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Convergent and divergent synthesis of dihydroisoquinoline-1,4-diones enabled by a photocatalytic skeleton-editing [4 + 2] strategy†

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Dihydroisoquinolinediones are ubiquitous nitrogen-containing fused heterocyclic units in natural products, drug molecules, and functional materials. However, straightforward synthesis of dihydroisoquinolinediones from simple and readily available precursors remains challenging and underdeveloped. Herein, we developed an unprecedented photocatalytic [4 + 2] skeleton-editing strategy enabled direct synthesis of dihydroisoquinoline-1,4-diones from vinyl azides and carboxylic NHPI esters. The key to success is the use of NHPIs as bifunctional reagents and in the skeleton-edit enabled [4 + 2] cyclization cascade. Notably, vinyl azides serve as α-primary amino alkyl radicals followed by a radical initiated ring-enlargement event. Impressively, the reaction provides convergent access to identical dihydroisoquinolinedione from different NHPIs and divergent access to different dihydroisoquinolinediones from identical NHPI. The reaction cleaves two C–N bonds and forges one C–N bond, two C–C bonds and a ring.

Introduction

Dihydroisoquinolinediones represent an important class of nitrogen-containing fused heterocyclic units which are widely found in natural products and bioactive molecules (Fig. 1a).[1] Therefore, developing straightforward strategies for the synthesis of dihydroisoquinolinediones is of great significance in the synthetic community. However, the synthesis of dihydroisoquinolin-1,4-diones remains underdeveloped compared to that of dihydroisoquinolin-1,3-diones and dihydroisoquinolin-3,4-diones. The only reported examples rely on the use of advanced precursors in the presence of stoichiometrically strong acids (HCl and H_2SO_4) and bases (NaOH), which undoubtedly limited the scope and synthetic applications (Fig. 1b).[2] To this end, a general platform for the synthesis of dihydroisoquinolin-1,4-diones with diverse substitution patterns under mild conditions is highly desirable. On the other

hand, bifunctional reagents were first defined by Piers in 1988,[3] and their use has been recognized as a valuable synthetic strategy for introducing two functional groups into one molecule in a single step for the synthesis of value-added targets.[4] It features improved atom economy and fewer steps, offering a potential platform to access molecular complexity from simple starting materials (Fig. 1c).[5] However, one major challenge in this area is to identify new robust bifunctional reagents which could offer new chemical space for structural diversity and variability in an atom-economic manner. *N*-Hydroxyphthalimide (NHPI) esters of aliphatic carboxylic acids are well-known as alkyl radical precursors in single electron enabled decarboxylation reactions, which waste major molecular weight of NHPI esters.[6] In 2020, Glorius used NHPI esters as bifunctional reagents to facilitate 1,4-aminoalkylation of 1,3-dienes, in which NHPI esters act as radical precursors and nitrogen nucleophiles.[7] To date, no example of using NHPI esters as bifunctional reagents with skeleton editing has been reported. Herein, we described a photocatalytic skeleton-editing [4 + 2] strategy enabled direct synthesis of dihydroisoquinoline-1,4-diones from redox-active NHPI esters and vinyl azides under mild conditions (Fig. 1d). Redox-active NHPIs were used as bifunctional reagents, serving as alkyl radicals and dihydroisoquinoline-1,4-dione precursors. Vinyl azides were used as latent α-amino substituted radical precursors, which allows for the direct access to dihydroisoquinoline-1,4-diones by ring enlargement with NHPIs.[8]

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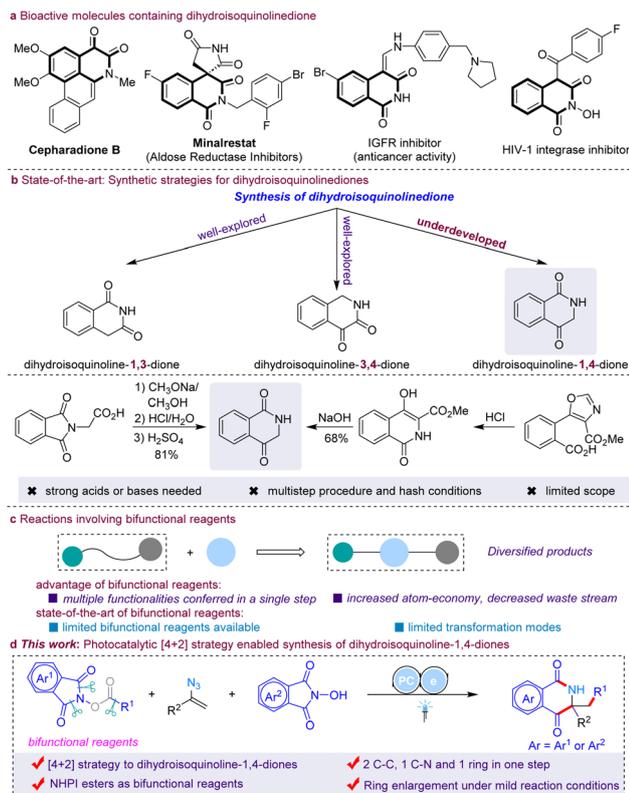
Fig. 1 Significance and impetus for the synthesis of dihydroisoquinoline-1,4-diones. (a) Bioactive molecules containing dihydroisoquinolinedione; (b) state-of-the-art: synthetic strategies for dihydroisoquinolinediones; (c) reactions involving bifunctional reagents; (d) this work: photocatalytic [4 + 2] strategy enabled synthesis of dihydroisoquinoline-1,4-diones.

Table 1   Reaction condition optimization[a]

Entry	Variation from "standard conditions"	Yield of 3a
1	None	68%
2	4CzIPN	56%
3	4CzIPN-Cl	52%
4	Ir(ppy)$_3$	Trace
5	Ru(bpy)$_3$(PF$_6$)$_2$	34%
6	[Mes–Acr–3,6-^{t}Bu$_2$–Ph$^+$]BF$_4^-$	Trace
7	DCE as solvent	41%
8	PhCl as solvent	44%
9	THF as solvent	N.D.
10	MeCN as solvent	22%
11	2,6-Lutidine as base	48%
12	DMAP as base	59%
13	DABCO as base	56%
14	K$_2$HPO$_4$ as base	58%
15	In air	31%
16	W/o base	43%
17	W/o A1	11%
18	W/o PC/HE/light	N.D.
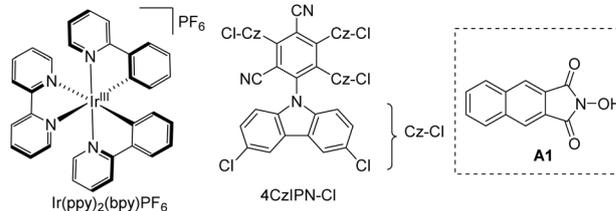
[a] Reaction conditions: unless otherwise noted, a mixture of 1a (0.18 mmol), 2a (0.10 mmol), A1 (0.25 mmol), Ir(ppy)$_2$(bpy)PF$_6$ (0.002 mmol), HE (0.40 mmol) and 2,4,6-collidine (0.08 mmol) in DCM (1.8 mL) was irradiated with 30 W blue LEDs at 35 °C for 16 h. Yield of 3a was determined by ^{1}H NMR of the crude mixture using mesitylene as an internal standard. PC = photocatalyst. NHPI = N-hydroxyphthalimide. HE = Hantzsch ester. A1 = N-hydroxy-2,3-naphthalimide. N.D. = not detected. DCM = dichloromethane. DCE = 1,2-dichloroethane. THF = tetrahydrofuran. DMAP = 4-dimethylaminopyridine. DABCO = triethylenediamine.

Results and discussion

To test the feasibility of the reaction, we set out to evaluate reaction conditions for the photocatalytic [4 + 2] reaction using bifunctional reagent NHPI ester (1a) and vinyl azide (2a) as model substrates. After evaluation of several reaction parameters (Tables S1–S6†),[9] dihydroisoquinolin-1,4-dione compound 3a was formed in 68% yield in dichloromethane (0.056 M) using Ir(ppy)$_2$(bpy)PF$_6$ (2 mol%) as a photosensitizer, N-hydroxy-2,3-naphthalimide (A1, 2.5 equiv.) as an additive, Hantzsch ester (HE, 4.0 equiv.) and 2,4,6-collidine (80 mol%) as a base under the irradiation of 30 W blue LEDs at 35 °C for 16 h (Table 1, entry 1). The structure of 3a was unambiguously confirmed by X-ray crystallography diffraction analysis. Next, the evaluation of the photocatalyst revealed the use of other metal-free photocatalysts, such as 4CzIPN and 4CzIPN-Cl, which provided desired product 3a in 56% and 52% yields (Table 1, entries 2 and 3). Other tested photocatalysts delivered 3a in inferior yields (Table 1, entries 4–6). Moreover, evaluation of the solvent effect on the [4 + 2] reaction indicated that aprotic solvents DCE and PhCl reduced the yields of 3a to 41% and 44%, respectively (Table 1, entries 7 and 8). However, the reaction failed to deliver 3a in THF (Table 1, entry 9). Conducting the reaction in MeCN

decreased the yield of desired product 3a to 22% (Table 1, entry 10). Replacing the base 2,4,6-collidine with 2,6-lutidine gave 3a in 48% yield (Table 1, entry 11). The reaction proceeded smoothly in organic and inorganic bases (DMAP, DABCO and K$_2$HPO$_4$), affording 3a in 56–59% yields (Table 1, entries 12–14). In addition, conducting the reaction in air furnished 3a in 31% yield (Table 1, entry 15). Notably, the use of thebase and additive is essential for the reaction, delivering 3a in 43% and 11% yields in the absence of the base or additive (Table 1, entries 16 and 17). Control experiments indicated that the photocatalyst, Hantzsch ester (HE) and light are all required for this [4 + 2] reaction. No desired product was detected in the absence of any of these elements (Table 1, entry 18).
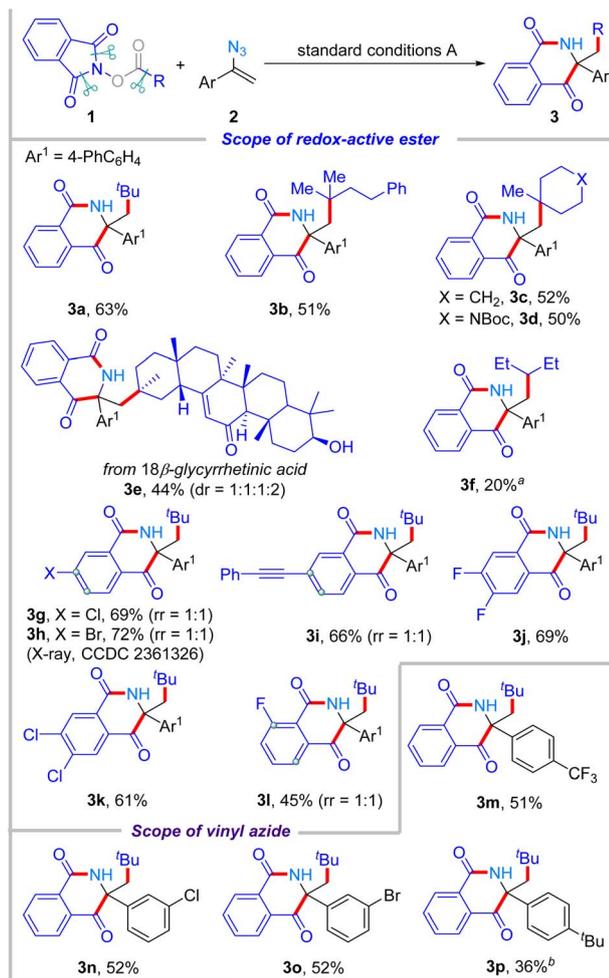
Fig. 2 Substrate scope for the photocatalytic two-component [4 + 2] reaction. Unless otherwise noted, the reaction was conducted under conditions **1** (0.18 mmol), **2** (0.10 mmol), Ir(ppy)₂(bpy)PF₆ (2 mol%), Hantzsch ester (0.4 mmol), **A1** (0.25 mmol) in DCM (0.56 M) irradiated with 30 W blue LEDs at 35 °C for 16 h. ^{a}The reaction was conducted using 4CzIPN (2 mol%), DIPEA (80 mol%), and DCM (1.0 mL). ^{b}HOAc (80 mol%) was added.

With the optimized conditions in hand, we turned to evaluate the scope of this photocatalyzed two-component [4 + 2] strategy using carboxylic acid redox active ester as a bifunctional reagent to provide dihydroisoquinoline-1,4-diones. The results are summarized in Fig. 2. Bifunctional reagents NHPI esters of tertiary substituted aliphatic carboxylic acids efficiently delivered the desired products (**3a** and **3b**) in 63% and 51% yields. Cyclic or heterocyclic tertiary carboxylic acid NHPI esters also successfully afforded corresponding products (**3c** and **3d**) with 52% and 50% yields. Gratifyingly, the NHPI ester derived from natural product ^{18}β-glycyrrhetinic acid reacted smoothly under standard conditions to furnish the corresponding dihydroisoquinoline-1,4-dione product (**3e**) in 44% yield (1 : 1 : 1 : 2 dr). The secondary carboxylic acid NHPI ester was successfully converted into the desired product (**3f**) in 20% yield. When NHPI esters bearing unsymmetric substitution patterns on arenes were used as bifunctional reagents, the

reaction proceeded smoothly to provide corresponding [4 + 2] products (**3g–3i**) as a mixture of regioisomers. 5-Chloro-substituted NHPI ester delivered **3g** in 69% yield with 1 : 1 rr. Similarly, 5-bromo-substituted NHPI ester afforded the dihydroisoquinoline-1,4-dione product (**3h**) in 72% yield with 1 : 1 rr. 5-Alkynyl-substituted NHPI ester also delivered the desired [4 + 2] product **3i** in 66% yield with 1 : 1 rr. Moreover, 5,6-difluoro- or dichloro-substituted NHPI esters afforded the dihydroisoquinoline-1,4-dione compounds **3j** and **3k** in 69% and 61% yields, respectively. Additionally, 4-fluoro- substituted NHPI ester gave the desired product **3l** in 45% yield with 1 : 1 rr. Subsequently, we explored the substrate scope of vinyl azides as α-primary amino alkyl radical precursors. The electron-withdrawing group (such as *p*-CF₃, *m*-Cl and *m*-Br) and electron-donating group (*p*-ʰBu) substituted aryl vinyl azides were well-tolerated to furnish dihydroisoquinoline-1,4-dione compounds (**3m–3p**) in 36–52% yields.

Surprisingly, it was found that the reaction of carboxylic NHPI esters with vinyl azides in the presence of external NHPIs gave dihydroisoquinolin-1,4-diones derived from external NHPIs. Inspired by this encouraging result, different dimensions of parameters were evaluated to investigate the photo-catalytic three-component [4 + 2] reaction (Tables S7–S12†) using 5-methyl-substituted NHPI ester of carboxylic acid, vinyl azide and NHPI **4a**. Dihydroisoquinolin-1,4-diones compound **3a** was formed in 78% yield using 4CzIPN-Cl (2 mol%) as a photosensitizer and HE (4.0 equiv.) as a reductant in DCM (0.1 M).

Next, the scope of the photocatalytic three-component [4 + 2] reaction was further examined and the results are summarized in Fig. 3. Tertiary carboxylic acid derived NHPI esters with diverse substitution patterns, such as ethyl, trifluoromethyl and alkenes, were all good substrates for this three-component reaction with external NHPI (**4a**) in the presence of vinyl azide **2** to provide target products (**3q–3s**) in 50–68% yields. The NHPI ester synthesized from the drug molecule delivered the desired product (**3t**) containing gemfibrozil in 59% yield under standard conditions. Moreover, different vinyl azides were also applicable to the three-component [4 + 2] reaction conditions. Phenyl vinyl azide afforded the desired product (**3u**) in 50% yield. Monosubstituted phenyl vinyl azides with electron-donating groups or electron-withdrawing groups at the *para*-position were all suitable substrates for this photocatalytic three-component [4 + 2] reaction and provided corresponding products (**3v–3z**) in 42–67% yields. Aryl vinyl azide containing a free hydroxyl group was successfully transformed into **3z** in 53% yield. *Meta*-substituted phenyl vinyl azides, such as fluorine and methyl, reacted smoothly to furnish desired products (**3aa** and **3ab**) in synthetically useful yields. Additionally, 3,5-difluoro-substituted phenyl vinyl azides were successfully converted to corresponding dihydroisoquinoline-1,4-dione (**3ac**) in 65% yield. Notably, no dihydroisoquinoline-1,4-dione product derived from *N*-hydroxy-5-methylphthalimide was detected, probably due to the difference in redox potentials and solubility of *N*-hydroxyphthalimides.

To further explore the synthetic diversity and utility of this photocatalytic [4 + 2] protocol, convergent synthesis of
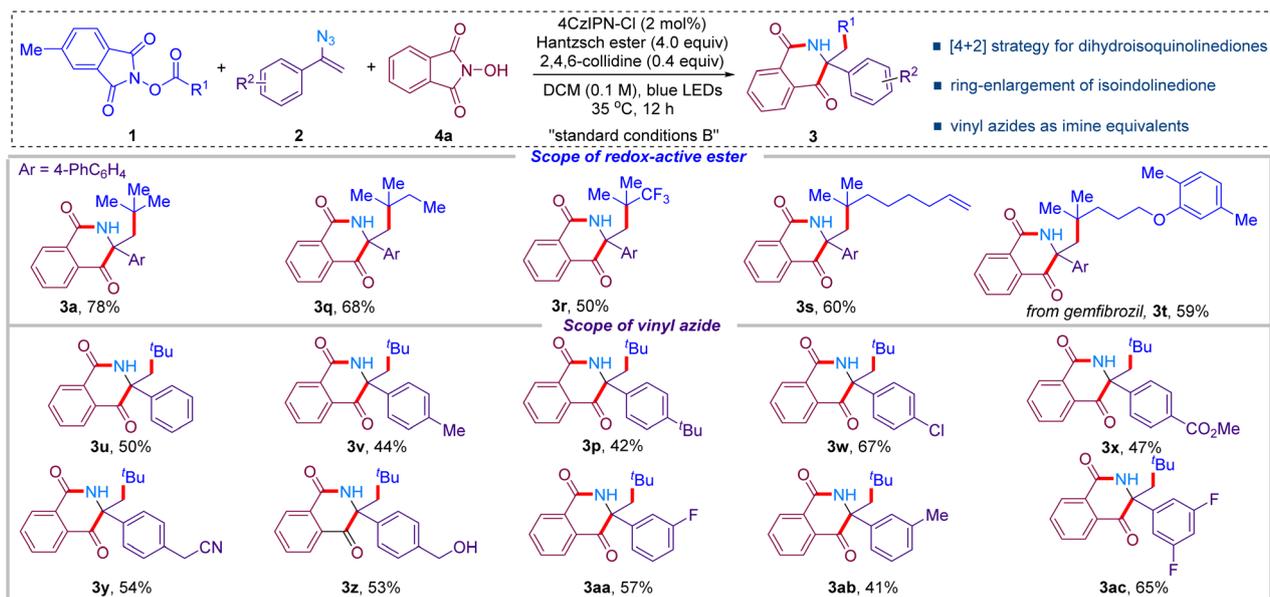
Fig. 3 Substrate scope of the photocatalytic three-component [4 + 2] reaction. The reaction was conducted using **1** (0.18 mmol), **2** (0.10 mmol), 4CzIPN-Cl (2.0 mol%), **4a** (0.25 mmol), Hantzsch ester (0.40 mmol) and 2,4,6-collidine (0.04 mmol) in DCM (0.10 M) irradiated with 30 W blue LEDs at 35 °C for 12 h.
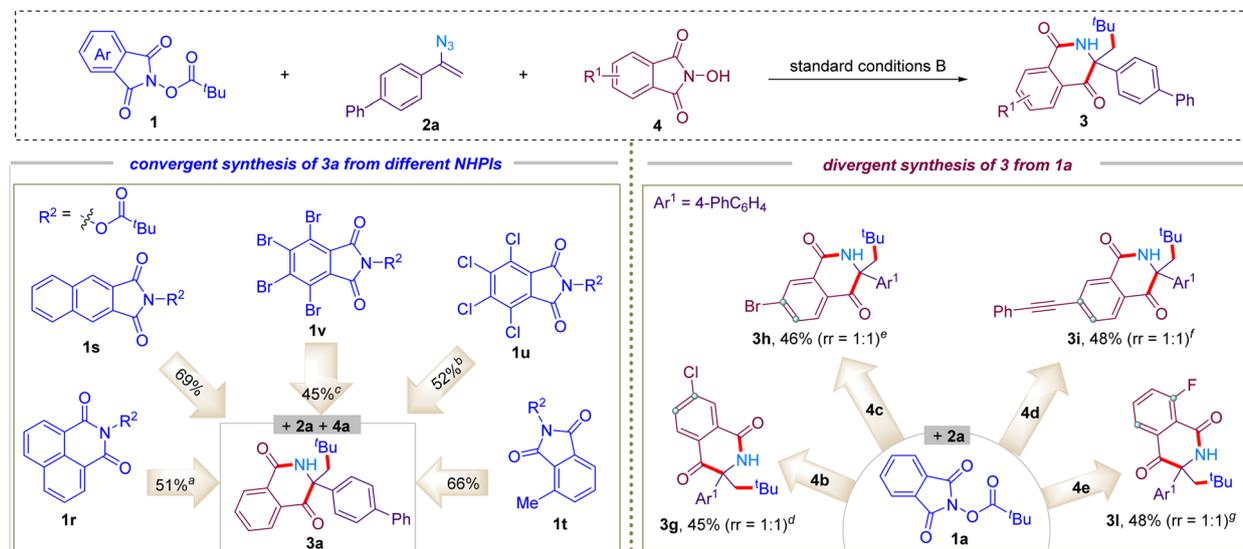

Fig. 4 Convergent and divergent synthesis of dihydroisoquinoline-1,4-diones by a photocatalytic three-component [4 + 2] reaction. Unless otherwise noted, the reaction was conducted using **1** (0.18 mmol), **2a** (0.10 mmol), 4CzIPN-Cl (2.0 mol%), **4** (0.25 mmol), Hantzsch ester (0.40 mmol) and 2,4,6-collidine (0.04 mmol) in DCM (0.10 M) irradiated with 30 W blue LEDs at 35 °C for 12 h. [a]**4a** (2.0 equiv.) was used. [b]**1u** (1.2 equiv.) was used. [c]**1v** (1.6 equiv.) was used. [d]**1a** (0.12 mmol) and **4b** (0.12 mmol) were used. [e]The reaction was conducted using **1a** (0.18 mmol), **4c** (0.18 mmol), DABCO (0.1 mmol) in DCM (1.5 mL). [f]The reaction was conducted using **1a** (0.18 mmol), **4d** (0.18 mmol) and DMAP (0.1 mmol) in DCM (2.0 mL). [g]Ir(ppy)$_2$(bpy)PF$_6$ (2 mol%) and DABCO (0.05 mmol) were used.

dihydroisoquinoline-1,4-dione from different NHPI esters with identical NHPI and divergent synthesis of different dihydroisoquinoline-1,4-diones from identical NHPI esters with different NHPIs have been investigated (Fig. 4). In the presence of N-hydroxyphthalimide, convergent synthesis of dihydroisoquinoline-1,4-dione (**3a**) was achieved in 45–69%

yields from different NHPI esters of pivalic acid (**1r–1v**) with **2a** (Fig. 4, left). Moreover, divergent synthesis of different dihydroisoquinoline-1,4-diones (**3g–3i** and **3l**) was successfully achieved in moderate yields from NHPI ester of pivalic acid (**1a**) with vinyl azide (**2a**) in the presence of different NHPIs (Fig. 4, right).
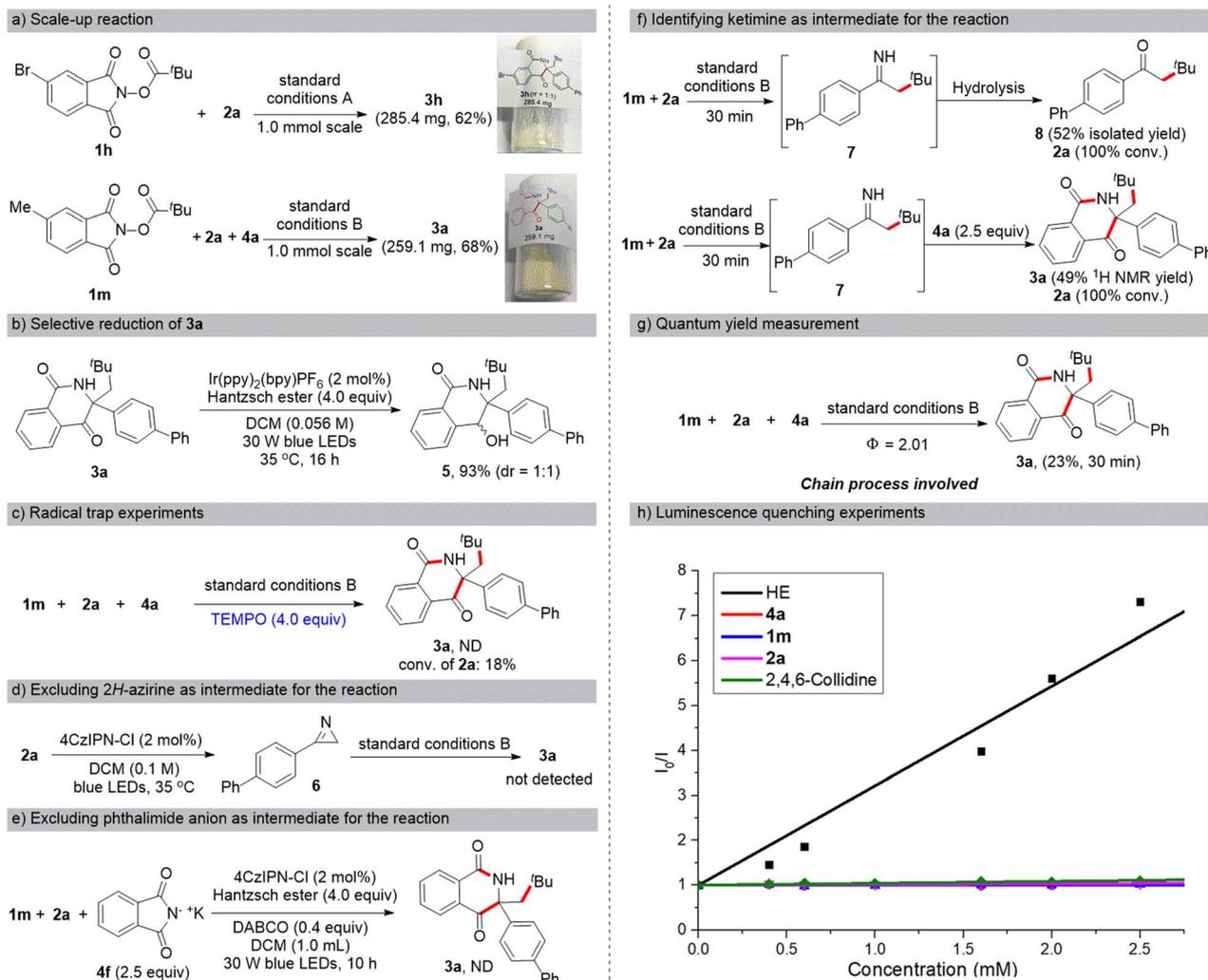
Fig. 5   Synthetic applications and mechanistic investigations. (a) Scale-up reaction; (b) selective reduction of 3a; (c) radical trap experiments; (d) excluding 2H-azirine as intermediate for the reaction; (e) excluding phthalimide anion as intermediate for the reaction; (f) identifying ketimine as intermediate for the reaction; (g) quantum yield measurement; (h) luminescence quenching experiments.

Furthermore, the synthetic robustness of this photocatalytic [4 + 2] strategy was further highlighted by a scaling up reaction (Fig. 5a). The reaction of using NHPI ester 1h as a bifunctional reagent on a 1.0 mmol scale to react with vinyl azide 2a under standard conditions provided dihydroisoquinoline-1,4-dione 3h in 62% yield (285.4 mg). The photocatalytic [4 + 2] three-component reaction of 1m with 2a in the presence of 4a provided dihydroisoquinoline-1,4-dione 3a in 68% yield (259.1 mg). Dihydroisoquinoline-1,4-dione 3a could be selectively reduced to synthesize β-amino alcohol compound 5 in 93% yield (dr = 1 : 1) (Fig. 5b), which further showcased the further elaboration of the final products. Moreover, the reaction of 1m with 2a and 4a in the presence of TEMPO ((2,2,6,6-tetramethylpiperidin-1-yl)oxyl, 4.0 equiv.) under otherwise identical standard conditions was carried out (Fig. 5c). The formation of 3a was completely inhibited, indicating the radical nature of this photocatalytic [4 + 2] process.[10] EPR studies were further conducted; it was confirmed that alkyl radicals formed

during the reaction (A_H = 21.20, A_N = 14.69, and g = 2.0048) (Fig. S1†).[11] In addition, the use of 2H-azirines to replace vinyl azides for this reaction under standard conditions led to no formation of desired product 3a, ruling out the possibility of 2H-azirine as an intermediate of the reaction (Fig. 5d).[12] In the three-component reaction, replacing NHPI with phthalimide anions failed to furnish the desired product 3a, which excluded the conversion of NHPI into phthalimide anions to participate in the reaction (Fig. 5e). Next, upon treating 1m and 2a under standard condition B in the absence of NHPI for 30 min, ketone 8 was formed in 52% yield after hydrolysis (Fig. 5f, top). Instead of hydrolysis, adding 4a into the reaction mixture resulted in the formation of target product 3a in 49% yield. These control experiments indicated that ketimine 7 may be an intermediate for this process (Fig. 5f, bottom). Furthermore, the measured quantum yield (Φ = 2.01) of the model reaction under blue light irradiation indicated that a radical-chain process might be involved in the reaction (Fig. 5g).[13] To gain further insights into
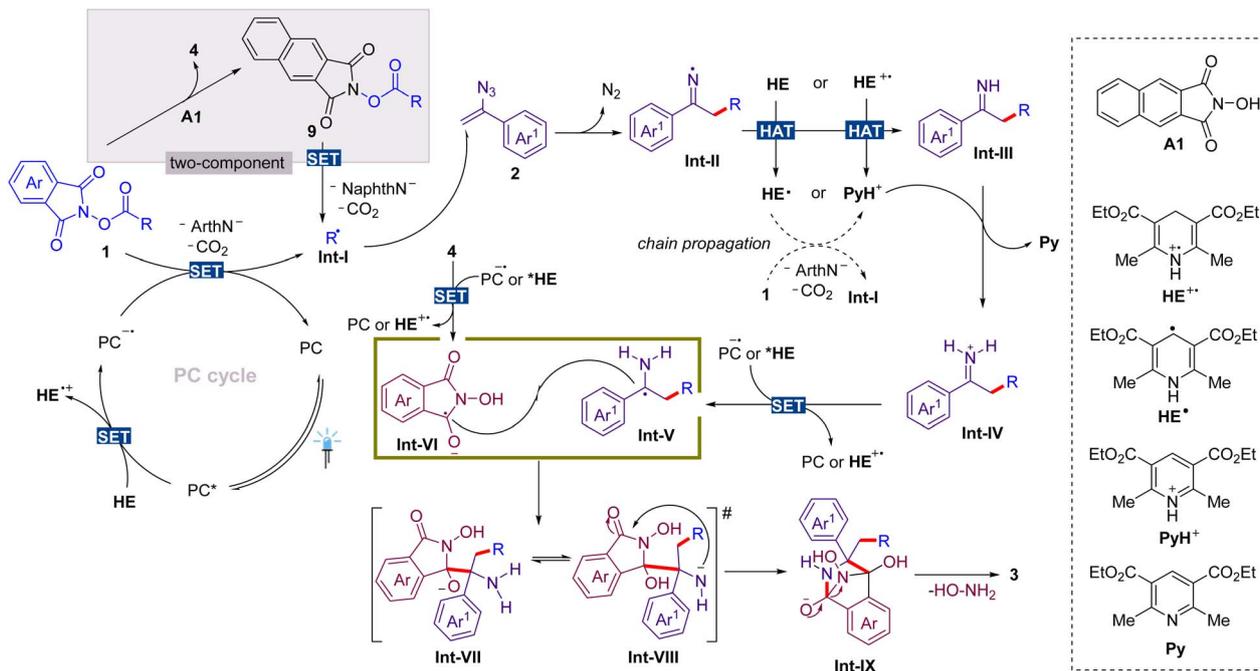
Fig. 6 Proposed mechanism for the photocatalytic [4 + 2] reaction for the synthesis of dihydroisoquinolin-1,4-diones.

the reaction mechanism, luminescence-quenching experiments for each reaction component, including HE, NHPI **4a**, NHPI ester **1m**, vinyl azide **2a** and 2,4,6-collidine, were conducted (Fig. 5h). The results showed that HE significantly quenched excited photocatalyst PC* and **1m**, **2a**, **4a** and 2,4,6-collidine showed no significant quenching effect of excited photocatalyst PC*, indicating that the reaction may be initiated by quenching the photocatalyst with HE.

Based on these experimental results and literature precedence,[8,14] a possible mechanism is proposed and depicted in Fig. 6. Irradiation of the PC using light generates the excited state PC*, which undergoes reductive quenching by HE ($E_{1/2}$red = +0.79 V *vs.* SCE) to generate PC$^{\bullet-}$ and HE$^{\bullet+}$.[15] Single electron transfer (SET) between PC$^{\bullet-}$ and redox-active NHPI esters **1** delivered the ground state photocatalyst (PC) and alkyl radical species **Int-I** by further decarboxylative fragmentation and release of a phthalimide anion.[16] In terms of the two-component reaction, **1** undergoes transesterification with **A1** to form a new NHPI ester **9** by releasing NHPI, which could be converted to alkyl radical **Int-I**. Subsequently, the **Int-I** radical adds to vinyl azide **2** to form iminyl radical species **Int-II** by release of nitrogen gas. A hydrogen atom transfer (HAT) process between **Int-II** and the HE or its radical cation HE$^{\bullet+}$ delivers ketimine **Int-III**.[8,17] Meanwhile, the radical HE$^{\bullet}$ might initiate a new chain propagation through an SET event with NHPI esters **1**. Then, protonation of **Int-III** affords iminium species **Int-IV**, facilitating the reduction by PC$^{\bullet-}$ or *HE ($E_{1/2}$red [*HE/HE$^{\bullet+}$] = −2.28 V *vs.* SCE) to yield α-primary amino alkyl radical species **Int-V**.[12] In the meantime, NHPI **4** ($E_{1/2}$red [**4a/4a**$^{\bullet-}$] = −2.17 V *vs.* SCE) (Fig. S10†) and PC$^{\bullet-}$ or *HE undergo a SET process to produce radical anion species **Int-VI**. Next, the radical–radical coupling between α-amino alkyl radical species **Int-V** and

radical anion species **Int-VI** leads to the formation of oxygen anion intermediate **Int-VII**, which undergoes tautomerization to nitrogen anion intermediate **Int-VIII**. Finally, **Int-VIII** undergoes an intramolecular nucleophilic addition reaction to obtain intermediate **Int-IX**, followed by extrusion of HO-NH$_2$ to deliver the dihydroisoquinoline-1,4-diones **3** as the final product.

Conclusions

In summary, a photocatalytic [4 + 2] reaction of NHPI esters of carboxylic acids with vinyl azides to access dihydroisoquinoline-1,4-diones has been developed. The key success of this method is the use of NHPI esters of carboxylic acids as bifunctional reagents to react with vinyl azides, enabled by cleavage of two C–N bonds along with formation of one C–N bond and two C–C bonds to enlarge a ring system. Notably, a three-component version of this reaction was realized in the presence of appropriate external NHPIs to afford dihydroisoquinolin-1,4-diones. Moreover, convergent synthesis of dihydroisoquinoline-1,4-dione from different NHPI esters with identical NHPI and divergent synthesis of diverse dihydroisoquinoline-1,4-diones from identical NHPI esters with different NHPIs have been realized, which further showcased the synthetic versatility of this photocatalytic protocol.

Data availability

The data supporting this article have been included as part of the ESI.† Crystallographic data for **3a** (CCDC 2361327) and **3h** (CCDC 2361326) have been deposited at the Cambridge Crystallographic Data Centre. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

Author contributions

W. S. conceived and directed the project. H. W. D. developed the reaction, performed the experiments, and collected the data. Y. L. L. and Q. Y. co-supervised the project. H. W. D., J. S. J., X. Y. C., Z. Y. Y., J. N. L., Y. L. L., Q. Y. and W. S. analyzed the data and wrote the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

Notes and references

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