

Conference paper

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Organocatalytic asymmetric synthesis of chiral nitrogenous heterocycles and natural products

Abstract: Nitrogen-containing chiral heterocycles represent important structural elements with wide occurrence in natural and unnatural compounds exhibiting important biological activities. Herein, we describe our recent endeavors directed toward the Brønsted acid-catalyzed 1,3-dipolar cycloaddition and alkylation reactions, together with the metal/Brønsted acid relay catalytic cascade reactions to access some typical nitrogenous heterocyclic structures and natural alkaloids, including (+)-folicanthine and (+)-gliocladin C.

Keywords: asymmetric organocatalysis; Brønsted acid; chiral heterocycles; ICHC-24; multicomponent reactions; natural alkaloids; relay catalysis.

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Introduction

Optically pure nitrogenous heterocyclic compounds have long been receiving a great deal of attention due to their frequent occurrence in natural and unnatural products with a diverse range of pharmaceutical activities [1]. For example (Fig. 1), chiral pyrrolidines, spirooxindoles, tetrahydroquinolines, and related heterocyclic compounds not only constitute core structural elements in the medicinally relevant compounds, but also serve as key synthetic intermediates for the total synthesis of alkaloids. In particular, as highlighted in Fig. 1, L-689560 (**4**), a potent N-methyl-D-aspartate, is a promising drug candidate for the treatment of Alzheimer's disease and for reducing ischemic brain damage [2]. The alkaloid, gliocladin C (**8**) exhibited cytotoxic activity against murine P388 lymphocytic leukemia cells [3]. Thus, the development of novel synthetic protocols to readily access these targets in excellent levels of stereoselectivity and highly structural diversity is undoubtedly appealing in organic and medicinal chemistry as well as other related fields.

Among numerous facile synthetic pathways to access nitrogenous heterocycles, chiral Brønsted acid-catalyzed asymmetric multicomponent reactions have emerged as robust and privileged tools for building up enantioenriched heterocyclic skeletons with high structural diversity and complexity [4]. As shown in Scheme 1, if a substrate bearing both nucleo- and electrophilic functionalities, it may undergo an enantioselective addition (path **a**) to an imine generated from an aldehyde and primary amine to give rise to an intermediate **I**, which then undergoes cyclization reaction to furnish heterocyclic compounds. Because either of the reaction components is structurally tunable, such a multicomponent protocol is principally able to provide a general approach to building up collections of optically active nitrogenous heterocycles (Scheme 1, A) [5]. On the other hand, if one of the reaction components contains both an electrophile

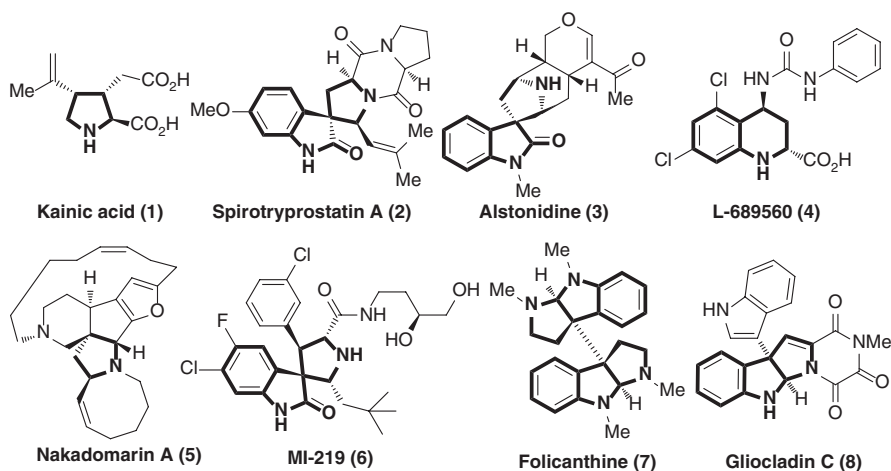
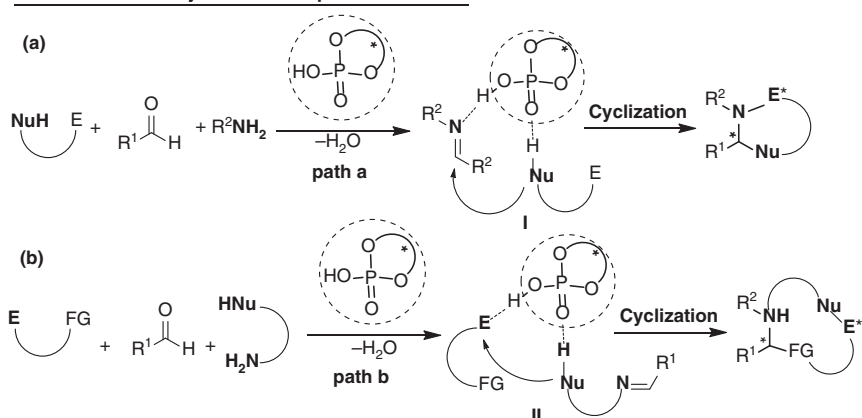
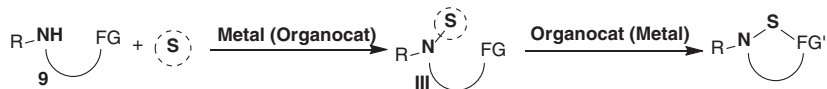


Fig. 1 The structural significance of five and six membered nitrogenous heterocycles.

A. Brønsted acid catalyzed multicomponent reactions



B. Metal/Brønsted acid relay catalytic cascade reactions



Scheme 1 General strategy to access nitrogenous heterocycles.

(E) and a functional group (FG), and the amine bears a nucleophilic moiety, the chiral Brønsted acid should promote an asymmetric cyclization reaction via intermediate **II** generated from the path **b**. In addition to the strategy shown in Scheme 1, we have recently proposed an asymmetric relay catalysis (ARC) comprising binary chiral Brønsted acids and metal complexes, which have enabled the discovery of unprecedented enantioselective cascade transformations with high enantioselectivities. We envisaged that the functionalized amines (**9**) are basically able to undergo a coupling reaction under the catalysis of either a metal or an organocatalyst to give an intermediate **III**, which would presumably participate in the cyclization reaction under the promotion of either organo- or metal catalyst to generate heterocycles (Scheme 1, B) [6].

In this article, we will describe our recent efforts directing at the discovery of asymmetric reactions to access these nitrogenous structures basically using the strategies described in Scheme 1. In addition, the organocatalytic enantioselective synthesis of (+)-folicanthine (**7**) and (+)-gliocladin C (**8**) will also be reported.

Results and discussion

Asymmetric 1,3-dipolar cycloaddition catalyzed by bisphosphoric acid

The 1,3-dipolar cycloaddition of azomethine ylides with olefins gives rise to pyrrolidines **13** and spiro[pyrrolidin-3,3'-oxindole] derivatives **17**, which represent two of the important structural elements, frequently found in natural products and artificial biologically active molecules [7]. In recent decades, elegant processes have been described in this field using either chiral metal complex [8] or organocatalyst [9]. We have found that chiral binol-derived phosphoric acids were good catalysts for three-component 1,3-dipolar cycloaddition reactions [10].

The examination of BINOL-based phosphoric acids revealed that the bisphosphoric acid **14** was the best catalyst for the three-component 1,3-dipolar cycloaddition with a wide range of aldehydes **10** and amino-malonates as well as α -arylglycine esters and phenylalanine esters, which allowed the formation of multiple substituted pyrrolidine derivatives in high yields and excellent enantioselectivities [10a]. DFT calculations performed on the transition states suggested that one phosphate of the bisphosphoric acid **14** acts as the Lewis base to activate the 1,3-dipole and the two hydroxyl groups of the catalyst may form two hydrogen-bonds with the two ester groups of maleate, respectively (**TS-1**), to make it more electron-deficient as a much stronger dipolarophile to conduct a concerted 1,3-dipolar cycloaddition with azomethine ylide **IV** (Fig. 2) [10b].

A diverse spectrum of dipolarophiles, including maleates **12** [10a,b], methyleneindolinones **16** [10c], *N*-aryl imines **18** [10d], allenates **19** [10e], quinones **20** [10f] and ynones **21** [10g], were able to react with azomethine ylides **IV** derived from aldehydes **10** by using either the bisphosphoric acid **14** or chiral phosphoric acids **15** as a chiral catalyst, to give several collections of pyrrolidine derivatives in high levels of enantioselectivity and structural diversity (Scheme 2).

Very recently, a spiro[pyrrolidin-3,2'-oxindole] core **23**, similar to spiro[pyrrolidin-3,3'-oxindole] derivatives **17**, is also a privileged heterocyclic ring system which is featured in a large family of medicinally relevant compounds [11]. Encouraged by our previous achievements on the 1,3-dipolar cycloaddition reactions and in view of the absence of enantioselective version of the cycloaddition reactions involving azomethine ylides generated from unsymmetrical cyclic ketones, an asymmetric 1,3-dipolar cycloaddition of isatin-based azomethine ylides efficiently catalyzed by the bisphosphoric acid **14** was subsequently developed, affording the spiro[pyrrolidin-3, 2'-oxindole] scaffolds **23** with contiguous quaternary stereogenic centers in excellent stereoselectivities (eq. 1) [12]. This protocol represents the first example of catalytic 1,3-dipolar cycloaddition involving azomethine ylides generated in situ from unsymmetrical cyclic ketones. Moreover, the preliminary bioassay revealed that some of these spiro[pyrrolidin-3,2'-oxindole] derivatives have shown moderate cytotoxicity to SW116 cells.

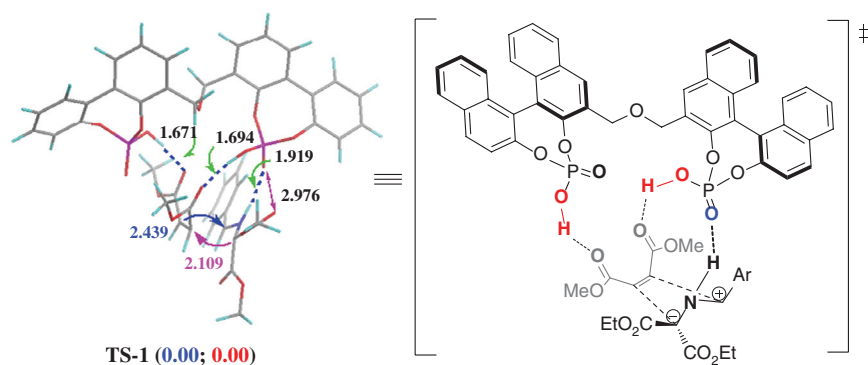
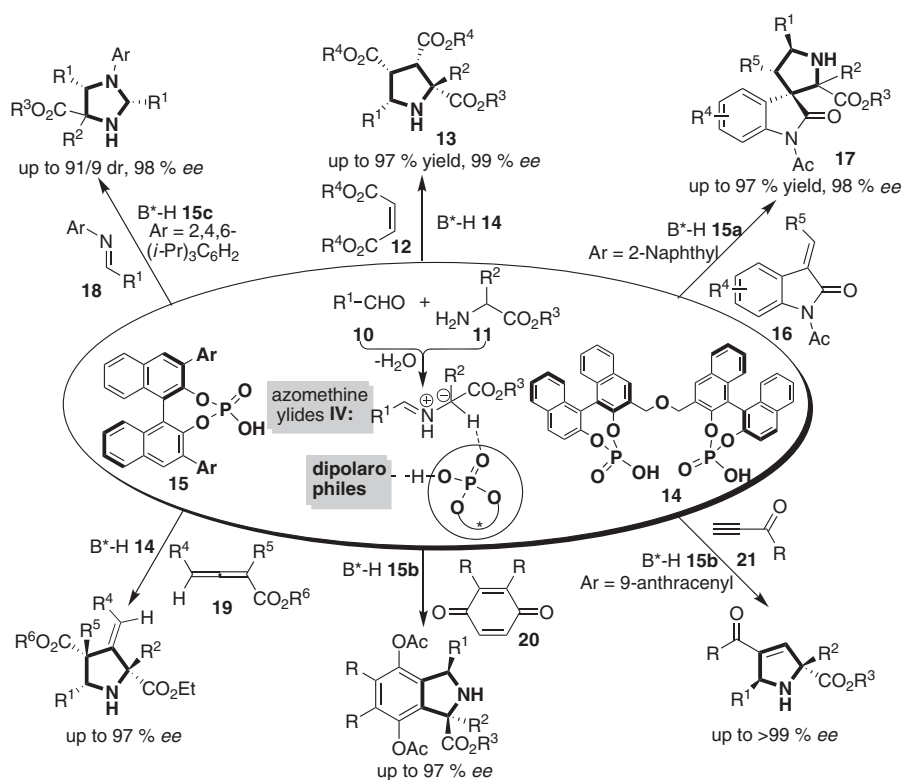
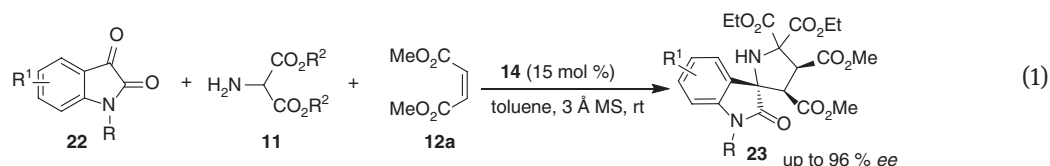


Fig. 2 Transition states of [3+2] cycloaddition catalyzed by bisphosphoric acid **14**.



Scheme 2 Asymmetric catalytic 1,3-dipolar cycloaddition reactions.



Organocatalytic enantioselective total synthesis of cyclotryptamine alkaloids

Enantioselective total synthesis of (+)-folicanthine from organocatalytic alkylation of 3-hydroxyoxindoles

The fascinating cyclotryptamine alkaloids (Fig. 3), which contain an octahydro-3a,3a'-bispyrrolo[2,3-*b*]indole subunit (Fig. 3, core structure 24) with vicinal all-carbon quaternary stereogenic centers, exhibit important biological activities [13] and have therefore led to a great demand for enantioselective and efficient synthetic

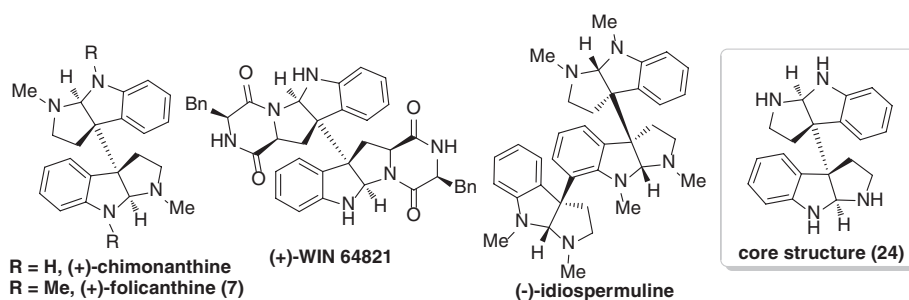
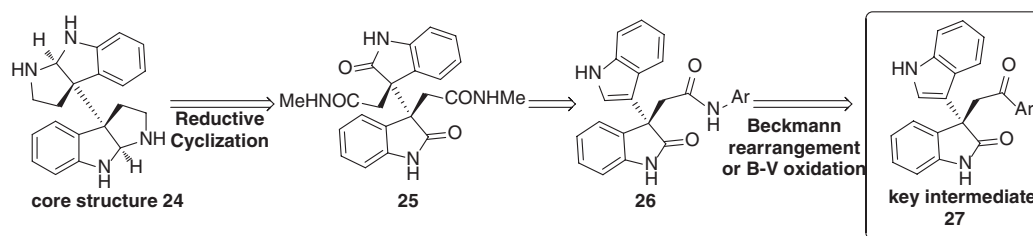


Fig. 3 Representative cyclotryptamine alkaloids.

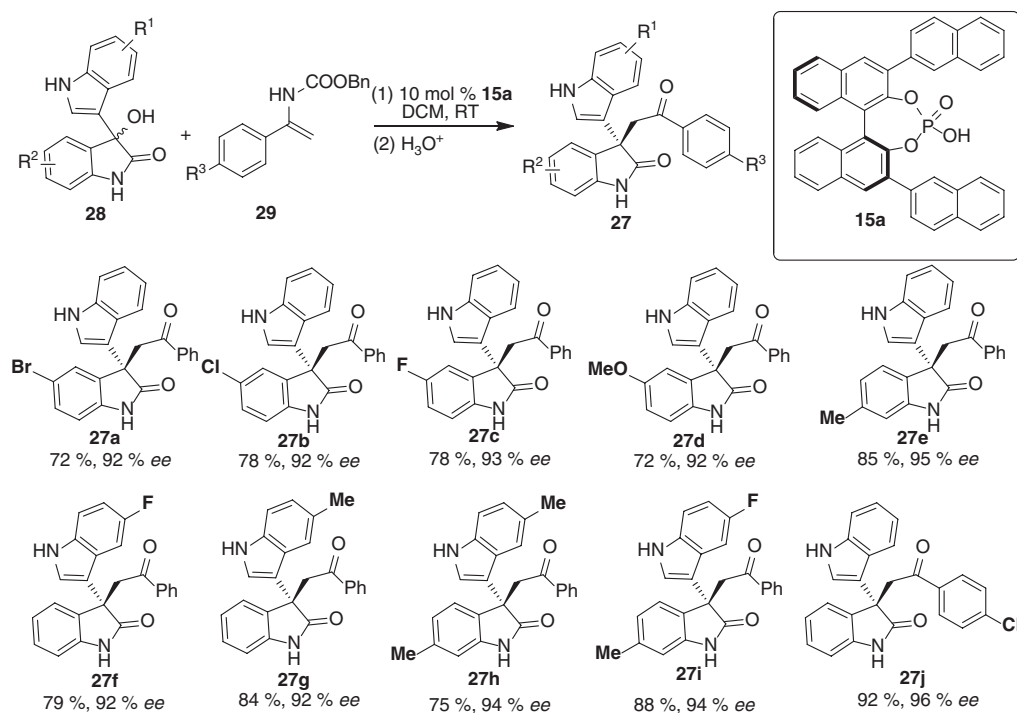
methods. As a consequence, important contributions have been directed to the development of novel protocols for accessing hexahydropyrroloindole skeletons [14]. Overman has reported enantioselective syntheses of optically pure chimonanthines [15], wherein the related quaternary stereocenters were built up from a naturally occurring chiral pool, a tartaric acid derivative. Starting from the bromocyclization of naturally available tryptophan and tryptamine derivatives, Movassaghi and coworkers established a radical coupling reaction to directly access hexahydropyrroloindoles. This synthetic strategy has allowed efficient total synthesis of several members of cyclotryptamine alkaloids [16].

In spite of these achievements, an enantioselective catalytic method to access a chiral intermediate for the synthesis of 3a,3a'-bispyrrolo[2,3-*b*]indoline skeleton still remains elusive. As indicated in Scheme 3, the core structure **24** could be prepared from diamide **25** via reductive cyclization. The intermediate **25** was planned to be accessed by classical transformations from **26**, which is principally able to be prepared from **27** by Beckmann rearrangement or sequential Baeyer–Villiger oxidation/amidation reaction. Obviously, the development of asymmetric catalytic reaction to generate compound **27** is the key point of the total synthesis [17].

Thus, an asymmetric enantioselective substitution reaction of 3-hydroxyoxindoles **28** with enamide **29** was first investigated and found that chiral phosphoric acid **15a** turned out to be the best catalyst. The protocol was very general for 3-hydroxyoxindoles **28** with enamide **29**, giving a diverse spectrum of 3,3'-disubstituted oxindoles **27** in high yields with excellent enantioselectivities (Scheme 4).



Scheme 3 Retrosynthetic analysis of core structure **24**.

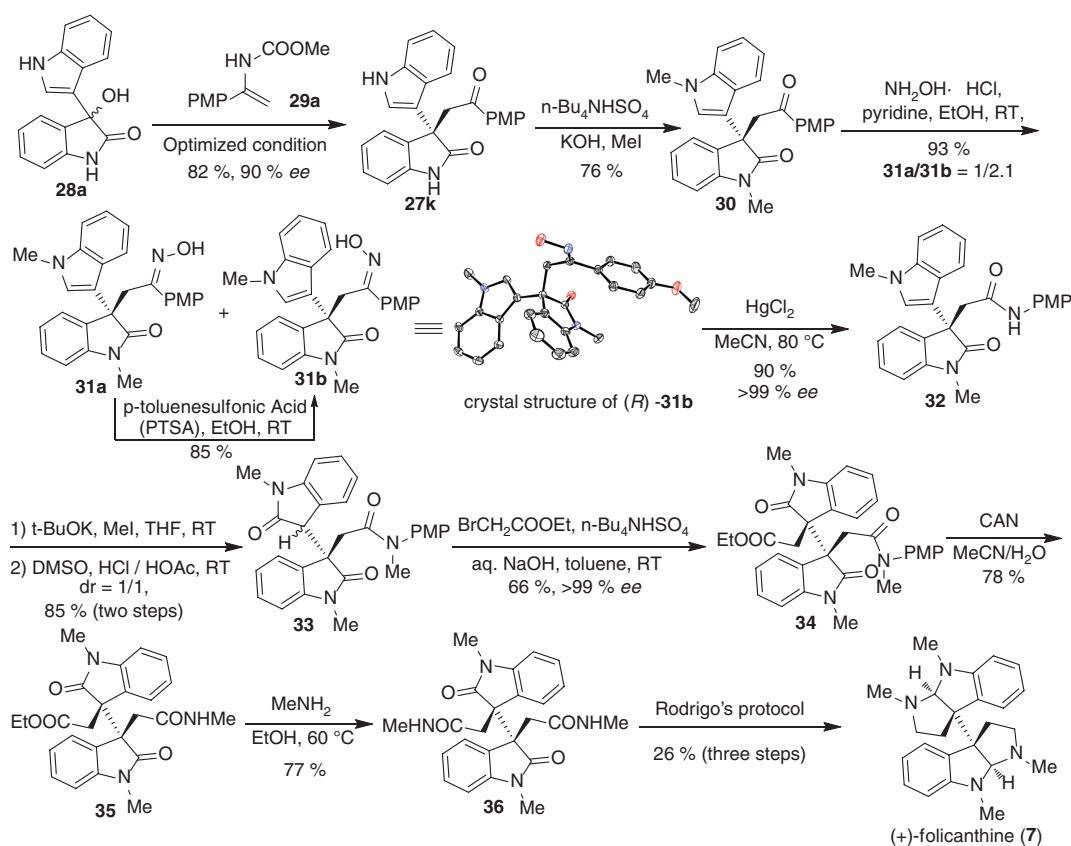


Scheme 4 The scope of asymmetric alkylation of 3-hydroxyoxindoles.

Then, we started to synthesize (+)-folicanthine **7** by using this asymmetric alkylation to build up the stereogenic centers (Scheme 5). The enantioselective substitution reaction of **28a** and enamide **29a** generated **27k** in 90 % *ee*. The subsequent dimethylation of **27k** furnish **30** in 76 % yield. Since the Baeyer–Villiger oxidation of **30** failed to give desired products, we turned our attention to the Beckmann rearrangement, a reliable reaction to transform ketones into amides. However, the treatment of **30** with $\text{NH}_2\text{OH}\cdot\text{HCl}$ in EtOH gave an isomeric mixture of ketoximes **31a** and **31b** (**31a**/**31b** = 1/2.1). Fortunately, the ketoxime **31a** could be completely converted into ketoxime **31b** in the presence of *p*-toluenesulfonic acid. A clean Beckmann rearrangement of **31b** promoted by HgCl_2 was achieved to give rise to amide **32** in 90 % yield [18]. After the amide nitrogen was methylated, the resultant crude product was directly oxidized with DMSO/HCl, to produce bisoxindole **33** in high yield. The exposure of bisoxindole **33** to $\text{BrCH}_2\text{COOEt}$ under basic conditions allowed an alkylation to afford **34** in 66 % yield. The removal of the *p*-methoxyphenyl group by means of ceric ammonium nitrate (CAN) furnished the compound **35**. The amidation of **35** with methyl amine afforded the intermediate **36** in 77 % yield. Following the procedure reported by Rodrigo [19], compound **36** was transformed into (+)-folicanthine **7** in 26 % overall yield.

Total synthesis of (+)-gliocladin C via organocatalytic α -alkylation of aldehydes

Owing to the significant biological activity of (+)-gliocladin C (**8**) [3], Overman and Shin established the first total synthesis of this molecule and confirm its stereochemical assignment in 2007 [20a]. Subsequently, Overman et al., developed a concise and elegant enantioselective synthesis of (+)-gliocladin C (**8**) and illustrated the importance of gliocladin C as a key intermediate for the construction of other C3–C3' bisindole alkaloids [20b]. Stephenson and co-workers also completed the total synthesis of (+)-gliocladin C (**8**) by using photoredox catalysis to introduce an indolyl substructure as a key step [20c]. The most recent synthesis of

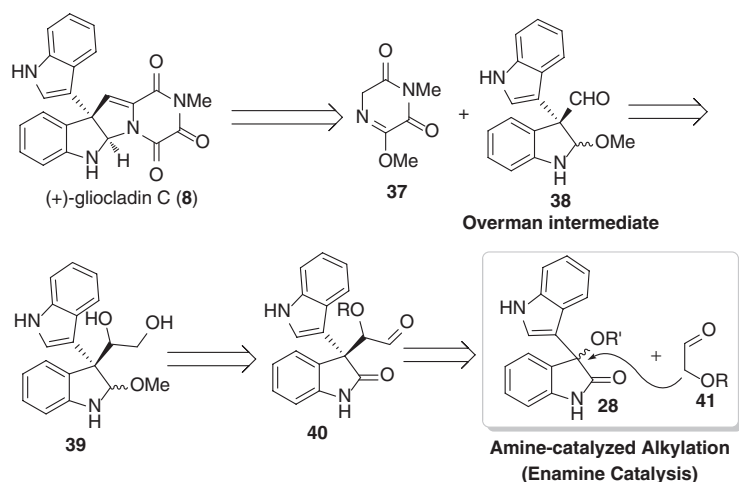


Scheme 5 Enantioselective total synthesis of (+)-folicanthine **7**.

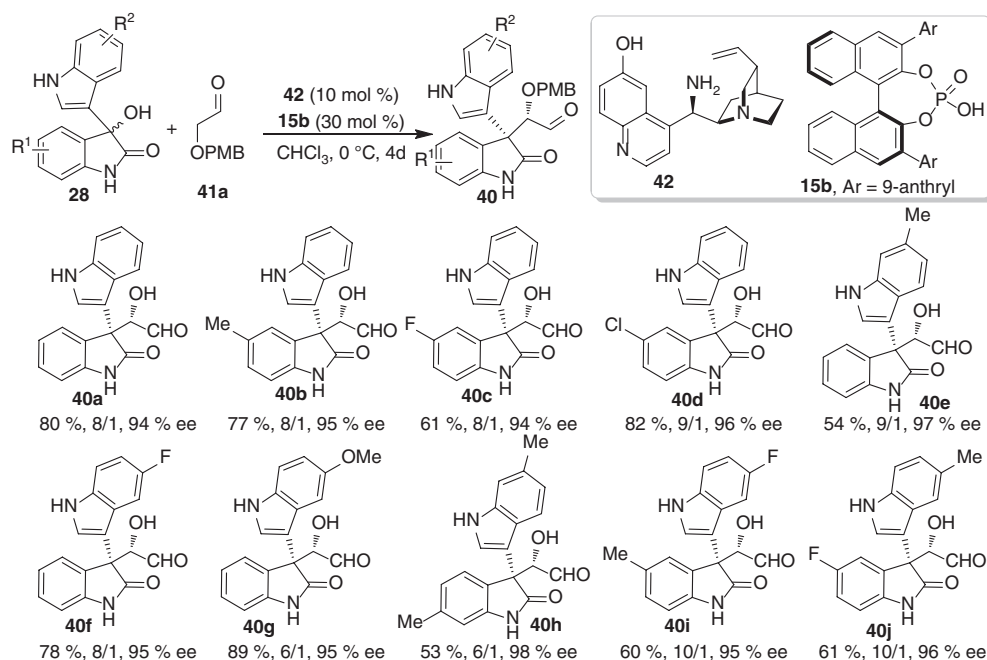
(+)-gliocladin C (**8**), reported by Movassaghi et al., used a Friedel–Crafts-based coupling strategy to access the C3-(3'-indolyl)hexahydropyrroloindole substructure [20d].

As illustrated in Scheme 6, the core skeleton of (+)-gliocladin C (**8**) could be obtained from the intermediates **37** and **38**. The indoline aldehyde **38** (Overman intermediate) [20b] could be easily synthesized from biindolin-1,2-diol **39**, which would be accessed by reduction of the aldehyde **40**. Thus, we developed an enantioselective alkylation reaction of 3-hydroxyindoles **28** with enalizable aldehydes **41** for the preparation of the key building block **40** [21].

The cinchona-based primary amines have been proved to be successful in either iminium or enamine catalyzed asymmetric transformations [22]. Inspired by these achievements, we screened several families of chiral organocatalysts for the alkylation of 3-hydroxyindoles **28a** with 2-alkyloxy-acetaldehyde **41** and found that the combined use of cinchona alkaloid-based primary amine **42** and chiral phosphoric acid **15** provided the highest levels of stereoselectivity [23]. The desired key intermediate **40a** was obtained in 80 % yield



Scheme 6 Retrosynthetic analysis of (+)-gliocladin C.



Scheme 7 The scope of asymmetric alkylation of 3-hydroxyindoles with 2-alkyloxy-acetaldehyde.

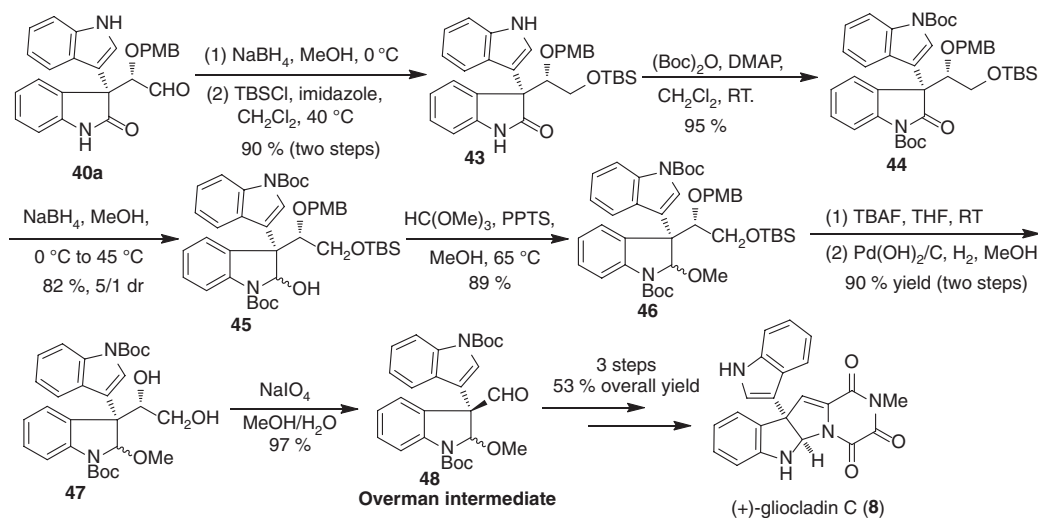
with 8:1 *dr* and 94 % *ee* under the optimized conditions. The expansion of the reaction conditions to other 3-hydroxyindole derivatives was also successful to generate alkylation products in high yields and excellent stereoselectivities (Scheme 7).

Then we applied this organocatalytic reaction to the enantioselective total synthesis of (+)-gliocladin C (**8**) (Scheme 8). The reduction of the chiral aldehyde **40a** to the corresponding alcohol, followed by protection with TBS group afforded **43** in 90 % yield. After the introduction of two Boc groups to the nitrogen atoms of **43** furnished **44** in 95 % yield, the reduction of oxindole carbonyl group with NaBH₄ afforded **45** in 5:1 *dr*. The treatment of **45** with trimethyl orthoformate in the presence of pyridinium *p*-toluenesulfonate (PPTS) led to the formation of **46** in 89 % yield. The O-protecting groups in **46** were then cleanly removed by treatment with TBAF and subsequently subjecting to hydrogenolysis catalyzed by Pd(OH)₂/C, provided diol **47** in 90 % yield (two steps). The indoline aldehyde **48** (Overman intermediate) was successfully accessed by the oxidative cleavage of the diol **47** with NaIO₄. Following Overman's procedure [20b], (+)-gliocladin C **8** finally was obtained from **48** in 53 % yield over 3 steps. The highly enantioselective total synthesis of (+)-gliocladin C **8** was presented within 12 steps from 3-hydroxyoxindole **28a** in an overall 19 % yield.

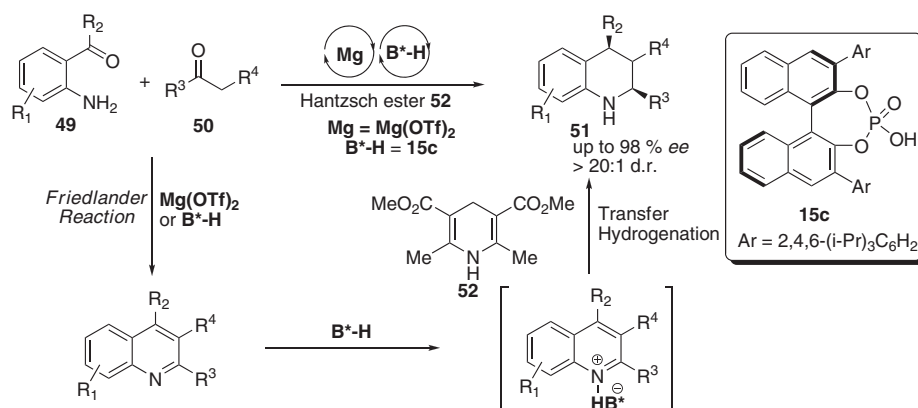
Asymmetric relay catalytic Friedländer condensation/transfer hydrogenation

Recently, the combination of metal complexes and organic molecules in relay and cooperative catalysis has gained increasing attention, because it could combine multiple transformations in one synthetic operation [6]. More importantly, asymmetric relay catalysis (ARC) holds great potential in creation of new step economy transformations wherein either type of catalyst failed to afford alone. The combination of transition metal and organocatalysts has enabled a diverse range of unprecedented transformations, providing efficient methods to access optically active heterocycles [6, 24].

We found that Lewis acids, such as Mg(OTf)₂, and chiral phosphoric acid **15c** were highly compatible and were able to catalyze a cascade Friedländer condensation [25]/asymmetric hydrogen transfer reaction (Scheme 9) [26]. Starting from commercially available 2-aminobenzaldehyde or 2-amino phenyl ketones **49** and β -ketoester **50**, this step-economical protocol provides an efficient approach to highly substituted tetrahydroquinolines **51** in excellent levels of stereoselectivity. The kinetic experiments suggested that the asymmetric hydrogen transfer process was solely catalyzed by chiral phosphoric acid, while Lewis and Brønsted acids cooperatively catalyzed the Friedländer condensation. The compatibility and synergism of the Lewis



Scheme 8 Total synthesis of (+)-gliocladin C.



Scheme 9 Step-economical synthesis of tetrahydroquinolines by asymmetric relay catalytic Friedländer condensation/transfer hydrogenation.

acid and chiral Brønsted acid may provide a new reaction mode potentially amenable to disclosing other relay catalytic asymmetric transformations.

Conclusions

In the field of organic synthesis, the development of new asymmetric transformations leading to novel scaffolds with unprecedented chemical and biological activities always hold great importance, but still represents a formidable challenge. Our recent development in the synthesis of nitrogenous heterocyclic structures via Brønsted acid catalyzed [3 + 2] cycloaddition reactions or metal/Brønsted acid catalytic relay cascade reactions provides a diverse range of protocols for the preparation of nitrogenous five- or six-membered heterocycles in highly structural diversity and excellent stereoselectivities. Remarkably, the organocatalytic alkylation of 3-hydroxyoxindoles has been established to synthesize the building blocks for total synthesis of cyclotryptamine alkaloids, including (+)-folicanthine and (+)-gliocladin C.

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References

- [1] *Modern Alkaloids: Structure, Isolation, Synthesis and Biology*. E. Fattorusso, O. Tagliatalata-Scafati (Eds.) Wiley-VCH, Weinheim, Germany (2008).
- [2] K. S. Atwal, B. N. Swanson, S. E. Unger, D. M. Floyd, S. Moreland, A. Hedberg, B. C. O'Reilly. *J. Med. Chem.* **34**, 806 (1991).
- [3] Y. Usami, J. Yamaguchi, A. Numata. *Heterocycles*. **63**, 1123 (2004).
- [4] For leading literatures of chiral phosphoric acid catalysis: (a) T. Akiyama, J. Itoh, K. Yokota, K. Fuchibe. *Angew. Chem. Int. Ed.* **43**, 1566 (2004); (b) D. Uraguchi, M. Terada. *J. Am. Chem. Soc.* **126**, 5356 (2004); for recent reviews, see: (c) T. Akiyama. *Chem. Rev.* **107**, 5744 (2007); (d) A. Zamfir, S. Schenker, M. Freund, S. B. Tsogoeva. *Org. Biomol. Chem.* **8**, 5262 (2010); (e) M. Terada. *Synthesis*. 1929 (2010).
- [5] J. Yu, F. Shi, L. -Z. Gong. *Acc. Chem. Res.* **44**, 1156 (2011).
- [6] For reviews, see: (a) Z. Shao, H. Zhang. *Chem. Soc. Rev.* **38**, 2745 (2009); (b) J. Zhou. *Chem. Asian J.* **5**, 422 (2010). (c) C. Zhong, X. Shi. *Eur. J. Org. Chem.* 2999 (2010); (d) A. S. K. Hashmi, C. Hubbert. *Angew. Chem. Int. Ed.* **49**, 1010 (2010); for first example illustrating the compatibility: (e) K. Sorimachi, M. Terada. *J. Am. Chem. Soc.* **130**, 14452 (2008).
- [7] For some reviews, see: (a) I. Coldham, R. Hufton. *Chem. Rev.* **105**, 2765 (2005); (b) G. Pandey, P. Banerjee, S. R. Gadre. *Chem. Rev.* **106**, 4484 (2006).
- [8] For early reports, see: (a) J. M. Longmire, B. Wang, X. Zhang. *J. Am. Chem. Soc.* **124**, 13400 (2002); (b) A. S. Gothelf, K. V. Gothelf, R. G. Hazell, K. A. Jørgensen. *Angew. Chem. Int. Ed.* **41**, 4236 (2002); for reviews, see: (c) C. Nájera, J. M. Sansano.

- Angew. Chem. Int. Ed.* **44**, 6272 (2005); (d) L. M. Stanley, M. P. Sibi. *Chem. Rev.* **108**, 2887 (2008); (e) J. Adrio, J. C. Carretero. *Chem. Commun.* **47**, 6784 (2011) and references cited therein.
- [9] (a) J. L. Vicario, S. Reboredo, D. Badía, L. Carrillo. *Angew. Chem. Int. Ed.* **46**, 5168 (2007); (b) I. Ibrahim, R. Rios, J. Vesely, A. Córdova. *Tetrahedron Lett.* **48**, 6252 (2007); (c) M. -X. Xue, X. -M. Zhang, L. -Z. Gong. *Synlett* 691 (2008); (d) Y. -K. Liu, H. Liu, W. Du, L. Yue, Y. -C. Chen. *Chem. Eur. J.* **14**, 9873 (2008).
- [10] (a) X. -H. Chen, W. -Q. Zhang, L. -Z. Gong. *J. Am. Chem. Soc.* **130**, 5652 (2008); (b) L. He, X. -H. Chen, D. -N. Wang, S. -W. Luo, W. -Q. Zhang, J. Yu, L. Ren, L. -Z. Gong. *J. Am. Chem. Soc.* **133**, 13504 (2011); (c) X. -H. Chen, Q. Wei, S. -W. Luo, H. Xiao, L. -Z. Gong. *J. Am. Chem. Soc.* **131**, 13819 (2009); (d) W. -J. Liu, X. -H. Chen, L. -Z. Gong. *Org. Lett.* **10**, 5357 (2008); (e) J. Yu, L. He, X. -H. Chen, J. Song, W. -J. Chen, L. -Z. Gong. *Org. Lett.* **11**, 4946 (2009); (f) C. Wang, X. -H. Chen, L. -Z. Gong. *Chem. Commun.* 1275 (2010); (g) F. Shi, S. -W. Luo, Z. -L. Tao, L. He, J. Yu, S. -J. Tu, L. -Z. Gong. *Org. Lett.* **13**, 4680 (2011).
- [11] For examples, see: (a) A. S. Girgis. *Eur. J. Med. Chem.* **44**, 91 (2009); (b) R. Murugan, S. Anbazhagan, S. S. Narayanan. *Eur. J. Med. Chem.* **44**, 3272 (2009); (c) S. U. Maheswari, K. Balamurugan, S. Perumal, P. Yogeeswari, D. Sriram. *Bioorg. Med. Chem. Lett.* **20**, 7278 (2010); (d) R. S. Kumar, S. M. Rajesh, S. Perumal, D. Banerjee, P. Yogeeswari, D. Sriram. *Eur. J. Med. Chem.* **45**, 411 (2010); (e) A. Thangamani. *Eur. J. Med. Chem.* **45**, 6120 (2010); (f) P. Prasanna, K. Balamurugan, S. Perumal, P. Yogeeswari, D. Sriram. *Eur. J. Med. Chem.* **45**, 5653 (2010); (g) M. A. Ali, R. Ismail, T. S. Choon, Y. K. Yoon, A. C. Wei, S. Pandian, R. S. Kumar, H. Osman, E. Manogaran. *Bioorg. Med. Chem. Lett.* **20**, 7064 (2010).
- [12] F. Shi, Z. -L. Tao, S. -W. Luo, S. -J. Tu, L. -Z. Gong. *Chem. Eur. J.* **18**, 6885 (2012).
- [13] (a) “Bisindole Alkaloids”: G. A. Cordell, J. E. Saxton in *The Alkaloids: Chemistry and Physiology*, R. H. F. Manske, R. G. A. Rodrigo (Eds.) Academic Press, New York, Vol. 20, p 3–294 (1981); (b) “Chemistry and Reactions of Cyclic Tautomers of Tryptamines and Tryptophans”: T. Hino, M. Nakagawa in *The Alkaloids: Chemistry and Pharmacology*, A. Brossi (Ed.) Academic Press, New York, Vol. 34, p 1–75 (1989); (c) “Alkaloids from the Medicinal Plants of New Caledonia”: T. Sévenet, J. Pusset in *The Alkaloids: Chemistry and Pharmacology*, G. A. Cordell (Ed.) Academic Press, New York, Vol. 48, p 58–59 (1996); (d) “Naturally Occurring Cyclotryptophans and Cyclotryptamines”: U. Anthoni, C. Christophersen, P. H. Nielsen in *Alkaloids: Chemical & Biological Perspectives*, S. W. Pelletier (Ed.) Wiley, New York, Vol. 13, p 163–236 (1999); (e) D. Crich; A. Banerjee, *Acc. Chem. Res.* **40**, 151 (2007).
- [14] A. Steven, L. E. Overman. *Angew. Chem. Int. Ed.* **46**, 5488 (2007).
- [15] (a) L. E. Overman, D. V. Paone, B. A. Stearns. *J. Am. Chem. Soc.* **121**, 7702 (1999); (b) L. E. Overman, J. F. Larrow, B. A. Stearns, J. M. Vance. *Angew. Chem. Int. Ed.* **39**, 213 (2000).
- [16] (a) M. Movassaghi, M. A. Schmidt. *Angew. Chem. Int. Ed.* **46**, 3725 (2007); (b) M. Movassaghi, M. A. Schmidt, J. A. Ashenurst. *Angew. Chem. Int. Ed.* **47**, 1485 (2008); (c) J. Kim, J. A. Ashenurst, M. Movassaghi. *Science*. **324**, 238 (2009); (d) J. Kim, M. Movassaghi. *J. Am. Chem. Soc.* **132**, 14376 (2010).
- [17] C. Guo, J. Song, J. -Z. Huang, P. -H. Chen, S. -W. Luo, L. -Z. Gong. *Angew. Chem. Int. Ed.* **51**, 1046 (2012).
- [18] C. Ramalingam, Y. -T. Park. *J. Org. Chem.* **72**, 4536 (2007).
- [19] C. -L. Fang, S. Horne, N. Taylor, R. Rodrigo. *J. Am. Chem. Soc.* **116**, 9480 (1994).
- [20] (a) L. E. Overman, Y. Shin. *Org. Lett.* **9**, 339 (2007); (b) J. E. Delorbe, S. Y. Jabri, S. M. Mennen, L. E. Overman, F. Zhang. *J. Am. Chem. Soc.* **133**, 6549 (2011); (c) L. Furst, J. M. R. Narayanam, C. R. J. Stephenson. *Angew. Chem. Int. Ed.* **50**, 9655 (2011); (d) N. Boyer, M. Movassaghi. *Chem. Sci.* **3**, 1798 (2012).
- [21] J. Song, C. Guo, A. Adele, H. Yin, L. -Z. Gong. *Chem. Eur. J.* **19**, 3319 (2013).
- [22] For a review on primary amine catalysis: (a) L. -W. Xu, J. Luo, Y. Lu. *Chem. Commun.* 1807 (2009); for reviews focusing on the reasons that have brought about the development of cinchona-based primary amines, see: (b) L. Jiang, Y. -C. Chen. *Catal. Sci. Technol.* **1**, 354 (2011); (c) G. Bartoli, P. Melchiorre. *Synlett* 1759 (2008); (d) Y. -C. Chen. *Synlett* 1919 (2008); (e) P. Melchiorre. *Angew. Chem. Int. Ed.* **51**, 9748 (2012).
- [23] (a) J. -W. Xie, X. Huang, L. -P. Fan, D. -C. Xu, X. -S. Li, H. Su, Y. -H. Wen. *Adv. Synth. Catal.* **351**, 3077 (2009); (b) X. Tian, C. Cassani, Y. Liu, A. Moran, A. Urakawa, P. Galzerano, E. Arceo, P. Melchiorre. *J. Am. Chem. Soc.* **133**, 17934 (2011); (c) G. Bergonzini, S. Vera, P. Melchiorre. *Angew. Chem. Int. Ed.* **49**, 9685 (2010); (d) O. Lifchits, C. M. Reisinger, B. List. *J. Am. Chem. Soc.* **132**, 10227 (2010).
- [24] For our recent contributions on relay catalysis, see: (a) Z. Y. Han, H. Xiao, X. H. Chen, L. Z. Gong. *J. Am. Chem. Soc.* **131**, 9182 (2009); (b) C. Wang, Z. Y. Han, H. W. Luo, L. Z. Gong. *Org. Lett.* **12**, 2266 (2010); (c) Z. -Y. Han, R. Guo, P. -S. Wang, D. -F. Chen, H. Xiao, L. -Z. Gong. *Tetrahedron Lett.* **52**, 5963 (2011); (d) H. Wu, Y. -P. He, L. -Z. Gong. *Adv. Syn. Catal.* **354**, 975 (2012); (e) Z. -Y. Han, D. -F. Chen, Y. -Y. Wang, L. -Z. Gong. *J. Am. Chem. Soc.* **134**, 6532 (2012); (f) H. Wu, Y. -P. He, L. -Z. Gong. *Org. Lett.* **15**, 460 (2013); (g) Y. -P. He, H. Wu, D. -F. Chen, J. Yu, L. -Z. Gong. *Chem. Eur. J.* **19**, 5232 (2013); (h) P. -S. Wang, K. -N. Li, X. -L. Zhou, X. Wu, Z. -Y. Han, R. Guo, L. -Z. Gong. *Chem. Eur. J.* **19**, 6234 (2013); (i) D. -F. Chen, P. -Y. Wu, L. -Z. Gong. *Org. Lett.* **15**, 3958 (2013).
- [25] (a) P. Friedländer. *Berichte* **15**, 2572 (1882); (b) C. C. Cheng, S. J. Yan. *Org. React.* **28**, 37 (1982); (c) J. M. Contelles, E. P. Mayoral, A. Samadi, M. C. Carreiras, E. Soriano. *Chem. Rev.* **109**, 2652 (2009).
- [26] L. Ren, T. Lei, J. -X. Ye, L. -Z. Gong. *Angew. Chem. Int. Ed.* **51**, 771 (2012).