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Methylene Blue-Catalyzed Oxidative Cleavage of N-Carbonylated Indoles

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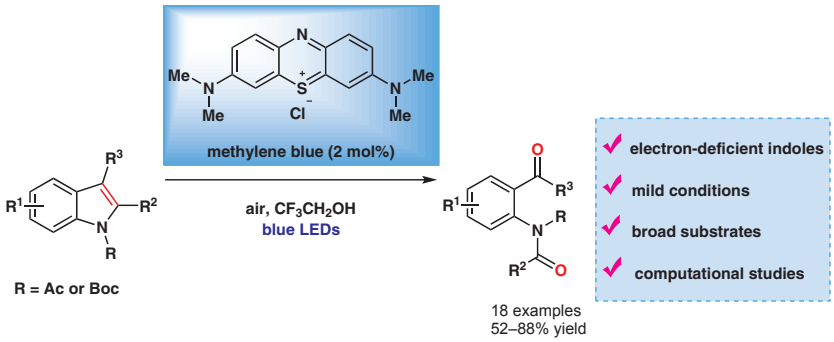

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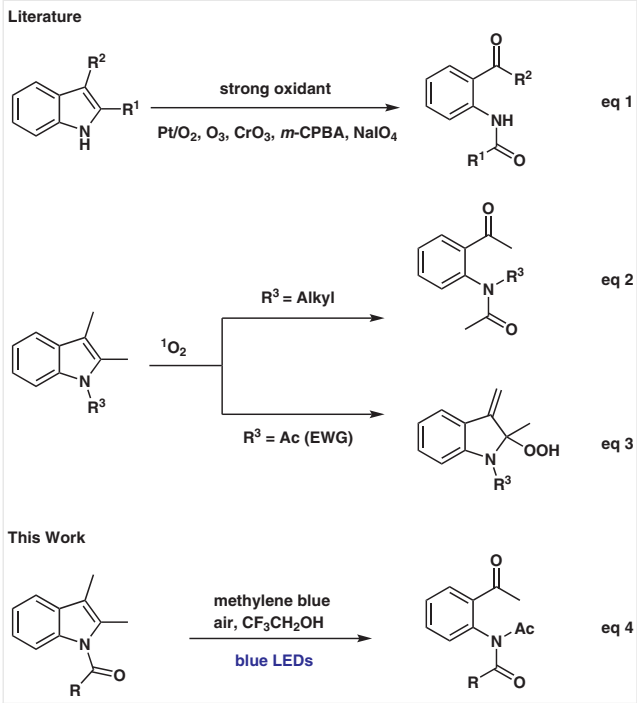
Abstract The development of a visible-light-mediated oxidative cleavage of electron-deficient indoles is reported. Methylene blue serves as an effective catalyst and the transformation shows a broad substrate scope. A variety of functional groups are well accommodated in the mild reaction conditions. The photo-mediated single electron transfer and oxidative cleavage mechanisms were investigated via density functional theory and Marcus theory calculations.

Key words methylene blue, visible light, electron-deficient indoles, Witkop–Winterfeldt oxidation, photocatalysis

Oxidative cleavage reaction of aromatic rings is a wide spread occurrence in nature.[1] Particularly, the oxidative transformation of tryptophan to *N*-formylkynurenine, catalyzed by tryptophan 2,3-dioxygenease, is the major oxidative and metabolic pathway of tryptophan.[2] It is also the first key step leading to the biosynthesis of coenzyme NAD. In 1951, Witkop reported the first chemically oxidative cleavage of the C-2–3 double bond of indoles by catalytic oxidation (Pt/O_2) as well as autoxidation.[3] Different synthetic procedures were then developed using various reagents including peracids, periodic acid, chromic acid, and ozone (Scheme 1, eq 1).[4] Winterfeldt later disclosed a direct procedure to convert Witkop oxidation intermediate to the Camps cyclization product by using NaH/O_2 and KO*t*-Bu/O_2 as oxidant.[5] Since then, the synthetic strategy (Witkop–Winterfeldt oxidation) has been widely applied in the synthesis of natural products and pharmaceutical agents. However, N-substituted indoles are liable to resist oxidation with such oxidizing agents. Singlet oxygen was then reported to react with N-alkylated indoles to give carbonyl and amide fragments (Scheme 1, eq 2);[4,6] but such transformation could not be realized on electron-deficient *N*-acetylindoles, presumably due to their poor nucleophilicities. Instead, an ene-type allylic oxidation product was obtained (Scheme 1, eq 3).[7] More recently, aerobic C–C oxidative

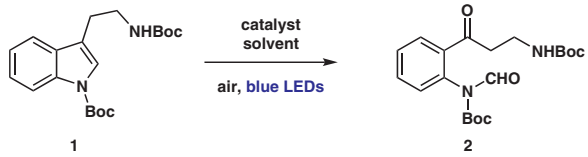


Scheme 1 Oxidative cleavage of N-carbonylated indoles

cleavages of N-alkylated indoles were reported by visible light photocatalysis,[8] where dicyanopyrazine-derived chromophore (DPZ) and $Ru(bpy)_3^{2+}$ were used as photocatalysts.[9] Yet, no N-carbonylated substrates were studied in the reports. Since a major class of protecting group on nitrogen center is carbonyl-containing groups (Ac, Boc, Cbz, Fmoc, etc.), we reasoned that new catalytic methods for the oxidative cleavage of such indole substrates under mild conditions might provide a significant synthetic benefit (Scheme 1, eq 4). Continuing our interest in organic photoredox catalysis,[10] herein we report a mild and efficient way to oxidize N-carbonylated indoles via methylene blue-catalyzed phototransformation.

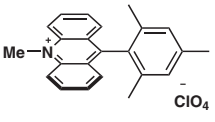
To test the idea, we started our investigations by screening different catalysts (catalysts A–D) for the oxidation of tryptamine derivative **1** (Table 1, entries 1–4). Gladly, it was found that methylene blue successfully catalyzed the oxidation process in MeOH upon irradiation with blue light-emitting diodes (LEDs), providing oxidative cleavage product **2** in 20% yield (entry 4). Various reaction solvents were then carefully screened (entries 5–11). We found that the reaction only proceeded in protic solvents, and more polar solvent tends to result in better yields (entries 9–11). Trifluroethanol was found to be the optimal solvent, providing **2** in yield of 88% (entry 11). Unfortunately, reactants are decomposed in the medium of hexafluoroisopropanol (HFIP,

Table 1 Optimization of Reaction Conditions[a]

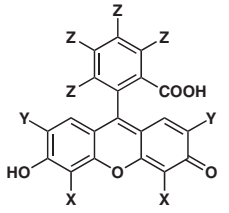


1 2

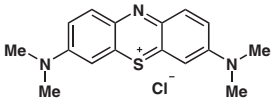
Entry	Photocatalyst	Solvent	Yield (%)[b]
1	A	MeOH	0
2	B	MeOH	0
3	C	MeOH	0
4	D	MeOH	20
5	D	CH_2Cl_2	0
6	D	DMF	0
7	D	MeCN	0
8	D	$MeNO_2$	0
9	D	$ClCH_2CH_2OH$	33
10	D	CCl_3CH_2OH	47
11	D	CF_3CH_2OH	88
12	D	HFIP	0
13	A	CF_3CH_2OH	24
14	B	CF_3CH_2OH	35
15	C	CF_3CH_2OH	0
16[c]	D	CF_3CH_2OH	0
17	–	CF_3CH_2OH	0



A. 9-Mesityl-10-methylacridinium perchlorate



B. Eosin Y (Y = Br, Z = H)
C. Rose Bengal (Y = I, Z = Cl)



D. Methylene Blue

[a] Reactions irradiated with two 12 W, 450 nm light-emitting diode (LED) flood lamps for 10 h.
[b] Isolated yield.
[c] Reaction conducted in the dark.

entry 12). We then tested other catalysts A–C in trifluroethanol, confirming that the methylene blue provided the best outcome (entries 13–15). Control experiments verified that both catalyst and the light irradiation are necessary for the success of this transformation (entries 16 and 17).

Encouraged by these results, our attention was next focused on exploring the scope of the photocatalytic oxidation reaction. Table 2 summarizes experiments probing a variety of substituted indoles. We were pleased to find that both acetyl (Ac) and *tert*-butoxycarbonyl (Boc)-protected indoles could be oxidized under the optimized conditions, providing the corresponding products in good yields (Table 2, entry 1, **a**–**c**). In addition, C-3 substituted indole **3d**, C-2 substituted indole **3e**, and C-2,3-disubstituted indole **3f** are well tolerated, providing the corresponding products **4d**,**e** in good yields of 85%, 68%, and 78%, respectively (entry 1, **d**,**e**). Tryptophan derivative **5** and tryptamine derivative **7** could be oxidized smoothly in excellent yields (entries 2 and 3). Excitingly, a free hydroxyl group was tolerated in this oxidation reaction (entry 4), demonstrating the mild nature of the reaction condition. Additionally, a variety of electron-donating and electron-withdrawing substituents at C-5 and C-6 positions are accommodated (entries 5–7). Moreover, oxidizing the cyclic structure frameworks under the optimized conditions furnished medium-size cyclic amides in good yields (entries 8 and 9).

Table 2 Scope of Oxidative Cleavage of Indoles[a]

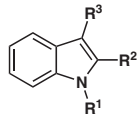
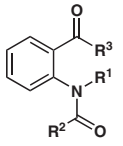
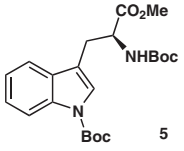
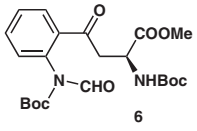
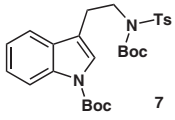
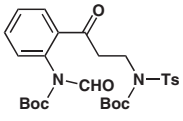
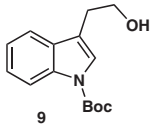
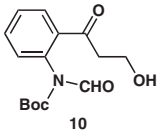
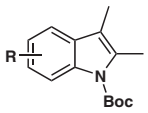
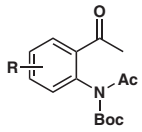
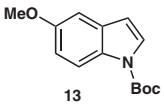
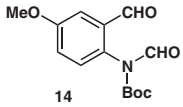
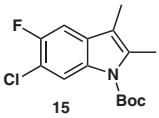
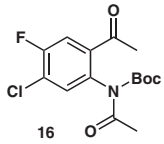
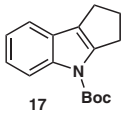
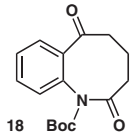
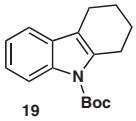
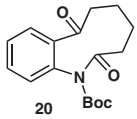
Entry	Indole	Product	Yield (%)[b]
1	 **3a**: R^1 = Ac, R^2 = R^3 = Me **3b**: R^1 = Ac, R^2 = H, R^3 = Me **3c**: R^1 = Boc, R^2 = R^3 = H **3d**: R^1 = Boc, R^2 = H, R^3 = Me **3e**: R^1 = Boc, R^2 = Me, R^3 = H **3f**: R^1 = Boc, R^2 = R^3 = Me	 **4a**: R^1 = Ac, R^2 = R^3 = Me **4b**: R^1 = Ac, R^2 = H, R^3 = Me **4c**: R^1 = Boc, R^2 = R^3 = H **4d**: R^1 = Boc, R^2 = H, R^3 = Me **4e**: R^1 = Boc, R^2 = Me, R^3 = H **4f**: R^1 = Boc, R^2 = R^3 = Me	**4a**: 68 **4b**: 84 **4c**: 75 **4d**: 85 **4e**: 68 **4f**: 78
2	 **5**	 **6**	86
3	 **7**	 **8**	81
4	 **9**	 **10**	74

Table 2 (continued)

Entry	Indole	Product	Yield (%)[b]
5	 11a: R = 5-F 11b: R = 5-Cl 11c: R = 6-Cl 11d: R = 5-OMe	 12a: R = 5-F 12b: R = 5-Cl 12c: R = 6-Cl 12d: R = 5-OMe	**12a**: 72 **12b**: 52 **12c**: 86 **12d**: 70
6	 13	 14	79
7	 15	 16	74
8	 17	 18	70
9	 19	 20	62

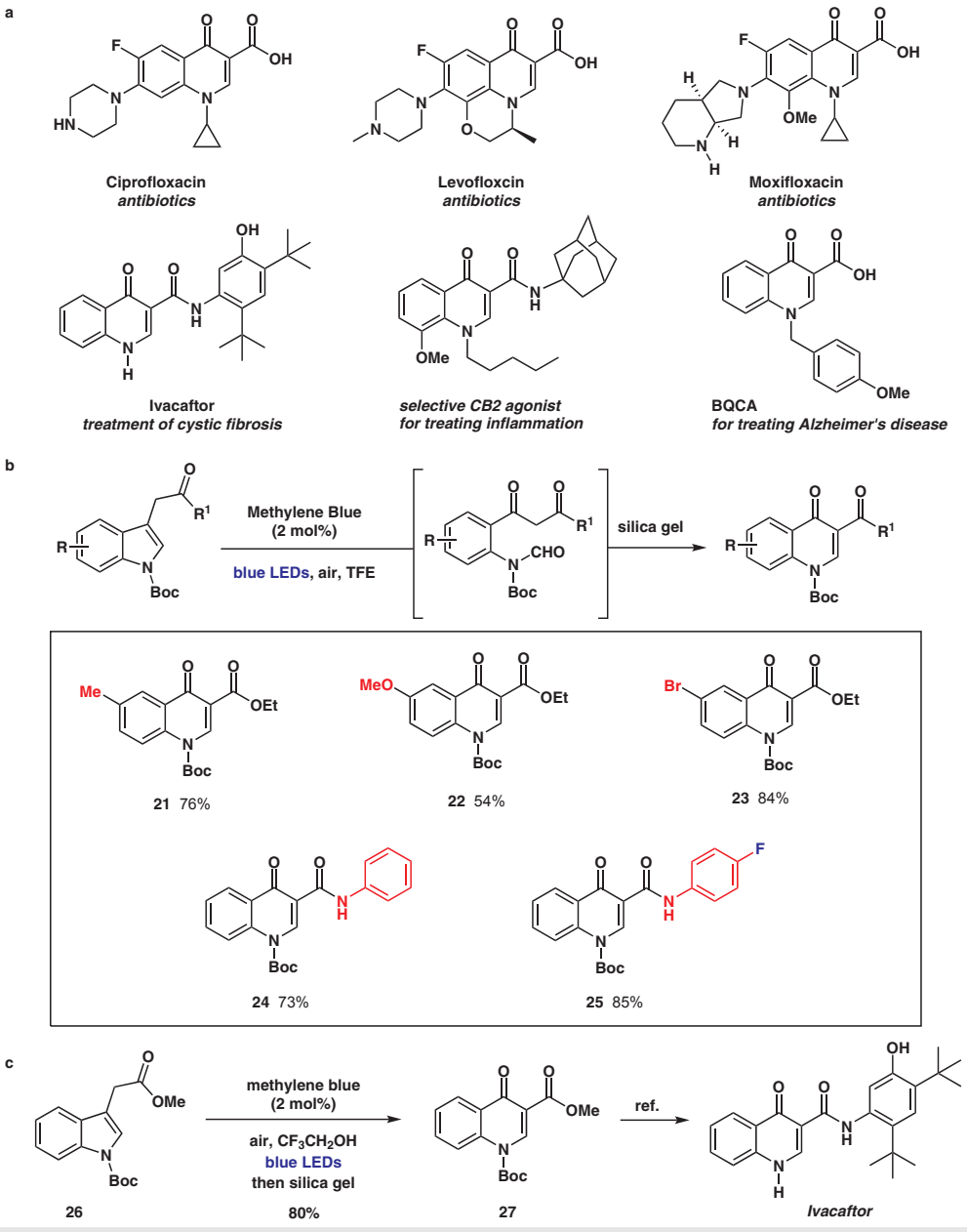
[a] Reactions irradiated with two 12 W, 450 nm LED flood lamps for 10 h at r.t. under air at 1 atm.
[b] Isolated yield.

Having demonstrated the high efficiency of the visible-light-mediated indole oxidation, the applicability of this chemistry to enable the Witkop–Winterfeldt oxidation to synthesize 4-quinolone-3-carboxylic acid derivatives was next investigated. 4-Quinolone-3-carboxylic acid derivatives are privileged structural frameworks in medicinal chemistry.[11] They widely exist in marketed drugs and biological active agents, such as synthetic antibiotics Ciprofloxacin, Levofloxacin, and Moxifloxacin.[11] Moreover, the amide derivative Ivacaftor[12] was recently approved by FDA for treatment of cystic fibrosis. In addition, this class of compounds also exhibit a broad array of biological activities, including antitumor, antiviral, anti-inflammation, antiparasitic activities, and activities towards Alzheimer's disease (Scheme 2a).[13] Given that the 4-quinolone-3-carboxylate skeleton may represent attractive template for medicinal evaluation, we were prompted to develop an efficient and mild access to this structure motif. We were pleased to find that the Witkop–Winterfeldt reaction, oxidative C-2–3 bond cleavage followed by Camps cyclization, could be achieved smoothly by treatment of silica gel once the indole substrates were consumed completely. The indole acetic acid derivatives with different substitutions at C-5 position are well tolerated, providing **21**–**23** in good yields. Amide equivalent **24** and fluoro-substituted aryl amide **25** could also be obtained in good yields of 73% and 85%, respectively. Under this mild reaction condition, protected indoleacetic acid **26** could be converted to quinolone **27** in 80% yield, which is the key precursor in the synthesis of Ivacaftor (Scheme 2b,c).[14]

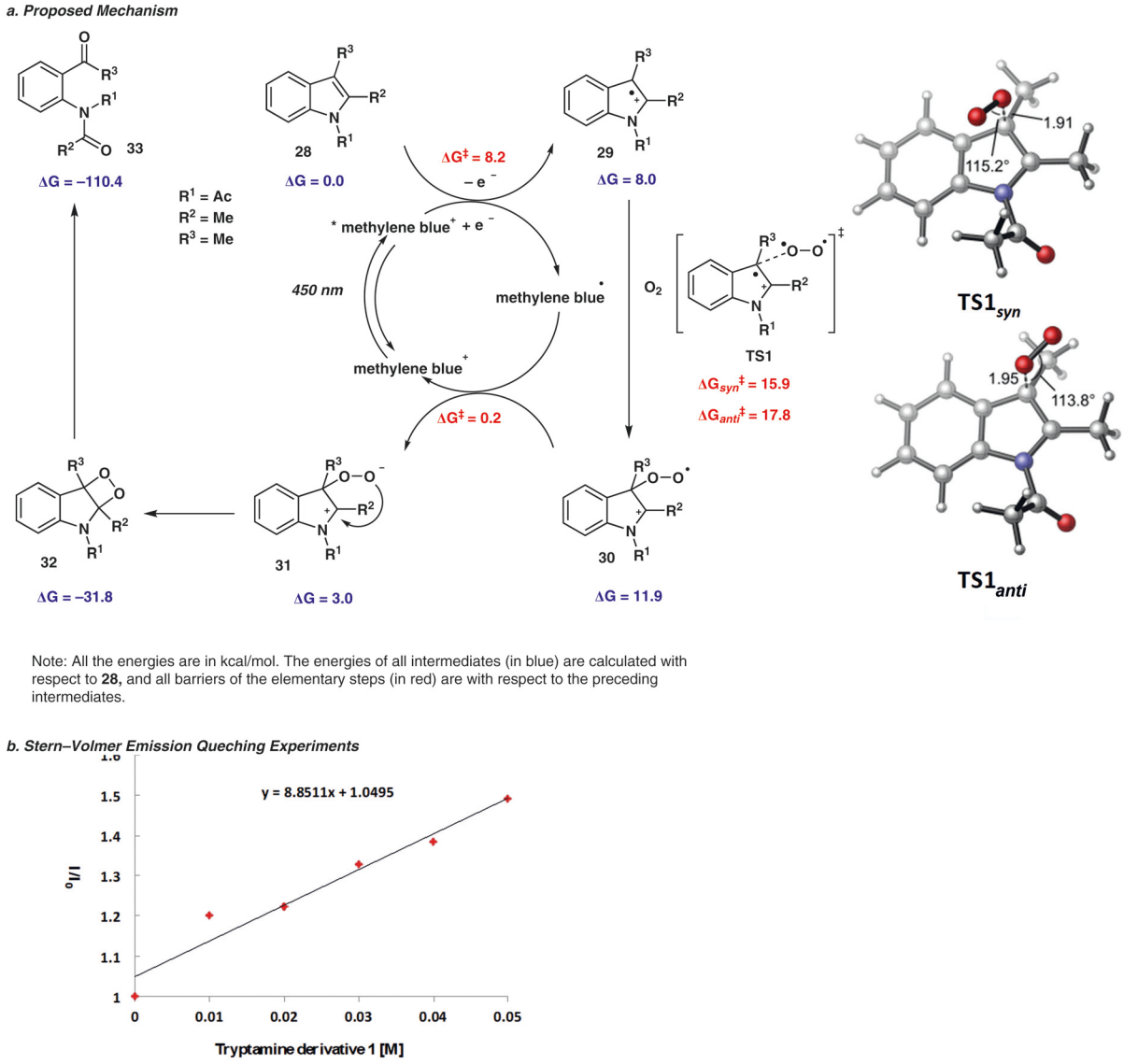
A plausible mechanism for the reaction is outlined in Scheme 3. Although we could not rule out the possible singlet oxygen involvement during the process,[7e] our Stern–Volmer emission quenching experiments (Scheme 3b) showed that there is redox activity between tryptamine derivative **28** and the catalyst methylene blue (M.B.$^+$). Therefore, we propose that the indole was oxidized via single electron transfer by methylene blue. The resulting radical cation **29** was then coupled with a molecule of oxygen to generate peroxy radical intermediate **30**. The peroxy radical

30 could be converted to **31** by accepting an electron from reduced methylene blue species, where the photoactive catalyst (M.B.$^{+}$) was regenerated. 1,2-Dioxetane formation followed by quick decomposition gave oxidative cleavage product **33**.

We next investigated the proposed mechanism via density functional theory (DFT) and Marcus theory calculations. The single electron transfer from **28** to the excited state M.B.$^{+*}$ to form **29** and M.B.$^{\cdot}$ requires a relatively low Gibbs free energy barrier of 8.2 kcal/mol. The spin density of radical cation **29** is mostly localized on the benzylic carbon (see Supporting Information), which promotes subsequent dioxygen addition to the benzylic radical center. Two different dioxygen addition transition states to the radical cation were located. The '*syn*' isomer (**TS1**$_{syn}$), in which the dioxygen points towards the indole nitrogen, has a 1.8 kcal/mol lower barrier than the '*anti*' transition state (**TS1**$_{anti}$) in which the dioxygen points away from the indole nitrogen. The preference for *syn*-dioxygen addition transition state is consistent with previous computational studies on dioxygen addition to π-systems.[15] Here, **TS1**$_{syn}$ and **TS1**$_{anti}$ are both computed as doublets, and are only 15.9



Scheme 2 Witkop–Winterfeldt indole oxidation



Scheme 3 Proposed mechanism and mechanistic studies

and 17.8 kcal/mol, respectively, higher in energy compared to the separate radical cation **29** and a triplet dioxygen. Although our DFT calculations cannot rule out the reaction of **29** with singlet dioxygen,[16] the computed barrier to the dioxygen addition indicates **29** is reactive enough with the ground state triplet dioxygen to form peroxy radical **30**. Single electron reduction of **30** to form the zwitterionic complex **31** is exergonic and facile. Subsequent steps, including collapse of **31** to 1,2-dioxetane **32** and decomposition of **32** to form the final product **33**, are both highly exergonic. The mechanism of thermal decomposition of 1,2-dioxetane has been well established in the literature,[17] and therefore was not investigated in detail here.

In summary, we have developed a visible-light-mediated oxidative cleavage of electron-deficient indoles. A broad range of electron-donating and electron-withdrawing groups are tolerated on the indole backbone. A variety of functional groups are well accommodated in the mild reaction conditions. Witkop–Winterfeldt reactions were then investigated in this photocatalytic system. A reaction mechanism was proposed and studied via density functional theory and Marcus theory calculations.

All commercially available chemicals were used without further purification, unless otherwise noted. Reactions were monitored by TLC using silica gel 60-F254 plates. TLC plates were visualized by UV fluorescence (254 nm) or stained by Cerium Molybdate followed by heat-

ing. Purification of the reaction products was carried out by column chromatography using Siliaflash-P60 (40–63 μm) silica gel available from Silicycle. 1H-NMR spectra were recorded on a Bruker AV-400 (400 MHz) and ^{13}C NMR spectra were recorded on a Bruker AV-400 or AV-600 (100 MHz or 150 MHz). Data for ^{1}H NMR are recorded as follows: chemical shift (δ, ppm), multiplicity (standard abbreviations), coupling constant(s) in hertz (Hz) and integration. Data for ^{13}C NMR are reported in terms of chemical shift (δ, ppm). IR spectra were recorded on a PerkinElmer Spectrum Two IR spectrometer and only major peaks were reported in cm^{-1}. High-resolution mass spectral analysis (HRMS) data were obtained using Agilent Technologies 6530 Accurate Mass Q-TOF LC/MS. Optical rotations were measured on a PerkinElmer 351 polarimeter at 589 nm with a 100 mm path length cell. Irradiation of photochemical reactions was carried out using two 12W PAR38 blue LED flood lamps from ABi LED lighting. Yields refer to chromatographically and spectroscopically purified compounds.

The syntheses of all the indoles in Table 2 and Scheme 2 are described in the Supporting Information.

Photo-Oxidative Cleavage of Indoles; General Procedure 1

To a 0.1 M solution of indole substrate (0.2 mmol, 1 equiv) in trifluoroethanol was added methylene blue (2 mol%) was added. The reaction mixture was irradiated under blue LEDs in the open air for 10 h. The reaction was quenched with H_2O and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine and dried (Na_2SO_4). After removal of the solvent under reduced pressure, the residue was purified on column chromatography to give the corresponding desired product (Table 2).

tert-Butyl (2-{3-[(*tert*-Butoxycarbonyl)amino]propanoyl}phenyl)(formyl)carbamate (2)

Following the general procedure **1**, compound **1** (72 mg) gave **2** as a colorless oil; yield: 69 mg (88%).

IR (CH_2Cl_2): 1743, 1698, 1503, 1368, 1295, 1242, 1154 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.32 (s, 1 H), 7.83 (d, *J* = 7.6 Hz, 1 H), 7.59 (t, *J* = 7.6 Hz, 1 H), 7.50 (t, *J* = 7.6 Hz, 1 H), 7.19 (d, *J* = 7.6 Hz, 1 H), 5.06 (s, 1 H), 3.45 (dd, *J* = 5.8, 5.5 Hz, 2 H), 3.12 (t, *J* = 5.5 Hz, 2 H), 1.48 (s, 9 H), 1.42 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.88, 163.23, 155.84, 151.90, 134.52, 132.92, 132.85, 130.76, 129.53, 128.97, 84.54, 79.15, 40.49, 35.54, 28.34, 27.88.

ESI-HRMS: *m*/*z* calcd for $C_{20}H_{28}N_2O_6Na$ [M + Na]$^+$: 415.1840; found: 415.1842.

N-Acetyl-*N*-(2-acetylphenyl)acetamide (4a)

Following the general procedure **1**, compound **3a** (37 mg) gave **4a** as a yellowish oil; yield: 29 mg (68%).

IR (CH_2Cl_2): 1701, 1368, 1274, 1243, 1019, 747, 598 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.84 (dd, *J* = 7.6, 1.6 Hz, 1 H), 7.61 (td, *J* = 7.6, 1.6 Hz, 1 H), 7.57–7.50 (td, *J* = 7.6, 1.1 Hz, 1 H), 7.19 (dd, *J* = 7.7, 1.1 Hz, 1 H), 2.55 (s, 3 H), 2.26 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.09, 173.05, 137.50, 135.94, 133.03, 130.66, 129.91, 129.13, 28.71, 26.74.

ESI-HRMS: *m*/*z* calcd for $C_{12}H_{13}NO_3Na$ [M + Na]$^+$: 242.0788; found: 242.0791.

N-(2-Acetylphenyl)-*N*-formylacetamide (4b)

Following the general procedure **1**, compound **3b** (35 mg) gave **4b** as a yellow oil; yield: 35 mg (84%).

IR (CH_2Cl_2): 1730, 1701, 1367, 1272, 1245, 764 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.41 (s, 1 H), 7.87 (dd, *J* = 7.6, 1.4 Hz, 1 H), 7.64 (td, *J* = 7.6, 1.5 Hz, 1 H), 7.57 (td, *J* = 7.6, 1.2 Hz, 1 H), 7.20 (dd, *J* = 7.6, 0.9 Hz, 1 H), 2.55 (s, 3 H), 2.10 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.73, 172.51, 162.68, 135.81, 133.58, 133.15, 130.69, 130.07, 129.66, 28.61, 23.98.

ESI-HRMS: *m*/*z* calcd for $C_{11}H_{11}NO_3Na$ [M + Na]$^+$: 228.0631; found: 228.0640.

tert-Butyl Formyl(2-formylphenyl)carbamate (4c)

Following the general procedure **1**, compound **3c** (43 mg) gave **4c** as a reddish oil; yield: 37 mg (75%).

IR (CH_2Cl_2): 1744, 1699, 1371, 1353, 1291, 1239, 1058, 846, 759, 617 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.97 (s, 1 H), 9.42 (s, 1 H), 7.92 (dd, *J* = 7.6, 1.6 Hz, 1 H), 7.69 (td, *J* = 7.6, 1.6 Hz, 1 H), 7.60 (td, *J* = 7.6, 0.9 Hz, 1 H), 7.23 (d, *J* = 7.6 Hz, 1 H), 1.47 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.57, 163.00, 151.66, 134.75, 134.51, 132.93, 132.08, 130.33, 129.35, 84.96, 27.80.

ESI-HRMS: *m*/*z* calcd for $C_{13}H_{15}NO_4Na$ [M + Na]$^+$: 272.0893; found: 272.0897.

tert-Butyl (2-Acetylphenyl)(formyl)carbamate (4d)

Following the general procedure **1**, compound **3d** (46 mg) gave **4d** as a yellowish oil; yield: 44 mg (85%).

IR (CH_2Cl_2): 1742, 1692, 1356, 1295, 1251, 1153, 1052, 762 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.32 (s, 1 H), 7.85 (d, *J* = 7.7 Hz, 1 H), 7.58 (t, *J* = 8.0 Hz, 1 H), 7.50 (t, *J* = 7.6 Hz, 1 H), 7.18 (d, *J* = 9.6 Hz, 1 H), 2.54 (s, 3 H), 1.48 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.12, 163.25, 151.90, 135.04, 132.98, 132.70, 130.66, 129.93, 128.89, 84.42, 28.53, 27.84.

ESI-HRMS: *m*/*z* calcd for $C_{14}H_{17}NO_4Na$ [M + Na]$^+$: 286.1050; found: 286.1052.

tert-Butyl Acetyl(2-formylphenyl)carbamate (4e)

Following the general procedure **1**, compound **3e** (46 mg) gave **4e** as a white solid; yield: 36 mg (68%); mp 80 °C.

IR (CH_2Cl_2): 1743, 1701, 1371, 1255, 1155, 764, 731 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.99 (s, 1 H), 7.88 (dd, *J* = 7.6, 1.3 Hz, 1 H), 7.65 (td, *J* = 7.6, 1.3 Hz, 1 H), 7.54 (t, *J* = 7.6 Hz, 1 H), 7.17 (d, *J* = 7.6 Hz, 1 H), 2.68 (s, 3 H), 1.34 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.96, 173.42, 139.32, 134.45, 132.44, 132.00, 130.01, 128.56, 83.61, 27.69, 26.36.

ESI-HRMS: *m*/*z* calcd for $C_{14}H_{17}NO_4Na$ [M + Na]$^+$: 286.1050; found: 286.1050.

tert-Butyl Acetyl(2-acetylphenyl)carbamate (4f)

Following the general procedure **1**, compound **3f** (49 mg) gave **4f** as a colorless oil; yield: 43 mg (78%).

IR (CH_2Cl_2): 1743, 1689, 1371, 1282, 1157, 731 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80 (d, *J* = 7.8 Hz, 1 H), 7.52 (t, *J* = 7.8 Hz, 1 H), 7.42 (t, *J* = 7.8 Hz, 1 H), 7.12 (d, *J* = 7.8 Hz, 1 H), 2.61 (s, 3 H), 2.51 (s, 3 H), 1.34 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.35, 173.54, 152.15, 137.32, 134.61, 132.59, 130.37, 129.79, 128.07, 83.00, 28.60, 27.71, 26.52;

ESI-HRMS: *m*/*z* calcd for $C_{15}H_{19}NO_4Na$ [M + Na]$^+$: 300.1206; found: 300.1208.

Methyl 2-[(*tert*-Butoxycarbonyl)amino]-4-{2-[*N*-(*tert*-butoxycarbonyl)formamido]phenyl}-4-oxobutanoate (6)

Following the general procedure **1**, compound **5** (83 mg) gave **6** as a reddish oil; yield: 87 mg (86%); $[\alpha]_D^{20}$ +97.8 (*c* 1.5, $CHCl_3$).

IR (CH_2Cl_2): 1744, 1708, 1497, 1368, 1295, 1155, 761 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.28 (s, 1 H), 7.82 (s, 1 H), 7.58 (t, *J* = 7.7 Hz, 1 H), 7.48 (t, *J* = 7.6 Hz, 1 H), 7.17 (d, *J* = 7.8 Hz, 1 H), 5.44 (s, 1 H), 4.60 (s, 1 H), 3.70 (s, 3 H), 3.56 (s, 1 H), 3.41 (d, *J* = 17.7 Hz, 1 H), 1.46 (s, 9 H), 1.44 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.12, 197.56, 171.77, 171.63, 163.12, 162.98, 155.48, 151.78, 151.70, 134.08, 133.40, 133.10, 132.96, 130.92, 130.81, 130.11, 129.58, 129.04, 129.00, 84.56, 84.44, 79.97, 79.89, 52.56, 52.46, 49.42, 42.51, 42.30, 28.24, 27.88, 27.76.

ESI-HRMS: *m*/*z* calcd for $C_{22}H_{30}N_2O_8Na$ [M + Na]$^+$: 473.1894; found: 473.1897.

***tert*-Butyl (2-{3-[*N*-(*tert*-Butoxycarbonyl)-4-methylphenylsulfonamido]propanoyl}phenyl)(formyl)carbamate (8)**

Following the general procedure **1**, compound **7** (130 mg) gave **8** as a colorless oil; yield: 111 mg (81%).

IR (CH_2Cl_2): 1697, 1355, 1289, 1154, 746, 567, 546 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.32 (s, 1 H), 7.90 (dd, *J* = 8.0, 1.0 Hz, 1 H), 7.78 (d, *J* = 8.0 Hz, 2 H), 7.59 (td, *J* = 7.7, 1.2 Hz, 1 H), 7.51 (td, *J* = 7.6, 1.2 Hz, 1 H), 7.30 (d, *J* = 8.0 Hz, 2 H), 7.19 (d, *J* = 8.0 Hz, 1 H), 4.13 (t, *J* = 7.6 Hz, 2 H), 3.40 (t, *J* = 7.6 Hz, 2 H), 2.43 (s, 3 H), 1.47 (s, 9 H), 1.35 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.03, 163.14, 151.91, 150.71, 144.30, 137.06, 134.31, 133.08, 132.87, 130.72, 129.58, 129.30, 128.97, 127.72, 84.48, 84.46, 43.01, 40.92, 27.83, 21.55.

ESI-HRMS: *m*/*z* calcd for $C_{27}H_{34}N_2O_8SNa$ [M + Na]$^+$: 569.1928; found: 569.1937.

***tert*-Butyl Formyl[2-(3-hydroxypropanoyl)phenyl]carbamate (10)**

Following the general procedure **1**, compound **9** (52 mg) gave **10** as a yellowish oil; yield: 43 mg (74%).

IR (CH_2Cl_2): 1744, 1296, 1153, 731 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.31 (s, 1 H), 7.83 (dd, *J* = 7.7, 1.3 Hz, 1 H), 7.59 (td, *J* = 7.7, 1.3 Hz, 1 H), 7.50 (td, *J* = 7.6, 1.3 Hz, 1 H), 7.20 (dd, *J* = 7.8, 0.9 Hz, 1 H), 3.98–3.84 (m, 2 H), 3.12 (t, *J* = 5.4 Hz, 2 H), 2.41 (s, 1 H), 1.48 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.09, 163.34, 151.91, 134.79, 132.90, 132.82, 130.72, 129.48, 128.99, 84.70, 58.19, 42.70, 27.85.

ESI-HRMS: *m*/*z* calcd for $C_{15}H_{19}NO_5Na$ [M + Na]$^+$: 316.1155; found: 316.1155.

***tert*-Butyl Acetyl(2-acetyl-4-fluorophenyl)carbamate (12a)**

Following the general procedure **1**, compound **11a** (52 mg) gave **12a** as a yellowish oil; yield: 42 mg (72%).

IR (CH_2Cl_2): 1743, 1701, 1276, 1254, 1156, 1100, 732, 701 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47 (dd, *J* = 8.7, 2.9 Hz, 1 H), 7.21(td, *J* = 8.8, 2.9 Hz, 1 H), 7.10 (dd, *J* = 8.7, 5.1 Hz, 1 H), 2.60 (s, 3 H), 2.49 (s, 3 H), 1.35 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.07, 197.05, 173.51, 162.59, 160.11, 152.01, 136.27, 136.21, 133.16, 133.13, 132.11, 132.03, 119.38, 119.16, 116.69, 116.46, 83.31, 28.46, 27.70, 26.43.

ESI-HRMS: *m*/*z* calcd for $C_{15}H_{18}FNO_4Na$ [M + Na]$^+$: 318.1112; found: 318.1113.

***tert*-Butyl Acetyl(2-acetyl-4-chlorophenyl)carbamate (12b)**

Following the general procedure **1**, compound **11b** (56 mg) gave **12b** as a yellowish oil; yield: 33 mg (52%).

IR (CH_2Cl_2): 1744, 1697, 1371, 1281, 1245, 1156, 1102, 845 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 2.3 Hz, 1 H), 7.50 (dd, *J* = 8.4, 2.3 Hz, 1 H), 7.07 (d, *J* = 8.4 Hz, 1 H), 2.61 (s, 3 H), 2.51 (s, 3 H), 1.36 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.07, 173.45, 151.83, 136.06, 135.75, 133.84, 132.40, 131.72, 129.72, 83.48, 28.51, 27.73, 26.43.

ESI-HRMS: *m*/*z* calcd for $C_{15}H_{18}ClNO_4Na$ [M + Na]$^+$: 334.0817; found: 334.0818.

***tert*-Butyl Acetyl(2-acetyl-5-chlorophenyl)carbamate (12c)**

Following the general procedure **1**, compound **11c** (56 mg) gave **12c** as yellow solid; yield: 54 mg (86%); mp 86 °C.

IR (CH_2Cl_2): 1745, 1692, 1371, 1276, 1247, 1156, 1105, 764 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 8.4 Hz, 1 H), 7.41 (dd, *J* = 8.4, 2.1 Hz, 1 H), 7.15 (d, *J* = 2.1 Hz, 1 H), 2.62 (d, *J* = 8.7 Hz, 3 H), 2.50 (s, 3 H), 1.36 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.14, 173.39, 151.67, 138.62, 138.15, 133.01, 130.82, 130.77, 128.27, 83.56, 28.54, 27.72, 26.45.

ESI-HRMS: *m*/*z* calcd for $C_{15}H_{18}ClNO_4Na$ [M + Na]$^+$: 334.0817; found: 334.0817.

***tert*-Butyl Acetyl(2-acetyl-4-methoxyphenyl)carbamate (12d)**

Following the general procedure **1**, compound **11d** (49 mg) gave **12d** as a yellowish oil; yield: 39 mg (70%).

IR (CH_2Cl_2): 1738, 1693, 1370, 1281, 1252, 1157, 1042 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29 (d, *J* = 1.3 Hz, 1 H), 7.03 (d, *J* = 1.3 Hz, 2 H), 3.86 (s, 3 H), 2.60 (s, 3 H), 2.49 (s, 3 H), 1.36 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.19, 173.73, 158.68, 152.47, 135.59, 131.20, 129.86, 116.98, 115.74, 82.96, 55.58, 28.56, 27.75, 26.56.

ESI-HRMS: *m*/*z* calcd for $C_{16}H_{21}NO_5Na$ [M + Na]$^+$: 330.1312; found: 330.1316.

***tert*-Butyl Formyl(2-formyl-4-methoxyphenyl)carbamate (14)**

Following the general procedure **1**, compound **13** (43 mg) gave **14** was obtained as a yellowish oil; yield: 39 mg (79%).

IR (CH_2Cl_2): 1742, 1696, 1500, 1276, 1256, 1152, 748 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.90 (s, 1 H), 9.43 (s, 1 H), 7.41 (d, *J* = 2.9 Hz, 1 H), 7.19 (dd, *J* = 8.6, 2.9 Hz, 1 H), 7.12 (d, *J* = 8.6 Hz, 1 H), 3.89 (s, 3 H), 1.47 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.12, 163.23, 159.95, 151.98, 132.90, 131.25, 127.76, 120.43, 116.20, 84.92, 55.74, 27.83.

ESI-HRMS: *m*/*z* calcd for $C_{14}H_{17}NO_5Na$ [M + Na]$^+$: 302.0999; found: 302.1000.

tert-Butyl Acetyl(2-acetyl-5-chloro-4-fluorophenyl)carbamate (16)

Following the general procedure **1**, compound **15** (59 mg) gave **16** as a colorless oil; yield: 48 mg (74%).

IR (CH_2Cl_2): 1747, 1696, 1371, 1281, 1155, 1102, 732 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.57 (d, *J* = 9.0 Hz, 1 H), 7.22 (d, *J* = 6.6 Hz, 1 H), 2.61 (s, 3 H), 2.49 (s, 3 H), 1.38 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.02, 196.00, 173.41, 158.22, 155.71, 151.61, 134.48, 134.43, 133.79, 133.74, 132.68, 125.11, 124.92, 117.58, 117.35, 83.84, 28.43, 27.73, 26.41.

ESI-HRMS: *m*/*z* calcd for $C_{15}H_{17}ClFNO_4Na$ $[M + Na]^+$: 352.0722; found: 352.0724.

tert-Butyl 2,6-Dioxo-3,4,5,6-tetrahydrobenzo[*b*]azocine-1(2*H*)-carboxylate (18)

Following the general procedure **1**, compound **17** (51 mg) gave **8** as a white solid; yield: 40 mg (70%); mp 88 °C.

IR (CH_2Cl_2): 1772, 1730, 1676, 1243, 1145, 731 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.98 (dd, *J* = 7.8, 1.6 Hz, 1 H), 7.58 (td, *J* = 7.8, 1.6 Hz, 1 H), 7.46 (t, *J* = 7.6 Hz, 1 H), 7.27 (d, *J* = 7.6 Hz, 1 H), 2.95 (t, *J* = 8.0 Hz, 2 H), 2.47 (t, *J* = 7.3 Hz, 2 H), 2.09–1.96 (m, 2 H), 1.37 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.38, 172.29, 150.48, 138.67, 136.45, 133.41, 130.73, 129.75, 128.86, 84.03, 40.73, 33.89, 27.69, 21.12.

ESI-HRMS: *m*/*z* calcd for $C_{16}H_{19}NO_4Na$ $[M + Na]^+$: 312.1206; found: 312.1205.

tert-Butyl 2,7-Dioxo-2,3,4,5,6,7-hexahydro-1*H*-benzo[*b*]azonine-1-carboxylate (20)

Following the general procedure **1**, compound **19** (54 mg) gave **20** was obtained as a white solid; yield: 38 mg (62%); mp 135 °C.

IR (CH_2Cl_2): 1732, 1698, 1451, 1288, 1152, 1115 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.51 (td, *J* = 7.6, 1.0 Hz, 1 H), 7.47 (dd, *J* = 7.6, 1.0 Hz, 1 H) 7.39 (td, *J* = 7.6, 1.0 Hz, 1 H), 7.23 (d, *J* = 7.6 Hz, 1 H), 3.26 (s, 1 H), 2.76 (d, *J* = 4.8 Hz, 2 H), 2.46 (s, 1 H), 2.08 (s, 1 H), 1.90 (d, *J* = 5.7 Hz, 3 H), 1.46 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.32, 177.82, 151.85, 139.26, 136.88, 131.43, 129.07, 128.25, 128.02, 83.97, 41.50, 38.51, 27.84, 26.26, 24.55.

ESI-HRMS: *m*/*z* calcd for $C_{17}H_{21}NO_4Na$ $[M + Na]^+$: 326.1363; found: 326.1361.

4-Quinolone-3-carboxylic Acid Derivatives; General Procedure 2 (Scheme 2)

To a 0.1 M solution of indole-3-acetic acid derivative (0.2 mmol, 1 equiv) in trifluoroethanol was added methylene blue (2 mol%). The reaction mixture was irradiated with blue LEDs in the open air for 36 h. The mixture was filtered and the filter cake was rinsed with EtOAc. The filtrate was treated with 10 equiv of silica gel and the mixture was stirred overnight. After removal of the solvent under reduced pressure, the residue was purified by column chromatography to give the corresponding desired 4-quinolone-3-carboxylic acid derivative.

1-tert-Butyl 3-Ethyl 6-Methyl-4-oxoquinoline-1,3(4*H*)-dicarboxylate (21)

Following the general procedure **2**, quinolone **21** was obtained as a white solid; yield: 50 mg (76%); mp 190 °C.

IR (CH_2Cl_2): 1611, 1277, 1234, 1136, 763 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.11 (s, 1 H), 8.38 (d, *J* = 8.9 Hz, 1 H), 8.22 (s, 1 H), 7.47 (dd, *J* = 8.9, 1.8 Hz, 1 H), 4.40 (q, *J* = 7.1 Hz, 2 H), 2.45 (s, 3 H), 1.69 (s, 9 H), 1.40 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.94, 164.81, 149.21, 144.63, 136.06, 135.35, 134.02, 127.79, 126.80, 119.60, 113.08, 87.66, 61.19, 27.83, 20.81, 14.26.

ESI-HRMS: *m*/*z* calcd for $C_{18}H_{21}NO_5Na$ $[M + Na]^+$: 354.1312; found: 354.1304.

1-tert-Butyl 3-Ethyl 6-Methoxy-4-oxoquinoline-1,3(4*H*)-dicarboxylate (22)

Following the general procedure **2**, quinolone **22** was obtained as a yellow solid; yield: 37 mg (54%); mp 310 °C.

IR (CH_2Cl_2): 1744, 1682, 1489, 1244, 1137, 1020, 734 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.12 (s, 1 H), 8.45 (d, *J* = 9.5 Hz, 1 H), 7.86 (d, *J* = 3.1 Hz, 1 H), 7.25 (dd, *J* = 9.5, 3.1 Hz, 1 H), 4.41 (q, *J* = 7.1 Hz, 2 H), 3.91 (s, 3 H), 1.70 (s, 9 H), 1.42 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.54, 164.95, 157.45, 149.17, 144.22, 131.59, 129.47, 122.35, 121.49, 112.49, 107.04, 87.75, 61.22, 55.66, 27.82, 14.26.

ESI-HRMS: *m*/*z* calcd for $C_{18}H_{21}NO_6Na$ $[M + Na]^+$: 370.1261; found: 370.1254.

1-tert-Butyl 3-Ethyl 6-Bromo-4-oxoquinoline-1,3(4*H*)-dicarboxylate (23)

Following the general procedure **2**, quinolone **23** was obtained as a yellow solid; yield: 66 mg (84%); mp 341 °C.

IR (CH_2Cl_2): 1682, 1421, 1264, 1137, 733 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.14 (s, 1 H), 8.55 (d, *J* = 2.3 Hz, 1 H), 8.44 (d, *J* = 9.3 Hz, 1 H), 7.75 (dd, *J* = 9.3, 2.4 Hz, 1 H), 4.41 (q, *J* = 7.1 Hz, 2 H), 1.70 (s, 9 H), 1.41 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.50, 164.35, 148.81, 145.01, 136.32, 135.75, 129.85, 129.39, 121.79, 120.15, 113.52, 88.40, 61.42, 27.81, 14.24.

ESI-HRMS: *m*/*z* calcd for $C_{17}H_{18}BrNO_5Na$ $[M + Na]^+$: 418.0261; found: 418.0254.

tert-Butyl 4-Oxo-3-(phenylcarbamoyl)quinoline-1(4*H*)-carboxylate (24)

Following the general procedure **2**, compound **24** was obtained as a yellowish oil; yield: 53 mg (73%).

IR (CH_2Cl_2): 1766, 1681, 1605, 1552, 1473, 1279, 1232, 1136, 663 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 11.88 (s, 1 H), 9.52 (s, 1 H), 8.61 (d, *J* = 8.8 Hz, 1 H), 8.52 (d, *J* = 8.1 Hz, 1 H), 7.77 (t, *J* = 8.7 Hz, 3 H), 7.56 (t, *J* = 8.4 Hz, 1 H), 7.37 (t, *J* = 7.8 Hz, 2 H), 7.14 (t, *J* = 7.1 Hz, 1 H), 1.74 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.08, 161.71, 144.95, 137.85, 133.49, 128.91, 126.82, 126.21, 124.13, 120.46, 119.86, 113.14, 88.37, 27.81.

ESI-HRMS: *m*/*z* calcd for $C_{21}H_{20}N_2O_{44}Na$ $[M + Na]^+$: 387.1315; found: 387.1312.

tert-Butyl 3-[(4-Fluorophenyl)carbamoyl]-4-oxoquinoline-1(4*H*)-carboxylate (25)

Following the general procedure **2**, compound **25** was obtained as a yellowish solid; yield: 32 mg (85%); mp 360 °C.

IR (CH_2Cl_2): 1760, 1662, 1621, 1525, 1481, 1280, 1199, 1121 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.49 (s, 1 H), 8.59 (d, *J* = 8.8 Hz, 1 H), 8.49 (dd, *J* = 8.0, 1.2 Hz, 1 H), 7.74 (ddd, *J* = 9.0, 7.8, 3.2 Hz, 3 H), 7.54 (t, *J* = 7.5 Hz, 1 H), 7.05 (t, *J* = 8.7 Hz, 2 H), 1.73 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.05, 161.67, 160.45, 158.04, 149.05, 144.91, 137.83, 134.39, 134.36, 133.52, 126.82, 126.78, 126.23, 122.03, 121.95, 119.86, 115.61, 115.39, 112.92, 88.43, 27.80.

ESI-HRMS: *m*/*z* calcd for $C_{21}H_{19}FN_2O_4Na$ $[M + Na]^+$: 405.1221; found: 405.1220.

1-*tert*-Butyl 3-Methyl 4-oxoquinoline-1,3(4*H*)-dicarboxylate (27)

Following the general procedure **2**, quinolone **27** was obtained as a white solid; yield: 48 mg (80%); mp 154 °C.

IR (CH_2Cl_2): 1646, 1611, 1470, 1278, 1262, 1137, 732 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.15 (s, 1 H), 8.48 (d, *J* = 8.8 Hz, 1 H), 8.45 (dd, *J* = 8.0, 1.6 Hz, 1 H), 7.72–7.64 (m, 1 H), 7.46 (t, *J* = 11.5 Hz, 1 H), 3.95 (s, 3 H), 1.70 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.79, 165.45, 149.13, 145.22, 137.43, 132.86, 127.94, 127.32, 126.05, 119.70, 112.97, 87.98, 52.38, 27.82.

ESI-HRMS: *m*/*z* calcd for $C_{16}H_{17}NO_5Na$ $[M + Na]^+$: 326.0999; found: 326.0998.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1592006.

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