

Photocatalysis

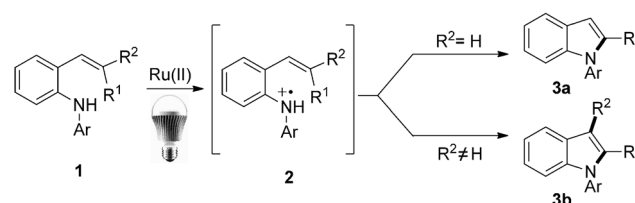
A Visible-Light-Mediated Oxidative C–N Bond Formation/Aromatization Cascade: Photocatalytic Preparation of *N*-Arylindoles**

Soumitra Maity and Nan Zheng*

Indoles are heterocyclic motifs that are embedded in a large number of bioactive natural products and pharmaceuticals.^[1] As such, the search for sustainable and more efficient methods for the preparation of indoles is of constant interest.^[2,3] Amination of vinyl C–H bonds of styryl anilines would provide direct and potentially more efficient access to indoles, particularly because styryl anilines are readily prepared by the Buchwald–Hartwig amination^[4] of 2-bromostyrene. When this approach was first reported by the research group of Hegedus, it employed a palladium complex under reaction conditions of high temperature.^[5a,b] However, its use in indole synthesis has been limited, although one notable example, in the form of a palladium-catalyzed cyclization of 2-chloro-*N*-(2-vinyl)aniline, was recently reported by Tselikhovsky and Buchwald.^[5c]

Recently, visible-light photocatalysis has become the subject of a flurry of activity in organic chemistry.^[6] In parallel with the efforts of other research groups in this field,^[7–11] our research group^[12] has been engaged in exploring new types of reactivity of nitrogen-centered radical cations that are generated through direct oxidation of the corresponding amines by using photoexcited ruthenium–polypyridyl complexes.^[13] Although this type of oxidation was first discovered in the late 1970s,^[14] its potential in organic synthesis has not been extensively explored before recent efforts. Under visible-light photoredox conditions, the fate of nitrogen-centered radical cations has been shown to follow one of three reaction pathways: conversion into an iminium ion with concomitant release of a hydrogen radical,^[15] conversion into an α -amino radical by deprotonation,^[16] or coupling with an irreversible ring-opening process to form a carbon-centered radical that is distal to the nitrogen atom.^[12b] We speculated that other reaction pathways that nitrogen-centered radical cations are known to follow, including electrophilic addition to alkenes, might be amenable to visible-light photocatalysis under similar reaction

conditions. Herein, we report that nitrogen-centered radical cation **2**, which is generated from styryl aniline **1**, can undergo electrophilic addition to the tethered alkene, thus triggering a cascade reaction involving either aromatization (when $R^2 = H$ in **2**) or C–C bond migration followed by aromatization (when $R^2 \neq H$) to form indoles **3a** and **3b** (Scheme 1). This new photocatalytic approach for preparing indoles is especially attractive because mild aerobic oxidation condi-



Scheme 1. Visible-light-mediated indole synthesis.

tions (visible light, open to air, and room temperature) are employed.

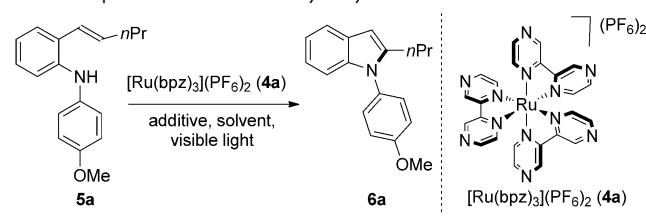
Styryl aniline **5a** was chosen as the model substrate for initial investigation (Table 1). $[\text{Ru}(\text{bpz})_3](\text{PF}_6)_2$ (**4a**)^[17] was employed as the photocatalyst and an 18 W white-light LED was used as the source of visible light. Using 2 mol % of **4a** in CH_3CN and leaving the reaction mixture open to air, we were pleased to find that the desired indole product **6a** was formed in 31 % yield, although, even after 24 hours, the reaction had not proceeded to completion (Table 1, entry 1). Either the use of O_2 in the place of ambient atmosphere (Table 1, entry 2) or the use of TFE^[18] as the solvent (Table 1, entry 3) did not improve the yield. Addition of silica gel^[18] to the reaction mixture significantly accelerated the reaction, which was complete after 12 hours, thus providing indole **6a** in 68 % yield (Table 1, entry 4). Doubling the catalyst loading further shortened the time necessary for full conversion to 5 hours and led to an increase in the yield of indole **6a** to 88 % (Table 1, entry 5). $[\text{Ru}(\text{bpy})_3](\text{PF}_6)_2$ (**4b**; bpy = 2,2'-bipyridine)^[17b] was found to be inferior to **4a**.^[19] Control studies showed that the catalyst, light, and air were all essential for this transformation (Table 1, entries 7–9). Notably, a *p*-alkoxyphenyl group on the nitrogen atom is also critical for the reaction.^[18] When the *p*-methoxyphenyl group of **5b** was replaced by a phenyl group (*N*-phenyl-2-vinylaniline, **5b'**), no reaction was observed under the same reaction conditions. We are currently investigating the role of the *p*-alkoxyphenyl group in the reaction.^[20]

[*] Dr. S. Maity, Prof. Dr. N. Zheng
Department of Chemistry and Biochemistry, University of Arkansas
Fayetteville, AR 72701 (USA)
E-mail: nzheng@uark.edu

[**] We thank the University of Arkansas, the Arkansas Bioscience Institute, and the NIH NCCR COBRE grant (P30 RR031154 and P30 GM103450) for generous support of this research. We also thank Prof. Bill Durham for insightful discussions on photochemistry.

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201205137>.

Table 1: Optimization of the catalytic system.



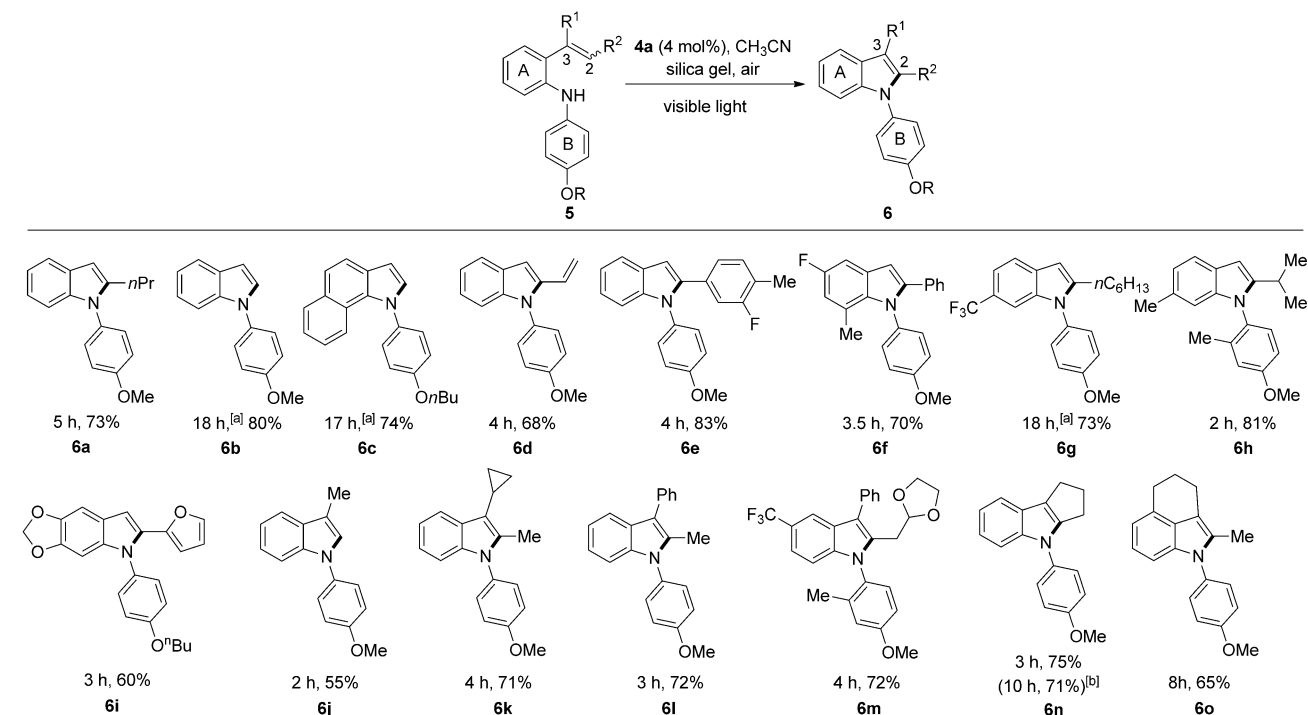
Entry	Reaction conditions ^[a]	t [h]	Conv. of 5a [%] ^[b]	Yield of 6a [%] ^[b]
1	4a (2 mol %), CH ₃ CN	24	44	31
2	4a (2 mol %), CH ₃ CN, O ₂	24	49	33
3	4a (2 mol %), TFE	24	42	21
4	4a (2 mol %), silica gel, CH ₃ CN	12	100	68
5	4a (4 mol %), silica gel, CH ₃ CN	5	100	88
6	4b (2 mol %), silica gel, CH ₃ CN	24	100	19
7	silica gel, CH ₃ CN, no 4a, light	24	8	4
8	4a (2 mol %), silica gel, CH ₃ CN, no light	24	4	2
9	4a (2 mol %), silica gel, CH ₃ CN, degassed	24	8	0

[a] Reaction conditions: 5a (0.2 mmol), solvent, open to air, irradiation with a white-light LED at RT. [b] Measured by GC using dodecane as an internal standard. bpz = 2,2'-bipyrazine, TFE = trifluoroethanol.

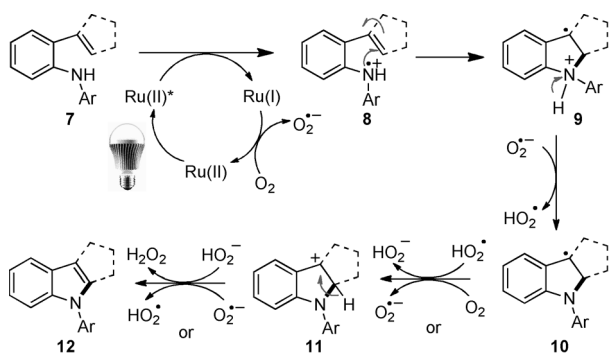
To examine the substrate scope of this method, a series of styryl anilines **5** were prepared using the Buchwald–Hartwig amination of a 2-bromostyrene derivative with anilines. Under the optimized reaction conditions (Table 1, entry 5), styryl anilines **5** were converted into the desired indole

products **6** in moderate to good yields (Scheme 2). The presence of electron-donating and electron-withdrawing groups on the aryl ring A were tolerated. A number of alkenes containing various functional groups such as alkanes, alkenes, arenes, and furans were good substrates for this reaction as long as the C2 position was monosubstituted. Disubstituted (2,3- and 3,3-) and trisubstituted (2,3,3-) alkenes were all converted into 2-substituted, 3-substituted, and 2,3-disubstituted indoles, respectively. This method represents a general method for the regioselective introduction of substituents at the C2 and C3 positions of indoles,^[2b,e,f] a need that is currently unmet in indole synthesis. Substrates that are sterically hindered in the vicinity of the alkene moiety are well tolerated (**6h**; Scheme 2). When the alkene was part of a carbocycle, fused indoles were obtained as the products (**6n** and **6o**; Scheme 2); the yield of **6n** was high, although the reaction took a longer time to reach completion when it was scaled up to 1 g.

We propose the catalytic cycle that is outlined in Scheme 3. The key steps include: (i) conversion of amine **7** into nitrogen-centered radical cation **8** through oxidation using a photoexcited [Ru(bpz)₃](PF₆)₂ (**4a**), (ii) electrophilic addition of nitrogen-centered radical cation **8** to a tethered alkene to generate benzylic radical **9**,^[21] (iii) oxidation of benzylic radical **10** to its corresponding benzylic cation **11**, and finally (iv) aromatization through deprotonation, thus forming indole **12**. A control study using tetraphenylporphyrin (TPP)^[22] in place of **4a** did not lead to the desired indole. This result strongly indicates that the reaction is not mediated by singlet oxygen (see the Supporting Information for details).



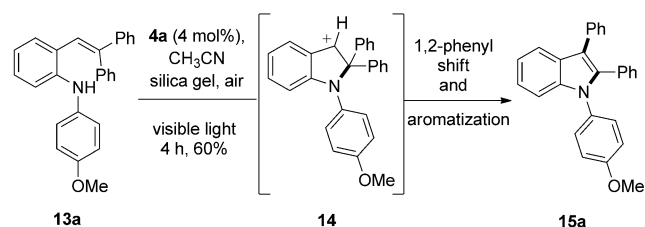
Scheme 2. Substrate scope of the reaction involving C–N bond formation and aromatization. Reaction conditions, unless otherwise noted, 4 mol % [Ru(bpz)₃](PF₆)₂, silica gel, air, CH₃CN, irradiation with a 18 W white-light LED. The newly formed C–N bonds are shown in bold. Yields of products isolated using column chromatography are given. [a] Using 6 mol % [Ru(bpz)₃](PF₆)₂. [b] Gram-scale reaction.



Scheme 3. Proposed mechanistic model.

We suspect that silica gel might play several roles in the reaction, including adsorbing oxygen, being a source of protons, which ensures that the nitrogen-centered radical cation **8** is protonated, and facilitating the oxidation through a proton-coupled electron transfer process.^[23] The presence of silica gel alone, that is, in the absence of the ruthenium catalyst, led to no reaction (Table 1, entry 7). Replacing silica gel with either HCl or TsOH led to the decomposition of the starting amine. The use of either AcOH or PPTS in place of silica gel gave the desired indole, although they were not as effective as silica gel (see the Supporting Information for the details). More studies are needed to understand the role(s) of silica gel.

Having proposed that a benzylic carbocation is an intermediate, we suspected that substrates lacking a C2 C–H bond might participate in a 1,2-carbon shift, thus forming a new C–C bond (Scheme 4). The research group



Scheme 4. Cyclization involving a 1,2-carbon shift.

of Driver has extensively explored the synthetic utility of this 1,2-carbon shift in their studies of rhodium-catalyzed decomposition of styryl azides, a transformation that presumably involves similar benzylic carbocations.^[24] To test this hypothesis, *gem*-diphenyl styryl aniline **13a** was prepared and subjected to the optimized visible-light photocatalytic conditions (Scheme 4). To our delight, the expected 2,3-diphenyl indole **15a** was isolated in 60 % yield. This result lent further credence to the possible involvement of benzylic carbocation **14** in the visible-light-mediated reaction.

To further explore the synthetic potential of this 1,2-carbon shift in indole synthesis, a series of *gem*-disubstituted styryl anilines were synthesized and tested under the

optimized reaction conditions (Table 2). Whether the substituents were independent (**13b**), part of a carbocycle (**13c** and **13d**), or part of an oxocycle (**13e**), aryl groups prefer-

Table 2: Scope of substrate in the C–N bond formation/1,2-carbon shift/aromatization cascade reaction.^[a]

Entry	Styryl anilines	Indole product	<i>t</i> [h]	Yield [%] ^[b]
1			4.5	62
2			6	52
3			6	60
4			6	58
5 ^[c]			16	40

[a] Reaction conditions, unless otherwise noted: 4 mol % [Ru(bpz)₃](PF₆)₂, silica gel, air, CH₃CN, irradiation with a 18 W white-light LED. The newly formed C–N and C–C bonds are shown in bold. [b] Yields of product isolated using column chromatography. [c] Using 6 mol % [Ru(bpz)₃](PF₆)₂.

entially migrated over alkyl groups. However, the 1,2-carbon shift is not limited to the migration of aryl groups only. When the C2 position formed part of a cyclopentane ring, the desired ring-expansion product **15f** was formed, although the efficiency of the transformation was not as high as those involving aryl shifts (Table 2, entry 5). However, when the C2 position bore two methyl groups, the desired methyl-migration product was not formed. Notably, when a tetralene product was formed, further oxidation to a fully aromatized product was observed (Table 2, entry 2).

Published online: ■■ ■■, ■■■■

Keywords: domino reactions · homogeneous catalysis · indoles · photochemistry · ruthenium

- [1] For selected recent reviews on biological activities and synthesis of indoles, see: a) S. Cacchi, G. Fabrizi, *Chem. Rev.* **2011**, *111*, PR215; b) A. J. Kochanowska-Karamyan, M. T. Hamann, *Chem. Rev.* **2010**, *110*, 4489; c) M. Bandini, A. Eichholzer, *Angew. Chem.* **2009**, *121*, 9786; *Angew. Chem. Int. Ed.* **2009**, *48*, 9608.
- [2] For selected recent examples, see: a) L. Ackermann, A. V. Lygin, *Org. Lett.* **2012**, *14*, 764; b) M. Inman, A. Carbone, C. J. Moody, *J. Org. Chem.* **2012**, *77*, 1217; c) B. Lu, Y. Luo, L. Liu, L. Ye, Y. Wang, L. Zhang, *Angew. Chem.* **2011**, *123*, 8508; *Angew. Chem. Int. Ed.* **2011**, *50*, 8358; d) J. Bonnamour, C. Bolm, *Org. Lett.* **2011**, *13*, 2012; e) Y. Tan, J. F. Hartwig, *J. Am. Chem. Soc.* **2010**, *132*, 3676; f) T. P. Pathak, K. M. Gligorich, B. E. Welm, M. S. Sigman, *J. Am. Chem. Soc.* **2010**, *132*, 7870; g) T.-S. Mei, X. Wang, J.-Y. Yu, *J. Am. Chem. Soc.* **2009**, *131*, 10806; h) Z. Shi, C. Zhang, S. Li, D. Pan, S. Ding, Y. Cui, N. Jiao, *Angew. Chem.* **2009**, *121*, 4642; *Angew. Chem. Int. Ed.* **2009**, *48*, 4572; i) R. Bernini, G. Fabrizi, A. Sferazza, S. Cacchi, *Angew. Chem.* **2009**, *121*, 8222; *Angew. Chem. Int. Ed.* **2009**, *48*, 8078; j) D. R. Stuart, M. Bertrand-Laperle, K. M. N. Burgess, K. Fagnou, *J. Am. Chem. Soc.* **2008**, *130*, 16474; k) O. Leogane, H. Lebel, *Angew. Chem.* **2008**, *120*, 356; *Angew. Chem. Int. Ed.* **2008**, *47*, 350; l) S. Würtz, S. Rakshit, J. J. Neumann, T. Dröge, F. Glorius, *Angew. Chem.* **2008**, *120*, 7340; *Angew. Chem. Int. Ed.* **2008**, *47*, 7230; m) B. J. Stokes, H. Dong, B. E. Leslie, A. L. Pumphrey, T. G. Driver, *J. Am. Chem. Soc.* **2007**, *129*, 7500; n) T. Tokuyama, T. Yamashita, M. T. Reding, Y. Kaburagi, T. Fukuyama, *J. Am. Chem. Soc.* **1999**, *121*, 3791; o) T. Fukuyama, X. Chen, G. Peng, *J. Am. Chem. Soc.* **1994**, *116*, 3127.
- [3] S. Jana, M. D. Clements, B. K. Sharp, N. Zheng, *Org. Lett.* **2010**, *12*, 3736.
- [4] a) D. S. Surry, S. L. Buchwald, *Chem. Sci.* **2011**, *2*, 27; b) J. F. Hartwig, *Acc. Chem. Res.* **2008**, *41*, 1534.
- [5] a) P. J. Harrington, L. S. Hegedus, *J. Org. Chem.* **1984**, *49*, 2657; b) P. J. Harrington, L. S. Hegedus, K. F. McDaniel, *J. Am. Chem. Soc.* **1987**, *109*, 4335; c) D. Tselikhovsky, S. L. Buchwald, *J. Am. Chem. Soc.* **2010**, *132*, 14048.
- [6] For recent reviews on photoredox catalysis, see: a) J. Xuan, W.-J. Xiao, *Angew. Chem.* **2012**, *124*, 6934; *Angew. Chem. Int. Ed.* **2012**, *51*, 6828; b) J. W. Tucker, C. R. J. Stephenson, *J. Org. Chem.* **2012**, *77*, 1617; c) J. M. R. Narayanan, C. R. J. Stephenson, *Chem. Soc. Rev.* **2011**, *40*, 102; d) F. Teplý, *Collect. Czech. Chem. Commun.* **2011**, *76*, 859; e) T. P. Yoon, M. A. Ischay, J.

- d) D. P. Hari, B. König, *Org. Lett.* **2011**, *13*, 3852; e) M. Rueping, S. Zhu, R. M. Koenigs, *Chem. Commun.* **2011**, *47*, 12709; f) M. Rueping, D. Leonori, T. Poisson, *Chem. Commun.* **2011**, *47*, 9615; g) J. Xuan, Y. Cheng, J. An, L.-Q. Lu, X.-X. Zhang, W.-J. Xiao, *Chem. Commun.* **2011**, *47*, 8337; h) A. G. Condie, J. C. González-Gómez, C. R. J. Stephenson, *J. Am. Chem. Soc.* **2010**, *132*, 1464.
- [16] a) Y. Miyake, K. Nakajima, Y. Nishibayashi, *J. Am. Chem. Soc.* **2012**, *134*, 3338; b) P. Kohls, D. Jadhav, G. Pandey, O. Reiser, *Org. Lett.* **2012**, *14*, 672; c) A. McNally, C. K. Prier, D. W. C. MacMillan, *Science* **2011**, *334*, 1114.
- [17] a) R. J. Crutchley, A. B. P. Lever, *J. Am. Chem. Soc.* **1980**, *102*, 7128; b) D. P. Rillema, G. Allen, T. J. Meyer, D. Conrad, *Inorg. Chem.* **1983**, *22*, 1617.
- [18] Fluorocarbon solvents and silica gel enhance the solubility of molecular oxygen, see: H. B. Lee, M. J. Sung, S. C. Blackstock, J. K. Cha, *J. Am. Chem. Soc.* **2001**, *123*, 11322.
- [19] The effectiveness of the catalysts correlates with the redox potentials of $\text{Ru}^{2+}/\text{Ru}^{1+}$ (versus SCE): $[\text{Ru}(\text{bpz})_3]$, 1.3 V; $[\text{Ru}(\text{bpy})_3]$, 0.78 V. The values are taken from Ref. [17a].
- [20] Electron-rich *p*-alkoxyphenyl groups lower the oxidation potential of anilines: see cyclic voltammogram of **5b** and **5b'** in the Supporting Information.
- [21] The formation of 3-cyclopropyl indole **6k** in high yield does not rule out our proposed mechanism. Bullock reported that, because of the stabilization provided by the benzyl group, ring opening of the cyclopropylbenzyl radical is much slower (2.7×10^5) than that of the cyclopropylmethyl radical (2.1×10^8), which would allow for competitive oxidation of benzylic radical **10** to benzylic cation **11**; see: J. Masnovi, E. G. Samsel, R. M. Bullock, *J. Chem. Soc. Chem. Commun.* **1989**, 1044.
- [22] For the use of TPP as a photosensitizer to generate singlet oxygen, see: G. Jiang, J. Chen, J.-S. Huang, C.-M. Che, *Org. Lett.* **2009**, *11*, 4568.
- [23] For a review on proton-coupled electron transfer, see: M. H. V. Huynh, T. J. Meyer, *Chem. Rev.* **2007**, *107*, 5004.
- [24] a) B. J. Stokes, S. Liu, T. G. Driver, *J. Am. Chem. Soc.* **2011**, *133*, 4702; b) K. Sun, S. Liu, P. M. Bec, T. G. Driver, *Angew. Chem.* **2011**, *123*, 1740; *Angew. Chem. Int. Ed.* **2011**, *50*, 1702; c) M. Shen, B. E. Leslie, T. G. Driver, *Angew. Chem.* **2008**, *120*, 5134; *Angew. Chem. Int. Ed.* **2008**, *47*, 5056.

Communications



Photocatalysis

S. Maity, N. Zheng* ——— ■■■■—■■■■

A Visible-Light-Mediated Oxidative C–N Bond Formation/Aromatization Cascade: Photocatalytic Preparation of *N*-Arylindoles



Just add light and air: Structurally diverse *N*-arylindoles can be prepared from readily prepared *o*-styryl anilines through visible-light photocatalysis. The reaction, which is conducted open to air, is mediated by $[\text{Ru}(\text{bpz})_3](\text{PF}_6)_2$ ($\text{bpz} = 2,2'$ -bipyrazine) and involves both C–N bond formation and aromatization (see scheme). Using suitably substituted substrates, a 1,2-carbon shift can be also incorporated into this cascade reaction.