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Base-promoted cascade β-F-elimination/electrocyclization/Diels–Alder/retro-Diels–Alder reaction: efficient access to δ-carboline derivatives†

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A serendipitous and highly efficient approach for the construction of a variety of δ-carboline derivatives was developed through base-promoted cascade β-F-elimination/electrocyclization/Diels–Alder/retro-Diels–Alder reaction of *N*-2,2,2-trifluoroethylisatin ketoimine esters with alkynes in good to high yields with excellent regio-/chemoselectivity control. Moreover, a reasonable reaction pathway was proposed, which was in accordance with the prepared reaction intermediate and control experiment results. The δ-carboline product could be easily converted into a new chiral Py-box-type ligand through simple synthetic transformations. This salient strategy featured the advantages of metal-free conditions, excellent regio-/chemoselectivity, good to high yields, and outstanding substrate tolerance. Importantly, the potential application of these fascinating δ-carboline derivative products is well demonstrated in the recognition of ferric ions.

Introduction

Carbolines, usually known as pyrido[*x*,*y*-*b*]indoles, have emerged as important N-heterocycles with a broad spectrum of biological activities, which could be divided into α-, β-, γ- and δ-carbolines according to the position of the N atom.[1,2] Among these various types of carbolines, δ-carbolines are identified as privileged units in plenty of natural alkaloids, pharmaceuticals, and functional materials (Scheme 1a).[2] For example, CzBPDCb was used as an electron transport unit bipolar host material for blue phosphorescent organic light emitting didoes,[2a] N^5-ω-cyclohexylpentyl-N^1-methyl-δ-carbolinium displayed antibacterial and antifungal activities,[2b] PIQ could serve as a potential structure-selective G-quadruplex binding molecule,[2c] natural alkaloid Jusbetonin was isolated from *Justicia betonica*,[2d] and SYUIQ-5 is a potential anticancer therapeutic.[2e,f] Great efforts have been devoted to the development of the synthesis of these promising synthetic target δ-carboline derivatives, but limited efficient synthetic protocols have been explored until now.[3] Yao and coworkers disclosed a metal-free protocol to construct δ-carboline derivatives through the I_2-promoted cycloaddition of indolylchalcone oxime esters.[3c] Tang's group[3e] and Chang's group[3b] respectively developed different [2 + 2 + 2] cycloadditions as attractive approaches for the synthesis of δ-carbolines. Reddy and coworkers developed $Yb(OTf)_3$-catalyzed decarboxylative condensation of 2-aminoindole-3-carboxylates with ynals, followed by uncommon [3 + 2]-spirocycloaddition and 2,3-aza migration to afford dihydrochromeno-fused δ-carbolines in moderate yields.[3f]

On the other hand, quaternary α-trifluoromethyl α-amino acids (α-Tfm-AAs) and derivatives as important subunits have been extensively distributed in many bioactive molecules.[4] And we are interested in the synthesis of these important molecules using the easily available arylethynylenes as the nucleophilic reagents, which would suffer from the challenge of umpolung functionalization of α-trifluoromethyl ketoimine esters[5] (Scheme 1b left). However, the expected α-Tfm-AA derivative product was not found in the initial investigation. To our surprise, an unexpected compound was obtained, whose structure was clearly assigned as a δ-carboline derivative. This biologically important product δ-carboline derivative is intriguing, and we speculated that this transformation may undergo an unprecedented cascade β-F-elimination/electrocyclization/Diels–Alder/retro-Diels–Alder reaction (Scheme 1b right). Considering these current scarce synthetic methods, the intriguing structures and the biological relevance of δ-carboline derivatives, we decided to investigate this transformation in detail and establish another facile and efficient synthetic protocol.

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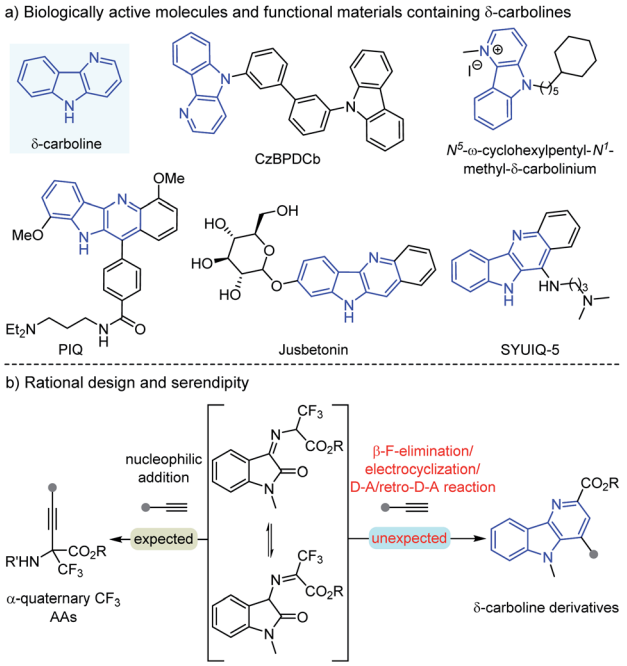


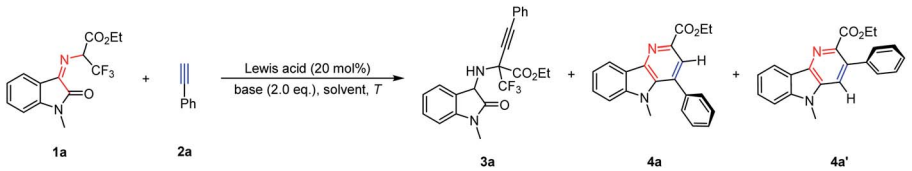
Scheme 1 Examples of biologically active molecules and functional materials containing δ-carboline motifs and synthesis of δ-carboline derivatives.

Results and discussion

In order to optimize the reaction conditions, the reactions between trifluoroethylisatin ketimine ester **1a** and phenylacetylene **2a** as model substrates were carried out in the presence of different Lewis acids and NEt_3. A series of Lewis acids, such as $Zn(OTf)_2$, $Cu(OTf)_2$, $InCl_3$ and $Sc(OTf)_3$, were then applied in this transformation. Although the expected α-quaternary trifluoromethyl amino acid derivative **3a** was not observed, structurally important δ-carboline derivative **4a** could be obtained in poor yields and exclusive regioselectivity, and another δ-carboline derivative **4a′** was not observed (8–15% yields, Table 1, entries 1–4). In order to improve the reactivity, chemoselectivity and regioselectivity, other bases like Cs_2CO_3 and DBU were then investigated, but no better result was afforded (Table 1, entries 5 and 6). When this transformation was performed in toluene, higher reactivity was provided with excellent selectivity (Table 1, entry 7). To our delight, when the reaction temperature was increased to 100 °C, the reactivity was greatly improved, the δ-carboline derivative **4a** could be obtained with high yield and exclusive regioselectivity (82% yield, >20 : 1 rr, Table 1, entry 8). In addition, it was found that very poor reactivity was furnished in the absence of a base (Table 1, entry 9). Remarkably, this transformation could be performed smoothly just promoted by NEt_3, leading to the product **4a** in good yield with exclusive regioselectivity (Table 1, entry 10). These results demonstrated that a Lewis acid was not essential in this cascade reaction. And we speculated that ketoimine ester **1a** and phenylacetylene **2a** may go through the cascade β-F-elimination/electrocyclization/Diels–Alder/retro-Diels–Alder reaction to produce δ-carboline derivative **4a**.

With the optimal reaction conditions in hand, the substrate generality of this protocol was then assessed. As shown in Table 2, *N*-2,2,2-Trifluoroethylisatin ketoimine ester **1a** was treated with a wide range of aromatic alkynes, and a variety of desired δ-carboline derivatives **4** were furnished with excellent results. When aryl alkynes were applied as reaction partners, the electronic properties of the substituted groups on the phenyl ring have little influence on the reactivities and regioselectivities. We found that the electron-neutral, electron-donating and electron-

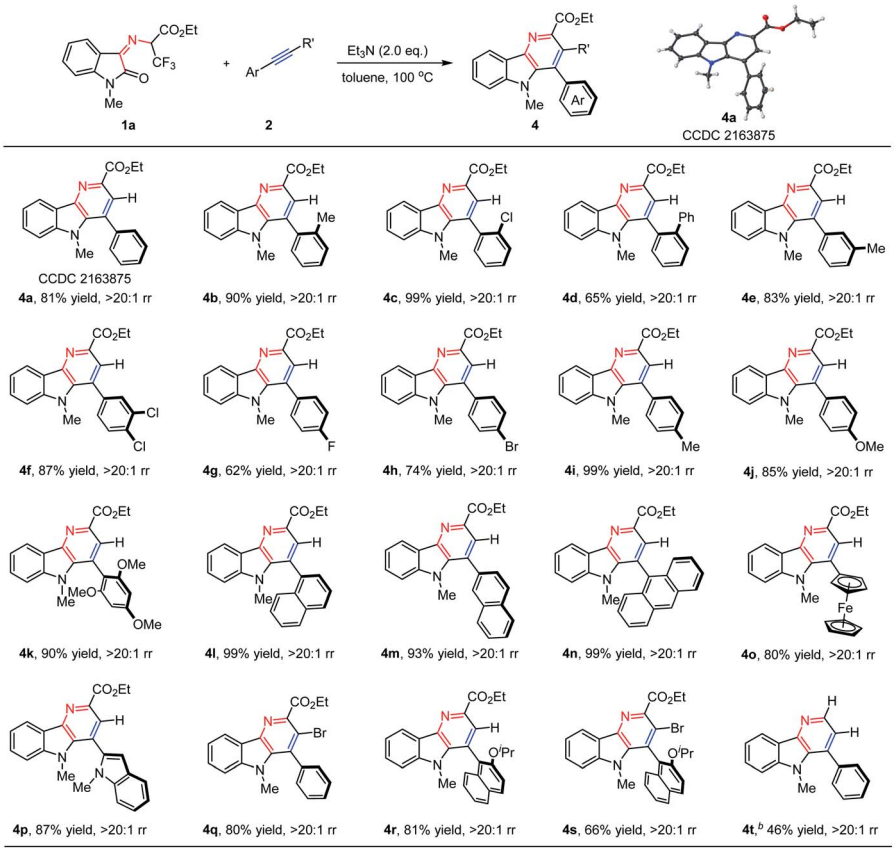
Table 1 Optimization of reaction conditions for the cascade β-F-elimination/electrocyclization/Diels–Alder/retro-Diels–Alder reaction of ketoimine ester **1a** and phenylacetylene **2a**[a]



Entry	Lewis acid	Base	Solvent	T (°C)	**3a**/**4a**/**4a′**[b]	Yield[c] (%)
1	$Zn(OTf)_2$	NEt_3	DCM	25	0/100/0	15
2	$Cu(OTf)_2$	NEt_3	DCM	25	0/100/0	8
3	$InCl_3$	NEt_3	DCM	25	0/100/0	8
4	$Sc(OTf)_3$	NEt_3	DCM	25	0/100/0	9
5	$Zn(OTf)_2$	Cs_2CO_3	DCM	25	0/100/0	11
6	$Zn(OTf)_2$	DBU	DCM	25	—	—
7	$Zn(OTf)_2$	NEt_3	Toluene	25	0/100/0	25
8	$Zn(OTf)_2$	NEt_3	Toluene	100	0/100/0	82
9	$Zn(OTf)_2$	—	Toluene	100	—	—
10	—	NEt_3	Toluene	100	0/100/0	81

[a] All reactions were carried out with 0.20 mmol ketoimine ester **1a**, 0.40 mmol phenylacetylene **2a**, 20 mol% Lewis acid, and 0.4 mmol base in 2 mL solvent. [b] The selectivity was determined by using a ^{1}H NMR analysis. [c] Isolated yield.

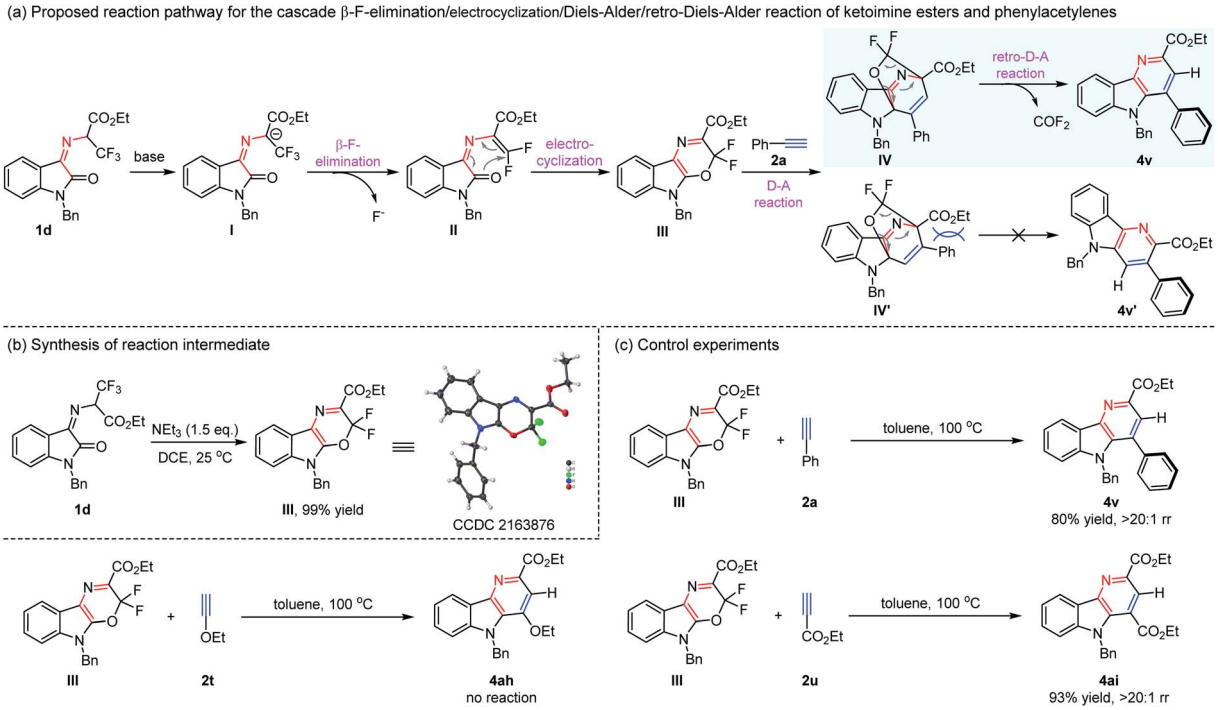
Table 2 Substrate scope study for arylacetylenes[a]



[a] All reactions were carried out with 0.20 mmol ketoimine ester **1a**, 0.40 mmol arylalkyne **2**, and 0.4 mmol NEt_3 in 2 mL toluene at 100 °C. The regioselectivity was determined by ^1H NMR analysis. The yield is isolated yield. [b] (*Z*)-1-Methyl-2-methylene-*N*-(2,2,2-trifluoroethyl)indolin-3-imine **1b** was used as the substrate.

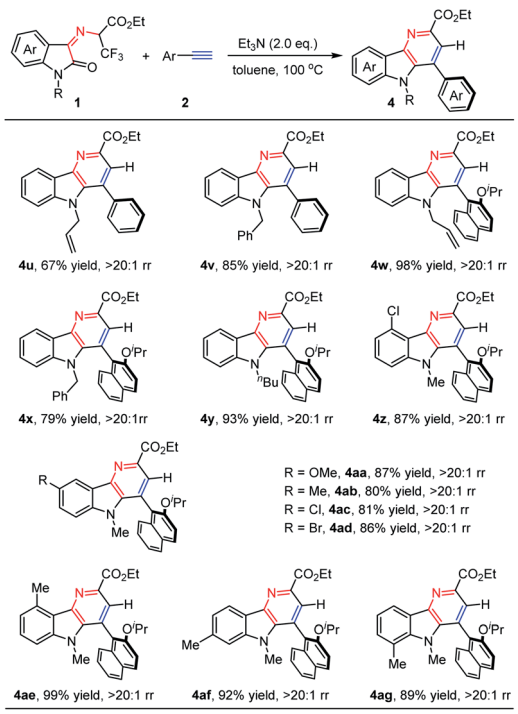
withdrawing groups could be well tolerated, resulting in the corresponding δ-carboline products **4a–4k** in moderate to high yields with exclusive regioselectivity (62–99% yields, >20 : 1 rr). The structure of product **4a** was determined by X-ray analysis (CCDC 2163875†). It is worth noting that other polycyclic aromatic substituted alkynes bearing steric hindrance, such as 1-naphthyl (**2l**), 2-naphthyl (**2m**), 9-anthracyl (**2n**) and 2-indolyl (**2p**) groups, underwent cascade β-F-elimination/electrocyclization/Diels–Alder/retro-Diels–Alder reaction smoothly to give the desired products **4l–4n** and **4p** in 87–99% yields. In addition, the ferrocenyl substituted alkyne (**2o**) was also surveyed, and the corresponding product (**4o**) could be obtained in 80% yield. Remarkably, compared with an aryl-terminated alkyne, disubstituted (bromoethynyl)benzene **2q** was also amenable under the standard reaction conditions, giving the desired product **4q** in 80% yield. Notably, bulky 1-ethynyl-2-isopropoxynaphthalene **2r** and 1-(bromoethynyl)-2-isopropoxynaphthalene **2s** also performed well to deliver the desired products **4r** and **4s** with satisfying results (81% yield and 66% yield, respectively). In addition, ethyl-(*Z*)-2-((1-methyl-2-oxoindolin-3-ylidene)amino)acetate **1b** could be tolerated in this cascade reaction, delivering the desired product **4t** in 46% yield. When ethyl-(*Z*)-2-((1-methyl-2-oxoindolin-3-ylidene) amino)-2-phenylacetate was then examined in this reaction system, no expected δ-carboline derivative was obtained with 3,3-difluoro-5-methyl-2-phenyl-3,5-dihydro-[1,4]oxazino[2,3-*b*] indole **III′** being separated in 80% yield as the intermediate (*vide infra* in Scheme 2b).

Next, we turned our attention to extending the above synthetic methodology for *N*-2,2,2-trifluoroethylisatin ketoimine esters. As shown in Table 3, the influence of protecting groups on the N atom of isatin moieties, such as allyl (**1c**), benzyl (**1d**), and *n*-butyl (**1e**) substituted groups, was first evaluated. They worked as compatible partners with phenylacetylene (**2a**) and steric 1-ethynyl-2-isopropoxynaphthalene (**2r**) smoothly, generating the corresponding products **4u–4y** in moderate to high yields with exclusive regioselectivity (67–98% yields, >20 : 1 rr). These reaction results demonstrated that the *N*-substituent of the *N*-2,2,2-trifluoroethylisatin ketoimine esters has little influence on the reactivity and selectivity. In addition, the effect of substitution at the benzene ring of the isatin motif was further explored. It was found that the substituted groups, such as halogen, methyl, and methoxy groups at different positions could be well tolerated. They



Scheme 2 Proposed reaction pathway, synthesis of the reaction intermediate and the control experiment.

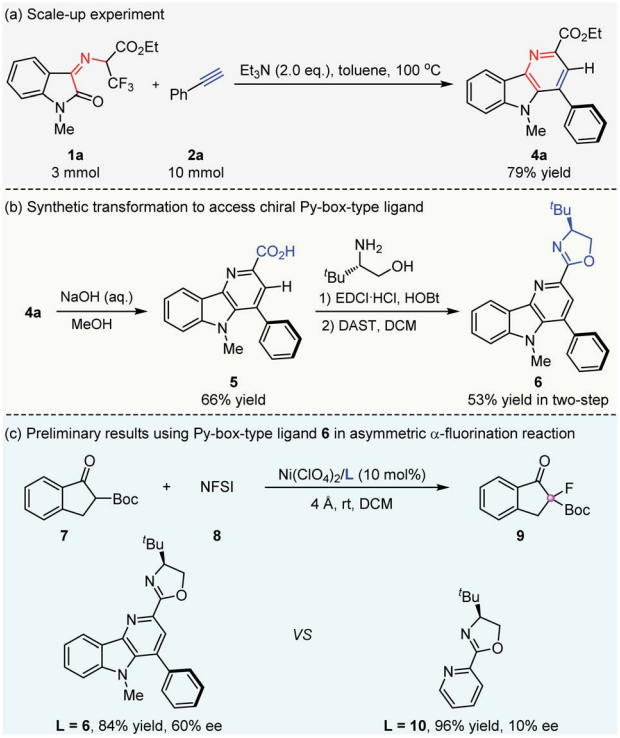
Table 3 Substrate scope study for ketoimine esters[a]



[a] All reactions were carried out with 0.20 mmol ketoimine ester **1**, 0.40 mmol arylalkyne **2**, and 0.4 mmol NEt_3 in 2 mL toluene at 100 °C. The regioselectivity was determined by ^1H NMR analysis. The yield is isolated yield.

reacted with steric 1-ethynyl-2-isopropoxynaphthalene (**2r**) efficiently, and excellent results were generally achieved for a wide range of *N*-2,2,2-trifluoroethylisatin ketoimine esters. A series of desired products (**4z–4ag**) were obtained with good to high yields (80–99% yields).

Having explored the new cascade β-F-elimination/electrocyclization/Diels–Alder/retro-Diels–Alder reaction, we were intrigued by the reaction mechanism. As depicted in Scheme 2a, a possible pathway for the synthesis of δ-carboline derivatives was proposed. Owing to the strong electron-withdrawing property of the trifluoromethyl group and ester group, the cascade transformation could be easily initiated by the loss of a proton in the presence of a base to form carbon anion **I**. Subsequently, it was converted to intermediate **II** *via* the β-F-elimination reaction, which underwent an intramolecular 6π-electrocyclic reaction to afford compound **III**.[6] The following Diels–Alder reaction with phenylacetylene **2a** gave the cyclization products **IV** and **IV′**. The product **IV′** should be more thermodynamically disfavored due to the steric repulsion, and the more preferential **IV** proceeded retro-Diels–Alder reaction smoothly, delivering the desired δ-carboline compound **4v** with high regioselectivity *via* extrusion of carbonyl fluoride. To further explore and confirm the reaction pathway, control experiments were conducted as shown in Scheme 2b. *N*-2,2,2-Trifluoroethylisatin ketoimine ester **1d** was treated with NEt_3, and it was found that 3,3-difluoro-3,5-dihydro-[1,4]oxazino[2,3-*b*]indole-2-carboxylate ester **III** is the sole product in nearly quantitative yield, and its structure was confirmed by X-ray diffraction analysis (CCDC 2163876,† Scheme 2b).[7] Moreover, the intermediate **III** could react with phenylacetylene **2a** easily to give the desired product **4v** in 80% yield (Scheme 2c). These results demonstrated that



Scheme 3 Scale-up experiment and application in asymmetric synthesis.

this transformation should go through intermediate **III**, which is consistent with the above-proposed pathway through the β-F-elimination/electrocyclization/Diels–Alder reaction. When electron-rich ethoxyacetylene **2t** was allowed to react with intermediate **III**, no reaction was observed. We found that electron-deficient ethyl propiolate **2u** reacted smoothly to furnish the corresponding δ-carboline compound **4ai** in 93% yield. Therefore, it is possible that the normal Diels–Alder reaction between the intermediate diene **III** with alkyne molecules proceeded in this reaction system.

To demonstrate the potential practicality of this cascade methodology, a scale-up experiment on 3 mmol was carried out smoothly, and the desired product δ-carboline derivative **4a** could be obtained in 79% yield (Scheme 3a). In addition, a further synthetic transformation of the δ-carboline derivative product was explored. The development of chiral ligands with a new skeleton is an important research topic in the field of asymmetric catalysis. A chiral oxazoline backbone has been regarded as a privileged structure for chiral ligands in the field of asymmetric catalytic synthesis.[8] As shown in Scheme 3b, a structurally novel chiral Py-box-type ligand could be easily prepared through simple transformations.[9] The ester group of a δ-carboline derivative was easily hydrolyzed to give carboxylic acid **5** under basic conditions, which underwent condensation with the commercially available chiral (*S*)-*tert*-leucinol and the subsequent intramolecular cyclization to give a new functionalized chiral Py-box-type ligand **6** smoothly with 53% yield in two steps. To our delight, chiral ligand **6** could be well utilized in the Ni-catalyzed asymmetric α-fluorination reaction of 2-*tert*-butoxycarbonyl-1-indanone **7** with *N*-fluorobenzenesulfonimide (NFSI) **8**, and preliminary results could be obtained to give the desired product **9** in good yield and moderate enantioselectivity. Ligand **6** was found to be more superior than the commonly used Py-box ligand **10**, which displayed poor enantioselective control in this asymmetric transformation (Scheme 3c).

In view of such a δ-carboline derivative containing π-conjugated system, we then turned our attention to investigate their

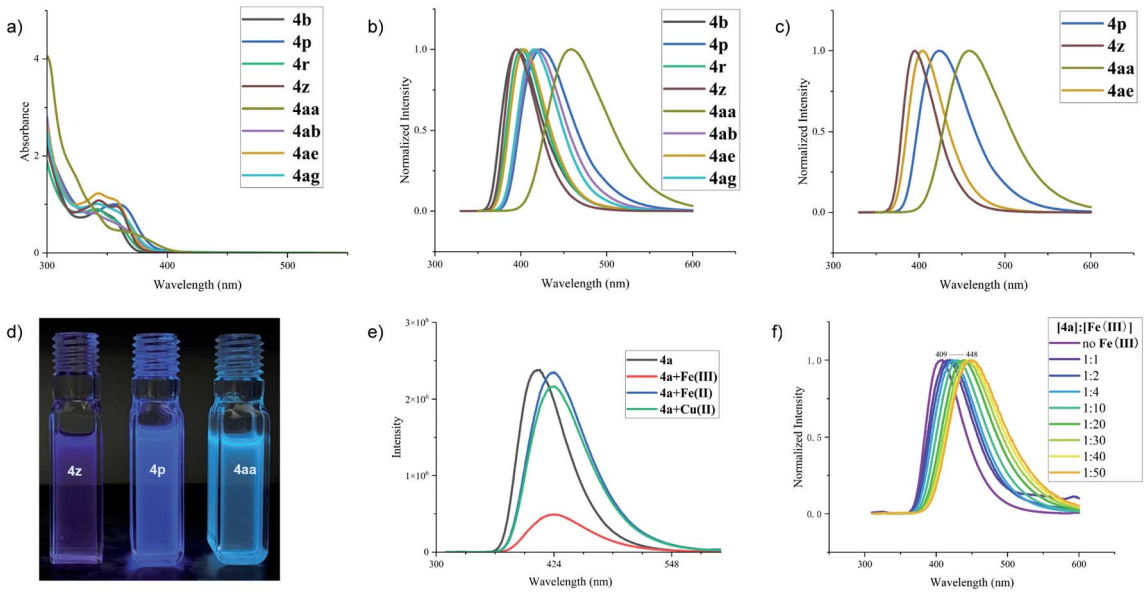


Fig. 1 (a) UV-vis absorption spectra. (b and c) Fluorescence spectra of δ-carboline derivatives. (d) Photographs of δ-carboline derivatives under irradiation with UV light (λ_{ex} = 365 nm) in DCM. (e) Fluorescence spectra of **4a** at 5×10^{-5} M with or without metal precursors (2×10^{-4} M) in CH_3CN. (f) Fluorescence spectra of **4a** with gradual addition of different amounts of Fe^{3+}.

spectral properties and potential application. The UV-visible absorption of a series of δ-carboline derivatives, including **4b**, **4p**, **4r**, **4z**, **4aa**, **4ab**, **4ae**, and **4ag**, has shown the adsorption ranges up to the visible light region within 460 nm in anhydrous dichloromethane (DCM) solution (Fig. 1a).[10] The fluorescence spectra of these molecules showed that the emission band maxima fell in the range between 395 (**4z**) and 460 nm (**4aa**) with a slight red-shift (Fig. 1b and c). As shown in Fig. 1d, the δ-carboline derivatives **4p**, **4z** and **4aa** exhibited different fluorescence emissions and colors under irradiation with UV light (λ_{ex} = 365 nm) in DCM. All these useful findings would offer a promising opportunity for these δ-carboline derivatives as potential fluorescent materials, metal ion recognition reagents, and biosensors.[11] Therefore, considering the possibility of the recognition ability of δ-carboline derivatives towards metal ions, we then focused on the investigation of the metal ion recognition effect of product **4a** in acetonitrile. As shown in Fig. 1e, the addition of $Fe(OTf)_3$ to the solution of **4a** led to a slight redshift but a great reduction of fluorescence intensity, while the addition of $Fe(OTf)_2$ or $Cu(OTf)_2$ only resulted in a slight redshift of the fluorescence. In addition, we found that the wavelength led to a redshift effect in the range of 409–448 nm in the process of gradual increase of the $Fe(OTf)_3$ concentration. These results demonstrated that ferric ions (Fe^{3+}) could be selectively recognized by δ-carboline derivative **4a**.[12]

Conclusions

In summary, we developed a new and highly efficient base-promoted cascade β-F-elimination/electrocyclization/Diels–Alder/retro-Diels–Alder reaction of *N*-2,2,2-trifluoroethylisatin ketoimine esters with alkynes, which provided a facile and efficient approach to access a wide range of nitrogen-containing heterocyclic δ-carboline derivatives in good to high yields. This synthetic strategy had the advantages of metal-free conditions, excellent regio-/chemoselectivity, good to high yields, wide substrate generality, and various synthetic transformations. Moreover, a possible reaction pathway was proposed for this cascade protocol, which was confirmed by the reaction intermediate and control experiment results. Importantly, the δ-carboline derivative product had good recognition ability of ferric ions through fluorescence spectrum analysis.

Data availability

The ESI† contains method description, product characterization data, and NMR spectra.

Author contributions

CJW conceptualized the project. CJW and XQD supervised the investigation. XSS and XYD performed the research. CJW and XQD co-wrote the paper. All authors analyzed the data, discussed the results, and commented on the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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