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Visible-Light-Enabled Aerobic Denitrative C3-Alkenylation of Indoles with β-Nitrostyrenes

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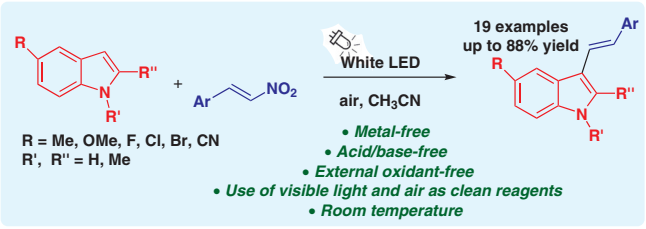

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Abstract Herein, we unveil the first visible-light-mediated alkenylation reaction of indoles. The reaction follows a denitrative radical pathway where β-nitrostyrenes have been utilized as the alkene precursors for the C3-styrenylation of indoles under visible-light irradiation to afford biologically and synthetically important 3-alkenylindoles. High regioselectivity, absence of any photocatalyst, metal, external oxidant, acid or base, and the use of visible light and air as inexpensive clean reagents are the key highlights of the developed method.

Key words indoles, β-nitrostyrenes, 3-alkenylindoles, visible light, radical reaction, photocatalyst-free

Even after 150 years of its discovery,[1] indole continues to fuel significant developments in the field of synthetic chemistry.[2] In fact, various functionalizations of indole constitute an array of reactions which have had noteworthy impact on synthetic organic chemistry. This is because of the wide occurrence of indole and its derivatives in natural products and their extensive use in synthetic and medicinal chemistry.[2,3] Furthermore, in the past decade, visible-light photoredox catalysis has emerged as a powerful tool to facilitate radical reactions in the most sustainable fashion (though expensive photocatalysts, e.g., Ir complexes have been used in some reports).[4] Consequently, this methodology has been applied for the functionalizations of indoles by alkylation, carbonylation, carboxylation, annulation, arylation, and other carbon–heteroatom bond formation, dearomatization and ring-cleavage reactions, elegantly covered in a review by Eycken and co-workers.[2e] However, an alkenylation of indoles enabled by visible-light photoredox catalysis has not been reported to date, although it could lead to the synthesis of highly valuable products.

3-Alkenylindoles are biologically and pharmaceutically extremely important compounds, ubiquitous in natural products[5] and can be used as building blocks in organic synthesis[6] employing various notable processes including pericyclic reactions[6a–d] and macrocyclizations.[6h,i] They are also known for exhibiting excellent anticancer[3b–d] and other therapeutic properties[3e,f] (Figure 1). Thus, their direct or indirect synthesis from indole has drawn significant attention. The indirect approach requires prefunctionalization of indoles, which increases the number of steps in the synthetic route and makes the method less efficient.[2d] As regards the direct approach, the most common method employed for the synthesis of 3-alkenylindoles involves transition-metal-catalyzed cross-coupling reactions.[2d] The pioneering work of Fujiwara et al.[7] regarding the 3-alkenylation of indoles under palladium catalysis paved the way for several other similar reports (Scheme 1, a).[8] Another approach, which has been employed, involves the 1,4- or 1,2-addition of indoles to α,β-enones or carbonyl compounds followed by oxidation/elimination or elimination, respectively (Scheme 1, b).[2d,9] For example, Jiao et al. developed an oxidative dehydrogenation coupling reaction between indole and α,β-unsaturated aldehydes in the presence of morpholin-4-ium trifluoroacetate as an organocatalyst and a stoichiometric amount of DDQ to achieve C3–H alkenylation of indoles.[9a]

In 2017, Maji et al. reported the synthesis of 3-alkenylindoles from indoles and aliphatic aldehydes by one-pot sequential Brønsted acid/base catalysis.[9b] However, these methods suffer from several drawbacks such as the use of expensive and difficult-to-remove transition metals, oxidants in stoichiometric amounts, and/or strong acids/bases. Therefore, the development of simpler and milder methods for the synthesis of 3-alkenylindoles remains of interest.

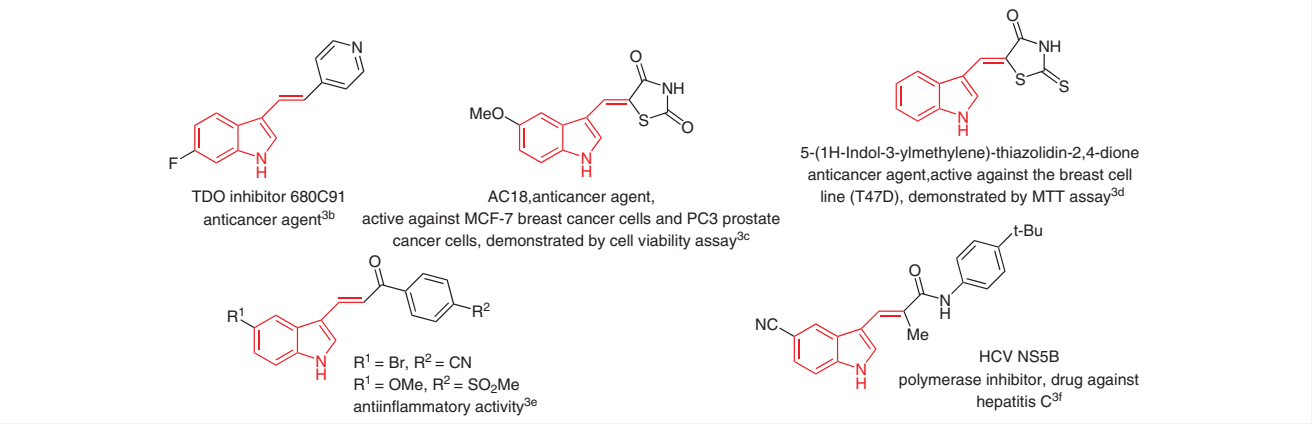
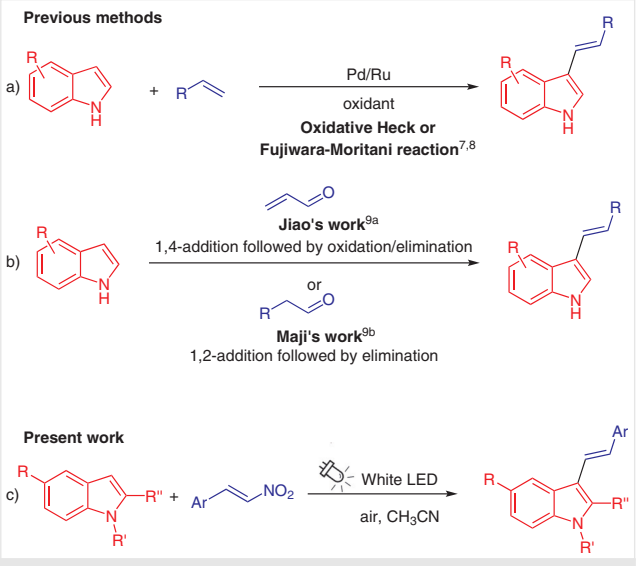


Figure 1 Some 3-alkenylindole-based therapeutic agents

β-Nitrostyrenes are attractive synthetic intermediates in organic synthesis.[10] They are also well known for their ability to act as radical acceptors for the formation of carbon–carbon bonds.[11] In radical reactions, β-nitrostyrenes are known to behave as alkene precursors since the addition of any radical to nitroalkenes is followed by elimination of a nitrosyl radical, leading to β-substituted styrenes.[11i] A number of radical transformations driven by visible-light photoredox catalysis has been reported with β-nitrostyrenes for the construction of chalcones,[11f] cinnamic acids,[11g] and *trans*-stilbenes.[11h] However, to the best of our knowledge, there are no reports on visible-light photoredox catalysis mediated functionalization of β-nitrostyrenes using indoles for the preparation of valuable 3-alkenylindoles. Although the literature has many reports of attack of various types of radicals on the indole moiety,[2e] the number of reports in which the indole radical has initially been generated under visible-light photoredox catalysis is limited.[12] All the above factors and our work on visible-light-mediated reactions[13] and β-nitrostyrenes[11f,g,14] prompted us to develop a visible-light-mediated reaction for the synthesis of 3-alkenylindoles by *sp*^{2} C–H radical functionalization of indoles using β-nitrostyrenes (Scheme 1, c).

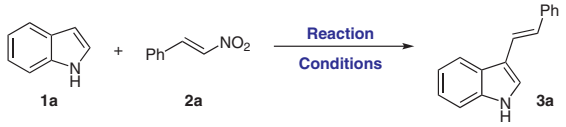


Scheme 1 Synthetic strategies for the construction of 3-alkenylindoles

With indole (**1a**) and β-nitrostyrene (**2a**) as model substrates, our first trial was performed using $Ru(bpy)_3Cl_2$ as a photoredox catalyst in CH_3CN under irradiation with 7.0 W white LED at room temperature in an open flask, monitoring by TLC after 12 hours. Encouragingly, under these conditions, the desired 3-alkenylindole **3a** was obtained in 51% yield (Table 1, entry 1). With this positive lead in hand, it was imperative to confirm the roles of the photocatalyst, visible light, and air in the reaction. We found that, in the absence of the photocatalyst, almost the same yield of the product could be obtained (Table 1, entry 2). However, when the light source was removed, product **3a** could be obtained only in traces (Table 1, entry 3), as well as when the reaction was performed under N_2 atmosphere (Table 1, entry 4). Thus, the necessity of the light source and oxygen was confirmed and the need of the photocatalyst was precluded, in accordance with earlier observations.[12c] With the objective of improving the efficiency of the reaction, we focused our efforts on choosing the best solvent system. In place of CH_3CN, other solvents such as THF, CH_2Cl_2, DMF, DMSO, EtOH, H_2O, and a combination of CH_3CN/H_2O were examined (Table 1, entries 5–11) but CH_3CN remained the best choice (Table 1, entry 2). The reaction time was also varied and on increasing the reaction time to 18 hours, a substantial increase in the yield of the product was obtained (Table 1, entry 12).

However, changing the reaction time to 24 hours led to no further increase in the yield (Table 1, entry 13), but decreasing the time to 9 hours decreased the yield of the product significantly (Table 1, entry 14). As far as the ratio of **1a** and **2a** is concerned, the best result was obtained

Table 1 Optimization of Reaction Conditions for the Denitrative C3-Styrenylation of Indoles[a]



Entry	Photocatalyst (mol%)	Solvent	Time (h)	Yield (%)[b]
1	$Ru(bpy)_3Cl_2$ (1)	CH_3CN	12	51
2	–	CH_3CN	12	50
3	$Ru(bpy)_3Cl_2$ (1)	CH_3CN	12	traces[c]
4	$Ru(bpy)_3Cl_2$ (1)	CH_3CN	12	traces[d]
5	–	THF	12	37
6	–	DCM	12	33
7	–	DMF	12	28
8	–	DMSO	12	24
9	–	EtOH	12	traces
10	–	H_2O	12	traces
11	–	CH_3CN/H_2O (9:1)	12	39
12	–	CH_3CN	18	70
13	–	CH_3CN	24	70
14	–	CH_3CN	9	38
15	–	CH_3CN	18	62[e]
16	–	CH_3CN	18	77[f]
17	–	CH_3CN	18	78[g]
18	–	CH_3CN	18	69[f,h]
19	–	CH_3CN	18	57[f,i]

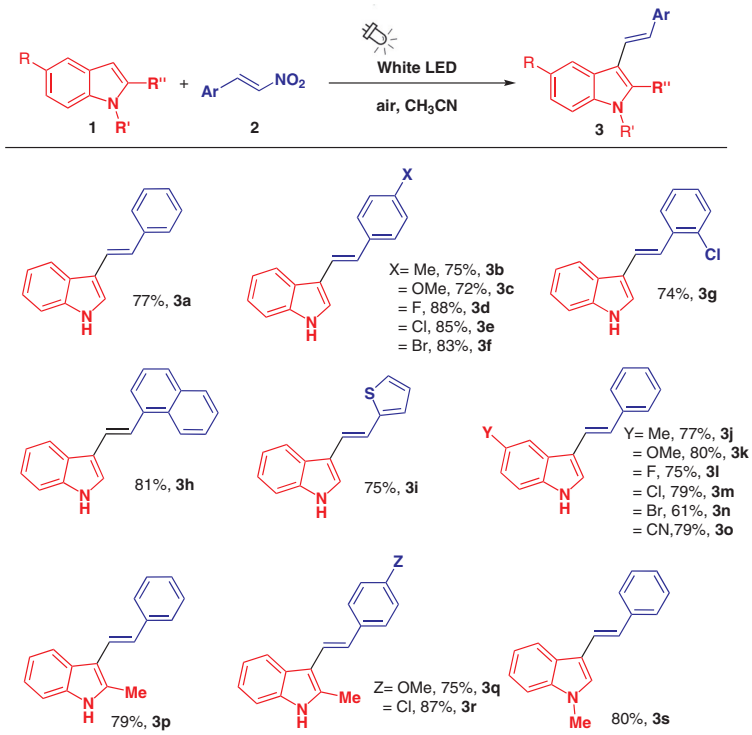
[a] Reaction conditions: indole (**1a**, 1.2 mmol), (*E*)-β-nitrostyrene (**2a**, 1.0 mmol), solvent (3 mL), irradiation using 7.0 W white LED in an open flask at r.t.
[b] Isolated yield of the pure product **3a**.
[c] Absence of light.
[d] N_2 atmosphere.
[e] **1a**, 1.0 mmol.
[f] **1a**, 1.5 mmol.
[g] **1a**, 2.0 mmol.
[h] Solvent 4 mL.
[i] Solvent 2 mL.

when the ratio was kept at 1.5:1 (Table 1, entries 12 and 15 vs. entry 16). Any further increase in the ratio did not produce an appreciable change in the yield of **3a** (Table 1, entry 17). When we changed the concentration of the reaction mixture, a decrease in the efficiency of the reaction was observed on increasing as well as on decreasing the concentration (Table 1, entries 18 and 19 vs. entry 16).

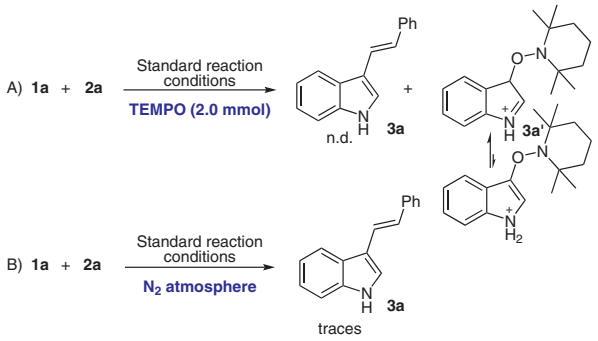
After optimizing conditions (Table 1, entry 16), we next examined the scope of the reaction with respect to a range of readily available β-nitrostyrenes and indoles (Scheme 2). β-Nitrostyrenes containing a range of substituents such as methyl, methoxy, fluoro, chloro, and bromo groups at the *para* position of the phenyl ring reacted with indole **1a** to give the corresponding 3-alkenylated products **3b–f** in moderate to excellent yields (72–88%). Even the *ortho*-chloro group was well tolerated, and the corresponding product **3g** was obtained in 74% yield. Such good compatibility of the halogenated nitroalkenes with this mild and base-free protocol is highly advantageous as it avoids the competitive cleavage of the C–halogen bond, which occurs in the case of transition-metal-catalyzed approaches (Scheme 1, a) via Heck reaction. Moreover, naphthyl and thiophene nitrostyrene derivatives also produced good to excellent yields (75–81%) of products **3h**,**i**. Subsequently, a variety of indoles bearing electron-donating and electron-withdrawing groups at the C5 position of the heteroarene was treated with β-nitrostyrene (**2a**) and all of them performed well under the reaction conditions (**3j–o**).

Furthermore, a variety of 2-methylindoles was amenable to the optimized protocol, leading to the formation of products **3p–r** in good yields (75–87%). As a representative of *N*-substituted indoles, *N*-methylindole could also be coupled to **2a** to furnish the corresponding product **3s** in 80% yield.

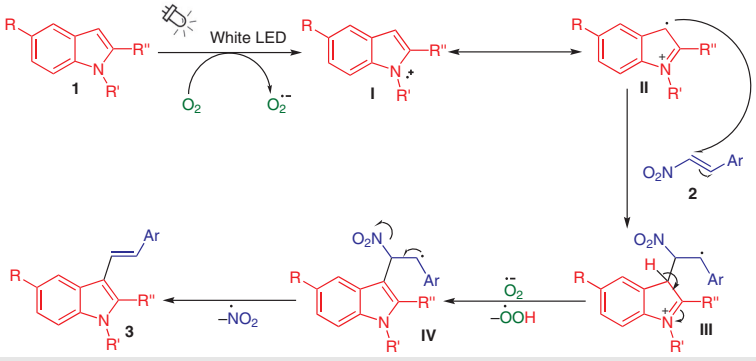
With the objective of gaining insight into the mechanism of the reaction, control experiments were performed in the presence of the radical scavenger 2,2,6,6-tetramethylpiperidinoxyl (TEMPO), where it was observed that the reaction was inhibited. The TEMPO–indole adduct **3a′** (*m/z* = 273.1978, calcd 273.1967) was observed during mass analysis of the reaction mixture and the mass peak due to the product **3a** could not be detected, indicating that the reaction was following a radical pathway (Scheme 3, A). When the reaction was carried out under N_2 atmosphere, the product was again formed in traces (Scheme 3, B). On the basis of these observations and earlier reports,[11d,12c] a plausible mechanism for the formation of 3-alkenylindoles is proposed in Scheme 4. Indole **1**, on irradiation with white light in the presence of oxygen, can result in indolyl radical cation **I** that is interconvertible with form **II** via resonance. Indolyl radical cation **II** could then add to β-nitrostyrene **2**, forming β-nitro radical cation **III** (a radical Michael addition of **II** to **2** is also possible).[12b,d] The superoxide radical anion generated in the first step would abstract a proton from **III**, forming the β-nitro radical **IV** and perhydroxyl radical $HO_2^{\bullet}$. The β-nitro radical **IV** could then be finally converted into product **3** with the elimination of $NO_2^{\bullet}$. In the second cycle, the perhydroxyl radical $HO_2^{\bullet}$ could abstract an electron from **1** and subsequent removal of a proton from **III** would generate H_2O_2. Detection of H_2O_2 by KI/starch indicator supports the formation of the superoxide radical anion.[15] Moreover, the excited-state oxidation potential of **1a** is –2.59 V[12c] and the reduction potential of oxygen to hydrogen peroxide is +0.65 V (vs. SCE),[12c] which are supportive of the fact that the oxidation of indole by oxygen is feasible to generate indolyl radical cation **I** and superoxide radical anion. It may be noted that the excited-state reduction potential of β-nitrostyrene (**2a**) is +1.90 V,[16] hence its interaction with oxygen is far less likely.



Scheme 2 Substrate scope. *Reagents and conditions*: indole **1** (1.5 mmol), (*E*)-β-nitrostyrene **2** (1 mmol), CH_3CN (3 mL), irradiation using 7.0 W white LED in an open flask at r.t. Yield of the pure isolated products **3**.



Scheme 3 Control experiments



Scheme 4 Plausible mechanistic pathway for the denitrative C3-styrenylation of indoles

In summary, we have developed the first visible-light-mediated alkenylation reaction of indoles via the sp^2–sp^2 coupling of indoles and β-nitrostyrenes.[17] The reaction has been exploited for the construction of 3-alkenylindoles through a denitrative visible-light-mediated radical pathway using β-nitrostyrenes as the styrenylating agent under metal, external oxidant, and acid/base-free conditions. The protocol is highly regioselective and exhibits good substrate scope. In this strategy, visible light and air have been used with β-nitrostyrenes as readily available coupling partners to accomplish the denitrative alkenylation of indoles in a benign manner.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1707099.

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(17) **General Procedure for the Synthesis of 3-Alkenylindoles 3**

A mixture of indole **1** (1.5 mmol) and β-nitrostyrene (**2**, 1.0 mmol) in CH_3CN (3 mL) was irradiated with visible light (white-light-emitting diode, 7.0 W) at a distance of 0.75 cm in a 10 mL round-bottom flask with stirring at r.t. for 18 h. Upon completion of the reaction (monitored by TLC), water (5 mL) was added, and the mixture was extracted with EtOAc (3 × 15 mL). The combined organic phases were dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was purified by silica gel column chromatography (EtOAc/*n*-hexane, 1:19) to afford an analytically pure sample of 3-alkenylindole **3**.

Characterization Data of Representative 3-Alkenylindoles 3

(*E*)-3-(4-Methoxystyryl)-1*H*-indole (3c)[18,9b]

^{1}H NMR (400 MHz, DMSO): δ = 11.25 (s, 1 H), 7.98 (d, *J* = 8.0 Hz, 1 H), 7.58 (d, *J* = 2.4 Hz, 1 H), 7.50 (d, *J* = 8.8 Hz, 2 H), 7.42 (d, *J* = 8.0 Hz, 1 H), 7.26 (d, *J* = 16.6 Hz, 1 H), 7.15 (t, *J* = 7.6 Hz, 1 H), 7.10 (t, *J* = 6.9 Hz, 1 H), 7.04 (d, *J* = 16.4 Hz, 1 H), 6.92 (d, *J* = 8.2 Hz, 2 H), 3.76 (s, 3 H). ^{13}C NMR (100 MHz, DMSO): δ = 158.0, 137.0, 131.2, 126.6, 125.3, 125.2, 123.2, 121.7, 120.3, 119.8, 119.5, 114.1, 113.9, 111.9, 55.1. HRMS (ESI): *m/z* calcd for $C_{17}H_{16}NO$ $[M + H]^+$: 250.1226; found: 250.1196.

3-[(*E*)-2-(Thiophen-2-yl)vinyl]-1*H*-indole (3i)[18,19]

^{1}H NMR (400 MHz, DMSO): δ = 11.34 (s, 1 H), 7.94 (d, *J* = 7.6 Hz, 1 H), 7.64 (s, 1 H), 7.41 (d, *J* = 7.6 Hz, 1 H), 7.32–7.31 (m, 2 H), 7.17–7.10 (m, 4 H), 7.01 (s, 1 H). ^{13}C NMR (100 MHz, DMSO): δ = 144.1, 137.0, 127.8, 126.4, 124.9, 124.3, 123.0, 122.3, 121.8, 119.8, 119.7, 117.1, 113.2, 111.9. HRMS (ESI): *m/z* calcd for $C_{14}H_{12}NS$ $[M + H]^+$: 226.0685; found: 226.0681.

(*E*)-5-Fluoro-3-styryl-1*H*-indole (3l)[19]

^{1}H NMR (400 MHz, DMSO): δ = 11.47 (s, 1 H), 7.82 (d, *J* = 10.0 Hz, 1 H), 7.75 (s, 1 H), 7.60 (d, *J* = 7.2 Hz, 2 H), 7.45–7.41 (m, 2 H), 7.35 (t, *J* = 6.8 Hz, 2 H), 7.19 (t, *J* = 6.6 Hz, 1 H), 7.10 (d, *J* = 17.1 Hz, 1 H), 7.03 (t, *J* = 8.4 Hz, 1 H). ^{13}C NMR (100 MHz, DMSO): δ = 159.0, 138.9, 134.0, 129.0, 128.1, 126.7, 126.0, 125.8, 123.9, 122.4, 114.4, 113.3, 110.4, 105.3. HRMS (ESI): *m/z* calcd for $C_{16}H_{13}FN$ $[M + H]^+$: 238.1027; found: 238.1007.

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