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Rose bengal as photocatalyst: visible light-mediated Friedel–Crafts alkylation of indoles with nitroalkenes in water†

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A novel and facile visible-light-mediated alkylation of indoles and nitroalkenes has been developed. In this protocol, rose bengal acts as a photosensitizer, and environmentally benign water was used as the green and efficient reaction medium. Indoles reacted smoothly with nitroalkenes under the irradiation of visible-light and generated corresponding 3-(2-nitroalkyl)indoles in moderate to good yields (up to 87%).

Introduction

Indole is a versatile building block that is widely used to synthesize bioactive natural products and drugs. The addition of indoles to electron-deficient-olefins, which can be considered as a Friedel–Crafts type alkylation, is a significant reaction in the formation of key C–C bonds.¹

Many useful methods for preparing 3-(2-nitroalkyl)indoles have been reported by predecessors. For the past few years, several groups have been devoted to realizing asymmetric Friedel–Crafts alkylation of indoles with nitroalkenes by designing various kinds of new chiral catalysts, such as thio-urea, azaindole, sulfonamide² and organic metal complexes catalysts.^{3,4} In spite of the efficiency and generality of these reactions, it remains not enough for green and sustainable chemistry because these methods still involve the use of organic solvents, such as toluene and chloroform. Therefore, the development of a facile, efficient, economic and eco-friendly method to construct 3-(2-nitroalkyl)indoles is still highly desirable. Taking into account the ecological and sustainable point of view, water-soluble organic catalytic systems⁵ have attracted continuously increasing attention for applications in organic synthesis. Nevertheless, as a green alternative to organic solvents, the catalysis of reaction in water is still a major challenge in synthetic chemistry.⁶ In 2008, water has previously been found to drive the Michael reaction of indoles with nitroalkenes without the assistance of any catalyst, as reported by Jérôme and co-workers,⁷ but this method has the disadvantages of high reaction temperature (90 °C) and long reaction

time (24 h). Besides, although impressive works have been accomplished in various Lewis acid catalytic systems in water, such as InBr₃, CeCl₃ and Sc(OTf)₃,⁸ little is still known in the aqueous organic catalytic system.

In 2016, Jagdamba and coworkers developed a novel visible-light mediated method on the synthesis of 3-substituted indoles, employing green LED as light source in ethanol. The reaction has mild conditions and good to excellent yields, but only eight substrates were expanded.⁹ Wu and co-workers further investigated into the direct alkylation of unfunctionalized C–H bonds *via* photoredox induced radical cation deprotonation.⁹ Organic photoredox catalyst eosin-Y and 9-mesityl-10-methylacridinium ion (Mes–Acr⁺) have been employed in C–H bond activation for electron-deficient olefins. Compared with metal-containing photocatalyst, organic dyes such as eosin Y, rose bengal and fluorescein¹⁰ are mild in reaction conditions and easier to modify. In recent years, numerous works were reported using organic dyes¹¹ as photoredox catalysts under visible light irradiation from low power source.

According to R. Lambert's research¹² in 1997, which reported the triplet state rose bengal's reduction potential was 1.77 eV. That is, the reduction quenching will be thermodynamically favorable for indoles with relatively lower reduction potentials.¹³ To the best of our knowledge, rose bengal involved, visible light-mediated Friedel–Crafts alkylation of indoles with nitroalkenes in water has not been reported yet. In this process, the reaction was performed under a more gentle conditions in totally green solvent, combining the advantage of the high efficiency of photoinduced electron transfer (PET) process (Scheme 1).¹⁴

Results and discussion

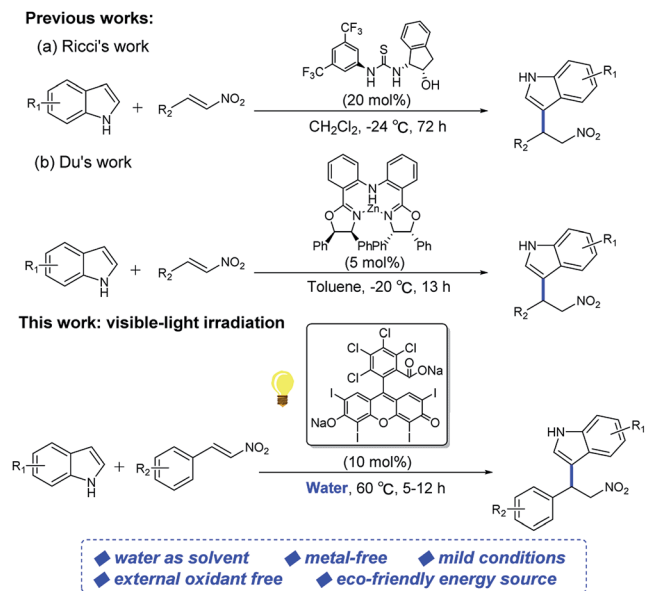
Initially, the visible light mediated alkylation of indoles with nitroalkenes was probed with *N*-methyl indole (**1a**) and (*E*)-2-nitroethenylbenzene (**2a**) as model substrates. Various kinds of photosensitizers were firstly investigated for the process. The

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Scheme 1 Comparative approaches for direct synthesis of 3-(2-nitroalkyl)indoles between the reported and this work.

reaction was carried out in tetrahydrofuran under the irradiation of 21 W white LED light (Table 1, entries 1–5). Among the photosensitizers tested, rose bengal showed the best catalytic

Table 1 Alkylation of *N*-methyl indole (**1a**)^a and (*E*)-2-nitroethenylbenzene (**2a**)^a

| Entry | Catalyst | Solvent | Yield ^b (%) |
|-------------------|---|---------------|------------------------|
| 1 | Eosin Y | THF | 26 |
| 2 | Eosin B | THF | 21 |
| 3 | Mes-Acr ⁺ (ClO ₄ [−]) | THF | Trace |
| 4 | Rose bengal | THF | 31 |
| 5 | Methylene blue | THF | Trace |
| 6 | Rose bengal | Toluene | Trace |
| 7 | Rose bengal | Paraxylene | 21 |
| 8 | Rose bengal | Cyclohexane | Trace |
| 9 | Rose bengal | Diethyl ether | 35 |
| 10 | Rose bengal | Ethyl acetate | 20 |
| 11 | Rose bengal | Acetone | 24 |
| 12 | Rose bengal | Methanol | Trace |
| 13 | Rose bengal | Water | 54 |
| 14 ^c | Rose bengal | Water | 61 |
| 15 ^{c,d} | Rose bengal | Water | 18 |
| 16 ^c | None | Water | 32 |
| 17 ^{c,d} | None | Water | 17 |

^a Unless otherwise specified, *N*-methyl indole **1a** (39.4 mg, 0.3 mmol), (*E*)-2-nitroethenylbenzene **2a** (44.7 mg, 0.3 mmol), and catalyst (0.015 mmol, 5 mol%), were added to a test tube equipped with a stirring bar and dissolved in 3 mL solvent. The mixture was stirred in air with exposure to 21 W white LED lamps at 20 °C for 24 h.

^b Isolated yields. ^c Reaction was performed at 60 °C for 6 h. ^d Reaction was performed in darkness.

effect, **3a** was obtained in 31% yield. In spite of different kinds of organic solvents were examined for this catalytic system, poor yields were obtained (Table 1, entries 6–12). In contrast, reactions in THF and diethyl ether which have lower solubility to the system achieved relatively high yields (Table 1, entries 1, 9). Therefore, it is reducing the solubility of reaction system that may promote the reaction. To our delight, when water was used as the solvent, **3a** was obtained in 54% yield (Table 1, entry 13). Control experiments were carried out in darkness or in the absence rose bengal, the yield decreased dramatically, thus verifying light and rose bengal are pivotal in the reaction (Table 1, entries 14–17).

To further optimize the reaction conditions, the effect of reaction temperature was investigated. To our delight, when reaction temperature raised from 20 °C to 60 °C, yield increased from 54% to 61% (Table 2, entries 1–3). What's more, reaction time reduced from 18 hours to 7 hours. On the contrary, when the reaction temperature continued to rise, side reaction increased, and the yield decreased to 53% (Table 2, entry 4). Taking the effect of the catalyst loading into account, the loading of catalyst was firstly reduced from 5 mol% to 0.5 mol%. However, as the catalyst loading reduced, reaction yield decreased from 61% to 52% (Table 2, entries 4–7), and the reaction time increased from 7 h to 12 h. Increasing catalyst loading to 10 mol%, yield of **3a** raised to 64% (Table 2, entry 8). However, yield of **3a** did not increase obviously when the catalyst loading raised to 20 mol% (Table 2, entry 9). Therefore, 10 mol% of rose bengal was chosen as the best photosensitizer loading. Subsequently, the molar ratio of substrates was

Table 2 Optimization of reaction conditions^a

| Entry | 1a : 2a | Cat (%) | Temp (°C) | Time (h) | Yield ^b (%) |
|-------|----------|---------|-----------|----------|------------------------|
| 1 | 1 : 1 | 5 | 20 | 18 | 54 |
| 2 | 1 : 1 | 5 | 40 | 10 | 58 |
| 3 | 1 : 1 | 5 | 60 | 7 | 61 |
| 4 | 1 : 1 | 5 | 80 | 2 | 53 |
| 5 | 1 : 1 | 3 | 60 | 9 | 58 |
| 6 | 1 : 1 | 1 | 60 | 10 | 56 |
| 7 | 1 : 1 | 0.5 | 60 | 12 | 52 |
| 8 | 1 : 1 | 10 | 60 | 5 | 64 |
| 9 | 1 : 1 | 20 | 60 | 5 | 66 |
| 10 | 1 : 1.5 | 10 | 60 | 5 | 69 |
| 11 | 1 : 1.25 | 10 | 60 | 5 | 63 |
| 12 | 1 : 1 | 10 | 60 | 5 | 58 |
| 13 | 1.25 : 1 | 10 | 60 | 5 | 43 |
| 14 | 1.5 : 1 | 10 | 60 | 5 | 42 |

^a *N*-Methyl indole **1a** (39.4 mg, 0.3 mmol), (*E*)-2-nitroethenylbenzene **2a** and catalyst were added to a test tube equipped with a stirring bar and dissolved in water (3 mL) under the exposure of 21 W white LED lamps.

^b Isolated yields.



screened, when the ratio of *N*-methyl indole and (*E*)-2-nitroethenylbenzene was 1 : 1.5, **3a** was generated in the highest yield of 69% (Table 2, entries 10–14).

Under the optimum reaction conditions, indoles and (*E*)-2-nitroethenylbenzenes with different kinds of substituents were investigated and the results were summarized in Table 3. (*E*)-2-Nitroethenylbenzene with divers functional groups at *para* position can smoothly carry out the Friedel–Crafts alkylation reaction with *N*-methyl indoles and afforded the desired products (**3b–3d**) in 75–81% yields, the *para*-fluoro-substituted (*E*)-2-nitroethenylbenzene substrate is capable of achieving a yield of up to 82%. Substrates with different functional groups attached to the indole ring were further investigated. It was gratifying to find that the substrates with both electron donating and electron withdrawing groups reacted smoothly and generated corresponding products (**3f–3n**) in 57–81% yields. In order to further demonstrate the tolerance of functional group, several

substrates with substituents on the benzene ring of (*E*)-2-nitroethenylbenzenes were performed under this protocol. To our delight, (*E*)-2-nitroethenylbenzenes with electron withdrawing groups generated desired products (**3p–3t**) in 82–87% yields. What's more, 2-nitrovinylthiophene also reacted with 2-methylindole smoothly, and the corresponding product (**3o**) was obtained in 81% yield.

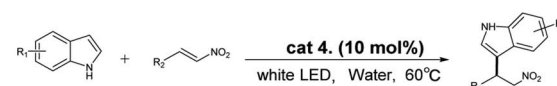
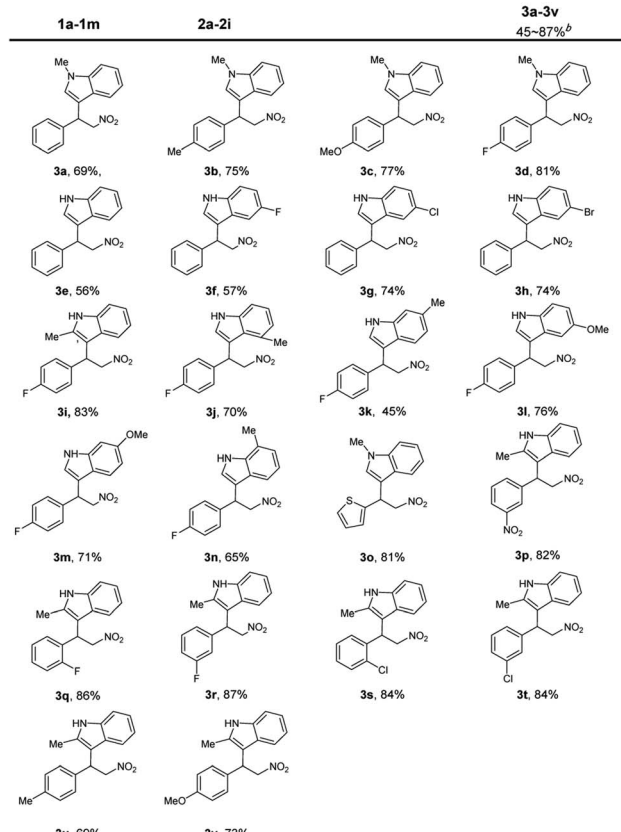
The reaction was scaled up to gram scale. Under the optimized reaction conditions, 2-methylindole **1i** (1.318 g, 10 mmol) was treated with 4-fluoro-β-(*E*)-2-nitroethenylbenzene **2e** (2.51 g, 15 mmol). Corresponding alkylated product **3i** was obtained in 82% yield (Scheme 2).

In order to expound the mechanism of the process, a series of control experiments were carried out (Scheme 3). A trace amount of expected product **3a** was observed in the presence of 2 equiv. of radical scavenger (TEMPO). And the raw material **1a** was nearly quantitatively recovered (Scheme 3a). To further investigate whether oxygen is involved in this process, control experiments under oxygen and nitrogen atmosphere were performed (Scheme 3b). The results turned that oxygen is unnecessary in the reaction.

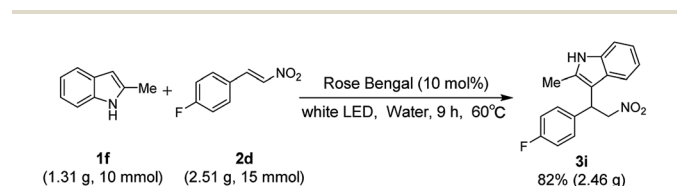
Cyclic voltammetry experiments were performed in a CH Instruments Electrochemical Analyzer. From the result, $E_{1/2ox}$ (**4**) = −1.211 V vs. SCE (Fig. 1) is higher than $E_{1/2red}$ (**1a**) = −1.977 V vs. SCE (Fig. 2) so the photoredox reaction between rose bengal **4** and *N*-methyl indole (**1a**) could occur spontaneously. (Fig. S1 and S2†).

Based on the experiment results and relevant references, plausible mechanism of this transformation was established. Due to the high oxidizing power of excited state rose bengal,^{14,15} olefins could be conveniently oxidized to radical cations by **4**^{*}. We proposed that the radical cation **I** tends to deprotonate to give the radical **II**.³ Addition of **II** to a Michael acceptor such as (*E*)-2-nitroethenylbenzene **2a** will give alkyl **III**. Electron-

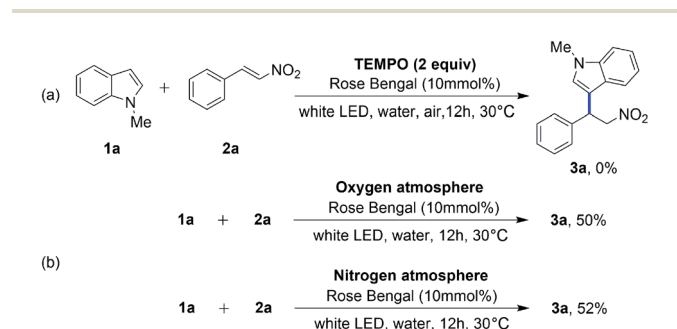
Table 3 Visible-light induced Friedel–Craft alkylation of indoles with nitroalkenes in the presence of rose bengal^a

|  | |
|--|-----------------|
| 1a-1m | 2a-2i |
|  | |
| 3a , 69% | 3b , 75% |
| 3c , 77% | 3d , 81% |
| 3e , 56% | 3f , 57% |
| 3g , 74% | 3h , 74% |
| 3i , 83% | 3j , 70% |
| 3k , 45% | 3l , 76% |
| 3m , 71% | 3n , 65% |
| 3o , 81% | 3p , 82% |
| 3q , 86% | 3r , 87% |
| 3s , 84% | 3t , 84% |
| 3u , 69% | 3v , 73% |

^a Indole **1a–1m** (1 equiv. 0.3 mmol), *trans*-β-nitrostyrenes **2a–2j** (1.5 equiv. 0.45 mmol), water (3 mL) and 10 mol% of the rose bengal under a 21 W white LED lamps at 60 °C for 12 h. ^b Isolated yield by column chromatography.

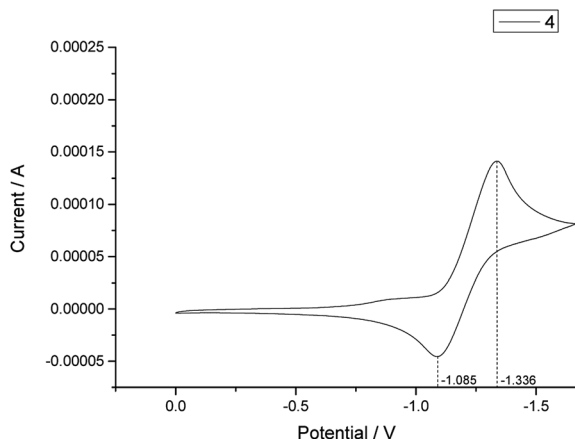
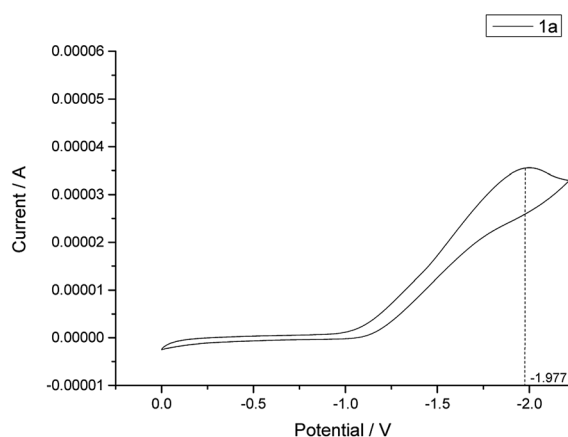


Scheme 2 Gram scale Friedel–Crafts alkylation reaction.

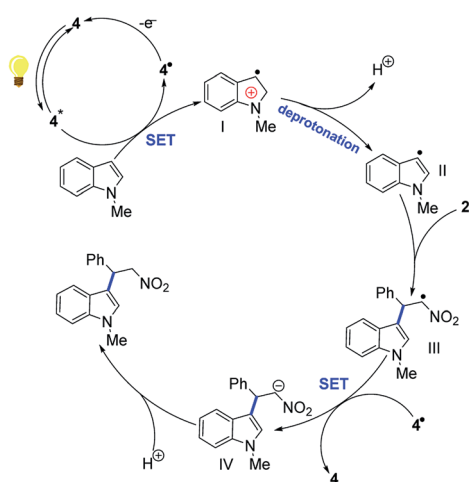


Scheme 3 Control experiment.



Fig. 1 Cyclic voltammetry experiment of **4**.Fig. 2 Cyclic voltammetry experiment of **1a**.

concentrating group **III** was reduced by the rose bengal catalyst **4**^{*}, and deliver the alkylated product **3a** after protonation while regenerating the photocatalyst **4** (Scheme 4).¹⁶



Scheme 4 Plausible mechanism.

Conclusions

In summary, we have developed a visible-light-mediated alkylation of indoles with nitroalkenes employing rose bengal as the photocatalyst. Various types of nitroalkylated indoles were obtained in 45–87% yields. Compared with the previous methods, this process is environmental friendly, using water as the solvent without any bases and metals being involved. As a result, the method is simple in operation, mild in condition and high in atomic economy.

Experimental

General

Unless otherwise stated, all commercial reagents and solvents were used without further additional purification. Purification of reaction products was carried out with chromatography on silica gel 60 (200–400 mesh). ¹H NMR (400 MHz) or (500 MHz) spectra was obtained at 25 °C; ¹³C NMR (101 MHz) were recorded on a Varian INOVA-400M and AVANCE II 400 spectrometer at 25 °C. Chemical shifts are reported as δ (ppm) values relative to TMS as internal standard and coupling constants (*J*) in Hz. HPLC analysis were performed on a waters liquid chromatograph equipped with a Yilite SinoChrom ODS-BP 5 μ m column (4.6 mm \times 250 mm), using mixtures of methanol/H₂O as mobile phase, at 25 °C. HRMS analysis were performed on LTQ Orbitrap XL of Thermo Scientific. Cyclic voltammetry (CV) experiments were performed on CHI600E of Chenhua.

General procedure for the catalytic Friedel–Crafts reaction

In a dry vial bottle equipped with magnetic stirrer was added rose bengal (33.9 mg, 0.03 mmol), *N*-methylindole (41.0 mg, 0.3 mmol) and nitroalkenes (69.2 mg, 0.45 mmol) under an air atmosphere followed by the addition of water (3 mL). The solution was stirred under the irradiation of 21 W white LED lamps for 5 hours at 60 °C. The resulting suspension was cooled to room temperature. The aqueous layer was extracted with ethyl acetate (5 \times 3 mL). The combined organic layer was dried over anhydrous Na₂SO₄ and filtered. The solvent was evaporated under reduced pressure. The residue was purified through silica gel column chromatography using hexane/ethyl acetate (5 : 1) as the eluent to afford 1-methyl-3-(2-nitro-1-phenylethyl)-1*H*-indole. There is about 5.0 cm distance between the lamps and reactors. The light intensity of the reaction system is 50 000 lux.

1-Methyl-3-(2-nitro-1-phenylethyl)-1*H*-indole (**3a**)

Compound **3a** was purified through silica gel column chromatography using hexane/ethyl acetate (5 : 1) as the eluent and was obtained as a yellow liquid, yield: 0.061 g, 71%; ¹H NMR (500 MHz, CDCl₃): δ 7.44 (d, *J* = 8.0 Hz, 1H), 7.37–7.17 (m, 7H), 7.07 (t, *J* = 7.5 Hz, 1H), 6.85 (s, 1H), 5.17 (t, *J* = 8.0 Hz, 1H), 5.04 (dd, *J* = 12.5, 7.5 Hz, 1H), 4.92 (dd, *J* = 12.6, 8.5 Hz, 1H), 3.73 (s, 3H).

1-Methyl-3-(2-nitro-1-(*p*-tolyl)ethyl)-1*H*-indole (**3b**)

Compound **3b** was purified through silica gel column chromatography using hexane/ethyl acetate (5 : 1) as the eluent and was obtained as a yellow liquid, yield: 0.066 g, 75%; ¹H NMR (500 MHz, CDCl₃): δ 7.43 (d, *J* = 8.0 Hz, 1H), 7.25 (d, *J* = 8.2 Hz, 1H),



7.20 (dd, $J = 7.6, 4.6$ Hz, 3H), 7.09 (d, $J = 7.8$ Hz, 2H), 7.04 (t, $J = 7.5$ Hz, 1H), 6.80 (s, 1H), 5.11 (t, $J = 8.1$ Hz, 1H), 4.98 (dd, $J = 12.5, 7.5$ Hz, 1H), 4.86 (dd, $J = 12.5, 8.6$ Hz, 1H), 3.66 (s, 3H), 2.28 (s, 3H).

3-(1-(4-Methoxyphenyl)-2-nitroethyl)-1-methyl-1H-indole (3c). Compound **3c** was purified through silica gel column chromatography using hexane/ethyl acetate (5 : 1) as the eluent and was obtained as a yellow liquid, yield: 0.071 g, 77%; ^1H NMR (500 MHz, CDCl_3): δ 7.43 (dd, $J = 8.2, 1.2$ Hz, 1H), 7.36–7.14 (m, 4H), 7.05 (ddd, $J = 8.0, 7.0, 1.1$ Hz, 1H), 6.83 (d, $J = 8.6$ Hz, 3H), 5.11 (t, $J = 8.0$ Hz, 1H), 5.00 (dd, $J = 12.4, 7.4$ Hz, 1H), 4.86 (dd, $J = 12.4, 8.6$ Hz, 1H), 3.74 (s, 3H), 3.70 (s, 3H).

3-(1-(4-Fluorophenyl)-2-nitroethyl)-1-methyl-1H-indole (3d). Compound **3d** was purified through silica gel column chromatography using hexane/ethyl acetate (5 : 1) as the eluent and was obtained as a yellow liquid, yield: 0.073 g, 81%; ^1H NMR (500 MHz, CDCl_3): δ 7.39 (d, $J = 8.0$ Hz, 1H), 7.28 (dt, $J = 8.9, 2.5$ Hz, 3H), 7.21 (dd, $J = 9.5, 5.8$ Hz, 1H), 7.06 (t, $J = 7.5$ Hz, 1H), 6.98 (t, $J = 8.5$ Hz, 2H), 6.82 (s, 1H), 5.14 (t, $J = 8.0$ Hz, 1H), 5.00 (dd, $J = 12.5, 7.4$ Hz, 1H), 4.86 (dd, $J = 12.6, 8.7$ Hz, 1H), 3.71 (s, 3H).

3-(2-Nitro-1-phenylethyl)-1H-indole (3e). Compound **3e** was purified through silica gel column chromatography using hexane/ethyl acetate (5 : 1) as the eluent and was obtained as a yellow liquid, yield: 0.045 g, 56%; ^1H NMR (500 MHz, CDCl_3): δ 8.02 (s, 1H), 7.42 (d, $J = 8.0$ Hz, 1H), 7.29 (d, $J = 6.9$ Hz, 5H), 7.25–7.20 (m, 1H), 7.17 (t, $J = 7.6$ Hz, 1H), 7.05 (t, $J = 7.5$ Hz, 1H), 6.93 (d, $J = 2.5$ Hz, 1H), 5.15 (t, $J = 8.0$ Hz, 1H), 5.01 (dd, $J = 12.5, 7.7$ Hz, 1H), 4.90 (dd, $J = 12.6, 8.4$ Hz, 1H).

5-Fluoro-3-(2-nitro-1-phenylethyl)-1H-indole (3f). Compound **3f** was purified through silica gel column chromatography using hexane/ethyl acetate (5 : 1) as the eluent and was obtained as a yellow liquid, yield: 0.051 g, 57%; ^1H NMR (500 MHz, CDCl_3): δ 8.11 (s, 1H), 7.33–7.16 (m, 6H), 7.05–7.00 (m, 2H), 6.90 (td, $J = 9.0, 2.5$ Hz, 1H), 5.08 (t, $J = 7.9$ Hz, 1H), 5.00 (dd, $J = 12.4, 8.0$ Hz, 1H), 4.89 (dd, $J = 12.3, 7.9$ Hz, 1H).

5-Chloro-3-(2-nitro-1-phenylethyl)-1H-indole (3g). Compound **3g** was purified through silica gel column chromatography using hexane/ethyl acetate (5 : 1) as the eluent and was obtained as a yellow liquid, yield: 0.067 g, 74%; ^1H NMR (500 MHz, CDCl_3): δ 8.15 (s, 1H), 7.39–7.21 (m, 7H), 7.12 (dd, $J = 8.6, 2.0$ Hz, 1H), 7.04 (dd, $J = 10.8, 2.5$ Hz, 1H), 5.11 (t, $J = 8.0$ Hz, 1H), 5.06–4.94 (m, 1H), 4.90 (dd, $J = 12.5, 7.9$ Hz, 1H).

5-Bromo-3-(2-nitro-1-phenylethyl)-1H-indole (3h). Compound **3h** was purified through silica gel column chromatography using hexane/ethyl acetate (5 : 1) as the eluent and was obtained as a yellow liquid, yield: 0.076 g, 74%; ^1H NMR (500 MHz, CDCl_3): δ 8.14 (s, 1H), 7.54 (d, $J = 1.7$ Hz, 1H), 7.32 (t, $J = 1.3$ Hz, 1H), 7.31–7.28 (m, 2H), 7.29–7.25 (m, 2H), 7.24 (d, $J = 1.7$ Hz, 1H), 7.18 (d, $J = 8.6$ Hz, 1H), 7.03 (d, $J = 2.6$ Hz, 1H), 5.11 (t, $J = 8.0$ Hz, 1H), 5.03–4.97 (m, 1H), 4.90 (dd, $J = 12.6, 8.0$ Hz, 1H).

3-(1-(4-Fluorophenyl)-2-nitroethyl)-2-methyl-1H-indole (3i). Compound **3i** was purified through silica gel column chromatography using hexane/ethyl acetate (5 : 1) as the eluent and was obtained as a yellow liquid, yield: 0.105 g, 83%; ^1H NMR (500 MHz, CDCl_3): δ 8.09 (s, 1H), 7.45 (d, $J = 1.6$ Hz, 1H), 7.27–7.21 (m, 1H), 7.20–7.07 (m, 5H), 6.98 (d, $J = 2.5$ Hz, 1H), 5.08 (t, $J =$

8.0 Hz, 1H), 4.99 (dd, $J = 12.4, 8.0$ Hz, 1H), 4.88 (dd, $J = 12.4, 7.9$ Hz, 1H), 2.29 (s, 3H).

3-(1-(4-Fluorophenyl)-2-nitroethyl)-4-methyl-1H-indole (3j). Compound **3j** was purified through silica gel column chromatography using hexane/ethyl acetate (5 : 1) as the eluent and was obtained as a yellow liquid, yield: 0.062 g, 70%; ^1H NMR (500 MHz, CDCl_3): δ 8.15–7.95 (m, 1H), 7.32–7.27 (m, 2H), 7.26 (d, $J = 4.7$ Hz, 1H), 7.09–6.81 (m, 5H), 5.16 (t, $J = 8.0$ Hz, 1H), 5.05 (dd, $J = 12.5, 7.4$ Hz, 1H), 4.90 (dd, $J = 12.5, 8.6$ Hz, 1H), 2.47 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3): δ 163.29, 160.85, 136.13, 129.40, 129.32, 125.51, 123.34, 121.15, 120.69, 120.30, 116.57, 115.91, 115.70, 114.77, 79.54, 40.99, 16.51. HRMS (m/z): (ESI) calcd for $\text{C}_{17}\text{H}_{15}\text{FN}_2\text{O}_2$ [$\text{M} + \text{H}$] $^+$: 219.1190, found: 219.1196.

3-(1-(4-Fluorophenyl)-2-nitroethyl)-6-methyl-1H-indole (3k). Compound **3k** was purified through silica gel column chromatography using hexane/ethyl acetate (5 : 1) as the eluent and was obtained as a yellow liquid, yield: 0.041 g, 45%; ^1H NMR (500 MHz, CDCl_3): δ 7.98 (s, 1H), 7.35–7.21 (m, 3H), 7.15 (s, 1H), 7.06–6.96 (m, 2H), 6.96–6.83 (m, 2H), 5.14 (t, $J = 8.0$ Hz, 1H), 5.04 (dd, $J = 12.5, 7.4$ Hz, 1H), 4.88 (dd, $J = 12.4, 8.6$ Hz, 1H), 2.43 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3): δ 163.31, 160.87, 137.03, 135.09, 132.80, 129.43, 123.83, 121.85, 120.83, 118.52, 115.92, 115.71, 114.13, 111.40, 79.60, 40.97, 21.66. HRMS (m/z): (ESI) calcd for $\text{C}_{17}\text{H}_{15}\text{FN}_2\text{O}_2$ [$\text{M} + \text{H}$] $^+$: 219.1190, found: 219.1197.

3-(1-(4-Fluorophenyl)-2-nitroethyl)-5-methoxy-1H-indole (3l). Compound **3l** was purified through silica gel column chromatography using hexane/ethyl acetate (5 : 1) as the eluent and was obtained as a yellow liquid, yield: 0.072 g, 76%; ^1H NMR (500 MHz, CDCl_3): δ 8.04 (s, 1H), 7.25 (dd, $J = 8.3, 5.3$ Hz, 2H), 7.18 (d, $J = 8.8$ Hz, 1H), 6.96 (t, $J = 8.5$ Hz, 2H), 6.93–6.89 (m, 1H), 6.84 (dd, $J = 8.8, 2.3$ Hz, 1H), 6.79 (d, $J = 2.5$ Hz, 1H), 5.08 (t, $J = 8.0$ Hz, 1H), 4.98 (dd, $J = 12.4, 7.5$ Hz, 1H), 4.84 (dd, $J = 12.5, 8.5$ Hz, 1H), 3.75 (s, 3H).

3-(1-(4-Fluorophenyl)-2-nitroethyl)-6-methoxy-1H-indole (3m). Compound **3m** was purified through silica gel column chromatography using hexane/ethyl acetate (5 : 1) as the eluent and was obtained as a yellow liquid, yield: 0.067 g, 71%; ^1H NMR (500 MHz, CDCl_3): δ 8.00 (s, 1H), 7.35–7.17 (m, 3H), 7.04–6.93 (m, 2H), 6.88 (dd, $J = 2.5, 0.9$ Hz, 1H), 6.82 (d, $J = 2.2$ Hz, 1H), 6.73 (dd, $J = 8.7, 2.3$ Hz, 1H), 5.10 (t, $J = 7.9$ Hz, 1H), 5.01 (dd, $J = 12.4, 7.4$ Hz, 1H), 4.86 (dd, $J = 12.4, 8.5$ Hz, 1H), 3.80 (s, 3H). HRMS (m/z): (ESI) calcd for $\text{C}_{17}\text{H}_{15}\text{FN}_2\text{O}_3$ [$\text{M} + \text{H}$] $^+$: 315.1140, found: 315.1140.

3-(1-(4-Fluorophenyl)-2-nitroethyl)-7-methyl-1H-indole (3n). Compound **3n** was purified through silica gel column chromatography using hexane/ethyl acetate (5 : 1) as the eluent and was obtained as a yellow liquid, yield: 0.058 g, 65%; ^1H NMR (500 MHz, CDCl_3): δ 8.15 (s, 1H), 7.28–7.14 (m, 3H), 7.14–7.04 (m, 2H), 7.03–6.94 (m, 2H), 6.81 (d, $J = 7.2$ Hz, 1H), 5.52 (t, $J = 8.1$ Hz, 1H), 4.95 (dd, $J = 12.6, 8.3$ Hz, 1H), 4.81 (dd, $J = 12.6, 7.9$ Hz, 1H), 2.53 (s, 3H). HRMS (m/z): (ESI) calcd for $\text{C}_{17}\text{H}_{15}\text{FN}_2\text{O}_2$ [$\text{M} + \text{H}$] $^+$: 219.1190, found: 219.1194.

1-Methyl-3-(2-nitro-1-(thiophen-2-yl)ethyl)-1H-indole (3o). Compound **3o** was purified through silica gel column chromatography using hexane/ethyl acetate (5 : 1) as the eluent and was



obtained as a yellow liquid, yield: 0.070 g, 81%; ^1H NMR (500 MHz, CDCl_3): δ 7.49 (d, J = 8.0 Hz, 1H), 7.28 (d, J = 8.2 Hz, 1H), 7.22 (t, J = 7.6 Hz, 1H), 7.16 (d, J = 5.1 Hz, 1H), 7.08 (t, J = 7.5 Hz, 1H), 7.00–6.87 (m, 3H), 5.42 (t, J = 7.9 Hz, 1H), 4.96 (qd, J = 12.6, 8.0 Hz, 2H), 3.69 (s, 3H).

2-Methyl-3-(2-nitro-1-(3-nitrophenyl)ethyl)-1H-indole (3p).

Compound **3p** was purified through silica gel column chromatography using hexane/ethyl acetate (5 : 1) as the eluent and was obtained as a yellow liquid, yield: 0.079 g, 82%; ^1H NMR (500 MHz, CDCl_3): δ 7.81 (s, 1H), 7.46 (d, J = 7.8 Hz, 1H), 7.36 (td, J = 7.8, 1.8 Hz, 1H), 7.21–7.13 (m, 2H), 7.11–6.95 (m, 4H), 5.38 (dd, J = 9.3, 6.8 Hz, 1H), 5.18 (dd, J = 12.7, 6.8 Hz, 1H), 5.11 (dd, J = 12.7, 9.3 Hz, 1H), 2.32 (s, 3H).

3-(1-(2-Fluorophenyl)-2-nitroethyl)-2-methyl-1H-indole (3q).

Compound **3q** was purified through silica gel column chromatography using hexane/ethyl acetate (5 : 1) as the eluent and was obtained as a yellow liquid, yield: 0.077 g, 86%; ^1H NMR (500 MHz, CDCl_3): δ 8.18 (t, J = 2.0 Hz, 1H), 8.08 (ddd, J = 8.2, 2.3, 1.0 Hz, 1H), 8.01 (s, 1H), 7.69–7.61 (m, 1H), 7.46 (t, J = 8.0 Hz, 1H), 7.33–7.20 (m, 2H), 7.17–7.09 (m, 1H), 7.03 (td, J = 7.5, 7.1, 1.0 Hz, 1H), 5.33–5.23 (m, 2H), 5.16–5.06 (m, 1H), 2.43 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 148.53, 141.88, 135.50, 133.49, 133.19, 129.84, 126.33, 122.29, 121.77, 120.16, 118.02, 111.03, 107.68, 77.90, 40.14, 29.73, 12.07. HRMS (m/z): (ESI) calcd for $\text{C}_{17}\text{H}_{15}\text{FN}_2\text{O}_2$ [$\text{M} + \text{H}$] $^+$: 219.1190, found: 219.1197.

3-(1-(3-Fluorophenyl)-2-nitroethyl)-2-methyl-1H-indole (3r).

Compound **3r** was purified through silica gel column chromatography using hexane/ethyl acetate (5 : 1) as the eluent and was obtained as a yellow liquid, yield: 0.078 g, 87%; ^1H NMR (500 MHz, CDCl_3): δ 7.86 (s, 1H), 7.31 (d, J = 7.9 Hz, 1H), 7.26–7.17 (m, 2H), 7.13–7.05 (m, 2H), 7.04–6.94 (m, 2H), 6.89 (td, J = 8.4, 2.6 Hz, 1H), 5.20–5.11 (m, 2H), 5.09–4.99 (m, 1H), 2.31 (s, 3H). HRMS (m/z): (ESI) calcd for $\text{C}_{17}\text{H}_{15}\text{FN}_2\text{O}_2$ [$\text{M} + \text{H}$] $^+$: 219.1190, found: 219.1195.

3-(1-(2-Chlorophenyl)-2-nitroethyl)-2-methyl-1H-indole (3s).

Compound **3s** was purified through silica gel column chromatography using hexane/ethyl acetate (5 : 1) as the eluent and was obtained as a yellow liquid, yield: 0.079 g, 84%; ^1H NMR (500 MHz, CDCl_3): δ 7.81 (s, 1H), 7.54–7.44 (m, 2H), 7.34 (dd, J = 7.6, 1.8 Hz, 1H), 7.22–7.12 (m, 3H), 7.11–6.98 (m, 2H), 5.47 (dd, J = 8.8, 7.3 Hz, 1H), 5.16–5.06 (m, 2H), 2.31 (s, 3H).

3-(1-(3-Chlorophenyl)-2-nitroethyl)-2-methyl-1H-indole (3t).

Compound **3t** was purified through silica gel column chromatography using hexane/ethyl acetate (5 : 1) as the eluent and was obtained as a yellow liquid, yield: 0.079 g, 84%; ^1H NMR (500 MHz, CDCl_3): δ 7.91 (s, 1H), 7.36–7.30 (m, 1H), 7.29–7.22 (m, 2H), 7.22–7.15 (m, 3H), 7.11 (ddd, J = 8.0, 7.1, 1.1 Hz, 1H), 7.03 (td, J = 7.5, 7.0, 1.1 Hz, 1H), 5.22–5.11 (m, 2H), 5.06 (dd, J = 11.2, 7.7 Hz, 1H), 2.37 (s, 3H). HRMS (m/z): (ESI) calcd for $\text{C}_{17}\text{H}_{15}\text{ClN}_2\text{O}_2$ [$\text{M} + \text{H}$] $^+$: 315.0895, found: 315.0881.

2-Methyl-3-(2-nitro-1-(p-tolyl)ethyl)-1H-indole (3u).

Compound **3u** was purified through silica gel column chromatography using hexane/ethyl acetate (5 : 1) as the eluent and was obtained as a yellow liquid, yield: 0.061 g, 69%; ^1H NMR (500 MHz, CDCl_3): δ 7.83 (s, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.27–7.22 (m, 1H), 7.19 (d, J = 8.0 Hz, 2H), 7.13–7.06 (m, 3H), 7.02 (td, J =

7.6, 7.1, 1.1 Hz, 1H), 5.20 (dd, J = 11.1, 6.5 Hz, 1H), 5.17–5.12 (m, 1H), 5.08 (dd, J = 11.1, 8.2 Hz, 1H), 2.37 (s, 3H), 2.29 (s, 3H).

3-(1-(4-Methoxyphenyl)-2-nitroethyl)-2-methyl-1H-indole (3v).

Compound **3v** was purified through silica gel column chromatography using hexane/ethyl acetate (5 : 1) as the eluent and was obtained as a yellow liquid, yield: 0.068 g, 73%; ^1H NMR (500 MHz, CDCl_3): δ 7.84 (s, 1H), 7.35 (d, J = 7.9 Hz, 1H), 7.23–7.15 (m, 3H), 7.10–7.04 (m, 1H), 7.00 (ddd, J = 8.2, 7.1, 1.1 Hz, 1H), 6.82–6.76 (m, 2H), 5.18–5.07 (m, 2H), 5.03 (dd, J = 10.6, 7.8 Hz, 1H), 3.71 (s, 3H), 2.28 (s, 3H).

Conflicts of interest

There are no conflicts to declare.

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Notes and references

- (a) G. A. Olah, R. Khrisnamurthi and G. K. S. Prakash, in *Comprehensive Organic Synthesis*, Pergamon Press, New York, 1st edn, 1991, pp. 293–339; (b) R. M. Roberts and A. A. Khalaf, *Friedel–Crafts Alkylation Chemistry A Century of Discovery*, Marcel Dekker, New York, 1984.
- (a) R. P. Herrera, V. Sgarzani, L. Bernardi and A. Ricci, *Angew. Chem., Int. Ed.*, 2005, **44**(40), 6576–6579; (b) N. Takenaka, R. S. Sarangthem and S. K. Seerla, *Org. Lett.*, 2007, **9**(15), 2819–2822; (c) E. M. Fleming, T. McCabe and S. J. Connon, *Tetrahedron Lett.*, 2006, **47**(39), 7037–7042; (d) F. Yang, P. Curtis and K. S. Robert, *J. Org. Chem.*, 2018, **83**, 10855–10863; (e) W. Zhuang, R. G. Hazell and K. A. Joergensen, *Org. Biomol. Chem.*, 2005, **3**(14), 2566–2571; (f) G. Yanlong, B. Joel and J. Francois, *Adv. Synth. Catal.*, 2008, **350**, 2007–2012; (g) H. Liu and D. M. Du, *Adv. Synth. Catal.*, 2010, **352**, 1113–1118.
- (a) D. A. Evans, K. A. Scheidt, K. R. Fandrick, H. W. Lam and J. Wu, *J. Am. Chem. Soc.*, 2003, **125**, 10780–10781; (b) K. A. Joergensen, *Synthesis*, 2003, **2003**(07), 594–605; (c) S. F. Lu, D. A. Daming and J. X. Xu, *Org. Lett.*, 2006, **8**(10), 2115–2118; (d) S. Z. Lin and T. P. You, *Tetrahedron*, 2010, **40**(23), 1010–1016; (e) M. Bandini, M. Fagioli, P. Melchiorre, A. Melloni and A. U. Ronchi, *Tetrahedron Lett.*, 2003, **44**(31), 5843–5846.
- (a) G. Bartoli, M. Bosco, S. Giuli, A. Giuliani, L. Lucarelli and E. Torregiani, *J. Org. Chem.*, 2005, **70**(5), 1941–1944; (b) M. M. Alam, R. Varala and S. R. Adapa, *Tetrahedron*, 2003, **44**(27), 5115–5119; (c) M. Bandini, P. G. Cozzi and M. J. Giacomini, *J. Org. Chem.*, 2002, **33**(44), 3700–3704; (d) M. Agnusdei, M. Bandini and A. J. Melloni, *J. Org. Chem.*, 2003, **68**(18), 7126–7129; (e) H. Firouzabadi, N. Iranpoor and F. Nowrouzi, *Chem. Commun.*, 2005, 789–791; (f) J. Xie, X. Zhu, M. Huang, M. Wang and Y. Wan, *Synth. Commun.*, 2010, **40**(21), 3259–3267; (g) R. S. Kumar, *J. Heterocycl.*



- Chem.*, 2006, **43**(5), 1383–1385; (h) C. Lin, J. Hsu and M. N. V. Sastry, *Tetrahedron*, 2006, **37**(12), 11751–11757; (i) K. Venkatanna, S. Y. Kumar, M. Karthick, R. Padmanaban and C. R. Ramanathan, *Org. Biomol. Chem.*, 2019, **17**(16), 4077–4086; (j) N. Azizi, F. Arynassab and M. R. Saidi, *Org. Biomol. Chem.*, 2006, **4**(23), 4275.
- 5 (a) Z. C. Fu, N. Chen and Z. H. Yang, *Green Chem.*, 2018, **20**, 4484; (b) Z. H. Yang, Z. P. Zhu and R. Luo, *Green Chem.*, 2017, **19**, 3296.
- 6 (a) Z. H. Yang, R. S. Luo and Z. P. Zhu, *Organometallics*, 2017, **36**, 4095–4098; (b) Z. H. Yang, Z. P. Zhu and R. S. Luo, *Green Chem.*, 2017, **19**, 3296–3301; (c) D. S. Merel and J. L. Renaud, *ChemCatChem*, 2013, **5**(10), 2939–2945.
- 7 Y. L. Gu, J. I. Barrault and F. Jérôme, *Adv. Synth. Catal.*, 2008, **350**, 2007–2012.
- 8 (a) G. Bartoli, M. Bosco, S. Giuli, A. Giuliani, L. Lucarelli, E. Marcantoni, L. Sambri and E. Torregiani, *J. Org. Chem.*, 2005, **70**, 1941–1944; (b) M. Agnusdei, M. Bandini, A. Melloni and A. U. Ronchi, *J. Org. Chem.*, 2003, **68**, 7126–7129; (c) J. W. Xie, X. H. Zhu, M. Huang, F. Meng, M. Wang and Y. Wan, *Synth. Commun.*, 2010, **40**(21), 3259–3267; (d) R. S. Kumar and P. T. Perumal, *J. Heterocycl. Chem.*, 2006, **43**, 1383; (e) M. Damodiran, R. S. Kumar, P. M. Sivakumar, M. Doble and P. T. Perumal, *J. Chem. Sci.*, 2009, **121**(1), 65–73; (f) H. Firouzabadi, N. Iranpoor and F. Nowrouzi, *Chem. Commun.*, 2005, 789–791.
- 9 (a) S. Yadav, M. Srivastava and J. Singh, *New J. Chem.*, 2016, **40**, 9694; (b) R. Zhou, H. Liu, H. Tao and J. Wu, *Chem. Sci.*, 2017, **8**, 4654–4659; (c) Y. Pan, C. W. Kee, L. Chen and C. H. Tan, *Green Chem.*, 2011, **13**(10), 2682; (d) L. Y. Xie, T. G. Fang, J. X. Tan and W. M. He, *Green Chem.*, 2019, **21**(15), 3858; (e) Y. Liang, L. Teng, Y. Wang and H. Cao, *Green Chem.*, 2019, **21**(15), 4025–4029; (f) H. P. Deng, Q. Zhou and J. Wu, *Angew. Chem., Int. Ed.*, 2018, **57**, 12661–12665; (g) X. Z. Fan, J. W. Rong, H. L. Wu and J. Wu, *Angew. Chem., Int. Ed.*, 2018, **57**, 8514–8518; (h) J. H. Xu, W. B. Wu and J. Wu, *Org. Lett.*, 2019, **21**, 5321–5325; (i) D. Chandrasekhar, S. Adhikary, J. B. Nanubolu and R. A. Maurya, *Org. Lett.*, 2016, **18**, 2974–2977; (j) A. S. Jadhav and R. V. Anand, *Org. Biomol. Chem.*, 2017, **15**, 56–60.
- 10 (a) Y. Pan, C. W. Kee, L. Chen and C. H. Tan, *Green Chem.*, 2011, **13**(10), 2682; (b) Q. Liu, Y. N. Li, H. H. Zhang, B. Chen, C. H. Tung and L. Z. Wu, *Chem.–Eur. J.*, 2012, **18**, 620–627; (c) D. P. Hari and B. König, *Org. Lett.*, 2011, **13**(15), 3852–3855; (d) K. Wang, L. G. Meng, Q. Zhang and L. Wang, *Green Chem.*, 2016, **18**, 2864–2870.
- 11 (a) F. Lima, L. Grunenberg, H. B. A. Rahman and R. Labes, *Chem. Commun.*, 2018, **54**, 5606–5609; (b) I. Ghosh and B. König, *Angew. Chem., Int. Ed.*, 2016, **55**, 7676–7679; (c) G. Kibriya, A. K. Bagdi and A. Hajra, *J. Org. Chem.*, 2018, **83**, 10619–10626; (d) G. Y. Zhao, S. Kaur and T. Wan, *Org. Lett.*, 2017, **19**, 3291–3294; (e) J. D. Tibbetts, D. R. Carbery and E. A. C. Emanuelsson, *ACS Sustainable Chem. Eng.*, 2017, **5**, 9826–9835; (f) I. I. Roslan, K. Ng, M. A. Gondal, C. Basheer, M. A. Dastageerb and S. J. G. K. Chuah, *Adv. Synth. Catal.*, 2018, **360**(8), 1584–1589.
- 12 (a) N. A. Romero and D. A. Nicewicz, *Chem. Rev.*, 2016, **116**(17), 10075–10166; (b) L. Buzzetti, G. E. M. Crisenza and P. Melchiorre, *Angew. Chem., Int. Ed.*, 2019, **58**(12), 3730–3747; (c) Y. Y. Chen, L. Q. Lu, D. G. Yu, C. J. Zhu and W. J. Xiao, *Sci. China: Chem.*, 2019, **62**, 24–57; (d) C. R. Lambert and I. E. Kocheva, *Photochem. Photobiol.*, 1997, **66**(1), 15–25; (e) P. C. C. Lee and M. A. J. Rodgers, *Photochem. Photobiol.*, 1987, **45**(1), 79–86; (f) P. M. Suardi, E. Gassmann, M. Braun and E. Oliveros, *Helv. Chim. Acta*, 1987, **70**, 1760–1773.
- 13 (a) I. Willner and E. Joselevich, *J. Phys. Chem. B*, 1999, **103**(43), 9262–9268; (b) L. Ludvikova, P. Stacko, J. Sperry and P. Klan, *J. Org. Chem.*, 2018, **83**, 10835–10844; (c) H. G. Roth and D. A. Nicewicz, *Synlett*, 2016, **27**, 714–723.
- 14 (a) N. A. Romero and D. A. Nicewicz, *Chem. Rev.*, 2016, **116**(17), 10075–10166; (b) D. S. Merel and J. L. Renaud, *ChemCatChem*, 2013, **5**(10), 2939–2945.
- 15 (a) Y. Pan, S. Wang, C. W. Kee, E. Dubuisson and C. H. Tan, *Green Chem.*, 2011, **13**, 3341–3347; (b) Y. Pan, C. W. Kee, L. Chen and C. H. Tan, *Green Chem.*, 2011, **13**, 2682–2689; (c) C. R. Lambert and I. E. Kocheva, *Photochem. Photobiol.*, 1997, **66**(1), 15–25.
- 16 R. Zhou, H. Liu, H. Tao and J. Wu, *Chem. Sci.*, 2017, **8**, 4654–4659.

