



Showcasing research from Professor Chi-Ming Che's laboratory, Department of Chemistry, Southern University of Science and Technology, Shenzhen, Guangdong, P. R. China.

Direct photo-induced reductive Heck cyclization of indoles for the efficient preparation of polycyclic indolinyl compounds

Photo-induced cleavage of $C(sp^2)$ -Cl bonds is an appealing synthetic tool in organic synthesis but usually requires the use of high UV light, photocatalysts and/or photosensitizers. In this study, the authors describe a metal- and photocatalyst-free, light-induced strategy for chloroarene activation that can be used in the reductive Heck cyclization of indoles for the preparation of polycyclic compounds and functionalization of natural product analogues under 365 or 410 nm LEDs irradiation. The chloroarene compounds examined display room temperature phosphorescence in the solid state and long-lived excited states that undergo bimolecular redox reactions with amines leading to the activation of $C(sp^2)$ -Cl bonds in solution.

As featured in:



See Chi-Ming Che *et al.*, *Chem. Sci.*, 2021, **12**, 14050.

Cite this: *Chem. Sci.*, 2021, 12, 14050

All publication charges for this article have been paid for by the Royal Society of Chemistry

Direct photo-induced reductive Heck cyclization of indoles for the efficient preparation of polycyclic indolinyll compounds†

Daohong Yu,¹ Wai-Pong To,² Yungen Liu,³ Liang-Liang Wu,⁴ Tingjie You,⁵ Jesse Ling⁶ and Chi-Ming Che^{1*}

The photo-induced cleavage of C(sp²)-Cl bonds is an appealing synthetic tool in organic synthesis, but usually requires the use of high UV light, photocatalysts and/or photosensitizers. Herein is described a direct photo-induced chloroarene activation with UVA/blue LEDs that can be used in the reductive Heck cyclization of indoles and without the use of a photocatalyst or photosensitizer. The indole compounds examined display room-temperature phosphorescence. The photochemical reaction tolerates a panel of functional groups including esters, alcohols, amides, cyano and alkenes (27 examples, 50–88% yields), and can be used to prepare polycyclic compounds and perform the functionalization of natural product analogues in moderate to good yields. Mechanistic experiments, including time-resolved absorption spectroscopy, are supportive of photo-induced electron transfer between the indole substrate and DIPEA, with the formation of radical intermediates in the photo-induced dearomatization reaction.

Received 4th August 2021
Accepted 16th September 2021

DOI: 10.1039/d1sc04258k

rsc.li/chemical-science

Introduction

Aryl halides are commonly used as building blocks in organic synthesis.¹ Due to the high negative reduction potential and bond energy of C(sp²)-Cl bonds [*e.g.*, for PhCl, $E_{\text{red}}(\text{PhCl}/\text{PhCl}^{\cdot-}) = -2.78$ V vs. SCE;² BDE (C-Cl) = 97.1 kcal mol⁻¹],³ the reduction of aryl chloride to give an aryl radical usually requires harsh conditions, such as a strong base under thermal conditions⁴ or ultraviolet (UV) light irradiation⁵ is usually used. Highly reactive organic super-electron donors,⁶ consecutive visible light-induced electron transfer reactions⁷ and electro-photocatalysis⁸ are also employed to activate aryl chlorides, *via* one-electron reduction. Recent studies on photochemical C-Cl bond activation often entailed the use of a photocatalyst that

initiates the reaction by electron transfer upon light irradiation.⁹

For decades, UV light-excitation of aryl halides has been known to induce homolytic carbon-halide bond cleavage and lead to cyclization if an arene/alkene is in close proximity.¹⁰ Nonetheless, application studies of this strategy in the synthesis of indoles with complexity are sparse, as the decomposition of indole, photo-Fries rearrangement and photo-dehalogenation were usually observed, leading to low product yields and undesirable regioselectivity.^{10b,c,g} Tin and radical initiators or transition metal catalysts are usually required for free radical cyclization¹⁰ or reductive Heck cyclization,¹¹ in which the C-Br or C-I bond is involved (Scheme 1a). Reactions involving the C-Cl bond are comparatively less developed and they often entail an electron-rich phosphine ligand and high temperature.^{11c,f-i} Reductive Heck cyclization without a radical initiator and transition metal catalyst has not been reported so far.

We conjecture that organic compounds which could attain a reactive, triplet excited state in solution can be harnessed for achieving photoredox reactions without the need for a photocatalyst/photosensitizer. During our study on organic amide compounds, we found that *N*-(2-chlorobenzoyl)indoles display long-lived phosphorescence at room temperature, suggesting that this class of compounds may attain long-lived excited states in solution.¹² Since carbonyl compounds exhibit rich photochemistry,^{13–16} we examined the photochemical reactivity of these *N*-benzoylindoles and discovered that they can undergo efficient photocyclization to give indolinyll compounds in the presence of a base. Herein, we describe a general light-induced

¹Department of Chemistry, Southern University of Science and Technology, Shenzhen, Guangdong 518055, China. E-mail: cmche@hku.hk

²State Key Laboratory of Synthetic Chemistry, HKU-CAS Joint Laboratory on New Materials, Department of Chemistry, The University of Hong Kong, Pokfulam Road, Hong Kong, China

³Key Laboratory of Organo-Pharmaceutical Chemistry of Jiangxi Province, Gannan Normal University, Ganzhou, 341000, China

⁴HKU Shenzhen Institute of Research and Innovation, Shenzhen, Guangdong 518057, China

⁵Laboratory for Synthetic Chemistry and Chemical Biology Limited, Units 1503-1511, 15/F, Building 17W, Hong Kong Science Park, New Territories, Hong Kong, China

† Electronic supplementary information (ESI) available: Experimental details, photophysical data, DFT calculations and NMR spectral data. CCDC 2101130 and 2101131. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1sc04258k





Scheme 1 Reported strategies for (a) the cyclization of indole. (b) Our metal- and photocatalyst-free strategy for chloroarene activation and dearomatization of indole, and synthesis of complex molecules.

Heck cyclization of aryl chlorides with broad substrate scope and its synthetic applications (Scheme 1b). During the preparation of the present manuscript, photo-induced [2 + 2] cycloaddition and reductive arylcarboxylation of indole derivatives which require the use of a photosensitizer were reported by several groups.¹⁷

Results and discussion

Considering both the halogen atom effect and $n \rightarrow \pi^*$ transition of carbonyl groups in facilitating singlet-to-triplet inter-system crossing,¹⁸ we synthesized a class of indole compounds containing a 2-chlorobenzoyl group (e.g., *N*-(2-chlorobenzoyl) indole; **S1**). Upon excitation at 355 nm, **S1** exhibits a broad, structureless emission band with λ_{max} at \sim 435 nm and decay

time constants (τ) of 4.7 and 22 μs in the solid state at room temperature (Fig. 1). The pulse excitation (355 nm) of **S1** at 77 K results in a short (\sim 0.2 s) blue afterglow visible to the naked eye. In 2-methyltetrahydrofuran at 77 K, the decay of the blue afterglow of **S1** is lengthened to a few seconds (Fig. S3[†]). Nanosecond time-resolved absorption difference (ns-TA) spectroscopic measurement on **S1** in MeCN revealed a positive $\Delta\text{O.D.}$ signal from 380 to \sim 550 nm, which decays to the baseline in 1 μs (Fig. 1). Similarly, *N*-(2-chlorobenzoyl)-5-chloroindole (**S3**) in the solid form exhibits fluorescence with a peak maximum at 453 nm ($\tau = 58$ ns; Fig. S4 and S5[†]) and a structured emission profile (500–700 nm), which slowly fades with a lifetime of 111 ms (Fig. S5[†]). The ns-TA spectra of **S3** in degassed MeCN revealed a long-lived signal, which persists for at least 10 μs (Fig. S6[†]). The above two examples suggest that this class of amide compounds could attain a long-lived triplet excited state in solution upon light excitation.

We are intrigued to utilize the long-lived excited state of *N*-benzoylindoles for C(sp²)-Cl bond activation as proposed in Scheme 2. A long-lived excited state of *N*-(2-chlorobenzoyl) indole, **A**, undergoes a bimolecular redox reaction with the reductant (amine) to form the radical anion, **B** (reductive quenching by amine).¹⁹ This radical anion would undergo intramolecular C(sp²)-Cl bond activation, fragmenting into a phenyl radical **C** and chloride ion.²⁰ The ensuing intramolecular radical cyclization of **C** generates benzylic radical **D**. Finally, the hydrogen atom abstraction²¹ with DIPEA⁺ or further reduction of **D** to carbanion **E** followed by protonation generates the reductive Heck cyclization product **1**.

We selected the reductive Heck cyclization of **S1** under LED irradiation to examine the feasibility of photocyclization. Several sacrificial electron donors were screened. In the presence of 2.5 equivalents of *N,N*-diisopropylethylamine (DIPEA), the reaction proceeded smoothly with a 76% product yield under 410 nm LED irradiation (12 W; Fig. S1[†]), with an *N*-benzoylindole byproduct in 5% yield (Table 1, entry 1). The use of *N,N,N',N'*-tetramethylethane-1,2-diamine (TMEDA) and Et₃N also gave the product in 5–10% yields (Table 1, entries 2 and 3). Electron donors such as 1,4-diazabicyclo[2.2.2]octane (DABCO) or bases such as K₂CO₃ and pyridine did not afford the corresponding product, with **S1** recovered quantitatively (Table 1,



Fig. 1 (a) Time-resolved emission spectra of **S1** in the solid state (excitation, 355 nm; the arrow indicates the change in emission intensity). (b) ns-TA spectra of **S1** (0.1 M) in degassed MeCN (excitation, 355 nm).



Scheme 2 Proposed reaction pathway.



Table 1 Reaction condition optimization for the reductive Heck cyclization of **S1**^a

Entry ^a	Additive	X	Time (h)	Yield (%)
1	DIPEA	2.5	8	76
2	TMEDA	2.5	8	10
3	Et ₃ N	2.5	8	5
4	DABCO	2.5	8	0 ^b
5	K ₂ CO ₃	2.5	8	0 ^b
6	Me ₂ S	2.5	8	0 ^b
7	Pyridine	2.5	8	0 ^b
8	—	—	12	0 ^b
9 ^c	DIPEA	2.5	8	0 ^b
10 ^d	DIPEA	2.5	8	0 ^b
11 ^e	DIPEA	2.5	12	80
12 ^{e,f}	DIPEA	2.5	12	65 (52 ^g)

^a **S1** (0.2 mmol), DIPEA (0.5 mmol) and acetonitrile (2.0 mL), under argon and 410 LED irradiation at 30–35 °C for 8–12 hours. Yields were determined by ¹H NMR using dibromomethane or 1,3,5-trimethoxybenzene as an internal standard. ^b The substrate was recovered completely. ^c Reaction conducted in the dark. ^d 450 nm LEDs were used. ^e 365 nm LEDs were used. ^f Under air. ^g Averaged isolated yield of three trials.

entries 4–7). As **S1** was also fully recovered in the reaction without an additive (Table 1, entry 8), the reaction is unlikely to proceed *via* direct light-induced homolysis of **S1**. The product yield decreased to 21–33% and low substrate conversion was observed when DIPEA was decreased to 1 or fewer equivalents (Table S1, entries 12 and 13[†]). Shortening the reaction time was deleterious to the reaction (Table S1, entries 1–3[†]). The solvent effect was evaluated, with MeCN yielding the best results (Table S1, entries 4–11[†]). The reaction did not proceed when performed in the dark (Table 1, entry 9), or under 450 nm LEDs (Table 1, entry 10). Upon 365 nm LED irradiation for 12 h, the cyclized product was obtained in 80% yield (Table 1, entry 11), which is higher than that obtained with Ir(III) photocatalysts (Table S1, entries 18 and 19,† 50–59%). When the chlorine atom in substrate **S1** was replaced by a bromo or iodo group, the reaction also proceeded to give **1** in 70% or 72% yield, respectively, under 410 nm LED irradiation (Table 2).

Under the optimized conditions, we examined the scope of the reductive Heck cyclization reaction (Table 2; see Scheme S1[†] for a list of substrates). A wide variety of functional groups, including both electron-donating and -withdrawing ones, were well tolerated and the corresponding products were obtained in good yields (**1**–**16**). The bromo or chloro substituent on the indole moiety remained intact (**2**–**3**, **11**); this can benefit further transformation, such as the cross-coupling reaction. Sterically hindered *N*-(2-chlorobenzoyl)-2-methylindole (**S18**) afforded the product with one quaternary carbon centre in 60% yield with the use of 365 nm LEDs (**18**). The substrate with both bromo

Table 2 Photo-induced reductive Heck cyclization reaction^{a,e}

^a Substrate (0.5 mmol), DIPEA (1.25 mmol), MeCN (5 mL) under 410 nm LED irradiation at 30–35 °C for 10–14 h; isolated yield. ^b The reaction was irradiated with 365 nm LEDs. ^c Averaged yield of two trials in two independent laboratories. ^d *N*-(2,4,6-Trichlorobenzoyl)indole as the substrate. ^e X = Cl unless otherwise noted.

and hydroxyl groups on indole afforded the product in 73% yield (**19**).

We found that when both *ortho* C–Cl and C–F bonds are present, only C–Cl bond cleavage occurred, with a product yield of 68% (**20**). When *N*-(2,4-dichlorobenzoyl)indole was subjected to the reaction, only the *ortho* C–Cl bond reacted to afford **21** in 80% yield. Interestingly, for *N*-(2,4,6-trichlorobenzoyl)indole, which has two *ortho* C–Cl bonds, the cyclized product **21** with both *ortho* C–Cl bonds cleaved was obtained in 58% yield. We speculated that the reaction first gave the 2,4-dichloro-substituted cyclized product, followed by photoreduction with amine to give **21**. Other electron-donating (AcNH and OMe) or





Scheme 3 Natural products containing an indole moiety.

electron-withdrawing (F and CF₃) functional groups on the benzoyl moiety were tolerated, affording the corresponding products in moderate yields (22–25). However, no reaction occurred for substrates having phenol, aldehyde, pyridine or azide groups (Scheme S1†). When *N*-(2-chlorobenzoyl)-5-nitroindole (**S28**) was subjected to the reaction, the cyclization reaction did not occur; the nitro group was reduced to an amino group to give the amino product (**S36**) in 80% yield.²² Increasing the amount of DIPEA to 5 molar equivalents and extending the reaction time to 24 hours still resulted in **S36** being the major product (81% yield).

Since indole alkaloids are prevalent in natural products and pharmaceuticals (examples are shown in Scheme 3),^{23–25} this photocyclization strategy was applied to the modifications of indole-containing polycycles (Scheme 4). As shown in Scheme 4a, the treatment of Uhle's ketone,²⁶ a key intermediate in the synthesis of lysergic acid,²⁷ α -ergocryptine,²⁷ *N*-methyl-welwistatin²⁸ and cycloclavine,^{23,29} with 2-chlorobenzoyl chloride followed by reduction afforded **26** (Scheme S4†). By subjecting **26** to our photochemical reaction conditions,

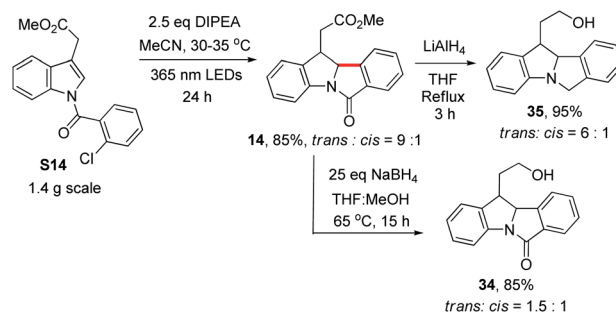


Scheme 4 Modification of polycyclic compounds.

compound **27** was obtained in 66% yield (overall yield of 55% from Uhle's ketone). We also explored the modification of selected medicinal compounds and drug-like molecules. Indometacin analogue **28** cyclized into product **29** in 32% yield upon 365 nm LED excitation with excellent diastereoselectivity (Scheme 4b). Glioperazine C is known to display appealing bioactivity and anti-inflammatory effects. Similarly, when we subject compound **30**, a structural analogue of anti-inflammatory alkaloid glioperazine C,^{25a} to our photochemical reaction conditions, diketopiperazine **31** was produced in 71% yield as a single diastereomer without affecting the pre-existing stereogenic centres (Scheme 4c). Finally, tricyclic lactam **32** underwent photochemical cyclization to afford pentacyclic compound **33** in 72% yield (Scheme 4d).

To demonstrate the synthetic utility of our method, we chose to derivatize **14**, **15** and **16** (see Table 2), with their functionalized side chains serving as handles for further transformations. The reaction of **S14** was scaled up to 1.4 grams. Product **14** (*trans* : *cis* = 9 : 1) was obtained in 85% yield by prolonging the reaction time to 24 h. Further reduction of **14** was effected with LiAlH₄ as the reductant, generating indoline **35** in 95% yield with a slight decrease in the *trans* : *cis* ratio. However, when **14** was reduced with NaBH₄ in THF/MeOH, alcohol **34** was obtained in 85% yield but with a significant drop in the *trans* : *cis* ratio to 1.5 : 1 (Scheme 5). We noted that when **1** was treated with NaBH₄ in a THF/CD₃OD mixture at 65 °C, the incorporation of deuterium at C2 was observed, suggesting that the H at C2 could undergo exchange in the presence of a base and protic solvent (Fig. S7†), thus accounting for the drop in the *trans* : *cis* ratio.

Recently, we have developed an iron-catalyzed intramolecular C(sp³)-H insertion reaction of alkyl azides.³⁰ To prepare complex indoline-containing compounds with this synthetic strategy, we converted *trans*-**34** into azide **36**. Using iron(II) phthalocyanine as the catalyst, pentacyclic indoline **37** was successfully prepared from **36** in 89% yield (27% from **S14**, 4 steps) (Scheme 6a). This indoline, incorporated with a quaternary aminal carbon centre, was characterized by X-ray crystallography (Fig. S14†). Compound **39** was synthesized using the same strategy in four steps, with an overall yield of 53% from **S14** (Scheme 6b). A panobinostat³¹ derivative, **41**, was obtained from **15** and methyl (*E*)-3-(4-(bromomethyl)-phenyl) acrylate **40** in moderate yield (Scheme 6c). Compound **31** was also synthesized in an overall 74% yield from **16** (Scheme 6d).

Scheme 5 Further transformation of **14**.



Scheme 6 Synthesis of complex compounds.

We conducted several experiments to examine the photochemical reaction and found the following: (1) when TEMPO was added, no product was formed and the substrate was recovered quantitatively, suggesting the involvement of radical(s) in the photochemical reaction (Table 3, entry 1). However, no TEMPO-trapped intermediate was detected by mass spectrometry. When 0.5 equivalent of butylated hydroxytoluene (BHT) was added, the product was obtained in only 50% yield (Table 3, entry 2). Hydroquinone and 1,4-dinitrobenzene are commonly used as single electron transfer (SET) inhibitors.³² With hydroquinone present, the product yield plummeted to 30% (Table 3, entry 3). No reaction was observed when 1-chloro-2,4-dinitrobenzene was added (Table 3, entry 4). These results indicate that a SET process is involved in the reaction.

(2) The use of *N*-(2-chlorobenzyl)indole **42** (no carbonyl group) did not give the desired cyclized product, **43**; the substrate remained intact (Scheme 7a). Hence, the presence of the carbonyl group is critical for the photochemical cyclization

Table 3 Mechanistic experiments

Entry	Additive	Yield (%) ^a
1	TEMPO (1.0 eq.)	0
2	BHT (0.5 eq.)	50
3	Hydroquinone (0.5 eq.)	30
4	1-Chloro-2,4-dinitrobenzene (0.5 eq.)	0

^a Yields were determined by ¹H NMR spectroscopy using dibromomethane or 1,3,5-trimethoxybenzene as the internal standard.



Scheme 7 Mechanistic experiments.

reaction. (3) When using CD₃CN as the solvent, product **1** was obtained without deuteration (Scheme 7b). A solvent mixture with D₂O, however, produced deuterated **1** with deuterium incorporated at the C3 position and C2 position to a lesser extent, (Scheme 7c). As D₂O served as an external proton source in competition with DIPEA⁺, these results suggest the formation of the product as a consequence of protonation of anion intermediate **E** instead of hydrogen atom abstraction.^{10g,33} The deuteration at the C2 position could be a result of proton exchange after the product was formed (similar to the treatment of **1** with NaBH₄ as aforementioned) because deuteration at the C2 position was also observed when the non-deuterated product **1** was subjected to the same reaction conditions shown in Scheme 7c (Fig. S7[†]). (4) When *N*-(2-chlorobenzoyl)-3-(2-bromoethyl)indole (**S27**) was subjected to the reaction, **44** was obtained in 30% yield and a spiro cyclopropane, **45**, was formed in 43% yield. We surmised that the radical intermediate **D'** is further reduced by DIPEA to afford the anion intermediate **E'**, giving product **45** via nucleophilic substitution (Scheme 7d). The results depicted in Scheme 7b–d support the mechanism of protonation of cyclized anion intermediates **E** with water in solvent or an aminium radical cation (DIPEA⁺).^{17d,21,34} (5) The quantum yield for the photochemical conversion of **S1** to **1** with 365 nm LEDs was estimated using potassium ferrioxalate as a chemical actinometer (see the ESI[†]); the photon flux of the LEDs was 3.91×10^{-6} einstein s⁻¹. By subjecting **S1** to the reaction conditions b depicted in Table 2, 89.2 μmol of **1** was formed in 40 minutes (18% yield). Thus, the quantum yield of





Fig. 2 (a) ns-TA spectra recorded at 4 μs after pulse excitation at 355 nm, and (b) $\Delta\text{O.D.}$ intensity at 500 nm for degassed MeCN solutions containing **S1** (0.1 M; black line), **S1** (0.1 M) and DIPEA (0.25 M; red line) or DIPEA (0.25 M; blue line).

the reaction is 2.1%, suggesting that a light-induced catalytic pathway is favored over a radical chain process.³⁵

(6) ns-TA spectral measurements in degassed MeCN revealed that, at 4 μs after pulse excitation (355 nm), **S1** or DIPEA alone showed no discernible signal. However, the solution containing both **S1** and DIPEA displayed a broad ns-TA band (maximum at ~ 500 nm) at the same time point (Fig. 2a). The signal with the $\Delta\text{O.D.}$ at 500 nm assigned to the ketyl radical anion³⁶ was relatively long-lived showing a decay time constant of 28 μs . The excited state potential $E(\text{S1}^*/\text{S1}^-)$ was estimated to be 1.15 V vs. Ag/AgCl (**S1**'s $E_{0-0} = 2.9$ eV; $E_{\text{pc}}(\text{S1}/\text{S1}^-) = -1.75$ V), which is higher than the reported potential of $E(\text{DIPEA}^{*+}/\text{DIPEA})$ (0.9 V vs. Ag/AgCl).³⁷ Therefore, upon excitation, **S1** attains a triplet excited state, which accepts an electron from DIPEA to give one-electron reduced **S1** (Scheme 2, species B) and DIPEA^{*+} . (7) *In situ* formation of electron donor-acceptor complexes is another strategy for light-induced C-Cl bond activation.³⁸ In MeCN,

DIPEA (0.25 M) shows an intense absorption at 250–300 nm and weak absorption beyond 325 nm. For indole substrate **S1** (0.1 M), there is an intense absorption at 250–330 nm, with absorption tail ending at ~ 390 nm (Fig. S11[†]). As the mixture of **S1** and DIPEA used in the photochemical experiment showed no new absorption band, the possibility of *in situ* formation of an electron donor-acceptor complex is disfavored.^{38a,39}

DFT calculations (Fig. 3) revealed that the calculated transition state (**TS**) energy for carbon-halogen bond cleavage of radical-anion **S1**^{•-} is 8.9 kcal mol⁻¹. On the other hand, the direct homolytic cleavage of the aryl-halogen bond in the triplet state (**TS1'**, 14.7 kcal mol⁻¹) and concerted bond cleavage and C-C formation (**TS1''**, 17.1 kcal mol⁻¹) have higher **TS** energy. Therefore, the photoexcited **S1** (triplet state) is more likely to undergo electron transfer with DIPEA to form the radical-anion species, which then undergoes C-Cl cleavage to form intermediate **C**. The subsequent cyclization of **C** is facile with a barrier of 9.5 kcal mol⁻¹ (Fig. S16[†]). The computational results further lend support to the proposed radical-anion decomposition pathway as depicted in Scheme 2.

Conclusions

Herein, we have described a general and operationally simple direct photo-induced reductive Heck cyclization reaction of indole derivatives. This reaction has a high tolerance to functional groups, such as esters, amides, alcohols, allylics and alkenes. More importantly, this method can be applied to the functionalization of natural product derivatives and preparation of complex polycyclic indolinyll compounds.

Data availability

CCDC 2101130, and 2101131 containing the supplementary crystallographic data for this paper. Experimental and computational data associated with this work are provided in the article. Additional data supporting the findings reported in this paper are available as ESI.[†] All other data are available from the authors upon reasonable request.

Author contributions

D. Yu performed the majority of the reactions and wrote the first draft of the manuscript. W.-P. To conducted the time-resolved spectroscopic studies and photochemical reaction quantum yield measurement. L.-L. Wu performed the DFT calculations. T. You contributed to the iron-catalyzed reactions. W.-P. To, J. Ling, Y. Liu and C.-M. Che revised writing of the manuscript. Y. Liu helped C.-M. Che to supervise the research. All authors have given approval to the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.



Fig. 3 DFT calculated transition states at the M06-2X-D3/6-311++G**/PCM//B3LYP-D3/6-311G*/PCM level of theory. Critical bond lengths are given in Å.



Acknowledgements

This work was supported by the Guangdong Major Project of Basic and Applied Basic Research (2019B030302009), the Science, Technology and Innovation Commission of Shenzhen Municipality (JCYJ20180508162429786), the China Postdoctoral Science Foundation (2018M633043), the Laboratory for Synthetic Chemistry and Chemical Biology under the Health@InnoHK Program launched by the Innovation and Technology Commission and the CAS-Croucher Funding Scheme for Joint Laboratories. We also thank the Southern University of Science and Technology for financial support. We thank Dr Qingyun Wan for the help with DFT calculations. Dr Zhou Tang and Dr Hua-Hua Wang were thanked for their help with EPR analysis and optical rotation measurement, respectively.

Notes and references

- P. Ruiz-Castillo and S. L. Buchwald, *Chem. Rev.*, 2016, **116**, 12564.
- L. Pause, M. Robert and J.-M. Savéant, *J. Am. Chem. Soc.*, 1999, **121**, 7158.
- S. J. Blanksby and G. B. Ellison, *Acc. Chem. Res.*, 2003, **36**, 255.
- (a) W. Liu, H. Cao, H. Zhang, H. Zhang, K. H. Chung, C. He, H. Wang, F. Y. Kwong and A. Lei, *J. Am. Chem. Soc.*, 2010, **132**, 16737; (b) E. Shirakawa, K.-I. Itoh, T. Higashino and T. Hayashi, *J. Am. Chem. Soc.*, 2010, **132**, 15537; (c) C. Adouama, M. E. Budén, W. D. Guerra, M. Puiatti, B. Joseph, S. M. Barolo, R. A. Rossi and M. Médebielle, *Org. Lett.*, 2019, **21**, 320.
- (a) S.-C. Lu, X.-X. Zhang, Z.-J. Shi, Y.-W. Ren, B. Li and W. Zhang, *Adv. Synth. Catal.*, 2009, **351**, 2839; (b) C. Uyeda, Y. Tan, G. C. Fu and J. C. Peters, *J. Am. Chem. Soc.*, 2013, **135**, 9548; (c) K. Chen, M. S. Cheung, Z. Lin and P. Li, *Org. Chem. Front.*, 2016, **3**, 875; (d) A. M. Mfuh, J. D. Doyle, B. Chhetri, H. D. Arman and O. V. Larionov, *J. Am. Chem. Soc.*, 2016, **138**, 2985; (e) A. M. Mfuh, V. T. Nguyen, B. Chhetri, J. E. Burch, J. D. Doyle, V. N. Nesterov, H. D. Arman and O. V. Larionov, *J. Am. Chem. Soc.*, 2016, **138**, 8408; (f) K. Chen, P. He, S. Zhang and P. Li, *Chem. Commun.*, 2016, **52**, 9125; (g) T. Fukuyama, Y. Fujita, H. Miyoshi, I. Ryu, S.-C. Kao and Y.-K. Wu, *Chem. Commun.*, 2018, **54**, 5582; (h) A. Steiner, J. D. Williams, J. A. Rincón, O. de Frutos, C. Mateos and C. O. Kappe, *Eur. J. Org. Chem.*, 2019, 5807.
- (a) E. Cahard, F. Schoenebeck, J. Garnier, S. P. Y. Cutulic, S. Zhou and J. A. Murphy, *Angew. Chem., Int. Ed.*, 2012, **51**, 3673; (b) L. Zhang and L. Jiao, *J. Am. Chem. Soc.*, 2017, **139**, 607; (c) G. Nocera, A. Young, F. Palumbo, K. J. Emery, G. Coulthard, T. McGuire, T. Tuttle and J. A. Murphy, *J. Am. Chem. Soc.*, 2018, **140**, 9751; (d) A. J. Smith, D. L. Poole and J. A. Murphy, *Sci. China: Chem.*, 2019, **62**, 1425; (e) S. Rohrbach, R. S. Shah, T. Tuttle and J. A. Murphy, *Angew. Chem., Int. Ed.*, 2019, **58**, 11454; (f) L. Zhang and L. Jiao, *J. Am. Chem. Soc.*, 2019, **141**, 9124; (g) K. Liang, T. Li, N. Li, Y. Zhang, L. Shen, Z. Ma and C. Xia, *Chem. Sci.*, 2020, **11**, 2130; (h) K. Liang, Q. Liu, L. e. Shen, X. Li, D. Wei, L. Zheng and C. Xia, *Chem. Sci.*, 2020, **11**, 6996.
- (a) I. Ghosh, T. Ghosh, J. I. Bardagi and B. König, *Science*, 2014, **346**, 725; (b) A. Graml, I. Ghosh and B. König, *J. Org. Chem.*, 2017, **82**, 3552; (c) C. Kerzig and O. S. Wenger, *Chem. Sci.*, 2019, **10**, 11023.
- (a) H. Kim, H. Kim, T. H. Lambert and S. Lin, *J. Am. Chem. Soc.*, 2020, **142**, 2087; (b) N. G. W. Cowper, C. P. Chernowsky, O. P. Williams and Z. K. Wickens, *J. Am. Chem. Soc.*, 2020, **142**, 2093; (c) J. P. Barham and B. König, *Angew. Chem., Int. Ed.*, 2020, **59**, 11732.
- (a) H. Yin, Y. Jin, J. E. Hertzog, K. C. Mullane, P. J. Carroll, B. C. Manor, J. M. Anna and E. J. Schelter, *J. Am. Chem. Soc.*, 2016, **138**, 16266; (b) M. Jiang, H. Li, H. Yang and H. Fu, *Angew. Chem., Int. Ed.*, 2017, **56**, 874; (c) A. U. Meyer, T. Slanina, A. Heckel and B. König, *Chem. Eur. J.*, 2017, **23**, 7900; (d) I. Ghosh, R. S. Shaikh and B. König, *Angew. Chem., Int. Ed.*, 2017, **56**, 8544; (e) R. Matsubara, T. Yabuta, U. Md Idros, M. Hayashi, F. Ema, Y. Kobori and K. Sakata, *J. Org. Chem.*, 2018, **83**, 9381; (f) T. U. Connell, C. L. Fraser, M. L. Czyn, Z. M. Smith, D. J. Hayne, E. H. Doeven, J. Agugiaro, D. J. D. Wilson, J. L. Adcock, A. D. Scully, D. E. Gómez, N. W. Barnett, A. Polyzos and P. S. Francis, *J. Am. Chem. Soc.*, 2019, **141**, 17646; (g) D. Yu, W.-P. To, G. S. M. Tong, L.-L. Wu, K.-T. Chan, L. Du, D. L. Phillips, Y. Liu and C.-M. Che, *Chem. Sci.*, 2020, **11**, 6370; (h) F. Glaser, C. B. Larsen, C. Kerzig and O. S. Wenger, *Photochem. Photobiol. Sci.*, 2020, **19**, 1035; (i) H. Cheng, T.-L. Lam, Y. Liu, Z. Tang and C.-M. Che, *Angew. Chem., Int. Ed.*, 2020, **60**, 1383; (j) M. Cybularczyk-Cecotka, J. Szczepanik and M. Giedyk, *Nat. Catal.*, 2020, **3**, 872.
- Selected literature on the photochemistry of aryl halides: (a) M. Ohashi, K. Tsujimoto and K. Seki, *J. Chem. Soc., Chem. Commun.*, 1973, 384a; (b) M. Somei and M. Natsume, *Tetrahedron Lett.*, 1973, **14**, 2451; (c) W. Carruthers and N. Evans, *J. Chem. Soc., Perkin Trans. 1*, 1974, 1523; (d) G. R. Lenz, *J. Org. Chem.*, 1974, **39**, 2839; (e) T. Kametani, T. Sugai, Y. Shoji, T. Honda, F. Satoh and K. Fukumoto, *J. Chem. Soc., Perkin Trans. 1*, 1977, 1151; (f) O. Tsuge, T. Hatta and H. Tsuchiyama, *Chem. Lett.*, 1998, 155; (g) J. Grimshaw and A. P. de Silva, *Chem. Soc. Rev.*, 1981, **10**, 181.
- Selected examples of thermal dearomatization of indoles: (a) W. Zhang and G. Pugh, *Tetrahedron Lett.*, 1999, **40**, 7591; (b) W. Zhang and G. Pugh, *Tetrahedron*, 2003, **59**, 3009; (c) D. A. Petrone, A. Yen, N. Zeidan and M. Lautens, *Org. Lett.*, 2015, **17**, 4838; (d) C. Shen, R.-R. Liu, R.-J. Fan, Y.-L. Li, T.-F. Xu, J.-R. Gao and Y.-X. Jia, *J. Am. Chem. Soc.*, 2015, **137**, 4936; (e) R.-R. Liu, Y.-G. Wang, Y.-L. Li, B.-B. Huang, R.-X. Liang and Y.-X. Jia, *Angew. Chem., Int. Ed.*, 2017, **56**, 7475; (f) M. Marković, P. Kooš, T. Čarný and T. Gracza, *Tetrahedron Lett.*, 2020, **61**, 152370; (g) X. Qin, M. W. Y. Lee and J. S. Zhou, *Angew. Chem., Int. Ed.*, 2017, **56**, 12723; (h) N. Zeidan, T. Beisel, R. Ross and M. Lautens, *Org. Lett.*, 2018, **20**, 7332; (i) C. Shen, N. Zeidan, Q. Wu, C. B. J. Breuers, R.-R. Liu, Y.-X. Jia and M. Lautens, *Chem. Sci.*, 2019, **10**, 3118.



- 12 (a) S. Xu, R. Chen, C. Zheng and W. Huang, *Adv. Mater.*, 2016, **28**, 9920; (b) J. Chavez, J. Kimball, L. Ceresa, E. Kitchner, T. Shtoyko, R. Fudala, J. Borejdo, Z. Gryczynski and I. Gryczynski, *J. Lumin.*, 2021, **230**, 117724; (c) W. Z. Yuan, X. Y. Shen, H. Zhao, J. W. Y. Lam, L. Tang, P. Lu, C. Wang, Y. Liu, Z. Wang, Q. Zheng, J. Z. Sun, Y. Ma and B. Z. Tang, *J. Phys. Chem. C*, 2010, **114**, 6090; (d) C. Hausteiner, W. D. Savage, C. F. Ishak and R. T. Pflaum, *Talanta*, 1989, **36**, 1065; (e) J. Chavez, L. Ceresa, E. Kitchner, J. Kimball, T. Shtoyko, R. Fudala, J. Borejdo, Z. Gryczynski and I. Gryczynski, *J. Photochem. Photobiol., B*, 2020, **208**, 111897; (f) S. Cai, H. Shi, J. Li, L. Gu, Y. Ni, Z. Cheng, S. Wang, W.-W. Xiong, L. Li, Z. An and W. Huang, *Adv. Mater.*, 2017, **29**, 1701244.
- 13 (a) D. O. Cowan and R. L. Drisko, *Photochemical Techniques and the Photochemistry of Ketones*, in *Elements of organic photochemistry*, Springer, Boston, 1976; (b) P. Klán and J. Wirz, in *Photochemistry of Organic Compounds*, John Wiley & Sons, Hoboken, 2009, p. 227; (c) J. A. Dantas, J. T. M. Correia, M. W. Paixão and A. G. Corrêa, *ChemPhotoChem*, 2019, **3**, 506.
- 14 (a) Y. Li, M. Lei and L. Gong, *Nat. Catal.*, 2019, **2**, 1016; (b) Y. Shen, Y. Gu and R. Martin, *J. Am. Chem. Soc.*, 2018, **140**, 12200; (c) A. Dewanji, P. E. Krach and M. Rueping, *Angew. Chem., Int. Ed.*, 2019, **58**, 3566; (d) J.-B. Xia, C. Zhu and C. Chen, *J. Am. Chem. Soc.*, 2013, **135**, 17494.
- 15 Á. Péter, S. Agasti, O. Knowles, E. Pye and D. J. Procter, *Chem. Soc. Rev.*, 2021, **50**, 5349.
- 16 (a) C. Kerzig and M. Goez, *Phys. Chem. Chem. Phys.*, 2015, **17**, 13829; (b) M. Brautzsch, C. Kerzig and M. Goez, *Green Chem.*, 2016, **18**, 4761; (c) M. Schmalzbauer, I. Ghosh and B. König, *Faraday Discuss.*, 2019, **215**, 364; (d) M. Schmalzbauer, M. Marcon and B. König, *Angew. Chem., Int. Ed.*, 2021, **60**, 6270.
- 17 Recent examples of light-induced cyclization of indoles: (a) M. V. Popescu, A. Mekereeya, J. V. Alegre-Requena, R. S. Paton and M. D. Smith, *Angew. Chem., Int. Ed.*, 2020, **59**, 23020; (b) Z. Zhang, D. Yi, M. Zhang, J. Wei, J. Lu, L. Yang, J. Wang, N. Hao, X. Pan, S. Zhang, S. Wei and Q. Fu, *ACS Catal.*, 2020, **10**, 10149; (c) M. Zhu, X. Zhang, C. Zheng and S.-L. You, *ACS Catal.*, 2020, **10**, 12618; (d) W.-J. Zhou, Z.-H. Wang, L.-L. Liao, Y.-X. Jiang, K.-G. Cao, T. Ju, Y. Li, G.-M. Cao and D.-G. Yu, *Nat. Commun.*, 2020, **11**, 3263; (e) M. S. Oderinde, E. Mao, A. Ramirez, J. Pawluczyk, C. Jorge, L. A. M. Cornelius, J. Kempson, M. Vetrichelvan, M. Pitchai, A. Gupta, A. K. Gupta, N. A. Meanwell, A. Mathur and T. G. M. Dhar, *J. Am. Chem. Soc.*, 2020, **142**, 3094; (f) M. S. Oderinde, A. Ramirez, T. G. M. Dhar, L. A. M. Cornelius, C. Jorge, D. Aulakh, B. Sandhu, J. Pawluczyk, A. A. Sarjeant, N. A. Meanwell, A. Mathur and J. Kempson, *J. Org. Chem.*, 2021, **86**, 1730; (g) K. A. McDaniel and N. T. Jui, *Org. Lett.*, 2021, **23**, 5576.
- 18 (a) O. Bolton, K. Lee, H.-J. Kim, K. Y. Lin and J. Kim, *Nat. Chem.*, 2011, **3**, 205; (b) W. Zhao, Z. He, J. W. Y. Lam, Q. Peng, H. Ma, Z. Shuai, G. Bai, J. Hao and B. Z. Tang, *Chem*, 2016, **1**, 592; (c) T. Liu, G. Zhang, R. E. Evans, C. O. Trindle, Z. Altun, C. A. DeRosa, F. Wang, M. Zhuang and C. L. Fraser, *Chem. Eur. J.*, 2018, **24**, 1859; (d) S. Cai, H. Shi, D. Tian, H. Ma, Z. Cheng, Q. Wu, M. Gu, L. Huang, Z. An, Q. Peng and W. Huang, *Adv. Funct. Mat.*, 2018, **28**, 1705045; (e) Z. Yang, C. Xu, W. Li, Z. Mao, X. Ge, Q. Huang, H. Deng, J. Zhao, F. L. Gu, Y. Zhang and Z. Chi, *Angew. Chem., Int. Ed.*, 2020, **59**, 17451.
- 19 (a) S. G. Cohen, G. A. Davis and W. D. K. Clark, *J. Am. Chem. Soc.*, 1972, **94**, 869; (b) S. G. Cohen, A. Parola and G. H. Parsons, *Chem. Rev.*, 1973, **73**, 141.
- 20 (a) A. N. Santiago, K. Takeuchi, Y. Ohga, M. Nishida and R. A. Rossi, *J. Org. Chem.*, 1991, **56**, 1581; (b) A. E. Lukach, D. G. Morris, A. N. Santiago and R. A. Rossi, *J. Org. Chem.*, 1995, **60**, 1000; (c) R. A. Rossi, A. B. Pierini and A. B. Peñeñory, *Chem. Rev.*, 2003, **103**, 71.
- 21 H. Kim and C. Lee, *Angew. Chem., Int. Ed.*, 2012, **51**, 12303.
- 22 (a) T. Hirao, J. Shiori and N. Okahata, *Bull. Chem. Soc. Jpn.*, 2004, **77**, 1763; (b) S. Gazi and R. Ananthakrishnan, *Appl. Catal., B*, 2011, **105**, 317.
- 23 (a) F. R. Petronijevic and P. Wipf, *J. Am. Chem. Soc.*, 2011, **133**, 7704; (b) W. Wang, J.-T. Lu, H.-L. Zhang, Z.-F. Shi, J. Wen and X.-P. Cao, *J. Org. Chem.*, 2014, **79**, 122; (c) N. Netz and T. Opatz, *J. Org. Chem.*, 2016, **81**, 1723.
- 24 K. Douki, H. Ono, T. Taniguchi, J. Shimokawa, M. Kitamura and T. Fukuyama, *J. Am. Chem. Soc.*, 2016, **138**, 14578.
- 25 (a) P. Wang, L. Miao, H. Zhao, D. Wu, L. Wang, Y. Teng, H. Sun and P. Yu, *J. Chem. Pharm. Res.*, 2015, **7**, 85; (b) Y. Wang, P. Wang, H. Ma and W. Zhu, *Expert Opin. Ther. Pat.*, 2013, **23**, 1415.
- 26 (a) F. C. Uhle, *J. Am. Chem. Soc.*, 1949, **71**, 761; (b) K. Teranishi, S. Hayashi, S.-i. Nakatsuka and T. Goto, *Tetrahedron Lett.*, 1994, **35**, 8173.
- 27 I. Moldvai, E. Temesvári-Major, M. Incze, É. Szentirmay, E. Gács-Baitz and C. Szántay, *J. Org. Chem.*, 2004, **69**, 5993.
- 28 M. Ruiz, P. López-Alvarado and J. C. Menéndez, *Org. Biomol. Chem.*, 2010, **8**, 4521.
- 29 M. Incze, G. Dörnyei, I. Moldvai, E. Temesvári-Major, O. Egyed and C. Szántay, *Tetrahedron*, 2008, **64**, 2924.
- 30 (a) K.-P. Shing, Y. Liu, B. Cao, X.-Y. Chang, T. You and C.-M. Che, *Angew. Chem., Int. Ed.*, 2018, **57**, 11947; (b) T. You, S.-H. Zeng, J. Fan, L. Wu, F. Kang, Y. Liu and C.-M. Che, *Chem. Commun.*, 2021, DOI: 10.1029/d1cc04573c.
- 31 P. G. Richardson, R. L. Schlossman, M. Alsina, D. M. Weber, S. E. Coutre, C. Gasparetto, S. Mukhopadhyay, M. S. Ondovik, M. Khan, C. S. Paley and S. Lonial, *Blood*, 2013, **122**, 2331.
- 32 F. Wu, B. Huang and W. Huang, *Chin. J. Org. Chem.*, 1993, **13**, 449.
- 33 (a) W. K. Smothers, K. S. Schanze and J. Saltsiel, *J. Am. Chem. Soc.*, 1979, **101**, 1895; (b) N. L. Holy, *Chem. Rev.*, 1974, **74**, 243; (c) L. M. Dorfman, *Acc. Chem. Res.*, 1970, **3**, 224.
- 34 J. Du, L. R. Espelt, I. A. Guzei and T. P. Yoon, *Chem. Sci.*, 2011, **2**, 2115.
- 35 M. A. Cismesia and T. P. Yoon, *Chem. Sci.*, 2015, **6**, 5426.
- 36 Selected examples of the ketyl radical or radical anion of benzophenone: (a) C. Pac, K. Mizuno, T. Tosa and H. Sakurai, *J. Chem. Soc., Perkin Trans. 1*, 1974, 561; (b) T. S. Godfrey, J. W. Hilpern and G. Porter, *Chem. Phys. Lett.*,



- 1967, **1**, 490; (c) M. von Raumer and P. Suppan, *Chem. Phys. Lett.*, 1996, **250**, 91; (d) J. Pérez-Prieto, F. Boscá, R. E. Galian, A. Lahoz, L. R. Domingo and M. A. Miranda, *J. Org. Chem.*, 2003, **68**, 5104; (e) E. Haselbach, E. Vauthey and P. Suppan, *Tetrahedron*, 1988, **44**, 7335.
- 37 Y. Imada, Y. Okaka and K. Chiba, *ChemElectroChem*, 2020, **7**, 1619.
- 38 (a) J. Davies, S. G. Booth, S. Essafi, R. A. W. Dryfe and D. Leonori, *Angew. Chem., Int. Ed.*, 2015, **54**, 14017; (b) B. Liu, C.-H. Lim and G. M. Miyake, *J. Am. Chem. Soc.*, 2017, **139**, 13616; (c) J. Yuan, W.-P. To, Z.-Y. Zhang, C.-D. Yue, S. Meng, J. Chen, Y. Liu, G.-A. Yu and C.-M. Che, *Org. Lett.*, 2018, **20**, 7816; (d) G. E. M. Crisenza, D. Mazzarella and P. Melchiorre, *J. Am. Chem. Soc.*, 2020, **142**, 5461.
- 39 L. Candish, M. Teders and F. Glorius, *J. Am. Chem. Soc.*, 2017, **139**, 7440.

