BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

All-carbon [3 + 2] cycloaddition in natural product synthesis

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Review

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Keywords:
all-carbon; cyclization; [3 + 2] cycloaddition; natural product synthesis; stereocenters

Beilstein J. Org. Chem. **2020,** *16,* 3015–3031.
https://doi.org/10.3762/bjoc.16.251

Received: 25 August 2020
Accepted: 21 November 2020
Published: 09 December 2020

Associate Editor: D. Y.-K. Chen

Abstract

Many natural products possess interesting medicinal properties that arise from their intriguing chemical structures. The highly-substituted carbocycle is one of the most common structural features in many structurally complicated natural products. However, the construction of highly-substituted, stereo-congested, five-membered carbocycles containing all-carbon quaternary center(s) is, at present, a distinct challenge in modern synthetic chemistry, which can be accessed through the all-carbon [3 + 2] cycloaddition. More importantly, the all-carbon [3 + 2] cycloaddition can forge vicinal all-carbon quaternary centers in a single step and has been demonstrated in the synthesis of complex natural products. In this review, we present the development of all-carbon [3 + 2] cycloadditions and illustrate their application in natural product synthesis reported in the last decade covering 2011–2020 (inclusive).

Introduction

The highly-substituted, stereo-congested, five-membered carbocycle containing contiguous stereocenters is one of the most common structural features in many structurally complicated, biologically important natural products [1-7] (Figure 1). Meanwhile, the construction of quaternary carbon stereocenter(s) is, at present, a distinct challenge in modern synthetic chemistry [8-11]. Therefore, the synthesis of highly-substituted five-membered carbocycles bearing congested arrays of stereocenters within the polycyclic framework of complex natural products usually require a sophisticated synthetic planning. This issue is not trivial because only a few strategies are available for the efficient synthesis of such an intriguing molecular architecture. More importantly, the all-carbon [3 + 2] cycloaddition can forge vicinal all-carbon quaternary centers [12] in a single-step operation and provides a direct access to various substituted five-membered carbocycles. These characteristics make the all-carbon [3 + 2] cycloaddition an appealing method and/or strategy in the synthesis of complex natural products (Figure 2).

The 1,3-dipolar cycloaddition has been well-documented and widely used for the construction of five-membered heterocycles since the 1960s [13]. However, the development of the

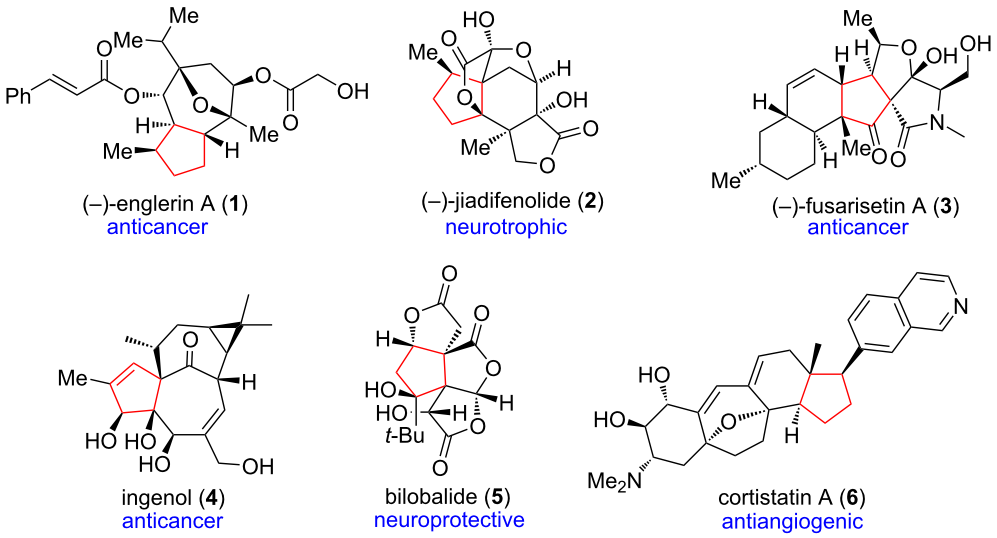


Figure 1: Highly-substituted five-membered carbocycle in biologically significant natural products.

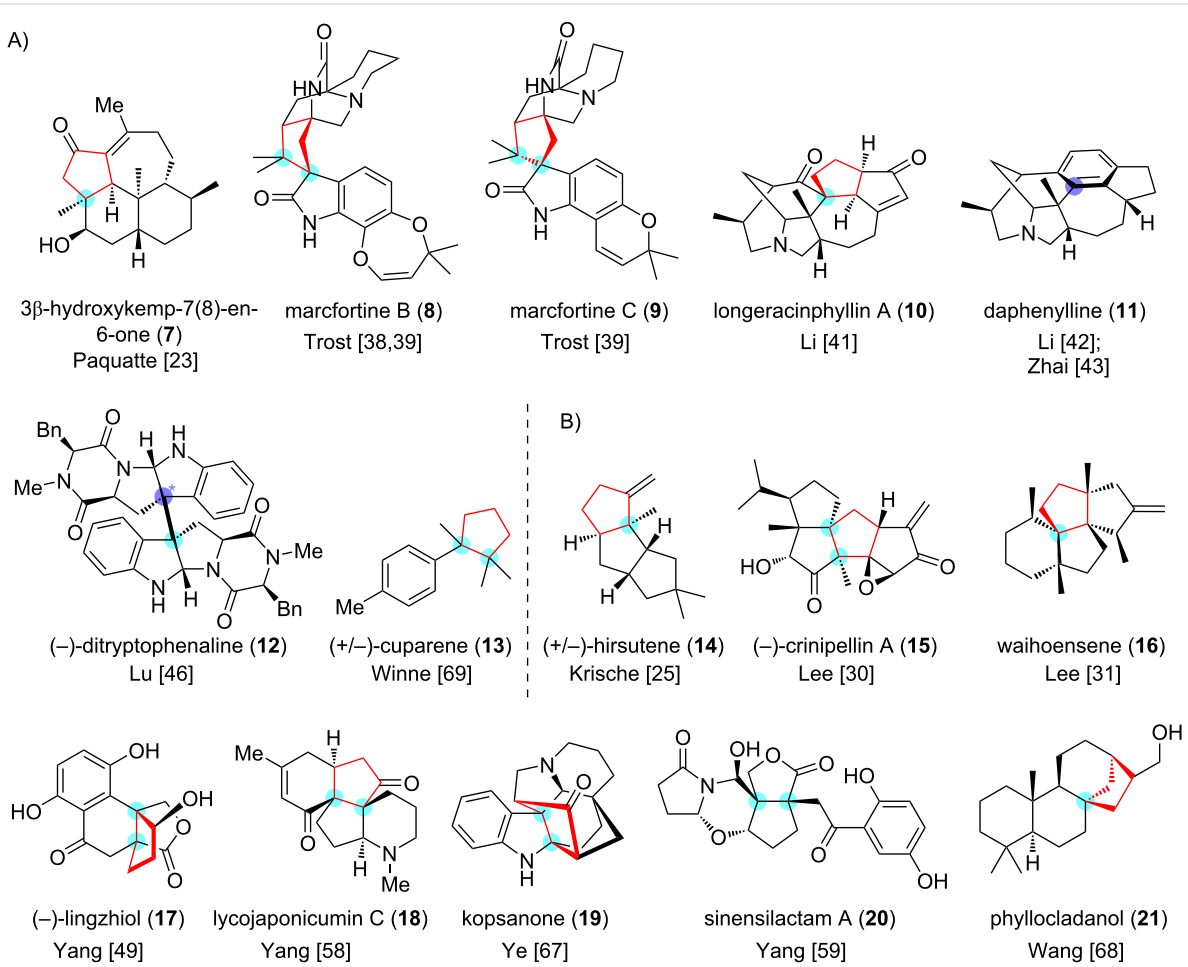


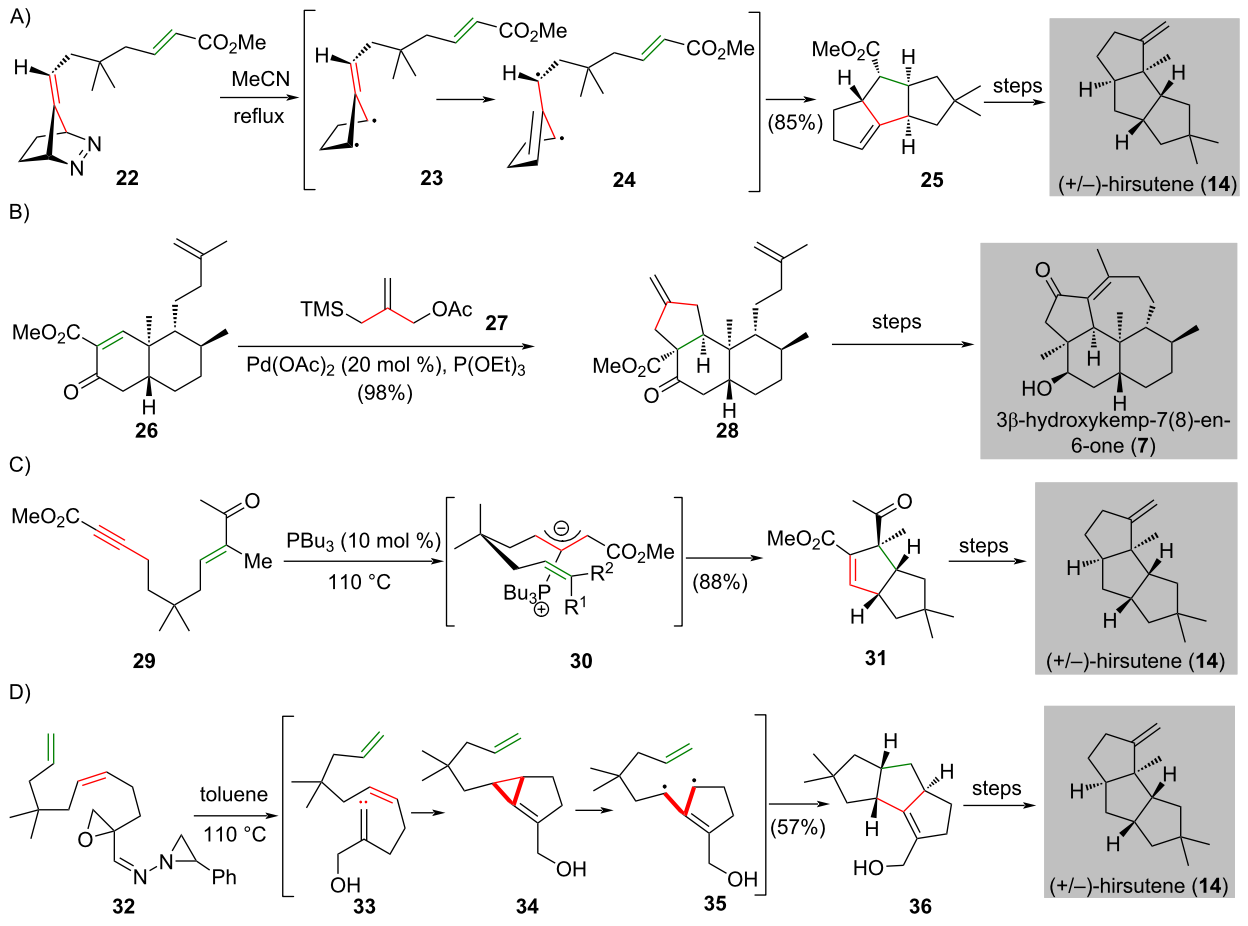
Figure 2: Natural product synthesis featuring the all-carbon [3 + 2] cycloaddition. (Quaternary carbon center(s) created by all-carbon [3 + 2] cyclization are highlighted in cyan; quaternary carbon center(s) created that are removed by subsequent transformations are highlighted in lilac; cyclopentane structures forged by the all-carbon [3 + 2] cyclization are labeled in red). (A) The intermolecular all-carbon [3 + 2] cyclization features as the key reaction. (B) The intramolecular all-carbon [3 + 2] cycloaddition features as the key reaction.

all-carbon [3 + 2] cycloaddition, for instance, Berson's and Little's [3 + 2] cycloaddition through diyl trapping with an olefin [14,15] and Trost's palladium-catalyzed trimethylenemethane cycloaddition [16], which allows the preparation of five-membered carbocycles, have been emerged since the 1970s. Thereafter, many novel and important all-carbon [3 + 2] cycloaddition reactions, such as the phosphine-catalyzed [3 + 2] cycloaddition [17], platinum-catalyzed [3 + 2] cycloaddition [18], and Rhodium-catalyzed [3 + 2] cycloaddition [12], were invented and have been extensively used in natural product synthesis in the last decade. Many reviews focusing the method development of the all-carbon [3 + 2] cycloaddition have been published [19-21]. However, there is no review effort, to the best of our knowledge, has been paid attention to the development of the all-carbon [3 + 2] cycloaddition with an emphasis on the natural product synthesis. Therefore, we are motivated to provide a timely and focused review of all-carbon [3 + 2] cycloadditions in natural product synthesis.

In this review, we present the development of the all-carbon [3 + 2] cycloaddition and discuss its application in natural product synthesis reported from 2011–2020. We begin with describing the brief history of the all-carbon [3 + 2] cycloaddition with selected natural product syntheses reported before 2011 [22-26]. Next, we discuss the synthetic methods including the proposed mechanism and/or catalytic cycle and focus on illustrative examples of natural product syntheses. Moreover, several natural product syntheses featuring all-carbon [3 + 2] annulation are elaborated. Lastly, we discuss future directions and opportunities for the all-carbon [3 + 2] cycloaddition.

Review

In 1981, Little and co-workers utilized a trimethylenemethane (TMM) cycloaddition as the key reaction to synthesize the tricyclic compound **25**, which led to the synthesis of (±)-hirsutene (**14**) [22] (Scheme 1A). Refluxing azo compound **22** in acetonitrile generated the proposed biradical intermediate



Scheme 1: Representative natural product syntheses that feature the all-carbon [3 + 2] cyclization as the key reaction, reported before 2011. (A) TMM cycloaddition of diyl **24** resulted from dinitrogen extrusion/isomerization is used to prepare tricycle **25**, which is a synthetic precursor of (±)-hirsutene (**14**) [22]. (B) Synthesis of 3β-hydroxykemp-7(8)-en-6-one (**7**) features a palladium-catalyzed intermolecular [3 + 2] cycloaddition to generate tricycle **28** [23]. (C) A stereospecific phosphine-catalyzed [3 + 2] cycloaddition completes the synthesis of (±)-hirsutene (**14**) [25]. (D) Linear alkylidene carbenes involved TMM [3 + 2] cycloaddition produces tricycle **36** in the preparation of (±)-hirsutene (**14**) [24].

23 through nitrogen extrusion. This intermediate underwent isomerization to **24** and intramolecular diyl trapping through a [3 + 2] cycloaddition to give fused tricycle **25** in 85% yield. The synthesis of the hydroxykempenone 3β-hydroxykemp-7(8)-en-6-one (**7**) features Trost's palladium-catalyzed trimethylenemethane [3 + 2] cycloaddition [27] and was reported by Paquette and co-workers in 1992 [23] (Scheme 1B). Catalytic TMM [3 + 2] cycloaddition of activated octalone **26** and the trimethylenemethane precursor **27** selectively produced adduct **28** in 98% yield, which is a synthetic precursor of 3β-hydroxykemp-7(8)-en-6-one (**7**).

Another two syntheses of (±)-hirsutene (**14**), after Little's pioneering work [22], were accomplished by Krische [25] and Lee [24] independently in 2003. (Scheme 1C and Scheme 1D) In Krische's synthesis, a stereospecific intramolecular phosphine-catalyzed [3 + 2] cycloaddition of 2-butynoate with electron-deficient alkene **29** afforded cycloadduct **31** in 88% yield as a single diastereomer [25] (Scheme 1C). Later, Lee`s synthesis of (±)-hirsutene (**14**) used an alkylidene carbene as source of TMM diyl in the intramolecular [3 + 2] cycloaddition [24] (Scheme 1D). Heating of epoxyaziridinyl imine **32** produced tricyclic compound **36** in 57% yield as a single product. The authors proposed that heating of epoxyaziridinyl imine **32** generates alkylidene carbene **33**. Transformation of **33** to TMM diyl **35** enables an intramolecular [3 + 2] cycloaddition to give the desired tricyclic product **36**.

Trimethylenemethane (TMM) cycloaddition

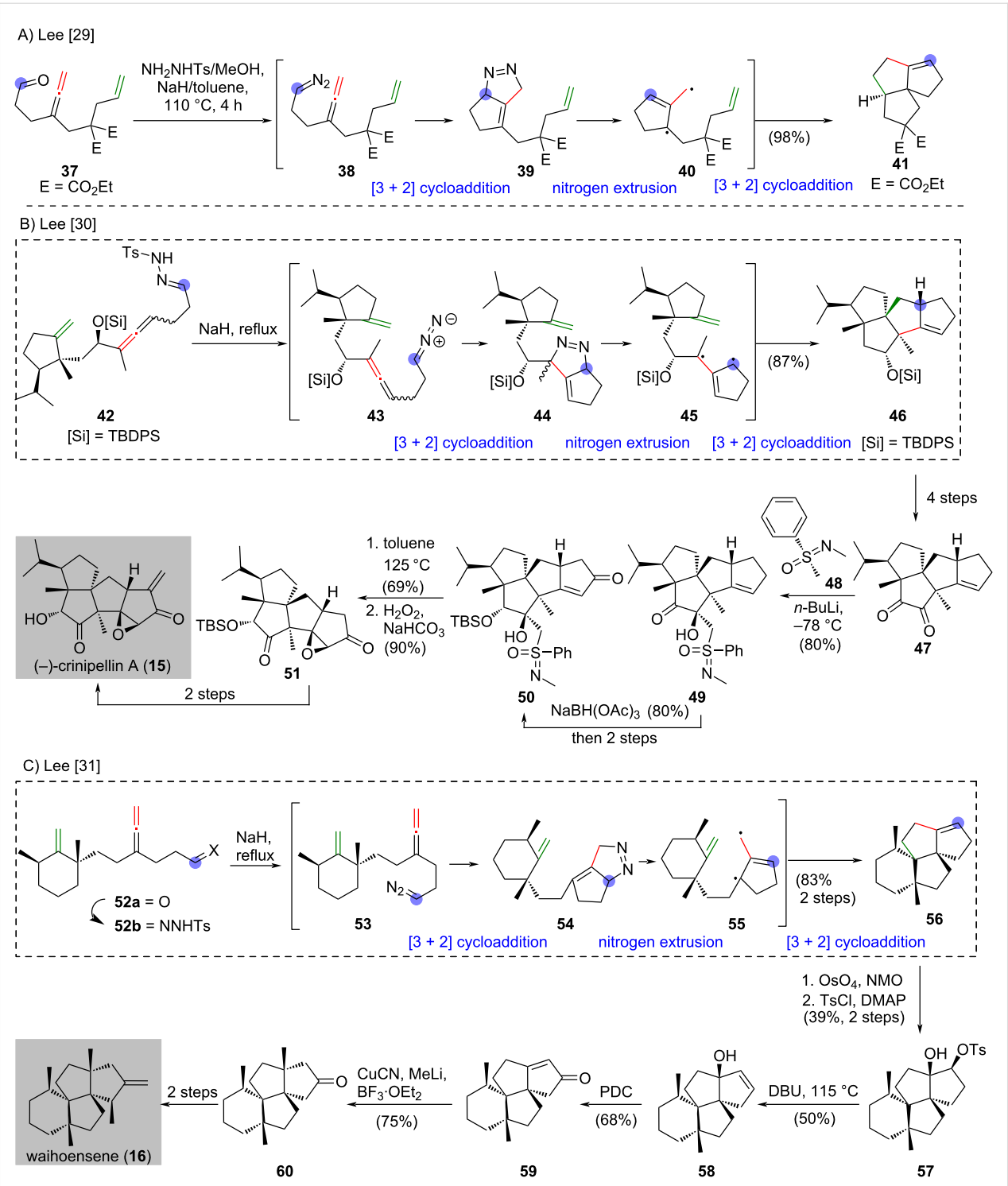
An intramolecular trimethylenemethane diyl [3 + 2] cycloaddition was reported by Berson [28] and Little [14] independently in the late 1970s, which was used to prepare (±)-hirsutene (**14**) in 1981 [22] (Scheme 1A). In 2003, Lee and co-workers disclosed an intramolecular trimethylenemethane diyl [3 + 2] cycloaddition with a linear alkylidene carbene as diyl source and was applied in the synthesis of linearly fused triquinane (±)-hirsutene (**14**) [24] (Scheme 1D). In 2011, the same research group used allenyl diazo compound **38**, which was generated from the reaction between aldehyde **37** and *p*-toluenesulfonehydrazide in the presence of sodium hydride upon heating, to produce diyl **40** [29] (Scheme 2A). The intramolecular trimethylenemethane diyl [3 + 2] cycloaddition of **40** led to the formation of angular fused triquinane **41** in 98% yield. The authors suggested that an intramolecular cycloaddition of the diazo group and allene **38** produces tetrahydrocyclopentapyrazole **39**. Extrusion of nitrogen from the newly formed **39** produces diyl **40**, which undergoes [3 + 2] cycloaddition to produce the angular fused triquinane **41**.

With the successful preparation of angular fused triquinane **41** by trimethylenemethane diyl [3 + 2] cycloaddition [29], enabled the synthesis of (−)-crinipellin A (**15**) [30] and waihoensene (**16**) [31] by Lee and co-workers in 2014 and 2017, respectively (Scheme 2B and Scheme 2C). The synthesis of (−)-crinipellin A (**15**) began with the treatment of hydrazone **42** with sodium hydride under reflux to produce the tetraquinane **46** in 87% yield [30] (Scheme 2B). The authors suggested that the diazo compound **43** formed undergoes an intramolecular cycloaddition to give **44**. Freshly prepared **44** was converted to diyl **45** followed by another cycloaddition to give the tetraquinane **46**. A four-step synthesis from the tetraquinane **46** gave diketone **47**. Treatment of sulfoximine **48** with *n*-butyllithium generated the corresponding anion, which selectively attacked the C-8 ketone moiety of **47** to give alcohol **49** in β-configuration in 80% yield [32]. Chemoselective and stereoselective reduction of the C-9 ketone of **49** was accomplished by treatment with $NaBH(OAc)_3$ [33] and produced **50** after a two-step synthesis. Removal of the sulfoximine group in **50** upon refluxing in toluene and subsequent epoxidation afforded **51** [32], which was converted to (−)-crinipelline A (**15**) in two steps.

The synthesis of waihoensene (**16**) commenced with the conversion of aldehyde **52a** to the corresponding hydrazone **52b**, which was treated with sodium hydride under reflux to give **56** in 83% yield over two steps [31] (Scheme 2C). This transformation was rationalized as follows: freshly prepared **52b** was converted to diazo **53**, which was subjected to [3 + 2] cycloaddition to give adduct **54**. Formation of diyl **55** from **54** and subsequent [3 + 2] cycloaddition produced the tetracyclic compound **56**. Dihydroxylation of freshly prepared **56** with OsO_4 and then selective tosylation afforded **57** in 39% yield over two steps. Exposure of **57** to DBU upon heating gave the elimination product **58**, which was subjected to an oxidative rearrangement with PDC to give enone **59** in 68% yield. Copper-mediated conjugated addition of methyllithium to enone **59** in the presence of boron trifluoride ether [34,35] produced desired ketone **60** in 75% yield. The resultant ketone **60** was converted to waihoensene (**16**) in two steps.

Palladium-catalyzed carboxylative trimethylenemethane cycloaddition

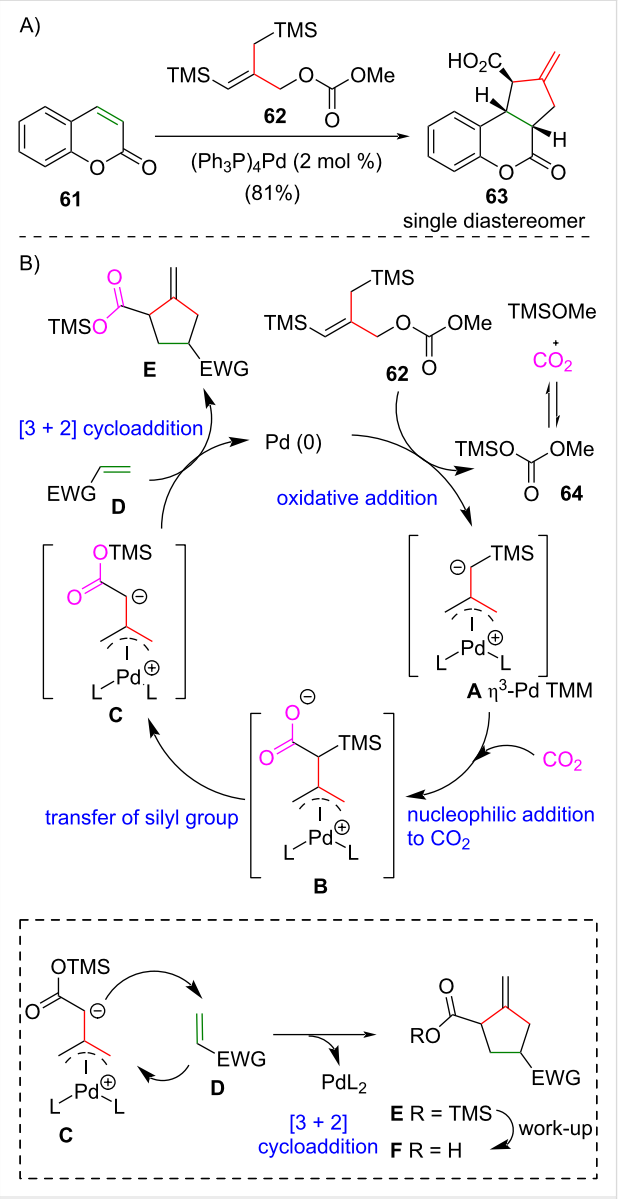
In 1986, Trost and co-workers disclosed the palladium-catalyzed intermolecular carboxylative TMM [3 + 2] cycloaddition [36] (Scheme 3). Exposure of coumarin **61** to the silyl-substituted TMM precursor **62** in the presence of a catalytic amount of $Pd(PPh_3)_4$ afforded adduct **63** in 81% yield as a single diastereomer (Scheme 3A). Trost and co-workers proposed that the catalytic mechanism involves an oxidative addition of palladium(0) into **62** affording the η^3-Pd TMM complex **A** [37] (Scheme 3B). Methyl trimethylsilyl carbonate (**64**) is formed as side product, which is in equilibrium with carbon dioxide and



Scheme 2: (A) An intramolecular trimethylenemethane diyl [3 + 2] cycloaddition with allenyl diazo compound **38** as a key intermediate to give angular-fused triquinane **41** [29]. (B) Synthesis of (–)-crinipellin A (**15**) [30]. (C) Synthesis of waihoensene (**16**) [31].

methyl trimethylsilyl ether. The electron-rich end of complex **A** attacks the carbon dioxide to give carboxylate **B**. Migration of the TMS group on carboxylate **B** generates the 1,3-dipole on **C** in the form of TMS carboxylate. An intermolecular [3 + 2] cycloaddition of **C** and alkene **D** (see Scheme 3B, inset) gives the cycloaddition adduct **E**, which is converted to the corresponding carboxylic acid (not shown) upon reaction work-up. This elegant reaction was applied in the synthesis of marcfor-

tine B (**8**), reported by Trost and co-workers in 2007 [38] and 2013 [39].



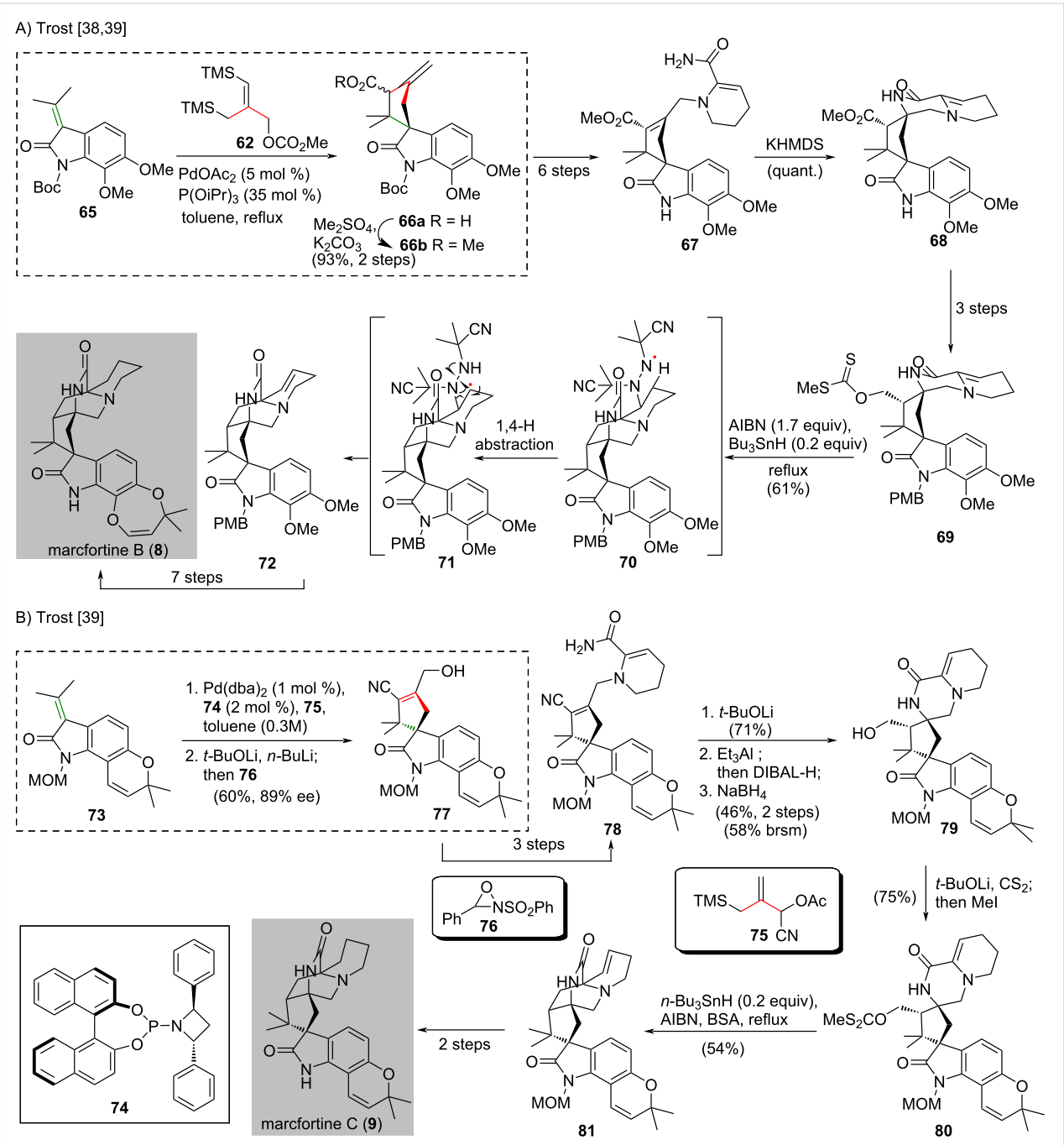
Scheme 3: (A) Palladium-catalyzed intermolecular carboxylative TMM cycloaddition [36]. (B) The proposed mechanism.

The synthesis of marcfortine B (**8**) began with palladium-catalyzed intermolecular carboxylatve TMM [3 + 2] cycloaddition [36] of enone **65** and TMM donor **62** to forge the highly-substituted spirocyclic cyclopentane **66a** [38] (Scheme 4A). Methylation of the resultant cyclopentane **66a** gave methyl ester **66b** in 93% yield over two steps. A six-step synthesis from ester **66b** gave α,β-unsaturated amide **67**, which was treated with KHMDS to facilitate an intramolecular Michael addition to give lactam **68** in quantitative yield. The conversion of freshly prepared lactam **68** to xanthante ester **69** was achieved in three steps. Exposure of xanthante ester **69** to AIBN and a catalytic amount of tributylstannane [40] led to a radical cyclization, in which the resultant alkyl radical formed was trapped by AIBN to give a proposed nitrogen-centered radical **70**. An 1,4-hydrogen abstraction of the nitrogen-centered radical on **70** produced carbon-centered radical **71**, which underwent fragmentation to afford alkene **72** in 61% yield. Marcfortine B (**8**) was synthesized from alkene **72** in seven steps.

The enantioselective synthesis of marcfortine C (**9**) commenced with a catalytic asymmetric cyano-substituted TMM cycloaddition of oxindole **73** and TMM donor **75** with $Pd(dba)_2$/**74** as catalyst to give a cycloaddition adduct (not shown) [39] (Scheme 4B). Subsequent treatement with *t*-BuOLi resulted in the isomerization of the *exo*-olefin followed by exposure to *n*-butyllithium and Davis' oxaziridine **76** to give **77** in 60% yield with 89% ee. A three-step synthesis from **77** gave α,β-unsaturated amide **78**, which underwent successive intramolecular Michael addition and hydrolytic nitrile reduction to give **79** in 46% yield in two steps. Extensive studies of the nitrile reduction eventually identified that Et_3Al and DIBAL-H could effectively reduce the nitrile group to the corresponding aldehyde and treatment with $NaBH_4$ afforded alcohol **79**. Alcohol **79** was converted into the corresponding xanthate ester **80**. This ester **80** was exposed to an excessive amount of AIBN and *N,O*-bis(trimethylsilyl)acetamide in the presence of a catalytic amount of tributylstannane producing bicyclo[2.2.2]diazaoctane **81** in 54% yield. The authors mentioned that the employment of the previously reported conditions for the radical cyclization in the synthesis of marcfortine B (**8**) led to the decomposition of the starting material. It was suggested that the MOM group of **80** may contribute to undesired side reactions. Synthesis of marcfortine C (**9**) was accomplished from **81** in two steps.

Phosphine-catalyzed [3 + 2] cycloaddition

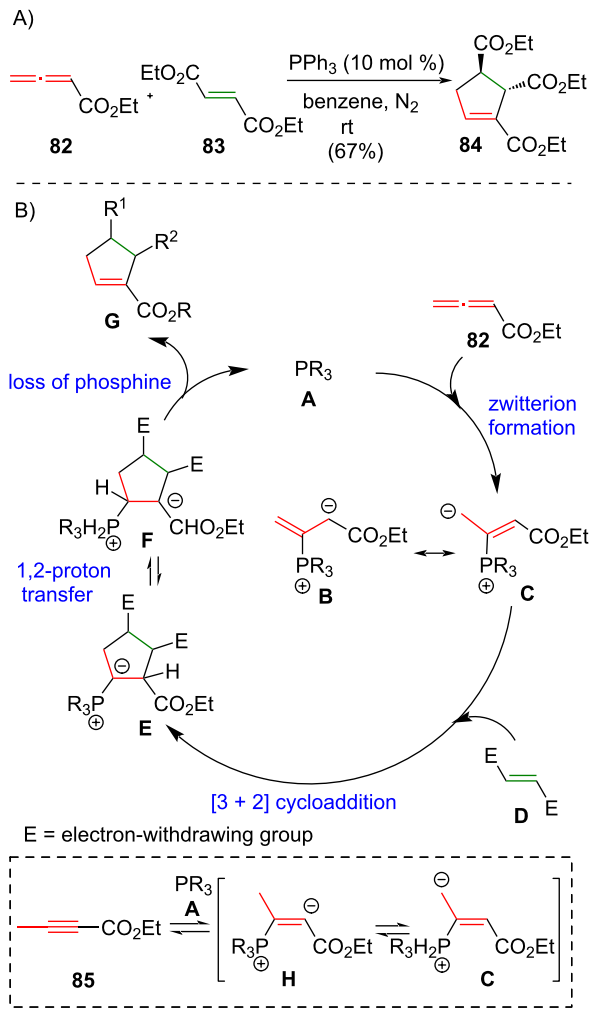
In 1995, Lu and co-workers reported a phosphine-catalyzed [3 + 2] cycloaddition, employing electron-deficient olefins and either 2,3-butadienoates or 2-butynoates to give a cyclopentene as product [17] (Scheme 5A). The reaction between ethyl 2,3-butadienoate (**82**) and diethyl fumarate (**83**) in the presence of 10 mol % of triphenylphosphine afforded *trans*-**84** in 67% yield. Under the same conditions, the use of diethyl maleate in place of diethyl fumarate (**83**) will give *cis*-**84** in 46% yield (not shown). Lu and co-workers proposed that the catalytic mechanism involves a reaction between phosphine catalyst **A** and allene **82** to give **B** and/or **C** (Scheme 5B). Catalytic [3 + 2] cycloaddition of **B** and/or **C** and alkene **D** gives the cyclic intermediates **E** and **F** in an equilibrium state through a 1,2-proton transfer. The loss of phosphine catalyst from **E** or **F** affords the cycloaddition product **G** and the catalyst is regenerated. It is noteworthy that ethyl 2-butynoate (**85**) can be used as substrate



Scheme 4: Natural product syntheses that make use of palladium-catalyzed intermolecular [3 + 2] cycloadditions of TMM. (A) Synthesis of marcfortine B (**8**) uses a palladium-catalyzed carboxylatve TMM [3 + 2] cycloaddition [38,39]. (B) Enantioselective synthesis of marcfortine C (**9**) features a palladium-catalyzed asymmetric cyano-substituted TMM [3 + 2] cycloaddition [39].

in place of ethyl 2,3-butadienoate (**82**) in the phosphine-catalyzed [3 + 2] cycloaddition. Ethyl 2-butynoate (**85**) enters the catalytic cycle by reacting with phosphine catalyst **A** to give **H** and **C**.

Some total syntheses of hexacyclic *Daphniphyllum* alkaloids were reported by Li's group (longeracinphyllin A (**10**) [41] and daphenylline (**11**) [42]) and Zhai's group (daphenylline (**11**) [43]), applying Lu's [3 + 2] cycloaddition (Scheme 6). The synthesis of longeracinphyllin A (**10**), which was reported by Li and co-workers in 2017, used a 1,1'-bis(diphenylphosphino)ferrocene-promoted [3 + 2] cycloaddition [44] of enedione **86** and allenoate **87** to give adduct **88** in 45% yield. This adduct **88** was treated with an excess of $LiCH_2PO(OMe)_2$



Scheme 5: (A) Phosphine-catalyzed [3 + 2] cycloaddition [17]. (B) The proposed mechanism.

to afford β-ketophosphonate **89** in 86% yield (Scheme 6A) [41]. Hydrogenation of **89** followed by an intramolecular Horner–Wadsworth–Emmons olefination produced hexacyclic enone **90** in 91% yield over two steps. The conversion of enone **90** to longeracinphyllin A (**10**) was achieved in three steps.

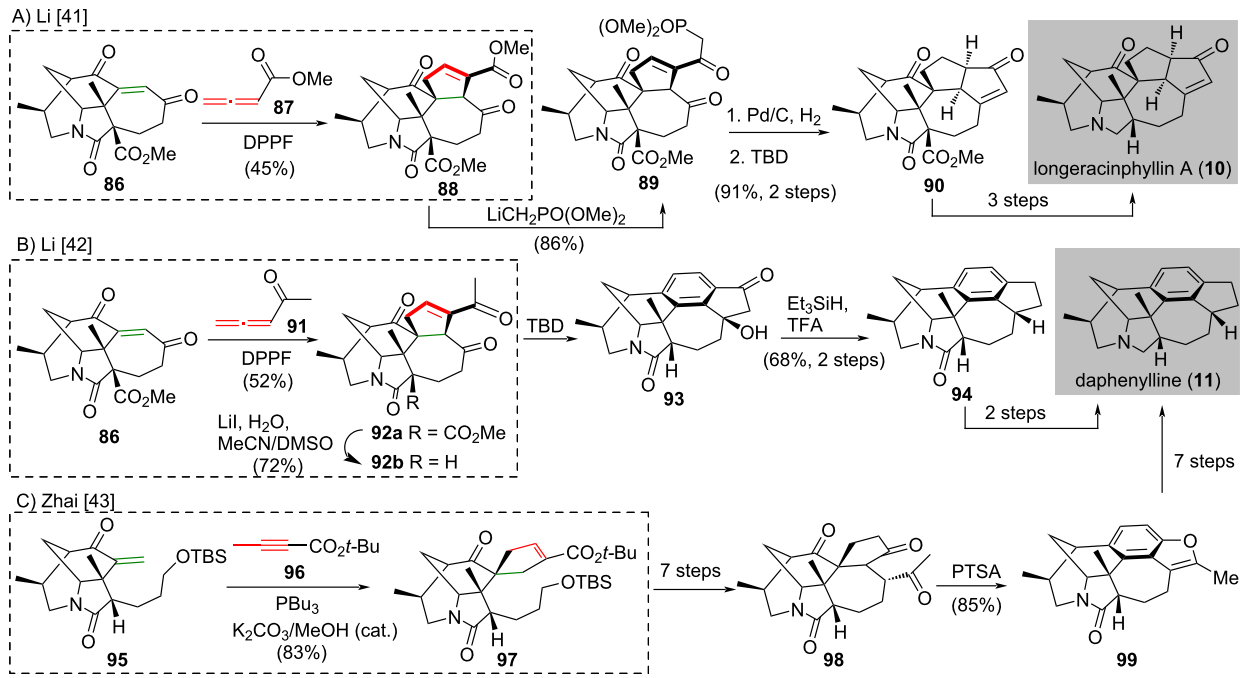
The syntheses of daphenylline (**11**) were reported by Li's group [42] and Zhai's group [43] independently in 2017 (Scheme 6B and Scheme 6C). In Li's synthesis, the common intermediate dienone **86** was subjected to a 1,1'-bis(diphenylphosphino)ferrocene-promoted [3 + 2] cycloaddition [41] with allenyl ketone **91** to give adduct **92a** in 52% yield (Scheme 6B). This adduct **92a** underwent decarboxylation to afford **92b** in 72% yield [42]. Exposure of freshly prepared **92b** to triazabicyclodecene [45] led to a ring-expansion/aromatization/aldol cascade producing **93**, which was reduced with Et_3SiH/TFA smoothly to give indane **94** in 68% yield over two steps. The freshly prepared indane **94** was converted to daphenylline (**11**) in two steps. The preparation of daphnipaxianine A and himalenine D (not shown) were also disclosed in the same work but are not described here.

Zhai's synthesis of daphenylline (**11**) used Lu's phosphine-catalyzed [3 + 2] cycloaddition [17] of enone **95** and *tert*-butyl 2-butynoate (**96**) with PBu_3 and K_2CO_3/MeOH as additive to give the cycloaddition adduct **97** in 83% yield [43] (Scheme 6C). A seven-step synthesis from **97** gave pentacyclic ketone **98**. Pentacyclic ketone **98** was exposed to PTSA under reflux to give the Wagner–Meerwein rearrangement product **99** in 85% yield. The synthesis of daphenylline (**11**) was completed by a seven-step synthesis from benzofuran **99**.

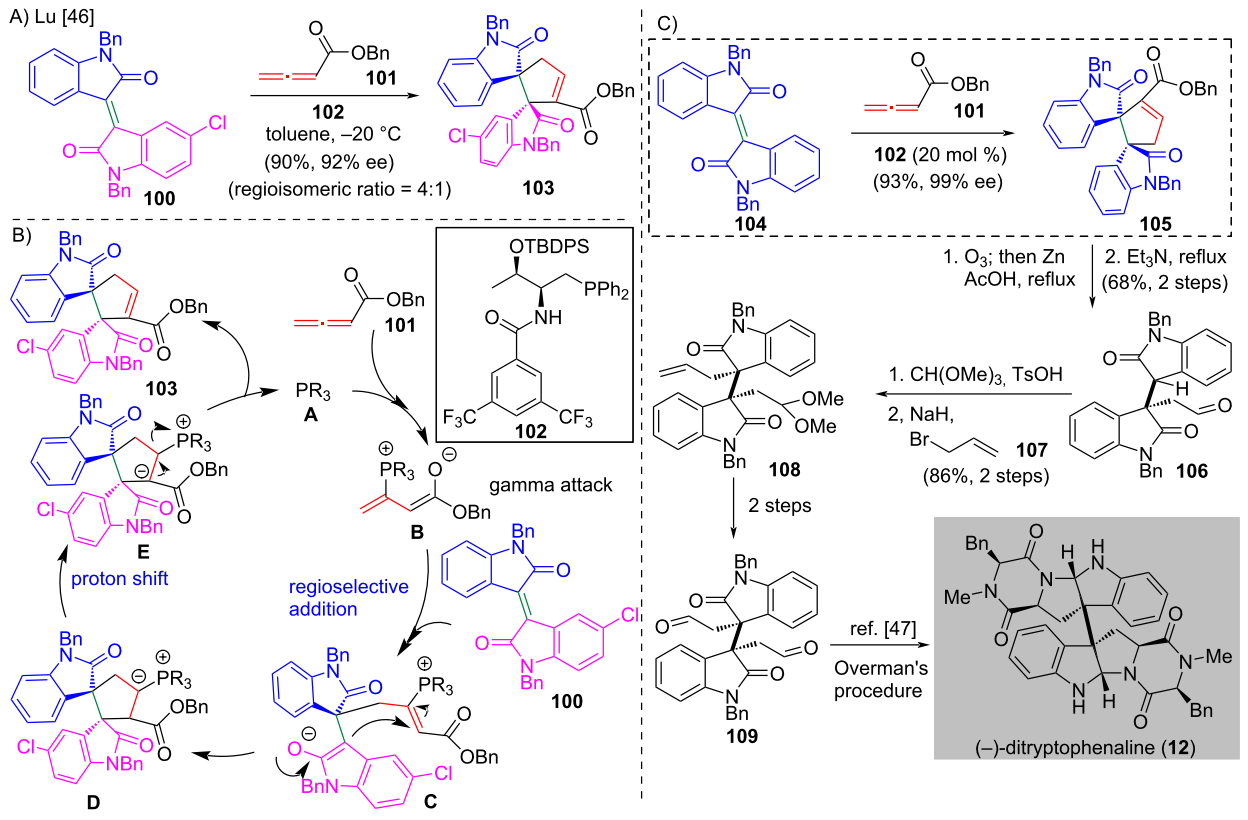
Phosphine-catalyzed enantioselective [3 + 2] annulation

In 2019, Lu and co-workers disclosed a novel chiral-phosphine-catalyzed enantioselective [3 + 2] annulation of allenes and isoindigos to give an enantioenriched annulation adduct bearing vicinal quaternary stereocenters [46] (Scheme 7A). Both symmetric and unsymmetric isoindigos can undergo enantioselective [3 + 2] annulation with an allene and produced a chiral adduct with high yield and high ee value. When unsymmetric isoindigo **100** was used as substrate, enantioselective [3 + 2] annulation with allene **101** in the presence of amino acid-derived bifunctional phosphine **102** produced adduct **103** in 90% yield with 92% ee and 4:1 regioisomeric ratio (rr). The authors suggested that the observed regioselectivity could be rationalized by the proposed catalytic mechanism (Scheme 7B). The phosphine (i.e., PR_3, **A**) attacks the allene **101** to generate zwitterion intermediate **B**, which is subjected to a less hindered attack by the isoindigo **100**. The oxindole bearing a chlorine atom on isoindigo **100** makes C-3 more electron deficient than C-3', which results in the regioselective formation of intermediate **C**. Cyclization of intermediate **C** gives **D** and subsequent proton transfer produces isomer **E**. It undergoes elimination to afford the annulation product **103** and the phosphine catalyst **A** is regenerated.

In the same work, Lu and co-workers applied the enantioselective [3 + 2] annulation to complete the formal synthesis of (−)-ditryptophenaline (**12**) [46] (Scheme 7C). The synthesis began with the catalytic asymmetric [3 + 2] annulation of symmetric isoindigo **104** and allene **101** with chiral phosphine catalyst **102** to give spirocyclic adduct **105** in 93% yield with 99% ee. The freshly prepared enantioenriched adduct **105** was subjected to ozonolysis [47] followed by decarboxylation to give bisoxindole **106** in 68% yield over two steps. Conversion of **106** to the corresponding acetal and subsequent allylation afforded **108** in 86% yield over two steps. A two-step synthesis from **108**



Scheme 6: Lu's [3 + 2] cycloaddition in natural product synthesis. (A) Synthesis of longeracinphyllin A (**10**) [41]. (B) Synthesis of daphenylline (**11**) [42]. (C) Synthesis of daphenylline (**11**) [43].

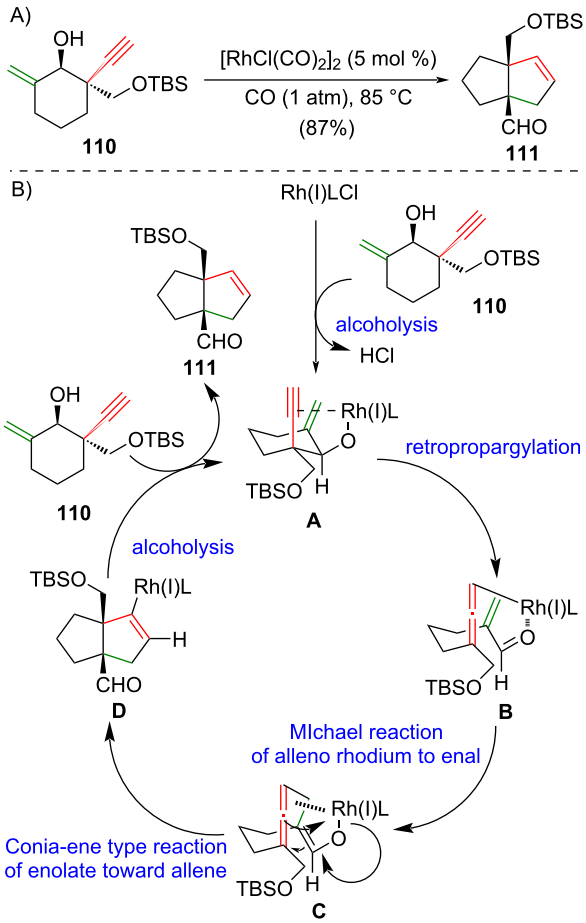


Scheme 7: (A) Phosphine-catalyzed [3 + 2] annulation of unsymmetric isoindigo **100** with allene in the preparation of spiro adduct **103** [46]. (B) The proposed catalytic cycle. (C) Application of phosphine-catalyzed asymmetric [3 + 2] annulation to prepare the chiral adduct **105** with symmetric isoindigo **104** in the formal synthesis of (–)-ditryptophenaline (**12**).

produced **109**, which was converted to (−)-ditryptophenaline (**12**) by using Overman's protocol [48].

Rhodium-catalyzed [3 + 2] cycloaddition

In 2014, Yang and co-workers reported an efficient rhodium-catalyzed intramolecular [3 + 2] cycloaddition of **110** to give [3.3.0] and [3.4.0] bicyclic systems bearing two quaternary atoms at the bridgehead position [49]. For instance, enynol **110** was treated with 5 mol % of $[RhCl(CO)_2]_2$ and carbon monoxide to afford a [3.3.0] bicycle **111** in 87% yield (Scheme 8A). The proposed catalytic cycle of this elegant rhodium-catalyzed intramolecular [3 + 2] cycloaddition begins with the reaction between the rhodium catalyst Rh(I)LCl and alcohol **110** to give complex **A** through alcoholysis [50,51] (Scheme 8B). Rh(I)-mediated retro-propargylation of the homopropargyl alcohol **A** afforded complex **B**. It undergoes an intramolecular Michael addition [52,53] with the allenyl rhodium to the enal and gives the allenyl rhodium species **C**. A Conia-ene-type reaction [54] between the Rhoda-enolate species and the allene of complex **C** produces the desired [3.3.0] bicycle **D**. Protonolysis [55-57] of complex **D** with the alcohol **110** gives bicyclic product **111** and regenerates the rhodium complex **A**. This elegant method has been successfully applied by the same research group in their synthesis of lingzhiol (**17**) [49], lycojaponicumin C (**18**) [58] and sinensilactam A (**20**) [59] (Scheme 9).

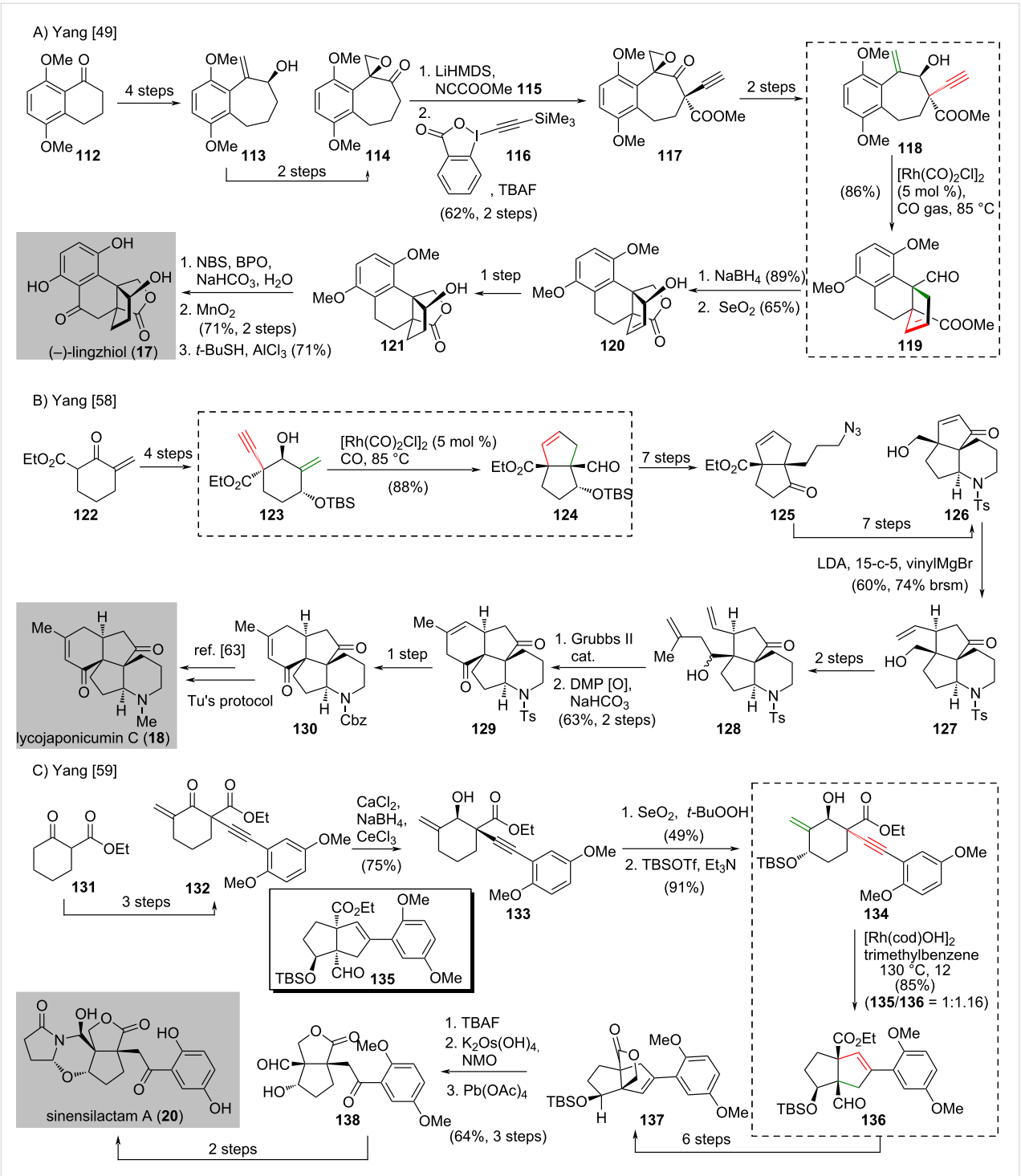


Scheme 8: (A) Rhodium-catalyzed intracmolecular [3 + 2] cycloaddition [49]. (B) The proposed catalytic cycle of the reaction.

The synthesis of (−)-lingzhiol (**17**) was reported by Yang and co-workers in 2014 [49] (Scheme 9A). The synthesis began with the conversion of ketone **112** into alcohol **113** in four steps, which involved a hypervalent iodine-mediated ring expansion [60]. A two-step synthesis from **113** gave epoxide **114**. Epoxide **114** was converted to the corresponding β-ketoester and subsequent treatment with Waser's reagent **116** [61] afforded alkyne **117** in 62% yield over two steps. Enyne **118**, which was prepared in two steps from **117**, was subjected to rhodium-catalyzed intramolecular [3 + 2] cycloaddition in the presence of carbon monoxide to give tricycle **119** bearing the desired vicinal quaternary carbon stereocenters in 86% yield. Reduction of aldehyde **119** and subsequent transesterification produced a lactone (not shown). It was exposed to SeO_2 to install the allylic hydroxy group to give **120** in 65% yield. Upon catalytic hydrogenation of **120,** alcohol **121** was formed. This alcohol **120** was subjected to a bromination [62]/oxidation sequence followed by demethylation to produce (−)-lingzhiol (**17**).

After the elegant synthesis of (−)-lingzhiol (**17**) was reported by Yang's group [49], the same research group disclosed the synthesis of lycojaponicumin C (**18**) [58] and sinensilactam A (**20**) [59] in 2017 and 2018, respectively, featuring the rhodium-catalyzed intramolecular [3 + 2] cycloaddition as the key reaction (Scheme 9B and Scheme 9C). Enyne **123**, which was prepared from enone **122** in four steps, was subjected to the rhodium-catalyzed intramolecular [3 + 2] cycloaddition under carbon monooxide to give the desired bicyclic [3.3.0] aldehyde **124** in 88% yield. A seven-step synthesis from aldehyde **124** gave azide **125**. It was converted to alcohol **126** in seven steps. Alcohol **126** was treated with LDA and vinylMgBr to facilitate a γ-OH directed 1,4-addition [63] to give C-7-vinylated tricycle **127** in 60% yield (74% yield, brsm). A two-step synthesis from **127** produced diene **128**, which was subjected to ring-closing metathesis and subsequent Dess–Martin oxidation to give **129** in 63% yield over two steps. Tetracycle **130**, which was prepared from **129** in one step, was converted to lycojaponicumin C (**18**) via Tu's protocol [64].

The synthesis of sinensilactam A (**20**) commenced with a three-step synthesis from ketoeseter **131** to give enone **132** [59] (Scheme 9C). Selective reduction of the ketone moiety of **132** was accomplished under Luche's conditions [65] in the presence of calcium chloride [63] to produce the desired alcohol



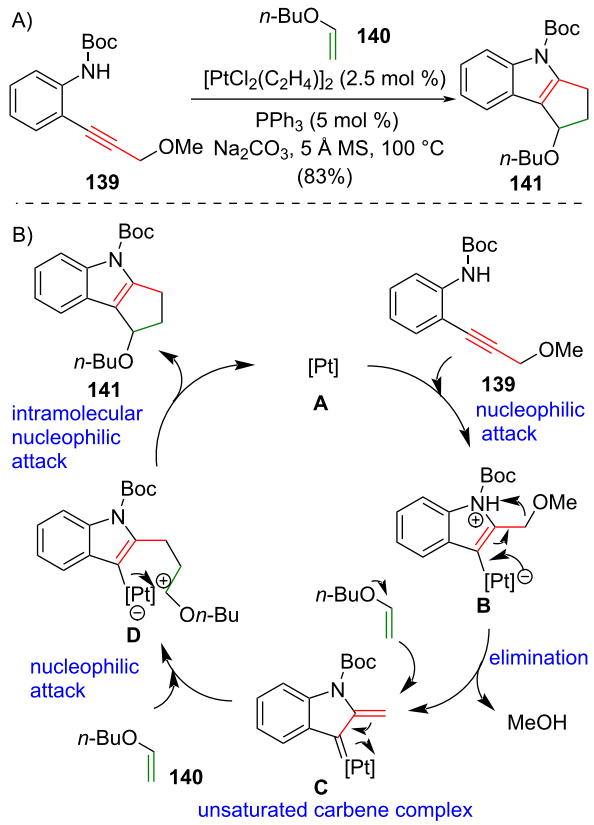
Scheme 9: Total synthesis of natural products reported by Yang and co-workers applying rhodium-catalyzed intramolecular [3 + 2] cycloaddition. (A) Synthesis of (–)-lingzhiol (**17**) [49]. (B) Synthesis of lycojaponicumin C (**18**) [58]. (C) Synthesis of sinensilactam A (**20**) [59].

133 in 75% yield as a single diastereomer. Allylic oxidation of freshly prepared **133** with SeO_2 followed by silylation with TBSOTf/Et_3N afforded enyne **134**. Enyne **134** was subjected to rhodium-catalyzed intramolecular [3 + 2] cycloaddition with a catalytic amount of $[Rh(cod)OH]_2$ to produce **135** and **136** in 85% yield in the ratio of 1:1.16. A six-step synthesis from the major product **136** gave lactone **137**. This compond was subjected to successive desilylation, OsO_4-mediated dihydroxylation and subsequent oxidative cleavage of the C=C double bond with $Pb(OAc)_4$ to give ketoaldehyde **138** in 64% yield

over three steps. The conversion of **138** to sinensilactam A (**20**) was achieved in two steps.

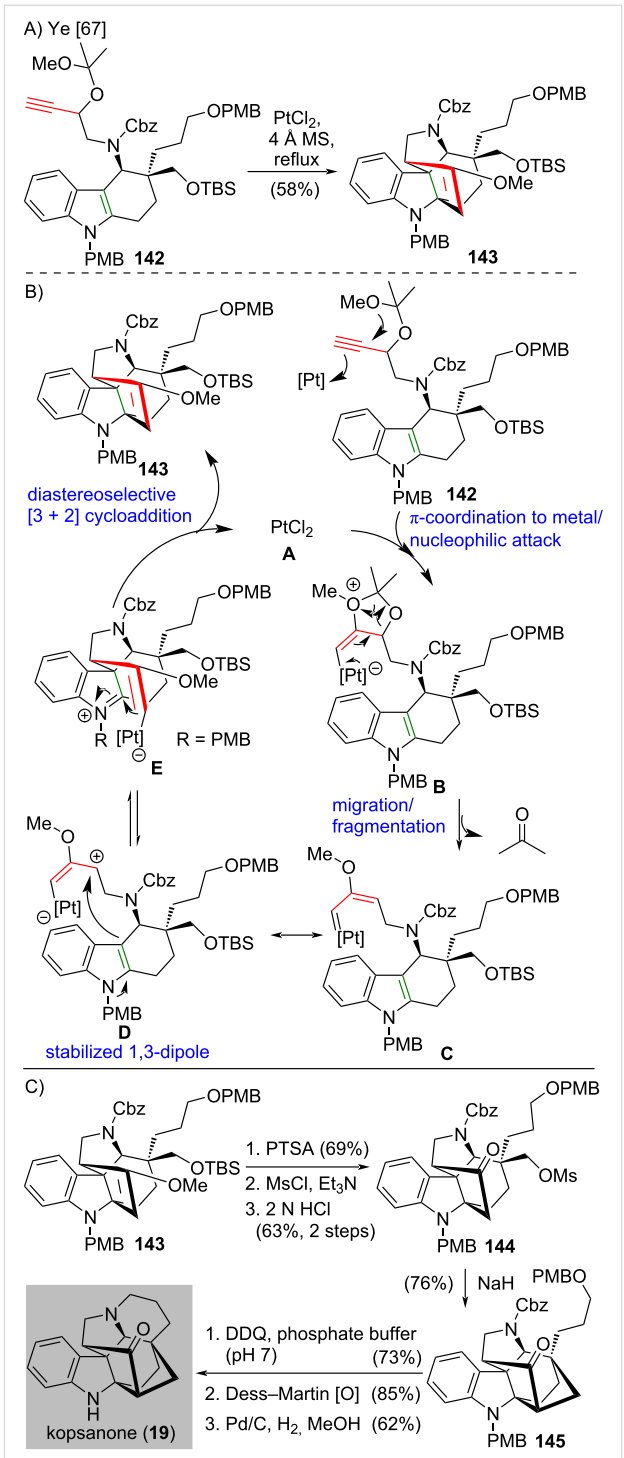
Platinum-catalyzed [3 + 2] cycloaddition

The platinum-catalyzed intermolecular [3 + 2] cycloaddition of propargyl ether derivatives and vinyl ether producing polycyclic indoles was disclosed by Iwasawa and co-workers in 2011 [18,66] (Scheme 10A). Treatment of Boc-protected aniline **139** and *n*-butyl vinyl ether (**140**) with a platinum(II) catalyst afforded tricyclic indole **141** in 83% yield. The authors suggested that this catalytic [3 + 2] cycloaddition reaction may involve an α,β-unsaturated carbene complex intermediate and a mechanism was proposed (Scheme 10B). An nucleophilic attack of the amine nitrogen onto the alkyne **139** under the effect of activated Pt(II) **A** produces zwitterionic intermediate **B**. Elimination of the methoxy group from zwitterion **B** generates the α,β-unsaturated carbene complex intermediate **C**. **C** is subjected to the nucleophilic attack of *n*-butyl vinyl ether (**140**) and generates alkenyl metallic intermediate **D**. Intramolecular nucleophilic attack onto the oxonium carbon of **D** affords the [3 + 2] cycloaddition product **141** with regeneration of the catalyst **A**.



Scheme 10: (A) Platinum(II)-catalyzed intermolecular [3 + 2] cycloaddition of propargyl ether **139** and *n*-butyl vinyl ether (**140**) gives tricyclic indole **141** [18,66]. (B) The proposed mechanism.

In 2020, Ye and co-workers used a platinum-catalyzed intramolecular [3 + 2] cycloaddition of a propargylic ketal derivative to complete the total synthesis of Kopsia indole alkaloids [67] (Scheme 11). The platinum-catalyzed intramolecular [3 + 2]



Scheme 11: (A) Platinum-catalyzed intramolecular [3 + 2] cycloaddition of propargylic ketal derivative **142** to give indoline **143** [67]. (B) The proposed catalytic mechanism. (C) The completion of total synthesis of kopsanone (**19**).

cycloaddition of propargylic ketal derivative **142** afforded indoline **143** in 58% yield, which possesses three contiguous stereocenters with vicinal all-carbon quaternary centers. (Scheme 11A). According to the proposed mechanism, coordination of the triple bond of **142** to the electrophilic platinum complex **A** followed by intramolecular nucleophilic attack by the methoxy group gives complex **B** (Scheme 11B). A facile migration–fragmentation process of complex **B** eliminates a ketone through fragmentation and produces metal-carbene intermediate **C**. The freshly prepared metal-carbene **C** is equilibrated to stabilized 1,3-dipole **D**. **D** undergoes a diastereoselective [3 + 2] cycloaddition to give indoline **143** and the active platinum catalyst **A** is regenerated. After the successful preparation of indoline **143**, the synthesis of kopsanone (**19**) is accomplished (Scheme 11C). Indoline **143** was converted to ketone **144** in three steps, which was subjected to a nucleophilic substitution to give the cyclization product **145** in 76% yield. The hexacyclic compound **145** was converted to kopsanone (**19**) in three steps.

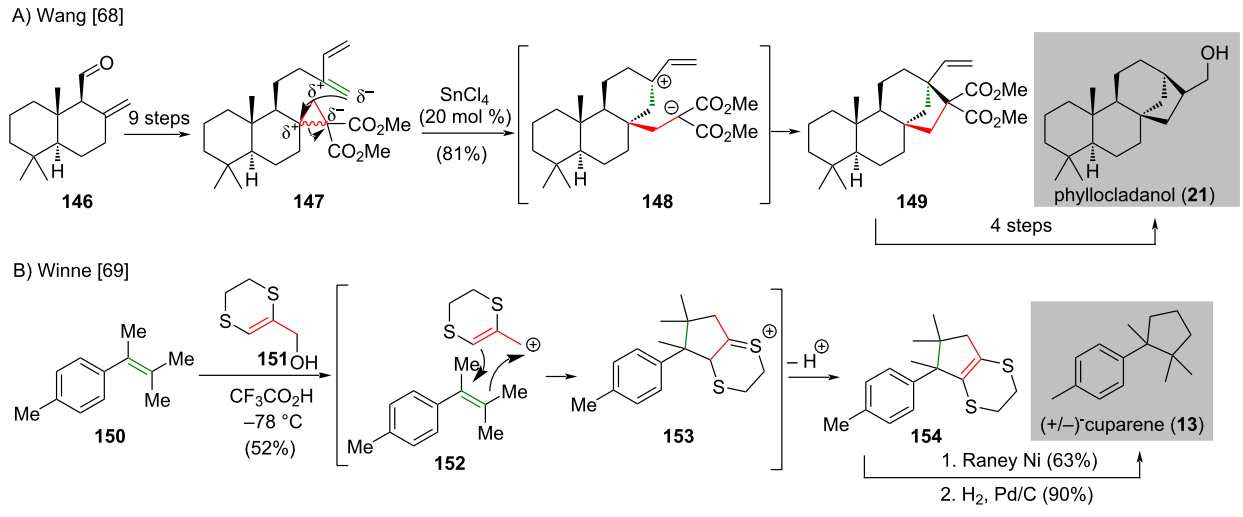
Miscellaneous

In 2012, Wang and co-workers reported a Lewis acid-catalyzed intramolecular [3 + 2] cross-cycloaddition (IMCC) of cyclopropane 1,1-diesters with non-activated alkene to generate bridged [*n*.2.1] carbocyclic skeletons, which is applied to the synthesis of phyllocladanol (**21**) [68] (Scheme 12A). The IMCC precursor **147** was prepared from aldehyde **146** in nine steps. The IMCC precursor **147** underwent an intramolecular cross-cycloaddition catalyzed by tin tetrachloride to give tetracycle **149** in 81% yield. The authors suggested that the intramolecular [3 + 2] cross-cycloaddition of the less-substituted external carbon atom in the C=C double bond results in the formation of the more stable internal carbenium (i.e., **148**) and promotes IMCC to give the bridged [3.2.1] octane **149**. The transformation of **149** to phyllocladanol (**21**) was accomplished in four steps.

In 2016, Winne and co-workers reported that (5,6-dihydro-1,4-dithiin-2-yl)methanol (**151**) can be served as a allyl-cation equivalent for the [3 + 2] cycloaddition and was applied in the synthesis of (±)-cuparene (**13**) [69] (Scheme 12B). An intermolecular [3 + 2] cycloaddition of tetrasubstituted alkene **150** and the dhdt-2-methanol reagent **151** under the effect of trifluoroacetic acid produced adduct **154** in 52% yield. The authors identified that the cyclic nature of the dhdt-2-methanol reagent **151** is essential for the cycloaddition to take place. The use of noncyclic analogues did not give the cycloaddition product. It is suggested that the restricted rotational freedom of **151** and the related enforced conjugation of the sulfur lone pair may block certain undesired cation reactions. Cycloaddition product **154** was subjected to the hydrodesulfurization with Raney nickel as catalyst and subsequent catalytic hydrogenation produced (±)-cuparene (**13**) in 90% yield.

All-carbon [3 + 2] annulation in natural product synthesis

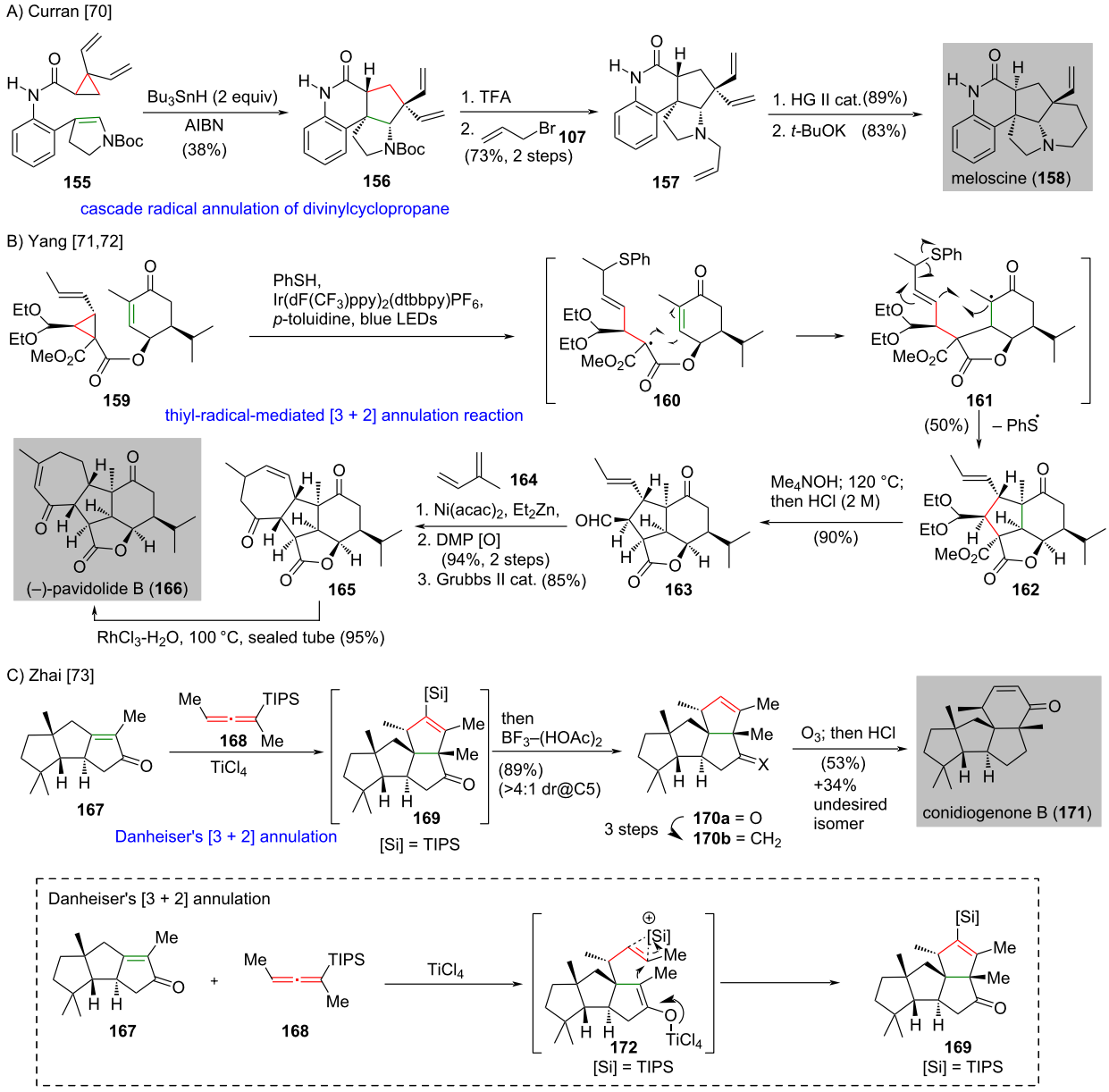
The all-carbon [3 + 2] cycloaddition demonstrated the ability to assemble intricate polycyclic structures in the synthesis of complex natural products. Besides the all-carbon [3 + 2] cycloaddition reactions and the corresponding applications described above, the all-carbon [3 + 2] annulation, which undergoes other possible mechanistic pathways other than cycloaddition, proved



Scheme 12: (A) Synthesis of phyllocladanol (**21**) features a Lewis acid-catalyzed formal intramolecular [3 + 2] cross-cycloaddition of cyclopropane 1,1-diesters with alkenes [68]. (B) (5,6-Dihydro-1,4-dithiin-2-yl)methanol **151** used as a versatile allyl-cation equivalent in [3 + 2] cycloaddition in the synthesis of (±)-cuparene (**13**) [69].

its usefulness in forging highly-substituted five-membered carbocycles. These reactions have been applied successfully in the synthesis of complex natural products. In 2011, Curran and co-workers reported the synthesis of meloscine (**158**) featuring a tandem radical cyclization of a divinylcyclopropane [70] (Scheme 13A). Slow addition of tributylstannane and AIBN to a refluxing solution of cyclopropane **155** afforded **156** in 38% yield. It was subjected to cleavage of the Boc group followed by *N*-allylation to give **157** in 73% yield over two steps. A ring-closing metathesis of freshly prepared **157** was effected by the second generation Hoveyda–Grubbs (HG II) catalyst and subsequent base-promoted epimerization produced meloscine (**158**) in 83% yield.

In 2017, Yang and co-workers disclosed the synthesis of (−)-pavidolide B (**166**) by using a thiyl-radical-mediated [3 + 2] annulation reaction to create four contiguous stereocenters on tricycle **162** in one step [71,72] (Scheme 13B). Exposure of ester **159** to PhSH [75], *p*-toluidine and a catalytic amount of $Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$ under the irradiation of blue LED



Scheme 13: The recent advances of [3 + 2] annulation in natural product synthesis. (A) The preparation of meloscine (**158**) features a cascade radical annulation of divinylcyclopropane [70]. (B) Thiyl-radical-mediated [3 + 2] annulation reaction realizes the synthesis of (–)-pavidolide B (**166**) [71,72]. (C) A Danheiser's [3 + 2] annulation en route to conidiogenone B (**171**) [73] (inset, the suggested mechanism based on Danheiser's proposal disclosed in 1981 [74].)

light [76,77] afforded tricycle **162** in 50% yield. The authors suggested that this process involves an intramolecular 5-*exo*-conjugated addition of a radical on **160** to the enone and produces **161**. The newly formed **161** was subjected to 5-*exo* radical addition to the allyl sulfane and subsequent loss of a thiyl radical produces **162**. A successive hydrolysis/decarboxylation upon heating and cleavage of acetal on **162** afforded aldehyde **163** in 90% yield. Coupling of aldehyde **163** and isoprene (**164**) with $Ni(acac)_2$ and diethylzinc [78] and then Dess–Martin oxidation gave a diene (not shown, 94% yield over two steps), which was subjected to ring-closing metathesis to give enone **165** in 85% yield. Isomerization of the freshly prepared **165** to more stable α,β-unsaturated enone with $RhCl_3$ [79] afforded pavidolide B (**166**) in 95% yield.

The synthesis of (−)-conidiogenone B (**171**) featured a Danheiser's [3 + 2] annulation [74,80] and was reported by Zhai and co-workers in 2020 [73] (Scheme 13C). Treatment of tricycle **167** with allene **168** in the presence of $TiCl_4$ gave the desired **169** carrying two vicinal quaternary carbons. A one-pot desilylation of the newly formed **169** with a trifluoride–acetic acid complex produced the tetraquinane **170a** in 89% yield with a 4:1 dr. The conversion of the freshly prepared ketone **170a** to **170b** was achieved in three steps. Ozonolysis of the C=C double bond of **170b** gave a keto aldehyde (not shown), which was subjected to an acid-mediated aldol reaction to give conidiogenone B (**171**) in 53% yield. The undesired isomer with β,γ-C=C double bond (not shown) was formed in 34% yield and can be isomerized to the more stable α,β-unsaturated enone to afford conidiogenone B (**171**) in 32% yield upon treatment with $RhCl_3$ in microwave.

The reaction mechanism of Danheiser's [3 + 2] annulation is shown according to the Danheiser's proposal [74] (Scheme 13C, inset). Initial complexation of the α,β-unsaturated ketone **167** and titanium tetrachloride produces an alkyoxy allylic carbocation (not shown). This carbocation is subjected to a regiospecific electrophilic substitution of allene **168** to generate a vinyl cation **172**, which is stabilized by an adjacent carbon–silicon bond. The 1,2-shift of the silyl group in **172** produces an isomeric vinyl cation, which is intercepted by the titanium enolate and results in the new C–C bond formation to give the five-membered carbocycle **169**.

Conclusion

The all-carbon [3 + 2] cycloaddition, together with the [3 + 2] annulation, continue to be an attractive class of reactions for the synthesis of highly-substituted and stereo-congested five-membered carbocycles. Also, one or more quaternary carbons can be created in a single reaction making this class of reactions appealing to complex natural product syntheses. This review outlines the development of the all-carbon [3 + 2] cycloaddition and its application in natural product synthesis reported from 2011–2020 (inclusive). The intermolecular all-carbon [3 + 2] cycloaddition offers a facile approach to install functionalized five-carbon carbocycles, including fused-rings (e.g., longeracinphyllin A (**10**)) and/or spiro-ring (e.g., marcfortine B (**8**)), at later stage of the synthesis without the need of pre-installation of necessary functional groups as a reaction precursor, for instance, ring-closing metathesis, intramolecular aldol condensation, and others.

One major issue that still needs to be addressed is the selectivity of the all carbon [3 + 2] cycloadditions, which are usually under substrate-control. Remarkable innovation of the stereoselective palladium-catalyzed trimethylenemethane cycloaddition reported by Trost's group, which makes use of catalytic amounts of palladium and chiral phosphine ligand **74**, was applied successfully in the enantioselective synthesis of marcfortine C (**9**, Scheme 4B). Another brilliant example is the development of a chiral-phosphine-catalyzed [3 + 2] annulation reported by Lu in 2019, in which the chiral phosphine catalyst confers high stereocontrol on the formation of a spiro adduct bearing two vicinal all-carbon quaternary stereocenters (Scheme 7). We believe that the enantioselective all-carbon [3 + 2] cycloaddition provides a new strategy for the preparation of sp^3-carbon-enriched complex scaffolds [81,82] for biological studies and potential new drug development.

The all-carbon [3 + 2] cycloaddition is undoubtedly an efficient synthetic transformation that creates two C–C bonds in a single reaction. However, the prior protection of the reactive functional groups, such as the hydroxy and amino groups, are still necessary for most of the all-carbon [3 + 2] cycloaddition reactions. We predict that further development of the all-carbon [3 + 2] cyclization with the reactive functional groups' compatibilities and/or without the use of protecting groups [83,84] can improve the synthetic efficiency and make this class of reactions more attractive to the synthetic scientist for applications. Lastly, we anticipate that the all-carbon [3 + 2] cycloaddition will gain further attention from the synthetic community, including scientists from academia and pharmaceutical industry, for methodic innovation and the efficient synthesis of biologically important natural products.

Acknowledgements

The author thanks C. Hui (Max Planck Institute of Molecular Physiology) for helpful discussion during the preparation of this manuscript. The authors would like to thank the anonymous reviewers for their thought-provoking comments and apologize to colleagues whose work was not cited owing to selected coverage.

Funding

Financial support from the Shenzhen Human Resources and Social Security Bureau (50820190066) to Z. Wang is gratefully acknowledged. J. Liu acknowledges the financial support from Shenzhen Science and Technology Innovation Committee (grant nos. JCYJ20190809181011411).

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