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Photochemical Synthesis of Complex Carbazoles: Evaluation of Electronic Effects in Both UV- and Visible-Light Methods in Continuous Flow

Augusto C. Hernandez-Perez, Antoine Caron, and Shawn K. Collins*[a]

Abstract: An evaluation of both a visible-light- and UV-light-mediated synthesis of carbazoles from various triarylamines with differing electronic properties under continuous-flow conditions has been conducted. In general, triarylamines bearing electron-rich groups tend to produce higher yields than triarylamines possessing electron-withdrawing groups. The incorporation of nitrogen-based heterocycles, as well as halogen-containing arenes in carbazole skeletons, was well tolerated, and often synthetically useful complementarity was observed between the UV-light and visible-light (photoredox) methods.

Introduction

The synthesis of complex, highly functionalized carbazoles has been an active field of study due to their application in both pharmaceuticals[1] and materials science.[2] Recent advances in synthetic strategies, which involve functionalization of carbon–hydrogen (C–H) bonds has provided chemists with new tools for the formation of the parent carbazole skeleton, as well as their late-stage functionalization. One of the more popular strategies for carbazole synthesis involves formation of a carbon–nitrogen (C–N) bond from an amino-functionalized biaryl to form the central five-membered ring of the carbazole. Oxidative transformations under palladium catalysis can prepare carbazoles in good to excellent yields employing $Cu(OAc)_2/O_2$ or hypervalent iodine reagents as stoichiometric oxidants. Alternatively, rhodium catalysis can be employed to transform azide-functionalized biaryls to carbazoles in a redox neutral process. Each of the aforementioned technologies studied the effects of substitution on the outcome of the transformation. In particular, the effect of a substituent placed in a *meta*-position of the biaryl can afford mixtures of products (see R^1 and products **2 para** and **2 ortho**, Figure 1). Photochemical strategies are attractive synthetic routes to carbazoles as light is viewed as a "green" reagent. The synthesis of carbazoles via a UV-mediated electrocyclic process has been known since the 1970s,[3] and despite considerable interest in the reaction mechanism,[4,5] has been only used sparingly in the preparation of natural products.[6–8] In 2014, our group reported a UV-light continuous-flow set-up and demonstrated its utility in the formation of derivatives of carprofen, a carbazole-based drug used for the treatment of pain in veterinarian science.[9] In addition, our group has reported that visible-light photoredox catalysis can be used to prepare carbazoles through a C–C bond-forming process.[10] The transformation used a Cu-based sensitizer **3** and exploited continuous-flow conditions to improve the yields and reaction time. The visible-light-mediated reaction was shown to afford trisubstituted *N*-aryl or *N*-alkyl carbazoles, but no effort was made to explain the regiochemical preferences observed during the synthesis of complex car-

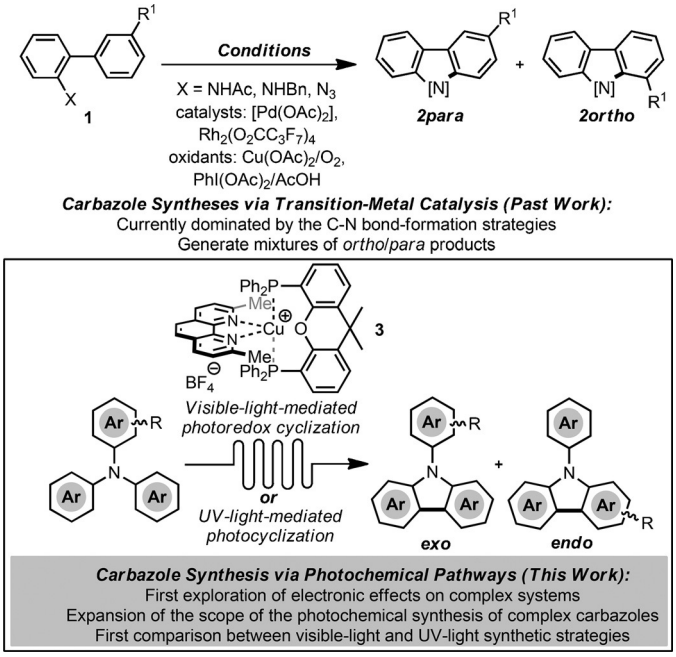

Figure 1. Synthesis of carbazoles via transition-metal catalysis and photochemical pathways.

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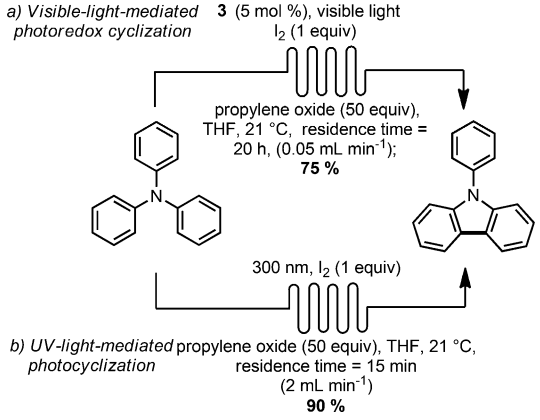
bazoles. Herein, we describe a full account of the substrate scope with regards to the visible-light-mediated synthesis of carbazoles employing a copper-based sensitizer, with an emphasis on exploring the electronic effects of substituent. In addition, we report a comparative study of the synthesis and substituent effects in the preparation of complex carbazoles by using a UV-light-mediated strategy.[11]

Results and Discussion

The synthesis of carbazoles from the corresponding triarylamine derivatives under photochemical conditions was carried out in continuous-flow conditions. The use of continuous-flow photochemistry has been shown to result in significant reductions in reaction time and rendering scale-up more "user-friendly".[12] In the visible-light-mediated synthesis of carbazoles, continuous-flow conditions resulted in an approximately 12-fold decrease in reaction time.[10] The photoredox methodology exploited the in situ formation of a copper-based sensitizer **3**, which outperformed other sensitizers for the process (Scheme 1 a). Continuous-flow conditions were also responsible for the ability to explore a UV-light-mediated synthesis of carbazoles. Using a previously developed flow system,[9] cyclizations could be performed at various wavelengths with even shorter reaction times than observed for the analogous photoredox methods (Scheme 1 b).



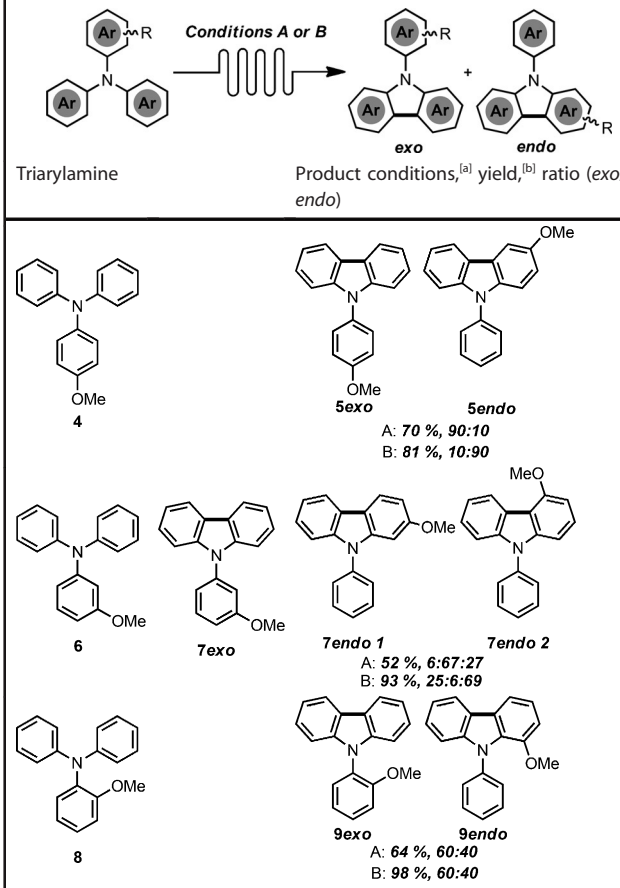
Scheme 1. Synthesis of an unsubstituted carbazole by a) visible-light-mediated photoredox catalysis and b) UV-light-mediated photocyclization.

The following study employed the identical oxidant system used in the visible-light syntheses under irradiation at 300 nm. In the cyclization of triarylamines to form carbazoles, the incorporation of the substituted aryl group is defined as the "*endo*" product, whereas exclusion of the substituted aryl (which becomes in the *N*-aryl group in the resulting carbazole) is defined as the "*exo*" substituent.

Evaluation of electron-rich substrates

In evaluating the transformation of electron-rich triarylamines to the corresponding carbazoles, the choice of a methoxy group as a typical electron-donating substituent was also made considering the number of biologically active carbazole natural products that contain such a motif.[13] Using either visible-light-mediated photoredox cyclization or UV-light-mediated electrocyclization, a series of triarylamines adorned with methoxy substituents were prepared and evaluated (Table 1).[14] First, triarylamine derivatives bearing a single methoxy substituent in either the *ortho*-, *meta*-, or *para*-positions of one of the N-aryl groups were examined. When the methoxy group was in the *para* position (triarylamine **4**), visible-light-mediated photoredox cyclization afforded a 70% yield of products as a 90:10 ratio of **5 exo**/**5 endo**. Interestingly, the UV-light-mediated cyclization afforded a 81% yield of products, with the opposite regiochemical preference for cyclization (10:90 **5 exo**/**5 endo**). When the *meta*-methoxy triaylamine **6** was subject to both photochemical syntheses, an *endo* product was favored in both cases. However, under visible-light photoredox conditions, the carbazole **7 endo1** was obtained in the highest yield, whereas UV-light electrocyclization gave the **7 endo2** as the favored product. When the methoxy substitu-

Table 1. Photocyclization of electron-rich triarylamines.

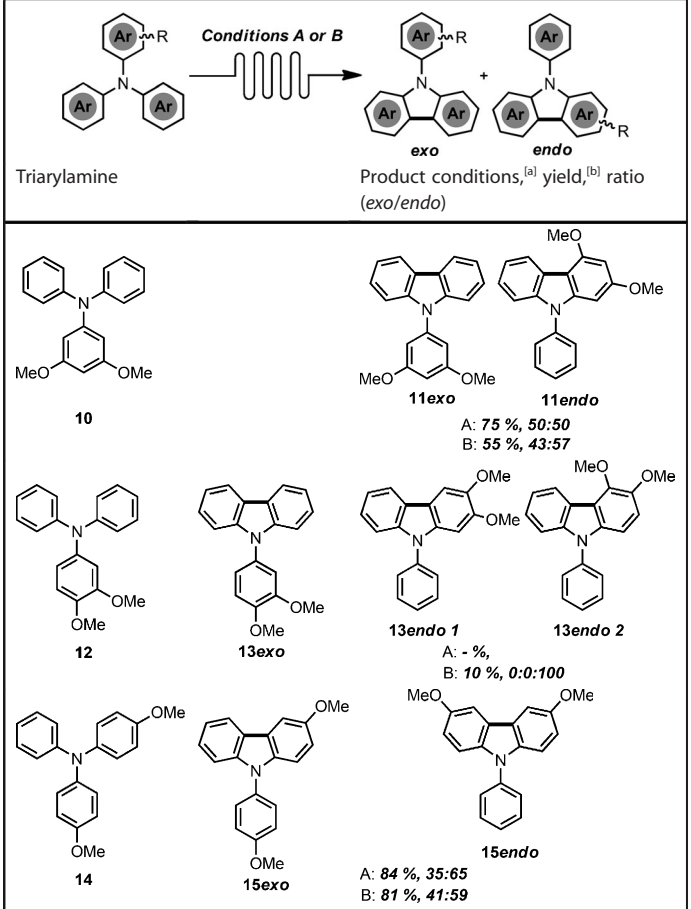


[a] A) Visible light, [Cu(Xantphos)(dmp)](BF_4), **3** in situ (5 mol%), visible light, I_2 (1 equiv), propylene oxide (50 equiv), THF, 21 °C, residence time 20 h, (0.05 mL min^{-1}); B) UV Light 300 nm, I_2 (1 equiv), propylene oxide (50 equiv), THF, 21 °C, residence time 15 min (2 mL min^{-1}). [b] Yields are based on chromatography.

ent was placed in an *ortho*-position on the *N*-aryl group (triarylamine **8**), both photochemical reaction conditions gave a similar ratio of products, slightly favoring the *exo*-product, **9 exo** (60:40 **9 exo**/**9 endo** in both cases); however, the UV-mediated method gave higher yields (98 vs. 64% yield).

Next, more complex patterns of methoxy-substituted triarylamines were examined (Table 2). A triarylamine bearing a 3,5-dimethoxy N-aryl group **10** was evaluated. Although a single *meta*-methoxy group exhibited preference in forming *endo*-products, no selectivity was now observed under visible-light conditions (75%, 50:50 **11 exo**/**11 endo**). Similar ratios were observed under UV-light irradiation (43:57 **11 exo**/**11 endo**), but the very electron-rich compounds were formed in lower yield (55%). The lower yields may be due to sensitivity of the final products to the UV-light conditions. When a similarly electron-rich triarylamine bearing a 3,4-dimethoxy *N*-aryl group **12** was evaluated, very little productive cyclization occurred in either photochemical manifold. Visible-light-mediated photoredox cyclization afforded only traces of cyclized carbazoles with significant amounts of by-products observed by ^{1}H NMR. The UV-light-mediated cyclization of the more electron-rich substrate **12** gave a low 10% yield, with selectivity for a single isomer **13 endo2**. When the retention time was decreased from 15 to 6 min, a yield of 56% was observed. In addition, at a reduced retention time, all three possible products were observed (10:26:64 **13 exo**/**13 endo1**/**13 endo2**), suggesting that certain products degrade more rapidly than others under the reaction conditions (although **13 endo2** was the major product in either case). Finally, when a triarylamine derivative having two of its *N*-aryl groups *para*-substituted with methoxy groups (**14**), the *endo* product was isolated as the major product under either photochemical conditions (photoredox: 84%, 35:65 **15 exo**/**15 endo**, UV light: 81%, 41:59 **15 exo**/**15 endo**).

Table 2. Photocyclization of complex electron-rich triarylamines.



[a] A) Visible light, [Cu(Xantphos)(dmp)](BF$_4$), **3** in situ (5 mol%), visible light, I_2 (1 equiv), propylene oxide (50 equiv), THF, 21 °C, residence time 20 h, (0.05 mL min^{-1}); B) UV light 300 nm, I_2 (1 equiv), propylene oxide (50 equiv), THF, 21 °C, residence time 15 min (2 mL min^{-1}). [b] Yields are based on chromatography.

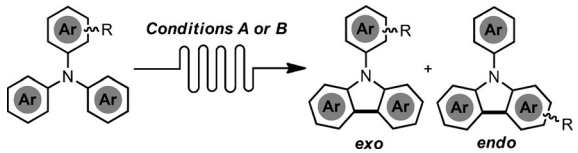
Evaluation of electron-poor substrates

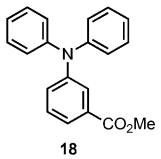
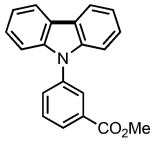
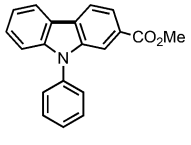
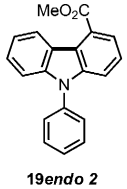
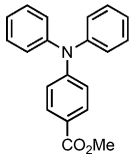
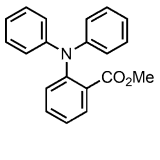
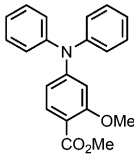
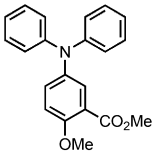
Next, triarylamine derivatives bearing a methyl ester substituent were examined to determine the effects of an electron-withdrawing group on the photochemical cyclizations to form carbazoles (Table 3). A methyl ester group was again placed in either the *ortho*-, *meta*-, or *para*-positions of one of the *N*-aryl groups of the corresponding triarylamines. The only cyclization, which proceeded with the formation product was when the methyl ester substituent was placed in the *meta*-position of an *N*-aryl group, in which cyclization could be observed under visible-light using the Cu-based sensitizer (37% of **19 exo**). Irradiation of the triarylamines having a methyl ester group was in the *ortho*- or *para*-positions did not result in cyclization under either visible-light-mediated photoredox cyclization or UV-light-mediated electrocyclization conditions (in general, quantitative recovery of starting material was observed). Because the photoredox transformation is thought to proceed through a nitrogen-centered radical cation, it was believed that the presence of a strong electron-withdrawing group renders the amine too electron-poor to undergo oxidation. In addition, two triarylamines were prepared having an N-aryl group with both an electron-donating and -withdrawing substituent (**22** and **24**), but both photochemical conditions failed to produce significant quantities of carbazole products.[15]

Evaluation of heterocycle-containing substrates

Complex carbazoles having additional nitrogen atoms within their framework form an important class of heterocycles. For example, both α- and β-carbolines[16] are prevalent in biologically active natural products. The photocyclization of triarylamines having a nitrogen heterocycle as an N-aryl group were explored under the photochemical conditions (Table 4). The photochemical transformation of the pyridine-substituted **26** was first explored and afforded a 55% yield of **27 endo** under visible-light conditions. UV-light-mediated cyclization afforded an excellent yield, again with selectivity for the **27 endo** isomer (98%). For the pyrimidine-substituted derivative **28**, both the visible-light and UV-light conditions afforded solely the **29 endo** product in similar yield (60 vs. 64% respectively).

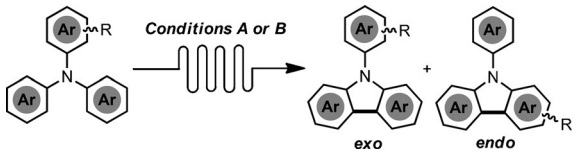
Table 3. Photocyclization of electron-poor triarylamines.

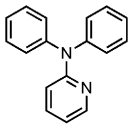
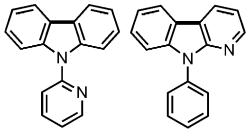
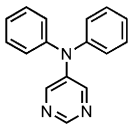
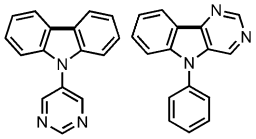
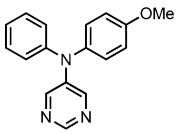
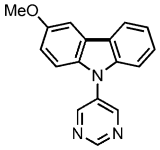
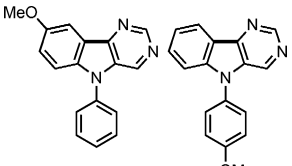


Triarylamine	Product conditions,[a] yield,[b] ratio (*exo*/*endo*)
 **18**	
 **19*exo***	
 **19*endo 1***	
 **19*endo 2*** A: ***37 % 100:0:0*** B: ***<5 % 100:0:0***	
 **16**	
 **20**	
 **22**	
 **24**	

[a] A) Visible light, [Cu(Xantphos)(dmp)](BF_4), **3** in situ (5 mol%), visible light, I_2 (1 equiv), propylene oxide (50 equiv), THF, 21 °C, residence time 20 h, (0.05 mL min^{-1}); B) UV light 300 nm, I_2 (1 equiv), propylene oxide (50 equiv), THF, 21 °C, residence time 15 min (2 mL min^{-1}). [b] Yields are based on chromatography. Only trace products were formed, recovered starting material was generally isolated.

Table 4. Photocyclization of heterocycle-containing triarylamines.



Triarylamine	Product conditions,[a] yield,[b] ratio (*exo*/*endo*)
 **26**	 **27*exo*** **27*endo*** A: ***55 % 0: 100*** B: ***98 % 0: 100***
 **28**	 **29*exo*** **29*endo*** A: ***60 % 0: 100*** B: ***64 % 0: 100***
 **30**	 **31*exo***
	 **31*endo1*** **31*endo2*** A: ***95 %, 0: 26: 74*** B: ***46 %, 0: 33: 67***

[a] A) Visible light, [Cu(Xantphos)(dmp)](BF_4), **3** in situ (5 mol%), visible light, I_2 (1 equiv), propylene oxide (50 equiv), THF, 21 °C, residence time 20 h, (0.05 mL min^{-1}); B) UV light 300 nm, I_2 (1 equiv), propylene oxide (50 equiv), THF, 21 °C, residence time 15 min (2 mL min^{-1}). [b] Yields are based on chromatography.

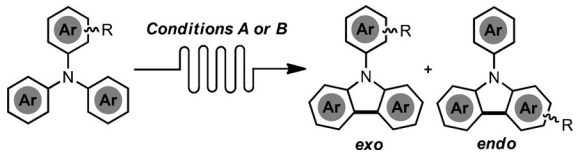
Finally, a more complex triarylamine having both a pyridine and an anisole substituent **30** was evaluated. Although three different products could be obtained, under photoredox conditions, only the *endo* products **31 endo1** and **31 endo2** were obtained (95%, 26:74 respectively). Although the yields of the cyclization under UV light were lower (46%), similar selectivity was observed, whereby the *endo* products were again favored (33:67 **31 endo1**/**31 endo2**). Given that both photochemical syntheses involving heterocycles showed a selectivity for inclusion of the heterocycle into the carbazole nuclei, the formation of the *endo* products is perhaps not surprising.

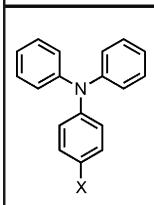
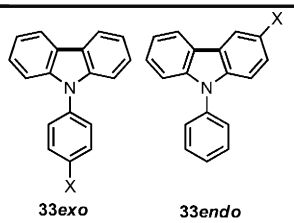
Evaluation of halogen-containing substrates

Halogens are important substituents in heterocyclic chemistry. Although chloride, bromide, and iodide substituents can be exploited in cross-coupling chemistry for further functionalization of a heterocyclic core, a fluoride substituent can be exploited in medicinal chemistry to inhibit metabolic degradation.[17]

Consequently, the behavior of triarylamines having a halogen substituent in the *para*-position of N-aryl group were explored under the photochemical conditions (Table 5). Given the difficulty of cyclizing triarylamines to carbazoles with electron-withdrawing methyl ester substituents, the photochemical transformation of the fluoride-substituted **32** was initially considered to be challenging. Surprisingly, excellent yields were obtained for photocyclization of **32** under visible light (94%) and UV light (86%). Under photoredox conditions, a preference for the *endo*-product was observed (10:90 **33 exo**/**33 endo**), whereas the opposite trend was observed under UV-light-mediated electrocyclization (87:13 **33 exo**/**33 endo**). Next, the chloro-derivative **34** was explored. Although the photoredox conditions under visible light afforded an excellent 95% of only **35 exo**, the UV-light conditions failed to give either **35 exo** or **35 endo**. A complex reaction mixture was observed, and none of the starting chloride **34** was recovered.[18] When the bromo-derivative **36** was evaluated under the photoredox conditions employing the copper-based sensitizer, only a 19% of the **37 endo** carbazole was obtained (the *exo* has been preferred for the fluoride and chloride derivatives) Under UV-light conditions, neither **37 exo** or **37 endo** was observed. A small amount of *N*-phenylcarbazole was observed (16%), along with 71% of recovered bromoamine **36**.[19] Under photoredox conditions, the iodo-derivative **38** gave a 50% of the **39 exo** carbazole. The productive cyclization of **38** is highly advantageous and provides a handle to install other electron withdrawing via cross-coupling.[20] In the case of the iodo-derivative **38**, the UV-light conditions afforded a clean reaction mixture, which produced a 95% of *N*-phenylcarbazole.[21] It is known that UV-light conditions can cleave C_{aryl}–X bonds; however, it is difficult to

Table 5. Photocyclization of halogen-containing triarylamines.



Triarylamine	Product conditions,[a] yield,[b] ratio (*exo/endo*)
	
	33*exo* **33*endo***
32 X = F	A: ***94 %, 10:90*** B: ***87 %, 87:13***
	35*exo* **35*endo***
34 X = Cl	A: ***95 %, 100:0*** B: ***- %***
	37*exo* **37*endo***
36 X = Br	A: ***19 %, 100:0*** B: ***16 % of N-phenylcarbazole, 71 % recovered 36***
	39*exo* **39*endo***
38 X = I	A: ***50 %, 100:0*** B: ***95 % of N-phenylcarbazole***

[a] A) Visible light, [Cu(Xantphos)(dmp)](BF$_4$), **3** in situ (5 mol%), visible light, I_2 (1 equiv), propylene oxide (50 equiv), THF, 21 °C, residence time 20 h, (0.05 mL min^{-1}); B) UV light 300 nm, I_2 (1 equiv), propylene oxide (50 equiv), THF, 21 °C, residence time 15 min, (2 mL min^{-1}). [b] Yields are based on chromatography.

assess whether in the case of **34**, **36**, or **38** if the C_{aryl}—X bond is undergoing homolysis before or after cyclization to the carbazole moiety.[22,23]

Conclusion

An evaluation of the visible-light-mediated synthesis of carbazoles from various electronically different triarylamines employing Cu-based sensitizer **3** under continuous-flow conditions has been conducted. In comparison, all of the triarylamines were also cyclized under UV-light irradiation using the identical oxidant system and the yields and regiochemical preferences have been compared. In general, the following conclusions come to light:

1) The synthesis of carbazoles from triarylamines bearing electron-rich methoxy groups tend to produce higher yields. In all cases, UV-light irradiation provided shorter reaction times and in general, higher yields as well. Preferences for either *exo* or *endo* products tend to be similar except in cases when the group is located in the *para* position with respect to the nitrogen atom.

2) The synthesis of carbazoles from electron-poor substrates is difficult under both visible-light photoredox conditions and UV-light conditions; however, in most cases, yields tend to be higher by using UV-light irradiation at 300 nm. The inclusion of an electron-donating group does not negate the influence of an electron-withdrawing substituent in the *para* position. Electron-withdrawing groups are also problematic even when present on identical rings as an electron-donating group.

3) The use of electron-poor nitrogen-based heterocycles as aryl groups on the triarylamine starting materials was well tolerated. In general, UV-light irradiation provided higher yields. The cyclization of a triarylamine having a pendant heterocycle and an aryl group with an electron-donating methoxy substituent provided inversed regiochemical preferences depending on the method of irradiation.

4) The cyclization of the halogen-containing triarylamines was well tolerated using a photoredox, visible-light-mediated approach, often with high selectivity for one regioisomer. Although UV-light methods tended to afford higher yields with the other substrate classes, for most halogen-containing substrates (Cl, Br, and I) photodehalogenation was observed.

Despite the general guidelines provided by the above-described study, it is worth noting that copper-based sensitizers have been known to play distinct and different roles in photocatalysis compared to more common Ru- and Ir-based sensitizers and the above-presented study does elucidate whether such interaction may be responsible for the observed selectivities.[24] The study demonstrates the efficiency of photochemical methods utilizing continuous flow for the synthesis of carbazoles, as well as the complementarity that can be obtained between UV-light and visible-light (photoredox) methods for the preparation of complex heterocycles. Given the widespread interest in carbazoles in medicinal chemistry, as well as material science, it is expected that photochemical methods described herein will interest a wide variety of researchers. The application of both UV- and visible-light-mediated strategies to other heterocyclic skeletons is currently under study.

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Keywords: carbazoles · continuous flow · photochemistry · photoredox catalysis · UV/Vis spectroscopy

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