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Metal-hydride hydrogen atom transfer (MHAT) reactions in natural product synthesis

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The metal-hydride hydrogen atom transfer (MHAT) reaction plays an important role in the field of natural product synthesis. MHAT, as a powerful method, has been employed by chemists to construct C–C, C–H, and C–heteroatom bonds. In this review, we summarize the recent total synthesis of natural products using MHAT to functionalize olefins with first-row transition metal catalysts such as cobalt, manganese and iron.

1. Introduction

Functionalization of olefins has been an important transformation in synthetic chemistry. In particular, functionalization of unactivated olefins is a difficult task. The metal-hydride hydrogen atom transfer (MHAT) reaction plays an important role in functionalization of olefins.

In 1979, Tabushi achieved the hydration of cyclohexene under Mn-catalyzed conditions employing $NaBH_4$ and air.[1] In 1989, Mukaiyama reported Co-catalyzed hydration of olefins utilizing alcohol as the solvent and reductant,[2] and he subsequently used silicon hydride as the hydrogen source instead of alcohols.[3] In the following decades, the hydride atom transfer reaction using silicon hydride as the hydrogen source has been greatly developed, and diverse types of MHAT reactions have been reported. Researchers including Carreira,[4] Shenvi,[5] Herzon,[6] Baran,[7] and Boger[8] and many others expanded the MHAT reaction. They reported the construction of carbon–carbon, carbon–heteroatom and carbon–hydrogen bonds from olefins, based on the generation of carbon-centered radicals. In light of the development, the application of MHAT reactions in total synthesis of natural products is booming, especially in recent years. In 2016 and 2018, Shenvi reviewed the development of metal-hydride hydrogen atom transfer reactions.[9] There were also some related reviews disclosed afterward.[10] This review focuses on the natural product synthesis employing the MHAT reaction as the key strategy, and basically covers

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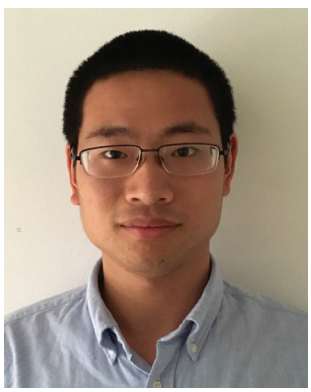

Jinghua Wu

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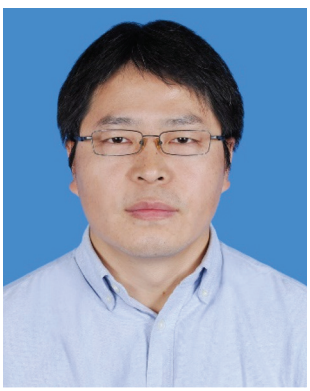

Zhiqiang Ma

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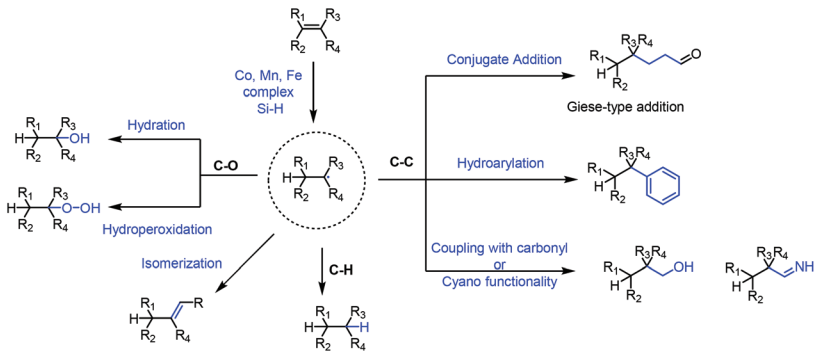


Fig. 1 MHAT-based reactions of olefins.

the examples reported after 2016. We have basically divided the review into four sections based on the type of bond formation, including C–C, C–O, and C–H bonds, and isomerization as shown in Fig. 1. We will summarize the construction of C–C bonds from olefins through MHAT first, including conjugate addition, hydroarylation, and addition to carbonyl or cyano groups. Next, hydration and hydroperoxidation of olefins are discussed. Hydrogenation of olefins and isomerization are discussed last.

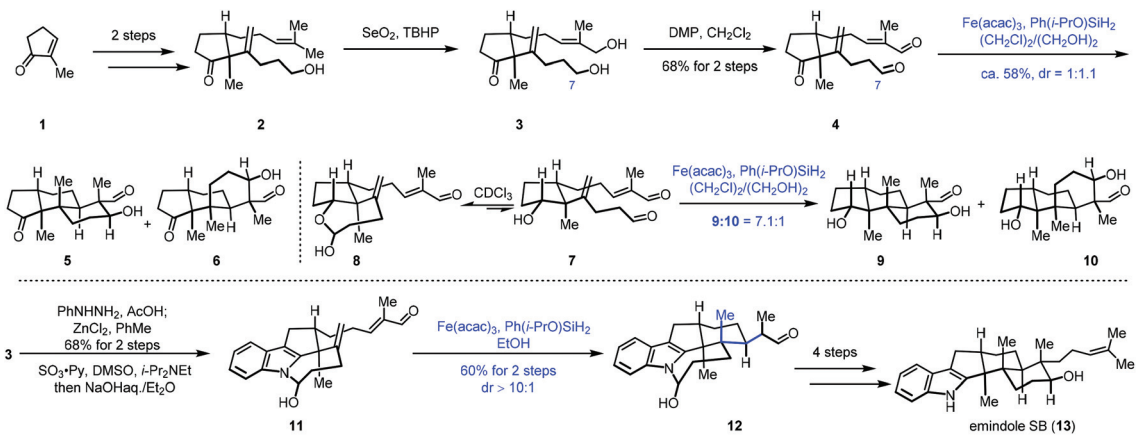
2. C–C bond formation

Based on the proposed mechanism of the MHAT reaction, carbon-centered radicals would be formed from olefins *via* MHAT, and diverse types of reactions, such as conjugate addition, hydroarylation, and addition to carbonyl or cyano groups, occur when different radical acceptors are present.

2.1 Conjugate addition

Addition of nucleophilic radicals to electron-deficient olefins is called the Giese reaction,[11] which is a useful approach for C–C bond construction. In 2010, Ishibashi reported iron-catalyzed radical cyclization of 1,6-dienes.[12] Subsequently in 2014, Baran developed cross-coupling of unactivated olefins and electron-deficient olefins under mild conditions with $Fe(acac)_3$ or $Fe(dibm)_3$ as catalysts and $PhSiH_3$ as the hydrogen source. Baran's work has greatly expanded the application of MHAT in the construction of C–C bonds. They further realized the cross-coupling reaction of heteroatom-substituted olefins with electron-deficient olefins.[7]

This powerful method was uitilized by Pronin to accomplish the synthesis of emindole SB (**13**).[13] In 2015, Pronin and co-workers employed iron-catalyzed intramolecular conjugate addition and aldol reaction to achieve polycyclization (Scheme 1). Their synthesis commenced with the cyclopentanone derivative **1**, which was transformed to **2** *via* a two-step sequence. Continuous oxidation gave **4**. The authors then tried to achieve polycyclization of **4** to establish the tricyclic core of emindole SB (**13**) *via* Fe-catalyzed HAT reaction. Under the conditions ($Fe(acac)_3$, $Ph(i\text{-}PrO)SiH_2$, $(CH_2Cl)_2$, and EtOH), the polycyclization occurred through conjugate addition and aldol reaction, giving tricyclic core products **5** and **6** with a 1 : 1.1 dr. The authors found that the C7 aldehyde of **4** existed predominantly in its hemiacetal form in alcoholic solvents, and then they proposed that reversible cyclic hemiacetal intermediates would be formed when a hydroxyl group instead of a ketone group is present in the precursor. Indeed, substrate **7** existed



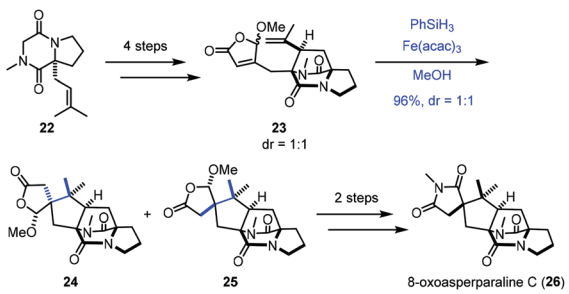
Scheme 1 Pronin's synthesis of emindole SB (**13**).

as a 1 : 2 mixture with the corresponding cyclic hemiacetal **8**. The authors envisioned that the cyclic hemiacetal of **8** could allow for the desired stereocontrol over the initial radical cyclization. As expected, exposure of **7** to similar polycyclization conditions with lower temperature delivered a mixture of **9** and **10** with a 7.1 : 1 dr, favoring the desired scaffold **9**. Accordingly, the authors speculated that the hemiaminal intermediate resulting from an indole N–H could induce similar stereoselective cyclization. A Fischer indole synthesis from **3** followed by oxidation furnished a dialdehyde, which was transformed to hemiaminal **11** in the presence of NaOH. Upon exposure of hemiaminal **11** to the conditions of $Fe(acac)_3$ and $Ph(i\text{-}PrO)SiH_2$, conjugate addition occurred, providing the pentacyclic intermediate **12** in 60% yield over two steps. In this conversion, three stereocenters were established with excellent selectivity. Lastly, a four-step sequence was performed to give emindole SB (**13**).

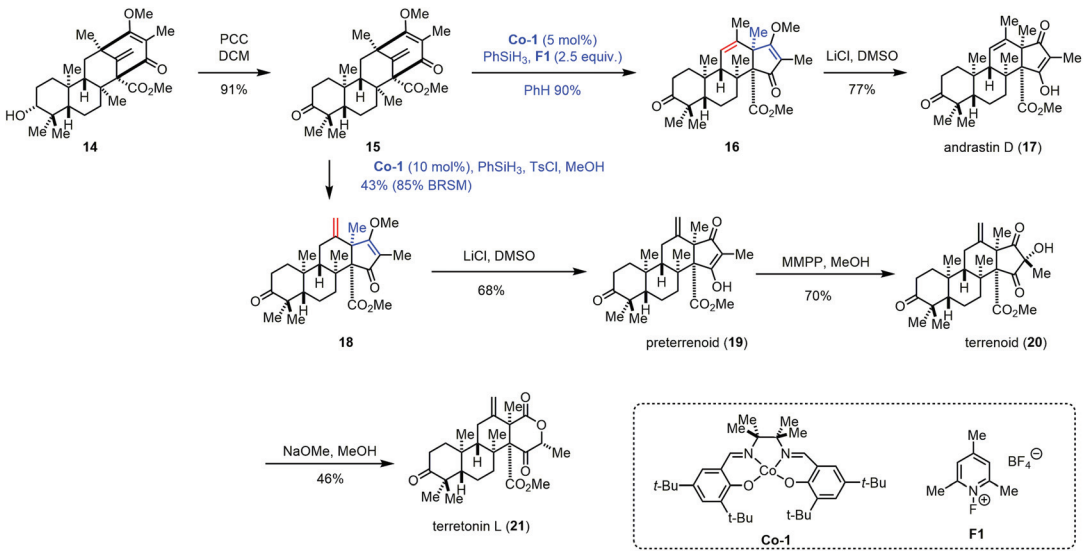
In 2017, Maimone and co-workers achieved the syntheses of andrastin D (**17**), preterrenoid (**19**), terrenoid (**20**), and terretonin L (**21**) (Scheme 2).[14] Their syntheses started with **14**, an intermediate in the synthesis of berkeleyone A.[15] **14** could be oxidized to **15** with PCC, which was further converted into **16** *via* a rearrangement reaction with the intermediacy of carbocations that were generated by the modified Shigehisa conditions (cat. Co-**1**, $PhSiH_3$, and **F1**).[16] The authors observed that increasing the equivalents of **F1** and $PhSiH_3$ from 1.0 to 2.5 could furnish **16** in 90% yield. The authors also tested a variety of Brønsted acids, and it turned out that these acidic conditions failed to induce the expected rearrangement. With **16** in hand, a Krapcho-type demethylation provided andrastin D (**17**). In 2008, Carreira reported the hydrochlorination of unactivated olefins under Co-catalyzed HAT in the presence of *para*-toluenesulfonyl chloride (TsCl).[4f] Compared to conventional hydrochlorination reactions, Carreira's method has good functional group compatibility. Under Carreira's conditions,[4f] Maimone and co-workers observed that a terretonin core skeleton (**18**) could be formed preferentially from **15**, which was then advanced to preterrenoid (**19**), terrenoid (**20**), and terretonin L (**21**).

In 2017, Jahn employed Baran's reductive radical cyclizations to achieve the synthesis of 8-oxoasperparaline C (**26**) (Scheme 3).[17] In the event, γ-methoxybutenolide **23** was prepared from **22** *via* a four-step sequence. Treatment of **23** with $Fe(acac)_3$ and $PhSiH_3$ generated the corresponding tertiary radical, which underwent Giese-type radical conjugate addition with an unsaturated γ-butyrolactone moiety to give **25** and the undesired diastereomer **24**. The authors proposed that the methoxy group controls the stereoselectivity of cyclization, in which the tertiary radical approached the butenolide moiety from the opposite face. A subsequent two-step sequence led to 8-oxoasperparaline C (**26**) from **25**.

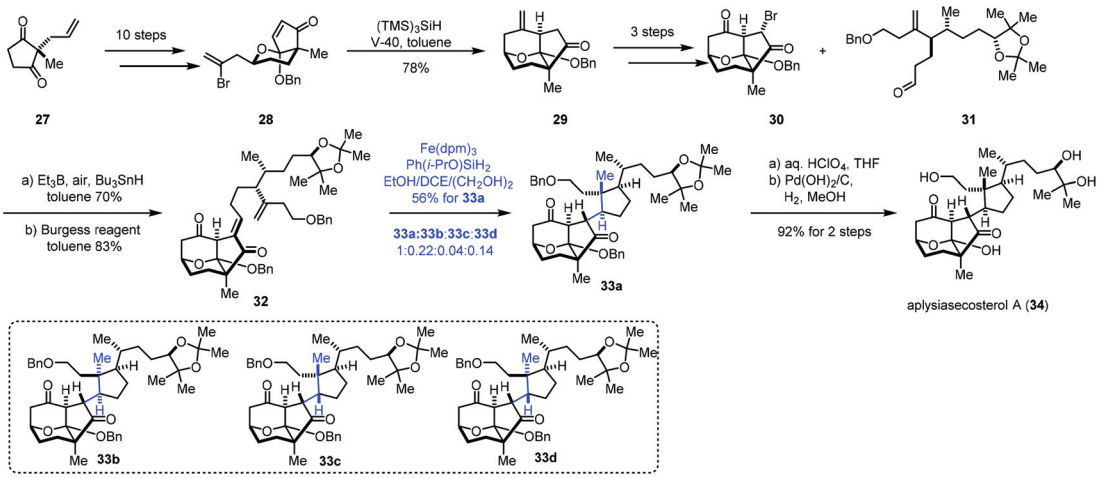
In 2018, Li and co-workers employed MHAT-based radical cyclization to complete the synthesis of aplysiasecosterol A (**34**) (Scheme 4).[18] α,β-Unsaturated enone **28** could be obtained from **27** *via* a ten-step sequence. An intramolecular radical cyclization took place under the conditions of V-40 and $(TMS)_3SiH$ furnishing the tricyclic scaffold **29**. Subsequently, a three-step sequence provided **30**. Coupling of **30** and another



Scheme 3 Jahn's synthesis of 8-oxoasperparaline C (**26**).



Scheme 2 Maimone's synthesis of andrastin and terretonin meroterpenes.

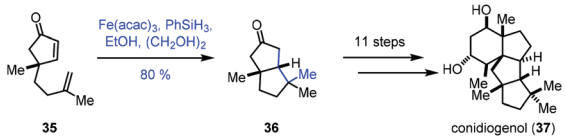


Scheme 4 Li's synthesis of aplysiasecosterol A (**34**).

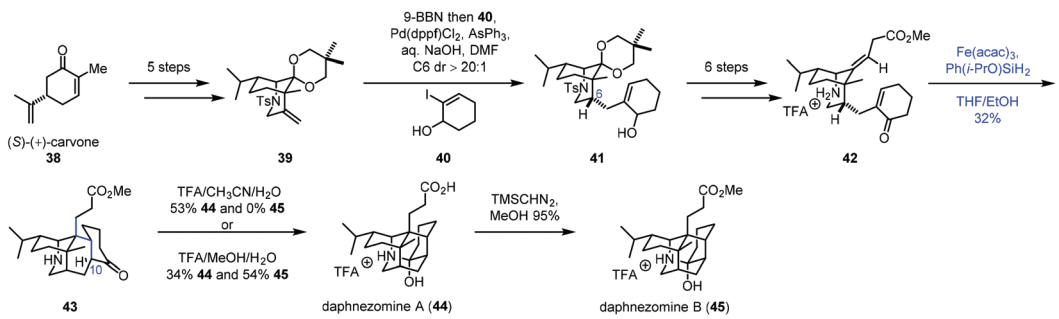
segment **31** under the Oshima conditions let to an *anti*-aldol product, which was dehydrated to give **32**. Initially, the authors tried the conditions ($Fe(acac)_3$, $PhSiH_3$, $EtOH/(CH_2OH)_2$) reported by Baran, and a mixture of four cyclization products (**33a–33d**) was obtained in 60% yield, in which the desired product **33a** was obtained in just 25% yield due to the poor diastereoselectivity (**33a** : **33b** : **33c** : **33d** = 1 : 0.33 : 0.47 : 0.58). Switching the silicon reagent to the more reactive Ph(*i*-PrO)SiH_2 used by Shenvi improved the diastereoselectivity (**33a** : (**33b** + **33c** + **33d**) = *ca.* 1 : 1). The authors then screened other iron complexes. They observed that the more bulky 1,3-diketone ligands like diisobutyrylmethanate (dibm) and dipivaloylmethanate (dpm) gave better stereoselectivity (**33a** : (**33b** + **33c** + **33d**) = *ca.* 1.7–2.5 : 1). Finally, under the optimal conditions ($Fe(dpm)_3$, Ph(*i*-PrO)SiH_2, and $EtOH/DCE/(CH_2OH)_2$), **33a** was prepared in 56% yield. Aplysiasecosterol A (**34**) was obtained from **33a** in two steps including acetonide hydrolysis and debenzylation.

In 2019, Snyder reported the synthesis of conidiogenol (**37**) by a quaternary-centre-guided synthetic strategy (Scheme 5).[19] They employed radical conjugate addition initiated by iron-catalyzed HAT to furnish the bicyclic ketone **36** as a single diastereomer.

In 2020, Li and co-workers employed radical cyclization *via* iron-catalyzed HAT to accomplish the synthesis of (−)-daphnezomines A (**44**) and B (**45**) (Scheme 6).[20] In practice, carvone was transformed to **39** *via* a five-step sequence. Upon exposure of **39** to 9-BBN, followed by Suzuki–Miyaura coupling with **40**, desired **41** was obtained. Treatment of **41** with a six-step sequence gave **42**. To build the core skeleton structure, they tried *ene* cyclization and anionic cyclization, which turned out to be unfruitful. They finally resorted to MHAT-based radical cyclization. Under the conditions developed by Baran ($Fe(acac)_3$, $PhSiH_3$, and EtOH), the *trans*-fused adduct **43** was afforded in 16% yield as a single product. The authors proposed that the C10–H of **43** was delivered from the ammonium proton of **42** *via* a 1,5-proton transfer, which accounts for the *trans*-fused ring junction. Further screening of the conditions revealed that the desired cyclization product **43** could be prepared in 32% yield under the conditions of $Fe(acac)_3$ and



Scheme 5 Snyder's synthesis of conidiogenol (**37**).



Scheme 6 Li's synthesis of (−)-daphnezomines A (**44**) and B (**45**).

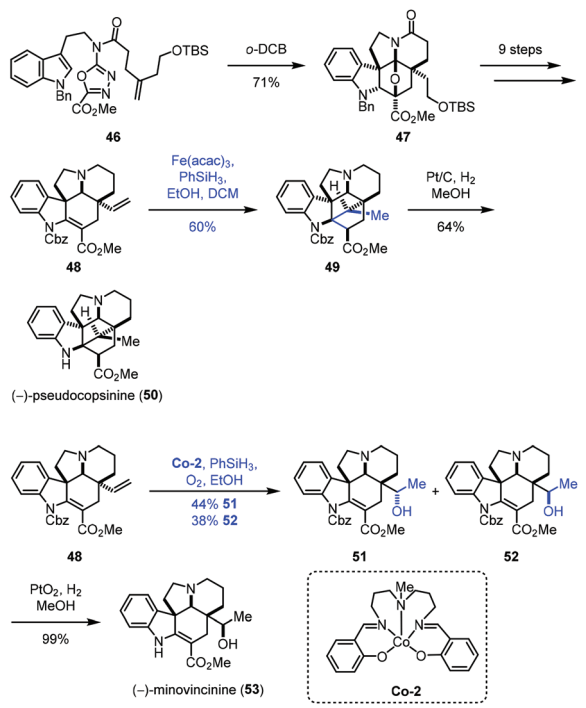
$Ph(i\text{-}PrO)SiH_2$ in THF/EtOH. The fact that the radical pathway worked in this case is perhaps a testament to its insensitivity to steric crowding.[7b] Lastly, in the presence of TFA, **43** was transformed to daphnezomines A (**44**) and B (**45**).

In 2020, Boger and co-workers disclosed the synthesis of (−)-pseudocopsinine (**50**) and (−)-minovincinine (**53**) (Scheme 7).[21] They employed the diene **48** as the common intermediate, from which different MHAT conditions were adopted to approach the target molecules. A sequential intramolecular [4 + 2] cycloaddition and [3 + 2] cycloaddition of **46** led to **47**, which was followed by functional group transformations to give the key intermediate **48**. Treatment of **48** with Fe $(acac)_3$ and phenylsilane provided **49** and its undesired epimer in 80% yield with good diastereoselectivity (3 : 1), favoring **49**. The authors observed that the yield of the cyclization increased with increasing $Fe(acac)_3$ catalyst (1.5 *vs.* 0.5 equiv.) and time (2 *vs.* 16 h) and using a less reactive silicon reductant ($PhSiH_3$ *vs.* $Ph(i\text{-}PrO)SiH_2$). (−)-Pseudocopsinine (**50**) was then obtained from **49** under conditions of Pt/C and H_2. Meanwhile, treating **48** with the Co catalyst **Co-2** furnished a pair of hydration products, the desired diastereomer **52** and its epimer in a nearly 1 : 1 ratio. Other attempted metal complexes such as Mn $(acac)_3$, $Fe_2(ox)_3$, FePc, $Fe(NO_3)_3$, $Fe_2(SO_4)_3$, $Fe(acac)_3$, $Fe(dpm)_3$ and $Co(acac)_2$ all gave inferior results. (−)-Minovincinine (**53**) was formed after deprotection of **52**.

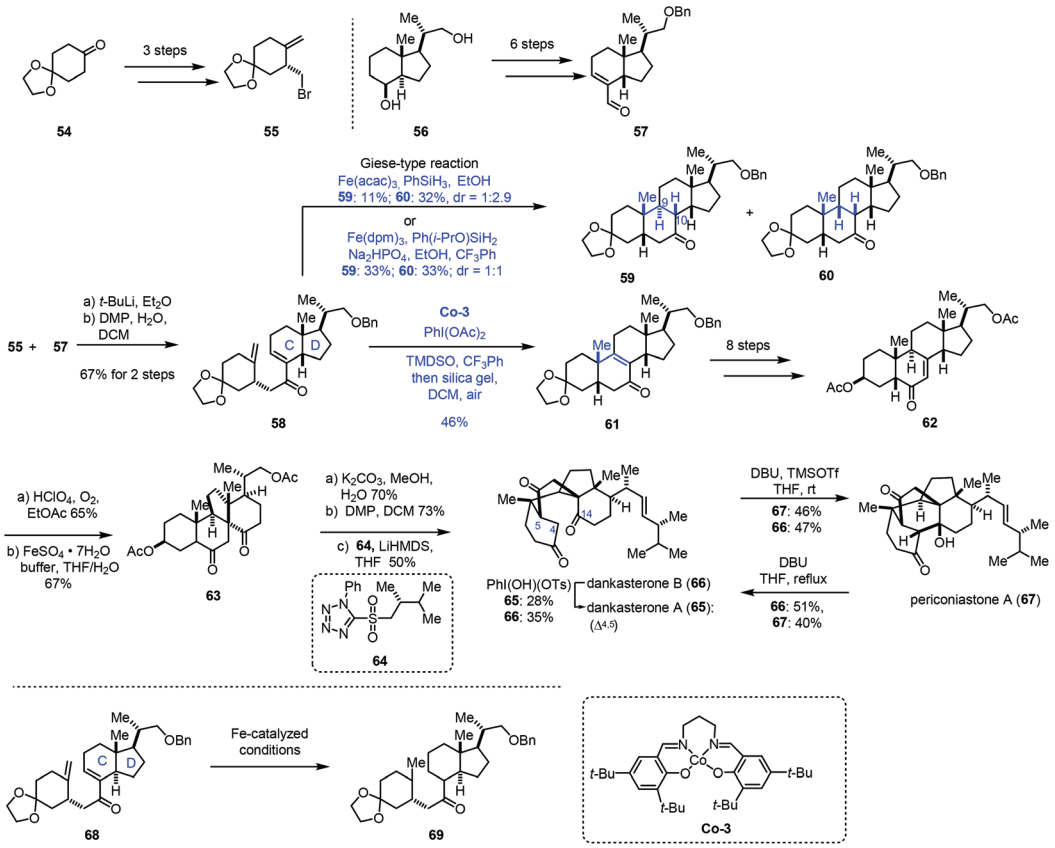
In 2021, Ma and co-workers achieved the synthesis of dankasterones A (**65**) and B (**66**) and periconiastone A (**67**) (Scheme 8).[22] They employed Co-catalyzed HAT-based radical cyclization to furnish a [6,6,6,5] tetracyclic core. Fragment **55** could be prepared from **54** *via* a three-step sequence. In parallel, fragment **57** was afforded from **56** in six steps. **55** and **57** were coupled through halogen lithium exchange and nucleophilic addition, which was followed by oxidation to give enone **58**. Exposure of the *cis*-fused C/D ring substrate **58** to Fe-catalyzed HAT conditions ($Fe(acac)_3$, $PhSiH_3$, EtOH) gave a pair of diastereomers **59** and **60** (dr = 1 : 2.9) *via* Giese-type radical conjugate addition, favoring undesired **60**. Screening of different Fe(III) catalysts, silane reagents, additives, solvents and temperatures showed that the optimal conditions ($Fe(dpm)_3$, $Ph(i\text{-}PrO)SiH_2$, Na_2HPO_4, EtOH, and CF_3Ph) resulted in better diastereoselectivity (dr = 1 : 1). Since the yield of the desired cyclization product **59** from a Giese type reaction mediated by Fe was still low, the authors extended the catalyst to Mn and Co. While the Mn-catalyzed systems used were messy, subjecting **58** to **Co-3**-catalyzed HAT conditions with an *N*-fluoropyridinium oxidant afforded the cycloisomerization product **61** in 23–27% yield. Screening of oxidants revealed that $PhI(OAc)_2$ was optimal, delivering **61** in 46% yield. In this conversion, $PhI(OAc)_2$ might serve as the oxidant to oxidize Co(II) to Co(III) and facilitate the dehydrogenation. It is noteworthy that, in contrast to the *cis*-fused C/D ring substrate **58**, they found that the *trans*-fused C/D ring substrate **68** under Fe-catalyzed HAT conditions just gave the bis-reduced product **69** without cyclization. Enone **62** was then furnished from **61** in eight steps. Through C–H oxidation and radical rearrangement, **63** was afforded. Lastly, deacetylation, oxidation and Julia–Kocienski olefination gave dankasterone B (**66**), which could be transformed into dankasterone A (**65**) and periconiastone A (**67**).

In their synthetic studies towards wortmannin, Zhou and co-workers used HAT-based radical cyclization to install the tetracyclic core of wortmannin with an Fe catalyst (Scheme 9).[23] Their findings also demonstrated that a *cis*-fused C/D ring was the key to the desired cyclization since they observed that the substrate containing a *trans*-fused C/D ring failed to produce the desired product under the same conditions.

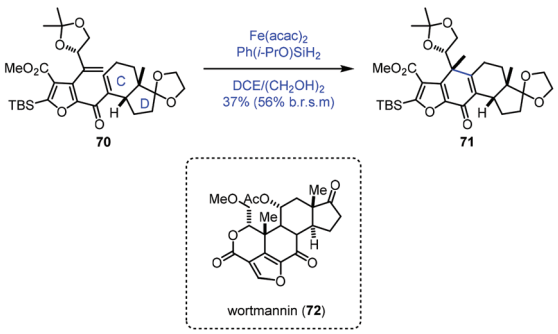
In 2017, Liu and co-workers accomplished the synthesis of hispidanin A (**82**),[24,25] in which they creatively employed iron-catalyzed radical polyene cyclization to furnish *trans*-decalin (Scheme 10). Compound **74** could be provided from **73** in four steps. Coupling **74** with Grignard reagent **75** in the presence of $FeCl_3$ afforded **76**. Oxidative operation of furan of **76** and a subsequent rearrangement provided the cyclization precursor **77**. Under the conditions of $Co(acac)_2$ or $Mn(dpm)_3$ as the catalyst, no desired product was detected probably because of the failure of radical initiation at the terminal alkene. Switching the catalyst to $Fe(acac)_3$ resulted in the desired radical polyene cyclization, giving the tricyclic compound **78** with 45% yield over 2 steps, along with an inseparable mixture of another three diastereomers in 19% combined yield. In this conversion, the radical initiated at the *gem*-disubstituted alkene went through a stereoselective cascade radical polycyclization process. As a result, the desired *trans*-decalin architecture bearing four contiguous stereogenic centers was obtained as



Scheme 7 Boger's synthesis of (−)-pseudocopsinine (**50**) and (−)-minovincinine (**53**).



Scheme 8 Ma's synthesis of dankasterones A (**65**) and B (**66**) and periconiastone A (**67**).



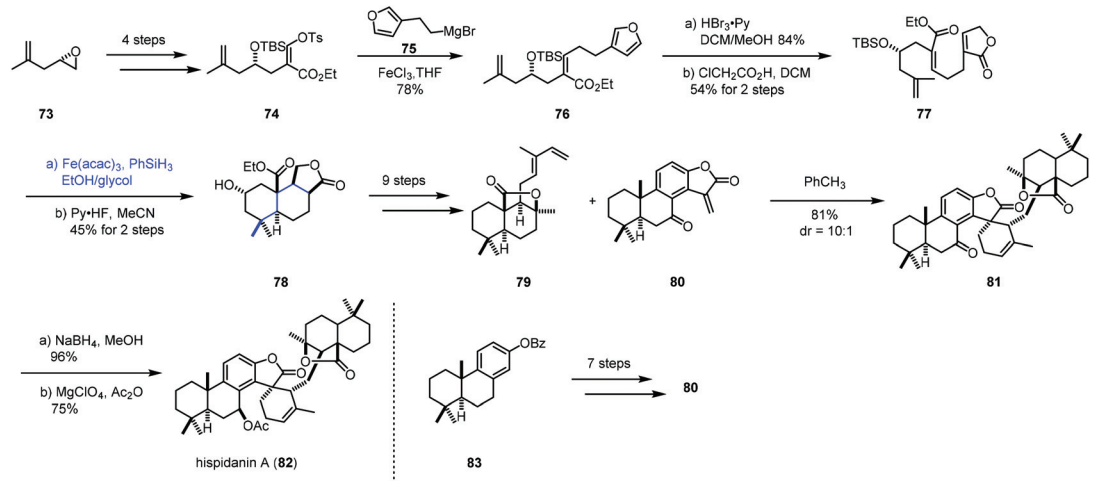
Scheme 9 Zhou's synthesis of the tetracyclic core of wortmannin.

the major product. In comparison, Pattenden's work[26] showed that the *cis*-isomer was isolated as the major product when an acyl radical initiated the polyene process with a similar substrate. After nine steps of transformations from **78**, **79** was obtained. At the same time, the dienophile fragment **80** was constructed using Yamamoto's cationic polyene cyclization. Next, a Diels–Alder cycloaddition between diene **79** and dienophile **80** occurred, furnishing **81**. Reduction with $NaBH_4$ followed by acetylation gave hispidanin A (**82**).

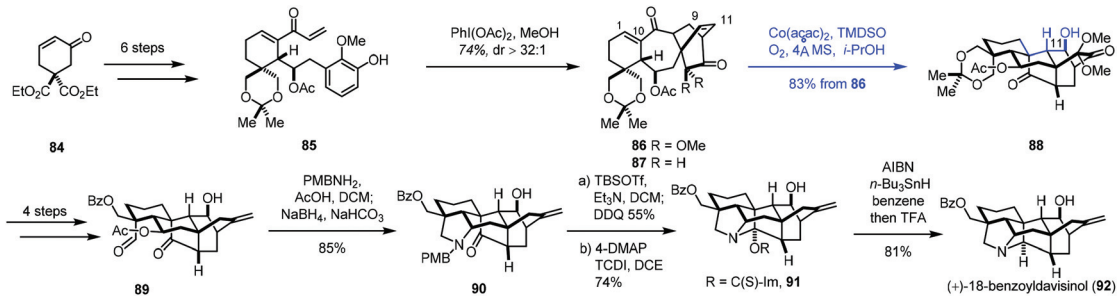
Very recently, Ding and co-workers communicated the synthesis of (+)-18-benzoyldavisinol (**92**) featuring a HAT-initiated transannular redox radical cyclization (Scheme 11).[27] Commercially available cyclohexenone **84** could be advanced to **85** in six steps. An oxidative dearomatization-induced-Diels–Alder cycloaddition furnished **86**. Additional transformations gave **87**. Initially, the authors expected to achieve reductive radical cyclization with an epoxide precursor (epoxidation of C9–C11 double bonds); however, the epoxidation of **87** was difficult. As such, the authors resorted to MHAT-based radical cyclization to create the core skeleton. After using the Fe catalysts, the expected cyclization products were not obtained.

They observed a hydration reaction occurring at the C1–C10 olefin of **86** under $Mn(acac)_2$ conditions, giving the corresponding alcohol at the C10 position. Encouraged by the results, the authors began to investigate Co catalysts. They found that the expected radical cyclization reaction took place from **86** under the conditions ($Co(acac)_2$, TMDSO, *i*-PrOH, O_2, 4 Å MS), giving **88** in 83% yield. The reaction is remarkable as two highly strained rings and three contiguous stereogenic centers were created in the cascade process. With **88** in hand, a four-step sequence and a reductive amination reaction furnished **90**. (+)-18-Benzoyldavisinol (**92**) was then prepared *via* hemiaminal formation and ensuing deoxygenation.

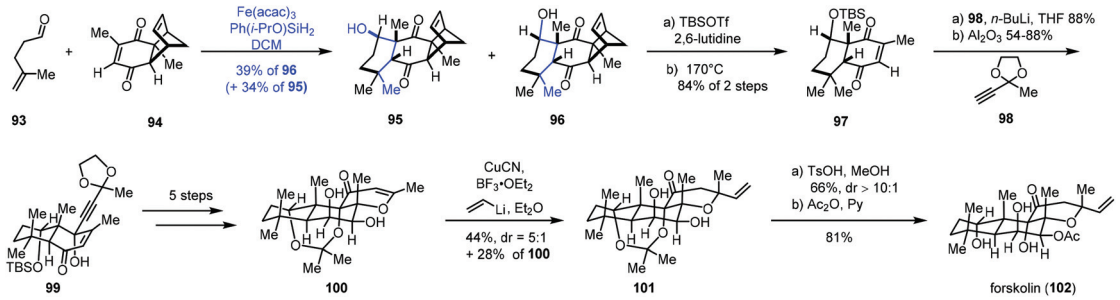
In 2019, Pronin and co-workers developed a new intermolecular annulation method between α,β- and γ,δ-unsaturated carbonyl compounds to furnish six-membered carbocycles through MHAT-initiated radical-polar crossover reaction. By taking advantage of the new method, they com-



Scheme 10 Liu's synthesis of hispidanin A (**82**).



Scheme 11 Ding's synthesis of (+)-18-benzoyldavisinol (**92**).



Scheme 12 Pronin's synthesis of forskolin (**102**).

pleted the synthesis of forskolin (**102**) (Scheme 12).[28] A radical tandem reaction between γ,δ-unsaturated aldehyde **93** and enone **94** gave cyclization products **95** and desired **96** as a pair of diastereomers (dr = 1 : 1). Although the diastereoselectivity was low, the reaction was scalable and allowed for the production of multigram quantities of **96**. In addition, the undesired epimer **95** could be converted to **96** after an oxidation and reduction process in 87% yield. Treatment of **96** with a two-step sequence including protection and retro-Diels–Alder reaction, followed by nucleophilic addition and epimerization, gave **99**. After five steps, **99** could be transformed to **100**. Forskolin (**102**) was then afforded through conjugate addition, deprotection and acetylation.

2.2 Hydroarylation

In addition to electron-deficient olefins corresponding to conjugate addition, aryl groups could be used as the terminator in MHAT reactions. We will systematically introduce applications of hydroarylations of unactivated olefins triggered through MHAT-based reactions in this section. Traditional methods such as Friedel–Crafts alkylation usually require vigorous reaction conditions to activate olefins.[29] There are also many

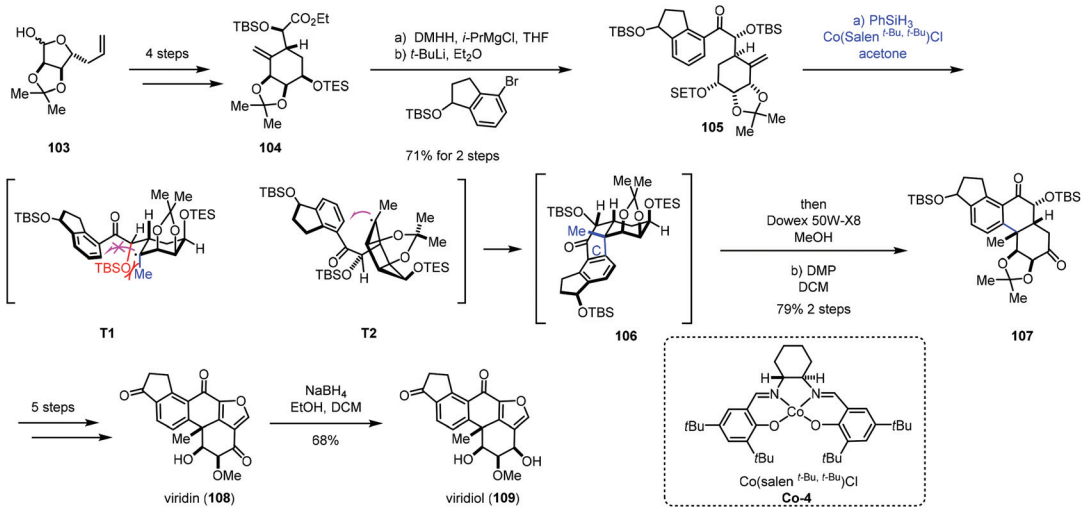
reports showing transition metal-mediated addition of aromatic C–H bonds across olefins with high regio- and chemoselectivity.[30] While metal catalysts usually involve expensive and toxic metals, compared to the above methods, MHAT-based hydroarylations would serve as an alternative to hydroarylation of unactivated olefins.

In 2019, Gao and co-workers completed the total synthesis of viridin and viridiol,[31] in which they employed Co-catalyzed hydroarylation reaction to close the C-ring (Scheme 13). Their synthesis commenced with **104**, which was prepared from **103** *via* a four-step sequence. Treatment of **104** with DMHH and *i*-PrMgBr afforded Weinreb amide, which was attacked by aryl lithium to furnish **105**. Under conditions of **Co-4** and $PhSiH_3$, the intramolecular radical hydroarylation occurred to form the tetracyclic core **106** with excellent diastereoselectivity. The authors rationalized the stereochemistry of MHAT cyclization through analysis of the radical intermediates **T1** and **T2**. There is a steric effect between the OTBS and the methyl in **T1** and no such effect in **T2**. Therefore, the intermediate **T2** is a favorable transition state to generate the tetracyclic core **106**. Sequential deprotection and oxidation delivered **107**. Five additional steps were carried out to give viridin (**108**). Viridin (**108**) could be converted to viridiol (**109**) by selective reduction.

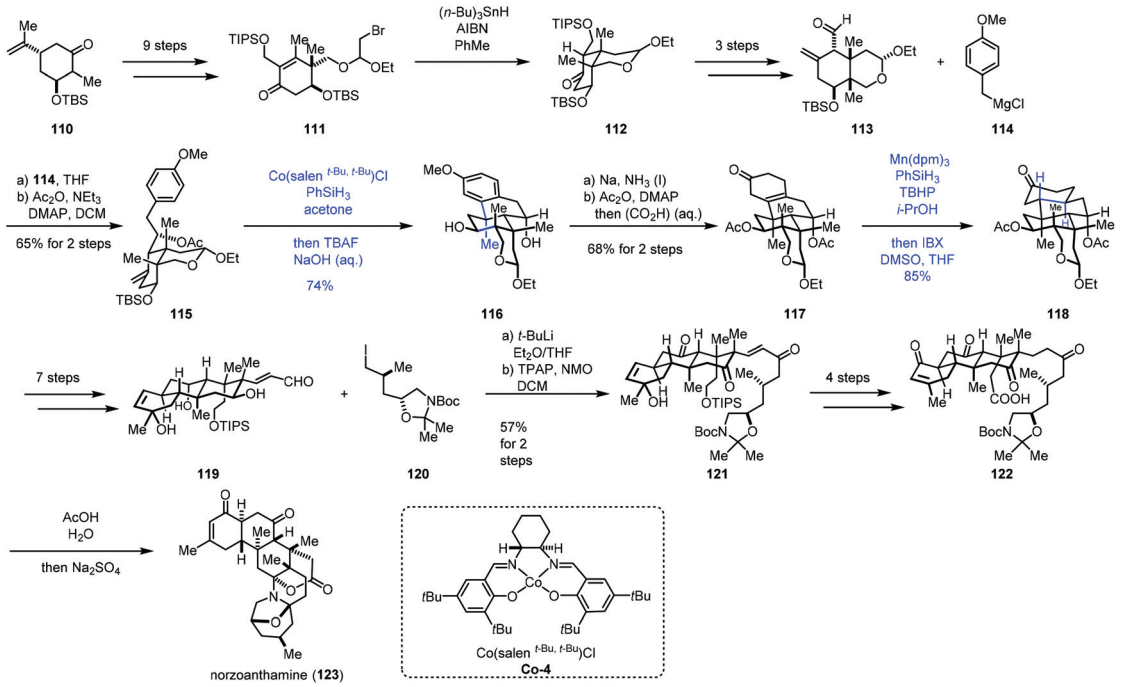
Recently, Gao and co-workers accomplished the synthesis of norzoanthamine using the same hydroarylation strategy to create the tetracyclic core (Scheme 14).[32] A carvone derivative could be converted into **111** in nine steps. Ueno–Stork radical cyclization furnished **112** through radical conjugate addition. **112** went through a three-step sequence to deliver aldehyde **113**, which was reacted with Grignard reagent **114**, followed by acetylation to afford compound **115**. Treatment of **115** with Co-catalyzed hydroarylation conditions reported by Shenvi gave the tetracyclic core **116** after deprotection of TBS. Subsequent Birch reduction and acetylation led to **117**. The following task was hydrogenation of the *tetra*-substituted olefin. The authors proposed that the desired product with the *trans–anti–trans*-fused perhydrophenanthrene A–B–C ring was more thermodynamically stable than other relative configurations, so the *anti*-addition of hydrogen was expected. Subjecting **117** to Shenvi's hydrogenation conditions ($Mn(dpm)_3$ and $PhSiH_3$) afforded **118** with a *trans*-fused A–B ring with good diastereoselectivity but low yield.

After optimization, the authors discovered that excess of $PhSiH_3$ (>4.0 equiv.) and *t*-butyl hydroperoxide (>4.0 equiv.) could ensure the complete conversion of **117**, accompanied by the reduction of the carbonyl group. Subsequent oxidation gave **118** with 85% yield. **118** could be transformed to the unsaturated aldehyde **119** in seven steps. Reaction of **120** and aldehyde **119** followed by oxidation gave rise to ketone **121**. **122** was then prepared from **121** in four steps. Deprotection of **122** followed by bis-aminoacetalization gave norzoanthamine (**123**).

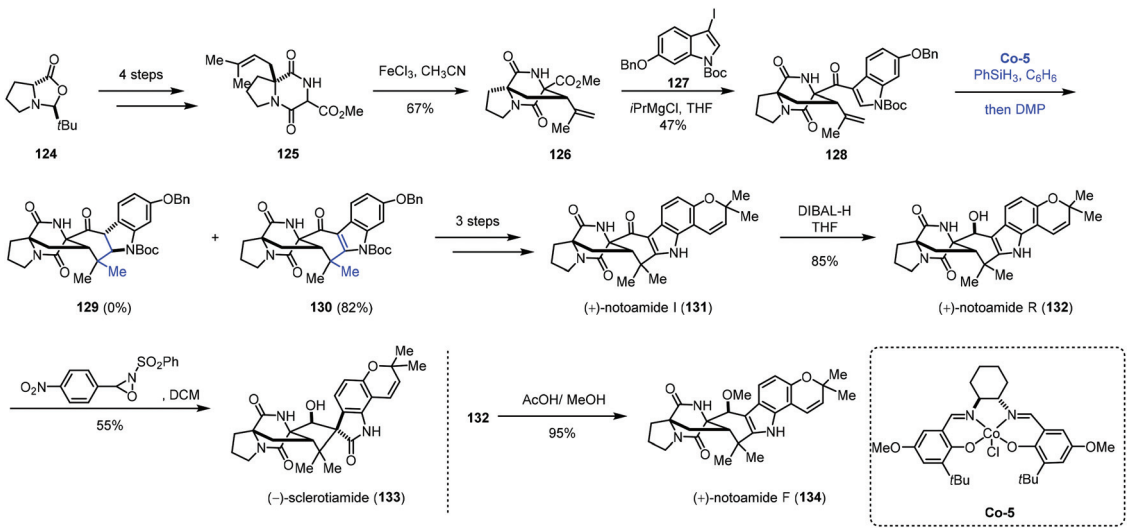
Besides phenyl groups, indoles have also been used as radical acceptors in MHAT-based reactions. In 2016, Li and co-workers employed cobalt-catalyzed HAT reaction to achieve desired cyclization in the total syntheses of (+)-notoamides F (**134**), I (**131**), and R (**132**) and (−)-sclerotiamide (**133**) (Scheme 15).[33] The starting material **124** was subjected to the reaction to give **125** in four steps. Under the optimal conditions, bicyclo[2,2,2]diazaoctane **126** was formed through oxidative aza-Prins cyclization with $FeCl_3$. The reaction of **126** with **127** delivered ketone **128**. With Shenvi's method, the desired product could not be obtained. While switching the cobalt catalyst to **Co-5**, the authors were able to obtain the desired products **130** along with 2,3-dihydroindole **129**, both in poor yields. After optimization, they discovered that using a slight excess of $PhSiH_3$ would increase the yields of **129** and **130**, and they also envisioned that **129** could be elaborated to **130** through oxidation. Thus, when using the optimized conditions and quenching the reaction mixture with Dess–Martin periodinane (DMP), **130** was synthesized in 82% yield. In this



Scheme 13 Gao's synthesis of viridin (**108**) and viridiol (**109**).



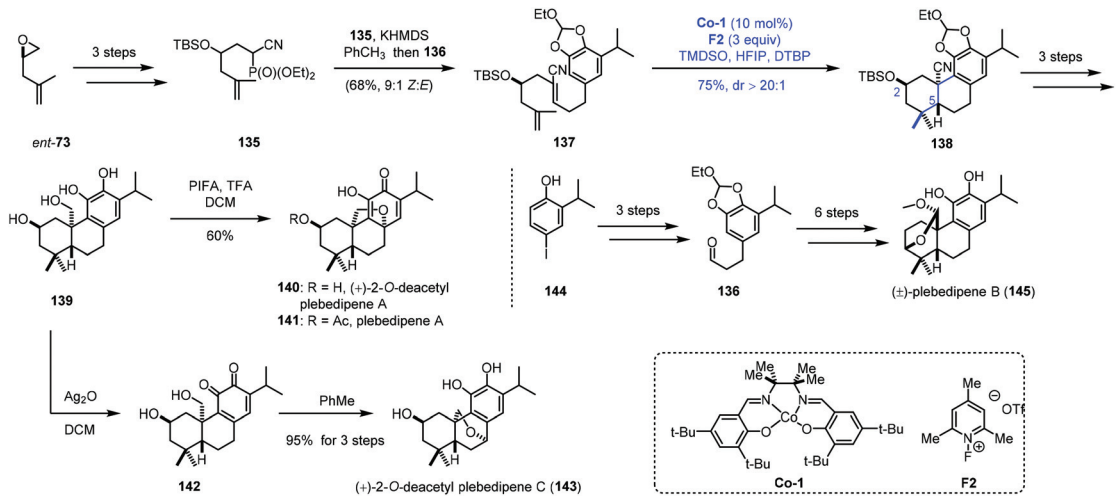
Scheme 14 Gao's synthesis of norzoanthamine (**123**).



Scheme 15 Li's synthesis of (+)-notoamides F (**134**), I (**131**), and R (**132**) and (−)-sclerotiamide (**133**).

reaction, the indole moiety is the radical acceptor. Compound **130** could be converted to (+)-notoamides F (**134**), I (**131**), and R (**132**) and (−)-sclerotiamide (**133**) featuring an allenyl Claisen rearrangement.

MHAT-initiated polyene cyclization was extensively investigated by Vanderwal and co-workers. They employed this strategy to complete the synthesis of a few oxidized abietane diterpenoids (Scheme 16).[34] In their synthesis, *ent*-**73** as the starting material was transformed to **135** *via* epoxide ring opening and hydroxyl protection. Another fragment **136** was furnished from **144**. Next, **135** was reacted with **136** to deliver the bicyclization precursor **137**. With **Co-1** as the catalyst, TMDSO as the hydrogen source and 2,6-di-*tert*-butylpyridine (DTBP) as the additive, a bicyclization took place *via* a radical process giving **138**. The reaction process was similar to that in Liu's work,[24,25] and the chiral center C2 would control the stereochemistry of the radical bicyclization. In particular, in their studies with model substrates, the authors found that oxygen substitution at C2 was associated with efficient polyene cyclization (>81% yield, dr > 20 : 1) for the equatorial group with both the free hydroxyl



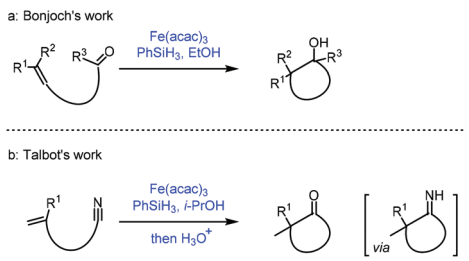
Scheme 16 Vanderwal's synthesis of (+)-2-*O*-deacetyl plebedipenes A (**140**) and C (**143**), and plebedipene B (**145**).

group and its corresponding silyl ether. The common intermediate **139** was then afforded through continuous reduction and deprotection. (+)-2-*O*-Deacetyl plebedipene A (**140**) was eventually obtained by oxidation of **139** with PIFA, and (+)-2-*O*-deacetyl plebedipene C (**143**) was obtained by oxidation with Ag_2O. Plebedipene B (**145**) could be obtained from **136** through similar reactions.

2.3 Reductive coupling with carbonyl or cyano functionalities

The reductive coupling of an olefin to a carbonyl functionality has been reported.[35a] Most of these reductive coupling reactions have been carried out under a hydrogen atmosphere in the presence of precious metal catalysts such as Rh. In 1989, Mukaiyama reported Co-catalyzed reductive coupling of α,β-unsaturated nitrile with aldehydes in the presence of phenylsilane.[35b]

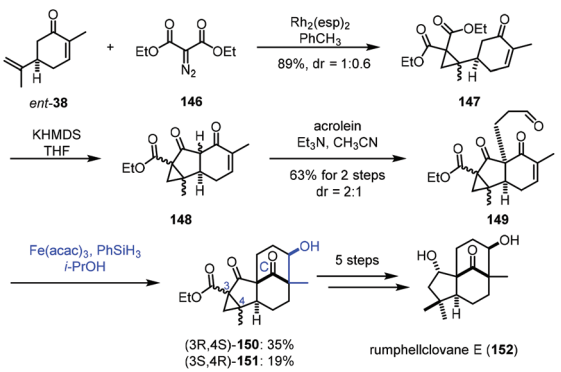
In 2018, Bonjoch[36a] and Talbot[36b] independently disclosed their accomplishment in MHAT reactions. They extended the radical acceptor to ketone and cyano groups when unactivated olefins were employed. Bonjoch discovered that the radical-centered carbon center from MHAT to the olefin was able to attack the proximal ketone group giving the corresponding tertiary alcohol (Scheme 17a), while Talbot observed that the resulting carbon radical would attack the cyano group leading to a ketone *via* an imine intermediate (Scheme 17b).



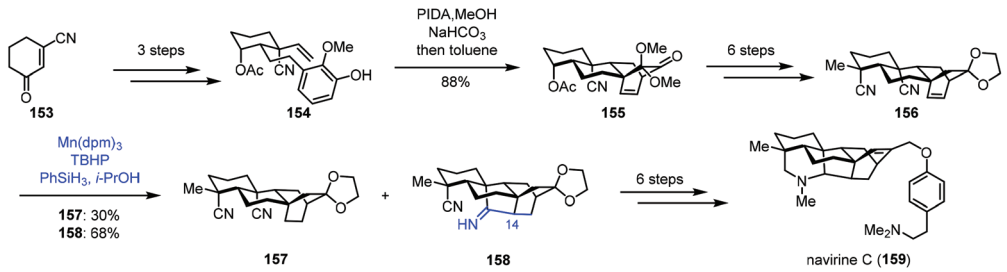
Scheme 17 (a) Bonjoch's work and (b) Talbot's work.

In 2021, Liu and co-workers applied iron-catalyzed reductive aldol reaction in the synthesis of rumphellclovane E (**152**) (Scheme 18).[37] Cyclopropanation between *ent*-**38** and **146** catalyzed by $Rh_2(esp)_2$ afforded **147**, which could be transformed to **149** *via* acylation and Michael addition. To assemble the tetracyclic core, they tried different reductive aldol conditions including Rh, Pd or Cu as catalysts, and all attempts failed. The authors thus resorted to MHAT-based conditions. The conditions of Mn and Co catalysts did not afford the desired cyclization product. Fortunately, a tetracyclic compound was obtained by the Fe-catalyzed radical process. After optimization, the authors observed that the treatment of **149** with $Fe(acac)_3$ and $PhSiH_3$ in *i*-PrOH led to the desired products **150**/**151**. With respect to the mechanism, the authors proposed that MHAT to enone **149** provides the radical intermediate, which is further reduced by Fe(II) to provide the enolate, which reacts with the aldehyde through an aldol process to form tetracyclic **150**/**151**. Next, a five-step transformation furnished rumphellclovane E (**152**).

In 2018, Ma and co-workers reported the synthesis of navirine C (**159**) (Scheme 19).[38] Their synthesis started with **153**,



Scheme 18 Liu's synthesis of rumphellclovane E (**152**).



Scheme 19 Ma's synthesis of navirine C (**159**).

which could be transformed to **154** *via* a three-step sequence. Oxidative dearomatization of **154** and Diels–Alder cycloaddition gave **155**. Then dinitrile **156** was obtained in six steps. Under MHAT reaction conditions ($Mn(dpm)_3$, $PhSiH_3$, and TBHP) reported by Shenvi and co-workers, the desired reductive cyclization occurred, delivering **158** in 68% yield, along with the reduction product **157** in 30% yield. The authors proposed that $HMn(dpm)_2$ reacted with an alkene to produce the corresponding C14 radical intermediate, which might attack the cyano group to produce the cyclized intermediate. Further reduction generated **158**. An additional six-step sequence gave avirine C (**159**).

Talbot's method was subsequently used by Zhai and co-workers in their synthesis of (−)-conidiogenone B (**166**), (−)-conidiogenone (**167**), and (−)-conidiogenol (**168**) (Scheme 20).[39] The starting material **160** could be transformed to **161** *via* a three-step sequence involving Corey–Bakshi–Shibata reduction, tandem vinyl etherification/Claisen rearrangement, and van Leusen reaction. Under Talbot's conditions, alkene–nitrile cyclization was achieved, providing the bicyclic ketone **163**, which was elaborated to deliver **164** by an additional nine steps. Subsequently, ozonolysis, followed by aldol reaction, provided (−)-conidiogenone B (**166**). After epoxidation and reduction, (−)-conidiogenone (**167**) was prepared. Reduction of (−)-conidiogenone (**167**) gave rise to (−)-conidiogenol (**168**).

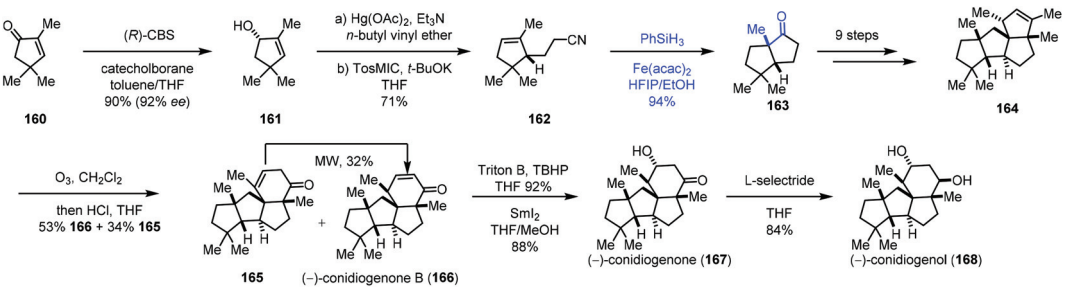
3. C–O bond formation

Mukaiyama developed the Co-catalyzed hydration of olefins in the presence of silane and oxygen in 1989.[3] Since then, the reaction has seen applications in natural product synthesis.[40,41] In Shenvi's excellent review published in 2016, they carefully summarized examples of olefin hydration under MHAT conditions in natural product synthesis. So next we will mainly focus on the examples that appeared after 2016. Hydration and hydroperoxidation will be discussed separately.

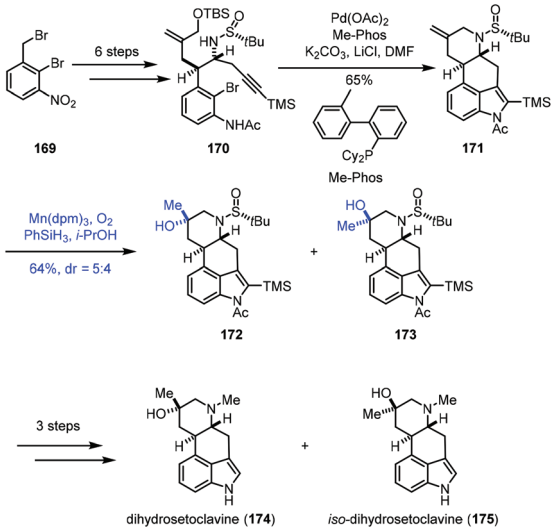
3.1 Hydration

Mukaiayama hydration reaction is a mild way to hydrate exocyclic double bonds to obtain tertiary hydroxyl groups. In 2017, Jia and co-workers applied Mukaiyama hydration in their synthesis of dihydrosetoclavine (Scheme 21).[42] The starting material **169** was converted into **170** in six steps. Larock indole annulation of **170** afforded **171**. Under Mn-catalyzed Mukaiyama hydration conditions, a diastereomeric mixture of tertiary hydroxyl **172** and **173** was furnished. The authors noticed that using a similar substrate (changing the *tert*-butanesulfinyl group of **171** to CO_2Me) with hydration conditions failed to give the desired hydration product, indicating that the carbamate moiety has a negative effect on the hydration. Dihydrosetoclavine (**174**) and *iso*-dihydrosetoclavine (**175**) were then synthesized in three steps.

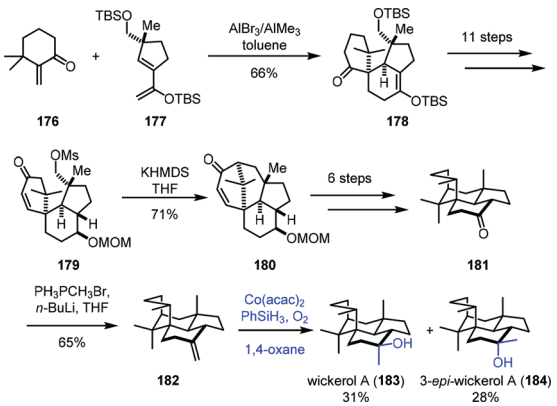
In 2017, Trauner and co-workers employed Mukaiyama hydration at the last step to furnish wickerol A (**183**) (Scheme 22).[43] A Diels–Alder cycloaddition between the known enone **176** and diene **177** was performed to afford **178**. The key intermediate **179** could be accessed from **178** in necessary functional group transformations. Treatment of **179** with KHMDS induced intramolecular alkylation to provide **180**. Ketone **181** was afforded after the introduction of the missing methyl group. Initially, they carried out the methyl nucleophilic addition to the ketone carbonyl with methyl Grignard or



Scheme 20 Zhai's synthesis of (−)-conidiogenone B (**166**), (−)-conidiogenone (**167**), and (−)-conidiogenol (**168**).



Scheme 21 Jia's synthesis of dihydrosetoclavine (**174**).



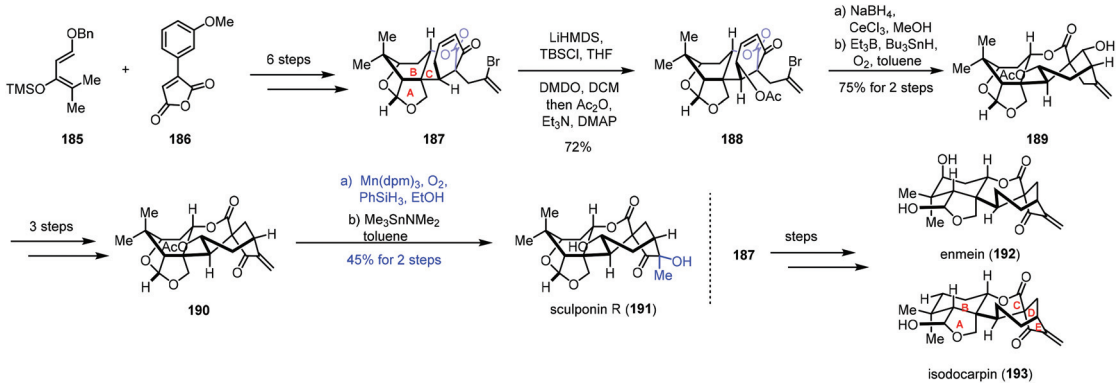
Scheme 22 Trauner's synthesis of wickerol A (**183**).

methyllithium, but unfortunately, undesired 3-*epi*-wickerol A (**184**) was produced as the sole product. Addition of the Lewis acid MAD to the system still favored undesired **184** (**183** : **184** = 1 : 4). The authors ultimately found that a two-step transformation including Wittig reaction and Mukaiyama hydration gave a better ratio. Olefination of ketone led to **182**, which underwent Mukaiyama hydration reaction with $Co(acac)_2$ as the catalyst to afford wickerol A (**183**) and 3-*epi*-wickerol A (**184**) in an almost 1 : 1 ratio.

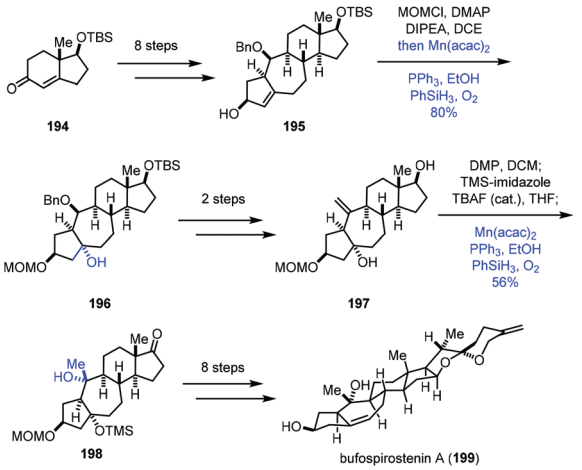
In 2018, a divergent total synthesis of enmein-type natural products was reported by Dong and co-workers (Scheme 23).[44] The common intermediate **187** containing the A/B/C rings of (−)-enmein (**192**), (−)-isodocarpin (**193**), and (−)-sculponin R (**191**) was synthesized from diene **185** and anhydride **186** involving Diels–Alder cycloaddition and Birch reduction. γ-Hydroxylation was achieved with vinylogous enol ether formation and DMDO oxidation to afford ester **188**, which was reduced by Luche reduction, followed by radical annulation to give **189**. A three-step conversion furnished **190**. Finally, functionalization of the exocyclic double bond was carried out under the Mn-catalyzed Mukaiyama hydration conditions (Mn(dpm)$_3$, $PhSiH_3$, O_2, and EtOH) to furnish (−)-sculponin R (**191**) after deacetylation in 45% yield over two steps. The common intermediate **187** could be also converted to (−)-enmein (**192**) and (−)-isodocarpin (**193**) in a few steps.

In 2020, Li and co-workers reported the synthesis of bufospirostenin A (**199**), in which Mukaiyama hydration was adopted two times (Scheme 24).[45] This synthesis began with **194**, which was transformed to tetracyclic **195** in eight steps. Treatment of **195** with MOMCl, followed by a standard Mukaiyama hydration ($Mn(acac)_2$, $PhSiH_3$, PPh_3, O_2, and EtOH), gave the tertiary alcohol **196** in 80% yield. Afterwards, a two-step conversion furnished **197**, poised for another Mukaiyama hydration. Then the tertiary alcohol **198** with the desired configuration was furnished *via* the same hydration process from the exocyclic double bond of **197** in 56% yield. A further eight steps of transformation afforded the natural product bufospirostenin A (**199**).

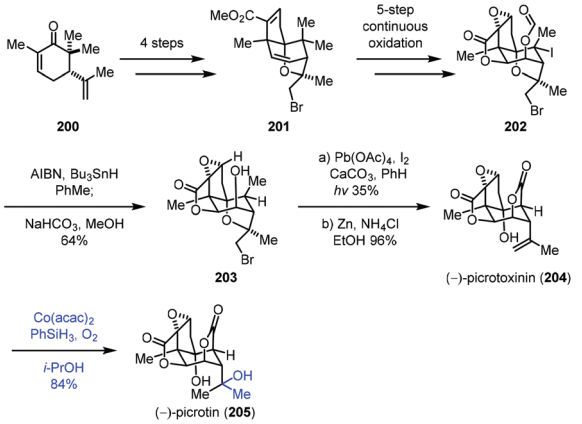
In 2020, Shenvi reported the synthesis of picrotoxinin (**204**), which could be transformed to picrotin (**205**) by Mukaiyama hydration (Scheme 25).[46] Their synthesis commenced with **200**, which could be converted to **201** *via* a four-step sequence. **201** went through a five-step continuous oxidation process to



Scheme 23 Dong's synthesis of (−)-enmein (**192**), (−)-isodocarpin (**193**), and (−)-sculponin R (**191**).



Scheme 24 Li's synthesis of bufospirostenin A (**199**).



Scheme 25 Shenvi's synthesis of picrotoxinin (**204**) and picrotin (**205**).

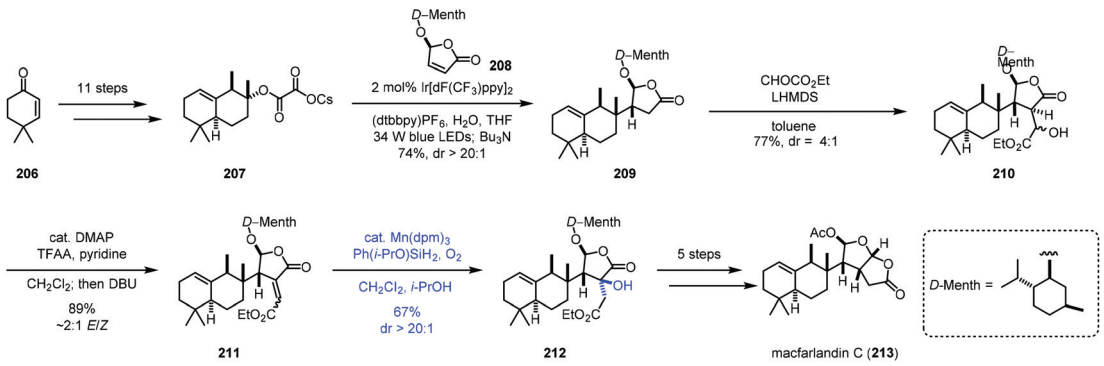
give **202**. Treatment of **202** with AIBN and Bu_3SnH removed the tertiary iodide, followed by the cleavage of the formyl group to furnish **203**. Picrotoxinin (**204**) was obtained from **203** through functionalization of the methyl group and cleavage of bromoether. Finally, a Mukaiyama hydration under Co $(acac)_2$, $PhSiH_3$, O_2, and *i*-PrOH conditions installed the tertiary hydroxyl from the exocyclic double bond of **204** to deliver the desired picrotin (**205**) in 84% yield.

In 2020, Overman and co-workers reported the synthesis of macfarlandin C (**213**), in which Mukaiyama hydration was used (Scheme 26).[47] The oxalate radical precursor **207** was obtained from **206** after eleven steps of transformations. Irradiation of **207** and D-menthol-derived chlorobutenolide **208** in the presence of an Ir-catalyst installed the vicinal quaternary and tertiary stereocenters generating **209**. Two more steps gave **211**. Mukaiyama hydration with $Mn(dpm)_3$ and Shenvi's more reactive $Ph(i\text{-}PrO)SiH_2$ [48] and O_2 provided **212** in a regio- and stereoselective manner in 67% yield. In this case, the electron-rich olefin remained untouched. Macfarlandin C (**213**) was then obtained in five additional steps.

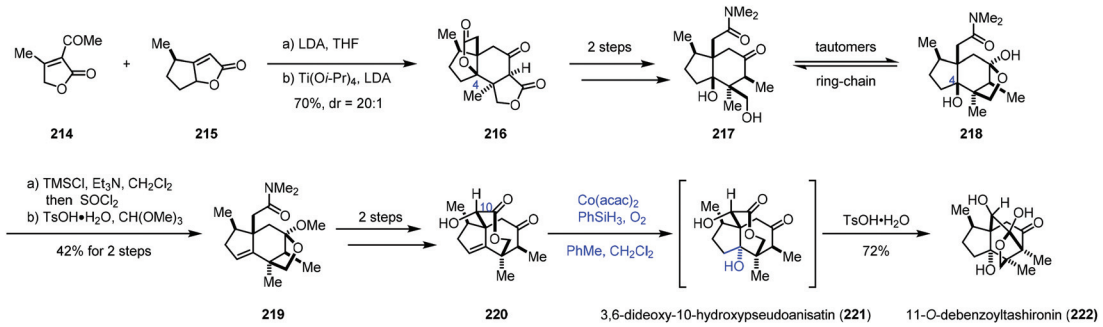
The above-mentioned examples are related to the hydration of exocyclic double bonds. Next, the hydration of endocyclic double bonds will be summarized.

In 2017, Shenvi and co-workers reported a seven-step synthesis of (−)-11-*O*-debenzoyltashironin (**222**) from butenolide (Scheme 27).[49] Butenolide heterodimerization of **215** to **214**, followed by the addition of titanium tetraisopropoxide and lithium diisopropylamide, gave tetracyclic **216**. To invert C4, the authors planned to eliminate the lactone to an alkene, and then use Mukaiyama hydration reaction to construct the tertiary hydroxyl group with the desired configuration. In accordance with the strategy, a two-step sequence afforded **217**/**218**, which was converted to **219** featuring a dehydration step. Seven-membered lactone **220** was afforded in two more steps. Mukaiyama hydration of the endocyclic double bond of **220** with $Co(acac)_2$ followed by the addition of *p*-toluenesulfonic acid produced **222** with a *trans*-hydrindane framework in 72% yield. *trans*-Hydrindane is thought to be thermodynamically disfavoured. The authors suspected that, in the current case, C10 alcohol might determine the stereochemistry of hydration as C10 alcohol shields the β-face. In addition, the authors mentioned that the hydration had to be arranged at the late stage since attempts with earlier intermediates resulted in a complex mixture or the undesired *cis*-hydrindane product.

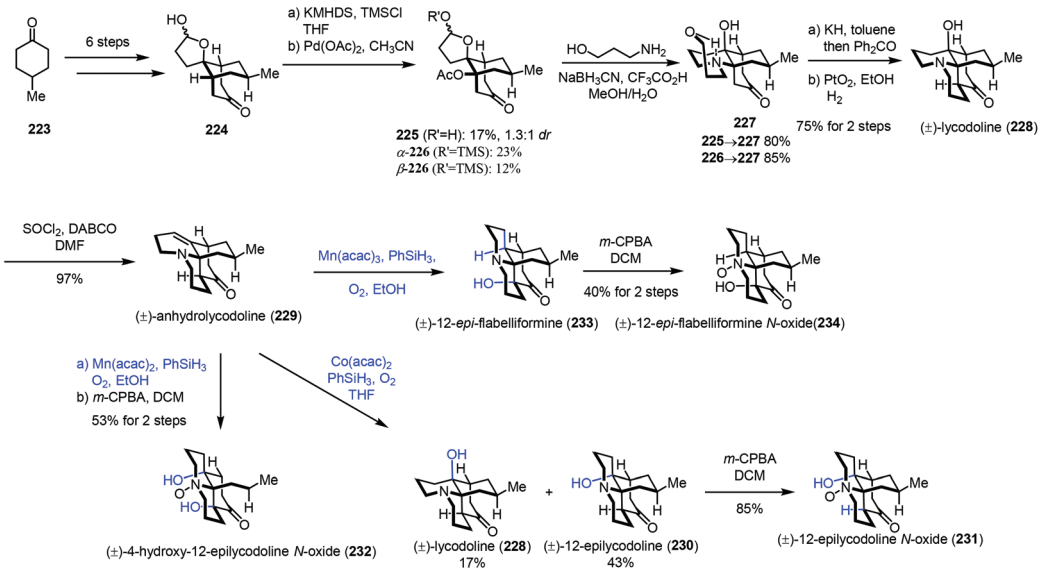
In 2017, Fan and co-workers communicated their synthesis of lycodoline-type *Lycopodium* alkaloids (Scheme 28).[50] In this case, subjecting the common intermediate anhydrolycodoline



Scheme 26 Overman's synthesis of macfarlandin C (**213**).



Scheme 27 Shenvi's synthesis of (−)-11-*O*-debenzoyltashironin (**222**).



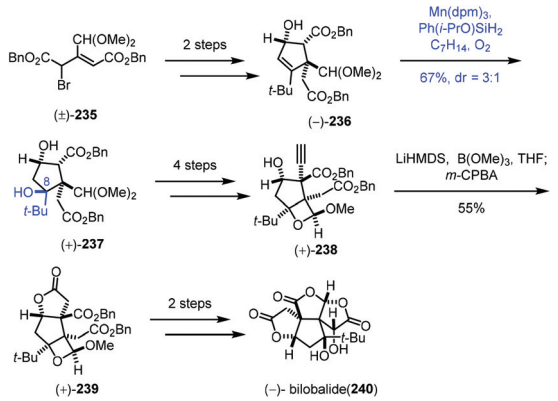
Scheme 28 Fan's synthesis of lycodoline-type *Lycopodium* alkaloids.

(**229**) to different hydration conditions could give different types of products. This synthesis commenced with the preparation of **224** from 4-methylcyclohexone **223**. Treatment of **224** with KHMDS and TMSCl, followed by tandem oxidative dehydrogenation and oxa-Michael reaction, gave **225**/**226**. Then tandem reductive amination and bridgehead aminolysis reaction were performed to give **227**. Lastly, lycodoline (**228**) was obtained through a sequence of Oppenauer oxidation, aldol condensation and hydrogenation of the olefin. Anhydrolycodoline (**229**) was furnished *via* dehydration from lycodoline (**228**).

Under Mukaiyama hydration conditions with $Co(acac)_2$ in THF, anhydrolycodoline (**229**) could be elaborated to 12-epilycodoline (**230**) and lycodoline (**228**). **230** could be further oxidized with *m*-CPBA to provide 12-epilycodoline *N*-oxide (**231**). In comparison, when anhydrolycodoline (**229**) was treated with $Mn(acac)_2$ and phenylsilane in EtOH, followed by oxidation with *m*-CPBA, it turned out that not only the C–C double bond was hydrated, but also α-hydroxylation occurred, providing 4-hydroxy-12-epilycodoline *N*-oxide (**232**). It is interesting to note that hydration with $Mn(acac)_3$ gave the α-hydroxylation product 12-*epi*-flabelliformine (**233**), which could be oxidized into **234**.

In 2019, Shenvi and co-workers described a solvent-controlled Mukaiyama hydration in total synthesis of (−)-bilobalide (**240**) (Scheme 29).[51a,b] In the process of the synthesis of bilobalide, with respect to the hydration step of **236** to **237**, Shenvi and co-workers observed that there is strong correlation between solvent polarity and diastereoselectivity. For example, under standard Mukaiyama conditions, $Mn(dpm)_3$/$PhSiH_3$/*i*-PrOH, **237** was delivered with no diastereoselectivity. Switching to Ph(*i*-PrO)SiH_2 and ethereal solvent such as *tert*-butyl methyl ether led to undesired diastereomer as the major product (dr = 1 : 1.8), while methylcyclohexane as solvent favoured the desired product **237** in a 3 : 1 ratio. An additional 4 steps gave **238**. Shenvi and co-workers then developed a new method for alkyne oxidation to form **239**. Finally, (−)-bilobalide (**240**) was accessed through a skeletal rearrangement and oxidation.

In 2019, Maimone and co-workers published a semisynthetic strategy to the *Illicium* sesquiterpenes from cedrol by their site-selective C(sp^3)–H bond functionalization reactions.

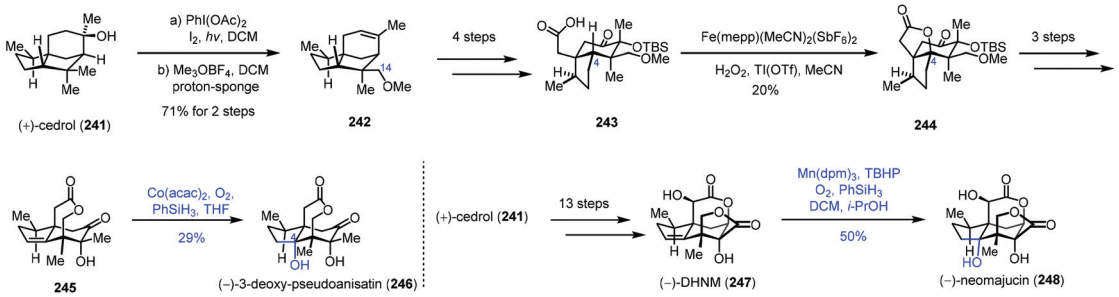


Scheme 29 Shenvi's synthesis of (−)-bilobalide (**240**).

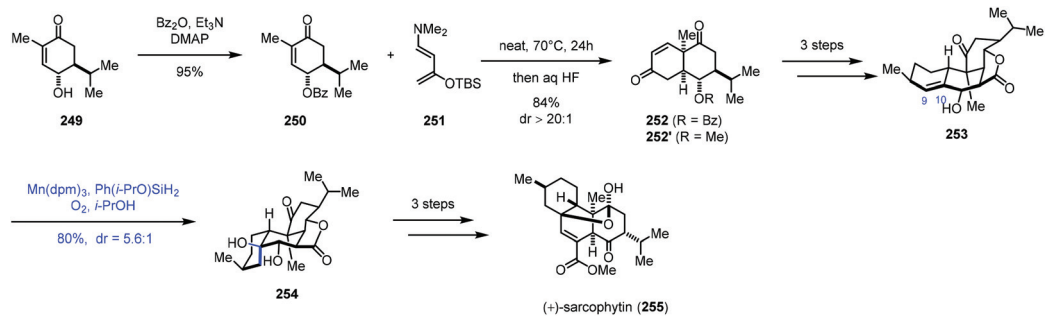
They employed Mn or Co-catalyzed hydration to install the C4 hydroxyl group (Scheme 30).[52] A hypoiodite photolysis of **241** with $PhI(OAc)_2$ and I_2 furnished a strained tetrahydrofuran intermediate by oxidation of C14 of cedrol, which underwent alkylation and concomitant elimination to provide **242**. The C4 oxidation precursor **243** was furnished from **242** in four steps. Fe-Catalyzed selective C–H oxidation of C4 afforded **244**, which was then transformed to alkene **245**. Under Co-catalyzed conditions, **246** was afforded in 29% yield as the minor product through the hydration process due to the modest diastereocontrol. Meanwhile, cedrol (**241**) could be converted to **247** in thirteen steps. A hydration reaction was conducted with a Mn-catalyst to give **248** in 50% yield.

In 2019, Ding and co-workers accomplished the synthesis of cembrane ditepeniond, (+)-sarcophytin (**255**) (Scheme 31).[53] They employed Mukaiyama hydration to introduce the tertiary alcohol. The synthesis commenced with the construction of bicyclic **252**, which was accessed through double-Mukaiyama Michael addition between **250** and the Rawal diene **251** and elimination. **253** was then furnished in three steps from **252**. The authors speculated that the subsequent hydration would take place from the β-face since the proximate pseudoaxial hydroxy group blocks the α-face. As expected, subjecting **253** to Shenvi's optimized hydration conditions ($Mn(dpm)_3$, $Ph(i\text{-}PrO)SiH_2$, O_2, and THF) formed **254** and its epimer in a 5.6 : 1 ratio with 80% yield, favouring desired **254**. In comparison, using other hydride sources ($EtSiH_3$, $PhSiH_3$, and $NaBH_4$) and metal catalysts ($Co(acac)_2$, $Co(tfa)_2$, $Mn(acac)_3$, and $Fe(acac)_3$) led to inferior yield (15–60%) and diastereoselectivity (1.2 : 1–4.5 : 1). Necessary functional group transformations eventually led to (+)-sarcophytin (**255**).

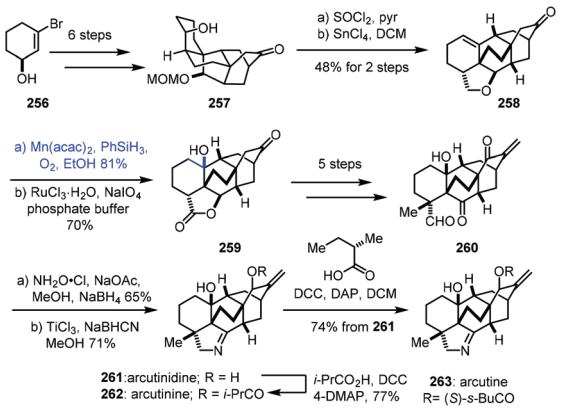
In 2019, Li and co-workers reported the synthesis of arcutinidine, arcutinine, and arcutine. Mukaiyama hydration was adopted (Scheme 32).[54] Alcohol **257** was made from alcohol **256** through sequential intermolecular and anionic Diels–Alder reactions. A dehydration reaction of **257** with $SOCl_2$ furnished a trisubstituted olefin which could further be converted to **258** through a Prins/Wagner–Meerwein cascade reaction. Mukaiyama hydration of **258** with $Mn(acac)_2$ and $PhSiH_3$ furnished tertiary alcohol **259** with the desired stereochemistry after site-selective C–H oxidation. In addition, the authors



Scheme 30 Maimone's synthesis of *Illicium* sesquiterpenes.



Scheme 31 Ding's synthesis of (+)-sarcophytin (**255**).



Scheme 32 Li's synthesis of arcutinidine (**261**), arcutinine (**262**) and arcutine (**263**).

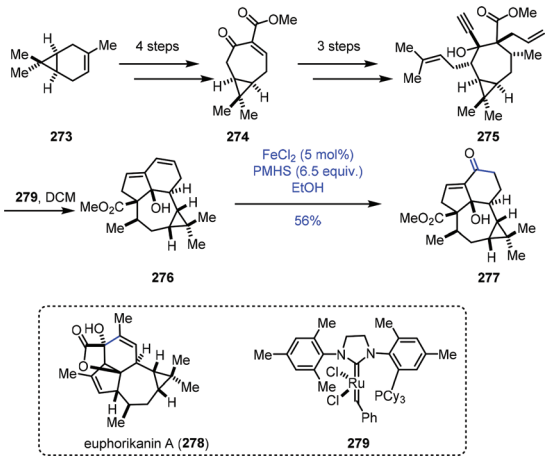
found that $Mn(acac)_2$ as a precatalyst was superior to $Co(acac)_2$ for this olefin hydration. Diketoaldehyde **260** was then prepared in five steps. Chemoselective condensation and 1,2-reduction provided the corresponding oxime, followed by cleavage of the N–O bond and reduction giving arcutinidine (**261**).

Arcutinine (**262**) and arcutine (**263**) were afforded from arcutinidine (**261**) *via* acylation, respectively.

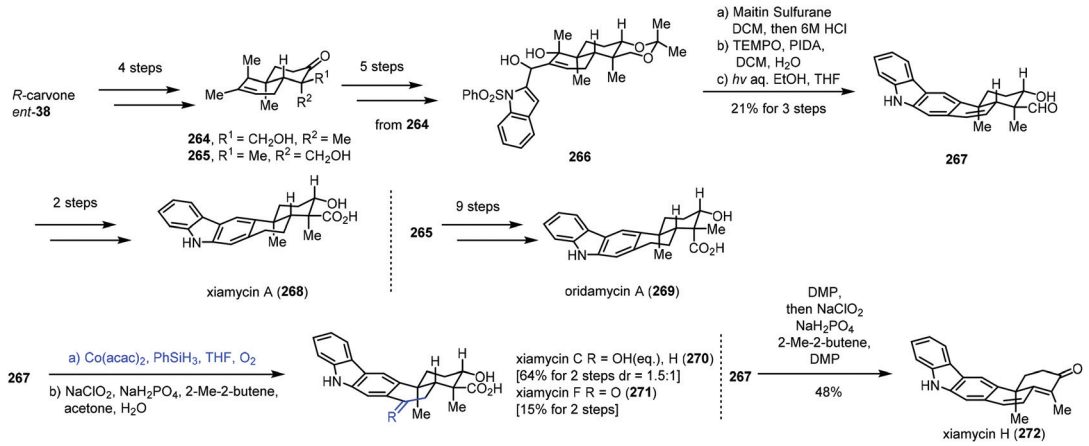
In 2019, Sarpong and co-workers reported total synthesis of xiamycins A (**268**), C (**270**), F (**271**), and H (**272**) and oridamycin A (**269**) (Scheme 33).[55] In this case, they employed Mukaiyama hydration to achieve functionalization of endocyclic disubstituted olefins. Their synthesis commenced with the assembly of the *trans*-decalin framework. (*R*)-Carvone was transformed to **264** and **265** in four steps. Diol **266** was furnished from **264**. Dehydration of **266**, followed by oxidation and key photocyclization–desulfonylation, led to aldehyde **267**. Xiamycin A (**268**) was obtained after two more steps. Subjecting **267** to Mukaiyama hydration conditions ($Co(acac)_2$, $PhSiH_3$, THF, and O_2) followed by Pinnick oxidation provided xiamycin C (**270**) and its C-19 epimer and xiamycin F (**271**). Meanwhile, xiamycin H (**272**) was generated from **267** in steps.

A similar conversion was performed by Yang and co-workers in the synthesis of the core structure of euphorikanin A (Scheme 34).[56] The 7/3-bicyclic **274** was synthesized from (+)-3-carene **273** in four steps. Three more steps of conversions gave the key dienyne precursor **275**. A domino RCM reaction of **275** with Grubbs second-generation catalyst **279** proceeded well to deliver the tetracyclic skeleton **276** in excellent yield. To realize the transformation of the conjugated double bonds into the α,β-unsaturated ketone, they tested diene **276** with various Wacker reactions, such as $PdCl_2$ and CuCl, which led to no reaction, probably due to the high rigidity of the ring system. Then they resorted to HAT-initiated oxidation. Screening of different Fe(II) catalysts, silane reagents, solvents, temperatures and reaction times revealed that $FeCl_2$/PMHS/EtOH was optimal, and the desired enone **277** could be obtained successfully in 56% yield.

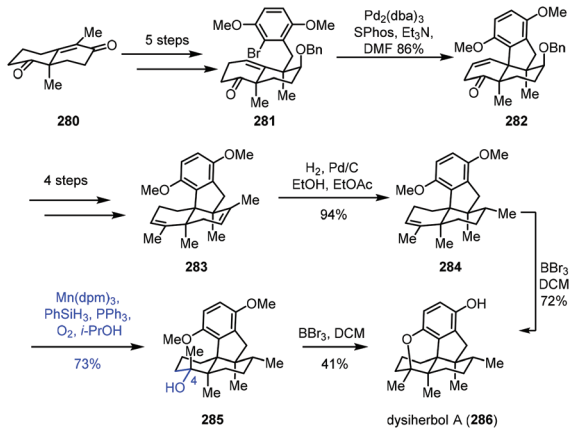
In 2021, Lu and co-workers described the synthesis of dysiherbol A (**286**) (Scheme 35).[57] The Wieland–Miescher ketone derivative **280** could be advanced to ketone **281** in five steps. The Pd-catalyzed intramolecular Heck reaction was carried out



Scheme 34 Yang's synthesis of the core structure of euphorikanin A.



Scheme 33 Sarpong's synthesis of xiamycins A (**268**), C (**270**), F (**271**), and H (**272**) and oridamycin A (**269**).

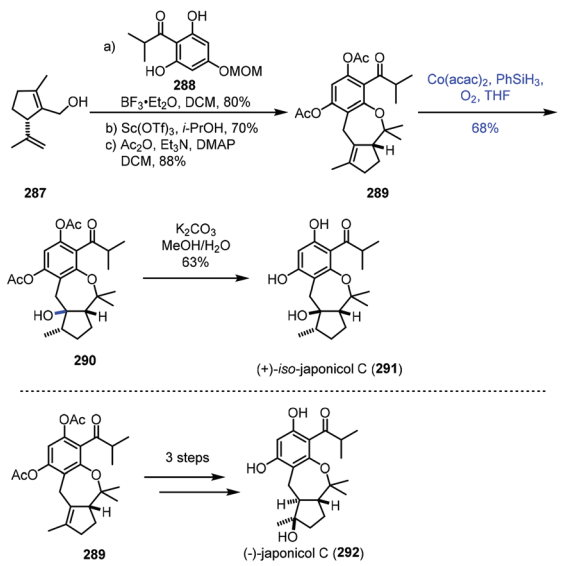


Scheme 35 Lu's synthesis of dysiherbol A (**286**).

to obtain tetracyclic **282**, which was advanced to diene **283** in four steps. Mono-alkene **284** was created from diene **283** *via* chemo- and diastereoselective reduction. The authors observed that the epoxidation of alkene **284** with H_2O_2, *m*-CPBA, TBHP or $Vo(acac)_2$ and TBHP led to the skeleton rearrangement presumably due to the strain of the 6/5-fused ring system. Dihydroxylation of alkene **284** with OsO_4, $K_2OsO_4{\cdot}H_2O$ or AD-mix-α also failed.

Fortunately, Mukaiyama hydration of **284** worked, giving **285** under optimized conditions ($Mn(dpm)_3$, $PhSiH_3$, O_2, and PPh_3) in 73% yield. They further separated the natural product dysiherbol A (**286**) upon exposure of **285** to BBr_3. Monitoring of the reaction revealed that the tertiary alcohol of **285** dehydrated in the presence of BBr_3 to return to compound **284**. Therefore, **284** was then transformed into dysiherbol A (**286**) directly with BBr_3.

In 2021, Dethe and Nirpal disclosed the synthesis of japonicol C (**292**) (Scheme 36).[58] **289** was obtained from **287** through Friedel–Crafts reaction, deprotection and acetylation. The



Scheme 36 Dethe's synthesis of japonicol C (**292**).

authors then tested the hydration reaction using various metal catalysts. Treatment of **289** with Mn or Fe complexes in the presence of $PhSiH_3$ or $EtSiH_3$ in solvents like 1,2-dichloroethane, EtOH or i-PrOH led to no reaction. Under Mukaiyama hydration conditions, $Co(acac)_2$ and phenylsilane in THF under O_2, undesired tertiary alcohol **290** was isolated in 68% yield. The authors proposed that the stereochemical outcome of the hydration could be due to the less hindered β-face. Deacetylation of **290** gave **291**, a regioisomer of the natural product japonicol C. Since **290** turned out to be an undesired hydration product, to overcome the regioselectivity issue, the authors attempted Fuch's C–H oxidation method and accessed the desired tertiary alcohol from **289**, which was finally elaborated to japonicol C (**292**).

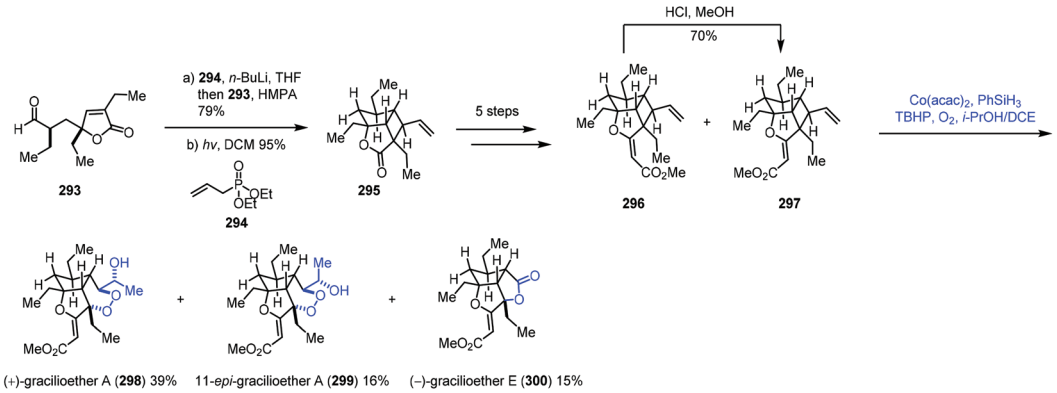
3.2 Hydroperoxidation

In this sub-section, we will introduce hydroperoxidation of olefins and its application in natural product synthesis. A number of important works have been summarized in other reviews,[9,10] such as those by Maimone[59] and Inoue.[60] We will focus on the studies published in recent years.

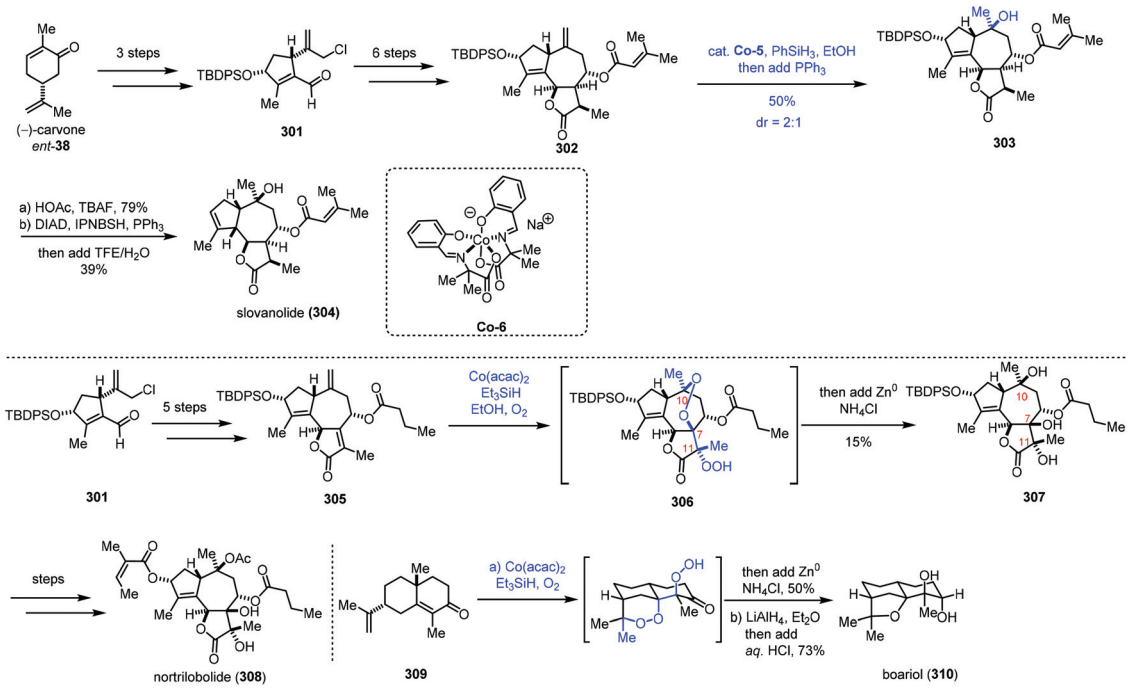
In 2018, Tang and co-workers used the Co-catalyzed HAT to oxygenation of vinylcyclobutane in the syntheses of (+)-gracilioether A (**298**) and (−)-gracilioether E (**300**) (Scheme 37).[61] A Horner–Wadsworth–Emmons reaction of **293** with **294** furnished a diene, which cyclized into vinylcyclobutane **295** through [2 + 2] photocycloaddition, which was advanced to the key compound **297**. They initially tried to construct a six-membered peroxy ring through a radical process as reported by Feldman;[62] however, they failed to get the desired result. Inspired by Maimone's[59] experience in the synthesis of (+)-cardamom peroxide using the Mn-catalyzed HAT to construct a peroxy group, the authors tested Maimone's MHAT conditions ($Mn(dpm)_3$, $PhSiH_3$, TBHP, O_2, and *i*-PrOH/DCM), and only 5% of gracilioether A (**298**) and 7% of gracilioether E (**300**) were isolated. Further optimization revealed that the Mukaiyama/Isayama hydrosilyl peroxidation reaction system was superior ($Co(acac)_2$, $PhSiH_3$, TBHP, O_2, and i-PrOH/DCE), and **297** could be converted to gracilioether A (**298**), **299** and gracilioether E (**300**) in acceptable yields. Mechanistically, the authors proposed that the radical is generated from the terminal alkene **297** by HAT from HCo(III), which undergoes cyclobutane ring-opening, dioxygen trapping of the resulting radical, 6-*exo-trig* cyclization, and second dioxygen insertion to give the corresponding peroxy radical. Subsequent hydrogen abstraction and peroxide reduction deliver **298** and **300**.

In 2019, Maimone and co-workers reported the synthesis of complex guaianolide sesquiterpenes (Scheme 38).[63] In the synthesis of nortrilobolide (**308**), they creatively employed the radical tandem reaction under Co-catalyzed HAT conditions to introduce three hydroxyl groups through reduction of the peroxy bond generated.

301 was prepared from carvone in three steps. Then **301** was converted to the 5,7,5-fused ring system **302** through a six-step sequence. Under MHAT conditions of a Co complex, $PhSiH_3$ and PPh_3 in EtOH, the exocyclic olefin was trans-



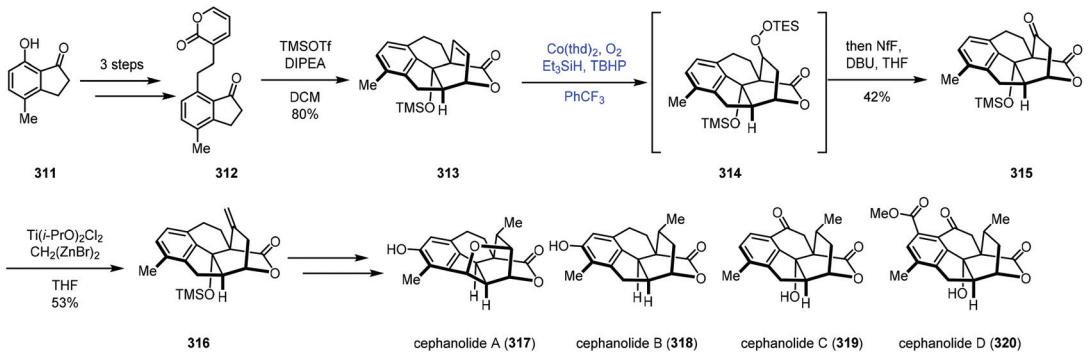
Scheme 37 Tang's synthesis of (+)-gracilioether A (**298**) and (–)-gracilioether E (**300**).



Scheme 38 Maimone's synthesis of complex guaianolide sesquiterpenes.

formed to the corresponding tertiary alcohol, furnishing **303**. Deprotection and reductive allylic transposition were conducted to give slovanolide (**304**). Regarding the synthesis of heavily oxidized nortrilobolide (**308**), they prepared **305** from **301** at first. Inspired by their synthesis of cardamom peroxide,[59] the authors envisioned that a polyoxygenation cascade with molecular oxygen may be applicable to secure the requisite hydroxyl groups at C10, C7, and C11 of nortrilobolide. Subjecting **305** to Co-catalyzed Mukaiyama hydroperoxidation conditions, followed by reduction with metal Zn provided **307** in 15% yield. Although the yield of the step is low, the cascade process is rather impressive as three hydroxyl groups were installed with the desired configurations in a single operation. The authors noted that any variation of these conditions did not lead to desired **307**. Based on the experimental results, the authors found that the major side reactions are premature reduction of the first peroxy radical intermediate and formation of an unstable peroxide. Lastly, **307** could be transformed to nortrilobolide (**308**). Maimone and co-workers also completed the synthesis of boariol *via* a similar radical process.

In 2021, Sarpong reported divergent syntheses of cephanolides A–D *via* the common intermediate **316** (Scheme 39).[64] They employed Co-catalyzed radical hydroperoxidation to achieve olefin functionalization. The indanone derivative **312** was created from 7-hydroxy-4-methylindanone (**311**). Exposure of **312** to two equivalents of TMSOTf induced Diels–Alder cycloaddition conditions to provide the core skeleton **313**. Functionalization of the bridging olefin group of **313** proved



Scheme 39 Sarpong's synthesis of cephanolides A–D.

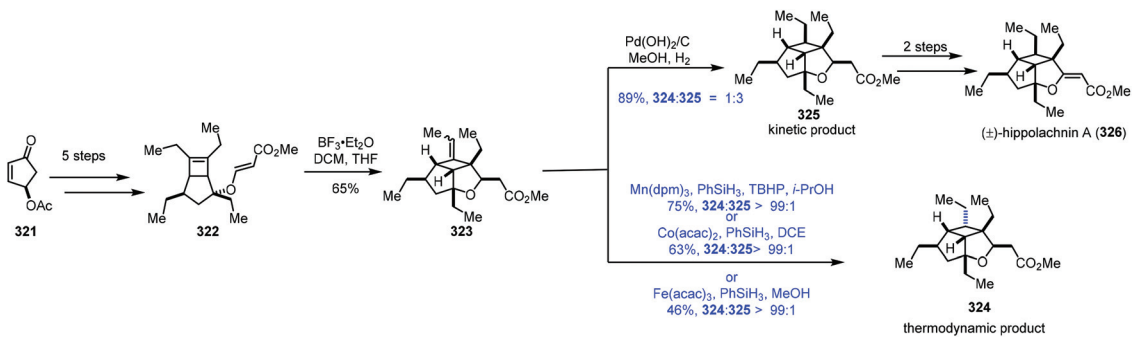
unfruitful. Due to the electron deficiency of olefins, conventional methods such as hydroboration and epoxidation all failed. Thus the authors turned their attention to the MHAT process. A modified Mukaiyama hydration process by Inoue was feasible ($Co(thd)_2$, O_2, Et_3SiH, and TBHP), giving ketone **315** in 42% yield after treatment of the mixture with DBU. The authors proposed that the regioselectivity of the hydrocobaltation likely correlates with the proximal oxygen lone pair of the lactone. Next, olefination with a combination of $Ti(i\text{-}PrO)_2Cl_2$ and Nysted reagent gave **316**, which could be elaborated to cephanolides A–D, respectively.

4. Hydrogenation

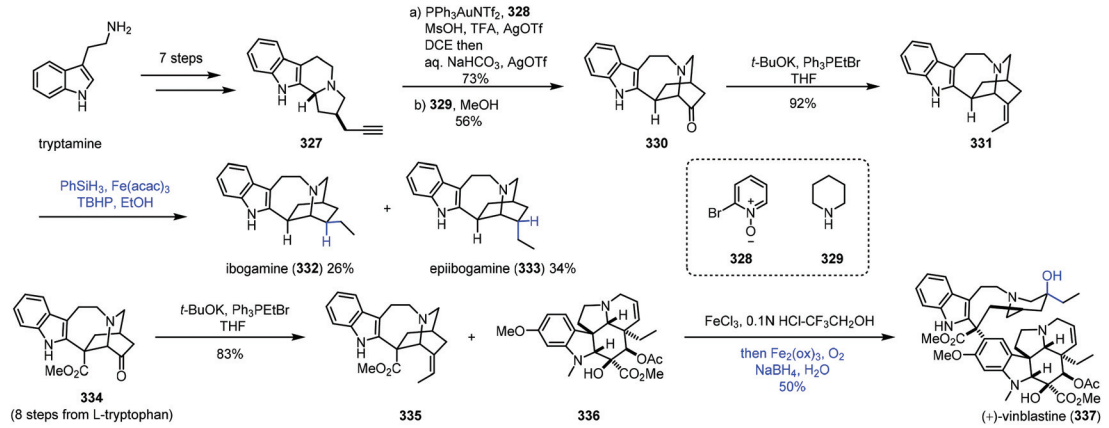
In the process of studying the hydration reaction of olefins with Co catalysts in secondary alcohols in 1989, Mukaiyama noted that the hydrogenation product was obtained as the minor product.[2] In 2000, Magnus discovered that under the conditions of $Mn(dpm)_3$/phenylsilane with the exclusion of air, α,β-unsaturated ketones could be transformed to saturated ketones.[65] In 2014, Shenvi[5a] and Herzon[6] independently reported using MHAT to achieve hydrogenation of unactivated olefins or alkenyl halides, greatly expanding the substrate scope. Since then, hydrogenation of olefins under MHAT conditions has been serving as an alternative to the conventional methods, and has been widely used in organic synthesis.

In their synthesis of hippolachnin A (**326**) in 2015, Carreira tested MHAT-based hydrogenation of exocyclic double bonds (Scheme 40).[66] Cyclopentenone **321** could be transformed to the bicyclic compound **322** *via* a five-step sequence. An ene cyclization with $BF_3{\cdot}Et_2O$ furnished **323**. When $Mn(dpm)_3$ or $Co(acac)_2$ or $Fe(acac)_3$ was used as the catalyst in the presence of $PhSiH_3$, they found that the undesired thermodynamic product **324** predominated. In contrast, the use of Pearlman's catalyst under a H_2 atmosphere gave a mixture of the desired kinetic product **325** and **324** (dr = 3 : 1), favouring **325**. Hippolachnin A (**326**) could be obtained from **325** in two steps.

In 2016, Luo and co-workers finished the synthesis of various iboga alkaloids,[67] in which iron-catalyzed HAT was performed to achieve hydrogenation and hydration of alkenes (Scheme 41). Starting from tryptamine, tertiary amine **327** was obtained in seven steps, which could be transformed to **330** *via* gold-catalyzed oxidation, alkylation and stevens rearrangement. The Wittig reaction furnished alkene **331**, and the double bond could be reduced to ibogamine (**332**) and epiibogamine (**333**) *via* Fe-catalyzed HAT-based hydrogenation, slightly preferring undesired **333**. Manganese and cobalt-based catalysts were inferior in this case since **333** was afforded as the predominant product with these catalysts. Moreover, activated Pd/C and H_2 conditions also gave **333** in high yield. In the synthesis of vinblastine (**337**), the advanced intermediate **334** was furnished from L-tryptophan in eight



Scheme 40 Carreira's synthesis of hippolachnin A (**326**).

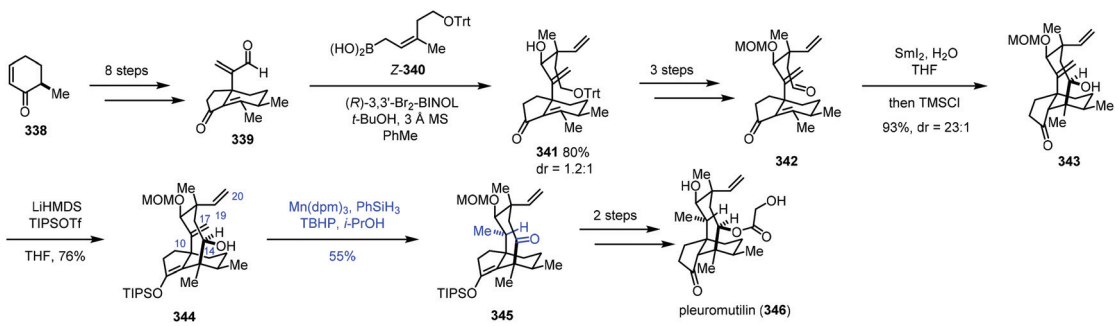


Scheme 41 Luo's synthesis of various iboga alkaloids.

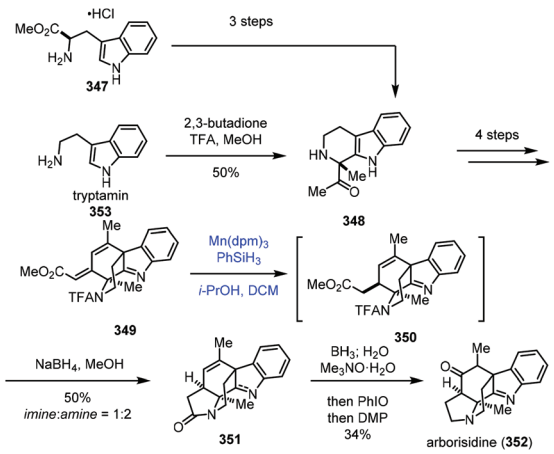
steps. Wittig reaction of **334** furnished the fragment **335**. Using the conditions reported by Boger and co-workers,[8] Fe (III)-promoted coupling of **335** with the commercially available vindoline **336** gave the coupled product, which was treated with an Fe(III)-$NaBH_4/O_2$ solution to selectively hydrate the resulting trisubstituted alkene and reduce the iminium ion, providing vinblastine (**337**) in 50% yield.

In Reisman's synthesis of pleuromutilin,[68] regarding the HAT-based hydrogenation step, an intramolecular abstraction of protons to rationalize the formation mechanism of the unexpected product **345** was proposed (Scheme 42). Bicycle **339** was synthesized from enone **338** in eight steps. Asymmetric allylboration with *Z*-**340** gave desired **341**, which could be transformed to **342** by a three-step sequence. An eight-membered ring was formed through a SmI_2-promoted cyclization, delivering tricyclic **343**. Enol ether **344** was then prepared. To finish the synthesis of pleuromutilin, chemoselective reduction of the C10–C17 exocyclic olefin was required. However, under the standard hydrogenation conditions with a cationic transition metal, hydrogenation of the more accessible C19–C20 vinyl group occurred. Thus the authors turned to MHAT reactions. HAT-type hydrogenation of **344** under the conditions $Mn(dpm)_3/PhSiH_3$/TBHP/*i*-PrOH led to unexpected **345** in 55% yield, in which the C10–C17 olefin was reduced and C14 alcohol was oxidized to ketone. Only trace amounts of products arising from C19–C20 vinyl reduction were noticed, which is in stark contrast to the standard hydrogenation conditions with a cationic transition metal. The authors thus proposed that a transannular [1,5]-HAT process occurs and cleavage of O–H bonds to form a ketone is a driving force of this conversion. The hypothesis is supported by deuterium-labeling experimental results. Besides, HAT-type hydrogenation of the protected C14 alcohol substrate gave the corresponding C10 alcohol as a mixture of diastereomers with only 6–10% conversion. Finally, pleuromutilin (**346**) was obtained after reduction, acylation and deprotection.

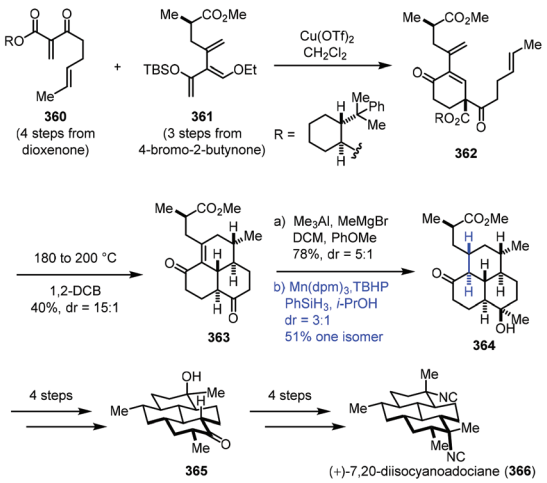
In 2019, Snyder and co-workers reported the synthesis of arborisidine (Scheme 43).[69] They conducted a Mn-catalyzed hydrogenation process to realize the 1,4-reduction of dienoate. In their synthesis, the racemic **348** was obtained from tryptamine (**353**) *via* Pictet–Spengler reaction, while an enantioselective synthesis of **348** was achieved by a three-step sequence from D-tryptophan methyl ester. **348** was then advanced to tetracyclic dienoate **349**. Conventional dienoate hydrogenation and conjugate reduction methods failed with **349**. Under such circumstances, they tried radical hydrogenation conditions with $Mn(dpm)_3/PhSiH_3$, and the desired 1,4-reduction product **350** could be produced. The optimization results showed that the best conversion required using Mn $(dpm)_3$ in a 50% loading, excess amounts of $PhSiH_3$ and trace air as the activator of the catalyst. Arborisidine (**352**) was thus



Scheme 42 Reisman's synthesis of pleuromutilin (**346**).



Scheme 43 Snyder's synthesis of arborisidine (**352**).



Scheme 45 Shenvi's synthesis of (+)-7,20-diisocyanoadociane (**366**).

synthesized after lactamization and functional group conversions.

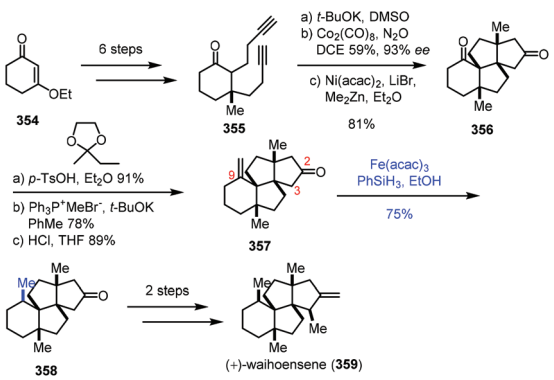
In Yang's synthesis of waihoensene (**359**) in 2020 (Scheme 44),[70] it is interesting to note that HAT-type hydrogenation gave a higher yield of the desired product with the tetracyclic substrate **357**. The tetracyclic substrate **357** was synthesized from enone **354** through Conia-ene type cyclization and Pauson–Khand reaction. Conventional hydrogenation with common metal catalysts led to an undesired diastereomer. HAT-type hydrogenation with $Fe(acac)_3$ as the catalyst, in contrast, generated desired **358** in 75% yield. The authors envisioned that the resulting C9 radical from **357** would abstract a proton from the proximal C3 next to the C2 carbonyl group through an intramolecular HAT, and the proposed pathway might account for the high diastereoselective reduction. They also conducted a density functional theory (DFT) experiment to further rationalize the observed selectivity. Waihoensene (**359**) was then furnished *via* methylation and methylenation.

In 2016, Shenvi and co-workers accomplished the synthesis of (+)-7,20-diisocyanoadociane (Scheme 45).[71] They employed Mn-catalyzed radical hydrogenation of a conjugated tetrasubstituted olefin to access the thermodynamic product. Starting materials **360** and **361** were obtained from dioxenone and 4-bromo-2-butynone, respectively. An intermolecular Diels–Alder cycloaddition between **360** and **361** with $Cu(OTf)_2$ furnished **362**, which was transformed to tricyclic **363** by an intramolecular Diels–Alder cycloaddition at 180 °C and removal of the auxiliary at 200 °C. Methylation generated the corresponding alcohol. Upon exposure of the alcohol to a Pd, Pt, or Rh catalyst, undesired deconjugation occurred. They eventually found that the hydrogenation of the highly strained alkene could be realized under MHAT conditions ($Mn(dpm)_3$, TBHP, $PhSiH_3$, and *i*-PrOH), delivering the thermodynamic product **364** in 51% yield as the major isomer. Tricyclic **364** was advanced to (+)-7,20-diisocyanoadociane (**366**) in eight steps.

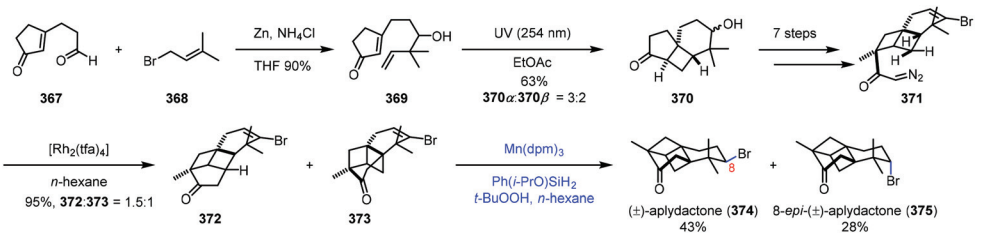
In the synthesis of aplydactone in 2017,[72] Zhang and co-workers employed a strategy to realize hydrogenation of vinyl bromide (Scheme 46). Coupling of **367** and **368** led to **369**. Irradiation of **369** afforded tricyclic **370** *via* [2 + 2] photocycloaddition, which was converted to **371** in seven steps. Transannular C–H insertion was performed to form the skeletal structure of aplydactone **373** as the minor product. Traditional hydrogenation conditions with Pd/C or PtO_2 as catalysts under H_2 turned out to be ineffective for the reduction of vinyl bromide of **373**. To their delight, subjecting **373** to Shenvi's conditions[5b] afforded uneventfully aplydactone (**374**) and its C8-epimer **375** in 43 and 28% yield, respectively.

In 2018, Dethe completed the synthesis of (+)-taondiol (**381**) (Scheme 47).[73] Enone **376** was prepared through ketal protection and Robinson-type annulation. Treatment of **376** with a four-step sequence gave **377**. Under MHAT conditions with Mn $(dpm)_3$ and phenylsilane, hydrogenation of the olefin was achieved to give **378**. It should be noted that the usual hydrogenation conditions with Pd/C and H_2 were able to reduce the olefin; however, undesired debenzylation occurred concomitantly. Moving forward, Friedel–Crafts reaction of **379** and **383** with $BF_3{\cdot}Et_2O$ was carried out to attain pentacyclic **380**, which was then advanced to (+)-taondiol (**381**).

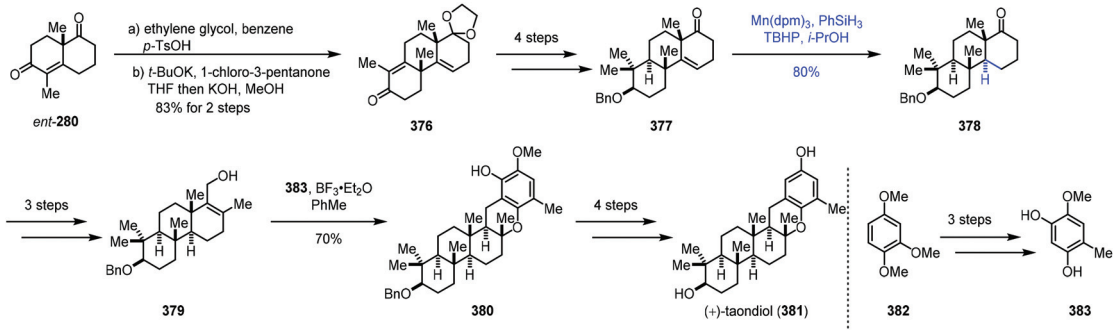
Using the MHAT-based hydrogenation approach, Krische and co-workers completed the synthesis of andrographolide



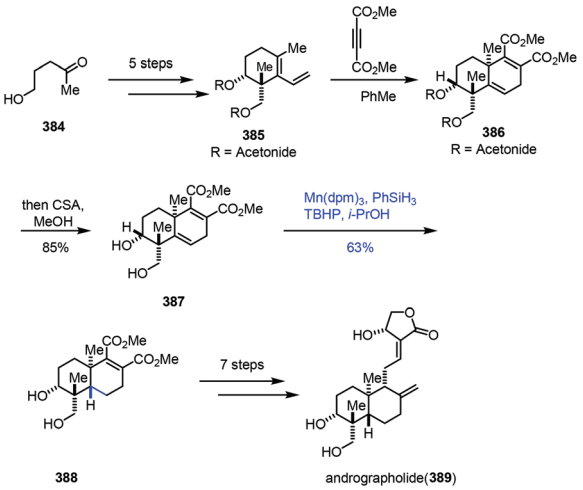
Scheme 44 Yang's synthesis of waihoensene (**359**).



Scheme 46 Zhang's synthesis of aplydactone (**374**).



Scheme 47 Dethe's synthesis of (+)-taondiol (**381**).

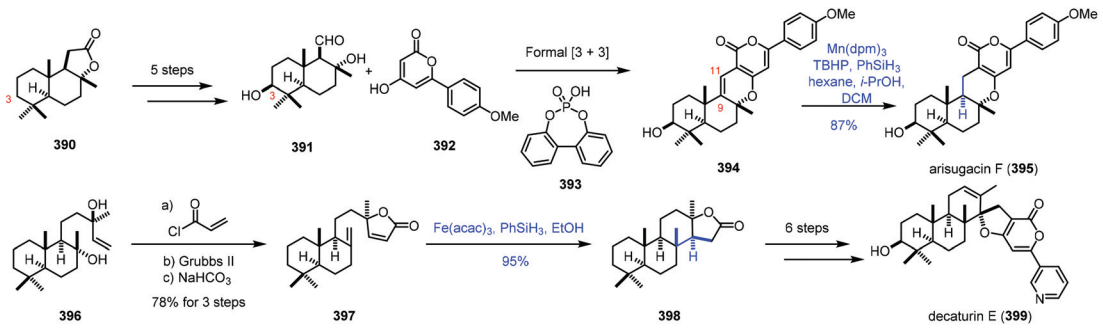


Scheme 48 Krische's synthesis of andrographolide (**389**).

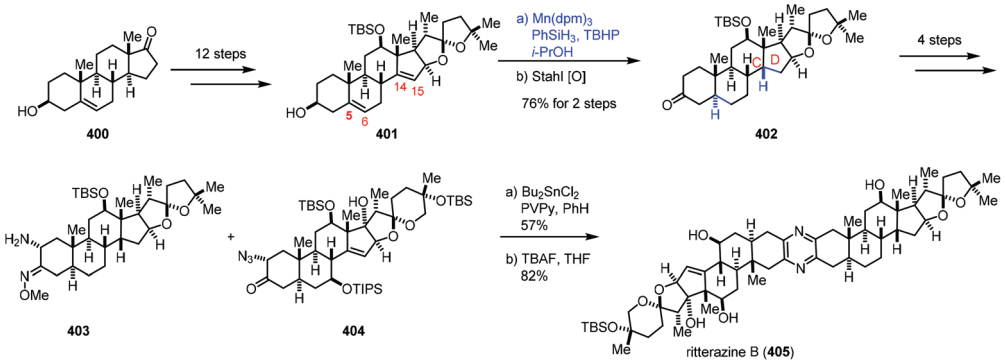
(Scheme 48).[74] Diene **385** was attained from 5-hydroxy-2-pentanone (**384**) in five steps. Diels–Alder cycloaddition of diene **385** and dimethyl acetylene dicarboxylate followed by hydrolysis gave diol **387**. Chemo- and stereoselective reduction of the alkene was achieved by the Mn-catalyzed hydrogenation reaction in the presence of phenylsilane to give *trans*-decalin **388** in 63% yield. In comparison, a *cis*-decalin product was exclusively formed upon subjecting acetonide **386** to identical reaction conditions. Andrographolide (**389**) was obtained from **388** in seven steps.

In 2020, Renata and co-workers applied biocatalytic C–H oxidations and MHAT reactions as the main methods to achieve the synthesis of eight meroterpenoid natural products (Scheme 49).[75] The key common intermediate **391** was obtained from sclareolide **390** by a five-step sequence, featuring biocatalytic C3-hydroxylation. A formal [3 + 3] union of **391** and **392** led to **394**. Under the conventional hydrogenation conditions, with Rh, Pt and Pd as catalysts, the reductions occurred at the pyrone moiety. The authors reasoned that MHAT-based reactions would be feasible. The bulky metal catalyst might suppress the reduction of the tetrasubstituted alkene. Among two trisubstituted alkenes, reduction of the C9–C11 alkene would be preferred due to the greater stability of the resulting C9 tertiary radical. Besides, Shenvi discovered that MHAT-based hydrogenation could provide the thermodynamically stable *trans*-decalin product. In practice, the authors discovered that arisugacin F (**395**) could be accessed by Mn-catalyzed HAT-based hydrogenation ($Mn(dpm)_3$, TBHP, and $PhSiH_3$) in 87% yield. In addition, HAT-based intramolecular Giese coupling served as the key step in the synthesis of decaturin E (**399**), in which the *trans*-decalin product **398** was afforded from **397** with complete diastereoselectivity and excellent yield under the conditions of $Fe(acac)_3$ and $PhSiH_3$.

In 2021, Reisman reported the synthesis of ritterazine B (Scheme 50).[76] The advanced diene intermediate **401** was prepared in twelve steps from *trans*-dehydroandrosterone **400**. MHAT-based reduction of the C5–C6 and C14–C15 alkenes of **401** proceeded well to give rise to **402** after oxidation. In this case, *cis*-fusion at the C/D ring-junction would be a thermodynamically stable configuration as supported by DFT studies. The authors found that it was difficult to reduce the C14–C15 double bond under conventional hydrogenation conditions. Ritterazine B (**405**) was accessed by heterodimerization of two advanced fragments **403** and **404** and deprotection.



Scheme 49 Renata's synthesis of oxidized meroterpenoids.

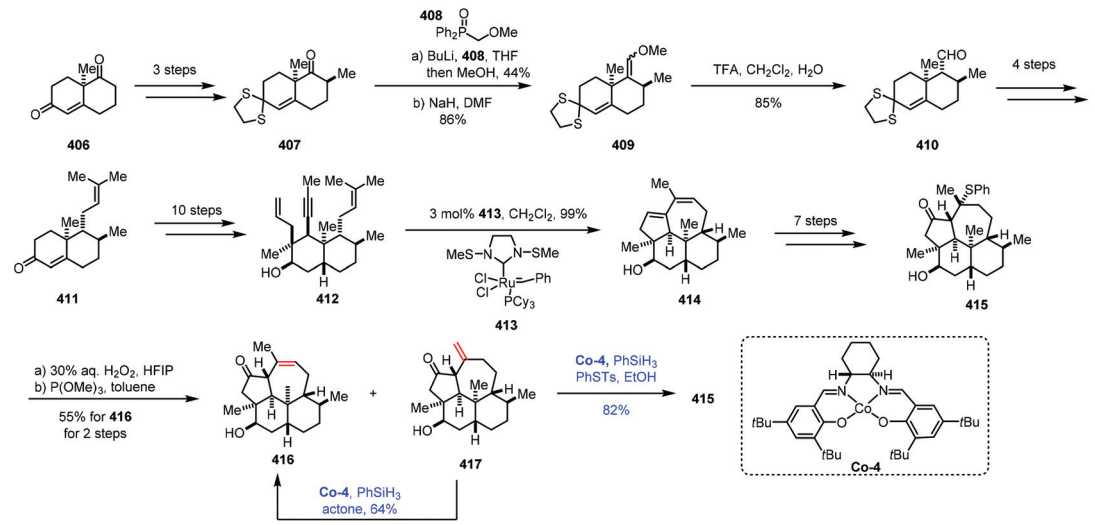


Scheme 50 Reisman's synthesis of oxidized meroterpenoids.

5. Isomerization

The isomerization of olefins is a redox neutral process, which could avoid surplus oxidation state manipulation. Mechanistically, the isomerization of olefins mainly proceeds with two different pathways: either a metal hydrogen mechanism or a π-allyl mechanism.[77,78] However, the isomerization of olefins through MHAT follows a different pathway. In 2014, Holland reported Co-catalyzed isomerization of terminal alkenes to internal *Z*-alkenes *via* most likely the metal hydrogen mechanism.[79] In 2017, Shenvi reported that Co-catalyzed HAT was used to isomerize a terminal alkene to an internal olefin by one position.[5a]

Metz and co-workers subsequently employed Shenvi's method in their synthesis of 3β-hydroxy-7β-kemp-8(9)-en-6-one



Scheme 51 Metz's synthesis of 3β-hydroxy-7β-kemp-8(9)-en-6-one (**416**).

(**416**) in 2017 (Scheme 51).[80] The synthesis commenced with Wieland–Miescher ketone **406**, which was transformed to **407** *via* chemoselective thioketalization, alkylation and epimerization. The carbonyl group underwent olefination to give compound **409**, followed by acid hydrolysis to lead to **410**. Prenylation provided **411**. A ten-step sequence provided ketone **412**. An olefin metathesis with Grubbs catalyst **413** gave tetracyclic dienol **414**, which could be transformed to **415** *via* a seven-step sequence. Upon treatment of **415** with aqueous hydrogen peroxide followed by heating the resulting mixture, **416** and the exocyclic olefin **417** were isolated. Under the conditions of the cobalt complex **Co-4** and $PhSiH_3$, the exocyclic double bond of **417** could be isomerized to an endocyclic double bond to provide **416** in 64% yield. It should be mentioned that **417** could be used to produce **415** through Co-catalyzed Markovnikov addition of thiophenol.

6. Conclusion

The metal-hydride hydrogen atom transfer (MHAT) reaction is a powerful method to functionalize olefins. Here we summarized the applications of MHAT in natural product synthesis. As demonstrated by the aforementioned examples, in many cases, MHAT reactions occur under mild conditions, with high chemoselectivity and high tolerance of functional groups. Besides, Fe, Co, and Mn, the often used metal catalysts in MHAT reactions, are relatively cheap. Based on the aforementioned examples, presumably due to the different reactivities of the metal catalysts, reductive coupling reactions like the Giese reaction and reductive coupling with carbonyl or cyano groups often involve the use of Fe complexes. Hydrogenations use both Mn and Fe metals. With respect to the redox neutral process and hydration and hydroperoxidation reactions, Co and Mn complexes are usually adopted. In particular, Co complexes are the preferred catalysts in hydroarylation and isomerization reactions.

Many reports have shown that C–N or C–X bonds could be formed by MHAT-induced reactions, such as Carreira's hydrohydrazination and Shigehisa's intramolecular hydroamination. However, regarding synthetic applications, there are just limited examples, indicating that in-depth application of these newly developed methods in complex molecule synthesis needs to be exploited in future. Furthermore, a few examples like Liu's synthesis of hispidanin A and Vanderwal's synthesis of plebedipene B have demonstrated the power of MHAT-based polyene cyclization. As such, more sophisticated designs of the MHAT-based cascade strategy in polycyclic or caged architectures, in which multiple bonds could be forged in a single operation, are highly expected.

Conflicts of interest

There are no conflicts to declare.

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