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Enantioselective formation of quaternary carbon stereocenters in natural product synthesis: a recent update

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Covering: 2013–2018

Natural products bearing quaternary carbon stereocenters have attracted tremendous interest from the synthetic community due to their diverse biological activities and fascinating molecular architectures. However, the construction of these molecules in an enantioselective fashion remains a long-standing challenge because of the lack of efficient asymmetric catalytic methods for installing these motifs. The rapid progress in the development of new-generation efficient chiral catalysts has opened the door for several asymmetric reactions, such as Michael addition, dearomative cyclization, polyene cyclization, α-arylation, cycloaddition, allylation, for the construction of quaternary carbon stereocenters in a highly enantioselective fashion. These asymmetric catalytic methods have greatly facilitated the synthesis of complex natural products with improved output and overall efficiency. In this concise review, we highlight the progress in the last six years in complex natural product synthesis, in which at least one quaternary carbon stereocenter has been constructed *via* asymmetric catalytic technologies, with particular emphasis on the analysis of the stereochemical model of each enantioselective transformation.

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1 Introduction

Quaternary carbon stereocenters ubiquitously exist in numerous natural products, which exhibit significant and diverse bioactivities. Fig. 1 shows some biologically active polycyclic alkaloids, terpenes, and polyketides that bear one or

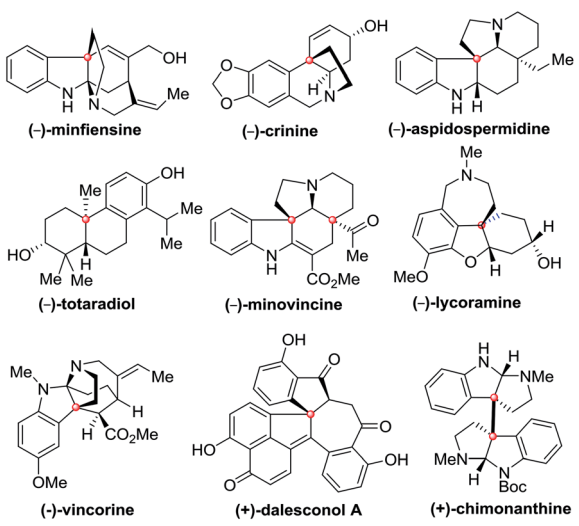

Fig. 1 Some natural products containing quaternary carbon stereocenters.

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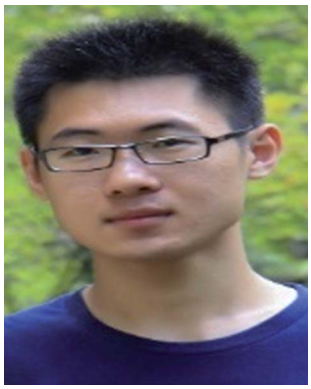
more quaternary carbon stereocenters in their structures. For example, (−)-minfiensine,[1] one of the strychnos alkaloids isolated from *Strychnos minfiensis*, possesses potent anticancer activity; (−)-crinine,[2] an *Amaryllidaceae* alkaloid with a 5,10*b*-ethanophenathridine skeleton, also shows remarkable anticancer properties; (−)-totaradiol[3] is a diterpene natural product that exhibits good antimicrobial properties; (−)-dalesconol A[4] is a unusual polyketide that exhibits strong immunosuppressive activities; and several other alkaloids such as (−)-minovincine, (+)-chimonanthine, (−)-aspidospermidine, and (−)-vincorine all exhibit various biological properties including anticancer, antimalarial, and anti-inflammatory activities.[5]

However, the efficient synthesis of chiral natural products bearing quaternary carbon stereocenters remain a significant challenge. Because of the generally higher steric hindrance of chiral quaternary carbons compared to other chiral units, the efficient asymmetric construction of these chiral motifs is much more difficult and only a limited number of enantioselective transformations are available or applicable to complex natural product synthesis. Despite the tremendous development on a number of asymmetric transformations such as asymmetric alkylation, radical reaction, photochemical reaction, pericyclic reaction, and many others toward natural product synthesis in the last two decades,[6] their synthetic efficiency is hampered by the scope limitations and deficiency in enantioselective control.

In the past five years, a few highly enantioselective catalytic reactions have been developed involving asymmetric Michael addition, asymmetric cycloaddition, asymmetric dearomative cyclization, and others, which have enabled the efficient construction of quaternary carbon stereocenters applicable to natural product synthesis. The implementation of these asymmetric catalytic methods has not only improved the synthetic



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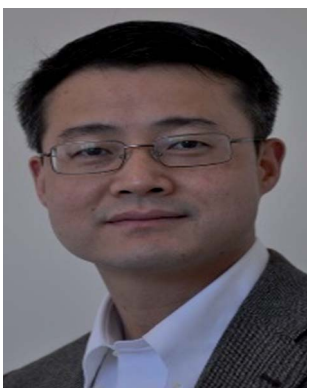


Prof. Wenjun Tang was born in 1974 in Zhejiang Province, China. He received his B. Eng. degree in 1995 from East China University of Sciences and Technology, his M.S. in 1998 from SIOC, CAS, and his PhD in 2003 from the Pennsylvania State University. After two year of postdoctoral research at the Scripps Research Institute, he worked for six years as a Process Chemist at Boehringer Ingelheim Pharmaceuticals Inc. In 2011, he became a Research Professor at SIOC. His research interests are in the areas of asymmetric catalysis, total synthesis of natural products, and development of efficient chemical processes.

output and overall efficiency of their total synthesis, but also allowed their access in ample quantities, further facilitating their biological studies.

The purpose of this review is to highlight the latest advances in asymmetric catalytic methods for the construction of quaternary carbon stereocenters and their applications in the total synthesis of several bioactive complex natural products. An in-depth analysis on each enantioselective transformation is provided, with particular emphasis on its stereochemical translation. It is our hope that this analysis will stimulate the development and application of asymmetric catalytic transformations, which can significantly improve the overall efficiency of natural product synthesis.

2 Asymmetric catalytic methods for the construction of quaternary carbon stereocenters

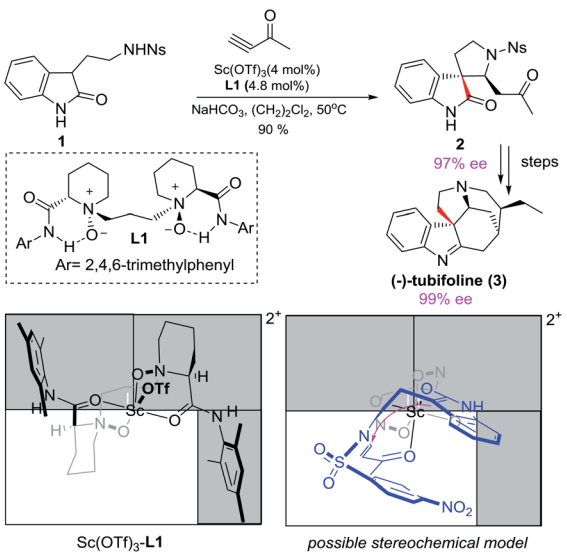
Despite the development of several asymmetric catalytic reactions, only a few efficient catalytic methods are available for the construction of quaternary carbon stereocenters. More strikingly, even less methods are applicable to natural product synthesis due to the limitation of the substrate scope. In the following sections, we summarize the enantioselective strategies that have been successfully employed in the synthesis of bioactive natural products bearing quaternary carbon stereocenters, with the examples covering the period of 2013–2018. Specifically, the recent applications of asymmetric Michael addition, asymmetric dearomative cyclization, asymmetric polyene cyclization, α-arylation, cycloaddition, allylation, and some others, in the synthesis of chiral natural products are detailed.

2.1 Asymmetric Michael addition

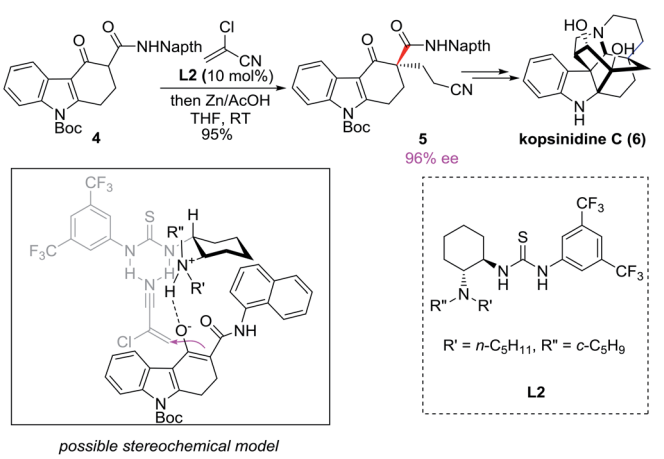
Asymmetric Michael addition is an important and powerful method for the enantioselective construction of quaternary carbon stereocenters. During this process, a quaternary carbon center is generated when an α,α-disubstituted enolate or equivalent adds to a Michael acceptor or a carbon nucleophile adds to a β,β-disubstituted Michael acceptor. Interestingly, the former transformation can be catalyzed by either a chiral organocatalyst or metal catalyst, which has been greatly studied recently. With the development of chiral *N*,*N*′-dioxides and chiral thiourea catalysts, several efficient asymmetric Michal additions have been observed in natural product synthesis.

In 2018, Xie and coworkers[7] developed a highly enantioselective tandem Michael addition of tryptamine-derived oxindoles to alkynones (Scheme 1) using a chiral Sc(OTf)$_3$-*N*,*N*′-dioxide complex Sc(OTf)$_3$-**L1** as the catalyst, allowing the facile preparation of enantioenriched spiro[pyrrolidine-3,3′-oxindole] compounds. Based on Feng's studies,[8] a stereochemical model of an Sc(OTf)$_3$-**L1** complex for catalysing the intramolecular Michael addition of the adduct of oxindole **1** with but-3-yn-2-one was proposed, where the *N*,*N*′-dioxide **L1** behaves as a neutral tetradentate ligand coordinating to the scandium center through two oxygens of *N*-oxides and two oxygens of the two amide groups on the opposite sides in a bibrachial manner. The apical site of the Sc(OTf)$_3$-**L1** complex where the triflate group resides together with the unoccupied site at the bottom provide opportunities for substrate coordination. There is a great steric hindrance in the top two quadrants as well as the right bottom quadrant. During the tandem Michael addition process, **1** presumably proceeds *via* the 1st Michael addition with but-3-yn-2-one in the presence of a base to form an enamide adduct. Coordination of the adduct to the scandium center in the presence of a base is proposed through double coordination. A scandium enolate is formed, in which the amide oxygen presumably coordinates at the apical site, and the oxygen of the unsaturated ketone coordinates at the bottom position. Intramolecular attack of the scandium enolate to the unsaturated ketone forms the observed spirocycle **2**.

This novel reaction was successfully employed for the asymmetric total synthesis of three strychnos alkaloids, (−)-dehydrotubifoline, (−)-tubifoline, and (−)-tubifolidine, in 10 to 11 steps (Scheme 1). The synthesis started with



Scheme 1 Xie's synthesis of (−)-tubifoline.



Scheme 2 Ma's synthesis of kopsinidine C.

preparation of spirooxindole **2** in a decagram scale in 90% yield and 97% ee. After several transformations to form two additional rings, (−)-tubifoline (**3**) was furnished in 97% ee.[9]

In the same year, Ma and coworkers[10] discovered a bifunctional thiourea catalyst for the highly enantioselective construction of 3,3-disubstituted carbazolones through the efficient Michael addition of carbazolone **4** to 2-chloroacrylonitrile (Scheme 2). They succeeded in scaling up the reaction to 9 g with excellent yield and enantioselectivity at 5 mol% catalytic loading. The role of the thiourea catalyst is to activate both substrates and bring them in close proximity through hydrogen bonding, allowing the reaction to occur. Thus, fine tuning the catalyst structure is pivotal for both reactivity and enantioselectivity.[11,12] Thus, the authors prepared a series of thioureas with different substituents at either the amine part or the aromatic unit.[12,13] The results revealed that a subtle structural change in the amine part not only affected the reaction rate, but also influenced the enantioselectivity. The best outcome in enantioselectivity was observed when the *n*-pentyl-substituted catalyst was employed.

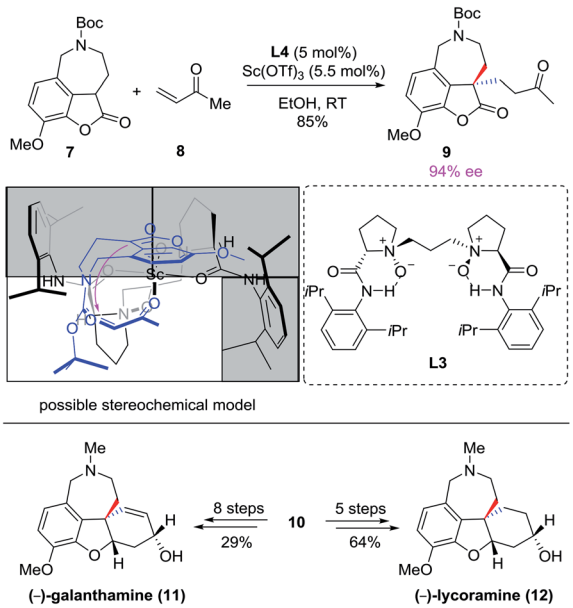
A stereochemical model of the transformation was proposed as depicted in Scheme 2. 2-Chloroacrylonitrile was presumably activated by interaction with the thiourea part of **L2** through hydrogen-bonding interaction, while the β-keto carboxamide **4** was converted to an enolate form by reacting the tertiary amine unit of **L2** through ionic interaction. Attack of the enolate to the acrylonitrile within the ternary complex formed the Michael product, which after reduction by treatment with Zn/AcOH provided **5** in 96% ee and 95% yield. The asymmetric reaction was applied to the total synthesis of three *Kopsia* alkaloids, namely, demethoxycarbonylkopsin, 5,22-dioxokopsane, and kopsinidine C. During the synthetic sequence, an Mn^{III}-mediated oxidative cyclization was conducted to install the cage-like core architecture of **6**, which proved to be a reliable strategy to construct the indole C3 quaternary stereocenter that exists in the structures of numerous indole alkaloids.

(−)-Galanthamine (**11**) is a representative member of the *Amaryllidaceae* alkaloids, which has been clinically used for the treatment of Alzheimer's disease and other memory impairments.[14] (−)-Lycoramine (**12**) has similar but less potent activity as an acetylcholinesterase inhibitor and an allosteric potentiating ligand.[15] In 2015, Jia's group[16] developed a palladium-catalyzed intramolecular Larock annulation for the rapid preparation of 3,4-fused benzofurans, which was successfully applied to the synthesis of (−)-galanthamine (**11**) and (−)-lycoramine (**12**) (Scheme 3). For the enantioselective construction of the quaternary carbon stereocenter, an asymmetric Michael addition between benzofuranone **7** and MVK (**8**) was implemented by employing the chiral *N*,*N*′-dioxide ligand **L3** (5 mol%) and $Sc(OTf)_3$ (5.5 mol%) as the catalyst, and the desired product **10** was obtained in 85% yield with 94% ee. A stereochemical model of the asymmetric Michael addition with $Sc(OTf)_3$-**L3** is depicted in Scheme 3, where the enolate of **7** coordinates to the scandium center at the apical position and MVK coordinates at the open low left quadrant. With **10** in hand, Jia completed the synthesis of (−)-galanthamine (**11**) after eight steps in 29% overall yield and (−)-lycoramine (**12**) after five steps in 64% overall yield.

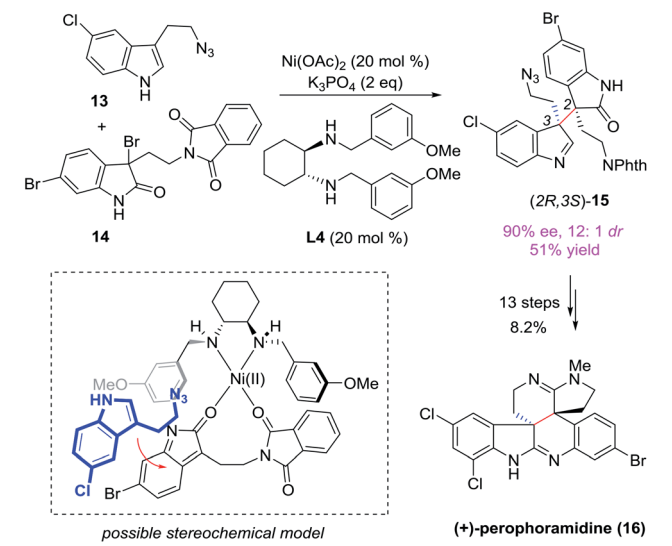
It is evident that both organo- and metal-catalyzed asymmetric Michael additions will collectively provide a wide spectrum of complex and highly enantioselective Michael adducts bearing quaternary carbon stereocenters that can be applied extensively in the total synthesis of numerous complex natural products.

2.2 Asymmetric dearomatization

Chemists have taken significant efforts in developing new and efficient asymmetric catalytic synthetic methods and strategies to synthesize complex polycyclic alkaloids, terpenes, and polyketides.[17] Because of the easy accessibility of arene compounds,



Scheme 3 Jia's synthesis of (−)-galanthamine and (−)-lycoramine.



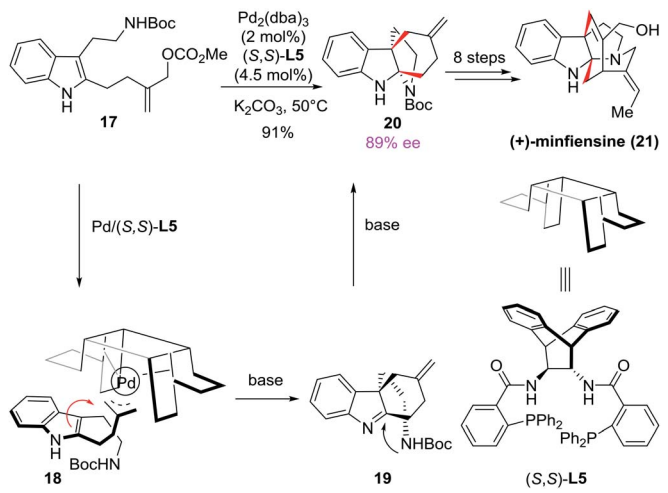
Scheme 4 Wang's synthesis of (+)-perophoramidine.

the recent development on asymmetric dearomatization including asymmetric dearomative alkylation and arylation has attracted significant interest and the applications of these methods have led to the concise and elegant synthesis of several complex natural products.[18]

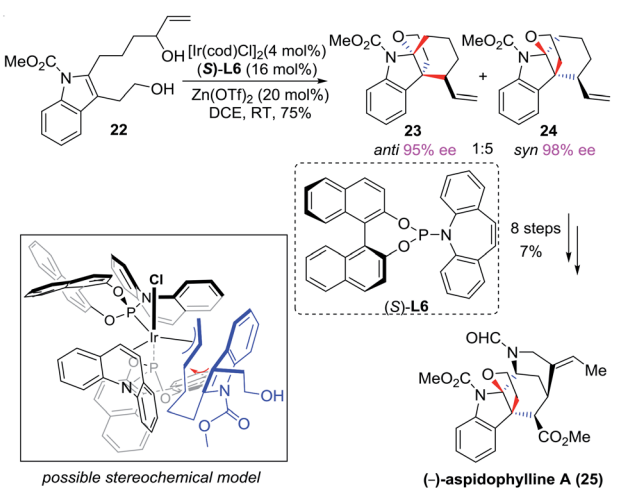
2.2.1 Asymmetric dearomative alkylation. (+)-Perophoramidine[19] is an architecturally intriguing natural product that has a multicyclic skeleton containing two vicinal quaternary centers. In 2013, Wang's group[20] developed an asymmetric nickel(II)-catalyzed alkylation of 3-bromooxindoles with 3-substituted indoles, leading to the formation of indolenines containing two vicinal chiral quaternary centers (Scheme 4). The reaction of 3-substituted indole **19** and 3-bromooxindole **20** proceeded with K_3PO_4 (2 equiv.) as the base in the presence of $Ni(OAc)_2$/**L5** (10 mol%, 1 : 1) and molecular sieves (5 Å), and the coupling adduct **21** was isolated in 51% yield and 92% ee with a diastereomeric ratio of 12 : 1. The stereochemical model of the dearomative alkylation is proposed in Scheme 4, where the bidentate chiral diamine **L4** coordinates to the nickel(II) center through a chelating fashion. Under basic conditions, 3-bromooxindole **14** after elimination of HBr forms an indolone intermediate, which is presumably coordinated with the nickel catalyst through two carbonyl groups. Next, the nucleophilic attack of indole **13** determines the stereochemistry of both vicinal quaternary centers. The left bottom face is apparently blocked by an aryl group from the ligand **L4**. Thus, the nucleophilic attack of **13** is proposed from the top face with a maximum secondary aryl–aryl interaction, leading to the formation of (2*R*,3*S*)-**15**. After 13 steps from **15**, (+)-perophoramidine (**16**) was obtained in 8.2% overall yield.

In 2016, Jiao and coworkers[21] developed a concise and enantioselective synthesis of (+)-minfiensine based on the asymmetric catalytic dearomatization of indole (Scheme 5). In the presence of $[Pd_2(dba)_3]$ (2 mol%) and (*S*,*S*)-**L5** (4.5 mol%) as the catalysts, indole **17** proceeded through a dearomative cyclization cascade, providing the tetracyclic product **20** in 91% yield with 89% ee. Mechanistically, the allylic carbonate **17** was first converted to the π-allylic palladium complex **18**, which underwent intramolecular nucleophilic attack in the presence of a base. The resulting imine component **19** was further attacked by the NHBoc moiety, forming the bridged tetracyclic product **20**. The stereochemistry of the quaternary center was determined during the intramolecular attack of the indole component to the π-allylic Pd moiety, which was fully controlled by the chiral pocket established by the Pd-(*S*,*S*)-**L5** complex. After an additional eight steps from **20**, the elegant total synthesis of (+)-minfiensine (**21**) was accomplished. This asymmetric dearomative cyclization cascade enabled the efficient syntheses of several structure-related polycyclic natural products.

(−)-Aspidophylline A (**25**)[22] was isolated from *Malayan Kopsia singapurensis* by Kam and coworkers in 2007 and was found to have significant biological activity. Its structure features a tricyclic furoindoline motif, a complex multi-substituted cyclohexyl ring containing five contiguous stereocenters, and a bridged [3,3,1]bicycle. In 2016, Yang's group[23] developed an asymmetric Ir-catalyzed dearomative cyclization cascade for the first enantioselective total synthesis of (−)-aspidophylline A (**25**) (Scheme 6). 2,3-Disubstituted indole derivative **22** was treated with $[Ir(cod)Cl]_2$ (4 mol%) and (*S*)-**L6** (16 mol%) as catalysts in the presence of $Zn(OTf)_2$ (20 mol%) to form the cyclization products **23** (95% ee) and **24** (98% ee) in a highly enantioselective fashion with a ratio of 1 : 5 as an inseparable diastereomeric mixture (Scheme 6). Presumably, the allylic alcohol was first converted into a π-allylic iridium complex under the action of Ir-(*S*)-**L6**. This was followed by the intramolecular nucleophilic attack of the indole component to provide an imine intermediate bearing an quaternary center. A 2nd ring formation under acidic conditions formed the hemiketals **23** and **24**. The high enantioselectivities observed in both **23** and **24** can be explained by the stereochemical model shown in Scheme 6. The Ir complex was coordinated with a chlorine atom at the apical position, and two molecules of **L6**, with one chelating to the Ir center through both P and olefin coordination and the other coordinating alone through the P atom. Apparently, the top and left sites were occupied by the ligands, and the π-allylic moiety was only



Scheme 5 Jiao's synthesis of (+)-minfiensine.



Scheme 6 Yang's synthesis of (−)-aspidophylline A.

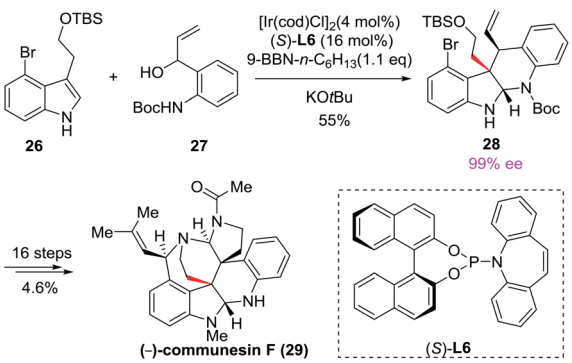
allowed to coordinate with Ir from the right-bottom site, leading to the formation of **23** and **24** in excellent enantioselectivities. Treatment of the mixture of **23** and **24** with OsO_4 removed the terminal vinyl group to give a single product, which after 8 steps furnished (−)-aspidophylline A (**25**) in a highly enantioselective fashion.

(−)-Communesin F (**29**) was isolated from marine and terrestrial *Penicillium* fungi, providing significant cytotoxicity and insecticidal activity.[24] Structurally, it has a challenging heptacyclic core, arrayed with five stereocenters, two of which are quaternary carbons. In 2007, Qin's group[25] reported the first total synthesis of (±)-communesin F *via* a cyclopropanation strategy.

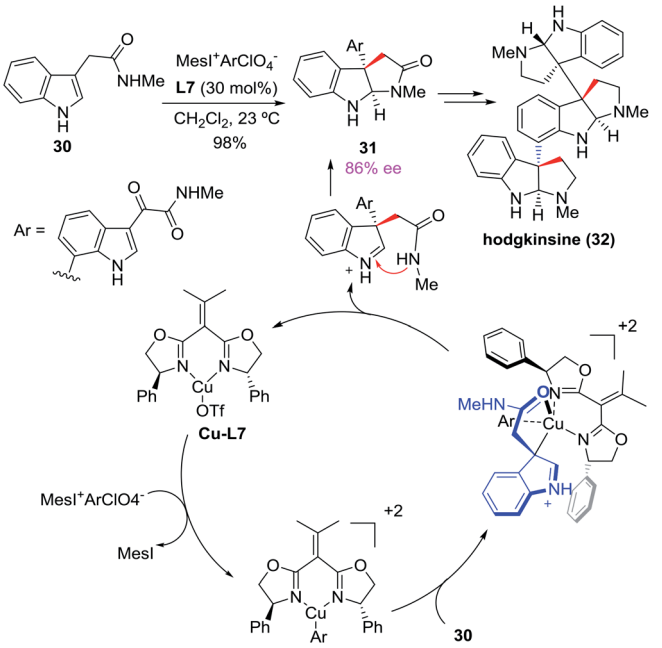
In 2010, Ma and coworkers[26] completed the first asymmetric synthesis of (−)-communesin F, employing an intramolecular oxidative coupling strategy. Recently, Yang group[27] reported the first asymmetric catalytic total synthesis of (−)-communesin F (Scheme 7). The key transformation was an iridium-catalyzed asymmetric intermolecular cascade cyclization. As illustrated in Scheme 7, with $[Ir(cod)Cl]_2$ (4 mol%) as the catalyst precursor and (*S*)-**L6** (16 mol%) as the ligand, the reaction between indole **26** and allylic alcohol **27** proceeded to give the dearomatized tetracyclic intermediate **28** in 55% yield and 99% ee with the use of 9-BBN-*n*-C_6H_{13} as an additive. A gram–scale reaction was also demonstrated, providing **28** (1.7 g) in excellent yield and enantioselectivity. Finally, the enantioselective total synthesis of the heptacyclic alkaloid (−)-communesin F (**29**) was accomplished after 16 steps from **28** in 4.6% overall yield.

2.2.2 Asymmetric dearomative arylation. The polypyrroloindolines, isolated primarily from shrubs of the genera *Chimonanthus*, *Calycanthus*, *Psychotria*, and *Hodgkinsonia*, are an interesting class of oligomeric natural products that have diverse therapeutic properties such as analgesic, antibacterial, antifungal, and antiviral activities.[28] Structurally, they are composed of multiple cyclotryptamine subunits. In 2017, MacMillan and co-workers[29] developed an asymmetric copper-catalyzed arylation/cyclization strategy for the total syntheses of a series of oligomeric polypyrroloindoline natural products (Scheme 8).

The critical enantioselective coupling between the nucleophilic tryptamide **30** and the electrophilic tryptamide iodonium $MesI^+ArClO_4^-$ was accomplished with the employment of the



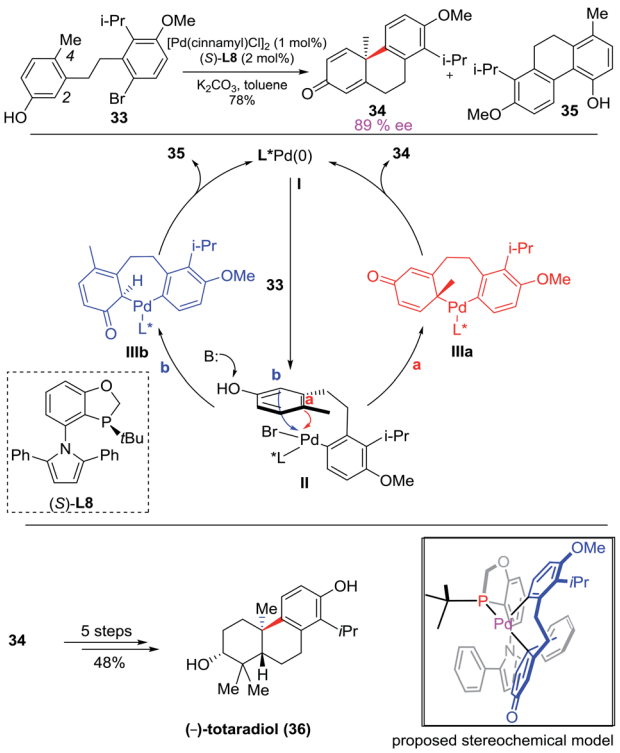
Scheme 7 Ma's synthesis of (−)-communesin F.



Scheme 8 MacMillan's synthesis of hodgkinsine.

chiral copper catalyst **Cu–L7** (30 mol%), leading to the formation of the pyrroloindoline–indole dimer **31** in 98% yield and 86% ee. Mechanistically, **Cu–L7** was firstly oxidatively added by $MesI^+ArClO_4^-$ to form an electrophilic Cu^{III}–Ar species. The nucleophilic tryptamide **30** then ligated to the Cu center through a chelating fashion, with the amide oxygen coordinating at the apical position and the indole part positioning at low-left corner, where less steric influence is available from the bisoxazoline ligand **L7**. Reductive elimination followed by ring formation gave rise to **31** in excellent enantioselectivity. MacMillan's group successfully applied this strategy to the enantioselective total synthesis of hodgkinsine **32**, hodgkinsine B, and several oligomeric polypyrroloindoline natural products, with high efficiency. The enantioselective copper-catalyzed arylation was scalable on a multigram scale.

Tang's group[30] reported an asymmetric palladium-catalyzed intramolecular dearomative arylation and a series of chiral phenanthrenone derivatives bearing quaternary centres were constructed in excellent enantioselectivities (Scheme 9). During this transformation, bromo phenol **33** was treated with a palladium precursor (2 mol% Pd) and the chiral monophosphorus ligand[30b] (*S*)-**L8** bearing a 2,5-diphenylpyrrole moiety (2 mol%) in the presence of potassium carbonate to deliver the chiral phenanthrenone **34** in 78% yield and 89% ee. Mechanistically, the Pd(II) complex **II** was formed after the oxidative addition step. Nucleophilic substitution in the presence of a base took place either at the 4-position of the phenol moiety (path a) to form **IIIa** leading to chiral phenanthrenone **34** or at the 2-position of the phenol moiety (path b) to form the achiral product **35**. Although **35** is thermodynamically more stable than **34**, the formation of **34** was kinetically more favorable in the presence of the Pd-(*S*)-**L8** catalyst. The stereochemical model in Scheme 9 at the reductive elimination step was provided to

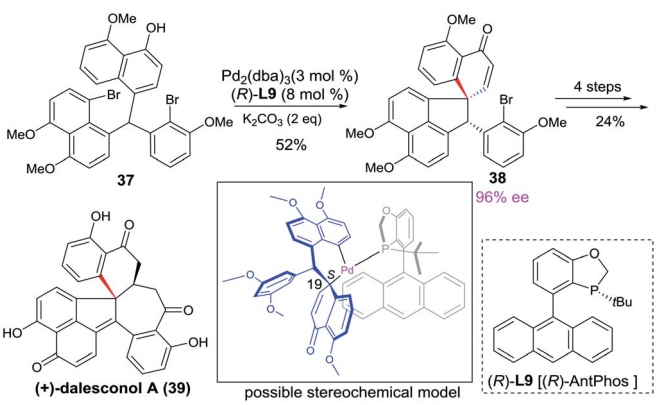


Scheme 9 Tang's synthesis of (−)-totaradiol.

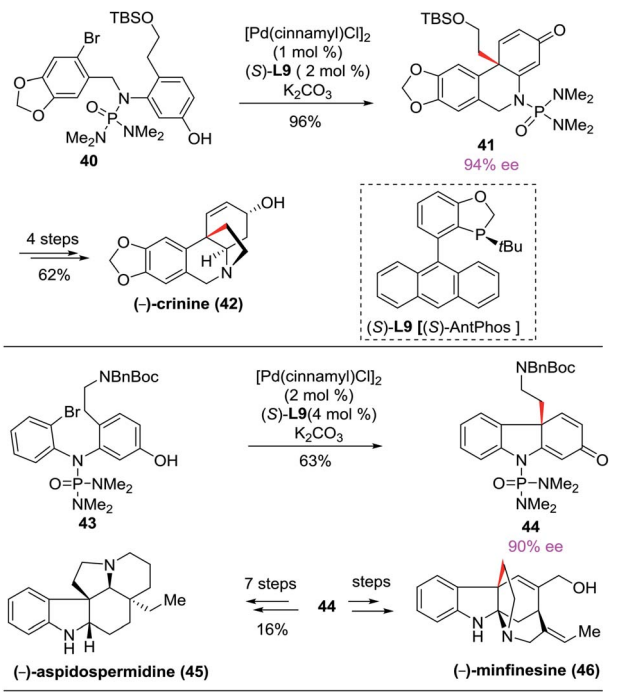
rationalize the observed high enantioselectivity. Apparently, the 2,5-diphenylpyrrole moiety of (*S*)-**L8** blocks the backside of the Pd(II) complex and its bulky *tert*-butyl group dictates the orientation of substrate coordination. Reductive elimination delivers the cyclization product **34** with the observed *R* configuration. Tang's group exploited this method in the enantioselective total synthesis of the antimicrobial (−)-totaradiol[4] (**36**), a tricyclic terpene bearing a quaternary carbon stereocenter (Scheme 9). After five steps from **34** in 48% overall yield, the enantioselective synthesis of (−)-totaradiol (**36**) was successfully accomplished.

Dalesconol A and B were initially isolated by Tan and coworkers[31] in 2008 from the mantis-associated fungus *Daldinia eschscholzii*, which were found to exhibit strong immunosuppressive activities. Both of them possess a highly dense carbon skeleton, which contains seven fused rings of various sizes and two stereocenters, including one sterically congested quaternary carbon. The enantioselective synthesis of dalesconol A or B has become a significant challenge.[32] In 2017, Tang and coworkers[33] accomplished the first enantioselective syntheses of (+)-dalesconol A and B in a highly efficient and concise manner (Scheme 10). The key intramolecular dearomative cyclization from dibromonaphthol **37** to spiro ketone **38** was realized with $Pd_2(dba)_3$ (3 mol%) as the catalyst precursor and (*R*)-**L9** [(*R*)-AntPhos] (8 mol%) as the chiral monophosphorus ligand. The cyclization product **38** was isolated in 52% yield and 96% ee as a single diastereomer. Four additional synthetic steps completed the total synthesis of (+)-dalesconol A (**39**) in 24% overall yield from **38**. The dearomative cyclization was proposed to proceed through the stereochemical model depicted in Scheme 10. The naphthol moiety of the substrate coordinated to the Pd center from the left side in order to avoid steric interaction with the *tert*-butyl group of the ligand. Since the back face was blocked by the anthracenyl group of the ligand, the naphthalenone moiety preferred to protrude upward, leading to the formation of **38** with the 19*S* configuration.

The same authors[34] also applied the enantioselective palladium-catalyzed dearomative cyclization in constructing the polycyclic skeletons of crinine,[2] aspidospermidine[35] (**45**), and minfiensine[1] (**46**) (Scheme 11). Bromophenol **40** was prepared for the enantioselective cyclization and the employment of the bulky *N*-phosphoramide protecting group [*N*-$P(O)(NMe_2)_2$] in its structure was crucial in the formation of the



Scheme 10 Tang's synthesis of (+)-dalesconol A.



Scheme 11 Tang's syntheses of (−)-crinine, (−)-aspidospermidine and (−)-minfiensine.

desired dearomative cyclization product. In the presence of [Pd(cinnamyl)Cl]$_2$ (1 mol%) and (*S*)-**L9** (2 mol%) and potassium carbonate as the base, the key cyclized intermediate **41** bearing a quaternary center was isolated in 96% yield and 94% ee. (−)-Crinine (**42**) was then successfully prepared from **41** in 62% overall yield through four transformations. Over 1 g of (−)-crinine was successfully obtained, demonstrating the practicality of this synthetic route and the palladium-catalyzed dearomative cyclization protocol. Under similar reaction conditions, the chiral carbazolone **44** was afforded in 63% yield and 90% ee from the cyclization substrate **43**. The enantioselective total synthesis of (−)-aspidospermidine (**45**) was accomplished from **44** through seven steps in 16% overall yield. Moreover, the formal synthesis of (−)-minfiensine (**46**) was achieved through eight steps from **44**.

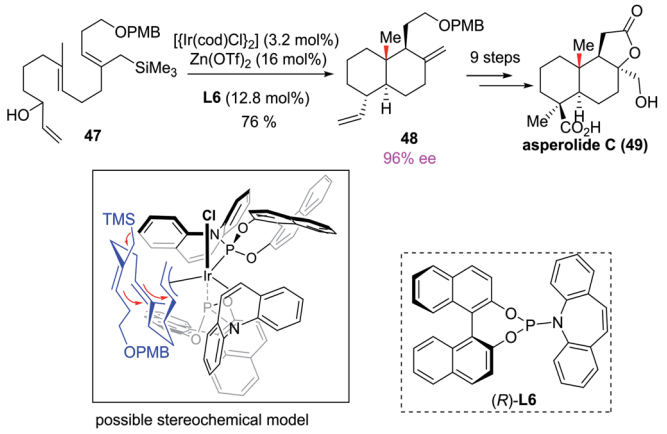
The work highlighted above captured some of the most impressive examples of asymmetric dearomative alkylation and arylation in the total synthesis of complex natural products. It is evident that this strategy provides a powerful method for constructing various multicyclic skeletons bearing at least one quaternary carbon stereocenter. More elegant syntheses with asymmetric dearomative transformations can be foreseen, which will undoubtedly promote the research and discovery of new therapeutic agents and drugs.

2.3 Asymmetric polyene cyclization

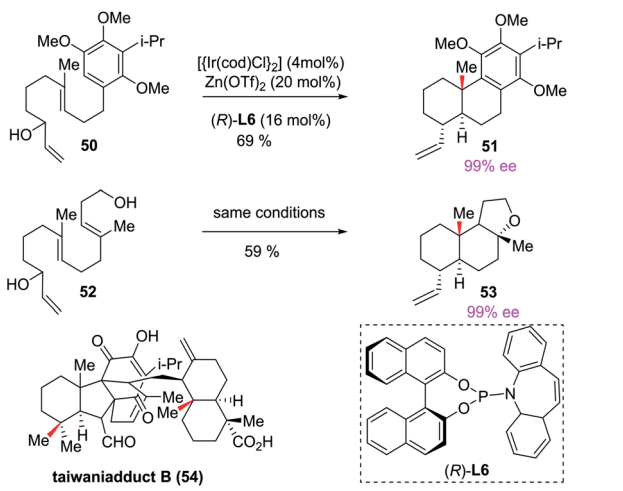
Polyene cyclization is considered as one of the most fundamental transformations in biosynthetic chemistry and one of most efficient synthetic methods for complex terpenes and steroids containing polycyclic frameworks and multiple contiguous chiral centers, including quaternary carbons.[36] Hence, much efforts have been taken in developing efficient enantioselective polyene cyclization. The first enantioselective polyene cyclization was described by Yamamoto and Ishihara[37] in 1999 by employing a BINOL-SnCl$_4$ derivative as a chiral Lewis-acid-assisted Brønsted acid (LBA). Subsequently, several Lewis-base-assisted Brønsted acids[38] and other catalysts were developed to achieve the catalytic enantioselective polyene cyclization. All these cyclizations are initiated with enantioselective protonation or electrophilic halogenation[39] of terminal isoprene. The recent development of efficient chiral catalysts have enabled the enantioselective synthesis of diverse terpenes and steroids.

In 2013, Carreira and co-workers[40] developed an efficient chiral iridium catalyst for asymmetric polyene cyclization[41] to construct chiral carbobicyclic scaffolds. With [{Ir(cod)Cl}$_2$] (3.2 mol%) and (*R*)-**L6** (12.8 mol%) as the catalytic system together with Zn(OTf)$_2$ (16 mol%) as the additive, triene **47** underwent asymmetric polyene cyclization to deliver the chiral bicyclic compound **48** in 73% yield and with excellent stereoselectivity (dr 9 : 1 and 96% ee). As shown in the stereochemical model (Scheme 12), the π-allylic moiety was only allowed to coordinate with Ir from the left-down site because of the steric hindrance possessed by the ligands at the up and right sites. Cyclization of the polyene *via* the loss of a TMS cation through a chair-like transition state led to the formation of **48** in excellent enantioselectivity. The *trans*-decalin **48** is a valuable intermediate for the synthesis of various labdane or labdane-type diterpenoids. After 9 steps, Carreira's group finished the first total synthesis of the tetranorlabdane diterpenoid asperolide C **49**, isolated from *Aspergillus wentii* EN-48.[42]

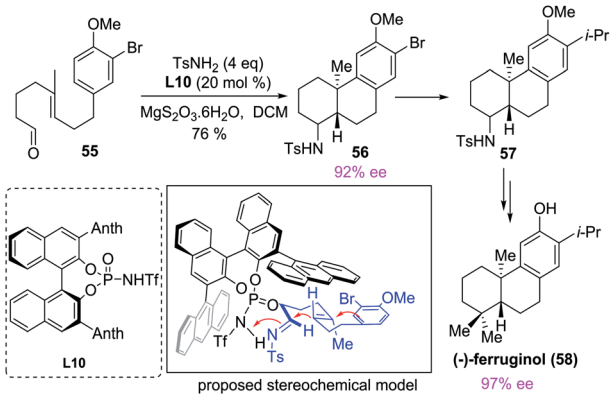
In 2014, Li and co-workers[43] applied Carreira's method to accomplish the first total synthesis of three biologically active diterpenoids, taiwaniadducts B, C, and D. Based on the inherent similarity between **51** and **53** (Scheme 13), Li applied the Ir-catalyzed asymmetric polyene cyclization as a general tool to construct the carbon skeletons of both compounds. Thus, by employing Carreira's catalyst system {[Ir(cod)-Cl]$_2$, (*R*)-**7**, and Zn(OTf)$_2$}, compound **50** was transformed to tricycle **51** (69%) with excellent stereoselectivities (>99% ee, a single detectable diastereomer). The reaction was also conducted on a 15 g scale with consistent efficiency and selectivity. Under similar reaction conditions, the 6,6,5-tricycle **53** was obtained from the diol **52** in 59% yield and >99% ee. Intermediates **51** and **53** were transformed through several steps to form a diene and dienenophile, respectively, which were then subjected to an intermolecular Diels–Alder reaction to form the core of taiwaniadduct B (**54**).



Scheme 12 Carreira's synthesis of asperolide C.



Scheme 13 Li's synthesis of taiwaniadduct B.

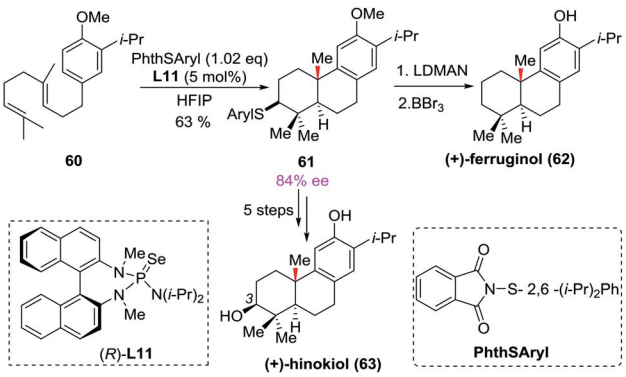


Scheme 14 Zhao's synthesis of (+)-ferruginol.

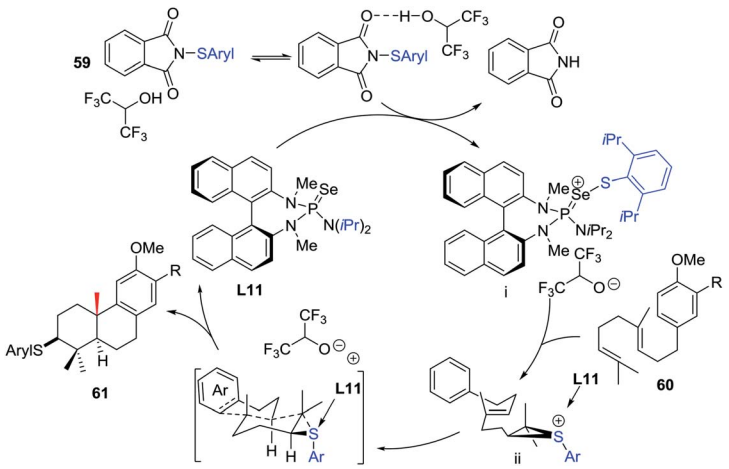
In 2018, Zhao's group[44] reported the first enantioselective polyene cyclization catalysed by a chiral BINOL-derived *N*-phosphoramide (NPA). The process was initiated by the protonation of the imine to form an iminium ion. This method provided efficient access to a fused tricyclic framework with three contiguous stereocenters, which are found in the structures of numerous terpene natural products. (+)-Ferruginol **58**, isolated from *Lamiaceae* plants, has shown various biological activities such as antitumor, antifungal, antimicrobial, and anti-inflammatory properties[45] (Scheme 14). Zhao implemented an NPA-catalyzed enantioselective polyene cyclization in the total synthesis of **58**, where the key step was the asymmetric cyclization of **55** in the presence of $TsNH_2$ with **L10** (20 mol%) as the catalyst. The cyclization product **56** was isolated in 72% yield and 92% ee. A stereochemical model was provided to rationalize the high enantioselectivity of the transformation. The terminal aldehyde was transformed to *N*-Ts imine, which accepted a proton from **L10** to form an ion pair. The iminium ion underwent cationic cyclization under the influence of the chiral counter anion, forming **56** in excellent enantioselectivity. The non-covalent interactions including the cation–π interaction and the steric interactions between the substrate and the anthryl substituents of **L10** may play an important role in the asymmetric induction. Further installation of an isopropyl group on the aryl ring of **56** by cross-coupling and hydrogenation furnished **57**, which after six additional steps afforded (+)-ferruginol (**58**) in 97% ee.

In the same year, Denmark's group[46] reported the efficient enantioselective Lewis base-catalyzed sulfenocyclization of polyenes. The transformation involved the generation of an enantiomerically enriched thiiranium ion from a terminal alkene of the substrate and a sulfenylating agent. As shown in the catalytic cycle[47] proposed in Scheme 15, hexafluoroisopropanol provided a proton, which helped the sulfenylating agent **59** to transfer the arylthio group to catalyst **L11**, generating the cationic complex **i**, which, in turn, reacted with the distal alkene of the polyene substrate **60** to generate the enantiomerically enriched thiiranium ion **ii** and regenerate the Lewis base catalyst **L11**. In the cationic cascade process, species **ii** was diastereospecifically opened and finally terminated by an electron-rich arene to afford the observed tricyclic product **61**.

The utility of this method was demonstrated by the enantioselective syntheses of (+)-ferruginol **62** and (+)-hinokiol **63**, which share the same pattern of arene substitution and differ only in the C(3) substituent. The total syntheses started with the



Scheme 16 Denmark's synthesis of (+)-ferruginol and (+)-hinokiol.



Scheme 15 Proposed catalytic cycle.

enantioselective sulfenocyclization of linear polyene **60** to form the common intermediate (+)-**61**. In the presence of **L11** (5 mol%) as the catalyst and PhthSAryl as the sulfenylating agent, compound **60** (3.0 mmol scale) was transformed into **61** in 63% yield and 84% ee. Subsequent reductive cleavage of *S*-aryl and demethylation afforded (+)-ferruginol (**62**) in 84% yield over 2 steps. (+)-Hinokiol (**63**) was also synthesized from (+)-**61** through five steps (Scheme 16).

2.4 Asymmetric α-arylation

The construction of benzylic quaternary centers have attracted significant interest. Among the various methods, the enantioselective palladium-catalyzed α-arylation has emerged as one of the most attractive and effective methods. However, most known catalytic systems are only applicable for non-hindered aryl halides, and effective examples with sterically bulky aryl halides such as *ortho*-substituted aryl halide are rare.[48] Consequently, the applications of asymmetric α-arylation in natural product synthesis have been rarely explored. In 2011, Hartwig[49] reported a rare example of asymmetric α-arylation in the enantioselective total synthesis of (−)-taiwaniaquinone H and (−)-taiwaniaquinol B. In 2018, Tang's group[50] reported an efficient asymmetric α-arylation for sterically hindered aryl halides. The method featured excellent enantioselectivities and good functional group compatibility. By employing a P-chiral monophosphorus ligand BI-DIME (**L12**), a series of chiral ketones bearing benzylic quaternary carbon stereocenters were formed in excellent yields and ee.

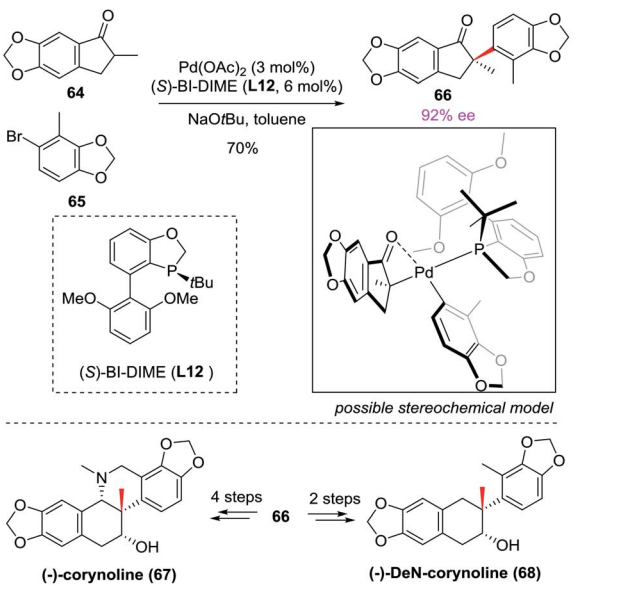
The key enantioselective palladium-catalyzed α-arylation of indanone **64** with aryl bromide **65** was accomplished in the presence of $Pd(OAc)_2$ (3 mol%) and (*S*)-BI-DIME (6 mol%), and the product **66** was obtained in 70% yield and 92% ee. A stereochemical model was provided at the reductive elimination stage (Scheme 17), wherein the Pd-aryl group preferred to adopt a position away from the bulky *tert*-butyl group and adjacent to the oxophosphole ring of the ligand. Because the back face was blocked by the dimethoxy-substituted phenyl ring of BI-DIME, the aryl part of the ketone protruded upward to minimize the steric interaction with the ligand. Reductive elimination led to the coupling product with observed *R* configuration. They applied this protocol in the synthesis of (−)-corynoline (**67**), an acetylcholinesterase inhibitor isolated from *Corydalis incisa* with diverse pharmacological effects.[51] Subsequently, four steps from **66** resulted in the concise and enantioselective synthesis of (−)-corynoline (**67**). Following a two-step procedure from chiral ketone **66**, the potent anti-inflammatory (−)-DeN-corynoline (**68**)[52] was successfully synthesized from indanone **69** in 40% overall yield.

The antidepressant (*S*)-nafenodone (**71**) and the *sceletium* alkaloid (+)-sceletium A-4 (**74**) were synthesized in a very short sequence (Scheme 18). Thus, the reaction of tetralone **69** with PhBr using Pd-(*S*)-BI-DIME as the catalyst afforded **70** in 75% yield and 80% ee. Subsequent ozonolysis and reductive amination furnished (*S*)-nafenodone[53] (**71**) in 70% yield. The chiral ketone **73** (85% ee and 70% yield) was obtained when Pd-(*S*)-AntPhos was used as the catalyst for the α-arylation of the heterocyclic substrate **72** with 3,4-$(MeO)_2C_6H_3Br$. Subsequent ozonolysis and reductive amination completed the asymmetric synthesis of (+)-sceletium A-4 (**74**).

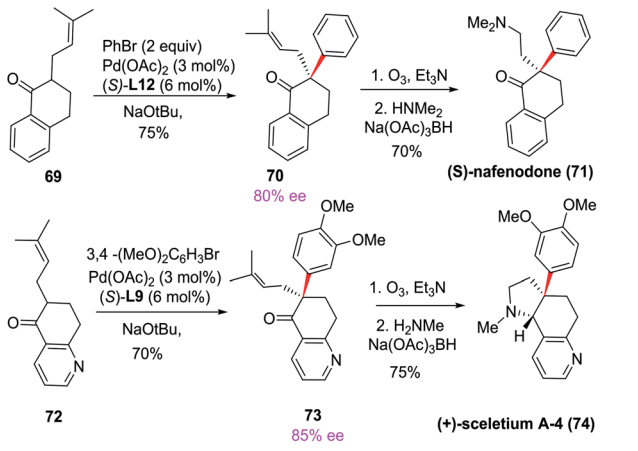
2.5 Asymmetric cycloaddition

Cycloaddition reactions such as the Diels–Alder reaction are a powerful method of forming complex polycyclic structures containing many stereocenters through a single step.[54] In recent years, the enantioselective construction of quaternary carbon stereocenters by cycloaddition reactions has progressed significantly, leading to the elegant synthesis of many complex natural products.

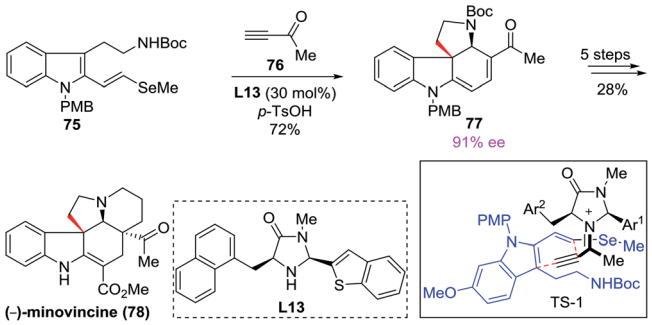
MacMillan's group developed a series of [4 + 2] cycloaddition reactions *via* the catalytic generation of iminium ion intermediates,[55] which have made great contributions to the enantioselective synthesis of various indole alkaloids.[56] Recently, they[57] used a chiral organocatalyst to activate a dienophile and



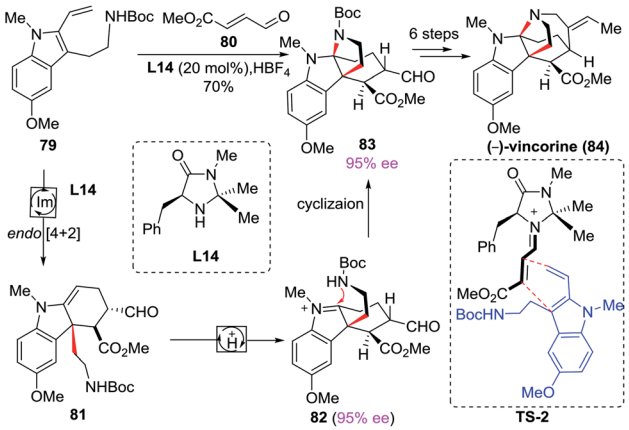
Scheme 17 Synthesis of (−)-corynoline and (−)-DeN-corynoline.



Scheme 18 Synthesis of (*S*)-nafenodone and (+)-sceletium A-4.



Scheme 19 MacMillan's synthesis of (−)-minovincine.



Scheme 20 Synthesis of (−)-vincorine with enantioselective organocatalytic cascade sequence.

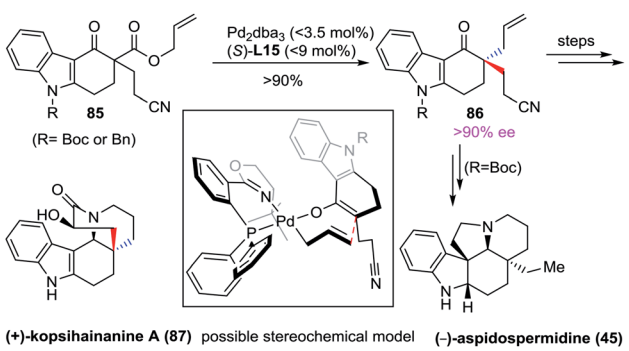
successfully realized a Diels–Alder/β-elimination/conjugate addition cascade to rapidly construct the tetracyclic framework of (−)-minovincine[58] in a highly efficient manner. As shown in Scheme 19, the [4 + 2] cycloaddition between but-3-yn-2-one (**76**) and vinyl selenide **75** proceeded in the presence of **L13** (30 mol%) as the catalyst, providing the desired tetracycle **77** in 72% yield and 91% ee. The use of *p*-toluenesulfonic acid as the co-catalyst was important for the high yield and enantioselectivity. The authors proposed that the condensation between **76** and the imidazolidinone catalyst **L13** generated an iminium ion, wherein the acetylenic group of the conjugated system was projected towards the benzylic unit on the catalyst scaffold. A possible cation–π stabilization between the terminal alkyne and the naphthalene ring of **L13** was present in this geometry. Because one π-face of the iminium ion was effectively shielded by the catalyst substituents, the *endo*-selective Diels–Alder cycloaddition proceeded from the opposite side and the adduct underwent a β-elimination/hetero-conjugate addition cascade, forming **77** in excellent selectivity (TS-1, Scheme 19). After five chemical steps from spiroindoline **77**, the first enantioselective total synthesis of (−)-minovincine (**78**) was accomplished in 28% overall yield.

In the same year, the concise and highly enantioselective total synthesis of the akuammiline alkaloid (−)-vincorine[59] was also accomplished through only nine steps by MacMillan's group.[60] Structurally, (−)-vincorine features a tetracyclic core incorporating a strained seven-membered azepanyl ring and a pyrroloindoline motif. A similar organocatalytic Diels–Alder/amine cyclization cascade was employed in the synthesis. In the key reaction, the tetracyclic vincorine core **83** was formed in 70% yield and 95% ee from diene **79** and enal **80** with **L14** (20 mol%) as the organic catalyst and HBF_4 as the Brønsted acid. It was proposed that the iminium ion formed from **80** and catalyst **L14** preferred to form a geometry where the olefin moiety was *trans* to the *gem*-dimethyl group and *cis* to the benzyl substituent of the catalyst (TS-2). Because one π-face of the iminium ion was shielded by the benzyl substituent of the catalyst, the *endo*-selective Diels–Alder cycloaddition proceeded from the opposite side to form the enamine cycloadduct **81**. The ammonium salt of **L14** would realize the Brønsted acid-catalyzed interconversion from enamine **81** to iminium ion **82**, ensuring the subsequent intramolecular 5-exo amine cyclization *via* the pendant carbamate group to afford the tetracyclic product **83**.[61] The total synthesis of (−)-vincorine (**84**) was achieved after six chemical transformations from **83** in 19% overall yield (Scheme 20).

2.6 Asymmetric allylation reaction

Decarboxylative coupling reactions[62] utilize decarboxylative metalation to generate organometallic intermediates that are coupled *via* reductive elimination. In recent years, many chemists utilized the asymmetric metal-catalyzed decarboxylative allylation for the construction of chiral quaternary centers for complex natural product synthesis.[63] There are several attractive features with this mothod:[64] (1) carboxylic acid derivatives as the reactants are ubiquitous and inexpensive, (2) the only stoichiometric byproduct is CO_2 and (3) the reactive intermediates can be generated under neutral conditions. As a result, the decarboxylative allylation reaction is increasingly employed in natural product synthesis.

Lupton and co-workers[65] reported a Pd-catalyzed decarboxylative allylation for the enantioselective synthesis of carbazolone and indolone heterocycles bearing quaternary carbon stereocenters, and accomplished the formal synthesis of (+)-kopsihainanine.[66] As illustrated in Scheme 21, treatment of the *N*-Boc-protected carbazolone **85** with $[Pd_2(dba)_3]$ (3.5 mol%)



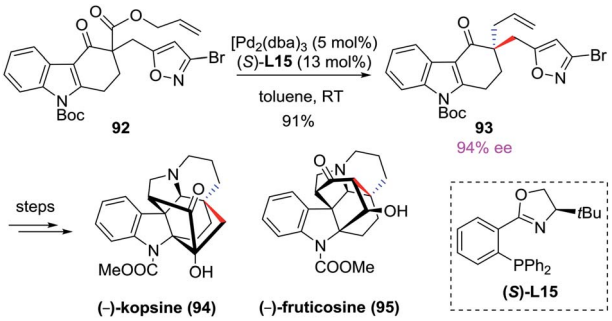
Scheme 21 Synthesis of (+)-kopsihainanine A and (−)-aspidospermidine.

and (*S*)-**L1** (9 mol%) in toluene at 50 °C resulted in the corresponding carbazolone **86** in 90% yield and 94% ee. An inner-sphere mechanism was postulated according to Stoltz's studies.[67] Oxidative addition of substrate **85** by the Pd^0–PHOX complex led to the formation of a Pd(allyl)PHOX complex, which after rearrangement and decarboxylation formed a Pd(allyl)PHOX enolate. Because of the steric bulk of the *tert*-butyl group in (*S*)-**L1**, the carbazole moiety preferred to direct away from it. Reductive-elimination through a cyclic seven-membered pericyclic transition state (boat conformation), similar to a sigmatropic rearrangement, provided product **91** with the observed stereochemistry. Consequently, the formal synthesis of (+)-kopsihainanine (**87**) was achieved after eight chemical steps from **86** in 19% overall yield.

In the same year, Shao and co-workers[68] demonstrated the divergent total synthesis of both kopsihainanine A (**87**) and (−)-aspidospermidine (**45**) using a similar Pd-catalyzed decarboxylative allylation protocol, where an *N*-benzyl carbazolone substrate was employed.

(+)-Sibirinine[69] is a tricyclic alkaloid, which contains an *N*,*O*-acetal, a tertiary amine *N*-oxide, and two vicinal stereocenters including a chiral quaternary center (Scheme 22). In 2015, Stoltz and co-workers[70] accomplished the enantioselective synthesis of (−)-isonitramine (**95**) and (+)-sibirinine (**96**). The key transformation was an asymmetric palladium-catalyzed decarboxylative allylation. As illustrated in Scheme 22, the β-keto ester **88** was converted to the desired product **89** in 94% yield with 86% ee at ambient temperature, in the presence of $[Pd_2(dba)_3]$ (2.5 mol%) and electron-deficient ligand **L16** (6.25 mol%). A six-step sequence from **89** furnished (−)-isonitramine (**90**). The first total synthesis of (+)-sibirinine (**91**) was accomplished from (−)-isonitramine (**90**) by treatment with acetaldehyde followed by the oxidation of *m*-CPBA.

Kopsia indole alkaloids,[71] which are isolated from various *Kopsia* (*Apocynaceae*) species distributed mainly in Southeast Asia, India, and China, belong to a large family of natural products with impressive biological activity. Some of their representative alkaloids include (−)-isokopsine, (+)-methyl chanofruticosinate,[72] (−)-kopsine,[73] (−)-kopsanone,[73] and (−)-fruticosine. Structurally, they are complex polycyclic natural products possessing three quaternary carbon stereocenters. In 2017, Qin and coworkers[74] successfully accomplished the enantioselective syntheses of all these natural products using the decarboxylative allylation strategy. As shown in Scheme 23, compound **92** was transformed to the chiral core structure **93** in



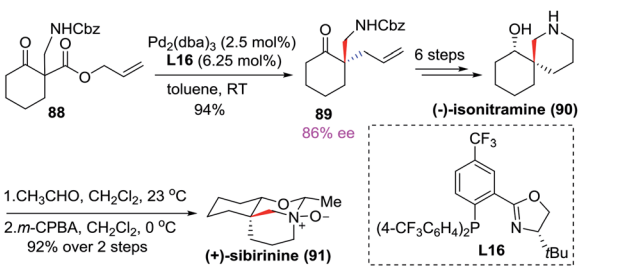
Scheme 23 Qin's synthesis of (−)-kopsine, and (−)-fruticosine.

91% yield and 94% ee using palladium/(*S*)-**L15** as the catalytic system, furnishing the first chiral quaternary center.[75] The asymmetric total synthesis of (−)-kopsine (**94**), (−)-fruticosine (**95**), and other related *Kopsia* alkaloids was accomplished after a series of chemical transformations.

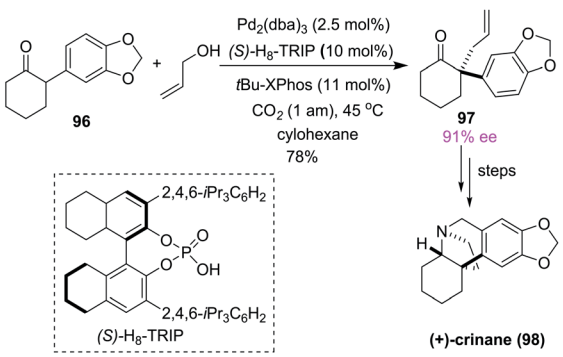
By employing a chiral phosphoric acid catalyst together with a nonchiral palladium catalyst, List and coworkers[76] developed a direct enantioselective α-allylation of branched ketones using allylic alcohol as the reagent in the presence of CO_2 as the promoter (Scheme 24). Thus, under the atmospheric pressure of CO_2, ketone **96** reacted with allylic alcohol in the presence of $Pd_2(dba)_3$ (2.5 mol%), *t*Bu-XPhos (11 mol%), and (*S*)-H_8-TRIP (10 mol%) as the catalyst delivered ketone **97** bearing a quaternary carbon stereocenter in 91% ee and 78% yield. The total synthesis of (+)-crinane (**98**) was then accomplished after three steps from **97**.

Stephadiamine, isolated from the snake vine *Stephania japonica*,[77] is an unusual hasubanan alkaloid. Structurally, it consists of a unique pentacyclic skeleton with an aza[4.3.3] propellane core, bearing four stereocenters including a benzylic quaternary carbon. In 2018, Trauner and coworkers[78] finished the first asymmetric total synthesis of stephadiamine.

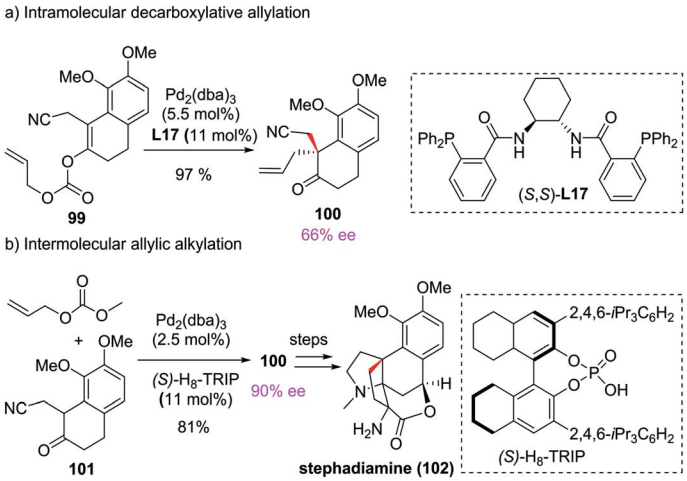
Two different methods were applied to the asymmetric formation of the key intermediate **100** with the benzylic quaternary carbon (Scheme 25). The asymmetric decarboxylative allylation of allylic carbonate **99** using Pd-**L17** as the chiral catalyst gave product **100** in 97% yield and 66% ee.[79] A single recrystallization provided **100** in almost enantiomerically pure form. An alternative approach employed List's protocol[77,80]



Scheme 22 Stoltz's synthesis of (+)-sibirinine.



Scheme 24 List's synthesis of (+)-crinane.

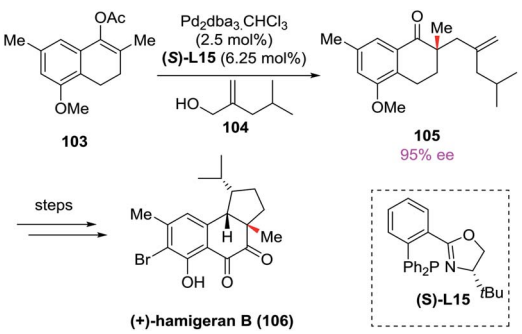


Scheme 25 Trauner's synthesis of stephadiamine.

for the asymmetric allylation of **101** using allylic carbonate as the electrophile. By using $Pd_2(dba)_3$ (2.5 mol%) as the palladium precursor and (*S*)-H_8-TRIP (11 mol%) as the chiral phosphorus acid catalyst, **101** reacted with allyl methyl carbonate to form **100** in 81% yield and 90% ee. A series of transformations from **100** completed the total synthesis of stephadiamine (**102**).

The antiviral (+)-hamigeran B (**106**) was isolated from the poecilosclerid sponge *Hamigera tarangaensis*.[81] In 2018, Aponick and coworkers[82] developed an asymmetric Tsuji allylation for the generation of α-quaternary stereocenters and accomplished the formal synthesis of (+)-hamigeran B (**106**). In the presence of $Pd_2dba_3{\cdot}CHCl_3$ (2.5 mol%) and PHOX ligand (*S*)-**L15** (6.25 mol%), the reaction of enol acetate **103** with iso-butyl-containing allylic alcohol **104** proceeded to provide product **105** in 67% yield and in 95% ee, which was subjected to the formal synthesis of (+)-hamigeran B (**106**) (Scheme 26).[83]

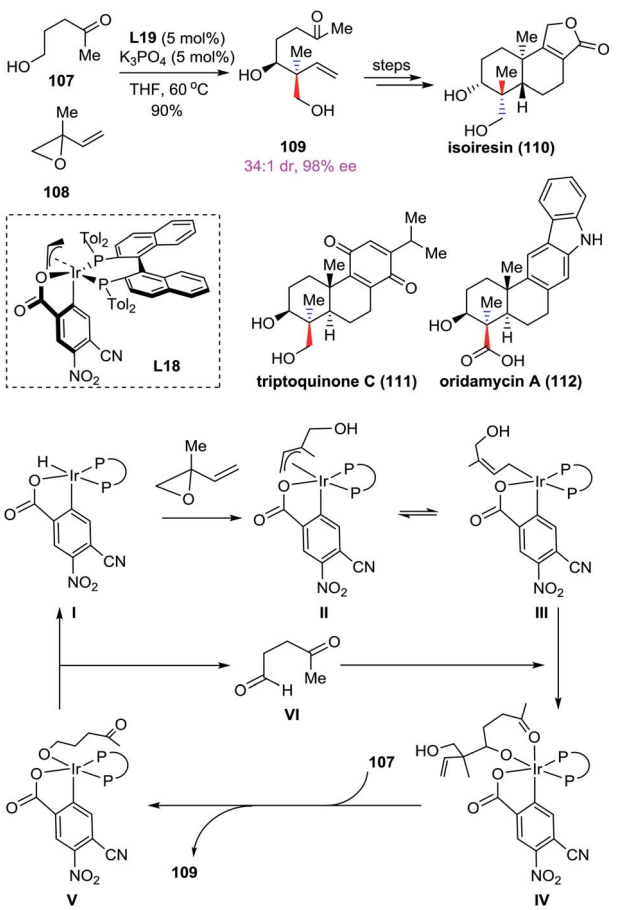
The asymmetric allylation remains one of most important asymmetric catalytic methods in natural product synthesis. The above examples showcased variants of this transformation including the decarboxylative allylation, the combination of a palladium catalyst with a chiral phosphorus acid, and the employment of various allylic electrophiles. Thus, these latest developments have significantly expanded the applicability of asymmetric allylation for the construction of quaternary carbon stereocenters.



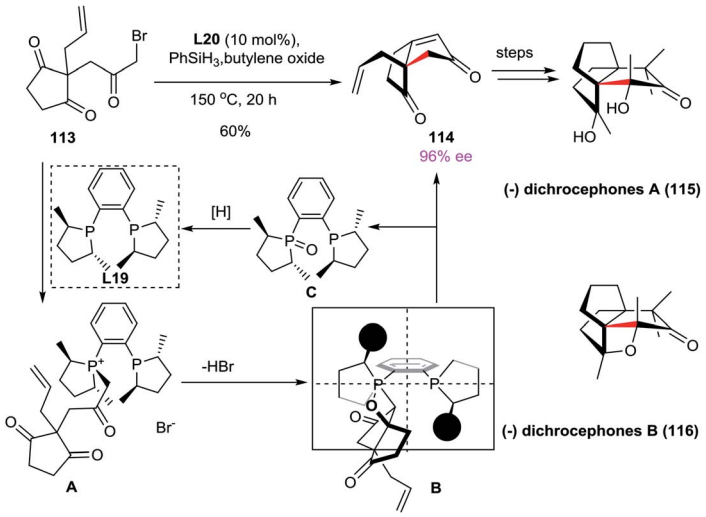
Scheme 26 Aponick's synthesis of (+)-hamigeran B.

2.7 Other asymmetric reactions

Besides the abovementioned asymmetric catalytic reactions, some newly discovered transformations have provided attractive solutions for the construction of quaternary carbons. Two notable examples will be highlighted in this section.



Scheme 27 Krische's synthesis of isoiresin, triptoquinone C and oridamycin A.



Scheme 28 Synthesis of dichrocephones A and B.

In 2016, Krische's group[84] accomplished the enantioselective total synthesis of isoiresin (**110**), triptoquinones C (**111**), and oridamycin A (**112**), using an iridium-catalyzed alcohol C–H *t*-(hydroxy)prenylation to form a quaternary stereocenter with excellent control of the diastereo- and enantioselectivity[85] (Scheme 27). By employing the π-allyliridium *C*,*O*-benzoate complex **L18** as the catalyst, the commercially available alcohol **107** was exposed to isoprene oxide **108**, and the diol product **109** was obtained in 90% yield and 98% ee with a dr ratio of 34 : 1. Mechanistically, **L18** is proposed to be transformed to an iridium hydride species **I**, which is oxidatively added to **108** to form a π-allyliridium intermediate **II**. Tautomerization of **II** to σ-allyliridium **III** followed by coordination of aldehyde **IV** and subsequent allylation form species **IV**. Ligand exchange with starting material **112** gives rise to product **111** and forms alkoxy iridium complex **V**. β-Hydride elimination regenerates iridium hydride species **I** and aldehyde **VI**. The total synthesis of isoiresin (**110**), triptoquinone C (**111**), and oridamycin A (**112**) was successfully accomplished through multiple transformations from chiral **109**.

(−)-Dichrocephones A (**115**) and B (**116**) were isolated from *Asteraceae* and emerged as the highest oxidized modhephanes known to date.[86] Structurally, they possess three contiguous quaternary carbon stereocenters embedded in a fully substituted cyclopentanone fused with two cyclopentanes or substituted oxetane. Tantillo and Christmann[87] recently reported the first enantioselective synthesis of dichrocephones A and B by applying a catalytic asymmetric Wittig reaction. During the key asymmetric Wittig reaction, the prochiral triketone **113** was converted into the bicyclic enone **114** bearing a quaternary carbon in 60% yield and 96% ee, with (*R*,*R*)-Me-DuPhos (**L19**, 10 mol%) as the catalyst, phenylsilane as the reducing reagent, and butylene oxide as the HBr scavenger. Mechanistically, triketone **113** was proposed to react with (*R*,*R*)-Me-DuPhos to form a phosphonium salt **A**, which after elimination of HBr generated an ylide **B**. Because of the well-defined chiral environment created by (*R*,*R*)-Me-DuPhos, the Wittig reaction through a 4-membered transition state took place preferentially at left-down quadrant, forming product **114** in high ee. Phosphine oxide **C** was reduced by phenylsilane to regenerate (*R*,*R*)-Me-DuPhos. Further several transformations from **114** completed the total synthesis of (−) dichrocephones A (**115**) and B (**116**) (Scheme 28).

3 Conclusion and outlook

This concise review highlights some of most impressive work on the enantioselective synthesis of complex natural products bearing quaternary carbon stereocenters due to the recent advances in the development of several asymmetric catalytic methods, namely, asymmetric Michael addition, dearomative cyclization, α-arylation, polyene cyclization, cycloaddition, allylation, and some others. Because of the increasing number of efficient asymmetric catalytic methods and the advent of powerful ligands and catalysts, several biologically important and structurally complex natural products have been synthesized with improved efficiency, including higher overall yields, shorter synthetic steps, and on a larger scale (many accomplished on the gram scale). Long-term progress should help the biological studies of these natural products and facilitate the discovery of new drugs.

Nonetheless, the total synthesis of complex natural products bearing quaternary carbon stereocenters remains one of the most challenging tasks in organic chemistry mainly because of the lack of efficient asymmetric catalytic methods. A few scientific and synthetic issues include: (1) most known methods are only applicable for some specific substrates, and subtle structural variation will lead to unsatisfactory results; (2) the catalyst loadings are often too high to be applicable for scale-up activities; (3) most metal catalysts are late transition metal catalysts, which are expensive for further development; (4) more efficient and greener asymmetric transformations and catalysts are yet to be discovered; and (5) the stereochemical model of each asymmetric catalytic reaction is not fully understood.

Hence, this review focused on discussing the stereochemical model of each asymmetric catalytic transformation to rationalize the origin of its enantioselectivity and reactivity. We hope that this effort will help develop more effective ligands and catalysts, resulting in the discovery of more efficient asymmetric transformations for natural product synthesis.

Undoubtedly, the total synthesis of chiral complex natural products bearing quaternary carbon stereocenters will flourish with the development of more general and effective asymmetric reactions and more efficient ligands and catalysts. The significant development of asymmetric catalytic methods can be foreseen in the area of radical chemistry, photochemistry, and non-precious metal-catalyzed reactions. Progress in these budding areas together with sophisticated advances in the developed fields will certainly facilitate the chemical synthesis of bioactive natural products and drug research.

4 Conflicts of interest

The authors declare no conflicts of interest.

5 Acknowledgments

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