Organic & Biomolecular Chemistry

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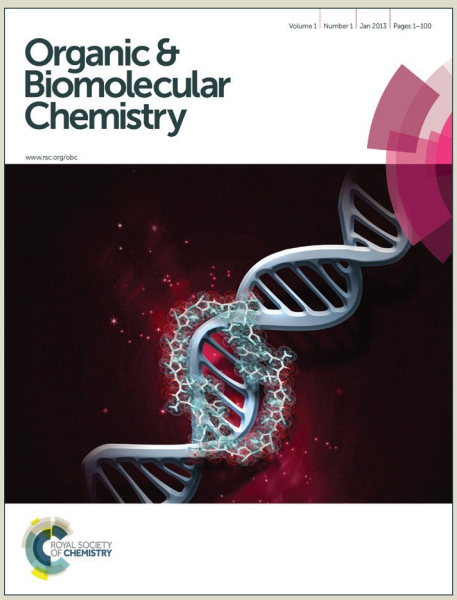

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REVIEW

Alkaloid Synthesis using Chiral Secondary Amine Organocatalysts

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Over the last decade, several excellent enantioselective total syntheses of important alkaloids using asymmetric reactions mediated by chiral secondary amine organocatalysts as a key step have been accomplished. This perspective article examines the full strategies of these alkaloid syntheses, especially the application of the organocatalytic reaction to construct the alkaloid scaffolds.

Introduction

Alkaloids containing a basic amine portion in the molecule are widespread in nature. Thus, a huge number of alkaloids have been isolated from plants, bacteria, and animals.[1] In addition, they have several attractive properties, such as potent bioactivity for development of drugs, and unique architecture for total synthesis. On the other hand, interest in organocatalyst-mediated asymmetric reactions has grown rapidly in recent developments. In particular, chiral secondary amine organocatalysts such as proline (**1**),[2] diphenylprolinol silyl ether catalyst (**2**, Hayashi–Jørgensen catalyst),[3] and 2,3,5-trisubstituted-4-imidazolidinone catalyst (**3**, MacMillan catalyst),[4] have been used to catalyze several important enantioselective reactions, such as asymmetric aldol, Michael, Mannich, Diels–Alder and ene-reactions, as well as α-oxidations, and epoxidations (Fig. 1).[5] These reactions induce a high enantioselectivity via optically active enamine or iminium ion intermediates formed by the catalyst and the carbonyl compound to promote stereoselective nucleophilic or electrophilic additions, or pericyclic reactions. Organocatalysts have several advantages. For instance, there are usually fewer toxicity issues associated with organocatalysts and the reactions are tolerant of water and air. Furthermore, the organocatalytic reactions can be easily applied to domino reactions and one-pot operations, because the secondary-amine catalyst is tolerant of several subsequent reactions.[6] As a result, they are quite attractive methods for preparation of biologically active natural products in both academic and industrial chemistry.

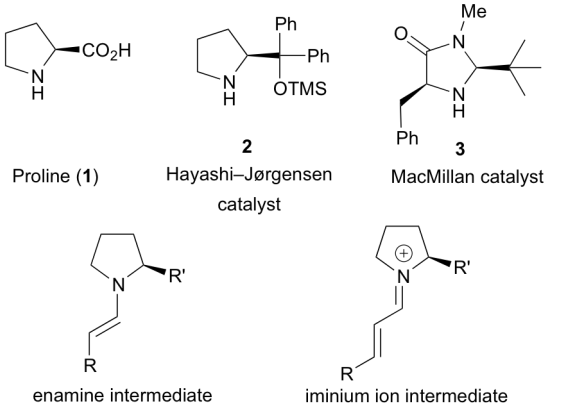

Fig. 1 Representative chiral secondary amine organocatalysts and their proposed reaction intermediates.

Over the last decade, several enantioselective total syntheses of alkaloids using chiral secondary amine organocatalysts have been reported.[7] This perspective article examines the strategies of these alkaloid syntheses, especially the application of organocatalytic reactions to construct the alkaloid scaffolds.

Indole and indoline alkaloids

Indole and indoline alkaloids exist widely in nature and these alkaloids are mainly derived from tryptophan, which is one of the essential amino acids in biosynthesis as a secondary metabolite.[1] Several important bioactivities of these alkaloids have been reported and a number of important naturally occurring indole and indoline alkaloids, such as vinblastine, vincristine, reserpine, and physostigmine are already employed in medicines for human health.[8] In addition, a wide variety of unique architectures of these alkaloids have been identified. Therefore, indole and indoline alkaloids continue to attract the attention of synthetic chemists.

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† Footnotes relating to the title and/or authors should appear here.
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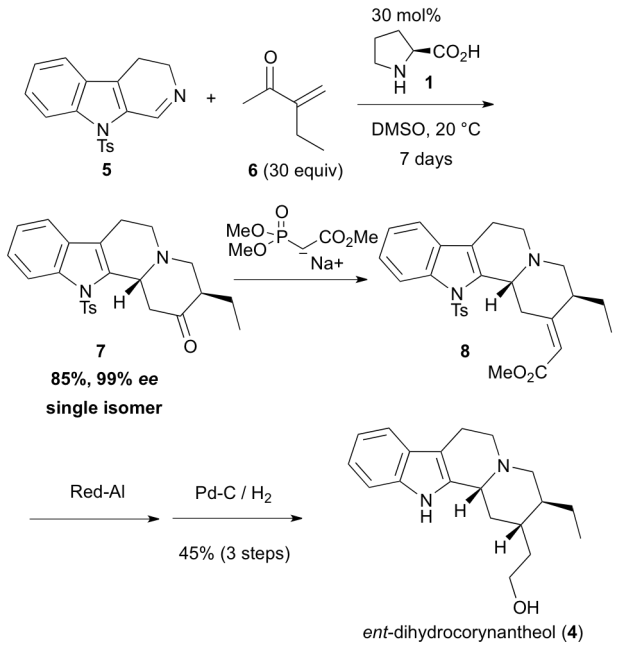
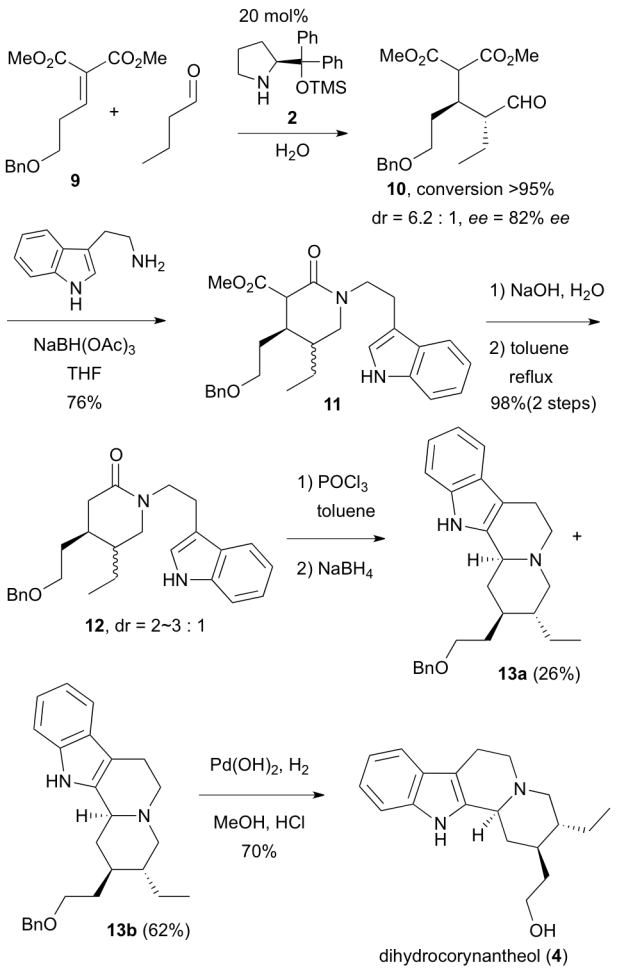
In 2006, Itoh and coworkers reported an enantioselective total synthesis of *ent*-dihydrocorynantheol (**4**), which is belongs to the *Corynanthe*-type monoterpenoid indole alkaloids (Scheme 1).[9] The key reaction was the proline-catalyzed domino asymmetric Mannich/Michael reaction using 3,4-dihydro-β-carboline derivative **5** and α,β-unsaturated ketone **6**. Thus, carboline derivative **5** treated with α,β-unsaturated ketone **6** in the presence of 30 mol% (*S*)-proline (**1**) in dimethyl sulfoxide (DMSO) provided 2,5-substituted 4-piperidinone derivative **7** as a single isomer in superb yield with excellent enantioselectivity (85%, 99% *ee*). Even though an excess amount of ketone (30 equiv) and long reaction time were required, this work is a landmark for not only the synthesis of *Corynanthe*-type monoterpenoid indole alkaloids, but also showing the potential of the domino process using an organocatalyst. A further three-step transformation including the Horner–Emmons reaction, Red–Al treatment for removal of the tosyl group and reduction of the methoxycarbonyl group, and stereoselective hydrogenation provided *ent*-dihydrocorynantheol (**4**) effectively.



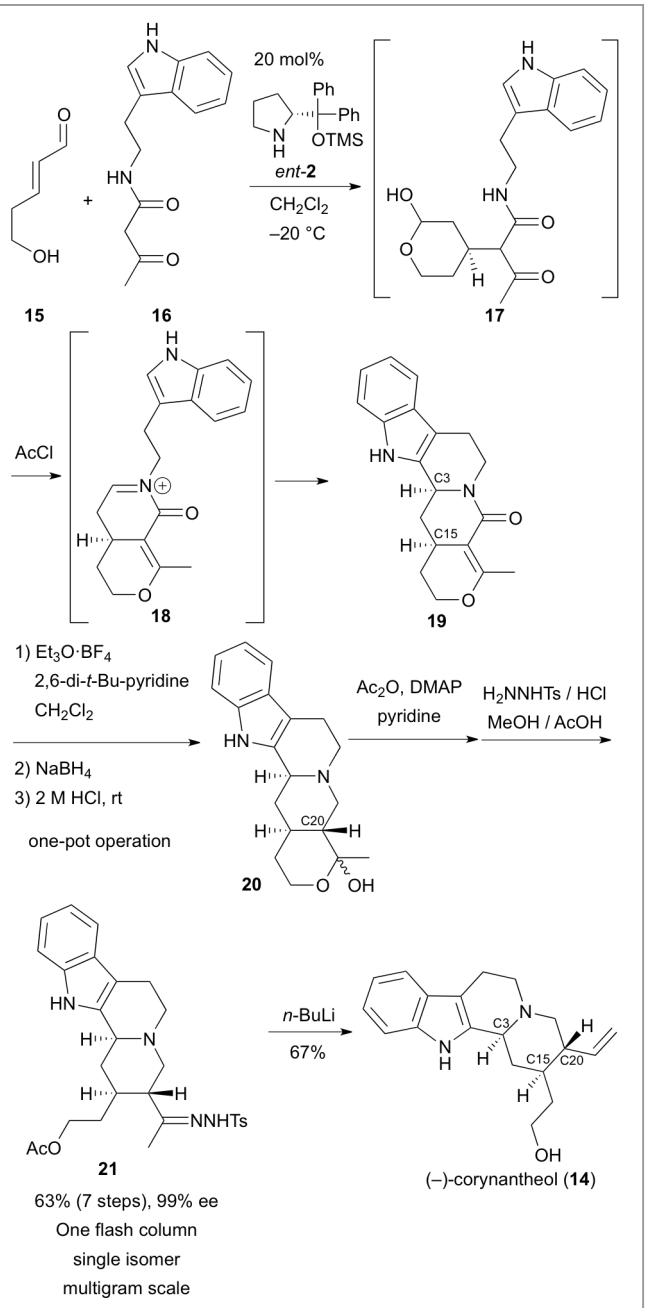
Scheme 1 Synthesis of *ent*-dihydrocorynantheol by Itoh *et al.* in 2006.

Another approach to the synthesis of dihydrocorynantheol and related alkaloids was reported by Ma and Sun in 2011 (Scheme 2).[10] Their synthesis started from an enamine-mediated asymmetric Michael reaction using diphenylprolinol silyl ether catalyst **2**. Thus, when alkylidene malonate **9** was treated with *n*-butanal in the presence of 20 mol% catalyst **2** in H_2O, the desired key Michael adduct **10** was obtained in excellent yield and good enantioselectivity (>95% conversion and 82% *ee*). For completion of the synthesis, reductive amination with tryptamine followed by an intramolecular amidation reaction was carried out to provide **11** as a diastereomeric mixture in good yield. Subsequent saponification and decarboxylation gave lactam **12** in superb yield. Further ring construction to provide tetracyclic compounds **13a** and **13b** was achieved using Bischler–Napieralski cyclization followed by reduction of the yielded iminium intermediate by $NaBH_4$. At this stage, two diastereomers were separated, and major diastereomer **13b** was obtained in 62% yield. Finally, target molecule **4** was obtained by hydrogenation in 70% yield. In addition, Ma and Sun reported not only additional total and formal syntheses of related *Corynanthe*-type indole alkaloids such as corynantheidol and mitragynine, but also the *ipecac* alkaloids that also contain the optically active isoquinoline ring, such as protoemethiol and protoemetine. The methodology developed by Ma and Sun can be widely applied to the divergent synthesis of monoterpenoid indole alkaloids and *ipecac* alkaloids.[10]



Scheme 2 Synthesis of dihydrocorynantheol by Ma and Sun in 2011.

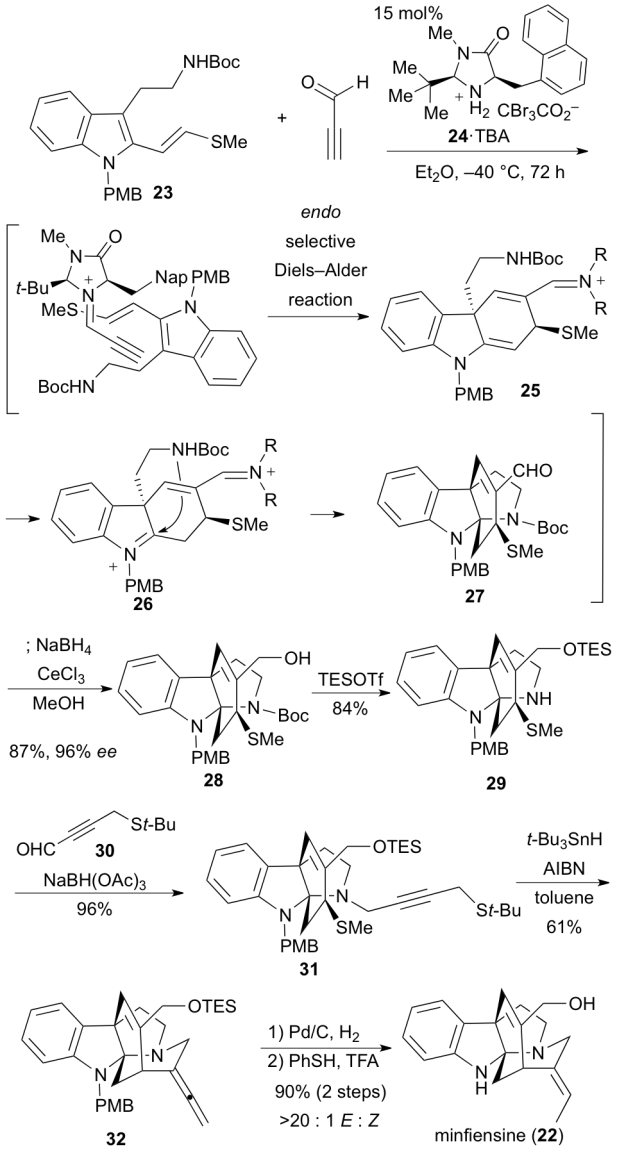
Six months after Ma's report, Franzén and coworkers also reported highly efficient synthetic strategies for synthesis of *Corynanthe*-type indole alkaloids such as corynantheol (**14**) (Scheme 3).[11] Their synthesis started from an enantioselective Michael reaction via an optically active iminium ion intermediate using α,β-unsaturated aldehyde **15** and indole-containing β-ketoamide **16** in the presence of 20 mol% diphenylprolinol silyl ether catalyst *ent*-**2** to provide hemiacetal compound **17**. Hemiacetal **17** was directly treated with AcCl to generate iminium intermediate **18**. Subsequently, **18** was smoothly converted to tetrahydro-β-carboline derivative **19** via a diastereoselective Pictet–Spengler-type cyclization. All steps were carried out in a one-pot operation and the desired compound **19** was obtained in high yield and enantio- and diastereoselectivity (isolation at this stage; 85%, C3 dr ≥ 95:5, 99% *ee*). Without purification, compound **19** was directly converted to pentacyclic compound **20** via reduction of the amide carbonyl group and hydrolysis of the enol ether moiety. Further opening of the hemiacetal followed by introduction of a hydrazone group provided **21**. The chemical yield of the seven-step transformation starting from the organocatalytic Michael reaction was excellent (63%) and all stereocenters such as C3, C15, and C20 were controlled by careful optimization (the numbering comes from biosynthesis of monoterpenoid indole alkaloids). In addition, purification was only needed at the last stage and multigram quantities of key intermediate **21** were obtained. The final transformation to corynantheol (**14**) was achieved by treatment with *n*-BuLi in 67% yield. Total yield of this synthesis was 42% from easily accessible β-ketoamide **16**. Notably, the author's strategy was applied to divergent syntheses of C3 and C20 epimers via optimization using thermodynamic or kinetic controls. Thus, five related *Corynanthe* indole alkaloids were prepared effectively. In addition, these protocols were expanded to divergent syntheses of *ipecac* alkaloids such as protoemetine and protoemethiol.



Scheme 3 Synthesis of corynantheol by Franzén *et al.* in 2011.

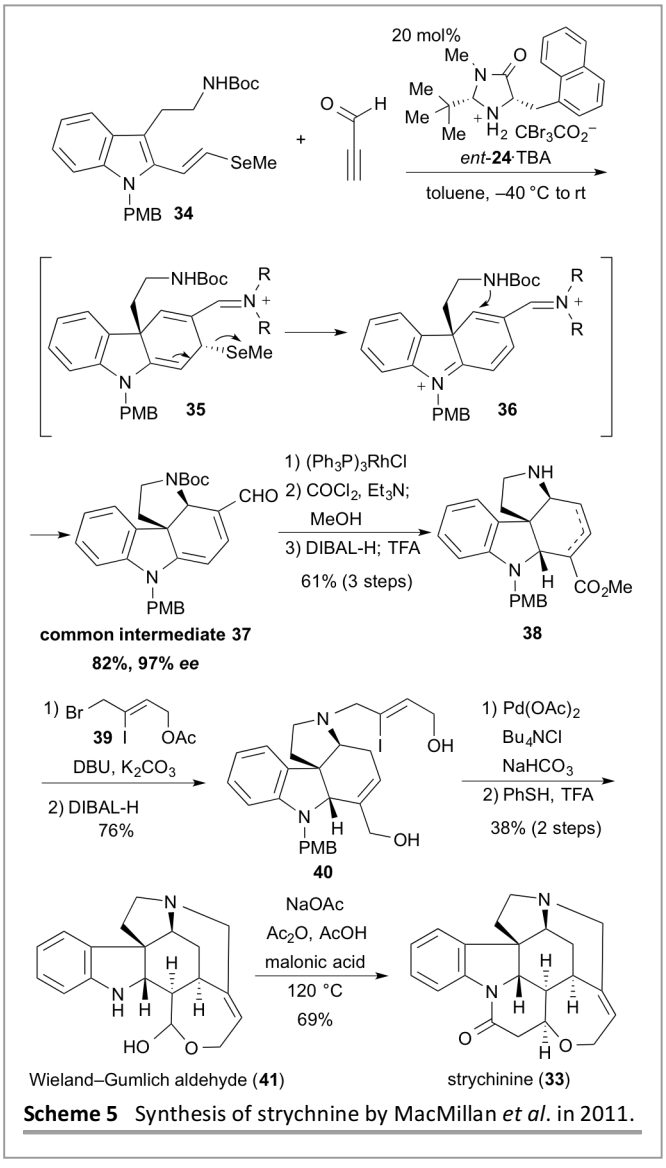
The elegant total synthesis of minfiensine (**22**) using an organocatalytic asymmetric Diels–Alder reaction was reported by MacMillan *et al.* in 2009 (Scheme 4).[12] Their key organocatalytic reaction was originally developed as a highly efficient Diels–Alder reaction using diene **23** containing an indole moiety and propynal in the presence of only 15 mol% tribromoacetic acid (TBA) salt of 2,3,5-trisubstituted-4-imidazolidinone catalyst **24**. The key transformation for construction of the cage structure of **22** involves an asymmetric organocatalytic reaction. Thus, the *endo*-selective Diels–Alder reaction proceeded to provide cyclic diene compound **25** containing a newly generated quaternary carbon center at the C3 position and the yielded enamine moiety was isomerized to the iminium ion intermediate **26**. Subsequent amine cyclization from the terminal NHBoc group was promoted to provide tetracyclic α,β-unsaturated aldehyde **27**. Without purification, direct reduction using the Luche condition in a one-pot operation provided alcohol **28** in 87% yield with excellent enantioselectivity (96% *ee*). Subsequent transformations to synthesize **22** included an important and impressive radical cascade reaction. Protection of the primary alcohol and removal of the Boc group on the secondary amine of compound **28** were carried out using TESOTf. The reductive amination with propynal derivative **30** yielding **29** in the presence of $NaBH(OAc)_3$ was achieved to provide radical cyclization precursor **31**. The key radical cascade cyclization to form the piperidine ring system in **22** was accomplished using sterically bulky tBu_3SnH in the presence of catalytic AIBN under reflux conditions to produce pentacyclic allene **32** in good yield (61%). Final regio- and diastereoselective hydrogenation followed by removal of the protective groups by two-step sequences provided minfiensine (**22**) in superb yield (90%). The short and straightforward synthesis was completed in a

total of only nine steps and 21% overall yield from commercial materials.



Scheme 4 Synthesis of Minfiensine by MacMillan *et al*. in 2009.

In 2011, the MacMillan group expanded the organocatalytic cascade strategies to the divergent total synthesis of six different *Strychnos*, *Aspidosperma*, and *Kopsia* alkaloids, namely, strychnine (**33**), akuammicine, aspidospermidine, vincadifformine, kopsinine, and kopsanone (Scheme 5).[13] In the key organocatalytic reaction, diene **34**, which has a –SeMe group on the side chain instead of the –SMe as in **23** was employed. Thus, after the Diels–Alder reaction using diene **34** and propynal in the presence of 20 mol% catalyst *ent*-**24**·TBA salt, the SeMe group was eliminated from intermediate **35** to give conjugated diene **36**. Subsequent stereoselective Michael addition of the Boc-protected primary amine group to the α,β-unsaturated imine moiety proceeded to form tetracyclic key common intermediate **37** in superb yield and excellent enantioselectivity (82%, 97% *ee*). The synthesis of strychnine (**33**) is illustrated in Scheme 5. From common intermediate **37**, a decarbonylation reaction using a stoichiometric amount of Wilkinson's catalyst followed by insertion of a methoxy carbonyl group at the dienamine α-position by treatment with phosgene and quenching with MeOH provided the dienamine intermediate. Reduction of the enamine portion and removal of the Boc group using DIBAL-H / TFA at low temperature provided the desired product containing a *cis* junction as a mixture of double-bond isomers **38** in good yield (61%, three steps). Subsequent alkylation of the secondary amine **38** with vinyl iodide **39** and base isomerization of the double bond into conjugation with the ester were achieved by treatment with DBU and K_2CO_3, then DIBAL-H reduction of the methyl ester to the allyl alcohol and cleavage of the acetate on the side chain gave **40** in 76% yield. An intramolecular Heck cyclization/lactol formation sequence to set the six-member ring system and removal of the PMB group with thiophenol as a cation scavenger provided the Wieland–Gumlich aldehyde (**41**) in moderate yield (38%, two steps). Under this beautiful cascade sequence, the authors pointed out that the PMB

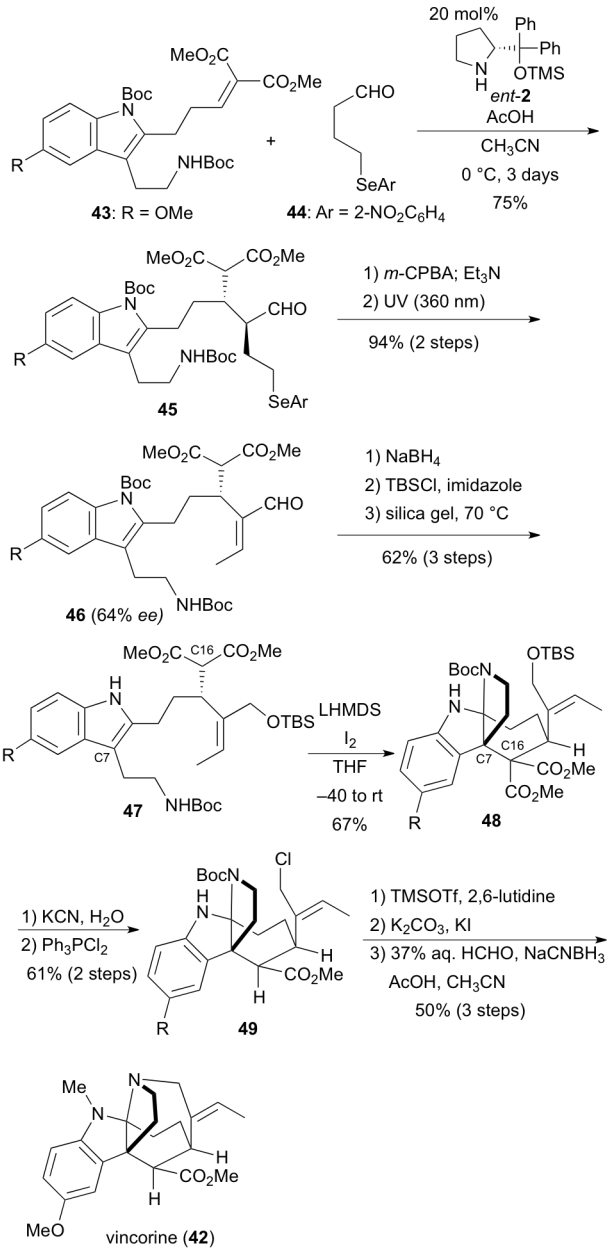


Scheme 5 Synthesis of strychnine by MacMillan *et al*. in 2011.

group was essential for direction of β-hydride elimination of the Heck reaction to form the enal. Final conversion from **41** to strychnine (**33**) using known reaction conditions proceeded smoothly and the total synthesis of **33** was completed in 12 steps and a total 6.4% yield from commercially available materials. The key intermediate **37** or another intermediate with Bn group instead of PMB group of **37** served as starting material to access five additional, structurally different alkaloids in high yield (8.9% up to 24%). On the other hand, the MacMillan group also published an elegant total synthesis of vincorine (**42**), which belongs to the akuammiline-type alkaloids in a nine-step sequence in 9% overall yield with 95% *ee* using a similar Diels–Alder and radical cyclization strategy in 2013.[14] All syntheses of these historically important molecules by the MacMillan group using organocatalytic cascade methodologies are remarkably efficient; they have a smaller number of steps and higher total yield than previously reported syntheses. In addition, these approaches have shown that domino or cascade reactions using organocatalysts work well for the total synthesis of complex molecules. The interested reader is referred to the original report by MacMillan *et al*. for further details.[13, 14]

Before disclosure of MacMillan's vincorine (**42**) synthesis, Ma and coworkers reported the total synthesis of vincorine (**42**) using an enamine-mediated organocatalytic asymmetric Michael and an intramolecular oxidative coupling reaction as key steps (Scheme 6).[15] Synthetic precursor **43** of the first key organocatalytic reaction was prepared in a six-step transformation including the author's previously developed C–H functionalization of the indole C2 position, from 5-methoxy tryptamine. The organocatalytic Michael reaction using alkylidene malonate **43** as an electrophile and aldehyde **44** containing an aryl selenide moiety as a nucleophile in the presence of diphenylprolinol silyl ether catalyst *ent*-**2** provided optically active Michael adduct **45** in 75% yield with high diastereoselectivity (dr = 5:1) after 3 days at 0 °C. For construction of the α,β-unsaturated aldehyde moiety, oxidation followed by elimination of the aryl selenide group was carried out. However, the product was obtained as a ~1.7:1 mixture of *E* / *Z* isomers. The proportion of the desired *E* isomer **46** was enriched by exposure to UV light (360 nm); final ratio was 30:1. The enantiomeric excess was determined at this stage and the *ee* value for **46** was 64% *ee*. Next, reduction of aldehyde **46** using $NaBH_4$ and TBS protection of the yielded primary alcohol followed by selective removal of the Boc group on the indole core by silica gel provided **47** in good yield (62%). The second key step of this synthesis was a stereoselective oxidative coupling reaction between the indole β-position (C7) and α-position (C16) of the malonic ester moiety. Thus, **47** was treated with LHMDS for deprotonation, then iodine was added at –40 °C to allow formation of the C7–C16 bond followed by amine cyclization. The desired tetracyclic compound **48** was obtained in 67% yield. To achieve the synthesis of vincorine (**42**), an additional five steps were required. Thus, decarboxylation at the C16 position using Krapcho's reaction conditions and direct chlorination of the TBS-protected hydroxy group provided **49** in 44% yield. A further three-step sequence including removal of the Boc group, seven-membered ring construction and reductive amination to install a methyl group on the indoline core gave vincorine (**42**) in 47% yield (three steps). Ma's synthesis of **42** was accomplished in 18 steps from commercially available materials and the overall yield was 5%.

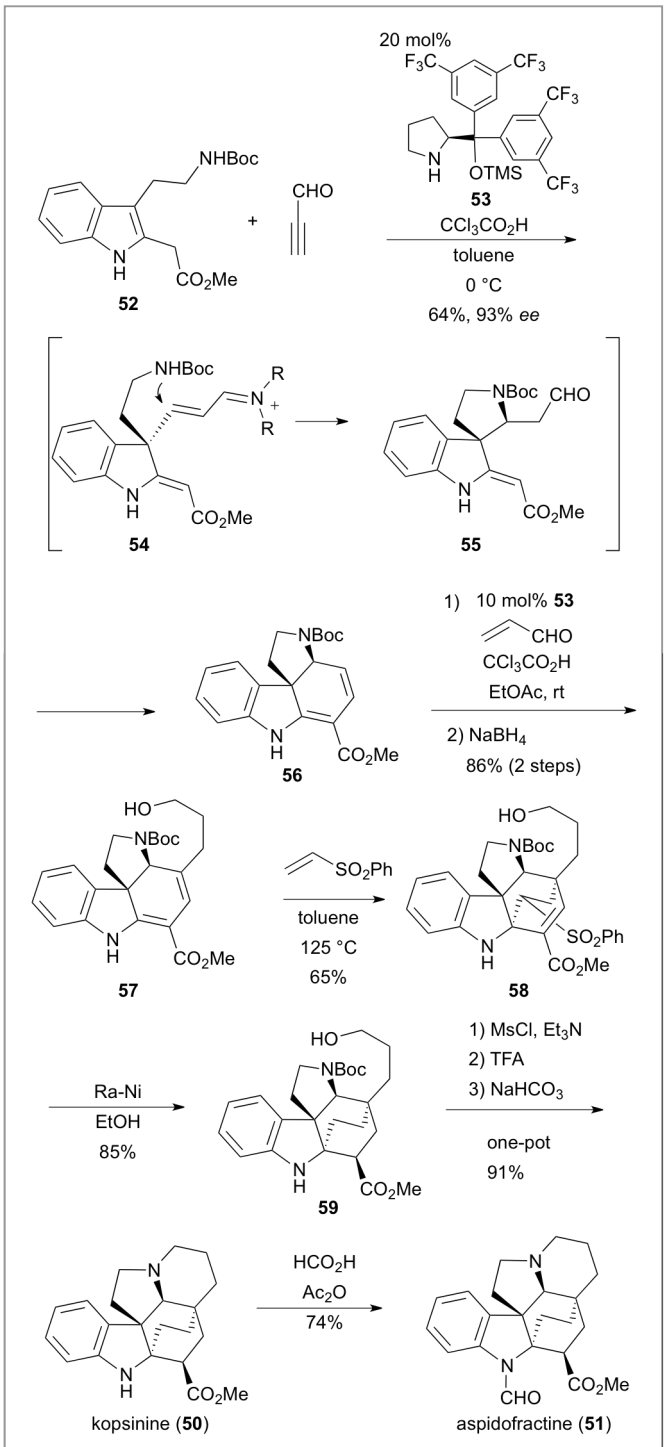
In 2014, Wu and coworkers reported the total synthesis of



Scheme 6 Synthesis of vincorine by Ma *et al*. in 2012.

kopsinine (**50**) and aspidofractine (**51**), which belong to the *Kopsia* alkaloids, using an organocatalytic Michael/*aza*-Michael/cyclization cascade sequence (Scheme 7).[16] The synthesis was started from a key cascade reaction. Thus, known tryptamine derivative **52** was treated with propynal and 20 mol% catalyst **53**, which is known as the Jørgensen catalyst, in the presence of 1 equiv of trichloroacetic acid to provide tetracyclic dienamine compound **56** in 64% yield

with 93% *ee*. The key reaction contained several unique transformations: asymmetric Michael addition from the indole C3 position to activated iminium ion to generate intermediate **54**, diastereoselective *aza*-Michael addition from terminal NHBoc group followed by hydrolysis to generate aldehyde **55**, and cyclization via the addition of the enamine to the aldehyde moiety followed by a dehydration reaction to form **56**. The condensation reaction with acrolein at the γ-position of the dienamine in the presence of catalyst **53** followed by reduction of the yielded aldehyde was achieved in 86% yield. The ethylene bridge of the target molecule was installed by exposing **57** to a large excess amount of phenyl vinyl sulfonate in toluene at 125 °C, affording the Diels–Alder adduct **58** in 65% yield. Removal of the sulfonate moiety and stereoselective hydrogenation of the α,β-unsaturated ester moiety were achieved by treatment with Raney-Ni to provide **59** in 85% yield. Following a three-step sequence containing mesylation of the primary alcohol, removal of the Boc group, *N*-alkylation to complete the pentacyclic ring system were carried out in a one-pot operation to afford the natural product kopsinine (**50**) in 91% yield. Transformation of **50** to aspidofractine (**51**) was accomplished by *N*-formylation in 74% yield. The strategies disclosed by Wu's group are also a very efficient approach to synthesis of this alkaloid family.

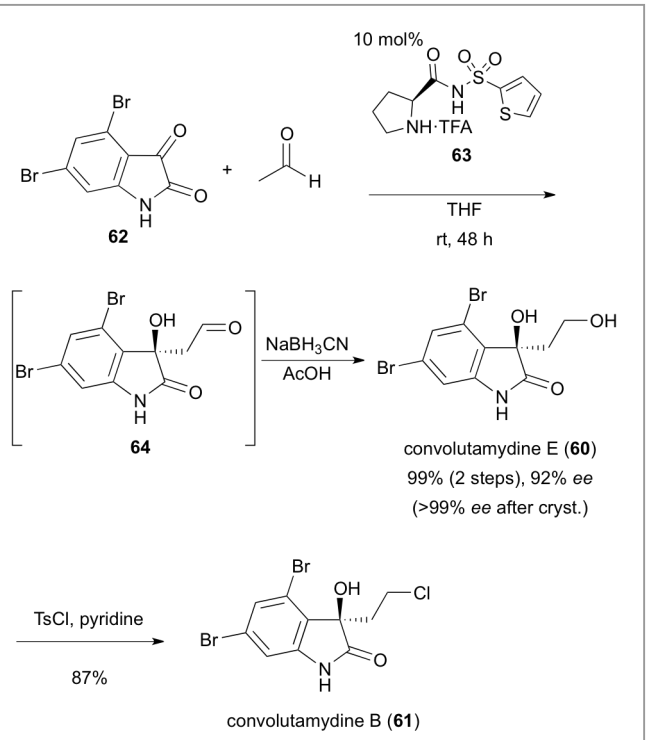


Scheme 7 Synthesis of kopsinine and aspidofractine by Wu *et al*. in 2014.

Oxindole alkaloids

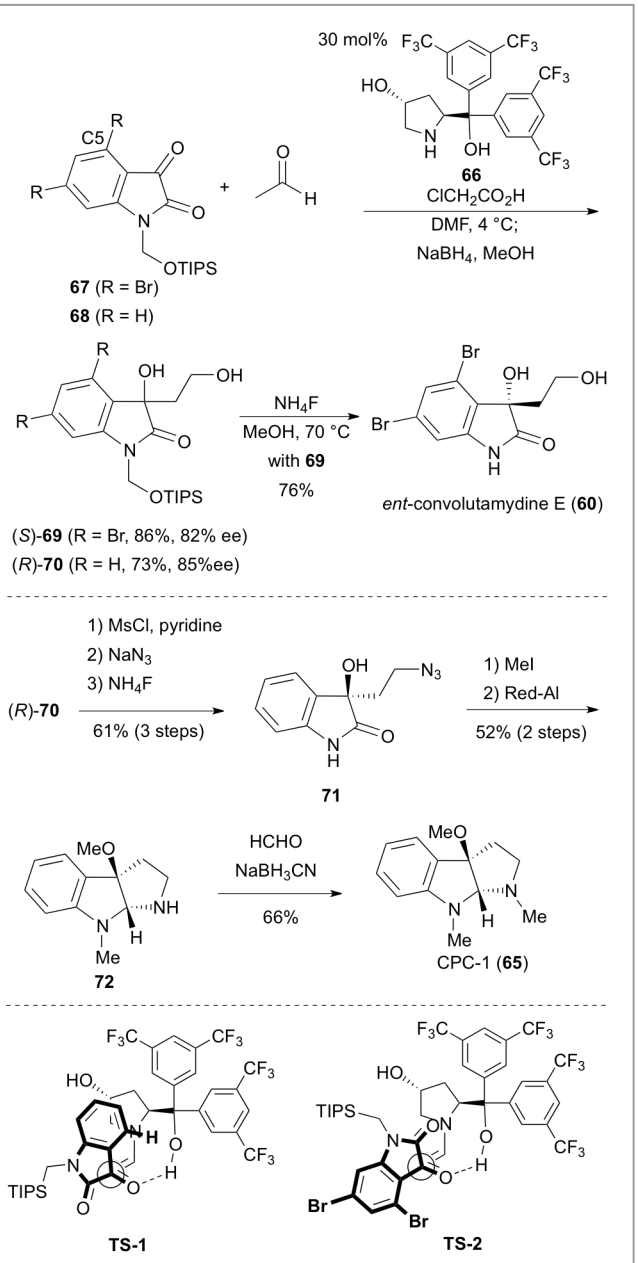
Large numbers of oxindole alkaloids have been isolated from nature and several reported important biological activities. Usually, in biosynthesis oxindoles are synthesized by an oxidation reaction of indole alkaloids. Therefore, oxindole alkaloids are also classified as indole alkaloids. On the other hand, organocatalytic reactions used in syntheses of oxindole alkaloids employ a starting material containing the oxindole moiety –here the C3 position of oxindole or its derivatives can perform both as nucleophile or electrophile. Thus, in this perspective article, indole and oxindole alkaloids are described as separatory alkaloids.

In 2009, Nakamura and coworkers reported excellent total syntheses of the simple alkaloids convolutamydines E (**60**) and B (**61**) (Scheme 8).[17] Their key organocatalytic asymmetric aldol reaction employed isatin derivative **62**, which has strong electrophilicity on the C3 position of the oxindole moiety, and acetaldehyde as a nucleophile in the presence of originally developed *N*-heteroarylsulfonylprolinamide catalyst **63**[18] to provide optically active aldehyde intermediate **64**. Without purification, the reaction mixture was directly treated with $NaBH_3CN$ in acetic acid to afford convolutamydine E (**60**) in superb yield with excellent enantioselectivity. Subsequent chlorination of **60** gave convolutamydine B in excellent yield. In addition, Nakamura and coworkers reported the synthesis of convolutamydine A using a similar strategy with acetone as the nucleophile in 2008.[18]



Scheme 8 Synthesis of *ent*-convolutamydine E and B by Nakamura *et al*. in 2009.

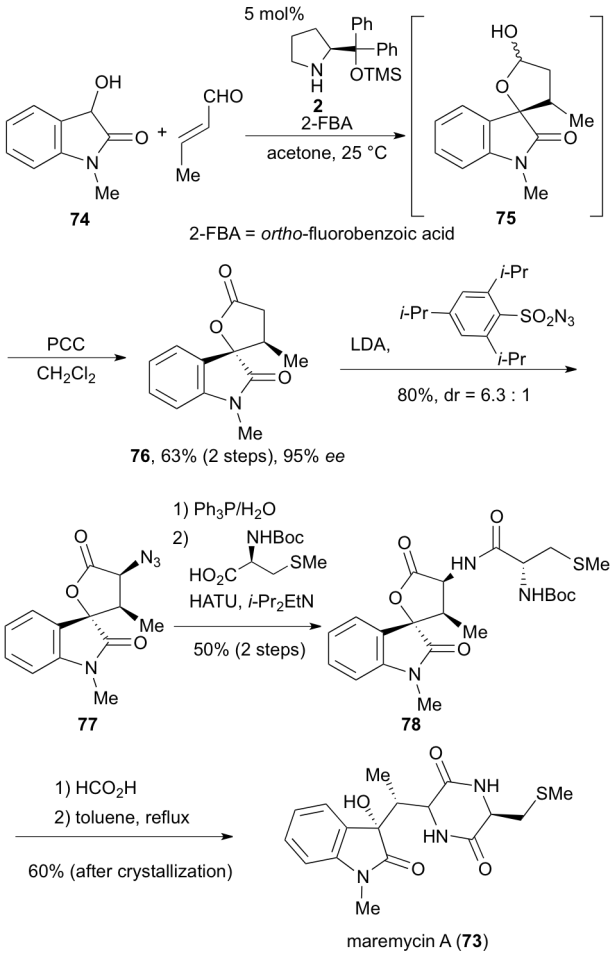
At almost the same time as Nakamura's report, Hayashi and coworkers reported syntheses of convolutamydine E (**60**), CPC-1 (**65**), and a fragment for the synthesis of madindolines A and B using an organocatalytic aldol reaction facilitated by diarylprolinol catalyst **66** (Scheme 9).[19] Substrates of the key reaction were *N*-protected isatin derivatives **67** and **68**. Thus, both isatin derivatives were treated with acetaldehyde in the presence of catalyst **66** followed by $NaBH_4$ reduction to provide optically active compound **69** and **70** in good yield and *ee*. Importantly, using **67**, S-configured **69** was obtained, whereas **68** gave the opposite (*R*)-enantiomer **70** under exactly the same reaction conditions. These differences were rationalized by the authors as the steric effect of the C5-substituent (Br vs H). Therefore, the reaction with both substrates proceeded via different transition states (**68** via TS-1, **67** via TS-2, see reference 19 for details). The prepared **69** was easily converted to *ent*-convolutamydine E (**60**) by treatment with NH_4F for removal of the triisopropylsiloxymethyl group. In addition, oxindole **70** was employed to synthesize CPC-1. Thus, the primary alcohol moiety of **70** was converted to the azide group via a two-step sequence including mesylation followed by displacement of azide. After removal of the protective groups of nitrogen in the oxindole moiety, double methylation of the C3 alcohol and the amide moiety followed by partial reduction with Red–Al provided tricyclic pyrrolidinoindoline compound **72**. The final transformation was reductive amination to install a methyl group on the secondary amine, thus achieving the total synthesis of CPC-1 (**65**). In addition, intermediate **70** was converted by a two-step sequence to a key fragment for the synthesis of madindolines A and B.



Scheme 9 Synthesis of *ent*-convolutamydine E, CPC-1 by Hayashi *et al*. in 2009.

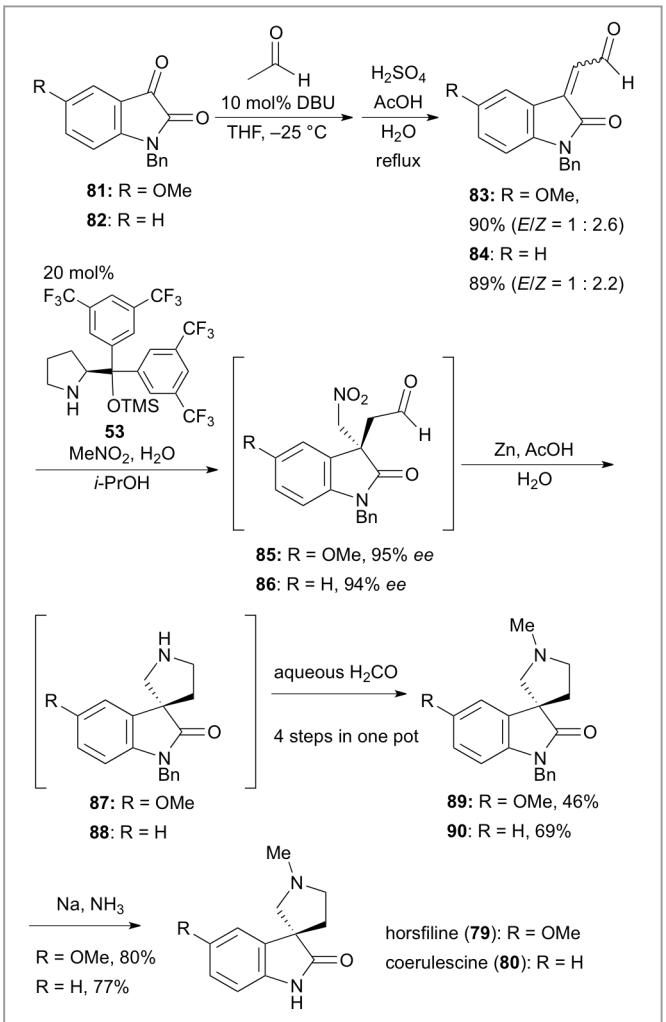
Melchiorre and Bergonzini reported an elegant total synthesis of diketopiperazine oxindole alkaloid maremycin A (**73**) using organocatalytic asymmetric Michael addition / Lactol cyclization with unique dioxindoles (3-hydroxy oxindoles) as nucleophiles in 2012 (Scheme 10).[20] Usually, dioxindoles are very unstable under basic condition because they undergo aerobic oxidation to form isatin followed by dimerization with another dioxindole. Therefore, effective cross-coupling reactions of dioxindole with suitable electrophiles are not easy and mild conditions are required. Melchiorre and Bergonzini showed that such an asymmetric Michael addition using dioxindole as a nucleophile can be achieved under mild organocatalytic conditions. Thus, the domino asymmetric Michael addition / Lactol cyclization reaction for the synthesis of **73** was carried out with *N*–Me dioxindole **74** and

crotonaldehyde in the presence of 5 mol% catalyst **2** and *ortho*-fluorobenzoic acid as additive at ambient temperature to afford optically active lactol **75** containing a chiral quaternary carbon center. Subsequent PCC oxidation of the mixture of four diastereomers provided the desired lactone **76** and minor diastereomers in good yield with excellent enantioselectivity (major diastereomer **76**; 63% yield, 95% *ee*, minor diastereomer; 15% yield, 65% *ee*). The α-azidation of the lactone ring of **76** was achieved by treatment of Li-enolate with trisylazide in 80% yield as a diastereomeric mixture (dr = 6.3:1). The Staudinger reaction was followed by condensation with *N*-Boc-*S*-methyl-L-cysteine. After purification, compound **78** was obtained as a single isomer in 50% yield. Maremycin A (**73**) was finally accessed after removal of the Boc group and formation of the diketopiperazine ring in 60% yield. The overall yield of this synthesis was 15% starting from dioxindole **74**.



Scheme 10 Synthesis of maremycin A by Melchiorre and Bergonzini in 2012.

More recently, three highly effective one-pot syntheses of horsfiline (**79**) and coerulescine (**80**) were achieved by Hayashi and coworkers (Scheme 11).[21] The first key reaction was the straightforward synthesis of 2-oxoindoline-3-ylidene acetaldehydes **83** and **84** from *N*-protected isatin derivatives **81** and **82** with acetaldehyde. Here, isatin derivatives **81** and **82** were treated with a catalytic amount of DBU for a condensation reaction with acetaldehyde, then subsequent treatment with sulfuric acid for dehydration in a one-pot operation to afford **83** and **84** as an *E* and *Z* mixture in excellent yield. The second key step was an organocatalytic Michael reaction for construction of the chiral quaternary center at the C3 position with nitromethane using diarylprolinol silyl ether catalyst **53**. Interestingly, the Michael reaction provided **85** and **86** containing chiral quaternary carbon centers in high yield and high enantioselectivity, regardless of the ratio of E/Z isomers in the starting materials. These results indicated that the isomerization reaction between the *E* and *Z* isomers occurred in situ to provide a single enantiomer. The one-pot sequence was continued. Zinc and acetic acid were added to the same flask to promote reduction of the nitro group to the amine, followed by cyclization via reductive amination with the aldehyde moiety. Crude **87** or **88** was directly treated with aqueous formaldehyde in the presence of zinc, again in the same flask to provide the desired compound **89** or **90** in excellent yield via a one-



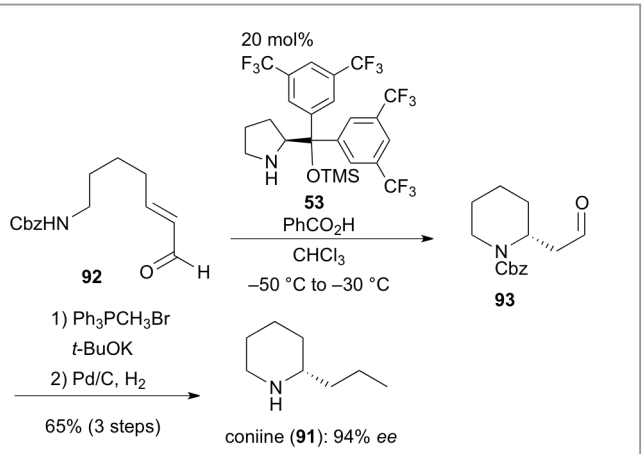
Scheme 11 Synthesis of horsfiline and coerulescine by Hayashi *et al.* in 2014.

pot sequence containing four steps. Subsequent removal of the benzyl group gave natural products horsfiline (**79**) and coerulescine (**80**). In addition, the absolute stereochemistry of **80** was determined. The efficient total syntheses of **79** and **80** by Hayashi *et al.* were accomplished in only three isolated steps in overall yields of 33% and 46%, respectively.

Piperidine alkaloids

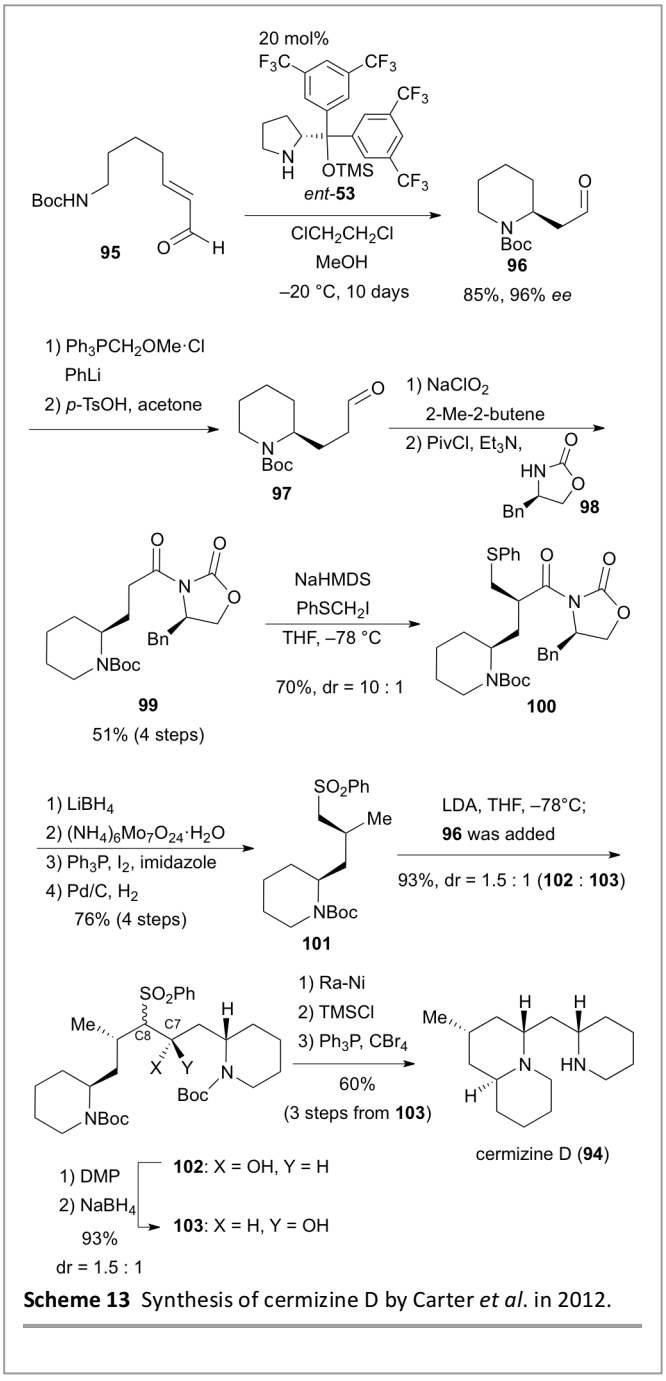
Multiply substituted chiral piperidine ring systems occur in a wide variety of natural products and biologically significant compounds.[22] These alkaloids are biosynthetically derived from L-lysine or L-ornithine. In addition, a wide variety of unique architectures of these alkaloids were identified. Therefore, the development of new methodologies for unified total syntheses of piperidine alkaloids is an important area in organic chemistry. Recently, several total syntheses of piperidine alkaloids using secondary amine-catalyzed reactions for the construction of these scaffolds as key steps were reported.

In 2007, an efficient construction protocol of chiral C2 alkylated piperidines via an organocatalytic intramolecular *aza*-Michael reaction was reported by Fustero and coworkers In their synthesis of simple piperidine alkaloid coniine (**91**) (Scheme 12).[23] Thus, when α,β-unsaturated aldehyde **92**, prepared by cross-metathesis of acrolein and the corresponding alkenes, was treated with 20 mol% catalyst **53** in the presence of benzoic acid at –50 to –30 °C, intramolecular *aza*-Michael reaction proceeded in an excellent enantioselective manner to provide C2-substituted piperidine **93** (94% *ee*). After a two-step sequence including Wittig olefination and removal of the Cbz group, the synthesis of coniine (**91**) was accomplished in 65% yield over three steps. Almost the same protocol was reported by Carter *et al.* a few months later.[24] In addition, the Fustero and Pozo group employed this methodology to synthesize quinolizidine alkaloids such as myrtine and lupinine in 2011.[25] Both simple synthetic protocols can be widely applied to more complex piperidine alkaloids.



Scheme 12 Synthesis of coniine by Fustero *et al.* in 2007.

Carter and coworkers established a total synthesis of cermizine D (**94**) using the same strategy (Scheme 13).[26] Thus, treatment of α,β-unsaturated aldehyde **95** with catalyst *ent*-**53** at –20 °C for 10 days provided optically active C2-substituted piperidine **96** in excellent yield with superb enantioselectivity (85%, 96% *ee*). C_1 elongation of the aldehyde moiety in **96** was achieved by Wittig olefination and enol ether cleavage to afford **97**. Kraus–Pinnick oxidation followed by coupling with Evans oxazolidinone **98** generated **99** in 51% yield over four steps. Diastereoselective alkylation using α-iodomethyl phenyl sulfide was carried out in the presence of NaHMDS as base at –78 °C to provide the desired thioether **100** with high diastereoselectivity (70%, dr = 10:1). A subsequent four-step transformation, including removal of oxazolidinone with $LiBH_4$, sulfide oxidation, and deoxygenation, provided the Julia coupling precursor **101** in 76% yield (four steps).

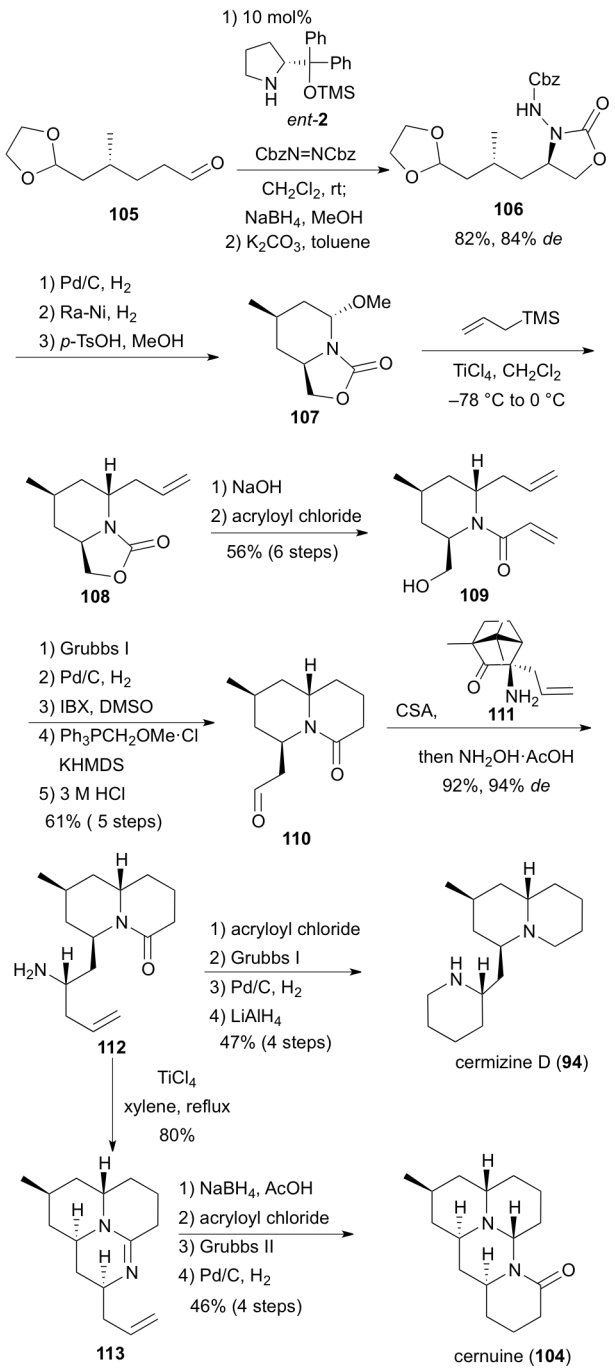


Scheme 13 Synthesis of cermizine D by Carter *et al.* in 2012.

Deprotonation of sulfone **101** using LDA followed by addition of aldehyde **96** gave the hydroxy sulfones **102** and **103** as a diastereomeric mixture at both C7 and C8. The undesired C7 diastereomeric mixture was recycled via oxidation followed by reduction to regenerate an almost equal diastereomeric ratio. Final transformation to cermizine D (**94**) was achieved by desulfurization using Raney-Ni, removal of the Boc group and S_N2 cyclization reaction in good yield. Carter's approach to the synthesis of **94** required 16 linear steps from commercially available materials.

Before disclosure of Carter's total synthesis, Takayama and coworkers published the first asymmetric total syntheses of cernuane-type *Lycopodium* alkaloids, namely cermizine D (**94**) and cernuine (**104**) in 2008 (Scheme 14).[27,28] One of the key steps was a diastereoselective organocatalytic α-amination reaction. Precursor **105** of this key step was prepared by a two-step transformation from commercially available (+)-citronellal. Then, aldehyde **105** was treated with dibenzyl azodicarboxylate in the presence of 10 mol% catalyst *ent*-**2** followed by reduction with $NaBH_4$ and cyclization under basic conditions to provide oxazolidinone **106** in excellent yield and high diastereoselectivity. Next, stepwise reductive *N*–*N* bond cleavage was achieved by removal of the Cbz group followed by hydrogenation with Raney-Ni. Subsequent conversion of the acetal moiety to an aldehyde followed by aminoacetal formation provided cyclic compound **107**. Without purification, stereoselective allylation via axial attack on the acyliminium ion was perfomed by treatment of aminoacetal **107** with allyltrimethylsilane in the presence of $TiCl_4$ to provide **108** as a single diastereomer. Hydrolysis of the oxazolidinone moiety in **108** followed by acryloylation gave acrylamide **109** in 56% yield over six steps. Subsequent ring-closing metathesis with first-generation Grubbs catalyst followed by hydrogenation of the α,β-unsaturated amide provided the quinolizidinone compound. Next, a three-step transformation including oxidation of the primary alcohol to the aldehyde with IBX, Wittig olefination followed by acid-mediated hydrolysis provided aldehyde **110** in 61% yield over five steps. Transfer aminoallylation as a second key step was accomplished by Kobayashi's procedure. Thus, using **111** derived from (1*R*)-camphor quinone, homoallylamine **112** was obtained in high yield and excellent diastereoselectivity (92%, 94% *de*). Now, **112** was converted to a piperidine ring by a four-step sequence that included acryloylation, ring-closing metathesis, hydrogenation, and reduction of the bisamide in 47% yield over four steps.

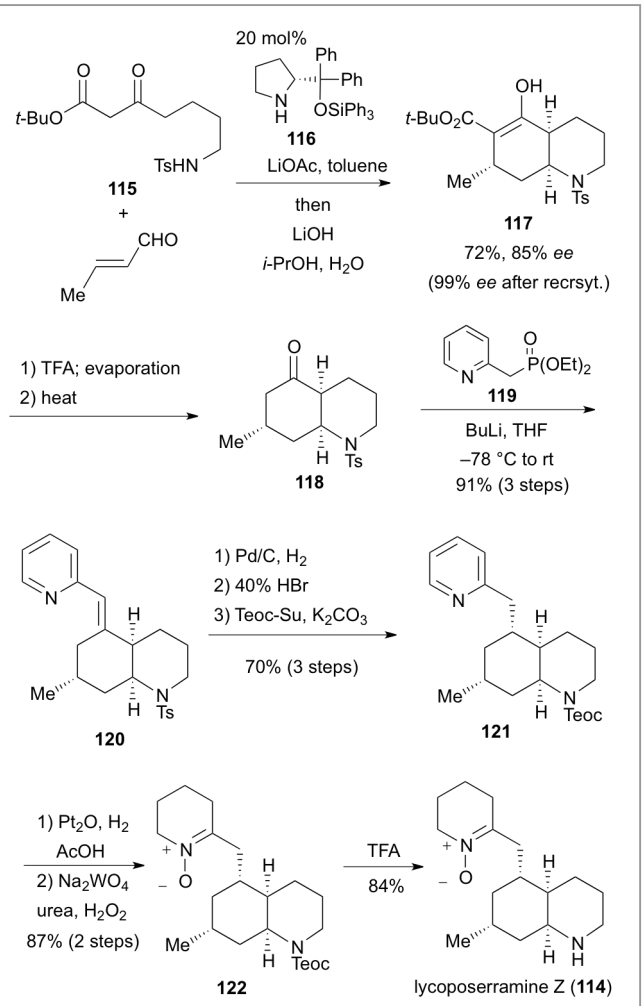
On the other hand, toward the synthesis of cernuine (**104**), amidine **113** was prepared by treatment with $TiCl_4$ under reflux conditions. Stereoselective reduction was conducted with $NaBH_4$ in the presence of acetic acid to provide the corresponding secondary amine compound. The final three-step conversion including acryloylation, ring-closing metathesis, and hydrogenation provided cernuine (**104**). The overall yield of the total synthesis of cermizine D (**94**) and cernuine (**104**) was 11% (18 steps) and 14% (19 steps), respectively.



Scheme 14 Synthesis of cermizine D and cernuine by Takayama *et al*. in 2008.

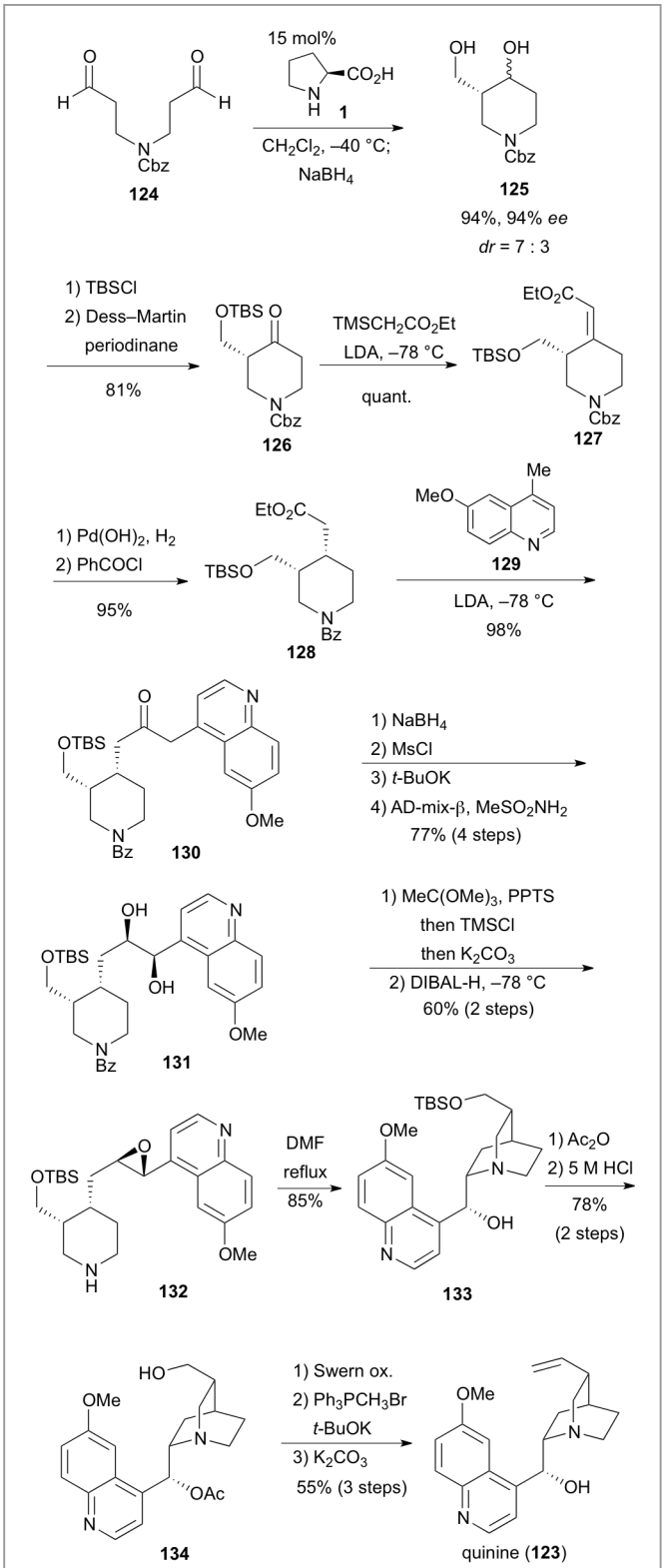
The total synthesis of lycoposerramine Z (**114**), which belongs to the *Lycopodium* alkaloids was reported by the Bradshaw and Bonjoch group in 2013 (Scheme 15).[29] The key one-pot transformation included an organocatalytic asymmetric Michael reaction using diphenylprolinol triphenylsilyl ether (**116**) as catalyst and a domino Robinson annulation/intramolecular *aza*-Michael reaction. Thus, β-keto ester **115**, which was prepared in three steps from commercially available 5-aminopentenoic acid, was treated with crotonaldehyde in the presence of catalyst **116** and LiOAc.

After completion of the Michael reaction, LiOH was added to the reaction flask to promote Robinson annulation for construction of the cyclohexenone intermediate followed by *aza*-Michael reaction to provide azabicyclic compound **117**. The chemical yield of the one-pot sequence was 75% and enantiomeric excess was 85% *ee*. Further recrystallization provided enantiomerically pure **117** in 65% yield. Removal of the *t*-butoxycarbonyl group was accomplished by treatment with TFA followed by heating to afford ketone **118**. After Horner–Emmons reaction with phosphonate **119**, desired **120** was obtained in 91% yield as a mixture of *E* and *Z* isomers. Stereoselective hydrogenation of the *E* and *Z* mixture was achieved under normal conditions. Subsequent removal of the tosyl group and reprotection with the Teoc group provided **121**. Reduction of the pyridine moiety followed by oxidation to form a nitrone moiety, then removal of the Teoc group gave lycoposerramine Z (**114**) in good yield. The total synthesis was completed in only 10 steps and overall yield was 20%. In 2014, the Bradshaw and Bonjoch group also reported the highly efficient total synthesis of cermizine B, which also belongs to the *Lycopodium* alkaloids, in an uninterrupted eight-step operation that allowed a gram scale synthesis.[30]



Scheme 15 Synthesis of lycoposerramine Z by Bradshaw *et al.* in 2013.

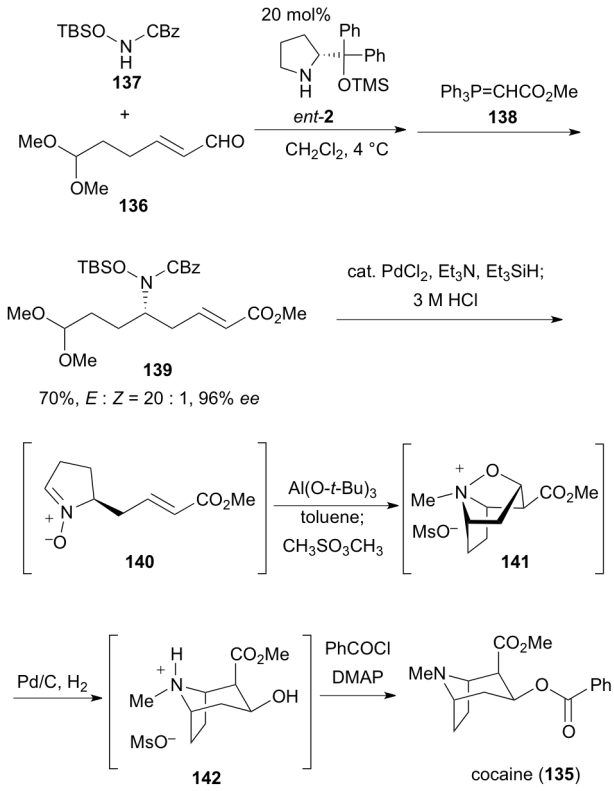
Quinine (**123**), which belongs to the monoterpenoid indole alkaloids in biosynthesis, was an historically important molecule because it was one of the best medicines for malaria infection. In addition, *cinchona* alkaloids such as quinine (**123**) and quinidine work as organocatalysts to promote several important reactions. In 2011, Hatakeyama and coworkers



Scheme 16 Synthesis of quinine by Hatakeyama *et al.* in 2011.

reported the total synthesis of quinine (**123**) and quinidine using a proline-catalyzed intramolecular aldol reaction (Scheme 16).[31] The key aldol reaction was carried out with amine containing bisaldehyde **124** (synthesized by a four-step transformation from commercially available materials) in the presence of 15 mol% L-proline (**1**). The subsequent reduction with $NaBH_4$ provided diol **125** in excellent yield and enantioselectivity as a diastereomeric mixture (94%, 94% *ee*). After silylation of the primary alcohol and oxidation of the secondary alcohol of **125**, Peterson olefination provided the desired α,β-unsaturated ester **127** without epimerization at the C3 position. Subsequent stereoselective hydrogenation and benzoylation of the obtained secondary amine provided **128** in good yield. Installation of 6-methoxylepidine (**129**) was achieved by lithiation of **129** followed by condensation with the ester moiety of **128** to provide the desired ketone **130** in almost quantitative yield. Subsequent reduction of the ketone, mesylation and elimination generated the conjugated olefin compound which was treated with AD-mix-β to provide (*R*, *R*)-diol **131** as a single diastereomer. Then, conversion to the epoxide **132** was carried out with trimethyl orthoformate, trimethylsilyl chloride, and K_2CO_3 in one pot. After removal of the benzoyl group by reduction with DIBAL-H, the quinuclidine-formation reaction was achieved by simple heating to afford **133**. Next, acetylation of the secondary alcohol followed by removal of the silyl group afforded alcohol **134**. A further three-step conversion including oxidation of the primary alcohol followed by Wittig olefination, and hydrolysis of the acetate group provided quinine (**123**). The synthesis of **123** was accomplished in a total of 23 steps and 10% overall yield. In addition, the Hatakeyama group also reported the total synthesis of quinidine, which was achieved via the (*S*, *S*)-diol intermediate using the AD-mix-α dihydroxylation reaction.[31]

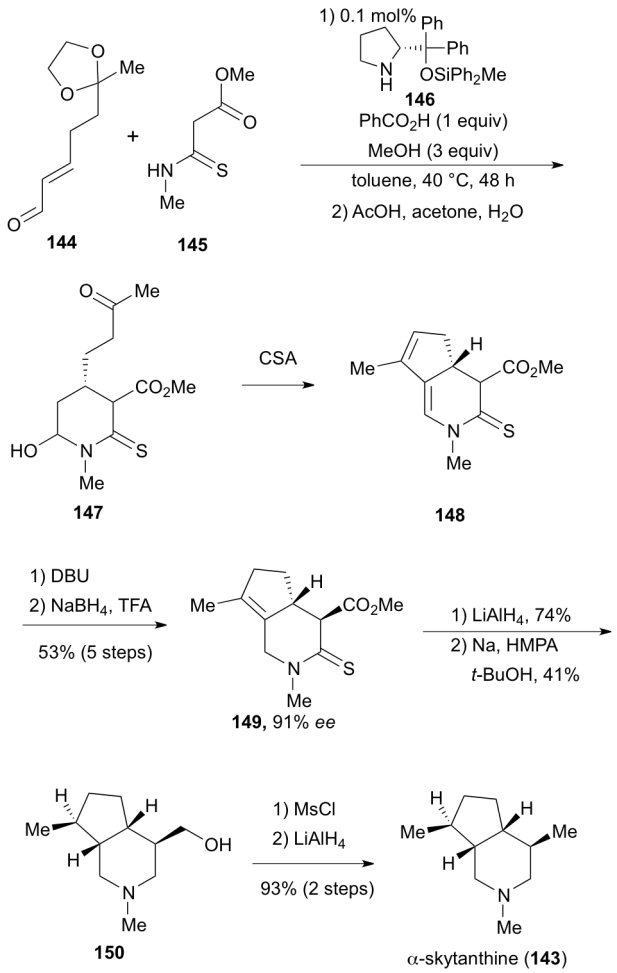
In 2012, Córdova and coworkers reported concise total syntheses of cocaine (**135**) and related alkaloids, which belong to the tropane alkaloids family, using a one-pot organocatalytic three-component domino *aza*-Michael/Wittig reaction and Lewis acid catalyzed intramolecular [1,3] dipolar cycloaddition reaction as key steps (Scheme 17).[32] The three-component domino *aza*-Michael/Wittig reaction was carried out with acetal-functionalized enal **136** and 4 equiv of hydroxylamine derivative **137** in the presence of 20 mol% catalyst *ent*-**2** followed by addition of 2-(triphenylphosphoranylidene)acetate **138** to provide δ-amino-α,β-unsaturated ester **139**. The chemical yield was 70% for this one-pot sequence, and excellent enantioselectivity was observed. (96% *ee*). A subsequent five-step conversion to complete the synthesis of cocaine (**135**) was followed: 1) removal of the Cbz group using cat. $PdCl_2$ in the presence of Et_3SiH; 2) acid-mediated acetal and silyl group deprotection and cyclization to form the nitrone moiety; 3) Al(O*t*-Bu)$_3$-catalyzed intramolecular [1,3] dipolar cycloaddition followed by methylation using $MeSO_3Me$ to provide the cage structure **141**; 4) *N*–*O* bond cleavage using hydrogenation conditions; and 5) benzoylation of the yielded secondary alcohol of **142**. This five-step sequence provided cocaine (**135**) in good yield (39% over five steps) and this total synthesis required only two purifications with column chromatography. The overall yield was 27%. In addition, total syntheses of related alkaloids such as *ent*-cocaine, methylecgonine, and ferruginine were published by Córdova's group.[32]



Scheme 17 Synthesis of cocaine by Córdova *et al*. in 2012.

More recently, Ishikawa and coworkers disclosed a highly efficient construction reaction of a C4-alkyl-substituted piperidine ring using an organocatalytic formal *aza*-[3 + 3] cycloaddition reaction and accomplished a concise total synthesis of α-skytanthine (**143**), which is a monoterpene piperidine alkaloid (Scheme 18).[33] The synthesis of **143** started with the key organocatalytic reaction. Thus, treatment of acetal-containing aldehyde **144** and *N*-methyl thiomalonamate **145** with 0.1 mol% steric bulky diphenylprolinol catalyst **146** in the presence of benzoic acid and MeOH as additive provided the cycloadduct cleanly. In this key reaction, careful optimizations by the authors led to only 0.1 mol% catalyst loading within acceptable reaction time and all carbon and nitrogen units of **143** were introduced in one step with high enantioselectivity. To cleave the acetal moiety, the diastereomeric mixture of cycloadduct was treated with acetic acid in the presence of water. Subsequent treatment of the latter with (+)-10-camphorsulfonic acid provided **148** by enamine formation followed by intramolecular aldol condensation reaction to the bicyclic compound, thereby constructing the 3-azabicyclo[4.3.0]nonane core. Epimerization of the methoxy carbonyl group to the thermodynamically stable *trans* isomer was accomplished by

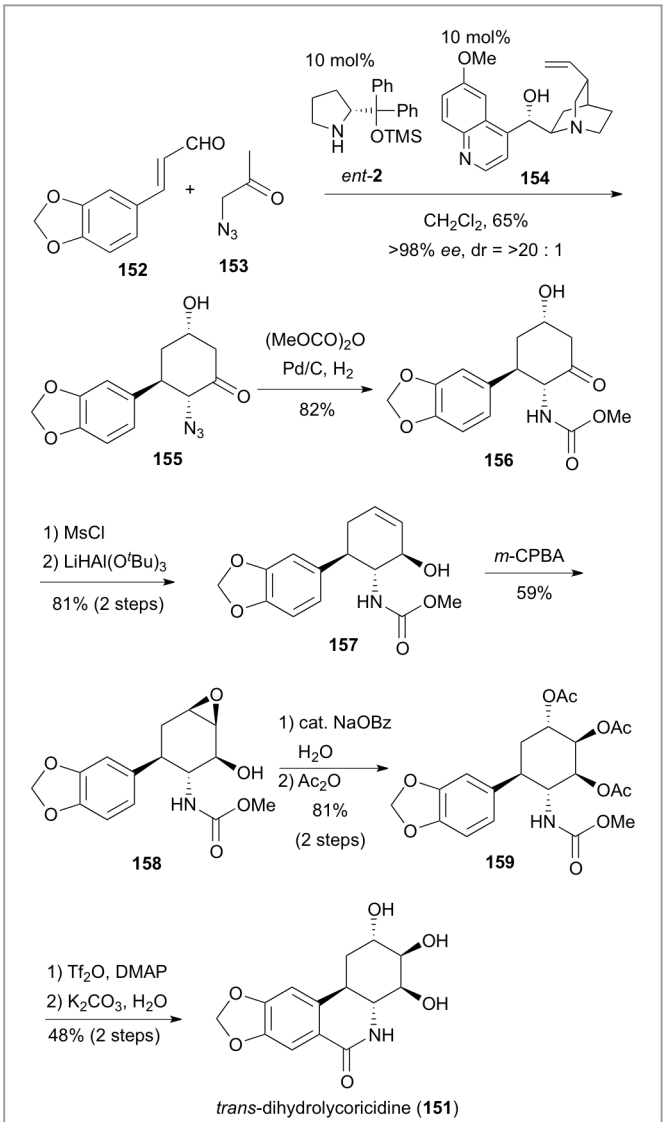
treatment with DBU followed by reduction with $NaBH_4$ in the presence of trifluoroacetic acid to provide bicyclic thiolactam derivatives **149**. The yield of the synthetic route over five steps was excellent (53%, five steps) and purification with silica gel-column chromatography was required only once. In addition, the excellent enantiomeric excess of the key reaction was confirmed at this stage (91% *ee*). Subsequent ester reduction to the corresponding primary alcohol and thiolactam reduction to the corresponding piperidine followed by diastereoselective formal hydrogenation of the tetraalkyl-substituted double bond was achieved using sodium in the presence of hexamethylphosphoric triamide (HMPA) and *t*-BuOH were achieved to afford **150**. Finally, mesylation of the primary alcohol of **150** followed by $LiAlH_4$-mediated reduction provided α-skytanthine (**143**). The overall yield was 15% from thiomalonamate **145**.



Scheme 18 Synthesis of α-skytanthine by Ishikawa *et al*. in 2015.

Other alkaloids

In 2014, two excellent total syntheses of *Lycoris* alkaloids, which contain a multisubstituted tetrahydroisoquinoline moiety, using a secondary amine organocatalyst were reported. McNulty and Zepeda-Velázquez reported a total synthesis of *trans*-dihydrolycoricidine (**151**) using an organocatalytic stepwise [3 + 3]-type Michael/aldol sequence (Scheme 19).[34] To install the nitrogen of tetrahydroisoquinoline, α-azideketone **153** was employed as a nucleophile. Thus, α,β-unsaturated aldehyde **152** and ketone **153** were treated with 10 mol% catalyst *ent*-**2** in the presence of an additional 10 mol% cinchonidine **154** as co-catalyst to provide **155** in high yield with excellent enantio- and diastereoselectivity. During optimization, the authors discovered that while other tertiary amines like diisopropylethylamine also enhanced the enantioselectivity, cinchonidine **154** was found to be the most suitable additive not only for enantioselectivity but also diastereoselectivity. The azide group of **155** was reduced and the resulting amine was converted to the methoxycarbonylamino group in good yield. Subsequent treatment with methanesulfonyl chloride for elimination provided an α,β-unsaturated ketone followed by

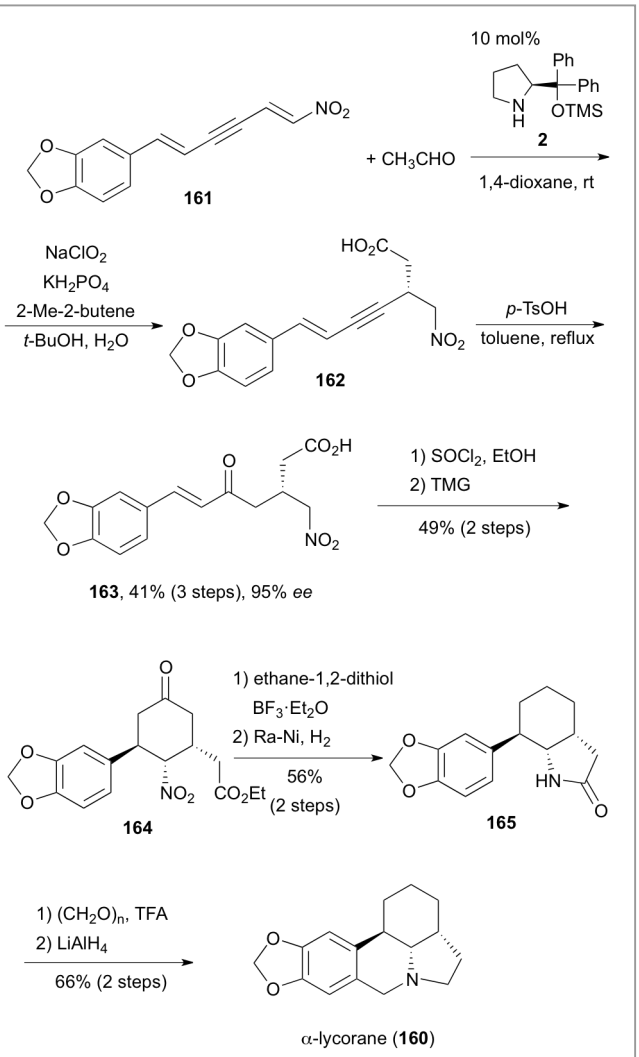


Scheme 19 Synthesis of trans-dihydrolycoricidine by McNulty *et al*. in 2014.

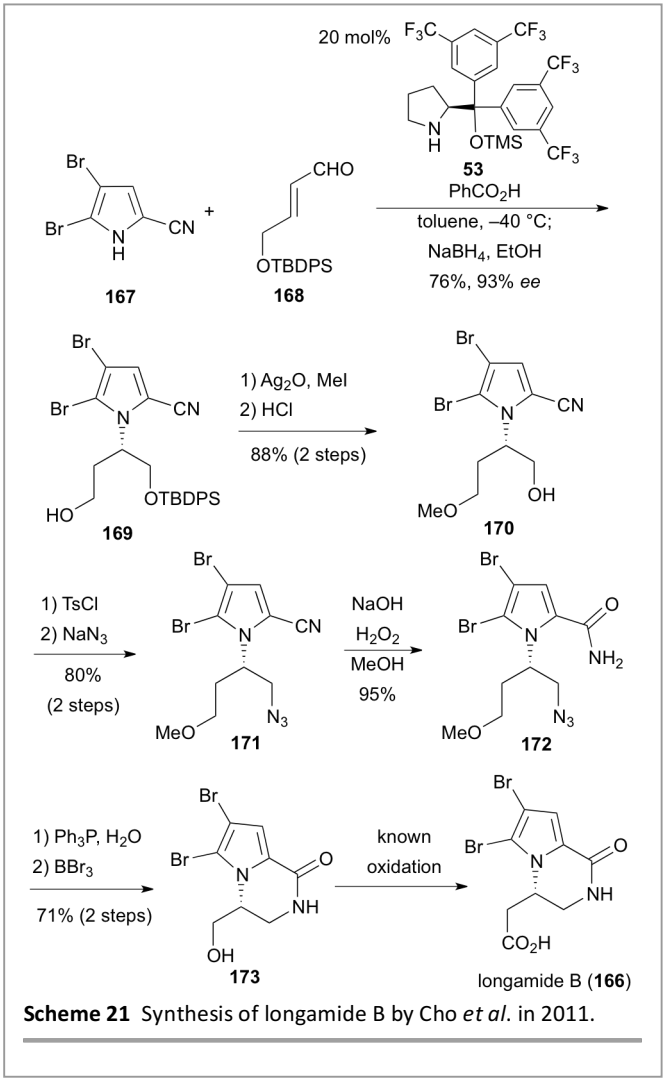
chemoselective reduction with a bulky reductant gave equatorial alcohol **157**. Epoxidation of **157** was achieved using *m*-CPBA, yielding a mixture of the β-epoxide **158** and the α-epoxide in a 4:1 ratio. Stereospecific opening of the epoxide via axial attack and acetyl group protection of the yielded triol moiety provided **159** as a single isomer. Subsequent Bischler–Napieralski reaction followed by hydrolysis of the acetoxy groups gave *trans*-dihydrolycoricidine (**151**) in 48% yield in two steps. This synthesis of anticancer natural product **151** was achieved in only nine steps from readily available starting materials.

The total synthesis of α-lycorane (**160**) was reported by the Peng and Shao group in 2014 (Scheme 20).[35] The organocatalyst-mediated key reaction was an enamine-mediated regioselective Michael addition of acetaldehyde to a highly conjugated nitroalkene **161**. Thus, the conjugate-addition reaction of highly reactive acetaldehyde with **161** in the presence of 10 mol% catalyst **2** followed by Kraus–Pinnick oxidation provided the desired optically active carboxylic acid **162** as a single isomer in 65% yield, 95% *ee*. Subsequent unique TsOH-mediated alkyne hydration discovered by the authors gave ketone **163** in moderate yield over three steps. The carboxylic acid moiety was converted to the corresponding ethyl ester and cyclized in an intramolecular Michael reaction to provide cyclohexanone derivative **164** as a single diastereomer in 49% yield (two steps). For removal of the ketone moiety, ketone **164** was transformed to a thioketal. Then, a three-reaction cascade reaction in one pot including desulfurization and reduction of the nitro group by Raney-Ni followed by intramolecular amidation gave lactam **165** in 56% yield (two steps). Finally, Pictet–Spengler cyclization with paraformaldehyde followed by $LiAlH_4$ reduction of the amide carbonyl group afforded the natural product α-lycorane (**160**).

A secondary amine-mediated asymmetric reaction was also applied to the synthesis of a pyrrole alkaloid. In 2011, Cho and coworkers established a formal total synthesis of longamide B (**166**) and related alkaloids using an originally developed organocatalytic *aza*-Michael reaction with a pyrrole derivative as a nucleophile (Scheme 21).[36] The siloxy group-containing α,β-unsaturated aldehyde **168** and 4,5-dibromo-1*H*-pyrrole-2-carbonitrile **167** were employed as starting materials. Thus, substrates **167** and **168** were treated with 20 mol% catalyst **53** in the presence of 40 mol% benzoic acid as additive at low



Scheme 20 Synthesis of α-lycorane by Peng *et al.* in 2014.



Scheme 21 Synthesis of longamide B by Cho *et al.* in 2011.

temperature to form an enantioselective C–N bond, followed by $NaBH_4$ reduction to provide the desired primary alcohol **169** in 76% yield and superb enantioselectivity (93% *ee*). Importantly, the authors pointed out the TBDPS group on the electrophile and nitrile group on the nucleophile are essential to obtain a good yield and enantioselectivity. After methylation of the primary alcohol of **169** followed by removal of the siloxy group under acidic conditions, the primary alcohol of **170** was converted to azide **171** via a two-step sequence including mesylation followed by azidation. Hydrolysis of the nitrile group with hydrogen peroxide and base provided amide **172** in superb yield. Subsequent lactamization was achieved using Staudinger reaction conditions for conversion of azide to amine. Finally, the methyl ether moiety was converted to alcohol by treatment with BBr_3 to provide **173**. Primary alcohol compound **173** is a known synthetic precursor of longamide B (**166**), thus formal total synthesis was accomplished. In addition, key intermediate **173** can be widely applied to this class of marine bromopyrrole alkaloids such as hanishin, cycloorotidine, agesamide A, and B via known procedures.

Conclusions

In the listed total syntheses of alkaloids, we can easily recognize that asymmetric organocatalytic reactions are growing to be an important methodology for preparation of chiral centers. In several of these example (e.g. minfiensine , strychnine, aspidofractine), significant complexity has been created through the organocatalytic step. This highlights the power of organocatalytic approaches. The future of this fileld should continue to strive for reactions that generate significant chemical complexity from easily accessible achiral precursors. In addition secondary amine-catalyzed organocatalytic reactions have several advantages, such as easy handling, scalablility, high stereoselectivity, and the combination thereof in one-pot. Although progress with secondary amine-catalyzed reactions in the synthesis of alkaloids has been made, it is still a developing field in current organic chemistry. The full potential of chiral secondary amine-catalyzed asymmetric reactions for total synthesis has not been realized yet. Thus, further exciting discoveries of new reactions using chiral secondary amine catalysts and their applications to impressive total syntheses of complex molecules are to be expected in the near future.

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