

# Manuscript

## Visible Light-Induced Sulphide Anion-Catalysed Decarboxylative Alkylations in Batch and Continuous Flow

Meng-Ting Liu,<sup>2,†</sup> De-Guang Liu,<sup>1,†</sup> Zhi-Wei Qin<sup>2</sup>, Guang-Zu Wang<sup>1,2</sup>

<sup>1</sup> Department of Chemistry, University of Science and Technology of China, Hefei 230026, China

<sup>2</sup> Institute of Advanced Technology, University of Science and Technology of China, Hefei 230031, China

<sup>†</sup>These authors contributed equally: Meng-Ting Liu and De-Guang Liu.

Correspondence and requests for materials should be addressed to G.-Z.W. (email: wgz@mail.ustc.edu.cn).

### Abstract

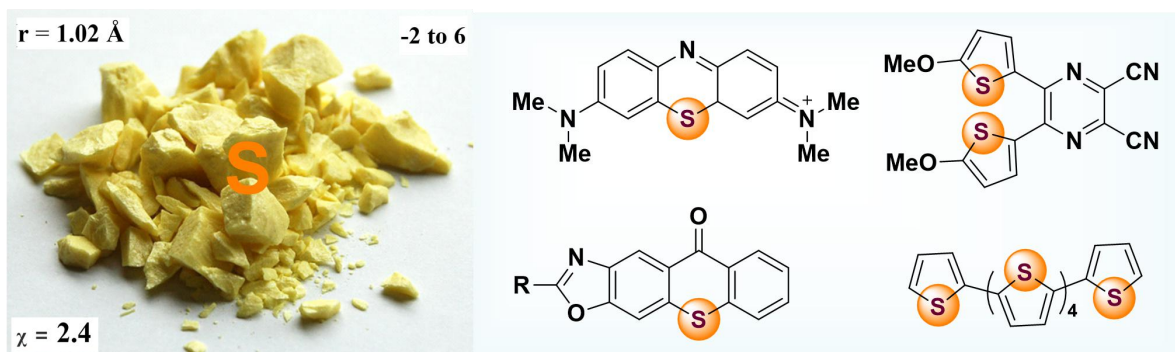
We demonstrated herein a versatile protocol for visible-light-induced sulphide anion-catalysed decarboxylative cross-couplings. An array of primary, secondary, tertiary and amino acid-derived redox-active esters (RAEs) were all amenable substrates to undergo radical decarboxylation to be coupled with a diverse range of nucleophiles, creating challenging C(sp<sup>3</sup>)-C(sp<sup>3</sup>) and C(sp<sup>3</sup>)-C(sp<sup>2</sup>) bonds with high efficiency. We note that Katritzky's salt and Togni's reagent were also suitable substrates, affording deaminative alkylation and trifluoromethylation products in high yields. Density functional theory calculations and mechanism experiments indicate that a charge-transfer complex was formed between sulphide anions and RAEs in the amide solvent. Additionally, a one-pot two-step telescoped procedure and continuous-flow process further increase the synthetic utility of this catalytic system.

### Introduction

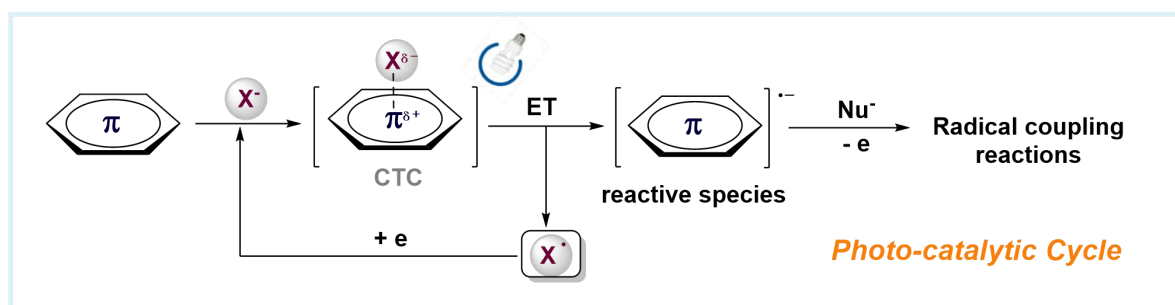
Sulphur atoms are found in a wide variety of natural products, drugs, organic materials, agrochemicals, and small molecules of medicinal interest<sup>[1-3]</sup>. The large size (1.02 Å) and low electronegativity (2.4) of the sulphur atom make the outer electron shell more prone to accept and

donate electrons, resulting in its multiplicity of valence (Figure 1A)<sup>[4]</sup>. Almost every atom (except inert elements) can bond with sulphur atoms, and its valence state can vary from -2 to 6<sup>[5]</sup>. The excellent electron-transfer ability and radical properties of sulphur-containing backbones make them ideal candidates for catalysis<sup>[6]</sup>, particularly in the photoredox pathway<sup>[7]</sup>. To date, numerous sulphur-containing photosensitizers have been synthesized and employed in visible-light-induced transformations, such as disodium benzophenondisulphonate (BPSS)<sup>[8]</sup>, thiazine dyes<sup>[9]</sup>, thiophene derivatives<sup>[10]</sup> and N-phenylphenothiazine (PTH)<sup>[11]</sup>. Although considerable progress has been made in this area, the high cost and complex synthesis of the catalysts have impeded their application in large-scale industrial processes. Consequently, developing a new photocatalyst based on this inexpensive and abundant element is highly desirable.

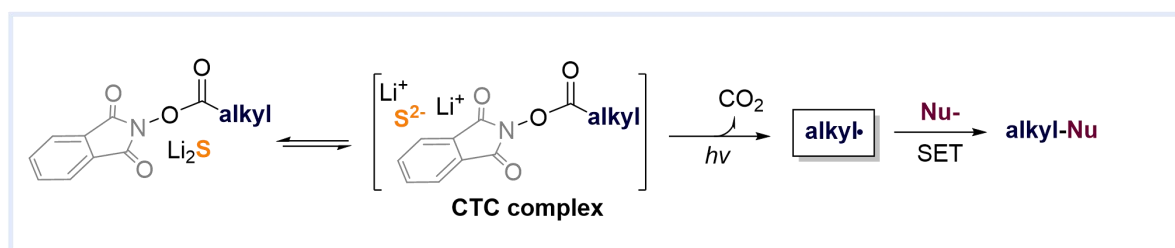
**(A) Sulfur and Sulfur-containing photocatalysts**



**(B) Charge-transfer complex (CTC) enabled photoredox process via anion- $\pi$  bonding**



**(C) Visible-light-induced sulfide anions-catalyzed decarboxylative alkylations (*This work*)**



**Figure 1 | Sulphide anion-catalysed decarboxylative alkylation via photoactivation of the anion- $\pi$  interaction-assembled charge transfer complex (CTC)**

Noncovalent interactions are of fundamental importance in many areas of modern chemistry and have been vital in the development of fast chemical dynamics<sup>[12-13]</sup>. Anion- $\pi$  bondings, which was commonly defined as an attraction of anions to the electron-deficient (olefinic or aromatic)

$\pi$ -systems, have recently emerged as one of the most interesting noncovalent interactions<sup>[14-16]</sup>. The anion- $\pi$  assembled charge-transfer complex (CTC) was found to be activated via photoactivation to undergo intermolecular electron transfer (IET), thus affording reactive radical ion pairs and anion radical intermediates (Figure 1B)<sup>[17-18]</sup>. In 2019, Shang and Fu reported the first photocatalysed decarboxylative alkylations enabled by  $\text{PPh}_3$  and  $\text{NaI}$ <sup>[19]</sup>. It is worthy noted that the CTC was formed with a cheap iodized salt, a sample phosphorus ligand, and an electron-accepting substrate, avoiding the use of the traditional metal- or dye complex-based photosensitizer<sup>[20-22]</sup>. Inspired by this, we questioned whether sulphide anions with better electron-transfer ability and radical properties could also exhibit the similar catalytic reactivity (Figure 1C).

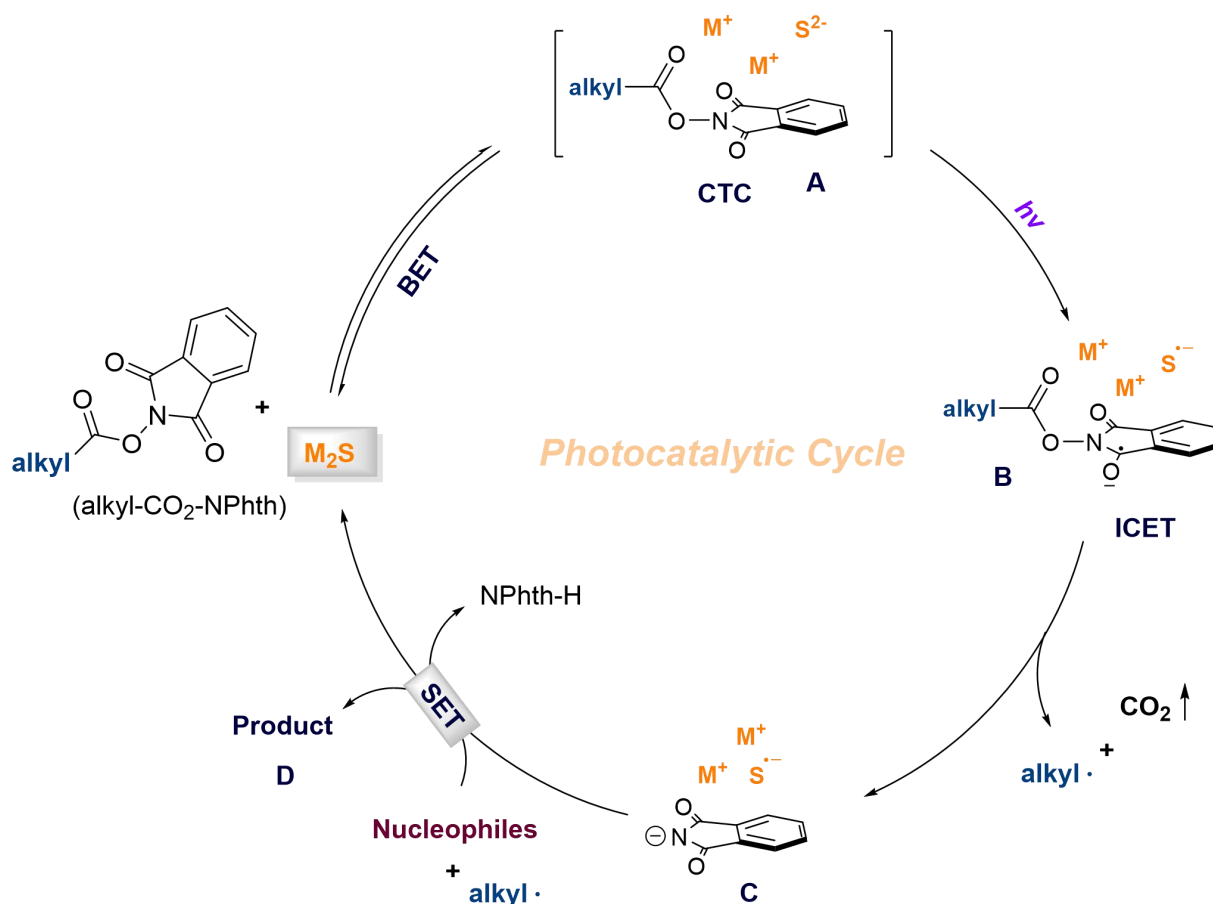


Figure 2 | Proposed photocatalytic cycle

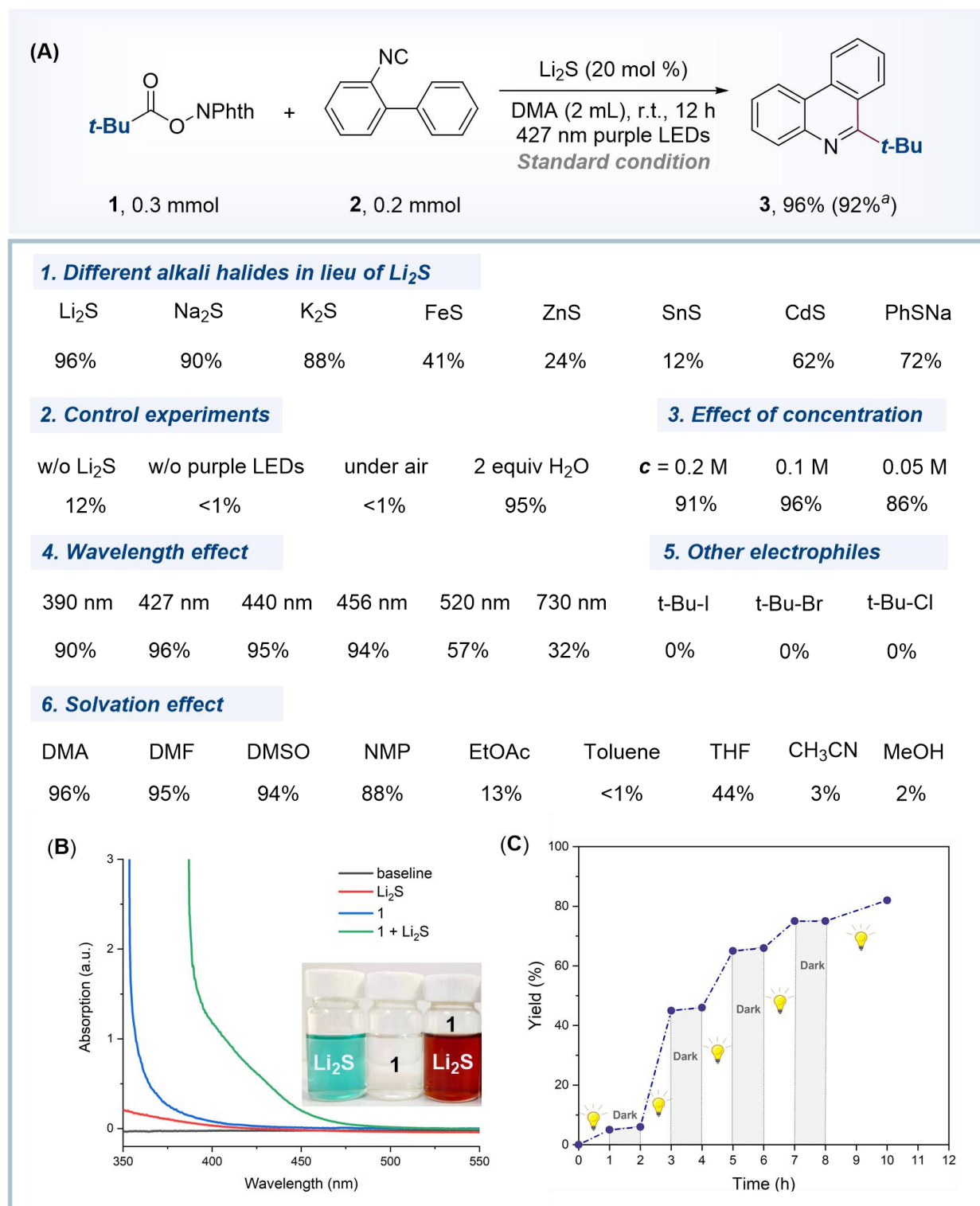
The proposed mechanism for sulphide anion-catalysed decarboxylative alkylation is illustrated in Figure 2. Initially, charge transfer complex **A** is dynamically formed with redox-active esters (RAEs) and sulphide anions through anion- $\pi$  interactions in the solvent cage. Then, intermolecular electron transfer (ICET) from sulphide anions to RAEs is induced through photoactivation of CTC, thus affording radical ion pair intermediate **B**. (Note: this step is critical, because the photoexcitation state **B** can either return to **A** through the back electron transfer pathway<sup>[23]</sup> or collapse to form the free sulphide radicals and alkyl radicals). Afterwards, the fragmentation of **B** occurs via decarboxylation to generate alkyl radicals and sulphide radical intermediate **C**. Finally, the alkyl radical attacks the

nucleophiles, followed by single electron transfer and deprotonation by  $\text{Nphth}^-$  to deliver alkylation product **D**.

## Results and Discussion

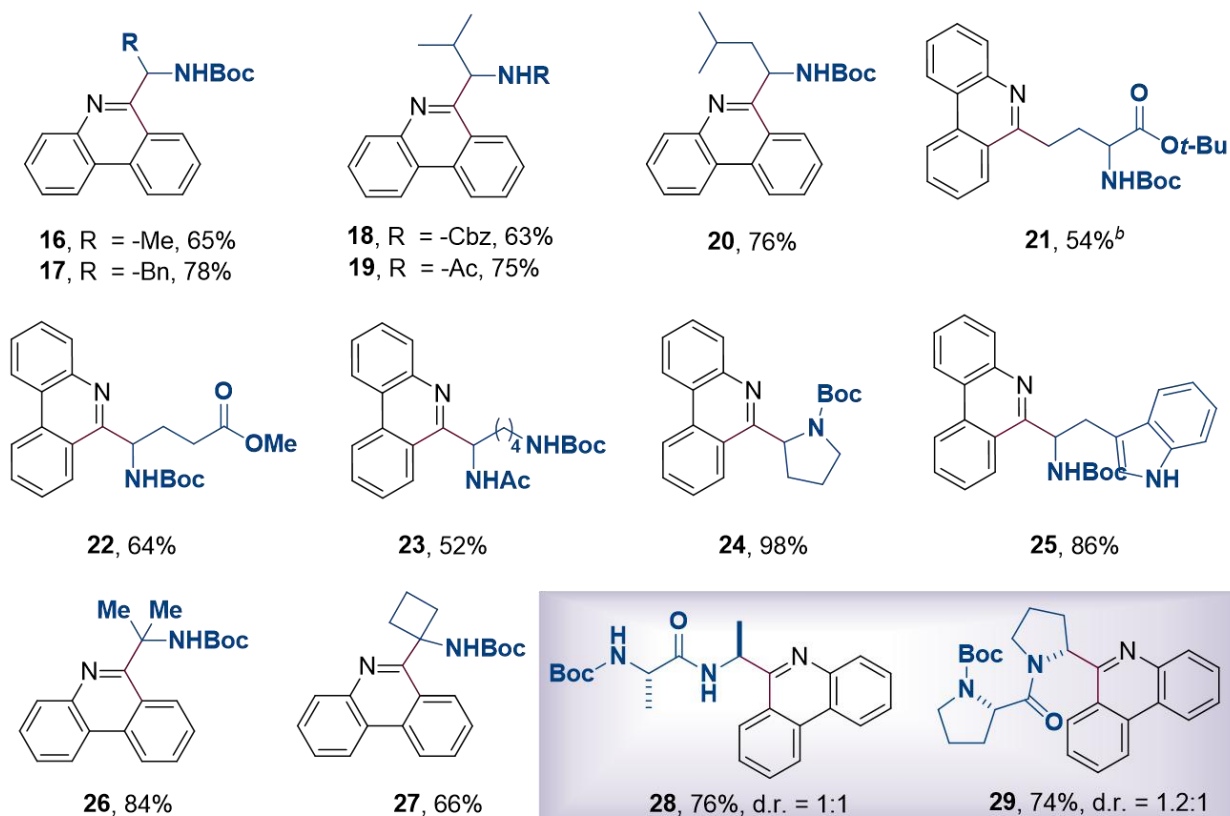
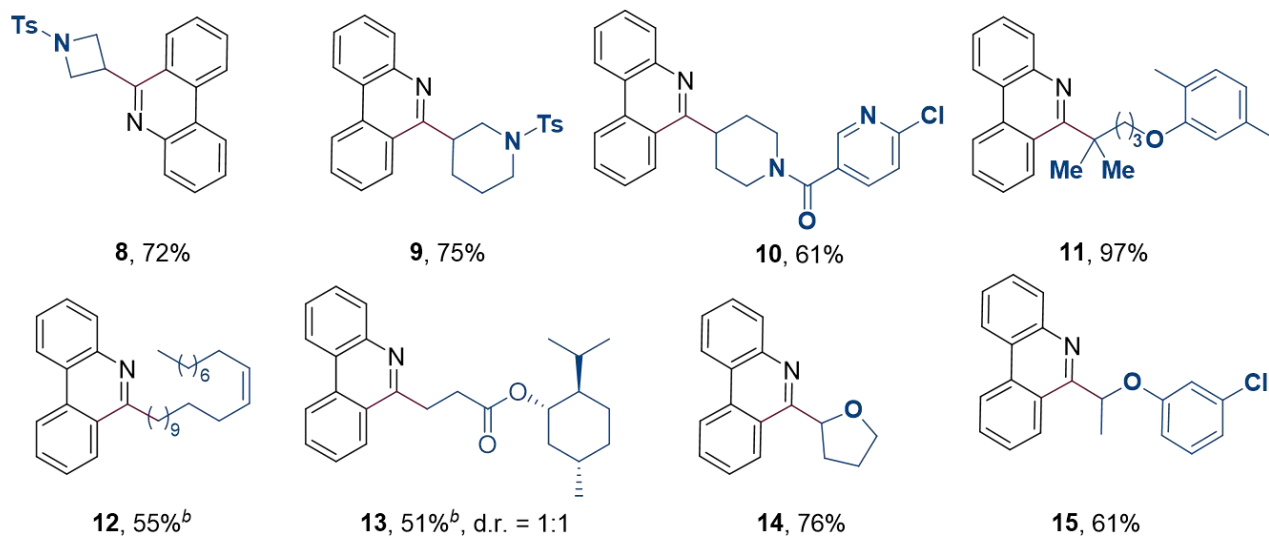
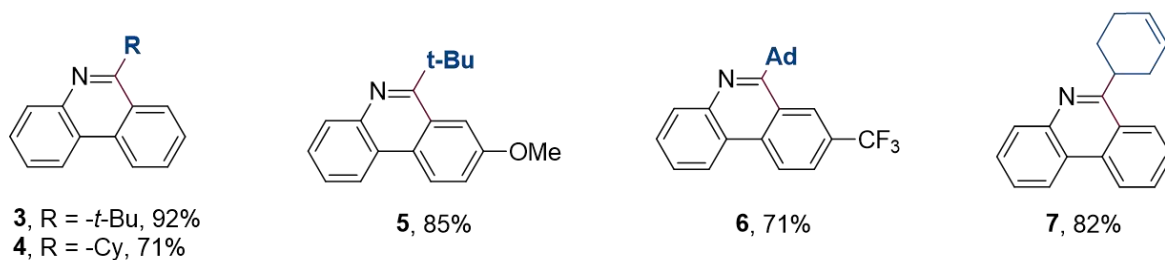
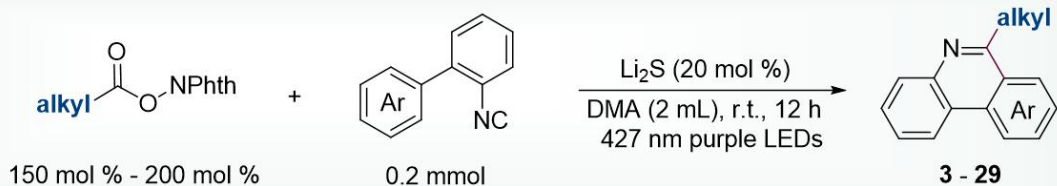
**Substrates scope.** The optimized reaction conditions for the decarboxylative alkylation of isocyanide are demonstrated in Figure 3. Irradiation the reaction mixture of N-(tert-butylacetoxy)phthalimide (**1**, 0.3 mmol), 2-isocyanato-1,1'-biphenyl (**2**, 0.2 mmol) and  $\text{Li}_2\text{S}$  (20 mol %) in DMA (2.0 mL) solvent by purple LEDs (427 nm) for 12 h, delivering the desired alkylation product (**3**) in 96% yield. The key parameters that affect the reaction are summarized in Figure 3A. In addition to  $\text{Li}_2\text{S}$ ,  $\text{Na}_2\text{S}$  and  $\text{K}_2\text{S}$  are also suitable catalysts to deliver **3** in good yields. However, other sulphide salts, such as  $\text{FeS}$ ,  $\text{ZnS}$ ,  $\text{SnS}$  and  $\text{CdS}$ , were less effective. Organic sulphides  $\text{PhSNa}$  exhibited good catalytic activity in this reaction system. Control experiments revealed that catalyst and light irradiation are both crucial. This catalytic system is highly sensitive to oxygen but is not sensitive to water. Moreover, the concentration effect is also significant to this reaction, and a relatively high concentration is necessary. We also investigated the dependence of the reaction on the light wavelength, and it was found that the purple LEDs (427 nm) and blue LEDs (440 nm, 456 nm) exhibited better performance than the other light sources, including ultraviolet radiation (390 nm), green LEDs (520 nm) and red LEDs (730 nm). It is noteworthy that alkyl halides (iodide, bromide and chloride) were all ineffective, which is attributed to their inability to form CTC complexes. For solvent optimization, we found that amide solvents (DMA, DMF, NMP) and dimethyl sulphoxide were all favourable solvents for this photoinduced sulphide-catalysed reaction.

To provide a further understanding of the charge transfer complex-enabled photoredox system, the UV-Vis absorption spectrum<sup>[24]</sup> of the reaction mixture was then measured with the same concentration used in the standard reaction condition (Figure 2B). No obvious absorption in the visible region was observed for the  $\text{Li}_2\text{S}$  solution, and the RAE (**1**) showed an absorption onset at approximately 390 nm<sup>[25]</sup>. A strong bathochromic shift, tailing into the wavelength range of purple LEDs and even blue LEDs occurred when  $\text{Li}_2\text{S}$  was mixed with **1**. It is important to note that the solution developed an amber colour change from colourless when **1** was mixed with  $\text{Li}_2\text{S}$  (aquamarine blue) in DMA. This phenomenon is in accordance with the bathochromic shift of UV-Vis absorption that is diagnostic of charge transfer complex formation in the reaction system. Finally, a light “on/off” experiment was conducted to indicate that uninterrupted irradiation is necessary for this transformation (Figure 3C)<sup>[26]</sup>.



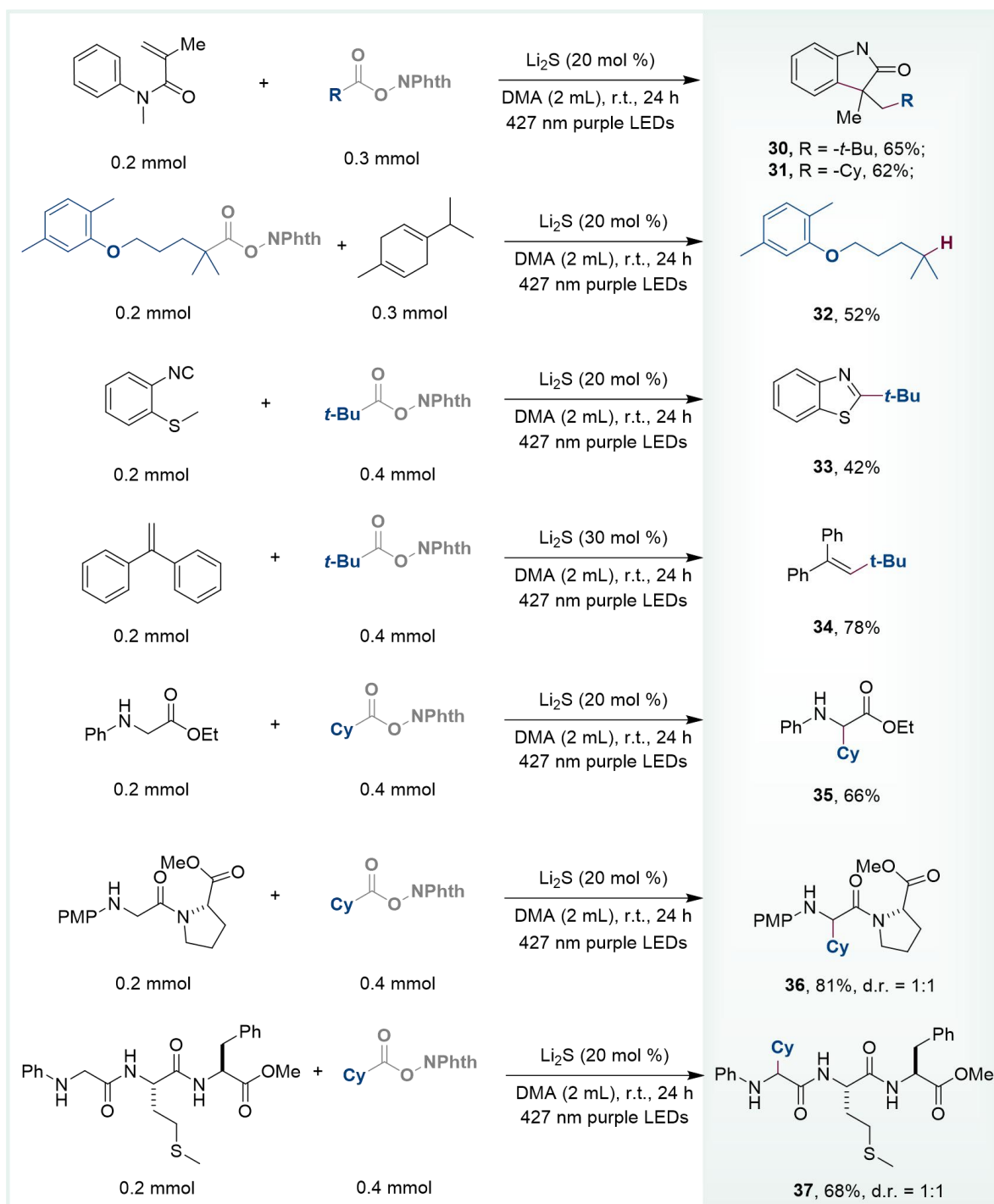
**Figure 3 | (A) Parameters affecting the sulphide anion-catalysed decarboxylative alkylations. (B) UV-Vis absorption spectrum of reactant mixtures and Electronic photos of different components in DMA solution. (C) On/off experiment. Yield determined by gas chromatography (GC) using diphenylmethane as an internal standard. <sup>a</sup>Isolated yield.**

**Substrates scope.** Encouraged by these results, we set out to explore the scope of this transformation. Satisfyingly, this catalytic system featured broad substrate scope and good functional group compatibility under the optimized reaction conditions (Table 1). Isocyanides substituted with electron-neutral (**3**, **4**) and electron-donating (**5**) and electron-groups (**6**) all gave good to excellent yields.



**Table 1 | Sulphide anion-catalysed decarboxylative alkylation of isocyanides.** <sup>a</sup>Reaction conditions: Isocyanides (0.2 mmol), RAEs (0.3 mmol) in DMA (2 mL), irradiation with purple LEDs (427 nm, 40 W) at room temperature for 12 h under argon atmosphere. <sup>b</sup>RAEs (0.4 mmol).

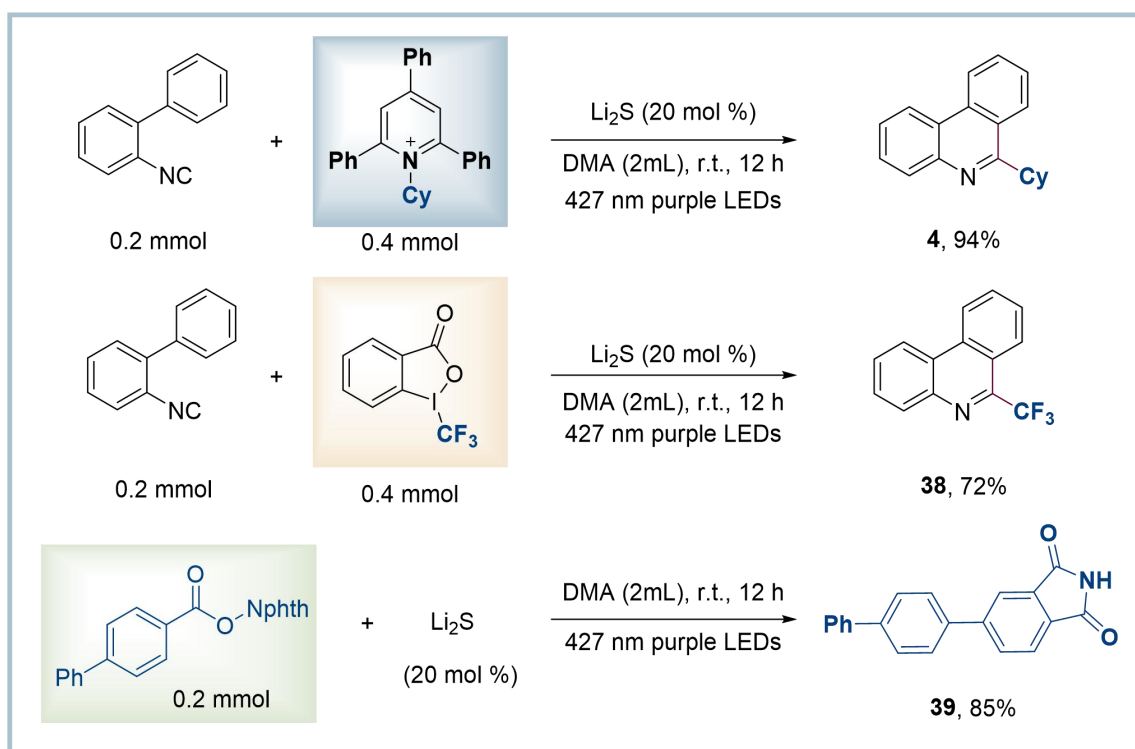
A variety of primary, secondary and even tertiary RAEs (**3** – **29**) were all amenable substrates to deliver the corresponding decarboxylative alkylation products in moderate to excellent yields (51% – 98%). Moreover, pharmaceutically relevant aliphatic structures, such as substituted piperidine (**9**, **10**), and even more strained four-membered rings (**8**), are also effective in this reaction manifold. Excitingly, RAEs derived from natural product, such as Erucic acid (**12**), and drug molecules, like gemfibrozil (**11**) and monomethyl succinate (**13**), were all tolerated. It is important to mention that  $\alpha$ -alkoxy acid (**14**, **15**), amino acid (**16** – **27**) and even peptide (**28**, **29**)-derived redox esters were all amenable substrates for obtaining alkylation products in good to excellent yields<sup>[27]</sup>.



**Scheme 1** | Photoinduced sulphide anion-catalysed decarboxylative alkylation of RAEs with other nucleophiles via charge-transfer complex



To further expand the scope of the photoinduced sulphide anion catalytic system, we examined decarboxylative alkylation of RAEs with other nucleophilic reagents (Scheme 1), including *N*-alkyl-*N*-phenylalkacrylamides<sup>[28]</sup> (**30**, **31**),  $\gamma$ -terpinene<sup>[29]</sup> (**32**), (2-isocyanophenyl)(methyl)sulphane<sup>[30]</sup> (**33**), ethene-1,1-diyl dibenzene<sup>[31]</sup> (**34**) and arylglycine derivatives and peptides<sup>[32]</sup> (**35** – **37**). It was found that all of these compounds could undergo photoinduced decarboxylation to yield alkylation products in moderate to good yields. In addition to RAEs, Katritzky's salt<sup>[33]</sup> and Togni's reagent<sup>[34]</sup> were also demonstrated to be suitable substrates, affording deaminative alkylation and trifluoromethylation products with high efficiency (Scheme 2). Moreover, we were delighted to find that aryl carboxylic acid-derived redox-active esters<sup>[35]</sup> were also amenable substrates, delivering the intramolecular decarboxylative arylation product (**39**) in high yield.



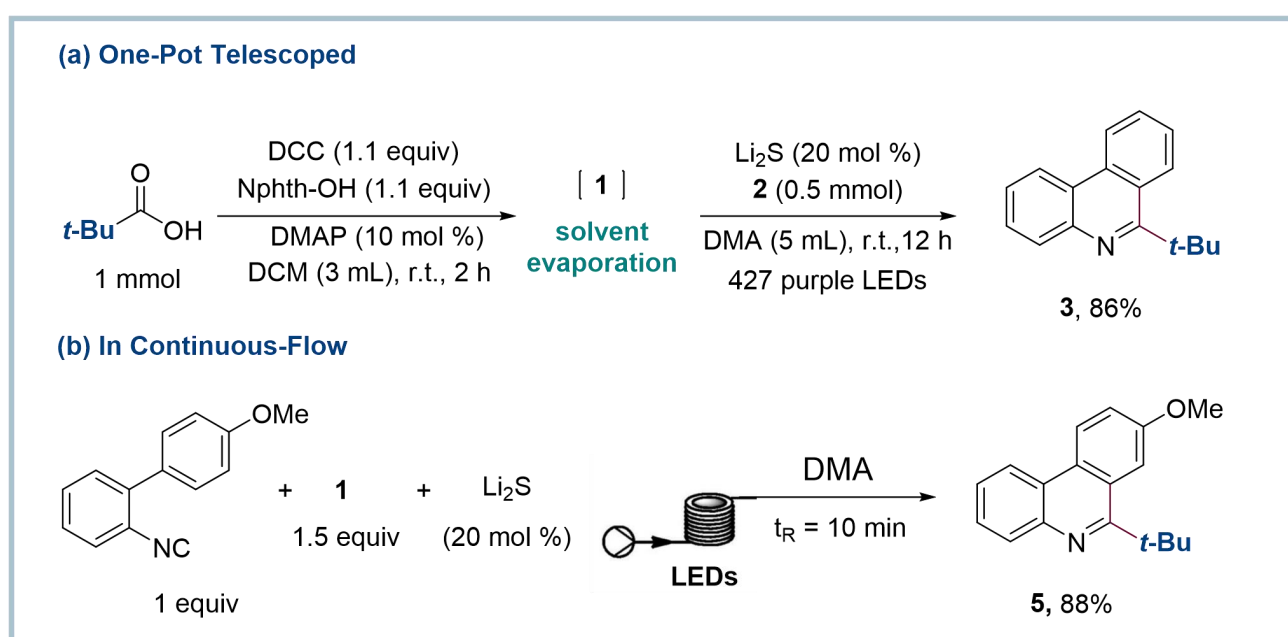
Scheme 2 | CTC-enabled sulphide anion-catalysed alkylations with other electrophiles

To increase the synthetic utility of this catalytic system, we implemented a two-step telescoped sequence to form RAE **1** in situ and use it without further purification (Scheme 3). A comparable yield was obtained under the optimum conditions, thus adding a synthetically valuable dimension to the CTC catalytic platform. Moreover, we also applied this sample catalytic system to the continuous-flow condition<sup>[36-37]</sup>. The same results can be achieved in just 10 minutes compared with the standard conditions (12 h), further enhancing the synthetic application value of this approach.

**Mechanism studies:** Finally, density functional theory (DFT) calculations were conducted to

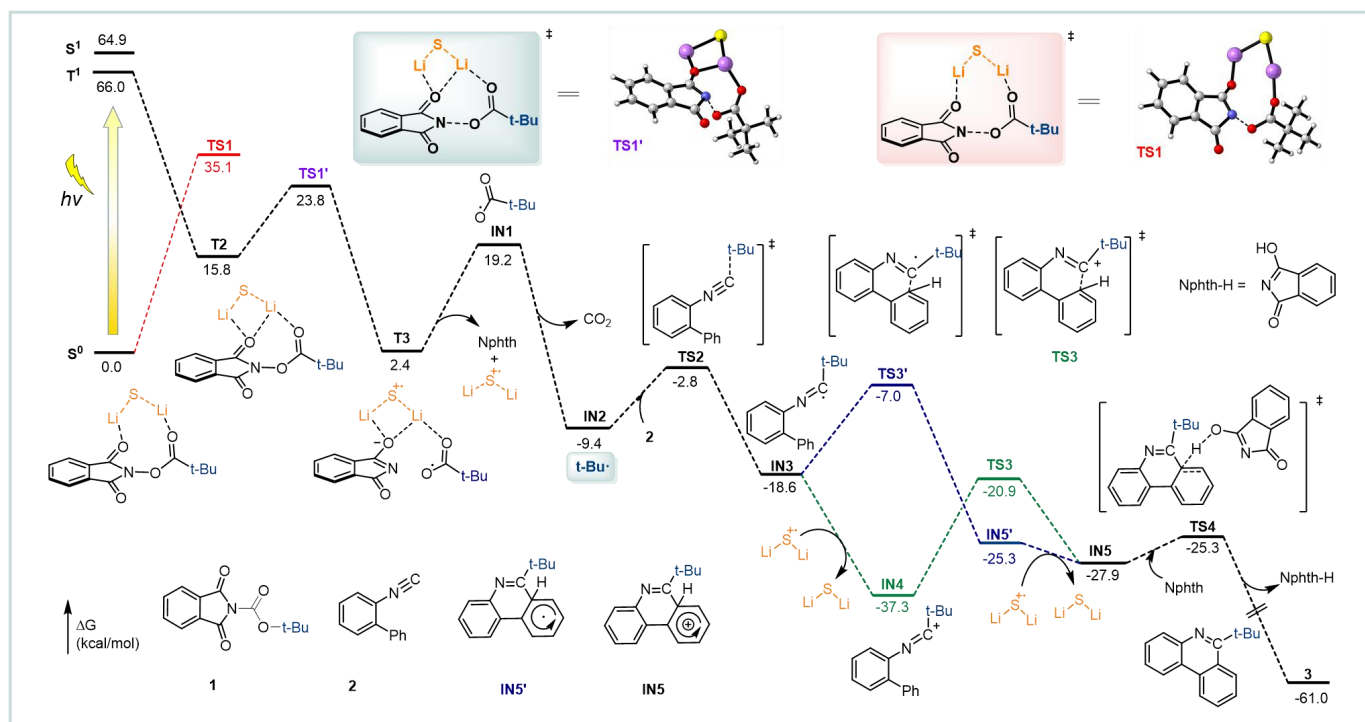


further elucidate the reaction pathway (Scheme 4)<sup>[38]</sup>. Initially, the charge-transfer complex (CTC) was spontaneously assembled with Li<sub>2</sub>S and RAEs (**1**) in *N,N*-dimethyl acetamide solvent. The ground state complex (**S**<sup>o</sup>) was activated with purple LEDs (427 nm) to generate a singlet excited **S**<sup>1</sup> state. Then, the **S**<sup>1</sup> state decays via intersystem crossing (ISC) to the corresponding triplet excited state **T**<sup>1</sup> and transforms to the optimized triplet excited state (**T**<sub>2</sub>) via relaxation process. Subsequently, photo-induced intermolecular single electron transfer (ISET) proceeded (**T**<sub>2</sub> → **TS**<sub>1</sub><sup>1</sup>,  $\Delta G^\ddagger = 8.0$  kcal/mol), leading to decarboxylation and generating tert-butyl free radicals (**IN**<sub>2</sub>) and sulphide radical cations. It is important to note that an enormous activation energy barrier must be overcome (**S**<sup>o</sup> → **TS**<sub>1</sub><sup>1</sup>,  $\Delta G^\ddagger = 35.1$  kcal/mol) in the absence of visible light, proving further proof for the necessity of irradiation.



Scheme 3 | Decarboxylative alkylation with a one-pot two-step Telescoped procedure and in continuous-flow conditions

In the following step, the obtained alkyl radical **IN**<sub>2</sub> will attack the aryl isocyanide (**2**) to form the corresponding radical intermediate **IN**<sub>3</sub> ( $\Delta G^\ddagger = 6.6$  kcal/mol). Subsequently, **IN**<sub>3</sub> may undergo a single electron transfer (SET) pathway with lithium sulphide cation radicals to obtain intermediate cation **IN**<sub>4</sub>, followed by cyclization to form intermediate **IN**<sub>5</sub> via the electrophilic attack on the aromatic ring. It is worthy noted that **IN**<sub>3</sub> may also undergo radical cyclization first to obtain the cyclized radical intermediate **IN**<sub>5</sub><sup>1</sup> and then obtain **IN**<sub>5</sub> through the SET pathway with lithium sulphide cation radicals. Finally, deprotonation with Nphth<sup>−</sup> to deliver the alkylation product (**3**) is facile with an energy barrier of only 2.6 kcal/mol.



Scheme 4 | DFT calculations

## Conclusions

In summary, we found that a charge-transfer complex spontaneously assembled with commercially available lithium sulphide and redox-active esters (RAEs) in amide solvents. An array of primary, secondary, tertiary and amino acid-derived RAEs were all amenable electron-acceptor substrates for undergoing radical decarboxylation and coupled with a diverse range of nucleophiles under 427 nm purple LED irradiation. Moreover, Katritzky's salt and Togni's reagent were also demonstrated to be suitable substrates, affording deaminative alkylation and trifluoromethylation products with high efficiency. This novel manifold featured a broad substrate scope and good functional group compatibility and was amenable to conducting the reaction in continuous-flow conditions, further enhancing its potential for application in large-scale synthesis. Mechanistic studies are consistent with the proposed reaction pathway in which CTC was activated with visible-light irradiation to undergo IEC, producing an alkyl radical and a sulphide anion radical intermediate. This new photoactivation concept presented in our work is anticipated to inspire future development of photocatalysis.

## Methods

**General procedure for decarboxylative alkylation of isocyanides.** isocyanide (0.2 mmol, if it is solid), RAEs (150 mol % - 200 mol %), Li<sub>2</sub>S (20 mol %) were placed in a 10 mL transparent Schlenk tube equipped with a stirring bar. The tube was evacuated and filled with argon (repeated for three times). To these solids, isocyanide (0.2 mmol, if it is liquid) and anhydrous DMA (1 mL) were added

using a gastight syringe under argon atmosphere. The reaction mixture was stirred under irradiation with purple LEDs (427 nm), maintained at approximately room temperature ( $30 \pm 2$  °C) by a desk fan in the air-conditioned room of 25 °C for 12 h. The mixture was then quenched with saturated NaCl solution and extracted with ethyl acetate ( $3 \times 10$  mL). The organic layers were combined and concentrated under reduced atmospheric pressure. The product was purified by flash column chromatography on silica gel using petroleum ether/ethyl acetate as eluent.

## Data availability

The authors declare that the data supporting the findings of this study are available within the article and Supplementary Information files, or from the corresponding author upon reasonable request. The experimental procedures, computational results, and characterization of all new compounds are provided in the Supplementary Information.

## Acknowledgements

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## Author contributions

M.-T.L. and D-G.L. contributed equally to this work. G-Z.W. conceived the idea, directed the project and wrote the manuscript. D-G.L. performed the DFT calculations. M.-T.L. and Z.-W.Q. performed the experiments and analyzed the data. All the authors participated in the preparation of the manuscript.

## Competing interests

The authors declare no competing interests.

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- 38 All calculations were performed with the Gaussian 16 program. The DFT functional of  $\omega$  B97XD /def2TZVP was used for geometry optimization, frequency analysis and single-point energy calculations of all intermediates and transition states. The solvent effects were taken into account in all calculations by employing the SMD (N, N-DiMethylAcetamide) solvation model. Further details are given in the ESI.

## TOC

