REVIEW

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Recent advances in the total synthesis of alkaloids using chiral secondary amine organocatalysts

Yuta Nakashima, Kenta Rakumitsu [ID] and Hayato Ishikawa [ID] *

Since the early 21st century, organocatalytic reactions have undergone significant advancements. Notably, numerous asymmetric reactions utilizing chiral secondary amine catalysts have been developed and applied in the total synthesis of natural products. In this review, we provide an overview of alkaloid syntheses reported since 2017, categorized by scaffold, with a focus on key steps involving asymmetric reactions catalyzed by secondary amine organocatalysts.

Introduction

Originally, the term 'alkaloid' referred to a basic compound isolated from plants. However, it is now used more broadly to describe nitrogen-containing secondary metabolites, which are found not only in plants but also in bacteria and animals. Among the vast number of alkaloids discovered in nature, many have already been utilized as medicines due to their potent biological activities. Due to their complex structures and significant biological activities, many alkaloids have become popular targets for total synthesis, driving advancements in synthetic organic chemistry.

Since the early 21st century, organocatalytic reactions have undergone significant advancements. In particular, chiral secondary amine organocatalysts, such as proline (**1**),[1] the

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diphenylprolinol trimethylsilyl ether catalyst (**2**, Hayashi–Jørgensen catalyst),[2] and the 2,3,5-trisubstituted-4-imidazolidi-none catalyst (5-benzyl-2-(*tert*-butyl)-3-methylimidazolidin-4-one (**3**), MacMillan catalyst),[3] have been employed to catalyze several key enantioselective reactions, including asymmetric aldol, Michael, Mannich, Diels–Alder, and ene reactions, as well as α-oxidation and epoxidation (Fig. 1).[4] These reactions consistently proceed with high stereoselectivity (both enantio- and diastereoselectivity) and do not require stringent conditions, such as anhydrous or anoxic environments. Furthermore, organocatalytic reactions are easily adapted to domino reactions, where multiple reactions occur in succession, as well as to one-pot reactions, where several chemical transformations are carried out simultaneously in a single flask.[5] This adaptability is due to the catalyst, which is a small molecule with a secondary amine moiety and does not interfere with subsequent reactions. Therefore, they are widely employed in the total synthesis of natural products and phar-

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Kenta Rakumitsu was born in Fukuoka Prefecture, Japan. He received his BSc and PhD degrees in science from Kumamoto University in 2016 and 2021, respectively. In 2021, he moved to Seikei University of Science and Technology as an assistant professor. In 2024, he joined the Faculty of Pharmaceutical Sciences, Chiba University as an assistant professor. He focuses on the total synthesis of natural products and the structural chemistry of organic compounds.
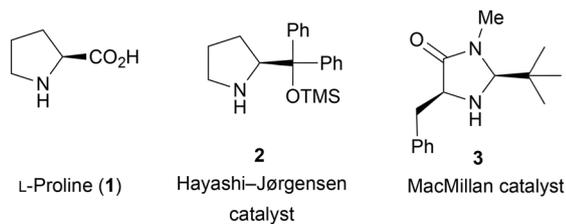
Kenta Rakumitsu

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Fig. 1 Representative chiral secondary amine organocatalysts.

maceuticals.[6] In 2016, we published a review article on the asymmetric total synthesis of 21 alkaloids utilizing chiral secondary amine organocatalysts.[7] This perspective article outlines synthetic strategies and highlights the use of asymmetric organocatalytic reactions as a key step in the synthesis of a total of 24 alkaloids published from 2017 to early 2024.

Indole alkaloids

Indole alkaloids represent one of the largest classes of alkaloids and are predominantly biosynthesized from tryptophan.[8] Several of these alkaloids, such as vinblastine, vincristine, and reserpine, have important bioactivities and are already employed as therapeutic agents. Additionally, a wide variety of scaffolds are found due to the high reactivity of the indole core. As a result, indole alkaloids continue to capture the attention of synthetic chemists.

In 2017, divergent total syntheses of naucleamide-related alkaloids were reported by Jia and coworkers (Scheme 1).[9] The key reaction in their synthesis was a contiguous organocatalyzed asymmetric Michael addition/Pictet–Spengler cyclization to construct a tetracyclic ring system. Thus, an α,β,γ,δ-unsaturated aldehyde **9**, the precursor for the Michael reaction, was synthesized in four steps from commercially
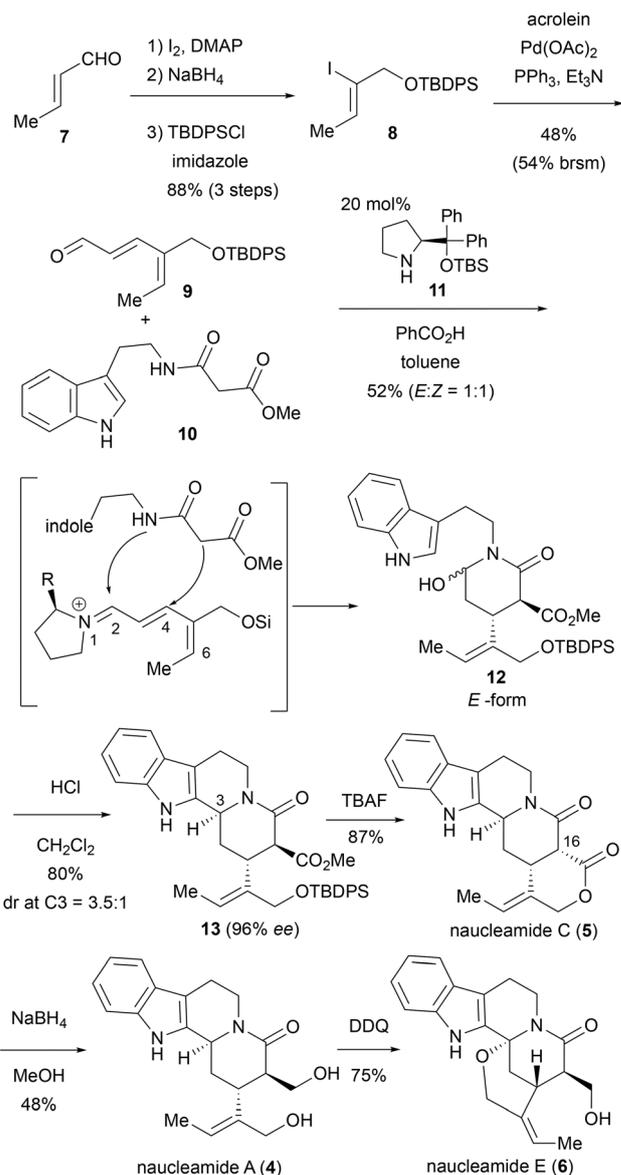
Scheme 1 Synthesis of naucleamide-related indole alkaloids by Jia *et al.* in 2017.

Hayato Ishikawa

Hayato Ishikawa received a PhD degree from Chiba University in 2004. After postdoctoral work (2004–2006) in the Scripps Research Institute, he was promoted to the rank of assistant professor at the same institute (2006–2007). In 2007, he moved to Tokyo University of Science as an assistant professor. In 2011, he moved to Kumamoto University and was promoted to associate professor. He was promoted to full professor at Kumamoto University in 2018. He joined the Faculty of Pharmaceutical Sciences, Chiba University in 2021 as a full professor.

available crotonaldehyde (**7**). These steps included α-iodination, reduction of the aldehyde followed by silylation of the resulting primary alcohol, and a Heck reaction to couple with acrolein. The Michael reaction, catalyzed by secondary amine **11**, between aldehyde **9** and indole-containing malonamate **10** in the presence of catalytic benzoic acid proceeded selectively *via* 1,4-addition, rather than 1,2- or 1,6-addition, to generate the iminium ion intermediate *in situ*. Spontaneous cyclization through nucleophilic addition of the amine to the aldehyde produced hemiaminal **12** in the *E* form and its geometrical isomer (*Z* form) as a 1 : 1 mixture in moderate yield. The subsequent Pictet–Spengler reaction under acidic conditions yielded **13**, possessing the C3*S* configuration, in good yield and selectively. At this stage, the enantiomeric excess

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was found to be 96%. After removal of the silyl group, the generated alcohol spontaneously cyclized to form lactone **5** along with the isomerized methoxycarbonyl group at C16. This lactone **5** is a monoterpenoid indole alkaloid found in plants of the genus *Nauclea* and named naucleamide C. Reduction of natural product **5** with NaBH$_4$ resulted in a lactone-selective reduction, followed by thermodynamic isomerization at the C16 position to yield the natural product naucleamide A (**4**) in moderate yield. The total synthesis of naucleamide E (**6**) was achieved by a biomimetic oxidation using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) with **4** as the substrate. In addition, Jia and coworkers also synthesized geissoschizine and three related alkaloids from the key intermediate **13**. Their synthetic strategy allows access to natural products in a reduced number of steps (6–11 steps from commercially available materials) and enables divergent total syntheses of naucleamide- and geissoschizine-related monoterpenoid indole alkaloids.

Yang and coworkers achieved the total synthesis of actinophyllic acid (**14**), a unique monoterpenoid indole alkaloid containing a 1-azabicyclo[4.2.1]nonane ring system (Scheme 2).[10] To date, several asymmetric total syntheses and formal total syntheses of **14** have been reported by the groups of Overman,[11] Kwon,[12] and Qin.[13] The key reaction in Yang's synthesis is the modified dual iridium/amine catalytic allylation developed by Carreira's group.[14] In this reaction, indole-containing allyl alcohol **15** and aldehyde **16** were treated with an iridium catalyst (iridium and chiral phosphine ligand **17**) and an amine catalyst **18** in the presence of (MeO)$_2$PO$_2$H as a promoter, resulting in the coupling product **19** in excellent yield, enantioselectivity (>99% ee), and diastereoselectivity (dr = 12 : 1). Subsequent diastereoselective addition of the enolate derived from **20** to the aldehyde of **19** followed by TBS protection afforded **21** as a single isomer, with four contiguous stereocenters being controlled. The stereocontrol at C20 was explained using the Felkin–Anh model. For the inversion of the C19 stereocenter, kinetic protonation at low temperature was conducted. Next, the vinyl group of **22** was converted into a methoxycarbonyl group in a three-step transformation involving oxidative cleavage of the olefin moiety, oxidation of the resulting aldehyde to carboxylic acid, and methylation with TMSCHN$_2$ (from compound **22** to **23**). The construction of the seven-membered ring was achieved by amide-selective partial reduction with LiBHEt$_3$ and Mannich-like reaction with Tf$_2$O on the generated hemiaminal (from compound **23** to **24**). To close the 1-azabicyclo[4.2.1]nonane ring system, the mesyl group was attached as the leaving group in two steps. Following selective deprotection of *N*-Boc on the pyrrolidine core followed by cyclization under basic condition afforded pentacyclic product **25** in 70% yield for four steps. Finally, actinophyllic acid (**14**) was accessed after desilylation, oxidation of the resulting alcohol, deprotection of *N*-Boc, Overman's aldol reaction with formaldehyde for installation of the tetrahydrofuran ring, and hydrolysis.[11]

In recent years, concerted asymmetric reactions involving secondary amine catalysts and metal catalysts have made
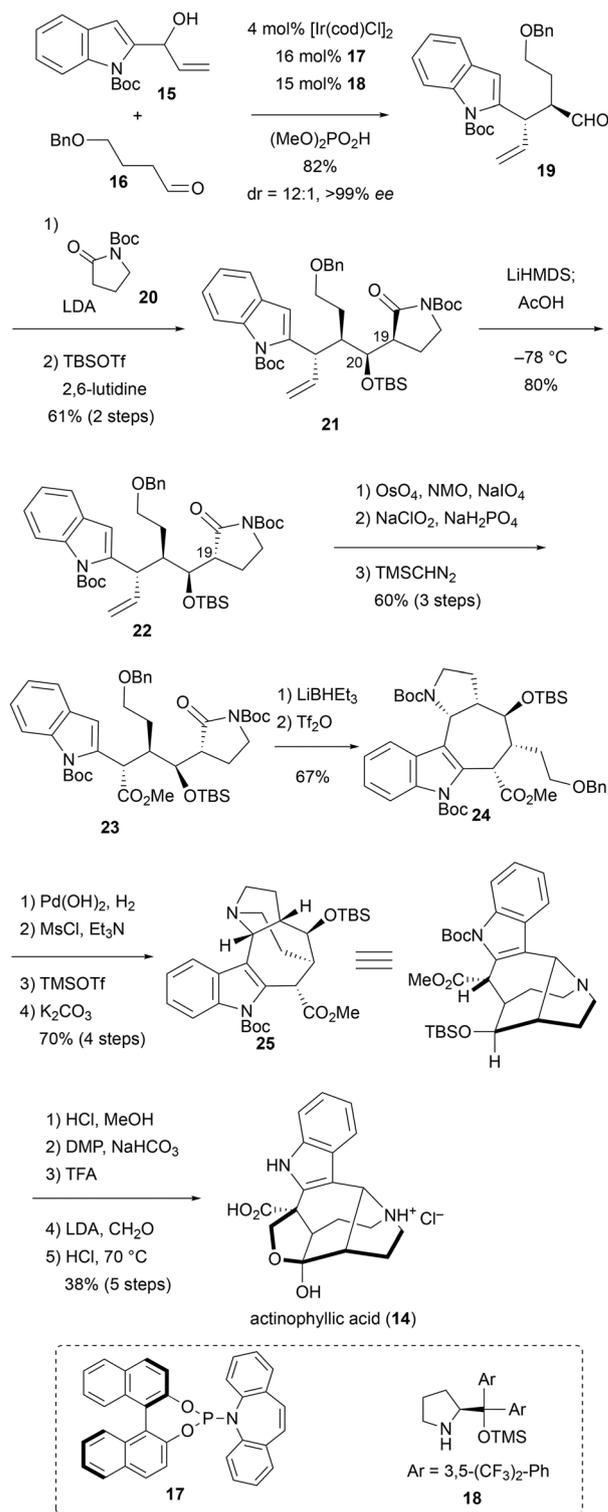
Scheme 2 Synthesis of actinophyllic acid by Yang et al. in 2018.

significant progress. In particular, the dual iridium/amine catalytic allylation developed by Carreira et al. has been employed in numerous total syntheses. In the synthesis by Yang et al., this reaction was carried out in the presence of an

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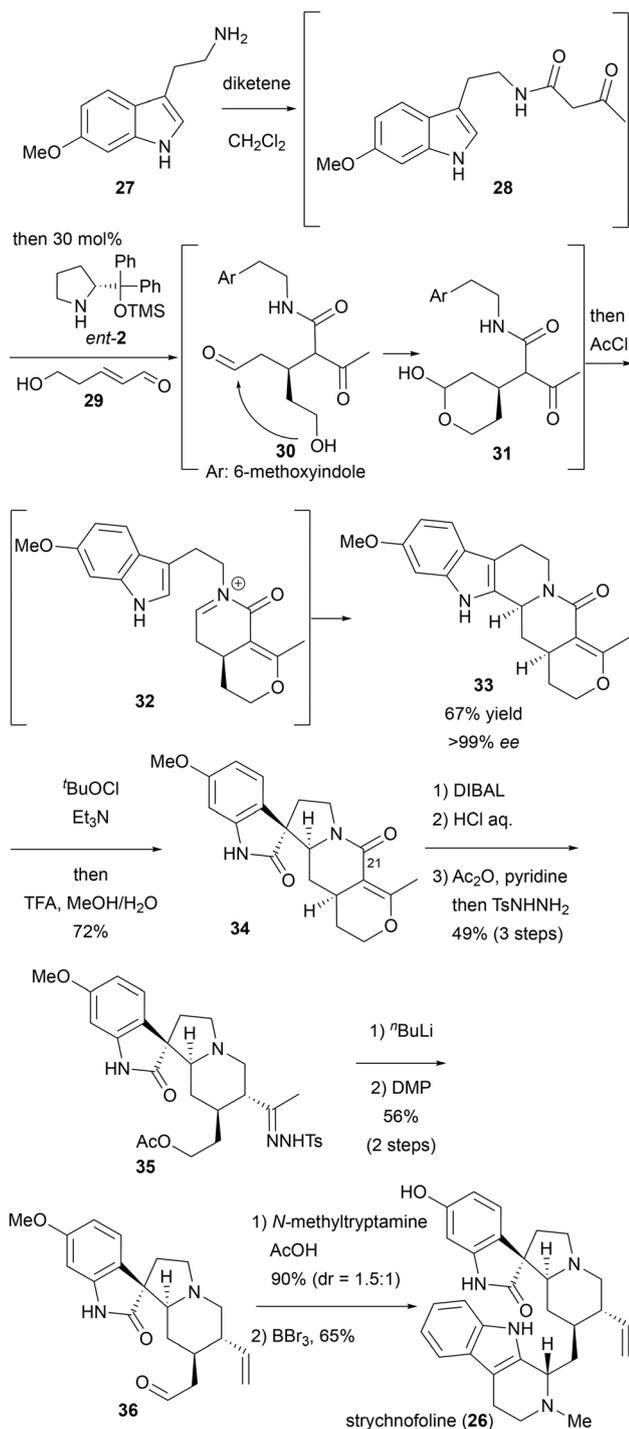*Org. Biomol. Chem.*, 2024, **22**, 9319–9341 | 9321

indole ring and the approach proved to be a powerful tool for the total synthesis of indole alkaloids.

In 2018, Xu and coworkers reported the total synthesis of the *Strychnos* alkaloid strychnofoline (**26**), which possesses significant anticancer activity (Scheme 3).[15] First, the one-pot acylation/asymmetric Michael reaction/Pictet–Spengler reaction developed by Franzén *et al.* in 2011 was performed to construct
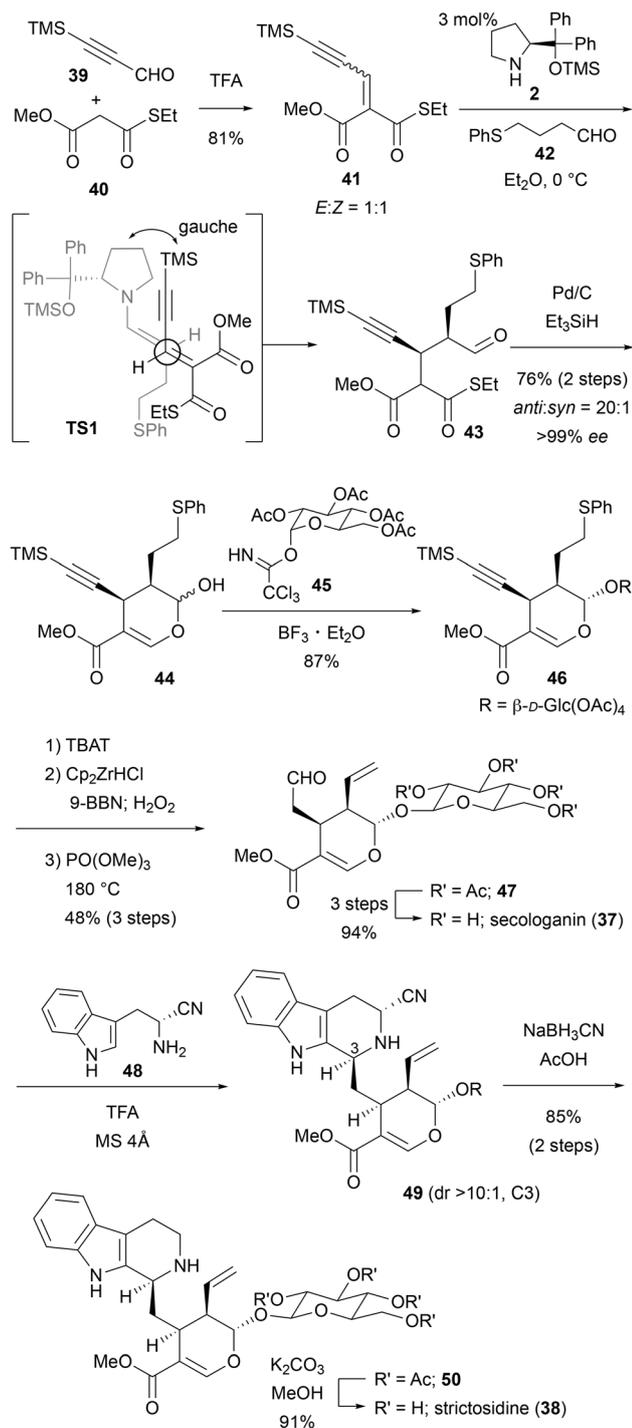
the pentacyclic ring system.[16] Thus, 6-methoxytryptamine (**27**) was treated with diketene to afford β-ketoamide **28**. Next, the addition of α,β-unsaturated aldehyde **29** and the Hayashi–Jørgensen catalyst (*ent*-**2**) to the same reaction vessel initiated an asymmetric Michael addition, yielding **30**, followed by spontaneous cyclization to give intermediate lactol **31**. The subsequent addition of AcCl to lactol **31** led to the ring opening of the lactol, hemiaminal formation, and a diastereoselective Pictet–Spengler reaction *via* intermediate **32**, resulting in the formation of **33** in good yield with excellent enantioselectivity (67% yield, >99% ee). Treatment of *t*BuOCl with indole **33** yielded chloroindolenine intermediate, which subsequently underwent a rearrangement reaction under acidic methanol conditions to produce oxindole **34** as a single isomer. Following selective reduction of the C21 amide using DIBAL, hydrolysis of the cyclic enol ether under acidic conditions, acetylation of the generated primary alcohol, and transformation of the ketone to tosylhydrazone, hydrazone **35** was obtained. After the Shapiro reaction and deacetylation of **35**, the resulting primary alcohol was oxidized with Dess–Martin reagent to produce aldehyde **36**. Finally, the total synthesis of strychnofoline (**26**) was achieved through the Pictet–Spengler reaction with *N*-methyltryptamine, followed by demethylation using BBr₃. In this total synthesis, the one-pot cascade reaction, which included the asymmetric Michael addition and Pictet–Spengler reaction to construct the pentacyclic system, enabled the efficient synthesis of strychnofoline (**26**) from simple 6-methoxytryptamine (**27**) in just nine steps.

In 2019, Ishikawa and coworkers reported the first total synthesis of secologanin (**37**), the monoterpene moiety in the biosynthesis of monoterpenoid indole alkaloids (Scheme 4).[17] In addition, the Ishikawa group achieved the synthesis of strictosidine (**38**), a common intermediate in the biosynthesis of more than 3000 monoterpenoid indole alkaloids.[18a] Having established a straightforward synthetic method for secologanin (**37**) and strictosidine (**38**), they successfully achieved the total synthesis of 33 indole alkaloids by fully utilizing bioinspired reactions.[17,18] The key reactions in the synthesis of **37** were contiguous organocatalytic Michael addition followed by Fukuyama reduction[19] and spontaneous cyclization to construct the dihydropyran ring. The precursor of the Michael reaction **41** was synthesized by Knoevenagel condensation of commercially available aldehyde **39** and a malonic acid derivative **40**. Subsequent enantioselective Michael reaction using electrophile **41** and aldehyde **42** containing a sulfide moiety as a nucleophile in the presence of catalyst **2** provided Michael adduct **43**. An important factor in achieving the unusual *anti*-selectivity required for the total synthesis was the substitution of an alkynyl group on the electrophile (**TS1**). Without purification, reduction of adduct **43** under Fukuyama conditions selectively converted the thioester into the aldehyde followed by spontaneous cyclization to provide dihydropyran **44** in good yield with excellent enantio- and diastereoselectivity. When hemiacetal **44** was treated with glycosyl donor **45** in the presence of BF₃·Et₂O, diastereoselective glycosylation proceeded to afford **46** as a single isomer in 87% yield. A further three-step

Scheme 3 Synthesis of strychnofoline by Xu *et al.* in 2018.

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Scheme 4 Syntheses of secologanin and strictosidine by Ishikawa et al. in 2019.
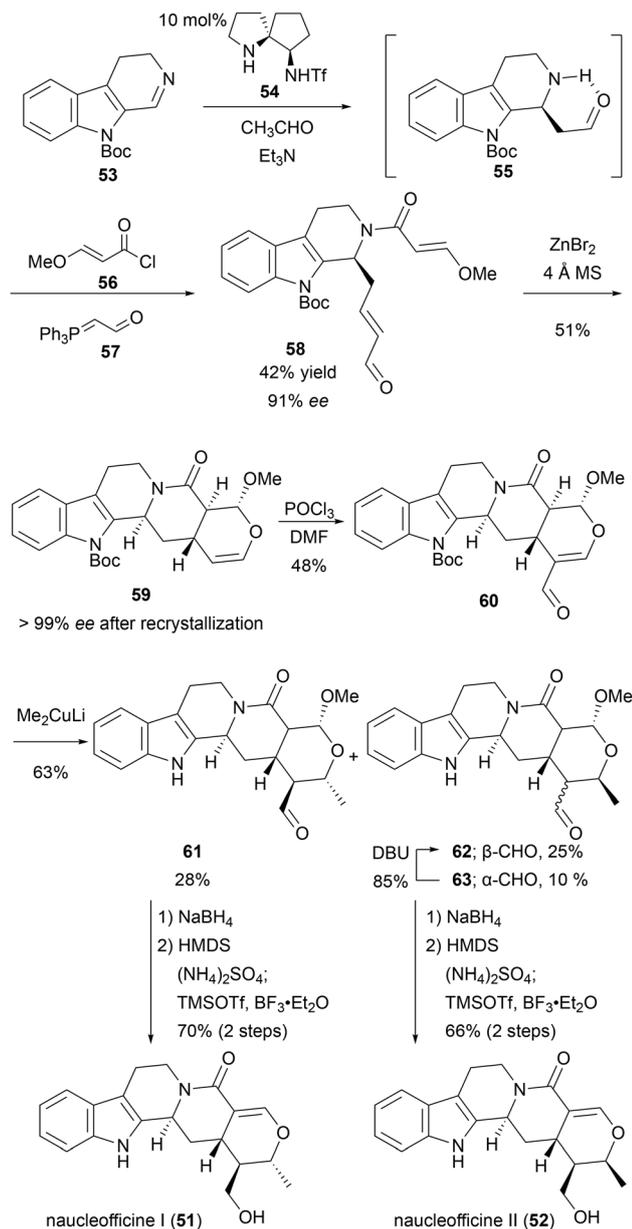
transformation to prepare the aldehyde and terminal olefin, including deprotection of TMS group, hydroboration-oxidation, and elimination of sulfoxide by heating, provided secologanin tetraacetate (47), which is a key intermediate for the collective synthesis of monoterpenoid indole alkaloids on the decagram scale. Finally, the total synthesis of secologanin (37) was achieved by removing the acetyl group from the sugar

moiety. The total synthesis of strictosidine (38) was subsequently achieved as shown in Scheme 4. Thus, the diastereoselective Pictet–Spengler reaction with 47 and a α-cyanotryptamine 48 afforded 49 as almost single isomer (dr = >10 : 1). The reasons for this intriguing diastereoselectivity have been experimentally and computationally verified; for details, see the original report.[18a] Next, the reductive decyanation of 49 with sodium cyanoborohydride in the presence of acetic acid provided strictosidine tetraacetate (50) in excellent yield (85% over two steps). Finally, removal of the four acetyl groups yielded strictosidine (38). The total synthesis of 38 was accomplished with a yield of 20% over ten steps and was achieved on a gram scale.

Tu and coworkers reported the total syntheses of naucleofficine I (51) and II (52) (Scheme 5).[20] The key reaction was a four-component asymmetric Mannich/acylation/Wittig reaction, catalyzed by the originally developed bifunctional spirocyclic pyrrolidine 54. Thus, 3,4-dihydro-β-carboline 53 was treated with acetaldehyde in the presence of secondary amine catalyst 54, which contains a sulfonamide moiety, to yield 55. Acyl chloride 56 and Wittig reagent 57 were then added to the same reaction vessel, resulting in the desired compound 58 in 42% yield over three steps and 91% ee. Subsequently, the intramolecular hetero-Diels–Alder reaction with ZnBr₂ gave pentacyclic product 59 in 51% yield and superb diastereoselectivity (dr >20 : 1). Then, recrystallization of 59 enhanced the enantio-purity to >99% ee in 85% yield. X-ray crystallographic analysis confirmed the absolute configuration. After a Vilsmeier–Haack reaction, methylation with Me₂CuLi afforded the diastereomeric products 61–63. Undesired 63 could be converted into 62 by isomerization of the α position of aldehyde with 1,8-diazabicyclo[5.4.0]-7-undecene (DBU). A further two-step transformation including reduction of the aldehyde to alcohol followed by elimination of the methoxy group with 1,1,1,3,3,3-hexamethyl-disilazane (HMDS) via the oxonium cation provided naucleofficine I (51) and II (52) from 61 and 62 in good yield, respectively. A one-pot, four-component asymmetric reaction using a secondary amine catalyst developed by Tu et al. completed the total synthesis of the complex pentacyclic alkaloids 51 and 52 in just seven steps.
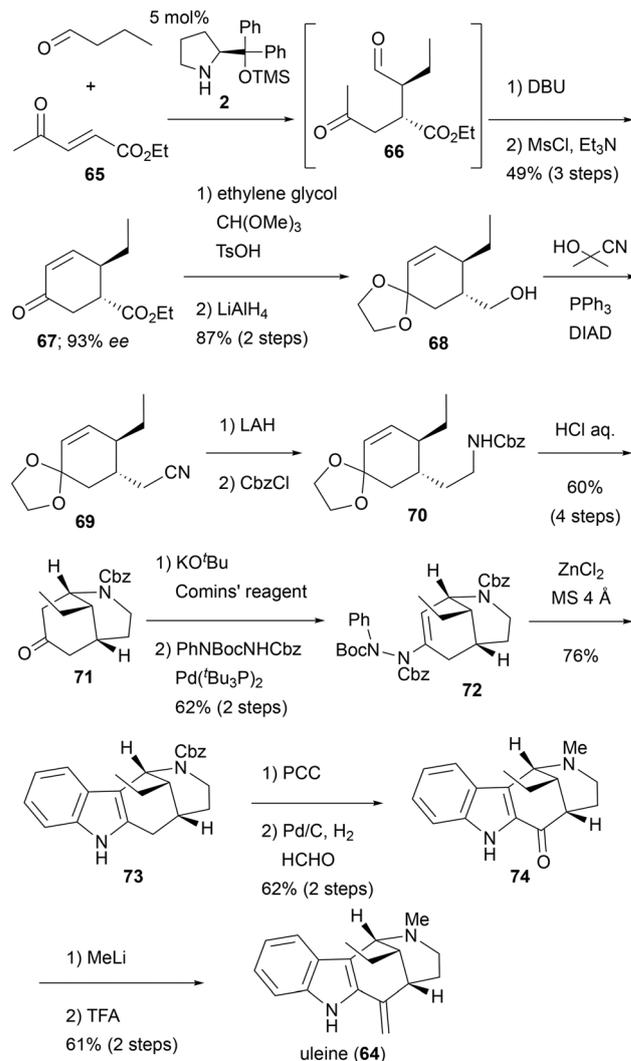
The Cho group reported the total synthesis of uleine (64) with modified Fischer indolization and asymmetric organocatalytic reaction as the key steps (Scheme 6).[21] Their synthesis started from Ma's organocatalytic chiral cyclohexanone synthesis.[22] Thus, γ-keto-α,β-unsaturated ester 65 was treated with n-butanal in the presence of catalyst 2 to afford the Michael adduct 66. Subsequently, the adduct 66 underwent intramolecular aldol reaction in the presence of DBU. Without purification, a mesylation of the generated alcohol gave cyclohexanone 67 in good yield and excellent enantioselectivity (49% over three steps and 93% ee). Conversion of the ketone into the cyclic acetal and reduction of the ester provided alcohol 68. The installation of the cyano group onto compound 68 was achieved via the Mitsunobu reaction, utilizing acetone cyanohydrin as the cyanide source to yield compound 69. Following

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Scheme 5 Syntheses of naucleofficine I and II by Tu *et al.* in 2019.

Scheme 6 Synthesis of uleine by Cho *et al.* in 2020.

a two-step transformation, which involved the reduction of the cyano group and the protection of the resulting primary amine with CbzCl, compound **70** was obtained. Subsequently, the removal of the acetal protection, followed by a spontaneous intramolecular aza-Michael addition, yielded the 2-azabicyclo[3.3.1]nonane core **71**, with an overall yield of 60% over four steps. For regioselective indolization, the ene-hydrazide **72** was prepared by palladium-catalyzed Buchwald–Hartwig coupling reaction *via* the enol triflate. The Zn-mediated indolization proceeded efficiently to afford the desired indole **73** in 76% yield. Regioselective oxidation of the benzyl position was achieved with PCC. Next, continuous deprotection of *N*-Cbz and *in situ* reductive methylation afforded **74** in good yield.
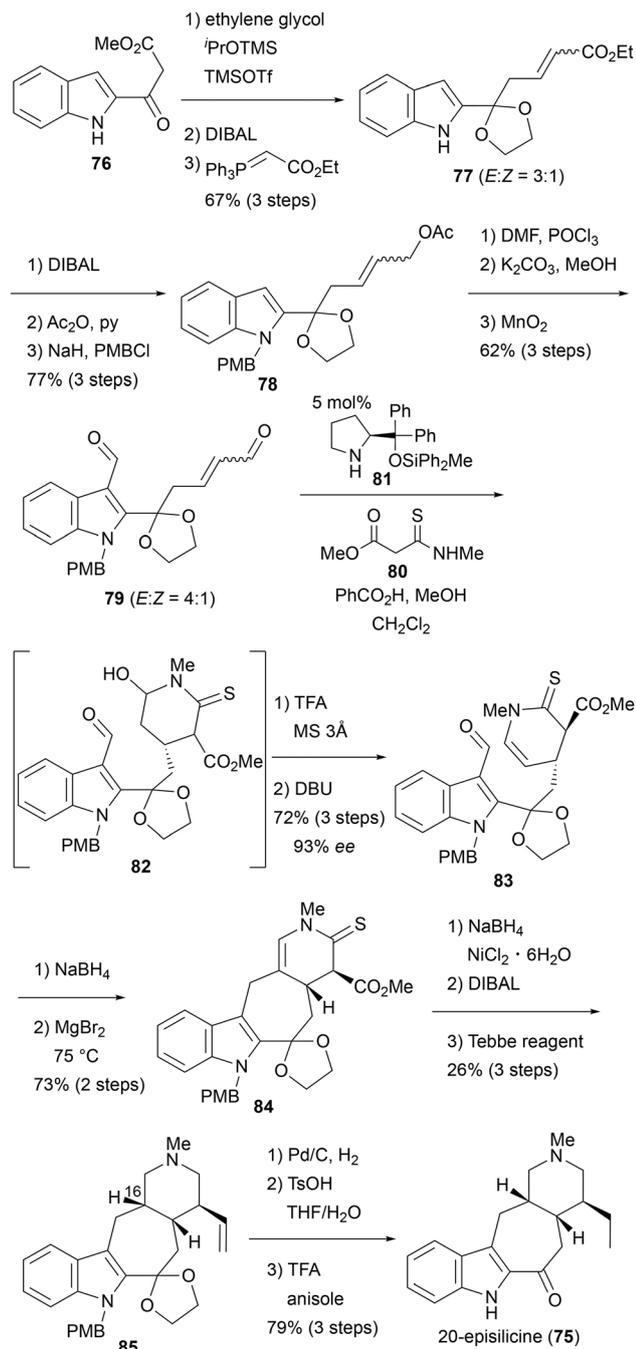
The final two-step transformation, including addition of MeLi and dehydration under acidic conditions, gave uleine (**64**). The Cho group also reported the formal synthesis of tubifolidine, an indole alkaloid containing a pentacyclic core. Cho *et al.* efficiently synthesized the 2-azabicyclo[3.3.1]nonane core from the chiral cyclohexanone developed by Ma. Modified Fishier indole synthesis thus enables the late-stage introduction of indole using ketones as substrates, where regioselectivity is an issue.

More recently, the Ishikawa group reported the first total synthesis of 20-episilicine (**75**) using an organocatalytic reaction they had previously developed (Scheme 7).[23] Their synthesis started from the preparation of **79**, a substrate for the key organocatalytic reaction. First, Noyori's protocol[24] achieved indole-conjugated ketone selective acetalization using β-esters **76**. Reduction of the ester and Wittig reaction of resulting aldehyde afford α,β-unsaturated ester **77** in good yield (67% over three steps). Next, the ester was reduced, and the generated alcohol was protected with an acetyl group. The following pro-

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Scheme 7 Synthesis of 20-episilicine by Ishikawa *et al.* in 2023.

tection with PMBCl and NaH provided PMB-protected indole **78** in 77% yield over three steps. The three-step conversion, including the Vilsmeier–Haack reaction to install a formyl group, removal of the acetyl group, and oxidation with MnO$_2$ of the yielded primary alcohol, gave the α,β-unsaturated aldehyde **79** as an *E/Z* mixture. Treatment of the mixture of **79** and thiomalonamate **80** with secondary amine catalyst **81** in the presence of benzoic acid and three equivalents of MeOH in CH$_2$Cl$_2$ constructed the chiral piperidine ring of intermediate **82**. Without purification, crude **82** was treated with trifluoroa-
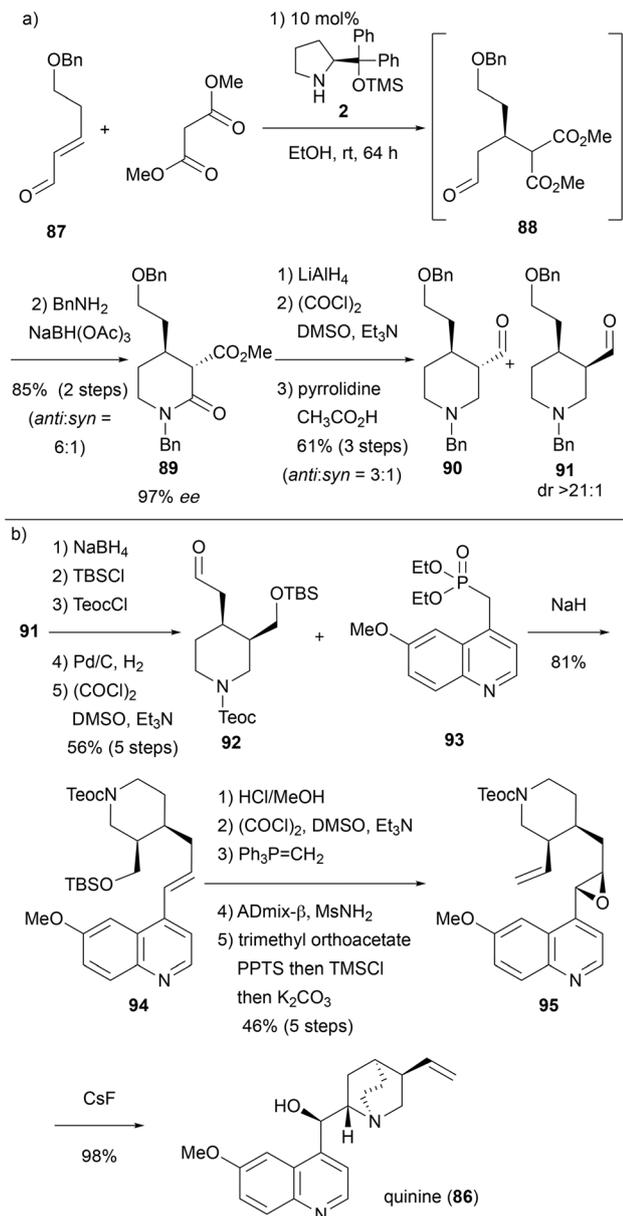
cetic acid (TFA) to convert the hemiaminal into an enamine. Subsequently, the mixture of stereoisomers of the methoxycarbonyl group was epimerized with DBU to afford **83** as a single isomer. The chemical yield of these three key steps was 72%, and the enantiomeric excess was 93%. After reducing the aldehyde of **83**, the construction of the seven-membered ring was accomplished under heating in the presence of MgBr$_2$ to provide **84** in 73% yield over two steps. Reduction of **84**, containing a methoxycarbonyl group, with nickel boride selectively reduced the thiocarbonyl group and enamine to give **85** as a single isomer. The conversion of the methoxycarbonyl group into an ethyl group was accomplished by a three-step reaction, including reduction with DIBAL, transformation of the resulting aldehyde into a terminal alkene with Tebbe reagent, and reduction under hydrogenation conditions. Finally, 20-episilicine (**75**) was obtained by reduction, removing the PMB group, and conversion of the acetal into a carbonyl group. In addition, the Ishikawa group achieved the total synthesis of silicine from common intermediate **84**. Ishikawa *et al.* achieved an efficient total synthesis of indole alkaloids, indicating the applicability of the originally developed organocatalytic piperidine ring synthesis.

Cinchona alkaloids

Cinchona alkaloids, which belong to the monoterpenoid indole alkaloids in biosynthesis, are historically significant molecules.[25] For instance, quinine (**86**) was one of the most effective medicines for treating malaria. Additionally, *Cinchona* alkaloids such as quinine (**86**), quinidine, and their derivatives function as organocatalysts, promoting several important reactions.[26]

In 2019, Córdova *et al.* reported the enantioselective synthesis of quinine (**86**) utilizing the diphenylprolinol silyl ether catalyst **2** (Scheme 8).[27] The key step in this synthesis is an enantioselective Michael addition followed by imine formation, reductive amination, and lactamization in a cascade reaction (Scheme 8a). Thus, when α,β-unsaturated aldehyde **87** and dimethyl malonate are used as substrates, and 10 mol% of secondary amine catalyst **2** is employed in ethanol, the Michael addition proceeds stereoselectively to form the Michael adduct **88**. After the reaction is complete, the solvent is removed under reduced pressure, and the resulting crude product is stirred with magnesium sulfate and benzylamine in dichloromethane to form an imine, which is subsequently converted into the corresponding benzyl amine by reduction with sodium triacetoxyborohydride. The reaction mixture is then stirred at room temperature for an additional 17 hours to allow lactamization, yielding compound **89** in high yield (85% over two steps) and excellent enantioselectivity (97% ee). The ester of compound **89** is formed in a 6 : 1 ratio of the *anti* and *syn* forms. However, since the *syn* form was required for the synthesis of quinine (**86**), epimerization was carried out using the following three-step chemical transformations. First, the ester and amide groups of **89** were simultaneously reduced
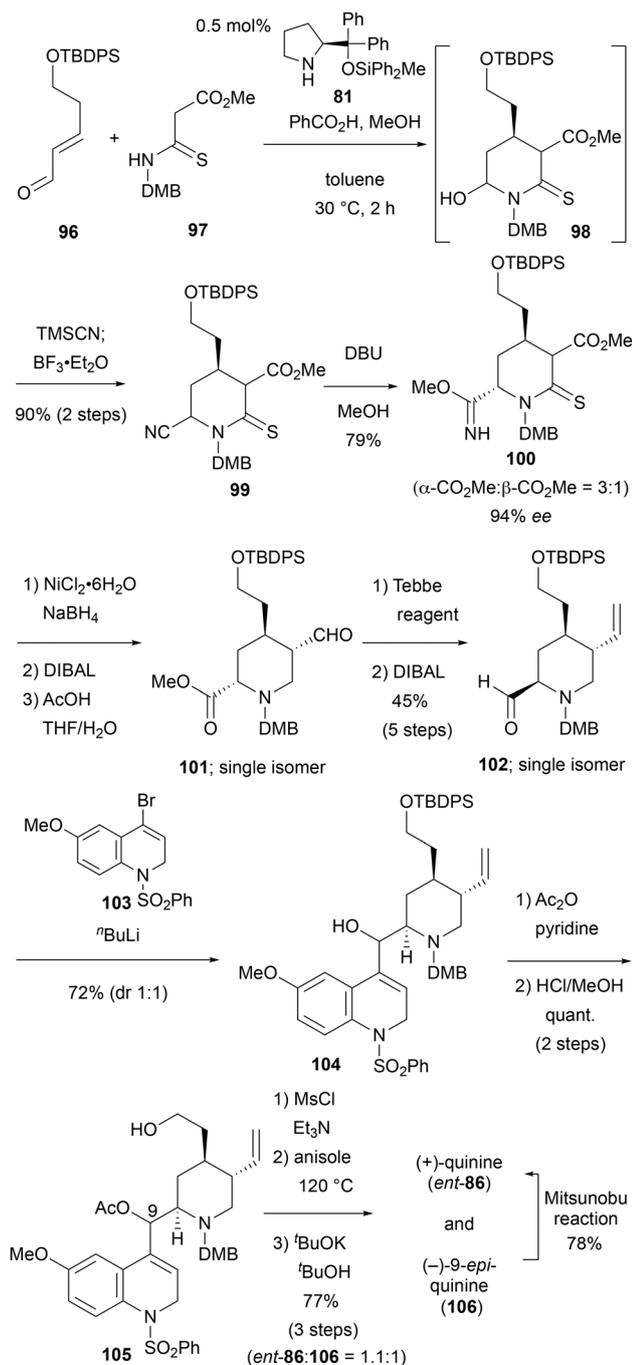
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Scheme 8 Synthesis of quinine by Córdova et al. in 2019.

conversion of **94** into quinine (**86**) was achieved in six steps, including Sharpless asymmetric dihydroxylation and quinuclidine formation via an S_N2 reaction, with a 45% yield, by following the method of Jacobsen et al.[29] Additionally, the Córdova group synthesized quinidine from synthetic intermediate **91**. This synthesis serves as a good example of the application of one-pot cascade reactions, where organocatalysis plays a key role in total synthesis.

The supply of cinchona alkaloids still relies on isolation from plants, making it challenging to obtain the enantiomers of quinine (**86**) and quinidine. However, this does not pose a major obstacle to developing asymmetric reactions, as cinchonidine and cinchonine, also isolated from the same plant, can serve as pseudoenantiomers of quinine (**86**) and quinidine. Nonetheless, quinine (**86**) and quinidine are diastereomers, and their chemical reactivity and ability to induce chirality are not identical. Therefore, efficient preparation of the enantiomers of quinine (**86**) and quinidine through total synthesis is highly significant. In 2019, Ishikawa and coworkers achieved the asymmetric total synthesis of ent-**86** using less than 1 mol% of catalysts in key asymmetric organocatalytic reactions, aiming to provide a quantitative supply of unnatural quinine (ent-**86**) through chemical synthesis (Scheme 9).[30] The key reaction in Ishikawa's synthesis was an enantioselective Michael addition/hemiamination/Strecker reaction, catalyzed by Hayashi–Jørgensen catalyst using thiomalonamate as the nucleophile. Thus, when α,β-unsaturated aldehyde **96** and thiomalonamate **97** react with secondary amine catalyst **81** in the presence of benzoic acid and methanol, the asymmetric Michael addition was followed by a hemiamination reaction to produce thiolactam **98**. Stirring the crude materials with trimethylsilyl cyanide under solvent-free conditions results in the rapid silylation of the hemiacetal. Upon completion of this reaction, the addition of boron trifluoride diethyl ether complex at low temperature promoted the Strecker reaction, yielding the desired cyanothiolactam **99** in two steps in 90% yield. To obtain key intermediate **102** from **99**, a stepwise and functional group-selective reduction of the ester, nitrile, and thiolactam was essential. This challenge was addressed by converting the cyano group into an imidate group. Thus, when **99** was stirred in methanol under basic conditions, imidate **100** was obtained as a diastereomeric mixture (α/β = 3 : 1). The enantioselective excess of **100** was 94%, confirming that the initial catalytic asymmetric reaction proceeded with high enantioselectivity. Imidate **100** was then converted into piperidine **101** through thiolactam-selective reduction using nickel boride. When the obtained amine intermediate was treated with DIBAL at low temperature, only the ester was reduced to an aldehyde. This imidate moiety was then rapidly hydrolyzed to an ester under acidic conditions in aqueous THF, resulting in piperidine-5-carbaldehyde **101**. The aldehyde in **101** was converted into a terminal double bond using Tebbe reagent. Subsequent reduction of the ester with DIBAL yielded the trisubstituted piperidine **102** in good yield (5 steps, 45%). During purification, the aldehyde moiety of **102** was isomerized to the equatorial position, adopting a thermodynamically stable

with LiAlH$_4$ to give the corresponding amino alcohol. This was then oxidized to the aldehyde via a Swern oxidation reaction, followed by mild epimerization with pyrrolidine, producing a diastereomeric mixture of **90** and **91** with an anti/syn ratio of 3 : 1. The mixture was purified using silica gel column chromatography, isolating the pure syn form **91** (dr >21 : 1). The conversion of aldehyde **91** into quinine (**86**) was carried out by following the route developed by Kobayashi et al.[28] (Scheme 8b). First, **91** was reduced to the corresponding alcohol and protected with a silyl group. The nitrogen protecting group was then switched from a benzyl group to a Teoc group, followed by Swern oxidation to form aldehyde **92**. Aldehyde **92** was converted into the coupling product **94** through a Horner–Wadsworth–Emmons (HWE) reaction with phosphate **93**. The

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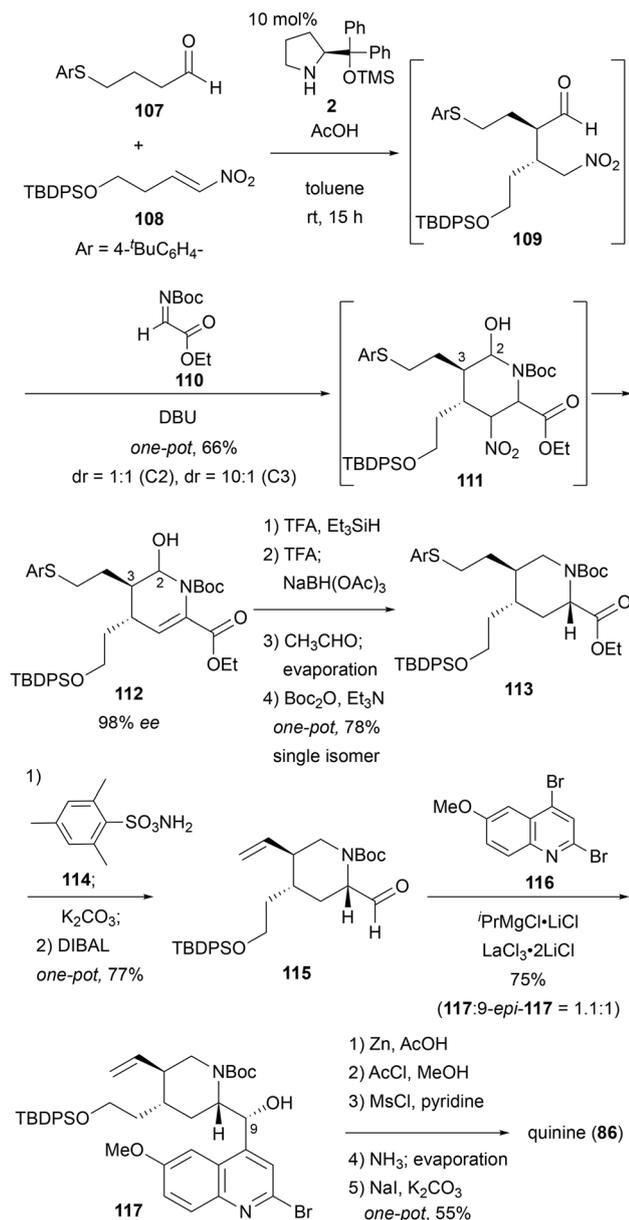This journal is © The Royal Society of Chemistry 2024

Scheme 9 Synthesis of unnatural enantiomers of quinine by Ishikawa *et al.* in 2019.

chair configuration due to the epimerization process; as a result, it was obtained as a single isomer required for the synthesis of *ent*-**86**. In the subsequent reaction to introduce the quinoline ring, a 1,2-dihydroquinoline derivative **103**, which lacks quinoline resonance to enhance reactivity, was lithiated and reacted with **102**. As a result, the desired coupling product **104** was obtained in 72% yield. Although the hydroxyl group of **104** was generated as a 1 : 1 ratio of α- and β-isomers, the

synthesis proceeded with this diastereomeric mixture. The secondary hydroxyl group of **104** was first acetylated, and the silyl group was removed using hydrochloric acid/methanol to yield **105**. Compound **105** was then mesylated and heated at 120 °C in toluene, facilitating an intramolecular S_N2 reaction. The 1,3-dimethoxybenzyl (DMB) group of the ammonium salt produced during cyclization was captured by added anisole, resulting in a quinuclidine intermediate. This process combined cyclization and deprotection in a single step. Finally, the removal of the acetyl group and the simultaneous desulfonation/oxidation of dihydroquinoline were carried out, leading to the total synthesis of unnatural quinine (*ent*-**86**) and 9-*epi*-quinine (**106**) in three steps with a 77% yield. 9-*epi*-Quinine (**106**) is also an important molecule as an organocatalyst.[25] The synthesis of *ent*-**86** and **106** could be interconverted with high yield *via* the Mitsunobu reaction. The synthesis of (+)-quinine (*ent*-**86**) is highly efficient, involving a total of 15 steps, including Mitsunobu reactions, with an overall yield of 16%. Furthermore, a synthesis that uses only 0.5 mol% of catalyst to construct chiral carbon centers is considered excellent for asymmetric total synthesis.

In 2022, Hayashi and Terunuma reported an extremely efficient total synthesis of quinine (**86**) using their originally developed asymmetric organocatalytic reaction and one-pot protocols (Scheme 10).[31] The key step for introducing the chiral carbon centers was the asymmetric Michael reaction, catalyzed by **2**, using sulfide-containing aldehyde **107** and nitroalkene **108** as substrates. The resulting intermediate **109** was then treated with an appropriate reactive imine **110** which was prepared *in situ* in the presence of DBU. This allows the successive aza-Henry reaction and hemiaminalization to proceed. The cyclized product **111** was kept under basic conditions, leading to the elimination of HNO_2 and affording the tetrahydropyridine derivative **112** in 66% yield and 98% ee. In this first one-pot reaction, five transformations occurred, including the preparation of compound **110**, with the reaction conducted on a decagram scale. The second one-pot reaction was an ingenious five-step process that began with the reductive removal of the hydroxyl group at the C2 position. Cyclized compound **112** was treated with Et_3SiH in the presence of TFA to remove both the Boc and hydroxyl groups, and the enamine double bond was further reduced using $NaBH(OAc)_3$. At this stage, the ethoxycarbonyl group adopted a thermodynamically stable *S*-form. The excess reducing agent was then decomposed with acetaldehyde, and volatile reagents were removed under reduced pressure. Finally, the Boc group was reintroduced, affording compound **113** in 78% yield with full control over the three stereocenters. The third one-pot reaction involved the construction of a terminal double bond and the conversion of an ester to an aldehyde. The allyl thioether moiety of compound **113** was converted into an alkene using the elimination reaction conditions developed by Matsuo *et al.*[32] Additionally, DIBAL was directly introduced into the reaction vessel, converting the ester into an aldehyde. This one-pot reaction proceeded in 77% yield. The fourth one-pot reaction involved the introduction of the quinoline ring.

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Scheme 10 Synthesis of quinine by Hayashi and Terunuma in 2022.

Hayashi *et al.* successfully incorporated 2,4-dibromoquinoline **116** into the aldehyde of compound **115** using an organolanthanide species developed by Knochel *et al.*[33] The diastereoselectivity at the C9 position was nearly 1 : 1, but the undesired 9-*epi*-**117** was converted into the desired **117** through oxidation and stereoselective reduction. The final one-pot reaction for quinine synthesis involves five steps, including the construction of the quinuclidine ring. First, the bromine on the quinoline ring of **117** was removed under zinc/acetic acid conditions. Next, AcCl was added in methanol to generate hydrochloric acid, which removed the Boc and TBDPS groups. MsCl was used for selective mesylation of the primary hydroxyl group, followed by treatment with ammonia to activate the nitrogen on the piperidine ring, which was temporarily pro-

tected as a hydrochloride salt. Finally, the quinuclidine ring was constructed *via* an S_N2 reaction, completing the total synthesis of quinine (**86**). The quinine synthesis reported by Hayashi and Terunuma was achieved through a 17-step chemical transformation. Compared to previous total syntheses, this 17-step process is relatively short and efficient. Additionally, they refined the synthesis to be completed using only five reaction vessels. The overall yield was 14%, demonstrating the practicality of the approach. Notably, the first asymmetric organocatalytic reaction and the aza-Henry reaction were crucial and unique steps that significantly contributed to the success of this total synthesis.
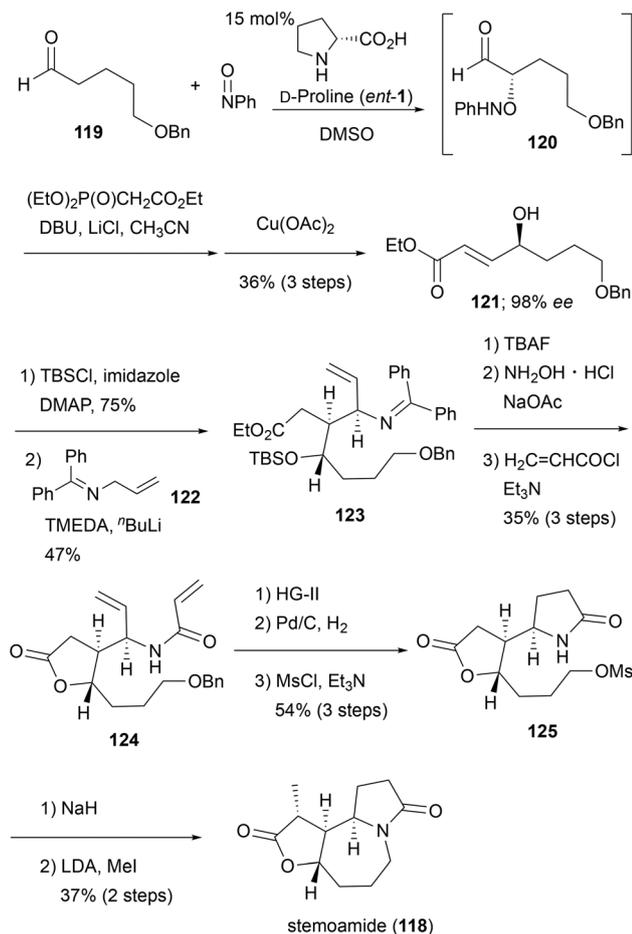
Stemona alkaloids

Stemona alkaloids were primarily isolated from *stemonaceous* plants, which were used in folk medicine in East Asian countries.[34] In addition, those alkaloids have attractive skeletons characterized by a 5/7/5 tricyclic core. Therefore, they have historically been the target of total synthesis studies.

In 2020, Prasad *et al.* reported the formal total synthesis of stemoamide (**118**) using sequential organocatalytic α-oxyamination and originally developed the conjugate addition of aza-allylanion (Scheme 11).[35] Their synthesis commenced from MacMillan sequencing to afford chiral γ-hydroxy α,β-unsaturated ester **121**.[36] Thus, treatment of the known aldehyde **119** with nitrosobenzene in the presence of D-proline furnished α-oxyamino aldehyde **120**, which upon *in situ* HWE olefination followed by reduction of the N–O bond with Cu(OAc)₂ gave **121** in 36% yield over three steps and 98% ee. After protection of the secondary alcohol with the TBS group, addition of the lithium anion of 2-aza-pentadiene **122** to the unsaturated ester diastereoselectively provided **123** in 47% yield. Deprotection of the TBS group proceeded with successive lactonization, and subsequent generation of free amine with hydroxylamine and treatment with acryloyl chloride gave unsaturated amide **124** in 35% yield over three steps. The three-step conversion, including ring-closing metathesis (RCM), simultaneous reduction of resulting olefine and benzyl group, and mesylation, afforded lactam **125** (54% over three steps), which is an intermediate in Narasaka's total synthesis of stemoamide (**118**).[37] Therefore, the formal total synthesis was accomplished.

Elegant collective total synthesis of *Stemona* alkaloids using tailored dyotropic rearrangement of β-lactone was reported by Tang in 2021.[38] Scheme 12 shows the total synthesis of bisdehydroneostemoninine (**126**). First, MacMillan's organo-SOMO catalyzed α-allylation[39] using ceric ammonium nitrate (CAN) as a single-electron oxidant and subsequent reduction converted aldehyde **127** into **129** in high yield and excellent enantioselectivity (72%, 93% ee). Reduction of amide **129** with alane provided **130**. Due to the instability of the produced aldehyde, the oxidation and subsequent conversion of **130** were extremely difficult. After extensive trials, the synthesis of **133** was achieved by modified Ley–Griffith oxidation

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Scheme 11 Synthesis of stemoamide by Prasad *et al.* in 2020.

followed by rhodium-catalyzed reductive aldol reaction with α,β-unsaturated ester **132** in the presence of catalyst **131** in 30% yield for two steps. β-Lactone **134**, obtained by hydrolysis of **133** followed by lactonization reactions, underwent dyotropic rearrangement using silica gel in the absence of acid (**TS2**). In this reaction, the electron-rich pyrrole ring rearranged and generated **135** in a nearly quantitative yield. Methylenation of **135** with Petasis reagent gave enol ether **136**. Oxaspirolactone was constructed by photoredox-catalyzed formal [3 + 2] cycloaddition with α-bromocarboxylic acid **137**, which afforded two pairs of diastereomer **138a/b** and **139a/b** in 63% and 22% yields, respectively. The undesired isomer **138a/b** could be converted with TFA into the desired **139a/b** *via* ring opening/closing equilibrium. Finally, the total synthesis of bisdehydroustemoninine (**126**) was accomplished by β-elimination with DBU followed by ruthenium-catalyzed double-bond isomerization (from compound **139** to **126** *via* **140**). In addition, Tang reported not only the total syntheses of *Stemona* alkaloids including stemoamide, tuberostemospiroline, saxorumamide, isosaxorumamide, and stemonine, but also the application of photoredox-catalyzed formal [3 + 2] cycloaddition with eight substrates. Their synthesis of **126** was accomplished in 12 steps from **127** and the
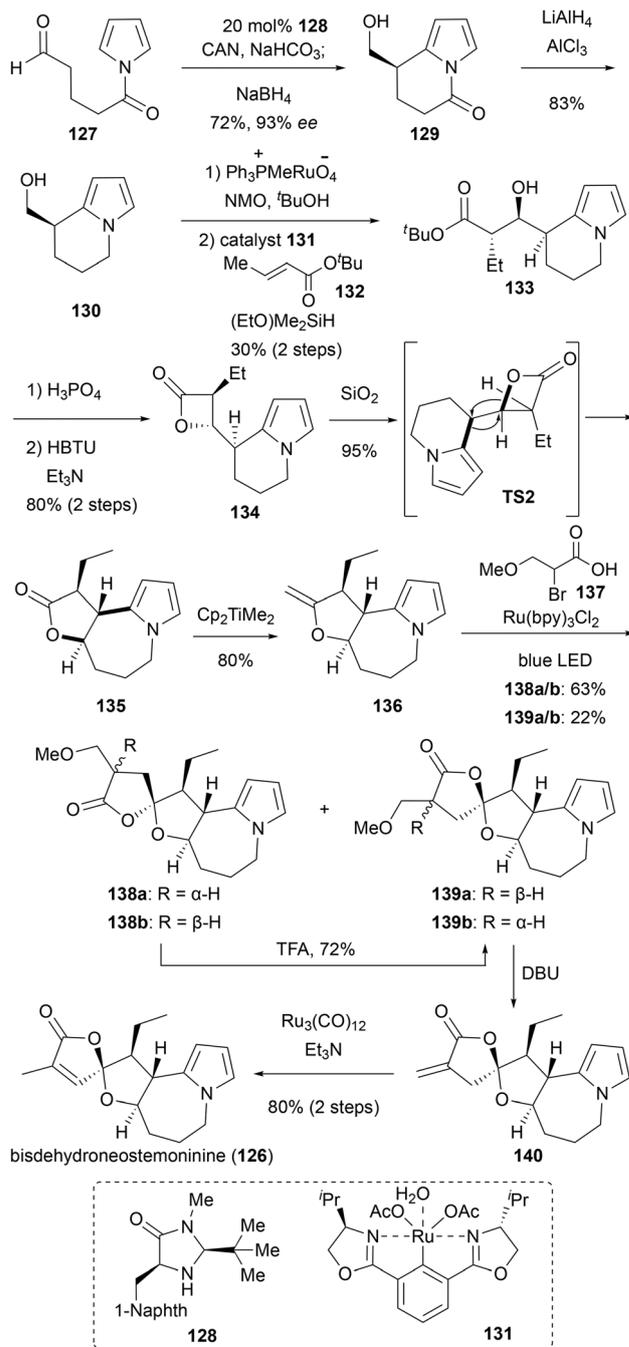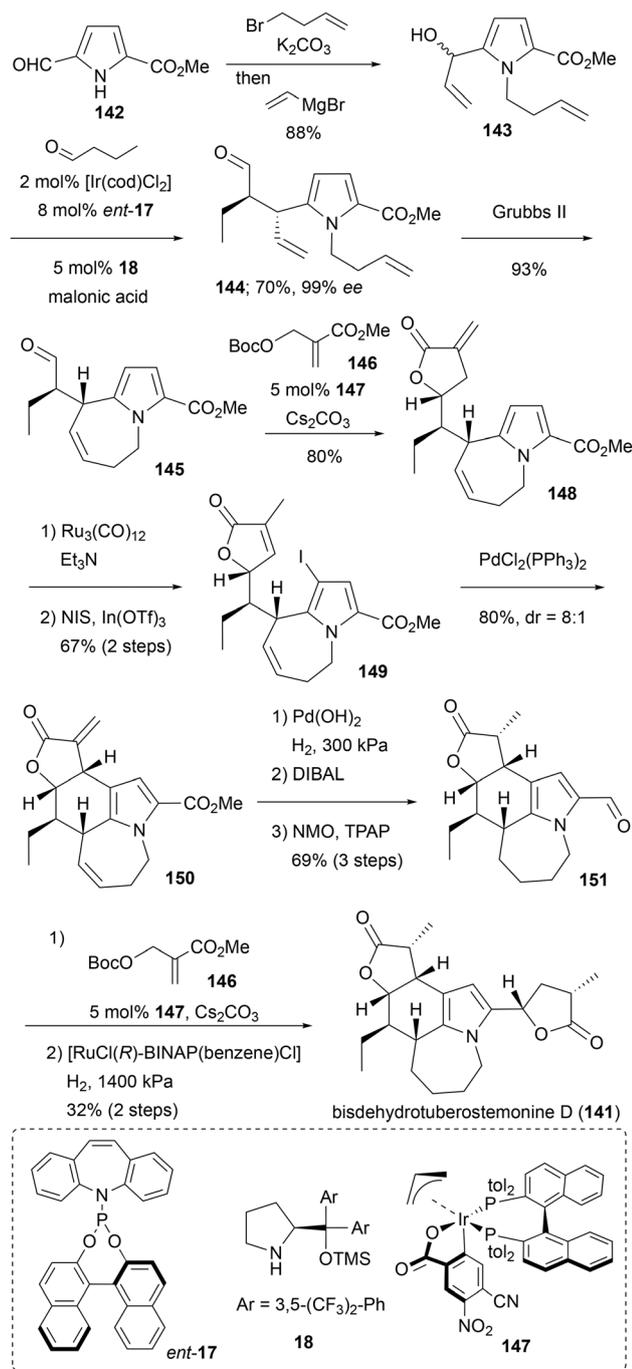

Scheme 12 Synthesis of bisdehydroneostemoninine by Tang *et al.* in 2021.

overall yield was 5.9%. The reader, interested in the dyotropic rearrangement of β-lactone, is referred to the original report by Tang *et al.*[38]

Yang and coworkers reported an efficient total synthesis of bisdehydrotuberostemonine D (**141**) (Scheme 13).[40] These two alkaloids in a diastereomeric relationship were synthesized *via* Carreira's Ir/amine dual catalytic stereodivergent reaction, respectively. Thus, **143**, converted by *N*-alkylation and addition of vinylmagnesium bromide from **142**, and butanal were
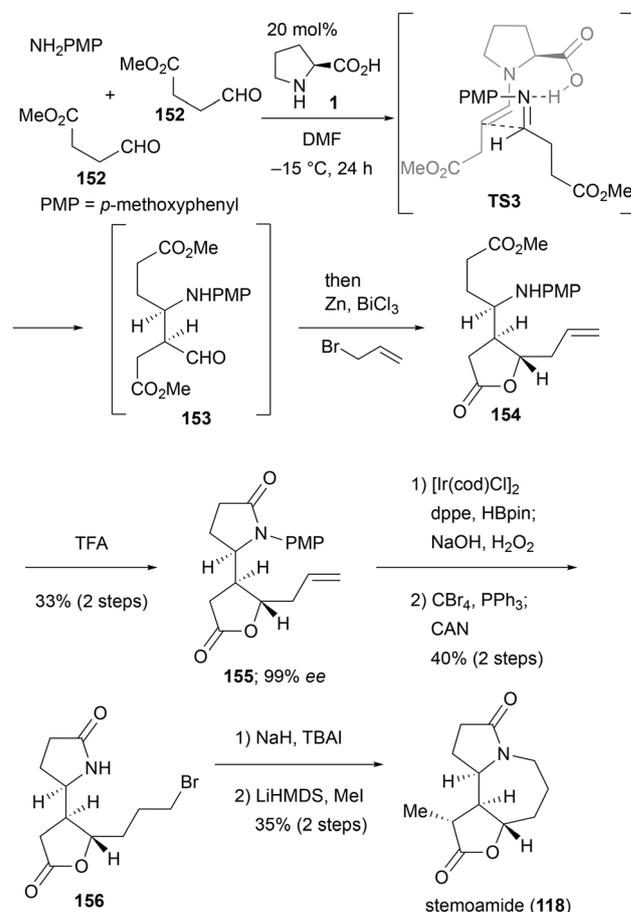
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Scheme 13 Synthesis of bisdehydrotuberostemonine D by Yang *et al.* in 2021.

treated with catalytic Ir/*ent*-**17** and **18** in the presence of malonic acid to obtain **144** with two newly generated stereocenters in good yield and superb enantio- and diastereoselectively (70%, dr >50 : 1, 99% ee). The RCM reaction of **144** using Grubbs' second-generation catalyst proceeded with excellent yield to form a seven-membered ring, resulting in the formation of **145**. Subsequently, Krische's allylation[41] using Ir-catalyst **147** with acrylic acid derivative **146** and spontaneous

lactonization gave γ-butyrolactone **148** as a single isomer in 80% yield. After ruthenium-catalyzed isomerization of *exo*-methylene, site-selective iodination followed by intramolecular Heck reaction afforded tetracyclic **150** *via* compound **149**. The aldehyde **151**, the precursor for the second Krische allylation, was provided by a three-step transformation including the hydrogenation of two double bonds, reduction of the methoxy-carbonyl group, and oxidation of the generating primary alcohol. Finally, the second Krische allylation followed by hydrogenation under Takaya's protocol[42] gave bisdehydrotu-berostemonine D (**141**) in 32% yield over two steps. Their stereodivergent syntheses using one Carreira Ir/amine dual catalytic reaction and two Krische allylations allowed them to efficiently provide pyrrole *Stemona* alkaloids.

More recently, Cernak and coworkers reported a short and straightforward total synthesis of stemoamide (**118**), utilizing a computer-aided key step and enhancements by chemists (Scheme 14).[43] Their synthesis started from proline-catalyzed self-Mannich reaction developed independently by Hayashi and Barbas in 2003.[44] Thus, two equivalents of aldehyde **152** and one equivalent of *p*-toluidine were treated with 20 mol% of L-proline (**1**), affording **153** through the addition of the enamine, formed from L-proline (**1**) to the imine formed from

Scheme 14 Synthesis of stemoamide by Cernak *et al.* in 2023.

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p-toluidine (**TS3**). Subsequently, the direct addition of allyl bromide, zinc, and bismuth chloride to the reaction vessel produced lactone **154**. Without purification, the crude mixture of **154** was treated with TFA for lactamization, yielding **155**. This two-step sequence rapidly formed three contiguous stereocenters and two rings in 33% yield with excellent enantioselectivity (99% ee). Next, the alkene was converted into an alcohol *via* hydroboration using [Ir(cod)Cl]$_2$, followed by bromination and *in situ* removal of the PMP group to yield **156** in 40% over two steps. The two known reactions, the construction of the azepane ring and the diastereoselective introduction of a methyl group, led to the total synthesis of stemoamide (**118**). In addition, they accomplished a three-step total synthesis of **118** using an alternative protocol, which included allylation, Michael addition, and the Schmidt–Aubé rearrangement, following a computer-suggested synthetic route. Their synthesis was the shortest of the 32 total syntheses of natural product **118** reported to date, an impressive achievement made possible with the assistance of computational science.

Daphniphyllum alkaloids

Daphniphyllum alkaloids, isolated from the plant genus *Daphniphyllum*, are part of a group of over 320 natural triterpenoids.[45] They share a distinctive polycyclic ring-fused framework with multiple contiguous stereogenic centers and exhibit potential bioactivity against tumors and the human immunodeficiency virus. Their fascinating structures and promising bioactivities have made these molecules highly attractive to synthetic chemists and biologists alike. In this perspective article, two total syntheses of *Daphniphyllum* alkaloids are presented, each incorporating asymmetric reactions using secondary amine catalysts in the initial stages.

Himalensine A (**157**) is an alkaloid with a [6-6-5-7-5] pentacyclic core, belonging to the calyciphylline A sub-family. In 2023, Dixon *et al.* reported the synthesis of this complex alkaloid using a practical and efficient dual amine/palladium catalyst system to construct the morphan skeleton (Scheme 15).[46] The synthesis of the substrate for the key desymmetrization reaction began with a monoprotected diketone **158**. Thus, arylamine **159** was condensed with ketone **158** in a reductive alkylation reaction, and the cyclic acetal moiety was reverted to a ketone. The secondary amine was then protected with a tosyl group, yielding substrate **160**. A considerable amount of examination was needed to develop the novel asymmetric carbon–carbon bond-formation reaction the authors were aiming for. Ultimately, they identified optimal conditions: 20 mol% of *cis*-4-hydroxyproline **161** as a secondary amine catalyst, 5 mol% of Pd(OAc)$_2$ and 15 mol% tris [*p*-(trifluoromethyl)phenyl] phosphine as metal catalysts, with dipotassium hydrogen phosphate as a base, and the reaction conducted in methanol at 85 °C. As a result, an optically active morphan compound **162**, with the α-position of the ketone coupled to the vinyl bromide, was obtained in excellent yields and enantioselectivity on a gram scale (92%, 94% ee). The reaction mechanism was
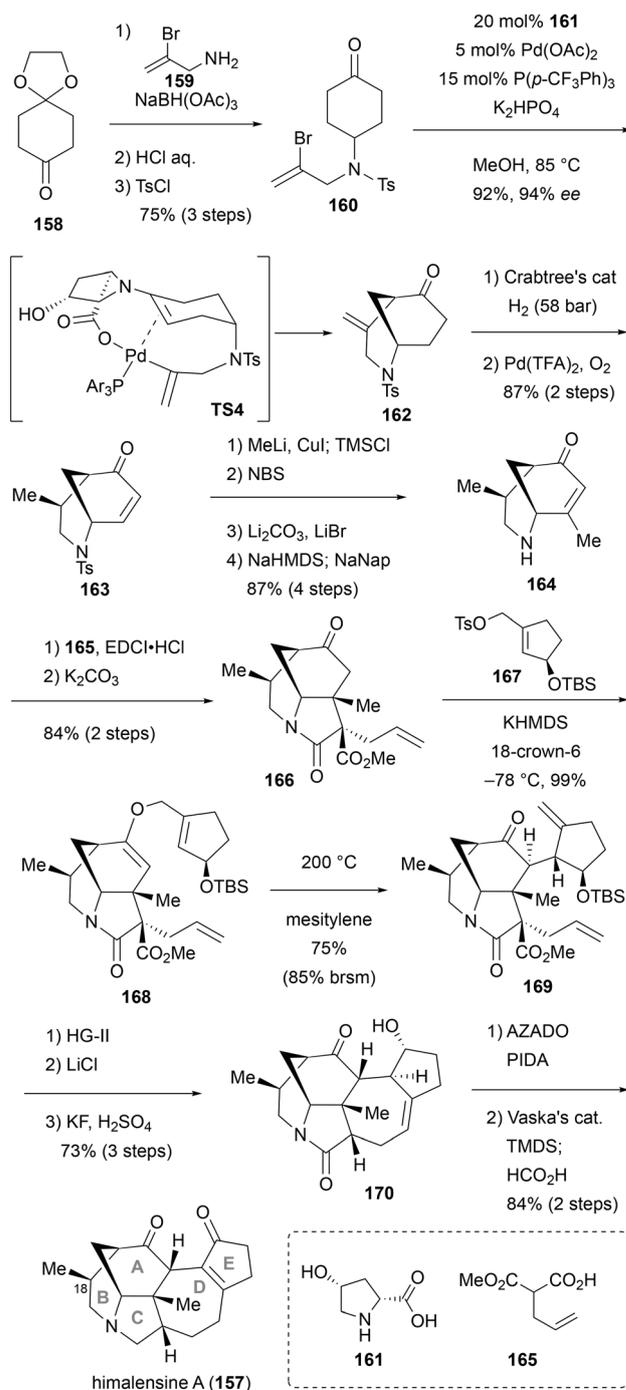

Scheme 15 Synthesis of himalensine A by Dixon *et al.* in 2023.

analyzed using computational chemistry, and an impressive transition state (**TS4**) was proposed, in which the carboxylic acid of the secondary amine catalyst forms a bridge with Pd. To construct the methyl group at C18 of the natural product, a diastereoselective reduction was performed using Crabtree's catalyst in a hydrogenation reaction. It was subsequently converted into compound **163** using the catalytic enone synthesis protocol developed by Stahl *et al.*[47] Enone **163** underwent 1,4-addition with methylcopper reagent, followed by silyl enol

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formation with TMSCl, bromination and elimination at the α-position, and removal of the tosyl group with sodium naphthalenide with the enone moiety protected as an enolate. This sequence of reactions yielded cyclic amine **164** in high yield (87%, 4 steps). The construction of the *C*-ring was achieved through the condensation of malonic acid derivative and intramolecular Michael reaction. Thus, dehydration condensation of allylated malonate **165** with **164**, followed by treatment with a base, leads to a diastereoselective intramolecular Michael reaction. This process results in compound **166**, where the *C*-ring is constructed along with the formation of two contiguous quaternary chiral carbon centers. Next, they developed and applied the *O*-allylation/Claisen rearrangement/RCM sequence for constructing the *D*-ring. First, ketone **166** was treated with potassium hexamethyldisilazide (KHMDS) at low temperature, followed by the addition of **167**, resulting in the *O*-allylated product **168**. When **168** was heated to 200 °C in mesitylene, a diastereoselective Claisen rearrangement reaction proceeded, yielding **169** in good yield. Following the ring-closing olefin metathesis reaction for *D*-ring construction, decarboxylation and removal of the silyl group were carried out, resulting in the preparation of the pentacyclic compound **170**. Finally, after oxidation of the secondary alcohol **170**, subsequent isomerization of the double bond, and amide-selective reduction with Vaska's complex,[48] the total synthesis of himalensine A (**157**) was achieved. This synthesis involves 19 steps, which is highly efficient given the structural complexity of **157**. The success of this impressive total synthesis is largely attributed to the discovery of a novel concerted reaction between secondary amines and transition-metal catalysts.

Most recently, Yang and coworkers reported the total synthesis of daphenylline (**171**), which features a benzene ring—an uncommon characteristic for a *Daphniphyllum* alkaloid (Scheme 16).[49] The key reaction for introducing the asymmetric carbon center is the Ir/amine dual-catalyzed allylation methodology developed by Carreira's group, which controls the stereochemistry of the methyl group at C18 on the *D*-ring. Thus, subjecting phenyl vinyl carbinol **172** and propanal to conditions using Ir/*ent*-**17** and secondary amine *ent*-**18** as catalysts, with dichloroacetic acid as the promoter, yielded aldehyde **173** in 64% yield and >99% ee. The optically active **173** was converted into the Boc-protected amine *via* reductive amination with BocNH₂, followed by transformation of the terminal double bond into a carboxylic acid using the radical hydrocarboxylation reaction developed by Wickens *et al.*[50] A subsequent intramolecular Friedel–Crafts acylation was achieved by heating carboxylic acid **175** in the presence of polyphosphoric acid (PPA), resulting in the formation of a cyclized ketone with good conversion. The construction of the morphan skeleton was achieved by applying the copper-catalyzed α-amination reaction developed by MacMillan *et al.* to an intramolecular reaction.[51] The ketone was then converted into allylic bridgehead amine **176** *via* a Wittig reaction. The secondary amine of compound **176** was condensed with an alkynyl carboxylic acid **177** to afford precursor **178** for reductive 1,6-enyne cyclization. Krische's Rh-catalyzed reductive 1,6-enyne
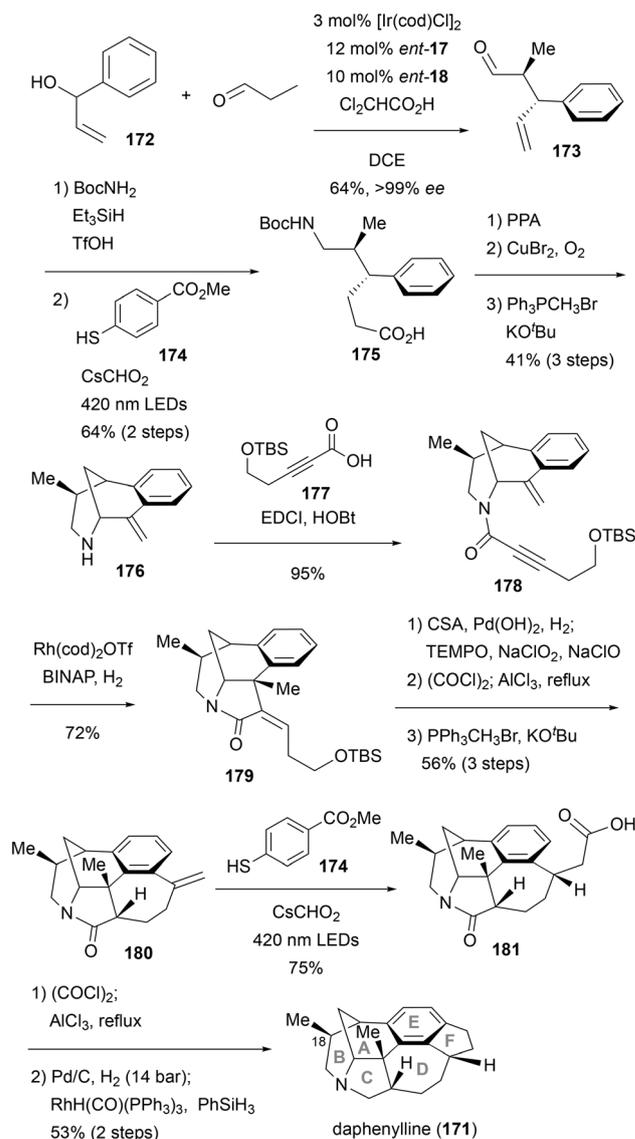
Scheme 16 Synthesis of daphenylline by Yang *et al.* in 2024.

cyclization was used to construct the *C*-ring.[52] The cyclization reaction of **178** proceeded stereoselectively, yielding tetracyclic compound **179** in high yield. The stereoselective reduction of the double bond and simultaneous removal of the silyl group are carried out. The resulting primary alcohol was then oxidized to a carboxylic acid, which was subsequently converted into an acid chloride. An intramolecular Friedel–Crafts reaction was performed to construct the *D*-ring, and finally, the ketone was converted into an alkene, completing the synthesis of **180**. Again, compound **180** underwent a radical hydrocarboxylation reaction to introduce the carboxylic acid moiety and achieve a one-carbon elongation and yielding compound **181**. Furthermore, a third intramolecular Friedel–Crafts reaction was employed to construct the *E*-ring. After decarbonylation, the total synthesis of daphenylline (**171**) was completed. The total synthesis was completed in just 14 steps, starting with Carreira's Ir/amine dual-catalyzed allylation. The

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impressive efficiency is due to the use of multiple catalytic reactions and the central benzene ring in the Friedel–Crafts reactions to form three key C–C bonds.

Pyrrolizidine and quinolizidine alkaloids

Multiply substituted chiral pyrrolizidine and quinolizidine ring systems are found in a wide variety of natural products, and several of these alkaloids have important biological activities such as sedative, anticonvulsant, anti-inflammatory, and antivirus actions.[53] These alkaloids are mainly biosynthesized from L-lysine or L-ornithine. In addition, these alkaloids have a wide range of structural diversity and substituent variation. Therefore, numerous total syntheses of these alkaloids or the construction of their scaffolds have been reported.

In 2020, Appayee et al. reported the total syntheses of all four stereoisomers of 1-hydroxymethylpyrrolizine alkaloids, namely, (+)- and (−)-isoretronecanol (**182** and *ent*-**182**), (+)-laburnine (**183**), and (−)-trachelanthamidine (*ent*-**183**) using organocatalytic self-Mannich reactions (Scheme 17).[54] When 4-oxobutanoate **152** and p-toluidine were treated with 10 mol% catalyst **2** in the presence of benzoic acid, the *anti*-selective self-Mannich reaction proceeded to provide aldehyde **184** (Scheme 17a). After completion of the Mannich reaction, aldehyde **184** was reduced with NaBH₄, followed by lactonization under acidic conditions to provide lactam **185** in excellent yield with high enantio- and diastereoselectivity (80% yield, dr = 4 : 1, 98% ee). After removal of the PMP group, a selective lactam reduction using Meerwein reagent (Me₃OBF₄) and NaBH₄, and a cyclization, primary alcohol was protected with the benzoyl group to provide bicyclic lactam **186**. Finally, the reduction of the lactam followed by removal of the benzoyl group gave (+)-isoretronecanol (**182**). Next, the total synthesis of (−)-isoretronecanol (*ent*-**182**) was also accomplished. Thus, in the asymmetric Mannich reaction, the opposite enantiomer *ent*-**2** was used as an organocatalyst to synthesize (−)-isoretronecanol (*ent*-**182**). In addition, total syntheses of (+)-laburnine (**183**) and (−)-trachelanthamidine (*ent*-**183**) using an organocatalytic *syn*-selective self-Mannich reaction were accomplished (Scheme 17b). Thus, when L-proline (**1**) was employed as a catalyst in the asymmetric Mannich reaction, the selectivity was reversed from that of the diphenylprolinol silyl ether catalyst **2**, and *syn*-self-Mannich reaction proceeded, followed by reduction using NaBH₄ and lactone formation to afford lactam **187** in excellent yield with high enantio- and diastereoselectivity (80% yield, dr = 7 : 1, 93% ee). Subsequent removal of the PMP group, lactam selective reduction, formation of the bicyclic lactam, and protection of primary alcohol proceeded. Reduction of the lactam and removal of the benzoyl group then afforded (+)-laburnine (**184**). The total synthesis of (−)-trachelanthamidine (*ent*-**183**) was also achieved by using D-proline in the *syn*-selective self-Mannich reaction. By using a different catalyst, namely, diphenylprolinol silyl ether catalyst
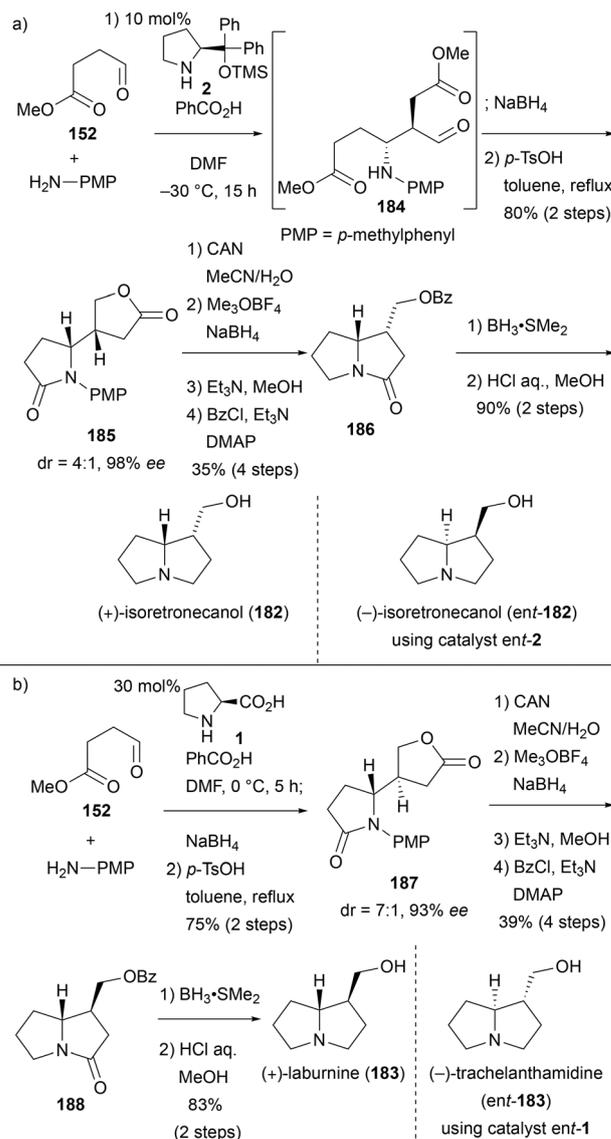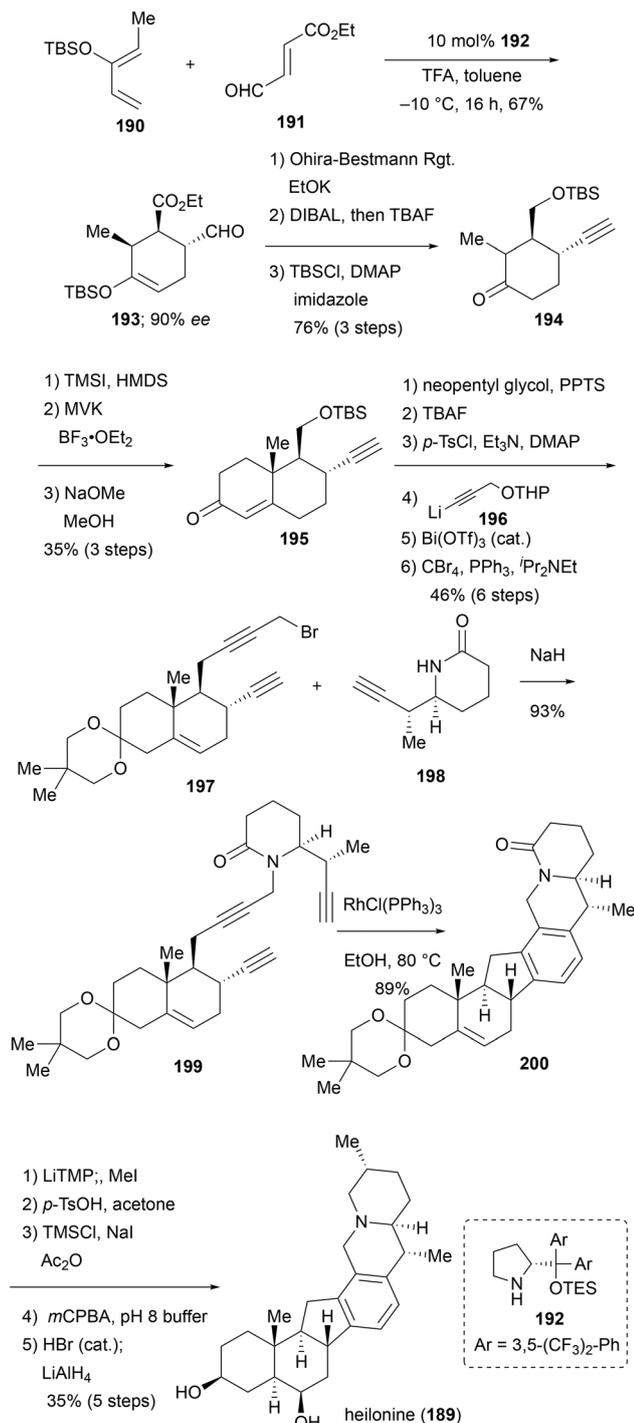

Scheme 17 Synthesis of isoretronecanol, laburnine, and trachelanthamidine by Appayee et al. in 2020.

2 and proline in a self-Mannich reaction, the total synthesis of four 1-hydroxymethylpyrrolizine alkaloids was achieved in eight steps and 20–21% overall yield. This difference in stereoselectivity arises because in proline catalysts, the carboxylic acid moieties form hydrogen bonds, whereas in diphenylprolinol silyl ether catalysts, selectivity is influenced by the steric bulk of the substituents. Using different catalysts allows for the collective total synthesis of diastereomers.

In 2021, Rawal et al. reported excellent total synthesis of the steroidal alkaloid heilonine (**189**) (Scheme 18).[55] One of the key steps was an organocatalytic Diels–Alder reaction using siloxydiene **190** and commercially available ethyl *trans*-4-oxo-2-butenoate (**191**) developed by the Hayashi group.[56] Thus, when siloxydiene **190** was treated with aldehyde **191** and TFA in the presence of catalyst **192**, regio- and stereoselective asymmetric
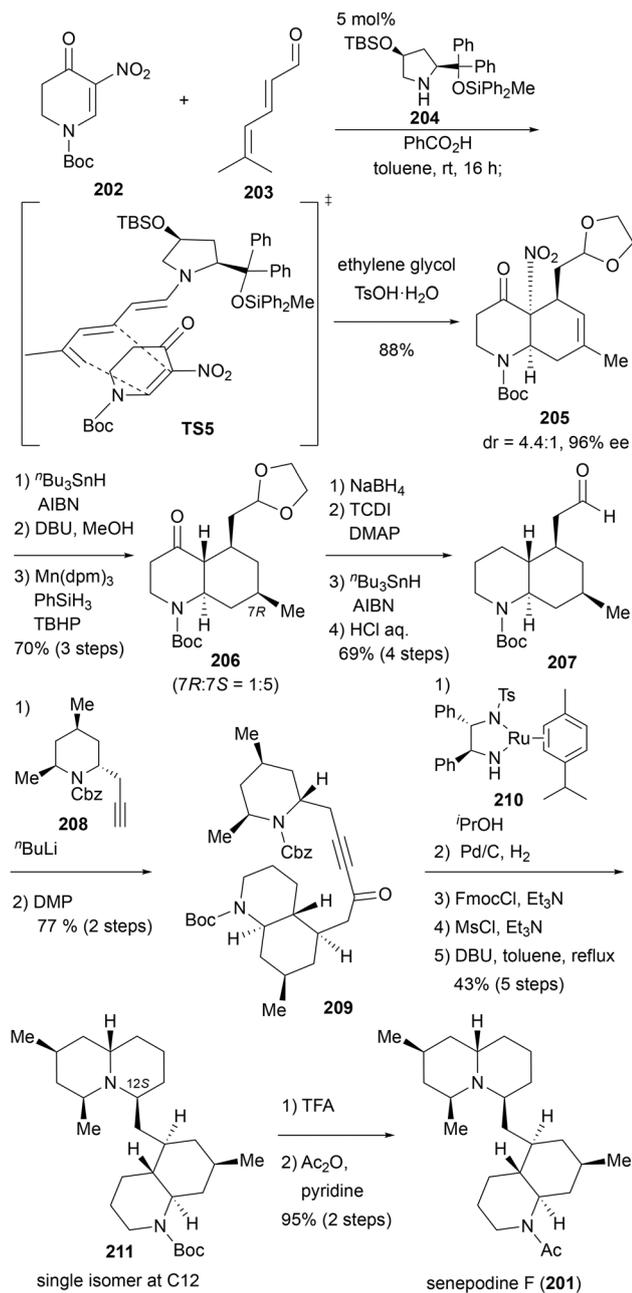
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Scheme 18 Synthesis of heilonine by Rawal et al. in 2021.

Diels–Alder reaction proceeded to provide cycloadduct **193** in 67% yield and 90% ee. Subsequent Gilbert–Seferth reaction using Ohira–Besmann reagent, reduction of ethyl ester, removal of the TBS group, and protection of the primary alcohol afforded cyclohexanone **194** as a mixture of diastereomers at the α-methyl group. After conversion into its thermodynamic silyl enol ether using TBSI and HMDS, the

Mukaiyama–Michael reaction with methyl vinyl ketone (MVK) and subsequent aldol/dehydration sequence afforded bicyclic ketone **195**.[57] In this three-step Robinson annulation protocol, the Mukaiyama–Michael reaction afforded an inseparable mixture of diastereomer (3 : 1); however, only the major (desired) isomer cyclized to provide **195**. Subsequent protection of the ketone moiety with neopentyl glycol, removal of the silyl group, and sulfonylation of the primary alcohol provided the tosylated compound. The coupling reaction with lithium acetylide **196** proceeded smoothly, and subsequent removal of the THP group and Appel reaction transformed diyne **197** in high yield (46%, 6 steps). The coupling reaction between propargyl bromide **197** and alkyne-containing lactam **198** (synthesized by seven-step protocol from commercially available materials) was carried out using NaH to provide triyne **199** in 93% yield. To construct a benzene ring, the authors performed [2 + 2 + 2] cycloaddition using a transition-metal catalyst. Thus, when triyne **199** was treated with 10 mol% RhCl(PPh$_3$)$_3$ in EtOH at 80 °C, alkyne trimerization proceeded smoothly to afford the six-membered ring product **200** in 89% yield. Further diastereoselective introduction of a methyl group at the α-position was carried out using MeI and LiTMP as a base, followed by removal of the acetal moiety using p-TsOH and enolization using TMSCl, NaI and Ac$_2$O to afford dienol acetate. Subsequent oxidation of the γ-position was performed with mCPBA, followed by isomerization to the γ-diketone using HBr as a catalyst and reduction of two ketones with LiAlH$_4$ to accomplish the total synthesis of heilonine (**189**) in a total of 21 steps from ethyl trans-4-oxo-2-butenoate (**191**). This elegant approach to the coupling of the two fragments and subsequent construction of the benzene ring in the late stage enabled the first total synthesis of heilonine (**189**).

The total synthesis of senepodine F (**201**) using an organocatalytic asymmetric Diels–Alder reaction was reported by Ishikawa and coworkers in 2023 (Scheme 19).[58] Their key organocatalytic reaction was originally developed as a Diels–Alder reaction using a 5-nitro-2,3-dihydro-4-pyridone derivative **202** as a dienophile. Thus, pyridone derivative **202** was treated with α,β,γ,δ-unsaturated aldehyde **203** and benzoic acid in the presence of 5 mol% of catalyst **204**, to afford the optically active endo-cycloadduct **205** in excellent yield with high regio-, enantio-, and diastereoselectivity (88% yield, dr 4.4 : 1, 96% ee). In this reaction, the trienamine intermediate generated from aldehyde **203** and catalyst **204** induced high stereoselectivity (**TS5**). Further, a denitration reaction under reductive conditions (^{n}Bu$_3$SnH, cat. AIBN) followed by isomerization to the thermodynamically stable trans-fused octahydroquinoline under basic conditions and a diastereoselective hydrogen atom transfer (HAT) reaction afforded 7R-decahydroquinoline **206** in high yield and diastereoselectivity (70% in 3 steps, dr at C7 = 5 : 1). Following reduction of the ketone using NaBH$_4$, thiocarbonylation of a secondary alcohol, deoxygenation using ^{n}Bu$_3$SnH, and removal of the acetal moiety under acidic hydrolysis conditions provided aldehyde **207**. After a coupling reaction with piperidine fragment **208** (synthesized in eight steps from commercially available materials) was achieved using

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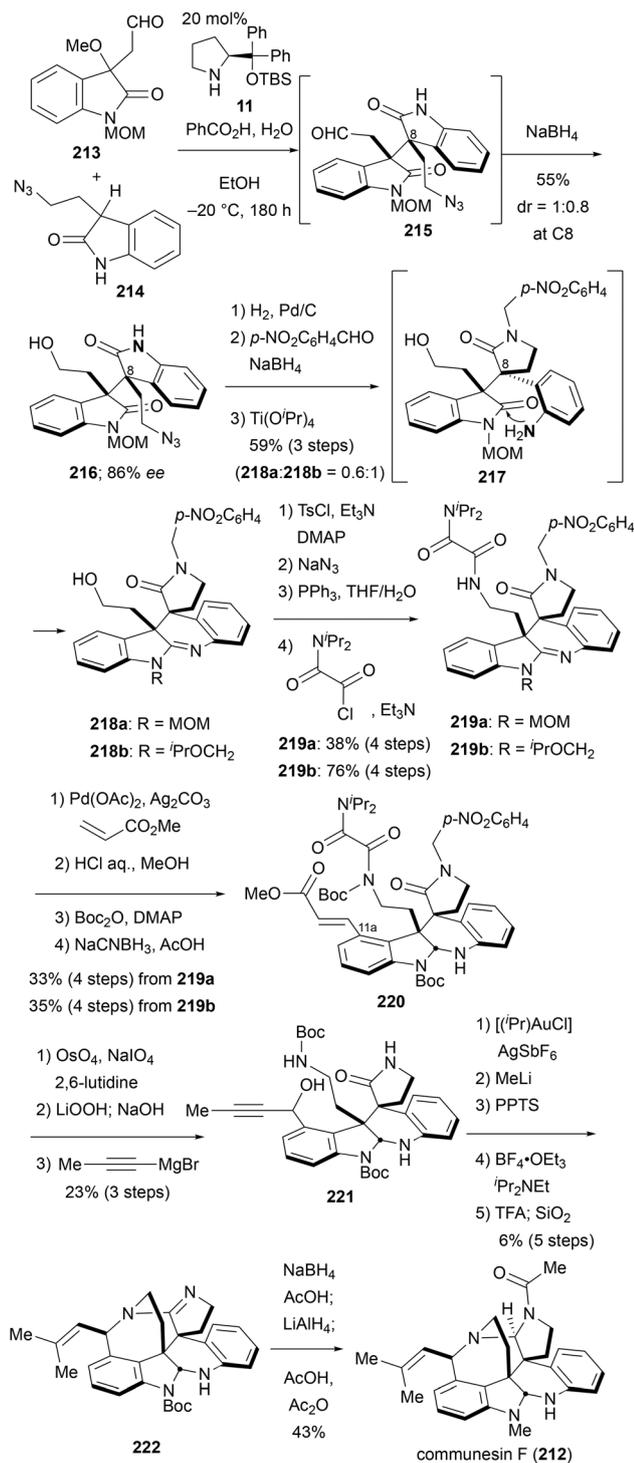**Scheme 19** Synthesis of senepodine F by Ishikawa et al. in 2023.

^{n}BuLi as a base, Dess–Martin oxidation of the secondary alcohol was performed to provide the coupling product **209**. Subsequent diastereoselective reduction of the ketone moiety under Noyori reduction conditions[59] using catalyst **210**, reduction of the alkyne and removal of the Cbz group under catalytic hydrogenation conditions, protection of the amine afforded a precursor of quinolizidine cyclization. Mesylation of the secondary hydroxyl group followed by deprotection of the Fmoc group and S$_N$2 cyclization using DBU were carried out to successfully provide **211** in 40% over five steps as a single isomer. Finally, the deprotection of the Boc group and acetyl-

ation sequence afforded senepodine F (**201**). The asymmetric Diels–Alder reaction developed by them is a powerful method to provide the optically active decahydroquinoline scaffold and will be used in the synthesis of other alkaloids with this scaffold in near future.
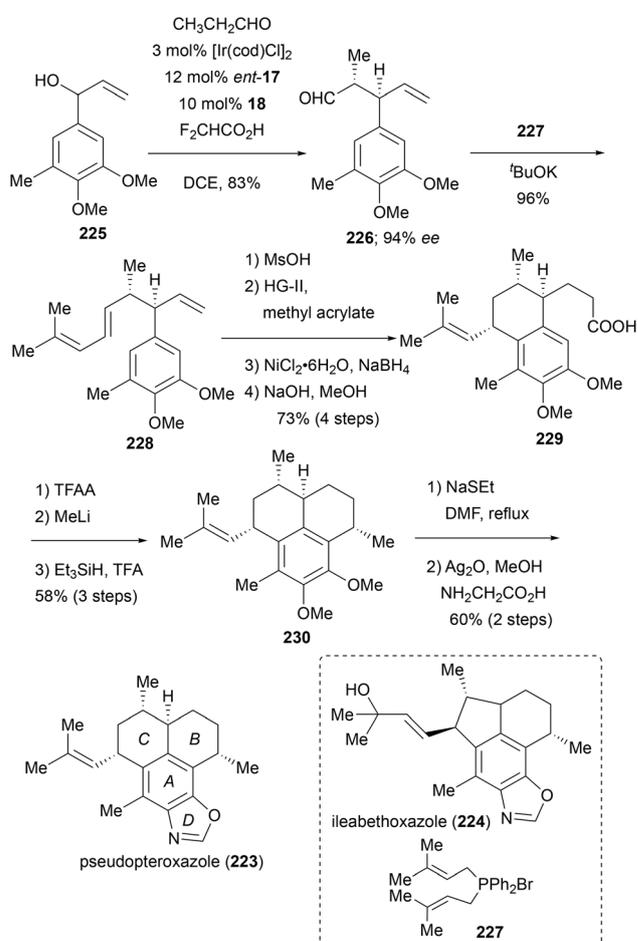
Other alkaloids

In 2017, Chen and coworkers achieved the total synthesis of communesin F (**212**), a member of the communesin family of polycyclic bis-aminal alkaloids (Scheme 20).[60] In the synthesis of communesins, the construction of a contiguous quaternary chiral center within the ring is crucial. Chen et al. elegantly constructed this challenging contiguous stereocenter using a secondary amine organocatalyst. The electrophile of the key organocatalytic reaction was an oxindole derivative **213**, which has a methoxy group—a leaving group—at the β-position of the aldehyde. The nucleophile was oxindole **214**, with an azide side chain. When the substrates and catalyst **11** were mixed in ethanol and stirred at low temperature, **213** and **11** condensed to form activated α,β-unsaturated iminium ion intermediates. Subsequently, another oxindole **214** was added, leading to the construction of a contiguous quaternary chiral center. The aldehyde of the generated intermediate **215** was reduced and isolated as alcohol **216**. This challenging coupling reaction proceeded with high enantioselectivity in moderate yield (86% ee, 55%). The azide group of **216** was reduced, and a p-nitro-benzyl group was introduced into the resulting amine. Subsequent treatment with the Ti(O^{i}Pr)$_4$ as Lewis acid induced skeletal rearrangement to form a pentacyclic lactam **218** via intermediate **217**. In this rearrangement, part of the originally present MOM group was converted into an isopropoxymethyl group. The primary hydroxyl group in compound **218** was converted into a primary amine in three steps. This was followed by the introduction of diisopropyl oxalamide, a directing group for C–H functionalization as reported by Zhao et al.[61] The second key reaction in this total synthesis is the introduction of the acrylic acid unit via C–H activation at C11a. Thus, methyl acrylate was introduced at the C11a position of **219**, with direct activation using palladium acetate and silver carbonate. The etheric protecting group was then removed using hydrochloric acid, and the resulting amino group was protected with a Boc group. The imidate moiety linked to aniline was stereoselectively reduced to form **220**. The acrylic acid moiety of **220** was cleaved by dihydroxylation/oxidation process to yield an aldehyde. The diisopropyl oxalamide group, used as a directing group, was then removed under hydrolysis conditions. Subsequently, the alkynyl group was introduced into the aldehyde to produce alcohol **221**. The Au-catalyzed Meyer–Schuster rearrangement[62] using alkynes was performed to construct additional ring structures. The resulting α,β-unsaturated ketone was then converted into 2-methylpropene moiety through methylation and dehydration. Subsequently, selective removal of the Boc group, followed by intramolecular dehydration and cyclization, led from the lactam ring to the cyclic

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Scheme 20 Synthesis of communesin F by Chen *et al.* in 2017.

In 2019, Hu's group achieved the total syntheses of two marine benzoxazole alkaloids, pseudopteroxazole (**223**) and ileabethoxazole (**224**), which were isolated from the Caribbean sea whip *Pseudopterogorgia elisabethae* (Scheme 21).[63] The key reaction for introducing the chiral centers is Carreira's asymmetric dual catalytic allylation, which utilizes allyl alcohol **225**. The combination of amine catalyst **18** and [Ir/*ent*-**17**] was employed to introduce the two desired stereocenters in **223**. In this reaction, the addition of various acids was explored to improve diastereoselectivity and yields. Ultimately, excellent selectivity and chemical yields were achieved with the addition of difluoroacetic acid (dr = 10 : 1, 83%). The enantioselectivity was excellent (94% ee). Subsequently, the aldehyde **226** was converted into **228**, featuring a diene structure, through Wittig–Vedejs *E*-selective olefination with **227**.[64] The construction of the *C*-ring proceeded diastereoselectively by treating **228** with methanesulfonic acid. Hu *et al.* proposed an interesting reaction mechanism, involving a 1,2-shift pathway. The terminal double bond was elongated *via* a cross-metathesis reaction with methyl acrylate, followed by 1,4-reduction and hydrolysis to yield carboxylic acid **229**. *B*-Ring construction was achieved through intramolecular Friedel–Crafts acylation, and the result-

imidate **222**. The total synthesis of communesin F (**212**) was achieved in three steps, including the reduction and acetylation of the imidate. Alkaloids from the communesin family consistently feature a contiguous quaternary chiral center. The organocatalytic protocols developed by Chen *et al.* will be highly useful for synthesizing these alkaloids.

Scheme 21 Synthesis of pseudopteroxazole by Hu *et al.* in 2019.

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ing ketone was converted into **230** *via* methylation followed by reduction. Finally, the *D*-ring was constructed using the oxazole motif synthesis reported by Kerr *et al.*,[65] completing the total synthesis of pseudopteroxazole (**223**). Using the same strategy, they also achieved the total synthesis of ileabethoxazole (**224**), which features a five-membered *C*-ring. The total synthesis is a concise and practical process that effectively utilizes the aldehydes and terminal double bonds generated through asymmetric dual catalytic allylation, a concerted reaction involving both organocatalysts and metal catalysts.

Morphine (**231**) is a crucial drug used to alleviate all types of pain. Additionally, codeine (**232**), a derivative of morphine, is commonly used as a cough suppressant. These alkaloids have a pentacyclic structure with five contiguous chiral centers, one of which is a quaternary carbon center. In 2019, Tu, Zhang, and coworkers synthesized this important drug using intramolecular asymmetric organocatalytic Michael reaction (Scheme 22).[66] The secondary amine catalyst used in the organocatalytic reactions was originally developed by Tu
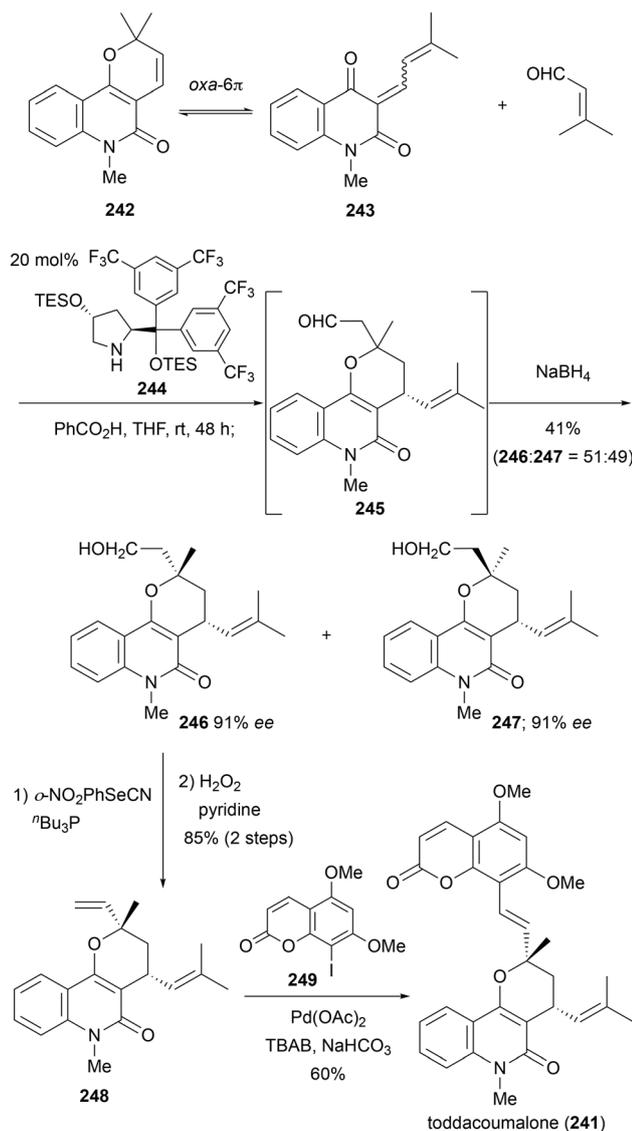
et al.[66] It efficiently induces chirality through its rigid spirocycles and the siloxy groups extending from them. The key organocatalytic reaction precursor, aldehyde **233**, was prepared in four steps starting from commercially available materials. When catalyst **234** and bulky 2,4,6-triisopropylbenzoic acid are added to compound **233** in CH_2Cl_2 at low temperature, the enantioselective intramolecular Michael reaction proceeded, leading to the formation of an all-carbon quaternary chiral center. The crude mixture of **235** was directly treated with *p*-toluenesulfonic acid (PTSA) under heating conditions, resulting in an aldol condensation reaction that provided the tricyclic product **236**. The enantioselectivity of **236** was 94% ee, which was further improved by recrystallization. The α-position of the ketone moiety of compound **236** was subsequently allylated to give **237** as a diastereomeric mixture. Next, selective ozonolysis of the electron-rich double bond of **237** was performed, followed by intramolecular Friedel–Crafts-type cyclization using a catalytic amount of PPA, yielding phenanthrofuran **238** as a single diastereomer. Then, site- and diastereoselective epoxidation of the α,β-unsaturated ketone, followed by the Wharton transposition sequence was carried out to afford allyl alcohol. Subsequent debenzylation yielded diol **239**. Selective sulfonamidation of the primary hydroxyl group under Mitsunobu conditions, followed by a sequential one-pot oxidation–reduction process, generated Guillou's intermediate **240**.[67] The total synthesis of codeine (**232**) was achieved through one-electron reduction of compound **240**, followed by a hydroamination reaction. Further demethylation then led to the total synthesis of morphine (**231**). The intramolecular Michael reaction catalyzed by spiro-secondary amines, developed by Tu, Zhang, and coworkers is highly useful for synthesizing natural products with a *cis*-hydroxybenzofuran skeleton. In fact, they also reported the total syntheses of galanthamine and lycoramine, which have similar structural motifs, shortly after their synthesis of morphine.[68]

Toddacoumalone (**241**) is a known phosphodiesterase-4 (PDE4) inhibitor and features a dimeric structure composed of coumarin and quinolone.[69] Since natural product **241** was isolated as a racemic mixture, structure–activity relationship studies using the optically active forms and its diastereomers are desired. In 2020, Xiong *et al.* developed an intriguing organocatalytic asymmetric inverse electron-demand Diels–Alder reaction, which was employed to achieve the first asymmetric total synthesis of toddacoumalone (**241**) (Scheme 23).[70] They found that the non-isolable diene **243** exists as a stable and isolable ring-closing pyranoquinolinone **242**, which could be in equilibrium *via* an oxa-6π electrocyclic pathway. They then investigated the asymmetric Diels–Alder reaction using this diene and 3-methyl-2-butenal as the dienophile. After careful catalyst screening, catalyst **244**, derived from *trans*-4-hydroxyproline, was identified. The Diels–Alder reaction with the highly reactive quinolinone-derived diene produced the cyclized product **245**. Subsequent reduction of the aldehyde moiety yielded the alcohol **246** and **247** as diastereomers. The chemical yield was 41%, with a diastereomeric ratio of 1 : 1 at the quaternary carbon center; each diastereomer having an
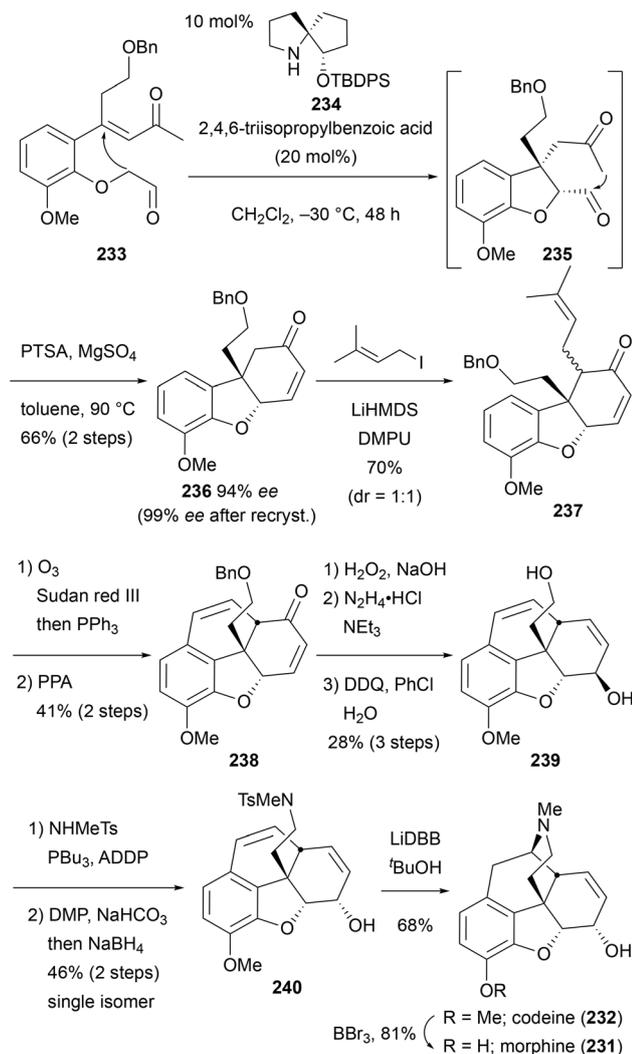
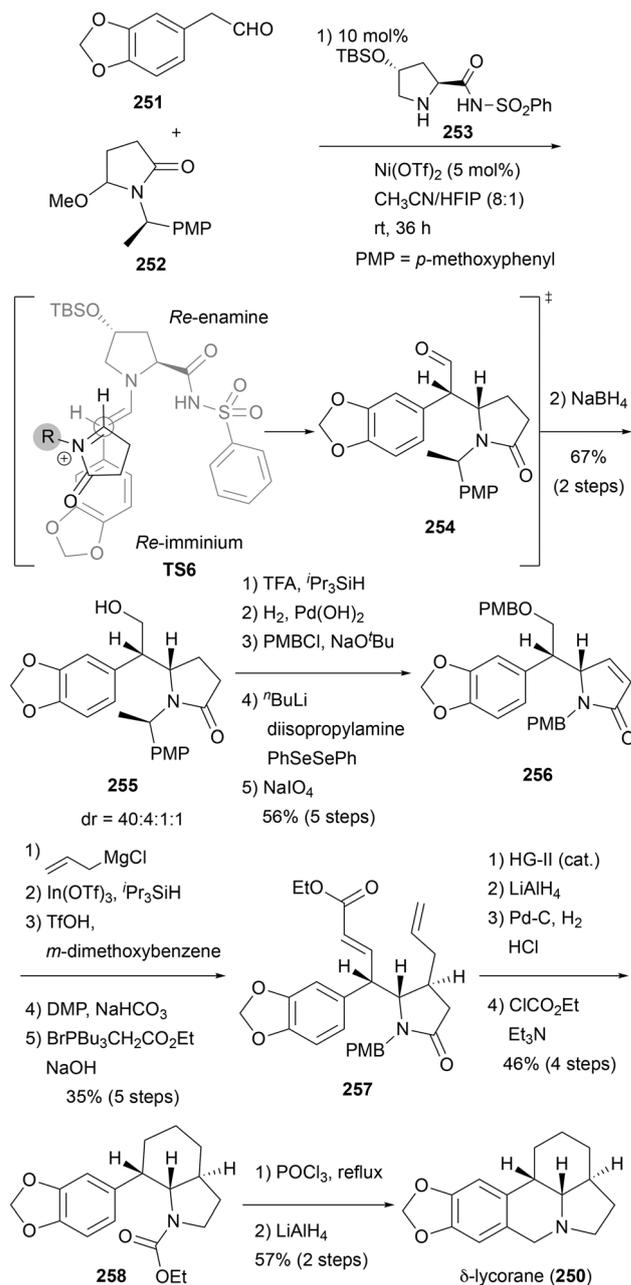**Scheme 22** Synthesis of morphine and codeine by Tu *et al.* in 2019.

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Scheme 23 Synthesis of toddacoumalone by Xiong *et al.* in 2020.

Scheme 24 Synthesis of δ-lycoran by Koley *et al.* in 2023.

enantiomeric excess of 91% ee. The resulting primary alcohol was converted into a terminal double bond using the Grieco–Nishizawa protocol, yielding compound **248**. This was followed by the condensation of the known coumarin derivative **249** *via* the Heck reaction, leading to the total synthesis of **241**. Xiong *et al.* subsequently prepared enantiomers, diastereomers, and their derivatives for structure–activity relationship studies. This is a notable achievement as it involves an organocatalytic reaction utilizing active intermediates that are not visible as isolated compounds (such intermediates might be inferred from biosynthesis).

The total synthesis of δ-lycorane (**250**) was reported by Koley and coworkers in 2023 (Scheme 24).[71] One of the key reactions was a diastereoselective organocatalytic Mannich reaction using optically active δ-methoxylactam **252** (prepared by a four-step transformation from commercially available materials) and phenylacetaldehyde **251** to construct 5-substituted-2-

pyrrolidone derivative **254**. Thus, treatment of the lactam **252** with the aldehyde **251** in the presence of 10 mol% organocatalyst **253** and 5 mol% Ni(OTf)$_2$, proceeded a diastereoselective Mannich reaction, followed by reduction using NaBH$_4$ to provide 5-substituted-2-pyrrolidone derivative **255** with good yield and diastereoselectivity (67% yield, dr = 40:4:1:1). The diastereoselectivity in this reaction was proposed by Koley to stem from the most sterically vacant *Re* face of enamines generated from organocatalyst and aldehyde reacting with the *Re* face of *N*-acyliminium (**TS6**). The lactam **255** was treated with TFA/triisopropylsilane followed by hydrogenation using Pd(OH)$_2$, and PMB protection of alcohol and amide. Subsequent α-selenylation and

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oxidation were performed to afford enamide **256**. The diastereoselective 1,4-addition of enamide **256** was carried out using an allyl magnesium reagent, followed by treatment of the crude reaction mixture with In(OTf)$_3$ and triisopropylsilane to decompose the inseparable byproduct and afford the adduct. After the PMB group on alcohol was removed, Dess–Martin oxidation and Wittig reaction provided dialkene **257**. Subsequent RCM with Hoveyda–Grubbs II catalyst, reduction of amide, reduction of the alkene, removal of the PMB group under catalytic hydrogenation conditions, and formation of the carbamate afforded a precursor of cyclization **258**. Finally, the total synthesis of δ-lycorane (**250**) was achieved by a two-step transformation. Thus, the Bischler–Napieralski reaction of **258** was performed in the presence of POCl$_3$ followed by amide reduction to provide δ-lycorane (**250**). The two vicinal stereocenters of **250** were efficiently constructed by Mannich reaction using organocatalysts **253** and Ni(OTf)$_2$, and this method could also be used for the total synthesis of other *Amaryllidaceae* alkaloids.

Conclusion

In the alkaloid syntheses listed in this article, many examples of domino and one-pot reactions were used to significantly increase the efficiency of the total synthesis. Since many alkaloids contain polycyclic structures, these sequential reactions are particularly effective for constructing multifunctionalized ring systems. This effectiveness may be due to the fact that the secondary amine catalyst does not inhibit subsequent domino or one-pot reactions. Furthermore, of the 24 cases discussed in this article, 7 involve concerted reactions between organocatalysts and metal reagents (mostly catalysts). Notably, the use of dual iridium/amine catalytic allylation, developed by Carreira *et al.*, is used in four of these cases. The terminal double bonds produced in this reaction can be utilized in hydroboration, hydrocarbonylation, olefin metathesis, and other transformations, thereby introducing diversity into synthetic strategies. In all syntheses, high enantioselectivity was achieved through organocatalysis, highlighting the reliability of organocatalysis, which has been well-established science around 2000. The full potential of chiral secondary-amine-catalyzed asymmetric reactions for total synthesis has not been realized yet. Currently, advanced research is underway to apply the active species generated by secondary amine organocatalysts to photoreactions and radical reactions, with the expectation that these methods will soon be applied to alkaloid synthesis. Consequently, elegant and attractive syntheses of alkaloids using secondary amine catalysts are expected to continue appearing.

Data availability

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

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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