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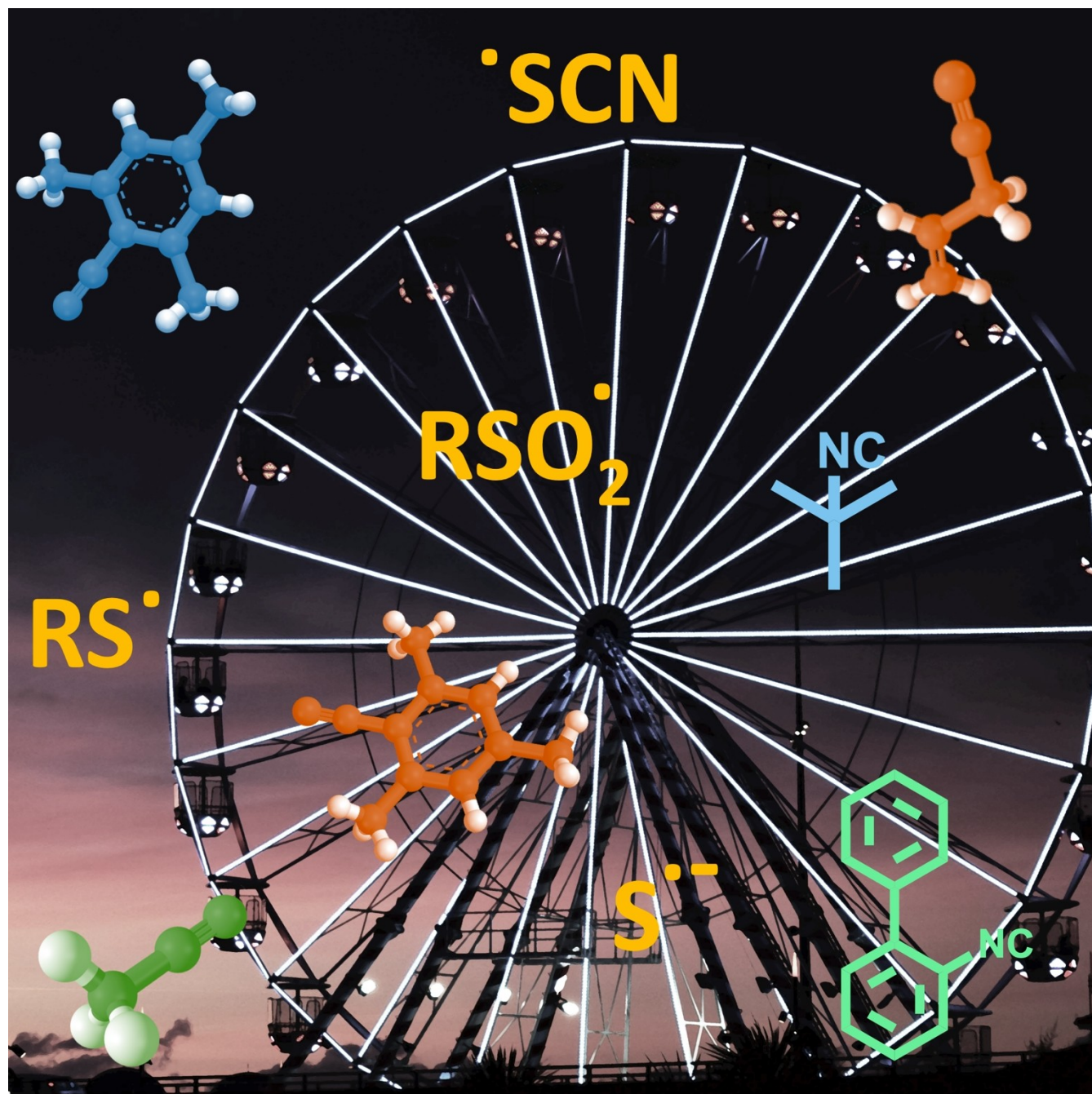


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Sulfur-Centered Radicals in Visible Light Isocyanide Photochemistry

Camilla Russo,^[a] Francesca Brunelli,^[b] Gian Cesare Tron,^{*,[b]} and Mariateresa Giustiniano^{*,[a]}



Sulfur-centered radicals have a key role in a plethora of synthetic organic transformations, whose scope has been further expanded thanks to the possibility to generate such species under visible light photocatalytic conditions. This review focuses on those transformations involving isocyanides and

sulfur-centered radicals with the aim to highlight the chemical space accessible, both in terms of complexity and diversity, and the mechanistic rational underpinning the current and future development of such chemical methodologies.

1. Introduction

The chemistry of sulfur-centered radicals represents a source of fundamental tools both for the study of oxidative stress and repair mechanisms in biological processes and in synthetic applications to efficiently forge new chemical bonds as in the thiol-ene and -yne reactions and in radical chain polymerizations.^[1–3] In this context, the reactivity of thiyl radicals has provided versatile processes spanning from the addition to unsaturated systems – alkenes, alkynes, isocyanides, and thiocarbonyl groups – to highly selective hydrogen atom abstraction.^[4–10] Isocyanides are considered a class of very special organic compounds, thanks to their chameleonic electronic properties and multiple reactivity modes including nucleophile/carbene reactivities, extensively exploited in multi-component reactions, and a somophilic behavior, which has been undergoing a renewed interest only recently, thanks to the impressive progresses in the development of light driven synthetic methodologies.^[11–15] The latter have also boosted the application of sulfur-centered radicals in the search for either sustainable synthetic routes to new chemical entities or unprecedented disconnections to known compounds. The main advantages include the generation of such open-shell species under mild reaction conditions, which enable improved chemo-, regio-, and in some cases stereo-selectivities, important issues also in the late-stage modification^[16,17] of complex structures such as drugs and natural compounds. The current review seeks to highlight the potentialities and the limitations of using sulfur-centered radicals in photochemical reactions involving isocyanides via a critical analysis of the current literature. Four main sections will treat the generation and the reactivity of 1) thiyl radicals from thiols and disulfides; 2) sulfonyl radicals from sulfones, sulfinate salts, and sulfonyl chlorides; 3) C-centered

radicals from C=S bond containing radical precursors, and 4) sulfonium salts as precursors of a trifluoromethyl radical (via Umemoto's reagent), aryl radicals (via thianthrenium salts), and alkyl radicals (via diarylsulfonium salts). A miscellaneous section will finally highlight the use of inorganic salts such as thiocyanate and will mention those photochemical reactions involving sulfur-centered radicals where the isocyanide has been used in tandem transformations. The recent developments herein outlined will help to disclose the current gaps in the field thus stimulating new trends and delineating future directions.

2. Thiyl Radicals

Thiyl radicals have a high relative stability, which can be affected by substituents by over 30 kcal mol⁻¹, as shown by M. L. Coote *et al.*,^[3] and represents a compromise between electron delocalization and σ -withdrawal. More in details, lone-pair donation (and π -acceptance by the thiyl radical) has a stabilizing effect, while an opposite influence is given by σ -withdrawing substituents such as carbonyl and pyridines. On the other hand, depending on the substituents' stabilization, in the absence of a suitable radical trap, they can be prone to undergo a rapid self-annihilation via radical dimerization, thermodynamically favored by the heat of formation of the new bond (73 kcal mol⁻¹ for Me–S–S–Me). Notwithstanding these potential limitations, the current section will deal with the use of isocyanides as efficient thiyl radical acceptors to build up both linear and heterocyclic compounds under visible light irradiation.

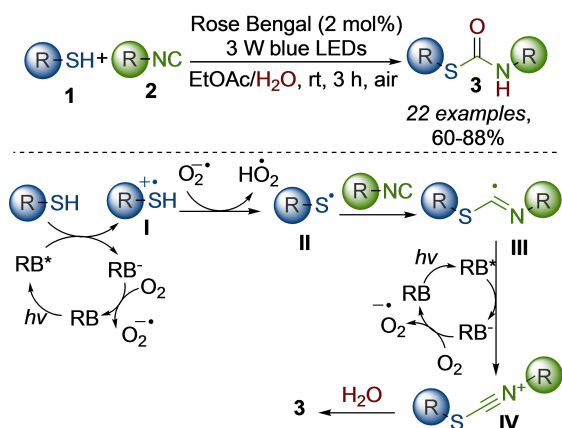
2.1. Thiols as thiyl radical precursors

Historically, the first report about the addition of thiyl radicals to isocyanides dates back to the 60s, when Saegusa *et al.* observed the formation of thioformimidates and isothiocyanates depending on the alkyl group of the thiol.^[18] When the reaction was performed at low temperatures a copper catalyst was needed, while at 100 °C, thiols reacted quite rapidly even in the absence of any catalyst. Soon after, the same authors disclosed the ability of UV light to accelerate thiyl radical formation and thus promote its addition to an isocyanide.^[19–21] It was not until recently that both aliphatic and aromatic thiols have been exploited for the formation of thiocarbamates under visible light irradiation.^[22a] The method required rose bengal (RB, 2 mol% loading) as an organic photocatalyst and an environmentally benign ethyl acetate/water solvent mixture (Scheme 1). The reaction proceeded under air at room temper-

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Scheme 1. Synthesis of thiocarbamates **3** from thiols **1**, isocyanides **2** and water.

ature, in short times, and the mild conditions enabled optimum yields for both electron-rich and electron-poor aromatic thiols as well as aliphatic ones. The isocyanide scope was mainly explored with aliphatic ones – excepting for 2,6-dimethylisocyanobenzene- proving to be good for primary, secondary, and tertiary substrates with yields ranging from 60 to 88%. From a mechanistic point of view, the reaction proceeded via RB mediated oxidation of the thiol **1** to radical cation **I**, which upon loss of a proton, formed the thiyl radical **II**. The latter added to the isocyanide to form an imidoyl radical intermediate **III**, oxidized by the excited photocatalyst to nitrilium ion **IV**, to eventually undergo hydrolysis to thiocarbamate **3**. After both the single electron transfers (SETs) from the thiol and the imidoyl radical to the excited RB, the ground-state photocatalyst was regenerated by molecular oxygen (Scheme 1). Interestingly, this method stands for a green alternative to traditional approaches requiring the use of carbamoyl chlorides, alkylchlorothioformates, and other toxic phosgene/triphosgene

derived reagents and suffering from limitations such as the need for pre-functionalized starting materials, harsh reaction conditions, poor atom economy, narrow scope, and low yields.^[22b–d]

The conversion of thiophenols and isocyanides to thiocarbamates has also been reported by using either carbazolic^[23] or 1,2,3-triazole-based^[24] conjugated microporous polymer (CMPs), which proved to be effective even on a gram scale. Shortly after, Tran C. C. *et al.* reported how *o*-diisocyanoarenes **4** could afford thylquinoxalines **5** when reacted under metal- and additive- free conditions and irradiated with a xenon lamp ($\lambda > 300$ nm) in deuterated chloroform (CDCl₃) as a solvent, under argon atmosphere, at room temperature (Scheme 2).^[25]

Optimum yields (62–89%, 14 examples) were obtained by adding 2 equivalents of thiol, whose scope was good for both aliphatic and aromatic ones, the latter including electron-rich and electron-poor substituents.

On the other hand, more complex thiols such as (iPr)₃SiSH and those bearing either unprotected alcohols or amino groups led to complex mixtures. Albeit an ionic pathway was not fully excluded, mechanistic studies in the presence of TEMPO as a radical-trapping agent supported the involvement of a thiyl radical **I** generated upon irradiation with near-UV or visible light, which could add to an isocyanide to generate an imidoyl radical intermediate **II**. Interestingly, the latter would intramolecularly intercept the second isocyanide at the *ortho*-position to afford a cyclized imidoyl radical **III** eventually undergoing hydrogen abstraction from the thiol **1** and thus generating a second thiyl radical **I** in a chain mechanism.

A different type of *ortho*-substituted arylisocyanides, namely *o*-alkenyl isocyanides **6**, have been shown as valuable tools to get 2-sulfenylindoles **7** via a radical cascade process (Scheme 3).^[26]

The latter required [Ru(bpy)₃](PF₆)₂ as a photoredox catalyst and *p*-toluidine **1** as electron-transfer mediator, in DMSO under blue LEDs light irradiation. Interestingly, a thiyl radical **III** was



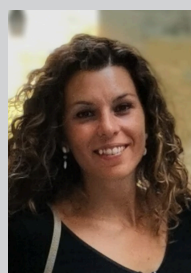
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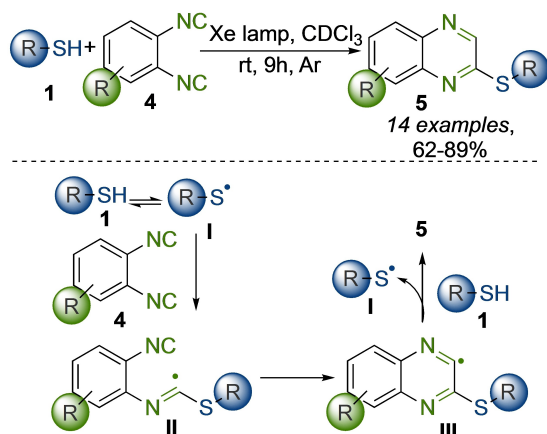
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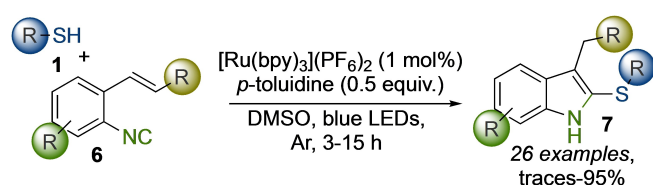
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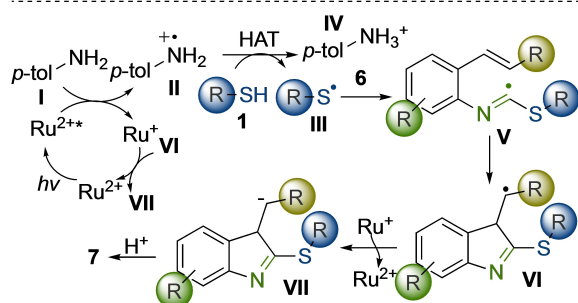
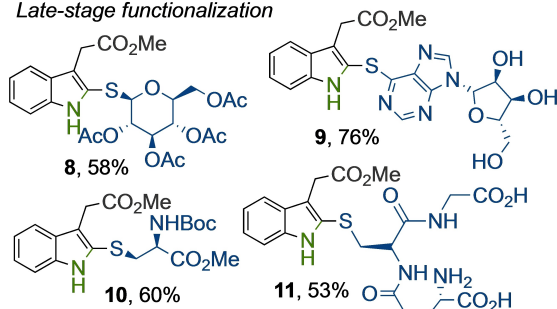
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Scheme 2. Synthesis of thiolquinoxalines 5 from thiols 1 and *o*-diisocyanoarenes 4.



Late-stage functionalization

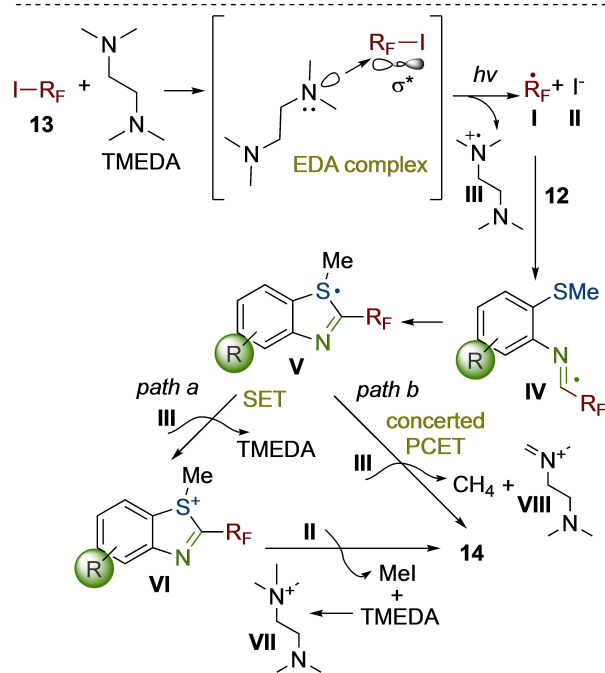
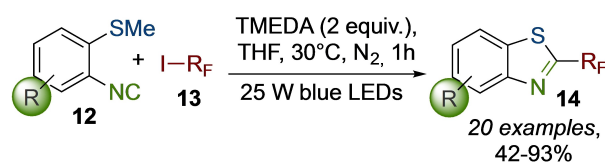


Scheme 3. Synthesis of 2-sulfonylindoles 7 from thiols 1 and *o*-alkenyl isocyanides 6.

generated upon hydrogen atom abstraction mediated by the amine radical cation II, which derived from the oxidation of I by the excited ruthenium catalyst. Hence, the reaction proceeded via thiyl radical insertion to the isocyanide and further addition of the imidoyl radical V to the tethered alkene, giving a radical intermediate VI, which got reduced to anion VII regenerating the ground state photocatalyst. The mild developed conditions enabled a broad substrate scope and excellent functional group tolerance, further proved in the late-stage functionalization of

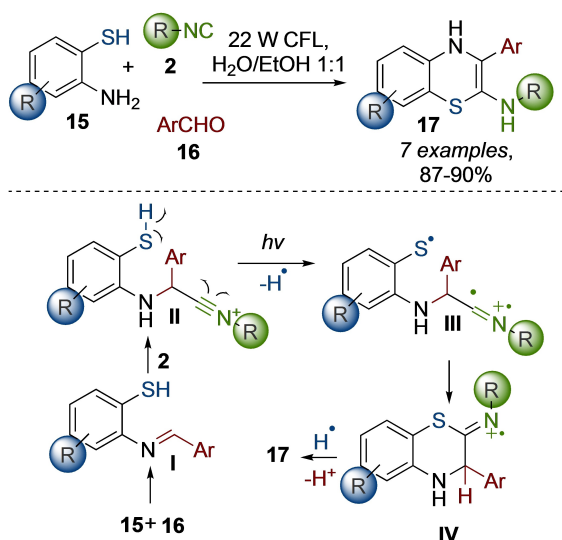
biomolecules such as saccharides (8 and 9, Scheme 3) and amino acids (10 and 11, Scheme 3) in 53–76% yields. Furthermore, a continuous flow implementation allowed smooth scalability with a residence time of 5 minutes (660 mg of methyl 2-(2-(phenylthio)-1*H*-indol-3-yl)acetate in 7 hours of infusion rate- 94 mg/h). A sulfur-centered radical is also involved in the formation of 2-perfluoroalkylbenzothiazoles 14 starting from 2-isocyanarylthioethers 12 and perfluoroalkyl iodides 13 (Scheme 4).^[27] The process would exploit the formation of a photoactive complex between the perfluoroalkyl iodide and a base such as *N,N*-tetramethylethylenediamine (TMEDA), which upon irradiation with visible light at 30 °C afforded the cyclized products. The latter would form upon addition of a perfluoroalkyl radical I to the isocyanide group and further intramolecular addition of the imidoyl radical IV to the tethered thiol. The sulfur-centered radical V would then afford 14 via two different pathways, one occurring via SET from TMEDA radical cation III (path a) and the second one proceeding via PCET from III (path b) to give the corresponding iminium ion of TMEDA and methane. Given the importance of organofluorine compounds for pharmaceutical and material chemistry, this method represents a valuable approach to get perfluoroalkyl-substituted heterocycles without requiring metals and/or initiators.

A similar visible light photoinduced cascade process to 3-aryl-4*H*-benzo[1,4]thiazin-2-amines 17- probably involving a sulfur-centered radical- occurred when 2-aminobenzenethiols

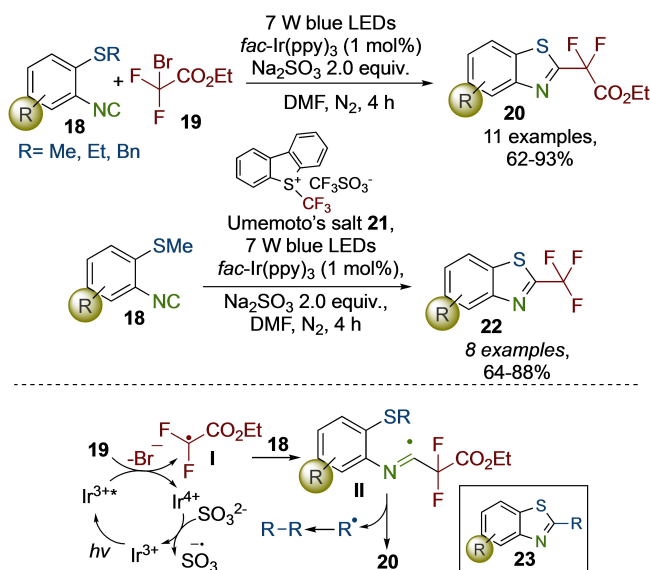


Scheme 4. Synthesis of 2-perfluoroalkylbenzothiazoles 14 from 2-isocyanarylthioethers 12 and perfluoroalkyl iodides 13.

15 were reacted with aldehydes 16 and isocyanides 2 under metal- and additive-free conditions (Scheme 5).^[28] The reaction was performed in a 1:1 ethanol/water mixture, at room temperature, under irradiation with a 22 W CFL. The reaction scope for the isocyanides and the 2-aminobenzenethiols was poorly investigated, while aromatic aldehydes tolerated both electron-withdrawing (such as the nitro group) and electron-donating (free hydroxy group) substituents (7 examples, 87–90% yields). Albeit the involvement of a sulfur-centered radical was suggested by the inhibition of the reaction in the presence of a radical trap such as TEMPO, the mechanistic hypothesis provided by the authors and relying on the formation of a species III with three unpaired electrons was not fully convincing and would deserve further investigation.



Scheme 5. Synthesis of 3-aryl-4H-benzo[1,4]thiazin-2-amines 17 from 2-aminobenzenethiols 15, aryl aldehydes 16, and isocyanides 2.

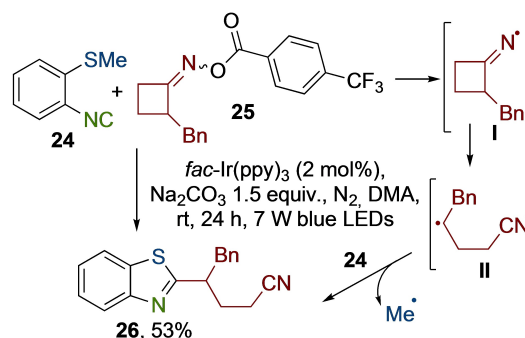


Scheme 6. Synthesis of difluoroalkyl- and trifluoromethyl-benzothiazoles 20 and 22 from 2-isocyanoaryl thioethers 18.

2.2. Sulfides as imidoyl radical traps

While thioethers are in general not reactive in photochemical reactions of isocyanides,^[29] sulfur functional groups tethered at the *ortho*-position of isocyanoaryls have been exploited as intramolecular traps for imidoyl radicals generated upon addition of either carbon- or heteroatom-centered radicals to the isocyanide. Such an approach provided a handful of methodologies to smoothly access 2-substituted benzothiazoles, with visible light photoredox catalytic methods reported quite recently. For example, Yuan Y. *et al.* reported a radical cascade addition/cyclization of 2-isocyanoaryl thioethers 18 with either 2-bromo-2,2-difluoroacetate 19 or 5-(trifluoromethyl)-5H-dibenzo[*b,d*]thiophen-5-ium trifluoromethane-sulfonate 21 (Umemoto's reagent) to get difluoroalkyl- and trifluoromethyl-benzothiazoles 20 and 22, respectively (Scheme 6).^[30] Standard reaction conditions required *fac*-Ir(ppy)₃ as a photoredox catalyst and sodium sulfite as an over-stoichiometric additive (2 equiv.) in DMF as a solvent under irradiation with 7 W blue LEDs and a nitrogen atmosphere at room temperature. Interestingly, sodium sulfite acted as a reductant to regenerate the ground state Ir^{III} from the oxidized Ir^{IV}, the latter formed upon SET from the difluoroalkylbromide 19 via oxidative quenching of Ir^{III} in its excited state (Scheme 6). The difluoroalkyl radical I then added to the isocyanide functional group, forming an imidoyl radical II, which underwent intramolecular cyclization onto the thioether with concomitant formation of the benzothiazole 20 and an alkyl radical R[•]. In the absence of sodium sulfite such a radical would be oxidized to carbocation that could be attacked by the isocyanide and eventually form byproduct 23. The reaction scope was wide, including both electron-rich and electron-poor isocyano thioethers, with yields up to 93% for difluoroalkylated benzothiazoles (11 examples). Similarly, a library of eight trifluoromethylated benzothiazoles have been obtained in 64–88% yields with poor difference in reactivity of differently substituted isocyanoaryl thioethers.

A similar radical cascade pathway has been exploited in combination with cyclobutanone oxime ester 25, which upon PET with a suitable photoredox catalyst such as *fac*-Ir(ppy)₃, formed an iminyl radical I finally affording a γ -cyanoalkyl radical II upon selective C–C bond cleavage (Scheme 7).^[31] The robust-

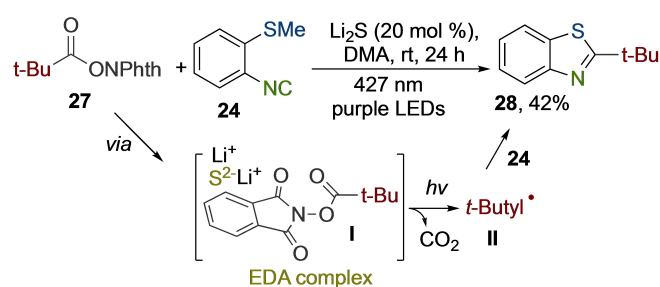


Scheme 7. Synthesis of benzothiazole 26 from 2-isocyanoaryl thioether 24 and cyclobutanone oxime ester 25.

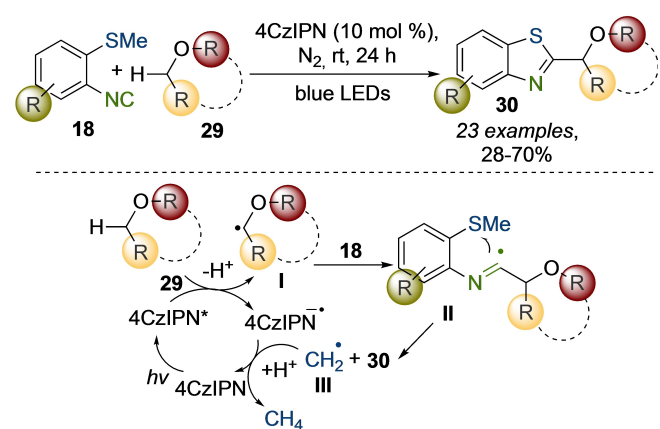
ness of the procedure was mainly shown for aryl isocyanides, which after the addition of a benzyl radical II, underwent a cascade cyclization with the tethered nitrile, while only one example has been reported with an isocyanoyl thioether, i.e., compound 26.

As for the introduction of alkyl chains via radical addition/cyclization cascades, one representative compound (28, Scheme 8) has been obtained by using a redox-active ester (RAE 27), which was able to form a visible light photoactive electron-donor acceptor complex (EDA) complex I with sulfide anions (anion- π assembled EDA complex).^[32] Such a complex would harvest visible light, reach an excited state and allow an electron transfer to trigger the reductive decarboxylative formation of a *t*-butyl radical II. The substrate scope mainly involved *ortho*-isocyanobiaryls except for compound 28. The formation of the latter would likely involve addition of radical II to the isocyanide functional group of 24 with formation of an imidoyl radical, followed by intramolecular cyclization of the latter onto the thioether with release of a methyl radical.

A third type of C-centered radicals which have been reported to be suitable partners in cascade reactions of isocyanoyl thioethers 18 are α -oxyalkyl radicals I generated from ethers 29 (Scheme 9).^[33] The corresponding benzothiazole derivatives 30 have been obtained in medium to good yields and with a wide scope (23 examples, 28–70% yield) with methoxy-, methyl-, bromo-, and fluoro-substituted isocyanoyl thioethers, while the ethers 29 included both cyclic substrates



Scheme 8. Synthesis of benzothiazole 28 from 2-isocyanoyl thioether 24 and RAE 27.

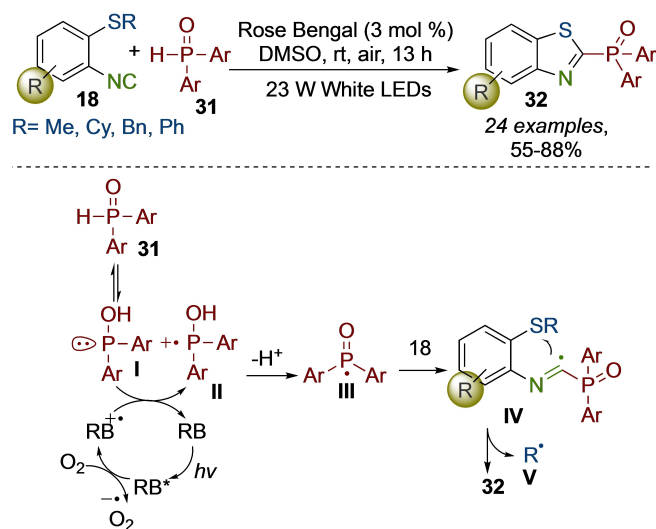


Scheme 9. Synthesis of benzothiazoles 30 from 2-isocyanoyl thioethers 18 and ethers 29.

such as THF, 1,4-dioxan, and 1,3-dioxolane and linear compounds such as ethylene glycol diethyl ether and 1,2-dimethoxyethane. The process required 4CzIPN as an organic photoredox catalyst undergoing, in its excited state, a reductive quenching with the ether 29 and regenerated by the methyl radical III released upon intramolecular cyclization of the imidoyl radical II onto the thioether functional group. The ethers were used as the solvent (0.1 M concentration for 18) and reaction mixture was irradiated with 3 W blue LEDs under a nitrogen atmosphere at room temperature for 24 h.

On the other hand, heteroatom centered radicals included P-centered ones, generated from H-phosphorous oxides 31, to give phosphoryl benzothiazoles 32 (Scheme 10).^[34] The reaction was promoted by rose bengal (RB) under irradiation with 23 W white LEDs in DMSO at room temperature and open to air. Interestingly, the reaction scope investigated also the effect of different substituents on the sulfur atom of the thioether moiety, with the most effective ones being methyl-, cyclohexyl-, and benzyl- respectively. Such a trend would represent a compromise between the radical acceptor ability of the thioether and the stability of the corresponding radical V upon cleavage. A wide range of isocyanoyl thioethers 18 and aromatic H-phosphorous oxides 31 reacted smoothly under standard conditions to give a library of 24 benzothiazole derivatives 32 with yields spanning from 55 to 88%, while phosphonate esters and aliphatic phosphine oxides revealed to be unable to afford the desired products. As for the reaction mechanism, the excited photocatalyst RB* was oxidatively quenched by molecular oxygen to give RB radical cation; the latter oxidized the H-phosphorous oxide 31 to give III upon further loss of a proton. III then added to the isocyanide affording intermediate IV and thus triggering a cascade cyclization to 32.

Alternative photoredox catalytic conditions were developed by Liu Y. *et al.* and featured the use of 4CzIPN-*t*Bu able to trigger a proton-coupled electron transfer to generate the P-

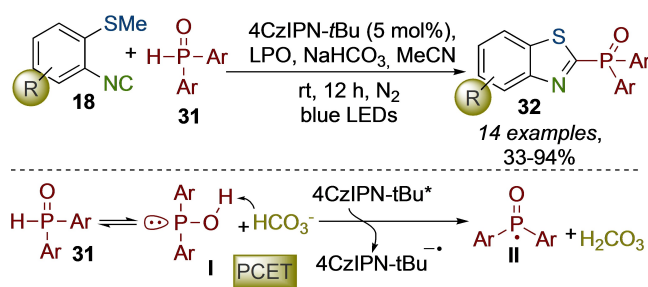


Scheme 10. Synthesis of benzothiazoles 32 from 2-isocyanoyl thioethers 18 and H-phosphorous oxides 31.

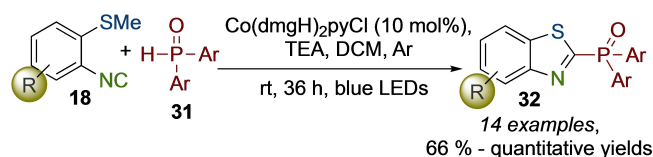
centered radicals **II** (Scheme 11).^[35] A library of fourteen 2-phosphorylated benzothiazoles (33–94% yield) were synthesized by reacting both electron-rich and electron-poor isocyanaryl thioethers **18** and diphenylphosphine oxides **31** in MeCN, with 5 mol% of 4CzIPN-tBu, lauroyl peroxide (LPO), sodium bicarbonate at room temperature under a nitrogen atmosphere and irradiation with blue LEDs.

The introduction of P-centered radicals on isocyano functional groups has also been accomplished via cobaloxime photocatalysis (Scheme 12).^[36] The mild conditions involved Co(dmgH)₂pyCl as the photocatalyst, TEA as a base, DCM as a solvent under irradiation with blue LEDs and argon atmosphere for 36 hours. With respect to the previous methods the scope of this procedure was extended to phosphine oxides with alkyl substituents (products **33** and **34**, Scheme 12), with a scaling-up to a gram scale and a couple of representative sunlight promoted reactions.

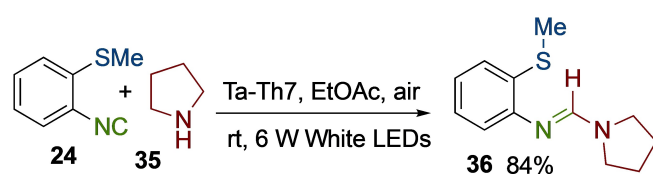
Worthy of note, the addition of a N-centered radical to the isocyanide functional group promoted by 1,2,3-triazole based-CMPs (Ta–Th7, Scheme 13) did not led to a cyclized product, but the imidine **36**, formed upon N–H insertion of pyrrolidine, was isolated in 84%.^[24] The scope was mainly investigated with



Scheme 11. Synthesis of benzothiazoles **32** from 2-isocyanaryl thioethers **18** and H-phosphorous oxides **31**.



Scheme 12. Synthesis of benzothiazoles **32** from 2-isocyanaryl thioethers **18** and H-phosphorous oxides **31**.



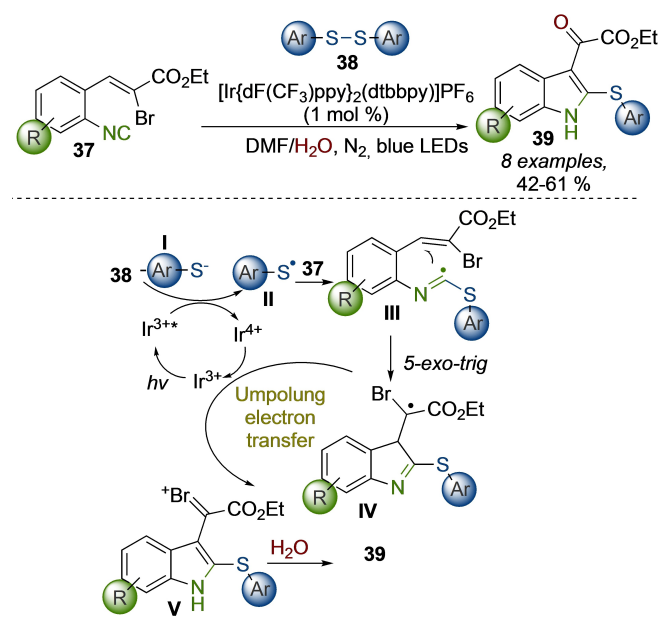
Scheme 13. Synthesis of imidine **36** from 2-isocyanaryl thioether **24** and pyrrolidine **35**.

a plethora of aromatic isocyanides, with **36** being the only compound coming from an isocyano thioether. Interestingly, the authors suggested a hydrogen atom abstraction mediated by an imidoyl radical intermediate from another molecule of the amine.

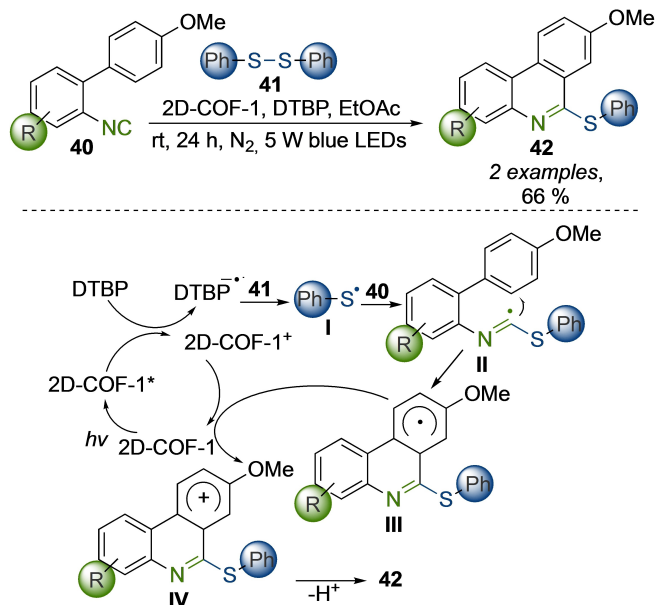
2.3. Disulfide as thiyl radical precursors

Despite a low carbon-radical capturing ability, disulfides could be harnessed in the formation of C–S bonds via UV light photoinduced homolytic cleavage of the S–S bond.^[37–42] On the other hand, visible light promoted conditions require the use of a photocatalyst able to reduce the disulfide to radical anion, which undergoes fragmentation to give a thiyl radical and a thiolate. Such an approach has been described by O. Reiser *et al.* in the radical tandem cyclization to 2-substituted indole-3-glyoxylates **39** of aryl disulfides **38** and *ortho*-isocyano- α -bromo cinnamates **37** (Scheme 14).^[43] The reaction was promoted by [Ir{dF(CF₃)ppy}₂(dtbbpy)]PF₆ as a photocatalyst in DMF with 2 equivalents of water, under irradiation at 455 nm and nitrogen atmosphere, at room temperature for 48 hours. Interestingly, according to the mechanistic hypothesis provided by the authors, the presence of a bromo or methoxy group in the starting alkenyl isocyanides **37** could reverse the electron flow typical of radicals next to a carbonyl center (less prone to get oxidized, E° = +1.85 V vs SCE) by forming the intermediate **V** and thus closing the catalytic cycle.

Alternatively, diphenylsulfide **41** could form 6-substituted phenanthridines **42** from 2-aryl phenyl isocyanides **40** by using recyclable covalent organic frameworks (2D-COF-1) as a photosensitizer and di-*tert*-butylperoxide (DTBP) as an additive in ethyl acetate as a solvent under a nitrogen atmosphere and blue LEDs irradiation at room temperature (Scheme 15).^[44]



Scheme 14. Synthesis of indoles **39** from *o*-alkenyl isocyanides **37** and diarylsulfides **38**.



Scheme 15. Synthesis of phenanthridines **42** from 2-aryl phenyl isocyanides **40** and diphenylsulfide **41**.

The reaction proceeded via a radical addition of a thiyl radical **I** to the isocyanide followed by an intramolecular cyclization of imidoyl radical **II** to form a cyclohexadienyl radical **III** able to close the catalytic cycle regenerating the ground state catalyst and forming a cation intermediate **IV**. The latter was eventually deprotonated to the final phenanthridine **42**. The catalyst retained excellent activity even after multiple runs and the versatility of the protocol was further highlighted in a gram scale reaction under continuous flow conditions.

3. Sulfonyl Radicals

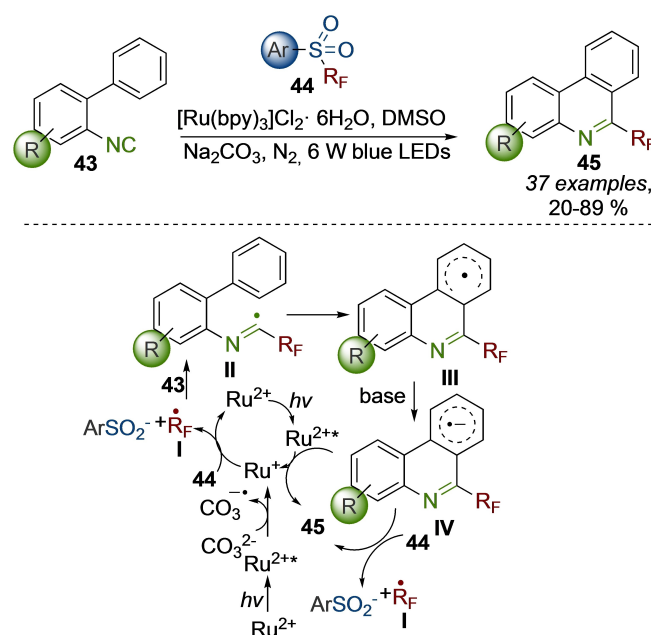
Sulfonyl containing compounds such as sulfonamides and sulfones are broadly found in biologically relevant compounds, agrochemicals, and materials. Accordingly, the development of new synthetic methods to access them with ease and to introduce SO_2 groups into complex structures such as drugs and natural compounds are receiving increasing attention as recently reported by D. W. C. MacMillan team.^[45] To this end, many interesting applications also arose from the use of DABSO, a charge-transfer complex generated from the combination of DABCO and sulfur dioxide.^[46,47] Most commonly, visible light photoredox catalytic methods harnessed the opposite transformation, i.e., the $\text{C}(sp^3)\text{-SO}_2$ bond cleavage with release of SO_2 and formation of C-centered radicals. The current section will deal with the use of sulfones and sulfonyl chlorides as radical precursors able to trigger oxidative cycles of photoexcited catalysts, thus undergoing reductive cleavages. Conversely, sulfinic acid salts could be useful precursors which would be oxidized to sulfonyl radicals, thus requiring photocatalyst suitable to efficiently engage in reductive quenching cycles.

3.1. Sulfones as radical precursors

Sulfones are considered important synthetic tools for carbon–carbon bond formation thanks to essential hallmarks such as ease of preparation, robustness and useful physical-chemical properties including bench-stability and crystallinity.^[48] In the realm of visible light photoredox catalysis a wide range of mono-, di-, and trifluoromethyl heteroaryl sulfones **44** have been conveniently harnessed for the radical fluoroalkylation of *ortho*-isocyanobiphenyls **43** under mild conditions (Scheme 16).^[49]

The latter featured the use of a ruthenium based photocatalyst and sodium carbonate in DMSO as a solvent at room temperature under a nitrogen atmosphere and irradiation with 6 W blue LEDs. Interestingly, the fluoroalkyl heteroaryl sulfones **44** revealed to be versatile and reactivity-tunable reagents, with the redox potential changing by varying both the substitution pattern of the aromatic moiety of the sulfone and the degree of fluorination of the fluoroalkyl chain. The reaction scope was wide – yields ranging from 20 to 89% (37 examples)- with electron-rich *ortho*-isocyanobiphenyls being the less reactive. The proposed mechanism entailed a SET from the reduced photocatalyst Ru^+ – formed upon PET from the carbonate anion to the excited Ru^{2+*} to the fluoroalkylsulfone **44**. The latter, hence underwent a reductive cleavage to form a fluoroalkyl radical **I** and a sulfonate ion. **I** then added to the isocyanide **43**, forming an imidoyl radical **II**, which underwent an intramolecular radical cyclization to form the cyclohexadienyl radical **III**. Deprotonation to **IV** and further oxidation by the excited photocatalyst closed the catalytic cycle and afforded the 6-substituted phenanthridine **45**.

Structurally related arylthiodifluoromethyl 2-pyridyl sulfone derivatives **46** revealed to be shelf-stable and scalable



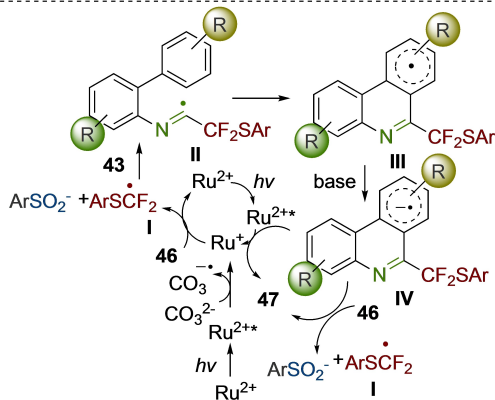
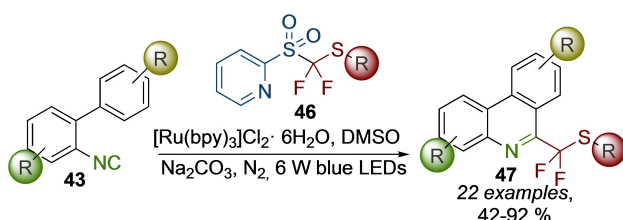
Scheme 16. Synthesis of 6-substituted phenanthridines **45** from *ortho*-isocyanobiphenyls **43** and heteroaryl sulfones **44**.

arylthiodifluoromethylation agents when reacted with *o*-isocyanobiphenyls **43** in the same reaction conditions, namely, [Ru(bpy)₃]Cl₂·6H₂O as the photocatalyst, DMSO as a solvent, sodium carbonate as a base, at room temperature under a nitrogen atmosphere and irradiation with 6 W blue LEDs (Scheme 17).^[50] A library of 22 different 6-arylthiodifluoromethyl-phenanthridines **47** have been reported in good to excellent yields (42–92%), with a wide substrate scope -in terms of electron-withdrawing and electron-donating substituents- for both the isocyanides **43** and the 2-pyridyl sulfone reagents **46**.

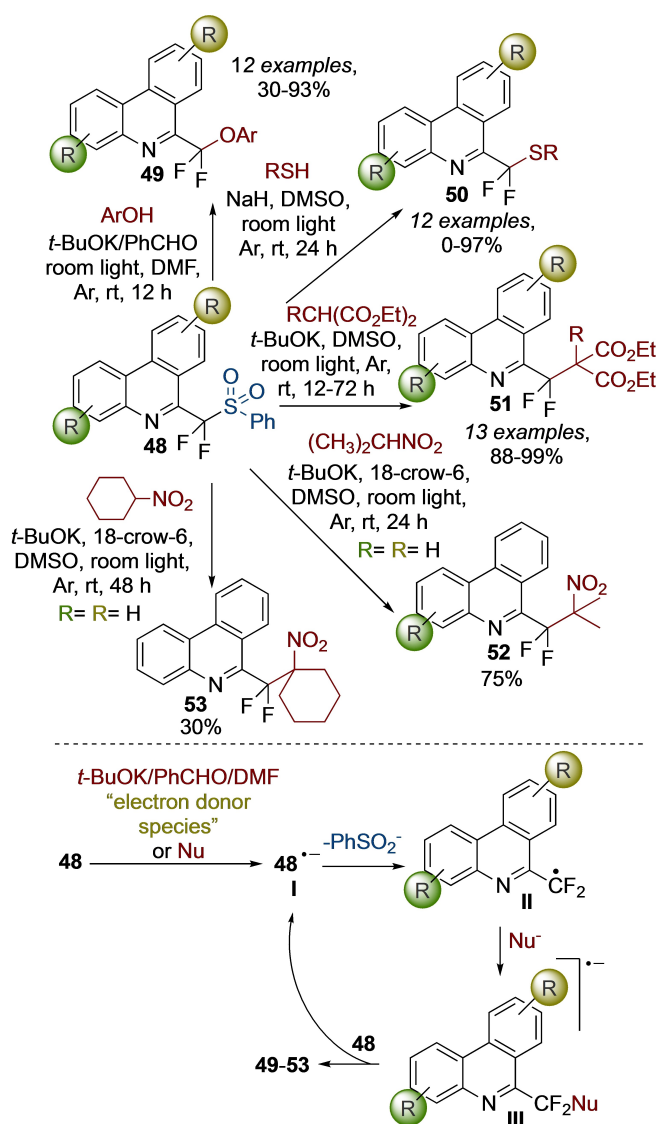
Unfortunately, aliphatic sulfones were not reactive at all. Similar to the previous reported mechanism, the 2-pyridyl sulfone **46** underwent a reductive fragmentation to ArSCF₂· radical I upon a SET from the photocatalyst (Ru^I) reduced by the carbonate anion CO₃²⁻. The catalytic cycle then featured the addition of the arylthiodifluoromethyl radical I to the isocyanide **43**, followed by an intramolecular cyclization of II and further aromatization via oxidation/deprotonation of the cyclohexadienyl radical intermediate III.

Shortly after, the high versatility of fluoroalkyl sulfones was explored in the substitution of (phenylsulfonyl)difluoromethyl phenanthridines **48** (obtained via cyclization of *ortho*-isocyanobiphenyls) with a range of O-, S-, Se-, and C-nucleophiles such as alcohols (potassium *tert*-butoxide), phenols, aromatic thiols, diphenyldiselenide, diethylmalonate salts, and nitroalkane salts (Scheme 18).^[51]

In the case of O-nucleophiles the reaction was promoted by the formation *in situ* of an electron-donating species via interaction of *t*-BuOK, benzaldehyde (PhCHO), and the solvent DMF, which could effectively initiate the SET to the fluoroalkyl aryl sulfone **48**. In the other cases, the nucleophiles could be able to reduce the fluoroalkyl aryl sulfone **48** inducing a reductive cleavage to fluoroalkyl radical intermediate II, which



Scheme 17. Synthesis of 6-arylthiodifluoromethyl-phenanthridines **47** from *ortho*-isocyanobiphenyls **43** and arylthiodifluoromethyl 2-pyridyl sulfones **46**.

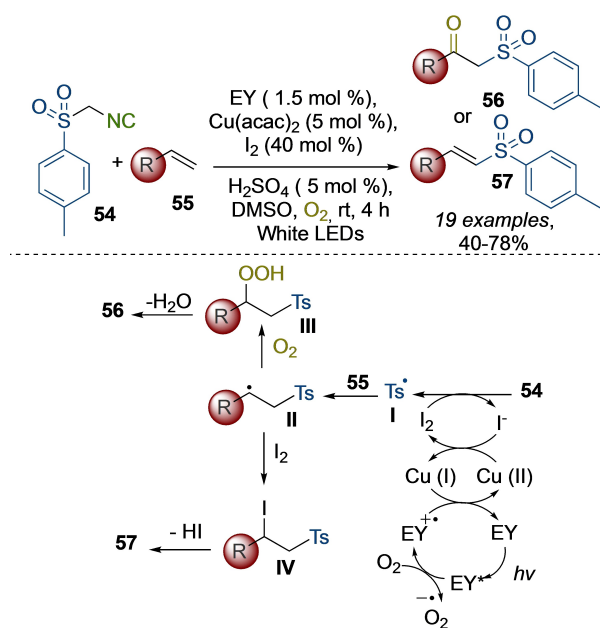


Scheme 18. Substitution of (phenylsulfonyl)difluoromethyl phenanthridines **48** with different nucleophiles.

was intercepted by the nucleophile to form a radical anion III with the latter able to reduce the fluoroalkyl aryl sulfone **48** in a chain mechanism. The reported transformations efficiently proceeded at room temperature under room light illumination. The nucleophile substrate scope was good, with yields up to 99% for diethylmalonate salts.

3.2. TosMIC as radical precursor

Albeit the isocyanide functional group was not directly involved in the formation of the final products, it is worth mentioning the use of *p*-toluenesulfonylmethyl isocyanide (TosMIC, **54**, Scheme 19) as a source of sulfonyl radical.^[52–56] To this end, Min W. *et al.* reported its ability to promote sulfonylation and sulfonylcarbonylation of alkenes **55**, namely styrenes and either acrylates or acrylamides under visible light conditions



Scheme 19. TosMIC **54** as sulfonyl radical precursor.

(Scheme 19).^[57] The reaction was performed using eosin Y (EY) as an organic photoredox catalyst, molecular iodine I_2 , $Cu(acac)_2$, and H_2SO_4 as additives in DMSO with an O_2 balloon under irradiation with white LEDs. As for the alkene substrates the reaction scope was good tolerating both electron-withdrawing and electron-donating substituents on the styrene aromatic ring (10 examples, 40–78% yields) and both aliphatic and aromatic alcohol moiety on the acrylate esters (6 examples, 63–70% yields; 3 examples for acrylamides, 66–69% yields).

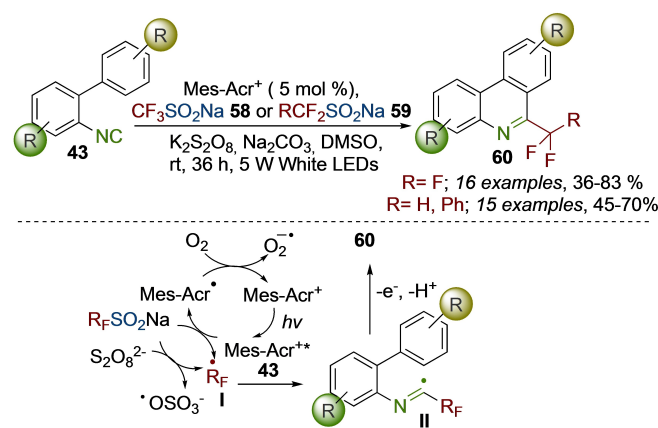
Unfortunately, only TosMIC **54** was used as sulfonyl radical precursor, with no information about the possibility of getting different substituents on the aromatic ring of the sulfone moiety. Albeit not detailed, a working mechanistic hypothesis relied on the PET from the excited photocatalyst to molecular oxygen and regeneration of the ground state eosin Y by copper (I). The latter was generated from copper (II) by an iodine anion formed in the molecular iodine promoted fragmentation of TosMIC **54** to form the sulfonyl radical I. Depending on the alkene, two different pathways have then been proposed: I added to styrene to form a benzyl radical II, prone to react with molecular oxygen to give β -ketosulfones **56**, while, when the intermediate II was formed upon addition of Ts radical I to acrylates, it was most likely to react with molecular iodine to form β -iodosulfone IV. Eventually, the elimination of HI from the latter under acidic conditions afforded vinyl sulfones **57**.

3.3. Sulfinic acid salts as radical precursors

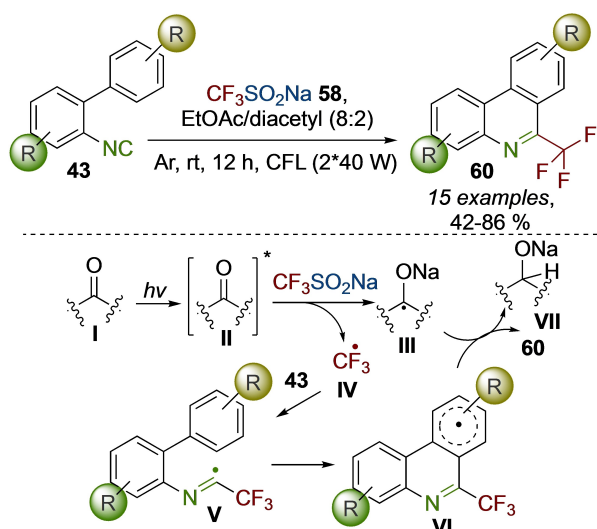
The fluoroalkylation of isocyanides with sulfone derivatives as in section 3.1 could be complemented by methods exploiting salts of sulfinic acids (RSO_2H). Sulfinic acid salts are generally acknowledged as useful synthetic tools to forge C–C and C–heteroatom bonds via sulfur dioxide (SO_2) extrusion. They are colorless,

odorless, and non-corrosive solids, easily synthesized via a plethora of smooth and scalable approaches.^[58] The first report focusing on the fluoroalkylation of isocyanide derivatives **43** with sulfinate salts **58** and **59** dates back to 2017 and exploited the use of *N*-methyl-9-mesityl acridinium ($Mes-Acr^+$) as an organic photoredox catalyst, potassium persulfate as an oxidant, sodium carbonate as the base in DMSO, at room temperature and under irradiation with 5 W white LEDs (Scheme 20).^[59] A library of 16 different trifluoromethylated phenanthridine derivatives **60** was obtained in good yields starting from either electron-rich or electron-poor 2-isocyanobiaryls **43** and sodium trifluoromethanesulfinate (CF_3SO_2Na , **58**), also known as the Langlois reagent. Analogously, di- and mono-fluoroalkyl derivatives were obtained from the corresponding sodium salts **59** (15 more examples, 45–70% yields). Interestingly, the standard reaction conditions proved to be enough robust even on a gram scale with up to 68% yield.

Following the mechanistic hypothesis in Scheme 20, the excited catalyst $Mes-Acr^{+*}$ would promote the oxidative fragmentation of the sulfinate salt upon PET, thus triggering the formation of a fluoroalkyl radical I. The latter would then be involved in cascade radical addition/annulation to afford the fluoroalkyl phenanthridines **60**. Li J. *et al.* in 2018 reported a protocol for a metal-free photocatalytic cascade addition/annulation reaction of 2-isocyanobiaryls **43** with Langlois reagent **58** affording 6-trifluoromethyl-phenanthridines **60** (Scheme 21).^[60] Such a method provided a smooth and simple installation of a trifluoromethyl group via generation of a CF_3 radical IV from a photoexcited 2,3-butandione (diacetyl, I): more in detail, CF_3SO_2Na underwent an oxidative fragmentation upon PET with loss of SO_2 . The CF_3 radical IV added to the isocyanate functional group to form an imidoyl radical intermediate V, further undergoing an intramolecular homolytic aromatic substitution (HAS) towards the phenanthridine derivatives **60**. The substrate scope was investigated for 15 different 2-isocyanobiaryls **43** with yields ranging from 42 to 86% and poor difference in the reactivity between electron-rich and electron-poor substituents. An alternative protocol involved the use of recyclable covalent organic frameworks (2D-COF-1) as a



Scheme 20. Synthesis of phenanthridine derivatives **60** from *ortho*-isocyanobiaryls **43** and sulfinate salts **58** and **59**.

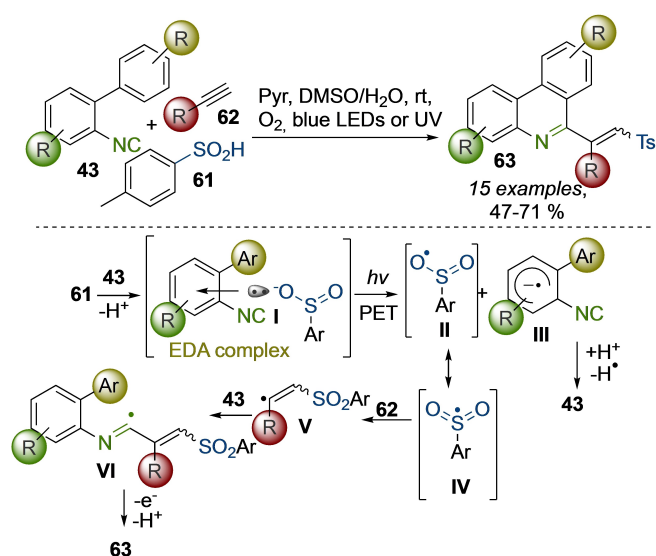


Scheme 21. Synthesis of phenanthridine derivatives **60** from *ortho*-isocyanobiaryls **43** and Langlois reagent **58**.

photosensitizer and di-tert-butylperoxide (DTBP) as already seen for aryl disulfides (see section 2.3).^[44]

Sulfinate salts could also be formed in situ starting from sulfinic acids **61**, as shown by Li Y. *et al.* who reported a photo-induced three-component reaction leading to 6-polyfunctionalized phenanthridines **63** (Scheme 22).^[61]

Worthy of note, the authors revealed that 2-isocyanobiaryls **43** and sulfinate anions are able to form a visible light photoactive electron donor-acceptor (EDA) complex **I** thus providing a photocatalyst-free protocol. The reaction proceeded in a mixture of DMSO/H₂O as the solvent system, with pyridine as an organic base, at room temperature under irradiation with either 3 W blue LEDs (450 nm) or 3 W UV (365 nm). Variable mixtures of *E/Z* isomers were obtained depending on the light source.



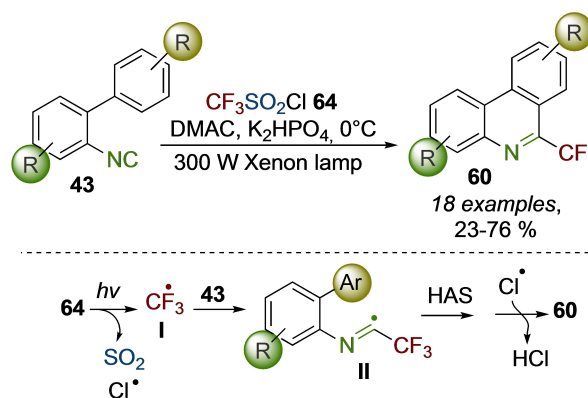
Scheme 22. Synthesis of phenanthridine derivatives **63** from *ortho*-isocyanobiaryls **43**, alkynes **62** and sulfinic acids **61**.

The mechanistic hypothesis featured for the first time the formation of an isocyanide radical anion **III** upon PET from the sulfinate salt. The latter, once oxidized to **II**, did not collapse to form a radical species and SO₂ as previously seen for the fluoroalkyl radicals, but underwent a radical addition to the alkyne to form a vinyl radical **V**, which added to the isocyanide group triggering the cascade annulation typical of the 2-isocyanobiaryl systems. The success of this elegant transformation is also due to a poor attitude of the RSO₂ radicals to undergo addition to the isocyanide as shown for example by Malacarne M. *et al.* in the radical arylation of isocyanides.^[62] Herein, indeed, the authors obtained aromatic amides by exploiting photoactive arylazosulfones, which upon excitation underwent a homolytic fragmentation to form an aryl radical – readily reacting with the isocyanide- and a sulfonyl radical, which promoted the oxidation of the imidoyl radical to nitrilium ion.

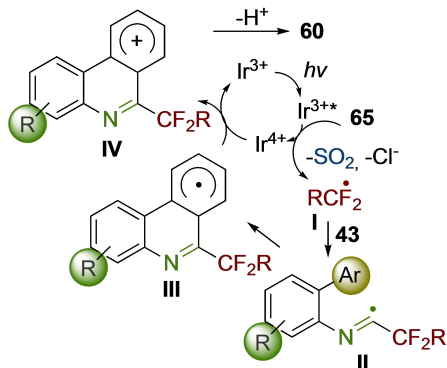
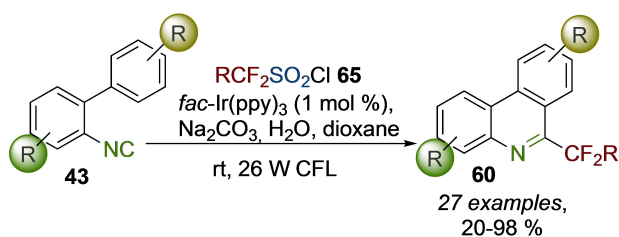
3.4. Sulfonyl chlorides as radical precursors

While sulfones need to be reduced and sulfinate salts should be oxidized in order to form fluoroalkyl radicals, it has been shown that CF₃SO₂Cl could undergo homolytic cleavage upon direct excitation by using a 300 W Xenon lamp (280–780 nm) as the light source.^[63] These photocatalyst-free conditions have been reported by Tang X. *et al.* for the synthesis of 6-trifluoromethylphenanthridines **60**, with a wide substrate scope and good yields (Scheme 23).

While a previous attempt of getting trifluoromethyl derivatives by using 3 W blue LEDs and fluorescein as an organic photocatalyst in DMF was not successful,^[64] *fac*-Ir(ppy)₃ was conveniently exploited as a photoredox catalyst for the synthesis of 6-(difluoromethyl)- and 6-(1,1-difluoroalkyl)phenanthridines **60** via a tandem addition/cyclization/oxidation process (Scheme 24).^[65] In this case, the fluoroalkyl sulfonyl chloride **65** should be reduced by the excited iridium-photocatalyst to generate the corresponding carbon radical **I** and Cl⁻, with release of SO₂. The reaction was performed in dioxane and the mild conditions afforded a library



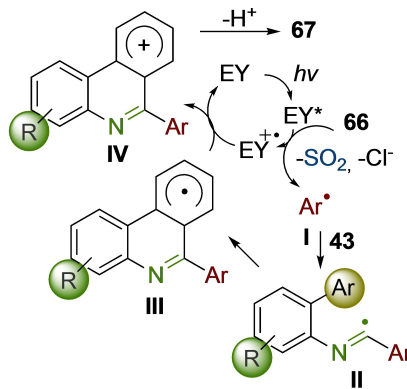
Scheme 23. Synthesis of phenanthridine derivatives **60** from *ortho*-isocyanobiaryls **43** and trifluoromethylsulfonyl chloride **64**.



Scheme 24. Synthesis of phenanthridine derivatives **60** from *ortho*-isocyanobiaryls **43** and fluoroalkyl sulfonyl chloride **65**.

of 27 examples in good to excellent yields (53–98%), excepting for 2-isocyanobiaryls containing ketone and ester functional groups (24 and 20% yield, respectively).

The scope of the sulfonyl chlorides involves also aryl derivatives as shown by Gu L. *et al.* who developed a transition metal- and additive-free procedure to get 6-arylated phenanthridines **67** (Scheme 25).^[66] Standard conditions required eosin Y as an organic photocatalyst, which upon excitation promoted



Scheme 25. Synthesis of 6-arylated phenanthridines **67** from isocyanides **43** and arylsulfonyl chlorides **66**.

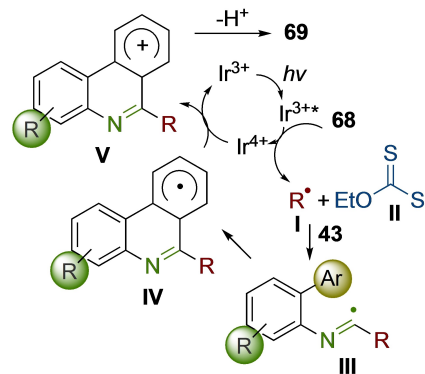
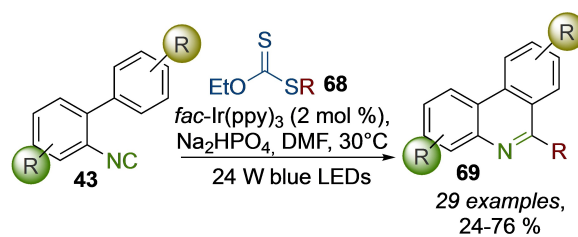
a PET to the arylsulfonyl chloride **66**, which once reduced, fragmented to aryl radical **I**, SO₂ and a chloride anion Cl[−]. The aryl radical **I** added to the isocyanide thus triggering an intramolecular HAS. Both the aryl sulfonyl chloride and the 2-isocyanobiaryl scope was good – involving also heterocyclic derivatives- as shown for the synthesis of 16 derivatives with yields ranging from 53 to 79%.

4. Radical Precursors Involving C=S Functional Groups

While visible light photoredox reactions involving thioketones, thioamides, and benzothioates mainly afforded desulfurization products^[67,68] and heterocyclic compounds such as thiazoles^[69] and thiadiazoles,^[70,71] the current section will highlight the handful of transformations harnessing C=S containing compounds to form C-centered radicals, such as xanthates and *N*-hydroxy-2-thiopyridones.

4.1. Xanthates as radical precursors

Xanthates represents a valuable source of C-centered radical precursors with the possibility of introducing a variety of alkyl moieties bearing functional groups such as esters, nitriles, ketones, amides and malonate derivatives.^[72–74] Recently, López-Mendoza P. and Miranda L. D. reported a visible light photoredox catalytic radical addition/cyclization cascade towards 6-alkylated phenanthridines **69** (Scheme 26).^[75] The mild conditions involved *fac*-Ir(ppy)₃ as a photocatalyst, Na₂HPO₄ as a



Scheme 26. Synthesis of 6-alkylated phenanthridines **69** from isocyanides **43** and xanthates **68**.

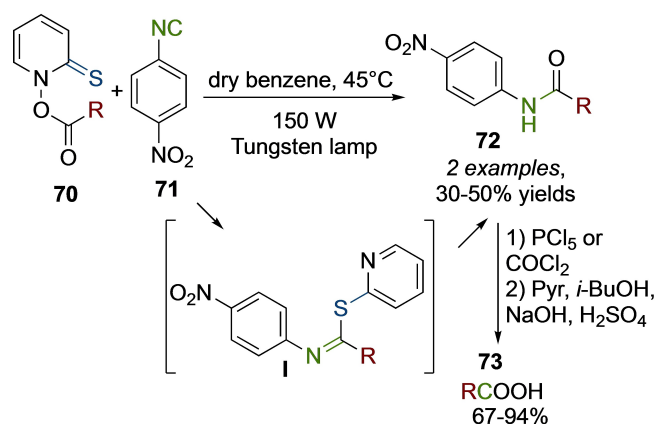
base, in DMF, under irradiation with 24 W blue LEDs at room temperature.

A library of 29 derivatives with yields ranging from 24 to 76% accounted for the wide scope of this transformation. According to the mechanism showed in Scheme 26, the excited photocatalyst would promote a reductive fragmentation of the xanthate **68** to give an alkyl radical **I** and *O*-ethyl dithiocarbonate **II**. The alkyl radical **I** then was trapped by the isocyanide **43**, forming an imidoyl radical **III** that further underwent intramolecular cyclization to cyclohexadienyl radical **IV**. The latter underwent a SET oxidation to **V**, thus regenerating the ground state Ir³⁺. Eventually, **V** afforded phenanthridine **69** upon loss of a proton.

4.2. *N*-hydroxy-2-thiopyridones as radical precursors

Besides arabinosyl-6-mercaptapurine used as complex substrate in the late-stage functionalization as in section 2.1,^[26] examples of compounds bearing C=S functional groups are quite poor. Thiohydroxamic esters have been elegantly exploited as photoactive alkyl radical precursors by Professor Sir D. H. R. Barton and coworkers for the synthesis of amides derivatives of different aromatic isocyanides.^[76] In a Tetrahedron article titled "The invention of radical chemistry part XVIII. A convenient solution to the 1-carbon problem ($R\text{-CO}_2\text{H} \rightarrow R\text{-}^{13}\text{C}_2\text{O}_2\text{H}$)" written in 1988, the Nobel Prize winner Professor Sir D. H. R. Barton described how the photolysis of thiohydroxamic esters **70** could be accomplished via irradiation with a 150 W tungsten lamp in dry benzene at 45 °C (Scheme 27).

The isocyanides were selected as the most suitable to be enough stable to be reacted in the standard reaction conditions, but sufficiently labile to be cleaved under reasonable conditions to afford carboxylic acid derivatives. To this end the best performing ones were found to be 4-nitrophenyl isocyanide **71** (corresponding amide cleaved via imidoyl chloride upon treatment with either PCl₅ or phosgene) and 3-pyridyl isocyanide (corresponding amide cleaved via thiol-acid upon treatment with hexamethyldisilazane/*n*-BuLi/CS₂/NaOH aq.). An experiment with an isocyanide labelled on the carbon

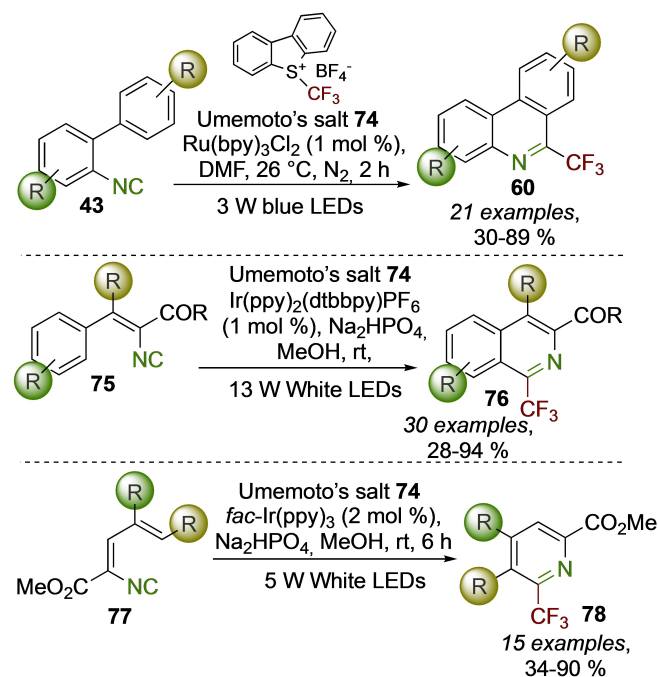


Scheme 27. Synthesis of benzamides **72** and further hydrolysis to carboxylic acids **73**.

atom (¹³C, 7.5% enriched) suggested the current protocol as a powerful tool to get labeled amides and carboxylic acids.

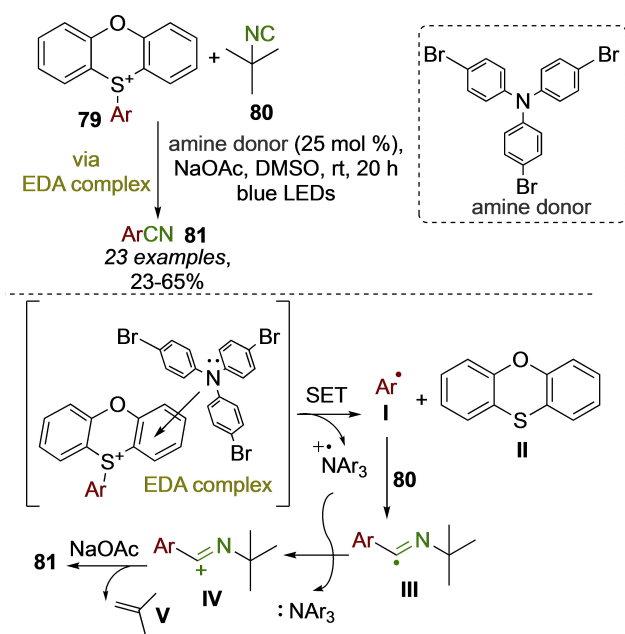
5. Sulfonium Salts as Radical Precursors

The current section would further highlight the efficacy and the value of S-based reagents in photochemical reactions involving isocyanides by bringing to attention aryl sulfonium salts. Between the most popular reagents, Umemoto's salts have been conveniently exploited to provide trifluoromethylated heterocycles. More in detail, the Yu S. lab reported the synthesis of 6-trifluoromethylphenanthridines^[64] **60** and either 1-trifluoromethylisoquinolines^[77] **76** or *ortho*-trifluoromethylpyridines^[78] **78** via visible light promoted insertion of a CF₃ radical onto isocyanobiphenyls **43** and vinyl isocyanides **75** and **77**, respectively (Scheme 28). The cascade reaction involving 2-isocyanobiaryls was promoted by a ruthenium catalyst, in DMF, under irradiation with blue LEDs and a nitrogen atmosphere. A library of twenty-one trifluoromethyl phenanthridines **60** involving both electron-donating and electron-withdrawing substituents was obtained in good yields (30–89%). The reactions involving vinyl isocyanides **75** and **77** were catalyzed by an iridium photocatalyst in methanol, with Na₂HPO₄ as a base under white LEDs irradiation at room temperature (Scheme 28). In all the cases the excited photocatalyst underwent an oxidative quenching with the Umemoto's reagent **74** to form the trifluoromethyl radical, further adding to the isocyanide functional group and triggering an intramolecular cyclization leading to either isoquinolines **76** or pyridines **78** depending on the isocyanide substitution pattern.

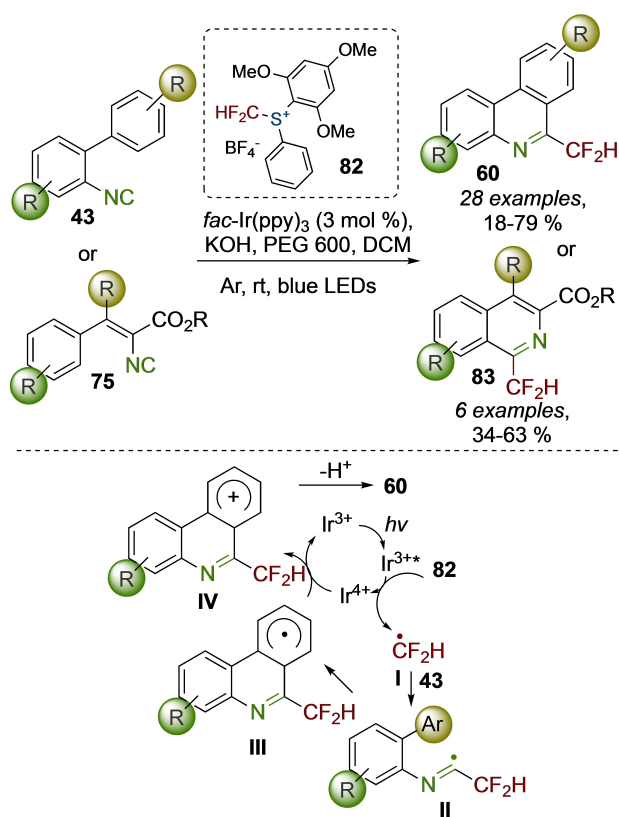


Scheme 28. Synthesis of 6-trifluoromethylphenanthridines **60**, 1-trifluoromethylisoquinolines **76**, and *ortho*-trifluoromethylpyridines **78**.

Another class of sulfonium salts which has been gaining more and more popularity thanks to their high versatility, wide scope, and suitability for site-selective late-stage functionalization of complex structures such as drugs and natural com-



Scheme 29. Synthesis of cyanoarenes **81** from triarylsulfonium salts **79** and *tert*-butyl isocyanide **80**.



Scheme 30. Synthesis of difluoromethylated phenanthridines **60** and isoquinolines **83** from diarylsulfonium salts **82**.

pounds is that involving thianthrenium salts for the generation of aryl radicals. The exploitation of the latter in visible light photoredox catalytic protocols has been pioneered by T. Ritter group in 2019,^[79] with further synthetic applications and mechanistic studies published shortly after.^[80,81] Very recently the group of D. J. Procter introduced triarylsulfonium salts **79** as acceptors in EDA complexes, which could be used in combination with catalytic amounts of a donor amine (Scheme 29).^[82]

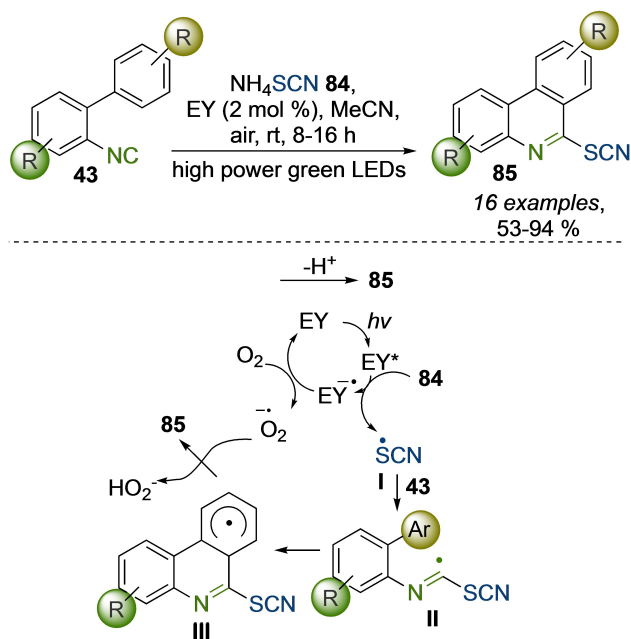
This elegant approach bypassed the need for specific electronic features of the aryl radical precursors and provided a metal-free protocol for cyanation of arenes by using commercially available *tert*-butyl isocyanide **80**. The substrate scope demonstrated with a library of twenty-three different cyanoarenes highlighted an exceptional functional group tolerance and involved pharmaceuticals and agrochemical compounds such as boscalid, estrone, naproxen, gemfibrozil and mexiletine which gave the corresponding products in good yields as single regioisomers under standard reaction conditions.

Finally, such section would include diarylsulfonium salts **82** which have been conveniently used as fluoroalkyl radical precursors for the synthesis of difluoromethylated phenanthridines **60** and isoquinolines **83** starting from isocyanobiaryls **43** and vinyl isocyanides **75**, respectively (Scheme 30).^[83] The protocol featured the oxidative quenching of an excited iridium catalyst to form the fluoroalkyl radical **I**, which was then engaged in the addition/cyclization cascade typical of isocyanobiaryls.

6. Miscellaneous

Besides the organic sulfonium salts, the literature focusing on sulfur-centered radicals involved in cascade addition/cyclization processes with *ortho*-isocyanobiaryls also provided a nice exploitation of the inorganic salt ammonium thiocyanate to get 6-thiocyanatophenanthridines **85** (Scheme 31).^[84] The metal-free reaction conditions required eosin Y as a photoredox catalyst and MeCN as a solvent under air and irradiation with green LEDs. The excited photocatalyst would be able to promote a SET oxidation of SCN⁻ to the corresponding radical **I**, which would then add to the isocyanide, forming the imidoyl radical **II** and thus triggering the cascade intramolecular cyclization to phenanthridines **85**. The mild conditions enabled excellent functional group tolerance (halogen-, nitrile-, ester-, methoxy-, alkyl-, and trifluoromethyl- functional groups) in the synthesis of sixteen derivatives in 53–94% yields.

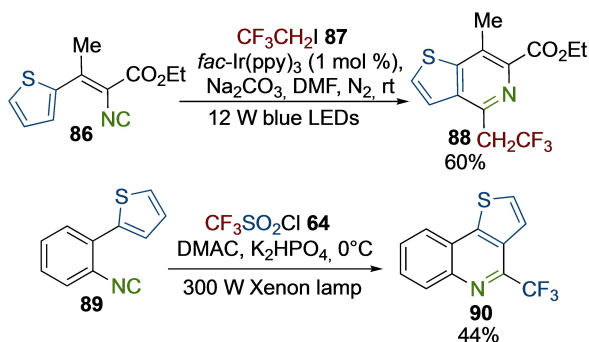
Albeit not directly being the focus of the current review manuscript, there are synthetic procedures where isocyanides have been used in tandem after photoredox catalytic processes involving sulfur-centered radicals^[85] and alkynes^[86,87] and cyclic disulfides.^[88] The advantages of exploiting isocyanide chemistry in combination with visible light photochemical processes have also been nicely highlighted in the generation of Ugi 4-CR adducts and their further modification in combination with aryl sulfonyl chlorides under blue LEDs irradiation to give sulfonated dibenzazepines.^[89] Worthy of note, the photoactivity of pyreneacyl sulfide was exploited to generate in situ a thioaldehyde



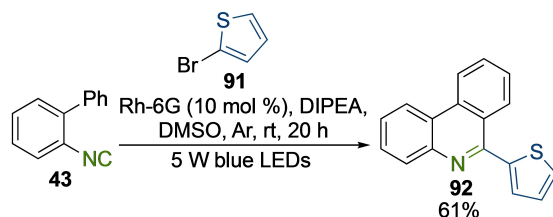
Scheme 31. Synthesis of 6-thiocyanatophenanthridines **85** from isocyanides **43** and ammonium thiocyanate **84**.

in a visible-light induced Passerini multicomponent polymerization under very mild reaction conditions leading to soft matter materials.^[90]

Interestingly, S-containing heterocycles such thiophene have been shown to be suitable intramolecular traps for imidoyl radicals as shown in the formation of 1-trifluoroethyl isoquinolines **88** from vinyl isocyanide^[91] **86** and in the photocatalyst-



Scheme 32. Thiophene as intramolecular trap.



Scheme 33. Synthesis of phenanthridine **92** from 2-bromothiophene.

free addition/cyclization cascade of isocyanoheterobiaryl^[63] **89** to give product **90** (Scheme 32).

While in the latter processes a thiophene radical cation was formed upon intramolecular addition of the imidoyl radical, the formation of a neutral thiophene radical was accomplished via reductive cleavage of 2-bromothiophene promoted by rhodamine 6G (Rh-6G) in DMSO under blue LEDs irradiation (Scheme 33).^[92] The product **92** -the only example to be reported- was obtained in 61% yield via addition/cyclization cascade with 2-isocyanobiphenyl **43**.

7. Summary and Outlook

In conclusion, organosulfur compounds emerged as valuable sulfur-centered radical precursors able to either trigger the formation of thiocarbamates or introduce alkyl and fluoroalkyl chains into heterocyclic compounds upon loss of sulfur dioxide. As for the latter, isocyanobiaryls and vinyl isocyanides stands for useful chemical platforms to efficiently trap the carbon- and sulfur-centered radicals mainly generated via SET reduction of sulfur-containing substrates, as in the case of disulfides, sulfones, sulfonyl chlorides, thioxanthes, and sulfonium salts. Conversely, thiols and sulfinic acid salts would get oxidized to afford thyl and sulfonyl radicals, respectively. Sulfonamides and sulfonic esters are in general orthogonal to both reductive and oxidative conditions as well as sulfides, albeit the latter could be exploited as imidoyl trapping agents when tethered at the *ortho*- position of isocyanoarenes such as in isocyanoyl thioethers. Interestingly, inorganic salts could also be useful reagents to promote either the formation of C–S bonds as for thiocyanate or to close a catalytic cycle by regenerating the photocatalyst as shown for the conversion of Ir^{IV} to Ir^{III} mediated by sodium sulfite. While most of the reactions involve biaryl isocyanides as substrates, the utilization of simpler substrates could constitute a significant breakthrough. Accordingly, future directions would be focused on the implementation of intermolecular visible light photoredox catalytic processes involving isocyanides as radical acceptors. To this end, considering the high versatility and compatibility with the isocyano functional group, organosulfur compounds herein highlighted could be definitely further exploited as useful precursors of both carbon- and sulfur-centered radicals.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Keywords: sulfur-centered radicals · isocyanides · visible light photocatalysis · organosulfur compounds · isocyanobiaryls

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