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

Fangqing Zhang, Bing-Tao Ren, Yuqiao Zhou, Yangbin Liu* and Xiaoming Feng**

Cite this: Chem. Sci., 2022, 13, 5562

Received 13th March 2022
Accepted 14th April 2022
DOI: 10.1039/d2sc01458k

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,N0,N0-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 such as minovincine, kopsinine, vindoline, and aeruginosin 298-A, pharmaceutical products such as the antihypertensive drug perindopril, and proline analogue organocatalysts (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.12,13b,c,d14c,d 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,d,14,15 Therefore, the development of a general and novel strategy for concise and efficient

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.\(^\text{16,17}\) By retrosynthetic analysis of cis-hydroindole, this chiral motif can be readily assembled from an electron-deficient diene and electron-rich cyclic enamine\(^\text{18}\) 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 semi-aromatic and adjustable electronic properties, electron-deficient 2-pyrones have become a favored diene component in the IEDDA reaction with a wide range of applications in aromatic compounds and complex natural product synthesis.\(^\text{19,20}\) Particularly, the Cai group demonstrated the enantioselective IEDDA reaction of 3-carboalkoxy-2-pyrones with electron-rich dienophiles, such as 2,2-dimethyl-1,3-dioxole,\(^\text{21}\) silyl cyclohexadienol\(^\text{22}\) and 1-naphthyl acetylenes,\(^\text{23}\) 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).\(^\text{24}\) Herein, we describe our efforts towards an enantioselective IEDDA reaction catalyzed by the chiral N,N'-dioxide/Mg(OTf)\(_2\) complex\(^\text{25}\) using 3-carboalkoxy-2-pyrene 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 (+)-mino-vincine 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-pyrene 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/Mg(OTf)\(_2\) complex\(^\text{22}\) using 3-carboalkoxy-2-pyrene 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 (+)-mino-vincine alkaloid was furnished concisely and enantioselectively by subsequent transformation of the enantiomerically enriched products.

[Table 1: Optimization of the reaction conditions]

| 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\(_2\)-PiPr\(_2\) | 12   | 97              | 69         |
| 7     | Mg(OTf)\(_2\) | L\(_2\)-PiPr\(_2\) | 12   | 99              | 79         |
| 8     | Mg(OTf)\(_2\) | L\(_3\)-PiMe\(_2\) | 17   | 91              | 12         |
| 9     | Mg(OTf)\(_2\) | L\(_3\)-PiMe\(_2\) | 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\(_2\)Br\(_2\) 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.

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-Pyrones 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-pyrene contained a phenyl group at the C6 position, the IEDDA reaction did not occur, probably due to the steric effect.
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-pyrole 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 3q was obtained in one pot through the tandem Diels–Alden reaction and in situ retro-[4 + 2] extrusion of CO2 at an elevated temperature. We found that the methyl and benzoxyl 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-pyrene 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 CO2 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 minovicnine,23 characterized by a spiroindoline pentacyclic framework with contiguous stereocenters, is considered as a “biogenetic turntable” between the vindoline 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 (−)-minovicnine.27–29 Based on our present approach and

![Table 2 Substrate scope of substituted 2-pyrones and cyclic enamines](image)

| Substrate | Yield | Enantiomeric Excess |
|-----------|-------|---------------------|
| 2-Pyrones |       |                     |
| Cyclic    |       |                     |

 outbreaks

![Table 3 Substrate scope of substituted 2-pyrones and acyclic enamines](image)

| Substrate | Yield | Enantiomeric Excess |
|-----------|-------|---------------------|
| Acyclic   |       |                     |

Scheme 2 (a) Scale-up synthesis; (b) further transformation of the product. Yield and enantiomeric excess were determined after recrystallization.
interest in synthesis of natural alkaloids, 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 CO2 and methyl esterification by using TMSCH2N2 to afford the cis-hydroindole derivative 5 in 91% overall yield. Protection of the hydroxyl of 5 with tert-butylidemethylsilyl chloride (TBSCI) furnished 6 in almost quantitative yield. Subsequent deprotection of the benzoxycarbonyl (Cbz) group of 6 (H2, 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 P2S5 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.

Based on the crystal structures of chiral N,N’-dioxide-metal complexes 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 L1,PMé2 with Mg(OTf)2 in a tetradentate manner generates an octahedral structure. Then 2-pyrene 1a coordinates tightly to the Lewis acid catalyst through the 1,3-dimethyl-tetrahydropyrimidin-2(1H)-one.

**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.

**Data availability**

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

We are grateful for the financial support from National Natural Science Foundation of China (No. 22001177) and Shenzhen Bay Laboratory (No. S201100003 and S211101001-1).

**Notes and references**

1. M. E. Amer, M. Shamma and A. J. Freyer, *J. Nat. Prod.*, 1991, 54, 329–363.
2. J. Leonard, *Nat. Prod. Rep.*, 1999, 16, 319–338.
For asymmetric metal-catalyzed reactions, see:
(a) 5566
(b) 15 For selected reviews, see: (a) H. F. Zheng, X. H. Liu, C. R. Xu, Y. Xia, L. L. Lin and X. M. Feng, Angew. Chem., Int. Ed., 2015, 54, 10958–10962; (b) Y. Lu, Y. H. Zhou, L. L. Lin, H. F. Zheng, K. Fu, X. H. Liu and X. M. Feng, Chem. Commun., 2016, 52, 8255–8258; (c) Y. H. Zhou, Y. Lu, X. Y. Hu, H. J. Mei, L. L. Lin, X. H. Liu and X. M. Feng, Chem. Commun., 2017, 53, 2060–2063.

For an important application of cyclic enamines, see: L. Bai, Y. Ma and X. Jiang, J. Am. Chem. Soc., 2021, 143, 20609–20615.

For selected reviews, see: (a) K. Afarinkia, V. Vinader, T. D. Nelson and G. H. Posner, Tetrahedron, 1992, 48, 9111–9171; (b) X. Jiang and R. Wang, Chem. Rev., 2013, 113, 5515–5546; (c) Q. Cai, Chin. J. Chem., 2019, 37, 946–976; (d) X.-G. Si, Z.-M. Zhang and Q. Cai, Synlett, 2021, 32, 947–954; (e) G. Huang, C. Kouklevsky and A. de la Torre, Chem.–Eur. J., 2021, 27, 4760–4788.

For selected examples, see: (a) G. H. Posner, J.-C. Carry, J. K. Lee, D. S. Bull and H. Dai, Tetrahedron Lett., 1994, 35, 1321–1324; (b) I. E. Markó, G. R. Evans and J.-P. Declercq, Tetrahedron, 1994, 50, 4557–4574; (c) G. H. Posner, H. Dai, D. S. Bull, J.-K. Lee, F. Eydoux, Y. Ishihara, W. Welsh, N. Pryor and S. Petr, J. Org. Chem., 1996, 61, 671–676; (d) I. E. Markó, I. Chellé-Regnaut, B. Leroy and S. L. Warriner, Tetrahedron Lett., 1997, 38, 4269–4272; (e) Y. Hashimoto, R. Abe, N. Morita and O. Tamura, Org. Biomol. Chem., 2018, 16, 8913–8916; (f) Y. Zhou, Z. Zhou, W. Wu and Y. Chen, Acta Chim. Sin., 2018, 76, 382–386; (g) X.-W. Liang, X. Zhao, X.-G. Si, M.-M. Xu, J.-H. Tan, Z.-M. Zhang, C.-G. Zheng, C. Zheng and Q. Cai, Angew. Chem., Int. Ed., 2019, 58, 14562–14567; (h) C. J. F. Cole, L. Fuentes and S. A. Snyder, Chem. Sci., 2020, 11, 2175–2180; (i) X.-G. Si, Z.-M. Zhang, C.-G. Zheng, Z.-T. Li and Q. Cai, Angew. Chem., Int. Ed., 2020, 59, 18412–18417; (j) M.-M. Xu, X.-Y. You, Y.-Z. Zhang, Y. Lu, K. Tan, L. Yang and Q. Cai, J. Am. Chem. Soc., 2021, 143, 8993–9001; (k) M.-M. Xu, L. Yang, K. Tan, X. Chen, Q.-T. Lu, K. N. Houk and Q. Cai, Nat. Catal., 2021, 4, 892–900; (l) Y. Lu, M.-M. Xu, Z.-M. Zhang, J. Zhang and Q. Cai, Angew. Chem., Int. Ed., 2021, 60, 26610–26615.

(a) M. Feng and X. Jiang, Chem. Commun., 2014, 50, 9690–9692; (b) N. Wang, S. Du, D. Li and X. Jiang, Org. Lett., 2017, 19, 3167–3170; (c) N. Wang, J. Liu, C. Wang, L. Bai and X. Jiang, Org. Lett., 2018, 20, 292–295.

For selected reviews about the properties of chiral N,N′-dioxide-Lewis acid complexes, see: (a) X. H. Liu, L. L. Lin and X. M. Feng, Acc. Chem. Res., 2011, 44, 574–587; (b) X. H. Liu, L. L. Lin and X. M. Feng, Org. Chem. Front., 2014, 1, 298–302; (c) X. H. Liu, H. F. Zheng, Y. Xia, L. L. Lin and X. M. Feng, Acc. Chem. Res., 2017, 50, 2621–2631; (d) X. H. Liu, S. X. Dong, L. L. Lin and X. M. Feng, Chin. J. Chem., 2018, 36, 791–797; (e) M. Y. Wang and W. Li, Chin. J. Chem., 2021, 39, 969–984; (f) S. Dong, X. H. Liu and X. M. Feng, Acc. Chem. Res., 2022, 55, 415–428.

For isolation of minovincine, see: (a) M. Plat, J. LeMen, M.-M. Janot, H. Budzikiewicz, J. M. Wilson, L. J. Durham and C. Djerassi, Bull. Chem. Soc. Chim. Fr., 1962, 2237–
241; (b) M. P. Cava, S. S. Tjoa, Q. A. Ahmed and A. I. Da Rocha, *J. Org. Chem.*, 1968, 33, 1055–1059.

24 W. Zi, Z. Zuo and D. Ma, *Acc. Chem. Res.*, 2015, 48, 702–711.

25 For a racemic total synthesis, see: (a) M. E. Kuehne and W. G. Earley, *Tetrahedron*, 1983, 39, 3707–3714; (b) M. E. Kuehne and W. G. Earley, *Tetrahedron*, 1983, 39, 3715–3717; (c) G. Kalaus, I. Juhász, I. Greiner, M. Kajtár-Peredy, J. Brlič, L. Szabó and C. Szántay, *J. Org. Chem.*, 1997, 62, 9188–9191; (d) G. Kalaus, L. Léder, I. Greiner, M. Kajtár-Peredy, K. Vékey, L. Szabó and C. Szántay, *Tetrahedron*, 2003, 59, 5661–5666.

26 For a semisynthesis, see: N. Langlois and R. Z. Andriamialisoa, *J. Org. Chem.*, 1979, 44, 2468–2471.

27 B. N. Laforteza, M. Pickworth and D. W. C. MacMillan, *Angew. Chem., Int. Ed.*, 2013, 52, 11269–11272.

28 T. Morikawa, S. Harada and A. Nishida, *J. Org. Chem.*, 2015, 80, 8859–8867.

29 S. Varga, P. Angyal, G. Martin, O. Egyed, T. Holczbauer and T. Sóós, *Angew. Chem., Int. Ed.*, 2020, 59, 13547–13551.

30 (a) J. Xu, Z. W. Zhong, M. Y. Jiang, Y. Q. Zhou, X. H. Liu and X. M. Feng, *CCS Chem.*, 2021, 3, 1894–1902; (b) J. Xu, R. Z. Li, N. Xu, X. H. Liu, F. Wang and X. M. Feng, *Org. Lett.*, 2021, 23, 1856–1861.