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Construction of all-carbon quaternary stereocenters by catalytic asymmetric conjugate addition to cyclic enones in natural product synthesis

Zhuo Wang

Asymmetric catalysis for chiral compound synthesis is a rapidly growing field in modern organic chemistry and provides enantioselective materials to meet the demands of various fields. However, the construction of all-carbon quaternary stereocenters poses a distinct challenge in organic synthesis. The development of catalytic asymmetric conjugate additions that require only a catalytic amount of a transition metal with a chiral ligand or organocatalyst has provided an efficient approach to the preparative-scale synthesis of enantioselective and/or diastereoselective conjugate adducts. Such reactions have been used in various synthetic applications such as natural product synthesis and reports of the use of this approach are becoming increasingly common in the literature. In particular, tandem copper-catalyzed asymmetric conjugate addition/enolate trapping by a carbon electrophile enables diastereoselective synthesis of α,β-substituted ketones with contiguous stereogenic centers, which is still an intricate task in organic synthesis. In this review, the use of asymmetric conjugate addition in natural product synthesis is described and discussed in depth.

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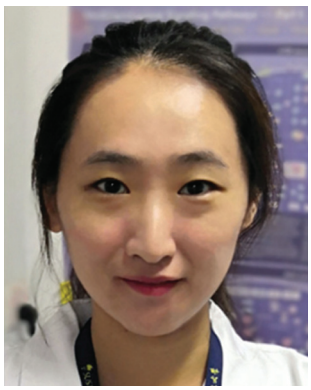


Zhuo Wang

Zhuo Wang received her BSc from Wuhan University (2009) and PhD from The Hong Kong Polytechnic University (2014) working under the direction of Dr Tao Ye. After working as a research associate in the same university for one year, she joined the lab of Prof. Hongmin Zhang at the Southern University of Science and Technology (aka. SUSTech) from 2016 to 2018 for post-doctoral research, followed by working as a senior research fellow. In late 2019, she accepted her professional appointment as a Research Assistant Professor from the School of Medicine of SUSTech. Her research interests include studying synthesis and biological evaluation of active natural products and small molecules, exploring pathogenesis of diseases, and investigating novel molecular-targeted therapeutic strategies.

1. Introduction

Asymmetric catalysis for chiral compound synthesis is a rapidly growing field in modern organic chemistry and provides enantioselective materials that meet the demands of various fields. However, the construction of all-carbon quaternary stereocenters still poses a distinct challenge in organic synthesis and the development of methods for constructing such centers is imperative.[1–11] Innovative chiral catalysts have enabled the efficient construction of all-carbon quaternary centers by various asymmetric reactions such as dearomative cyclization,[12,13] polyene cyclization,[14,15] arylation,[16] allylation,[17–19] and Michael addition.[20] Catalytic asymmetric conjugate addition can be used to synthesize ketones containing all-carbon quaternary centers from enones and is an indispensable method for accessing enantiopure and/or enantioenriched materials for various synthetic purposes.

The recent success of catalytic asymmetric conjugate addition has attracted much attention from the synthetic community in terms of the development of methods for natural product synthesis. The advantages of this class of reactions, which include the use of readily accessible transition metals and chiral ligands in catalytic amounts, the ability to produce highly enantioselective and/or diastereoselective ketones containing all-carbon quaternary stereocenters, and applicability to preparative-scale reactions, collectively make catalytic asym-

metric conjugate addition appealing for natural product synthesis. Alkylation and/or acylation at the α-position through enolate trapping after copper-catalyzed asymmetric conjugate addition (*i.e.*, a tandem reaction) provides diastereoselective ketones with contiguous stereocenters at the α- and β-positions. This approach provides access to structures with congested arrays of stereocenters. Organocatalytic asymmetric conjugate addition can establish an all-carbon quaternary stereocenter without the use of a transition-metal catalyst to generate an organometallic nucleophile. Much effort has been devoted to the development of methods for achieving catalytic asymmetric conjugate addition and this has become a facile approach to the construction of a wide range of important enantioenriched scaffolds for use in organic chemistry, medicinal chemistry, and the pharmaceutical industry. Many reviews of catalytic asymmetric conjugate addition and its applications have been published.[21–26] The upsurge in the use of this class of reactions has enabled the synthesis of many structurally elusive natural products (Fig. 1). These important results have motivated us to provide a timely and focused review of catalytic asymmetric conjugate additions in natural product synthesis.

In this review, we begin with an introduction to method development and representative examples of natural product syntheses that make use of catalytic asymmetric conjugate

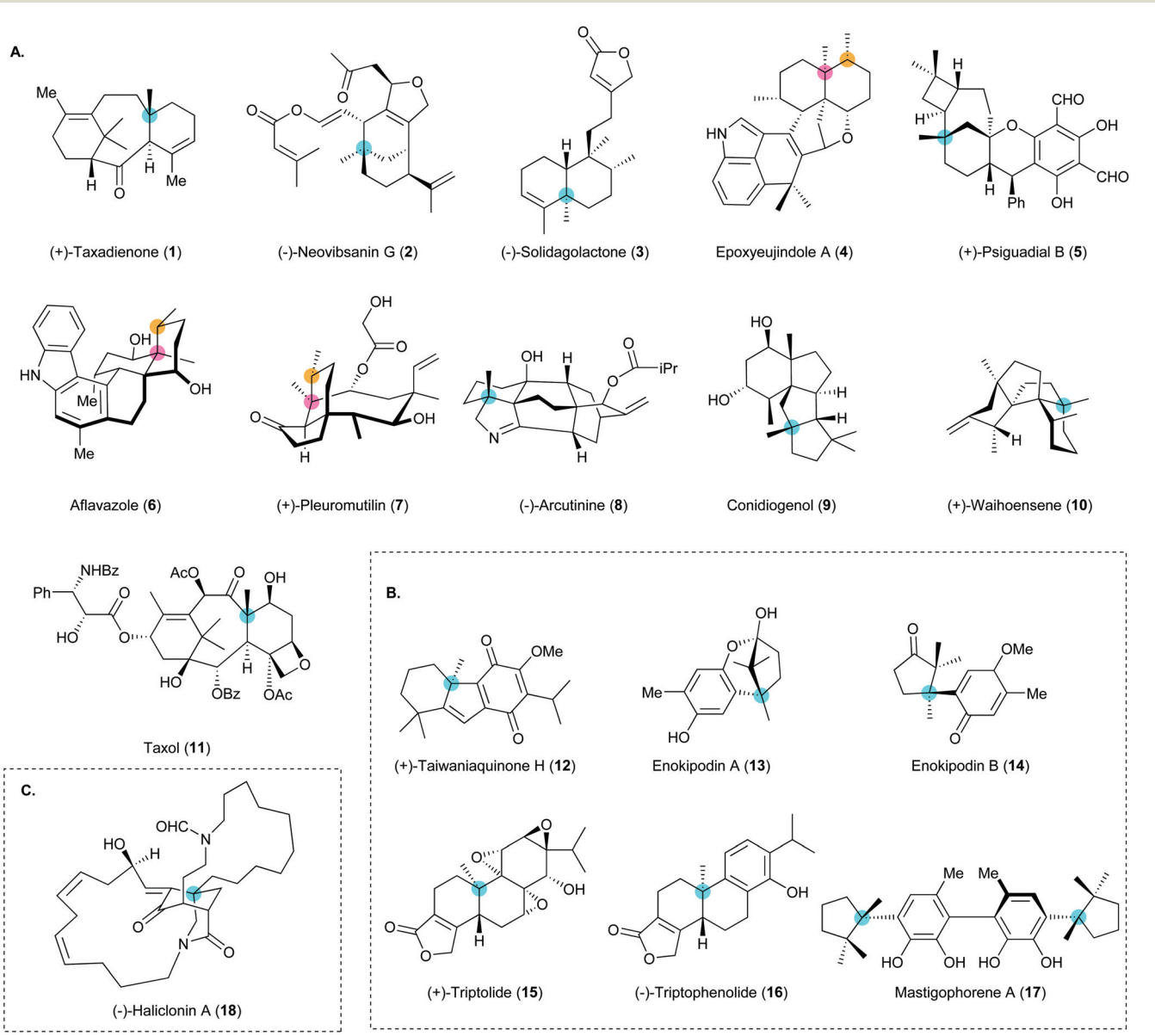
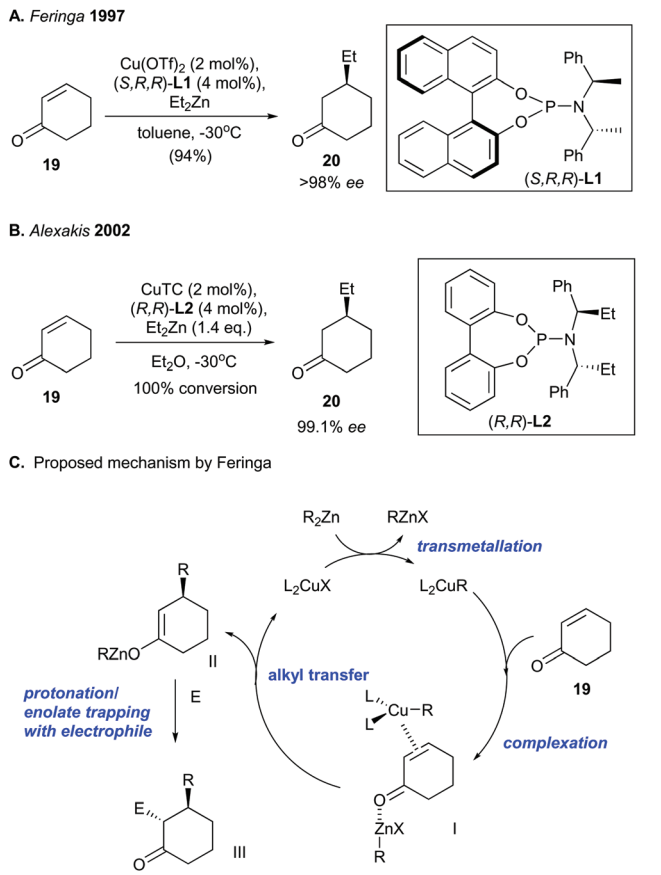


Fig. 1 Some natural product syntheses that make use of *catalytic asymmetric conjugate addition* (CACA) to create all-carbon quaternary stereocenters. (A) Quaternary carbon(s) created directly by copper-catalyzed asymmetric conjugate addition or indirectly by subsequent enolate trapping by carbon electrophile. (B) Quaternary carbon(s) created by palladium-catalyzed asymmetric conjugate addition. (C) Quaternary carbon(s) created by organocatalytic asymmetric conjugate addition. [Quaternary stereocenter(s) created by CACA are highlighted in cyan; stereocenter(s) created by CACA are highlighted in orange; and quaternary stereocenter(s) formed by enolate trapping immediately after CACA are highlighted in pink.]

addition and were reported before 2016. We discuss natural product syntheses reported in 2016–2020 (inclusive) that feature this important synthetic method, with an emphasis on the key factors and transformations that led to their success. We classify the natural product syntheses according to the catalyst used in the asymmetric conjugate addition to build the all-carbon quaternary stereocenter, namely copper catalysts, palladium catalysts, and organocatalysts. Finally, we discuss potential developments and envisage future opportunities for the use of catalytic asymmetric conjugate additions.

2. Construction of all-carbon quaternary stereocenters by copper-catalyzed asymmetric conjugate addition

The pioneering discovery of copper-catalyzed asymmetric conjugate addition was made independently by Feringa[27] and Alexakis.[28] They used a copper catalyst and a chiral phosphine ligand to facilitate asymmetric conjugate addition of an enone to give an enantioenriched ketone (Scheme 1). Chirality was introduced by using a chiral phosphoramidite ligand [*e.g.*, (*S*,*R*,*R*)-**L1** and (*R*,*R*)-**L2**]. The copper-catalyzed asymmetric conjugate addition of cyclohexenone (**19**) with diethylzinc produced the enantioenriched ketone **20** with a high ee value of 98% to 99.1% (Scheme 1A and B). Feringa and co-workers[29] proposed that the catalytic mechanism involves alkyl transfer from dialkylzinc (*i.e.*, R_2Zn) to a copper(I)–phosphoramidite complex, which generates a copper(I)–alkyl complex (*i.e.*, L_2CuR) (Scheme 1C). Complexation of an alkylzinc halide (*i.e.*, RZnX) to the enone carbonyl of **19** and coordination of a copper–alkyl complex (*i.e.*, L_2CuR) to the enone olefin of **19** results in the formation of π-complex **I**. The authors reasoned that high levels of stereocontrol can result from bimetallic complex formation, which fixes the enone conformation. Next, alkyl transfer from the π-coordinated copper complex to the enone generates zinc enolate **II**. Finally, either protonation or trapping of the zinc enolate by an electrophile (**E**) produces **III**.



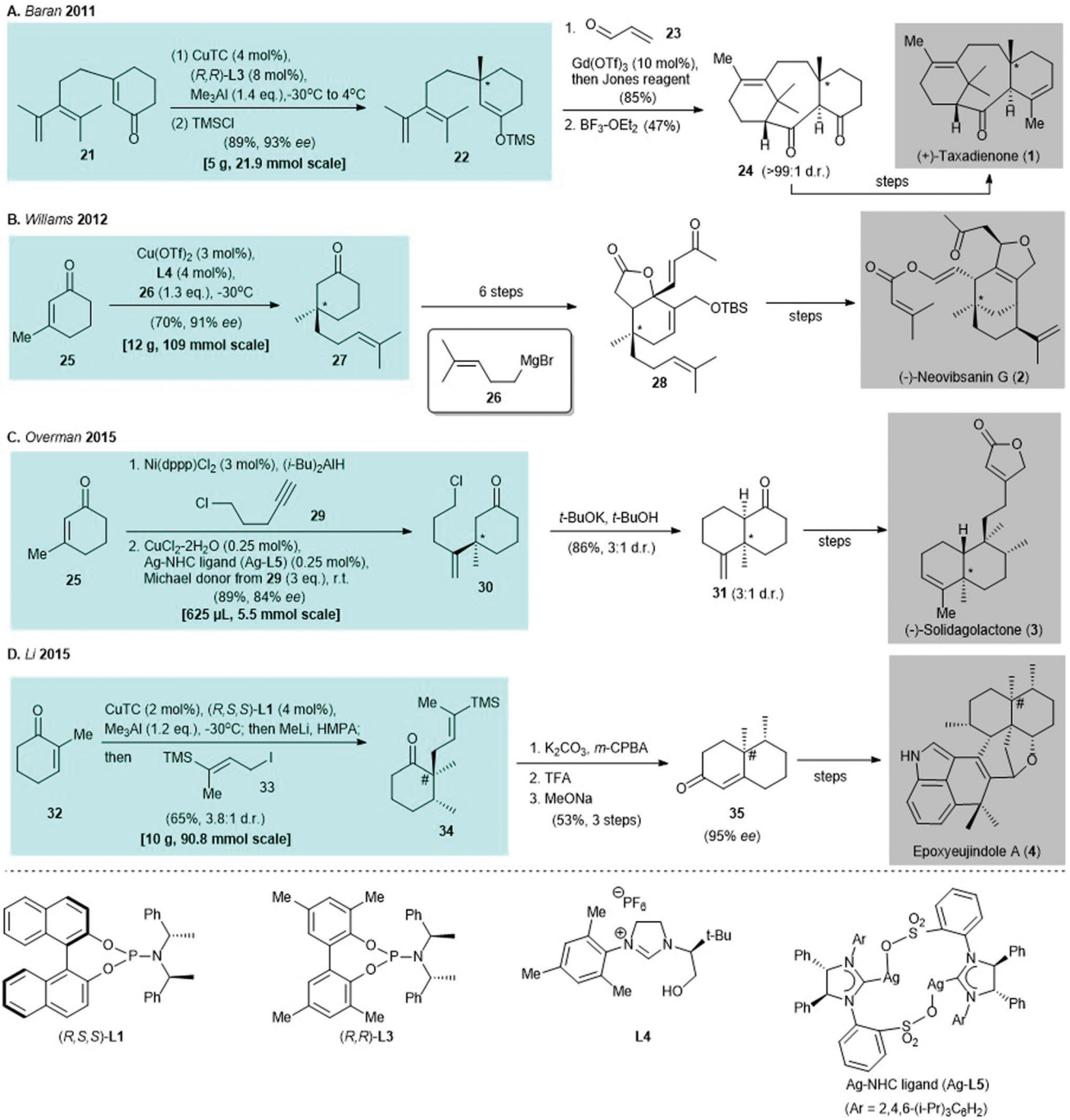
Scheme 1 Pioneering reports of copper-catalyzed asymmetric conjugate addition by (A) Feringa (1997)[27] and (B) Alexakis (2002).[28] (C) Mechanism proposed by Feringa.[29]

Since the report of copper-catalyzed asymmetric conjugate addition to set the enone β-stereocenter, the construction of all-carbon quaternary stereocenters has become possible and has been widely used in natural product synthesis. Representative syntheses of natural products reported before 2016 are shown in Scheme 2.

In 2011, the preparation of (+)-taxadienone (**1**) was reported by Baran and co-workers. The synthesis featured asymmetric conjugate addition and the enantioenriched TMS-enolate **22** was prepared in 89% yield with 93% ee[30] (Scheme 2A). In 2012, Williams and co-workers synthesized (−)-neovibsanin G (**4**) by using a $Cu(OTf)_2$–chiral nitrogen-heterocyclic carbene (NHC) ligand (**L4**) to catalyze a conjugate addition. Use of a Grignard reagent (*i.e.*, **26**) as the alkylating agent afforded the intermediate cyclohexanone **27** in 70% yield with 91% ee[31] (Scheme 2B). Synthesis of (−)-solidagolactone (**5**), which was reported by Overman and co-workers in 2015, involved tandem nickel-catalyzed regioselective hydroalumination[32,33]/asymmetric copper-catalyzed conjugate addition[34] of enone **25** under the effect of a Ag–NHC complex (Ag-**L5**)[35] to give adduct **30** in 89% yield with 84% ee[36] (Scheme 2C). In the same year, epoxyeujindole A (**6**) was synthesized by Li and co-workers by asymmetric conjugate addition under the Alexakis protocol,[37] followed by enolate trapping with iodide **33** to give cyclohexanone **34** in 65% yield with a 3.8 : 1 dr[38] (Scheme 2D).

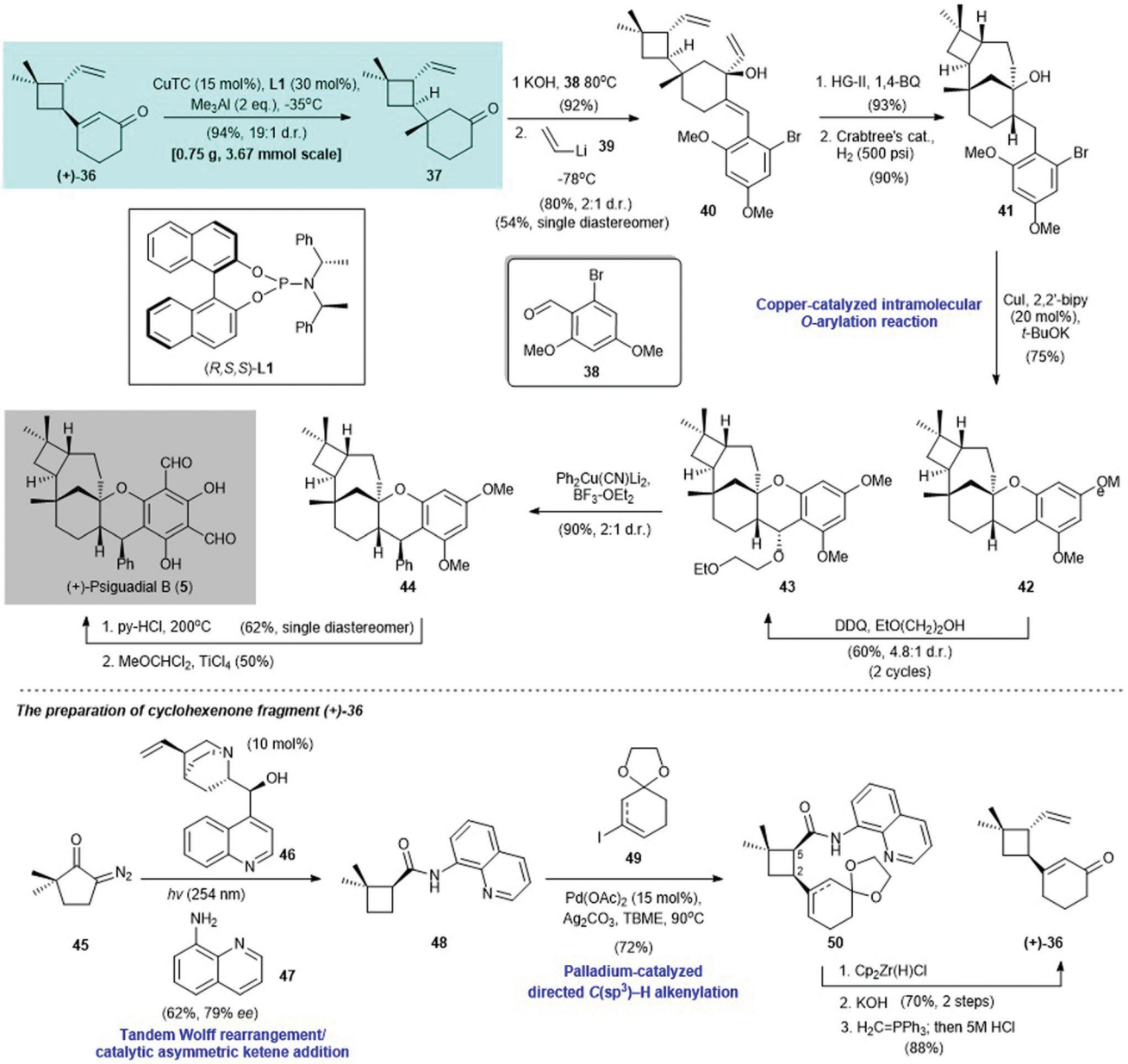
2.1. (+)-Psiguadial B (Reisman 2016)[39]

(+)-Psiguadial B (**5**) is a diformyl phloroglucinol-containing meroterpenoid. It was isolated from the leaves of *Psidium guajava* by Ye and co-workers in 2010.[40] This compound shows potent antiproliferative activity against human hepatoma cells (HepG2 IC_{50} = 46 nM).[40] In 2016, Reisman and co-workers reported the first enantioselective synthesis of **5** (Scheme 3)[39] Cyclohexenone (+)-**36**, which was prepared from diazoketone **45** in five steps (Scheme 3, bottom section), was subjected to copper-catalyzed asymmetric conjugate addition *via* the Alexakis protocol [*i.e.*, with CuTC/(*R*,*S*,*S*)-**L1** as the catalyst][41] to afford adduct **37** in 94% yield with a 19 : 1 dr. Aldol condensation of chiral adduct **37** with benzaldehyde **38** and sub-



Scheme 2 Selected examples of natural product syntheses reported before 2016 that use copper-catalyzed asymmetric conjugate addition. [All-carbon quaternary stereocenter(s) created by (i) copper-catalyzed asymmetric conjugate addition are denoted by *; (ii) copper-catalyzed asymmetric conjugate addition/enolate trapping is denoted by #]. (A) Asymmetric conjugate addition of **21** and immediate trapping of enolate with trimethylsilane chloride (TMSCl) gives TMS-enolate **22** in the synthesis of (+)-taxadienone (**1**). (B) Synthesis of (–)-neovibsanin G (**2**) makes use of chiral NHC ligand **L4** in catalytic conjugate addition for the preparation of enantioenriched cyclohexanone **27**.[31] (C) Tandem nickel-catalyzed regioselective hydroalumination[35]/asymmetric copper-catalyzed conjugate addition produces **30** in the presence of Ag–NHC complex (Ag-**L5**)[47] as a catalyst in synthesis of (–)-solidagolactone (**3**).[36] (D) Tandem asymmetric conjugate addition/α-alkylation produces cyclohexanone **34**, which is a precursor in the preparation of epoxyeujindole A (**4**).[38]

sequent 1,2-addition with vinyllithium (**39**) gave alcohol **40** in 81% yield with a 2 : 1 dr; **40** was subjected to HG-II catalyst-promoted ring-closing metathesis (product not shown, 93% yield). Subsequent catalytic hydrogenation with Crabtree's catalyst produced **41** in 90% yield. Copper-catalyzed intramolecular *O*-arylation[42] of **41** afforded **42** in 75% yield; **42** was



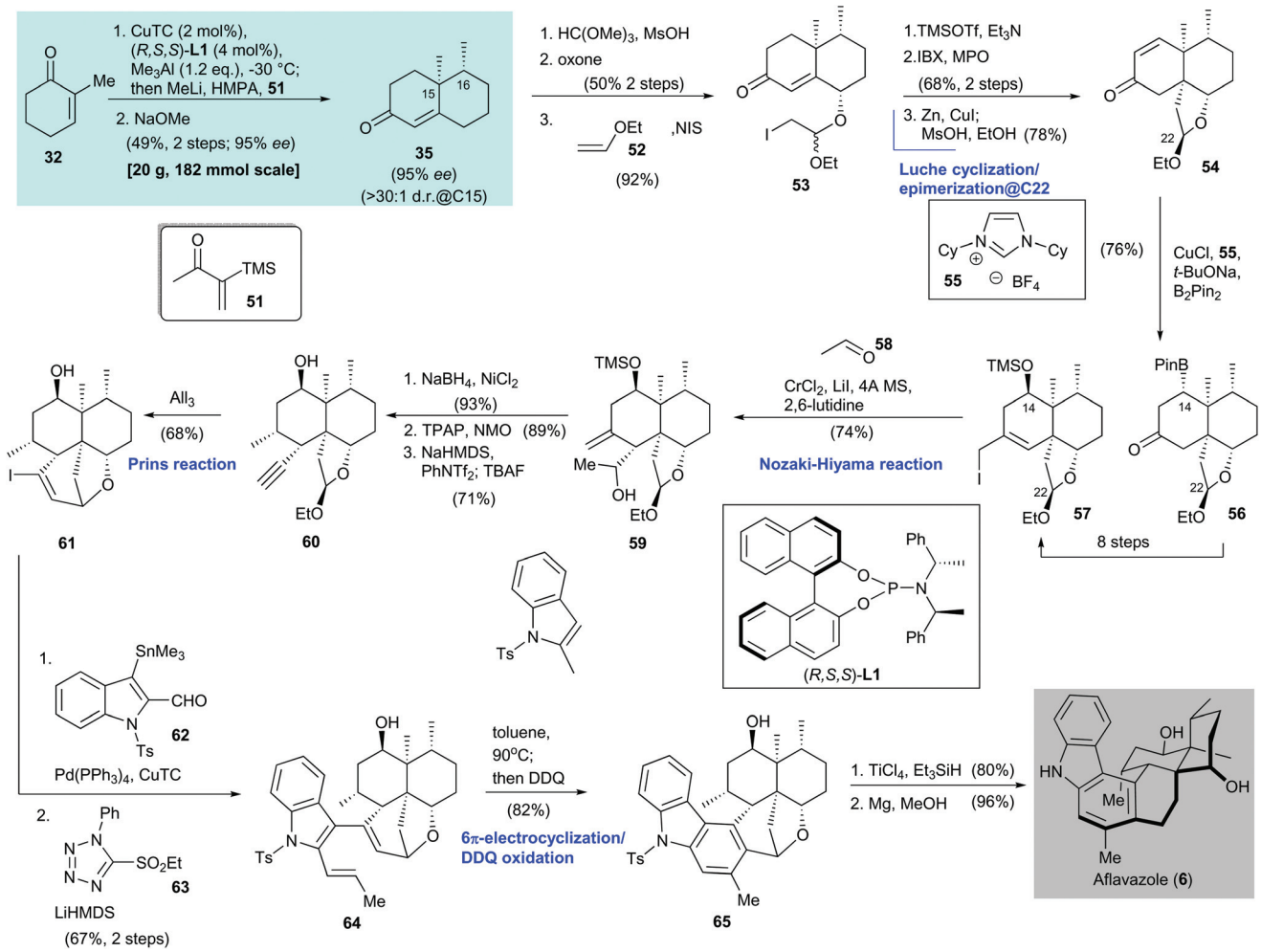
Scheme 3 Enantioselective synthesis of (+)-psiguadial B (**5**) (Reisman, 2016).[39] Bottom section: preparation of cyclohexanone fragment (+)-**36**.

treated with DDQ/ethoxyethanol[43] to effect benzylic oxidation to give **43** in 60% yield with a 4.8 : 1 dr. Treatment of **43** with $Ph_2Cu(CN)Li_2$ [44,45] and BF_3–OEt_2 afforded **44** in 90% yield with a 2 : 1 dr; **44** was subjected to demethylation (62% yield, single diastereomer) and simultaneous formylation *via* the Rieche procedure[46] to give (+)-psiguadial B (**5**) in 50% yield.

The synthesis of cyclohexenone (+)-**36** began with a tandem Wolff-rearrangement[48]/asymmetric ketene addition[49,50] of **45** with aniline **47**, and (+)-cinchonine (**46**) as the catalyst, to afford enantioenriched cyclobutane **48** in 62% yield with 79% ee (Scheme 3, bottom section). Enantiomerically pure **48** can be obtained *via* single recrystallization by layer diffusion. Palladium-catalyzed cross-coupling of freshly prepared **48** with iodide **49** afforded **50** in 72% yield. Reduction of the amide group in **50** by $Cp_2Zr(H)Cl$ afforded a *cis*-aldehyde intermediate (not shown), which was subjected to C-5 epimerization with KOH/methanol, followed immediately by Wittig olefination to produce the desired enone (+)-**36** in 88% yield.

2.2. Aflavazole (Li 2016)[51]

Aflavazole (**6**) is an indole diterpenoid. It is a metabolite of the sclerotia of *Aspergillus flavus* and was identified by Dowd and co-workers in 1990.[52] The first total synthesis of **6** was reported by Li and co-workers in 2016 (Scheme 4).[51] Asymmetric conjugate addition of 2-methylcyclohexenone (**32**), catalyzed by CuTC/(*R*,*S*,*S*)-**L1**,[38] enolate synthesis with methyllithium and



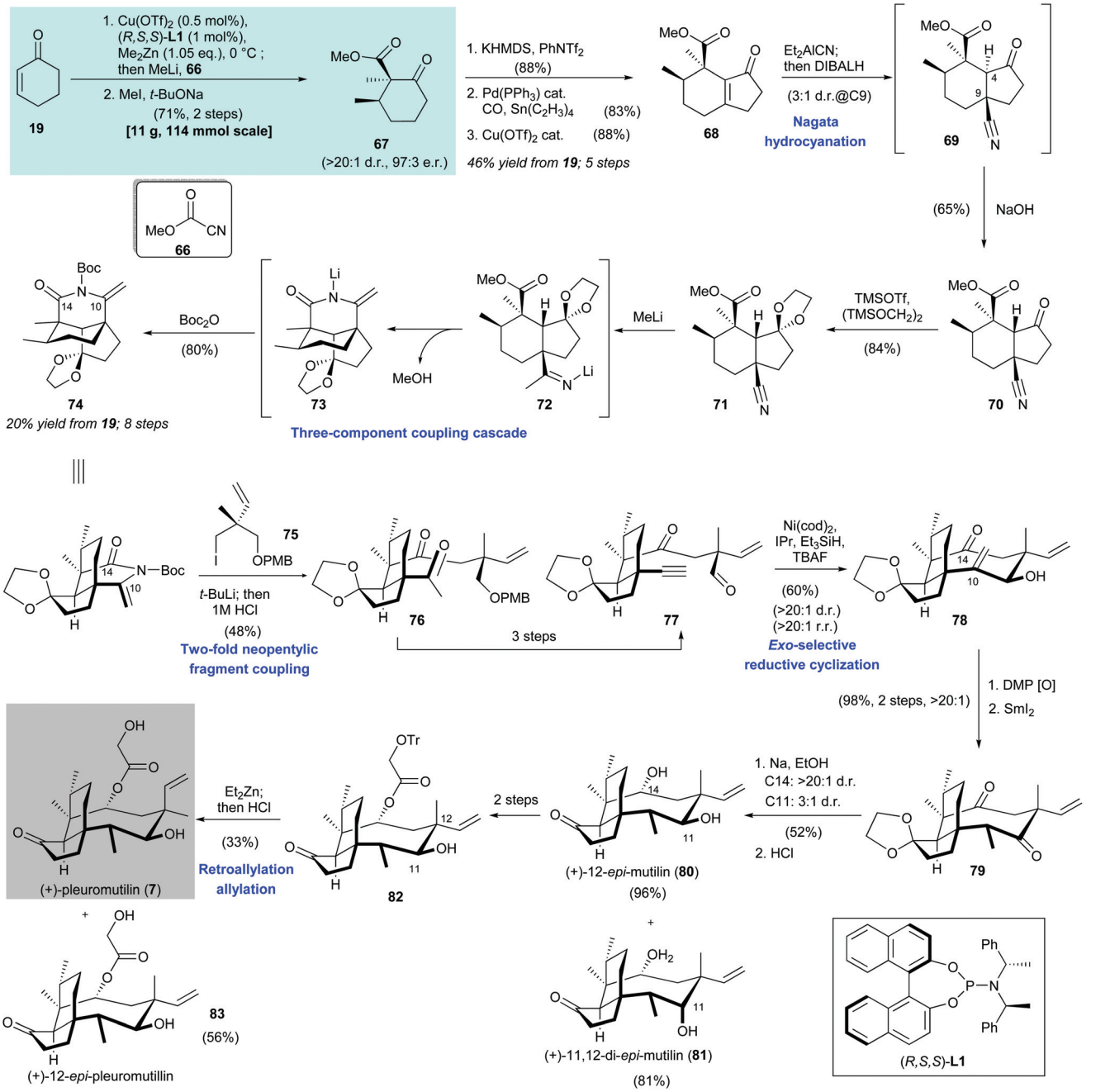
Scheme 4 Enantioselective synthesis of aflavazole (**6**) (Li, 2016).[51]

HMPA, and subsequent attack by the Stork–Ganem reagent **51**[53] gave an α-silyl ketone (not shown). Exposure of the freshly prepared α-silyl ketone to NaOMe produced **35** in 49% yield over two steps with 95% ee.

A three-step synthesis from enone **35** gave iodide **53**, which was subjected to silyl enol ether formation and IBX oxdation[54] to give a bis-enone (not shown, 68% yield over two steps). The enone underwent Luche cyclization and epimerization at C-22[38] to afford enone **54** in 78% yield over two steps. Boron conjugate addition[55,56] of enone **54** gave boronate **56** in 76% yield; **56** was converted to iodide **57** with the desired stereochemistry at C-14 through an eight-step transformation. Freshly prepared iodide **57** was subjected to a Nozaki–Hiyama reaction with acetaldehyde **58** to give alcohol **59** in 74% yield as a single diastereomer. A three-step transformation from alcohol **59**, namely facial selective reduction of the *exo*-olefin (product not shown, 93% yield), secondary alcohol oxidation (product not shown, 89% yield), and triflation/TBAF-mediated elimination[57] and desilylation, gave alkyne **60** in 71% yield. Treatment of **60** with AlI_3 facilitated a Prins cyclization and provided the cyclization product **61** in 68% yield. Stille–Migita coupling of vinyl iodide **61** with tin compound **62** and subsequent Julia–Kocienski olefination afforded triene **64** in 67% yield over two steps. Heating of triene **64** resulted in 6π-electrocyclization, and subsequent DDQ oxidation[58] gave arene **65** in 82% yield. Reductive cleavage of the benzyl ether in **65** and then desulfonation with magnesium afforded aflavazole (**6**) in 96% yield. The enantioselective synthesis of 14-hydroxyaflavinine (not shown) was also reported in the same publication, but is not discussed here.

2.3. (+)-Pleuromutilin (Herzon 2017)[59]

The enantioselective synthesis of (+)-pleuromutilin (**7**) was disclosed by Herzon and co-workers in 2017;[59,60] **7** is a tricyclic diterpene fungal metabolite (Scheme 5). Biologically, **7** shows inhibitory activities against the growth of Gram-positive pathogens.[61,62] Because of its unique mode of action, *i.e.*, binding to the highly conserved peptidyl transferase center of the bacterial ribosome, the development of resistance to pleuromutilin has been delayed. The synthesis of (+)-pleuromutilin (**7**) and its derivatives has therefore attracted wide interest in the context of the development of new antibiotics.[63–66]



Scheme 5 Enantioselective synthesis of (+)-pleuromutilin (**7**) (Herzon, 2017).[59]

Herzon's synthesis of (+)-pleuromutilin (**7**) began with asymmetric copper-catalyzed conjugate addition of dimethylzinc and cyclohexenone (**19**). Acylation at the α-position with Mander's reagent **66**[67] and subsequent diastereomeric α-methylation[68] produced **67** in 71% yield with >20 : 1 dr and 97 : 3 er. Exposure of the freshly prepared β-ketoester **67** to KHMDS/$PhNTf_2$ afforded the corresponding enol triflate (not shown, 88% yield), which was subjected to palladium-catalyzed carbonylative coupling[69] (product not shown, 83% yield). Subsequent $Cu(OTf)_2$-catalyzed Nazarov cyclization[70] gave cyclopentenone **68** in 88% yield. Conjugate addition of Et_2AlCN[71] to cyclopentenone **68** gave adduct **69** with a 3 : 1 dr; the undesired epimer (not shown) was reduced selectively with DIBAL-H. Immediate treatment of the formed crude product **69** with dilute sodium hydroxide resulted in inversion of the C-4 stereocenter to produce **70** in 65% yield. After protection of ketone **70** as ketal **71**,[72] addition of excess methyllithium facilitated functionalization of the nitrile moiety in **71** and subsequent addition of Boc_2O afforded cyclic enimide **74** in 80% yield. The authors proposed that this three-component coupling cascade takes place as follows. Nucleophilic addition of methyllithium to the nitrile group in **71** produced **72**, which

underwent lactamization and then deprotonation to give **73**. Boc protection of **73** produced enimide **74**.

The organolithium reagent generated *in situ* from the reaction between iodide **75** and *tert*-butyllithium was treated with enimide **74** to provide methyl ketone **76** in 48% yield after acid hydrolysis. The authors suggested that electronic activation of the C-14 carbonyl group and minimization of nearby nonbonding interactions by construction of a cyclic enimide functional group were detrimental to the success of this two-fold neopentylic fragment coupling. A three-step transformation from **76** gave aldehyde **77**, which was subjected to nickel-catalyzed reductive cyclization,[73] followed by immediate desilylation to give allylic alcohol **78** in 60% yield with >20 : 1 dr and >20 : 1 rr. The authors suggested that the limited number of rotatable bonds along the cyclization precursor **77** reduces the entropic penalty of cyclization and enhances stereo- and regio-control. The sp^2-carbons at C-10 and C-14 in the cyclization product **78** can relieve transannular nonbonding interactions in the eight-membered ring, which enables the unprecedented reductive cyclization of a medium-sized ring to be achieved. Oxidation of alcohol **78** and subsequent stereoselective enone reduction with samarium diiodide produced **79** in 98% yield with >20 : 1 dr. Single-electron reduction of ketone **79** was accomplished by treatment with sodium in the presence of ethanol. Ketal hydrolysis then afforded **80** and **81** in 96% and 81% yield, respectively. A two-step transformation from **80** gave ester **82**, which was subjected to C-12 epimerization *via* a retro-allylation–allylation process.[74] Subsequent cleavage of the trityl group afforded (+)-pleuromutilin (**7**) in 33% yield and (+)-12-*epi*-pleuromutilin (**83**) in 56% yield.

2.4. (−)-Arcutinine (Qin 2019)[75]

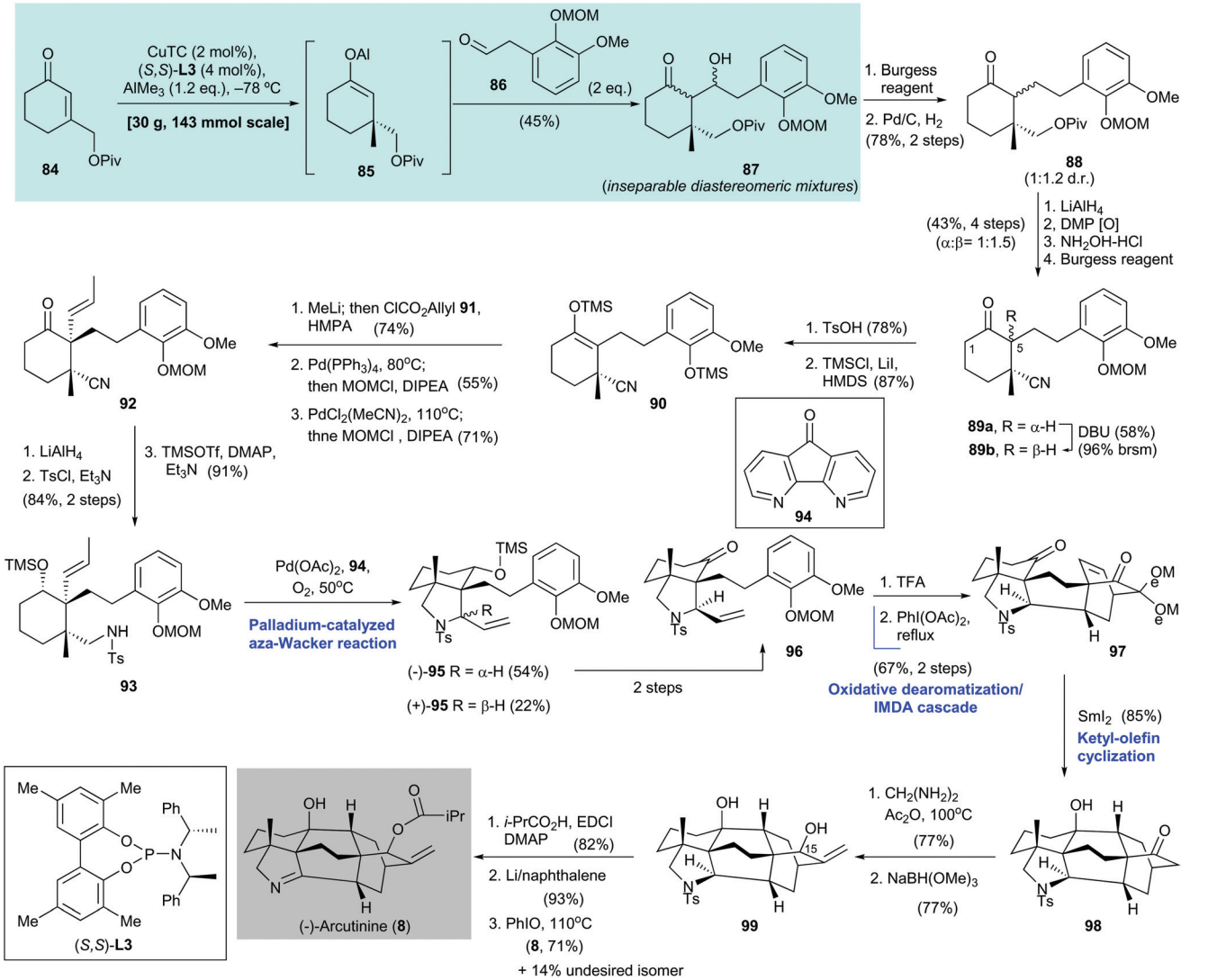
Arcutinine (**8**) is an arcutine-type C20 diterpenoid alkaloid.[76] It was isolated from *Aconitum arcuatam* in a 1 : 2 mixture with arcutine (not shown) by Saidkhodzhaeva and co-workers in 2001.[77] Shortly after the first enantioselective synthesis of (−)-arcutinine (**8**), which was reported by Qin and co-workers[75] in 2019, Li and co-workers reported their asymmetric synthesis of **8**.[78] The enantioselective synthesis of **8** reported by Qin is as follows[75] (Scheme 6). Asymmetric conjugate addition of enone **84**[79] with $AlMe_3$ was effected with CuTC/(*S*,*S*)-**L3** as the catalyst.[37] The obtained adduct, *i.e.*, aluminum enolate **85**, was trapped by aldehyde **86** to give hydroxy ketone **87** in 45% yield. Hydrolysis of aluminum enolate **85** gave the corresponding cyclohexanone (not shown) with 92% ee. A two-step transformation from hydroxy ketone **87** gave **88**, which was subjected to a sequence of reactions, namely simultaneous ketone and pivalate reduction, Dess–Martin oxidation, selective oxime formation with hydroxylamine, and dehydration with Burgess reagent, to afford nitriles **89a** and **89b** with a 1 : 1.5 dr in 43% yield over four steps. Removal of the MOM group in **89b** (R = β-H) with TsOH (product not shown, 78% yield) resulted in selective silyl enol ether formation at C-5 over C-1. The resultant phenol was treated with TMSCl/LiI in the presence of HMDS to afford the desired silyl enol ether **90** in 87% yield with the phenol moiety as the silylated form. Epimerization of **89a** to **89b** was accomplished by treatment with DBU.

Treatment of **90** with methyllithium and $ClCO_2$allyl (**91**) in the presence of HMPA gave a carbonate (not shown, 74% yield), which was subjected to decarboxylative allylic alkylation/MOM protection of the phenol group (product not shown, 55% yield). Subsequent palladium-catalyzed olefin isomerization to an internal olefin,[80] followed by MOM protection of the phenol group, gave cyclohexanone **92** in 71% yield. A three-step synthesis from **92**, which involved simultaneous ketone and nitrile reduction, *N*-tosylation (product not shown, 84% yield over two steps), and alcohol silylation, gave amine **93** in 91% yield. The use of the aza-Wacker reaction *via* Stahl's protocol[81] converted **93** to pyrrolidine **95** as a mixture of diastereomers. The desired isomer, *i.e.*, (−)-**95**, which was obtained in 54% yield, was converted to the corresponding ketone **96** in two steps. Cleavage of the MOM group in **96** with TFA, followed by an oxidative dearomatization/intramolecular Diels–Alder reaction cascade of the resulting phenol, produced the cycloaddition adduct **97** in 67% yield over two steps. Ketyl–olefin cyclization of freshly prepared **97**, mediated by samarium diiodide, gave the cyclization product **98** in 85% yield; **98** was subjected to α-methylenation (product not shown, 77% yield) and then reduction to give diol **99** in 77% yield. Selective installation of an isobutyryl group at the C-15 alcohol of **99** (product not shown, 82% yield), detosylation effected by Li/naphthalene (product not shown, 93% yield), and subsequent oxidation of the resultant pyrrolidine with PhIO afforded (−)-arcutinine (**8**) in 71% yield along with the undesired isomer (not shown) in 14% yield.

2.5. Conidiogenones and conidiogenol (Snyder 2019)[82]

Conidiogenone B (**110**), conidiogenone (**111**), and conidiogenol (**9**) are tetracyclic diterpenes. They were isolated from fermentation broths and marine-derived endophytic fungi of the *Penicillium* genus.[83,84] Biologically, conidiogenone (**111**) and conidiogenol (**9**) have potent conidiation-inducing activities, and conidiogenone B (**110**) shows high antibacterial activity against methicillin-resistant *Staphylococcus aureus*, *Pseudomonas fluorescens*, *P. aeruginosa*, and *S. epidermidis*.[85] In 2016, Tu and co-workers disclosed the total syntheses and absolute configurations of **110**, **111**, and **9**.[86] In 2019, Snyder and co-workers reported the enantioselective syntheses of several conidiogenones (**110**, **111**, **114**, and **115**) and conidiogenol (**9**). They described the concept of quaternary-center-guided synthesis of complex polycyclic terpenes[82] (Scheme 7).

Snyder's syntheses of conidiogenone B (**110**), conidiogenone (**111**), and conidiogenol (**9**) featured asymmetric conjugate addition of enone **100** *via* Hoveyda's protocol [*i.e.*, with a $Cu(OTf)_2$/Ag–NHC (Ag-**L6**) catalyst][87] to give cyclopentane **101** in 79% yield with 88% ee[82] (Scheme 7). Conversion of freshly prepared **101** to **102** was accomplished in two steps; **102** was then subjected to Baran's reductive coupling[88] to give **103** in 80% yield as a single diastereomer. Corey hydrazine-mediated alkylation[89] of **103** with iodide **104** afforded an α-alkylation product (not shown), which was transformed into the corres-



Scheme 6 Enantioselective synthesis of (–)-arcutinine (**8**) (Qin, 2019).[75]

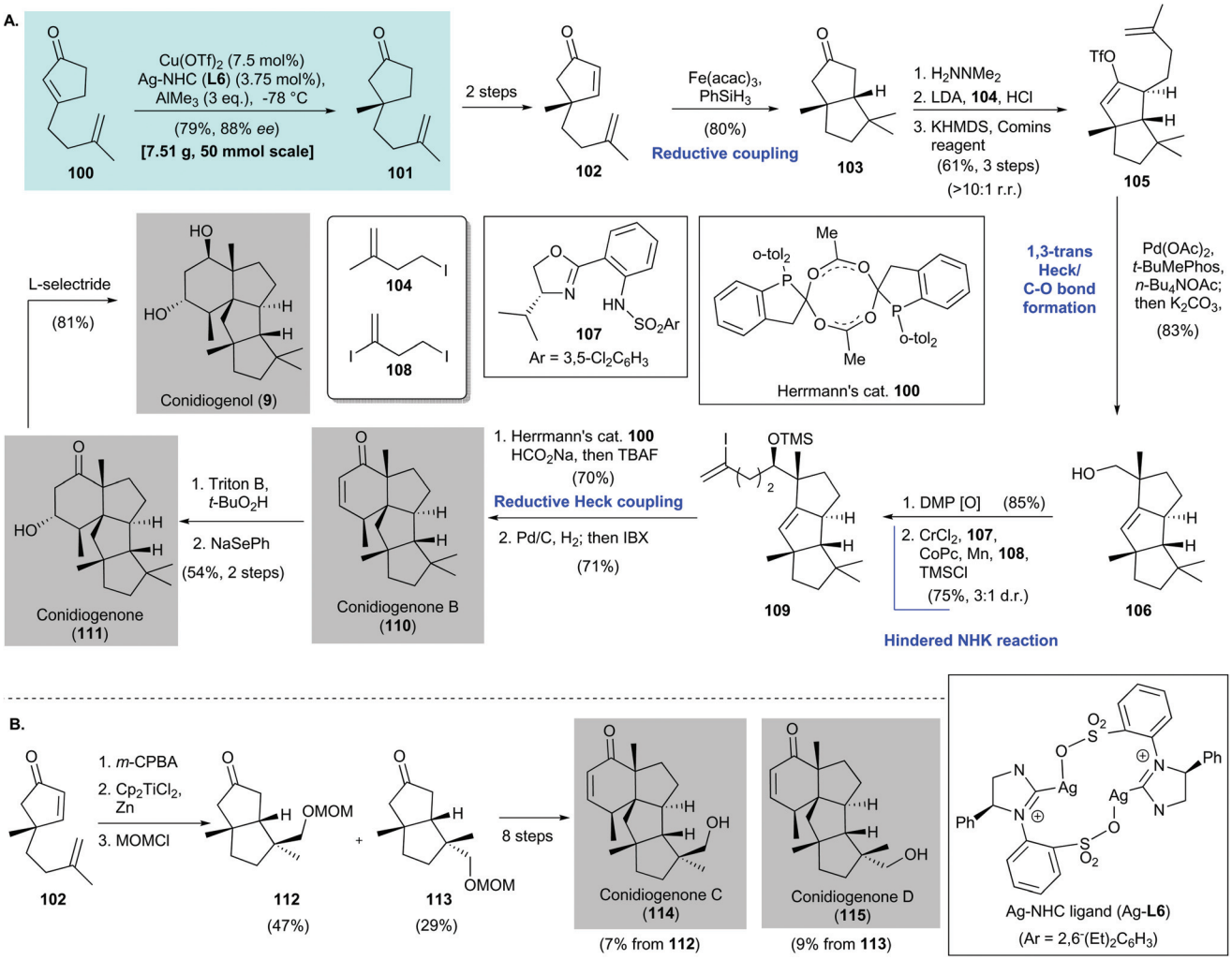
ponding vinyl triflate **105** by using KHMDS/Comins' reagent. The yield was 61% over three steps and the rr was >10 : 1. Cyclization of vinyl triflate **105** was achieved with a palladium catalyst (*i.e.*, $Pd(OAc)_2$/*t*-BuMePhos) in the presence of *n*-Bu_4NOAc[90] as an oxygen source to give a tricyclic acetate (not shown), which was subjected to saponification to give the corresponding alcohol **106** in 83% yield as a single diastereomer. Oxidation of alcohol **106** with Dess–Martin periodinane gave an aldehyde (not shown), which was subjected to a radical-based Nozaki–Hiyama–Kishi reaction[91,92] with diiodide **108**. Subsequent silylation gave vinyl iodide **109** in 75% yield with a 3 : 1 dr. Reductive Heck coupling[93] with Herrmann's catalyst[94] in the presence of HCO_2Na gave the tetracyclic core (not shown, 70% yield), which was subjected to catalytic hydrogenation of the olefin. Desaturation with IBX produced conidiogenone B (**110**) in 71% yield. Conversion of **110** to conidiogenone (**111**) and conidiogenol (**9**) was achieved by using Tu's reported conditions.[86]

In the same work, Snyder and co-workers synthesized conidiogenones C (**114**) and D (**115**)[82] (Scheme 7B). Treatment of **102** with *m*-CPBA and cyclization with Cp_2TiCl_2 [95] produced **112** and **113**, which were used in an eight-step synthesis to give conidiogenone C (**114**) and conidiogenone D (**115**), respectively.

2.6. (+)-Waihoensene (Yang 2020;[96] Snyder 2020 [97])

Waihoensene (**10**) is a tetracyclic diterpene; it was isolated from the New Zealand podocarp *Podocarpus totara* var *waihoensis* by Weavers and co-workers in 1997.[98] After the first racemic synthesis of **10** by Lee and co-workers in 2017,[99] the asymmetric synthesis of (+)-waihoensene (**10**) was reported by Yang's group[96] and Snyder's group[97] independently in 2020. A copper-catalyzed asymmetric conjugate reaction was the key synthetic step in each synthesis (Scheme 8).

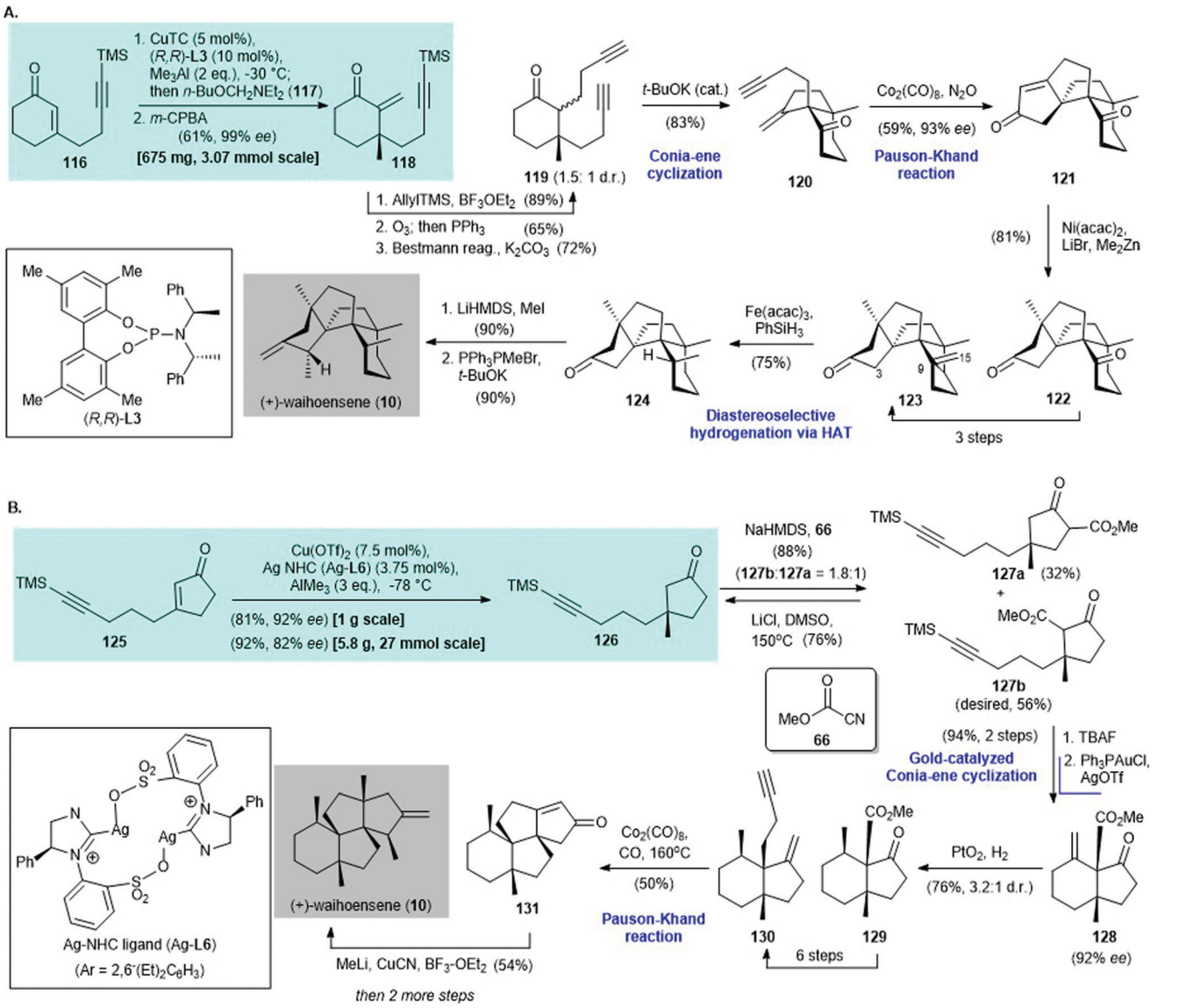
In Yang's synthesis,[96] asymmetric conjugate addition of trimethylaluminum and **116** with CuTC/(*R*,*R*)-**L3** as the cata-



Scheme 7 (A) Quaternary-center-guided synthesis of conidiogenone B (**110**), conidiogenone (**111**), and conidiogenol (**9**) (Snyder, 2019).[82] (B) Synthesis of conidiogenones C (**114**) and D (**115**) achieved in the same work *via* a similar synthetic approach.[82]

lyst,[100] followed by α-methylenation, afforded enone **118** in 61% yield with 99% ee (Scheme 8A). Conversion of enone **118** to diyne **119** was accomplished in three steps. Diyne **119** was subjected to a *t*-BuOK-catalyzed Conia-ene type cyclization[101] to give enyne **120** in 83% yield. A Pauson–Khand reaction[102] of enyne **120** mediated by $Co_2(CO)_8$ in the presence of N_2O[103] gave cyclized enone **121** in 59% yield with 93% ee. This was subjected to nickel-catalyzed methylation[104] to produce diketone **122** in 81% yield as a single diastereomer. A three-step synthesis from diketone **122** gave ketone **123**, which was subjected to diastereoselective hydrogenation through radical-mediated hydrogen-atom transfer[88] to give **124** in 75% yield. α-Methylation of **124** (product not shown, 90% yield) and then a Wittig reaction gave (+)-waihoensene (**10**) in 90% yield.

In Snyder's synthesis of (+)-waihoensene (**10**),[97] asymmetric conjugate addition of trimethylaluminum and cyclopentenone **125** *via* Hoveyda's protocol, with $Cu(OTf)_2$/Ag–NHC ligand (Ag-**L6**) as the catalyst,[47,105] afforded cyclopentanone **126** in 81% yield with 92% ee (Scheme 8B). Treatment of cyclopentanone **126** with NaHMDS and subsequent trapping of the enolate intermediate with Mander's reagent **66** afforded **127b** and **127a** in a 1.8 : 1 ratio and 88% combined yield. The authors suggested that the potential regioselectivity observed on treatment with a base (*i.e.*, NaHMDS) can be ascribed to a weak directing effect by the alkyne.[82,106] The undesired isomer **127a** was recycled to **126** by Krapcho decarboxylation.[107] Desilylation of **127b**, followed by a Conia–ene reaction in the presence of catalytic amounts of $Ph_3PAuCl/AgOTf$,[108] afforded alkene **128** in 94% yield over two steps. Catalytic hydrogenation of **128** with PtO_2 as the catalyst provided **129** in 76% yield with a 3.2 : 1 dr. Enyne **130** was obtained in six steps from **129**. A Pauson–Khand reaction of **130** at 160 °C afforded the tetracyclic enone **131**[99] in 50% yield. The authors mentioned that a high reaction temperature is critical for a successful reaction because it is likely to increase the reaction rate and overcome the energy barrier required for quaternary center formation.[96] A three-step synthesis from **131** afforded (+)-waihoensene (**10**).

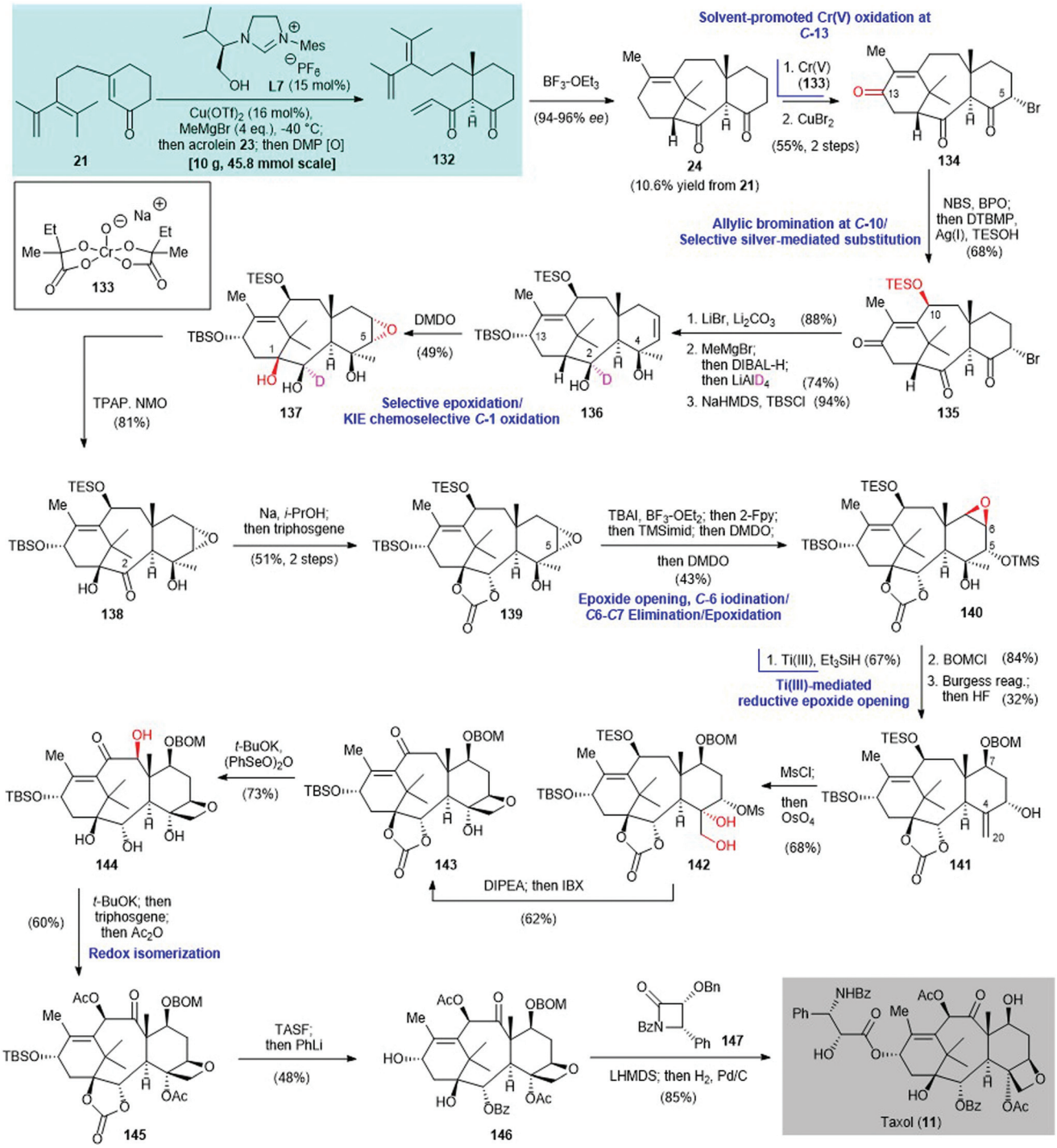


Scheme 8 Enantioselective synthesis of (+)-waihoensene (**10**) reported independently by (A) Yang (2020)[96] and (B) Snyder (2020).[97]

2.7. Taxol® (Baran 2020)[109]

The prominent biological profile of Taxol® (**11**) has made it an important synthetic target since 1994.[110–120] The concept of two-phase terpene synthesis was introduced by Baran and co-workers in 2009 [121,122] Since then, the same laboratory has focused on the total synthesis of **11** *via* the two-phase approach.[30,123,124] In 2020, Baran and co-workers achieved the total synthesis of **11** by using a two-phase approach[109] (Scheme 9). The previously achieved enantioselective synthesis of (+)-taxadienone (**1**) featured a copper-catalyzed asymmetric conjugate addition to build the 6–8–6 tricyclic core **24** with >99 : 1 dr (*see* Scheme 2A); **24** is also an intermediate in Baran's Taxol® synthesis. In a new version of the method for preparing tricycle **24**, a copper-catalyzed asymmetric conjugate addition of MeMgBr as the alkylating agent to enone **21** was effected by the chiral NHC ligand **L7**.[125] Enolate trapping with acrolein **23** gave triene **132** after oxidation with Dess–Martin periodinane. An intramolecular Diels–Alder reaction of triene **132**, mediated by BF_3–OEt_2, gave the desired tricycle **24** in 10.6% yield from enone **21**. The complex framework **24** is regarded as the end-product of the cyclase phase.

With the cyclase phase end-product **24** in hand, strategic oxidation of the cyclic framework completed the terpene (in this case Taxol®) synthesis. This is called the oxidase phase. Selective allylic oxidation at the C-13 position was achieved by using the Cr(v)-based oxidant **133** [124,126] and HFIP : TMSOH (2 : 1) as the solvent. Selective bromination with $CuBr_2$ at the C-5 position gave triketone **134** in 55% yield over two steps. Allylic bromination of **134** with NBS/BPO at the C-10 position gave a C-5/C-10 dibromide (not shown). Subsequent radical-based oxidation[124] mediated by Ag(I) selectively replaced the

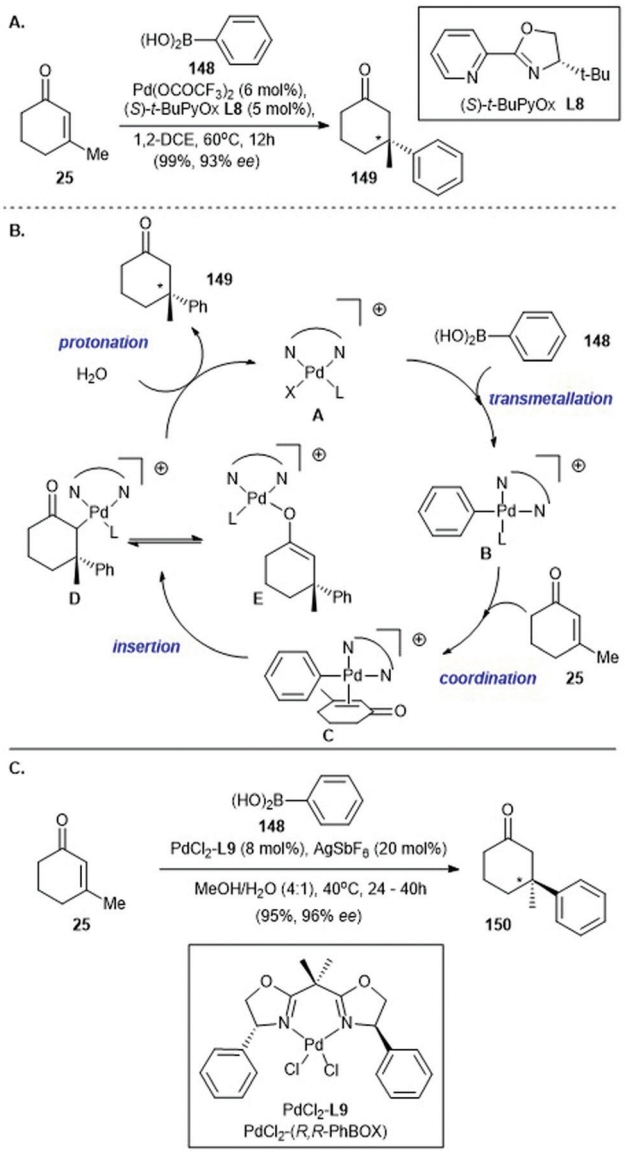


Scheme 9 Synthesis of Taxol® (**11**) *via* a two-phase synthetic approach (Baran, 2020).[109] (Newly introduced oxygen atom(s) in the synthetic step is/are highlighted in red).

C-10 bromide by TESOH to give **135** in 68% yield. Deuterated **136** was obtained in three steps from triketone **135**; these steps were elimination of the C-5 bromide using LiBr, 1,2-addition to the C-4 ketone using MeMgBr, selective reduction of the C-13 ketone with DIBAL-H, reduction of the C-2 ketone with $LiAlD_4$, and selective silylation of the C-13 hydroxy group with TBSCl to give **136.** Chemo- and stereo-selective oxidation of the deuterated alcohol **136** with DMDO afforded the epoxy-triol **137** in 49% yield.[127] It was subjected to TPAP-mediated[128] oxidation to give ketone **138** in 81% yield. The C-11–C-12 olefin in **136** is shielded by the C-10 and C-13 substituents, and is therefore protected from DMDO oxidation.[129,130] The deuterium

atom at the C-2 position of **136** promotes chemoselective oxidation at C-1 *via* the kinetic isotopic effect[131] and simultaneously acts as a blocking group[132] to prevent oxidation of the C-2 hydroxy group to the corresponding ketone.

Thermodynamic reduction of the C-2 carbonyl group of **138** by Na/i-PrOH and then exposure to triphosgene produced carbonate **139** in 51% yield. This was subjected to a sequence of reactions: (i) selective epoxide opening of **139** with BF_3–OEt_2 and iodination at the C-6 position, followed by addition of 2-fluoropyridine (2-Fpy) to sequester the boron salt, gave an iodide (not shown), (ii) immediate protection of the C-5 hydroxy group from epoxide opening with TMS-imidazole and oxidation of the C-6 iodide by DMDO, which led to elimination and generated a silylated alcohol with a C=C double bond at the C-6 and C-7 positions (not shown) and (iii) further oxidation by DMDO to generate epoxytaxane **140** in 43% overall yield. The regioselective reductive opening of **140** was sterically guided by Ti(III)[133] in the presence of Et_3SiH to give an alcohol (not shown, 67% yield), which was protected by BOMCl (not shown, 84% yield); subsequent Burgess dehydration produced **141** in 32% yield. Mesylation of **141** and then dihydroxylation with OsO_4 gave **142** in 68% yield. This was treated with a hindered amine base (*i.e.*, diisopropylethylamine) to give an oxetane and subsequent exposure to IBX produced enone **143** in 62% yield. α-Hydroxylation of enone **143** with *t*-BuOK/$(PhSeO)_2O$ gave **144** in 73% yield, with unintended cleavage of the cyclic carbonate. Redox isomerization of **144** by treatment with *t*-BuOK and acylation with Ac_2O regenerated the cyclic carbonate and acetylated C-4/C-10 simultaneously to produce taxane **145** in 60% yield. Desilylation of **145**, followed by treatment with PhLi, gave BOM-group-bearing baccatin III **146** in 48% yield.[115] Subsequent Ojima acylation[134] with β-lactam **147** in the presence of the lithium alkoxide of **146**, followed by catalytic hydrogenation, produced Taxol® (**11**) in 85% yield.

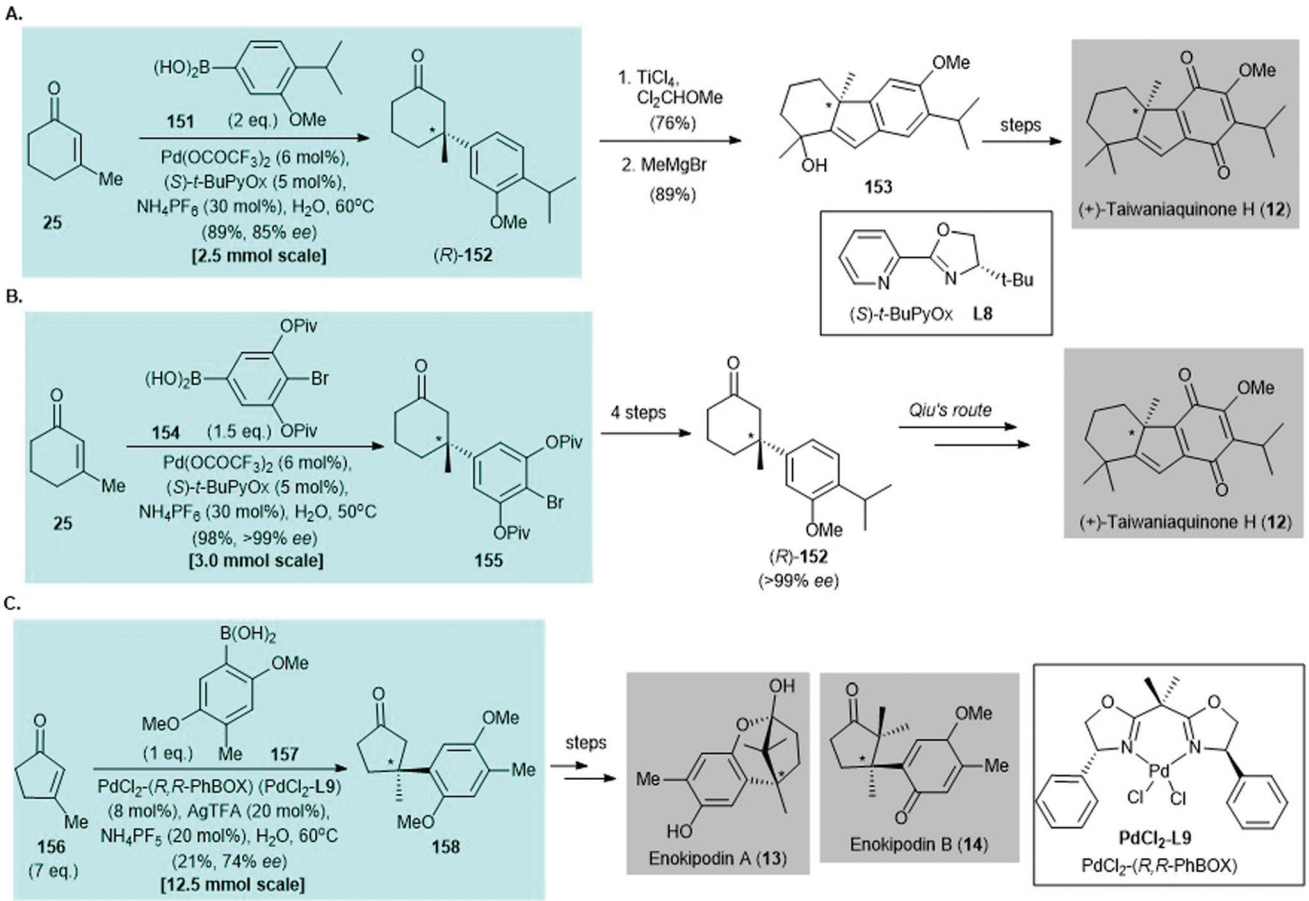


Scheme 10 (A) Palladium-catalyzed asymmetric conjugate addition of arylboronic acid **148** to β-substituted cyclic enone **25** (Stoltz, 2011).[135] (B) Proposed catalytic cycle reported by the same group in 2013.[138] (C) Palladium catalyzed asymmetric conjugate addition of arylboronic acid **148** to β-substituted cyclic enone **25**, effected by the $PdCl_2$(*R*,*R*-PhBox) ($PdCl_2$**L9**) catalyst (Minnaard, 2012).[136]

3. Construction of all-carbon quaternary stereocenters by palladium-catalyzed asymmetric conjugate addition

Palladium-catalyzed asymmetric conjugate addition of arylboronic acids to β-substituted cyclic enones was reported by Stoltz's group[135] and Minnaard's group[136] in 2011 and 2012, respectively, shortly after Lu's report of a racemic version in 2010 [137] (Scheme 10). In Stoltz's work, asymmetric conjugate addition of phenylboronic acid (**148**) to 3-methylcyclohex-2-enone (**25**), with catalytic amounts of $Pd(OCOCF_3)_2$ and (*S*)-*t*-BuPyOx (**L8**) as the chiral ligand, afforded cyclohexanone **149** in 99% yield with 93% ee[135] (Scheme 10A). Later in 2013, the same group suggested a possible mechanism for this elegant method[138] (Scheme 10B). The catalytic cycle begins with transmetalation of **148** with the cationic palladium catalyst **A** to give the cationic arylpalladium intermediate **B**. Coordination of enone **25** to arylpalladium intermediate **B** produces a cationic π-complex **C**, which undergoes rate- and enantioselectivity-determining insertion of the aryl moiety into the enone π-system to give carbon-bound palladium enolate **D**, which either tautomerizes to the corresponding oxygen-bound palladium enolate **E** or undergoes protonation to give the enantioenriched conjugate addition product **149**. Regeneration of the cationic palladium catalyst **A** completes the catalytic cycle.

In 2012, Minnaard and co-workers disclosed the palladium-catalyzed asymmetric conjugate addition of an arylboronic acid to a β-substituted cyclic enone by using a $PdCl_2$(*R*,*R*-



Scheme 11 Selected examples of construction of all-carbon quaternary stereocenters by palladium-catalyzed asymmetric conjugate addition of arylboronic acid to enone in natural product syntheses reported before 2016. (A) Synthesis of (+)-taiwaniaquinone H (**12**) (Qin, 2014).[139] (B) Another synthesis of (+)-taiwaniaquinone H (**12**) (Stoltz, 2014).[140] (C) Formal syntheses of enokipodin A (**13**) and enokipodin B (**14**) (Minnaard, 2014).[143]

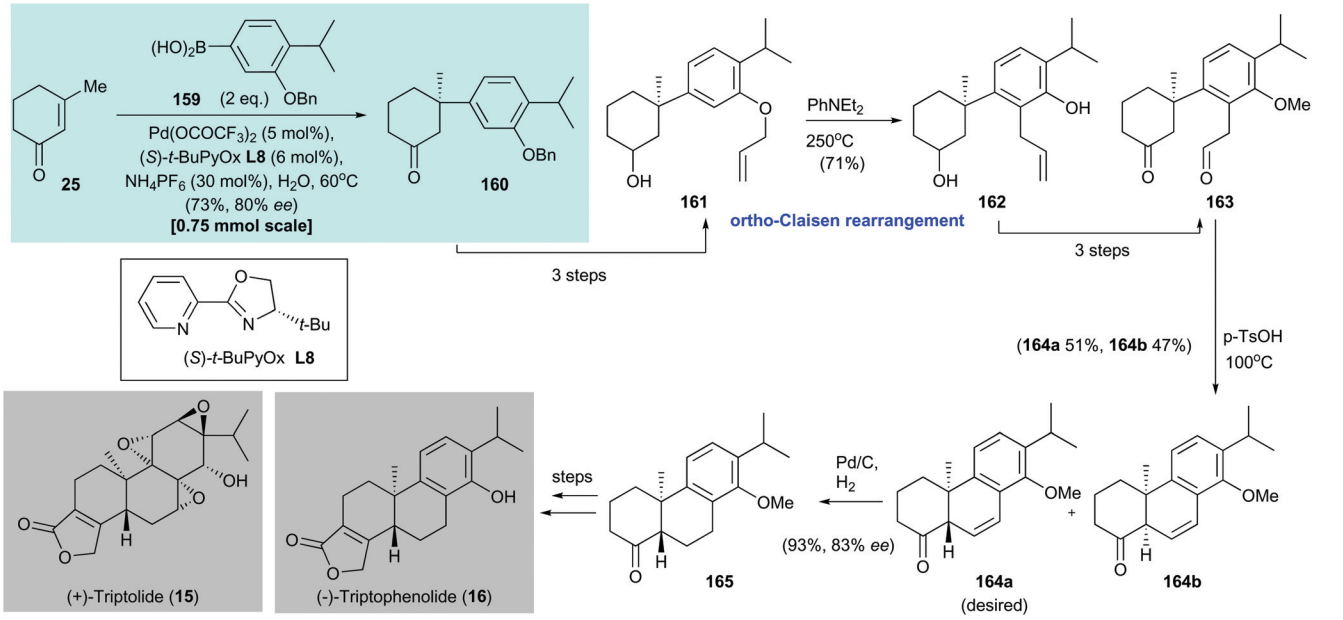
PhBox) ($PdCl_2$**L9**) catalyst and 20 mol% $AgSbF_6$ as an additive[136] (Scheme 10C). Under the optimized conditions, asymmetric conjugate addition of phenylboronic acid (**148**) to 3-methylcyclohex-2-enone (**25**) gave the conjugate addition adduct **150** in 95% yield with 96% ee. These elegant methods reported by Stoltz[135] and Minnaard,[136] which enable the efficient construction of β-aryl-substituted all-carbon quaternary stereocenters, have been used in natural product synthesis.

Synthesis of (+)-taiwaniaquinone H (**12**) was accomplished by Qin[139] and Stoltz[140] independently in 2014 (Scheme 11A and B). The palladium-catalyzed asymmetric conjugate addition of arylboronic acids to enones, which was developed by Stoltz and co-workers in 2011,[135] features as the key reaction in both syntheses. In Qin's work,[139] catalytic asymmetric conjugate addition of arylboronic acid **151** to enone **25** afforded the enantioenriched conjugate adduct (*R*)-**152** in 89% yield with 85% ee. The synthesis of (+)-taiwaniaquinone H (**12**) was completed by using a reported procedure.[141,142] In Stoltz's synthesis,[140] palladium-catalyzed asymmetric conjugate addition of arylboronic acid **154** to enone **25** gave aryl bromide **155** in 98% yield with >99% ee; **155** was converted to Qin's intermediate (*R*)-**152** in four steps.[139] The synthesis of (+)-taiwaniaquinone H (**12**) was achieved by using a reported protocol.[139] The preparation of (+)-dichroanone (not shown) was also accomplished in studies by Qin[139] and Stoltz[140] but is not described here.

In 2014, Minnaard and co-workers reported the enantioselective synthesis of enokipodin A (**13**) and enokipodin B (**14**) *via* asymmetric conjugate addition of arylboronic acid **148** to 3-methyl-2-pentenone (**156**) with $PdCl_2$(*R*,*R*-PhBOX) ($PdCl_2$**L9**) as the catalyst.[143] The enantioenriched conjugate **158** was obtained in 21% yield with 74% ee[143] (Scheme 11C). The synthesis of herbertenediol (not shown) was also disclosed in the same work but is not discussed here.

3.1. (+)-Triptolide and (−)-triptophenolide (Qin 2016)[144]

Triptolide (**15**) is a potent antitumor and immunosuppressive agent. It was isolated by Kupchan and co-workers from the Chinese medicinal plant *Tripterygium wilfordii* Hook F in 1972.[145] In 2016, Qin and co-workers disclosed the formal syntheses of (+)-triptolide (**15**) and (−)-triptophenolide (**16**)[144] (Scheme 12). The enantioenriched conjugate adduct **160** was prepared by asymmetric conjugate addition of arylboronic acid **159** to enone **25** by using Stoltz's protocol;[135] **160** was isolated



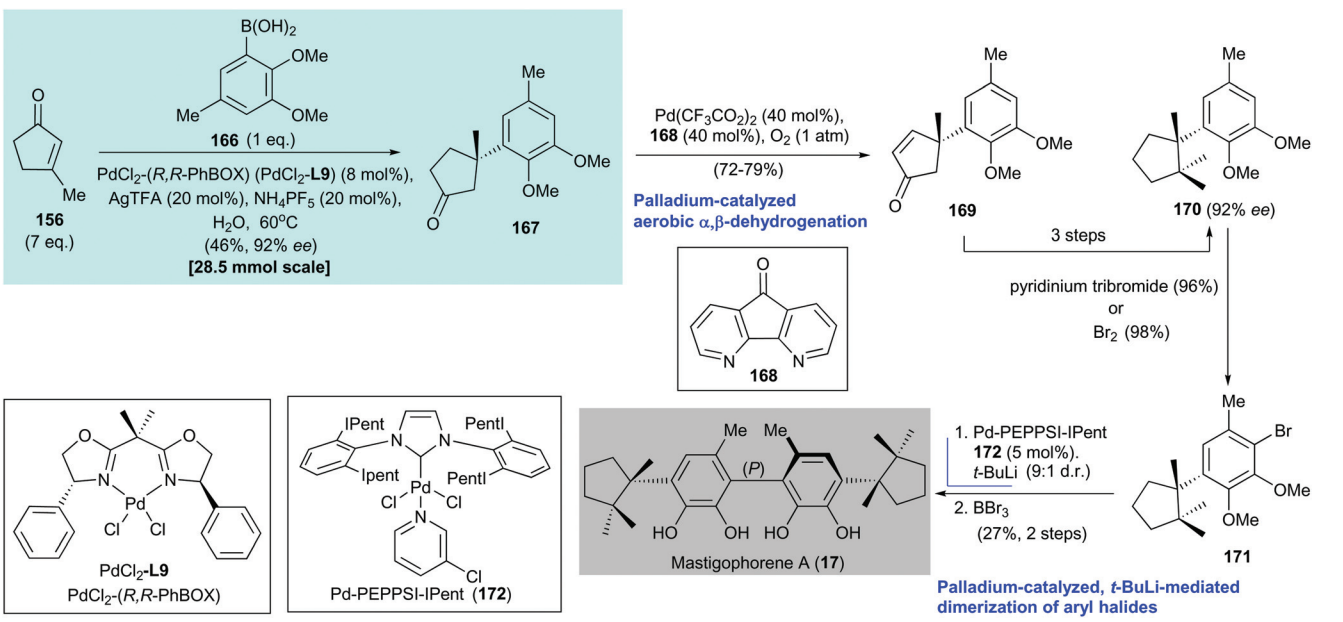
Scheme 12 Formal syntheses of (+)-triptolide (**15**) and (–)-triptophenolide (**16**) (Qin, 2016).[144]

in 73% yield with 80% ee. Allyl ether **161**, which was synthesized in three steps from conjugate addition adduct **160**, underwent an *ortho*-Claisen rearrangement on heating to afford phenol **162** in 71% yield. Conversion of freshly prepared phenol **162** to aldehyde **163** was accomplished in three steps. An acid-catalyzed intramolecular aldol condensation of **163** produced a mixture of **164a** (51% yield) and **164b** (47% yield). Catalytic hydrogenation of the major isomer **164a** gave **165** in 93% yield with 83% ee. This is the precursor for synthesizing (+)-triptolide (**15**) and (–)-triptophenolide (**16**).[146]

3.2. Mastigophorene A (Minnaard and Feringa 2016 [147])

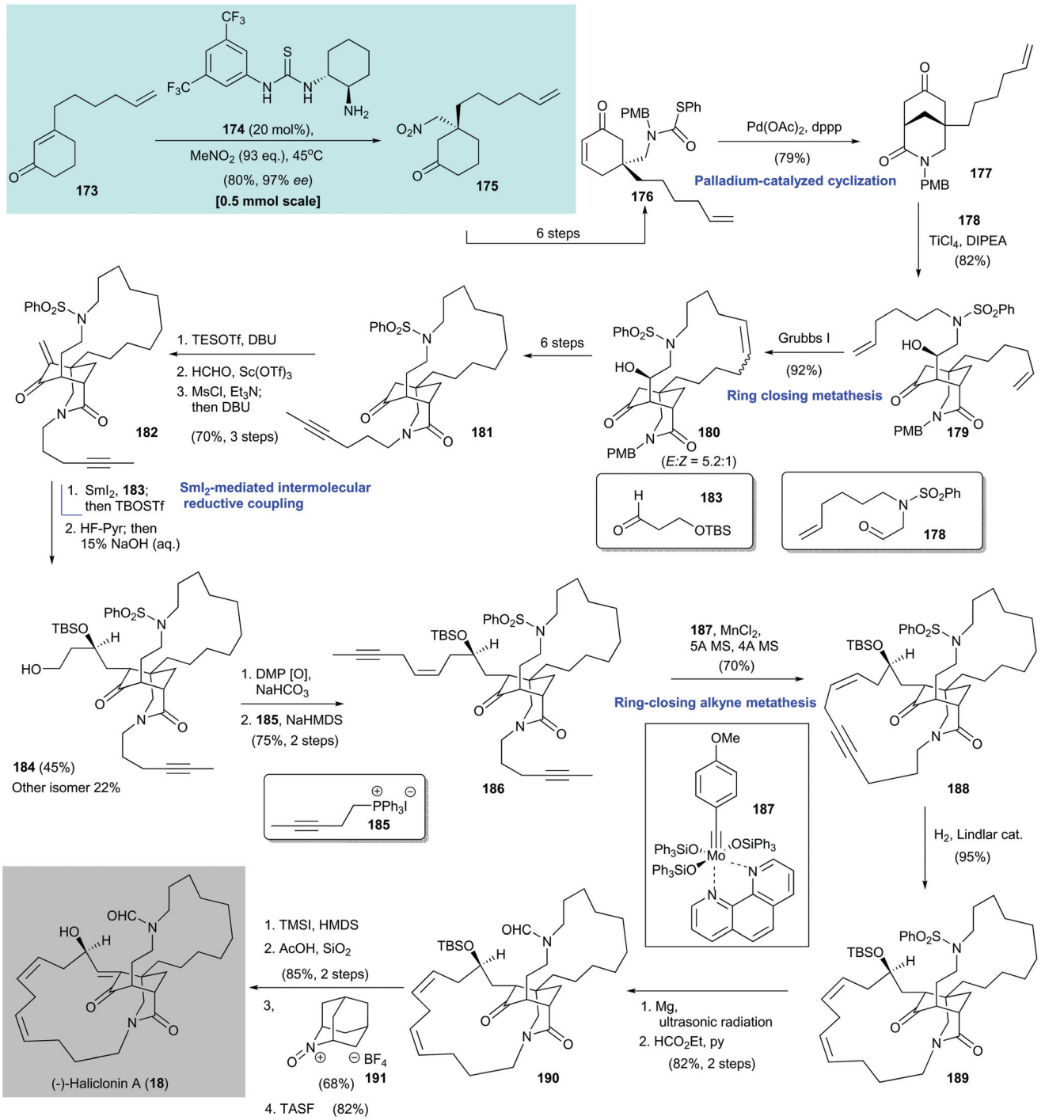
Mastigophorene A (**17**) is a dimeric sesquiterpene. It was isolated from the liverwort *Mastigophora diclados* by Asakawa and co-workers in 1988.[148] It shows neurotrophic activity at concentrations as low as 0.1–1 μM.[149,150]

In 2016, Minnaard and Feringa reported the atroposelective total synthesis of mastigophorene A (**17**) *via* palladium-catalyzed, *tert*-butyllithium-mediated dimerization of an aryl halide (Scheme 13).[147] The preparation of mastigophorene A



Scheme 13 Atroposelective total synthesis of mastigophorene A (**17**) (Minnaard and Feringa, 2016).[147]

(**17**) began with a palladium-catalyzed asymmetric conjugate addition of arylboronic acid **166** to 3-methylcyclopent-2-enone (**156**) under Minnaard's conditions[143] to afford adduct **167** in 55% yield with 92% ee. Dehydrogenation[151] of freshly prepared adduct **167** generated enone **169,** which was converted to dimethylherbertenediol (**170**) in three steps. Aryl bromide **171** was obtained by bromination of **170.** Homocoupling of the enantiomerically pure mastigophorene building block **171** was achieved with 5 mol% Pd-PEPPSI-IPent (**172**). The homocoupling involved conversion of **171** to the corresponding lithium salt *via* halogen/lithium exchange with *tert*-butyllithium (1.2 equiv.) to produce a biaryl product with a 9 : 1 dr (major *P* helicity of the biaryl axis). Subsequent treatment of the biaryl with BBr_3 afforded mastigophorene A (**17**) in 27% yield over two steps from **171.** The authors reasoned that the observed diastereoselectivity was the result of a catalyst-induced point-



Scheme 14 Organocatalytic, asymmetric total synthesis of (–)-haliclonin A (**18**) (Huang, 2016).[164]

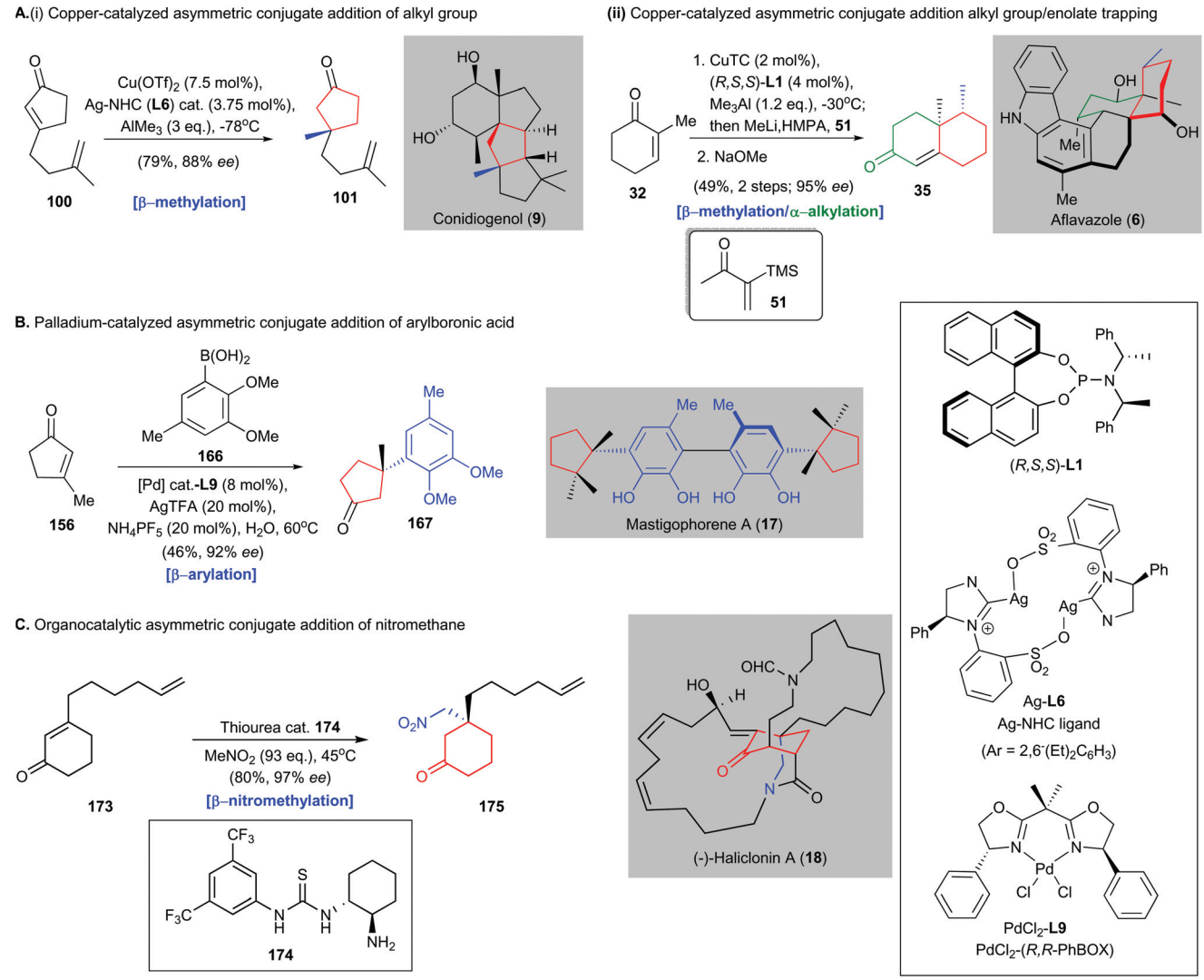
to-axial chirality transfer involving a steric interaction between the aromatic residues of the catalyst (Pd-PEPPSI-Ipent **172**) and the benzylic quaternary stereocenter at the *para* position.

4. Construction of all-carbon quaternary stereocenters by organocatalytic asymmetric conjugate addition

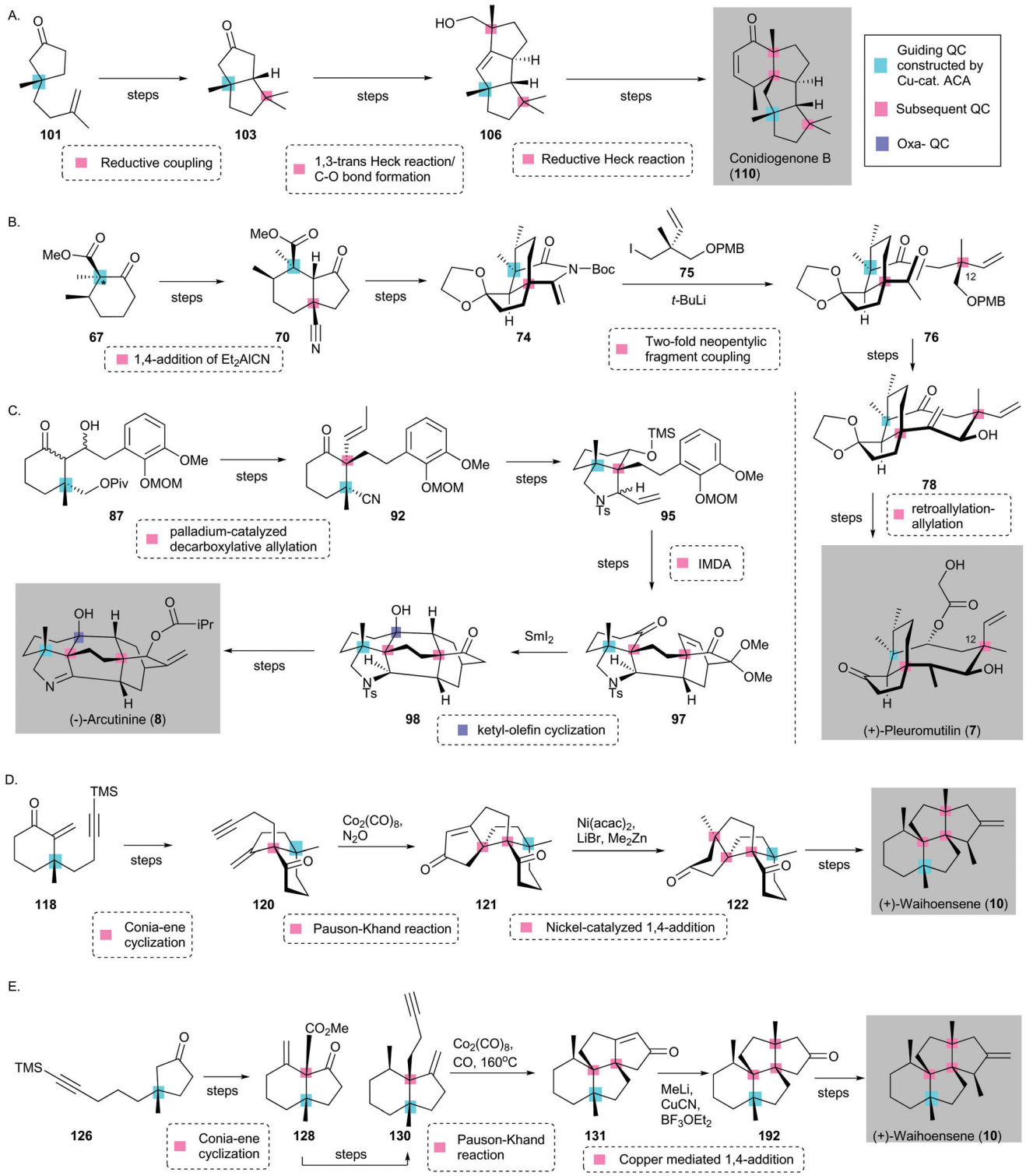
The construction of quaternary stereocenters by organocatalytic reactions has long been a research interest in organic chemistry.[10,152,153] It not only enables the construction of stereocenter(s) without the use of metal catalysts but also is useful in the synthesis of complex natural products.[154–157] However, only a few examples of all-carbon quaternary stereocenter construction *via* organocatalytic asymmetric conjugate addition in natural product synthesis have been reported.[158] In 2016, Huang and co-workers reported an elegant synthesis of (−)-haliclonin A (**18**) by using a novel organocatalytic asymmetric conjugate addition of nitromethane[159–163] to enone **173**, with the thiourea catalyst **174** (Scheme 14).[164]

4.1. (−)-Haliclonin A (Huang 2016)[164,165]

(−)-Haliclonin A (**18**) is a macrocyclic alkaloid. It was first isolated from a marine sponge *Haliclona* sp. by Shin and co-



Scheme 15 Asymmetric conjugate additions with three different catalysts, to give different transformations, which have been successfully used in complex natural product synthesis. (A) (i) Synthesis of conidiogenol (**9**) *via* copper-catalyzed asymmetric conjugate addition of the methyl group to afford intermediate **101**.[82] (ii) Tandem copper-catalyzed asymmetric conjugate addition/enolate trapping with Stork–Ganem reagent (**51**) and subsequent condensation to give functionalized enone **35** in the synthesis of aflavazole (**6**).[51] (B) Palladium-catalyzed asymmetric conjugate addition of arylboronic acid **166** to enone **156** to generate β-aryl-substituted all-carbon quaternary stereocenter on **167**, which is an intermediate in the synthesis of mastigophorene A (**17**).[147] (C) Organocatalytic asymmetric conjugate addition of nitromethane to enone **173** produces a nitro-group-containing adduct **175**, which is used in the total synthesis of (−)-haliclonin A (**18**).[164]



Scheme 16 Quaternary-center-guided synthetic analysis of natural product synthesis with multiple quaternary centers (QCs) using selected examples in this review. (Guiding QC is highlighted in cyan; subsequent QC is highlighted in pink, and Oxa-QC is highlighted in lilac.) (A) Synthesis of conidiogenone B (**110**) reported by Snyder [*three subsequent QCs*]. (B) Synthesis of (+)-pleuromutilin (**7**) reported by Herzon[59] [*two subsequent QCs*]. (*Guiding QC is synthesized through enolate trapping and α-methylation after asymmetric conjugate addition.) (C) Synthesis of (–)-arcutinine (**8**) reported by Qin[75] [*two subsequent QCs and one oxa-QC*]. Syntheses of (–)-waihoensene (**10**) reported by (D) Yang[96] and (E) Snyder[97] [*three subsequent QCs*]. Cu ACA = copper-catalyzed asymmetric conjugate addition.

workers in 2009.[166] It shows moderate antibacterial activity and cytotoxicity against the K562 leukemia cell line. An asymmetric total synthesis of **18** was reported by Huang and co-workers in 2016.[164] They used an organocatalytic asymmetric conjugate addition of nitromethane to enone **173** to configure the stereochemistry of the all-carbon quaternary stereocenter (Scheme 14).[164,165] The synthesis began with asymmetric conjugate addition of nitromethane to enone **173**, with chiral thiourea **174** as the catalyst, to give adduct **175** in 80% yield with 97% ee. Enone **176**, which was formed in six steps from the enantioenriched adduct **175**, was subjected to palladium-promoted cyclization[167] to form the 3-azabicyclo[3,3,1]nonane core **177** in 79% yield. A $TiCl_4$/Hünig base-mediated aldol reaction[168] of **177** with aldehyde **178**[167] produced **179** in 82% yield; **179** underwent ring-closing metathesis with Grubbs I catalyst[169] to give **180** as a geometric mixture in 92% yield.

A six-step synthesis from **180** gave alkyne **181**, which was subjected to α-methylenation *via* a sequence of reactions, namely silyl enol ether formation with TESOTf/DBU, α-hydroxymethylation with formalin/$Sc(OTf)_3$,[170] and mesylation/elimination by DBU. Enone **182** was obtained in 70% yield over three steps. Intermolecular reductive coupling of freshly prepared **182** with aldehyde **183** was facilitated by samarium diiodide[171] and the resultant alcohol was subjected to silylation with TBSOTf. Selective desilylation of the primary silyl ether gave the desired diastereomer **184** in 45% yield and the undesired isomer (not shown) in 22% yield. Oxidation of newly formed **184** with Dess–Martin periodinane and a subsequent Wittig reaction with **185**[172] afforded enediyne **186** in 75% yield over two steps. Ring-closing alkyne metathesis[173,174] of enediyne **186** with Fürstner's catalyst **187**[175] gave the cyclization product **188** in 70% yield. Controlled hydrogenation of **188** by using Lindler's catalyst gave the tetracyclic diene (13*Z*,16*Z*)-**189** in 95% yield. Desulfonylation of **189** with magnesium in methanol under ultrasonic irradiation[176] and immediate formylation of the liberated amine with ethyl formate/pyridine afforded **190** in 82% yield over two steps. Treatment of freshly prepared ketone **190** with TMSI–HMDS[177] gave the corresponding silyl enol ether, which was subjected to desilylation with AcOH/silica gel to give an enol (not shown, 85% yield over two steps). The enol could have been formed *via* intramolecular hydrogen-bond formation with the lactam.[178] Oxidation of the resultant enol to the corresponding enone was achieved by using an oxoammonium salt ($AZADO^+BF_4^-$, **191**).[179,180] Subsequent cleavage of the TBS group by using tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF)[181] furnished (−)-haliclonin A (**18**) in 82% yield.

5. Summary and outlook

All-carbon quaternary stereocenter construction poses a distinct challenge in modern synthetic organic chemistry. The overall efficiency of a natural product synthesis is frequently governed by the methods used to install the all-carbon quaternary stereocenters.[13] This issue is not trivial because few effective methods are available for achieving inversion of undesired configurations of all-carbon quaternary stereocenters to the desired ones. In this review, the use of catalytic asymmetric conjugate additions in natural product synthesis was discussed. Such reactions can be used to build all-carbon quaternary stereocenters with high enantioselectivities, and possibly on a preparative scale (*i.e.*, decagram scale). Only catalytic amounts of a catalyst and a chiral ligand are necessary, which makes this an attractive synthetic method.

In this review, we have summarized many recent developments (2016–2020) in the use of catalytic asymmetric conjugate addition in natural product synthesis. The role of this class of reactions in the synthesis of structurally elusive natural products has been highlighted. Asymmetric conjugate additions with different catalysts, *i.e.*, copper catalysts, palladium catalysts, and organocatalysts, give different transformations, which have been successfully used in complex natural product synthesis (Scheme 15). Examples are copper-catalyzed asymmetric conjugate addition of alkyl groups (*e.g.*, Snyder's synthesis of conidiogenol **9**), tandem copper-catalyzed asymmetric conjugate addition/enolate trapping (*e.g.*, Li's synthesis of aflavazole **6**), palladium-catalyzed asymmetric conjugate addition of arylboronic acids (*e.g.*, Minnaard and Feringa's synthesis of mastigophorene A **17**), and organocatalytic asymmetric conjugate addition of nitromethane [*e.g.*, Huang's synthesis of (−)-haliclonin A **18**]. These transformations can work complementarily and expand the range of synthetic methods available for constructing all-carbon quaternary stereocenters with diverse functionalities. Recently, Snyder and co-workers completed their enantioselective synthesis of conidiogenones and postulated the concept of quaternary-center-guided synthetic analysis in the synthesis of natural products containing multiple quaternary stereocenters[82] (Scheme 16). We attempted to apply this logic to show how a quaternary center forged by catalytic asymmetric conjugate addition could guide successive assembly of subsequent quaternary centers and enable enantioselective synthesis of complex natural products, particularly those bearing congested arrays of stereocenters, including all-carbon quaternary stereocenter(s).

Asymmetric conjugate addition catalyzed by a transition metal such as copper or palladium requires the use of a chiral ligand such as a phosphine ligand [*e.g.*, (*S*,*R*,*R*)-**L1**], a silver–chiral NHC complex (*e.g.*, Ag-**L5**), or a chiral NHC ligand (*e.g.*, **L4**) to achieve stereocontrol. The synthesis of (−)-haliclonin A (**18**) reported by Huang[164] shows that construction of an all-carbon quaternary stereocenter can be achieved by using chiral thiourea **174**, which acts as an organocatalyst and can be easily prepared by using an economical and optically pure 1,2-diamine as the starting material.[182] This provides an excellent example of how the structure of the chiral thiourea catalyst **174** can be conveniently varied by altering the source of the 1,2-diamine. We predict that further investigation of readily available chiral ligands in transition-metal catalysts and/or novel organocatalysts will promote the development of this method and broaden the range of synthetic applications of asymmetric

conjugate additions. Palladium-catalyzed asymmetric conjugate additions of β-aryl groups, which make use of various commercially available, air- and/or moisture-stable arylboronic acids bearing a wide range of functionalities such as halo and nitro groups, undoubtedly provide a convenient and useful approach to the construction of enantioenriched β-aryl ketones[135–138,143] (see Schemes 10 and 11). Unlike palladium-catalyzed asymmetric conjugate additions of boronic acids, the copper-catalyzed counterparts usually require air- and/or moisture-sensitive organometallic nucleophiles generated from arylmagnesium,[125,183] arylaluminum,[47,184,185] and arylzinc reagents,[105,186,187] which are incompatible with many reactive functional groups because of their reactivity with the nucleophiles used. Recently, Zhou achieved asymmetric conjugate addition of organoboron reagents to acyclic enones by combining cost-effective copper catalysts and air-stable organoboron reagents.[188] However, the use of cyclic enones as substrates is yet to be reported. Finally, we anticipate that enantioenriched scaffolds containing all-carbon quaternary stereocenters constructed by catalytic asymmetric conjugate addition and from chiral pools[189] will cooperatively provide a wide range of enantioenriched substances. This will improve the synthetic efficiency to meet the demands of academia, materials science, and the pharmaceutical industry.

Conflicts of interest

There are no conflicts to declare.

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