REVIEW

Recent Applications of Asymmetric Organocatalytic Methods in Total Synthesis

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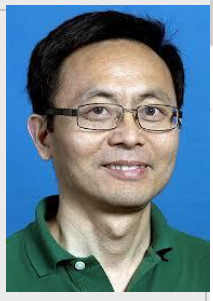
Satish Jakkampudi received his MSc degree in organic chemistry from Acharya Nagarjuna University, India, in 2008. After six years industrial career, then moved to Graduate school of science, Hiroshima University, Japan, where he obtained his PhD degree under the supervision of Prof. Manabu Abe in 2017. Since November 2017, he has been working as a postdoctoral researcher in the research group of Professor John C.-G. Zhao, University of Texas at San Antonio (San Antonio, USA). His current research focuses on organocatalytic asymmetric reactions with a special emphasis on diastereo- and enantiodivergent synthesis using modularly designed organocatalysts (MDOs).



John C.-G. Zhao received his MS degree from the Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences in1995 and his Ph.D. degree from the University of Würzburg, Germany, in 1999 under the supervision of Prof. Waldemar Adam with the support of a DAAD scholarship. From 2000-2001 he was a post-doctoral fellow at the University of Texas at San Antonio (UTSA). He then held a visiting Assistant Professor position at UTSA from 2001-2002. In 2002 he became an Assistant Professor at the Department of Chemistry, UTSA, where he is now a Professor. His research interests include asymmetric catalysis and synthesis, methodology development, oxidation, and organophosphorus compounds.

Abstract: Natural products are the great sources of drugs and leading compounds in drug discovery, as it has been estimated that most of the current medicines are derived from natural products. Total synthesis of natural products, especially those of biological activities, has been an important part of organic chemistry, which, besides its potential practical utilities, also provides new inspirations and novel synthetic methodologies. Over the past two decades, organocatalysis has been shown to be very effective in controlling the stereochemistry of the reaction products and has found many applications in the asymmetric synthesis of natural products and related compounds. In this review we will attempt to summarize some applications of asymmetric organocatalysis in the total synthesis of natural products and related compounds in the past seven years.

Introduction

While the first organocatalytic conversion was reported in 1860 by Justus von Liebig in the transformation of cyanogen to oxamide in the presence of acetaldehyde,[1] the first asymmetric organocatalytic reaction was not reported until 1912, when Bredig and Fiske worked on the addition of hydrogen cyanide to benzaldehyde using cinchona alkaloids as the catalyst and obtained cyanohydrins in ~10% ee.[2] Later, Pracejus in 1960 reported the addition of methanol to ketenes with ee's up to 74%.[3] One of the milestones in organocatalysis is the intramolecular aldol reaction catalyzed by proline, which was developed independently by the pharmaceutical companies Hoffman-La Roche[4] and Schering AG.[5] This reaction, also known as the Hajos-Parrish-Eder-Sauer-Wiechert reaction, allows the preparation of intermediates for the synthesis of steroids and other enantiomerically enriched molecules. Nonetheless, it was not until 2000, two pioneering reports by MacMillan[6] and List, Lerner, and Barbas,[7] reignited the modern age of organocatalysis and triggered the "gold rush" in the last two decades. MacMillan first introduced the term "organocatalysis" to define the phenomenon of the acceleration of a chemical transformation through addition of a substochiometric amount of an organic compound that does not contain a metal atom.[6]

After twenty years of extensive developments, organocatalysis has now been established as the third pillar of asymmetric catalysis[8] and still remains a popular area of contemporary asymmetric catalysis research. The easy availability, inexpensiveness, robustness, operational simplicity, low toxicity, and chemical efficiency render organocatalysis advantageous over metal and biocatalysis. It also finds more and more applications in academia and industrial sectors.

This fast developing field has been constantly reviewed and several review articles have appeared recently to cover the applications of specific types of organocatalysts in the total synthesis of natural products or the total synthesis of specific classes of natural products using organocatalysts.[9-20] Nonetheless, an overview of these developments is still lacking. This current short review focuses on selected recent examples of

total synthesis of natural products and related compounds enabled by all types of known organocatalysts. The aim of this review is to highlight the exciting advances in this area and their growing impact in scalable natural product synthesis. The organocatalysts can be classified as covalent or noncovalent catalysts by means of their interactions with the substrate or "mode of action", which include enamine catalysis,[21] iminium catalysis,[22] general base catalysis,[23] Brønsted acid catalysis,[24] and *N*-heterocyclic carbene catalysis.[25] Nonetheless, because the reported organocatalysts may have more than one mode of activation during the catalysis and/or not of all of the activation modes were explicitly described in the original reports, which makes the discussion based on activation mode difficult, in this review, for simplicity purpose, we divided the examples on the application of organocatalysis in the total synthesis of natural products and related compounds collected into seven sections based on the types of organocatalysts that were employed to achieve the desired organocatalytic reactions for the total synthesis.

(a) Secondary and primary amine catalysts: This section deals with the total synthesis of natural products and related compounds involving reactions catalyzed by chiral secondary and primary amine organocatalysts.

(b) Cinchona alkaloid catalysts: This section deals with the total synthesis of natural products involving reactions catalyzed by cinchona alkaloid organocatalysts.

(c) Bifunctional organocatalysts: This section deals with the total synthesis of natural products involving reactions catalyzed by (thio)urea-type and squaramide-type bifunctional organocatalysts.

(d) Chiral guanidine and guanidinium catalysts: This section deals with the total synthesis of natural products involving reactions catalyzed by chiral guanidine and guanidinium organocatalysts.

(e) Catalysis conducted with two organocatalysts: This section deals with the total synthesis of natural products and related compounds involving reactions catalyzed by two organocatalysts via a one-pot isolated sequential catalysis or a cooperative catalysis.

(f) Chiral phosphoric acid catalysts: This section deals with the total synthesis of natural products and related compounds involving reactions catalyzed by chiral phosphoric acids.

(g) *N*-heterocyclic carbene catalysts: This section deals with the total synthesis of natural products involving reactions catalyzed by chiral *N*-heterocyclic carbenes.

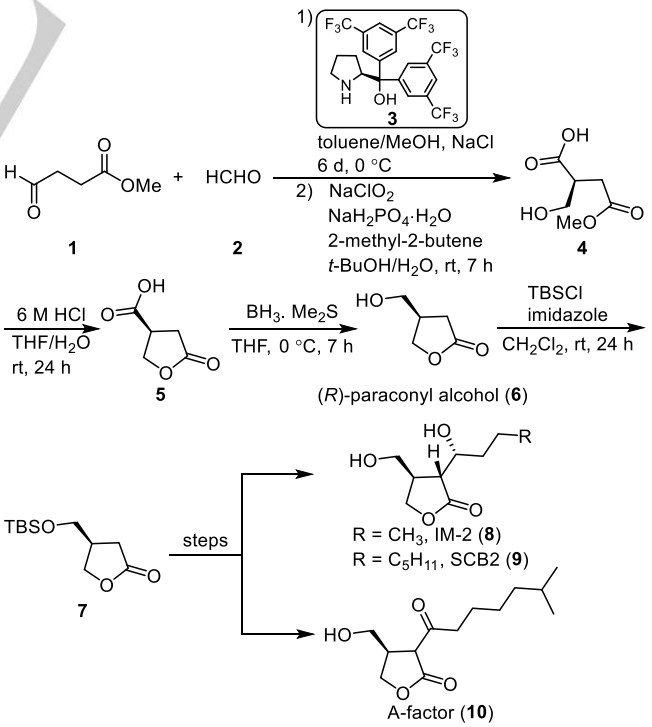
Applications in Natural Product Synthesis

(a) Secondary and primary amine catalysts

In this section, we will discuss the total synthesis of natural products involving reactions catalyzed by amine-based organocatalysts via enamine or iminium intermediates. As mentioned above, while the initial report of the asymmetric enamine catalysis mediated by proline was reported in 1971,[5] List, Lerner, and Barbas were the first to bring this into an extraordinary research field.[7] Simultaneously, another breakthrough in organocatalyzed asymmetric transformation via the iminium intermediate was achieved by MacMillan's group.[6] However, due to the low catalytic efficiency and/or the low capability in asymmetric induction of the free amino acids (i.e., proline etc.) via the iminium/enamine intermediates, different primary or secondary amines ranging from amino acid derivatives to alkaloid derivatives have been developed and frequently used as the organocatalysts. For example, among these improved chiral amine organocatalysts there are diarylprolinol silyl ethers, reported separately by Jørgensen[26] and Hayashi,[27] which are the most versatile chiral secondary amine catalysts for a variety of asymmetric transformations, including the applications in the total synthesis of natural products.[9]

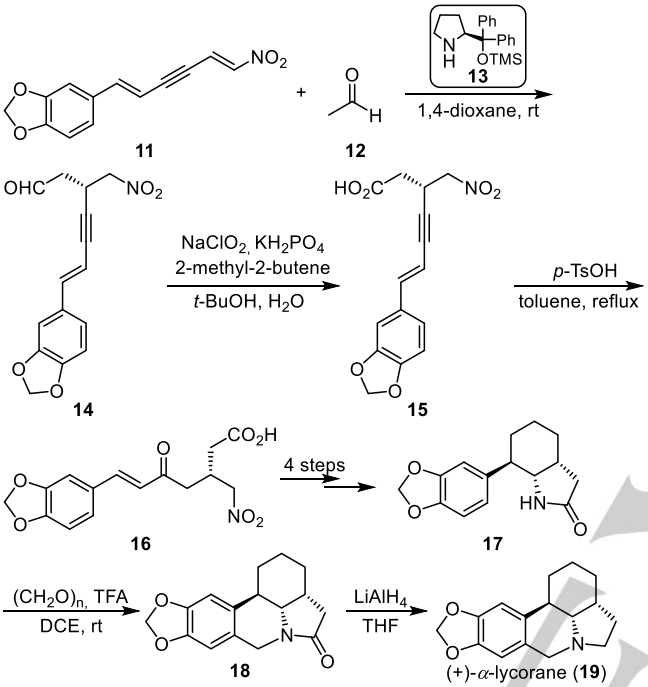
(1) Secondary amine catalysts

In 2018, Appayee and co-workers reported a short synthesis of IM-2 (**8**), SCB2 (**9**), and A-factor (**10**) γ-butyrolactone autoregulators (Scheme 1).[28] The organocatalytic aldol reaction between methyl 4-oxobutanoate (**1**) and formaldehyde (**2**) using (*S*)-diaryl prolinol **3** as the catalyst was used as an express method to access the key intermediate **4**, which was then converted to the common intermediate (*R*)-paraconyl alcohol (**6**) for the synthesis of these three natural products (Scheme 1).[28]



Scheme 1. Total synthesis of IM-2, SCB2, and A-factor γ-butyrolactone autoregulators via an organocatalyzed asymmetric aldol reaction.

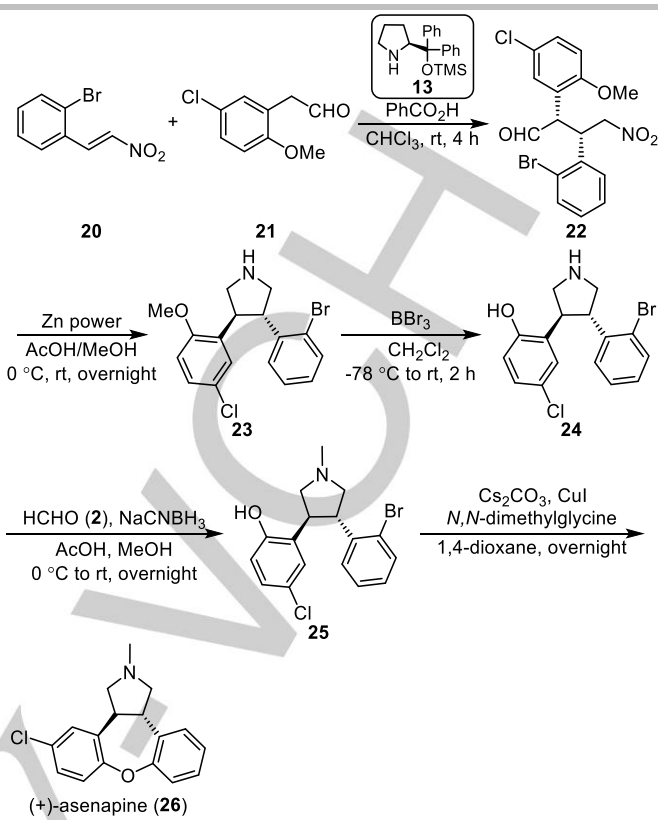
In 2014, Peng, Shao, and co-workers reported an organocatalyzed enantioselective total synthesis of (+)-α-lycorane (**19**) (Scheme 2).[29] The organocatalytic Michael addition reaction of acetaldehyde (**12**) to nitrodienyne **11**, catalyzed by the Jørgensen-Hayashi diarylprolinol silyl ether **13**, afforded the optically active product **14** in good enantioselectivity and yield, which served as a key intermediate for the synthesis. Further transformations of **14** afforded **19** via a multistep sequence, which includes Pinnick oxidation, alkyne hydration, Pictet-Spengler-type cyclization, and $LiAlH_4$ reduction.[29]



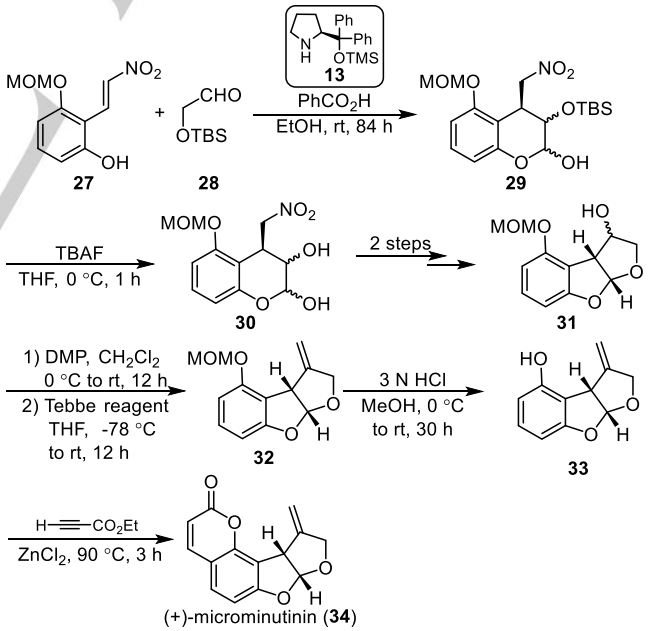
Scheme 2. Total synthesis of (+)-α-lycorane via an organocatalyzed asymmetric Michael addition reaction.

In 2014, Szcześniak, Mlynarski, and co-workers reported the enantioselective total synthesis of (+)-asenapine (**26**) (Scheme 3).[30] They demonstrated that an organocatalytic Michael addition of aldehyde **21** to nitroalkene **20** using **13** as the catalyst led to the formation of an optically active γ-nitroaldehyde **22**. The later could be used as the key intermediate for the synthesis of **26**. As shown in Scheme 3, further transformations of **22** afforded (+)-asenapine (**26**) in five steps, which include the reductive cyclization, *O*-demethylation, *N*-methylation, and an intramolecular Ullmann condensation.[30]

In 2017, Hong and co-workers reported the enantioselective total synthesis of (+)-microminutinin (**34**) (Scheme 4).[31] It was shown that an organocatalytic one-pot Michael-hemiacetalization of nitrostyrene **27** and aldehyde **28** led to the formation the optically active hemiacetal **29**. Again, the Jørgensen-Hayashi catalyst **13** was used to obtain the desired stereoselectivities in this reaction. A multistep transformation of **29**, which included deprotection, oxidation, olefination, and Pechmann-type condensation reaction, afforded the natural product (+)-microminutinin (**34**). Apparently, the organocatalytic reaction that affords the precursor **29** is the key step of this total synthesis (Scheme 4).[31]



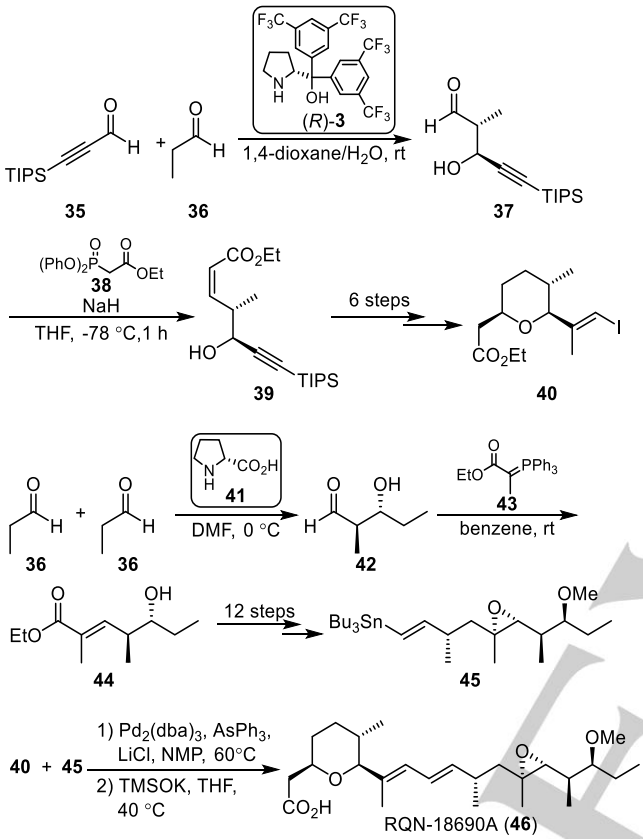
Scheme 3. Total synthesis of (+)-asenapine via an organocatalytic asymmetric Michael addition reaction.



Scheme 4. Total synthesis of (+)-microminutinin via an organocatalyzed domino Michael/hemiacetalization reaction.

In 2016, Hayashi and co-workers reported an enantioselective total synthesis of RQN-18690A (**46**) (Scheme 5).[32] The synthesis highlights the application of two organocatalyzed aldol reactions in the process of obtaining the key intermediates for the total synthesis. First, the cross-aldol reaction between 3-(triisopropylsilyl)propynal (**35**) and propanal (**36**) catalyzed by diarylprolinol derivative (*R*)-**3** led to the formation of the optically

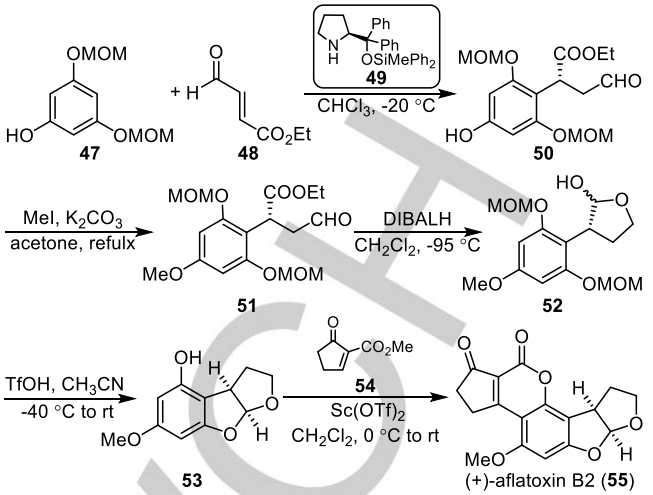
active aldehyde **37**, which was further converted to the key pyran intermediate **40** via several steps of synthetic maneuvers. Next, compound **42** was prepared via a self-aldol reaction of **36** using D-proline (**41**) as the catalyst. Compound **42** was further transformed to the other key intermediate **45** via a series of reactions. Finally, the Stille coupling between **40** and **45** afforded RQN-18690A (**46**) (Scheme 5).[32]



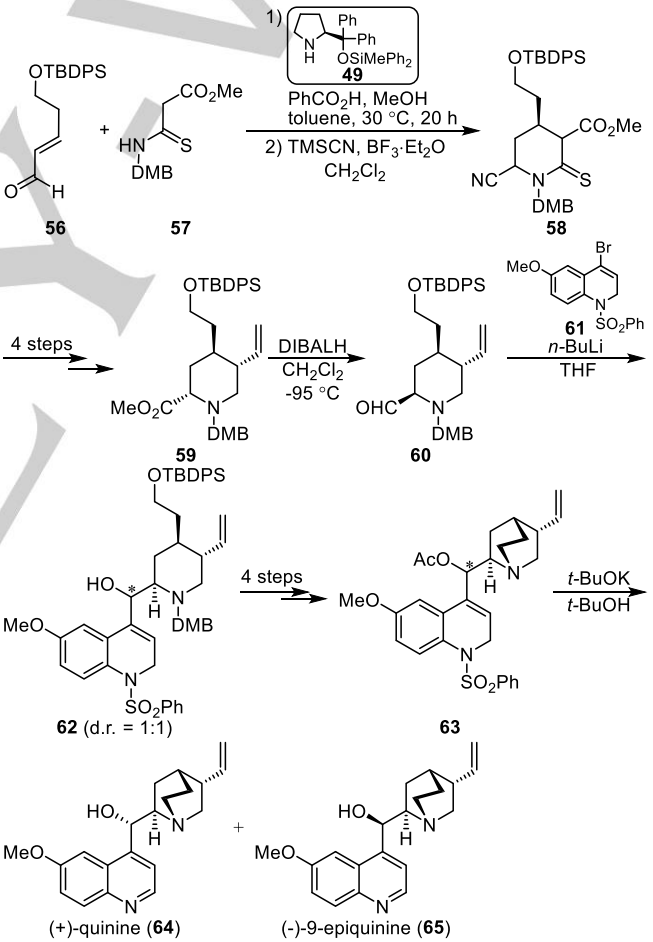
Scheme 5. Total synthesis of RQN-18690A via organocatalytic aldol reactions.

In 2019, Zu and co-workers reported an enantioselective total synthesis of (+)-aflatoxin B_2 (**55**) (Scheme 6).[33] They demonstrated that the organocatalytic Friedel-Crafts alkylation of naphthol **47** by enal **48**, using diphenylprolinol silyl ether **49** as the catalyst, could be used to obtain compound **50** via a *para*-selective alkylation. Further synthetic transformations of **50** provided the key intermediate **53**, which reacts with compound **54** to afford (+)-aflatoxin B_2 (**55**) (Scheme 6).[33]

In 2019, Ishikawa and co-workers reported an enantioselective total synthesis of (+)-quinine (**64**, enantiomer of quinine) and (-)-9-*epi*-quinine (**65**) (Scheme 7).[34] With the diarylprolinol silyl ether derivative **49** as the catalyst, the aza-[3+3] cycloaddition between 5-hydroxypentenal derivative **56** and thiomalonamate **57**, followed by a Strecker-type cyanation, led to the formation of the tetrasubstituted piperidine derivative **58**, which serves a key intermediate to both natural products. A multistep transformation of **58** yielded compound **60**, which subsequently yielded **62** as a 1:1 diastereomeric mixture via the coupling reaction with **61**. Further transformations of **62** yielded both **64** and **65** (Scheme 7).[34]



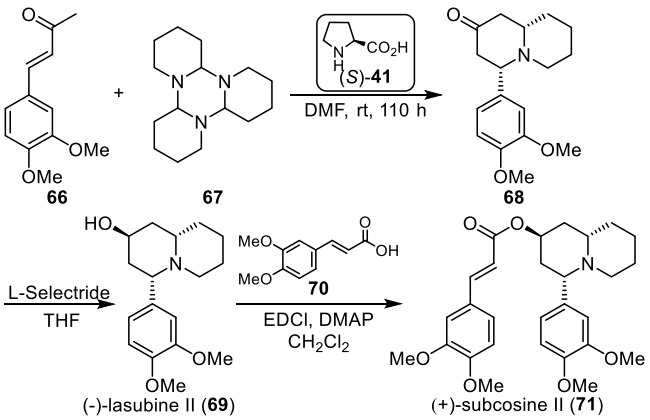
Scheme 6. Total synthesis of (+)-aflatoxin B_2 via organocatalyzed Friedel-Crafts alkylation.



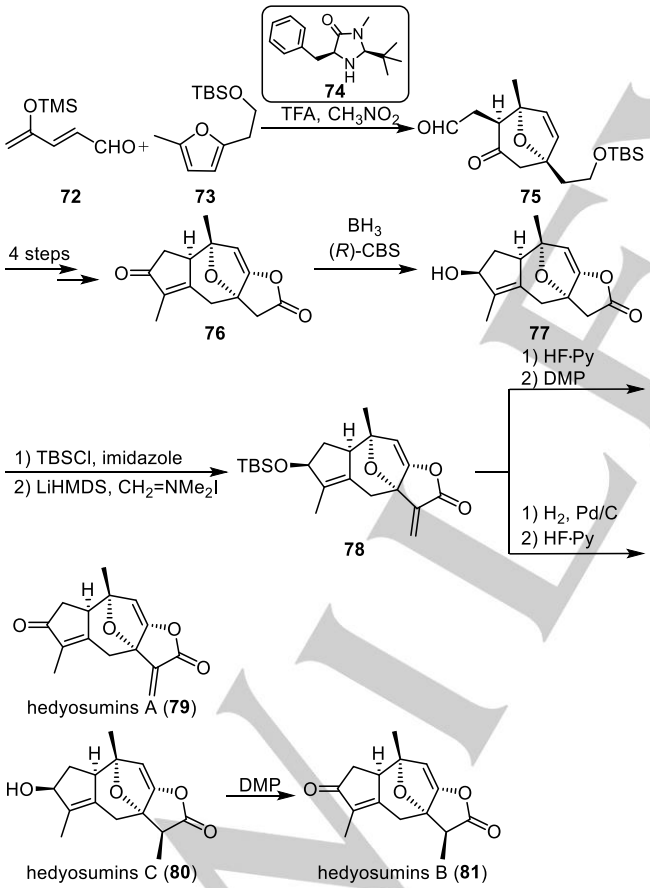
Scheme 7. Total synthesis of the (+)-quinine and (-)-9-epi-quinine via an organocatalyzed enantioselective aza-[3+3] cycloaddition (DMB = 2,4-dimethoxybenzyl).

In 2019, Pansare and Virk reported the enantioselective total synthesis of (-)-lasubine II (**69**) and (+)-subcosine II (**71**) (Scheme 8).[35] They demonstrated that the key precursor to these natural products, 4-aryl quinolizidin-2-one (**68**), could be obtained in a single step via an organocatalytic enantioselective domino Mannich/aza-Michael reaction of 3,4-dimethoxybenzylidene

acetone (**66**) and tripiperideine (**67**) using L-proline [(*S*)-**41**] as the catalyst. Further transformations of **68** afforded both **69** and **71** in short steps (Scheme 8).[35] It should be pointed out that this methodology can be used to access intermediates similar to **68** that have been used for the synthesis of (+)-abresoline, (+)-dihydrolyfoline, (−)-decinine, lythrine, and decaline.[35]

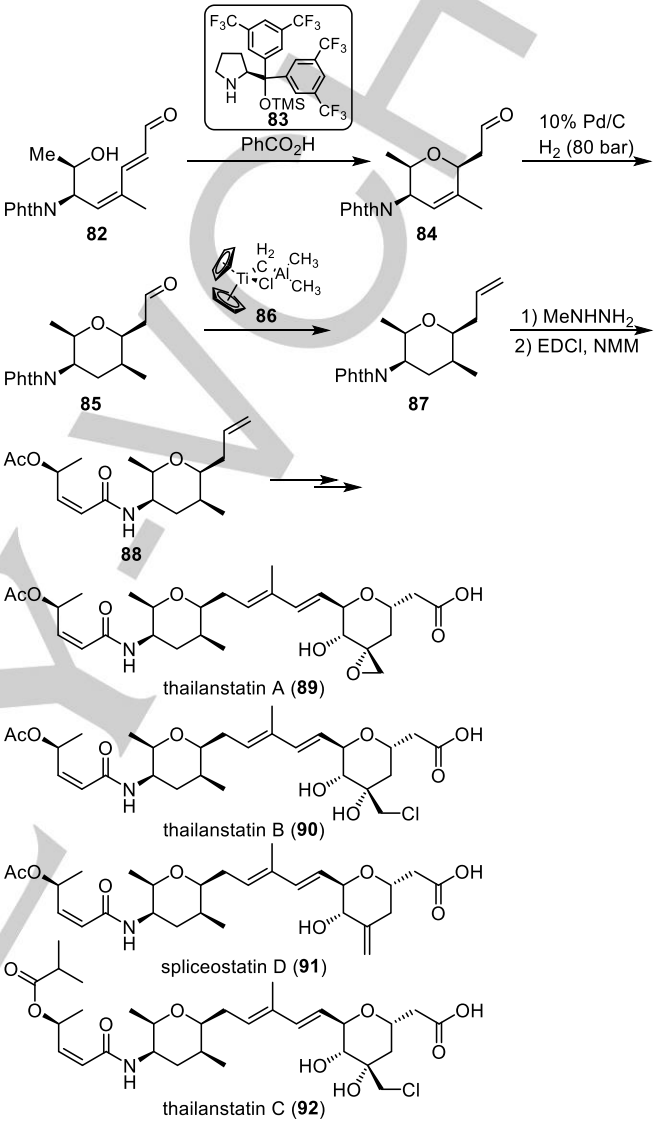


Scheme 8. Synthesis of (-)-lasubine II and (+)-subcosine II via an organocatalyzed domino Mannich/aza-Michael reaction.



Scheme 9. Synthesis of hedyosumins A, B, and C via an organocatalyzed [4+3] cycloaddition reaction.

In 2016, Sun and co-workers developed an enantioselective total synthesis of hedyosumins A, B, and C (**79**-**81**) using an organocatalytic reaction as the key step (Scheme 9).[36] Using catalyst **74**, they achieved an organocatalytic enantioselective [4+3] cycloaddition between dienal **72** and furan **73** for the synthesis of an optically active tetracyclic skeleton **76**, which was further elaborated to afford **79**-**81** via a multistep sequence (Scheme 9).[36]

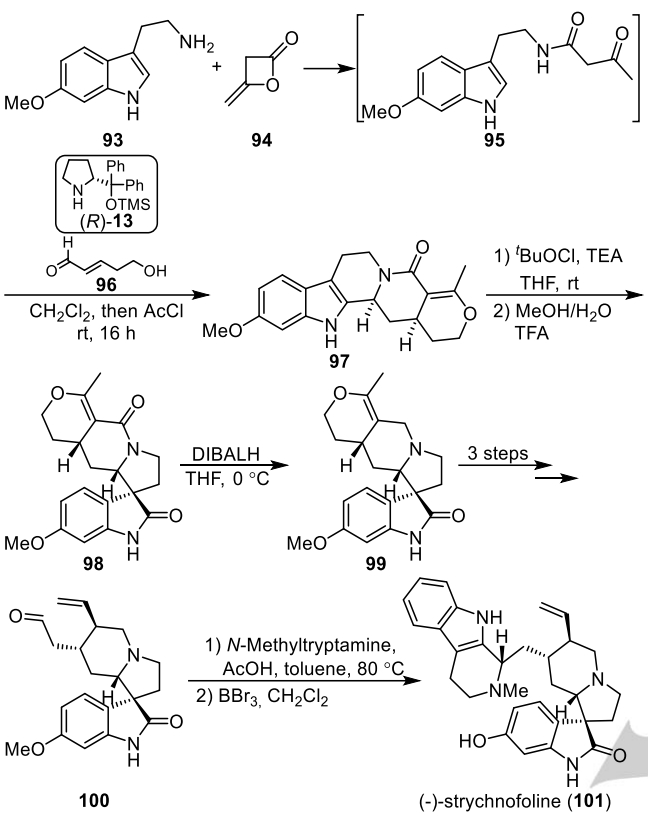


Scheme 10. Total synthesis of thailanstatins A-C and spliceostatin D via an organocatalyzed intramolecular oxa-Michael addition reaction.

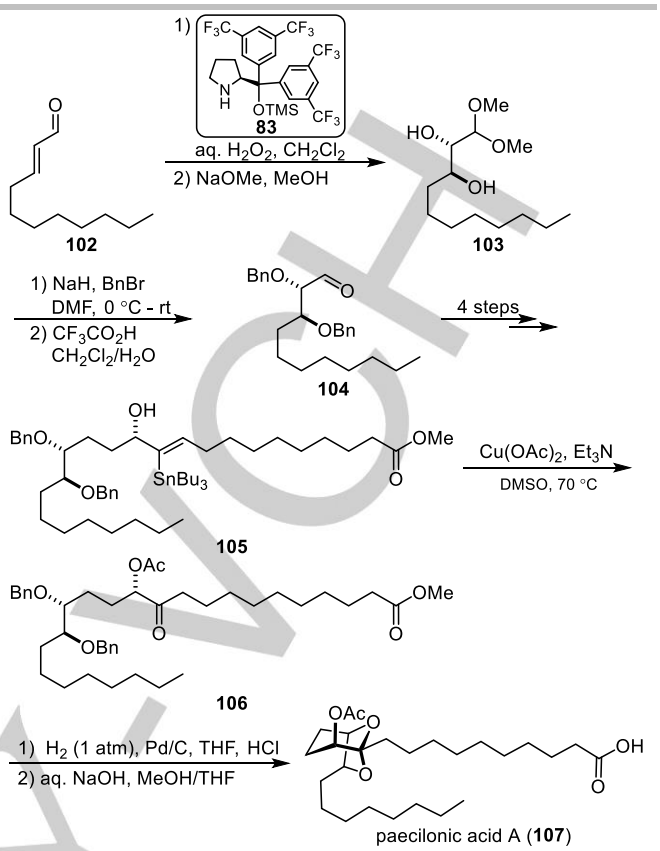
In 2018, the enantioselective total synthesis of thailanstatins A-C (**89**-**90**, **92**) and spliceostatin D (**91**) was reported by Nicolaou and co-workers (Scheme 10).[37] An organocatalytic intramolecular oxa-Michael cyclization of unsaturated aldehyde **82**, catalyzed by the chiral catalyst **83**, was applied to obtain the optically active dihydropyran **84**, which was converted to **87** in a few steps. The later served as a key intermediate for the synthesis of the natural products thailanstatins A-C (**89**-**90, 92**) and spliceostatin D (**91**) (Scheme 10).[37]

In 2018, Xu and co-workers reported the enantioselective total synthesis of (-)-strychnofoline (**101**, Scheme 11).[38] The synthesis involves an asymmetric Michael addition/Pictet-Spengler reaction

between **95** and the acrolein derivative **96** catalyzed by (*R*)-**13** to access the quinolizidine derivative **97** as the key intermediate of



Scheme 11. Total synthesis of (-)-strychnofoline via an organocatalyzed domino Michael addition/Pictet-Spengler reaction.

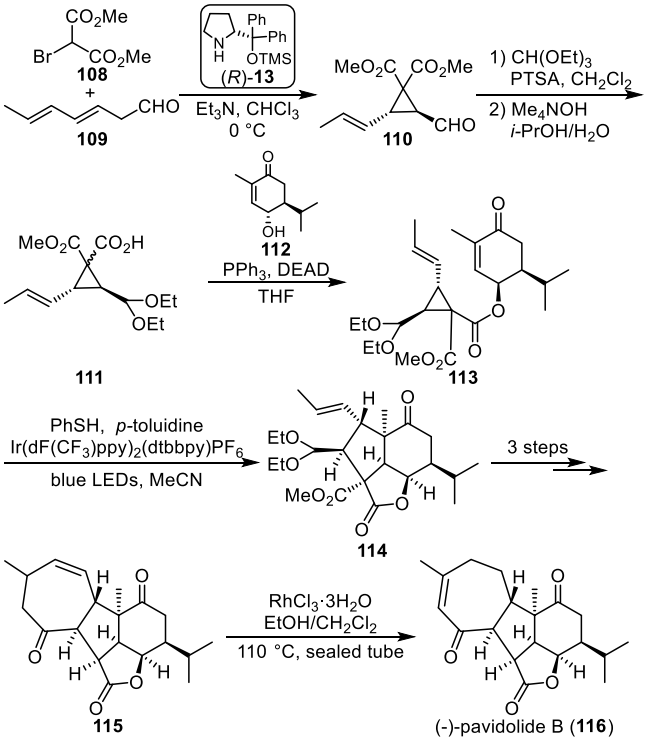


Scheme 12. Total synthesis of paecilonic acid A via an organocatalyzed epoxidation and an ensuing one-pot ring-opening reaction.

this synthesis. Compound **95** was obtained in-situ from the reaction of 6-methoxytryptamine (**93**) with diketene (**94**). Further elaboration of **97** afforded (-)-strychnofoline (**101**) via a nine-step sequence that included oxidative rearrangement, amide reduction, and diacylation (Scheme 11).[38]

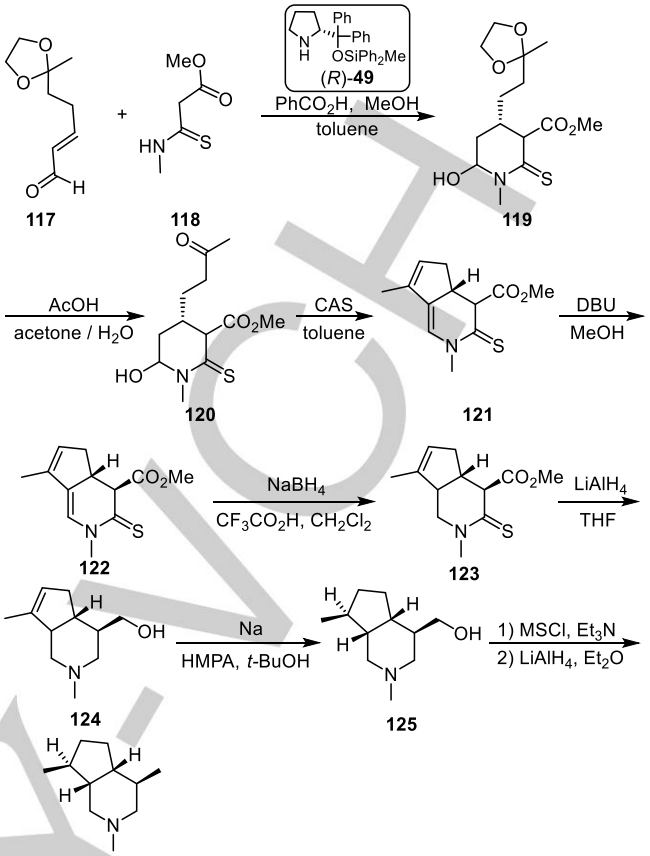
In 2017, Fürstner and co-workers reported enantioselective total synthesis of Paecilonic acid A (**107**, Scheme 12).[39] They employed an asymmetric epoxidation of enal **102** with H_2O_2 catalyzed Hayashi-Jørgensen catalyst **83**, followed by the ring-oping and acetalization with NaOMe to obtain the key synthetic intermediate **103** as a single diastereomer with an excellent ee value. Paecilonic acid A (**107**) was obtained via a 10-step sequence from **103**, which include *trans*-hydrostannation, acetylation, and hydrogenolysis (Scheme 12).[39]

In 2017, Yang and co-workers developed the total synthesis of (-)-pavidolide B (**116**, Scheme 13), involving an enantioselective organocatalytic cyclopropanation reaction as the key step.[40] They demonstrated that the asymmetric Michael addition/intramolecular-alkylation reaction of dimethyl 2-bromo-malonate (**108**) and hexadienal **109** catalyzed by the amine catalyst (*R*)-**13** led to the cyclopropane derivative **110**. Further elaboration of **110** afforded (-)-pavidolide B (**116**) via a multistep sequence that included the Mitsunobu reaction, an annulation reaction, and the isomerization of the γ,δ-unsaturated enone **115** to the more stable α,β-unsaturated enone **116** (Scheme 13).[40]



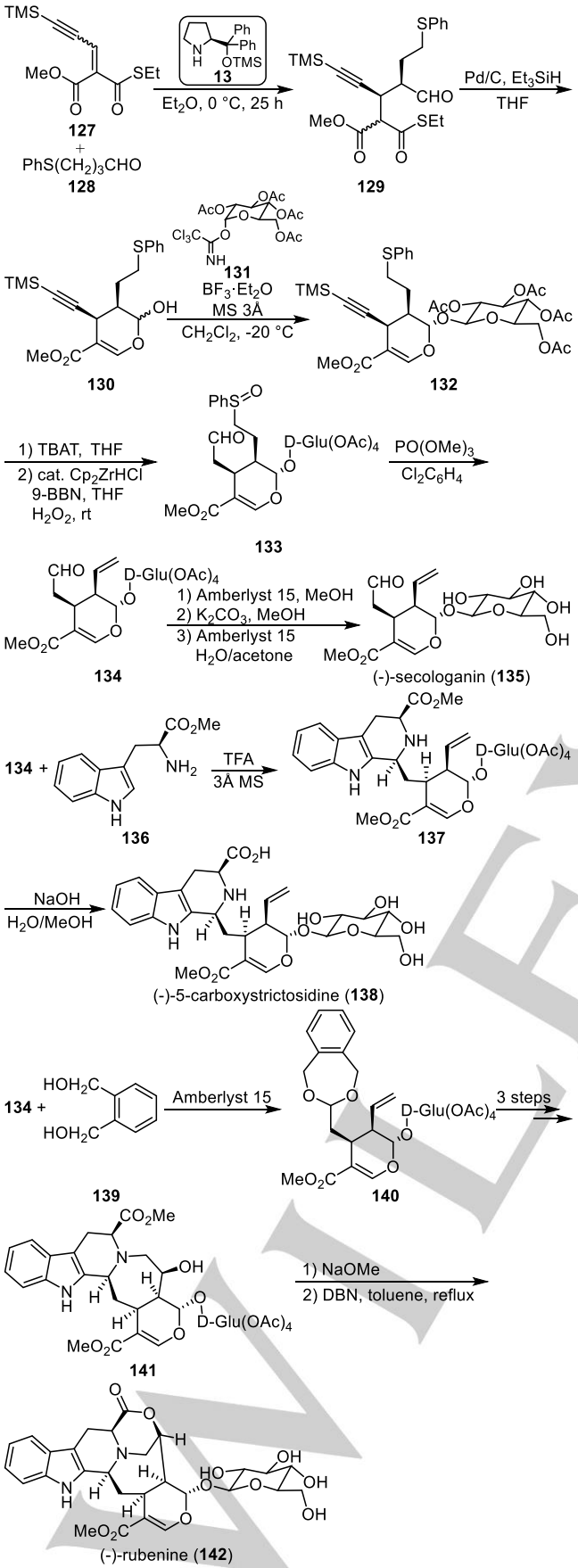
Scheme 13. Total synthesis of (-)-pavidolide B via organocatalyzed cyclopranation reaction.

In 2015, Ishikawa and co-workers developed an enantioselective total synthesis of (+)-α-skytanthine (**126**, Scheme 14).[41] In this synthesis the organocatalyzed asymmetric aza-[3+3] cycloaddition reaction of α,β-unsaturated aldehyde **117** and thiomalonamate derivative **118** served as a key step. In the presence of a chiral secondary amine (*R*)-**49**, the reaction led to the formation of a chiral piperidine **119**. Further elaborations of **119** afforded (+)-α-skytanthine (**126**) (Scheme 14).[41]

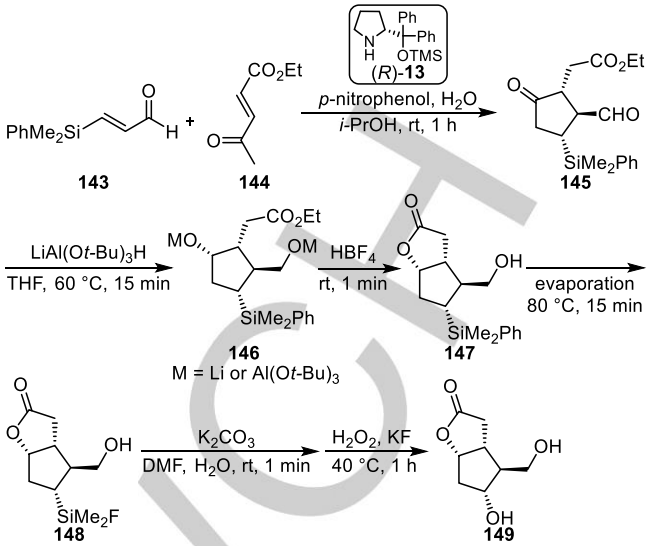


Scheme 14. Total synthesis of (+)-α-skytanthine via an organocatalyzed aza-[3+3] cycloaddition

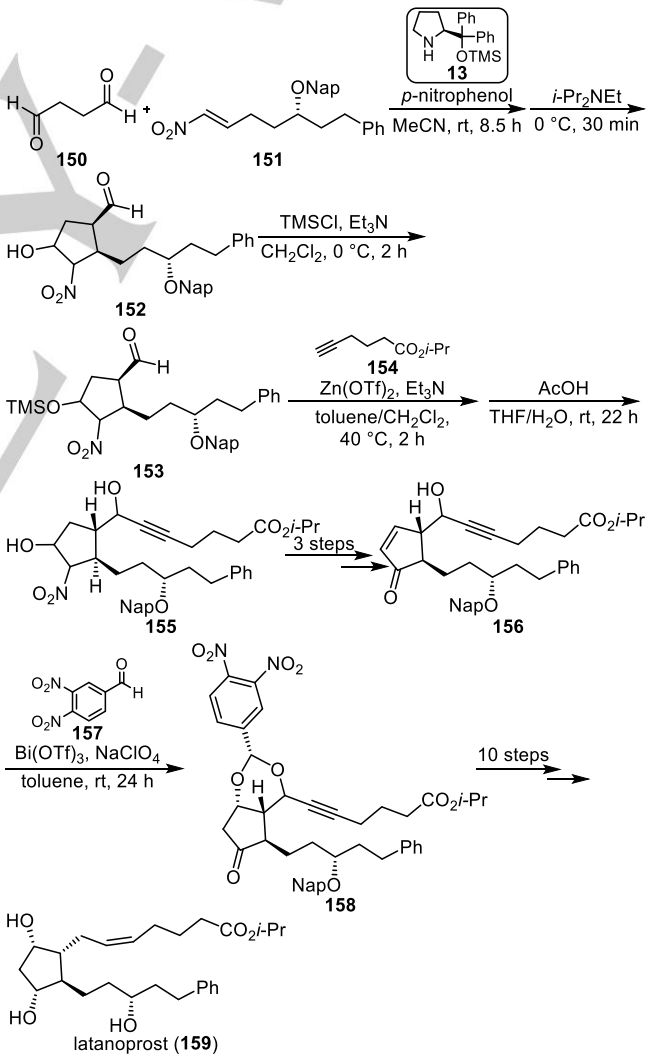
In 2019, the same group reported an enantioselective total synthesis of (-)-secologanin (**135**), (-)-5-carboxystrictosidine (**138**), and (-)-rubenine **(142)**.[42] As shown in Scheme 15, the synthesis of these three natural products all relies on the key intermediate **134** [(-)-secologanin tetraacetate], which was synthesized from the asymmetric Michael reaction of malonate derivative **127** and aldehyde **128**, catalyzed by diphenylprolinol trimethylsilyl ether (**13**), followed by a Fukuyama reduction/spontaneous cyclization, glycosylation, desilylation/isomerization, and sulfur oxidation/elimination sequence. Deacetylation of **134** led to the natural product (-)-secologanin (**135**). The reaction of **134** and **136** led to the formation of **137** as a major diastereomer (dr: 2.6:1) via a Pictet-Spengler reaction, which gave (-)-5-carboxystrictosidine (**138**) after deacetylation. The reaction of **134** and **139** led to compound **140**, which gave the natural product (-)-rubenine (**142**) after further transformations (Scheme 15).[42]



Scheme 15. Total synthesis of (-)-secologanin, (-)-5-carboxystrictosidine, and (-)-rubenine.



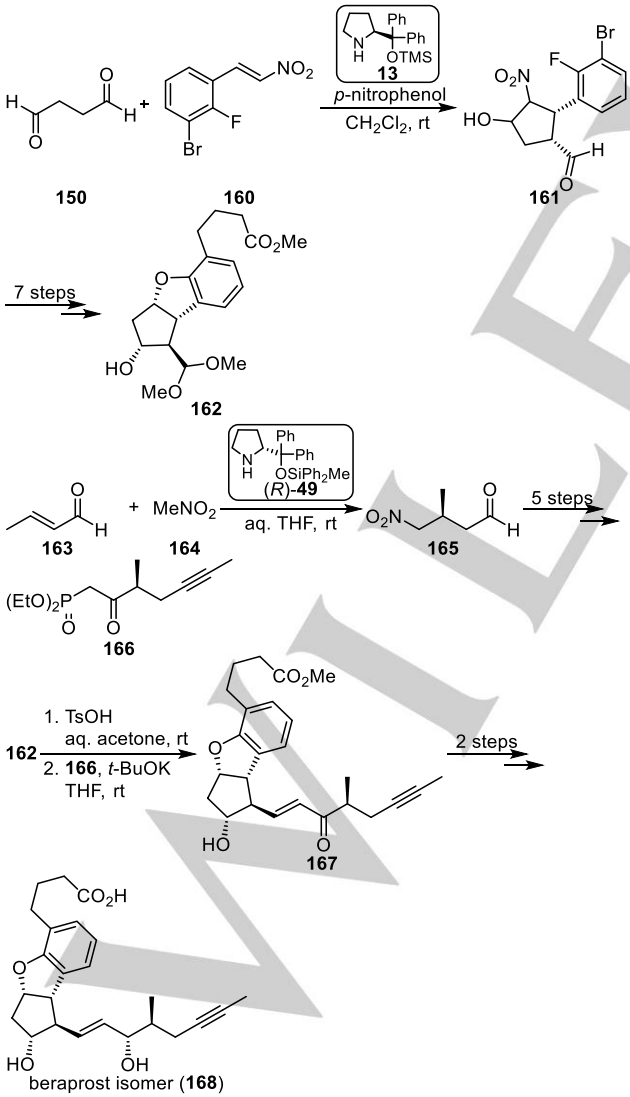
Scheme 16. One-pot synthesis of Corey lactone via an organocatalyzed domino Michael/Michael reaction.



Scheme 17. Total synthesis of latanoprost via an organocatalyzed formal [3+2]-cycloaddition reaction.

In 2020, Hayashi, and co-workers reported the total synthesis of Corey lactone **149** (Scheme 16).[43] They demonstrated that an asymmetric domino Michael/Michael reaction between 3-(dimethylphenylsilyl)propenal (**143**) and ethyl 4-oxo-2-pentenoate (**144**) in the presence of diphenylprolinol trimethylsilyl ether catalyst (**13**) could be used to access the trisubstituted cyclopentanone **145** as a single diastereomer with an excellent enantioselectivity. Compound **145** served as a key intermediate for this total synthesis, which afforded **149** after a few steps of synthetic maneuvers (Scheme 16).[43]

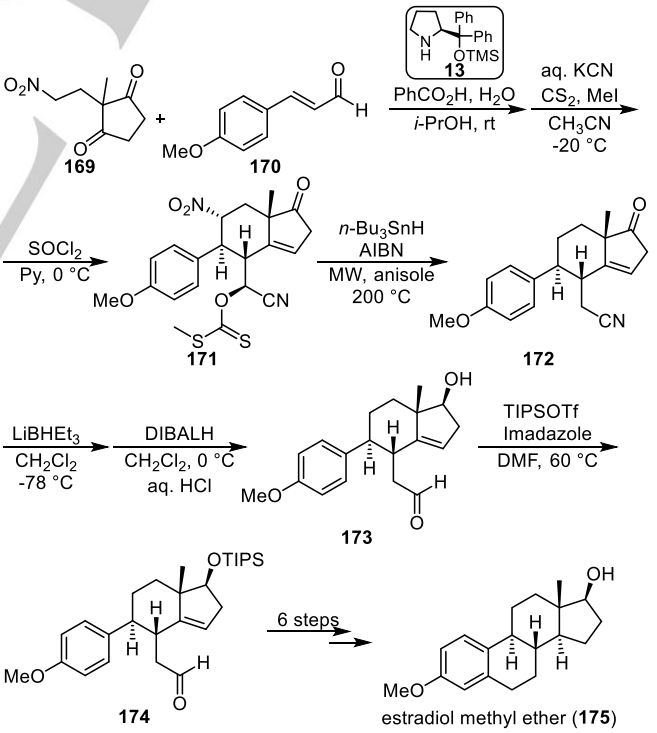
In 2020, the same group reported a diastereo- and enantioselective total synthesis of latanoprost (**159**) starting from succinaldehyde (**150**) and nitroalkene **151** (Scheme 17).[44] The formal [3+2]-cycloaddition reaction between **150** and **151** (actually a domino Michael/Henry reaction) afforded cyclopentanecarbaldehyde derivative **152**, catalyzed by diphenylprolinol silyl ether (**13**) and Hünig's base sequentially. Further elaboration of this key intermediate afforded latanoprost (**159**) via a multistep sequence, which included $Zr(OTf)_2$-catalyzed epimerization and side-chain elongation (Scheme 17).[44]



Scheme 18. Convergent total synthesis of a beraprost isomer via organocatalyzed formal [3+2]-cycloaddition reaction and Michael reaction.

In 2017, the same group developed a convergent organocatalytic approach for the enantioselective synthesis of the most active isomer of beraprost **168** (Scheme 18).[45] A similar formal [3+2] cycloaddition reaction of succinaldehyde (**150**) with nitroalkene **160** catalyzed by **13** was adopted to obtain the cyclopentanal derivative **161**, which was further transformed to **162**, which is the structural backbone of **168**. The side-chain unit **166** was also synthesized via an organocatalytic Michael reaction: *trans*-Crotonaldehyde (**163**) reacted with nitromethane (**164**) under the catalysis of (*R*)-**49** to yield the γ-nitroaldehyde **165**, which was further converted to the side-chain unit **166** in five steps. The final assembly of **162** and **166** was achieved through deprotecting the acetal group in **162** followed by a Horner−Wadsworth−Emmons reaction to give **167**, which was then converted to **168** in just two steps (Scheme 18).[45]

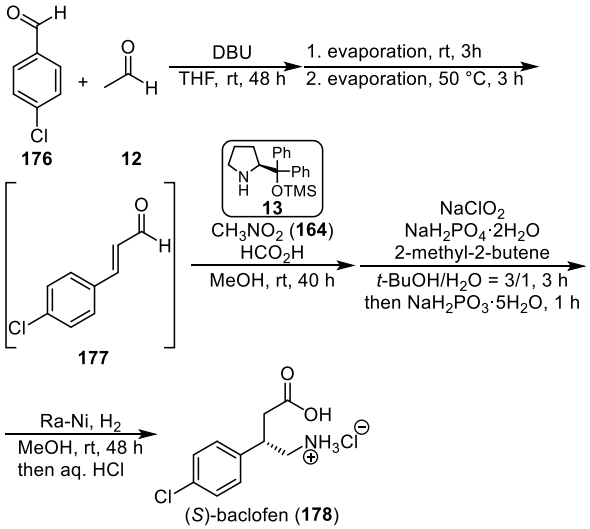
In 2017, the same group also reported an enantioselective synthesis of estradiol methyl ether **175** (Scheme 19).[46] The key step of this reaction is to assemble the intermediate **171**, which was achieved through a domino reaction of **169** and 4-methoxycinnamaldehyde (**170**) catalyzed by **13**. Further transformations of **171** afforded the aldehyde **174**, which was finally converted to the desired product via a multistep synthetic maneuver (Scheme 19).[46]



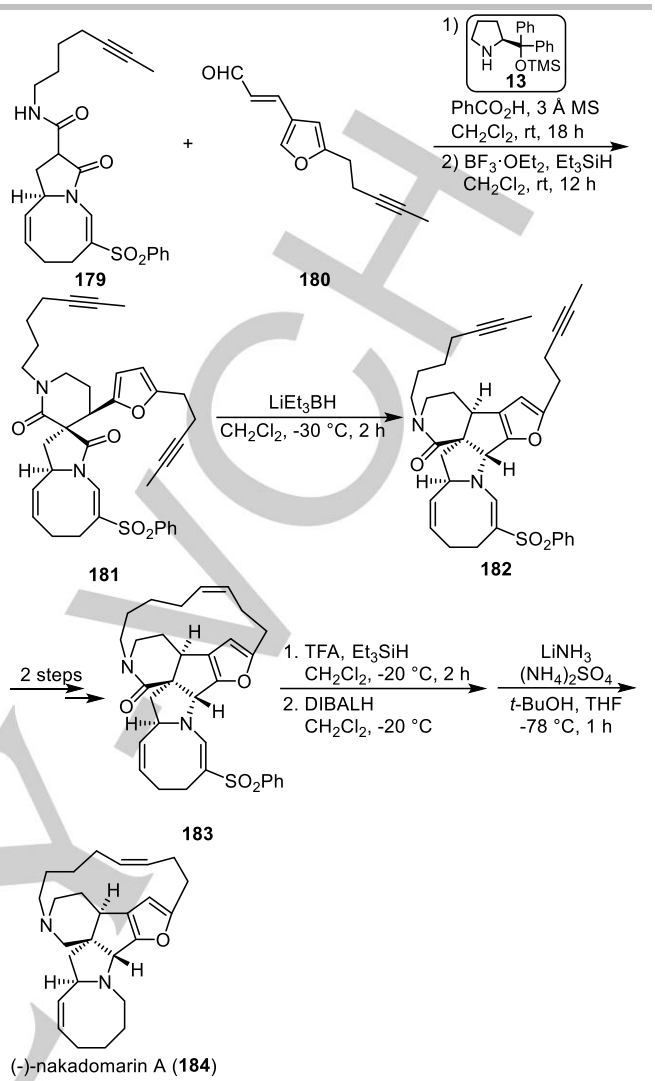
Scheme 19. Total synthesis of estradiol methyl ether via an organocatalyzed domino reaction.

In 2016, the same group developed an improved one-pot asymmetric synthesis of (*S*)-baclofen hydrochloride (**178**, Scheme 20).[47] They demonstrated that the condensation of 4-chlorobenzaldehyde (**176**) and acetaldehyde (**12**) could be

achieved by using DBU as the catalyst and careful evaporation procedures to give the desired condensation product *trans*-4-chlorocinnamaldehyde (**177**) in a good yield (not isolated). An in-situ asymmetric Michael reaction between **177** and nitromethane



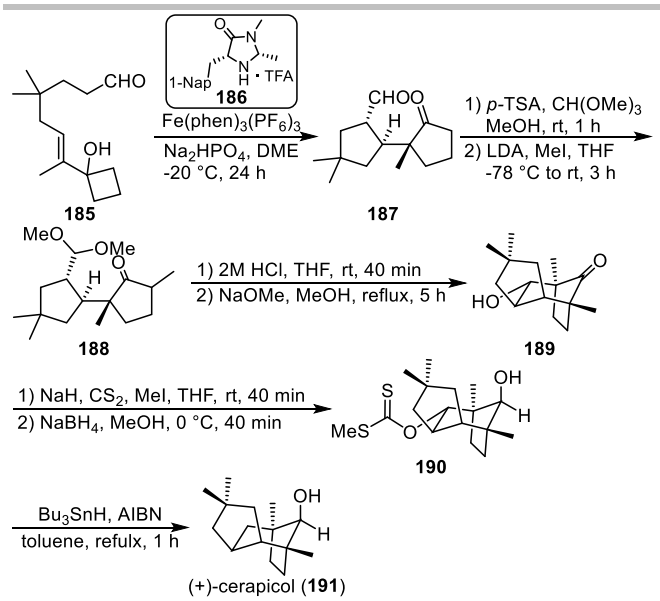
Scheme 20. One-pot total synthesis of (*S*)-baclofen via a one-pot organocatalyzed condensation and Michael reactions.



Scheme 21. Total synthesis of (−)-nakadomarin A *via* Michael/spirocyclization.

(**164)** catalyzed by **13** led to the formation of (*S*)-baclofen as a hydrochloride salt (**178**) after oxidation of the aldehyde to carboxylic acid group, reduction of the nitro to an amino group, and acidification of the final product with aqueous hydrochloric acid, all conducted in a one-pot manner (Scheme 20).[47]

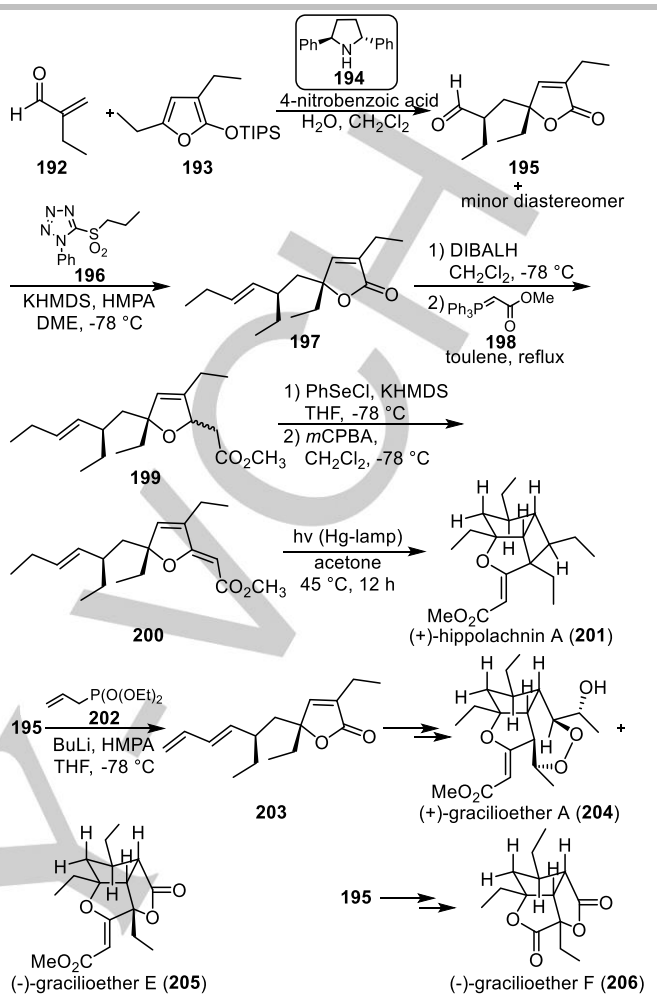
In 2016, Boeckman and co-workers reported an enantioselective total synthesis of (−)-nakadomarin A (**184**, Scheme 21).[48] The key intermediate of this synthesis, the spiro compound **181**, was obtained by a cascade organocatalyzed Michael addition and spirocyclization between malonamide **179** and enal **180**, promoted by diphenylprolinol silyl ether (**13**) and BF_3, separately. Further transformations of **181** via a multistep sequence led to the formation of **184** (Scheme 21).[48]



Scheme 22. Total synthesis of (+)-cerapicol via organo-SOMO catalytic aldehyde α-alkylation/semipinacol rearrangement (1-Nap =1-naphthyl).

In 2020, Zhang, Tu, and co-workers reported the enantioselective total synthesis of (+)-cerapicol **191** (Scheme 22).[49] The asymmetric aldehyde α-alkylation/semipinacol rearrangement of allylic alcohol **185** was achieved with secondary amine catalyst **186** in the presence of an iron(III) oxidant. This SOMO catalysis led to the formation of an enantioenriched α-quaternary cyclopentanone **187**, which was further transformed to afford (+)-cerapicol via a multistep sequence, including α-methylation, intramolecular aldol cyclization, thioxoester formation, reduction of the ketone group, and Barton–McCombie radical deoxygenation (Scheme 22).[49]

In 2018, Enders, Tang, and co-workers developed an elegant and efficient enantioselective synthesis of (+)-hippolachnin A (**201**), (+)-gracilioether A (**204**), (−)-gracilioether E (**205**), and (−)-gracilioether F (**206**) from one common intermediate (Scheme 23).[50] The key intermediate **195** was synthesized by an organocatalytic asymmetric Mukaiyama-Michael reaction between enal **192** and 1-silyloxyfuran **193** in the presence of a chiral pyrrolidine catalyst **194**. 1-Silyloxyfuran **193** was prepared from the corresponding α,β-unsaturated lactone and was used in-situ in the catalytic reaction.[50] Further elaborations of **195** led to formation of the four natural products via multistep sequences, as exemplified for (+)-hippolachnin A (**201**) in Scheme 23.[50]

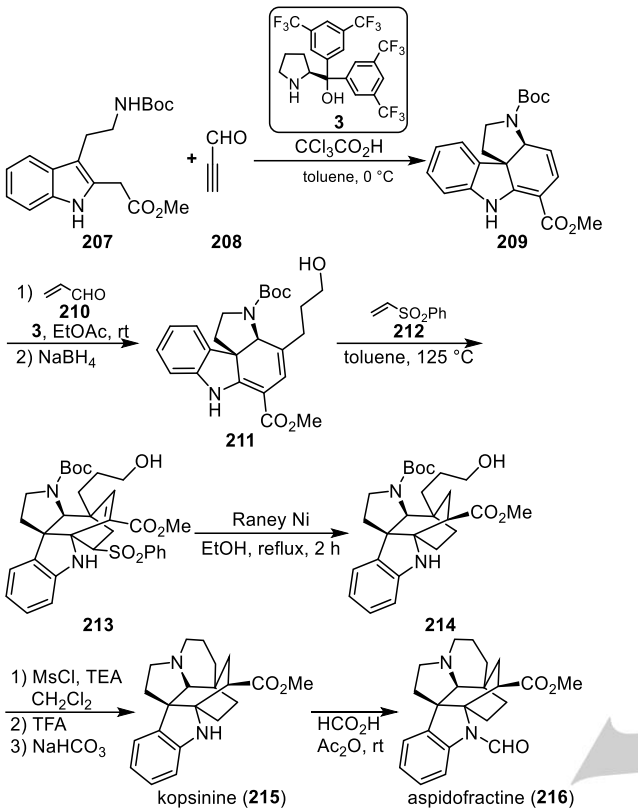


Scheme 23. Total synthesis of (+)-hippolachnin A, (+)-gracilioether A, (−)-gracilioether E, and (−)-gracilioether F via an organocatalyzed Mukaiyama-Michael reaction.

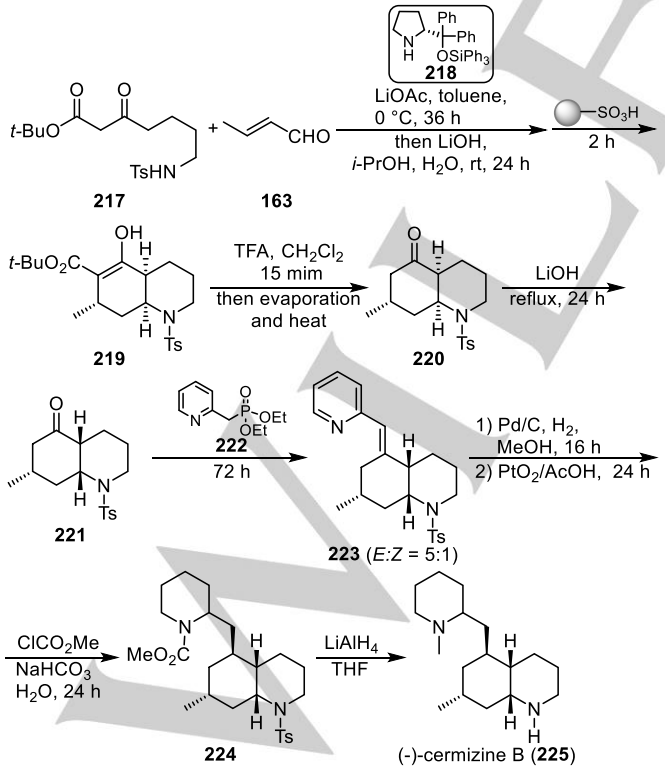
In 2014, Wu and co-workers demonstrated an efficient asymmetric total synthesis of kopsinine (**215**) and aspidofractine (**216**) (Scheme 24).[51] They developed an organocatalyzed enantioselective domino Michael addition/aza-Michael addition/cyclization of 2,3-disubstituted indole **207** and aldehyde **208**, using **3** as the catalyst. The reaction led to the formation of a highly functionalized tetracyclic spiroindoline **209**, which served as the key intermediate for the total synthesis. Further transformations on this intermediate, which included $NaBH_4$ reduction, *endo*-Diels-Alder cycloaddition, desulfonation, and cyclization afforded kopsinine (**215**) and aspidofractine (**216**) (Scheme 24).[51]

In 2014, Bradshaw, Bonjoch and their co-worker realized an asymmetric total synthesis of (-)-cermizine B (**225**) (Scheme 25).[52] They adopted an enantioselective Michael addition of β-keto ester **217** and *trans*-crotonaldehyde (**163**), catalyzed by compound **218**, followed by an aldol cyclization and an aza-Michael addition, to access the highly functionalized bicyclic *cis*-decahydroquinoline **219**, which served as the key intermediate for the total synthesis. Further elaborations of **219** via a multistep process, including decarboxylation, *retro*-aza-Michael ring-opening and recyclization, Wittig-Horner reaction, hydrogenation,

and $LiAlH_4$ reduction, afforded (-)-cermizine B (**225**, Scheme 25).[52]

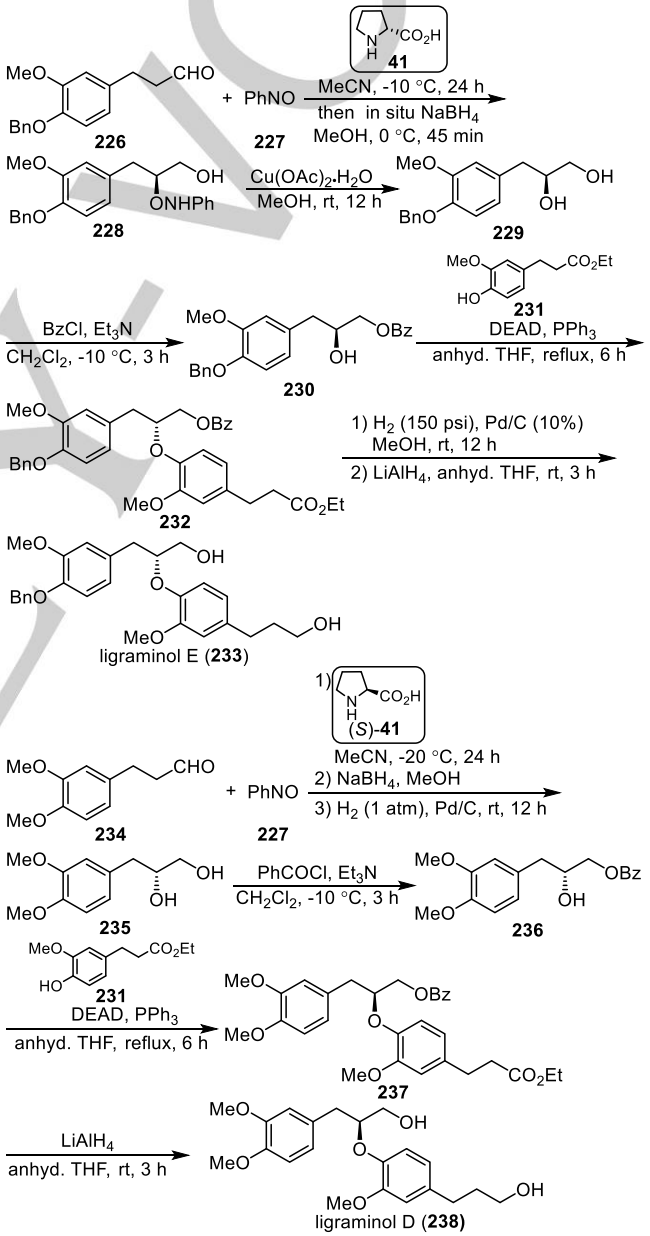


Scheme 24. Total synthesis of Kopsinine and Aspidofractine via an organocatalyzed Michael addition/aza-Michael addition/cyclization.



Scheme 25. Total synthesis of (-)-cermizine B via an organocatalyzed Michael addition followed by aldol cyclization and aza-Michael addition reaction.

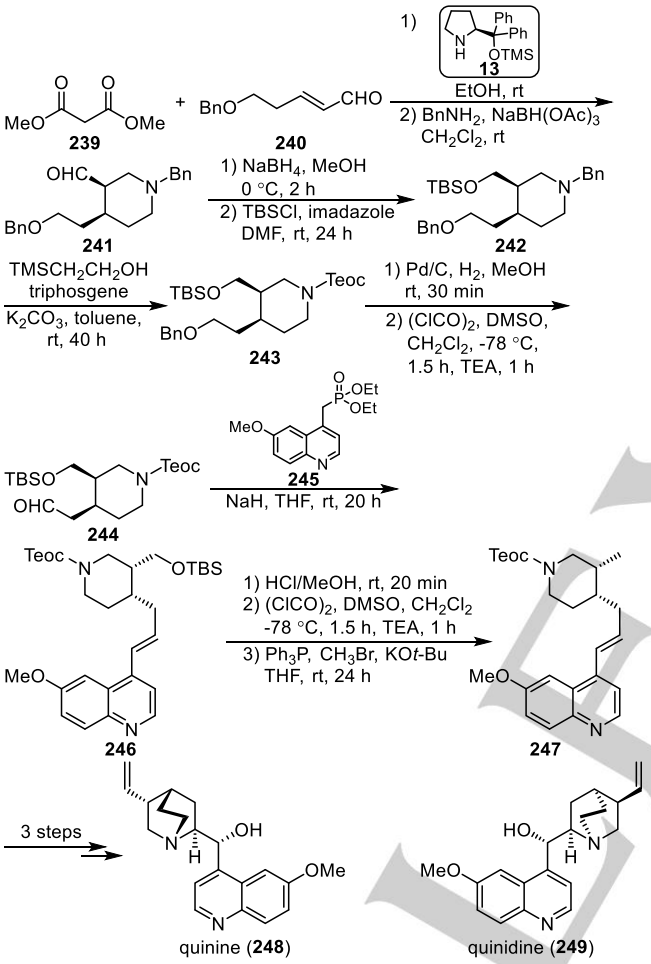
In 2019, Waghmode and co-workers developed an asymmetric total synthesis of both ligraminol D (**238**) and ligraminol E (**233**) using a similar strategy (Scheme 26).[53] To obtain the diol **229**, the key intermediate for the synthesis of ligraminol E (**233**), an organocatalyzed enantioselective α-aminooxylation of aldehyde **226** with nitrosobenzene (**227**) using D-proline (**41**) as the catalyst was employed. The obtained α-aminooxy alcohol **228** was then converted to **229**, which underwent benzoylation of the primary alcohol, Mitsunobu reaction, hydrogenation, and reduction with $LiAlH_4$ to give ligraminol E (**233**) (Scheme 26).[53] Ligraminol D (**238**) was synthesized in a similar way from the aldehyde **234** using L-proline [(*S*)-**41**] as the catalyst (Scheme 26).[53]



Scheme 26. Total synthesis of ligraminol D and ligraminol E via a proline-catalyzed α-aminooxylation reaction.

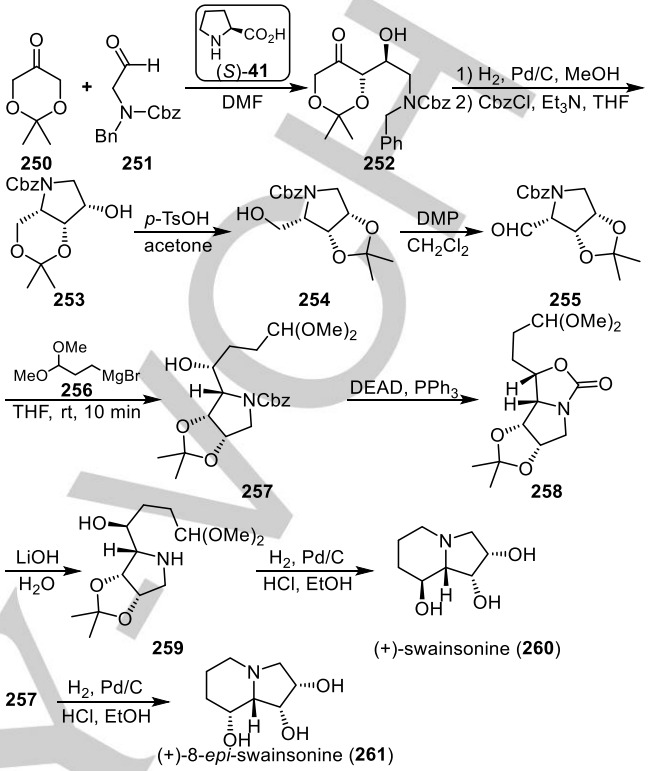
In 2019, Córdova and co-workers reported an enantioselective total synthesis of quinine (**248**) and quinidine (**249**) (Scheme 27).[54] They employed an asymmetric Michael reaction between

methyl malonate **239** and aldehyde **240** catalyzed by compound **13**, and the reductive amination of the primary Michael addition product led to the formation of the disubstituted piperidine **241**. Further transformations of **241** afforded compound **247** via a multistep sequence, which served as the key intermediate for the synthesis of quinine (**248**) (Scheme 27).[54] Starting from compound **241** and through similar synthetic maneuvers, quinidine (**249**) was also synthesized. This synthesis highlights the use of a common early-stage intermediate that can be used for the total synthesis of different enantiomers or epimers of quinine and quinidine. [54]

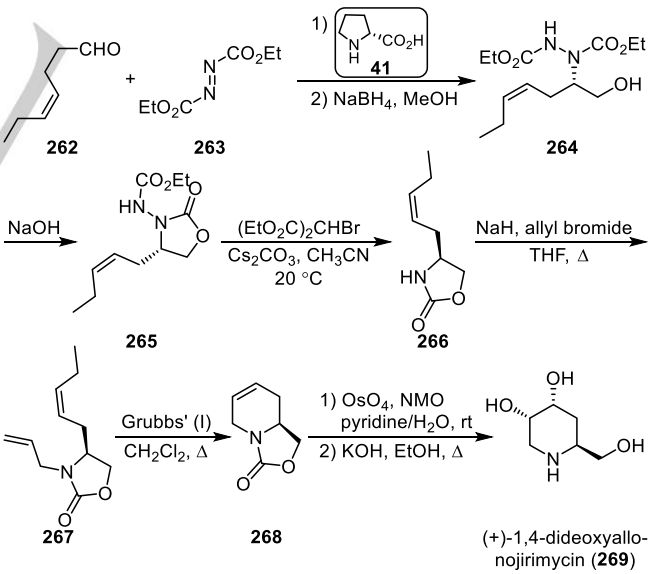


Scheme 27. Total synthesis of quinine and quinidine via an organocatalyzed Michael reaction.

In 2014, Ferjancic, Saicic, and co-workers developed an efficient asymmetric total synthesis of (+)-swainsonine (**260**) and (+)-8-*epi*-swainsonine (**261**) using L-proline [(*S*)-**41**] as the catalyst (Scheme 28).[55] The enantioselective aldol reaction between dioxanone **250** and α-aminoacetaldehyde **251** catalyzed by (*S*)-**41** led to the formation of compound **252**, which gave a highly functionalized heterocyclic system **253** after a reductive amination. Further transformation of this products afforded the intermediate **257**. A reductive amination using **257** as the substrate led to the formation of (+)-8-*epi*-swainsonine **(261**) (Scheme 28). Alternatively, the hydroxy-substituted stereogenic center in **257** can be flipped in an intramolecular Mitsunobu reaction to give a lactone **258**, which underwent hydrolysis/decarboxylation, followed by a similar reduction amination, to give (+)-swainsonine (**260**) (Scheme 28).[55]



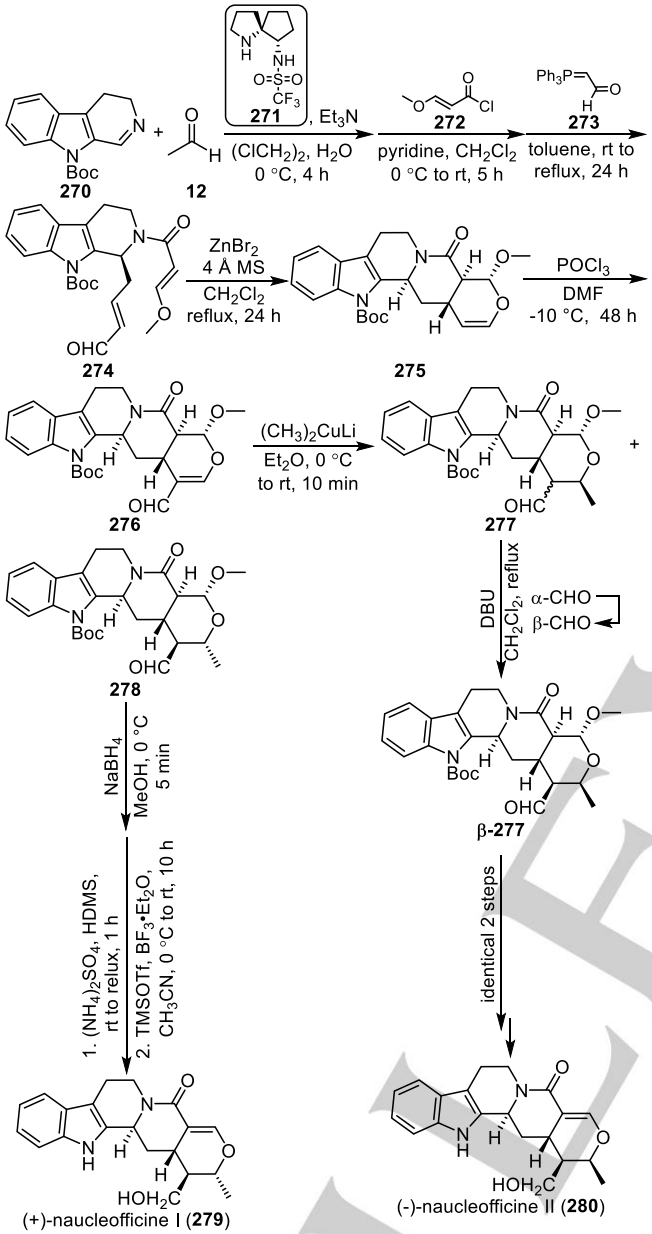
Scheme 28. Total synthesis of (+)-swainsonine and (+)-8-*epi*-swainsonine via a L-proline-catalyzed aldol reaction.



Scheme 29. Total synthesis of (+)-1,4-dideoxyallonojirimycin via an organocatalyzed α-hydrazination reaction.

In 2015, Hunter and co-workers reported the total synthesis of (+)-1,4-dideoxyallonojirimycin (**269**, Scheme 29).[56] They first developed an organocatalyzed asymmetric α-hydrazination reaction of aldehyde **262** using azodicarboxylate **263** in the presence of D-proline (**41**) as the catalyst. The α-hydrazination product was reduced and cyclized to give the crucial oxazolidinone hydrazide intermediate **265**. The N-N cleavage of

265 via an E1cB mechanism followed by *N*-allylation yielded **267**, which was then cyclized by using the Grubbs'(I) catalyst to give compound **268**, which was dihydroxylated to yield (+)-1,4-dideoxyallonojirimycin (**269**, Scheme 29).[56]

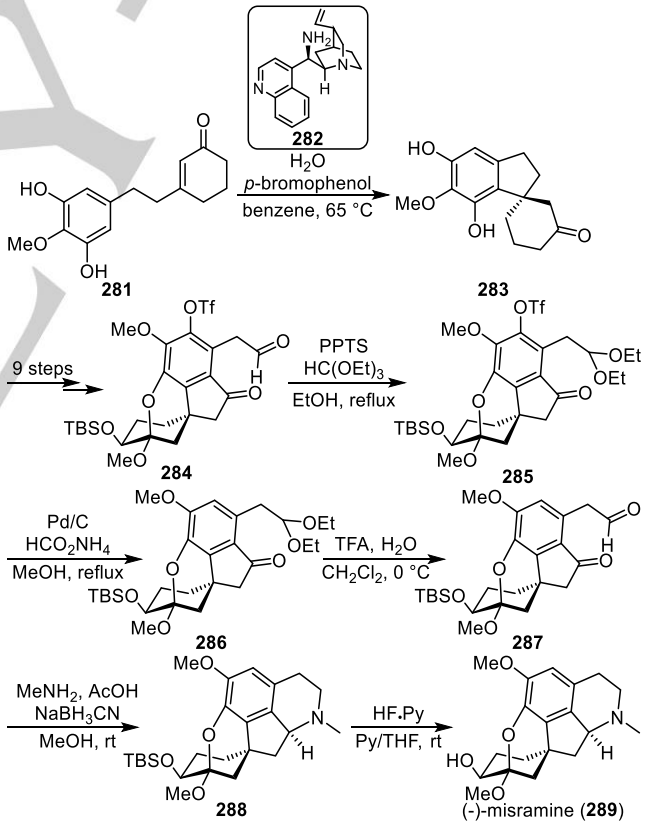


Scheme 30. Total synthesis of (+)-naucleofficine I and (-)-naucleofficine II via an organocatalyzed enantioselective Mannich reaction.

In 2019, Tu and coworkers developed a spirocyclic pyrrolidine catalyst **271** and applied it in the asymmetric Mannich reaction of 3,4-dihydro-β-carboline derivatives and acetaldehyde (**12**).[57] This method was then applied for the total synthesis of monoterpenoid alkaloids (+)-naucleofficine I (**279**) and (-)-naucleofficine II (**280**). As shown in Scheme 30, under the catalysis of **271**, the reaction between **270** and **12** yielded compound **274** after the subsequent *N*-acylation with **272** and Wittig reaction with **273**. This compound served as the key intermediate for the synthesis of the two natural products. The intramolecular *O*-hetero-Diels-Alder cyclization reaction of **274** catalyzed by $ZnBr_2$ gave the desired pentacyclic **275**. Formylation of **275** followed by Michael addition with $(CH_3)_2CuLi$ led to the formation of three separable diastereomers **α-277**, **β-277**, and **278**. The reduction of diastereomer **278** followed by the elimination of methoxy group and deprotection of the *N*-Boc group yielded the desired natural product (+)-naucleofficine I (**279**). On the other hand, by treating with DBU, diastereomer **α-277** could be epimerized to the desired **β-277**, which could be further converted to the natural product (-)-naucleofficine II (**280**) in a similar manner as **278** (Scheme 30).[57]

(2) Primary amine catalysts

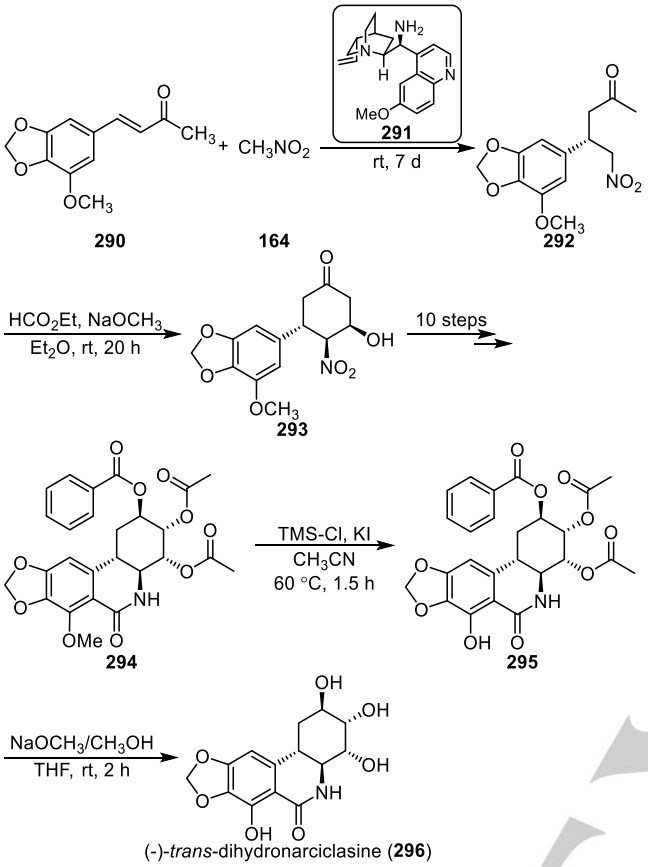
In 2018, Yoshida, Takao, and co-workers reported an enantioselective total synthesis of (-)-misramine (**289**, Scheme 31).[58] They established an organocatalytic intramolecular Friedel-Crafts-type Michael addition of cyclohexenone-resorcinol derivative **281** using cinchonine-derived amine **282** as the catalyst to obtain the spiroindane skeleton **283**, which served as the key intermediate for the total synthesis. Further synthetic maneuvers afforded eventually (-)-misramine (**289**) via a multistep sequence (Scheme 31).[58]



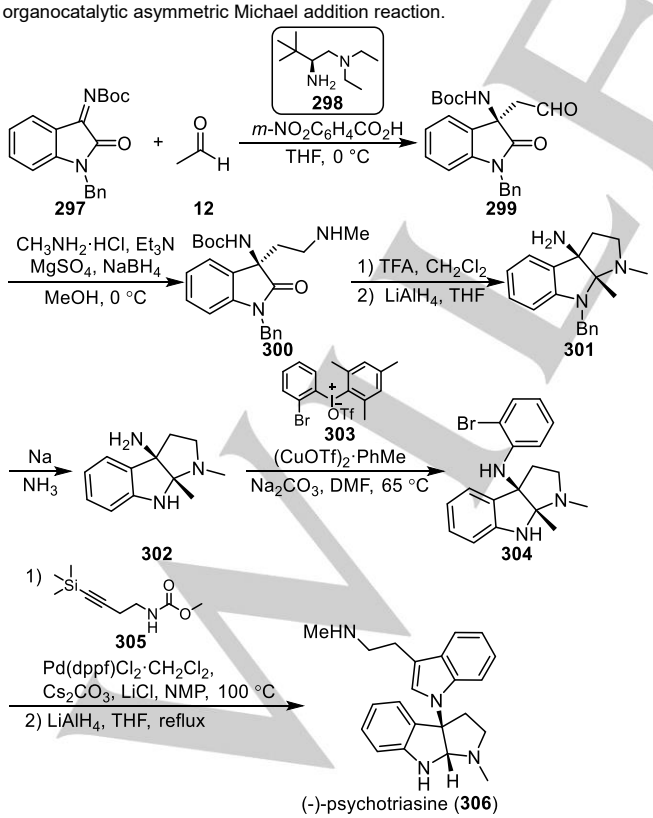
Scheme 31. Total synthesis of (-)-misramine via an organocatalyzed enantioselective intramolecular Friedel−Crafts-type Michael reaction.

In 2017, K das and co-workers reported an enantioselective total synthesis of (-)-*trans*-dihydronarciclasine (**296**) starting from a simple organocatalytic Michael addition of nitromethane (**164**) to butenone derivative **290**, using a quinine-derived amine (**291**) as the catalyst (Scheme 31).[59] The reaction led to the formation of nitropentanone derivative **292**, which was extensively elaborated

to afford the natural product (-)-*trans*-dihydronarciclasine (**296**, Scheme 32).[59]



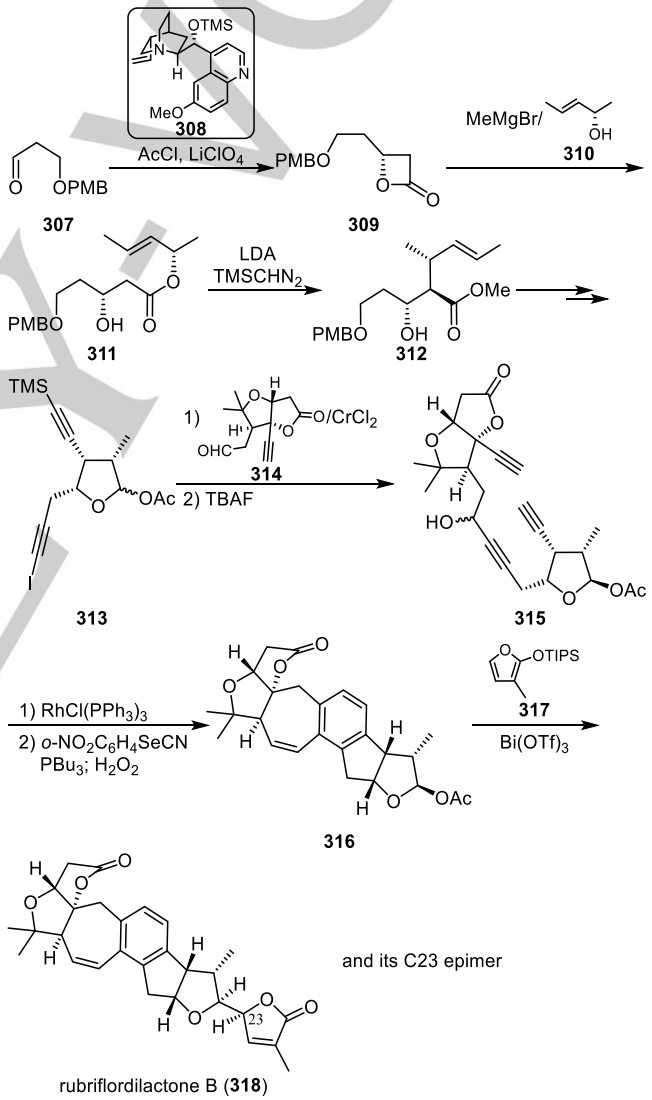
Scheme 32. Total synthesis of (-)-*trans*-dihydronarciclasine via an organocatalytic asymmetric Michael addition reaction.



Scheme 33. Total synthesis of (-)-psychotriasine via an organocatalyzed Mannich reaction.

In 2017, Shao and co-workers realized the enantioselective total synthesis of (-)-psychotriasine (**306**, Scheme 33).[60] Using an asymmetric Mannich reaction between the *N*-Boc-isatin ketimine **297** and acetaldehyde (**12**) catalyzed by a chiral primary amine catalyst **298**, they obtained the key isatin intermediate **299**. Further transformations of **299** afforded the tricyclic intermediate **300** after several steps of synthetic maneuvers. *N*-Arylation of **302** followed by a palladium-catalyzed cyclization afforded (-)-psychotriasine (**306**, Scheme 33).[60]

(b) Cinchona alkaloid catalysts



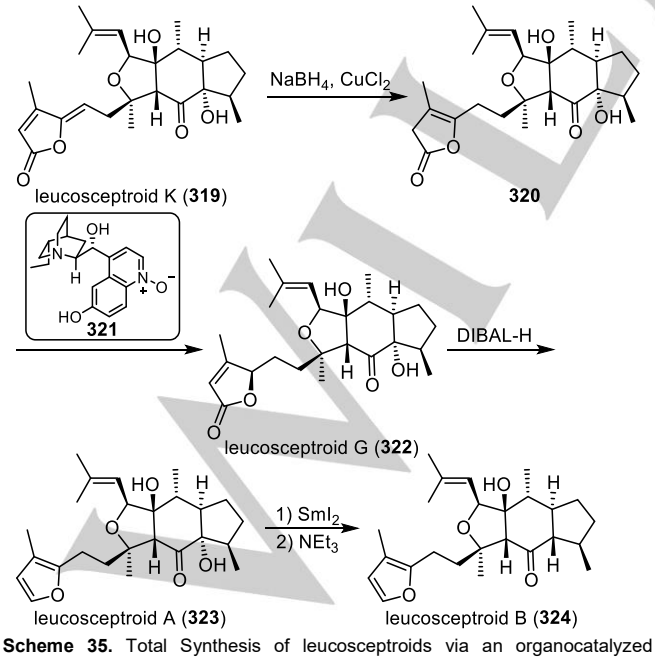
Scheme 34. Total synthesis of rubriflordilactone B via an organocatalyzed [2+2] cycloaddition (PMB = 4-methoxybenzyl).

In this section, we will discuss the total synthesis of natural products reactions catalyzed by of cinchona alkaloid and their derivatives. These compounds have a tertiary nitrogen atom in the quinuclidine core, which is more basic than the quinoline nitrogen. Thus, the tertiary nitrogen is responsible for the basic character of these catalysts. In 1960, Pracejus reported that

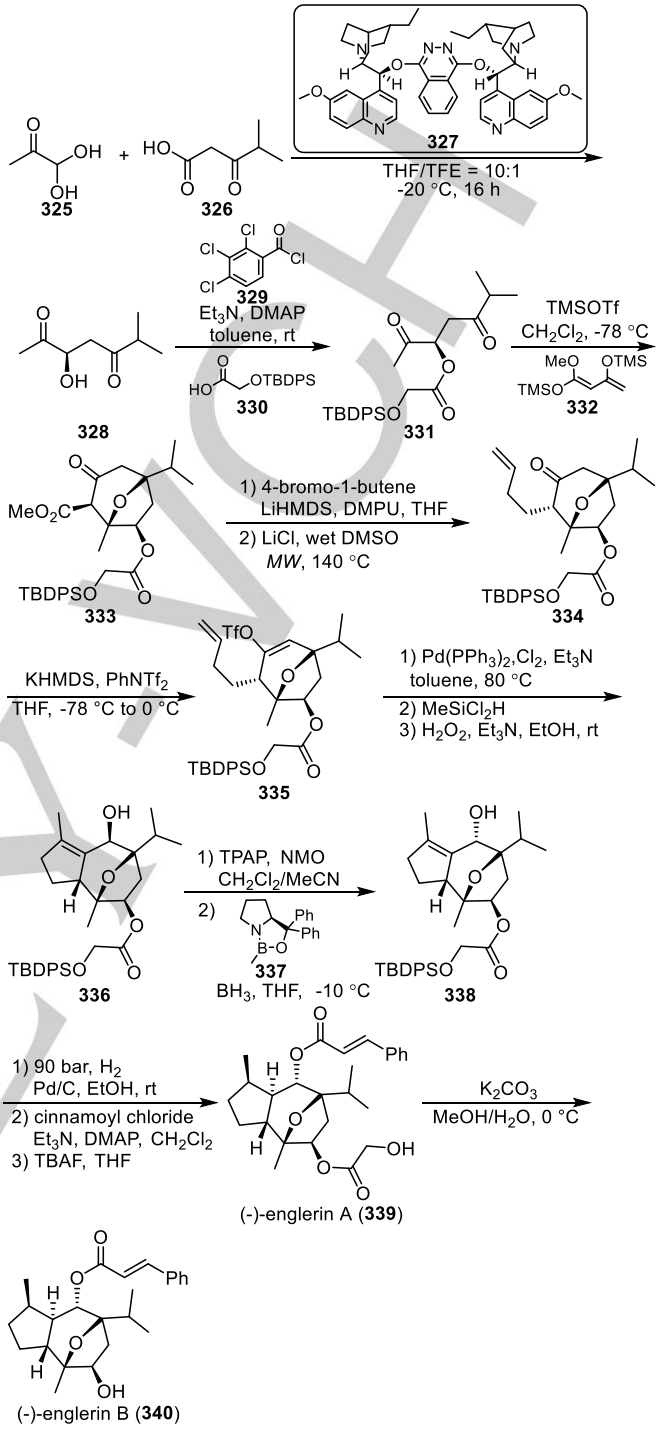
methyl phenyl ketene was converted to (*S*)-methyl hydratropate in 74% ee using *O*-acetylquinine as the catalyst.[3] This is one of the earliest examples of cinchona alkaloid-catalyzed asymmetric reactions. Wynberg and co-workers later carried out extensive studies on the application of cinchona alkaloids as chiral Brønsted base/nucleophilic catalysts, which were shown to be versatile catalysts for promoting a plethora of asymmetric 1,2- or 1,4-addition reactions of a wide range of nucleophiles to carbonyl compounds.[61] However, with a few exceptions, low enantioselectivities were usually obtained in these reactions with simple cinchona alkaloids as the catalyst and, therefore, their applications in the total synthesis of natural products was rather limited.

In 2016, Anderson and co-workers, reported an enantioselective total synthesis of (-)-rubriflordilactone B (**318**, Scheme 34).[62] An asymmetric enantioselective [2+2] cycloaddition between aldehyde **307** and acetyl chloride catalyzed by the quinine-derived catalyst **308** led to the formation of lactone **309**. Further elaboration of this intermediate afforded **313**, which was coupled with **314** via $CrCl_2$ catalysis and yielded **315** after desilylation. A Rhodium-catalyzed cyclotrimerization followed by elimination gave the desired hexacyclic compound **316**, which was converted to (-)-rubriflordilactone B (**318**) and its epimer by reacting with **317** under the catalysis of $Bi(OTf)_3$ (Scheme 34).[62]

In 2015, Magauer and Hugelshofer reported an enantioselective total synthesis of leucosceptroids A (**323**), B (**324**), and G (**322**), in which an organocatalyzed isomerization was the key step (Scheme 35).[63] The synthesis started with leucosceptroid K (**319**), which was converted to compound **320** via a 1,6-addition. The asymmetric isomerization of β,γ-unsaturated butanolide **320** in the presence of a cinchona alkaloid-derived catalyst **321** led to the formation of leucosceptroid G (**322**), which was further converted to leucosceptroid A (**323**) and leucosceptroid B (**324**) (Scheme 35).[63]



Scheme 35. Total Synthesis of leucosceptroids via an organocatalyzed isomerization of β,γ-unsaturated butanolide.



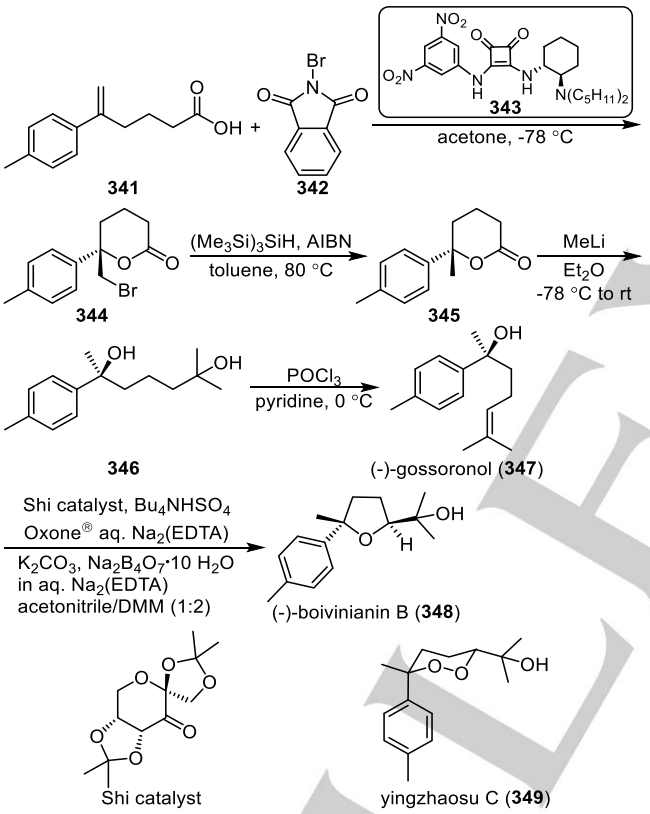
Scheme 36. Total synthesis of (-)-englerins A and B via an organocatalyzed enantioselective decarboxylative aldol reaction.

In 2019, Plietker and Guo demonstrated an efficient asymmetric total synthesis of (-)-englerin A (**339**) and (-)-englerin B (**340**) (Scheme 36).[64] Using $(DHQD)_2PHAL$ (**327**) as the catalyst, they first developed an enantioselective decarboxylative aldol reaction of methylglyoxal (**325**) with β-ketoacids, such as **326**. The obtained optically active alcohol derivative **328** was used as the starting material for the total synthesis. Through a two-step process, compound **328** was converted to the key intermediate **333**. Further elaborations afforded (-)-englerin A (**339**) and (-)-englerin B (**340**) via a multistep sequence, which included an

intramolecular Heck reaction and an asymmetric Corey-Bakshi-Shibata (CBS) reduction (Scheme 36).[64]

(c) Bifunctional organocatalysts

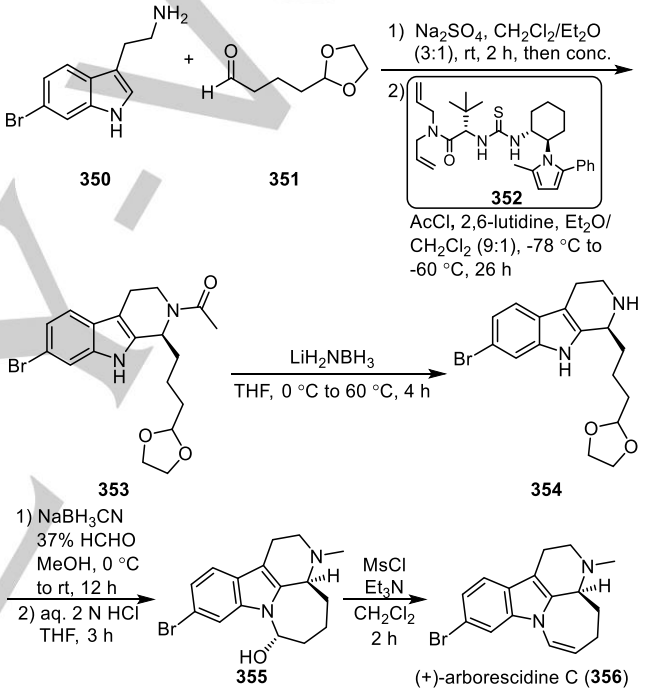
It should be pointed out that during his study of the cinchona alkaloid catalysts for asymmetric reactions, Wynberg has recognized the bifunctional nature of some of these catalysts that contain a C-9 hydroxy group.[61] Jacobsen,[65] Takemoto,[66] Soós,[67] Connon,[68] and Rawal[69] were among the first to introduce the thiourea, urea, and squaramide moieties, which are more effective in hydrogen-bonding than a simple hydroxy group, to a variety of chiral backbones, including the cinchona alkaloids, to obtain a plethora of highly effective and stereoselective organocatalysts. In this section, we will discuss the application of these bifunctional organocatalysts in the total synthesis of natural products.[13]



Scheme 37. Synthesis of (-)-gossoronol and (-)-boivinianin B via an organocatalyzed bromolactonization reaction

In 2016, Hansen and co-workers reported an enantioselective total synthesis of (-)-gossoronol (**347**) and (-)-boivinianin B (**348**) (Scheme 37).[70] They utilized the organocatalytic enantioselective bromolactonization reaction of *δ*-unsaturated carboxylic acids with *N*-bromophthalimide (**342**) developed in the paper for converting **341** to **344** using the chiral squaramide **343** as the catalyst. Further transformations of this intermediate afforded compound **347**, which is the natural product (-)-gossoronol. Compound **347** was further converted to the natural product (-)-boivinianin B (**348**) via an epoxidation with Shi's catalyst, followed by an epoxide ring-opening reaction (Scheme 37). Compound **347** may also serve as a precursor for the synthesis of the natural product yingzhaosu C (**349**, Scheme 37).[70]

In 2019, Hong and co-workers reported enantioselective total synthesis of (+)-arborescidine C (**356**, Scheme 38).[71] The synthesis started from tryptamine **350** and aldehyde **351**, which underwent an organocatalytic enantioselective acyl-Pictet-Spengler reaction under the catalysis of a Jacobsen-type thiourea organocatalyst (**352**). The reaction led to the formation of the tricyclic product **353**, which served as the key intermediate for the total synthesis (Scheme 38).[71] Further elaborations of this product afforded (+)-arborescidine C (**356**) through a multistep sequence that included amide reduction with LiH_2NBH_3, reductive amination and cyclization reaction, and elimination reaction (Scheme 38).[71]

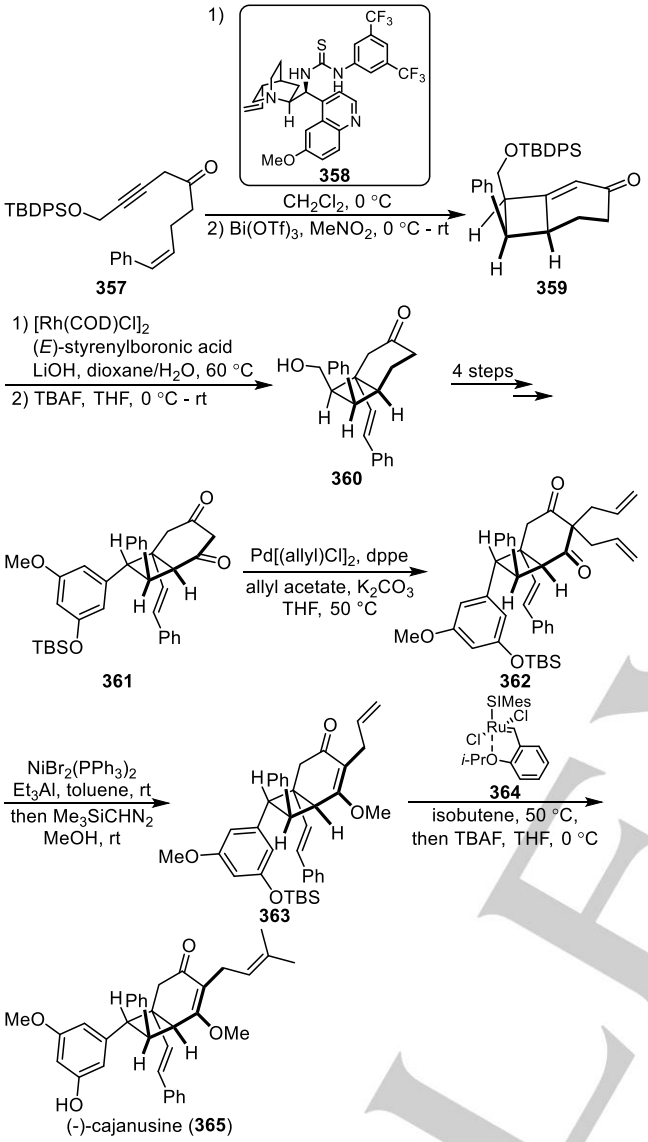


Scheme 38. Total synthesis of (+)-arborescidine C via an organocatalyzed enantioselective acyl-Pictet-Spengler reaction.

In 2020, Brown and co-workers reported an enantioselective synthesis of (−)-cajanusine (**365**, Scheme 39).[72] The asymmetric intramolecular [2+2]-cycloaddition reaction of **357** catalyzed by the quinine thiourea catalyst (**358**) led to the formation of an intermediate, which, upon the treatment with $Bi(OTf)_3$ in situ, yielded the bicyclic compound **359**. Compound **359** contains the same skeleton as the desired natural product and served as the key intermediate of the total synthesis. Further synthetic maneuvers on this intermediate led to the successful synthesis of (−)-cajanusine (**365**, Scheme 39).[72]

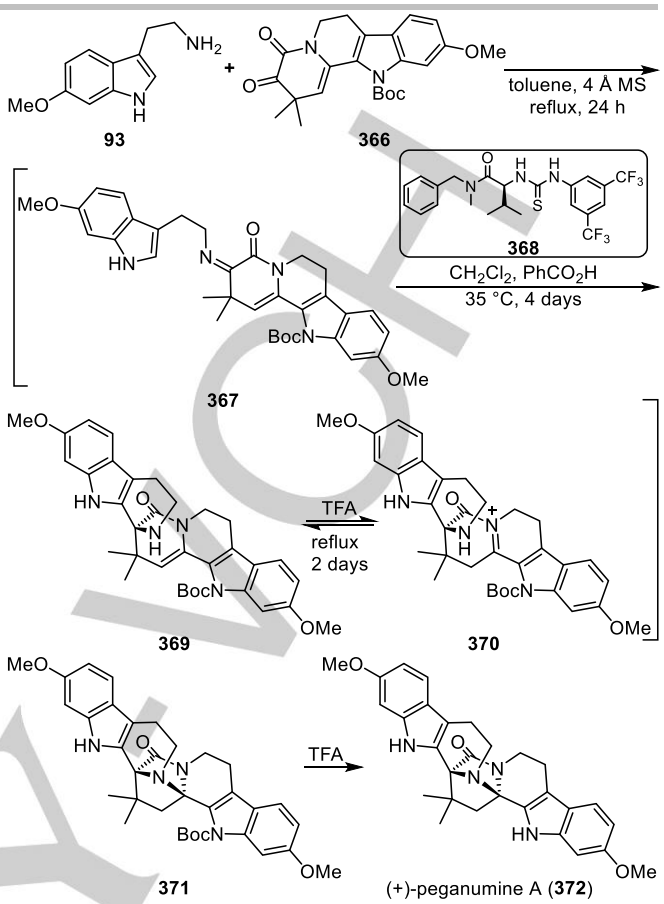
In 2016, Zhu and co-workers developed a highly efficient asymmetric total synthesis of (+)-peganumine A (**372**, Scheme 40).[73] They first developed a novel strategy to access the tetracyclic *α*-ketolactam **366**.[73] Then it was condensed with 6-methoxytryptamine (**93**) to give an intermediate **367**, which was treated in situ with the chiral thiourea catalyst **368** and TFA

subsequently. An enantioselective Pictet−Spengler reaction catalyzed by **368** followed by a TFA-catalyzed transannular cyclization directly led to the desired natural product (+)-peganumine A (**372**) in a single step (Scheme 40).[73]



Scheme 39. Total synthesis of (−)-cajanusine via an organocatalyzed [2+2]-cycloaddition reaction.

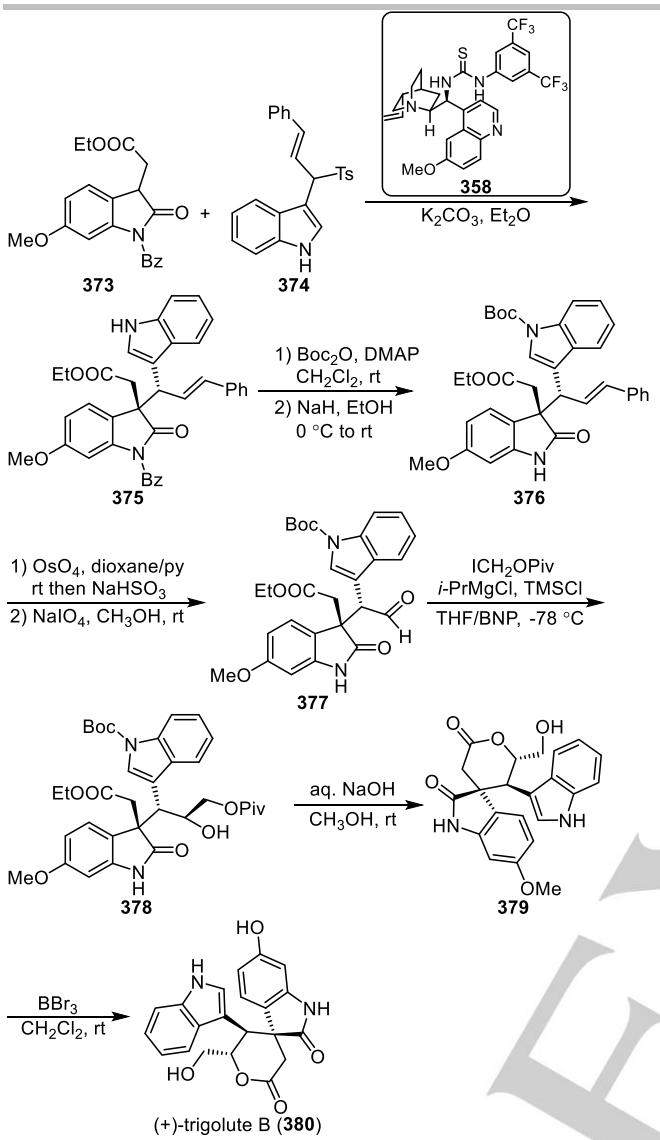
In 2015, Gong and co-workers reported a total synthesis of (+)-trigolute B (**380**) as an application of the synthetic method developed in the paper.[74] As shown in Scheme 41, the asymmetric substitution reaction between 3-(1-tosylalkyl)indole derivative **374** and oxindole derivative **373**, under the catalysis of the quinine thiourea (**358**), led to the formation of the highly functionalized optically active indole derivative **375**. Further transformations of this key intermediate afforded (+)-trigolute B (**380**) after a multistep sequence, which included oxidative cleavage of the styrene group to introduce the aldehyde group, stereoselective introduction of a diol via the Knochel's method, and final cyclization and deprotection (Scheme 41).[74]



Scheme 40. Total synthesis of (+)-peganumine A via an organocatalyzed enantioselective Pictet-Spengler reaction.

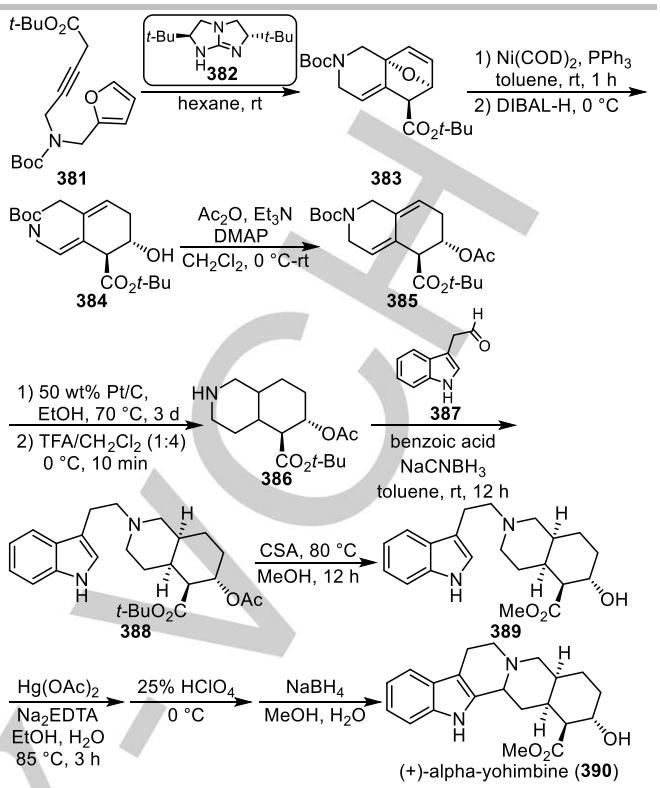
(d) Chiral guanidine and guanidinium catalysts

The guanidine functional group exhibits Brønsted basicity and hydrogen bond donating and accepting abilities. On the other hand, protonated guanidinium salt shows weak Brønsted acidity and cationic hydrogen bond donating capability. In catalytic reactions, guanidine and guanidinium salt possess similar structural feature and capability as urea and thiourea, such as dual hydrogen bonding, which is very important in the electrophilic activation as well as in the transition state organization. Najera and co-workers were among the first to use chiral guanidines as organocatalysts in enantioselective reactions. In 1994, they applied an open-chain chiral guanidine in an organocatalyzed Henry reaction and obtained the products in up to 54% ee.[75] In 1999, Corey and Grogan reported a bicyclic chiral guanidine organocatalyst for the Strecker reaction.[76] Later Nagasawa and Tan developed pentacyclic[77] and bicyclic[78] guanidine organocatalysts, respectively. With the developments of new guanidine catalysts, more and more asymmetric reactions that can be catalyzed these catalysts were discovered.[79]. In this section, we are going to discuss the most recent applications of chiral guanidine organocatalysts in the total synthesis of natural products.

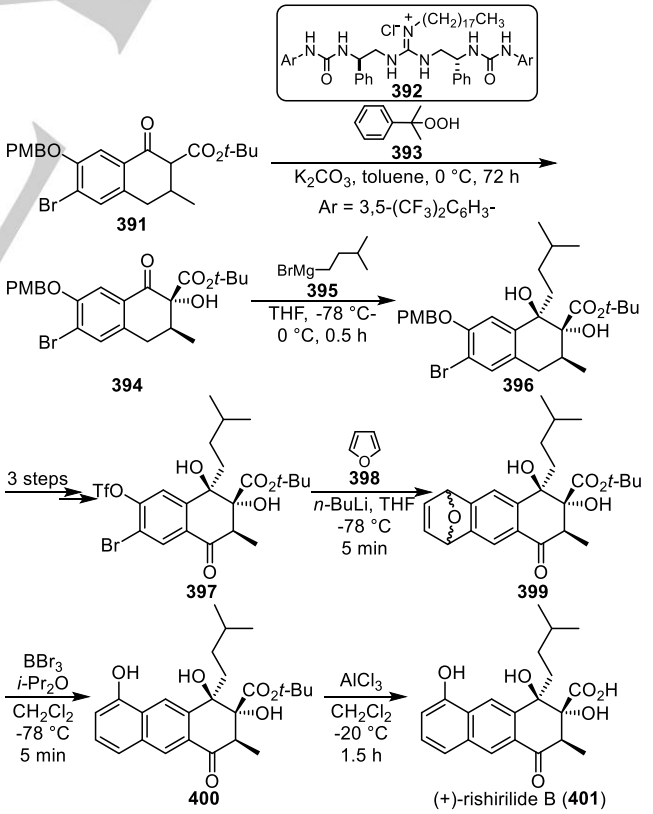


Scheme 41. Total synthesis of (+)-trigolute B via an organocatalyzed asymmetric substitution reaction.

In 2016, Tan and co-workers reported the first enantioselective total synthesis of (+)-alpha-yohimbine (**390**) using an organocatalyzed domino isomerization/intramolecular Diels-Alder reaction.[80] As shown in Scheme 42, under the catalysis of a C2-symmetric bicyclic guanidine catalyst **382**, the domino isomerization/intramolecular Diels-Alder reaction of alkynoate **381** yielded the tricyclic product **383**, which was ring-opened and reduced to produce compound **384**, which served as the key intermediate for the total synthesis. Further elaborations via an eight-step sequence, including reductive amination with aldehyde **387** and oxidative cyclization of the intermediate **389**, afforded (+)-alpha-yohimbine (**390**) (Scheme 42).[80]



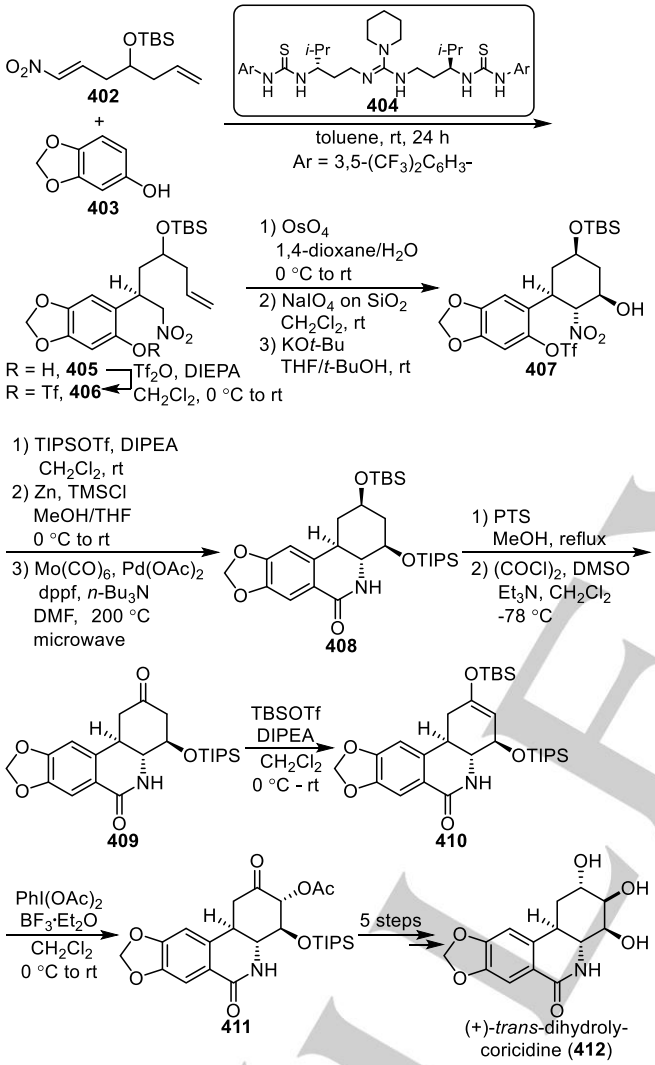
Scheme 42. Total synthesis of (+)-alpha-yohimbine via an organocatalyzed domino isomerization/intramolecular Diels-Alder reaction.



Scheme 43. Total synthesis of (+)-rishirilide B via an organocatalyzed oxidative kinetic resolution reaction. (PMB = *para*-methoxybenzyl)

In 2017, Odagi, Nagasawa, and co-workers reported the total synthesis of (+)-rishirilide B (**401**) starting from a guanidinium

catalysis (Scheme 43).[81] They developed an oxidative kinetic resolution of 1-tetralone derivative **391** by cumene hydroperoxide (**393**) using guanidinium salt **392** as the catalyst, which led to the formation of **394** in 48% yield with 90% *ee*. A single recrystallization increased the enantiopurity of **394** to 99% *ee*.[81] Further transformations of this key intermediate via a seven-step sequence, including reacting with Grignard reagent **395**, benzyne-mediated Diels-Alder reaction with furan (**398**), and regioselective ring isomerization, afforded (+)-rishirilide B (**401**, Scheme 43).[81]



Scheme 44. Total synthesis of (+)-*trans*-dihydrolycoricidine via an organocatalytic Friedel-Crafts reaction.

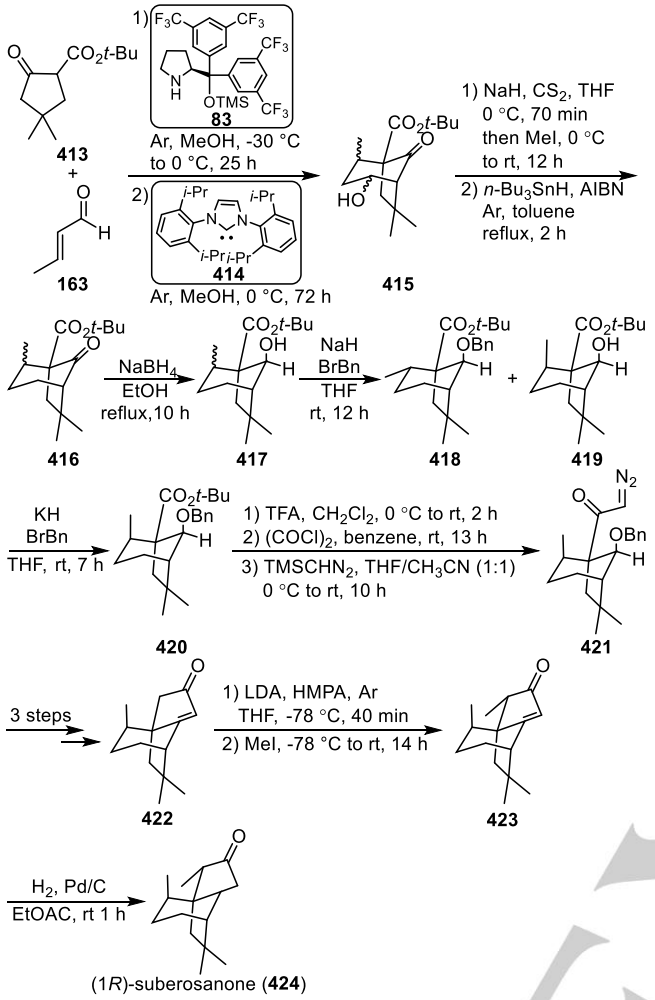
In 2016, Nagasawa and co-workers reported an enantioselective total synthesis of (+)-*trans*-dihydrolycoricidine (**412**, Scheme 44).[82] They first achieved an asymmetric 1,4-Friedel-Crafts reaction between racemic nitroalkene **402** and sesamol (**403**), using guanidine-bisthiourea **404** as the organocatalyst. The reaction led to the formation of an optically active **405** as an inseparable diastereomeric mixture. After the hydroxy group has been protected (to **406**), the alkene group was converted to an aldehyde and an intramolecular Henry reaction took place to yield compound **407** and its diastereomer, which could be separated from each other. Compound **407** served as the key intermediate for the total synthesis, and further transformations afforded (+)-*trans*-dihydrolycoricidine (**412**) via a multistep sequence (Scheme 44).[82]

(e) Catalysis conducted with two organocatalysts

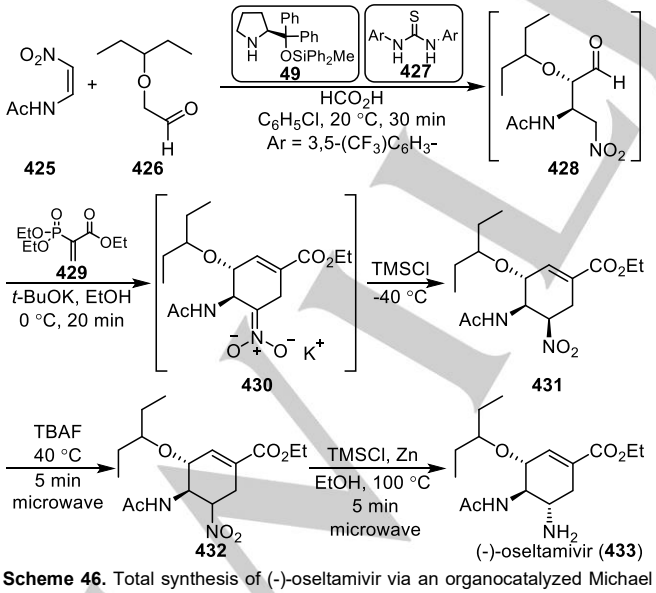
When two or more catalysts are applied in a one-pot chemical transformation, depending on the timing of the catalyst deployment and the involvement of the catalysts in the reaction mechanisms, it can be an example of either an isolated sequential catalysis,[83] an orthogonal tandem catalysis,[83] or a cooperative catalysis.[84] If not all of the catalysts are present from the very beginning of the reaction, then it is a case of the isolated sequential catalysis. If all of the catalysts are present from the very beginning of the reaction but operate sequentially in two or more mechanistically distinct catalytic cycles, then the situation is referred to as an orthogonal tandem catalysis. On the other hand, if all of the catalysts are present at the very beginning of the reaction and operate by sharing the same catalytic cycle by activating different substrates separately, then the situation is referred to as a cooperative catalysis. In cooperative catalysis, since more than one catalyst is used in the same catalytic cycle to activate the substrates separately, it is possible to generate synergistic effects during catalysis, which can be either positive or negative. However, from practical point of view, only a positive synergism is desirable. In this section, we will discuss the total synthesis of natural products involving reactions catalyzed by two organocatalysts via an isolated sequential catalysis or a cooperative catalysis mode.

In 2016, Rodriguez, Coquerel, and co-workers developed an enantioselective total synthesis of (1*R*)-suberosanone (**424**) using a sequential catalysis of an enamine catalyst and an NHC catalyst (Scheme 45).[85] The key step of the total synthesis was achieved via the reaction of β-ketoester **413** and crotonaldehyde (**163**), catalyzed sequentially by a secondary amine catalyst **83** followed by an NHC catalyst **414**, to yield a bridged bicyclic compound **415** as a mixture of four diastereomers. While the reaction was conducted in one-pot, the catalyses were isolated events and, therefore, it is an example of the isolated sequential catalysis. Compound **416** was then dehydroxylated and stereoselectively reduced to give compound **417** as a mixture of two diastereomers. Selectively benzylation of equatorial-methyl diastereomer to **418** achieved the separation the desired axial-diastereomer **419**. Further transformations of this diastereomer afforded (1*R*)-suberosanone (**424**) via a 10-step sequence, including benzylation, Arndt-Eistert homologation, α-methylation, and hydrogenation (Scheme 45).[85]

In 2016, Hayashi and Ogasawara reported highly efficient enantioselective one-pot total synthesis of (-)-oseltamivir (**433**, Scheme 46).[86] An organocatalytic asymmetric Michael reaction between nitroalkene **425** and aldehyde **426** was conducted in the presence of dual catalysts **49** and **427**. This reaction is an example of cooperative catalysis and led to the formation of the key intermediate **428**. Reacting this intermediate with compound **429** formed the cyclic intermediate **430**, which was in-situ converted to (-)-oseltamivir (**433**) via epimerization and reduction (Scheme 46).[86]

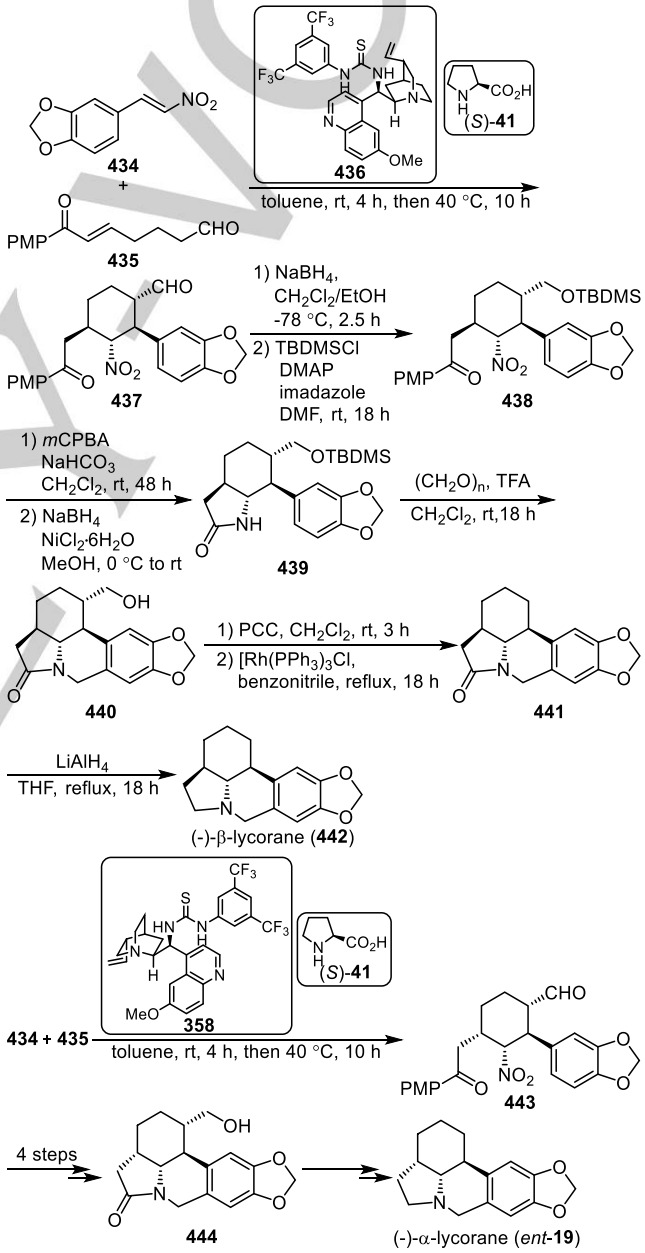


Scheme 45. Total synthesis of (1*R*)-suberosanone via a dual organocatalytic Michael/aldolization reaction.



Scheme 46. Total synthesis of (-)-oseltamivir via an organocatalyzed Michael reaction.

In 2014, we reported a diastereodivergent synthesis of (-)-α-lycorane (*ent*-**19**) and (-)-β-lycorane (**442**) using domino Michael/Michael reactions between the nitroalkene **434** and the enal **435** (Scheme 47).[87] When pseudodiastereomeric modular designed organocatalysts (MDOs),[88] self-assembled from L-proline [(*S*)-**41**] and cinchona alkaloid thioureas **436** and **358**, respectively, were applied, two diastereomeric cyclohexanecarbaldehydes **437** and **443** were obtained in high diastereo- and enantioselectivities. Further transformations of **437** via a multistep sequence afforded the natural product (-)-β-lycorane (**442**). In a similar manner, compound **443** could be transformed to compound **444**, which can serve as a key intermediate for the synthesis of (-)-α-lycorane (**19**) according to a reported synthesis (Scheme 47).[87] These reactions are also examples of cooperative catalysis.[87]

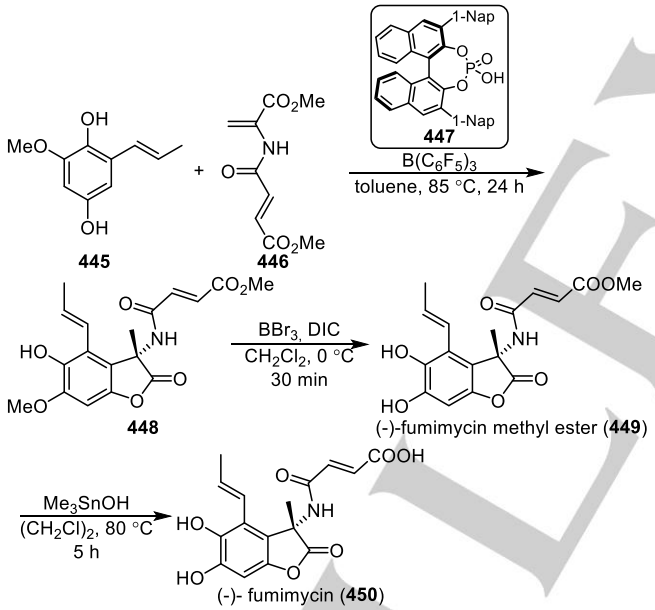


Scheme 47. Total synthesis of β-lycorane and formal synthesis of α-lycorane via organocatalyzed diastereodivergent domino Michael/Michael reactions.

(f) Chiral phosphoric acid and their derivatives

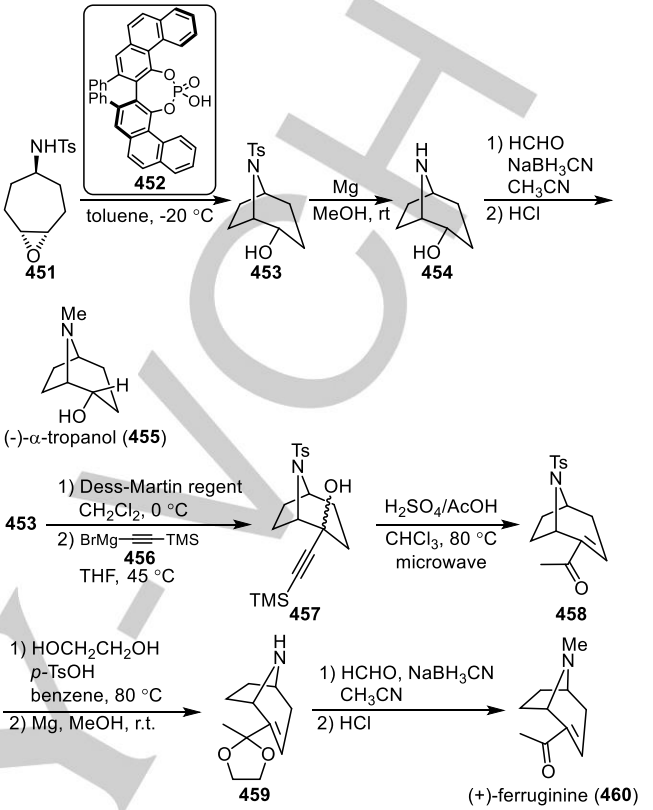
Since the pioneering reports of Akiyama[89] and Terada,[90] axial chiral phosphoric acids have been widely used as organocatalysts for the simultaneous activation of nucleophiles and/or electrophiles in asymmetric reactions.[91–94] Chiral BINOL-derived phosphoric acids have been proved to be powerful Brønsted acid catalysts for a variety of chemical transformations and have been applied in the total synthesis of natural products.[14-19] In this section, we will discuss the recent applications of these catalysts in the total synthesis of natural products and related compounds.

In 2019, Piersanti and co-workers reported an enantioselective total synthesis of (-)-fumimycin (**450**) and its enantiomer (+)-fumimycin via an organocatalytic asymmetric aza-Friedel-Crafts reaction (Scheme 48).[95] Using the BINOL-derived chiral phosphoric acid **447** as the catalyst, an asymmetric aza-Friedel-Crafts reaction between highly substituted hydroquinone **445** and dehydroalanine derivative **446** led to the formation of the desired optically active lactone **448** regioselectively. Removing the methyl protecting group in **448** yielded (-)-fumimycin methyl ester (**449**). Cleavage of the methyl ester of **449** gave (-)-fumimycin (**450**) (Scheme 48). Use the enantiomer of **447** as the catalyst, (+)-fumimycin was obtained with the same yield and almost opposite enantioselectivity.[95]



Scheme 48. Total synthesis of (+)- and (-)-fumimycin via an organocatalyzed asymmetric aza-Friedel-Crafts reaction (1-Nap = 1-naphthyl).

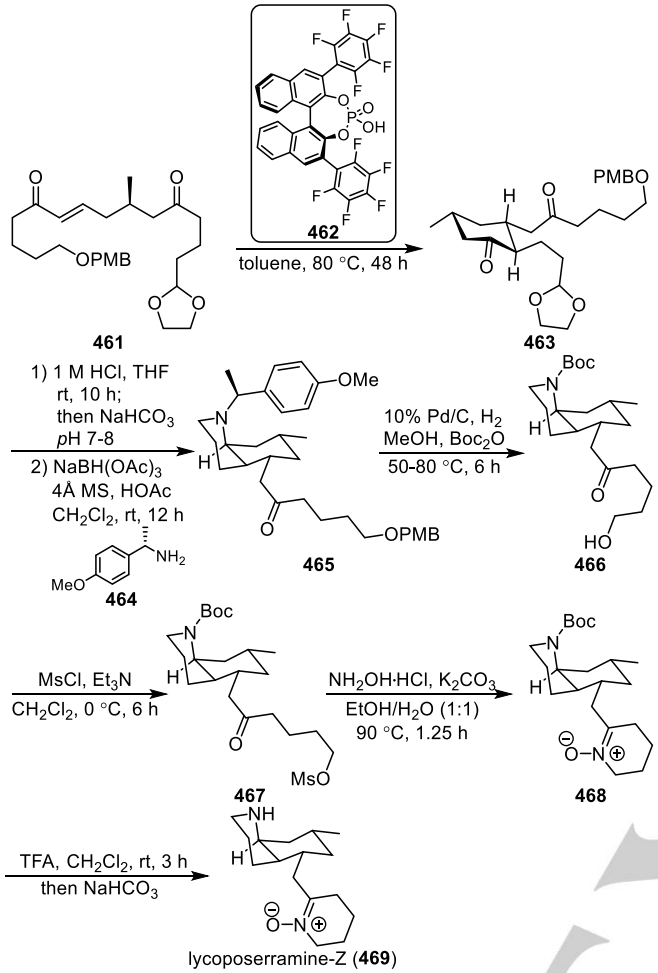
In 2020, Uria, Merino, Vicario, and co-workers reported an enantioselective total synthesis of (-)-α-tropanol (**455**) and (+)-ferruginine (**460**, Scheme 49).[96] They first realized an asymmetric pseudotransannular ring-opening of epoxycycloheptylamines using a chiral phosphoric acid **452** as the catalyst. Then they applied the method for the total synthesis of two natural products from the tropane family. As shown in Scheme 49, the epoxycycloheptylamine **451** was ring-opened to give an optically active 8-azabicyclo[3.2.1]octane scaffold **453** under the catalysis of **452**. Deprotecting the *N*-tosyl group and reprotecting it with a methyl group afforded (-)-*α*-tropanol (**455**). Starting from the scaffold **453**, they also synthesized (+)-ferruginine (**460**) via a multistep sequence that included oxidation, alkynylation, Rupe rearrangement, and detosylation/*N*-methylation (Scheme 49).[96]



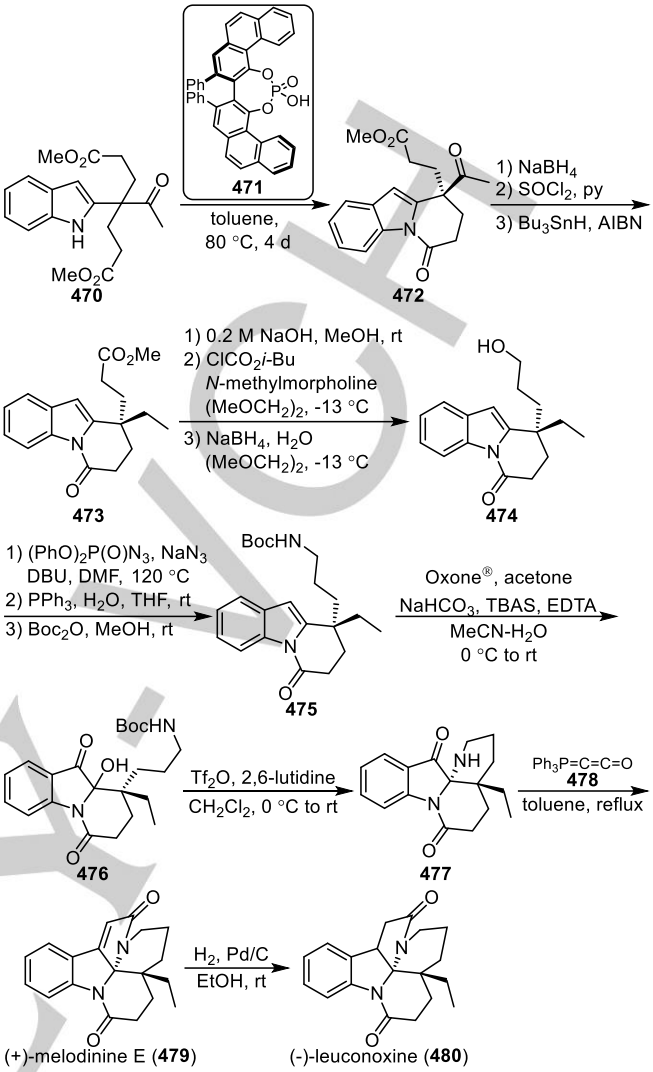
Scheme 49. Total synthesis of (-)-*α*-tropanol and (+)-ferruginine via an organocatalyzed asymmetric pseudotransannular ring-opening reaction

In 2016, Yang, Yao, and co-workers reported an enantioselective total synthesis of lycoposerramine-Z (**469**, Scheme 50).[97] To obtain the key intermediate **463**, they carried out an asymmetric intramolecular Michael addition of *α,β*-unsaturated ketone **461** using chiral phosphoric acid **462** as the catalyst. The reaction led to the formation of the desired highly substituted cyclohexanone **463** in high stereoselectivities after optimizations. Further elaboration of **463** afforded lycoposerramine-*Z* (**469**) via a multistep sequence that included reductive amination, hydrogenolysis, mesylation, and nitrone formation reaction (Scheme 50).[97]

In 2015, Higuchi, Kawasaki, and co-workers reported the enantioselective total synthesis of (+)-melodinine E (**479**) and (-)-leuconoxine (**480**) (Scheme 51).[98] The desymmetrization of a prochiral diester **470** under the catalysis of the chiral phosphoric acid **471** led to the formation of an optically active lactam derivative **472**, which underwent further transformations to afford (+)-melodinine E (**479**) via a multistep sequence that included $NaBH_4$ reduction/deoxygenation, azidation, Staudinger reduction, indole oxidation, and lactamization with Bestmann's ylide (**478**). The hydrogenation of **479** produced (-)-leuconoxine (**480**) (Scheme 51).[98]

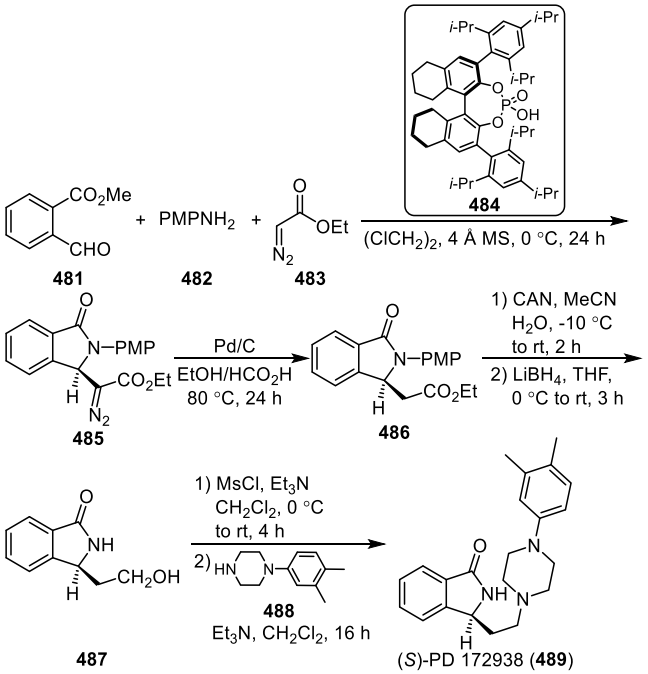


Scheme 50. Total synthesis of lycoposerramine-Z via an organocatalyzed asymmetric intramolecular Michael addition.



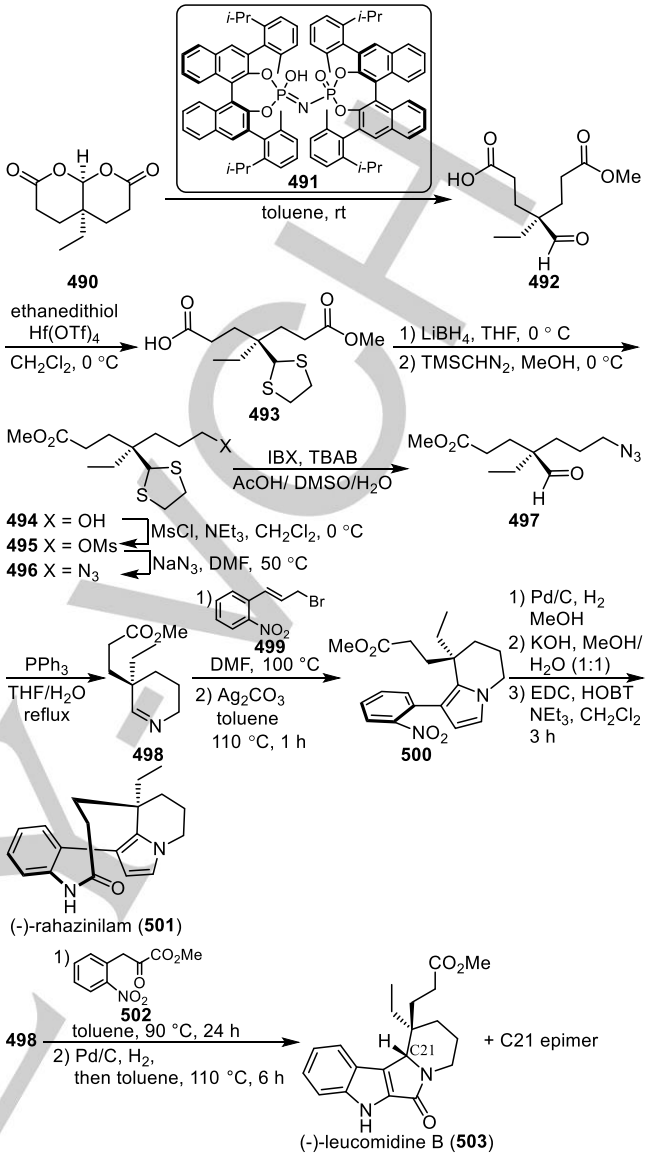
Scheme 51. Total synthesis of (+)-melodinine E and (-)-leuconoxine via an organocatalyzed desymmetric lactamization.

In 2019, Singh and co-workers reported an enantioselective total synthesis of (*S*)-PD 172938 (**489**, Scheme 52).[99] The asymmetric tandem Mannich-lactamization of methyl 2-formylbenzoate (**481**) and *p*-anisidine (**482**) with ethyl diazoacetate (**483**) in the presence of the phosphoric acid **484** as the catalyst produced an optically active chiral isoindolinone containing α-diazo ester (**485**). This compound was further transformed to (*S*)-PD 172938 (**489**), which is a dopamine D_4 ligand, via a multistep sequence including removal of the diazo and the PMP groups, reduction the ester with $LiBH_4$, and the final assembly with piperazine **488** (Scheme 52). Apparently, an organocatalytic reaction afforded the key intermediate **485** for this synthesis.[99]



Scheme 52. Total synthesis of (*S*)-PD 172938 via an organocatalyzed tandem Mannich-lactamization and aldol-lactonization reaction.

In 2014, Zhu and co-workers realized an efficient asymmetric total synthesis of (-)-rhazinilam (**501**) and (-)-leucomidine B (**503**) (Scheme 53).[100] They developed an organocatalyzed desymmetrization of bicyclic bislactones, such as compound **490**, by alcohols using an imidodiphosphoric acid **491** as the catalyst. One of the obtained enantiomerically enriched products, compound **492**, was used to access the cyclic imine **498**, which served as the key intermediate for the concise synthesis of both (-)-rhazinilam (**501**) and (-)-leucomidine B (**503**) (Scheme 53).[100]



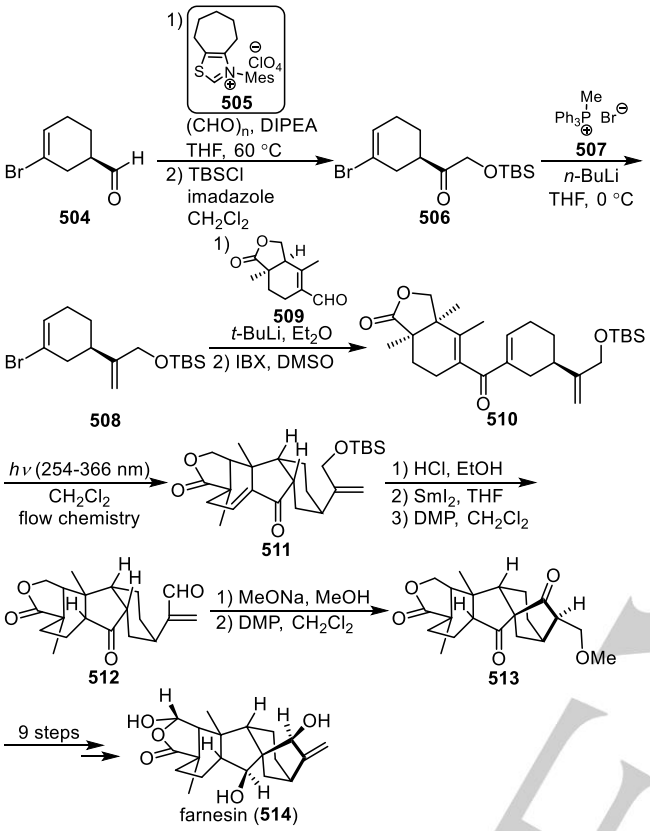
Scheme 53. Total synthesis of (-)-rhazinilam and (-)-leucomidine B.

(g) *N*-heterocyclic carbene catalysts

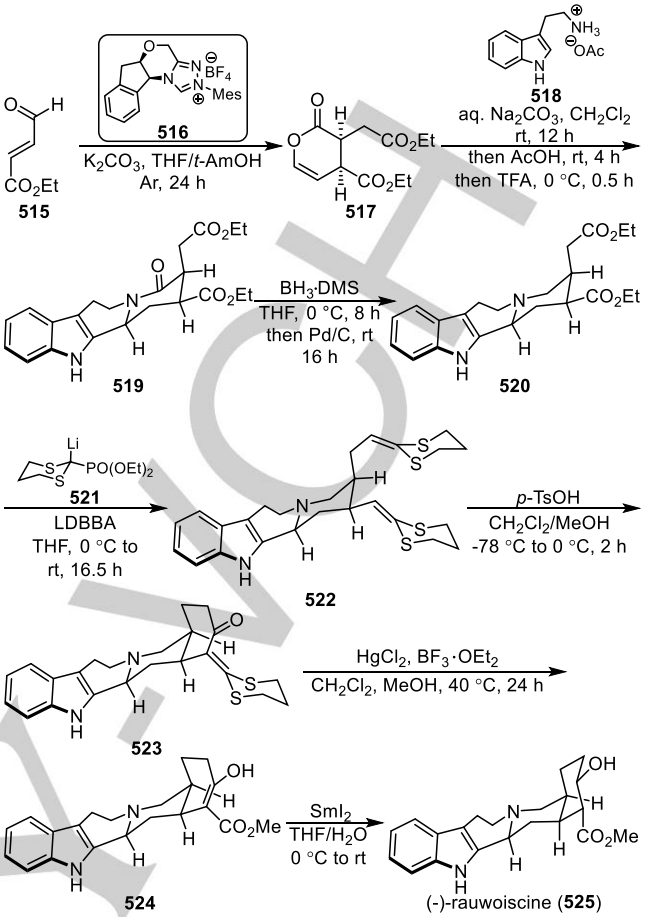
N-Heterocyclic carbenes (NHC) have found a lot of applications as excellent organocatalyst in organocatalysis due to their unique activation mode and the new reactivities they introduced.[13] In addition, besides aldehydes and ketones, *N*-heterocyclic carbene catalysts can also activate unactivated esters, which cannot be activated by the amine catalysts.[25] In this section, we will discuss the application these catalysts in the total synthesis of natural products.[20]

In 2020, Gao and co-workers reported a convergent approach for the total synthesis of farnesin (**514**, Scheme 54).[101] One of the key intermediates of this synthesis, intermediate **506**, was obtained from an NHC-catalyzed reaction. As shown in Scheme 54, they first synthesized the aldehyde **504**, which was allowed to react with formaldehyde under the catalysis of the NHC catalyst generated in-situ from the thiazolium salt **505**. The hydroxymethylation reaction and ensuing silyl protection of the alcohol product led to the formation compound **506**, which was

further converted to compound **508** via a Wittig reaction. The assembly of **508** and the other key intermediate **509** gave compound **510**. Further elaborations of this molecule afforded farnesin (**514**) via a multistep sequence that included photo-Nazarov reaction, intramolecular aldol reaction, and oxidation (Scheme 54).[101]

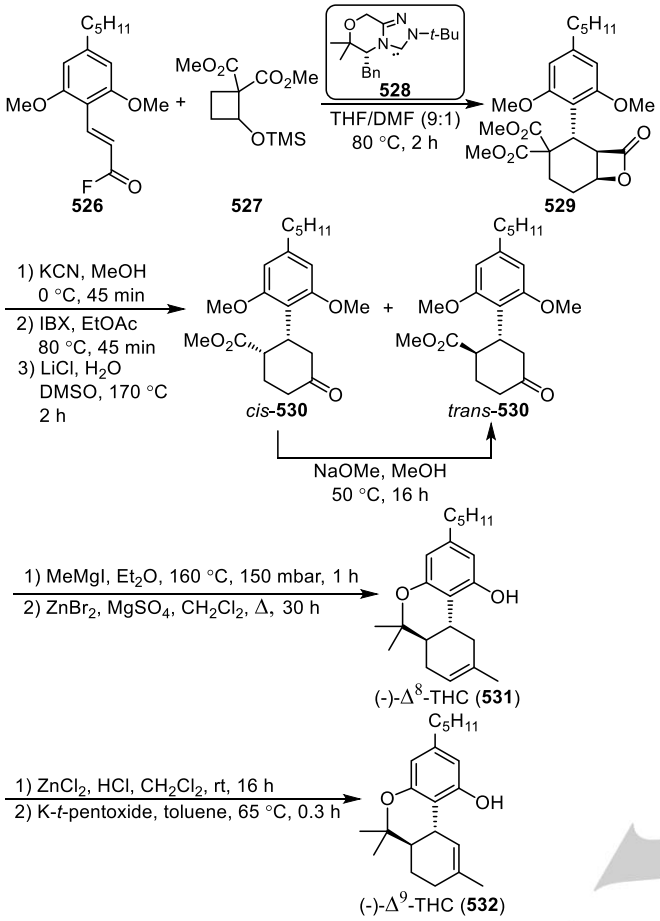


Scheme 54. Total synthesis of farnesin via an organocatalyzed hydroxymethylation reaction (DMP = Dess-Martin periodinane).



Scheme 55. Total synthesis of rauwolscine via an organocatalyzed annulation reaction (LDBBA = lithium diisobutyl-*tert*-butoxyaluminum hydride).

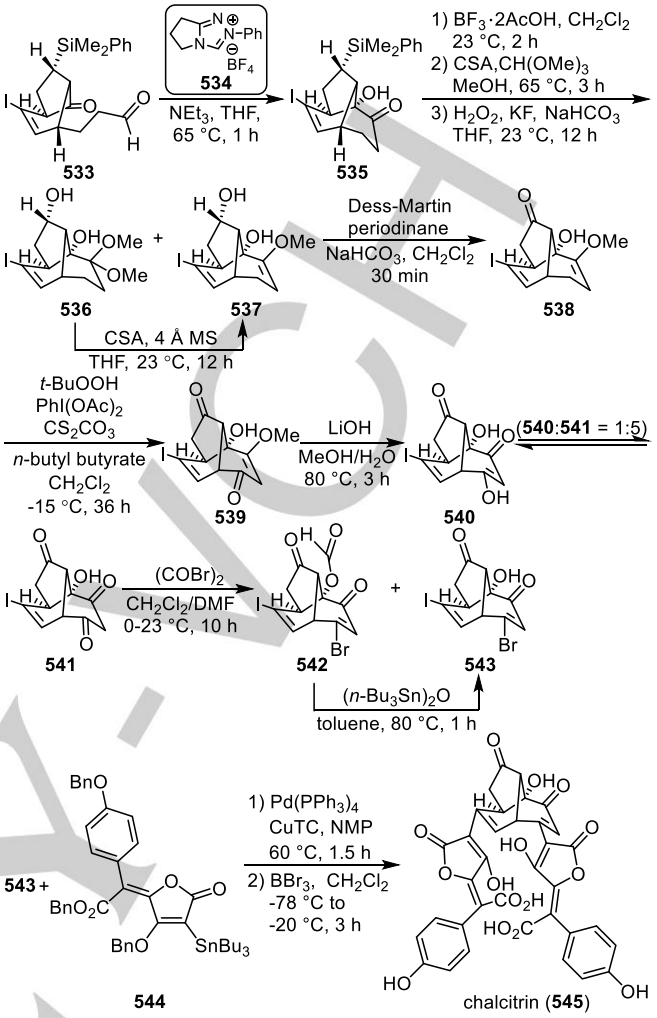
In 2020, Scheidt and co-workers reported total synthesis of rauwolscine (**525**, Scheme 55).[102] The key intermediate for this synthesis, an enantioenriched enol lactone **517**, was obtained by an NHC-catalyzed annulation reaction of the commercially available aldehyde **515**, using **516** as the catalyst. Reacting this compound with **518** yielded the tetracyclic product **519**, Further transformations of **519** afforded intermediate **524**, from which rauwolscine (**525**) was obtained via a SmI_2 reduction. (Scheme 55).[102] From the same intermediate **524**, (-)-alloyohimbane and (-)-17-epirauwolscine were also synthesized. The synthesis is also amenable to access all of the eight stereoisomers of the yohimbines.[102]



Scheme 56. Total synthesis of (−)-Δ9-tetrahydrocannabinol via an organocatalyzed [4+2] annulation reaction.

In 2019, Lupton and Ametovski reported an enantioselective total synthesis of (−)-Δ^9-tetrahydrocannabinol (**532**, Scheme 56).[103] They employed an enantioselective *N*-heterocyclic carbene (NHC)-catalyzed [4+2] annulation of cinnamoyl fluorides **526** and donor-acceptor cyclobutane **527** to access the optically active bicyclic β-lactone **529**, using **528** as the catalyst. Further transformations of **529** afforded a mixture of both diastereomers (*cis*- and *trans*-**530**), for which the *cis*-diastereomer could be further converted to the *trans*-**530** via epimerization. Compound *trans*-**530** was then converted to Δ^8-tetrahydrocannabinol (**531**) and then to (−)-Δ^9-tetrahydrocannabinol (**532**) (Scheme 56).[103]

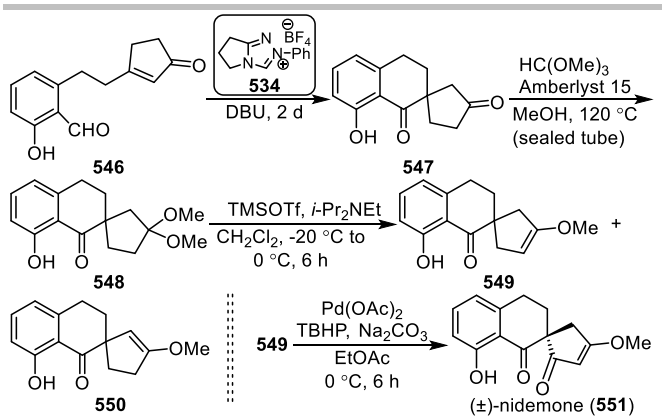
In 2019, Snyder and co-workers reported the total synthesis of chalcitrin (**545**, Scheme 57).[104] The synthesis relies on the successful synthesis of the full carbon framework of the bridged tricyclic core **543**, in which the NHC-catalysis plays a key role. As shown in Scheme 57, the authors first synthesized the optically enriched bicyclic keto-aldehyde compound **533** from cyclohexenone via a multistep sequence.[104] An acyloin addition reaction of this keto-aldehyde catalyzed by *N*-heterocyclic carbene salt **534** yielded the tricyclic compound **535** diastereoselectively, which was then converted compound **543** via further synthetic maneuvers. The assembly of compound **543** with compound **544**, which was synthesized separately, via Pd-catalyzed double Stille couplings followed by deprotection to give chalcitrin (**545**) (Scheme 57).[104]



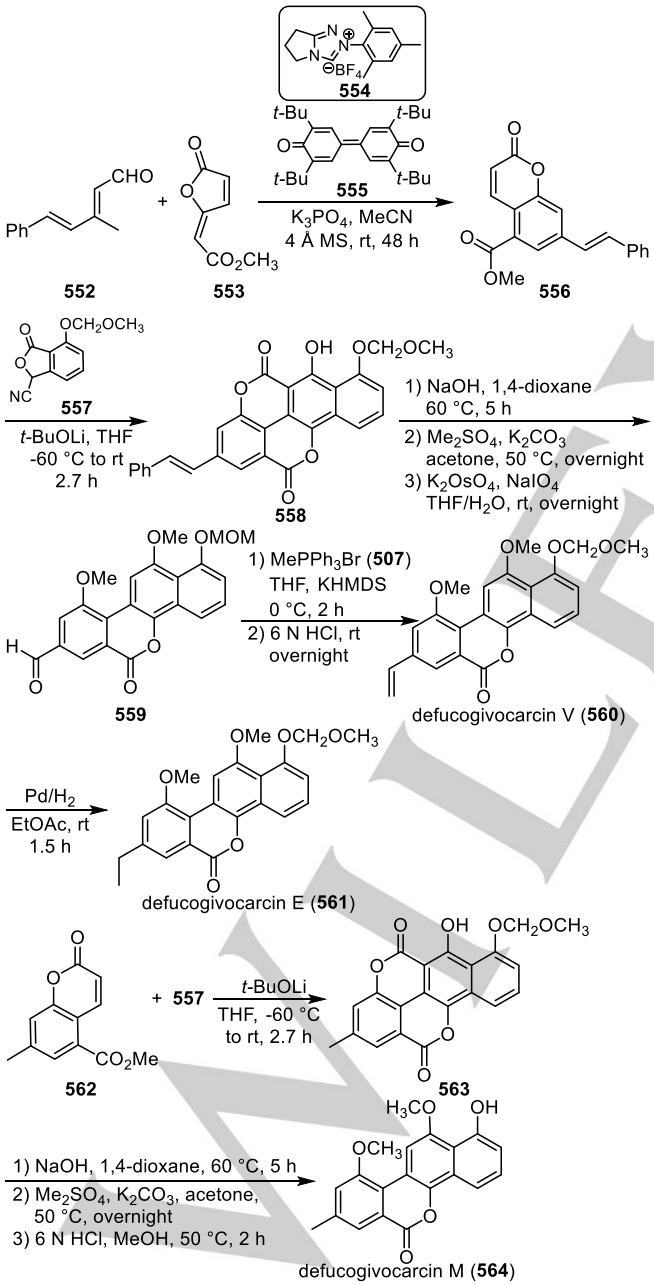
Scheme 57. Total synthesis of chalcitrin via acyloin addition.

In 2018, Hsu and Liou reported a total synthesis of racemic nidemone (**551**, Scheme 58).[105] They demonstrated that an intramolecular Stetter reaction of enone-benzaldehyde **546** catalyzed by the NHC salt catalyst **534** led to the formation of compound **547**, which contains the key spiro core of nidemone. Further transformations afforded racemic nidemone (**551**) via a multistep sequence that included ketal formation, a regioselective elimination, and a Pd-catalyzed regioselective oxidation of the major regioisomer **549** (Scheme 58).[105]

In 2017, Chi and co-workers reported the total synthesis of defucogilvocarcins E (**561**), M (**564**), and V (**560**) (Scheme 59).[106] Compounds **556** and **562**, the key intermediates for the total synthesis of these natural products, were obtained from an NHC-catalyzed formal [5+5] Hauser annulation reaction, using the *N*-heterocyclic carbene salt **554** as the catalyst, as exemplified for synthesis of compound **556**. Further elaborations of compounds **556** and **562** afforded the nature products defucogilvocarcins E (**561**) and V (**560**), and M (**564**), respectively (Scheme 59).[106]

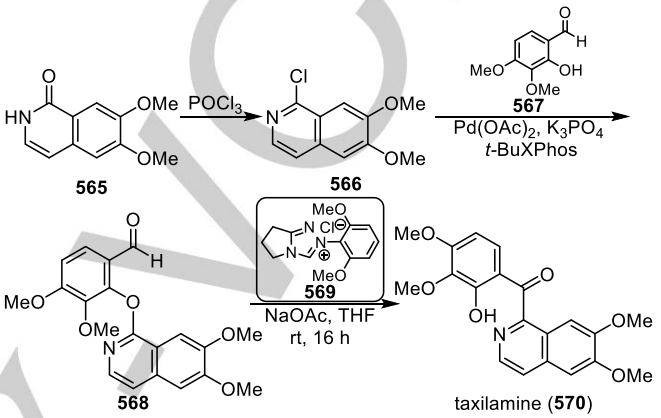


Scheme 58. Total synthesis of (±)-nidemone via an organocatalyzed intramolecular Stetter reaction.



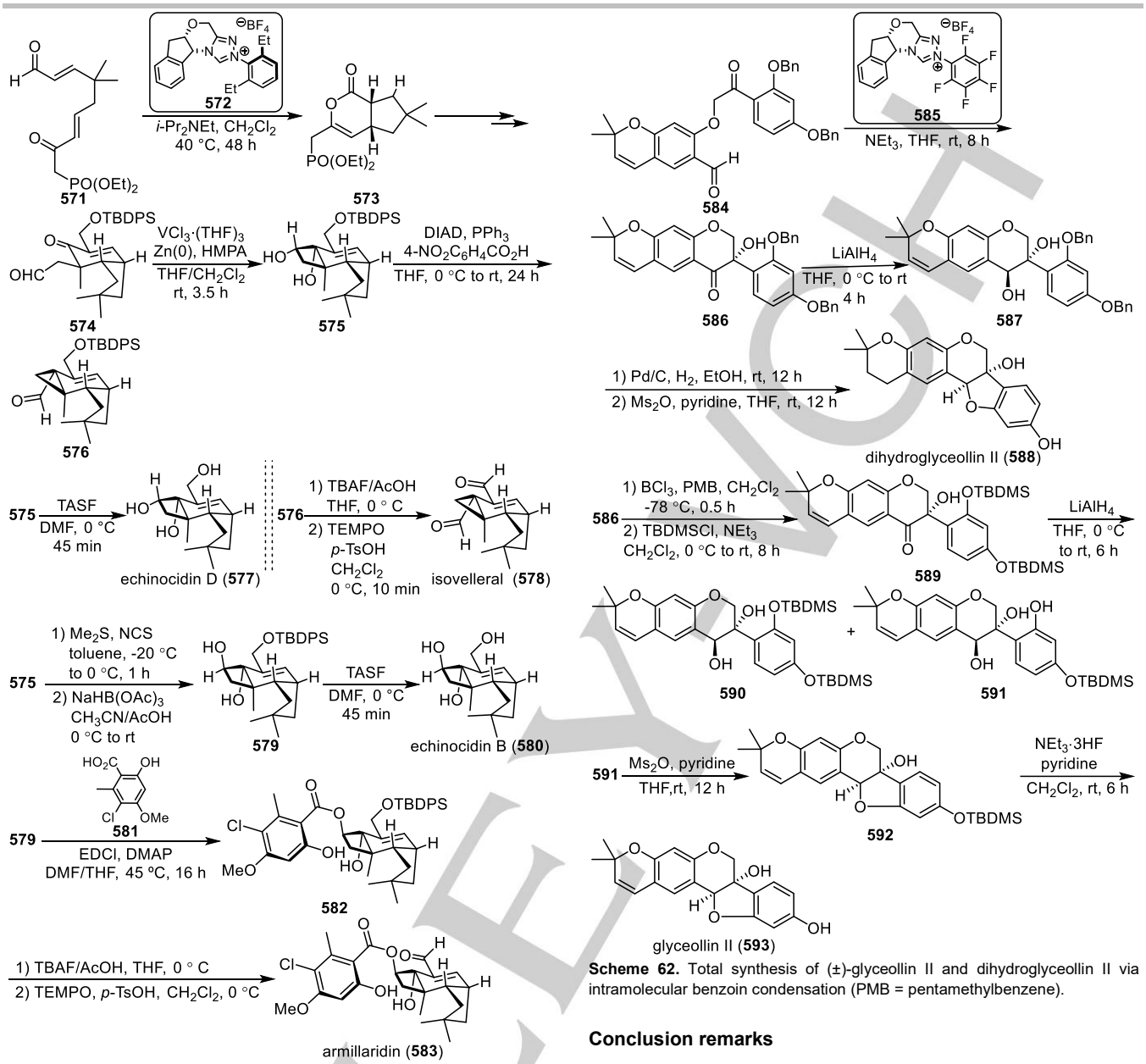
Scheme 59. Total synthesis of defucogilvocarcins via an organocatalyzed formal [5+5] reaction.

In 2017, Glorius and co-workers developed an NHC-catalyzed Truce–Smiles rearrangement of *O*-aryl salicylaldehyde derivatives via the in-situ generated acyl-anion equivalent.[107] As an application of this novel synthetic method, they developed a three-step total synthesis of taxilamine (**570**). As shown in Scheme 60, from compound **565**, the desired *O*-aryl salicylaldehyde derivative **568** was synthesized in just two steps. Finally, a Truce–Smiles rearrangement was carried out under the catalysis of the *N*-heterocyclic carbene salt **569**, which yield the desired natural product **570** in a single step. (Scheme 60).[107]



Scheme 60. Total synthesis of taxilamine via aryl migration and C-H functionalization.

In 2017, Scheidt and co-workers developed a unified strategy for the enantioselective total synthesis of protoilludane, mellolide, and marasmane families of natural products, in which the NHC-catalysis played a key role.[108] As shown in Scheme 61, the annulation reaction of acyclic enone-enal **571** under the catalysis of the *N*-heterocyclic carbene salt **572** led to the formation the vinyl lactone product **573** in a high yield and high stereoselectivities. Further elaborations afforded the tricyclic *cis*-diol **575** and the ring-contracted tricyclic aldehyde **576**, which served as the key intermediates for the total synthesis. De silylation of **575** yielded echinocidin D (**577**), whereas a desilylation of **576** followed by an oxidation led to isovelleral (**578**). Epimerization of **575** led to the *trans*-diol **579**, which yielded echinocidin B (**580**) after desilylation. Coupling **579** with the benzoic acid derivative **581**, followed by desilylation and oxidation, led to the formation of armillaridin (**583**). Among these natural products, echinocidins B (**580**) and D (**577**) belong to the protoilludane family; armillaridin (**583**) belongs to the mellolide family; and isovelleral (**578**) belongs to the marasmane family (Scheme 61).[108]



Scheme 61. Total synthesis of echinocidins B and D, isovelleral, and armillaridin via an organocatalyzed annulation reaction.

In 2015, Erhardt and co-workers reported the total synthesis of (±)-glyceollin II (**593**) and (±)-dihydroglyceollin II (**588**) (Scheme 62).[109] They achieved the synthesis of the key intermediate **586** as a racemate through an NHC-catalyzed intramolecular benzoin condensation reaction of the keto-aldehyde **584**, using the *N*-heterocyclic carbene salt **585** as the catalyst. Reducing the ketone group and saturation of the double bond of **585**, followed by an intramolecular etherification afforded (±)-dihydroglyceollin II (**588**). In a similar manner, glyceollin II (**593**) was synthesized from the selective reduction/deprotection product **591** (Scheme 62).[109]

Scheme 62. Total synthesis of (±)-glyceollin II and dihydroglyceollin II via intramolecular benzoin condensation (PMB = pentamethylbenzene).

Conclusion remarks

As organocatalysis has been established as the third pillar of asymmetric catalysis, it has found more and more applications in the total synthesis of natural products and related compounds. This short review summarizes those cases reported in the last seven years or so where organocatalytic reactions were employed to access the key intermediates of the total synthesis. It is evident from the above summary that organocatalysis is able to construct complex molecules in a highly efficient and stereoselective manner. In addition, almost all types of known organocatalysts have found applications in the total synthesis of natural products, although some of them apparently found more applications than others. In most cases, the disparity was mainly due to the maturity of the specific type of organocatalysts instead of the limitation of these catalysts. Looking forward to the future, we are very confident that organocatalysis will be an indispensable tool for organic chemists working in the total synthesis arena. While we foresee continued applications of the amine catalysts in total synthesis, we believe chiral phosphoric acid catalysis and NHC catalysis will become more and more

popular as these catalytic methods mature. In addition, tandem catalysis and cooperate catalysis involving the use of multiple organocatalysts in one-pot reactions are also very promising.

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Keywords: Asymmetric catalysis · Natural product · Organocatalysis · Total synthesis · Synthetic method

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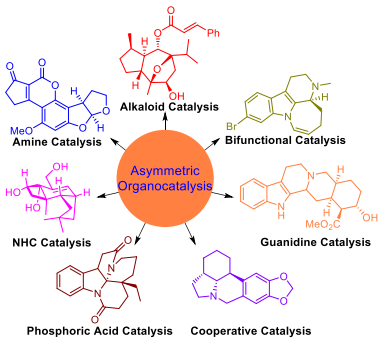
TOC entry



As organocatalysis is now established as the third pillar of asymmetric catalysis, it has found many applications in the total synthesis of natural products. This review summarizes the selected examples reported in the past seven years where organocatalytic methods were employed to achieve the key intermediates for the total syntheses. As is evident from our summary, organocatalysis is able to construct a wide range of important and complex organic structures in a highly efficient and stereoselective manner and it has become an indispensable tool of synthetic chemists.