Carbamoylation of azaarenes and olefins with formamides through dual photoredox/HAT catalysis

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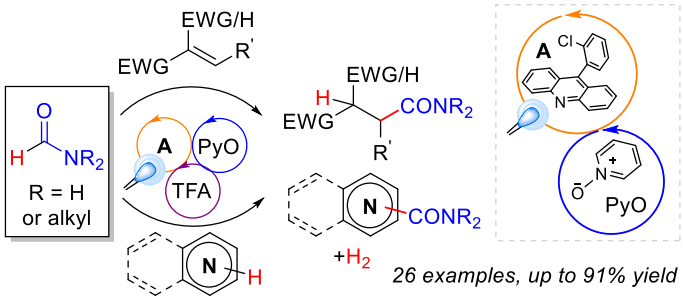
Supporting Information Placeholder



ABSTRACT: Among the different methods to synthesize amides, radical amidation of suitable acceptors is appealing. In this context, we have developed a methodology for the photoinduced Minisci and Giese carbamoylation with readily available formamides. This approach avoids using less atom-efficient carbamoyl precursors (*e.g.*, oxamic acids) and sacrificial oxidants, relying on dual photoredox/hydrogen atom transfer (HAT) catalysis.

1. Introduction

Known for over a hundred years now,[1,2] the formation of amide bonds is still one of the most important transformations in synthetic and bioorganic chemistry. Amide linkages are present in bioactive compounds, including peptides and proteins, but also almost a quarter of all commercialized drugs.[3] In addition, this versatile moiety in synthetic organic chemistry is also present in mass-produced polymers.[4] Over the last few decades, research has steered from classic amide formation by coupling acids and amines with significant developments in the direct amidation of compounds *via* oxidative radical reactions (Scheme 1A).[5] This approach mitigates operational issues related to using commonly insoluble carboxylic acids and poorly atom-economic coupling reagents while providing a complementary scope. One seminal contribution to this field is the iron-catalyzed carbamoylation of azaarenes with formamide in the presence of hydrogen peroxide as a sacrificial oxidant, reported by Minisci in 1970 (Scheme 1B).[6] Although many different substrates and conditions have been explored since then, the fundamental working principle is mostly based on adding a carbamoyl radical (·$CONR_2$) to a suitable acceptor.[7] These radicals are long-lived and nucleophilic owing to strong conjugation of the non-bonding electrons of the oxygen with the SOMO.[8]

Photocatalytic approaches provide a sustained and controlled radical formation from suitable precursors under milder operating conditions than conventional approaches.[9] In this context, a myriad of possibilities has been explored for the photocatalytic generation of carbamoyl radicals (Scheme 1B). For example, the photoinduced oxidation of oxamic acids[10–14] with concomitant decarboxylation or semicarbazides with loss of N_2[15] has been reported in recent years. On the other hand, photooxidation of 4-carboxamido-1,4-dihydropyridines has proved to be a competent method to obtain carbamoyl radicals but generate the corresponding pyridine as waste.[16,17] Moreover, photoinduced reduction of moisture-sensitive carbamoyl chlorides[18] or using *N*-hydroxyphtalimido esters are also popular approaches.[19,20]

Despite the efficiency of many of the above-commented methods, formamides are more readily available and convenient substrates, providing the highest atom economy in generating carbamoyl precursors. The sustainability of the carbamoylation with formamides would be optimal in the absence of sacrificial reagents. In this context, Prieto and Taillefer have recently reported the photoinduced hydrocarbamoylation of styrenes with formamides, relying on decatungstate/disulfide catalysis.[21] To our best knowledge, this is the only carbamoylation reported in the absence of sacrificial reagents, and developing new methodologies would be highly desirable in terms of sustainability.

This work presents a protocol for the direct photoinduced carbamoylation of nitrogenated heterocycles and electron-deficient olefins with formamides**.** Our approach relies on dual photoredox/HAT catalysis, using readily made 9-(2-chlorophenyl)acridine (**A**) and inexpensive pyridine *N*-oxide (PyO) as catalysts under blue light. Importantly, this method avoids the need for sacrificial oxidants and tolerates the presence of air and moisture, making this protocol sustainable and user-friendly (Figure 1C).

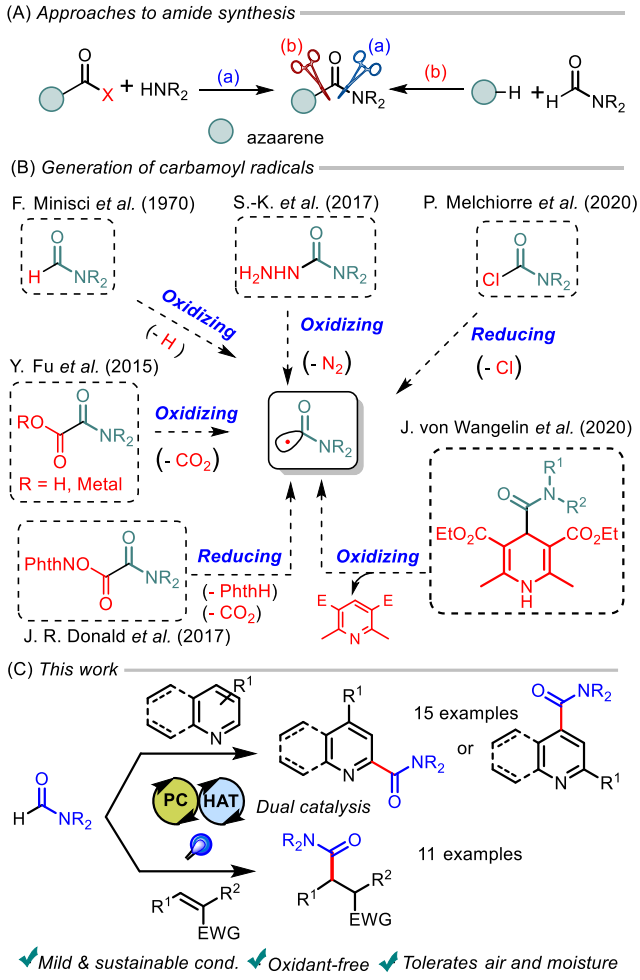


Figure 1. Background of carbamoylation and the present work.

2. Results and discussion

Due to the relevance of nitrogenated heterocyclic scaffolds in medicinal chemistry, we selected the Minisci reaction to first assay the performance of our system in radical carbamoylation reactions. In an earlier report, we established the capability of **A** ($E_{red}^{[A-H+]*}$ = 2.2 V *vs.* SCE) to efficiently generate a HAT catalyst by oxidation of PyO in the presence of TFA under irradiation at 450 nm.[22] The resulting *N*-oxyl radical (BDE = 99 kcal·mol^{-1})[23] should then be capable of abstracting a hydrogen atom from the formamide (BDE = 95 kcal·mol^{-1}),[24] generating the corresponding carbamoyl radical, which would then undergo addition to the protonated heterocycle. Thus, we selected the carbamoylation of lepidine with formamide as the model reaction to test this hypothesis. Using the optimized conditions from our earlier report on the Minisci alkylation of azaarenes,[22] we observed the desired product in a modest 26% yield. After extensive optimization studies (Table S2), we found the optimal conditions to be 10 equivalents of formamide, 5 mol% of **A**, 30 mol% of PyO and 2 equivalents of TFA at a concentration of 0.1 M in acetonitrile for 48 hours at room temperature (around 30 to 35 ºC). In contrast to our earlier report, the use of hexafluoroisopropanol (HFIP) was found to be detrimental to the reaction. With the optimized conditions set, we explored the scope of the reaction (Figure 2).

Quinolines reacted smoothly, affording the corresponding products in moderate to good yields with good functional group tolerance. Quinaldine was a particularly convenient substrate, as the low solubility of the product meant it could be obtained pure after filtration and washing with hexane (compound **2**). Plain quinoline reacted preferentially at C2, although the C4 derivative and disubstituted products were also obtained (compounds **4**), likely due to the lower steric hindrance at the C2 position. Notably, the DL-menthol functionalized **5** could be obtained in moderate yield. Isoquinolines were challenging substrates in our previous protocol for the alkylation of azaarenes. In this case, they reacted cleanly, so we obtained the corresponding 1-carbamoylisoquinolines in good yields. This is further highlighted by obtaining product **8** pure after simple filtration and washing with hexane. Phenanthridines exhibited similar behavior, affording the corresponding products in good-to-excellent yields after simple filtration and washing with hexane (compounds **9** and **10**). Other azaarenes were also assayed, and good results were obtained. Quinazoline and quinoxaline were also well tolerated, affording products **11** and **12** in good yield and selectivity. Pyridines were more challenging substrates, with several failed attempts (Figure S3). In addition to azaarenes, we tested several different *N*-substituted formamides in combination with isoquinoline. Amides bearing alkyl groups, including the heavily sterically hindered diisopropylformamide, were well tolerated, which led to **15** in moderate yield. Aryl groups resulted in no reactivity whatsoever. Prieto and Taillefer had previously observed this behavior.[21] It could be attributed to the relatively low rate of addition leading to side products, particularly isocyanates obtained by oxidation of the carbamoyl radical, which were detected by GC-MS and are known to form under such conditions.[25]

After studying the Minisci reaction, we shifted our attention towards the Giese-type addition of carbamoyl radicals to olefins. This redox-neutral process allows for the direct preparation of a variety of masked 1,4-dicarbonyl amides. Thus, we selected the carbamoylation of diethyl ethylidenemalonate as the model reaction. Under the standard conditions for the Minisci reaction, we were delighted to observe the desired product in 90% GC yield (based on unreacted substrate) after 24 h. As the Giese acceptor does not require activation by acid, only one equivalent of TFA was used. Encouraged by this result, we briefly re-optimized the reaction (Table S3). We found the ideal conditions to be 5 equivalents of formamide, the same amount of both catalysts (5 and 30 mol% for **A** and PyO, respectively), and one equivalent of TFA at a concentration of 0.1 M in acetonitrile for 24 hours. With these conditions in hand, we set on exploring the scope of this transformation (Figure 3).

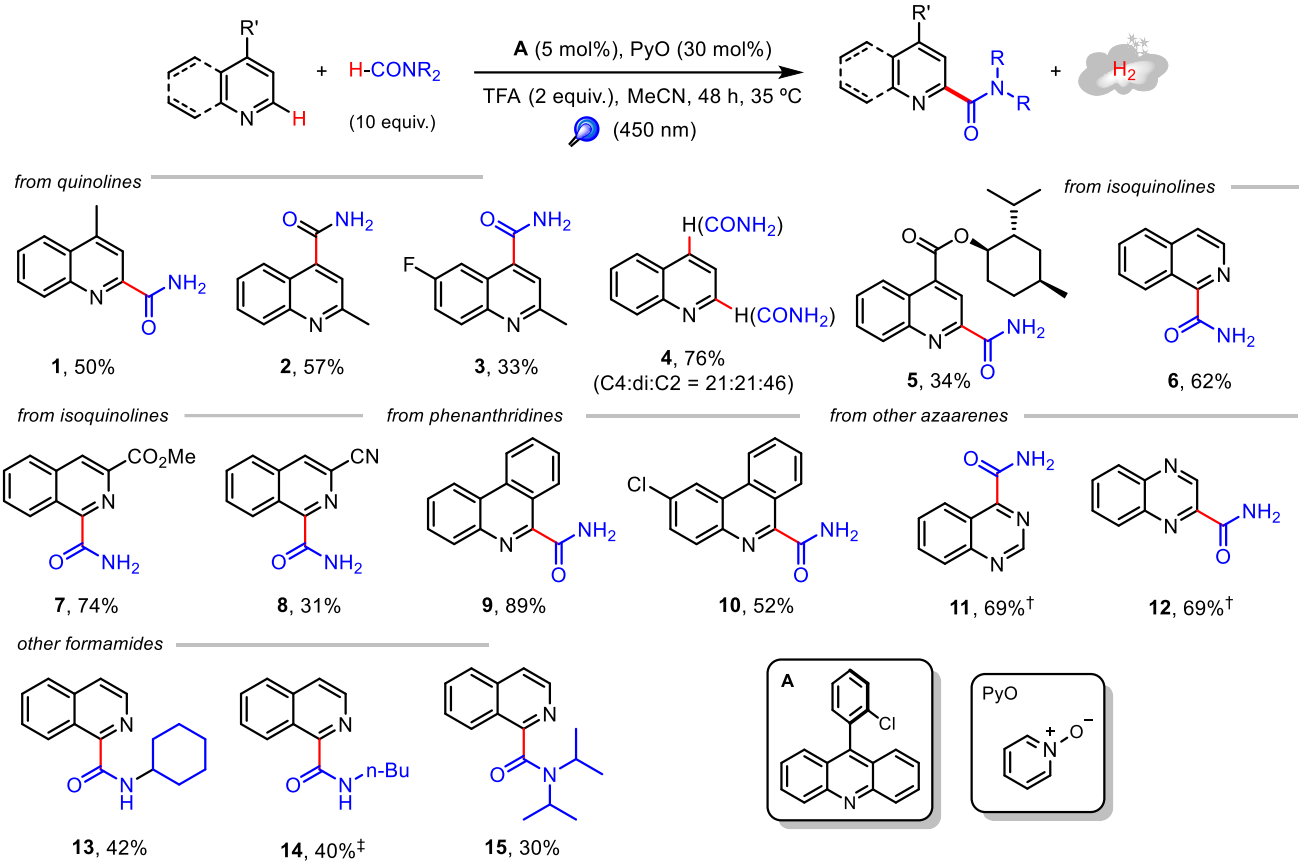


Figure 2. Substrate scope of the Minisci carbamoylation. Yields for isolated pure products. †4 equiv. of TFA were used. ‡ After 60 h.

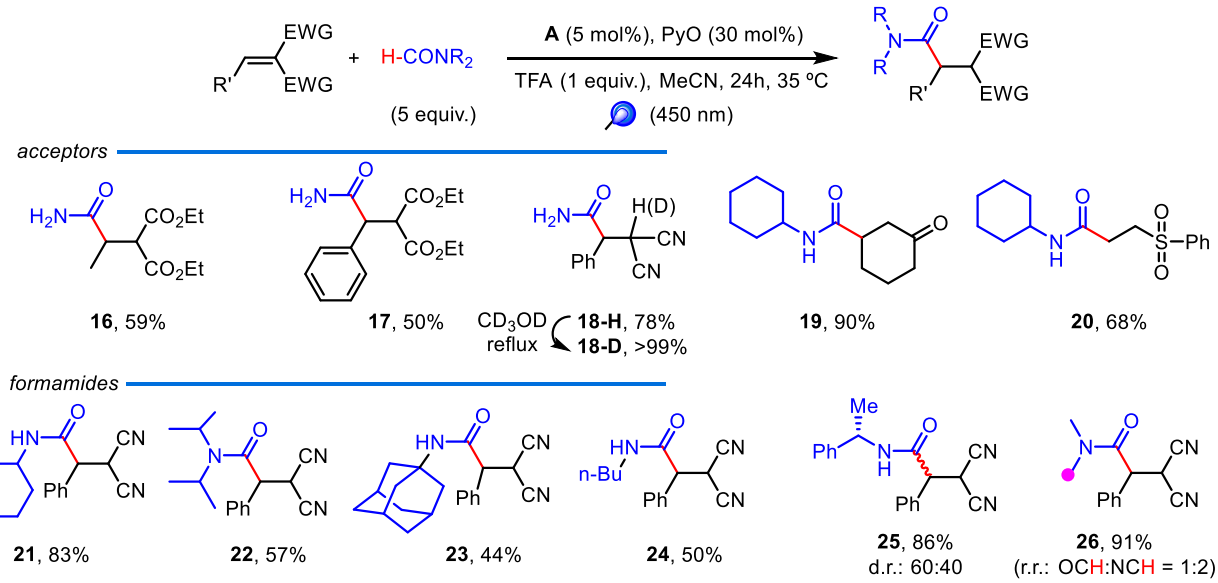


Figure 3. Substrate scope of the Giese-type carbamoylation of olefins. Yields for isolated pure products.

In general, good results were obtained across the board. As expected, the more electron-withdrawing benzylidenemalononitrile performed the best among the substrates paired with formamide (compound **18** *vs.* **16** and **17**). Interestingly, this product could be easily deuterated between the nitrile groups by refluxing it in deuterated methanol, affording **18-D** in quantitative yield. Deuteration can be reversed following the same protocol in regular methanol. Cyclohexanone afforded **19** in excellent yield in combination with *N*-cyclohexylformamide, demonstrating that only one electron-withdrawing group is enough. Notably, vinylphenylsulfone was a suitable substrate, affording the synthetically useful **20** in good yield.[26] We then focused on exploring different formamides in combination with benzylidenemalononitrile. This reaction tolerates a broader

scope of formamides than the Minisci reaction, although we are still limited to alkyl substituents (products **21** - **26**). Sterically challenged formamides were successful substrates, affording the desired products in moderate to good yield (compounds **22** and **23**). Interestingly, a formamide prepared from the chiral auxiliary (*S*)-1-phenethylamine was successfully employed (compounds **25**). Although the diastereoselectivity was low, the diastereomers were easily separated by column chromatography. This method offers the opportunity to prepare enantioenriched compounds. Finally, *N*,*N*-dimethylformamide was also examined as substrate, showing preference towards forming the methylene radical, thus affording a 1:2 mixture of the carbamoylated and alkylated products, respectively (compounds **26**). This selectivity had been previously observed in this type of transformation and is consistent with the number of N-CH bonds (6) overcoming the lower BDE of the OC-H bond.[27] It is worth noting that considering the number of C-H bonds (1 vs. 6), the normalized selectivity for the formyl substitution is still high (3 (OCH): 1 (NCH)), in line with the selectivity observed for monoalkylformamides and even with diisopropylformamide.

We then performed some experiments to gain insight into the mechanism of the reactions (Figure 4A). Using phenanthridine as a substrate, removing either **A**, TFA, or PyO shuts down the reaction completely, as does running it in the dark. As expected, adding two equivalents of TEMPO completely inhibits the reaction. No adduct could be detected, which can be attributed to the short lifetime of the adduct, which is an unstable carbamic acid ester. Deoxygenation experiments point towards a closed catalytic cycle, as 80% of the product (GC) was formed under these conditions. Based on this, literature precedents, and our previous investigations,[22] we propose the mechanism depicted in Figure 4B. The protonated photocatalyst **[A-H$^+$]** is photoexcited and undergoes single electron oxidation of the PyO, forming the active HAT catalyst. This *N*-oxyl radical can then abstract a hydrogen atom from formamide, generating the carbamoyl radical. The radical addition to the protonated heterocycle affords the intermediate radical cation **I**, which is reduced to intermediate **II,** cycling back the active photocatalyst. Regarding the HAT catalyst, the resulting PyOH is significantly more acidic than TFA and can protonate the azaarene, regenerating the PyO. The dihydroquinoline **II** can then be oxidized to the product *via* a self-oxidation mechanism with hydrogen evolution. A unit of radical cation **I** can accept a hydride from intermediate **II**, generating molecular hydrogen and intermediates **IV** and **III**, the former being the protonated product and the latter a captodative radical. A simple proton transfer between these intermediates affords the final product and regenerates the intermediate **I**.

Our proposal for the Giese-type addition is similar to the one of the Minisci reaction in the initial steps (Figure 5). The addition of the carbamoyl radical to the electron-deficient olefin is followed by the reduction of radical intermediate **I** to the anionic intermediate **II**, regenerating the active photocatalyst. Eventually, anion **II** can be protonated by the PyOH, regenerating the HAT catalyst and affording the final product.

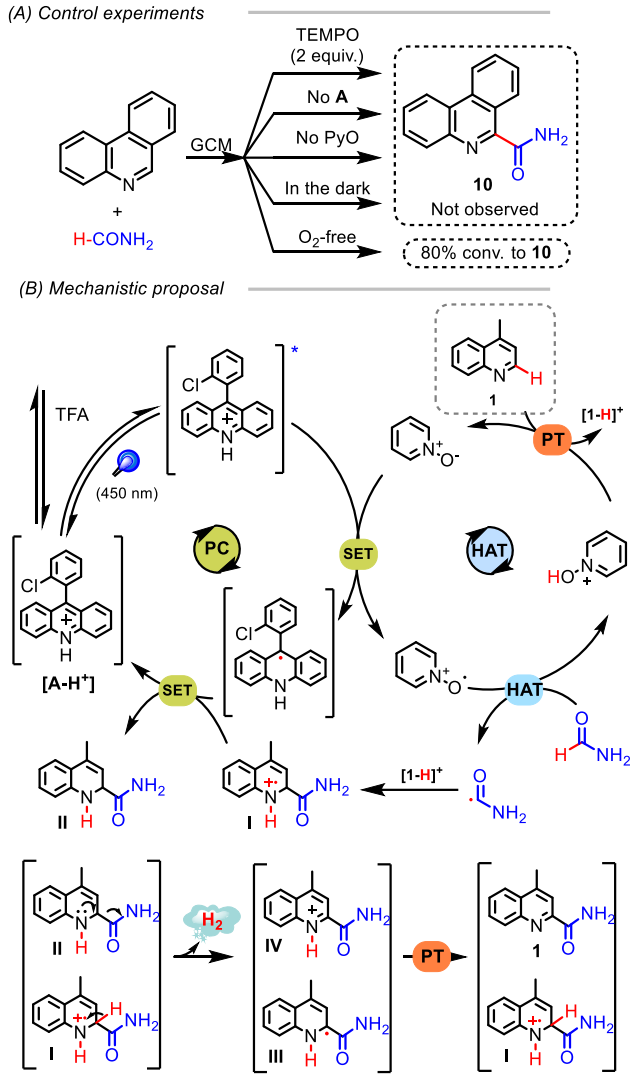


Figure 4. (a) Control experiments. (b) Mechanistic proposal for the Minisci carbamoylation.

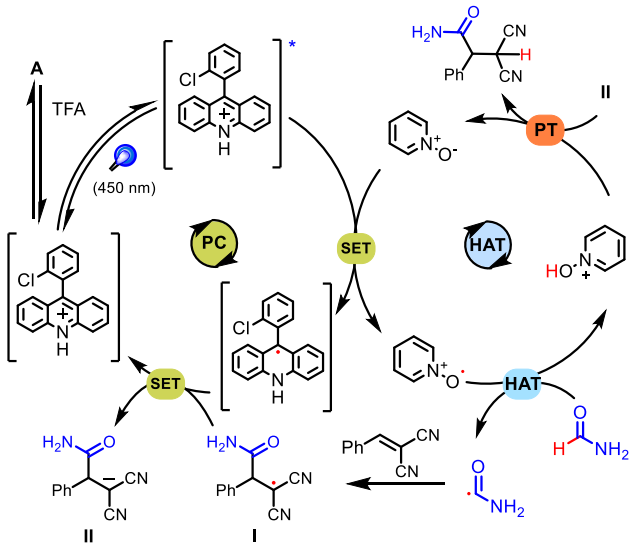


Figure 5. Mechanistic proposal for the Giese carbamoylation.

3. Conclusions

We have developed a methodology for the oxidant-free carbamoylation of azaarenes and olefins *via* dual photoredox/HAT catalysis. Our protocol is compatible with a wide array of substrates, affording valuable carboxamides in good to excellent yields while using readily available catalysts and visible light at room temperature. In addition, this methodology tolerates air and water, thus resulting in an inexpensive, user-friendly and sustainable protocol.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and optimization, mechanistic studies, and full characterization (including NMR spectra) of all products (PDF)

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Author Contributions

All authors have given approval to the final version of the manuscript. / ‡These authors contributed equally.

Notes

The authors declare no competing financial interest.

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