ORGANIC CHEMISTRY
FRONTIERS

CHINESE CHEMICAL SOCIETY
ROYAL SOCIETY OF CHEMISTRY

REVIEW

View Article Online
View Journal | View Issue

Cite this: *Org. Chem. Front.*, 2022, **9**, 499

The applications of catalytic asymmetric halocyclization in natural product synthesis

Jiahang Yan,[a] Zhiqiang Zhou,[a] Qiaoqiao He,[a] Guzhou Chen,[a] Hongbo Wei *[a] and Weiqing Xie *[a,b]

Received 16th September 2021,
Accepted 17th November 2021

DOI: 10.1039/d1qo01395e

rsc.li/frontiers-organic

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.

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 SbF_5–SO_2 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

Jiahang Yan

Jiahang Yan was born in 1989 in Tianshui, Gansu Province, China. He received his M.S. in Chemistry from Northwest A&F University in 2018. Currently, he is pursuing his Ph.D. degree under the supervision of Prof. Weiqing Xie. His research interests focus on the asymmetric synthesis of indole alkaloids via *asymmetric catalysis.*

Zhiqiang Zhou

Zhiqiang Zhou was born in Shandong province. After receiving his B.S. degree in 2019 at Northwest A&F University, he has been a master's student under the guidance of Prof. Weiqing Xie. He is currently working on the development of catalytic asymmetric methodology towards the asymmetric synthesis of diterpenoids.

---

[a] *Shaanxi Key Laboratory of Natural Products & Chemical Biology, College of Chemistry & Pharmacy, Northwest A&F University, 22 Xinong Road, Yangling 712100, Shaanxi, China. E-mail: xiewq@nwafu.edu.cn*
[b] *Key Laboratory of Botanical Pesticide R&D in Shaanxi Province, Yangling, Shaanxi 712100, China*

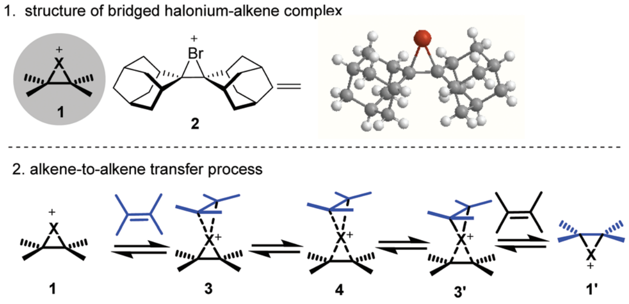


Fig. 1 The cyclic halonium–alkene complex and alkene-to-alkene transfer process.

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)$_2$PHAL-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-

Qiaoqiao He

Qiaoqiao He was born in Gansu Province. In 2019, he began to pursue his M.S. degree under the guidance of Prof. Weiqing Xie. He is currently concentrating on the asymmetric synthesis of aspidospermа indole alkaloids.

Guzhou Chen

Guzhou Chen gained her B.S. degree in applied chemistry in 2014 and M.S. degree in organic chemistry in 2017 from Shenyang Pharmaceutical University. In 2021, she obtained her Ph.D. degree in chemical biology from Northwest A&F University under the supervision of Prof. Weiqing Xie. Her current research interests included developing asymmetric methodologies and applications in the synthesis of polymeric cyclotryptamine alkaloids.

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 alkaloids 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 C_2- (*e.g.* (−)-chimonanthine) or a *meso*-symmetric (*e.g.* hodgkinsines) 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 C_4 or C_7 of indole, were accommodated, giving C_{3a}-bromo-HPIs in good to excellent enantioselectivities (Scheme 1). It is noteworthy that C_2-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 methodologies 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.

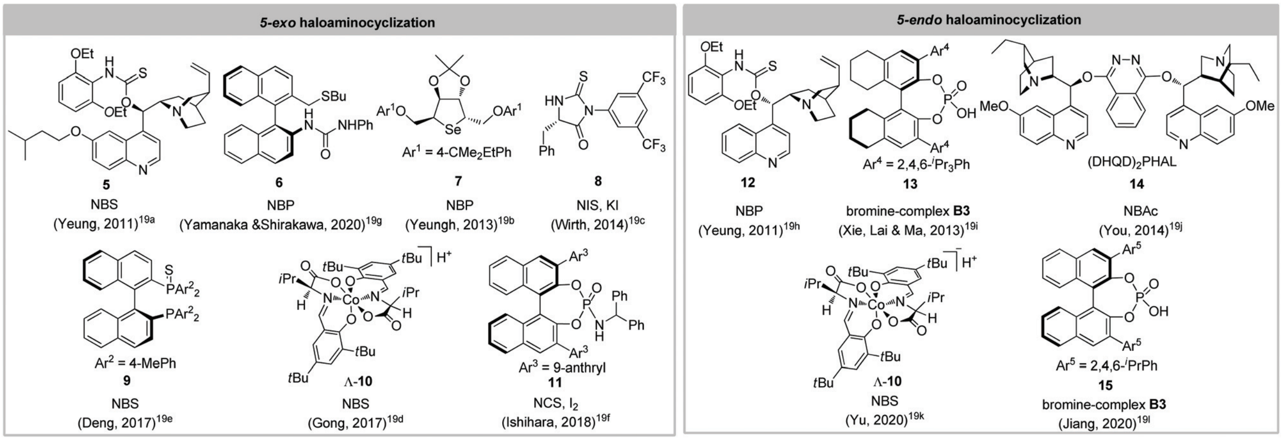


Fig. 2 Reported catalysts and halogenating reagents employed for the catalytic asymmetric haloaminocyclization of olefinic amines.

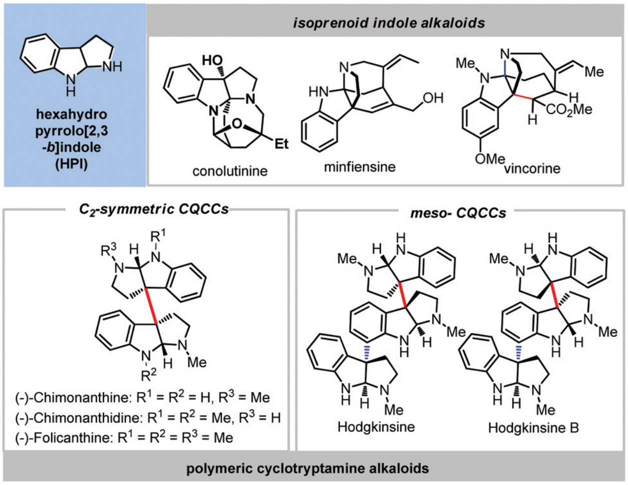
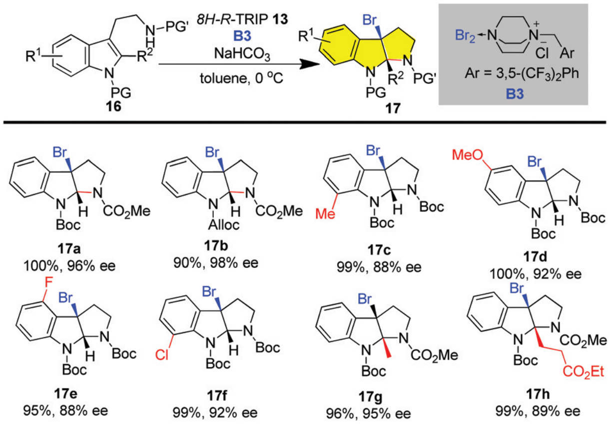


Fig. 3 Monoterpenoid indole alkaloids with one HPI unit and representative polymeric cyclotryptamine indole alkaloids.



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)$_2$PHAL) 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 facilely 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(PPh$_3$)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

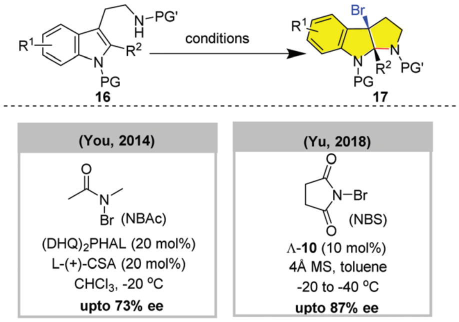
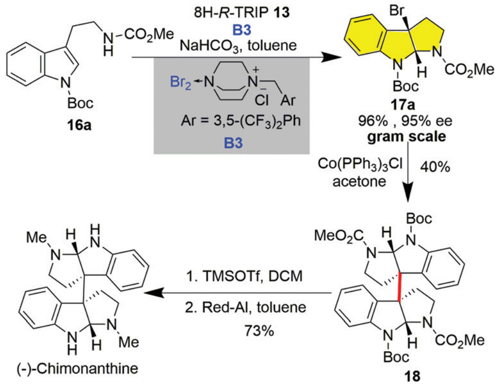


Fig. 4 Other catalyst systems for the enantioselective bromocyclization of tryptamine.

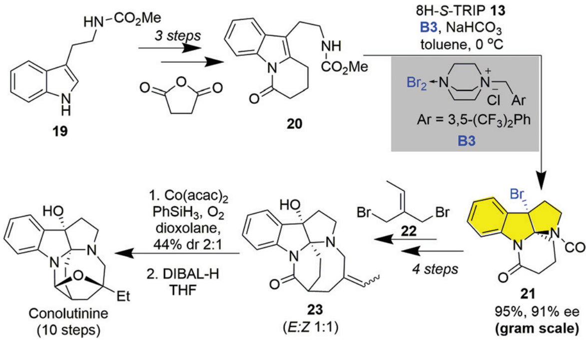


Scheme 2 Four-step synthesis of (−)-chimonanthine (Xie, Lai and Ma).

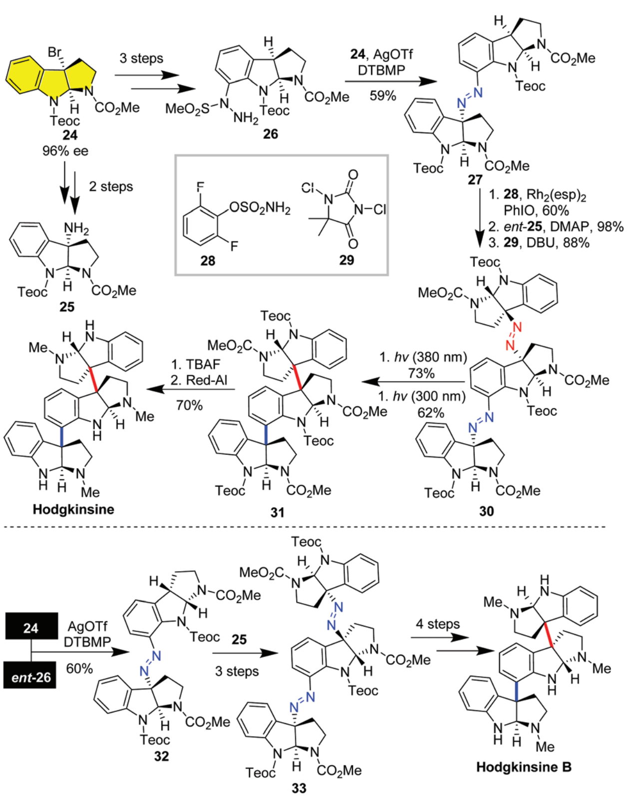
indole alkaloids. Conolutinine, isolated from Malaysian *Tabernaemontana*, is a rearranged monoterpenoid indole alkaloid with a featured HPI ring, bridged diaza[4.2.2]decane ring system.[24a] In 2015, Xie and Lai accomplished the asymmetric synthesis of conolutinine based on the catalytic asymmetric bromocyclization of tryptamine (Scheme 3).[24b] The synthesis commenced with the three-step preparation of tetrahydropyrido[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 enantioenriched C_{3a}-bromo-HPI could serve as an ideal building block for the modular synthesis of polymeric cyclotryptamine alkaloids. 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 C7-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.

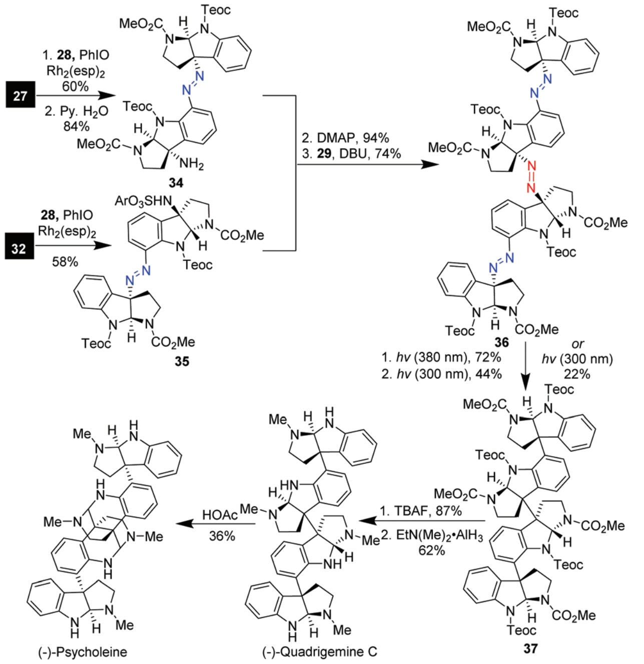
The diazene assembly approach was also amenable to the modular synthesis of tetrameric cyclotryptamine alkaloids.[25g]



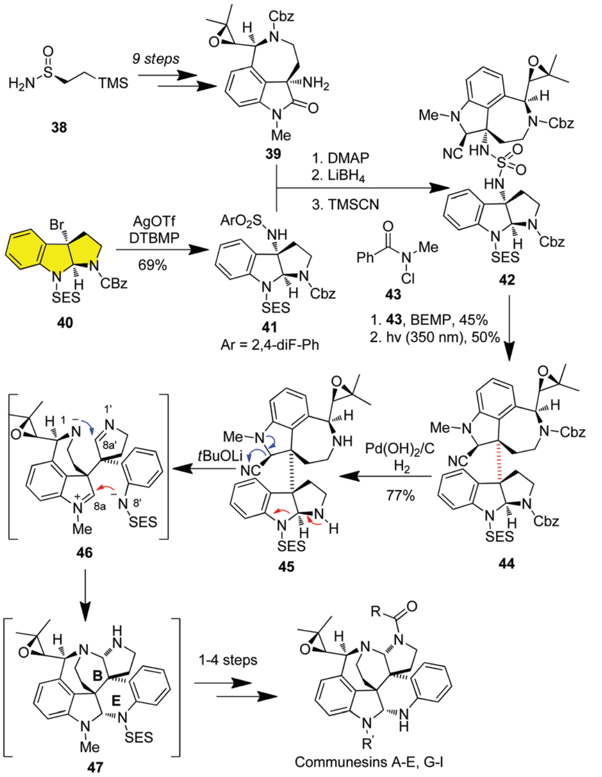
Scheme 3 Ten-step asymmetric synthesis of conolutinine (Xie and Lai).



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



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



Scheme 6 Collective asymmetric synthesis of communesins (Movassaghi).

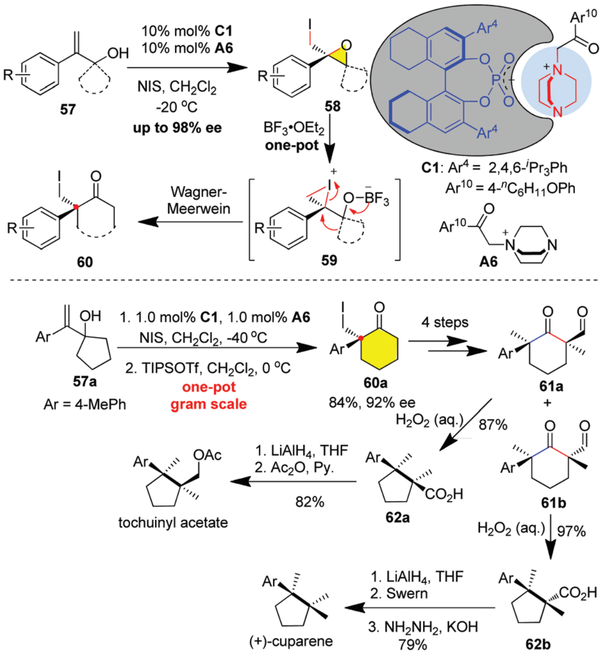
As depicted in Scheme 5, the introduction of the benzylic amino to dimer **27** *via* C–H amination and hydrolysis of the resulting sulfamide gave the amino-substituted dimer **34**. On the other hand, Rh(esp)$_2$-catalyzed C–H benzyl amination of **32** led to sulfamate ester **35**, which was coupled with amine **34** followed by DCDHM-mediated oxidative desulfonylation 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 (−)-quadrigemine in 54% yield in two steps. Further treatment of (−)-quadrigemine 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 aminal linkages, and up to six stereogenic centers, of which two are vicinal and quaternary (C_{3a}–$C_{3a'}$).[26] The communesins possess interesting biological profiles, including potent cytotoxicity, and insecticidal, antiproliferative, and vasculogenetic 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 coworkers achieved the collective synthesis of epoxy-communesins by utilizing the diazene-directed fragment coupling strategy for stereospecifically forging the C_{3a}–$C_{3a'}$ bond.[27g] As shown in Scheme 6, the synthesis commenced with the asymmetric 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 I_2 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 enantioenriched halogenated tetrahydrofuran and tetrahydro-2*H*-pyran scaffolds.[31]

In 2016, Xie and colleagues designed an ion-pair organocatalyst **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 $BF_3{\cdot}OEt$ for producing enantioenriched 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 H_2O_2-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

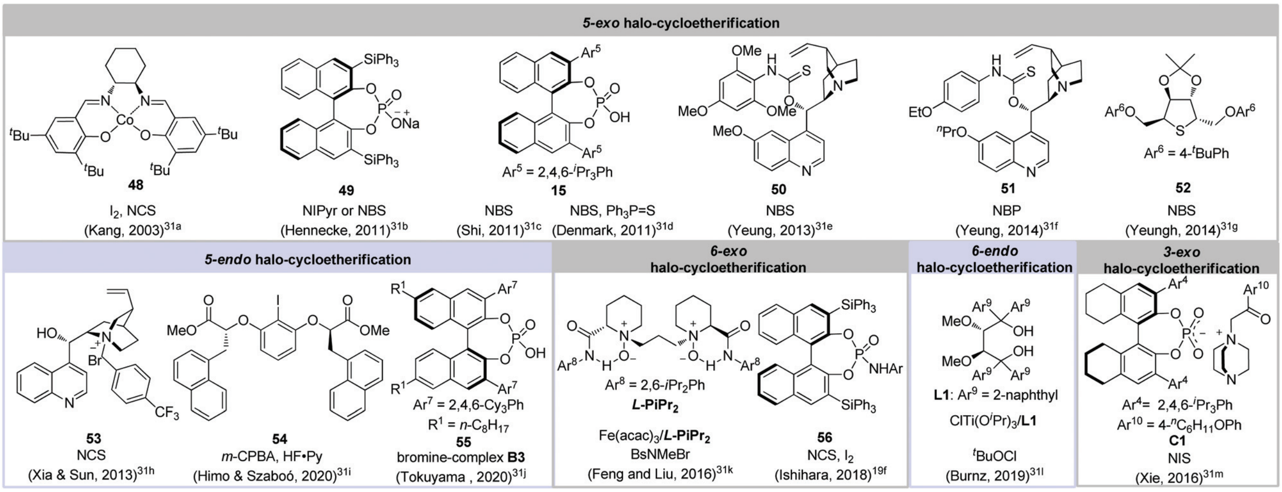
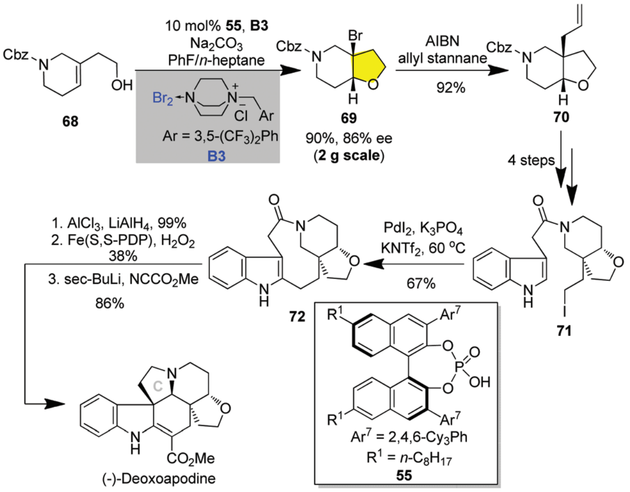


Fig. 5 Developed catalysts and halogenating reagents employed for the catalytic asymmetric halo-cycloetherification.

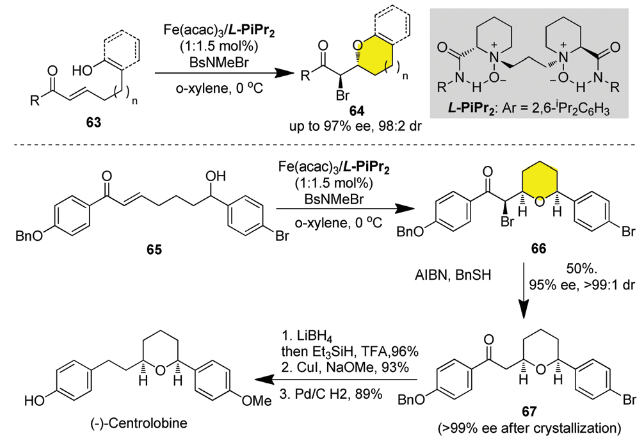
with 92% ee on a gram scale only in the presence of 1.0 mol% ion-pair organocatalyst **C1** (Scheme 7). Subsequent transformations of cyclohexanone **60a** *via* the removal of iodine, formylation followed by methylation delivered the two separable diastereoisomers **61a** and **61b**, which were respectively subjected to H_2O_2-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/Et$_3$N to give ketone **67** in 50% yield over two steps and 95% ee with >99 : 1 dr. Reduction of the ketone **67** with LiBH$_4$ followed by the removal of the resulting secondary alcohol mediated by Et$_3$SiH/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 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 bromofuran **70** under the effect of AIBN/allylstannane 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 PdI$_2$/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.

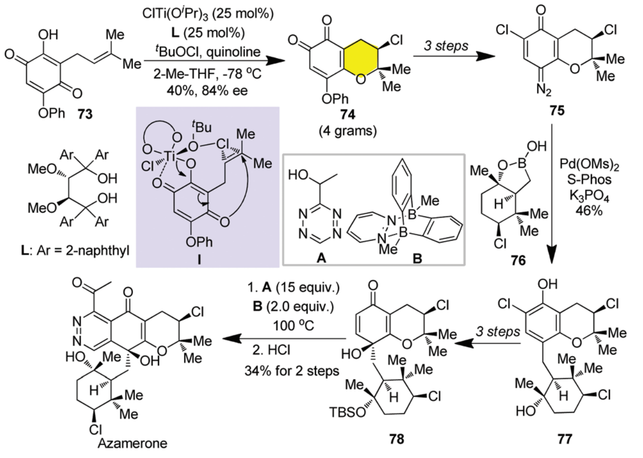


Scheme 9 Asymmetric synthesis of (−)-deoxoapodine relying on catalytic asymmetric 5-*endo* bromo-cycloetherification (Tokuyama).



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

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).[31l] 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 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 Bougoult 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] Fujioka[39n] 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 organocatalyst (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

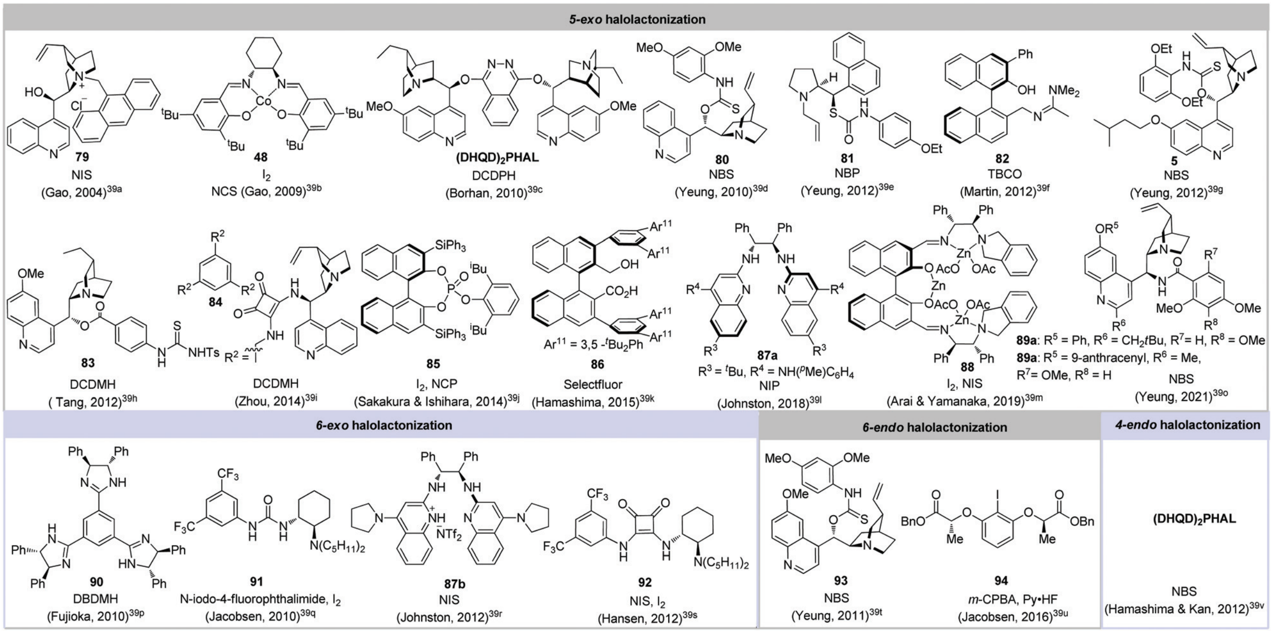
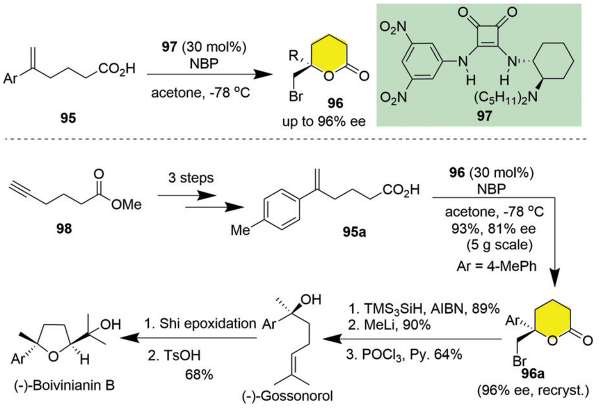
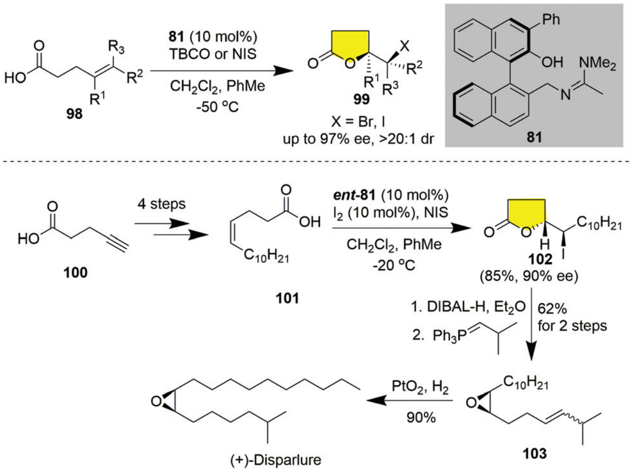


Fig. 6 Developed catalysts and halogenating reagents employed for catalytic asymmetric halolactonization of alkenoic acids.



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



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

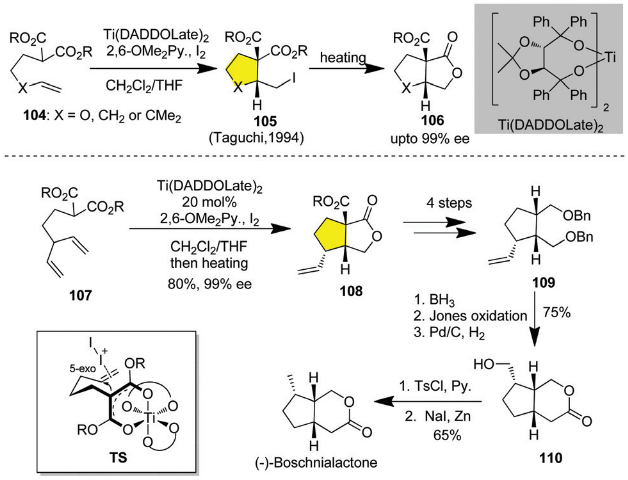
alcohol, which could be elaborated to natural products. In 2016, Hansen and co-workers reported the 6-*exo* asymmetric bromolactonization of δ-unsaturated carboxylic acids in the presence of 30 mol% chiral squaramide organocatalyst **97** (Scheme 11).[40] To demonstrate its synthetic potential, chiral 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 TMS_3SiH/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.

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 $Ti(TADDOLate)_2$, 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 $Ti(TADDOLate)_2$ 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* $Ti(TADDOLate)_2$-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 thiophosphoramide **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.

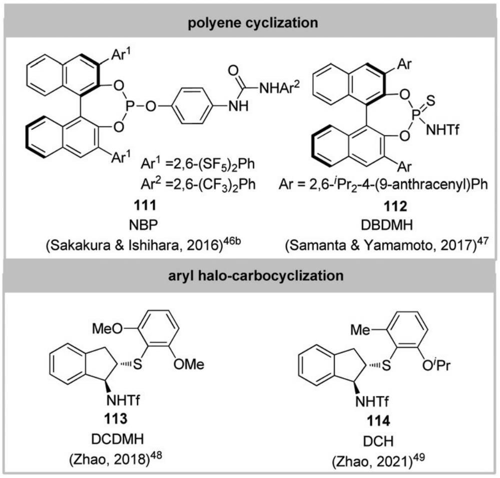


Fig. 7 Other described organocatalysts and halogenating reagents employed for catalytic asymmetric halo-carbocyclization.

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.

Acknowledgements

We are grateful for financial support from the National Natural Science Foundation of China (grants 21722206, 21672171). Financial support from the Scientific Fund of Northwest A&F University is also acknowledged.

Notes and references

1 (*a*) K. E. Harding and T. H. Tiner, in *Comprehensive Organic Synthesis*, ed. B. M. Trost and I. Fleming, Pergamon Press, Oxford, 1991, vol. 4, p. 363; (*b*) J. Mulzer, in *Organic Synthesis Highlights*, ed. J. Mulzer, H. J. Altenbach, M. Braun, K. Krohn and H. U. Reissig, VCH, Weinheim, 1991, p. 157; (*c*) F. Rodríguez and F. J. Fañanás, in *Handbook of Cyclization Reactions*, ed. S. Ma, Wiley-VCH, New York, 2010, vol. 4, pp. 951–990; (*d*) M. D. Dowle and D. I. Davies,

Synthesis and Synthetic Utility of Halolactones, *Chem. Soc. Rev.*, 1979, **8**, 171–197; (*e*) G. Cardillo and M. Orena, Stereocontrolled cyclofunctionalizations of Double Bonds through Heterocyclic Intermediates, *Tetrahedron*, 1990, **46**, 3321–3408; (*f*) S. Robin and G. R. Rousseaur, Electrophilic Cyclization of Unsaturated Amides, *Tetrahedron*, 1998, **54**, 13681–13736; (*g*) O. Kitagawa and T. Taguchi, Iodocarbocyclization and Iodoaminocyclization Reactions Mediated by a Metallic Reagent, *Synlett*, 1999, 1191–1199; (*h*) A. N. French, S. Bissmire and T. Wirth, Iodine Electrophiles in Stereoselective Reactions: Recent Developments and Synthetic Applications, *Chem. Soc. Rev.*, 2004, **33**, 354–362; (*i*) S. Ranganathan, K. M. Muraleedharan, N. K. Vaish and N. Jayaraman, Halo- and Selenolactonisation: the Two Major Strategies for Cyclofunctionalisation, *Tetrahedron*, 2004, **60**, 5273–5308; (*j*) G. Li, S. R. S. Saibabu Kotti and C. Timmons, Recent Development of Regio- and Stereoselective Aminohalogenation Reaction of Alkenes, *Eur. J. Org. Chem.*, 2007, 2745–2758; (*k*) V. S. C. de Andrade and M. C. S. de Mattos, N-Halo Reagents: Modern Synthetic Approaches for Heterocyclic Synthesis, *Synthesis*, 2019, **51**, 1841–1870; (*l*) H. China, R. Kumar, K. Kikushima and T. Dohi, Halogen-Induced Controllable Cyclizations as Diverse Heterocycle Synthetic Strategy, *Molecules*, 2020, **25**, 6007.

2 (*a*) B.-G. Wang, J. B. Gloer, N.-Y. Ji and J.-C. Zhao, Halogenated Organic Molecules of Rhodomelaceae Origin: Chemistry and Biology, *Chem. Rev.*, 2013, **113**, 3632–3685; (*b*) W.-J. Chung and C. D. Vanderwal, Stereoselective Halogenation in Natural Product Synthesis, *Angew. Chem., Int. Ed.*, 2016, **55**, 4396–4434; (*c*) I. Saikia, A. J. Borah and P. Phukan, Use of Bromine and Bromo-Organic Compounds in Organic Synthesis, *Chem. Rev.*, 2016, **116**, 6837–7042.

3 I. Roberts and G. E. Kimball, The Halogenation of Ethylenes, *J. Am. Chem. Soc.*, 1937, **59**, 947–948.

4 (*a*) G. A. Olah and J. M. Bollinger, Stable Carbonium Ions. XLVIII. Halonium ion Formation via neighboring Halogen Participation. Tetramethylethylene Halonium Ions, *J. Am. Chem. Soc.*, 1967, **89**, 4744–4752; (*b*) G. A. Olah, J. M. Bollinger and J. Brinich, Stable carbonium ions. LXII. Halonium Ion Formation via Neighboring Halogen Participation: Ethylenehalonium, Propylenehalonium, and 1,2-Dimethylethylenehalonium Ions, *J. Am. Chem. Soc.*, 1968, **90**, 2587–2594; (*c*) J. Strating, J. H. Wieringa and H. Wynberg, The Isolation of a Stabilized Bromonium Ion, *J. Chem. Soc. D*, 1969, 907–908; (*d*) H. Slebocka-Tilk, R. G. Ball and R. S. Brown, The Question of Reversible Formation Of Bromonium Ions During the Course of Electrophilic Bromination of Olefins. 2. The Crystal and Molecular Structure of the Bromonium Ion of Adamantylideneadamantane, *J. Am. Chem. Soc.*, 1985, **107**, 4504–4508.

5 (*a*) R. E. Buckles, J. M. Bader and R. J. Thurmaier, Stereospecificity of the Addition of Bromine to cis- and trans-Stilbene, *J. Org. Chem.*, 1962, **27**, 4523–4527; (*b*) R. C. Fahey and C. Schubert, Polar Additions to Olefins. I. The Chlorination of 2-Butene and 1-Phenylpropene, *J. Am. Chem. Soc.*, 1965, **87**, 5172–5179; (*c*) J. H. Rolston and K. Yates, Polar Additions to the Styrene and 2-Butene Systems. I. Distribution Stereochemistry Of Bromination Products in Acetic Acid, *J. Am. Chem. Soc.*, 1969, **91**, 1469–1476; (*d*) J. H. Rolston and K. Yates, Polar Additions to the Styrene and 2-Butene Systems. II. Medium Dependence of Bromination Products, *J. Am. Chem. Soc.*, 1969, **91**, 1477–1483; (*e*) J. H. Rolston and K. Yates, Polar Additions to the Styrene and 2-Butene Systems. III. Kinetics annd Linear Free Energy Relations, *J. Am. Chem. Soc.*, 1969, **91**, 1483–1491; (*f*) K. Yates and R. S. McDonald, Kinetics and Mechanisms of Electrophilic Addition. II. Thermochemical-kinetic Approach to Transition State Structure, *J. Org. Chem.*, 1973, **38**, 2465–2478.

6 (*a*) K. D. Ashtekar, M. Vetticatt, R. Yousefi, J. E. Jackson and B. Borhan, Nucleophile-Assisted Alkene Activation: Olefins Alone Are Often Incompetent, *J. Am. Chem. Soc.*, 2016, **138**, 8114–8119; (*b*) N. S. Marzijarani, R. Yousefi, A. Jaganathan, K. D. Ashtekar, J. E. Jackson and B. Borhan, Absolute and Relative Facial Selectivities in Organocatalytic Asymmetric Chlorocyclization Reactions, *Chem. Sci.*, 2018, **9**, 2898–2908; (*c*) R. Yousefi, A. Sarkar, K. D. Ashtekar, D. C. Whitehead, T. Kakeshpour, D. Holmes, P. Reed, J. E. Jackson and B. Borhan, Mechanistic Insights into the Origin of Stereoselectivity in an Asymmetric Chlorolactonization Catalyzed by (DHQD)2PHAL, *J. Am. Chem. Soc.*, 2020, **142**, 7179–7189; (*d*) R. Van Lommel, J. Bock, C. G. Daniliuc, U. Hennecke and F. De Proft, A Dynamic Picture of the Halolactonization reaction through a Combination of Ab Initio Metadynamics and Experimental Investigations, *Chem. Sci.*, 2021, **12**, 7746–7757.

7 (*a*) G. Bellucci, R. Bianchini, C. Chiappe, F. Marioni, R. Ambrosetti, R. S. Brown and H. Slebocka-Tilk, The Solution Behavior of the Adamantylideneadamantane-Bromine System: Existence of equilibrium Mixtures of Bromonium-Polybromide Salts and a Strong 1 : 1 Molecular Charge-Transfer Complex, *J. Am. Chem. Soc.*, 1989, **111**, 2640–2647; (*b*) A. J. Bennet, R. S. Brown, R. E. D. McClung, M. Klobukowski, G. H. M. Aarts, B. D. Santarsiero, G. Bellucci and R. Bianchini, An unprecedented Rapid And Direct Bromine(1 +) Ion Transfer from theBbromonium Ion of Adamantylideneadamantane to Acceptor Olefins, *J. Am. Chem. Soc.*, 1991, **113**, 8532–8534; (*c*) R. S. Brown, R. W. Nagorski, A. J. Bennet, R. E. D. McClung, G. H. M. Aarts, M. Klobukowski, R. McDonald and B. D. Santarsiero, Stable Bromonium and Iodonium Ions of the Hindered Olefins Adamantylideneadamantane and Bicyclo[3.3.1]nonylidenebicyclo[3.3.1]nonane. X-Ray Structure, Transfer of Positive Halogens to Acceptor Olefins, and ab Initio Studies, *J. Am. Chem. Soc.*, 1994, **116**, 2448–2456; (*d*) R. S. Brown, Investigation of the Early Steps in Electrophilic Bromination through the Study of the

Reaction with Sterically Encumbered Olefins, *Acc. Chem. Res.*, 1997, **30**, 131–137.

8 (*a*) D. C. Braddock, S. A. Hermitage, L. Kwok, R. Pouwer, J. M. Redmond and A. J. P. White, The Generation and Trapping of Enantiopure Bromonium ions, *Chem. Commun.*, 2009, 1082–1084; (*b*) S. E. Denmark, M. T. Burk and A. J. Hoover, On the Absolute Configurational Stability of Bromonium and Chloronium Ions, *J. Am. Chem. Soc.*, 2010, **132**, 1232–1233.

9 (*a*) O. Kitagawa, T. Hanano, K. Tanabe, M. Shiro and T. Taguchi, Enantioselective Halocyclization Reaction Using a Chiral Titanium Complex, *J. Chem. Soc., Chem. Commun.*, 1992, 1005–1007; (*b*) R. B. Grossman and R. J. Trupp, The First Reagent-Controlled Asymmetric Halolactonizations. Dihydroquinidine-Halogen Complexes as Chiral Sources of Positive Halogen Ion, *Can. J. Chem.*, 1998, **76**, 1233–1237; (*c*) X.-L. Cui and R. S. Brown, Mechanistic Evaluation of the Halocyclization of 4-Penten-1-ol by Some Bis(2-substituted pyridine) and Bis(2,6-di-substituted pyridine)bromonium Triflates, *J. Org. Chem.*, 2000, **65**, 5653–5658; (*d*) J. Haas, S. Piguel and T. Wirth, Reagent-Controlled Stereoselective Iodolactonizations, *Org. Lett.*, 2002, **4**, 297–300.

10 T. Inoue, O. Kitagawa, O. Ochiai, M. Shiro and T. Taguchi, Catalytic Asymmetric Iodocarbocyclization reaction, *Tetrahedron Lett.*, 1995, **36**, 9333–9336.

11 or selected reviews on organocatalysis, see: (*a*) *Enantioselective Organocatalyzed Reactions*, ed. R. Mahrwald, Springer, New York, 2011; (*b*) *Comprehensive Enantioselective Organocatalysis: Catalysts, Reactions, and Applications*, ed. P. I. Dalko, Wiley-VCH, Weinheim, 2013; (*c*) D. W. C. MacMillan, *Nature*, 2008, **455**, 304–308; (*d*) S. Mukherjee, J. W. Yang, S. Hoffmann and B. List, *Chem. Rev.*, 2007, **107**, 5471–5569; (*e*) A. Vega-Penaloza, S. Paria, M. Bonchio, L. Dell'Amico and X. Companyo, *ACS Catal.*, 2019, **9**, 6058–6072; (*f*) T. Akiyama, *Chem. Rev.*, 2007, **107**, 5744–5758; (*g*) R. J. Phipps, G. L. Hamilton and F. D. Toste, *Nat. Chem.*, 2012, **4**, 603–614; (*h*) M. Mahlau and B. List, *Angew. Chem., Int. Ed.*, 2013, **52**, 518–533.

12 (*a*) M. P. Brochu, S. P. Brown and D. W. C. MacMillan, Direct and Enantioselective Organocatalytic α-Chlorination of Aldehydes, *J. Am. Chem. Soc.*, 2004, **126**, 4108–4109; (*b*) N. Halland, A. Braunton, S. Bachmann, M. Marigo and K. A. Jørgensen, Direct Organocatalytic Asymmetric α-Chlorination of Aldehydes, *J. Am. Chem. Soc.*, 2004, **126**, 4790–4791.

13 (*a*) R. Britton and B. Kang, α-Haloaldehydes: versatile building blocks for natural product synthesis, *Nat. Prod. Rep.*, 2013, **30**, 227–236; (*b*) P. J. Chevis and S. G. Pyne, Synthesis of enantioenriched α-heteroatom functionalised aldehydes by chiral organocatalysis and their synthetic applications, *Org. Chem. Front.*, 2021, **8**, 2287–2314.

14 For review: (*a*) J. Bock, S. Guria, V. Wedek and U. Hennecke, Enantioselective Dihalogenation of Alkenes, *Chem. – Eur. J.*, 2021, **27**, 4517–4530 For selected examples: (*b*) K. C. Nicolaou, N. L. Simmons, Y. Ying, P. M. Heretsch and J. S. Chen, Enantioselective Dichlorination of Allylic Alcohols, *J. Am. Chem. Soc.*, 2011, **133**, 8134–8137; (*c*) S. M. Banik, J. W. Medley and E. N. Jacobsen, Catalytic, Diastereoselective 1,2-Difluorination of Alkenes, *J. Am. Chem. Soc.*, 2016, **138**, 5000–5003; (*d*) W.-S. Huang, L. Chen, Z.-J. Zheng, K.-F. Yang, Z. Xu, Y.-M. Cui and L.-W. Xu, Catalytic asymmetric Bromochlorination of Aromatic Allylic Alcohols Promoted by Multifunctional Schiff Base Ligands, *Org. Biomol. Chem.*, 2016, **14**, 7927–7932; (*e*) V. Wedek, R. Van Lommel, C. G. Daniliuc, F. De Proft and U. Hennecke, Organocatalytic, Enantioselective Dichlorination of Unfunctionalized Alkenes, *Angew. Chem., Int. Ed.*, 2019, **58**, 9239–9243.

15 (*a*) D. X. Hu, G. M. Shibuya and N. Z. Burns, Catalytic Enantioselective Dibromination of Allylic Alcohols, *J. Am. Chem. Soc.*, 2013, **135**, 12960–12963; (*b*) D. X. Hu, F. J. Seidl, C. Bucher and N. Z. Burns, Catalytic Chemo-, Regio-, and Enantioselective Bromochlorination of Allylic Alcohols, *J. Am. Chem. Soc.*, 2015, **137**, 3795–3798; (*c*) M. L. Landry, D. X. Hu, G. M. McKenna and N. Z. Burns, Catalytic Enantioselective Dihalogenation and the Selective Synthesis of (−)-Deschloromytilipin A and (−)-Danicalipin A, *J. Am. Chem. Soc.*, 2016, **138**, 5150–5158 For review on the synthetic applications: (*d*) M. L. Landry and N. Z. Burns, Catalytic Enantioselective Dihalogenation in Total Synthesis, *Acc. Chem. Res.*, 2018, **51**, 1260–1271.

16 For reviews on catalytic asymmetric halocyclization, see: (*a*) S. France, A. Weatherwax and T. Lectka, Recent Developments in Catalytic, Asymmetric α-Halogenation: A New Frontier in Asymmetric Catalysis, *Eur. J. Org. Chem.*, 2005, 475–479; (*b*) G. Chen and S. Ma, Enantioselective Halocyclization Reactions for the Synthesis of Chiral Cyclic Compounds, *Angew. Chem., Int. Ed.*, 2010, **49**, 8306–8308; (*c*) A. Castellanos and S. P. Fletcher, Current Methods for Asymmetric Halogenation of Olefins, *Chem. – Eur. J.*, 2011, **17**, 5766–5776; (*d*) C. K. Tan, L. Zhou and Y.-Y. Yeung, Organocatalytic Enantioselective Halolactonizations: Strategies of Halogen Activation, *Synlett*, 2011, 1335–1339; (*e*) S. E. Denmark, W. E. Kuester and M. T. Burk, Catalytic, Asymmetric Halofunctionalization of Alkenes—A Critical Perspective, *Angew. Chem., Int. Ed.*, 2012, **51**, 10938–10953; (*f*) U. Hennecke, New Catalytic Approaches towards the Enantioselective Halogenation of Alkenes, *Chem. – Asian J.*, 2012, **7**, 456–465; (*g*) C. K. Tan and Y.-Y. Yeung, Recent advances in stereoselective bromofunctionalization of alkenes using N-bromoamide reagents, *Chem. Commun.*, 2013, **49**, 7985–7996; (*h*) C. B. Tripathi and S. Mukherjee, Catalytic Enantioselective Halocyclizations beyond Lactones: Emerging Routes to Enantioenriched Nitrogenous Heterocycles, *Synlett*, 2014, **25**, 163–169; (*i*) S. Zheng, C. M. Schienebeck, W. Zhang, H.-Y. Wang and W. Tang, Cinchona Alkaloids as Organocatalysts in Enantioselective Halofunctionalization of Alkenes and Alkynes, *Asian J. Org. Chem.*, 2014, **3**, 366–376; (*j*) M. H. Gieuw, Z. Ke and Y.-Y. Yeung, Lewis Base Catalyzed Stereo- and Regioselective Bromocyclization,

Chem. Rec., 2017, **17**, 287–311; (*k*) Y. Kawato and Y. Hamashima, Enantioselective Bromocyclization of Allylic Amides Mediated by Phosphorus Catalysis, *Synlett*, 2018, **29**, 1257–1271; (*l*) B. Maji, Stereoselective Halonium, Thiiranium and Seleniranium Ion-Triggered Friedel–Crafts-Type Alkylations for Polyene Cyclizations, *Adv. Synth. Catal.*, 2019, **361**, 3453–3489; (*m*) J. Wong and Y.-Y. Yeung, Recent Advances in C–Br Bond Formation, *Synlett*, 2021, **32**, 1354–1364 For the example of constucting polyclic scaffolds *via* catalytic asymmetric cascade cyclization, see: (*n*) T. Zheng, X. Wang, W.-H. Ng, Y.-L. S. Tse and Y.-Y. Yeung, Catalytic enantio- and diastereoselective domino halocyclization and spiroketalization, *Nat. Catal.*, 2020, **3**, 993–1001.

17 (*a*) D. O'Hagan, Pyrrole, Pyrrolidine, Pyridine, Piperidine and Tropane Alkaloids, *Nat. Prod. Rep.*, 2000, **17**, 435–446; (*b*) F.-X. Felpin and J. Lebreton, Recent Advances in the Total Synthesis of Piperidine and Pyrrolidine Natural Alkaloids with Ring-Closing Metathesis as a Key Step, *Eur. J. Org. Chem.*, 2003, 3693–3712; (*c*) X. Wen-Fang, C. Xian-Chao, W. Qiang and F. Hao, Advances in Matrix Metalloproteinase Inhibitors Based on Pyrrolidine Scaffold, *Curr. Med. Chem.*, 2008, **15**, 374–385.

18 For selected examples of applications of halo-aminocyclization in natural product synthesis: (*a*) Y. G. Kim and J. K. Cha, DivergentSyntheses of Stereoisomers of Swainsonine: (−)-8-epi-, (−)-8a-epi- and (−)-8,8a-diepi-Swainsonine, *Tetrahedron Lett.*, 1989, **30**, 5721–5724; (*b*) Y.-Y. Yeung, S. Hong and E. J. Corey, A Short Enantioselective Pathway for the Synthesis of the Anti-Influenza Neuramidase Inhibitor Oseltamivir from 1,3-Butadiene and Acrylic Acid, *J. Am. Chem. Soc.*, 2006, **128**, 6310–6311; (*c*) D. C. Beshore and A. B. Smith, Total Syntheses of (+)-Lyconadin A and (−)-Lyconadin B, *J. Am. Chem. Soc.*, 2007, **129**, 4148–4149; (*d*) D. C. Beshore and A. B. Smith, The Lyconadins: Enantioselective Total Syntheses of (+)-Lyconadin A and (−)-Lyconadin B, *J. Am. Chem. Soc.*, 2008, **130**, 13778–13789; (*e*) S. G. Davies, A. L. A. Figuccia, A. M. Fletcher, P. M. Roberts and J. E. Thomson, Asymmetric Syntheses of (−)-1-Deoxymannojirimycin and (+)-1-Deoxyallonojirimycin via a Ring-Expansion Approach, *Org. Lett.*, 2013, **15**, 2042–2045.

19 For catalytic asymmetric 5-*exo* aminocyclization: (*a*) L. Zhou, J. Chen, C. K. Tan and Y.-Y. Yeung, Enantioselective Bromoaminocyclization Using Amino–Thiocarbamate Catalysts, *J. Am. Chem. Soc.*, 2011, **133**, 9164–9167; (*b*) F. Chen, C. K. Tan and Y.-Y. Yeung, C2-Symmetric Cyclic Selenium-Catalyzed Enantioselective Bromoaminocyclization, *J. Am. Chem. Soc.*, 2013, **135**, 1232–1235; (*c*) P. Mizar, A. Burrelli, E. Günther, M. Söftje, U. Farooq and T. Wirth, Organocatalytic Stereoselective Iodoamination of Alkenes, *Chem. – Eur. J.*, 2014, **20**, 13113–13116; (*d*) H.-J. Jiang, K. Liu, J. Yu, L. Zhang and L.-Z. Gong, Switchable Stereoselectivity in Bromoaminocyclization of Olefins: Using Brønsted Acids of Anionic Chiral Cobalt(III) Complexes, *Angew. Chem., Int. Ed.*, 2017, **56**, 11931–11935; (*e*) S.-N. Yu, Y.-L. Li and J. Deng, Enantioselective Synthesis of 2-Bromomethyl Indolines via BINAP(S)-Catalyzed Bromoaminocyclization of Allyl Aniline, *Adv. Synth. Catal.*, 2017, **359**, 2499–2508; (*f*) Y. Lu, H. Nakatsuji, Y. Okumura, L. Yao and K. Ishihara, Enantioselective Halo-oxy- and Halo-azacyclizations Induced by Chiral Amidophosphate Catalysts and Halo-Lewis Acids, *J. Am. Chem. Soc.*, 2018, **140**, 6039–6043; (*g*) T. Nakamura, K. Okuno, K. Kaneko, M. Yamanaka and S. Shirakawa, Chiral Bifunctional Sulfide-Catalyzed Asymmetric Bromoaminocyclizations, *Org. Biomol. Chem.*, 2020, **18**, 3367–3373 For 5-*endo* catalytic asymmetric aminocyclization: (*h*) J. Chen, L. Zhou and Y.-Y. Yeung, A Highly Enantioselective Approach towards 2-Substituted 3-Bromopyrrolidines, *Org. Biomol. Chem.*, 2012, **10**, 3808–3811; (*i*) W. Q. Xie, G. D. Jiang, H. Liu, J. D. Hu, X. X. Pan, H. Zhang, X. L. Wan, Y. S. Lai and D. W. Ma, Highly Enantioselective Bromocyclization of Tryptamines and Its Application in the Synthesis of (-)-Chimonanthine, *Angew. Chem., Int. Ed.*, 2013, **52**, 12924–12927; (*j*) Q. Cai, Q. Yin and S.-L. You, Chiral-Amine-Catalyzed Asymmetric Bromocyclization of Tryptamine Derivatives, *Asian J. Org. Chem.*, 2014, **3**, 408–411; (*k*) K. Liu, H.-J. Jiang, N. Li, H. Li, J. Wang, Z.-Z. Zhang and J. Yu, Enantioselective Bromocyclization of Tryptamines Induced by Chiral Co(III)-Complex-Templated Brønsted Acids under an Air Atmosphere, *J. Org. Chem.*, 2018, **83**, 6815–6823; (*l*) H. Wang, H. Zhong, X. Xu, W. Xu and X. Jiang, Catalytic Enantioselective Bromoaminocyclization and Bromocycloetherification, *Adv. Synth. Catal.*, 2020, **362**, 5358–5362.

20 (*a*) H. Huang, H. Pan, Y. Cai, M. Liu, H. Tian and Y. Shi, Enantioselective 6-endo bromoaminocyclization of 2,4-dienyl N-tosylcarbamates catalyzed by a chiral phosphine oxide-Sc(OTf)$_3$ complex. A dramatic additive effect, *Org. Biomol. Chem.*, 2015, **13**, 3566–3570; (*b*) Z. Li and Y. Shi, Chiral Phosphine Oxide–Sc(OTf)$_3$ Complex Catalyzed Enantioselective Bromoaminocyclization of 2-Benzofuranylmethyl N-Tosylcarbamates. Approach to a Novel Class of Optically Active Spiro Compounds, *Org. Lett.*, 2015, **17**, 5752–5755; (*c*) W. Liu, H. Pan, H. Tian and Y. Shi, Enantioselective 6-exo-Bromoaminocyclization of Homoallylic N-Tosylcarbamates Catalyzed by a Novel Monophosphine-Sc(OTf)$_3$ C omplex, *Org. Lett.*, 2015, **17**, 3956–3959; (*d*) H. Pan, H. Huang, W. Liu, H. Tian and Y. Shi, Phosphine Oxide–Sc(OTf)$_3$ C atalyzed Highly Regio- and Enantioselective Bromoaminocyclization of (E)-Cinnamyl Tosylcarbamates. An Approach to a Class of Synthetically Versatile Functionalized Molecules, *Org. Lett.*, 2016, **18**, 896–899.

21 For reviews, see: (*a*) U. Anthoni, C. Christophersen and P. H. Nielsen, in *Alkaloids: Chemical and Biological Perspectives*, ed. S. W. Pelletier, Pergamon, New York, 1999, vol. 13, pp. 163–236; (*b*) G. A. Cordell and J. E. Saxton, in *The Alkaloids: Chemistry and Physiology*, ed. R. H. F. Manske and R. G. A. Rodrigo, Academic Press, New York, 1981, vol.

20, pp. 3–295; (*c*) T. Hino and M. Nakagawa, in *The Alkaloids: Chemistry and Pharmacology*, ed. A. Brossi, Academic Press, New York, 1989, vol. 34, pp. 1–75; (*d*) T. S. Pvenet and J. Pusset, in *The Alkaloids: Chemistry and Pharmacology*, ed. G. A. Cordell, Academic Press, New York, 1996, vol. 48, pp. 1–73 For synthesis of cyclotryptamine alkaloids: (*e*) D. Crich and A. Banerjee, Chemistry of the Hexahydropyrrolo[2,3-b]indoles: Configuration, Conformation, Reactivity, and Applications in Synthesis, *Acc. Chem. Res.*, 2007, **40**, 151–161; (*f*) P. Ruiz-Sanchis, S. A. Savina, F. Albericio and M. Álvarez, Structure, Bioactivity and Synthesis of Natural Products with Hexahydropyrrolo[2,3-b]indole, *Chem. – Eur. J.*, 2011, **17**, 1388–1408; (*g*) L. M. Repka and S. E. Reisman, Recent Developments in the Catalytic, Asymmetric Construction of Pyrroloindolines Bearing All-Carbon Quaternary Stereocenters, *J. Org. Chem.*, 2013, **78**, 12314–12320; (*h*) M. Büschleb, S. Dorich, S. Hanessian, D. Tao, K. B. Schenthal and L. E. Overman, Synthetic Strategies toward Natural Products Containing Contiguous Stereogenic Quaternary Carbon Atoms, *Angew. Chem., Int. Ed.*, 2016, **55**, 4156–4186.

22 (*a*) A. R. Pape, K. P. Kaliappan and E. P. Kundig, Transition-Metal-Mediated Dearomatization Reactions, *Chem. Rev.*, 2000, **100**, 2917–2940; (*b*) S. P. Roche and J. A. Porco Jr., Dearomatization Strategies in the Synthesis of Complex Natural Products, *Angew. Chem., Int. Ed.*, 2011, **50**, 4068–4093; (*c*) C. X. Zhuo, W. Zhang and S. L. You, Catalytic Asymmetric Dearomatization Reactions, *Angew. Chem., Int. Ed.*, 2012, **51**, 12662–12686; (*d*) C. Zheng and S. L. You, Catalytic Asymmetric Dearomatization by Transition-Metal Catalysis: A Method for Transformations of Aromatic Compounds, *Chem*, 2016, **1**, 830–857; (*e*) W. C. Wertjes, E. H. Southgate and D. Sarlah, Recent advances in chemical dearomatization of nonactivated arenes, *Chem. Soc. Rev.*, 2018, **47**, 7996–8017.

23 For reviews: for selected recent examples: (*a*) M. Movassaghi and M. A. Schmidt, Concise total synthesis of (-)-calycanthine, (+)-chimonanthine, and (+)-folicanthine, *Angew. Chem., Int. Ed.*, 2007, **46**, 3725–3728; (*b*) H. Mitsunuma, M. Shibasaki, M. Kanai and S. Matsunaga, Catalytic Asymmetric Total Synthesis of Chimonanthine, Folicanthine, and Calycanthine through Double Michael Reaction of Bisoxindole, *Angew. Chem., Int. Ed.*, 2012, **51**, 5217–5221; (*c*) R. R. Liu and J. L. Zhang, Organocatalytic Michael Addition of Indoles to Isatylidene-3-acetaldehydes: Application to the Formal Total Synthesis of (-)-Chimonanthine, *Org. Lett.*, 2013, **15**, 2266–2269; (*d*) S. P. Lathrop and M. Movassaghi, Application of diazene-directed fragment assembly to the total synthesis and stereochemical assignment of (+)-desmethyl-meso-chimonanthine and related heterodimeric alkaloids, *Chem. Sci.*, 2014, **5**, 333–340; (*e*) M. Ding, K. J. Liang, R. Pan, H. B. Zhang and C. F. Xia, Total Synthesis of (+)-Chimonanthine, (+)-Folicanthine, and (-)-Calycanthine, *J. Org. Chem.*, 2015, **80**, 10309–10316; (*f*) K. N. Babu, A. Roy, M. Singh and A. Bisai, Thiourea-Catalyzed Enantioselective Malonate Addition onto 3-Sulfonyl-3 ‘-indolyl-2-oxindoles: Formal Total Syntheses of (-)-Chimonanthine, (-)-Folicanthine, and (+)-Calycanthine, *Org. Lett.*, 2018, **20**, 6327–6331.

24 (*a*) K.-H. Lim, T. Etoh, M. Hayashi, K. Komiyama and T.-S. Kam, Conolutinine, a Hexacyclic Indole Alkaloid with a Novel Ring System Incorporating a Diazaspiro Center and Fused Oxadiazepine–Tetrahydrofuran Rings, *Tetrahedron Lett.*, 2009, **50**, 752–754; (*b*) X. Feng, G. Jiang, Z. Xia, J. Hu, X. Wan, J.-M. Gao, Y. Lai and W. Xie, Total Synthesis of (−)-Conolutinine, *Org. Lett.*, 2015, **17**, 4428–4431.

25 (*a*) A. D. Lebsack, J. T. Link, L. E. Overman and B. A. Stearns, Enantioselective Total Synthesis of Quadrigemine C and Psycholeine, *J. Am. Chem. Soc.*, 2002, **124**, 9008–9009; (*b*) J. J. Kodanko and L. E. Overman, Enantioselective Total Syntheses of the Cyclotryptamine Alkaloids Hodgkinsine and Hodgkinsine B, *Angew. Chem., Int. Ed.*, 2003, **42**, 2528–2531; (*c*) L. E. Overman and E. A. Peterson, Enantioselective Total Synthesis of The Cyclotryptamine Alkaloid Idiospermuline, *Angew. Chem., Int. Ed.*, 2003, **42**, 2525–2528; (*d*) K. Foo, T. Newhouse, I. Mori, H. Takayama and P. S. Baran, Total Synthesis Guided Structure Elucidation of (+)-Psychotetramine, *Angew. Chem., Int. Ed.*, 2011, **50**, 2716–2719; (*e*) R. H. Snell, R. L. Woodward and M. C. Willis, Catalytic Enantioselective Total Synthesis of Hodgkinsine B, *Angew. Chem., Int. Ed.*, 2011, **50**, 9116–9119; (*f*) C. R. Jamison, J. J. Badillo, J. M. Lipshultz, R. J. Comito and D. W. C. MacMillan, Catalyst-Controlled Oligomerization for the Collective Synthesis of Polypyrroloindoline Natural Products, *Nat. Chem.*, 2017, **9**, 1165–1169; (*g*) P. Lindovska and M. Movassaghi, Concise Synthesis of (-)-Hodgkinsine, (-)-Calycosidine, (-)-Hodgkinsine B, (-)-Quadrigemine C, and (-)-Psycholeine via Convergent and Directed Modular Assembly of Cyclotryptamines, *J. Am. Chem. Soc.*, 2017, **139**, 17590–17596.

26 (*a*) A. Numata, C. Takahashi, Y. Ito, T. Takada, K. Kawai, Y. Usami, E. Matsumura, M. Imachi, T. Ito and T. Hasegawa, Communesins, Cytotoxic Metabolites of a Fungus Isolated from a Marine Alga, *Tetrahedron Lett.*, 1993, **34**, 2355–2358; (*b*) H. Hayashi, H. Matsumoto and K. Akiyama, New Insecticidal Compounds, Communesins C, D and E, from Penicillium expansum Link MK-57, *Biosci. Biotechnol. Biochem.*, 2004, **68**, 753–756; (*c*) R. Jadulco, R. A. Edrada, R. Ebel, A. Berg, K. Schaumann, V. Wray, K. Steube and P. Proksch, New Communesin Derivatives from the Fungus Penicillium sp. Derived from the Mediterranean Sponge Axinella verrucosa, *J. Nat. Prod.*, 2004, **67**, 78–81; (*d*) P. W. Dalsgaard, J. W. Blunt, M. H. G. Munro, J. C. Frisvad and C. Christophersen, Communesins G and H, New Alkaloids from the Psychrotolerant Fungus Penicillium Rivulum, *J. Nat. Prod.*, 2005, **68**, 258–261.

27 For reviews: (*a*) P. Siengalewicz, T. Gaich and J. Mulzer, It All Began with an Error: The Nomofungin/Communesin

Story, *Angew. Chem., Int. Ed.*, 2008, **47**, 8170–8176; (*b*) Z. Zuo and D. Ma, Synthetic Studies toward Communesins, *Israel J. Chem.*, 2011, **51**, 434–441; (*c*) B. M. Trost and M. Osipov, Recent Advances on the Total Syntheses of Communesin Alkaloids and Perophoramidine, *Chem. – Eur. J.*, 2015, **21**, 16318–16343 For recent syntheses: (*d*) S. P. Lathrop, M. Pompeo, W. T. T. Chang and M. Movassaghi, Convergent and Biomimetic Enantioselective Total Synthesis of (-)-Communesin F, *J. Am. Chem. Soc.*, 2016, **138**, 7763–7769; (*e*) X. Liang, T. Y. Zhang, X. Y. Zeng, Y. Zheng, K. Wei and Y. R. Yang, Ir-Catalyzed Asymmetric Total Synthesis of (-)-Communesin F, *J. Am. Chem. Soc.*, 2017, **139**, 3364–3367; (*f*) J. Park, A. Jean and D. Y.-K. Chen, Asymmetric Total Syntheses of Communesin F and a Putative Member of the Communesin Family, *Angew. Chem., Int. Ed.*, 2017, **56**, 14237–14240; (*g*) M. M. Pompeo, J. H. Cheah and M. Movassaghi, Total Synthesis and Anti-Cancer Activity of All Known Communesin Alkaloids and Related Derivatives, *J. Am. Chem. Soc.*, 2019, **141**, 14411–14420.

28 For selected reviews: (*a*) J. Marco-Contelles, M. T. Molina and S. Anjum, Naturally Occurring Cyclohexane Epoxides: Sources, Biological Activities, and Synthesis, *Chem. Rev.*, 2004, **104**, 2857–2900; (*b*) J. Rutkowski and B. Brzezinski, Structures and Properties of Naturally Occurring Polyether Antibiotics, *BioMed. Res. Int.,*, 2013, **2013**, 162513; (*c*) J. W. Blunt, B. R. Copp, R. A. Keyzers, M. H. G. Munro and M. R. Prinsep, Marine natural products, *Nat. Prod. Rep.*, 2016, **33**, 382–431.

29 For selected reviews: (*a*) A. Deiters and S. F. Martin, Synthesis of Oxygen- and Nitrogen-Containing Heterocycles by Ring-Closing Metathesis, *Chem. Rev.*, 2004, **104**, 2199–2238; (*b*) M. Inoue, Convergent Strategies for Syntheses of trans-Fused Polycyclic Ethers, *Chem. Rev.*, 2005, **105**, 4379–4405; (*c*) I. Kadota and Y. Yamamoto, Synthetic Strategies of Marine Polycyclic Ethers via Intramolecular Allylations: Linear and Convergent Approaches, *Acc. Chem. Res.*, 2005, **38**, 423–432; (*d*) N. Li, Z. Shi, Y. Tang, J. Chen and X. Li, Recent Progress On The Total Synthesis of Acetogenins from Annonaceae, *Beilstein J. Org. Chem.*, 2008, **4**, 48; (*e*) I. Vilotijevic and T. F. Jamison, Epoxide-Opening Cascades in the Synthesis of Polycyclic Polyether Natural Products, *Angew. Chem., Int. Ed.*, 2009, **48**, 5250–5281; (*f*) T. Nakata, SmI2-Induced Reductive Cyclizations for the Synthesis of Cyclic Ethers and Applications In Natural Product Synthesis, *Chem. Soc. Rev.*, 2010, **39**, 1955–1972; (*g*) R. L. Davis, J. Stiller, T. Naicker, H. Jiang and K. A. Jørgensen, Asymmetric Organocatalytic Epoxidations: Reactions, Scope, Mechanisms, and Applications, *Angew. Chem., Int. Ed.*, 2014, **53**, 7406–7426; (*h*) T. Martín, J. I. Padrón and V. S. Martín, Strategies for the Synthesis of Cyclic Ethers of Marine Natural Products, *Synlett*, 2014, **25**, 12–32.

30 Selected examples: (*a*) Y. Adachi, N. Kamei, S. Yokoshima and T. Fukuyama, Total Synthesis of (−)-Histrionicotoxin, *Org. Lett.*, 2011, **13**, 4446–4449; (*b*) S. A. Snyder, A. P. Brucks, D. S. Treitler and I. Moga, Concise Synthetic Approaches for the Laurencia Family: Formal Total Syntheses of (±)-Laurefucin and (±)-E- and (±)-Z-Pinnatifidenyne, *J. Am. Chem. Soc.*, 2012, **134**, 17714–17721; (*c*) N. Alnafta, J. P. Schmidt, C. L. Nesbitt and C. S. P. McErlean, Total Synthesis of (+)-Panacene, *Org. Lett.*, 2016, **18**, 6520–6522; (*d*) J. Clarke, K. J. Bonney, M. Yaqoob, S. Solanki, H. S. Rzepa, A. J. P. White, D. S. Millan and D. C. Braddock, Epimeric Face-Selective Oxidations and Diastereodivergent Transannular Oxonium Ion Formation Fragmentations: Computational Modeling and Total Syntheses of 12-Epoxyobtusallene IV, 12-Epoxyobtusallene II, Obtusallene X, Marilzabicycloallene C, and Marilzabicycloallene D, *J. Org. Chem.*, 2016, **81**, 9539–9552; (*e*) Y. Ogura, H. Sato and S. Kuwahara, Total Synthesis of Amphirionin-4, *Org. Lett.*, 2016, **18**, 2399–2402; (*f*) Y. Yoshikawa, M. Yamakawa, T. Kobayashi, K. Murai, M. Arisawa, M. Sumimoto and H. Fujioka, First Asymmetric Total Synthesis and Insight into the Structure of Laurenidificin, *Eur. J. Org. Chem.*, 2017, **2017**, 2715–2718; (*g*) A. Matsuzawa, J. Shiraiwa, A. Kasamatsu and K. Sugita, Enantioselective, Protecting-Group-Free Total Synthesis of Boscartin F, *Org. Lett.*, 2018, **20**, 1031–1033.

31 For 5-*exo* halo-cycloetherifications: (*a*) S. H. Kang, S. B. Lee and C. M. Park, Catalytic Enantioselective Iodocyclization of γ-Hydroxy-cis-alkenes, *J. Am. Chem. Soc.*, 2003, **125**, 15748–15749; (*b*) U. Hennecke, C. H. Müller and R. Fröhlich, Enantioselective Haloetherification by Asymmetric Opening of meso-Halonium Ions, *Org. Lett.*, 2011, **13**, 860–863; (*c*) D. Huang, H. Wang, F. Xue, H. Guan, L. Li, X. Peng and Y. Shi, Enantioselective Bromocyclization of Olefins Catalyzed by Chiral Phosphoric Acid, *Org. Lett.*, 2011, **13**, 6350–6353; (*d*) S. E. Denmark and M. T. Burk, Enantioselective Bromocycloetherification by Lewis Base/Chiral Brønsted Acid Cooperative Catalysis, *Org. Lett.*, 2012, **14**, 256–259; (*e*) Y. Zhao, X. Jiang and Y.-Y. Yeung, Catalytic, Enantioselective, and Highly Chemoselective Bromocyclization of Olefinic Dicarbonyl Compounds, *Angew. Chem., Int. Ed.*, 2013, **52**, 8597–8601; (*f*) Z. Ke, C. K. Tan, F. Chen and Y.-Y. Yeung, Catalytic Asymmetric Bromoetherification and Desymmetrization of Olefinic 1,3-Diols with C2-Symmetric Sulfides, *J. Am. Chem. Soc.*, 2014, **136**, 5627–5630; (*g*) D. W. Tay, G. Y. C. Leung and Y.-Y. Yeung, Desymmetrization of Diolefinic Diols by Enantioselective Amino-thiocarbamate-Catalyzed Bromoetherification: Synthesis of Chiral Spirocycles, *Angew. Chem., Int. Ed.*, 2014, **53**, 5161–5164 For 5-*endo* halo-cycloetherifications: (*h*) X. Zeng, C. Miao, S. Wang, C. Xia and W. Sun, Asymmetric 5-endo Chloroetherification of Homoallylic Alcohols toward the Synthesis of Chiral β-chlorotetrahydrofurans, *Chem. Commun.*, 2013, **49**, 2418–2420; (*i*) Q. Wang, M. Lübcke, M. Biosca, M. Hedberg, L. Eriksson, F. Himo and K. J. Szabó, Enantioselective Construction of Tertiary Fluoride Stereocenters by Organocatalytic Fluorocyclization, *J. Am. Chem. Soc.*, 2020,

142, 20048–20057; (*j*) K. Yoshida, K. Okada, H. Ueda and H. Tokuyama, A Concise Enantioselective Total Synthesis of (−)-Deoxoapodine, *Angew. Chem., Int. Ed.*, 2020, **59**, 23089–23093 For 6-*exo* halo-cycloetherification: (*k*) P. Zhou, Y. Cai, X. Zhong, W. Luo, T. Kang, J. Li, X. Liu, L. Lin and X. Feng, Catalytic Asymmetric Intra- and Intermolecular Haloetherification of Enones: An Efficient Approach to (−)-Centrolobine, *ACS Catal.*, 2016, **6**, 7778–7783 For 6-*endo* halo-cycloetherification: (*l*) M. L. Landry, G. M. McKenna and N. Z. Burns, Enantioselective Synthesis of Azamerone, *J. Am. Chem. Soc.*, 2019, **141**, 2867–2871 For 3-*exo* halo-cycloetherification: (*m*) Z. Shen, X. Pan, Y. Lai, J. Hu, X. Wan, X. Li, H. Zhang and W. Xie, Chiral Ion-pair Organocatalyst Promotes Highly Enantioselective 3-exo Iodo-cycloetherification of Allyl Alcohols, *Chem. Sci.*, 2015, **6**, 6986–6990.

32 (*a*) C. Enzell and H. Erdtman, The Chemistry of the Natural Order Cupressales—XXI: Cuparene and Cuparenic Acid, Two Sesquiterpenic Compounds with a New Carbon Skeleton, *Tetrahedron*, 1958, **4**, 361–368; (*b*) Y. Asakawa, R. Matsuda, W. B. Schofield and S. R. Gradstein, Cuparane- and isocuparane-type sesquiterpenoids in liverworts of the genus Herbertus, *Phytochemistry*, 1982, **21**, 2471–2473; (*c*) H. Irita, T. Hashimoto, Y. Fukuyama and Y. Asakawa, Herbertane-type sesquiterpenoids from the liverwort Herbertus sakuraii, *Phytochemistry*, 2000, **55**, 247–253.

33 For selected recent examples: (*a*) B. R. Aavula, Q. Cui and E. A. Mash, Synthesis of (S)-(-)-beta-Cuparenone and (S)-(-)-Cuparene, *Tetrahedron: Asymmetry*, 2000, **11**, 4681–4686; (*b*) T. Cohen, T. Kreethadumrongdat, X. J. Liu and V. Kulkarni, Use of Aromatic Radical-anions in the Absence of THF. Tandem Formation and Cyclization of Benzyllithiums Derived From the Attack of Homo- and Bishomoallyllithiums on alpha-Methylstyrenes: Two-pot Synthesis of Cuparene, *J. Am. Chem. Soc.*, 2001, **123**, 3478–3483; (*c*) F. G. Favaloro, C. A. Goudreau, B. P. Mundy, T. Poon, S. V. Slobodzian and B. L. Jensen, Natural Products via Reetz Chemistry Synthesis of (+ /-)-Cuparene, *Synth. Commun.*, 2001, **31**, 1847–1855; (*d*) R. S. Grainger and A. Patel, Photomediated Asymmetric Synthesis of (2)-Cuparene, *Chem. Commun.*, 2003, 1072–1073; (*e*) A. Nayek, M. G. B. Drew and S. Ghosh, Convenient Route to Enantiopure aryl Cyclopentanes via Diels-Alder reaction of Asymmetric Dienes. Total synthesis of (+)-Herbertene and (+)-Cuparene, *Tetrahedron*, 2003, **59**, 5175–5181; (*f*) T. Paul, A. Pal and D. Mukherjee, Stereocontrolled total Synthesis of (+ /-)-Tochuinyl Acetate and Facile Total Synthesis of (+ /-)-alpha-Cuparenone and (+ /-)-Cuparene, *ARKIVOC*, 2003, 104–114; (*g*) R. J. Boxall, L. Ferris and R. S. Grainger, Synthesis of C-13 Oxidised Cuparene and Herbertane Sesquiterpenes via a Paterno-Büchi Photocyclisation-Oxetane Fragmentation Strategy: Total Synthesis of 1,13-Herbertenediol, *Synlett*, 2004, 2379–2381; (*h*) F. Secci, A. Frongia, J. Ollivier and P. P. Piras, Convenient Formal Synthesis of (+ /-)-Cuparene, (+ /-)-Enokipodins A and B, and (+ /-)-Cuparene-1,4-quinone, *Synthesis*, 2007, 999–1002; (*i*) A. Srikrishna, G. Satyanarayana and K. R. Prasad, RCM-Based Approach to (+ /-)-Cuparene, *Synth. Commun.*, 2007, **37**, 1511–1516; (*j*) M. R. Luderer, M. J. Mealy and W. F. Bailey, Asymmetric Intramolecular Carbolithiation of Achiral Substrates: Synthesis of Enantioenriched (R)-(+)-Cuparene and (R)-(+)-Herbertene, *J. Org. Chem.*, 2014, **79**, 10722–10726.

34 X. Yu, J. Hu, Z. Shen, H. Zhang, J.-M. Gao and W. Xie, Stereospecific Construction of Contiguous Quaternary All-Carbon Centers by Oxidative Ring Contraction, *Angew. Chem., Int. Ed.*, 2017, **56**, 350–353.

35 L. V. Alegrio, R. Braz-filho and O. R. Gottlieb, Diarylheptanoids and Isoflavonoids from Centrolobium Species, *Phytochemistry*, 1989, **28**, 2359–2362.

36 A.-M. Bui, B. C. Das and P. Potier, Étude Chimiotaxonomique de Hazunta Modesta, *Phytochemistry*, 1980, **19**, 1473–1475.

37 (*a*) G. W. Gribble, Naturally Occurring Organohalogen Compounds, *Acc. Chem. Res.*, 1998, **31**, 141–152; (*b*) F. H. Vaillancourt, E. Yeh, D. A. Vosburg, S. Garneau-Tsodikova and C. T. Walsh, Nature's Inventory of Halogenation Catalysts: Oxidative Strategies Predominate, *Chem. Rev.*, 2006, **106**, 3364–3378.

38 J. Y. Cho, H. C. Kwon, P. G. Williams, P. R. Jensen and W. Fenical, Azamerone, a Terpenoid Phthalazinone from a Marine-Derived Bacterium Related to the Genus Streptomyces (Actinomycetales), *Org. Lett.*, 2006, **8**, 2471–2474.

39 For 5-*exo* halolactonization: (*a*) M. Wang, L. X. Gao, W. P. Mai, A. X. Xia, F. Wang and S. B. Zhang, Enantioselective Iodolactonization Catalyzed by Chiral Quaternary Ammonium Salts Derived from Cinchonidine, *J. Org. Chem.*, 2004, **69**, 2874–2876; (*b*) Z. Ning, R. Jin, J. Ding and L. Gao, Enantioselective Iodolactonizations of 4-Pentenoic Acid Derivatives Mediated by Chiral Salen-Co (II) Complex, *Synlett*, 2009, 2291–2294; (*c*) D. C. Whitehead, R. Yousefi, A. Jaganathan and B. Borhan, An Organocatalytic Asymmetric Chlorolactonization, *J. Am. Chem. Soc.*, 2010, **132**, 3298–3300; (*d*) L. Zhou, C. K. Tan, X. Jiang, F. Chen and Y.-Y. Yeung, Asymmetric Bromolactonization Using Amino-thiocarbamate Catalyst, *J. Am. Chem. Soc.*, 2010, **132**, 15474–15476; (*e*) X. Jiang, C. K. Tan, L. Zhou and Y.-Y. Yeung, Enantioselective Bromolactonization Using an S-Alkyl Thiocarbamate Catalyst, *Angew. Chem., Int. Ed.*, 2012, **51**, 7771–7775; (*f*) C. K. Tan, C. Le and Y.-Y. Yeung, Enantioselective Bromolactonization of cis-1,2-Disubstituted Olefinic Acids Using an Amino-Thiocarbamate Catalyst, *Chem. Commun.*, 2012, **48**, 5793–5795; (*g*) D. H. Paull, C. Fang, J. R. Donald, A. D. Pansick and S. F. Martin, Bifunctional Catalyst Promotes Highly Enantioselective Bromolactonizations To Generate Stereogenic C–Br Bonds, *J. Am. Chem. Soc.*, 2012, **134**, 11128–11131; (*h*) W. Zhang, N. Liu, C. M. Schienebeck, K. Decloux, S. Zheng, J. B. Werness and W. Tang, Catalytic Enantioselective Halolactonization of Enynes and Alkenes, *Chem. – Eur. J.*, 2012, **18**, 7296–7305; (*i*) X. Han, C. Dong and H.-B. Zhou, C3-Symmetric Cinchonine-Squaramide-

Catalyzed Asymmetric Chlorolactonization of Styrene-Type Carboxylic Acids with 1,3-Dichloro-5,5-dimethylhydantoin: An Efficient Method to Chiral Isochroman-1-ones, *Adv. Synth. Catal.*, 2014, **356**, 1275–1280; (*j*) H. Nakatsuji, Y. Sawamura, A. Sakakura and K. Ishihara, Cooperative Activation with Chiral Nucleophilic Catalysts and N-Haloimides: Enantioselective Iodolactonization of 4-Arylmethyl-4-pentenoic Acids, *Angew. Chem., Int. Ed.*, 2014, **53**, 6974–6977; (*k*) H. Egami, J. Asada, K. Sato, D. Hashizume, Y. Kawato and Y. Hamashima, Asymmetric Fluorolactonization with a Bifunctional Hydroxyl Carboxylate Catalyst, *J. Am. Chem. Soc.*, 2015, **137**, 10132–10135; (*l*) M. T. Knowe, M. W. Danneman, S. Sun, M. Pink and J. N. Johnston, Biomimetic Desymmetrization of a Carboxylic Acid, *J. Am. Chem. Soc.*, 2018, **140**, 1998–2001; (*m*) T. Arai, K. Horigane, O. Watanabe, J. Kakino, N. Sugiyama, H. Makino, Y. Kamei, S. Yabe and M. Yamanaka, Association of Halogen Bonding and Hydrogen Bonding in Metal Acetate-Catalyzed Asymmetric Halolactonization, *iScience*, 2019, **12**, 280–292; (*n*) Y.-C. Chan, X. Wang, Y.-P. Lam, J. Wong, Y.-L. S. Tse and Y.-Y. Yeung, A Catalyst-Controlled Enantiodivergent Bromolactonization, *J. Am. Chem. Soc.*, 2021, **143**, 12745–11275 For 6-*exo* halolactonization: (*o*) K. Murai, T. Matsushita, A. Nakamura, S. Fukushima, M. Shimura and H. Fujioka, Asymmetric Bromolactonization Catalyzed by a C3-Symmetric Chiral Trisimidazoline, *Angew. Chem., Int. Ed.*, 2010, **49**, 9174–9177; (*p*) G. E. Veitch and E. N. Jacobsen, Tertiary Aminourea-Catalyzed Enantioselective Iodolactonization, *Angew. Chem., Int. Ed.*, 2010, **49**, 7332–7335; (*q*) M. C. Dobish and J. N. Johnston, Achiral Counterion Control of Enantioselectivity in a Brønsted Acid-Catalyzed Iodolactonization, *J. Am. Chem. Soc.*, 2012, **134**, 6068–6071; (*r*) J. E. Tungen, J. M. J. Nolsøe and T. V. Hansen, Asymmetric Iodolactonization Utilizing Chiral Squaramides, *Org. Lett.*, 2012, **14**, 5884–5887 For 6-*endo* halolactonization: (*s*) C. K. Tan, L. Zhou and Y.-Y. Yeung, Aminothiocarbamate-Catalyzed Asymmetric Bromolactonization of 1,2-Disubstituted Olefinic Acids, *Org. Lett.*, 2011, **13**, 2738–2741; (*t*) E. M. Woerly, S. M. Banik and E. N. Jacobsen, Enantioselective, Catalytic Fluorolactonization Reactions with a Nucleophilic Fluoride Source, *J. Am. Chem. Soc.*, 2016, **138**, 13858–13861 For 4-*exo* halolactonization: (*u*) K. Ikeuchi, S. Ido, S. Yoshimura, T. Asakawa, M. Inai, Y. Hamashima and T. Kan, Catalytic Desymmetrization of Cyclohexadienes by Asymmetric Bromolactonization, *Org. Lett.*, 2012, **14**, 6016–6019.

40 M. Aursnes, J. E. Tungen and T. V. Hansen, Enantioselective Organocatalyzed Bromolactonizations: Applications in Natural Product Synthesis, *J. Org. Chem.*, 2016, **81**, 8287–8295.

41 (*a*) B. A. Bierl, M. Beroza and C. W. Collier, Potent Sex Attractant of the Gypsy Moth: Its Isolation, Identification, and Synthesis, *Science*, 1970, **170**, 87–89; (*b*) A. M. Liebhold and P. C. Tobin, Population Ecology of Insect Invasions and Their Management, *Annu. Rev. Entomol.*, 2008, **53**, 387–408.

42 D. W. Klosowski and S. F. Martin, Synthesis of (+)-Disparlure via Enantioselective Iodolactonization, *Org. Lett.*, 2018, **20**, 1269–1271.

43 For review: (*a*) A. Sakakura and K. Ishihara, Stereoselective Electrophilic Cyclization, *Chem. Rec.*, 2015, **15**, 728–742; (*b*) A. C. A. D'Hollander, L. Peilleron, T. D. Grayfer and K. Cariou, Halonium-Induced Polyene Cyclizations, *Synthesis*, 2019, **51**, 1753–1769 For selected examples: (*c*) E. E. van Tamelen and E. J. Hessler, The Direct Brominative Cyclization of Methyl Farnesate, *Chem. Commun.*, 1966, 411–413; (*d*) A. G. González, J. D. Martín, C. Pérez and M. A. Ramírez, Bromonium ion-induced Cyclization of Methyl Farnesate: Application to the Synthesis of Snyderol, *Tetrahedron Lett.*, 1976, **17**, 137–138; (*e*) L. E. Wolinsky and D. J. Faulkner, Biomimetic Approach to the Synthesis of Laurencia Metabolites. Synthesis of 10-bromo-alpha-Chamigrene, *J. Org. Chem.*, 1976, **41**, 597–600; (*f*) Y. Yamaguchi, T. Uyehara and T. Kato, Biogenetic type synthesis of (±)-concinndiol and (±)-aplysin 20, *Tetrahedron Lett.*, 1985, **26**, 343–346; (*g*) J. Barluenga, M. Trincado, E. Rubio and J. M. González, Intramolecular Arylation Reactions of Alkenes: A Flexible Approach to Chromans and Tetrahydroquinoline Derivatives, *J. Am. Chem. Soc.*, 2004, **126**, 3416–3417; (*h*) S. A. Snyder and D. S. Treitler, $Et_2SBr\cdot SbCl_5Br$: An Effective Reagent for Direct Bromonium-Induced Polyene Cyclizations, *Angew. Chem., Int. Ed.*, 2009, **48**, 7899–7903; (*i*) S. A. Snyder, D. S. Treitler and A. P. Brucks, Simple Reagents for Direct Halonium-Induced Polyene Cyclizations, *J. Am. Chem. Soc.*, 2010, **132**, 14303–14314.

44 T. Sakan, Y. Hayashi, Y. Honda, T. Shono, M. Nakajima and M. Kato, Structure and Stereochemistry of Boschniakine, Boschnialactone, and Boschnialinic acid, an Oxidation Product of Boschnialactone, *Tetrahedron*, 1967, **23**, 4635–4652.

45 T. Inoue, O. Kitagawa, A. Saito and T. Taguchi, Catalytic Asymmetric Iodocarbocyclization Reaction of 4-Alkenylmalonates and Its Application to Enantiotopic Group Selective Reaction, *J. Org. Chem.*, 1997, **62**, 7384–7389.

46 (*a*) A. Sakakura, A. Ukai and K. Ishihara, Enantioselective Halocyclization Of Polyprenoids Induced By Nucleophilic Phosphoramidites, *Nature*, 2007, **445**, 900–903; (*b*) Y. Sawamura, Y. Ogura, H. Nakatsuji, A. Sakakura and K. Ishihara, Enantioselective Bromocyclization of 2-Geranylphenols induced by Chiral Phosphite–urea Bifunctional Catalysts, *Chem. Commun.*, 2016, **52**, 6068–6071.

47 R. C. Samanta and H. Yamamoto, Catalytic Asymmetric Bromocyclization of Polyenes, *J. Am. Chem. Soc.*, 2017, **139**, 1460–1463.

48 Q. Cao, J. Luo and X. Zhao, Chiral Sulfide Catalysis for Desymmetrizing Enantioselective Chlorination, *Angew. Chem., Int. Ed.*, 2019, **58**, 1315–1319.

49 J. Luo, Y. Zhang, F. Zhong and X. Zhao, Catalytic Enantioselective Construction of Chiral Benzo-Fused N-Heterocycles through Friedel–Crafts-Type Electrophilic Chlorination, *CCS Chem.*, 2021, DOI: 10.31635/ccschem.021.202100777.