ARTICLE

Recent Applications of Asymmetric Organocatalytic Annulation Reactions in Natural Products Synthesis

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The past two decades have witnessed remarkable growth of asymmetric organocatalysis, which is now a firmly etabished synthetic tool, serving as a powerful platform for the production of chiral molecules. Ring structures are ubiquitous in organic compounds, and in the context of natural products synthesis, strategic construction of ring motifs is often crucial, fundamentally impacting the eventual fate of the whole synthetic plan. In this review, we provide a comprehensive and updated summary of asymmetric organocatalytic annulation reactions, in particular, the applications of these annulation strategies to natural products synthesis will be highlighted.

1. Introduction

Natural products have played pivotal roles in medicinal chemistry and drug discovery.[1] The molecular architectures of natural products often serve as valuable starting points for drug development. Consequently, there are significant number of drugs and drug candidates having their origin in natural products. With the rapid development of modern organic chemistry, organic synthesis has contributed enormously to biology and medicine, providing opportunities to transform pharmaceutical industry.[2] In the past few decades, the emergence of numerous catalytic asymmetric synthetic strategies empowered the field of natural products total synthesis, greatly accelerating drug discovery processes.[3] Traditionally, asymmetric catalysis was referred to transition metal-mediated catalytic reactions. Organocatalysis, on the other hand, makes use of small organic molecules to catalyze organic reactions, is a relatively new research field. Through the intensive investigations since the turning of this century, asymmetric organocatalysis has gained more and more recognitions as an important tool in asymmetric synthesis,[4] often complementary to well-established powerful methodologies mediated by metals. Compared to transition-metal-mediated processes, organocatalytic reactions are often carried out mild reaction conditions, and they are also more tolerant to air and moisture, being more environmentally benign and less toxic. However, the key drawbacks of organocatalytic reactions include: high catalyst loading, less efficient reaction, and limited modes of activation.

Annulation reactions are synthetically valuable, representing a powerful strategy for the construction of cyclic molecular frameworks. Given the ready availability of chiral organic catalysts, as well as their high efficiency and convergence in promoting a diverse range of ring-forming reactions, asymmetric organocatalytic annulation reactions have found wide applications in natural products synthesis. An annulation reaction, by IUPAC definition, is a transformation that involves fusion of a new ring to a molecule via two new bonds.[5] An annulation is very different from a cyclization reaction, which refers to the transformation of a chain structure to a ring motif via a new bond-forming event. In this review, we will be discussing a number of classic reactions, including Diels–Alder reaction, Robinson annulation, Pictet–Spengler reaction, among others. In addition, various cascade processes that fit in the above definition of an annulation reaction are also the topic of our discussion. Different cascade sequences, for instance Michael/Michael cascade, tandem Michael/aldol, will be elaborated in the subsequent sections. We will be organizing our review based on different types of annulation reactions, from more common [4+2], [3+2], [3+3] annulations, to less common [5+1], [4+3], [2+2] annulation reactions. Within each mode of annulation, we will be arranging our discussion based on different types of catalysts employed for the reaction activations. Figure 1 summarizes all the organic catalysts utilized in the studies that have been described in this review. Among Brønsted acid catalysts, chiral phosphoric acids and thioureas are the most common and extensively used catalyst classes. Squaramides also found wide applications in different annulation reactions. From a mechanistic viewpoint, Brønsted acid catalysts rely on non-covalent interactions between the catalyst and the substrate, which can be generally referred to hydrogen-bonding catalysis. Among Lewis base catalysts, amines are most widely employed, phosphine catalysts, on the hand, are less common. Mechanistically, Lewis base catalysts

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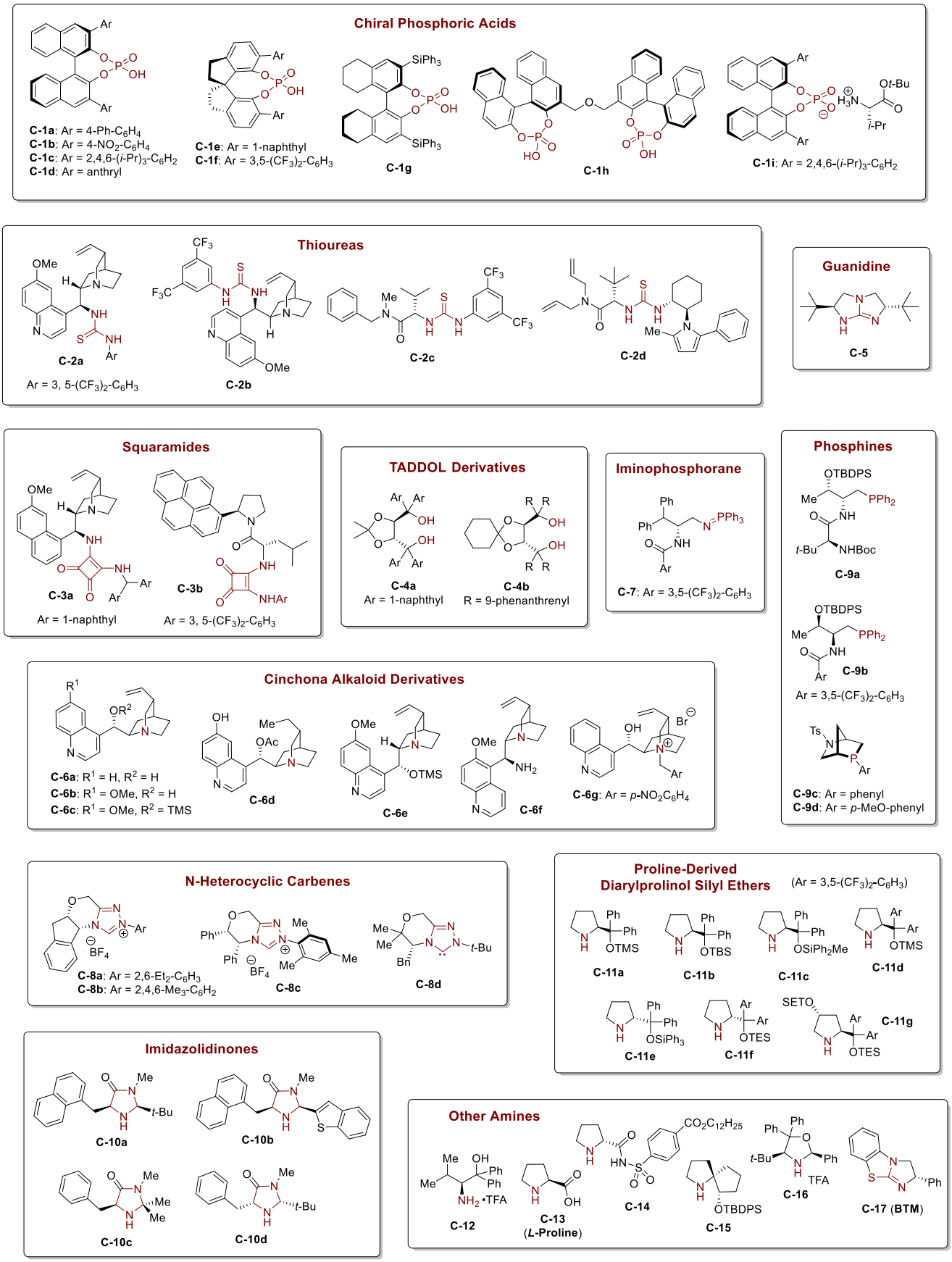


Figure 1 A collection of organic catalysts utilized in studies described in this review.

mostly form active species via a covalent bond formation, termed as covalent catalysis. Specifically, major activation modes that will be described in the following sections include: enamine catalysis, iminium catalysis, nucleophilic catalysis, *N*-hetereocyclic carbine (NHC) catalysis, and counterion catalysis (including phase-transfer catalysis), among others.[6]

There were a few early review articles summarizing applications of organocatalytic reactions in total synthesis, which were either relatively specific, for instance focusing on cascade reactions, or less comprehensive.[7] Over the years, many excellent review articles on asymmetric organocatalytic reactions for the natural products total synthesis were published, and those articles were organized according to the catalytic modes of reactions reported, or organic catalysts utilized in the reaction, or certain reaction types. Specifically, the following topics relating to total synthesis were reviewed: Brønsted acid catalysis,[8] covalent catalysis,[9] NHC catalysis,[10] phosphine catalysis,[11] secondary amine catalysis,[12] diarylprolinol silyl ethers-enabled catalysis,[13] proline catalysis,[14] bifunctional catalysis,[15] Michael and Friedel–Crafts reactions.[16] In addition, a number of other review articles were dedicated to the synthesis of target natural product classes e.g. indole alkaloids,[17] and tetrahydropyrans and related natural products,[18] by riding on the power of organocatalytic reaction methods.

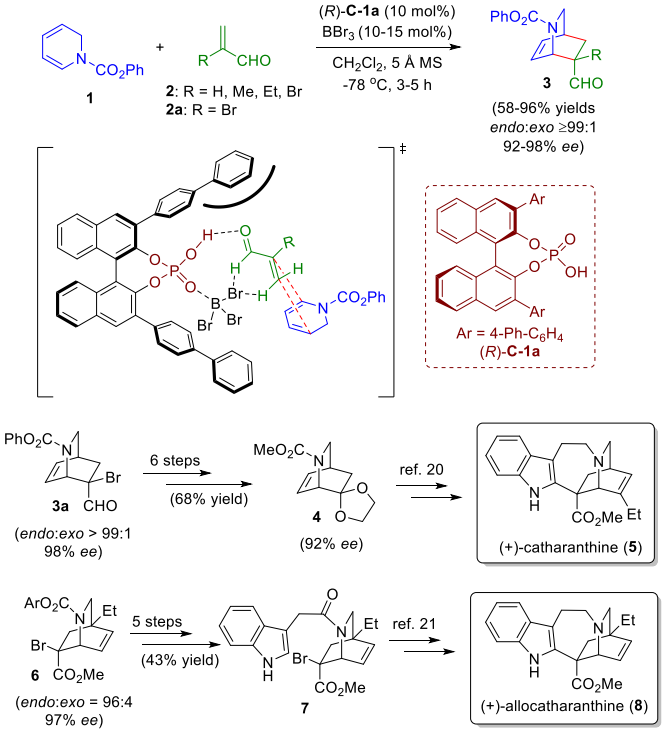
Given the power and efficiency of asymmetric organocatalytic annulation reactions in constructing ring structures, and their remarkable applications in natural products synthesis, a comprehensive review summarizing recent progress in organic catalyst-empowered enantioselective annulation reactions and related applications in the total synthesis of natural products is timely and highly desirable. In this review, we compile literature examples from 2011 to 2020, and attempt to provide a panoramic view of this interesting research topic. We hope this review will provide our readers an updated broad picture of this exciting research field, inspiring practitioners to further develop novel annulation strategies enabling creative and practical synthesis of complex natural products.

2. [4+2] Annulation

The [4+2] annulation reaction represents a powerful direct approach for the construction of 6-membered carbon- and hetero-cyclic compounds. The Diels–Alder reaction, despite being discovered almost a century ago, is still one of the most important reactions for building 6-membered ring structures. Other than the commonly employed dienes, alkenes, and alkynes, α,β-carbonyls and *o*-quinone methides have also been employed for oxo-Diels–Alder reaction. With the advent of organic catalysis, a range of formal [4+2] annulations have been developed, often consisting of domino reaction processes. Whereas the Michael addition is often a designated reaction process, its combination with other reactions, e.g. aldol condensation, acetalization, Mannich reaction, and Friedel–Crafts reaction, renders the resulting formal [4+2] annulations amazing power, allowing for efficient creation of a wide variety of structural motifs. Yet, another group of less common [4+2] annulation reactions involved NHC catalysis. In our following discussions, we shall describe different types of [4+2] annulations in detail.

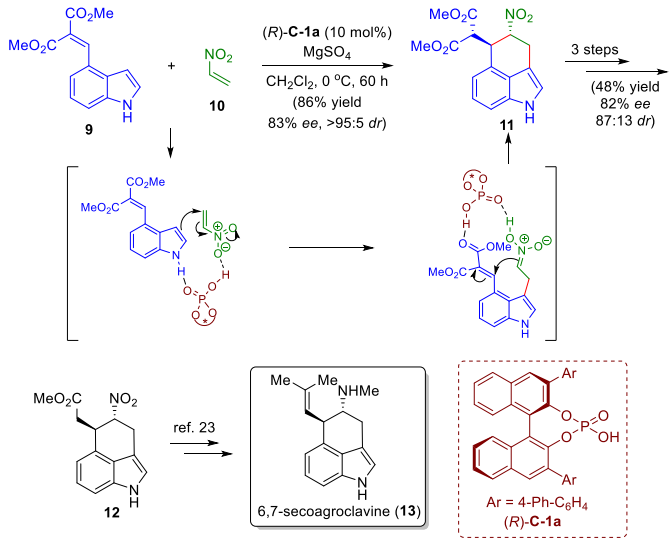
2.1 Catalysis with chiral phosphoric acid

In 2015, the Ishihara group developed a BBr_3-assisted chiral phosphoric acid (*R*)-**C-1a** catalyzed enantioselective Diels–Alder reaction between 1,2-dihydropyridine **1** and α-substituted acroleins **2**.[19] Acroleins bearing different substituents at the 2-position such as methyl, ethyl, and bromine could be used, and the bridged cyclic amines **3** were obtained in moderate to high yields (58–96%) and with excellent enantioselectivities (92–98%) (Scheme 1). The [4+2] annulation products obtained were shown to be valuable in the total synthesis of natural products. Cyclic amine **3a** was elaborated in six steps to form the key intermediate **4**, which can be transformed into (+)-catharanthine (**5**) following the literature procedures reported by Doris et al.[20] In comparison with Doris' approach, the Ishihara synthesis is more efficient and was completed in shorter reaction sequence, although the enantiomeric excess of the product was slightly inferior. In another application, key intermediate **7** was formed via a five-step reaction sequence from **6**, which was synthesized via a Diels–Alder reaction between ethyl-substituted dihydropyridine and 2-bromoacrylaldehyde **2a** with (*S*)-**C-1a** as the catalyst. The formal total synthesis of (+)-allocatharanthine (**8**) was thus established, following procedures reported[21] by the Szántay group.



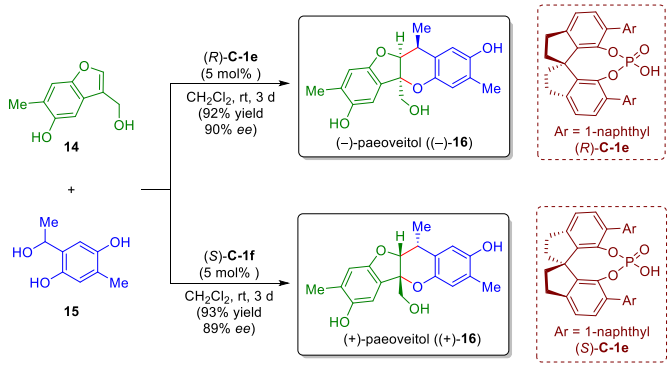
Scheme 1 BBr_3-assisted phosphoric acid-catalyzed Diels–Alder reaction and the formal synthesis of (+)-catharanthine and (+)-allocatharanthine (Ishihara, 2015).

Santoro, Fochi, Bernardi, and co-workers developed formal [4+2] annulation reaction between indole **9** and nitroalkene **10** via a phosphoric acid-catalyzed domino Friedel–Crafts/Michael process, which furnished tricyclic **11** in 86% yield with 83% *ee* and >95:5 *dr* (Scheme 2).[22] The transformation of **11** into key intermediate **12** was completed in one-pot via a three-step sequence, and the latter could be transformed into 6,7-secoagroclavine (**13**) following Somei et al.'s early report.[23]



Scheme 2 Domino Friedel–Crafts/nitro-Michael catalyzed by phosphoric acid and formal synthesis of 6,7-secoagroclavine (Santoro, Fochi, Bernardi, 2015).

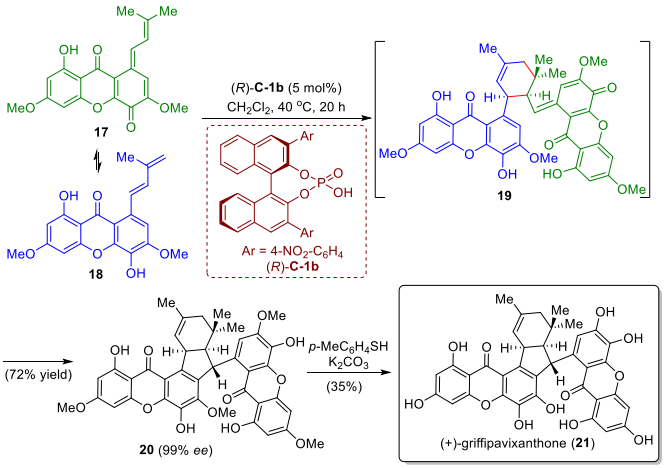
(±)-Paeoveitol (**16**) is a pair of new norditerpene enantiomers isolated from the root of *Paeonia veitchii*, a well-known Chinese medicine.[24] The Chen group accomplished the first asymmetric total synthesis of (+)-paeoveitol and (−)-paeoveitol.[25] The key step of the synthesis is a chiral phosphoric acid ((*R*)-**C-1e**)-catalyzed oxo-Diels–Alder reaction. Paeoveitol D (**14**) was reacted with *o*-quinone methide (*o*-QM), generated *in situ* from compound **15**, to give the (−)-paeoveitol ((−)-**16**) in 92% yield with 90% *ee*. Similarly, (+)-paeoveitol ((+)-**16**) was prepared with the employment of (*S*)-**C-1e** as the catalyst (Scheme 3).



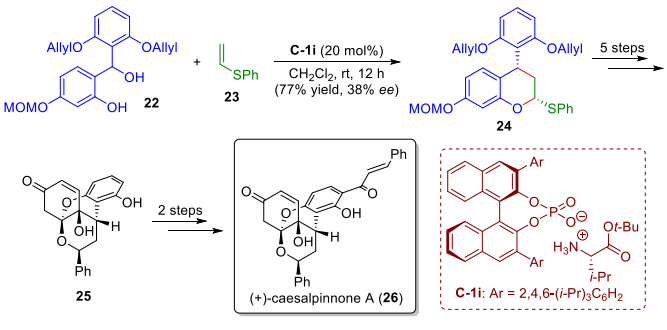
Scheme 3 The oxo-Diels–Alder reaction and total synthesis of (+)-paeoveitol and (−)-paeoveitol (Chen, 2017).

Schaus, Porco, and co-workers reported the total synthesis of (+)-griffipavixanthone (**21**) via dimerization of a *p*-quinone methide using a chiral phosphoric acid catalyst (**C-1b**).[26] The Diels–Alder reaction between *p*-quinone methide **17** and its tautomer **18** formed the key precursor, dimer **20**, in 72% yield with 99% *ee*. Finally, global demethylation afforded (+)-griffipavixanthone (**21**) in 35% yield. Mechanistic studies confirmed that the formation of syncyclohexene moiety (intermediate **19**) is the enantiodetermining step (Scheme 4).

(+)-Caesalpinnone A (**26**) is a flavan-chalcone hybrid isolated from *Caesalpinnea enneaphylla*, and has displayed anticancer activities.[27] Recently, the Zheng group accomplished the total synthesis of (+)-caesalpinnone A.[28] The key reaction is the construction of flavonoid skeleton through an asymmetric oxo-Diels–Alder reaction. In the presence of a chiral phosphoric acid catalyst (**C-1i**), diol **22** was converted *in situ* into *o*-quinone methide (*o*-QM), which underwent annulation with phenyl vinyl sulfide **23** to give benzodihydopyran **24** in 77% yield with 38% *ee*. The bridged ketal **25** was next synthesized via a five-step reaction sequence, including palladium-catalyzed deallylation and oxa-Michael addition. Subsequently, selective phonolic esterification and photo-Fries rearrangement then completed the total synthesis of (+)-caesalpinnone A (**26**) (Scheme 5).



Scheme 4 Total synthesis of (+)-griffipavixanthone via dimerization of a *p*-quinone methide (Schaus, Porco, 2019).

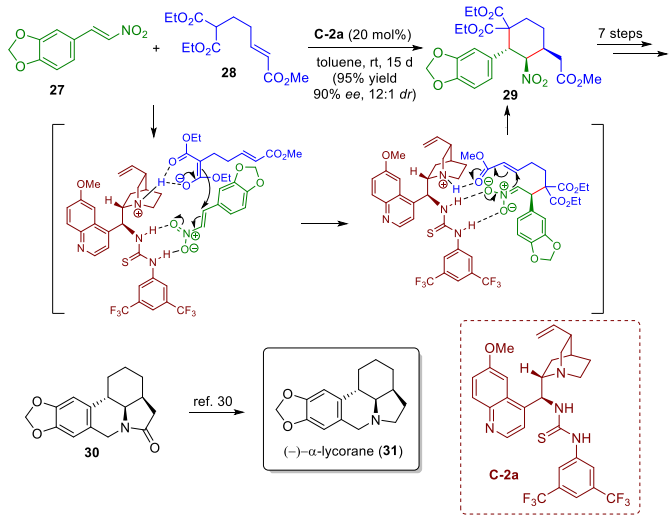


Scheme 5 Total synthesis of (+)-caesalpinnone A (Zheng, 2020).

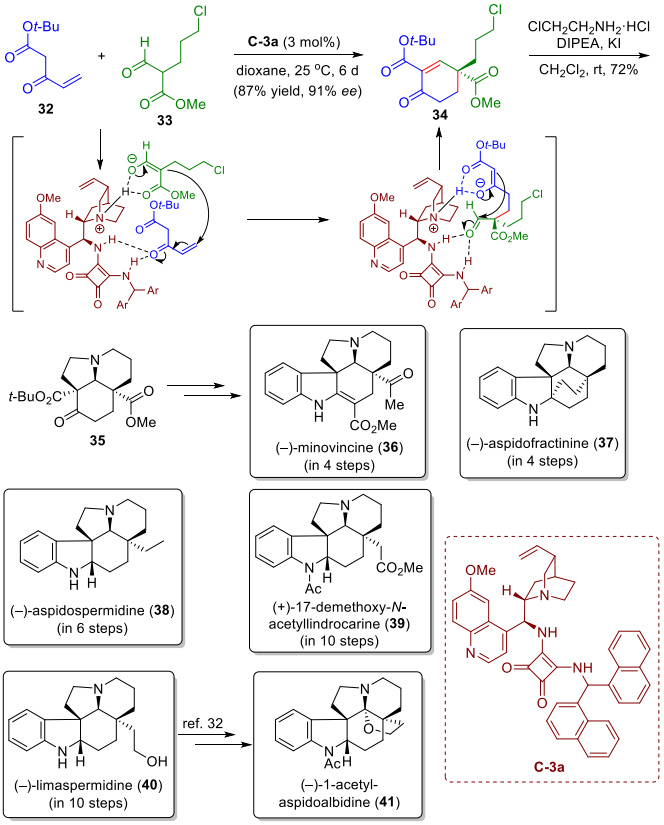
2.2 Catalysis with bifunctional tertiary amine-thiourea/ squaramide

The Xu group designed a double Michael cascade reaction for the construction of the tetracyclic core of lycorine-type alkaloid, and accomplished the formal synthesis of (–)-α-lycorane (**31**).[29] Employing cinchona alkaloid derived bifunctional tertiary amine-thiourea **C-2a**, the cascade Michael/Michael reaction between nitroalkene **27** and unsaturated ester **28** led to the formation of nitrocyclohexane **29** in 95% yield with 90% *ee* and 12:1 *dr*. The annulation product **29** was elaborated into advanced lactam **30** through seven trivial reaction steps, and the final reduction with $LiAlH_4$ as reported in the literature[30] completed the formal total synthesis of (–)-α-lycorane (**31**) (Scheme 6).

Very recently, Soós and co-workers achieved divergent asymmetric total syntheses of *aspidosperma* alkaloids.[31] The formation of key intermediate relied on an organocatalytic Robinson annulation reaction. In the presence of quinine-squaramide **C-3a**, the cascade Michael/aldol condensation between Nazarov reagent **32** and ω-chloro-formylpentenoate **33** took place smoothly and furnished the anticipated enone **34** in 87% yield with 91% *ee*, notably at 100 g reaction scale. Subsequently, a nucleophilic cascade strategy was employed to form the key tricyclic aminoketone **35**. The authors established that the tricyclic ketone **35** could serve as a key common intermediate, leading to the total syntheses of (–)-minovincine (**36**), (–)-aspidofractinine (**37**), (–)-aspidospermidine (**38**), (+)-17-demethoxy-*N*-acetyllindrocarine (**39**), and (–)-limaspermidine (**40**). Moreover, (–)-limaspermidine was transformed through two established steps[32] into (–)-1-acetylaspidoalbidine (**41**) (Scheme 7).



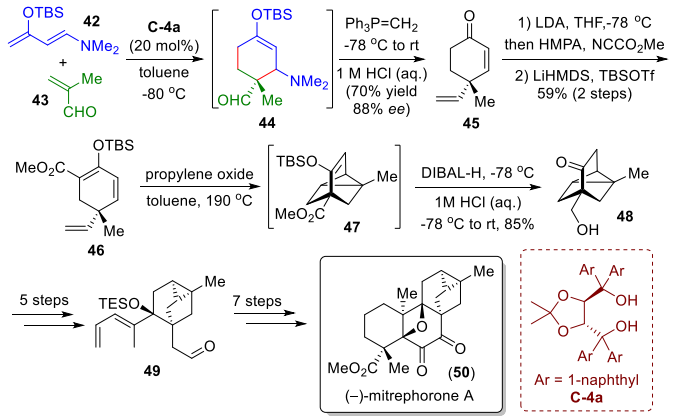
Scheme 6 Double Michael cascade and the formal synthesis of (–)-α-lycorane (Xu, 2012).



Scheme 7 Cascade Robinson annulation and divergent total syntheses of a range of *aspidosperma* alkaloids (Soós, 2020).

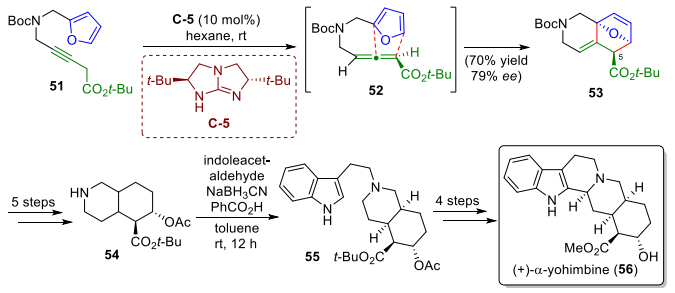
2.3 Catalysis with TADDOL derivative

(–)-Mitrephorone A (**50**) was isolated from the Bornean shrub *Mitrephora glabra*, and has shown promising antimicrobial activities.[33] Structurally, (–)-mitrephorone A contains a fully substituted oxetane embedded in a pentacyclic carbon skeleton as well as the tricyclo[3.2.1.$0^{2,7}$]-octane scaffold, making its synthesis highly challenging. In 2018, the Carreira group disclosed the first total synthesis of (–)-mitrephorone A, and the key feature of the synthesis is an efficient assembly of all carbocycles by three [4+2] annulations.[34] The synthesis commenced with a TADDOL-catalyzed Diels–Alder reaction between Rawal's diene **42** and methacrolein **43**, affording cyclohexene intermediate **44**, which was transformed into unsaturated ketone **45** in 70% yield with 88% *ee* via a Wittig reaction. Introduction of a methyl ester and subsequent TBS protection furnished triene **46**, which set the stage for the intramolecular cycloaddition, affording tricyclooctane **47** as a single product. Reduction with DIBAL-H then formed the key hydroxyketone intermediate **48**. Synthetic elaborations of tricyclooctane core were followed, and aldehyde **49** was then obtained. The subsequent reaction of **49** with lithiated alkyne set the stage for another Diels–Alder reaction, creating the core structural motif. Finally, a few trivial synthetic manipulations completed the total synthesis of mitrephorone A (**50**) (Scheme 8).



Scheme 8 TADDOL-catalyzed Diels–Alder reaction and the first total synthesis of (–)-mitrephorone A (Carreira, 2018).

2.4 Catalysis with chiral bicyclic guanidine

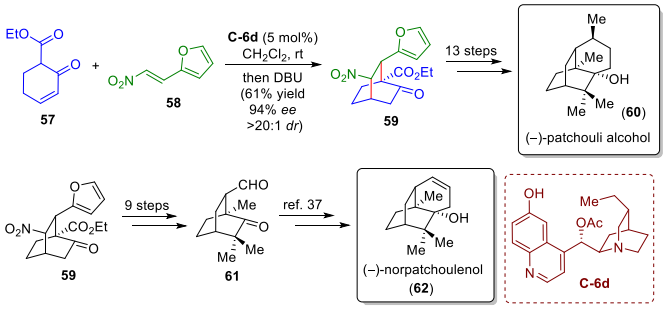


Scheme 9 Tandem isomerization/intramolecular-Diels–Alder reaction and the total synthesis of (+)-α-yohimbine (Tan, 2016).

The Tan group devised a bicyclic guanidine-catalyzed asymmetric tandem isomerization/intramolecular-Diels–Alder reaction, and accomplished the first catalytic enantioselective total synthesis of (+)-α-yohimbine (**56**).[35] In the presence of bicyclic guanidine **C-5**, alkynyl amine **51** was isomerized to a chiral allene **52**, which underwent intramolecular Diels–Alder reaction to afford adduct **53** in 70% yield with 79% *ee*. Key intermediate **54** was derived from **53** via a five-step reaction sequence. At last, reductive amination with indoleacetaldehyde, followed by a few standard operations completed the total synthesis of (+)-α-yohimbine (**56**) (Scheme 9).

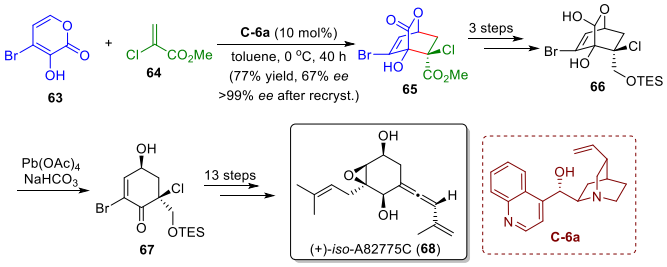
2.5 Catalysis with cinchona alkaloid derivatives

The Sun group reported an asymmetric total synthesis of (−)-patchouli alcohol (**60**) and a formal total synthesis (−)-norpatchoulenol (**62**).[36] Since both natural products possess a tricyclo-[5.3.1.0^{3,8}]undecane skeleton, the authors developed an efficient asymmetric synthesis of common key intermediate. In the presence of quinidine derivative **C-6d**, a cascade Michael/Michael reaction between enone **57** and nitroolefin **58** took place smoothly, leading to the formation of bicyclo[2.2.2]octane **59** in 61% yield with 94% *ee*. Subsequently, elaboration of **59** completed the total synthesis of (−)-patchouli alcohol (**60**). Alternatively, **59** could be transformed into advanced intermediate **61**, which could be further elaborated to (−)-norpatchoulenol (**62**) by following known procedures[37] in the literature (Scheme 10).



Scheme 10 Formal [4+2] annulation catalyzed by cinchona alkaloid and the total synthesis of (−)-patchouli alcohol and (−)-norpatchoulenol (Sun, 2017).

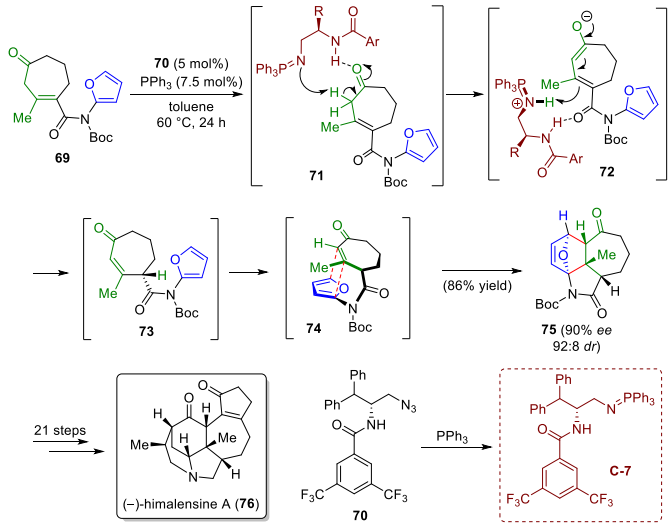
(+)-*Iso*-A82775C (**68**) was isolated from the plant endophytic fungus *Pestalotiopsis fici*.[38] The first enantioselective total synthesis of (+)-*iso*-A82775C was achieved by Suzuki, Tanino, and their co-workers.[39] The key step of the reaction is a Diels–Alder reaction between pyrone **63** and methyl 2-chloroacrylate **64**, catalyzed by cinchonine (**C-6a**). The *endo* product **65** was obtained with 67% *ee*, and further improved to >99% *ee* after recrystallization. With the key intermediate **67** in hand, through routine structural elaborations, the authors achieved the total synthesis of (+)-*iso*-A82775C (Scheme 11).



Scheme 11 The Diels–Alder reaction of pyrone and the total synthesis of (+)-*iso*-A82775C (Suzuki, Tanino, 2017).

2.6 Catalysis with iminophosphorane

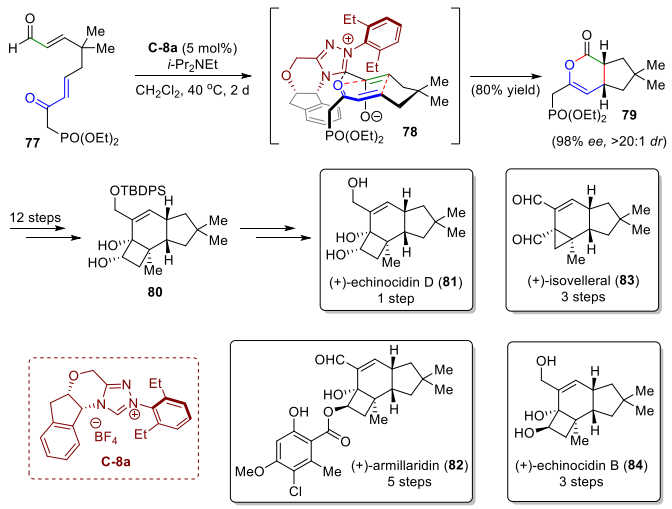
The first asymmetric total synthesis of (−)-himalensine A (**76**) was accomplished by Paton, Dixon, and co-workers.[40] Pivotal to their synthetic strategy is the enantioselective construction of the key 5,6,7-tricyclic core structure, which was formed via a prototropic shift, followed by an intramolecular Diels–Alder reaction. When *N*-Boc protected furan **69** was treated with a chiral bifunctional iminophosphorane superbase **C-7**, which was *in situ* derived from pre-catalyst **70**, a prototropic shift took place to form intermediate **73**. Subsequently, an enantio- and diastereoselective intramolecular Diels–Alder enabled the creation of tricyclic core **75** in 86% yield with 90% *ee* and 92:8 *dr*. The tone for the total synthesis was well set, and the key intermediate **75** was transformed into (−)-himalensine A (**76**) in multi-step synthetic manipulations (Scheme 12). It is noteworthy that the super basic iminophosphorane catalyst **C-7** effectively facilitated facile proton abstraction, which was believed to the key to the success of described synthetic strategy. In comparison, when cinchona alkaloid catalysts (20 mol%) were employed, the reactions required 7 days to reach similar yields.



Scheme 12 Total synthesis of (−)-himalensine A (Paton, Dixon, 2017).

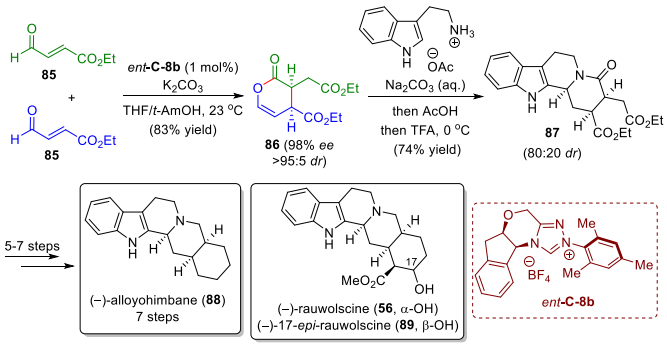
2.7 Catalysis with *N*-heterocyclic carbenes

The Scheidt group accomplished divergent enantioselective total syntheses of various sesquiterpenoids, i.e. (+)-echinocidin D (**81**), (+)-armillaridin (**82**), (+)-isovelleral (**83**), and (+)-echinocidin B (**84**).[41] The key to their successful syntheses was a chiral NHC-catalyzed intramolecular [4+2] annulation of acyclic achiral enal **77** to construct the *cis*-fused cyclohexyl/cyclopentyl ring skeleton **79**. NHC pre-catalyst **C-8a** was used in the reaction to induce asymmetry, and the computational studies revealed that the NHC tended to interact with the enone oxygen through electrostatic attraction, to form a formal Diels–Alder transition state (**78**), leading to the formation of *cis*-fused product. The key bicyclic lactone **79** was obtained in 80% yield with 98% *ee*. The eventual divergent syntheses of sesquiterpenoids all made use of a common 1,2-cyclobutanediol intermediate **80**, which was derived from **79** using an intramolecular pinacol reductive coupling strategy. Impressively, starting from cyclobutanediol **80**, all the target natural products were synthesized in less than five reaction steps (Scheme 13).



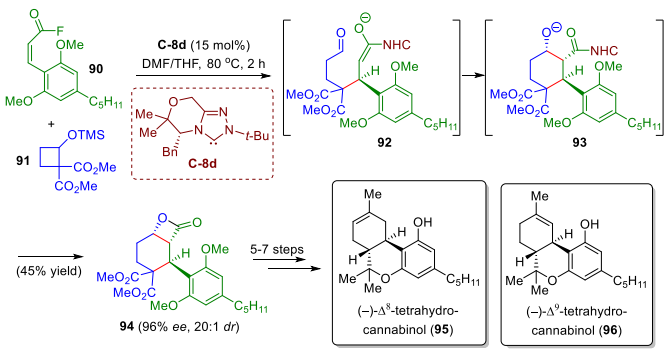
Scheme 13 NHC-catalyzed [4+2] annulation and divergent total syntheses of sesquiterpenoids (Scheidt, 2017).

Very recently, the Scheidt group disclosed a concise enantioselective approach for the synthesis of yohimbine alkaloids, utilizing a chiral NHC-catalyzed intermolecular [4+2] annulation of ethyl (*E*)-4-oxobut-2-enoate **85** as the key transformation.[42] In the presence of 1 mol% of pre-catalyst *ent*-**C-8b**, the dimerization of **85** took place via an NHC-catalyzed formal [4+2] annulation to furnish the key enol lactone **86** in 83% yield with 98% *ee*. Treatment of enol lactone **86** with tryptamine triggered the amidation/*N*-acyliminium ion cyclization sequence to deliver tetracyclic lactam **87** in 74% yield with 80:20 *dr*. Lactam **87** was readily transformed in short reaction sequences into target natural products, i.e. (−)-alloyohimbane (**88**), (−)-rauwolscine (**56**) and (−)-17-*epi*-rauwolscine (**89**) (Scheme 14).



Scheme 14 NHC-catalyzed dimerization and total synthesis of (−)-alloyohimbane, (−)-rauwolscine and (−)-17-*epi*-rauwolscine (Scheidt, 2020).

In 2019, the Lupton group reported the total syntheses of (−)-Δ^8 and Δ^9-tetrahydrocannabinol (**95** & **96**).[43] The key transformation is an NHC (**C-8d**)-catalyzed [4+2] annulation between cinnamoyl fluoride **90** and cyclobutene **91**. This formal [4+2] annulation started with cyclobutene ring-opening reaction, which added to NHC-activated enone to generate intermediate **92**. The subsequent intramolecular aldol-type reaction then formed intermediate **93**. Subsequently, lactonization delivered cyclohexyl β-lactone **94** in overall 45% yield with 96% *ee* and 20:1 *dr*. With the key precursor **94** in hand, (−)-Δ^8-tetrahydrocannabinol (**95**) was synthesized in five steps, and further two-step sequence completed the total synthesis of (−)-Δ^9-tetrahydrocannabinol (**96**) (Scheme 15).

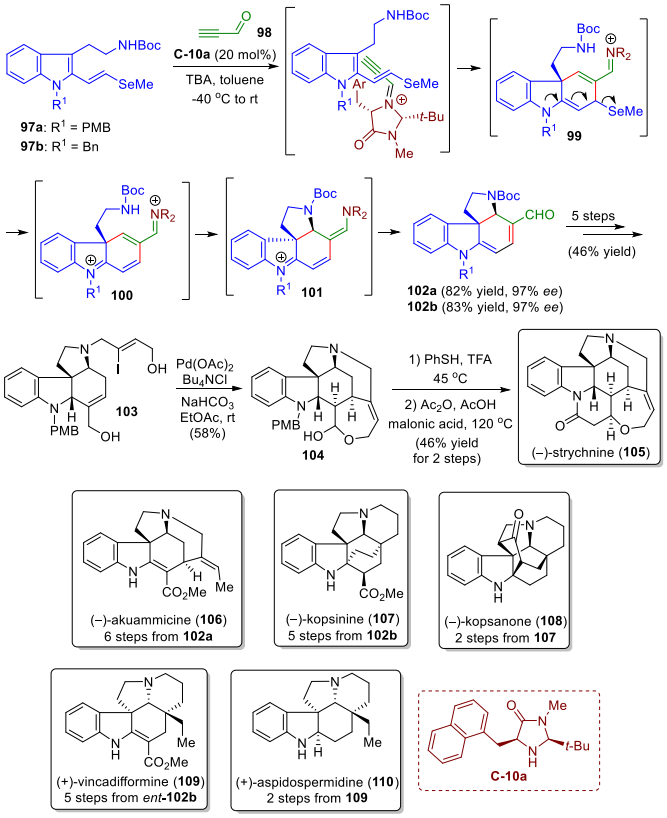


Scheme 15 Enantioselective total syntheses of (−)-Δ^8- and (−)-Δ^9-tetrahydrocannabinols (Lupton, 2019).

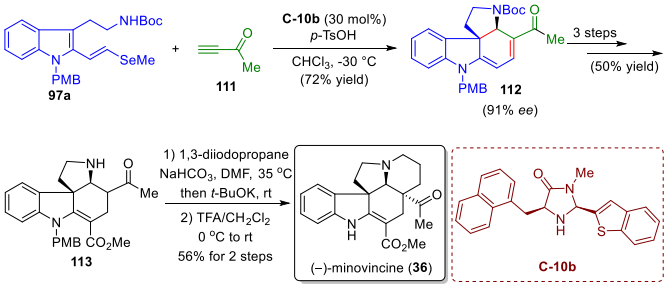
2.8 Catalysis with imidazolidinones

The MacMillan group devised an organocascade catalytic sequence, which led to the collective enantioselective total syntheses of *strychnos*, *aspidosperma*, and *kopsia* families of alkaloids.[44] Exposing tryptamine **97** and propynal **98** in the presence of imidazolidinone **C-10a** resulted in an *endo*-selective Diels–Alder reaction, forming adduct **99**. The subsequent β-elimination of methyl selenide and conjugate addition then delivered the key tetracyclic spiroindoline intermediate **102** in high yield with 97% *ee*. Through a few standard transformations, **102a** was elaborated into vinyl iodide **103**. The successful Jeffery–Heck cyclication/lactol formation then formed Wieland–Gumlich aldehyde **104**. Finally, cleavage of PMB group and heating in a mixture of malonic acid, acidic anhydride and sodium acetate completed the total synthesis of (–)-strychnine (**105**). Using the common intermediate **102**, the authors also accomplished the total syntheses of a number of alkaloids, i.e. (–)-akuammicine (**106**), (–)-kopsinine (**107**), (–)-kopsanone (**108**), (+)-vincadifformine (**109**), and (–)-aspidospermidine (**110**) within eight steps (Scheme 16).

The MacMillan group subsequently extended their cascade sequence of Diels–Alder reaction/elimination/conjugate addition to include ketone dienophile.[45] In the presence of catalyst **C-10b** and co-catalyst *p*-TsOH, the projected cascade reaction worked well and led to the formation of enantiomerically enriched key tetracyclic core structure **112** in 72% yield with 91% *ee*. A few trivial reaction steps then delivered natural product (–)-minovincine (**36**), which was formed in a yield of 13% for an overall nine-step sequence (Scheme 17).

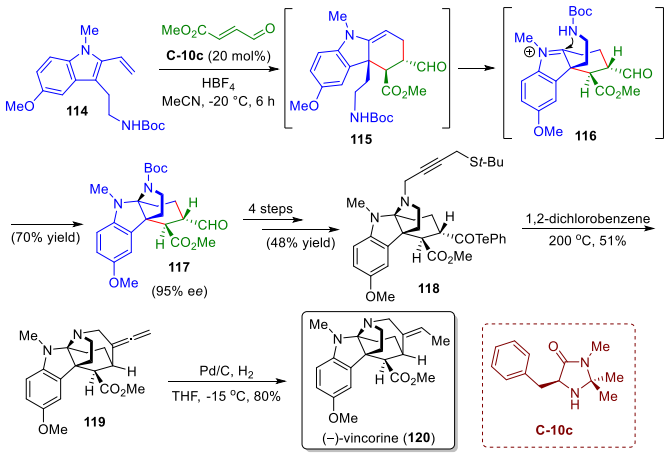


Scheme 16 Organocascade catalysis and collective asymmetric total syntheses of *strychnos*, *aspidosperma*, and *kopsia* alkaloids (MacMillan, 2011).



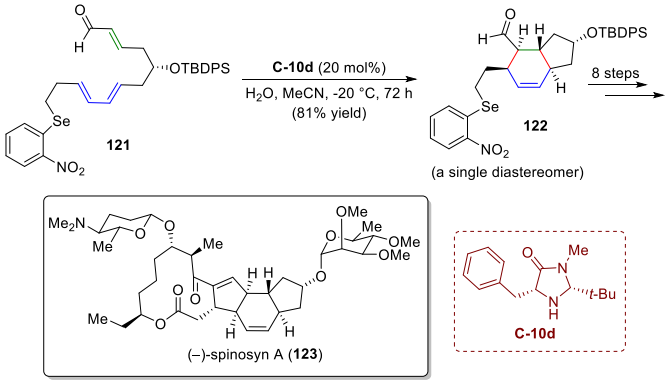
Scheme 17 Total synthesis of (–)-minovincine via an organocascade sequence employing ketone substrate (MacMillan, 2013).

In a similar fashion, MacMillan and co-workers achieved the total synthesis of (–)-vincorine (**120**), relying on a cascade Diels–Alder reaction/cyclization strategy to construct the core intermediate.[46] The iminium formation with imidazolidinone activated enal substrate, enabling a Diels–Alder reaction with indole derivative **114** to take place, delivering stereoselective *endo* adduct **115**. Brønsted acid-catalyzed enamine to iminium interconversion, followed by an intramolecular amine cyclization afforded the key tetracyclic intermediate **117** in 70% yield with 95% *ee*. Further elaborations into (–)-vincorine (**120**) required a six-step reaction sequence, including a crucial radical cyclization (Scheme 18).



Scheme 18 The Diels–Alder/iminium cyclization cascade and total synthesis of (–)-vincorine (MacMillan, 2013).

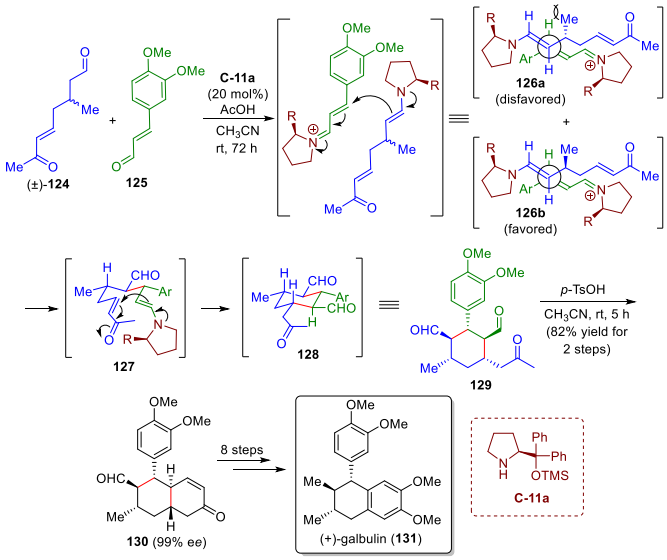
The Dai group accomplished the total synthesis of (–)-spinosyn A (**123**), a major component of insecticide Spinosad.[47] One key feature of the designed strategy is a chiral amine-catalyzed intramolecular Diels–Alder reaction of advanced diene-enal **121**. In the presence of imidazolidinone **C-10d**, the [4+2] annulation product **122** was obtained in 81% yield as a single diastereomer, which was transformed to (–)-spinosyn A (**123**) in an 8-step reaction sequence (Scheme 19).



Scheme 19 Intramolecular Diels–Alder reaction and the total synthesis of (–)-spinosyn A (Dai, 2016).

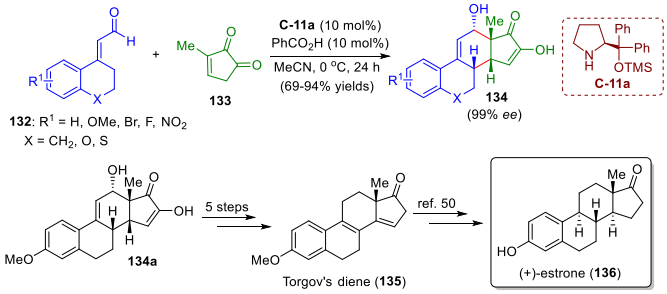
2.9 Catalysis with diarylprolinol silyl ethers

The Hong group accomplished the total synthesis of (+)-galbulin (**131**) using kinetic asymmetric transformation strategy.[48] In the presence of diarylprolinol silyl ether **C-11a**, a domino Michael/Michael/aldol condensation between racemic ketoaldehyde **124** and aldehyde **125** took place to afford hexahydronaphthalenone **130** in 82% yield with 99% *ee*, enabled via the formation of enamine/iminium intermediates. Whereas (*S*)-**124** reacted smoothly, (*R*)-**124** did not tend to react due to the steric hindrance. Finally, bicyclic **130** was ready converted into (+)-galbulin (**131**) through an 8-step reaction sequence (Scheme 20).



Scheme 20 Michael/Michael/aldol cascade and the total synthesis of (+)-galbulin (Hong, 2011).

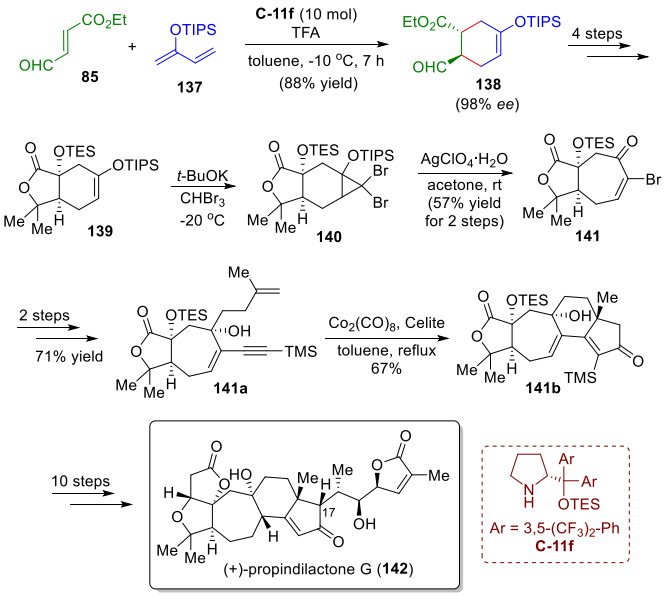
The Jørgensen group developed an amine-catalyzed Diels–Alder reaction for the asymmetric construction of chiral steroids.[49] The condensation between the aminocatalyst **C-11a** and enals **132** formed either a dienamine or trienamine, which are electron-donating in nature, and readily underwent Diels–Alder reaction with dienophile **133** to afford steroid core motifs (**134**) in high yields with excellent stereoselectivities (Scheme 21). In particular, the authors showed that Torgov's diene **135** was readily prepared, leading to the formal total synthesis of (+)-estrone (**136**).[50]



Scheme 21 Amine-catalyzed Diels–Alder reaction and formal synthesis of (+)-estrone (Jørgensen, 2014).

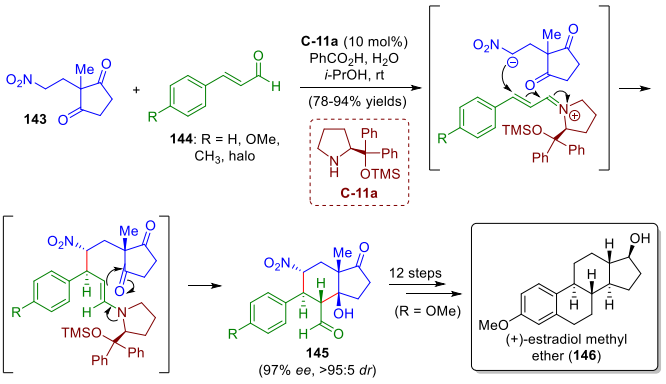
(+)-Propindilactone G (**142**) is a nortriterpenoid isolated from species of *Schisandracea* family.[51] In 2015, Chen, Yang, and co-workers accomplished the first asymmetric total synthesis of (+)-propindilactone G.[52] One key step in their synthesis is amine **C-11f** catalyzed Diels–Alder reaction between the dienophile **85** and diene **137**, which formed chiral scaffold **138** in 88% yield with 98% *ee*. Subsequently, after a few trivial transformations, lactone **139** was obtained. The following cyclopropanation and ring expansion then furnished enone **141**. At last, structural elaborations of **141** through a 13-step synthetic sequence, including a key Pauson–Khand reaction, accomplished the asymmetric total synthesis of (+)-propindilactone G (Scheme 22). It should be mentioned that the structure of (+)-

propindilactone G was revised through their synthetic studies, and the originally proposed structure has been reassigned as C17-*epi*-(+)-propindilactone G.



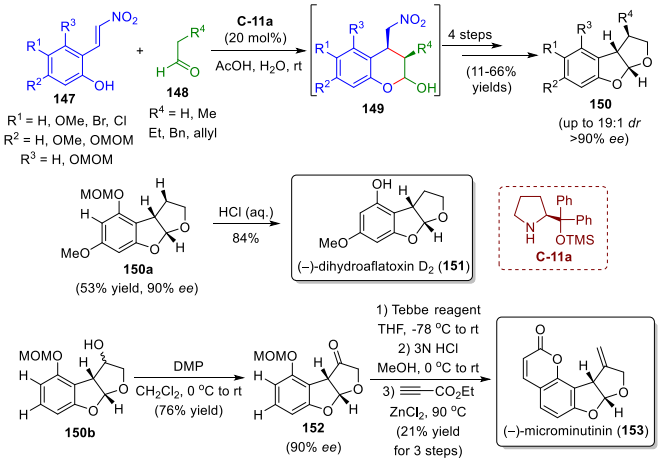
Scheme 22 Total synthesis of (+)-propindilactone G (Chen, Yang, 2015).

The Hayashi group accomplished the total synthesis of (+)-estradiol methyl ether (**146**) in a pot-economical manner.[53] The key reaction is a diphenylprolinol silyl ether (**C-11a**)-mediated cascade Michael/aldol reaction between nitroalkane **143** and substituted-cinnamaldehydes **144**, which effectively formed aldehyde **145** in good yield with excellent enantio- and diastereoselectivities. Subsequently, standard synthetic manipulations of **145** led to the total synthesis of (+)-estradiol methyl ether (Scheme 23). Impressively, Hayashi and co-workers utilized only five reaction vessels and performed four purifications to realize their above total synthesis.



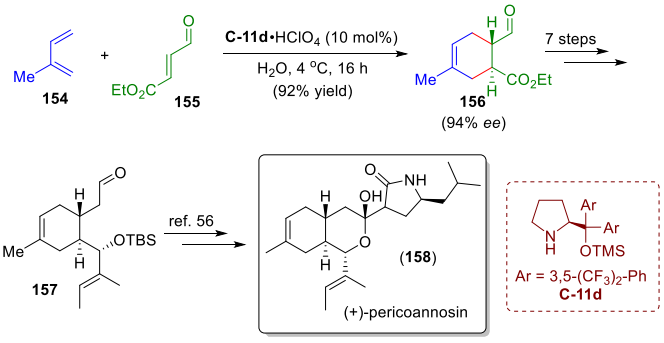
Scheme 23 Total synthesis of (+)-estradiol methyl ether (Hayashi, 2017).

The Hong group developed an organocatalytic Michael/acetalization/reduction/Nef cascade sequence for one-pot construction of the functionalized aflatoxin system.[54] In the presence of diphenylprolinol silyl ether (**C-11a**), the projected sequential reaction between nitroalkene **147** and aldehyde **148** smoothly delivered product **150** in overall 53% yield with 90% *ee*. Subsequently, the cleavage of the MOM group of **150a** led to the formation of (−)-dihydroaflatoxin D_2 (**151**). Similarly, alcohol **150b** was prepared, which was subjected to Dess–Martin oxidation, treated with Tebbe reagent, and underwent the Pechmann-type condensation to produce (−)-microminutinin (**153**) (Scheme 24).



Scheme 24 The Michael/acetalization/reduction/Nef cascade and total synthesis of (−)-dihydroaflatoxin D_2 and (−)-microminutinin (Hong, 2017).

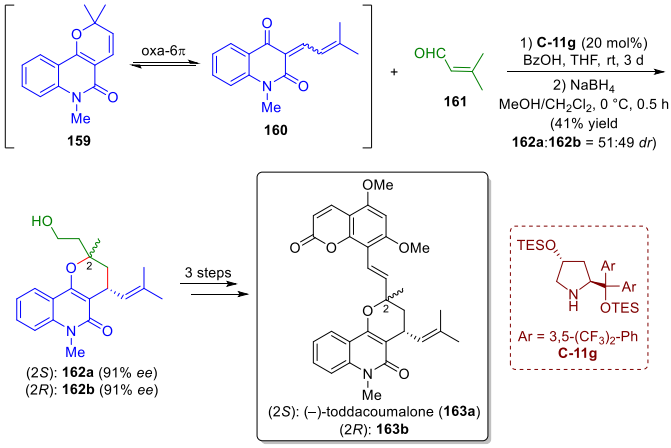
The Lindsley group disclosed a formal total synthesis of (+)-pericoannosin A (**158**) (Scheme 25).[55] In the presence of prolinol catalyst (**C-11d**), the Diels–Alder reaction between the diene **154** and enal **155** delivered aldehyde **156** in 92% yield with 94% *ee*. Further transformations were established to convert **156** to advanced intermediate **157**, which could be elaborated into (+)-pericoannosin A (**158**) following earlier report by Kalesse and co-workers.[56]



Scheme 25 Formal total synthesis of (+)-pericoannosin A (Lindsley, 2019).

Toddacoumalone was isolated from *Toddalia asiatica* and exists naturally in a racemic form.[57] The stereochemistry of the two chiral centers was not established until 2020 when Xiong et al. disclosed an asymmetric total synthesis of toddacoumalone (**163**).[58] The key transformation was a prolinol (**C-11g**)-promoted oxo-Diels–Alder reaction between 3-methyl-crotonaldehyde **161** and enone **160**, which was derived from pyranoquinolinone **159** *in situ* via an oxa-6π electrocyclic

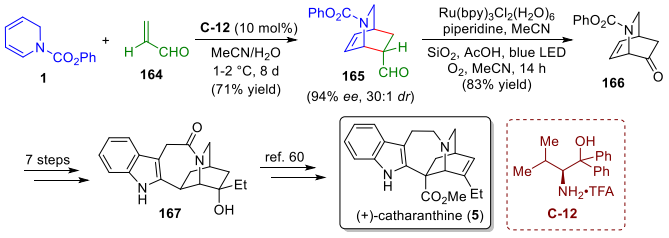
pathway. Following a reduction, diastereoisomers **162a** and **162b** were obtained in a total yield of 41% with 91% *ee* for both isomers. Further transformations led to the synthesis of **163a** and **163b**, as well as their enantiomers, obtained through catalysis of *ent*-**C-11g** (Scheme 26). Finally, NMR and single X-ray crystal studies established the configuration of naturally separated (–)-toddacoumalone (**163a**).



Scheme 26 Total synthesis of (–)-toddacoumalone (Xiong, 2020).

2.10 Catalysis with other chiral amines

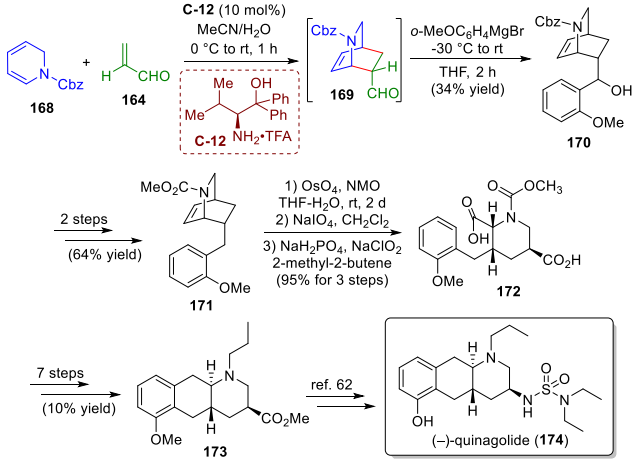
The Batey group reported a formal total synthesis of (+)-catharanthine (**5**) (Scheme 27).[59] The key transformation is a Diels–Alder reaction between diene **1** and acrolein **164** in the presence of primary amine catalyst **C-12**, delivering isoquinuclidine core **165** in 71% yield with 94% *ee*. Interestingly, the authors converted aldehyde **165** to ketone **166** via photoredox catalyzed cleavage with molecular oxygen in 83% yield. With ketone **166** in hand, the authors proceeded to accomplish the formal total synthesis of (+)-catharanthine (**5**).[60]



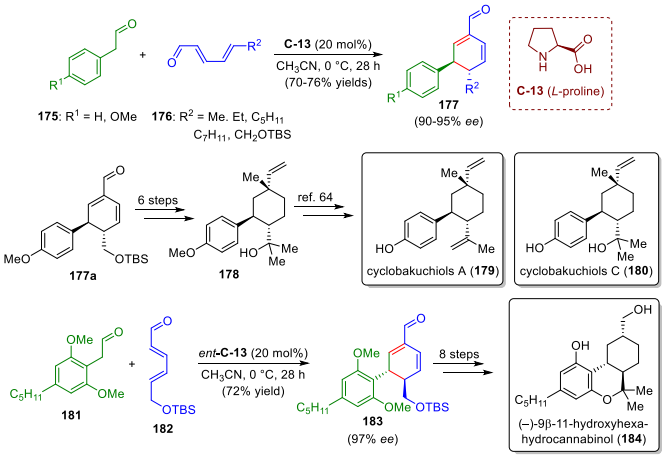
Scheme 27 Primary amine-catalyzed Diels–Alder reaction and formal total synthesis of (+)-catharanthine (Batey, 2018).

The Chavan group accomplished the formal synthesis of (–)-quinagolide (**174**) from simple pyridine and acrolein **164** (Scheme 28).[61] The key transformation is a primary amine (**C-12**)-catalyzed Diels–Alder reaction to construct bicyclic intermediate **170**. The deoxygenation of **170** under Birch reduction conditions furnished bicyclic amine, which was protected as a carbamate derivative **171**. Following dihydroxylation-diol cleavage and Pinnick oxidation, dicarboxylic acid **172** was obtained. Following an intramolecular Friedel–Crafts cyclization, the tricyclic core structure was obtained, which after further elaborations and following known literature report[62] was converted to (–)-quinagolide.

The Appayee group disclosed an asymmetric total synthesis of cyclobakuchiols A (**179**) and C (**180**) by using inverse-electron-demand Diels–Alder (IEDDA) to construct the key structural motif.[63] In the presence of *L*-proline, the IEDDA reaction between α,β,γ,δ-unsaturated aldehydes **176** and arylacetaldehydes **175** effectively created 3,4-disubstituted cyclohexadiene carboaldehydes **177** in good chemical yields with excellent *ee* values. With **177** in hand, the authors accomplished formal total synthesis of cyclobakuchiols A and C following literature reports.[64] Very recently,[65] utilizing similar synthetic strategy, Appayee and co-workers completed the formal total synthesis of (–)-9β-11-hydroxyhexahydrocannabinol (**184**) (Scheme 29).



Scheme 28 Formal total synthesis of (–)-quinagolide (Chavan, 2019).

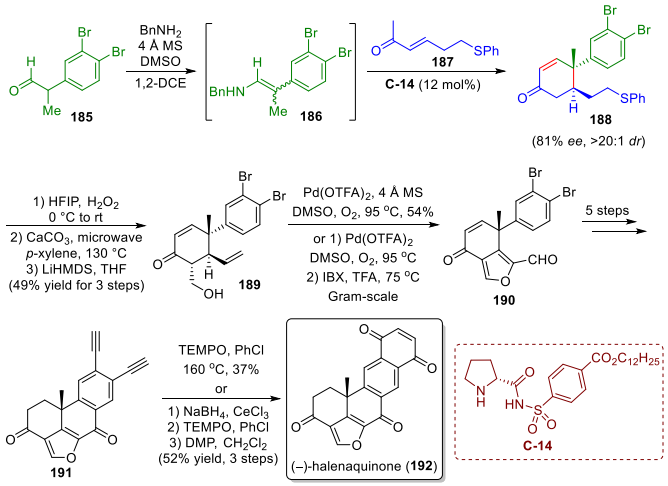


Scheme 29 Formal total synthesis of cyclobakuchiols A and C, and (–)-9β-11-hydroxyhexahydrocannabinol (Appayee, 2018, 2020).

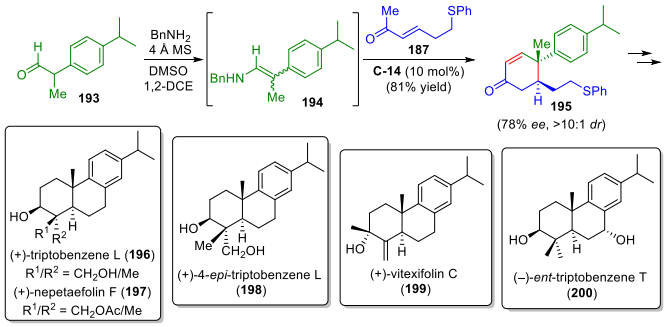
The Carter group disclosed an enantioselective total synthesis of (–)-halenaquinone (**192**).[66] One highlight of the synthetic sequence is proline sulfonamide (**C-14**)-catalyzed Yamada–Otani reaction between benzylic aldehyde **185** and ketone **187** to construct the advanced cyclohexanone intermediate **188**. Both enamine formation and iminium activation were crucial for the reaction to take place. With

alkene **189** in hand, a palladium-catalyzed furanyl aldehyde formation was developed, yielding furan **190**. Further structural elaboration led to the formation of dialkyne furan **191**, and the subsequent Bergmann cyclization formed the final quinone ring, resulting in the eventual completion of the total synthesis of (–)-halenaquinone (**192**) (Scheme 30).

Utilizing similar key synthetic strategy, the Carter group accomplished the divergent syntheses of multiple abietane diterpenoids.[67] In the presence of proline sulfonamide **C-14**, benzylic aldehyde **193** and ketone **187** underwent Yamada–Otani reaction to form enone **195**. The subsequent Pummerer cyclization pathways created the common tricyclic cyclohexanone intermediates, which were subjected to further synthetic manipulations, leading to the completion of total syntheses of (+)-triptobenzene L (**196**), (+)-nepetaefolin F (**197**), (+)-4-epi-triptobenzene L (**198**), (+)-vitexifolin C (**199**), and (–)-*ent*-triptobenzene T (**200**) (Scheme 31).



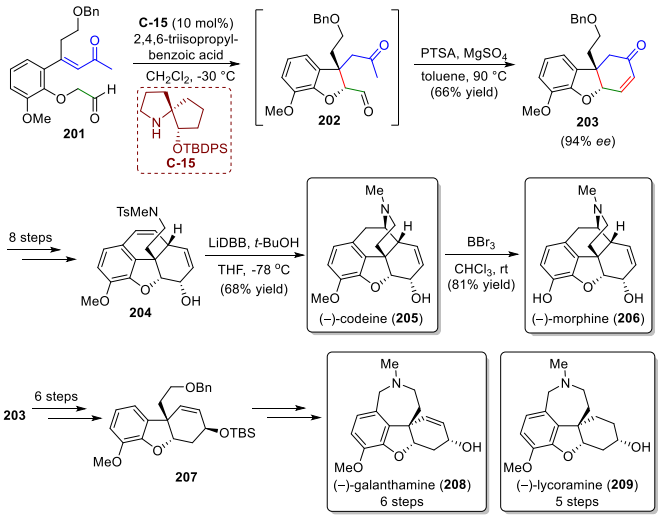
Scheme 30 Enantioselective total synthesis of (–)-halenaquinone (Carter, 2018).



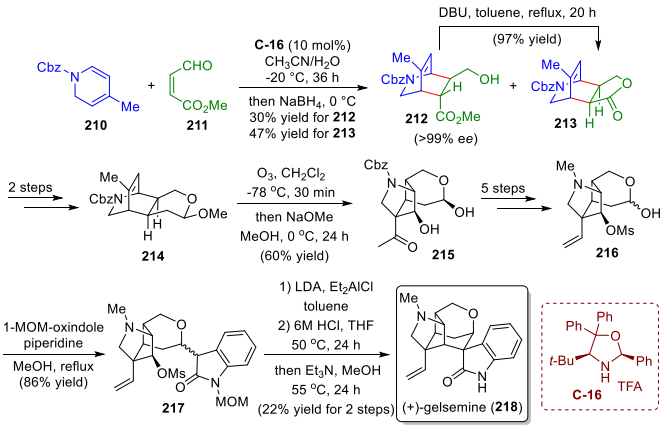
Scheme 31 Divergent syntheses of abietane diterpenoids (Carter, 2018).

Zhang, Tu, and co-workers developed an efficient approach to access *cis*-hydrodibenzofuran framework, which was applied to the total syntheses of a number opioid alkaloids.[68] The Robinson annulation of enone **201** was promoted by spirocyclic pyrrolidine **C-15** to deliver the crucial *cis*-hydrodibenzofuran core **203** in 66% yield with 94% *ee*. Further transformations of benzofuran **203** led to the formation of Guillou's intermediate, which underwent hydroamination reaction to form (–)-codeine (**205**), and the subsequent demethylation produced (–)-morphine (**206**). Alternatively, benzofuran **203** was converted to common intermediate **207**, from which the total syntheses of (–)-galanthamine (**208**) and (–)-lycoramine (**209**) were readily accomplished (Scheme 32).

Zhai, Qiu, and co-workers reported an organocatalytic Diels–Alder reaction and an asymmetric total synthesis of (+)-gelsemine (**218**).[69] The key transformation was a Diels–Alder reaction between dihydropyridine **210** and enoate **211**, which was followed by a $NaBH_4$ reduction to afford bridged **213**, and its double bond isomerized product **212**, which could be converted to **213** by treatment with DBU. Acetal **214** was readily obtained in two steps, which was transformed to hemiacetal **216** following a few trivial transformations. After a condensation with oxindole, intermediate **217** with all the core structural features of the natural product was obtained, further transformations of which completed the total synthesis of (+)-gelsemine (**218**) (Scheme 33).

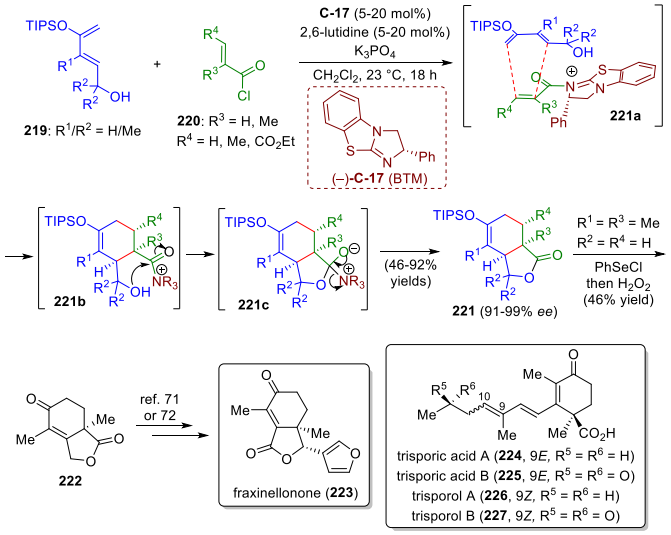


Scheme 32 Organocatalytic Robinson annulation and applications to the total syntheses of (–)-codeine, (–)-morphine, (–)-galanthamine and (–)-lycoramine (Zhang, Tu, 2019).



Scheme 33 Total synthesis of (+)-gelsemine (Zhai, Qiu, 2015).

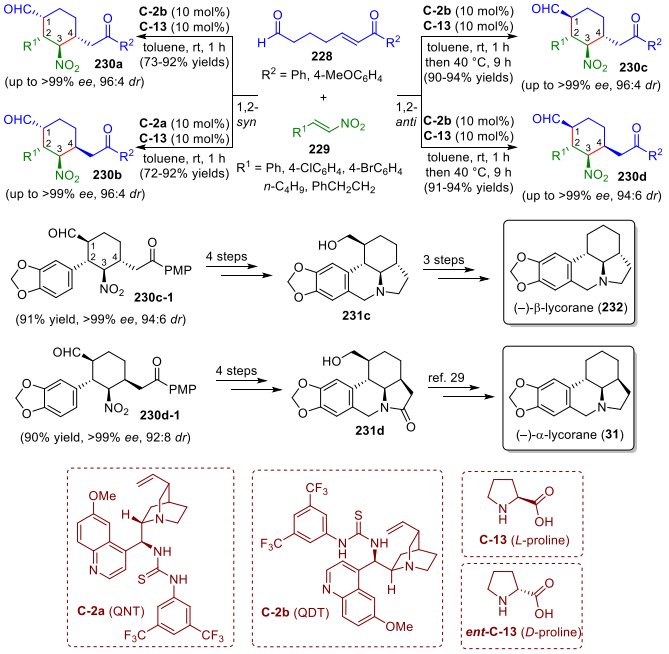
The Romo group disclosed a highly stereoselective Diels–Alder reaction/lactonization cascade sequence between diene **219** and dienophilic α,β-unsaturated acylammonium salts, which was derived from α,β-unsaturated acid chlorides **220** (Scheme 34).[70] Under the catalysis of isothiourea **C-12** (BTM), *cis*- and *trans*-fused bicyclic γ- and δ-lactones **221** bearing multiple stereogenic centers were readily obtained. Subsequent α-selenylation, followed by oxidative elimination gave key intermediate enone **222**, from which the formal syntheses of fraxinellonone (**223**),[71] trisporic acids (**224** & **225**) and trisporols (**226** & **227**)[72] were well-established.



Scheme 34 A Diel–Alder/lactonization cascade and the formal syntheses of fraxinellone, trisporic acids, and trisporols (Romo, 2014).

2.11 Catalysis with dual catalysts

Zhao and co-workers utilized modularly designed organic catalysts to promote a tandem Michael/Michael cascade to construct up to eight stereoisomers among possible 16 tetrasubstituted cyclohexanes.[73] In the presence of L-proline **C-13** and thioureas **C-2a**/**C-2b**, the projected cascade reaction between nitroalkene **229** and compound **228** occurred smoothly to afford **230** in high yields with excellent *ee* values. The advanced cyclohexane intermediates were applied to the total synthesis of (–)-β-lycorane (**232**), and a shorter and more efficient formal total synthesis of (–)-α-lycorane (**31**) as reported by Xu[29] (Scheme 35).



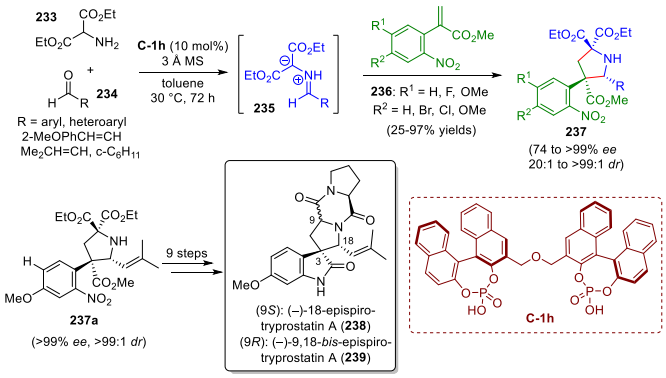
Scheme 35 Michael/Michael cascade catalyzed by modularly designed organic catalysts and syntheses of (–)-β-lycorane and (–)-α-lycorane (Zhao, 2014).

3. [3+2] Annulation

The [3+2] annulation reactions are synthetic very useful, as the common five-membered ring structures are prevalent in natural products and bioactive molecules. One type of [3+2] annulations is 1,3-diploar cycloaddition reaction, in which 1,3-dipoles are reacted with dipolarphiles. Alternatively, a range of formal [3+2] annulations have emerged, which rely on cascade organocatalytic reaction sequence to construct 5-membered ring systems. Common organic reactions, such as Michael addition, nucleophilic substitution, are often an elementary reaction step in these formal [3+2] annulation strategies. Moreover, NHC-catalyzed annulation reactions, and phosphine-mediated annulations have also drawn much attention from synthetic organic chemists. In following sections, different types of [3+2] annulation reactions will be discussed in detail, and their applications to natural products total synthesis will be presented.

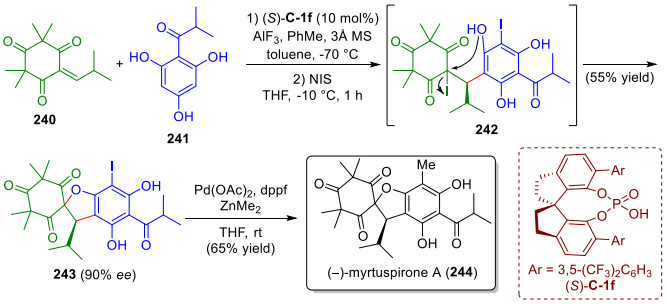
3.1 Catalysis with chiral phosphoric acids

Spirotryprostatin A was originally isolated from *Aspergillus fumigatus*, and exhibited potential in inhibiting cell division.[74] The Gong group reported the total syntheses of two diastereomers of spirotryprostatin A.[75] The key transformation is an enantioselective 1,3-dipolar cycloaddition between the azomethine ylide **235** and acrylate **236**. In the presence of chiral bisphosphoric acid **C-1h**, the 1,3-dipolar cycloaddition produced polysubstitutied pyrrolidine **237** in 25-97% yields with 74% to >99% *ee* and 20:1 to >99:1 *dr*. Further transformations formed 18-epispirotryprostatin A (**238**) and 9,18-*bis*-epispirotryprostatin A (**239**) (Scheme 36).



Scheme 36 Total syntheses of (–)-18-epispirotryprostatin A and (–)-9,18-*bis*-epispirotryprostatin A (Gong, 2011).

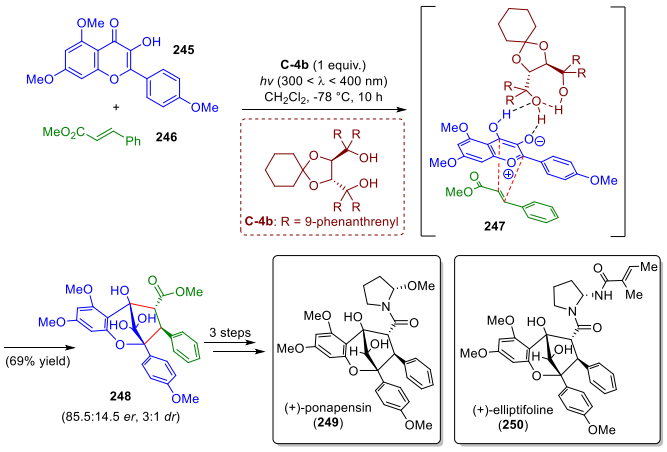
Myrtuspirone A (**244**) was isolated from *Myrtus communis*, which is a medicinal herb with antibacterial and insecticidal effects.[76] Li, Wang, Ye, and co-workers disclosed a Michael/NIS-mediated [3+2] annulation strategy, which was applied to the total synthesis of (–)-myrtuspirone A.[77] The sequence commenced with a Friedel–Craft-type Michael addition of enone **240** to phloroglucinol **241** catalyzed by chiral phosphoric acid (*S*)-**C-1f**, followed by NIS-mediated cyclization, giving product **243** in 55% yield with 90% *ee*. Subsequently, treatment of **243** with $ZnMe_2$ triggered a Negishi coupling to furnish (–)-myrtuspirone A (**244**) in 65% yield with 90% *ee* (Scheme 37).



Scheme 37 Michael-NIS-mediated [3+2] annulation and total synthesis of (–)-myrtuspirone A (Li, Wang, Ye, 2019).

3.2 Catalysis with TADDOL derivative

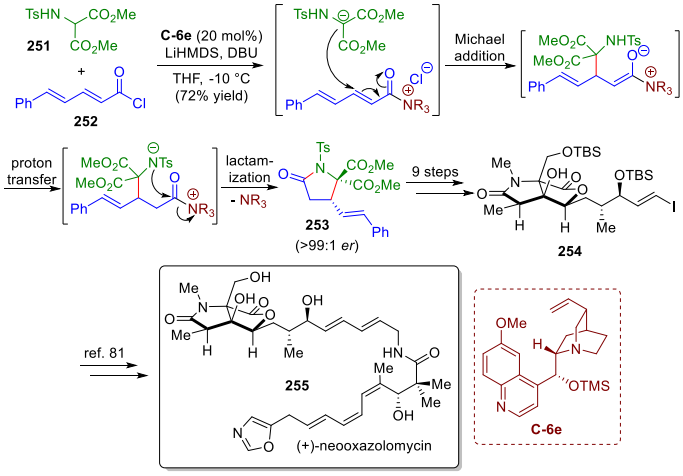
(+)-Ponapensin (**249**) and (+)-elliptifoline (**250**) were secondary metabolites produced by the plant genus *Aglaia*, and (+)-ponapensin displayed potent NF-κB inhibitory activity.[78] The Porco group first assigned the absolute configurations of those two natural products via their enantioselective total synthesis,.[79] The formation of the crucial backbone relied on the [3+2] photo-cycloaddition of oxidopyrylium, tautomerized from 3-hydroxyflavones **245**, and methyl cinnamate **246**. Tetrakis-9-phenanthrenyl TADDOL **C-4b** was used as catalyst to promote the stereoselectivity through a host–guest complexation **247**, forming **248** in 69% yield with 85.5:14.5 *er* (Scheme 38).



Scheme 38 Photo [3+2] annulation of 3-hydroxyflavones, and total syntheses of (+)-ponapensin and (+)-elliptifoline (Porco, 2012).

3.3 Catalysis with cinchona alkaloid derivative

Very recently, the Romo group accomplished the formal total synthesis of (+)-neooxazolomycin (**255**).[80] The key step is a Lewis base catalyzed cascade Michael/proton transfer/lactamization reaction to construct the core pyrrolidinone scaffold **253**. In the presence of cinchona alkaloid derivative **C-6e**, the [3+2] annulation between sulfonamido malonate **251** and acid chloride **252** under the catalysis of cinchona alkaloid derivative **C-6e** took place smoothly to give pyrrolidinone **253** in 72% yield with excellent enantioselectivity (Scheme 39). Further transformations produced advanced intermediate **254**, which was readily converted to (+)-neooxazolomycin (**255**) following known procedures.[81]

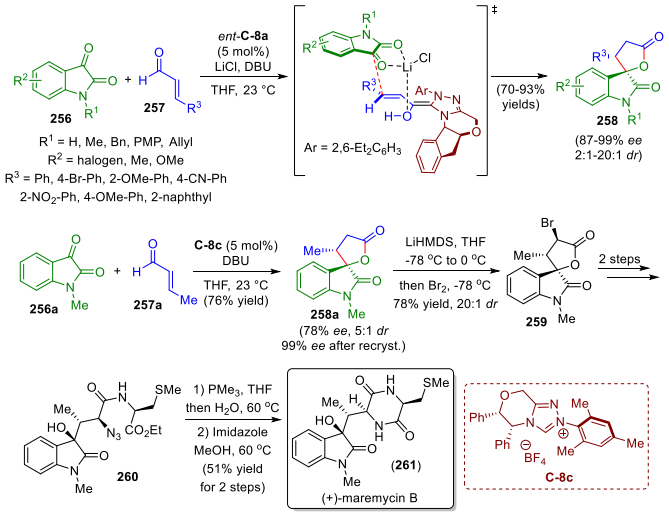


Scheme 39 Formal synthesis of (+)-neooxazolomycin (Romo, 2020).

3.4 Catalysis with *N*-Heterocyclic carbenes

The Scheidt group accomplished the total synthesis of (+)-maremycin B (**261**), which is featured by a NHC-catalyzed enantioselective [3+2] annulation as the key transformation.[82] Under NHC catalysis, the [3+2] annulation of isatin **256** with enal **257** rendered spirooxindole lactone **258** in 76% yield with good stereoselectivity. α-Bromination of **258** by treating with LiHMDS/Br_2 yielded α-bromo lactone **259**, which was

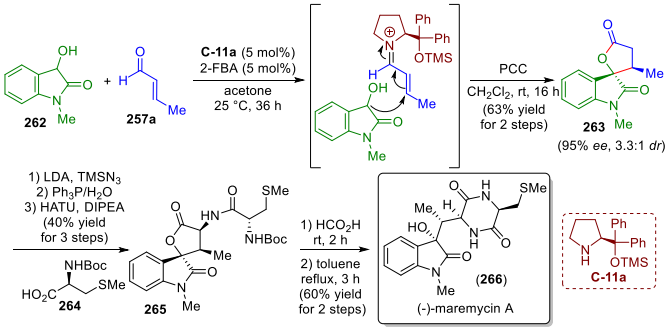
transformed to amide **260** bearing an azido group. Finally, **260** was converted into (+)-maremycin B (**261**) via a Staudinger reduction followed by a lactamization (Scheme 40).



Scheme 40 NHC-catalyzed [3+2] annulation and total synthesis of (+)-maremycin B (Scheidt, 2012).

3.5 Catalysis with diarylprolinol silyl ethers

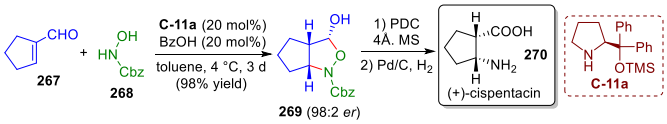
The Melchiorre group developed a route to access enantioenriched 3-substituted 3-hydroxyoxindoles and achieved the total synthesis (−)-maremycin A (**266**).[83] In the presence of amine catalyst **C-11a**, an asymmetric sequential Michael addition/acetalization/oxidation reaction created spirooxindole lactone **263** in 63% yield with 95% *ee* as a mixture of diastereoisomers. Subsequently, the introduction of azide group, followed by Staudinger reaction and condensation with protected cysteine, and the final cleavage of Boc protection completed the total synthesis of (−)-maremycin A (Scheme 41).



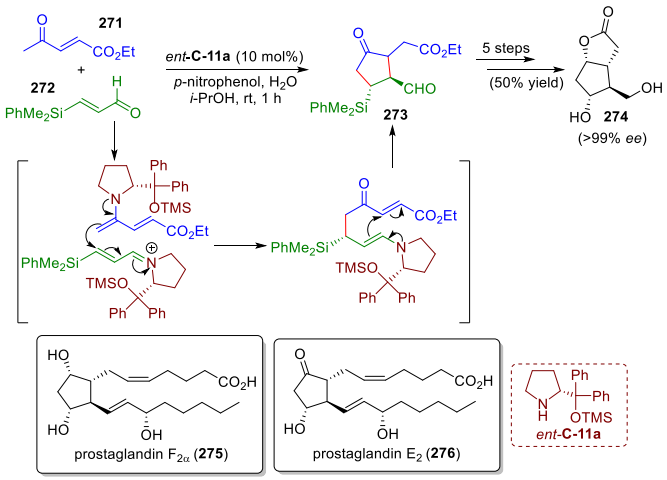
Scheme 41 Michael addition/acetalization/oxidation cascade and total synthesis of (−)-maremycin A (Melchiorre, 2012).

The Moyano group reported a short synthesis of (+)-cispentacin (**270**).[84] In the presence of **C-11a**, the aza-Michael addition of hydroxylamine **268** to cyclopentene-2-carbaldehyde **267** took place, followed by a hemiacetalization reaction, isoxazolidine **269** was obtained in excellent yield and enantioselectivity. Finally, oxidization Cbz cleavage produced (+)-cispentacin (**270**) (Scheme 42).

The Hayashi group disclosed a time-economic one-pot enantioselective synthesis of the Corey lactone **274**, an important intermediate for synthesizing prostaglandins.[85] With the employment of prolinol silyl ether **C-11a**, domino Michael/Michael addition between 3-(dimethylphenylsilyl)-propenal **272** and ethyl 4-oxo-2-pentenoate **271** provided cyclopentanone **273**. At last, the one-pot six-step reaction sequence afforded the Corey lactone **274** in a total yield of 50% and >99% *ee* within 152 minutes (Scheme 43). The Corey lactone **274** was readily transformed into various prostaglandins such as prostaglandins $F_{2\alpha}$ (**275**) and E_2 (**276**), following procedures reported earlier.[86]



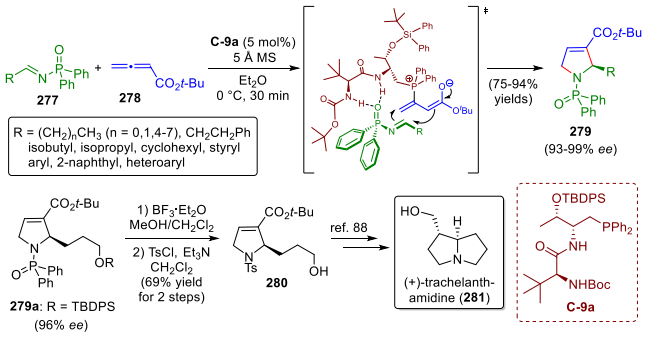
Scheme 42 A short enantioselective synthesis of (+)-cispentacin (Moyano, 2013).



Scheme 43 Time-economic one-pot synthesis of the Corey lactone (Hayashi, 2020).

3.6 Catalysis with phosphines

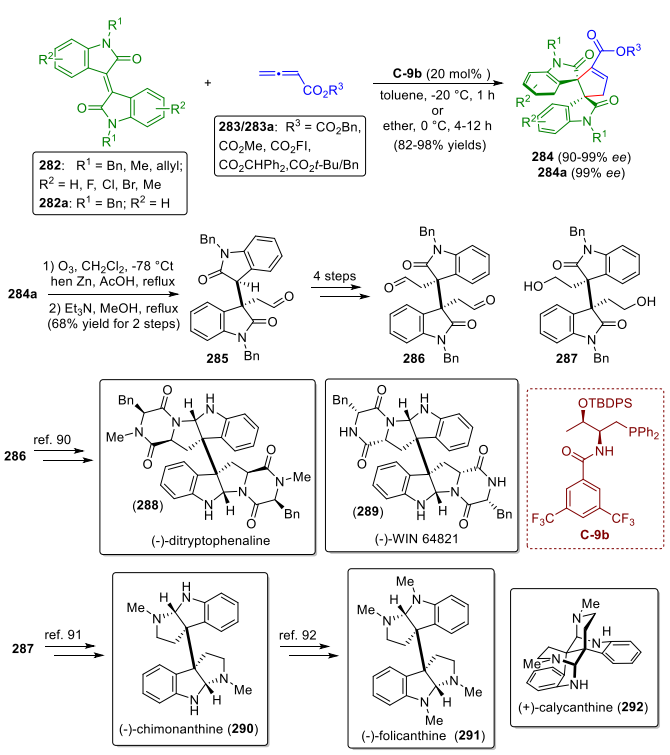
The Lu group developed a phosphine-catalyzed enantioselective [3+2] annulation reaction between imine **277** and *tert*-butyl allenoate **278** (Scheme 44).[87] The reaction was effectively promoted by dipeptide-derived phosphine catalysts, and pyrrolines **279** with aryl and alkyl substituents were formed in high yields with excellent enantioselectivities. The [3+2] annulation product **279a** was easily converted to intermediate **280**, which could be elaborated into (+)-trachelanthamidine (**281**) using procedures described in the literature.[88]



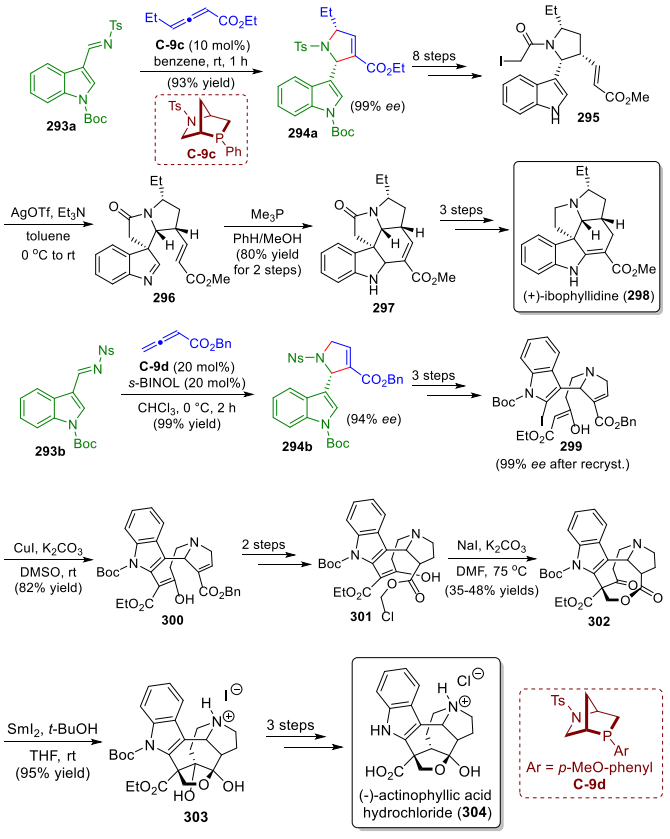
Scheme 44 Phosphine-catalyzed [3+2] annulation of imines and formal synthesis of (+)-trachelanthamidine (Lu, 2012).

Recently, the Lu group employed isoindigos in phosphine-catalyzed [3+2] annulation with allenes, which allowed for effective formation of two vicinal quaternary stereogenic centers.[89] In the presence of threonine-derived phosphine **C-9b**, spirocyclic bisindolines **284** were obtained in high yields (82-98%) with excellent stereoselectivities (90-99% *ee*) (Scheme 45). The reported strategy represents a powerful and versatile method for the synthesis of dimeric hexahydropyrroloindole (HPI) alkaloids. The annulation product **284a** was readily converted to aldehyde **285**, which was further elaborated into dialdehyde **286** and diol **287**. Following procedures established in literature, **286** could be transformed into natural product (–)-ditryptophenaline (**288**) and (+)-WIN 64821 (**289**),[90] while **287** could be elaborated into (–)-chimonanthine (**290**),[91] and further converted into (–)-folicanthine (**291**) and (+)-calycanthine (**292**) via known methods.[92]

Kwon and co-workers constructed five-membered nitrogen-containing ring systems via phosphine-catalyzed [3+2] annulation, which was used as a key intermediate for the total synthesis of (+)-ibophyllidine (**298**) and (–)-actinophyllic acid hydrochloride (**304**).[93] The [3+2] annulation between *N*-tosyl imine **293a** and allenoate in the presence of chiral [2.2.1] bicyclic phosphine catalyst **C-9c** gave the desired pyrroline **294a** in 99% yield with 99% *ee*. Following multi-step standard transformations, the cyclization precursor **295** was obtained. Activation of the iodide with silver trifluoromethanesulfonate resulted in spirocyclic indolenine **296**, which was treated with trimethylphosphine to trigger an intramolecular aza-Morita–Baylis–Hillamn reaction, yielding the pentacyclic **297**. After a few trivial transformations, (+)-Ibophyllidine (**298**) was synthesized. Pyrrolidine **294b**, derived via **C-9d**-catalyzed [3+2] annulation, was converted to iodoketoester **299**, which was treated with CuI, forming cyclization product **300**. Subsequent conversion to chloromethyl ester **301** was straightforward, treatment with NaI furnished lactone **302**. SmI_2 was found to promote pinacol coupling well, yielding coupling product **303**, which was then readily elaborated into (–)-actinophyllic acid hydrochloride (**304**) (Scheme 46).



Scheme 45 Phosphine-catalyzed [3+2] annulation of isoindigos and formal syntheses of dimeric HPI alkaloids (Lu, 2019).



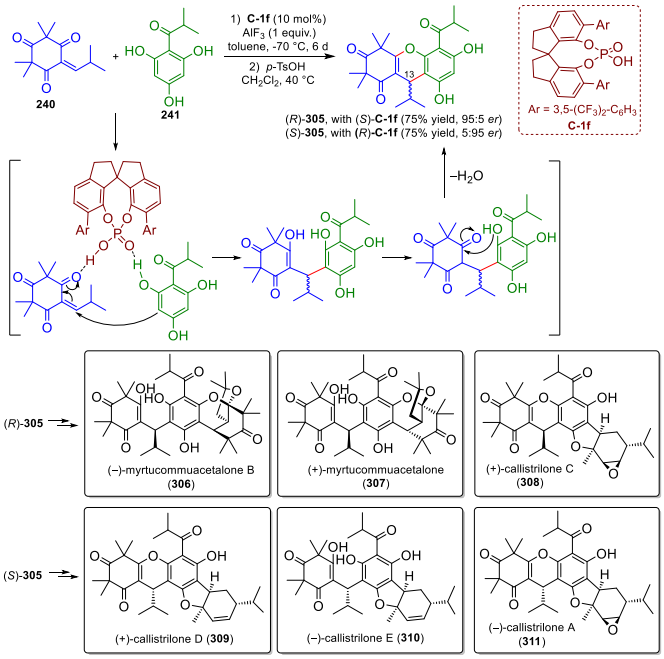
Scheme 46 Phosphine-mediated [3+2] annulation of imines and total syntheses of (+)-ibophyllidine and (–)-actinophyllic acid hydrochloride (Kown, 2012, 2016).

4. [3+3] Annulation

[3+3] annulation also constructs six-membered ring systems. In comparison with the [4+2] annulation, [3+3] annulation reactions are relatively less explored. In what follows, we describe examples of [3+3] annulations, placing them into the context of natural products total synthesis; most of such [3+3] annulations are cascade processes, in which Michael addition is often a key element in the cascade.

4.1 Catalysis with chiral phosphoric acids

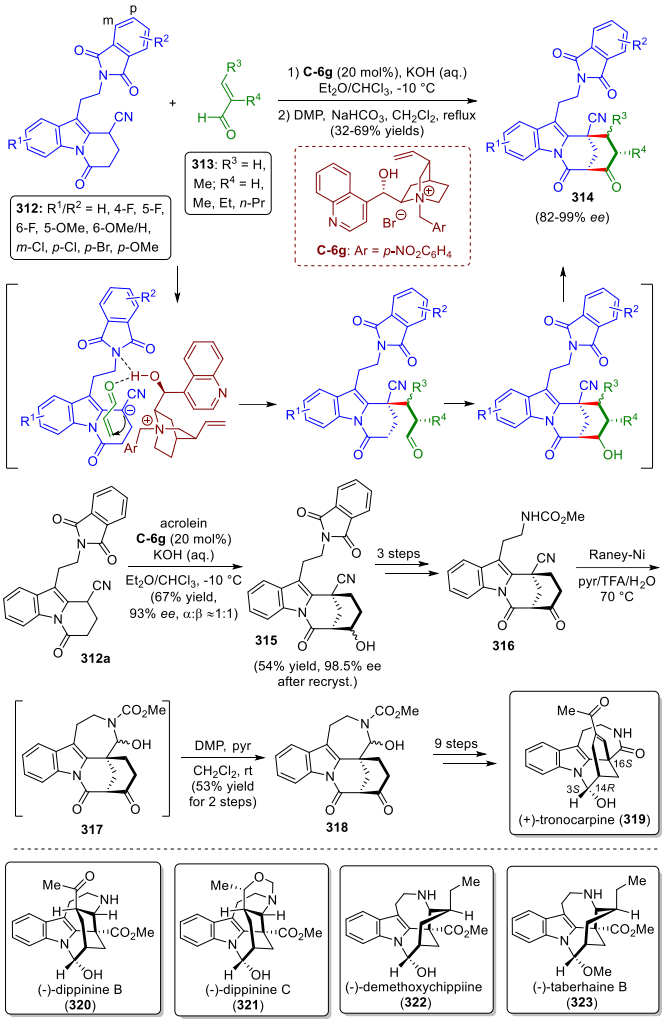
Wang, Ye, Li, and co-workers developed an efficient [3+3] annulation process between enone **240** and phloroglucinol **241**.[94] In the presence of chiral phosphoric acid **C-1f**, the tandem Friedel–Craft-type Michael addition, followed by a *p*-TsOH-mediated cyclization, delivered fused tricyclic product **305** in moderate yield with high enantiomeric excess. This unique [3+3] annulation reaction formed basis for the authors to accomplish total syntheses of a group of diverse polycyclic polymethylated phloroglucinols, i.e. (–)-myrtucommuacetalone B (**306**), (+)-myrtucommuacetalone (**307**), (+)-callistrilone C (**308**), (+)-callistrilone D (**309**), (–)-callistrilone E (**310**), and (–)-callistrilone A (**311**) (Scheme 47).



Scheme 47 Tandem [3+3] annulation and total syntheses of polycyclic polymethylated phloroglucinols (Wang, Ye, Li, 2018).

4.2 Catalysis with phase-transfer catalyst

Han and co-workers disclosed the first enantioselective total syntheses of post-iboga indole alkaloids.[95] The key to their success is a chiral phase-transfer-catalyst (PTC) catalyzed Michael/aldol cascade reaction between indole derivatives **312** and acroleins **313** for efficient construction of bridged bicyclo[3,3,1] structure **314**. Bifunctional phase-transfer catalyst **C-6g** derived from cinchona alkaloids was found to be effective. With the key structural motif in hand, the authors proceeded to accomplish the total syntheses of a number of natural products, i.e. (+)-tronocarpine (**319**), (–)-dippinine B (**320**), (–)-dippinine C (**321**), (–)-demethoxychippiine (**322**), (–)-taberhaine B (**323**) (Scheme 48).



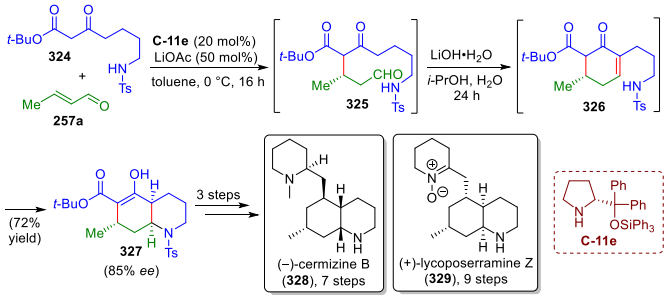
Scheme 48 Total syntheses of post-iboga indole alkaloids (Han, 2020).

4.3 Catalysis with diarylprolinol silyl ethers

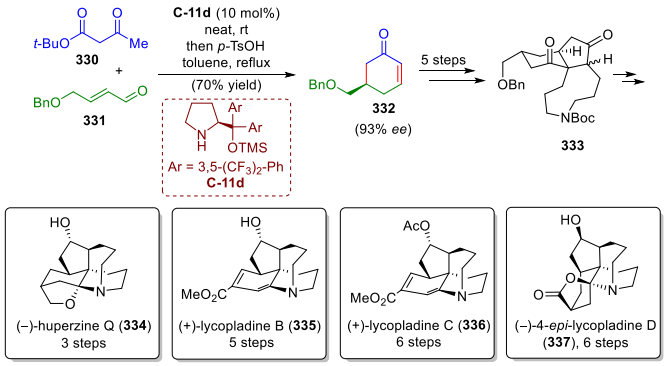
The practical total syntheses of *lycopodium* alkaloids (–)-cermizine B (**328**) and (+)-lycoposerramine Z (**329**) were accomplished by the Bonjoch group in a "pot-economy" manner.[96] Catalyzed by diarylprolinol silyl ether **C-11e**, the key intermediate **326** was formed by a tandem Michael/aldol reaction between β-keto ester **324** and enal **257a**, and the subsequent aza-Michael addition produced hydroquinoline **327** in an overall yield of 72% with 85% *ee*. Further structural elaborations, including dealkoxycarbonylation, retro aza-Michael/aza-Michael, followed by Horner-Wadsworth-Emmons reaction, completed the total synthesis of (–)-cermizine B and (+)-lycoposerramine Z (Scheme 49).

The Lei group achieved divergent total syntheses of *lycopodium* alkaloids, including (–)-huperzine Q (**334**), (+)-lycopladine B (**335**), (+)-lycopladine C (**336**), and (–)-4-*epi*-lycopladine D (**337**).[97] In the presence of diarylprolinol silyl ether **C-11d**, a cascade Michael/aldol reaction between α,β-

unsaturated aldehyde **331** and acetoacetate **330** led to the formation of enone **332** in 70% yield with 93% *ee*. Subsequent synthetic transformations, including Michael/aldol annulation and carbonyl-olefin metathesis generated the key intermediate **333**, with the common 6/5/9 tricyclic structural motif in place. Further elaborations led to efficient total syntheses of target natural products (Scheme 50).



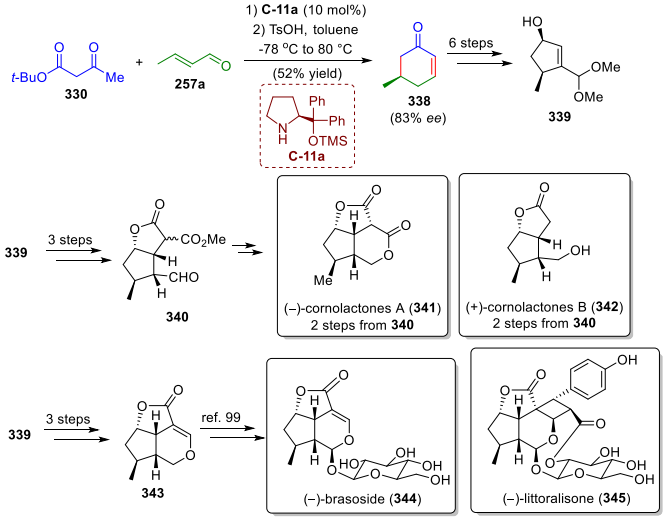
Scheme 49 Organocatalytic tandem Michael/aldol/aza-Michael tandem and total synthesis of (–)-cermizine B and (+)-lycoposerramine Z (Bonjoch, 2013, 2014).



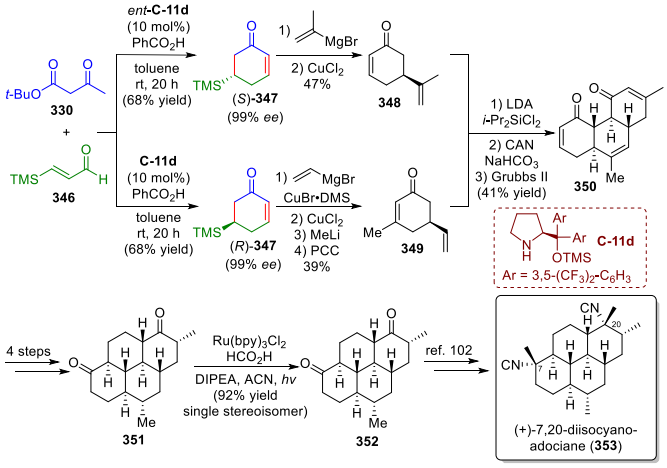
Scheme 50 Divergent asymmetric total syntheses of *lycopodium* alkaloids (Lei, 2017).

The Sun group reported asymmetric total syntheses of (–)-cornolactones A (**341**) and (+)-cornolactones B (**342**), as well as the formal total syntheses of (–)-brasoside (**344**) and (–)-littoralisone (**345**) (Scheme 51).[98] Acetoacetate **330** and crotonaldehyde **257a** underwent a cascade Michael/aldol reaction in the presence of catalyst **C-11a**, affording the cyclohexenone **338** in 52% yield with 83% *ee*. Cyclohexenone **338** was then converted in a few steps, including a crucial intramolecular aldol condensation, to produce the common intermediate **339** which is pivotal for target natural products synthesis. When **339** was transformed to bicyclic lactone **340**, (–)-cornolactones A (**341**) and (+)-cornolactones B (**342**) were readily synthesized. Alternatively, conversion of **339** to tricyclic lactone **343**, which could be transformed to (–)-brasoside (**344**) and (–)-littoralisone (**345**) following procedures reported in the literature.[99]

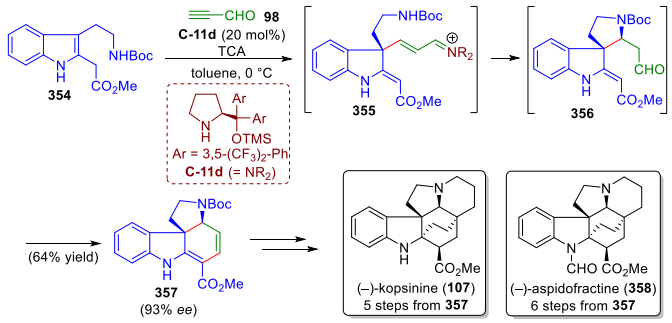
The Thomson group devised a strategy for convergent and stereoselective assembly of polycyclic structures, and the formal total synthesis of (+)-7,20-diisocyanoadociane (**353**) testified the efficiency of their approach (Scheme 52).[100] Two TMS enone building blocks, (*S*)-**347** and (*R*)-**347**, were readily prepared via prolinol-catalyzed cascade Michael/aldol reaction between acetoacetate **330** and enal **346**.[101] The two enones were further converted to building blocks **348** and **349**, which through the 3-step couple and close strategy established the crucial tricyclic dienone structure **350**. After a few more transformations, the Corey dione **352** was obtained, which could be elaboration into (+)-7,20-diisocyanoadociane (**353**) in 3 steps following the literature report.[102]



Scheme 51 Divergent syntheses of (–)-cornolactones A, (+)-cornolactones B, (–)-brasoside and (–)-littoralisone (Sun, 2018).



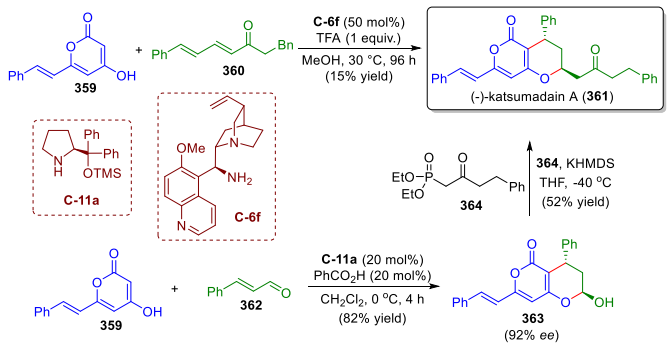
Scheme 52 Formal total synthesis of (+)-7,20-diisocyanoadociane (Thomson, 2018).



Scheme 53 Cascade Michael/aza-Michael/cyclization and total syntheses of (–)-kopsinine and (–)-aspidofractine (Wu, 2014).

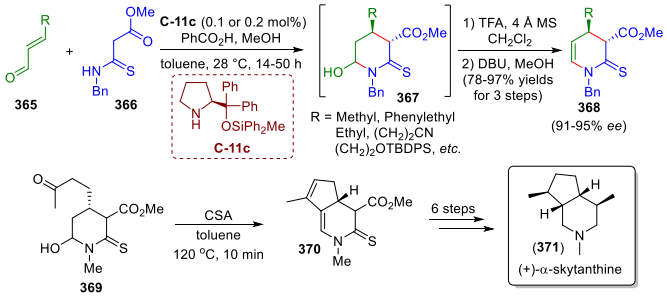
Inspired by MacMillan's earlier synthesis of tetracyclic spiroindolines,[44] Wu and co-workers reported the concise total syntheses of (–)-kopsinine (**107**) and (–)-aspidofractine (**358**).[103] The synthetic strategy for the construction of the core structure **357** was a cascade Michael/aza-Michael/cyclization sequence between tryptamine-derivative **354** and propargyl aldehyde **98**. In the presence of prolinol catalyst **C-11d**, common intermediate **357** was formed in 64% yield with 93% *ee*. With the enantiomerically enriched tetracyclic spiroindoline **357** in hand, the subsequent synthetic transformations were straightforward, and the total syntheses of (–)-kopsinine (**107**) and (–)-aspidofractine (**358**) were accomplished (Scheme 53).

(–)-Katsumadain A (**361**), originated from Chinese herbal *Alpinia katsumadai Hayata* for alleviating emesis,[104] was first asymmetrically synthesized by the Tang group using a biomimetic approach.[105] In the proposed biosynthetic pathways, katsumadain A (**361**) may be derived, from styryl-2-pyranone **359**, or alnustone **360**, via 1,6-conjugate addition, or oxa-Michael addition. Accordingly, when 9-amino-9-deoxyepicinchona alkaloid **C-6f** was utilized to promote the reaction, katsumadain A was only obtained in 15% yield. Alternatively, with the employment of enal **362**, the cascade process furnished intermediate **363** in 82% yield with 92% *ee*, which could be transformed to (–)-katsumadain A (**361**) in a single step with a yield of 52% (Scheme 54).



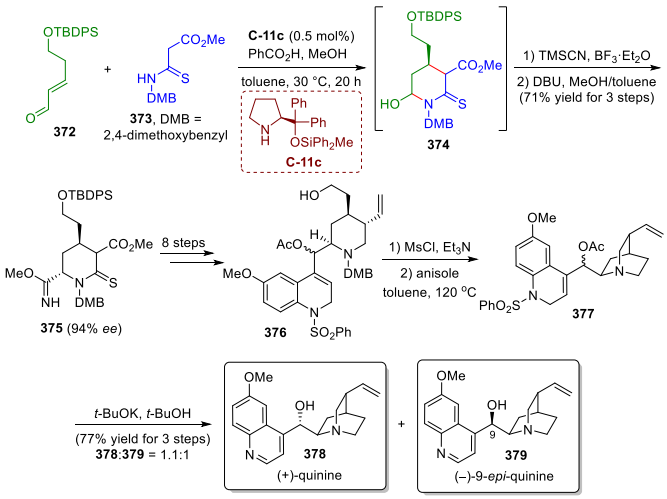
Scheme 54 Biomimetic total synthesis of (–)-Katsumadain A (Tang, 2013).

The Ishikawa group disclosed an effective method for the construction of chiral 4-alkyl piperdines via [3+3] annulation, which was utilized for the total synthesis of (+)-α-skytanthine (**371**).[106] The cascade sequence started with the Michael addition of thiomalonamate **366** to α,β-unsaturated aldehydes **365**, catalyzed by prolinol silyl ether **C-11c**. The subsequent aza-Mannich reaction, followed by hydrolysis furnished intermediate **367**, which was subjected to dehydration to afford products **368** in good yields with 91-95% *ee* values. Specifically, when ketone **369** was treated with CSA, bicyclic **370** was constructed via a dehydration/intramolecular aldol sequence. Following a few trivial transformations, the total synthesis of (+)-α-skytanthine (**371**) was accomplished (Scheme 55).



Scheme 55 Formal [3+3] annulation and total synthesis of (+)-α-skytanthine (Ishikawa, 2015).

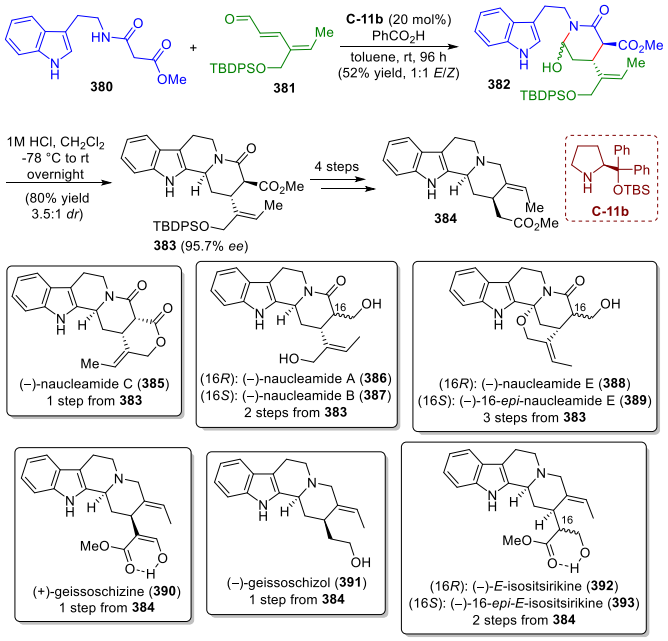
Subsequently, the Ishikawa group took a similar approach and accomplished the total synthesis of (+)-quinine (**378**) and (–)-9-*epi*-quinine (**379**).[107] Prolinol silyl ether **C-11c**-catalyzed [3+3] annulation between enal **372** and thiomalonamate **373** afforded the intermediate **374**, which was subjected to cyanation and alcoholysis to give **375** in 71% yield with 94% *ee*. Following subsequent multi-step synthetic transformations, (+)-quinine (**378**) and (–)-9-*epi*-quinine (**379**) were synthesized (Scheme 56).



Scheme 56 The [3+3] annulation and total syntheses of (+)-quinine and (–)-9-*epi*-quinine (Ishikawa, 2019).

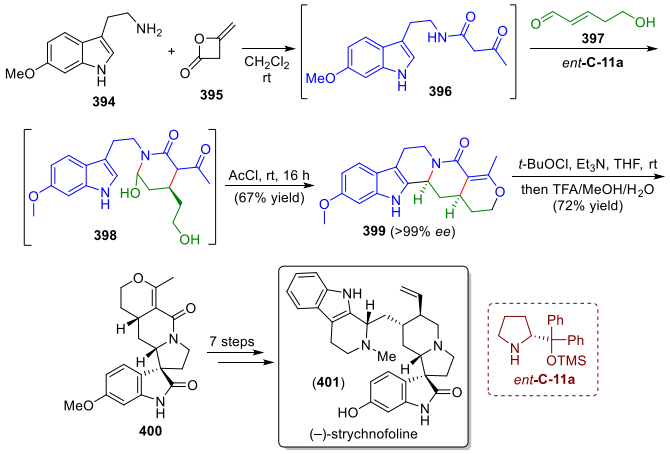
Jia and co-workers reported the total syntheses of eight monoterpenoid indole alkaloids, relying on an organocatalytic formal [3+3] annulation.[108] The total synthesis was featured by a prolinol **C-11b**-catalyzed cascade Michael/aza-Mannich reaction between amidomalonate **380** and dienal **381** to construct advanced intermediate **382**. Subsequently,

Pictet–Spengler reaction produced **383** with 95.7% *ee*, which possesses the key structural motifs embedded in a range of monoterpenoid indole alkaloids. Through a 4-step reaction sequence and following procedures reported in the literature,[109] total syntheses of (–)-naucleamides C (**385**), A (**386**), B (**387**), and E (**388**), (–)-16-*epi*-naucleamide E (**389**), (+)-geissoschizine (**390**), (–)-geissoschizol (**391**), (–)-(*E*)-isositsirikine (**392**), and (–)-16-*epi*-(*E*)-isositsirikine (**393**) were accomplished (Scheme 57).



Scheme 57 Divergent total syntheses of monoterpenoid indole alkaloids (Jia, 2017).

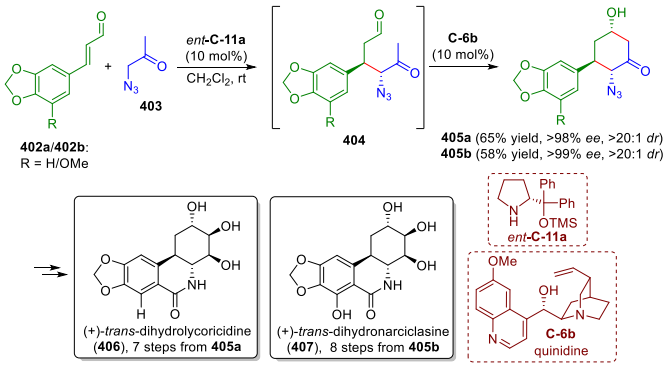
(–)-Strychnofoline (**401**) is a *Strychnos* alkaloid isolated from the leaves of *Strychnos usambarensis* and exhibited promising antimitotic activity.[110] Xu et al. accomplished the asymmetric total synthesis of (–)-strychnofoline (**401**) in nine steps.[111] The one-pot sequence to construct the key skeleton started with the acylation of commercially available methoxytryptamine **394**, followed by the prolinol silyl ether **C-11a** catalyzed cascade Michael/aza-Mannich reaction with enal **397** to produce intermediate **398**, which underwent a Pictet–Spengler reaction to create polycyclic **399** in a total 67% yield with >99% *ee*. Subsequently, an oxidative rearrangement formed the core spirooxindole structural motif of (–)-strychnofoline. Further transformations, including a selective amide reduction and a Shapiro tosylhydrazone decomposition, completed the total synthesis of target natural product (Scheme 58).



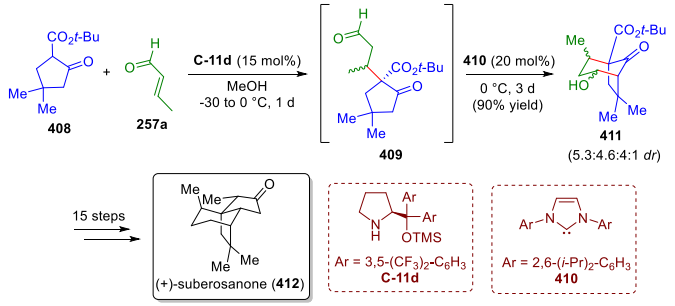
Scheme 58 Total synthesis of (–)-strychnofoline (Xu, 2018).

4.4 Catalysis with dual catalysts

The McNulty group reported the total syntheses of two amaryllidaceae alkaloids, i.e. (+)-*trans*-dihydrolycoricidine (**406**)[112] and (+)-*trans*-dihydronarciclasine (**407**),[113] in 2014 and 2016, respectively. The key element of these syntheses is a secondary amine-catalyzed *syn*-Michael addition followed by an intramolecular aldol condensation. The [3+3] annulation reaction between substituted cinnamaldehyde (**402a** or **402b**) and azidoacetone (**403**) in the presence of diarylprolinol silyl ether *ent*-**C-11a** and quinidine **C-6b** furnished cyclohexane derivative **405a** or **405b** in moderate yield with excellent stereoselectivity. It is interesting to note that dual catalysts were used for this transformation; while secondary amine catalyst was responsible for inducing asymmetry, the bulky tertiary amine catalyst was crucial for achieving high diastereoselectivity, which was believed to be pivotal for promoting proton shuffling to permit sequential Michal/aldol sequence. With the advanced hexane intermediates constructed, the subsequent structural elaborations to the target natural products were straightforward (Scheme 59).



Scheme 59 Cascade Michael/aldol and total syntheses of (+)-*trans*-dihydrolycoricidine and (+)-*trans*-dihydronarciclasine (McNulty, 2014, 2016).



Scheme 60 Secondary amine/NHC dual catalytic system and total synthesis of (+)-suberosanone (Rodriguez, Coquerel, 2016).

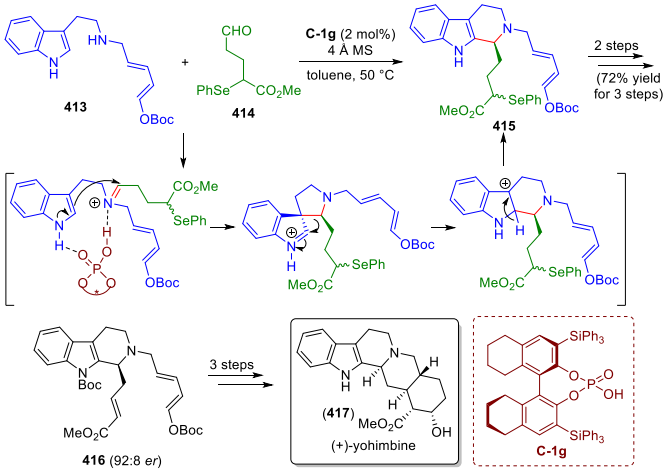
Coquerel, Rodriguez, and co-workers presented a dual organocatalytic system and documented the total synthesis of (+)-suberosanone (**412**).[114] The [3+3] annulation between β-Ketoester **408** and enal **257a** catalyzed by dual secondary amine and NHC catalysts, via a sequential Michael/aldol reaction, generated 6-membered ketone **411** in 90% as a mixture of diastereoisomers. While prolinol **C-11d** promoted the first Michael addition via iminium activation, the NHC catalyst **410** operated as the reactivity switch and was important for the subsequent aldol condensation. With intermediate **411** in hand, the authors continued to complete the total synthesis of (+)-suberosanone (**412**) in a 15-step reaction sequence (Scheme 60).

5. [5+1] Annulation

The [5+1] annulation serves as another method for constructing common six-membered ring structural motifs. The asymmetric total syntheses of natural products utilizing [5+1] annulation was mostly based on Pictet–Spengler reaction, in which arylethylamines undergo condensation with ketones or aldehydes. Other asymmetric [5+1] annulations make use of cascade reactions. The details of all the [5+1] annulation processes and their applications in natural products total synthesis are described in the following sections.

5.1 Catalysis with chiral phosphoric acids

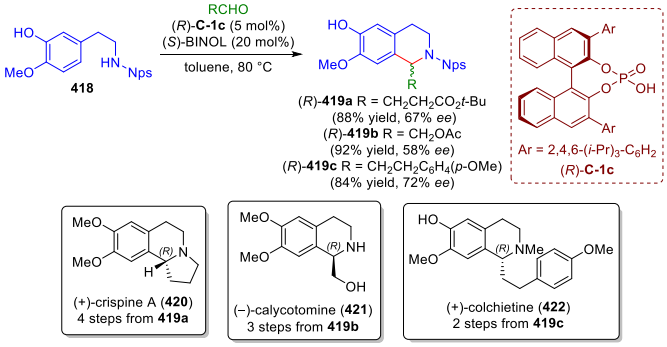
In 2011, the Hiemstra group disclosed the total synthesis of (+)-yohimbine (**417**).[115] The key reaction of their synthesis is a chiral phosphoric acid (**C-1g**)-catalyzed Pictet–Spengler reaction to construct tricyclic indoline structures. In the presence of **C-1g**, the Pictet–Spengler reaction between tryptamine derivative **413** and aldehyde **414** led to the formation of **415**, which was subjected to oxidation/elimination sequence to produce **416** in 72% overall yield with a 92:8 *er*. Subsequent transformations, including an intramolecular Diels–Alder reaction completed the total synthesis of (+)-yohimbine (**417**) (Scheme 61). Taking a similar approach, and following the literature reports established by Sato et al.,[116] the same authors achieved the formal total synthesis of corynantheidine.



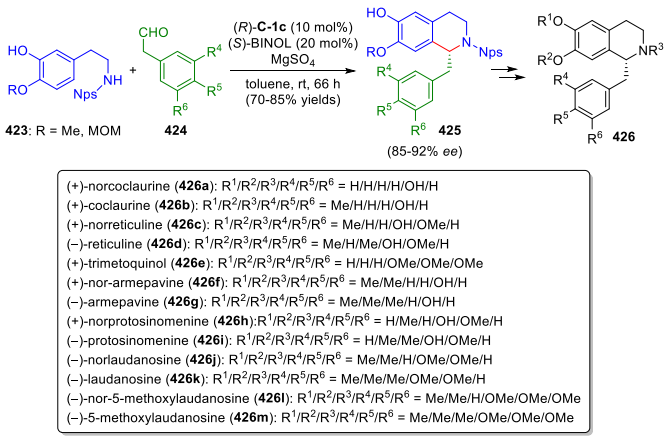
Scheme 61 The Pictet–Spengler reaction and total synthesis of (+)-yohimbine (Hiemstra, 2011).

The Hiemstra group next extended their previously developed asymmetric Pictet–Spengler reaction for the enantioselective syntheses of a number of 1-substituted 1,2,3,4-tetrahydroisoquinolines.[117] Notably, the employment of *N*-*o*-nitrophenylsulfenyl group (Nps) in phenylethylamine **418** was crucial for the smooth occurrence of the Pictet–Spengler reactions. With common intermediates **419** in hand, through short reaction sequences, the total syntheses of (+)-crispine A (**420**), (–)-calycotomine (**421**) and (+)-colchietine (**422**) were conveniently accomplished (Scheme 62).

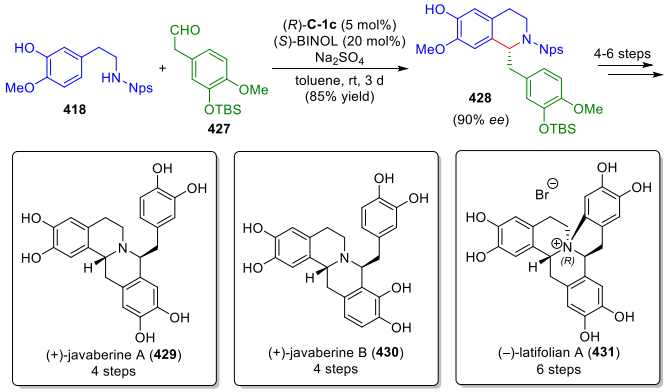
Hiemstra and co-workers further demonstrated the powerful of their phosphoric acid-catalyzed Pictet–Spengler approach, and amply demonstrated their applications in natural products synthesis.[118] With the construction of different 1-substituted 1,2,3,4-tetrahydroisoquinolines, they achieved the total syntheses of (+)-norcoclaurine (**426a**), (+)-coclaurine (**426b**), (+)-norreticuline (**426c**), (–)-reticuline (**426d**), (+)-trimetoquinol (**426e**), (+)-nor-armepavine (**426f**), (–)-armepavine (**426g**), (+)-norprotosinomenine (**426h**), (–)-protosinomenine (**426i**), (–)-norlaudanosine (**426j**), (–)-laudanosine (**426k**), (–)-nor-5-methoxylaudanosine (**426l**), and (–)-5-methoxylaudanosine (**426m**) (Scheme 63).



Scheme 62 Total syntheses of (+)-crispine A, (–)-calycotomine and (+)-colchietine using the Pictet–Spengler reaction as a key step (Hiemstra, 2014).



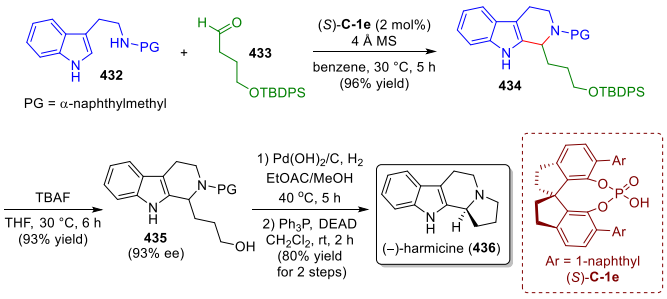
Scheme 63 Divergent total syntheses of alkaloids (Hiemstra, 2015).



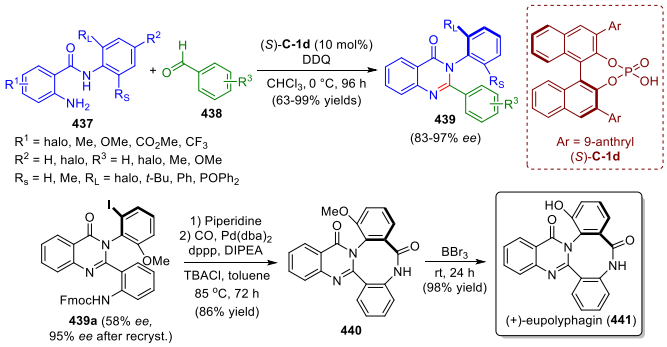
Scheme 64 The Pictet–Spengler reaction towards 8-benzylprotoberberines and related total syntheses (Hiemstra, 2016).

Through phosphoric acid-catalyzed consecutive Pictet–Spengler condensations, the Hiemstra group accomplished the total syntheses of tetrahydroprotoberberine alkaloids[119] The first Pictet–Spengler between phenylethylamine **418** and aldehydes **427** produced tetrahydroisoquinoline **428**, which was then subjected to another Pictet–Spengler condensation, followed by trivial synthetic manipulations, accomplished the total syntheses of (+)-javaberine A (**429**), (+)-javaberine B (**430**), and (–)-latifolian A (**431**). (Scheme 64).

Lin, Wang, co-workers reported a phosphoric acid-catalyzed Pictet–Spengler reaction and accomplished the total synthesis of (–)-harmicine (**436**)[120] and the formal total synthesis of (–)-quinolactacin B.[121] In the presence of SPINOL phosphoric acid **C-1e**, the Pictet–Spengler reaction between the tryptamine **432** and aldehyde **433** led to the formation of condensation product **434**, which was subjected to desilylation to yield **435** with 93% ee. At last, a few simple steps delivered (–)-harmicine (**436**) (Scheme 65).



Scheme 65 Phosphoric acid-catalyzed Pictet–Spengler reaction and total synthesis of (–)-harmicine (Lin, Wang, 2012).

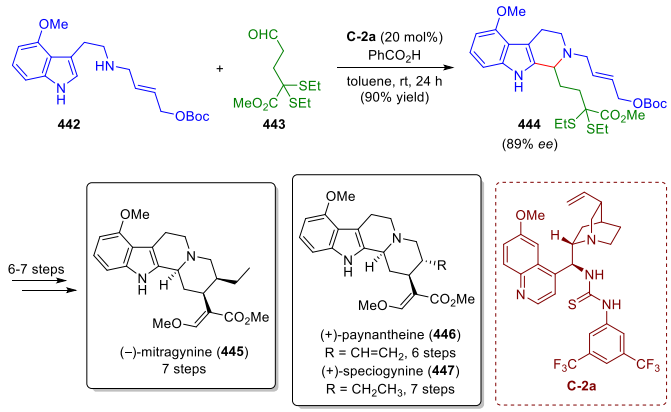


Scheme 66 Brønsted acid-catalysed construction of axially chiral arylquinazolinones and total synthesis of (+)-eupolyphagin (Tan, 2017).

Eupolyphagin (**441**) was an axially chiral arylquinazolinone that was first isolated from Chinese insect medicine *Eupolyphaga sinensis*.[122] The Tan group accomplished an asymmetric total synthesis of (+)-eupolyphagin, relying on an efficient phosphoric acid-catalyzed one-pot method to access axially chiral arylquinazolinones.[123] Phosphoric acid (*S*)-**C-1d** effectively promoted the [5+1] annulation between *N*-aryl anthranilamides **437** and aldehyde **438**, via a cascade imination/*N,N*-aminal cyclization/dehydrogenation, to afford axially chiral **439** in 63-99% yield with 83-97% *ee*. The total synthesis precursor **439a**, with an *ee* value of 95% after recrystallization, was further converted in a few steps including a palladium-catalyzed carbonylation reaction to deliver (+)-eupolyphagin (**441**) (Scheme 66).

5.2 Catalysis with thioureas and squaramide

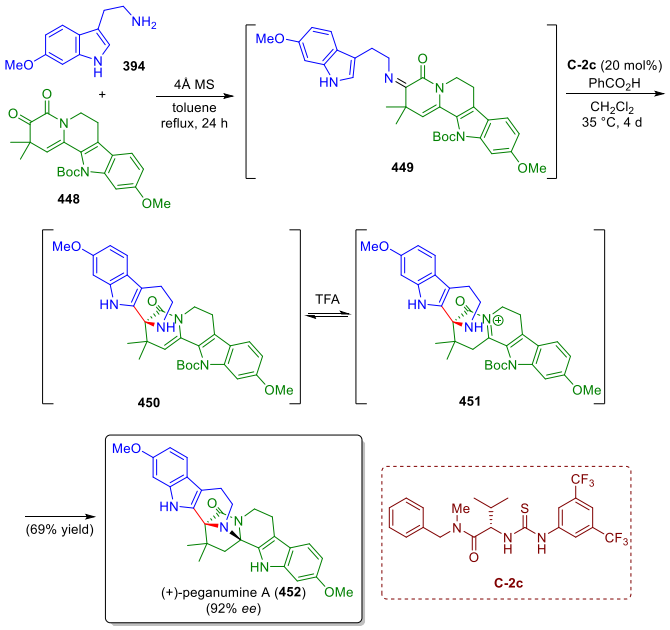
Other than phosphoric acid catalysts, Hiemestra and co-workers also employed chiral thioureas to promote enantioselective Pictet–Spengler reaction.[124] In the presence of quinine-derived thiourea catalyst **C-2a**, tryptamine derivative **442** condensed with aldehyde **443** to afford product **444** in 90% yield with 89% *ee*. Treatment of **444** with silver triflate formed α-ketoester, which is an ideal precursor for the subsequent palladium-catalyzed Tsuji–Trost cyclization. Following the construction of critical tetracyclic ring structure, a few further transformations completed the total syntheses of (–)-mitragynine (**445**), (+)-paynantheine (**446**) and (+)-speciogynine (**447**) (Scheme 67).



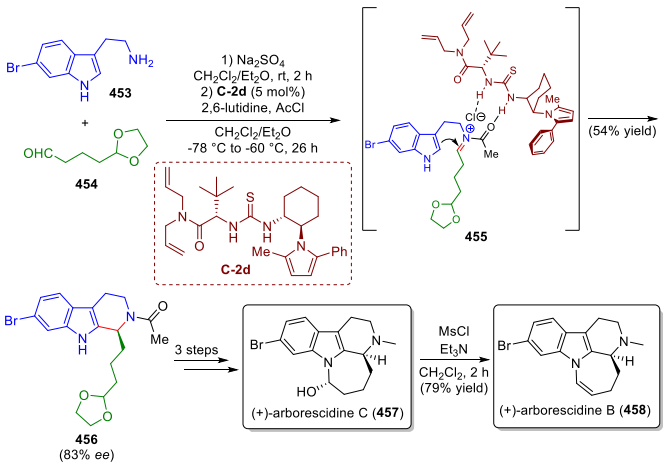
Scheme 67 Thiourea-promoted Pictet–Spengler reaction and total syntheses of (–)-mitragynine, (+)-paynantheine and (+)-speciogynine (Hiemstra, 2012).

Peganumine was a dimeric tetrahydro-β-carboline alkaloid isolated from *Peganum harmala* L.[125] In 2016, the Zhu group accomplished the first asymmetric total synthesis of (+)-peganumine (**452**).[126] The most important step of their synthesis is a one-pot organocatalytic process merging two achiral building blocks into 2,7-diazabicyclo[2.2.1]heptan-3-one structural motif. In the presence of thiourea catalyst **C-2c** and co-catalyst $PhCO_2H$, the Pictet–Spengler reaction between tryptamine **394** and tetracyclic α-ketoamide **448** formed the condensation intermediate **450**. The treatment of **450** with TFA triggered an enamine–iminium tautomerization, resulting in a transannular cyclization to deliver natural product (+)-peganumine (**452**) in total 69% yield with 92% *ee* (Scheme 68).

Hong and co-workers developed a thiourea-catalyzed Pictet–Spengler reaction, which was utilized for the total syntheses of (+)-arborescidine C (**457**) and (+)-arborescidine B (**458**).[127] The Pictet–Spengler condensation between tryptamine **453** and aldehyde **454** catalyzed by thiourea **C-2d** delivered **420** in 54% yield with 83% ee. Notably, acetyl chloride was crucial for this reaction, because it facilitated the formation of *N*-acyliminium chloride–thiourea complex **455**, pivotal for asymmetric induction. The synthetic manipulations of **456** were straightforward, and the total syntheses of (+)-arborescidine C (**457**) and (+)-arborescidine B (**458**) were readily accomplished (Scheme 69).

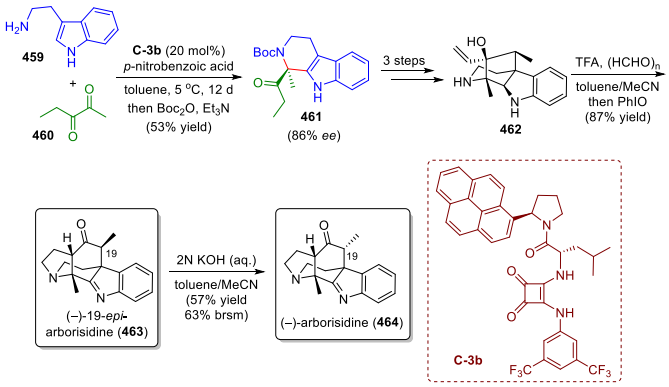


Scheme 68 Total synthesis of (+)-peganumine (Zhu, 2016).



Scheme 69 Total syntheses of (+)-arborescidine C and (+)-arborescidine B (Hong, 2017).

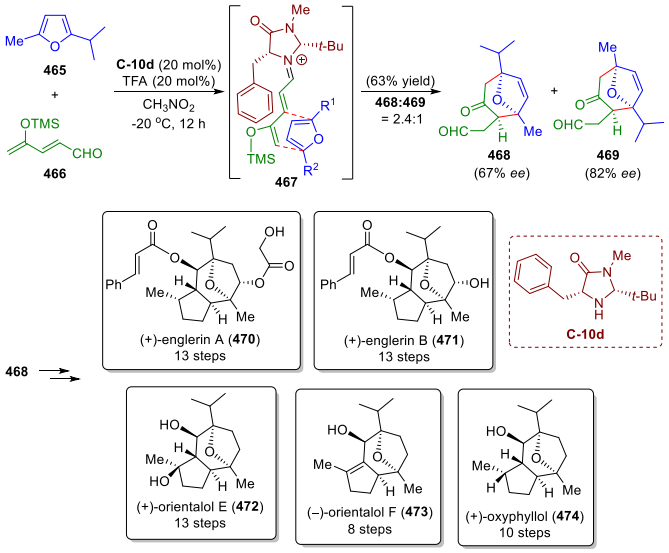
Very recently, Zhu and co-workers disclosed the asymmetric total syntheses of (–)-19-*epi*-arborisidine (**463**) and (–)-arborisidine (**464**), enabled by a squaramide-catalyzed enantioselective Pictet–Spengler reaction.[128] Under the catalysis of squaramide **C-3b**, tryptamine **459** underwent Pictet–Spengler condensation with diketone **460** to deliver advanced ketone intermediate **461** in 53% yield with 86% *ee*. Following a three-step reaction transformation including an intramolecular oxidative coupling, allyl alcohol **462** was obtained. Finally, treatment with TFA/$(HCHO)_n$, followed by PhIO triggered an aza-Cope/Mannich/oxidation cascade process to furnish (–)-19-*epi*-arborisidine (**463**). Epimerization of **463** with 2N KOH (aq.) in toluene/MeCN gave (–)-arborisidine (**464**) in 57% yield (Scheme 70).



Scheme 70 Total syntheses of (−)-19-*epi*-arborisidine and (−)-arborisidine enabled by catalytic Pictet-Spengler reaction (Zhu, 2020).

6. [4+3] Annulation

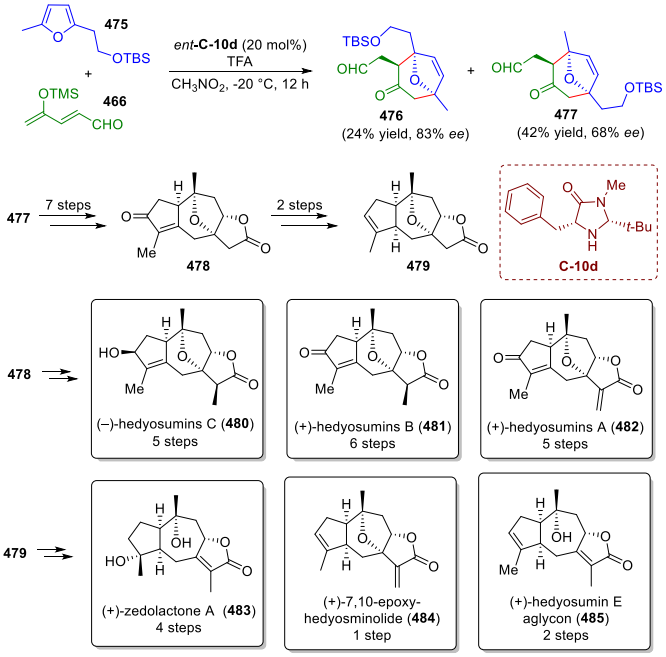
The asymmetric [4+3] annulation reactions are rather uncommon, and very limited applications to natural products total synthesis relied on the [4+3] annulation reaction of furan derivatives, catalyzed by imidazolidinones.



Scheme 71 Divergent total syntheses of terpenes (Sun, Lin, Xu, 2011-2013).

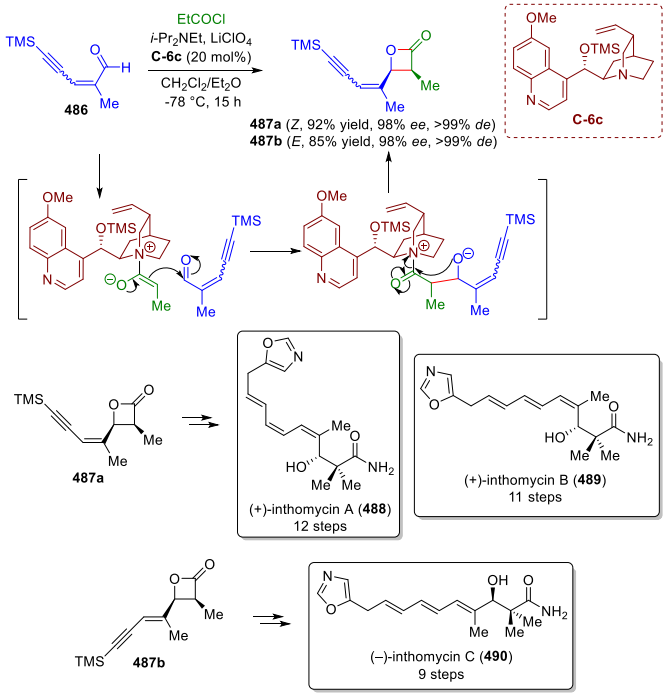
Sun, Lin, Xu, and co-workers accomplished divergent total syntheses of a range of terpenes.[129] The transformation crucial for the total syntheses was the construction of oxo-bridged cycloheptanone skeleton. The MacMillan catalyst **C-10d** was employed to promote a [4+3] cycloaddition between the furan **465** and dienal **466**, creating key common oxygen-bridged intermediates **468** and **469**, in 67% *ee* and 82% *ee*, respectively. With the oxygen-bridged skeleton efficiently constructed, subsequent structural elaborations led to the total syntheses of (+)-englerin A (**470**) and B (**471**), (+)-orientalol E (**472**), (–)-orientalol F (**473**), and (+)-oxyphyllol (**474**) (Scheme 71).

Utilizing the same strategy, Lin, Sun, and co-workers subsequently achieved divergent total syntheses of guaianolides.[130] In the presence of *ent*-**C-10d**, the [4+3] annulation between furan **475** and dienal **466** formed the desired regioisomer **477** in 42% yield with 68% *ee*. The elaboration of **477** to lactone **478**, and subsequently to alkene lactone **479** were easily realized. With advanced intermediates **478** and **479** in hand, the authors proceeded to accomplish the total syntheses of (–)-hedyosumins C (**480**), (+)-hedyosumins B (**481**), (+)-hedyosumins A (**482**), as well as (+)-zedolactone A (**483**), (+)-7,10-epoxy-hedyosminolide (**484**), and (+)-hedyosumin E aglycon (**485**) (Scheme 72).



Scheme 72 Divergent total syntheses of guaianolides (Lin, Sun, 2016).

7. [2+2] Annulation



Scheme 73 Total syntheses of (+)-inthomycin A, (+)-inthomycin B and (−)-inthomycin C (Hatakeyama, 2012).

Stereoselective [2+2] annulations in fact are rare, and their applications to asymmetric total synthesis of natural products are scarce. In 2012, the Hatakeyama group reported organocatalytic asymmetric syntheses of inthomycins A (**488**), B (**489**) and C (**490**).[131] One key reaction in the synthesis is a quinidine TMS ether **C-6c**-catalyzed [2+2] annulation between aldehyde **486** and ketene, *in situ* generated from propionyl chloride. The reaction was applicable to both *Z* and *E* type substrates, and β-lactones **487** were obtained in good yield with excellent enantio- and diastereoselectivities. Lactone intermediates **487a** and **487b** served as common intermediates, from which the total syntheses of (+)-inthomycin A (**488**), (+)-inthomycin B (**489**) and (−)-inthomycin C (**490**) were accomplished (Scheme 73).

8. Conclusions and outlook

We have summarized the latest progress of asymmetric organocatalytic annulation reactions, placing them in the context of natural products total synthesis. The state-of-the-art of annulation reactions whereby different molecular moieties are annealed via organic catalysis are fascinating, through which optically enriched 4-, 5-, 6- and 7-membered carbo- or heteroatom- ring structural motifs are effectively constructed. The annulation reactions are often featured with the following: 1) readily available starting materials; 2) easily obtainable organic catalysts; 3) mild reaction conditions, insensitive to air and moisture at most times; 4) frequently being non-toxic and environmentally benign; 5) atom-, step-, pot-economy, efficiently constructing structural complexity from simple starting motifs. Moreover, it is noteworthy that certain types of organic catalysts have been shown to be privileged in promoting a variety of different types of reactions, often with excellent stereochemical controls. Such catalyst families include: chiral phosphoric acids, thioureas, squaramides, cinchona alkaloids, iminophosphoranes, *N*-heterocyclic carbenes, and phosphines, among others. When the reaction discovery is concerned, employment of powerful privileged catalyst classes is advantageous, such practice will make reaction exploration and development more likely to be successful. Despite the astonishing progress of asymmetric organocatalytic annulation reactions and their applications in natural products synthesis, certain drawbacks persist. High catalyst loadings are usually required, and the reaction times are often too long. Furthermore, the activation modes are limited, which in turn place constraints on the substrates that can be employed. We anticipate more efforts will be devoted to the development of truly efficient processes in the future, which will facilitate industrial scale production, as well as make multi-step total synthesis practical. To make synthetic approaches more powerful and versatile, we strongly believe that various organocatalytic modes of activations will be utilized in a synergistic manner with other well-established catalytic platforms, for instance, transition metal catalysis, photoredox catalysis, thus elevating the power of annulation reactions to new heights. We hope this review will provide an overview to synthetic chemists so that recent marvellous advancement in organocatalytic annulation reactions and related beautiful applications in natural products synthesis can be better appreciated and recognized. More importantly, we hope the current exciting adventure will inspire organic practitioners to develop even more powerful and versatile synthetic methods to advance the state-of-the-art of ring construction strategies, leading to a new chapter in the total synthesis of natural products.

Conflicts and interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

1. (a) D. J. Newman and G. M. Cragg, *J. Nat. Prod.*, 2012, **75**, 311-335; (b) M. S. Butler, A. A. Robertson and M. A. Cooper, *Nat. Prod. Rep.*, 2014, **31**, 1612-1661; (c) D. J. Newman and G. M. Cragg, *J. Nat. Prod.*, 2016, **79**, 629-661; (d) T. Rodrigues, D. Reker, P. Schneider and G. Schneider, *Nat. Chem.*, 2016, **8**, 531-541; (e) D. J. Newman and G. M. Cragg, *J. Nat. Prod.*, 2020, **83**, 770-803.

2. (a) D. C. Blakemore, L. Castro, I. Churcher, D. C. Rees, A. W. Thomas, D. M. Wilson and A. Wood, *Nat. Chem.*, 2018, **10**, 383-394; (b) K. C. Nicolaou and S. Rigol, *Nat. Prod. Rep.*, 2020, **37**, 1404-1435.
3. (a) M. Waser, *Asymmetric Organocatalysis in Natural Product Syntheses*, Springer, Berlin, 2012; (b) P.-Q. Huang, Z.-J. Yao and R. P. Hsung, *Efficiency in Natural Product Total Synthesis*, Wiley, Hoboken, 2018.
4. (a) B. List, *Asymmetric Organocatalysis*, Springer, Heidelberg, 2010; (b) P. I. Dalko, *Comprehensive Enantioselective Organocatalysis Catalyst*, Wiley, Weinheim, 2013; (c) K. N. Houk and B. List, *Acc. Chem. Res.*, 2004, **37**, 487-487; (d) A. G. Doyle and E. N. Jacobsen, *Chem. Rev.*, 2007, **107**, 5713-5743; (e) H. Pellissier, *Tetrahedron*, 2007, **63**, 9267-9331; (f) A. Dondoni and A. Massi, *Angew. Chem. Int. Ed.*, 2008, **47**, 4638-4660; (g) S. Bertelsen and K. A. Jorgensen, *Chem. Soc. Rev.*, 2009, **38**, 2178-2189; (h) G. Bartoli, G. Bencivenni and R. Dalpozzo, *Chem. Soc. Rev.*, 2010, **39**, 4449-4465; (i) F. Giacalone, M. Gruttadauria, P. Agrigento and R. Noto, *Chem. Soc. Rev.*, 2012, **41**, 2406-2447; (j) P. Chauhan and S. S. Chimni, *RSC Adv.*, 2012, **2**, 737-758; (k) L. Bernardi, M. Fochi, M. Comes Franchini and A. Ricci, *Org. Biomol. Chem.*, 2012, **10**, 2911-2922; (l) R. Dalpozzo, G. Bartoli and G. Bencivenni, *Chem. Soc. Rev.*, 2012, **41**, 7247-7290; (m) J. Aleman and S. Cabrera, *Chem. Soc. Rev.*, 2013, **42**, 774-793; (n) U. Scheffler and R. Mahrwald, *Chem. - Eur. J.*, 2013, **19**, 14346-14396; (o) P. Chauhan, S. Mahajan and D. Enders, *Chem. Rev.*, 2014, **114**, 8807-8864; (p) G. Zhan, W. Du and Y.-C. Chen, *Chem. Soc. Rev.*, 2017, **46**, 1675-1692; (q) Y.-B. Wang and B. Tan, *Acc. Chem. Res.*, 2018, **51**, 534-547; (r) A. Ding, M. Meazza, H. Guo, J. W. Yang and R. Rios, *Chem. Soc. Rev.*, 2018, **47**, 5946-5996; (s) A. Franconetti and G. de Gonzalo, *ChemCatChem*, 2018, **10**, 5554-5572; (t) M. P. van der Helm, B. Klemm and R. Eelkema, *Nat. Rev. Chem.*, 2019, **3**, 491-508; (u) D. Kristofikova, V. Modrocka, M. Meciarova and R. Sebesta, *ChemSusChem*, 2020, **13**, 2828-2858; (v) X. Xiao, B.-X. Shao, Y.-J. Lu, Q.-Q. Cao, C. Xia and F.-E. Chen, *Adv. Synth. Catal.*, 2021, **363**, 352-387; (w) A. Ghosh and A. T. Biju, *Angew. Chem. Int. Ed.*, 2020, **60**, 13712-13724.
5. P. Muller, *Pure Appl. Chem.*, 1994, **66**, 1077-1184.
6. (a) A. Moyano and R. Rios, *Chem. Rev.*, 2011, **111**, 4703-4832; (b) D. W. MacMillan, *Nature*, 2008, **455**, 304-308.
7. (a) C. Grondal, M. Jeanty and D. Enders, *Nat Chem*, 2010, **2**, 167-178; (b) E. Marques-Lopez, R. P. Herrera and M. Christmann, *Nat. Prod. Rep.*, 2010, **27**, 1138-1167; (c) B.-F. Sun, *Tetrahedron Lett.*, 2015, **56**, 2133-2140.
8. J. Merad, C. Lalli, G. Bernadat, J. Maury and G. Masson, *Chem. - Eur. J.*, 2018, **24**, 3925-3943.
9. M. E. Abbasov and D. Romo, *Nat. Prod. Rep.*, 2014, **31**, 1318-1327.
10. J. Izquierdo, G. E. Hutson, D. T. Cohen and K. A. Scheidt, *Angew. Chem. Int. Ed.*, 2012, **51**, 11686-11698.
11. C. Gomez, J.-F. Betzer, A. Voituriez and A. Marinetti, *ChemCatChem*, 2013, **5**, 1055-1065.
12. Z. Wang, *Molecules*, 2019, **24**, 3412-3450.
13. G. J. Reyes-Rodriguez, N. M. Rezayee, A. Vidal-Albalat and K. A. Jorgensen, *Chem. Rev.*, 2019, **119**, 4221-4260.
14. P. Kumar and B. Sharma, *Synlett*, 2018, **29**, 1944-1956.
15. M. Odagi and K. Nagasawa, *Asian J. Org. Chem.*, 2019, **8**, 1766-1774.
16. O. V. Matsev, I. P. Beletskaya and S. G. Zlotin, *Russian Chemical Reviews*, 2011, **80**, 1067-1113.
17. (a) H. Ishikawa and S. Shiomi, *Org. Biomol. Chem.*, 2016, **14**, 409-424; (b) J. Song, D.-F. Chen and L.-Z. Gong, *Natl. Sci. Rev.*, 2017, **4**, 381-396.
18. F. Vetica, P. Chauhan, S. Dochain and D. Enders, *Chem. Soc. Rev.*, 2017, **46**, 1661-1674.
19. M. Hatano, Y. Goto, A. Izumiseki, M. Akakura and K. Ishihara, *J. Am. Chem. Soc.*, 2015, **137**, 13472-13475.
20. (a) L. Moisan, P. Thuery, M. Nicolas, E. Doris and B. Rousseau, *Angew. Chem. Int. Ed.*, 2006, **45**, 5334-5336; (b) G. Büchi, P. Kulsa, K. Ogasawara and R. L. Rosati, *J. Am. Chem. Soc*. 1970, **92**, 999-1005.
21. C. Szántay, H. Bölcskei and E. Gács-Baitz, *Tetrahedron*, 1990, **46**, 1711-1732.
22. S. Romanini, E. Galletti, L. Caruana, A. Mazzanti, F. Himo, S. Santoro, M. Fochi and L. Bernardi, *Chem. - Eur. J.*, 2015, **21**, 17578-17582.
23. M. Somei, F. Yamada and Y. Makita, *Heterocycles*, 2007, **72**, 599-620.
24. W.-J. Liang, C.-A. Geng, X.-M. Zhang, H. Chen, C.-Y. Yang, G.-Q. Rong, Y. Zhao, H.-B. Xu, H. Wang, N.-J. Zhou, Y.-B. Ma, X.-Y. Huang and J.-J. Chen, *Org. Lett.*, 2014, **16**, 424-427.
25. T.-Z. Li, C.-A. Geng, X.-J. Yin, T.-H. Yang, X.-L. Chen, X.-Y. Huang, Y.-B. Ma, X.-M. Zhang and J.-J. Chen, *Org. Lett.*, 2017, **19**, 429-431.
26. M. J. Smith, K. D. Reichl, R. A. Escobar, T. J. Heavey, D. F. Coker, S. E. Schaus and J. A. Porco, Jr., *J. Am. Chem. Soc.*, 2019, **141**, 148-153.
27. L.-J. Zhang, D.-W. Bi, J. Hu, W.-H. Mu, Y.-P. Li, G.-H. Xia, L. Yang, X.-N. Li, X.-S. Liang and L.-Q. Wang, *Org. Lett.*, 2017, **19**, 4315-4318.
28. Z. Liu, Y. Meng, P. Yuan, Z. Wang, J. M. Gao and H. Zheng, *Org. Lett.*, 2020, **22**, 520-522.
29. Y. Wang, Y.-C. Luo, H.-B. Zhang and P.-F. Xu, *Org. Biomol. Chem.*, 2012, **10**, 8211-8215.
30. L. D. Miranda and S. Z. Zard, *Org. Lett.*, 2002, **4**, 1135-1138.
31. (a) S. Varga, P. Angyal, G. Martin, O. Egyed, T. Holczbauer and T. Soos, *Angew. Chem. Int. Ed.*, 2020, **59**, 13547-13551; (b) G. Martin, P. Angyal, O. Egyed, S. Varga and T. Soos, *Org. Lett.*, 2020, **22**, 4675-4679.
32. K. L. White and M. Movassaghi, *J. Am. Chem. Soc.*, 2016, **138**, 11383-11389.
33. C. Li, D. Lee, T. N. Graf, S. S. Phifer, Y. Nakanishi, J. P. Burgess, S. Riswan, F. M. Setyowati, A. M. Saribi, D. D. Soejarto, N. R. Farnsworth, J. O. I. Falkinham, D. J. Kroll, A. D. Kinghorn, M. C. Wani and N. H. Oberlies, *Org. Lett.*, 2005, **7**, 5709-5712.
34. M. J. R. Richter, M. Schneider, M. Brandstatter, S. Krautwald and E. M. Carreira, *J. Am. Chem. Soc.*, 2018, **140**, 16704-16710.
35. W. Feng, D. Jiang, C.-W. Kee, H. Liu and C.-H. Tan, *Chem. Asian J.*, 2016, **11**, 390-394.
36. G.-Q. Xu, G.-Q. Lin and B.-F. Sun, *Org. Chem. Front.*, 2017, **4**, 2031-2033.
37. M. Bertrand, P. Teisseire and G. Pelerin, *Tetrahedron Lett.*, 1980, **21**, 2051-2054.
38. L. Liu, S. Liu, L. Jiang, X. Chen, L. Guo and Y. Che, *Org. Lett.*, 2008, **10**, 1397-1400.
39. T. Suzuki, S. Watanabe, S. Kobayashi and K. Tanino, *Org. Lett.*, 2017, **19**, 922-925.
40. H. Shi, I. N. Michaelides, B. Darses, P. Jakubec, Q. N. N. Nguyen, R. S. Paton and D. J. Dixon, *J. Am. Chem. Soc.*, 2017, **139**, 17755-17758.
41. M. T. Hovey, D. T. Cohen, D. M. Walden, P. H. Cheong and K. A. Scheidt, *Angew. Chem. Int. Ed.*, 2017, **56**, 9864-9867.

42. E. R. Miller, M. T. Hovey and K. A. Scheidt, *J. Am. Chem. Soc.*, 2020, **142**, 2187-2192.
43. A. Ametovski and D. W. Lupton, *Org. Lett.*, 2019, **21**, 1212-1215.
44. S. B. Jones, B. Simmons, A. Mastracchio and D. W. MacMillan, *Nature*, 2011, **475**, 183-188.
45. B. N. Laforteza, M. Pickworth and D. W. Macmillan, *Angew. Chem. Int. Ed.*, 2013, **52**, 11269-11272.
46. B. D. Horning and D. W. MacMillan, *J. Am. Chem. Soc.*, 2013, **135**, 6442-6445.
47. Y. Bai, X. Shen, Y. Li and M. Dai, *J. Am. Chem. Soc.*, 2016, **138**, 10838-10841.
48. B. C. Hong, C. S. Hsu and G. H. Lee, *Chem. Commun.*, 2012, **48**, 2385-2387.
49. K. S. Halskov, B. S. Donslund, S. Barfusser and K. A. Jorgensen, *Angew. Chem. Int. Ed.*, 2014, **53**, 4137-4141.
50. Y. Y. Yeung, R. J. Chein and E. J. Corey, *J. Am. Chem. Soc.*, 2007, **129**, 10346-10347.
51. C. Lei, S.-X. Huang, J.-J. Chen, L.-B. Yang, W.-L. Xiao, Y. Chang, Y. Lu, H. Huang, J.-X. Pu and H.-D. Sun, *J. Nat. Prod.*, 2008, **71**, 1228-1232.
52. L. You, X. T. Liang, L. M. Xu, Y. F. Wang, J. J. Zhang, Q. Su, Y. H. Li, B. Zhang, S. L. Yang, J. H. Chen and Z. Yang, *J. Am. Chem. Soc.*, 2015, **137**, 10120-10123.
53. (a) Y. Hayashi, S. Koshino, K. Ojima and E. Kwon, *Angew. Chem. Int. Ed.*, 2017, **56**, 11812-11815; (b) S. Koshino, E. Kwon and Y. Hayashi, *Eur. J. Org. Chem.*, 2018, 5629-5638.
54. W. L. Huang, A. Raja, B. C. Hong and G. H. Lee, *Org. Lett.*, 2017, **19**, 3494-3497.
55. M. G. Fulton, J. L. Bertron, C. W. Reed and C. W. Lindsley, *J. Org. Chem.*, 2019, **84**, 12187-12191.
56. D. Lucke, Y. Linne, K. Hempel and M. Kalesse, *Org. Lett.*, 2018, **20**, 4475-4477.
57. H. Ishii, J.-I. Kobayashi and T. Ishikawa, *Tetrahedron Lett.*, 1991, **32**, 6907-6910.
58. K.-Q. Hou, X.-P. Chen, Y. Huang, A. S. C. Chan, H.-B. Luo and X.-F. Xiong, *Org. Lett.*, 2020, **22**, 584-588.
59. S. J. Kim and R. A. Batey, *Org. Chem. Front.*, 2018, **5**, 2934-2939.
60. G. Buchi, P. Kulsa, K. Ogasawara and R. L. Rosati, *J. Am. Chem. Soc.*, 1970, **92**, 999-1005.
61. S. P. Chavan, A. L. Kadam and R. G. Gonnade, *Org. Lett.*, 2019, **21**, 9089-9093.
62. R. Nordmann and T. J. Petcher, *J. Med. Chem.*, 1985, **28**, 367-375.
63. V. Maurya and C. Appayee, *Org. Lett.*, 2018, **20**, 4111-4115.
64. (a) H. Kawashima, Y. Kaneko, M. Sakai and Y. Kobayashi, *Chem. - Eur. J.*, 2014, **20**, 272-278; (b) H. Kawashima, M. Sakai, Y. Kaneko and Y. Kobayashi, *Tetrahedron*, 2015, **71**, 2387-2392.
65. V. Maurya and C. Appayee, *J. Org. Chem.*, 2020, **85**, 1291-1297.
66. S. Goswami, K. Harada, M. F. El-Mansy, R. Lingampally and R. G. Carter, *Angew. Chem. Int. Ed.*, 2018, **57**, 9117-9121.
67. X. Li and R. G. Carter, *Org. Lett.*, 2018, **20**, 5546-5549.
68. (a) Q. Zhang, F.-M. Zhang, C.-S. Zhang, S.-Z. Liu, J.-M. Tian, S.-H. Wang, X.-M. Zhang and Y.-Q. Tu, *Nat. Commun.*, 2019, **10**, 2507-2514; (b) Q. Zhang, F.-M. Zhang, C.-S. Zhang, S.-Z. Liu, J.-M. Tian, S.-H. Wang, X.-M. Zhang and Y.-Q. Tu, *J. Org. Chem.*, 2019, **84**, 12664-12671.
69. X. Chen, S. Duan, C. Tao, H. Zhai and F. G. Qiu, *Nat. Commun.*, 2015, **6**, 7204-7211.
70. M. E. Abbasov, B. M. Hudson, D. J. Tantillo and D. Romo, *J. Am. Chem. Soc.*, 2014, **136**, 4492-4495.
71. H. Okamura, K. Yamauchi, K. Miyawaki, T. Iwagawa and M. Nakatani, *Tetrahedron Lett.*, 1997, **38**, 263-266.
72. J. D. White, K. Takabe and M. P. Prisbylla, *J. Org. Chem.*, 1985, **50**, 5233-5244.
73. N. K. Rana, H. Huang and J. C. Zhao, *Angew. Chem. Int. Ed.*, 2014, **53**, 7619-7623.
74. C.-B. Cui, H. Kakeya and H. Osada, *Tetrahedron*, 1997, **53**, 59-72.
75. M.-N. Cheng, H. Wang and L.-Z. Gong, *Org. Lett.*, 2011, **13**, 2418-2421.
76. G. Alipour, S. Dashti and H. Hosseinzadeh, *Phytother. Res.*, 2014, **28**, 1125-1136.
77. M.-J. Cheng, X.-Y. Yang, J.-Q. Cao, C. Liu, L.-P. Zhong, Y. Wang, X.-F. You, C.-C. Li, L. Wang and W.-C. Ye, *Org. Lett.*, 2019, **21**, 1583-1587.
78. A. A. Salim, A. D. Pawlus, H. B. Chai, N. R. Farnsworth, A. Douglas Kinghorn and E. J. Carcache-Blanco, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 109-112.
79. N. J. Lajkiewicz, S. P. Roche, B. Gerard and J. A. Porco, Jr., *J. Am. Chem. Soc.*, 2012, **134**, 13108-13113.
80. C. M. Chaheine, P. T. Gladen, M. E. Abbasov and D. Romo, *Org. Lett.*, 2020, **22**, 9282-9286.
81. A. S. Kende, K. Kawamura and R. J. DeVita, *J. Am. Chem. Soc.*, 1990, **112**, 4070-4072.
82. J. Dugal-Tessier, E. A. O'Bryan, T. B. Schroeder, D. T. Cohen and K. A. Scheidt, *Angew. Chem. Int. Ed.*, 2012, **51**, 4963-4967.
83. G. Bergonzini and P. Melchiorre, *Angew. Chem. Int. Ed.*, 2012, **51**, 971-974.
84. A. Pou and A. Moyano, *Eur. J. Org. Chem.*, 2013, 3103-3111.
85. (a) N. Umekubo, Y. Suga and Y. Hayashi, *Chem. Sci.*, 2020, **11**, 1205-1209; (b) N. Umekubo and Y. Hayashi, *Eur. J. Org. Chem.*, 2020, 6221-6227.
86. E. J. Corey, N. M. Weinshenker, T. K. Schaaf and W. Huber, *J. Am. Chem. Soc.*, 1969, **91**, 5675-5677.
87. X. Han, F. Zhong, Y. Wang and Y. Lu, *Angew. Chem. Int. Ed.*, 2012, **51**, 767-770.
88. S. Ishikawa, F. Noguchi and A. Kamimura, *J. Org. Chem.*, 2010, **75**, 3578-3586.
89. W.-L. Chan, X. Tang, F. Zhang, G. Quek, G.-J. Mei and Y. Lu, *Angew. Chem. Int. Ed.*, 2019, **58**, 6260-6264.
90. L. E. Overman and D. V. Paone, *J. Am. Chem. Soc.*, 2001, **123**, 9465-9467.
91. L. E. Overman, D. V. Paone and B. A. Stearns, *J. Am. Chem. Soc.*, 1999, **121**, 7702-7703.
92. H. Mitsunuma, M. Shibasaki, M. Kanai and S. Matsunaga, *Angew. Chem. Int. Ed.*, 2012, **51**, 5217-5221.
93. (a) I. P. Andrews and O. Kwon, *Chem. Sci.*, 2012, **3**, 2510-2514; (b) L. Cai, K. Zhang and O. Kwon, *J. Am. Chem. Soc.*, 2016, **138**, 3298-3301.
94. M.-J. Cheng, J.-Q. Cao, X.-Y. Yang, L.-P. Zhong, L.-J. Hu, X. Lu, B.-L. Hou, Y.-J. Hu, Y. Wang, X.-F. You, L. Wang, W.-C. Ye and C.-C. Li, *Chem. Sci.*, 2018, **9**, 1488-1495.
95. (a) D.-X. Tan, J. Zhou, C.-Y. Liu and F.-S. Han, *Angew. Chem. Int. Ed.*, 2020, **59**, 3834-3839; (b) D.-X. Tan, J. Zhou and F.-S. Han, *Tetrahedron*, 2020, **76**, 131641; (c) J. Zhou, D. X. Tan and F. S. Han, *Angew. Chem. Int. Ed.*, 2020, **59**, 18731-18740.
96. (a) B. Bradshaw, C. Luque-Corredera and J. Bonjoch, *Org. Lett.*, 2013, **15**, 326-329; (b) B. Bradshaw, C. Luque-Corredera and J. Bonjoch, *Chem. Commun.*, 2014, **50**, 7099-7102.
97. B. Hong, D. Hu, J. Wu, J. Zhang, H. Li, Y. Pan and X. Lei, *Chem. Asian J.*, 2017, **12**, 1557-1567.
98. H. Hou, Q. Gu, X. Wang, D.-Q. Sun and B.-F. Sun, *Org. Chem. Front.*, 2018, **5**, 358-360.
99. I. K. Mangion and D. W. MacMillan, *J. Am. Chem. Soc.*, 2005, **127**, 3696-3697.

100. E. E. Robinson and R. J. Thomson, *J. Am. Chem. Soc.*, 2018, **140**, 1956-1965.
101. P. Bolze, G. Dickmeiss and K. A. Jørgensen, *Org. Lett.*, 2008, **10**, 3753-3756.
102. E. J. Corey and P. A. Magriotis, *J. Am. Chem. Soc.*, 1987, **109**, 287-289.
103. X. Wu, J. Huang, B. Guo, L. Zhao, Y. Liu, J. Chen and W. Cao, *Adv. Synth. Catal.*, 2014, **356**, 3377-3382.
104. Y. Yang, K. Kinoshita, K. Koyama, K. Takahashi, T. Tai, Y. Nunoura and K. Watanabe, *J. Nat. Prod.*, 1999, **62**, 1672-1674.
105. Y. Wang, R. Bao, S. Huang and Y. Tang, *Beilstein J. Org. Chem.*, 2013, **9**, 1601-1606.
106. S. Shiomi, E. Sugahara and H. Ishikawa, *Chem. - Eur. J.*, 2015, **21**, 14758-14763.
107. S. Shiomi, R. Misaka, M. Kaneko and H. Ishikawa, *Chem. Sci.*, 2019, **10**, 9433-9437.
108. L. Li, P. Aibibula, Q. Jia and Y. Jia, *Org. Lett.*, 2017, **19**, 2642-2645.
109. (a) M. Lousnasmaa, R. Jokela, P. Hanhinen, J. Miettinen and J. Salo, *Tetrahedron*, 1994, **50**, 9207-9222; (b) A. Deiters, K. Chen, C. T. Eary and S. F. Martin, *J. Am. Chem. Soc.*, 2003, **125**, 4541-4550.
110. R. Bassleer, M.-C. Depauw-Gillet, B. Massart, J.-M. Marnette, P. Wiliquet, M. Caprasse and L. Angenot, *Planta Med.*, 1982, **45**, 123-126.
111. Q. Yu, P. Guo, J. Jian, Y. Chen and J. Xu, *Chem. Commun.*, 2018, **54**, 1125-1128.
112. J. McNulty and C. Zepeda-Velazquez, *Angew. Chem. Int. Ed.*, 2014, **53**, 8450-8454.
113. O. Revu, C. Zepeda-Velázquez, A. J. Nielsen, J. McNulty, R. H. Yolken and L. Jones-Brando, *ChemistrySelect*, 2016, **1**, 5895-5899.
114. Y. Ren, M. Presset, J. Godemert, N. Vanthuyne, J. V. Naubron, M. Giorgi, J. Rodriguez and Y. Coquerel, *Chem. Commun.*, 2016, **52**, 6565-6568.
115. B. Herle, M. J. Wanner, J. H. van Maarseveen and H. Hiemstra, *J. Org. Chem.*, 2011, **76**, 8907-8912.
116. T. Mizuno, Y. Oonishi, M. Takimoto and Y. Sato, *Eur. J. Org. Chem.*, 2011, 2606-2609.
117. E. Mons, M. J. Wanner, S. Ingemann, J. H. van Maarseveen and H. Hiemstra, *J. Org. Chem.*, 2014, **79**, 7380-7390.
118. A. Ruiz-Olalla, M. A. Wurdemann, M. J. Wanner, S. Ingemann, J. H. van Maarseveen and H. Hiemstra, *J. Org. Chem.*, 2015, **80**, 5125-5132.
119. J. Kayhan, M. J. Wanner, S. Ingemann, J. H. van Maarseveen and H. Hiemstra, *Eur. J. Org. Chem.*, 2016, 3705-3708.
120. D. Huang, F. Xu, X. Lin and Y. Wang, *Chem. - Eur. J.*, 2012, **18**, 3148-3152.
121. X. Zhang, W. Jiang and Z. Sui, *J. Org. Chem.*, 2003, **68**, 4523-4526.
122. H.-L. Jiang, X.-H. Luo, X.-Z. Wang, J.-L. Yang, X.-J. Yao, P. Crews, F. A. Valeriote and Q.-X. Wu, *Fitoterapia*, 2012, **83**, 1275-1280.
123. Y.-B. Wang, S.-C. Zheng, Y.-M. Hu and B. Tan, *Nat. Commun.*, 2017, **8**, 15489-15498.
124. I. P. Kerschgens, E. Claveau, M. J. Wanner, S. Ingemann, J. H. van Maarseveen and H. Hiemstra, *Chem. Commun.*, 2012, **48**, 12243-12245.
125. K.-B. Wang, Y.-T. Di, Y. Bao, C.-M. Yuan, G. Chen, D.-H. Li, J. Bai, H.-P. He, X.-J. Hao, Y.-H. Pei, Y.-K. Jing, Z.-L. Li and H.-M. Hua, *Org. Lett.*, 2014, **16**, 4028-4031.
126. C. Piemontesi, Q. Wang and J. Zhu, *J. Am. Chem. Soc.*, 2016, **138**, 11148-11151.
127. V. M. Sheth, B. C. Hong and G. H. Lee, *Org. Biomol. Chem.*, 2017, **15**, 3408-3412.
128. R. Andres, Q. Wang and J. Zhu, *J. Am. Chem. Soc.*, 2020, **142**, 14276-14285.
129. (a) B.-F. Sun, C.-L. Wang, R. Ding, J.-Y. Xu and G.-Q. Lin, *Tetrahedron Lett.*, 2011, **52**, 2155-2158; (b) J.-Y. Xu, G.-Q. Lin, B.-F. Sun, C.-L. Wang, S.-G. Chen, R. Ding and Y.-J. Shang, *Synlett*, 2011, **2012**, 263-266; (c) J. Wang, S.-G. Chen, B.-F. Sun, G.-Q. Lin and Y.-J. Shang, *Chem. - Eur. J.*, 2013, **19**, 2539-2547.
130. (a) W.-B. Sun, X. Wang, B.-F. Sun, J.-P. Zou and G.-Q. Lin, *Org. Lett.*, 2016, **18**, 1219-1221; (b) X. Wang, W.-B. Sun, J.-P. Zou, G.-Q. Lin and B.-F. Sun, *Org. Biomol. Chem.*, 2016, **14**, 10581-10584.
131. M. Yoshino, K. Eto, K. Takahashi, J. Ishihara and S. Hatakeyama, *Org. Biomol. Chem.*, 2012, **10**, 8164-8174.

