Organic LETTERS
Letter
Cite This: Org. Lett. XXXX, XXX, XXX−XXX
pubs.acs.org/OrgLett

Bromo- or Methoxy-Group-Promoted Umpolung Electron Transfer Enabled, Visible-Light-Mediated Synthesis of 2-Substituted Indole-3-glyoxylates

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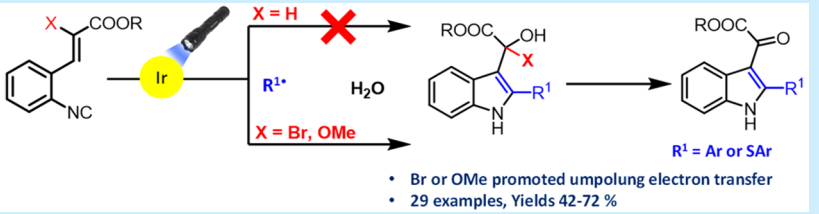
Supporting Information



ABSTRACT: A visible-light-mediated radical tandem cyclization of *ortho*-isocyano-α-bromo cinnamates to 2-substituted indole-3-glyoxylates is achieved by formation of both C−C/C−S and C−O bonds. The reaction proceeds through a hitherto unprecedented bromine- or methoxy-group-promoted umpolung back electron transfer from an α-carbonyl radical to the photocatalyst. This method allows preparation of diverse 2-arylated or 2-thioarylated indole-3-glyoxylates. The glyoxylate group installed in the products can be utilized for several biologically relevant manipulations.

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Nitrogen-containing heterocyclic compounds, and in particular indoles, are prevalent structures in many natural alkaloids and biologically important pharmacophores.[1] Among them, 2-(2-phenyl-1*H*-indol-3-yl)acetic acids represent a prominent subclass, which exhibit a wide range of biological activities.[2] The importance of these molecules is reflected in the number of synthetic methods developed over the past years,[3] and especially *o*-alkenylarylisonitriles have been popular precursors for construction of the indol-3-acetic acid framework.[4] Related to our work described here, Fukuyama et al. disclosed a Bu_3SnH-mediated radical reaction of *o*-alkenylarylisonitriles to synthesize 2-stannylated indole derivatives (Figure 1a).[5] This method has gained much attention, being manifested in several indole-based natural product syntheses.[6] Later, Chatani et al. developed a tin-free, copper-catalyzed method to synthesize 2-borylated derivatives (Figure 1a).[7] Both methods subsequently allow a palladium-mediated coupling to attain 2-substituted indoles. Very recently, Jamison and co-workers developed a copper-catalyzed method to cyclize **1** with arylboronic acids to obtain the corresponding 2-arylated indole derivatives.[8]

Visible-light photocatalysis[9] has emerged as a powerful tool for the generation of radicals and thus might provide an alternative to achieve the title reaction in a step economic way without the need to use stoichiometric amounts of boron or tin reagents. Radical addition onto **1** followed by 5-exo-trig cyclization provides an α-carbonyl radical intermediate **A** (Figure 1b, c), which can be easily reduced to its enolate[10] (Figure 1c, path B). Very recently, this pathway has been demonstrated with the cyclization of **1** induced by visible-light-mediated generation of P-radicals utilizing a reductive quenching cycle of a ruthenium-based photocatalyst.[11] In contrast, the radical intermediate **A** is difficult to oxidize (Figure 1c, Path A, E° = +1.85 V vs SCE)[12] due to the generation of a positive charge adjacent to the carbonyl group. The latter, however, is necessary when radicals are generated by the commonly encountered oxidative quenching cycle of a photocatalyst to keep the catalytic photoredox system alive.

A suitable modification of the cinnamyl ester group could allow such an umpolung in a photoredox process. Thus, moving to the readily available α-bromo cinnamates **2a**, we questioned if the extra bromo group introduced might allow oxidation (umpolung electron transfer) of radical **A** by altering its redox potential and/or stabilizing the carbocation formed next to the carbonyl center to complete the photoredox cycle. Thus, we envisioned that the synthesis of indol-3-glyoxylates should become directly possible, generating a moiety which has been proven to be versatile for the generation of a great variety of functional groups[13] (diols, amino alcohols, amino acids; Figure S4, Supporting Information (SI)) that would be useful for the synthesis of various indole-based bioactive compounds. Especially maleimide derivatives are readily accessible from indol-3-glyoxylates, which have several biological activities *viz.* cyclin D1/CDK4,[14] Angiogenisis,[15] Protein Kinase C,[16] and Mdm2 inhibition properties.[17]

Given that α-bromo cinnamates are capable substrates themselves in accepting electrons in a visible-light-mediated photoredox process (e.g., E_{red} (**2a**) = −1.33 V vs SCE),[18] the redox potentials of an external radical generated by an SET

Received: August 25, 2018

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DOI: 10.1021/acs.orglett.8b02725
Org. Lett. XXXX, XXX, XXX−XXX

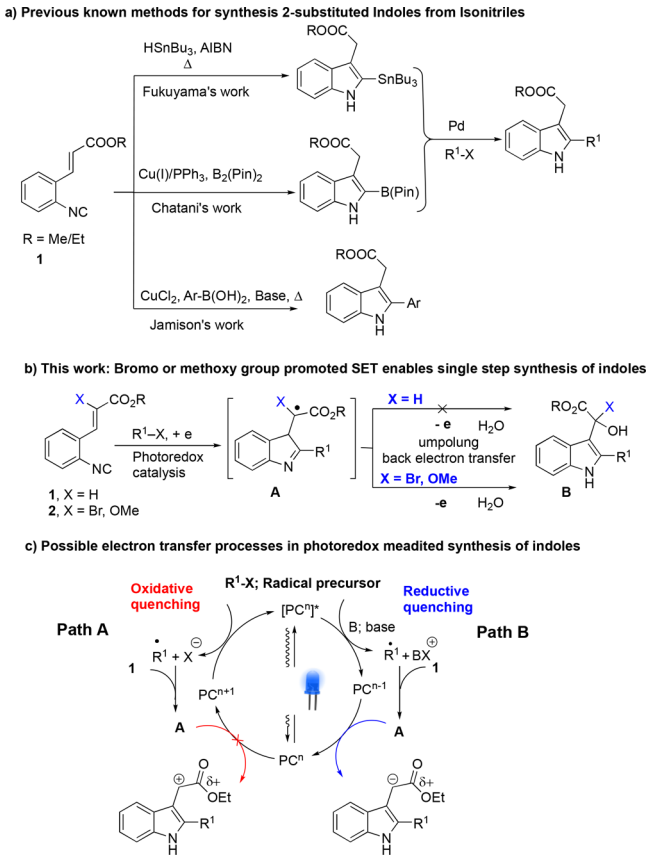


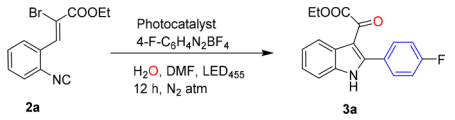
Figure 1. Previous known methods for indole synthesis from *o*-alkenylaryl isonitriles and present method.

must be carefully matched. Thus, we have initially chosen aryl diazonium salts as aryl radical precursors with a relatively low reduction potential (E_{red} = −0.03 to −0.5 V vs SCE),[19] which can be reduced by many common photocatalysts.

Indeed, treating **2a** with 4-fluorophenyl diazonium tetrafluoroborate[20] in the presence of various common photoredox catalysts (1 mol %, Table 1, entries 1−6) and H_2O as a terminal nucleophile resulted in the complete consumption of the starting material after 12 h, and 2-(4-fluorophenyl)-indole-3-glyoxylate (**3a**) was obtained. [Ir{dF(CF$_3$)ppy}$_2$(dtbbpy)]-PF$_6$ ($E_{Ir(IV)/Ir(III)*}$ = −0.89 V vs SCE; $E_{Ir(III)/Ir(IV)}$ = +1.69 V vs SCE; dF(CF$_3$)ppy = 2-(2,4-difluorophenyl)-5-trifluoromethyl-pyridine, dtb-bpy = 4,4′-di-*tert*-butyl-2,2′-dipyridyl; Table 1, entry 6) performed best, giving rise to **3a** in 66% isolated yield, which is attributed to its high oxidation potential necessary to achieve the oxidation of an α-carbonyl radical intermediate of type **A** (Figure 1b,c). It is noteworthy that the reaction also proceeds without a photocatalyst, albeit with significantly reduced yield, suggesting that the reaction can also be carried on via a radical chain process (Table 1, entry 11). Attempts to increase the reaction yield by varying the amount of diazonium salt, water or replacing the latter by alcohols to avoid hydrolysis of the isontrile that was observed as a competing process were not successful (Table S2, Supporting Information).

With the optimized reaction conditions in hand, we explored the substrate scope: a variety of substituted isonitriles (**2a−f**) could be transformed into the corresponding indole derivatives. Both electron-withdrawing and -donating groups containing aryl diazonium salts reacted smoothly with **2** to

Table 1. Optimization of Reaction Conditions[a]

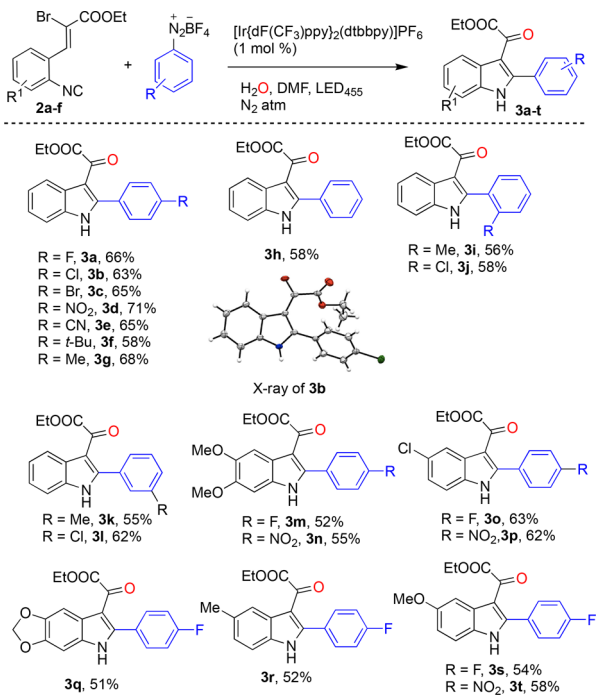


entry	catalyst	yield (%)
1[b]	Eosin Y	37
2	[Ir{(dtbbpy)(ppy)$_2$}]PF$_6$	41
3	[Ru(bpy)$_3$Cl$_2$]	38
4[b]	[Cu(dap)$_2$]Cl	21
5	Ir(ppy)$_3$	42
6	[Ir{dF(CF$_3$)ppy}$_2$(dtbbpy)]PF$_6$	69 (66[c])
7[d]	[Ir{dF(CF$_3$)ppy}$_2$(dtbbpy)]PF$_6$	ND
8[e]	[Ir{dF(CF$_3$)ppy}$_2$(dtbbpy)]PF$_6$	25
9[f]	[Ir{dF(CF$_3$)ppy}$_2$(dtbbpy)]PF$_6$	28
10[g]	[Ir{dF(CF$_3$)ppy}$_2$(dtbbpy)]PF$_6$	36
11	No catalyst	29

[a]Reaction conditions: **2a** (0.25 mmol), photocatalyst (1 mol %), aryldiazonium salt (2 equiv), H_2O (2 equiv), irradiation at 455 nm for 12 h; NMR yields with diphenylmethane as an internal standard. [b]Irradiation at 530 nm. [c]Isolated yield. [d]No light. [e]1 equiv of aryldiazonium salt. [f]No water added. [g]1 equiv of H_2O. ND: not detected.

produce diverse arylated indole derivatives **3a−t** (Scheme 1), which were confirmed by NMR and MS data and further by the X-ray structure of **3b**.

Scheme 1. Arylation Substrate Scope[a]



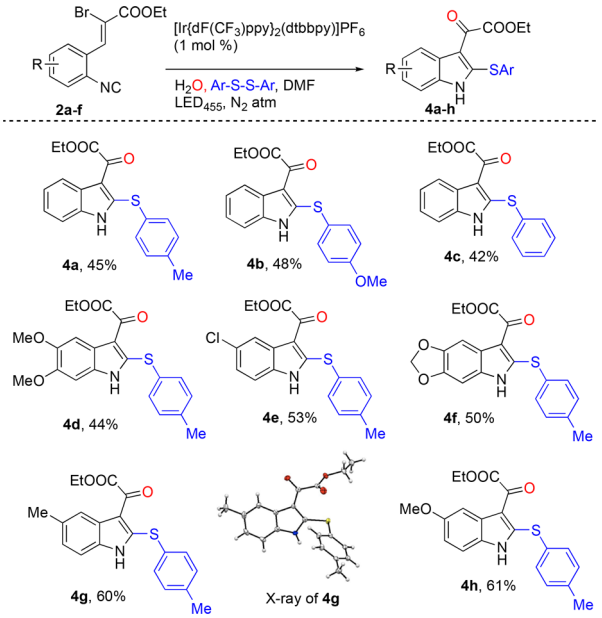
[a]Reaction conditions: see Table 1, isolated yields.

To extend the scope of this reaction, thiyl radicals, generated from the corresponding disulfides,[21] underwent the analogous reaction with **2a−f** to provide 2-arylthio-indole-3-glyoxylates **4a−h** (Scheme 2). This transformation is oxygen sensitive. Proper degassing is required to avoid the formation of 3-

DOI: 10.1021/acs.orglett.8b02725
Org. Lett. XXXX, XXX, XXX−XXX

bromo-2-quinolones as a side product (Scheme S3, Supporting Information).

Scheme 2. Aryl Thiiyl Substrate Scope[a]



[a]Reaction conditions: **2a−f** (0.25 mmol), diaryl disulfide (2 equiv), H_2O (2 equiv), and irradiation at 455 nm for 48 h, isolated yields.

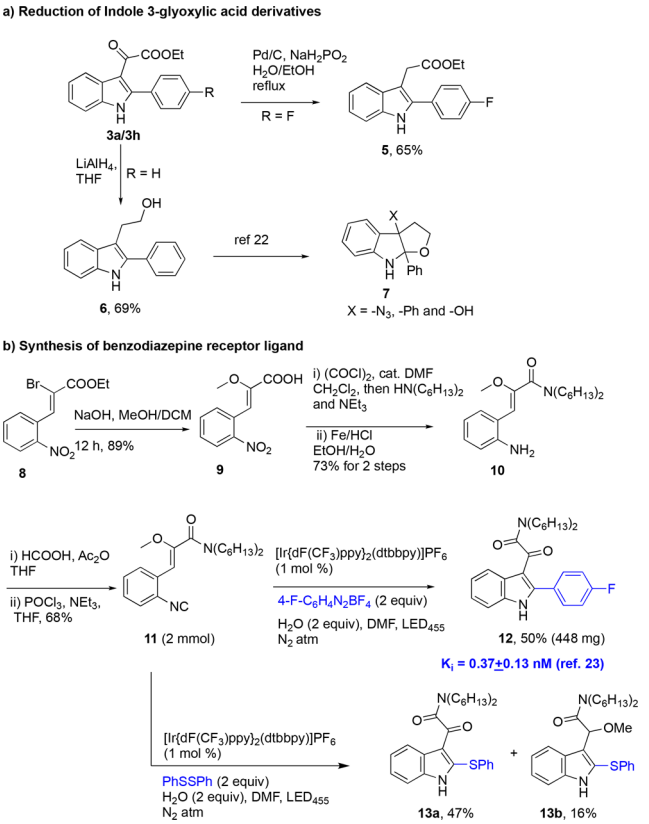
Besides many transformations known for the functionalization of indole-3-glyoxylates[13−17] (Figure S4, Supporting Information), the selective reduction of this moiety is possible as demonstrated for derivatives **3a** and **3h**, thus bridging glyoxylates **3** to the likewise medicinally important 2-(2-phenyl-1*H*-indol-3-yl)acetic acids of type **5** (Scheme 3a). The exhaustive reduction of **3h** with $LiAlH_4$ provided alcohol **6** in 69% yield (Scheme 3a), which can be converted into differently functionalized furoindolines **7**.[22]

Indole-3-glyoxylamide derivatives are well-known ligands for peripheral benzodiazepine receptor (translocator protein) at nanomolar/subnanomolar concentrations and stimulators for steroid biosynthesis in rat C glioma cells.[23] Aiming for the synthesis of a representative member of this compound class, we converted the carboxylic ester in **8** to an amide **11** via the carboxylic acid **9**, which unexpectedly was accompanied by an exchange of Br for OMe (Scheme 3b). Alternatively, **9** was synthesized in three steps from *ortho*-nitrotoluene on a 10 g scale, avoiding the use of ethyl bromoacetate, which is a potent lacrymator (see SI). Gratifyingly, the methoxy group can take the role of bromo, and thus, the photocyclization of **11** with 4-fluorobenzenediazonium tetrafluoroborate under optimized conditions previously established furnished **12** in 50% yield on a 2.5 mmol scale (Scheme 3b). Likewise, the photoreaction of **11** with PhSSPh to **13a** proceeded smoothly, but in this case **13b** was identified as a byproduct, which arises by H atom transfer from the radical intermediate **II** (Scheme 4).

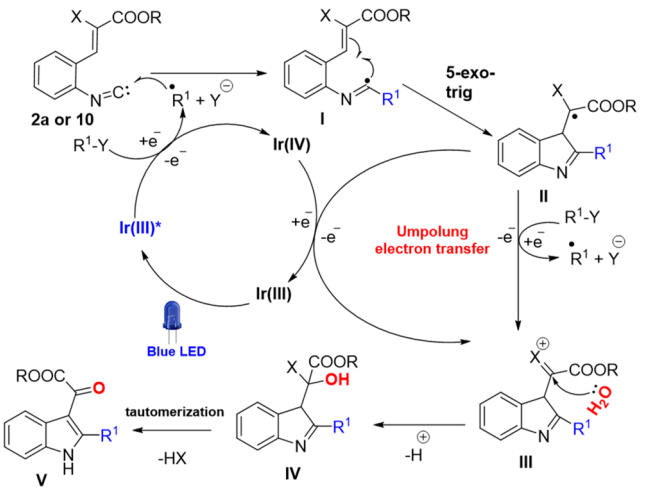
A plausible mechanism for the reaction can be proposed (Scheme 4) in agreement with control experiments that were carried out. Upon excitation of the iridium photocatalyst by visible light, an electron transfer to the radical precursor (aryl diazonium salt or diaryl disulfide) occurs to generate a radical $R^1\cdot$, which adds onto the isonitrile (**2a** or **10**) to produce imidoyl radical **I**.[24] The imidoyl radical then undergoes a 5-exo-trig cyclization to produce intermediate **II**, i.e., an α-carbonyl radical.[25] In general, radicals next to a carbonyl center (E° = +1.85 V vs SCE)[12] resist oxidation; however, the tactically introduced bromo or methoxy group can now reverse the electron flow (umpolung), thereby closing the photoredox cycle.

When the reaction was performed between compound **1**,[26] having no bromine group in the cinnamate moiety, and *p*-tolyl disulfide, only the formation of **14a** and **14b** occurred in minor amounts (Scheme 5a and Figure S3, Supporting Information),

Scheme 3. Functionalization of Indole 3-Glyoxylate Derivatives and Application in Synthesis Benzodiazepine Receptor Ligand



Scheme 4. Plausible Reaction Mechanism



R = Et or $N(C_6H_{13})_2$; X = Br or OMe; R^1-Y = Aryl diazonium salt or diaryl disulfide.

DOI: 10.1021/acs.orglett.8b02725
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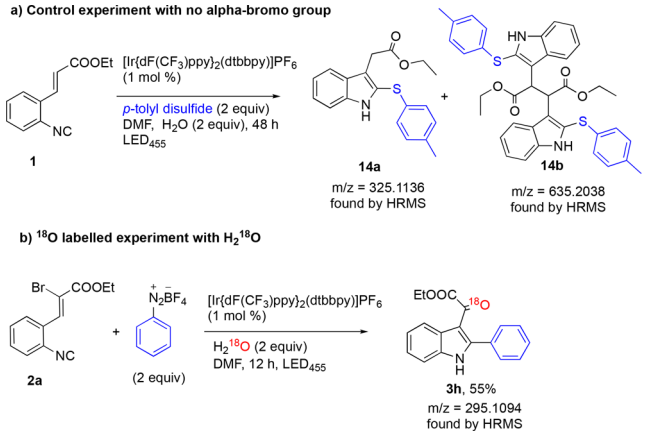
Scheme 5. Mechanistic and Control Experiments



again proving that the role of the bromo group in the back electron transfer process to the catalyst or to substrate serving as the radical precursor is crucial. HRMS of the product **3h** formed with ^{18}O enriched water (Scheme 5b and Figure S2, Supporting Information) showed a high level (>50%) of incorporation of ^{18}O in to the product, confirming that the resulting radical **II** is oxidized to carbocation **III** and subsequently trapped with H_2O. Successive elimination of H^+ and HBr followed by tautomerization via intermediate **IV** results in formation of the product. We assume that the oxidation of **II** to **III** is more facile for the bromo containing starting materials **2** compared to methoxy compound **11** since a reduced product such as **13b** formed by H-abstraction (PhSH as H-donor via PhSSPh → PhS· + PhS^- → PhSH) is not observed in the sequence of **2** to **4** (Scheme 2).

In conclusion, we have developed a photoredox-mediated radical process to synthesize 2-aryl or 2-phenylthio-indole-ethyl-3-glyoxylates. We propose that a bromine-/methoxy-group-promoted umpolung electron transfer from an α-carbonyl radical (oxidation) to the photocatalyst or to the radical precursor is the driving force for the reaction to occur. The present method shows a uniquely different method for the utilization of vinyl bromides in photoredox catalysis beyond the generation of vinyl radicals. The synthesized derivatives are important building blocks for many natural products and pharmaceutically important compounds. The glyoxylate functional group can be utilized for further manipulations to install different groups onto the indole core.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02725.

Experimental procedures, compound characterizations and copies of the ^1H, ^{13}C NMR, ^{19}F NMR spectra, and X-ray data (PDF)

Accession Codes

CCDC 1862130−1862131 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the Deutsche Forschungsgemeinschaft (GRK 1626 Photocatalysis), the Alexander von Humboldt Foundation (fellowship for A.V.), and the China Scholarship councel (CSC, fellowship for J.S.). We are also thankful to the following colleagues (all University of Regensburg): Dr. Santosh Pagire and Mr. Asik Hossain for fruitful discussions, Ms. B. Hischa for carrying out the X-ray crystal structure analyses of **3b** and **4g**, and Mrs. R. Hoheisel for cyclic voltammetry measurements.

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