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Synthetic Methods

# Allenes in Catalytic Asymmetric Synthesis and Natural Product Syntheses

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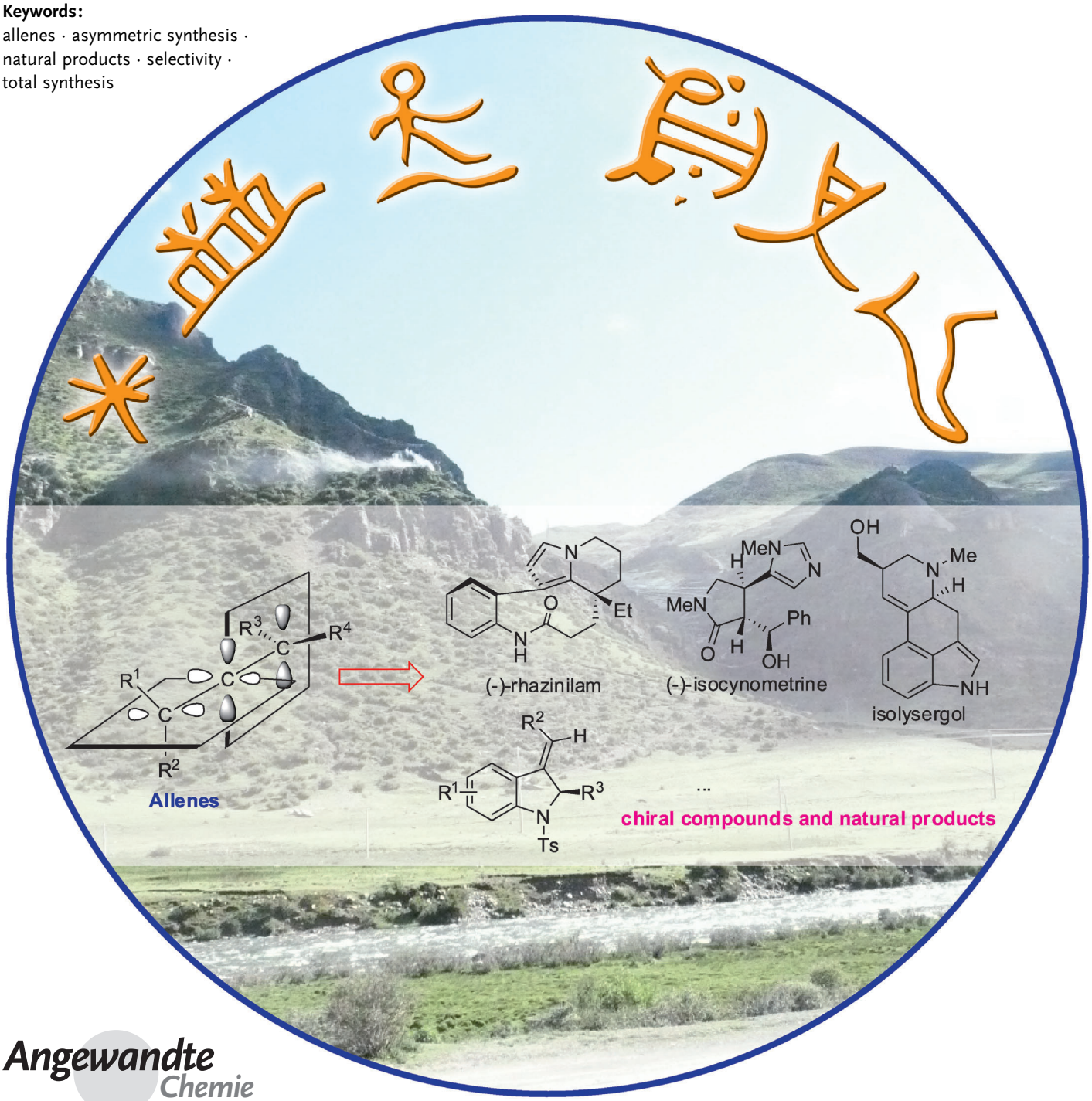
allenes · asymmetric synthesis · natural products · selectivity · total synthesis



*Allenes are the simplest class of cumulenes, with two contiguous C=C bonds, and show unique physical and chemical properties. These features make allenes particularly attractive in modern organic chemistry. In this Review, attention is paid to the advances made in catalytic asymmetric synthesis and natural product syntheses based on well-established reactions of allenes, such as propargylation, addition, cycloaddition, cycloisomerization, cyclization, etc., with or without catalysts. Their versatile reactivity, substituent-loading ability, axial to center chirality transfer, and controllable selectivity allow access to target molecules by unique and efficient approaches. The main topics in this Review are presented with selected examples from 2003 to 2011.*

**From the Contents**



## 1. Introduction

Allenes, which show interesting and varied reactivity patterns as a result of their unique chemical properties, are now becoming an integral part of modern synthetic methods. The higher reactivity of allenic compounds, compared with their alkenyl and alkynyl analoges, allows controllable selectivity to be achieved under mild reaction conditions. The unsaturation of allenes spread over three carbon atoms demonstrates the excellent flexibility and opportunity to perform tandem or multistep reactions. As a consequence of their substituent-loading ability, less-hindered linear structures, and the intrinsic axial chirality,[1] the reactions of allenes can be implemented with high levels of stereocontrol at multiple stereocenters, and even quaternary carbon atoms can be installed highly efficiently. With the development of more and more readily available methods for the synthesis of allenes[2] and the recent demonstration of their reactivities,[3,4] the utility of allenes in the synthesis of optically active compounds and natural products has been increasing, and the potential of allene chemistry has been nicely demonstrated. This Review will highlight with selected examples from the literature (2003 to April 2011) the current status of this area.

## 2. Reactions of Carbonyl Compounds with Allenylmetal Reagents

The propargylation of carbonyl compounds by allenylmetal reagents is not very attractive, partly because of the low selectivity caused by the rearrangement of allenylmetal reagents to the corresponding propargylic organometallic compounds, thereby affording mixtures of homopropargylic and α-allenic carbinols.[5] It has been observed that the selectivity is influenced by the nature of the metal center, steric hindrance of the participated reagents, and the reactivity of the electrophile.[6] For example, deprotonation or halogen–lithium exchange are the most common methods to access allenyllithium reagents, which react with electrophiles or serve as precursors for the synthesis of allenylzinc, -stannane, -silane, -titanium, and -boronate compounds. Reissig's series of studies on lithiated alkoxyallenes led to the synthesis of a variety of useful heterocycles such as furans, pyrroles, pyridines, pyrimidines, and 1, 2-oxazines in a new efficient way.[7–10] Allenyl vinyl ketone with an alkoxyl substituent was highly reactive and ready underwent a Nazarov cyclization.[11,12] Deprotonation of 2,3-allenoates with lithium diisopropylamide (LDA) or tetrabutylammonium fluoride (TBAF) gave alkynylenolates, which could react with a variety of electrophiles, such as organohalides[13] and electron-withdrawing alkenes,[14] to afford highly functionalized α,α-disubstituted β-alkynyl esters in good to excellent yields under mild conditions, with a number of functional groups tolerated. When the alkynylenolate intermediate was trapped with a fluorinating agent, it reacted exclusively at the α-carbon atom, thereby forming α-fluoro-β-alkynyl esters. Interestingly, the addition of $I_2$ to the alkynyl enolate intermediate protected as a silyl ether gives solely 4-iodo-2,3-allenoates.[15] The oxidative addition of aluminum to propargylic bromides in the presence of $PbCl_2$ forms allenic aluminum reagents. These organoaluminum reagents react with carbonyl compounds to afford the corresponding allenic alcohols (from nonterminal primary propargylic bromides) or homopropargylic alcohols (from propargyl bromide or nonterminal secondary propargylic bromides) in good to excellent yields with high regio- and diastereoselectivity. Various

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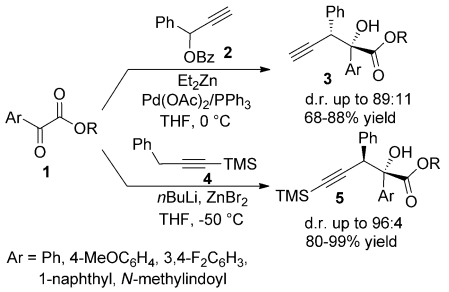
functional groups such as ester, cyanide, amino groups, and acidic methylene groups are tolerated in this reaction.[16]

### 2.1. Allenylzinc Reagents

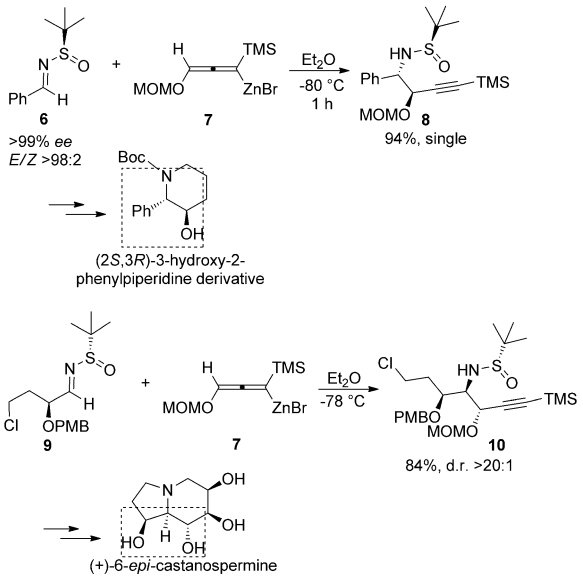
Allenylzinc compounds are commonly prepared through oxidative addition with zinc metal or by transmetalation.[17] Cossy, Bellosta, and co-workers prepared two types of allenylzinc compounds by Pd/Zn exchange from propargylic benzoates or by metalation of alkynes (Scheme 1). These reagents showed divergent diastereoselectivity in the propargylation of aryl glyoxylates.[18]




***Scheme 1.*** Propargylation of aryl glyoxylates. TMS = trimethylsilyl, Bz = benzoyl.

The addition of 1-trimethylsilyl-3-(methoxymethoxy)propadienyl zinc reagent **7** to chiral *tert*-butylsulfinylimines **6** and **9** afforded synthetically useful 3-alkynyl-1,2-amino alcohol **8** and 2-amino-1,3-diol **10** in a stereoselective fashion.[19] These two products have been used for the asymmetric syntheses of naturally occurring and/or bioactive alkaloids, such as a (2*S*,3*R*)-3-hydroxy-2-phenylpiperidine derivative,[20] L-1-deoxyallonojirimycin and L-1-deoxymannojirimycin,[21] (+)-6-*epi*-castanospermine,[22] and sphingoid-type bases (Scheme 2).[23]

Baker, Caddick et al. reported that the allenylzinc reagent **12** with a chlorine substituent may condense with 2-trimethylsilylacetynyl ketone **11** through a Darzens-like sequence




***Scheme 2.*** Propargylation of chiral imines to give nitrogen heterocycles as segments of natural products. Boc = *tert*-butyloxycarbonyl, MOM = methoxymethyl, PMB = *para*-methoxybenzyl.

to yield chlorohydrin **13**, which readily cyclizes to propargylic epoxide **14** upon treatment with base (Scheme 3).[24]

Marshall and Mulhearn accomplished the synthesis of the C20–C26 segment of superstolide A by a sequence where the key strategic step was the addition of a chiral allenylzinc reagent to an α-chiral aldehyde (Scheme 4).[25] The allenylzinc compound **17** was prepared in situ by palladiozincation of (*S*)-5-pivalyloxy-3-butyn-2-ol mesylate (**16**). The reaction of this reagent with chiral α-amino aldehyde **15** resulted in an excellent reagent-controlled stereoselectivity that led to the *anti*,*anti*-diastereoisomer **18** in a diastereomeric ratio of 95:5. The reduction of the carbon–carbon triple bond with Red-Al yielded allylic alcohol **19**. Sharpless asymmetric epoxidation led to epoxide **20**, which underwent a ring-opening reaction with a higher order methyl cyanocuprate reagent to introduce the methyl group diastereoselectively.

Other natural products that were successfully synthesized by this strategy include (+)-zincophorin,[26] dictyostatin,[27]

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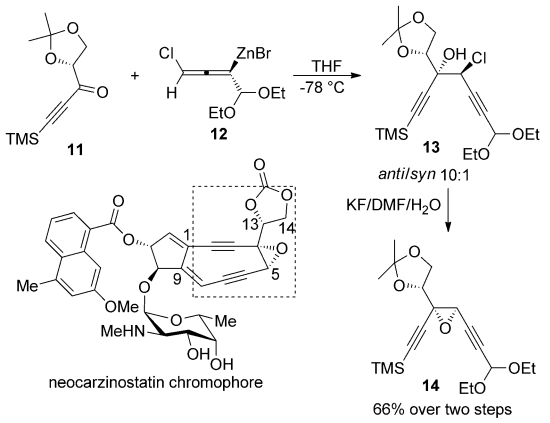
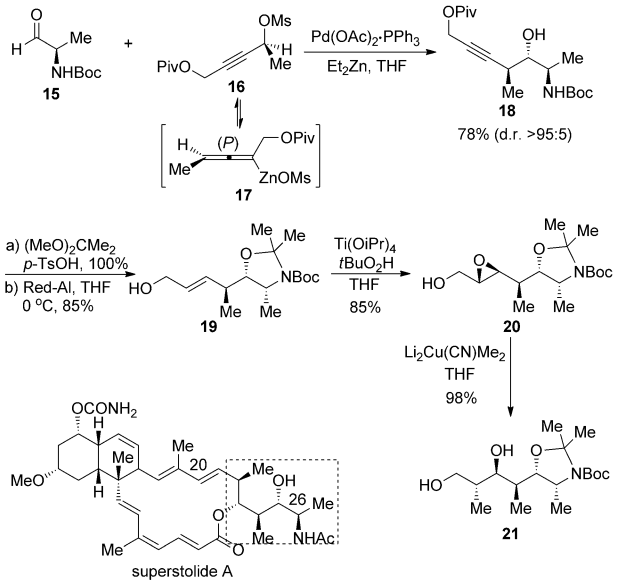
*Shichao Yu, was born in 1977 in Hubei, China, studied chemistry at the Shanghai Institute of Organic Chemistry (SIOC), and received his PhD with Professor Shengming Ma. He then carried out postdoctoral research with Prof. Xumu Zhang at Pennsylvania State University (2005–2006) and Rutgers University, New Jersey (2007–2009). In 2010 he joined the research group of Professor Ma at SIOC as an assistant professor. In mid 2011 he left the SIOC to join his family in the USA.*




***Scheme 3.*** Diastereoselective synthesis of an epoxydiyne. DMF = *N*,*N*-dimethylformamide.

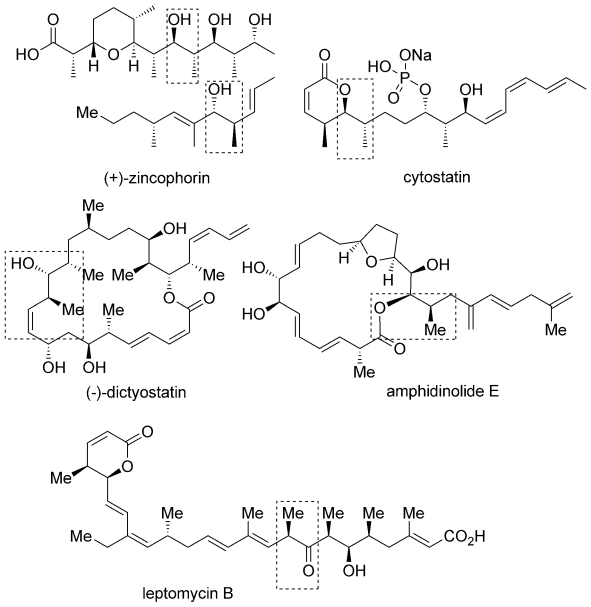



***Scheme 4.*** Synthesis of the C20–C26 segment of superstolide A. Ms = methanesulfonyl, Piv = pivaloyl, Red-Al = sodium bis(2-methoxyethoxy)aluminumhydride, Ts = *para*-toluenesulfonyl.

cytostatin,[28] amphidinolide E,[29] and leptomycin B[30] (Scheme 5).

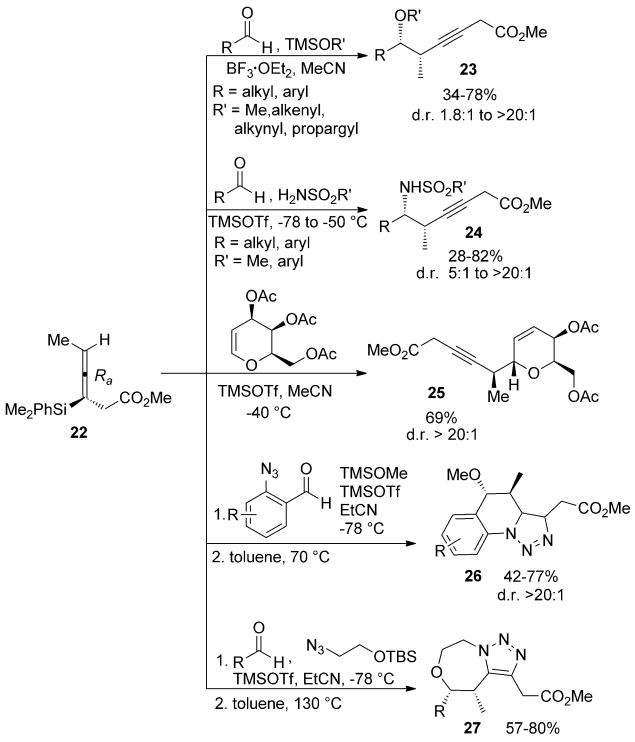
### 2.2. Allenylsilane Reagents

Allenylsilanes have emerged as an important class of reagents in organic synthesis.[31] Like their alkene variants, these allenes are good carbon nucleophiles, and add to carbonyl compounds as well as iminum and oxonium ions with stereospecific formation of functionalized alkynes.[32–34] Homopropargylic ethers, sulfonamides, and dihydrofurans are synthesized in a highly *syn* manner. Chiral allenylsilane **22** react diastereoselectively with aldehydes and silyl ethers to give *syn*-homopropargylic ethers **23**, or with aldehydes and sulfonamides to give *syn*-homopropargylic amines **24**. *syn*-




***Scheme 5.*** Natural products, whose synthesis involved the reaction of an in situ generated chiral allenylzinc reagent.

Homopropargylic ethers **23** then undergo thermally induced 1,3-dipolar cycloaddition reactions with an azide moiety or another azide compound to form fused 1,2,3-triazole ring systems **26** and **27**. Allenylsilane **22** can also undergo a $S_N2'$ substitution with an allylic acetate derivative to give a *syn*-allylic compound **25** (Scheme 6).[35] Likewise, the electro-

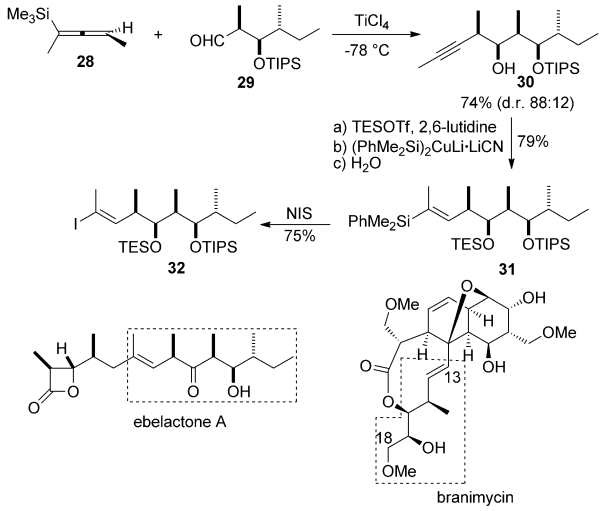



***Scheme 6.*** Reactions of chiral allenylsilanes. Tf = trifluoromethanesulfonyl.

philic fluorodesilylation of enantioenriched allenylsilanes was reported by Gouverneur and co-workers. It was found that the reaction proceeds with efficient transfer of chirality.[36]

Such Lewis acid catalyzed addition of allenylsilanes to aldehydes was applied in the synthesis of the branched structure of ebelactone A by Fleming and co-workers.[37] This reaction showed a preference for the formation of the *syn* diastereoisomer **30**. Treatment of the carbon–carbon triple bond with the silylcuprate reagent yielded the desired vinylsilane **31** with high regioselectivity. Iododesilylation gave *E* iodide **32**, which was ready for the subsequent coupling reaction. This approach represents an exquisite example in which all of the stereochemical relationships are controlled by silicon reagents. In a similar way, this strategy was also applied to the synthesis of the C13–C18 segement of branimycin, which has a high activity against *Streptomyces viridochromogenes* combined with a low toxicity (Scheme 7).[38]

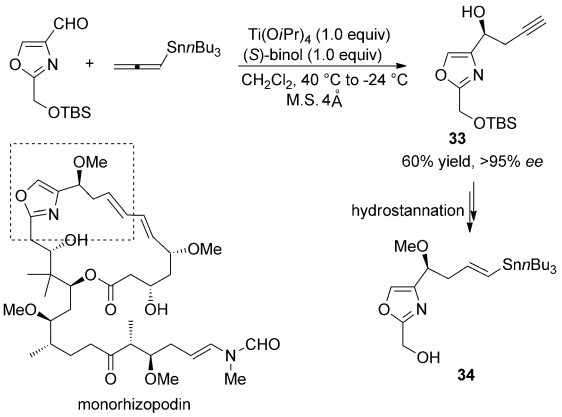



***Scheme 7.*** Synthesis of the branch structure of ebelactone A by addition of an allenylsilane to an aldehyde. TES = triethylsilyl, TIPS = triisopropylsilyl.

### 2.3. Allenyltin Reagents

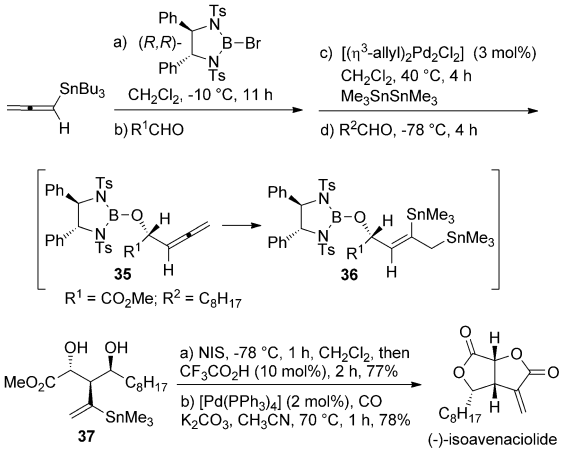
In their recent approach to monorhizopodin, which exhibits potent antitumor activity, Nicolaou et al. utilized a stoichiometric amount of a chiral Ti(O*i*Pr)$_4$/(*S*)-binol complex to promote the addition of allenyl(tri-*n*-butyl)stannane to an aldehyde. This provided the chiral homopropargyl product **33** in 60% yield and greater than 95% *ee*. Regio- and stereoselective hydrostannation of the terminal acetylene unit under palladium catalysis afforded vinyl stannane **34**, which was later used to construct the macrocycle of the natural product (Scheme 8).[39]

A sequential allylic transfer reaction for the stereoselective synthesis of 2-(1-stannylvinyl)-1,3-diols was investigated by Yu et al., and subsequently applied to the synthesis of (−)-avenaciolide and (−)-isoavenaciolide (Scheme 9).[40] Their synthetic strategy involved propargylboration with an aldehyde to yield an allenic species **35**, distannation of the allene




***Scheme 8.*** The use of chiral a Ti(O*i*Pr)$_4$/(*S*)-binol complex to promote the addition of allenyl(tri-*n*-butyl)stannane to an aldehyde in the total synthesis of monorhizopodin. Binol = 2,2'-dihydroxy-1,1'-binaphthyl, TBS = *tert*-butyldimethylsilyl.

moiety to form the allylic tin reagent **36**. An allylic transfer process with a second aldehyde, mediated by the tethered boronyl group, yielded 2-(1-stannylvinyl)-1,3-diol **37**. Treatment of **37** with NIS followed by addition of $CF_3CO_2H$ (10 mol%) at −78°C resulted in the formation of a lactone with a vinyl iodide substituent in 77% yield, which was subjected to modified Stille coupling conditions to complete the synthesis of (−)-isoavenaciolide. (−)-Avenaciolide could be synthesized starting from the enantiomer of the corresponding 2-(1-stannylvinyl)-1,3-diol in a similar way.

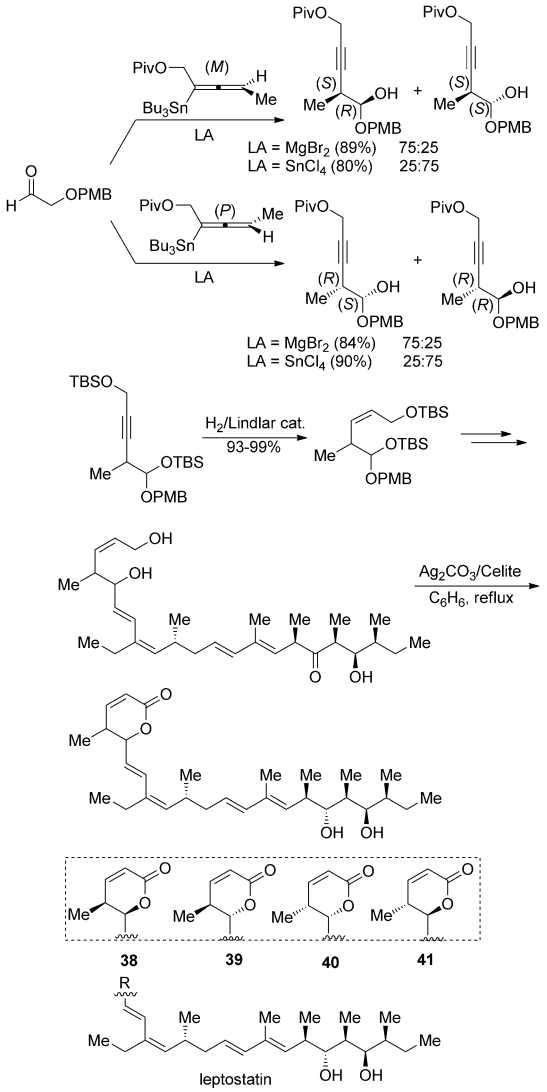



***Scheme 9.*** Synthesis of (−)-isoavenaciolide by a sequential allylic transfer reaction. NIS = *N*-iodosuccinimide.

Marshall et al. completed the syntheseis of leptostatins **38**–**41** by utilizing Lewis acid catalyzed addition of chiral allenylstannane to an aldehyde (Scheme 10).[41] The four precursors of the pyranone segment were each obtained in a 3:1 ratio by applying $MgBr_2$ or $SnCl_4$ as a promoter with a chiral *M*- or *P*-allenylstannane. The *syn* and *anti* adducts were not separable at this stage. However, the isomeric diols generated from the pivalic ester group by reaction with

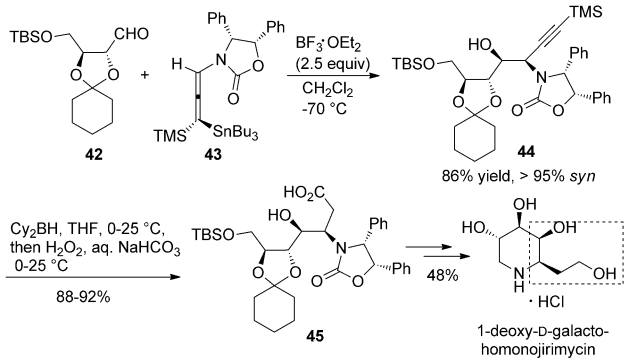
DIBAL-H were readily separated by flash chromatography. Lindlar hydrogenation afforded the *Z* alkenes in high yields. After attachment of the acyclic polyketide segment, the conversion of the diols into a pyranone ring was realized by means of Fetizon's reagent.




***Scheme 10.*** Synthesis of leptostatins **38**–**41** by using a chiral allenylstannane. LA = Lewis acid.

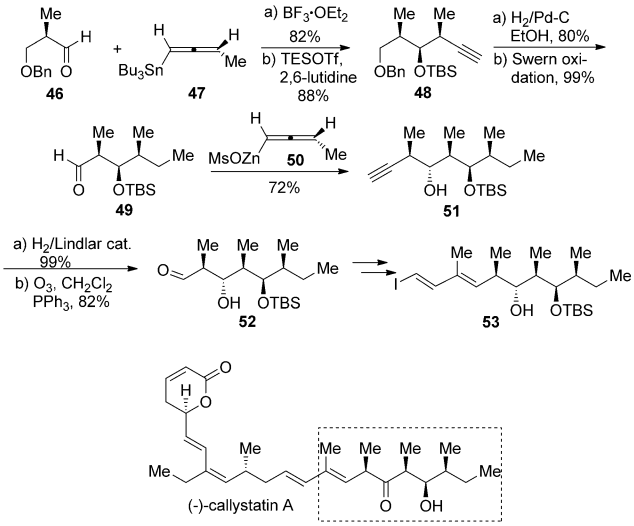
Achmatowicz and Hegedus synthesized 1-deoxy-D-galactohomonojirimycin by using the addition of optically pure allenylstannane **43** to L-lactate-derived aldehyde **42** as the key step. The protected aminotetraol **44** was produced in 86% yield with greater than 95% *syn* selectivity; its absolute configuration was confirmed by X-ray crystallography. Hydroboration/oxidation of the carbon–carbon triple bond gave carboxylic acid **45** in an excellent yield, which was then converted into 1-deoxy-D-galactohomonojirimycin (Scheme 11).[42]

An iterative synthesis of the polypropionate segment of (−)-callystatin A has been developed by Marshall and




***Scheme 11.*** Synthesis of 1-deoxy-D-galactohomonojirimycin. Cy = cyclohexyl.

Bourbeau which involves $BF_3{\cdot}OEt_2$-promoted addition of *M*-allenylstannane **47** to *R* aldehyde **46** to give *syn*,*syn* adduct **48**. Addition of the *M*-allenylzinc reagent **50** to aldehyde **49** afforded the expected *anti* adduct **51** in 72% yield as a single diastereoisomer. Partial hydrogenation of the carbon–carbon triple bond and ozonolysis of the resulting olefin led to aldehyde **52**. This product was further manipulated to obtain the necessary vinyl iodide **53**, which coupled with another segment under Suzuki-coupling conditions to finish (−)-callystatin A (Scheme 12).[43]

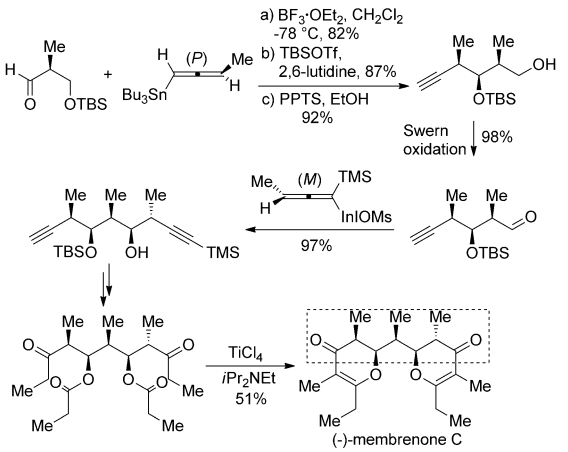



***Scheme 12.*** Synthesis of the polypropionate segment of (−)-callystatin A. Bn = benzyl.

In a similar way, the four stereocenters in the polypropionate marine defense substance (−)-membrenone C were introduced by a sequence involving the addition of chiral allenylmetal reagents to aldehydes, which was followed by a double intramolecular hydrosilylation/oxidation process to install the β-hydroxy ketone subunits, and a double intramolecular aldol reaction to finalize the total synthesis (Scheme 13).[44]

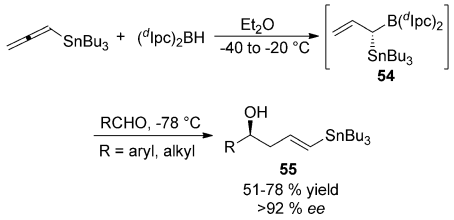
Diastereoselective hydroboration of allenylstannane with diisopinocampheylborane [($^d$Ipc)$_2$BH] at −40 to −20 °C




***Scheme 13.*** Synthesis of the four stereocenters of (−)-membrenone C by sequential addition of chiral allenyltin and -indium reagents. PPTS = pyridinium *p*-toluenesulfonate.

followed by a kinetically controlled highly diastereoselective 1,3-boratropic shift afforded chiral allylborane **54**. A subsequent allylboration reaction with aldehydes provides *E*-configured *δ*-stannyl homoallylic alcohols **55** in good yields and excellent enantioselectivity (Scheme 14).[45]

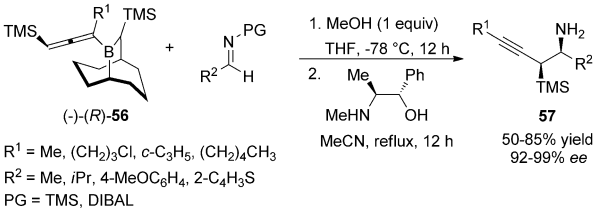



***Scheme 14.*** Hydroboration of 1,2-propadienylstanne and the allylation with aldehydes.

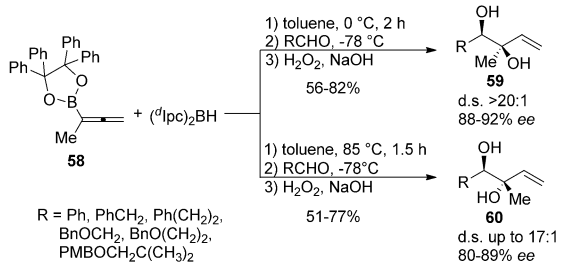
### 2.4. Allenylboranes

Allenylborane reagents react with electrophiles, such as aldehydes, imines, and related compounds to give homopropargylic derivatives.[46] Recently, a new class of chiral allenylborane reagents was developed by Soderquist and coworkers. In particular, the more bulky *B*-allenyl-10-TMS-9-BBDs **56** (BBD = borabicyclo[3.3.2]decane) underwent addition to imines in a highly selective process (92–99% *ee*), which led to the synthesis of the homopropargylic amines **57**. This was the case even for the more challenging substrates such as acetaldimine. These reagents could also be transformed into the corresponding optically pure allenylsilanes through simple protonolysis (Scheme 15).[47–49]

The hydroboration of 1,2-butadien-3-yl boronate **58** with ($^d$Ipc)$_2$BH followed by allylboration of an aldehyde and oxidative workup gave the 1,2-*syn*- or 1,2-*anti*-diol diastereomers **59** or **60**; which diastereomer was obtained could be controlled by the hydroboration conditions (Scheme 16).[50,51]

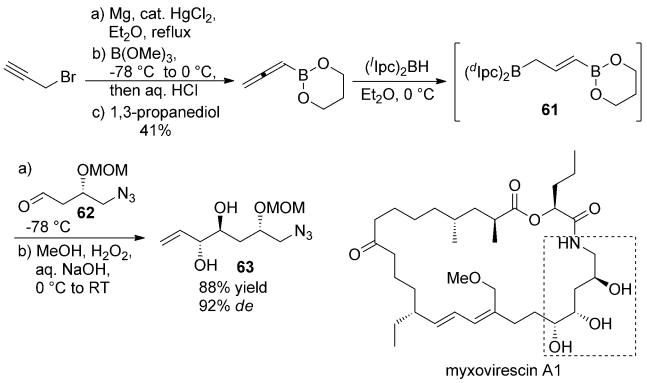



***Scheme 15.*** Diastereoselective propargylation of imines. DIBAL = diisobutylaluminum hydride.




***Scheme 16.*** Hydroboration of allenylboronate and subsequent allylation with an aldehyde.

In Fürstner's approach to the antibiotic macrolide myxovirescin A1, one of the segments was prepared from chiral aldehyde **62** by means of Brown's *anti*-selective allylboration. Thus, addition of the substituted allylborane **61**, generated from allenylboronate and ($^l$Ipc)$_2$BH, delivered the required adduct **63** in 88% yield and 92% *de* (Scheme 17).[52]




***Scheme 17.*** Application of Brown's *anti*-selective allyboration in the synthesis of myxovirescin A1.

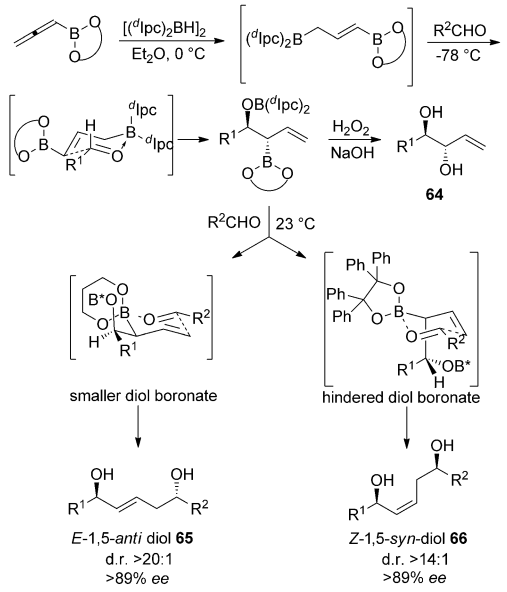
Based on such a protocol, Flamme and Roush exploited a double allylboration sequence for the synthesis of 1,5-diols enantio- and diastereoselectively by subjecting Brown's γ-borylallylboronates sequentially to two different aldehydes.[53] The steric bulkiness of the boronate moiety determines the outcome of the second allylboration: with a smaller boronate, the reaction is presumed to proceed through a chair-equatorial transition state to afford *E*-1,5-*anti* diol **65**, while the bulkier boronate prefers a transition state with the

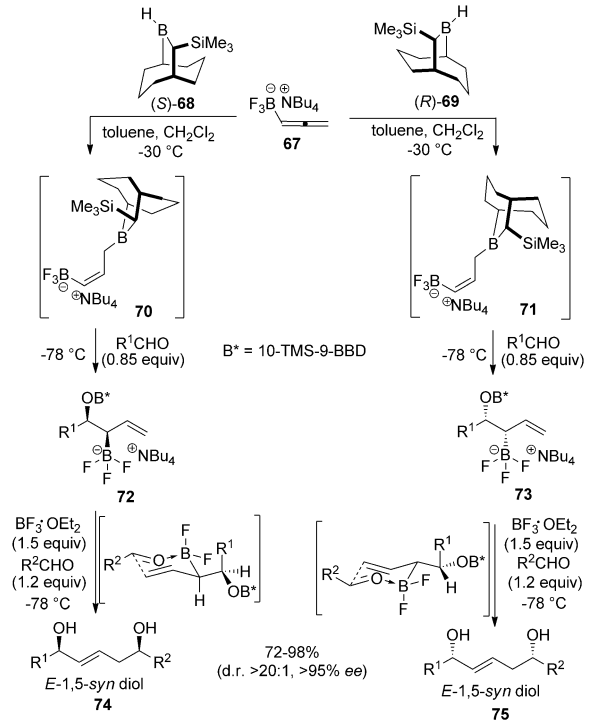
substituent α to the boron atom in an axial orientation, and results in the formation of *Z*-1,5-*syn* diol **66**. The complementary methods afford 1,5-*anti* adducts (in a ratio of > 20:1) and 1,5-*syn* adducts (in a ratio of > 14:1); both variants showed high enantioselectivity (> 89 % *ee*; Scheme 18).

A new double allylboration reagent for the enantio- and diastereoselective synthesis of *E*-1,5-*syn* diols was further developed by the Roush research group (Scheme 19).[54] The requisite *Z*-configured reagents **70** and **71** were prepared by hydroboration of allenylboron difluoride with the Soderquist borane, 10-TMS-9-borabicyclo[3.3.2]decane [(*R*/*S*)-10-TMS-9-BBD-H], at low temperature (kinetically controlled). The smaller difluoroborane moiety helps maintain a transition state with the substituent α to the boron atom in an equatorial orientation. Both enantiomers of the *E*-1,5-diol, **74** and **75**, can be obtained by starting with each enantiomer of the Soderquist borane. The *E*-1,5-*syn* diols are usually obtained in 72–98 % yield and with excellent enantio- and diastereoselectivity (> 95 % *ee*, d.r. > 20:1, and *E*/*Z* > 20:1).

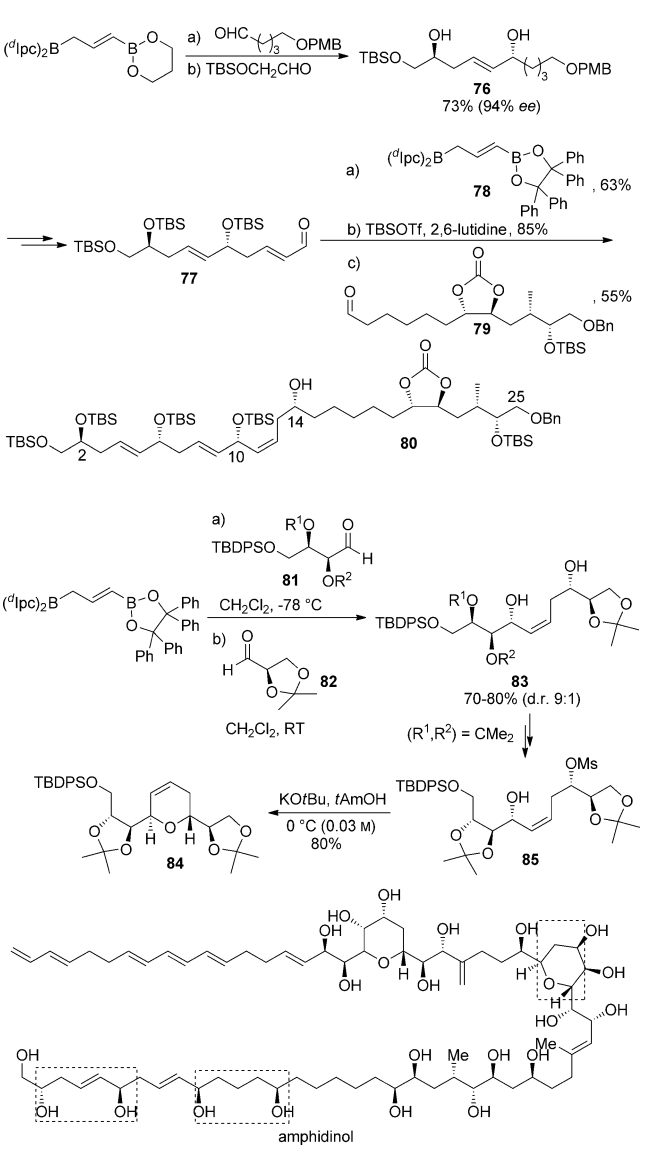
The potential of Roush's modified double allylboration sequence was fully demonstrated in the enantioselective total synthesis of amphidinol, in which this protocol was employed three times to construct the two 1,5-diol segments and the tetrahydropyran segment (Scheme 20). In the C1–C15 segment, the Brown borylallylborane reagent coupled with two




***Scheme 18.*** Enantio- and diastereoselective synthesis of 1,5-diols by double allylboration.




***Scheme 19.*** Enantio- and diastereoselective synthesis of *E*-1,5-syn diols by double allylboration.

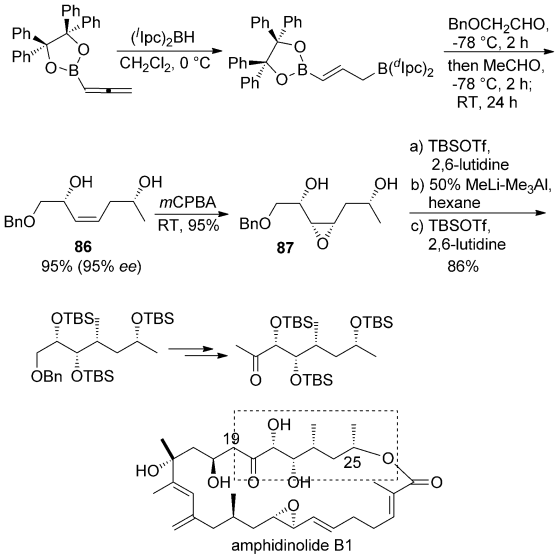



***Scheme 20.*** Application of double allylboration in the synthesis of amphidinol. TBDPS = *tert*-butyldiphenylsilyl.

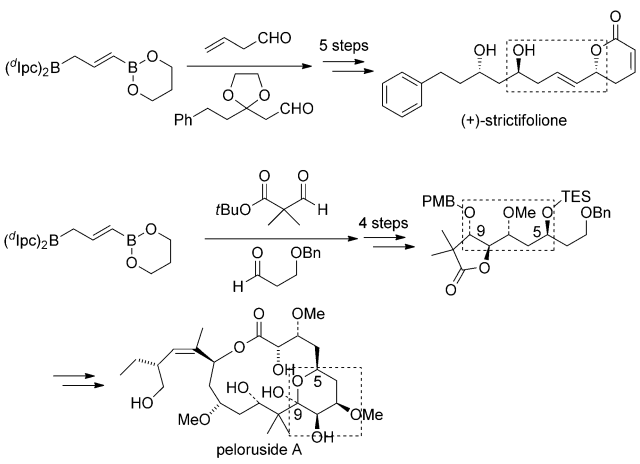
  

aldehydes to furnish *E*-1,5-*anti* diol in 73% yield and with good enantioselectivity. After several steps, the resulting α,β-unsaturated aldehyde underwent an allylboration with a bulky boronate moiety to establish the *syn* relationship between C10 and C14. The tetrahydropyran ring moiety was also synthesized by utilizing the double allylboration sequence and the base-mediated cyclization of the resulting hydroxy mesylate.[55,56]

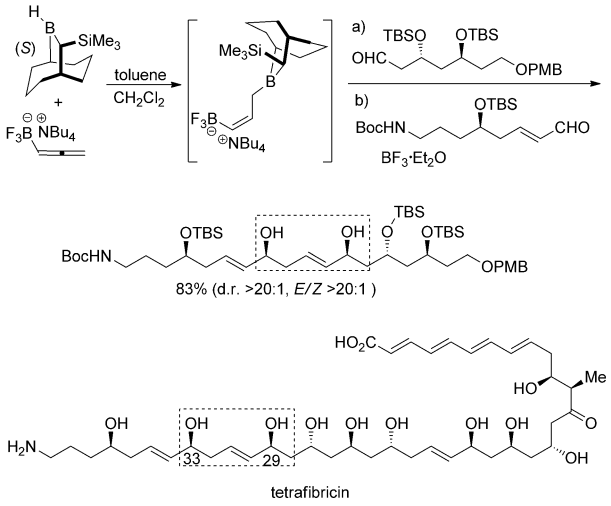
This double allylboration reaction was utilized in the stereoselective synthesis of the C19–C25 fragment of amphidinolide B1 by Crews and co-workers (Scheme 21).[57] Their synthetic strategy relied on an enantioselective/diastereoselective double allylboration to prepare 1,5-*syn*-diol **86**. Epoxidation with *m*CPBA furnished epoxy alcohol **87** (in an 8:1 diastereoisomeric ratio), which underwent a regioselective and stereoselective ring opening with $Me_3Al$ in refluxing hexane. Further straightforward manipulations of the functional groups provided the desired fragment.




***Scheme 21.*** Synthesis of the C19–C25 fragment of amphidinolide B1 by double allylboration. *m*CPBA = *meta*-chloroperbenzoic acid.




***Scheme 22.*** Total synthesis of (+)-strictifolione and the synthesis of the C5–C9 fragment of peloruside A by double allylboration.




***Scheme 23.*** Syntheses of a tetrafibricin fragment by double allylboration.

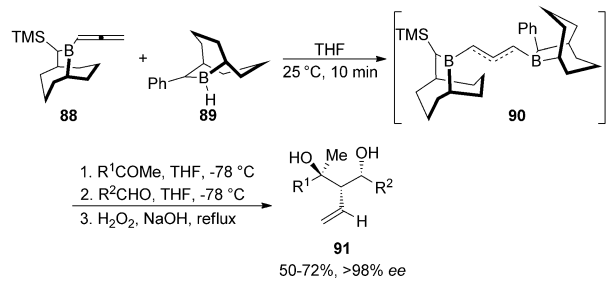
Another simple polyol natural product that was made by means of double allylboration is (+)-strictifolione, which was synthesized in five steps with an overall yield of 23% from readily available 3-butenal (Scheme 22).[58] The C1–C11 fragment of peloruside A[59] and the C1–C19 fragment of tetrafibricin[60] were also constructed by such a stereoselective double allylboration.

The newly defined double allylboration was also employed by Roush and co-workers in the synthesis of the C23–C40 tetrafibricin fragment, which contains the typical *E*-1,5-*syn*-diol structure (Scheme 23).[54] By using the double allylboration reagent derived from (*S*)-10-TMS-9-BBD-H, the desired diastereomer was generated in 83% yield with >20:1 diastereoselectivity and an *E*/*Z* selectivity of >20:1 in a one-pot convergent coupling of two aldehydes.

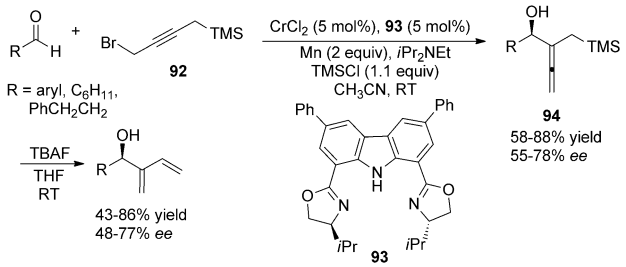
Furthermore, Soderquist and co-workers further prepared a new double allylating reagent by hydroboration of allenylborane **88** with the 10-Ph-9-BBD-H reagent **89**, which gives a 60:40 mixture of regioisomeric *trans*-1,3-diborylpropene adduct **90**. Sequential addition of ketones and aldehydes then resulted in the creation of three stereogenic centers in a single operation, with the final diols **91** having excellent enantiopurity (Scheme 24).[61]

### 2.5. Allenylchromium Reagents

Instead of homopropargylic alcohols, optically active 2-(trimethylsilylmethyl)allenyl-2,3-allenols **94** were efficiently synthesized from aldehydes and (4-bromobut-2-ynyl)trimethylsilane **92** in the presence of a catalytic amount of $CrCl_2$ and tridentate carbazole ligand **93** (Scheme 25).[62a] The reaction could be extended to the synthsis of homoallenols by using allenyl bromide.[62b]



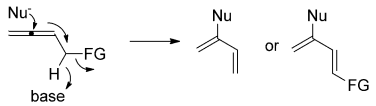

***Scheme 24.*** Diastereoselective synthesis of a chiral 2-vinyl-1,3-diol.




***Scheme 25.*** Allenylation of aldehydes with $CrCl_2$.

## 3. Reactions of Allenes with an α-Functional Group

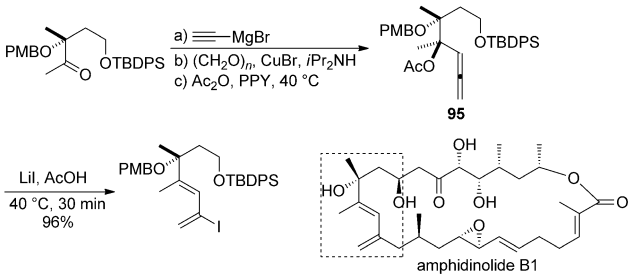
It has been found that allenes with an α-functional group can undergo isomerization or an addition/elimination sequence in the presence of bases, acids, or nucleophiles to give 1,3-coujugated dienes (Scheme 26).[63]




***Scheme 26.*** SN2′ reaction or isomerization of the allenic skeleton to 1,3-dienes. Nu = nucleophile, FG = functional group.

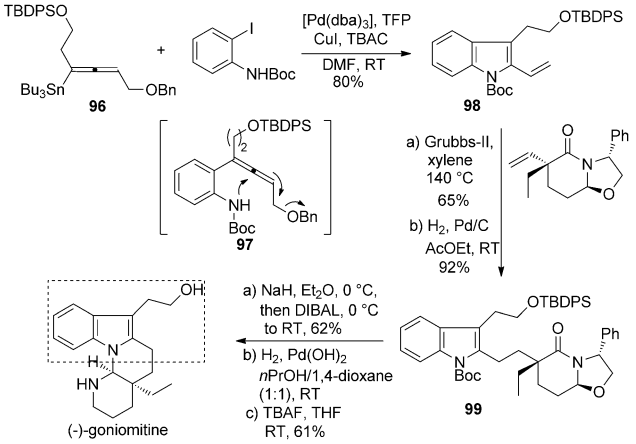
In the synthetic strategy by Crews and co-workers for the synthesis of amphidinolide B1,[64] the requisite 1,3-diene iodide was synthesized by an iodide-mediated SN2′ reaction.[63a] The allenic acetate was prepared by a three-step protocol. The chelation-controlled addition of ethynylmagnesium bromide to the ketone, followed by homologatation with $(CH_2O)_n$/$iPr_2NH$/CuBr gave the allenol.[65] Acetylation was achieved by using $Ac_2O$/4-pyrrolidinopyridine (Scheme 27). Treatment of the allenic acetate with acetic acid and lithium iodide produced the stereodefined *E*-1,3-diene iodide in an excellent yield.[63] The exclusive formation of *E*-1,3-diene was rationalized by an *anti*-$S_N2'$ attack of the iodide on the central carbon atom of the allene of **95** to afford an acetate with a conformation that has less 1,3-allylic strain. The diene structure in amphidinolides G and H could also be prepared in a similar way.[66]

Mukai et al. applied a cyclic variant of the reaction in the highly stereoselective synthesis of (−)-goniomitine. The




***Scheme 27.*** Synthesis of a diene fragment for amphidinolide B1. PPY = 4-pyrrolidinopyridine.

precursor **97** was obtained by the Stille coupling of an *N*-acyl-2-iodoaniline with 1-(tributylstannyl)-1-substituted allenes. The natural product was obtained in 10 steps starting from commercially available 3-butyn-1-ol (Scheme 28).[67,68]

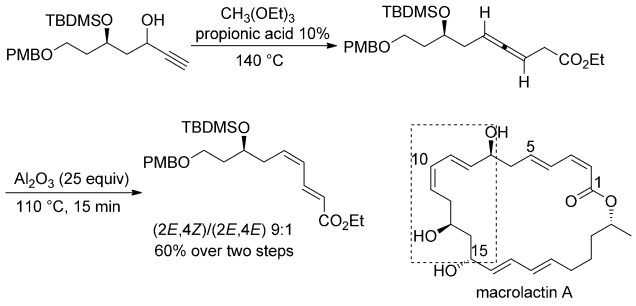



***Scheme 28.*** Total synthesis of (−)-goniomitine from a 2-vinylindole derivative. dba = *trans*,*trans*-dibenzylideneacetone, TBAC = tetrabutylammonium cyanoborohydride, TBAF = tetra(*n*-butyl)ammonium fluoride, TFP = tris(2-furyl)phosphine.

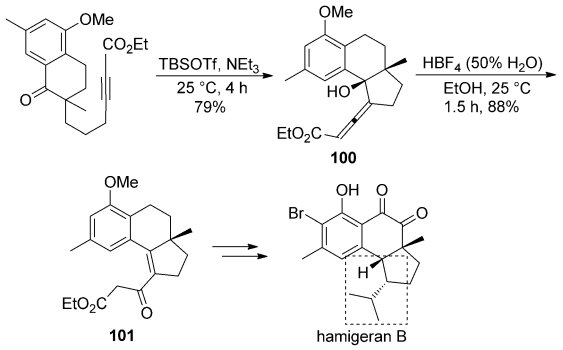
A stereoselective synthesis of the *E*,*Z* diene unit in macrolactin A has been achieved by using an allene→1,3-diene isomerization sequence (Scheme 29).[69] Treatment of propargyl alcohol with ethyl orthoacetate/propionic acid at 140 °C gave an allene, which could be used directly for an isomerization conducted at 110 °C with alumina for 15 min. This afforded the conjugated diene in 60% yield with a d.r. of 9:1.

Miesch et al. reported the total synthesis of hamigeran B by utilizing an intramolecular alkynylogous Mukaiyama aldol reaction[4i] as the key step to form the ring junction (Scheme 30).[70] The $HBF_4$-promoted acidic hydrolysis transformed the allene moiety in **100** into the α,β-unsaturated keto moiety in **101**, which was then converted into hamigeran B in a multistep sequence.




***Scheme 29.*** Synthesis of the diene fragment in macrolactin A.

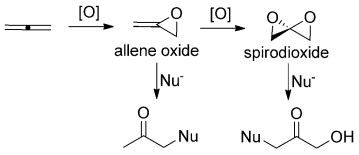



***Scheme 30.*** Allene-enone transformation in the synthesis of hamigeran B.

## 4. Epoxidations

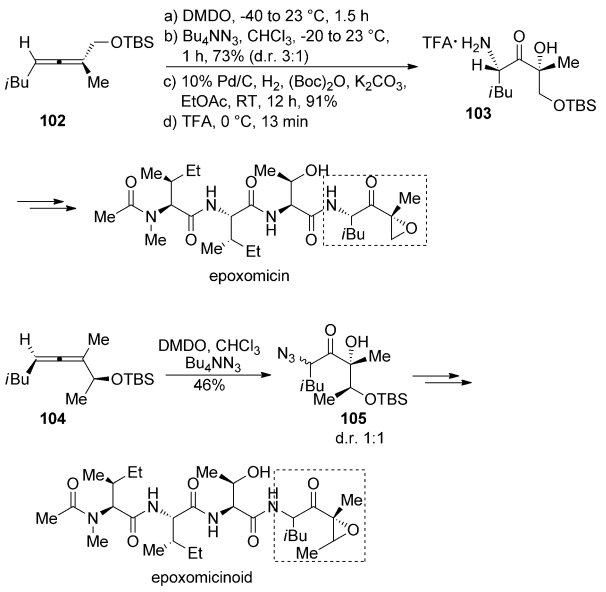
The epoxidation of allenes can, depending on the reaction conditions, proceed via allene oxide to the spirodioxide (Scheme 31).[71] Dimethydioxirane (DMDO) is usually the reagent of choice since it permits clean sequential epoxidation of allenes to isolable spirodioxides under neutral conditions in the absence of nucleophiles. The initial epoxidation of DMDO occurred at the more-substituted electron-rich internal double bond,[72] with the stereochemistry being controlled by attack of the epoxidizing agent from the π face of the less sterically hindered double bond.[73] The resulting allene oxide intermediate undergoes a subsequent rapid, often stereochemically less-discriminating, epoxidation to afford a spirodioxide. Both allene oxides and spirodioxides readily react in an intra- or intermolecular manner with a wide range of nucleophiles to give stable acyclic ketones with the nucleophiles as α substituents. Ring opening of substituted spirodioxides by nucleophiles in the absence of acid generally takes place at the less-substituted epoxide terminus with inversion of the configuration.[74] For intramolecular nucleophilic process, for example of a hydroxy group, the regiochemistry is largely controlled by the relative position of the hydroxy group, so as to afford the more-stable five- and six-membered heterocyclic rings.[73] This reaction sequence represents a very good example that exquisitely maneouvers the three carbon atoms of the allene into the synthesis of a complex molecule with multiple different functionalities.[75]

The synthesis of the proteasome inhibitor epoxomicin highlights the practical utility of this epoxidation and




***Scheme 31.*** Epoxidation of allenes and ring opening by a nucleophile.

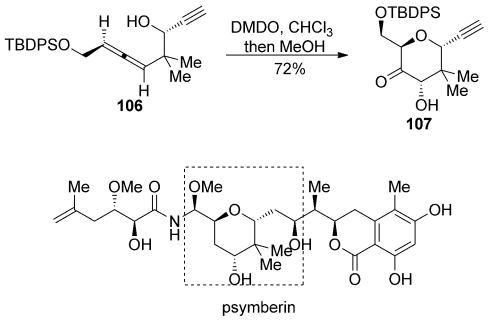
nucleophilic ring-opening sequence (Scheme 32).[76] An allene derived from isovaleraldehyde underwent oxidation with DMDO followed by addition of an azide and reduction of the unstable azidoketone to furnish an α-amino-α′-hydroxy ketone with moderate diastereoselectivity. Peptide condensation followed by transformation of the tertiary alcohol into the requisite epoxide gave epoxomicin. This sequence proceeded in very good overall yield starting from allene **102** (33%, nine steps). This spirodiepoxide-based strategy was further applied to the synthesis of analogues of epoxomicin.[76] Allene **104** underwent epoxidation and subsequent ring-opening with azide to give two separable isomers of **105** in a 1:1 ratio, which were used for the synthesis of epoxomicinoids.




***Scheme 32.*** Synthesis of epoxomicin and its analogue by a sequence of epoxidation and nucleophilic ring opening. DMDO = dimethyldioxirane, TFA = trifluoroacetic acid.

The diastereoselective synthesis of psymberin has also been accomplished by using the spirodiepoxide-based strategy (Scheme 33).[77] The epoxidation of allene by DMDO **107**, followed by the addition of methanol gave the cyclized product dihydropyranone, which was further transformed into a known intermediate in the synthesis of psymberin. The addition of methanol is necessary for the formation of the desired *trans*-substituted pyran. It was assumed that protic solvent destroyed the hydrogen bond between the hydroxy group and the adjacent epoxide moiety, thus favoring the

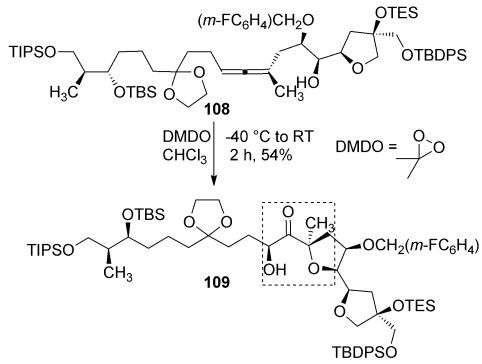
  




***Scheme 33.*** Synthesis of the tetrahydropyran moiety of psymberin.

formation of the conformer preferred for generation of the *trans* isomer.

A spirodiepoxide was utilized in the synthesis of the C1–C19 sector **109** of pectenotoxin (Scheme 34).[78] Conversion of the allene moiety **108** into spirodiepoxide by DMDO followed by an intramolecular nucleophilic attack by the hydroxy group afforded the targeted fragment **109** as a single diastereoisomer.

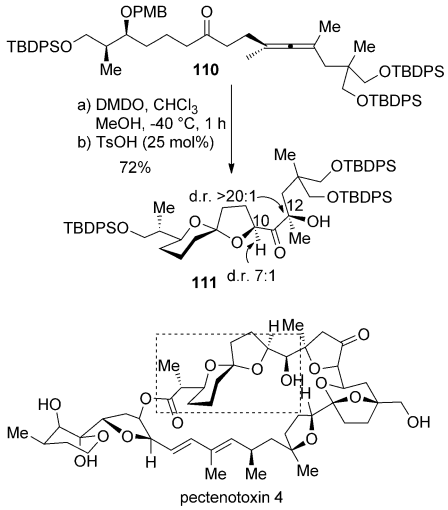



***Scheme 34.*** Synthesis of the C1–C19 fragment of pectenotoxin.

The spirocyclic AB ring system of pectenotoxin 4 has been accessed using a spirodiepoxide as a key intermediate (Scheme 35).[79] The bisepoxide derived from **110** was intercepted by the pendant ketone to generate an oxocarbenium ion, which was then captured by the hydroxy group (obtained by PMB cleavage) to give a spirocycle featuring the AB ring system of pectenotoxin 4. The diastereoselectivities for both oxidations were good, >20:1 for C12 with the hydroxy group and 7:1 for C10 of the tetrahydrofuran ring. This method was applied to the synthesis of precursors toward erythromycin[80] and epicitreodiol.[81]

## 5. Transition-Metal-Catalyzed Additions of Arylboronic Acids to Allenes[4h]

In 2003, our research group and Oh et al. independently reported the highly regio- and stereoselective palladium-catalyzed hydroarylation or hydroalkenylation of allenes with




***Scheme 35.*** Synthesis of the AB ring system of pectenotoxin 4.

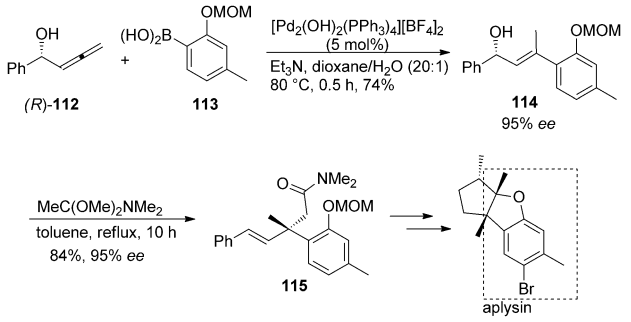
organic boronic acids to give tri- or tetrasubstituted alkenes.[82] This method tolerates a substrate with high substituent loading and a variety of substituents. ESI-FTMS studies confirmed that the reaction might proceed by oxidative addition of AcOH and $Pd^0$, hydropalladation of the less sterically hindered terminal C=C bond in the allene moiety, transfer of the aryl group, and reductive elimination to yield the final product and regenerate the $Pd^0$.[82b] Yoshida et al. later disclosed that the selectivity of the addition of arylboronic acids to allenes could be altered by the choice of the transition metal and base. In contrast to the formation of *endo* olefins as products in the reactions with a hydroxopalladium complex, *exo* olefins were the predominant products in the reaction with platinum[83] or rhodium complexes.[84] The observed *E* configuration for the double bond in the *endo* olefins resulted form the attack of the organoboronic acids on the less hinderic side of the allene. The use of a nickel catalyst in the addition reaction of arylboronates to allenes results in a quite different regioselectivity: the aryl groups selectively add to the terminal carbon atom of the allenes.[85]

In the formal synthesis of aplysin by Yoshida et al., the palladium-catalyzed addition of arylboronic acid **113** to allenol (*R*)-**112** was combined with a Claisen-type rearrangement to access stereospecifically the amide **115** with a quaternary carbon center in 84% yield and 95% *ee*. This amide was then subjected to further manipulations to generate aplysin (Scheme 36).[86]

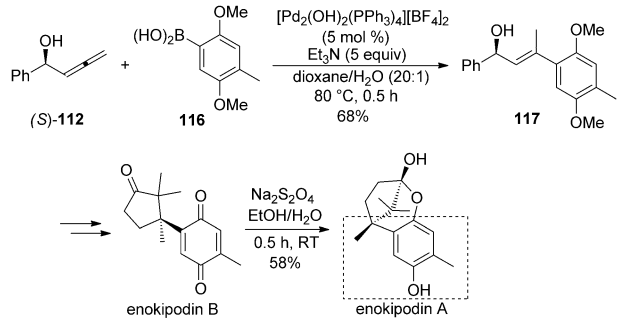
This palladium-catalyzed coupling reaction was further applied to the total synthesis of enokipodins A and B (Scheme 37).[87] In a similar way, the quaternary carbon center was constructed enantiospecifically by a sequence involving a palladium-catalyzed addition of arylboronic acid **116** to allenol (*S*)-**112** followed by an Eschenmoser–Claisen rearrangement.

The regiocontrolled addition of arylboronic acid **118** to allene **119** using the platinum catalyst led to the formation of the *exo* olefin **120** in high yields and regioselectivity (>20:1). Shishido and co-workers applied this method as the starting

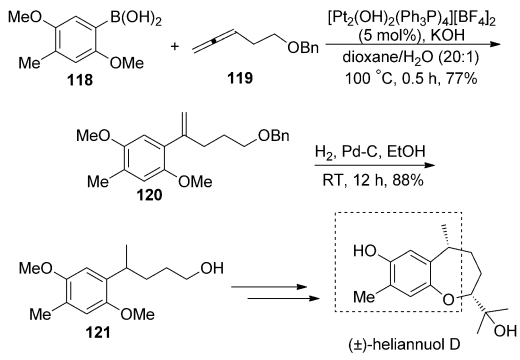



***Scheme 36.*** Synthesis of the quaternary carbon center in aplysin.



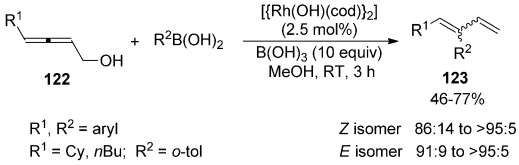

***Scheme 37.*** Synthesis of the quaternary carbon center in enokipodins A and B.

step in the total synthesis of (±)-heliannuol D, which was followed by catalytic hydrogenation to give the alcohol **121** in 88% yield. This intermediate was then transformed in several steps into the target. In total, the total synthesis was achieved in 11 steps and 6.9% overall yield from the arylboronic acid **118** (Scheme 38).[88]




***Scheme 38.*** Synthesis of (±)-heliannuol D starting from a platinum-catalyzed addition of arylboronic acids to allenes.

In contrast, the reaction of 2,3-allenol **122** with boronic acids in the presence of a rhodium(I) catalyst proceeds through the regioselective addition of organorhodium(I) species across the carbon–carbon double bond of the allene moiety and subsequent elimination of $Rh^{I}$-OH to afford 1,3-dienes (Scheme 39).[89]




***Scheme 39.*** Rhodium-catalyzed reaction of organoboronic acids with 2,3-allenols. cod = cycloocta-1,5-diene.

## 6. Cyclizations[4a,c]

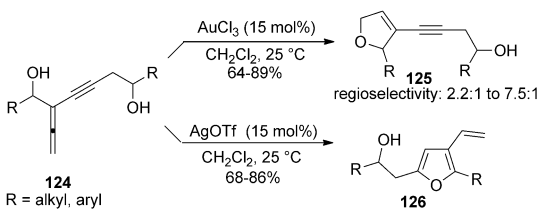
### 6.1. Transition-Metal-Catalyzed Cyclizations of Allenes with a Nucleophilic Functional Group[4d]

#### 6.1.1. Lewis Acidic Transition-Metal-Catalyzed Cycloisomerizations[4f,g,k–m,p]

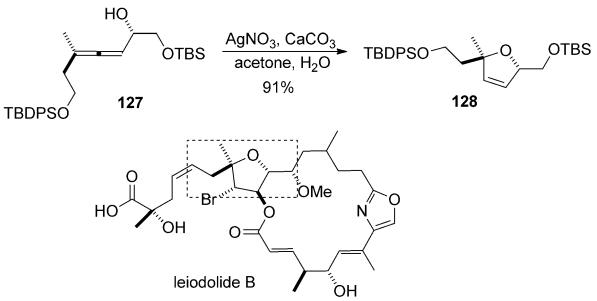
The intermolecular hydroalkoxylation of allenes in the presence of [AuCl($PPh_3$)]/AgOTf as a catalyst at ambient temperature produces primary allylic ethers, whereas the use of an NHC–gold catalyst in DMF and excess alcohol affords tertiary allylic ethers.[90] No transfer of chirality is observed in this process, which is quite different from the corresponding hydroamination process.[91] The reaction may also take place in the presence of a catalytic amount of [$AuNO_3(PPh_3)$] and $H_2SO_4$.[92] A dihydroalkoxylation reaction of allenes with platinum as the catalyst was reported to give aliphatic acetals by attack of two molecules of alcohol on the terminal carbon atom of the allene moiety.[93] When water was used as the nucleophile, the hydration of allenes in the presence of [AuCl(IPr)]/AgOTf afforded *E*-allylic alcohols efficiently.[94] The addition usually took place at the less sterically hindered C=C bond of allenes. However, DFT calculations have suggested that the tertiary allyl ether should be the kinetic product, and subsequent gold-catalyzed isomerization possibly occurs to produce the observed (and more stable) primary allylic ether.[95] Since 2001, Krause, Hoffmann-Röder, and co-workers have developed a series of gold-catalyzed cyclization reactions of highly functionalized α- or β-hydroxyallenes to afford the corresponding 2,5-dihydrofurans or dihydropyrans, respectively.[96–99] Notably, 2,5-dihydrofuran or furan derivatives **125** or **126** were produced selectively in good to excellent yields when allenyne-1,6-diols **124** were treated with gold or silver catalysts, respectively. The reason for this difference lies in the selective activation and differentiation of the double and triple bonds in allenyne-1,6-diols **124** (Scheme 40).[100]

Fürstner and co-workers used the silver-induced cyclization of chiral allenol **127** to form the polysubstituted THF rings of amphidinolide X[101] and leiodolide B.[102] The chiral information in the allene moiety was transmitted to the exigent tertiary ether site (Scheme 41).

Krause and co-workers have shown that α-hydroxyallenes[103] and other functionalized allenes[104] can be converted into five- or six-membered heterocycles with efficient axis-to-center chirality transfer by using a gold catalyst.[105] They demonstrated the power of this method with the stereoselective synthesis of three natural products bearing a 2,5-trisubstituted tetrahydrofuran ring: (2*S*,5*R*)-(+)-linalool oxide, (−)-isocyclocapitelline, and (−)-isochrysotricine

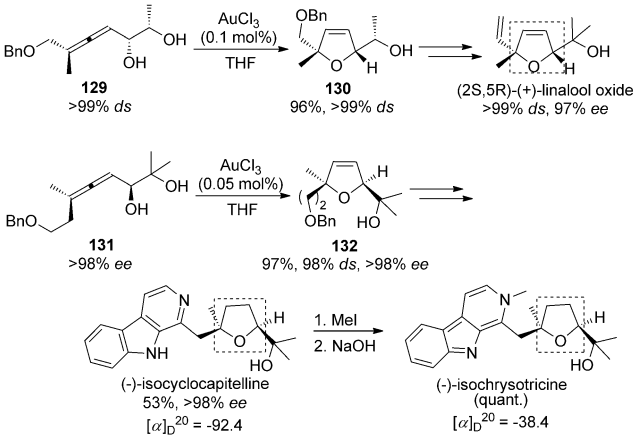



***Scheme 40.*** Selective cyclization of allenols **124**.



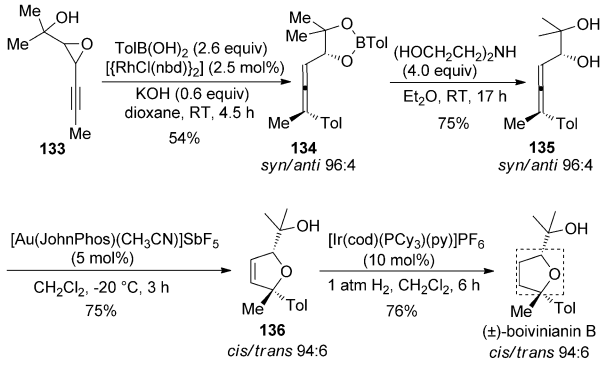

***Scheme 41.*** Silver-catalyzed cyclization of an allenol for the synthesis of leiodolide B.

(Scheme 42).[106] The key intermediate was obtained from the corresponding axially chiral α,β-dihydroxyallenes **129** and **131** with complete axis-to-center chirality transfer by the use of only 0.05–0.1 mol% of gold(III) chloride in THF. The synthesis of naturally occurring sesquiterpenoid (*R*,*R*,*R*)-bejarol and its 3*R*,5*S*,9*R* isomer was also accomplished in a similar manner by using the gold-catalyzed cyclization of β-hydroxyallene to the dihydropyran as the key step.[107]



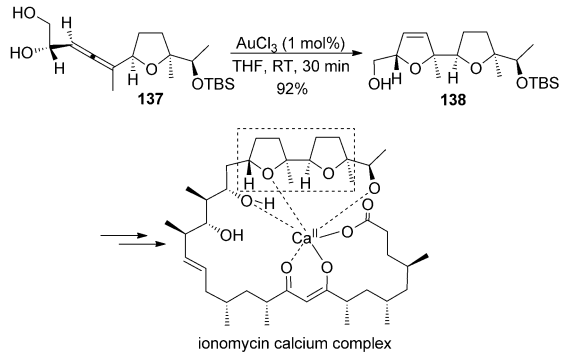

***Scheme 42.*** Synthesis of the dihydrofuran core of (2*S*,5*R*)-(+)-linalool oxide and the tetrahydrofuran core of (−)-isocyclocapitelline and (−)-isochrysotricine.

A similar synthetic strategy was used by Murakami, Krause, and co-workers to forge the 2,5-trisubstituted tetrahydrofuran ring in the total synthesis of (±)-boivinianin B (Scheme 43).[108] The reaction was conducted at −20 °C with the cationic complex [Au(JohnPhos)(CH$_3$CN)]SbF$_6$ as the catalyst, which resulted in the chiral information in **135** being transferred completely to the product. The *syn*-configured α-allenol **135** was accessed by a rhodium-catalyzed reaction of alkynyl oxirane **133** with arylboronic acid.




***Scheme 43.*** Synthesis of the tetrahydrofuran core of (+/−)-boivinianin B. nbd = norbornadiene, py = pyridine, Tol = tolyl.

Kocienski and co-workers reported the total synthesis of ionomycin and its calcium complex (Scheme 44).[109] One of the key intermediates, the dihydrofuran ring moiety **138**, was constructed by the gold-catalyzed cyclization of α-hydroxyallene **137**.

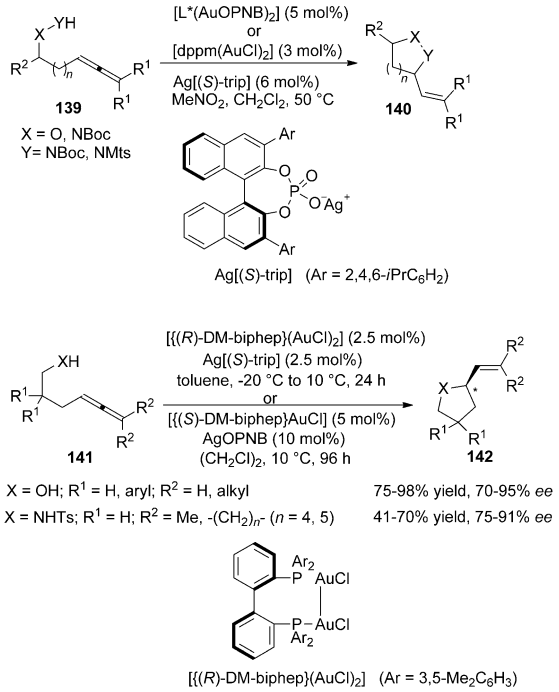



***Scheme 44.*** Synthesis of a segment for the total synthesis of ionomycin.

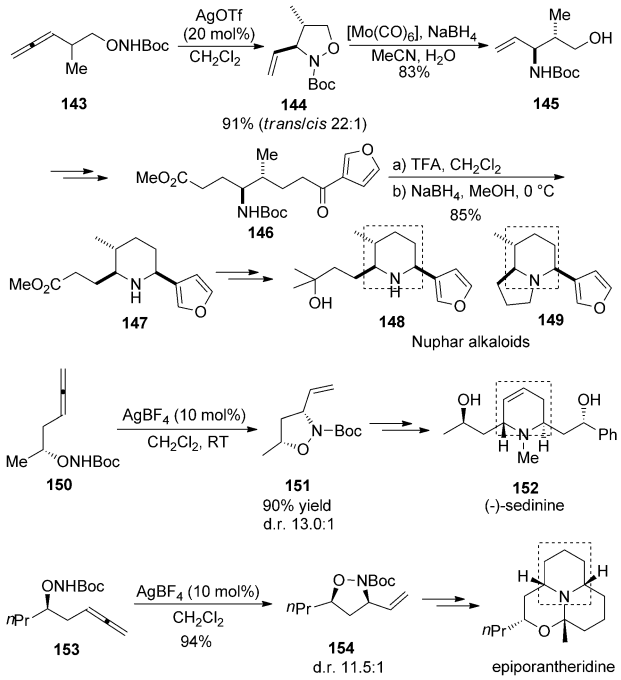
The research groups of Toste and Widenhoefer independently developed an enantioselective intramolecular hydroamination and hydroalkoxylation of allenes with hydroxyamines and hydrazines **139**. The combination of chiral ligands (L*) and the chiral anion (*S*)-trip with a gold(I) catalyst afforded chiral vinyl isoxolidines, oxazines, and pyrazolidines **140**, which thus offers the possibility to use such a reaction for the synthesis of natural products (Scheme 45). It was found that gold(I) complexes of chiral biarylphosphines are suitable catalysts for the enantioselective addition of nitrogen nucleophiles to allenes, whereas the addition of oxygen nucleophiles requires the use of chiral anions.[110] Extra examples were recently reportal by Mikami and co-workers.[111,112]

Cyclic hydroamination of allenyl amines have been used by Bates et al. to complete their formal synthesis of swainso-



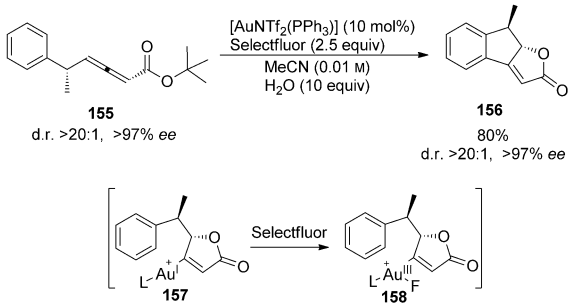

***Scheme 45.*** Enantioselective cycloisomerization of allenyl alcohols or amines. dppm = 1,1-bis(diphenylphosphanyl)methane, Mts = mesitylenesulfonyl, PNB = *para*-nitrobenzyl.




***Scheme 46.*** Silver-catalyzed cyclizations of allenic hydroxylamines for natural product syntheses.

nine.[113] In addition, they have developed an efficient strategy for the enantioselective synthesis of 1,3-amino alcohols through a gold- or silver-catalyzed cyclization of allenic hydroxylamines.[114] Recently, this method was used in the synthesis of nuphar alkaloids **148** and **149**.[115] The *trans*-isoxazolidine **144** was obtained in 91% yield and 22:1 selectivity from **143** by using silver triflate in anhydrous dichloromethane. These two isomers could be separated by chromatography after hexacarbonylmolybdenum-catalyzed cleavage of the N–O bond. The resulting 1,3-amino alcohol was elongated to an ester over several steps. Removal of the Boc group followed by reductive amination yielded the desired piperidine as a single diastereomer, which was converted into nupharamine by using a literature method (Scheme 46). The *Sedum* alkaloid (−)-sedinine[116] and epiporantheridine were synthesized by the same research group in a similar manner.[117]

In early 1990, Marshall et al. demonstrated that allenoic acids or ketones may undergo $Ag^+$- or $H^+$-catalyzed cycloisomerization.[118] Multisubstituted *N*-aminopyrroles were obtained in good to excellent yields when β-allenylhydrazones were subjected to the gold(I)-catalyzed cyclization. The reaction proceeded by the nucleophilic attack of nitrogen on the central carbon atom of the allene, followed by an intramolecular 1,2-alkyl or 1,2-aryl migration.[119] A similar Brønsted acid catalyzed reaction of 3,4-allenals with amines has also been reported.[120] Interestingly, it was recently reported that the carbonyl oxygen atom of the ester or amide group could also act directly as the nucleophile in the gold-catalyzed formation of the C–O bond.[121] Gouverneur and co-workers reported a gold-catalyzed reaction cascade involving the C–O cyclization of chiral benzyl-substituted allenoate **155** followed by intramolecular oxidative C–C formation with Selectfluor as the oxidant. Axis-to-center chirality transfer took place with no erosion of the enantiomeric excess (Scheme 47).[122] Examples of the cyclization of 2,3-allenoates with terminal alkynes and allylic halides have also been observed.[123]

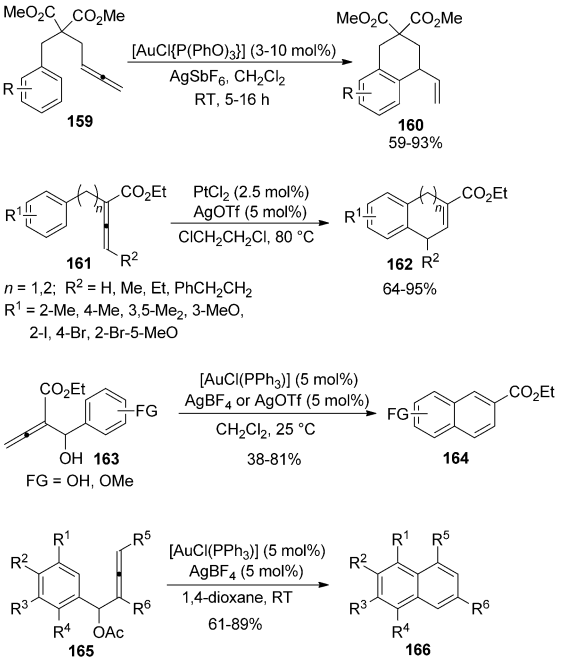



***Scheme 47.*** Gold-catalyzed cyclization of 2,3-allenoates.

Skouta and Li reported the addition of arenes to allenes in the presence of commercially available $AuCl_3$ and AgOTf.[124] The arene adds at the terminal allenic carbon atom to generate *E*-allylation products. The reactivity was greatly enhanced when the gold complex was modified with a phosphite ligand.[125] A highly selective palladium-catalyzed allylation of 1,3,5-trimethoxybenzene, anisole, or phenol in TFA with 2,3-allenoates under mild conditions afforded 4,4-diarylbut-2(*E*)-enoates in moderate yields.[126] Substituted

indoles added intermolecularly to simple allenes or allenamides in the presence of a gold(I) N-heterocyclic carbene complex[127] or $[Au(NTf_2)(PPh_3)]$ [128] to afford 3-allylindoles. The $PtCl_4$-catalyzed intermolecular reaction of indoles with β-allenols in THF at room temperature afforded indole derivatives containing a six-membered ether ring at the 3-position in moderate isolated yields.[129]

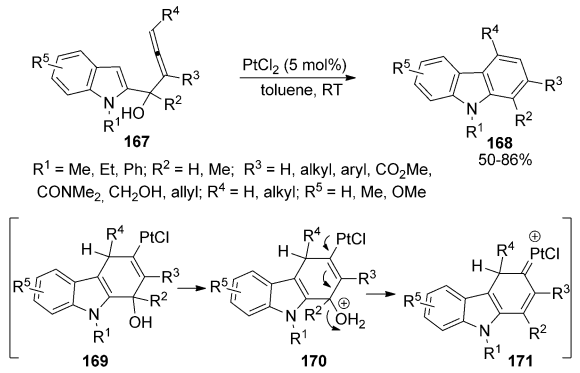
Analogous intramolecular reactions have also been developed.[130] Notably, Gagné and co-workers have identified gold complexes for the intramolecular hydroarylation of allenic arenes,[131] while Liu and Widenhoefer reported the intramolecular hydroarylation of 2-(allenyl)indoles to form substituted, polycyclic, indole derivatives.[132] The *endo* cyclization of α-hydroxyalkyl allenic esters **163** possessing strong electron-donating aryl groups cyclized to naphthalene derivatives **164** through intramolecular C-arylation in the presence of gold salts as catalysts.[133] Differently polysubstituted naphthalenes **166** have been efficiently prepared through a gold-catalyzed cyclization reaction of 1-arylalka-2,3-dienyl acetates **165** (Scheme 48).[134]



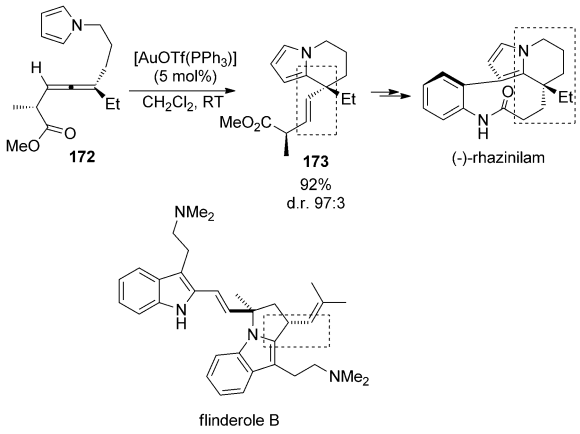

***Scheme 48.*** Transition-metal-catalyzed intramolecular hydoarylation of allenes.

The $PtCl_2$-catalyzed reaction of 1-(indol-2-yl)-2,3-allenols **167** occurred smoothly to afford differently substituted carbazoles **168** in good yields under very mild conditions via the metal carbene intermediate **171** (Scheme 49).[135] This reaction may be useful for the synthesis of naturally occurring carbazoles.

A novel strategy for the enantioselective construction of quaternary carbon atoms was applied by Nelson and co-workers in the total synthesis of (−)-rhazinilam (Scheme 50).[136a] By using a cationic gold catalyst, tetrahydroindolizine **173** was obtained in high yield and with




***Scheme 49.*** Platinum-catalyzed synthesis of carbazoles.

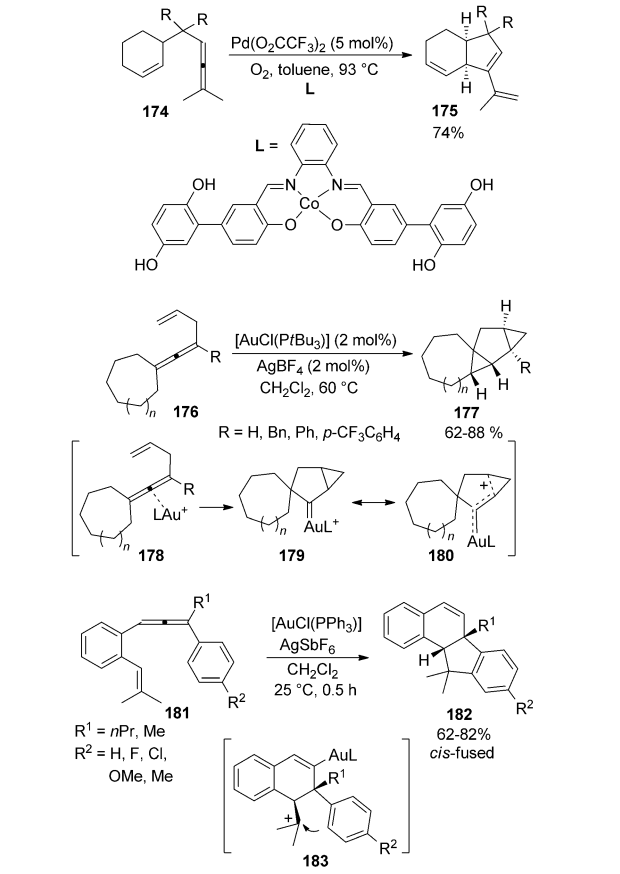



***Scheme 50.*** Gold-catalyzed annulation in the total synthesis of (−)-rhazinilam and flinderole B.

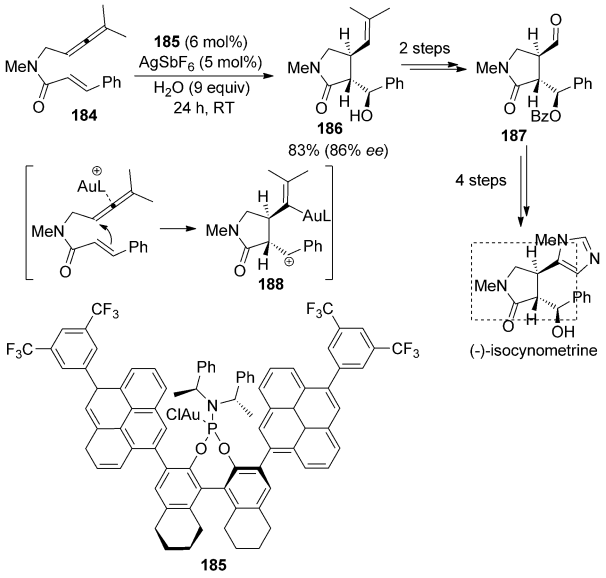
excellent chirality transfer by the nucleophilic attack of the pyrrole ring on the chiral allene in **172**. It is suggested that the coordination of the Lewis acidic gold catalyst to the carbonyl group is essential for the high diastereoselectivity. By following this method, Zeldin and Toste constructed the pyrrolidine and isobutenyl functionalities of flinderole B by a gold-catalyzed annulation of indole tethered to an allene moiety.[136b]

Bäckvall and co-workers reported the palladium(II)-catalyzed aerobic carbocyclization of enallenes[137] or dieneallenes.[138] Recently, an interesting study on a gold(I)-catalyzed sequential cycloisomerization/C($sp^3$)–H bond functionalization of 1,4-enallenes **176** to generate tetracyclotridecane derivatives **177** was reported by Horino, Toste et al. (Scheme 51).[139] The key feature of this reaction is the insertion of a cationic gold(I)-carbenoid intermediate **179** into a C($sp^3$)–H bond. Liu and co-workers reported the gold-catalyzed intramolecular annulation of 1-aryl-1-allen-6-enes **181** in $CH_2Cl_2$, which selectively yields *cis*-fused [4.3.0]carbocycles **182** via the intermediacy of **183** (Scheme 51).[140]

Gagné and co-workers reported the [{(*R*)-3,5-xylyl-binap}$(AuCl)_2$]-catalyzed enantioselective cyclization of eneallenes with moderate enantioselectivity.[141] A cyclization/alkoxylation catalyzed by a chiral gold(I)–phosphine complex was used in the formal synthesis of (−)-isocynometrine by



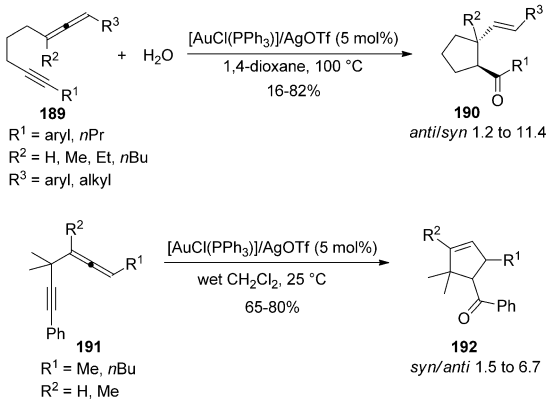

***Scheme 51.*** Intramolecular hydroalkylation of allenes with alkenes.




***Scheme 52.*** Enantioselective synthesis of (−)-isocynometrine.

Toste and co-workers for the conversion of ene-allene into *trans*-3,4-disubstituted γ-lactam (Scheme 52).[142] Exposure of ene-allene **184** to the cationic gold(I) catalyst in the presence of water yielded γ-lactam **186** in 83% yield and 86% *ee*. Conversion of the resulting secondary alcohol into its benzoyl ester and oxidative cleavage of the carbon–carbon double bond with ozone gave aldehyde **187** in 80% yield, which could then be used in the synthesis of (−)-isocynometrine according to a literature procedure. The use of AuI complex **185** with a bulky monodentate phosphorus ligand was essential for achieving the high diastereo- and enantioselectivity. The reaction proceded via a carbocationic intermediate **188**, which was trapped by water.

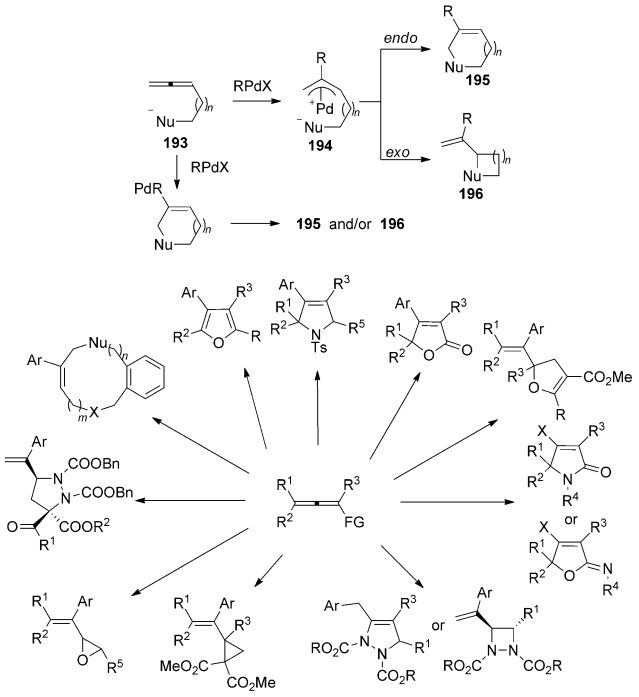
The metal-catalyzed cycloisomerizations and nucleophilic carbocyclizations of allenynes are usually mediated by π-alkyne species that form stable allylcation intermediates through an *exo* or *endo* attack of the central allene carbon atom on the π-alkyne (Scheme 53).[143] In the [AuCl(PPh$_3$)]/AgOTf-catalyzed hydrative carbocyclization of 1,5- and 1,7-allenynes **189** and **191**, Liu and co-workers found that hydration occurred regioselectively at the outer C≡C carbon atom.[144] They proposed on the basis of the chirality transfer of allenyne substrates, control experiments, and theoretical calculations that this hydrative carbocyclization proceeds through an initial π-allene complex with a small energy barrier.




***Scheme 53.*** Intramolecular hydroalkylation of allenes with alkynes.

### 6.1.2. *Cyclizations in the Presence of Organic Halides or HX*

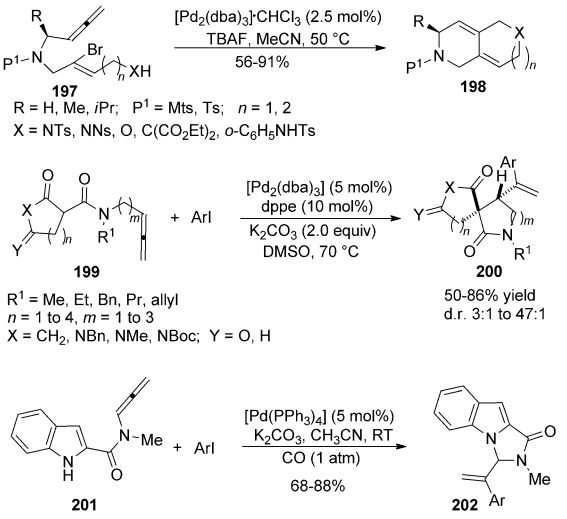
The π-allylpalladium intermediate initially formed by regioselective carbopalladation of organic halides with allenes in the presence of nucleophiles reacts intramolecularly to furnish allylic derivatives **195** or **196**. Aternatively, these cyclic products may be formed by nucleometalation followed by reductive elimination (Scheme 54).[145] A related process involving the formation with a π-allylpalladium intermediate through a hydropalladation step and interception by intramolecular trapping by a carbon nucleophile is also known.[146] This strategy has been explored for the synthesis of a series of heterocycles, such as γ-butenolides, γ-lactams, γ-iminolactones, vinylic epoxides, 4-amino-2-alkenols, 2-amino-3-alkenols, 2,5-dihydrofurans, furans, vinylic cyclopropanes, cyclopentenes, *trans*-1,2-diazetidines,[147] 2,3-dihydro-1*H*-pyrazoles,[148] and nine- to twelve-membered rings,[149] from the reaction of aryl halides with allenes containing a nucleophilic function in the α position. A



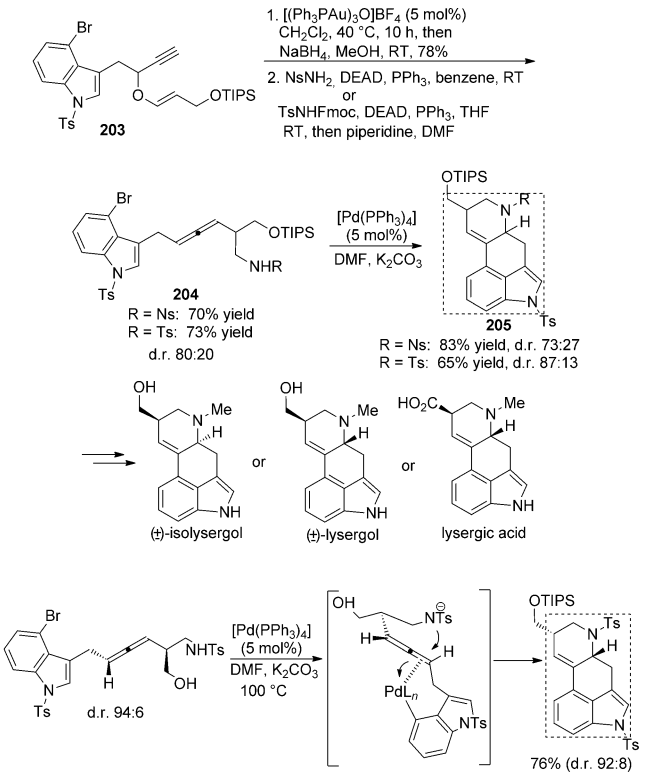
***Scheme 54.*** Cyclization of allenes with a nucleophilic functional group.

palladium(0)-catalyzed three-component tandem double addition and cyclization reaction of 2-(2,3-allenyl)malonate, iodobenzene, and an imine has also been disclosed for the stereoselective synthesis of *cis*-pyrrolidine derivatives.[150] Scheme 55 shows examples of the application of such reactions for the synthesis of bicyclic and tricyclic products such as **198**, **200**, and **202**.[151–153]

Fujii, Ohno, and co-workers have successfully applied such a strategy for the ring system of (±)-lysergic acid, (±)-lysergol, and (±)-isolysergol (Scheme 56).[154] The requisite



***Scheme 55.*** Synthesis of biyclic compounds from allenes with a nucleophilic functional group. dppe = 1,2-bis(diphenylphosphanyl)-ethane, Ns = 2-nitrophenylsulfonyl.



***Scheme 56.*** Synthesis of the ring system of (±)-lysergic acid, (±)-lysergol, and (±)-isolysergol. DEAD = diethylazodicarboxylate, Fmoc = 9-fluorenyloxycarbonyl.

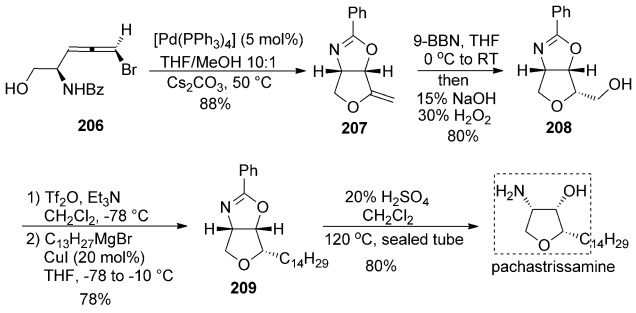
amino allene unit in **204** was obtained by gold-catalyzed Claisen rearrangement of enol ether **203**, followed by a Mitsunobu reaction with $NsNH_2$ or TsNHFmoc. The palladium-catalyzed domino cyclization was suggested to proceed through an aminopalladation/reductive elimination sequence, which enabled the direct construction of the ring system of the lysergol and its analogues in one pot. (±)-Lysergic acid, (±)-lysergol, and (±)-isolysergol could then be easily prepared through several reaction steps. The enantioselective total synthesis of the (+)-lysergol, (+)-isolysergol, and (+)-lysergic acid could be achieved in a similar way by starting from enantiopure aminoallenes.[155]

In the total synthesis of pachastrissamine, Fujii, Ohno, and co-workers used the palladium(0)-catalyzed cascade cyclization of chiral 5-bromo-2-amino-3,4-allenol **206** with two internal nucleophiles as the key step for the diastereoselective synthesis of the functionalized tetrahydrofuran core **207** in 88% yield as a single enantiomer. This intermediate can be easily converted into pachastrissamine in a four-step sequence (Scheme 57).[156]

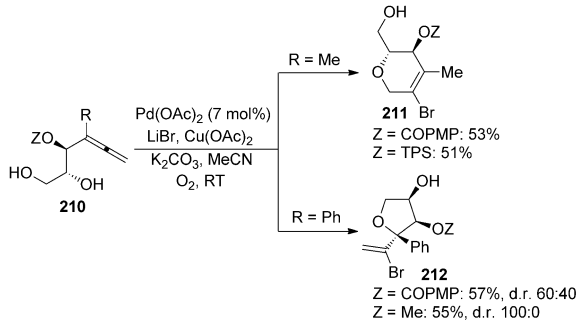
This type of reaction may also be initiated by the bromopalladation of allenes. Alcaide et al. have demonstrated that β,γ- and γ,δ-allendiols **210** undergo intramolecular cyclization to a variety of enantiopure oxacycles **211** or **212** of different ring sizes in the presence of LiBr (Scheme 58).[157]

However, there are only a few examples of the catalytic enantioselective cyclic allylation by carbopalladation. In 1991,

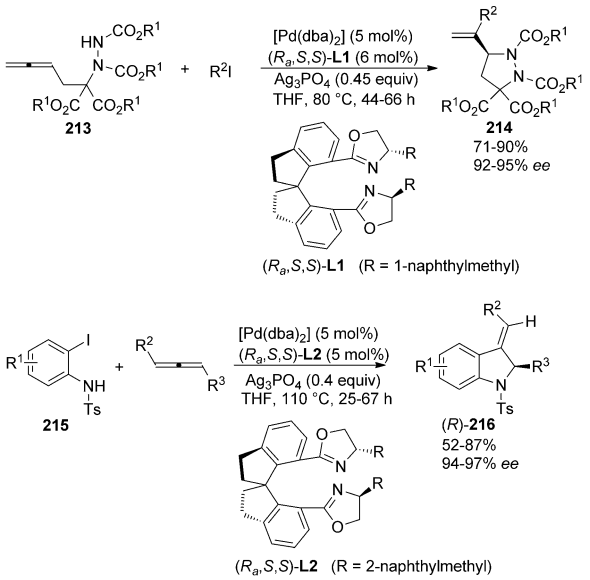



***Scheme 57.*** Total synthesis of pachastrissamine.




***Scheme 58.*** Cyclization of allenols by bromopalladation. PMP = *para*-methoxyphenyl, TPS = triphenylsilyl.

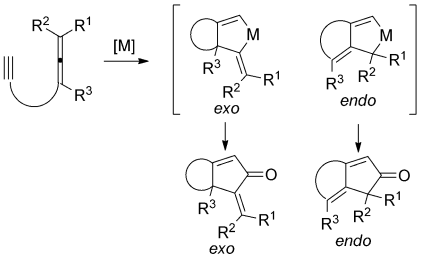
Larock et al. reported the first regio- and enantioselective annulation of cyclic and acyclic allenes with aryl halides possessing a nucleophilic amino group; the use of (*R*)-Bn-BOX as a ligand resulted in the formation of five- and six-membered heterocycles.[158] Hiroi et al. subsequently disclosed that the use of chiral [1′,2-(bisdiphenylphosphanyl)-ferrocenyl]ethyl acetate (BPPFOAc) and modified binap as the ligands resulted in the intermolecular reaction of 1-phenyl-1,2-butadiene with sodium malonate[159] and the intramolecular cyclization of 2-(*N*-allenyl)aminophenyl iodides,[160] thereby giving the corresponding asymmetric products in 96 and 88% *ee*, respectively; (*R*)-Bn-BOX has also been employed in the cyclization of allenic carboxylic acids and 2,3-allenyl hydrazines with aryl iodides with moderate enantioselectivity (< 84%).[161,162] The limited success in the asymmetric allylation of allenes with nucleophiles by carbopalladation in the presence of most of the known ligands resulted in the development of a new bisoxazoline ligand ($R_a$,*S*,*S*)-**L1** with a spiro skeleton and an α-naphthylmethyl substituent. This ligand has been successfully applied to the highly enantioselective cyclic allylation of 3,4-allenyl hydrazines **213** in 92–95% *ee*.[163] Ligand ($R_a$,*S*,*S*)-**L2** with β-naphthylmethyl substituents could also be used for the palladium-catalyzed cyclization of 2-iodoanilines **215** with allenes, and resulted in enantioselectivities ranging from 94 to 97% *ee* (Scheme 59).[164] This finding offers new possibilities for such reactions.




***Scheme 59.*** Allylation by using the new bisoxazoline ligands with naphthylmethyl substituents.

### *6.2. Pauson–Khand Reactions of Allenes*

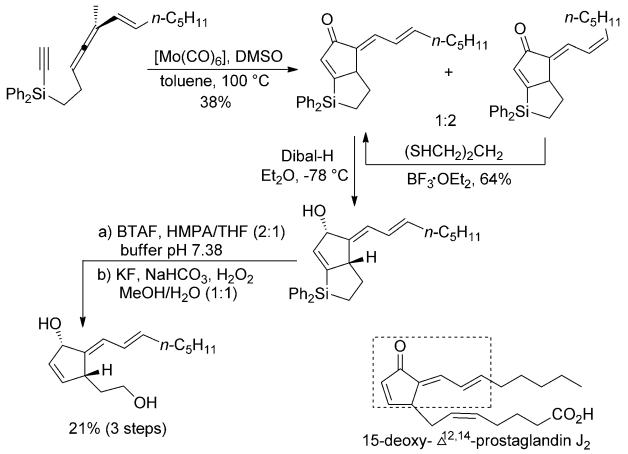
Intramolecular Pauson–Khand-type cyclizations of allenynes provide a wealth of routes to hetero- and carbobicyclic compounds (Scheme 60).[165] Experiments indicate that the nature of the transition metals, substitutents at the internal carbon–carbon double bond of the allene moiety, and the distance between the reacting entities are the major factors for controlling the regioselectivity.[166] For example, rhodium(I) catalysis was found to generally favor the formation of *endo*-cyclized products, while the corresponding molybdenum-mediated reactions led to *exo*-cyclized products. However, when a substituent was present at the internal carbon–carbon double bond of the allene moiety (i.e. $R^3 \neq H$), the formation of *endo*-cyclized products was preferred even with the molybdenum catalyst.




***Scheme 60.*** Intramolecular Pauson–Khand reaction of allenynes.

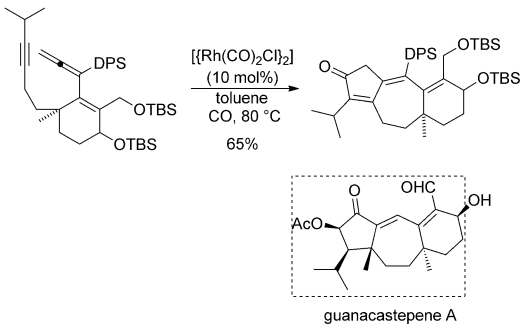
A silicon-tethered allenyl Pauson–Khand-type reaction was employed by Brummond et al. to obtain the highly unsaturated cyclopentenone ring in their total synthesis of the 15-deoxy-$\Delta^{12,14}$-prostaglandin $J_2$ (Scheme 61).[167] The cyclization of an alkynylallene in the presence of hexacarbonylmolybdenum and dimethyl sulfoxide afforded the desired cyclo-

adduct in a moderate yield and low selectivity for the *E* alkene. However, the undesired *Z* isomer could be transformed to the desired *E* isomer by a Lewis acid catalyzed isomerization. The product contains all of the necessary functionality, and thus the synthesis of 15-deoxy-$\Delta^{12,14}$-prostaglandin $J_2$ can be completed in a few simple steps.



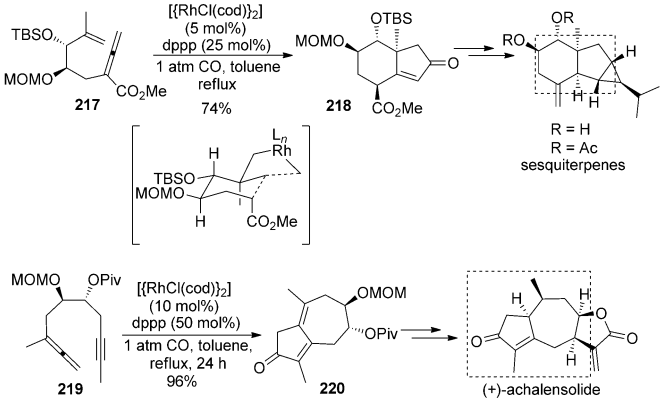

***Scheme 61.*** Synthesis of a segment in the total synthesis of 15-deoxy-$\Delta^{12,14}$-prostaglandin $J_2$. BTAF = benzyltriethylammonium fluoride, DMSO = dimethylsulfoxide, HMPA = hexamethylphosphoric triamide.

A formal synthesis of guanacastepenes A was attempted by Brummond and Gao by using a rhodium-catalyzed allenyl Pauson–Khand reaction to assemble its 7,5-bicyclic system (Scheme 62).[168]




***Scheme 62.*** Synthesis of the 5,7,6-ring system of guanacastepenes A by a rhodium-catalyzed allenyl Pauson–Khand reaction. DPS = dimethylphenylsilyl.

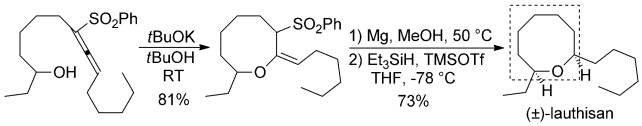
In the total synthesis of sesquiterpenoids by Mukai and co-workers, the reaction of allenene **217** in the presence of 5 mol% of [{RhCl(cod)}$_2$] and 25 mol% of dppp under CO produced exclusively the bicyclo[4.3.0]nonenone derivative **218** with the desired stereochemistry in 74% yield (Scheme 63).[169] A key intermediate in the synthesis of (+)-achalensolide was also generated by a rhodium(I)-catalyzed intramolecular Pauson–Khand reaction of allenyne **219**.[170]




***Scheme 63.*** Applications of rhodium(I)-catalyzed Pauson–Khand reactions of allenynes in the total synthesis of sesquiterpenoids and (+)-achalensolide. dppp = 1,3-bis(diphenylphosphanyl)propane.

### 6.3. Intramolecular Nucleophilic Conjugate Additions

The intramolecular nucleophilic addition of a hydroxy group to an allene with an electron-withdrawing phenylsulfonyl group was employed in the synthesis of the eight-membered oxacycle of (±)-lauthisan (Scheme 64).[171] Exposure of the allene to *t*BuOK in *t*BuOH at room temperature for 40 min furnished (*E*)-8-ethyl-2-hexylidene-3-(phenylsulfonyl)oxocane in 81% yield. Dephenylsulfonylation with Mg in MeOH followed by the reduction of the enol ether moiety with $Et_3SiH$ afforded (±)-lauthisan in 73% yield.




***Scheme 64.*** Synthesis of the eight-membered oxacycle of (±)-lauthisan by base-mediated intramolecular addition of a hydroxy group to an allenyl sulfone.

### 6.4. Electrophilic Cyclizations

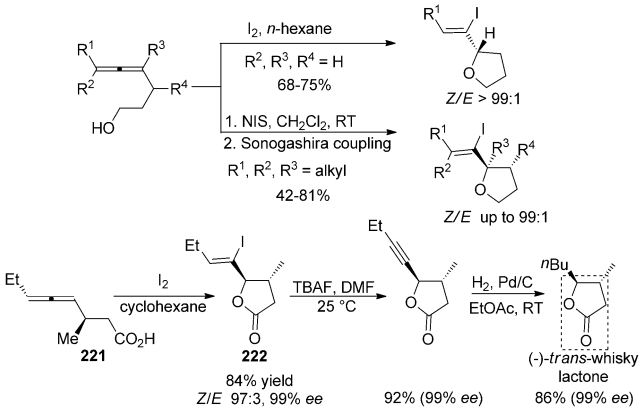
Halocyclization of functionalized allenes is a powerful method for the synthesis of various substituted heterocycles.[172] The electrophilic cyclization of functionalized allenes to afford heterocycles, such as butenolides, furans, and lactams, iminolactones, have been carefully explored.[173]

Recently, it was disclosed that the cyclic iodoetherification of 4,5-allenols with a substituent in the 3-position afforded the *trans*-2,3-disubstituted tetrahydrofurans with very high diastereoselectivity. Highly optically active *Z* products could be prepared by using NIS in $CH_2Cl_2$, followed by kinetic resolution through a Sonogashira coupling reaction with propargyl alcohol.[174] In contrast to this cyclization reaction, Gockel and Krause observed that the cyclic iodoetherification reaction of the β-hydroxyallenes in the presence of a catalytic

amount of a gold catalyst afforded iodinated 6-*endo*-dihydropyrans in good yield.[175]

Our research group used the iodolactonization of chiral 4,5-allenoic acids[176] as the key step in the total synthesis of (−)- and (+)-*trans*-whisky lactones to construct the five-membered ring (Scheme 65).[177] Treatment of chiral γ-allenoic acid **221** with iodine in cyclohexane furnished the desired iodolactone **222** in 84% yield with a complete axial-to-center chirality transfer. Dehydroiodination in the presence of TBAF and hydrogenation afforded the target (−)-*trans*-whisky lactone in 86% yield and 99% *ee*. The overall synthesis of (−)-*trans*-whisky lactone was realized in 11 steps and 8% yield from propargyl alcohol. The (+)-*trans*-whisky lactone was also prepared by a similar strategy.



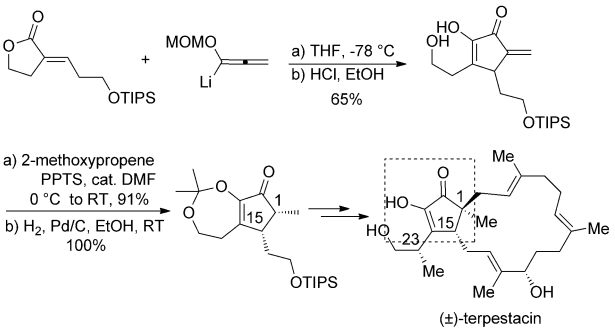

***Scheme 65.*** Total synthesis of (−)-whisky lactones by iodolactonization of the chiral 4,5-allenoic acid.

### 6.5. Nazarov Cyclizations of Allenes

The Nazarov reaction is one of the most powerful processes for constructing five-membered carbocyclic skeletons.[178] Allenyl Nazarov-type cyclizations have been exploited to form diverse highly functionalized cyclopentenones in a single step.[11,179]

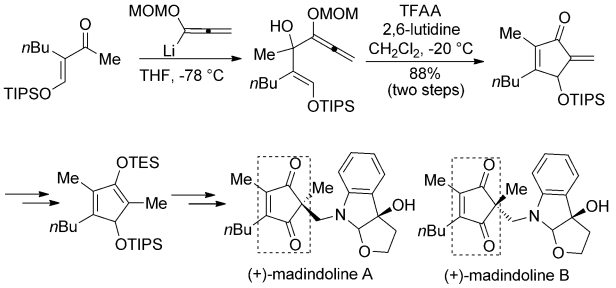
Berger and Tius used Nazarov cyclizations of allenes as the key steps to construct the α-hydroxycyclopentenone ring system during the total synthesis of (±)-terpestacin and its epimers (Scheme 66).[180] Treatment of a lactone with 1-lithio-1-(methoxymethoxy)allene led to a cyclopentenone in 65% yield. Protection of the diol functionality and selective hydrogenation of the exocyclic double bond afforded the cyclopentenone as a single diastereomer in quantitative yield. The configuration at C15 was later used to control the configurations at C1 and C23.

This Nazarov cyclization was further used by Wan and Tius to install the cyclopentenedione portion of madindolines A and B (Scheme 67).[181] The allenylation of an enone with 1-lithio-1-(methoxymethoxy)allene formed the substrate for the Nazarov cyclization. The substrate cyclized upon exposure to trifluoroacetic anhydride and 2,6-lutidine to give




***Scheme 66.*** Total synthesis of (±)-terpestacin.

the cyclopentenone in 88% yield over two steps. Conversion of the resulting cyclopentenone into triethylsilyl enol ether, followed by a Mannich reaction with hydroxyfuroindoline gave the main skeleton of madindolines A and B.



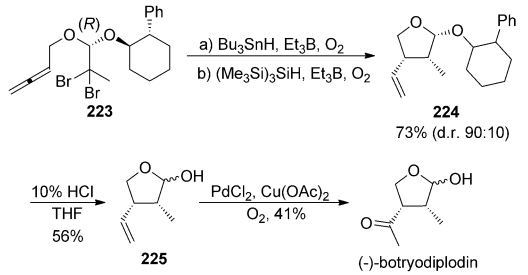

***Scheme 67.*** Synthesis of madindolines A and B. TFAA = trifluoroacetic anhydride.

### 6.6. Radical Cyclizations

Intramolecular radical cycloadditions of allenes, in particular for constructing five-membered rings with an adjacent olefinic π system, are getting more and more important.[182] Radical cyclizations of allenes can proceed via the *dig* (β addition) or the *exo-trig* mode of ring closure (α addition) depending on the chain length between the reacting entities and the stereoelectronic interactions between the radical and the π system. This method allows the synthesis of complex target molecules derived from natural products to be accomplished in cases where ionic transformations have failed to provide similar selectivities.[183]

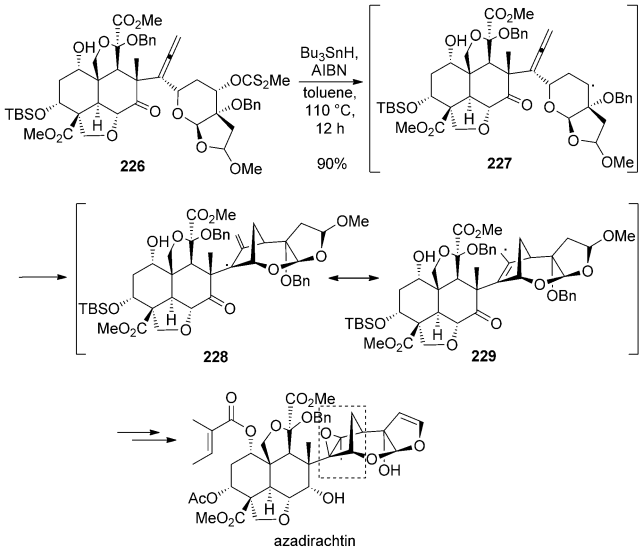
The asymmetric synthesis of (−)-botryodiplodin was accomplished by Nouguier et al. by using the radical cyclization of an allenyl bromoacetal as the key step (Scheme 68).[184] The configuration of the resulting 4-vinyl-substituted tetrahydrofuran was controlled by the stereogenic acetal center, where (1*R*,2*S*)-2-phenylcyclohexanol was applied as a chiral auxiliary. Stereoselective reduction followed by a Wacker oxidation to convert the vinyl moiety into an acetyl group led to (−)-botryodiplodin.

The first total synthesis of azadirachtin was accomplished by Ley et al., who applied the 5-*exo* radical cyclization to generate the crucial bicyclo[3.2.1] system **229** (Scheme 69).[185]




***Scheme 68.*** Enantioselective synthesis of (−)-botryodiplodin.

It was suggested that the efficiency of the 5-*exo* cyclization was due to the closeness of the central allene carbon atom and the radical center in the favored conformation of the reactive radical intermediate **227**.

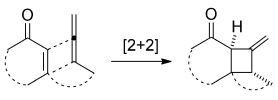



***Scheme 69.*** Synthesis of azadirachtin by radical cyclization. AIBN = azobisisobutyronitrile.

## 7. Cycloaddition Reactions[4e,n,O]

### 7.1. [2+2] Cycloadditions

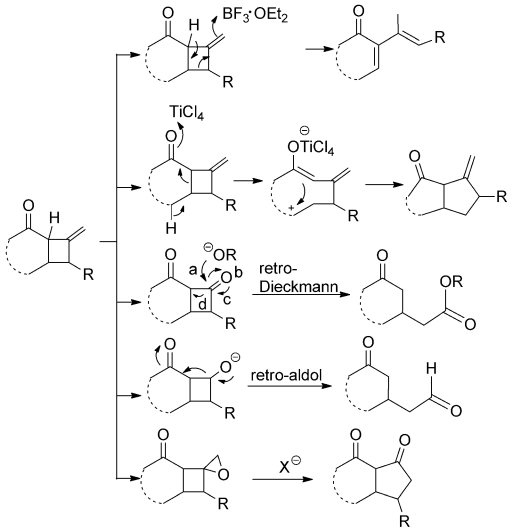
[2+2] Cycloadditions of allenes and enones are one of the most synthetically useful reactions of allenes in natural product synthesis (Scheme 70).[186] They usually occur with moderate to good site- and regioselectivities, and the regioselectivity is quite high for the intramolecular formation




***Scheme 70.*** [2+2] Cycloaddition of allenes with enones.

of five-membered rings. In most cases, head-to-head cycloadducts are preferred.

Except for the direct use of [2+2] cycloadditions to construct products containing four-membered rings, the facile fragmentation and ring expansion of the alkyledine cyclobutanes are often used to construct new functionality or polycyclic frameworks.[187] Typical fragmentation and ring-expansion patterns for the generic cycloadducts are summarized in Scheme 71. The electrophilic attack of a Lewis or Brønsted acid on the olefinic C–C double bond or carbonyl oxygen atom leads to the fission of the cyclobutane ring.[188] The transformation of the C–C double bond in the alkylidene cyclobutane ring to a carbonyl group or epoxide gives intermediates that readily undergo retro-aldol reactions, retro-Dieckmann reactions, etc.[189]

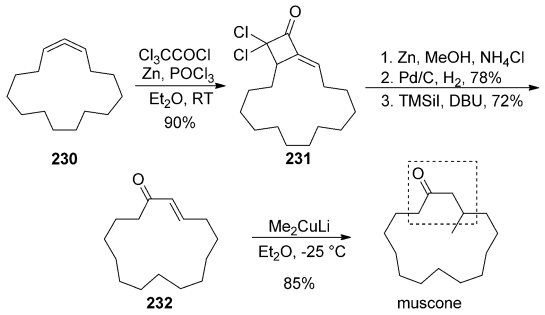



***Scheme 71.*** Fragmentation and ring expansion of alkylidine cyclobutanes.

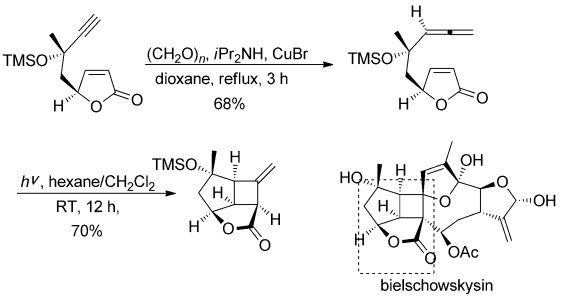
A general approach to the macrocyclic enones and a total synthesis of muscone has been reported by Erden et al. This approach involves a [2+2] cycloaddition between dichloroketene and the cyclic allene **230**. Dechlorination of the resulting cycoadduct **231**, followed by hydrogenation and cyclobutanone ring opening mediated by trimethylsilyl iodide provided the corresponding macrocyclic enone **232**, which was converted into muscone with $(CH_3)_2CuLi$ (Scheme 72).[190]

The substrate-controlled photoinitiated [2+2] cycloaddition of an allene-linked γ-butenolide was employed by Lear and co-workers as the key step in the formation of the tricyclo[3.3.0]oxoheptane core of bielschowskysin (Scheme 73).[191] The allene substrate could be easily prepared in 68% yield by homologation of the corresponding acetylene with $(CH_2O)_n$ in refluxing dioxane.[65] Irradiation of the ene-allene in dichloromethane/hexane (1:1) afforded a single diastereomeric photoadduct in 70% yield. The tertiary carbinol in the bridge to the allene was believed to play an important role in determining the stereochemical outcome by helping the allene unit to adopt the "correct" conformation.



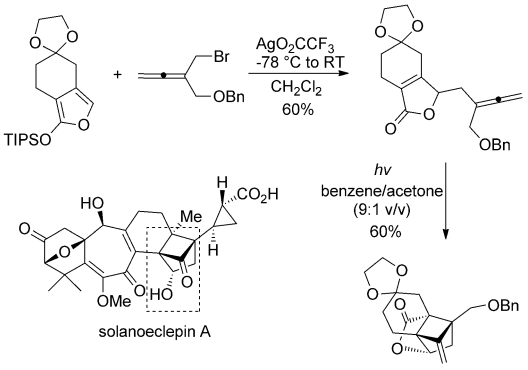

***Scheme 72.*** Total synthesis of muscone by a [2+2] cycloaddition. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, TMSiI = trimethylsilyl iodide.




***Scheme 73.*** Synthesis of the tricyclo[3.3.0]oxoheptane core of bielschowskysin by a photoinitiated [2+2] cycloaddition.

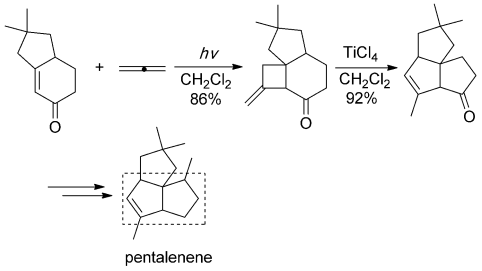
An intramolecular [2+2] photocyclization of an allenyl butenolide was employed for the synthesis of the bicyclo-[2.1.1]hexane substructure of solanoeclepin A (Scheme 74).[192] The substituted allenyl butenolide was obtained by the silver-mediated coupling between the substituted allenic bromide and a silyloxyfuran. The cyclobutane photoadduct was formed exclusively as a single diastereomer in 60% yield upon irradiation. The regioselectivity of the photocycloaddition was explained by the preferential 1,5-closure during the cyclization process.

A formal synthesis of (±)-pentalenene based on a sequence involving a [2+2] photocycloaddition of cyclohexenone with an allene and Lewis acid induced rearrangement



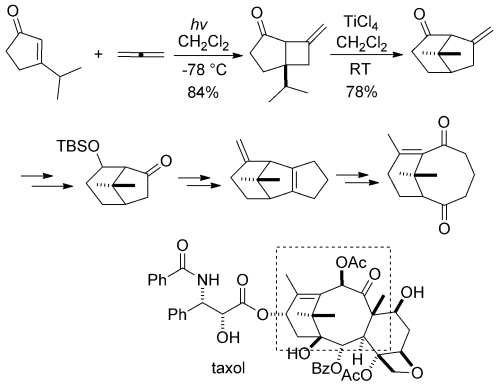

***Scheme 74.*** Synthesis of the bicyclo[2.1.1]hexane substructure of solanoeclepin A.

was achieved by Kakiuchi and co-workers.[188a] Irradiation of the propadiene with the bicyclic cyclohexenone afforded the tricyclo [6.3.0.0$^{1,4}$]undecanone in 86% yield (Scheme 75). Treatment of the cyclobutane ring with $TiCl_4$ afforded the key triquinane intermediate, which had previously been used for the synthesis of (±)-pentalenene by Paquette and Annis.[193]




***Scheme 75.*** Formal synthesis of (±)-pentalenene.

In the construction of the AB ring system of taxol by Kakiuchi and co-workers, irradiation of the cyclopentenone with allene in $CH_2Cl_2$ at −78 °C afforded the head-to-head photoadduct in 84% yield (Scheme 76). The skeletal rearrangement of the bicyclo[3.2.0] ketone in the presence of $TiCl_4$ at room temperature resulted in the formation of a bicyclo[3.2.1]octanone with an isopropylidene bridge (78% yield).[194]

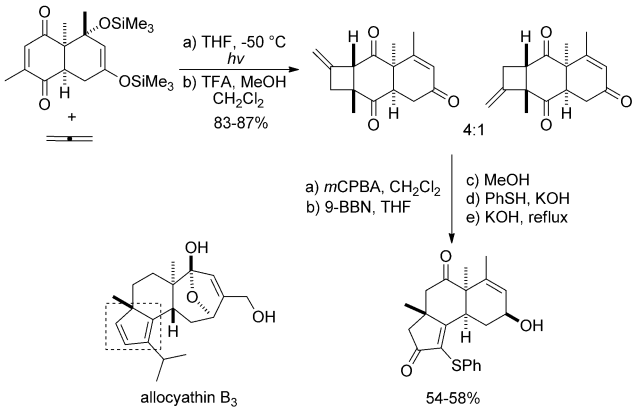



***Scheme 76.*** Construction of the AB ring system of taxol by a [2+2] photocycloaddition and acid-catalyzed rearrangement.

Ward's approach towards the total synthesis of (±)-allocyathin $B_3$ also relies on a [2+2] photocycloaddition of an allene to a bicyclic enone.[195] The photocycloadduct was obtained in up to 87% yield with a regioselectivity of 4:1 for the desired isomer and was used directly for further manipulation to give the skeletally rearranged tricyclic compound (54–58% overall yield, Scheme 77).

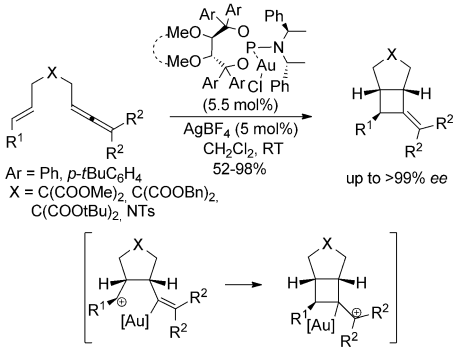
Such an enantioselective reaction was reported by the research groups of Toste[196] and Fürstner.[197] A new class of taddol-derived phosphoramidite ligands was developed for the gold-catalyzed asymmetric [2+2] cycloaddition of ene-allenes by a nonconcerted mechanism involving cationic gold




***Scheme 77.*** Total synthesis of (±)-allocyathin $B_3$.

intermediates (Scheme 78). This development will further promote the application of this type of reaction in natural product synthesis.

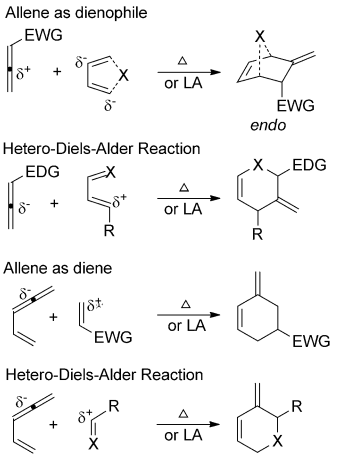



***Scheme 78.*** Enantioselective [2+2] cycloaddition.

### *7.2. [4+2] Cycloadditions*

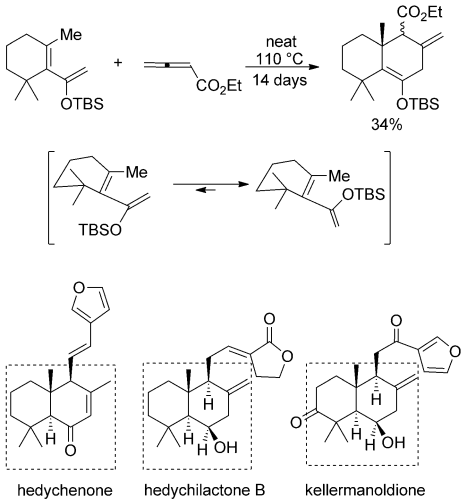
[4+2] Cycloaddition reactions of allenes with unsaturated compounds provide a powerful method for the synthesis of six-membered ring systems.[198] Simple allenes usually act as a dienophile in the Diels–Alder [4+2] cycloaddition,[199] whereas vinylallenes and conjugated bisallenes participate in the cycloadditions mainly as the diene component. Electronic effects, steric effects, and secondary orbital interactions play important roles in the determination of the regioselectivity and stereoselectivity.[200] The general reaction patterns for allenes are summarized in Scheme 79. The Diels–Alder reactions are usually carried out under thermal conditions or in the presence of Lewis acids. The use of a Lewis acid can lead for the need to a lower reaction temperature and improve the yield and regioselectivity.

Jung et al. have shown that functionalized trimethyldecalin systems can be prepared by using a stepwise [4+2] cycloaddition (Scheme 80).[201] The reaction between the hindered silyloxydiene and allenoate afforded the *exo* adduct as the major product. The steric repulsion between the substituents




***Scheme 79.*** General modes of Diels–Alder reactions with allenes. EWG = electron-withdrawing group. EDG = electron-donating group.

around the dienes results in the diene unit not being in a coplanar conformation, which is a requirement for a concerted [4+2] cycloaddition.

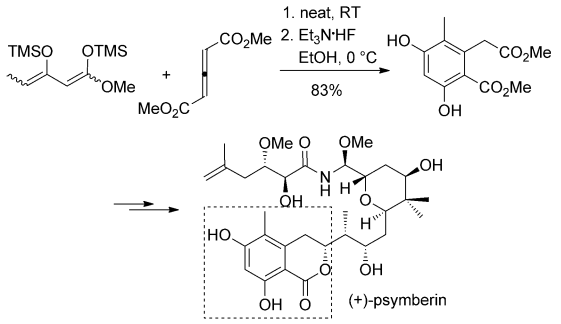



***Scheme 80.*** Synthesis of functionalized trimethyldecalin systems by stepwise [4+2] cycloaddition.

In the course of the total synthesis of the marine sponge cytotoxin (+)-psymberin, the research groups of Smith III,[202] Crimmins,[203] and Floreancig[204] have all taken advantage of the Diels–Alder reaction between 1,3-bis(trimethylsiloxy)-1,3-pentadiene and dimethyl 1,3-allene dicarboxlate to construct the multisubstituted aromatic ring (Scheme 81). After a Diels–Alder reaction followed by aromatization with $HF{\cdot}NEt_3$, this fragment was obtained in 83% yield.

Suzuki and Kobayashi constructed the chloropupukeananin core skeleton by a biomimetic process, which involved a reverse-electron-demand Diels–Alder reaction of a maldoxin derivative with vinylallene and a TFA-promoted intramolecular carbonyl-ene reaction.[205] The intermolecular Diels–Alder reaction only occurred under high pressure, whereby

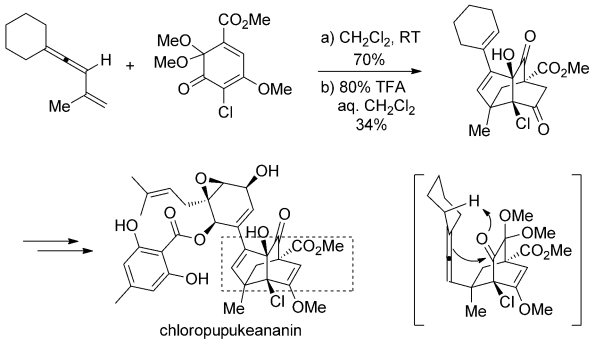
  




***Scheme 81.*** Synthesis of a highly substituted aromatic ring by [4+2] cycloaddition.

the alkene unit of the vinylallene reacted with the diene moiety of the masked *o*-benzoquinone. Treatment of the resulting cycloadduct with TFA in $CH_2Cl_2$ gave the desired tricyclo[4.3.1.$0^{3,7}$]decane skeleton in 34% yield (Scheme 82).

The [4+2] cycloaddition of chiral allene-1,3-dicarboxylates with *N*-Boc-pyrrole in the presence of $AlCl_3$ proceeded with high diastereoselectivity to afford the *endo* adduct exclusively in good yield (Scheme 83).[206] The highly selective

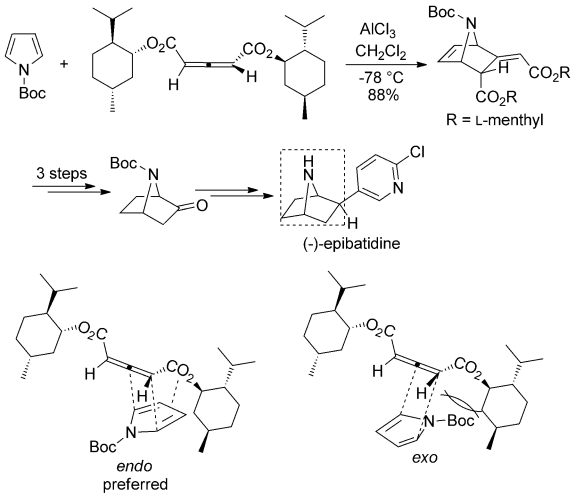



***Scheme 82.*** Synthesis of the core skeleton of chloropupukeananin.

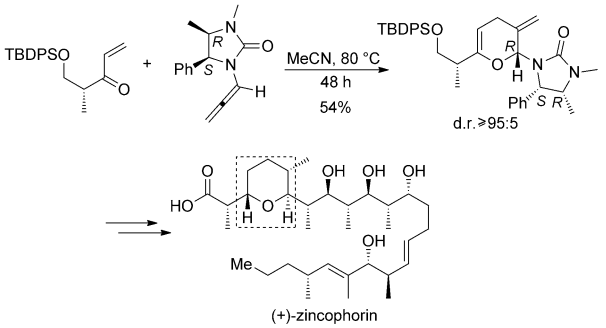
formation of the *endo* adduct was attributed to the severe steric repulsion between the Boc group and the L-menthyl group in the allenic ester moiety. By taking advantage of this reaction, (−)-epibatidine was formally synthesized in a few steps.

A [4+2] hetero-cycloaddition between an allenamide having a chiral auxiliary and an α,β-unsaturated carbonyl compound was successfully applied as the key reaction in the total synthesis of (+)-zincophorin (Scheme 84).[207] It was found that the chirality of the allenamide controlled the configuration of the cycloadduct, irrespective of the chiral information of the heterodiene.

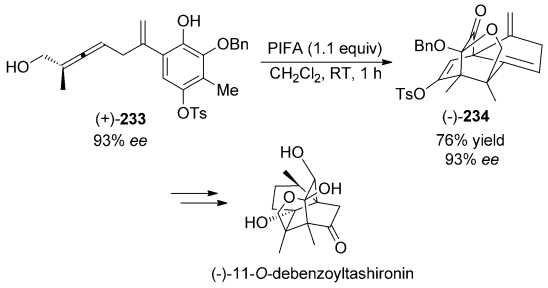
Danishefsky and co-workers reported an enantioselective total synthesis of (+)-11-*o*-debenzoyltashironin (Scheme 85).[208] The key intermediate was accessed through the use of the optically active allene (+)-**233**, which underwent an oxidative dearomatization and transannular Diels–Alder reaction to yield the enantiomerically enriched tetracyclic adduct (−)-**234**.




***Scheme 83.*** Synthesis of (−)-epibatidine by the [4+2] cycloaddition of a chiral allene-1,3-dicarboxylate.




***Scheme 84.*** [4+2] Hetero-cycloaddition of a chiral allenamide with a chiral enone.

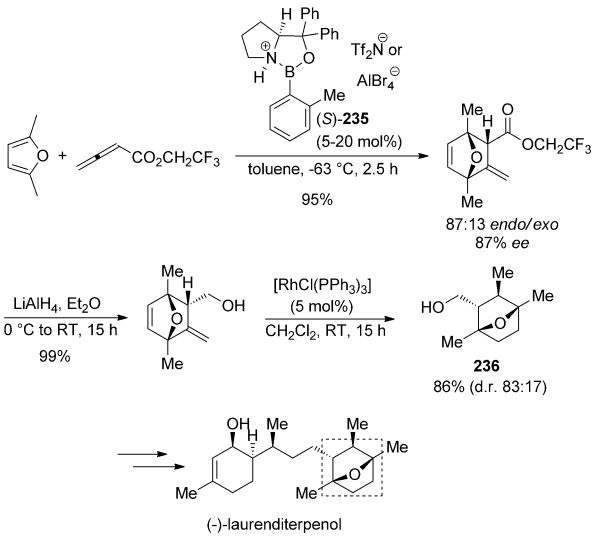



***Scheme 85.*** Intramolecular oxidative dearomatization and transannular Diels–Alder reaction for the enantioselective synthesis of the tetracyclic substructure of (+)-11-*O*-debenzoyltashironin. PIFA = phenyliodine-(III) bis(trifluoroacetate).

An asymmetric Diels–Alder reaction of an allenoate as the dienophile with 2,5-dimethylfuran under the catalysis of the chiral oxazaborolidinium triflimide **235** was employed in the synthesis of the subunit of (−)-laurenditerpenol.[209] Reduction of the ester group followed by hydrogenation of the cabon–carbon double bond with the Wilkinson catalyst

provided the desired diastereomer **236** with good diastereoselectivity (d.r. 83:17; Scheme 86).

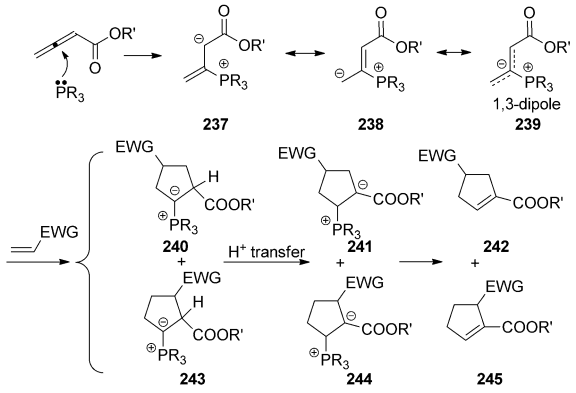



***Scheme 86.*** Application of a catalytic asymmetric Diels–Alder reaction with an allenoate for the synthesis of a subunit of (−)-laurenditerpenol.

### *7.3. [m+n] Cycloadditions*

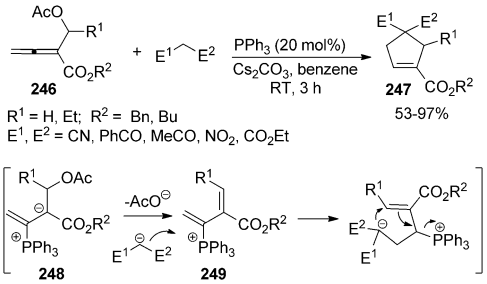
#### *7.3.1. Phosphine-Catalyzed Formation of Five-Membered Rings*

Phosphine-catalyzed [3+2] cycloadditions of allenoates with electron-deficient olefins and aldehydes/imines have received considerable attention since the pioneering work of Lu et al.[210,211] The nucleophilic addition of the phosphine to the β-carbon atom of the allenoate initiates the reaction, the cycloaddition of the resulting zwitterionic enolate intermediate with electron-deficient C=C bonds, followed by proton transfer and elimination of the catalyst to generate regioisomeric cyclopentenes **242** or **245** (Scheme 87). Investigations have revealed that the electronic and steric properties of phosphines can exert significant influence on the chemoselectivity of the reaction.[211]



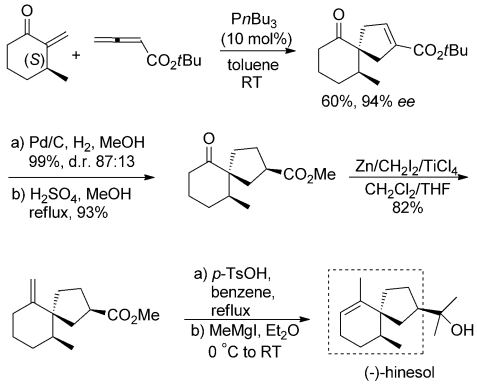

***Scheme 87.*** Mechanism for the phosphine-catalyzed [3+2] cycloaddition.

Such phosphine-catalyzed [3+2] cyclizations of 2,3-butadienoates with substituted alkylidenemalononitriles[212] and nitroalkenes[213] have recently been reported. Interestingly, a $PPh_3$-catalyzed annulation of α-acetoxyalkyl allenoates **246** with carbon nucleophiles provided a facile synthetic method for the synthesis of cyclopentene derivatives **247** (Scheme 88).[214] The acetate group in the substrate was crucial and acted as a leaving group for the formation of the extra C=C bond in **249**.




***Scheme 88.*** Phosphine-catalyzed [4+1] cycloaddition.

An asymmetric synthesis of the spirocyclic skeleton of (−)-hinesol has been achieved using a phosphine-catalyzed [3+2] cycloaddition of *tert*-butyl 2,3-butadienoate and (*S*)-3-methyl-2-methylenecyclohexanone (Scheme 89).[215]

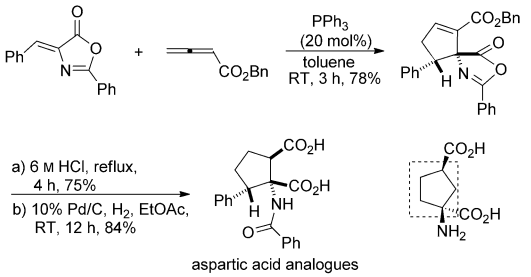



***Scheme 89.*** Synthesis of (−)-hinesol by a phosphine-catalyzed [3+2] cycloaddition.

Aspartic acid derivatives could be accessed using a phosphine-catalyzed [3+2] cycloaddition of 4-benzylidene-2-phenyloxazol-5(4*H*)-one and benzyl 2,3-butadienoate to afford fused oxazolones.[216] Acid hydrolysis and palladium-mediated hydrogenation of the obtained cycloadduct afforded the structurally diverse aspartic acid analogues in an overall yield of 59% (Scheme 90).

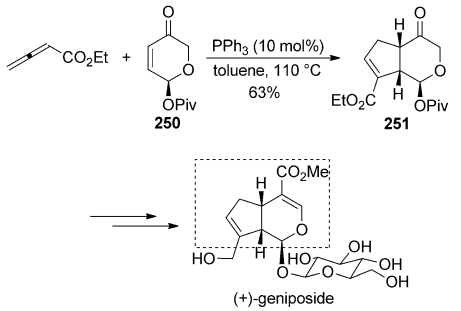
This reaction was also used by Jones and Krische to construct the *cis*-fused cyclopenta[*c*]pyran ring system of the natural product (+)-geniposide (Scheme 91).[217] The annulation between ethyl butadienoate and cyclic chiral enone **250** in the presence of 10 mol% $PPh_3$ produced the bicyclic




***Scheme 90.*** Synthesis of aspartic acid derivatives.

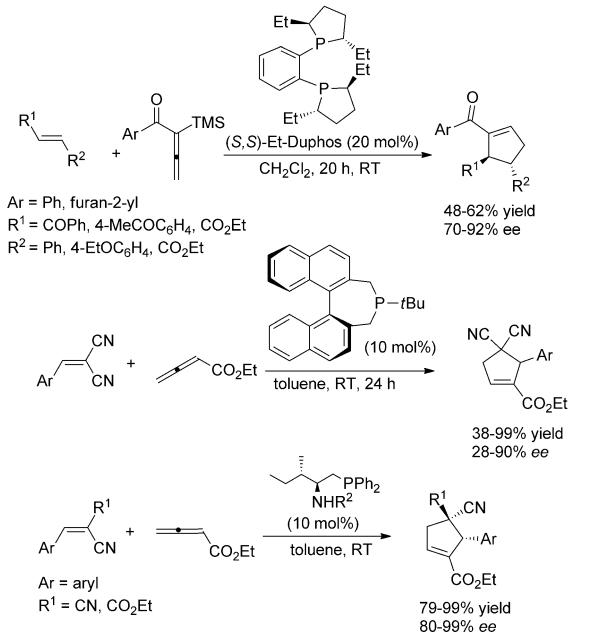
product **251** in 63% yield with high levels of regio- and stereocontrol. This product was then elaborated to (+)-geniposide in ten steps.




***Scheme 91.*** Application of a phosphine-catalyzed [3+2] cycloaddition in the total synthesis of (+)-geniposide.

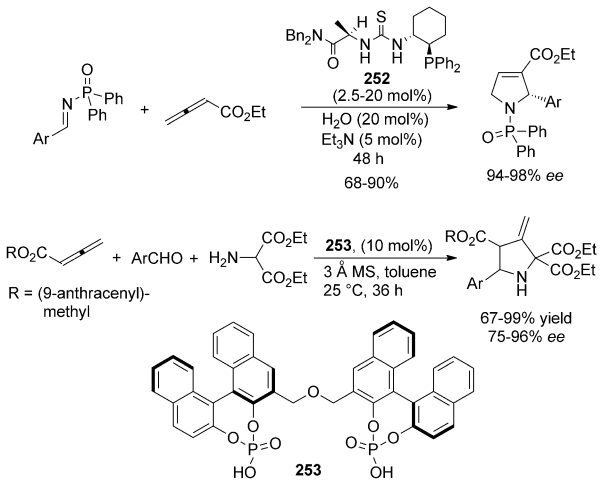
Following Zhang's first report on the enantioselective cycloaddition of allenoates catalyzed by chiral phosphines,[218] various new catalysts, such as binaphthyl-derived phosphines,[219] amino acid based phosphines,[220] and chiral 2-phospha[3]ferrocenophanes,[221] have been reported. Recently, Sampath and Loh described a highly efficient phosphine-catalyzed [3+2] cycloaddition of α-trimethylsilyl-substituted aryl allenones with electron-deficient olefins. The steric hindrance of the silyl group helps to suppress the bimolecular [4+2] reaction and leads to the preferential formation of γ adducts when β-unsubstituted olefins, such as methyl acrylate and methyl methacrylate, are used.[222] The asymmetric version of the reaction with (*S*,*S*)-Et-Duphos leads to [2+3] cycloadducts with moderate to high enantioselectivity. Such reactions have also been reported by the research groups of Marinetti[223] and Zhao[224] (Scheme 92).

Analogous enantioselective cyclization reactions with imines have also been developed. The use of chiral bifunctional thiourea catalysts derived from readily accessible *trans*-2-amino-1-(diphenylphosphino)cyclohexane **252** for the [3+2] cycloaddition between allenes and imines led to excellent enantioselectivities for a variety of aryl and heteroaryl imines (Scheme 93).[225] Electron-rich imines exhibited low reactivity and required the use of higher catalyst loadings (20 mol%). It was proposed that the $H_2O$ additive helps to protonate the basic ylide intermediate to form a pentavalent hydroxyphosphorane intermediate, and the $Et_3N$ promoted




***Scheme 92.*** Enantioselective phosphine-catalyzed [3+2] cycloadditions with alkenes.

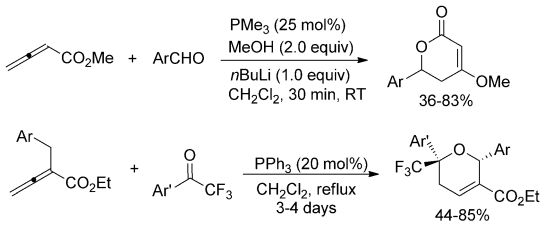
the elimination and liberation of the phosphine catalyst by either $E_2$ or $E_{1cb}$ mechanisms. Gong and co-workers developed a 1,3-dipolar cycloaddition of buta-2,3-dienoate with azomethine ylides catalyzed by bisphosphoric acid **253** to yield 3-methylenepyrrolidine derivatives with excellent enantioselectivity (Scheme 93).[226]




***Scheme 93.*** Enantioselective phosphine-catalyzed [3+2] cycloadditions with imines.

### *7.3.2. Phosphine-Catalyzed Formation of Six-Membered Rings*

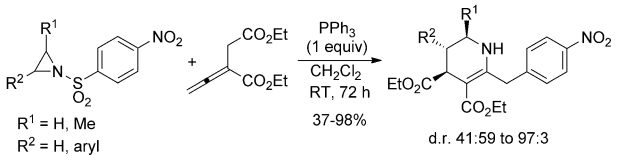
Kwon and co-workers found in their research on phosphine-catalyzed annulation of allenoate with aldehydes that the addition of an alcohol to the reaction system can promote the formation of disubstituted dihydropyrones (Scheme 94).




***Scheme 94.*** Phosphine-catalyzed [4+2] cycloadditions of butadienoates with aldehydes or ketones.

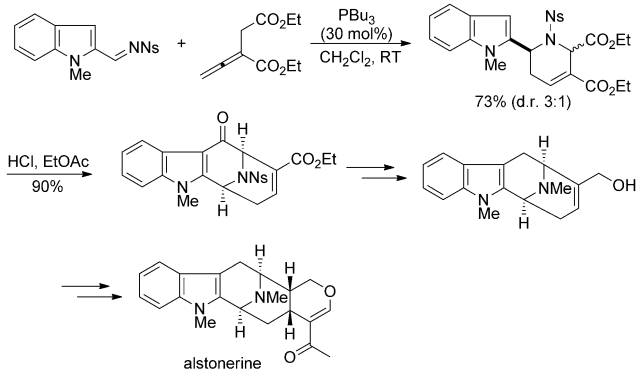
The presence of alcohol allowed preferable formation of the *s-cis*-phosphonium dienolate and subsequent lactonization after its addition to the aldehyde.[227] Wang and Ye found that 6-trifluoromethyl-5,6-dihydropyran derivatives could be synthesized with high diastereoselectivity by the phosphine-catalyzed [4+2] annulation of α-benzylbutadienoate and trifluoromethyl ketones (Scheme 94).[228]

A new phosphine-mediated [3+3] cycloaddition with aziridine derivatives was reported recently (Scheme 95).[229] The reaction produces highly functionalized tetrahydropyridines in good to excellent yields with high levels of diastereoselectivity.




***Scheme 95.*** Phosphine-catalyzed [3+3] cycloaddition of butadienoates with aziridines.

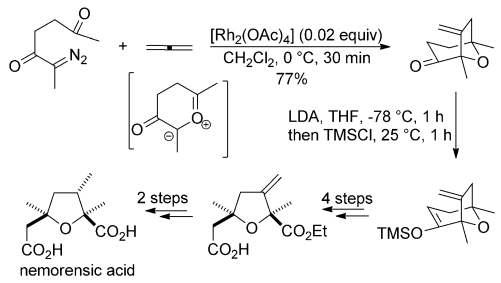
Tran and Kwon assembled the fused tetracyclic ring skeleton of alstonerine by a phosphine-catalyzed formal [4+2] reaction between imine and α-substituted allenoate (Scheme 96).[230] A subsequent intramolecular Friedel–Crafts acylation with HCl in ethyl acetate provided the bridged tetracycle, which could be easily transformed to the target alstonerine by a literature method.[231]




***Scheme 96.*** Application of the phosphine-catalyzed [4+2] annulation in the formal synthesis of alstonerine.

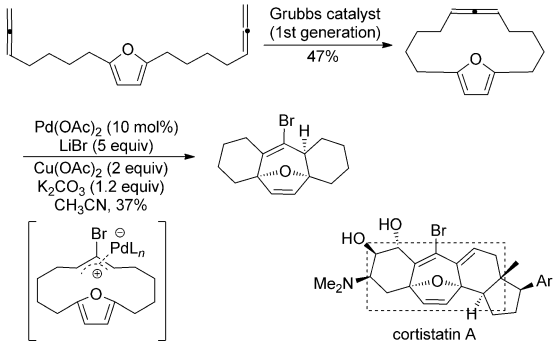
### *7.3.3. Miscellanous Cycloadditions*

A synthesis of nemorensic acids has been accomplished by Hodgson et al. through a $[Rh_2(OAc)_4]$-catalyzed tandem formation of a carbonyl ylide and intermolecular 1,3-dipolar cycloaddition of a diazodione with an allene (Scheme 97).[232] The reaction of a diazodione with allene in the presence of $[Rh_2(OAc)_4]$ afforded the desired cycloadduct in 77 % yield as a single regioisomer. Subsequent oxidative cleavage of the newly formed internal carbon–carbon double bond provided straightforward access to the polysubstituted tetrahydrofuran.




***Scheme 97.*** $Rh_2(OAc)_4$-catalyzed 1,3-dipolar cycloadditions of a diazodione with allene in the synthesis of nemorensic acid.

A 14-membered macrocycle with a cyclic allene moiety was subjected to a palladium-catalyzed [4+3] cycloaddition to obtain the tetracyclic ring structure of cortistatin A (Scheme 98).[233] The desired macrocyclic precursor was synthesized by an allene ring-closing metathesis reaction, which formed a π-allylpalladium intermediate by bromopalladation of one of the C–C double bonds in the allene. This species was intercepted intramolecularly by the furan moiety to afford the tetracyclic compound in 37 % yield.

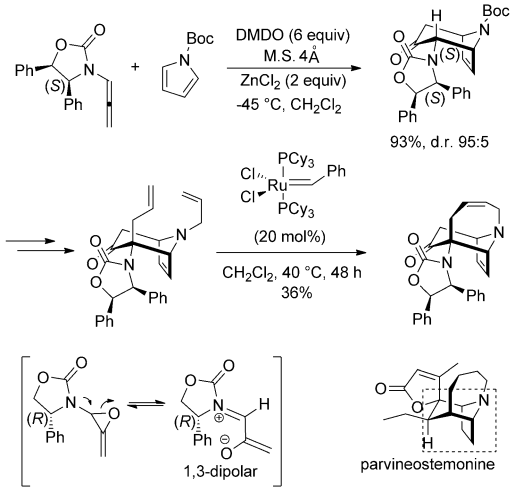



***Scheme 98.*** Palladium-catalyzed [4+3] cycloaddition for the synthesis of the tetracyclic ring structure of cortistatin A.

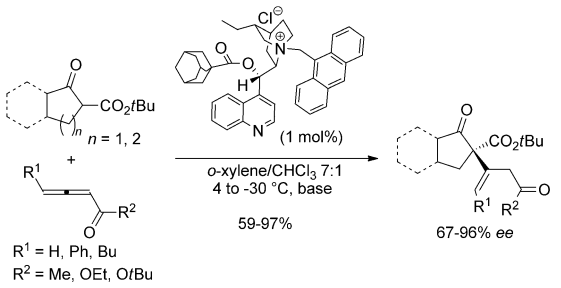
A [4+3] cycloaddition between a chiral oxyallyl cation derived from allenamide and *N*-Boc-pyrrole was examined by Hsung and co-workers and applied to the synthesis of the fused azatricycle core of parvineostemonine (Scheme 99).[234] The epoxidation of chiral allenamides by DMDO gave nitrogen-stabilized oxyallyl cations, which underwent highly diastereoselective [4+3] cycloadditions with allenes in the

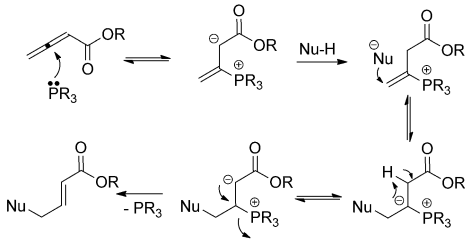
presence of $ZnCl_2$ to afford an *endo* cycloadduct in 93% yield. After introducing the allyl groups at the nitrogen atom and α position of the chiral auxilary, the resulting allyl derivative was subjected to ring-closing metathesis conditions to give the azatricyclic core of parvineostemonine.




***Scheme 99.*** Synthesis of the azatricycle core of parvineostemonine.




***Scheme 100.*** Enantioselective conjugate addition of allyl ketones and carboxylates.




***Scheme 101.*** Mechanism for the phosphine-catalyzed γ addition of electron-deficient allenes.

## 8. Perspective

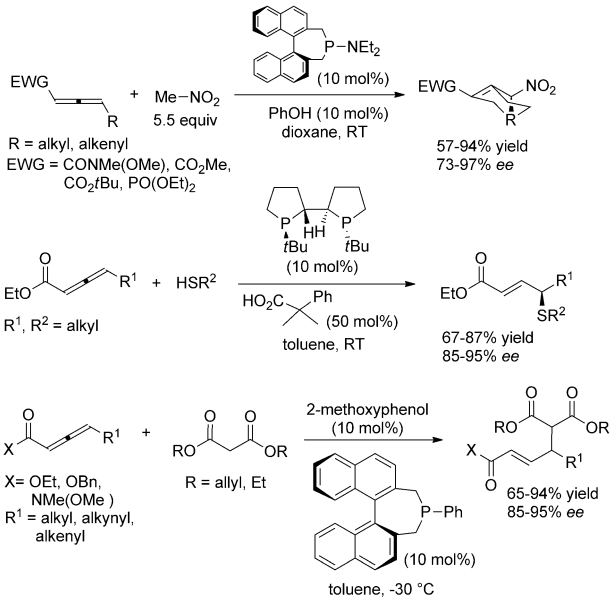
In addition to the reactions that have already been used in the syntheses of the natural products, there are also some well-established reactions of allenes which may potentially be applied to target syntheses in the near future. They are briefly discussed here.

### 8.1. Nucleophilic Additions

Allenes with electron-withdrawing substituents react readily with nucleophiles such as alcohols, phenols, carboxylates, primary and secondary amines, thiols,[235] halides,[236] stabilized carbonuclephiles,[237] organometallic reagents,[238] and phosphine–borane complexes.[239] Such reactions involving the addition at the electron-deficient inner C=C bond provides efficient routes for the synthesis of β,γ-unsaturated functionalized alkenes and cyclic products. A remarkable advance is the enantioselective conjugate addition of cyclic β-ketoesters to electron-deficient allenes to afford the corresponding chiral β,γ-unsaturated carbonyl compounds in high yields and excellent enantioselectivities (Scheme 100).[240]

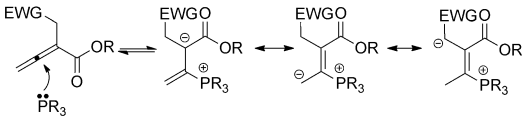
Lu et al.[211] have established that organophosphines may undergo nucleophilic addition to 2,3-allenoates to form a phosphine–allenoate zwitterion, which undergoes proton transfer with acidic pronucleophilies to give the electrophilic vinylphosphonium species, and finally providing γ-addition products (Scheme 101).

Recently, such highly enantioselective reactions have also been reported, with typical examples shown in Scheme 102 for the efficient synthesis of chiral products that are otherwise not easily achieved.[241–244]



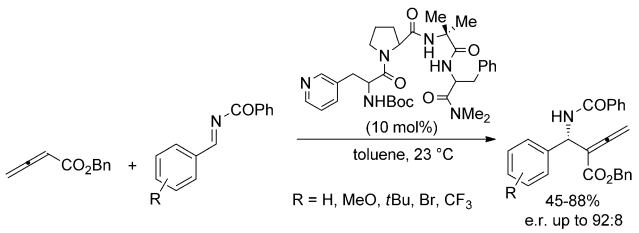

***Scheme 102.*** Selected enantioselective phosphine-catalyzed γ additions of electron-deficient allenes.

The research groups of Kwon and He expanded the phosphine-mediated reactions to allenoates. The addition of phosphines to these substrates results in the generation of a new zwitterionic intermediate with the anionic center localized at the β′-carbon atom. This approach enables the synthesis of dienes[245] and cyclic compounds[246] (Scheme 103).



***Scheme 103.*** Resonance structures for the key intermediate in phosphine-mediated reactions of α-substituted allenoates.

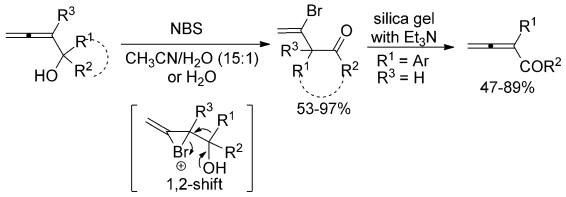
Aza-Baylis–Hillman-type reactions of electron-deficient allenes with imines are less precedented in the literature because the reagents can undergo a wide range of reactions.[247] The reactivities of both the imines and the catalysts have an influence on the final products.[248] Miller and coworkers developed a series of pyridylalanine-based peptides to catalyze the addition of benzyl 2,3-butadienoate to *N*-acyl imines, thereby forming a new type of allenyl-substituted amino acid derivatives in moderate to good yields and good enantioselectivity (Scheme 104).[249]



***Scheme 104.*** Enantioselective aza-Baylis–Hillman-type reaction of a 2,3-butadienoate with imines.

### *8.2. Electrophilic Additions*

Electrophilic additions of allenes have been demonstrated to be powerful reactions in organic synthesis, with two functionalities being introduced while one of the carbon–carbon double bonds stays intact. However, this method had often been considered to be synthetically less attractive due to the lack of simple control of the regio- and stereoselectivity. Studies have shown that the steric and electronic effects of the substituents on the allenes, the nature of the electrophiles, and the reaction conditions have a strong influence on the regio- and stereoselectivity. Many electrophilic reagents, such as halogens, hydrohalides, ArSCl, and ArSeCl, have been used for the halohydroxylation and selenohydroxylations of functionalized allenes with defined regio- and stereoselectivity. The halohydroxylation reaction of 1,2-allenyl sulfoxides, sulfones, sulfides, phosphine oxide, β-butenolides, and selenides results in the electrophilic halogen attacking the central carbon atom of the allene moiety.[172] The different electronic properties of the two C=C bonds in these allenes determine the regioselectivity of these reactions. The stereoselectivity is determined by the nature of the substituents: *E* isomers are formed with sulfoxides, phosphine oxide, and sulfones, while *Z* isomers are produced from sulfides, selenides, and β-butenolides.[172,173o,250] In a few limited cases, chlorine is installed at the 3-position of the starting allenes instead of the usual hydroxy group with Z selectivity.[173i,251] The hydration and oxidative hydroacetoxylation of 1,2-allenylic sulfoxides follows a similar mechanism as that of halohydroxylation.[252,253] Interestingly, Barluenga et al. observed that electron-rich arenes may be used as the nucleophiles in the intermolecular electrophilic addition of simple allenes with $I^+$.[254] In addition, it was observed that the reaction of secondary or tertiary 2,3-allenols with $X^+$ provides 2-halo-2-propenyl ketones or 3-halo-3-enals, which are otherwise not readily available, by a 1,2-shift of the aryl or alkyl group (Scheme 105).[173k,255]

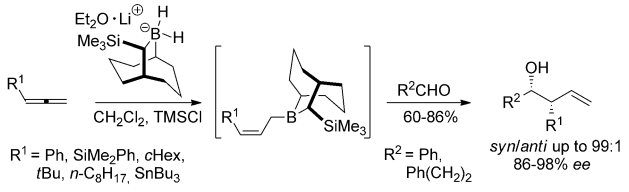


***Scheme 105.*** Synthesis of 2-halo-2-propenyl ketones or 3-halo-3-enals from 2,3-allenols. NBS = *N*-bromosuccinimide.

### *8.3. Hydrometalation*

#### *8.3.1. Hydroborations*

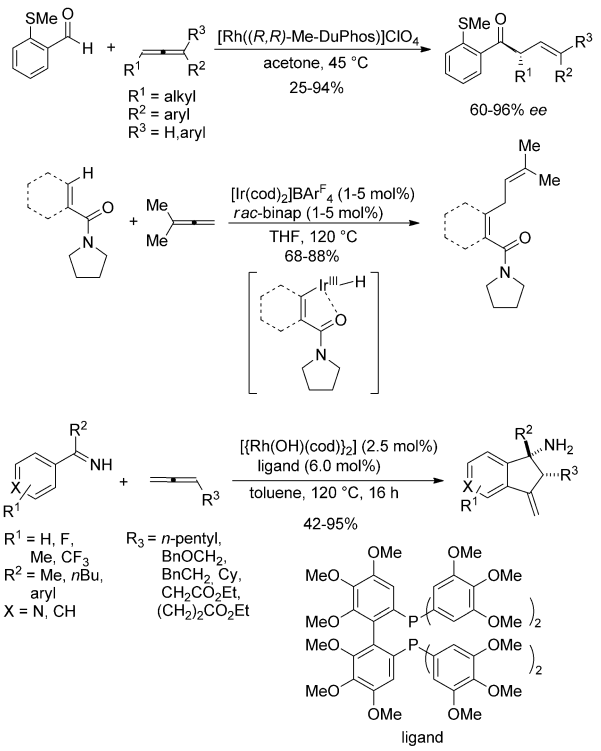
The hydroboration of allenes is especially versatile because the vinylic or allylic boron groups in the products could undergo oxidative cleavage of the C–B bond or participate in a wide range of allylations with carbonyl and imine derivatives.[256] In most cases, allylboranes can only be smoothly prepared starting from 1,1-disubstituted allenes and secondary boranes, with the best hydroborating agent being 9-borabicyclo[3.3.1]nonane (9-BBN). An enantioselective version of such a reaction has been developed: It was found that chiral dialkylborane (Soderquist borane) hydroborated allenes with high *Z* stereoselectivity (Scheme 106).[257] The resulting allylboranes underwent allylborations with aldehydes to afford *syn* diols with up to 99:1 diastereoselectivity (60–86% yields and 86–98% *ee*). DFT calculations showed this phenomenon to be attributed to the interaction of the 10-TMS group with the π-allyl group in the transition state of the [1,3] sigmatropic shift. This interaction raises the barrier for rearrangement, thus allowing kinetic control of the allene hydroboration.



***Scheme 106.*** Hydroboration of allenes and subsequent allylation of aldehydes.

### 8.3.2. Hydrometalations Based on C–H Bond Activation

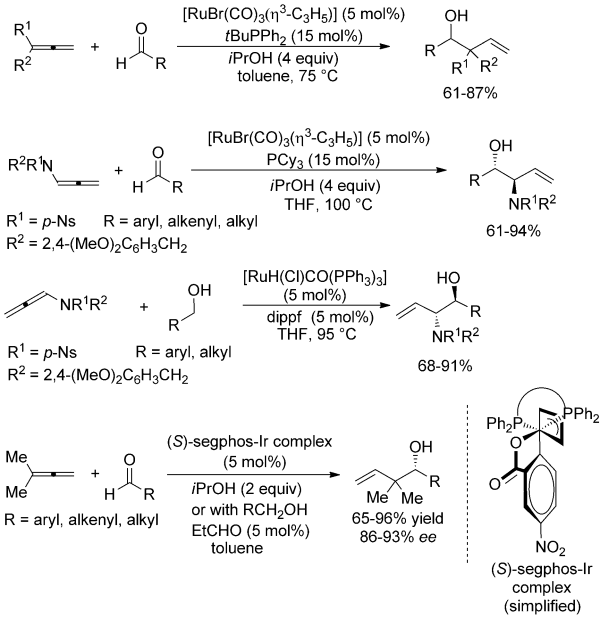
Willis and co-workers developed the enantioselective hydroacylation reactions of β-SMe-substituted enals and *o*-SMe-aryl aldehydes with simple allenes that provided a direct and efficient route to synthetically challenging chiral β,γ-unsaturated ketones.[258] A rhodium complex with chiral Me-Duphos displayed the highest levels of reactivity and selectivity.[259] Krische and co-workers have developed an iridium-catalyzed prenylation of aromatic and α,β-unsaturated carboxamides by C–H oxidative addition and allene insertion. The reaction occurs with a broad range of functional groups and regioselectively affords the prenylated adducts in high yields.[260] Recently, Tran and Cramer found that the allylrhodium intermediates formed in the rhodium(I)-catalyzed C–H functionalization of unsubstituted ketimines with terminal allenes enable additions to the directing imine moiety and lead to cyclized products in a highly regio- and diastereoselective manner.[261] A similar variant catalyzed by a rhenium complex was disclosed by Kuninobu, Yu, and Takai (Scheme 107).[262]




***Scheme 107.*** Reactions of allenes based on the activation of C–H bonds.

### 8.3.3. Hydrometalations Based on β-Hydride Elimination

Krische and co-workers disclosed that 1,1-disubstituted allenes or sulfonamido allenes reductively coupled with aldehydes in the presence of transition metals as catalysts to furnish homoallylic alcohols.[263–266] In all cases, the reductive coupling occurs regioselectively to deliver branched homoallylic alcohols. Furthermore, an enantioselective variant of this process was developed. A cyclometalated iridium C,O-benzoate complex was prepared from allyl acetate, *m*-nitrobenzoic acid, and (*S*)-segphos, and employed for the inverse prenylation of aldehydes by 1,1-dimethylallene (Scheme 108).[264]

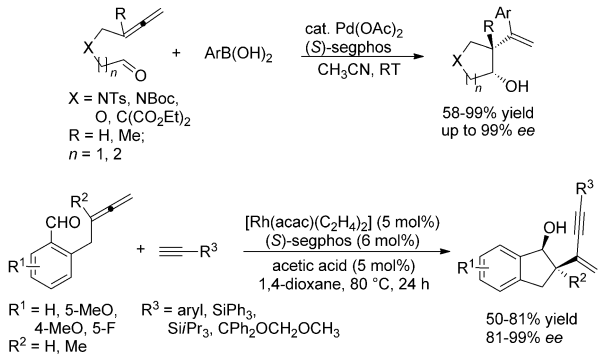



***Scheme 108.*** Synthesis of homoallylic alcohols from allenes. dippf = 1,1′-bis(diisopropylphosphino)ferrocene.

### 8.4. Intramoleculer Cyclizations of Allenes with Aldehydes or Ketones

The interception of π-allylpalladium intermediates with aldehyde groups provides a route to homoallyl alcohols.[267] In 2002, Kang et al. reported the palladium-catalyzed reaction of allene aldehydes or ketones with ArI in the presence of distannane or indium metal. The latter changed the electrophilic π-allylpalladium species into a nucleophilic indium species.[268] In 2004, Malinakova and co-workers realized the intermolecular three-component coupling of an arylboronic acid with allenes and aldehydes by using a β-pinene-derived π-allylpalladium dimer as the catalyst.[269] Yu and co-workers have found that the reaction of allenoate-aldehydes with hexamethylditin in the presence of a palladium complex gave the dehydrated cyclic diene as a single product in moderate to good yields.[270] In addition, Tsukamoto et al. have disclosed a palladium(0)-catalyzed arylative cyclization of allenals that affords cyclic alcohols.[271] An interesting advance is that a palladium(II)–bisphosphine catalyst system may be used with this type of substrates to give *cis*-fused five- and six-membered cyclic homoallylic alcohols in excellent diastereo- and enantioselectivity (Scheme 109).[272] This palladium(II)-catalyzed arylative cyclization was further extended to C1-, C2-, and C3-tethered allenyl enones.[273] Yu and Lu have developed an annulation reaction of 2-formylarylboronic acids and allenes catalyzed by the cationic palladium complex

$[Pd(dppp)(H_2O)_2]^{2+}(BF_4^-)_2$.[274] The use of chiral bisphosphine ligands enabled the indanol derivatives to be obtained with moderate diastereo- and enantioselectivity.




***Scheme 109.*** Palladium- or rhodium-catalyzed cyclization of allenals.

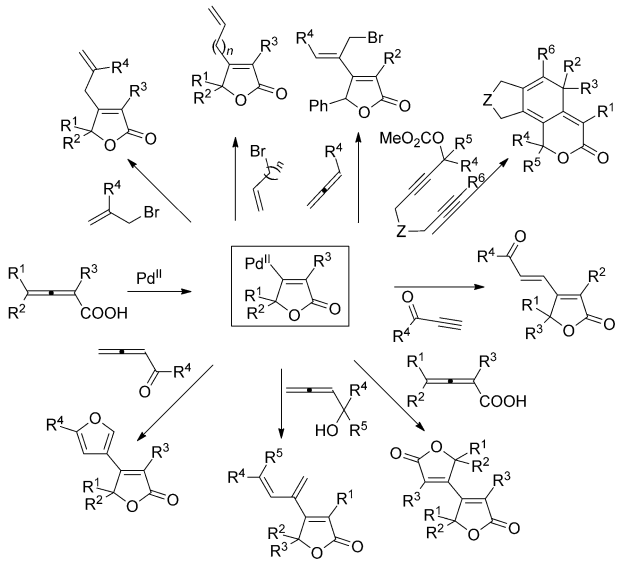
Furthermore, Hayashi, Nishimura, and co-workers expanded their asymmetric hydroalkynylation reaction to allenyl aldehydes (Scheme 109).[275] Indanol derivatives were formed regioselectively in the presence of a [Rh(acac)L*] (L* = binap or segphos) complex with high yields and enantioselectivity. The acetylacetonate (acac) ligand at the rhodium center is important for the selective formation of the indanol derivatives without their isomerization to indanones.

### 8.5. Cyclization Reactions Initiated by Nucleometalation

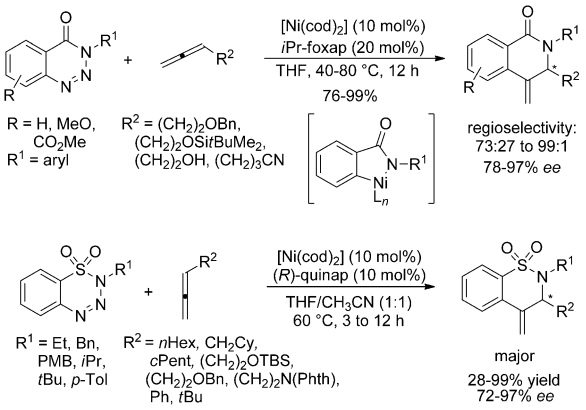
Since the first report of the palladium(II)-catalyzed cycloisomerization of 1,2-allenyl ketones by an oxypalladation process by Hashmi et al. in 1997,[276] palladium(II)-catalyzed cyclization/coupling reactions of allenoic acids, amides, allenols, allenic ketones, 1,2-allenyl phosphonic acids, and allenic amines in the presence of allylic halides,[277] or ω-1-alkenyl halides,[278] alkenes,[279] alkynes,[280] allenylic alcohols or acetates,[281] allenes,[282] and bisallenes[283] have been established. These transformations allow the synthesis of a variety of different cyclic products, which are commonly observed units in natural products, with high efficiency of chirality transfer by an *anti*-nucleometalation mechanism (Scheme 110).[284]

### 8.6. Eliminative Cycloadditions

Murakami and co-workers developed a nickel-catalyzed enantioselective denitrogenative annulation reaction of 1,2,3-benzotriazin-4(3*H*)-ones with allenes, in which a five-membered azanickelacycle was formed as the intermediate (Scheme 111).[285] Similarly, they found that an azanickelacycle could be generated from 1,2,3,4-benzothiatriazine-1,1(2*H*)-dioxide through extrusion of $N_2$ and then treated with a variety of allenes to give substituted 3,4-dihydro-1,2-benzothiazine-1,1(2*H*)-dioxides in good to high regio- and enantioselectivity (Scheme 111).[286]




***Scheme 110.*** Selected examples of nucleometalation-based reactions with unsaturated partners.




***Scheme 111.*** Transition-metal-catalyzed enantioselective denitrogenative annulations. *i*Pr-Foxap = (*S*,*S*)-[2-(4′-isopropyloxazolin-2′-yl)ferrocenyl]-diphenylphosphane, quinap = 1-(2-diphenylphosphino-1-naphthyl)isoquinoline.

## 9. Conclusions

The wide variety of reactions presented in this Review demonstrates the power of allenes in the synthesis of target molecules and optically active compounds, thus proving that allenes are becoming an irreplaceable class of compounds in organic transformations. An impressive range of reactions, including additions, cycloadditions, cyclizations, cycloisomerizations, transition-metal-catalyzed coupling, and annulations, have been used successfully in the synthesis of natural products and chiral products with remarkably good regio- and stereoselectivity. The variable set of functional groups or molecular structures thus introduced are often unique or difficult to access by other means. Additionally, the range of natural products amenable to the allene approach is vast—spanning relatively simple conjugated polyenes or polyols up to highly complex, polycyclic structures. Despite the out-

standing progress that has been accomplished, a number of challenges slow down the progress of using allenes in natural products synthesis. First, the diverse reactivities of allenes make the control of chemoselectivity, regioselectivity, and stereoselectivity less predictable. The substituent effect also plays an important role in product distribution. These uncertainties increase the risk and difficulty of using allene chemistry, and thus there is enormous potential for further development. Second, the stereoselective generation of axial chiral allenes and axis-to-center transformation of allenes without loss of chirality are still challenging. Until now, only a limited number of asymmetric versions of these reactions have been reported. This is due to the fact that the axial chirality of allenes spreads over three carbon atoms, and further studies are expected to be devoted towards improvements in this area. Extensive structural and mechanistic studies are necessary for elucidating the interactions of allenes with catalysts as well as the origin of the stereocontrol during those transformations. The future of allene chemistry will rely heavily on the development of efficient methods for the synthesis of allenes, especially those in a highly enatioselective manner, the control of reactivity as well as selectivity, and chirality transfer efficiency, as well as new catalytic asymmetric reactions of allenes. Further creative research and continued investigation of allenes will not only enrich the chemistry of allenes but will also result in further applications in the synthesis of natural products and pharmaceuticals as well as in materials science.

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