



**HAL**  
open science

# Visible-light-driven carboxylic amine protocol (clap) for the synthesis of 2-substituted piperazines under batch and flow conditions

Robin Gueret, Lydie Pelinski, Till Bousquet, Mathieu Sauthier, Vincent Ferey, Antony Bigot

## ► To cite this version:

Robin Gueret, Lydie Pelinski, Till Bousquet, Mathieu Sauthier, Vincent Ferey, et al.. Visible-light-driven carboxylic amine protocol (clap) for the synthesis of 2-substituted piperazines under batch and flow conditions. *Organic Letters*, 2020, *Organic Letters*, 22 (13), pp.5157-5162. 10.1021/acs.orglett.0c01759 . hal-04312599

**HAL Id: hal-04312599**

**<https://hal.univ-lille.fr/hal-04312599>**

Submitted on 28 Nov 2023

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

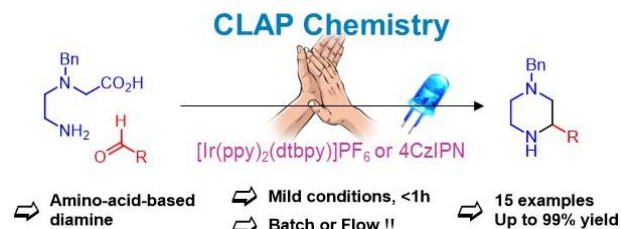
# Visible light-driven CarboxyLic Amine Protocol (CLAP) for the synthesis of 2-substituted piperazines in batch and flow conditions

Robin Gueret, Lydie Pelinski, Till Bousquet,\* Mathieu Sauthier, Vincent Ferey, Antony Bigot\*

Supporting Information Placeholder

[Paste publication-size TOC graphic here]

**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. Iridium-based complex  $[\text{Ir}(\text{ppy})_2(\text{dtbbpy})]\text{PF}_6$  or carbazolyl dicyanobenzene 4CzIPN were found to be the photocatalysts of choice to perform efficiently 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).<sup>1</sup> The construction of this saturated 6-membered ring scaffold has thus been extensively investigated.<sup>2</sup> However, efficient synthetic pathways to access  $\alpha$ -substituted piperazines are somewhat limited. Available approaches include the di- or monoketopiperazine reduction, the Mitsunobu transformation,<sup>3</sup> hydroamination,<sup>4</sup> condensation of diamines on diols,<sup>5</sup>  $\alpha$ -bromo ester or epoxide derivatives,<sup>6</sup> lithiation/trapping of *N*-Boc piperazines,<sup>7</sup> and photoredox catalysis.<sup>8</sup> In 2013, a breakthrough was achieved by Bode's group when first developing the SnAP (Tin Amine Protocole)<sup>9</sup> shortly followed by the photocatalytic SLAP (SiLicon Amine Protocole)<sup>10</sup> variant (Scheme 1). 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 thus the development by Bode's group of a safer, tin-free SLAP protocole making use of diaminosilyl reagents. In both protocols, these key reagents react either with 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 6-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, based on 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 4-alkyl Hantzsch ester moiety can lead to the corresponding alkyl radical by oxidative single electron transfer.<sup>11</sup>

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

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

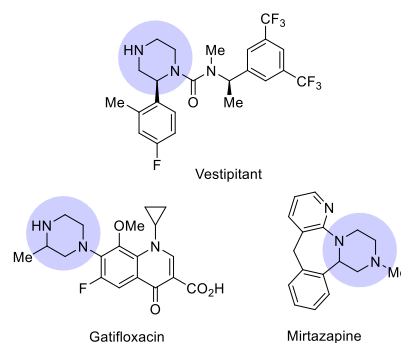
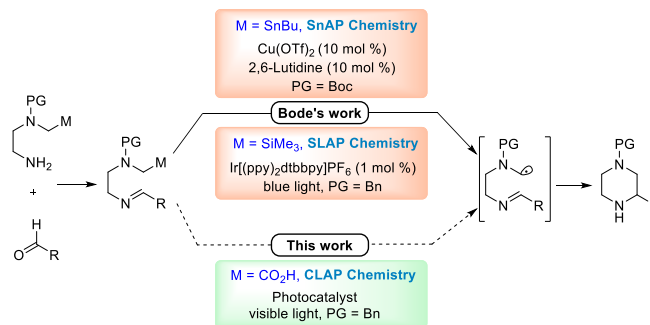


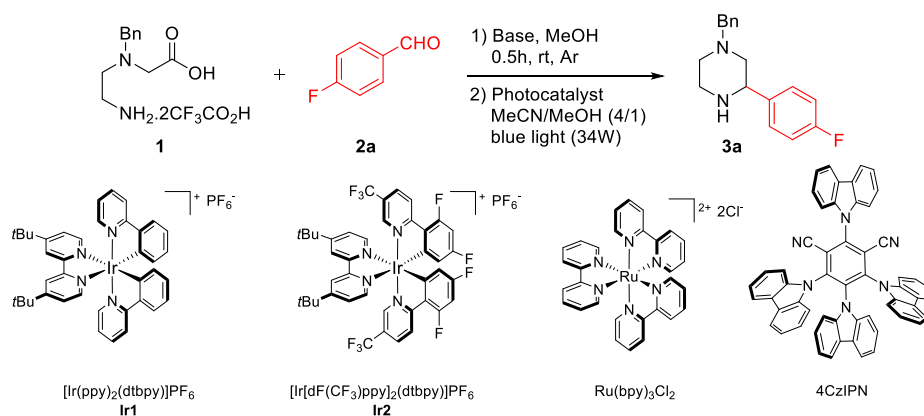
Figure 1. Exemple of drugs containing piperazine core



Scheme 1. Synthesis of 2-substituted piperazines

In this paper, we describe our work towards 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 CarboxyLic Amine Protocol (CLAP).

The viability of our approach was initially investigated on a model reaction between the diamino acid **1** (easily available from natural amino-acid glycine) and 4-fluorobenzaldehyde **2a**. The reaction was performed under blue light irradiation in the presence of 1 mol% of the  $[\text{Ir}(\text{ppy})_2(\text{dtbbpy})]\text{PF}_6$  (**Ir1**) photocatalyst (Table 1). In a first set of experiments, **2a** was reacted in a one to one ratio with diamino carboxylic acid **1**. Several inorganic bases (KOH,

**Table 1. Optimization of the piperazine synthesis<sup>a</sup>**

entry	base	aldehyde <b>2a</b> (eq.)	photocatalyst (mol %)	irradiation time (h)	yield (%) <sup>b</sup>
1	KOH	1	<b>Ir1</b> (1)	3	90
2	Cs <sub>2</sub> CO <sub>3</sub>	1	<b>Ir1</b> (1)	3	60
3	K <sub>2</sub> HPO <sub>4</sub>	1	<b>Ir1</b> (1)	3	25
4	CsF	1	<b>Ir1</b> (1)	3	38
5	TMG	1	<b>Ir1</b> (1)	3	57
6	DBU	1	<b>Ir1</b> (1)	3	60
7	KOH	1.4	<b>Ir1</b> (1)	3	95
8	KOH	1.4	<b>Ir1</b> (1)	0.5	95
9	KOH	1.4	<b>Ir1</b> (1)	3	90
10	KOH	1.4	<b>Ir1</b> (1)	3	85
11	KOH	1.4	<b>Ir1</b> (1)	3	75
12	KOH	1.4	<b>Ir1</b> (0.5)	3	90
13	KOH	1.4	<b>Ir1</b> (0.1)	3	85
14	KOH	1.4	<b>Ir2</b> (1)	3	33
15	KOH	1.4	Ru(bpy) <sub>3</sub> Cl <sub>2</sub> (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 <sup>c</sup>	KOH	1.4	<b>Ir1</b> (1)	3	0

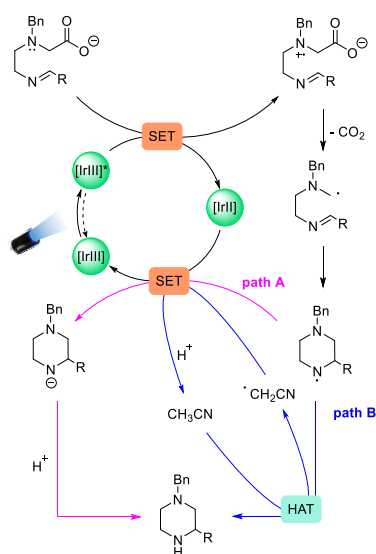
<sup>a</sup>Each reaction was performed at room temperature, under blue light irradiation (34W) on a 0.1 mmol scale of **1** in 0.05 M concentration in a MeCN/MeOH (4/1) degassed solution, in the presence of 4.1 eq. of base. <sup>b</sup>NMR yields using 1,3,5-trimethoxybenzene as internal standard. 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

Cs<sub>2</sub>CO<sub>3</sub>, K<sub>2</sub>HPO<sub>4</sub> 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 3h 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<sub>2</sub>CO<sub>3</sub>, 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 eq. led to an increase in yield to 95% regardless of whether the irradiation time was maintained at 3h or more interestingly decreased to 30 min (entries 7-8).

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 16-17). Blank experiments were conducted either in the absence of photosensitizer (entry 18) or without photoexcitation (entry 19) and this suggested that both are necessary to promote the reaction.<sup>15</sup> From this first successful set of experiments, a plausible mechanism can be already proposed starting from the imine, generated prior to irradiation by condensation between the diamine **1** and the aldehyde **2a** (Scheme 2). In a first step, the amino moiety is suspected to be oxidized by the photoexcited iridium catalyst [Ir(ppy)<sub>2</sub>(dtbbpy)]PF<sub>6</sub>. A consecutive decarboxylation would lead to the α-amino radical, which then would undergo an intramolecular addition onto the imine. From the resulting N-centered radical,

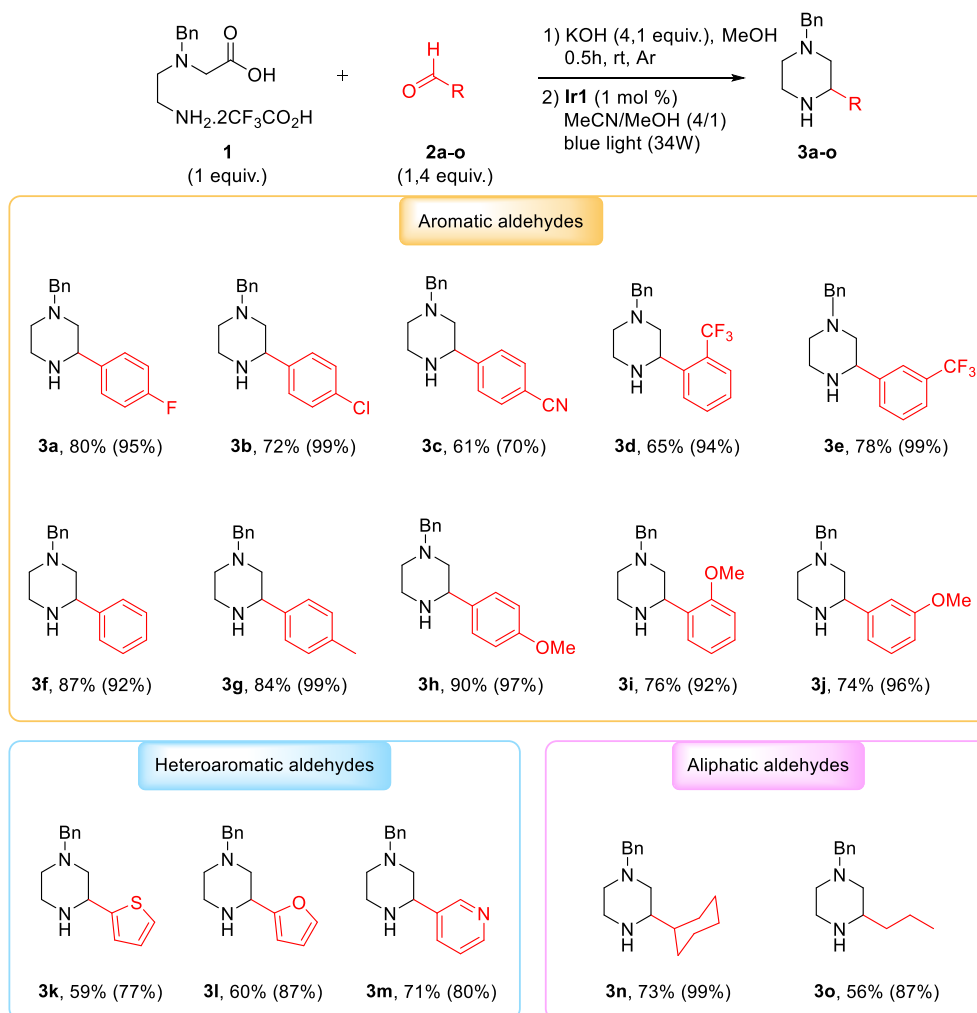
## Scheme 2. Proposed Mechanism for Ir-based catalyst



two pathways can be hypothesized. In accordance with the literature, following the 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 ( $E_{1/2}^{\text{red}} = -1.70$  V vs SCE for dialkylaminy radicals and  $E_{1/2}^{\text{red}}[\text{Ir(III)/Ir(II)}] = -1.51$  V vs SCE), Bode has proposed a stabilizing effect of the adjacent substituents, thus rendering the reduction feasible.<sup>10</sup> As we found that the reaction could be performed in the presence of 4CzIPN, which has an even less favorable reduction potential ( $E_{1/2}^{\text{red}}(4\text{CzIPN}/4\text{CzIPN}^-) = -1.21$  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  $D_{298}(\text{H}-\text{CH}_2\text{CN}) = 405.8 \pm 4.2$  kJ.mol<sup>-1</sup>)<sup>16</sup> to afford the piperazine and the cyanomethyl radical  $\cdot\text{CH}_2\text{CN}$ . This latter can be readily reduced by the photocatalyst ( $E_{1/2}^{\text{red}}[\cdot\text{CH}_2\text{CN}/-\text{CH}_2\text{CN}] = -0.72$  V)<sup>17</sup> thereby closing the catalytic cycle.

With suitable conditions established, *i.e.* 1 equivalent of amino acid, 1.4 equivalent of aldehyde, 4.1 equivalent of KOH, 1 mol % of **Ir1**, the scope of the annulation process was examined with a variety of aldehydes (Scheme 3).

## Scheme 3. Variation of Substrates<sup>a,b</sup>



<sup>a</sup>Each reaction was performed at room temperature, under blue light irradiation (34W) on a 0.1 mmol scale of **1** in 0.05 M concentration in a MeCN/MeOH (4/1) degassed solution. <sup>b</sup>The values outside bracket are the isolated yields and the values inside brackets are the NMR yields using 1,3,5-trimethoxybenzene as internal standard.

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 *ortho*, *meta* or *para* position is well tolerated, furnishing the corresponding piperazines with up to 92% yield. As exceptions, 4-cyanobenzaldehyde led to a lower, albeit satisfactory, yield of 70% while 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. Amongst the aliphatic aldehydes, cyclohexanecarboxaldehyde and propanal yielded the corresponding annulated adducts **3n** and **3o** with 99 and 87%, 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 intramolecular lactamization of the substrate **1**, with no traces of the desired ketimine.

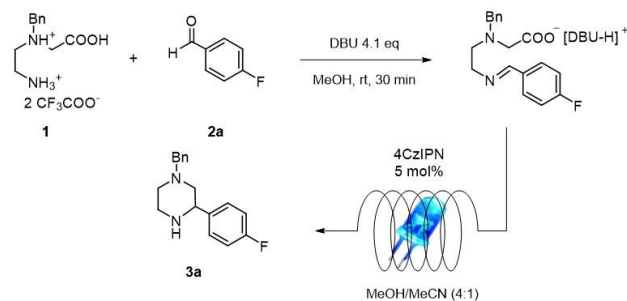
Following the development of the above carboxylic amine protocol, we discovered that the transformation proceeds very quickly in batch conditions, the reaction being over in approximately 30 minutes. This observation prompted us to transpose this reaction from batch to continuous mode. Compared to classical 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.<sup>18</sup> 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.<sup>19</sup> In the photocatalysis area, a good number of batch transformations have been transposed to continuous flow processes.<sup>20</sup>

The batch conditions for the carboxylic amine protocol were not directly transposable to flow conditions due to the presence of solids which 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 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 pricy 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 (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 Vapourtec® photoreactor at an initial flow rate of 1.5 mL.min<sup>-1</sup> within 6.7 min of residence time. This led to the piperazine **3a** with 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 photo-annulated adduct with 77% isolated yield within approximately 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 natural amino-acid glycine, the use of purely organic photoredox catalyst

**Table 2. Continuous process optimization**



entry	flow rate (mL.min <sup>-1</sup> )	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% <sup>a</sup>

<sup>a</sup> Reaction performed with 2.5 mmol (1.09 g) of diamine.

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 on the ACS Publications website.

Experimental procedures and accompanying analytical data (<sup>1</sup>H and <sup>13</sup>C NMR, IR, and MS) for all new compounds

## AUTHOR INFORMATION

### Corresponding Authors

**Till Bousquet** – Univ. Lille, CNRS, Centrale Lille, ENSCL, Univ. Artois, UMR 8181, Unité de Catalyse et Chimie du Solide, F-59000 Lille, France; orcid.org/0000-0003-3022-3494. Email: till.bousquet@univ-lille.fr

**Antony Bigot** – Pre Development Science Chemical Synthesis, Sanofi, 13 quai Jules Guesde, 94403 Vitry-Sur-Seine, Cedex, France; orcid.org/0000-0003-3320-3755, Email: antony.bigot@sanofi.com.

### Authors

**Robin Gueret** – Univ. Lille, CNRS, Centrale Lille, ENSCL, Univ. Artois, UMR 8181, Unité de Catalyse et Chimie du Solide, F-59000 Lille, France

**Lydie Pelinski** – Univ. Lille, CNRS, Centrale Lille, ENSCL, Univ. Artois, UMR 8181, Unité de Catalyse et Chimie du Solide, F-59000 Lille, France

**Mathieu Sauthier** – Univ. Lille, CNRS, Centrale Lille, ENSCL, Univ. Artois, UMR 8181, Unité de Catalyse et Chimie du Solide, F-59000 Lille, France

**Vincent Ferey** – PDP Innovation, Sanofi, 371 rue du Professeur Joseph Blayac, 34184 Montpellier, France

## Notes

Any additional relevant notes should be placed here.

## ACKNOWLEDGMENT

Sanofi is gratefully acknowledged for financial support and for a post-doctoral grant (R. G.). CNRS, Chevreul institute (FR 2638), Ministère de l'Enseignement Supérieur et de la Recherche, Région Nord – Pas de Calais and FEDER are acknowledged for supporting and funding partially this work.

We also would like to thank Céline Delabre (UCCS) for their technical support and Mr Alexandre Farag (trainee in Sanofi) for initial experiments demonstrating the validity of the described approach. Finally, we would like to thank Dr Andrew Van-Sickle (Vitry Drug Substance, Sanofi) for help in proofreading.

## REFERENCES

- (1) Vitaku, E.; Smith, D. T.; Njardarson, J. T. Analysis of the Structural Diversity, Substitution Patterns, and Frequency of Nitrogen Heterocycles among U.S. FDA Approved Pharmaceuticals. *J. Med. Chem.* **2014**, *57*, 10257–10274
- (2) Gettys, K. E.; Ye, Z.; Dai, M. Recent Advances in Piperazine Synthesis **2017**, *49*, 2589–2604
- (3) Crestey, F.; Witt, M.; Jaroszewski, J. W.; Franzyk, H. Expedite Protocol for Construction of Chiral Regioselectively N-Protected Monosubstituted Piperazine, 1,4-Diazepane, and 1,4-Diazocane Building Blocks. *J. Org. Chem.* **2009**, *74*, 5652–5655
- (4) (a) Nakhla, J. S.; Wolfe, J. P. A. Concise Asymmetric Synthesis of *cis*-2,6-Disubstituted *N*-Aryl Piperazines via Pd-Catalyzed Carboamination Reactions. *Org. Lett.* **2007**, *9*, 3279–3282. (b) Cochran, B. M.; Michael, F. E. Synthesis of 2,6-Disubstituted Piperazines by a Diastereoselective Palladium-Catalyzed Hydroamination Reaction. *Org. Lett.* **2008**, *10*, 329–332. (c) James, T.; Simpson, I.; Grant, J. A.; Sri-dharan, V.; Nelson, A. Modular, Gold-Catalyzed Approach to the Synthesis of Lead-like Piperazine Scaffolds. *Org. Lett.* **2013**, *15*, 6094–6097.
- (5) (a) Nordstrøm, L. U.; Madsen, R. Iridium catalysed synthesis of piperazines from diols. *Chem. Commun.* **2007**, 5034–5036. (b) Lorentz-Petersen, L. L. R.; Nordstrøm, L. U.; Madsen, R. Iridium-Catalyzed Condensation of Amines and Vicinal Diols to Substituted Piperazines. *Eur. J. Org. Chem.* **2012**, 6752–6759.
- (6) Vidal-Albalat, A.; Rodríguez, S.; González, F. V. Nitroepoxides as Versatile Precursors to 1,4-Diamino Heterocycles. *Org. Lett.* **2014**, *16*, 1752–1755
- (7) (a) Berkheij, M.; van der Sluis, L.; Sewing, C.; den Boer, D. J.; Terpstra, J. W.; Hiemstra, H.; Iwema Bakker, W. I.; van den Hoogenband, A.; van Maarseveen, J. H. Synthesis of 2-substituted piperazines via direct  $\alpha$ -lithiation. *Tetrahedron Lett.* **2005**, *46*, 2369–2371. (b) Robinson, S. P.; Sheikh, N. S.; Baxter, C. A.; Coldham, I. Dynamic thermodynamic resolution of lithiated *N*-Boc-*N'*-alkylpiperazines. *Tetrahedron Lett.* **2010**, *51*, 3642–3644. (c) Barker, G.; O'Brien, P.; Campos, K. R. Diamine-Free Lithiation-Trapping of *N*-Boc Heterocycles using *s*-BuLi in THF. *Org. Lett.* **2010**, *12*, 4176–4179.
- (8) (a) Musacchio, A. J.; Nguyen, L. Q.; Beard, G. H.; Knowles, R. R. Catalytic Olefin Hydroamination with Aminium Radical Cations: A Photoredox Method for Direct C–N Bond Formation. *J. Am. Chem. Soc.* **2014**, *136*, 12217–12220. (b) McNally, A.; Prier, C. K.; MacMillan, D. W. C. Discovery of an  $\alpha$ -Amino C–H Arylation Reaction Using the Strategy of Accelerated Serendipity. *Science* **2011**, *334*, 1114–1117. (c) Prier, C. K.; MacMillan, D. W. C. Amine  $\alpha$ -heteroarylation via photoredox catalysis: a homolytic aromatic substitution pathway. *Chem. Sci.* **2014**, *5*, 4173–4178. (d) Noble, A.; MacMillan, D. W. C. Photoredox  $\alpha$ -Vinylolation of  $\alpha$ -Amino Acids and *N*-Aryl Amines. *J. Am. Chem. Soc.* **2014**, *136*, 11602–11605. (e) Bissonnette, N. B.; Ellis, J. M.; Hamann, L. G.; Romanov-Michailidis, F. Expedient access to saturated nitrogen heterocycles by photoredox cyclization of imino-tethered dihydropyridines. *Chem. Sci.* **2019**, *10*, 9591–9596. (f) Pantaine, L. R. E.; Milligan, J. A.; Matsui, J. K.; Kelly, C. B.;

Molander, G. A. Photoredox Radical/Polar Crossover Enables Construction of Saturated Nitrogen Heterocycles. *Org. Lett.* **2019**, *21*, 2317–2321.

(9) (a) Vo, C.-V. T.; Mikutis, G.; Bode, J. W. SnAP Reagents for the Transformation of Aldehydes into Substituted Thiomorpholines—An Alternative to Cross-Coupling with Saturated Heterocycles. *Angew. Chem. Int. Ed.* **2013**, *52*, 1705–1708. (b) Luescher, M. U.; Vo, C.-V. T.; Bode, J. W. SnAP Reagents for the Synthesis of Piperazines and Morpholines. *Org. Lett.* **2014**, *16*, 1236–1239. (c) Luescher, M. U.; Bode, J. W. Catalytic Synthesis of *N*-Unprotected Piperazines, Morpholines, and Thiomorpholines from Aldehydes and SnAP Reagents. *Angew. Chem. Int. Ed.* **2015**, *54*, 10884–10888.

(10) Hsieh, S.-Y.; Bode, J. W. Silicon amine reagents for the photocatalytic synthesis of piperazines from aldehydes and ketones. *Org. Lett.* **2016**, *18*, 2098–2101.

(11) Nakajima, K.; Nojima, S.; Sakata, K.; Nishibayashi, Y. Visible-Light-Mediated Aromatic Substitution Reactions of Cyanoarenes with 4-Alkyl-1,4-dihydropyridines through Double Carbon–Carbon Bond Cleavage. *ChemCatChem* **2016**, *8*, 1028–1032.

(12) Zuo, Z.; MacMillan, D. W. C. Decarboxylative Arylation of  $\alpha$ -Amino Acids via Photoredox Catalysis: A One-Step Conversion of Biomass to Drug Pharmacophore. *J. Am. Chem. Soc.* **2014**, *136*, 5257–5260.

(13) (a) Jin, Y.; Fu, H. Visible-Light Photoredox Decarboxylative Couplings. *Asian J. Org. Chem.* **2017**, *6*, 368–385. (b) Li, Y.; Ge, L.; Muhammad, M.; Bao, H. Recent Progress on Radical Decarboxylative Alkylation for Csp<sup>3</sup>–C Bond Formation. *Synthesis* **2017**, *49*, 5263–5284. (c) Xuan, J.; Zhang, Z.-G.; Xiao, W.-J. Visible-Light-Induced Decarboxylative Functionalization of Carboxylic Acids and Their Derivatives. *Angew. Chem. Int. Ed.* **2015**, *54*, 15632–15641. (d) Patra, T.; Maiti, D. Decarboxylation as the Key Step in C–C Bond-Forming Reactions. *Chem. Eur. J.* **2017**, *23*, 7382–7401.

(14) Fava, E.; Millet, A.; Nakajima, M.; Loescher, S.; Rueping, M. Angew. Reductive Umpolung of Carbonyl Derivatives with Visible-Light Photoredox Catalysis: Direct Access to Vicinal Diamines and Amino Alcohols via  $\alpha$ -Amino Radicals and Ketyl Radicals. *Angew. Chem. Int. Ed.* **2016**, *55*, 6776–6779.

(15) In addition, it is worth noticing that residual oxygen is deleterious for the transformation and mixtures has to be degassed prior to irradiation.

(16) Luo, Y R , Comprehensive Handbook of Chemical Bond Energies, CRC Press, Boca Raton, FL, 2007

(17) Bortolamei, N.; Isse, A. A.; Gennaro, A. Estimation of Standard Reduction Potentials of Alkyl Radicals Involved in Atom Transfer Radical Polymerization. *Electrochim. Acta* **2010**, *55*, 8312–8318.

(18) Sambiagio, C.; Noël, T. Flow Photochemistry: Shine Some Light on Those Tubes! *Trends Chem.* **2019**, *2*, 92–106.

(19) (a) Harsanyi, A.; Conte, A.; Pichon, L.; Rabion, A.; Grenier, S.; Sandford, G. One-Step Continuous Flow Synthesis of Antifungal WHO Essential Medicine Flucytosine Using Fluorine. *Org. Process Res. Dev.* **2017**, *21*, 273–276. (b) Bogdan, A. R.; Dombrowski, A. W. Emerging Trends in Flow Chemistry and Applications to the Pharmaceutical Industry. *J. Med. Chem.* **2019**, *62*, 6422–6468. (c) Hughes, D. L. Applications of Flow Chemistry in Drug Development: Highlights of Recent Patent Literature. *Org. Process Res. Dev.* **2018**, *22*, 13–20. (d) May, S. A. Flow Chemistry, Continuous Processing, and Continuous Manufacturing: A Pharmaceutical Perspective. *J. Flow Chem.* **2017**, *7*, 137–145. (e) Gutmann, B.; Cantillo, D.; Kappe, C. O. Continuous-flow technology—a tool for the safe manufacturing of active pharmaceutical ingredients. *Angew. Chem., Int. Ed.* **2015**, *54*, 6688–6728.

(20) (a) Su, Y.; Straathof, N. J. W.; Hessel, V.; Noël, T. Photochemical Transformations Accelerated in Continuous-Flow Reactors: Basic Concepts and Applications. *Chem. Eur. J.* **2014**, *20*, 10562–10589. (b) Cambié, D.; Bottecchia, C.; Straathof, N. J. W.; Hessel, V.; Noël, T. Applications of Continuous-Flow Photochemistry in Organic Synthesis, Material Science, and Water Treatment. *Chem. Rev.* **2016**, *116*, 10276–10341. (c) Staveness, D.; Bosque, I.; Stephenson, C. R. J. Free Radical Chemistry Enabled by Visible Light-Induced Electron Transfer. *Acc. Chem. Res.* **2016**, *49*, 2295–2306. (d) Douglas, J. J.; Sevrin, M. J.; Stephenson, C. R. J. Visible Light Photocatalysis: Applications and New Disconnections in the Synthesis of Pharmaceutical Agents.

*Org. Process Res. Dev.* **2016**, *20*, 1134–1147. (e) Nguyen, J. D.; D'Amato, E. M.; Narayanam, J. M. R.; Stephenson, C. R. J. Engaging Unactivated Alkyl, Alkenyl and Aryl Iodides in Visible-Light-Mediated Free Radical Reactions. *Nat. Chem.* **2012**, *4*, 854–859. (f) Knowles, J. P.; Elliott, L. D.; Booker-Milburn, K. I. Flow Photochemistry: Old Light through New Windows. *Beilstein J. Org. Chem.* **2012**, *8*, 2025–2052. (g) Tucker, J. W.; Zhang, Y.; Jamison, T. F.; Stephenson, C. R. J. Visible-Light Photoredox Catalysis in Flow. *Angew. Chem. Int. Ed.* **2012**, *51*, 4144–4147. (h) Neumann, M.; Zeitler, K. Application of Microflow Conditions to Visible Light Photoredox Catalysis. *Org. Lett.*

**2012**, *14*, 2658–2661. (i) Atodiresei, I.; Vila, C.; Rueping, M. Asymmetric Organocatalysis in Continuous Flow: Opportunities for Impacting Industrial Catalysis. *ACS Catal.* **2015**, *5*, 1972–1985. (j) Jackl, M. K.; Legnani, L.; Morandi, B.; Bode, J. W. Continuous Flow Synthesis of Morpholines and Oxazepanes with Silicon Amine Protocol (SLAP) Reagents and Lewis Acid Facilitated Photoredox Catalysis. *Org. Lett.* **2017**, *19*, 4696–4699.