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Photocatalysis

Visible-Light-Induced Direct Photocatalytic Carboxylation of Indoles with CBr_4/MeOH

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Abstract: Photocatalysis enables the cascade reactions of indoles and CBr_4 in MeOH through a C(sp^2)–H functionalization/methanolysis sequence. The title reaction provides an efficient access to indole 2- and 3-carboxylates in a single operation (no preinstallation of protecting as well as directing groups was required) with good yields under mild reaction conditions.

Indoles and their derivatives have been widely recognized as a pivotal structural component of a diverse array of natural products and pharmacological agents of various therapeutic actions.[1] Among them, indole C(2)-carboxylates are present as privileged cores in numerous biologically active molecules and still represent pivotal building blocks for the synthesis of naturally occurring compounds (Figure 1).[2]

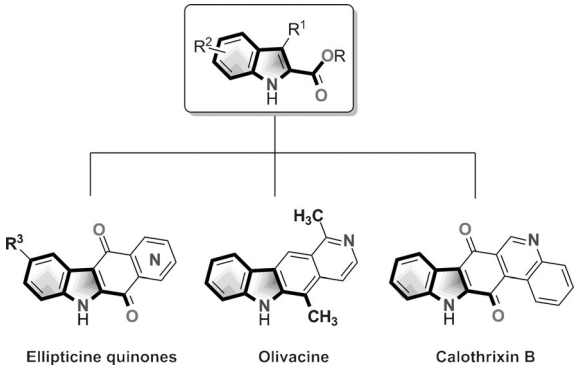
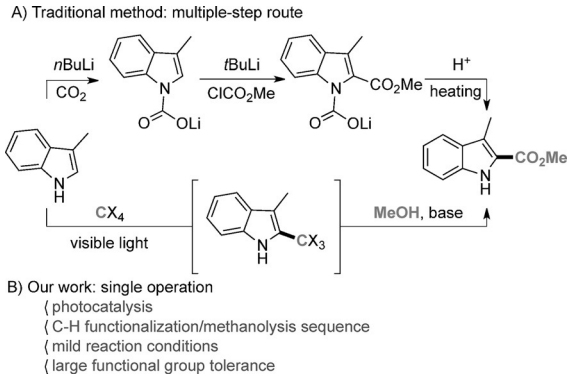


Figure 1. Representative indole C(2)-carboxylate-based natural products and biologically active compounds.

Accordingly, the development of highly efficient methods to access direct carboxylation of this pharmacophore, under protecting-group/prefunctionalization-free conditions, still remains an unsolved challenge in organic synthesis. As a matter of fact, besides the Fisher indole synthesis,[3] the direct C(2)-carboxylation of indolyl cores frequently involves multiple-step sequences based on aggressive reagents (i.e., organolithium compounds)[4] with consequent limitation of substrate scope and moderate yields (Scheme 1 A).[5,6] A straightforward and atom-economic route to this structural motif would deal with the direct C–H functionalization of the indole nucleus.[7] In this context, we drove our attention to the visible-light-induced photoredox catalysis that continues to receive a considerable amount of attention due to its inherent features of sustainability, operational simplicity, and selectivity.[8] In this scenario, visible photocatalysis already found elegant applications in both the synthesis[9] and peripheral functionalization of indoles[10] by means of metal/organic photosensitizers and electron-donor–acceptor complexes.[11] However, despite this blooming scenario, no example of photoassisted regioselective carboxylative C–H activation of arenes has been documented so far.[12]



Scheme 1. Synthesis of indole 2-carboxylates: A) traditional protecting-group-based approach; B) present study.

In this context we recognized in the tetrahalogenated methanes CX_4 (X = Cl, Br) potential carboxylating agents for arenes, due to their intrinsic attitude of generating electrophilic $^{\bullet}CX_3$ radicals (CCl_4 = −0.78 V vs. SCE and CBr_4 = −0.30 V vs. SCE)[13] by oxidative quenching of photoexcited photosensitizers.[14] The intercepting of these radical species by aromatic nucleus, followed by alcoholysis,[15] would deliver a rapid entry to mild C–H-type carboxylating events (Scheme 1B).

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It is worth mentioning that despite their wide use as stoichiometric sacrificial oxidative quenchers, their incorporation in the final target, by means of visible-light-induced photocatalytic tools has never been fully exploited so far. Indeed, besides the elegant photoinduced-ATRA (atom-transfer radical addition) to alkenes and alkynes reported by Stephenson[14a,c,16a] and Melchiorre,[16b] tetrahalomethanes found applications solely in the photochemical activation of oxygenated moieties such as: 1) halogenation of alcohols,[14a] 2) activation of carboxylic acids,[14b] 3) Losson and Beckmann rearrangements[14e,f] ($^{\bullet}CBr_3$ is trapped by the solvent—DMF—during the reaction course) or 4) halogenation of arenes and alkenes (CBr_4 is employed as the source of Br_2).[14d,g] The use of CX_4 as the latent source of „carboxylic groups" under light-driven conditions is still unknown.

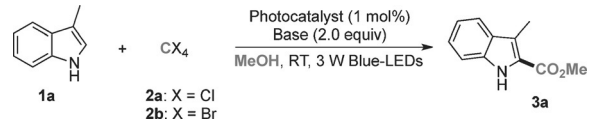
As part of our ongoing research program on the functionalization of indole derivatives,[17] we present here the direct and regioselective synthesis of indole carboxylates by site-selective photocatalytic C–H functionalization in the presence of CBr_4 and MeOH. The protecting-group-free methodology enables a range of functionalized C(2)- or C(3)-indolyl esters to be obtained under extremely mild conditions (Scheme 1 B). In this direction, it should be mentioned that CBr_4 and MeOH have been already employed by Mukminov in the iron-catalyzed C(2)-carboxylation of benzofuran.[18] However, in addition to the limited scope (only one substrate was reported), optimal reaction conditions involved 130 or 100 °C, in the absence or in the presence of radical initiator, respectively.

To explore the feasibility of our working plan, we initially investigated the reaction of 3-methylindole (**1a**) and CX_4 **2** (**2a**: CCl_4, **2b**: CBr_4, 3 equiv) in the presence of metal photosensitizer (1 mol%), DTBP (2.0 equiv), blue LEDs (3 W) irradiation, and MeOH as the reaction media.[19] Interestingly, while no reaction was observed with CCl_4 (Table 1, entry 1),[20] the use of more easily reducible **2b** furnished the desired **3a** in 32% yield (entry 2).

Next, we further optimized the reaction conditions by performing a survey of parameters involving: nature of the photosensitizer, light source, concentration, and base, identifying the following: $[Ru(bpy)_3](PF_6)_2$ (1 mol%), 7 W blue LEDs, 0.05 M, iPr_2NH (2 equiv) as the optimal reaction conditions. Here, compound **3a** was isolated in 90% yield as a single regioisomer upon 6 h irradiation (Table 1, entry 12). Additionally, a sunlight-induced process was also carried out (entry 15), delivering **3a** in comparable extents (yield: 81%).

With the optimal conditions in hand, we probed the scope of this photocatalytic carboxylation reaction. As summarized in Scheme 2, a series of C(3)-substituted indoles (**1b–l**) were successfully applied to this reaction. The 3-substituted indoles containing linear and branched alkyl groups (i.e. ethyl, cyclopentyl, cyclohexyl) were observed to react smoothly with CBr_4 delivering products **3b–d** in good yields (70–84%). Focusing on functional-group tolerance, we also subjected N-protected tryptamines (**1e, 1f**) and tryptophol **1g** to best operating conditions. Gratifyingly, in all cases, the desired acyclic products were recorded in a satisfying manner (yield: 70–82%). It is worth noting that the present carboxylative process does not suffer brominating side events (both on the arene and alcoholic moiety **1g**) and that the *N*-Boc (Boc = *tert*-butoxycarbonyl)

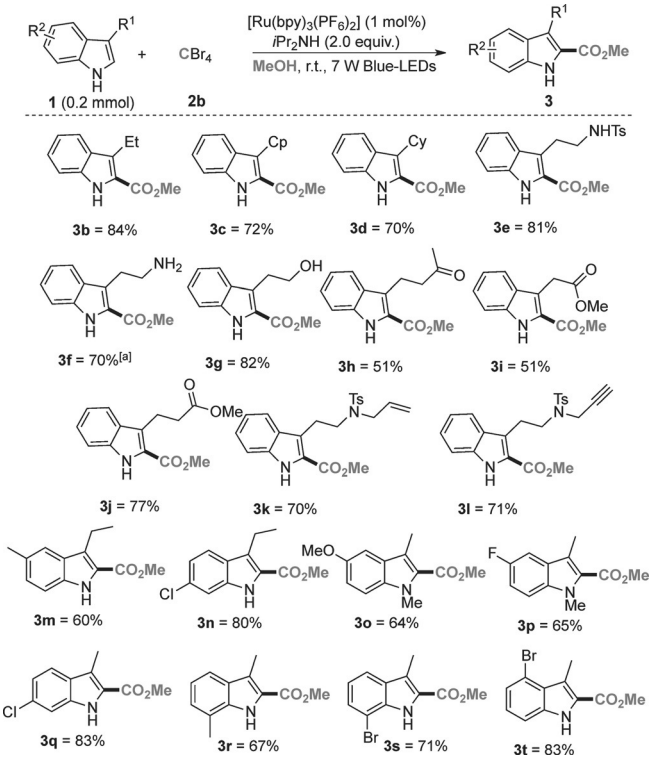
Table 1. Optimization of reaction conditions.[a]



1a — 2a: X = Cl, 2b: X = Br — 3a

Entry	Photocatalyst/**2**	Base	Time [h]	Yield [%][b]
1	$[Ir(diFppy)_2(dtb\text{-}bpy)]PF_6$/**2a**	DTBP	24	NR
2	$[Ru(bpy)_3]Cl_2 \cdot 6H_2O$/**2b**	DTBP	12	32
3	$[Ir(diFppy)_2(dtb\text{-}bpy)]PF_6$/**2b**	DTBP	72	50
4	fluorescein/**2b**	DTBP	48	trace
5	$[Ru(bpy)_3](PF_6)_2$/**2b**	DTBP	12	42
6	$[Ru(bpy)_3](PF_6)_2$/**2b**	$NaHCO_3$	24	33
7	$[Ru(bpy)_3](PF_6)_2$/**2b**	Et_3N	24	25
8	$[Ru(bpy)_3](PF_6)_2$/**2b**	Cy_2NH	48	66
9	$[Ru(bpy)_3](PF_6)_2$/**2b**	iPr_2NH	24	73
10[c]	$[Ru(bpy)_3](PF_6)_2$/**2b**	iPr_2NH	48	79
11[c,d]	$[Ru(bpy)_3](PF_6)_2$/**2b**	iPr_2NH	24	81
12[c,d,e]	$[Ru(bpy)_3](PF_6)_2$/**2b**	iPr_2NH	6	90
13[c,d,e]	–/**2b**	iPr_2NH	24	NR
14[c,d,f]	$[Ru(bpy)_3](PF_6)_2$/**2b**	iPr_2NH	24	trace
15[c,d,g]	$[Ru(bpy)_3](PF_6)_2$/**2b**	iPr_2NH	6	81

[a] Unless noted, reactions were performed on 0.2 mmol scale of **1a** (**1a**/**2** 1:3 ratio), in degassed reagent-grade MeOH. [b] Isolated yield. [c] CBr_4 (1.5 equiv) was used. [d] **1a**: 0.05 M in MeOH. [e] 7 W blue-LEDs was used. [f] In the dark. [g] In the sunlight. bpy = 2,2′-bipyridine; diFppy = 2-(2,4-difluorophenyl)pyridine; dtb-bpy = di-*tert*-butylbipyridine; DTBP = 2,6-di-*tert*-butylpyridine. NR = no reaction.

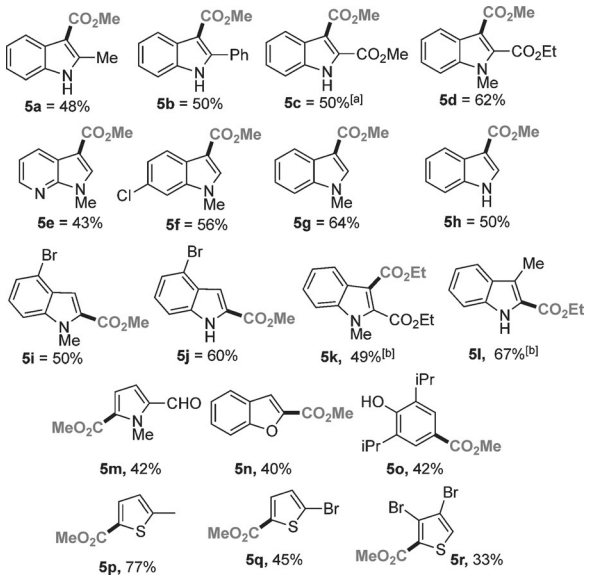


Scheme 2. Generality of the method towards C(3)-substituted indoles (isolated yields are reported for each example). [a] *N*-Boc-protected tryptamine **1f** was used as the starting material.

group is also selectively cleaved during irradiation (N-free tryptamine **3 f** was isolated as the major compound).

Besides amino and alcohol moieties, a wide range of different functional groups proved tolerance of the working conditions. Indoles carrying ketone (**1 h**), ester (**1 i**, **1 j**), alkene (**1 k**), and alkyne (**1 l**) substituents were proved competent in our protocol (yield: 51–77 %). Furthermore, the impact of the electronic properties of the benzene ring on the final chemical outcome was assessed. To this aim, substrates containing electron-deficient and -donating groups at the C(4)-, C(5)-, C(6)-, and C(7) arene-position were tested, furnishing the corresponding C(2)-carboxyl-indoles (**3 m**–**t**) in good yields (60–83 %).

Next, the generality of the process was further substantiated by subjecting a range of C(2)-substituted or-unsubstituted indoles and azaindoles to the best conditions. As highlighted in Scheme 3, 2-substituted indoles carrying Me, Ph, and CO_2Et

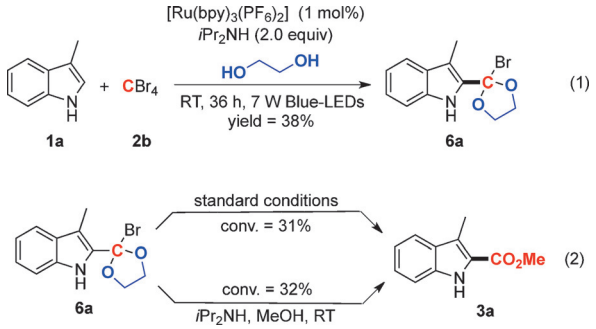


Scheme 3. Substrate scope. For reaction conditions see Scheme 2.[a] Complete trans-esterification occurred starting from ethyl indole 2-carboxylate **4 c**.[b] EtOH was used as the solvent.

units (**4 a**–**d**) successfully participated in the process, providing the corresponding products **5 a**–**d** in 48–62 % yields. Analogously, substrates without substituents at C(2)- and C(3)-positions were suitable in this reaction to furnish indole 3-carboxylates **5 e**–**h** (43–64 %). In contrast, the introduction of a substituent at the C(4)-position (i.e. Br) led to the carboxylation of the C(2) carbon atom exclusively (yield: 50–60 %) probably due to the steric hindrance (**5 i**–**j**). In addition, ethyl indole C(2)- and C(3)-carboxylates could also be easily accessible by the use of EtOH as the solvent (**5 k**–**l**, 49–67 % yields). Last but not least, preliminary encouraging results on different electron-rich heterocycles (i.e., pyrrole, benzofuran, phenol, and thiophene, **5 m**–**r**) were achieved in moderate to good yields (33–77 %).[18a]

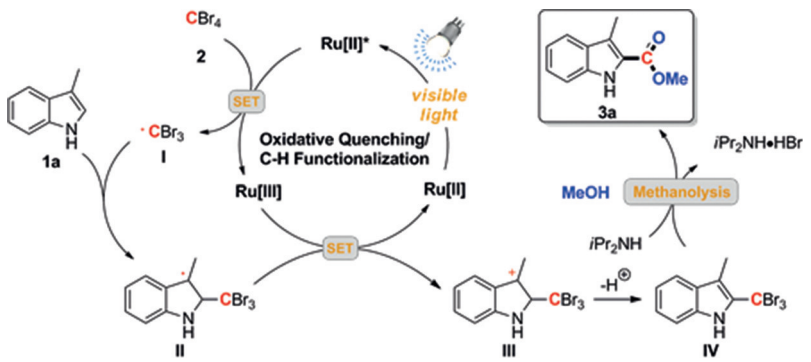
Preliminary insights into the reaction mechanism are provided by the additional experiments described in Equations (1) and (2). In particular, the isolation of the bromo derivative **6 a** when ethylene glycohol was used as the solvent [Eq. (1)] allows some conclusions to be drawn: 1) the carbon atom of the final carboxylic group comes from CBr_4 that exerts the initial indole C–H activation; 2) the alternative carbene-like mechanism can be excluded.[21]

In addition, the comparable results obtained by treating **6 a** under standard conditions ($[Ru(bpy)_3](PF_6)_2$ (1 mol %), 7 W blue LEDs, 0.05 M (**6 a**) in MeOH, iPr_2NH (2 equiv)) or simply by stirring **6 a** in iPr_2NH (2 equiv), MeOH at RT for 24 h [**3 a**: 31 and 32 % conversion, respectively, Eq. (2)] account for a classic methanolysis reaction as the conclusive chemical event of the cascade process.[13]



The reaction completely stopped in the dark and restarted when the light source was switched on once again (Figure S1, Supporting Information): this experiment clearly emphasized the pivotal role played by visible light in promoting the process.[22]

As shown in Scheme 4, a plausible mechanism is proposed using methoxycarboxylation of 3-methylindole (**1 a**) as an example of this novel photocatalytic process. Visible-light excita-



Scheme 4. Hypothesis of reaction mechanism.

tion of the reaction mixture yields its lowest energy triplet excited state of $[Ru(bpy)_3]^{2+}$, $*[Ru(bpy)_3]^{2+}$, since none of the other reagents is absorbing visible light (Figure S2, Supporting Information). $*[Ru(bpy)_3]^{2+}$ is quenched by CBr_4 (**2b**) with a quenching constant of $5.3\times10^6\ M^{-1}s^{-1}$ (see Figure S5, Supporting Information). The quenching process is the oxidation of $*[Ru(bpy)_3]^{2+}$ and the reduction of CBr_4, which generates $^{\bullet}CBr_3$ (**I**) and Br^-.[14a,23] Trapping of the electron-deficient radical by 3-methylindole formed a new benzyl radical **II**, which can be oxidized by $[Ru(bpy)_3]^{3+}$ to provide the intermediate **III**, regenerating the photocatalyst $[Ru(bpy)_3]^{2+}$. Rearomatization of the intermediate **III** followed by methanolysis furnished the observed product. The photoreaction quantum yield upon monochromatic excitation at 450 nm is approximately 2% (see the Supporting Information for more details), much lower than 100%. This result rules out a chain reaction mechanism, as supported also by the light on–off experiment described above. It is worth noting that at the end of the photoreaction no significant change in the absorption spectrum of the photosensitizer is observed (Figure S4, Supporting Information), meaning that $[Ru(bpy)_3]^{2+}$ does not decompose and can be reused.

In conclusion, we have developed a visible-light-induced site-selective carboxylation reaction of indoles by direct C–H functionalization, in the presence of CBr_4 and MeOH as the solvent. The mild conditions requested (RT, few hours, 7 W Blue LEDs) enable a wide functional-group tolerance. Further studies on photoredox-mediated carboxylation of different organic compounds are currently underway in our laboratory.

Experimental Section

Representative procedure

To a 10 mL Schlenk flask equipped with a magnetic stirrer bar was added MeOH (4 mL), which was bubbled with N_2. 3-Methylindole (**1a**) (0.2 mmol), CBr_4 (**2**) (0.3 mmol), $[Ru(bpy)_3(PF_6)_2]$ (0.002 mmol), and iPr_2NH (0.4 mmol). The resulting solution was stirred at room temperature under irradiation of 7 W blue LEDs at a distance of approximately 5 cm. Upon completion of the reaction, as monitored by TLC, the solvent was removed under reduced pressure. The crude residue was subjected to flash chromatography on silica gel (silica: 240–400; eluent: cyclohexane/ethyl acetate = 20:1) to provide pure methyl 3-methylindole 2-carboxylate (**3a**) as a white solid; yield: 90%.

Acknowledgements

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Keywords: carboxylation · indole functionalization · methanolysis · photocatalysis · visible light

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