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# Synthesis of Carbazoles by a Merged Visible Light Photoredox and Palladium Catalyzed Process

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**ABSTRACT:** Carbazoles have become of great interest in recent years for a variety of applications in organic and medicinal chemistry as well as in materials science. In this work, an efficient method for the synthesis of carbazoles through the intramolecular C–H bond amination of *N*-substituted 2-amidobiaryls has been developed. Under visible light and an aerobic atmosphere, the transformation requires only catalytic amounts of  $Pd(OAc)_2$  and  $[Ir(dFppy)_2phen]PF_6$  (dFppy = 2-(2,4difluorophenyl)pyridine; phen = 1,10-phenanthroline), the latter of which is utilized in synthetic chemistry for the first time. Spectroscopic and electrochemical studies revealed that the reaction is initiated by photoinduced electron transfer from a palladacycle intermediate, formed from the 2-amidobiaryl and Pd<sup>II</sup> species, to the photoexcited Ir catalyst. This step triggers reductive elimination in a Pd<sup>III</sup>-containing palladacycle to produce the carbazole and a Pd<sup>I</sup> species. The one electron-reduced photocatalyst is reoxidized by O<sub>2</sub> to generate the original form of the photocatalyst, and the Pd<sup>I</sup> species can be oxidized to the resting state through oxidative electron transfer to O<sub>2</sub> or the excited-state photocatalyst.

**KEYWORDS**: carbazole • amination • C-H activation • visible light • photocatalysis

# **1. INTRODUCTION**

Owing to their occurrence in a large number of bioactive natural products and pharmaceutical agents, carbazoles have garnered significant interest among synthetic organic and medicinal chemists (Figure 1).<sup>1</sup> The carbazole motif is also found in a variety of electronic materials, including photoconducting polymers and organic optoelectronic materials.<sup>2</sup>

compounds, transition metal-catalyzed intramolecular C–H bond amination of *N*-substituted 2-amidobiaryls are perhaps the most atom-economical route (Scheme 1).<sup>12, 13</sup>

Scheme 1. Intramolecular C–H Bond Amination Reactions of *N*-Substituted Amidobiaryls.



Figure 1. Molecules containing the carbazole structural motif.

Consequently, intense efforts have been devoted towards the development of methods that can be used to prepare substances containing carbazole moieties.<sup>1f, 3-13</sup> Among the various routes devised thus far to synthesize these target



In 2005, Buchwald and co-workers disclosed that the Pdcatalyzed intramolecular C–H bond amination of 2acetamidobiaryls resulted in the production of carbazole

derivatives by using Cu(OAc)<sub>2</sub> as the oxidant.<sup>12a</sup> Later, Gaunt and co-workers showed that *N*-alkyl (Me, <sup>*t*</sup>Bu, allyl, and benzyl)-substituted 2-aminobiaryls could be transformed to N-substituted carbazoles upon treatment with stoichiometric quantities of a hypervalent iodine complex in the presence of a Pd catalyst.<sup>126</sup> Hypervalent iodine complexes were also utilized as oxidants by Chang and coworkers to promote Cu-catalyzed or metal-free carbazole formation from N-substituted 2-amidobiaryls.<sup>12c</sup> Youn also reported that carbazoles could be produced by a Pdcatalyzed intramolecular C-H bond amination using oxone as the oxidant in the presence of *p*-TsOH.<sup>12d</sup> Miura and his co-workers developed a Cu-catalyzed synthesis using a picolinamide-based bidentate directing group and MnO<sub>2</sub> as terminal oxidant in the presence of AcOH in DMF.<sup>12e</sup> Recently, the same group reported an Ir-catalyzed process of 2-aminobiaryls to 9H-carbazoles using Cu(OAc), and molecular oxygen as oxidants (Scheme 1).<sup>12g</sup> In addition, organocatalytic intramolecular C-H bond amination of Nacetyl amidobiaryls was done by the Antonchick group using 2,2'-diiodo-4,4',6,6'-tetramethylbiphenyl and AcOOH as an organocatalyst and an oxidant, respectively.<sup>13</sup>

Despite these advances, the processes described above have limitations associated with the requirements of high reaction temperatures and stoichiometric use of strong ground-state oxidants. This raises concerns regarding atom economy and environmental issues. Therefore, a new approach for the highly efficient preparation of carbazoles, with minimal reagent use, is highly desirable.

In another arena, visible light photoredox catalysis has attracted substantial attention owing to its environmental compatibility and versatility in a large number of synthetically important reactions.<sup>14</sup> Recently, visible-light-promoted, single electron transfer (SET) processes have been devised for the oxidation or reduction of transition-metal complex intermediates in Ni-,<sup>15</sup> Cu-,<sup>16</sup> Rh-,<sup>17</sup> Au-,<sup>18</sup> and Pd<sup>19</sup>-catalyzed reactions.<sup>14f, 14h</sup> We envisioned that the combined use of photoredox and transition metal catalysis would be both environment-friendly and applicable to the synthesis of industrially important substances. In such processes, the use of photon energy would obviate the need to use strong chemical additives.

Experience gained in earlier studies of photoredox catalysis<sup>20</sup> and C–H bond amination reactions<sup>12</sup> enabled us to design a protocol for the synthesis of *N*-substituted carbazoles where an intramolecular C–H bond amination would take place by visible light irradiation of a solution of a *N*substituted 2-amidobiaryl in the presence of catalytic amounts of Pd<sup>II</sup> and a visible-light-absorbing, electronaccepting photocatalyst under an O<sub>2</sub> atmosphere (Scheme 1).

#### 2. RESULTS AND DISCUSSION

To explore this proposal, a study was conducted using *N*-benzenesulfonyl amidobiphenyl **1a** as the model substrate (Table 1). Visible light irradiation of a solution of **1a** in air-saturated DMSO, containing 10 mol % of Pd(OAc)<sub>2</sub> and 1 mol % of [Ru(bpy)<sub>3</sub>]Cl<sub>2</sub>, at 80 °C led to the production of

desired carbazole 2a in a 52% yield (Table 1, entry 1). Notably, strong ground-state oxidants were not required for this Pd-catalyzed reaction. A variety of Pd catalysts were employed in the reaction; Pd(OAc)<sub>2</sub>, the most widely used catalyst in C–H bond functionalization reactions, was found to be optimal (Table 1, entries 1–6). Control experiments revealed that visible light, the Pd catalyst, the photocatalyst, and molecular oxygen were essential for transformation of **1a** to **2a** (Table 1, entries 1 vs 7–10). When the reaction was performed at room temperature, a lower yield of **2a** was obtained (Table 1, entry 11).



NHSO <sub>2</sub> Ph	1 mol % Ru(bpy) <sub>3</sub> Cl <sub>2</sub> 10 mol % Pd catalyst, O <sub>2</sub> DMSO (0.2 M), 80 °C blue LEDs (7 W), 15 h	SO <sub>2</sub> Ph N 2a
Entry	catalyst	Yield (%) <sup>b</sup>
1	Pd(OAc) <sub>2</sub>	52
2	Pd(PPh <sub>3</sub> ) <sub>2</sub> Cl <sub>2</sub>	9
3	Pd(CH <sub>3</sub> CN) <sub>4</sub> (BF <sub>4</sub> ) <sub>2</sub>	16
4	Pd(dba) <sub>2</sub>	4
5	Pd(PPh <sub>3</sub> ) <sub>4</sub>	27
6	K <sub>2</sub> PdCl <sub>4</sub>	trace
7	no Pd catalyst	-
8 <sup>c</sup>	$Pd(OAc)_2$ and no $O_2$	-
9	$Pd(OAc)_2$ and no $Ru(bpy)_2Cl_2$	17
10	Pd(OAc) <sub>2</sub> and no blue LEDs	18
11	Pd(OAc) <sub>2</sub> at r.t.	25

<sup>*a*</sup>Reaction scale: **1a** (0.1 mmol). <sup>*b*</sup>The yield was determined using gas chromatography. <sup>*c*</sup>The reaction mixture was deoxygenated by repeating vacuum-freeze-thaw cycles.

### Table 2. Photocatalyst Screening.<sup>a,b</sup>



<sup>*a*</sup>Reaction scale: **1a** (0.1 mmol). <sup>*b*</sup>The yield was determined using gas chromatography.

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The new, merged catalytic, carbazole-forming process, was optimized in an exploration examining a variety of Ru, Pt, and Ir based photocatalysts (1 mol %) in the presence of 10 mol % Pd(OAc)<sub>2</sub> in oxygenated DMSO (Table 2). The investigated photoredox catalysts included Pt(ppy)2acac (4),  ${}^{20i}$  [Ir(ppy)<sub>2</sub>(dtbbpy)]PF<sub>6</sub> (5),  ${}^{21}$  fac-Ir(ppy)<sub>3</sub> (6), and fac- $Ir(dFppy)_3$  (7) (Table 2; ppy = 2-phenylpyridinato, acac = 2-acetylacetonate, and dtb-bpy = 4,4'-di-tert-butyl-2,2'bipyridine). Interestingly, Ir<sup>III<sup>\*</sup></sup> complexes containing electron-withdrawing ligands, such as fac-Ir(dFppy)<sub>3</sub> (7),  $[Ir(dFppy)_2phen]PF_6$  (8), and  $[Ir(dCF_3ppy)_2phen]PF_6$  (9;  $dCF_3ppy = 2-(2,4-bis(trifluoromethyl)phenyl)pyridine),$ promoted the highest yielding reactions (7, 83%; 8, 95%; 9, 95%). Based on these observations,  $[Ir(dFppy)_2phen]PF_6$  (8) was selected for use in further studies because it is more readily available than  $[Ir(dCF_3ppy)_2phen]PF_6$  (9). It is noted that synthetic utility of the complexes, 8 and  $9^{22}$  has yet to be fully evaluated to date.

The effects of several parameters including solvent, temperature, and concentration, on the efficiency of the reaction were also examined. Among various solvents including DCM, DMSO, DMF, and MeOH, DMSO showed the best reactivity for the transformation. Although the reaction proceeded at lower temperatures (25 °C, 40 °C and 60 °C), 80 °C was chosen for the higher efficiency and reproducibility of the process. The highest vielding process occurred when 10 mol %  $Pd(OAc)_2$  and 1 mol % [Ir(dFppy)<sub>2</sub>(phen)]PF<sub>6</sub> (8) were utilized in 0.20 M DMSO under an oxygen atmosphere and visible-light irradiation at 80 °C. Using these conditions, the substrate scope of the carbazole forming process was investigated. A variety of N-benzenesulfonyl amidobiaryls were converted to the corresponding N-benzenesulfonyl carbazoles in good to excellent yields (Table 3). Importantly, while the efficiencies of previous reactions employed in other methods depended on the substitution pattern of the amidobiaryls,<sup>12c</sup> the yields obtained using this approach were not significantly altered by the electronic properties or position of aryl ring substituents. Substrates 1d and 1i, which contain Cl groups at different positions but both generate 3-chloro-9-(phenylsulfonyl)-9H-carbazole (2d), reacted with nearly equal efficiencies (Table 3, entries 4 and 9). Notably, the reactions of 1h and 1i, which have the potential of producing two regioisomeric carbazoles, generated single carbazoles, 2h and 2i respectively, as a consequence of steric effects (Table 3, entries 8 and 9).

Not only *N*-benzenesulfonyl amidobiaryls but also heteroatom-containing substrates worked for this process. Although the reactivity was not as good as those of simple biaryl systems, the reaction of *N*-(2-(thiophen-3-yl)phenyl)benzenesulfonamide (10) smoothly underwent C-H amination to produce the tricyclic system 11 (Scheme 2). Notably, the process was highly regioselective, producing only single isomer 11 where heteroatoms N and S have a *syn* orientation

 Table 3. Substrate Scope of the Intramolecular C-H Bond

 Amination Reaction of N-Benzenesulfonyl Amidobiaryls.<sup>a</sup>



<sup>*a*</sup>Reaction scale: 1 (0.3 mmol). <sup>*b*</sup>Isolated yield based on an average of two runs. <sup>*c*</sup>15 mol % of Pd(OAc)<sub>2</sub> was used.

#### Scheme 2. Intramolecular C–H Amination of *N*-(2-(thiophen-3-yl)phenyl)benzenesulfonamide.



The effects of *N*-substituents on the efficiencies of the reaction were also explored (Table 4). Notably, *N*-sulfonyl-(*p*-toluenesulfonyl (**12**) and methylsulfonyl (**14**)) and *N*acetyl (**16a**)-containing substrates reacted to produce the corresponding *N*-substituted carbazoles (Table 4, entries 1–3). However, 2-aminobiphenyl (**18**) and *N*-alkylsubstituted aminobiphenyls, such as benzyl (**20**) and ethyl (**22**), did not undergo the intramolecular C–H amination (Table 4, entries 4–6).<sup>23</sup>

Table 4. N-Substituent Effects.<sup>a</sup>



<sup>*a*</sup>Reaction scale: Substrate (0.3 mmol). <sup>*b*</sup>Isolated yield based on an average of two runs. <sup>*c*</sup>15 mol % of Pd(OAc)<sub>2</sub> was used.

Specifically, *N*-acetyl amidobiaryls containing both electron-donating and electron-withdrawing aryl substituents reacted smoothly to form the corresponding *N*acetylcarbazoles (Table 5). The reactivities of the *N*-acetyl substrates were lower than those of their *N*-benzenesulfonyl analogs, as 15 mol % of Pd(OAc)<sub>2</sub> was required to drive these reactions to completion. However, the relatively facile removal of *N*-acetyl as compared to *N*-sulfonyl groups makes the use of *N*-acetyl amidobiaryls (**16**) more practical.

The results described above clearly demonstrate the feasibility and scope of the merger of  $Pd(OAc)_2$  and  $Ir^{III}$  photoredox catalysts for transformation of amidobiaryls to the corresponding carbazoles. To further explore utility of our method, we attempted preparation of clausine C (an alkaloid, Figure 1) using the merged catalysts. The intermediate, an acetylated carbazole **17d** (Table 5, entry 4), was prepared according to our protocol. **17d** was then converted to clausine C by deacetylation under a basic condition (Scheme 3). This demonstration illustrates that the merged catalysis is applicable to production of pharmaceutically and industrially relevant compounds.

 Table 5. Substrate Scope of the Intramolecular C-H Bond

 Amination Reaction of N-acetyl Amidobiaryls.<sup>a</sup>



<sup>*a*</sup>Reaction scale: **1** (0.3 mmol). <sup>*b*</sup>Isolated yield based on an average of two runs.

Scheme 3. Synthesis of an alkaloid, clausine C, through deacetylation of 17d.



As the final phase of our study, spectroscopic and electrochemical investigations were performed in order to gain insight into the reaction mechanism. Notably, the UV-vis absorption spectrum of a DMSO solution containing Pd(OAc)<sub>2</sub> and **1a** preincubated at 80 °C for 12 h under an anaerobic atmosphere differed significantly from that of DMSO solutions of 1a or Pd(OAc)<sub>2</sub> (Supporting Information (SI), Figure S1). This observation may be indicative of generation of a palladacycle. We obtained the ESI-MS (positive) spectra that revealed presence of  $[KPd^{II}(1a-H)(DMSO)_3]^+$ , supporting this notion (SI, Figure S2). The formation of a trinuclear carbopalladacycle of amidobiaryls under similar conditions was reported by Gaunt and co-workers.<sup>12b</sup> We hypothesized that the palladacycle might be the key species responsible for SET with the photoexcited Ir catalyst. Comparisons of the oxidation potentials ( $E_{ox}$ ) of **1a** (1.86 V vs SCE), **2a** (1.83 V vs SCE), and the palladacycle of 1a (1.21 V vs SCE) with that of the excited-state reduction potential of 8 ( $E^*_{red} = 1.49$  V

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59 60 vs SCE) revealed that exoergic SET to the excited-state of 8 (8\*) is allowed only from the palladacycle with a positive driving force of 0.28 eV (SI, Figure S3). Actually, the phosphorescence lifetime of 8\* decreased in a concentration-dependent manner from 1.48 µs to 0.986 µs upon the addition of the palladacycle (0-0.800 mM; Figure 2(a)). A pseudo-linear fit of the data yielded an electron-transfer rate constant of  $4.33\pm0.09 \times 10^8$  M<sup>-1</sup> s<sup>-1</sup>, which corresponded to a SET rate that was ca. 15 and 2 times faster than those for the radiative ( $k_r = 5.73 \times 10^4 \text{ s}^{-1}$ ) and nonradiative ( $k_{nr} = 4.64 \times 10^5 \text{ s}^{-1}$ ) decay of 2.0 mM 8 (Figure 2(b)).<sup>22</sup> The SET involved oxidation of Pd<sup>II</sup> in the palladacycle, as similar photoinduced reductive quenching of  $8^*$  by Pd(OAc)<sub>2</sub> occurred at a relative smaller the rate constant  $(3.98\pm0.12\times10^8 \text{ M}^{-1} \cdot \text{s}^{-1}; \text{ SI}, \text{ Figure S4})$ . As expected, phosphorescence quenching of 8\* did not take place in the presence of 1a and 2a (SI, Figure S5).

In the ensuing steps in the mechanistic pathway, the one electron-reduced photocatalyst is oxidized to reform **8** upon donation of the extra electron to  $O_2$ . The Pd<sup>III</sup> palladacycle undergoes reductive elimination to produce a C–N bond as part of the carbazole ring system, as well as a Pd<sup>I</sup> species. Since the redox potential of Pd<sup>II/I</sup> should be more cathodic than that of Pd<sup>III/II</sup>, the Pd<sup>I</sup> species should be capable of reducing the photoexcited catalyst. However, direct monitoring of this process was hampered presumably by the short lifetime of this transient species.



**Figure 2**. (a) Phosphorescence decay traces of 1.00 mM  $[Ir(dFppy)_2(phen)]PF_6$  (8) (deaerated DMSO) with increasing concentrations of the palladacycle (0–0.800 mM) ( $\lambda_{ex} = 377$  nm, temporal resolution = 8 ns). (b) A pseudo-linear fit of the electron transfer rates, which were obtained from electron transfer rate =  $1/\tau - 1/\tau_0$ , to the concentration of palladacycle:  $\tau$  and  $\tau_0$  correspond to the observed phosphorescence lifetimes in the presence and absence of palladacycle, respectively.

These results enabled us to postulate the plausible mechanism for the carbazole-forming reaction (Figure 3). In the initial step of the route, coordination of the amido group of **1a** to Pd(OAc)<sub>2</sub> facilitates cyclopalladation, leading to the six-membered palladacycle **1A**.<sup>12a</sup> The palladacycle, having a Pd<sup>II</sup> oxidation state, is oxidized to a Pd<sup>III</sup> complex by SET to the photoexcited Ir catalyst (i.e., \*[Ir<sup>IV</sup>(dFppy)<sub>2</sub>phen<sup>•</sup>]<sup>+</sup>), with generation of the one electron-reduced catalyst [Ir<sup>III</sup>(dFppy)<sub>2</sub>phen<sup>•</sup>]<sup>0</sup>. Reductive elimination of the Pd<sup>III</sup>palladacycle leads to the formation of carbazole **2a** and a

Pd<sup>I</sup> species (Path A). The Pd<sup>I</sup> species is subsequently oxidized to generate the original Pd<sup>II</sup> complex through SET to the photoexcited Ir catalyst or molecular oxygen. However, it is not possible to rule out a mechanism that follows path B, in which one electron transfer to the photoexcited catalyst from Pd<sup>III</sup> intermediate occurs prior to reductive elimi-\* $[Ir^{IV}(dFppy)_2phen^{-}]^+$  + Pd<sup>III</sup> nation (i.e.,  $\rightarrow$  $[Ir^{III}(dFppy)_2phen^{-1}]^0 + Pd^{IV})^{24}$  In either case, the one electron-reduced Ir catalyst donates one electron to dioxygen with a positive driving force of 0.65 eV  $(e \cdot [E_{red}([Ir(dFppy)_2phen]^+))$  $E_{red}(O_2)];$  $E_{\text{red}}([\text{Ir}(\text{dFppy})_2\text{phen}]^+) = -1.30 \text{ V vs SCE and } E_{\text{red}}(O_2) =$ -0.75 V vs SCE), being restored to its original state. Alternatively,  $*[Ir^{IV}(dFppy)_2phen^-]^+$  can be oxidatively quenched to  $[Ir^{IV}(dFppy)_2phen^{2+}$  by O<sub>2</sub>, followed by SET from the palladacycle (i.e.,  $[Ir^{IV}(dFppy)_2phen^{2+} + Pd^{II} \rightarrow [Ir^{III}(dFppy)_2phen^+ + Pd^{III})$ . Since one-electron oxidation of 8 occurs at 1.58 V vs SCE, the driving force for the generation of the Pd<sup>III</sup> species is greater than the case by 8\* by 0.09 eV. This may be indicative of preference for the oxidative quenching pathway, but it is likely that both (reductive and oxidative quenching of 8\*) would be operative.



**Figure 3**. Proposed mechanism for C–H bond amination reactions of *N*-substituted amidobiaryls.

#### **3. CONCLUSION**

In conclusion, in the investigation described above we have developed an efficient method for the synthesis of *N*-substituted carbazoles, which involves intramolecular C–H bond amination of *N*-substituted 2-amidobiaryls. The process utilizes the merged visible light photoredox and Pd catalysis and, as such, does not require strong oxidants for regeneration of the Pd catalyst. In addition, observations made in electrochemical and transient photoluminescence spectroscopy studies showed that the catalysis is initiated by SET from a palladacycle intermediate to the photoexcited Ir complex. Moreover, the photocatalyst is regenerated by molecular oxygen-promoted oxidation of its reduced

form, and the catalytic Pd<sup>II</sup> species is regenerated by SET from a Pd<sup>I</sup> species to molecular oxygen or the excited photocatalyst. The strategy employed in this study, which combines transition metal catalysis and photocatalysis and negates the use of stoichiometric amounts of harsh or potentially toxic chemical additives, might be applicable in the formation of other environmentally benign reactions.

# 4. EXPERIMENTAL SECTION

**Synthesis of N-Benzenesulfonyl Carbazole (2):** An oven-dried resealable tube equipped with a magnetic stir bar was charged with N-benzenesulfonyl aminobiaryl compound **1** (0.3 mmol), Pd(OAc)<sub>2</sub> (10 mol %, 0.03 mmol) and [Ir(dFppy)<sub>2</sub>(phen)]PF<sub>6</sub>, **8** (1 mol%, 0.003 mmol) in DMSO (1.5 mL, 0.2 M). Then oxygen gas was bubbled through the reaction mixture for 3 minutes and the tube was sealed with a silicone septum screw cap. The test tube was then placed under blue LEDs (7 W) at 80 °C. The progress of the reaction was checked by TLC or gas chromatography. The reaction mixture was then diluted with dichloromethane (DCM) and washed with brine. The organic layer was dried over MgSO<sub>4</sub>, concentrated in vacuum, and purified by flash column chromatography to furnish the pure *N*benzenesulfonyl carbazole, **2**.

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# Author Contributions

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#### Notes

The authors declare no competing financial interest.

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#### ASSOCIATED CONTENT

#### Supporting Information.

Experimental procedures, additional experimental data, analytical data, and copies of <sup>1</sup>H and <sup>13</sup>C NMR spectra of compounds. This information is available free of charge via the Internet at http://pubs.acs.org/.

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An efficient protocol for intramolecular C-H bond amination of *N*-substituted amidobyaryls, leading to the formation of a library of *N*-substituted carbazoles using a merged palladium and visible light photoredox catalysis, has been developed. This method avoids the use of stoichiometric amounts of expensive and/or toxic chemical additives, which merits special mention.



160x47mm (300 x 300 DPI)