

# ASYMMETRIC SYNTHESIS OF AXIALLY CHIRAL ALLENES

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## INTRODUCTION

Allenes are attracting increasing attention in organic synthesis, both as interesting building blocks and synthetic targets. However, since the first correct illustration of their structure in 1875<sup>1</sup> and synthesis in 1887,<sup>2</sup> allenes have largely been considered highly unstable and thus poorly suited for synthesis. Only during the last decade has the use of allenes in organic synthesis undergone rapid development.

At present about 150 allene containing natural products have been isolated,<sup>3</sup> and considerable effort has been given to their synthesis, as well as to the study of their biological activity. Methods for transforming allenes into various other functionalities, often in a stereoselective manner, have attracted even more attention. Allenes can participate in cycloaddition, radical reactions, metalations and other processes.<sup>4</sup> Furthermore, the superb ability of allenes to transfer axial chirality to new stereogenic centers is being increasingly exploited in synthetic applications. Therefore, it is not surprising that asymmetric methods to prepare axially chiral allenic structures are currently the focus of active development.<sup>5, 6</sup> Several of the most popular methods are highlighted in this review, including nucleophilic S<sub>N</sub>2' substitution of propargyl derivatives, Stereoselective rearrangements, olefination with chiral auxiliaries and asymmetric catalysis.

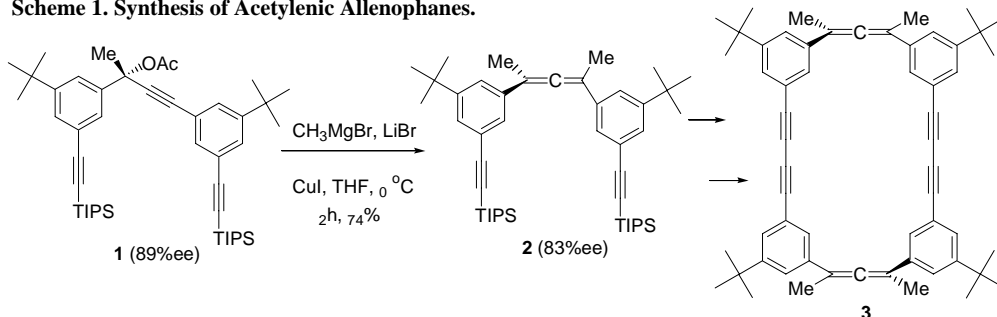
## DIASTEREOSELECTIVE SYNTHESIS OF AXIALLY CHIRAL ALLENES

### From Organocuprate and Propargyl Derivatives

**Synthetic Applications.** After the first report by Crabbe in 1963,<sup>7</sup> the S<sub>N</sub>2' reaction of organocuprates with propargyl derivatives to yield allenes is becoming one of the most popular methods to prepare allenes, including axially chiral forms. Effective as leaving groups are acetates, carbonates, sulfonates, ethers,

acetals, halides, oxiranes and aziridines, and cuprates range from simple Gilman reagents to more functionalized ones.

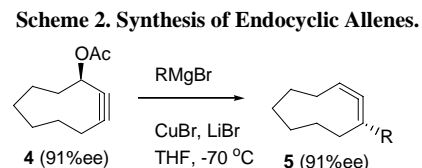
Scheme 1. Synthesis of Acetylenic Allenophanes.



This reaction has been used as a key step in many syntheses.

A recent example is the synthesis of the acetylenic allenophanes **3** (Scheme 1), which possesses novel helical asymmetry due to the axially chiral allenic moiety.<sup>8</sup> The (S)-allene in structure **2** was formed by the addition of methyl cuprate to the chiral propargyl acetate **1**. The central chirality of the propargyl system was transferred to the axial chirality of the allene with little erosion.

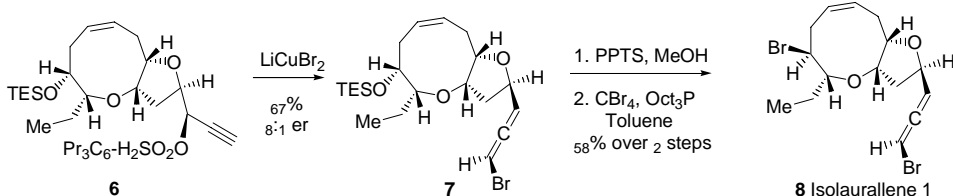
Endocyclic allenes can also be obtained using this method.<sup>9</sup> The 9-membered ring compound **5**, containing a chiral allenic moiety, was formed from the propargyl acetate **4** without loss of optical purity (Scheme 2). The R group tested included n-butyl, t-butyl and isopropyl with chemical yields ranging from 49% to 80%.



The copper-mediated  $S_N2'$  substitution reaction is not restricted to carbon-carbon bond formation. Bromoallenes, silylallenes and stannylallenes can also be formed using heterocuprate reagents. One example

is illustrated in the total synthesis of isolaurallene **1** (**8**, Scheme 3).<sup>10</sup>

**Scheme 3. Application in the Total Synthesis of Isolaurallene 1**

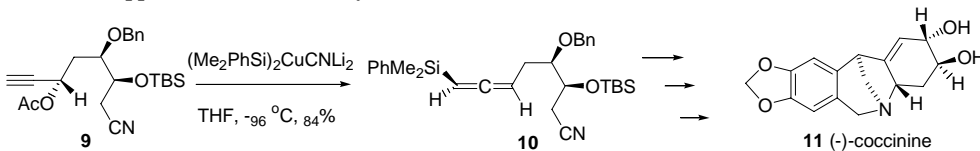


The bromoallene

moiety in the advanced intermediate **7** is formed diastereoselectively by treatment of propargyl trisylate **6** with lithium bromocuprate. This resulted in a 67% yield of an 8:1 mixture favoring the desired diastereoisomer. Further elaboration of this advanced intermediate allowed the formal total synthesis of isolaurallene **1**.

The wide scope of the heterocuprates in this reaction is further demonstrated in the construction of the core skeleton of (-)-coccinine (**11**, Scheme 4). Reaction of the silyl cuprate with propargyl acetate **9** proceeded with anti  $S_N2'$  substitution stereochemistry to furnish the imino silylallene **10** in 84% yield.<sup>11</sup> This intermediate

**Scheme 4. Application in the Total Synthesis of (+)-Coccinine.**

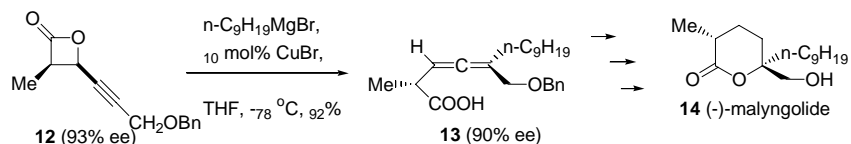


was further transformed into the final natural product (-)-coccinine.

Besides propargyl ethers,  $\beta$ -lactones, epoxides and aziridines are attractive variant leaving groups for the construction of

allenes. The addition of the nonyl cuprate to the disubstituted

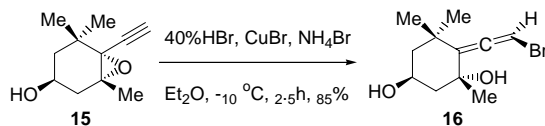
**Scheme 5. Application in the Total Synthesis of (-)-Malyngolide.**



oxetanone **12** (Scheme 5) afforded the tri-substituted allene **13** in 92% yield and 95:5 er, which upon further transformation led to the naturally occurring antibiotic (-)-malyngolide **14**.<sup>12</sup>

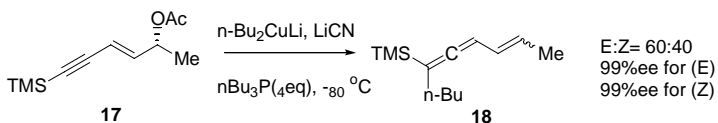
The total synthesis of 6'-epi-peridinin exploited copper-mediated S<sub>N</sub>2' substitution of an oxirane with bromide ion. Thus, the alkynyl oxirane **15** (Scheme 6), under the conditions of Chemla<sup>13</sup> (40% HBr, CuBr, NH<sub>4</sub>Br, Et<sub>2</sub>O, -10 °C, 2.5h), yielded exclusively the anti S<sub>N</sub>2' displacement product, allene **16**, in 85% yield. Further transformations of **16** furnished an epimer of the natural product peridinin.<sup>14</sup> Likewise, amino allenes can also be obtained from chiral alkynyl aziridines<sup>15</sup> and allenic alcohols from propargylic cyclic carbonates or sulfinates.<sup>16</sup>

Scheme 6. Application in the Total Synthesis of 6'-epi-Peridinin.



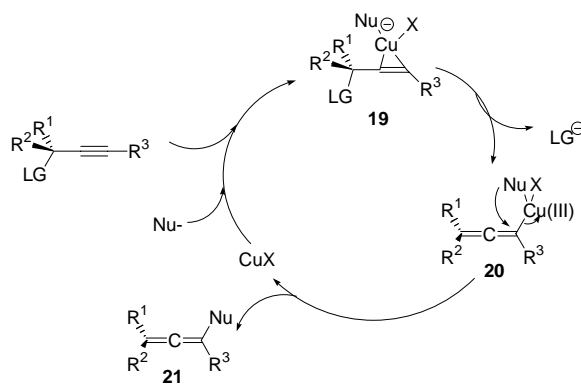
Interestingly, vinyl allenes can be accessed through 1,5-addition of cuprates to enyne acetates.<sup>17</sup> However, in this case, two types of stereoselectivity should be taken into account: the configuration of the allenic chirality axis (S or R) and of the olefinic double bond (Z or E). As shown below, the relatively long distance between the stereogenic center and the nucleophilic attack position in this 1,5-substitution reaction provides a rare example of “remote stereo control”.<sup>18</sup> Thus, the best stereoselectivity was observed in the reaction of the trimethylsilyl substituted enyne acetate **17** (Scheme 7) with di-n-butylcuprate, lithium cyanide and tri-n-butyl phosphine at -80 °C. This combination afforded vinylallene **18** as a 40:60 mixture of E/Z isomers both with er's as high as 99.5:0.5. The absolute configuration of the products was not determined.

Scheme 7. Diastereoselective 1,5-Substitution of Cuprate to Enyne Acetate.



**Stereochemical Rationale.** The S<sub>N</sub>2' substitution of propargyl derivatives by organocuprates was proposed to proceed through a copper(III) intermediate **19** (Scheme 8).<sup>19</sup> The in situ generated organocuprate coordinated with the acetylenic moiety of the propargyl derivative to form a copper(III) π-complexes **19**, which underwent subsequent elimination of the leaving group when the copper and the leaving group possessed an antiperiplanar disposition. Besides the interaction between the copper p, d orbitals and acetylenic π, π\* orbitals, the electron donation from a copper d orbital to the antibond of the C-O σ\* bond is also conceivable. It was proposed that this latter interaction initiated the dissociation of the leaving group.

Scheme 8. Mechanistic Explanation on Stereochemistry.



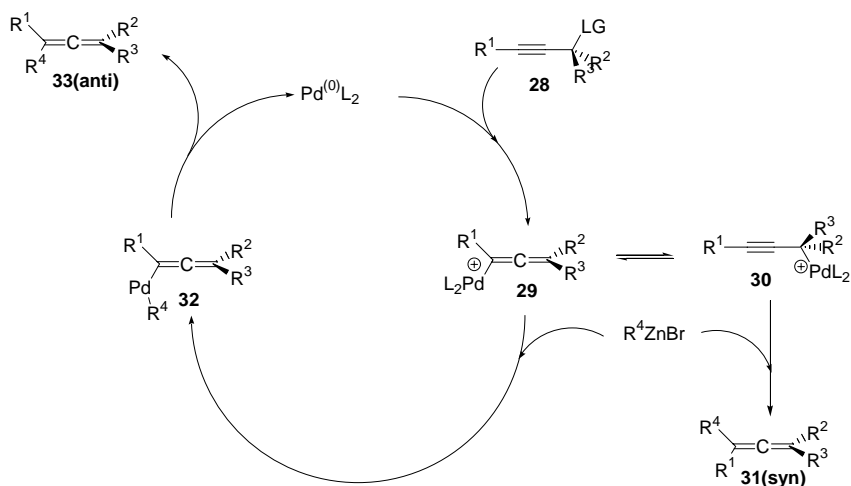
The resulting allenic cuprate **20** collapsed by reductive elimination, regenerating the halocopper and giving the allene product **21** with an overall anti-S<sub>N</sub>2' stereochemistry.

In some special cases, an overall syn-S<sub>N</sub>2' stereochemistry are observed, probably due to a syn elimination of the π-complex **19**.<sup>20</sup>

### Palladium Catalysed Substitution from Propargyl Derivatives.

**From Propargyl Derivatives.** It was found that catalytic amounts of tetrakis(triphenylphosphine)-palladium were able to effect the transformation of propargyl ethers or esters to the allenylpalladium intermediate **29** (Scheme 10). As illustrated in Scheme 9, this intermediate can be further transformed into allenes stereoselectively with zinc reagents.<sup>23</sup> The proposed

Scheme 9. Mechanism of Palladium Catalyzed Coupling of Allenyl Halides

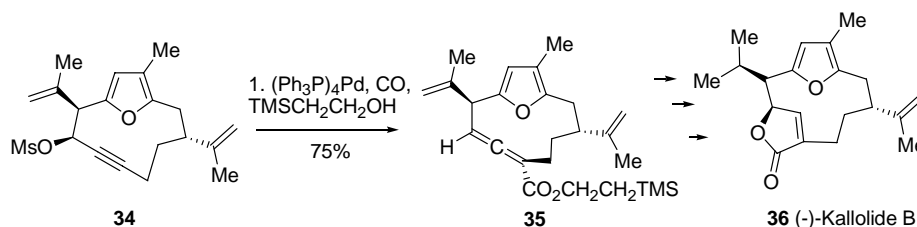


mechanism is as follows (Scheme 10): the palladium(0) assumes a nucleophilic attack antiperiplanar to the leaving group, forming the chiral allenylpalladium intermediate **29** which couples with the organozinc reagent; subsequent reductive elimination regenerates the palladium(0) catalyst and gives the

chiral allene **33** through an anti-S<sub>N</sub>2' process. In some cases, however, the palladium undergoes a [1,3]-sigmatropic rearrangement to afford the propargylpalladium intermediate **30**, which is directly displaced by the organozincate to give syn-S<sub>N</sub>2' chiral allene **31**, resulting in erosion of stereoselectivity.

Carbonylation can be added to the above reaction cycle. For example, the nonracemic propargyl mesylate **34** (Scheme 10), when treated with carbon monoxide, trimethylsilyl ethanol and a palladium catalyst, gave trimethylsilyl ethyl allenyl ester **35** as a single isomer. The product was an intermediate in the synthesis of (-)-Kallolide B **36**, the enantiomer of the natural product.<sup>24</sup>

### Scheme 10. Application in the Total Synthesis of (-)-Kallolide B.



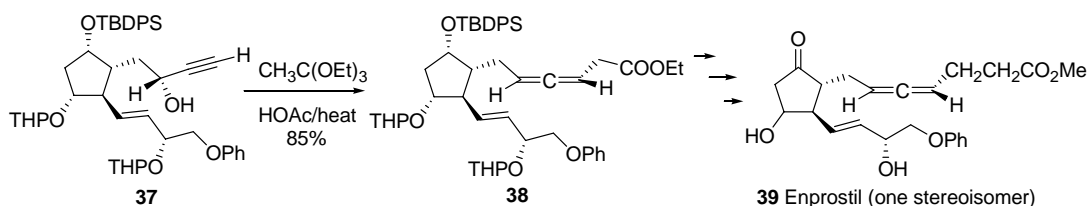
## STEREOSPECIFIC REARRANGEMENT FROM PROPARGYL DERIVATIVES

The stereospecific Wittig rearrangement of chiral propargyl ethers and the ortho ester Claisen rearrangement of chiral propargyl alcohols constitute important and convenient methods to prepare axially chiral allenes.

### Orthoester Claisen Rearrangement

Scheme 11 depicts the stereospecific conversion of propargylic alcohol **37** via an orthoester Claisen rearrangement, resulting from treatment with triethyl orthoacetate and acetic acid, to allenic ester **38**, the product of syn elimination. Further transformations lead to **39**, one stereoisomer of enprostil.<sup>25</sup>

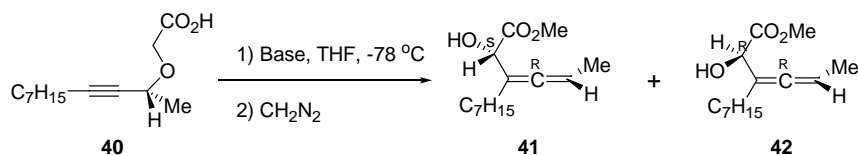
**Scheme 11. An Orthoester Claisen Rearrangement in Synthesis of One Stereoisomer of Enprostil.**



### Wittig [2,3]-Rearrangement

Under basic conditions, certain propargyl ethers can undergo a Wittig [2,3]-rearrangement to give allenols or allenic esters. The process is stereoselective on the propargyl carbon if the substrate is chiral or a chiral base is used.<sup>26</sup> As demonstrated in Scheme 13, when an achiral base such as LDA was used to effect the Wittig rearrangement of the enantiopure propargyloxy acetic acid **40**, allenic  $\alpha$ -hydroxyl ester was obtained as two enantiomers **41** and **42** in a 93:7 enantiomeric ratio. This ratio increased to 99:1 when the matched chiral base ((*R,R*)-amide) was used and lowered to 81:19 with the mismatched (*S,S*)-amide base.

**Scheme 12. Wittig Rearrangement to Afford Axially Chiral Allenes.**

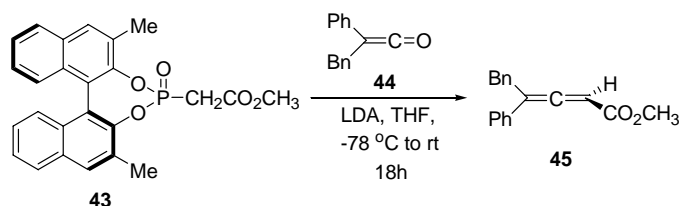


Base	Yield (%)	( <i>S,aR</i> )/( <i>R,aR</i> )
( <i>S,S</i> )-[PhCH(Me)] <sub>2</sub> NLi	81	81/19
LDA	80	93/7
( <i>R,R</i> )-[PhCH(Me)] <sub>2</sub> NLi	79	>99/1

## OLEFINATION WITH CHIRAL AUXILIARIES

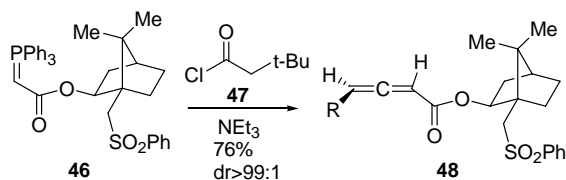
Wittig or Horner-Emmons olefination are important methods to form carbon-carbon double bonds, so it is not surprising that they had been used to form the double bonds in allenes. Chiral auxiliaries can be used to prepare axially chiral allenes stereoselectively, the best results being obtained with reagents having chiral phosphorus groups, such as phosphonoacetic acid methyl ester **43** (Scheme 13) that bears a chiral binol group.<sup>27</sup> The phenyl benzyl ketene **44**, generated in situ from the corresponding disubstituted acetic acid phenyl ester, underwent Horner-Wadsworth-Emmons reaction with **43** to give axially chiral allenic ester **45** with chemical yield 55% and ee as high as 89%.

### Scheme 13. Olefination to Form Allenes with Binol as a Chiral Auxiliary.



An alternative approach places the chiral auxiliary on the ester group as illustrated in Scheme 14.<sup>28</sup> The isoborneol phosphorus ylide **46** reacted with in situ-generated ketenes to give the corresponding chiral allene **48** as a single diastereomers, with chemical yields as high as 76%. Cleavage of the chiral auxiliary can be achieved by alkaline hydrolysis to afford the corresponding allenic ester.

### Scheme 14. Olefination to Form Allenes with Isoborneol As Chiral Auxiliary.

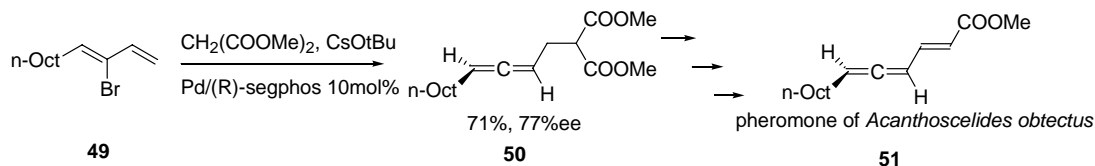


## ASYMMETRIC CATALYSIS

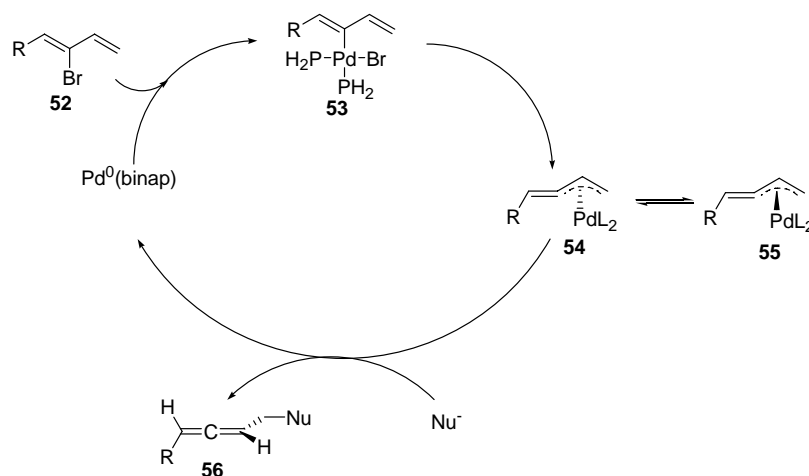
Increasing attention has been paid to the synthesis of axially chiral allenes via catalytic asymmetric synthesis; yet, since the first report in 1993, this protocol is still not yet well developed. Several ways have been reported to date: palladium-catalyzed hydroboration<sup>29</sup> and hydrosilylation<sup>30</sup> of enynes, rhodium-catalyzed hydrosilylation of butadiynes,<sup>31</sup> palladium-catalyzed substitution of 2-bromo-1,3-dienes,<sup>32</sup> and 1,6-addition to enynones.<sup>33</sup> However, each protocol is restricted to specific substrates and reagents, and is thus limited in application. Only nucleophilic substitution of 2-bromo-1,3-dienes has been used in total synthesis. Utilizing this method, efficient synthesis of the sex attractant of the male dried bean beetle,<sup>34</sup> methyl trienoate **51** (Scheme 15), has been achieved from prochiral bromo diene **49** via intermediate **50**. Axially chiral ligands, such as BINAP and segphos

proved effective in the catalysis, though in this case segphos was superior. With this method, alkyl allenes and allenyl silanes can also be accessed with er's up to 94:6.

**Scheme 15. Application in Total Synthesis of the Sex Attractant of Male Dried Bean Beetle.**



A probable mechanism for the above asymmetric reaction was proposed (Scheme 16):<sup>32</sup> the palladium insertion in bromodiene **52** resulted in the key alkylidene- $\pi$ -allyl palladium intermediate, which equilibrates between two diastereomers **54** and **55**. The enantiomer **54** enjoys much less steric congestion from the chiral environment created around the Pd(II) ion and is therefore energetically favored, giving the enantioenriched allene **56** upon attack of a soft nucleophile.



**Scheme 16. Catalytic Cycle of Asymmetric Synthesis From Bromodiene**

**CONCLUSION**

Various methods leading to the asymmetric synthesis of axially chiral allenes are illustrated here, including substitution of propargyl derivatives with organometallic reagents, rearrangement of propargyl ethers and esters, olefination of phosphorous reagents carrying chiral auxiliaries with in situ generated ketenes, and the newly developed enantioselective catalytic protocols. Key challenges remaining include the construction of several specific allenic structures, such as chiral tetra-substituted allenes and allenyl metal reagents, as well as further developments in catalytic enantioselective methods. Because of the vigorous research in this area, one can expect more applications of these methods in total synthesis and varied synthetic transformations.

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