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Squaraines as Near-Infrared Photocatalysts for Organic Reactions

Nicolas Sellet,^a Malik Sebbat,^a Mourad Elhabiri,^b Morgan Cormier,^{*a} and Jean-Philippe Goddard,^{*a}

Herein, unprecedented uses of squaraine derivatives as new organic near-infrared photocatalysts are reported. These efficient molecular tools are able to promote oxidation and reduction for organic transformations through photocatalytic conditions. A mechanistic investigation is performed to discriminate competitive Single Electron Transfer and Energy Transfer pathways.

Photoredox catalysis can be considered as a cutting-edge method in organic synthesis to create challenging bonds under mild conditions.¹ To implement a photocatalytic reaction, a photocatalyst (Pcat) is required to convert light-energy into chemical energy. During such process, high reactive intermediates can be generated through various type of mechanisms including Single Electron Transfer (SET) or Energy Transfer (EnT). Usually, photocatalysts are organic dyes² or metal complexes³ that absorb light between 380 to 550 nm. This spectral window presents several drawbacks. First, the light energy is relatively high, involving selectivity issues and the formation of by-products. Second, the penetration of light into the reaction medium is limited when short wavelengths are used, what can affect the scalability of the reaction.⁴ To circumvent these problems, the development of NIR-photoredox catalysis has recently gained in interest.⁵ The remaining challenge is to find appropriate photocatalysts that can absorb low energetic NIR-light ($\lambda > 750$ nm) and promote organic transformations at the excited state. Following this concept, metal nanoparticles⁶ and transition metal complexes⁷ have been reported and their efficiencies appeared remarkable. However, their challenging preparation, storage, and stability render them difficult to handle, which limit their synthetic applications to specialists.

To provide alternative photocatalytic systems, we have recently developed NIR-organic photocatalysts based on a cyanine (Cy) scaffold.^{8a} The Cy746 photocatalyst was the first example of organic NIR-photocatalysts applied to organic transformations (Figure 1). Later, Kamino and Tanioka published a bridged eosin Y (BEY)) capable of acting as a NIR-photocatalyst in the reduction of diazonium salts.^{8b} Thus, Cy746 and BEY were found to be the only photocatalysts currently available in the NIR field that are capable of efficiently promoting various organic reactions. To extend the toolbox of organic NIR-photocatalysts, we investigated herein the family of squaraine (Sq) dyes (Figure 1). Their differences and complementarity with the reactivity of cyanines is highlighted as well as their unprecedentedly reported physicochemical and photophysical properties.

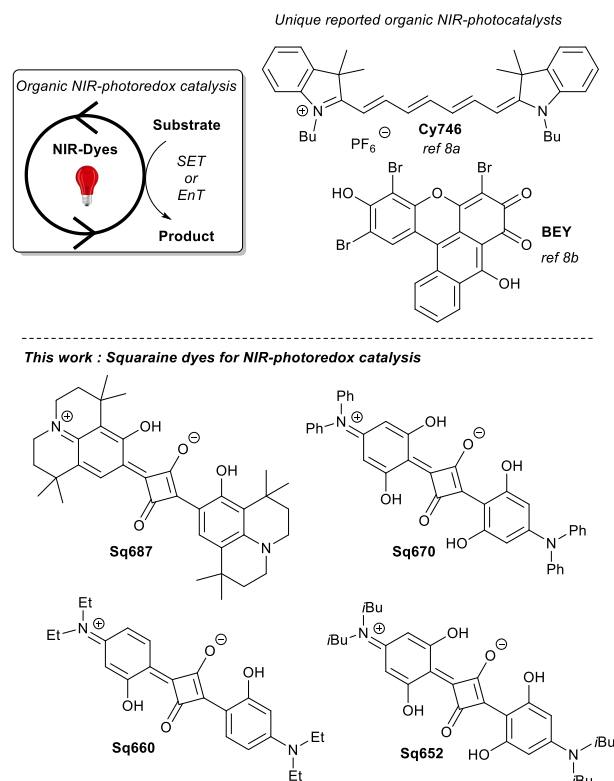


Figure 1 : State of the art about organic NIR-photocatalyst and this work.

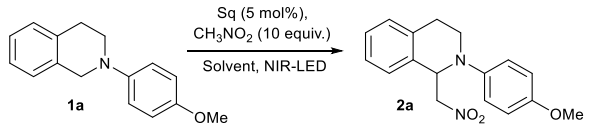
Squaraines (Sq) have a characteristic four membered unsaturated ring derived from squaric acid. This class of organic dyes displays valuable NIR-fluorescent properties that have been exploited to probe biomolecules, for example.⁹ Sq-derivatives are also well-known dyes used for organic photovoltaic cells,¹⁰ or as singlet oxygen photosensitizers.¹¹ Taking advantage of these photophysical and redox properties, we decided to evaluate whether this family of molecules could play the role of NIR- photocatalyst in organic synthesis. To do so, four Sq-dyes (Sq687, Sq670, Sq660, Sq652, Figure 1) have been selected according to their ability to absorb NIR photons (see §2.1 in ESI). These compounds are commercially available, which makes them accessible for the whole chemist's community. Prior to the catalytic activity investigation, we first measured their spectroscopic properties and redox potentials in DMSO (Table 1 and §2.2 in ESI). Their excited redox potentials $E^*_{red/ox}$ were then estimated by means of the simplified Rehm-Weller equation on the basis of their ground-state redox potentials (adjusted to the SCE reference) and their absorption spectra.¹² These values are comparable for each NIR dye (-1.22 V $< E^*_{ox} < -1.58$ V and 0.84 V $< E^*_{red} < 1.22$ V) and thus encouraged us to evaluate the photocatalytic activity of these selected Sq-dyes.

Table 1: Redox potentials of selected squaraines.

P _{cat}	Measured vs Ag/AgCl (V)		Referenced to SCE (V)		E* _{red/ox} vs SCE (V)	
	E _{ox}	E _{red}	E _{ox}	E _{red}	E* _{ox}	E* _{red}
Sq652	0.26	-0.76	0.23	-0.80	-1.58	1.01
Sq660	0.39	-0.71	0.36	-0.75	-1.44	1.05
Sq670	0.46	-0.39	0.43	-0.43	-1.22	1.22
Sq687	0.26	-0.80	0.23	-0.83	-1.45	0.84

E_{red/ox} of squaraines measured by cyclic voltammetry (CV) with Ag/AgCl (3M KCl) reference electrode and then corrected for referencing against SCE¹³. E*_{red/ox} were calculated according to the Rehm-Weller theory.¹²

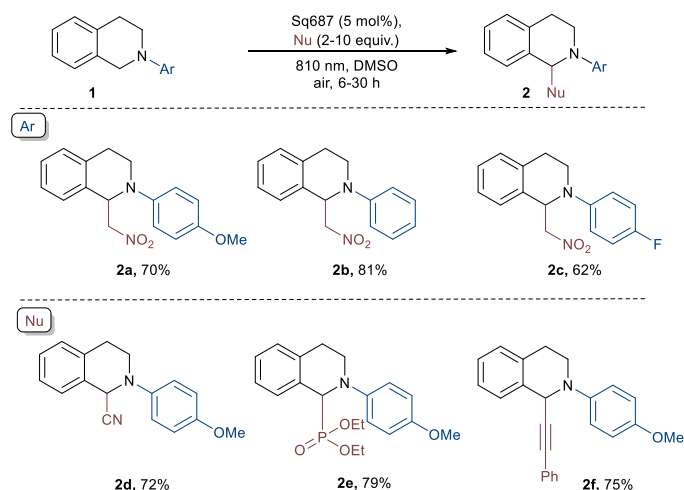
First, we investigated the oxidative aza-Henry reaction with the tetrahydroisoquinoline **1a** (E_{ox} = 0.62 V vs SCE)¹⁴ into **2a** as a model reaction (Table 2). Interestingly, after 24 h of irradiation at 810 nm, full conversion of **1a** was observed with Sq652 and Sq687 in DMSO. However, many undetermined byproducts were formed during the process and **2a** was isolated in only 48% yield (Table 2, entry 4) while the reaction with Sq652 resulted in an inseparable mixture that did not allow **2a** to be quantified. To optimize the formation of **2a**, Sq687 was selected as the most promising photocatalyst. Then, by changing the solvent from very polar and protic HFIP to polar DMF no improvement was observed (Table 1, entries 5-10). Finally, the DMSO was kept for the rest of the study. Decreasing the reaction time to 6 h gave an interesting equilibrium between the formation of **2a** and its degradation (see §4.2 in ESI).¹⁵ Under these specific conditions, the aza-Henry reaction was performed in 70% isolated yield (Table 2, entry 11). As Sq687 absorb in a wide spectral window (see §2.1 in ESI), we decided to compare its photocatalytic activity upon irradiation by two light-sources (LED-810 nm and LED-660 nm). Although the absorption of Sq687 is higher at 660 nm, the yield was not improved as **2a** was isolated in 56% yield (Table 2, entry 12). We observed a lower selectivity with the formation of many side products. To ensure the essential role of Sq687 on the reaction, we performed several control experiments (Table 2, entries 13-14). In the absence of Sq687, only 7% of conversion was observed while no conversion of **1a** was recorded in the dark. An additional control reaction has been done (Table 2, entry 15) under nitrogen atmosphere. No reaction was observed, indicating the importance of air (oxygen) for the transformation. To then, the extension of the aza-Henry reaction to different tetrahydroisoquinolines confirmed the photocatalytic activity of Sq687, which was still found to be effective (Scheme 1). Decreasing the electron density on the nitrogen by changing the aryl pending substituent from methoxy group to H or F, does not impact deeply the efficiency of the reaction. The aza-Henry products **2b** and **2c** were obtained in 81% and 62% respectively.

Table 2: Optimization of the aza-Henry reaction with squaraine-based dyes.


Param.	entry	Conditions ^a	conv. (yield) ^b in %
PCat	1	Sq660, 810 nm, DMSO, 24 h	11
	2	Sq670, 810 nm, DMSO, 24 h	10
	3	Sq652, 810 nm, DMSO, 24 h	100 (nd)
	4	Sq687, 810 nm, DMSO, 24 h	100 (48)
Solvent	5	Sq687, 810 nm, CH ₃ CN, 24 h	38
	6	Sq687, 810 nm, <i>i</i> PrOH, 24 h	35
	7	Sq687, 810 nm, HFIP, 24 h	29
	8	Sq687, 810 nm, CH ₃ NO ₂ , 24 h	8
	9	Sq687, 810 nm, DMF, 24 h	5
	10	Sq687, 810 nm, DCM, 24 h	5
Time	11	Sq687, 810 nm, DMSO, 6 h	70 (70)
Light	12	Sq687, 660nm, DMSO, 6 h	100 (56)
	13	810 nm, DMSO, 6 h	7
Control	14	Sq687, dark, DMSO, 6 h	0
	15	Sq687, 810 nm, DMSO, 6 h, N ₂	0

^a 0.1 mmol scale c = 0.1 M, under air except for entry 15 where the reaction has been run under nitrogen. ^b Conversions were determined on the crude by ¹H-NMR and yields were obtained after purification by flash-chromatography. nd = non determined.

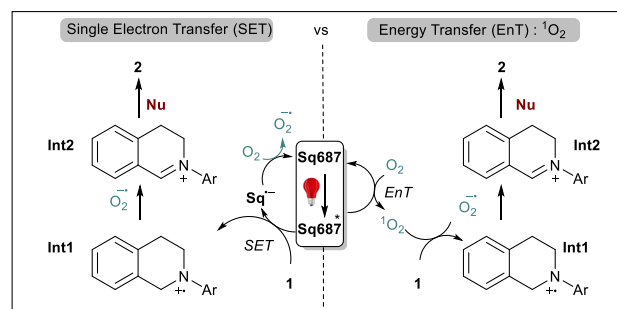
This NIR-photocatalytic system is also compatible with different type of nucleophiles under the optimized conditions. The transfer of cyanide was confirmed by the formation of **2d** in 72% yield using TMSCN as a precursor of nucleophile. Addition of diethyl phosphite to **1a** gave the phosphonate **2e** in 79% yield under the same experimental conditions. Sq687 is always as reactive in the presence of organometallic species as demonstrated by the catalytic addition of copper(I) phenylacetylide to **1a**. By merging these two catalytic cycles, **2f** was obtained in 75% yield. Then, we decided to investigate the mechanism which is involved in this catalytic process. The photocatalytic aza-Henry reaction of tetrahydroisoquinoline is known to proceed via two types of mechanism depending on the photocatalytic conditions, namely SET and EnT (Scheme 2a).¹⁶ In the SET process, the Sq excited state directly oxidizes **1** to form the radical cation **Int1** which is transformed further into the corresponding iminium **Int2**. The same intermediates could be generated via the EnT mechanism. In this case, photosensitization of ³O₂ into ¹O₂ by Sq could promote the oxidation of **1** to lead **Int1** and **Int2**. To determine which mechanism controls the Sq687 photocatalyzed reaction, we performed a series of experiments (Scheme 2b).



Scheme 1 : Substrate scope of squaraine-based-NIR aza-Henry type reactions.

First, we confirmed the essential role of dioxygen for the reaction to proceed since the starting material was integrally recovered after 24 h of irradiation when the reaction was carried out under N_2 -atmosphere. On the other hand, the **1a** to **2a** conversion decreased to 30% after 24 h of irradiation when sodium azide was used as a singlet oxygen quencher.¹⁷ This reveals that 1O_2 is not essential for the photocatalyzed reaction. However, we also observed a progressive degradation of Sq687 in presence of NaN_3 , that could also affect the conversion of **1a** (see §4.6 in ESI). To rule out the implication of 1O_2 in the photocatalytic transformation we then explore the [4+2]-cycloaddition between the tetraphenylcyclopentadienone (**3**) and 1O_2 (Scheme 2c). This reaction is well known to be efficient with different photosensitizers upon visible and NIR-light.^{8a, 18} In our case, no reaction occurred since only traces of **4** were observed and the starting material was almost fully recovered (Scheme 2c) suggesting that Sq687 is not able to generate high concentration of 1O_2 under these conditions. To confirm that the SET mechanism is the predominant process in this reaction, dioxygen was replaced by an alternative co-oxidant (1,3-dinitrobenzene, $E_{red} = -0.85$ V vs SCE)¹⁹, which could be able to regenerate the photocatalyst ($Sq^{\cdot-}$ to Sq).²⁰ Under these conditions, generation of 1O_2 is not possible and only the SET catalytic cycle should occur. Interestingly, after 24 h of irradiation at 810 nm, the conversion of **1a** into **2a** is observed at 62%. A UV-Vis. spectroscopic study suggested that no Electron Donor-Acceptor (EDA)-complex is formed between the photocatalyst and 1,3-dinitrobenzene (see § 4.6 in ESI). Additionally, no reaction was observed in control experiment with 1,3-dinitrobenzene either in the dark or in absence of Sq687. These results support that the SET mechanism is possible under N_2 by adding a co-oxidant, suggesting the high probability of this pathway. Finally, we explored other types of reactions to emphasize the broad synthetic potential of this NIR-photocatalyst (Scheme 3). Oxidation of aniline **5** followed by a [4+2]-cycloaddition with *N*-phenylmaleimide **6** gives **7** in 63% yield. Sq687 is also able to oxidize ylide **8** and catalyze its dimerization to afford **9** in 65%.²¹

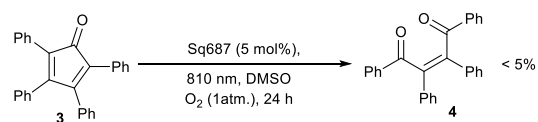
a) Proposed mechanistic pathways



b) Mechanistic investigation

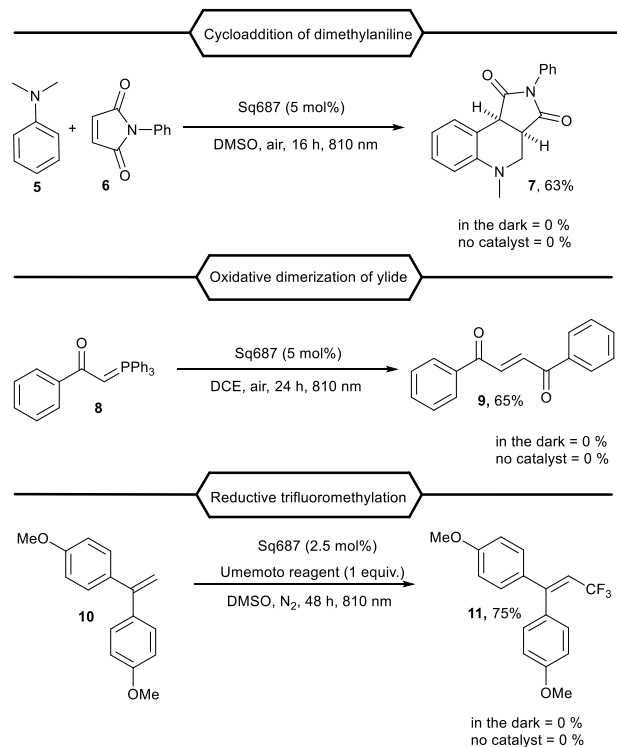
1a	Sq687 (5 mol%), CH_3NO_2 (10 equiv.)	810 nm, DMSO	Conversion of 1a	
			6 h	24 h
	optimized conditions		70%	100%
	N_2 instead of air		0%	0%
	1O_2 quencher : NaN_3 (2 equiv.)		26%	30%
	N_2 , 1,3-dinitrobenzene (2 equiv.)		13%	62%
	N_2 , dark, 1,3-dinitrobenzene (2 equiv.)		0%	0%
	N_2 , no Pcat, 1,3-dinitrobenzene (2 equiv.)		0%	0%

c) 1O_2 control reaction



Scheme 2 : Study of mechanism.

Even more interesting, Sq687 is able to initiate the photoreduction of sulfonium salt (Umemoto's reagent, $E_{red} = -0.75$ V vs Fc/Fc^+)²² to achieve the trifluoromethylation of **10** into **11** in 75%.



Scheme 3 : Selection of other NIR-photoredox reactions.

In summary, we have reported a new NIR-photocatalyst based on squaraine derivatives and provided new photophysical data (UV-Vis,

fluorescence and redox potentials) for this series of molecules. Under our optimized conditions, Sq687 proved to be the most efficient to promote organic transformations. Trifluoromethylation, cycloaddition, oxidative homocoupling reactions as amine oxidation are some representative reactions. The first mechanistic insights that we obtained reveals that this photocatalyst is able to transfer electron in oxidative or reductive manner while the EnT pathway is less probable. It should be noted that squaraine family presents several differences compared to previously reported NIR-organic photocatalysts (Cyanines): both NIR-photocatalytic systems are complementary in term of mechanisms and kinetics. Further investigations would confirm the high potential of squaraines as photocatalysts.

Conflicts of interest

There are no conflict to declare

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