

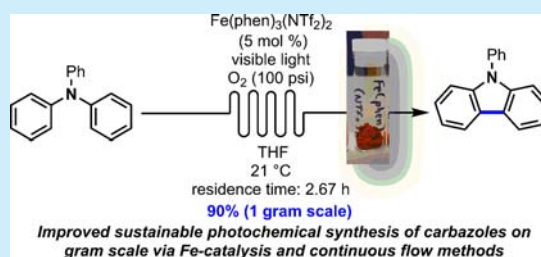
Photochemical Synthesis of Carbazoles Using an $[\text{Fe}(\text{phen})_3](\text{NTf}_2)_2/\text{O}_2$ Catalyst System: Catalysis toward Sustainability

Shawn Parisien-Collette, Augusto C. Hernandez-Perez, and Shawn K. Collins*

Département de Chimie, Centre for Green Chemistry and Catalysis, Université de Montréal, CP 6128 Station Downtown, Montréal, Québec H3C 3J7 Canada

S Supporting Information

ABSTRACT: An increasingly sustainable photochemical synthesis of carbazoles was developed using a catalytic system of $\text{Fe}(\text{phen})_3(\text{NTf}_2)_2/\text{O}_2$ under continuous flow conditions and was demonstrated on gram-scale using a numbering-up strategy. Photocyclization of triaryl and diarylamines into the corresponding carbazoles occurs in general in higher yields than with previously developed photocatalysts.



Photocatalysis has experienced a resurgence in interest as a tool for organic synthesis, particularly as the use of light as an energy source is widely viewed as a green technology.¹ The harvesting of light by sensitizers and subsequent electron transfer to different molecules can promote a number of important organic transformations via catalysis. In parallel, continuous flow methods have complemented the development of new photochemical technologies, allowing faster reactions times and improved scale-up to synthetically relevant scales.² Among metal-based sensitizers for photoredox catalysis, Ru- and Ir-based complexes possessing polypyridine and associated ligands have demonstrated utility in a host of transformations.³ However, questions of sustainability have led to the exploration of heterogeneous photocatalysis via sensitized TiO_2 ⁴ or mesoporous carbon nitride polymers,⁵ as well as homogeneous photocatalysis using organic dyes.⁶

The use of Cu-based sensitizers⁷ has now attracted attention as a cheaper and more abundant metal source for photocatalysis, although they remain underexplored in comparison to their Ru- and Ir-based counterparts. Our group previously described the use of heteroleptic copper complexes for the synthesis of carbazole heterocycles (Scheme 1).⁸ The complex $\text{Cu}(\text{Xantphos})(\text{neo})\text{BF}_4$ formed in situ promoted the oxidative cyclization of di- and triarylamines to the corresponding carbazoles using visible light irradiation and a continuous flow

setup. Despite the good yields and wide substrate scope, several key drawbacks were identified (Figure 1), especially when scale-



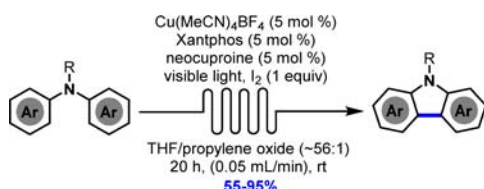
Photocatalysis via Cu complexes (Past Work):	
1) Required toxic oxidant/solvent system (I_2/THF)	Cu 
2) Utility demonstrated on small scales (< 100 mg)	
3) Relatively long residence times for a continuous process (approx. 20 h)	
Photocatalysis via Fe complexes (This Work):	
1) Exploit molecular oxygen as a benign oxidant	Fe 
2) Demonstrate scalability in continuous flow synthesis	
3) Improved reactivity/residence times	

Figure 1. Limitations of the Cu-based sensitizer/ I_2 catalyst system and targets for a new catalyst system.

up would be considered. Although copper remains a more abundant and cheaper metal than Ru or Ir, both metal and ligand costs would have to be revisited. A change from molecular iodine to molecular oxygen or air would permit a more benign oxidant system. Lastly, the copper-catalyzed reaction required relatively long residence times for a continuous flow process, and decreasing the residence time through either chemical reactivity or reaction engineering would be valued. Herein, we report the synthetic utility of a soluble Fe-based sensitizer complex for a photocatalytic oxidative transformation under continuous flow conditions.

The first goal was to survey photocatalysts that could efficiently form the carbazole nucleus using molecular oxygen as an oxidant. Molecular oxygen can accept an electron and act as a reagent to promote organic oxidative transformations.⁹ As such, a variety of sensitizers were evaluated in an oxidative cyclization to form 9-phenylcarbazole employing molecular oxygen (Figure 2). All reactions were performed in continuous flow using household lightbulbs as the light source. To achieve the goal of using molecular oxygen as the stoichiometric oxidant,¹⁰ a tube-

Scheme 1. Photoredox Synthesis of Carbazoles Using a Cu-Based Sensitizer/ I_2 Catalyst System

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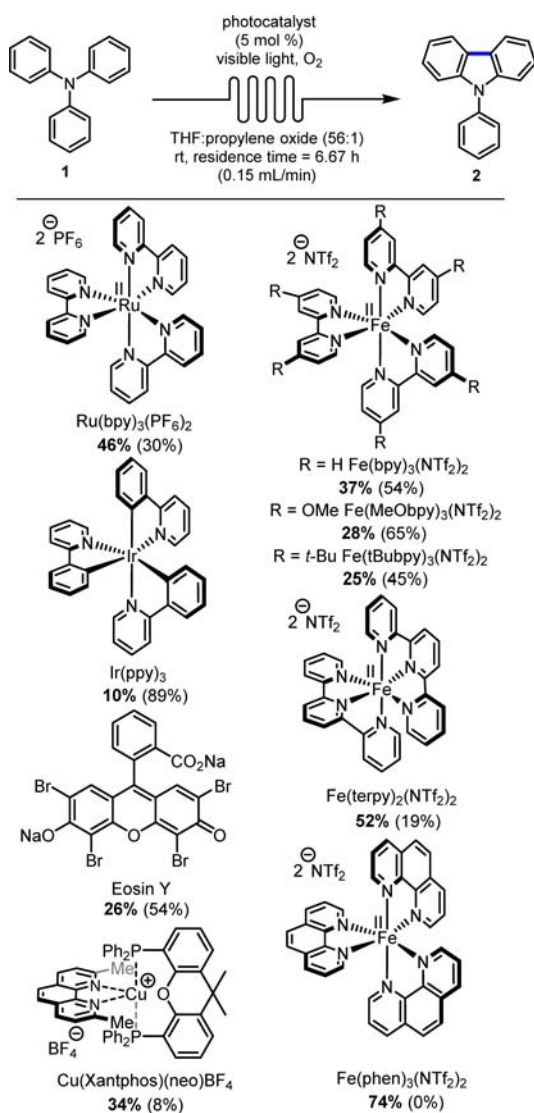


Figure 2. Optimization evaluation of photocatalysts for the synthesis of 9-phenylcarbazole. Yields following flash chromatography. Recovered starting material **1** indicated in brackets.

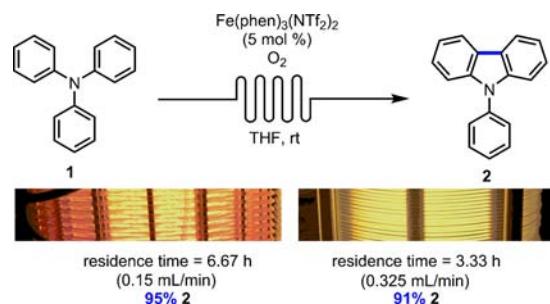
in-tube reactor¹¹ was used to ensure a high concentration of dissolved oxygen in THF.¹² For convenience, a flow rate of 0.15 mL/min (irradiation time = 6.67 h) was employed. First, the synthesis of carbazole **2** was performed in the dark, and >90% of the starting material **1** was recovered. In addition, attempts to promote the reaction thermally also failed (heating in batch, 80% recovered **1**). The reaction also failed to afford significant yields of carbazole **2** (13% **2**, 86% recovered **1**) when performed in the absence of any photocatalyst. When a Ru- [Ru(bpy)₃Cl₂] and Ir-based sensitizer [Ir(ppy)₃] were studied, each afforded modest to low yields of the desired carbazole (46 and 10% yield, respectively). Next, a previously developed Cu-based sensitizer [Cu(Xantphos)(neo)BF₄, 34% yield] and an organic sensitizer (eosin Y,¹³ 26% yield) were also evaluated but provided low yields, as well. An Fe-based catalyst [Fe(bpy)₃(NTf₂)₂]¹⁴ afforded a 37% yield of carbazole **2**. The NTf₂⁻ counterion was chosen specifically to augment the solubility of the Fe complex for its use in continuous flow. Other Fe-based complexes were also investigated, and the phen-derived complex **3**¹⁵ provided the desired carbazole in the highest yield (74%). Finally, further optimization via the removal of the propylene oxide additive,

previously used to trap any acidic byproducts, improved the isolated yield of **2** to 95%.

It should be noted that the excited states of polypyridyl complexes of the type ^{*}FeL₃²⁺ are short compared to analogous Ru-based analogues^{16,17} and hence should not operate via the single electron transfer mechanisms common in photoredox catalysis. Given the abundance of literature data which support that photoredox catalysis via metal-to-ligand charge transfer for Fe(II)–polypyridyl complexes is not possible in solution,¹⁸ it is reasonable to assume that some other mechanism must be promoting the photochemical transformation. It may also be possible that catalysis is achieved through Fe(III)-based impurities. A control experiment was performed where commercially available Fe(II)Cl₂ was purified using a reported protocol to remove any Fe(III)-based impurities, and the corresponding catalyst **3** was prepared. Once again, the transformation (**1** → **2**) occurred in high yield (~80% of **2**) and required visible light irradiation (in the absence of light, 5% **2**, 94% recovered **1**). Given the necessity of the iron complex, light, and oxygen for the reaction to occur, the oxidation of the amines to carbazoles could proceed mechanistically via formation of superoxide.¹⁹ The improved mixing of O₂²⁰ made possible via the flow tube-in-tube system likely helps accelerate the reaction rate. In addition, when the transformation (**1** → **2**) was performed with Fe(III)(phen)₃PF₆ in either catalytic or stoichiometric quantities, no productive formation of the desired carbazole **2** was observed.

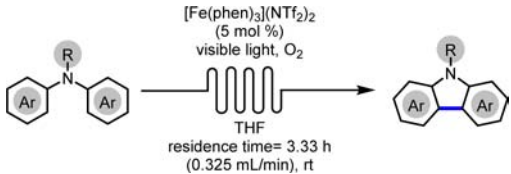
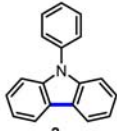
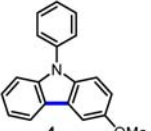
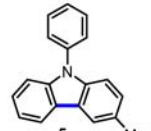
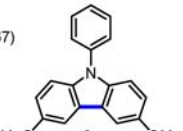
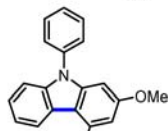
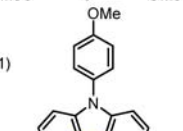
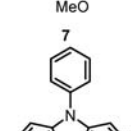
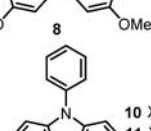
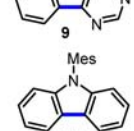
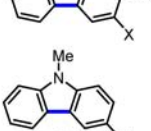
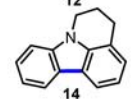
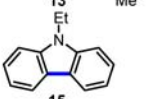
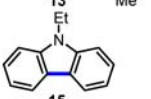
A second goal to improve the synthesis of carbazoles was to decrease the reaction time. The use of continuous flow techniques is crucial to the success of the Fe(phen)₃(NTf₂)₂/O₂ photocatalytic system. When the analogous carbazole synthesis (**1** → **2**) was performed in batch with a reaction time of 6.67 h, only traces of **2** could be isolated from the reaction mixtures. When a reaction time of 50 h was used, the desired carbazole could be isolated in 15% yield. In addition, in the absence of the tube-in-tube reactor, the yields of the carbazole **2** ranged from 46 to 95% yield, highlighting the need for efficient dissolution of molecular oxygen in the reaction media. To decrease the residence time, modifications to the continuous flow reactor were made so that the tubing was no longer in an interwoven pattern. Consequently, improved irradiation allowed a decrease in the residence time to 3.33 h, while maintaining high yields of **2** (91%) (Scheme 2).

Scheme 2. Improved Irradiation with Reactor Design



To probe the efficiency of the Fe(phen)₃(NTf₂)₂/O₂ system, a series of carbazoles were prepared from the corresponding diaryl- or triaryl amines (Table 1). First, triaryl amines bearing an electron-donating OMe or Me substituent were cyclized using the optimized conditions. The carbazoles **4** and **5** were isolated in 85 and 81% yields, respectively. The synthesis of carbazoles

Table 1. Efficiency of the $\text{Fe}(\text{phen})_3(\text{NTf}_2)_2/\text{O}_2$ System for the Synthesis of Carbazoles

			
product	yield (%) ^a (exo:endo)	product	yield (%) ^a (exo:endo)
	91		85 (11:89)
	81 (33:67)		68 (56:44)
	76 (29:71)		63
	91		10 X = F 76 (7:93)
	77		11 X = Cl 87 (5:95)
	67		80
			80

^aIsolated yields following flash chromatography. Major product is shown. In the cyclization of substituted triaryl amines, the incorporation of the substituted aryl group is defined as the *endo* product, while exclusion of the substituted aryl is defined as the *exo* substituent.

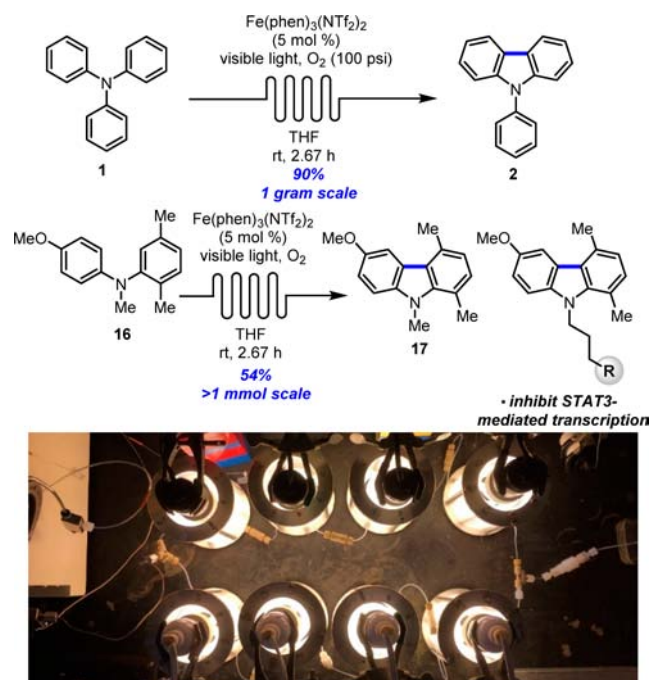
having an even greater number of electron-donating methoxy groups could also be prepared. The dimethoxy carbazoles **6** and **7** were prepared in 68 and 76% yields, and the trimethoxy derivative **8** was isolated in 63% yield. The synthesis of a pyrimidoindole was also possible as **9** was synthesized in 91% yield.

When we explored the scope of the synthesis of carbazoles, two halogenated substrates underwent productive cyclization to provide halogenated carbazoles **10** and **11** in good yields (76 and 87%, respectively). Both the fluoro- and chlorocarbazoles were isolated as predominantly the *endo* isomers. A sterically encumbered mesityl group was also tolerated and afforded the carbazole **12** in 77% yield. Three different N-alkylated carbazoles were also evaluated and isolated in good yields, with the N-Me carbazole **13** in 80% yield, the N-Et carbazole **14** in 80% yield, and the tetracyclic heterocycle **15** in 67% yield. In addition, upon comparison with the previously developed catalyst system employing a Cu-based catalyst and I_2 as molecular oxidant,⁹

the yields were all higher when the Fe-based sensitizer/ O_2 catalyst system was employed and performed in a much shorter reaction time (residence times 3.33 vs 20 h for Fe- vs Cu-based catalyst systems).

The improved protocol utilizing molecular oxygen and shorter residence times was explored on ~40 mg scales. We decided to explore the scalability in the photochemical synthesis of carbazoles up to a gram-scale. Using an experimental setup which involved five tubing reactors in series, at ~40 mg scales, the desired carbazole **2** was obtained in 91%. When the scale of the reaction was increased to 1 g, the reaction profile remained highly reproducible (88% of **2**). A drawback was the long overall process time required for the scale-up: the 1 g transformation (**1** → **2**) required approximately 50 h to complete. To demonstrate improved protocols for scale-up, proof-of-principle for the utility of a “numbering-up” strategy²¹ was explored (Scheme 3). The

Scheme 3. Numbering-up Strategy for the Synthesis of Simple and Complex Carbazoles



reaction mixture was first pumped through a tube-in-tube reactor where the O_2 pressure was increased (40 → 100 psi) compared to smaller scales. After elution from the gas/liquid reactor, the flow was “split” into the two reactor sequences with two 8 bar back pressure regulators connected to the end of the flow system. As such, **2** was obtained in 90% yield, and the overall process time was reduced by more than 50% (approximately ~1 g/day). The optimized photocatalytic synthesis of carbazoles was also applied to the synthesis of the carbazole core of recently reported inhibitors of STAT3,²² an emerging biomarker in tumor therapy.²³ The photocyclization of diarylamine **16** was performed on a >1 mmol scale using the numbering-up reactor design. The desired and highly substituted carbazole **17** was obtained in 54% yield.

In summary, a new photochemical synthesis of carbazoles has been developed. Key improvements include the following: (1) a catalytic system of $\text{Fe}(\text{phen})_3(\text{NTf}_2)_2$ allows the use of O_2 as a stoichiometric oxidant; (2) employing a tube-in-tube-type reactor under continuous flow conditions improved the reaction

time compared to previous methods; and (3) the photochemical synthesis of carbazoles was demonstrated in scale-up via a numbering-up strategy. The $\text{Fe}(\text{phen})_3(\text{NTf}_2)_2/\text{O}_2$ system could also promote photocyclization for the synthesis of carbazoles in yields higher than those of the first-generation copper-based catalyst system. Further fundamental work is currently directed toward a better understanding of the mechanism via Fe complexes and application in other photochemical syntheses.

■ ASSOCIATED CONTENT

■ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: [10.1021/acs.orglett.6b02456](https://doi.org/10.1021/acs.orglett.6b02456).

Experimental procedures and characterization data for all new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: shawn.collins@umontreal.ca.

Notes

The authors declare no competing financial interest.

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