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NHC-catalyzed asymmetric synthesis of natural products and pharmaceutical drugs

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Asymmetric processes catalyzed by *N*-heterocyclic carbenes (NHCs) have become extremely important as strategic tools for the efficient synthesis of bioactive molecular scaffolds. Over the past few years, these catalysts have been widely employed for the total synthesis of pharmaceutical drugs and structurally distinct natural products. This review provides an integrated survey of the asymmetric formal and total synthesis of biologically active natural products and medicinally important compounds using triazolium, imidazolium, and thiazolium-based NHC catalysts from 2016 onwards. This review covers the asymmetric synthesis of different classes of natural products, such as alkaloids, terpenoids, lignans, polyketides, pentadecaketides, and flavonoids, along with pharmaceutical drugs, such as NSAIDs, antidepressants, antibacterial and analgesic agents, by harnessing NHC catalysis.

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1 Introduction

N-Heterocyclic carbenes (NHCs) are defined as singlet carbenes, having a divalent carbon atom in their ring structure that is linked to one or more nitrogen atoms to form a heterocyclic scaffold.¹ As carbenes have six electrons in their valence shell, their incompletely filled valence shell and coordinative unsaturation make free carbenes unstable in nature.^{2,3} Depending on the number of nitrogen atoms in the ring structure, a wide variety of carbene compounds exist with different substituents and ring sizes (Fig. 1).^{3,4} Because of the easily accessible starting materials, sustainable reaction conditions and ease of use, NHCs have been acknowledged as versatile and efficient organocatalysts for the rapid synthesis of a broad range of cyclic and acyclic compounds of pharmacological and biological significance.^{5–11} Along with C–C bond formation, C–heteroatom bond formation can also take place by utilizing NHC organocatalysts.^{5,12–15}

Since the mid-19th century, chemists have been trying to isolate carbenes, but all attempts have failed.¹⁶ Carbenes

typically play the role of extremely reactive intermediates and have a short lifespan. However, the characteristics of *N*-heterocyclic carbenes, where the carbene center is positioned on an *N*-heterocyclic ring, are distinct.^{17,18} NHCs continue to intrigue researchers because these compounds are not only employed as organocatalysts^{3,5,19–22} but also serve as ligands for transition-metal catalysis,^{23–26} and they are also used in materials science^{27,28} and nanoparticle applications.^{29–32} Tschugajeff prepared the first complex of a carbene ligand stabilized by an adjacent heteroatom in 1925.³³ The first metal carbene complex was constructed and evaluated by Fischer in 1964.³⁴ In the 1960s, Wanzlick made efforts to prepare and isolate stable NHC, but instead, the corresponding dimer was obtained.³⁵ In 1991, Arduengo *et al.* isolated and identified the first crystalline NHC, IAd, named 1,3-di(adamantly)imidazole-2-ylidene, which was obtained by the removal of a proton from the 1,3-imidazolium salt (Fig. 2).³⁶

Different types of NHC-bound intermediates have been generated as a result of organocatalytic reactions. These can be categorized as Breslow intermediates, radical intermediates, azolium intermediates, homoenolate intermediates, azolium enolate intermediates, acyl azolium intermediates and azolium dienolate intermediates.^{11,37–40} The polarity of carbonyl compounds is inverted when NHC compounds are used as organocatalysts. As a result, a number of nucleophilic addition reactions can take place by utilizing different electrophiles.^{41–52} Hence, NHCs are utilized in a number of transformations or annulation reactions,^{53–55} including Stetter,^{56,57} benzoin,^{58,59} radical,^{60,61} Mannich, and Michael reactions, as well as Claisen rearrangements, C–C/C–H activation and cycloaddition reactions.^{41–52}

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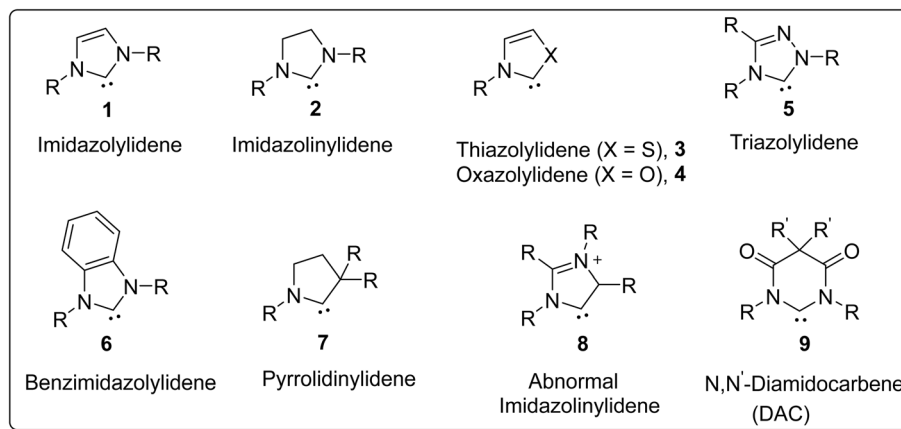



Fig. 1 Structures of the most widely used NHCs.

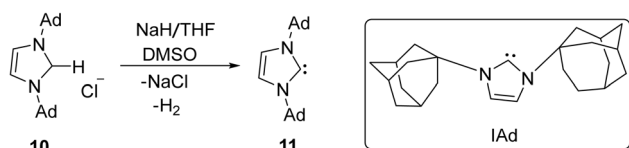
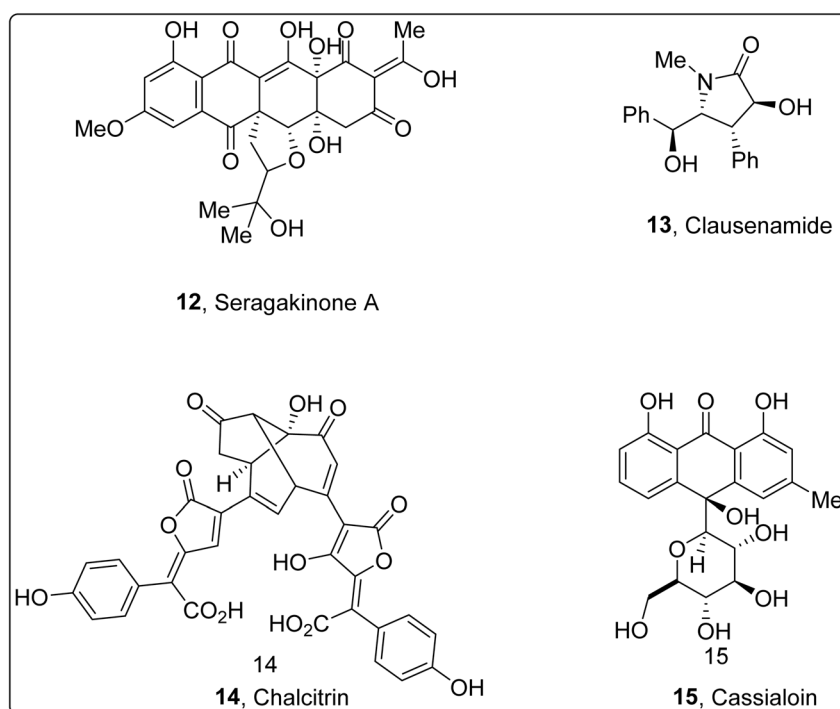


Fig. 2 Synthesis and isolation of the first NHC.

Natural products play a crucial role in the drug discovery process due to their distinctive and physiologically active scaffolds.^{62–64} In natural products and pharmaceutical research, chemists have been focused on the synthesis of enantiomeric compounds, and designing drugs with defined stereochemistry is one of the core challenges in organic synthesis. For example, one enantiomer may have beneficial pharmacological features,

while the other enantiomer may have unfavorable side effects. Therefore, there can be significant risks associated with using racemic substances as pharmaceutical medications.⁶⁵ *N*-Heterocyclic carbenes catalysis is recognized as a potent and adaptable method for the stereoselective synthesis of various compounds,^{3,5,12,15,19,66–71} and natural products such as seragakinone A,⁷² clausenamide,⁷³ cassialoin⁷⁴ and chalcitrin⁷⁵ have been accessed *via* NHC catalysis (Fig. 3). NHC catalysis has also been employed to synthesize fragments of natural products⁷⁶ and pharmaceuticals-related compounds.^{77–79} Over a prolonged timespan, a range of NHC precursors have been constructed for asymmetric organocatalysis. First, Sheehan and Hunneman harnessed precatalyst chiral thiazolium salts for the enantioselective benzoin condensation reaction about half

Fig. 3 Natural products synthesized *via* NHC catalysis.

a century ago.⁸⁰ Then, in 1996, a triazolium-based NHC salt was used as a precatalyst by Enders and co-workers in the Stetter reaction.⁸¹ Since then, there has been notable progress in NHC-catalyzed asymmetric synthesis.

A number of review articles have been published over many years on the versatile utility of NHCs as catalysts, cooperative catalysts, and ligands.^{82,83} Zhang *et al.*, in 2025, presented a review on asymmetric axial and planar chirality construction through the use of NHC organocatalysis.⁸⁴ Another review was published by Li *et al.* in 2025 on asymmetric electrophilic activation of carbonyl compounds by NHC catalysis.⁸⁵ In 2024, Cai *et al.* presented a review on radical reactions carried out by the SET reduction of NHC-derived acyl azoliums.⁸⁶ In 2020, Que *et al.* reviewed the advances in NHC catalysis for natural product synthesis.⁸⁷ Moreover, in 2012, Scheidt and coworkers also summarized the application of NHC catalysis in the total synthesis of natural products.⁶⁷ Since then, much more progress has been made on the applications of NHC catalysis. Thus, this review provides an overview of various NHC catalysts that have been utilized (Table 1) for the synthesis of different classes of natural products and pharmaceutical drugs, reported since 2016.

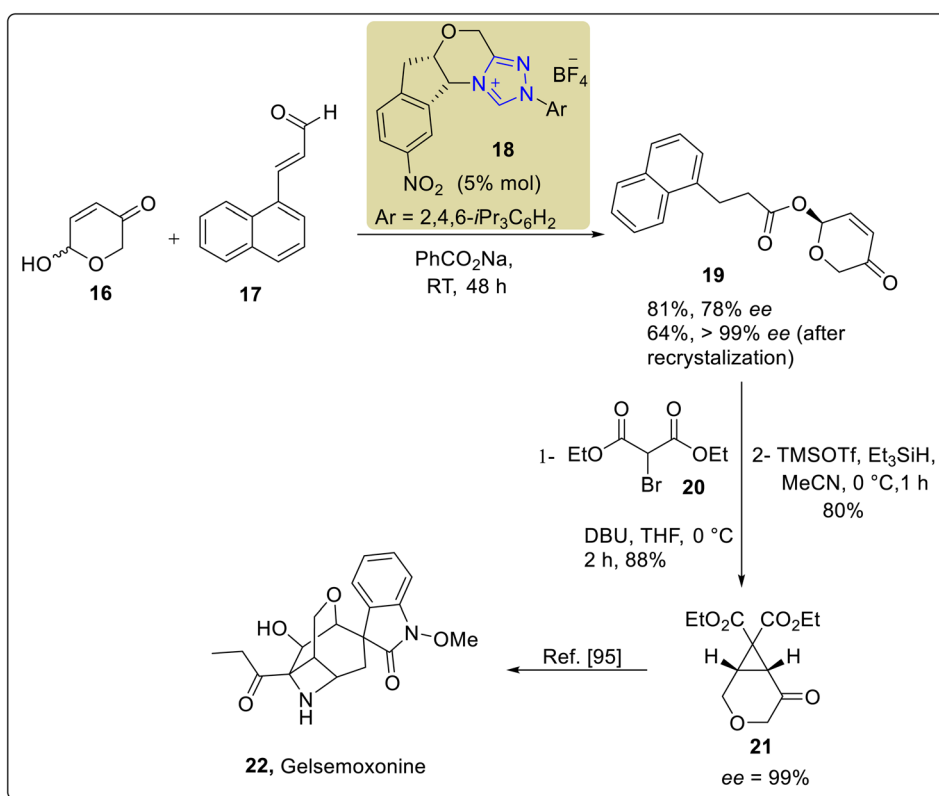
2 Applications of NHC catalysts in asymmetric synthesis

2.1 Natural products

2.1.1 Synthesis of alkaloids. Gelsemoxonine **22**, a gelsemium alkaloid, was first extracted from the foliage of *Gelsemium elegans* Benth., by the research group of Clardy in 1991.⁸⁸ The

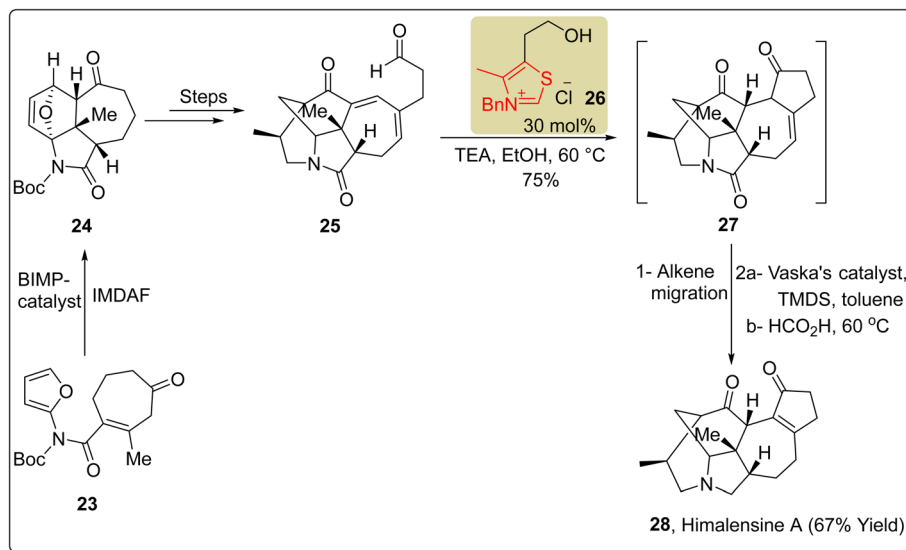
original structure of Gelsemoxonine (**22**) was revised in 2003 by Aimi, based on X-ray crystallographic analysis, as the initial proposed structure was misassigned.⁸⁹ Gelsemium alkaloids exhibit analgesic, anti tumor and antispasmodic activity; furthermore, they are also used to treat skin ulcers.^{90–93} In 2016, an asymmetric synthesis of Gelsemoxonine **22** was reported by Zhao *et al.* by utilizing indanol-triazolium-based NHC **18** as a catalyst. In this synthetic protocol, redox esterification of 6-hydroxy pyranone **16** and enal **17** was observed in the presence of triazolium-based NHC **18** (catalyst) and sodium benzoate (base) at room temperature. As a result, ester **19** was generated with 64% yield and 99% ee after recrystallization. The ester **19** was then reacted with bromomalonate **20** by employing DBU in THF at 0 °C. The resulting compound was allowed to react further with triethyl silane in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) and MeCN to synthesize the key intermediate **21** with 99% ee.⁹⁴ The fabricated key intermediate **21** had been reported earlier, in 2011, by Shimokawa *et al.* and used for the synthesis of Gelsemoxonine **22** (Scheme 1).⁹⁵

Himalensine A **28**, which belongs to the *Daphniphyllum* class of alkaloids with a trinorcalyciphylline A type skeleton, was first isolated in 2016 by Yue and coworkers from *Daphniphyllum himalense*, found in the Himalaya Mountains.^{96–98} In 2017, Dixon and coworkers reported a novel strategy for the enantioselective synthesis of Himalensine A **28** by utilizing NHC **26** as a catalyst *via* 22-steps. In this unique synthetic protocol, *N*-Boc protected furan **23** was allowed to undergo intramolecular Diels–Alder furan (IMDAF) cycloaddition reaction in the presence of bifunctional iminophosphorane (BIMP) catalyst to



Scheme 1 Asymmetric synthesis of gelsemoxonine **22**.





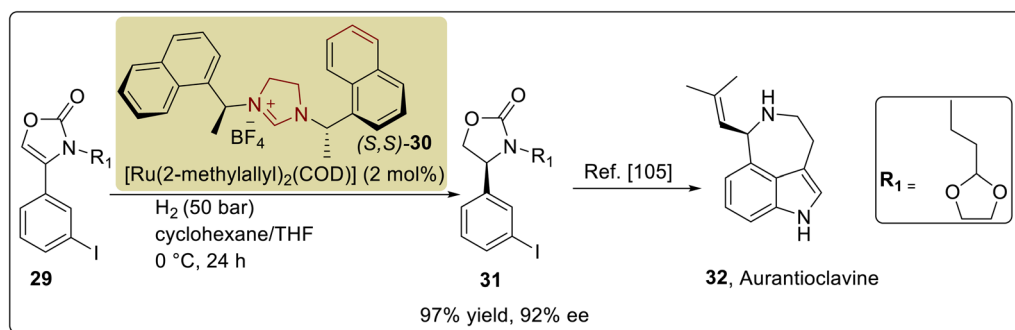
Scheme 2 Asymmetric synthesis of himalensine A 28.

furnish the tricyclic core structure **24**. Over a few steps, this tricyclic core structure **24** was converted into the aldehyde moiety **25**. The aldehyde **25** was then reacted with thiazolium-based NHC **26** (catalyst) and TEA (base) in ethanol at 60 °C to obtain an intermediate, *i.e.* the pendant cyclopentenone **27**, with 75% yield *via* Stetter cyclization. An alkene migration of intermediate cyclopentenone **27** generated the enone that underwent further reduction in the presence of Vaska's catalyst [Ir(CO)(PPh₃)₂Cl] and formic acid at 60 °C to generate (–)-himalensine A **28** in 67% yield (Scheme 2).⁹⁹

Aurantioclavine **32** is an ergot alkaloid that was first extracted from the *Penicillium aurantiovirens* in 1981.¹⁰⁰ Its tricyclic indole core structure has been utilized as a biosynthetic precursor for the synthesis of complex communesin alkaloids,^{101,102} which demonstrate cytotoxic activity against blood cancer cells.¹⁰³ In 2018, Glorius and coworkers introduced an asymmetric approach to synthesize (–)-aurantioclavine **32** by utilizing NHC (*S,S*)-**30** as a ligand, with ruthenium metal catalyst. In their synthetic route, 2 moles of Ru–NHC complex accelerated the asymmetric hydrogenation of 2-oxazolones **29** under 50 bar H₂ in cyclohexane and tetrahydrofuran (solvent) at

0 °C to obtain 2-oxazolidinone **31** in 97% yield with 92% enantioselectivity.¹⁰⁴ The synthesized key intermediate 2-oxazolidinone **31** was employed by Park *et al.* in 2016 for the total asymmetric synthesis of aurantioclavine **32** (Scheme 3).¹⁰⁵

Cruciferane is a naturally occurring alkaloid composed of fused rings of pyrroloindoline and quinazolinone. Cruciferane was first extracted from the non-woody plant *Isatis indigotica* (Chinese woad) in 2012.¹⁰⁶ The desiccated roots and foliage of *Isatis indigotica* have traditionally been employed to cure influenza, erysipelas, epidemic hepatitis, encephalitis B and carbuncles.^{107–109} Moreover, it exhibits hepatoprotective and antipyretic activity.¹¹⁰ In 2019, Mhaske and coworkers introduced a novel approach to synthesize the asymmetric deoxy-cruciferane **41** by utilizing the triazolium-based NHC **40** as a catalyst for the intramolecular [3 + 2] annulation reaction. The synthetic protocol commenced with the Heck coupling reaction of methyl acrylate **33** and *o*-bromoaniline **34** in the presence of Pd(PPh₃)₂Cl₂ and TEA at 100 °C to generate amine **35**. After that, unstable benzoxazinone **37** was furnished by the reaction of anthranilic acid **36** and triethyl orthoformate in the presence of *p*-TsOH. Next, amine **35** and unpurified benzoxazinone **37** were

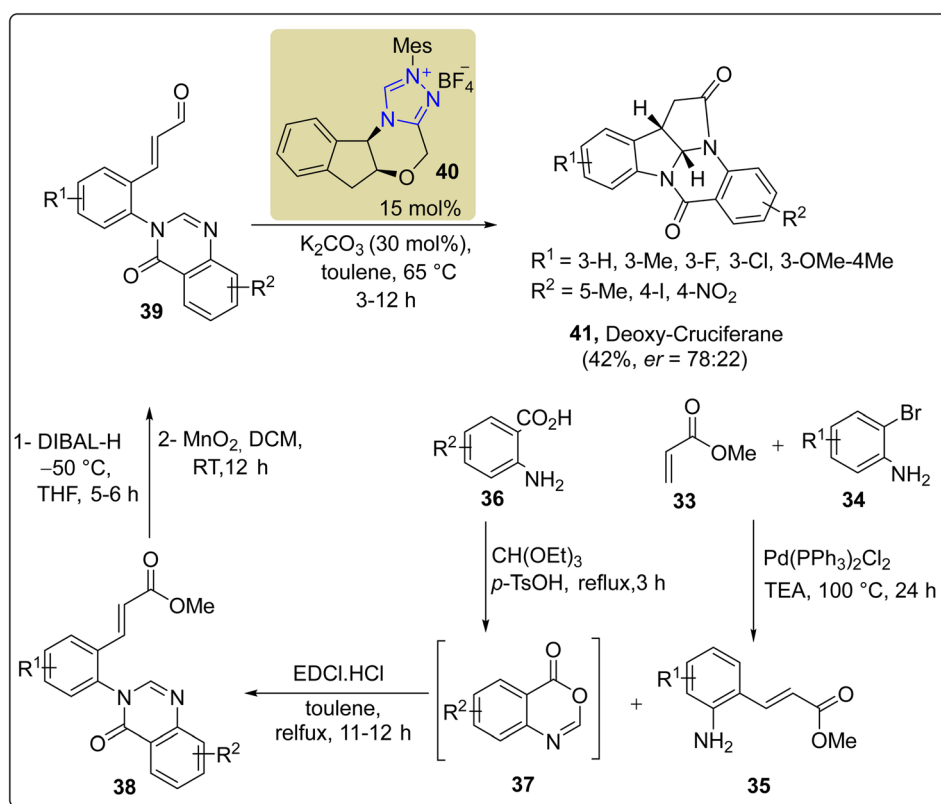
Scheme 3 Asymmetric synthesis of aurantioclavine **32**.

allowed to react to deliver quinazolinone ester **38** in the presence of EDCI in toluene. In the next step, ester **38** was subjected to reduction in the presence of DIBAL-H and THF at $-50\text{ }^{\circ}\text{C}$ to synthesize the corresponding alcohol, which further underwent oxidation in crude form by utilizing MnO_2 in DCM at room temperature to synthesize the aldehyde **39**. Finally, enal **39** was made to undergo intramolecular [3 + 2] cycloaddition reaction with quinazolinone's internal imine in the presence of NHC **40** (catalyst) and K_2CO_3 (base) in toluene at $65\text{ }^{\circ}\text{C}$ to deliver deoxy-cruciferane **41** in 42% yield with 78:22 enantiomeric ratio (Scheme 4).¹¹¹

The *clausena* alkaloids, clausenamide and its derivatives, including neoclausenamide **47**, were obtained from the hydrous extract of the Chinese traditional medicinal plant *Clausena lansium* Skeels in 1988. As a traditional medicine, the water extract of *Clausena lansium* obtained by decoction is used for the treatment of various diseases, including dermatological diseases and hepatitis.¹¹² Moreover, it also shows a wide range of bioactivities, including hepatoprotective activity, anti-aging activity, anti-ischemic activity and nootropic activity.^{113–117} Hu *et al.*, in 2019, discovered an efficient approach to synthesize an asymmetric derivative of clausenamide, known as *epi*-neoclausenamide **47**, by utilizing NHC **44** as a catalyst. In this new strategy, α -bromoenal **42** and α -aminoketone **43** were made to undergo [3 + 2] annulation reaction in the presence of triazolium-based NHC **44** (catalyst) derived from the amino indanol core structure and TEA (base) in 1,4-dioxane to synthesize the γ -lactam **45** with 98% ee, 20 : 1 dr and 84% yield.

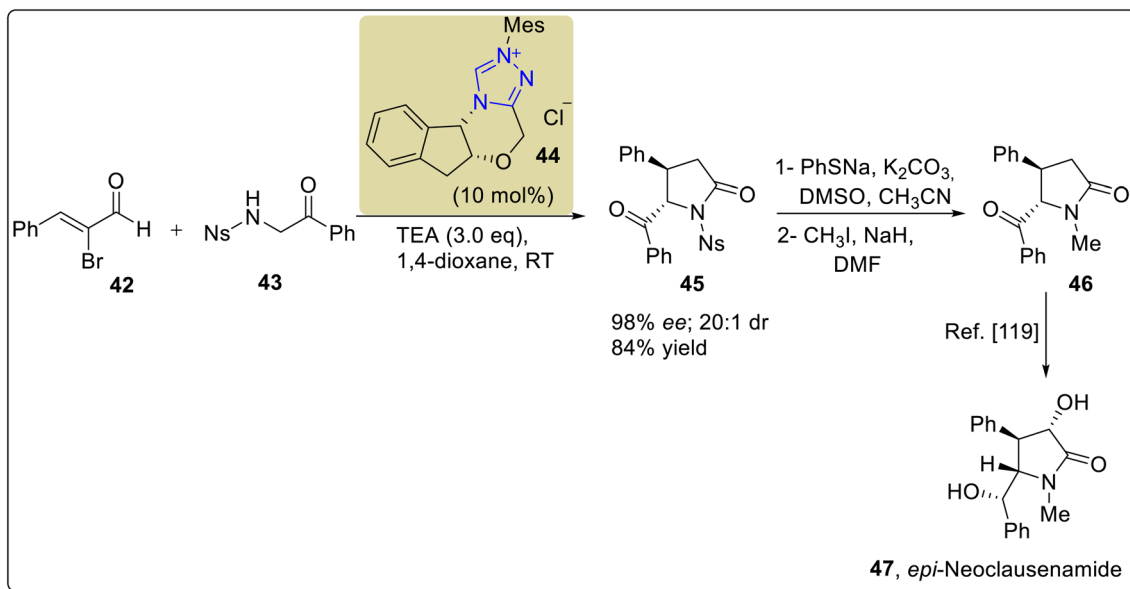
Next, the Ns group in the γ -lactam **45** was removed by using sodium benzenethiolate, potassium carbonate, dimethyl sulfide and acetonitrile, and subsequent methylation was achieved in the presence of methyl iodide and sodium hydride in DMF to synthesize 5-benzoyl-1-methyl-4-phenylpyrrolidin-2-one **46**.¹¹⁸ The synthesized compound **46** was reported earlier in 2015 and utilized for the total synthesis of *epi*-neoclausenamide **47** (Scheme 5).¹¹⁹

Pumiliotoxin B is a dendrobatid alkaloid that was first isolated from *Dendrobates pumilio*, a poison frog, in 1967. Pumiliotoxin B **54** shows cardiotoxic and myotonic activity.¹²⁰ The marine-sponge-derived triannular guanidine alkaloid netamine **69** was extracted from *Biemna laboutei* in 2006 by Kashman and coworkers. Netamine **69** was inferred to exhibit cytotoxic activity against colon (HT29), breast (MDS-MB-231), and lung (A549) cancer cells.¹²¹ In this regard, Hoveyda and coworkers, in 2019, introduced enantioselective routes to generate netamine **69** and the fragment of pumiliotoxin B **54** by utilizing NHC **50** as a ligand with Cu metal catalyst. For the synthesis of pumiliotoxin B **54**, *Z*-trisubstituted alkenyl-B (pin) **48**, mono-substituted alkene **49** and polymethylhydrosilane (PMHS) were reacted to generate 1,5-diene **51** by utilizing NHC **50** (ligand) with copper metal catalyst. Over a few steps, 1,5-diene **51** was converted into compound **52**, which was further reacted with LDA in THF to synthesize the alkyne **53**.¹²² The synthesized intermediate, *i.e.*, alkyne **53**, had been reported earlier by Lin *et al.* in 1996, leading toward the synthesis of pumiliotoxin B **54** (Scheme 6).¹²³



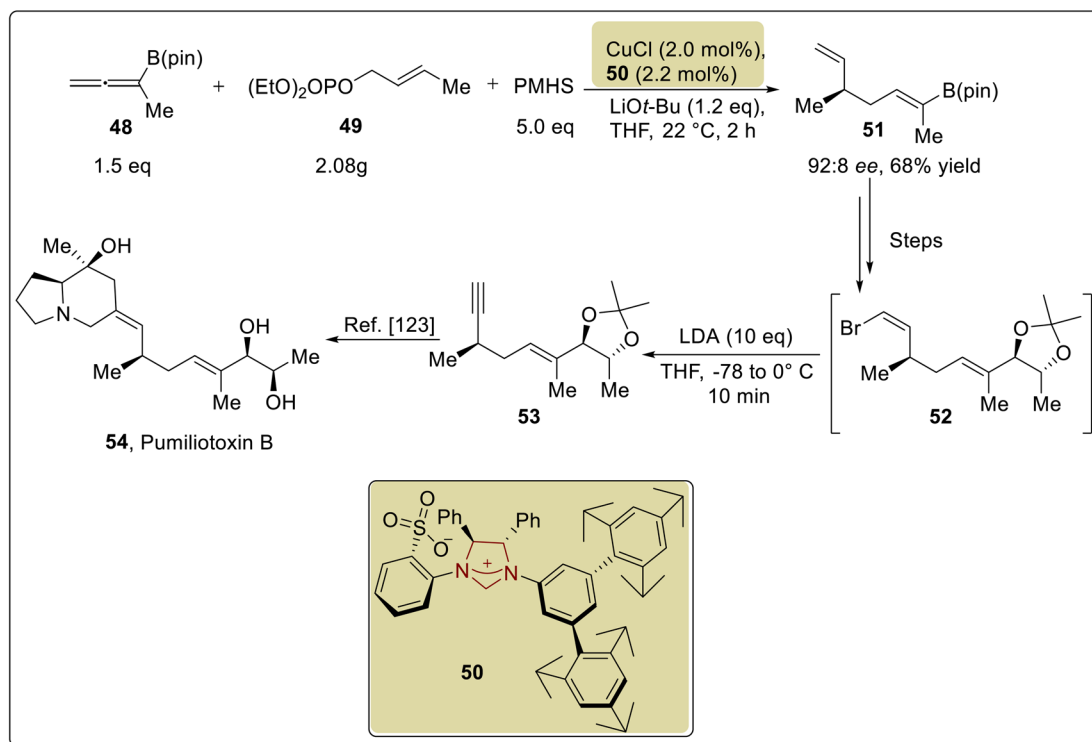
Scheme 4 Asymmetric synthesis of deoxy-cruciferane **41**.



Scheme 5 Asymmetric synthesis of *epi*-neoclausenamide 47.

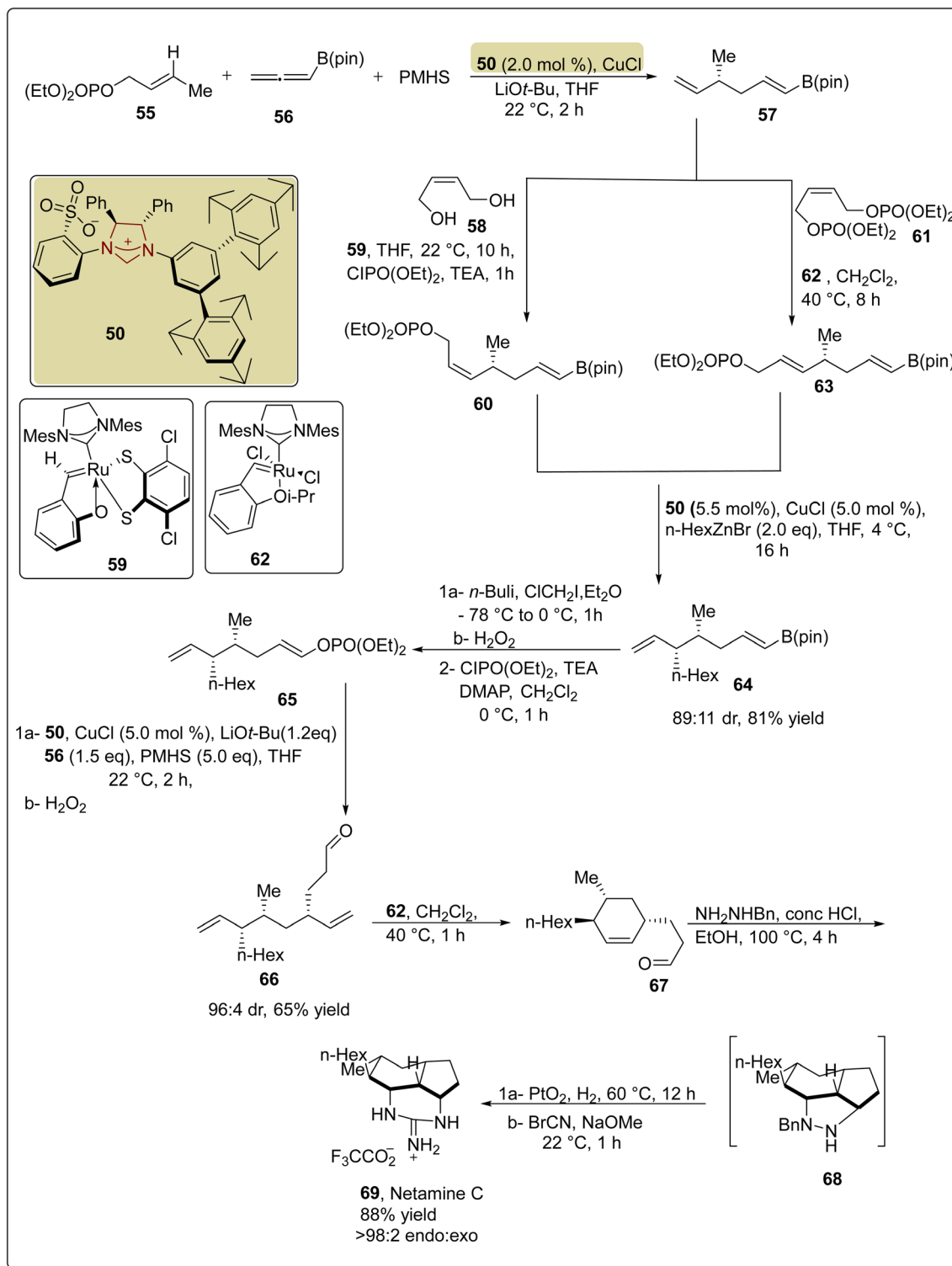
To synthesize netamine C 69 through a novel synthetic strategy, allylic phosphate 55, allenyl-B(pin) 56 and polymethylhydrosiloxane (PMHS) were reacted in the presence of Cu catalyst with NHC 50 as ligand and LiOt-Bu in THF at 22 °C to furnish 1,5-diene 57. After cross-metathesis of 57 with diol 58 and bis-phosphate 61 separately, in the presence of Ru catalysts 59 and 62, respectively, *Z*-60 and *E*-63 allylic phosphates were obtained. Both *E*- and *Z*-compounds (60 and 63) produced the same isomer 64 when they underwent reaction with *n*-hexylzinc

bromide by utilizing the Cu–NHC complex (formed *in situ* from 50). Then, compound 64 was allowed to react with *n*-BuLi, ClCH₂I, Et₂O and H₂O₂ to synthesize the alcohol, which was subsequently converted into the corresponding phosphate 65 by utilizing ClPO(OEt)₂, TEA, DMAP, and CH₂Cl₂. Next, another allylic substitution was made between *n*-hexylphosphate 65 and allenyl-B(pin) 56 by utilizing a Cu catalyst with NHC 50 and followed by oxidation to furnish the corresponding aldehyde 66. Ring closure of aldehyde 66 through metathesis generated



Scheme 6 Asymmetric synthesis of pumiliotoxin B 54.





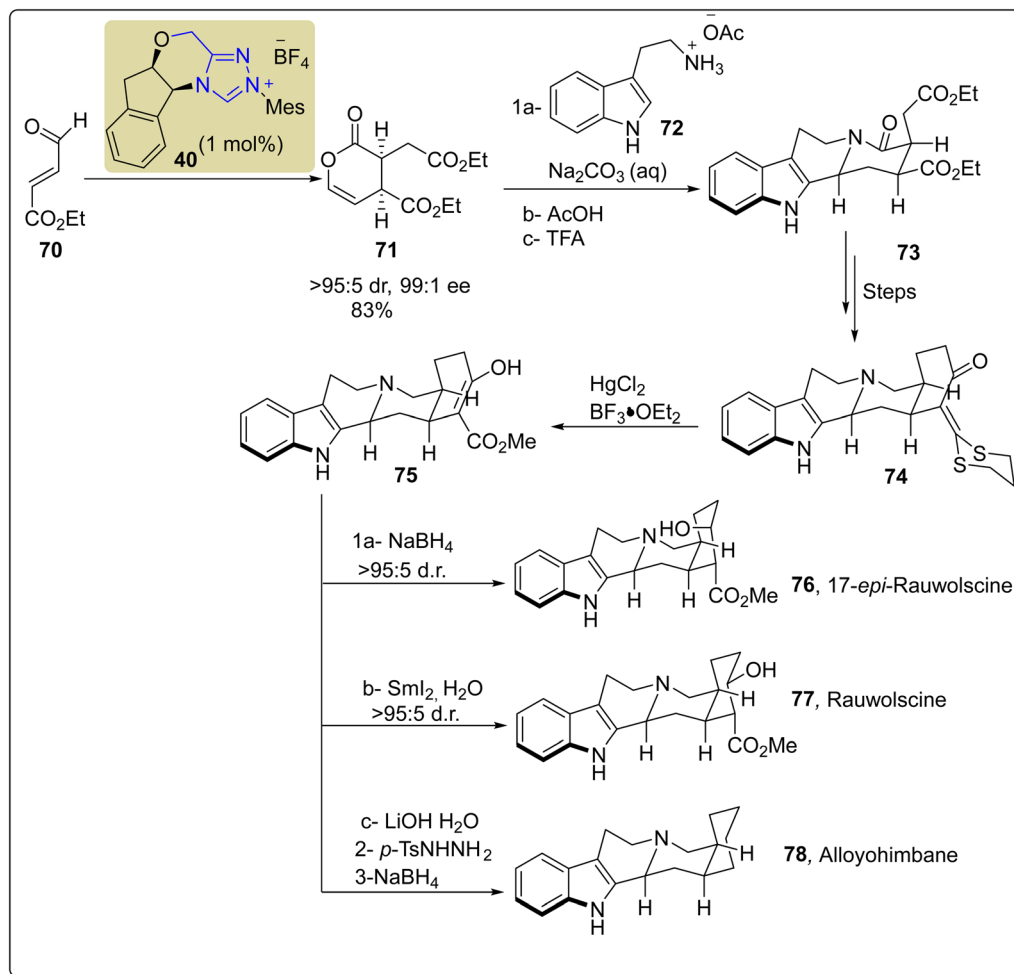
Scheme 7 Asymmetric synthesis of netamine C 69.

cyclohexenyl intermediate **67**, which further underwent a [3 + 2] cycloaddition reaction in the presence of NH₂NHBn, HCl and EtOH at 100 °C to generate **68**. Finally, netamine C **69** was obtained by catalytic hydrogenation of **68** (Scheme 7).¹²²

A monoterpenoid indole-based alkaloid, *i.e.* yohimbine, was first extracted from the outer covering of a tree found in

Western Africa named *Pausinystalia yohimbe*. On the basis of stereochemistry around the D-ring, these alkaloids are further classified into four subfamilies; *normal*, *allo*, *pseudo* and *epiallo*. Yohimbine alkaloids demonstrate anti-adrenaline, antidiuretic, mydriatic, prototypical α₂-receptor antagonistic and serotonin antagonistic activity.¹²⁴ Scheidt and coworkers, in 2020,





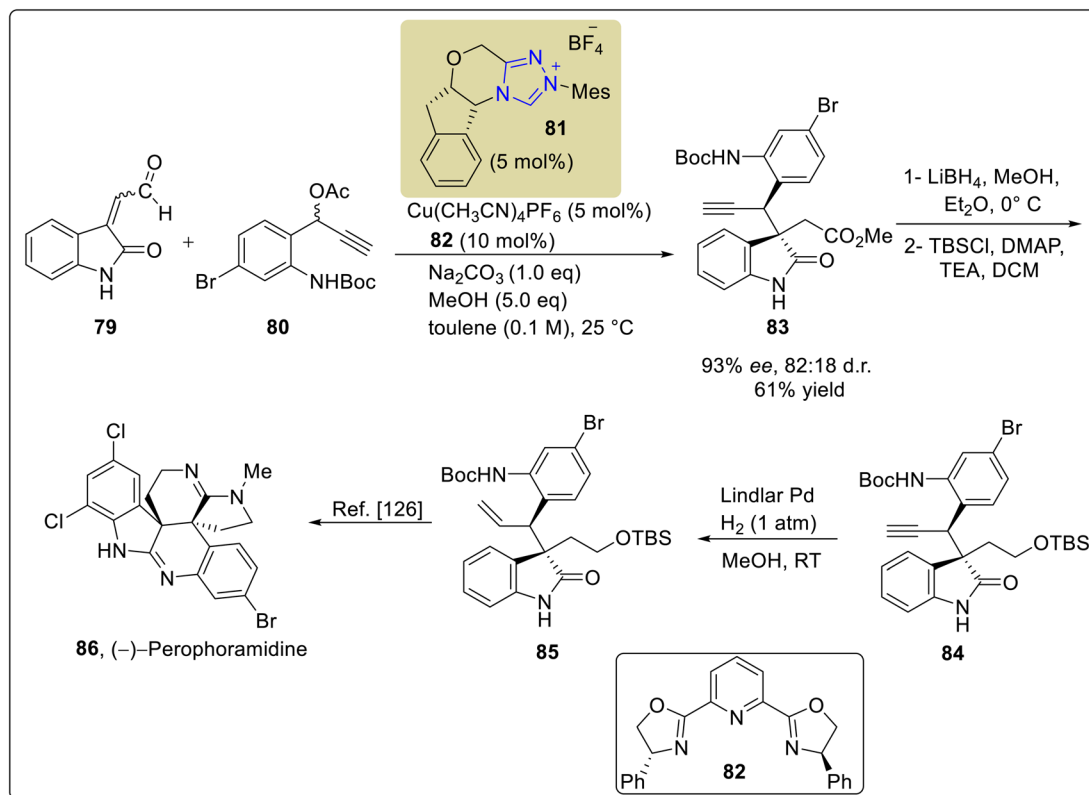
Scheme 8 Asymmetric synthesis of yohimbine alkaloids.

reported an enantioselective approach to synthesize the yohimbine alkaloid by utilizing NHC **40** as a catalyst. In this synthetic protocol, enol lactam **71** was obtained with 99 : 1 ee, >95 : 5 dr and 83% yield by dimerization of aldehyde **70** by utilizing triazolium-based NHC **40**. Next, the enal lactam **71** was made to undergo amidation/*N*-acyliminium ion cyclization in a three-step sequence. Initially, the enal lactam **71** was treated with tryptamine **72** and Na_2CO_3 in CH_2Cl_2 ; subsequent acidification was done with AcOH, then treatment with TFA favored the cyclization to synthesize compound **73**. Over a few steps, compound **73** was converted into α -oxo-ketene dithioacetal **74**. In the next step, the α -oxo-ketene dithioacetal **74** was treated with mercury(II) chloride and $\text{BF}_3 \cdot \text{OEt}_2$ to generate the main component, *i.e.* methyl ester **75**. Finally, ester **75** was treated in three different ways to produce yohimbine-based natural products. Asymmetric reduction of methyl ester **75** was performed in the presence of NaBH_4 to obtain 17-*epi*-rauwolscine **76**. On the other hand, methyl ester **75** was treated with SmI_2 and H_2O to produce (–)-rauwolscine **77**. Finally, decarboxylation of β -ketoester **75** was done by using $\text{LiOH} \cdot \text{H}_2\text{O}$ with subsequent Wolff–Kishner deoxygenation to synthesize alloyohimbane **78** (Scheme 8).¹²⁵

Verbitski *et al.*, in 2001, extracted the polyannular alkaloid perophoramidine **86** for the first time from *Perophora namei*, an organism found in the Philippines.¹²⁶ Perophoramidine **86** exhibits cytotoxic activity against the HCT116 colon cancer cell line.¹²⁷ In 2022, Gong and coworkers reported a novel strategy for the asymmetric synthesis of perophoramidine **86** by exploring Cu/NHC **81** cooperative catalysis. In this new synthetic protocol, enal **79** and propargylic acetate **80** were made to undergo a stereoselective propargylic alkylation reaction in the presence of the copper/NHC **81** dual catalyst, pyridine bisoxazoline **82** (ligand), Na_2CO_3 and methanol in toluene at 25 °C to obtain oxindole derivative **83** with 61% yield with 93% ee and 82 : 18 d.r. Next, the oxindole **83** was reduced by employing LiBH_4 , methanol and diethyl ether at 0 °C to generate the primary alcohol, which was subsequently protected with TBSCl in the presence of DMAP, TEA and DCM. Finally, the TBS-protected oxindole derivative **84** underwent Lindlar reduction to generate the key component, *i.e.* alkene **85**.¹²⁸ The synthesized alkene **85** had been reported earlier by Trost *et al.*, in 2015, and utilized to furnish asymmetric perophoramidine **86** (Scheme 9).¹²⁶

Debromoflustramine B **99a** is a pyrrolidinoindoline alkaloid that was first extracted from *Flustra foliacea*, a marine bryozoan,



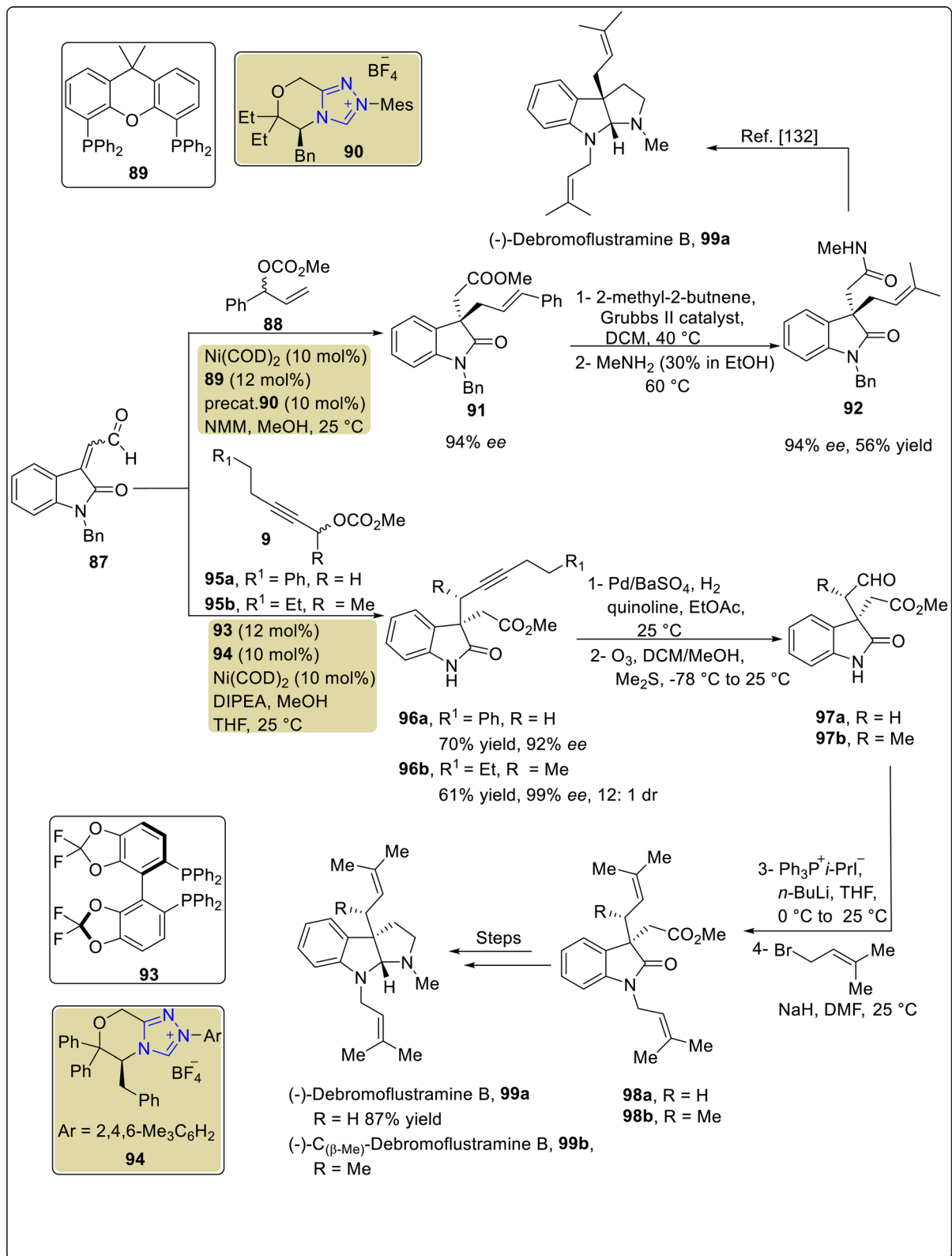
Scheme 9 Asymmetric synthesis of perophoramidine **86**.

in 1994. Debromoflustramine B **99a** has been found to demonstrate bactericidal activity against methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococci*.¹²⁹ In 2022, Fan *et al.* introduced an asymmetric approach to generate debromoflustramine B **99a** by utilizing Ni–NHC **90** synergistic catalysis. In this synthetic pathway, enal **87** and allylic carbonate **88** were made to undergo allylic alkylation reaction in the presence of Ni(COD)₂ catalyst along with NHC **90** (precatalyst), Xantphos **89** (ligand) and *N*-methylmorpholine (NMM) (base) in methanol at 25 °C to furnish 3,3'-disubstituted oxindole **91** with 94% ee. Next, the cross-metathesis reaction of oxindole **91** with 2-methyl-2-butene, in the presence of Grubbs II catalyst, generated the required alkene, which further underwent amidation reaction with methylamine to obtain methyl amide **92** in 56% yield with 94% ee.¹³⁰ The synthesized key component, methyl amide **92**, had been reported earlier, in 2013, by Miyamoto *et al.* and utilized for the total synthesis of debromoflustramine B **99a**.¹³¹ After one year, Peng *et al.* demonstrated another distinguished and efficient asymmetric approach towards the total synthesis of debromoflustramine B **99a** by using Ni–NHC **94** synergistic catalysis. In this synthetic protocol, enal **87** and propargylic carbonate **95a** and **95b** were allowed to undergo stereochemically divergent propargylation reactions under combined catalysis of Ni–NHC **94** by utilizing diphosphine ligand **93**, DIPEA and MeOH, in THF at room temperature to generate asymmetric 3,3'-disubstituted oxindoles **96a** and **96b** in 70% yield with 92% ee and 61% yield with 99% ee, respectively. The alkyne groups in oxindoles **96a** and

96b were allowed to undergo Lindlar reduction, followed by ozone-mediated oxidation, resulting in the synthesis of aldehydes **97a** and **97b**, respectively. Next, Wittig olefination of aldehydes **97a** and **97b** was performed by reaction with triphenylisopropylphosphonium iodide to furnish the corresponding compounds, which were further treated with 1-bromo-3-methylbut-2-ene to generate esters **98a** and **98b**, respectively. Over a few steps, ester **98a** was converted into the final natural product, *i.e.* debromoflustramine B **99a**. Synthesis of the methyl analogue of debromoflustramine B, *i.e.* (–)-C(β-Me)-debromoflustramine B **99b**, was also achieved by this research group (Scheme 10).¹³²

The alkaloid physostigmine **107** was extracted from the poisonous Calabar bean (*Physostigma venenosum*), a vine native to tropical Africa. Physostigmine **107** demonstrates therapeutic potential against Alzheimer's disease.¹³³ Dutta *et al.*, in 2023, reported an enantioselective approach to the synthesis of esermethole **106** and physostigmine **107** by utilizing NHC **102** as the catalyst. In this unique strategy, acylation of diol **100** was achieved by utilizing benzaldehyde **101** as an acylation source in the presence of NHC **102** as a catalyst, with MnO₂ and DABCO in THF at 0 °C to generate the mono-ester **103**. The ester **103** was then treated with PPh₃, imidazole I₂ and THF at 80 °C to furnish its iodo derivative **104**. In the next step, iodo derivative **104** was converted into an inseparable mixture by utilizing (TMS)₃SiH and azobisisobutyronitrile (AIBN) in toluene at 85 °C, which was subsequently exposed to hydrazine hydrate to furnish a key component, *i.e.* the asymmetric alcohol **105**.¹³⁴ The synthesized



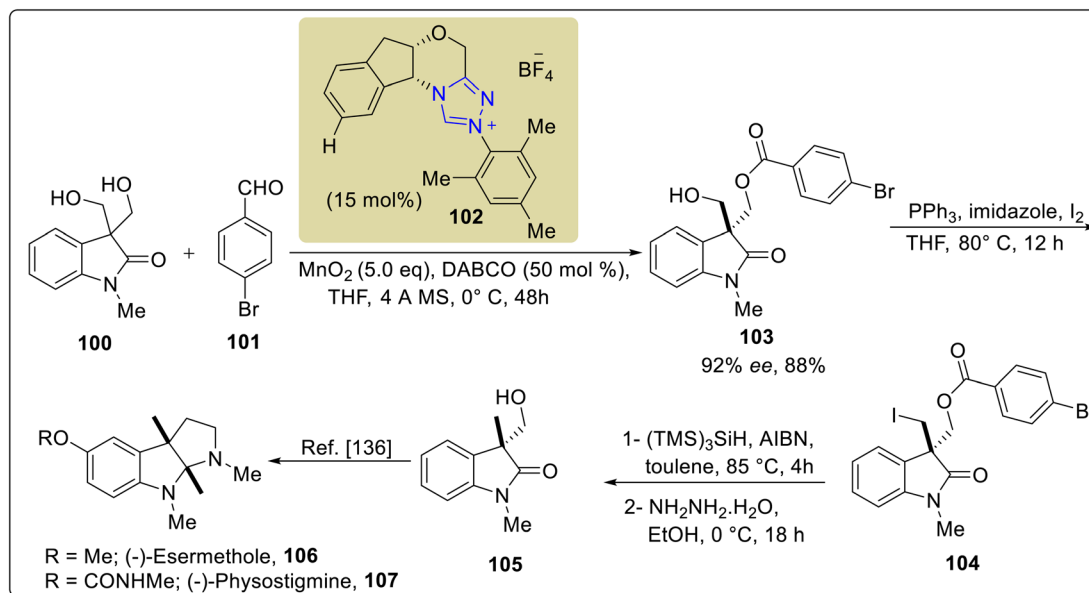


Scheme 10 Asymmetric synthesis of debromoflustramine B 99a.

key intermediate **105** had been reported earlier to be utilized for the total synthesis of esermethole **106** and physostigmine **107** (Scheme 11).^{135,136}

Cryptowolinol **117** is a dibenzopyrrocoline alkaloid that was extracted from the Lauraceae plant *Cryptocarya phyllostemon*, which is endemic to New Caledonia, in 1989.¹³⁷⁻¹³⁹ Miyakoshi





Scheme 11 Asymmetric synthesis of esermethole **106** and physostigmine **107**.

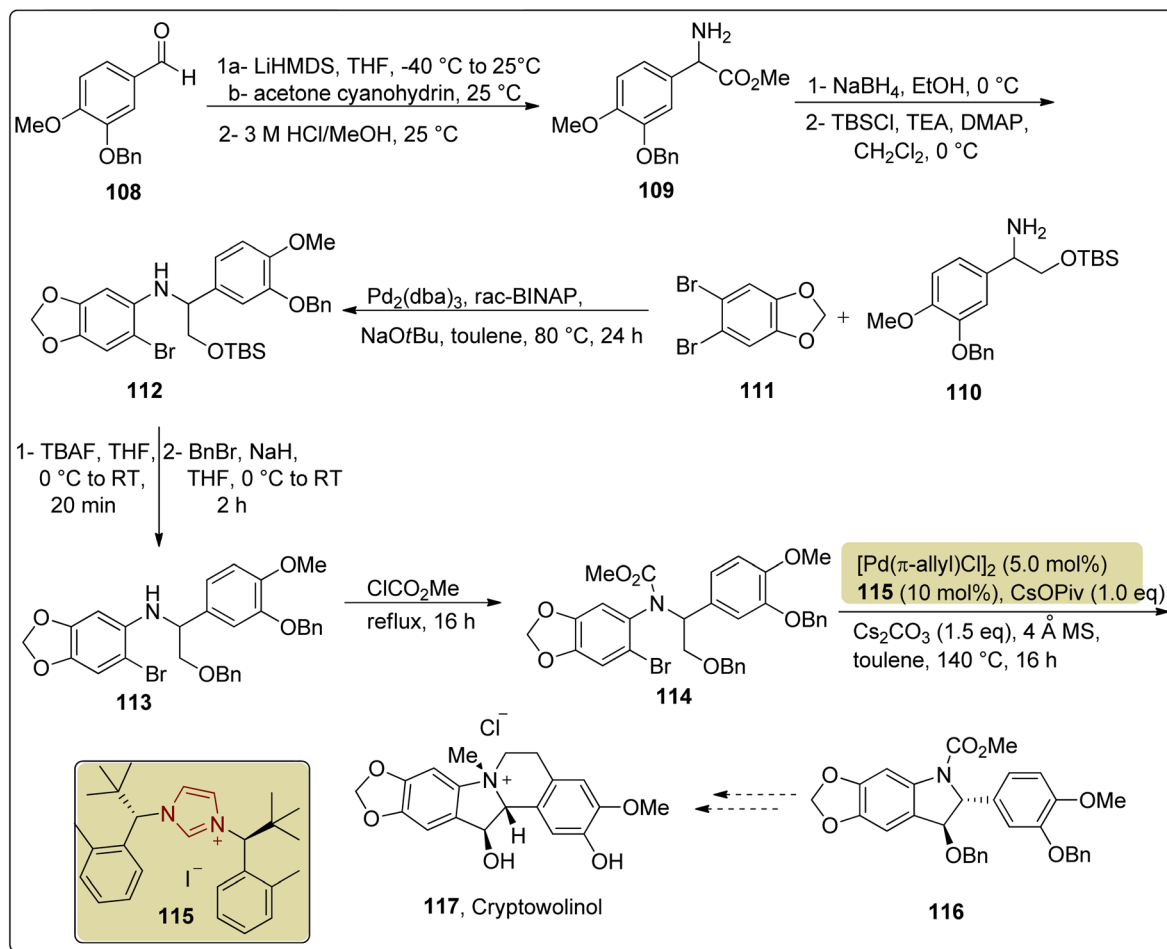
et al., in 2024, reported an enantioselective strategy towards the synthesis of a key component en route to cryptowolinol **117** by utilizing NHC **115** as ligand with Pd-catalyst *via* parallel kinetic resolution. In this synthetic protocol, benzaldehyde **108** was made to undergo the Strecker reaction in the presence of acetone cyanohydrin to synthesize crude aminonitrile, which subsequently underwent the Pinner reaction in the presence of HCl/MeOH to generate 2-amino ester **109**. Reduction of amino ester **109** generated the alcohol, which was then masked with TBSCl to give **110**, and further reacted with dibromide **111** *via* Buchwald-Hartwig *N*-arylation to synthesize the intermediate **112**. Deprotection of the TBS-protected alcohol **112** and subsequent re-protection were done with TBAF and BnBr, respectively, to furnish the benzyl-protected alcohol **113**, which was further reacted with methyl chloroformate to protect the amine in order to generate methyl carbamate **114**. Next, methyl carbamate **114** was cyclized in the presence of Pd catalyst with NHC **115** as ligand, CsOPiv, Cs₂CO₃ and toluene at 140 °C to furnish indoline **116**, a potential intermediate to obtain cryptowolinol **117**. Despite various experimentations, the total synthesis of cryptowolinol **117** was not successful *via* this approach; however, the significant intermediate **116** was afforded (Scheme 12).¹³⁹

2.1.2 Synthesis of polyketides. In 1974, Hesseltine and colleague extracted equisetin **125** from the secondary metabolites of *Fusarium heterosporum*, which demonstrates strong antibacterial and HIV-inhibiting activities.¹⁴⁰ In this regard, Meng *et al.* (2016) reported an enantioselective approach to synthesize equisetin **125** by utilizing imidazole-based NHC **120** and CuCl as a catalyst. In this synthetic protocol, dienolate **118** and allenyl-B(pin) **119** were allowed to undergo 1,6-conjugate addition in the presence of NHC **120** and CuCl (as catalyst) with NaO*t*-Bu and NaOPh in THF at 22 °C to synthesize the enyne **121** in 72% yield with 92 : 8 ee. Next, the enyne **121** was allowed to

undergo regio- and stereo-controlled proto-boryl addition by utilizing compound **122** and CuCl to furnish compound **123**. Over a few steps, compound **123** was converted into compound **124**, an intermediate¹⁴¹ that was reported earlier, in 2001, by Yuki *et al.* and utilized for the total synthesis of equisetin **125** (Scheme 13).¹⁴²

The isocoumarin-based polyketide mellein **129** was first extracted from the fungus *Aspergillus melleus* in 1933. Mellein **129** demonstrates mycocidal and antibacterial activities.^{143,144} In 1965, Steyn and fellow researchers isolated ochratoxin A **134** from *Aspergillus ochraceus*.¹⁴⁵ In 2017, Li *et al.* disclosed an enantioselective route to furnish *O*-methylmellein **128**, mellein **129** and ochratoxin A **134** by harnessing NHC (*R,R*)-**30**-diamine-**127** as ligand with a ruthenium transition-metal catalyst. In this unique synthetic protocol, 8-methoxy-3-methylisocoumarin **126** was allowed to undergo reduction by utilizing the Ru-NHC (*R,R*)-**30**-diamine **127** catalytic system in the presence of NaO*t*-Bu, H₂ gas at 50 bar pressure and *n*-hexane at 15–25 °C to obtain *O*-methylmellein **128** in 64% yield with 99% ee. Next, *O*-methylmellein **128** was demasked by employing BCl₃ and CH₂Cl₂ at 0 °C to furnish another natural product, mellein **129**, with 99% ee. In order to synthesize ochratoxin A **134**, *O*-methylmellein **128** was treated with *N*-chlorosuccinimide (NCS) to synthesize its chloro-derivative, which further underwent demethylation in the presence of BCl₃ and CH₂Cl₂ at 0 °C to generate 5-chloromellein **130**. Next, chloromellein **130** was made to undergo Rieche formylation in the presence of Cl₂-CHOMe/TiCl₄ to furnish aldehyde **131**, which was converted into the corresponding acid *via* Pinnick oxidation, and subsequently treated with *L*-phenylalanine **132** to generate the amide **133**. Finally, the *t*-butyl ester group was removed from amide **133** by utilizing TFA and CH₂Cl₂ to obtain ochratoxin A **134** (Scheme 14).¹⁴⁶

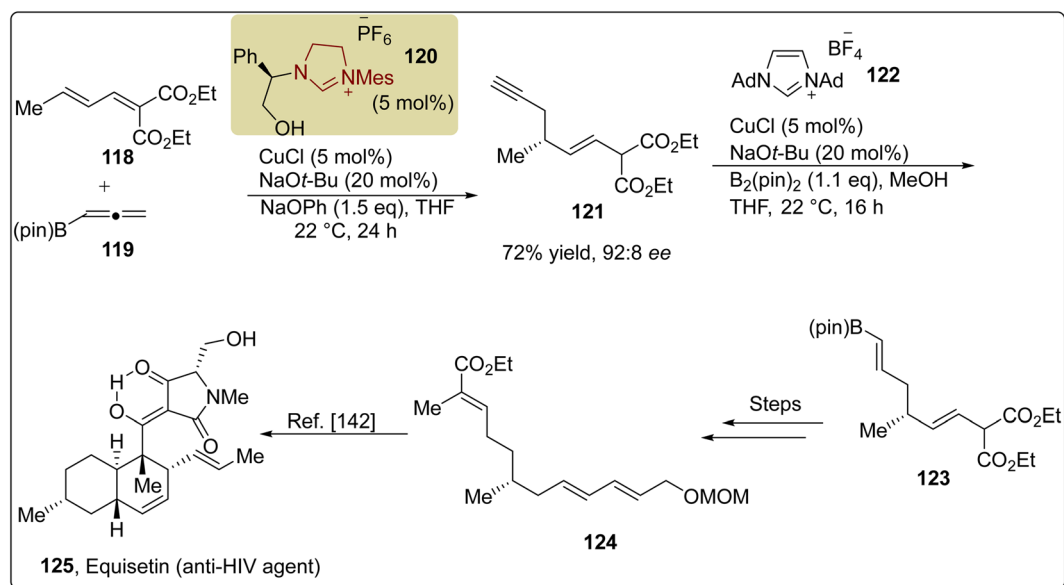




Scheme 12 Asymmetric synthesis of cryptowolinol 117.

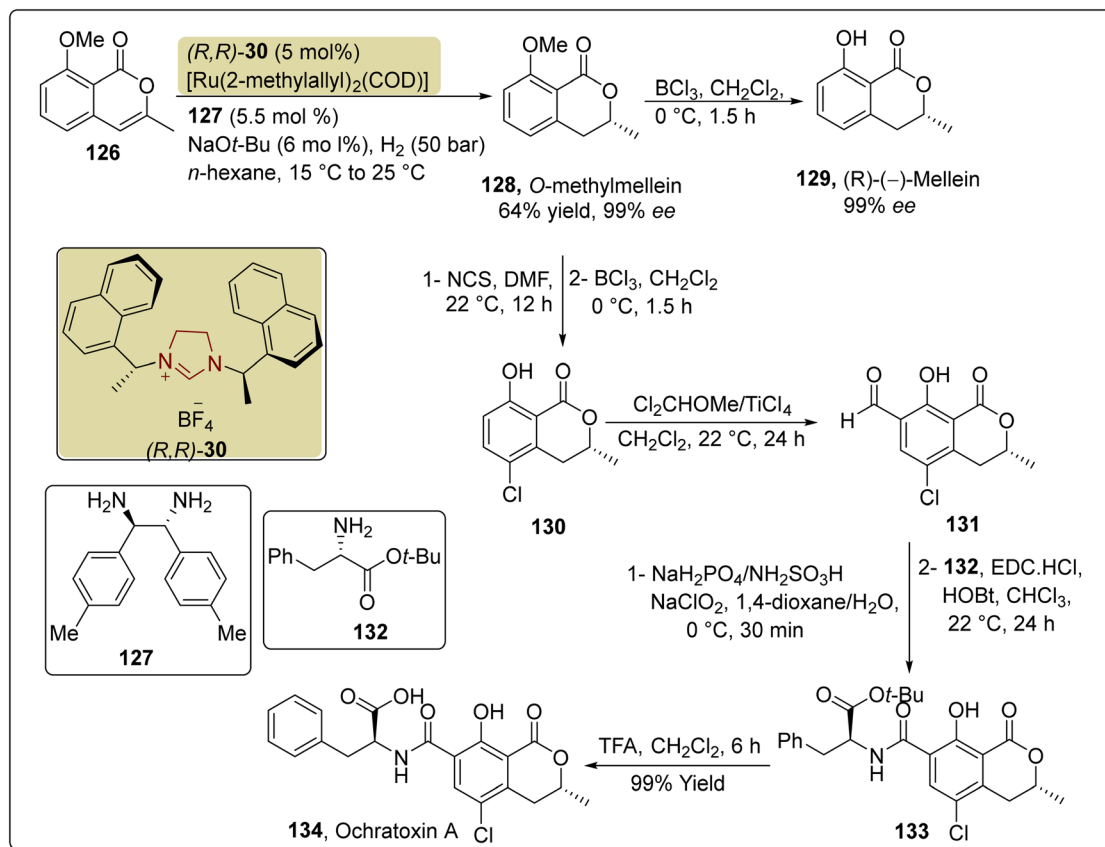
Tanikolide **143** is a polyketide with a lactonic core structure that was isolated from the lipid extract of the marine cyanobacterium *Lyngbya majuscula* by Gerwick and coworkers in

1999.¹⁴⁷ Tanikolide **143** shows molluscicidal, antifungal and narcotic activities.¹⁴⁸ In 2018, Yakura and coworkers introduced an asymmetric route to furnish tanikolide **143** by employing



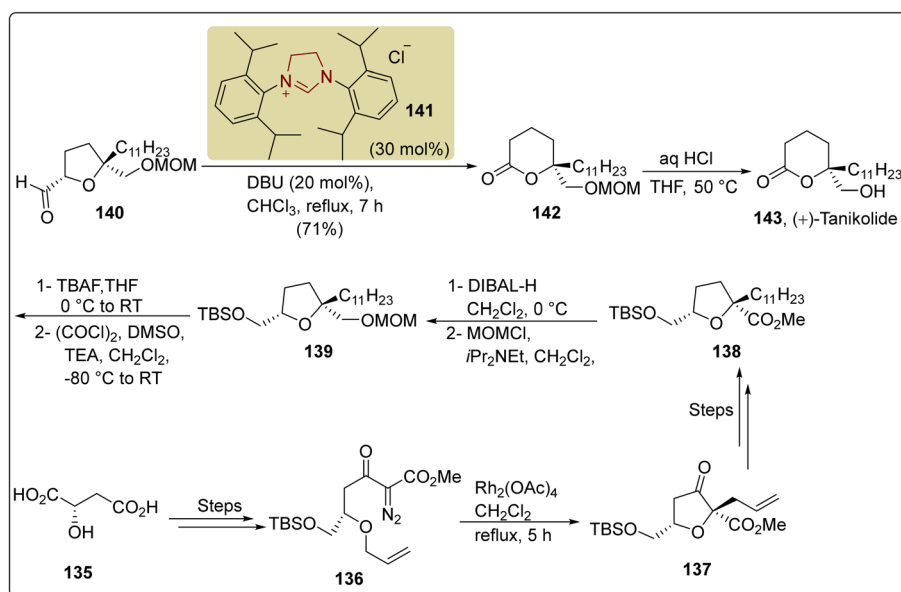
Scheme 13 Asymmetric synthesis of equisetin 125.

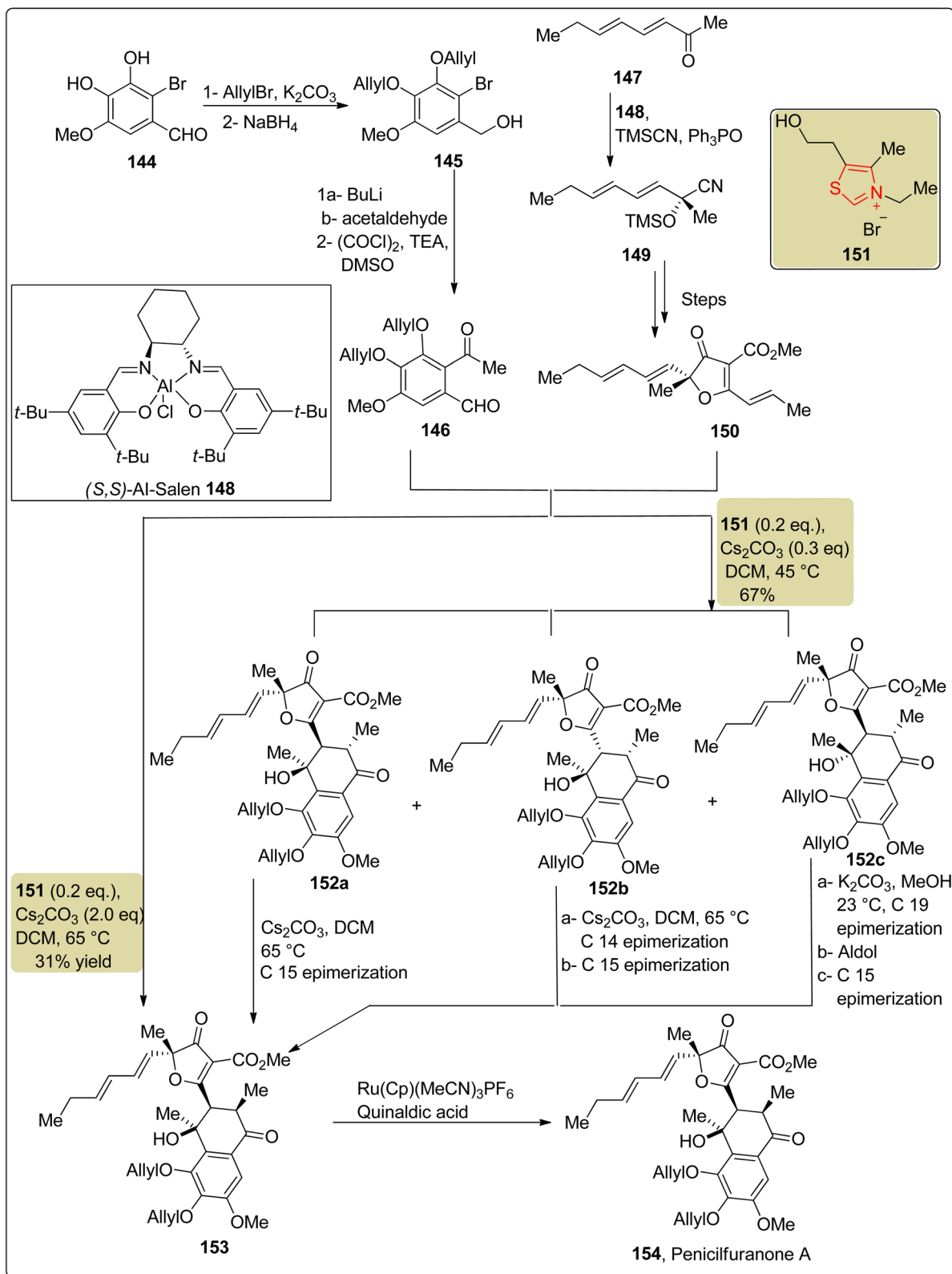


Scheme 14 Asymmetric synthesis of mellein **129**, O-methylmellein **128** and ochratoxin A **134**.

NHC **141** as a catalyst. In this synthetic protocol, L-malic acid **135** was transformed into diazoketoester **136** over a number of steps, and subsequently submitted to [2,3]-sigmatropic rearrangement in the presence of dirhodium(II) tetraacetate and refluxing in dichloromethane for 5 hours to synthesize

dihydrofuranone **137** in 93% yield. Dihydrofuranone **137** was then converted into the tetrahydrofuran **138** over a few steps. The methyl ester of tetrahydrofuran **138** was then converted into the alcohol by reduction with DIBAL-H, and further protected with methoxy methyl ether to generate compound **139**. In the

Scheme 15 Asymmetric synthesis of tanikolide **143**.



Scheme 16 Asymmetric synthesis of penicilfuranone A 154.

next step, MOM-protected tetrahydrofuran **139** underwent desilylation by utilizing TBAF, and subsequent Swern oxidation furnished the corresponding aldehyde **140**. Ring expansion of

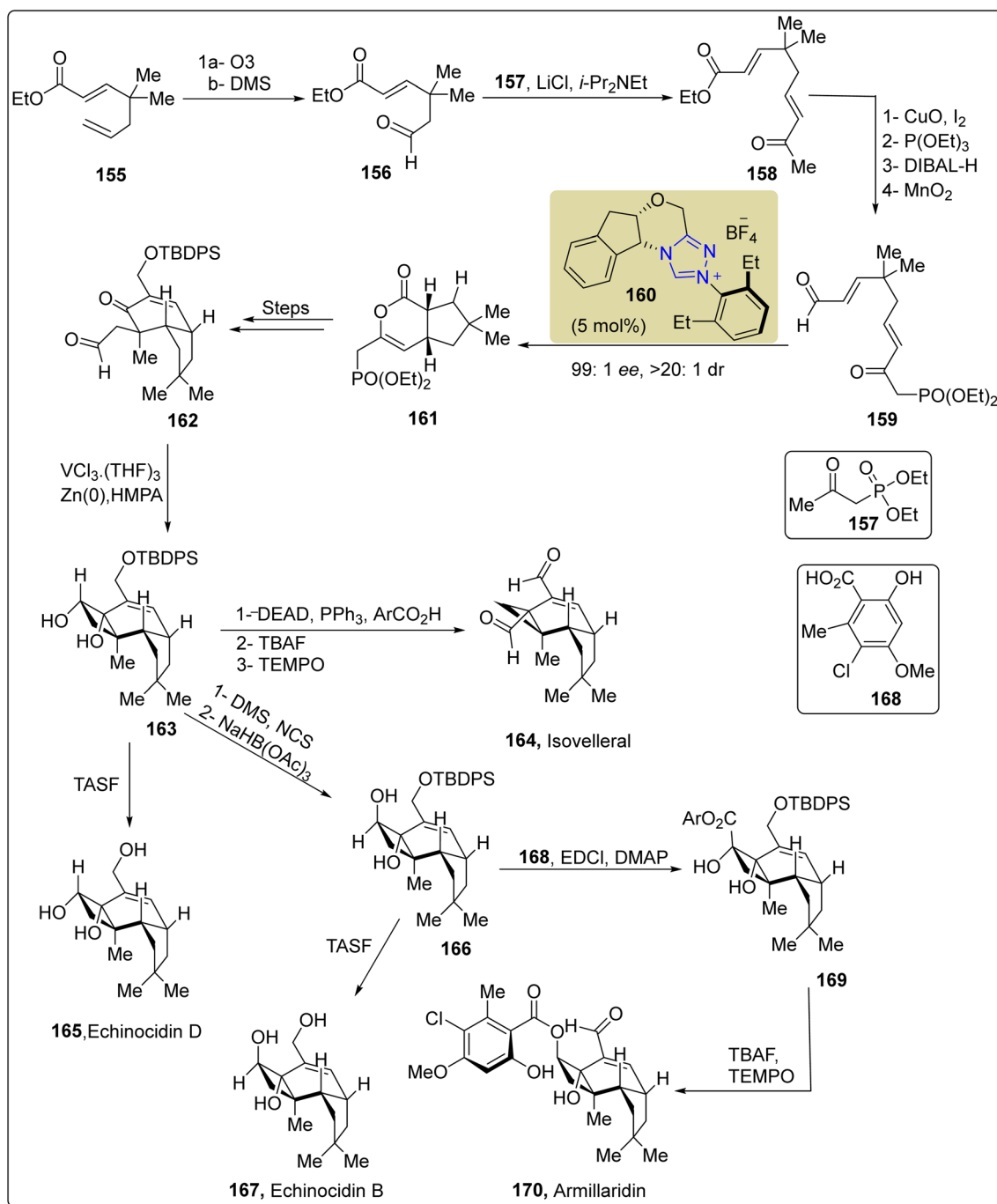
the aldehyde-containing tetrahydrofuran **140** to the δ -lactone **142** proceeded with 71% yield by employing imidazolium-based NHC **141** as a catalyst with the aid of DBU in chloroform at



reflux for 7 hours. Finally, MOM-deprotection of δ -lactone **142** was achieved to furnish tanikolide **143** (Scheme 15).^{149,150}

Penicilfuranone A **154**, a furancarboxylic acid that belongs to the class of tricyclic aromatic polyketides, was obtained from *Penicillium* sp. Sh18 that was extracted from the stem of the plant *I. ericalyx* var. *Laxiflora* in 2016 by Pu and fellow researchers.^{151,152} Penicilfuranone A **154** shows fibrosis attenuating effects in fibrogenic hepatic stellate cells and is considered an important compound to treat hepatic fibrosis. In 2025, Ding *et al.* reported the first asymmetric approach to the

synthesis of penicilfuranone A **154** by employing thiazolium-based NHC **151** as a catalyst. The synthetic protocol commenced with the synthesis of benzaldehyde **146**, which was produced in a three-step reaction involving allyl bromide protection, aldehyde reduction to generate alcohol **145** and subsequent Swern oxidation. On the other hand, gregatin A **150** was generated by utilizing Al-salen **148** to catalyze the asymmetric cyanosilylation of methyl ketone **147**, yielding intermediate **149**. Over a few steps, compound **149** was then converted into gregatin A **150**. Next, benzaldehyde **146** and gregatin A **150**



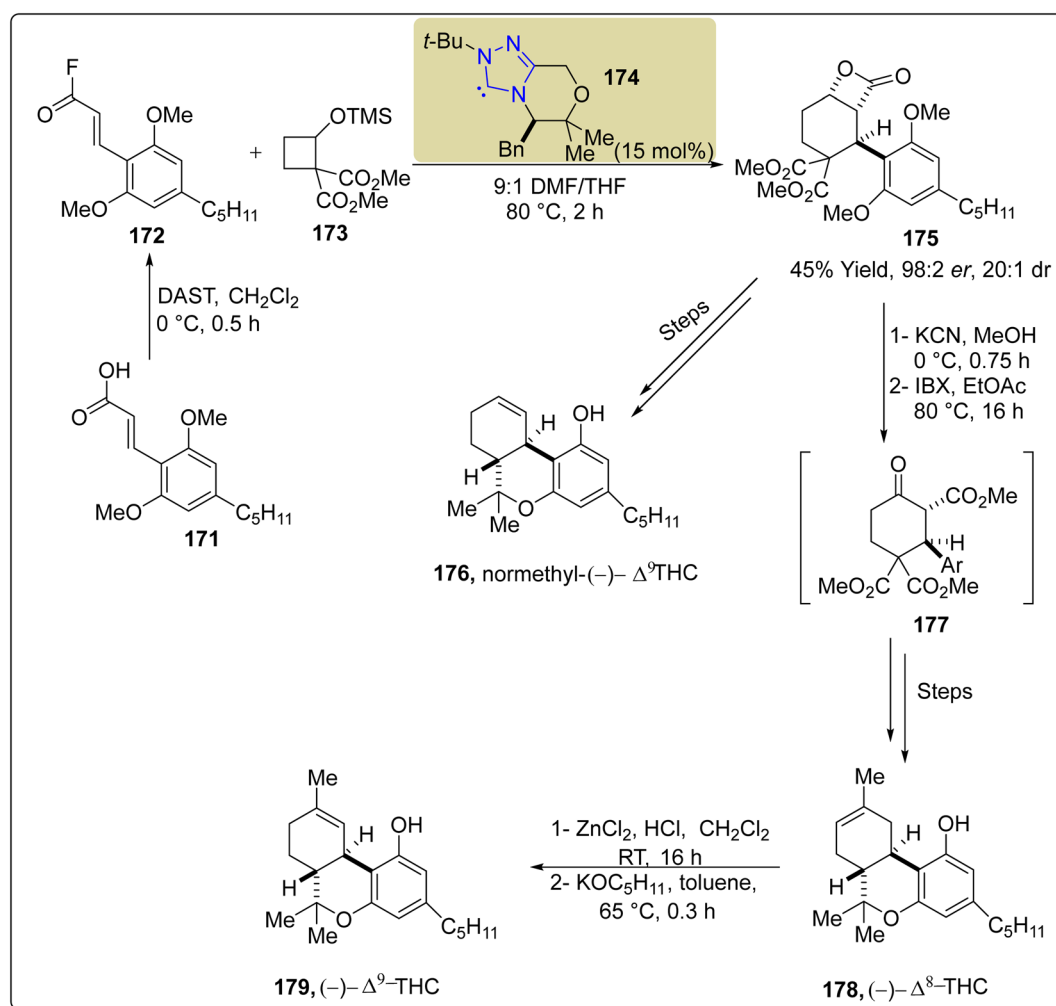
Scheme 17 Asymmetric synthesis of isovelleral **164**, echinocidin D **165** and B **167**, and armillaridin **170**.



were allowed to undergo dimerization in the presence of NHC **151** as a catalyst, 0.3 eq. of Cs_2CO_3 and DCM at 65 °C to generate three diastereomers, **152a**, **152b** and **152c**, which were subsequently converted into the precursor of penicilfuranone A **153**, individually. Benzaldehyde **146** and gregatin A **150** were also converted directly into penicilfuranone A precursor **153** when they were treated with NHC **151**, 2 eq. of Cs_2CO_3 and DCM at 45 °C. Finally, compound **153** was allowed to undergo deallylation in the presence of a ruthenium catalyst to furnish penicilfuranone A **154** (Scheme 16).¹⁵²

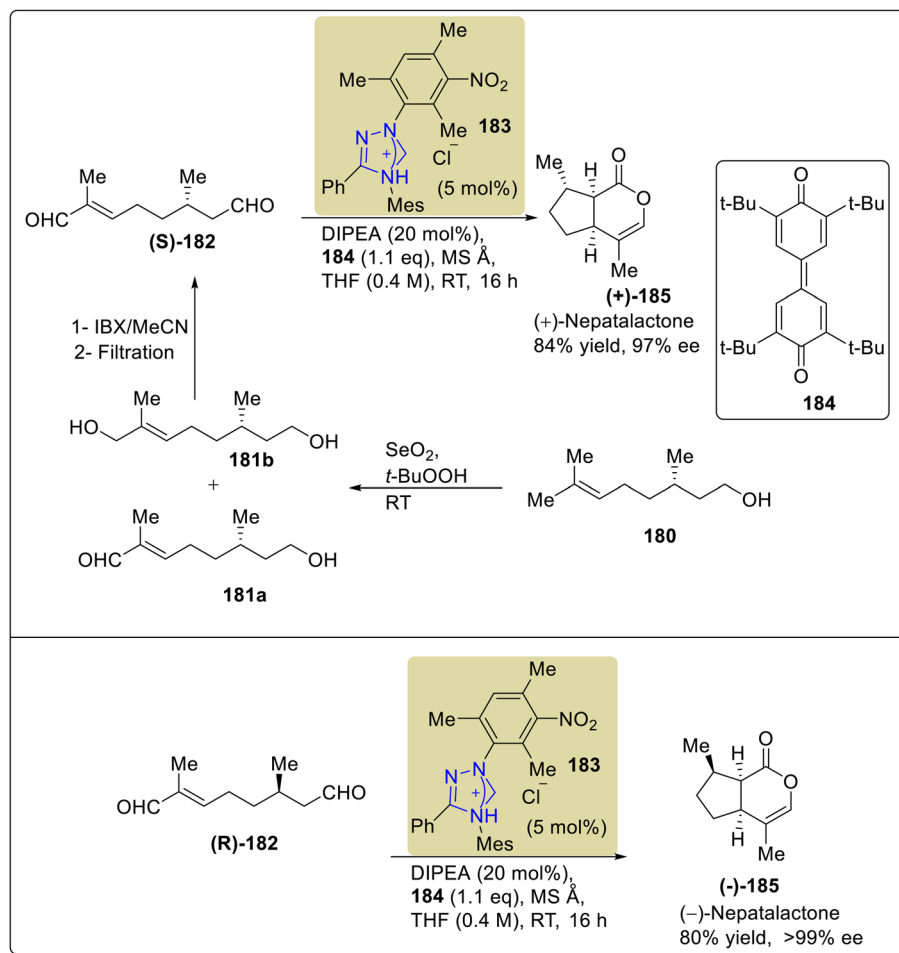
2.1.3 Synthesis of terpenoids. The sesquiterpenoid natural products, marasmane and protoilludane, were isolated from the parasitic basidiomycete fungus species *Lactarius vellereus* and *Armillaria mellea* in the 1960s. Protoilludane demonstrates antimicrobial activity, and marasmane shows anti-feedant and wide-spectrum antimicrobial activity. Moreover, mellolite sesquiterpenoid exhibits radiosensitizing and apoptotic activity against various malignant cell lines. Owing to its high pharmaceutical importance, Hovey *et al.*, in 2017, introduced a unified synthetic approach to generate echinocidin D **165** and B **167** (protoilludane), isovelleral **164** (marasmane) and

armillaridin **170** (mellolite) natural products by employing NHC **160** as an efficient catalyst. The total synthesis began with the ozonolysis of 1,5-dienoate **155** to generate aldehyde **156**, which was subjected to Masamune–Roush modified Horner–Wadsworth–Emmons (HWE) olefination to furnish enone **158**. In the next step, enone **158** was subjected to α -iodination and subsequent Arbuzov reaction, in conjunction with reduction, followed by oxidation in the presence of manganese oxide to generate enal **159**. Next, enal **159** underwent an annulation reaction by employing triazolium-based NHC **160** (catalyst) to afford lactone **161** with 99 : 1 *er* and >20 : 1 *dr*. Over a few steps, lactone **161** was converted into aldehyde **162**, which was further subjected to intramolecular pinacol reductive coupling to convert it into *cis*-cyclobutane-diol **163** by employing a vanadium(II)/zinc(II) bimetallic complex generated *in situ*. After desilylation of *cis*-cyclobutane-diol **163** by utilizing TASF, echinocidin D **165** (protoilludane) was accessed. On the other hand, when *cis*-diol **163** was exposed to *para*-nitrobenzoic acid, cyclopropane was obtained, which further underwent desilylation with TBAF, followed by oxidation with TEMPO to furnish isovelleral **164** (marasmane). In order to synthesize armillaridin

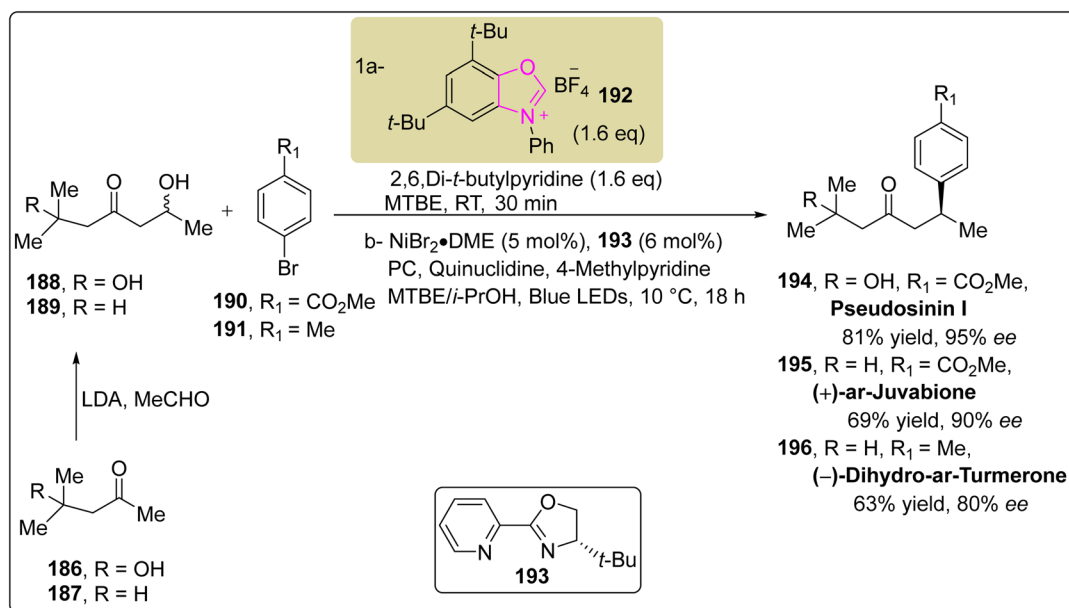


Scheme 18 Asymmetric synthesis of normethyl (-)- Δ^9 -THC **176**, (-)- Δ^8 -THC **178** and (-)- Δ^9 -THC **179**.





Scheme 19 Asymmetric synthesis of (+)-nepetalactone (+)-185 and (-)-nepetalactone (-)-185.



Scheme 20 Asymmetric synthesis of pseudosinin I 194, (+)-ar-juvabione 195 and (-)-dihydro-ar-turmerone 196.



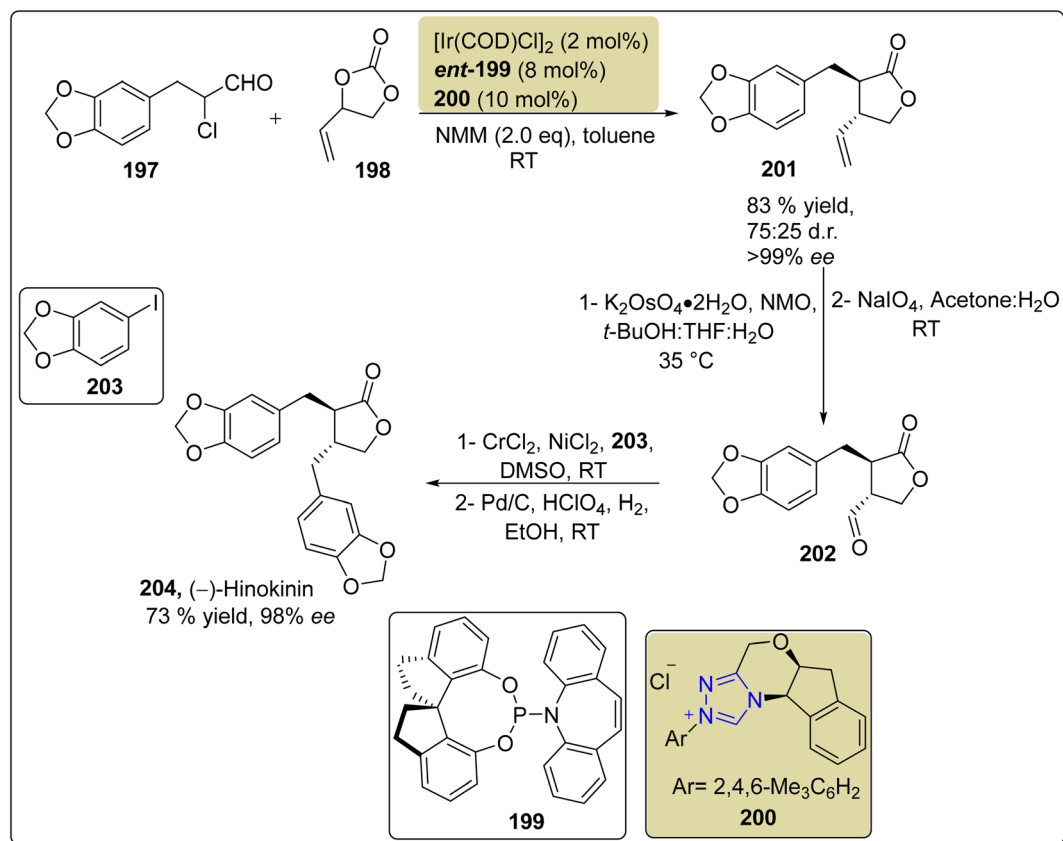
170 (melloide), *cis*-diol **163** was allowed to undergo reduction by employing sodium triacetoxyborohydride to furnish the *trans*-diol **166**, followed by esterification with orsellinic acid derivative **168** to deliver orsellinate ester **169**, with subsequent desilylation with TBAF and oxidation with TEMPO to afford armillaridin **170**. Desilylation of *trans*-diol **166** with TASF afforded echinocidin B **167** (Scheme 17).¹⁵³

Delta-9-tetrahydrocannabinol (Δ^9 -THC) **179** is a monoterpene natural product extracted in 1964 from the *Cannabis sativa* L in its *trans*-form. Δ^9 -THC **179** demonstrates anti-glaucoma, antiemetic, analgesic and antinauseant activities.^{154,155} In this regard, Ametovski *et al.*, in 2019, reported an enantioselective approach to synthesize normethyl (-)- Δ^9 -THC **176**, (-)- Δ^8 -THC **178** and (-)- Δ^9 -THC **179** by utilizing triazolium-based NHC **174** as a catalyst. The total synthesis commenced from the commercially and easily available cinnamate **171**, which was converted into acyl fluoride **172** by employing diethylaminosulfur trifluoride (DAST) in CH_2Cl_2 at 0 °C. In the next step, [4 + 2] annulation reaction was performed between acyl fluoride **172** and cyclobutane **173** by utilizing NHC **174** (catalyst) in DMF/THF at 80 °C to afford β -lactone **175** in 45% yield with 98:2 enantioselectivity and 20:1 diastereoselectivity ratio. Over a few steps, β -lactone **175** was converted into normethyl(-)- Δ^9 -THC **176** in 62% yield. Treatment of β -lactone **175** with KCN and MeOH at 0 °C and subsequent oxidation with IBX and EtOAc at 80 °C afforded β -

ketoester **177**. Next, β -ketoester **177** was transformed into (-)- Δ^8 -THC **178** in 40% yield *via* multiple steps. Furthermore, (-)- Δ^8 -THC was isomerized into (-)- Δ^9 -THC **179** in two steps by utilizing ZnCl_2 and HCl, and then $\text{KOC}_5\text{H}_{11}$ in toluene (Scheme 18).¹⁵⁶

Nepetalactone **185** belongs to the class of iridoid monoterpene, which are present in several plants of the genus *Nepeta*, which includes about 300 species in the Lamiaceae family of mints.¹⁵⁷ Nepetalactone **185** is the key component of mosquito repellents, aphid sex pheromones and insects. Moreover, they show euphoric effects in cats. In 2020, Harnying *et al.* reported an enantiospecific strategy to synthesize nepetalactone **185** by employing triazolium-based NHC **183** as a catalyst. The synthesis began with the allylic oxidation of (*S*)-citronellol **180** with $\text{SeO}_2/t\text{-BuOOH}$ to obtain an unrefined mixture of **181a** and **181b**, which subsequently underwent IBX oxidation to deliver 8-oxocitronellal (*S*)-**182**. In the next step, oxidative bicyclization took place to convert 8-oxocitronellal (*S*)-**182** into (+)-nepetalactone (+)-**185** in 84% yield and 97% enantiomeric excess in the presence of NHC **183** (catalyst) by utilizing quinone **184** (oxidant) and DIPEA (base) in THF. Moreover, (-)-nepetalactone (-)-**185** was also furnished in 80% yield and >99% enantiomeric excess *via* the same synthetic protocol (Scheme 19).¹⁵⁸

Pseudosinin I **194** and dihydro-*ar*-turmerone **196** are naturally occurring sesquiterpenoids that were isolated separately



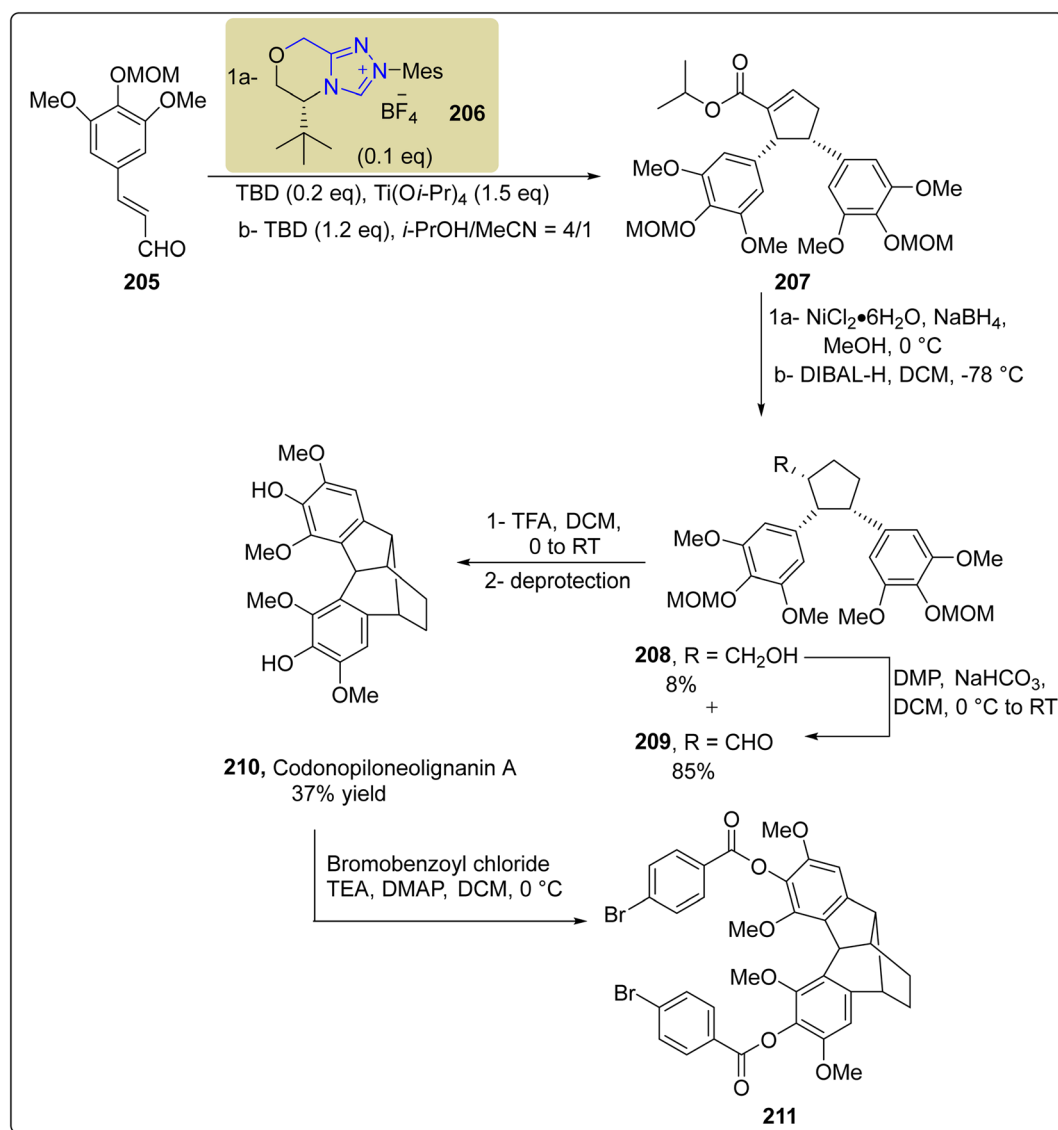
Scheme 21 Asymmetric synthesis of hinokinin **204**.



from *Pseudotsuga sinensis* and the wood of *Himalayan Cedar*, respectively.^{159–161} Zhang *et al.*, in 2024, reported an enantioselective approach to synthesize pseudosinin I **194**, (+)-*ar*-juvabione **195** and dihydro-*ar*-turmerone **196** by utilizing oxazole-based NHC **192** as a catalyst. In this synthetic protocol, ketones **186** and **187** were allowed to react with MeCHO and LDA to furnish the corresponding β -hydroxy ketones **188** and **189**. In the next step, the β -hydroxy ketones **188** and **189** were subjected to deoxygenative asymmetric reductive cross-coupling with aryl bromides **190** and **191** in the presence of NHC **192** (catalyst) to furnish final natural products, pseudosinin I **194**, (+)-*ar*-juvabione **195** and (–)-dihydro-*ar*-turmerone **196** (Scheme 20).¹⁶²

2.1.4 Synthesis of lignans. Hinokinin **204** is a dibenzylbutyrolactone-lignan that was isolated from the heartwood of *L. formosana* Florin.¹⁶³ Hinokinin **204** demonstrates antimicrobial, antiinflammatory and regulatory effects on

human γ -aminobutyric acid (GABA) translocation activities.^{164,165} Owing to its high medicinal importance, Singha *et al.*, in 2020, reported the use of NHC **200** and iridium cooperative catalysis to achieve the enantioselective and diastereodivergent synthesis of hinokinin **204** via a [3 + 2] annulation reaction. The total synthesis commenced with [3 + 2] annulation reaction between α -chloro aldehyde **197** and vinyl ethylene carbonate **198** in the presence of NHC **200**/Ir cooperative catalyst by utilizing 1,1'-spirobiindane-7,7'-diol (SPINOL) ligand *ent*-**199** and NMM (base) in toluene to generate *trans*-lactone **201** in 83% yield with 99% enantiomeric excess. In the next step, dihydroxylation of the double bond and subsequent oxidative cleavage delivered the aldehyde **202**. Next, the Nozaki–Hiyama–Kishi reaction was performed between aldehyde **202** and aryl iodide **203**, followed by hydrogenolysis utilizing Pd/C (catalyst) to furnish the final compound (–)-hinokinin **204** in 73% yield with 98% enantiomeric excess (Scheme 21).¹⁶⁶

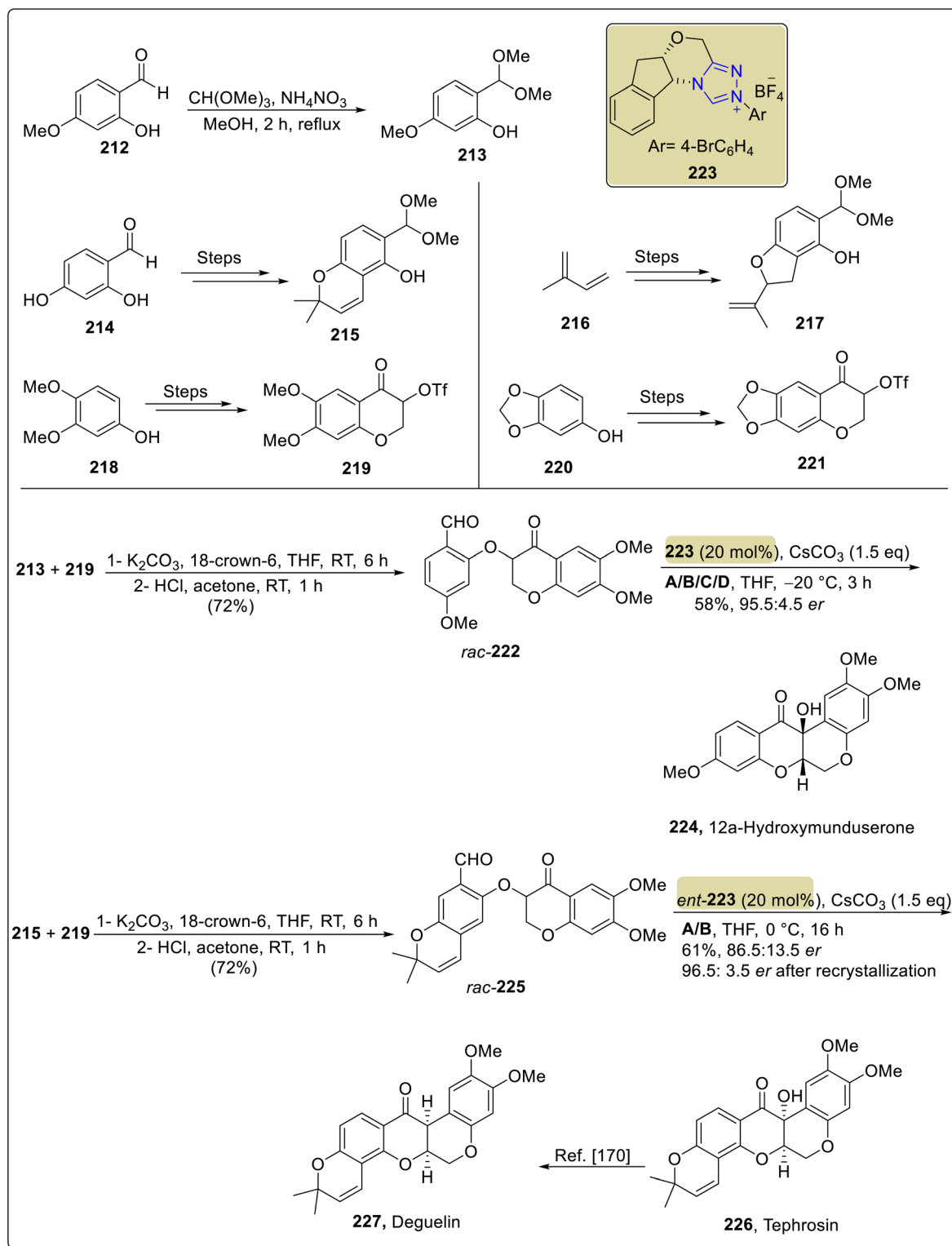


Scheme 22 Asymmetric synthesis of codonopiloneolignanin A **210**.



Shi and colleagues isolated a unique polycyclic neolignan named codonopiloneolignanin A **210** in 2016 from the roots of *C. pilosula*.¹⁶⁷ In 2021, Li *et al.* demonstrated the use of NHC **206** and titanium(IV) cooperative catalysis to deliver asymmetric codonopiloneolignanin A **210** in four steps. The total synthesis

commenced with asymmetric dimerization of cinnamaldehyde **205** to furnish *cis*-cyclopentene **207** in the presence of Ti(IV)/NHC **206** as a cooperative catalyst, TBD (base) and a mixture of isopropanol and acetonitrile (MeCN) (solvent). Next, reduction of the double bond of *cis*-cyclopentene **207** was achieved by



Scheme 23 Asymmetric synthesis of 12a-hydroxymunduserone **224**, tephrosin **226**, and deguelin **227**.

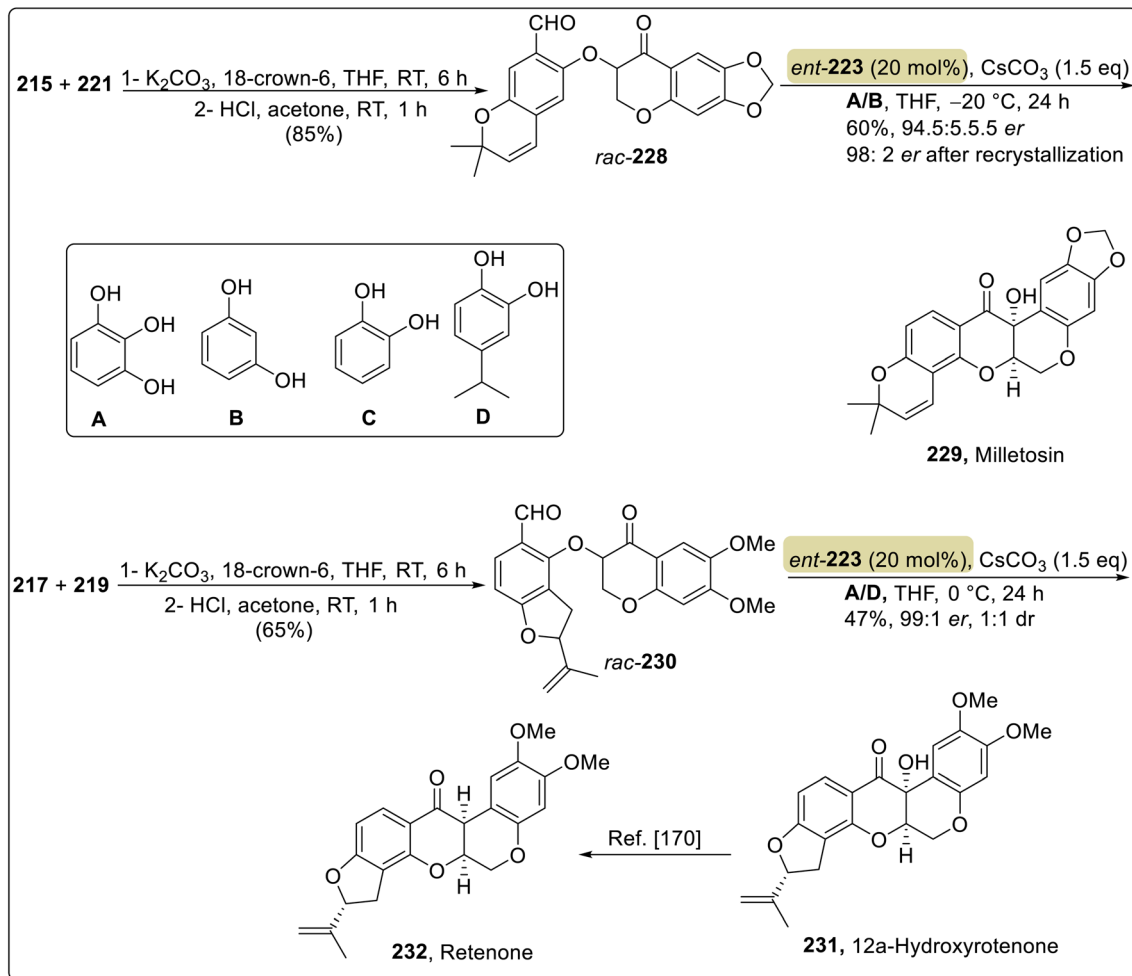


utilizing sodium borohydride (NaBH_4) and nickel chloride hexahydrate, with further subsequent reduction using DIBAL to convert the ester intermediate into aldehyde **209**. Due to over-reduction, a small amount of alcohol **208** was also formed, which was re-oxidized back to aldehyde **209** by utilizing Dess–Martin periodinane. In the next step, aldehyde **209** was subjected to transannular intramolecular Prins reaction followed by cation-mediated cyclization by utilizing TFA in DCM, and the product was subjected to deprotection to form the final natural product codonopiloneolignanin A **210**. Codonopiloneolignanin A **210** was further treated with bromobenzoyl chloride along with TEA in DMAP and DCM at 0 °C to furnish the codonopiloneolignanin A derivative **211** (Scheme 22).¹⁶⁸

2.1.5 Synthesis of flavonoids. Rotenoids are a significant class of naturally occurring compounds that have been discovered in the *Derris* and *Lonchocarpus* species. In 2019, Perveen *et al.* demonstrated an approach by utilizing NHC **223** as a catalyst that enabled the efficient construction of the *cis*-fused tetrahydrochromeno[3,4-*b*]chromene central scaffold of rotenoids. The approach has been utilized for the synthesis of various rotenoids, including 12a-hydroxymunduserone **224** (antitumor activity), tephrosin **226** (pesticides), milletosin **229**,

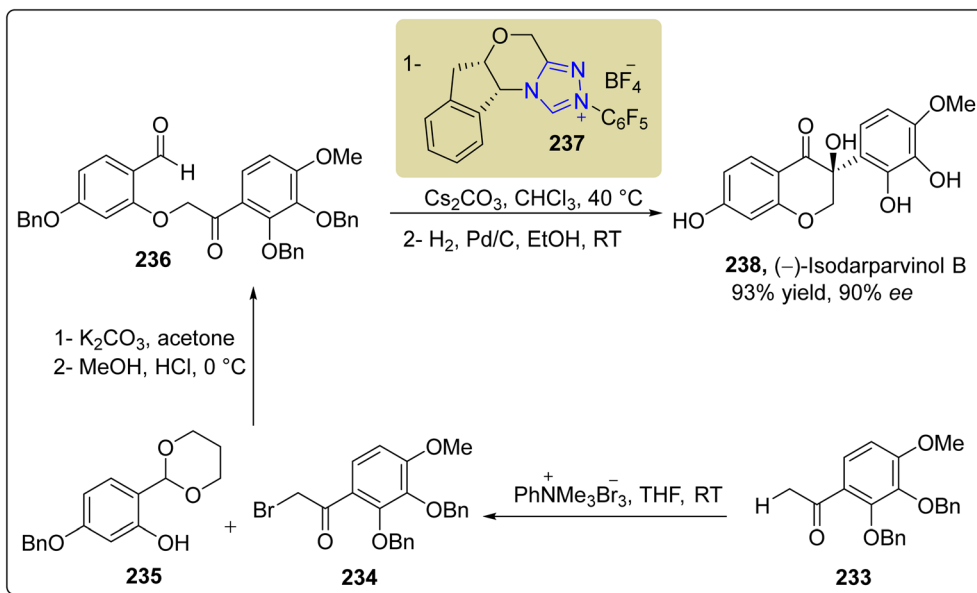
12a-hydroxyrotenone **231**, rotenone **232** (anticancer activity) and deguelin **227**. In order to synthesize naturally occurring rotenoids, three aldehyde modules **213**, **215**, and **217** and two ketone modules **219** and **221** were first generated. Next, the conjunction of modules **213** and **219** took place, followed by deprotection to generate *rac*-**222**, which was further submitted to an intramolecular annulation reaction utilizing NHC **223** as a catalyst with Cs_2CO_3 and additives **A**, **B**, **C**, **D** in THF at –20 °C to furnish 12a-hydroxymunduserone **224** in 58% yield with 95.5 : 4.5 *er* (Scheme 23). By utilizing similar optimized conditions, tephrosin **226**, milletosin **229** and 12a-hydroxyrotenone **231** were also synthesized.¹⁶⁹ Next, deguelin **227** from tephrosin **226** and rotenone **232** from 12a-hydroxyrotenone **231** were also achieved by utilizing the method reported by XiaoHui and coworkers (Scheme 24).¹⁷⁰

Umehara and co-researchers isolated an isoflavanonol derivative named isodarparvinol B **238** from the duramen of the medicinal plant *Dalbergia parviflora*, which is native to Thailand.¹⁷¹ Iwai *et al.*, in 2020, demonstrated an enantioselective approach to furnish isodarparvinol B **238** by utilizing NHC **237** as a catalyst. The total synthesis commenced with the bromination of ketone **233** with phenyltrimethylammonium



Scheme 24 Asymmetric synthesis of milletosin **229**, 12a-hydroxyrotenone **231** and rotenone **232**.

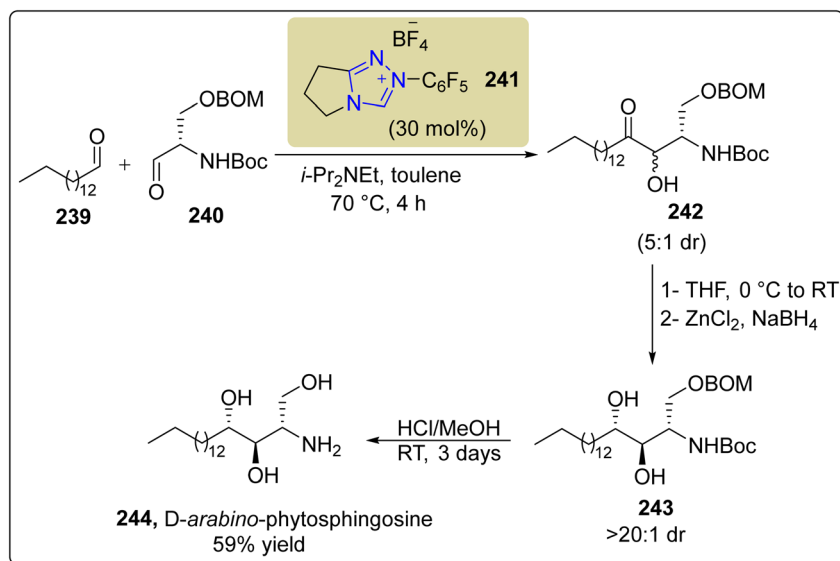


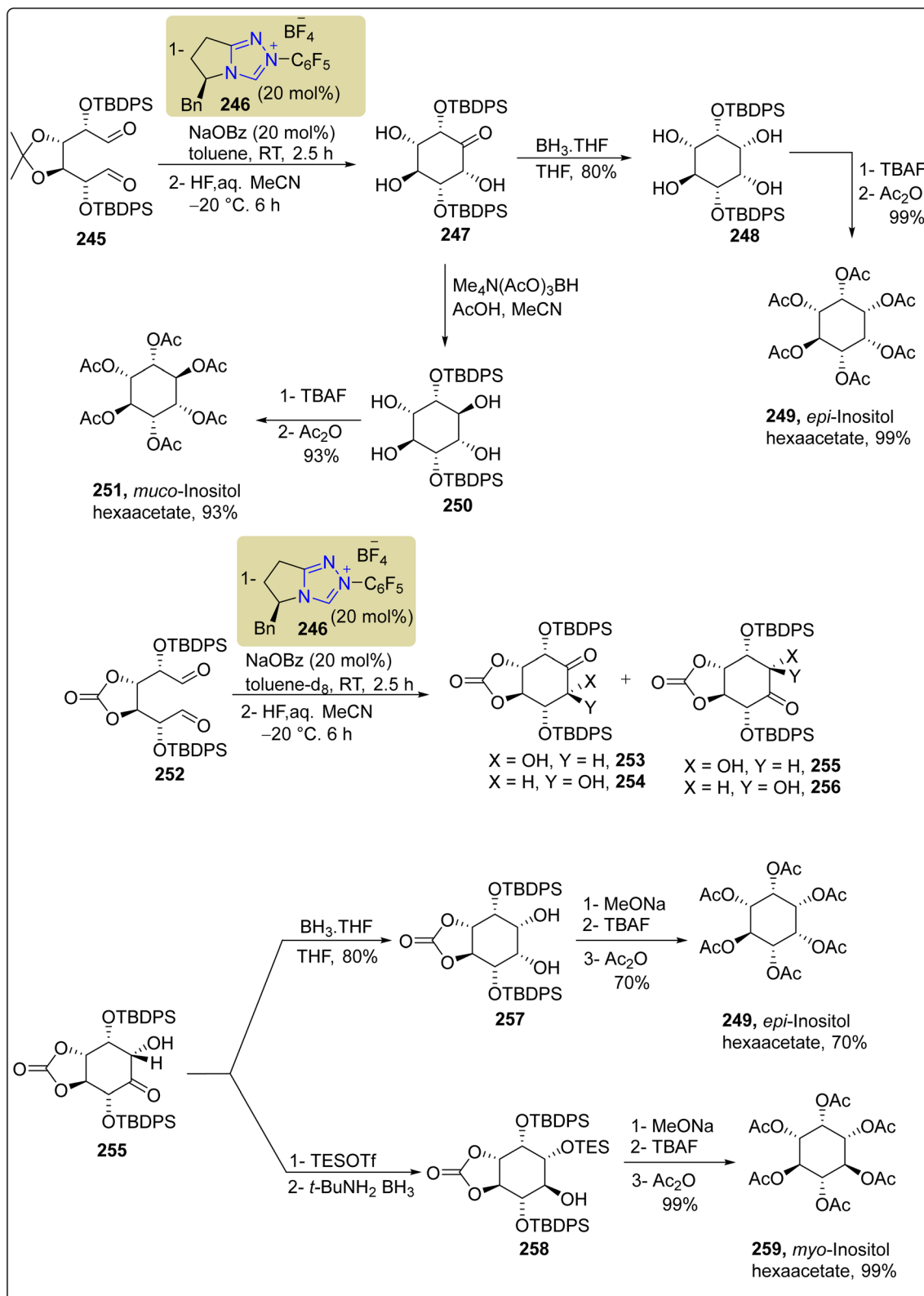
Scheme 25 Asymmetric synthesis of isodarparvinol B **238**.

tribromide to generate compound **234**. Next, compounds **234** and **235** were subjected to Williamson ether synthesis followed by acetal deprotection to generate aldehyde **236** in 62% yield. In the next step, aldehyde **236** was allowed to undergo intramolecular benzoin reaction in the presence of NHC **237** (catalyst) by utilizing Cs_2CO_3 in CHCl_3 at $40\text{ }^\circ\text{C}$ to afford the 4-chromanone, which subsequently underwent hydrogenation to generate (-)-isodarparvinol B **238** in 93% yield with 90% ee (Scheme 25).¹⁷²

2.1.6 Miscellaneous natural products. *D-ribo*-Phytosphingosine exhibits cytotoxic activity against a cell line derived from human leukemia and also serves as an indicator of thermal stress in yeast cells. Several analogues of *D-ribo*-phytosphingosine have been observed to demonstrate antitumor,

antiviral and immunostimulatory activities.¹⁷³ In 2016, Haghshenas *et al.* reported a diastereoselective strategy to synthesize a derivative of *D-ribo*-phytosphingosine named *D-arabino*-phytosphingosine **244** by employing NHC **241** as a catalyst. The total synthesis began with the cross-benzoin reaction between aliphatic aldehyde **239** and *N*-Boc-protected amino aldehyde **240** in the presence of triazolium-based NHC **241** (catalyst) to furnish a mixture of **242** with 5 : 1 diastereoselectivity ratio. In the next step, the diastereomeric mixture **242** was reduced with $\text{ZnCl}_2/\text{NaBH}_4$ to generate the amino diols **243** with >20 : 1 dr. Finally, amino diol **243** was subjected to deprotection to furnish the final natural product *D-arabino*-phytosphingosine **244** (Scheme 26).¹⁷⁴

Scheme 26 Asymmetric synthesis of *D-arabino*-phytosphingosine **244**.

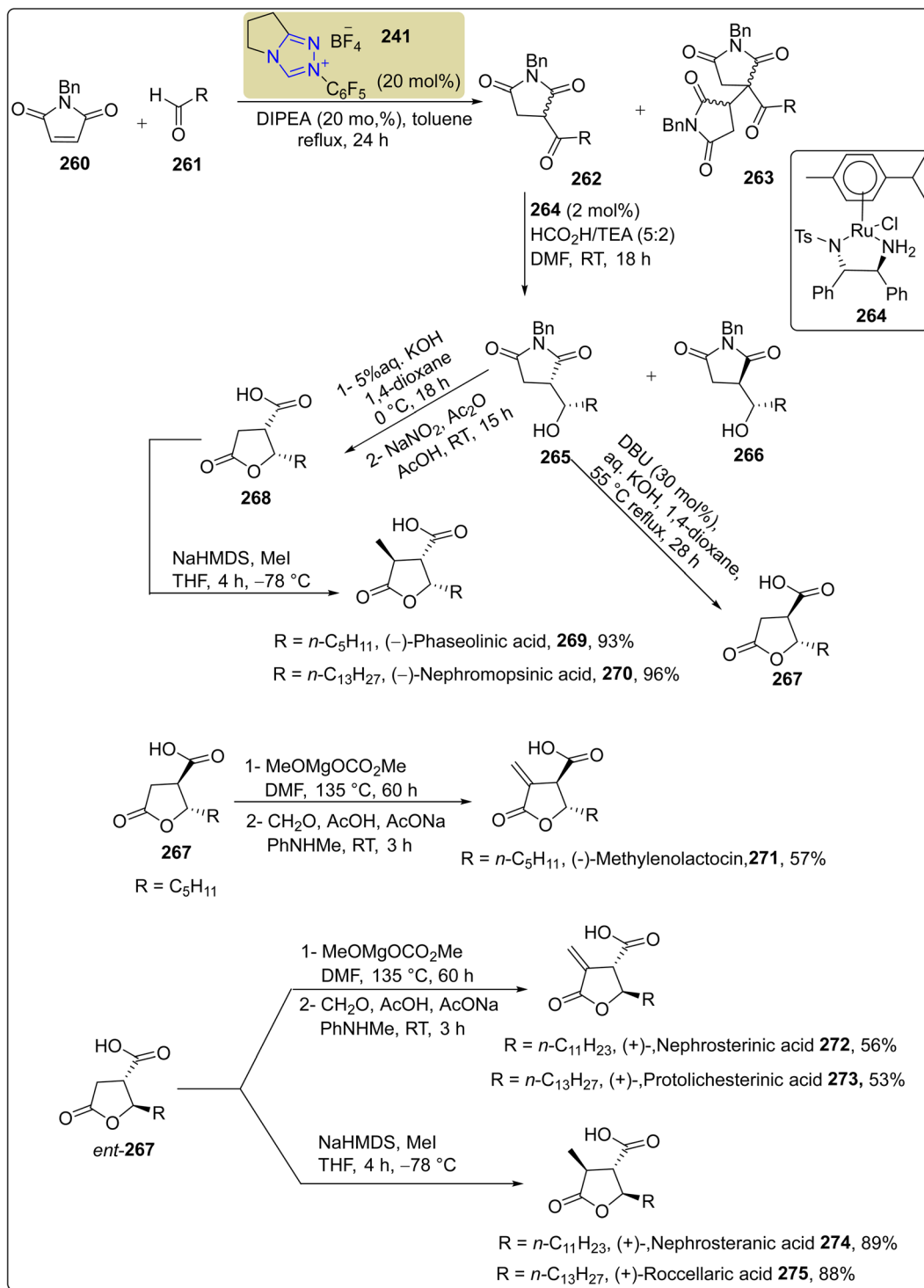


Scheme 27 Asymmetric synthesis of *epi*-inositol hexaacetate **249**, *muco*-inositol hexaacetate **251** and *myo*-inositol hexaacetate **259**.

In 2017, Kang *et al.* reported a cross-benzoin type cyclization reaction by utilizing NHC **246** as a catalyst to furnish *epi*-inositol hexaacetate **249**, *muco*-inositol hexaacetate **251** and *myo*-inositol

hexaacetate **259**. Among them, *myo*-inositol **259** and its derivatives have been extensively investigated due to their abundance and wide range of biological characteristics.¹⁷⁵ *myo*-Inositol **259**



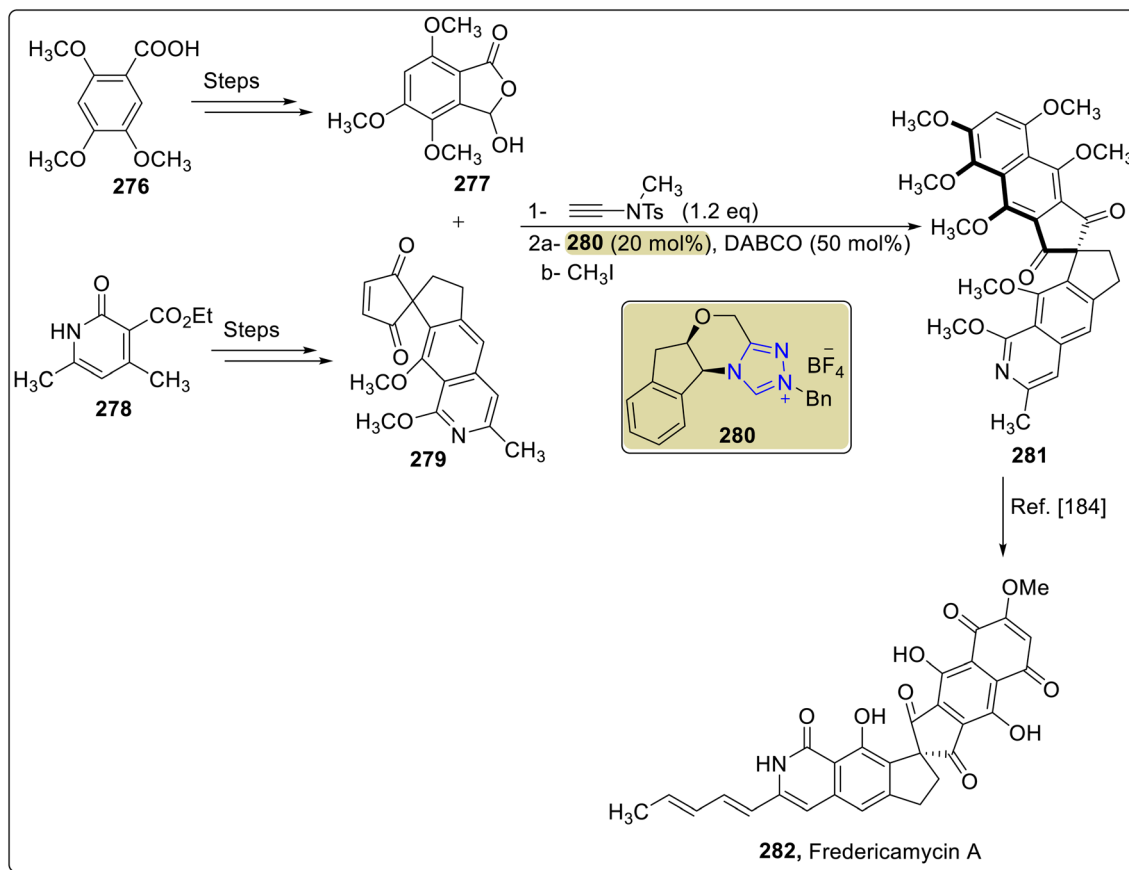


Scheme 28 Asymmetric synthesis of (-)-phaseolinic acid **269**, (-)-nephromopsinic acid **270**, (-)-methylenolactocin **271**, (+)-nephrosterinic acid **272**, (+)-protolichesterinic acid **273**, (+)-nephrosteranic acid **274** and (+)-roccellaric acid **275**.

exhibits diverse functionalities, including roles in regulating phosphate levels, ion-channel permeability, metabolic flux, embryonic development and insulin signaling.¹⁷⁶ The total synthesis began with the benzoin cyclization reaction of 3,4-*O*-acetonide **245** masked with TBDPSO groups in the presence of triazolium-based NHC **246** (as a catalyst) with NaOBz (as base) in toluene to furnish a crude product, which was further treated

with HF in aq. MeCN at $-20\text{ }^{\circ}\text{C}$ to generate the inosose **247**. Next, compound **247** was subjected to reduction by utilizing $\text{BH}_3\cdot\text{THF}$ to synthesize compound **248**, which was further deprotected with TBAF and then acylated with Ac_2O to furnish the final compound *epi*-inositol hexacetate **249**. Parallel to this, compound **247** was also allowed to undergo reduction in the presence of $\text{Me}_4\text{N}(\text{AcO})_3\text{BH}$, AcOH and MeCN to synthesize **250**,



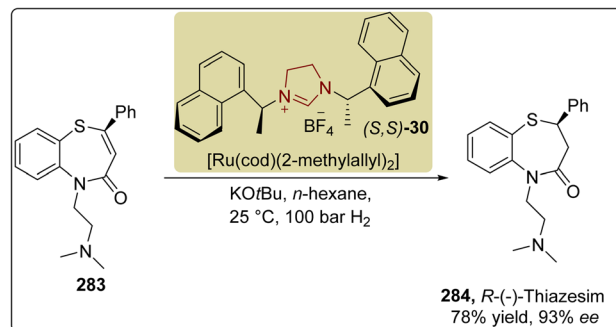


Scheme 29 Asymmetric synthesis of fredericamycin A 282.

which was further deprotected with TBAF and acylated with Ac_2O to furnish another natural product, *muco*-inositol hexaacetate 251. Next, another unsymmetrical dialdose 252 was allowed to undergo benzoin cyclization reaction under similar conditions to synthesize compounds 253, 254, 255 and 256. In the next step, compound 255 was reduced with $\text{BH}_3 \cdot \text{THF}$ to deliver compound 257, which was further treated with MeONa, followed by deprotection with TBAF in conjunction with acylation using Ac_2O to synthesize *epi*-inositol hexaacetate 249. Parallel to this, compound 255 was also protected with TESOTf, then reduced with $\text{BuNH}_2 \cdot \text{BH}_3$ to generate compound 258. Finally, compound 258 was treated with MeONa followed by deprotection with TBAF and then subjected to acylation to synthesize *myo*-inositol hexaacetate 259 (Scheme 27).¹⁷⁵

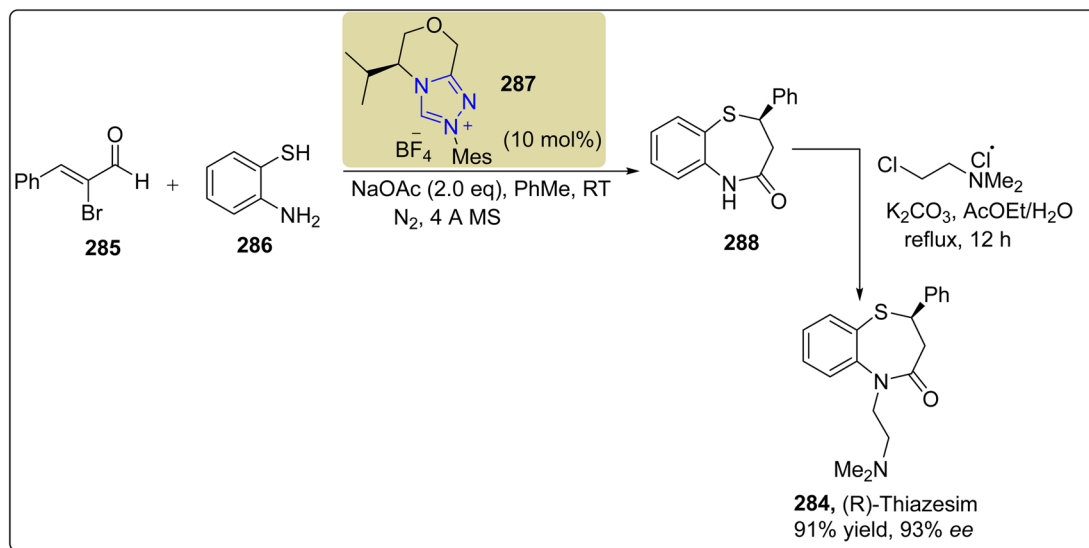
Asymmetric, naturally occurring paraconic acids exhibit various biological activities, including anti-HIV-1, antibiotic and antimicrobial activity, depending on their substitution and chiral configuration.^{177–180} In this regard, Sarkale *et al.*, in 2019, reported a stereodivergent approach to synthesize paraconic acids by utilizing triazolium-based NHC 241 as a catalyst. In this synthetic protocol, alkyl aldehyde 261 and *N*-benzylmaleimide 260 were allowed to react in the presence of NHC 241 (catalyst) by utilizing DIPEA (base) in toluene to synthesize 3-acylsuccinimide 262. Next, asymmetric transfer hydrogenation (ATH), along with dynamic kinetic resolution (DKR) of 3-

acylsuccinimide 262, was performed to generate a diastereomeric mixture of alcohols 265 and 266, which could not be separated, by employing 264 with $\text{HCO}_2\text{H}/\text{TEA}$ in DMF at room temperature. In the next step, alcohol 265 was treated with DBU and aq. KOH in 1,4-dioxane at 55 °C to synthesize *trans*-paraconic acid 267. Parallel to this, alcohol 265 was also subjected to hydrolysis of the imide by employing 5% aqueous KOH, followed by treatment with NaNO_2 and Ac_2O in acetic acid to furnish *cis*-paraconic acid 268. Next, the *cis*-paraconic acid 268 was treated with NaHMDS and MeI in THF to synthesize (–)-phaseolinic acid 269 in 93% yield and (–)-nephromopsinic



Scheme 30 Asymmetric synthesis of (R)-(-)-thiazesim 284.

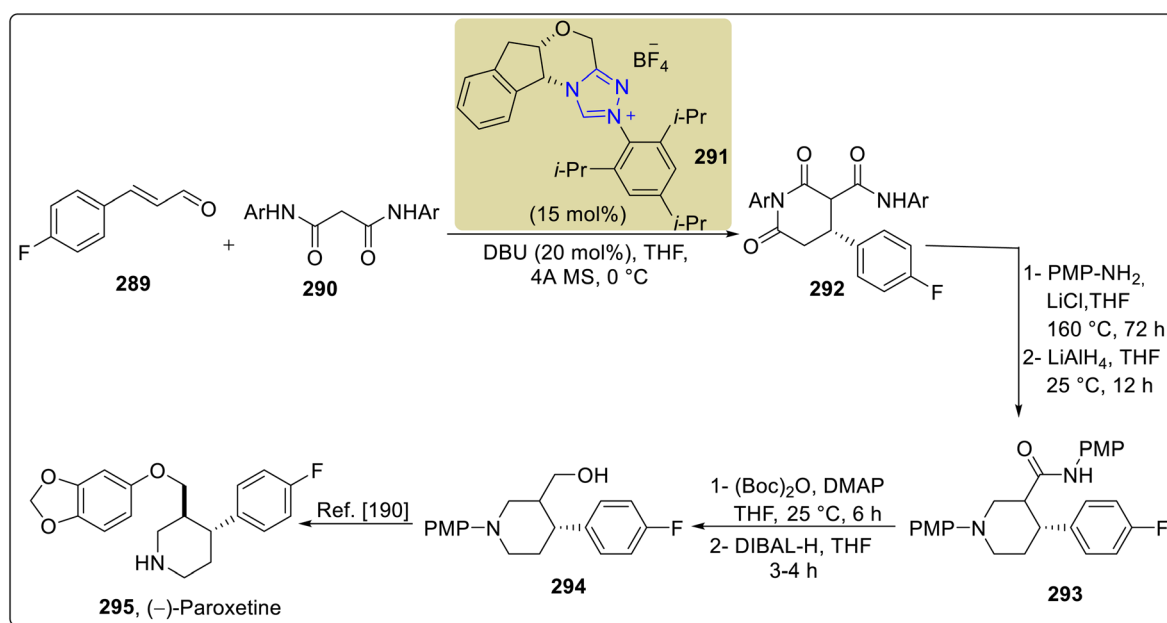


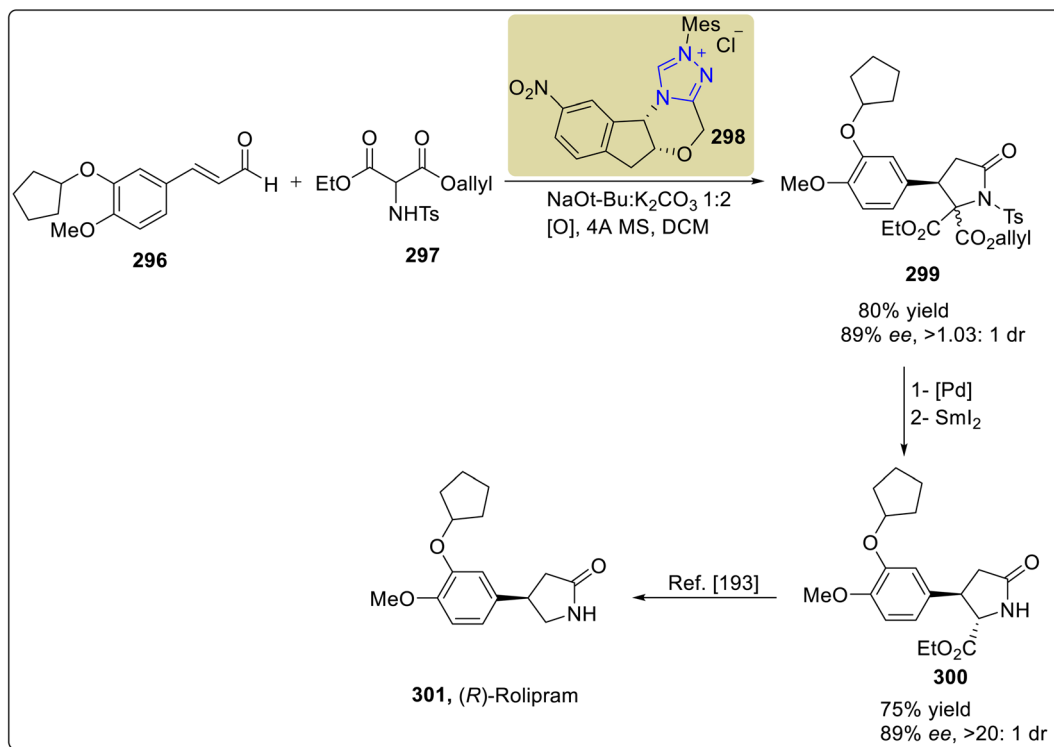
Scheme 31 Asymmetric synthesis of (*R*)-(-)-thiazesim **284**.

acid **270** in 96% yield. When *ent*-**267** was treated under similar conditions, nephrosteranic acid **274** was obtained in 89% yield, and (+)-roccellaric acid **275** was obtained in 88% yield. (-)-Methylenolactocin **271** was furnished from **267** upon treatment with MeOMgOCO₂Me in DMF and then with CH₂O, AcOH, AcONa and PhNHMe. Moreover, when *ent*-**267** was treated under similar conditions, (+)-nephrosterinic acid **272** and (+)-protolichesterinic acid **273** were obtained in 56% and 53% yield, respectively (Scheme 28).¹⁸¹

Fredericamycin A **282** is a naturally occurring aromatic pentadecaketide that was isolated from the *Streptomyces griseus* by Pandey and co-workers in 1981.^{182,183} Fredericamycin A **282** was observed to exhibit cytotoxic activity against a number of

cell lines and moderate anticancer bioactivity.¹⁸³ Owing to its medicinal importance, Ren *et al.*, in 2025, reported an efficient asymmetric approach to synthesize fredericamycin A **282** by utilizing NHC **280** as a catalyst. Initially, phthalide **277** was prepared from compound **276** in a few steps. Parallel to this, dienophile **279** was furnished from compound **278** in a few steps. Next, phthalide **277** and dienophile **279** were allowed to undergo NHC **280** catalyzed asymmetric reaction in the presence of *N*-methyltoluenesulfonamide as coupling reagent and DABCO as base to generate the intermediate **281**,¹⁸² which was reported earlier by Kita *et al.*, in 1999, and utilized for the synthesis of fredericamycin A **282** (Scheme 29).¹⁸⁴

Scheme 32 Asymmetric synthesis of paroxetine **295**.

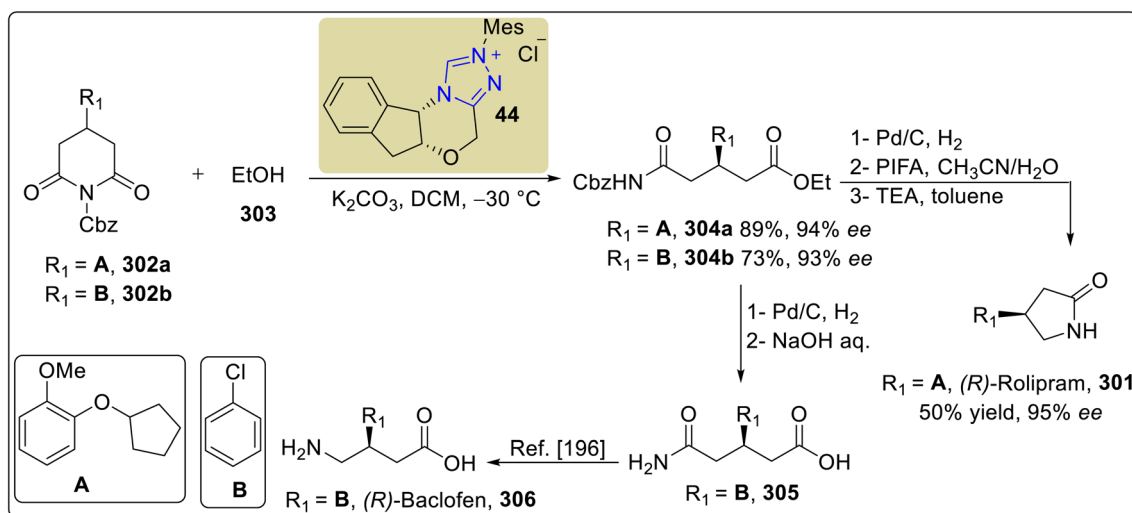
Scheme 33 Asymmetric synthesis of (*R*)-rolipram **301**.

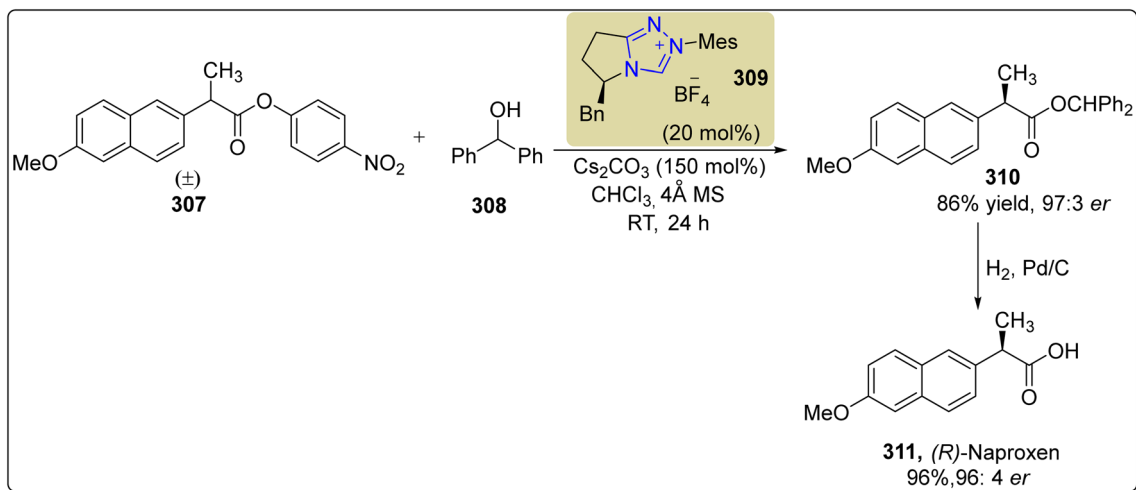
2.2 Pharmaceutical drugs

2.2.1 Synthesis of antidepressant drugs. (*R*)-(-)-Thiazesim **284** is an antidepressant drug that is available as its hydrochloride salt, *i.e.*, Altinil and diltiazem. (*R*)-(-)-Thiazesim **284** is utilized for the amelioration of hypertension and angina.¹⁸⁵ Owing to its pharmaceutical importance, Li *et al.*, in 2016, reported an asymmetric hydrogenation approach to furnish (*R*)-(-)-thiazesim **284** by utilizing ruthenium NHC (*S,S*)-**30** as a catalyst in a single step. The synthesis began with the

asymmetric hydrogenation of unsaturated 1,5-benzothiazepinone **283** in the presence of NHC (*S,S*)-**30** as ligand with ruthenium catalyst by employing *KOtBu* in *n*-hexane under 100 bar H₂ at room temperature to synthesize (*R*)-(-)-thiazesim **284** in 78% yield with 93% enantiomeric excess (Scheme 30).¹⁸⁶

In 2017, Fang *et al.* also reported a novel enantioselective strategy to synthesize (*R*)-thiazesim **284** by utilizing the triazolium-based NHC **287** as a catalyst. The synthesis commenced with the [3 + 4] annulation of α -bromoenal **285** with

Scheme 34 Asymmetric synthesis of (*R*)-rolipram **301** and (*R*)-baclofen **306**.

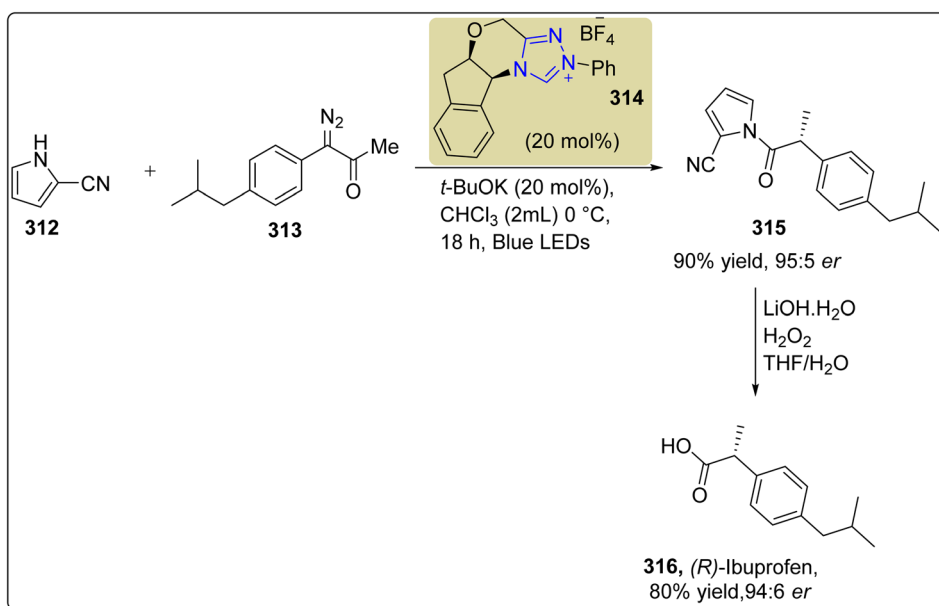
Scheme 35 Asymmetric synthesis of naproxen **311**.

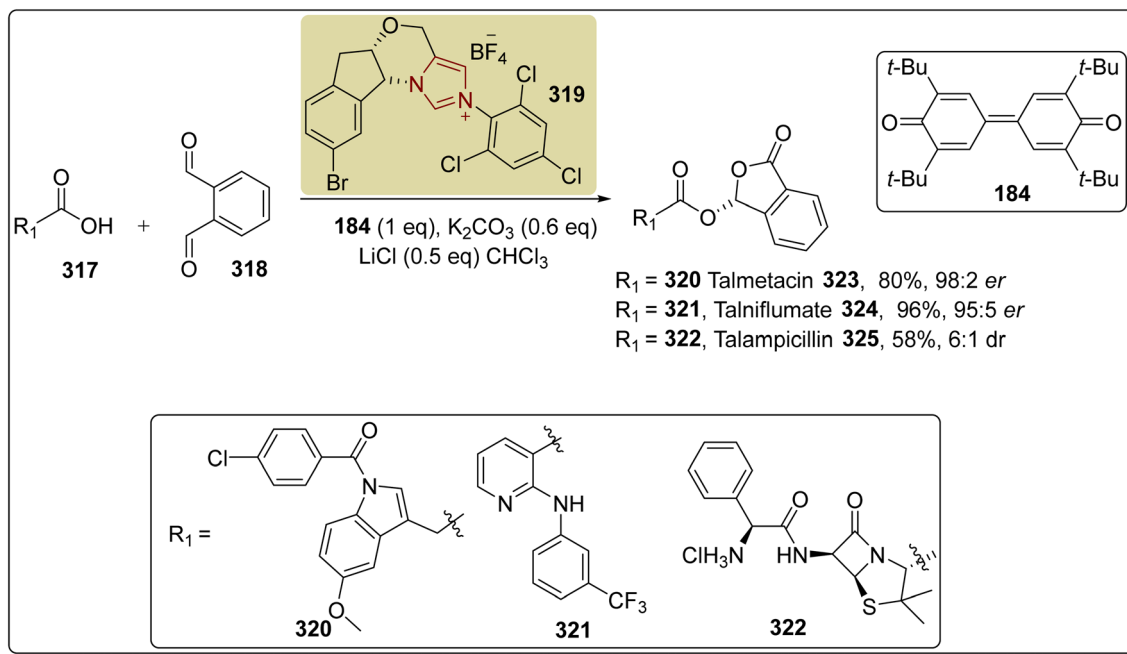
2-aminobenzenethiol **286** in the presence of NHC **287** (catalyst) and NaOAc (base) in PhMe (solvent) at room temperature to furnish 1,5-benzothiazepine **288** in 53% yield with 90.7% ee. In the next step, 1,5-benzothiazepine **288** was refluxed with 2-chloro-*N,N*-dimethylethan-1-amine and K_2CO_3 in AcOEt/ H_2O for 12 hours to generate (*R*)-thiazesim **284** in 91% yield with 93% ee (Scheme 31).¹⁸⁷

The pharmaceutical product paroxetine **296** has been used to treat a number of anxiety disorders, namely generalized anxiety disorder, major depressive disorder, obsessive-compulsive disorder, premenstrual dysphoric disorder, panic disorder, post-traumatic disorder, and social anxiety disorder.¹⁸⁸ Owing to its high medicinal importance, Porey *et al.*, in 2019, demonstrated an enantioselective strategy towards the formal synthesis of paroxetine **295** by utilizing oxidative NHC **291**

catalysis. The synthesis commenced with the [3 + 3] annulation of enal **289** and malonamide **290** by utilizing NHC **291** (catalyst) and DBU in THF to furnish compound **292** in 72% yield, 97% enantioselectivity and 4 : 1 diastereoselectivity. In the next step, compound **292** was allowed to undergo transamidation to install the PMP-group, followed by imide reduction by utilizing $LiAlH_4$ in THF to synthesize compound **293**. Next, Boc-protection of compound **293** was performed, and subsequent DIBAL reduction generated the important intermediate alcohol **294**.¹⁸⁹ The synthesized intermediate **294** had been reported earlier by Hughes *et al.* in the synthesis of paroxetine **295** (Scheme 32).¹⁹⁰

Rolipram **301** is a phosphodiesterase inhibitor that was initially formulated to treat depression, but has also been used to treat asthma, Huntington's disease, arthritis, multiple

Scheme 36 Asymmetric synthesis of ibuprofen **316**.

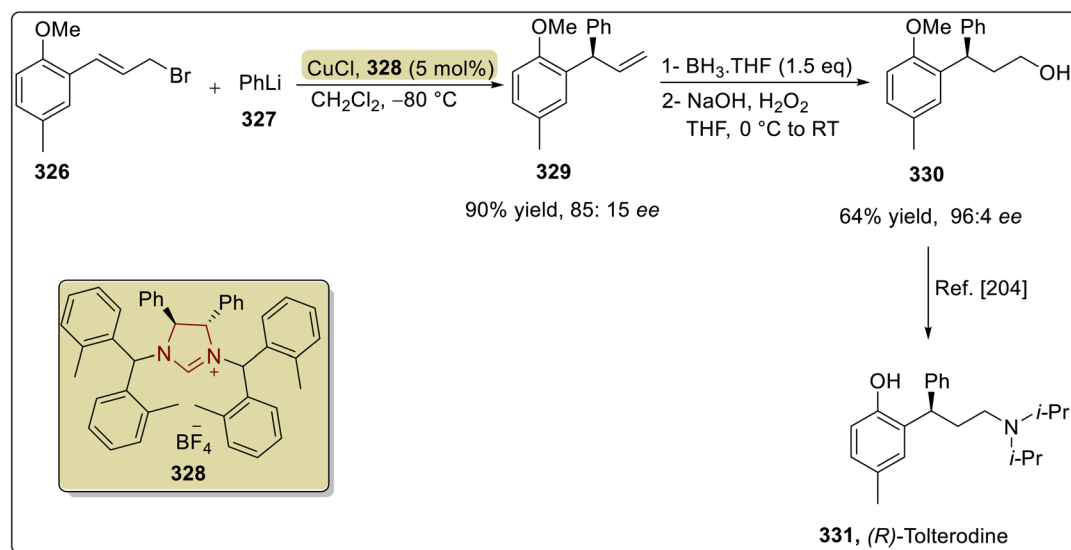


Scheme 37 Asymmetric synthesis of talmecatin **323**, talniflumate **324** and talampicillin **325**.

sclerosis, human immunodeficiency virus (HIV) infections, traumatic brain injury (TBI) and Alzheimer's disease.¹⁹¹ In this regard, Zhang *et al.*, in 2021, reported an asymmetric strategy towards the formal synthesis of (*R*)-rolipram **301** by employing oxidative NHC **298** catalysis. In this synthetic protocol, enal **296** and *N*-Ts allyl-ethyl aminomalonate **297** were allowed to undergo [3 + 2] annulation by utilizing NHC **298** (catalyst) and NaOtBu : K₂CO₃ (base) in DCM to furnish the γ -lactam **299** in 80% yield, 90% enantiomeric excess and 1.03 : 1 diastereoselectivity ratio. Next, the γ -lactam **299** was treated with a palladium catalyst to remove the allyl ester, followed by detosylation using SmI₂ to synthesize an intermediate γ -lactam

300,¹⁹² which was reported earlier for the synthesis of rolipram **301** (Scheme 33).¹⁹³

A year later, in 2022, Hu *et al.* reported an asymmetric approach towards the total synthesis of (*R*)-rolipram **301** by utilizing NHC **44** as a catalyst. The synthesis began with the imide C–N bond cleavage for the desymmetrization of *N*-Cbz cyclic imide **302a** with alcohol **303** in the presence of triazolium-based NHC **44** (as a catalyst) with K₂CO₃ (base) in DCM at –30 °C to furnish the amido ester **304a** in 89% yield with 94% enantiomeric excess. In the next step, amido ester **304a** was allowed to undergo decarbobenzyloxylation followed by decarbonylation in conjunction with intramolecular lactamization



Scheme 38 Asymmetric synthesis of tolterodine **331**.



Table 1 Summary of the discussed NHC catalysts

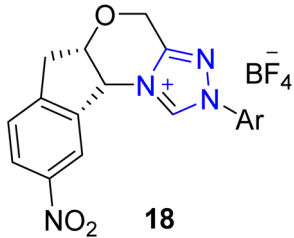
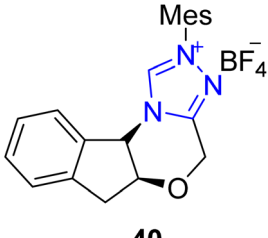
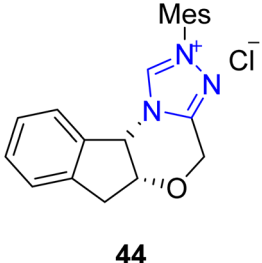
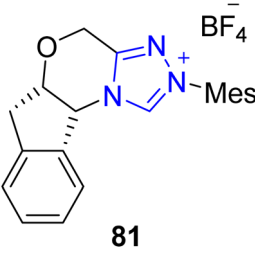
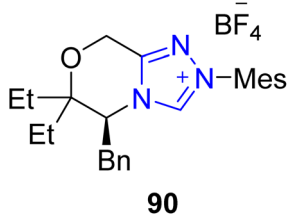
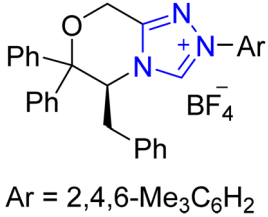
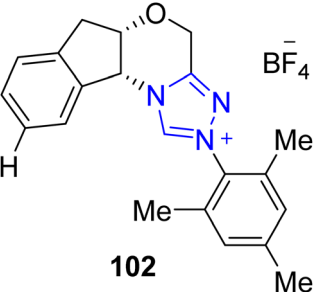
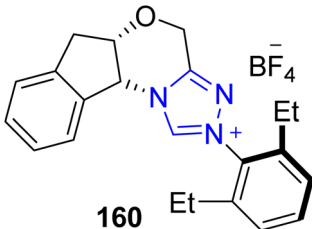
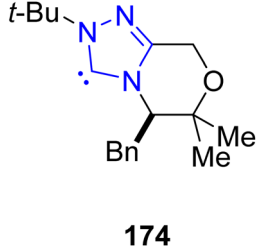
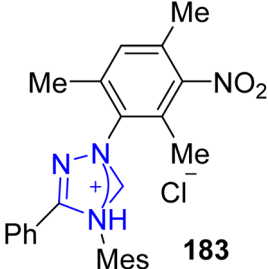
S. no.	NHC catalyst	S. no.	NHC catalyst
Triazolium-based NHCs			
1	 18 Ar = 2,4,6- <i>i</i> Pr ₃ C ₆ H ₂	2	 40
3	 44	4	 81
5	 90	6	 Ar = 2,4,6-Me ₃ C ₆ H ₂ 94
7	 102	8	 160
9	 174	10	 183



Table 1 (Contd.)

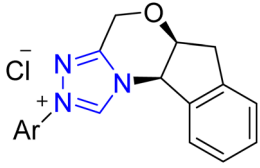
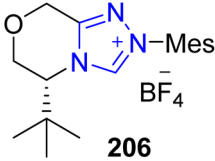
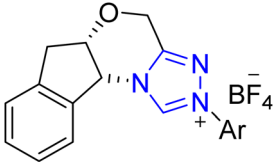
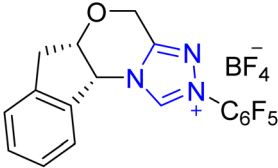
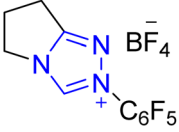
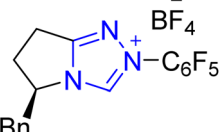
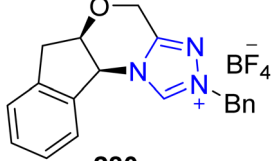
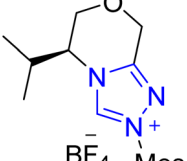
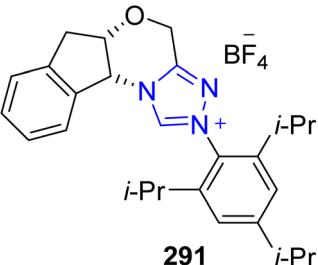
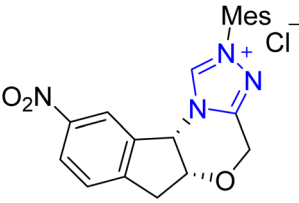
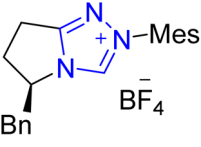
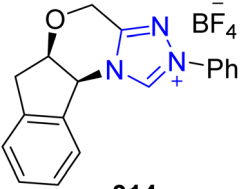
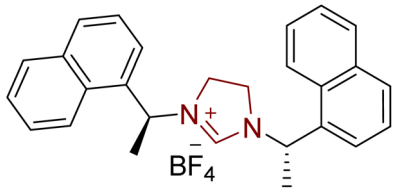
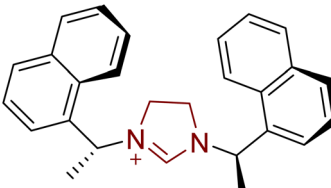
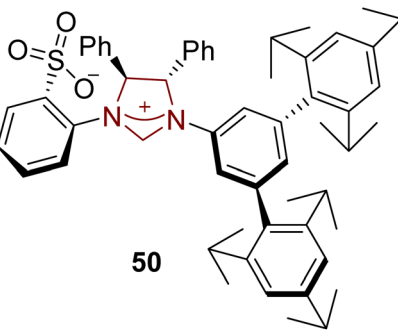
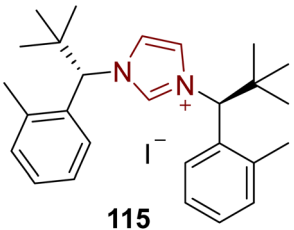
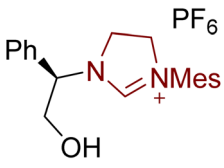
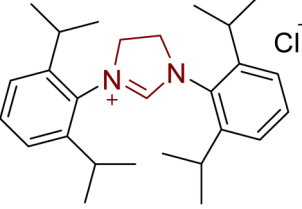
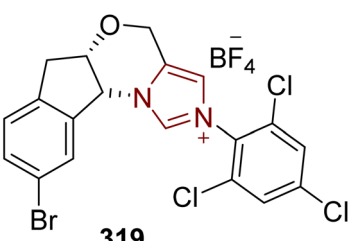
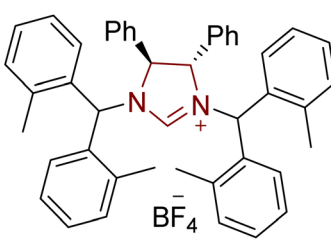
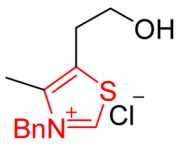
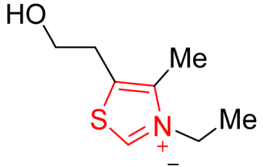
S. no.	NHC catalyst	S. no.	NHC catalyst
11	 <p>Ar = 2,4,6-Me₃C₆H₂</p> <p>200</p>	12	 <p>206</p>
13	 <p>Ar = 4-BrC₆H₄</p> <p>223</p>	14	 <p>237</p>
15	 <p>241</p>	16	 <p>246</p>
17	 <p>280</p>	18	 <p>287</p>
19	 <p>291</p>	20	 <p>298</p>
21	 <p>309</p>	22	 <p>314</p>



Table 1 (Contd.)

S. no.	NHC catalyst	S. no.	NHC catalyst
Imidazolium-based NHCs			
23	 (<i>S,S</i>)-30	24	 <i>(R,R)</i> -30
25	 50	26	 115
27	 120	28	 141
29	 319	30	 328
Thiazolium-based NHCs			
31	 26	32	 151

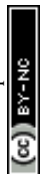
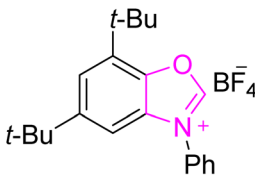


Table 1 (Contd.)

S. no.	NHC catalyst	S. no.	NHC catalyst
Oxazole-based NHC			
33		192	

to furnish (*R*)-rolipram **301** in 50% yield with 95% enantioselectivity.¹⁹⁴ Along with (*R*)-rolipram **301**, Hu *et al.* also reported the formal synthesis of (*R*)-baclofen **306**, which is used to treat spasticity linked to brain and spinal cord injuries, alcoholism and drug addiction, overactive bladder and cancer pain.¹⁹⁵ (*R*)-Baclofen **306** synthesis commenced with the desymmetrization of *N*-Cbz cyclic imide **302b** with alcohol **303**, under similar conditions to those used for **304a**, to furnish the amido ester **304b**. Next, amido ester **304b** was subjected to decarboxylation in conjunction with hydrolysis to synthesize the key intermediate **305**,¹⁹⁴ which was reported earlier by Ji *et al.* for the synthesis of (*R*)-baclofen **306** (Scheme 34).¹⁹⁶

2.2.2 Synthesis of NSAIDs. Naproxen **311**, containing free carboxylic acid functionality has been known to demonstrate analgesic, anticancer, antipyretic and antiinflammatory activity.¹⁹⁷ Owing to its high pharmaceutical importance, Chen *et al.*, in 2016, reported a synthetic protocol to synthesize asymmetric (*R*)-naproxen **311** by utilizing NHC **309** as a catalyst. The synthesis commenced with dynamic kinetic resolution (DKR) of racemic α,α -disubstituted carboxylic ester **307** with alcohol **308** in the presence of triazolium-based NHC **309** (as a catalyst) with Cs₂CO₃ (as base) in CHCl₃ at room temperature to deliver the transesterified product **310** in 86% yield with 97 : 3 enantioselectivity ratio. Next, compound **310** was allowed to undergo hydrogenolysis to furnish (*R*)-naproxen **311** in 96% yield and 96 : 4% enantioselectivity ratio (Scheme 35).¹⁹⁸

Ibuprofen **316** is an important non-steroidal anti-inflammatory drug (NSAID) used to treat rheumatoid arthritis, musculoskeletal pain and osteoarthritis.¹⁹⁹ Owing to its medicinal importance, Wang *et al.*, in 2024, reported an asymmetric approach to furnish (*R*)-ibuprofen **316** by utilizing visible-light-induced NHC **314** cooperative catalysis. In this synthetic protocol, pyrrole-2-carbonitrile **312** and α -diazoketones **313** were allowed to undergo α -amination by utilizing NHC **314** (as a catalyst), potassium *t*-butoxide (as base), in CHCl₃ (as solvent) under blue LED irradiation to synthesize the chiral product **315** in 90% yield with 95 : 5 enantioselectivity ratio. Next, compound **315** was treated with LiOH·H₂O and H₂O₂ in THF/H₂O to deliver (*R*)-ibuprofen **316** in 80% yield with 94 : 6 enantioselectivity ratio (Scheme 36).²⁰⁰

2.2.3 Synthesis of analgesics and antibacterial drugs. In 2019, Liu *et al.* reported an asymmetric approach to synthesize

talmecacin **323** (analgesic), talniflumate **324** (analgesic) and talampicillin **325** (antibacterial) drugs by utilizing triazolium-based NHC **319** as a catalyst. In this synthetic protocol, carboxylic acid **317** was allowed to undergo acetalization with *o*-phthalaldehyde **318** in the presence of NHC **319** (catalyst), quinone **184** (oxidant), K₂CO₃ (base) and LiCl (additive) in CHCl₃ to synthesize talmecacin **323** in 80% yield and 98 : 2 enantioselectivity ratio, talniflumate **324** in 96% yield and 95 : 5 enantioselectivity ratio, and talampicillin **325** in 58% yield with 6 : 1 diastereoselectivity ratio (Scheme 37).²⁰¹

A muscle relaxant exhibiting anticholinergic pharmacology called tolterodine tartrate **331** is used to treat discomfort, urgency and frequency of urination in patients with unstable bladders.²⁰² In this regard, Guduguntla *et al.* (2017) demonstrated an asymmetric strategy to synthesize tolterodine **331** by utilizing NHC **328** as a ligand, with a copper catalyst. The synthesis commenced with the enantioselective allylic arylation of aryl bromide **326** with aryllithium reagent **327** in the presence of Cu/NHC **328** (catalyst/ligand) in CH₂Cl₂ at -80 °C to furnish compound **329**, which was further allowed to undergo hydroboration-oxidation to synthesize a key intermediate **330**,²⁰³ which was reported earlier by Sun *et al.* in 2014 and utilized for the synthesis of tolterodine **331** (Scheme 38).²⁰⁴

3 Conclusion

This review provides a comprehensive perspective on NHC-catalyzed asymmetric formal and total synthesis of natural products, along with pharmaceutical drugs, reported since 2016. The synthesis of different classes of natural products, including alkaloids, terpenoids, lignans, polyketides, penta-decaketides, and flavonoids, alongwith pharmaceutical drugs, such as NSAIDs, antidepressants, antibacterial and analgesics, employing asymmetric NHC catalysis, has been summarized. During the thorough assessment, it was observed that asymmetric NHC catalysis delivered products with excellent stereochemical selectivity and substantial yields. Despite various synthetic applications of NHCs, the enhanced synthetic use of NHC catalysis in the synthesis of a wide range of other natural products and pharmaceutical drugs is yet to be explored. Further studies are needed on asymmetric NHC catalysis, which might open new doors to access more important bioactive



molecular scaffolds, drugs and important natural products. Moreover, greener, more economical and sustainable synthetic protocols (utilizing asymmetric NHC catalysis) targeting diverse stereoenriched organic compounds need to be developed.

Conflicts of interest

The authors declare no conflicts of interest.

Data availability

All data are contained in the manuscript.

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