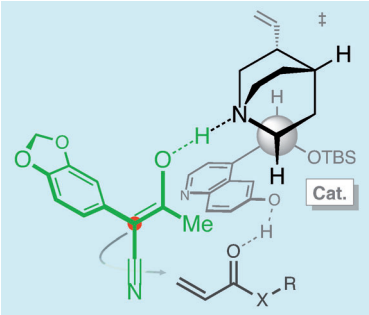
COMMUNICATION

Cat. on a hot tin roof: Enantioselective catalytic Michael addition of α-cyanoketones to acrylates under bifunctional organocatalysis was used to construct the unique arylic all-carbon quaternary stereocenter, which is synthetically crucial in the chemical synthesis of optically pure *cis*-aryl hydroindole alkaloids. The protocol offers an asymmetric route to (+)-vittatine, (+)-*epi*-vittatine, and (+)-buphanisine.



Asymmetric Synthesis

*Meng-Xue Wei, Cheng-Tao Wang, Ji-Yuan Du, Hu Qu, Pei-Rong Yin, Xu Bao, Xiao-Yan Ma, Xian-He Zhao, Guo-Biao Zhang, Chun-An Fan** ——— ▮▮▮▮–▮▮▮▮

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Enantioselective Synthesis of *Amaryllidaceae* Alkaloids (+)-Vittatine, (+)-*epi*-Vittatine, and (+)-Buphanisine

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The naturally occurring alkaloids having a *cis*-aryl hydroindole nucleus are widely distributed in the plants of the *Amaryllidaceae* and *Aizoaceae* families (Figure 1),[1] and such alkaloids have attracted considerable interest in the chemistry community due to their intriguing molecular architectures and broad range of biological activities.[1] Notably from a synthetic point of view, the asymmetric creation of the arylic all-carbon quaternary stereocenter in the above *cis*-aryl hydroindole nucleus constitutes one critical element in the total synthesis of these bioactive alkaloids. The asymmetric synthesis of chiral all-carbon quaternary stereogenic centers is one of the most challenging and dynamic research areas in modern organic synthesis.[2] Encompassing the asymmetric assembly of the quaternary stereocenters in *cis*-aryl hydroindole alkaloids, various approaches for the direct formation of a carbon–carbon bond centered on the sterically congested chiral quaternary carbon atom have been extensively developed over the past four decades, as mainly exemplified by: 1) 3,3-sigmatropic rearrangement;[3] 2) semipinacol rearrangement;[4] 3) α-alkylation of carbonyls or addition of enolates generated in situ by oxy-Cope rearrangement;[5] 4) Mannich reaction initiated by aza-Cope rearrangement.[6] 5) cycloaddition reaction;[7] 6) Michael addition;[8] 7) epoxide ring opening;[9] 8) intramolecular Heck reaction;[10] 9) intramolecular carbene insertion;[11] 10) intramolecular carbonyl–ene reaction;[12] 11) intramolecular radical cyclization;[13] and 12) intramolecular zirconium-mediated diene reductive cyclization.[14] Among them, however, asymmetric access to the vital quaternary centers was entirely achieved by the diastereoselective induction of the pre-existing stereocenters in chiral substrates or auxiliaries. In addition, the diastereoselective and enantioselective desymmetrization strategies, which were based on lactonization[15a,b] and intramolecular aza-Michael addition,[15c–f,16] have also been elegantly utilized to indirectly access such quaternary stereocenters of *cis*-aryl hydroindole alkaloids from the prochiral quaternary carbon atom. Despite the above-mentioned substantial progress in the construction of the related chiral all-carbon quaternary centers, the exploration of alternative strategies, especially to create such stereocenters in a catalytic enantioselective manner, is still of high demand in the asymmetric synthesis of *cis*-aryl hydroindole alkaloids.[3–16]

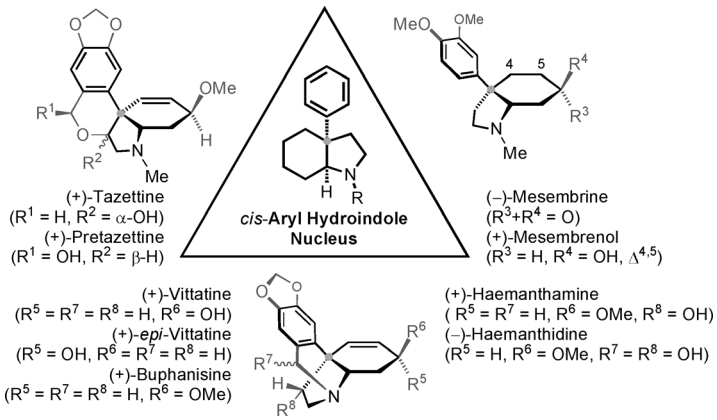

Figure 1. Selected representative *Amaryllidaceae* and *Aizoaceae* alkaloids.

To address this topic, three biologically interesting *Amaryllidaceae* alkaloids, (+)-vittatine, (+)-*epi*-vittatine, and (+)-buphanisine (Figure 1), were selected as our synthetic targets for developing a method-oriented strategy. These structurally related molecules with a bridged polycyclic ring system were originally found in some *Amaryllidaceae* plants such as *Hippeastrum vittatum*, *Nerine bowdenii*, *Crinum erubescens*, and *Sternbergia sicula*.[1a] It should be noted that only one route to the asymmetric synthesis of (+)-vittatine has been disclosed by Chida and co-workers,[3c,e] in which the stereodefined construction of the key chiral quaternary carbon center was successfully achieved by a diastereoselective Claisen rearrangement using chiral allylic alcohol pre-

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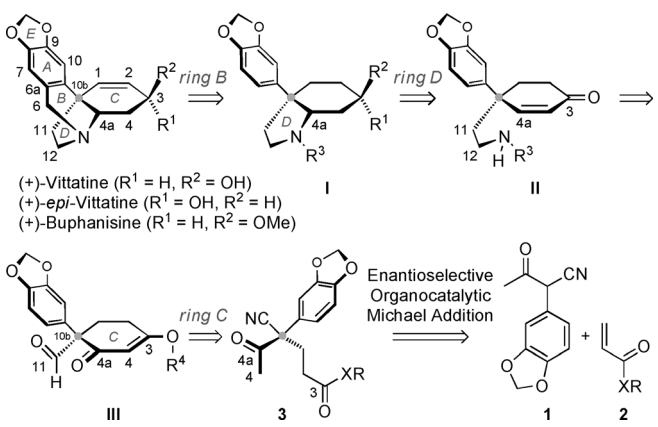
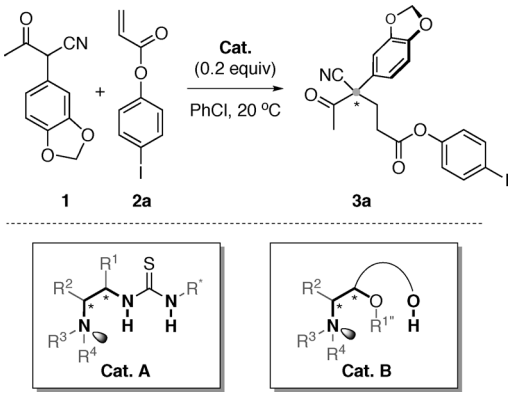
cursor derived from chiral pool D-glucose. However, there was no report on the asymmetric synthesis of (+)-*epi*-vittatine[17] and (+)-buphanisine.[18] In connection with our recent interest in the enantioselective synthesis of polycyclic alkaloids with *cis*-hydrodibenzofuran cores,[19] we have previously demonstrated the synthetic potential of organocatalytic Michael addition of α-cyanoketones to acrylates in the catalytic asymmetric establishment of highly functionalized chiral all-carbon quaternary stereocenters. As a continuing exploration of such organocatalysis in the arena of natural product synthesis,[20] herein we report our results on the enantioselective synthesis of some *cis*-aryl hydroindole alkaloids.

Our retrosynthetic analysis of (+)-vittatine, (+)-*epi*-vittatine, and (+)-buphanisine (Scheme 1) commenced with the disconnection of C6–C6a and C6–N in the hydroisoquinoline ring B, giving a promising *cis*-aryl hydroindole synthon **I**. Logically, the formation of pyrolidine ring D in **I** could be envisioned by a diastereoselective intramolecular aza-Michael addition of enone synthon **II**, which could be chemically derived from the aldehyde synthon **III** through one-carbon homologation at C11 and the carbonyl transposition from C4a to C3. Subsequently, the scission of the C3–C4 bond in ring C of **III** could be conceived to deliver the functionalized acyclic synthon **3** having the crucial quaternary carbon center, which would be accessed by a novel enantioselective organocatalytic Michael addition as a key step.



Scheme 1. Retrosynthetic analysis.

According to the above synthetic considerations (Scheme 1), the target-oriented model using α-cyanoketone **1** as Michael donor and the acrylate **2a** as Michael acceptor was then built for our synthetic study (Scheme 2), in which two types of multifunctional organocatalysts (**Cat. A** and **Cat. B**) were selected in the current Michael addition. Based on our previous investigation on the Michael addition of α-cyanoketones to acrylates,[19] several **Cat. A**-type chiral tertiary amine thioureas **4a**–**4e** (Figure 2),[21] which were derived from the structural combinations of cyclic and acyclic chiral diamines with nonchiral and chiral *N*-thiourea substituents, were firstly evaluated at 20 °C in the presence of



Scheme 2. The key enantioselective organocatalytic Michael addition.

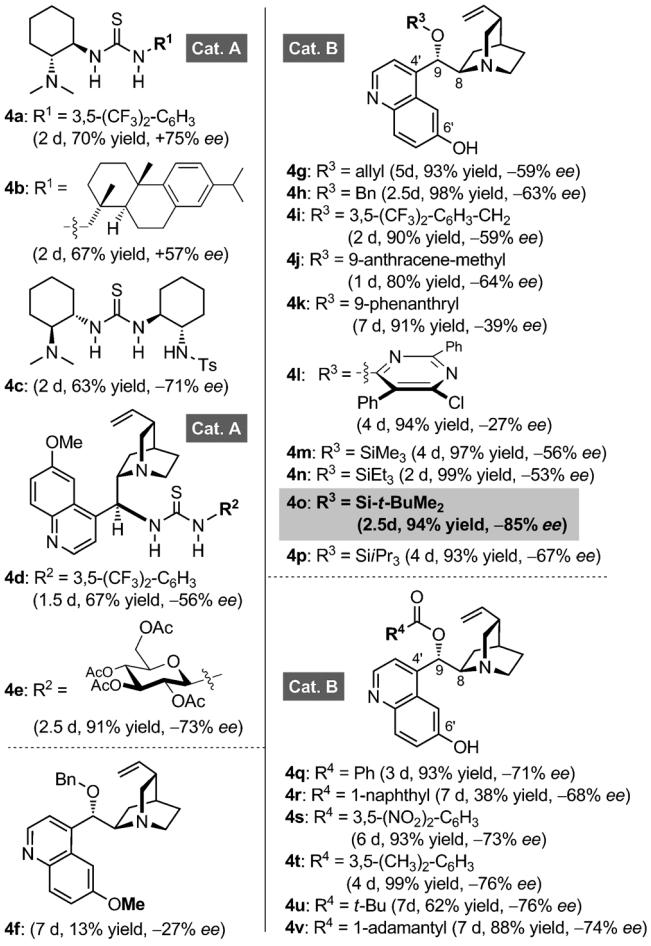


Figure 2. Evaluation of organocatalysts for the synthesis of **3a** by Michael addition of **1** to **2a**. Ts = 4-methylbenzenesulfonyl.

PhCl as solvent.[22] In the cases using **4a**–**4e** as catalyst, the desired Michael adduct **3a** was afforded in 63–91% yields, but with 56–75% *ee*, showing an appeal for the further improvement of enantioselectivity.

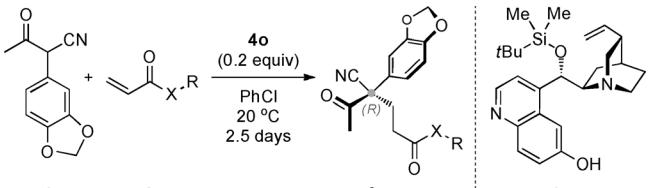
Following the above mode of acid–base catalysis, the **Cat. B**-type chiral tertiary amine phenols **4g**–**4v** (Figure 2),[23]

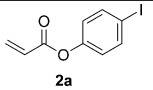
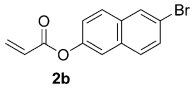
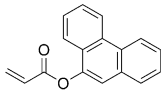
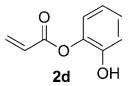
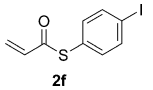
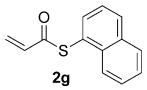
which were grafted to the chiral 1,2-amino alcohol backbone bearing a Brønsted acidic ω-OH instead of the acidic thiourea moiety in **Cat. A**, were then investigated. The presence of the acidic ω-OH in **Cat. B** proved to be pivotal for the reactivity and stereoselectivity of this Michael addition, and for example the quinidine-derived ether catalyst **4f** gave a very low yield and *ee* (13% yield, 27% *ee*). Subsequently, a series of R^3 and R^4 protecting groups, which included alkyl (**4g**–**4j**), aryl (**4k**–**4l**), silyl (**4m**–**4p**), aryl-acyl (**4q**–**4t**) and alkyl-acyl (**4u**–**4v**), were installed on the C(sp^3)-OH of cupreidine (*O*-demethylquinidine) to probe the potential influence on the reactivity and enantioselectivity. It is known that the size and property of groups located on the aliphatic secondary hydroxy group of *Cinchona* alkaloids can adjust the spatial orientation of the appended isoquinoline motif by rotation around the C4′–C9 and C9–C8 bonds (Figure 2), which would consequently impact the stereocontrol in the cinchona-related chiral catalysis. In comparison with the results by using the ester-type catalysts **4q**–**4v** (68–76% *ee*), generally the ether-type catalysts **4g**–**4l** showed an inferior asymmetric induction (27–64% *ee*). However, the silyl ether-type catalyst **4o**,[24] which was derived from the alcoholic silylation of *Cinchona* alkaloid cupreidine, could give an improved stereocontrol (85% *ee*) in the construction of quaternary stereogenic center of the key building block **3a**. When other silyl ether-type catalysts bearing less sterically bulky trimethylsilyl (**4m**) and triethylsilyl (**4n**) or more hindered triisopropylsilyl (**4p**) were used, the enantioselectivity of the model Michael addition of **1** to **2a** was eroded (53–67% *ee*), demonstrating the stereoselective influence of the slight conformation change of the cupreidine skeleton on this transformation.

In addition to the optimization of catalysts mentioned above, we also investigated the effect of Michael acceptors **2** in terms of our target-directed analysis (Scheme 1). As shown in Table 1, some acrylates and thioacrylates were subjected to the optimized conditions. Compared with 4-iodophenyl acrylate **2a** (Table 1, entry 1), either the bulky aryl acrylates (**2b**,**c**) or the acrylate with additional hydrogen-bonding site (**2d**) gave an obviously reduced induction (41–57% *ee*; Table 1, entries 2–4). But surprisingly, the alkyl acrylate **2e** (Table 1, entry 5) was ineffective in current conditions, probably due to the lower electrophilicity of the acrylate double bond caused by the electron-donating nature of the C(sp^3)-hybridized alkyl substituent in the acceptor. Besides, two more electrophilically reactive thioacrylates **2f** and **2g** were examined at −20 °C (Table 1, entries 6–7), and unexpectedly the Michael addition did not exhibit the positive improvement of the enantioselectivity (60–74% *ee*).

In order to further enhance the enantiopurity of the corresponding Michael adduct (*R*)-**3a** (85% *ee*; Table 1, entry 1), chiral enrichment by crystallization was employed. Gratifyingly, the enantiomeric purity of the mother liquor was readily enriched through an interesting heterochiral crystallization[25] to deliver (*R*)-**3a** in 99% *ee* and 78% yield after separation of the racemate crystals by filtration, providing an alternative opportunity for highly enantioselective

Table 1. Effect of Michael acceptors on the enantioselectivity.[a,b]



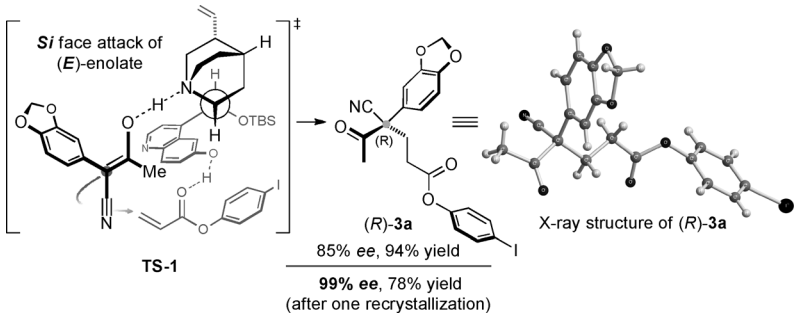
Entry	2	3	Yield [%][c]	*ee* [%][d]
1	 2a	(*R*)-**3a**[b]	94	85
2	 2b	**3b**	94	57
3	 2c	**3c**	93	49
4	 2d	**3d**	90	41
5	 2e	**3e**	trace	–
6	 2f	**3f**[e]	73	74
7	 2g	**3g**[e]	94	60

[a] To an oven-dried 10 mL Schlenk tube were sequentially added **4o** (0.01 mmol), α-cyanoketone **1** (0.05 mmol), PhCl (0.25 mL), and acrylic (thio)esters **2** (0.10 mmol). The reaction mixture was stirred for 2.5 days at 20 °C (unless otherwise noted). [b] The (*R*) absolute configuration of **3a** was determined by X-ray crystallographic analysis,[26] and then the enantioselectivity for other cases was tentatively assigned by analogy. [c] Yield of isolated product. [d] Determined by chiral HPLC analysis. [e] Performed at −20 °C.

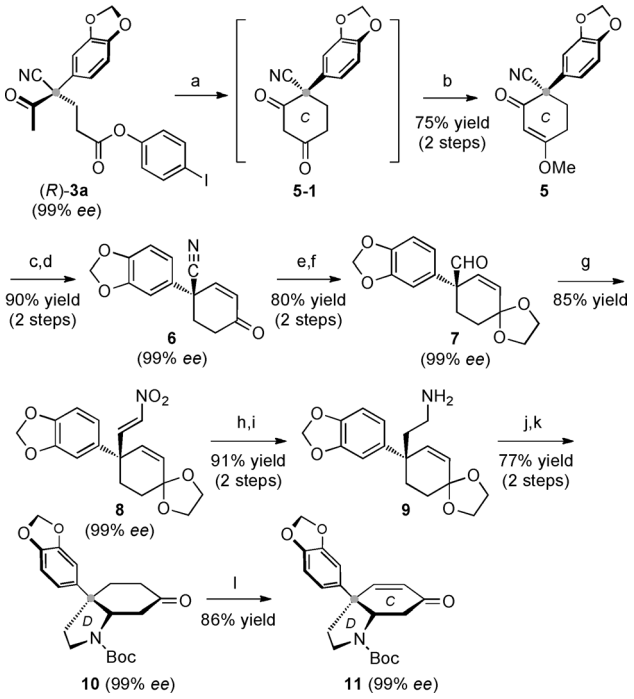
access to the crucial chiral all-carbon quaternary stereocenters in the designed asymmetric synthesis of *cis*-aryl hydroindole alkaloids. Due to the importance of the requisite stereochemistry depicted in our retrosynthetic analysis (Scheme 1), the absolute configuration of crystal (*R*)-**3a** (> 99% *ee*), which was further obtained by a gradual recrystallization of the resulting mother liquor (99% *ee*) from a mixed solvent of $CHCl_3$ and *n*-hexane, was unambiguously determined by the X-ray crystallographic analysis (Scheme 3).[26]

Accordingly, a bifunctional activation mode **TS-1** for the organocatalytic Michael addition of **1** to **2a** was also proposed for the observed stereocontrol under the catalysis of **4o**, in which the preferential *Si* face attack of the energetically favorable (*E*)-enolate was involved.

Based on the asymmetric establishment of the functionalized acyclic synthon (*R*)-**3a** (99% *ee*) having the crucial chiral quaternary stereogenic center (Scheme 4), an intramolecular ketone–ester condensation and subsequent regio-



Scheme 3. Stereochemical assignment of (*R*)-**3a** and proposed enantioselectivity mode. TBS = *tert*-butyldimethylsilyl.

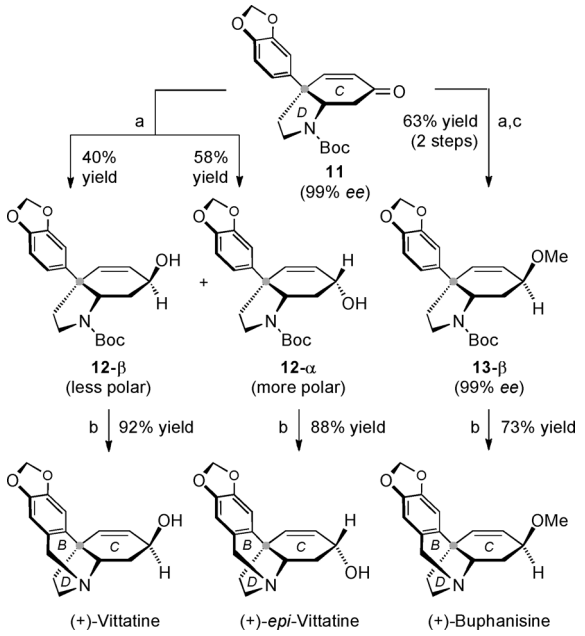


Scheme 4. Enantioselective synthesis of aryl hydroindole synthon **11**. a) *t*BuONa (2.5 equiv), *t*BuOH/THF (1:1), −20 °C; b) *p*-TsOH·H_2O (cat.), toluene/MeOH (10:1), 0 °C to rt; c) $NaBH_4$, $CeCl_3$, MeOH/THF (3:1), −20 °C; d) $MeSO_3H$, toluene, 0 °C; e) $HO(CH_2)_2OH$, *p*-TsOH·Py (cat.), benzene, reflux; f) *i*Bu_2AlH, CH_2Cl_2, −78 °C; g) $MeNO_2$, NEt_3, rt; and then MsCl, NEt_3, CH_2Cl_2, 0 °C to rt; h) $NaBH_4$, EtOH, 0 °C to rt; i) Zn (powder), aq. NH_4Cl (sat.), EtOH, 50 °C; j) 2 M HCl, THF, reflux; k) Boc_2O, NEt_3, CH_2Cl_2, 0 °C to rt; l) TMSOTf, NEt_3, CH_2Cl_2, −78 °C to −40 °C; and then $Pd(OAc)_2$, MeCN, 0 °C to rt. Boc = *tert*-butoxycarbonyl, Ms = methanesulfonyl, Py = pyridine, THF = tetrahydrofuran, Tf = trifluoromethanesulfonyl, TMS = trimethylsilyl, *p*-TsOH = *p*-toluenesulfonic acid.

selective etherification were used to construct the all-carbon six-membered ring C, leading to the cyclic vinylogous ester **5** via 1,3-diketone intermediate **5-1** in 75% yield over two steps. Then, the carbonyl transposition protocol involving the Luche reduction of enone moiety of **5** and subsequent acidic hydrolysis of enol ether group afforded the desired γ-quaternary cyclohexenone **6** (99% *ee*) in 90% overall yield. Following the protection of enone carbonyl with cyclic ketal, the aldehyde **7** (99% *ee*) was obtained by a subsequent diisobutylaluminum hydride reduction of the cyano group in 80% yield over two steps. With the aldehyde **7** in hand, one-carbon homologation by a Henry reaction was conducted, and the desired nitroolefin **8** (99% *ee*) was smoothly formed through successive elimination of the derived mesylate in 85% overall yield. After a sequential reduction of the conjugated nitroalkene **8** using $NaBH_4$ and zinc powder, the primary amine **9** was afforded in 91% overall yield. The removal of ketal protection in **9** under acidic conditions resulted in the in situ formation of enone intermediate, which rapidly underwent a stereospecific intramolecular aza-Michael addition in one pot, followed by N-carbamation with di-*tert*-butyl dicarbonate, to give the expected D ring containing hydroindolone **10** (99% *ee*) in 77% yield over two steps. Subsequently, a Saegusa–Ito oxidation protocol consisting of the enol silylation and palladium-mediated oxidative dehydrogenation was adopted for the regioselective introduction of the enone functionality, furnishing the desired functionalized hydroindolenone synthon **11** (99% *ee*) in 86% overall yield.

After the stereocontrolled assembly of *cis*-aryl hydroindole skeleton with rings C and D, the further elaboration directed to the construction of ring B was then carried out. Upon treatment of the synthon **11** with lithium tri-*sec*-butylborohydride (L-selectride), as shown in Scheme 5, 1,2-reduction of the enone motif delivered two chromatographically separable diastereoisomers **12-β** (less polar) and **12-α** (more polar) in 40% yield and 58% yield, respectively, in which the relative stereochemistry was confirmed by comparison with the literature.[27] Accompanied by the acidic deprotection of the *N*-Boc group in **12-β** and **12-α**, the methylene unit in ring B was readily installed via a Pictet–Spengler reaction, leading to the completion of (+)-vittatine and (+)-*epi*-vittatine in 92% yield and 88% yield, respectively. As a continuing pursuit in the enantioselective synthesis of *cis*-aryl hydroindole alkaloids, the stereoselective conversion of the common building block **11** to the allyl methyl ether **13-β** was achieved in 63% overall yield through a stepwise protocol including the L-selectride reduction of the enone moiety, the mesylation of an unpurified mixture of resulting allylic alcohols, and the regio- and diastereoselective S_N1-like methanolysis of allylic mesylates.[28] Following the removal of the *N*-Boc protecting group of **13-β** under acidic conditions, the incorporation of hydroisoquinoline ring B was analogously accomplished by the Pictet–Spengler protocol, delivering the expected (+)-buphanisine in 73% overall yield.

In conclusion, towards the catalytic asymmetric construction of the unique arylic all-carbon quaternary stereocenter,



Scheme 5. Asymmetric synthesis of (+)-vittatine, (+)-*epi*-vittatine, and (+)-buphanisine. a) L-selectride, THF, −78 °C; b) CF_3CO_2H, $Cl(CH_2)_2Cl$, 0 °C to rt; and then 37% HCHO (aq.), 6 M HCl, MeOH; c) NEt_3, Ms_2O, THF; and then MeOH, 0 °C to rt. L-selectride = lithium tri-*sec*-butylborohydride.

which synthetically crucial in the chemical synthesis of optically pure *cis*-aryl hydroindole alkaloids, an alternative strategy featuring a key enantioselective organocatalytic Michael addition of α-cyanoketones to acrylates was revealed. Importantly, the catalytic efficiency of the axially chiral tertiary amine-phenol **4o** as a novel cupreidine-derived bifunctional organocatalyst was unprecedentedly explored in our target-oriented Michael addition, providing an opportunity to organocatalytically access the chiral quaternary carbon center in high yield and good enantioselectivity. Based on the preliminary investigation of such key conjugate addition and combined with the further enantioenrichment by unusual heterochiral crystallization, the enantioselective synthesis of (+)-vittatine was presented, and also the first asymmetric syntheses of (+)-*epi*-vittatine and (+)-buphanisine were divergently achieved. Our current study not only enriches the synthetic chemistry of *cis*-aryl hydroindole alkaloids, but also extends the synthetic potential of organocatalytic Michael addition of α-cyanoketones to acrylates in the asymmetric synthesis of natural products.[20]

Acknowledgements

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Keywords: alkaloids · asymmetric synthesis · Michael addition · organocatalysis · quaternary carbon

[1] a) *Dictionary of Alkaloids*, *2nd ed.* (Eds.: J. Buckingham, K. H. Baggaley, A. D. Roberts, L. F. Szabó), CRC Press, **2010**; for selected reviews, see: b) S. F. Martin in *The Alkaloids*, *Vol. 30* (Ed.: A. Brossi), Academic Press, New York, **1987**, pp. 251; c) O. Hoshino in *The Alkaloids*, *Vol. 51* (Ed.: G. A. Cordell), Academic Press, New York, **1998**, pp. 323; d) J. R. Lewis, *Nat. Prod. Rep.* **1998**, *15*, 107; e) Z. Jin, Z. Li, R. Huang, *Nat. Prod. Rep.* **2002**, *19*, 454; f) Z. Jin, *Nat. Prod. Rep.* **2005**, *22*, 111; g) Z. Jin, *Nat. Prod. Rep.* **2009**, *26*, 363.

[2] For selected reviews on the catalytic asymmetric construction of all-carbon quaternary centers, see: a) K. Fuji, *Chem. Rev.* **1993**, *93*, 2037; b) E. J. Corey, A. Guzman-Perez, *Angew. Chem.* **1998**, *110*, 402; *Angew. Chem. Int. Ed.* **1998**, *37*, 388; c) J. Christoffers, A. Mann, *Angew. Chem.* **2001**, *113*, 4725; *Angew. Chem. Int. Ed.* **2001**, *40*, 4591; d) I. Denissova, L. Barriault, *Tetrahedron* **2003**, *59*, 10105; e) J. Christoffers, A. Baro, *Angew. Chem.* **2003**, *115*, 1726; *Angew. Chem. Int. Ed.* **2003**, *42*, 1688; f) J. Christoffers, *Chem. Eur. J.* **2003**, *9*, 4862; g) M. Shibasaki, E. M. Vogl, T. Ohshima, *Adv. Synth. Catal.* **2004**, *346*, 1533; h) C. J. Douglas, L. E. Overman, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5363; i) J. Christoffers, A. Baro, *Adv. Synth. Catal.* **2005**, *347*, 1473; j) *Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis* (Eds.: J. Christoffers, A. Baro), Wiley-VCH, Weinheim, Germany, **2005**; k) B. M. Trost, C. Jiang, *Synthesis* **2006**, 369; l) J. T. Mohr, B. M. Stoltz, *Chem. Asian J.* **2007**, *2*, 1476; m) P. G. Cozzi, R. Hilgraf, N. Zimmermann, *Eur. J. Org. Chem.* **2007**, 5969; n) A. Alexakis, M. Vuagnoux-d'Augustin, D. Martin, S. Kehrli, L. Palais, H. Hénon, C. Hawner, *Chimia* **2008**, *62*, 461; o) M. Bella, T. Gasperi, *Synthesis* **2009**, 1583; p) S. Jautze, R. Peters, *Synthesis* **2010**, 365; q) C. Hawner, A. Alexakis, *Chem. Commun.* **2010**, *46*, 7295; r) J. P. Das, I. Marek, *Chem. Commun.* **2011**, *47*, 4593.

[3] For examples using a diastereoselective 3,3-sigmatropic rearrangement in the synthesis of (−)-mesembrine, (+)-mesembrine, (+)-vittatine, (+)-haemanthamine, and (+)-amabiline, see: a) H. F. Strauss, A. Wiechers, *Tetrahedron Lett.* **1979**, *20*, 4495; b) H. Kosugi, Y. Miura, H. Kanna, H. Uda, *Tetrahedron: Asymmetry* **1993**, *4*, 1409; c) M. Bohno, H. Imase, N. Chida, *Chem. Commun.* **2004**, 1086; d) T. Paul, W. P. Malachowski, J. Lee, *Org. Lett.* **2006**, *8*, 4007; e) M. Bohno, K. Sugie, H. Imase, Y. B. Yusof, T. Oishi, N. Chida, *Tetrahedron* **2007**, *63*, 6977; f) E. A. Ilardi, M. J. Isaacman, Y.-c. Qin, S. A. Shelly, A. Zakarian, *Tetrahedron* **2009**, *65*, 3261; g) A. D. Findlay, M. G. Banwell, *Org. Lett.* **2009**, *11*, 3160; h) Q.-Q. Zhang, J.-H. Xie, X.-H. Yang, J.-B. Xie, Q.-L. Zhou, *Org. Lett.* **2012**, *14*, 6158.

[4] For examples using a diastereoselective semipinacol rearrangement of chiral epoxides formed in situ in the synthesis of (−)-mesembrine, see: a) H. Nemoto, T. Tanabe, K. Fukumoto, *Tetrahedron Lett.* **1994**, *35*, 6499; b) H. Nemoto, T. Tanabe, K. Fukumoto, *J. Org. Chem.* **1995**, *60*, 6785.

[5] For examples using a diastereoselective α-alkylation of carbonyls in the synthesis of (−)-mesembrine, (+)-mesembrine, as well as the chiral hydroindolone synthon, see: a) S. Takano, Y. Imamura, K. Ogasawara, *Tetrahedron Lett.* **1981**, *22*, 4479; b) A. I. Meyers, R. Hanreich, K. T. Wanner, *J. Am. Chem. Soc.* **1985**, *107*, 7776; c) P. I. Dalko, V. Brun, Y. Langlois, *Tetrahedron Lett.* **1998**, *39*, 8979; d) D. J. Watson, A. I. Meyers, *Tetrahedron Lett.* **2000**, *41*, 1519; for an example using a diastereoselective addition of enolates generated in situ by oxy-Cope rearrangement in the synthesis of (−)-mesembrine, see: e) S. Arns, M.-E. Lebrun, C. M. Grisé, I. Denissova, L. Barriault, *J. Org. Chem.* **2007**, *72*, 9314.

[6] For an example using a diastereoselective Mannich reaction initiated by aza-Cope rearrangement in the synthesis of (−)-crinine, see: L. E. Overman, S. Sugai, *Helv. Chim. Acta* **1985**, *68*, 745.

[7] For examples using a diastereoselective cycloaddition reaction in the synthesis of (−)-mesembrine, (−)-amabiline, (−)-augustamine, (+)-pretazettine, and (+)-tazettine, see: a) S. Takano, K. Samizu, K.

Ogasawara, *Chem. Lett.* **1990**, 1239; b) W. H. Pearson, F. E. Lovering, *J. Am. Chem. Soc.* **1995**, *117*, 12336; c) S. E. Denmark, L. R. Marcin, *J. Org. Chem.* **1997**, *62*, 1675; d) W. H. Pearson, F. E. Lovering, *J. Org. Chem.* **1998**, *63*, 3607; e) S. W. Baldwin, J. S. Debenham, *Org. Lett.* **2000**, *2*, 99.

[8] For examples using a diastereoselective Michael addition in the synthesis of (+)-mesembrine, (−)-mesembrine, and (+)-sceletium A-4, see: a) S.-i. Yamada, G. Otani, *Tetrahedron Lett.* **1971**, *12*, 1133; b) G. Otani, S.-i. Yamada, *Chem. Pharm. Bull.* **1973**, *21*, 2130; c) T. Kamikubo, K. Ogasawara, *Chem. Commun.* **1998**, 783.

[9] For an example using a diastereoselective epoxide ring opening in the synthesis of (−)-mesembrine, see: D. F. Taber, Y. He, *J. Org. Chem.* **2005**, *70*, 7711.

[10] For an example using a diastereoselective intramolecular Heck reaction in the synthesis of (+)-mesembrine and (+)-mesembranol, see: K. Geoghegan, P. Evans, *J. Org. Chem.* **2013**, *78*, 3410.

[11] For an example using a diastereoselective intramolecular carbene insertion in the synthesis of (−)-mesembrine, see: D. F. Taber, T. D. Neubert, *J. Org. Chem.* **2001**, *66*, 143.

[12] For examples using a diastereoselective intramolecular carbonyl–ene reaction in the synthesis of (+)-crinamine, (−)-haemanthidine, and (+)-pretazettine, see: a) T. Nishimata, M. Mori, *J. Org. Chem.* **1998**, *63*, 7586; b) T. Nishimata, Y. Sato, M. Mori, *J. Org. Chem.* **2004**, *69*, 1837.

[13] For an example using a diastereoselective intramolecular radical cyclization in the synthesis of (−)-mesembrine and (+)-sceletium A-4, see: O. Yamada, K. Ogasawara, *Tetrahedron Lett.* **1998**, *39*, 7747.

[14] For an example using a diastereoselective intramolecular zirconium-mediated diene reductive cyclization in the synthesis of (−)-mesembrane and (−)-mesembrine, see: M. Mori, S. Kuroda, C.-S. Zhang, Y. Sato, *J. Org. Chem.* **1997**, *62*, 3263.

[15] For examples using a diastereoselective desymmetrization strategy for the synthesis of (+)-mesembrine and (−)-mesembrine via a lactonization, see: a) T. Yokomatsu, H. Iwasawa, S. Shibuya, *Tetrahedron Lett.* **1992**, *33*, 6999; b) T. Yoshimitsu, K. Ogasawara, *Heterocycles* **1996**, *42*, 135; for the synthesis of (+)-maritidine and (+)-plicamine via an intramolecular aza-Michael addition, see: c) S.-i. Yamada, K. Tomioka, K. Koga, *Tetrahedron Lett.* **1976**, *17*, 57; d) K. Tomioka, K. Koga, S.-i. Yamada, *Chem. Pharm. Bull.* **1977**, *25*, 2681; e) Y. Kita, T. Takada, M. Gyoten, H. Tohma, M. H. Zenk, J. Eichhorn, *J. Org. Chem.* **1996**, *61*, 5857; f) I. R. Baxendale, S. V. Ley, C. Piutti, *Angew. Chem.* **2002**, *114*, 2298; *Angew. Chem. Int. Ed.* **2002**, *41*, 2194.

[16] For an example using an enantioselective desymmetrization strategy for the synthesis of (−)-mesembrine via an intramolecular aza-Michael addition, see: Q. Gu, S.-L. You, *Chem. Sci.* **2011**, *2*, 1519.

[17] For the synthesis of (±)-*epi*-vittatine, also named (±)-*epi*-crinine, see Ref. [7d] and: a) H. Muxfeldt, R. S. Schneider, J. B. Mooberry, *J. Am. Chem. Soc.* **1966**, *88*, 3670; b) T. Kametani, T. Kohno, *Tetrahedron Lett.* **1971**, *12*, 3155; c) T. Kametani, T. Kohno, R. Charubala, S. Shibuya, K. Fukumoto, *Chem. Pharm. Bull.* **1972**, *20*, 1488; d) W. H. Pearson, F. E. Lovering, *Tetrahedron Lett.* **1994**, *35*, 9173; e) S. Kodama, H. Takita, T. Kajimoto, K. Nishide, M. Node, *Tetrahedron* **2004**, *60*, 4901; f) C. Bru, C. Guillou, *Tetrahedron* **2006**, *62*, 9043; g) J.-D. Liu, S.-H. Wang, F.-M. Zhang, Y.-Q. Tu, Y.-Q. Zhang, *Synlett* **2009**, *18*, 3040; h) G. Pandey, N. R. Gupta, S. R. Gadre, *Eur. J. Org. Chem.* **2011**, 740.

[18] For the synthesis of (±)-buphanisine, see Ref. [17f] and: a) S. F. Martin, C. L. Campbell, *Tetrahedron Lett.* **1987**, *28*, 503; b) S. F. Martin, C. L. Campbell, *J. Org. Chem.* **1988**, *53*, 3184.

[19] P. Chen, X. Bao, L.-F. Zhang, M. Ding, X.-J. Han, J. Li, G.-B. Zhang, Y.-Q. Tu, C.-A. Fan, *Angew. Chem.* **2011**, *123*, 8311; *Angew. Chem. Int. Ed.* **2011**, *50*, 8161.

[20] For selected reviews on the application of asymmetric organocatalysis in natural-product synthesis, see: a) R. Marcia de Figueiredo, M. Christmann, *Eur. J. Org. Chem.* **2007**, 2575; b) A. Dondoni, A. Massi, *Angew. Chem.* **2008**, *120*, 4716; *Angew. Chem. Int. Ed.* **2008**, *47*, 4638; c) E. Marqués-López, R. P. Herrera, M. Christmann, *Nat. Prod. Rep.* **2010**, *27*, 1138; d) C. Grondal, M. Jeanty, D. Enders, *Nat. Chem.* **2010**, *2*, 167; e) M. Rueping, J. Dufour, F. R. Schoepke, *Green Chem.* **2011**, *13*, 1084; f) Recent Advances on Stereoselective Organocatalytic Reactions. Organocatalytic Synthesis of Natural Products and Drugs. M. Raj, V. K. Singh in *Catalytic Methods in Asymmetric Synthesis: Advanced Materials, Techniques, and Applications* (Eds.: M. Gruttadauria, F. Giacalone), Wiley, **2011**, Chap. 11; g) B. Bradshaw, J. Bonjoch, *Synlett* **2012**, *23*, 337; h) Asymmetric Organocatalysis in Natural Product Syntheses. M. Waser in *Progress in the Chemistry of Organic Natural Products*, *Vol. 96*, Springer, **2012**; i) Enantioselective Organocatalysis: A Powerful Tool for the Synthesis of Bioactive Molecules. M. Shoji, Y. Hayashi in *Modern Tools for the Synthesis of Complex Bioactive Molecules* (Eds.: J. Cossy, S. Arseniyadis), Wiley, **2012**, Chap. 6; j) R. Marcia de Figueiredo, A. Mazziotta, D. P. de Sant′Ana, C. Palumbo, T. Gasperi, *Curr. Org. Chem.* **2012**, *16*, 2231; k) P. Kumar, N. Dwivedi, *Acc. Chem. Res.* **2013**, *46*, 289.

[21] For selected reviews concerning bifunctional-thiourea organocatalysis, see: a) Y. Takemoto, *Org. Biomol. Chem.* **2005**, *3*, 4299; b) S. J. Connon, *Chem. Eur. J.* **2006**, *12*, 5418; c) M. S. Taylor, E. N. Jacobsen, *Angew. Chem.* **2006**, *118*, 1550; *Angew. Chem. Int. Ed.* **2006**, *45*, 1520; d) A. G. Doyle, E. N. Jacobsen, *Chem. Rev.* **2007**, *107*, 5713; e) S. J. Connon, *Chem. Commun.* **2008**, 2499; f) Z. Zhang, P. R. Schreiner, *Chem. Soc. Rev.* **2009**, *38*, 1187; g) Bifunctional Thiourea Catalysts. Y. Takemoto, T. Inokuma in *Asymmetric Synthesis II: More Methods and Applications* (Eds.: M. Christmann, S. Bräse), Wiley, **2012**, Chap. 29.

[22] For details on the solvent screening, see the Supporting Information.

[23] For recent excellent reviews on the bifunctional asymmetric organocatalysis mediated by phenolic hydroxy groups and tertiary amines, see: a) T. Marcelli, J. H. van Maarseveen, H. Hiemstra, *Angew. Chem.* **2006**, *118*, 7658; *Angew. Chem. Int. Ed.* **2006**, *45*, 7496; b) P. Chauhan, S. S. Chimni, *RSC Adv.* **2012**, *2*, 737.

[24] The 6′-OH *Cinchona* alkaloids bearing a 9-silyl ether group as organocatalysts were first explored by Deng and co-workers in 2011, in which 9-*tert*-butyldimethylsilyl dihydrocupreidine, an analogue of catalyst **4o** (9-*tert*-butyldimethylsilyl cupreidine), was reported. For its pioneering catalytic asymmetric [4+2] addition, see: K. J. Bartelson, R. P. Singh, B. M. Foxman, L. Deng, *Chem. Sci.* **2011**, *2*, 1940.

[25] For selected examples of heterochiral crystallization, see: a) A. Ishii, M. Kanai, K. Higashiyama, K. Mikami, *Chirality* **2002**, *14*, 709; b) Homo- and Heterochirality in Crystals. P. A. Levkin, V. Yu. Torbeev, D. A. Lenev, R. G. Kostyanovsky in *Topics in Stereochemistry*, *Vol. 25* (Eds.: S. E. Denmark, J. S. Siegel), Wiley, **2006**, Chap. 4; c) W.-W. Chen, M.-H. Xu, G.-Q. Lin, *Tetrahedron Lett.* **2007**, *48*, 7508; d) F. Faigl, E. Fogassy, M. Nógrádi, E. Pálovics, J. Schindler, *Org. Biomol. Chem.* **2010**, *8*, 947 and references therein.

[26] CCDC 935127 for (*R*)-**3a** contains the supplementary crystallographic data for this paper. The data can be also obtained free of charge via the Internet at www.ccdc.cam.ac.uk/data_request/cif.

[27] For the synthesis of (±)-**12-α** and (±)-**12-β**, see Ref. [17g].

[28] For analougous stereoselective S_N1-like methanolysis of allylic mesylates, see Ref. [18b].

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