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## Visible light amination/Smiles cascade: access to phthalazine derivatives†

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We report the synthesis of various phthalazines *via* a new cascade reaction, initiated by visible light photocatalysis, involving a radical hydroamination reaction followed by a radical Smiles rearrangement. Phthalazine derivatives are obtained in high yields and from a broad scope readily accessible *ortho*-alkynylsulfonohydrazone precursors. The mild photoredox conditions ensure an excellent functional group tolerance. Application of this strategy to a one-pot protocol starting from the corresponding carbonyl compounds, and subsequent functionalization allow the rapid synthesis of structurally diverse structures.

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## Introduction

Since the early beginning of organic chemistry, the synthesis of nitrogen-containing heterocycles constantly attracted interest from the chemistry community, due to their ubiquitous presence in natural products.<sup>1</sup> Until now, despite many synthetic efforts, phthalazine structures have been less explored and therefore synthetic methods are still desirable. Moreover, these heterocycles are found in many important biological relevant compounds possessing properties, such as antibacterial<sup>2</sup> or antitumor<sup>3</sup> agents (Fig. 1).

Current strategies for the synthesis of these heterocycles are limited to the use of hydrazine on diaryldiketones or *ortho*

alkynyl-phenylketones<sup>4</sup> and Diels–Alder reactions.<sup>4a,5</sup> These reactions require sometimes harsh reaction conditions and/or use toxic hydrazine reagents, limiting the access to phthalazine structures.<sup>4,5</sup> Therefore, looking for a general strategy to build phthalazine derivatives is still highly requested. We were thus interested in developing a milder and general protocol focusing on the formation of the C–N bond *via* a photoredox strategy. Carbon–nitrogen bonds are ubiquitous and essential in countless important organic compounds.<sup>1</sup> Thus, chemists have developed a plethora of strategies to synthesize C–N bonds leading to diversified structures.<sup>6,7</sup> Tremendous improvements were made over the last decades especially thanks to transition metal catalysis, such as Buchwald–Hartwig amination<sup>6</sup> or oxidative amination reactions.<sup>7</sup> Nevertheless, C–N bond formation reactions remain of great interest, particularly in developing more general, milder and ecofriendly conditions.

In this context, carbo-amination and hydro-amination reactions, especially *via* radical mechanisms, are currently under investigation.<sup>8</sup> By taking advantage of photocatalyzed reactions,<sup>9</sup> we propose an unprecedented photo-induced radical cascade reaction combining a hydro-amination reaction step followed by a Smiles rearrangement.

The reported examples of C–N bond formation using photoredox catalysis mainly differ in nitrogen radical precursors (hydrazone, azide, *N*-acyloxyphthalimides, *N*-oxyl sulfonylcarbamates...).<sup>10</sup> Among them, hydrazone precursors were initially converted into radicals using stoichiometric quantities of TEMPO<sup>11</sup> or azodicarboxylate reagents<sup>12</sup> yielding pyrazoline derivatives, *via* an intramolecular 5-*exo*-trig cyclisation process. In these cases, the heterocyclic products were obtained predominantly as adducts with the radical initiator<sup>13</sup> (Scheme 1A). Last year, Chen, Xiao and coworkers were able to replace stoichiometric oxidation with catalytic photo-oxidation, using visible light, leading to pyrazolines, thanks to the base-

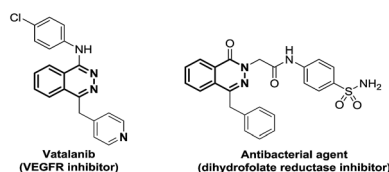


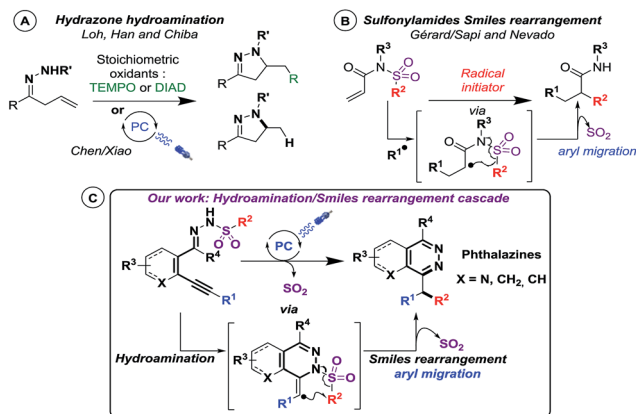
Fig. 1 Phthalazines bioactive compounds.

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Scheme 1 State of art in radical hydro- and oxo-amination reactions and in the radical Smiles rearrangement (A and B); our photocatalyzed cascade (C).

mediated photocatalytic conversion of the N–H bond into an N-centered radical.<sup>14</sup> In both cases, the nitrogen radical, generated on a hydrazone precursor, makes an intramolecular attack on an alkenyl residue (Scheme 1A). It is noteworthy that all reported photo-induced cyclization reactions of nitrogen-based radicals on unsaturated moieties happen on alkenyl residues.<sup>9f</sup> Intriguingly, cyclization reactions of nitrogen-based radicals on alkynyl residues have never been investigated under visible light catalysis.<sup>9f,10g–j</sup> Therefore, our findings are of particular interest since we designed new alkynyl-substituted arylsulfonylhydrazone precursors (Scheme 1C) involved in intramolecular photo-induced hydro-amination to alkynes. To our delight, we were thrilled to isolate benzhydryl-substituted phthalazine structures through a subsequent radical Smiles rearrangement. Indeed, only a few recent examples of radical Smiles rearrangements (aryl migration<sup>15</sup>) from Gérard/Sapi<sup>16</sup> and Nevado,<sup>17</sup> using sulfonylamides precursors, demonstrated that this process could happen in a radical fashion (Scheme 1B), but no report included an arylsulfonylhydrazone scaffold. Therefore, we describe here the behavior of novel phenylsulfonylhydrazone moieties in an unprecedented photo-induced reaction cascade.<sup>18</sup> We found that they were able to undergo an intramolecular hydroamination reaction followed by a Smiles rearrangement, providing a new strategy to build phthalazine derivatives, under visible light catalysis (Scheme 1C).

## Results and discussion

We started our investigation on a model substrate, *N'*-(2-(phenylethynyl)benzylidene)benzenesulfonylhydrazone **1a**, easily prepared from the corresponding carbonyl<sup>19a</sup> and sulfonylhydrazide moieties (Table 2). We optimized the reaction conditions (see ESI† for full details) modifying the nature of the base, of the solvent, of the photocatalyst and the crucial presence of a drying agent. Starting from reaction conditions using Ru(bpy)<sub>3</sub>Cl<sub>2</sub>·6H<sub>2</sub>O as the photocatalyst, and NaOH as the base in CHCl<sub>3</sub>, we were pleased to isolate the desired product **2a** with an encouraging yield of 25% (Table 1, entry 1). The X-ray

Table 1 Optimization of the reaction conditions

Reaction scheme: **1a** (N'-(2-(phenylethynyl)benzylidene)benzenesulfonylhydrazone) reacts under photocatalytic conditions (Photocatalyst, base, solvent, additives, Blue LED, 12h @ RT) to form **2a** (benzhydryl-substituted phthalazine).

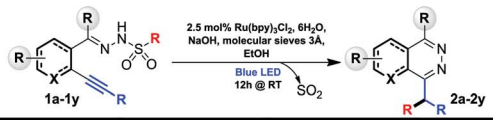
Entry	PC (2.5 mol%)	Base (1.5 equiv.)	Solvent	Additives (100 mg)	Yield [%] <sup>[a]</sup>
1	A	NaOH	CHCl <sub>3</sub>	-	25
2	A	<i>t</i> BuONa	CHCl <sub>3</sub>	-	10
3	A	NaOH	MeCN	-	17
4	A	NaOH	EtOH	-	75
5	B	NaOH	EtOH	-	10
6	C	NaOH	EtOH	-	5
7	A	NaOH	EtOH	3 Å M.S.	81
8	A (1 mol%)	NaOH	EtOH	3 Å M.S.	54
9	A	NaOH	EtOH	3 Å M.S.	0 <sup>[b]</sup>
10	-	NaOH	EtOH	3 Å M.S.	0
11	A	-	EtOH	3 Å M.S.	0

<sup>a</sup> Isolated yields. <sup>b</sup> Without light.

analysis of **2a** (Table 2) unambiguously confirmed the structure. Changing the base from NaOH to *t*BuONa leads to a lower 10% yield (entry 2). Investigation on the nature of the solvent (Entries 3 and 4) allowed us to increase the isolated yield from 25% to 75% with EtOH (entry 4). The influence of the photocatalyst was then evaluated with Eosin Y<sup>9</sup> and Fukuzumi's catalyst.<sup>9</sup> However, the reaction was inefficient in both cases, leading to a 10% or 5% product yield, respectively, for entries 5 and 6. Additives were then screened and we were pleased to find that, with the use of 3 Å molecular sieves, we were able to avoid the formation of a side product, thus improving the yield of the desired product **2a** to 81% (see ESI†). Decreasing the amount of the ruthenium catalyst from 2.5 mol% to 1 mol% led to a lower yield of 54% (entry 8). The presence of the photocatalyst, a base and light proved to be crucial for the reaction since the lack of one of them prevented the formation of product **2a** (entries 9–11). Finally, the optimized reaction conditions are: 2.5 mol% of Ru(bpy)<sub>3</sub>Cl<sub>2</sub>·6H<sub>2</sub>O, 1.5 equivalents of NaOH and 100 mg of 3 Å molecular sieves in EtOH (0.08 M) under blue light irradiation (~450 nm). With these conditions in hand, we explored the reaction scope. At first, we examined the impact of alkyne substitution by evaluating various aryls with *ortho*, *meta* or *para* substituents, exhibiting electron-donating or electron-withdrawing properties (**1b–h**, Fig. 2 and **2b–h**, Table 2). Electron-donating groups are well tolerated; *para*-methyl or *meta*-methoxy substituted derivatives **2b** and **2c** provided good product yields, 71 and 79%, respectively. 3,4,5-Trimethoxybenzene derivative **1d** gave the expected product **2d** in 60% yield (Table 2). Electron-withdrawing groups are also well tolerated, producing *para*- and *ortho*-fluoro or *para*-trifluoromethyl derivatives **2g/2h/2f** with moderate to good isolated yields of 83%, 61% or 55%, respectively. However, *para*-nitro derivative **1e** was unreactive under these conditions due to



Table 2 Scope of the reaction<sup>a</sup>

Reaction scheme: 

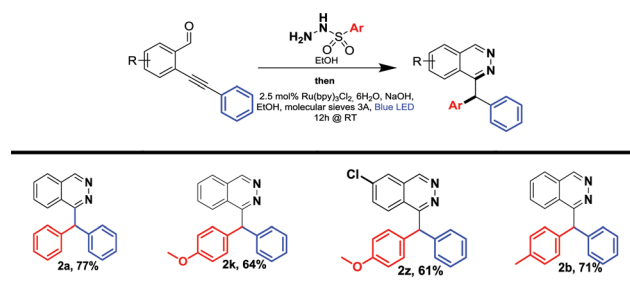
Sulfonohydrazones	Products
<p>1a: R = -Ph</p> <p>1b: R = -4Me-Ph</p> <p>1c: R = -3OMe-Ph</p> <p>1d: R = -3,4,5(OMe)-Ph</p> <p>1e: R = -4NO<sub>2</sub>-Ph</p> <p>1f: R = -4CF<sub>3</sub>-Ph</p> <p>1g: R = -4F-Ph</p> <p>1h: R = -2F-Ph</p> <p>1i: R = -C<sub>6</sub>H<sub>5</sub></p> <p>1j: R = -C<sub>6</sub>H<sub>9</sub></p>	<p>2a, 81%</p> <p>2b, 71%</p> <p>2c, 79%</p> <p>2d, 60%</p> <p>2e, 0%</p> <p>2f, 55%</p> <p>2g, 83%</p> <p>2h, 61%</p> <p>2i, 55%</p> <p>2j, 66%</p>
<p>1k: R = -4OMe-Ph</p> <p>1l: R = -4Me-Ph</p> <p>1m: R = -2,5(Me)-Ph</p> <p>1n: R = -1-naphthyl</p> <p>1o: R = -Me</p> <p>1p: R = -4Br-Ph</p> <p>1q: R = -4COMe-Ph</p> <p>1r: R = -4Me-thiophene</p>	<p>2k, 69%</p> <p>2l, 30%</p> <p>2m, 0%</p> <p>2n, 0%</p> <p>2o, 73%</p> <p>2p, 68%</p> <p>2q, 71%</p>
<p>1r: R<sup>1</sup> = -Me; R<sup>2</sup>=R<sup>3</sup>=R<sup>4</sup>= -H</p> <p>1s: R<sup>1</sup> = -Ph; R<sup>2</sup>=R<sup>3</sup>=R<sup>4</sup>= -H</p> <p>1t: R<sup>2</sup> = -F; R<sup>1</sup>=R<sup>3</sup>=R<sup>4</sup>= -H</p> <p>1u: R<sup>2</sup> = -Cl; R<sup>1</sup>=R<sup>3</sup>=R<sup>4</sup>= -H</p> <p>1v: R<sup>2</sup> = -OMe; R<sup>1</sup>=R<sup>3</sup>=R<sup>4</sup>= -H</p> <p>1w: R<sup>1</sup> = -H; R<sup>2</sup>=R<sup>3</sup>=R<sup>4</sup>= -OMe</p>	<p>2r, 78%</p> <p>2s, 57%</p> <p>2t, 49%</p> <p>2u, 46%</p> <p>2v, 68%</p> <p>2w, 64%</p>
<p>1x: R = -Ph</p> <p>1y: R = -Ph</p>	<p>2x, 71%</p> <p>2y, 64%</p>

<sup>a</sup> Reaction conditions: **1a–y** (0.15 mmol, 1 eq.), 3 Å M.S. (100 mg), Ru(bpy)<sub>3</sub>Cl<sub>2</sub>·6H<sub>2</sub>O (3.5 μmol, 2.5 mol%) and NaOH (0.225 mmol, 1.5 eq.) in dry EtOH (0.08 M) was irradiated for 12 h under blue light (450 nm) at 20 °C.

low solubility in ethanol. Cyclohexenyl derivative **1j** reacted chemoselectively, yielding **2j** in 66% yield (Table 2). Starting from pentyne derivative **1i**, we obtained product **2i** in a moderate 55% yield.

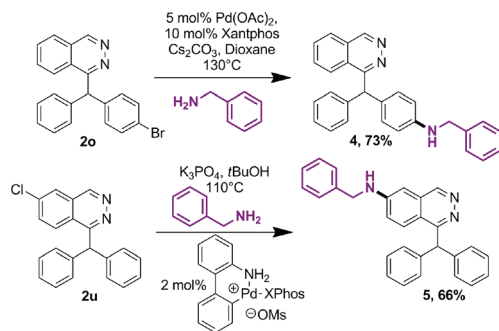
Then, we investigated the reaction scope for the sulfonyl part (**1b'–r**, Fig. 2) of the starting materials, thus modifying the migrating moiety.

Derivatives bearing electron donating-groups, such as *para*-methoxy or *para*-tolyl on the phenyl ring of sulfonohydrazone, gave the desired products **2k** and **2b** in 69% and 78% yields, respectively (Table 2). Steric congestion is detrimental to the reaction: xylene substitution provided the desired product **2l** in only 30% yield; 1-naphthalene substitution (**1m**) is unreactive under these conditions and the starting material is almost fully recovered. Bromo-substituted phenylsulfonohydrazone reacted nicely to **2o** in 73% yield; this derivative could be further functionalized using cross-coupling reactions. Derivatives bearing electron-withdrawing groups, such as *para*-acetyl on the phenylsulfonohydrazone moiety, yield product **2p** in 68% yield. Alkyl-substituted sulfonohydrazones are not tolerated under our conditions. Indeed methylsulfonohydrazone **1n** (or benzyl-sulfonohydrazone, data not shown) did not yield any reaction product. Finally, heteroarene-derived sulfonohydrazones, 2-methylthiophene **1q**, was successfully transferred giving the desired product **2q** in 71% yield. Differently substituted benzaldehyde units on the carbamoyl or aromatic part were synthesized and evaluated in the reaction (**1r–y**, Table 2). Thus, 1-substituted phthalazines became accessible *via* our new process and compounds **2r** and **2s** were obtained with yields of 78% and 57%, respectively. Then, the aromatic part was substituted by electron-donating or -withdrawing groups and we isolated products (**2t–w**) in moderate to good yields (46–68%). Finally, we applied the method to the synthesis of other heterocycles and obtained pyridazine **2x** and pyridopyridazine **2y** in 71% and 64% yield, respectively. The reaction was also attempted in a sequential one-pot process. This one-pot strategy was successfully applied to the synthesis of four compounds with yields ranging from 61 to 77%, which are similar compared to the two-steps procedure for compounds **2a**, **2b** and **2k**, (Tables 2 and 3) and one new disubstituted analog **2z**. The one-

Table 3 One-pot two-step synthesis of benzhydrylphthalazines<sup>a</sup>

<sup>a</sup> Reaction conditions: benzaldehyde (0.15 mmol, 1 eq.) and sulfonylhydrazine (0.15 mmol, 1 eq.) were mixed at room temperature in EtOH (1 mL) for 1 hour, then we followed our optimized conditions.





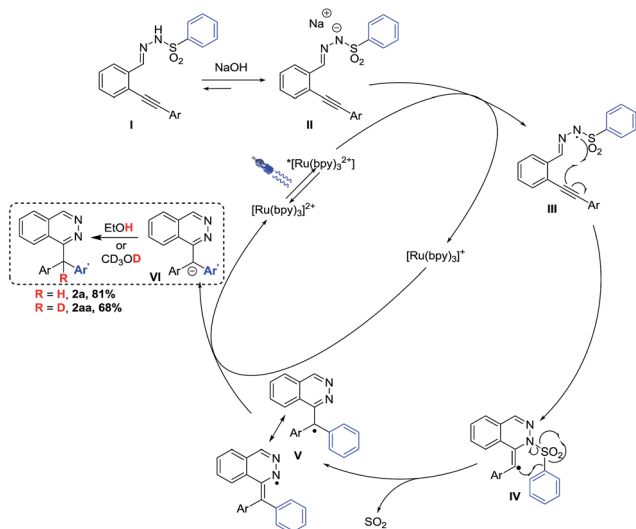
Scheme 2 Functionalization of halogenobenzhydrylphthalazines.

pot process could be particularly attractive for the synthesis of phthalazine or pyridazine compound libraries (Table 3).

Further functionalization of phthalazine derivatives is possible, since the presence of a halogen atom is compatible with our cascade process, either on a phthalazine substituent (**2o**, Table 3) or directly on the phthalazine core (**2u**). As an example, the Buchwald–Hartwig cross-coupling reaction of compounds **2o** and **2u** with benzylamine provided products **4** and **5** in 73% and 66% yield, respectively (Scheme 2).<sup>19</sup>

## Mechanistic study

A proposed mechanism based on the observations of several control experiments and measurements is depicted in Scheme 3. The reaction in MeOH-d<sub>4</sub> gave deuterated product **2aa** in 68% yield with more than 85% incorporation of deuterium, confirming that the solvent is the proton source. Cyclic voltammetry measurements suggest that only a deprotonated sulfonohydrazone **II** ( $E_{\text{III/II}} = 0.54$  eV vs. SCE) can be photo-oxidized by the excited ruthenium-based photocatalyst ( $E_{\text{RuII}^*/\text{RuI}} = 0.77$  eV vs. SCE), confirmed by further fluorescence experiments (see ESI† for data). Then, the N-centered radical **III**



Scheme 3 Proposed mechanism.

may add to the triple bond and the loss of sulfur dioxide in intermediate **IV** yields the phthalazine radical structure **V** (C-centered and N-centered radical species in equilibrium). The reduction of intermediate **V** through the regeneration of the catalyst yields anion **VI**, which can be protonated or deuterated by the solvent (**2a**, **2aa**). The quantum yield of the reaction was determined to be  $\Phi = 0.33$  indicating that the mechanism does not contain significant radical chain pathways.<sup>20</sup>

## Conclusions

In summary, we have developed a new photoredox cascade process combining a hydroamination reaction followed by a Smiles rearrangement. This unprecedented transformation provides an efficient access to highly diversified benzhydrylphthalazine structures. Moreover, mechanistic investigations confirmed the radical pathway displayed in our proposed mechanism. Halogen substituents are tolerated, allowing, through subsequent cross-coupling reaction, further functionalization of the phthalazines. The *in situ* preparation of the sulfonohydrazones from the corresponding carbonyl substrates allows a one-pot procedure. We currently investigate further applications of the photoredox Smiles reaction in our laboratory.

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