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Authors	Paula Pérez-Ramos, Raquel G. Soengas and Humberto Rodríguez-Solla
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ORCID® iDs	Raquel G. Soengas - https://orcid.org/0000-0001-8178-0034; Humberto Rodríguez-Solla - https://orcid.org/0000-0002-5394-5177

General Method for the Synthesis of Enaminones via Nickel Photocatalysis

Paula Pérez-Ramos,[1] Raquel G. Soengas,[1,*] Humberto Rodríguez-Solla[1,*]

[1] Department of Organic and Inorganic Chemistry, and Instituto Universitario de Química Organometálica Enrique Moles, University of Oviedo, Julián Clavería 8, 33006, Oviedo (Spain).

Email: Raquel G. Soengas – rsoengas@uniovi.es; Humberto Rodríguez-Solla – hrsolla@uniovi.es

* Corresponding author

In the memory of our friend and colleague Prof. Iván Lavandera García

Abstract

Enaminones are key intermediates in the synthesis of several derivatives with important applications in medicinal chemistry. Furthermore, many marketed drugs feature the enamine structural moiety. In this context, we have developed a photoredox and nickel catalytic system to rapidly forge the enaminone scaffold from 3-bromochromones via the formation of a nitrogen-centered radical and subsequent trapping by the electron-deficient alkene moiety. With this dual catalytic system, a range of structurally diverse enaminone derivatives have been achieved in good yields with total *trans* selectivity. Mechanistic studies indicate that the key to the success of this process is the formation of an unexplored ternary Ni-complex with 3-bromochromone and a pyridinium salt, which is crucial for the effective activation of the α,β-unsaturated system towards the radical addition.

Keywords

enaminones; chromones; metallophotoredox; nickel; photocatalysis.

Introduction

Enaminones are a class of enamines that have attracted significant attention due to their value in medicinal chemistry as intermediates in the synthesis of novel drug candidates [1–6]. These vinylogous amides consists of a conjugated system of an amino group linked through a carbon-carbon double bond to a carbonyl group, displaying a typical “push-pull” behavior where the carbonyl group pulls electron density to itself from the amino group [7]. This makes enaminones very reactive, providing an excellent scaffold for organic synthesis. Thus, enaminones are valuable building blocks in the preparation of several carbocyclic [8–11], heterocyclic [12–18] as well as acyclic compounds [19–23]. Furthermore, the enaminone structural moiety represents the key framework of many drug classes, including antibiotic **1** [24], anti-inflammatory **2** [25], antinociceptive **3** [26], anticonvulsant **4** [27], antitubercular **5** [28], and antitumor **6** [29] agents (Figure 1).

In view of the important biological roles of enamines and their relevance as synthetic intermediates, it is not surprising that there has been a continuous focus on developing general, straightforward, and efficient strategies for their synthesis. Enaminones are usually accessed by the means of the condensation of 1,3-dicarbonyl compounds with amines [30]. While this approach is simple and straightforward, it often leads to a mixture of constitutional isomers in which the two different α-positions of the ketone have been functionalized. In recent years, several novel methods for the synthesis of enaminones have been developed.

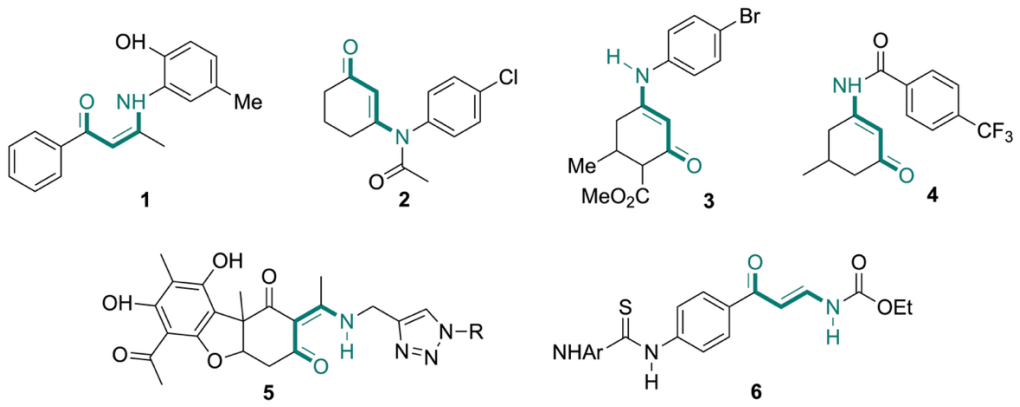


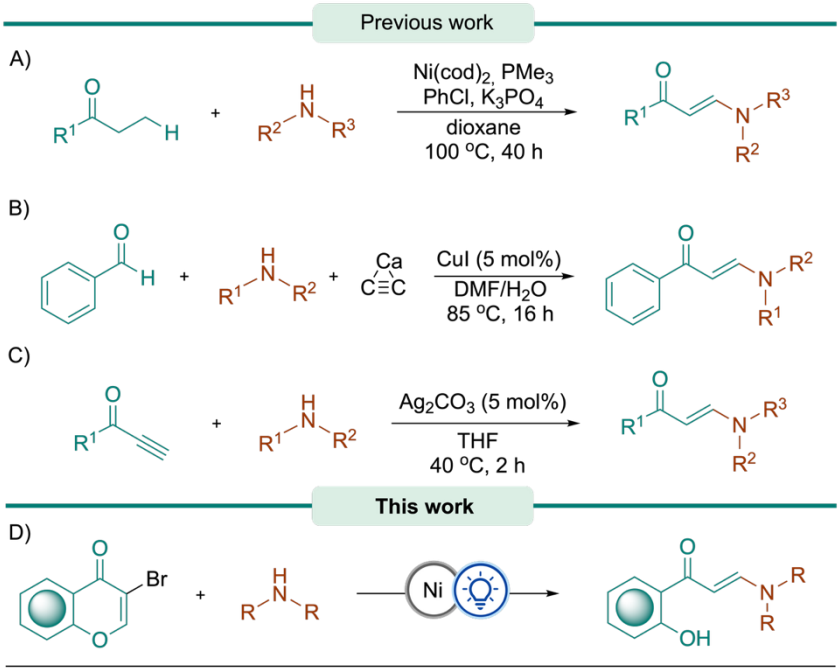
Figure 1. Medicinal chemistry of the enaminone scaffold.

Kuwano's group described a nickel-catalyzed formation of β-enaminone through amination at the β-position of alkyl ketones (Scheme 1A) [31]. Zhang's group reported a methodology to prepare enaminones from the reaction of aldehydes, calcium carbide and amines catalyzed by CuI (Scheme 1B) [32]. Li *et al.* disclosed the transformation of propargyl alcohols to enaminones in the presence of silver salts (Scheme 1C) [33]. Although these new methods provide a wide variety of enaminones, there are limitations such as expensive and unavailable reagents, long reaction times and drastic reaction conditions. Furthermore, the increasing emphasis on economic and environmental factors has highlighted the limitations of traditional methods for enaminone synthesis to align with the modern understanding of organic chemistry.

With the increasing concern on the environmental impact of organic synthesis, photocatalysis emerged as a powerful synthetic tool in organic chemistry, offering new ways to deliver diverse organic products via mild, easy to handle, and environmentally benign operations [34–36]. Thus, the use of visible light as an energy source provides more efficient chemical transformations and minimize the use of harmful reagents, the generation of waste and the consumption of energy, fulfilling several principles of Green Chemistry and promoting greener opportunities for organic synthesis [37, 38]. In this context, the reactivity of enaminones under visible-light mediated reaction

conditions has attracted significant attention [39]. However, it is rather surprising that a photocatalytic approach for the synthesis of enaminones has yet to be explored.

Herein, we report the first design of a light-mediated paradigm for synthesizing enaminones from 3-bromochromones (Scheme 1D). The protocol employs a photocatalytic system to generate a N-centered radical and a nickel catalyst to activate the α,β-unsaturated system towards radical addition, ultimately resulting in the opening of the heterocyclic ring to achieve the corresponding enamines. This transformation is simple, straightforward, and proceeds under mild conditions.



Scheme 1. Synthesis of enaminones.

Results and Discussion

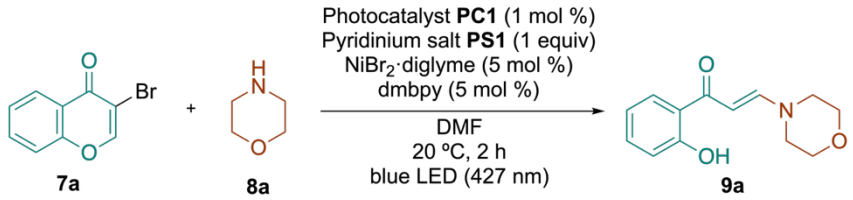
The initial challenge in achieving the desired reactivity was the activation of the unsaturated system towards the addition of the nitrogen-centered radical. The most common strategy to increase the reactivity of unsaturated esters towards the aza-Michael addition is the use of transition metal complexes as catalysts/promoters [40–

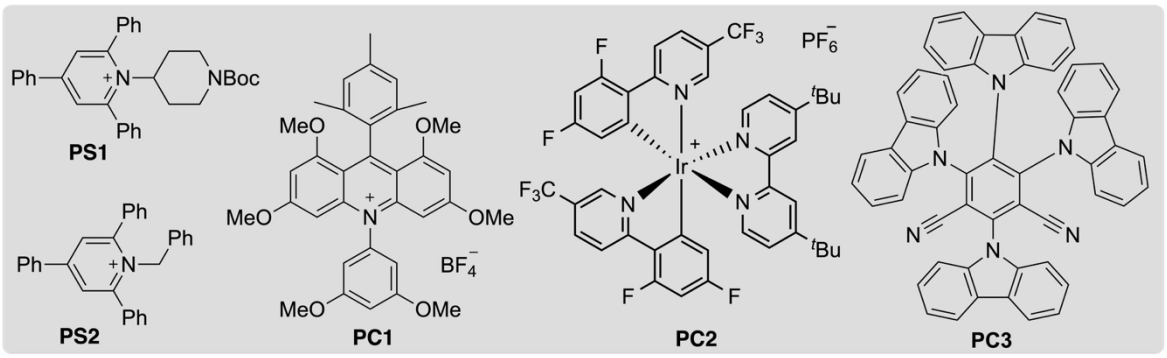
42]. Considering this background, we reasoned that Ni(II) could be a suitable catalyst for the Giese-type amination of unsaturated systems.

Initial investigations were carried out by using 3-bromochromone **7a** and morpholine **8a** as model substrates in the presence of Ni(II) salt (5 mol %) and ligand (5 mol %), a pyridinium salt (1 equiv) and a photocatalyst (1 mol %) under 427 nm blue LEDs. After carefully screening of the reaction parameters, we found that a combination of 1-[1-(*tert*-butoxycarbonyl)piperidin-4-yl]-2,4,6-triphenylpyridin-1-ium (**PS1**), $NiBr_2$·diglyme, 4,4'-dimethoxy-2,2'-bipyridine (dmbpy), and 10-(3,5-dimethoxyphenyl)-9-mesityl-1,3,6,8-tetramethoxyacridin-10-ium tetrafluoroborate (**PC1**) in *N*,*N*-dimethylformamide (DMF) at 20 °C afforded the best results, giving the desired product **9a** in a 70% isolated yield (Table 1, entry 1). Changing $NiBr_2$·diglyme to other nickel salts, such as $Ni(OTf)_2$ and $NiCl_2$·diglyme led to lower yields (Table 1, entries 2 and 3). Similarly, changing the ligand for dtbbpy or phenantroline also resulted in a decrease in the efficiency of the process (Table 1, entries 4, 5). The pyridinium salt has also a significant effect on reactivity; thus, when 1-benzyl-2,4,6-triphenylpyridin-1-ium (**PS2**) was used, enaminone **9a** was isolated in only a 28% yield (Table 1, entry 6). Replacing DMF by DME, DMSO or acetone diminished the product yields (Table 1, entries 7-9). The reactivity of acridinium **PC1** was superior to that of other photocatalysts, including 4-CzIPN (**PC2**) and $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (**PC3**) (Table 1, entries 10, 11).

Attempts to increase the temperature of the process resulted in a complex reaction mixture in which only traces of the desired enaminone **9a** were detected (Table 1, entry 12). Longer reaction times also led to significant degradation, isolating the desired enaminone in only a 18% yield (entry 13). Control experiments including the reaction in the absence of visible-light or photocatalyst, showed no product formation (Table 1, entries 16, 17). Interestingly, the yield of **9a** dropped to 30% in the absence of Ni salt and 33% in the absence of the pyridinium salt (Table 1, entries 14, 15).

Table 1. Optimization of the reaction conditions.





Entry	Deviation from the standard conditions[a]	Yield (%)[b]
1	None	70
2	$Ni(OTf)_2$ instead $NiBr_2$·diglyme	62
3	$NiCl_2$·diglyme instead $NiBr_2$·diglyme	49
4	dtbbpy instead dmbpy	66
5	phenantroline instead dmbpy	49
6	**PS2** instead **PS1**	34
7	acetone instead DMF	51
8	DMSO instead DMF	55
9	DME instead DMF	57
10	**PC2** instead **PC1**	46
11	**PC3** instead **PC1**	57
12	40 °C instead 20 °C	traces
13	16 h instead 2 h	18
14	no **PS**	33
15	no Ni salt and ligand	30
16	no **PC**	n.r.[c]
17	no light	n.r.

[a] 3-Bromochromone **7a** (0.2 mmol), morpholine **8a** (0.3 mmol), PC1 (1.0 mol %), $NiBr_2$·diglyme (5.0 mol %), dmbpy (5.0 mol %) and **PS1** (1 equiv) in DMF under N_2, irradiation with a 427 nm LED lamp at 20 °C for 2 hours. [b] Isolated yield of **9a** after flash column chromatography. [c] No reaction.

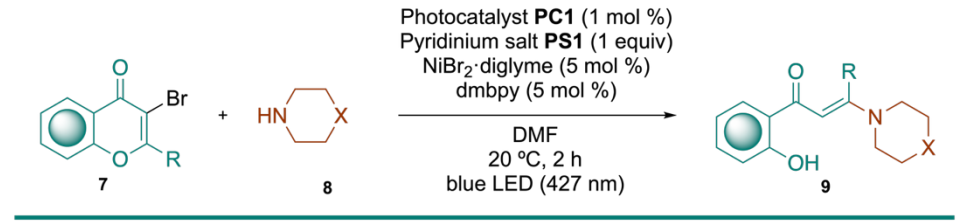
With the optimal reaction conditions, we first studied the substrate scope of 3-bromochromones **7** (Table 2). It was found that a wide range of halochromones bearing electron-donating (Me, OMe) or electron-withdrawing (F, Cl, Br) groups with different substituent patterns at the phenyl ring were all compatible with this transformation. The corresponding products **9a−9h** were obtained from moderate to good yields (45−70%). The successful synthesis of the expected enaminones **9d** and **9e** bearing bromo and chloro moieties was noteworthy, since they could provide an opportunity for additional synthetic elaboration. Unfortunately, when 2-methyl-3-bromochromone was employed as the substrate, the metallophotoredox process failed to afford the desired enaminone product, which was possibly caused by a combination of increased steric hindrance and decreased electrophilicity of the β-carbon due to the electron-donating nature of methyl group.

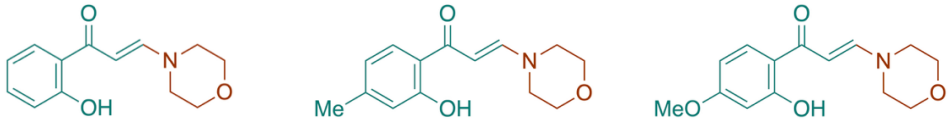
Subsequently, we turned our attention to investigate a range of amine derivatives **8** under the standard conditions. When morpholine was replaced by piperazine, the expected enaminone **9g** was provided, albeit in lower yield. Similarly, 4-methylpiperazine and *N-tert*-butoxycarbonylpiperazine afforded the corresponding enamines **9i** and **9j**, respectively, in moderate yields. Gratifyingly, 1-(pyridin-2-yl)piperazine was also tolerated, providing the expected product **9h** in 46% yield. Considering that pyridine is one of the core components of drug derivative formulations, present in more than 7,000 active pharmaceutical compounds [43], the introduction of a pyridine ring into the enaminone structure holds great promise for the development of new drug candidates.

When pyrrolidine was used as amine reagent, the target enaminone **9k** was obtained, albeit in low yield. Regrettably, this transformation failed to provide the corresponding enaminone products by replacing alicyclic amines by diisopropylamine, probably due to steric hindrance. Steric factors could also explain the lack of reactivity of seven-

membered azepane. In view of these results, it seems evident that six-membered cyclic amines have the optimal ring size for the metallophotocatalyzed enamine formation process.

Table 2. Substrate scope

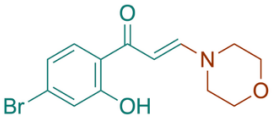




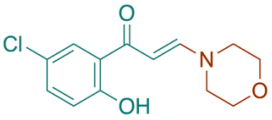
9a: 70% yield

9b: 52% yield

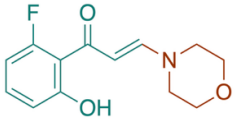
9c: 58% yield



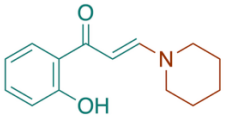
9d: 45% yield



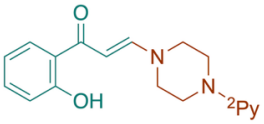
9e: 60% yield



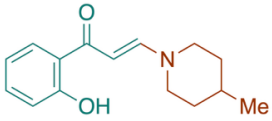
9f: 50% yield



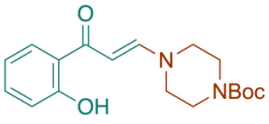
9g: 40% yield



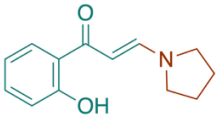
9h: 46% yield



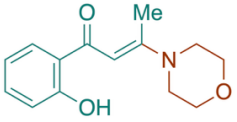
9i: 39% yield



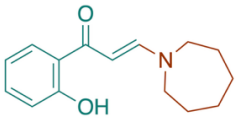
9j: 35% yield



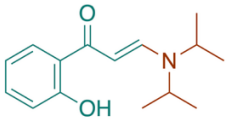
9k: 26% yield



n.r.



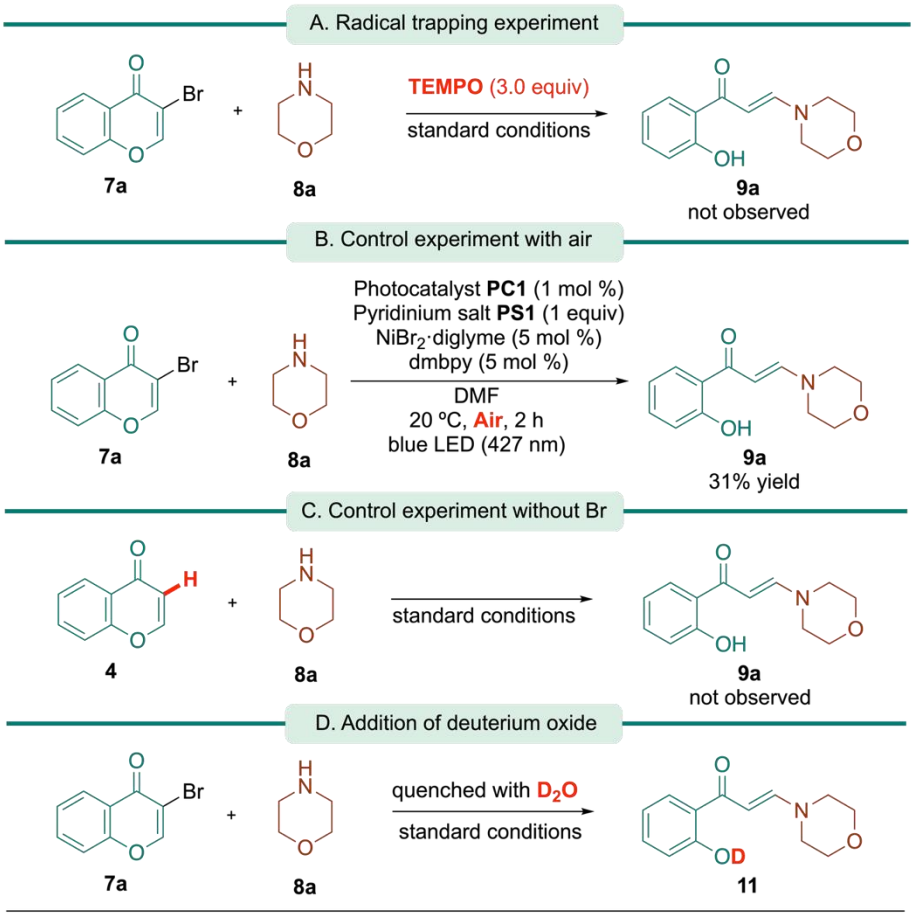
n.r.



n.r.

In terms of the reaction mechanism, TEMPO completely inhibited the reaction, indicating the possibility of a radical intermediate in the reaction (Scheme 2A). Air

treatment of the reaction mixture resulted in a 31% yield of the intended product **9a**, indicating that air influenced the interaction between the Ni-catalyst and the α,β-unsaturated carbonyl function (Scheme 2B). Furthermore, when the reaction of chromone **10** was carried out under standard conditions, the starting material was recovered unaltered, implying that the photocatalyzed dehalogenation step is crucial to enable the ring opening (Scheme 2C). Finally, deuterolysis of the reaction mixture led to the formation of the deuterated enamine **11** (Scheme 2D).



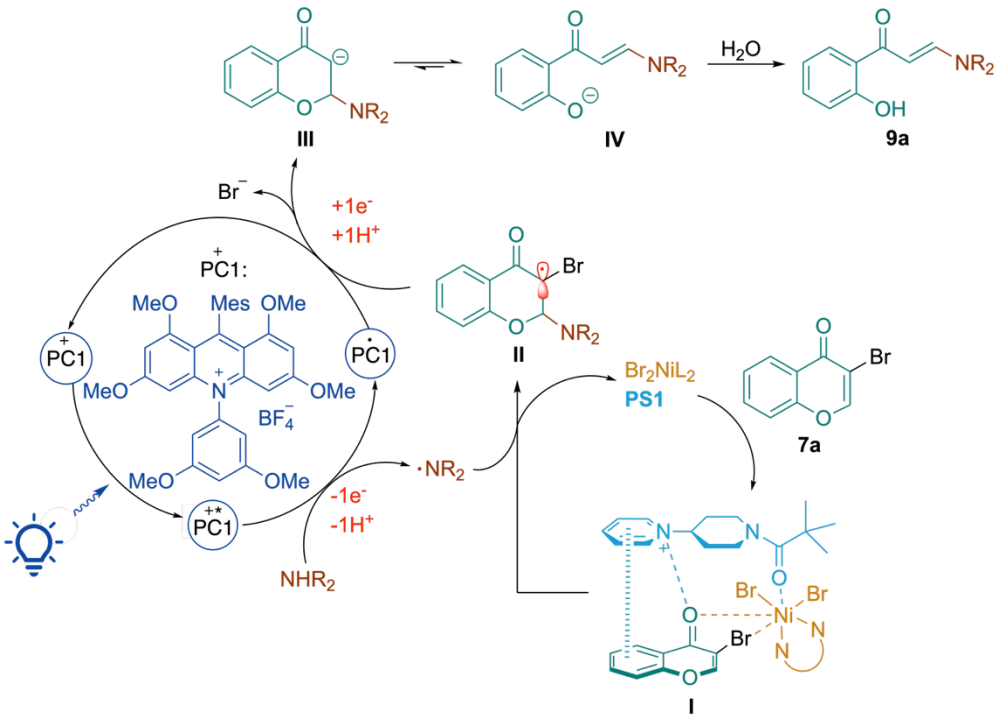
Scheme 2. Mechanistic studies.

Based on the above experiments, a possible mechanism for this reaction is proposed in Scheme 3. A ternary complex **I** is initially formed upon complexation of the 3-bromochromone **7a** with Ni-dmbpy, which is further activated on aggregation of the

pyridinium salt and the chromone aromatic ring through π−π stacking. By virtue of being coordinated to a Ni-center, the β-carbon is activated toward nucleophilic attack. Simultaneously, acridinium photocatalyst **PC1** absorbed energy and transitioned from the ground state to excited state under visible-light irradiation. This excited state **PC1*** is quenched by the amine **8**, generating nitrogen-centered radical and **PC1** radical via a single-electron transfer (SET) process. Radical addition of the amino radical to complex **I** then produces radical intermediate **II**, which is subsequently oxidized by the reactive **PC1** radical via a single-electron transfer (SET) process to give anion **III** and regenerate the ground state of **PC1**. Finally, anion **III** evolves to the more stable anion **IV**, which on protonation of affords the final enamine product **9a**.

Conclusion

In summary, a simple and effective metallophotocatalytic system for the direct formation of enaminones from 3-bromochromones is herein reported. This approach exploits the photocatalytic formation of nitrogen-centered radicals and their trapping with an electron-deficient alkene moiety, accomplishing a C–N bond formation. Mechanistic studies suggest that the key to the success of this transformation is the complexation of the starting 3-bromochromones to Ni(II) and a pyridinium salt, giving rise to a ternary Ni-complex which activates the α,β-unsaturated carbonyl compound towards radical addition. The present method is operationally simple and can be conducted using low catalyst loadings of a Ni-catalyst and an inexpensive organic photocatalyst.



Scheme 3. Proposed mechanism.

Supporting Information

Photochemical reactions set-up, experimental details, characterization data and NMR spectra for enaminones **9**.

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