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

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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  $\alpha,\beta$ -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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## 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 cyclization, 14,15 polyene 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  $\alpha$ - 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

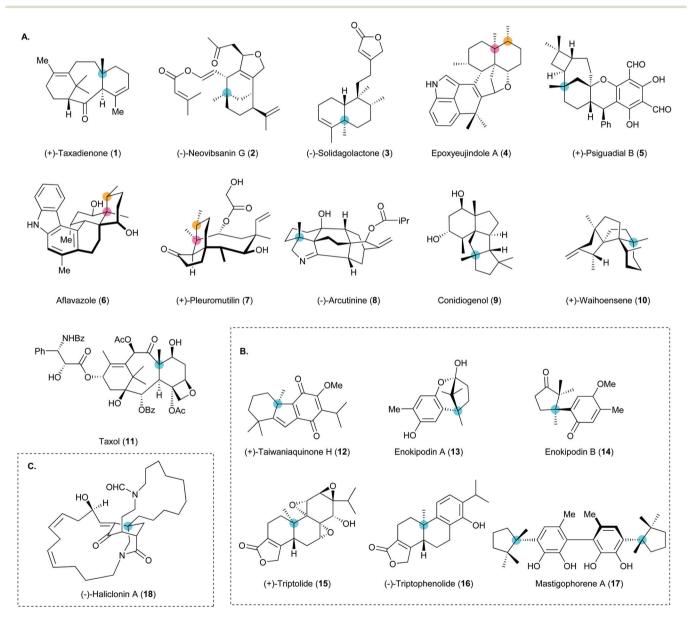


Fig. 1 Some natural product syntheses that make use of catalytic asymmetric conjugate addition (CACA) to create all-carbon quaternary stereocenters. (A) Quaternary carbon(s) created directly by copper-catalyzed asymmetric conjugate addition or indirectly by subsequent enolate trapping by carbon electrophile. (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.

## Construction of all-carbon quaternary stereocenters by coppercatalyzed asymmetric conjugate addition

The pioneering discovery of copper-catalyzed asymmetric conjugate addition was made independently by Feringa<sup>27</sup> 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

B. Alexakis 2002

C. Proposed mechanism by Feringa

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

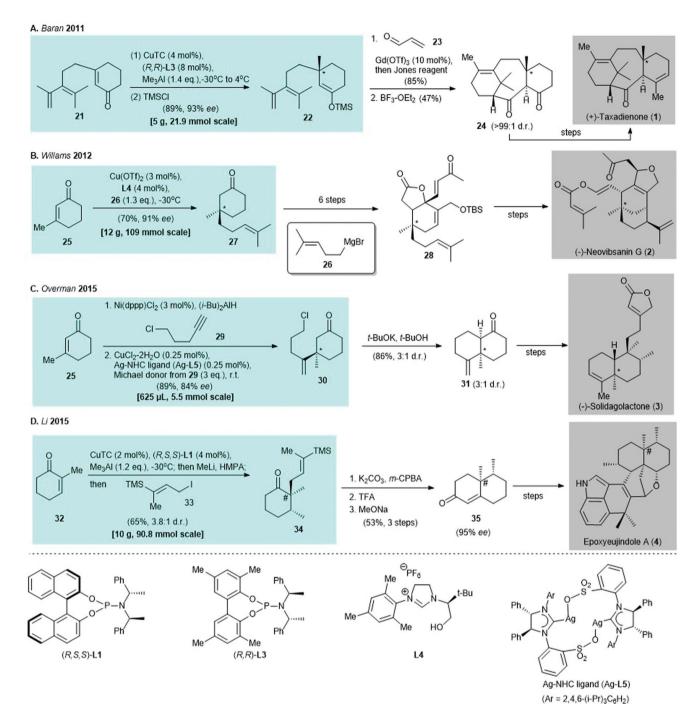
introduced by using a chiral phosphoramidite ligand [e.g., (S, R,R-L1 and (R,R)-L2]. The copper-catalyzed asymmetric conjugate addition of cyclohexenone (19) with diethylzinc produced the enantioenriched ketone 20 with a high ee value of 98% to 99.1% (Scheme 1A and B). Feringa and co-workers<sup>29</sup> proposed that the catalytic mechanism involves alkyl transfer from dialkylzinc (i.e., R<sub>2</sub>Zn) to a copper(1)-phosphoramidite complex, which generates a copper(1)-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., L2CuR) to the enone olefin of 19 results in the formation of  $\pi$ -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  $\pi$ -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.

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<sup>30</sup> (Scheme 2A). In 2012, Williams and co-workers synthesized (-)-neovibsanin G (4) by using a Cu(OTf)<sub>2</sub>-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<sup>31</sup> (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<sup>34</sup> of enone 25 under the effect of a Ag-NHC complex (Ag-L5)35 to give adduct 30 in 89% yield with 84% ee<sup>36</sup> (Scheme 2C). In the same year, epoxyeujindole A (6) was synthesized by Li and co-workers by asymmetric conjugate addition under the Alexakis protocol,<sup>37</sup> followed by enolate trapping with iodide 33 to give cyclohexanone 34 in 65% yield with a 3.8:1 dr<sup>38</sup> (Scheme 2D).

## 2.1. (+)-Psiguadial B (Reisman 2016)<sup>39</sup>

(+)-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).<sup>40</sup> In 2016, Reisman and co-workers reported the first enantioselective synthesis of 5 (Scheme 3)<sup>39</sup> 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]<sup>41</sup> 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. [Allcarbon 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 (TMSCI) 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<sup>35</sup>/asymmetric copper-catalyzed conjugate addition produces 30 in the presence of Aq-NHC complex (Aq-L5)<sup>47</sup> as a catalyst in synthesis of (–)-solidagolactone (3). $^{36}$  (D) Tandem asymmetric conjugate addition/ $\alpha$ -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 catalystpromoted 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).<sup>39</sup> Bottom section: preparation of cyclohexanone fragment (+)-36.

Palladium-catalyzed directed C(sp³)-H alkenylation

treated with DDQ/ethoxyethanol<sup>43</sup> 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<sup>46</sup> to give (+)-psiguadial B (5) in 50% yield.

(62%, 79% ee)

Tandem Wolff rearrangement/

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.

1. Cp<sub>2</sub>Zr(H)Cl

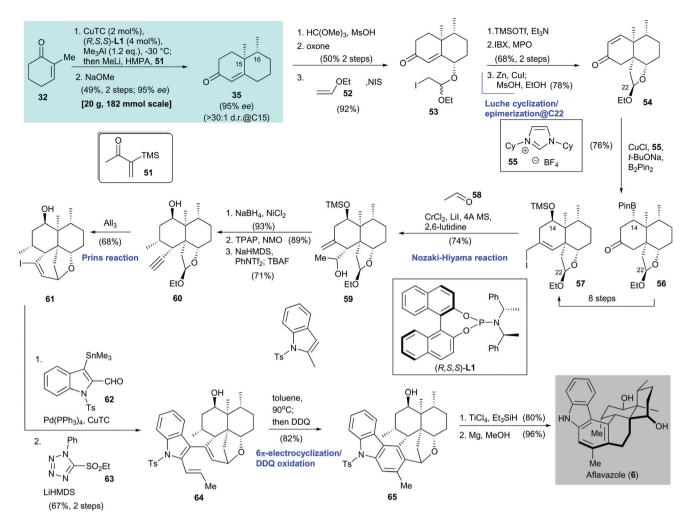
2. KOH (70%, 2 steps)

3. H2C=PPh3; then 5M HCl

(88%)

## 2.2. Aflavazole (Li 2016)<sup>51</sup>

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). Asymmetric conjugate addition of 2-methylcyclohexenone (32), catalyzed by CuTC/(R,S,S)-L1, 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  $\alpha$ -silyl ketone (not shown). Exposure of the freshly prepared α-silvl 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<sup>54</sup> 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<sup>55,56</sup> 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<sup>57</sup> and desilylation, gave alkyne **60** in 71% yield. Treatment of 60 with AlI<sub>3</sub> 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  $6\pi$ -electrocyclization, and subsequent DDQ oxidation<sup>58</sup> 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)<sup>59</sup>

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

(81%)

Scheme 5 Enantioselective synthesis of (+)-pleuromutilin (7) (Herzon, 2017).<sup>59</sup>

Herzon's synthesis of (+)-pleuromutilin (7) began with asymmetric copper-catalyzed conjugate addition of dimethylzinc and cyclohexenone (19). Acylation at the  $\alpha\text{-position}$  with Mander's reagent  $66^{\,67}$  and subsequent diastereomeric  $\alpha\text{-methylation}^{68}$  produced 67 in 71% yield with >20:1 dr and 97:3 er. Exposure of the freshly prepared β-ketoester 67 to KHMDS/PhNTf2 afforded the corresponding enol triflate (not shown, 88% yield), which was subjected to palladium-catalyzed carbonylative coupling<sup>69</sup> (product not shown, 83% yield). Subsequent Cu(OTf)<sub>2</sub>-catalyzed Nazarov cyclization<sup>70</sup> gave cyclopentenone 68 in 88% yield. Conjugate addition of

Et<sub>2</sub>AlCN<sup>71</sup> 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 Boc2O 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

(+)-12-epi-pleuromutillin

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,<sup>73</sup> 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<sup>2</sup>-carbons at C-10 and C-14 in the cyclization product 78 can relieve transannular nonbonding interactions in the eightmembered 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 (+)-12epi-pleuromutilin (83) in 56% yield.

## 2.4. (-)-Arcutinine (Qin 2019)<sup>75</sup>

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.<sup>77</sup> Shortly after the first enantioselective synthesis of (-)-arcutinine (8), which was reported by Qin and co-workers<sup>75</sup> in 2019, Li and co-workers reported their asymmetric synthesis of 8.78 The enantioselective synthesis of 8 reported by Qin is as follows<sup>75</sup> (Scheme 6). Asymmetric conjugate addition of enone 84 79 with AlMe3 was effected with CuTC/(S,S)-L3 as the catalyst.<sup>37</sup> 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

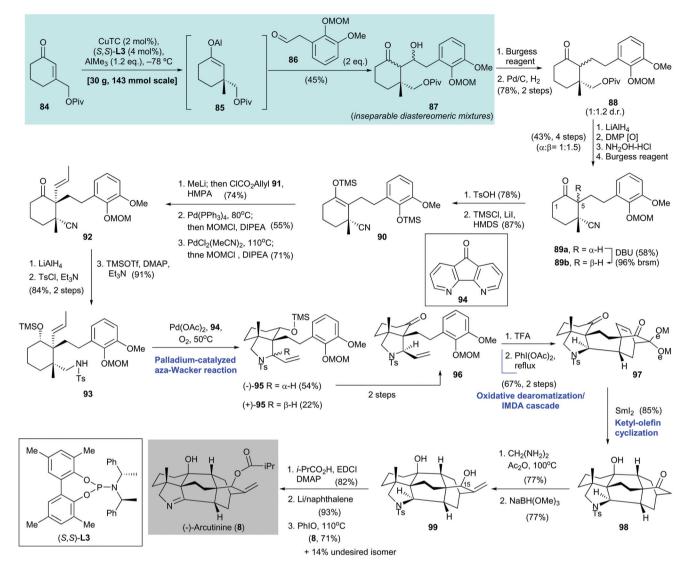
with the phenol moiety as the silvlated form. Epimerization of 89a to 89b was accomplished by treatment with DBU.

Treatment of 90 with methyllithium and ClCO2allyl (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 protocol81 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. Ketylolefin 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.

## 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 methicillin-resistant Staphylococcus against 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-centerguided synthesis of complex polycyclic terpenes<sup>82</sup> (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)<sub>2</sub>/Ag-NHC (Ag-L6) catalyst]<sup>87</sup> to give cyclopentane 101 in 79% yield with 88% ee<sup>82</sup> (Scheme 7). Conversion of freshly prepared 101 to 102 was accomplished in two steps; 102 was then subjected to Baran's reductive coupling88 to give 103 in 80% yield as a single diastereomer. Corey hydrazine-mediated alkylation<sup>89</sup> 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).<sup>75</sup>

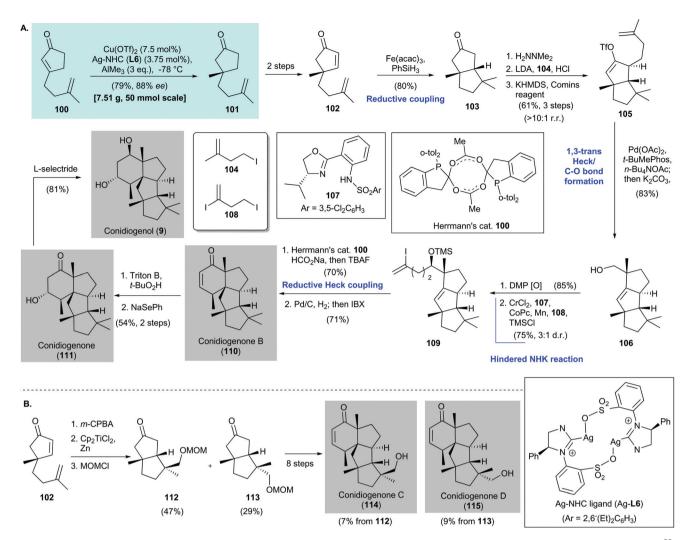
ponding vinyl triflate 105 by using KHMDS/Comins' reagent. The yield was 61% over three steps and the rr was >10:1. Cyclization of vinyl triflate 105 was achieved with a palladium catalyst (i.e., Pd(OAc)2/t-BuMePhos) in the presence of n-Bu<sub>4</sub>NOAc<sup>90</sup> as an oxygen source to give a tricyclic 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<sup>93</sup> with Herrmann's catalyst<sup>94</sup> in the presence of HCO<sub>2</sub>Na 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<sub>2</sub>TiCl<sub>2</sub> 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<sup>96</sup> and Snyder's group<sup>97</sup> 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-

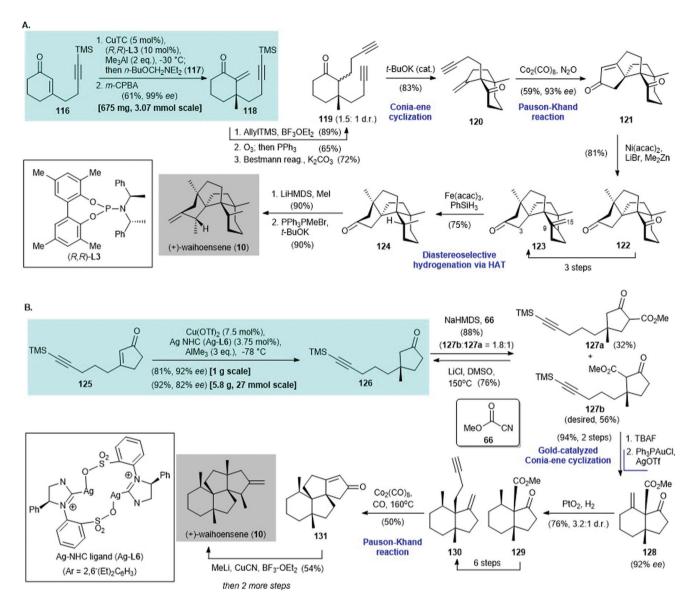


Scheme 7 (A) Quaternary-center-guided synthesis of conidiogenone B (110), conidiogenone (111), and conidiogenol (9) (Snyder, 2019). (B) Synthesis of conidiogenones C (114) and D (115) achieved in the same work via a similar synthetic approach.<sup>82</sup>

lyst,  $^{100}$  followed by  $\alpha$ -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 Co2(CO)8 in the presence of N2O103 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 radicalmediated hydrogen-atom transfer<sup>88</sup> 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 recycled to 126 by Krapcho decarboxylation. 107 Desilvlation of 127b, followed by a Conia-ene reaction in the presence of catalytic amounts of Ph<sub>3</sub>PAuCl/AgOTf, <sup>108</sup> afforded alkene 128 in 94% yield over two steps. Catalytic hydrogenation of 128 with PtO2 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.<sup>96</sup> A three-step synthesis from 131 afforded (+)-waihoensene (10).



Scheme 8 Enantioselective synthesis of (+)-waihoensene (10) reported independently by (A) Yang (2020)<sup>96</sup> and (B) Snyder (2020).<sup>97</sup>

### 2.7. Taxol® (Baran 2020)<sup>109</sup>

The prominent biological profile of Taxol® (11) has made it an important synthetic target since 1994. The concept of two-phase terpene synthesis was introduced by Baran and coworkers 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 BF3-OEt2, 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<sub>2</sub> 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 radicalbased oxidation124 mediated by Ag(I) selectively replaced the Review

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

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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<sub>4</sub>, and selective silylation of the C-13 hydroxy group with

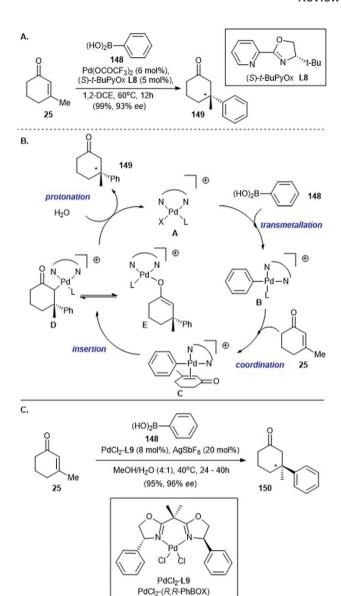
TBSCl to give **136**. Chemo- and stereo-selective oxidation of the deuterated alcohol **136** with DMDO afforded the epoxy-triol **137** in 49% yield. The Was subjected to TPAP-mediated oxidation to give ketone **138** in 81% yield. The C-11–C-12 olefin in **136** is shielded by the C-10 and C-13 substituents, and is therefore protected from DMDO oxidation. 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<sub>3</sub>-OEt<sub>2</sub> 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)<sup>133</sup> in the presence of Et<sub>3</sub>SiH 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 OsO4 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)<sub>2</sub>O 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<sub>2</sub>O 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.

# 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<sup>135</sup> and Minnaard's group<sup>136</sup> 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-2enone (25), with catalytic amounts of Pd(OCOCF<sub>3</sub>)<sub>2</sub> and (S)-t-BuPyOx (L8) as the chiral ligand, afforded cyclohexanone 149 in 99% yield with 93% ee135 (Scheme 10A). Later in 2013, the same group suggested a possible mechanism for this elegant method<sup>138</sup> (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



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  $\beta$ -substituted cyclic enone 25, effected by the PdCl<sub>2</sub>(R,R-PhBox) (PdCl<sub>2</sub>L9) catalyst (Minnaard, 2012). 136

enone 25 to arylpalladium intermediate B produces a cationic  $\pi$ -complex C, which undergoes rate- and enantioselectivitydetermining insertion of the aryl moiety into the enone  $\pi$ -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 palladiumcatalyzed asymmetric conjugate addition of an arylboronic acid to a β-substituted cyclic enone by using a PdCl<sub>2</sub>(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 (+)-taiwaniaguinone H (12) (Qin. 2014). (B) Another synthesis of (+)-taiwaniaguinone H (12) (Stoltz, 2014). 140 (C) Formal syntheses of enokipodin A (13) and enokipodin B (14) (Minnaard, 2014). 143

PhBox) (PdCl<sub>2</sub>L9) catalyst and 20 mol% AgSbF<sub>6</sub> 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<sup>135</sup> 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<sup>139</sup> and Stoltz<sup>140</sup> 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. <sup>139</sup> 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 Oin<sup>139</sup> and Stoltz<sup>140</sup> but is not described

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<sub>2</sub>(R,R-PhBOX) (PdCl<sub>2</sub>L9) as the catalyst. 143 The enantioenriched conjugate 158 was obtained in 21% yield with 74% ee143 (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)<sup>144</sup>

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)<sup>144</sup> (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

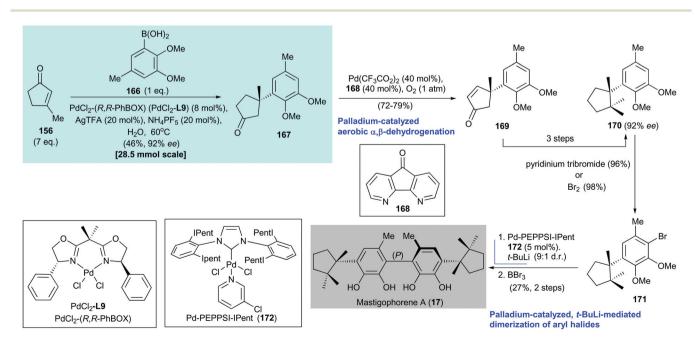
Scheme 12 Formal syntheses of (+)-triptolide (15) and (-)-triptophenolide (16) (Qin, 2016). 144

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  $\mu$ M. <sup>149,150</sup>

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 of freshly prepared adduct 167 generated enone 169, which was converted to dimethylherbertenediol (170) in three steps. Arvl 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<sub>3</sub> 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-

Organocatalytic, asymmetric total synthesis of (–)-haliclonin A (18) (Huang, 2016). 164

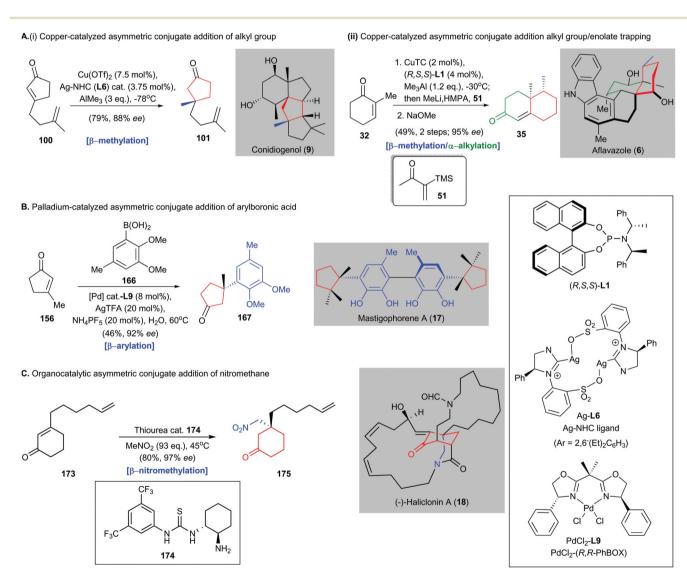
to-axial chirality transfer involving a steric interaction between the aromatic residues of the catalyst (Pd-PEPPSI-Ipent 172) and the benzylic quaternary stereocenter at the para position.

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

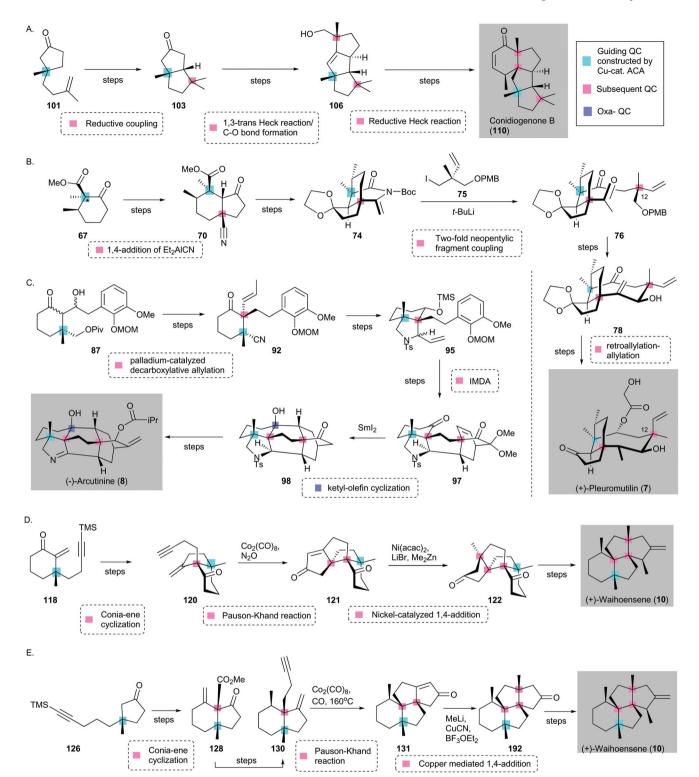
The construction of quaternary stereocenters by organocatalytic reactions has long been a research interest in organic chemistry. 10,152,153 It not only enables the construction of stereocenter(s) without the use of metal catalysts but also is useful in the synthesis of complex natural products. 154-157 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)<sup>164,165</sup>

(-)-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  $\beta$ -aryl-substituted all-carbon quaternary stereocenter on 167, which is an intermediate in the synthesis of mastigophorene A (17).<sup>147</sup> (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<sup>59</sup> [two subsequent QCs]. (\*Guiding QC is synthesized through enolate trapping and  $\alpha$ -methylation after asymmetric conjugate addition.) (C) Synthesis of (–)-arcutinine (8) reported by Qin<sup>75</sup> [two subsequent QCs and one oxa-QC]. Syntheses of (-)-waihoensene (10) reported by (D) Yang<sup>96</sup> and (E) Snyder<sup>97</sup> [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 coworkers 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 palladiumpromoted cyclization<sup>167</sup> to form the 3-azabicyclo[3,3,1]nonane core 177 in 79% yield. A TiCl<sub>4</sub>/Hünig base-mediated aldol reaction<sup>168</sup> of 177 with aldehyde 178 167 produced 179 in 82% yield; 179 underwent ring-closing metathesis with Grubbs I catalyst169 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 silvl enol ether formation with TESOTf/DBU, α-hydroxymethylation with formalin/Sc(OTf)<sub>3</sub>, <sup>170</sup> 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<sup>171</sup> and the resultant alcohol was subjected to silvlation with TBSOTf. Selective desilvlation 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 (13Z,16Z)-189 in 95% yield. Desulfonylation of 189 with magnesium in methanol under ultrasonic irradiation<sup>176</sup> 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<sup>177</sup> 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<sup>+</sup>BF<sub>4</sub><sup>-</sup>, 191). 179,180 Subsequent cleavage of the TBS group by using tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF)<sup>181</sup> furnished (–)-haliclonin A (18) in 82% yield.

# 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<sup>82</sup> (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 silverchiral 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<sup>164</sup> shows that construction of an allcarbon 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 1,2diamine 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 1,2diamine. 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 \beta-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 palladiumcatalyzed 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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