

REVIEW

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The applications of catalytic asymmetric halocyclization in natural product synthesis

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Halocyclization of olefinic substrate enables the establishment of cyclic skeletons *via* intramolecular halonium-induced nucleophilic addition, which has been well utilized as a practical strategy for constructing cyclic skeletons in natural product synthesis. Recently, the renaissance and rapid evolution of organocatalysis have accelerated the development of catalytic asymmetric halocyclization. In this context, natural product synthesis powered by catalytic asymmetric halocyclization has also achieved considerable progress in recent years. In some cases, these newly developed protocols enable more concise synthetic routes for accessing enantioenriched natural products. To this end, this review summarizes the applications of catalytic asymmetric halocyclization in natural product synthesis.

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The halonium-induced functionalization of the C–C double bond is one of the fundamental transformations in organic synthesis,¹ as it enables the difunctionalization of alkenes and also provides a versatile handle (the halogen) for further manipulation. In this regard, halocyclization, dihalogenation and other halo-functionalizations have found wide applications in the total synthesis of natural products.² Mechanistically, the reaction is initiated by the addition of halonium to the C–C double bond to form a cationic cyclic

halonium–alkene complex **1** (Fig. 1).³ However, little information was gained about this conceptual bridged halonium until Olah and co-workers observed this species in SbF₅–SO₂ solution using NMR spectroscopy.^{4a,b} In 1969, the bromonium of adamantylideneadamantane **2** was synthesized and isolated by Wynberg^{4c} and subsequently its structure was unambiguously established by X-ray crystallographic analysis.^{4d} For the halonium-induced reactions, the following capture of this intermediate usually results in high diastereoselectivities, which originate from the *anti*-addition of nucleophiles to the bridged halonium. However, this intermediate is not always involved in all the halonium-induced transformations of the olefin. Kinetic and mechanistic studies also support the existence of the β -halo-carbenium ion in some cases, which depends on the substituents on the olefin, additives, and the

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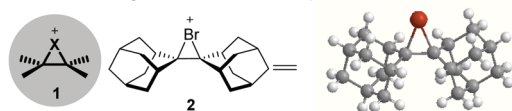
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Zhiqiang Zhou

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1. structure of bridged halonium-alkene complex



2. alkene-to-alkene transfer process

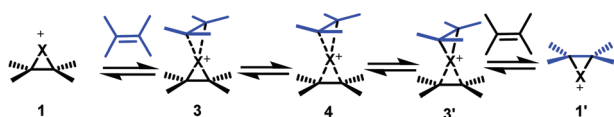


Fig. 1 The cyclic halonium-alkene complex and alkene-to-alkene transfer process.

reaction solvent.⁵ However, the stepwise pathway *via* cationic intermediates is not always followed. In this regard, concerted nucleophile-assisted alkene activation (NAAA) has been proposed for *syn*-addition in the (DHQD)₂PHAL-catalyzed asymmetric halolactonization of alkenoic acid.⁶

Although the halogenation of an alkene usually leads to excellent diastereoselectivities *via* the *anti*-addition of nucleophiles to the cyclic halonium intermediate, enantioselective halogenation remained elusive long after the discovery of halogenation reactions.¹ Brown and co-workers observed that the labile bridged bromonium-alkene complex 2 underwent rapid alkene-to-alkene transfer in the presence of an alkene acceptor, presumably *via* the associated complexes 3, 3' and 4 (Fig. 1).⁷ In this regard, the alkene acceptor could be considered the ancillary ligand to the bromonium. Later, Denmark and co-workers suggested that this process could lead to the epimerization of the enantioenriched halonium intermediate.⁸ The alkene-to-alkene process accounts for the low enantioselectivities when the reactions were performed using a chiral halogenating reagent.⁹ Therefore, it is not surprising that the catalytic asymmetric halonium-induced functionalization of the C-C double bond was not developed until 1995.¹⁰

During the past two decades, asymmetric organocatalysis has evolved into a general tool for asymmetric synthesis,¹¹

which is powering the development of catalytic asymmetric halogenation reactions.^{12–14} In this context, the catalytic asymmetric chlorination of an aldehyde promoted by prolinol derivatives for accessing enantioenriched α -chloro-aldehyde was concurrently reported by Jørgensen and MacMillan.¹² The following applications of this method in natural product synthesis have been well practised and reviewed.¹³ Besides this type of reaction, the catalytic asymmetric dihalogenation of olefins has also emerged, promoted by organocatalysts since Nicolaou's first report.^{14b} However, these protocols have not been employed in natural product synthesis owing to the limitations of substrate scope. More recently, the catalytic asymmetric dibromination, bromochlorination, and dichlorination of allylic alcohol with aliphatic substituents have been reported by Burns and co-workers by taking advantage of the chiral Ti(IV) complex as catalyst.^{15a–c} A host of structurally diverse halogenated natural products have been synthesized relying on these newly developed protocols, which have been summarized in Burns' recent account.^{15d}

On the other hand, halocyclization enables the establishment of cyclic skeletons *via* intramolecular halonium-induced nucleophilic addition.^{1d–i,k,l} A variety of N- and O-heterocycles as well as carbocycles could be easily accessed from olefinic amines, alcohols, and carboxylic acids. In this regard, halocyclization has also been well capitalized for the construction of the ring systems of natural products.^{1d,g,2b} During the last decades, catalytic asymmetric halocyclization has rapidly evolved, providing a facile entry to enantioenriched heterocycles and carbocycles.¹⁶ Based on these exciting advances, the strategic applications of catalytic asymmetric halocyclization in natural products have been nicely demonstrated. In this regard, the enantioenriched halogenated cyclic building blocks could be further transformed into advanced synthetic intermediates for natural product synthesis, relying on the versatile transformations of halogen. Additionally, catalytic asymmetric halocyclization could sometimes be directly applied in the synthesis of natural products with a stereogenic halogenated carbon center. In this review, we summarize recent pro-



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gress in natural product synthesis employing catalytic asymmetric halocyclizations. To this end, the contents are categorized by the type of catalytic asymmetric halogenation.

1. Catalytic asymmetric haloaminocyclization in natural product synthesis

N-Heterocycles (e.g. pyrrolidine, piperidine) are the privileged fragments of many natural products and pharmaceuticals.¹⁷ Enabling facile entry to N-heterocycles from unsaturated amines, haloaminocyclization has been well applied in the total synthesis of alkaloids.¹⁸ In 2011, Yeung and colleagues reported the first catalytic asymmetric 5-*exo* bromoaminocyclization of unsaturated sulfonamide using a chiral amino-thiocarbamate catalyst.^{19a} Subsequently, bifunctional organocatalysts, chiral Lewis bases, and chiral phosphoric acids have been developed for realizing catalytic asymmetric 5-*exo* and 5-*endo* haloaminocyclization (Fig. 2). However, most of the resulting chiral pyrrolidines are not suitable for further elaboration to natural products due to the substrate restriction. Surprisingly, the catalytic asymmetric 6-*exo* or 6-*endo* haloaminocyclization of olefinic amines remain unreported to date, despite the enantioselective haloaminocyclization of the corresponding olefinic hydrozone and *N*-tosylcarbamate having been documented.²⁰

Hexahydropyrrolo[2,3-*b*]indole (HPI) is a featured scaffold incorporated in a handful of indole alkaloids, which are also known as cyclotryptamine alkaloids (Fig. 3).²¹ The cyclotryptamine alkaloids could be categorized into two classes: monoterpenoid indole alkaloids (e.g. conolutinine, minfiensine and vincorine) with one HPI unit and polymeric cyclotryptamine alka-

loids with two or more HPIs. Interestingly, the HPIs of polymeric cyclotryptamines are connected by one C_{3a}–C_{3a'} bond and one or more C_{3a}–C_{7'} bonds. It is noteworthy that the C_{3a}–C_{3a'} linkage constitutes a contiguous quaternary carbon centers (CQCCs) skeleton, which could be a C₂- (e.g. (–)-chimonanthine) or a *meso*-symmetric (e.g. hodgekinsines) configuration. In this context, the formidable structural features and interesting biological activities of cyclotryptamine alkaloids have attracted a lot of attention from the synthetic community.²¹

The enantioselective construction of the HPI ring has witnessed tremendous advances *via* the asymmetric catalytic dearomatization (CADA) of tryptamine or tryptaphon.²² In this regard, a unified strategy could be envisioned by using an enantioenriched C_{3a}-bromo-HPI as a building block prepared from the catalytic asymmetric synthesis of cyclotryptamine alkaloids as bromine could be a versatile handle for subsequent cyclization and homo- or hetero-dimerization (*vide infra*). However, the catalytic asymmetric bromocyclization of tryptamine has posed significant challenges due to the fast uncatalyzed background reaction. To this end, Xie, Lai and Ma realized the highly enantioselective bromocyclization of tryptamine by employing 8*H*-*R*-TRIP using it as an anionic phase transfer catalyst and **B3** as a bromine source in 2013 (Scheme 1).¹⁹ⁱ This novel type of brominating reagent **B3** is a bench-stable yellowish solid and could be prepared on a decagram scale from easily available DABCO-derived ammonium salt and bromine. Various carbamate or sulfamide protecting groups and electron-withdrawing and donating substituents, even on the C₄ or C₇ of indole, were accommodated, giving C_{3a}-bromo-HPIs in good to excellent enantioselectivities (Scheme 1). It is noteworthy that C₂-alkylated tryptamines were also smoothly cyclized to C_{3a}-bromo-HPIs with continuous chiral tetra-substituted carbon centers in good enantioselectivities (Scheme 1, **17g** and **17h**).



Hongbo Wei

Hongbo Wei received his B.S. degree in 2010 and M.S. degree in 2013 from Lanzhou University. He then earned his Ph.D. degree under the supervision of Professor Hongbin Zhai at the same university. In 2016, he moved to the College of Chemistry & Pharmacy of Northwest A&F University and worked as a lecturer in Prof. Xie's group. His current research interests include developing asymmetry synthetic method-

ologies and the total synthesis of biologically active natural products.



Weiqing Xie

Weiqing Xie pursued his Ph.D. degree at Shanghai Institute of Organic Chemistry (SIOC) under the supervision of Prof. Dawei Ma after obtaining his BSc degree in chemistry from Lanzhou University in 2002. In 2007, he was appointed as assistant Professor at SIOC upon receiving his Ph.D. degree. From 2009 to 2011, he worked as postdoc in John R. Falck's group at UT Southwestern Medical Center at Dallas. Then he

returned to SIOC and began his academic career as associate professor in Prof. Ma's group. In 2015, he moved to Northwest A&F University and set up his research group. His research interests include the total synthesis of complex natural products and target-oriented synthetic methodologies.

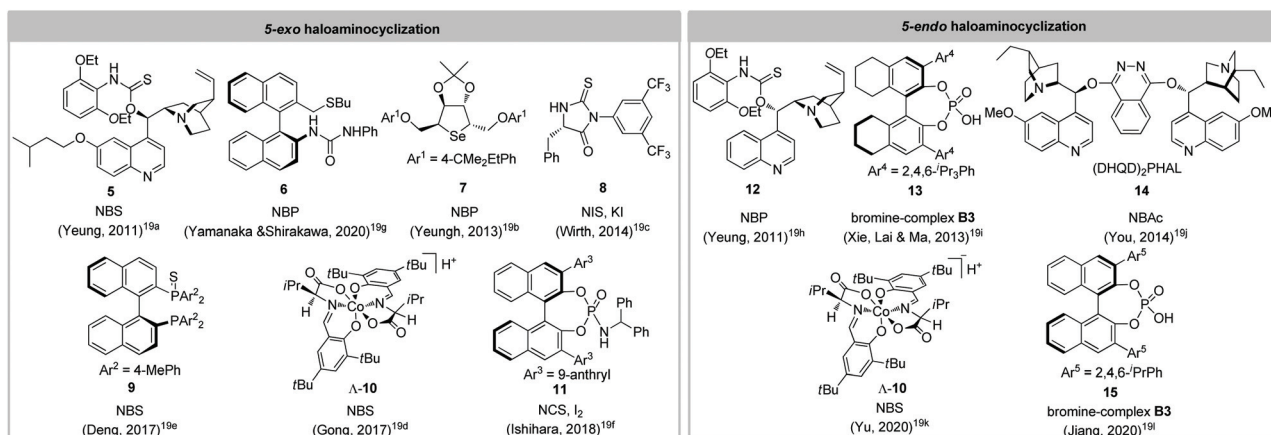


Fig. 2 Reported catalysts and halogenating reagents employed for the catalytic asymmetric haloaminocyclization of olefinic amines.

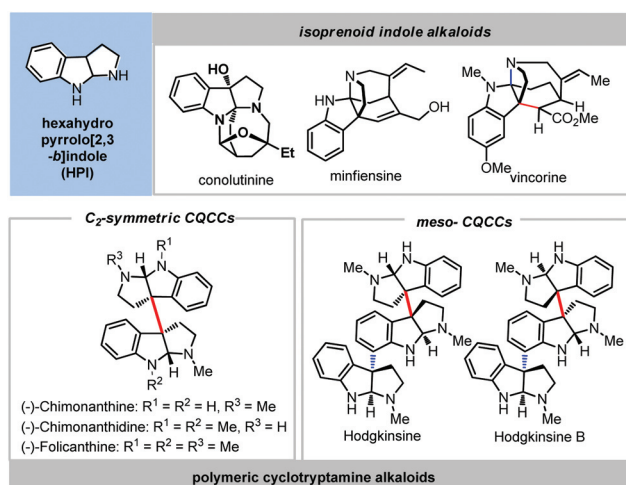
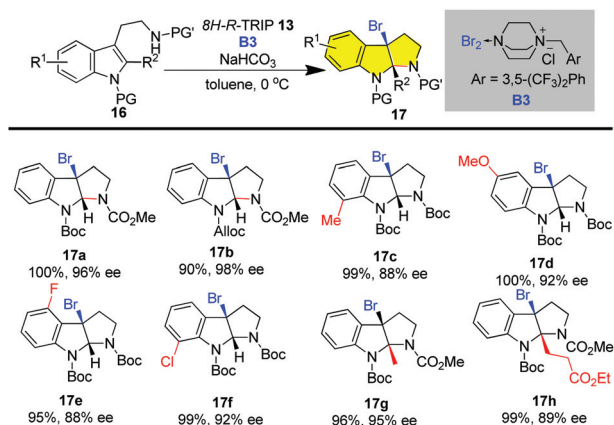


Fig. 3 Monoterpenoid indole alkaloids with one HPI unit and representative polymeric cyclotryptamine indole alkaloids.



Scheme 1 Catalytic asymmetric bromocyclization of tryptamine (Xie, Lai and Ma).

The enantioselective bromoaminocyclization of tryptamine could also be realized by using other types of catalyst system (Fig. 4).^{19j,k} In 2014, You and co-workers reported that the combination of hydroquinine 1,4-phthalazinediyl diether ((DHQ)₂PHAL) with (+)-camphorsulfonic acid (CSA) enabled the asymmetric bromocyclization of protected tryptamine in up to 74% ee using *N*-bromoacetamide (NBAC) as a brominating reagent.^{19j} In 2018, Yu reported that chiral Co(III)-complex-templated Brønsted acids catalyzed the enantioselective bromoaminocyclization of tryptamines by employing NBS as a bromine source in up to 87% ee.^{19k}

As the representative dimeric cyclotryptamine alkaloid, the asymmetric synthesis of (–)-chimonanthine has been extensively described.^{21e–h,23} However, the previously reported route took longer steps either on the establishment of the CQCCs or on building up the HPIs. As shown in Scheme 2, the C_{3a}-bromo-HPI 3 could be facily prepared at gram scale by taking advantage of the enantioselective bromocyclization of tryptamine with comparable enantioselectivity. Reductive dimerization^{23a} of C_{3a}-bromo-HPI 16a mediated by Co(PPh₃)Cl followed by removal of Boc and reduction of the methylcarbamates furnished (–)-chimonanthine in four steps.

The enantioselective bromocyclization of tryptamine also provides a new strategy for the synthesis of monoterpenoid

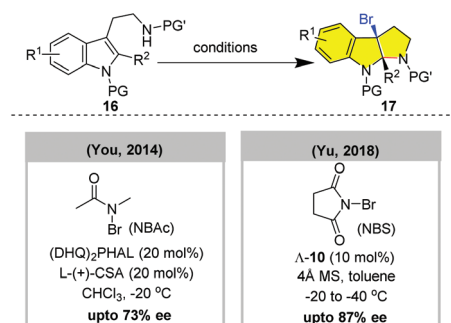
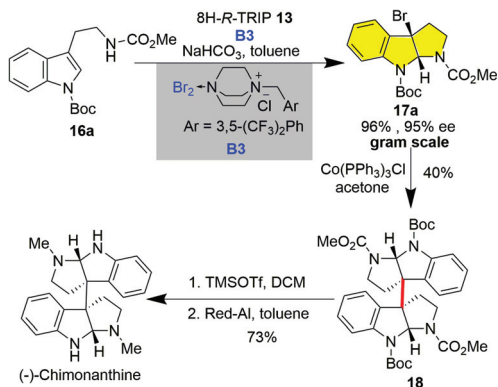


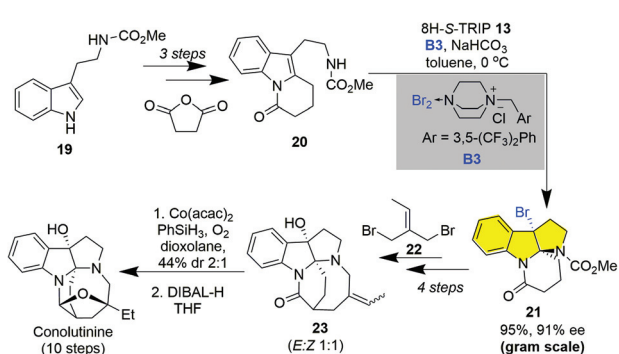
Fig. 4 Other catalyst systems for the enantioselective bromocyclization of tryptamine.



Scheme 2 Four-step synthesis of (–)-chimonanthine (Xie, Lai and Ma).

indole alkaloids. Conolutinine, isolated from Malaysian *Tabernaemontana*, is a rearranged monoterpene indole alkaloid with a featured HPI ring, bridged diaza[4.2.2]decane ring system.^{24a} In 2015, Xie and Lai accomplished the asymmetric synthesis of conolutinine based on the catalytic asymmetric bromocyclization of tryptamine (Scheme 3).^{24b} The synthesis commenced with the three-step preparation of tetrahydropyrindo[1,2-*a*]indole **20** from methylcarbamate-protected tryptamine. The 8*H*-*S*-TRIP **13** catalyzed bromocyclization of **20** smoothly gave *C*_{3a}-bromo-HPI **21** in 95% yield and 91% ee on a gram scale. Subsequently, the installation of the diaza[4.2.2]decane skeleton was realized *via* sequential *N*-alkylation and intramolecular cyclization in four steps. Eventually, Mukaiyama hydration of the double bond followed by reduction of the amide bond mediated by DIBAL-H accomplished the synthesis of conolutinine in ten longest linear steps (LLS).

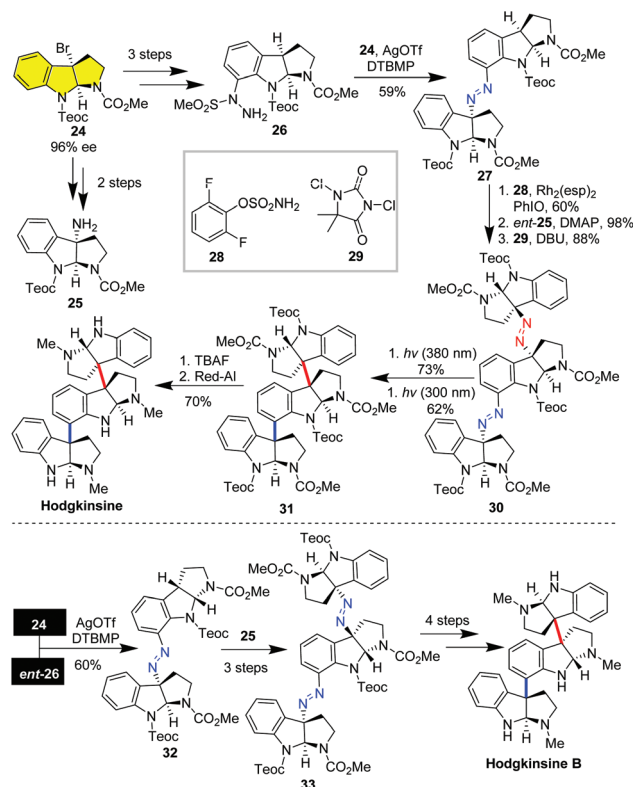
Higher-order polymeric cyclotryptamine alkaloids containing more than two HPIs (*e.g.* hodgkinsines) have posed significant challenges in the stereoselective construction of *C*_{3a}–*C*_{3a'} and multiple *C*_{3a}–*C*_{7'} bonds. To date, only five groups have accomplished the total synthesis of higher-order polymeric cyclotryptamine alkaloids.²⁵ In this respect, the enantio-enriched *C*_{3a}-bromo-HPI could serve as an ideal building block for the modular synthesis of polymeric cyclotryptamine alka-



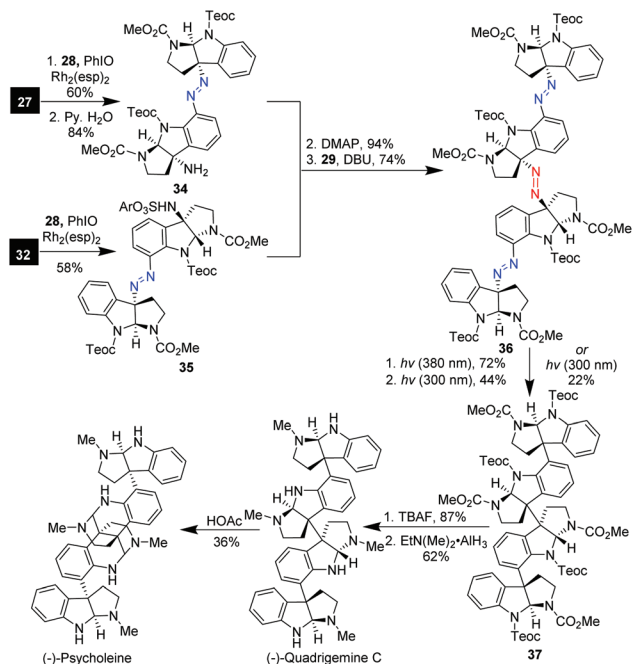
Scheme 3 Ten-step asymmetric synthesis of conolutinine (Xie and Lai).

loids. In 2017, Movassaghi and co-workers reported the collective synthesis of trimeric and tetrameric cyclotryptamine based on a stereospecific diazene-directed fragment assembly strategy.^{25g} As delineated in Scheme 4, the enantioenriched *C*_{3a}-bromo-HPI **24** was elaborated to *C*_{3a}-amino-HPI **25** and *C*_{7'}-hydrazinyl-HPI **26** in two and three steps, respectively. Subsequently, AgOTf-mediated aminolysis of *C*_{3a}-bromo-HPI **24** with *C*_{7'}-hydrazinyl-HPI **26** set up the first diazene linker between *C*_{3a} and *C*_{7'}. Then Rh(esp)₂-catalyzed benzyl *C*–H amination of **27**, coupling of the resulting sulfonamide with *C*_{3a}-amino-HPI *ent*-**25** followed by DCDHM-mediated oxidative desulfonylation built up the second diazene linker between *C*_{3a} and *C*_{3a'}. To this end, irradiation of a thin film of **30** under 380 nm light selectively activated the labile diazene between *C*_{3a} and *C*_{3a'}, stereospecifically forging the contiguous quaternary carbon centers. Further irradiation by 300 nm light forged the *C*_{3a}–*C*_{7'} bond *via* the second extrusion of nitrogen. Finally, hodgkinsine was obtained in 11 LLS *via* deprotection of 2-(trimethylsilyl)ethyl carbamates (Teoc) and overall reduction of the methylcarbamates of trimer **31**. By following the same procedure, assembly of *C*_{3a}-bromo-HPI **24** with the enantiomeric **26**, then coupling with the antipode of *C*_{3a}-amino-HPI **25** delivered diazene-tethered trimer **33**, which was transformed to hodgkinsine B in four steps.

The diazene assembly approach was also amenable to the modular synthesis of tetrameric cyclotryptamine alkaloids.^{25g}



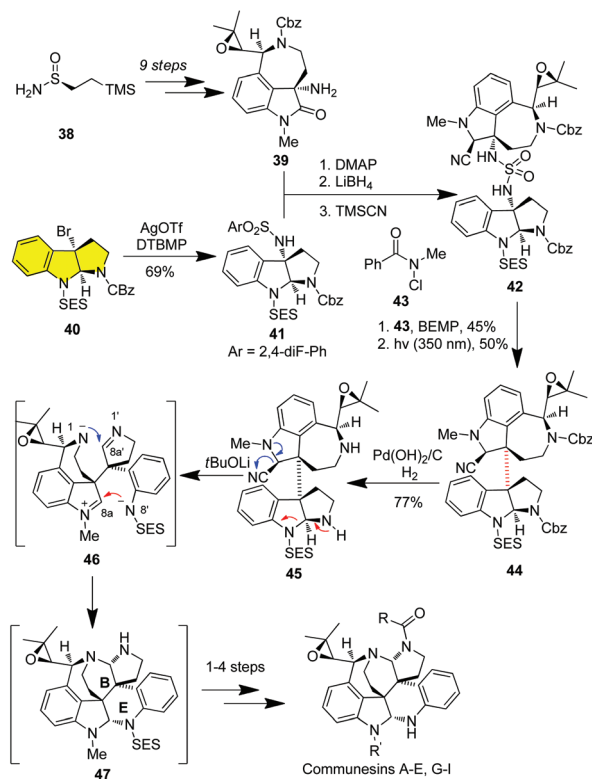
Scheme 4 Modular synthesis of hodgkinsine and hodgkinsine B (Movassaghi).



Scheme 5 Asymmetric synthesis of tetrameric cyclotryptamine (-)-quadrigimine C and (-)-psycholeine (Movassaghi).

As depicted in Scheme 5, the introduction of the benzylic amino to dimer **27** via C-H amination and hydrolysis of the resulting sulfamide gave the amino-substituted dimer **34**. On the other hand, $\text{Rh}(\text{esp})_2$ -catalyzed C-H benzyl amination of **32** led to sulfamate ester **35**, which was coupled with amine **34** followed by DCDHM-mediated oxidative desulfonation to deliver the triazene-tethered tetramer **36**. Selective photolysis of **36** under 380 nm ultraviolet light and subsequent irradiation with 300 nm ultraviolet light produced tetramer **37** in 32% overall yield. Notably, direct photolysis of **36** with 300 nm ultraviolet light could directly generate tetramer **20** in 22% yield with four quaternary carbon centers being stereospecifically set up in one operation. The eventual removal of Teoc and the overall reduction of methyl carbamates with allane afforded (-)-quadrigimine C in 54% yield in two steps. Further treatment of (-)-quadrigimine C with aqueous acetic acid led to (-)-psycholeine in 36% yield.

Communesins are a family of dimeric cyclotryptamines with a rearranged skeleton, containing a fused heptacycle, two amination linkages, and up to six stereogenic centers, of which two are vicinal and quaternary (C_{3a} - $\text{C}_{3a'}$).²⁶ The communesins possess interesting biological profiles, including potent cytotoxicity, and insecticidal, antiproliferative, and vasculogenic activities. The challenging structure of communesins has spurred widespread synthetic interest and 12 total syntheses have been concluded to date.²⁷ In 2019, Movassaghi and co-workers achieved the collective synthesis of epoxy-communesins by utilizing the diazene-directed fragment coupling strategy for stereospecifically forging the C_{3a} - $\text{C}_{3a'}$ bond.^{27g} As shown in Scheme 6, the synthesis commenced with the asym-



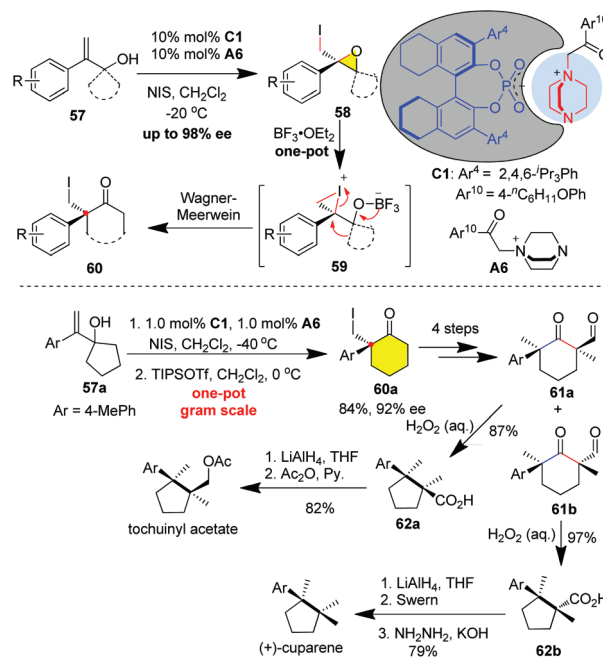
Scheme 6 Collective asymmetric synthesis of communesins (Movassaghi).

metric synthesis of the (-)-aurantioclavine derivative **39** from enantioenriched sulfinamide (-)-**38** in 9 steps on a gram scale. On the other hand, treatment of C_{3a} -bromo-HPI **40**, prepared from the enantioselective bromocyclization of a protected tryptamine, with AgOTf in the presence of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) afforded the sulfamate ester (+)-**41**. Union of the functionalized aurantioclavine fragment **39** with the HPI fragment **41** via sulfamidation, partial reduction of the oxindole entity with LiBH_4 followed by capture of the hemiaminal with TMSCN afforded aminonitrile **42** as a single diastereomer. Selective oxidation of the sulfuric diamide moiety with *N*-chloro-*N*-methylbenzamide in the presence of polystyrene-bound diazaphosphorine (BEMP) generated a sensitive diazene, which was subjected to photo-irradiation to yield heterodimer **44** in 50% yield as a single diastereoisomer via the extrusion of nitrogen. Hydrogenolysis of Cbz followed by *t*-BuOLi-mediated skeletal rearrangement enabled the stereoselective building up of B/E rings of the communesins. In this regard, the ring opening of the HPI moiety of **45** under basic conditions gave a sulfonamide anion, which attacked the iminium generated from the aminonitrile via elimination of cyanide to form the E ring. Meanwhile, the capture of cyclic imine by N_1 enabled concurrent B-ring closure. Eventual derivatization of pentacycle **20** in one to four steps thus furnished the collective asymmetric synthesis of communesins.

2. Catalytic asymmetric halo-cycloetherification in natural product synthesis

Saturated cyclic ethers (*e.g.* epoxide, tetrahydrofuran and tetrahydro-2*H*-pyran) are abundantly present in a large number of natural products and pharmaceutically active molecules.²⁸ In this context, a number of methodologies have been documented for building up cyclic ether skeletons.²⁹ In this regard, the halo-cycloetherification of olefinic alcohols has been widely utilized in natural product synthesis^{2,30} as olefinic alcohols are easily prepared and usually high diastereoselectivities could be obtained *via* the *anti*-addition of oxygen to the cyclic halonium intermediate. However, the catalytic asymmetric halo-cycloetherification achieved little progress until the first catalytic asymmetric halo-cycloetherification was reported by Kang in 2003, which employed salen-Co(II) as a catalyst and I₂ as a halogen source.^{31a} Since 2011, various organocatalysts including chiral phosphoric acid, bifunctional organocatalysts and chiral metallic catalysts have been developed for catalytic asymmetric halo-cycloetherification (Fig. 5). To this end, various types of asymmetric halo-cycloetherification (*e.g.* 5-*exo*, 5-*endo*, 6-*exo*, 6-*endo* cyclization) have been realized, enabling the construction of enantio-enriched halogenated tetrahydrofuran and tetrahydro-2*H*-pyran scaffolds.³¹

In 2016, Xie and colleagues designed an ion-pair organo-catalyst **C1** consisting of chiral phosphoric acid and DABCO-derived quaternary ammonium, which realized the challenging catalytic asymmetric 3-*exo* iodo-cycloetherification of allylic alcohol **57** to afford chiral epoxide **58** with up to 98% ee (Scheme 7).^{31m} Moreover, this protocol was amenable to the one-pot catalytic 3-*exo* cycloetherification/Wagner–Meerwein rearrangement promoted by BF₃·OEt for producing enantio-enriched cyclohexanone **60** with an aryl quaternary carbon center.



Scheme 7 Total synthesis of cuparene sesquiterpenoids based on catalytic asymmetric 3-*exo* iodo-cycloetherification (Xie).

Cuparene-type sesquiterpenoids feature a cyclopentane skeleton incorporating contiguous quaternary carbon centers (CQCCs), one of which is aryl-substituted.³² The stereoselective construction of the CQCCs constitutes the major challenge in the synthesis of cuparene sesquiterpenoids.³³ In this context, Xie and colleagues discovered H₂O₂-mediated ring contraction of α -formyl cycloketone for the stereospecific construction of CQCCs.³⁴ By strategically combining these two novel protocols, the same group accomplished the asymmetric synthesis of cuparene-type sesquiterpenoids. As drawn in Scheme 7, the gram-scale synthesis of cyclohexanone **60a** with an aryl quaternary carbon center was conveniently achieved in 85% yield

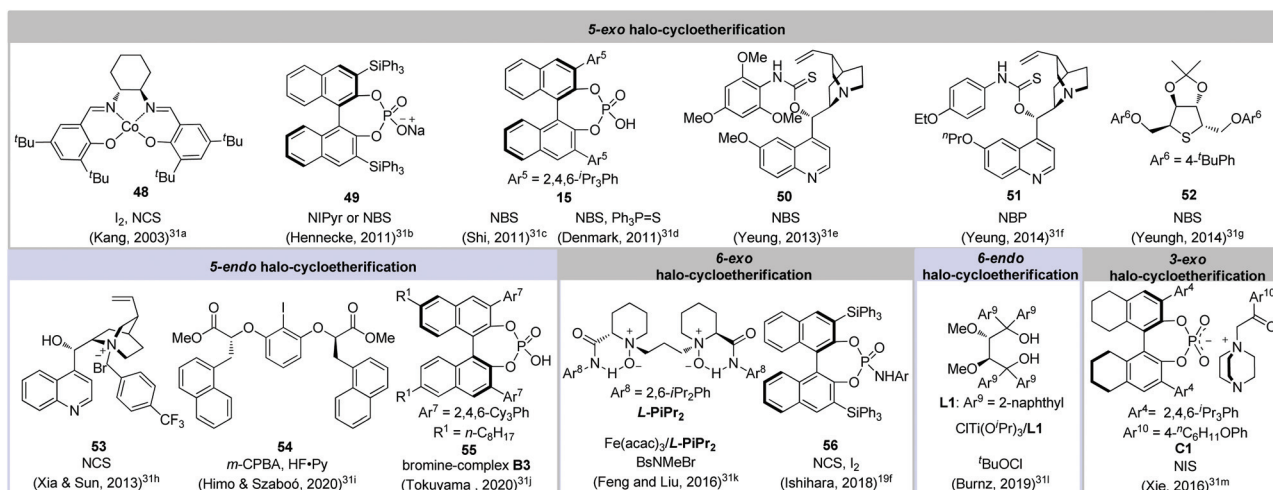
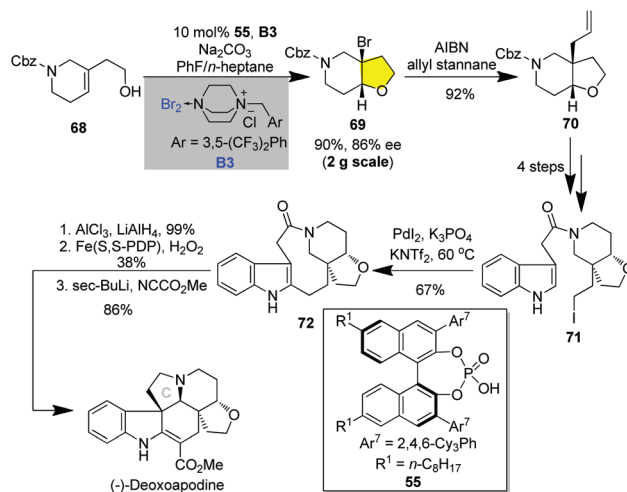


Fig. 5 Developed catalysts and halogenating reagents employed for the catalytic asymmetric halo-cycloetherification.

with 92% ee on a gram scale only in the presence of 1.0 mol% ion-pair organocatalyst **C1** (Scheme 7). Subsequent transformations of cyclohexanone **60a** via the removal of iodine, formylation followed by methylation delivered the two separable diastereoisomers **61a** and **61b**, which were respectively subjected to H₂O₂-mediated oxidative ring construction to stereospecifically forge the CQCCs. Reduction of carboxylic acid **62a** and acetylation of the resulting primary alcohol furnished tochuinyl acetate in 8 LLS. The other diastereoisomer **62b** could be converted to cuparene in 9 LLS through sequential reduction/oxidation/Huang–Kishner reduction.

More frequently, catalytic asymmetric halo-cycloetherification has been applied in the asymmetric synthesis of natural products with a chiral O-heterocycle skeleton. (–)-Centrolobine belongs to diarylheptanoids isolated from the heartwood of *Centrolobium robustum* and the stem of *Brosimum potabile* with a *cis*-disubstituted tetrahydro-2*H*-pyran ring, which exhibits anti-inflammatory, antibacterial, and antileishmanial activities (Scheme 8).³⁵ In 2016, Feng and Liu disclosed a catalytic asymmetric intra- and intermolecular haloetherification of enone **63** promoted by chiral *N,N'*-dioxides/Fe(acac)₃.^{31k} The authors disclosed that the kinetic resolution of alcoholic enone **65** could be readily realized by chiral *N,N'*-dioxides/Fe(acac)₃ catalyzed bromo-cycloetherification to deliver *cis*-substituted pyran **66**, which underwent debromination under the action of BnSH/Et₃N to give ketone **67** in 50% yield over two steps and 95% ee with >99:1 dr. Reduction of the ketone **67** with LiBH₄ followed by the removal of the resulting secondary alcohol mediated by Et₃SiH/TFA, Ullman coupling of aryl bromide with NaOMe and removal of benzyl by hydrogenation over Pd/C finally furnished (–)-centrolobine in 6 LLS.

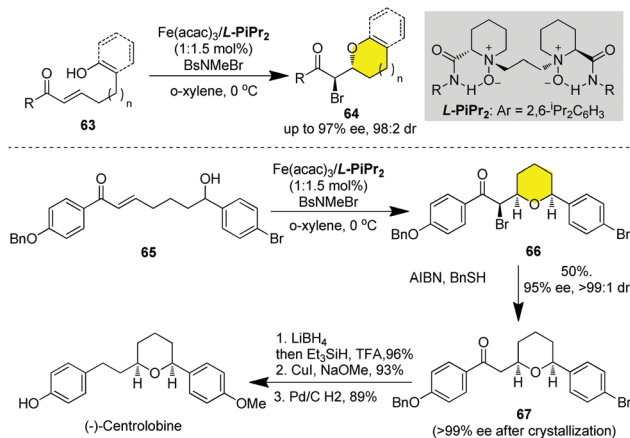
(–)-Deoxoapodine belongs to the *Aspidosperma* indole alkaloids incorporating a characteristic tetrahydrofuran ring.³⁶ In 2020, Tokuyama and co-worker accomplished a 10-step synthesis of (–)-deoxoapodine relying on chiral counter ionic



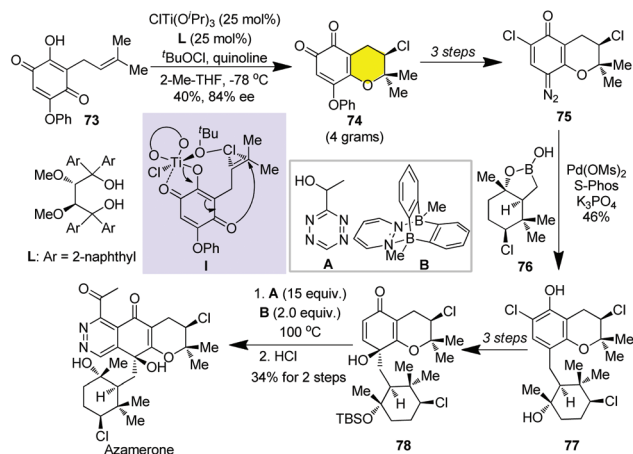
Scheme 9 Asymmetric synthesis of (–)-deoxoapodine relying on catalytic asymmetric 5-*endo* bromo-cycloetherification (Tokuyama).

directed 5-*endo* cycloetherification for forging the chiral tetrahydrofuran ring. As shown in Scheme 9, the catalytic asymmetric 5-*endo* bromocyclization of homoallylic alcohol **68** promoted by chiral phosphoric acid **CPA1** using bromine complex **B3** as the brominating reagent was readily realized in 76% yield with 86% ee on a two-gram scale.^{31j} Allylation of bromo-furan **70** under the effect of AIBN/allyl stannane successively installed the quaternary carbon centers. Subsequent cleavage of Cbz, introduction of indole-3-acetyl and transformation of the terminal alcohol to iodide gave iodide **71**. After a series of trials, the highly strained bridged nine-membered was successively established by PdI₂/norbornene catalyzed intramolecular C–H alkylation, which furnished petacycle **72** in 67% yield. Reduction of the amide moiety of **72**, oxidative cyclization catalyzed by Fe(S,S-PDP) for C-ring closure and the introduction of the methoxycarbonyl group delivered a sub-gram quantity (260 mg) of (–)-deoxoapodine in 10 LLS.

Halogenated natural products are widely found in nature.³⁷ The introduction of halogen may alter the physical properties, including electronic and steric effects, which can be of importance for increasing biological affinity and selectivity. In this regard, the synthesis of natural products with chiral halogenated carbon centers has attracted a lot of attention and a plethora of strategies for setting up the chiral halogenated carbon centers has been invented.^{2b} Azamerone is structurally unique among the napyradiomycin natural products containing two enantioenriched chlorinated tetrahydro-2*H*-pyran rings and an unprecedented phthalazinone ring.³⁸ Recently, Burns and co-workers accomplished the first enantioselective synthesis of azamerone by taking advantage of asymmetric 6-*endo* chloro-cycloetherification of prenylated hydroxyquinone **73** promoted by a TADDOL ligated Ti(IV) using *tert*-butyl hypochlorite as a chloronium source (Scheme 10).³¹ⁱ In this context, the initial formation of octahedral titanium complex **I** was proposed for the stereoselective transfer of chloronium to the prenyl side chain, which undergoes a stereoselective 6-*endo*



Scheme 8 Asymmetric synthesis of (–)-centrolobine via catalytic asymmetric intramolecular 6-*exo* bromo-etherification of enone (Feng and Liu).



Scheme 10 Enantioselective synthesis of azamerone (Burns).

cyclization to afford *o*-quinone **74**. Conversion of *o*-quinone to quinone diazide **75** was then achieved in three steps. On the other hand, chlorocyclohexane **76** was prepared from geranyl acetate *via* mercury-based polyene cyclization and resolution in six steps. The coupling of quinone diazide **75** with boronic hemiester **76** catalyzed by (SPhos)Pd-G3 successively provided phenol **77** in 46% yield. Dechlorination, protection of the tertiary alcohol with TBS and oxidation of phenol diastereoselectively gave quinone **78**. The installation of the phthalazinone moiety was realized though [4 + 2]/retro[4 + 2] cycloaddition of **78** with tetrazole **A** promoted by bisboron complex **B**, which was followed by *in situ* air oxidative rearomatization and benzyl alcohol oxidation. Eventual cleavage of TBS mediated by HCl furnished azamerone in 10 LLS.

3. Catalytic asymmetric halolactonization in natural product synthesis

The iodolactonization of alkenoic acid was first discovered by Bougault at the turn of 20th century.^{1d,h} Since then, halolactonization has received continuous attention from the synthetic community and has become a very useful and reliable strategy in natural product synthesis.^{1,2} However, the catalytic asymmetric halolactonization of olefinic acid remained underdeveloped until Gao reported the first asymmetric 5-*exo* iodolactonization by using cinchonine derived PTC **79** as a catalyst albeit in low enantioselectivities (Fig. 6).^{39a} Soon after, the same group further demonstrated that salen-Co(II) **48** was capable of promoting asymmetric 5-*exo* iodolactonization with up to 83% ee.^{39b} In 2010, Borhan,^{39c} Yeung,^{39d} Fujioka³⁹ⁿ and Jacobsen^{39p} respectively reported a highly enantioselective halolactonization capitalizing asymmetric organocatalyst, which unveiled a new strategy for catalytic asymmetric halocyclization.³⁹ Since then, the catalytic asymmetric halolactonization of olefinic acid has achieved considerable advances and various asymmetric types of cyclization (*e.g.* 4-*endo*, 5-*exo*, 6-*endo* and 6-*exo*) were realized by employing different kinds of organo-catalyst (Fig. 6).

Surprisingly, catalytic asymmetric halolactonization is scarcely utilized in natural product synthesis. This could be ascribed to the substrate restriction, as only aromatic substituted alkenoic acids resulted in high to excellent enantioselectivities. However, these protocols provide an alternative route for constructing the enantioenriched aryl tertiary

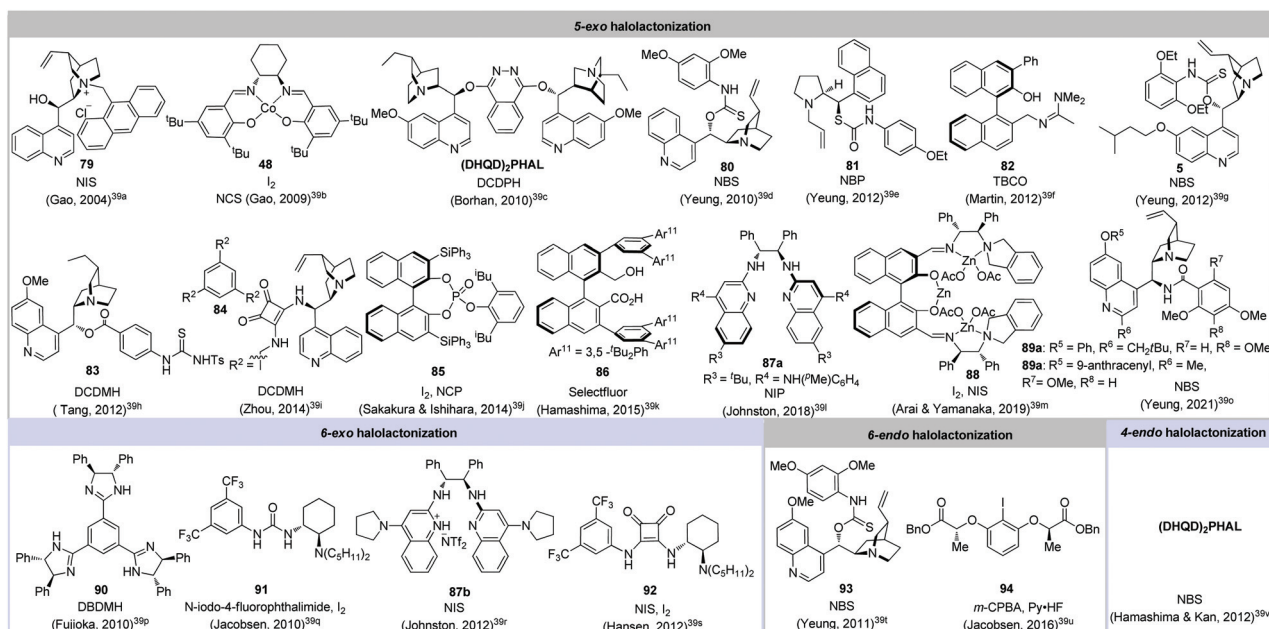
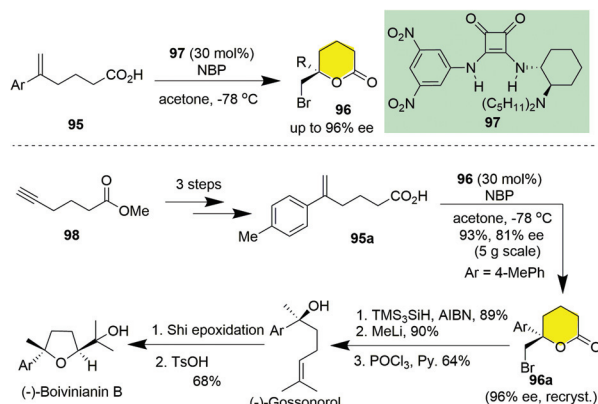


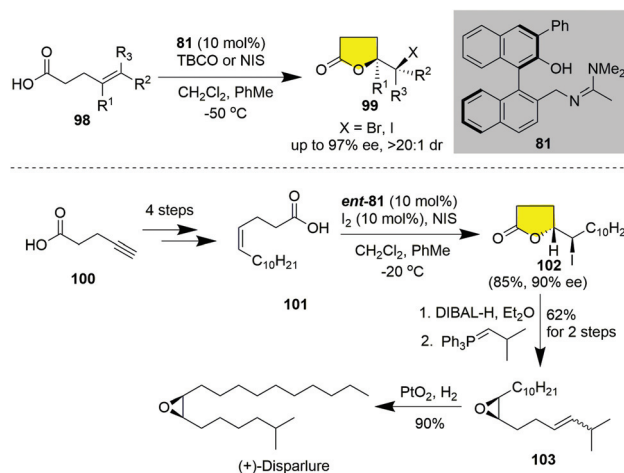
Fig. 6 Developed catalysts and halogenating reagents employed for catalytic asymmetric halolactonization of alkenoic acids.



Scheme 11 Hansen's asymmetric synthesis of (–)-gossonorol and (–)-boivinianin B by employing catalytic asymmetric 6-*exo* bromolactonization (Hansen).

alcohol, which could be elaborated to natural products. In 2016, Hansen and co-workers reported the 6-*exo* asymmetric bromolactonization of δ -unsaturated carboxylic acids in the presence of 30 mol% chiral squaramide organocatalyst **97** (Scheme 11).⁴⁰ To demonstrate its synthetic potential, chiral lactone **96a** was prepared from carboxylic acid **95a** via this protocol on a 5-gram scale in 93% yield with 81% ee, which was improved to 96% ee after recrystallization (Scheme 11). The sequence of radical debromination under the action of $\text{TMS}_3\text{SiH/AIBN}$, treatment with an excess of MeLi and chemoselective elimination of the aliphatic tertiary alcohol mediated with POCl_3 /pyridine eventually gave (–)-gossonorol over seven steps in 34% yield and >99% ee. Further Shi epoxidation of (–)-gossonorol followed by TsOH-promoted cyclization of the tetrahydrofuran ring afforded (–)-boivinianin B.

(+)-Disparlure,⁴¹ (Z)-7,8-epoxy-2-methyloctadecane, is a sex attractant emitted by the female gypsy moth and has been utilized as the major attractant component in pheromone-containing traps for managing gypsy moth populations. In 2017, Martin and co-workers completed an 8-step synthesis of (+)-disparlure by applying the enantioselective 5-*exo* halolactonization of alkenoic acids catalyzed by a BINOL-amidine organocatalyst **81**,⁴² which was previously developed by the same group.^{39f} In this regard, the resulting chiral iodo-lactone served as the precursor of the epoxide moiety of (+)-disparlure. As shown in Scheme 12, Z-olefinic acid **101**, prepared in 4 steps from pentynoic acid **100**, was subjected to BINOL-amidine **81** catalyzed asymmetric 5-*exo* iodolactonization to produce γ -lactone **102** in 85% yield with 90% ee. Sequential semi-reduction of the lactone followed by a Wittig reaction smoothly led to the requisite epoxide **103**. The selective reduction of the double bond of epoxide **102** was successively achieved by hydrogenolysis over PtO_2 in hexane, thus accomplishing the catalytic enantioselective synthesis of (+)-disparlure in 33% overall yield in eight steps.

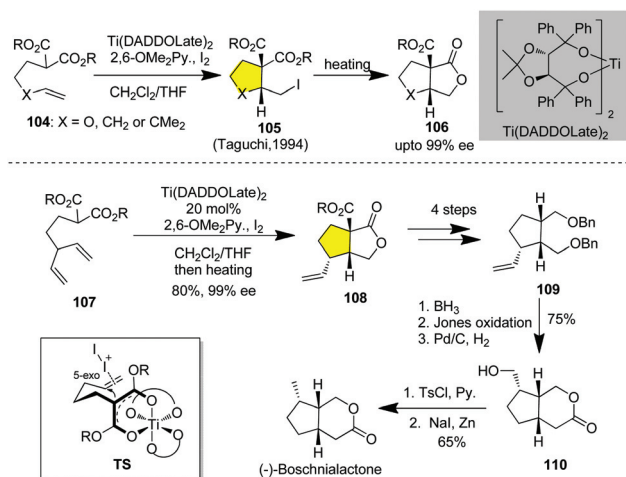


Scheme 12 Total synthesis of (+)-disparlure by taking advantage of catalytic asymmetric 5-*exo* halolactonization (Martin).

4. Catalytic asymmetric halo-carbocyclization in natural product synthesis

The construction of carbocycles constitutes one of the major challenges in the total synthesis of cyclic natural products. In this regard, halo-carbocyclizations provide a facile entry to carbocycles from an olefinic substrate. In particular, the halonium-induced biomimetic polyene cyclization has been developed as a powerful tool for generating polycyclic carbocycles from linear precursors in excellent diastereoselectivities. Relying on those protocols, the racemic synthesis of polycyclic natural products has been elegantly achieved.⁴³ However, catalytic asymmetric carbocyclization has achieved less progress compared with other types of catalytic asymmetric halocyclization. Unlike olefinic alcohols, acids and amines, the polyene substrate lacks the secondary interaction between the substrate and the catalyst in the transition state, thus leading to reduced or negligible enantioselectivities. To date, only limited successful examples of catalytic asymmetric halo-carbocyclization have been described.¹⁰

(–)-Boschnialactone is an iridoid monoterpene lactone isolated from *Boschniakia rossica* with insect-attracting and insecticidal activities.⁴⁴ In 1995, Taguchi and co-workers developed the catalytic asymmetric iodocarbocyclization of diene **104** in the presence of a catalytic amount of $\text{Ti}(\text{TADDOLate})_2$, leading to the bicyclic lactone **106** in 80% yield with 99% ee upon heating after the completion of iodocyclization (Scheme 13).¹⁰ As shown in the transition state **TS**, the anion was derived from malonate complexed with $\text{Ti}(\text{TADDOLate})_2$ to form an octahedral Ti complex, which dictated the enantiofacial selectivity of the incoming iodonium and the attack of the nucleophile. Relying on this method, the desymmetrization of diene **107** via $\text{Ti}(\text{TADDOLate})_2$ -catalyzed asymmetric iodocarbocyclization was achieved in 99% ee with >12:1 dr (Scheme 13).⁴⁵ Decarboxylation followed by reduction of the lactone and Bn-



Scheme 13 Catalytic asymmetric iodocarbocyclization of 4-alkenylmalonates and its application in the asymmetric synthesis of (–)-boschnialactone.

protection of the resulting diol gave bisbenzylether **109**. Hydroboration/oxidation of the terminal olefin, Jones oxidation of the resulting primary alcohol and removal of benzyl by hydrogenation over Pd/C delivered lactone **110** mediated by Zn/NaI, affording (–)-boschnialactone in 10 LLS.

More recently, organocatalyzed asymmetric halo-carbocyclization has also emerged (Fig. 7). In 2016, Ishihara and Sakakura realized the first catalytic asymmetric polyene cyclization by chiral phosphite-urea bifunctional catalysts **111**, albeit in low enantioselectivities, as a modification of their previous work.⁴⁶ Soon after, Yamamoto and Samanta described catalytic asymmetric polyene cyclization by using a chiral BINOL-derived thiophosphoramidate **112** and 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) as a bromonium source with up to 94% ee.⁴⁷ In 2018, Zhao and co-workers reported a chiral sulfide-catalyzed enantioselective chloro-carbocyclization of

aryl-tethered diolefins and diaryl-tethered olefins *via* desymmetrization.⁴⁸ By utilizing the same type of chiral sulfide **114**,⁴⁹ the same group developed the enantioselective carbocyclization of an aniline derivative for the construction of enantioenriched 3,4-functionalized tetrahydroquinolines. Although these protocols afford natural-like polycyclic skeletons, their strategic application in natural products remains unexplored.

5. Conclusions and perspective

The renaissance and blooming of asymmetric organocatalysis are powering the rapid development of catalytic asymmetric halocyclization. In this context, natural product synthesis relying on catalytic asymmetric halocyclization has achieved considerable progresses in recent years. The catalytic asymmetric halocyclization not only provides a facile access to the enantioenriched cyclic skeletons of natural products, but also installs a halogen for further elaboration. In this respect, the versatile halogen has indeed exhibited great synthetic potential in some cases. However, dehalogenation of the enantioenriched halogenated building block is usually performed, thus lowering the atom economy and synthetic efficiency. On the other hand, halonium-induced catalytic asymmetric carbocyclization has witnessed little progress and is sparsely applied in complex natural product synthesis. In this context, the unsolved challenges in catalytic asymmetric halocyclization still evoke the design of more robust catalysts and powerful transformations. On the other hand, the strategic application of the developed catalytic asymmetric halocyclization in natural product synthesis still needs extensive exploration.

Conflicts of interest

There are no conflicts to declare.

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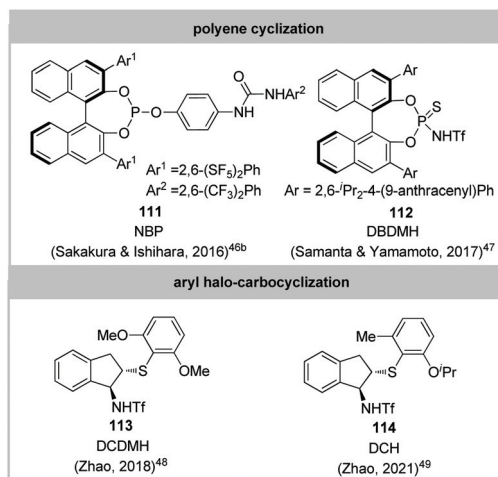


Fig. 7 Other described organocatalysts and halogenating reagents employed for catalytic asymmetric halo-carbocyclization.

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