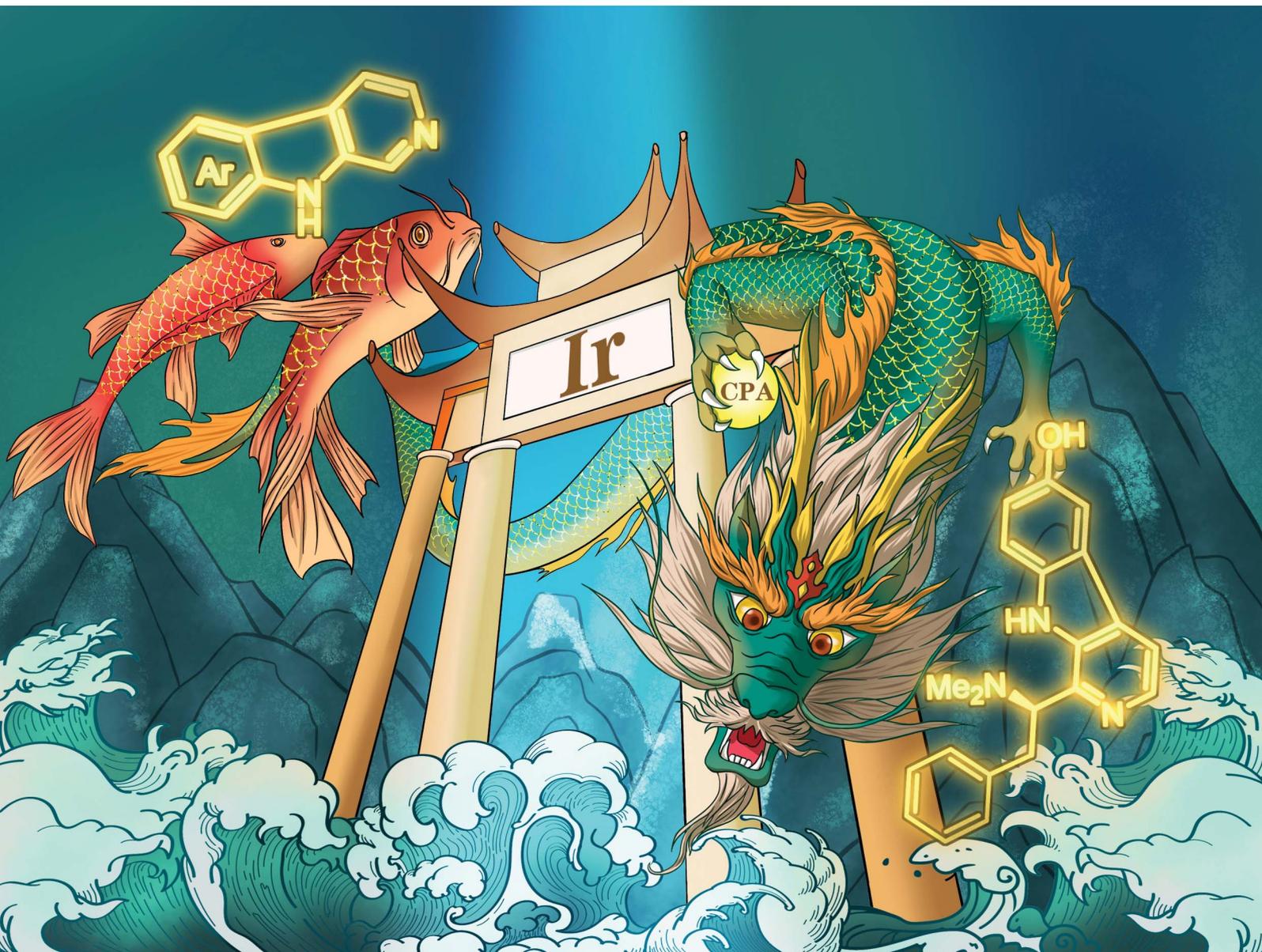


Chemical Science

rsc.li/chemical-science



ISSN 2041-6539

Cite this: *Chem. Sci.*, 2023, 14, 251

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

Received 23rd September 2022

Accepted 23rd November 2022

DOI: 10.1039/d2sc05313f

rsc.li/chemical-science

Photocatalytic enantioselective Minisci reaction of β -carboline and application to natural product synthesis†

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A highly efficient enantioselective direct C–H functionalization of β -carboline *via* a Minisci-type radical process under a photo-redox and chiral phosphoric acid cooperative catalytic system has been disclosed. Through this protocol, a wide range of C1 aminoalkylated β -carboline were constructed directly with high levels of enantioselectivities from readily available β -carboline and alanine-derived redox-active esters. This transformation allows straightforward access to highly valuable enantioenriched β -carboline, which are an intriguing structural motif in valuable natural products and synthetic bioactive compounds. This protocol has been utilized as a highly efficient synthetic strategy for the concise asymmetric total synthesis of marine alkaloids eudistomin X, (+)-eudistomidin B and (+)-eudistomidin I.

Introduction

Radical chemistry has exhibited enormous potential in direct C–H functionalization of *N*-heteroarenes to construct complex molecules.^{1–4} However, the corresponding catalytic asymmetric radical transformations remain a significant challenge due to the lack of compatible effective enantioselective catalytic systems and the high reactivity of radical species.^{4,5} Liu⁶ and Zhang^{7,8} have presented copper-catalyzed enantioselective C(sp²)-H alkylation of electron-deficient azoles *via* alkyl radical intermediates, forming valuable chiral azoles with good to excellent regio- and enantioselectivities. With the rapid development of photochemistry, it has been shown that the cooperative photo-catalysis strategy plays an essential role in catalytic asymmetric radical transformations.^{9–11} Jiang,¹² Phipps,^{13–17} and Fu¹⁸ have successfully developed catalytic asymmetric Minisci-type reactions of *N*-heteroarenes to achieve direct enantioselective C–H functionalization of electron-deficient *N*-heteroarenes with high level of enantiocontrol using chiral phosphoric acids as the catalysts under photoredox-catalytic conditions. Studer and co-workers reported an enantioselective cascade radical reaction *via* a Minisci-type process to form heterocyclic γ -amino acids and 1,2-diamine derivatives under a photoredox and chiral Brønsted

acid cooperative catalytic system.¹⁹ Recently, Xiao and coworkers presented a photo-promoted asymmetric Minisci reaction of 5-arylpyrimidines with α -amino-acid derived redox-active esters to construct axially and centrally chiral heterobiaryls with high levels of diastereo-, and enantioselectivities.²⁰ In spite of this impressive progress on various asymmetric C–H radical functionalizations of electron-deficient *N*-heteroarenes,²¹ such as quinolines, isoquinolines, pyridines, and pyrimidines, the catalytic direct C–H enantioselective functionalization of β -carboline *via* a radical process has not been touched.^{22–24} The reason for this might originate from the less electron-deficient nature of the β -carboline structure, or from its reduced reactivity due to the participation of the nitrogen lone pair of the indole moiety, or from other regioselectivity-related problems.²

Notably, chiral β -carboline have been shown to be attractive and privileged scaffolds in a variety of natural products, bioactive agents and approved drugs, displaying diverse potent biological activities.^{25–29} For instance, eudistomin marine alkaloids, which bears a chiral aminoalkylated β -carboline core motif, exhibited extremely potent antiviral and antitumor activities (Fig. 1A).^{30–32} Compared with the well-developed catalytic asymmetric synthesis of tetrahydro- β -carboline,^{33,34} the highly effective catalytic enantioselective construction of β -carboline has been less explored (Fig. 1B).

Herein, we report an enantioselective Minisci reaction of β -carboline *via* catalytic asymmetric C–H radical functionalization process under a photoredox and chiral phosphoric acid cooperative catalytic system to construct enantioenriched β -carboline. This strategy has been applied as a key step in the efficient and concise asymmetric synthesis of biologically important eudistomin marine alkaloids (Fig. 1C).

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† Electronic supplementary information (ESI) available. CCDC 2215559. For ESI and crystallographic data in CIF or other electronic format see DOI: <https://doi.org/10.1039/d2sc05313f>



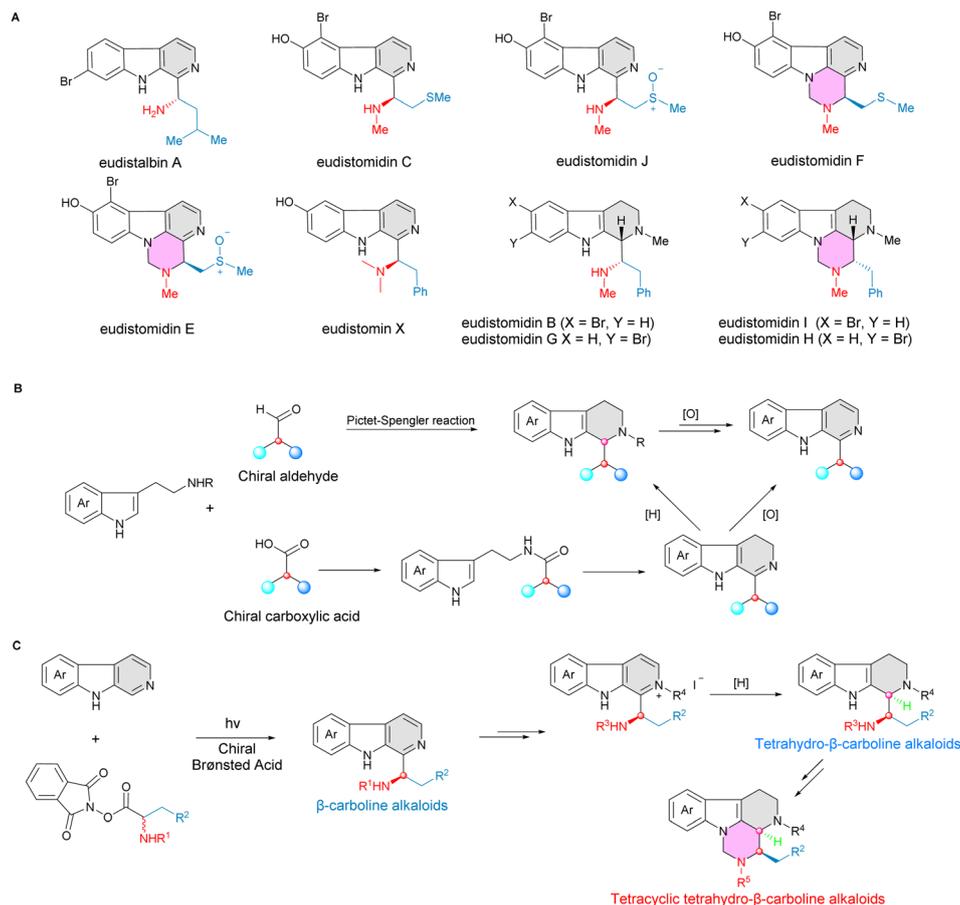


Fig. 1 Stereoselective synthesis of β -carboline and tetrahydro- β -carboline alkaloids. (A) Representative examples of naturally occurring C1-aminoalkylated bioactive β -carbolines and tetrahydro- β -carbolines. (B) Construction of β -carboline and tetrahydro- β -carboline skeletons by Pictet–Spengler reaction (well studied). (C) A new strategy for efficient construction of β -carboline and tetrahydro- β -carboline cores by photocatalytic Minisci reaction (this work).

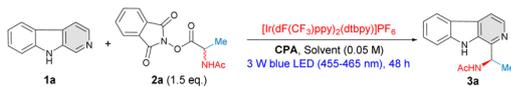
Results and discussion

Reaction optimization

Inspired by the work of Jiang¹² and Phipps,¹³ our study began with the reaction between β -carboline (**1a**) and racemic *N*-acetylalanine-derived redox-active ester (RAE) **2a** in the presence of 5 mol% of chiral phosphoric acid catalyst CPA-1 and 1 mol% of photocatalyst [Ir(dF(CF₃)ppy)₂(dtbpy)]PF₆ in 1,4-dioxane; the system was irradiated with blue LEDs (455–465 nm) for 48 h at 25 °C. To our delight, the reaction proceeded with excellent regioselectivity and only C1 C–H aminoalkylated product **3a** was obtained in an excellent yield, although without any enantiocontrol (92% yield, 0% ee) (Table 1, entry 1). In order to obtain high levels of asymmetric induction, different types of chiral phosphoric acid catalysts were evaluated (Table 1, entries 2–6). We were pleased to find that the 3,5-(CF₃)₂C₆H₃-substituted catalyst CPA-3 delivered **3a** in 83% yield with fair enantioselectivity (41% ee) (Table 1, entry 3). Notably, chiral phosphoric acids equipped with a chiral SPINOL backbone displayed a highly favorable catalytic performance, and CPA-6 (*R*)-STRIP gave a remarkable improvement on enantio-induction, affording **3a** in 83% yield and 68% ee (Table 1, entry 6). Further

screening of different solvents demonstrated that the solvent effect significantly influenced the enantioselectivity of this process (Table 1, entries 7–12). A notable improvement on both catalytic efficacy and enantioselectivity (90% yield, 80% ee) was observed when the reaction was carried out in THF (Table 1, entry 12), while other solvents showed inferior results (Table 1, entries 7–11). Lowering the reaction temperature revealed further increased enantioselectivities (Table 1, entries 13–14). Very good yield and excellent enantioselectivity (86% yield, 94% ee) was obtained when the reaction was conducted at –40 °C employing 10 mol% of CPA-6 (Table 1, entry 15). Thus, the optimal reaction conditions were established as 10 mol% of CPA-6, 1 mol% of photocatalyst [Ir(dF(CF₃)ppy)₂(dtbpy)]PF₆ in THF (0.05 M), irradiated by 3 W blue LEDs at –40 °C for 72 hours. The influence of *N*-protecting groups of the RAEs ranging from formyl, acetyl, *tert*-butyloxycarbonyl (-Boc), benzoyl (-Bz), to benzyloxycarbonyl (-Cbz) groups were also evaluated, indicating the *N*-acetylalanine-derived RAE was the most suitable substrate in terms of yield and ee (for more details, see ESI[†]). The effects of photocatalyst and light intensity of the reaction were also investigated (for more details, see ESI[†]).



Table 1 Optimization of reaction conditions^a


CPA-1: Ar = 2,4,6-Pr₃-C₆H₂
 CPA-2: Ar = 3,5-*i*Bu₂-4-MeO-C₆H₂
 CPA-3: Ar = 3,5-(CF₃)₂-C₆H₂

CPA-4: Ar = 3,5-(CF₃)₂-C₆H₂
 CPA-5: Ar = 2,4,6-Cy₃-C₆H₂
 CPA-6: Ar = 2,4,6-Pr₃-C₆H₂

Entry	Solvent	Cat. (mol%)	T (°C)	Yield ^b (%)	ee ^c (%)
1	1,4-Dioxane	CPA-1 (5)	25	92	0
2	1,4-Dioxane	CPA-2 (5)	25	58	19
3	1,4-Dioxane	CPA-3 (5)	25	83	41
4	1,4-Dioxane	CPA-4 (5)	25	81	46
5	1,4-Dioxane	CPA-5 (5)	25	82	58
6	1,4-Dioxane	CPA-6 (5)	25	83	68
7	MeCN	CPA-6 (5)	25	67	44
8	Toluene	CPA-6 (5)	25	91	56
9	CH ₂ Cl ₂	CPA-6 (5)	25	68	59
10	DME	CPA-6 (5)	25	92	59
11	EtOAc	CPA-6 (5)	25	74	73
12	THF	CPA-6 (5)	25	90	80
13	THF	CPA-6 (5)	-20	88	88
14 ^d	THF	CPA-6 (5)	-40	85	91
15 ^d	THF	CPA-6 (10)	-40	86	94

^a Reaction conditions: **1a** (0.1 mmol), **2a** (0.15 mmol), [Ir(dF(CF₃)ppy)₂(dtbbpy)]PF₆ (1 mol%), solvent (2.0 mL), 48 h. ^b Yield of isolated product. ^c Determined by HPLC analysis on a chiral stationary phase. ^d Reaction time: 72 h.

Substrate scopes

With the established reaction conditions in hand, the scope and generality of this protocol was investigated (Fig. 2). Firstly, a variety of β-carboline substrates were evaluated with *N*-acetylalanine-derived RAE **2a** under the optimal reaction conditions. Gratifyingly, variations in the structural and electronic properties of β-carboline substrates were all tolerated well. Different types of β-carbolines bearing either electron-rich (**2a–2h**, **2n–2o**) or electron-poor (**2i–2m**, **2p–2q**) substituents were smoothly transformed to the desired C–H aminoalkyl functionalized products with high yields and excellent levels of enantioselectivity. 6-Methyl-, 8-methyl-, 5-methyl-, 4-methyl-, and 6-methoxy substituted β-carbolines were all proven to be suitable substrates under this catalytic system, affording the corresponding products **3c–3g** in 72–82% yield with 94–96% ee. β-Carboline **1h** bearing a free hydroxyl group was well compatible in terms of both reactivity and asymmetric induction, giving the target product **3h** with 63% yield and 97% ee. Electron-withdrawing groups, such as Cl[−], Br[−] and F[−], at different positions on the β-carboline scaffold were demonstrated to have little influence on yield and enantioselectivity (**3i–3m**, 77–87% yield and 86–96% ee). Considering the fact that various eudistomin marine alkaloids exhibit a phenylalanyl moiety, *N*-acetylphenylalanine-derived RAE **4m** was also

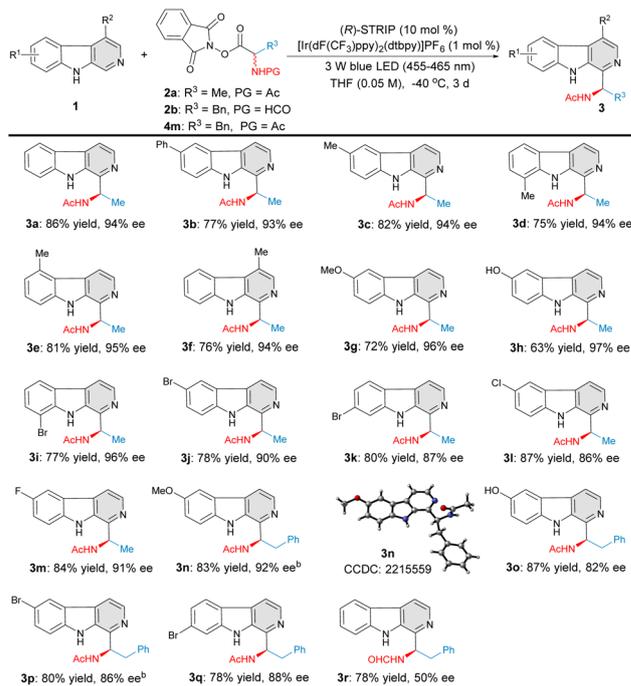


Fig. 2 Substrate scope of β-carbolines. ^aReaction conditions: **1** (0.2 mmol), **2a**, **2b**, or **4m** (0.3 mmol), [Ir(dF(CF₃)ppy)₂(dtbbpy)]PF₆ (1 mol%), (*R*)-STRIP (10 mol%), THF (0.05 M), 3 W Blue LEDs (455–465 nm), −40 °C, 3 d. ^bTHF (0.025 M).

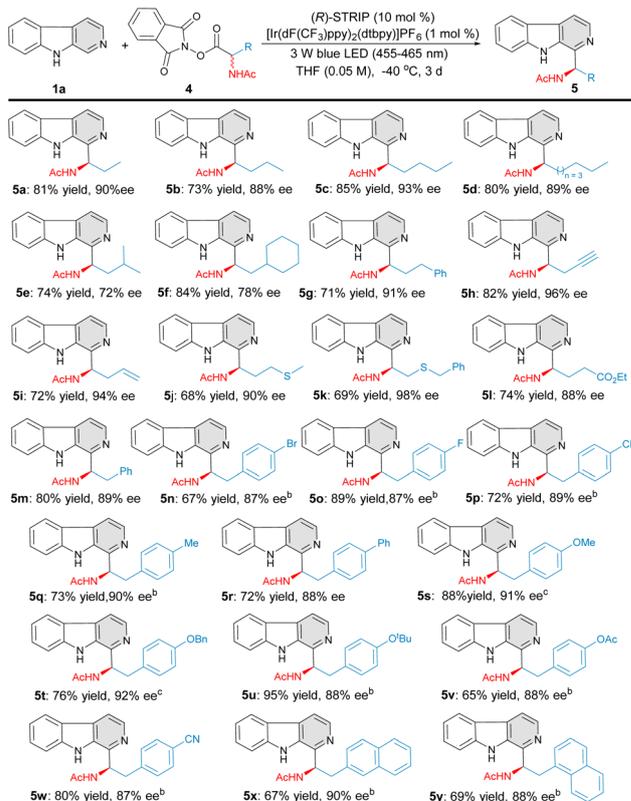


Fig. 3 Substrate scope of redox active esters (RAEs). ^aReaction conditions: **1a** (0.2 mmol), **4** (0.3 mmol), [Ir(dF(CF₃)ppy)₂(dtbbpy)]PF₆ (1 mol%), (*R*)-STRIP (10 mol%), THF (0.05 M), 3 W Blue LEDs (455–465 nm), −40 °C, 3 d. ^bTHF (0.025 M). ^cTHF (0.04 M).



examined in this transformation. Various C–H phenylalanyl-substituted β -carboline **3n–3q** were obtained with high level of yields and enantioselectivities (78–87% yield, 82–92% ee). Interestingly, product **3r** was obtained from the *N*-formylphenylalanine-derived RAE **2b** in good yield but moderate enantioselectivity, possibly due to the steric hindrance effect.

Encouraged by the above results, we further evaluated a wide range of amino-acid derived RAEs (Fig. 3). Alanine homologue substrates with different carbon chain length were first examined. Clearly, the carbon chain length of the amino-acid derived RAEs exhibits little influence on the yields and enantioselectivities, and the corresponding C–H aminoalkyl functionalization products **5a–5d** were effectively constructed (73–85% yield, 88–93% ee). Sterically more hindered amino-acid derived RAEs were also tolerated in this transformation, albeit with slightly decreased enantioselectivities (**5e–5f**, 72–78% ee).

Various functional groups, such as phenyl (**5g**), thioethers (**5j–5k**), and esters (**5l**), were well tolerated, providing the desired products with excellent asymmetric induction (**5g–5l**, 88–98% ee). To our delight, terminal alkenyl- and alkynyl-containing RAEs **4h–4i** transformed efficaciously under this reaction conditions to furnish the products **5h** and **5i** with excellent yields and enantioselectivities. A series of 4-substituted phenylalanine-derived RAEs were further evaluated, affording the products **5m–5w** in good yields and excellent level of enantiocontrol (65–95% yield, 87–92% ee). 1-Naphthyl and 2-naphthyl-substituted amino-acids were also tolerated in this catalytic system, affording the target products **5x–5y** smoothly in good yields and enantioselectivities (67–69% yield, 88–90% ee).

Total synthesis of eudistomin marine alkaloids

The synthetic potential and utility of this methodology were demonstrated in the total synthesis of eudistomin marine alkaloids (Fig. 4). Firstly, we introduced this enantioselective C–H bond aminoalkyl functionalization as a straightforward synthetic strategy for the concise synthesis of marine alkaloid eudistomin X. ^{35,36} Simple treatment of the optically pure C–H functionalization product **3o**, obtained after a simple recrystallization, with deacetylation and aminomethylation conditions afforded the target natural product eudistomin X directly with 82% yield without any loss of enantiomeric purity. We then focused our attention on applying this asymmetric Minisci reaction for the highly efficient synthesis of tetrahydro- β -carboline natural products eudistomidin B^{30,37} and eudistomidin I.^{32,38} To our great delight, compound **3p** underwent acetyl group cleavage and subsequent *N*-Boc protection successfully to furnish the desired product **9**. The transformation of compound **9** to the natural product (+)-eudistomidin B proceeded smoothly in a highly diastereoselective manner (>10 : 1 dr) by a three-step sequence, which included the formation of β -carboline methiodide **10**, selective reduction of pyridine methiodide with

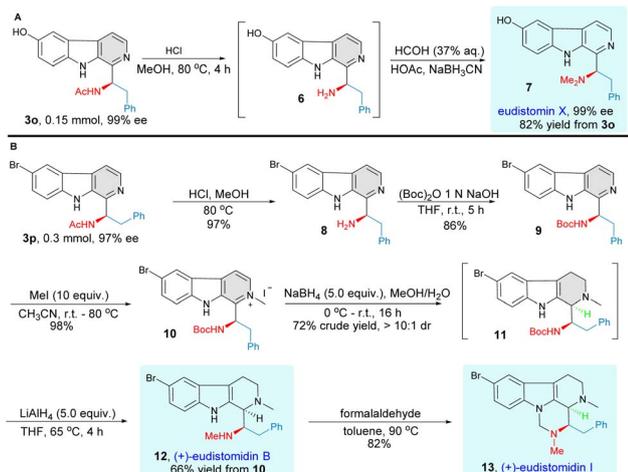


Fig. 4 Total synthesis of β -carboline marine alkaloids. (A) Total synthesis of eudistomin X. (B) Total synthesis of (+)-eudistomidin B and (+)-eudistomidin I.

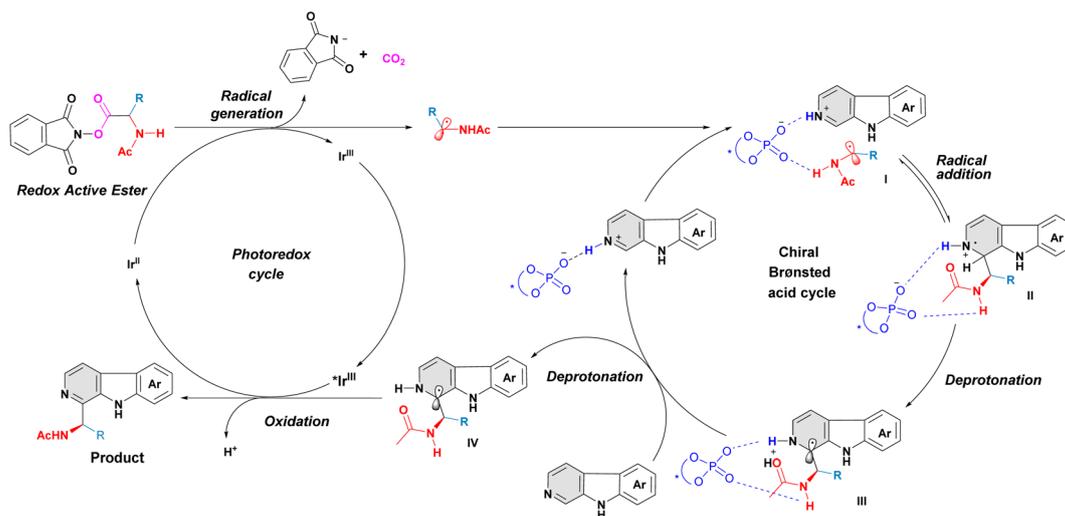


Fig. 5 Proposed catalytic cycle.



NaBH₄,³⁹ and reduction of *N*-Boc to *N*-Me. Then, treatment of (+)-eudistomidin B with formaldehyde *via* a cyclocondensation process readily afforded the desired (+)-eudistomidin I. The absolute configuration of optically pure compound **3n** was established as *R* by an X-ray crystallographic analysis and the structure of compounds **7**, **12** and **13** were confirmed by comparing the reported spectroscopic data and optical rotation of natural eudistomin X,^{35,36} eudistomin B^{30,37} and eudistomin I^{32,38} (for more details, see ESI†).

Proposed mechanism

A plausible mechanism for this asymmetric Minisci reaction of β -carboline is shown in Fig. 5.^{12–18} Firstly, the α -aminoalkyl radical, generated from α -amino-acid derived redox-active ester, interacts with β -carboline, aided by the bifunctional phosphoric acid catalyst, affording indeterminate **I**. A subsequent reversible radical addition results in a radical cation species **II**. The intermediate **II** then undergoes an internal proton abstraction promoted by the carbonyl oxygen of the *N*-acetyl group,¹⁵ giving intermediate **III**. Subsequently, the deprotonation of intermediate **III** occurs with the help of an external β -carboline and forms the neutral radical intermediate **IV**. This deprotonation is considered as an irreversible and enantiodetermining step in this transformation.¹⁵ Finally, the dissociated radical intermediate **IV** transforms into the desired C–H aminoalkyl-functionalized product *via* a single-electron oxidation process.

Conclusions

In summary, we present a photocatalytic direct C–H enantioselective functionalization of β -carboline *via* a Minisci-type radical process using a chiral phosphoric acid as the chiral catalyst. This transformation allows straightforward access to a wide range of highly functionalized β -carboline from simple and readily available starting materials with high level of enantioselectivity. This protocol has been applied as a highly efficient synthetic strategy for the concise asymmetric total synthesis of marine alkaloids. Further explorations on other catalytic asymmetric radical C–H functionalizations of *N*-heteroarenes in this field are on the way.

Data availability

All experimental and characterization data, as well as NMR spectra are available in the ESI.† Crystallographic data for compound **3n** has been deposited in the Cambridge Crystallographic Data Centre under accession number CCDC2215559.

Author contributions

M. P. performed the most experiments, collected and analyzed the data and wrote the draft; Y. J. assisted in some experiments and helped in synthesis of substrates; S. G. conceived the idea, guided this project and revised the manuscript.

Conflicts of interest

The authors declare no competing financial interests.

Acknowledgements

We are grateful to the National Natural Science Foundation of China (22001260); Shenzhen Science and Technology Innovation Committee (JCYJ20210324101810028); Guangdong Basic and Applied Basic Research Foundation (2021A1515010016); the Shenzhen Key Laboratory of Computer Aided Drug Discovery (ZDSYS20201230165400001); China Postdoctoral Science Foundation (2019M663172) and the Guangdong Provincial Key Laboratory of Catalysis (2020B121201002).

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