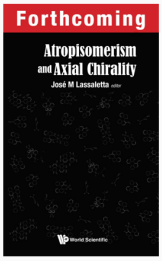

Atropisomerism and Axial Chirality

https://doi.org/10.1142/q0192 | June 2019
Pages: 676
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Atropisomerism and Axial Chirality provides a global survey of the chemistry of axially chiral compounds including biaryls, heterobiaryls, non-biaryl atropisomers, allenes and spyrocyclic derivatives. From the perspective of a synthetic organic chemist, this book provides a unique compilation of the available methodologies for their synthesis, with emphasis on the most efficient and modern strategies, a review of the huge amount of practical applications in the field of asymmetric catalysis, either as transition metal ligands or as organocatalysts, and an overview of their occurrence as bioactive compounds and natural products.

The first of its kind, this book serves as a general introduction and a practical reference to advanced chemistry students and researchers, while also offering creative ideas for further developments in the field.

Contents:

Readership: Advanced undergraduate and graduate students in chemistry chemists interested in asymmetric catalysis, organocatalysis, organic synthesis.

We recommend

Beltrami Fields in Chiral Media

Remarkably diastereoselective synthesis of a chiral

Chapter 6

Axial Chirality Beyond Atropoisomerism: Allenes And Related Compounds

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The ability to produce chiral molecules is a powerful feature of Nature. For example, both enantiomers of a molecule can be isolated from different natural sources and may exhibit different biological or therapeutic activities. From this knowledge, organic chemists have learnt the high importance for the developments of synthesis of enantiomerically pure molecules. Nowadays, contemporary organic chemists have many tools to successfully achieve the asymmetric synthesis of natural products and value-added products. In particular, central chirality of organic molecules has been studied in depth; however the efficient synthesis of molecules with axial chirality is under-developed. The present chapter is devoted to the most recent contributions of the chemistry of allenes and briefly to spirocycles with axial chirality. The synthesis of optically active allenes from enantiomeric pure molecules or from racemic mixtures has been covered. The organization has been done taking into account the type of starting material. In addition, a selection of different contributions with efficient transfer of axial-to-central chirality has been discussed, which has been organized by type of reactions. In some cases, a detailed explanation of the mechanism has also been included. Furthermore, the usefulness of chiral allenes as ligands in metal-catalyzed processes has also been covered. Finally, the most recent reports about the synthesis and applications of axially chiral spirocycles have also been discussed.

CONTENTS

1. Introduction

The term *axial chirality* is defined as a type of stereoisomerism resulting from the non-planar rearrangement of four substituents about a chiral axis.[1] Around this axis four different groups are organized in pairs but are not located in a plane. Allenes can present axial chirality when the terminal ends of the cumulative π-system hold different groups (Figure 1). The absolute configuration of allenes has been established by the Brewster-Lowe rules.[2] On the other hand, spirocycles can also exhibit axial chirality. For example, spiro[4,4]nonane is not a chiral molecule, however, the incorporation of substituents makes a chiral molecule (Figure 2). In this chapter we are going to discuss the axial chirality in both, allenes and briefly spirocycles.

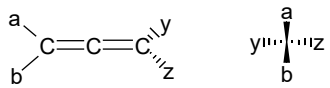


Figure 1. Axial chirality in allenes.

(a) Spiro[4,4]nonane (*achiral)*

(b) C_2-symmetric (*axially and centrally chiral rigid*)

Figure 2. Examples of spirocycles with no chirality (a) and with axial chirality (b).

The structure of allenes was first predicted by Van't Hoff in 1875;[3] however the first synthesis of a molecule containing an allene was achieved a few years later. In 1887, Burton and von Pechmann reported the synthesis of an allene skeleton.[4] For a long period of time, allenes have been considered unstable. Fortunately, during the last 20 years the chemistry of allenes has experimented a frenetic growing.[5,6] Thus, many synthetic methodologies have been developed[7,8,9] and their reactivity has been studied in depth.[10] Furthermore, the allene moiety is found in many natural products and pharmaceuticals.[11] In fact, around 150 natural compounds with an allenic or cumulenic skeleton have been characterized. In addition, due to the interesting biological activities of many allenic natural products, the allenic moiety has been introduced in pharmacologically active compounds such as steroids, amino acids and nucleosides, showing promising activities.

On the other hand, the term *spyrocyclane*, can be defined by a molecule formed by two rings with a common carbon atom (spiro carbon atom) and was first proposed by Adolf von Baeyer in 1900.[12] The spirocyclic skeleton is present in a high number of natural products with interesting biological activitites. Due to the tetrahedral hybridation of the spiro carbon atom and the perpendicular orientation of both two rings, the rotation is limited and as a result, axial chirality in this type of compounds can be observed. The especial characteristics of this spirocyclic compounds have been a good reason for the development of many synthetic methodologies.[13,14]

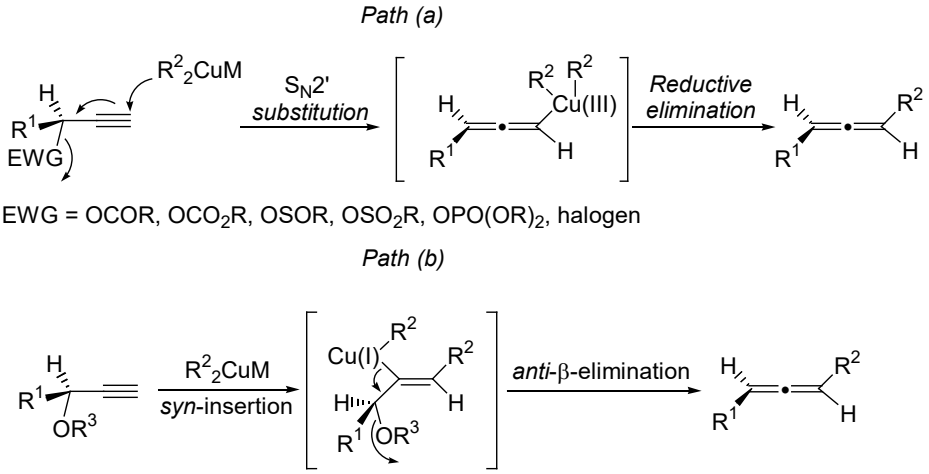
The aim of the present chapter is to provide a selection of the most relevant and recent contributions about the axial chirality in allenes and briefly in spirocyclic compounds. The chapter has been organized as follows. First, the more general methods for the synthesis of allenes are discussed according with the type of the starting material. Secondly, the reactivity of allenes is explained where an efficient axial-to-central chirality transfer is achieved. In some cases, a detailed mechanism has also been included. Next, a less explored area, the usefulness of chiral allenes in metal-catalyzed processes is covered. Finally, the synthesis and applications of spirocyclic compounds with axial chirality has been illustrated.

2 Enantioselective Synthesis of allenes

The preparation of optically active axially chiral allenes is an important topic in asymmetric synthesis. [15,16] Usually, stochiometric chiral sources are required and the catalytic version is less developed. In this section we are going to discuss some selected recent methodologies, the most representative, some of them already covered in previous reviews.

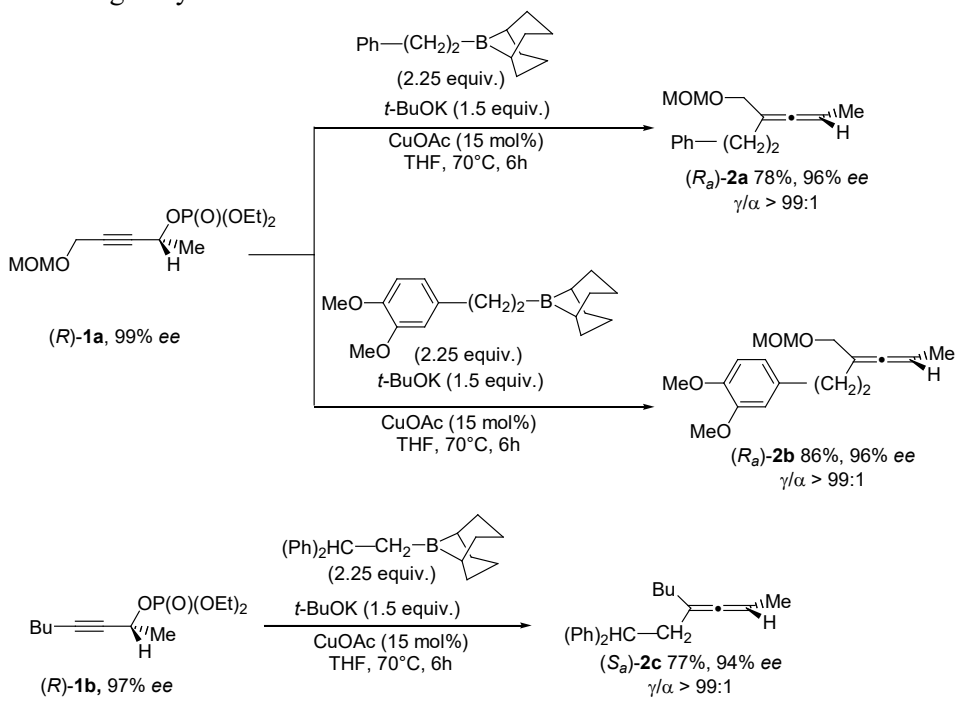
2.1. *From propargylic alcohols or their derivatives*

S_N2' reactions of enantiomerically pure propargylic derivatives such as acetates, ethers, halides, sulfinates, sulfonates and phosphates with organocopper reagents is one of the most standard and convenient methods for the enantioselective synthesis of allenes. The main advantage of this methodology relies on the use of readily available substrates which involves the formation of a new C–C bond. There are two possible reaction pathways to explain the mechanism of this processes as is shown in Scheme 1: *path (a)* via S_N2' followed by reductive elimination in propargylic derivatives with a good leaving group; and *path (b) syn*-insertion followed by *anti*-β-elimination in propargylic ethers or epoxides (poor leaving groups).



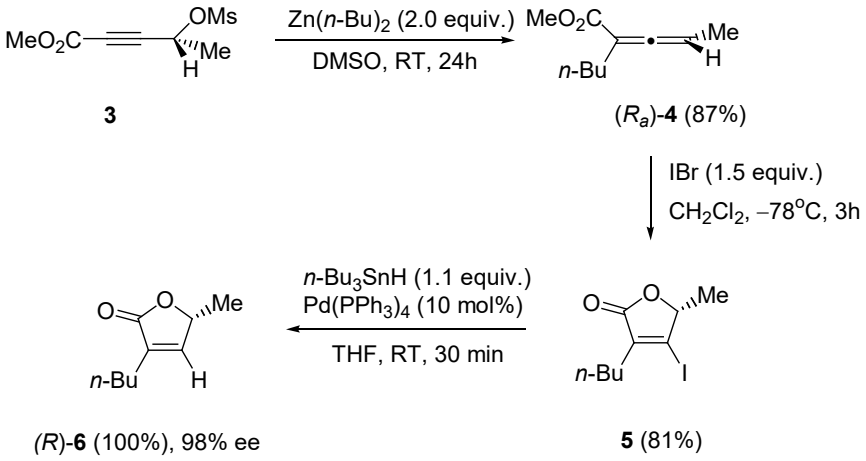
Scheme 1. Two possible reaction pathways to explain the chirality transfer in S_N2' reactions of propargylic derivatives.

Copper-catalyzed coupling between enantioenriched propargylic phosphates **1** and alkylboron compounds gives enantioenriched allenes **2** with excellent point-to-axial chirality transfer (Scheme 2).[17] Importantly, the reaction occurred cleanly with excellent γ-selectivity to give the geminally disubstituted terminal allene in good yields and enantioselectivities.



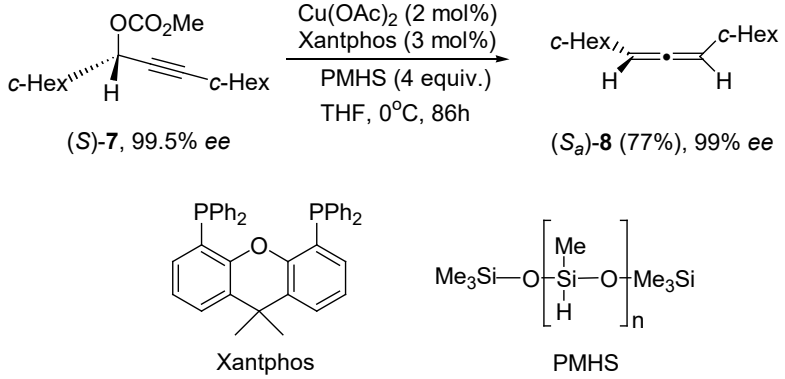
Scheme 2. Synthesis of optically pure allenes from propargylic phosphates and alkylboron compounds.

The S_N2' reaction of chiral propargyl mesylate **3** with an organozinc reagent (LiCl-free dibutylzinc) in DMF as solvent has allowed the synthesis of allene **4** (Scheme 3).[18] The absolute configuration of allene **4** has been determined as (R_a), with an optical purity of 98% *ee*, by conversion of **4** to the known chiral furanone **6**. This result indicates that the butyl group attacks the triple bond with *anti* stereochemistry in this S_N2'-type reaction. Then, the selectivity observed in this reaction is the same as with the conventional organocopper reagents.



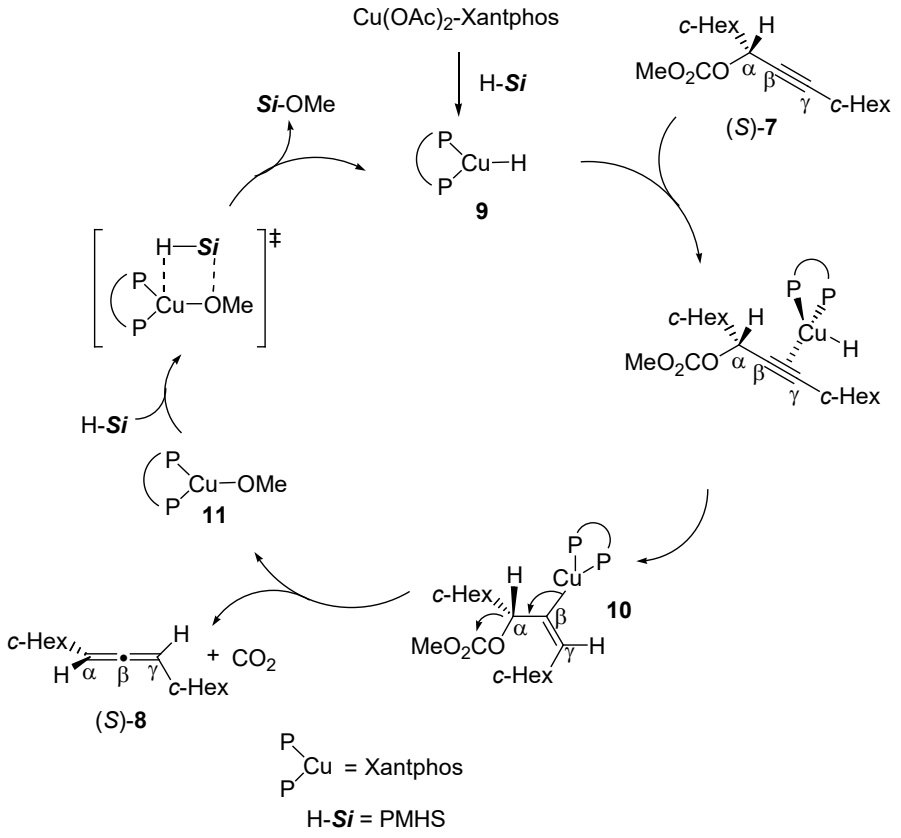
Scheme 3. Synthesis of chiral allene **4** from propargyl mesylate **3**.

The selective reduction of optically pure propargylic alcohols with transition metals is an attractive method for the synthesis of allenes with high enantiomeric purity. The regioselective and stereoselective reduction of propargylic carbonate **7** with polymethylhydroxysiloxane (PMHS) has afforded optically active allene **8**.[19] Chiral allene **8** has been obtained in 77% yield and 99% *ee* (Scheme 4).



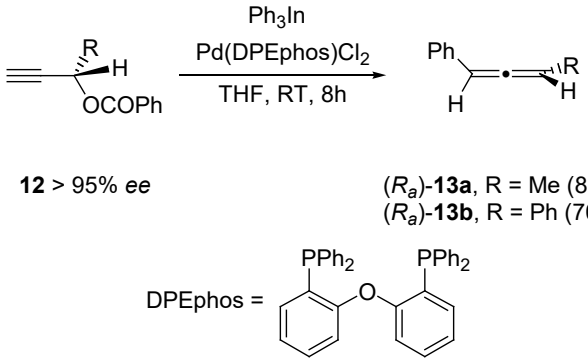
Scheme 4. Synthesis of optically active allene **8** via reduction of propargyl carbonate **7**.

The regio- and stereochemical result has been explained by the mechanism shown in Scheme 5. In presence of Xantphos, $Cu(OAc)_2$ is reduced by the hydrosilane to give Cu(I) hydride intermediate **9**. This species is coordinated by the triple bond of the substrate. Next, *syn*-addition of the Cu-H bond to the triple bond affords alkenyl copper specie **10**. Finally, *anti*-β-elimination of **10** gives the allene product, with the liberation of CO_2 giving copper alkoxide **11**. σ-Bond methatesis between **11** and the hydrosilane reproduce Cu(I) hydride **9**.



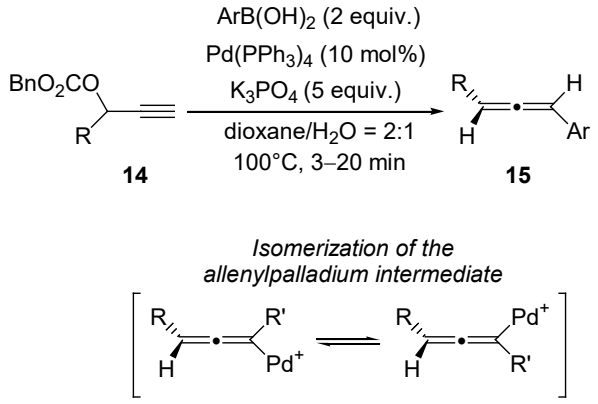
Scheme 5. Mechanistic explanation for the synthesis of allene **8**.

Palladium-catalyzed coupling reaction of enantiomerically pure propargylic compounds with a variety of organometallic compounds (organozinc,[20] organoindium, and arylboronic acid reagents) is another straightforward approach for the synthesis of enantioenriched allenes. However, in some cases, the chirality transfer of the process decreases. For example, triorganoindium reagents react with nonracemic propargylic esters **12** under palladium catalysis via an S_N2' rearrangement to afford allenes **13** in good yields, high regioselectivity and high enantiomeric excess (Scheme 6).[21]

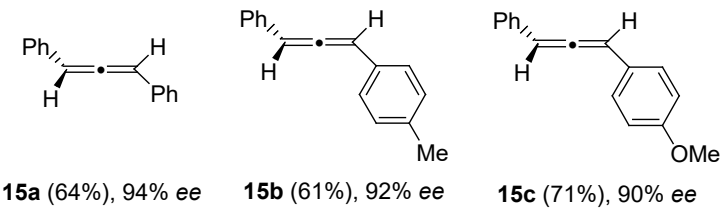


Scheme 6. Synthesis of optically active allenes **13** from propargyl esters **12** and triorganoindium reagents catalyzed by $Pd(DPEphos)Cl_2$.

The reaction of propargyl esters and carbonates **14** with arylboronic acids has been studied using a palladium catalyst.[22] The reaction has been carried out under basic aqueous conditions affording optically active 1,3-disubstitued allenes **15** (Scheme 7). The low enantioselectivity observed in some cases has been explained by isomerisation of the allenylpalladium intermediate.



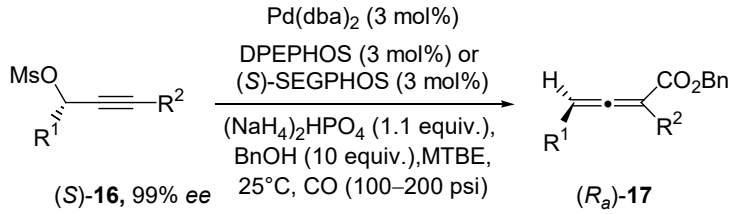
Selected examples:



15a (64%), 94% *ee* **15b** (61%), 92% *ee* **15c** (71%), 90% *ee*

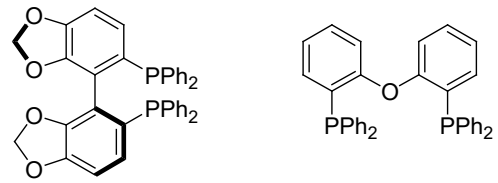
Scheme 7. Synthesis of optically active allenes from propargylic esters and arylboronic acids catalyzed by $Pd(PPh_3)_4$.

Recently, an efficient method for the synthesis of optically active 2,3-allenoates **17** from readily available enantioenriched secondary propargylic mesylates **16** has been reported.[23,24] Allene derivatives have been obtained with moderate to excellent yields and good stereoselectivities under mild reaction conditions using $Pd(dba)_2$ as catalyst and (*S*)-SEGPHOS or DPEPHOS as the ligand (Scheme 8).



R^1 = Me, Et, *n*-C_7H_{15}, *i*-Bu, Bn, allyl
R^2 = *n*-C_nH_{2n+1} (n = 1-4, 6,7), *t*-Bu, *i*-Bu, *i*-pent, allyl, 2-CH_3allyl, $Cl(CH_2)_4$, $Ph(CH_2)_2$

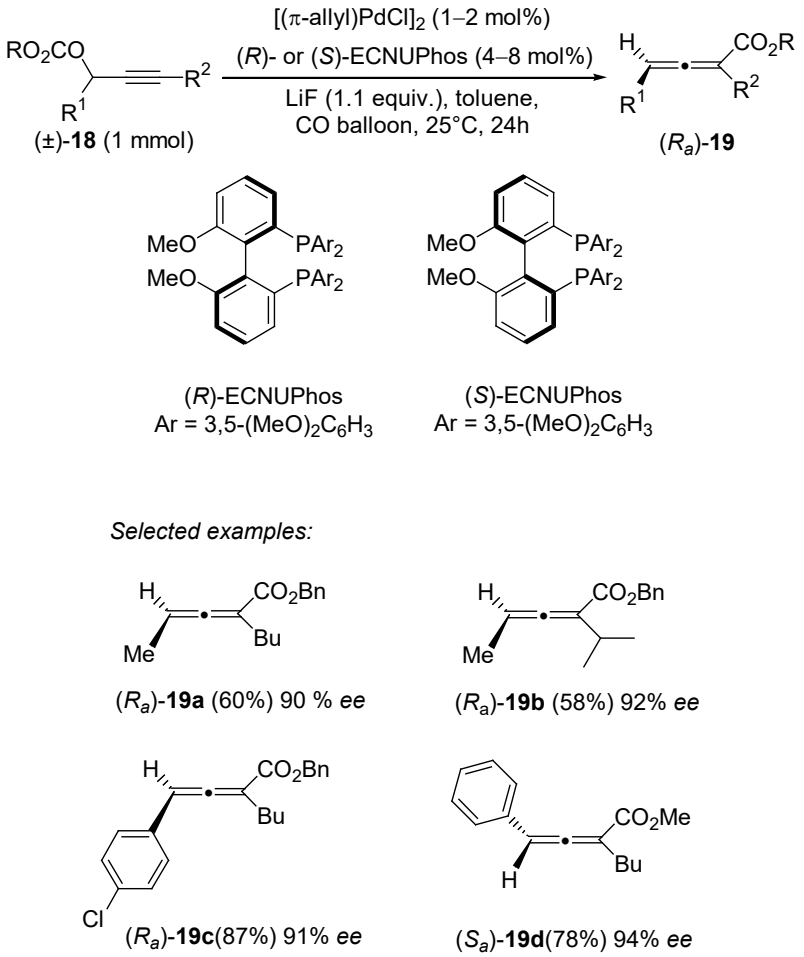
(*S*)-SEGPHOS: (69–90%), 90–97% *ee*
DPEphos: (69–86%), 96–99% *ee*



(*S*)-SEGPHOS DPEPHOS

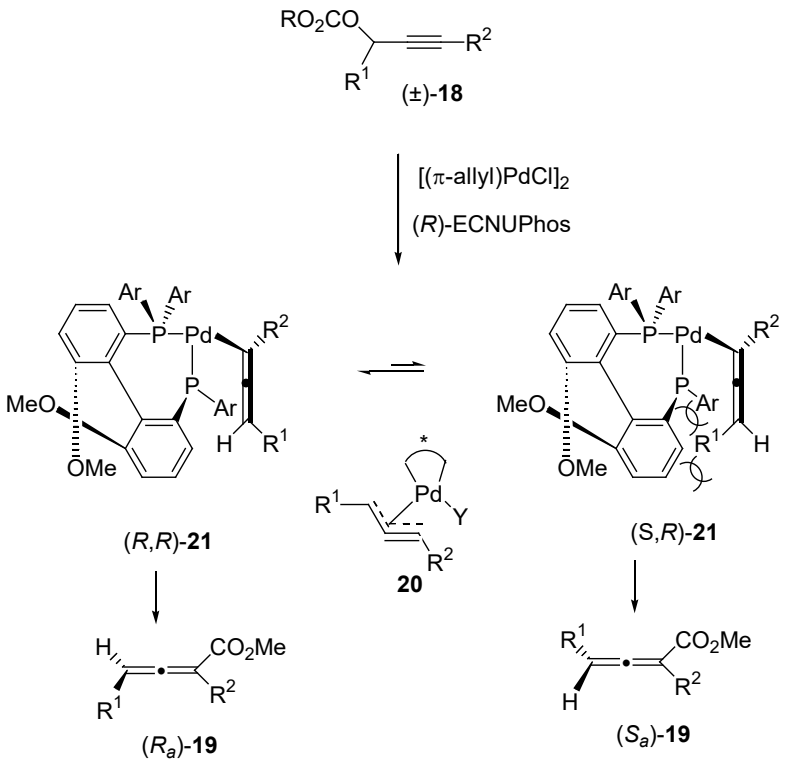
Scheme 8. Synthesis of optically active 2,3-allenoates **17** from enantioenriched propargylic mesylates **16**.

Later on, the same authors have developed a catalytic system to prepare optically active 2,3-allenoates **19** via carbonylation from readily available racemic propargylic derivatives **18**.[25] The authors have found that the combination of (*R*)- or (*S*)-ECNUPhos, a ligand which works at room temperature to prevent possible racemisation, with $[(\pi\text{-allyl})PdCl]_2$ as catalyst is a good system to obtain allenes with high enantioselectivity and efficiency (Scheme 9). In fact, both enantiomers of the allenoate can be obtained at room temperature and 1 atm of CO by applying either (*R*)- or (*S*)-ECNUPhos.



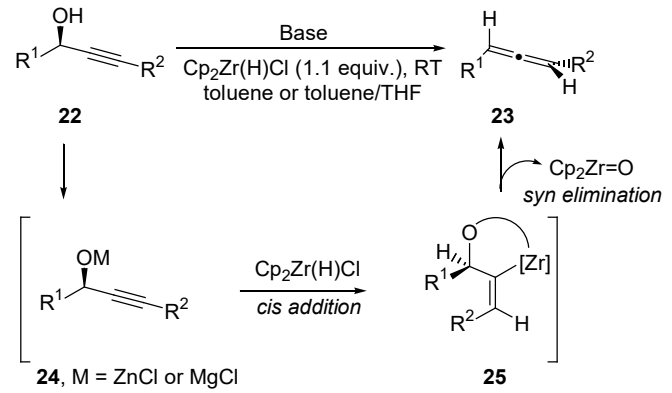
Scheme 9. Synthesis of optically active 2,3-allenoates **19** from racemic propargylic derivatives **18**.

The prediction of the absolute configuration of the allene moiety is shown in Scheme 10. First, oxidative addition of the (*R*)-ECNUPhos-coordinated Pd catalyst with propargylic derivative **18**, both (*R*)- and (*S*)-allenyl palladium species **21** would be formed. There should be an isomerisation process between these two diastereomers **21** involving a σ-π-σ rearrangement via the intermediacy of **20**. It has been showed by structural analysis that (*S*,*R*)-**21** is less favoured due to the steric interaction of each R^1 moiety with the biaryl skeleton and the Ar group of (*R*)-ECNU-Phos, which does not happen for intermediate (*R*,*R*)-**21**. Then, allenoate (R_a)-**19** is formed in high enantioselectivity from intermediate (*R*,*R*)-**21**.

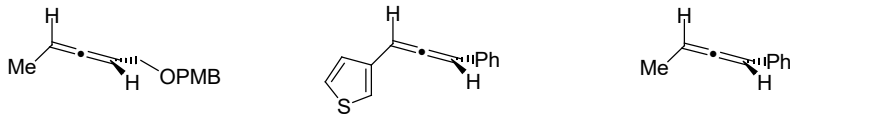


Scheme 10. Prediction of the absolute configuration of chiral allenes **19**.

The previous methodologies explained so far involve the use of propargylic derivatives with an adequate leaving group, but propargylic alcohols can also be the starting material for the preparation of chiral allenes. A direct stereospecific synthesis of allenes **23** from propargylic alcohols **22** has been achieved by reduction with Cp_2ZrHCl (Schwartz reagent), using EtMgCl or EtZnCl (formed *in situ* from Et_2Zn and $ZnCl_2$) as bases (Scheme 11).[26] This process involves the hydrozirconation of internal propargylic alcohols followed by addition of a base. The high efficiency of the chirality transfer is explained by *syn*-hydrozirconation followed by *syn*-elimination of Cp_2ZrO via intermediates **24** and **25**.



Selected examples:



23a (70%), 98% *ee*
98% *ee* of the starting material

23b (89%), 98% *ee*
98% *ee* of the starting material

23c (70%), 97% *ee*
99% *ee* of the starting material

Base = EtMgCl (R^1, R^2 saturated)

Et_2Zn, $ZnCl_2$ (R^1 or R^2 unsaturated)

Scheme 11. Synthesis of chiral allenes from porpargylic alcohols using Schwartz reagent. Selected examples.

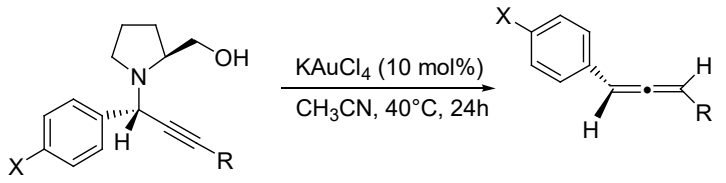
2.2. *From terminal alkynes*

The first synthesis of monosubstituted allenes from terminal alkynes in the presence of paraformaldehyde, *i*-Pr_2NH and CuBr, was developed by Crabbé *et al.* in 1979.[27] Since this discovery, several examples have been developed to optimize the reaction in terms of yield and scope of substrates. Thus, some of the modified procedures involve the use of Cy_2NH and CuI affording the corresponding allenes in higher yields, with the limitation of the use of paraformaldehyde.[28] In fact, when other aldehydes were tested, the expected allenes were not obtained. Fortunately, a related methodology promoted by ZnI_2 solves this drawback and gives access to 1,3-disubstituted allenes from 1-alkynes and different aldehydes.[29]

There are two ways for the synthesis of optically active 1,3-disubstitued allenes from terminal alkynes and aldehydes: *the chiral amine approach* and *the*

catalytic asymmetric synthesis of propargylic amine approach (using a chiral ligand). Both strategies will be covered in this section.

The synthesis of axially chiral allenes from chiral propargylamines has been achieved using a gold salt as catalyst.[30] First of all, chiral amines **26** have been prepared by a gold(III) salen complex-catalyzed coupling reaction of aldehydes, alkynes and amines derived from prolinol.[31] The expected propargylamines have been obtained in excellent enantioselectivities (Scheme 12). Next, propargylamines **26** were converted to enantioenriched allenes (up to 93% yield and up to 97% *ee*) by heating with $KAuCl_4$ in acetonitrile at 40°C for 24h. The study of this reaction has been carried out using chiral propargylamines bearing various functionalities. The scope of this reaction is restricted to the synthesis of 1,3-diarylallenes, and the enantiomeric excess of the allene products is limited on the electronic effect of substrates. In fact, electron-rich propargylamines led the corresponding allenes with low enantioselectivities. This result is explained by coordination of the gold catalyst to axially chiral allenes that subsequently leads to racemization.



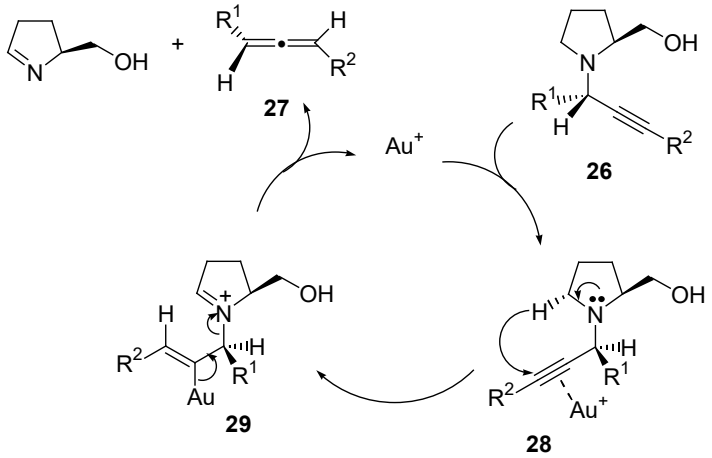
26, 99% *ee*

27
up to 93% yield
up to 97% *ee*

X = H, CF_3, Cl, Br
R = Ph, 4-$CF_3C_6H_4$

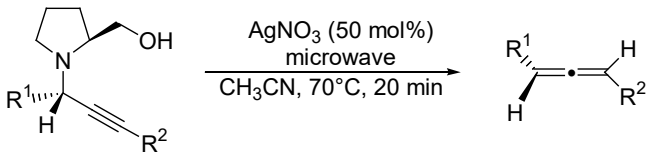
Scheme 12. Synthesis of chiral allenes from propargylic amine catalyzed by a gold(III) complex.

A tentative mechanism, based on ESI-MS analysis and deuterium-labeling experiments, has been proposed (Scheme 13). First of all, Au(I) is generated by reduction of the Au(III) salt ($AuCl_4^-$) by the amine moiety of the substrate. Then, Au(I) is coordinated to the C–C triple bond to give intermediate **28**, which would transform into **29** by intramolecular hydride transfer. Intermediate **29** should suffer deaminoauration to afford allene **27**.



Scheme 13. Tentative mechanism for the synthesis of chiral allenes **27**.

In this context, there are many examples revealing that the chirality of allenes is preserved in silver(I)-mediated organic transformations. Thus, it has been reported the transformation of optically active propargylamines to axially chiral allenes with excellent enantioselectivities.[32] The optimized reaction conditions involves the use of $AgNO_3$ (50 mol%) in acetonitrile at 70°C under microwave irradiation for 20 min (Scheme 14). The authors have observed that this protocol is useful for the synthesis of axially chiral 1,3-alkylarylallenes from propargylamines, affording products in high yields (up to 85%) with almost complete chirality transfer.

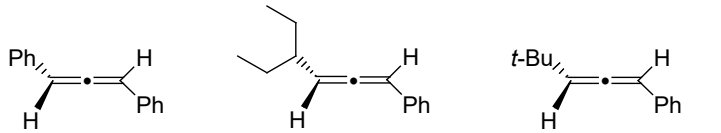


30, 99% *ee*

31 up to 93% yield
up to 97% *ee*

R^1 = aromatic and alkyl group
R^2 = Ph, *n*-Hex

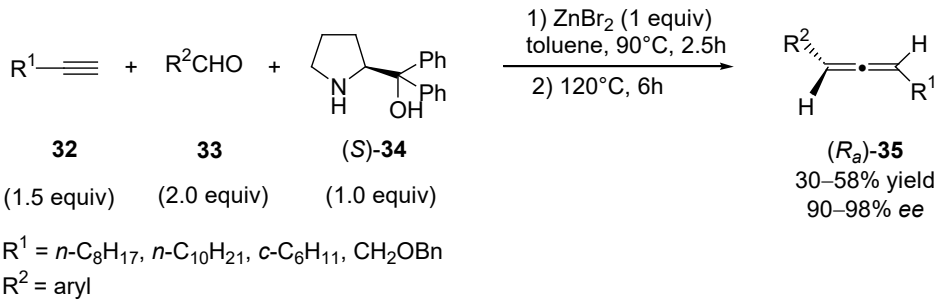
Selected examples:



31a (80%), 99% *ee* **31b** (69%), 98% *ee* **31c** (78%), 96% *ee*

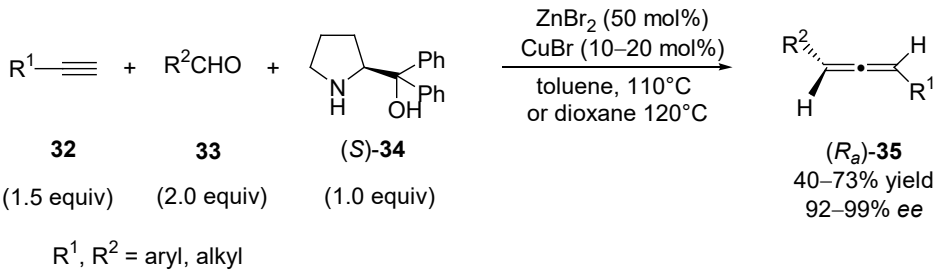
Scheme 14. Synthesis of chiral allenes from porpargylic amines catalyzed by a silver(I) salt.

A "chiral amine approach" has been developed using commercially available (*S*)-α,α-diphenylprolinol **34** as the chiral amine (Scheme 15).[33] The $ZnBr_2$-mediated reaction of alkynes **32**, aldehydes **33** and enantiopure prolinol **34** gives the corresponding allenes in low to moderated yields and good *ee's*. However, the scope of the reaction is very limited as only terminal alkynes with a sterically bulky group and aromatic aldehydes are suitable substrates. When the reaction was tested with simple alkynes with a less sterically bulky group, poor results were obtained.

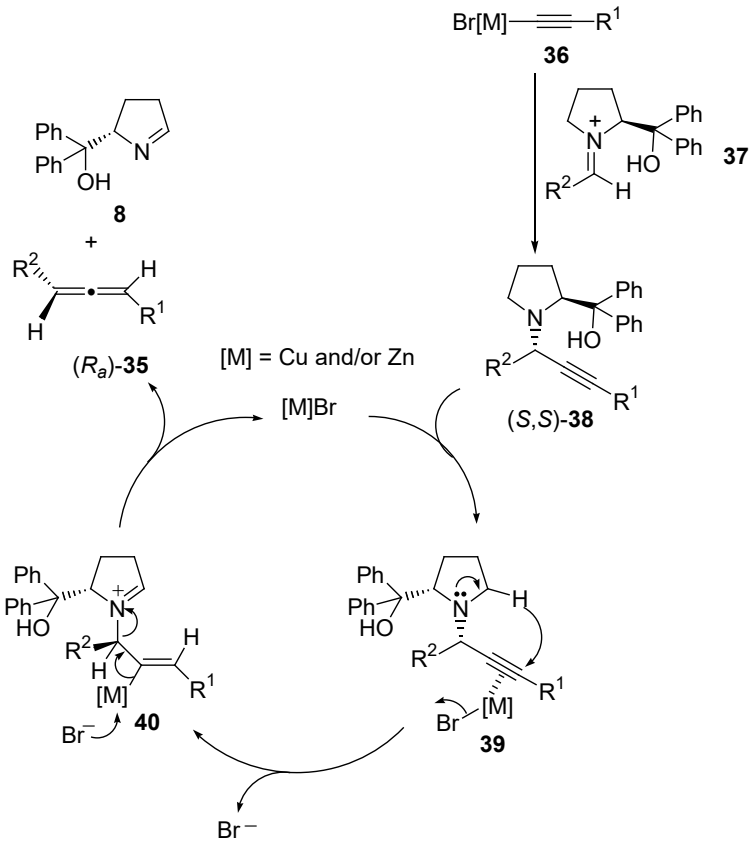


Scheme 15. Synthesis of chiral allenes **34** from (*S*)-α,α-diphenylprolinol.

To further improve the yield and enantioselectivity as well as the scope, the same authors have studied the process using a Cu^{+}/Zn^{2+} bimetallic complex. Reaction of alkynes and aldehydes using a chiral amine (*S*)-α,α-diphenyl-prolinol promoted by bimetallic Zn(II)/Cu(I) has afforded axially chiral allenes (Scheme 16).[34] Interestingly, aliphatic and both electron-poor and –rich aromatic aldehydes are suitable using the optimized conditions. A mechanistic explanation to understand the high enantioselectivity observed in the synthesis of allene (*R*)-**35** is shown in Scheme 17. The alkynylmetal species **36**, which are generated by deprotonation of the starting alkyne **32** in the presence of CuBr, $ZnBr_2$, and amine, reacted with the *in situ* generated intermediate **37** via *Re*-face attack, affording highly enantioenriched propargylic amine (*S*,*S*)-**38**. This species then undergoes highly stereoselective intramolecular 1,5-hydride transfer and β-elimination, via intermediates **39** and **40**, to generate the enantioenriched allene **35** under the participation of Cu(I) and $ZnBr_2$. It has been postulated that CuBr may play a privileged role in the efficient synthesis of chiral propargylic amine whereas both CuBr and $ZnBr_2$ are involved for the generation of allene products.

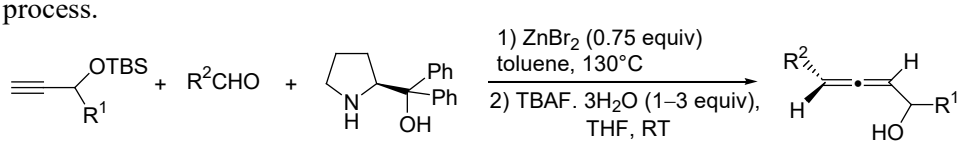


Scheme 16. Synthesis of chiral allenes **35** from (*S*)-α,α-diphenylprolinol.



Scheme 17. Mechanistic explanation for the highly enantioselective synthesis of chiral allenes **35**.

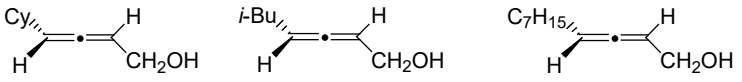
The synthesis of α-allenols from TBS-protected propargylic alcohols **41**, aldehydes **33** and (*S*)-α,α-diphenylprolinol **34** has been reported (Scheme 18).[35] The process is highly efficient and enantioselective using both racemic and optically active TBS-protected propargyl alcohols. In addition, the preparation of α-allenols, with both central and axial chiralities, from optically pure TBS-protected propargylic alcohols have been achieved. Interestingly, the role of the bulky TBS group is related with the excellent enantioselectivity observed in the process.



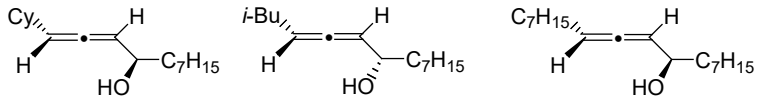
41 (1.1 equiv) **33** (1.5 equiv) (*S*)-**34** (1.0 equiv) **42**

R^1 = H, Cy, *n*-C_7H_{15}, Ph
R^2 = Cy, *c*-C_5H_9, *i*-Bu, *n*-C_7H_{15}, $Ph(CH_2)_2$, Et_2CH

Selected examples:



(*R*$_a$)-**42a** (68%), 99% *ee* (*R*$_a$)-**42b** (45%), 98% *ee* (*R*$_a$)-**42c** (65%), 97% *ee*

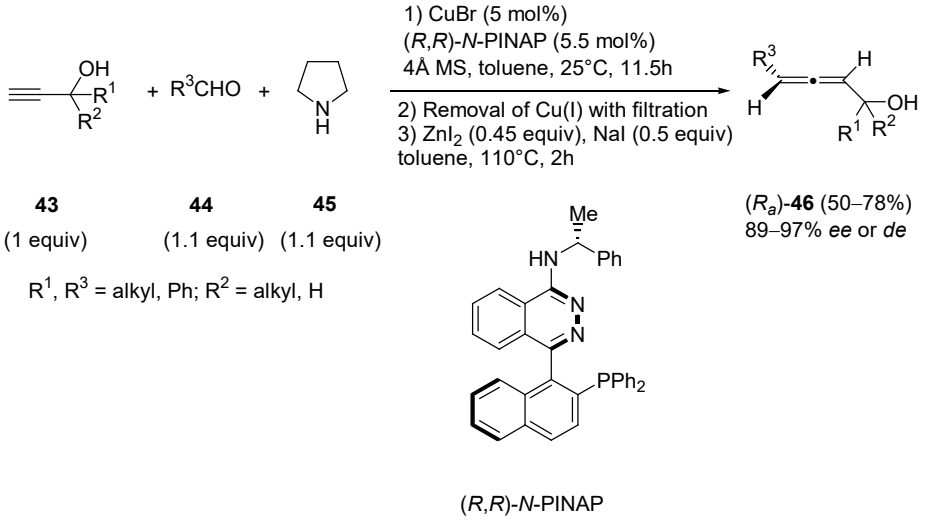


(*R*$_a$,*R*)-**42d** (71%) 99% de, >99% *ee* (*R*$_a$,*S*)-**42e** (74%) 99% de, 99% *ee* (*S*$_a$,*R*)-**42f** (68%) 99% de, >99% *ee*

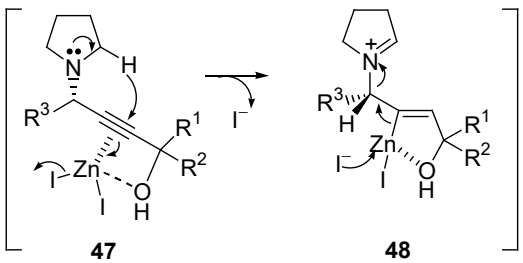
Scheme 18. Synthesis of chiral allenes **35** from (*S*)-α,α-diphenylprolinol.

Due to the expensive nature of the use of stoichiometric amounts of chiral amine **34** and the limitation in the use of protected propargyl alcohols, a second approach was pursued, which involves the use of an external ligand.[36] This approach involves the use of an external chiral ligand such as (*R*,*R*)-*N*-PINAP.[37] Reaction of alkynes **43**, aldehydes **44** and pyrrolidine **45** in the presence of the chiral ligand (*R*,*R*)-*N*-PINAP has afforded the corresponding optically enriched allenes **46** (Scheme 19). The reaction has been studied using racemic and optically active secondary and tertiary propargylic alcohols affording axially

chiral allenes in moderated yields and very practical *ee's*. It is presumed that the role of the hydroxyl group is crucial by coordination of the hydroxyl oxygen with Cu or Zn, via formation of intermediates **47** and **48** (Scheme 20).



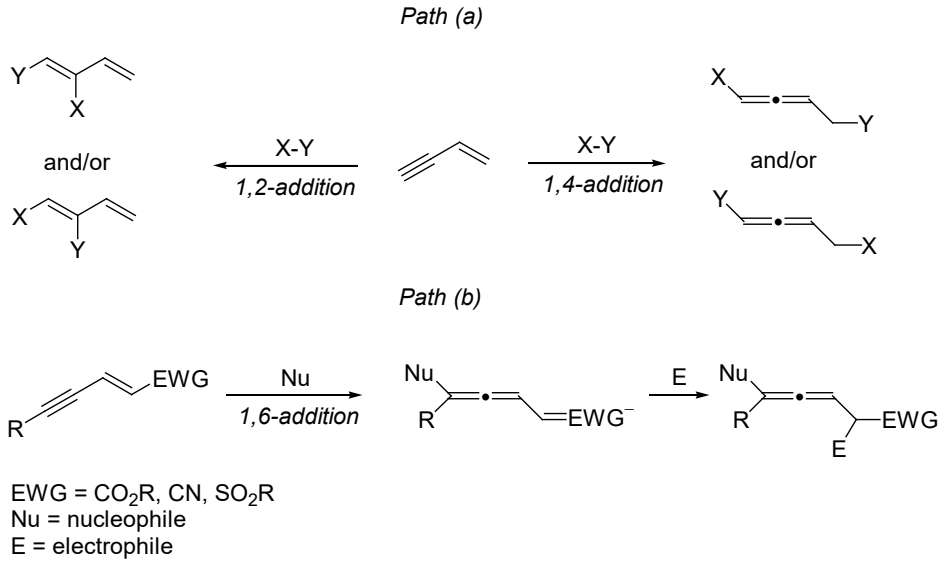
Scheme 19. Synthesis of optically enriched allenes **46** using a chiral ligand.



Scheme 20. Intermediates **47** and **48**, which may explain the absolute configuration of allenes **46**.

2.3. *From conjugated enynes by metal-catalyzed 1,4- or 1,6-addition reactions*

1,4-Addition of hydrosilanes or hydroboranes to conjugated enynes is an efficient synthetic tool to produce multi-substituted functionalized allenic derivatives (Scheme 21, *path a*). However, in some cases, 1,2-addition to the alkynyl moiety of the substrate competes to give a conjugated diene as by-product. On the other hand, the addition of organotitanate reagents to an acceptor-substituted enyne gives the corresponding allenic species via 1,6-addition reaction (Scheme 21, *path b*).

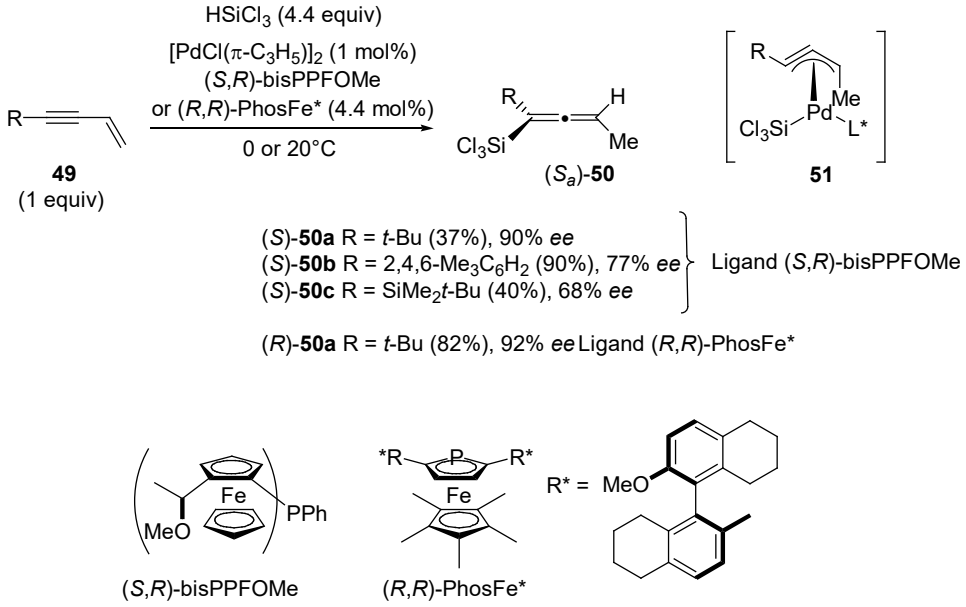


EWG = CO_2R, CN, SO_2R
Nu = nucleophile
E = electrophile

Scheme 21. Synthesis of allenes from conjugated enynes.

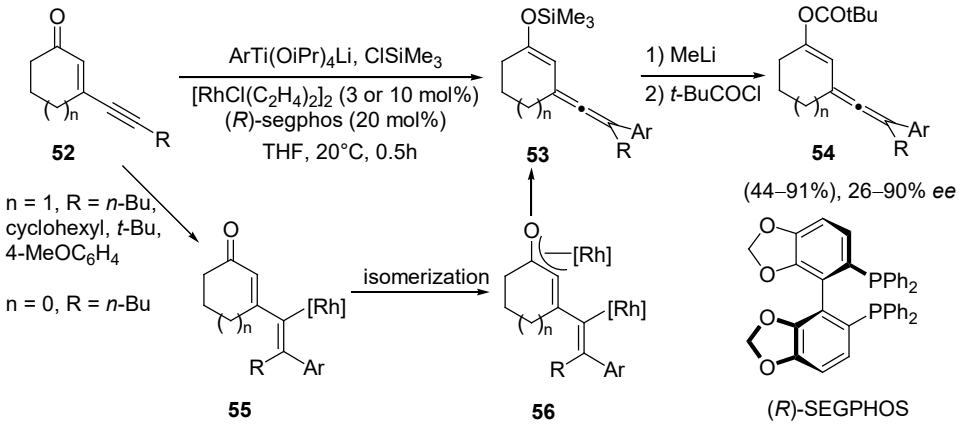
Pd-catalyzed 1,4-addition of hydrosilane to conjugated enynes is a successful methodology to obtain allenylsilanes.[38] A monodentate bulky chiral phosphine, (*S*,*R*)-bisPPFOMe, has been found to be effective and up to 90% *ee* was achieved (Scheme 22). This methodology has been studied in 1-buten-3-ynes **49** containing various types of substituents at 4-position and the authors have found that the selectivity in affording allenylsilane depends on the steric bulkiness of the substituent. In fact, the selectivity is high for 1-buten-3-ynes **49** substituted by sterically bulky groups such as *t*-butyl, mesityl, or *t*-butyldimethylsilyl, while it was low for those substituted with less bulky groups. This observation may imply that the hydrosilylation takes place through a catalytic cycle involving hydropalladation of the double bond in **49**, generating a π-propargyl(silyl)palladium intermediate **51**. Thus, the bulky substituent at the 4-position is essential for retarding the hydropalladation at the alkyne group in **49**.

More recently, the same research group has used a monodentate chiral phosphaferrocene (*R*,*R*)-PhosFe* as chiral ligand in the same asymmetric reaction giving enantioenriched allenes (*R*)-**50** in higher yield and with better enantioselectiviy (92% *ee*).[39] It has been presumed that the sterically demanding η^5-C_5Me_5 moiety in (*R*,*R*)-PhosFe* is important for the efficient performance of the chiral ligand.



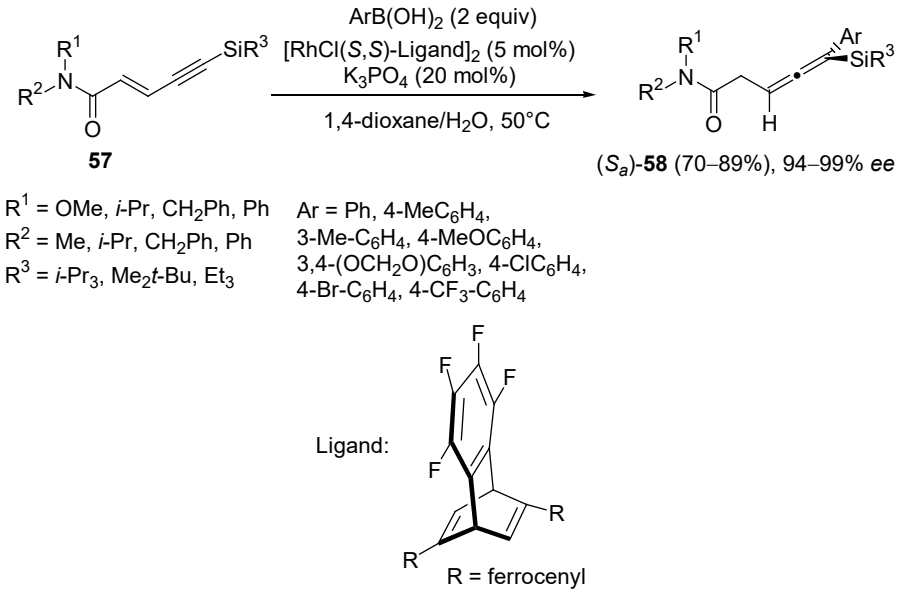
Scheme 22. Synthesis of enantioenriched allenylsilanes **50**.

The addition of aryltitanate reagents $ArTi(OiPr)_4Li$ to 3-alkynyl-2-en-1-ones **52** in the presence of chlorotrimethylsilane and a rhodium-(*R*)-SEGPHOS as catalyst is a synthetic methodology to obtain axially chiral allenylalkenyl silyl enol ethers **53** with up to 93% *ee* (Scheme 23).[40] Due to the instability of of silyl ethers **53**, these compounds were transformed into the pivalate esters **54** by reaction of **53** with MeLi in ether followed by reaction with pivaloyl chloride. The formation of the allenyl derivatives **53** may proceed through a catalytic cycle. First, insertion of the C–C triple bond of enynones **52** into the rhodium-aryl bond forms alkenylrhodium **55**. This intermediate would isomerize into the thermodynamically more stable oxa-π-allylrhodium species **56**. At this point, during the isomerisation step, the sterochemical outcome of the asymmetric 1,6-addition is settled. Finally, the silylation and transmetalation of intermediate **56**, would afford allenylalkenyl silyl ether **53** and regeneration of the catalyst.



Scheme 23. Synthesis of allenylalkenyl silyl enol ethers **53**.

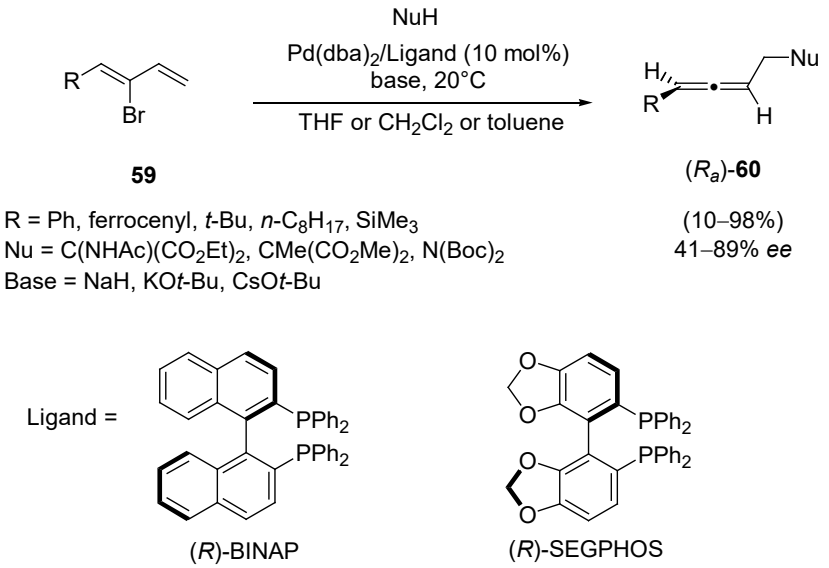
1,6-Addition of carbon nucleophiles to conjugated enynamides is an efficient approach for the preparation of funcionalized allenes. Usually, copper catalysts are used for the selective 1,6-addition of organometallic reagents to enynoates leading to allenes. However, the asymmetric version has not been reported using copper salts. In this context, rhodium-catalyzed asymmetric 1,6-addition of arylboronic acids to β-alkynyl acrylamides **57** substituted with a silyl group on the alkyne terminus to give allenylsilanes **58**, has been reported (Scheme 24).[41] Enynamides **57** substituted with *tert*-butyldimethylsilyl, triethylsilyl, diisopropyl, dibenzyl and diphenylamide were good substrates, affording the corresponding allenes **58** in good yields (70–89%) and enantioselectivities (94–98% *ee*). In addition, arylboronic acids with aryl groups bearing a variety of substituents were successfully introduced.



Scheme 24. Synthesis of enantioenriched allenylsilanes **58**.

2.4. *From dienes*

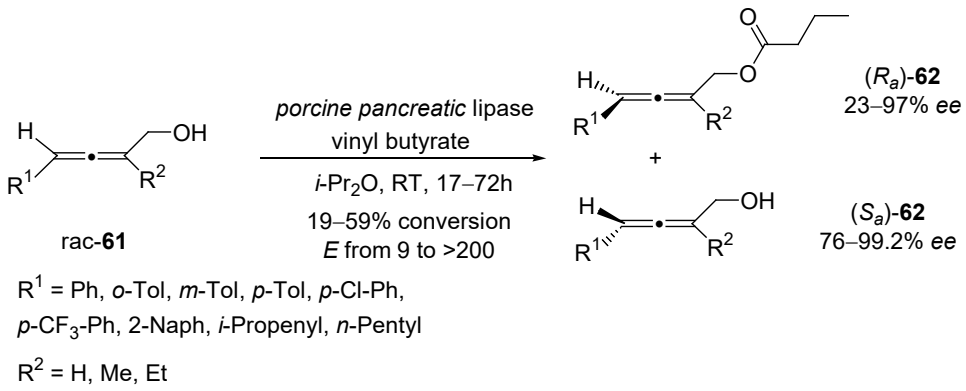
The synthesis of enantiomerically enriched allenes has been studied in depth using achiral conjugated dienes using a palladium-BINAP/SEGPHOS species as chiral catalyst.[42,43] Chiral allenes **60** have been obtained in low to good yields and low to moderate enantioselectivities (Scheme 25). The reaction of a diene **59** with a soft nucleophile must take place via a formal S_E2' pathway via an (alkylidene-π-allyl)palladium species. Interestingly, allenylsilanes have also been obtained, which are excellent synthetic intermediates in reactions with electrophiles.[44] The scope of this methodology has also been studied for the preparation of conjugated vinylallenes from 2-bromo-1,3,5-trienes.[45] Furthermore, a formal total synthesis of (*R*,*E*)-(−)-tetradeca-2,4,5-trienoate, a pheromone of male dried bean beetle, has been developed using this methodology.[46]



Scheme 25. Synthesis of enantioenriched allenes **60**.

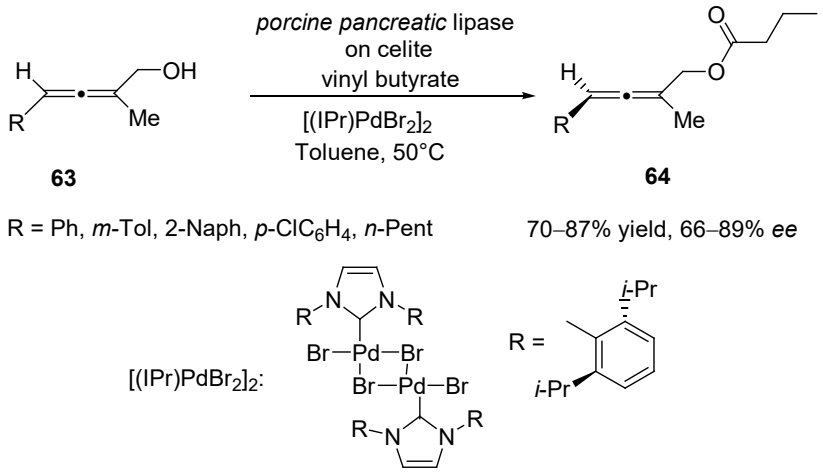
2.5. *From racemic allenes*

Kinetic resolution (KR) of racemic allenes is a valuable methodology which involves the use of enzymes. The kinetic resolution of primary allenic alcohols by enzymatic transesterification from vinyl esters using the cheap and commercially available *porcine pancreatic* lipase (PPL) has been reported.[47] A family of racemic α-allenols **61** with different substituents at the chiral allene was reacted to the PPL-catalyzed kinetic resolution (Scheme 26). Presumably, a substituent in the 2-position is decisive for the recognition by the protein. On the other hand, incrementing the bulkiness in the 2-position by changing from methyl to ethyl has not influence because a high enantioselectivity was observed. The effect of modifications at the aryl group in the 4-position of the allene remained insignificant and selectivity issues seem depend on the substitution position rather than the nature of the substituent.



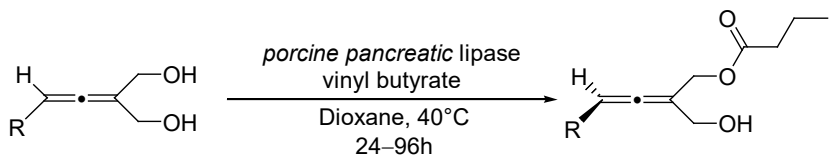
Scheme 26. Kinetic resolution of primary allenic alcohols using PPL.

However, an important limitation of this procedure is that a maximum theroretical yield of 50% can be obtained. In this sense, many efforts have been focused to solve this problem and to afford compounds with high enantiomeric purity, but with improved yields. Thus, classical kinetic resolution has grown up into dynamic kinetic resolution (DKR). In this process, it is possible to obtain a quantitative yield of one of the enantiomers.[48] DKR combines the resolution step of kinetic resolution with an in situ equilibration or racemisation of the chirally labile substrate. The first report on chemoenzymatic DKR of axially chiral allenes used a combination of a palladium catalyst, such as $[(IPr)PdBr_2]_2$ with porcine pancreatic lipase (PPL) in presence of vinyl butyrate as the acyl donor.[49] The DKR of allenic alcohols **63** have been achieved and the expected (S_a)-butyrates **64** were obtained in good yields and enantioselectivities (Scheme 27).



Scheme 27. Chemoenzymatic dynamic kinetic resolution of primary allenic alcohols **63** using the combination of a palladium catalyst and PPL.

An alternative strategy to resolve yield limitations in enzyme-catalyzed transformations is the use of prochiral substrates. Thus, by selective transformation of one of two enantiotopic groups, elements of symmetry are eliminated and optically active products can be obtained in high yield.[50] The enantioselective enzymatic desymmetrization of prochiral allenic diols has been reported.[51] It has been carried out the selective acylation of one of the enantiotopic hydroxyl groups of allenes **65** using PPL as catalyst affording enantioenriched allenes **66** in good yields and *ee's* (Scheme 28). The scope of the reaction has been studied using a variety of substituted allendiols through enzymatic transesterification.



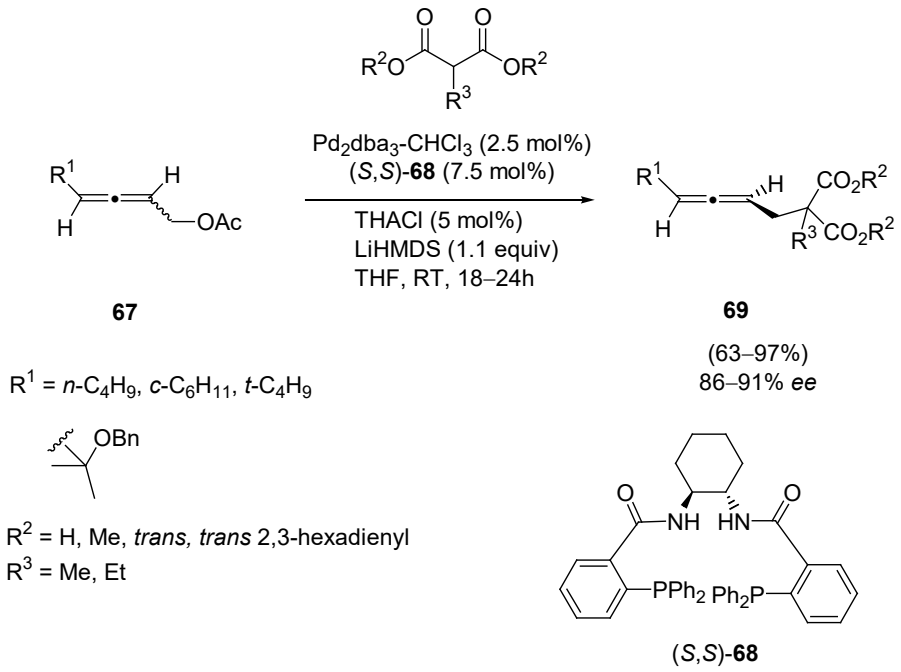
65 **66**

R = Ph, 3-MeC_6H_4, 4-Cl-C_6H_4, 4-MeOC_6H_4, 3,4-methylendioxyphenyl, 2-naphtyl, 2-trimethylsilylethynyl

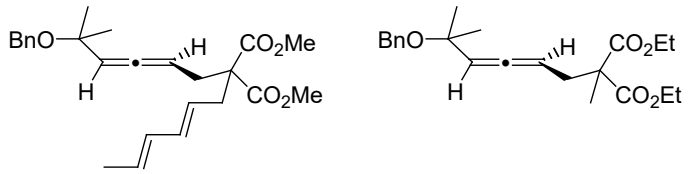
(89–96%), 98–99% *ee*

Scheme 28. Enzymatic desymmetrization of prochiral allenes **65** using PPL.

The development of a methodology coined "dynamic kinetic asymmetric transformation" (DYKAT) which involves the transformation of racemic compounds to useful chiral compounds using simple addition reactions has been presented.[52,53,54,55] In particular, it has studied the dynamic kinetic asymmetric allylic alkylation of racemic allenes **67** with malonates (Scheme 29).[56] After optimization of the reaction conditions, the authors found a good catalytic system composed of Pd_2dba_3-$CHCl_3$ (2.5 mol%), ligand **68** (7.5 mol%), and tetrahexylammonium chloride (THACl) (5 mol%). Then, asymmetric addition of malonates to allenes in presence of LiHMDS afforded allenes **69** in good yields and *ee's*. Increasing the size of the allene substituent slightly increased the enantiomeric excess. Unsubstituted malonates also afforded high enantioselectivity.



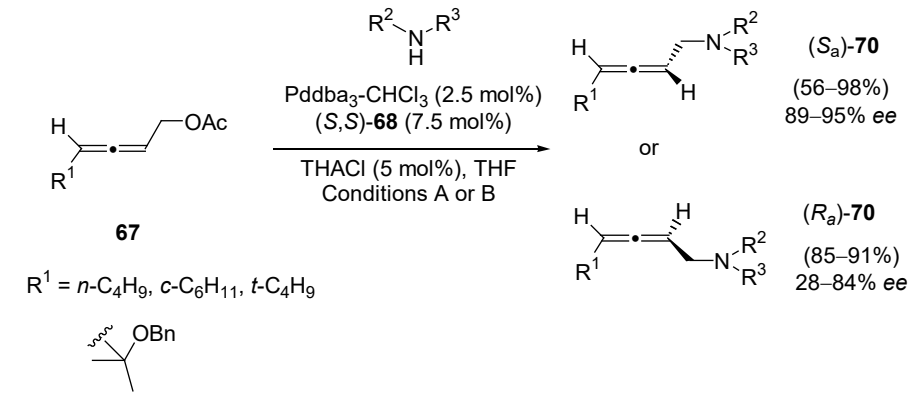
Selected examples:



(*S*$_a$)-**69a**, (97%), 90% *ee* (*S*$_a$)-**69b**, (95%), 91% *ee*

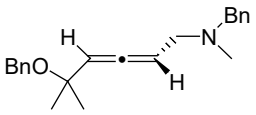
Scheme 29. Synthesis of axially chiral allenes **69** by dynamic kinetic asymmetric alkylation of allenes **67** with malonates.

The methodology has also been studied using amines instead of malonates (Scheme 30). Interestingly, chiral (+)-(*S*$_a$)-allenylamines **70** have been obtained with high enantioselectivities from allenes **67** using 1.1 equiv of the amine and excess of the base. However, the utilization of the same catalytic system and a 2-fold excess of the amine as base, resulted in the formation of the opposite enantiomer (*R*$_a$) with lower enantiomeric excess (28–65%). A more recent research, which involves the synthesis of optically pure tetrasubstituted allenes from racemic allenes under phase-transfer-catalysed conditions, has been described.[57]

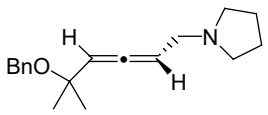


Conditions A: amine (1.1 equiv), Cs_2CO_3 (3 equiv), RT, 1 day.
Conditions B: amine (2.2 equiv), RT, 1 day.

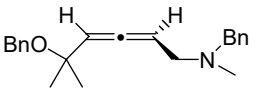
Selected examples:



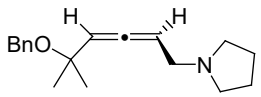
Conditions A: (S_a)-**70a** (98%), 95% *ee*



Conditions A: (S_a)-**70b** (86%), 89% *ee*



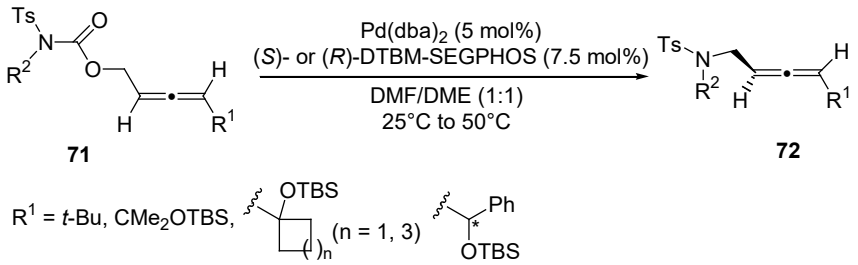
Conditions B: (R_a)-**70a** (91%), 65% *ee*



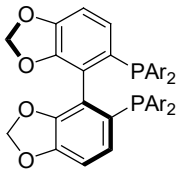
Conditions B: (R_a)-**70b** (90%), 28% *ee*

Scheme 30. Synthesis of axially chiral allenyl amines **70** by dynamic kinetic asymmetric alkylation of allenes **67** with amines.

An intramolecular decarboxylative amination protocol for the synthesis of axially chiral allenes **72** from allenyl *N*-tosylcarbamates **71**, has been developed using the chiral ligand (*S*)- or (*R*)-DTBM-Segphos.[58] For the high efficiency of the process, the authors have observed that a sterically bulky R^1 group on the allene **71** is essential to achieve good *ee's* values (Scheme 31).

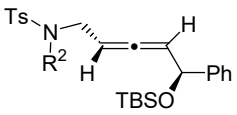


R^2 = Me, Et, *i*-Pr, *i*-pentyl, isoprenyl, Bn, 1-naphtylCH$_2$, 4-BrC$_6$H$_4$CH$_2$

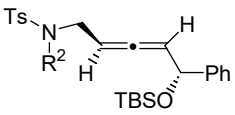


DTBM-SEGPHOS
Ar = 3,5-*t*-Bu$_2$-4-MeOC$_6$H$_2$

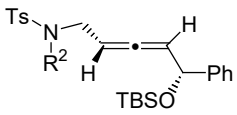
Selected examples:



(R_a,*S*)-**72a**
(85%), 97% *de*, >99% *ee*



(S_a,*R*)-**72b**
(83%), 97% *de*, >99% *ee*



(R_a,*R*)-**72c**
(80%), 92% *de*, >99% *ee*

Scheme 31. Synthesis of axially chiral allenyl amines **72** by decarboxylative amination of from allenyl *N*-tosyl carbamatos **71**.

3. Axial-to-central chiralily transfer from allenes

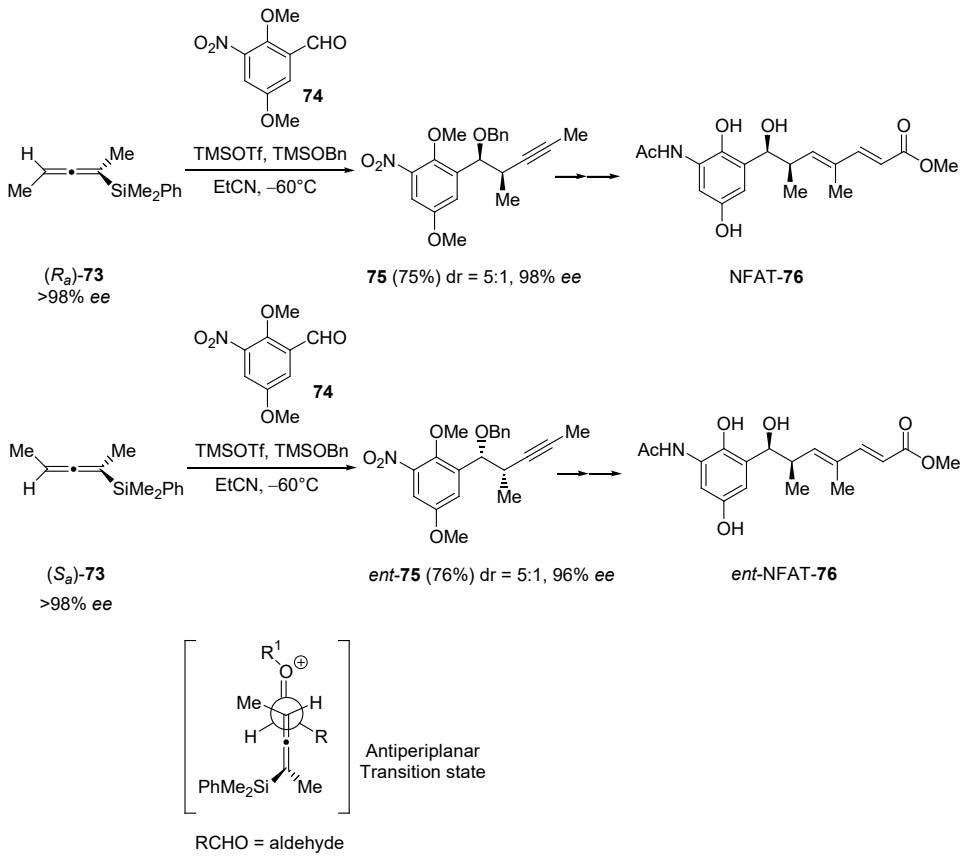
The development of efficient and practical methodologies capable to transfer axial-to-central chirality of allenes is not an easy task and has been reviewed recently.[59,60,61,62] Fortunately, many synthetic strategies have achieved this goal with good to excellent chirality transfer. In this section we have selected the most recent reports which have been classified by type of reaction.

3.1. *Organosilane reagents as carbon nucleophiles*

Allenylsilanes are versatile synthetic intermediates in organic synthesis, reacting with electrophiles to give the corresponding allylated and propargylated

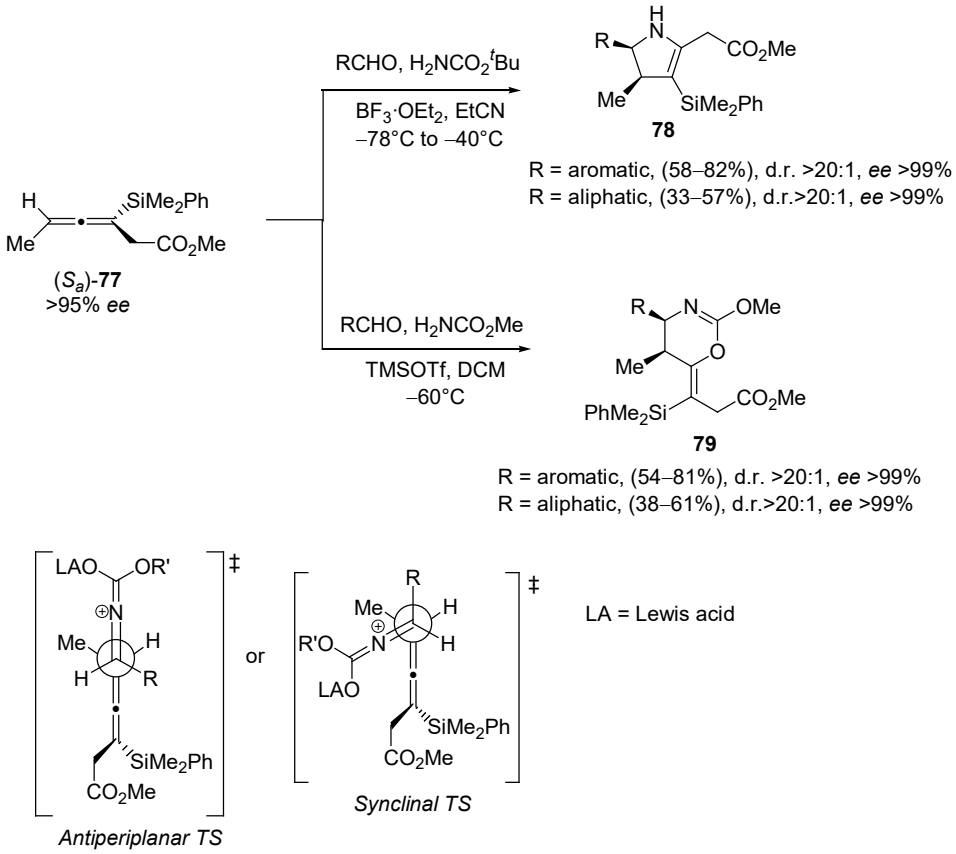
compounds.[63] The reaction takes place via a regio- and stereospecific S_E2' mechanism. In addition, enantioenriched allenes are capable to transfer their axial chirality into new formed stereogenic centers.

Metalated allenes have been used as nucleophiles in different organic transformations where the axial chirality of the allene is successfully transfer to central chirality in the final products. In particular, enantioenriched allenylsilanes have been used in a three-component reaction, catalyzed by a Lewis acid, to form homopropargylic ethers.[64] More recently, the same research group has described the use of chiral allenylsilanes in addition reactions to oxonium ions for the direct formation of stereochemically well-defined homopropargylic ethers. Besides, the application in the synthesis of both enantiomers of a polyketide natural product, NFAT-**76** has been reported.[65] The three-component propargylation reaction between aromatic aldehyde **74**, (benzyloxy)trimethylsilane, and chiral silane (*S*)-**73** or (*R*)-**73**, produced internal alkynes **75** and *ent*-**75** with good yield, diastereoselectivity and excellent *ee's* values (Scheme 29). In both cases, *syn* products are obtained as the major diastereomer. This result is in agreement with an antiperiplanar transition state, where the destabilizing interaction between the R moiety on the oxonium ion and the methylene groups of the allene is reduced. Further transformations made on products **75** afforded NFAT-**76** and *ent*-NFAT-**76**.



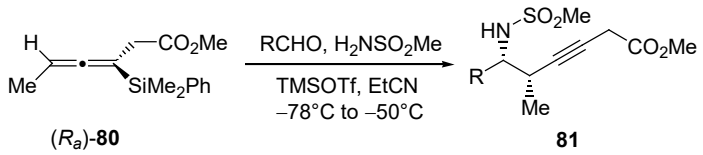
Scheme 32. Reaction of chiral allenylsilanes **73** with *in situ* generated oxonium ions. Application to the synthesis of both enantiomers of NFAT-**76**, a polyketide natural product.

Highly enantioenriched allenylsilane (*S*)-**77** reacts with *in situ* generated iminium ions under Lewis acid catalysis using a polar solvent (EtCN).[66] The products obtained, dihydropyrroles **78**, via a [3+2] annulation reaction, were prepared in good yields when aromatic aldehydes were used and with lower yields when aliphatic aldehydes were tested (Scheme 33). The stereochemical result is explained by either an antiperiplanar or synclinal transition state. Then, the axial chirality of the allenylsilane is effectively transferred to the *si* face of the iminium ion. By contrast, when the amine source was replaced by methyl carbamate, dihydrooxazines **79** via a [3+3] annulation reaction, were obtained (Scheme 33). The optimal conditions for their formation were the use of TMSOTf as Lewis acid and DCM as solvent.



Scheme 33. Reaction of chiral allenylsilanes with *in situ* generated iminium ions to give dihydropyrroles **78** and dihydrooxazines **79**.

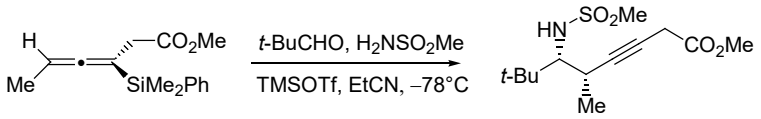
Later on, the same research group has described a three-component reaction of enantioenriched allenylsilanes **80**, aldehydes, and sulfonamides mediated by TMSOTf to give enantioenriched homopropargylic sulfonamides **81** (Scheme 34).[67] Primary aliphatic aldehydes gave compounds **81** in moderate to high yields while tertiary aliphatic aldehydes gave high yields using higher temperatures. However, the reactions with aromatic aldehydes were more difficult in terms of reaction time and selectivity. The axial chirality in compounds **80** was transferred into point chirality in products **81a** and *ent*-**81a**.



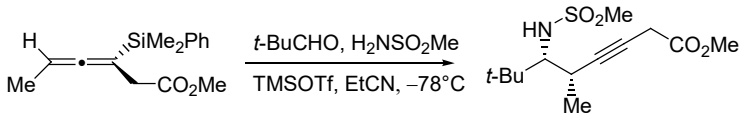
(R_a)-**80** **81**

RCHO = secondary aliphatic aldehydes, (77–81%), d.r.: >20:1
RCHO = primary aliphatic aldehydes, (64–81%), d.r.: 5:1–10:1
RCHO = tertiary aliphatic aldehydes, (82–82%), d.r.: >20:1
RCHO = aromatic aldehydes, (28–59%), d.r.: 6:1–13:1

Selected examples:



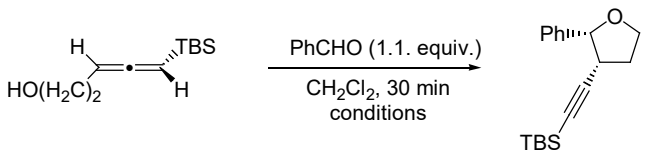
(R_a)-**80a**, 98% *ee* **81a** (76%), d.r.: 20:1, 98% *ee*



(S_a) **80**, >99% *ee* *ent*-**81a** (76%), d.r.: 20:1, 99% *ee*

Scheme 34. Reaction of chiralallenylsilanes **80**, aldehydes, and sulfonamides to give enantioenriched homopropargylic sulfonamides **81**.

β-Hydroxy allenyl silanes have been used for the synthesis of trisubstituted tetrahydrofurans, tetrahydropyrans, and pyrrolidines via Prins cyclization with carbonyl compounds.[68] In particular, the reaction of enantioenriched allene (*S*)-**82** (92% *ee*) with benzaldehyde and TMSOTf at 0°C afforded tetrahydrofuran **83** in 78% *ee* (Scheme 35). Interestingly, when TMSOTf was used in stochiometric amount, 85% *ee* in compound **83** was observed.



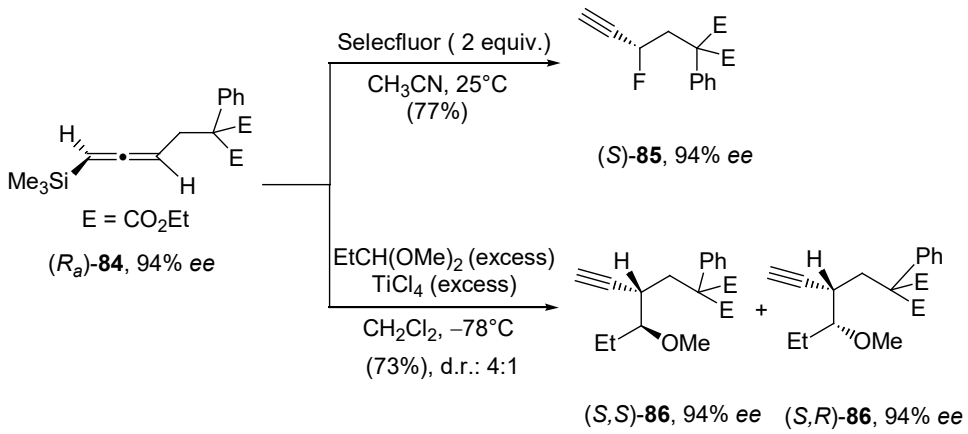
(S_a)-**82**, 92% *ee* (2*R*,3*R*)-**83**
d.r.: > 20:1

Conditions:

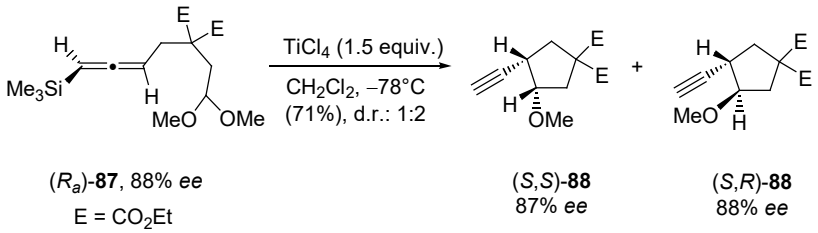
TMSOTf (0.1 equiv.), 0°C, (97%), 78% *ee*
TMSOTf (1.1. equiv.), –78°C, (97%), 85% *ee*

Scheme 35. Reaction of enantioenriched β-hydroxy allenyl silane **82** with benzaldehyde to give tetrahydrofuran **83**.

Axial-to-central chirality transfer of allenylsilanes to alkynes has also been reported.[69] Electrofilic fluorination of enantioenriched allene **84** with Selecfluor afforded propargylic fluoride **85** in 94% *ee* in 77% yield (Scheme 36). Reaction of allene **84** with propanal dimethylacetal at −78°C in the presence of $TiCl_4$ gave a (4:1) diastereomeric mixture of homopropargylic methyl ethers **86** in 73% and 94% *ee* (Scheme 36). In addition, the intramolecular nucleophilic addition to dimethylacetal has also been studied. Thus, reaction of acetal-tethered allenylsilane (*R*)-**87** with $TiCl_4$ gave a mixture of two diastereomers (*S*,*S*)-**88** and (*S*,*R*)-**88** in a 1.2 molar ratio (Scheme 37).



Scheme 36. Reaction of allenylsilane **84** with propanal dimethylacetal and Selectfluor.

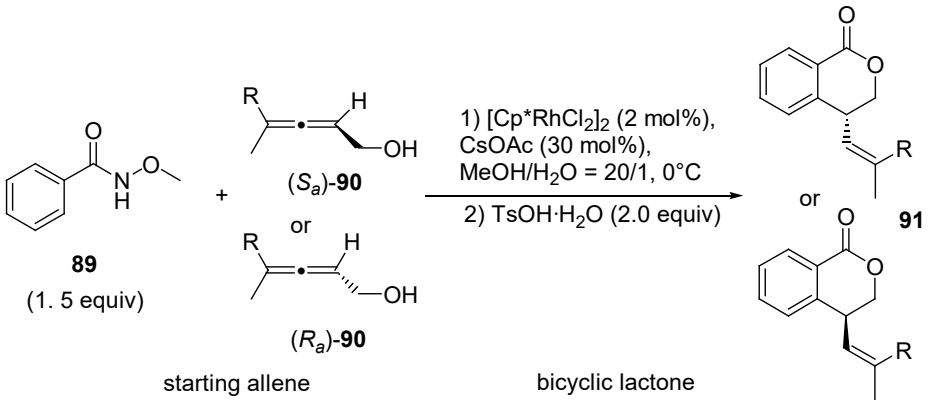


Scheme 37. Cyclization reaction of allenylsilane **87** with $TiCl_4$.

3.2. *Metal-catalyzed or metal-promoted cyclizations*

Metal-catalyzed cyclization reactions of unsaturated compounds, such as enynes, dienes or allenynes, are useful strategies to obtain cyclic compounds, when at

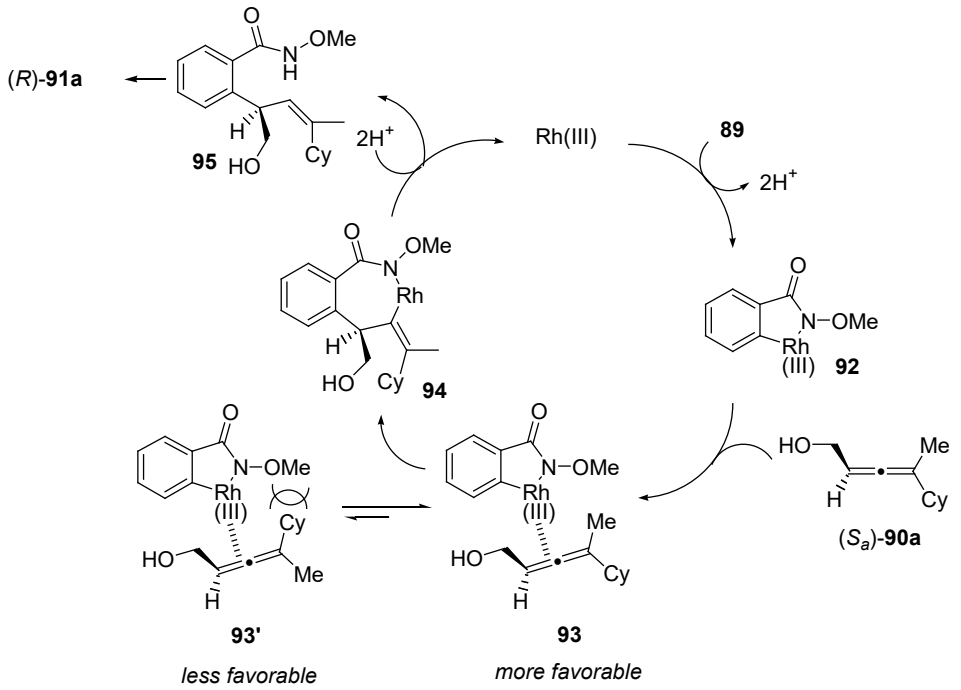
least one degree of unsaturation is consumed.[70] A Rh(III)-catalyzed hydroarylation reaction of enantiopure allenols **90** with *N*-methoxybenzamide **89** has been described (Scheme 38). The process takes place via C–H bond functionalization and allene insertion followed by lactonization.[71] The reaction is conducted under very mild conditions and high efficient axial chirality transfer has been observed.



starting allene	bicyclic lactone
(S_a)-**90a**, R = Cy, 99% *ee*	(*R*)-(*Z*)-**91a** (70%), 99% *ee*
(R_a)-**90a**, R = Cy, 97% *ee*	(*S*)-(*Z*)-**91a**, (67%), 97% *ee*
(S_a)-**90b**, R = BnCH$_2$, 99.7% *ee*	(*R*)-(*Z*)-**91b**, (56%), 99.7% *ee*
(R_a)-**90b**, R = BnCH$_2$, 99.7% *ee*	(*S*)-(*Z*)-**91b**, (54%), 99.6% *ee*

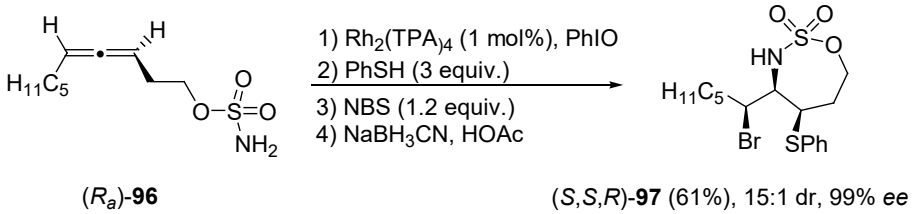
Scheme 38. Rh(III)-catalyzed hydroarylation of allenols **90** with *N*-methoxybenzamide to give bicyclic lactones **91**.

A probable mechanism for this reaction has been proposed in Scheme 39. The first step would be the arene electrophilic rhodation of *N*-methoxybenzamide **89** to give the cyclic intermediate **92**. The formation of this intermediate would be followed by coordination with the less-substituted C=C bond of the allene moiety. Mild insertion of this C=C bond would afford C(sp^2)-Rh intermediate **94**. The formation of **94** would explain the regioselectivity observed in the process. In addition, the steric interaction observed in **93** and **93'** may explain the observed *Z/E* stereoselectivity and axial chirality transfer of the allenes. Finally, protonolysis with in situ-generated H^+ would yield **95** with regeneration of the catalyst.



Scheme 39. Proposed mechanism for the Rh(III)-catalyzed hydroarylation of allenes to give bicyclic lactones.

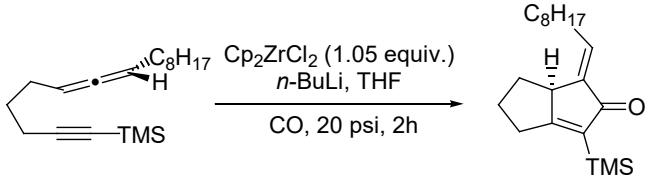
A methodology to prepare stereotriads containing three contiguous heteroatom-bearing carbons of the general pattern X/N/Y has been developed.[72] This transformation involves a Rh-catalyzed intramolecular conversion of an allenic sulfamate **96** into a highly reactive methylene aziridine, which in the presence of a nucleophile underwent regioselective ring-opening to yield the *E*-enesulfamate **97** exclusively in 61% yield and 99% *ee* (Scheme 40).



Scheme 40. Strategy for the preparation of a nitrogen-containing stereotriad from allenes.

Pauson-Khand reaction involving an allene moiety is an excellent strategy to give cyclopentenones.[73,74] Reaction of enantiopure allenyne **98** in the presence of a zirconium catalyst has afforded bicycle[3.3.0]octenone **99** in 39% yield and

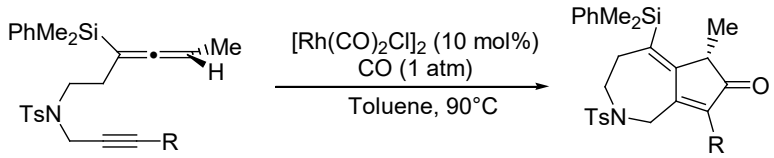
85% *ee* (Scheme 41).[75] The authors have explained that the loss of enantiomeric purity might be due to an isomerisation of the diastereomeric (*Z*)-α-alkylidene cyclopentenone to the (*E*)-α-alkylidene cyclopentenone.



98, 95% *ee* **99** (39%), 85% *ee*

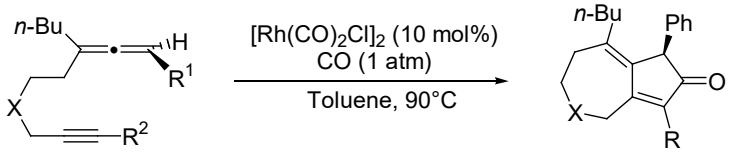
Scheme 41. Pauson-Khand reaction of allenyne **98** to give bicycle[3.3.0]octenone **99**.

More recently, the same research group has described the chirality transfer in an intramolecular Rh(I)-catalyzed allenic Pauson-Khand reaction to 5,7-bicyclic ring systems.[76] Thus, cyclocarbonylation reactions of allene-ynes **100** and **102** gave cycloadducts **101** and **103,** respectively, in moderate to good yields and excellent *ee* values. Scheme 42 shows some selected examples.



100 > 93% *ee*
R = Me, H, Ph, TMS, 2-thienyl, 3-thienyl, cyclopropyl

101 (66–95%)
ee >96–>99%



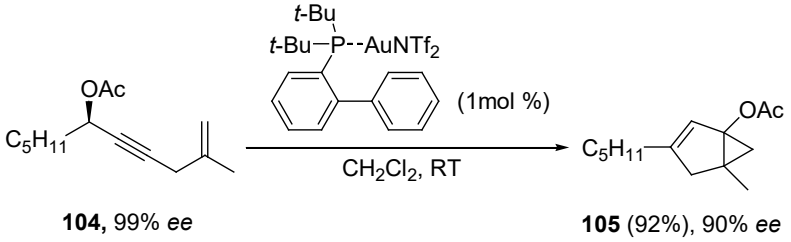
102 > 74% *ee* (R^1 = Ph), 99% *ee* (R^1 = Me)
X = NTs, O, $C(CO_2Et)_2$
R^1 = Me, Ph
R^2 = Me, Ph, TMS, cyclopropyl

103 (40–92%)
ee >22–>88%

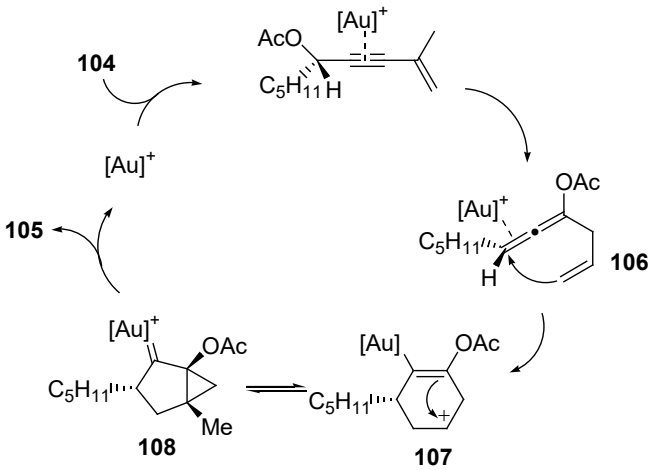
Scheme 42. Pauson-Khand reaction of allene-ynes **100** and **102** to give cycloadducts **101** and **103**.

Nobel metal catalyzed enyne cycloisomerizations is a very practical synthetic tool to create molecular complexity in a single step.[77] In this context, many research groups have focused their attention in the development of strategies involving enantiomerically pure allenes.[62]

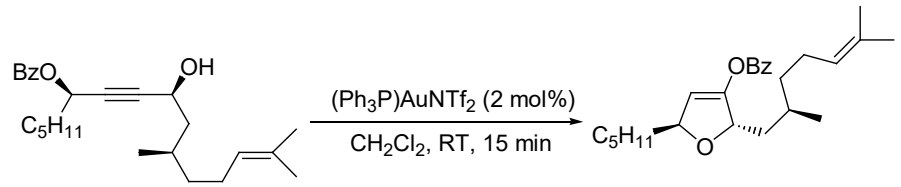
The use of a gold catalyst in the 1,3-acyloxy-migration of propargyl acetates gives the corresponding allenyl acetate, which can be involved in different cyclization processes.[78] For example, gold(I)-catalyzed cycloisomerization of enantioenriched propargyl acetate **104** has afforded bicycle[3.1.0]hexane **105** in excellent yield and enantioselectivity (Scheme 43).[79] The process implicate a enantioselective 1,3-migration of the acetoxy group giving an allenyl acetate intermediate. The mechanism involves the gold(I) activation of the triple bond in compound **104** to form allene **106** through a [3,3]-sigmatropic rearrangement (Scheme 44). Next, gold(I) activation of the allene promotes the nucleophilic attack of the alkene moiety to give a cationic vinyl-gold intermediate **107**. Next, formation of the cyclopropyl ring supported by electron donation from gold(I) affords gold(I) carbene **108**. Finally, 1,2-hydride shift regenerates the gold(I) catalyst and affords bicycle[3.1.0]hexane **105**. This methodology has been applied to the synthesis of enantiopure functionalized 2,5-dihydrofurans **110** from enantioenriched butynol **109** (Scheme 45).[80]



Scheme 43. Gold(I)-catalyzed cycloisomerization of enantioenriched propargylic acetate **104**.



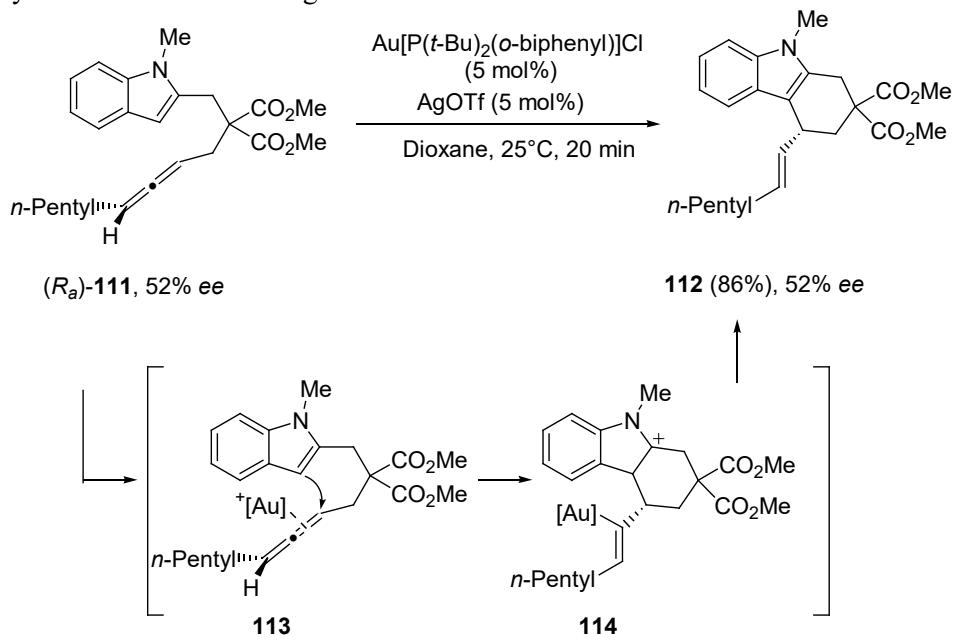
Scheme 44. Mechanism of gold(I)-catalyzed cycloisomerization of enantioenriched propargylic acetate via an allene intermediate.



109, 90:10 dr, 98% *ee* **110** (99%) 90:10 dr, 98% *ee*

Scheme 45. Application of the methodology to the synthesis of functionalized 2,5-dihydrofuran **110** from enantioenriched butynol **109**.

Gold-catalyzed hydroarylation of enantiomerically enriched 2-allenyl indole (*R*)-**111** using the catalytic system Au[P(*t*-Bu)$_2$(*o*-biphenyl)]Cl (5 mol %) and AgOTf (5 mol%) gave tetrahydrocarbazole **112** in 86% yield and 52% *ee* (Scheme 46).[81] Conversion of compound **111** to tetrahydrocarbazole **112** has been explained by nucleophilic attack of the electron-rich indole to the allene-gold complex **113** to give intermediate **114**. The *E*-olefin was obtained from the cyclization reaction as single isomer and no isomerisation was observed.

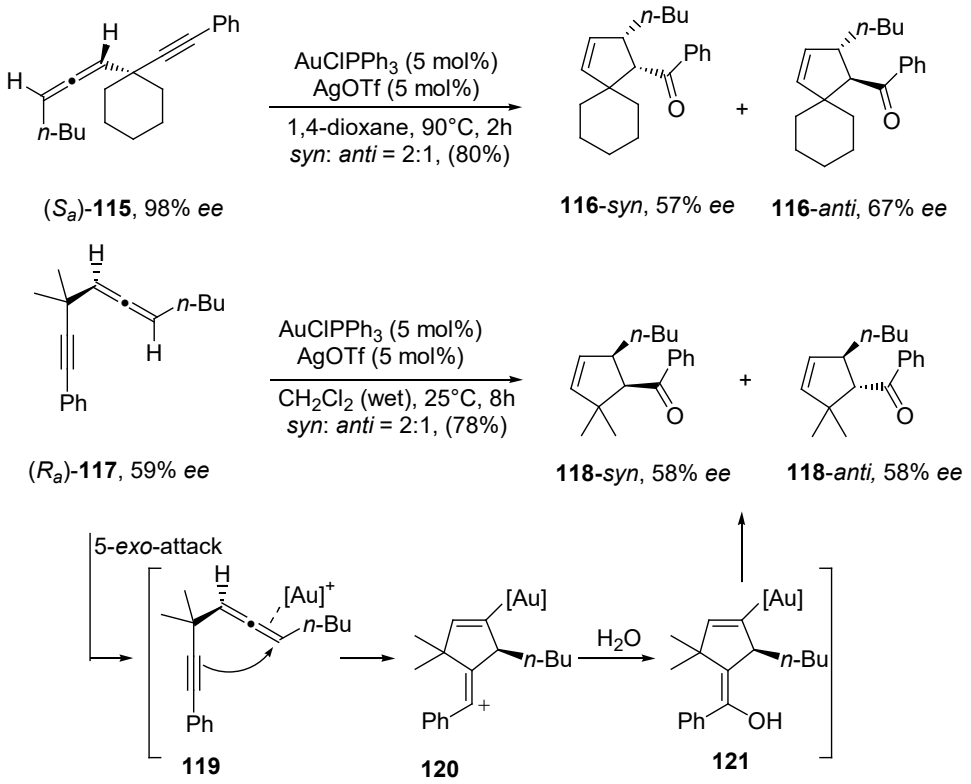


(R_a)-**111**, 52% *ee* **112** (86%), 52% *ee*

113 **114**

Scheme 46. Gold-catalyzed hydroarylation of enantiomerically enriched 2-allenylindole **111** to give tetrahydrocarbazole **112**.

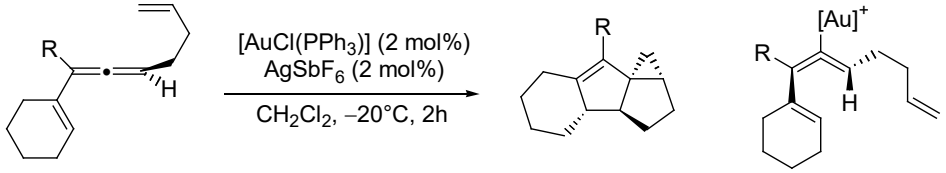
Carbocyclization of chiral 1,5-allenynes **115** and **117** has been studied using the catalytic system $PPh_3AuCl/AgOTf$ to give cyclic ketones **116** and **118** chemoselectively (Scheme 47).[82] The reaction pathway, based on the synthesis of tetrahydrocarbazoles **112**, involves the nucleophilic attack of the alkyne to the Au-complexed allene intermediate **119** to give **120**. Hydration of vinylcation **120** would give intermediate **124** which would furnish cyclic ketones (Scheme 47).



Scheme 47. Carbocyclization of chiral 1,5-allenynes **115** and **117** to give cyclic ketones **116** and **118**, respectively.

Gold-catalyzed cycloisomerization of enantioenriched ene-vinyl allenes **122b** and **122c** furnished enantioenriched compounds **123b** and **123c** in good yield with perfect transfer chirality (Scheme 48).[83] However, when non-substituted allene **122a** was treated under the same reaction conditions, racemic compound **123a** was obtained. This result confirms the role of C2-coordinated allenes, either as allylic cations, bent allenes **124**, in the reaction mechanism. Although this intermediate is cationic, this species preserves the stereochemical data of the

substrate. In fact, better chirality transfer is observed when the substitution of the allene increases. A more detailed study concerning the behaviour of allene-gold(I) complexes has also been reported.[84]



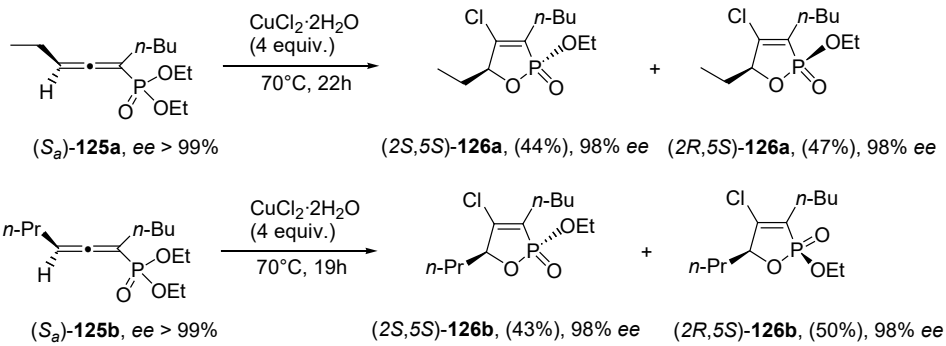
(S_a)-**122a**, R = H, 91% *ee*
(R_a)-**122b**, R = Me, 84% *ee*
(R_a)-**122c**, R = *t*-Bu, *ee* >88%

123a, (87%), 0% *ee*
123b, (90%), 84% *ee*
123c, (65%), 88% *ee*

Bent-allene
124

Scheme 48. Gold-catalyzed cycloisomerization of enantioenriched ene-vinyl allenes **122** to give compounds **123**.

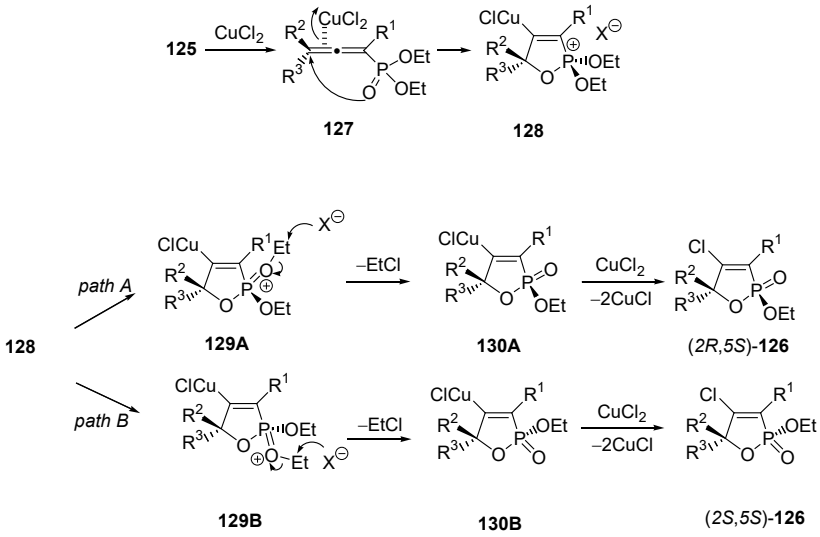
$CuCl_2$-mediated halocyclization of diethyl-1,2-allenylphosphonates **125** is a convenient and efficient synthesis of 4-halo-2,5-dihydro-1,2-oxaphosphole 2-oxides **126** (Scheme 49).[85] These compounds have been obtained in good yields and good *ee's*. Formation of compounds **126** can be explained by coordination of the copper salt to the relatively electron-rich C=C bonds to form complex **127** (Scheme 50). Then, *anti*-oxy-metalation gives the five-membered intermediate **128**. Arbuzov type dealkylation of the ethoxy substituents mediated by a chloride anion gives intermediates **130A** and **130B**. Next, C–X bond formation in the presence of a second molecule of $CuCl_2$ produces the final product **126** together with two molecules of CuCl.



(S_a)-**125a**, *ee* > 99%
(*2S*,*5S*)-**126a**, (44%), 98% *ee*
(*2R*,*5S*)-**126a**, (47%), 98% *ee*

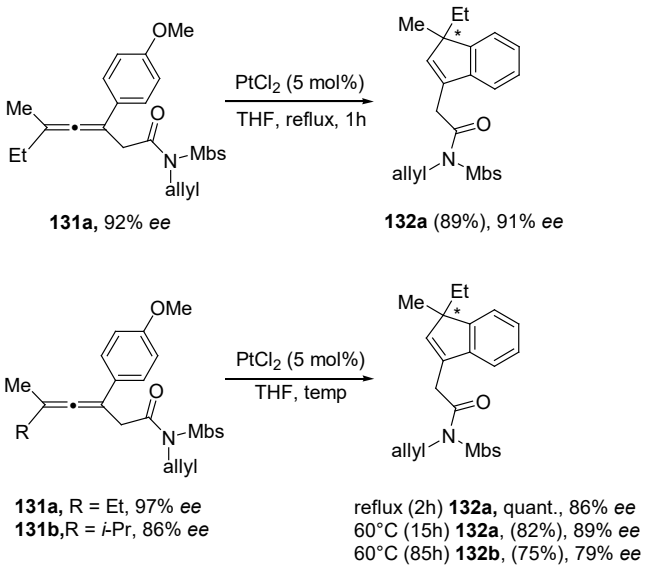
(S_a)-**125b**, *ee* > 99%
(*2S*,*5S*)-**126b**, (43%), 98% *ee*
(*2R*,*5S*)-**126b**, (50%), 98% *ee*

Scheme 49. $CuCl_2$-mediated halocyclization of diethyl-1,2-allenylphosphonates to give 4-halo-2,5-dihydro-1,2-oxaphosphole 2-oxides.



Scheme 50. Mechanism for the Cu-promoted halocyclization of 1,2-allenylphosphonates **125**.

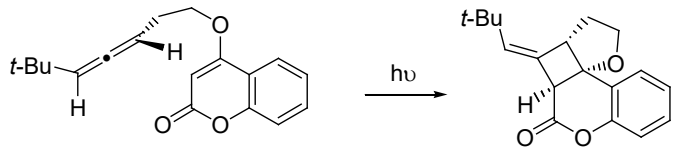
Tetrasubstituted allenes **131** have been obtained by addition of tertiary propargyl alcohols to ynamides to give propargyl vinyl ethers, which undergo *in situ* [3,3]-sigmatropic rearrangement. Enantioenriched tetrasubstituted allenes **131** have been used as starting materials to study intramolecular cyclizations to give indenes **132**.[86] The screening of the reaction has been studied using different catalysts [AgOTf, $(Ph_3P)AuOTf$, $InCl_3$ and $PtCl_2$] and the optimal conditions found were the used of $PtCl_2$ (5 mol%) in THF at reflux temperature. Indenes **132** have been obtained in good yields and good to excellent *ee's* (Scheme 51).[87]



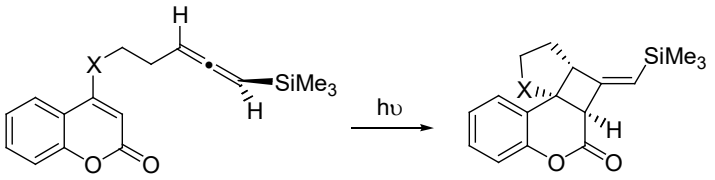
Scheme 51. Synthesis of indenes **132** from enantioenriched allenes **131**.

3.3. *Cycloaddition Reactions*

[2+2] Cycloadditions of allenes with alkenes and alkynes is a powerful synthetic tool which allows the preparation of cyclobutane and cyclobutene skeletons, respectively in a single step.[88] This type of reactions can be studied under thermal and photochemical conditions, via a stepwise biradical mechanism. Furthermore, metal-catalyzed [2+2] cycloadditions have been reported as well. In addition, [4+2] and [4+3] cycloaddition of allenes are efficient methodologies for the construction of six and seven membered rings.[89] Irradiation of optically active allene derived coumarin **133** afforded tetracycle **134** as a 10:1 mixture of olefin diastereomers with excellent asymmetric induction (Scheme 52).[90] Optically active allenylsilanes **135** have also reacted under photochemical conditions to afford cyclobutane adducts **136** in moderate to good yields and 67–90% *ee's*. Selected examples are depicted in Scheme 53.[91]



Scheme 52. [2+2] Cycloaddition reaction of enantioenriched allene derived coumarin **133** under photochemical conditions to give tetracycle **134**.

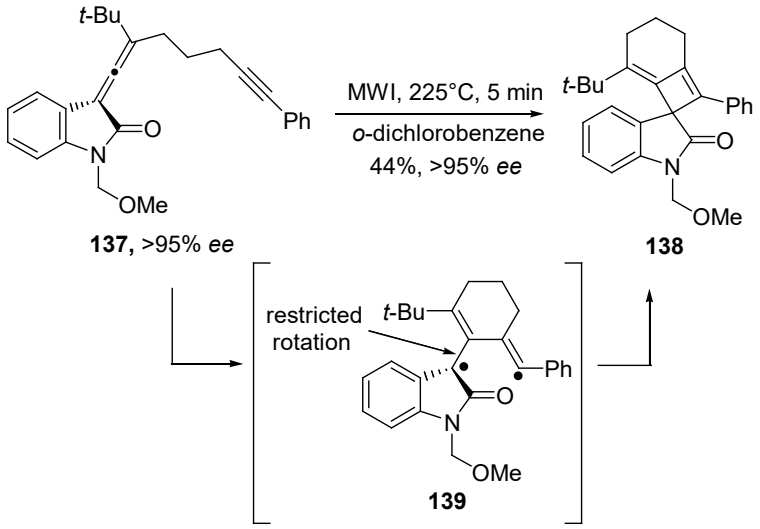


135a X = O, 99% *ee*
135b X = S, 99% *ee*

136a (90%), 99% *ee*
136b (80%), 89% *ee*

Scheme 53. [2+2] Cycloaddition reaction of optically active allenylsilanes **135** under photochemical conditions to give cyclobutane adducts **136**.

Intramolecular [2+2] cycloaddition between the allene and the tethered alkyne moieties of allenyl oxindole **137** takes place with total chirality transfer affording enantiopure spirooxindole **138**.[92] The reaction has been studied under microwave conditions at 225°C, affording compound **138** in 5 min. The mechanism of the reaction has been explained by formation of a thermally generated biradical intermediate **139**, where the *tert*-butyl group hinders rotation around carbon–carbon bond as shown in Scheme 54.[93]



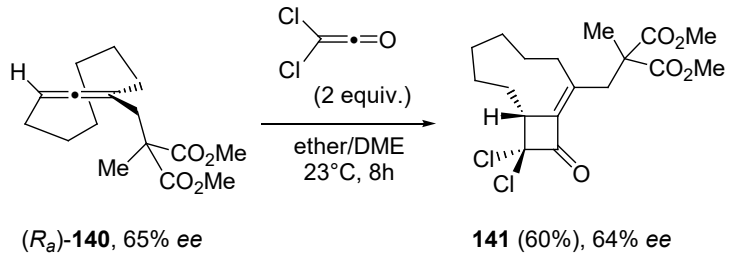
137, >95% *ee*

138

139

Scheme 54. [2+2] Cycloaddition reaction of optically active allenyl oxindole **137** under microwave conditions to give enantiopure spirooxindole **138**.

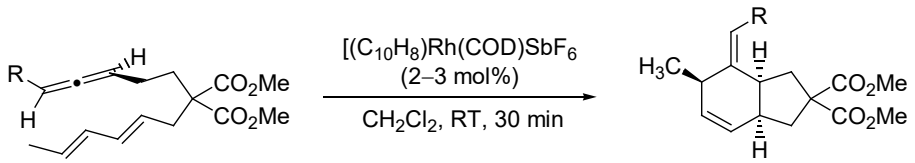
Enantiomerically enriched allene (R_a)-**140** was reacted with dichloroketene to give [2+2] cycloaddition product **141** in 60% yield and 64% *ee* (Scheme 55).[94] Interestingly, the chirality transfer of the reaction was estimated to be superior of 98%.



(R_a)-**140**, 65% *ee* **141** (60%), 64% *ee*

Scheme 55. [2+2] Cycloaddition reaction of enantienriched allene **140** with dichloroketene to give cycloadduct **141** under thermal conditions.

Intramolecular Diels-Alder cycloaddition of allene-dienes **142** catalyzed by a rhodium complex has afforded the corresponding bicyclic systems **143** efficiently with complete chirality transfer and as one diastereomer (Scheme 56).[56]

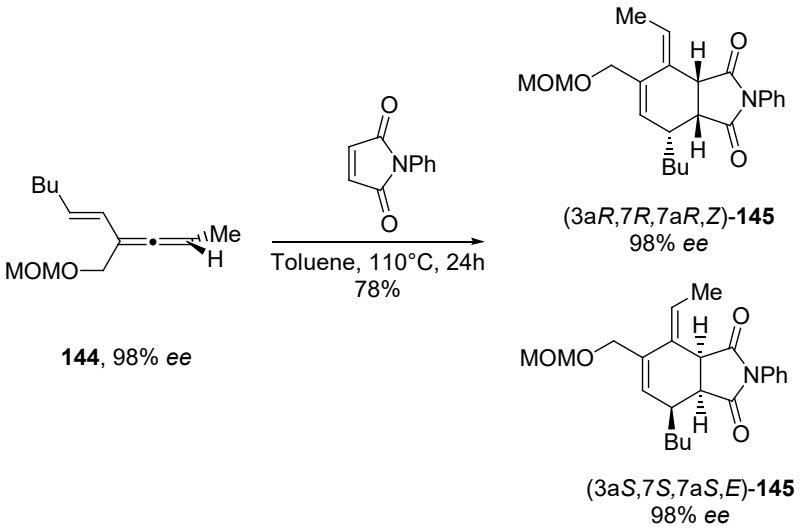


R = *n*-C_4H_9, (S_a)-**142a**, 87% *ee* **143a**, (93%), 87% *ee*

R =  , (S_a)-**142b**, 90% *ee* **143b**, (89%), 91% *ee*

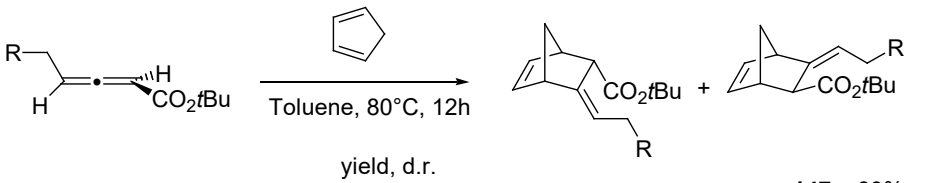
Scheme 56. Metal-catalyzed intramolecular Diels-Alder cycloaddition of allene-dienes **142** to give bicyclic systems **143**.

Alkenyl-conjugated allene **144** has reacted with *N*-phenylmaleimide as a dienophile, under thermal conditions, to give 6,5-fused bicyclic frameworks **145** with a high diastereofacial selectivity (92:8) and complete *endo/exo* selectivity (Scheme 57).[95] It is important to remark that three stereogenic centers are formed and a geometrically controlled exocyclic alkene is formed.



Scheme 57. Thermal intermolecular Diels-Alder cycloaddition of allene **144** with *N*-phenylmaleimide to give cycloadducts **145**.

The Diels-Alder reaction of enantioenriched allenoates **146** with cyclopentadiene has been studied to smoothly afford cycloadducts **147** (Scheme 58),[96] being the *endo* diastereomer **148** (olefin in *Z* configuration) the major isomer. The yields and chirality transfer were excellent in all cases.

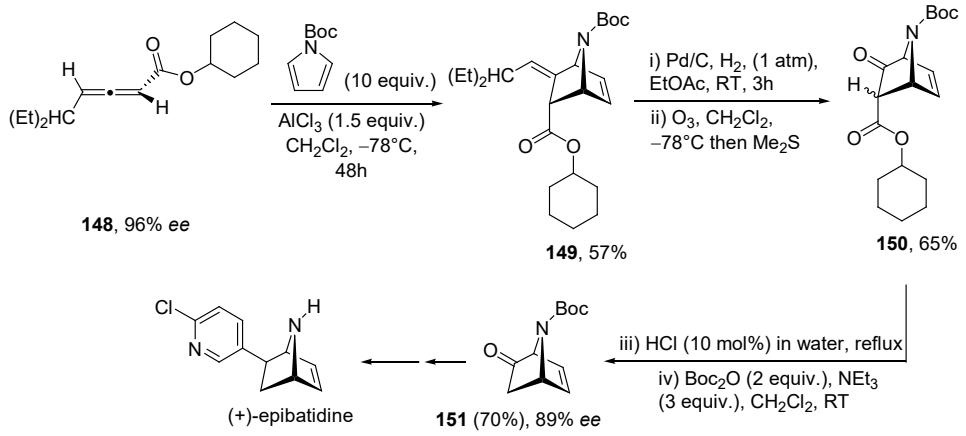


	yield, d.r.		
146a, R = OH, 86% *ee*	85%, 4:1	*endo*-**147a**, 85% *ee*	*exo*-**147a**, 89% *ee*
146b, R = NHCbz, 91% *ee*	98%, 3:1	*endo*-**147b**, 87% *ee*	*exo*-**147b**, 85% *ee*
146c, R = PhthN, 94% *ee*	99%, 2:1	*endo*-**147c**, 93% *ee*	*exo*-**147c**, 93% *ee*

Scheme 58. Thermal intermolecular Diels-Alder cycloaddition of allenes **146** with cyclopentadiene to give cycloadducts **147**.

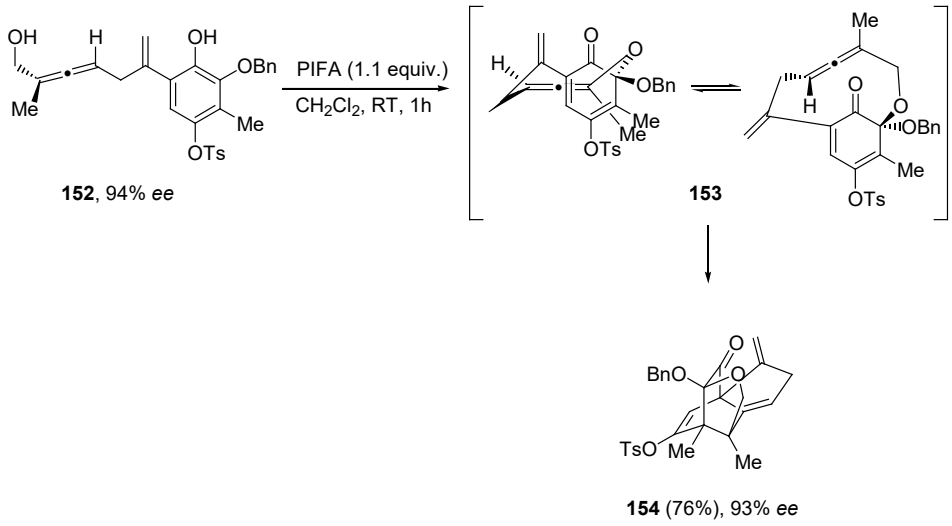
The formal total synthesis of (+)-epibatidine has been carried out using as key step the Diels-Alder reaction of enantioenriched allene.[97] Diels-Alder cycloaddition of allene **148** with excess of *N*-Boc pyrrole using $AlCl_3$ as catalyst, has afforded the corresponding *endo*-product **149** in 57% yield. Chemoselective

hydrogenation followed by ozonolysis yielded β-keto ester **150** in 65% overall yield. Next, decarboxylation followed by protection gave compound **151**, in 70% yield and 89% *ee* (Scheme 59).



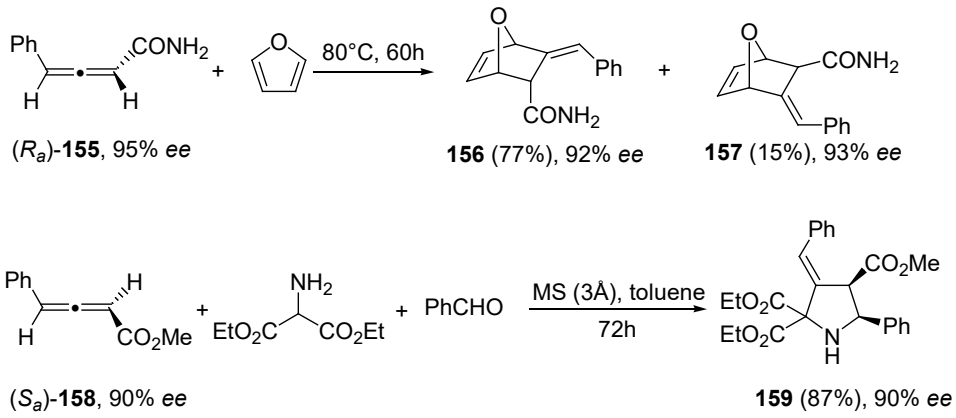
Scheme 56. Formal total synthesis of (+)-epibatidine from enantioenriched allene **148**.

The synthesis of a precursor of (–)-11-*O*-debenzoyltashironin, a natural product with neurotropic activity, has been described.[98] The synthesis of optically active allene **152** has been obtained by subjecting an enantioenriched propargylic substrate to nucleophilic conditions with organocopper reagents via S_N2' (Scheme 60). Tampura-Pelter oxidation with PIFA affords enantioenriched acetal intermediate **153**. The subsequent transanular Diels-Alder cyclization of **153** gave enantiomerically enriched tetracycle (–)-**154**.



Scheme 60. Synthesis of *O*-debenzoyltashironin (–)-**153**, a precursor of the natural product.

Chiral allene (R_a)-**155** has been reacted with furan under thermal conditions to give a mixture of *endo*-adduct **156** and *exo*- adduct **157** in 77% and 15% yields, respectively, with good *ee* values (Scheme 61).[99] 1,3-Dipolar cycloaddition reaction of methyl-2,3-allenoate (*S*)-**158** with an azomethine ylide, gave pyrrolidine **159** in 87% yield.

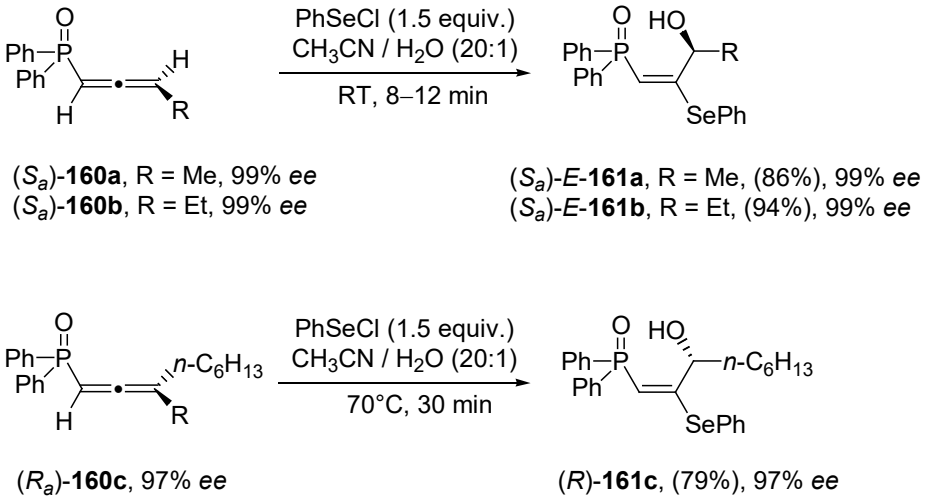


Scheme 61. Diels-Alder and 1,3-dipolar cycloadditions of chiral allenes **155** and **158**.

3.4. *Electrophilic reactions to give acyclic and cyclic compounds*

Reaction of allenyl compounds with electrophilic reagents is a powerful methodology to obtain acyclic and cyclic compounds.[100] Different methodologies involving the axial chirality transfer from enantiomerically pure allenes have been described and the most recent works have been discussed in this section.

Selenohydroxylation of enantiomerically pure 1,2-allenyl phosphine oxides **160** have been studied using PhSeCl in CH_3CN/H_2O (Scheme 62).[101] The products, 3-hydroxy-2-phenylselanyl-1-(*E*)-alkenyl diphenyl phosphine oxides **161** have been obtained in good yields with very high regio- and stereoselectivities. In addition, high efficiency of the axial chirality transfer has been observed.



(S_a)-**160a**, R = Me, 99% *ee*
(S_a)-**160b**, R = Et, 99% *ee*

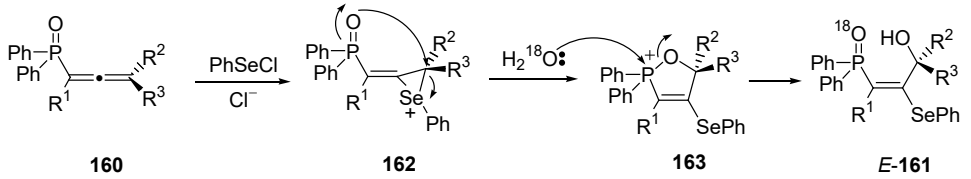
(S_a)-*E*-**161a**, R = Me, (86%), 99% *ee*
(S_a)-*E*-**161b**, R = Et, (94%), 99% *ee*

(R_a)-**160c**, 97% *ee*

(*R*)-**161c**, (79%), 97% *ee*

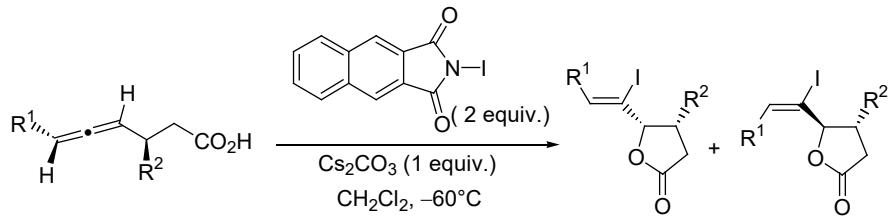
Scheme 62. Selenohydroxylation of enantiomerically pure 1,2-allenyl phosphine oxides.

The chirality transfer observed during formation of compounds **161** has been proposed based on labeling experiments (Scheme 63). First, electron-rich C=C double bond of the allene moiety would react with $PhSe^+$ to give intermediate **162**. Next, a five-membered cyclic intermediate **163** is formed via neighboring group participation of the oxygen atom of the diphenyl phosphine oxide group. Finally, a $H_2{}^{18}O$ molecule would attack at the positively charged phosphorous atom to cleave the P–O bond, which gives compound *E*-**161**.



Scheme 63. Mechanistic explanation of the chirality transfer observed in selenohydroxylation of compounds **160**.

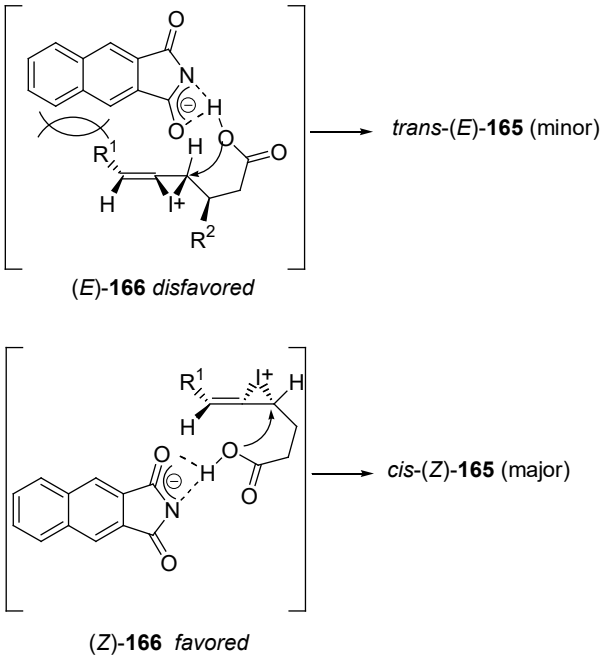
Iodolactonization of 4-allenoic acids **164** with a sterically demanding electrophilic iodination reagent has afforded optically active γ-butyrolactones **165** (Scheme 64).[102] The products are obtained with excellent axial chirality transfer and excellent *Z/E* selectivity. The *Z* stereoselectivity and the high efficiency of the chirality transfer have been explained as shown in Scheme 65. Iodination reaction would give iodonium intermediates (*Z*)-**166** and (*E*)-**166**, with the amide anion and the steric interaction with group R^1 playing an important role. Both factors determine the stereoselectivity observed in compounds **165**.



(*R*$_a$,*R*)-**164a** R^1 = C_2H_5, R^2 = Me
(*R*$_a$,*R*)-**164b** R^1 = *n*-C_4H_9, R^2 = Me
(*R*$_a$,*R*)-**164c** R^1 = *n*-C_4H_9, R^2 = allyl

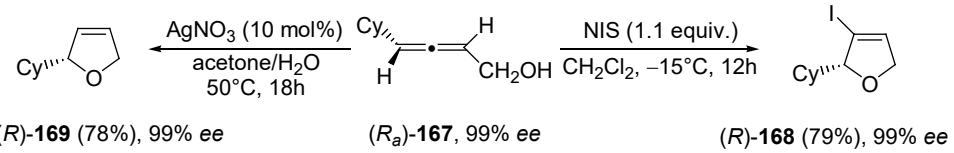
(4*R*,5*S*)-**165a**, (70%), (*Z*)-**165**/(*E*)-**165**, 97:3, 99% *ee*
(4*R*,5*S*)-**165b**, (71%), (*Z*)-**165**/(*E*)-**165**, 98:2, 99% *ee*
(4*R*,5*S*)-**165c**, (83%), (*Z*)-**165**/(*E*)-**165**, 99:1, 99% >*ee*

Scheme 64. Iodolactonization of optically active 4-allenoic acids.



Scheme 65. Explanation of the *Z*-stereoselectivity and the chirality transfer in the iodolactonization reaction of enantioenriched allenes **164**.

Analogously, the electrophilic oxycyclizations of enantioenriched allenol **167** in the presence of NIS or silver-nitrate have been studied, affording dihydrofurans **168** and **169**, respectively in good yields and with complete transfer of the axial chirality (Scheme 66).[103]

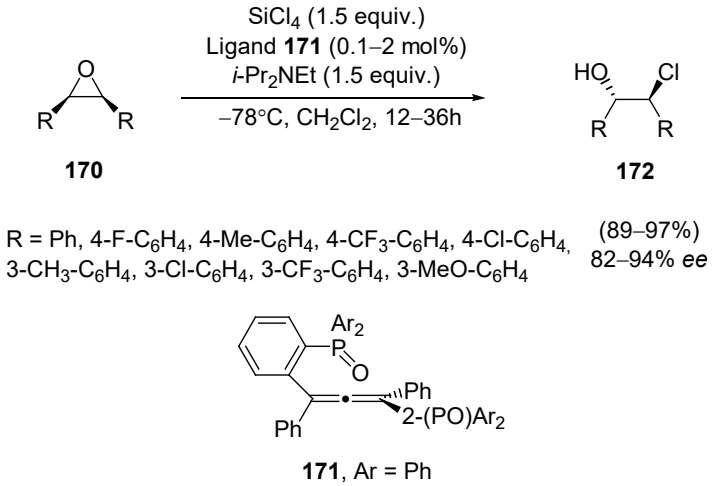


Scheme 66. Electrophilic oxycyclizations of enantioenriched primary allenols with NIS.

4. Chiral allenes as ligands in asymmetric catalysis

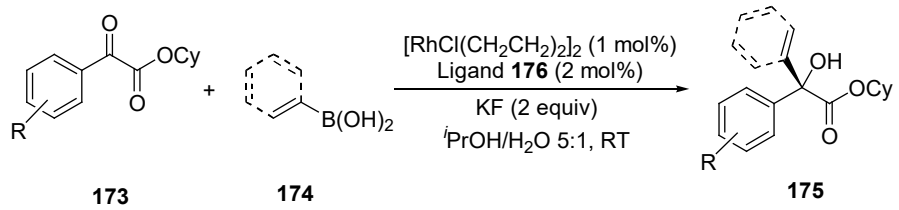
Taking into account that phosphine oxides are good chiral Lewis bases, the application of phosphine-containing allenes as ligands in transition metal catalysis has been reported. The synthesis of biphosphine oxides that contain an allene backbone has been described.[104] A family of meso-epoxides **170** has been exposed to $SiCl_4$ and iPr$_2$NEt in the presence of catalytic amounts of allene-

containing bisphosphine oxide **171** (Scheme 67). Interestingly, the authors have observed that ligand **171** induces the enantioselective formation of chlorohydrins **172**, which have been obtained in good yields (89–97%) and good *ee's* (82–94%).



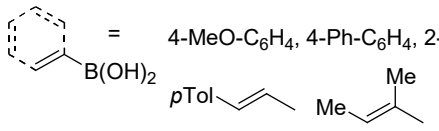
Scheme 67. Asymmetric ring-opening of *meso*-epoxides catalyzed by allene **171**.

Another interesting example which evaluates the use of of allene-containing phosphines in asymmetric catalysis has been reported.[105] The enantioselective Rh(I)-catalyzed addition of arylboronic acids **174** to α-keto esters **173** using catalytic amounts of ligand **176** gives tertiary alcohols **175** in moderate to good yields and *ee's* (Scheme 68). It has been observed that the additions were faster and more enantioselective with electron-deficient α-keto esters. In addition, the steric bulk around the allene is necessary for the process.

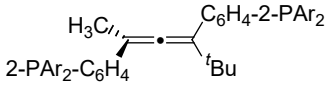


173 **174** **175**

R = H, 3,5-$(CF_3)_2$-, 4-CN, 4-F, 4-Me, 4-MeO, 4-Cl, 3-Cl, 2-CF_3, 4-F (41–98%), 48–95% *ee*



4-MeO-C_6H_4, 4-Ph-C_6H_4, 2-Napht, Ph, 4-ClC_6H_4, 4-Me_2N-C_6H_4



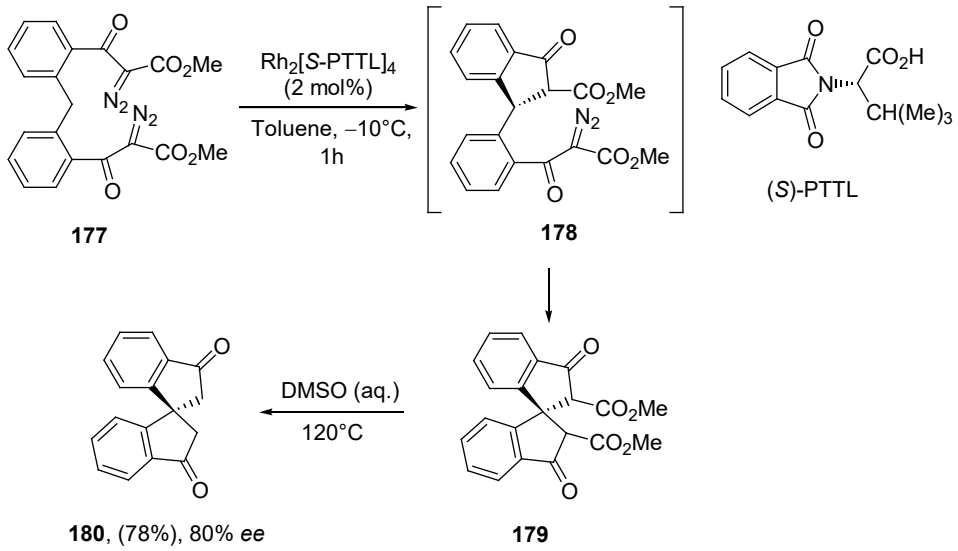
Ar = 3,5-$(CF_3)_2$-C_6H_3

176

Scheme 68. Enantioselective Rh(I)-catalyzed addition of arylboronic acids to α-keto esters.

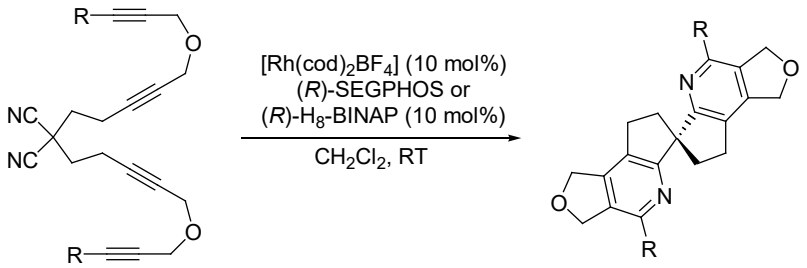
5. Axial chirality in spirocyclic compounds

The synthesis of 1,1'-spirobi[indan-3,3'-dione] **180** has been achieved by a double cyclization of bis(α-diazo-β-keto ester) **177** using Rh(II) catalysis (Scheme 69).[106] Spirocycle **180** has been obtained in 78% yield and 80% *ee*. The stereochemical result observed in the reaction is explained by a first insertion of the chiral rhodium(II) carbene intermediate **177** into the methylene C–H bond to give (3*S*)-indan-1-one derivative **178**. This intermediate undergoes a second C–H insertion at the methane C–H bond in **178** with retention of the configuration to provide (*R*)-**179**, which after demethoxycarbonylation gives (*R*)-**180**.



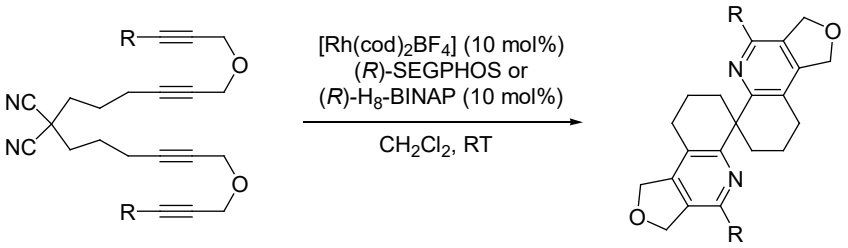
Scheme 69. Synthesis of 1,1'-spirobi[indan-3,3'-dione] **180**.

Spyrocyclic compounds **182** and **184** have been formed by an intramolecular [2+2+2] cycloaddition of bis-diynenitriles **181** and **183**, respectively (Scheme 70).[107] The reaction takes place in the presence of $[Rh(cod)_2]BF_4$ (10 mol%) and a ligand, (*R*)-SEGPHOS or (*R*)-H_8-BINAP. Spirobipyridines containing five and six-membered skeletons have been prepared in very good yields (70–99% yield) and moderate enantioselectivities (40–71% *ee*). Formation of spirocycles is explained in Scheme 71 from diynes **181**. First of all, coordination of Rh(I) with two alkyne moieties in compounds **181**, would form complexes **185**. Then, insertion of the nitrile and subsequent reductive elimination of Rh, gives pyridines **186** with regeneration of the rhodium catalyst. Finally, a second [2+2+2] cycloaddition would take place to form the spirocyclic compounds **182**.



181a, R = Ph
181b, R = 4-ClC_6H_4
181c, R = 4-$MeOC_6H_4$
181d, R = Me
181e, R = H

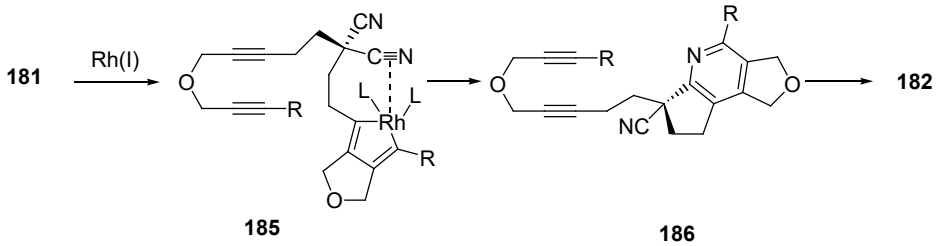
(*R*)-**182a**, (99%), 64% *ee*
(*S*)-**182b**, (89%), 71% *ee*
(*R*)-**182c**, (85%), 62% *ee*
(*R*)-**182d**, (98%), 49% *ee*
(*R*)-**182e**, (70%), 47% *ee*



183a, R = Ph
183b, R = Me

184a, (90%), 45% *ee*
184b, (98%), 40% *ee*

Scheme 70. Synthesis of spirocyclic compounds **182** and **184** via [2+2+2] cycloaddition reaction of bis-diynenitriles **181** and **183**.

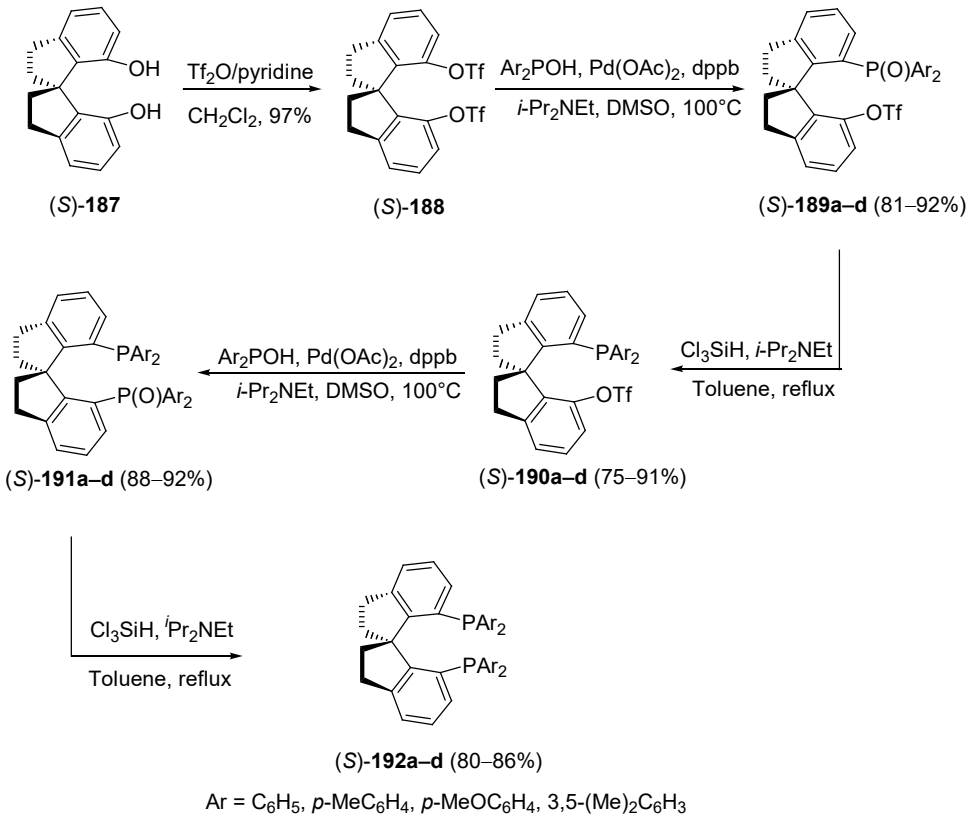


Scheme 71. Mechanistic explanation for the synthesis of spirocyclic compounds **182.**

The incomparable structural peculiarity of spirocyclic compounds has converted them in promising ligands.[108,109] However, their use as chiral ligands has been put in practice recently, probably due to the problems associated with their synthesis.

Chiral spiro phosphorus ligands (*R*)- and (*S*)-SDP containing a 1,1'-spirobiindane backbone have been synthetized from optically pure (*R*)- and (*S*)-

1,1'-spirobiindane-7,7'-diol (SPINOL).[110] First of all, diol (*S*)-**187** was transformed into triflate (*S*)-**188** in 97% yield (Scheme 72). Next, monophosphinylation of compound (*S*)-**188** with diarylphosphine oxide in presence of $Pd(OAc)_2$ and subsequent reduction with trichlorosilane gave spirobiindanes derivatives (*S*)-**190** in good yields. Then, phosphinylation and reduction of compounds (*S*)-**190** gave diphosphines (*S*)-**192** in 80–86% yields. Diphosphines (*S*)-**192** were transformed in ruthenium complexes for their use in the asymmetric hydrogenation of aromatic, heteroaromatic, and α,β-unsaturated ketones, affording the corresponding alcohols in excellent yields and enantioselectivities. Catalysts **193** (Figure 3) were prepared by reacting ligands **192** with $[(C_6H_6)RuCl_2]_2$ in DMF at 100°C followed by addition of 1,2-diphenylethylenediamine . In addition, the same authors have used these ligands in Pd-catalyzed allylic alkylations of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate and other nucleophiles.[111] SPINOL has also been used for the synthesis of chiral spiro phosphine-oxazoline ligands, which have been employed in the preparation of cationic iridium catalysts **194** (Figure 3).[112] These iridium complexes have shown excellent reactivity and enantioselectivity in the asymmetric reduction of imines.



Scheme 72. Synthesis of spiro diphosphines **192**.

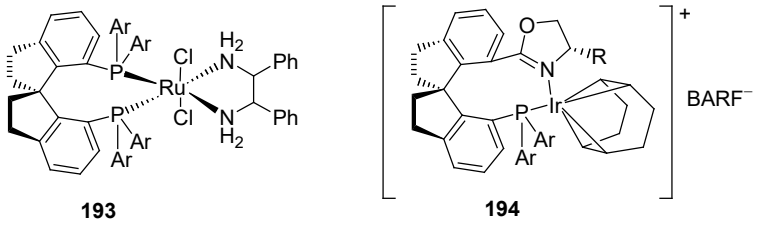
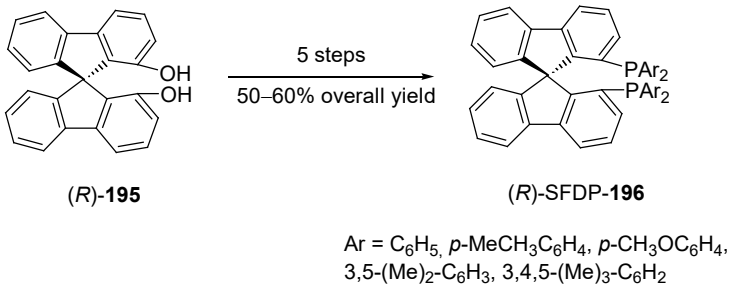


Figure 3. 1,1'-Spirobiindane-based Ru-catalyst **193** used in asymmetric hydrogenation of ketones and Ir-complex **194** used in asymmetric hydrogenation of imines.

Analogously, chiral ligands with a 9,9'-spirobifluorene backbone **196** have been prepared from enantiomerically pure 9,9'-spirobifluoren-1,1'-diol **195** following the same experimental procedure than for compounds **192** (Scheme 73).[113] The SFDP ligands have been transformed in Ru(II) complexes **197** (Figure

4) by reaction of diphosphine ligands with $[RuCl_2(C_6H_6)]_2$ in DMF followed by addition of NaOAc. The catalysts have been tested in the asymmetric hydrogenation of α,β-unsaturated acids, affording the corresponding products with excellent enantioselectivities. [114]



Scheme 73. Synthesis of chiral ligands **196** with a 9,9'-spirobifluorene backbone.

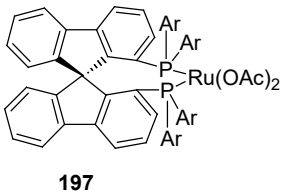
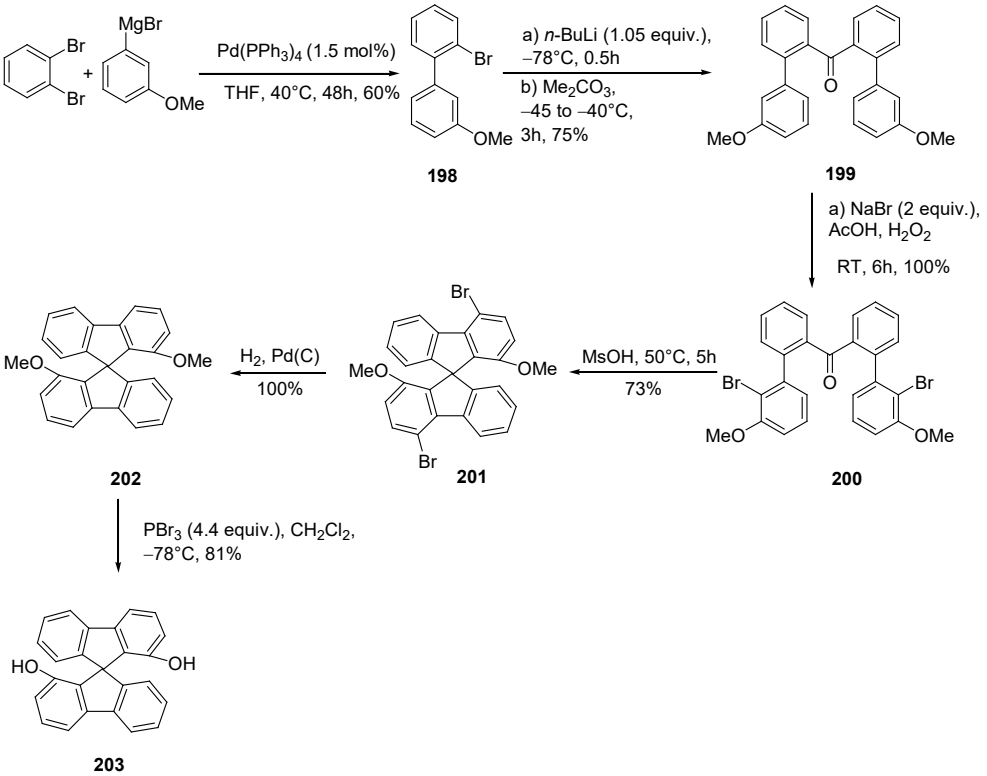
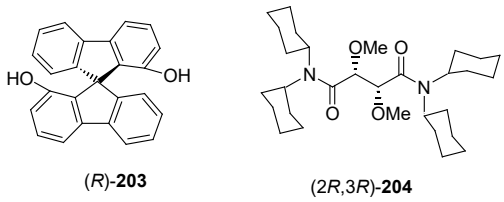


Figure 4. 9,9'-Spirobifluorene-based Ru(II) complex **197**.

Another methodology to obtain enantiomerically pure spirobifluorene derivatives involves the use of inclusion resolution.[115] The synthetic route to access racemic spirobifluorene is shown in Scheme 74. First, Kumada coupling of 1,2-dibromobenzene and the Grignard reagent of 3-bromoanisole, gave substituted biphenyl **198** in 60% yield. Then, treatment of coupling compound **198** with *n*-BuLi and dimethylcarbonate produced ketone **199** in 70% yield. Selective bromination reaction of ketone **199** at *ortho* positions of both methoxy-groups was achieved using NaBr in presence of H_2O_2, affording dibromoketone **200** in quantitative yield. Treatment of compound **200** with methanosulfonic acid gave the cyclization product, 9,9'-spirobifluorene **201**. The debromination step was carried out using H_2/Pd(C), while the demethylation was promoted by PBr_3, to afford compound **203** in 27% overall yield. The resolution of 9,9'-spirobifluorene-1,1'-diol **203** has been achieved using the chiral resolving reagent 2,3-dimethoxy-*N*,*N*,*N*',*N*'-tetracyclohexylsuccinamide **204** (Figure 5). After inclusion crystallization, both enantiomers (+)-**203** and (−)-**203** were obtained in 99% *ee*.



Scheme 74. Synthesis of spirobifluorene derivative **203**.



(*R*)-**203** (2*R*,3*R*)-**204**

Figure 5. Enantiomerically pure 9,9'-spirobifluorene-1,1'-diol (*R*)-**203** and resolving agent (2*R*,3*R*)-2,3-dimethoxy-*N*,*N*,*N*',*N*'-tetracyclohexylsuccinamide **204**.

5. Conclusions

In conclusion, the axial chirality in allenes and briefly in spiro compounds has been covered. A selection of the most representative and recent contributions has been selected. Many asymmetric tools to synthesize enantioenriched allenes have been exploited, and in some cases optimization of conditions and scope of the starting materials should be addressed in the future to get more general procedures. On the other hand, high efficiency on axial-to-central chirality transfer has been achieved in an important collection of reactions. Interestingly, some optically active allenic derivatives have been used as ligands in asymmetric synthesis, with good selectivities. Thus, these methodologies would be the starting point for future promising investigations. Finally, the synthesis of axially chiral spirocyclic compounds has been discussed and their applications as ligands in metal-catalyzed processes have been documented.

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Abbreviations

BARF	tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthalene
Boc	*t*-butoxycarbonyl
COD	1,5-cyclooctadiene
Cp	cyclopentadienyl
dba	dibenzylidenacetone
DMSO	dimethylsulfoxide
DMF	dimethylformamide
DPEphos	bis[*o*-(diphenylphosphino)phenyl]ether
dppb	1,4-bis(diphenylphosphino)butane
DTBM-SEGPHOS	5,5'-bis[di(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphino]-4,4'-bi-1,3-benzodioxole
EWG	electron withdrawing group
LiHMDS	lithium bis(trimethylsilyl)amide
MTBE	methyl *tert*-butyl ether
Mbs	*p*-methoxybenzenesulfonyl
Ms	methanesulfonyl
MOMO	methoxymethoxy
Naph	naphtyl
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
PIFA	phenyliodonium bis(trifluoroacetate)
PMHS	polymethylhydroxysiloxane
PPL	*porcine pancreatic* lipase

PTTL	*N*-phthaloyl-*t*-leucine
RT	room temperature
SDP	spiro diphosphine
SEGPHOS	5,5'-bis(diphenylphosphino)-4,4'-bi-1,3-benzodioxole
SFDP	spirobifluorene-based diphosphane
SPINOL	1,1'-spirobiindane-7,7'-diol
TBAF	tetra-*n*-butylammonium fluoride
TBS	*t*-butyldimethylsilyl
THACl	tetrahexylammonium chloride
THF	tetrahydrofuran
TMS	trimethylsilyl
Tf	trifluoromethanesulfonyl
Xantphos	4,5-(Bisdipehnylphosphino)-9,9-dimethylxanthene

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Título: Axial Chirality Beyond Atropisomerism: Allenes and Related Compounds, chp. 8, pp 541-609; https://doi.org/10.1142/9781786346469_0008

Libro: Atropisomerism and Axial Chirality, edited by José M. Lassaletta, World Scientific: Singapore, 2019 (https://doi.org/10.1142/q0192; ISBN: 978-1-78634-647-6 (ebook))