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Enantioselective C–H functionalization: logic and applications in the total synthesis of natural products

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Natural products, with their profound structural diversity and potent bioactivities, represent an invaluable source of inspiration for drug discovery and biomaterial development. The integration of enantioselective C–H functionalization into synthetic planning has emerged as a transformative strategy, offering streamlined and atom-economical routes to complex molecular architectures. This review comprehensively summarizes the pivotal role of these methodologies in the asymmetric total synthesis of natural products. We have organized recent breakthroughs according to three distinct C–H functionalization pathways: (1) radical hydrogen atom abstraction (HAA), (2) metallocarbene C–H insertion, and (3) C–H metalation. Through illustrative case studies, we dissect how these strategies function as the key steps to construct stereodefined frameworks, thereby enabling the concise synthesis of target molecules, confirming absolute configurations, and facilitating biological evaluation. We anticipate that the continued maturation of enantioselective C–H activation will further democratize and accelerate the synthesis of complex natural products and their analogues.

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1 Introduction

Natural products, isolated from living organisms, are a significant class of chemical compounds known for their diverse and unique bioactivities. Consequently, these natural products and their analogues have found extensive applications across pharmaceuticals, agrochemicals, cosmetics, and biomaterials science.¹ Since Wöhler accomplished the first total synthesis of urea **3** from inorganic salts—silver cyanate **1** and ammonium chloride **2**—in 1828 (Scheme 1a),² chemists have recognized the potential for artificially synthesizing bioactive organic compounds in abiotic systems. In 1917, the tropinone **7** was established by Robinson *via* a twofold Michael addition (Scheme 1b).³ Compared with the first 21-step approach reported by Willstätter,⁴ this landmark one-pot synthesis⁵ further highlighted the power of innovative methodologies for enhancing efficiency in total synthesis.⁶

Today, the advancements in organic chemistry have opened up new avenues for imaginative disconnections in the retrosynthesis of complex structures. It appears that nearly all natural products, regardless of their complexity, can be synthesized in the laboratory or industry,⁷ providing an alternative to biosynthesis for compounds that are insufficiently available from natural sources. However, challenges remain, as unsatisfactory overall yields and tedious synthetic procedures continue to limit the practical applications of many natural products.^{1,8} For example, Taxol (paclitaxel) **9**, a well-known and effective natural-source antitumor drug, still primarily relies on semi-synthesis from the isolated intermediate 10-deacetyl baccatin III (10-DAB) **8** (Scheme 1c).⁹ Thus, there is an urgent need to develop new synthetic protocols for the total syntheses

of complex molecules, which may achieve higher atom economy, yield, and stereoselectivity within shorter and scalable synthetic routes.¹⁰

The ubiquitous C–H bond in organic molecules presents an attractive target for direct and precise transformation without pre-functionalization. This approach offers a more convenient, cost-effective and sustainable pathway for target-oriented organic synthesis, and has a long-standing history in the total synthesis of natural products.¹¹ The pioneering work of Löffler and colleagues in 1909 applied a site-selective radical C–H functionalization in the synthesis of nicotine **11** through intramolecular 1,5-hydrogen atom transfer (HAT, Scheme 1d).^{12,13} In the following decades, significant contributions were made. In 1977, the Barton group utilized diastereoselective C–H oxidation as a key step in synthesizing aldosterone acetate **13** from a photochemically unstable nitrite ester by taking advantage of the rigid conformation of a steroid (Scheme 1e).¹⁴ Cory and colleagues employed intramolecular C–H insertion for the construction of isharane **16** with an *in situ* generated carbene (Scheme 1f),¹⁵ trimming the route to 6 steps from the original 16-step synthesis.¹⁶ Additionally, Trost demonstrated a Pd-catalyzed C–H activation/reductive Heck coupling in the total synthesis of ibogamine (Scheme 1g).¹⁷ Despite these advances, the generation of new chiral elements in these early examples often depended on pre-existing stereocenters within the molecules, necessitating the use of chiral precursors that are challenging to prepare in many cases, thereby restricting the enantioselective synthesis of chiral natural products.

Recently, transition metal-catalyzed enantioselective C–H functionalization—including radical hydrogen atom abstraction (HAA), metalcarbene/nitrene insertion, and C–H



Scheme 1 Advancements in the efficiency of total synthesis driven by innovations in synthetic methodology and strategy.



metalation strategies—has garnered significant attention.¹⁸ This approach offers an innovative avenue for the streamlined synthesis of chiral complex compounds from prochiral substrates and enables the late-stage decoration of highly functionalized intermediates under mild conditions, balancing reactivity and selectivity among numerous similar inert C–H bonds.¹¹ Over the past three decades, enantioselective C–H functionalization has emerged as a promising strategy for constructing both molecular skeletons and stereocenters in the total synthesis of natural products with minimized synthetic steps and waste (Scheme 1h). To summarize recent progress and offer new perspectives on this burgeoning field, this review will comprehensively discuss the contributions of total syntheses that benefit from transition metal-catalyzed enantioselective C–H functionalization. We will emphasize the interconnections between synthetic advancements and the corresponding innovations in methodology. To provide a clearer focus, this review will primarily cover the construction of chirality during the C–H activation step. Processes involving functionalization of unsaturated bonds after C–H activation to generate chirality are beyond the scope of this discussion.

2 Syntheses via HAA/radical relay

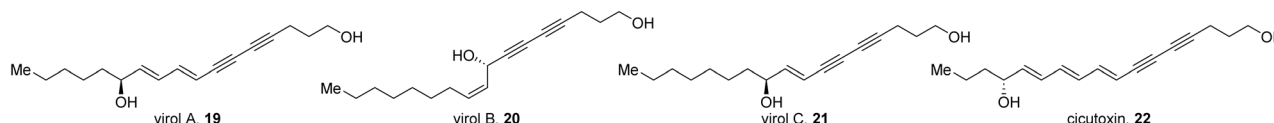
In the metabolism of organisms, C-centered radicals serve as prevalent intermediates for selective C–H functionalization *via*

a radical rebound pathway. This process can be facilitated by reactive metal–oxo species under mild conditions through enzyme catalysis.¹⁹ The precise manipulation of free radicals generated through hydrogen atom abstraction (HAA) poses a significant challenge due to their instability and high reactivity.²⁰ To address this issue, a second species—often a transition metal catalyst—is introduced to trap the diffusible C-centered radical intermediate, enabling excellent regio- and stereoselectivity. This approach is known as a radical relay process and is typically achieved using cobalt, copper, or nickel catalysts.^{18k,m,21}

2.1 Cu-catalyzed enantioselective C(sp³)-H oxidation

Polyacetylenic alcohols virol A **19**, virol B **20** and virol C **21** (Scheme 2a) are three minor toxic components isolated from water hemlock,²² *Cicuta virosa* (Umbelliferae), a plant widespread throughout temperate areas. These compounds are extremely poisonous for tonic and clonic convulsions and respiratory paralysis to both livestock and humans through their impact on the central nervous system. Compared with their analogue cicutoxin **22**, the major toxin of the plant,²³ virols A, B and C are more chemically stable compounds, which are suitable for pharmacological action investigations. In 1999, Oshima and coworkers disclosed a total synthesis of virols A and C from (*S*)-oct-1-yn-3-ol **24** and (*S,S*)-

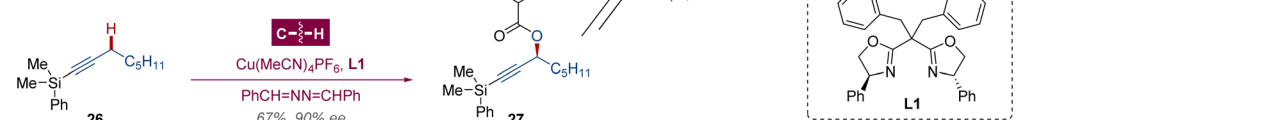
a) Structure of virol A, B, C and cicutoxin



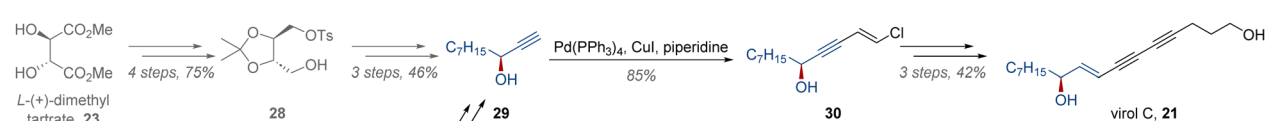
b) Oshima's total synthesis of virol A, 1999



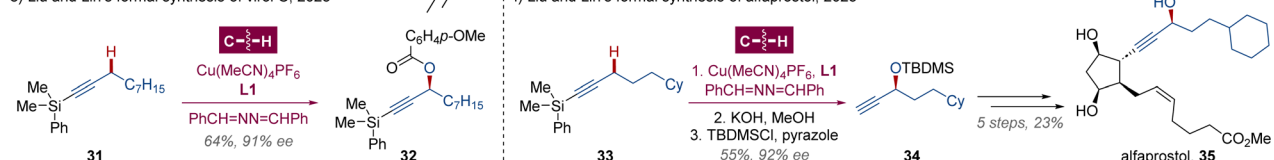
c) Liu and Lin's formal synthesis of virol A, 2025



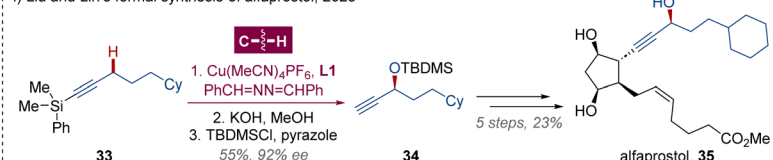
d) Oshima's total synthesis of virol C, 1999



e) Liu and Lin's formal synthesis of virol C, 2025



f) Liu and Lin's formal synthesis of alfaprostol, 2025



Scheme 2 Liu and Lin's formal syntheses of virol A, virol C and alfaprostol *via* Cu-catalyzed radical relay.





Scheme 3 Huo's total synthesis of (-)-indolizidine 201 and Kong and Ping's total synthesis of (-)-coniceine.

methylbenzenesulfonate **28** respectively,²⁴ which could be prepared from L-(+)-dimethyl tartrate **23** via several transformations in moderate yield (Scheme 2b and d).²⁵ Alternatively, the enantioselective Kharasch–Sosnovsky reaction, a copper-catalyzed direct oxidation of allyl, propargylic or benzylic C–H bonds,²⁶ is obviously a more ideal approach of these chiral propargyl alcohols, while the enantiocontrol was poor and an excessive amount of hydrocarbon substrate was required.^{26c} Very recently, building on their sustained endeavors in enantioselective C–H functionalization via Cu-catalyzed radical relay,^{21d,27} Liu, Lin and coworkers showcased a biomimetic propargylic C(sp³)–H acyloxylation with excellent site- and enantioselectivity assisted by chiral bisoxazoline (BOX) ligand **L1**.²⁸ Leveraging their radical C(sp³)–H oxidation methodology, the nearly 10-step syntheses of chiral fragments **25** and **29** could be simplified to 3 steps from dimethylphenylsilyl alkynes **26** and **31** in the absence of stoichiometric chiral synthons (Scheme 2c and e). Similarly, the formal synthesis of alfaprostol **35** was also performed with a chiral side chain constructed via this Cu-catalyzed radical relay (Scheme 2f).²⁹

2.2 Ni-catalyzed enantioselective C(sp³)–H alkylation and amination

Indolizidine and pyrrolizidine alkaloids, featuring a 5/6- or 5/5-membered fused azacycle system as the core skeleton, respectively (Scheme 3a), are widely present among a multitude of marine and terrestrial living beings, such as trees, fungi, frogs and so on, illustrating numerous distinctive biological activities.³⁰ For these natural products, a major synthetic challenge is the construction of an α -tertiary or quaternary chiral center on the fused N-heterocycle framework.

In 2022, Yu, Yuan and colleagues presented a total synthesis of (-)-indolizidine **201** **36** from N-Boc-2-formylpyrrolidine **44** in 27% yield over 8 steps by means of a photoexcited Cu/BOX-catalyzed kinetic resolution of alkenes as the key stereo-introducing step (Scheme 3b).³¹ Drawing from previous studies,³² in 2024, the Huo group demonstrated a photoredox nickel-catalyzed enantioselective α -C(sp³)–H alkylation of N-Bz-pyrrolidine **45** with *in situ* prepared N-hydrophthalimide (NHPI) ester utilizing chiral BOX ligand **L2**, and the (-)-indolizidine **201** **36** was obtained in 59% yield over 3 steps with additional acidic deprotection and diastereoselective reductive amination of the corresponding compound **46** to construct the 5/6-membered fused ring (Scheme 3c).³³

Very recently, Kong, Ping and collaborators revealed a similar enantioselective α -C(sp³)–H alkylation of saturated heterocycles with olefins enabled by Ni/L3 catalysis.³⁴ Applying this protocol, the 3-step total synthesis of the simplest indolizidine alkaloid (-)-coniceine **37** was performed (Scheme 3d), which was similar to Huo's route of (-)-indolizidine **201** **36** and more concise than the previous synthetic approach.³⁵ Meanwhile, the authors also achieved the enantio- and diastereoselective formation of secondary–secondary C(sp³)–C(sp³) bonds using alkenyl boronates as alkylation agents to restrain potential chain walking by stabilizing the branched organonickel intermediate,³⁶ which streamlined the construction of more complicated indolizidine and pyrrolizidine alkaloids (Scheme 4). The alkylated products **48** and **49** were oxidized to alcohol and benzylated with stereochemical retention in 66% and 77% yields, respectively. Cp₂ZrHCl-mediated debenzoylation was then performed at 0 °C, followed by desilylation for **50** with tetrabutylammonium fluoride (TBAF) or debenzoylation for **51** with trifluoroacetic acid (TFA). The alcohol **53** was oxidized to carboxylic acid by (1-hydroxycyclohexyl) phenylmethanone (1-HCPK) via a base-promoted hydrogen atom transfer,³⁷ and 8-hydroxy-5-indolizidinone **54** was afforded after amidation and debenzoylation as the key synthon for the formal synthesis of pumiliotoxin 251D **38**,³⁸ a major component in the secretion of *Dendrobates tricolor* (Ecuador) with myotonic and cardiotoxic properties.³⁹ The natural alkaloid (-)-1-hydroxypyrrolizidine **39** was generated in an overall yield of 12% after further Mitsunobu-type nucleophilic cyclization and debenzoylation of free alcohol **52**, as well as (-)-perhydro-8-indolizolinol **40** in 17% total yield via compound **53**. With a stereoconserving Matteson boronate rearrangement process of **48** and **49** for homologation followed by the same benzylolation–deprotection–cyclization–debenzoylation sequence





Scheme 4 Kong and Ping's total (or formal) syntheses of chiral indolizidine and pyrrolizidine alkaloids.

described above, pyrrolizidine (–)-trachelanthamidine **41** and indolizidine (–)-tashiromine **42** were formed in 7 steps with overall yields of 11% and 8%, respectively. Moreover, the azabicyclo[3.3.0]octane ring of (–)-trachelanthamidine **41** was a core framework of selective serotonin 5-HT₄ receptor agonists and antagonists, e.g. SC-53606 **43**.⁴⁰

Chiral pyrrolidines, usually bearing an α -C-stereocenter, are found as a common structural motif in numerous biologically active natural products, mainly prepared from enantiopure proline.⁴¹ As prevalent in approximately 20% of saturated N-heterocycle drugs, pyrrolidines are recognized as a treasure trove for pharmaceutical design.⁴² Evidently, the enantioselective α -C(sp³)-H alkylation developed by the Huo and Kong groups would be applicable in asymmetric pyrrolidine synthesis, especially for the rapid construction of an analogue library.^{33,34} Employing these methodologies, the synthesis of (–)-norbgugaine **61** and Ca-sensing receptor antagonist

precursor **62** was refined to 2 steps from N-Bz-pyrrolidine **45** via nickel-catalyzed enantioselective α -C(sp³)-H alkylation and Cp₂ZrHCl-mediated debenzoylation (Scheme 5a), compared with the original approach from L-proline.^{43a,b} (–)-Bgugaine **63** and (–)-irnidine **64**, two antibacterial and antimycotic natural alkaloids isolated from tubers of *Arisarum vulgare*,⁴⁴ were produced through a similar enantioselective α -C(sp³)-H alkylation and debenzoylation sequence with an additional methylation in improved overall yields of 47% and 39%, respectively (Scheme 5b).^{43c}

(+)- α -Lipoic acid **67** is identified as a coenzyme participating in a wide range of biological processes among animals, plants and microorganisms.⁴⁵ Especially, it is both an intracellular and an extracellular metabolic antioxidant for reactive oxygen species (ROS) scavenging, exhibiting potent neuroprotection, anti-inflammation, anti-cancer and anti-human immunodeficiency virus (HIV) activities and so on.⁴⁶ In both the enzymatic



Scheme 5 Huo's and Kong and Ping's total syntheses of chiral pyrrolidines.





Scheme 6 Kong and Ping's formal syntheses of (+)- α -lipoic acid and (-)-tetrahydrolipstatin.

and transition metal-catalyzed asymmetric syntheses of (+)- α -lipoic acid **67**, methyl (*S*)-6,8-dihydroxyoctanoate **66** was always involved as the key intermediate, which entailed multiple steps to build the stereocenter and the 1,3-diol structure.⁴⁷ To address this synthetic challenge, guided by their previous accomplishment in the asymmetric syntheses of chiral alcohol-derived drugs *via* photoredox C(sp³)-H arylation,⁴⁸ Kong, Ping and coworkers explored whether their enantioselective α -C(sp³)-H alkylation protocol would serve as a superior solution with an extended heterocycle scope to saturated oxacycles.³⁴ After replacement of the oxidant from dicumyl peroxide (DCP) to *tert*-butyl peroxide (DTBP) for the HAT process, the chiral segment **66** was obtained in 54% yield and 97% *ee* with BOX ligand *ent*-L3 (Scheme 6). In a similar manner, harnessing this convenient one-pot synthesis, key intermediate (*S*)-tetradecane-1,3-diol **68** was constructed with excellent enantioselectivity for the formal synthesis of (-)-tetrahydrolipstatin **69**,⁴⁹ a saturated counterpart of lipstatin with strong and irreversible inhibition to lipase isolated from *Streptomyces toytricini*, which is a medication against obesity marketed as Xenical.⁵⁰

Beyond enantioselective C-C formation, related transformations such as C-N bond formation have also been developed for complex molecule synthesis. For instance, Guo and coworkers reported a nickel-catalyzed electrochemical enantioselective dehydrogenative C-H amination.⁵¹ This method was successfully applied to the concise synthesis of bioactive agents, including the (+)- γ -secretase inhibitor and the agrochemicals (+)-flamprop-methyl and (+)-flamprop-isopropyl, illustrating the potential of these reactions in target-oriented synthesis.

3 Syntheses *via* metallocarbene C-H insertion

Direct carbene C-H insertion offers another valuable route to the formation of C(sp³)-C(sp³) bonds. The enantioselective version of this transformation was pioneered by chiral dirhodium(II) catalysts bearing carboxylate or carboxamidate ligands.^{18a,g,52} Subsequently, these same catalysts were successfully extended to asymmetric nitrene insertions into C(sp³)-H bonds.^{52a,53} More recently, the catalytic manifold has expanded

to include other transition metals—such as Fe, Co, Cu, Ru and Ir—for enantioselective alkylation and amination *via* carbene and nitrene transfer, respectively.^{53,54} Despite the rapid progress, the application of these methods in natural product total synthesis remains limited. To date, only asymmetric dirhodium-carbenoid C(sp³)-H insertion has been employed in a handful of cases to forge C(sp³)-C(sp³) bonds.^{11c,55} Furthermore, these applications often rely on diastereoselective control, achieved by combining a chiral dirhodium catalyst with a pre-installed chiral auxiliary;⁵⁶ they primarily establish stereogenicity on the diazo-derived fragment rather than on the functionalized hydrocarbon backbone.⁵⁷ As a result, enantioselective C-H functionalization *via* carbene or nitrene insertion has not yet been widely adopted to enable concise total syntheses, representing a significant area for future development.

3.1 Rh-catalyzed intramolecular C(sp³)-H carbene insertion

(-)-Enterolactone **77** is the most commonly synthesized lactone with anticarcinogenic and antiestrogenic properties in the lignan library widely distributed in plants,⁵⁸ which was fortuitously observed and characterized from female urine with a periodic excretion during the menstrual cycle as well as pregnancy⁵⁹ and then synthesized by Groen.⁶⁰ In a previous study, the fabrication of chiral γ -lactone ring was quite tricky and troublesome.⁶¹ As an efficient approach for the asymmetric γ -lactone construction, Doyle, Simonsen, Lynch and coworkers disclosed a refined synthesis of (-)-enterolactone **77** employing the dirhodium-catalyzed enantioselective intramolecular C(sp³)-H carbene insertion in 1995 (Scheme 7a).⁶² The C-C double bond in commercially available substrate *meta*-methoxycinnamic acid **70** was initially hydrogenated in the presence of 5% Pd/C, followed by the reduction of carboxyl group with LiAlH₄ to form 3-(*meta*-methoxyphenyl)propan-1-ol **71** in 98% yield over two steps. The diazoacetate reactant **72** was then delivered through esterification with diketene, diazotization with methanesulfonyl azide and deacetylation with LiOH·H₂O. After optimization of conditions for the key step in the entire route, the intramolecular C(sp³)-H carbene insertion, the authors uncovered that the carboxamidate-coordinated dirhodium catalyst Rh₂(*R*-MPPIM)₄ **Rh1** was preferable for this transformation, with the (*R*)- γ -lactone **76** afforded in 63% yield and 93% *ee*. The 2-substituent was introduced with outstanding diastereoselectivity by lithium diisopropylamide (LDA)-mediated deprotonation and nucleophilic substitution with *meta*-benzyl bromide. With methyl groups removed by BBr₃, the desired lignan (-)-enterolactone **77** was eventually produced in 26% yield over 8 steps. Meanwhile, with the enantiomer of dirhodium catalyst **Rh1** provided from *L*-asparagine, (+)-enterolactone **78** was also synthesized smoothly *via* the same procedure with Rh₂(*S*-MPPIM)₄ *ent*-**Rh1** in an overall yield of 27% with 91% *ee*.

Taking advantage of this efficient intramolecular C(sp³)-H carbene insertion for enantioselective γ -lactone construction catalyzed by newly designed dirhodium Rh₂(*R*-MPPIM)₄ **Rh1** and Rh₂(*S*-MPPIM)₄ *ent*-**Rh1**, Doyle and collaborators also



a) Doyle, Simonsen and Lynch's total synthesis of (–)– and (+)–enterolactone



b) Doyle, Simonsen and Lynch's total synthesis of (–)– and (+)–hinokinin



c) Doyle's total synthesis of (+)–arctigenin



d) Doyle's total synthesis of (+)–isodeoxydopphyllotoxin



e) Doyle's formal synthesis of (–)–matairesinol, (–)–anhydrosecoisolaricresinol, (–)–secoisolaricresinol and (+)–isolaricresinol



f) Doyle's total synthesis of (+)–imperanene



Scheme 7 Doyle, Simonsen and Lynch's total (or formal) syntheses of chiral lignan and phenolic natural products.

studied the streamlined synthesis of other lignan natural products.⁶² (–)-Hinokinin **82**,⁶³ (+)-hinokinin **83** and (+)-arctigenin **88** (ref. 64) were analogues of enterolactone with subtle differences in O-containing moieties on arenes, which were

unobstructedly synthesized with 94% *ee* in overall yields of 27%, 25% and 19% applying their enantioselective C(sp³)–H insertion to form the chiral γ -lactone cycle respectively (Scheme 7b and c). Similar to the total synthesis of (+)-hinokinin **83**, the key



chiral building block (*S*)- γ -lactone *ent*-**81** was delivered with $\text{Rh}_2(\text{S-MPPIM})_4$ *ent*-**Rh1** in 67% yield and 94% *ee*, and the target lignan (+)-isodeoxydopodophyllotoxin **87** (ref. 65) was provided through nucleophilic addition to 3,4,5-trimethoxybenzaldehyde and TFA-promoted Friedel-Crafts alkylation in 68% yield and >99% *ee* after crystallization (Scheme 7d). Additionally, the chiral lactone **90**, obtained from the corresponding diazoacetate **89** in 59% yield and 97% *ee* via $\text{Rh}_2(\text{R-MPPIM})_4$ **Rh1**-catalyzed enantioselective $\text{C}(\text{sp}^3)\text{-H}$ insertion, is also a key synthon in syntheses of lignan compounds,⁶⁶ including (–)-matairesinol **91**,^{61b,67} (–)-anhydrosecoisolariciresinol **92**,⁶⁸ (–)-secoisolariciresinol **93** (ref. 69) and (+)-isolariciresinol **94** (ref. 70) (Scheme 7e). Notably, this enantioselective $\text{C}(\text{sp}^3)\text{-H}$ insertion methodology was also viable for complex chiral lactam structures, such as bioactive (–)-rolipram.⁷¹

Furthermore, since the chiral γ -lactone scaffold could be easily opened through hydrolysis, nucleophilic substitution or other potential process, the rhodium catalysis mentioned above was also feasible for the asymmetric synthesis of linear natural products. Isolated from a diuretic and anti-inflammatory Chinese traditional medicine—*Imperata cylindrica*, (+)-imperanene **98** is a homoallylic alcohol with a tertiary C-stereocenter proximal to the C–C double bond, illustrating platelet aggregation inhibitory activity.⁷² In 2002, the Doyle group realized the first enantioselective total synthesis of (+)-imperanene **98** (Scheme 7f).⁷³ The *tert*-butyldiphenylsilyl (TBDPS)-protected diazoacetate **95** was prepared in 51% yield from the inexpensive starting material 4-hydroxyl-3-methoxycinnamic acid over 6 steps, and then the dirhodium $\text{Rh}_2(\text{S-MPPIM})_4$ *ent*-**Rh1**-catalyzed enantioselective $\text{C}(\text{sp}^3)\text{-H}$ carbene insertion/lactonization occurred, generating γ -lactone **96** with 68% yield and 93% *ee* in the *S* configuration. Compound **96** was reduced to a hemiacetal with diisobutylaluminum hydride (DIBAL-H), followed by stereospecific ring-opening nucleophilic addition with aryllithium to yield acyclic 1,4-diol **97** as an approximately 1:1 mixture of diastereomers. The primary hydroxy group was selectively silylated, and the 12-step total synthesis of homoallylic (+)-imperanene **98** was accomplished in 12% overall yield after the ultimate elimination and desilylation sequence.

3.2 Rh-catalyzed $\text{C}(\text{sp}^3)\text{-H}$ intermolecular carbene insertion

Pseudopterogorgia elisabethae (Octocorallia) is a Caribbean gorgonian coral found in the West Indies, where the gorgonian octocorals flourish more than anywhere else in the world.⁷⁴ Since the pioneering discovery of diterpene-glycoside secpseudopteosins by Fenical in 1987,⁷⁵ plenty of marine secondary metabolites in *Pseudopterogorgia elisabethae* have been isolated and characterized as a family of diterpenes. These compounds usually possess distinctive structural architectures which are rarely found in terrestrial organisms,⁷⁴ exhibiting diverse bioactivities including antibacterial, anti-inflammatory, antitubercular and anticancer properties.^{74,76} Originating from the common precursor (+)-elisabethatriene **99** in biological synthesis,⁷⁷ these natural products typically possess three stereocenters (Scheme 8a), which are daunting to be

constructed simultaneously in the correct configuration with excellent enantioselectivity and diastereoselectivity.

Leveraging their previous achievements in dirhodium-catalyzed intermolecular enantiodifferentiating $\text{C}(\text{sp}^3)\text{-H}$ carbene insertion/Cope rearrangement,⁷⁸ Davies and colleagues materialized the total synthesis of antitubercular marine diterpene (+)-erogorgiaene **100** (ref. 79) via a kinetic enantio-divergent functionalization in 2005 (Scheme 8b).⁸⁰ Using commercially available 4-oxo-4-*p*-tolylbutanoic acid as the starting reagent, racemic dihydronaphthalene **105** was obtained in 28% yield through a methylation–vinylation–hydrogenation–hydrolysis–cyclization–reduction–elimination sequence. Controlled by the steric effect of the chiral dirhodium catalyst $\text{Rh}_2(\text{R-DOSP})_4$ **Rh2**, the asymmetric $\text{C}(\text{sp}^3)\text{-H}$ carbene insertion proceeded at the 2-position for (*S*)-**105**, followed by an enantiospecific Cope arrangement to afford compound **107** bearing three aspired tertiary C-stereocenters in >49:1 *dr*. In contrast, under the same conditions, only a C–C double bond cyclopropanated product was detected for its enantiomer (*R*)-**105**, attaining the efficient resolution of enantiomers and establishing the fundamental architecture of the (+)-erogorgiaene **100**. The C–C double bond and carbomethoxy group were subsequently reduced to avoid the propensity of retro-Cope arrangement, and alcohol **109** was isolated from the corresponding 1:1 mixture of compounds **107** and **108** by chromatography in 34% yield over 3 steps from (\pm)-**105**, which could be transformed to (+)-erogorgiaene **100** by oxidation and Wittig olefination.

Undoubtedly, polycyclic diterpenes (–)-colombiasin A **101** (ref. 81) and (–)-elisapterosin B **102** (ref. 82) are more sophisticated and highly functionalized, featuring two quaternary and three tertiary C-stereocenters. Stimulated by previous approaches,⁸³ the authors envisioned that the late-stage intermediate **118** for [4 + 2] or [5 + 2] cycloaddition could be settled through the cascade asymmetric $\text{C}(\text{sp}^3)\text{-H}$ carbene insertion/Cope rearrangement with ease (Scheme 8c).⁸⁴ The core framework of dihydronaphthalene (\pm)-**113** was generated from diene **110** and dienophile **111** via Diels–Alder reaction after the cleavage of the TBS-enol group and migration of the C–C double bond.^{83a,b} Then the combined enantiodifferentiating $\text{C}(\text{sp}^3)\text{-H}$ allylation/Cope rearrangement was investigated with dirhodium $\text{Rh}_2(\text{R-DOSP})_4$ **Rh2** catalysis, and the TBS group was proven to be vital for excellent enantiocontrol with sufficient steric hindrance provided, since the highest enantiomeric excess (>95% *ee*) was measured for further reduced alcohol **116** from TBS-protected *p*-hydroquinone (\pm)-**113** compared to those from dimethyl **133** or diacetyl polyhydroxy dihydronaphthalene derivatives in proper stereochemistry. Within 4 standard steps, the late-stage *p*-quinone intermediate bearing a diene group was constructed, which could be smoothly transformed to (–)-colombiasin A **101** through Diels–Alder reaction/demethylation and (–)-elisapterosin B **102** undergoing a $\text{BF}_3\cdot\text{OEt}_2$ -mediated [5 + 2] cycloaddition as single diastereomers.⁸³ In a similar manner, assisted by a selective demethylation of adjacent methoxy groups with LiSEt developed by Schmalz,⁸⁵ gorgonian octocoral bicyclic metabolites (+)-elisabethadione **103** (ref. 86) and (+)-*p*-benzoquinone **104** (ref. 87) were



a) Biosynthetic route of selected marine diterpenes isolated from *Pseudopterogorgia elisabethae*

b) Davies' total synthesis of (+)-elisabethatriene



c) Davies' total synthesis of (-)-colombiasin A and (-)-elisapterosin B



d) Davies' total synthesis of (+)-elisabethadione and (+)-p-benzoquinone



Scheme 8 Davies' total syntheses of marine secondary metabolite diterpenes.

synthesized from trimethoxy-1,4-dihydronaphthalene **121**, which was obtained through $\text{Rh}_2(\text{R-DOSP})_4$ **Rh2** catalyzed enantiodivergent C–H functionalization of **120** respectively (Scheme 8d).⁸⁸

In addition to the chemodivergent kinetic resolution *via* $\text{C}(\text{sp}^3)\text{-H}$ carbene insertion/Cope rearrangement, the dirhodium(II)-catalyzed direct diastereoselective construction of two adjacent tertiary C-stereocenters located on both the C–H fragment and diazo skeleton has also been unveiled. Using





Scheme 9 Shaw's total syntheses of panowamycins A, B, TM-135 and veramyacin F.

dirhodium-catalyzed diastereo- and enantioselective C-H functionalization, the Sorensen group uncovered the rapid access toward several benzo-fused analogues of the indoxamycin natural product family in 2016.⁸⁹ Subsequently, Shaw and

collaborators employed this method in the construction of a multi-substituted isochroman skeleton,⁹⁰ which is a vital scaffold existing in a lot of natural products and biologically active compounds. Initially, the authors found that the



Scheme 10 Davies and Stoltz's total synthesis of (-)-cyclindrocyclophane A.

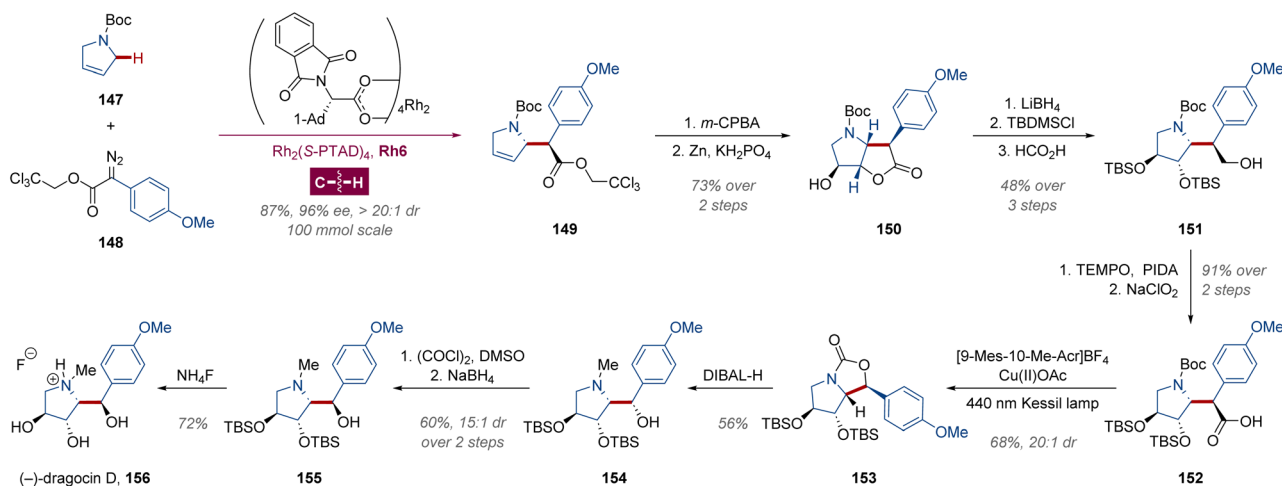


structure of panowamycin A **131** was misassigned by Ōmura,⁹¹ and the actual structure was predicted by computational NMR studies with Mahmud's updated spectra.⁹² Starting from benzyl alcohol **125**, the precursor of donor/donor carbene, phenyl-ethylidene hydrazine **127**, was prepared with (*S*)-Roche ester in 7 steps (Scheme 9). With hydrazone **127** treated with MnO₂ in MeCN, the generated diazo intermediate was added into the dilute solution of Rh₂(*S*-TCPTTL)₄ **Rh3** dropwise, and the isochroman-cored **128** and *epi*-**128** were produced in 79% yield and 4 : 1 *dr*. Fortunately, nearly complete *cis*-selectivity (>19 : 1 *cis/trans*) was measured at C10 and C11 position in both compounds **128** and *epi*-**128**, which is consistent with the configuration in the target molecules. Although the starting material **127** contains a chiral side chain, the stereoselectivity at C10 and C11 was predominantly governed by the chiral dirhodium catalyst **Rh3** during the C–H functionalization step. Lactone **129** was then obtained *via* oxidation with pyridinium chlorochromate (PCC) from **128**. Further elaboration of **129** yielded panowamycin A **131**, TM-135 **132**, and panowamycin B **133**. Meanwhile, *epi*-**128** was converted into veramycin F **134**, a compound isolated from *Streptomyces* sp. ST157608,⁹³ through sequential PCC oxidation and Wacker oxidation.

(–)-Cylindrocyclophane A **146** is a [7,7]paracyclophane natural product isolated from cytotoxic *Nostocaceae* blue-green algae in 1990,⁹⁴ and various synthetic attempts of this unique all-carbon macrocyclic structure have been reported with stereocenters settled by enzyme catalysis or chiral auxiliary ever since.⁹⁵ Building on the model synthesis of simplified [7,7]paracyclophane with previously developed dirhodium species **Rh5**,⁹⁶ Davies, Stoltz and coworkers demonstrated the asymmetric total synthesis of (–)-cylindrocyclophane A **146** *via* multifold C–H functionalizations (Scheme 10).⁹⁷ Controlled by sterically hindered catalyst Rh₂(*R-p*-PhTPCP)₄ **Rh4**, a site- and enantioselective primary C(sp³)–H alkylation of *trans*-2-hexene **136** was carried out with diazocompound **135** at the less crowded allylic position.^{96,98} The olefin **137** could be easily obtained in 25 g scale with 73% yield, >20 : 1 *rr* and 96% *ee*, and the aryl diazoacetate **138** was prepared after hydronation and a formal

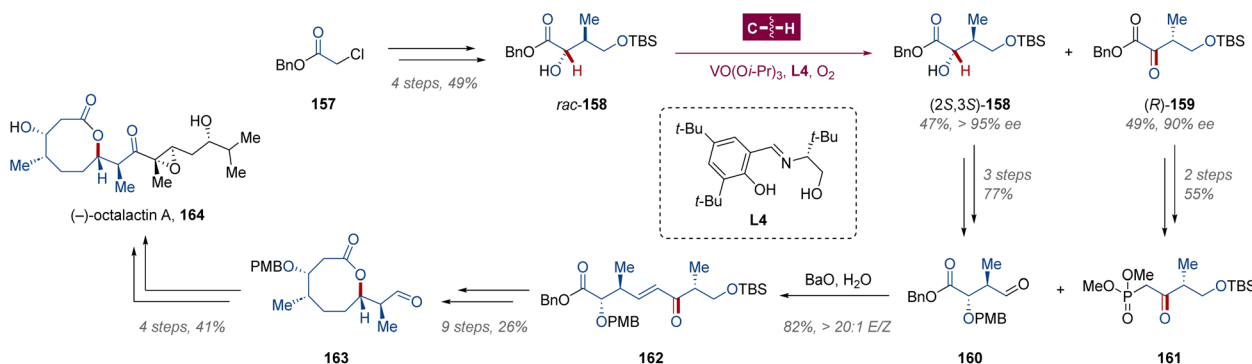
C–H arylation of α -diazo ester. Strikingly, the [7,7]-paracyclophane structure in **141** could be established within a one-pot direct cyclodimerization of **138** *via* Rh₂(*R*-2-Cl-5-BrTPCP)₄ **Rh5**-catalyzed twofold regio- and diastereoselective C(sp³)–H carbenoid insertion in 19% yield and 6 : 1 *dr*, while a superior result as 36% overall yield and 8 : 1 *dr* would be gained through a three-step macrocyclization process. Selective sequential deesterification and derivatization of the trichloroethyl and trifluoroethyl esters in **141** were conducted respectively, followed by the palladium-catalyzed acetoxylation of four C(sp²)–H bonds in macrocycle **143** with 5-(trifluoromethyl)pyridine-3-sulfonic acid used as a ligand.⁹⁹ Eventually, the asymmetric total synthesis of (–)-cylindrocyclophane A **146** was finished by installation of two alkyl side chains and final deprotection.

Very recently, the Davies group also illustrated an elegant total synthesis of the 2,3-dihydropyrrolidine natural product (–)-dragocin D, a cytotoxic metabolite of marine cyanobacteria,¹⁰⁰ with their newly developed dirhodium-catalyzed diastereoselective C(sp³)–H alkylation of *N*-Boc-2,5-dihydro-1H-pyrrole (Scheme 11).¹⁰¹ Modulated by Rh₂(*S*-PTAD)₄ **Rh6** at a mere catalyst loading of 0.05 mol%, the C–C bond in compound **149** was formed from Boc-protected 2,5-dihydropyrrole **147** *via* an 100 mmol scale diastereoselective intermolecular C–H insertion with aryl diazoacetate **148** in 87% yield, 96% *ee* and >20 : 1 *dr*. The C–C double bond was epoxidized by *m*-CPBA, and the epoxide ring was attacked from the opposite face *in situ* during the zinc-induced deprotection of the trichloroethyl group. Through a reduction–silylation–selective hydrolysis¹⁰²–reoxidation sequence, γ -butyrolactone **150** was converted into carboxylic acid **152** smoothly, followed by a photopromoted intramolecular decarboxylative carbamylation in 68% yield and 20 : 1 *dr*.¹⁰³ Subsequently, the bicyclic carbamate **153** was reduced by DIBAL-H, and the absolute configuration of the benzylic hydroxyl group of alcohol **154** was inverted, providing the corresponding hydrofluoride salt of (–)-dragocin D **156** in 15 : 1 *dr*.



Scheme 11 Davies' total synthesis of (–)-dragocin D.





Scheme 12 Toste's total synthesis of (-)-octalactin A.

3.3 V-catalyzed C(sp³)-H oxidative kinetic resolution

As an isoelectronic species of metal-carbenoid complex, metal-oxos are widely involved in the single-electron C-H functionalization process *via* HAA/radical rebound.^{19,104} Intriguingly, a unique two-electron HAA mechanism was observed in the vanadium-catalyzed enantioselective C-H oxidation,¹⁰⁵ which could be regarded as a special form of the two-electron C-H insertion with a metal-oxo intermediate. In 2008, the Toste group applied this C-H oxidative kinetic resolution in the *de novo* synthesis of (-)-octalactin A **164**,¹⁰⁶ which is a medium-ring metabolite isolated from the marine microorganism, *Streptomyces* sp.¹⁰⁷ As drawn in Scheme 12, the reactant *rac*-**158** for C-H oxidation was prepared within 4 steps from benzyl chloroacetate **157**. Catalyzed by VO(Oi-Pr)₃ and (*R*)-2-(3,5-di-*tert*-butylsalicylideneamino)-*tert*-butyl-1-ethanol **L4**, all three stereocenters in the retained (2*S*,3*S*)-**158** and generated (*R*)-**159** were constructed upon the pivotal asymmetric C-H oxidation of *rac*-**158** using 1 atm of molecular oxygen as the stoichiometric oxidant. Both (2*S*,3*S*)-**158** and (*R*)-**159** were utilized in subsequent transformation, and two modified resolution fragments, aldehyde **160** and ketophosphonate **161**, were recombined through olefination, affording the linear alkene **162** in 82% yield with complete *E*-selectivity. By employing Arndt-Eistert homologation/Wolff rearrangement for lactonization, the lactone **163** was obtained in 26% yield over 9 steps, which could be converted into (-)-octalactin A **164** with the installation of a side chain through Nozaki-Hiyama-Kishi coupling with vinyl iodide.

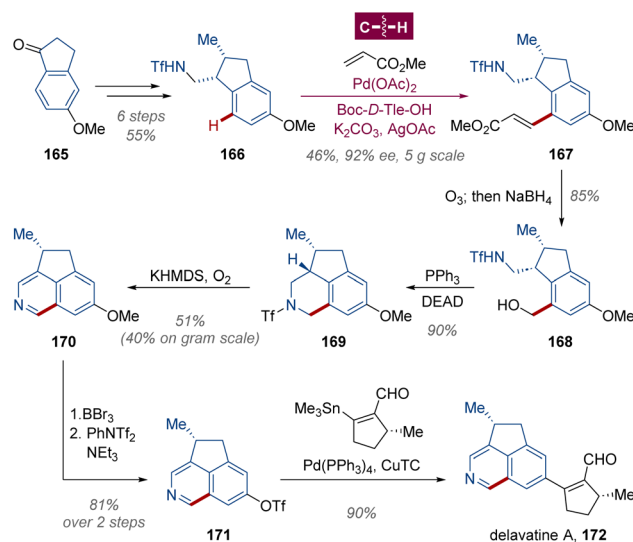
4 Syntheses *via* C-H metalation/functionalization

Opposite to the HAA/radical relay or metallocarbene C-H insertion processes discussed above, enantioselective C-H metalation/functionalization involves an inner-sphere mechanism C-H cleavage with the formation of a new carbon-metal bond, which is identified as the strictly speaking C-H activation.^{18e,f,108} Since the pioneering palladium catalysis developed by the Yu group with *N*-monoprotected amino acid (MPAA) as chiral ligands,¹⁰⁹ a variety of enantioselective C-H activation methodologies have been developed ranging from noble metal

Pd, Rh, and Ir to earth abundant metal Co, Ni, and Cu catalysis and so on.^{18h-j,l,110} To date, these transformations have become pivotal tools in the efficient synthesis of complex molecules, including the total synthesis of natural products.^{11a,o}

4.1 Pd-catalyzed enantioselective C(sp²)-H activation

The cyclopenta[*de*]isoquinoline alkaloid delavatine A **172** is a potential anticancer agent with considerable cytotoxicity isolated from *Incarvillea delavayi*, a mountain flowering plant in Chinese herbal medicine blooming at high altitudes in Southwest China.¹¹¹ In 2017, Zhang and Li hypothesized that the enantioenriched precursor **168** for the construction of an isoquinoline ring could be produced from kinetic resolution *via* triflamide-directed palladium-catalyzed enantioselective C(sp²)-H olefination followed by an ozonolysis quenched by NaBH₄ (Scheme 13).¹¹² After optimization of conditions, the intended alkenylated product **167** was obtained in 46% yield and 92% *ee* on 5-g scale from racemic indane **166** employing *N*-Boc-protected *D*-*tert*-leucine (*N*-Boc-*D*-Tle-OH) as a chiral ligand. With hydroxymethyl triflamide **168** in hand, the tetrahydroisoquinoline moiety was cyclized through Mitsunobu



Scheme 13 Zhang and Li's total synthesis of delavatine A.



substitution in 90% yield. Subsequently, the triflyl group was removed by E1cb-type reaction with KHMDS, and an oxidative aromatization took place *in situ* under O₂ atmosphere to afford isoquinoline **170**. A trifloxy group was installed in 81% yield from methoxy for the final Stille–Migita cross-coupling with stannane synthon arisen from (+)-pulegone. Notably, within this route, each of the steps could be amplified to gram-scale preparation with delavatine A **172** obtained over 1 g, illustrating the robustness and convenience of enantioselective C–H activation in total synthesis.^{10c}

Dibenzocyclooctadiene represents another significant class of natural lignan skeletons, comprising an additional unique chiral C–C axis within the biaryl framework which is arduous to be settled.^{58,113} Guided by their persistent efforts in asymmetric synthesis of axially chiral compounds *via* atroposelective C–H activation,¹¹⁴ Shi and coworkers assumed that the Pd-catalyzed enantioselective C–H alkylation facilitated by a chiral transient directing group (cTDG) would be a mature strategy¹¹⁵ for these cyclic axially chiral lignans,¹¹⁶ such as (+)-isoschizandrin **177** from *Schisandra chinensis*,¹¹⁷ (–)-steganone *ent*-**182** from *Steganotaenia araliacea*¹¹⁸ and their analogues. With an imine formed *in situ* as the cTDG group, the transannular C(sp²)–H activation was conducted, and the atroposelectivity was

modulated by the residue of amino acid *L*-tert-leucine (*L*-Tle-OH), generating axially chiral biaryls **174** and **179** in 2-gram and 3-gram scale respectively (Scheme 14a and b). Aldehyde **174** was transformed to dimethyl acetal for desilylation and homologation, and the *Z*-olefin **176**, a key intermediate for (+)-isoschizandrin **177**,¹¹⁹ was created in 1.35 g with 98% *ee* through stereoselective reduction by Ti(O*i*-Pr)₄ and *i*-PrMgCl.¹²⁰ Similarly, the precursor to (+)-steganone **182** (ref. 121) was then yielded in 1.11 g with 96% *ee* from C(sp²)–H alkynylated product **179**, avoiding the usage of stoichiometric sulfoxide as a chiral auxiliary in previous work *via* asymmetric C(sp²)–H alkenylation.¹²²

Capitalizing on a negligibly adjusted Pd/cTDG strategy for the establishment of axially chiral biaryls, in 2019, Shi and colleagues realized the enantioselective total synthesis of TAN-1085 **190** through axial-to-central chirality transfer (Scheme 14c),¹²³ which is a *trans*-9,10-dihydrophenanthrene-9,10-diol-cored antibiotic produced by *Streptomyces* sp. S-11106.¹²⁴ Prepared by Suzuki–Miyaura cross-coupling of aryl bromide **183** and pinacol boronate **184**, the reactant **185** was atroposelectively alkenylated by *n*-butyl acrylate catalyzed by Pd(OAc)₂ and *L*-Tle-OH, providing enantiopure biaryl **186** in 1.08 g with 99% *ee*. The C–C double bond was cleaved to form dialdehyde

a) Shi's formal synthesis of (+)-isoschizandrin



b) Shi's formal synthesis of (+)-steganone



c) Shi's total synthesis of TAN-1085



Scheme 14 Shi's total (or formal) syntheses of dibenzocyclooctadiene and dihydrophenanthrene-9,10-diol natural products.



186, followed by a SmI_2 -mediated radical cyclization with an *in situ* site-selective monobenzoylation of *trans*-9,10-diol to fabricate the fundamental scaffold of TAN-1085 **190**, which was eventually afforded after further glycosylation, oxidation and deprotection.

4.2 Co-catalyzed enantioselective $\text{C}(\text{sp}^2)$ -H annulation

Owing to its low toxicity, abundant availability, cost-effectiveness and unique reactivity, cobalt-catalyzed enantioselective C-H activation has attracted widespread attention in recent years.^{110a,b,125} With long-term interests in cobalt catalysis,¹²⁶ the Shi group reported an elegant protocol for asymmetric total syntheses of chiral 1-substituted tetrahydroisoquinoline (THIQ) natural alkaloids in 2023 (Scheme 15).¹²⁷ Combined with salicyloxazoline (Salox) **L5**, 1-(3,4-dimethylbenzyl)-1,2-dihydroisoquinoline **192** was obtained in 1.42 g with 98% *ee* via cobalt-catalyzed kinetic resolution (Scheme 15a). Enantiopure natural product (–)-norlaudanosine **195** was then synthesized from C-H annulated intermediate **192** undergoing a desilylation–hydrogenation–deacylation sequence seamlessly, which could be transformed to opium alkaloids (+)-laudanosine **196** and (–)-xylopinine **198** via reductive amination and Mannich aminomethylation in yields of 76% and 81% respectively,¹²⁸ as well as the morphinandienone alkaloid (+)-seberiferine **197** with further oxidative dearomatization/cyclization treated with the mixture of [bis(trifluoroacetoxy)iodo]benzene (PIFA), phosphotungstic acid (HPA) and $\text{BF}_3 \cdot \text{OEt}_2$ from (+)-laudanosine **196**.¹²⁹ For tetrahydroisoquinoline alkaloid (+)-cryptostyline II **202**, a probe for dopamine receptor D1 isolated from *Cryptostylis fulva*,¹³⁰ the authors carried out the

desymmetrization of benzhydrylamine derivative **199** via Co-catalyzed enantioselective C-H annulation with Salox **L6**, resulting in the enantioenriched product **200** in 1.52 g with 96% *ee* (Scheme 15b). Within 4 standard reactions similar to (+)-laudanosine **196**, the desired natural product (+)-cryptostyline II **202** was generated in 99% *ee*. Meanwhile, this strategy was also manifested as a fruitful method for the construction of N- α -chiral bioactive molecules, involving (+)-solifenacin,¹³¹ (+)-FR115427 (ref. 132) and (+)-NPS R-568.¹³³

4.3 Pd-catalyzed enantioselective $\text{C}(\text{sp}^3)$ -H arylation

In view of the inert molecular orbital profile and lower acidity than $\text{C}(\text{sp}^2)$ -H bond for metalation, the asymmetric $\text{C}(\text{sp}^3)$ -H activation has been relatively less investigated and mainly limited to palladium catalysis,^{18f,134} while the majority of applications in total synthesis are diastereoselective transformations.¹³⁵ Based on their intensive efforts on Pd(0) catalyzed enantioselective $\text{C}(\text{sp}^3)$ -H activation,¹³⁶ Baudoin and collaborators accomplished the asymmetric total synthesis and structural revision of (+)-indidene **C 212** (Scheme 16),¹³⁷ a prenylated polyketide with anticancer properties isolated from *Streblus indicus* grown in South Asia.¹³⁸ With the substrate **207** prepared through an $\text{S}_{\text{N}}2$ reaction between substituted benzyl bromide **204** and dimethyl malonate derivative **206**, the enantioselective $\text{C}(\text{sp}^3)$ -H intramolecular arylation was actualized by the cooperation with palladium and a bulky IBiox-type chiral N-heterocyclic carbene (NHC) ligand **L7** revealed in their previous study,¹³⁹ yielding cyclopentane compound (*R*)-**208** with 98% *ee*. Then the corresponding diol **209** was obtained through a cascade of diastereoselective Krapcho

a) Shi's total synthesis of (–)-norlaudanosine, (+)-laudanosine, (+)-seberiferine and (–)-xylopinine

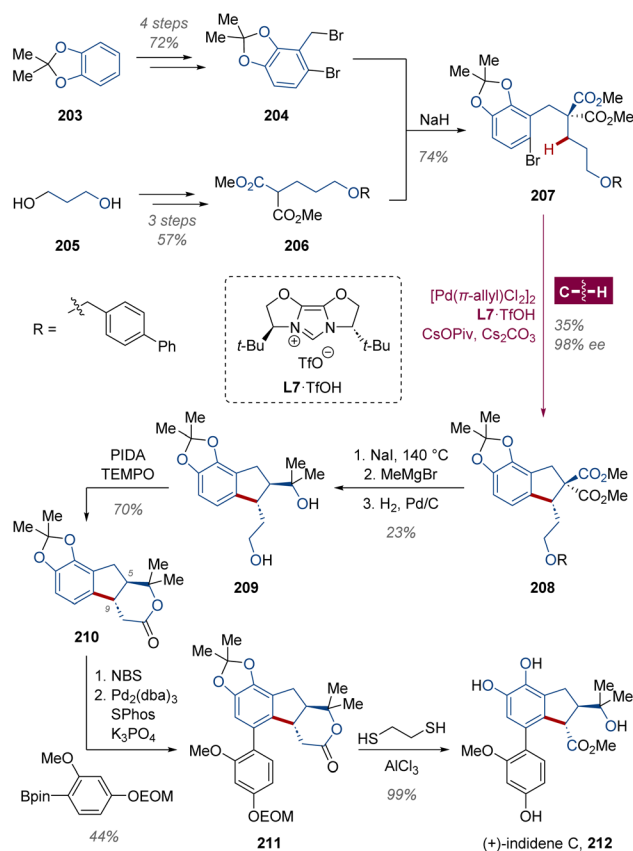


b) Shi's total synthesis of (+)-cryptostyline II



Scheme 15 Shi's total synthesis of chiral 1-substituted tetrahydroisoquinoline alkaloids.





Scheme 16 Baudoin's total synthesis of (+)-indidene C.

decarboxylation, double Grignard addition and Pd/C-catalyzed hydrogenolysis. After a mild oxidation of the primary hydroxyl group with 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) and (diacetoxyiodo)benzene (PIDA), the lactone **210** was created in 70% yield, of which the absolute configuration was determined as (5*S*,9*R*) by vibrational circular dichroism (VCD) analysis.¹⁴⁰ Followed by site-selective bromination, Suzuki–Miyaura cross-coupling and deprotection, (+)-indidene C **212** was ultimately generated within 13 steps.

5 Conclusion and outlook

In summary, with the flourishing methodologies of transition metal-catalyzed enantioselective C–H functionalization, a range of sophisticated natural products were synthesized from prochiral starting materials through streamlined and scaled-up procedures, facilitating the exploration of their potential bioactivities and applications as new pharmaceutical candidates and others. The HAA/radical relay strategy serves as an efficient approach for chiral alcohols and amines, especially for pyrrolidines bearing an α -C-stereocenter next to nitrogen atom, while the enantioselective metal–carbenoid insertion represents an alternative protocol for methylene C(sp³)-H functionalization within the aliphatic strain particularly in the absence of any heteroatoms. On the other side, those traditional asymmetric C–H activation methodologies undergoing an inner-sphere C–H metalation mechanism, significantly promote the

construction of multifarious compounds incorporating chirality elements other than C-centrally chiral molecules. Remarkably, considering the unnecessary of pre-functionalization, these highly stereoselective transformations could be expanded to gram scale or even decagram scale with minimum waste, accelerating their future adoption in industrial manufacturing.

Despite considerable progress, several challenges remain in applying stereoselective C–H functionalization to target-oriented synthesis. First, current methods are predominantly limited to C–C bond formations using a narrow set of well-established catalytic systems. The development of novel catalysis to directly forge C–N and C–O bonds—ubiquitous linkages in natural products—would therefore significantly broaden the scope and utility of this approach. Furthermore, these synthetic methodologies are frequently employed for chiral induction at an early stage rather than the establishment of key molecular scaffolds in complex natural products. There is a pressing need to apply these methods to access sophisticated biogenic molecules with multiple chiral elements, such as the glycopeptide antibiotic vancomycin, which features central, axial, and planar chirality.¹⁴¹ Finally, while asymmetric C–H functionalization offers clear benefits in step- and atom-economy, the complexity and cost of catalysts and ligands can hinder broader application. Simplifying catalytic systems and developing inexpensive, readily accessible chiral ligands are crucial for enabling more extensive and streamlined synthetic campaigns. In conclusion, we hope this review will inspire further innovations towards more efficient, sustainable, and simplified total syntheses of natural metabolites *via* enantioselective C–H functionalization, ultimately contributing to their practical application for human benefit.

Author contributions

B.-F. S. conceived the topic of this review. P.-F. Q. developed the conceptual framework and summarized the relevant literature. P.-F. Q. and B.-F. S. wrote the manuscript.

Conflicts of interest

The authors declare no conflict of interest.

Data availability

No primary research results, software or code have been included and no new data were generated or analyzed as part of this review.

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