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REVIEW

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Oxidation reactions in the current total synthesis of natural products

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Oxidation and oxidative reactions are fundamental types of transformations in organic chemistry, which are indispensable in organic synthesis, especially in the total synthesis of natural products. Although there are many reviews on a specific oxidation reaction or oxidation reagent, a general review on the diverse oxidation reactions and oxidation reagents in natural product synthesis has not yet been reported. In this review, we selected some total syntheses published during 2020 to 2025 from selected journals and surveyed the oxidation reactions and oxidative transformations employed therein to reflect the current status of oxidation reactions. This article is organized by functional groups for oxidation and subcategorized by reagents/methods used in natural product synthesis. In addition to the categorized reactions, we selected twenty total syntheses (in Sections 2 and 7) and analysed and discussed all the oxidative transformations involved. The information provided will not only be helpful for chemists in the field of total synthesis of natural products and medicinal chemists to plan their syntheses but also prompt synthetic organic chemists in general to develop modern oxidation reactions/reagents to suit the increasing needs of sustainable organic synthesis.

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1. Introduction

Oxidation reactions are one of the most important types of transformations in organic synthesis, as can be seen from the fact that there are more than 25 named oxidation reactions

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and reagents in organic chemistry,[1] such as the Baeyer–Villiger oxidation, Moffatt (Pfitzner–Moffatt) oxidation, Swern oxidation, Dess–Martin periodinane (DMP) reagent, Corey–Kim oxidation, Ley–Griffith oxidation, Sharpless asymmetric epoxidation, Sharpless asymmetric dihydroxylation, Shi asymmetric epoxidation, and Davis reagent. Sharpless was awarded the 2001 Nobel Prize in Chemistry for his outstanding contribution to catalytic asymmetric oxidation reactions.

As a class of fundamental organic transformations, oxidation reactions serve to introduce oxygen atoms in a selective site within a molecule and adjust the oxidation state, ranging from alcohols to aldehydes/ketones, aldehydes/ketones to acids and derivatives, and alcohols to acids and their derivatives. Moreover, oxidation reactions are a class of reactions enabling subsequent C–C bond forming reactions, such as aldol reactions and Grignard additions from alcohol to aldehyde/ketone transformations. Additionally, oxidation reactions can be used to create chirality in a catalytic enantioselective manner. Thus, oxidation reactions are indispensable for constructing complex molecules, particularly in the total synthesis of natural products. Indeed, a brief survey of the publications on total synthesis between 2015 to 2025 using SciFinder® revealed that 16% of them contain the term "oxidation" in their abstract, indicating its crucial role in natural product synthesis. Although many reviews have been reported on a specific oxidation reaction or oxidation reagent,[2] a general review on diverse oxidation reactions and oxidation reagents in natural product synthesis, to the best of our knowledge, has not yet been reported. However, this is very important because very often, several oxidation reactions and reagents are required for total synthesis.

To bridge this gap, this review aims to cover the applications of diverse oxidation methods in the synthesis of natural products, guiding readers to select suitable reactions, reagents and conditions for oxidative transformations. Nonetheless, considering the huge number of publications in this field, this article will be restricted to selected examples chosen from papers published in selected journals during 2020 to 2025 on the total synthesis of natural products to reflect the current status of oxidation reactions. This article is organized by functional groups for oxidation and subcategorized by reagents/methods used. Prior to the categorized oxidation reactions, we selected ten total syntheses and analysed and discussed all the oxidative transformations involved. The information provided will not only be helpful for the chemists in the field of total synthesis of natural products and medicinal chemists to plan their syntheses but also prompt synthetic organic chemists in general to develop modern oxidation reactions/reagents to suit the increasing needs of high chemo-, regio- and stereo-selectivity,[3] efficiency,[4] mild reaction conditions, reduced waste formation and environmental friendliness.[5]

2. Survey of oxidation reactions in ten selected total syntheses

To provide an overview on the diverse roles played by oxidation reactions in total synthesis, we selected ten cases from the recent literature. A closer inspection of these examples revealed unexpected and surprising results, where the oxidation steps comprised more than 40% of the total steps. Moreover, some oxidation reactions and oxidative transformations can constitute the basis of a synthetic strategy or be used as a key step of the total synthesis. Additionally, oxidation reactions are not only limited to adjusting the oxidation state

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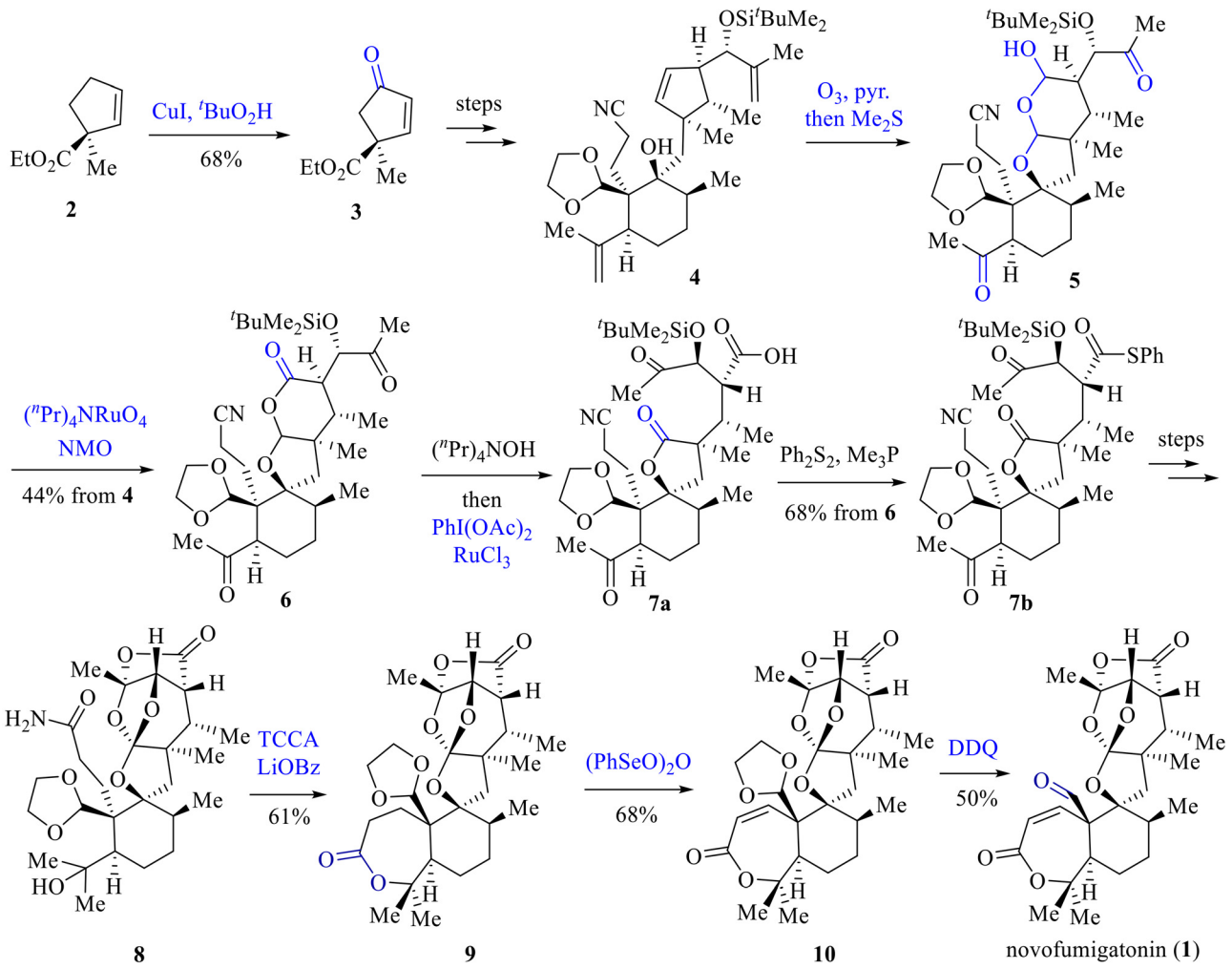
of a specific site or a functional group but also play vital roles in enabling transformations. These recent examples cover a variety of oxidation reactions and oxidation transformations, which serve, at least in part, to reflect the current status of oxidation chemistry.

2.1. Enantioselective total synthesis of (−)-novofumigatonin

Isolated in 2008, novofumigatonin **1** represents one of the most structurally complex and most highly oxidized members of the 3,5-dimethylorsenillic acid (DMOA)-meroterpenoid class of natural products isolated to date. In 2025, Carreira and co-workers achieved its first and enantioselective total synthesis (Scheme 1).[6] The central role of oxidation reactions in their total synthesis is highlighted by one of their conclusions, as follows: "A powerful anionic fragment coupling followed by a series of oxidative transformations led to the rapid construction of the highly oxygenated backbone of **1**".

The first oxidation reaction involved the allylic oxidation of olefin **2** to afford enone **3**, which was achieved using catalytic CuI/*t*-BuO_2H[7] (68% yield). This oxidation reaction not only introduced the first oxygen atom in the core structure, but also enabled subsequent transformations. Next, after the key anionic fragment coupling reaction, three consecutive oxidation reactions were employed to forge a highly oxygenated intermediate. Firstly, triple ozonolysis of **4** generated four carbonyl groups in the form of diketo hemiacetal **5**. Secondly, Ley–Griffith oxidation afforded lactone–acetal **6**. Finally, saponification of the δ-lactone followed by oxidation by $PhI(OAc)_2$ and $RuCl_3$·hydrate furnished γ-lactone **7a**. Because multifunctionalized compound **8** contains both acid-sensitive (ortholactone) and base-sensitive (bicyclic γ-lactone) functional groups, the oxidation method (trichloroisocyanuric acid, TCCA) recently reported by Bao and Wan[8] was employed for the primary amide (**8**) to ester (**9**) transformation. Interestingly, two oxidants were used to complete the total synthesis. One was $(PhSeO)_2O$[9] for the desaturation of **9** to afford α,β-unsaturated ε-lactone **10**, and the other was 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)[10] used to provide an acidic medium, enabling the selective cleavage of the acetal to afford **1** bearing an embedded ortholactone.



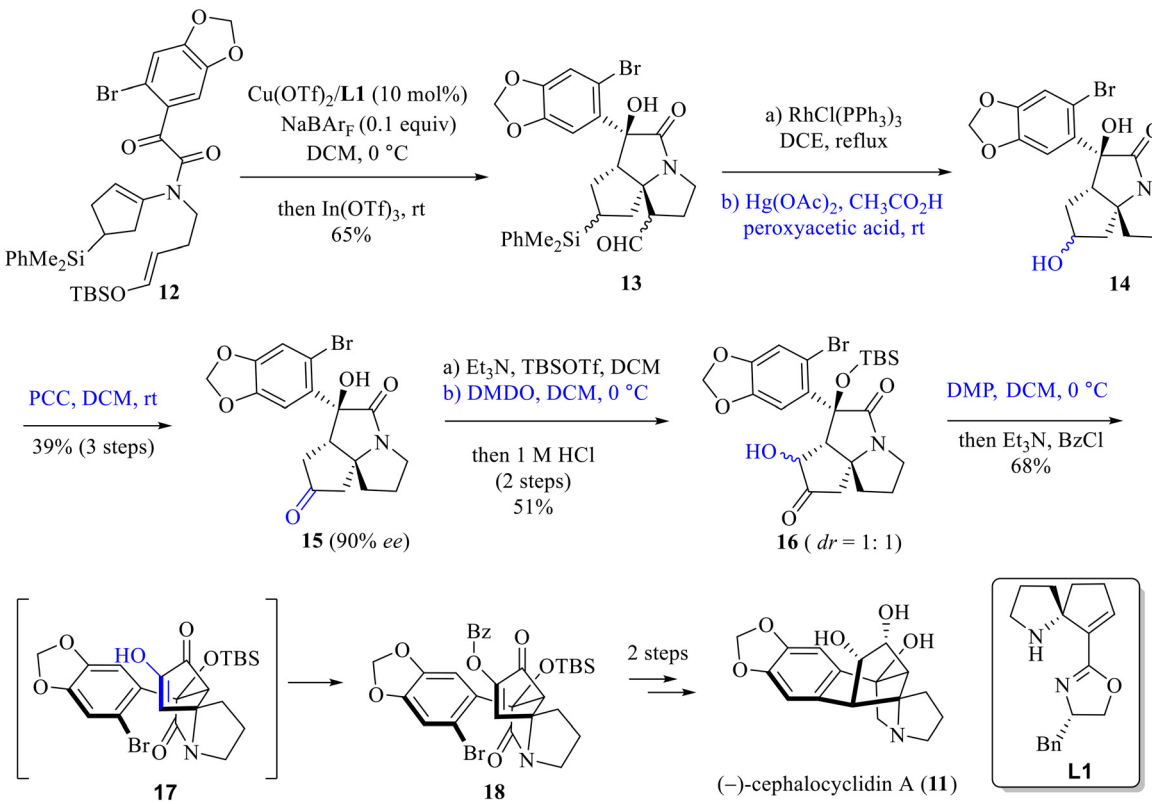
Scheme 1 First and enantioselective total synthesis of (−)-novofumigatonin by Carreira and co-workers.

2.2. Asymmetric total synthesis of (−)-cephalocyclidin A

(−)-Cephalocyclidin A (**11**) is a novel alkaloid isolated from the fruits of *Cephalotaxus harringtonia* var. *nana*. Its structure features a unique fused-pentacyclic skeleton and six consecutive chiral centres, making it a challenging target for total synthesis. Its first total synthesis was accomplished by Zhang/Tu and co-workers in 2023 in a quite efficient manner.[11] In this 10-step (from known compounds, 12 steps from commercially available materials) total synthesis, four steps involved different types of oxidation reactions, highlighting the crucial role of oxidation reactions in its total synthesis. They first developed a catalytic asymmetric polycyclization of tertiary enamide **12** with silyl enol ether employing Tu's chiral ligand **L1** to build tricyclic core **13** as a mixture of inconsequential diastereomers in 90% ee. The latter was subjected to Wilkinson's complex-catalyzed deformylation, Fleming–Tamao oxidation[12] (C–Si to C–OH, **14**), and Corey oxidation of the resulting alcohol with pyridinium chlorochromate (PCC) to afford ketone-lactam **15** in 39% yield over three steps. Regioselective α-oxidation of the ketone group was achieved by successive treatment of **15** with TBSOTf (2.1 equiv.) and dimethyldioxirane (DMDO),[2i] which afforded tricyclic α-hydroxy cyclopentanone **16** as a pair of inconsequential diastereomers. This transformation probably involved silyl enol ether formation and its oxidation with DMDO. Dess–Martin oxidation of α-hydroxy ketone **16** delivered the corresponding α-diketone in enol form **17**, which was benzoylated in one-pot to yield compound **18** in 68% yield. Finally, one-pot radical cyclization–desilylation, and reduction-debenzoylation furnished (−)-cephalocyclidin A (**11**) (Scheme 2). *It is worth noting that in this ten-step total synthesis (from a known compound, not shown), four steps are oxidation reactions covering Si to OH oxidation, alcohol oxidation, ketone α-hydroxylation, and oxidation of α-hydroxyketone*.

2.3. Divergent, enantioselective total syntheses of three calyciphylline A-type alkaloids

During the last decades, many modern variants of the classic named reactions appeared, which significantly expanded the scope of the original reactions. In this regard, Xu and co-workers developed the oxidative Nazarov-type reaction and used it as a key reaction in the divergent total syntheses of *Daphniphyllum* alkaloids.[13] The synthesis started from chiral ketone **22b**, which was derived in five steps from (*R*)-Wieland–Miescher ketone. The Saegusa–Ito oxidation afforded dienone **23** in high yield. For allylic oxidation at C9, the authors tried several reactions and found that Riley oxidation gave the best yield. A tandem oxidation with AZADOL/iodobenzene diacetate (PIDA)[14] afforded enone **25** in 77% yield over two steps. Lower yields were obtained with other oxidation methods. The transformation of enone **25** to 1,3-done **26** also involved Ley oxidation.[15] Two more oxidation reactions were employed for the conversion of **27** to tetracarbonyl compound **28**. After the reductive cyclization using Kagan's reagent, the resulting diol



Scheme 2 First and catalytic asymmetric total synthesis of (−)-cephalocyclidin A (**11**) by Zhang/Tu and co-workers.

was subjected, once again, to Ley oxidation, which afforded α-hydroxyketone **29a**. According to their original plan, the subsequent step was the transformation of unfunctionalized tertiary divinyl carbinol to the enone moiety in compound **33**. Unexpectedly, Xu discovered that under Iwabuchi's conditions ($TEMPO^+BF_4^-$, MeCN),[16] pentacycle **31** was formed in 80% yield. This reaction was coined as an oxidative Nazarov-type reaction. The resulting product was converted to (−)-10-deoxydaphnipaxianine A (**19**) in three more steps. Alternatively, treatment of key intermediate **30** with $TEMPO^+BF_4^-$ in dioxane yielded allylic alcohol **32**, which was subjected to oxidation with AZADOL/PIDA to give ketone **33** in 98% yield. Finally, chemoselective reduction of the amide carbonyl furnished (+)-daphlongamine E (**20**), which was further converted to (+)-calyciphylline R (**21**) *via* *N*-oxidation with *m*-CBPA (Scheme 3). *It is worth mentioning that in this 22-step total synthesis of (+)-calyciphylline R (**21**), more than 40% of the steps involve oxidation reactions*. More recently, Xu and co-workers applied their oxidative Nazarov-type reaction to the collective total synthesis of laurane and guaiane sesquiterpenoids.[17]

2.4. First and catalytic asymmetric total synthesis of tri-nor-meroterpenoid janthinoid A

Janthinoid A (**34**) is a novel 3,5-dimethylorsellinic acid (DMOA)-derived natural product that exhibits *in vivo* antitumor activities against NSCLC cells A549.[18] Soon after its isolation in 2021, Yang and co-workers accomplished its first catalytic asymmetric total synthesis.[19] This highly efficient 14-step, protecting group-free total synthesis started from the regioselective, catalytic asymmetric dihydroxylation[20,21] of geranylacetone (**35**) to produce diol **36** (97% yield, 92% ee), setting the stage for epoxide formation and subsequent double cyclization to afford bicyclic intermediate **38**. Although the transformation of **38** to **39** involved a routine oxidation (DMP)-reduction strategy to correct the stereochemistry (at C3), the protocol that they developed alleviated the need for protection of the hydroxy group. Another key step in its total synthesis is the regio- and stereo-selective oxidative cascade cyclization reaction of **40** to build the oxabicyclo[3.2.1]octane core. After extensive experimentation, this was achieved by treating bicyclic ketoester **40** with $Fe(ClO_4)_3{\cdot}9H_2O$[22] in CH_3CN, affording tetracyclic **41** in 55% yield. The latter was converted into janthinoid A (**34**) in just two steps, completing the highly concise total synthesis (Scheme 4). This total synthesis provides another example[23] demonstrating how oxidative reactions can be used, directly or indirectly, for rapidly building molecular complexity.

2.5. Divergent, enantioselective total syntheses of bryostatins 1, 7, 9 and an analogue

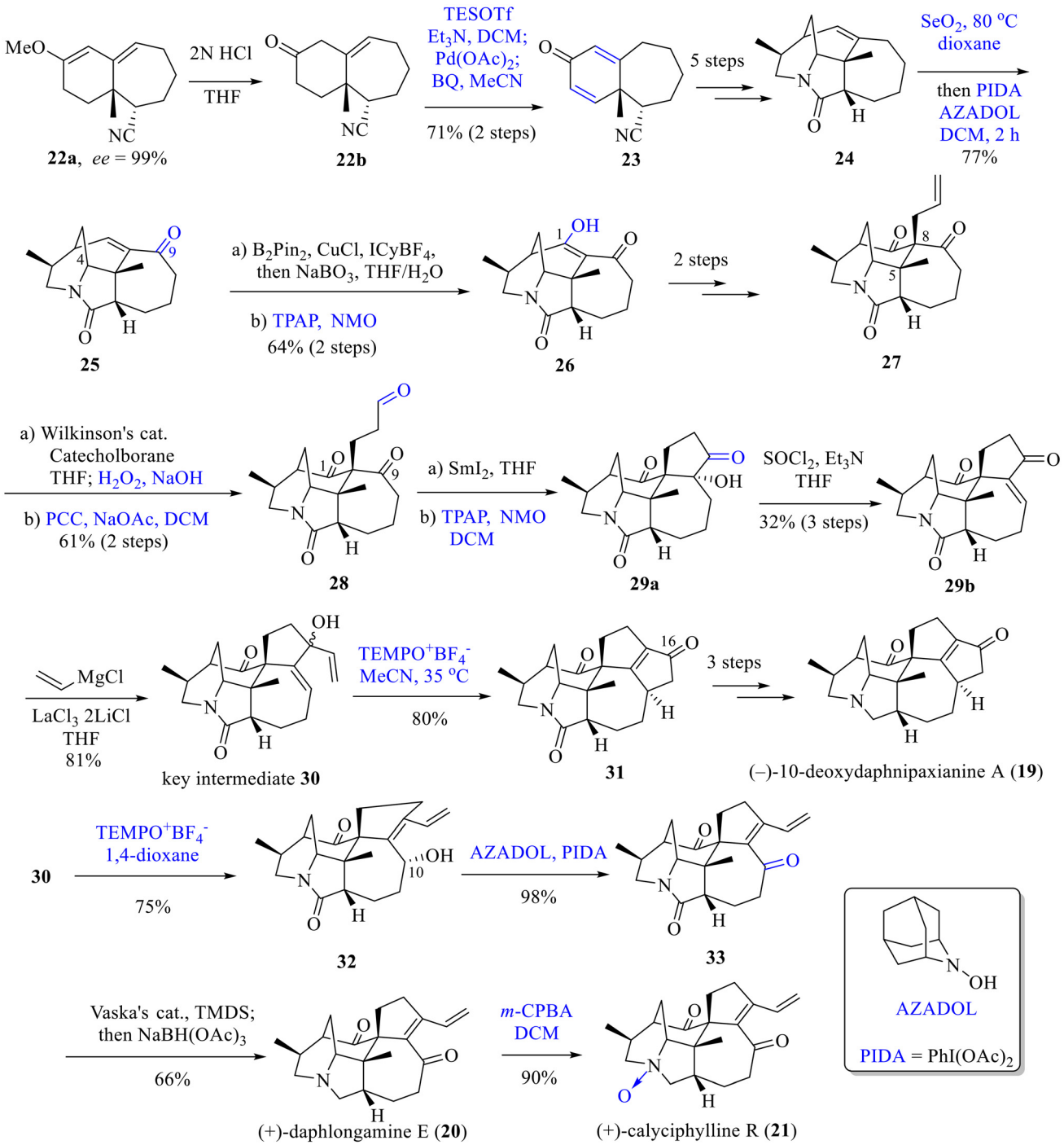
Bryostatins are a class of structurally complex marine macrolides displaying diverse and potent biological activities with more than 40 clinical trials conducted. In 2025, Song and co-workers achieved the divergent and scalable enantioselective total synthesis of bryostatins 1, 7, 9 and unnatural 9-N_3.[24,25] The synthesis of the southern fragment involved several oxidation reactions. Firstly, *in situ*-formed dihydropyran **45** was subjected to epoxidation with magnesium monoperoxyphthalate (MMPP) hexahydrate, *in situ* methanolysis, and Dess–Martin oxidation of the resulting C20 hydroxy group[26] to afford pyranone **46** in high yield. Secondly, oxidative deprotection of the PMB group in **47** with DDQ followed by Dess–Martin oxidation afforded enal **48**. Thirdly, Sharpless asymmetric dihydroxylation[27] (dr = 11 : 1) and selective protection of the C26 hydroxy group produced **49** in 72% yield (Scheme 5).

2.6. Modular, enantioselective synthesis of marine natural products dragocins A–C and analogues

In the recent modular synthesis and cytotoxicity evaluation of dragocins A–C disclosed by Liu/Li *et al.*,[28] one of the key reactions involved oxidation of the benzylic C–H bond. After attempting several methods, DDQ-induced CDC etherification was found to be suitable for the intramolecular cross-dehydrogenative etherification at the benzylic position,[29] which afforded the desired compound **54** and its C-5 epimer *epi*-**54** (dr = 1 : 1) in a combined yield of 56%. Employing the TEMPO/BAIB (bis(acetoxy)iodobenzene) combination, primary alcohol **54** was oxidized smoothly to carboxylic acid **55** in 87% yield. The decarboxylative chlorination reaction can be viewed as an oxidative transformation because the oxidation state of the carbon increased. This was achieved by employing Li's method[30] with minor modification. The desired mono-chlorination product **56**, formed in 60% yield, was converted into dragocin A (**50**) in two steps. Selective removal of the *N*-protecting group in **56** afforded **58** in 84% yield, which was converted to dragocin B (**51**) by reductive debenzoylation. On the other hand, subjecting **58** to Huang's *N*-methylation reaction (MeOH, H_2, Pd/C)[31] and reductive debenzoylation of the resulting *N*-methylpyrrolidine product produced dragocin C (**52**) in 59% yield over two steps (Scheme 6). It is worth noting that although Huang's *N*-methylation reaction using MeOH as the methylating agent appears to be performed under reduction conditions, the first and key step involves Pd/C-catalyzed dehydrogenation of MeOH to generate formaldehyde.[31]

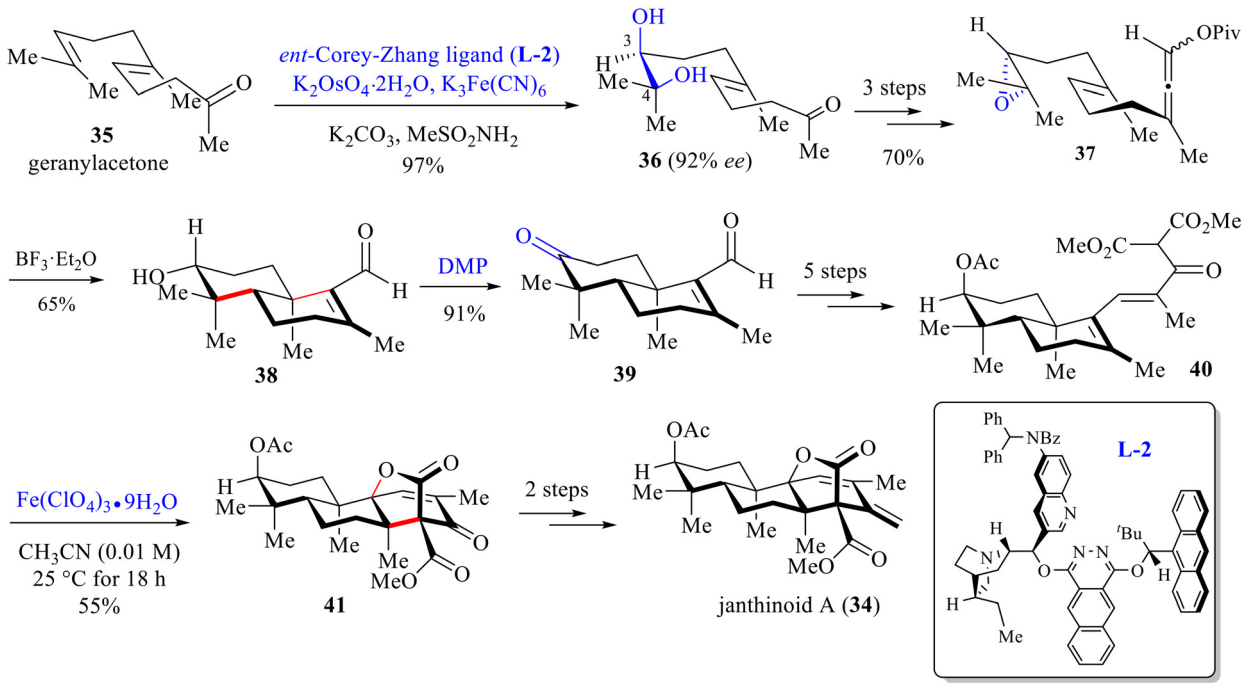
2.7. Twenty-step enantioselective total synthesis of tigliane diterpene (+)-phorbol

Tigliane diterpenes are a family of natural products possessing diverse and potent bioactivities, among which tigilanol tiglate (Stelfonta®) has been approved by the FDA to treat non-metastatic mast cell tumors in dogs. As a representative member, the total synthesis of (+)-phorbol (**60**) has attracted considerable attention. Very recently, Jia and co-workers disclosed a 20-step (longest linear steps) enantioselective total synthesis,[32] which represents one of the shortest total syntheses after Baran's elegant 19-step total synthesis of this natural product.[33] As a highly oxygenated molecule, it is not surprising that the total synthesis of (+)-phorbol (**60**) heavily relied on oxidation reactions. Indeed, in Jia's total synthesis, 35% of the steps (7 steps) are oxidation reactions. The synthesis com-

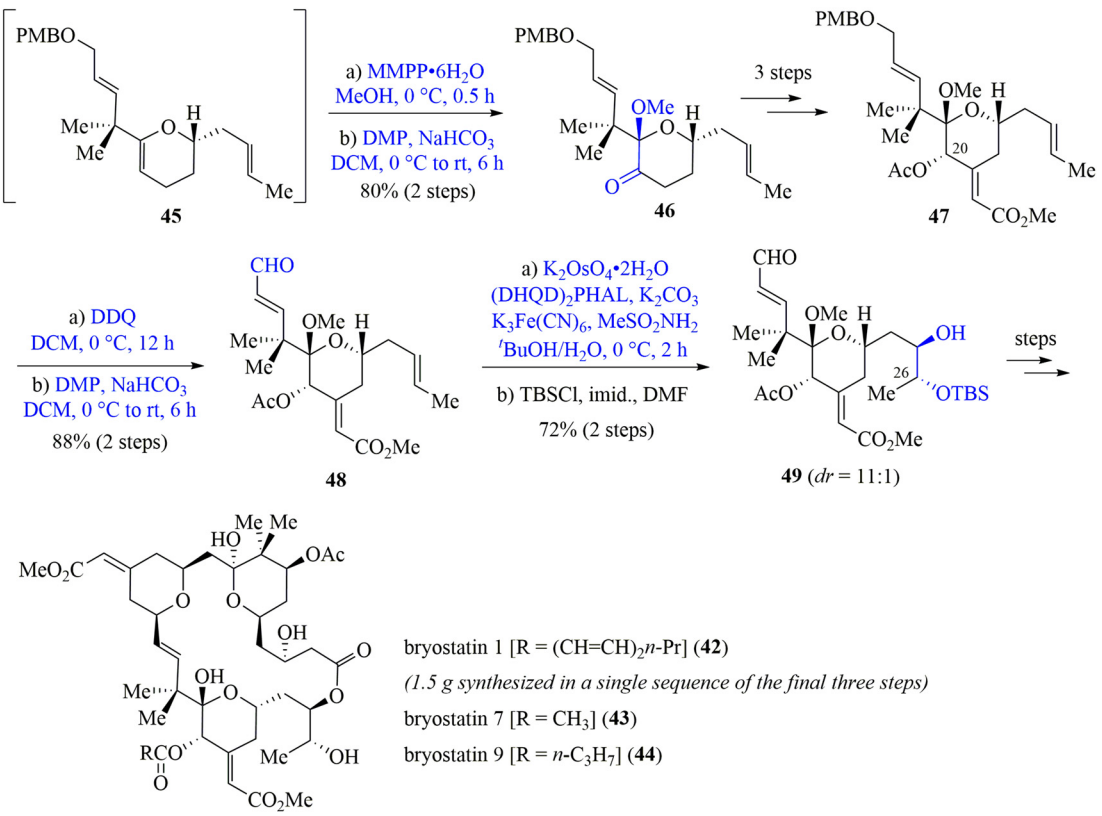


Scheme 3 Divergent, total syntheses of (–)-10-deoxydaphnipaxianine A, (+)-daphlongamine E, and (+)-calyciphylline R by Xu and co-workers.

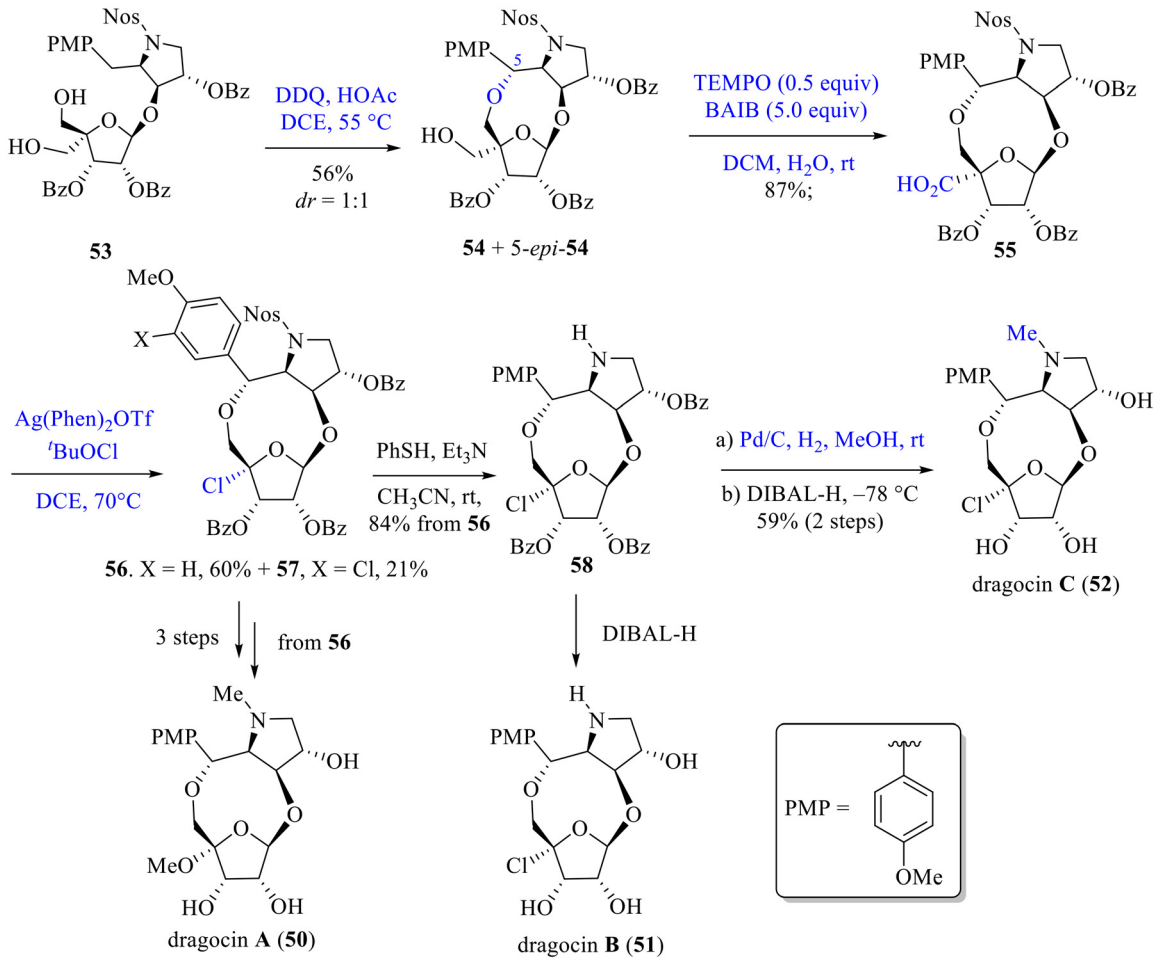
menced with the direct epoxidative transformation of (+)-carvone (**61**) to 3,4-epoxycaranone **62** by a known method. Because direct hydroxylation of **62** proved to be challenging, inspired by Fuchs' approach,[34] a pentamethyldisilyl group was introduced as a masked hydroxy group. Chemoselective oxidation of the less hindered C9 alcohol *versus* that at C12 in diol **63** was achieved using Mukaiyama reagent (**64**).[35] Subjecting silyl derivatives **66a and b** to Tamao–Fleming oxidation[36] delivered alcohols **67a and b** in 63% yield, respectively. Subsequent Swern oxidation yielded **68a and b**, respectively. Treatment of ketone **69** with LiHMDS and Mukaiyama reagent (**64**) was performed again for the generation of enone **70** from ketone **69**.[37] α-Hydroxylation of the fused cyclic enone proved to be challenging. After extensive experimentation, *t*-BuOK/O_2/P(OEt)$_3$ was found to be the reagent system of choice for this transformation, which afforded α-hydroxylated



Scheme 4 14-step, protecting group-free, total synthesis of janthinoid A by Yang and co-workers.



Scheme 5 Later stage of the gram-scale enantioselective total synthesis of bryostatin 1 and its congeners by Song and co-workers.



Scheme 6 Collective enantioselective synthesis of dragocins A–C and their analogues by Liu/Li and co-workers.

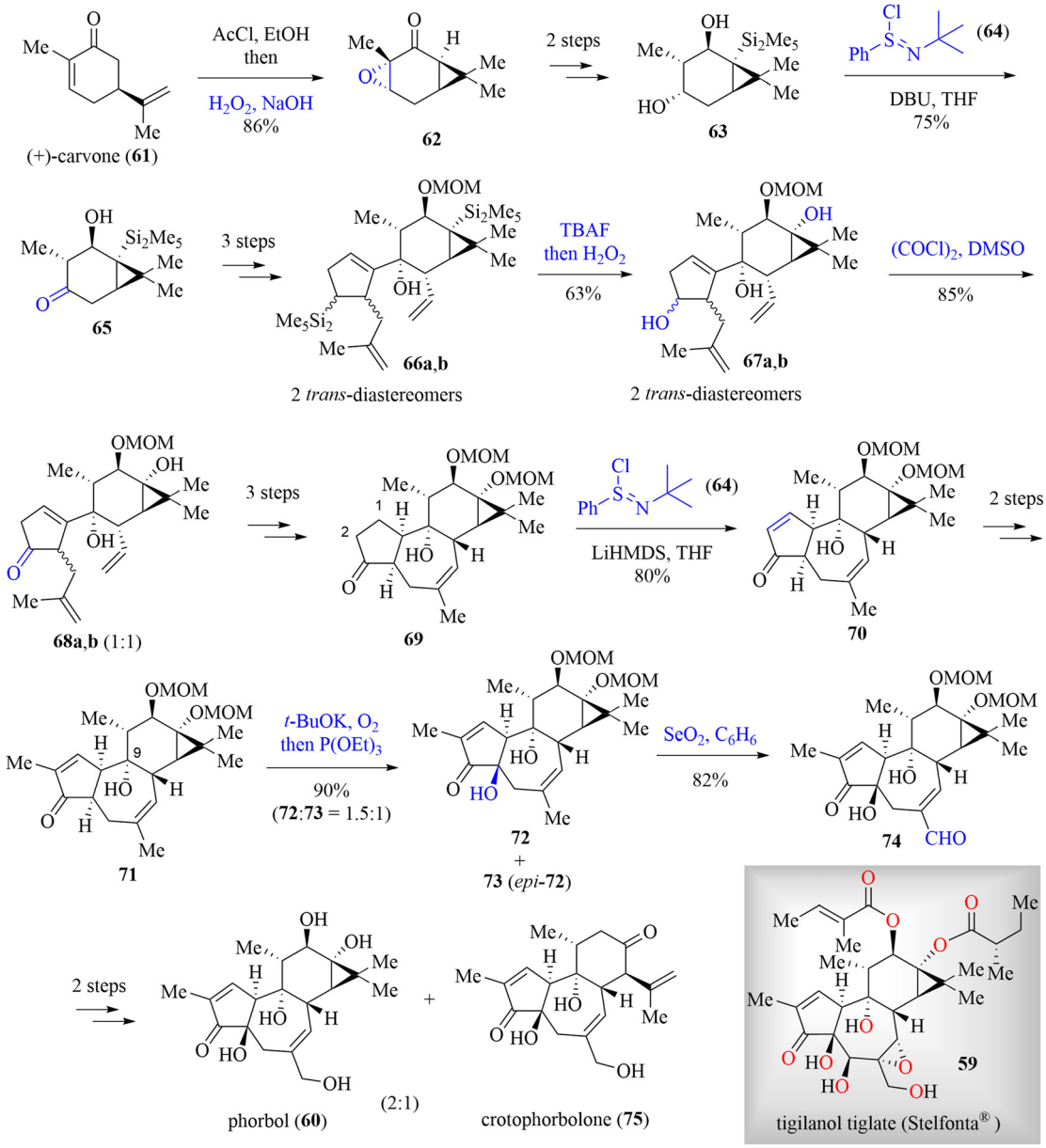
product **72** and its epimer **73** in a combined yield of 90%. Allylic oxidation of **72** with SeO_2 furnished enal **74** instead of the desired allylic alcohol. Finally, reduction and deprotection afforded (+)-phorbol (**60**) along with (+)-crotophorbolone (**75**) (Scheme 7).

2.8. First total synthesis of octacyclic caged *Kopsia* alkaloid kopsinitarine E

Kopsinitarine E is an alkaloid isolated from the genus *Kopsia* (Apocynaceae). Its intriguing octacyclic cage structure presents a formidable challenge for its total synthesis, which was overcome by Ma and co-workers in 2020.[38] In this total synthesis, only four oxidation reactions were employed, which illustrated the classical role of oxidation reactions in functional group manipulation. However, it is worth noting that in the stepwise transformation of ester **77** to aldehyde **78**, the classical Parikh–Doering oxidation showed good chemoselectivity for the oxidation of the primary alcohol intermediate resulting from DIBAL-H reduction, in the presence of an amine group (a piperidine moiety) prone to oxidation. Moreover, the unexpected DMP oxidation (of **80**)-triggered cascade Prins-type cyclization to give **81** inspired the authors to develop a method for the direct transformation of **79** to **81**. Additionally, successive treatment of ketone **84** with KHMDS and Davis oxaziridine[39] allowed the indispensable α-hydroxylation (Scheme 8).

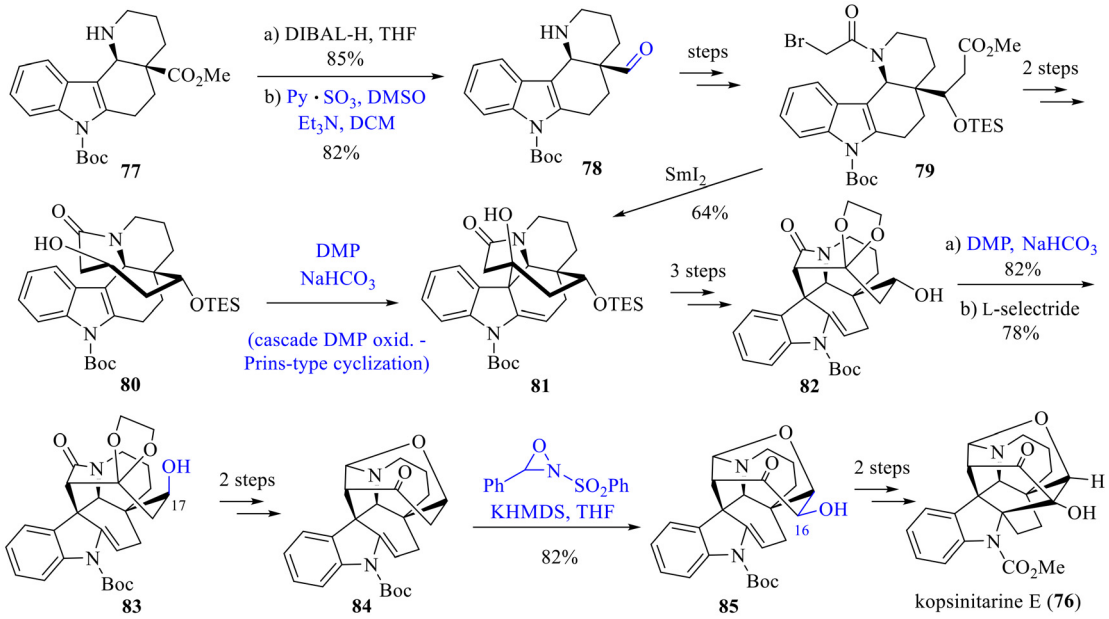
2.9. Total synthesis of ophiobolin-derived sesterterpenoids bipolarolide B and bipoladien B

Bipolarolides A and B and bipoladien B are sesterterpenoids that exhibit potent HMGR inhibitory activity and possess intriguing cage-like scaffolds. In 2024, Jia and co-workers accomplished the first and enantioselective total syntheses of bipolarolides A and B *via* a bioinspired strategy.[40] Very recently, Fan and co-workers reported a distinct bridgehead enone-directed,[41] divergent total synthesis of bipolarolide B (**86**) and bipoladien B (**87**).[42] The first oxidation reaction in Fan's synthetic approach involves the hydroxy group-directed diastereoselective dihydroxylation of **89** with $K_2[OsO_2(OH)_4]$(cat.)/4-methylmorpholine *N*-oxide (NMO), which, after subsequent chemoselective silylation of the resulting secondary diols with concomitant silyl enol etherification, and Conia-ene-type cyclization, afforded tricyclic ketone **90** in 51% yield. Next, for the key ketone **90** to bridgehead enone **91** transformation, a two-step protocol was first secured based on the Saegusa–Ito oxi-



Scheme 7 Highly efficient asymmetric total synthesis of (+)-phorbol by Jia and co-workers.

dation.[43] The moderate yield (43%) prompted them to explore a one-step method. After attempting the one-step method,[44] and inspired by Shvo's method,[44a] the one-step, catalytic dehydrogenation of **90** was achieved in 78% yield using $Pd(CF_3CO_2)_2$ as the catalyst. Remarkably, the reaction could be performed on a 30 g scale. The oxidative cleavage of the vicinal diol in **92** with $NaIO_4$ followed by piperidine-mediated regioselective intramolecular aldol condensation afforded the ring-contracted product, which was further transformed into compound **93**. Employing Brown's oxymercuration–demercuration method[45] as the key step, **93** was converted regio- and diastereo-selectively to compound **94** in three steps. Dehydrogenation of **95** by Barton's method $[(PhSeO)_2O]$[9] set the stage for conjugate addition to yield **97**. The resulting TMS enol ether **97** was subjected to Saegusa–Ito-type oxidation to produce trisubstituted enone **98** in 43% yield and recover ketone from **97** in 37% yield. Interestingly, compound **99** served as the common intermediate for the oxidative divergent total synthesis of bipolarolide B (**86**) and bipoladien B (**87**). Thus, regioselective allylic oxidation of **99** with SeO_2/*t*-BuO_2H[46] furnished bipolarolide B (**86**) in 79% yield, whereas Swern oxidation[47] of **99** afforded bipoladien B (**87**), completing its first total synthesis (Scheme 9). In this campaign, the ketone to enone transformation was performed three times at different stages of the total synthesis and by using different methods, highlighting the importance of developing versatile synthetic methods.



Scheme 8 20-step total synthesis of (±)-kopsinitarine E by Ma and co-workers.

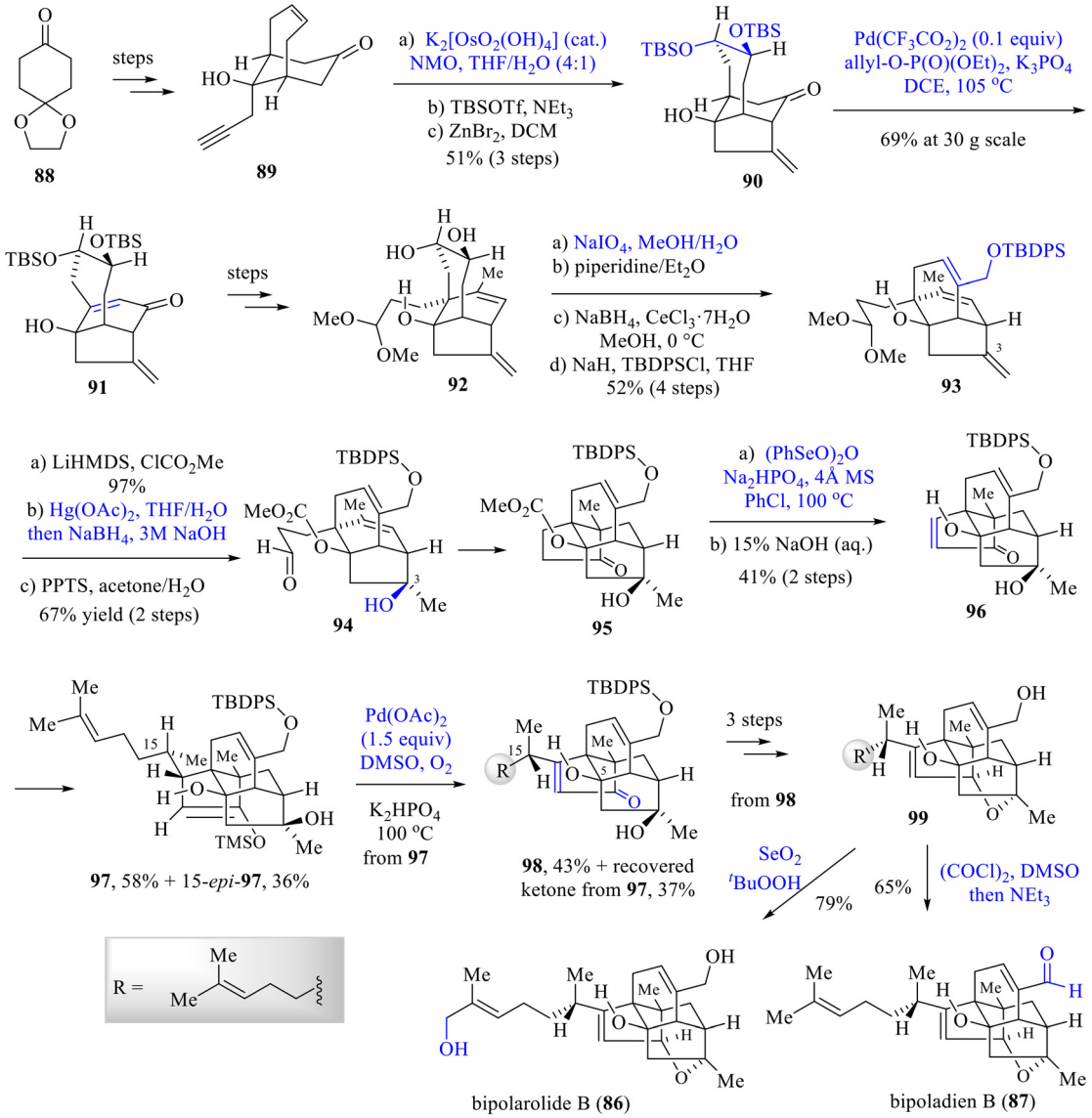
2.10. Collective total syntheses of nine elisapterane and relevant diterpenoids

Elisapterosins A–F are diterpenoids isolated from the West Indian Sea Whip *Pseudopterogorgia elisabethae* (Bayer). Among them, elisapterosin B (**101**) was reported to exhibit strong inhibitory activity against *Mycobacterium tuberculosis* H37Rv. The total synthesis of elisapterosin B was achieved first by Rychnovsky and co-workers,[48] and then by other groups. Most of its total syntheses used a similar D-ring first strategy. In 2025, Ding and co-workers conceived an unprecedented bio-inspired late-stage D-ring formation strategy, leading to the divergent syntheses of several elisapterane and relevant diterpenoids (Scheme 10).[49] The divergent syntheses feature norneoelisabane-like (ABC ring system) tricyclic enone **111** as a common intermediate, readily accessible *via* Ding's in-house developed oxidative dearomatization-induced (ODI)-(5 + 2) cycloaddition/1,2-acyl migration cascade methodology.[50] The synthesis of common intermediate **111** relied on the phenyliodine(III) bis(trifluoroacetate) (PIFA) and 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP)-mediated ODI-(5 + 2) cascade[50] of enantiopure **107**, affording tricyclic skeleton **108** in 60% yield. Epoxidation of **108** with urea hydrogen peroxide (UHP)/trifluoroacetic anhydride (TFAA) proceeded diastereoselectively to yield epoxide **109** in 70% yield. Ley–Griffith oxidation[15] of diol **110** furnished common intermediate **111** in 77% yield.

For the synthesis of aberrarone (**113**) from **111**, Albright–Goldman oxidation[51] was employed for the oxidation of the C17-alcohol, whereas in the synthesis of elisabanolide (**106**), three oxidation steps were used. The Mukaiyama hydration of **114** promoted the desired concomitant elimination of the C2-tertiary alcohol to give **115** in 86% yield. Dihydroxylation of **115** with OsO_4/pyridine[52] afforded **116** in 72% yield. Treatment of **116** with $VOCl_3$ and O_2 [53] resulted in the formation of elisabanolide (**106**) *via* sequential oxidative cleavage. Treatment of elisapterosin C (**102**), derived from **116** *via* elimination, with O_sO_4/Pyr., led to stereoselective dihydroxylation and spontaneous hemiketalization, affording the putative structure of elisapterosin F (**104**). On the other hand, for the conversion of elisapterosin C (**102**) to elisapterosin A (**100**), after many unsuccessful trials, benzeneseleninic anhydride[54] was found to be the reagent of choice, delivering the latter in 88% yield. Similarly, elisapterosin B (**101**) was oxidized to yield elisapterosin D (**103**). Employing Woerpel's alkene hydroperoxidation method[55] by treating elisapterosin B (**101**) with Co(pic)$_2$, *tert*-butyl hydroperoxide (TBHP) and O_2 resulted in an intramolecular oxygen atom transfer to provide **117** in 87% yield. Repeating the same protocol, the latter was further converted to elisapterosin A in 20% yield (25% brsm). Prolonged exposure of **118** to Woerpel's conditions afforded elisapterosin F (**105**). Similarly, elisapterosin D (**103**) was converted to elisapterosin A in 38% yield. It is important to note that in this total synthesis campaign, the structures of several natural products were found to be misassigned, which were revised *via* a combination of total synthesis and computer-assisted structure elucidation (CASE).

3. Oxidation of alcohols

Alcohols are some of the most prevalent functional groups in natural products. Depending on the synthetic purpose, primary alcohols can be oxidized to aldehydes or further to carboxylic acids or esters, whereas secondary alcohols are typically oxidized to ketones. Tertiary alcohols, which lack a hydrogen on the carbinol carbon, are generally resistant to oxidation. In the synthesis of a natural product, the selective oxidation of a specific alcohol in a complex structural setting with multiple functionalities often poses a challenge. Thus, a

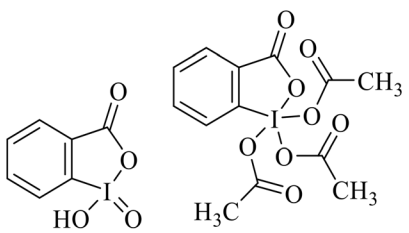


Scheme 9 Bridgehead enone-directed total synthesis of (±)-bipolarolide B and (±)-bipoladien B by Fan and co-workers.

plethora of methods have been developed for the selective oxidation of alcohols. This section will highlight examples of the total synthesis of natural products and pharmaceutical molecules applying greener, milder and catalytic alcohol oxidation methods, including hypervalent iodine reagents, TPAP/NMO, nitroxyl radicals, and alcohol dehydrogenation.

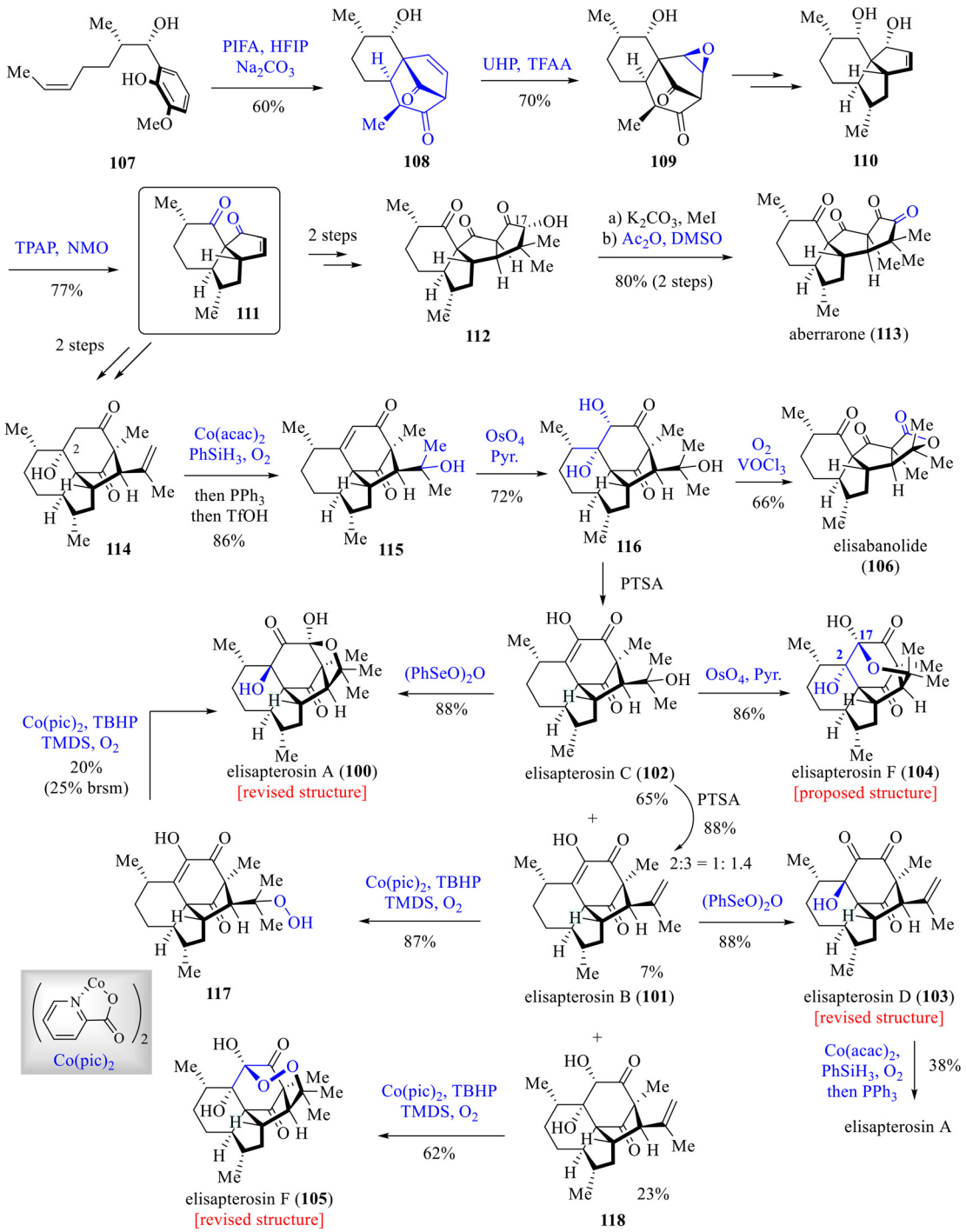
3.1 Hypervalent iodine(v) reagents (IBX and DMP)

Among the many methods for alcohol oxidation, the hypervalent iodine(v) oxidants 2-iodoxybenzoic acid (IBX, **119**) and Dess–Martin periodinane [DMP; 1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3-(1*H*)-one, **120**] have been widely used in natural product synthesis.[56,57] Although both oxidants are effective for the oxidation of alcohols to carbonyl compounds, DMP is usually preferred due to its superior solubility, milder conditions (room temperature), faster reaction rates, and higher yields; whereas the poor solubility of IBX in most organic solvents (except DMSO) limits its use to some extent. Nonetheless, both IBX and DMP are often the choice for alcohol oxidation in natural product syntheses, as highlighted in the selected examples below.



IBX (**119**) DMP (**120**)

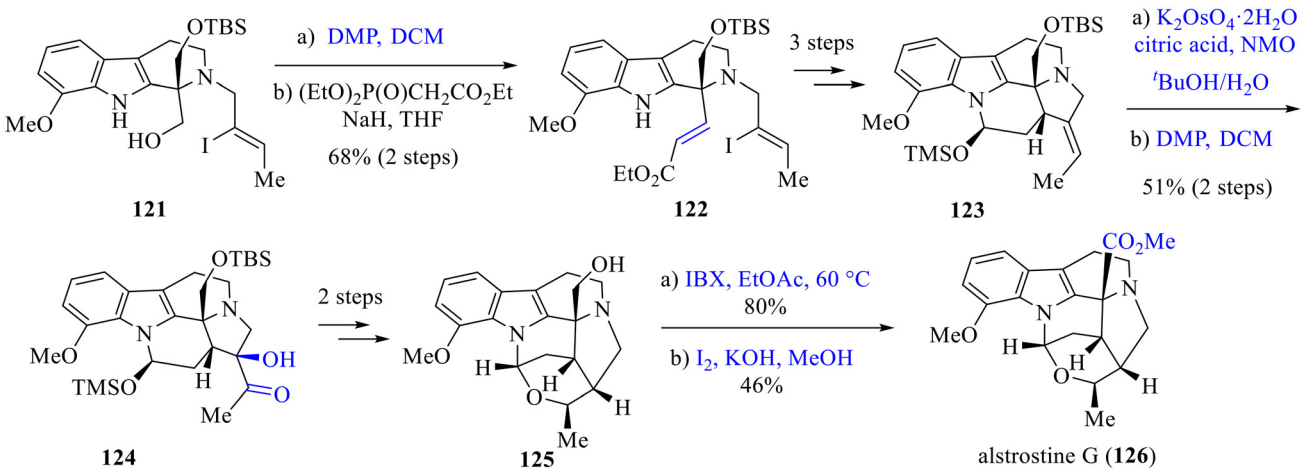
(−)-Alstrostine G (**126**) is an indole alkaloid isolated from the bark and trunks of *Alstonia rostrata*. This molecule contains an unusual 6/5/6/6/5/6 hexacyclic ring system with five stereocen-



Scheme 10 Bioinspired collective total syntheses of marine natural products elisapterosins A–F, aberrarone, elisabanolide, and 3-*epi*-elisabanolide by Ding/Xia and co-workers.

ters, rendering it a challenging target for total synthesis. Its first asymmetric total synthesis by Ma's group involves three DMP/IBX oxidation steps.[58] Dess–Martin oxidation of alcohol **121** followed by Horner–Wadsworth–Emmons (HWE) reaction provided α,β-unsaturated ester **122**. A subsequent 3-step transformation led to pentacyclic core **123**, in which the C19–C20 double bond was dihydroxylated and the resultant C19 alcohol was oxidized with DMP, providing α-hydroxy ketone **124**. Final IBX oxidation of the primary alcohol in alstrostine G precursor **125** followed by I_2-mediated oxidative esterification of the resulting aldehyde completed the synthesis of (−)-alstrostine G (**126**) (Scheme 11).

Although primary and secondary alcohols are generally not differentiable with IBX and DMP, some cases on the selective

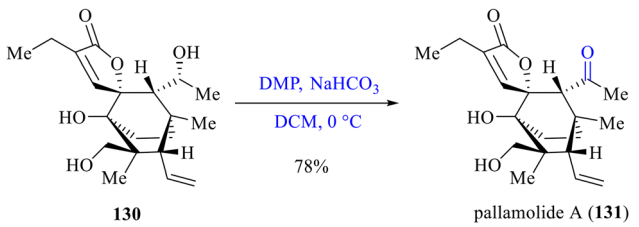


Scheme 11 IBX and Dess–Martin oxidation in the total synthesis of (–)-alstrostine G.

oxidation of either have been reported. For example, in the synthesis of tetrodotoxin (**129**) by Qi's group,[59] the primary alcohol in diol intermediate **127** was selectively oxidized with IBX (1.05 eq.) to the aldehyde (not shown), which was then reacted with the secondary alcohol to form the corresponding hemiacetal. Subsequent acetalization with trimethyl-orthoacetate provided acetal (**128**) in 88% yield in a one-pot operation (Scheme 12).

In the second example, in the total synthesis of pallamolide A (**131**) by Jia's group,[60] the authors found that the rate of Dess–Martin oxidation of the secondary hydroxy group in the pallamolide A precursor **130** was much faster than that of the primary one. Thus, oxidation of **130** with 1.2 equivalent of DMP at 0 °C furnished the total synthesis of pallamolide A in 78% yield, significantly simplifying selective oxidation at the final stage of synthesis (Scheme 13). Although the reason for this subtle selectivity was not clear, it could be due to the steric hindrance around the primary alcohol and its hydrogen-bonding to the tertiary alcohol.

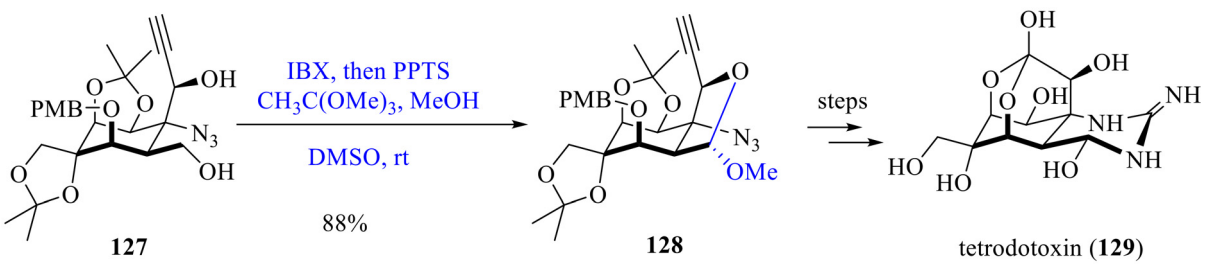
The selectivity of the oxidation of alcohols could also be influenced by the reaction temperature. For instance, in the synthesis of phomactins by Sarpong's group,[61] oxidation of advanced intermediate **132** with 2.0 eq. DMP at 0 °C selectively oxidized the C2 hydroxy group, providing ketone **133**, which was further converted to Sch 49027 (**134**) by deacetylation–



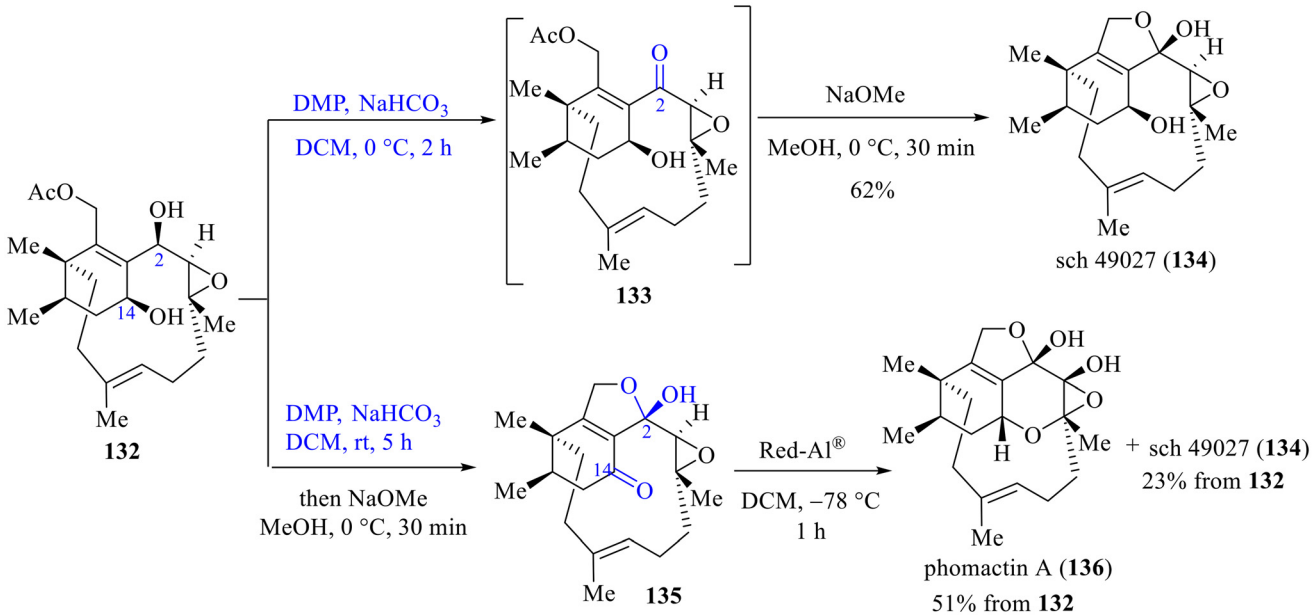
Scheme 13 Selective Dess–Martin oxidation in the total synthesis of pallamolide A.

hemiketalization. When the reaction was carried out at 21 °C with 4.0 eq. DMP, both the C2 and C14 hydroxy groups were oxidized with subsequent formation of C2 hemiketal **135** after deacetylation. Final reduction of C14 ketone in **135** by Red-Al® provided a mixture of phomactin A (**136**) and Sch 49027 (**134**), which was separated by HPLC (Scheme 14).

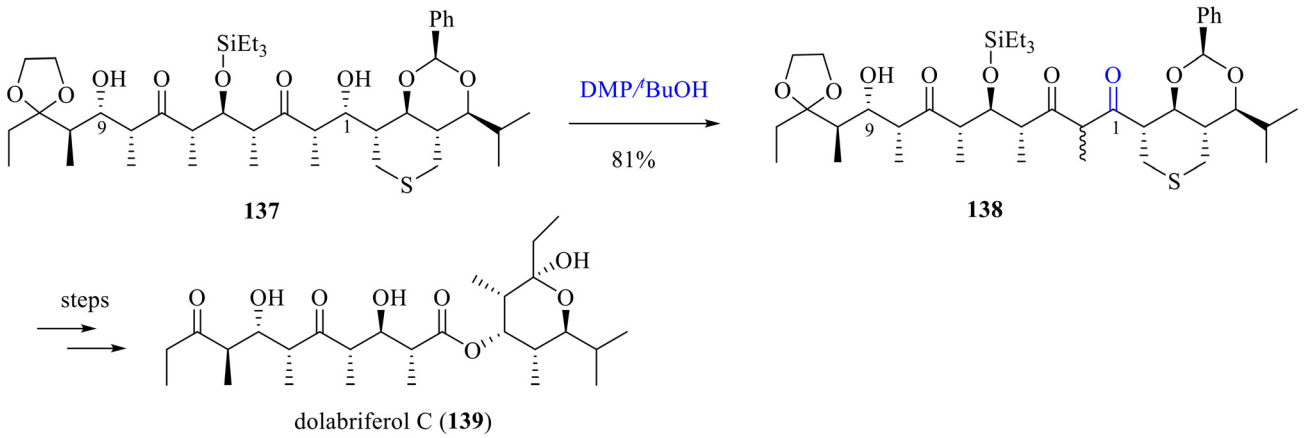
Additionally, DMP modified with *t*-butanol as a bulky ligand[62] has been applied to control the regioselectivity in alcohol oxidation. For example, in the total synthesis of dolabriferol C (**139**) by Ward's group,[63] 1,9-diol (**137**) was selectively oxidized at the C1 position to provide ketone **138** in >10 : 1 selectivity (Scheme 15), whereas DMP and IBX were much less selective (*ca.* 4 : 1 and 1.2 : 1, respectively).



Scheme 12 IBX oxidation in the total synthesis of tetrodotoxin.



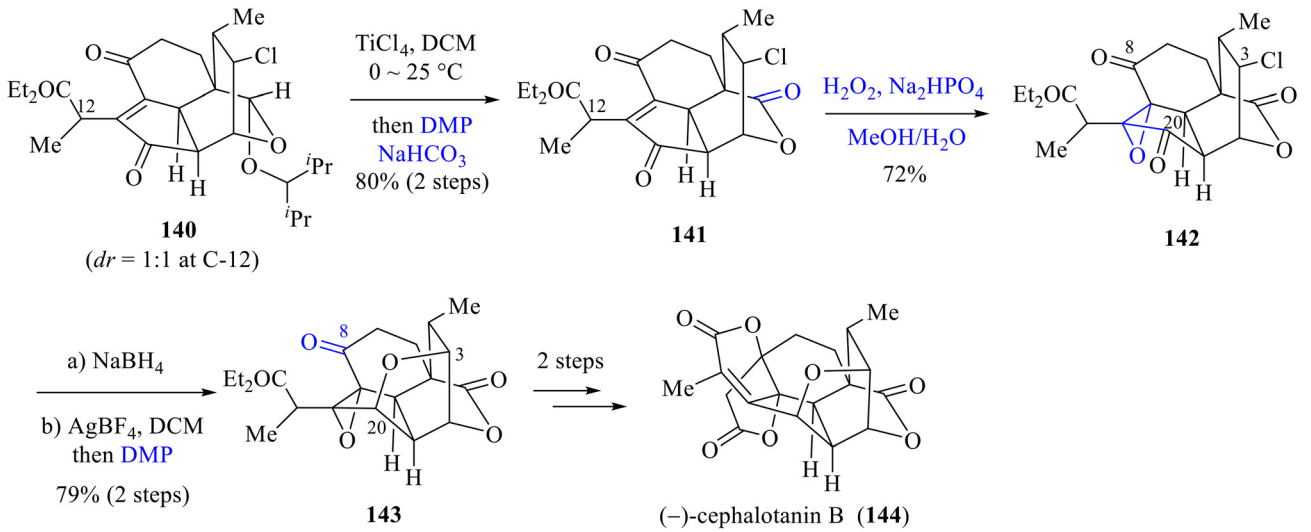
Scheme 14 Dess–Martin oxidation in the total synthesis of Sch 49027 and phomactin A.



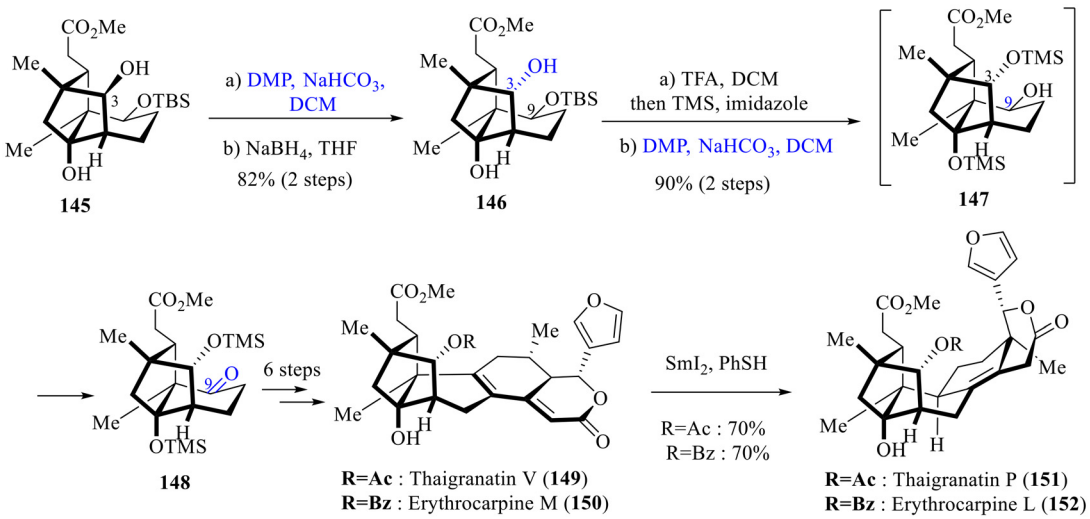
Scheme 15 Dess–Martin oxidation in the total synthesis of dolabriferol C.

Apart from alcohols, lactols can also be oxidized by IBX and DMP to form lactones. For example, in the total synthesis of (−)-cephalotanin B (**144**) by Hu's group,[64] deprotection of $(i\text{-Pr})_2$CH in acetal intermediate **140** followed by oxidation of the resulting lactol with DMP provided lactone **141** in 80% yield over 2 steps. The double bond in **141** was stereoselectively epoxidized with H_2O_2/Na_2HPO_4, providing α-epoxide **142**. Subsequent reduction of both C8 and C20 carbonyl groups with $NaBH_4$, followed by $AgBF_4$-promoted S_N2 displacement of the C3-chloride from the resultant C20-β-alcohol, installed ring G in **143** after reoxidation of the C8-alcohol with DMP. Final two-step transformation completed the total synthesis of (−)-cephalotanin B (Scheme 16).

Thaigranatins V (**149**) and P (**151**) and erythrocarpines M (**150**) and L (**152**) are phragmalin-type limonoids featuring a complex cage-like tricyclo[3.3.$1^{2,10}$.$1^{1,4}$]decane core, rendering them challenging targets for total synthesis studies. Two Dess–Martin oxidation steps were employed in the total synthesis of these phragmalin-type limonoid natural products by Newhouse's group.[65] Firstly, the undesired configuration of C3–alcohol in tricyclic intermediate **145** was corrected by Dess–Martin oxidation, followed by reduction with $NaBH_4$. Secondly, a one-pot operation on alcohol **146** by TBS deprotection, global TMS protection, selective C9 TMS deprotection and subsequent Dess–Martin oxidation of the resultant C9 alcohol **147** provided ketone **148**. Subsequent 6 steps of transformation led to thaigranatin V (**149**) and erythrocarpine M (**150**), which upon 1,6-reduction of the dienone with SmI_2/PhSH furnished thaigranatin P (**151**) and erythrocarpine L (**152**) (Scheme 17).



Scheme 16 Dess–Martin oxidation in the total synthesis of (–)-cephalotanin B.



Scheme 17 Dess–Martin oxidation in the total synthesis of phragmalin-type limonoids.

More examples on the application of the IBX and DMP oxidation of alcohols in natural product synthesis are provided in Table 1.

3.2 Ley–Griffith oxidation (TPAP/NMO)

Ley–Griffith oxidation is the oxidation of primary and secondary alcohols to the corresponding aldehydes and ketones, respectively, using a catalytic amount (5–10 mol%) of tetrapropylammonium perruthenate (TPAP) and *N*-methylmorphone *N*-oxide (NMO) as the co-oxidant. This reaction is named after William P. Griffith and Steven V. Ley, who first reported it in 1987.[81] This reaction is known for its mild conditions and broad functional group tolerance, though stringently anhydrous conditions are required to achieve the optimal reaction performance.[15] The application of this method in natural product synthesis is highlighted in selected examples below.

In the synthesis of Taxol (**236**) by Inoue's group,[82] the primary alcohol in **233** was oxidized with TPAP/NMO and the resulting aldehyde was reacted with methyllithium to provide alcohol **234** in 76% yield over 2 steps. Secondary alcohol **234** was in turn oxidized with TPAP/NMO, leading to ketone **235** (Scheme 18).

In the total synthesis of isoxeniolide A (**239**) by Altmann's group,[83] double oxidation of a lactol and a primary alcohol in intermediate **237** under Ley–Griffith conditions provided the desired lactone-aldehyde **238** in 70% yield (Scheme 19), whereas a number of other oxidants, including DMP, PCC, PDC, and TEMPO/DAIB alone or in combination with Yb $(OTf)_3$, were ineffective.

Table 1 More examples on the application of IBX and DMP oxidation of alcohols in natural product synthesis

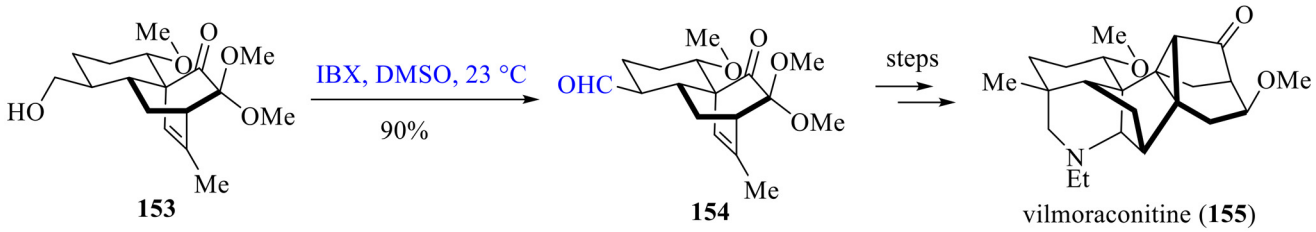
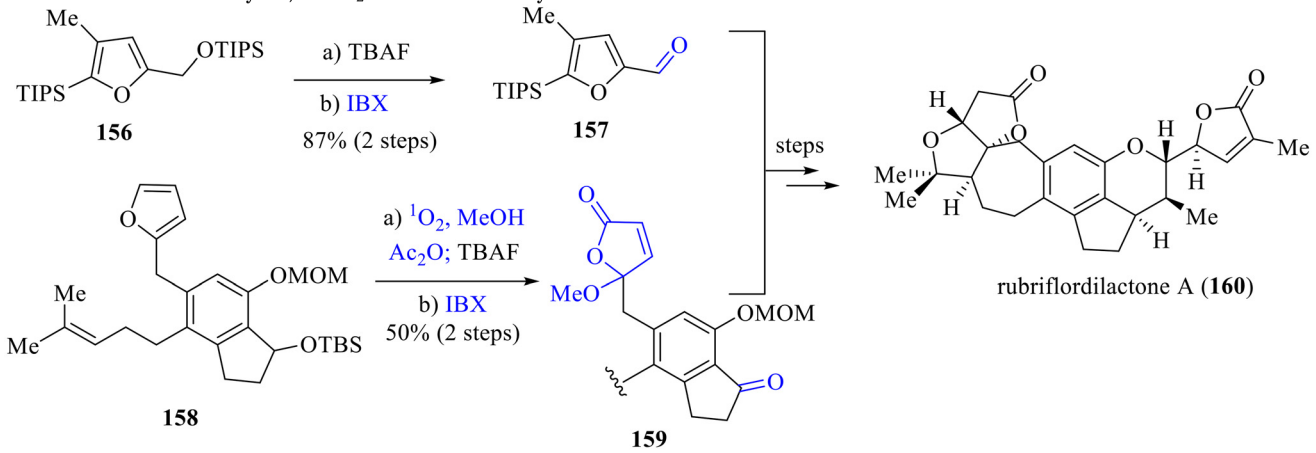
Entry	Source and significance of the natural product	Oxidation of alcohols using IBX and DMP
1	Vilmoraconitine (**155**) is a C_{19}-diterpenoid alkaloid isolated from the traditional Chinese medicinal herb *Aconitum vilmorinianum*, used to treat rheumatism and pains	 Comment:[66] IBX oxidation of alcohol **153** provided aldehyde **154** in excellent yield Other oxidation reactions used: $PhI(OAc)_2$ oxidation of phenol; Dess–Martin oxidation of alcohol to ketone; Ozonolysis of olefin; 2× AZADO oxidation of alcohol to aldehydes; and O_2/LDA oxidative decyanation to ketone
2	Rubriflordilactone A (**160**) is a highly oxygenated polycyclic triterpenoid with anti-HIV activity, which is isolated from the Chinese herbal medicinal plant *Schisandra rubriflora*.	 Comment:[67] O-TIPS deprotection of **156** followed IBX oxidation of the resultant primary alcohol provided aldehyde **157**. Oxidation of the furan in **158** with singlet oxygen followed TBS deprotection and IBX oxidation of the resulting benzylic alcohol afforded ketone **159** Other oxidation reactions used: 2× photocatalytic singlet oxygen oxidation of furan to butenolid

Table 1 *(Contd.)*

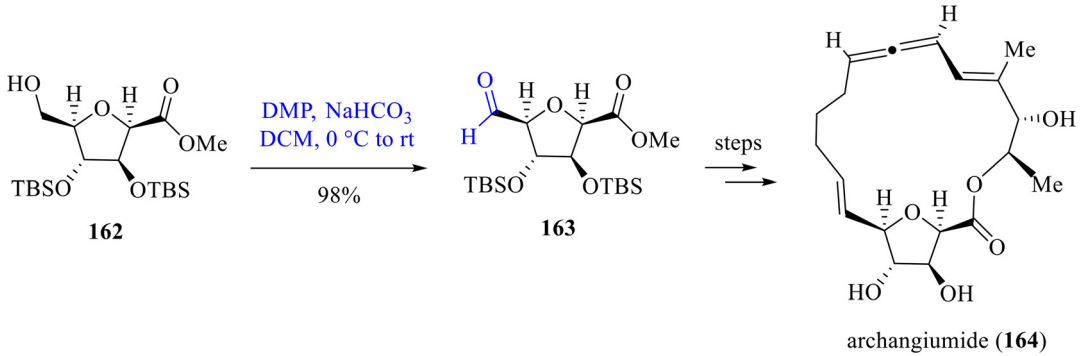
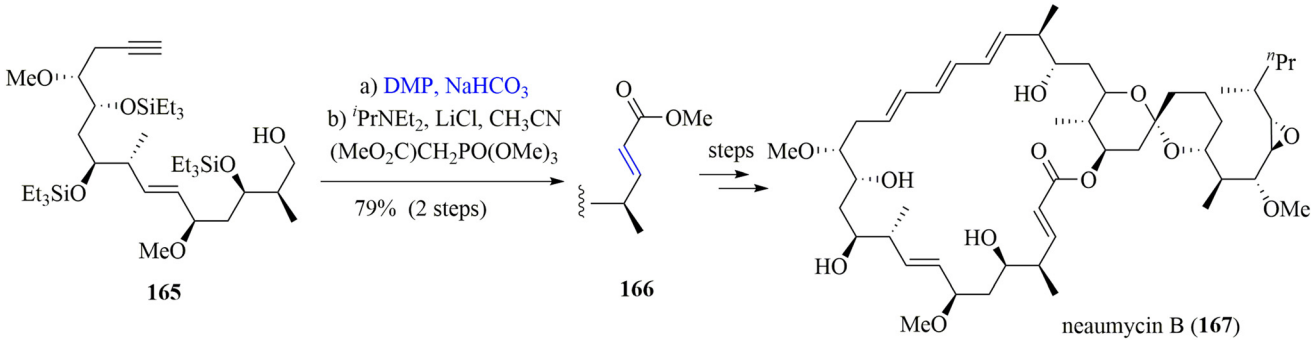
Entry	Source and significance of the natural product	Oxidation of alcohols using IBX and DMP
3	Archangiumide (**164**) is an unusual allenic macrolide isolated from the myxobacterium *Archangium violaceum* SDU8 collected in Shandong Province in China	 Comment:[68] DMP oxidation of alcohol **162** provided aldehyde **163** in 98% yield Other oxidation reactions used: N/A
4	Neaumycin B (**167**) was isolated from the marine microbe *Micromonospora* sp. (strain CNY-010) in the Bahamas Islands. This compound displayed significant potency against several cancer cell lines	 Comment:[69] Dess–Martin oxidation of alcohol **165** followed by Horner–Wadsworth–Emmons (HWE) olefination of the resultant aldehyde provided α,β-unsaturated ester **166** in 79% yield over 2 steps Other oxidation reactions used: $NaIO_4$ cleavage of 1,2-diol; 2× MnO_2 oxidation of allylic alcohol; TBHP/$VO(acac)_2$ epoxidation of allylic alcohol; TEMPO/PIDA oxidation of alcohol; and Stahl oxidation of alcohol

Table 1 *(Contd.)*

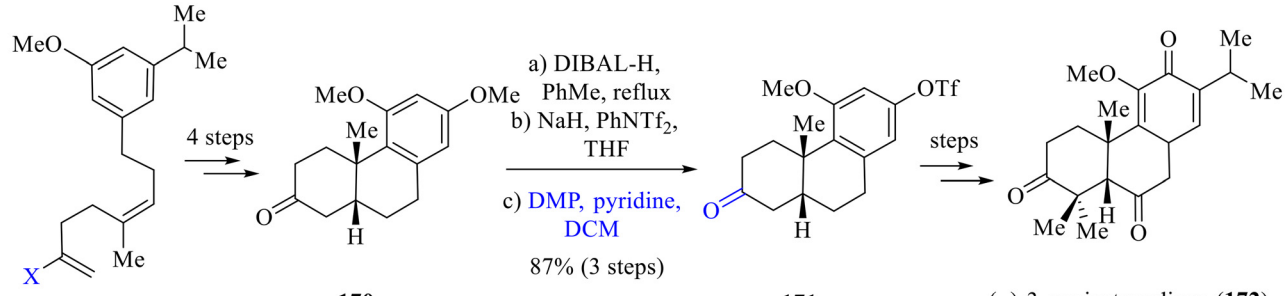
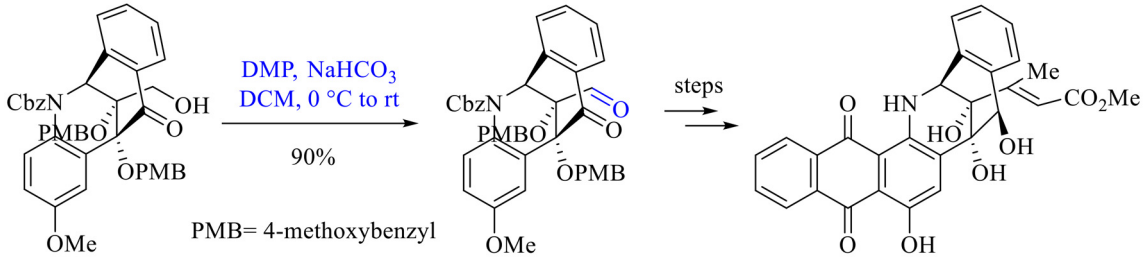
Entry	Source and significance of the natural product	Oxidation of alcohols using IBX and DMP
5	(−)-3-Oxoisotaxodione (**172**) was first isolated from the plant *Taiwana cryptomerioides* in 2005. This compound displayed promising anticancer, antibacterial, and antifungal activities	 **168**, X = CH_2OH ⟶ DMP, Py. ⟵ **169**, X = CHO **170** **171** (−)-3-oxoisotaxodione (**172**) Comment:[70] Two Dess–Martin oxidation steps were employed in the synthesis of **172** Firstly, alcohol **168** was oxidized to the aldehyde **169**. Secondly, the resultant alcohol after DIBAL-H demethylation-reduction of **170** was oxidized back to ketone **171** after selective triflation of the phenol Other oxidation reactions used: *m*-CPBA olefin epoxidation; HIO_5 epoxide cleavage; $(PhSeO)_2O$ phenol oxidation to quinone; and DMDO olefin epoxidation-rearrangement
6	Sealutomicin C (**175**) is an anthraquinone antibiotic isolated from fermentation of the marine *actinomycete Nonomuraea* sp. MM565M-173N2	 **173** **174** sealutomicin C (**175**) Comment:[71] Dess–Martin oxidation of alcohol **173** provided aldehyde **174** in excellent yield Other oxidation reactions used: $RuCl_3/NaIO_4$ dihydroxylation of olefin; $(NH_4)_2Ce(NO_3)_6$ oxidation of *p*-aminophenol ether to iminoquinone; and DDQ deprotection of PMB

Table 1 *(Contd.)*

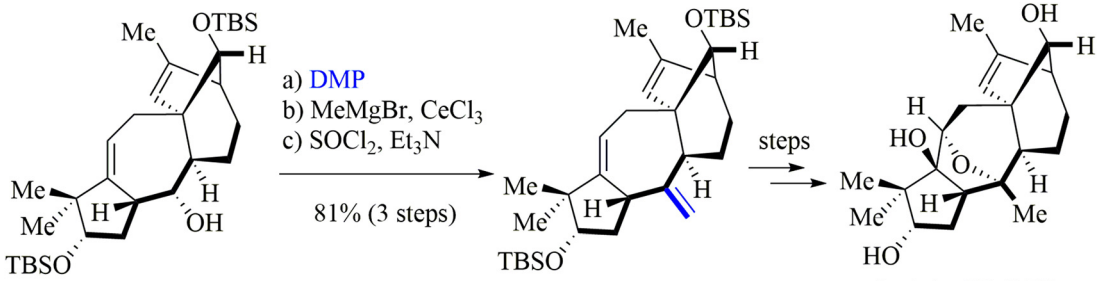
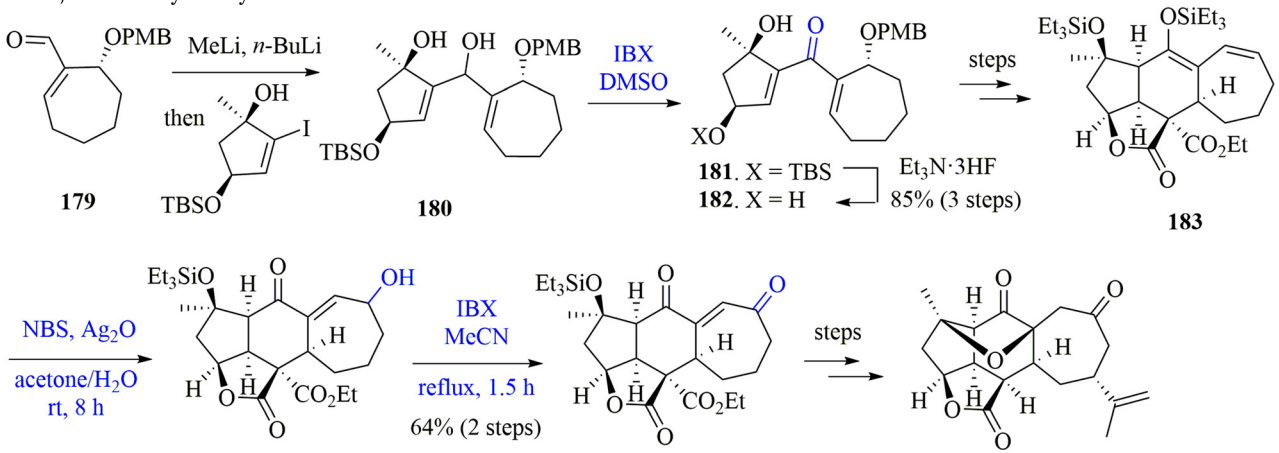
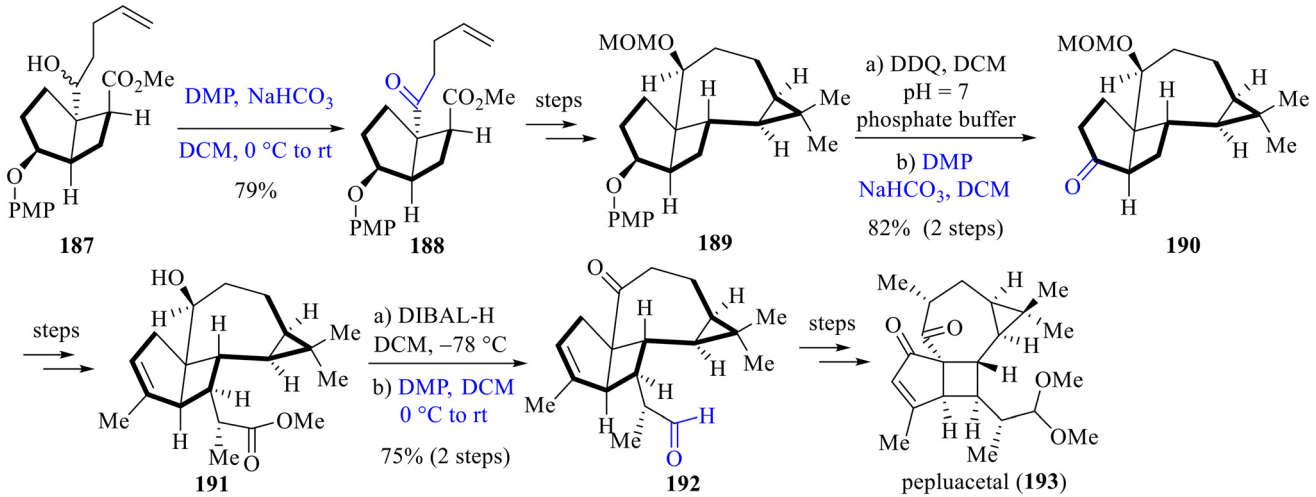
Entry	Source and significance of the natural product	Oxidation of alcohols using IBX and DMP
7	Principinol B (**178**) is a member of the grayanoid diterpenoids, isolated from *Rhododendron principis* growing in Tibet, China	 **176** **177** principinol B (**178**) Comment:[72] Dess–Martin oxidation of alcohol **176** followed by reacting the resultant ketone with methyl cerium generated *in situ* and further elimination of the formed tertiary alcohol with $SOCl_2/Et_3N$ provided triene **177** Other oxidation reactions used: Tamao-Fleming oxidation; Parikh-Doering oxidation; *m*-CPBA epoxidation of olefin; OsO_4 dihydroxylation of olefin; and Mukaiyama hydration of olefin
8	(−)-Sinulochmodin C (**186**) is a norcembranoid diterpenoid isolated from the *genus Sinularia*. This compound displayed anti-tumor and anti-inflammatory activities	 **179** **180** **181**. X = TBS, **182**. X = H **183** **184** (*dr* = 2.8:1) **185** (−)-sinulochmodin C (**186**) Comment:[73] IBX oxidation of alcohols **180** and **184** provided ketones **181** and **185**, respectively Other oxidation reactions used: DDQ deprotection of PMB; 3× Saegusa oxidation of ketone to enone; Mukaiyama hydration of olefin; and *m*-CPBA epoxidation of olefin

Table 1 *(Contd.)*

Entry	Source and significance of the natural product	Oxidation of alcohols using IBX and DMP
9	Pepluacetal (**193**), featuring a 5/4/7/3 tetracyclic core, was isolated from *Euphorbia peplus*, which is a traditional medicine to treat asthma and psoriasis	

Comment:[74] Three Dess–Martin oxidation steps were employed in the total synthesis of **193**. Oxidation of alcohol **187** to ketone **188**, the alcohol after PMB deprotection of **189** to ketone **190**, and the alcohol from DIBAL-H reduction of ester **191** to aldehyde **192**
Other oxidation reactions used: DDQ deprotection of PMB; Pinnick oxidation; Baeyer–Villiger oxidation; and CrO_3 oxidation of allylic methylene to ketone.

Table 1 *(Contd.)*

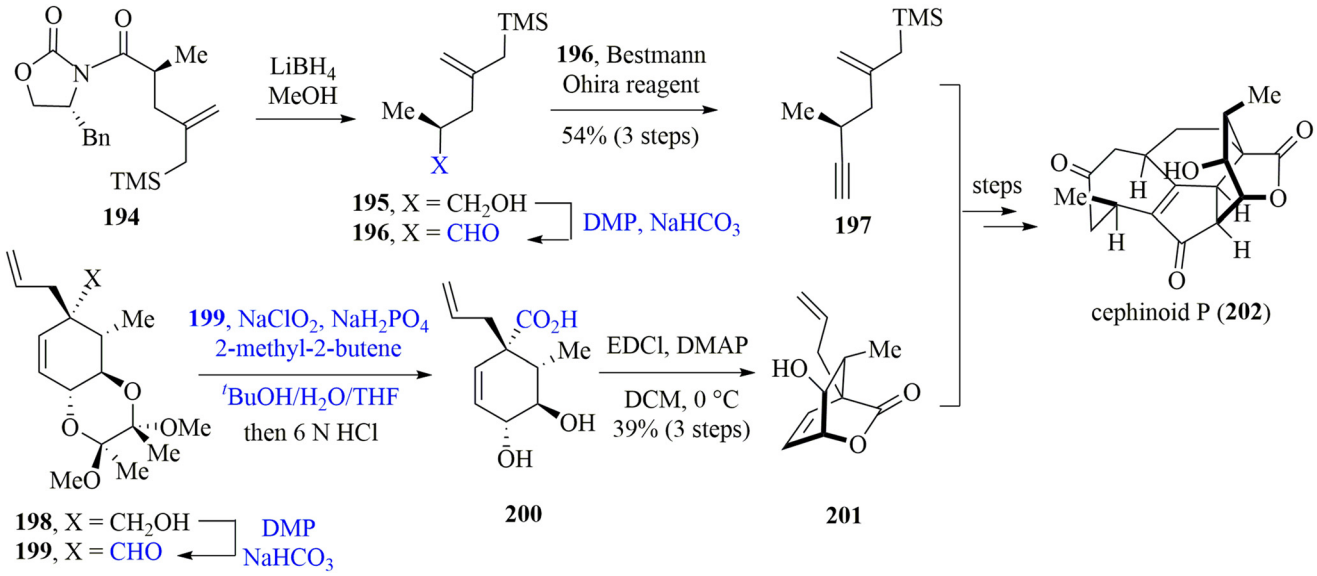
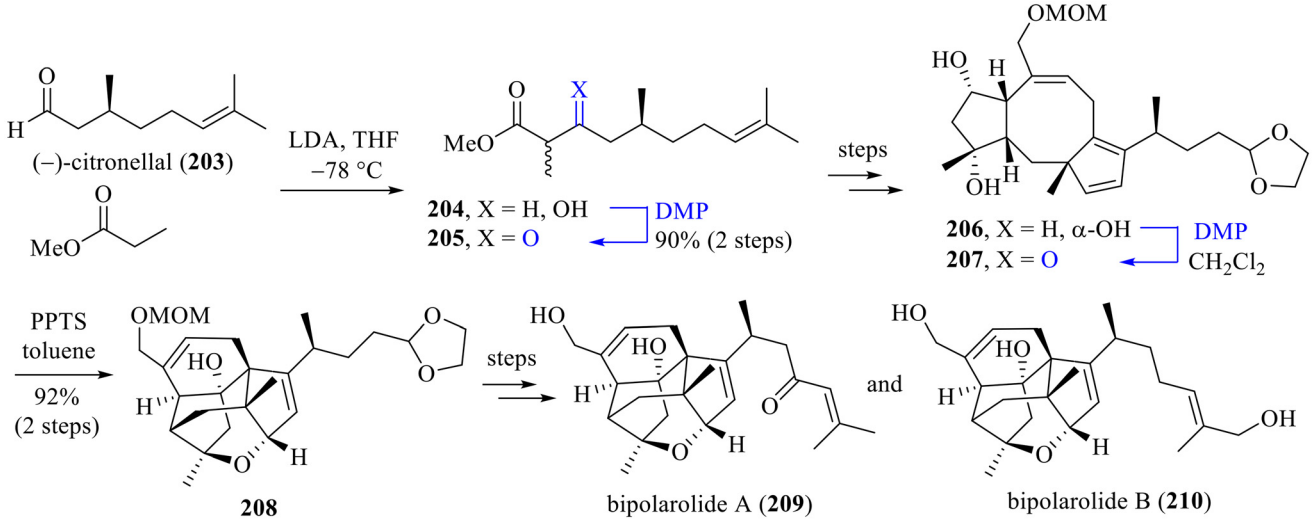
Entry	Source and significance of the natural product	Oxidation of alcohols using IBX and DMP
10	The cephalotaxus diterpenoids such as cephinoid P (**202**) are a family of structurally diverse diterpenoids isolated from different species of *Cephalotaxus*	 Comment:[75] Oxidation of primary alcohols **195** and **198** with DMP provided the corresponding aldehydes **196** and **199**, which were transformed to fragments **197** and **201**, respectively, for the synthesis of cephinoid P (**202**) and other members of the cephalotaxus diterpenoids Other oxidation reactions used: Lindgren-Kraus oxidation; Swern oxidation; and $OsO_4/NaIO_4$ cleavage of olefin.
11	Bipolarolides A (**209**) and B (**210**) are sesterterpenoids isolated from *Bipolaris* sp. TJ403-B1. Structurally they possess a caged 5/6/6/6/5 pentacyclic skeleton bearing seven contiguous stereocenters, making them challenging targets for total synthesis	 Comment:[40] Dess–Martin oxidation of alcohols **204** and **206** provided ketones **205** and **207**, respectively. Subsequent Prins reaction-ether formation cascade cyclization of **207** led to the 5/6/6/6/5 pentacyclic skeleton **208** of bipolarolides Other oxidation reactions used: Babler-Dauben oxidation; TEMPO/PIDA oxidation of alcohol; $K_2OsO_4/NMO/NaIO_4$ cleavage of olefin; methylene blue/O_2 and Babler-Dauben oxidation of olefin to enone

Table 1 *(Contd.)*

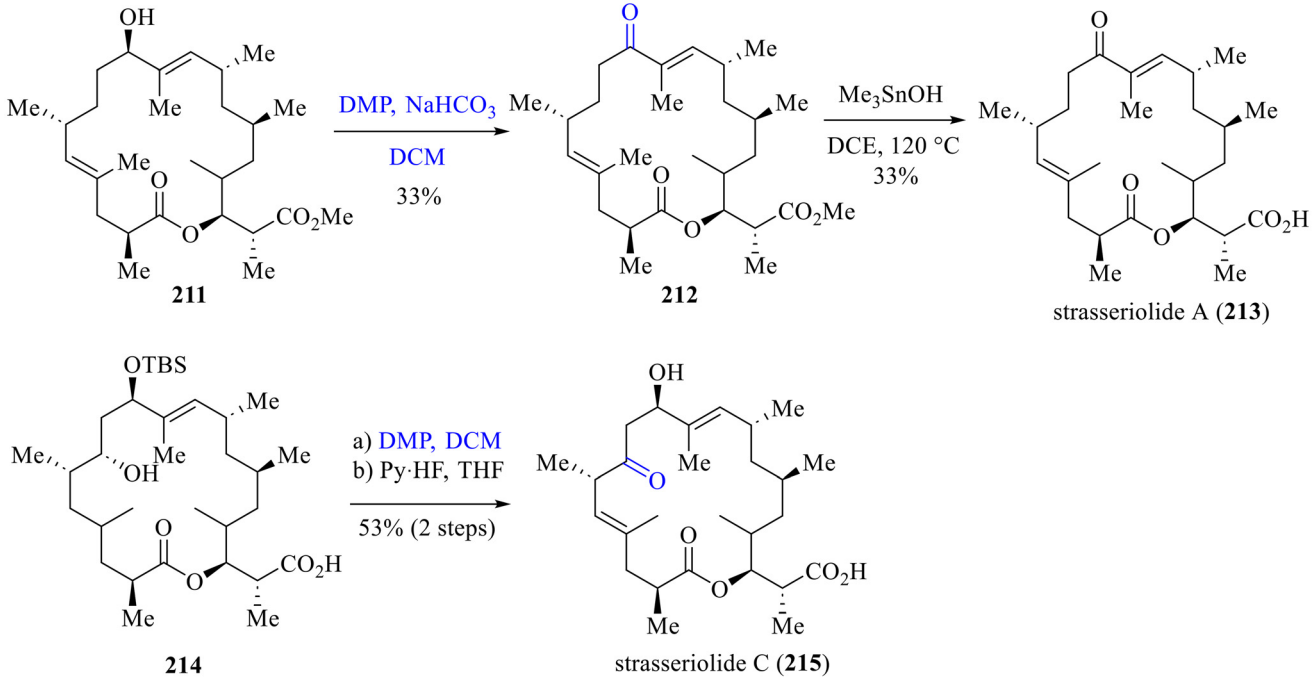
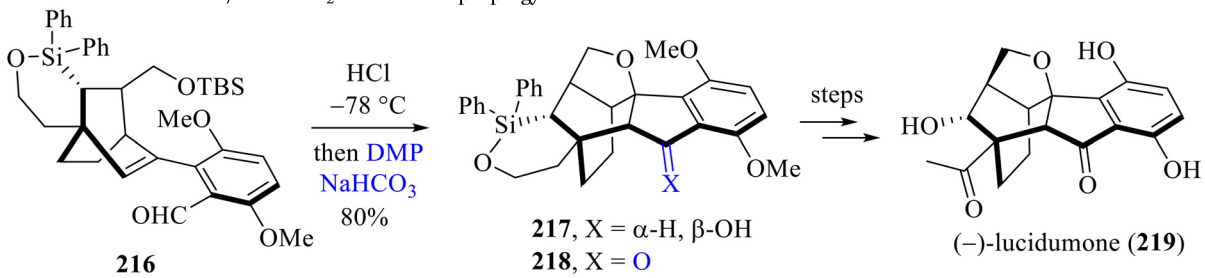
Entry	Source and significance of the natural product	Oxidation of alcohols using IBX and DMP
12	Strasseriolides A (**213**) and C (**215**) are 18-membered macrolides isolated from the fungus *Strasseria geniculata* CF-247, with strasseriolide C (**215**) displaying inhibitory activities against *P. falciparum* parasites	 Comment:[76] Dess–Martin oxidation of alcohol **211** followed by hydrolysis of ester **212** using Nicolaou's method provided strasseriolide A (**213**), while the same oxidation of alcohol **214** and subsequent deprotection of TBS group furnished strasseriolide C (**215**) Other oxidation reactions used: 2× Parikh Doering oxidation of alcohols; 2× ozonolysis; Ti-Salan-catalysed enantioselective epoxidation of unfunctionalized olefin; and MnO_2 oxidation of propargyl alcohol
13	Lucidumone (**219**) is a meroterpenoid isolated from the fruiting bodies of *Ganoderma lucidum* cultivated in the Yunnan Province in China. Its structure features a complex 6/5/6/6/5 polycyclic ring system	 Comment:[77] Acid-catalyzed *O*-deprotection/Prins cyclization/cycloetherification sequence on **216** led to hexacyclic alcohol **217**, which was oxidized with DMP to ketone **218** Other oxidation reactions used: Iron-catalyzed Wacker-type oxidation of terminal olefin to methyl ketone.

Table 1 *(Contd.)*

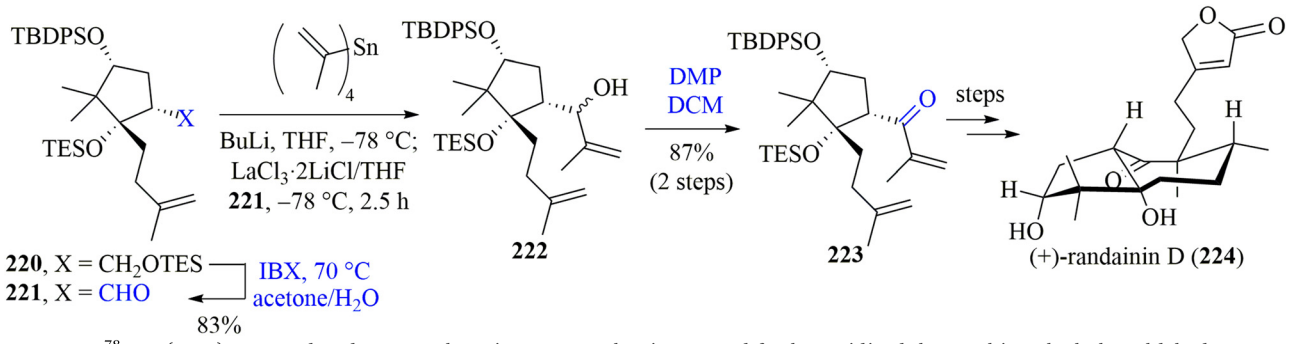
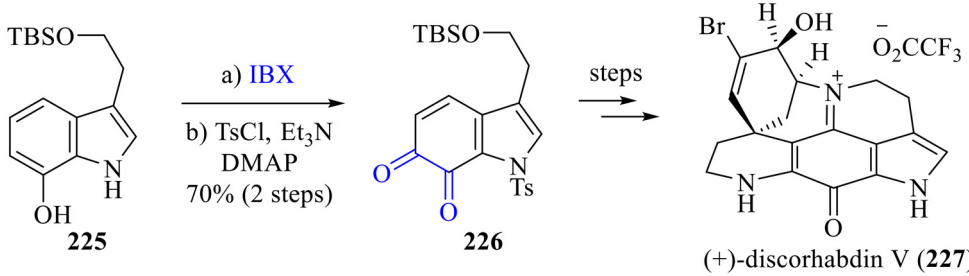
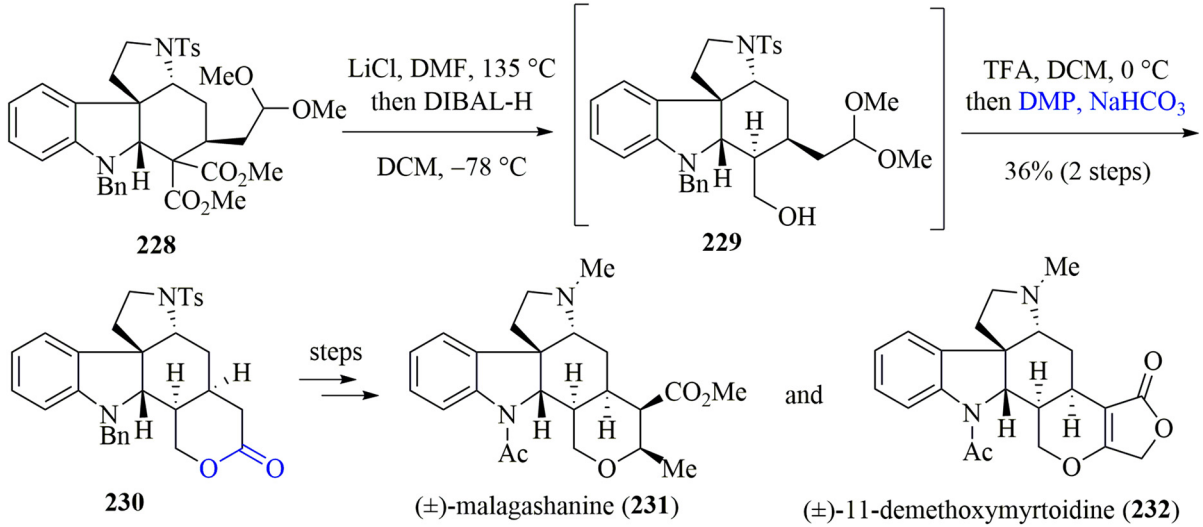
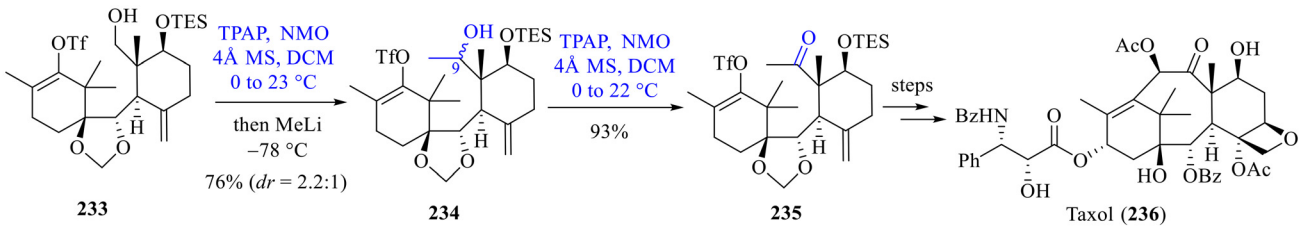
Entry	Source and significance of the natural product	Oxidation of alcohols using IBX and DMP
14	Randainin D (**224**) is a diterpenoid isolated from *Callicarpa randaiensis*. This compound inhibits elastase release and superoxide-anion generation	 Comment:[78] IBX (5 eq.) was used to deprotect the primary TES ether in **220** and further oxidized the resulting alcohol to aldehyde **221**. Subsequent isopropenylation provided alcohol **222**, which was oxidized with DMP to ketone **223** Other oxidation reactions used: Mukaiyama hydration of olefin to alcohol.
15	Discorhabdin V (**227**) is a member of the pyrroloimino-quinone alkaloids. This compound inhibits hypoxia-inducible factor 1 (HIF-1), a heterodimeric transcription factor that contributes to tumour development	 Comment:[79] Regioselective IBX oxidation of phenol **225** to *o*-quinone followed by *p*-toluenesulfonyl protection of N–H provided tosylamide **226** Other oxidation reactions used: Air oxidation of *o*-diphenol to *o*-quinone; Stahl oxidation of primary alcohol to aldehyde; and Swern oxidation

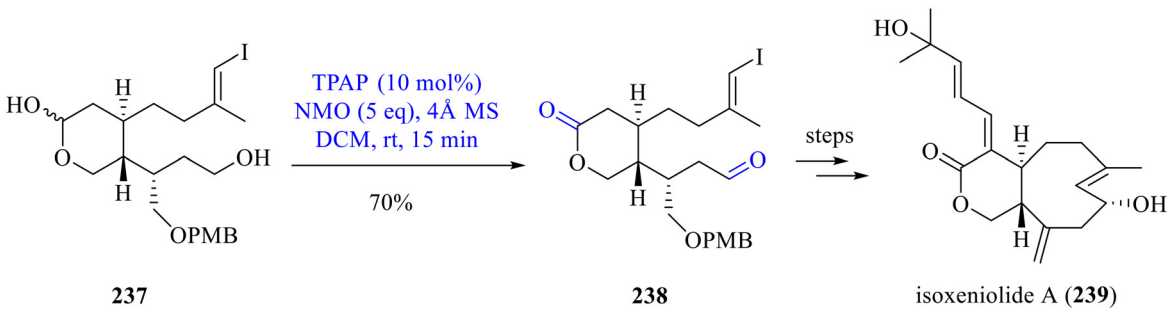
Table 1 *(Contd.)*

Entry	Source and significance of the natural product	Oxidation of alcohols using IBX and DMP
16	The Malagasy family of alkaloids (*e.g.*, **231** and **232**) are polycyclic indoline compounds featuring unique *trans*-fused C/D rings	

Comment:[80] Mono decarboxylation of **228** followed by DIBAL-H reduction provided alcohol **229.** Subsequent TFA-mediated one-pot deacetalization and intramolecular acetalization led to a lactol intermediate, which was oxidized to lactone **230** with DMP
Other oxidation reaction used: Riley allylic oxidation



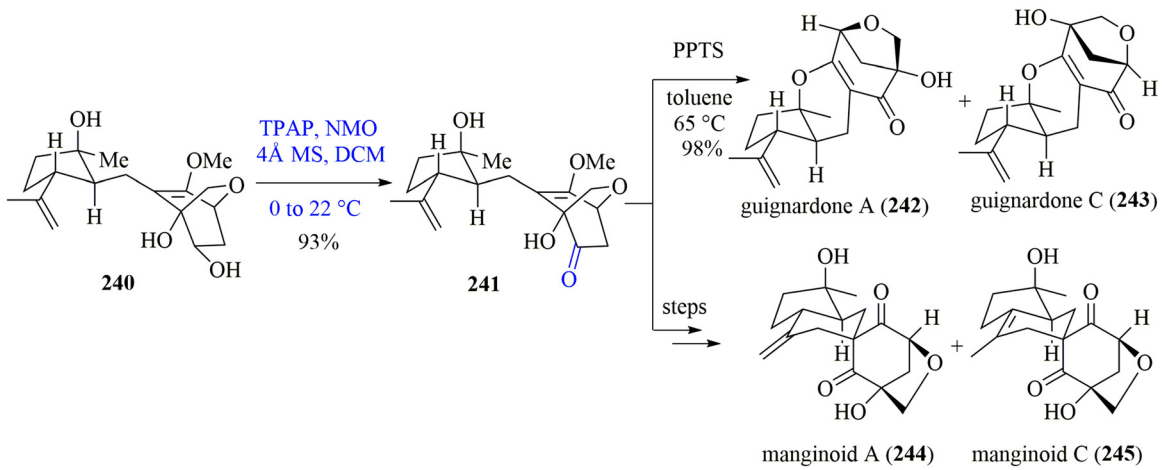
Scheme 18 Ley–Griffith oxidation in the synthesis of Taxol.



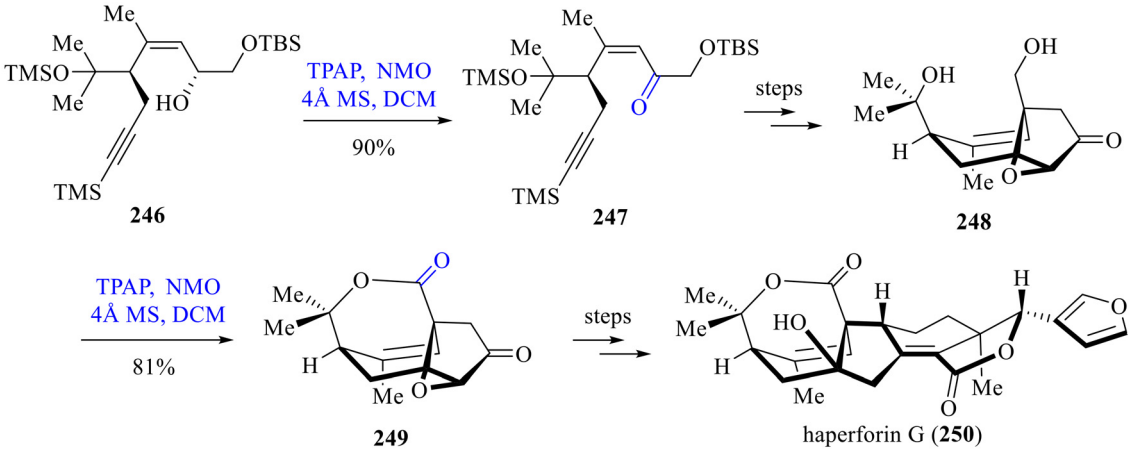
Scheme 19 Ley–Griffith oxidation in the synthesis of isoxeniolide A.

Manginoids and guignardones are two types of biogenetically related meroterpenoids found in the fungus *Guignardia mangiferae*. These natural products possess intriguing architectures and exhibit diverse biological activities. In the combined synthesis of guignardones A/C (**242** and **243**) and manginoids A/C (**244** and **245**) by Zong *et al.*,[84] oxidation of the secondary alcohol in **240** to the common intermediate ketone **241** was achieved by Ley–Griffith oxidation, while other methods, including PDC, DMP and IBX, failed due to the sensitivity of the other functional groups in the molecule. Treatment of **241** with pyridinium *p*-toluenesulfonate (PPTS) furnished guignardones A/C, which were separated by silica gel column chromatography. A longer sequence of transformations led to manginoids A and C (Scheme 20).

(+)-Haperforin G (**250**) is a potent inhibitor of human 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) isolated from *Harrisonia perforata*. In the total synthesis of (+)-haperforin G by Zhang's group,[85] two Ley–Griffith oxidation steps were employed. The first oxidation of alcohol **246** provided ketone **247** without affecting the two labile TMS groups. The second Ley–Griffith oxidation of diol intermediate **248** led directly to lactone **249** *via* the lactol intermediate formed from the resultant aldehyde with the tertiary alcohol (Scheme 21).



Scheme 20 Ley–Griffith oxidation in the synthesis of manginoids and guignardones.



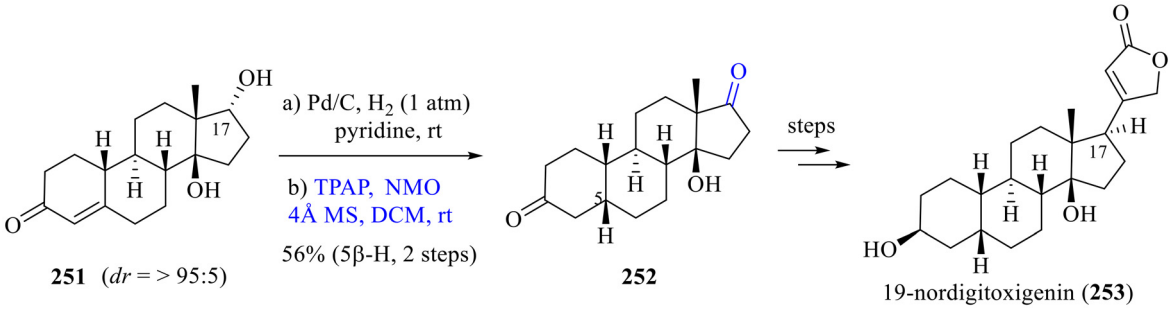
Scheme 21 Ley–Griffith oxidation in the synthesis of (+)-haperforin G.

19-Nordigitoxigenin (**253**) is an aglycon of antiroside Y, which is a 19-norcardenolide isolated from the bark of *Antiaris toxicaria*. Antiroside Y showed potent inhibitory activities against human cancer cell lines with a totally different mode of action, and hence is a potential candidate for cancer therapy. In the total synthesis of 19-norcardenolide by Nakazaki and co-workers,[86] hydrogenation of the double bond in **251** resulted in an 80 : 20 inseparable mixture of 5-β/α epimers. Interestingly, after Ley–Griffith oxidation of the C17-alcohol, the epimeric mixture was separable, providing the desired 5-β isomer (**252**) in 56% isolated yield over the two steps (Scheme 22).

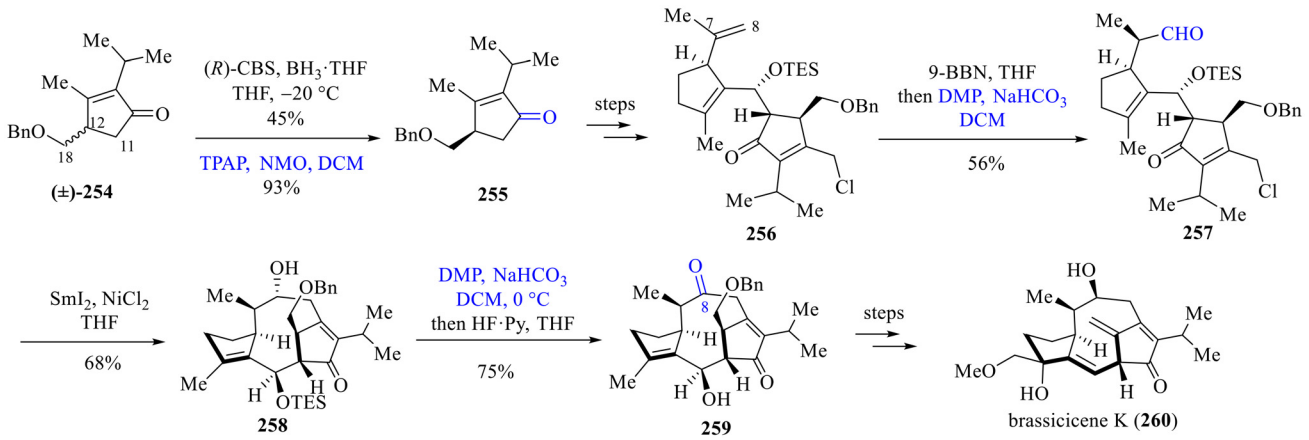
In the concise and divergent total synthesis of brassicicenes by Wang and Chen,[87] the initial racemic enone [(±)-**254**] was deracemized by (*R*)-CBS reduction followed by Ley–Griffith oxidation of the desired isomer, providing the enriched enone **255** in 57% ee. Subsequent two-step reactions led to triene intermediate **256**, which was converted to aldehyde **257** by regioselective hydroboration at the C7–C8 olefin and subsequent DMP oxidation. A critical Barbier reaction mediated by SmI_2 formed macrocycle **258**, in which the C8-alcohol was oxidized to ketone **259** with DMP. Further transformations led to brassicicene K (**260**) (Scheme 23).

3.3 Nitroxyl radical TEMPO and related reagents

Nitroxyl radicals are a class of stable organic free radicals used as catalysts for the oxidation of alcohols to aldehydes and ketones.[88] Among them, the most well-known is 2,2,6,6-tetramethylpiperidine *N*-oxyl (TEMPO, **261**)[89] but it often shows sluggish activity in the oxidation of hindered alcohols. To overcome this limitation, other nitroxyl radicals, such as AZADO (**262**)[14] and ABNO (**263**),[90] have been developed for enhanced reactivity. The nitroxyl radicals require a terminal oxidant (or co-oxidant) for alcohol oxidation to regenerate the active oxoammonium cation species to maintain the catalytic cycle. A variety of terminal oxidants, such as NaOCl, Oxone®, O_2/air, PhIO, phenyliodine(III) diacetate (PIDA or BAIB), trichloroisocyanuric acid (TCCA), *t*-butyl hydroperoxide (TBHP), and $KBrO_3$, have been used. The choice of a co-oxidant is often dictated by the specific reaction conditions, desired selectivity, and environmental considerations. Additionally, nitroxyl radicals can be used in combination with a metal co-catalyst, such as copper (Stahl oxidation)[91] or iron (Ma oxidation)[92] with molecular oxygen as a green oxidant. Apart from the often-used nitroxyl radical catalysts, their oxoammonium salt derivatives such as 4-acetamido-2,2,6,6-tetramethyl-1-oxopiperidinium tetrafluoroborate (Bobbitt's salt, **264**)[93] have also been

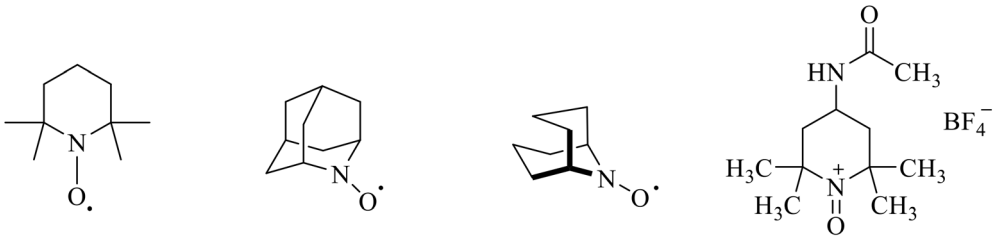


Scheme 22 Ley–Griffith oxidation in the synthesis of 19-nordigitoxigenin.



Scheme 23 Ley–Griffith oxidation in the synthesis of brassicicene.

used for alcohol oxidation, although a stoichiometric amount of the reagent is required. For primary alcohols, the aldehydes formed can be further oxidized to carboxylic acids in combination with a suitable co-oxidant such as PIDA, providing convenient access to carboxylic acids in an efficient one-step operation.

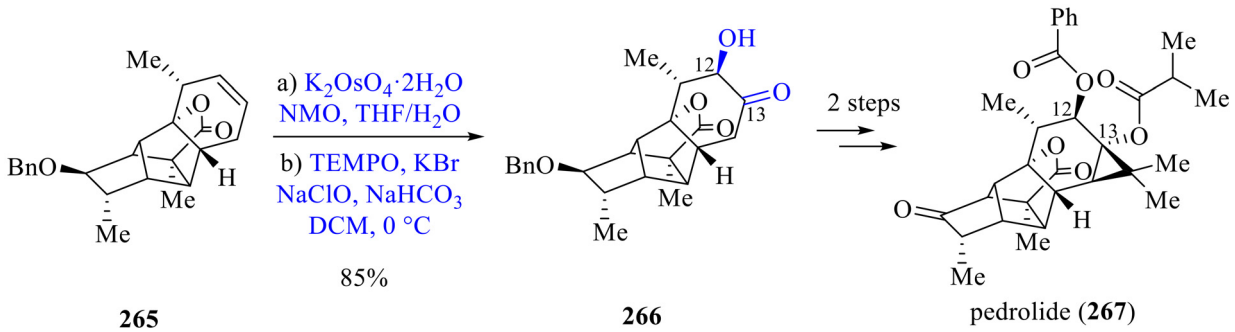


Alcohol oxidation using nitroxyl radicals has several notable advantages, including high chemoselectivity, mild reaction conditions, use of environmentally benign oxidants (*e.g.* O_2/air), choice of catalyst (TEMPO, AZADO and ABNO) for optimal outcome, and scalability. Thus, they are often the choice for alcohol oxidation in the synthesis of natural products and pharmaceutical compounds, as shown in the examples below.

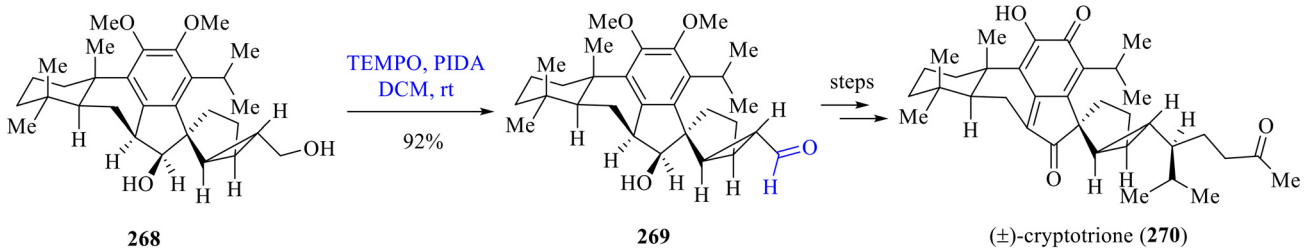
In the total synthesis of pedrolide (**267**) by Li and co-workers,[94] dihydroxylation of the olefin in **265** followed by regioselective oxidation of the less hindered C13-hydroxy group with TEMPO/KBr-NaOCl provided hydroxy ketone **266** in 85% yield in a one-pot operation (Scheme 24).

TEMPO with a suitable co-oxidant can selectively oxidize a primary alcohol in the presence of a secondary one, whereas it is difficult to achieve by using DMP or IBX. For example, in the total synthesis of (±)-cryptotrione (**270**),[95] the primary alcohol in the advance intermediate (**268**) was selectively oxidized to aldehyde (**269**) using TEMPO and PIDA in excellent yield without affecting the secondary alcohol (Scheme 25).

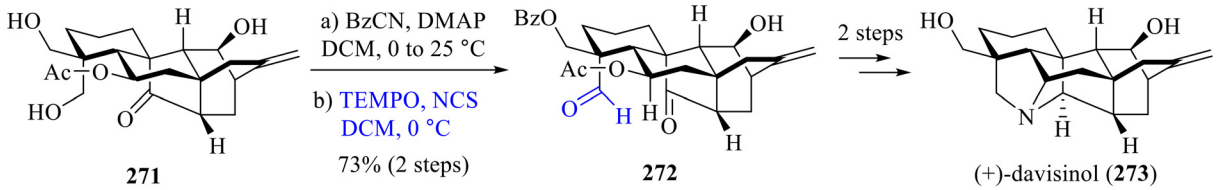
In another example, in the synthesis of (+)-davisinol (**273**) by Ding's group,[96] selective benzoylation of the equatorial hydroxymethyl group in **271**, followed by chemoselective oxidation of the primary alcohol in the resulting benzoate with



Scheme 24 TEMPO oxidation of alcohol in the synthesis of pedrolide.



Scheme 25 TEMPO-selective oxidation of primary alcohol in the synthesis of (±)-cryptotrione.



Scheme 26 TEMPO-selective oxidation of primary alcohol in the synthesis of (+)-davisinol.

TEMPO and NCS (*N*-chlorosuccinimide) at 0 °C provided the aldehyde (**272**) without affecting the secondary alcohol (Scheme 26).

As less hindered nitroxyl radicals than TEMPO, AZADO (**262**) and ABNO (**263**) have also been used in the selectivity oxidation of alcohols with enhanced activity for sterically hindered secondary alcohols, often in combination with a Cu(I) or Fe(III) co-catalyst. For example, at the final stage in the synthesis of vilmoraconitine (**155**) by Qin's group,[66] to overcome the challenge in selective reduction of the amide in the presence of the C14 ketone in **274**, both the amide and ketone were reduced with $LiAlH_4$ and the resulting alcohol (**275**) was reoxidized to ketone using AZADO/CuCl and air as the co-oxidant, completing the synthesis of vilmoraconitine (Scheme 27).

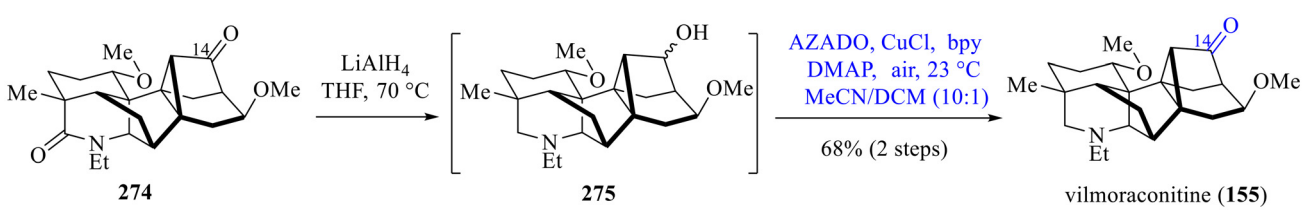
In another example, in the synthesis of C19 diterpenoid alkaloids (−)-talatisamine (**278**), (−)-liljestrandisine (**279**) and (−)-liljestrandinine (**280**) by Reisman and co-workers,[97] the diol from the deprotection of the cyclic silyl ether (**276**) was selectively oxidized at the allylic position using an ABNO/Cu(I)-^{MeO}bpy (4,4′-dimethoxy-2,2′-bipyridine) complex and *N*-methylimidazole (NMI).[98] Subsequent MOM protection of the remaining hydroxy group led to the common enone intermediate (**277**) in 75% yield over 3 steps (Scheme 28).

One of the prominent advantages of nitroxyl radical-mediated alcohol oxidation is that oxygen or air can be used as an inexpensive and environmentally benign terminal oxidant. For example, in the synthesis of (+)-discorhabdin V (**227**) by Burns' group,[79] the primary alcohol in diol **281** was selectively oxidized to aldehyde **282** under Stahl conditions (TEMPO, CuBr, bipy, NMI and air).[90] Subsequent double condensation and cyclization of **282** with NH_4OAc/AcOH/MeOH led to *N*,*O*-acetal **283**, which underwent reductive demethoxylation, providing cyclic amine **284** in 58% yield in an efficient one-pot operation (Scheme 29).

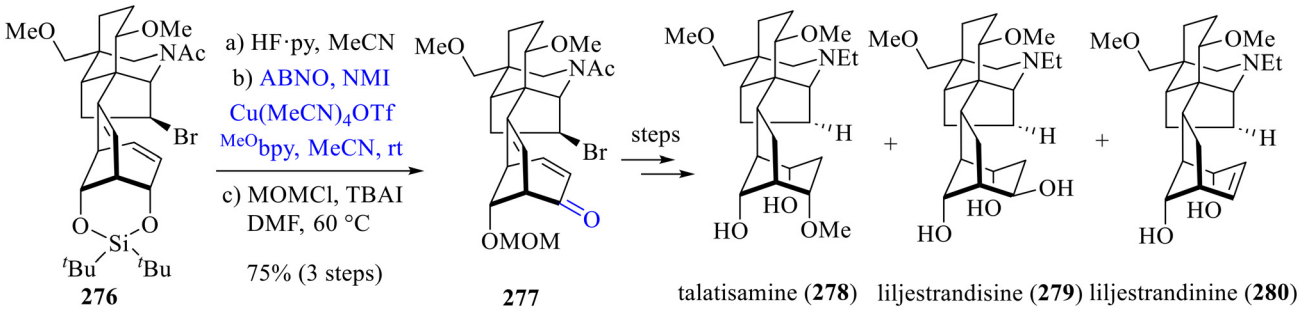
More examples of the nitroxyl radical-catalyzed oxidation of alcohols are provided in Table 2. Apart from converting primary alcohols to aldehydes, nitroxyl radicals in conjunction with a suitable co-oxidant can also oxidize primary alcohols directly to carboxylic acids, making it a selective and efficient transformation (see Section 4.2).

3.4 Oxidation by alcohol dehydrogenation

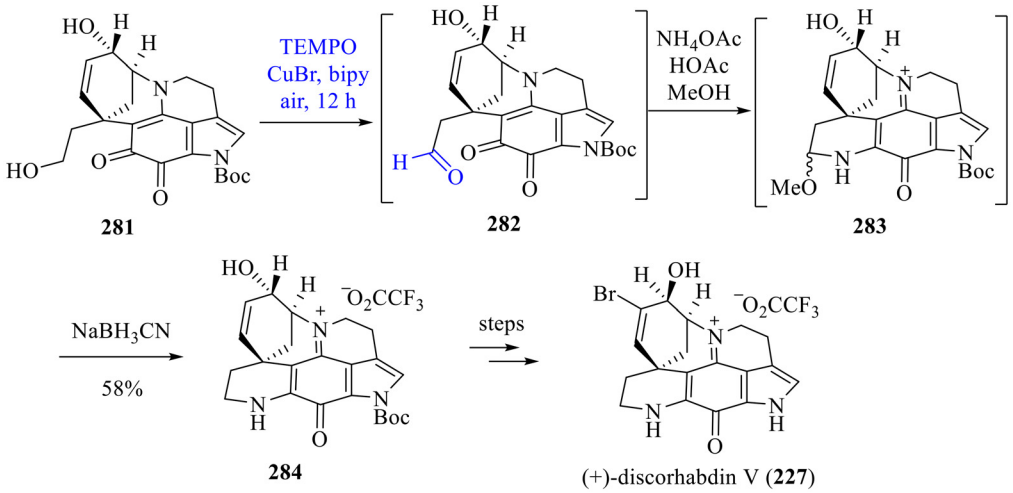
Alcohol oxidation *via* dehydrogenation is an important transformation in organic synthesis. It enables the conversion of primary and secondary alcohols into aldehydes and ketones, respectively, without the use of stoichiometric oxidants. This reaction typically employs transition metal catalysts that mediate the removal of a molecule of hydrogen from the hydroxy group and the carbon linked to it, releasing molecular hydrogen as the sole by-product, making the process highly atom-economical and environmentally attractive. The catalysts



Scheme 27 AZADO/Cu(I) oxidation of alcohol in the synthesis of vilmoraconitine.



Scheme 28 AZADO/Cu(I) oxidation of alcohol in the synthesis of (–)-talatisamine, (–)-liljestrandisine and (–)-liljestrandinine.



Scheme 29 TEMPO/Cu(I) selective oxidation of primary alcohol in the synthesis of discorhabdin V.

most often used for alcohol dehydrogenation are complexes of noble metals such as Ru, Ir, Pt, Pd, and Rh, although earth-abundant metals such as Mn, Fe, Co, Ni, and Cu have also been used. In addition, the carbonyl compounds formed in the reaction can be used for subsequent transformations before the catalyst returns the bonded hydrogen to liberate the product and regenerate the catalyst, which is a concept termed "hydrogen autotransfer" or "borrowing hydrogen".[107] In the presence of a chiral ligand, the reaction proceeds in an enantioselective manner, which is often required in natural product synthesis.[107c] The merits of mild conditions, high selectivity and reduced waste generation make alcohol dehydrogenation an attractive alternative to traditional stoichiometric oxidants in natural product synthesis. Significantly, owing to the discovery by Tu,[108] and Krische's innovative contribution,[109] the direct catalytic functionalization of carbinol C–H bonds (Scheme 30a) has become a redox-economical reaction.[108b,c,109] Particularly, Krische's elegant catalytic asymmetric version has rendered this methodology a powerful tool in the catalytic asymmetric total synthesis of natural products,[2g] as highlighted by the selected examples shown below.

In the total synthesis of leiodermatolide A (**324**) by Krische's group,[110] in the presence of an iridium-(*S*)-DM-SEGPHOS catalyst generated *in situ*, alcohol **321** underwent dehydrogenation to form the corresponding aldehyde (not shown), which was further reacted with the allenyliridium generated from the Ir–H complex with the conjugated enyne (**322**), providing **323** in 63% yield, 9 : 1 dr and 90% ee (Scheme 30b).

In the synthesis of neaumycin B (**167**) by Chen's group,[100] two homoallylic alcohol intermediates, **327** and **329**, were obtained *via* transfer hydrogenative crotylation. On the one hand, (*R*)-SEGPHOS-Ir catalyzed the dehydrogenative coupling of alcohol **325** with but-3-en-2-yl acetate (**326**) provided homoallylic alcohol **327** in high diastereo- and enantio-selectivity. On the other hand, coupling of alcohol **328** and **326** using the (*S*)-SEGPHOS-Ir catalyst afforded fragment **329** (Scheme 31).

In the total synthesis of the indolizidine alkaloid bipolamine I (**333**) by Pierce's group,[111] the resultant aldehyde (not shown) from the dehydrogenation of alcohol **330** was coupled with the allylruthenium intermediate formed from the acetylenic pyrrole (**331**), providing key intermediate **332** (Scheme 32).

In summary, hypervalent iodine reagents, Ley–Griffith oxidation, nitroxyl radicals, and alcohol dehydrogenation are common methods for alcohol oxidation in natural product total syntheses. Hypervalent iodine(v) reagents are mild, selective and metal-free reagents for the oxidation of alcohols to

Table 2 More examples of nitroxyl radical-mediated oxidation of alcohols in natural product synthesis

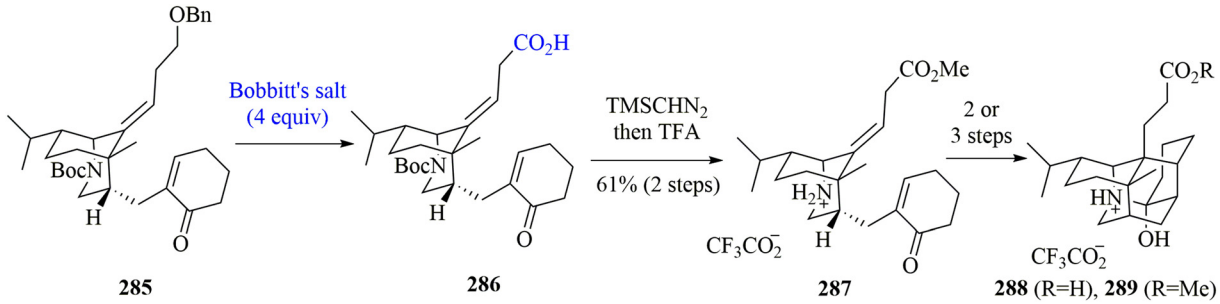
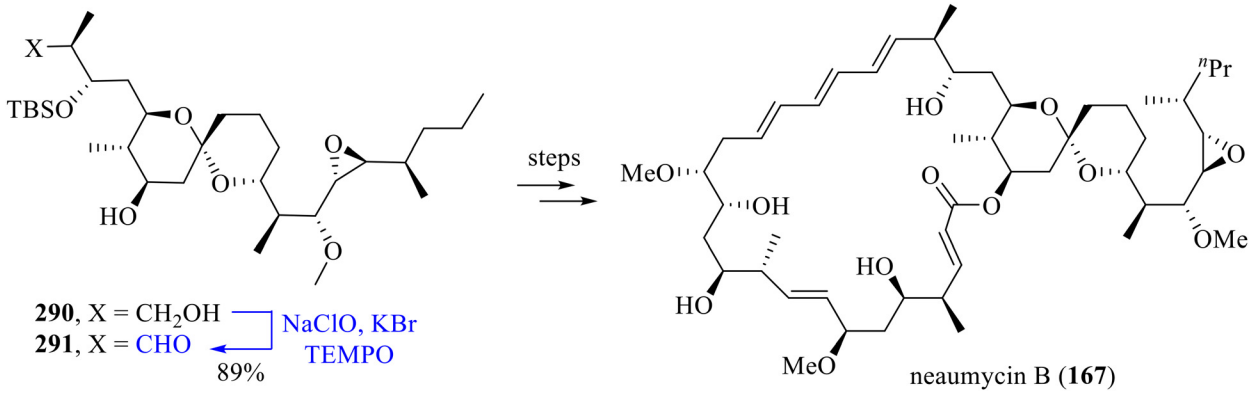
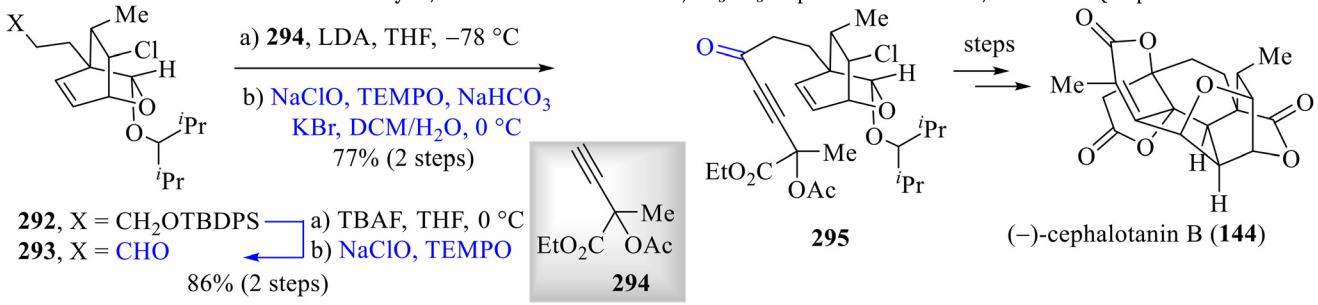
Entry	Source and significance of natural product	Oxidation of alcohols using nitroxyl radical and related reagents
1	Daphnezomines A (**288**) and B (**289**) are daphniphyllum alkaloids isolated from the leaves of *Daphniphyllum humile*. Daphnezomine B displayed notable cytotoxicity in murine lymphoma L1210 cells	 **285** **286** **287** **288** (R=H), **289** (R=Me) Comment:[99] Bobbitt's salt (4.0 eq.) cleaved the benzyl ether in **285** and further oxidized the resulting alcohol to carboxylic acid (**286**), which was further converted to methyl ester **287** Other oxidation reactions used: Dess–Martin oxidation
2	Neaumycin B (**167**) was isolated from the marine microbial *Micromonospora* sp. (strain CNY-010) in the Bahamas Islands. This compound displayed significant activities against several cancer cell lines	 **290**, X = CH_2OH ⟶ **291**, X = CHO (NaClO, KBr, TEMPO, 89%) neaumycin B (**167**) Comment:[100] The primary alcohol in **290** was selectively oxidized to aldehyde **291** without affecting the secondary alcohol and the epoxide Other oxidation reactions used: 3× ozonolysis; 5× Dess–Martin oxidation; CF_3CO_3H epoxidation of olefin; and 2× DDQ deprotection of PMB
3	Cephalotanin B (**144**) is a member of the *Cephalotaxus* diterpenoids found in Cephalotaxus plants. This molecule possesses a highly congested heptacyclic skeleton, three lactone units, and nine consecutive stereocenters	 (−)-cephalotanin B (**144**) Comment:[64] Alcohols from TBDPS deprotection of **292** and reaction of **293** were oxidized with TEMPO/NaOCl-KBr, providing aldehyde **293** and ketone **295**, respectively Other oxidation reactions used: 2× Dess–Martin oxidation

Table 2 *(Contd.)*

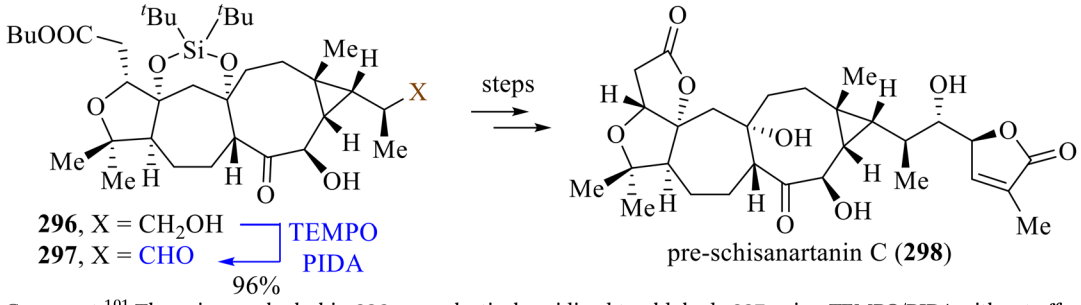
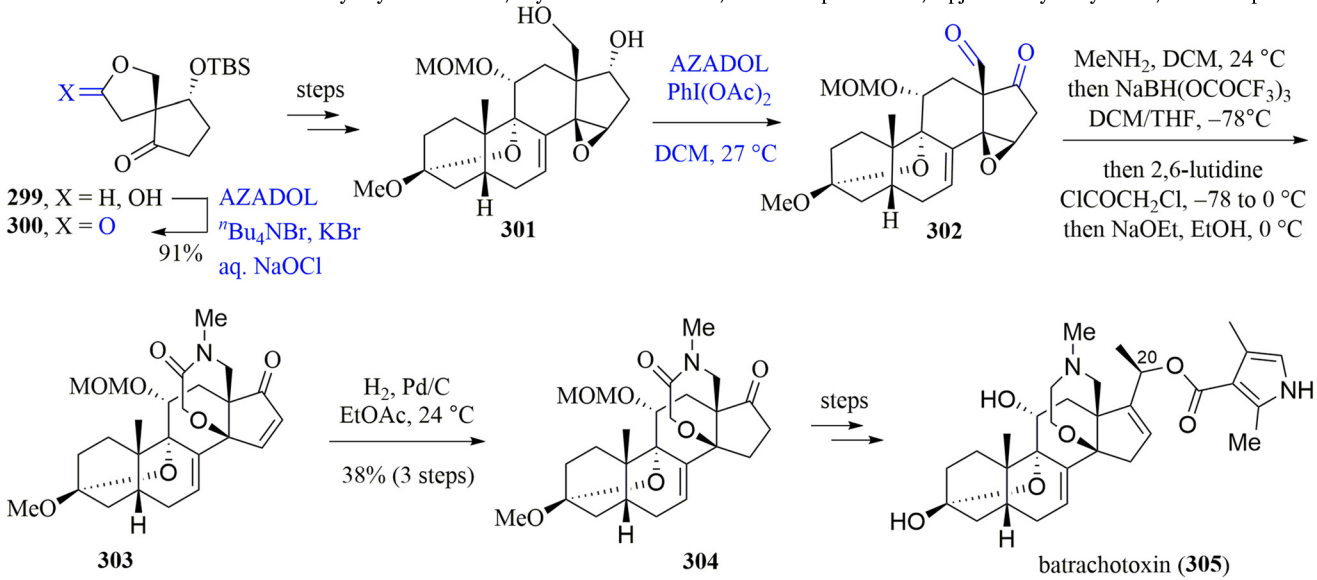
Entry	Source and significance of natural product	Oxidation of alcohols using nitroxyl radical and related reagents
4	Pre-schisanartanin C (**298**) is a nortriterpenoid isolated from the *Schisandra* genus. This compound exhibited potent anti-hepatitis, antitumor and anti-HIV activities	 Comment:[101] The primary alcohol in **296** was selectively oxidized to aldehyde **297** using TEMPO/PIDA without affecting the secondary alcohol Other oxidation reactions used: Riley allylic oxidation; Ley–Griffith oxidation; *m*-CPBA epoxidation; Upjohn dihydroxylation; and Sharpless AD
5	Batrachotoxin (**305**) is a steroidal alkaloid isolated as the toxic principle of *Phyllobates*. This compound is one of the most toxic natural substances known with an LD_{50} of 2 μg kg^{-1} (subcutaneous in mice)	 Comment:[102] AZADOL mediated the oxidation of lactol **299** to lactone **300** and β-diol **301** to β-keto aldehyde **302**, which was further converted to lactam **304** Other oxidation reactions used: $RuCl_3/NaIO_4$ cleavage of olefin; Ozonolysis; and $VO(O^iPr)_3/PhC(Me)_2OOH$ epoxidation of olefin

Table 2 *(Contd.)*

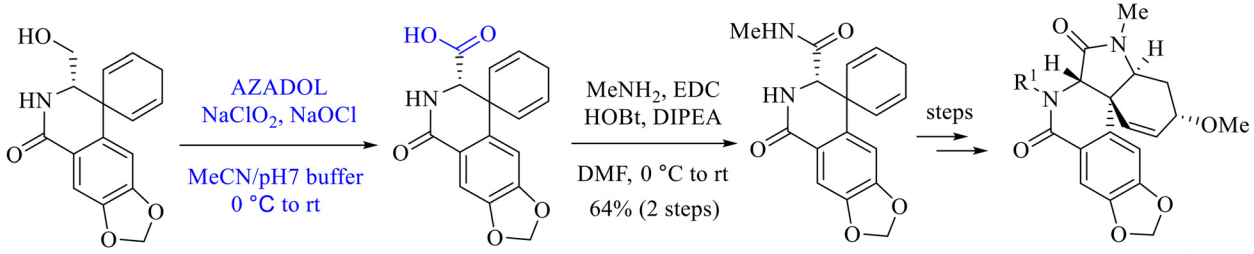
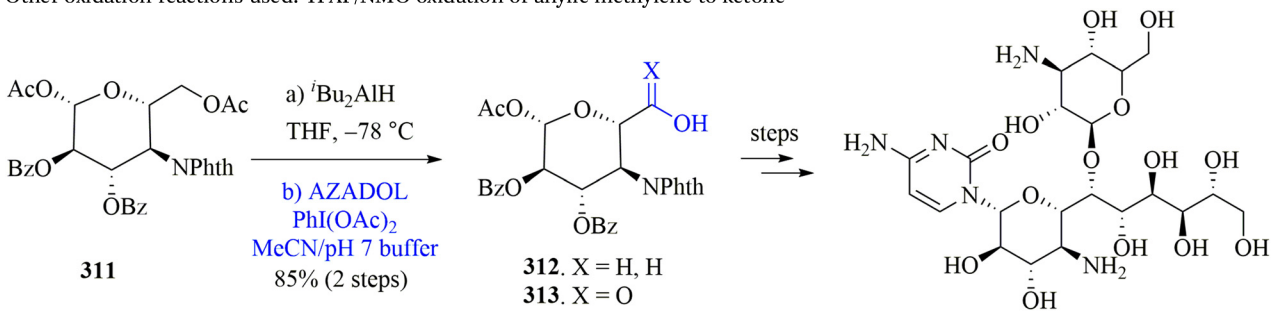
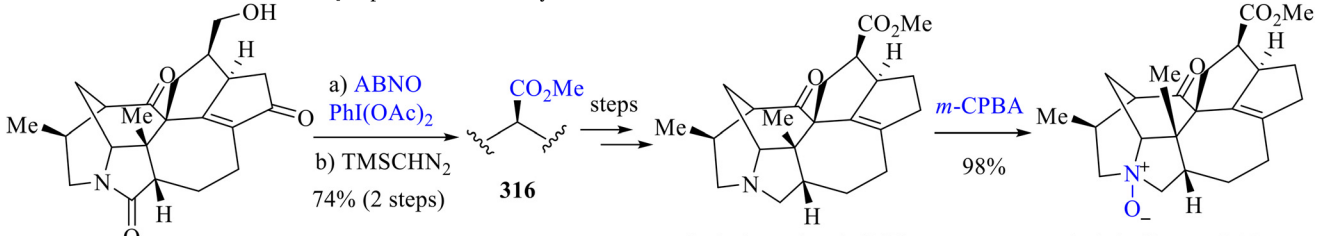
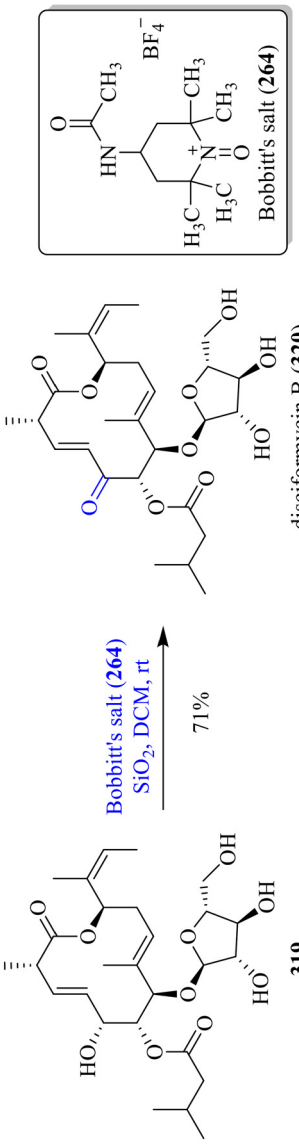
Entry	Source and significance of natural product	Oxidation of alcohols using nitroxyl radical and related reagents
6	Zephycarinatines C (**309**) and D (**310**) are plicamine-type alkaloids isolated from *Zephyranthes carinata*. They displayed cytotoxic properties against a variety of cancer cell lines and anti-inflammatory activities	 **306** **307** **308** zephycarinatine C (**309**, R^1 = isopentyl) zephycarinatine D (**310**, R^1 = Me) Comment:[103] Oxidation of the primary alcohol in **306** with AZADOL/$NaClO_2$-NaOCl led to carboxylic acid **307**, which was further converted to methyl amide **308** Other oxidation reactions used: TPAP/NMO oxidation of allylic methylene to ketone
7	Hikizimycin (**314**) is a nucleoside antibiotic natural product isolated from the fermentation broth of *Streptomyces* A-5. This compound inhibits protein synthesis and exhibits antiparasitic and antibiotic activities.	 **311** **312**. X = H, H **313**. X = O hikizimycin (**314**) Comment:[104] Primary alcohol **312** from the selective deacetylation of **311** was oxidized to carboxylic acid **313** using AZADOL/PIDA Other oxidation reaction used: DDQ deprotection of benzyl ether
8	Daphnilongeranin A (**317**) and calyciphylline A (**318**) are members of daphniphyllum alkaloids from the *genus Daphniphyllum*. This class of natural products possesses complex structures and diverse biological activities	 **315** **316** daphniyunnine A (**317**) calyciphylline A (**318**) Comment:[105] Oxidation of primary alcohol in **315** with ABNO/PIDA led to the carboxylic acid, which was methylated, providing methyl ester **316**. Further transformation led to daphnilongeranin A and calyciphylline A Other oxidation reactions used: UHP/TFAA epoxidation of olefin; *m*-CPBA oxidation of tertiary amine to *N*-oxide; ozonolysis; H_2O_2 oxidation of tertiary amine to *N*-oxide; and KHMDS/O_2/$P(EtO)_3$ α-hydroxylation of ketone

Table 2 *(Contd.)*

Entry	Source and significance of natural product	Oxidation of alcohols using nitroxyl radical and related reagents
9	Disciformycin A (**320**) is a polyketide-derived macrolide glycoside isolated from the myxobacterium *Pyxidicoccus fallax* strain AndGT8. This compound exhibits antibacterial activity against Gram-positive bacteria	 **319** disciformycin B (**320**) Comment:[106] At the final stage of synthesis, the allylic alcohol in tetrol **319** was selectively oxidized with Bobbitt's salt without protection of the sugar hydroxy groups Other oxidation reactions used: MnO_2 oxidation of allylic alcohol; DM oxidation of primary alcohol to aldehyde; Pinnick oxidation; and DDQ deprotection of PMB

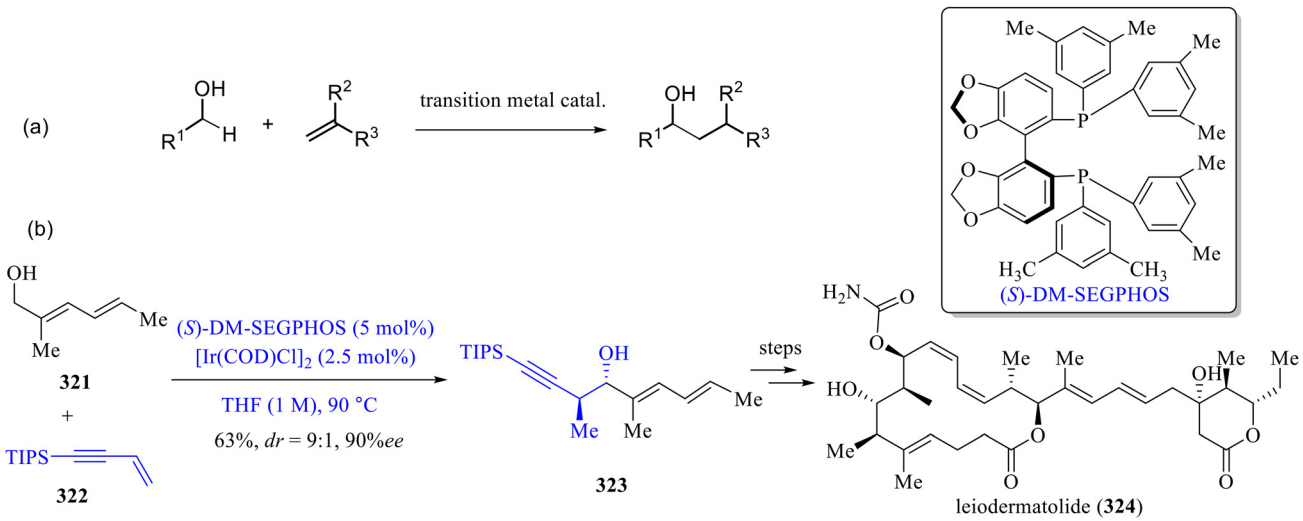
aldehydes or ketones with broad functional group tolerance, but require stoichiometric quantities, which generate waste. Ley–Griffith oxidation is efficient, high-yielding and compatible with a wide range of functional groups, but requires stringent anhydrous conditions, besides the high cost of the TPAP catalyst. Nitroxyl radicals are catalytic, selective for alcohols, and compatible with a wide range of functional groups. Additionally, when combined with environmentally friendly, inexpensive co-oxidants such as bleach and oxygen, hazardous waste is minimized, making nitroxyl radicals a more sustainable choice for alcohol oxidation, especially for large-scale reactions. Finally, alcohol dehydrogenation using transition metal catalysts is highly atom economical and environmentally attractive, though the requirement of higher temperatures and expensive transition metal catalysts limit its broad application to some degree. Together, these methods provide complementary tools for selective and efficient alcohol oxidation in natural product total syntheses.

4. Oxidation of aldehydes to carboxylic acids and esters

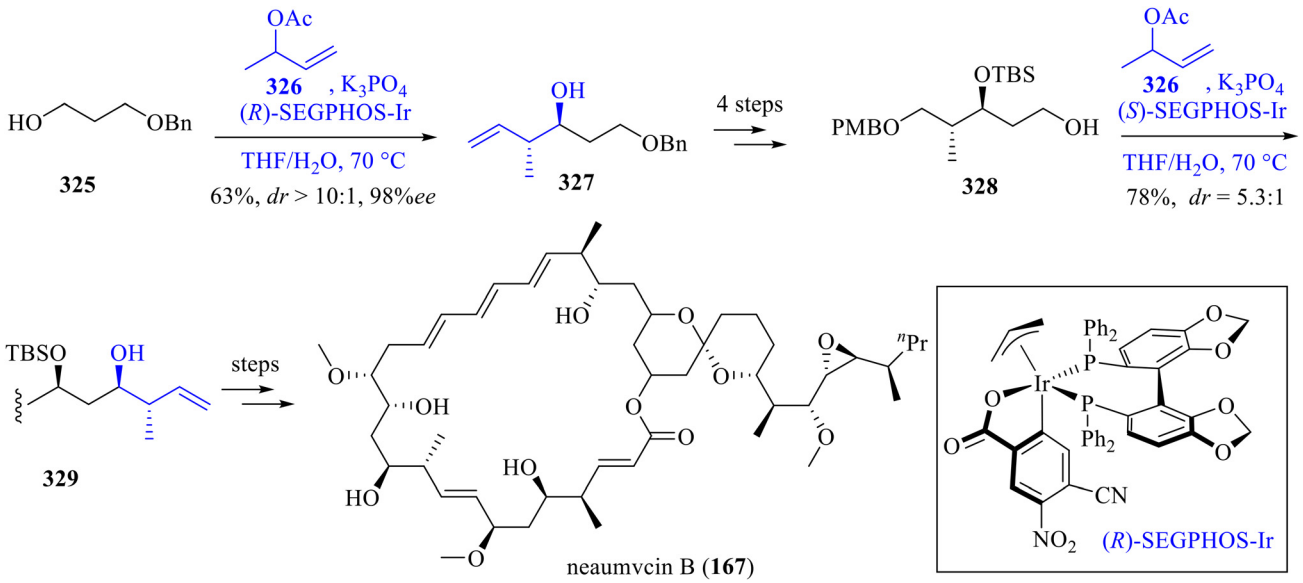
A number of methods have been developed for the oxidation of aldehydes to carboxylic acids and esters. Traditional methods employing reagents such as $KMnO_4$ and Cr(VI) (Jones oxidation) are inexpensive and reliable but suffer from poor selectivity and environmental concerns, leading to their reduced use. Hypervalent iodine reagents, such as PIDA and IBX, offer mild and versatile options but are limited by their cost and formation of stoichiometric waste. The Pinnick oxidation is often the method of choice for natural product synthesis owing to its high chemoselectivity, functional group compatibility and mild conditions. However, TEMPO-catalyzed oxidation is a more sustainable alternative as it utilizes inexpensive and green terminal oxidants, such as NaOCl or molecular oxygen. Apart from carboxylic acids, in the presence of a metal catalyst such as Pd, Cu, and Ag or stoichiometric iodine in combination with an alcohol, aldehydes can be converted to esters in one step under oxidative esterification conditions.

4.1 Pinnick oxidation

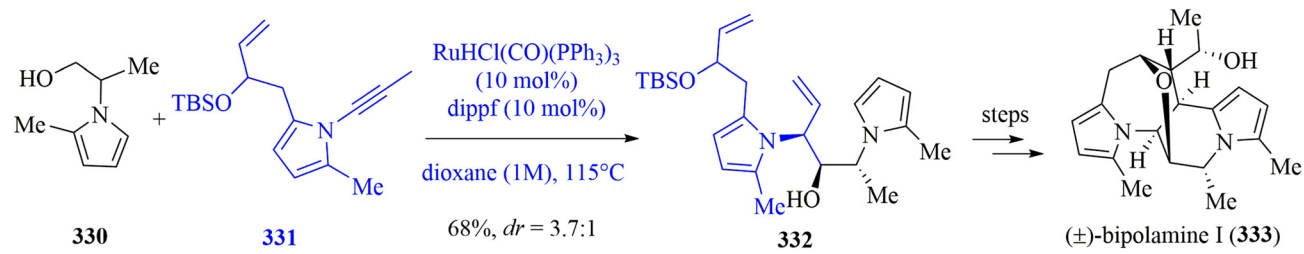
The Pinnick oxidation is a highly selective and mild method for oxidizing aldehydes to carboxylic acids.[112] In this reaction, inexpensive sodium chlorite ($NaClO_2$) is used as the oxidant. 2-Methyl-2-butene is often added to the reaction as a scavenger to prevent interference from the byproduct hypochlorous acid (HOCl) formed during the reaction. The advantages of the Pinnick oxidation include high chemoselectivity, and tolerance to a broad range of functional groups, such as double bonds, triple bonds and epoxides. The reaction is particularly effective for oxidizing α,β-unsaturated aldehydes, which are often problematic substrates with other oxidants.[113] Owing to these merits, the Pinnick oxidation has found wide application in natural product synthesis, as illustrated below.



Scheme 30 Catalytic enantioselective hydrogen autotransfer reaction in the synthesis of leiodermatolide.

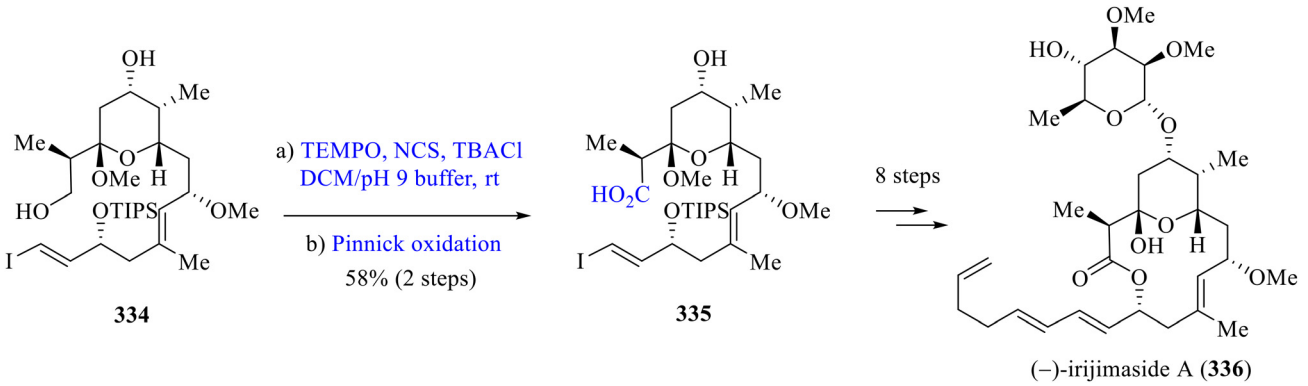


Scheme 31 Catalytic enantioselective hydrogen autotransfer reaction in the synthesis of neaumycin B.



Scheme 32 Catalytic hydrogen autotransfer reaction in the synthesis of (±)-bipolamine I.

Irijimasides are 14-membered macrolide glycosides isolated from the marine cyanobacterium *Okeania* sp. collected from Irijima, Okinawa, Japan. In the first total synthesis of (−)-irijimaside A (**336**) by Umehara and co-workers,[114] chemoselective oxidation of the primary alcohol in **334** with TEMPO/NCS and further Pinnick oxidation of the resultant aldehyde (not



Scheme 33 Pinnick oxidation in the synthesis of (–)-irijimaside A.

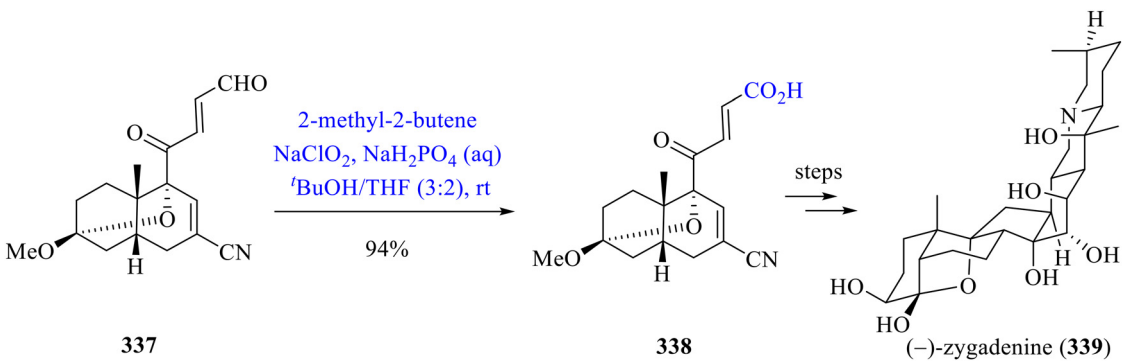
shown) provided carboxylic acid **335** in 58% yield over the two steps (Scheme 33).

(–)-Zygadenine (**339**) is one of the most highly oxygenated members of the *Veratrum* alkaloids. In the first total synthesis of zygadenine by Luo's group,[115] the aldehyde in the sensitive intermediate (**337**) underwent Pinnick oxidation smoothly, providing carboxylic acid **338** in excellent yield (Scheme 34).

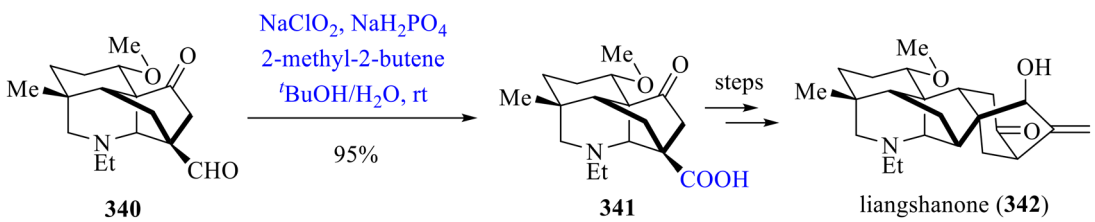
Liangshanone (**342**) is a hexacyclic *ent*-kaurane diterpenoid alkaloid with a range of biological activities. In the first total synthesis of liangshanone by Qin and co-workers,[116] Pinnick oxidation of aldehyde **340** provided carboxylic acid **341** in 95% yield without affecting the tertiary amine (Scheme 35).

In Aggarwal's synthesis of 10-deoxymethynolide (**345**),[117] Dess–Martin oxidation of alcohol **343** followed by Pinnick oxidation provided carboxylic acid **344** in 80% yield over two steps without affecting the enone and the silyl group (Scheme 36).

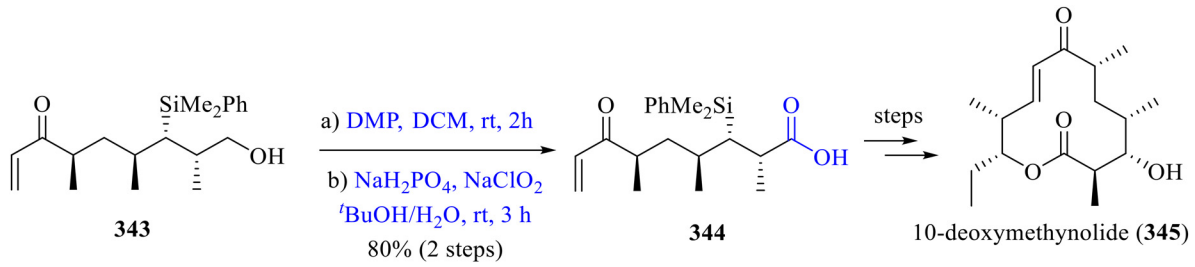
Arbophyllidine (**349**) is an unusual pentacyclic monoterpenoid indole alkaloid isolated from the bark of Malayan *Kopsia arborea*. This compound displayed growth inhibitory activity against HT-29 human cancer cells. In the first asymmetric total synthesis of arbophyllidine by Zhai and co-workers,[118] IBX oxidation of the primary alcohol in **346** followed by Pinnick oxidation of the resultant aldehyde **347** led to lactone **348** instead of the corresponding carboxylic acid (Scheme 37). The unusual lactonization is likely facilitated by the carbocation generated at C16 from free chlorine in the reaction medium, as suggested by their DFT calculation.



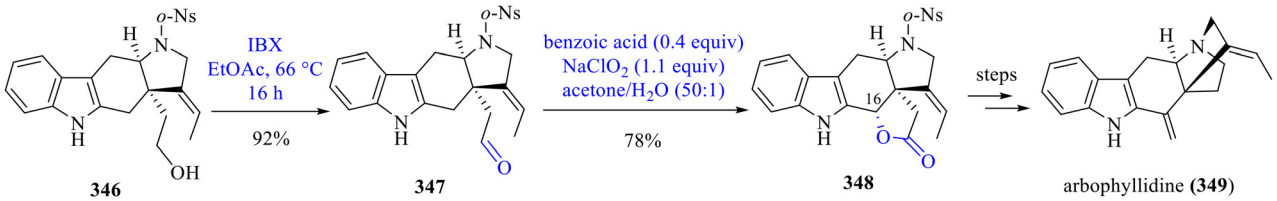
Scheme 34 Pinnick oxidation in the synthesis of (–)-zygadenine.



Scheme 35 Pinnick oxidation in the synthesis of liangshanone.



Scheme 36 Pinnick oxidation in the synthesis of 10-deoxymethynolide.



Scheme 37 Pinnick oxidation in the synthesis of arbophyllidine.

4.2 Nitroxyl radical-catalyzed oxidation

In the nitroxyl radical-catalyzed oxidation of primary alcohols, the aldehydes formed can be further oxidized to carboxylic acids in the presence of a suitable co-oxidant such as PIDA, TCCA and O_2. This one-pot operation provides direct selective and efficient access to carboxylic acids from primary alcohols. For example, in the synthesis of piperaborenine B (**352**),[119] exhaustive oxidation of both the aldehyde and alcohol in **350** under the Ma oxidation conditions[92] provided the dicarboxylic acid (**351**), which was converted to piperaborenine B by sequential reactions with oxalyl chloride and dihydropyridinone (Scheme 38).

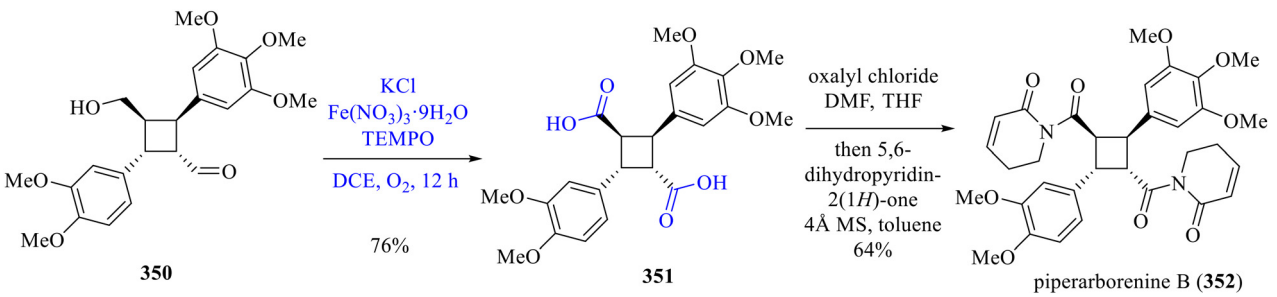
In the synthesis of tetrachlorovancomycin (**355**) as a new vancomycin analogue,[120] oxidation of the primary alcohol in **353** with TEMPO/PhI(OAc)$_2$ (2.5 eq.) provided the corresponding carboxylic acid (**354**) in excellent yield without affecting the electron-rich biaryl moiety (Scheme 39).

In the synthesis of (−)-isoscopariusin A (**358**), an immunosuppressive meroditerpenoid natural product isolated from the aerial parts of *Isodon scoparius*, oxidation of the primary alcohol in **356** with ABNO/PhI(OAc)$_2$ (2.4 eq.) provided carboxylic acid **357** in 89% yield (Scheme 40).[121]

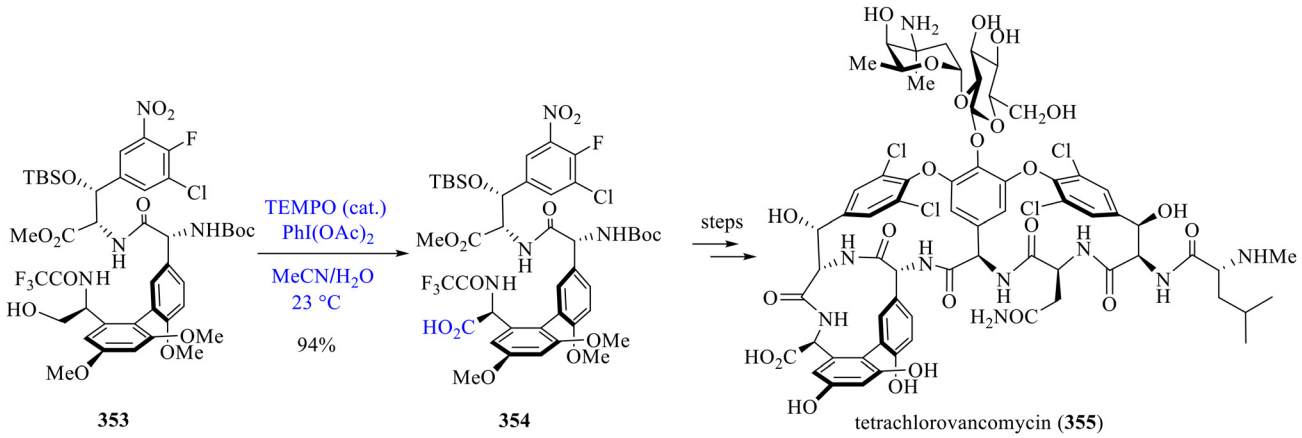
4.3 Oxidative esterification

Oxidative esterification of aldehydes enables the conversion of an aldehyde in conjunction with an alcohol directly to an ester without the need to isolate the carboxylic acid.[122] The transformation involves reacting the aldehyde with an alcohol to form a hemiacetal, which is then oxidized by a suitable catalyst or oxidant to form the ester. For example, in the synthesis of (−)-demethoxychippiine (**361**),[123] an aldehyde (**359**) was converted to a methyl ester (**360**) using an excess of iodine and KOH (Scheme 41). Ester intermediate **360** was transformed into (−)-demethoxychippiine and other members of post-iboga indole alkaloids.

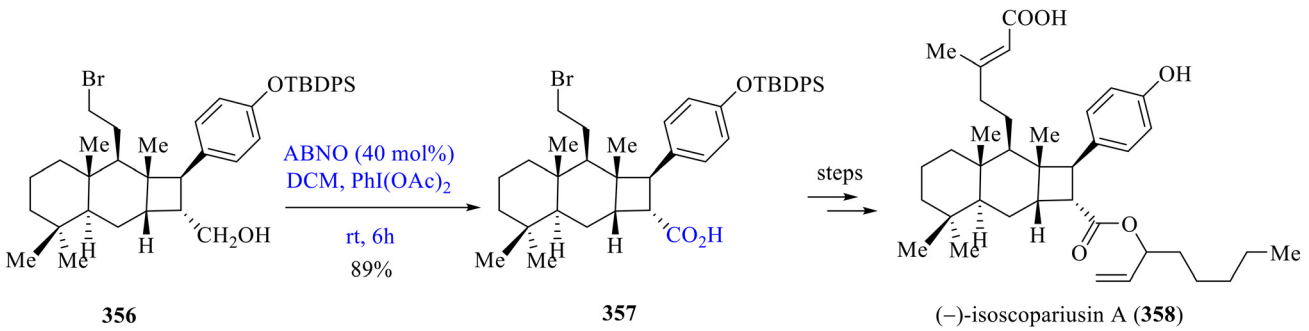
Apart from aldehydes, lactols can also undergo oxidative esterification to form lactones. For instance, in a unified synthesis of cephalotaxus diterpenoids by Zhao's group,[124] the advanced lactol intermediate **362** was oxidized to lactone **363** using silver carbonate supported on Celite. Subsequent hydrogenation of the carbonyl group in **363** led to a mixture of cephanolide E (**364**) and its 13-epimer (**365**) in a ratio of 1 : 4.2, which was separated by silica gel chromatography (Scheme 42).



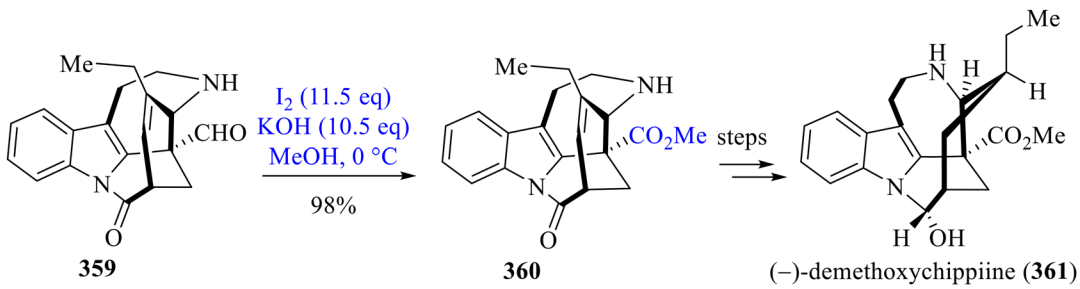
Scheme 38 TEMPO-catalyzed oxidation of alcohol/aldehyde to carboxylic acid in the synthesis of piperaborenine B.



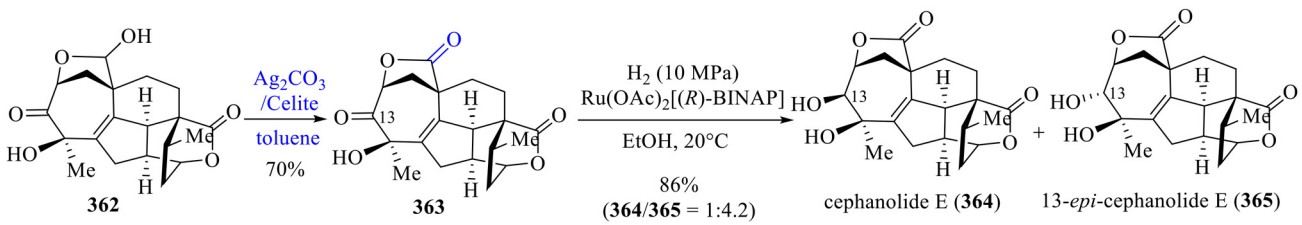
Scheme 39 TEMPO-catalyzed oxidation of alcohol to carboxylic acid in the synthesis of tetrachlorovancomycin.



Scheme 40 ABNO-catalyzed oxidation of alcohol to carboxylic acid in the synthesis of (–)-isoscopariusin A.



Scheme 41 Oxidative esterification in the synthesis of (–)-demethoxychippiine.



Scheme 42 Ag_2CO_3 oxidation of lactol to lactone in the synthesis of cephanolide E and its 13-epimer.

In summary, aldehydes can be oxidized to carboxylic acids *via* the Pinnick oxidation and nitroxyl radical-catalyzed oxidation. The Pinnick oxidation uses sodium chlorite under mild acidic conditions, offering broad functional group tolerance and efficiency for sensitive or sterically hindered substrates. Nitroxyl radical-catalyzed oxidation, often in conjunction with a base metal catalyst and benign co-oxidants such as oxygen, provides a selective, cost-efficient and greener method to convert aldehydes to carboxylic acids. Additionally, the reaction is often carried out under cascade or one-pot conditions, along with the previous step of alcohol oxidation to the aldehyde, making it a highly efficient operation to access carboxylic acids in natural product syntheses. Despite being less often employed and less atom economical, the direct conversion of aldehydes to esters through classical methods by using iodine and silver oxide remain a valuable methodology in certain structural settings.

5. Oxidation of alkenes

Alkene oxidations are a cornerstone for the synthesis of natural products, since they enable the conversion of carbon–carbon double bonds into oxygenated motifs such as epoxides, diols, carbonyls, and alcohols widely present in natural products. In addition, the oxygenated functionalities resulting from alkene oxidations often bridge the next stage of transformation in the synthesis. Modern alkene oxidation chemistry emphasizes not only chemo- and regio-selectivity, but also enantioselectivity, atom-economy, sustainability, and electrochemical and photo oxidations. This section will exemplify key alkene oxidation reactions, including epoxidation, dihydroxylation, carbonylation (Wacker oxidation) and hydroxylation, in recent studies on the synthesis of natural products.

5.1 Epoxidation of alkenes

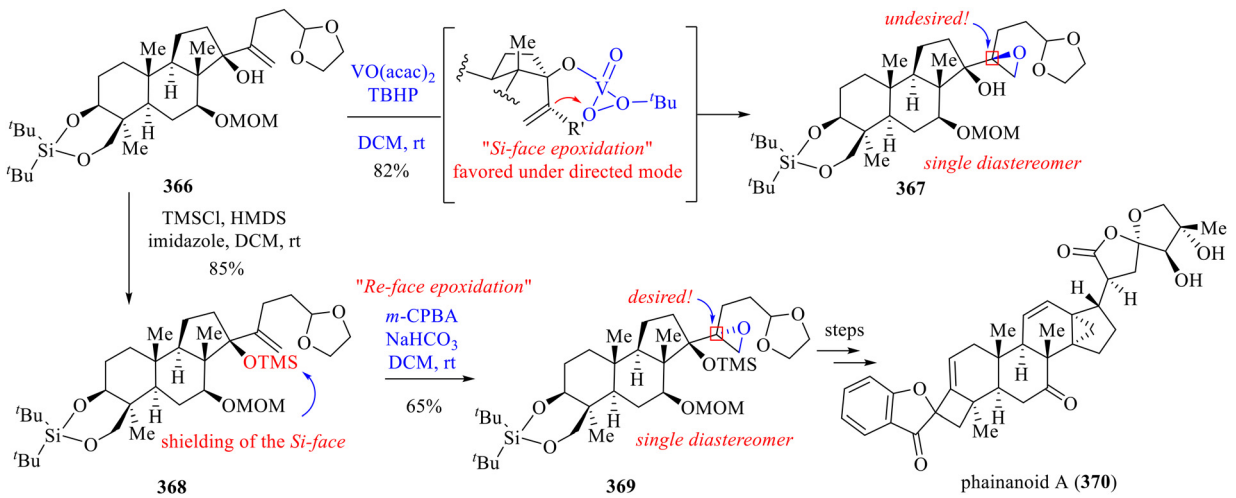
Epoxidation converts an alkene to an epoxide, which is widely present in natural products. Additionally, epoxides often serve as intermediate motifs for further transformations, notably *via* stereoselective ring-opening with diverse nucleophiles. Methods for alkene epoxidations involve the use of peroxyacids, peroxides (oxiranes, Oxone, H_2O_2), Shi and Mn(salen) catalysts for unfunctionalized alkenes, and Sharpless asymmetric epoxidations for allylic alcohols. With an emphasis on sustainability, greener oxidants (H_2O_2, oxone, and molecular oxygen) and electrochemical methods have been applied in epoxidation reactions.

5.1.1 Epoxidation using peroxide reagents. Peroxy reagents, such as organic peracids [*m*-chloroperbenzoic acid (*m*-CPBA) and trifluoroperacetic acid], alkyl peroxides [*t*-butyl hydroperoxide (TBHP) and dimethyldioxirane (DMDO)], inorganic peroxides [urea-hydrogen peroxide complex (UHP)], and [potassium peroxymonosulfate (Oxone®)], are often used for alkene epoxidation due to their low cost. Selected examples on the application of peroxy reagents in alkene epoxidations are highlighted below.

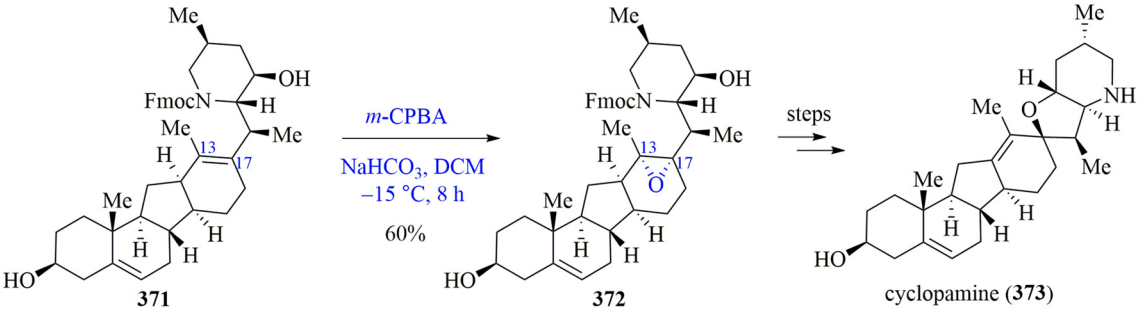
5.1.1.1 Peroxyacids. As a classical oxidant, *m*-CPBA[125] remains one of the most used oxidants for alkene epoxidation in natural product synthesis, owing to its easy accessibility and low-cost. However, due to its thermal instability, potential explosion hazard and poor atom-economy, *m*-CPBA is mostly limited to small-scale laboratory use.

In Dong's first total synthesis of phainanoid A (**370**),[126] they attempted VO-catalyzed, OH-directed epoxidation of the olefin in **366**, which resulted in epoxide **367** with undesired stereochemistry. Alternative *m*-CPBA epoxidation of TMS-protected alcohol **368** enabled epoxidation from the less hindered *Re*-face, providing the desired epoxide **369** in 65% yield as a single diastereomer (Scheme 43).

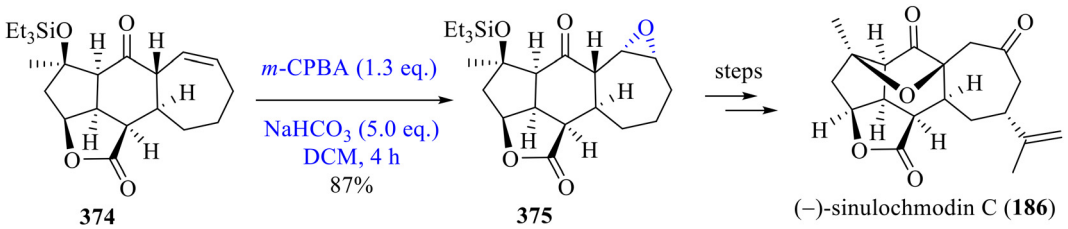
Cyclopamine (**373**) is a teratogenic steroidal alkaloid inhibiting the Hedgehog signalling pathway. In the total synthesis of cyclopamine by Gao's group,[127] selective *m*-CPBA epoxidation of the more electron-rich tetrasubstituted C13–C17 double bond in **371** from the less hindered α-face was achieved by careful control of the reaction time and temperature



Scheme 43 *m*-CPBA epoxidation of olefin in the synthesis of phainanoid A.



Scheme 44 *m*-CPBA epoxidation of olefin in the synthesis of cyclopamine.



Scheme 45 *m*-CPBA epoxidation of olefin in the synthesis of (−)-sinulochmodin C.

(−15 °C), providing the desired mono-epoxide **372** in 60% yield (Scheme 44).

In the total synthesis of (−)-sinulochmodin C (**186**) by Zhang's group,[73] epoxidation of the double bond in **374** with *m*-CPBA occurred preferentially from the less hindered bottom face, providing the desired α-epoxide **375** in 87% yield (Scheme 45).

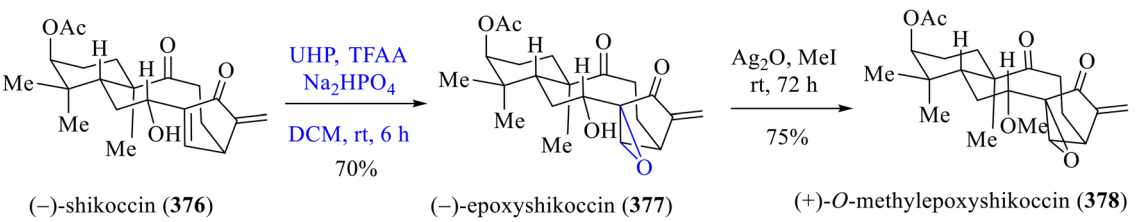
5.1.1.2 Urea hydrogen peroxide (UHP). Urea hydrogen peroxide [$CO(NH_2)_2{\cdot}H_2O_2$, UHP] is a safe and convenient alternative to anhydrous hydrogen peroxide, with the advantages of controlled release of H_2O_2, water-free reaction conditions, environmental friendliness and cost-effectiveness. As a result, UHP has been widely used for alkene epoxidation, often in combination with a promoter such as carboxylic anhydrides, nitriles, or metal catalysts.[128] Examples of the use of UHP in alkene epoxidation for natural product synthesis are highlighted below.

In the asymmetric total syntheses of 8,9-*seco*-*ent*-kaurane diterpenoids by Ding's group,[129] chemo- and stereo-selective epoxidation of the more electron-rich trisubstituted alkene in (−)-shikoccin (**376**) was achieved by using UHP in combination with trifluoroacetic anhydride (TFAA), providing (−)-epoxyshikoccin (**377**) without affecting the exocyclic olefin. Further methylation on the hydroxy group provided (+)-*O*-methylepoxyshikoccin (**378**) (Scheme 46).

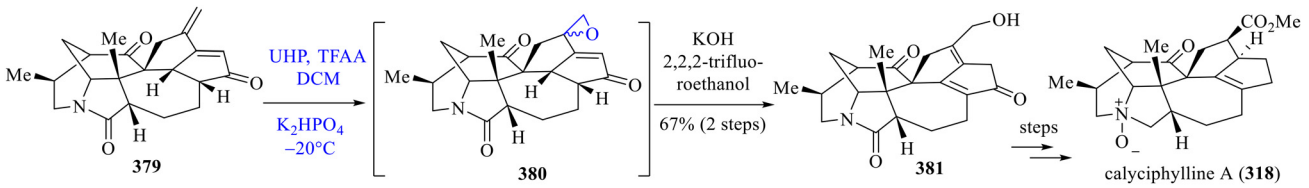
In Li's synthesis of daphniphyllum alkaloids,[105] selective epoxidation of the exocyclic double bond in **379** with UHP and TFAA at −20 °C provided epoxide **380**. Subsequently, base-promoted double bond migration-δ-alkoxy elimination cascade of the epoxide provided hydroxy dienone **381**, which was transformed to calyciphylline A (**318**) (Scheme 47).

In the synthesis of (−)-zygadenine (**339**) by Luo's group,[115] regio- and diastereo-selective epoxidation of the C15–C16 olefin in **382** was achieved by using UHP-TFAA at 0 °C, providing epoxide **383**. Subsequent cleavage of both the epoxide and carbonate by Ti-mediated radical reduction provided tetraol **384** in 57% yield over the two steps (Scheme 48).

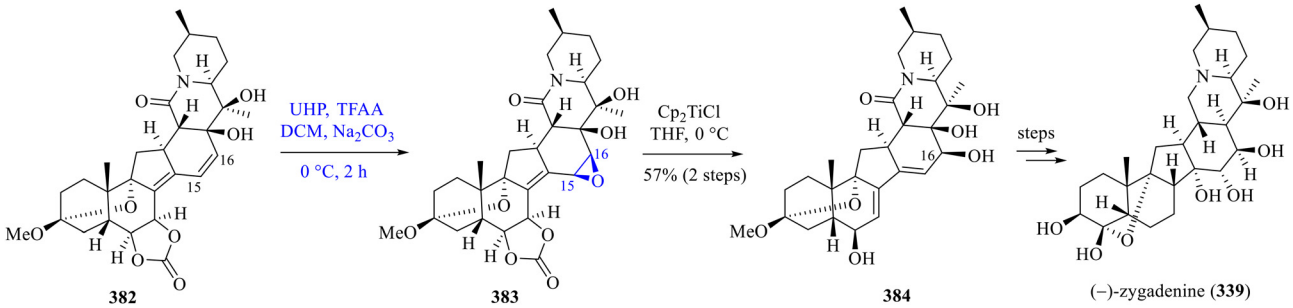
5.1.1.3 Sharpless asymmetric epoxidation. The Sharpless asymmetric epoxidation of prochiral allylic alcohols[130] is one of the most used methods for alkene epoxidation and has been applied in the synthesis of numerous natural products.[131] This epoxidation method continues to be a powerful tool in natural product synthesis, as illustrated in the examples below.



Scheme 46 UHP epoxidation of olefin in the synthesis of (−)-epoxyshikoccin.



Scheme 47 UHP epoxidation of olefin in the synthesis of calyciphylline A.



Scheme 48 UHP epoxidation of olefin in the synthesis of (–)-zygadenine.

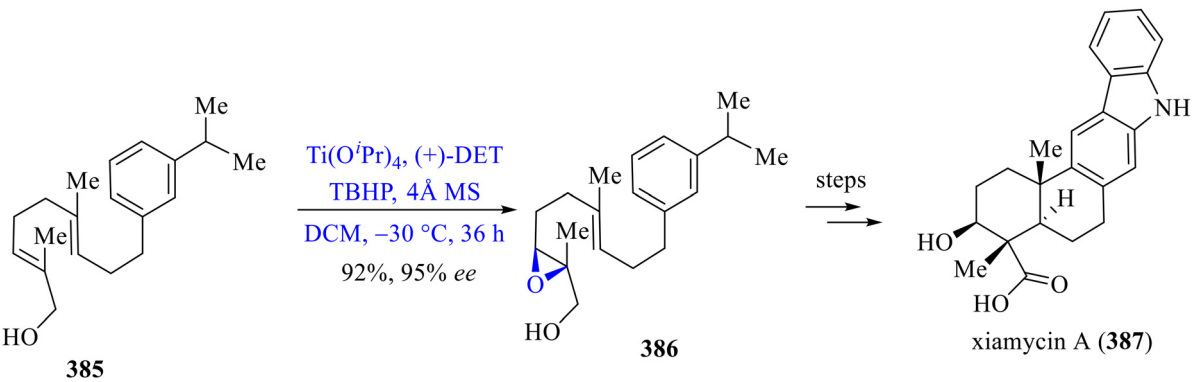
Xiamycin A (**387**) was isolated from *Streptomyces* sp. GT2002/1503, an endophyte from the mangrove plant *Bruguiera gymnorrhiza*. This indole alkaloid displayed anti-HIV activities and can form rare *N*–*N* atropisomers (dixiamycins) by dimerization at the indole nitrogen. In the total synthesis of xiamycin A by Bisai's group,[132] Sharpless asymmetric epoxidation of allylic alcohol **385** provided epoxide **386** in excellent yield and *ee* (Scheme 49).

In Fürstner's total synthesis of mycinolide IV (**391**),[133] Sharpless asymmetric epoxidation of allylic alcohol **388** using cumene hydroperoxide as the terminal oxidant provided epoxide **389** in 87% ee. Further transformations led to enyne fragment **390** for mycinolide IV synthesis (Scheme 50).

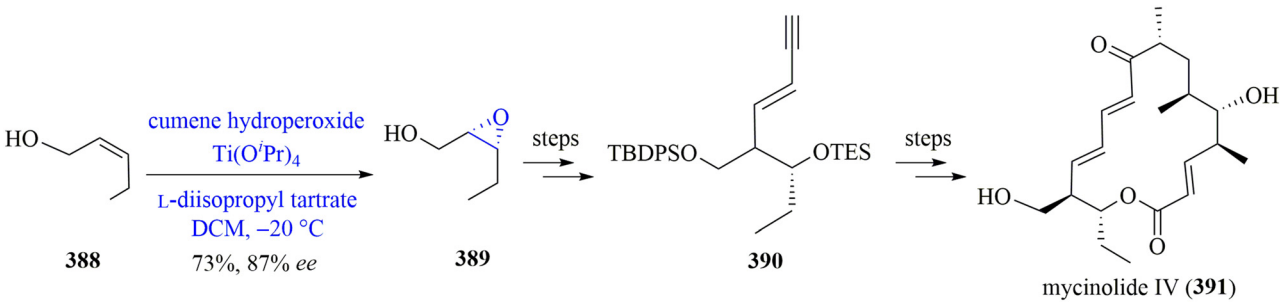
Mannopeptimycins (MPPs) are cyclic peptides isolated from *Streptomyces hygroscopicus* LL-AC98. These compounds displayed promising activities against clinically important resistant Gram-positive pathogens such as Methicillin-resistant *Staphylococcus aureus* (MRSA) and Vancomycin-resistant Enterococci (VRE). In the total synthesis of mannopeptimycin β (**398**) by Li's group,[134] Sharpless asymmetric epoxidation of two allylic alcohols (**392** and **395**) provided the corresponding epoxides (**393** and **396**), which were transformed to L- and D-β-hydroxyenduracididine (**394** and **397**) in suitably protected forms for the assembly of mannopeptimycin β, respectively (Scheme 51).

Angucyclinones are a large family of aromatic polyketide natural products with a wide range of biological activities. In the total synthesis of angucyclinones by Kaliappan's group,[135] Sharpless asymmetric epoxidation of geraniol (**399**) provided epoxide **400**, which was transformed to 4-hydroxy-8-*O*-methyltetrangomycin (**401**) and 4-keto-8-*O*-methyltetrangomycin (**402**) (Scheme 52).

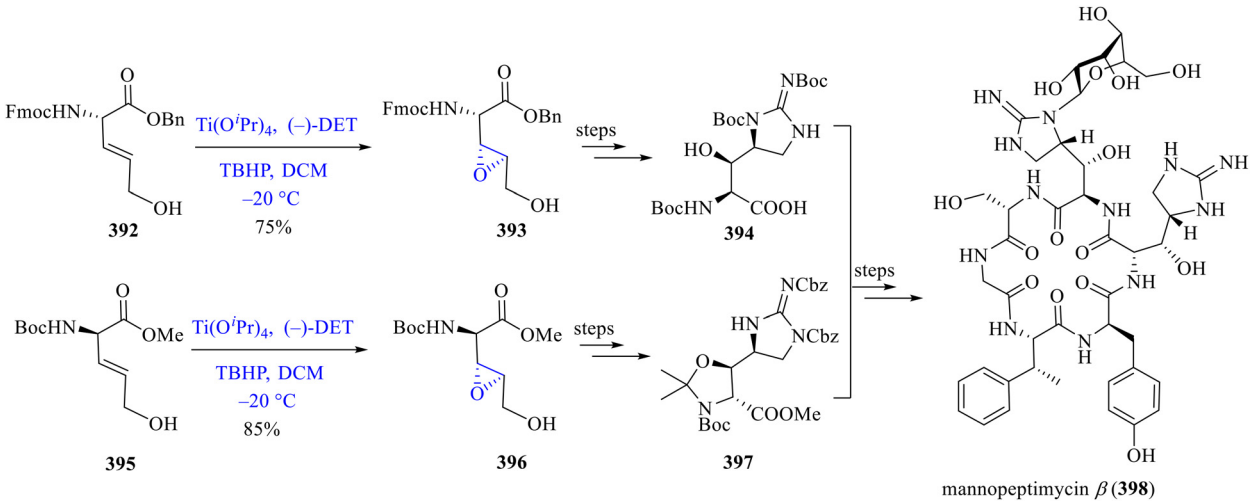
5.1.1.4 Other epoxidation methods. In addition to the aforementioned methods, there are several other methods/regents for the epoxidation of alkenes.



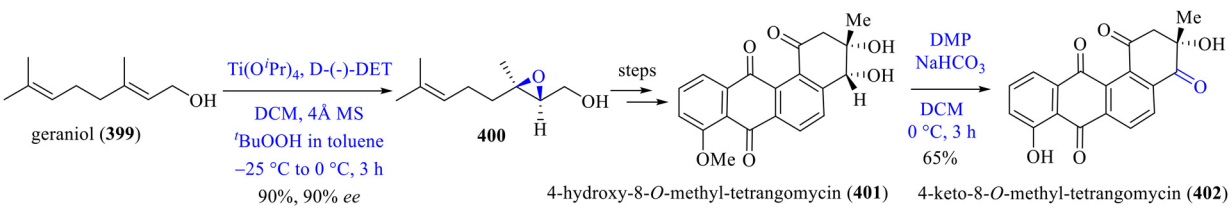
Scheme 49 Sharpless asymmetric epoxidation in the synthesis of xiamycin A.



Scheme 50 Sharpless asymmetric epoxidation in the synthesis of mycinolide IV.



Scheme 51 Sharpless asymmetric epoxidation in the synthesis of mannopeptimycin.

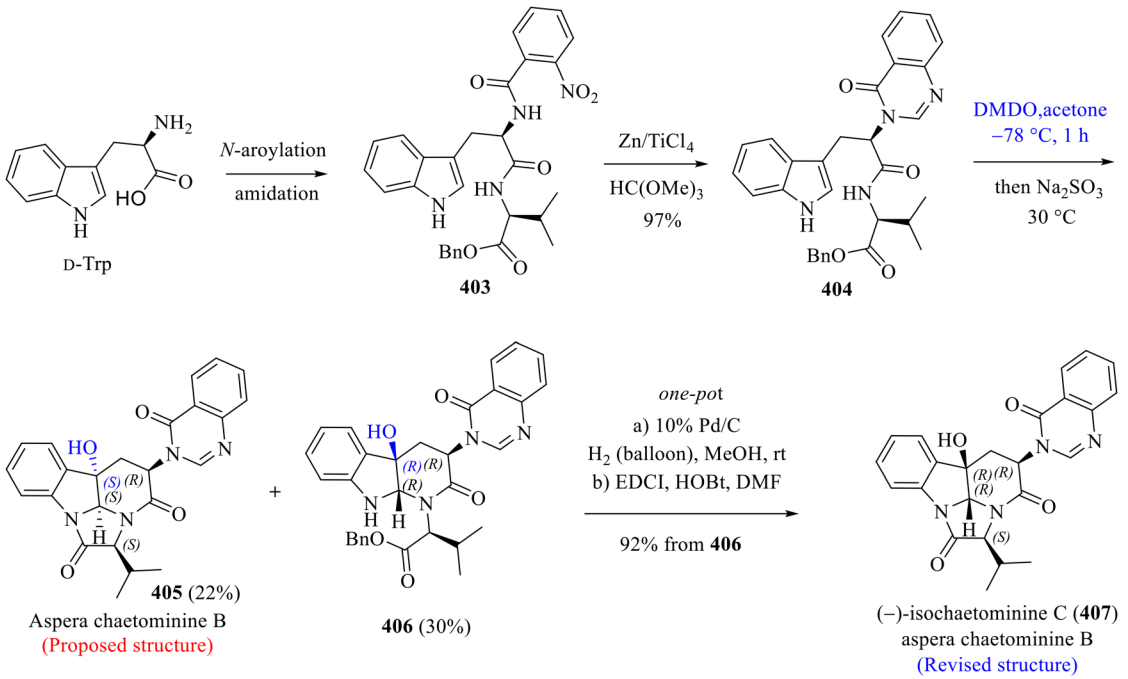


Scheme 52 Sharpless asymmetric epoxidation in the synthesis of 4-hydroxy-8-*O*-methyltetrangomycin and 4-keto-8-*O*-methyltetrangomycin.

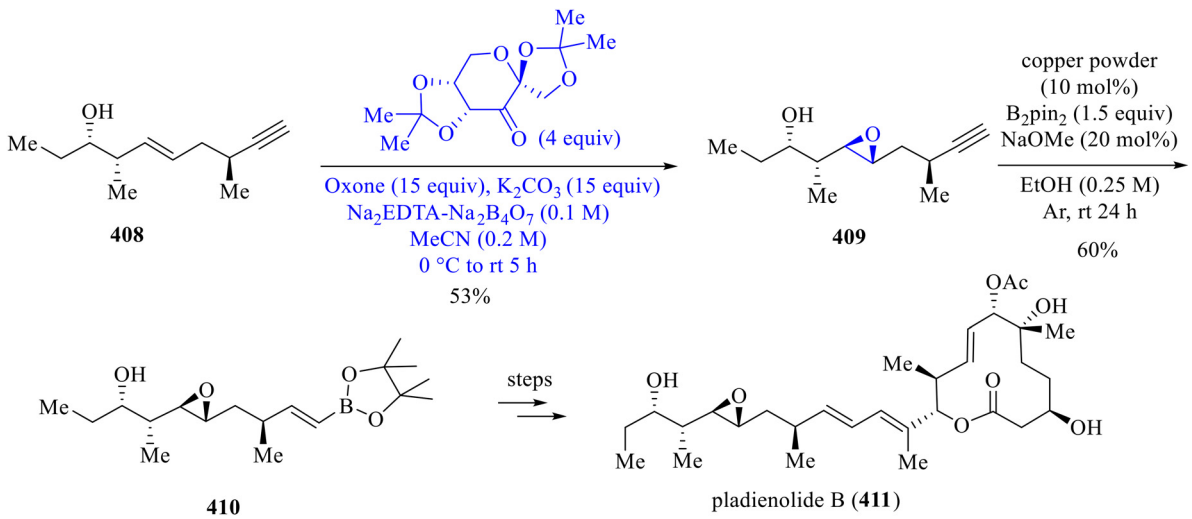
Dimethyldioxirane (DMDO) is an inexpensive yet versatile oxidant for the epoxidation of olefins. In 2014, Huang's group developed a DMDO-epoxidation-triggered double cyclization strategy enabling the four-step total synthesis of (−)-chaetominine.[136] Through further elaboration of this strategy, in 2025, this group disclosed the first enantioselective synthesis of both the proposed (**405**) and revised (**407**) structures of aspera chaetominine B, which was completed in five steps from the readily available D-tryptophan (Scheme 53).[137]

The Shi epoxidation[138] is an organocatalytic method for the asymmetric epoxidation of unfunctionalized olefins, which complements the Sharpless asymmetric epoxidation of allylic alcohols. This reaction uses a fructose-derived chiral ketone as the catalyst and potassium peroxymonosulfate (Oxone®) as the stoichiometric oxidant, which reacts with the chiral ketone to *in situ* form a chiral dioxirane intermediate for stereoselective epoxidation. This reaction is particularly effective for creating chiral epoxides from *trans*-disubstituted and trisubstituted alkenes with high enantioselectivity. For example, in the synthesis of the anti-cancer compound pladienolide B (**411**) by Krische's group,[139] diastereoselective Shi epoxidation of the double bond in **408** provided epoxide **409**. Subsequent hydroboration of the alkyne led to fragment **410** for the synthesis of pladienolide B (Scheme 54).

V and Ti complexes have been used for substrate-controlled epoxidation of chiral allylic alcohols without a chiral ligand.



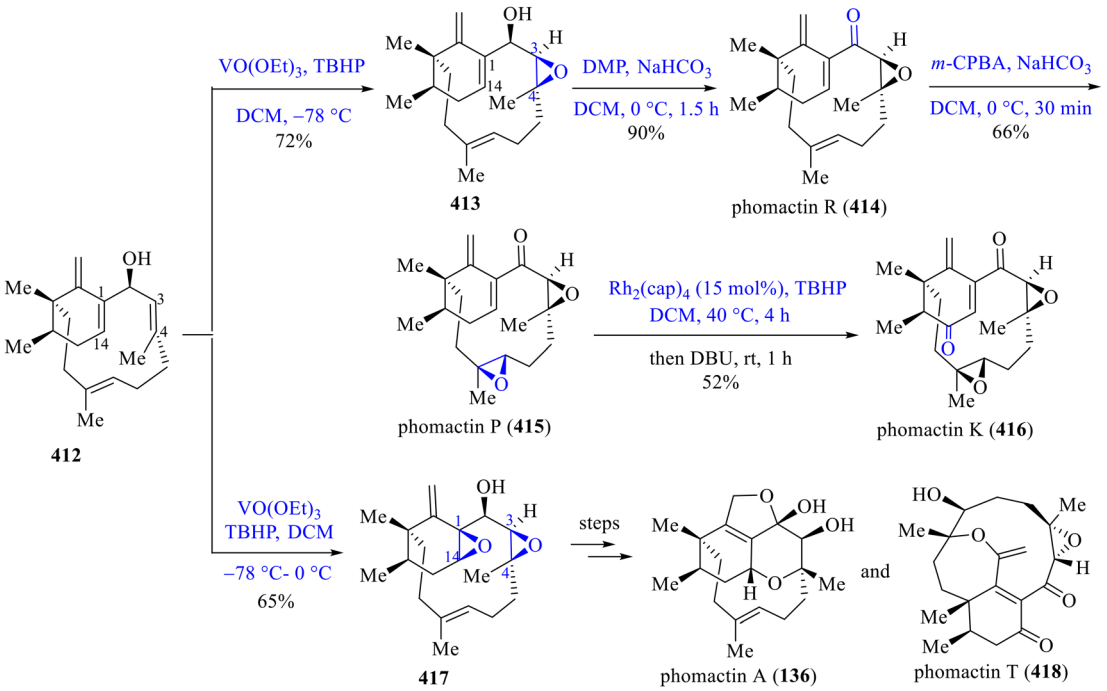
Scheme 53 DMDO epoxidation of indole in the synthesis of aspera chaetominine B.



Scheme 54 Shi epoxidation of olefin in the synthesis of pladienolide B.

For example, in a unified total synthesis of phomactins,[61] hydroxy group-directed selective epoxidation of one or both C1–C14 and C3–C4 allylic alcohols in tetraene **412** was achieved by using $VO(OEt)_3$ and *tert*-butylhydroperoxide (TBHP) at lower temperatures, while $VO(acac)_2$ at ambient temperature failed. On the one hand, OH-directed epoxidation at −78 °C selectively epoxidized the more electro-rich C3–C4 double bond, providing *syn*-epoxide **413**, which was transformed to phomactins R (**414**), P (**415**) and K (**416**) through elegantly planned sequential and selective oxidations. On the other hand, upon increasing the reaction temperature to 0 °C, both C3–C4 and C1–C14 olefins were epoxidized, affording bisepoxide (**417**), which was converted to phomactin A (**136**) and phomactin T (**418**) (Scheme 55).

Salarin C (**421**) is a cytotoxic nitrogenous marine macrolide featuring two epoxide groups. This natural product displayed high activities against a chronic myelogenous leukemia (CML) cell line (K562) with an IC_{50} of 5 nM. In the first total synthesis of salarin C by Britton's group,[140] stereoselective installation of the crucial C12–C13 epoxide in the heavily functionalized intermediate **419** was a challenge, as the allylic alcohol is kinetically mismatched for typical Sharpless epoxidation con-

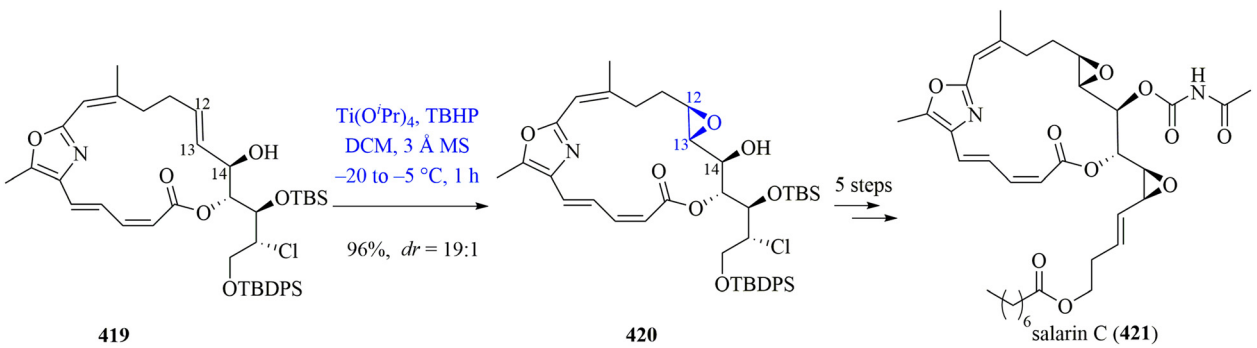


Scheme 55 $VO(OEt)_3$-catalyzed epoxidation of allylic alcohol in the synthesis of phomactins.

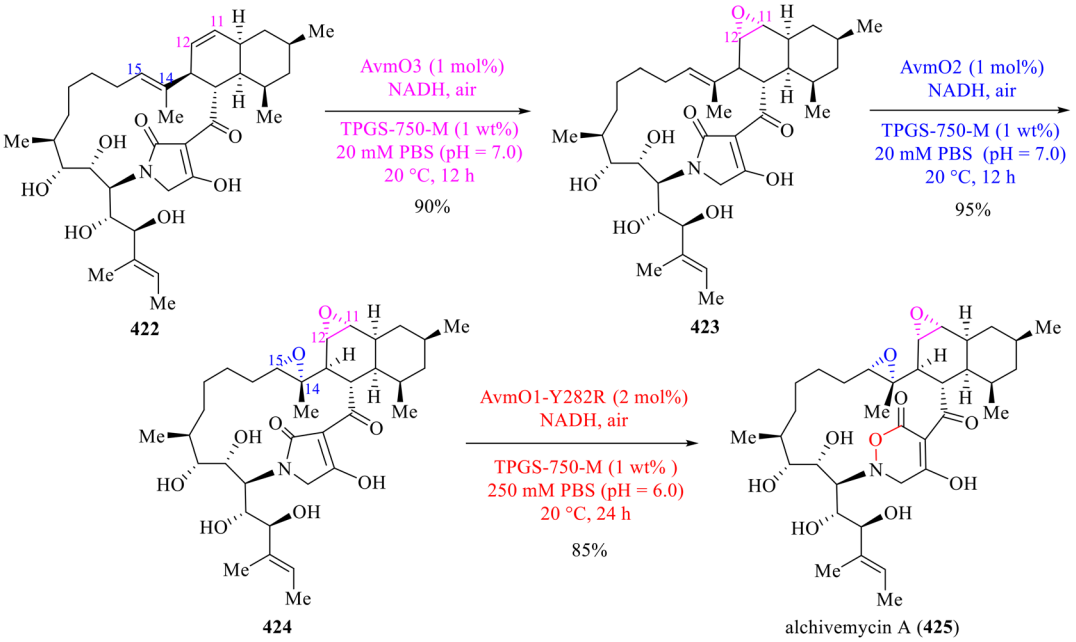
ditions. Consequently, the chiral C14–OH-directed epoxidation was explored. Investigation of $VO(acac)_2$ and $Ti(O^iPr)_4$ in combination with TBHP under a range of conditions identified the best conditions that provided the desired epoxide **420** in excellent yield and *threo*-selectivity (Scheme 56).

With the increasing awareness and emphasis on sustainability, enzymatic epoxidation of alkenes has attracted substantial attention[141] and has been applied in natural product synthesis. In a very recent example of the chemoenzymatic synthesis of the antibacterial and anti-tumour natural product alchivemycin A (**425**) by Lei's group,[142] consecutive selective epoxidation of the highly functionalized advanced intermediate **422** by using flavin adenine dinucleotide (FAD)-dependent monooxygenases AvmO3 and AvmO2 provided bisepoxide **424** in excellent yield. Final Baeyer–Villiger type oxidation of the tetramic acid ring by using an engineered AvmO1 (AvmO1-Y282R) converted it into the 2*H*-tetrahydro-4,6-dioxo-1,2-oxazine (TDO) ring, completing the efficient chemoenzymatic synthesis of alchivemycin A (Scheme 57).

In summary, the epoxidation of alkenes is a fundamental transformation in natural product syntheses, enabling access to versatile epoxides. Peroxyacids such as *m*-CPBA are widely used for direct epoxidation, offering simplicity but are limited in terms of stereochemical control and the generation of stoichiometric by-products. Peroxides such as H_2O_2, Oxone® and DMDO provide greener alternatives with good selectivity but lack of stereochemical control. The Sharpless asymmetric epoxidation provides a method for the highly enantioselective epoxidation of allylic alcohols with broad functional group compatibility. The Shi epoxidation, which complements the Sharpless asymmetric epoxidation, allows the highly enantioselective epoxidation of unfunctionalized alkenes under mild,



Scheme 56 $Ti(O^iPr)_4$-catalyzed epoxidation of allylic alcohol in the synthesis of salarin C.



Scheme 57 Enzymatic epoxidation of olefin in the synthesis of alchivemycin A.

environmentally friendly conditions using a fructose-derived catalyst with Oxone® as the oxidant. Finally, enzymatic epoxidation offers exceptional regio- and stereo-selectivity under aqueous, mild conditions, representing the most sustainable approach despite the need to screen and optimize an effective enzyme for each class of substrates. Overall, these methods provide a selection of tools for alkene epoxidation in natural product syntheses.

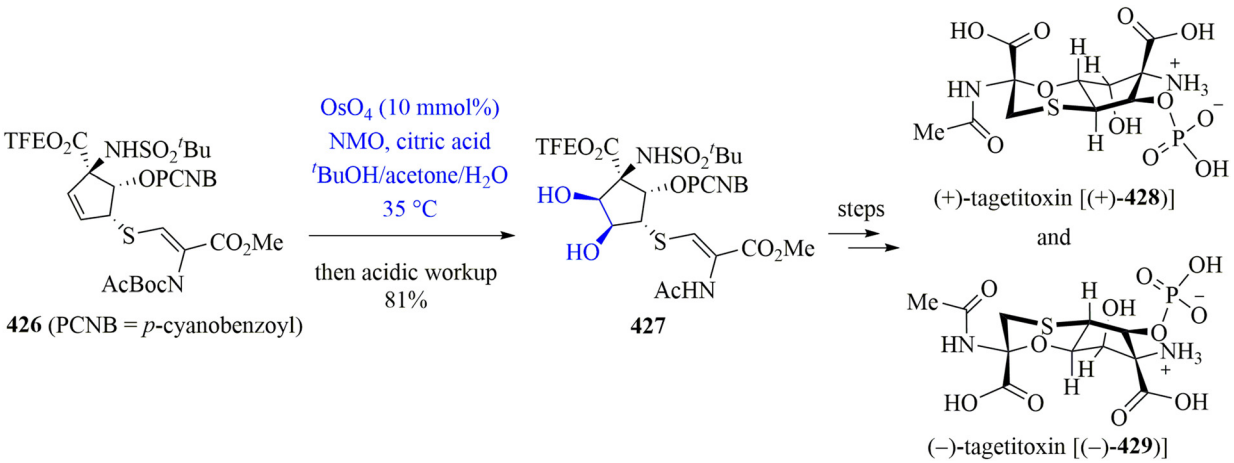
5.2 Dihydroxylation of alkenes

Dihydroxylation of alkenes enables the introduction of vicinal *syn*-diols, which are widely present in natural products. Three of the most often used methods for the dihydroxylation of alkene are Upjohn dihydroxylation, Sharpless asymmetric dihydroxylation (AD), and ruthenium-catalyzed dihydroxylation. The Upjohn dihydroxylation employs catalytic OsO_4 with a stoichiometric oxidant such as *N*-methylmorpholine *N*-oxide (NMO) or *t*-butyl hydroperoxide.[52] Despite its effectiveness in the *cis*-dihydroxylation of a wide range of alkenes, the reaction results in racemic products unless controlled by the substrate. The Sharpless asymmetric dihydroxylation (AD), an improved method of the Upjohn method, uses OsO_4 or its less toxic precursor $K_2OsO_2(OH)_4$ as the catalyst, potassium ferricyanide as a co-oxidant and chiral cinchona alkaloid-derived ligands [$(DHQ)_2$-PHAL and $(DHQD)_2$-PHAL], enabling the enantioselective dihydroxylation of a wide range of alkenes.[143] Sharpless AD has been used in numerous syntheses of natural products and pharmaceutical molecules.[144,145] Due to the cost and toxicity of the osmium catalyst, ruthenium catalysts such as $RuCl_3$ or RuO_4 have also been used as alternatives for alkene dihydroxylation in conjunction with $NaIO_4$ as a co-oxidant.[146] The reaction is generally less selective and more prone to over-oxidation by cleavage of the diol to carbonyl compounds. To overcome this drawback, an improved protocol was developed by the addition of $CeCl_3$ as an additive, which not only suppresses diol cleavage but also broadens the scope of the reaction and reduces the catalyst loading.[147] Same as the Upjohn dihydroxylation, the reaction produces racemic diols unless controlled by the substrate. Applications of these dihydroxylation methods in natural product synthesis are illustrated below.

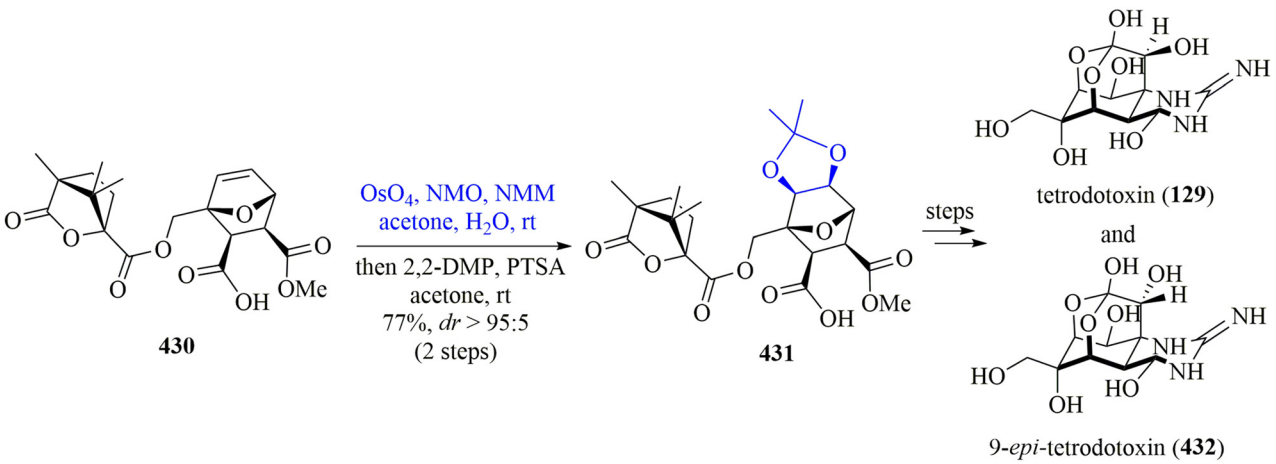
5.2.1 The Upjohn dihydroxylation. Tagetitoxin is a phytotoxin produced by *Pseudomonas syringae* pv. *Tagetis*. It inhibits RNA synthesis directed by chloroplast RNA polymerase. In the total synthesis and structural revisiting of tagetitoxin by Baran's group,[148] conditions for the OsO_4-catalyzed selective dihydroxylation of cyclopentene in the presence of an amidoacrylate side chain (**426**) were extensively screened. It was found that *N*-Boc protection of methyl 2-acetamidoacrylate greatly improved the selectivity for cyclopentene dihydroxylation, while the addition of citric acid as an additive was critical for the rate of the reaction. Under the optimized conditions, the required diol **427** was obtained as a single diastereomer in 81% yield after acidic workup, which concomitantly removed the *N*-Boc protection. This work achieved the synthesis of both (+)-tagetitoxin (**428**) and (−)-tagetitoxin (**429**) (Scheme 58), allowing the confirmation of (+)-tagetitoxin as the natural isomer through an RNA polymerase inhibition assay.[148]

In the synthesis of tetrodotoxin (**129**) and 9-*epi*tetrodotoxin (**432**) by Qi's group,[59] substrate-controlled Upjohn dihydroxylation of olefin **430** and subsequent 1,2-diol protection provided acetonide **431** in excellent diastereoselectivity (Scheme 59).

Cotylenin A (**436**) was initially isolated as a plant growth regulator, but later found to be able to induce the differen-



Scheme 58 Upjohn dihydroxylation in the synthesis of (+)-tagetitoxin and (−)-tagetitoxin.



Scheme 59 Upjohn dihydroxylation in the synthesis of tetrodotoxin and 9-*epi*tetrodotoxin.

tiation of murine and human myeloid leukemia cells and apoptosis in a wide range of human cancer cell lines by combined treatment with interferon-α. In the total synthesis of cotylenin A by Nakada's group,[149] methylenation of the ketone in **433** provided *exo*-alkene **434**, which was selectively dihydroxylated from the less hindered α-face under Upjohn conditions, providing diol **435** without affecting the other two more hindered olefins (Scheme 60).

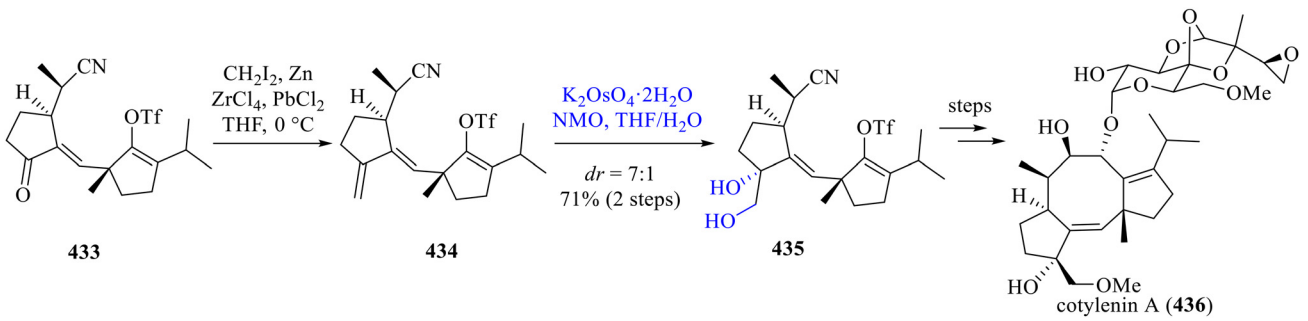
5.2.2 Sharpless asymmetric dihydroxylation. FD-594 (**439**) is a complex polycyclic xanthone-type natural product with inhibitory activities against P388 and HeLa tumour cells. In Gao's total synthesis of FD-594,[150] Sharpless asymmetric dihydroxylation of the C6–C7 olefin in **437** with OsO_4 and chiral ligand $(DHQ)_2PHAL$ afforded the desired diol **438** in excellent yield as a single diastereomer (Scheme 61).

In the total synthesis of pre-schisanartanin C (**298**) by Yang's group,[101] final-step regioselective Sharpless asymmetric dihydroxylation of the more reactive C23–C24 double bond in **440** with AD-mix-α and concomitant δ-lactonization of the C24-hydroxy group completed the synthesis of pre-schisanartanin C (Scheme 62).

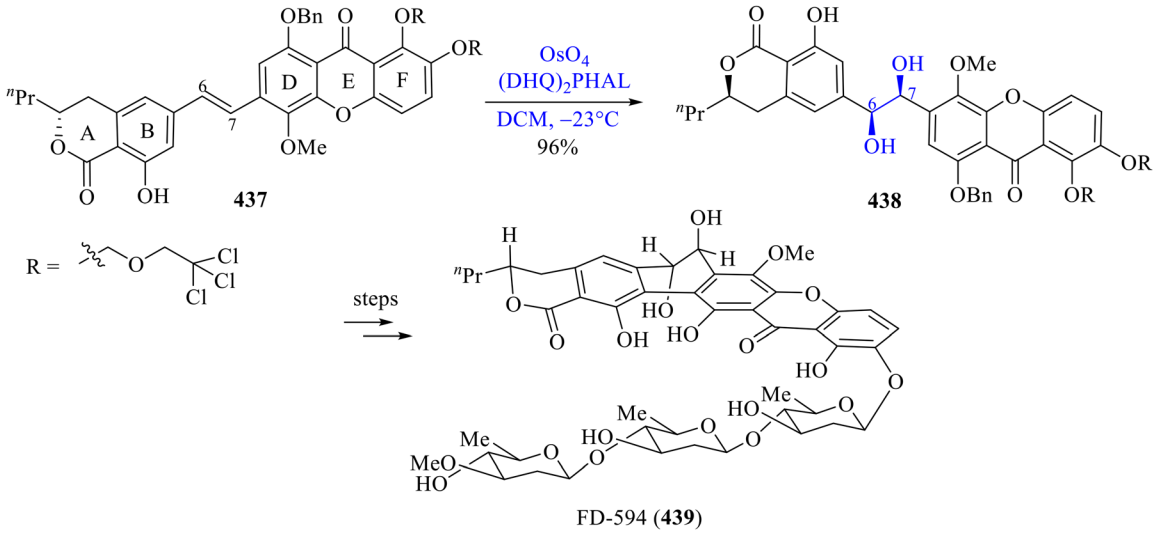
α-Amanitin (**443**) is a highly potent toxin isolated as the major product of the death cap mushroom (*Amanita phalloides*). This compound is a potent inhibitor of RNA polymerase II, which interrupts the basic transcription processes of eukaryotes, leading to apoptosis in their cells. This unique mechanism makes this toxin an ideal payload for antibody–drug conjugates (ADCs). In its recent total synthesis by Müller's group,[151] Sharpless asymmetric dihydroxylation of olefin **441** with AD-mix-β provided the required diol **442** in excellent ee (Scheme 63).

5.2.3 Ru-catalyzed alkene dihydroxylation. In Burton's total synthesis of sealutomicin C (**175**),[71] ruthenium-catalyzed dihydroxylation of the double bond in **444** proceeded from the less hindered α-face, providing diol **445** in 88% yield as a single diastereomer (Scheme 64).

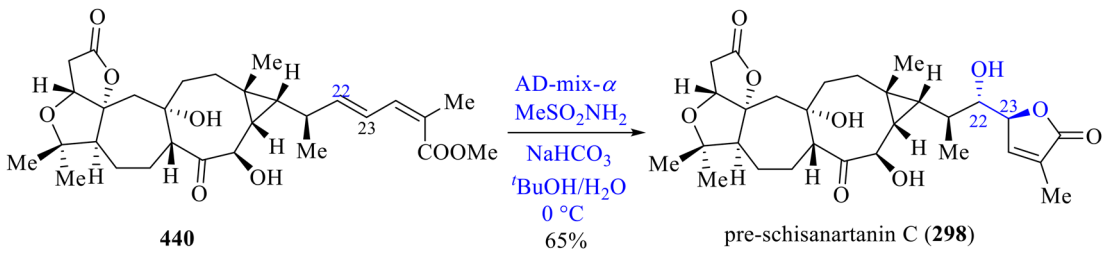
In summary, the Upjohn, Sharpless asymmetric and ruthenium-catalyzed dihydroxylations are the most often used



Scheme 60 Upjohn dihydroxylation in the synthesis cotylenin A.



Scheme 61 Sharpless asymmetric dihydroxylation in the synthesis of FD-594.

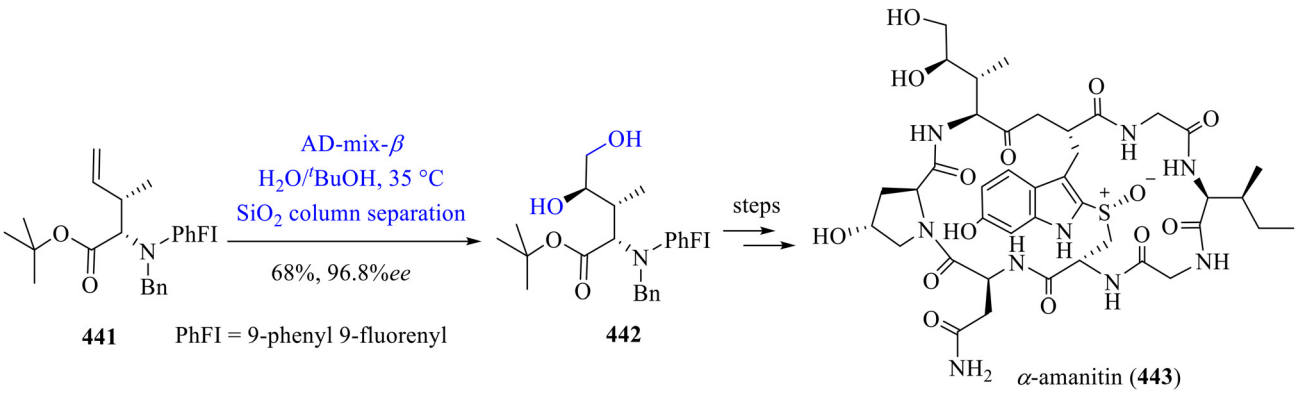


Scheme 62 Sharpless asymmetric dihydroxylation in the synthesis of pre-schisanartanin C.

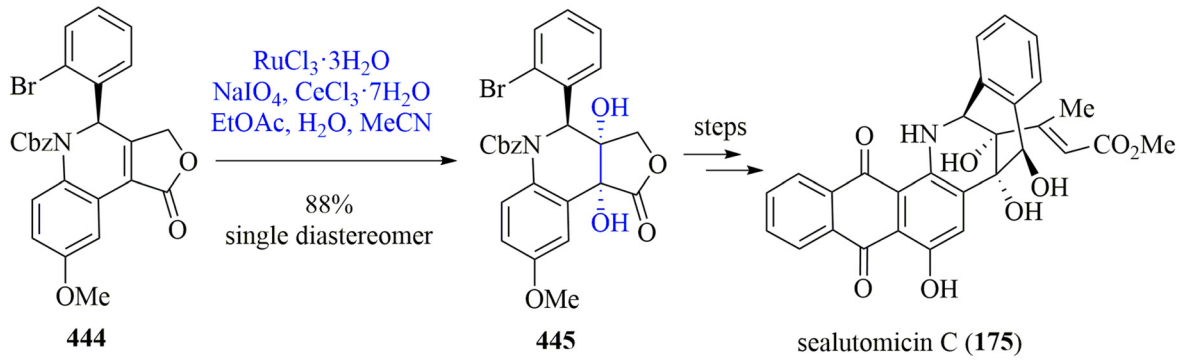
methods for alkene dihydroxylation to produce vicinal diols in natural product syntheses. The Upjohn dihydroxylation provides efficient *cis*-dihydroxylation under mild conditions, though it lacks stereochemical control. The Sharpless asymmetric dihydroxylation enables highly enantioselective dihydroxylation of prochiral alkenes with excellent selectivity and functional group tolerance. Ruthenium-catalyzed dihydroxylation is more effective for less reactive alkenes with a trade-off in terms of selectivity and over-oxidation.

5.3 Catalytic oxidation of alkenes using molecular oxygen

In the presence of a suitable metal catalyst, alkenes can undergo oxidation with molecular oxygen to form either carbonyl compounds or alcohols. Among the alkene oxidation reactions, the Wacker oxidation converts terminal alkenes into aldehydes or ketones, whereas Mukaiyama hydration and Schenck Ene reaction enable the conversion of alkenes to alcohols. These reactions utilize molecular oxygen as a green



Scheme 63 Sharpless asymmetric dihydroxylation in the synthesis of α-amanitin.



Scheme 64 $RuCl_3$-catalyzed dihydroxylation in the synthesis of sealutomicin C.

oxidant, and hence provide a route for the more sustainable transformation of alkenes. Thus, they are increasingly applied in natural product synthesis, as exemplified below.

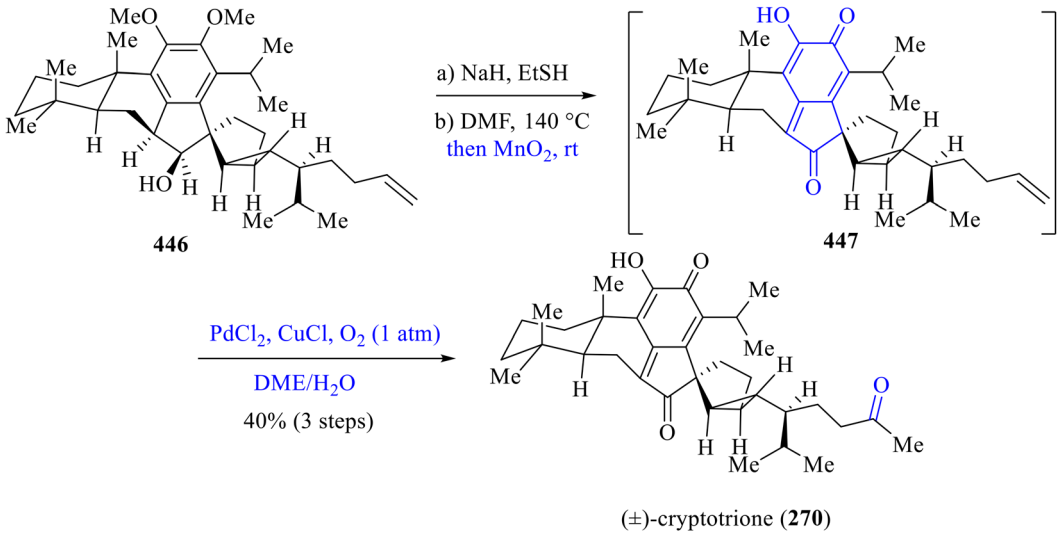
5.3.1 Conversion of alkenes to carbonyl compounds. The Wacker oxidation allows the conversion of terminal alkenes to aldehydes or methyl ketones *via* anti-Markovnikov or the Markovnikov addition of water, using palladium-based catalysts and oxygen as the oxidant. This reaction has been widely applied in the synthesis of natural products.[152] Nevertheless, considering the high cost of palladium catalysts, less expensive metals such as iron and cobalt have also been explored for Wacker-type oxidation of alkenes,[153] although their applications are less general than Pd catalysts.

In the first total synthesis of (±)-cryptotrione (**270**) by Peng and co-workers,[95] at the final stage of their synthesis, the catechol dimethyl ether in the precursor (**446**) was demethylated with EtSNa generated *in situ*. The resulting catechol intermediate was oxidized with MnO_2, leading to *p*-quinone methide **447**. Final Wacker oxidation of the terminal alkene installed the required methyl ketone in cryptotrione (Scheme 65).

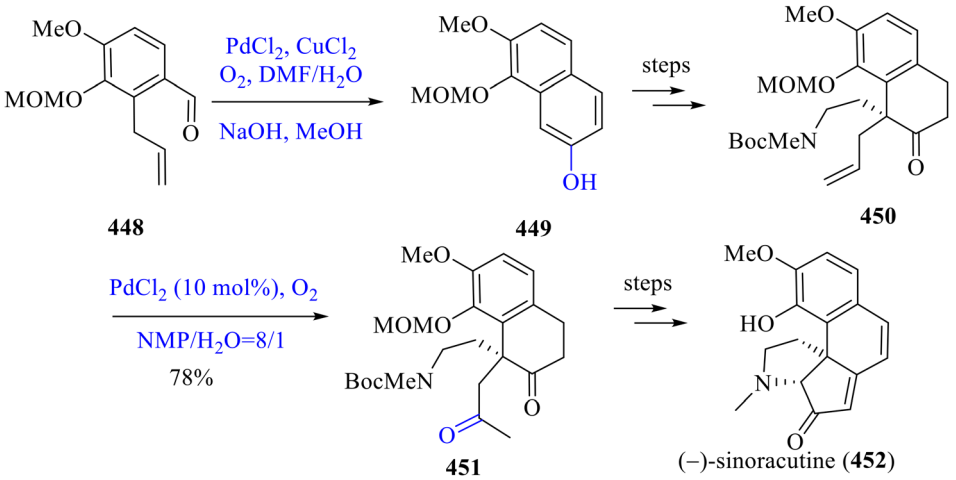
(−)-Sinoracutine (**452**) is a member of the hasubanan alkaloids with a 6/6/5/5 tetracyclic structure. This compound was isolated from *Sinomenium acutum* and displays potent antioxidant activity, indicating its potential in the treatment of neurodegenerative diseases. Wacker oxidation was applied twice in Zhu's total synthesis of (−)-sinoracutine.[154] The first Wacker oxidation converted terminal olefin **448** to the corresponding methyl ketone (not shown), which then underwent base-promoted aldol condensation and subsequent aromatization, providing β-naphthol **449**. Further transformations led to terminal olefin **450**, which underwent a second Wacker oxidation to form the required methyl ketone **451** in 78% yield (Scheme 66).

At a late stage in the synthesis of (−)-lucidumone (**219**) by Li's group,[77] they attempted the conversion of the terminal alkene in **453** to methyl ketone **454** under the standard Wacker oxidation conditions, resulting in the formation of the anti-Markovnikov aldehyde (not shown), likely caused by the steric effect from the bulky cage moiety. Alternatively, iron-catalyzed Wacker-type oxidation of the alkene[155] provided the required methyl ketone **454** in 65% yield. Final demethylation of hydroquinone dimethyl ether furnished the synthesis of (−)-lucidumone (Scheme 67).

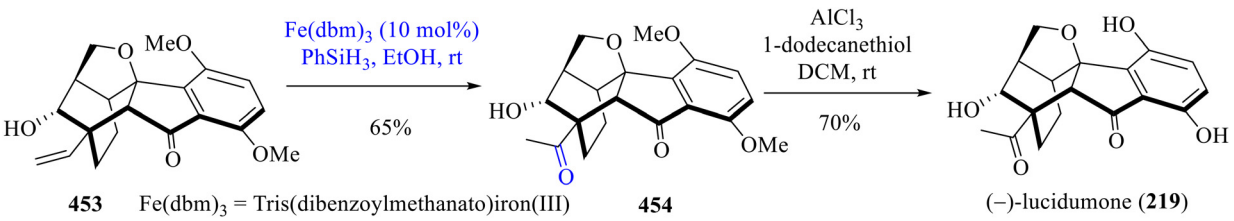
5.3.2 Conversion of alkenes to alcohols. In the presence of a suitable metal catalyst, alkenes can undergo hydration to form an alcohol. Among the methods for alkene hydration, the Mukaiyama hydration and Schenck ene reaction are the two commonly used methods owing to their mild conditions, versatility and functional group tolerance. The Mukaiyama hydration is a metal (Co or Mn complexes)-catalyzed radical hydration reaction using a hydrosilane and molecular



Scheme 65 Wacker oxidation in the synthesis of (±)-cryptotrione.



Scheme 66 Wacker oxidation in the synthesis of (−)-sinoracutine.



Scheme 67 Wacker oxidation in the synthesis of (−)-lucidumone.

oxygen.[156] This reaction converts alkenes to Markovnikov alcohols under mild conditions and is especially useful in complex structural settings. On the other hand, the Schenck ene reaction[157] is a photooxidation reaction involving singlet oxygen reacting with alkenes *via* an ene mechanism to form allylic hydroperoxides, which are subsequently reduced to allylic alcohols. Tetraphenylporphyrin (TPP) is often used as the photosensitizer to generate singlet oxygen. These alkene hydration methods provide valuable strategies in natural product synthesis, as highlighted in the examples below.

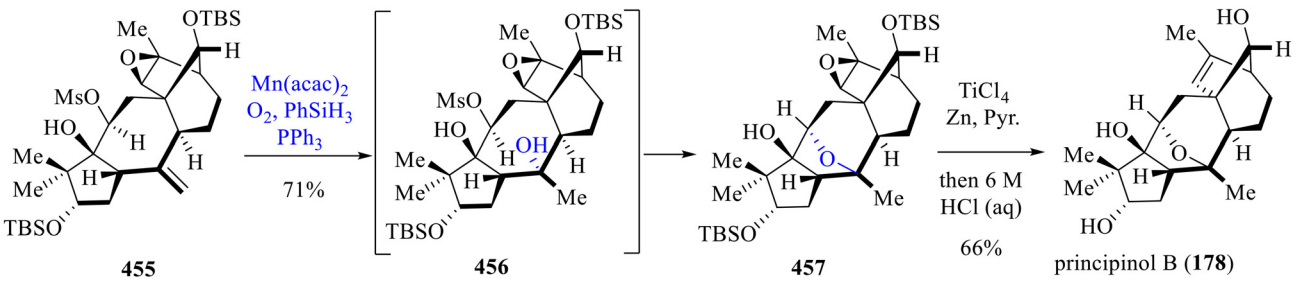
In Yang's total synthesis of principinol B (**178**),[72] Mukaiyama hydration of the exocyclic olefin in **455** provided

the Markovnikov alcohol **456**, which underwent S_N2 substitution at the preformed mesylate, leading to the pentacyclic compound **457** in 71% yield. Final reduction of the epoxide to alkene and TBS deprotection completed the synthesis of principinol B (Scheme 68).

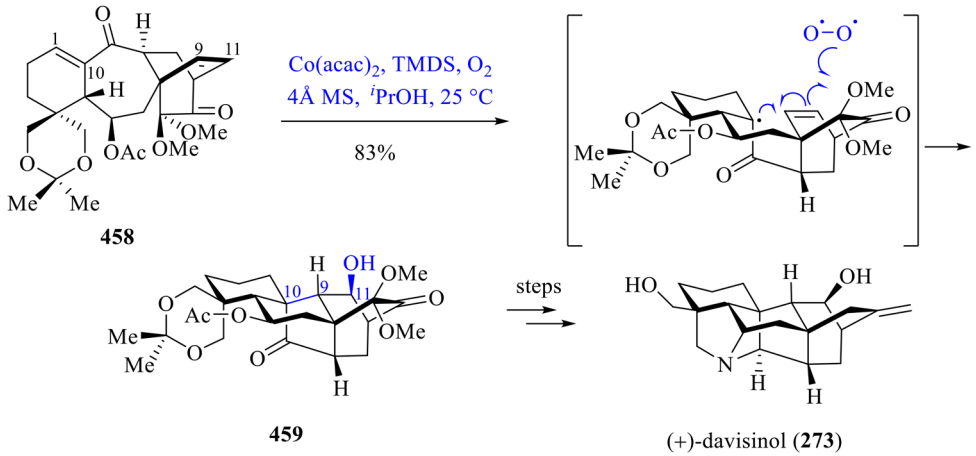
In the first asymmetric total synthesis of (+)-davisinol (**273**) by Ding's group,[96] radical transannular cyclisation between C9–C10 of the two olefins in **458** to introduce a C11-alcohol and concurrently form tricyclo[4.3.1.$0^{3,7}$]decane skeleton **459** was explored. After screening a range of conditions, it was found that in the presence of $Co(acac)_2$, tetramethyldisiloxane (TMDS) and molecular oxygen, a hydrogen atom transfer (HAT) redox radical cascade was successfully achieved, providing **459** in 83% yield as a single isomer. This elegant single-step operation formed two highly strained rings and three contiguous stereogenic centers (Scheme 69).

(−)-Garryine (**462**) is a veatchine-type C20-diterpenoid alkaloid isolated from the species of *Garrya*. In Qin's first asymmetric total synthesis of (−)-garryine,[158] Schenck ene reaction of the endocyclic olefin in **460** under the standard conditions (TPP, O_2, and *hν* then Me_3P) provided the allylic alcohol **461** in 73% yield as a single diastereomer (Scheme 70).

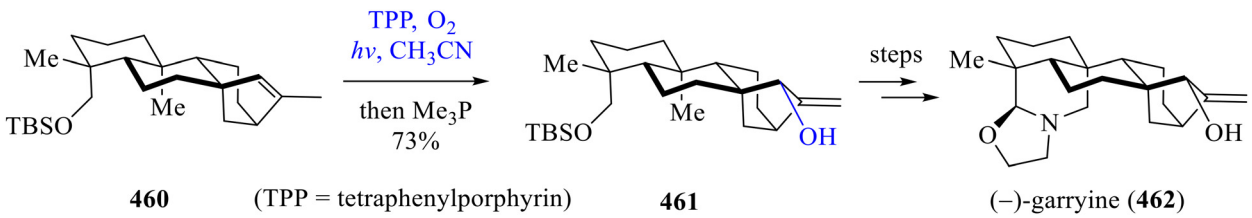
(−)-Daphenylline (**465**) and (−)-himalensine (**466**) are two C-30 alkaloids isolated from the *Daphniphyllum genus*. In their total synthesis by Qiu's group,[159] attempts to introduce the required 1,3-diene in **464** *via* allylic C–H oxidation or bromination of the alkene in **463** using several conventional protocols were unsuccessful. Alternatively, allylic transpositional oxi-



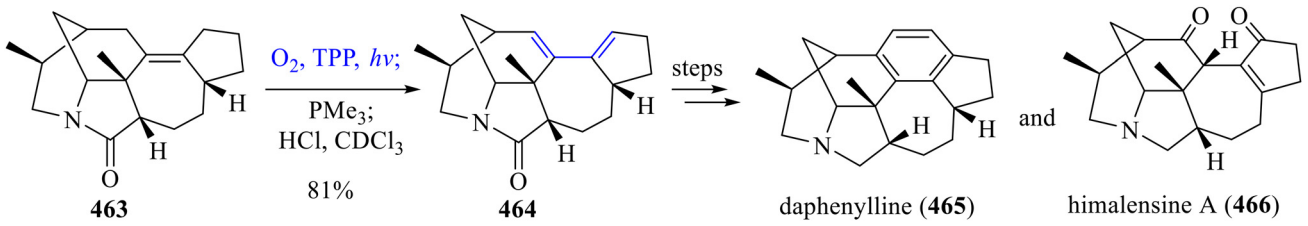
Scheme 68 Mukaiyama hydration of olefin in the synthesis of principinol B.



Scheme 69 $Co(acac)_2$-catalyzed radical transannular cyclization–hydration of olefin in the synthesis of (+)-davisinol.



Scheme 70 Schenck ene reaction in the synthesis of (−)-garryine.



Scheme 71 Schenck ene reaction in the synthesis of (–)-daphenylline and (–)-himalensine.

dation by Schenck ene reaction proceeded smoothly, providing the allylic alcohol (not shown), which, without isolation, was dehydrated using HCl in ethyl acetate, leading to the desired diene **464** in 81% yield (Scheme 71).

In summary, the catalytic oxidation of alkenes with O_2 provides a sustainable route to carbonyl compounds and alcohols. The Wacker oxidation uses $PdCl_2/CuCl_2$ catalysts to convert terminal alkenes into ketones or aldehydes with good selectivity. In addition, owing to the use of water as the oxygen source and O_2 as the terminal oxidant, this reaction is sustainable and industrially significant. The Mukaiyama hydration employs cobalt or manganese catalysts with molecular oxygen to hydrate alkenes directly, forming alcohols under mild, functional group-tolerant conditions. The Schenck ene reaction converts an alkene to an alcohol *via* a photochemical process with singlet oxygen. These methods provide a route for the more sustainable transformation of alkenes, and hence are increasingly applied in natural product syntheses.

6. Oxidation of sp^3 C–H bonds

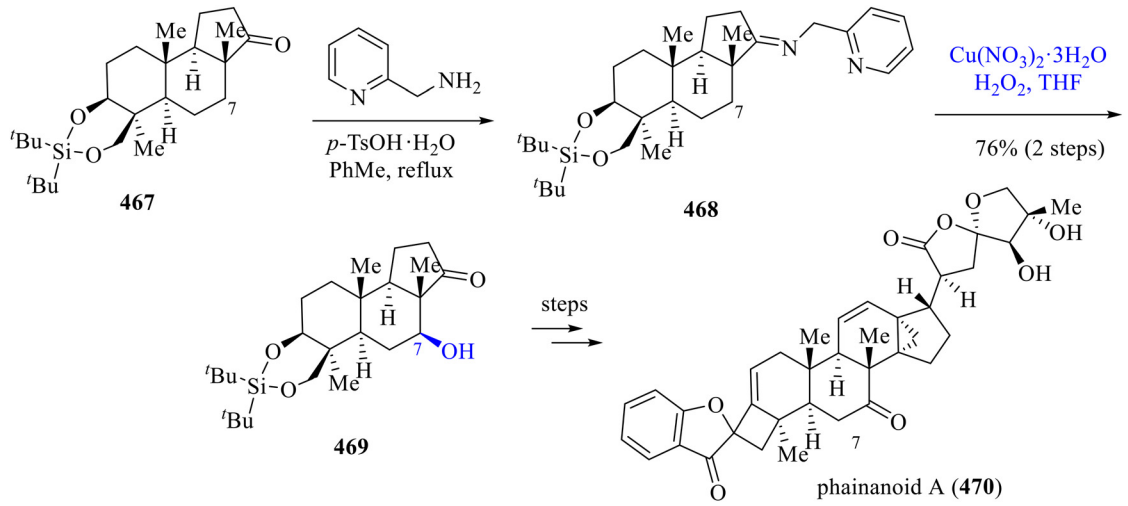
In recent years, oxidation of sp^3 C–H bonds has emerged as a revolutionary strategy in natural product synthesis, fundamentally changing retrosynthetic logic by allowing the direct oxygenation of non-activated sp^3 C–H bonds. This strategy circumvents the need for lengthy functional group manipulations, reduces the use of protecting groups, and enables late-stage functionalization and diversification, thereby significantly streamlining synthetic routes. In addition, this approach expands the choice of starting materials, especially those from natural sources, making the synthesis more sustainable. The most common methods for sp^3 C–H oxidation employ transition-metal catalysts or enzymes to achieve selective sp^3 C–H bond cleavage and oxygen insertion. In addition, photo- and electro-chemical methods have emerged as valuable tools for the oxidation of sp^3 C–H bonds. Owing to its high efficiency, conciseness and environmental friendliness, sp^3 C–H oxidation is being increasingly applied in the synthesis of natural products.[160]

6.1 Transition metal-catalyzed oxidation of sp^3 C–H bonds

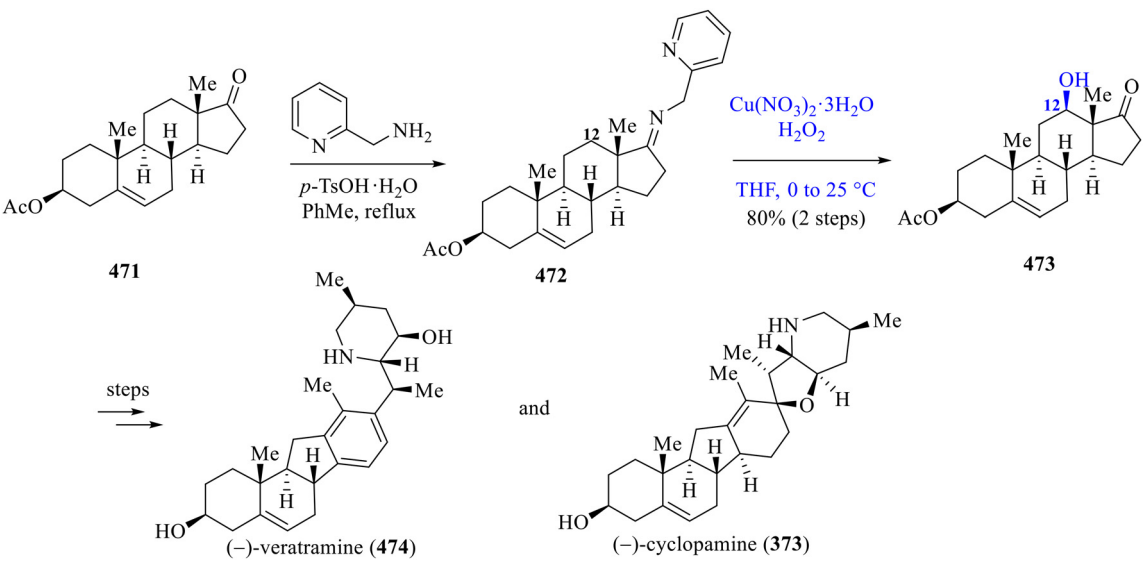
Transition metal (Pd, Mn, Cu, Ni, Co, Fe, *etc.*) catalysts in combination with an oxidant, such as oxygen, peroxides or hypervalent iodine, are often used in sp^3 C–H bond oxidations. Mechanistically, oxidation often proceeds through sp^3 C–H activation/functionalization, wherein the metal coordinates to the sp^3 C–H bond, leading to a metal–carbon species, which is converted to an oxygenated functionality, most often a hydroxy group. The site and stereo-selectivity of the reaction are controlled either by the inherent reactivity of the sp^3 C–H bonds or a directing group. In the directing group approach, a functional group already present or temporarily installed on the substrate coordinates to the metal, directing the catalyst in close proximity to a specific sp^3 C–H bond for the oxidation. In the absence of a directing group, the selectivity of the reaction is governed by the intrinsic electronic or steric differences among the sp^3 C–H bonds in the molecule, often favouring oxidation at the most electron-rich or least sterically hindered position. The latter approach, despite its conciseness in avoiding installation of a directing group, often results in a trade-off in selectivity, especially in molecules containing multiple sp^3 C–H bonds. The applications of transition metal-catalyzed sp^3 C–H oxidation in natural product synthesis have been reviewed previously.[160d] Accordingly, selected recent examples are highlighted below.

Phainanoid A (**370**) is a member of the cyclodammarane-type triterpenoids isolated from *Phyllanthus hainanensis* Merr., a shrub only found in Hainan Island of China. This compound possesses a unique [4.3.1]propellane architecture embedded in its core and a highly oxygenated 5,5-oxaspirolactone moiety on its side chain. In the total synthesis of this challenging natural product by Dong's group,[126] ketone **467** served as a substrate for Baran's modified Schönecker C–H oxidation to introduce a C7 alcohol in **469**. The pyridyl directing group was installed *via* imine formation of the ketone with 2-(aminomethyl)pyridine. The crude imine **468** was used for the directed C7–H oxidation using $Cu(NO_3)_2$ as the catalyst and hydrogen peroxide as the oxidant, leading to the C7-β-alcohol (**469**) in 76% yield with the desired equatorial selectivity (Scheme 72).

This pyridyl-directed sp^3 C–H oxidation was also applied to a divergent synthesis of (–)-veratramine (**474**) and (–)-cyclopamine (**373**), two representative members of the isosteroidal alkaloids.[161] In Qin's synthetic route, 3-acetyl dehydro-*epi*-androsterone (**471**) was subjected to Baran's C–H oxidation protocol[162] to introduce the required C12-β-OH *via* (imino)pyridine intermediate **472**. The hydroxy compound **473** was prepared in impressive 80% yield in >40-gram scale for the synthesis of both (–)-veratramine and (–)-cyclopamine (Scheme 73).



Scheme 72 Directed sp^3 C–H oxidation in the synthesis of phainanoid A.

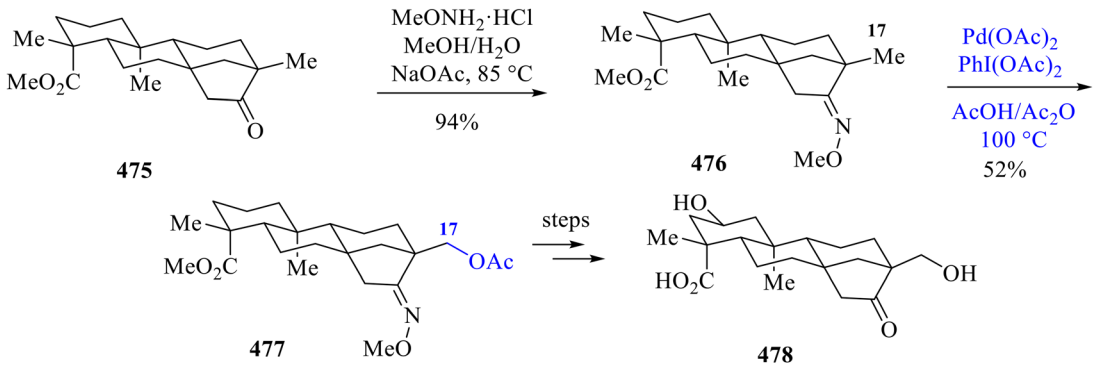


Scheme 73 Directed sp^3 C–H oxidation in the synthesis of (–)-veratramine and (–)-cyclopamine.

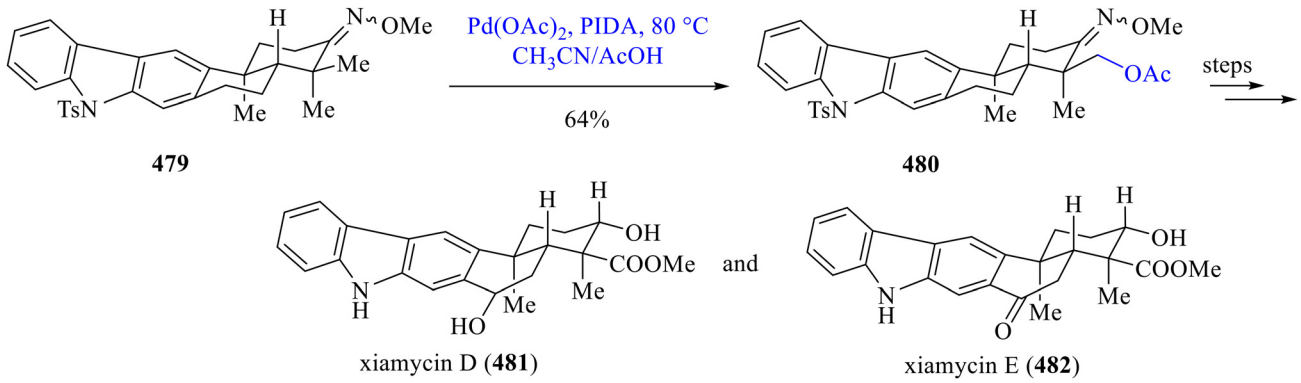
Apart from the pyridyl group, oxime has also been used as a directing group in Pd-catalyzed C–H oxidation in conjunction with $PhI(OAc)_2$ as the oxidant, resulting in acetoxylation of a suitably positioned sp^3 C–H bond.[163] For example, in the synthesis of an *ent*-beyerane metabolite (**478**) by de Lucca's group,[164] the ketone (**475**) was converted to oxime **476**, which directed Pd-catalyzed oxidation of the C17 methyl group, providing the C17 acetoxylated compound **477** in 52% yield (Scheme 74).

In another example, in the first total syntheses of the antiviral natural products xiamycins D (**481**) and E (**482**) by Dethe' group,[165] an oxime (**479**) was used to direct the selective oxidation of the equatorial methyl group with $Pd(OAc)_2$/PIDA in AcOH/acetonitrile, providing the desired acetate **480** in 64% yield (Scheme 75).

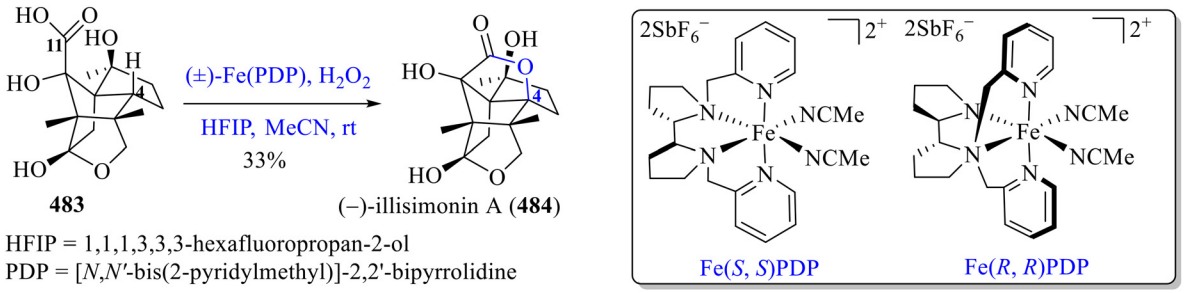
While directed sp^3 C–H oxidations provide high regio- and stereo-selectivity, oxidation without a directing group is advantageous in that it saves two steps in installation and removal of the directing group. However, there is often a trade-off in selectivity. Nevertheless, some excellent developments such as the White–Chen catalyst[166] have enabled selective sp^3 C–H oxidations with impressive applications in natural product synthesis. A recent example is illustrated in Kalesse's asymmetric total synthesis of (–)-illisimonin A (**484**), a sesquiterpenoid isolated from the fruits of *Illicium simonsii*.[167] In the final step of the synthesis, oxidation of the C4–H in precursor **483** using an (±)-Fe(PDP) catalyst [prepared by mixing equal amounts of (–)-Fe(*S*,*S*)PDP and (+)-Fe(*R*,*R*)PDP] and concomitant lactonization completed the synthesis of (–)-illisimonin A (Scheme 76).



Scheme 74 Directed sp^3 C–H oxidation in the synthesis of an *ent*-beyerane metabolite.



Scheme 75 Directed sp^3 C–H oxidation in the synthesis of xiamycins D and E.



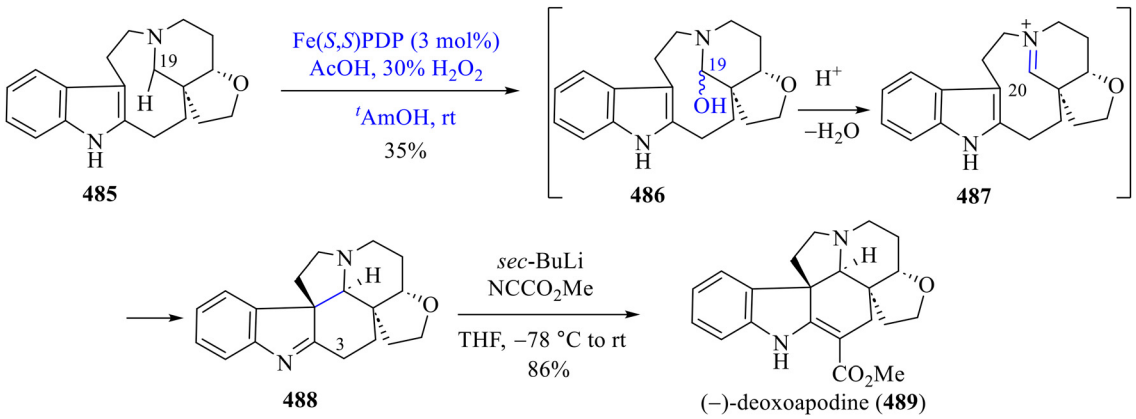
Scheme 76 Non-directed sp^3 C–H oxidation in the synthesis of (–)-illisimonin A.

(–)-Deoxoapodine (**489**) is a member of the aspidosperma alkaloids first isolated from *Tabernae armeniaca*. In the concise total synthesis of (–)-deoxoapodine by Tokuyama's group,[168] a later-stage oxidative transannular Mannich reaction on intermediate **485** using Fe(*S*,*S*) PDP, H_2O_2 and AcOH, *via* hemiaminal **486** from the oxidation of C19–H, provided hexacyclic compound **488** in 35% yield. Final methoxy carbonylation at C3 completed the synthesis of (–)-deoxoapodine (Scheme 77).

6.2 Enzymatic oxidation of sp^3 C–H bonds

Enzymatic oxidation of sp^3 C–H bonds is a crucial transformation in nature, enabling the biosynthesis of diverse oxygenated natural products that are essential for biological processes.[2d] These reactions are primarily catalyzed by metalloenzymes such as cytochrome P450s and non-heme iron oxygenases, which achieve remarkable site- and stereo-selectivity in the oxidation of unactivated sp^3 C–H bonds, often in complex structural settings. Harnessing and engineering these enzymes have provided powerful tools for the synthesis and late-stage diversification of complex natural products,[169] as highlighted in the recent examples below.

In the chemo-enzymatic first total synthesis of four *trans*–*syn*-fused drimane meroterpenoids by Renata and co-workers, enzymatic C–H hydroxylation was employed to install the pre-

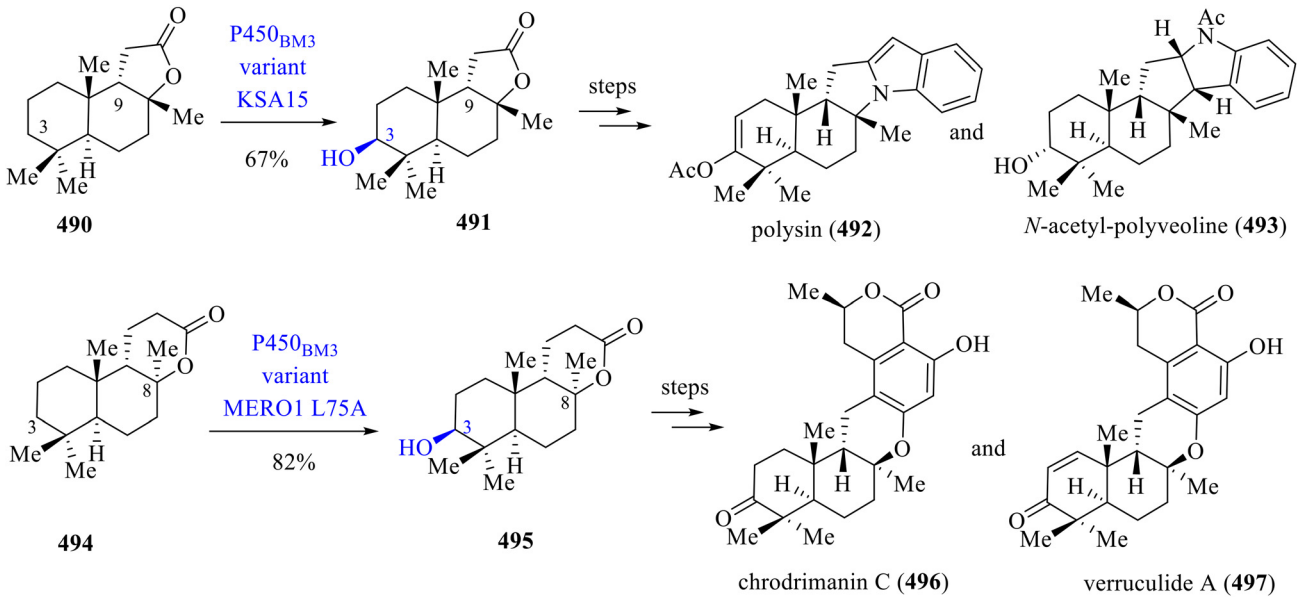


Scheme 77 Non-directed sp^3 C–H oxidation in the synthesis of (–)-deoxoapodine.

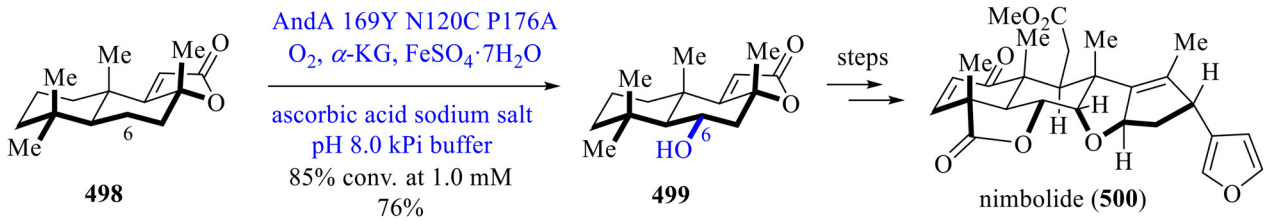
requisite C3 hydroxy group of the starting material 9-*epi*-sclareolide (**490**) and its 8-*epi*-δ-lactone analogue (**494**).[170] Screening a collection of $P450_{BM3}$ variants identified the KSA15 variant, which selectively oxidized the C3–β-H in **490**, providing the required 3-β-hydroxy compound **491** in 67% yield. On the other hand, the MERO1 L75A variant was found to be more effective for the C3–β-H oxidation of **494**, leading to the corresponding 3-β-hydroxy compound **495**. Subsequent chemical transformations of the two hydroxylated intermediates led to the synthesis of four *trans–syn*-fused drimane meroterpenoids, *i.e.* polysin (**492**), *N*-acetyl-polyveoline (**493**), chrodrimanin C (**494**), and verruculide A (**495**) (Scheme 78).

In another work on the synthesis of nimbolide (**500**) by Li's group,[171] screening an enzyme library of P450 monooxygenases and α-ketoglutarate (αKG)-dependent dioxygenases (AndA) against six labdane substrates led to the identification of 9,11-dehydrosclareolide (**498**) as a privileged substrate for selective C–H hydroxylation. Further directed evolution of AndA identified a mutant, AndA I69Y N120C L175A, which exhibited a better performance for C6 α-hydroxylation with 100% selectivity, 85% conversion and 76% yield, providing the required 6-α-hydroxy compound (**499**). Further chemical transformations led to the synthesis of the anti-cancer natural product nimbolide (Scheme 79).

The cyclopiane diterpenes are a family of natural products featuring a 6-5-5-5 tetracyclic carbon skeleton containing 6–9 stereogenic centres, rendering them challenging targets for total synthesis. While chemical routes are generally lengthy, enzymatic or chemoenzymatic routes can be more concise and efficient, as demonstrated by the recent work by Xu's group.[172] In their approach, a pivotal compound, deoxyconidiogenol (**501**), which contains a 6-5-5-5-fused tetracyclic cyclopiane core, was produced by an engineered *E. coli* strain XT02015 expressed with the corresponding terpene cyclase using



Scheme 78 Enzymatic C–H hydroxylation in the synthesis of drimane meroterpenoids.



Scheme 79 Enzymatic C–H hydroxylation in the synthesis of nimbolide.

prenol/isoprenol as the substrates. The crucial hydroxy group in deoxyconidiogenol served as the starting point for chemical transformations that led to A and B ring-modified cyclopiane diterpenes, *i.e.* conidiogenone B (**502**), conidiogenone (**503**), conidiogenol (**504**) and conidiogenone G (**505**) (Scheme 80).

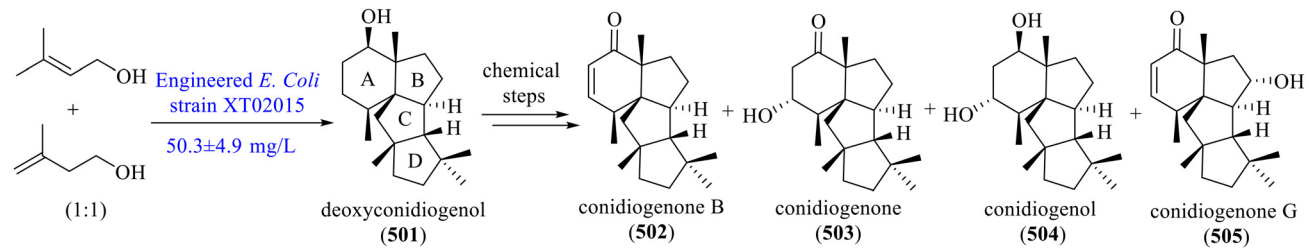
Further efforts to access ring D-functionalized cyclopianes by late-stage non-directed chemical sp^3 C–H oxidation *via* acetyl conidiogenone were unsuccessful due to the inert reactivity and poor selectivity of different types of C–H bonds within this molecule. Alternatively, a docking study and screening a library of P450-BM3 variants found that BM3-A3 combined with a phosphite dehydrogenase variant, Rnd6, for NADPH regeneration was effective in hydroxylating C12-β-H of conidiogenone (**503**), providing conidiogenone H (**506**) in 80% isolated yield on a gram scale. The C12-β-hydroxy group in **506** served as a pivotal functionality, enabling divergence to five other cyclopiane diterpenes (**507–511**) *via* chemical transformations (Scheme 81).[172]

6.3 Photo- and electro-chemical oxidation of sp^3 C–H bonds

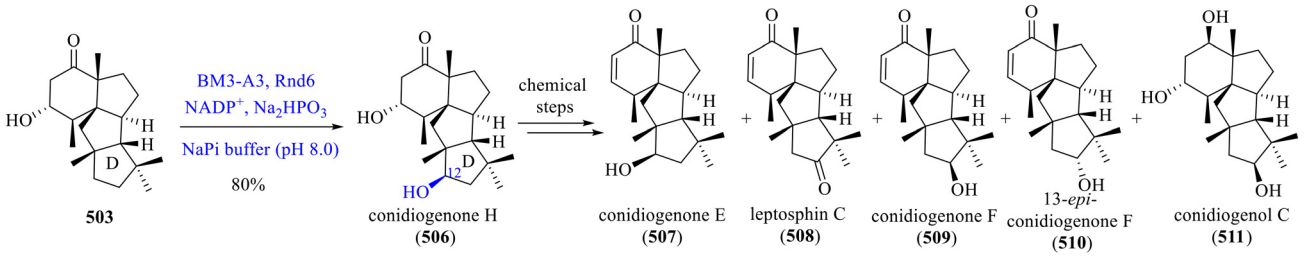
Photochemical sp^3 C–H oxidations involve the use of hydrogen-atom transfer (HAT) catalysts, photoexcited oxidants, or radical intermediates, enabling the activation of sp^3 C–H bonds, which are then oxidized by an oxidant.[173] On the other hand, electrochemical oxidation enables the oxidation of sp^3 C–H bonds *via* direct anodic oxidation or mediated routes, avoiding stoichiometric oxidants and harsh conditions.[174] Compared to the well-studied sp^2 C–H oxidation, oxidation of sp^3 C–H bonds by photo- and electro-chemical means is more challenging due to their inertness and selectivity. Nevertheless, the examples highlighted below have shown their potential in natural product synthesis.

6.3.1 Photochemical sp^3 C–H oxidation. Benzylic and allylic hydrogens generally have lower dissociation energies compared to most aliphatic C–H bonds, which is attributed to the resonance stabilization of the resulting radicals. Considering these different reactivities, photochemical sp^3 C–H oxidation is often applied to benzylic and allylic hydrogens to achieve useful selectivity.

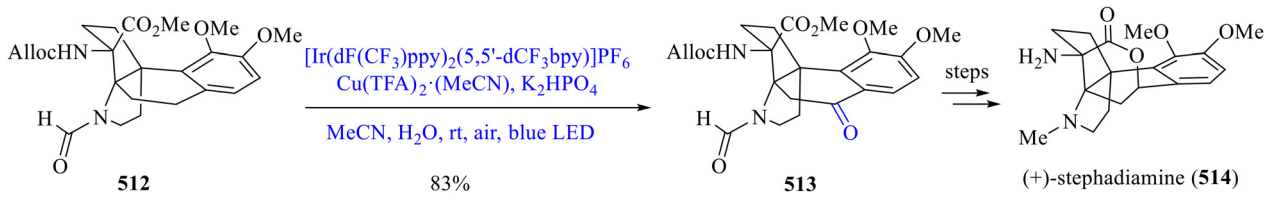
In Zhu's total synthesis of (+)-stephadiamine (**514**),[175] an alkaloid isolated from the vine *Stephania japonica*, photocatalytic aerobic oxidation of the benzylic C–H in **512** using {[Ir(dF(CF$_3$)ppy)$_2$(5,5′-dCF$_3$bpy)]}PF$_6$ as the photocatalyst and blue LED light provided ketone intermediate **513** in high selectivity and yield (Scheme 82).



Scheme 80 Enzymatic synthesis of deoxyconidiogenol for the divergent synthesis of cyclopiane diterpenes.

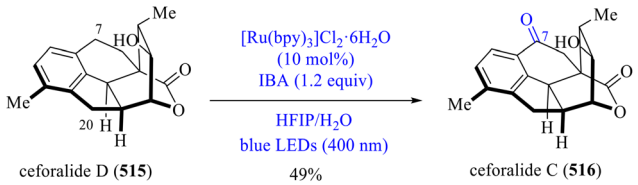


Scheme 81 Enzymatic hydroxylation of conidiogenone for the divergent synthesis of cyclopiane diterpenes.



Scheme 82 Photochemical sp^3 C–H oxidation in the synthesis of (+)-stephadiamine.

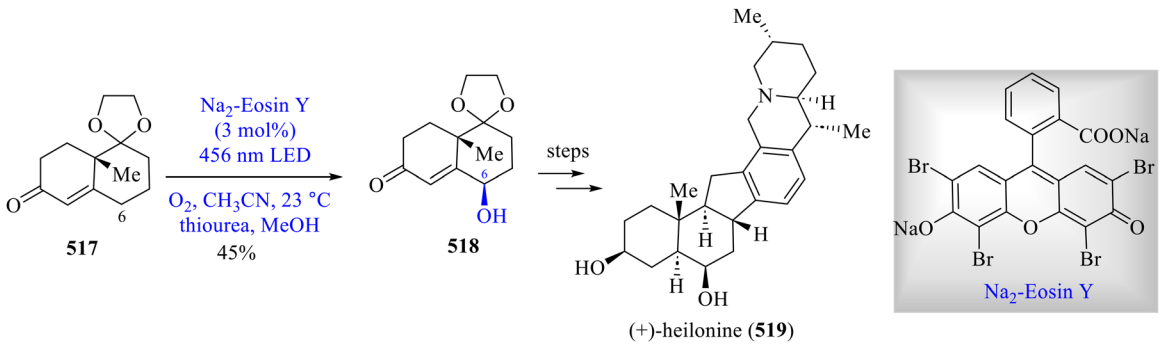
In the synthesis of ceforalide C (**516**) by Sarpong's group,[176] selective oxidation of the less hindered C7 benzylic hydrogens in ceforalide D (**515**) was achieved by using $[Ru(bpy)_3]Cl_2$ as the photocatalyst and 2-iodosobenzoic acid (IBA) as the oxidant (Scheme 83). Considering that there are four types of benzylic hydrogens and a secondary alcohol in this molecule, the selectivity was remarkable.



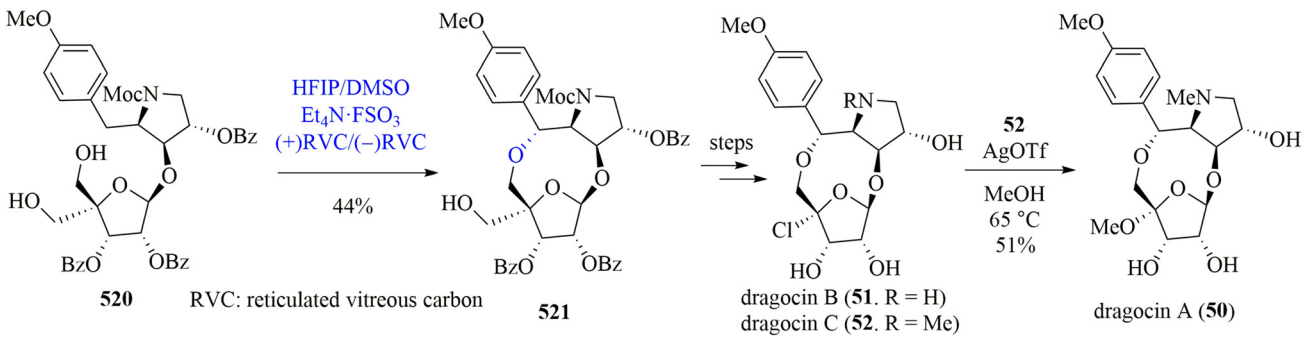
Scheme 83 Photochemical sp^3 C–H oxidation in the synthesis of ceforalide C.

(+)-Heilonine (**519**) is a member of *Veratrum* steroidal alkaloids isolated from *Fritillaria ussuriensis* Maxim. cultivated in the Hei-Long-Jiang Province in China. In a convergent total synthesis of (+)-heilonine by Dai's group,[177] stereoselective photooxidation of the allylic C6-β-hydrogen in enone **517** using Na_2-Eosin Y catalyst and visible light provided the C6-β-hydroxylated compound **518** in 45% yield (Scheme 84).

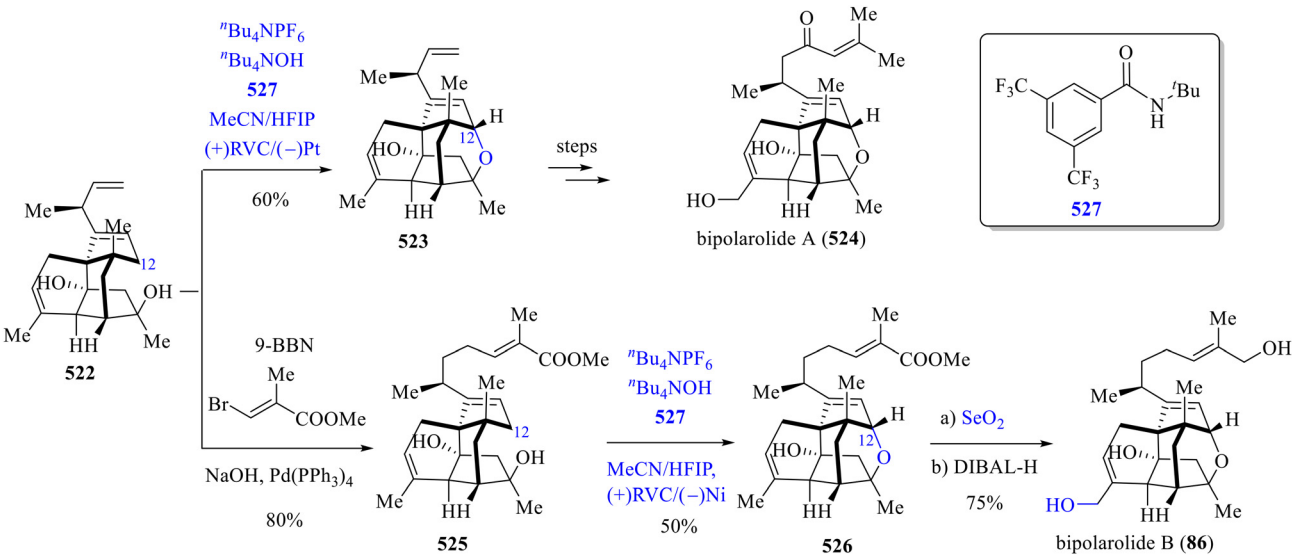
6.3.2 Electrochemical sp^3 C–H oxidation. The reactivity of sp^3 C–H bonds in electrochemical oxidation is primarily determined either by their bond dissociation energy (BDE) (in radical pathways) or oxidation potential (in direct electron transfer pathways). Based on these principles, the sp^3 C–H bonds adjacent to π systems or heteroatoms are the most reactive to oxidation. For example, in the recent first total synthesis of dragocins A, B and C (**50–52**) by Baran's group,[178] formation



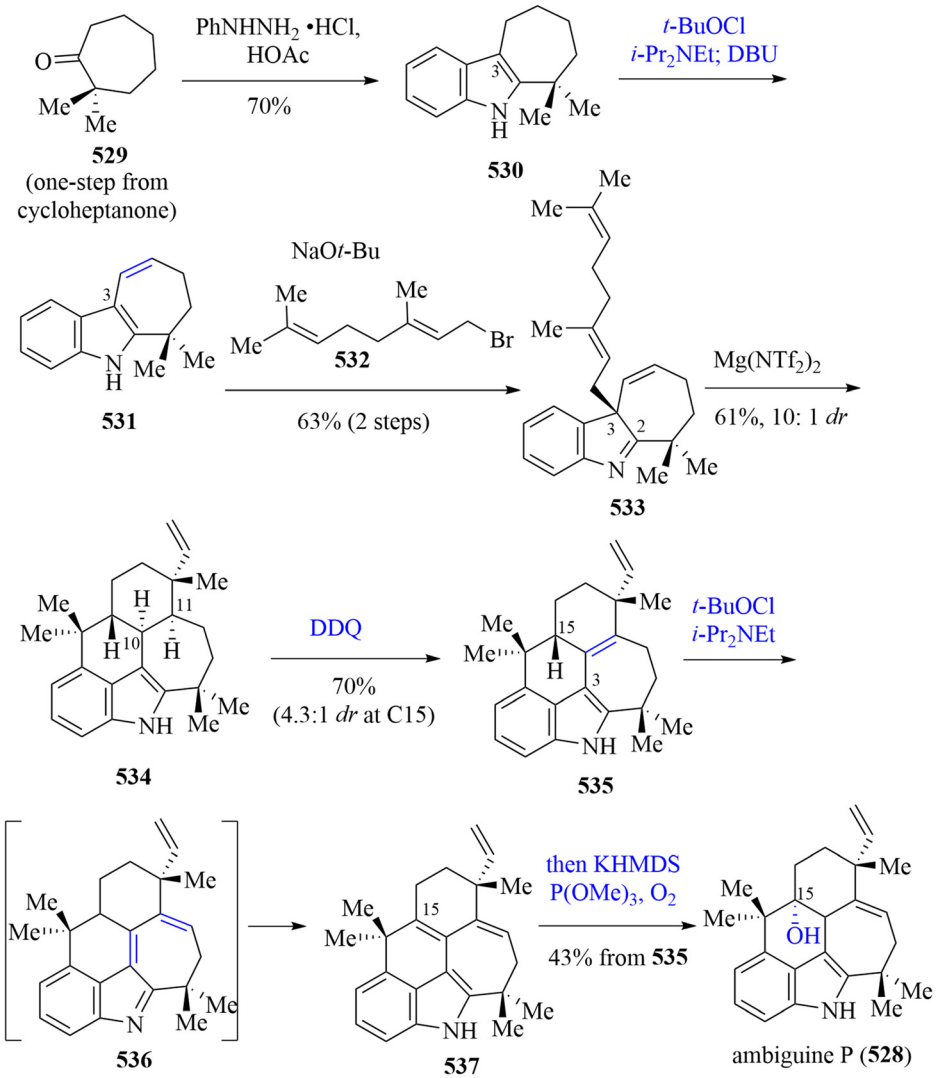
Scheme 84 Photochemical sp^3 C–H oxidation in the synthesis of (+)-heilonine.



Scheme 85 Electrochemical sp^3 C–H oxidation in the synthesis of dragocins.



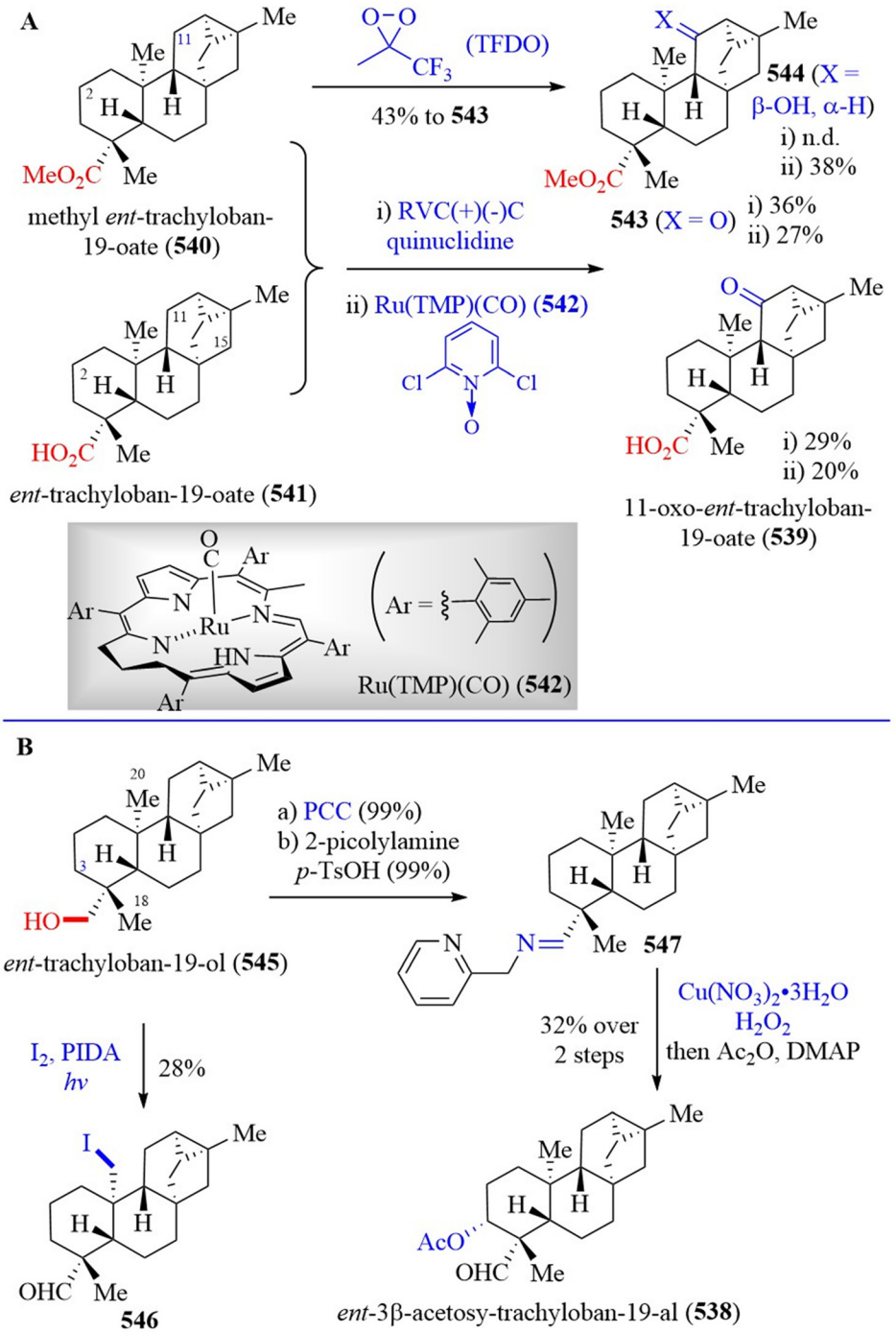
Scheme 86 Electrochemical sp^3 C–H oxidation in the synthesis of bipolarolides A and B.



Scheme 87 Concise total synthesis of ambiguine P by Yang/Li and co-workers.

of the critical 9-membered cyclic ether at the benzylic position in **520** was achieved by diastereoselective oxidative electrochemical cyclization. Under anodic oxidation conditions, precursor **520** was selectively oxidized at the benzylic position, providing the desired cyclic ether **521** in 44% yield (Scheme 85). The selectivity was remarkable considering the presence of multiple reactive C–H bonds and a pyrrolidine moiety within the molecule.

In another example, in Lu's divergent total synthesis of bipolarolides A (**526**) and B (**86**),[179] two members of the ophiobolin family of sesterterpenes possessing intricate cage-like structures, the crucial cyclic allylic ether was installed by electrochemical oxidation, while the conventional method for C–O bond formation using Suárez oxidation conditions [PhI$(OAc)_2$, I_2, and *hν*] failed. Electrochemical oxidative etherification of **522** at the C12 allylic axial-H mediated by the more



Scheme 88 Oxidase phase C–H oxidations of *ent*-trachylobanes **540**, **541**, and **545**: A. undirected C–H oxidations and B. directed C–H oxidations.

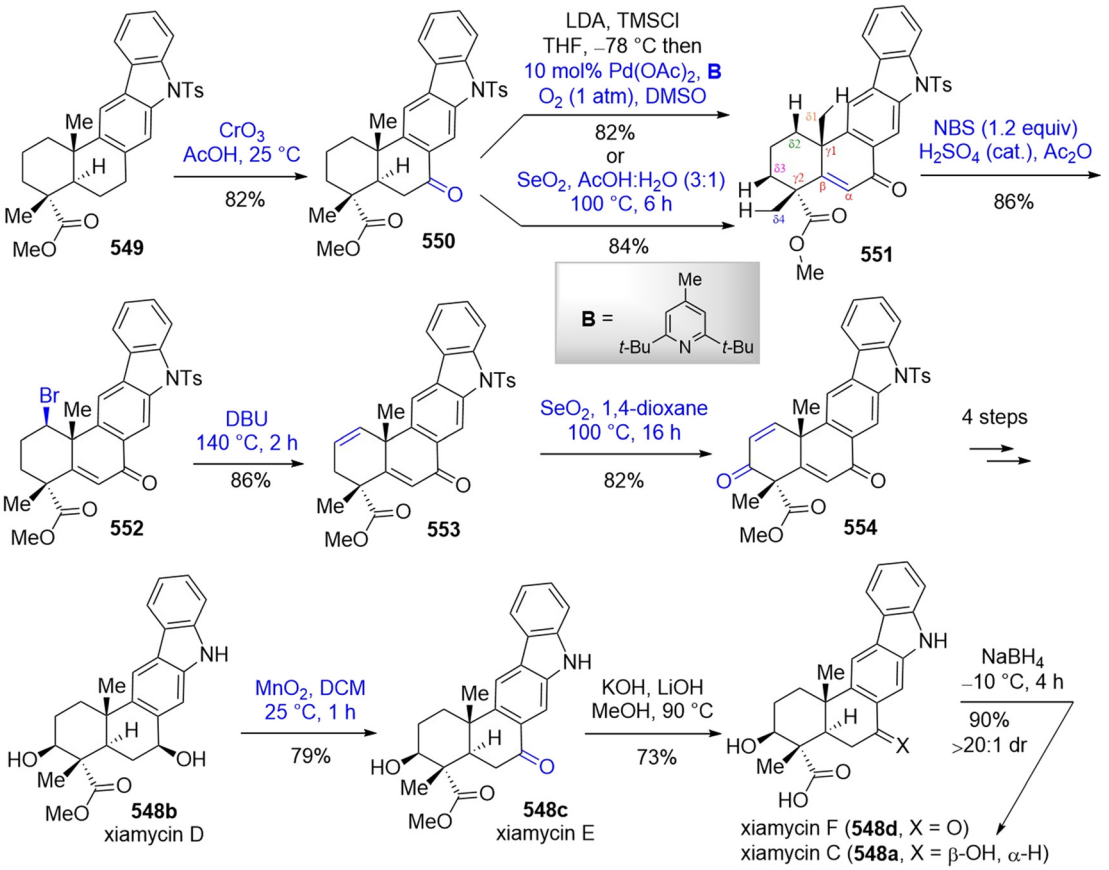
reactive secondary alcohol afforded cyclic ether **523**, which was then transformed to bipolarolide A (**524**). Under similar conditions, etherification of sidechain-elongated compound **525** led to cyclic ether **526**, which was converted to bipolarolide B (**86**) in a one-pot operation *via* allylic oxidation and ester reduction (Scheme 86). The authors found that the addition of amide **527** was crucial for the electrochemical oxidation as it effectively suppressed competing decomposition pathways, likely functioning as a sacrificial agent under high-voltage conditions that protected both the substrate and the products.

In summary, oxidation of sp^3 C–H bonds is a powerful strategy for functionalizing otherwise inert sites in organic molecules, significantly shortening and streamlining natural product syntheses. Transition-metal catalysts enable oxidation of sp^3 C–H bonds to alcohols or carbonyl compounds but often require a directing group or a carefully designed catalyst for effective site and stereochemical control. Enzymatic sp^3 C–H oxidation offers remarkable regio- and stereo-selectivity under mild aqueous conditions, making it highly attractive in natural product synthesis despite the need to screen and optimize the enzyme for a particular type of substrate. Photo- and electro-chemical methods utilize light and electrons as green energy inputs, eliminating stoichiometric oxidants, and thus facilitating sustainable sp^3 C–H oxidation. Overall, sp^3 C–H oxidation is still in its infancy, and hence more efficient and broadly applicable methods still need to be developed.

7. Addendum

7.1. Concise total synthesis of ambiguine P

Ambiguine P (**528**) belongs to the hapalindole-type natural products. In 2025, Li, Yang and co-workers reported a remarkably concise six-step synthesis of this challenging target from 2,2-dimethylcycloheptanone (Scheme 87).[180] Their synthetic strategy was inspired by the biosynthesis of this indole family and highlighted by a newly developed Cope/Prins/Friedel–Crafts cascade reaction. In this seven-reaction, six-step total synthesis, four reactions are oxidative transformations. Among them, three steps involve dehydration reactions: (1) C3-chlorination of tricyclic indole derivative **530** with *t*-BuOCl/i-Pr_2NEt, followed by DBU-promoted elimination of HCl and tautomerization to afford dehydrogenated product **531**; (2) DDQ-mediated dehydrogenation at C10–C11 of pentacyclic intermediate **534** delivered from the key Cope/Prins/Friedel–Crafts cascade reaction to afford compound **535** as an inseparable mixture; and (3) once again, *t*-BuOCl/i-Pr_2NEt-initiated chlorination–HCl elimination–tautomerization of **535** to afford



Scheme 89 Total syntheses of the naturally occurring antiviral indolosesquiterpene alkaloids, xiamycins C–F by Bisai and co-workers.

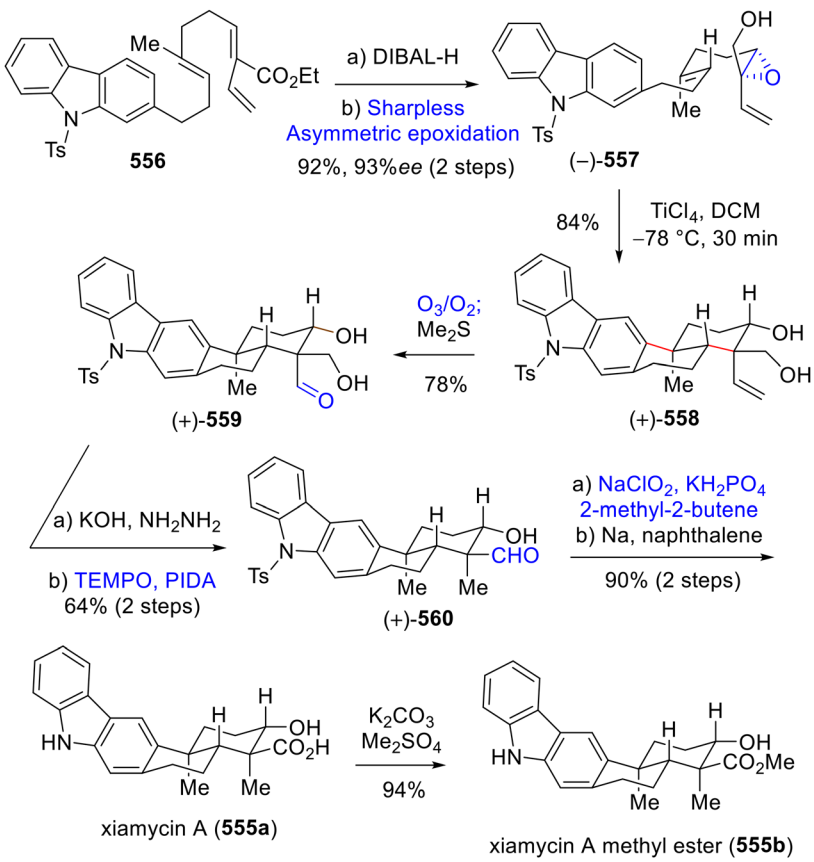
triene **537**, which was subjected to *in situ* hydroxylation of **537** at C15 under Rawal conditions[181] [KHMDS, $P(OMe)_3$, and O_2], producing the desired ambiguine P (**528**) in 43% yield, along with its C15-epimer in 19% yield. Notably, more than 100 mg of ambiguine P was prepared through this route.

7.2. Total synthesis and late-stage C–H oxidations of *ent*-trachylobane natural products

It is now recognized that a sophisticated two-phase strategy for terpene biosynthesis is adopted in nature, involving a cyclase phase to build the skeletons and oxidase phase to functionalize them.[2d,182,183] By mimicking this approach, the efficient total synthesis of several terpenes has been achieved, with the most well-known one being Baran's two-phase synthesis of Taxol.[184] For the "oxidase phase", chemical C–H oxidation constitutes a highly desirable yet challenging tactic. In 2022, Magauer and co-workers reported the total synthesis of *ent*-trachylobane natural products,[185] in which late-stage C–H oxidations were employed to synthesize *ent*-3β-acetoxy-trachyloban-19-al (**538**) and 11-oxo-*ent*-trachyloban-19-oate (**539**) (Scheme 88). After preparing ample amounts of *ent*-trachylobanes **540** and **541**, they first attempted the undirected C–H oxidation. Among the reported protocols tried, Curci's methyl (trifluoromethyl)dioxirane (TFDO),[186] Baran's electrochemical conditions, and Ru(TMP)(CO) (**542**) gave C-11 selective oxidation products **543**, **544**, and **539**, respectively. Next, alcohol **545** was employed for exploring directed oxidation. Employing the Suárez oxidation protocol, the reaction of **545** afforded C-20 iodide **546** in 28% yield as the sole product. Alternatively, by converting alcohol **545** to imine **547**, and exposing the latter to copper(II) nitrate trihydrate and hydrogen peroxide, followed by acetylation, terpene **538** was obtained in 32% yield.

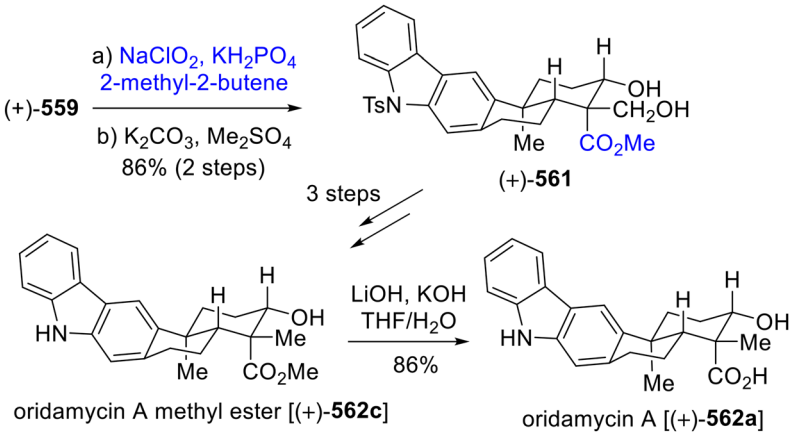
7.3. Total syntheses of naturally occurring antiviral indolosesquiterpene alkaloids xiamycins C–F

Indolosesquiterpene alkaloids including xiamycins and oridamycins are a class of architecturally complex natural products possessing important biological activities such as antimicrobial, antiviral, antitumor, immunomodulatory, and enzyme inhibitory activities, and are promising inhibitors against nsp10 of SARS-CoV-25 pathogenicity. In 2022, Bisai and co-workers reported the concise total syntheses of the naturally occurring antiviral indolosesquiterpene alkaloids xiamycin C (**548a**), D (**548b**), E (**548c**) and F (**548d**) *via* late-stage oxidative δ-Csp^3–H functionalization of an advanced pentacyclic enone intermediate.[187] The synthesis started from a naturally occurring diterpenoid, dehydroabietic acid methyl ester, which was converted to deoxyxiamycin A methyl ester in four steps. *N*-Tosylation followed by benzylic oxidation using CrO_3 in acetic acid (Jones oxidation) furnished ketone **549** in 70%

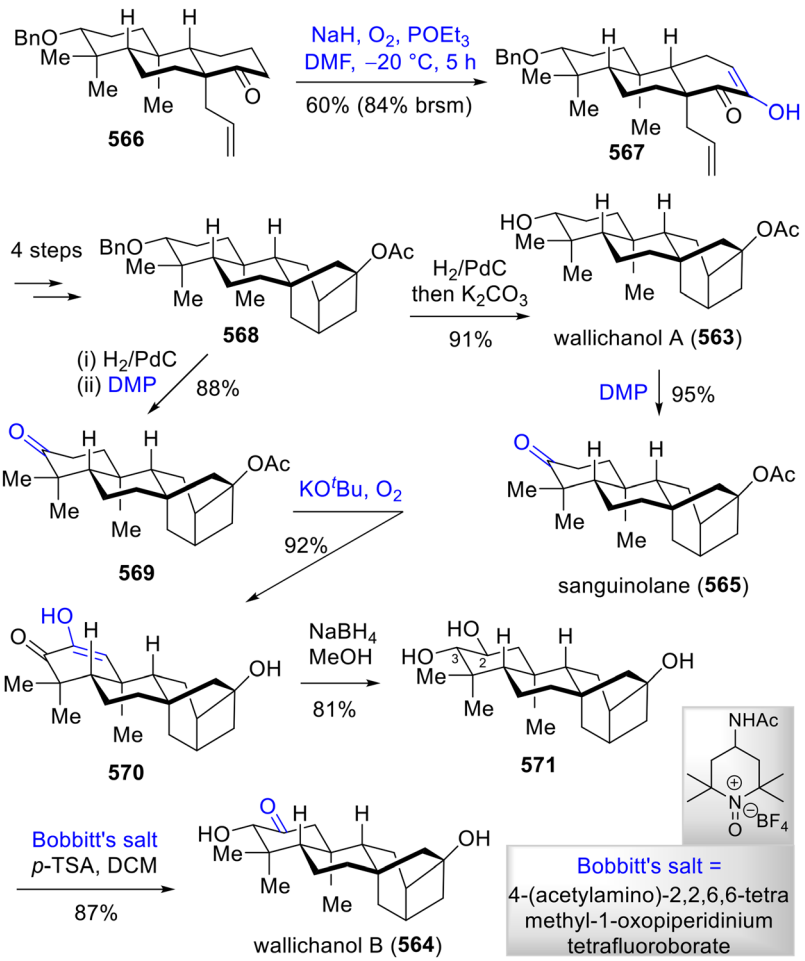


Scheme 90 Total synthesis of xiamycin A by Bisai and co-workers.

yield over 2 steps. After attempting several oxidative conditions for the ketone (**550**) to enone (**551**) transformation, three protocols including a two-step protocol and two one-pot methods, Saegusa–Ito oxidation and oxidation with SeO_2, were established for this desaturation reaction. After extensive experimentation, regioselective Csp^3–H functionalization of **551** was achieved by treating **551** with NBS in the presence of catalytic sulfuric acid in acetic anhydride to afford product **552** in 86%



Scheme 91 Total synthesis of oridamycin A by Bisai and co-workers.



Scheme 92 Concise enantioselective total syntheses of the rearranged *ent*-trachylobane diterpenoids, (–)-wallichanols A and B by Dethe and co-workers.

yield. DBU-promoted elimination followed by allylic oxidation with SeO_2 provided bis-enone **554** in 82% yield. The latter was converted into xiamycin D (**548b**) in four steps. Selective oxidation of the benzylic alcohol in xiamycin D (**548b**) with MnO_2 furnished xiamycin E (**548c**) in 79% yield. Saponification of xiamycin E (**548c**) yielded xiamycin F (**548d**) in 72% yield. The latter was converted to xiamycin C (**548a**) by diastereoselective reduction with $NaBH_4$ (Scheme 89).

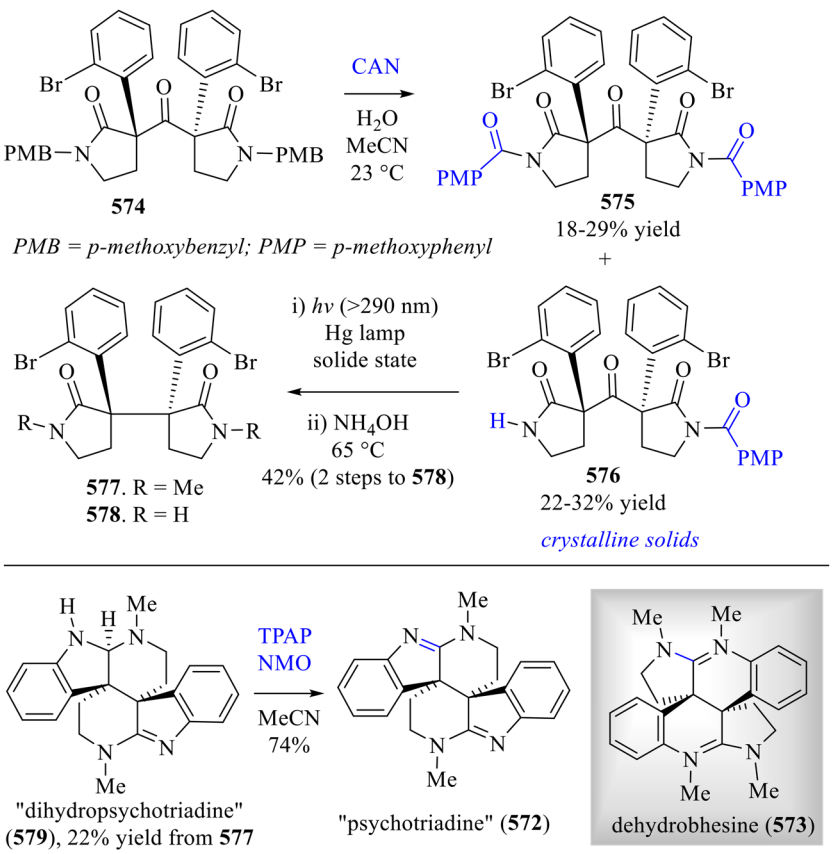
7.4. Total synthesis of (+)-oridamycins A and B

Continuing synthetic efforts by Bisai and co-workers on indolosesquiterpene alkaloids allowed them to report, in 2024, the collective total synthesis of (+)-oridamycins A and B and xiamycin A (**555a**) and xiamycin A methyl ester (**555b**) by a unified strategy.[188] Oxidation reactions were extensively employed in the second half of their synthesis. Firstly, Sharpless asymmetric epoxidation was employed not only to build the initial chiral centers, but also laid the foundation for the key $TiCl_4$-mediated epoxy-ene-aryl double cyclization to afford the common intermediate (+)-**558**. Oxidative cleavage of the vinyl moiety in **558** afforded dihydroxy aldehyde (**559**) in 78% yield. The latter was subjected to Wolff–Kishner reduction and chemoselective oxidation of the primary alcohol with TEMPO/PIDA, which provided the β-hydroxy aldehyde (**560**) in 64% yield over 2 steps. Pinnick oxidation of the aldehyde group in **560** furnished the corresponding carboxylic acid, which was detosylated to afford xiamycin A (**555a**) in 90% yield over 2 steps (Scheme 90).

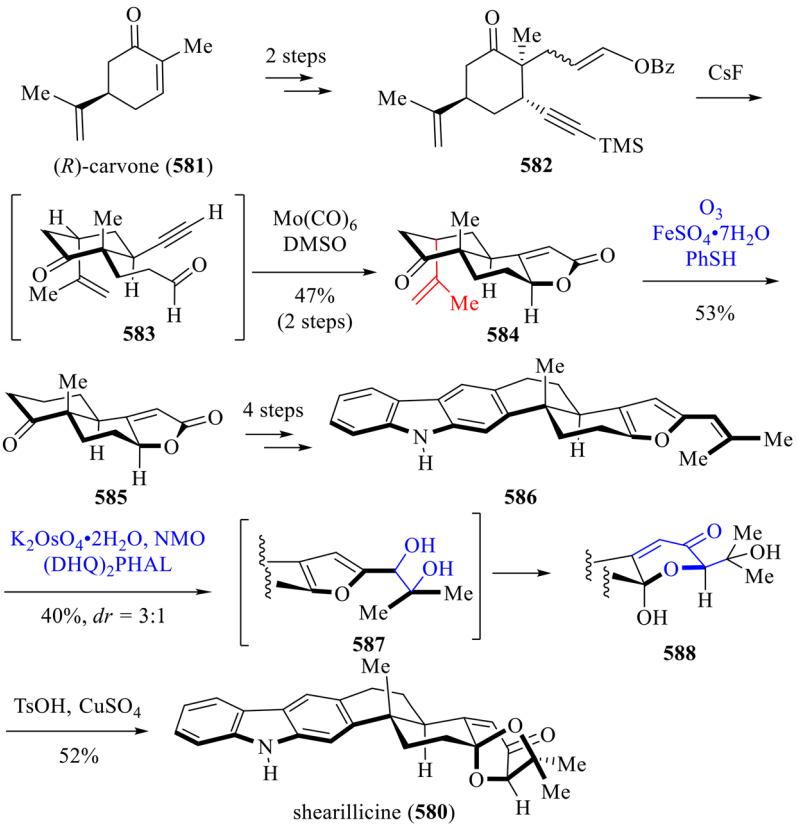
On the other hand, Pinnick oxidation of aldehyde (**559**) followed by esterification afforded *N*-tosyl oridamycin B methyl ester (**561**). Selective deoxygenation reaction of the primary alcohol in **561** by the Barton–McCombie protocol, *N*-detosylation, and saponification completed the total synthesis of oridamycin A (**562a**) (Scheme 91).

7.5. Concise enantioselective total syntheses of rearranged *ent*-trachylobane diterpenoids (–)-wallichanols A and B

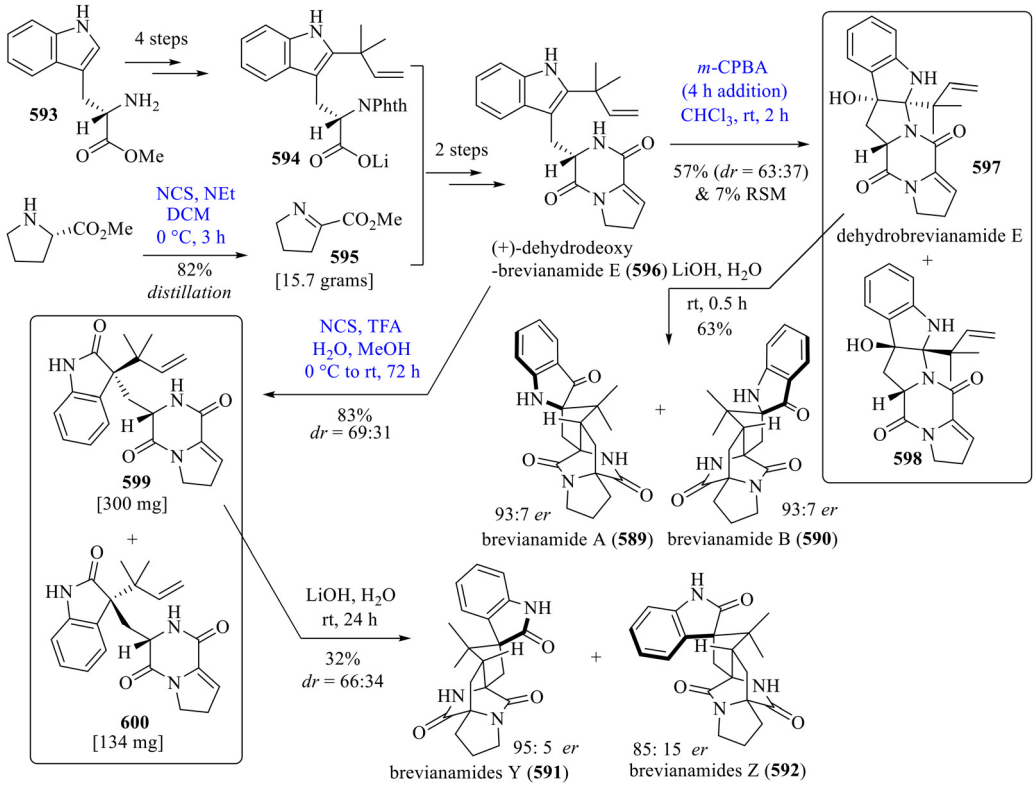
Wallichanol A (**563**) and wallichanol B (**564**) are two rearranged *ent*-trachylobane diterpenoids isolated from the medicinal herb *Euphorbia wallichii*, which has long been used in Tibetan folk medicine to treat edema and various skin ailments, including abscesses, eruptions, and anthrax infections. In 2025, Dethe and coworkers disclosed the first enantioselective total syntheses[189] of these two natural products, and structurally related sanguinolane (**565**), isolated from *Stillingia sanguinolenta*. Five oxidation reactions were employed in the total syntheses, with four carried out at the later stage of the total syntheses. Aerobic oxidation of the α-carbon adjacent to the carbonyl group in compound **566** based on literature precedents[190] proved to be non-trivial. After systematic screening



Scheme 93 Total synthesis of a bis(cyclotryptamine) alkaloid by Garcia-Garibay/Garg and co-workers.



Scheme 94 First total synthesis of shearilicine by Newhouse and co-workers.

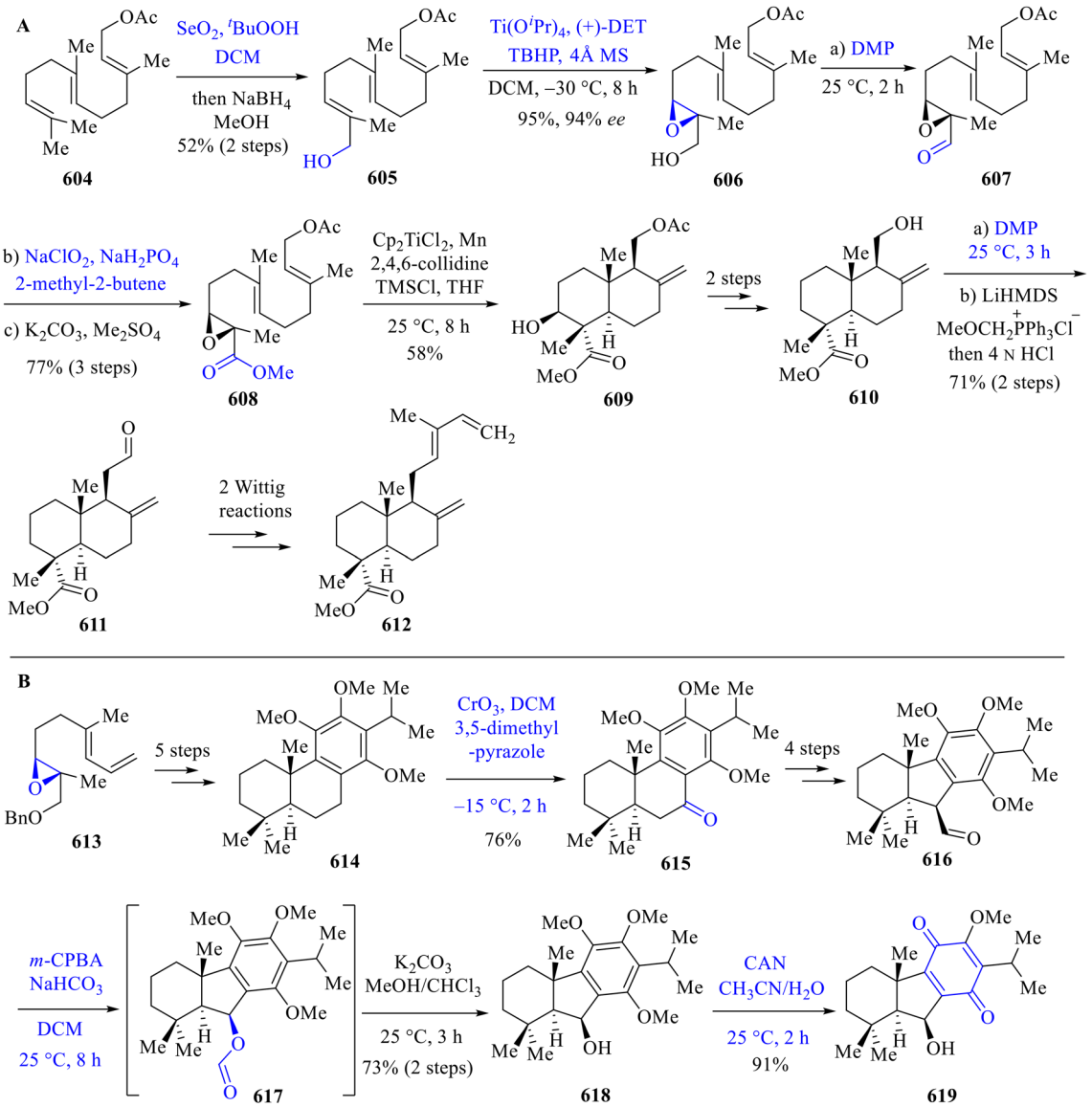


Scheme 95 Unified total synthesis of the brevianamide alkaloids by Lawrence and co-workers.

of several reaction parameters, the optimal conditions were defined, involving the use of NaH and $POEt_3$ in DMF under an O_2 atmosphere at −20 °C for 5 h. Under these conditions, the oxidized product **567** was obtained in 60% isolated yield (84% brsm). The Dess–Martin oxidation was used twice, one for the oxidation of wallichanol A (**563**) to sanguinolane (**565**), and the other for the transformation of the common intermediate **568** into ketone **569**. The latter was subjected to another aerobic oxidation of the ketone α-carbon, which was efficiently achieved using KO*t*Bu in *t*BuOH under an oxygen atmosphere and proceeded with concomitant deacetylation to afford **570**. The last required oxidation involved the challenging chemoselective mono-oxidation of the carbinol at C2 of triol **571**. After unsuccessful attempts with several oxidants such as PDC, PCC, and DMP, the combination of *p*-toluenesulfonic acid and Bobbitt's salt (4-AcNH-TEMP=O$^+$ BF4$^-$),[191–193] an oxoammonium salt, proved effective, affording the desired selective oxidation product (–)-wallichanol B (**564**) in 87% yield (Scheme 92).

7.6. Total synthesis of a bis(cyclotryptamine) alkaloid bearing the elusive piperidinoindoline scaffold

In their synthetic efforts towards bis(cyclotryptamine) alkaloids, Garcia-Garibay and Garg proposed that the product they obtained was a natural product, named "psychotriadine (**572**)".[194] Its synthesis features a stereospecific solid-state photodecarbonylation reaction to introduce the key vicinal quaternary stereocenters. In an attempt to perform oxidative cleavage of the *p*-methoxybenzyl (PMB) moieties from *N*,*N*′-diPMB-protected bis-pyrrolidin-2-one ketone using ceric ammonium nitrate (CAN), imides **575** and **576**, intermediates of PMB cleavage by CAN, were isolated in low yields. The unan-



Scheme 96 Syntheses of the two segments **612** (A) and **619** (B) for the total synthesis of taiwaniadducts I, J, and L.

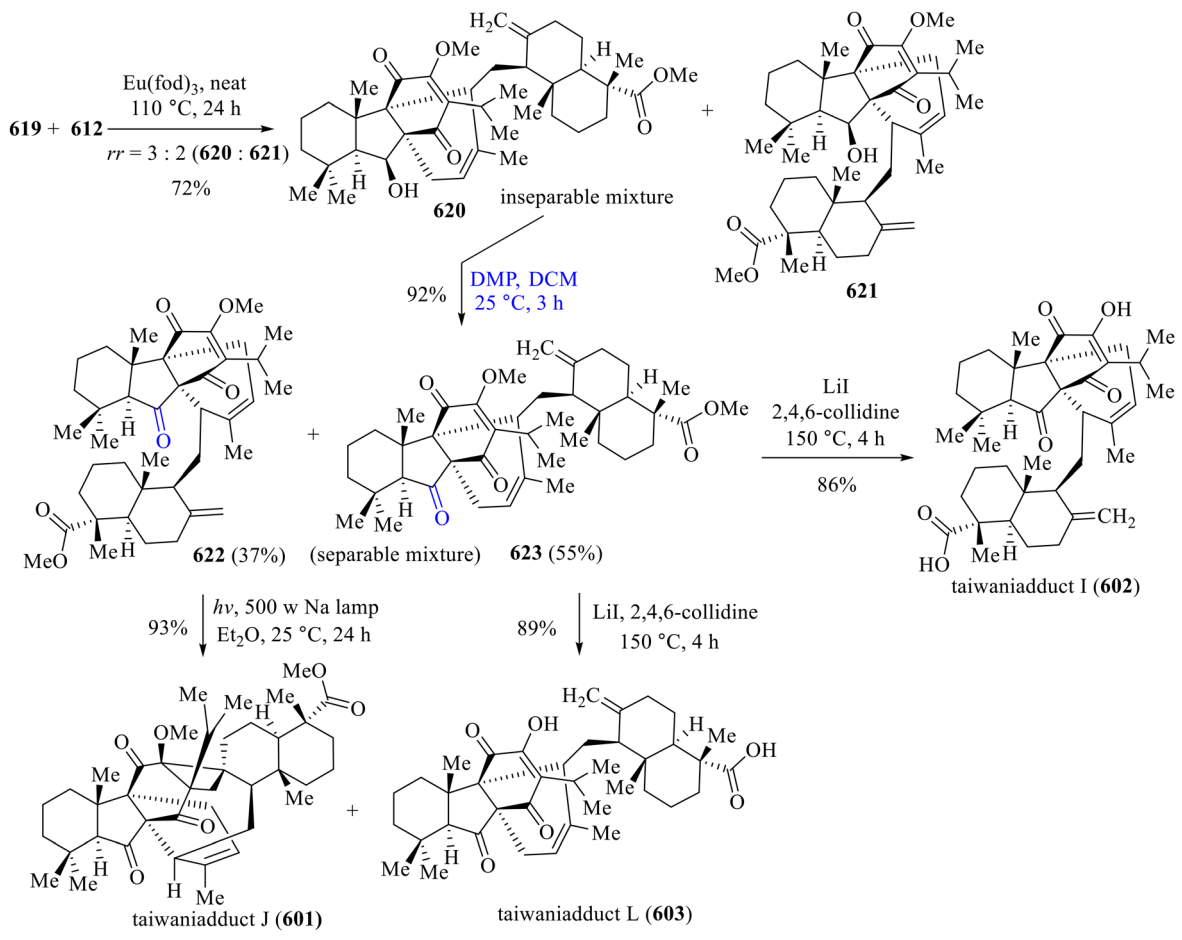
ticipated isolation of crystalline products allowed them to realize the key photodecarbonylation reaction of **576** to afford **578** after *N*-deprotection. In a late-stage, **579** was subjected to Ley–Griffith oxidation, affording compound **572** in 74% yield. This compound was found to spectroscopically match that of a previously unidentified compound during the isolation of dehydrobhesine (**573**)[195] and was named "psychotriadine" (Scheme 93).

7.7. Total synthesis of (+)-shearilicine

In 2023, Newhouse and co-workers reported the first total synthesis of the indole diterpenoid shearilicine, which was realized in 11 steps.[196] In their synthesis route, the isopropylidene moiety in **584** needed to be excised. Although oxidative cleavage of the C=C bond is a routine transformation realizable by several methods such as ozonolysis, $C(sp^3)$–$C(sp^2)$ bond cleavage is rare. They found that Kwon's hydrodealkenylative $C(sp^3)$–$C(sp^2)$ bond fragmentation method using ozone, an iron salt, and a hydrogen atom donor[197] was well-suited to achieve the desired transformation. Using this protocol, enantioenriched **585** was obtained in 53% yield. The highly oxidized terminal ring was constructed at a late-stage. When subjecting carbazole **586** to Sharpless dihydroxylation at low temperature with an extended reaction time, the furan diol product **587** underwent a tandem Achmatowicz rearrangement, affording the desired diol **588** in 40% yield with a dr of 3 : 1. Treatment of **588** with TsOH and $CuSO_4$ led to shearilicine (**580**) (Scheme 94).

7.8. Unified total synthesis of the brevianamide alkaloids enabled by chemical investigations into their biosynthesis

In 2022, Lawrence and co-workers reported the full details of their synthetic efforts to gain insight into the chemical feasibility of a proposed network of biosynthetic pathways towards the brevianamide family alkaloids, which resulted in the total synthesis of all known bicyclo[2.2.2]diazaoctane brevianamides.[198] Dehydroproline **595**, a component for the synthesis of their proposed (bio)synthetic intermediate (+)-dehydrodeoxybrevianamide E (**596**), was prepared in practical quantities from proline methyl ester using *N*-chlorosuccinimide as the oxidant (Scheme 95). Diastereoselective tandem oxidation–cyclization of **596** turned out to be challenging. A variety of oxidants (*e.g.* peroxy acids, singlet oxygen, dioxiranes, oxaziridines, and *m*-CBPA) were attempted for this transformation. However, they all led to the formation of two diastereomers, **597** and **598**, in low diastereoselectivities. Noteworthy is that



Scheme 97 Completion of the enantioselective total synthesis of taiwaniadducts I, J, and L by Bisai and co-workers.

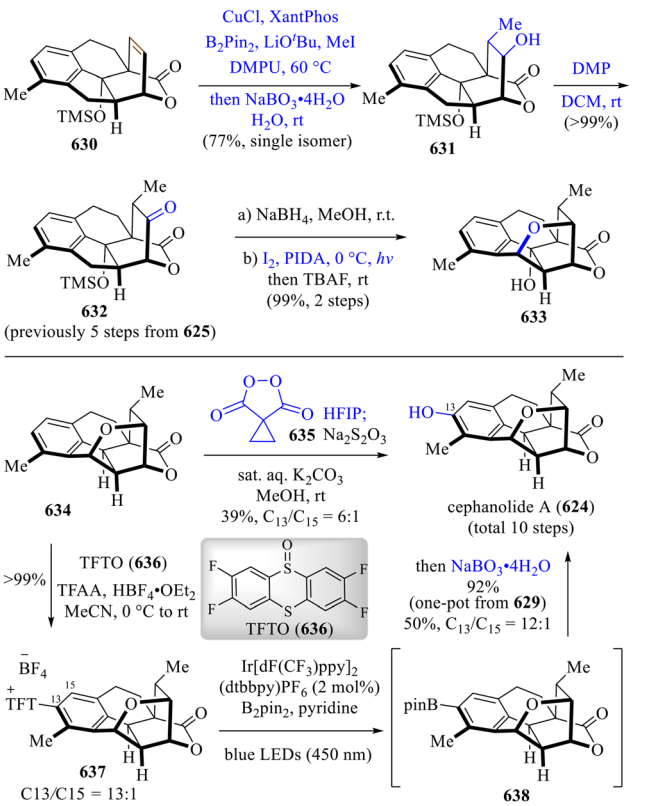
use of Davis chiral oxaziridine resulted in a relatively clean reaction but with no diastereoselectivity. The best result was obtained when using *m*-CBPA as the oxidant, which afforded dehydrobrevianamide E (**597**) and **598** in 57% combined yield with a modest dr of 63 : 37. Brief exposure of dehydrobrevianamide E (**597**) to LiOH in water at room temperature produced the natural (+)-enantiomers of brevianamide A (**589**) and B (**590**) with the bicyclo[2.2.2]diazaoctane ring system formed in a combined 63% yield. As an alternative to oxidation with *m*-CPBA, treating (+)-dehydrodeoxybrevianamide E (**596**) with *N*-chlorosuccinimide and aqueous trifluoroacetic acid resulted in the direct formation of oxindoles **599** and **600** in excellent yield and with a diastereoselectivity of 69 : 31. Exposing the major diastereomer oxindole **599** to LiOH led to the [4 + 2] adduct (+)-brevianamide Y (**591**) in 32% combined yield as the major diastereomer.

7.9. Enantioselective total synthesis of taiwaniadducts I, J, and L

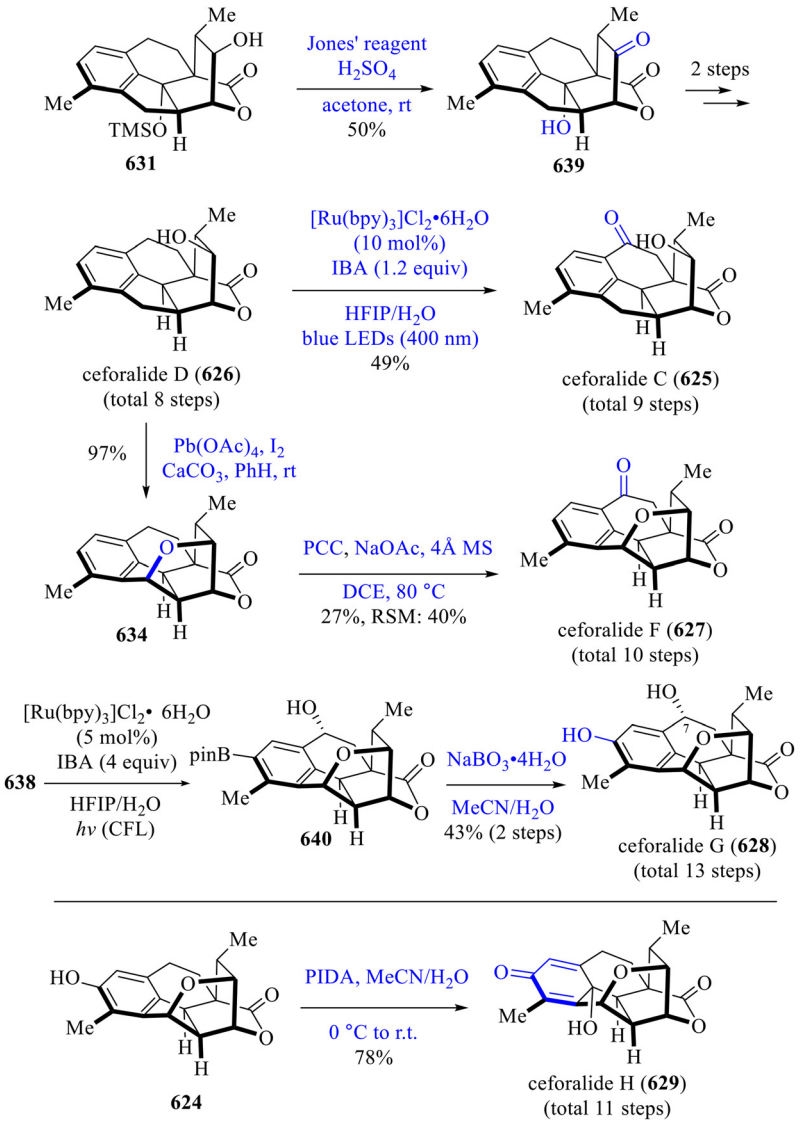
Taiwaniaquinoids are a class of tetraterpenoids isolated from the endemic evergreen species *Taiwania cryptomerioides*, which exhibited impressive biological activities. In 2025, Bisai and co-workers disclosed the enantioselective total synthesis of taiwaniadducts I, J, and L.[199] For the structurally most complex taiwaniaquinoid, taiwaniadduct J (**601**), bioinspired Diels–Alder cycloaddition and [2 + 2] cycloaddition were employed to construct its skeleton and multiple quaternary centers. In the asymmetric synthesis of *trans*-ozic acid methyl ester (diene), five oxidation reactions were used. (1) Site-selective allylic oxidation of commercially available 2*E*,6*E*-farnesyl acetate (**604**) afforded allylic alcohol **605** in 52% yield based on recovered starting materials (brsm) (Scheme 96). (2) Sharpless catalytic asymmetric epoxidation of **605** afforded epoxy alcohol **606** in 95% yield with 94% ee. (3) Dess–Martin periodinane (DMP) oxidation of **606** followed by (4) Pinnick oxidation and methylation of the resultant carboxylic acid gave **608** in 77% yield over 3 steps. In addition to the four consecutive oxidation reactions, the primary alcohol in **610** was oxidized with DMP to afford the corresponding aldehyde. This set the stage for three sequential Wittig reactions to afford the desired diene component **612**. For the asymmetric synthesis of abeo-abietane diterpenoid **619** as the dienophile component, enantiopure epoxy-ether diene **613** was converted, in five steps, to compound **614**. Following the protocol reported by Li,[200,201] **614** was converted to diazoketone **615** *via* benzylic oxidation with CrO_3/3,5-dimethylpyrazole. In the subsequent five-step transformations, three oxidation reactions were employed, including DMP oxidation, Bayer–Villiger oxidation of aldehyde **616**, and ceric(IV) ammonium nitrate (CAN)-mediated oxidative dearomatization to produce *p*-benzoquinone derivative **619** (Scheme 96). After the key Diels–Alder reaction, the resulting inseparable mixture was subjected, one again, to DMP oxidation, which facilitated the separation of two regioisomeric adducts **622** and **623**. Demethylation of **622** and **623** and light-promoted [2 + 2]-cycloaddition of compound **622** completed the first total syntheses of taiwaniadducts I, L and J respectively (Scheme 97).

7.10. Unified total syntheses of benzenoid cephalotane-type norditerpenoids: cephanolides and ceforalides

Cephanolides and ceforalides are benzenoid cephalotane-type norditerpenoids isolated by Yue's group from *Cephalotaxus sinensis*[202] and the seeds of *Cephalotaxus fortunei* var. *alpine*,[203] respectively. In 2022, Sarpong and co-workers developed a unified strategy for the total syntheses of all of the known cephanolides and five recently isolated ceforalides **624–629** in 8–13 steps from commercially available hydroxyindanone.[176] Although the authors did not mention the concept of two-phase synthesis, their approach is likely to be the case. The key pentacyclic core **630** was efficiently prepared in four steps from hydroxyindanone. For the elaboration of **630**, they first developed an efficient and highly regioselective method for direct alkene difunctionalization that relies on borocupration. Under the optimized conditions, **630** was converted into the desired methyl boronic ester in 83% yield as a single isomer. Subjecting **630** to tandem methyl-boration–oxidation led to methyl alcohol **631** in 77% yield as a single isomer. DMP oxidation of **631** and reduction of the resulting ketone yielded the desired *endo*-oriented alcohol, which was subjected to Suaŕez oxidation[204] and one-pot cleavage of TMS to afford hexacyclic compound **633** in excellent yield (99%) over two steps. Although compound **634**, obtained *via* Barton–McCombie's deoxygenation protocol, could be converted to cephanolide A by treating with malonoyl peroxide (**635**) and subsequent hydrolysis, the authors were not satisfied with the yield (39%)



Scheme 98 Total synthesis of the benzenoid cephalotane-type norditerpenoid, cephanolide A by Sarpong and co-workers.



Scheme 99 Total syntheses of the benzenoid cephalotane-type norditerpenoids, ceforalides C, D, F, G, H by Sarpong and co-workers.

and selectivity (6 : 1) and developed a stepwise approach consisting of C–H thianthrenation with TFTO (**636**), under photocatalytic borylation of **637** to yield boronic ester **633**, and one-pot oxidation of the resulting Bpin moiety gave rise to **624** in 92% yield. In this second phase, 4/5 or 4/6 steps involve oxidative transformations (Scheme 98).

In the synthesis of ceforalides, several oxidation reactions have been employed. The Jones oxidation of common intermediate **631** under acidic conditions resulted in concomitant alcohol oxidation and desilylation, affording ketoalcohol **639** in 50% yield, which was converted into ceforalide D (**626**) in three steps. Chemoselective selective benzylic oxidation in the presence of the free secondary alcohol group in **626** was achieved using a photoredox-catalysis strategy with hypervalent iodine[205] to afford ceforalide C (**625**) in 49% yield. For the synthesis of ceforalide F (**627**) from **626**, two consecutive oxidative transformations were used: photoirradiation of **626** with $Pb(OAc)_4$, I_2, and $CaCO_3$ gave **634** in 97% yield, and C7 benzylic oxidation of the latter using PCC gave ceforalide F (**627**). The three-step transformation of compound **637** to ceforalide G (**628**) also involved two oxidation reactions: (1) photoredox oxygenation of intermediate **638** using a compact fluorescent light (CFL) instead of blue light-emitting diodes (LEDs) (400 nm) afforded alcohol **640** selectively and (2) oxidation of the Bpin moiety with $NaBO_3{\cdot}4H_2O$ afforded ceforalide G (**628**) in 42% yield over 2 steps. Lastly, phenyliodine(III) diacetate (PIDA)-mediated oxidative dearomatization of **624** selectively gave rise to **629** in 78% yield as a single constitutional isomer (Scheme 99).

8. Summary and outlook

In summary, oxidation reactions are a class of indispensable transformations in organic synthesis, particularly in the total

synthesis of biologically active natural products. As can be seen from the twenty cases surveyed, oxidation reactions often serve as key steps in a total synthesis, and the percentage of the oxidation steps can exceed 40% of all the synthetic steps of a total synthesis. Because about 50% of the US FDA approved drugs are developed from/or inspired by natural products, the abovementioned conclusion could also reflect the situation in the pharmaceutical industry. Thus, it is our expectation that synthetic chemists, in particular those in the field of total synthesis of natural products, and medicinal chemists will find the information summarized in this review helpful for their research. Additionally, because both the total synthesis of natural products and the synthesis of structurally complex medicinal agents can rely heavily on oxidation reactions, this constitutes the major driving force for the development of oxidation chemistry. According to the highlighted total syntheses, on one hand, we witness how novel oxidation reactions, protocols, and reagents such as Mukaiyama hydration, oxidative cyclization/cycloaddition, and C–H oxidation can facilitate total syntheses. On the other hand, we have to admit that the chemistry of oxidation is underdeveloped. Actually, most oxidation protocols involve stoichiometric reactions, and the safety of oxidants remain a concern, even for the widely used IBX.[206] All these highlighted issues will prompt organic chemists to develop safer, catalytic oxidation reactions featuring high selectivity, versatility, and high redox economy.[207]

Author contributions

JFZ, AC and PQH wrote the paper. YJG was responsible for the artwork and references.

Conflicts of interest

The authors declare no other competing interests.

Data availability

The data supporting this article have been included as part of the article.

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