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Diastereoselective Oxidative C–N/C–O and C–N/C–N Bond Formation Tandems Initiated by Visible Light: Synthesis of Fused *N*-Arylindolines

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Abstract

The synthesis of fused *N*-arylindolines using visible light photoredox catalysis has been developed. We previously described that photogenerated amine radical cations generate substituted indoles through an intermediate benzylic carbocation. Herein, we expand the application of this chemistry by trapping the benzylic carbocation with tethered heteronucleophiles. The reactivity of the photogenerated benzylic carbocation is explored and applied to a range of substrates with various electronic characters and ring constraints. The method described provides C2 and C3 fused indolines bearing a tetrasubstituted carbon stereocenter with greater than 99:1 diastereoselectivity in moderate to good yields.

Keywords

Photocatalysis; Fused-ring systems; Cations; C–N bond formation; C–O bond formation; Heterocycles

Nitrogen-containing compounds have received much attention recently due to their prevalence in natural products and pharmaceuticals.^[1] Specifically, indole and indoline motifs constitute an important substructure of nitrogen-containing heterocycles.^[2] A subclass of the indoline motif is the fused indolines. Some notable approaches for the synthesis of these compounds include functionalization of oxindoles,^[3] C–H amination of properly designed aromatics,^[4] and manipulation of indole precursors.^[5]

Visible light photoredox catalysis has also been a subject of recent interest among synthetic chemists.^[6] The excitement in this topic of organic research is mainly due to new synthetic opportunities enabled by photocatalysis' ability to manipulate organic molecules' redox states. Since organic molecules do not absorb visible light efficiently, a variety of organometallic complexes^[7] and organic dyes^[8] have been developed as visible light photoredox catalysts. Upon excitation, they can act as either a single electron oxidant or

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Dedicated to Professor Stephen L. Buchwald of Massachusetts Institute of Technology) for his 60th Birthday.

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reductant. Photocatalysts' unique ability to participate in the two distinct redox processes has led to a recent surge of reported methodologies based on visible light photoredox catalysis.

Previously, our lab disclosed an oxidative C–N bond formation cascade triggered by visible light to generate a wide range of mono- and disubstituted indoles at the C2 and C3 positions (Scheme 1).^[9] The substrate was designed in which, under photoredox conditions, an oxidation could occur on the nitrogen atom to generate an amine radical cation. A subsequent C–N bond formation was then initiated in which the amine radical cation was added electrophilically to the styrene moiety of the molecule. After subsequent deprotonation and oxidation, a benzylic cation intermediate was proposed to undergo either direct aromatization or 1,2-aryl/carbon shift^[10] followed by aromatization to form the substituted indole. We hypothesized that by tethering a nucleophile to the styrene moiety and substituting R¹ with an alkyl group, the tethered nucleophile might be competitive against the 1,2-aryl/carbon shift to intercept the benzylic cation, providing a fused indoline (Scheme 1). Specifically, this approach would allow for formation of two new carbon-heteroatom bonds over an alkene in just a single step with complete diastereocontrol. Herein, we describe a one-step diastereoselective synthesis of fused indolines initialized by visible light.

We began our investigation using alcohol **1a**. Under similar conditions for the indole synthesis,^[9] we were able to obtain fused indoline **2a** in 43% yield (entry 1, Table 1). Upon further catalyst and solvent optimization (entries 2–6), we found that Ru(bpy)₃(PF₆)₂ in acetonitrile gave the highest yield (78%, entry 3). The reaction did not proceed when omitting photoredox catalyst (entry 7) and light (entry 8). Additionally, the reaction did not proceed when the reaction mixture was ran in N₂ atmosphere, suggesting atmospheric oxygen plays an important role in the transformation (entry 9). In order to further probe this observation, the reaction was ran under O₂ atmosphere, producing **2a** in a decreased yield, likely due to increasing decomposition caused by higher concentration of O₂ (entry 10). Omitting HOAc led to a slower reaction and a lower yield of **2a** (entry 11). On the other hand, use of an acid stronger than HOAc resulted in more decomposition and also a lower yield of **2a** (entry 12). Both phenomena are consistent with what we observed in the indole synthesis,^[9] stressing a tight range of *p*K_as for the acid to be effective. Lowering the catalyst loading to 2 mol % had no effect on the yield; therefore, we opted to use the 2 mol % catalyst loading for the optimal conditions (entry 13). Lastly, we applied the optimized conditions to **1b**, bearing a simple phenyl group rather than the *para*-methoxyphenyl (PMP) group, which was found to be unreactive after 36 h (entry 14). This observation is in accord with the indole synthesis, where we identified the need of a *para*-alkoxy phenyl aniline substituent in order to undergo the cascade triggered by visible light.^[9]

To set up the cascade, we would need to develop synthetic routes for accessing the starting material, styryl anilines bearing a trisubstituted alkene and a *para*-alkoxy phenyl aniline substituent. The first route we developed hinged on use of a Wittig reaction of **3** and **4** to set up the alkene (**6**) followed by a Buchwald-Hartwig Amination with **5** to install the *para*-alkoxy phenyl aniline substituent^[9] (Scheme 2, Method A). However, this route lacks convergence and thus leads to a lengthy synthesis of styryl anilines. To address this issue,

we developed an alternative and more convergent route that is centered on a Suzuki–Miyaura Cross Coupling of boronic ester **8** and vinyl iodide **7** (Scheme 2, Method B). Both boronic ester **8** and vinyl iodide **7** can be prepared in one or two steps from commercially available starting materials (see SI), thus allowing for a faster entry to styryl anilines. The use of the Suzuki–Miyaura Cross Coupling reaction also obviates the need of protecting the hydroxyl group.

Protodeboronation of boronic esters is a known side reaction in the Suzuki–Miyaura Cross Coupling reaction.^[11] Although a number of approaches were reported to remedy this issue,^[12] we spent considerable effort finding suitable conditions for the Cross Coupling reaction using boronic ester **8a** and vinyl iodide **7a** (Table 2). It quickly became apparent that Pd(PPh₃)₄ was inferior to the catalyst system composed of Pd(OAc)₂ with a Buchwald ligand (entries 1–4). In fact, of the Buchwald ligands examined, RuPhos yielded the most promising results in our initial screen using a 10:1 mixture of toluene to water (entry 4). Using RuPhos as the ligand, we then investigated other solvent mixtures. When toluene was replaced with THF, the yield was dramatically increased (entry 5). The yield was further increased when adding ethanol to give a 2:1:1 mixture of THF:EtOH:H₂O (entry 6). Replacement of THF by toluene in the three-solvent system gave slightly inferior results, confirming the THF/EtOH/H₂O mixture as the optimal solvent system (entry 7).

A variety of styryl anilines were successfully prepared using either route, which allowed us to turn our attention to study the substrate scope (Scheme 3). Varying the length of the nucleophilic tether to generate the corresponding indoline fused with a 5-, 6-, or 7-membered ring (**2a–c**) proceeded in good yields. However, attempts to synthesize the indoline fused with 4- or 8-membered ring met with little success (**1n** and **1o**). Significant decomposition and formation of multiple products were observed in both examples. Next, we modified the PMP group to a 2,4-dimethoxyphenyl group or a 3,4,5-trimethoxyphenyl group. In both cases (**2e** and **2f**), the reaction proceeded with slightly shorter reaction time, albeit modestly lower yields. We then probed the substituent effect at C5 and C6 of the indoline moiety. When a MeO group was installed at C5, the reaction proceeded rapidly (3 h) to afford **2g** in 71% yield. Conversely, when a CF₃ group was placed at C5, the reaction was found to be very sluggish (24 h) and product **2h** was obtained in a diminished yield (39%). Clearly, the substituent effect at C5 was quite pronounced. We also placed the pair of substituents at C6 to study the substituent effect. Interestingly, although both substrates proceeded sluggishly (24 h and 25 h), having the CF₃ group at C6 gave a higher yield (**2i**) than having the MeO group at C6 (**2j**). A final example of studying the substituent effect was to place a MeO group at C5 while N1 was substituted with a Ph group rather than the PMP group. The substrate was converted to the corresponding *N*-phenylindoline **2k** in 60% yield after 6 h. Finally, we evaluated the feasibility of using tethered amine nucleophiles to generate fused pyrrolo- and piperidoindolines. The requisite substrates were easily generated from the alcohol substrates using a Gabriel synthesis followed by a Boc protection. Pyrrolo- and piperidoindolines were produced in satisfactory yields (**2l**, 76%; **2m**, 52%). Notably, free amines (e.g., **2m**) were found to be incapable of undergoing the cyclization with or without HOAc. Lastly, it is worth mentioning that in all cases in which

the desired fused indoline was formed, >99:1 diastereoselectivity was uniformly observed, regardless of the styrene's alkene geometry.

In the substrate scope study discussed above, we installed a methyl group in all the substrates. This decision was made based on our concern that intramolecular S_N1 reaction might not be competitive against E1 elimination if R1 is hydrogen (Scheme 1). To test this hypothesis, we synthesized substrate **1p** and subjected it to the optimized conditions. Indeed, the corresponding indole **9a** was formed as expected (Scheme 4, eq. 1). Additionally, we subjected **2f**, bearing a 3,4,5-trimethoxyphenyl group, to CAN (ceric ammonium nitrate) with H_2SO_4 in order to remove the *N*-aryl group (Scheme 4, eq. 2).^[13] To our delight, fused indoline **10a** was successfully isolated in 57% yield. It is of note, however, that the oxidative cleavage conditions were not successful to cleave the PMP group.

In summary, diastereoselective oxidative C–N/C–O and C–N/C–N bond formation tandems were revealed to generate fused *N*-arylindolines using visible light. Two independent synthetic routes were also developed for accessing the starting materials, allowing for flexibility about how to decorate the *N*-arylindolines. Additionally, a variety of *N*-arylindolines were synthesized, ranging from good to moderate yields. Both oxygen and nitrogen nucleophiles were shown to intercept the photogenerated benzyl cation effectively. Lastly, the *N*-aryl group could be removed in synthetically useful yields when it is a 3,4,5-trimethoxyphenyl group, further expanding the substrate scope of this method. More studies are currently underway to uncover additional synthetic transformations associated with this method.

Experimental Section

A Representative Procedure for Preparation of *N*-Arylindolines by Visible Light Photocatalysis

To a test tube equipped with a stir bar were added styryl aniline (1 equiv, 0.2 mmol), $Ru(bpy)_3(PF_6)_2$ (2 mol %, 0.004 mmol, 3.5 mg), acetic acid (1 equiv), and CH_3CN (3 mL, 0.067 M). The tube was then sealed with a Teflon screw cap and pierced with a 16 gauge needle. The test tube was then clamped at a 6 cm distance from an 18 W focused white LED and stirred until completion by TLC. The reaction mixture was then diluted with diethyl ether and filtered through a pad of neutral alumina. The filtrate was then concentrated in vacuum and purified by flash chromatography on neutral alumina to afford the pure fused *N*-arylindoline.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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previous work:

this work:

Scheme 1.

Design of a new approach for fused indoline synthesis.

Method A **Method B**

Scheme 2.
Retrosyntheses of styryl anilines.

Scheme 3.

Substrate scope. Reaction conditions: 2 mol % $\text{Ru}(\text{bpy})_3(\text{PF}_6)_2$, HOAc, air, CH_3CN , irradiation with an 18 W focused white-light LED. Yields of products isolated using column chromatography are given.

Indole formation of **1p** (eq. 1) and oxidative cleavage of 3,4,5-trimethoxyphenyl group (eq. 2).

Table 1

Reaction Optimization.

Entry ^{a)}	Catalyst ^{b)}	Solvent	Conv. of 1 (%) ^{c)}	Yield (%) ^{c)}
1	A	MeCN	91	43
2	B	MeCN	59	35
3	C	MeCN	100	78
4	C	DMSO	96	33
5	C	DMF	94	11
6	C	CH ₃ NO ₂	100	14
7	None	MeCN	0	N.R. ^{d)}
8 ^{e)}	C	MeCN	0	N.R. ^{d)}
9 ^{f)}	C	MeCN	17	11
10 ^{g)}	C	MeCN	100	39
11 ^{h)}	C	MeCN	70	37
12 ⁱ⁾	C	MeCN	96	13
13 ^{j)}	C	MeCN	100	80 (73) ^{k)}
14 ^{j),l),m)}	C	MeCN	0	N.R. ^{d)}

^{a)} To a test tube equipped with a magnetic stir bar was added styryl aniline (1 equiv, 0.1 mmol), photoredox catalyst (4 mol %), HOAc (1 equiv), and 1.5 mL of solvent. The test tube was closed by a screw cap with a Teflon septum and exposed to air by a 16-gauge disposable needle. The resulting mixture was allowed to stir at a 6 cm distance from a single 18 W focused white LED for 8 h.

^{b)} Catalysts: A = Ru(bpz)₃(PF₆)₂; B = Ir(ppy)₂(dtb-bpy)(PF₆); C = Ru(bpy)₃(PF₆)₂.

^{c)} GC yield using a dodecane standard.

^{d)} No reaction, determined by GC analysis and ¹H NMR of the crude mixture.

^{e)} Reaction performed in the dark.

^{f)} N₂ atmosphere.

^{g)} O₂ atmosphere.

^{h)} No HOAc added.

ⁱ⁾ TFA (1 equiv) used instead of HOAc.

^{j)} Using 2 mol % of catalyst.

^{k)} Isolated yield.

^{l)} Using **1b**.

^{m)} Allowed to stir for 36 h.

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Table 2

The Suzuki–Miyaura Cross Coupling Screen.

Entry ^{a)}	Solvent	Ligand	Yield (%) ^{b)}
1 ^{c)}	toluene:H ₂ O (10:1)	None	9
2	toluene:H ₂ O (10:1)	XPhos	16
3	toluene:H ₂ O (10:1)	SPhos	30
4	toluene:H ₂ O (10:1)	RuPhos	55
5	THF:H ₂ O (10:1)	RuPhos	83
6	THF:EtOH:H ₂ O (2:1:1)	RuPhos	95 (88) ^{d)}
7	toluene:EtOH:H ₂ O (2:1:1)	RuPhos	91

^{a)} To a test tube equipped with a magnetic stir bar was added the boronic ester **8a** (1.5 equiv, 0.33 mmol), Pd(OAc)₂ (2 mol %, 0.0044 mmol), ligand (4 mol %, 0.0088 mmol), and ground K₃PO₄ (3 equiv, 0.66 mmol). The test tube was sealed and then subjected to three cycles of evacuation/refill with N₂. Alcohol **7a** (1 equiv, 0.22 mmol) and solvent (1 mL, degassed) were then added. The resulting mixture was stirred at 90 °C for 24 h.

^{b)} GC yield using dodecane as an internal standard.

^{c)} Using Pd(PPh₃)₄ (10 mol %, 0.022 mmol) and K₂CO₃ (3 equiv, 0.66 mmol).

^{d)} Isolated yield.