.7, 135.1, 133.1, 131.5, 131.2, 129.6, 129.2, 128.2, 128.0, 127.6, 127.1, 126.6, 126.3, 122.8, 122.4, 52.3
HR: EI-MS [$M^{+\cdot}$]
Calculated: 270.0448
Found: 270.0444

Ethyl 3-chlorophenanthrene-9-carboxylate (4o)[6]



^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 9.01 – 8.82 (m, 1H), 8.70 – 8.51 (m, 2H), 8.38 (s, 1H), 7.86 (d, *J* = 8.5 Hz, 1H), 7.76 – 7.64 (m, 2H), 7.56 (dd, *J* = 8.5, 2.0 Hz, 1H), 4.52 (q, *J* = 7.1 Hz, 2H), 1.51 (t, *J* = 7.1 Hz, 3H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 167.4, 135.0, 133.1, 131.2, 131.2, 129.6, 129.3, 128.3, 128.0, 127.6, 127.1, 126.8, 126.7, 122.8, 122.4, 61.3, 14.4
HR: EI-MS [$M^{+\cdot}$]
Calculated: 284.0604
Found: 284.0603

Dimethyl 3-chlorophenanthrene-9,10-dicarboxylate (4p)



4p

^{1}H NMR (300 MHz, $CDCl_3$):

δ ppm 8.67 (d, *J* = 2.1 Hz, 1H), 8.62 (d, *J* = 7.8 Hz, 1H), 8.14 (d, *J* = 8.8 Hz, 2H), 7.81 – 7.65 (m, 2H), 7.61 (dd, *J* = 8.9, 2.1 Hz, 1H), 4.04 (s, 3H), 4.03 (s, 3H)

^{13}C NMR (75 MHz, $CDCl_3$):

δ ppm 168.1, 167.9, 134.9, 132.2, 130.4, 130.0, 129.0, 128.8, 128.5, 128.3, 128.2, 127.3, 126.9, 125.4, 122.9, 122.6, 52.9, 52.9

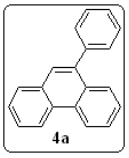
HR: EI-MS [$M^{+\cdot}$]

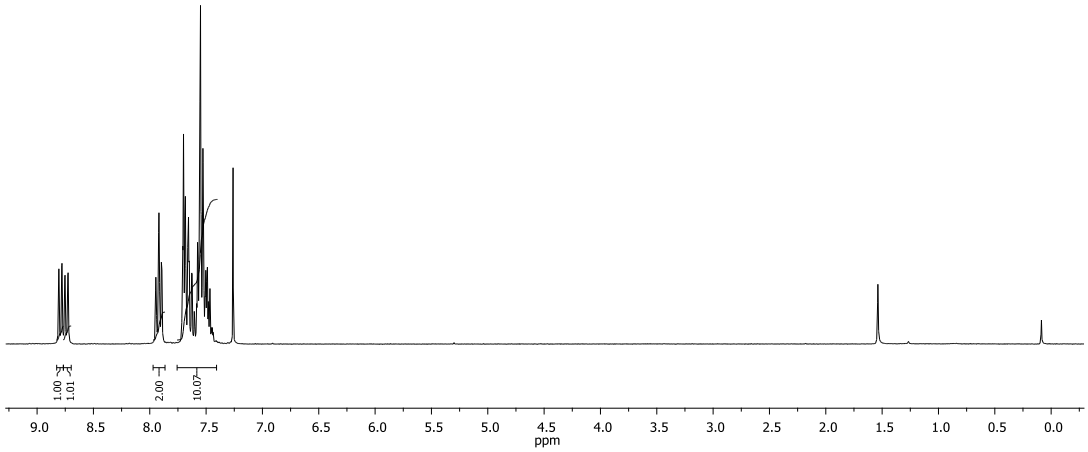
Calculated: 328.0502

Found: 328.0498

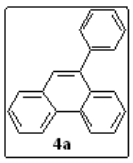
^{1}H and ^{13}C NMR spectra of selected compounds

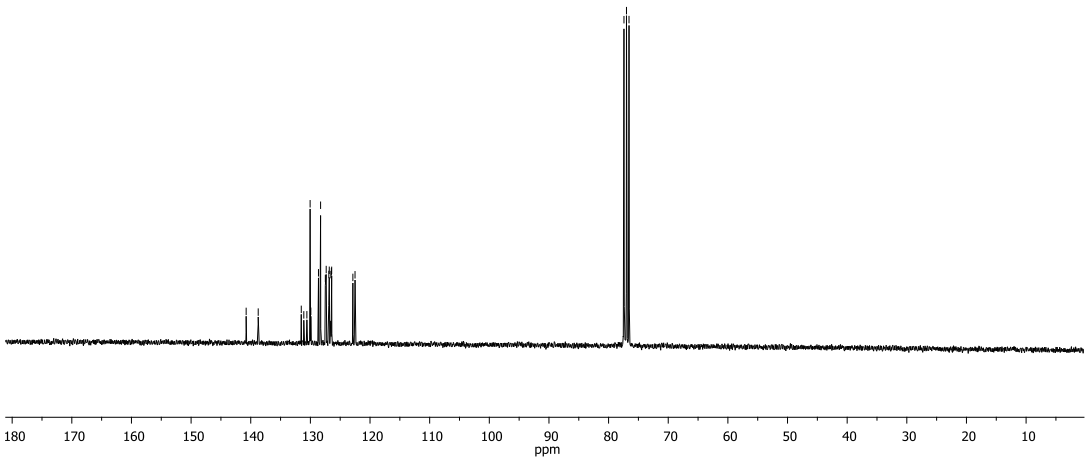
^{1}H NMR (300MHz, $CDCl_3$)



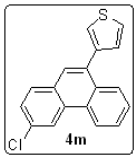


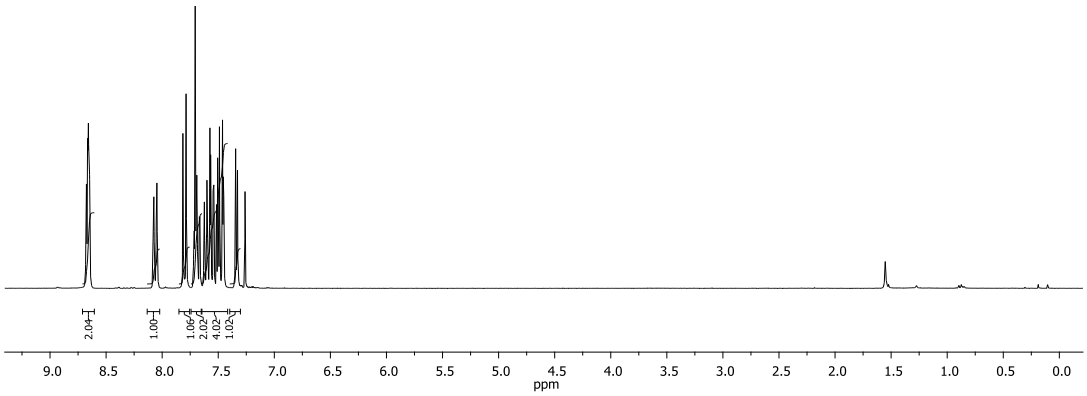
^{13}C NMR (75 MHz, $CDCl_3$)



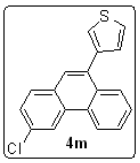


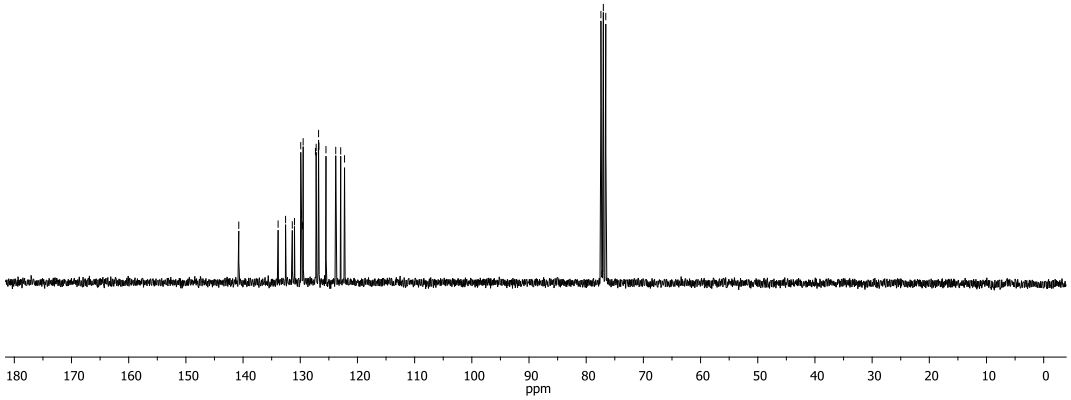
^{1}H NMR (300MHz, $CDCl_3$)



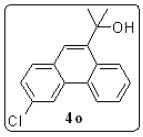


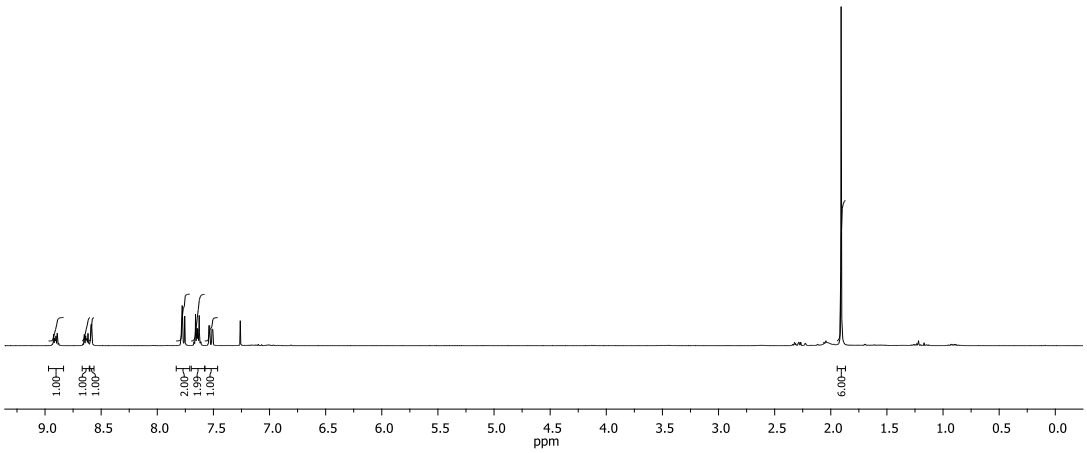
^{13}C NMR (75 MHz, $CDCl_3$)



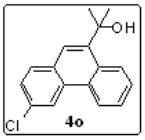


^{1}H NMR (300MHz, $CDCl_3$)

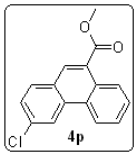


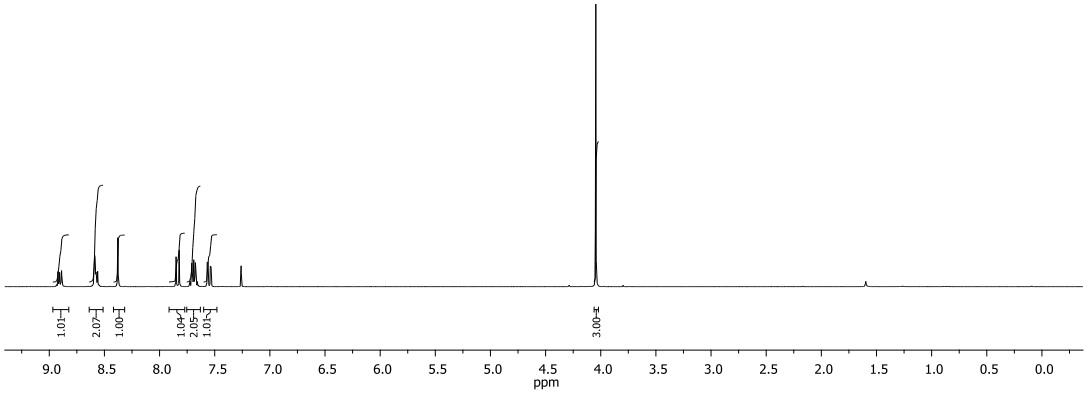


^{13}C NMR (75 MHz, $CDCl_3$)

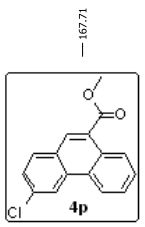


^{1}H NMR (300MHz, $CDCl_3$)

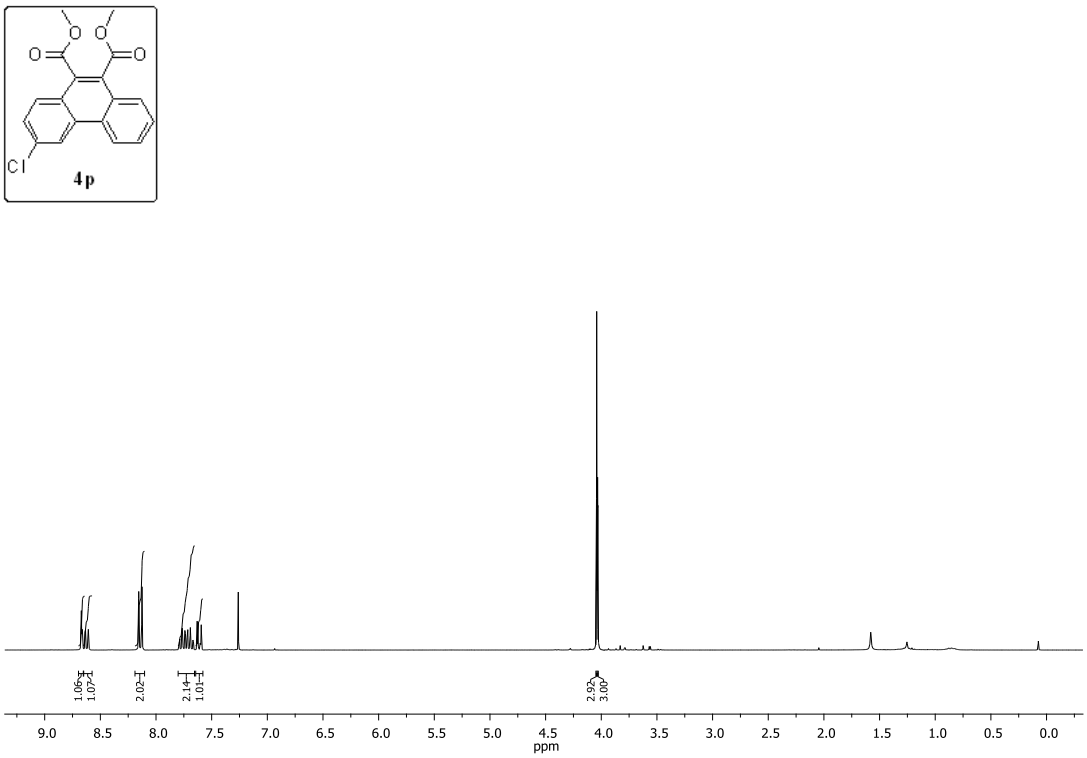




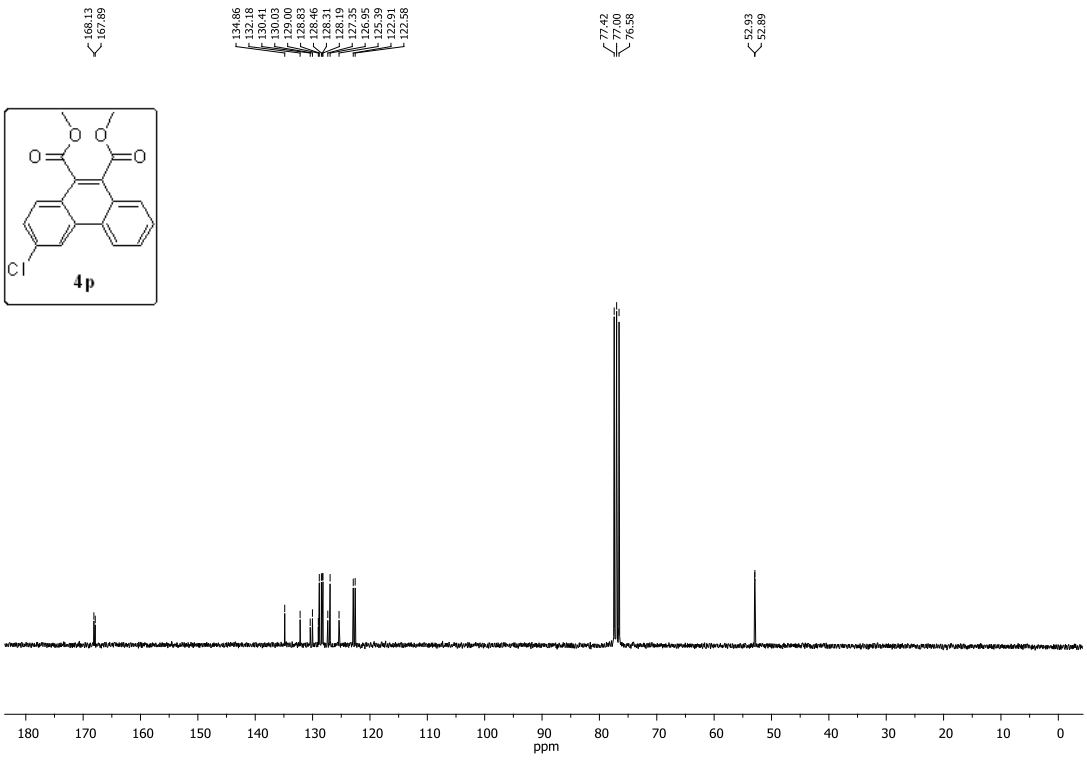
^{13}C NMR (75 MHz, $CDCl_3$)



^{1}H NMR (300MHz, $CDCl_3$)



^{13}C NMR (75 MHz, $CDCl_3$)



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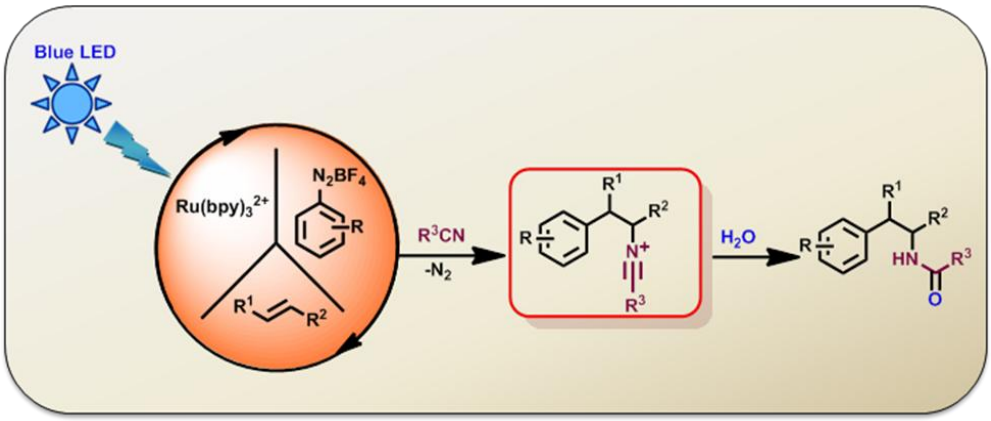
Chapter 5

5 The Photoredox Catalyzed Meerwein Addition Reaction: Intermolecular Amino-Arylation of Alkenes



A variety of amides are efficiently accessible at mild conditions by intermolecular amino-arylation using a visible light photo Meerwein addition. The protocol has a broad substrate scope, tolerates a large range of functional groups and was applied to the synthesis of 3-aryl-3,4 dihydroisoquinoline.

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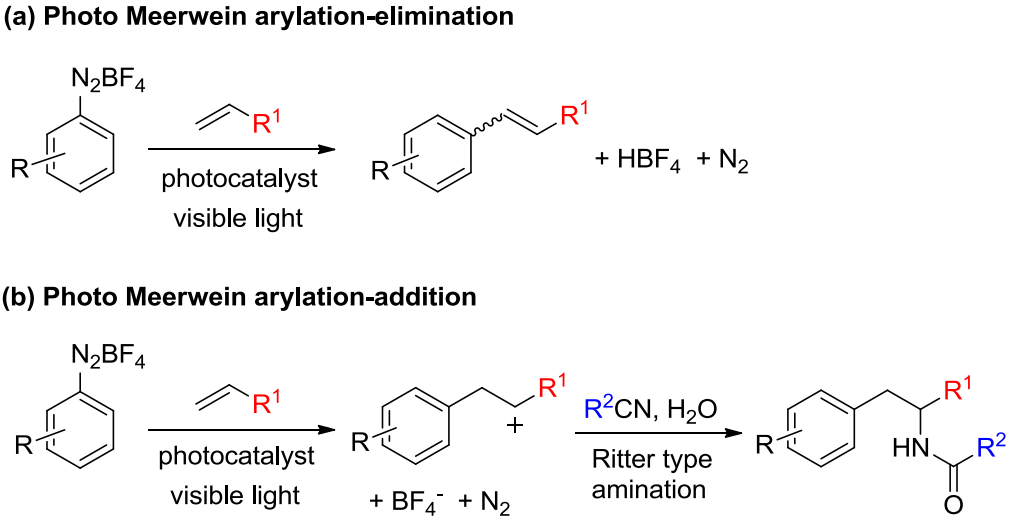
Author contributions:
DP carried out the photoreactions in Table 1, 2, 3 and wrote the manuscript; TH carried out the reactions in Table 4.

5.1 Introduction

The Meerwein arylation is a valuable synthetic transformation based on aryl radical chemistry.[1] The classic Meerwein arylation has two alternative reaction pathways: (a) Meerwein arylation-elimination, in which aryl-alkene cross coupling products are formed exclusively, and (b) Meerwein arylation-addition, in which the aryl radical and a halogen atom add to an olefinic substrate.[1b] The addition of other atoms instead of halogen has also been reported.[1b] However, photo Meerwein arylations were so far only applied for the formation of aryl-alkene coupling products and not extended to the valuable alkene addition products[2] obtainable under classical Meerwein arylation conditions.[3] The challenge in obtaining the addition product is the competing reaction of the trapping reagent or nucleophile with the diazonium salt leading to undesired products.[1b]



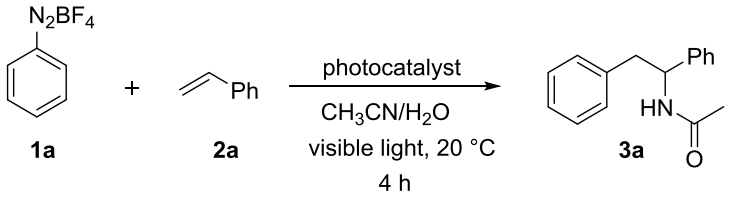
Scheme 1. Types of photo Meerwein arylation reactions: (a) photo Meerwein arylation-elimination, (b) photo Meerwein arylation-addition.

The Ritter-type amination reaction is a most useful transformation for the formation of C-N bonds and has been used in industrial processes for the synthesis of the anti-HIV drug Crixivan, the alkaloid aristotelone, and Amantadine.[2d,4] We utilize the Ritter reaction conditions to trap the carbenium ion, which is generated during the photoredox Meerwein arylation reaction leading to a photoredox catalyzed Meerwein arylation-addition process allowing the intermolecular amino-arylation of alkenes mediated by visible light.

5.2 Results and Discussion

Our initial studies began with an attempted reaction of diazonium salt **1a** (0.25 mmol) with 5 equiv of styrene **2a** using 2 mol% of $[Ru(bpy)_3]Cl_2$ in 1.0 mL of CH_3CN containing 10 equiv of water under visible light irradiation for 4 h at 20 °C; the desired product **3a** was obtained in 42% yield (Table 1, entry 1) along with 1,2-diphenylethanol as a byproduct.

Table 1. Optimizing reaction conditions.



Entry	Conditions	Yield (%)[a]
1	$[Ru(bpy)_3]Cl_2$ (2 mol%), **2a** (5 equiv)	42[b]
2	$[Ru(bpy)_3]Cl_2$ (2 mol%), **2a** (5 equiv)	75
3	$[Ru(bpy)_3]Cl_2$ (2 mol%), **2a** (5 equiv)	65[c]
4	$[Ru(bpy)_3]Cl_2$ (2 mol%), **2a** (5 equiv)	74[d]
5	$[Ru(bpy)_3]Cl_2$ (0.5 mol%), **2a** (5 equiv)	75
6	$[Ru(bpy)_3]Cl_2$ (0.5 mol%), **2a** (2 equiv)	88
7	$[Ru(bpy)_3]Cl_2$ (0.5 mol%), **2a** (1.1 equiv)	72
9	Eosin Y (0.5 mol%), **2a** (2 equiv)	38
10	$Ir(ppy)_3$ (0.5 mol%), **2a** (2 equiv)	76
11	Rhodamine B (0.5 mol%), **2a** (2 equiv)	5
12	Rose bengal (0.5 mol%), **2a** (2 equiv)	37
13	$C_{50}H_{40}CuF_6N_2OP_3$ (0.5 mol%), **2a** (2 equiv)	21
14	no photocatalyst, **2a** (2 equiv)	5
15	$[Ru(bpy)_3]Cl_2$ (0.5 mol%), **2a** (2 equiv), no light	0

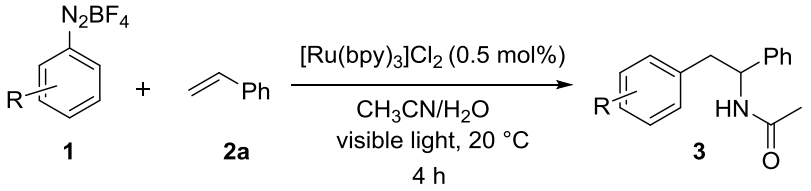
[a]GC yield determined by using a calibrated internal standard. [b]The reaction was carried out with 10 equiv of H_2O. [c]The reaction was carried out in 0.5 mL of CH_3CN. [d]The reaction was carried out in 2.0 mL of CH_3CN. Unless otherwise mentioned in all other cases the reactions were carried out in 1.0 mL of CH_3CN using 1 equiv of H_2O.

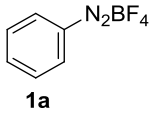
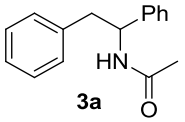
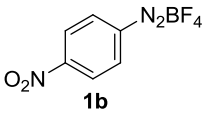
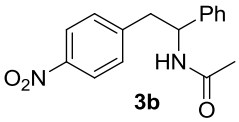
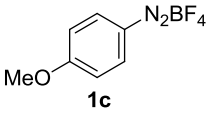
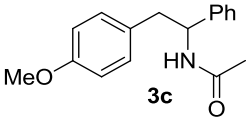
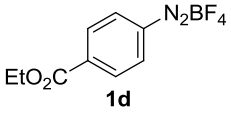
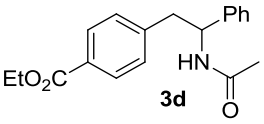
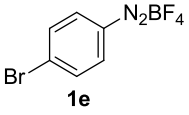
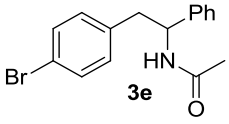
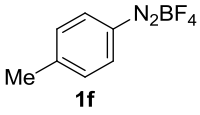
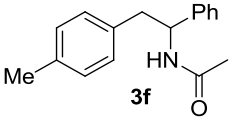
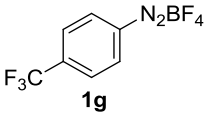
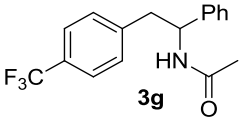
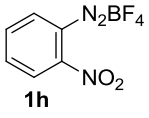
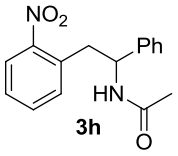
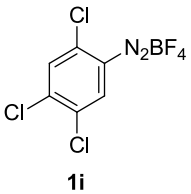
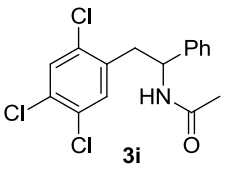
We examined the amount of water, catalyst loading and different equiv of styrene on this multi-component photoreaction. To our delight the desired product **3a** was obtained in 88% yield (Table 1, entry 6) when diazonium salt **1a** (0.25 mmol), 0.5 mol% of $[Ru(bpy)_3]Cl_2$, 2 equiv of styrene **2a** and 1 equiv of water were used in 1.0 mL of CH_3CN. The reaction yields of **3a** are significantly affected by the amount of water: a larger amount of water results in the formation of the 1,2-diphenylethanol (Table 1, entry 1 *vs.* 2).

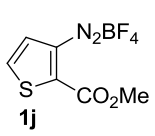
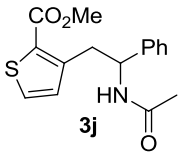
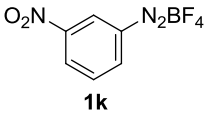
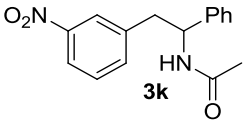
After having optimized the reaction conditions we screened different photocatalysts (Table 1, entries 6, 9-13).$[Ru(bpy)_3]Cl_2$ was found to be the best one for this transformation. To prove the significance of the photoreaction, we carried out control experiments without light and without photocatalyst $[Ru(bpy)_3]Cl_2$. As expected, we observed 0 and 5 % of product yield, respectively (Table 1, entries 15 and 14). When we employed dichloromethane as a solvent and 10 equiv of acetonitrile in this photoreaction, product **3a** was obtained in 70% yield.[5] This shows that the use of the organic nitrile as a solvent is not required. In addition, we also replaced the photocatalyst and visible light by copper catalysts, which are commonly employed in Meerwein arylations. However, under these conditions the reaction does not proceed showing that the photoredox system is essential.[5]

Furthermore, we investigated the scope of the diazonium salts for this photoreaction and the results were summarized in Table 2. Aryl diazonium salts bearing electron withdrawing, neutral and donating substituents react smoothly affording the corresponding products in good to excellent yields. Several functional groups including ester, nitro, halide, ether, alkyl groups are tolerated in the photoreaction. In addition to aryl diazonium salts, heteroaryl diazonium salt **1j** was used in this reaction to giving the corresponding product **3j** in 75% yield (Table 2, entry 10). Carbon-halogen bonds remain intact during the photoreaction providing access to halogen substituted amides in a single step (Table 2, entries 5 and 9). The halide functional groups can be used for further transformations by transition metal catalyzed or organometallic reactions.

Table 2. Scope of the aryl diazonium salts[a].



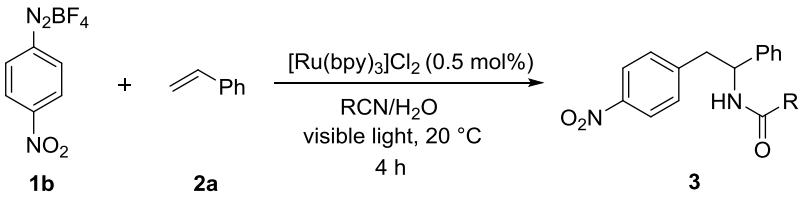
Entry	Substrate	Product	Yield (%)[b]
1	 **1a**	 **3a**	82
2	 **1b**	 **3b**	92
3	 **1c**	 **3c**	70
4	 **1d**	 **3d**	82
5	 **1e**	 **3e**	76
6	 **1f**	 **3f**	70
7	 **1g**	 **3g**	73
8	 **1h**	 **3h**	87
9	 **1i**	 **3i**	50

10	 1j	 3j	75
11	 1k	 3k	70

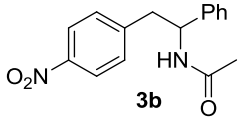
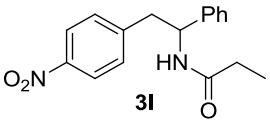
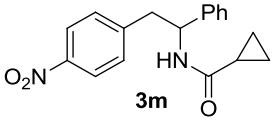
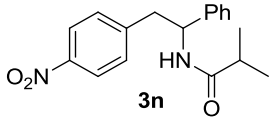
[a]The reaction was performed with **1** (0.25 mmol), styrene **2a** (2 equiv), $[Ru(bpy)_3]Cl_2$ (0.005 equiv) and 1 equiv of water in 1.0 mL of CH_3CN. [b]Isolated yields after purification by flash column chromatography using silica gel.

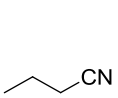
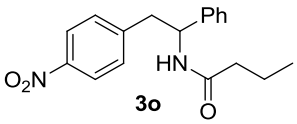
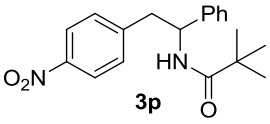
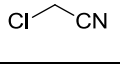
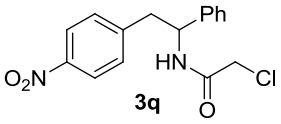
We then expanded the scope of the reaction by varying the nitrile, which proved to be of general applicability in the photoreaction. The products obtained from the reactions of diazonium salt **1b** and styrenes **2a** with different nitriles are shown in Table 3. The results demonstrate that primary, secondary, and tertiary alkyl nitriles undergo cleanly the transformation providing the corresponding products in good to excellent yields. We were also pleased to find that cyclopropane carbonitrile was tolerated well affording the corresponding product **3m** in 65% yield after 4 h blue light irradiation at room temperature (Table 3, entry 3).

Table 3. Scope of nitriles[a].



1b 2a 3

Entry	Nitrile	Product	Yield (%)[b]
1	CH_3CN	 3b	92
2		 3l	84
3		 3m	65
4		 3n	71

5		 **3o**	80
6		 **3p**	72
7		 **3q**	60

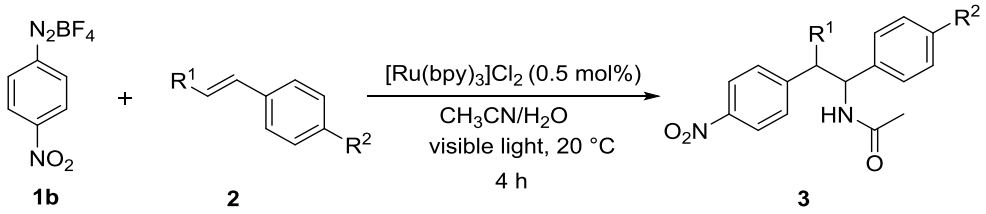
[a]The reaction was performed with **1b** (0.25 mmol), styrene **2a** (2 equiv), $[Ru(bpy)_3]Cl_2$ (0.005 equiv) and 1 equiv of water in 1.0 mL of nitrile. [b]Isolated yields after purification by flash column chromatography using silica gel.

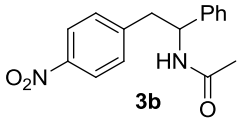
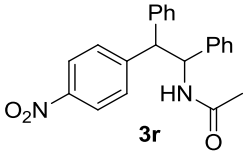
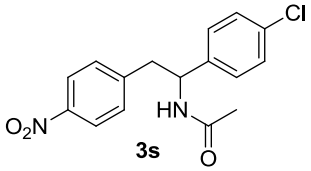
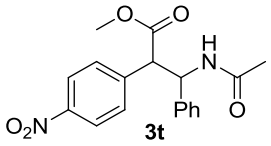
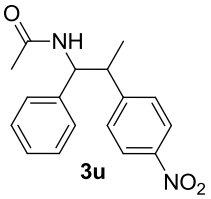
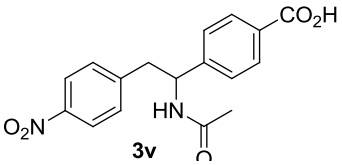
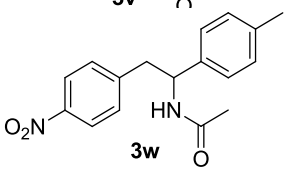
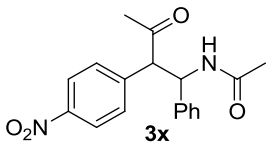
Having established the scope towards both diazonium salts and nitriles in this photoreaction, we investigated various alkenes. The results are summarized in the Table 4. Styrenes with electron withdrawing, neutral and donating substitution at *para* position smoothly give the corresponding products in moderate to excellent yields upon irradiation for 4 h (Table 4, entries 1, 3, 6, and 7). In addition, this photoreaction could also be applied to internal alkenes. The reaction of diaznoium salt **1b** with trans-*β*-methylstyrene regioselectively provided the corresponding product **3u** in 75% yield (dr 65:35).[2d] Notably, trans-stilbene, cinnamic acid ester, and benzalacetone can be used in this multi-component photoreaction and afford the corresponding products as single regioisomers in moderate yields (Table 4, entries 2, 4, and 8).

The photoreaction product **3a** was used for the synthesis of 3-aryl-3,4-dihydroisoquinoline to demonstrate its application by adopting a previously reported method by Larsen and co-workers (Scheme 2).[6] The reaction of diazonium salt **1a** with styrene **2a** under standard photoreaction conditions provided the corresponding product **3a**, which was then further converted into 3-aryl-3,4-dihydroisoquinoline **4** using oxalyl chloride and $FeCl_3$.[6a]

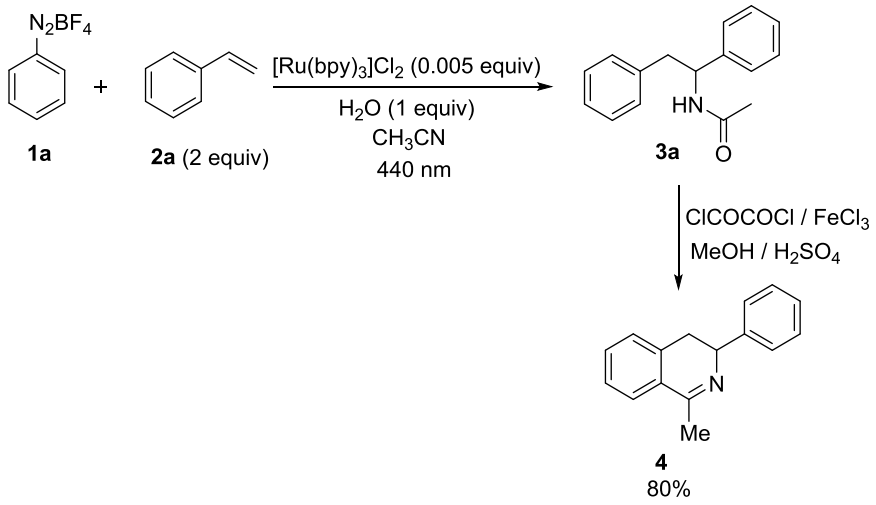
The suggested mechanism of the photoreaction based on trapping of intermediates and related literature reports is depicted in scheme **3**.[2d,3a,7] Aryl radical **5** is formed initially by a single electron transfer from the excited state of the photocatalyst $Ru(bpy)_3^{2+}$* to diazonium salt **1a**. Addition of aryl radical **5** to alkene **2** yields the corresponding radical intermediate **6**, which is then further oxidized to give carbenium intermediate **7**.[3e] Finally, the intermediate **7** is attacked by a nitrile (R^3CN), followed by hydrolysis to give the amino-arylated product **3a**.[2d]

Table 4. Scope of alkenes[a].



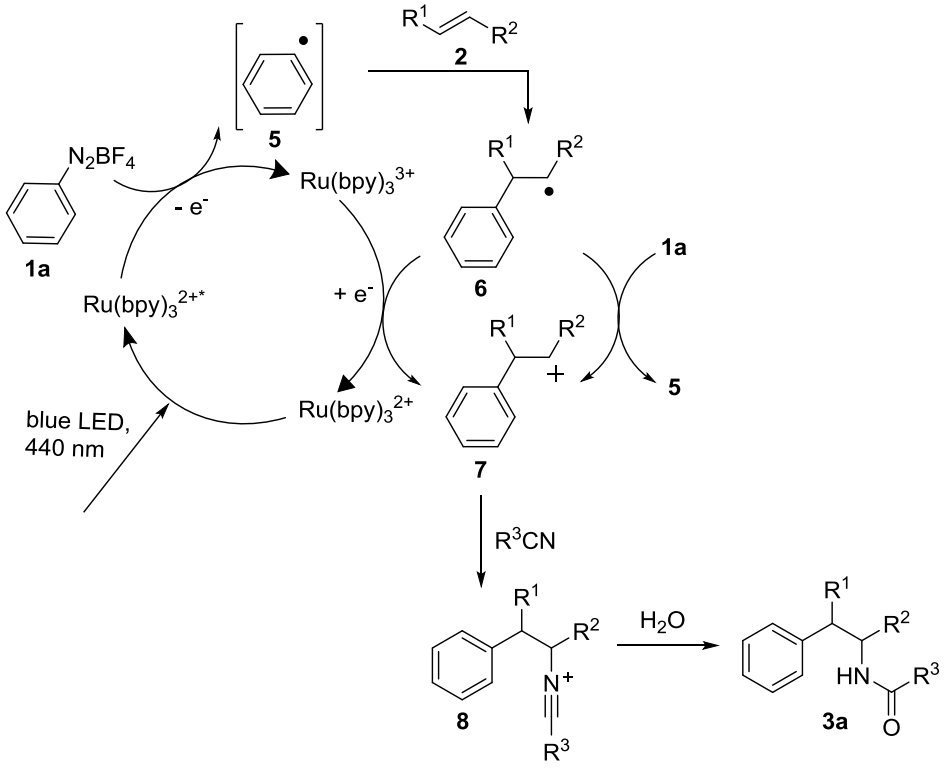
Entry	R^1	R^2	Product	Yield (%)[b]
1	H	H	 **3b**	92
2	Ph	H	 **3r**	53
3	H	Cl	 **3s**	87
4	COOMe	H	 **3t**	20
5	Me	H	 **3u**	75[c]
6	H	COOH	 **3v**	97
7	H	Me	 **3w**	55
8	COMe	H	 **3x**	43

[a]The reaction was performed with **1b** (0.25 mmol), alkene **2** (2 equiv), $[Ru(bpy)_3]Cl_2$ (0.005 equiv) and 1 equiv of water in 1.0 mL of CH_3CN. [b]Isolated yields after purification by flash column chromatography using silica gel. [c]dr (65:35).



Scheme 2. Application of the photoreaction in the synthesis of 3-aryl-3,4-dihydroisoquinoline.

Radical intermediate **6** is either oxidized by the strong oxidant $Ru(bpy)_3^{3+}$ to complete the photocatalytic cycle or by the diazonium salt **1a** in a chain transfer mechanism. Radical intermediates **5** and **6** were trapped with TEMPO, which supports radical intermediates during the photoreaction.[3c-e,5] In addition, the carbenium ion intermediate was also trapped with water and methanol, these results indicate the formation of intermediate **7** in the reaction.[5]



Scheme 3. Proposed mechanism for the Photo-Meerwein addition reaction.

5.3 Conclusion

In conclusion, the reported protocol allows the formation of C_{alkyl}-N bonds by an intermolecular amino-arylation of alkenes mediated by visible light. It is, to the best of our knowledge, the first example of a photocatalytic Meerwein addition reaction. The multi-component reaction gives efficient access to different types of amides under mild reaction conditions tolerating a broad range of functional groups. The substrate scopes of diazonium salts, nitriles, and alkenes are large. Many products of the photoreaction are not easily accessible by other methods and have due to the presence of halide functional groups the potential for further synthetic elaboration. Exemplarily, one photoreaction product was used for the synthesis of a 3-aryl-3,4-dihydroisoquinoline. Experiments to elucidate the mechanism of the reaction in detail, and applications of the reaction to the synthesis of other potential biologically active molecules are ongoing in our laboratory.

5.4 Experimental Part

General Information

Proton NMR spectra were recorded on a Bruker Avance 300 MHz spectrometer in $CDCl_3$ and dimethyl sulfoxide-d_6 solutions with internal solvent signal peak at 7.26 ppm and 2.50 ppm respectively. Carbon NMR were recorded at 75 MHz spectrometer in $CDCl_3$ and dimethyl sulfoxide-d_6 solutions and referenced to the internal solvent signal at 77.0 ppm and 39.52 ppm respectively. Proton NMR data are reported as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, dd = doublet of doublets, ddd = doublet of doublet of doublets, td = triplet of doublets, qd = quartet of doublets, m = multiplet, br. s. = broad singlet), and coupling constants (Hz). All reactions were monitored by thin-layer chromatography (TLC) using Merck silica gel plates 60 F254; visualization was accomplished with short wave UV light (254 nm). Standard flash chromatography was performed using silica gel of particle size 40−63 μm. All other commercially available reagents and solvents were used without any further purification.

Irradiation Sources:

High Power LEDs of different wavelengths were used for irradiation of the reaction mixtures: Philips LUXEON® Rebel (purple, λmax = 400 ± 10 nm, 1000 mA, 1.2 W)

Philips LUXEON® Rebel LXML-TRo1-0225 (blue, λmax = 440 ± 10 nm, 700 mA, 3.0 W) and Philips LUXEON® Rebel (green, λmax = 520 ± 15 nm, 145 lm @700mA, 1.0 W)

General Procedures

Procedure for the preparation of aryl diazonium tetrafluoroborates[8]

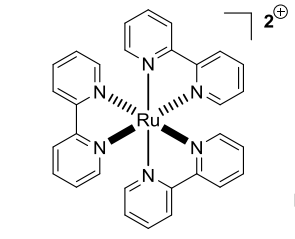
The appropriate aniline (10 mmol) was dissolved in a mixture of 3.4 mL of hydrofluoroboric acid (50%) and 4 mL of distilled water. The reaction mixture was cooled down to 0 °C using an ice-water bath, and then sodium nitrite ($NaNO_2$) solution (0.69 g in 1.5 mL) was added drop wise. The resulting reaction mixture was stirred for 40 min at 0-5 °C and the obtained precipitate was collected by filtration, dried and re-dissolved in a minimum amount of acetone. Diethyl ether was added until precipitation of diazonium tetrafluoroborate, which is filtered, washed several times with small portions of diethyl ether and dried under vacuum.

Photocatalytic reactions

General procedure for the reaction of arenediazonium tetrafluoroborates with alkenes

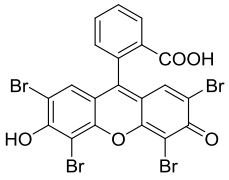
In a 5 mL snap vial equipped with magnetic stirring bar the catalyst $[Ru(bpy)_3]Cl_2$ (0.005 equiv), arenediazonium tetrafluoroborate 1 (1 equiv, 0.25 mmol), alkene 2 (2 equiv), and water (1 equiv) were dissolved in 1 mL of CH_3CN, and the resulting reaction mixture was degassed by three "pump-freeze-thaw" cycles via a syringe needle. The vial was irradiated through the vial's plane bottom side using 440 nm blue LEDs with cooling device maintaining a temperature around 20 °C. After 4 h of irradiation, the reaction mixture was transferred to a separating funnel, diluted with dichloromethane and washed with 15 mL of water. The aqueous layer was washed three times (3 x 15 mL) with dichloromethane. The combined organic phases were dried over Na_2SO_4, filtered and concentrated in vacuum. Purification of the crude product was achieved by flash column chromatography using petrol ether/ethyl acetate (1:1 to 1:3) as eluent.

Photocatalysts



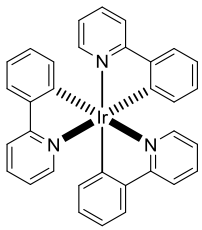
$Ru(bpy)_3Cl_2$

Irradiated at 440 nm



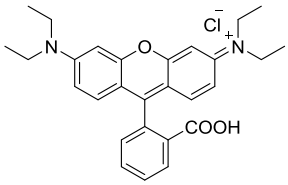
Eosin Y

Irradiated at 530 nm



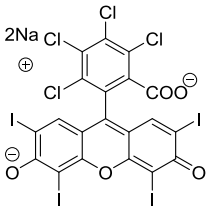
$Ir(ppy)_3$

Irradiated at 400 nm



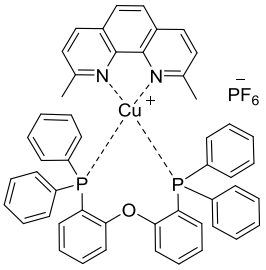
Rhodamine B

Irradiated at 530 nm



Rose bengal

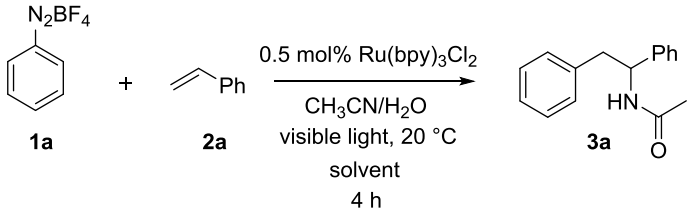
Irradiated at 530 nm



$C_{50}H_{40}CuF_6N_2OP_3$

Irradiated at 530 nm

Screening of Copper catalysts and Solvents[a]

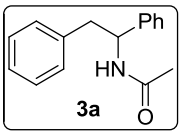


1a **2a** **3a**

Entry	Conditions	Yield (%)[b]
1	20 mol% Cu powder, no photocatalyst, no light, 1.0 mL CH_3CN	0
2	20 mol% CuCl, no photocatalyst, no light,1.0 mL CH_3CN	0
3	20 mol% $CuCl_2$, no photocatalyst, no light, 1.0 mL CH_3CN	0
4	$[Ru(bpy)_3]Cl_2$ (0.5 mol%), 10 equiv of CH_3CN, DMSO (0.850 mL), 440 nm	0[c]
5	$[Ru(bpy)_3]Cl_2$ (0.5 mol%), 20 equiv of CH_3CN, DMSO (0.700 mL), 440 nm	0[c]
6	$[Ru(bpy)_3]Cl_2$(0.5 mol%), 30 equiv of CH_3CN, DMSO (0.550 mL), 440 nm	0[c]
7	$[Ru(bpy)_3]Cl_2$ (0.5 mol%), 10 equiv of CH_3CN, DCM (0.850 mL), 440 nm	68
8	$[Ru(bpy)_3]Cl_2$ (0.5 mol%), 20 equiv of CH_3CN, DCM (0.700 mL), 440 nm	77
9	$[Ru(bpy)_3]Cl_2$ (0.5 mol%). 30 equiv of CH_3CN, DCM (0.550 mL), 440 nm	82

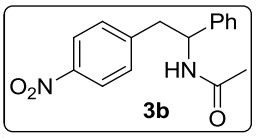
[a]The reaction was performed with **1a** (0.25 mmol), styrene **2a** (2 equiv), and 1 equiv of water. [b]GC yield determined by using a calibrated internal standard.[c]Obtained more than 80% of stilbene.

***N*-(1,2-Diphenylethyl)acetamide (3a)[6a]**



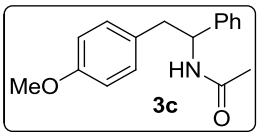
^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 7.48 – 7.12 (m, 8H), 7.13 – 6.92 (m, 2H), 5.81 (s, 1H), 5.28 (q, *J* = 7.3 Hz, 1H), 3.11 (d, *J* = 7.1 Hz, 2H), 1.93 (s, 3H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 169.4, 141.6, 137.4, 129.4, 128.7, 128.5, 127.5, 126.8, 126.7, 54.5, 42.6, 23.5
ESI-MS: [M+H^+]:
Calculated: 241.1416
Found: 241.1416
Mp: 150-152 °C

***N*-(2-(4-Nitrophenyl)-1-phenylethyl)acetamide (3b)**



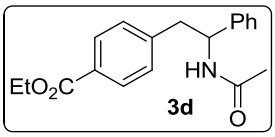
^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 8.06 (d, *J* = 8.7 Hz, 2H), 7.37 – 7.24 (m, 3H), 7.24 – 7.14 (m, 4H), 5.83 (d, *J* = 7.5 Hz, 1H), 5.25 (dd, *J* = 14.5, 7.8 Hz, 1H), 3.34 (dd, *J* = 13.5, 6.5 Hz, 1H), 3.16 (dd, *J* = 13.5, 8.1 Hz, 1H), 1.97 (s, 3H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 169.4, 146.7, 145.4, 140.2, 130.2, 129.0, 128.1, 126.8, 123.5, 54.7, 42.2, 23.4
ESI-MS: [M+H^+]:
Calculated: 285.1234
Found: 285.1234
Mp: 158-160 °C

***N*-(2-(4-Methoxyphenyl)-1-phenylethyl)acetamide (3c)**



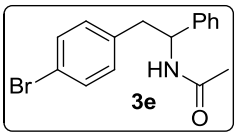
^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 7.35 – 7.23 (m, 3H), 7.22 – 7.16 (m, 2H), 6.94 (d, *J* = 8.7 Hz, 2H), 6.76 (d, *J* = 8.7 Hz, 2H), 5.83 (s, 1H), 5.22 (q, *J* = 7.2 Hz, 1H), 3.76 (s, 3H), 3.04 (d, *J* = 7.0 Hz, 2H), 1.93 (s, 3H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 169.4, 158.3, 141.7, 130.4, 129.3, 128.6, 127.5, 126.8, 113.8, 55.3, 54.6, 41.7, 23.5
ESI-MS: [M+H^+]:
Calculated: 270.1489
Found: 270.1490
Mp: 143-146 °C

Ethyl 4-(2-acetamido-2-phenylethyl)benzoate (3d)



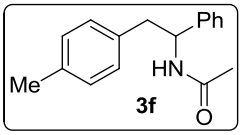
^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 7.89 (d, *J* = 8.3 Hz, 2H), 7.35 – 7.24 (m, 3H), 7.21 – 7.15 (m, 2H), 7.11 (d, *J* = 8.3 Hz, 2H), 5.81 (d, *J* = 7.1 Hz, 1H), 5.27 (q, *J* = 7.5 Hz, 1H), 4.34 (q, *J* = 7.1 Hz, 2H), 3.17 (qd, *J* = 13.6, 7.2 Hz, 2H), 1.94 (s, 3H), 1.37 (t, *J* = 7.1 Hz, 3H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 169.4, 166.7, 142.8, 140.9, 129.7, 129.4, 128.9, 128.8, 127.8, 126.8, 61.0, 54.6, 42.5, 23.5, 14.7
ESI-MS: [M+H$^+$]:
Calculated: 312.1594
Found: 312.1597
Mp: 144-146 °C

***N*-(2-(4-Bromophenyl)-1-phenylethyl)acetamide (3e)**



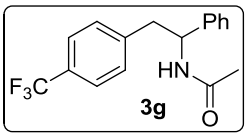
^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 7.36 – 7.24 (m, 5H), 7.22 – 7.13 (m, 2H), 6.90 (d, *J* = 8.3 Hz, 2H), 5.78 (d, *J* = 7.7 Hz, 1H), 5.22 (dd, *J* = 14.8, 7.5 Hz, 1H), 3.20 – 2.85 (m, 2H), 1.95 (s, 3H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 169.4, 140.9, 136.5, 131.5, 131.2, 128.8, 127.8, 126.8, 120.6, 54.6, 41.9, 23.6
ESI-MS: [M+H$^+$]:
Calculated: 318.0488
Found: 318.0488
Mp: 187-189 °C

***N*-(1-Phenyl-2-(p-tolyl)ethyl)acetamide (3f)**



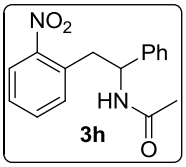
^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 7.34 – 7.19 (m, 5H), 7.03 (d, *J* = 7.8 Hz, 2H), 6.93 (d, *J* = 8.0 Hz, 2H), 5.89 (d, *J* = 7.7 Hz, 1H), 5.25 (q, *J* = 7.3 Hz, 1H), 3.06 (d, *J* = 7.1 Hz, 2H), 2.29 (s, 3H), 1.92 (s, 3H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 169.4, 141.8, 136.2, 134.2, 129.3, 129.1, 128.6, 127.4, 126.7, 54.5, 42.2, 23.5, 21.1
ESI-MS: [M+H$^+$]:
Calculated: 254.1539
Found: 254.1542
Mp: 134-136 °C

***N*-(1-Phenyl-2-(4-(trifluoromethyl)phenyl)ethyl)acetamide (3g)**



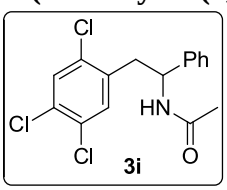
^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 7.46 (d, *J* = 8.1 Hz, 2H), 7.37 – 7.24 (m, 3H), 7.24 – 7.11 (m, 4H), 5.83 (d, *J* = 7.8 Hz, 1H), 5.27 (q, *J* = 7.5 Hz, 1H), 3.24 (dd, *J* = 13.6, 6.8 Hz, 1H), 3.13 (dd, *J* = 13.6, 7.7 Hz, 1H), 1.95 (s, 3H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 169.4, 141.7, 140.8, 129.7, 128.9, 127.9, 126.8, 125.3 (q, *J* = 3.6 Hz), 54.6, 42.3, 23.5
ESI-MS: [M+H^+]:
Calculated: 308.1257
Found: 308.1259
Mp: 177-179 °C

***N*-(2-(2-Nitrophenyl)-1-phenylethyl)acetamide (3h)**



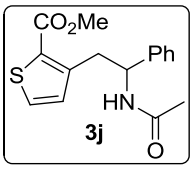
^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 7.86 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.54 (td, *J* = 7.6, 1.2 Hz, 1H), 7.47 – 7.26 (m, 7H), 6.38 (d, *J* = 8.2 Hz, 1H), 5.35 (ddd, *J* = 10.0, 8.5, 5.5 Hz, 1H), 3.43 (dd, *J* = 13.9, 10.2 Hz, 1H), 3.30 (dd, *J* = 13.9, 5.4 Hz, 1H), 1.84 (s, 3H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 169.5, 150.1, 141.6, 133.3, 133.0, 132.5, 128.9, 128.0, 127.9, 126.5, 124.8, 54.6, 38.6, 23.4
ESI-MS: [M+H^+]:
Calculated: 285.1234
Found: 285.1236
Mp: 170-172 °C

***N*-(1-Phenyl-2-(2,4,5-trichlorophenyl)ethyl)acetamide (3i)**



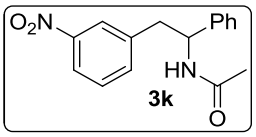
^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 7.44 (s, 1H), 7.39 – 7.23 (m, 6H), 5.89 (d, *J* = 8.0 Hz, 1H), 5.30 (dd, *J* = 15.0, 8.2 Hz, 1H), 3.26 – 3.09 (m, 2H), 1.94 (s, 3H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 169.4, 140.9, 135.9, 133.1, 132.5, 131.6, 131.1, 130.8, 129.0, 128.1, 126.6, 53.7, 39.2, 23.5
ESI-MS: [M+H^+]:
Calculated: 342.0214
Found: 342.0218
Mp: 170-172 °C

Methyl 3-(2-acetamido-2-phenylethyl)thiophene-2-carboxylate (3j)



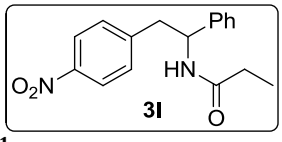
^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 7.44 (d, *J* = 5.1 Hz, 1H), 7.41 – 7.29 (m, 5H), 6.98 (m, 2H), 5.34 – 5.02 (m, 1H), 3.91 (s, 3H), 3.64 (dd, *J* = 13.7, 11.0 Hz, 1H), 3.19 (dd, *J* = 13.7, 4.3 Hz, 1H), 1.85 (s, 3H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 169.5, 164.5, 147.1, 142.7, 131.3, 131.2, 128.7, 127.5, 126.4, 55.3, 52.4, 35.9, 23.4
ESI-MS: [M+H$^+$]:
Calculated: 304.1002
Found: 304.1003
Mp: 199-201 °C

***N*-(2-(3-Nitrophenyl)-1-phenylethyl)acetamide (3k)**



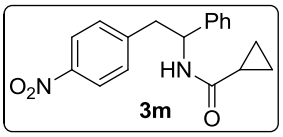
^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 8.03 (dt, *J* = 7.4, 2.1 Hz, 1H), 7.89 (d, *J* = 1.8 Hz, 1H), 7.45 – 7.37 (m, 2H), 7.37 – 7.24 (m, 3H), 7.23 – 7.14 (m, 2H), 5.95 (d, *J* = 7.6 Hz, 1H), 5.25 (q, *J* = 7.6 Hz, 1H), 3.30 (dd, *J* = 13.6, 7.0 Hz, 1H), 3.16 (dd, *J* = 13.6, 7.6 Hz, 1H), 1.95 (s, 3H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 169.5, 148.2, 140.4, 139.8, 135.6, 129.3, 129.0, 128.2, 126.8, 124.4, 121.8, 54.8, 42.1, 23.5
ESI-MS: [M+H$^+$]:
Calculated: 285.1234
Found: 285.1236
Mp: 172-174 °C

***N*-(2-(4-Nitrophenyl)-1-phenylethyl)propionamide (3l)**



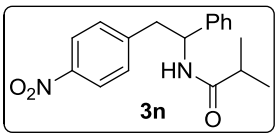
^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 8.05 (d, *J* = 8.7 Hz, 2H), 7.38 – 7.23 (m, 3H), 7.24 – 7.12 (m, 4H), 5.88 (d, *J* = 7.6 Hz, 1H), 5.25 (dd, *J* = 14.6, 7.7 Hz, 1H), 3.33 (dd, *J* = 13.5, 6.6 Hz, 1H), 3.16 (dd, *J* = 13.5, 8.0 Hz, 1H), 2.18 (q, *J* = 7.6 Hz, 2H), 1.10 (t, *J* = 7.6 Hz, 3H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 173.2, 146.9, 145.6, 140.4, 130.3, 129.0, 128.1, 126.8, 123.6, 54.6, 42.4, 29.8, 9.8
ESI-MS: [M+H$^+$]:
Calculated: 299.1390
Found: 299.1391
Mp: 163-165 °C

***N*-(2-(4-Nitrophenyl)-1-phenylethyl)cyclopropanecarboxamide (3m)**



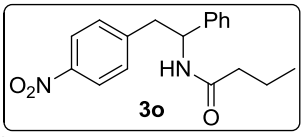
^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 8.05 (d, *J* = 8.7 Hz, 2H), 7.36 – 7.27 (m, 3H), 7.24 – 7.14 (m, 4H), 5.98 (s, 1H), 5.23 (dd, *J* = 14.2, 7.9 Hz, 1H), 3.37 (dd, *J* = 13.4, 6.2 Hz, 1H), 3.16 (dd, *J* = 13.4, 8.3 Hz, 1H), 1.41 – 1.27 (m, 1H), 0.98 – 0.85 (m, 2H), 0.84 – 0.57 (m, 2H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 173.1, 146.8, 145.6, 140.3, 130.3, 129.0, 128.2, 126.9, 123.6, 55.1, 42.5, 14.9, 7.6, 7.5
ESI-MS: [M+H^+]:
Calculated: 310.1317
Found: 310.1315
Mp: 180-182 °C

***N*-(2-(4-Nitrophenyl)-1-phenylethyl)isobutyramide (3n)**



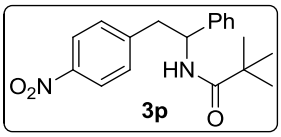
^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 8.06 (d, *J* = 8.8 Hz, 2H), 7.37 – 7.27 (m, 3H), 7.24 – 7.15 (m, 4H), 5.78 (d, *J* = 7.1 Hz, 1H), 5.25 (dd, *J* = 14.6, 7.6 Hz, 1H), 3.32 (dd, *J* = 13.5, 6.7 Hz, 1H), 3.18 (dd, *J* = 13.5, 7.8 Hz, 1H), 2.42 – 2.13 (m, 1H), 1.10 (t, *J* = 2.0 Hz, 3H), 1.08 (t, *J* = 3.5 Hz, 3H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 176.4, 146.8, 145.6, 140.4, 130.3, 129.0, 128.1, 126.8, 123.6, 54.4, 42.4, 35.8, 19.8, 19.5
ESI-MS: [M+H^+]:
Calculated: 313.1547
Found: 313.1550
Mp: 178-180 °C

***N*-(2-(4-nitrophenyl)-1-phenylethyl)butyramide (3o)**



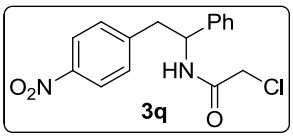
^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 8.05 (d, *J* = 11.0 Hz, 2H), 7.36 – 7.26 (m, 3H), 7.24 – 7.13 (m, 4H), 5.81 (d, *J* = 7.5 Hz, 1H), 5.27 (dd, *J* = 14.7, 7.7 Hz, 1H), 3.33 (dd, *J* = 13.5, 6.7 Hz, 1H), 3.16 (dd, *J* = 13.5, 7.9 Hz, 1H), 2.13 (t, *J* = 7.4 Hz, 2H), 1.61 (td, *J* = 14.4, 7.0 Hz, 2H), 0.87 (t, *J* = 7.4 Hz, 3H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 172.4, 146.8, 145.6, 140.4, 130.3, 128.9, 128.1, 126.7, 123.6, 54.6, 42.4, 38.8, 19.2, 13.8
ESI-MS: [M+H^+]:
Calculated: 312.1474
Found: 312.1475
Mp: 162-164 °C

***N*-(2-(4-nitrophenyl)-1-phenylethyl)pivalamide (3p)**



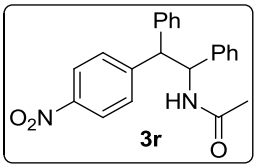
^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm δ 8.07 (d, *J* = 8.7 Hz, 2H), 7.37 – 7.26 (m, 3H), 7.25 – 7.12 (m, 4H), 5.91 (d, *J* = 7.4 Hz, 1H), 5.24 (q, *J* = 7.4 Hz, 1H), 3.30 (dd, *J* = 13.5, 6.7 Hz, 1H), 3.18 (dd, *J* = 13.5, 7.7 Hz, 1H), 1.14 (s, 9H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 177.9, 146.9, 145.6, 140.5, 130.3, 129.1, 128.1, 126.7, 123.6, 54.4, 42.4, 38.9, 27.6
ESI-MS: [M+H$^+$]:
Calculated: 327.1703
Found: 327.1709
Mp: 163-165 °C

2-Chloro-*N*-(2-(4-nitrophenyl)-1-phenylethyl)acetamide (3q)



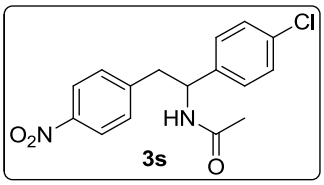
^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 8.08 (d, *J* = 8.7 Hz, 2H), 7.40 – 7.27 (m, 3H), 7.25 – 7.13 (m, 4H), 6.92 (d, *J* = 7.9 Hz, 1H), 5.26 (dd, *J* = 15.1, 7.5 Hz, 1H), 4.02 (s, 2H), 3.33 (dd, *J* = 13.5, 6.9 Hz, 1H), 3.22 (dd, *J* = 13.5, 7.6 Hz, 1H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 165.3, 147.0, 144.8, 139.5, 130.3, 129.2, 128.4, 126.7, 123.7, 54.9, 42.7, 42.4
ESI-MS: [M+H$^+$]:
Calculated: 319.0844
Found: 319.0848
Mp: 158-160 °C

***N*-(2-(4-Nitrophenyl)-1,2-diphenylethyl)acetamide (3r)**



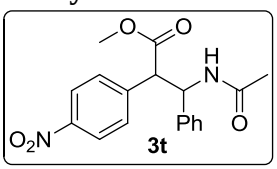
^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 8.16 (d, *J* = 8.8 Hz, 2H), 7.53 (d, *J* = 8.7 Hz, 2H), 7.25 – 6.99 (m, 10H), 6.04 – 5.84 (m, 1H), 5.77 (d, *J* = 9.4 Hz, 1H), 4.44 (d, *J* = 10.9 Hz, 1H), 1.80 (s, 3H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 169.1, 149.3, 146.9, 140.3, 139.9, 129.4, 128.8, 128.7, 128.4, 127.7, 127.3, 127.2, 123.9, 57.6, 55.6, 23.4
ESI-MS: [M+H$^+$]:
Calculated: 361.1547
Found: 361.1551
Mp: 210-212 °C

***N-(*1-(4-Chlorophenyl)-2-(4-nitrophenyl)ethyl)acetamide (3s)**



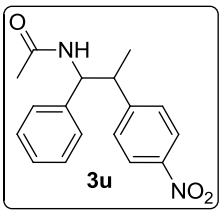
^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 8.07 (d, *J* = 8.8 Hz, 2H), 7.27 (d, *J* = 8.4 Hz, 2H), 7.20 (d, *J* = 8.7 Hz, 2H), 7.12 (d, *J* = 8.4 Hz, 2H), 5.96 (d, *J* = 7.8 Hz, 1H), 5.23 (q, *J* = 7.6 Hz, 1H), 3.28 (dd, *J* = 13.6, 6.9 Hz, 1H), 3.12 (dd, *J* = 13.6, 7.9 Hz, 1H), 1.95 (s, 3H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 169.5, 146.9, 145.1, 139.0, 133.9, 130.2, 129.1, 128.2, 123.7, 54.1, 42.1, 23.4
ESI-MS: [M+H^+]:
Calculated: 319.0844
Found: 319.0848
Mp: 190-192 °C

Methyl 3-acetamido-2-(4-nitrophenyl)-3-phenylpropanoate (3t)



^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 8.18 (d, *J* = 8.8 Hz, 2H), 7.56 (d, *J* = 8.8 Hz, 2H), 7.41 – 7.27 (m, 5H), 5.88 (d, *J* = 9.4 Hz, 1H), 5.77 (t, *J* = 9.7 Hz, 1H), 4.25 (d, *J* = 9.9 Hz, 1H), 3.52 (s, 3H), 1.76 (s, 3H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 170.8, 169.1, 147.8, 142.6, 139.1, 130.1, 129.0, 128.5, 127.4, 123.8, 57.2, 55.0, 52.6, 23.3
ESI-MS: [M+H^+]:
Calculated: 343.1288
Found: 343.1291
Mp: 191-193 °C

***N*-(2-(4-nitrophenyl)-1-phenylpropyl)acetamide (3u)**

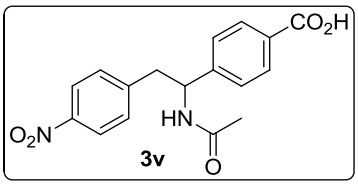


Major Isomer:
^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 8.15 (d, *J* = 8.8 Hz, 2H), 7.42 – 7.28 (m, 5H), 7.25 – 7.17 (m, 2H), 5.66 (d, *J* = 9.1 Hz, 1H), 5.24 (t, *J* = 9.0 Hz, 1H), 3.29 (dq, *J* = 14.0, 7.0 Hz, 1H), 1.78 (s, 3H), 1.18 (d, *J* = 7.0 Hz, 3H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 169.0, 151.1, 147.0, 140.3, 128.9, 128.8, 128.0, 127.2, 123.8, 58.1, 45.7, 23.4, 19.2

ESI-MS: [M+H$^+$]:
Calculated: 298.1301
Found: 298.1302
Mp: 195-196 °C

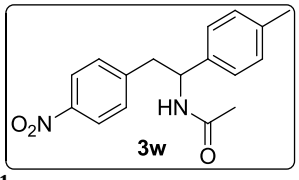
Minor Isomer:
^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 8.03 (d, *J* = 8.8 Hz, 2H), 7.24 – 7.12 (m, 5H), 7.05 – 6.91 (m, 2H), 5.85 (d, *J* = 8.7 Hz, 1H), 5.23 (t, *J* = 8.8 Hz, 1H), 3.47 – 3.10 (dq, *J* = 14.1, 7.0 Hz, 1H), 2.02 (s, 3H), 1.39 (d, *J* = 7.0 Hz, 3H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 169.6, 150.8, 146.7, 139.6, 129.1, 128.7, 127.9, 127.3, 123.5, 58.6, 45.5, 23.6, 18.4

4-(1-Acetamido-2-(4-nitrophenyl)ethyl)benzoic acid (3v)



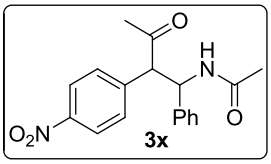
^{1}H NMR (300 MHz, DMSO-d_6):
δ ppm 12.91 (s, 1H), 8.51 (d, *J* = 8.7 Hz, 1H), 8.14 (d, *J* = 8.7 Hz, 2H), 7.90 (d, *J* = 8.3 Hz, 2H), 7.51 (dd, *J* = 13.5, 8.5 Hz, 4H), 5.17 (td, *J* = 9.1, 6.0 Hz, 1H), 3.11 (qd, *J* = 13.6, 7.8 Hz, 2H), 1.76 (s, 3H)
^{13}C NMR (75 MHz, DMSO-d_6):
δ ppm 168.6, 167.1, 147.8 146.8, 146.2, 130.5, 129.5, 129.4, 126.8, 123.2, 53.4, 41.9, 22.5
ESI-MS: [M+H$^+$]:
Calculated: 329.1132
Found: 329.1136
Mp: 248-250 °C

***N*-(2-(4-nitrophenyl)-1-(p-tolyl)ethyl)acetamide (3w)**



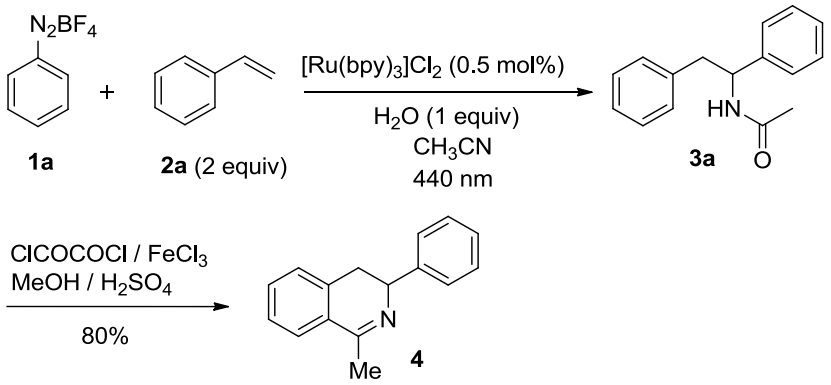
^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 8.01 (d, *J* = 8.8 Hz, 2H), 7.16 (d, *J* = 8.7 Hz, 2H), 7.12 – 6.98 (m, 4H), 5.75 (d, *J* = 7.7 Hz, 1H), 5.15 (dd, *J* = 14.3, 8.0 Hz, 1H), 3.29 (dd, *J* = 13.5, 6.3 Hz, 1H), 3.09 (dd, *J* = 13.5, 8.2 Hz, 1H), 2.28 (s, 3H), 1.91 (s, 3H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 169.4, 146.8, 145.7, 138.0, 137.2, 130.3, 129.7, 126.8, 123.6, 54.6, 42.4, 23.5, 21.2
ESI-MS: [M+H$^+$]:
Calculated: 299.1390
Found: 299.1391
Mp: 197-199 °C

***N*-(2-(4-Nitrophenyl)-3-oxo-1-phenylbutyl)acetamide (3x)**

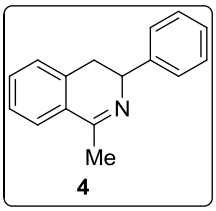


^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 8.16 (d, *J* = 8.8 Hz, 2H), 7.42 (d, *J* = 8.7 Hz, 2H), 7.34 – 7.16 (m, 5H), 7.03 (d, *J* = 9.2 Hz, 1H), 5.51 (dd, *J* = 9.2, 6.0 Hz, 1H), 4.55 (d, *J* = 6.0 Hz, 1H), 2.05 (s, 3H), 1.95 (s, 3H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 208.0, 169.6, 147.6, 142.5, 139.6, 129.7, 128.9, 127.9, 126.8, 124.2, 62.3, 55.8, 31.1, 23.5
Mp: 84-86 °C

Synthesis of 3-aryl-3,4-dihydroisoquinoline[6a]



1-Methyl-3-phenyl-3,4-dihydroisoquinoline (4)[6a]



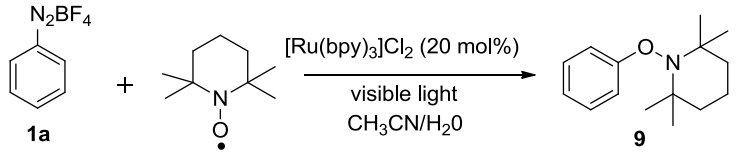
^{1}H NMR (400 MHz, $CDCl_3$):
δ ppm 7.57 (dd, *J* = 7.5, 1.2 Hz, 1H), 7.51 – 7.43 (m, 2H), 7.43 – 7.31 (m, 4H), 7.32 – 7.24 (m, 1H), 7.20 (d, *J* = 7.2 Hz, 1H), 4.57 (ddd, *J* = 13.8, 5.3, 2.2 Hz, 1H), 3.02 – 2.78 (m, 2H), 2.51 (d, *J* = 2.2 Hz, 3H)

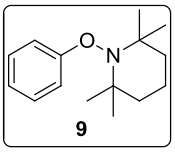
Radical Capturing Experiments

Experimental procedure for capturing intermediate radicals with TEMPO[3d,3e]

1) In a 5 mL snap vial equipped with magnetic stirring bar the catalyst $[Ru(bpy)_3]Cl_2$ (0.2 equiv), aryl diazonium tetrafluoroborate **1a** (0.25 mmol, 1 equiv) and TEMPO (2 equiv) were dissolved in CH_3CN containing 1 equiv of water and the resulting mixture was degassed by three "pump-freeze-thaw" cycles via a syringe needle. The vial was irradiated through the

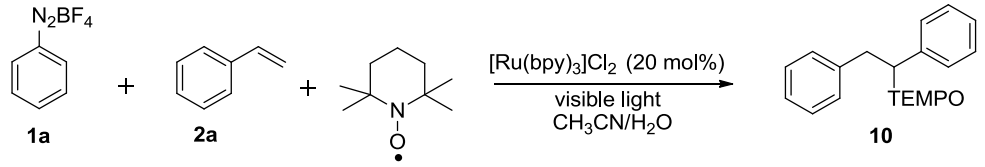
vial's plane bottom side using 440 nm LEDs. After 4 h of irradiation, a TEMPO trapped compound **9** was detected by mass spectra.

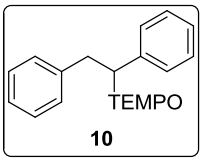




MS (CI): [MH^+]: 234.2

2) In a 5 mL snap vial equipped with magnetic stirring bar the catalyst $[Ru(bpy)_3]Cl_2$ (0.2 equiv), aryl diazonium tetrafluoroborate **1a** (0.25 mmol, 1 equiv), styrene **2a** (2 equiv) and TEMPO (2 equiv) were dissolved in CH_3CN containing 1 equiv of water and the resulting mixture was degassed by three "pump-freeze-thaw" cycles via a syringe needle. The vial was irradiated through the vial's plane bottom side using 440 nm LEDs. After 4 h of irradiation, a TEMPO trapped compound **10** was detected by mass spectra.





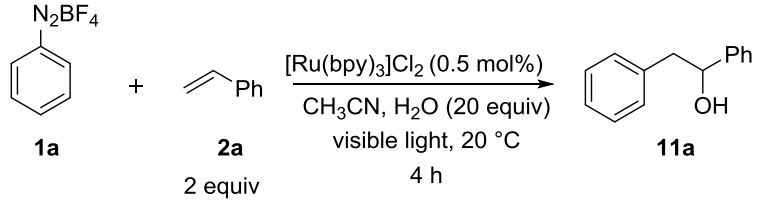
MS (ESI): [MH^+]: 338.2

Carbenium Ion Trapping Experiments

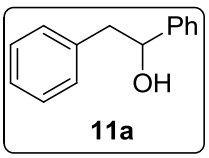
Experimental procedure for tapping carbenium intermediate with water

1) In a 5 mL snap vial equipped with magnetic stirring bar the catalyst $[Ru(bpy)_3]Cl_2$ (0.005 equiv), arenediazonium tetrafluoroborate (1 equiv, 0.25 mmol), alkene (2 equiv), and water (20 equiv) were dissolved in 1 mL CH_3CN, and the resulting reaction mixture was degassed by three "pump-freeze-thaw" cycles via a syringe needle. The vial was irradiated through the vial's plane bottom side using 440 nm blue LEDs. After 4 h of irradiation, the reaction mixture was transferred to a separating funnel, diluted with dichloromethane and washed with 15 mL of water. The aqueous layer was washed three times (3 x 15 mL) with

dichloromethane. The combined organic phases were dried over Na_2SO_4, filtered and concentrated in vacuum.

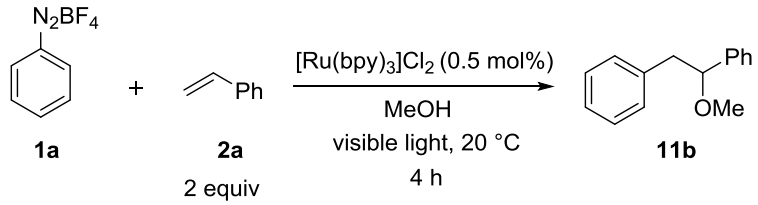


1,2-Diphenylethanol (11a)

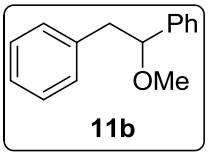


^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 7.46 – 7.12 (m, 10H), 4.91 (dd, *J* = 8.3, 5.1 Hz, 1H), 3.15 – 2.81 (m, 2H), 1.89 (s, 1H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 143.9, 138.7, 129.6, 128.7, 128.6, 127.8, 126.8, 126.0, 75.5, 46.2

2) In a 5 mL snap vial equipped with magnetic stirring bar the catalyst $[Ru(bpy)_3]Cl_2$ (0.005 equiv), arenediazonium tetrafluoroborate (1 equiv, 0.25 mmol), alkene (2 equiv), were dissolved in 1 mL CH_3OH, and the resulting reaction mixture was degassed by three "pump-freeze-thaw" cycles via a syringe needle. The vial was irradiated through the vial's plane bottom side using 440 nm blue LEDs. After 4 h of irradiation, the reaction mixture was transferred to a separating funnel, diluted with dichloromethane and washed with 15 mL of water. The aqueous layer was washed three times (3 x 15 mL) with dichloromethane. The combined organic phases were dried over Na_2SO_4, filtered and concentrated in vacuum.



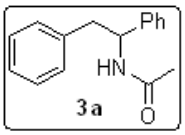
(1-Methoxyethane-1,2-diyl)dibenzene (11b)[2b,3e]

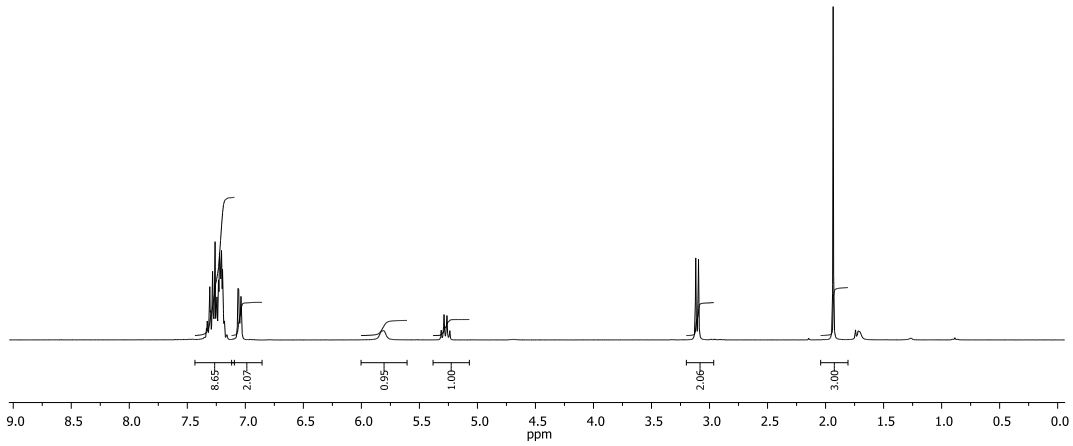


^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 7.34 – 7.14 (m, 10H), 4.32 (dd, *J* = 6.5, 5.9 Hz, 1H), 3.19 (s, 3H), 3.10 (dd, *J* = 13.9, 6.3 Hz, 1H), 2.89 (dd, *J* = 13.8, 5.8 Hz, 1H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 141.8, 138.6, 129.6, 128.5, 128.2, 127.8, 126.9, 126.2, 85.2, 56.9, 44.9

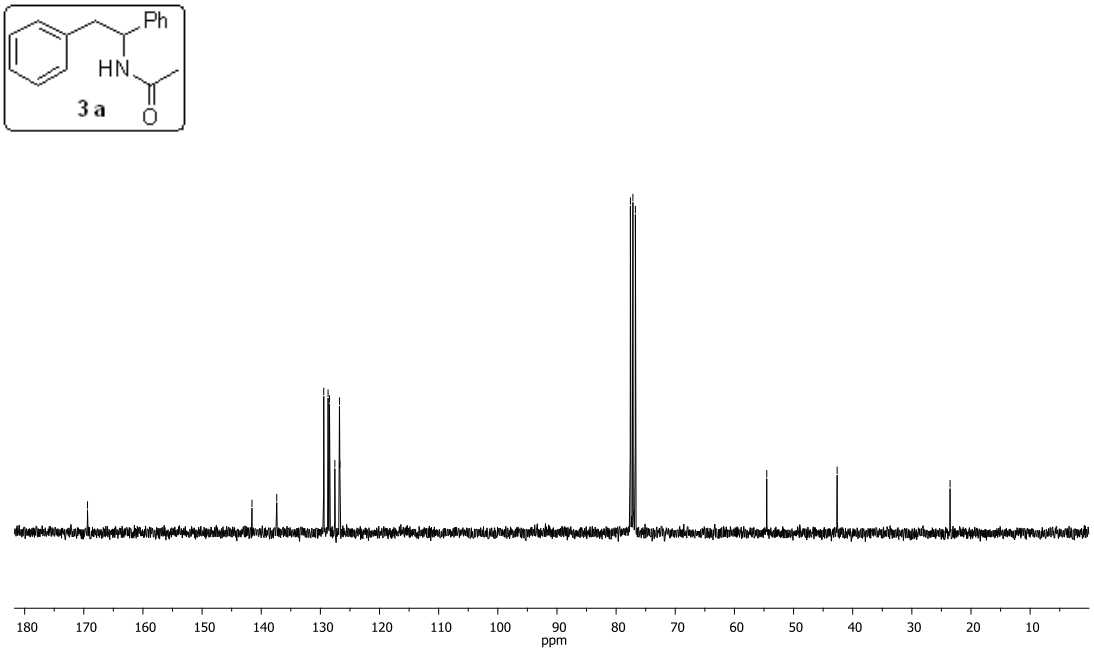
^{1}H and ^{13}C NMR spectra of selected compounds

^{1}H NMR (300MHz, $CDCl_3$)

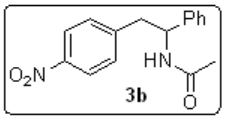


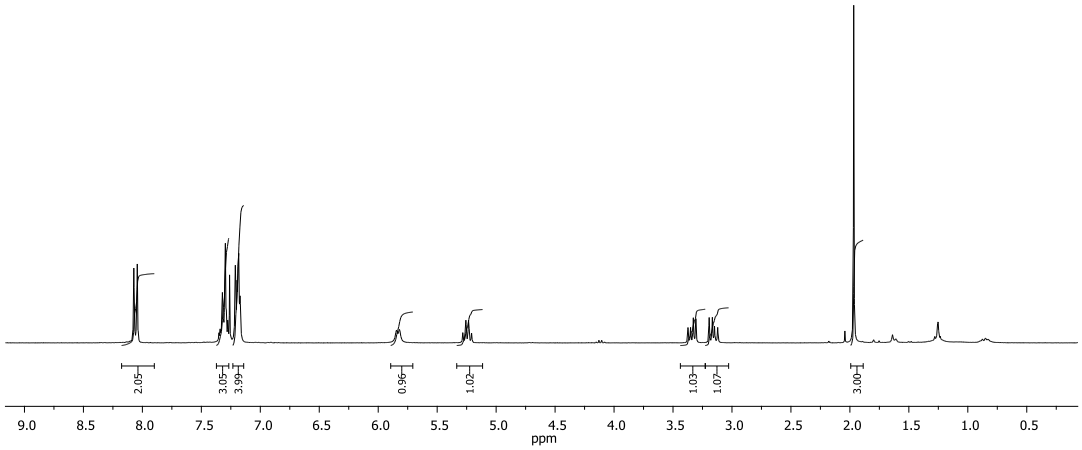


^{13}C NMR (75 MHz, $CDCl_3$)

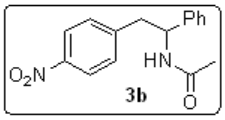


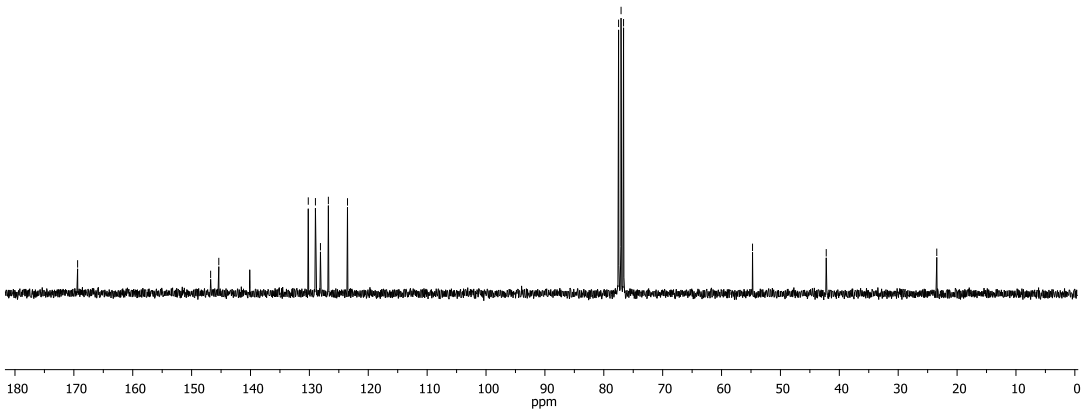
^{1}H NMR (300MHz, $CDCl_3$)



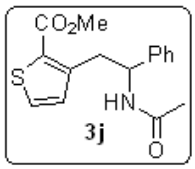


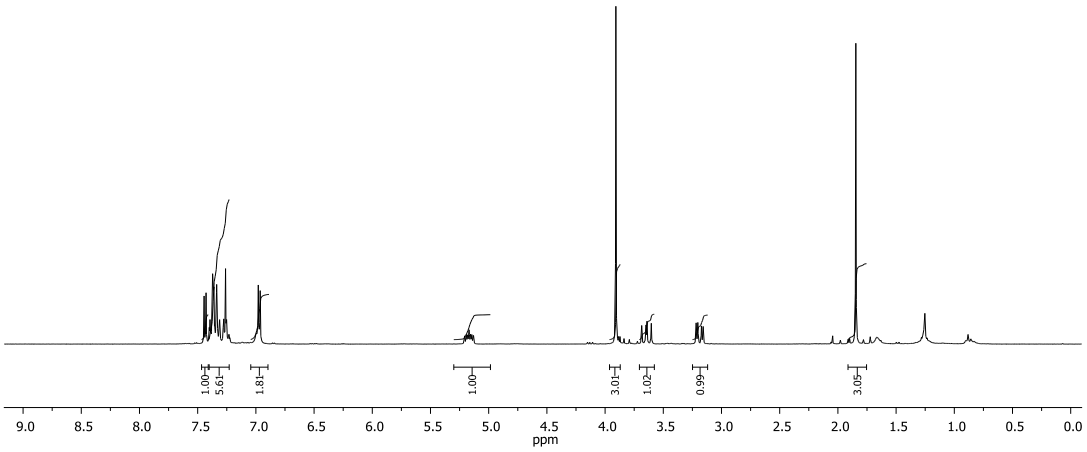
^{13}C NMR (75 MHz, $CDCl_3$)



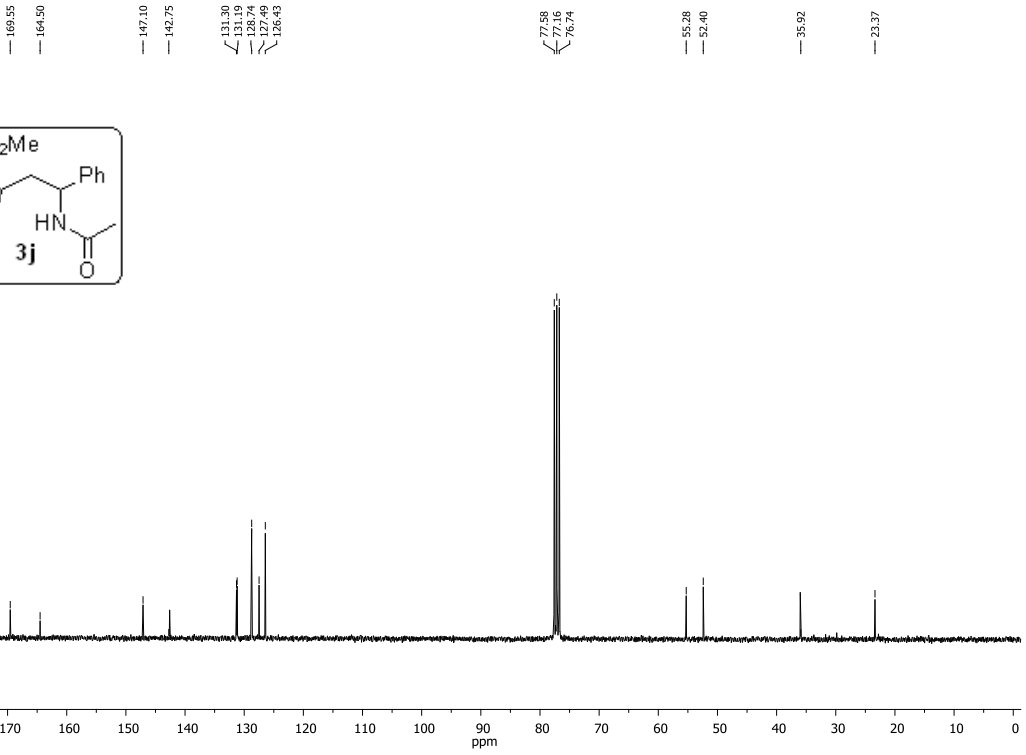


^{1}H NMR (300MHz, $CDCl_3$

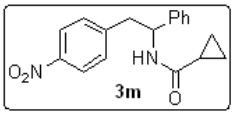


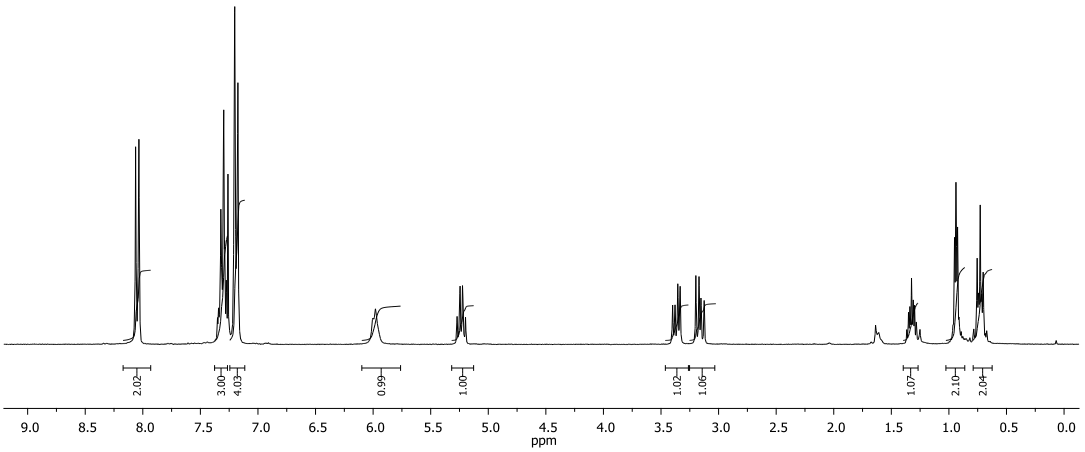


^{13}C NMR (75 MHz, $CDCl_3$)

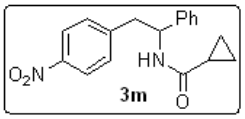


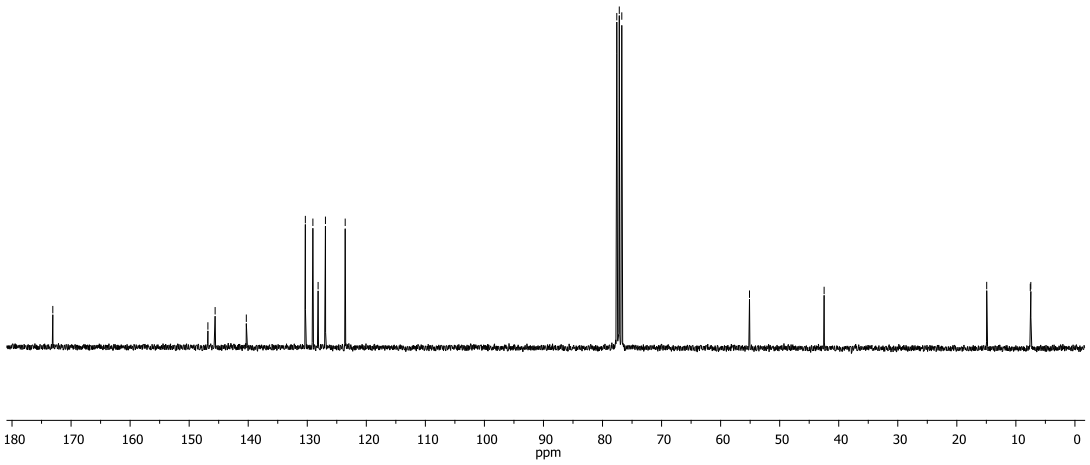
^{1}H NMR (300MHz, $CDCl_3$)





^{13}C NMR (75 MHz, $CDCl_3$)





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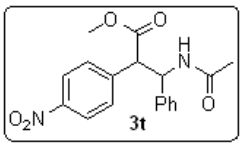

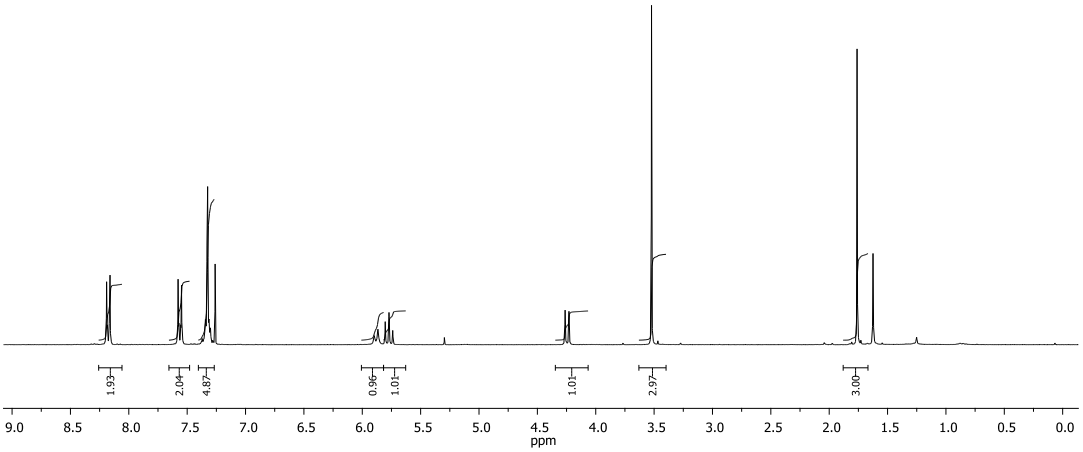

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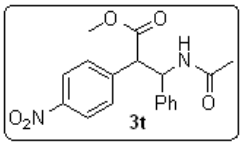

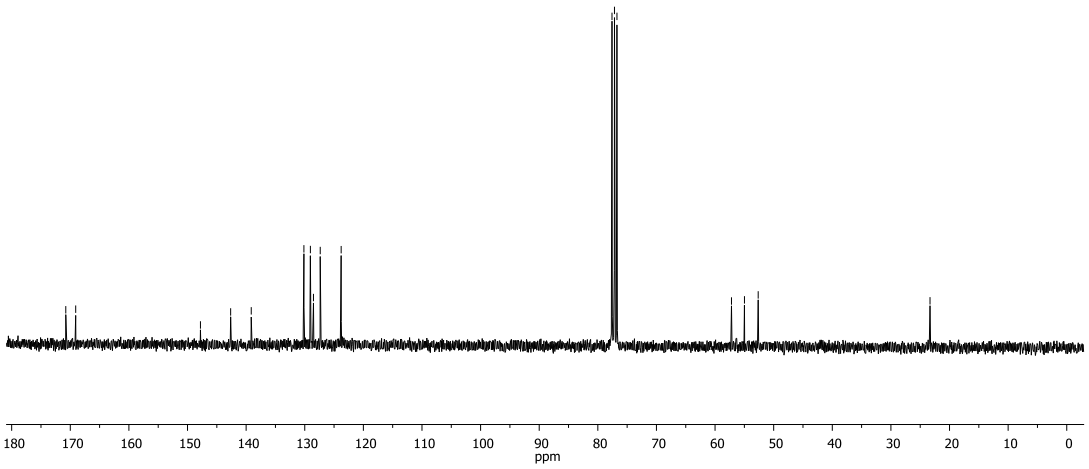

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(5) See the supporting information for more details.

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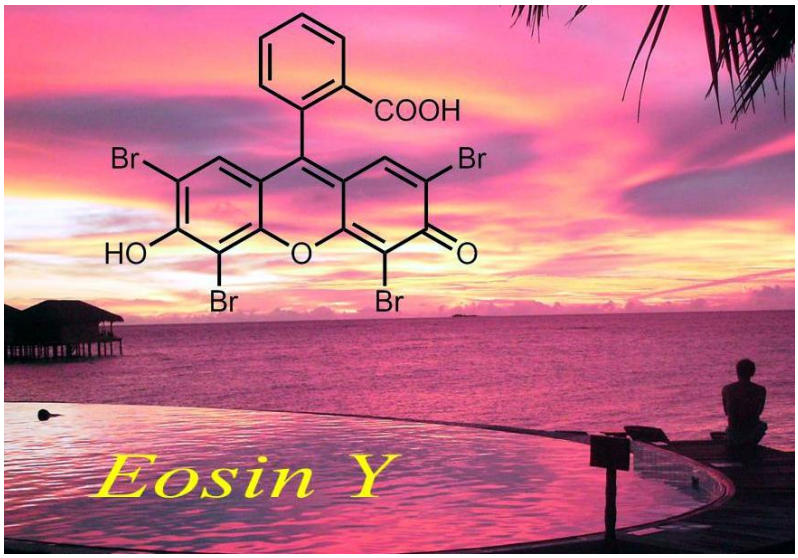
Chapter 6a

6a Synthetic Applications of Eosin Y in Photoredox Catalysis



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. In this chapter, we summarize the key photophysical properties of the dye and the recent synthetic applications in photoredox catalysis.

This chapter has been submitted:
D. P. Hari and B. König, *Chem. Commun.* **2014** (Feature Article).
Author contributions:
DP wrote the manuscript.

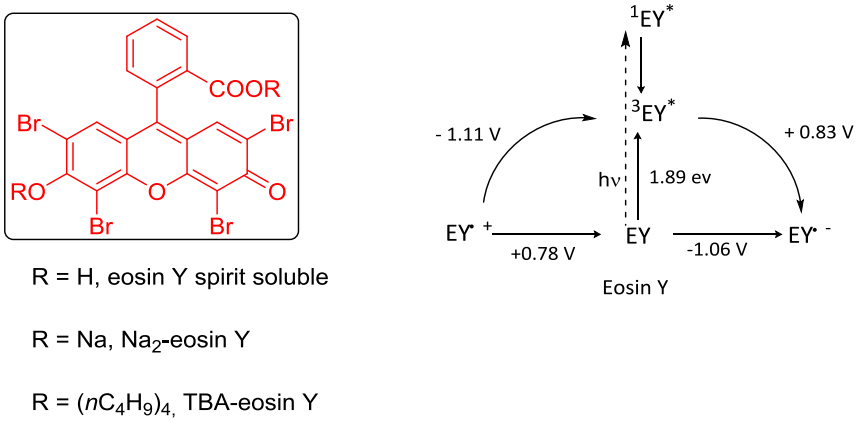
6a.1 Introduction

Visible light photoredox processes have recently found many applications in organic synthesis,[1] but the general interest in the field started much earlier.[2] 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.[2-3]

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.[4] Organic dyes have been used as an attractive alternative to transition metal complexes in photoredox catalysis. They are typically less expensive and less toxic, easy to handle and even outperform organometallic and inorganic catalysts in some cases.[4-5] 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,[6] as pH indicator,[7] as indicator in the analytical halide determination by Fajans[8] and as dye pigment, e.g. in lip sticks.[9] In this Chapter, we discuss recent applications of eosin Y as visible light photocatalyst in organic synthesis.

6a.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 2 ps in water.[10] 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.[11] In addition, the photo excited state of eosin Y may also undergo energy transfer.[12]



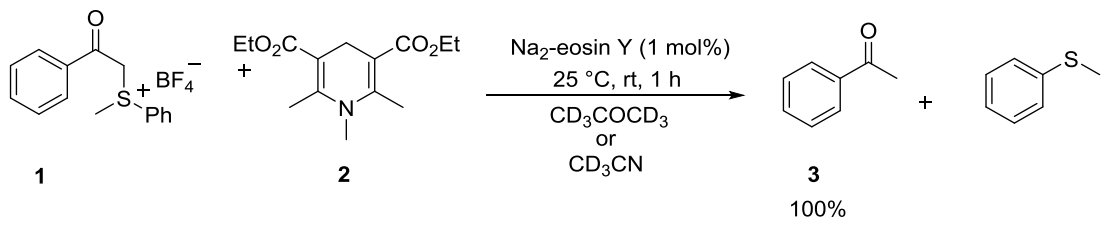
Scheme 1. Different forms of eosin Y and the redox potentials of eosin Y in CH_3CN/H_2O (1:1) in ground and corresponding excited states.

6a.3 Reduction reactions

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

6a.3.1 Reduction of phenacyl sulfonium salt

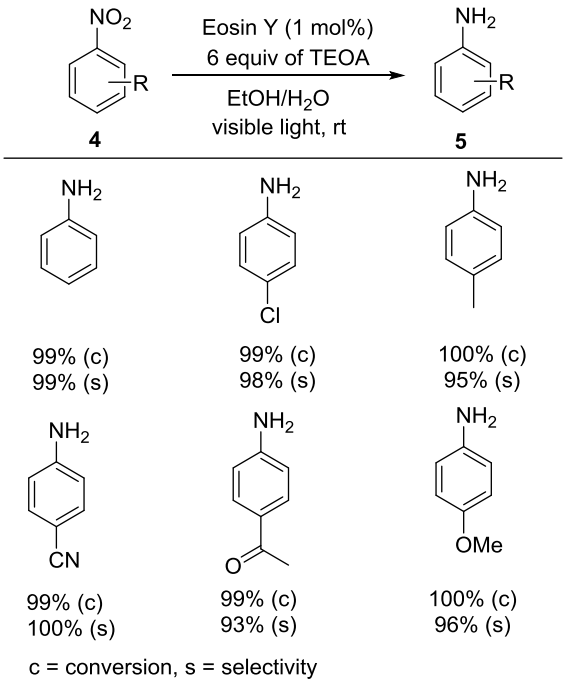
In 1978, Kellogg and co-workers reported the visible light induced reduction of phenacyl sulfonium salts by 1,4 dihydropyridines (Scheme 2).[13] Irradiation of a mixture of **1** and **2** in CD_3CN or CD_3COCD_3 without any photosensitizer provided the reduced product **3** in quantitative yield after 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 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.

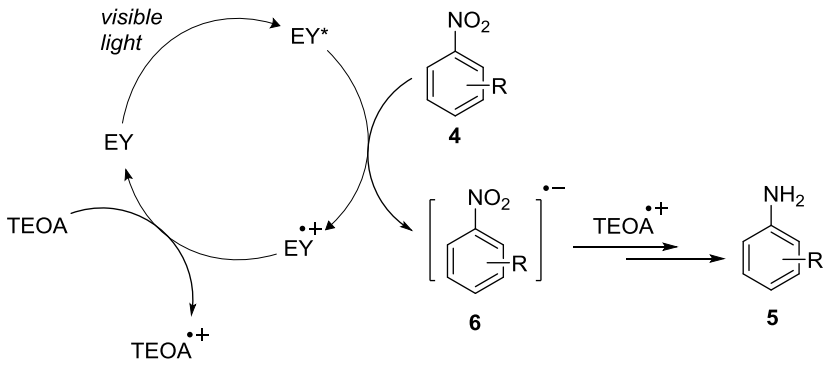
6a.3.2 Reduction of nitrobenzene

Tung and co-workers utilized eosin Y as photocatalyst and TEOA as sacrificial reducing agent for the efficient photocatalytic reduction of nitrobenzene under green light irradiation (Scheme 3).[14] 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.

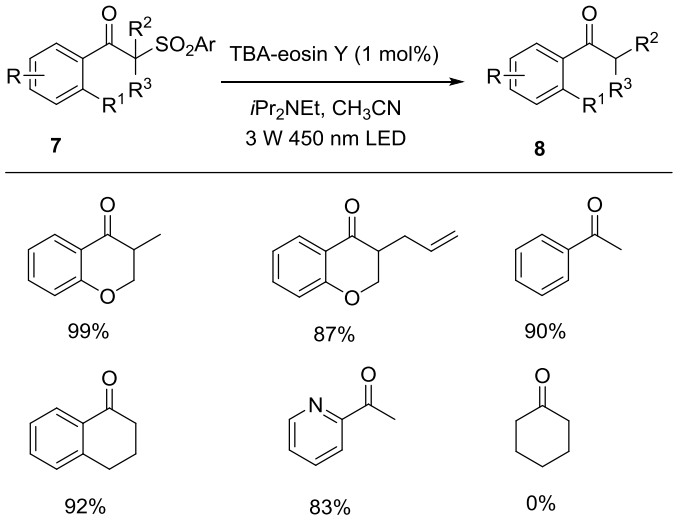
Based on quenching experiments and a flash photolysis study, the authors proposed a tentative mechanism for the photocatalytic reduction of nitrobenzene as shown in Scheme 4. A SET from eosin Y* to nitrobenzene generates **6** and the radical cation of eosin Y, which is reduced by TEOA to close the catalytic 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.

6a.3.3 Desulfonylation

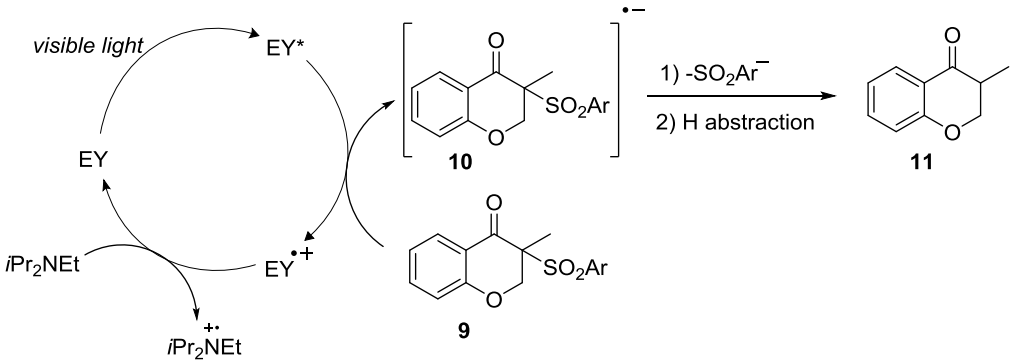
The use of sulfones as auxiliary groups is an efficient synthetic strategy to generate a wide range of important products. Commonly the sulfone group is removed using metal containing reducing agents, such as Bu_3SnH, Al (Hg), or $Sm/HgCl_2$. Recently an environmental friendly desulfonylation reaction was reported by Wu and co-workers using TBA-eosin Y as photo-catalyst and diisopropylethylamine (iPr$_2$EtN) as a reducing agent (Scheme 5).[15] 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.



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

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.

6a.4 Oxidation reactions

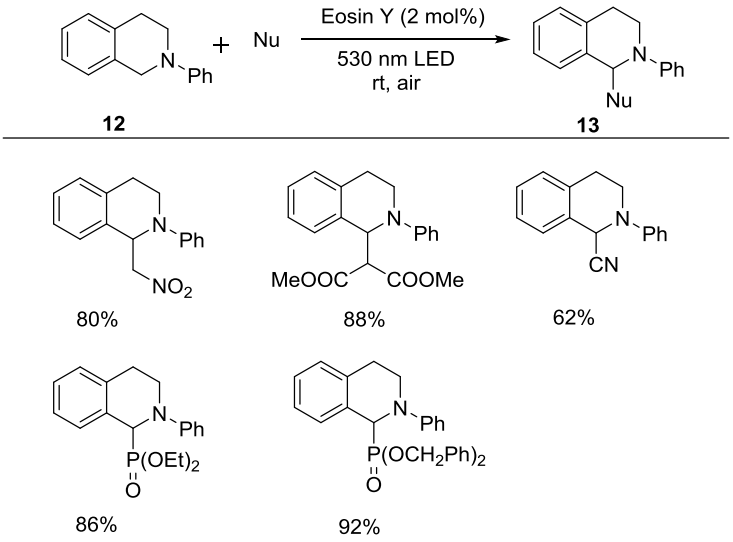
Eosin Y has been used to mediate photooxidation reactions in the presence of stochiometric amounts of electron acceptors. The reported reactions include the oxidation of amines, thioamides, and enol ethers.

6a.4.1 Oxidative iminium ion formation

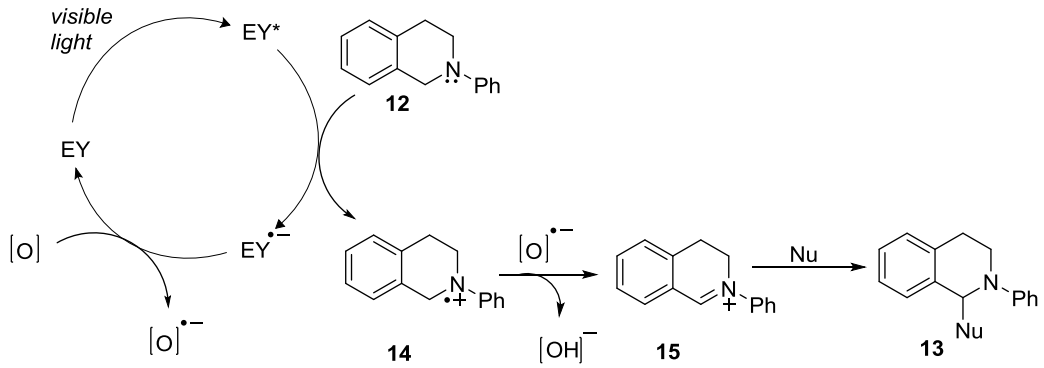
The construction of C-C and C-P bonds by C-H activation is an emerging research area in organic synthesis. Our group reported an efficient visible light mediated method for the formation of C-C and C-P bonds using eosin Y as photoredox catalyst in visible light (Scheme 7).[16] Nitroalkanes, dialkyl phosphonates, 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.

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 the oxidant present in the reaction. The radical anion of the oxidant 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**.



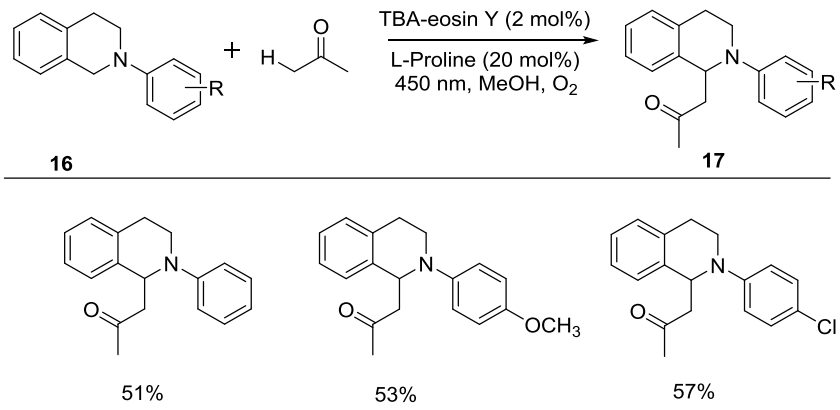
Scheme 7. Oxidative C-C and C-P bond formation.



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

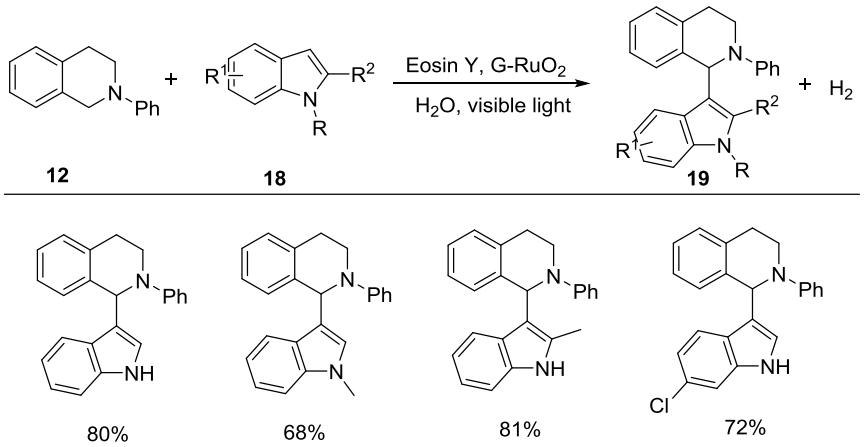
Later, Wu and co-workers reported the photocatalytic oxidative Mannich reaction under aerobic condition using molecular oxygen (Scheme 9).[17] Irradiation of TBA-eosin Y, L-proline, tetrahydroisoquinoline **16**, and acetone produce the synthetically important product **17** in moderate yields. The catalyst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

Wu and co-workers 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).[18] 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.



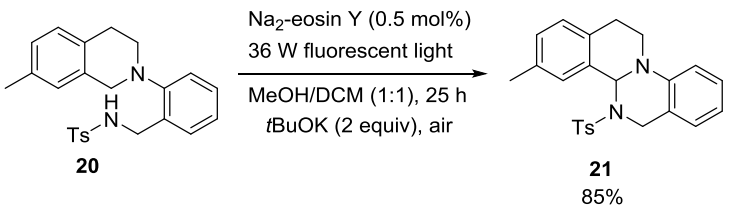
Scheme 9. The photocatalytic oxidative Mannich reaction.

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.

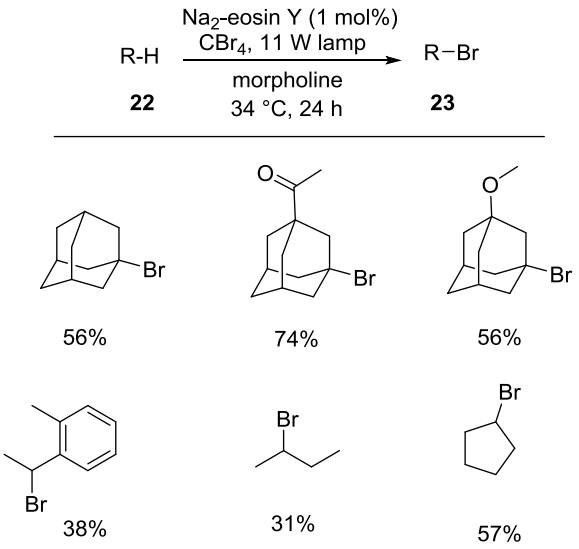
In the reactions described so far, the iminium ion and the nucleophile react intermolecularly. Recently, Xiao and co-workers reported the synthesis of isoquino[2,1-a]pyrimidine **21** *via* intramolecular trapping of the iminium ion with a pendant *N*-tosyl moiety using Na_2-eosin Y as photoredox catalyst (Scheme 11).[19] Irradiation of Na_2-eosin Y, *t*BuOK, 4-methyl-*N*-(2-(7-methyl-3,4-dihydroisoquinolin-2(1H)-yl)benzyl)benzenesulfonamide **20** in MeOH/DCM 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.

6a.4.2 Bromination

Selective bromination of C-H bonds under ambient conditions is an important synthetic method in organic synthesis. Recently, Tan and co-workers reported a selective method for the bromination of aliphatic and benzylic C-H bonds with visible light photoredox catalysis using eosin Y (Scheme 12).[20] 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 DCM 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.

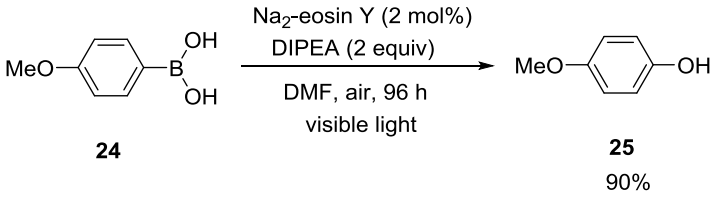


Scheme 12. Selective bromination of aliphatic and benzylic C-H bonds.

6a.4.3 Hydroxylation

Xiao and co-workers reported a highly efficient method for the hydroxylation of arylboronic acids to aryl alcohols using visible light photoredox catalysis under aerobic

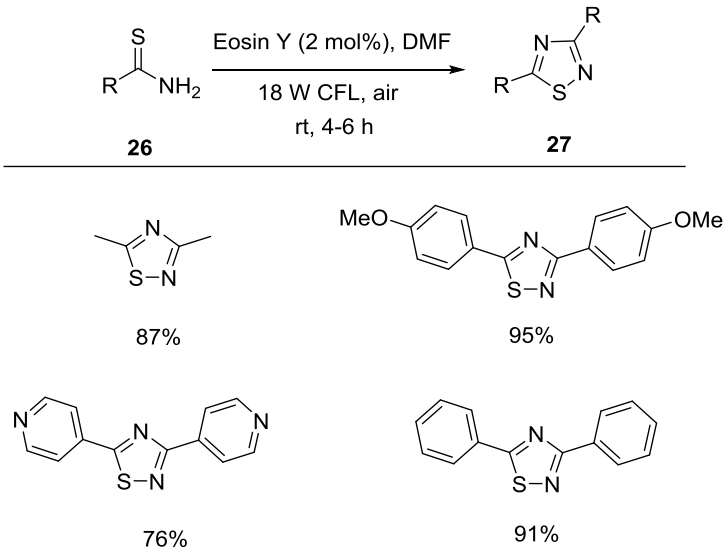
oxidative conditions (Scheme 13).[21] Typical reaction conditions used transition metal photocatalysts, but in a single example Na_2-eosin Y was successfully adopted. Irradiation of a mixture of 2 mol% Na_2-eosin Y, arylboronic acid **24** (0.5 mmol), *i*Pr_2NEt (2.0 equiv) in DMF provided the hydroxylated 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.

6a.4.4 Cyclization of thioamides

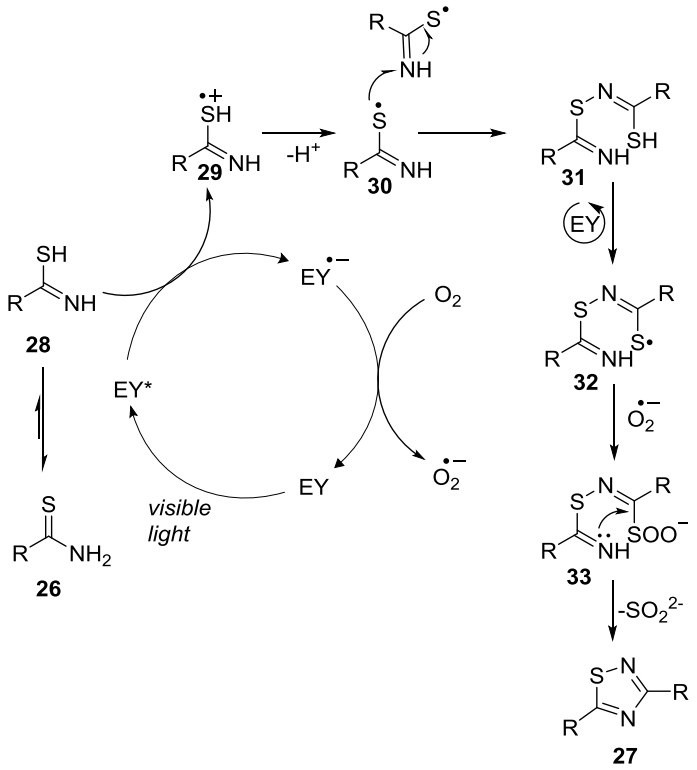
1,2,4-Thiadiazoles have found applications in biology and pharmaceutical sciences. An example is the clinically used antibiotic cefozopram, which contains a 1,2,4-thiadiazole moiety. Elegant methods have been reported for synthesis of the privileged structure, but most of them require oxidizing agents. Yadav and co-workers 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.[22]



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

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.

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-}.[23]

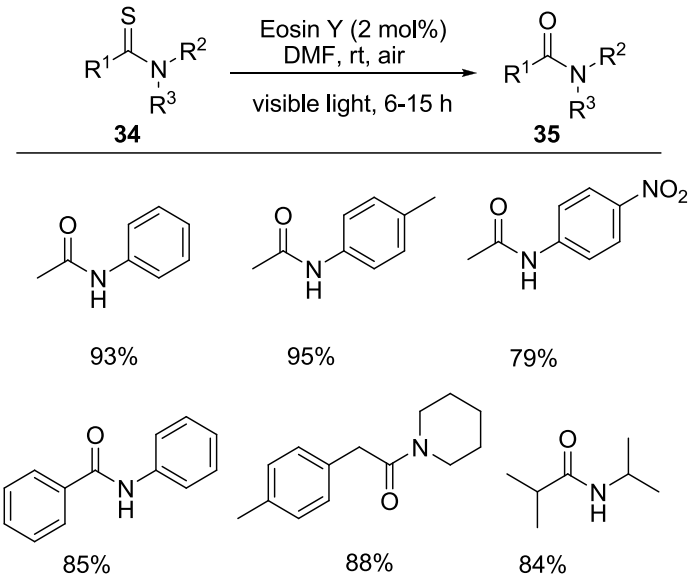


Scheme 15. Proposed mechanism of the cyclization of thioamides.

6a.4.5 Desulfurization

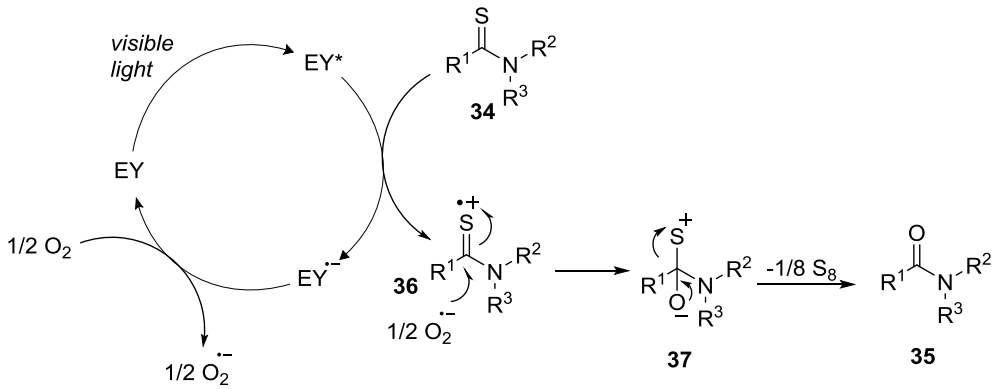
Aerobic desulfurization of thioamides to amides has been achieved by Yadav and co-workers under visible light photoredox catalysis using eosin Y as a photocatalyst (Scheme 16).[24] Green light irradiation of 2 mol% eosin Y, thioamide **34** in DMF under air atmosphere

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**, which is oxidized to the intermediate **37** which converts to the desired product **35** along with the formation of elemental sulfur as byproduct.

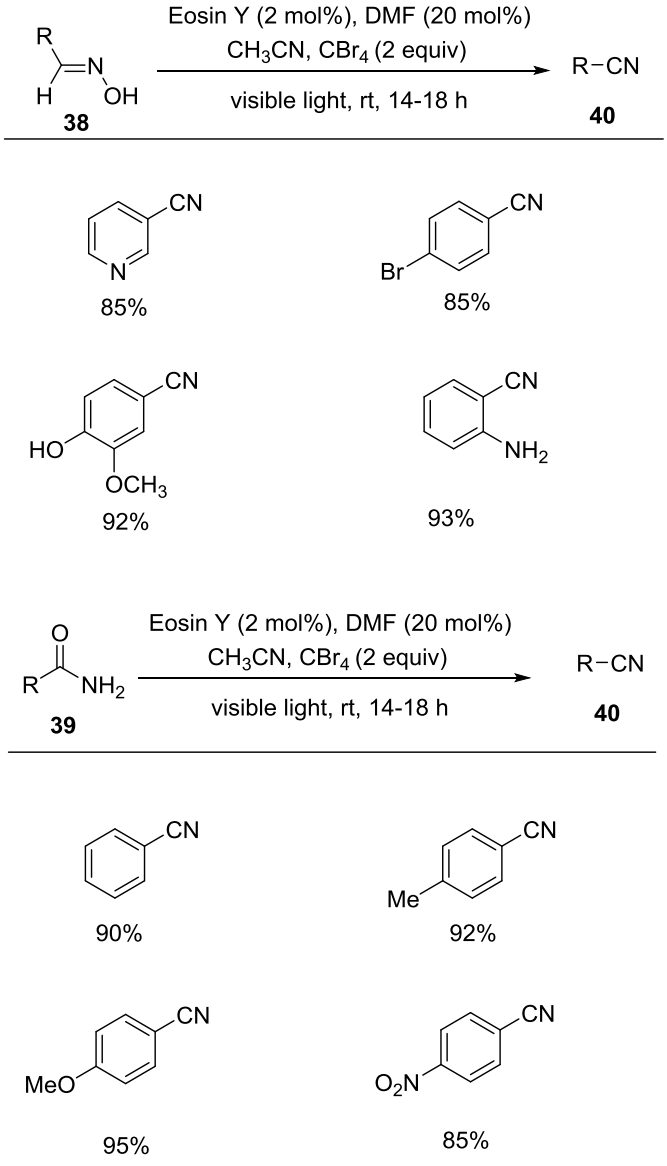


Scheme 17. Suggested mechanism for the desulfurization of thioamides into the amides.

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 DABCO or 2,3 dimethyl-2-butene.

6a.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 co-workers (Scheme 18).[25] 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.

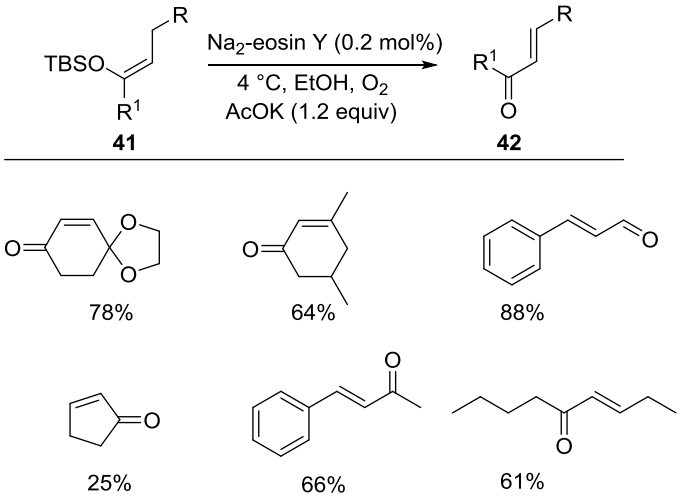


Scheme 18. Conversion of aldoximes and primary amides into nitriles.

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.

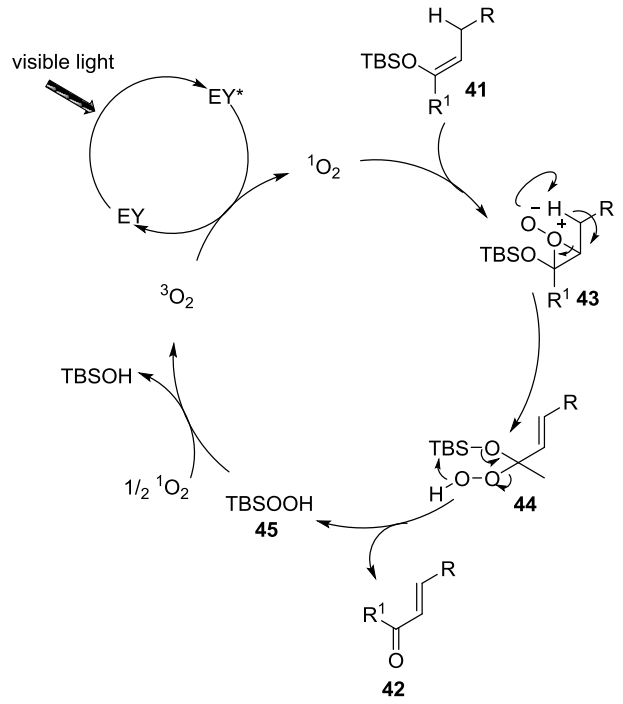
6a.4.7 Oxidation of silyl enol ethers

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 co-workers 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).[12] 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.

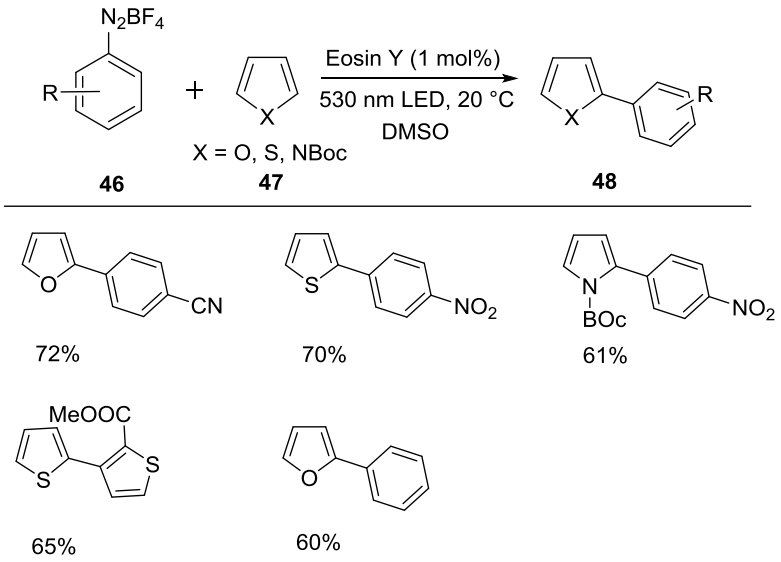
The authors proposed a singlet oxygen mechanism for this transformation based on radical clock experiments and literature reports (Scheme 20). First, singlet oxygen is generated from sensitization by Na_2-eosin Y*. An ene reaction between the silyl enol ether **41** and singlet oxygen produces the intermediate **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.

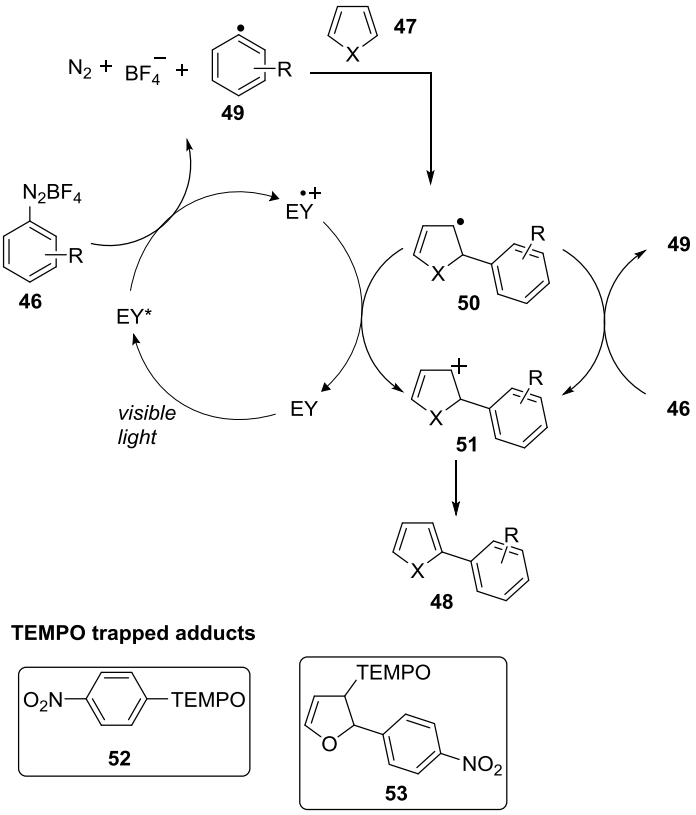
6a.5 Arylation reactions

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).[26]



Scheme 21. Direct photocatalytic C-H arylation of heteroarenes.

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.

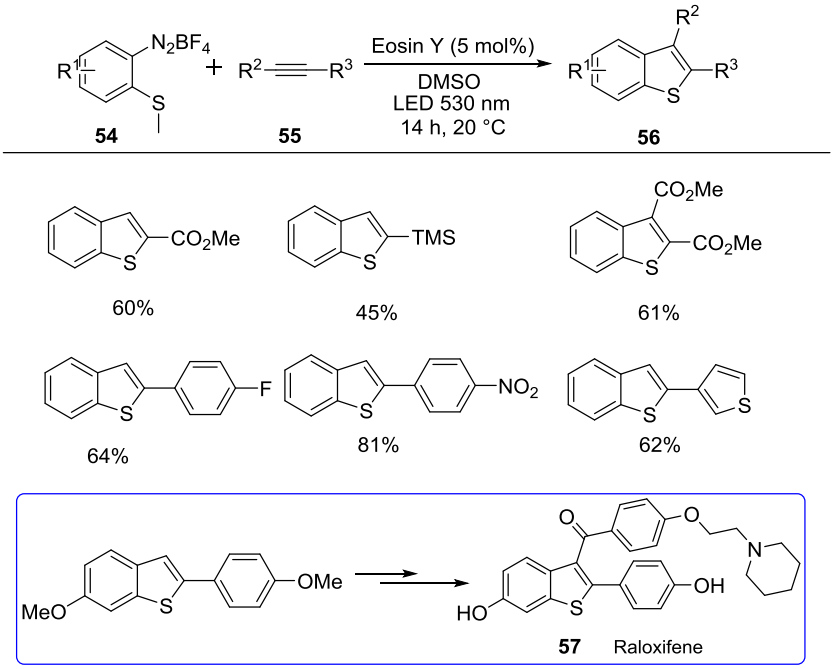


Scheme 22. Proposed mechanism for the direct photocatalytic C-H arylation of heteroarenes.

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**, **50** were trapped with TEMPO and the

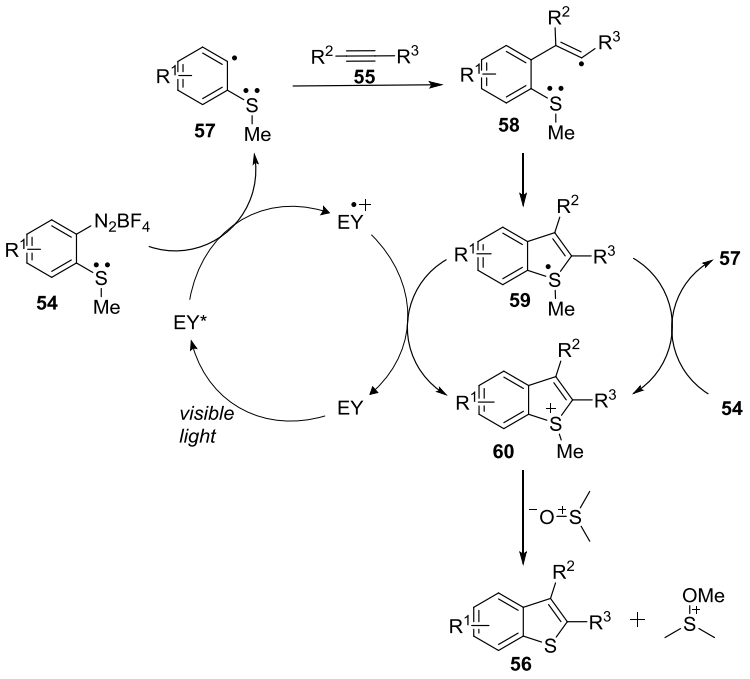
corresponding adducts **52**, **53** were confirmed by mass spectrometry.

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 were obtained in low yields. To obtain a single regioisomer, we decided to explore a radical annulation to obtain the benzothiophene moiety (Scheme 23).[27] 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**.



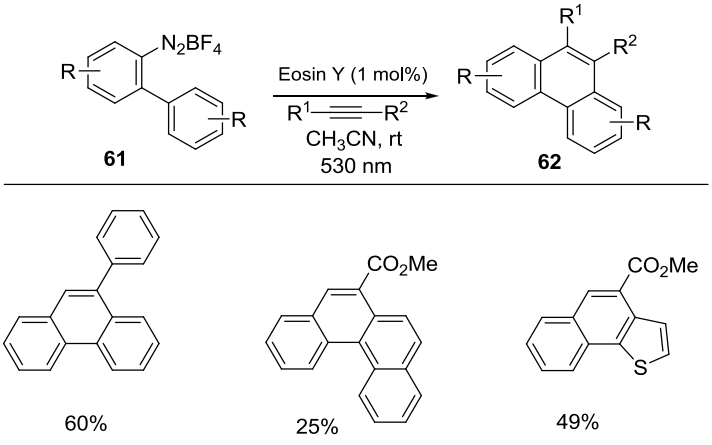
Scheme 23. Synthesis of substituted benzothiophenes via a photocatalytic radical annulation route.

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.



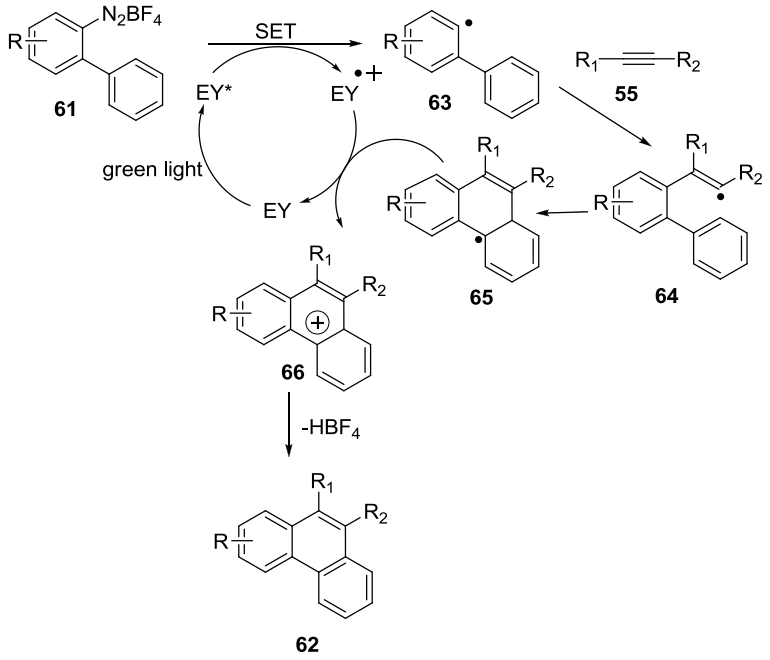
Scheme 24. Proposed mechanism of the photocatalytic radical annulation synthesis of benzothiophenes.

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).[28] Eosin Y (1 mol%), biphenyl diazonium 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. Addition 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.



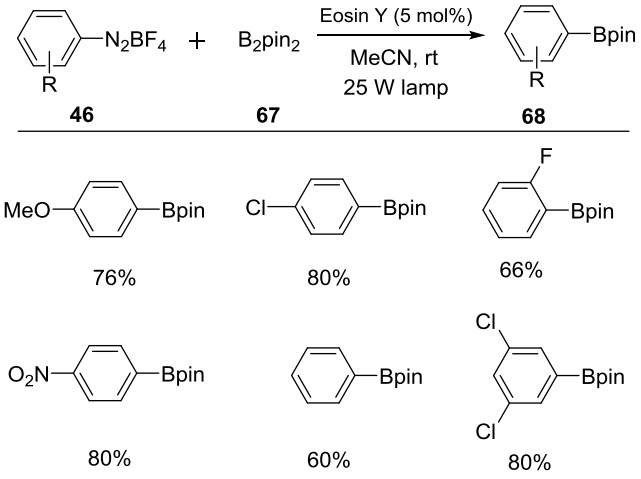
Scheme 25. Photocatalytic synthesis of phenanthrenes *via* a [4+2] benzannulation method.

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**.



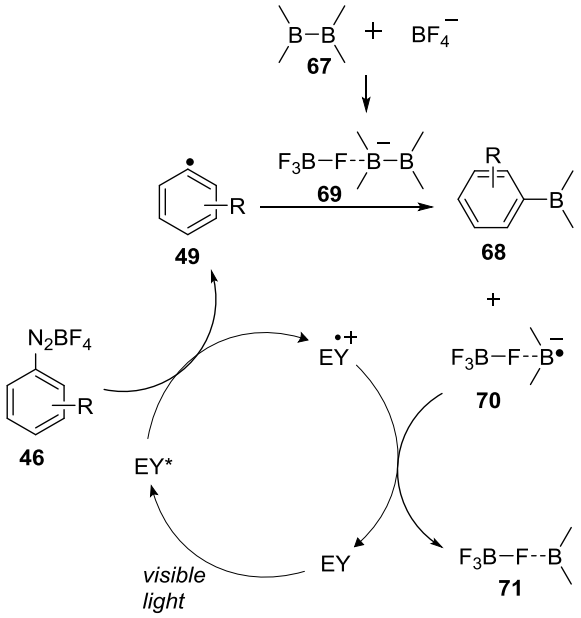
Scheme 26. Proposed mechanism for the synthesis of phenanthrenes.

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).[29] 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.

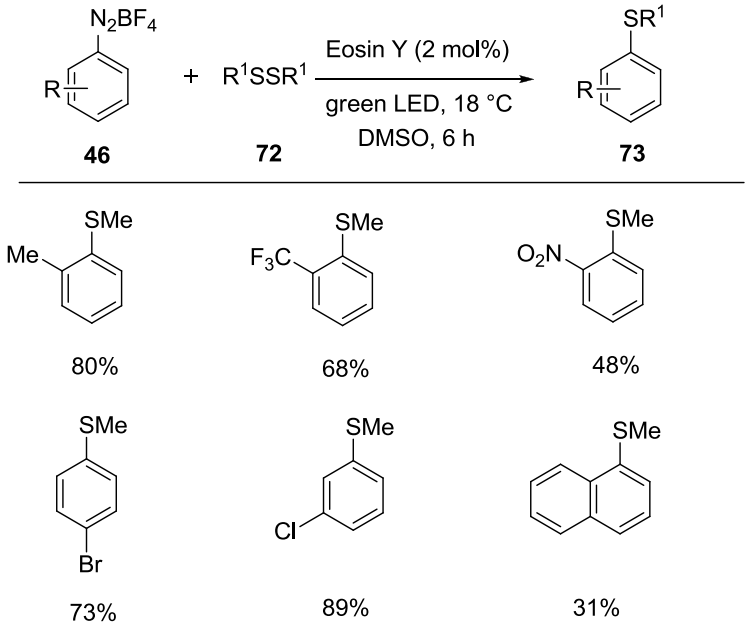
The proposed mechanism for the borylation of aryl diazonium salts is depicted in Scheme 28. Initially, a SET from eosin Y* to the aryl diazonium salt **46** gives the aryl radical **49** and the radical cation of eosin Y. Addition of the aryl radical **49** to the tetracoordinated complex **69**, which 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.

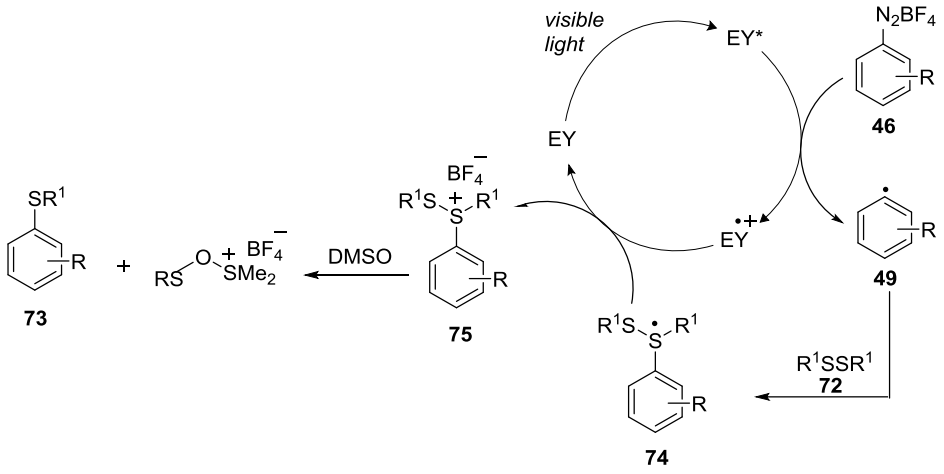
Arylsulfides are important structural motifs in synthetic and natural molecules and they are usually prepared by treatment of aryl diazonium salts with thiols under basic or neutral conditions. The intermediate diazosulfide, which is formed during the reaction, is a potent explosive. The recently reported method by Jacobi and co-workers 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).[30] 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.

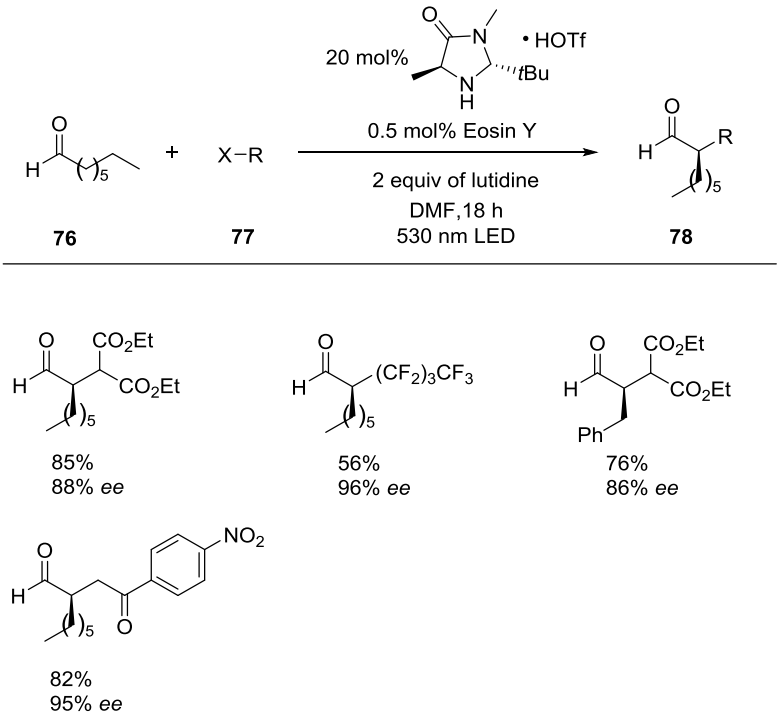
The suggested mechanism for the photocatalytic thiolation reaction as shown in Scheme 30. A SET reduction of aryl diazonium salt **46** by eosin Y* generates aryl radical **49** and the radical cation of eosin Y. The nucleophilic disulfide **72** attacks the aryl radical giving a trivalent sulfur radical **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.

6a.6 Cooperative catalysis

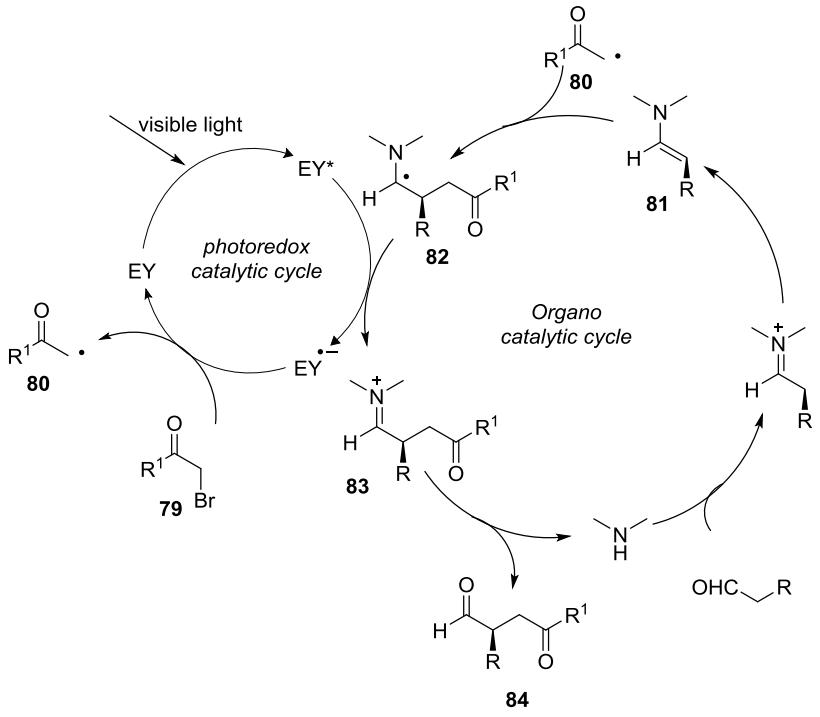
A dual catalytic combination of photocatalysis with organocatalysis was reported by Zeitler and co-workers for the enantioselective α-alkylation of aldehydes.[11b] Eosin Y and imidazolidinone were found to be capable of alkylating aldehydes with electron deficient alkyl halides to provide the corresponding products in good yields with high enantiomeric excess (Scheme 31).



Scheme 31. Asymmetric α-alkylation of aldehydes.

Eosin Y catalyzed reactions require a little longer reaction times compared to the ruthenium-trisbipyridine catalyzed MacMillan reaction,[31] 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.

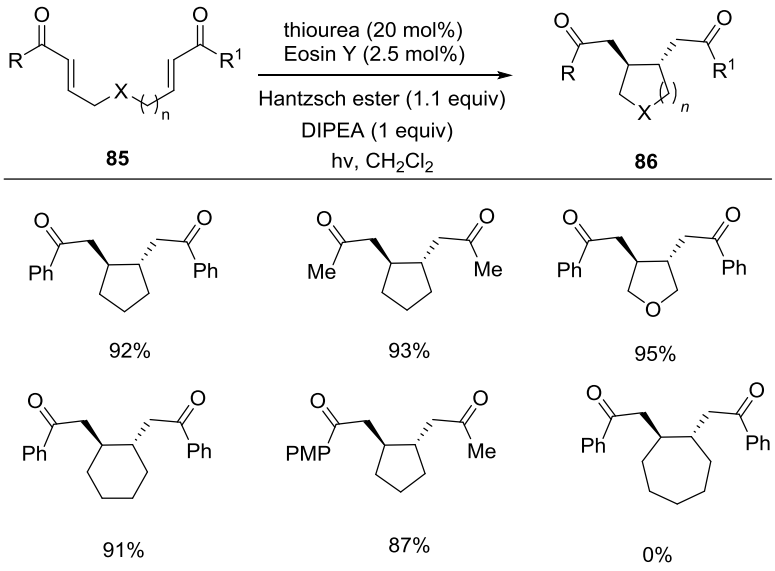
Following mainly the mechanism proposed by MacMillan and co-workers,[31] the authors suggested a mechanism for the eosin Y reaction, which is shown in Scheme 32. Initially, a catalytic amount of enamine is oxidized by eosin Y* to generate the radical anion of eosin Y that reduces the halide **79** to 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**.



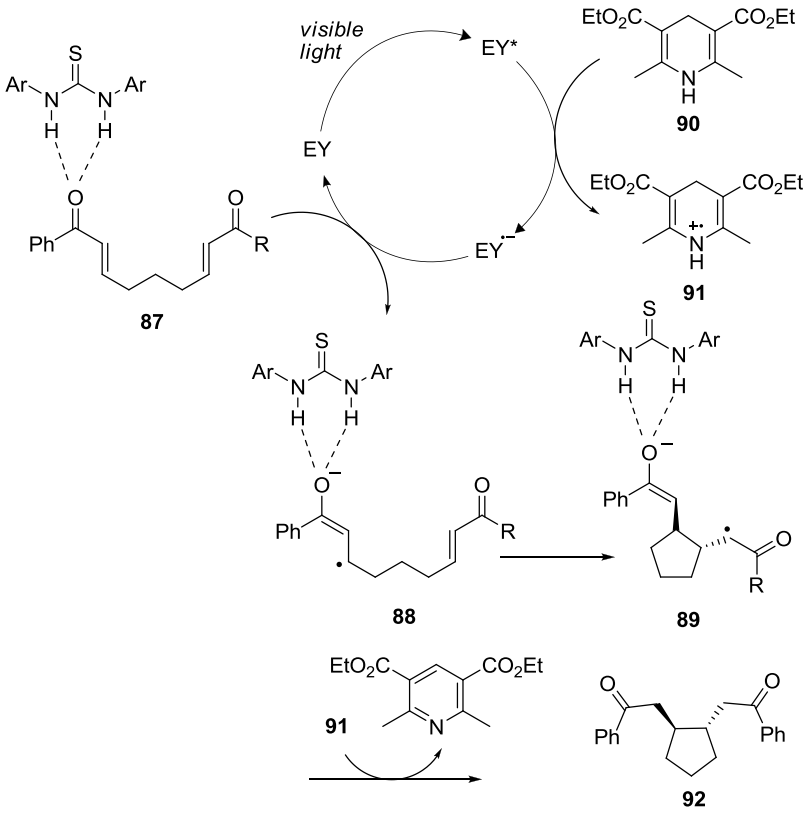
Scheme 32. Mechanism for the asymmetric alkylation of aldehydes.

Another dual catalytic mode of hydrogen bond promoted organophotoredox catalysis was applied for highly diastereoselctive reductive enone cyclization by Zeitler et al.[32] These reactions proceed smoothly at ambient temperature using Na_2-eosin Y as a photocatalyst and thiourea, TADDOL as organocatalysts (Scheme 33). The combination of Hantzsch ester and 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.

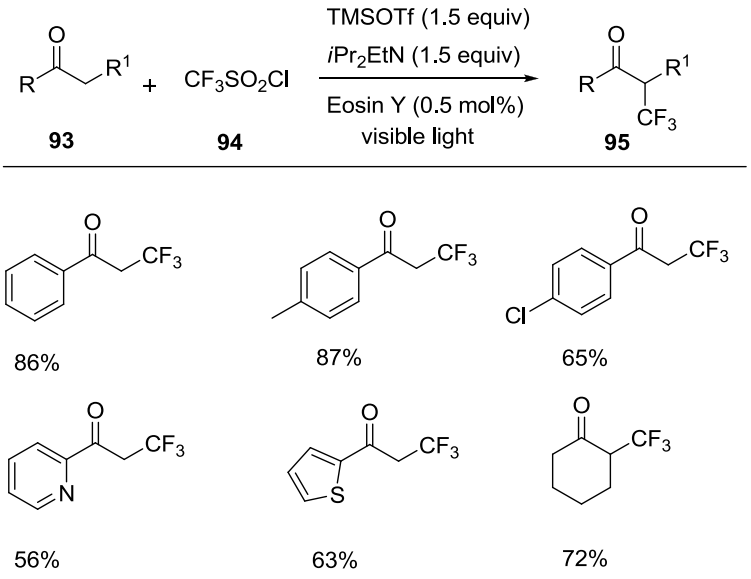


Scheme 34. Suggested mechanism for the reductive enone cyclization.

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** to give the final product **92**. An alternative mechanism is the oxidation of radical **89** followed by hydride transfer to give compound **92**.

6a.7 Trifluoromethylation

α-Trifluoromethylation of ketones has been reported by Kappe and co-workers using a continuous flow visible light photoredox catalysis with eosin Y (Scheme 35).[5d] The reaction proceeds in two steps: in the first step the ketones are converted into their respective silyl enol ethers by reaction with TMSOTf and *i*Pr_2NEt. 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.[33] Several ketones including acetophenones, heteroaromatic ketones, and aliphatic ketones were successfully trifluoromethylated.



Scheme 35. α-Trifluoromethylation of ketones.

6a.8 Conclusion

Visible light photoredox catalysis with metal complexes, such as $Ru(bpy)_3^{2+}$ 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.[5d] 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.[5d,34] 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 appealing and green photocatalysts for organic synthesis.

6a.9 References

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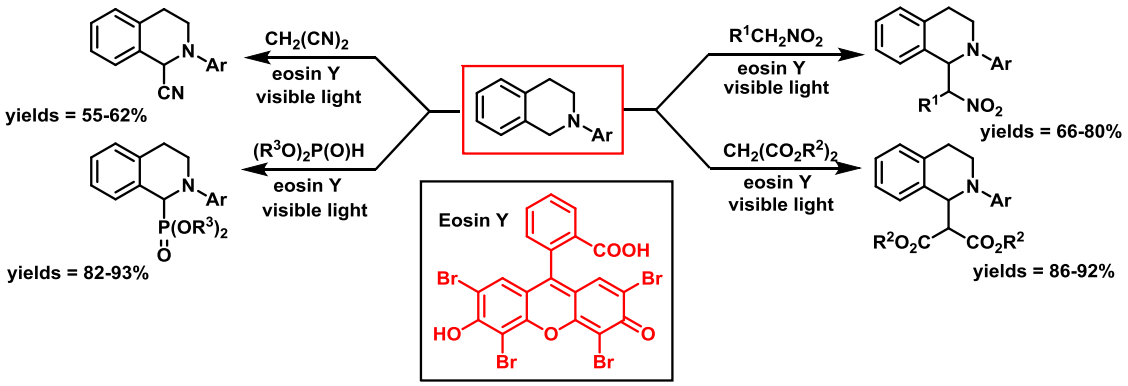
Chapter 6b

6b Eosin Y Catalyzed Visible Light Oxidative C-C and C-P bond Formation



Eosin Y catalyzes efficiently the visible light mediated coupling of sp^3 C-H bonds adjacent to the nitrogen atom in tetrahydroisoquinoline derivatives in the absence of an external oxidant. Nitroalkanes, dialkyl malonates, malononitrile, and dialkyl phosphonates were used as pronucleophiles in this metal free, visible light oxidative coupling reaction.

This chapter has been submitted:
D. P. Hari, B. König, *Org. Lett.* **2011**, *13*, 3852-3855.
Author contributions:
DP carried out all the reactions and wrote the manuscript.

6b.1 Introduction

Sunlight is an abundant, renewable and clean energy resource for chemistry.[1] Visible light accounts for the major part of the incoming solar radiation and therefore visible light should be used to drive chemical transformations. However, most organic molecules do not absorb light in the visible region of light. This restricts the application of photochemical reactions, and thus, motivates the development of efficient visible light photocatalysts for chemical transformations in organic synthesis.[2] Such photoredox catalysts absorb visible light and utilize the collected energy for electron transfer to or from organic molecules to initiate chemical reactions.

In the last decade tris(bipyridine) ruthenium and iridium complexes have been used as visible light photoredox catalysts in dehalogenation,[2d,3] reduction,[4] oxidation[5] and asymmetric alkylation reactions.[6] Yoon and co-workers have used the same ruthenium complex as photocatalyst in inter- and intramolecular [2+2] enone cycloadditions.[2b,7] Currently, Stephenson used these catalysts for oxidative coupling reaction of nitroalkanes with *N*-arylamines in visible light.[8] However, the iridium and ruthenium catalysts are expensive and toxic. The use of organic dyes, which are environmentally friendly, inexpensive and easy to handle as photoredox catalysts would be a superior alternative to inorganic transition metal photocatalysts.

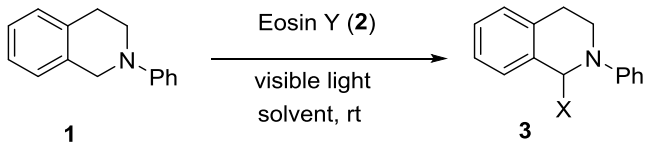
Direct formation of C-C and C-P bonds by C-H activation is a challenging research area in organic synthesis. In the past years many elegant methodologies were developed,[9] but those required transition metal catalysts and harsh conditions. We reported here the metal free visible light photoredox catalysis for C-C and C-P bond formation using the organic dye eosin Y to initiate a single electron transfer processes without exclusion of moisture or air in visible light.

6b.2 Results and discussion

We focused our initial studies on the oxidative coupling reaction of 1 with nitromethane using the reaction conditions reported by Stephenson and co-workers,[8] but replacing the tris(bipyridine) ruthenium complex as visible light photoredox catalyst by the organic dye eosin Y (2 mol %). The desired product **3** was obtained in 80% isolated yield after 8 h of irradiation with green LED light (Table 1, entry 2). Under these conditions (2 mol % of **2**, 530 nm) we also examined other pronucleophiles, such as dialkyl malonates, malononitrile and

dialkyl phosphonates at room temperature (Table 1, entries 4, 5, 6 and 7). In all cases, we obtained the desired products in good yields and found that for efficient conversion both light and catalyst are required (Table 1, entries 8 and 9).

Table 1. Oxidative trapping of iminium ion with different pronucleophiles.



Entry	Conditions[a]	Yield[b] (%)
1	**2** (1 mol %), CH_3NO_2, 12 h; X = CH_2NO_2	74
2	**2** (2 mol %), CH_3NO_2, 8 h; X = CH_2NO_2	80
3	**2** (5 mol %), CH_3NO_2, 8 h; X = CH_2NO_2	80
4	**2** (2 mol %), $C_7H_{12}O_4$, 10 h; X = $C_7H_{11}O_4$	92[c]
5	**2** (2 mol %), $C_5H_8O_4$, 10 h; X = $C_5H_7O_4$	88[c]
6	**2** (2 mol %), DMF , 6 h; X = CN	62
7	**2** (2 mol %), DMF, 3 h; X = $C_4H_{10}O_3P$	86
8	No catalyst, CH_3NO_2, 180 h; X = CH_2NO_2	78
9	**2** (2 mol %), no light, CH_3NO_2, 72 h; X = CH_2NO_2	0

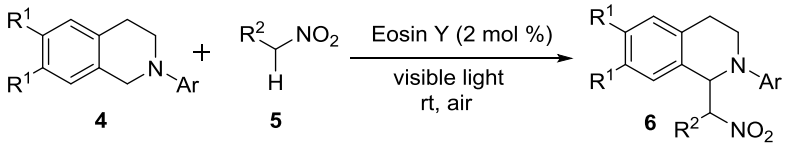
[a]With the exception of entry 6 and 7, in all cases nucleophiles were used as solvents. [b]Isolated yields after purification by chromatography. [c]Isolated yields after removal of the excess solvent by distillation.

Various *N*-aryl tetrahydroisoquinoline derivatives were reacted with nitromethane, nitroethane or 1-nitropropane and gave the desired coupling products in good yields (66-80%; Table 2). Nitromethane always gave better results than other nitroalkanes (**6a** vs **6e** and **6f**) and the reaction was insensitive to electronic effects on the aromatic rings (**6a**, **6b** and **6c**). In the case of non-activated amine (Scheme 1), a low yield was obtained after 96 h irradiation.

Dialkyl malonates gave β-diester amines in excellent yields from the reaction with tetrahydroisoquinoline derivatives using 2 mol % of eosin Y as photocatalyst and green light irradiation at 530 nm at room temperature. Excellent product yields (86-92%; Table 3) were obtained when dialkyl malonates were used as solvents. After the reaction excess dialkyl malonates were distilled off using Kugelrohr distillation[10] yielding the analytically pure

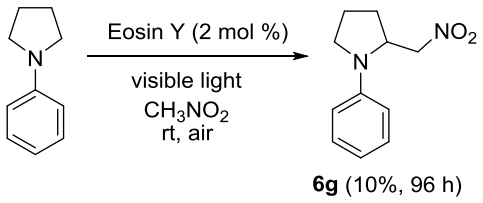
reaction products. These results compare favorably with literature reported results by Li and co-workers[11] and Liang et al.[12]

Table 2. Oxidative coupling reaction of tetrahydroisoquinolines with nitroalkanes[a].



Entry	R^1	Ar	R^2	Product	Time (h)	Yield[b] (%)
1	H	Ph	H	**6a**	8	80
2	H	4-BrC_6H_4	H	**6b**	10	76
3	H	4-$MeOC_6H_4$	H	**6c**	10	78
4	OMe	Ph	H	**6d**	8	74
5	H	Ph	Me	**6e**	12	75
6	H	Ph	Et	**6f**	14	66

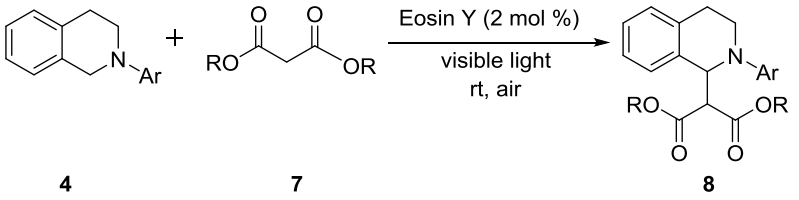
[a]The reaction was performed with **4** (0.25 mmol) and eosin Y (0.02 equiv) in 1.0 mL of **5**. [b]Isolated yield after purification on SiO_2. [c]dr = 2:1. [d]dr = 1.4:1.



Scheme 1. Reaction of 1-phenylpyrrolidine with nitromethane.

In addition to nitroalkanes, dialkyl malonates, the photocatalytic reaction was applied to malononitrile. Surprisingly, α-amino nitriles were obtained as the sole products instead of the expected β-dicyano substituted derivatives when malononitrile was treated with tetrahydroisoquinolines in DMF at room temperature (Table 4). Amino nitriles are synthetically useful intermediates. The nitrile functionality can be hydrolyzed to give α-amino acids or can be converted into α-amino aldehydes or α-amino alcohols. The photocatalytic reaction, which we report is an alternative synthetic route to α-amino nitriles avoiding toxic cyanides and expensive metals.[12,13]

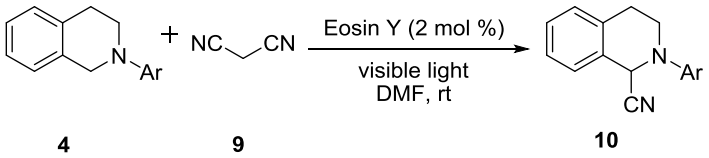
Table 3. Oxidative coupling reaction of tetrahydroisoquinolines with dialkyl malonates[a].



Entry	Ar	R	Product	Time (h)	Yield[b] (%)
1	Ph	Et	**8a**	10	92
2	Ph	Me	**8b**	10	88
3	4-$MeOC_6H_4$	Et	**8c**	12	91
4	4-$MeOC_6H_4$	Me	**8d**	12	90
5	2-$MeOC_6H_4$	Et	**8e**	14	89
6	2-$MeOC_6H_4$	Me	**8f**	14	86

[a]The reaction was performed with **4** (0.25 mmol) and eosin Y (0.02 equiv) in 1.0 mL of **7**.
[b]Isolated yield after distillation of excess solvent.

Table 4. Oxidative synthesis of α-amino nitriles[a].



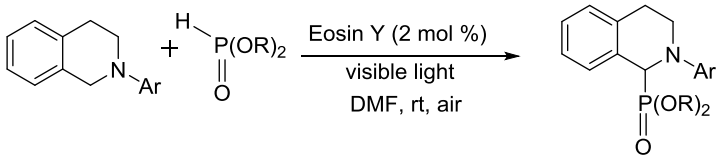
Entry	Ar	Product	Time (h)	Yield[b] (%)
1	Ph	**10a**	10	62
2	4-BrC_6H_4	**10b**	12	56
3	4-$MeOC_6H_4$	**10c**	10	60
4	2-$MeOC_6H_4$	**10d**	10	58

[a]The reaction was run with **4** (0.25 mmol), malononitrile (1.5 equiv), eosin Y (0.02 equiv) in 1.0 mL DMF. [b]Isolated yield after purification on SiO_2.

The success of C-C bond formation by using eosin Y encouraged us to investigate C-P bond reactions. A variety of methods have been described for the synthesis of α-amino phosphonates,[9r-9w] but those typically require metal catalysts and expensive reagents. To avoid these catalysts, we applied our methodology for the synthesis of α-amino phophonates.

Various tetrahydoisoquinolines were reacted with dialkyl phosphonates, and representative results are listed in Table 5. The desired products were obtained in good to excellent yields.

Table 5. Oxidative synthesis of α-amino phosphonates[a].

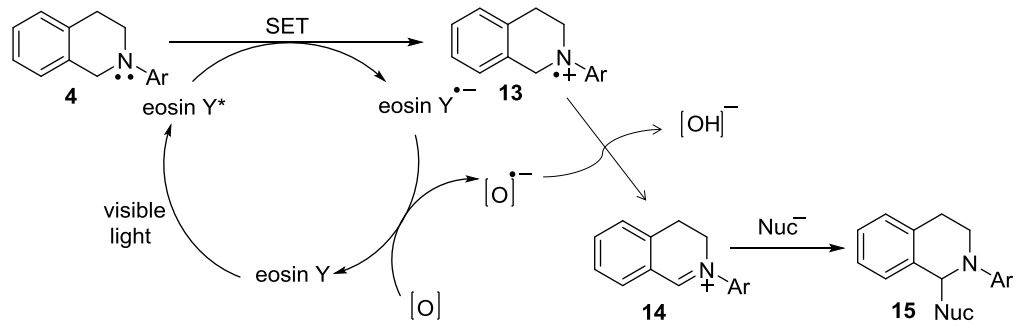


4 **11** **12**

Entry	Ar	R	Product	Time (h)	Yield[b] (%)
1	Ph	Et	**12a**	3	86
2	Ph	Bn	**12b**	4	92
3	4-BrC_6H_4	Et	**12c**	2	82
4	4-BrC_6H_4	Bn	**12d**	3	88
5	4-$MeOC_6H_4$	Et	**12e**	3	93
6	4-$MeOC_6H_4$	Bn	**12f**	3	91
7	2-$MeOC_6H_4$	Et	**12g**	3	91
8	2-$MeOC_6H_4$	Bn	**12h**	3	90

[a]The reaction was run with **4** (0.25 mmol), dialkyl phosphonate (4 equiv), eosin Y (0.02 equiv) in 1.0 mL DMF. [b]Isolated yield after purification on SiO_2.

The mechanism of the eosin Y photocatalysis has not been investigated in detail at this stage. However, on the basis of our results using nitroalkanes, dialkyl malonates, dialkyl phosphonates as pronucleophiles in the photoreaction and the litreature reports[8,14] the following mechanism can be suggested (Scheme 2). A single electron transfer from **4** to excited state of eosin Y gave an aminyl cation radical **13**, which then lost a hydrogen atom by radical anion to generate iminium ion **14**.[15] Subsequently, trapping of **14** with pronucleophiles resulted in the desired product **15**. The formation of α-amino nitriles may result from cyanide ion addition to the iminium ion **14**, whereby cyanide ions may be formed by oxidative cleavage of the malononitrile C-CN bond.[11,12a,16]



Scheme 2. Proposed reaction mechanism.

6b.3 Conclusion

Iridium- and ruthenium based photocatalysts mediate the visible light oxidative coupling of tetrahydroisoquinoline derivatives with nitroalkanes, as recently disclosed by Stephenson et al. Our experiments have shown that the transition metal catalysts can be replace by the redox active organic dye eosin Y yielding comparable yields. Using these organic photocatalysts, the scope of the reaction was extended to dialkyl malonate, malononitrile and dialkyl phosphonates as pronucleophiles. Continuing from these results we successfully replaced other reagents $PhI(OAc)_2$ (for cyanation) and $CuBr\text{-}O_2$ (for phosphonation). Due to the similar redox properties of eosin Y and the previously used $Ru(bpy)_3^{2+}$ complexes we propose a similar mechanism of the reaction. However, alternative mechanistic pathways are equally likely and ongoing investigations must prove the correct mechanistic picture.

6b.4 Experimental Part

General information

^1H NMR spectra were recorded on a Bruker Avance 300 MHz spectrometer in $CDCl_3$ solution and the chemical shifts were reported in parts per million (δ) referenced to the internal solvent signal peak at 7.26 ppm. Multiplicities are indicated, s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sept (septet), m (multiplet)); coupling constants (*J*) are in Hertz (Hz). ^{13}C NMR were obtained at 75 MHz spectrometer in $CDCl_3$ solution and referenced to the internal solvent signal (central peak is 77.00 ppm). ^{31}P NMR were obtained at 121 MHz and calibrated with peak at 0.00 ppm. All reactions were monitored by thin-layer chromatography using Merck silica gel plates 60 F254; visualization was accomplished with UV light and/or staining with appropriate stains (anisaldehyde, orphosphomolybdic acid). Standard flash chromatography procedures were followed (particle size 40−63 μm).

Commercially available reagents and solvents were used without further purification. Irradiation with green light was performed using high-power LEDs Philips LUXEON® Rebel (1W, λ = 530±10 nm, 145 lm @700mA).

General Procedures

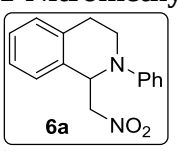
General procedure for the preparation of 2-aryl-1,2,3,4-tetrahydroisoquinolines[9h,17]

Copper (I) iodide (200 mg, 1.0 mmol) and potassium phosphate (4.25 g, 20.0 mmol) were put into a Schlenk-tube. The Schlenk-tube was evacuated and back filled with nitrogen. 2-Propanol (10.0 mL), ethylene glycol (1.11 mL, 20.0 mmol), 1,2,3,4-tetrahydro-isoquinoline (2.0 mL, 15.0 mmol) and iodobenzene (1.12 mL, 10.0 mmol) were added successively at room temperature. The reaction mixture was heated at 85-90 °C and kept for 24 h and then allowed to cool to room temperature. Diethyl ether (20 mL) and water (20 mL) were then added to the reaction mixture. The organic layer was extracted with diethyl ether (2 × 20 mL). The combined organic phases were washed with brine and dried over sodium sulfate. The solvent was removed by rotary evaporation and purified by column chromatography on silica gel using hexane/ethyl acetate as eluent.

General procedure for the preparation of β-nitro amine derivatives

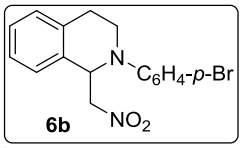
In a 5 mL snap vial equipped with magnetic stirring bar the tetrahydroisoquinoline derivative (1 eq) and eosin Y (0.02 eq) were dissolved in nitroalkane (0.25 mmol/mL) and the resulting mixture was irradiated through the vial's plane bottom side using green LEDs. After the reaction was completed (monitored by TLC), the reaction mixture was filtered and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel using hexane/ethyl acetate as eluent.

1-Nitromethyl-2-phenyl-1,2,3,4-tetrahydroisoquinoline (6a)[12b]



^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 7.33-7.13(m, 6H), 7.01-6.98(m, 2H), 6.87(t, *J* = 7.3 Hz, 1H), 5.57(t, *J* = 7.2 Hz, 1H), 4.88(dd, *J* = 11.8, 7.8 Hz, 1H), 4.57(dd, *J* = 11.8, 6.6 Hz, 1H), 3.70-3.58(m, 2H), 3.15-3.05(m, 1H), 2.84-2.76(m, 1H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 148.4, 135.3, 132.9, 129.5, 129.2, 128.1, 127.0, 126.6, 119.4, 115.1, 78.8, 58.2, 42.0, 26.4

2-(4-Bromophenyl)-1-nitromethyl-1,2,3,4-tetrahydroisoquinoline (6b)[12a]



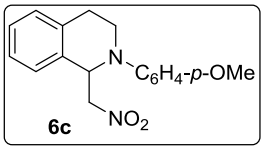
^{1}H NMR (300 MHz, $CDCl_3$):

δ ppm 7.34(d, *J* = 9.1 Hz, 2H), 7.27-7.12(m, 4H), 6.85(d, *J* = 8.8 Hz, 2H), 5.49(t, *J* = 7.6 Hz, 1H), 4.87-4.80(m, 1H), 4.59-4.53(m, 1H), 3.63-3.59(m, 2H), 3.09-3.04(m, 1H), 2.83-2.74(m, 1H)

^{13}C NMR (75 MHz, $CDCl_3$):

δ ppm 147.5, 135.0, 132.6, 132.2, 129.3, 128.3, 126.8, 126.8, 116.7, 111.5, 78.6, 58.1, 42.1, 26.2

2-(4-Methoxyphenyl)-1-nitromethyl-1,2,3,4-tetrahydroisoquinoline (6c)[11]



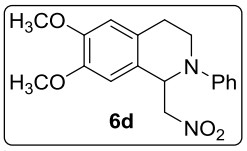
^{1}H NMR (300 MHz, $CDCl_3$):

δ ppm 7.26-7.22(m, 2H), 7.19-7.14(m, 2H), 6.94(d, *J* = 9.1 Hz, 2H), 6.83(d, *J* = 9.1 Hz, 2H), 5.41(dd, *J* = 8.6, 5.8 Hz, 1H), 4.83(dd, *J* = 11.9, 8.6 Hz, 1H), 4.57(dd, *J* = 11.9, 5.8 Hz, 1H), 3.76(s, 3H), 3.50-3.55(m, 2H), 3.08-2.97(m, 1H), 2.74-2.67(m, 1H)

^{13}C NMR (75 MHz, $CDCl_3$):

δ ppm 153.9, 143.0, 135.4, 132.9, 129.5, 127.9, 126.9, 126.6, 118.8, 114.7, 78.9, 58.9, 55.6, 43.1, 25.8

6,7-Dimethoxy-1-nitromethyl-2-phenyl-1,2,3,4-tetrahydroisoquinoline (6d)[8]



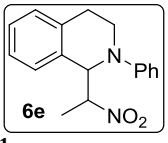
^{1}H NMR (300 MHz, $CDCl_3$):

δ ppm 7.29-7.23(m, 2H), 6.98(d, *J* = 8.1 Hz, 2H), 6.85(t, *J* = 7.3 Hz, 1H), 6.65(s, 1H), 6.61(s, 1H), 5.47(dd, *J* = 8.0, 6.3 Hz, 1H), 4.85(dd, *J* = 11.8, 8.1 Hz, 1H), 4.57(dd, *J* = 11.8, 6.3 Hz, 1H), 3.86(s, 3H), 3.85(s, 3H), 3.67-3.64(m, 1H), 3.57(m, 1H), 3.00(ddd, *J* = 15.4, 9.4, 5.6 Hz, 1H), 2.67(dt, *J* = 16.2, 4.5 Hz, 1H)

^{13}C NMR (75 MHz, $CDCl_3$):

δ ppm 148.8, 148.6, 147.7, 129.4, 127.4, 124.5, 119.5, 115.5, 111.7, 109.6, 78.8, 58.0, 56.1, 55.9, 42.0, 25.8

1-(1-Nitro-ethyl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline (6e)[11]

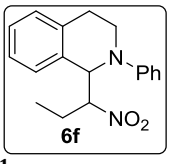


^{1}H NMR (300 MHz, $CDCl_3$):

The major isomer: δ ppm 5.23(d, *J* = 6.7 Hz, 1H), 5.10-5.00(m, 1H), 3.65-3.55(m, 2H), 1.55(d, *J* = 6.8 Hz, 3H); The minor isomer: δ ppm 5.24(d, *J* = 7.0 Hz, 1H), 4.91-4.86(m, 1H), 3.84(ddd, *J* = 13.6, 8.1, 5.7 Hz, 2H), 1.71(d, *J* = 6.8 Hz, 3H). Other overlapped peaks: δ ppm 7.30-7.21(m), 7.18-7.09(m), 7.02-6.98(m), 6.86-6.79(m), 3.11-3.00(m), 2.95-2.85(m)

^{13}C NMR (75 MHz, $CDCl_3$):
The major isomer: δ ppm 148.8, 135.5, 131.9, 129.4, 129.2, 128.3, 128.1, 126.1, 119.3, 115.3, 85.4, 62.7, 42.6, 26.3, 16.3; The minor isomer: δ ppm 149.1, 134.7, 133.8, 129.2, 129.0, 128.6, 127.2, 126.5, 118.7, 114.4, 88.9, 61.1, 43.5, 26.7, 17.4

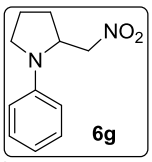
1-(1-Nitro-propyl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline (6f)[18]



6f

^{1}H NMR (300 MHz, $CDCl_3$):
The major isomer: δ ppm 5.18(d, *J* = 9.6 Hz, 1H), 4.95-4.87(m, 1H), 3.93-3.84(m, 1H); The minor isomer: δ ppm 5.29(d, *J* = 9.3 Hz, 1H), 4.76-4.68(m, 1H); Other overlapped peaks: δ ppm 7.34-7.15(m), 7.04-6.97(m), 6.88-6.80(m), 3.74-3.50(m), 3.16-2.85(m), 2.30-2.09(m), 1.90-1.82(m), 1.00-0.94(m)
^{13}C NMR (75 MHz, $CDCl_3$):
The major isomer: δ ppm 149.0, 135.4, 132.4, 129.3, 129.1, 128.6, 128.1, 125.8, 119.2, 115.7, 92.9, 62.1, 42.1; The minor isomer: δ ppm 148.9, 134.6, 133.8, 129.2, 128.6, 128.1, 127.1, 126.5, 118.4, 114.0, 96.0, 60.6, 43.4, 26.7, 24.9, 10.6; Other overlapped peaks: δ ppm 129.5, 129.5, 129.1, 128.5, 128.5, 128.1, 128.1, 127.1, 126.5, 125.8, 26.7, 25.6, 24.9, 24.5, 10.6

2-Nitromethyl-1-phenyl-pyrrolidine (6g)[9h]



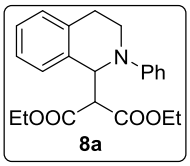
6g

^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 7.30-7.22(m, 2H), 6.81-6.76(m, 1H), 6.72-6.69(m, 2H), 4.64(dd, *J* = 11.3, 3.0 Hz, 1H), 4.45-4.37(m, 1H), 4.19(dd, *J* = 11.4, 9.8 Hz, 1H), 3.54-3.47(m, 1H), 3.26-3.17(m, 1H), 2.20-2.08(m, 4H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 145.7, 129.6, 117.2, 111.9, 75.8, 57.5, 48.2, 29.4, 22.9

General procedure for the preparation of β-diester amine derivatives

In a 5 mL snap vial equipped with magnetic stirring bar the tetrahydroisoquinoline derivative (1 eq) and eosin Y (0.02 eq) were dissolved in dialkyl malonates (0.25 mmol/mL) and the resulting mixture was irradiated through the vial's plane bottom side using green LEDs. After the reaction was completed (monitored by TLC), the reaction mixture was filtered and distilled off excess dialkyl malonates using a Kugelrohr apparatus yielding the analytically pure reaction products.

2-(2-Phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-malonic acid diethyl ester (8a)[11]



8a

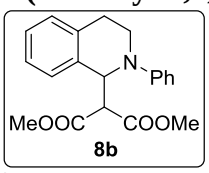
^{1}H NMR (300 MHz, $CDCl_3$):

δ ppm 7.35-7.08(m, 6H), 7.02(d, *J* = 8.0 Hz, 2H), 6.78(t, *J* = 7.3 Hz, 1H), 5.78(d, *J* = 9.2 Hz, 1H), 4.23- 3.98(m, 4H), 3.95(d, *J* = 9.2 Hz, 1H), 3.81-3.61(m, 2H), 3.14-3.04(m, 1H), 2.87(dt, *J* = 16.4, 5.2 Hz, 1H), 1.20(t, *J* = 7.1 Hz, 3H), 1.12(t, *J* = 7.1 Hz, 3H)

^{13}C NMR (75 MHz, $CDCl_3$):

δ ppm 167.9, 167.1, 148.8, 135.9, 134.8, 129.0, 128.8, 127.5, 127.1, 126.0, 118.4, 115.0, 61.5, 59.5, 57.8, 42.2, 26.1, 13.9, 13.8

2-(2-Phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-malonic acid dimethyl ester (8b)[12b]



8b

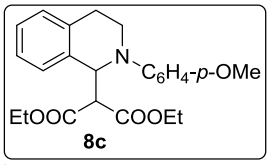
^{1}H NMR (300 MHz, $CDCl_3$):

δ ppm 7.30-7.10(m, 6 H), 7.03(d, *J* = 8.1 Hz, 2H), 6.80(t, *J* = 7.3 Hz, 1H), 5.76(d, *J* = 9.4 Hz, 1H), 4.00(d, *J* = 9.4 Hz, 1H), 3.78-3.66(m, 5H), 3.58(s, 3H), 3.15-3.03(m, 1H), 2.85(dt, *J* = 16.5, 5.2 Hz, 1H)

^{13}C NMR (75 MHz, $CDCl_3$):

δ ppm 168.2, 167.4, 148.7, 135.6, 134.7, 129.1, 128.9, 127.6, 126.9, 126.0, 118.6, 115.1, 59.0, 58.1, 52.5, 42.1, 26.0

2-[2-(4-Methoxy-phenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl]-malonic acid diethyl ester (8c)[11]



8c

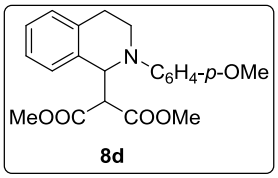
^{1}H NMR (300 MHz, $CDCl_3$):

δ ppm 7.28-7.22(m, 1H), 7.19-7.09(m, 3H), 6.92(d, *J* = 9.1 Hz, 2H), 6.78(d, *J* = 9.1 Hz, 2H), 5.52(d, *J* = 9.2 Hz, 2H), 4.15-4.01(m, 4H), 3.91(d, *J* = 9.2 Hz, 2H), 3.72(s, 3H), 3.69-3.63(m, 1H), 3.59- 3.53(m, 1H), 3.06-2.95(m, 1H), 2.76(dt, *J* = 16.6, 4.3 Hz, 1H), 1.17-1.10(m, 6H)

^{13}C NMR (75 MHz, $CDCl_3$):

δ ppm 167.9, 167.1, 153.0, 143.4, 135.5, 134.7, 129.0, 127.2, 127.1, 125.8, 117.9, 114.3, 61.3, 61.3, 59.4, 58.8, 55.4, 42.9, 25.5, 13.9, 13.8

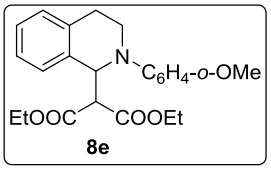
2-[2-(4-Methoxy-phenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl]-malonic acid dimethyl ester (8d)[11]



8d

^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 7.22-7.15(m, 2H), 7.13-7.08(m, 2H), 6.92(d, *J* = 9.1 Hz, 2H), 6.78(d, *J* = 9.1 Hz, 2H), 5.50(d, *J* = 9.4 Hz, 2H), 3.97(d, *J* = 9.4 Hz, 2H), 3.72(s, 3H), 3.69-3.63(m, 4H), 3.61(s, 3H), 3.58-3.53(m, 1H), 3.01(ddd, *J* = 16.6, 10.2, 6.3 Hz, 1H), 2.74(dt, *J* = 16.7, 4.4 Hz, 1H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 168.2, 167.4, 153.2, 143.3, 135.3, 134.7, 129.1, 127.4, 127.0, 125.9, 118.2, 114.3, 59.1, 55.5, 52.4, 52.4, 43.0, 25.5

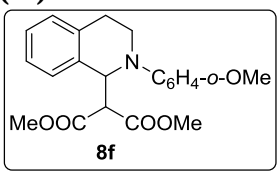
2-[2-(2-Methoxy-phenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl]-malonic acid diethyl ester (8e)[11]



8e

^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 7.29-7.08(m, 4H), 7.01-6.95(m, 1H), 6.83-6.77(m, 3H), 5.47(d, *J* = 8.5 Hz, 1H), 4.10-3.97(m, 4H), 3.95(d, *J* = 8.5 Hz, 1H), 3.81(s, 3H), 3.52-3.34(m, 2H), 2.94-2.83(m, 1H), 2.71-2.64(m, 1H), 1.13(t, *J* = 5.7 Hz, 3H), 1.08(t, *J* = 5.7 Hz, 3H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 168.0, 167.3, 152.6, 141.0, 139.4, 135.6, 135.0, 129.0, 127.0, 125.6, 123.2, 121.7, 120.6, 111.4, 61.2, 61.1, 58.9, 55.3, 42.7, 26.2, 13.7

2-[2-(2-Methoxy-phenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl]-malonic acid dimethyl ester (8f)[11]



8f

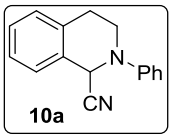
^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 7.24-7.09(m, 4H), 7.01-6.94(m, 1H), 6.85-6.77(m, 3H), 5.43(d, *J* = 8.9 Hz, 1H), 4.01(d, *J* = 8.9 Hz, 1H), 3.82(s, 3H), 3.66-3.51(m, 2H), 3.58(s, 3H), 3.56(s, 3H), 2.93-2.82(m, 1H), 2.72-2.64(m, 1H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 168.3, 167.5, 152.8, 139.3, 135.5, 135.0, 129.2, 127.1, 126.7, 125.7, 123.3, 121.9, 120.6, 111.5, 59.2, 58.7, 55.3, 52.3, 52.2, 42.8, 26.1

General procedure for the preparation of α-amino nitriles

In a 5 mL snap vial equipped with magnetic stirring bar the tetrahydroisoquinoline derivative (1 eq) and eosin Y (0.02 eq) were dissolved in DMF (0.25 mmol/mL). Then malononitrile (1.5 eq) was added and the resulting mixture was irradiated through the vial's plane bottom side using green LEDs. After the reaction was completed (monitored by TLC), the mixture was transferred to the separating funnel, diluted with diethyl ether and washed with water. The aqueous phase was extracted three times with diethyl ether. The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuum. Purification of

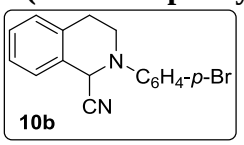
the crude product was achieved by flash column chromatography using hexane/ethyl acetate as eluent.

2-Phenyl-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile (10a)[9v]



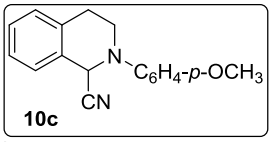
^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 7.42-7.24(m, 6H), 7.12-7.02(m, 3H), 5.54(s, 1H), 3.83-3.76(m, 1H), 3.55-3.46(m, 1H), 3.23-3.12(m, 1H), 2.96(td, *J* = 16.3, 3.6 Hz, 1H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 148.4, 134.6, 129.6, 129.4, 128.8, 127.1, 126.9, 121.9, 117.6, 117.6, 53.2, 44.2, 28.6

2-(4-Bromo-phenyl)-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile (10b)[12a]



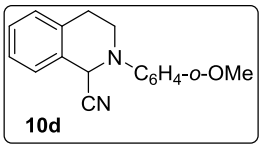
^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 7.46(d, *J* = 9.0 Hz, 2H), 7.34-7.23(m, 4H), 6.96(d, *J* = 9.0 Hz, 2H), 5.46(s, 1H), 3.69-3.75(m, 1H), 3.51-3.42(m, 1H), 3.21-3.10(m, 1H), 3.02-2.94(m, 1H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 147.4, 134.4, 132.54, 129.3, 129.2, 128.9, 127.0, 127.0, 119.1, 117.4, 114.4, 52.9, 44.2, 28.4

2-(4-Methoxy-phenyl)-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile (10c)[9v]



^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 7.34-7.22(m, 4H), 7.10(d, *J* = 9.0 Hz, 2H), 6.93(d, *J* = 9.0 Hz, 2H), 5.37(s, 1H), 3.80(s, 3H), 3.62-3.56(m, 1H), 3.48-3.39(m, 1H), 3.23-3.11(m, 1H), 2.97-2.90(m, 1H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 155.7, 142.6, 134.3, 129.7, 129.5, 128.6, 127.1, 126.7, 121.0, 117.6, 114.8, 55.6, 55.5, 44.9, 28.7

2-(2-Methoxy-phenyl)-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile (10d)



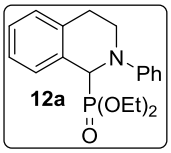
^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 7.34-7.13(m, 6H), 7.07-7.01(m, 1H), 6.96-6.93(m, 1H), 5.76(s, 1H), 3.87(s, 3H), 3.55-3.51(m, 2H), 3.31-3.20(m, 1H), 2.97-2.90(m, 1H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 155.7, 137.6, 133.9, 129.8, 129.4, 128.4, 127.1, 126.4, 125.0, 121.3, 120.8, 117.6, 111.3, 55.5, 53.0, 44.6, 28.6
mp: 162-164°C

IR: ν_{max} /cm^{-1} 2979, 2929, 2844, 2225 (C≡N), 1657, 1588, 1494, 1388, 1289, 1246, 1161, 1021, 966, 829, 806, 741
MS (EI, 70 eV): m/z = 120.1 (39.25), 233.1 (95.19), 264.2 (100.00) [M$^+$]

General procedure for the preparation of *α*-amino phosphonates

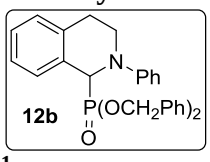
In a 5 mL snap vial equipped with magnetic stirring bar the tetrahydroisoquinoline derivative (1 eq) and eosin Y (0.02 eq) were dissolved in DMF (0.238 mmol/mL). Then dialkyl phosphonate (4 eq) was added and the resulting mixture was irradiated through the vial's plane bottom side using green LEDs. After the reaction was completed (monitored by TLC), the mixture was transferred to the separating funnel, diluted with ethyl acetate and washed with water. The aqueous phase was extracted three times with ethyl acetate. The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuum. Purification of the crude product was achieved by silica gel column chromatography using hexane/ethyl acetate as eluent.

1-Phenyl-2-diethylphosphonate-1,2,3,4-tetrahydroisoquinoline (12a)[9s]



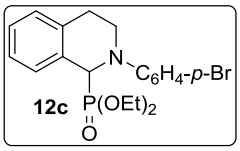
^{1}H NMR (300MHz, $CDCl_3$):
δ ppm 7.39-7.36(m, 1H), 7.29-7.13(m, 5H), 6.99(d, *J* = 8.3 Hz, 2H), 6.80(t, *J* = 7.3 Hz, 1H), 5.20(d, *J* = 20.0 Hz, 1H), 4.14-3.86(m, 5H), 3.65-3.61(m, 1H), 3.07-3.02(m, 2H), 1.25(t, *J* = 7.1 Hz, 3H), 1.15(t, *J* = 7.1 Hz, 3H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 149.4(d, *J* = 5.7 Hz), 136.4(d, *J* = 5.4 Hz), 130.7, 129.1, 128.7(d, *J* = 2.4 Hz), 128.1(d, *J* = 4.5 Hz), 127.4(d, *J* = 3.5 Hz), 125.9(d, *J* = 2.7 Hz), 118.4, 114.6, 63.3(d, *J* = 7.3 Hz), 62.3(d, *J* = 7.6 Hz), 58.8(d, *J* = 159.2 Hz), 43.5, 26.7, 16.4(d, *J* = 6.3 Hz), 16.4(d, *J* = 6.4 Hz)

1-Phenyl-2-dibenzylphosphonate-1,2,3,4-tetrahydroisoquinoline (12b)[9s]



^{1}H NMR (300MHz, $CDCl_3$):
δ ppm 7.38-7.11(m, 16H), 6.98(d, *J* = 8.3 Hz, 2H), 6.81(t, *J* = 7.2 Hz, 1H), 5.30(d, *J* = 19.6 Hz, 1H), 5.05-4.69(m, 4H), 4.07- 3.99(m, 1H), 3.67-3.59(m, 1H), 3.08- 2.99(m, 2H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 149.2(d, *J* = 5.4 Hz), 136.5(d, *J* = 5.5 Hz), 136.3(d, *J* = 6.1 Hz), 136.2(d, *J* = 6 Hz), 130.4, 129.2, 128.8(d, *J* = 2.4 Hz), 128.4(d, *J* = 6.4 Hz), 128.2, 128.2, 128.1, 128.0(d, *J* = 3.7 Hz), 127.5(d, *J* = 3.6 Hz), 126.0(d, *J* = 2.9 Hz), 118.6, 114.8, 68.6(d, *J* = 7.3 Hz), 67.7(d, *J* = 7.7 Hz), 59.0(d, *J* = 158.1 Hz), 43.5, 26.8

1-*(*4-Bromophenyl)-2-diethylphosphonate-1,2,3,4-tetrahydroisoquinoline (12c)



^{1}H NMR (300MHz, $CDCl_3$):

δ ppm 7.39-7.29(m, 3H), 7.22-7.14(m, 3H), 6.84(d, *J* = 9.1 Hz, 2H), 6.83-6.79(m, 2H), 5.10(d, *J* = 19.2 Hz, 1H), 4.20-3.73(m, 5H), 3.57-3.49(m, 1H), 3.20- 3.10(m, 2H), 1.23(t, *J* = 7.0 Hz, 3H), 1.14(t, *J* = 7.1 Hz, 3H)

^{13}C NMR (75 MHz, $CDCl_3$):

δ ppm 148.3(d, *J* = 5.0 Hz), 136.3(d, *J* = 5.6 Hz), 131.8, 130.3, 128.6(d, *J* =2.7 Hz), 128.1(d, *J* = 4.6 Hz), 127.6(d, *J* = 3.4 Hz), 126.0(d, *J* = 2.7 Hz), 116.1, 110.3, 63.3(d, *J* = 7.3 Hz), 62.4(d, *J* = 7.7 Hz), 58.7(d, *J* = 159.6 Hz), 43.6, 26.9, 16.4(d, *J* = 5.5 Hz), 16.4(d, *J* = 5.5 Hz)

^{31}P NMR (121 MHz, $CDCl_3$):

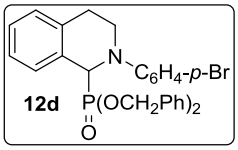
δ ppm 22.41(s)

IR: ν_{max} /cm^{-1} 3065, 3028, 2929, 2906, 1594, 1588, 1504, 1493, 1389, 1245, 1048, 1022, 964

HRMS:

Calculated for $C_{19}H_{23}BrNO_3P$ ($M^{+\cdot}$): 423.0599; Found: 423.0604

1-(4-Bromophenyl)-2-dibenzylphosphonate-1,2,3,4-tetrahydroisoquinoline (12d)



^{1}H NMR (300MHz, $CDCl_3$):

δ ppm 7.32-7.14(m, 14H), 7.11-7.08(m, 2H), 6.81(d, *J* = 9.1 Hz, 2H), 5.19(d, *J* = 18.7 Hz, 1H), 5.02-4.70(m, 4H), 3.98-3.89(m, 1H), 3.55-3.47(m, 1H), 3.12-2.96(m, 2H)

^{13}C NMR (75 MHz, $CDCl_3$):

δ ppm 148.1(d, *J* = 4.6 Hz), 136.3(d, *J* = 5.3 Hz), 136.1(d, *J* = 3.0 Hz), 136.0(d, *J* = 3.1 Hz), 131.8, 130.1, 128.7(d, *J* = 2.7 Hz), 128.6, 128.5, 128.4, 128.4, 128.3, 128.2(d, *J* = 5.0 Hz), 128.0, 127.9, 127.8(d, *J* = 3.5 Hz), 126.1(d, *J* = 2.9 Hz), 116.2, 110.4, 68.6(d, *J* = 7.4 Hz), 67.8(d, *J* = 7.9 Hz), 58.9(d, *J* = 158 Hz), 43.6, 27.0

^{31}P NMR (121 MHz, $CDCl_3$):

δ ppm 23.5(s)

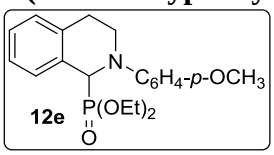
mp: 172-173°C

IR: ν_{max} /cm^{-1} 3031, 2946, 2895, 1508, 1495, 1259, 988, 994, 917, 764, 747

HRMS:

Calculated for $C_{29}H_{27}BrNO_3P$ ($M^{+\cdot}$): 547.0912; Found: 547.0919

1-(4-Methoxyphenyl)-2-diethylphosphonate-1,2,3,4-tetrahydroisoquinoline (12e)[9s]

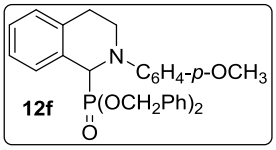


^{1}H NMR (300MHz, $CDCl_3$):

δ ppm 7.40-7.30(m, 1H), 7.18-7.10(m, 3H), 6.94-6.89(m, 2H), 6.81-6.78(m, 2H), 5.02(d, 1H, *J* = 21.5 Hz), 4.19-3.87(m, 5H), 3.73(s, 3H), 3.57-3.49(m, 1H), 2.94- 2.89(m, 2H), 1.25(t, *J* = 7.1 Hz, 3H), 1.15(t, *J* = 7.1 Hz, 3H)

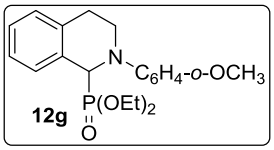
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 153.1, 144.1(d, *J* = 8.2 Hz), 136.4(d, *J* = 5.8 Hz), 130.5, 128.9(d, *J* = 2.4 Hz), 128.1(d, *J* = 4.4 Hz), 127.2(d, *J* = 3.5 Hz), 125.8(d, *J* = 2.9 Hz), 117.5, 114.5, 63.3(d, *J* = 7.3 Hz), 62.2(d, *J* = 7.6 Hz), 59.4(d, *J* = 158.6 Hz), 55.6, 44.6, 26.1, 16.5(d, *J* = 5.6 Hz), 16.4(d, *J* = 5.7 Hz)

1-(4-Methoxyphenyl)-2-dibenzylphosphonate-1,2,3,4-tetrahydroisoquinoline (12f)[9s]



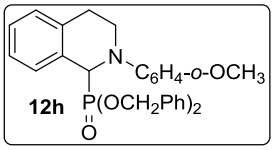
^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm 7.39-7.13(m, 14H), 6.93(d, *J* = 9.1 Hz, 2H), 6.81(d, *J* = 9.1 Hz, 2H), 5.16(d, *J* = 22.1 Hz, 1H), 5.08-4.82(m, 4H), 4.10-4.02(m, 1H), 3.75(s, 3H), 3.59-3.51(m, 1H), 3.02-2.88(m, 2H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 153.2, 144.0(d, *J* = 8.1 Hz), 136.5(d, *J* = 5.8 Hz), 136.3(d, *J* = 6.0 Hz), 130.2, 129.0(d, *J* = 2.7 Hz), 128.4(d, *J* = 5.8 Hz), 128.3, 128.2, 128.1, 128.0, 127.9, 127.4(d, *J* = 3.0 Hz), 125.9(d, *J* = 2.9 Hz), 117.7, 114.5, 68.7(d, *J* = 7.3 Hz), 67.7(d, *J* = 7.9 Hz), 59.7(d, *J* = 157.2 Hz), 55.6, 44.7, 26.2

1-*(*2-Methoxyphenyl)-2-diethylphosphonate-1,2,3,4-tetrahydroisoquinoline (12g)[9s]



^{1}H NMR (300MHz, $CDCl_3$):
δ ppm 7.46-7.43(m, 1H), 7.20-7-16(m, 2H), 7.12-7.09(m, 1H), 6.99-6.93(m, 1H), 6.91-6.81(m, 3H), 5.16(d, *J* = 21.8 Hz, 1H), 4.04- 3.80(m, 5H), 3.81(s, 3H), 3.61-3.54(m, 1H), 2.97-2.84(m, 1H), 2.75-2.69(m, 1H), 1.18(t, *J* =7.1 Hz, 3H), 1.07 (t, *J* = 7.1 Hz, 3H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 152.5, 140.1(d, *J* = 7.8 Hz), 135.8(d, *J* = 6.0 Hz), 130.7, 129.2(d, *J* = 2.5 Hz), 128.1(d, *J* = 4.0 Hz), 127.0(d, *J* = 3.6 Hz), 125.5(d, *J* = 3.1 Hz), 123.0, 121.7, 120.8, 111.6, 63.0(d, *J* = 7.3 Hz), 61.9(d, *J* = 7.3 Hz), 58.7(d, *J* = 146.9 Hz), 55.4, 44.3, 26.5, 16.3(d, *J* = 6.0 Hz)

1-(2-Methoxyphenyl)-2-dibenzylphosphonate-1,2,3,4-tetrahydroisoquinoline (12h)[9s]



^{1}H NMR (300MHz, $CDCl_3$):
δ ppm 7.47(d, *J* = 7.4 Hz, 1H), 7.37-7.09(m, 12H), 7.03-6.97(m, 1H), 6.92- 6.79(m, 3H), 5.29(d, *J* = 22.5 Hz, 1H), 5.06-4.90(m, 3H), 4.85-4.78(m, 1H), 4.16-4.10(m, 1H), 3.77(s, 3H), 3.67-3.60(m, 1H), 2.95-2.80(m, 1H), 2.74- 2.69(m, 1H)
^{13}C NMR (75 MHz, $CDCl_3$):
δ ppm 152.6, 141.3, 139.9(d, *J* = 8.5 Hz), 136.9(d, *J* = 6.8 Hz), 136.5(d, *J* = 6.1 Hz), 136.0(d, *J* = 6.3 Hz), 130.4, 129.4(d, *J* = 2.5 Hz), 128.6, 128.4, 128.3, 128.1, 128.0, 127.9, 127.6, 127.4, 127.2(d, *J* = 3.7 Hz), 125.7(d, *J* = 3.2 Hz), 123.3, 121.8, 120.9, 111.6, 68.5(d, *J* = 7.2 Hz), 67.4(d, *J* = 7.5 Hz), 59.3(d, *J* = 149.6 Hz), 55.3, 44.6, 26.3

Starch-Iodine test for the detection of H_2O_2

After the reaction was completed (monitored by TLC), aqueous potassium iodide was added. The aqueous layer turned to light brown-blue color and the color was enhanced by addition of starch. To the same aqueous layer, aqueous sodium thiosulfate was added and the solution immediately turned colorless.

The chemical equations involved in this reaction:

$$H_2O_2 + 2KI_{(aq)} \longrightarrow I_{2(aq)} + 2K^+_{(aq)} \text{ (light brown color solution)}$$

$$I_{2(aq)} + 2S_2O_3^{2-}{}_{(aq)} \longrightarrow 2I^-_{(aq)} + S_4O_6^{2-}{}_{(aq)} \text{ (colorless solution)}$$

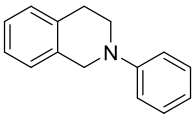
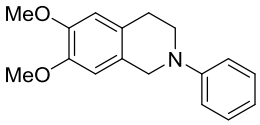
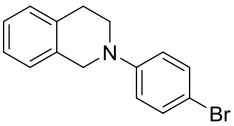
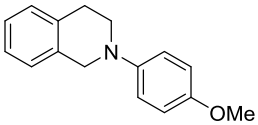
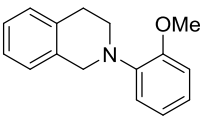
Δ*G* values for electron transfer calculated from Rehm-Weller equation

Singlet excited state energy of eosin Y[19]

E_{00} (^{1}S) = 2.31 V

Oxidation and reduction potentials of eosin Y[19, 2f]

$$\text{Eosin Y}^{\bullet+} \xrightarrow{+0.80\ \text{V}} \text{Eosin Y} \xrightarrow{-1.06\ \text{V}} \text{Eosin Y}^{\bullet-}$$

Tetrahydroisoquinoline	Oxidation potential / V	Δ*G* / kcal.mol^{-1}
	0.82	-11.3
	0.82	-11.3
	0.88	-7.6
	0.62	-15.9
	0.81	-11.5

Eosin Y potentials are in reference to SCE in acetonitrile. All oxidation potentials of tetrahydroisoquinoline derivatives are reported in reference to the SCE in acetonitrile (the potentials were measured in reference to ferrocene/ferrocenium and then converted in to SCE according to Pavlishchuk, V. V.; Addison, A. W. *Inorganica. Chimica. Acta* **2000**, *298*, 97-102.)

For rough estimation of excited state redox potentials we use the following equation[20]

$E^0 (D^{\cdot+}/D^*) = E^0 (D^{\cdot+}/D) - E_{00}$

$E^0 (A^*/A^{\cdot-}) = E^0 (A/A^{\cdot-}) + E_{00}$

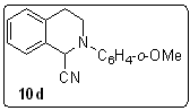
Gibbs free energy of the electron transfer from tetrahydroisoquinoline to the excited eosin Y in acetonitrile can be calculated using Rehm-Weller equation[21]

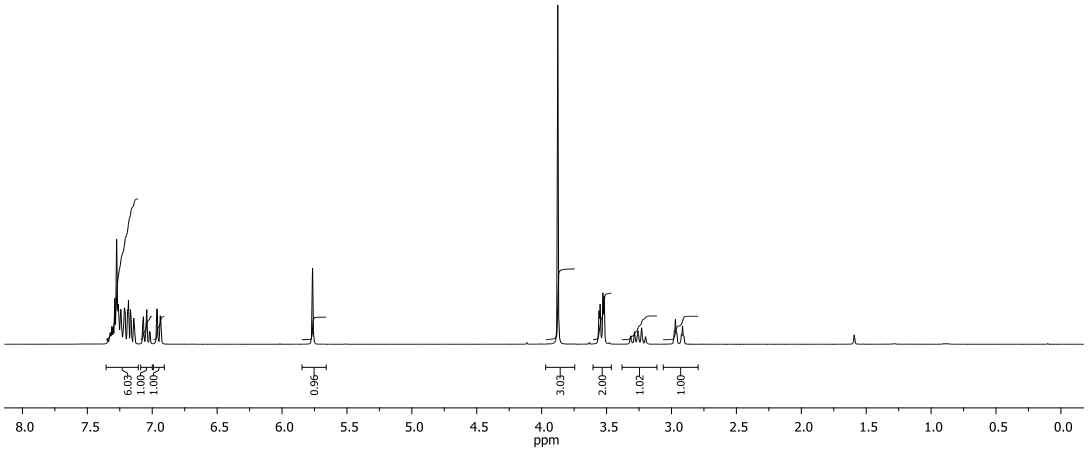
ΔG (kcal/mol) = $23.06(E_{ox} - E_{red} - e_0^2/a\varepsilon - E_{00})$

Where E_{ox} and E_{red} are the oxidation potential of tetrahydroisoquinoline and reduction potential of eosin Y respectively, $e^2/\varepsilon a$ is Coulombic term (0.06 kcal mol^{-1}; lit.[21]).

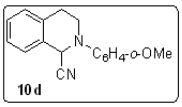
^{1}H and ^{13}C NMR spectra of selected compounds

^{1}H NMR (300MHz, $CDCl_3$)

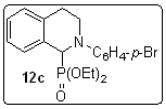


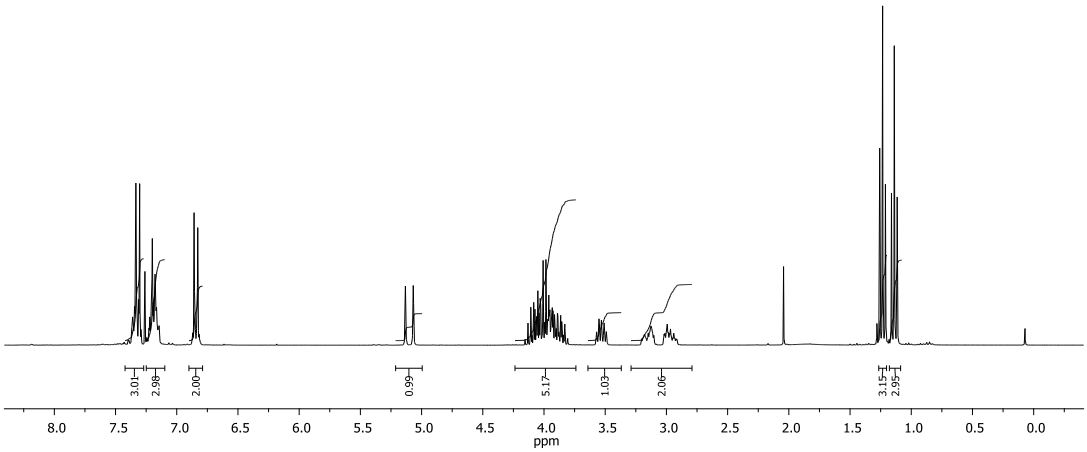


^{13}C NMR (75 MHz, $CDCl_3$)

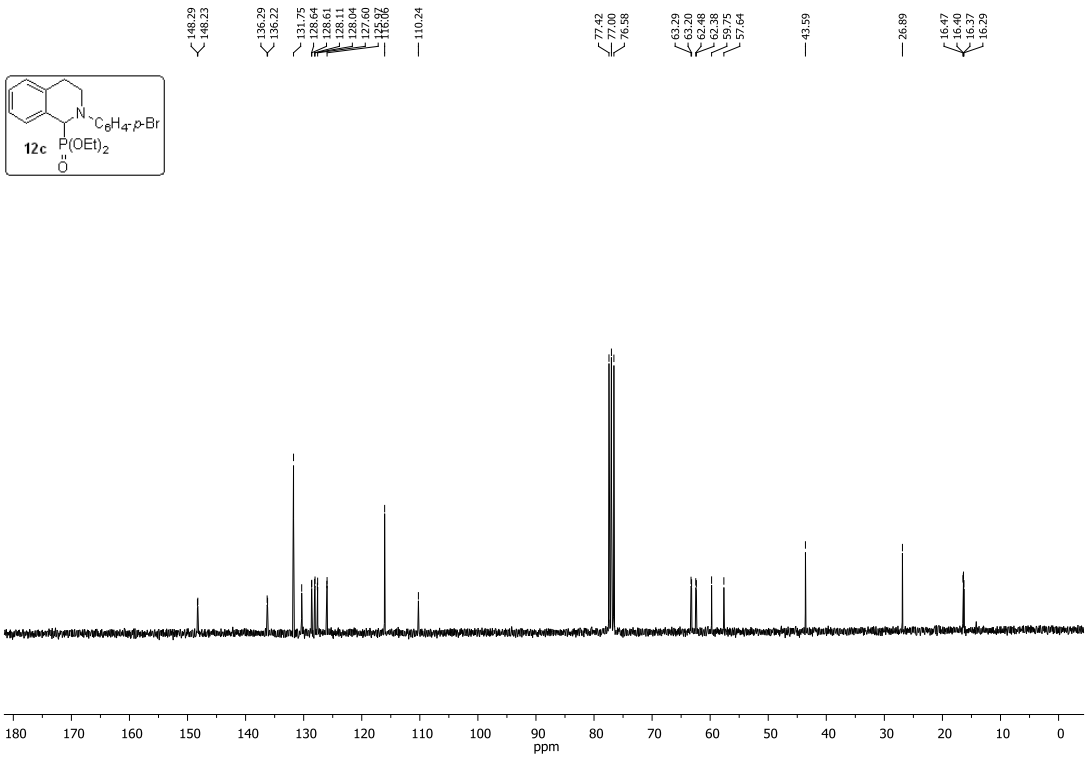


^{1}H NMR (300MHz, $CDCl_3$)

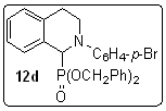


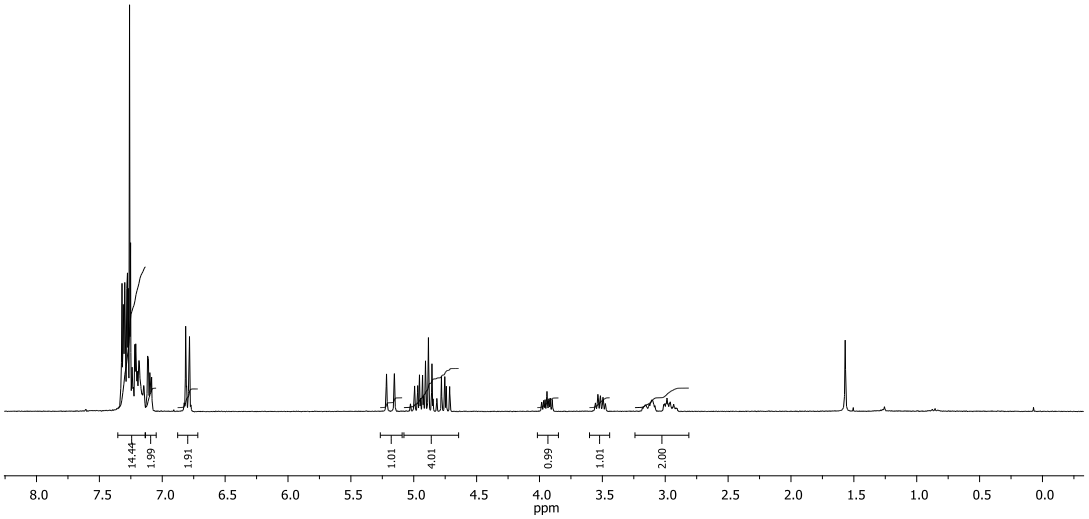


^{13}C NMR (75 MHz, $CDCl_3$)

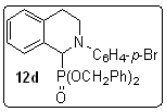


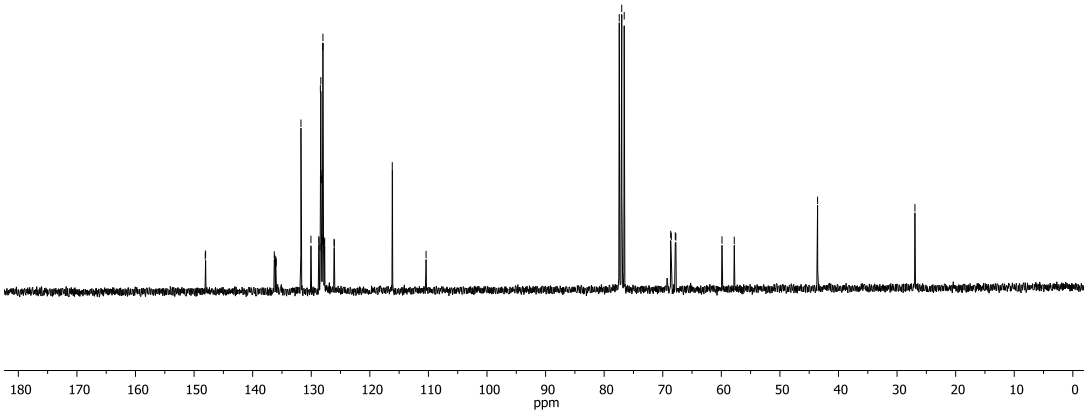
^{1}H NMR (300MHz, $CDCl_3$)





^{13}C NMR (75 MHz, $CDCl_3$)





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7 Summary

This thesis describes the applications of visible light photoredox catalysis with aryl diazonium salts and tetrahydroisoquinolines in organic synthesis.

Chapter 1 summarizes the origins of aryl radical chemistry using aryl diazonium salts and recent developments with their scope and applications in organic chemistry.

In chapter 2, a novel approach for the direct C-H arylation of heteroarenes with aryl diazonium salts in green light using organic dye eosin Y as a photoredox catalyst is described. Furan, thiophene, protected pyrroles, and nitro benzene are suitable substrates in this reaction. In addition, electron-neutral or -withdrawing groups bearing diazonium salts also reacted well in this reaction. Noteworthy, the addition of base to the reaction decreases the yield, which is attributed to the direct reaction of diazonium salt and base. Control experiments confirmed that for an efficient conversion both catalyst and light are necessary. The reaction mechanism is supported by trapping of the key radical intermediates with TEMPO.

In chapter 3, we describe a visible light mediated radical annulation process for the synthesis of benzothiophenes. Eosin Y was found to be a good catalyst for this transformation and terminal and internal alkynes are smoothly converted. A plausible single electron transfer mechanism was proposed for this reaction. Furthermore, the synthetic application of the photocatalytic annulations reaction was demonstrated by preparing the key intermediate in the synthesis of the drug molecule Raloxifene.

In chapter 4, we describe an efficient method for the synthesis of phenanthrenes from diazonium salts in visible light. We screened a set of photocatalysts and found that eosin Y was best for an efficient conversion. Aliphatic, aromatic, and hetero aromatic alkynes are suitable substrates in this reaction. A single electron transfer mechanism has been proposed for the reaction involving a cascade radical addition and cyclization sequence.

In chapter 5, we utilized the Ritter reaction conditions to trap the carbenium ion, which is generated during the photoredox Meerwein arylation reaction leading to the first photoredox catalyzed Meerwein arylation-addition reaction for the intermolecular amino-arylation of alkenes mediated by visible light. Different amides are synthesized in good to excellent yields. To further demonstrate the applicability of the reaction we applied it to the synthesis of 3-aryl-3,4-dihydroisoquinolines. Unfortunately, aliphatic alkenes were not suitable substrates in this multicomponent reaction.

The photochemical properties and applications of eosin Y as photoredox catalyst for organic transformations including oxidation, reduction, C-H functionalization and asymmetric reactions are summarized in the first part of chapter 6.

A metal-free visible light photoredox catalysis for C-C and C-P bond formation using the organic dye eosinY is then reported in the second part of chapter 6. Nitroalkanes, dialkyl malonates, malononitrile, and dialkyl phosphonates were used as pronucleophiles in this metal-free, visible light oxidative coupling reaction. Our experiments have shown that transition metal catalysts and stoichiometric oxidants can be replaced by the redox active organic dye eosin Y and green light yielding comparable coupling yields.

8 Zusammenfassung

Diese Arbeit beschäftigt sich mit der Anwendung von Photoredoxkatalyse mit sichtbarem Licht in organischen Synthesen. Als Substrate wurden hierbei Aryldiazoniumsalze und Tetrahydrochinoline eingesetzt.

Das erste Kapitel fasst die Ursprünge der Nutzung von Aryldiazoniumsalzen als Arylradikalquelle zusammen und diskutiert die neueren Entwicklungen auf diesem Gebiet sowie deren Anwendung in der organischen Chemie.

Im zweiten Kapitel wird ein neues, durch grünes Licht vermitteltes Verfahren zur direkten C–H- Arylierung von Heteroarenen unter Verwendung von Aryldiazoniumsalzen und dem organischen Farbstoff Eosin Y beschrieben. Dabei können Furan, Thiophen, geschützte Pyrrole sowie Nitrobenzol als Substrate in dieser Reaktion eingesetzt werden. Zudem zeigt die Reaktion eine hohe Toleranz gegenüber Aryldiazoniumsalzen mit elektronenziehenden sowie –neutralen Substituenten. Bemerkenswert ist, dass die Zugabe einer Base zu der Reaktionsmischung einen drastischen Rückgang der Ausbeute zur Folge hat, was auf eine direkte Reaktion des Diazoniumsalzes mit der Base zurückzuführen ist. Des Weiteren konnte durch Kontrollexperimente gezeigt werden, dass sowohl Licht als auch Katalysator für eine effizienten Umsatz zum Produkt erforderlich sind. Der postulierte Reaktionsmechanismus wurde durch TEMPO-Abfang der radikalischen Intermediate untermauert.

Kapitel 3 beschreibt eine durch sichtbares Licht vermittelte, radikalische Annelierungsreaktion zur Synthese von Benzothiophenen. Es konnte gezeigt werden, dass sich Eosin Y als Photokatalysator für diese Umsetzung eignet und so terminale und interne Alkine erfolgreich zur Reaktion gebracht werden konnten. Ein plausibler über Ein-Elektronenübertragung ablaufender Mechanismus wurde vorgeschlagen. Zudem konnte die synthetische Relevanz der beschriebenen photokatalytischen Annelierungsreaktion durch die Darstellung des Schlüsselproduktes in der Synthese des Wirkstoffes Raloxifene gezeigt werden.

In Kapitel 4 wird eine effiziente, photokatalytische Methode zur Synthese von Phenanthrenen aus Diazoniumsalzen beschrieben. Nach einem Screening verschiedener Photokatalysatoren erwies sich Eosin Y als am geeignetsten für diese Umsetzung. Aliphatische, aromatische sowie heteroaromatische Alkine können in dieser Reaktion umgesetzt werden. Der postulierte Reaktionsmechanismus läuft über zwei Ein-

Elektronenübertragungen ab und beinhaltet eine Radikalkaskade sowie einen Zyklisierungsschritt.

In Kapitel 5 wurden die Bedingungen der Ritter Reaktion auf unser System übertragen, um so das in der Photo-Meerwein Reaktion entstehende Carbeniumion abzufangen. So konnte die erste photo-redoxkatalysierte additive Meerweinarylierung zur intermolekularen Aminoarylierung von Alkenen entwickelt werden. Unterschiedliche Amide werden in guten bis exzellenten Ausbeuten erhalten. Um die Anwendbarkeit der Reaktion aufzuzeigen, nutzten wir sie für die Synthese von 3-Aryl-3,4-dihydroisochinolinen. Leider konnte diese Reaktion aber nicht auf aliphatische Alkene angewendet werden.

Die photochemischen Eigenschaften von Eosin Y, sowie dessen Nutzung als Photo-redoxkatalysator für organische Transformationen, wie Oxidationen, Reduktionen, C–H-Funktionalisierungen und enantioselektive Reaktionen, sind im ersten Teil von Kapitel 6 zusammengefasst.

Der zweite Teil von Kapitel 6 beschäftigt sich dann mit der metallfreien durch Eosin Y katalysierten C–C- und C–P-Bindungsknüpfung in sichtbarem Licht. Dabei wurden Nitroalkane, Dialkylmalonate, Malonitril sowie Dialkylphosphonate als Pronucleophile in dieser photokatalytischen, oxidativen Kupplung eingesetzt. Unsere Untersuchungen konnten zeigen, dass Übergangsmetallkatalysatoren und stöchiometrische Oxidationsmittel durch den redoxaktiven organischen Farbstoff Eosin Y und Bestrahlung mit grünem Licht ersetzt werden können und unter diesen Bedingungen vergleichbare Ausbeuten erhalten werden.

9 Abbreviations

ACN	Acetonitrile
$CDCl_3$	Deuterated chloroform
DCM	Dichloromethane
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
DMSO-d_6	Deuterated dimethyl sulfoxide
equiv	Equivalent
ee	Enantiomeric excess
ES	Electrospray
ESI	Electrospray ionization
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
EtOH	Ethanol
EY	Eosin Y
eV	Electron volts
GC	Gas chromatography
h	Hour
H^+	Proton
HR-MS	High resolution mass spectrometry
ISC	Inter system crossing
M	Molar concentration
$MeNO_2$	Nitromethane
MeOD	Deuterated methanol, MeOH-d_4
MeOH	Methanol
$MgSO_4$	Magnesium sulfate
MHz	Mega hertz
min	Minute
mL	Milli liter
mm	Milli meter
mmol	Milli mole
mol%	Mole percent
Mp	Melting point
MS	Mass spectrometry
nm	Nanometer
NMR	Nuclear magnetic resonance
Nu	Nucleophile
PC	Photocatalyst
PE	petroleum ether
ppm	Parts per million
SCE	Saturated calomel electrode
SET	Single electron transfer
TEMPO	(2,2,6,6-Tetramethyl-piperidin-1-yl)oxyl
TLC	Thin layer chromatography
TMS	Tetramethylsilane
UV	Ultra violet
V	Volt
W	Watt

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Finally, my deep and sincere thanks go to my fiancee (Durgasri) for her love, patience, support and encouragement during all this time in Germany, you also made my research easier by correcting all manuscripts. Thank you for taking me away all the stress and for brings me an infinite happiness every single day during last years. I pay my due respect and sincere regards to my parents, whose love, blessing and believe are always with me for the accomplishments that I had so far in my life.

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11 Curriculum Vitae

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Personal Information

Date of birth: July 1, 1986
Nationality: Indian
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University Education

Ph.D. in Chemistry, 08/2010–02/2014
Universität Regensburg (Regensburg, Germany)
Advisor: Prof. Dr. Burkhard König
Ph.D. thesis title: The Photoredox Catalyzed Meerwein Arylation

M.Sc. in Chemistry, 08/2008–07/2010
Indian Institute of Technology Madras (Chennai, India)
Advisor: Prof. Dr. S. Sanakararaman
M.Sc. thesis title: Synthesis and Properties of Triphenylene Derivatives.

B.Sc. in Chemistry, 08/2004–07/2007
Silver Jubilee Degree College (Kurnool, India)

Research Experience

Universität Regensburg, 08/2010–02/2014

- Developed a novel method for synthesis of tetrahydroisoquinoline derivatives using eosin Y as a photoredox catalyst in visible light.
- A metal free method for direct arylation of heteroarenes has been developed by photoredox catalysis using green light.
- Photocatalytic arylation of alkenes, alkynes and enones with diazonium salts has been developed.
- Synthesis of benzothiophene derivatives has been achieved using [3+2] annulation method and further utilized this methodology for synthesis of Raloxifene drug intermediate.
- A mild method has been developed for arylation of enol acetates by photoredox catalysis.
- [4+2] Benzannulation of biaryl diazonium salts with alkynes for synthesis of phenanthrene derivatives using eosin Y as photocatalyst.
- Intermolecular arylation of alkenes mediated by visible light has been developed.

Indian Institute of Technology Madras, 08/2008–07/2010

- Synthesized various triphenylene derivatives and studied their photo-physical properties.
- Synthesized as well as calculated the association constant of pyrene octaaldehyde derivative.

Skills

Instrumental techniques

- Strong background and extensive experience with the analytical techniques; NMR, HPLC, IR, LCMS, Elemental analysis and Cyclic voltammetry.
- Hands on experience on various purification techniques: Column chromatography, TLC, and GC.
- Well versed in handling the air/moisture sensitive reagents and Organometallic reactions.
- Fluorescence spectrometer (Perkin Elmer, Cary Eclipse, Edinburgh Instruments), UV spectrophotometer (JASCO, Cary).

Software

- MS Office (Word, Powerpoint, a n d Excel), EndNote, Adobe Illustrator, Adobe Photoshop, Chem draw, Scifinder and Web of Knowledge.

Teaching Experience

- Supervised two undergraduate and two master students during their research projects at the University of Regensburg.

Scholarships and Awards

- Selected for the "Reaxys PhD prize **2012**" (Finalist).
- Selected for the "BASF 123rd international summer course“ held at Ludwigshafen, Germany, **2012**.
- Fellowship of the “GRK 1626, Chemical Photocatalysis (**2010-2013**)”.
- Fellowship of the Council of Scientific and Industrial Research (CSIR) (for Ph.D. in India) – **2010**.
- Have qualified Graduate Aptitude Test in Engineering (GATE) (for Ph.D. in India) – **2010**.
- Awarded the "Merit scholarship" by Indian Institute of Technology Madras – **2008-2010**.
- Stood All India 1st rank in M.Sc. (Chemistry) entrance test conducted by Hyderabad Central University in **2008**.
- Stood All India 1st rank in M.Sc. (Chemistry) entrance test conducted by Pondicherry Central University in **2008**.
- Stood All India 3rd rank in M.Sc. (Chemistry) entrance test conducted by NIT, Warangal in **2008**.
- Gold medalist in B.Sc. (Chemistry) in **2007**.
- BREAD (Basic Research Education and Development) scholarship in 2004 for securing highest marks in 10+2 level in **2004**.
- Zakata Chartible Trust scholarship for scoring highest marks in (10+2) in **2004**.

Research Publications

1. **Durga Prasad Hari** and Burkhard Koenig
   Eosin Y Catalyzed Visible Light Oxidative C-C and C-P Bond Formation
   ***Org. Lett.* 2011, *13*, 3852 – 3855.**
2. **Durga Prasad Hari**, Peter Schroll, and Burkhard Koenig
   Metal free, Visible Light Mediated Direct C-H Arylation of Heteroarenes with Aryl Diazonium Salts
   ***J. Am. Chem. Soc.* 2012, *134*, 2958-2961.**

Highlighted in "*Synfacts*".

3. Peter Schroll, **Durga Prasad Hari**, and Burkhard König
   Photocatalytic Arylation of Alkenes, Alkynes and Enones with Diazonium Salts
   ***Chemistry Open*. 2012, *1*, 130-133.**
4. **Durga Prasad Hari**, Thea Hering, and Burkhard König
   Visible Light Photocatalytic Synthesis of Benzothiophenes
   ***Org. Lett.* 2012, *14*, 5334-5337.**
   Highlighted in "*Synfacts*".
5. Thea Hering, **Durga Prasad Hari**, and Burkhard König
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2. **Durga Prasad Hari**, Peter Schroll, and Burkhard König, "Metal free, Visible Light Photocatalysis for C-H Arylation of Heteroarenes", BASF 123rd international summer course" held at Ludwigshafen, Germany, **2012.**
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2. **Durga Prasad Hari**, Thea Hering, Peter Schroll and Burkhard König, "Organic Synthesis Powered by Visible Light Photoredox Catalysis ", INDIGO conference, Regensburg, Germany, **2013**.

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1. INDIGO conference held at University of Regensburg, Germany, **2010**
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