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# Visible-Light-Driven CarboxyLic Amine Protocol (CLAP) for the Synthesis of 2-Substituted Piperazines under Batch and Flow Conditions

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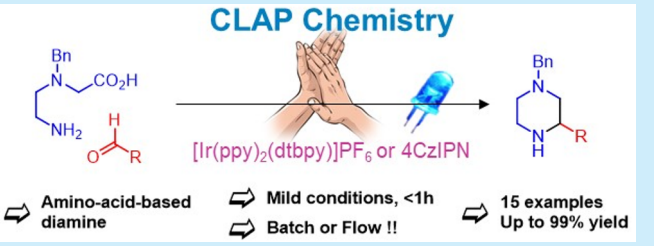
**ABSTRACT:** Piperazines are privileged scaffolds in medicinal chemistry. Disclosed herein is a visible-light-promoted decarboxylative annulation protocol between a glycine-based diamine and various aldehydes to access 2-aryl, 2-heteroaryl, as well as 2-alkyl piperazines. The iridium-based complex $[Ir(ppy)_2(dtbpy)]PF_6$ and carbazolyl dicyanobenzene 4CzIPN were found to be the photocatalysts of choice to efficiently perform the transformation under mild conditions, whether in batch or in continuous mode.






The piperazine skeleton is the third most common nitrogen heterocyclic core encountered in approved pharmaceuticals (Figure 1).[1] The construction of this saturated six-membered ring scaffold has thus been extensively investigated.[2] However, efficient synthetic pathways to access $\alpha$-substituted piperazines are somewhat limited. Available approaches include the di- or monoketopiperazine reduction, the Mitsunobu transformation,[3] hydroamination,[4] condensation of diamines on diols,[5] $\alpha$-bromo ester or epoxide derivatives,[6] lithiation/trapping of *N*-Boc piperazines,[7] and photoredox catalysis.[8] In 2013, a breakthrough was achieved by Bode's group when first developing the SnAP (Tin Amine Protocol),[9] shortly followed by the photocatalytic SLAP (SiLicon Amine Protocol) variant (Scheme 1).[10] These straightforward strategies allow access to a wide variety of saturated *N*-heterocycles including piperazines, morpholines, thiomorpholines, oxazepines, and diazepines. For the preparation of piperazines, the SnAP reagents are toxic diaminostannane compounds, hence the development by Bode's group of a safer, tin-free SLAP protocol making use of diaminosilyl reagents. In both protocols, these key reagents react with either aldehydes or ketones to generate the corresponding aldimines/ketimines, followed by carbon-centered radical generation. This nucleophilic radical then adds to the aldimine/ketimine group in a 6-*endo*-trig mode, to generate the six-membered ring and the nitrogen-centered aminyl radical, the reduction of which generates the nitrogen-anion that is finally protonated by the solvent. (See Scheme 1.) Very recently, on the basis of the same photoinitiated concept, an alternative strategy was described from amino-dihydropyridine (DHP) reagents. Indeed, similarly to alkyl silicon reagents, it was previously found that the 4-alkyl Hantzsch ester moiety can lead to the

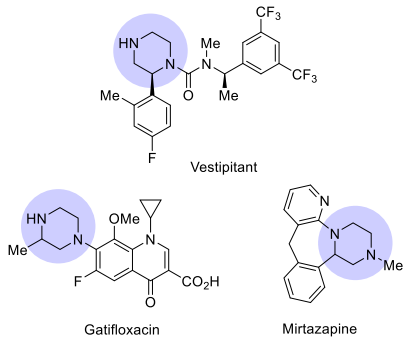



**Figure 1.** Examples of drugs containing a piperazine core.

**Scheme 1. Synthesis of 2-Substituted Piperazines**

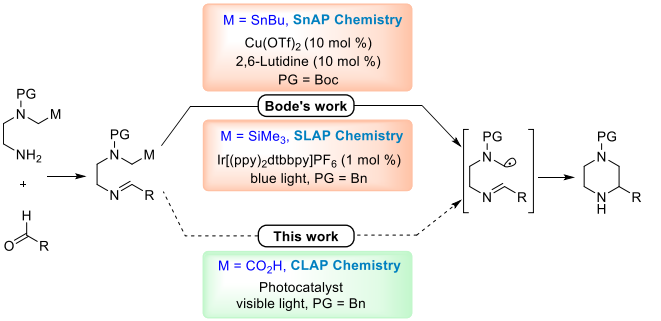



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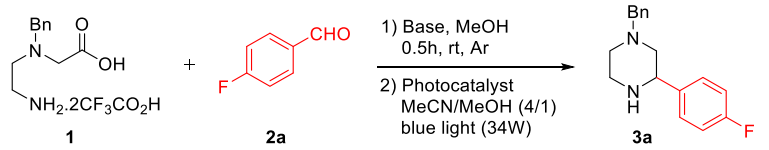
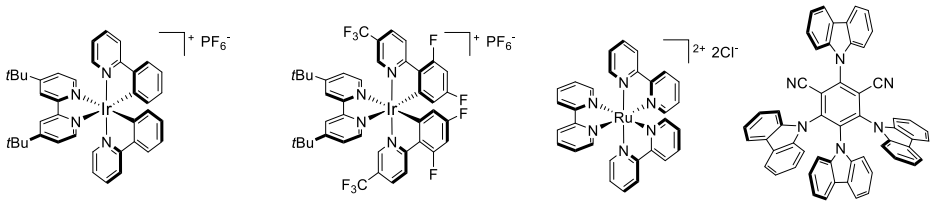
**Table 1. Optimization of the Piperazine Synthesis**[a]




| entry | base | aldehyde **2a** (equiv) | photocatalyst (mol %) | irradiation time (h) | yield (%)[b] |
|---|---|---|---|---|---|
| 1 | KOH | 1 | **Ir1** (1) | 3 | 90 |
| 2 | $Cs_2CO_3$ | 1 | **Ir1** (1) | 3 | 60 |
| 3 | $K_2HPO_4$ | 1 | **Ir1** (1) | 3 | 25 |
| 4 | CsF | 1 | **Ir1** (1) | 3 | 38 |
| 5 | TMG | 1 | **Ir1** (1) | 3 | 57 |
| 6 | DBU | 1 | **Ir1** (1) | 3 | 60 |
| 7 | KOH | 1.4 | **Ir1** (1) | 3 | 95 |
| 8 | KOH | 1.4 | **Ir1** (1) | 0.5 | 95 |
| 9 | KOH | 1.4 | **Ir1** (1) | 3 | 90 |
| 10 | KOH | 1.4 | **Ir1** (1) | 3 | 85 |
| 11 | KOH | 1.4 | **Ir1** (1) | 3 | 75 |
| 12 | KOH | 1.4 | **Ir1** (0.5) | 3 | 90 |
| 13 | KOH | 1.4 | **Ir1** (0.1) | 3 | 85 |
| 14 | KOH | 1.4 | **Ir2** (1) | 3 | 33 |
| 15 | KOH | 1.4 | $Ru(bpy)_3Cl_2$ (1) | 3 | 33 |
| 16 | KOH | 1.4 | 4CzIPN (1) | 3 | 70 |
| 17 | KOH | 1.4 | 4CzIPN (5) | 3 | 92 |
| 18 | KOH | 1.4 | none | 3 | 0 |
| 19[c] | KOH | 1.4 | **Ir1** (1) | 3 | 0 |

[a]Each reaction was performed at room temperature, under blue-light irradiation (34 W) on a 0.1 mmol scale of **1** in 0.05 M concentration in a MeCN/MeOH (4/1) degassed solution in the presence of 4.1 equiv of base. [b]NMR yields using 1,3,5-trimethoxybenzene as an internal standard. [c]Experiment performed in the dark.

corresponding alkyl radical by oxidative single-electron transfer.[11]

In 2014, the group of MacMillan extended the photocatalyzed oxidative decarboxylation on amino acids.[12] This triggered significant interest oriented toward the application of such processes in a wide variety of reactions.[13] Among them, Rueping demonstrated that the resulting $\alpha$-amino radical could undergo an *intermolecular* addition onto an imine.[14]

From these studies, we asked ourselves whether a *decarboxylative* photoredox cyclization process might be envisioned for the construction of 2-substituted piperazines.

In this Letter, we describe our work toward a photocatalytic approach to the synthesis of such scaffolds from easily available, environmentally benign amino-acid-based substrates. In line with the SnAP and SLAP chemistry, we propose to name this new annulation process the CarboxyLic Amine Protocol (CLAP).

The viability of our approach was initially investigated on a model reaction between the diamino acid **1** (easily available from the natural amino acid glycine) and 4-fluorobenzaldehyde **2a**. The reaction was performed under blue-light irradiation in the presence of 1 mol % of the $[Ir(ppy)_2(dtbpy)]PF_6$ (**Ir1**) photocatalyst (Table 1). In the first set of experiments, **2a** was reacted in a one to 1:1 ratio with diamino carboxylic acid **1**. Several inorganic bases (KOH, $Cs_2CO_3$, $K_2HPO_4$, and CsF) as well as organic ones (TMG, tetramethylguanidine; DBU, 1,8-diazabicyclo[5,4,0]undec-7-ene) were evaluated (entries 1−6). After 3 h of irradiation, we were delighted to observe, in all cases, the formation of the desired cyclized product piperazine **3a**. Although acceptable yields were obtained with both organic bases and $Cs_2CO_3$, the best result was achieved in the presence of KOH, yielding 90% of **3a** (entry 1). Increasing the proportion of aldehyde **2a** to 1.4 equiv led to an increase in yield to 95% regardless of whether the irradiation time was maintained at 3 h or, more interestingly, decreased to 30 min (entries 7 and 8).

Next, the catalytic performance of various photocatalysts, including iridium- or ruthenium-based complexes and the purely organic carbazolyl dicyanobenzene 4CzIPN, was evaluated (entries 11−17). From this survey, **Ir1** appears to be the most active and, interestingly, remains satisfactory with a catalyst loading as low as 0.1 mol % (entries 11−14). It should be emphasized that the easily accessible organophotocatalyst 4CzIPN showed remarkable effectiveness to perform the reaction, although 5 mol % loading was required (entries 16 and 17). Blank experiments were conducted either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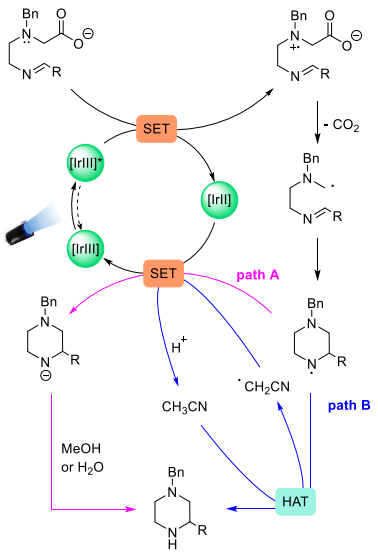
in the absence of photosensitizer (entry 18) or without photoexcitation (entry 19), and this suggested that both are necessary to promote the reaction.[15]

From this first successful set of experiments, a plausible mechanism can already be proposed starting from the imine, generated prior to irradiation by condensation between diamine **1** and aldehyde **2a** (Scheme 2). In the first step, the

**Scheme 2. Proposed Mechanism for Ir-based Catalyst**




amino moiety is suspected to be oxidized by the photoexcited iridium catalyst $[Ir(ppy)_2(dtbpy)]PF_6$.[16] A consecutive decarboxylation would lead to the $\alpha$-amino radical, which then would undergo an intramolecular addition onto the imine. From the resulting N-centered radical, two pathways can be hypothesized. In accordance with the literature, following path A, this latter radical might be reduced by the Ir(II) species to give, after protonation by methanol or water, the piperazine. Although this reduction might first seem to be unfavorable ($E_{1/2}^{red}$ = −1.70 V vs SCE for dialkylaminyl radicals and $E_{1/2}^{red}$[Ir(III)/Ir(II)] = −1.51 V vs SCE), Bode has proposed a stabilizing effect of the adjacent substituents, thus rendering the reduction feasible.[10] Because we found that the reaction could be performed in the presence of 4CzIPN, which has an even less favorable reduction potential ($E_{1/2}^{red}$(4CzIPN/4CzIPN$^-$) = −1.21 V vs SCE), we assume that another mechanism could occur through path B. As such, we envision that the N-centered radical could abstract a hydrogen atom from acetonitrile (bond dissociation energy $D_{298}$(H−$CH_2CN$) = 405.8 ± 4.2 kJ mol$^{-1}$)[17] to afford the piperazine and the cyanomethyl radical $^{\bullet}CH_2CN$. The latter can be readily reduced by the photocatalyst ($E_{1/2}^{red}$[$^{\bullet}CH_2CN/^{-}CH_2CN$] = −0.72 V),[18] thereby closing the catalytic cycle.

With suitable conditions established, that is, 1 equiv of amino acid, 1.4 equiv of aldehyde, 4.1 equiv of KOH, and 1 mol % of **Ir1**, the scope of the annulation process was examined with a variety of aldehydes (Scheme 3). These include diversely substituted benzaldehyde derivatives, heteroaromatics, as well as aliphatic aldehydes. For the benzaldehydes, this study revealed that a wide range of substituents, including electron-donating or -withdrawing ones attached to the benzaldehyde in the ortho, meta or para position, are well-tolerated, furnishing the corresponding piperazines in up to 92% yield. As exceptions, 4-cyanobenzaldehyde led to a lower, albeit satisfactory, yield of 70%, whereas 4-nitrobenzaldehyde failed to give the desired product. The heteroaromatics thiofurfural, furfural, and nicotinaldehyde were good performers in this CLAP transformation, furnishing **3k**, **3l**, and **3m** in 77, 87, and 80% yields, respectively. Among the aliphatic aldehydes, cylohexanecarboxaldehyde and propanal yielded the corresponding annulated adducts **3n** and **3o** in 99 and 87% yield, respectively. Unfortunately, when the annulation process was attempted with trifluoroacetaldehyde ethyl hemiacetal, the 2-trifluoromethyl piperazine was not obtained. Similarly, the reactions with ketones failed during the prerequisite ketimine formation. Despite several dehydration conditions tested, the predominant product was the 4-benzylpiperazin-2-one, resulting from the intramolecular lactamization of substrate **1**, with no traces of the desired ketimine.

Following the development of the above carboxylic amine protocol, we discovered that the transformation proceeds very quickly under batch conditions, with the reaction being over in ∼30 min. This observation prompted us to transpose this reaction from batch to continuous mode. Compared with classical batch processes, an increased surface exposed to light and more homogeneous irradiation are among the multiple benefits of continuous-flow conditions for light-mediated reactions.[19] As a powerful tool in organic synthesis, flow chemistry has now become common in a wide range of chemical industries, including the pharmaceutical sector for drug discovery, development, and manufacturing.[20] In the photocatalysis area, a good number of batch transformations have been transposed to continuous-flow processes.[21]

The batch conditions for the carboxylic amine protocol were not directly transposable to flow conditions due to the presence of solids that could clog the flow device. A precipitate, most probably potassium trifluoroacetate, forms during the course of the reaction when KOH is used. This led us to replace KOH by 1,8-diazabicyclo[5.4.0]undec-7-ene, which does not form a precipitate during the reaction. In addition, we decided to test the flow transformation in the presence of the 4CzIPN. This photocatalyst, despite its requirement for higher loading than **Ir1**, is particularly cost-attractive and, being purely organic, does not contain the expensive and potentially toxic iridium heavy metal, residual traces of which would have to be tightly controlled in the piperazine if the end use included biological testing. (The permitted daily exposure for Ir is 100 ppm/day for oral route administration and 10 ppm/day for I.V.)

Similarly to the batch procedure, the imine was preformed for 30 min before being mixed into a methanol/acetonitrile (4/1) solution containing the photoinitiator (Table 2). After degassing, the mobile phase was introduced into a Vaportec photoreactor at an initial flow rate of 1.5 mL·min$^{-1}$ within 6.7 min of residence time. This led to the piperazine **3a** in 65% isolated yield (entry 1). Gratifyingly, an improved yield of 80% was obtained when the residence time was reduced to only 3 min (entry 3). Finally, a scale-up continuous experiment from 0.2 to 2.5 mmol led to the photoannulated adduct in 77% isolated yield within ∼30 min (entry 5).

In summary, we have demonstrated that a straightforward synthesis of 2-aryl, 2-heteroaryl, as well as 2-alkyl piperazines is possible through a photoinitiated decarboxylative annulation protocol between a diamine and a large variety of aldehydes. Advantages include easy access to the building block **1** derived from the natural amino acid glycine, the use of a purely organic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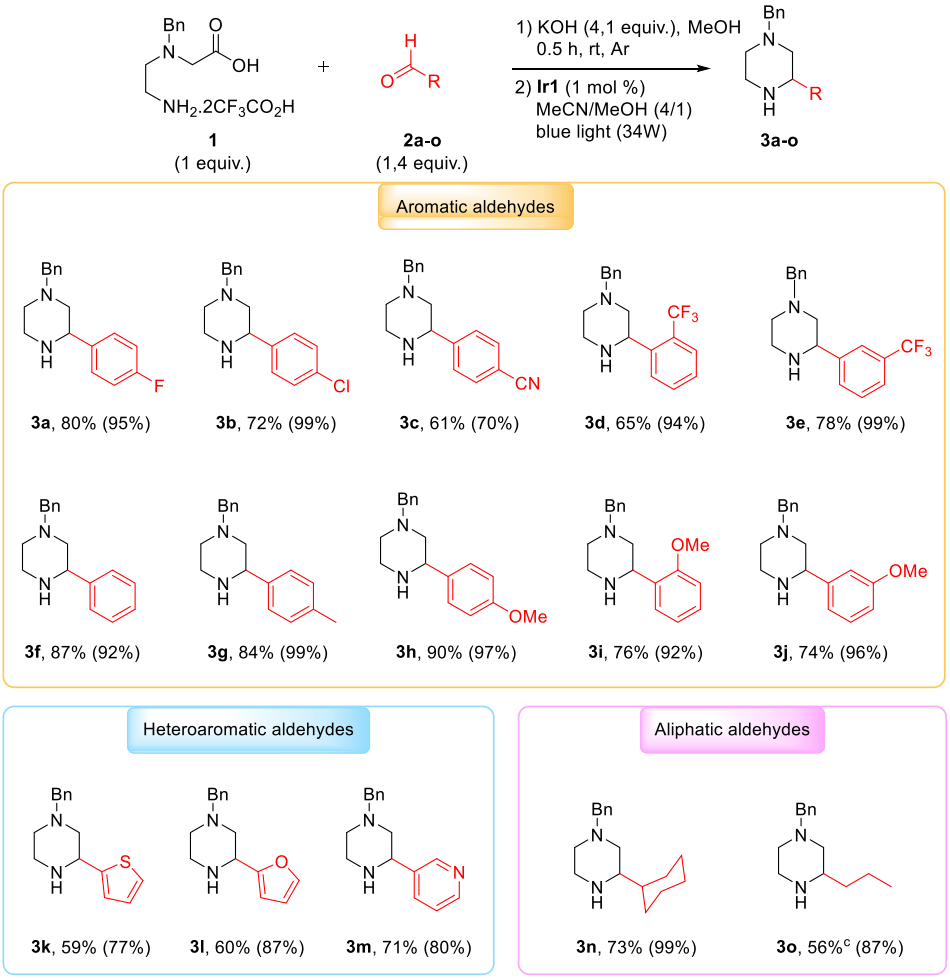
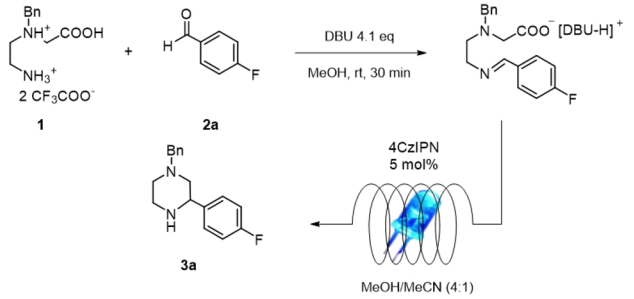
**Scheme 3. Variation of Substrates**[a,b]




[a]Each reaction was performed at room temperature under blue-light irradiation (34 W) on a 0.1 mmol scale of **1** in 0.05 M concentration in a MeCN/MeOH (4/1) degassed solution. [b]Values outside brackets are the isolated yields, and the values inside brackets are the NMR yields using 1,3,5-trimethoxybenzene as an internal standard. [c]Few impurities remain after isolation.

**Table 2. Continuous Process Optimization**




| entry | flow rate (mL·min$^{-1}$) | residence time (min) | yield (%) |
|---|---|---|---|
| 1 | 1.5 | 6.7 | 65 |
| 2 | 2.5 | 4 | 76 |
| 3 | 3.33 | 3 | 80 |
| 4 | 5 | 2 | 75 |
| 5 | 3.33 | 3 | 77[a] |

[a]Reaction performed with 2.5 mmol (1.09 g) of diamine.

photoredox catalyst, as well as the successful transposition of this reaction from batch to flow conditions. These render the newly developed CLAP protocol a powerful alternative to the current existing methods for the synthesis of 2-substituted piperazines.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01759.

Experimental procedures and accompanying analytical data ($^1$H and $^{13}$C NMR, IR, and MS) for all new compounds (PDF)

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## Notes

The authors declare no competing financial interest.

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