Article

s-Tetrazine Dyes: a facile generation of photoredox organocatalysts for routine oxidations

Tuan Le, Thibaut Courant, Jérémy Merad, Clémence Allain, Pierre Audebert, and Géraldine Masson

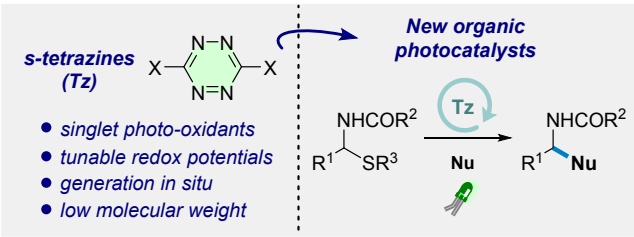
J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.9b02454 • Publication Date (Web): 13 Nov 2019

s-Tetrazine Dyes: a facile generation of photoredox organocatalysts for routine oxidations

Tuan Le,[§†] Thibaut Courant,[§‡] Jérémy Merad,[‡] Clémence Allain,[†]* Pierre Audebert[†] and Géraldine Masson[‡]*

[‡] Institut de Chimie des Substances Naturelles, CNRS UPR 2301, Université Paris-Sud, Université Paris-Saclay, 1, av. de la Terrasse, 91198 Gif-sur-Yvette Cedex, France

[†] PPSM, ENS Paris-Saclay, CNRS, Université Paris-Saclay, 94235 Cachan, France.



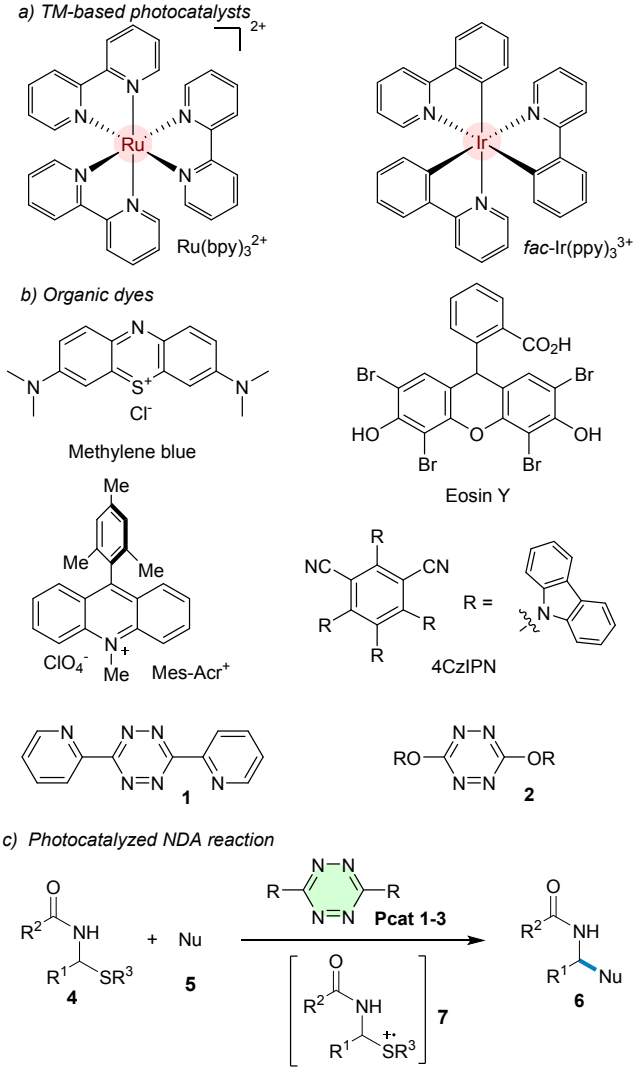
ABSTRACT: A series of organic dyes derived from s-tetrazine have been synthesized, and their photophysical and electrochemical properties systematically investigated. Testing these compounds as photoredox catalysts in a model oxidative C-S bond cleavage of thioethers has led us to identify new classes of active *s*-tetrazines. Moreover, some of them can be formed *in situ* from commercially available 3,6-dichlorotetrazine making this photocatalyzed C-S bond functionalization simple and highly practical.

INTRODUCTION

In recent years, visible light photoredox catalysis has turned out to become a powerful ally to drive ion-radical redox reactions under mild reaction conditions.[1] In this context, Ru(II) and Ir(III) polypyridyl complexes, have been extensively used as sensitizers, owing to their exceptional photophysical properties (Scheme 1, a).[1,2] On the other hand, this unique reactivity is offset by high costs, toxicity and scarcity in metal resources, a situation responsible for the limited exports of photoredox catalysis out of academic laboratories. An alternative is provided by the use of naturally occurring dyes as sensitizers (such as methylene blue and eosin Y, Scheme 1, b).[3] Consequently, identifying new organic scaffolds as non-toxic, inexpensive and eco-friendly photocatalysts has recently become a dynamic research area. As a result of these extensive investigations, original structures like cyanoarenes (i.e. 4CzIPN) and acridinium salts (i.e. Mes-Acr$^+$) have been brought to light (Scheme 1, b).[4] Although these examples of organic sensitizers represent important advances, the development of accessible and cheap metal-free photocatalysts is still highly desirable.

As part of our continuing efforts to develop novel photocatalytic processes[5] and design new organic fluorophores,[6] we have recently turned our attention to *s*-tetrazines (1,2,4,5-tetrazines **2**, Scheme 1). These electroactive heterocycles show high electron affinity and can be reversibly reduced into their anion-radical counterpart. Their reduction potential can be tuned by the nature of the aromatic substituents. In addition, we[6] and others [7] have demonstrated that appropriately substituted tetrazines absorb visible light while displaying long fluorescence lifetimes and high quantum yields. Despite this attractive profile, as far as we are aware, only 3,6-di(pyridin-2-yl)-1,2,4,5-tetrazine **1** has been employed as a photocatalyst by Biswas et *al.* (Scheme 1, b).[8] However, the imposed structure of this

Scheme 1. Selected photocatalysts. Oxidative C-S bond functionalizations

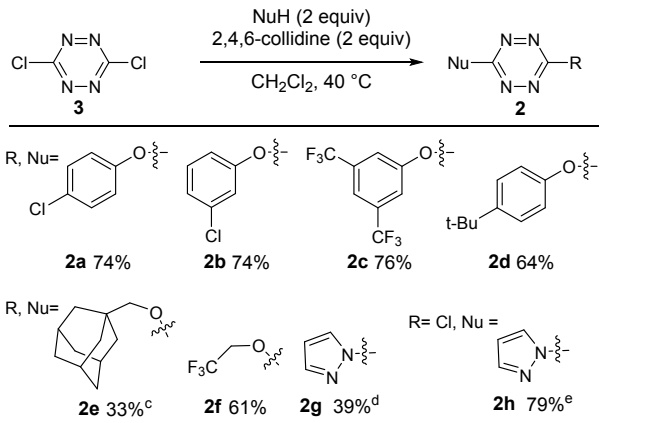


compound only offers a poor modularity of its photoredox performances. Since 3,6-dialkoxy and 3,6-diaryloxy tetrazines **2** exhibit significantly improved fluorescence quantum yields compared to **1**,[6c,6f] we have assumed that this general scaffold could be the starting point to design original, cheap and highly efficient photocatalysts. Herein is reported a comparative study accounting for the ability of various 3,6- dialkoxy and 3,6-diaryloxy tetrazines **2** to catalyze the C-S bonds cleavage of α-carbamoylsulfides under visible-light irradiation (Scheme 1, c). In addition, to their synthesis, their electrochemical and spectroscopic properties were investigated and compared to tetrazine **1**. Following this studies, we found that an active photocatalyst can be formed *in situ* from commercially available 3,6-dichlorotetrazine, improving the practical aspect of using tetrazines as photocatalysts.

RESULTS AND DISCUSSION

The study started with the synthesis of several substituted *s*-tetrazines **2**, easily prepared by a single nucleophilic aromatic substitution step between commercially available 3,6-dichlorotetrazine **3** and various nucleophiles (such as alcohols and pyrazole, Scheme 2).[6] Etherification process was efficiently conducted in the presence of 2,4,6-collidine with phenols and aliphatic alcohols, then affording tetrazines **2a-d** with moderate to good yields. Sterically demanding adamantan-1-ylmethanol gave only mono-substituted product and the addition of DMAP was required to promote the second substitution and deliver **2e** with 33% yield. The synthesis of 3,6-di(1H-pyrazol-1-yl)-tetrazine **2g** can be achieved by refluxing pyrazole and **3** in CH_3CN.

Scheme 2. Synthesis of 3,6-dialkoxy-tetrazines from 3,6-dichloro 1,2,4,5-tetrazine 3



[a] Reaction conditions: **3** (1.6 mmol), NuH (3.2 mmol), collidine (3.2 mmol) in CH_2Cl_2 (20 mL) at reflux. [b] Isolated yields. [c] **3** (1.6 mmol), NuH (3.2 mmol), collidine (1.6 mmol, 1 equiv.) in CH_2Cl_2 (20 mL) at reflux followed by addition of DMAP (3.2 mmol). [d] with CH_3CN as solvent. [e] (1.6 mmol), NuH (1.6 mmol,), collidine (1.6 mmol) in CH_2Cl_2 (20 mL) at reflux

The photophysical and electrochemical properties of synthesized *s*-tetrazines **2** were then recorded (Table 1). Dichloromethane solutions of tetrazines **2a** to **2g** display a strong absorption band in the UV region, corresponding to a π–π* allowed transition (See the UV-vis spectra, Figure S1 in Supporting Information). More interestingly, a less intense band was observed in the green region (520-530 nm) resulting from a mainly forbidden n-π* transition. Modifying the electronic properties of the substituents of *s*-tetrazines only had a small impact on the λ_{max} of this last band and all compounds showed decent molar extinction coefficient (>500 $cm^{-1}.L.mol^{-1}$). Irradiation of **2** in the green region produces fluorescence emission between 549 and 577 nm (recorded in dichloromethane) with high

fluorescence quantum yields (See the fluorescence spectra, Figure S2 in Supporting Information).

Table 1. Photophysical data for tetrazines 2a to 2h and 3 in CH_2Cl_2.

entry	Pcat **2**	λ_{abs} nm	ε	λ_{em} nm	ϕ_f	τ ns
1	**2a**[a]	531, 340, 232	600	577	0.14	60
2	**2b**[a]	525, 350	600	567	0.27	130
3	**2c**	528, 335, 258	640	563, 573	0.31	165
4	**2d**[a]	530, 345, 232	500	575	0.005	n.d.
5	**2e**[b]	523, 333	588	574	0.07	32
6	**2f**	520, 331, 272	680	556, 566	0.32	133
7	**2g**	520, 371, 290	600	556	0.02	8[c]
8	**2h**	517, 348, 270	420	553	0.15	94
9	**3**[d]	515, 307	460	555	0.14	58

λ_{abs} absorption wavelength. ε molar absorption coefficient ($M^{-1}.cm^{-1}$) for first λ_{abs} value, λ_{em}, emission wavelength, ϕ_f fluorescence quantum yield, measured using rhodamine 6G in EtOH as a reference (ϕ_{f_ref} =0.95), τ fluorescence lifetime. [a] Data from ref 6f. [b] Data from 6g [c]Pure at >95% contaminated by inseparable amount of **2h**. [d]Data from ref 6b

However, the presence of electron donor groups on the phenoxy moiety led to complete extinction of the fluorescence for tetrazines **2d** with no measurable quantum yield, this presumably due to an intramolecular electron-transfer from the electron-rich substituent to the tetrazine core. Similar results were observed with aliphatic alkyl groups such as the adamantyl. Interestingly, 3,6-bis-(2,2,2-trifluoroethoxy)-1,2,4,5-tetrazine (**2c**) is highly fluorescent. Excited state lifetimes were extrapolated from the rates of fluorescence decays and turned out to be long for compounds **2a-c, 2f** (60-165 ns, Figure S3, in Supporting Information). It is important to notice that commonly employed photoredox catalysts usually perform SET from their long living (up to ms) triplet excited state. However, it is established that direct photoexcitation of *s*-tetrazines does not lead to intersystem crossing (ISC) and phosphorescence is only observed in specific cases.[9] Theoretically, SET from singlet or triplet states are equally fast, only back electron transfer from the radical ionic product is faster in the case of singlet state.[10] This feature pushed us to believe that highly fluorescent *s*-tetrazines with long lifetime of excited state could emerge as unique singlet photoredox catalysts suitable for wide-range oxidations.

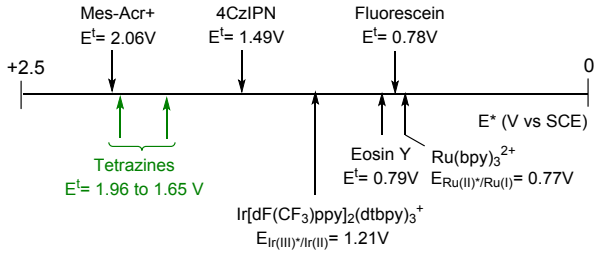
Electrochemical data for *s*-tetrazines **2a** to **2g** in dichloromethane and using ferrocene as internal reference are reported in Table 2 (See the cyclic voltammograms, Figure S4 in Supporting Information). Measured reduction potentials from –0.21V to –0.86V *vs* SCE for tetrazines **2a** to **2g** confirmed their high electron affinity as well as the opportunity to finely tune their reduction potential by modifying lateral chains. The geometry of tetrazines has been optimized using DFT/B3LYP/6-31G(d) method and their electronic properties as HOMO, LUMO levels were examined (see Figure S10 to S17 in Supporting Information). It is worth noting that a good correlation was obtained between the reduction potential determined experimentally and the LUMO level obtained from DFT calculations.[6c] An optical gap of 2.17V was then applied to calculate the reduction potential of the singlet excited state. The resulting values proved to be significantly higher than that displayed by the excited state of some benchmark photoredox catalysts such as $Ru(bpy)_3^{2+}$, eosin Y, fluorescein, 4CzIPN and similar to that of excited mesitylacridinium (E*= 2.06V *vs* SCE) (figure 1).

Table 2. Electrochemical data for tetrazines 2a to 2h and 3 in CH_2Cl_2.

entry	Pcat **2**	E^0(Tz/$Tz^{-\cdot}$ vs Fc+/Fc)[-]	E^0(Tz/$Tz^{-\cdot}$ vs SCE)	E^0(Tz*/$Tz^{-\cdot}$ vs Fc+/Fc)[-]	E^0(Tz*/$Tz^{-\cdot}$ vs SCE)
1	**2a**[a]	-0.92	-0.52	1.25	1.65
2	**2b**[a]	-0.92	-0.52	1.25	1.65
3	**2c**	-0.61	-0.21	1.56	1.96
4	**2d**[a]	-0.99	-0.59	1.18	1.58
5	**2e**[b]	-1.26	-0.86	0.91	1.31
6	**2f**	-0.98	-0.58	1.19	1.59
7	**2g**	-0.90	-0.50	1.27	1.67
8	**2h**	-0.78	-0.38	1.39	1.79
9	**3**[c]	-0.68	-0.28	1.49	1.89

E^0(Tz/$Tz^{-\cdot}$) measured in DCM with 1mM concentration of **2**, 0.1M $TBAPF_6$ and ferrocene as internal reference. [a] data from reference 6f. [b] Data from ref 6g [c] Data from ref 6c.

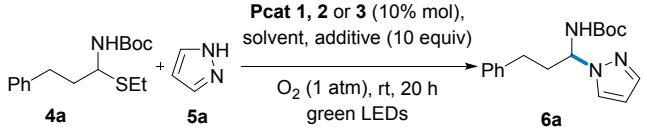
Figure 1. Electrochemical scale



In 2016, our group developed a $Ru(bpy)_3(PF)_6$-catalyzed coupling reaction of azoles with α-carbamoylsulfides through a single-electron oxidation of sulfides.[5b,c] In this studies, organic dyes such as eosin Y and 9-mesityl-10-methylacridinium provided disappointing results comparatively to $Ru(bpy)_3(PF_6)_2$. Therefore, identifying efficient organic dyes able to compete with Ru complexes in oxidative C-S bond functionalization is still highly motivating. This reaction was then selected as a model to evaluate the performances of s-tetrazine dyes **2**.[5b, c, g, 11]

Based on the singlet excited-state oxidation potentials shown in Table 2, most of *s*-tetrazines **2** should be able to oxidize the α-carbamoylsulfides (E_{ox} = +1.18 V *vs* SCE)[5c] through a SET oxidation. As a matter of fact, irradiation with green LEDs of **2a** (10 mol%) under O_2 atmosphere in CH_3CN in the presence of *tert*-butyl-(1-(ethylthio)-3-phenylpropyl)carbamate (**4a**) with pyrazole (**5a**) led to the formation of desired adduct **6a** with 33% yield after 20 h. (Table 3, entry 2). Meanwhile, tetrazine **1** was nearly unreactive under these conditions (entry 1). As speculated, dye **2b** (entry 3) with comparable photoredox properties gave a similar yield. *s*-Tetrazine **2c** (with higher quantum yield) incorporating *m*-bis-(trifluoromethyl)-group afforded **6a** with the higher yield (entry 4) while weakly fluorescent compound **2d** provided 33% yield of **6a** (entry 5). Surprisingly, better conversion was observed when using less fluorescent compound **2e** comparted to **2f** and **2g** (entry 6 *vs.* entry 7). *Bis*-pyrazole tetrazine **2g** showed also promising results as photocatalyst for the coupling reaction (entry 8). We then imagine that the addition of an acidic additive able to stabilize radical anions could improve the reaction efficiency.[5b, c, g, 11] Indeed, in the presence of 2,2,2-trifluoroethanol (TFE), **2c** and **2g** catalyze the formation of **6a** with an excellent yield of 93%

Table 3. Optimization of the oxidative C-S bond functionalization.[a]



4a **5a** **6a**

entry	Pcat	solvent	additive	yield (%)[b]
1	**1**	CH_3CN	-	trace
2	**2a**	CH_3CN	-	33
3	**2b**	CH_3CN	-	43
4	**2c**	CH_3CN	-	75
5	**2d**	CH_3CN	-	33
6	**2e**	CH_3CN	-	70
7	**2f**	CH_3CN	-	10
8	**2g**	CH_3CN	-	69
9	**2c**	CH_3CN	TFE	93
10	**2g**	CH_3CN	TFE	93
11	**3**	CH_3CN	TFE	79
12	**2h**	CH_3CN	TFE	86
13	**3**	CH_3CN	TFE	0[c]
14	**-**	CH_3CN	TFE	0[d]
15	**3**	CH_3CN	TFE	8[e]
16	4CzIPN	CH_3CN	TFE	42
17	$Ru(bpy)_3Cl_2$	CH_3CN	TFE	72
18	Mes-acr	CH_3CN	TFE	60
19	**2g**	CH_2Cl_2	TFE	25
20	**2g**	THF	TFE	trace
21	**2g**	CH_3CN	TFE	78[f]

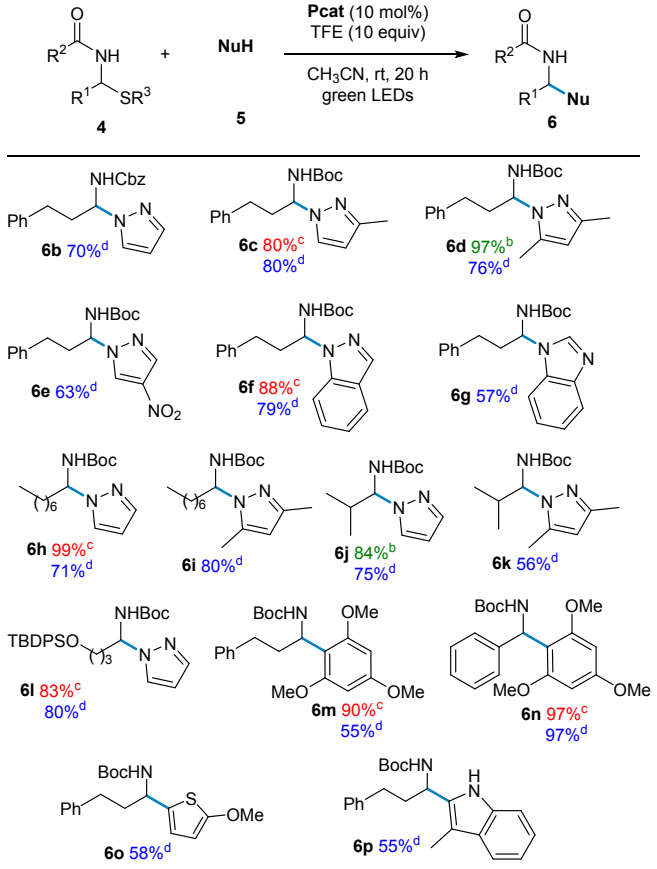
[a] General conditions: **4a** (0.10 mmol, 1 equiv.), **5a** (0.15 mmol), **2** (0.10 equiv), in CH_3CN (1 mL) irradiated with 5 W green LEDs at rt for 20 h. [b] Isolated yields. [c] Reaction performed in the dark. [d] Reaction conducted without Pcat. [e] Reaction conducted under argon atmosphere. [f] Reaction conducted with chlorocyclohexane.

(entries 9 and 10). To our delight, the use of commercially fluorescent 3,6-dichlorotetrazine **3** results in an efficient C-N bond formation (entry 11). However, a careful analysis of the reaction progress allows us to detect the *in situ* formation of 3-chloro-6-(1H-pyrazol-1-yl)-1,2,4,5-tetrazine (**2h**), resulting from a nucleophilic mono-substitution by pyrazole. We then synthesized this compound (See Supporting Information) and demonstrated it was the active catalytic species when the reaction was conducted with **3** (entry 12). As a confirmation, compound **2h** displayed similar photophysical properties (excited-state lifetime, absorption spectral features and fluorescence, Table 1) to **2c** while with a lower oxidation potential (Table 2). Other solvents and additives have been tested in combination with **3** without any significant improvement of the yields was observed (See Supporting information). Under these conditions, catalyst 4CzIPN, $Ru(bpy)_3Cl_2$ and 9-mesityl-10-methylacridinium tetrafluoroborate (Mes-acr)

afforded the adduct **6a** in lower yields (entries 16-18) thus clearly demonstrating the superiority of tetrazines over other photocatalysts in C-S bond functionalization (entry 16, Table 3). We also briefly screened other solvents for the process. However, the yield was substantially decreased when the reaction was conducted in CH_2Cl_2, or THF instead of CH_3CN (entries 19 and 20).

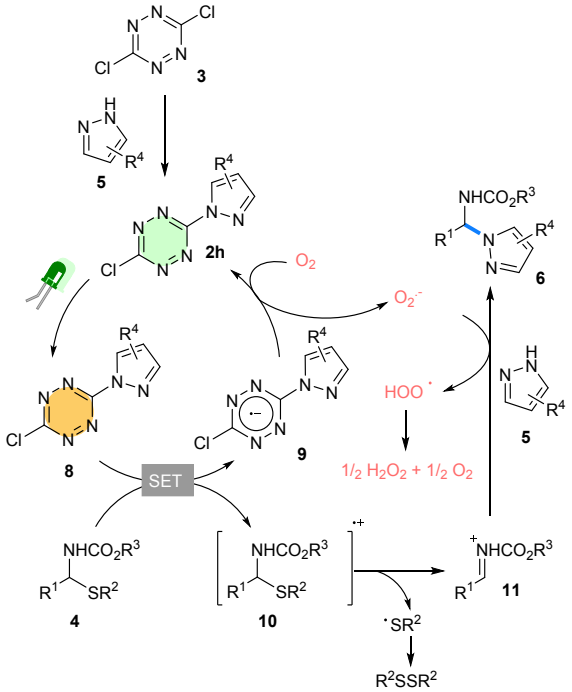
With the optimized reaction conditions, the scope of the photo-catalyzed oxidative C-S bond functionalization was next investigated (Scheme 3). In order to propose a turnkey process, the reaction scope was first explored by using the commercially available pre-catalyst **3**. Electron-rich and poor pyrazoles, as well as benzopyrazole and benzoimidazole are effective reaction partners since they afford the corresponding coupling products **6b-g** in moderate to good yields. In addition, α-carbamoyl sulfides bearing either linear and branched alkyl chains or silyl ethers reacted smoothly to deliver 56 to 80% of the desired adducts **6h-6l**. As expected, tetrazines **2c** and **2g** efficiently catalyze the C-N bond formation (**6c**, **6d**, **6f**, **6h**, **6j**, **6h** and **6l**). To our delight, when 1 equiv of chlorocyclohexane was added in the reaction of **4a** and **5a**, the desired coupling product was exclusively formed in similar yield, showing thus satisfactory tolerance with halogen groups (Table 3, entry 21).[12] The reaction of C-C bonds is also promoted by tetrazines **2g** and **3** when trimethoxybenzene was used instead of pyrazole (**6m**). Surprisingly, nearly no product **6m** was observed when using **2c** as a catalyst. To our delight, the photocatalytic aza-Friedel-Craft reaction can be applied to aromatic and aliphatic α-amidosulfides (**6n** and **6p**). Finally, thiophene and indole readily participate in nucleophilic addition giving rise, respectively, to **6o** and **6p** in descent yield. The model reaction could also be scaled-up to 1 mmol scale giving 89% of desired compound **6a** showing that tetrazine photocatalysis could be a very inexpensive way to perform photoredox reaction on large scale (see Supporting information).

Scheme 3 Scope of the reaction for oxidative C-S bond functionalization[a]



[a] Reaction conditions: **4** (0.10 mmol), **5** (0.15 mmol), **Pcat** (10 mol%), in CH_3CN (1 mL) irradiated with 5 W green LEDs at rt for 20h. [b] Isolated yields with **2c**. [c] Isolated yields with **2g**. [d] Isolated yields with **3**.

Scheme 4. Suggested reaction mechanism for electron rich substrates



In view to clarify the reaction mechanism, control experiments were conducted. They have pointed out that the reaction does not proceed in the absence of light (Table 3, entry 13) or photocatalyst (entry 14) while working under an oxygen atmosphere is essential to regenerate the ground state catalyst (entry 15). Stern-Volmer

fluorescence quenching experiments (see Figure S5 and S6 in Supporting Information) established that α-carbamoylsulfides is the fluorescence quencher for the excited state of s-tetrazine dye **2h**.

Based on our previous studies and the above results,[5b,c] a possible reaction mechanism is proposed in Scheme 4.[1] Upon irradiation, *s*-tetrazine **2h** *in situ* generated from **3**, is excited to its singlet state **8** and reductively quenched by α-carbamoylsulfides **4** to generate tetrazine radical anion **9** and sulfur radical cation **10** *via* single electron transfer (SET) oxidation. Subsequent C-S bond cleavage affords *N*-carbamoyl iminium **11** and thiyl radical **12** which dimerizes fast (isolation of disulfide supports the mechanism, See Figure S7 in Supporting Information). Meanwhile, photocatalyst **2h** is regenerated by the reduction of oxygen to superoxide radical anion ($O_2^{\bullet-}$). Nucleophilic addition of pyrazole **5** and deprotonation by $O_2^{\bullet-}$[13] ultimately afford the desired product **6**. To confirm the formation of $O_2^{\bullet-}$, the reactions between **4** and **5** were conducted in the presence of *p*-benzoquinone (*p*-BQ), as a superoxide scavenger.[14] Coupling product **6a** was obtained in only 20% yield (see Figure S8 in Supporting Information), indicating that the formation of a superoxide radical is crucial step in this photocatalyzed process. A control experiment using iodine-starch indicator (see Figure S9 in Supporting Information),[15] highlighted the presence of H_2O_2 (see Scheme 4) at the end of the reaction probably generated by disproportionation of hydroperoxyl radical ($HO_2^{\bullet}$). "

CONCLUSION

In conclusion, we have designed and prepared new s-tetrazine dyes displaying high oxidative ability. These compounds are among the smallest photoredox catalysts reported in the literature and can be generated *in situ* from commercially available compounds. Moreover, their redox properties can be tuned by modifying the substitution patterns. These advantages make them easy to handle and quickly accessible. Their efficiency has been demonstrated in a model C-S bond functionalization where they competed efficiently with benchmark catalysts like $Ru(bpy)_3^{2+}$. Finally, we expect this work could be the starting point of an increased use of simple tetrazines to perform routine day-to-day chemical oxidations.

EXPERIMENTAL SECTION

Materials and methods. Technical grade solvents were used for quantitative flash chromatography. HPLC grade solvents purchased from Sigma-Aldrich or freshly distilled solvents were used for flash chromatography for compounds undergoing full characterization. Reaction solvents were purchased from ACROS 99.8% grade on molecular sieves. All other commercially available reagents were purchased from Acros, Aldrich, Fluka, VWR, Aplichem or Merck and used without any further purification. 3,6-dichloro-1,2,4,5-*s*-tetrazine was purchased from Sigma-Aldrich. Chromatography was performed on silica gel (60-240 mesh) unless otherwise specified. Analytical thin layer chromatography (TLC) was performed on silica gel plates (Merck $60F_{254}$) visualized either with a UV lamp (254 nm) or by using permanganate, phosphomolbdic acid or ninhydrin stain. Organic extracts were dried over anhydrous $MgSO_4$. ^1H NMR and ^{13}C NMR spectra were recorded on Bruker DPX-500, at 500 MHz (^1H value) or 125 MHz (^{13}C value) in $CDCl_3$. Spectra were referenced to residual chloroform (7.26 ppm, ^1H; 77.0 ppm, ^{13}C) or TMS. Chemical shifts are reported in ppm, multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), qt (quintet), and m (multiplet or unresolved), br (broad signal). Coupling constants, *J*, are reported in hertz (Hz). All NMR spectra were obtained at 300K unless otherwise specified. High-resolution mass spectra (HRMS) were recorded using electrospray ionization (ESI) and a time-of-flight (TOF) analyzer in positive-ion or negative-ion detection mode. Reaction were irradiated using Flexled INSPIRE LED lamp (45 LEDs, 7.2W, λ = 535 nm) at a 5cm distance and using a cooling fan to keep temperature at 25° C. Amidosulfides starting materials were synthesized according literature procedure.[16]

General Protocol for azoles coupling. To a solution of amidosulfide (0.1 mmol, 1eq) in acetonitrile (0.1M), was added suitable nucleophile (0.15 mmol, 1.5eq) and *s*-tetrazine photocatalyst (0.01 mmol, 10% Mol) followed by TFE (1 mmol, 10eq, 80ul). The reaction was flushed with O_2 (bubbling) for 5 minutes and then stirred at room temperature overnight under O_2 atmosphere. The reaction was irradiated with green leds (535 nm) for 20h. Completion of the reaction was checked by TLC. Solvents were removed *in vacuo* and the residue was purified by flash chromatography (Pet. Ether / Ethyl acetate) to give desired product.

Compounds **6a** to **6p** except **6l** were previously described in literature. Data are in accordance with literature values.[5a,b]

*tert-butyl (3-phenyl-1-(1H-pyrazol-1-yl)propyl)carbamate (**6a**)*[5b] was obtained following general protocol for azoles coupling. With **2c** 28 mg, 93%, **2g** 28 mg, 93%, **3** 24 mg, 79%, (Pet. Ether / Ethyl acetate 4:1 as eluent) $^1H\{^{13}C\}$ NMR ($CDCl_3$, 300

MHz) δ (ppm): 7.63 (s, 1H), 7.57 (s,1H), 7.31 (t, J= 7.2 Hz, 2H), 7.22 (t, J= 7.1 Hz, 1H), 7.15 (d, J= 7.6Hz, 2H), 6.26 (s, 1H), 5.84 (d, J= 9.2 Hz, 1H), 5.77 (m, 1H), 2.54-2.51 (m, 3H), 2.43-2.36 (m, 1H), 1.42 (s, 9H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75MHz) δ (ppm): 154.7, 140.3, 140.2, 130.0, 128.6 (2C), 128.5 (2C), 126.3, 104.9, 80.3, 66.4, 36.0, 31.5, 28.3 (3C).

benzyl (3-phenyl-1-(1H-pyrazol-1-yl)propyl)carbamate (**6b**)[5b] was obtained following general protocol for azoles coupling. With **3** 23 mg, 70%, (Pet. Ether / Ethyl acetate 4:1 as eluent) $^1H\{^{13}C\}$ NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.65 (s, 1H), 7.60 (s, 1H), 7.40-7.20 (m, 8H), 7.14-7.11 (m, 2H), 6.41 (d br, J = 9.2 Hz, 1H), 6.28 (s, 1H), 5.81 (t, J = 8.1 Hz, 1H), 5.16 (d, J = 12.1 Hz, 1H), 5.00 (d, J = 12.3 Hz, 1H), 2.63-2.32 (m, 4H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz) δ (ppm): 155.5, 140.4, 140.1, 136.0, 130.1, 128.6 (2C), 128.5 (2C), 128.4 (2C), 128.2, 128.1, 126.3, 126.1, 105.0, 67.1, 66.8, 35.8, 31.4.

tert-butyl (1-(3-methyl-1H-pyrazol-1-yl)-3-phenylpropyl) carbamate (**6c**) [5b] was obtained following general protocol for azoles coupling. With **2c** 25 mg, 80%, **3** 25 mg, 80%, (Pet. Ether / Ethyl acetate 4:1 as eluent) $^1H\{^{13}C\}$ NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.47-7.40 (m, 1H), 7.28-7.24 (m, 2H), 7.20-7.15 (m, 1H), 7.12-7.09 (m, 2H), 5.98-5.96 (m, 1H), 5.82-5.75 (m, 1H), 5.63-5.56 (m, 1H), 2.56-2.40 (m, 3H), 2.29 (s, 3H), 2.25 (m, 1H), 1.38 (s, 9H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz) δ (ppm): 149.5, 139.5, 130.9, 128.6 (2C), 128.5, 126.3, 104.9, 104.5, 66.3, 62.5, 36.1, 31.6, 28.4 (3C), 13.9, 10.8;

tert-butyl (1-(3,5-dimethyl-1H-pyrazol-1-yl)-3-phenylpropyl) carbamate (**6d**) [5b] was obtained following general protocol for azoles coupling. With **2c** 32 mg, 97%, **3** 25 mg, 76%, (Pet. Ether / Ethyl acetate 4:1 as eluent) $^1H\{^{13}C\}$ NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.32-7.13 (m, 5H), 6.10 (d br, J= 9.2 Hz, 1H), 5.77 (s, 1H), 5.70 (m, 1H), 2.52-2.33 (m, 4H), 2.27(s, 3H), 2.24 (s, 3H), 1.42 (s, 9H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz) δ (ppm): 154.8, 148.4, 140.7, 139.6, 128.5 (2C), 128.4 (2C), 126.1, 104.7, 79.0, 62.2, 36.4, 31.5, 28.3 (3C), 13.7, 10.7;

tert-butyl (1-(4-nitro-1H-pyrazol-1-yl)-3-phenylpropyl) carbamate (**6e**) [5b] was obtained following general protocol for azoles coupling. With **3** 22 mg, 63%, (Pet. Ether / Ethyl acetate 4:1 as eluent) $^1H\{^{13}C\}$ NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.29 (s br, 1H), 8.15 (s, 1H), 7.36-7.23 (m, 3H), 7.16-7.13 (m, 2H), 5.73-5.57 (m, 2H), 2.67-2.32 (m, 4H), 1.44 (s, 9H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz) δ (ppm):154.3, 139.3, 136.4, 135.3, 128.8 (2C), 128.3 (2C), 126.7 (2C), 81.4, 68.2, 35.1, 31.3, 28.2 (3C).

tert-butyl (1-(1H-indazol-1-yl)-3-phenylpropyl)carbamate (**6f**) [5b] was obtained following general protocol for azoles coupling. With **2g** 31 mg, 88%, **3** 28 mg, 79%, (Pet. Ether / Ethyl acetate 3:1 as eluent) $^1H\{^{13}C\}$ NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.14 (s br,1H), 7.79 (dd, J= 8.8 and 0.9 Hz, 1H), 7.72 (dt, J= 8.4 and 1.0 Hz, 1H), 7.38-7.20 (m, 4H), 7.16-7.11 (m, 3H), 6.49 (d br, J= 9.0 Hz,1H), 6.07 (m, 1H), 2.72-2.48 (m, 4H), 1.39 (s, 9H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz) δ (ppm): 154.7, 143.6, 141.3, 139.5, 132.5, 128.7(2C), 128.4 (2C), 126.6, 123.2, 122.6, 120.3, 110.8, 80.8, 62.4, 36.0,31.7, 28.2 (3C).

tert-butyl (1-(1H-benzo[d]imidazol-1-yl)-3-phenylpropyl) carbamate (**6g**)[5b] was obtained following general protocol for azoles coupling. With **2g** 21 mg, 59%, (Pet. Ether / Ethyl acetate 1:1 as eluent) **$^1H\{^{13}C\}$ NMR** ($CD_3CN + D_2O$, 500 MHz) δ (ppm): 8.08 (s, 1H), 7.73-7.56 (m, 2H), 7.36-7.16 (m, 7H), 6.56 (bs, 1H), 5.92 (q, J=7.1Hz, 1H), 2.78-2.40 (m, 4H), 1.36 (s, 9H), **$^{13}C\{^1H\}$ NMR** ($CDCl_3$, 75 MHz) δ (ppm): 154.7, 143.6,141.3, 139.5, 132.5, 128.7 (2C), 128.4 (2C), 126.6, 123.2, 122.6, 120.3, 110.8, 80.8, 62.4, 36.0, 31.7, 28.2 (3C).

tert-butyl (1-(1H-pyrazol-1-yl)octyl)carbamate (**6h**)[5b] was obtained following general protocol for azoles coupling. With **2g** 29 mg, 99%, **3** 21 mg, 71%, (Pet. Ether / Ethyl acetate 4:1 as eluent) **$^1H\{^{13}C\}$ NMR** ($CDCl_3$, 300 MHz) δ (ppm): 7.48 (s, 2H), 6.13 (s, 1H), 5.72(br s, 1H), 5.52 (br s, 1H), 2.12 (br s, 1H), 1.98 (br s, 1H), 1.33 (s, 9H), 1.28-1.08 (m, 10H), 0.78 (t, J= 6.7 Hz, 3H). **$^{13}C\{^1H\}$ NMR** ($CDCl_3$, 75 MHz) δ (ppm): 154.8, 140.0, 129.6, 104.7, 80.2, 67.2, 34.7, 31.6, 29.1, 29.0, 29.0, 28.3 (×3), 25.3, 22.5, 14.0;

tert-butyl (1-(3,5-dimethyl-1H-pyrazol-1-yl)octyl) carbamate (**6i**)[5b] was obtained following general protocol for azoles coupling. With **3** 26 mg, 80%, (Pet. Ether / Ethyl acetate 4:1 as eluent) **$^1H\{^{13}C\}$ NMR** ($CDCl_3$, 300MHz) δ (ppm): 5.74 (s, 1H), 5.71-5.59 (m, 2H), 2.35 (s, 3H), 2.23(s, 3H), 2.16-1.88 (m, 2H), 1.41 (s, 9H), 1.34-0.99 (m, 10H), 0.87 (t, J= 6.7 Hz, 3H). **$^{13}C\{\{^1H\}$ NMR** ($CDCl_3$, 75 MHz) δ (ppm): 154.8,148.2, 134.4, 104.4, 79.8, 62.8, 35.3, 31.6, 29.0, 28.7, 28.2 (3C), 25.2, 22.5, 13.9, 13.6, 10.7;

tert-butyl (2-methyl-1-(1H-pyrazol-1-yl)propyl) carbamate (**6j**)[5b] was obtained following general protocol for azoles coupling. With **2c** 20 mg, 84%, **3** 18 mg, 75%, (Pet. Ether / Ethyl acetate 4:1 as eluent) $^1H\{^{13}C\}$ NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.55 (s, 1H),7.51 (s, 1H), 6.21 (s, 1H), 5.52 (d, J= 7.7 Hz, 1H), 5.37 (t, J= 9.0 Hz,1H), 2.38 (h, J= 6.5 Hz, 1H), 1.40 (s, 9H), 1.06 (d, J= 6.6 Hz, 3H), 0.70 (d, J= 6.6 Hz, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz)

δ (ppm): 155.2, 140.0, 130.0, 104.4, 80.1, 72.8, 33.1, 28.2 (3C), 18.8, 18.6.

tert-butyl (1-(3,5-dimethyl-1H-pyrazol-1-yl)-2-methyl propyl)carbamate (**6k**)[5b] was obtained following general protocol for azoles coupling. With 15 mg, 56%, (Pet. Ether / Ethyl acetate 4:1 as eluent). $^{1}H\{^{13}C\}$ NMR ($CDCl_3$, 300 MHz) δ (ppm): 5.73 (s, 1H), 5.70 (s, 1H), 5.27 (t, J= 9.9 Hz, 1H), 2.42-2.26 (m, 4H), 2.22 (s, 3H), 1.40 (s, 9H), 1.08 (d, J= 6.6 Hz, 3H), 0.64 (d, J= 6.6 Hz, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 75 MHz) δ (ppm): 155.3, 148.3, 139.8, 104.4, 79.9, 68.6, 33.9, 28.4 (3C), 19.2, 18.7, 13.8, 11.0.

tert-butyl (4-((tert-butyldiphenylsilyl)oxy)-1-(1H-pyrazol-1-yl)butyl)carbamate (**6l**) was obtained following general protocol for azoles coupling. Colorless oil. With **2g** 41 mg, 83%, **3** 39 mg, 80%, (Pet. Ether / Ethyl acetate 4:1 as eluent) $^{1}H\{^{13}C\}$ NMR ($CDCl_3$, 300 MHz) δ (ppm) : 7.74-7.18 (m, 12H), 6.11 (t, J= 1.8Hz, 1H), 5.79-5.40 (m, 2H), 3.55 (t, J= 6.2Hz, 2H), 2.25-1.91 (m, 2H), 1.46-1.19 (m + s, 2H + 9H), 0.96 (s, 9H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 75 MHz) δ (ppm): 154.7, 139.9, 135.5 (4C), 133.7, 129.6 (4C), 129.5, 127.7 (4C), 104.7, 80.2, 67.1, 63.0, 31.3, 28.3 (3C), 26.8 (3C), 19.2. IR (neat) cm^{-1} : 3217, 2947, 2858, 1697, 1532, 1366, 1268, 1254, 1109, 734; HRMS (ESI-TOF) anal. for $C_{28}H_{39}N_3O_3SiNa$ [M+Na] calc : 516.2653 found : 516.2663

tert-butyl (3-phenyl-1-(2,4,6-trimethoxyphenyl)propyl) carbamate (**6m**)[5c] was obtained following general protocol for azoles coupling. With **2g** 36 mg, 90%, (Pet. Ether / Ethyl acetate 4:1 as eluent) $^{1}H\{^{13}C\}$ NMR ($CDCl_3$, 300 MHz,) δ (ppm) 7.28-7.16 (m, 5H), 6.15 (s, 2H), 5.86 (br. d, J= 10.2 Hz, 1H), 5.43 (dd, 1H, J= 9.9 and 15.3 Hz), 3.84 (s, 3H), 3.83 (s, 6H), 2.75-2.65 (m, 1H), 2.53-2.43 (m, 1H), 2.19-1.92 (m, 2H), 1.46 (s, 9H). $^{13}C\{^{1}H\}$ NMR (CDC13, 75 MHz) δ (ppm): 160.2, 158.6, 155.5, 128.3 (3C), 128.1 (2C), 125.4 (2C), 111.0, 91.1, 91.0 (2C), 78.6, 55.8, 55.2, 45.9, 37.6, 32.9, 28.5 (3C);

tert-butyl (phenyl(2,4,6-trimethoxyphenyl)methyl) carbamate (**6n**)[5c] was obtained following general protocol for azoles coupling. With **2g** 36 mg, 97%, **3** 36 mg, 97%, (Pet. Ether / Ethyl acetate 5:1 as eluent) $^{1}H\{^{13}C\}$ NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.26-7.11 (m, 5H), 6.59 (br. d, J= 10.1 Hz, 1H), 6.25 (br. d, J= 10.2 Hz, 1H) 6.15 (s, 2H), 3.81 (s, 3H), 3.77 (s, 6H), 1.47 (s, 9H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 75 MHz) δ (ppm) 160.6, 158.6, 155.7, 127.8 (3C), 126.0 (2C), 126.0 (2C), 111.0 (3C), 91.2, 79.0, 55.9, 55.3, 48.2, 28.5 (3C).

tert-butyl (1-(5-methoxythiophen-2-yl)-3-phenylpropyl) carbamate (**6o**)[5c] was obtained following general protocol for azoles coupling. With **3** 20 mg, 58%, (Pet. Ether / Ethyl acetate 3:1 as eluent) $^{1}H\{^{13}C\}$ NMR ($CDCl_3$, 300 MHz) δ (ppm) : 7.22-7.07 (m, 5H), 6.49 (s, 1H), 5.95-5.93 (m, 1H), 4.74-4.59 (m, 2H), 3.78 (s, 3H), 2.65-2.55 (m, 2H), 2.05-1.97 (m, 2H), 1.37 (s, 9H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$,75 MHz) δ 165.4, 155.2, 141.5, 132.5, 128.6 (2C), 128.4 (2C), 126.1, 121.8, 103.1, 80.1, 60.4, 50.9, 38.5, 32.5, 28.5 (3C);

tert-butyl (1-(3-methyl-1H-indol-2-yl)-3-phenylpropyl) carbamate (**6p**)[5c] was obtained following general protocol for azoles coupling. With **3** 20 mg, 55%, (Pet. Ether / Ethyl acetate 2:1 as eluent) $^{1}H\{^{13}C\}$ NMR ($CDCl_3$, 300 MHz) δ (ppm) 8.46 (s, 1H, NHindole), 7.47 (d, J = 7.7Hz, 1H), 7.26-7.01 (m, 8H), 4.97 (br. s, 1H) 4.71-4.64 (m, 1H,), 2.65-2.48 (m, 2H), 2.36-2.12 (m, 2H), 2.19 (s, 3H), 1.37 (s, 9H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 75 MHz) δ (ppm) 156.0, 141.2, 135.5, 134.7, 129.1, 128.6 (2C), 128.5 (2C), 126.2, 121.9, 119.2, 118.7, 110.9, 107.8, 80.2, 48.0, 32.7, 28.5 (3C), 28.1, 8.8.

Synthesis and data for *s*-tetrazines 2c and 2e to 2h

s-tetrazines **2a**, **2b**, **2d** were prepared according reported procedures.[6f]

Procedure A: To a solution of 3,6-dichlorotetrazine (1.0 equiv) in anhydrous CH_2Cl_2 (8 x 10^{-2} M) were added a phenol derivative (2 equiv), then 2,4,6-collidine (2 equiv). The resulting mixture was then stirred and heated under reflux until complete conversion (monitored by TLC). The solvent was then removed under reduce pressure and the residue was purified by silica gel flask chromatography (CH_2Cl_2 /AcOEt or petroleum ether/CH_2Cl_2 gradient). In some cases, the desired product as a precipitate was filtered, washed with cold dichloromethane and used without further purification.

Procedure B: To a solution of 3,6-dichlorotetrazine (1.0 equiv) in anhydrous CH_2Cl_2 (8 x 10^{-2} M) were added a phenol derivative (2 equiv), then 2,4,6-collidine (1 equiv). The resulting mixture was then stirred and heated under reflux until complete conversion into monosubstituted product (monitored by TLC). DMAP (1 equiv) was added and the reaction was kept running for 1 hours. The solvent was then removed under reduce pressure and the residue was purified by silica gel flash chromatography (CH_2Cl_2 /AcOEt or petroleum ether/CH_2Cl_2 gradient).

3,6-bis(4-chlorophenoxy)-1,2,4,5-tetrazine (**2a**)[6f] Pink solid (397 mg, 74% yield). Reported (287 mg, 52% yield). $^{1}H\{^{13}C\}$ NMR (300 MHz, $CDCl_3$) δ (ppm): 7.43 (d, J = 8.9 Hz, 4H), 7.22 (d, J = 8.9 Hz, 4H); Mp: 165-166° C.

3,6-bis(3-chlorophenoxy)-1,2,4,5-tetrazine (**2b**)[6f] Pink solid (397 mg, 74% yield). Reported (110 mg, 33% yield). $^{1}H\{^{13}C\}$ NMR (300 MHz, $CDCl_3$) δ (ppm): 7.44 (t, J = 8.0 Hz, 2H), 7.37-7.31 (m, 4H), 7.20-7.18 (d, J = 8.0 Hz, 2H); Mp:128-130° C.

3,6-bis(3,5-bis(trifluoromethyl)phenoxy)-1,2,4,5-tetrazine (2c) Prepared according to general procedure **A** in 4 hours from 3,6-dichlorotetrazine (242 mg, 1.6 mmol), 3,5-bis(trifluoromethyl)phenol (0.6 mL, 3.2 mmol) and 2,4,6-collidine (0.4 mL, 3.2 mmol) in CH_2Cl_2 (20 mL). no purification needed. Pink solid (655 mg, 76% yield). $^1H\{^{13}C\}$ NMR (300 MHz, CD_3CN) δ (ppm): 8.02 (s, 2H), 7.98 (s, 4H); ^{19}F NMR (282 MHz, CD_3CN) δ (ppm): -63.54; $^{13}C\{^1H\}$ NMR (75 MHz, CD_3CN) δ (ppm): 167.0 (2C), 152.9 (2C), 132.9 (4C), 122.0 (4C), 120.2 (4C), 117.0 (2C); IR (neat) ν (cm^{-1}): 3055, 1406, 1347, 1264, 1174, 1133, 956, 902, 847, 732, 702; Mp: 215-217° C. HRMS (ESI-TOF) m/z: $[M+Cl]^-$ Calcd for $C_{18}H_6F_{12}N_4O_2Cl^-$ 572,9988; Found 572.9983

3,6-bis(4-(tert-butyl)phenoxy)-1,2,4,5-tetrazine (2d) [6f] Pink solid (387 mg, 64% yield). Reported (403 mg, 93% yield). $^1H\{^{13}C\}$ NMR (500 MHz, DMSO-d6) δ (ppm): 7.51 (d, J = 8.7 Hz, 4H), 7.29 (d, J = 8.7 Hz, 4H), 1.32 (s, 18H); Mp: 267-269° C;

3,6-bis(((1s,3s)-adamantan-1-yl)methoxy)-1,2,4,5-tetrazine (2e) Prepared according to general procedure **B** under reflux from 3,6-dichlorotetrazine (242 mg, 1.6 mmol), 1-adamantanemethanol (531 mg, 3.2 mmol), 2,4,6-collidine (0.2 mL, 1.6 mmol) and DMAP (195 mg, 1.6 mmol) in CH_2Cl_2 (20 mL). (CH_2Cl_2 / Ethyl acetate 99/1 to 1/1 as eluent) Pink solid (216 mg, 33% yield). $^1H\{^{13}C\}$ NMR (300 MHz, $CDCl_3$) δ (ppm): 4.12 (s, 4H), 2.04 (m, 6H), 1.79-1.69 (m, 24H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ (ppm): 166.4 (2C), 79.4 (2C), 39.1 (6C), 36.9 (6C), 33.7 (2C), 28.0 (6C); IR (neat) ν (cm^{-1}): 3676, 2988, 2902, 1451, 1407, 1394, 1242, 1230, 1075, 1066, 1057, 892, 880; Mp: 175-176° C. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{24}H_{35}N_4O_2^+$ 411.2760; Found 411.2752.

3,6-bis(2,2,2-trifluoroethoxy)-1,2,4,5-tetrazine (2f) Prepared according to general procedure **A** under reflux from 3,6-dichlorotetrazine (242 mg, 1.6 mmol), TFE (0.5 mL, 6 mmol), 2,4,6-collidine (0.4 mL, 3.2 mmol) in CH_2Cl_2 (20 mL) collection by filtration no purification needed. Pink solid (271 mg, 61% yield). $^1H\{^{13}C\}$ NMR (300 MHz, $CDCl_3$) δ (ppm): 5.01 (q, J = 7.9 Hz, 2H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ (ppm): 166.7, 122.4 (q, J = 277.6 Hz, CF_3), 65.1 (q, J = 37.7 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm): -73.8; IR (neat) ν (cm^{-1}): 3676, 2988, 2902, 1406, 1394, 1250, 1230, 1075,1066, 892, 879; Mp: 80-82° C. HRMS (ESI-TOF) m/z: $[M-CF_3]^+$ Calcd for $C_5H_4F_3N_4O_2^+$ 209.0286; Found 209.295

3,6-di(1H-pyrazol-1-yl)-1,2,4,5-tetrazine (2g) To a solution of 3,6-dichlorotetrazine (150 mg, 1 mmol) in acetonitrile 10 mL, was added pyrazole (136 mg, 2 mmol) The reaction was heated to reflux for 2h. Reaction was cooled to 0° C and the orange-pink precipitate was collected by filtration and washed with cold acetonitrile. The solid was purified by chromatography over silica gel (CH_2Cl_2 / Ethyl acetate 99/1 to 1/1) to give pure product as an orange solid (102 mg, 48% yield, 97% purity with 3% of 2h). $^1H\{^{13}C\}$ NMR (300 MHz, $CDCl_3$) δ (ppm) : 8.75 (m, 2H), 8.06 (m, 2H), 6.71 (m, 2H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ (ppm); 158.8 (2C), 146.1 (2C), 129.6 (2C), 110.1 (2C). IR (neat) ν (cm^{-1}): 3676, 3146, 2988, 1524, 1475, 1397, 1255, 1185, 1165, 1075, 1027, 953, 918, 888, 773; Mp: 256-259° C. HRMS (ESI-TOF) m/z: $[M+CH_3CN+Na]^+$ m/z: $[M+H]^+$ Calcd for $C_8H_7N_8^+$ 215.0794; Found 215.0794.

3-chloro-6-(1H-pyrazol-1-yl)-1,2,4,5-tetrazine (2h) To a solution of 3,6-dichlorotetrazine (150 mg, 1 mmol) in acetonitrile 10 mL, was added pyrazole (68 mg, 1 mmol). The reaction was stirred at reflux for 1h. Solvents were removed *in vacuo* and the resulting solid was purified by chromatography over silica gel (CH_2Cl_2 / Ethyl acetate 99/1 to 2/1) to give pure product as an orange solid (73 mg, 40% yield). $^1H\{^{13}C\}$ NMR (300 MHz, $CDCl_3$) δ (ppm) : 8.70-8.69 (m, 2H), 8.05-8.04 (m, 2H), 6.72-6.70 (m, 2H) ; $^{13}C\{^1H\}$ NMR (75 MHz, CD_3CN) δ (ppm) ; 166.4, 146.0, 130.0, 117.0, 110.7; IR (neat) ν (cm^{-1}) : 3676, 3152, 2988, 2901, 1532, 1499, 1478, 1393, 1259, 1210, 1066, 922, 781 ; Mp : 117-119° C HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_5H_4ClN_6^+$ 183.0186; Found 183.0172.

ASSOCIATED CONTENT

The Supporting Information is available free of charge via the Internet at http://pubs.acs.org. Control experiments, Electrochemical Data, UV-Vis data, DFT Calculation and ^1H, ^{13}C NMR data.

AUTHOR INFORMATION

Corresponding Author

* clemence.allain@ens-paris-saclay.fr

* geraldine.masson@cnrs.fr

§ T.L and T.C contributed equally to this work.

ACKNOWLEDGMENT

We thank ICSN for funding. T.C and J.M thanks the Labex Charm3at for postdoctoral fellowships and T.L thanks for a financial support of Master. P.A thanks the Institut Universitaire de France for personal and financial support. This work was granted access to the computing resources of CINES (Montpellier, allocation A0050810547 awarded by GENCI). We thank Arnaud Brosseau (PPSM) for his help with the fluorescence lifetime measurements.

REFERENCES

(1) For selected recent reviews on photoredox catalysis, see: (a) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. Visible Light Photoredox Catalysis with Transition Metal Complexes: Applications in Organic Synthesis. *Chem. Rev.* **2013**, *113*, 5322. (b) Schultz, D. M.; Yoon, T. P. Solar Synthesis: Prospects in visible light Photocatalysis *Science* **2014**, *343*, 1239176. (c) Kärkäs, M. D.; Matsuura, B. S.; Stephenson, C. R. J. Enchained by Visible Light-Mediated Photoredox Catalysis *Science*, **2015**, *349*, 1285. (d) Shaw, M. H.; Twilton, J.; MacMillan, D. W. C. Photoredox Catalysis in Organic Chemistry. *J. Org. Chem.* **2016**, *81*, 6898. (e) Courant, T.; Masson, G. Recent Progress in Visible-Light Photoredox-Catalyzed Intermolecular 1,2-Difunctionalization of Double Bonds via an ATRA-Type Mechanism *J. Org. Chem.* **2016**, *81*, 6945. (f) Skubi, K. L.; Blum, T. R.; Yoon, T. P. Dual catalysis Strategies in Photochemical Synthesis *Chem. Rev.* **2016**, *116*, 10035. (g) Ravelli, D.; Protti, S.; Fagnoni, M. Carbon-Carbon Bond Forming Reactions via Photogenerated *Chem. Rev.* **2016**, *116*, 9850. (h) Marzo, L.; Pagire, S.K.; Reiser, O.; Konig, B.; Visible-Light Photocatalysis: Does it Make a Difference in Organic Synthesis *Angew. Chem. Int. Ed.* **2018**, *57*, 10034.

(2) (a) Juris, A.; Balzani, V.; Barigelletti, F.; Campagna, S.; Belser, P.; von Zelewsky, A. Ru(II) Polypyridine Complexes: Photophysics, Photochemistry, Electrochemistry, and Chemiluminescence. *Coord. Chem. Rev.* **1988**, *84,* 85. (b) Tucker, J. W.; Stephenson, C. R. J. Shining Light on Photoredox Catalysis: Theory and Synthetic Applications. *J. Org. Chem.* **2012**, *77*, 1617. (c) Teegardin, K.; Day, J. I.; Chan, J.; Weaver, J. Advances in Photocatalysis: A Microreview of Visible Light Mediated Ruthenium and Iridium Catalyzed Organic Transformations. *Org. Process Res. Dev.* **2016**, *20*, 1156. (d) Blakemore, J. D.; Crabtree; R. H.; Brudvig, G. W. Molecular Catalysts for Water Oxidation. *Chem. Rev.* **2015**, *115*, 12974.

(3) For selected reviews, see: (a) Ravelli, D.; Fagnoni, M.; Albini, A. Photoorganocatalysis. What For? *Chem. Soc. Rev.* **2013**, *42*, 97. (b) Nicewicz, D.A. and Nguyen, T.M. Recent Applications of Organic Dyes as Photoredox Catalysts in Organic Synthesis. ACS Catal., **2014,** *4*, 355. (c) Romero, N. A.; Nicewicz, D. A. Organic Photoredox Catalysis *Chem. Rev.* **2016**, 116, 10075. (d) Ghosh, I.; Marzo, L.; Das, A.; Shaikh, R.; König, B. Visible Light Mediated Photoredox Catalytic Arylation Reactions *Acc. Chem. Res.* **2016**, *49*, 1566. (e). Pitre, S. P.; McTiernan, C. D.; Scaiano, J. C. Library of Cationic Organic Dyes for Visible-Light-Driven Photoredox Transformations *ACS Omega* **2016**, *1*, 66. (f) Zeitler, K. Metal-free Photo(redox) Catalysis. In Visible Light Photocatalysis in Organic Chemistry; Stephenson, C. R. J., Yoon, T. P., MacMillan, D. W. C., Eds.; Wiley-VCH: Weinheim, 2018. (g) Sideri, I. K.; Voutyritsa, E.; Kokotos, C. G. Photoorganocatalysis, Small Organic Molecules and Light in the Service of Organic Synthesis: the Awakening of a Sleeping Giant *Org. Biomol. Chem.* **2018,** *16*, 4596. (h) Ray, S.; Samanta, P. K.; Biswas, P. Recent Developments on Visible‐Light Photoredox Catalysis by Organic Dyes for Organic Synthesis. In Visible Light‐Active Photocatalysis: Nanostructured Catalyst Design, Mechanisms, and Applications; Ghosh, S., Ed.; Wiley-VCH: Weinheim, 2018.

(4) Selected examples: (a) Fukuzumi, S.; Ohkubo, K. Organic Synthetic Transformations Using Organic Dyes as Photoredox Catalysts *Org. Biomol. Chem.* **2014**, *12*, 6059. (b) Nicewicz, D. A.; Nguyen, T. M. Recent Applications of Organic Dyes as PhotoRedox Catalysts in Organic Synthesis *ACS Catal.* **2014**, *4*, 355. (c) Yang, C.; Yang, J. D.; Li, Y. H.; Li, X.; Cheng, J. P. 9,10-Dicyanoanthracene Catalyzed Decarboxylative Alkynylation of Carboxylic Acids under Visible-Light Irradiation *J. Org. Chem.* **2016**, *81*, 12357. (d) Joshi-Pangu, A.; Roth, H. G.; Oliver, S. F.; Campeau, L.-C.; Nicewicz, D. A.; DiRocco, D. A. Acridinium-Based Photocatalysts: A Sustainable Option in Photoredox Catalysis. *J. Org. Chem.* **2016**, *81*, 7244. (e) Le Vaillant, F.; Garreau, M.; Nicolai, S.; Gryn'ova, G.; Corminboeuf, C.; Waser, J. Fine-Tuned Organic Photoredox Catalysts for Fragmentation-Alkynylation Cascades of Cyclic Oxime Ethers, *Chem. Sci.* **2018**, *9*, 5883. (f) Speckmeier, E.; Fischer, T.; Zeitler, K. *J.* A Toolbox Approach to Construct Broadly Applicable Metal-Free Catalysts for Photoredox Chemistry – Deliberate Tuning of Redox Potentials and Importance of Halogens in Donor-Acceptor Cyanoarenes *J. Am. Chem. Soc.* **2018**, 140, 15353.

(5) (a) Courant, T.; Masson, G. Photoredox Initiated α-Alkylation of Imines via a Three-Component Radical/Cationic Reaction *Chem. Eur. J.* **2012**, *18*, 423. (b) Jarrige, L.; Levitre, G.; Masson, G. Visible-Light Photoredox-Catalyzed Coupling Reaction of Azoles with α-Carbamoyl Sulfides. *J. Org. Chem.* **2016**, *81*, 7230. (c) Lebée, C.; Languet, M.; Allain, C.; Masson, G. α-Carbamoylsulfides as N-Carbamoylimine Precursors in the Visible Light Photoredox-Catalyzed Synthesis of α,α-Disubstituted Amines. *Org. Lett.* **2016**, *18*, 1478. (d) Lanzi, M.; Merad, J.; Boyarskaya, D.V., Maestri, G.; Allain, C.; Masson, G. Visible Light-Triggered C-C and C-N Bonds Formation by C-S Bonds Cleavage of Benzylic Thioethers *Org. Lett.* **2018**, *20*, 5247.

(6) For a review, see: (a) Clavier, G.; Audebert, P. s-Tetrazines as Building Blocks for New

Functional Molecules and Molecular Materials. *Chem. Rev.* **2010**, 110, 3299. For selected examples, see (b) Audebert, P.; Miomandre, F.; Clavier, G.; Vernieres, M. C.; Badré, S.; Meallet-Renault, R. Synthesis and Properties of New Tetrazines Substituted by Heteroatoms: Towards the World's Smallest Organic Fluorophores. *Chem. – Eur. J.* **2005**, 11, 5667. (c) Gong, Y. H.; Miomandre, F.; Meallet-Renault, R.; Badre, S.; Galmiche, L.; Tang, J.; Audebert, P.; Clavier, G., Synthesis and Physical Chemistry of s-Tetrazines: Which Ones are Fluorescent and Why? *Eur. J. Org. Chem.* **2009**, 6121. (d) Jullien-Macchi, E.; Allain, C.; Alain-Rizzo, V.; Dumas-Verdes, C.; Galmiche, L.; Audibert, J.-F.; Berhe Desta, M.; Pansu, R. B.; Audebert, P. New Highly Electrodeficient Cationic Fluorescent Tetrazines: a Step Toward the Strongest Purely Organic Photooxidants. *New J. Chem.* **2014**, *38*, 3401.. (e) Qing, Z.; Audebert, P.; Clavier, G.; Miomandre, F.; Tang, J.; Vu, T. T.; Méallet-Renault, R. Tetrazines with Hindered or Electron Withdrawing Substituents: Synthesis, Electrochemical and Fluorescence Properties, *J. Electroanal. Chem.* **2009**, *632*, 39.

(7) (a) Gückel, F.; Maki, A. H.; Neugebauer, F. A.; Schweitzer, D.; Vogler, H., Spectroscopic Investigations of the Lowest Triplet-State of s-Tetrazines. *Chem. Phys.* **1992,** *164*, 217. (b) Myers, T. W. ; Snyder, C. J.; Chavez, D. E.; Scharff, R. J.; Veauthier, J. M.: Synthesis and Electrochemical Behavior of Electron-Rich s-Tetrazine and Triazolo-tetrazine Nitrate Esters, *Chem. Eur. J.* **2016**, *22*, 10590. (c) Chavez, D. E. ; Parrish, D. A.; Mitchell, L.: Energetic Trinitro- and Fluorodinitroethyl Ethers of 1,2,4,5-Tetrazines *Angew. Chem. Int. Ed.* **2016**, *55*, 8666.

(8) (a) Samanta, S.; Das, S. Biswas, P. Photocatalysis by 3,6-Disubstituted-s-Tetrazine: Visible-Light Driven Metal-Free Green Synthesis of 2-Substituted Benzimidazole and Benzothiazole *J. Org. Chem.* **2013**, *78,* 11184. (b) Samanta, S.; Biswas, P. Metal Free Visible Light Driven Oxidation of Alcohols to Carbonyl Derivatives Using 3,6-Di(pyridin-2-yl)-1,2,4,5-tetrazine (pytz) as catalyst *RSC Adv.* **2015**, *5*, 84328. (c) Samanta, S.; Ray, S.; Ghosh, A. B.; Biswas, P. 3,6-Di(pyridin-2-yl)-1,2,4,5-tetrazine (pytz) Mediated Metal-Free Mild Oxidation of Thiols to Disulfides in Aqueous Medium *RSC Adv.* **2016**, *6,* 39356.

(9) (a) Chowdhury, M.; Goodman, L. Nature of s-Tetrazine Emission Spectra, *J. Chem. Phys.* **1963**, *38*, 2979. (b) Ågren, H.; Vahtras, O.; Knuts, S. Jørgensen, P. Radiative Lifetimes of Triplet Spin Sublevels of the Azabenzenes, J. *Chem. Phys.* **1994**, *181*, 291

(10) (a) Yasunao, K.; Tatsuo, A.; Hirochika, S.; Katsumi, T. Effects of Sensitizer Spin Multiplicity on Electron-Transfer Initiated Isomerization of cis-Stilbene *Chem. Lett.* **1988**, *17,* 1193. (b) Akaba, R.; Ohshima, K.; Kawai Y.; Obuchi, Y.; Negishi, A.; Sakuragi, H.; Tokumaru, K. Triplet-Mediated Electron Transfer Oxygenation of Stilbene Derivatives with 2,4,6-Triphenylpyrylium Tetrafluoroborate *Tetrahedron Lett.* **1991**, *32*, 109.

(11) Wever, W. J.; Cinelli, M. A.; Bowers, A. A. Visible Light Mediated activation and *O*-Glycosylation of Thioglycosides *Org. Lett.* **2013**, *15*, 30.

(12) Chlorocyclohexane was totally recovered at the end of the reaction.

(13) For a selected review on superoxide anion radical acting as a base, see: Hayyan, M.; Hashim, M. A.; AlNashef, I. M. Superoxide Ion: Generation and Chemical Implications *Chem. Rev.* **2016** *116*, 3029.

(14) Samoilova, R. I.; Crofts, A R.; Dikanov S. A. Reaction of Superoxide Radical with Quinone Molecules *Phys. Chem. A,* **2011***, 115*, 11589.

(15) Hsu, C.W.; Sundén, H. α-Aminoalkyl Radical Addition to Maleimides via Electron Donor–Acceptor Complexes *Org. Lett.* **2018,** *20,* 2051.

(16) George, N.; Bekkaye, M.; Masson, G.; Zhu, J. A Practical, One-Pot Multicomponent Synthesis of α-Amidosulfides and Their Application as Latent *N*-Acylimines in the Friedel-Crafts Reaction Eur. *J. Org. Chem.* **2011**, 3695