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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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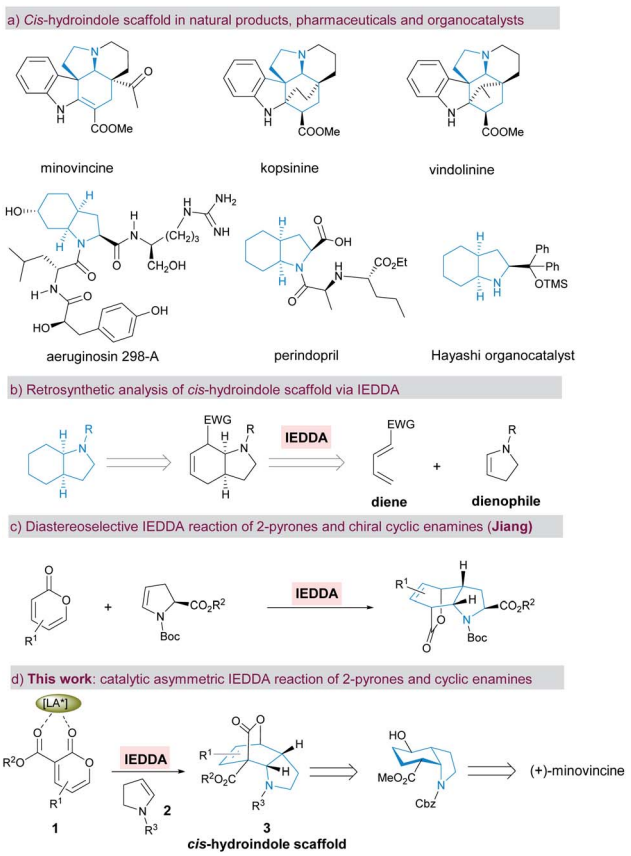
cis-Hydroindole scaffolds widely exist in a large number of natural products, pharmaceuticals, and organocatalysts. Therefore, the development of efficient and enantioselective methods for the construction of *cis*-hydroindoles is of great interest and importance. Herein, a novel approach for the enantioselective synthesis of *cis*-hydroindole scaffolds has been realized through a chiral *N*,*N*′-dioxide/$Mg(OTf)_2$ complex catalyzed asymmetric inverse-electron-demand Diels–Alder (IEDDA) reaction of 2-pyrones 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.

Introduction

Chiral *cis*-hydroindole is a privileged scaffold present in numerous biologically active natural products[1–8] such as minovincine, kopsinine, vindolinine, and aeruginosin 298-A, pharmaceutical products[9] such as the antihypertensive drug perindopril, and proline analogue organocatalysts[10,11] (Scheme 1a). Complex molecular architectures and fascinating biological properties have long motivated the development of synthetic methods towards enantioselective construction of chiral *cis*-hydroindoles.[12–15] In this context, most strategies for the stereoselective construction of *cis*-hydroindoles are primarily based on using optically active starting materials.[12,13a,b,13d] 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.[13c,14,15] Therefore, the development of a general and novel strategy for concise and efficient



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

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

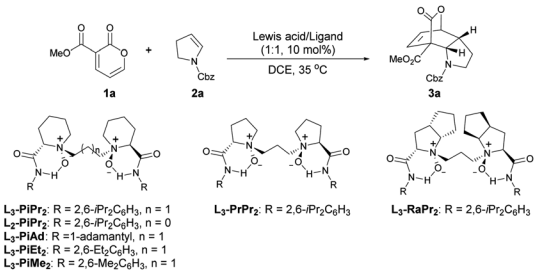
As one of the most important and fundamental reactions in organic chemistry, the Diels–Alder reaction between a conjugated diene and dienophile is widely applied to construct a six-membered carbo/hetero-cyclic ring.[16,17] By retrosynthetic analysis of *cis*-hydroindole, this chiral motif can be readily assembled from an electron-deficient diene and electron-rich cyclic enamine[18] *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.[19,20] 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,[20g] silyl cyclohexadienol[20i] and 1-naphthyl acetylenes,[20j] 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).[21] Herein, we describe our efforts towards an enantioselective IEDDA reaction catalyzed by the chiral *N*,*N*′-dioxide/$Mg(OTf)_2$ complex[22] 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_3-PiPr$_2$** were evaluated in DCE at 35 °C (entries 1–4). The results showed that $Sc(OTf)_3$ and $In(OTf)_3$ only led to trace yield of product **3a**, while $Yb(OTf)_3$ gave **3a** in 92% yield but 13% ee. To our delight, in the presence of the $Mg(OTf)_2$/**L_3-PiPr$_2$** 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 $Mg(OTf)_2$, including changes in the length of the linker, backbones of chiral amino acids, and substituents on the aromatic amide group (entries 5–10). It was found that **L_3-PiMe$_2$** 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 $CHCl_3$ 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.

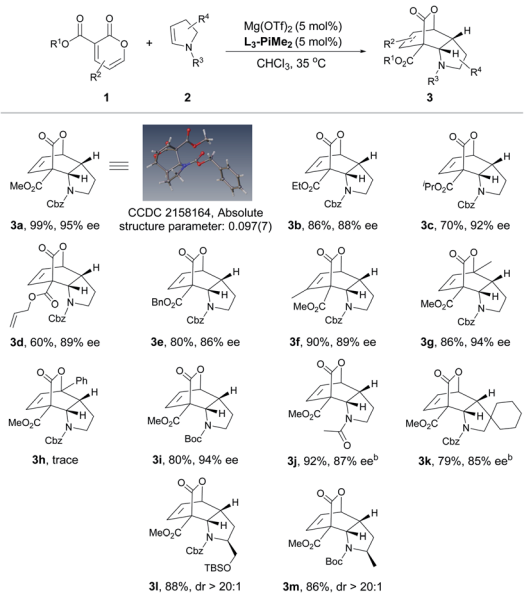
Table 1 Optimization of the reaction conditions[a]



Entry	Lewis acid	Ligand	t (h)	Yield[b] (%)	ee[c] (%)
1	$Sc(OTf)_3$	**L_3-PiPr$_2$**	24	Trace	—
2	$In(OTf)_3$	**L_3-PiPr$_2$**	24	Trace	—
3	$Yb(OTf)_3$	**L_3-PiPr$_2$**	3	92	13
4	$Mg(OTf)_2$	**L_3-PiPr$_2$**	3	73	78
5	$Mg(OTf)_2$	**L_2-PiPr$_2$**	12	99	68
6	$Mg(OTf)_2$	**L_3-PrPr$_2$**	12	97	69
7	$Mg(OTf)_2$	**L_3-RaPr$_2$**	12	99	79
8	$Mg(OTf)_2$	**L_3-PiAd**	17	91	12
9	$Mg(OTf)_2$	**L_3-PiEt$_2$**	6	95	82
10	$Mg(OTf)_2$	**L_3-PiMe$_2$**	3	97	88
11[d]	$Mg(OTf)_2$	**L_3-PiMe$_2$**	3	99	95
12[e]	$Mg(OTf)_2$	**L_3-PiMe$_2$**	3	99	95
13[f]	$Mg(OTf)_2$	**L_3-PiMe$_2$**	12	99	93

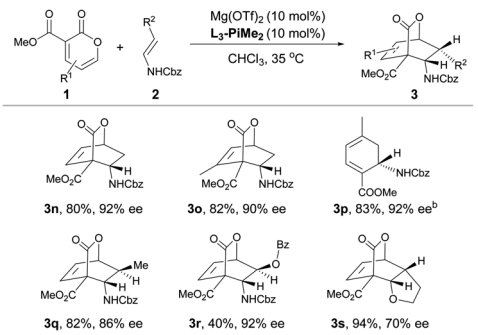
[a] Unless otherwise noted, all reactions were carried out with **1a** (0.10 mmol), **2a** (0.15 mmol), Lewis acid/ligand (1 : 1, 10 mol%) in DCE (0.5 mL) at 35 °C. [b] NMR yield detected by using CH_2Br_2 as an internal standard. [c] Enantiomeric excess determined by HPLC analysis on a chiral stationary phase. [d] Carried out in $CHCl_3$ (0.5 mL). [e] $Mg(OTf)_2$/**L_3-PiMe$_2$** (1 : 1, 5 mol%). [f] $Mg(OTf)_2$/**L_3-PiMe$_2$** (1 : 1, 2 mol%). DCE = 1,2-dichloroethane, Tf = trifluoromethanesulfonyl.

Table 2 Substrate scope of substituted 2-pyrones and cyclic enamines[a]



[a] All reactions were carried out with **1** (0.10 mmol), **2** (0.15 mmol), $Mg(OTf)_2$/**L_3-PiMe$_2$** (1 : 1, 5 mol%) in $CHCl_3$ (0.5 mL) at 35 °C. Isolated yield. Enantiomeric excess was determined by HPLC on a chiral stationary phase. [b] $Mg(OTf)_2$/**L_3-PiMe$_2$** (1 : 1, 10 mol%) was used.

Table 3 Substrate scope of substituted 2-pyrones and acyclic enamines[a]

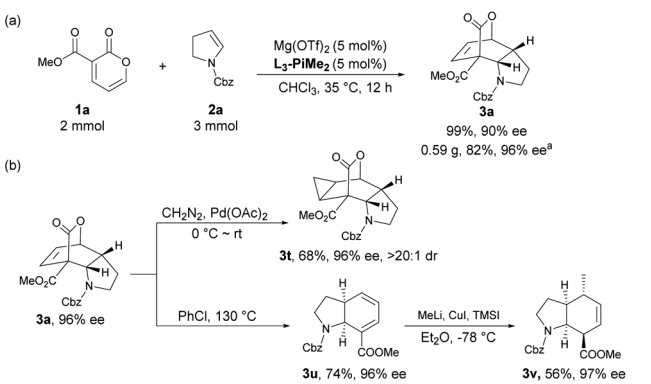


[a] All reactions were carried out with **1** (0.10 mmol), **2** (0.15 mmol), $Mg(OTf)_2$/**L_3-PiMe$_2$** (1 : 1, 10 mol%) in $CHCl_3$ (0.5 mL) at 35 °C. Isolated yield. Enantiomeric excess was determined by HPLC on a chiral stationary phase. [b] The reaction was conducted at 35 °C for 36 h, and then 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_2 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_2 *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,[23] characterized by a spiroindoline pentacyclic framework with contiguous stereocenters, is considered as a "biogenetic turntable" between the vindolinine and kopsinine classes of isolates.[24] Intrigued by its fascinating structural features and potential biological activities, minovincine has long attracted considerable interest within the chemical synthesis community.[25,26] However, there are few examples in the literature for the enantioselective total synthesis of (−)-minovincine.[27–29] Based on our present approach and



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

interest in synthesis of natural alkaloids,[30] 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_2 and methyl esterification by using $TMSCH_2N_2$ 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_2, 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 $PySO_3$ 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.[29]

Based on the crystal structures of chiral *N*,*N*′-dioxide-metal complexes[22a] 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_3-PiMe$_2$** with $Mg(OTf)_2$ 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 (3a*R*,4*R*,7*S*,7a*S*)-**3a** with excellent stereoselectivity.

Conclusions

In conclusion, we have developed a novel strategy for the highly enantioselective synthesis of the *cis*-hydroindole motif, involving a chiral *N*,*N*′-dioxide/$Mg(OTf)_2$ complex catalyzed asymmetric IEDDA reaction of 2-pyrones 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.

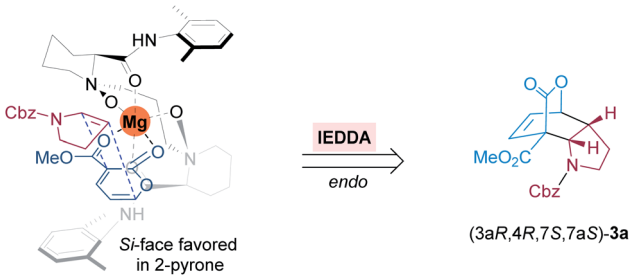
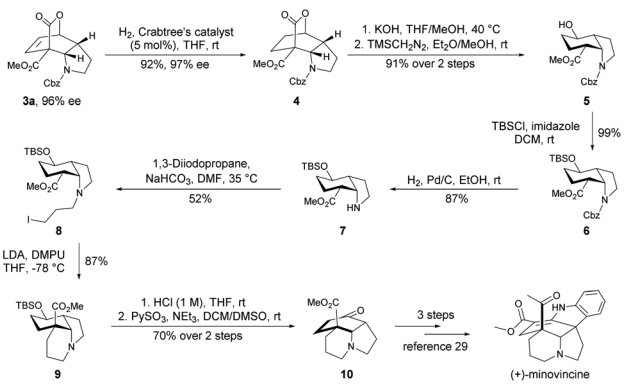


Fig. 1 Proposed stereochemical model.



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

Data availability

All experimental and characterization data in this manuscript are available in the ESI.† Crystallographic data for compound (3a*R*,4*R*,7*S*,7a*S*)-**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.

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