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# Enantioselective construction of *cis*-hydroindole scaffolds via an asymmetric inverse-electron-demand Diels–Alder reaction: application to the formal total synthesis of (+)-minovincine†

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*cis*-Hydroindole scaffolds widely exist in a large number of natural products, pharmaceuticals, and organocatalysts. Therefore, the development of efficient and enantioselective methods for the construction of *cis*-hydroindoles is of great interest and importance. Herein, a novel approach for the enantioselective synthesis of *cis*-hydroindole scaffolds has been realized through a chiral *N,N'*-dioxide/Mg(OTf)<sub>2</sub> complex catalyzed asymmetric inverse-electron-demand Diels–Alder (IEDDA) reaction of 2-pyrone and cyclic enamines. A series of substituted *cis*-hydroindole derivatives bearing multiple contiguous stereocenters and functional groups were obtained in good to excellent yields and enantioselectivities (up to 99% yield, and 95% ee) under mild reaction conditions. Moreover, the enantioselective formal total synthesis of (+)-minovincine was concisely furnished with high efficiency and stereoselectivity to demonstrate the synthetic potential of this method.

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## Introduction

Chiral *cis*-hydroindole is a privileged scaffold present in numerous biologically active natural products<sup>1–8</sup> such as minovincine, kopsinine, vindolinine, and aeruginosin 298-A, pharmaceutical products<sup>9</sup> such as the antihypertensive drug perindopril, and proline analogue organocatalysts<sup>10,11</sup> (Scheme 1a). Complex molecular architectures and fascinating biological properties have long motivated the development of synthetic methods towards enantioselective construction of chiral *cis*-hydroindoles.<sup>12–15</sup> In this context, most strategies for the stereoselective construction of *cis*-hydroindoles are primarily based on using optically active starting materials.<sup>12,13a,b,13d</sup> In contrast, catalytic asymmetric reactions that rely on the use of readily accessible prochiral substrates to achieve enantioenriched *cis*-hydroindoles are still relatively rare. Mechanistically, these synthetic tactics are largely carried out by asymmetric (aza-) Michael additions.<sup>13c,14,15</sup> Therefore, the development of a general and novel strategy for concise and efficient

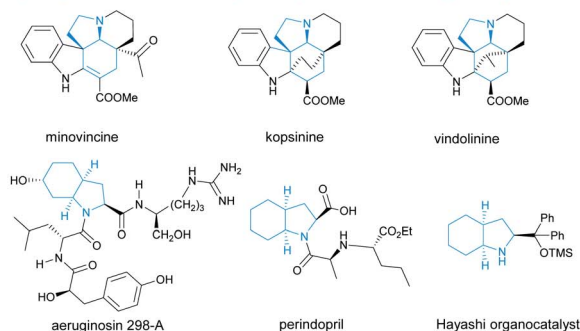
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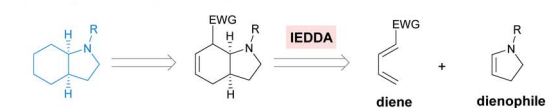
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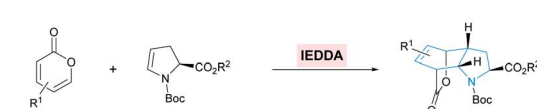
### a) *Cis*-hydroindole scaffold in natural products, pharmaceuticals and organocatalysts



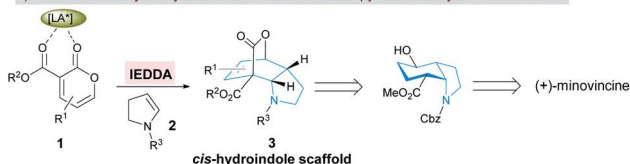
### b) Retrosynthetic analysis of *cis*-hydroindole scaffold via IEDDA



### c) Diastereoselective IEDDA reaction of 2-pyrone and chiral cyclic enamines (Jiang)



### d) This work: catalytic asymmetric IEDDA reaction of 2-pyrone and cyclic enamines

Scheme 1 Enantioselective synthesis of the *cis*-hydroindole scaffold.

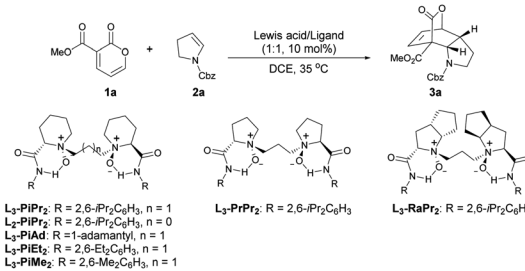
manipulation of densely functionalized *cis*-hydroindole derivatives with multiple stereocenters remains a significant challenge.

As one of the most important and fundamental reactions in organic chemistry, the Diels–Alder reaction between a conjugated diene and dienophile is widely applied to construct a six-membered carbo/hetero-cyclic ring.<sup>16,17</sup> By retrosynthetic analysis of *cis*-hydroindole, this chiral motif can be readily assembled from an electron-deficient diene and electron-rich cyclic enamine<sup>18</sup> *via* an enantioselective inverse-electron-demand Diels–Alder (IEDDA) reaction (Scheme 1b). Simultaneously, multiple stereocenters and dense functionalities can also be conveniently introduced into the resulting *cis*-hydroindole scaffolds in a single-step, which could be used for further functional group transformations and natural product synthesis. Due to the hemi-aromatic and adjustable electronic properties, electron-deficient 2-pyrone has become a favored diene component in the IEDDA reaction with a wide range of applications in aromatic compounds and complex natural product synthesis.<sup>19,20</sup> Particularly, the Cai group demonstrated the enantioselective IEDDA reaction of 3-carboalkoxyl-2-pyrone with electron-rich dienophiles, such as 2,2-dimethyl-1,3-dioxole,<sup>20g</sup> silyl cyclohexadienol<sup>20i</sup> and 1-naphthyl acetylenes,<sup>20j</sup> affording the products in high yield, excellent ee, and high dr. In spite of the above achievements, catalytic asymmetric synthesis of *cis*-hydroindoles *via* the enantioselective IEDDA reaction of 2-pyrones with cyclic enamines is still in its infancy so far. Recently, Jiang and co-workers disclosed an elegant diastereoselective IEDDA reaction of electron-deficient 2-pyrones with chiral cyclic enamines, affording the bridged *cis*-hydroindole derivatives in high yield with a moderate *exo/endo* ratio (Scheme 1c).<sup>21</sup> Herein, we describe our efforts towards an enantioselective IEDDA reaction catalyzed by the chiral *N,N'*-dioxide/Mg(OTf)<sub>2</sub> complex<sup>22</sup> using 3-carboalkoxyl-2-pyrone **1** and cyclic enamine **2** as the reaction partners (Scheme 1d). This reaction provided a facile and rapid route to access the bridged *cis*-hydroindole motif bearing four contiguous stereocenters with excellent levels of diastereo- and enantioselectivity. Furthermore, a formal total synthesis of bioactive (+)-minovincine alkaloid was furnished concisely and enantioselectively by subsequent transformation of the enantiomerically enriched products.

## Results and discussion

Our studies commenced by using 3-carbomethoxy-2-pyrone **1a** and cyclic enamine **2a** as model substrates to optimize the reaction conditions (Table 1). First of all, different metal salts coordinated with the *N,N'*-dioxide ligand **L**<sub>3</sub>-**PiPr**<sub>2</sub> were evaluated in DCE at 35 °C (entries 1–4). The results showed that Sc(OTf)<sub>3</sub> and In(OTf)<sub>3</sub> only led to trace yield of product **3a**, while Yb(OTf)<sub>3</sub> gave **3a** in 92% yield but 13% ee. To our delight, in the presence of the Mg(OTf)<sub>2</sub>/**L**<sub>3</sub>-**PiPr**<sub>2</sub> complex, the reaction occurred smoothly to generate the desired product **3a** in 73% yield with 78% ee (entry 4). Encouraged by these results, various chiral *N,N'*-dioxide ligands were investigated in cooperation with Mg(OTf)<sub>2</sub>, including changes in the length of the linker,

Table 1 Optimization of the reaction conditions<sup>a</sup>



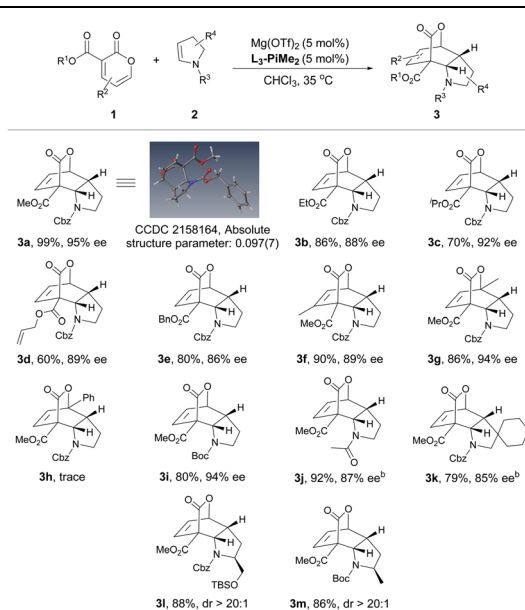
Entry	Lewis acid	Ligand	<i>t</i> (h)	Yield <sup>b</sup> (%)	ee <sup>c</sup> (%)
1	Sc(OTf) <sub>3</sub>	<b>L</b> <sub>3</sub> - <b>PiPr</b> <sub>2</sub>	24	Trace	—
2	In(OTf) <sub>3</sub>	<b>L</b> <sub>3</sub> - <b>PiPr</b> <sub>2</sub>	24	Trace	—
3	Yb(OTf) <sub>3</sub>	<b>L</b> <sub>3</sub> - <b>PiPr</b> <sub>2</sub>	3	92	13
4	Mg(OTf) <sub>2</sub>	<b>L</b> <sub>3</sub> - <b>PiPr</b> <sub>2</sub>	3	73	78
5	Mg(OTf) <sub>2</sub>	<b>L</b> <sub>2</sub> - <b>PiPr</b> <sub>2</sub>	12	99	68
6	Mg(OTf) <sub>2</sub>	<b>L</b> <sub>3</sub> - <b>PrPr</b> <sub>2</sub>	12	97	69
7	Mg(OTf) <sub>2</sub>	<b>L</b> <sub>3</sub> - <b>RaPr</b> <sub>2</sub>	12	99	79
8	Mg(OTf) <sub>2</sub>	<b>L</b> <sub>3</sub> - <b>PiAd</b>	17	91	12
9	Mg(OTf) <sub>2</sub>	<b>L</b> <sub>3</sub> - <b>PiEt</b> <sub>2</sub>	6	95	82
10	Mg(OTf) <sub>2</sub>	<b>L</b> <sub>3</sub> - <b>PiMe</b> <sub>2</sub>	3	97	88
11 <sup>d</sup>	Mg(OTf) <sub>2</sub>	<b>L</b> <sub>3</sub> - <b>PiMe</b> <sub>2</sub>	3	99	95
12 <sup>e</sup>	Mg(OTf) <sub>2</sub>	<b>L</b> <sub>3</sub> - <b>PiMe</b> <sub>2</sub>	3	99	95
13 <sup>f</sup>	Mg(OTf) <sub>2</sub>	<b>L</b> <sub>3</sub> - <b>PiMe</b> <sub>2</sub>	12	99	93

<sup>a</sup> Unless otherwise noted, all reactions were carried out with **1a** (0.10 mmol), **2a** (0.15 mmol), Lewis acid/ligand (1 : 1, 10 mol%) in DCE (0.5 mL) at 35 °C. <sup>b</sup> NMR yield detected by using CH<sub>2</sub>Br<sub>2</sub> as an internal standard. <sup>c</sup> Enantiomeric excess determined by HPLC analysis on a chiral stationary phase. <sup>d</sup> Carried out in CHCl<sub>3</sub> (0.5 mL). <sup>e</sup> Mg(OTf)<sub>2</sub>/**L**<sub>3</sub>-**PiMe**<sub>2</sub> (1 : 1, 5 mol%). <sup>f</sup> Mg(OTf)<sub>2</sub>/**L**<sub>3</sub>-**PiMe**<sub>2</sub> (1 : 1, 2 mol%). DCE = 1,2-dichloroethane, Tf = trifluoromethanesulfonyl.

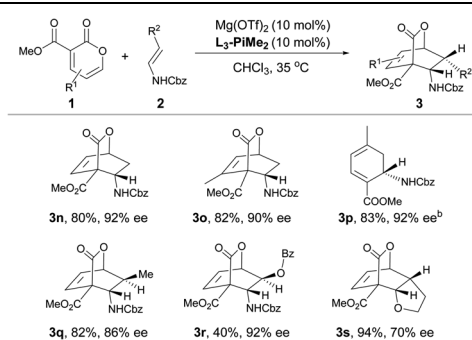
backbones of chiral amino acids, and substituents on the aromatic amide group (entries 5–10). It was found that **L**<sub>3</sub>-**PiMe**<sub>2</sub> derived from 2,6-dimethyl aniline could improve the result dramatically, providing the product **3a** in 97% yield with 88% ee (entry 10). The screening of other solvents suggested that CHCl<sub>3</sub> could further increase the enantioselectivity to 95% ee (entry 11). Notably, when the catalyst loading was reduced to 5 mol%, there was no obvious effect on the outcomes (entry 12). A further decrease to 2 mol% still demonstrated excellent reactivity and a slight deterioration of the enantioselectivity (99% yield with 93% ee, entry 13).

After the optimal reaction conditions were established, the substrate scope of this transformation was further investigated (Table 2 and 3). It was found that 2-pyrones bearing various ester groups such as methyl, ethyl, isopropyl, allyl and benzyl groups were well tolerated, affording **3a–3e** in good yields with excellent enantioselectivities (60–99% yields and 86–95% ee). Meanwhile, the absolute configuration of product **3a** was determined unambiguously by X-ray crystallography analysis. 2-Pyrone with a methyl group at the C4 or C6 position was also compatible, providing **3f** and **3g** in excellent yields (90% and 86% yields) and ee values (89% and 94% ee). Unfortunately, when 2-pyrone contained a phenyl group at the C6 position, the IEDDA reaction did not occur, probably due to the steric effect.



Table 2 Substrate scope of substituted 2-pyrones and cyclic enamines<sup>a</sup>

<sup>a</sup> All reactions were carried out with **1** (0.10 mmol), **2** (0.15 mmol), Mg(OTf)<sub>2</sub>/L<sub>3</sub>-PiMe<sub>2</sub> (1 : 1, 5 mol%) in CHCl<sub>3</sub> (0.5 mL) at 35 °C. Isolated yield. Enantiomeric excess was determined by HPLC on a chiral stationary phase. <sup>b</sup> Mg(OTf)<sub>2</sub>/L<sub>3</sub>-PiMe<sub>2</sub> (1 : 1, 10 mol%) was used.

Table 3 Substrate scope of substituted 2-pyrones and acyclic enamines<sup>a</sup>

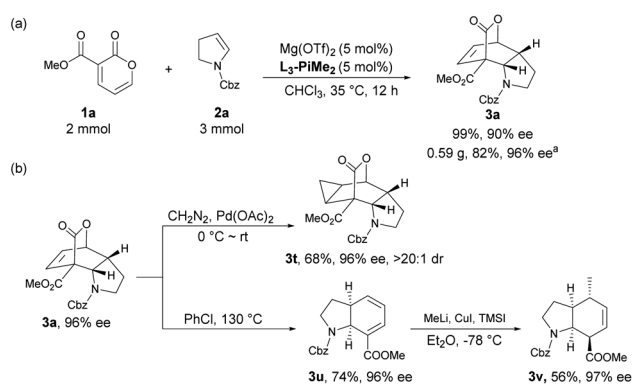
<sup>a</sup> All reactions were carried out with **1** (0.10 mmol), **2** (0.15 mmol), Mg(OTf)<sub>2</sub>/L<sub>3</sub>-PiMe<sub>2</sub> (1 : 1, 10 mol%) in CHCl<sub>3</sub> (0.5 mL) at 35 °C. Isolated yield. Enantiomeric excess was determined by HPLC on a chiral stationary phase. <sup>b</sup> The reaction was conducted at 35 °C for 36 h, and then heated at 110 °C for 2 h.

Next, the scope with respect to the substituted cyclic enamines was also examined. By changing different *N*-protecting groups of enamines, both Boc- and acetyl-protected cyclic enamines were confirmed to be well tolerated, affording **3i** and **3j** in good yields (80% and 92%) with high enantioselectivities (94% and 87% ee). The spiro-cyclic enamine **2k** was reactive as well to give desired product **3k** with moderate enantioselectivity. In addition, the chiral enamines **2l** and **2m** underwent the diastereoselective IEDDA reaction very well, delivering an exclusive diastereoisomer

**3l** and **3m**, respectively. Furthermore, the scope of acyclic enamines was also evaluated. As summarized in Table 3, terminal enamine **2n** reacted smoothly with 2-pyrone **1a** to afford the corresponding chiral bridged cyclolactone **3n** in 80% yield with 92% ee. C4- or C6-methyl substituted 2-pyrones were also tolerated (**3o** and **3p**), while cyclohexadiene **3p** was obtained in one pot through the tandem Diels–Alder reaction and *in situ* retro-[4 + 2] extrusion of CO<sub>2</sub> at an elevated temperature. We found that the methyl and benzyloxy substituted (*E*)-enamines **2q** and **2r** afforded the desired products in moderate to good yields and enantioselectivities. Gratifyingly, the IEDDA reaction of 2,3-dihydrofuran and 2-pyrone also occurred smoothly to provide **3s** in good yield but with a moderate ee (94% yield with 70% ee).

To illustrate the potential utility of the methodology, a scale-up synthesis of **3a** proceeded under the standard conditions. As shown in Scheme 2a, 2 mmol of compound **1a** reacted smoothly with 3 mmol of **2a**, furnishing the desired product **3a** in 82% yield with 96% ee after recrystallization. Meanwhile, several postcatalytic derivatizations were also conducted using enantiomerically pure product **3a**. By treatment with diazomethane and a catalytic amount of palladium acetate, the stereospecific cyclopropanation of the alkene motif in **3a** was accomplished, thus generating a complex polycyclic product **3t** in 68% yield with 96% ee and >20 : 1 dr. Complete extrusion of CO<sub>2</sub> *via* retro-Diels–Alder reaction led to the formation of a *cis*-tetrahydroindole structure **3u** without epimerization in chlorobenzene under reflux. Subsequent regioselective and stereoselective 1,6-Michael addition with MeLi and CuI afforded the corresponding *cis*-hexahydroindole derivative **3v** bearing multiple stereocenters in moderate yield with maintained enantioselectivity.

Natural product minovincine,<sup>23</sup> characterized by a spiroindoline pentacyclic framework with contiguous stereocenters, is considered as a “biogenetic turntable” between the vindolinine and kopsinine classes of isolates.<sup>24</sup> Intrigued by its fascinating structural features and potential biological activities, minovincine has long attracted considerable interest within the chemical synthesis community.<sup>25,26</sup> However, there are few examples in the literature for the enantioselective total synthesis of (–)-minovincine.<sup>27–29</sup> Based on our present approach and



Scheme 2 (a) Scale-up synthesis; (b) further transformation of the product. <sup>a</sup> Yield and enantiomeric excess were determined after recrystallization.

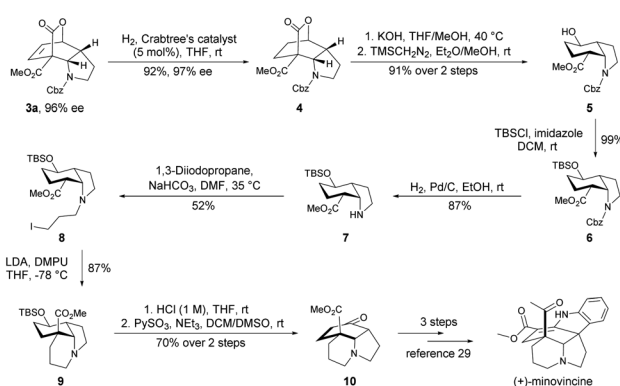


interest in synthesis of natural alkaloids,<sup>30</sup> the *cis*-hydroindole scaffold present in minovincine inspired us to develop a concise synthetic route for the enantioselective formal total synthesis of the naturally occurring enantiomer (+)-minovincine. As shown in Scheme 3, the enantiomerically pure product **3a** was readily reduced to **4** in 92% yield with 97% ee by treatment with 5 mol% Crabtree's catalyst under a hydrogen atmosphere. The hydrolysis of the tricyclic lactone **4** was then accomplished by using KOH, followed by extrusion of CO<sub>2</sub> and methyl esterification by using TMSCH<sub>2</sub>N<sub>2</sub> to afford the *cis*-hydroindole derivative **5** in 91% overall yield. Protection of the hydroxyl of **5** with *tert*-butyldimethylsilyl chloride (TBSCl) furnished **6** in almost quantitative yield. Subsequent deprotection of the benzyloxycarbonyl (Cbz) group of **6** (H<sub>2</sub>, Pd/C, EtOH, rt) led to **7** in good yield. Further *N*-alkylation of **7** with 1,3-diiodopropane produced **8** in 52% yield, then **8** was treated with LDA and DMPU to generate **9** bearing a key tricyclic framework. Exposure of **9** to aq. HCl (1 M) gave the corresponding alcohol, which was further oxidized by PySO<sub>3</sub> to form the common-core structure **10** in 70% yield over two steps. The absolute configuration of **10** was determined to be opposite to that reported by Soós, and then it could be converted into (+)-minovincine in three steps according to a known procedure.<sup>29</sup>

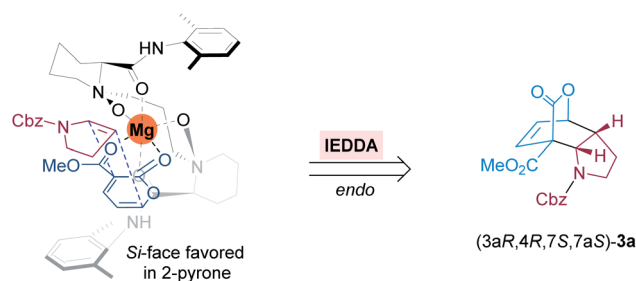
Based on the crystal structures of chiral *N,N'*-dioxide-metal complexes<sup>22a</sup> and the absolute configuration of this IEDDA reaction product, we proposed a putative stereochemical model to rationalize the stereoselectivity shown in Fig. 1. The coordination of the chiral *N,N'*-dioxide ligand L<sub>3</sub>-PIME<sub>2</sub> with Mg(OTf)<sub>2</sub> in a tetradentate manner generates an octahedral structure. Then 2-pyrone **1a** coordinates tightly to the Lewis acid catalyst through the two carbonyl groups of the ester motif, resulting in a decrease of its LUMO level to accelerate the IEDDA reaction. Simultaneously, due to the steric hindrance of the bulky amide group of the ligand, cyclic enamine **2a** prefers to attack from the *Si*-face of 2-pyrone to give *endo*-adduct (3*aR*,4*R*,7*S*,7*aS*)-**3a** with excellent stereoselectivity.

## Conclusions

In conclusion, we have developed a novel strategy for the highly enantioselective synthesis of the *cis*-hydroindole motif,



**Scheme 3** Enantioselective formal total synthesis of (+)-minovincine. TBSCl = *tert*-butyldimethylsilyl chloride, LDA = lithium diisopropylamide, DMPU = 1,3-dimethyl-tetrahydropyrimidin-2(1*H*)-one.



**Fig. 1** Proposed stereochemical model.

involving a chiral *N,N'*-dioxide/Mg(OTf)<sub>2</sub> complex catalyzed asymmetric IEDDA reaction of 2-pyrone and cyclic enamines. A range of *cis*-hydroindole derivatives were obtained in good yields with high stereoselectivities under mild reaction conditions (up to 99% yield, and 95% ee). This protocol was also compatible for acyclic enamines and 2,3-dihydrofuran. Meanwhile, the scale-up synthesis and further postcatalytic derivatizations were conducted to measure the synthetic potential of the method. Particularly, an alternative and facile access to efficient formal total synthesis of (+)-minovincine was demonstrated by employing the transformations. Further investigations of this reaction in total synthesis of other bioactive natural products are ongoing in our laboratory.

## Data availability

All experimental and characterization data in this manuscript are available in the ESI†. Crystallographic data for compound (3*aR*,4*R*,7*S*,7*aS*)-**3a** has been deposited at the Cambridge Crystallographic Data Center and assigned number 2158164.

## Author contributions

F. Q. Z. performed the experiments and prepared the ESI† and paper. B. T. R. performed some experiments. Y. Q. Z. helped with resolving the X-ray crystallographic data. Y. B. L. and X. M. F. conceived the concept, directed the project and helped with modifying the paper and ESI†.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

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