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Conquering three-carbon axial chirality of allenes†

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While one-carbon central chirality of organic molecules has been recognized and extensively studied for more than a century, far less attention has been paid to three-carbon axial chirality of allenes, although they exist in nature with interesting biological activity and have been demonstrated with great synthetic potentials. However, remarkable progress has been made in this field in recent years, giving rise to axially chiral allenes with a wide range of functionalities with practical enantioselectivity. This review provides a concise account of enantioselective syntheses of axially chiral allenes with a selection of published protocols.

1. Introduction

Chirality is an interesting phenomenon commonly existing in nature. A typical example is the hands of human beings: the left hand is a non-superimposable mirror image of the right hand. Nature also endows organic molecules with various types of chiralities such as central, axial, planar, and helical chiralities,[1] among which one-carbon central chirality is the most frequently encountered one closely connected to biological activity and thus has been extensively studied ever since Jacobus van't Hoff and Joseph Le Bel's prediction in as early as 1874 (Fig. 1).[2] Another type of chirality that has recently attracted broad interest of chemists is the axial chirality of allenes owing to the rapid development of allene chemistry in the last few decades as well as their occurrence in nature.[3] However, construction of the axial chirality of allenes proved to be much more challenging,[4] simply due to the fact that such an axial chirality spreads over a linear three-carbon atom unit.

Traditionally, axially chiral allenes are prepared *via* central-to-axial chirality transfer of enantioenriched propargylic alcohols or

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† Dedicated to Prof. Negishi on the occasion of his 80th birthday.

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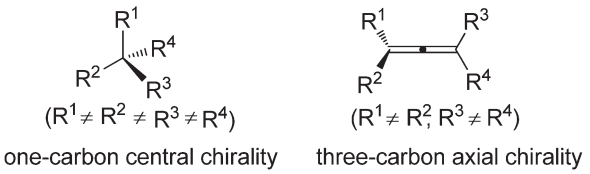
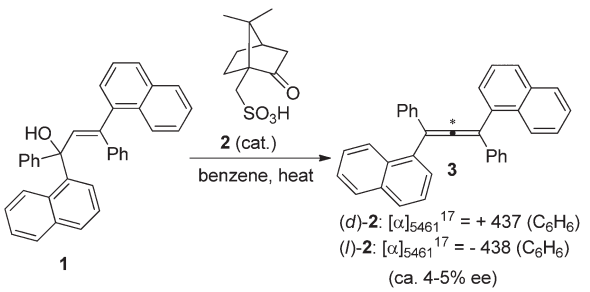


Fig. 1 One-carbon central chirality *vs*. three-carbon axial chirality.

their derivatives, kinetic resolution of racemic allenes, or olefination of ketenes with chiral ylide reagents.[4] However, all these methods require a stoichiometric amount of chiral sources. Loss of enantiopurity during the chirality transfer and lack of generality are the major problems. Accordingly, more attention has been paid to catalytic asymmetric synthesis of axially chiral allenes, which in fact has a long history as the first synthesized axially chiral allene was prepared *via* asymmetric catalytic dehydration by Maitland and Mills in 1935: in the presence of a catalytic amount of (D)- or (L)-camphorsulphonic acid **2**, allylic alcohol **1** was dehydrated to the corresponding optically active allenes **3** (Scheme 1),[5a] thereby experimentally verifying van't Hoff's early prediction[6] that unsymmetrically substituted allenes would exhibit enantiomorphism for the first time. However, the vast potential of this early finding was not recognized at that time, probably due to the low enantioselectivity observed.[5b]



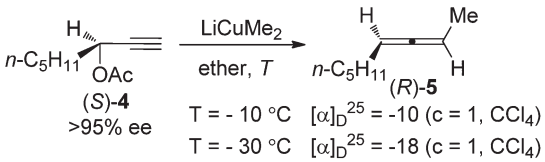
Scheme 1 Camphorsulphonic acid-catalyzed dehydration to axially chiral allene **3**.

Fortunately, with the rapid development of new protocols to form racemic allenes as well as the emergence of numerous types of easily available commercialized chiral ligand skeletons, chemists around the world have witnessed remarkable progress in this area over the last few years by identifying new approaches and/or new chiral ligands from the well-established chiral ligand skeletons. In this review, we present a critical (rather than exhaustive) account of enantioselective synthesis of axially chiral allenes, with a focus on the most privileged ones.[4]

2. From propargylic alcohols or their derivatives

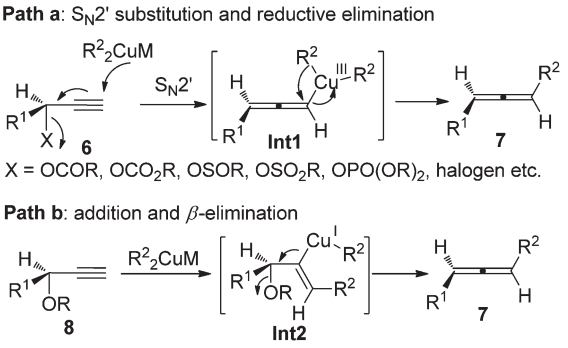
2.1 From propargylic alcohol derivatives

2.1.1 Copper-catalyzed or -mediated transformations. Since the pioneering work of Crabbé and co-workers in 1968,[7] S_N2' substitution of propargylic derivatives such as acetates, carbonates, sulfinates, sulfonates, phosphates, halides, and ethers with organocopper or cuprate reagents has become one of the most popular methods for the synthesis of allenes.[4] Crabbé *et al.* also observed that central chirality of the enantioenriched propargylic acetate (*S*)-**4** could be transferred to axial chirality of the allene product; however, the efficiency of chirality transfer was not clear due to the fact that the enantiomeric excess (ee) of the allene (*R*)-**5** was not determined (Scheme 2).[8a]



Scheme 2 Central-to-axial chirality transfer of enantioenriched propargylic acetate in the presence of $LiCuMe_2$.

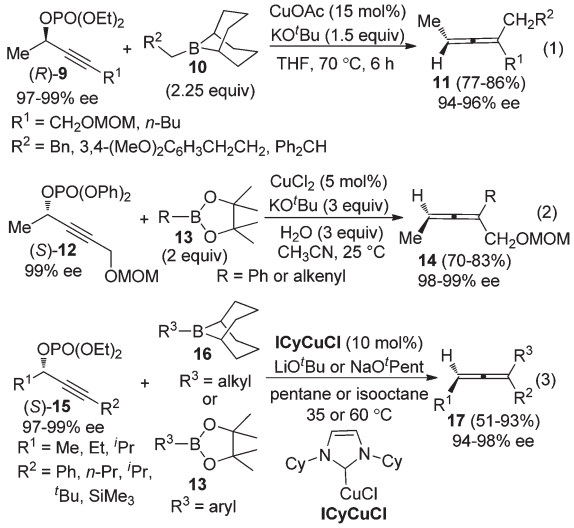
Given the high potential of this methodology, great effort has been made by Crabbé,[8a,b] Claesson,[8c,9a] Elsevier,[8d,e] and Alexakis *et al.*[8f–h] to broaden the substrate scope, improve the efficiency of chirality transfer, and elucidate the reaction mechanism. It turned out that the chirality transfer process is affected by a series of factors such as the nature of electrophiles, nucleophiles, leaving groups, ligands, solvent, temperature, and even reaction time.[8,9] In addition, *in situ* racemization of the allene products caused by organocopper or cuprate reagents that are derived from Grignard or organolithium reagents has also been observed.[9] Generally speaking, there are two possible reaction pathways for these reactions:[8f–h] (1) for propargylic derivatives with a good leaving group such as acetates, carbamates, sulfinates, sulfonates, phosphates, and halides, the reaction is more likely to proceed *via* S_N2' substitution followed by reductive elimination from the Cu(III) intermediate **Int1** (path a, Scheme 3); (2) for those with a poorer leaving group such as propargylic ethers or epoxides, a *syn*-insertion followed by *anti*-β-elimination may be operative (path b, Scheme 3). In both cases, an overall *anti* displacement was observed.



Scheme 3 Two possible pathways of the chirality transfer process.

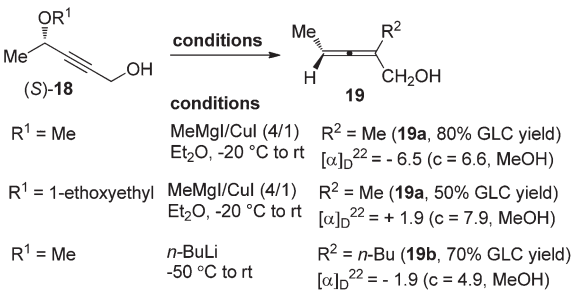
To avoid racemization in the traditional cuprate-based methods, Sawamura *et al.* employed alkylboranes **10**[10a] or

phenyl- and alkenylboronates **13**[10b] to couple with optically active propargylic phosphates **9** or **12**, under the catalysis of CuOAc or $CuCl_2$, furnishing trisubstituted allenes in good yields with excellent central-to-axial chirality transfer (eqn (1) and (2), Scheme 4). Almost at the same time, Lalic and co-workers independently demonstrated that, in the presence of N-heterocyclic carbene (NHC)-ligated copper complexes (**ICyCuCl**), propargylic phosphates **15** could be coupled with alkyl boranes or arylboronic esters to give trisubstituted axially chiral allenes in moderate to good yields without obvious loss of enantiomeric purity (eqn (3), Scheme 4).[11]



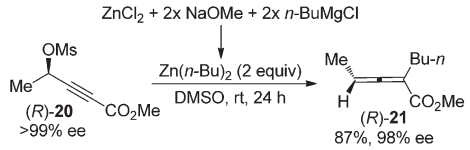
Scheme 4 Chirality transfer of propargylic phosphates with alkylboranes or aryl- and alkenylboronates.

However, in spite of all the advances mentioned above, direct access of highly enantioenriched 2-substituted α-allenols, which are versatile building blocks in organic synthesis,[12] was yet to be well established, probably due to the presence of a free hydroxyl group. Claesson *et al.* reported that 2-substituted α-allenols **19** could be obtained by reacting propargylic ethers **18** with methylmagnesium iodide–copper(I) iodide (4 : 1) or *n*-butyllithium; however, the efficiency of chirality transfer is very low (Scheme 5).[8c] Thus, further explorations in this area are still highly desirable.



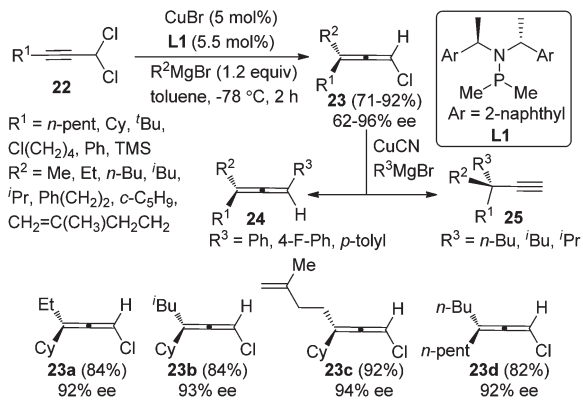
Scheme 5 Synthesis of optically active 2-substituted α-allenols *via* chirality transfer.

An alternative approach to circumvent the propensity of organocopper or cuprates to racemize enantioenriched allenes is to utilize organozinc reagents as the nucleophile, as demonstrated by Kondo and co-workers in the highly stereospecific S_N2' reaction of propargylic mesylate (*R*)-**20** (Scheme 6).[13] A dramatic solvent effect of DMSO was observed for achieving higher reactivity.



Scheme 6 Chirality transfer of propargylic mesylate with organozinc reagents without a catalyst.

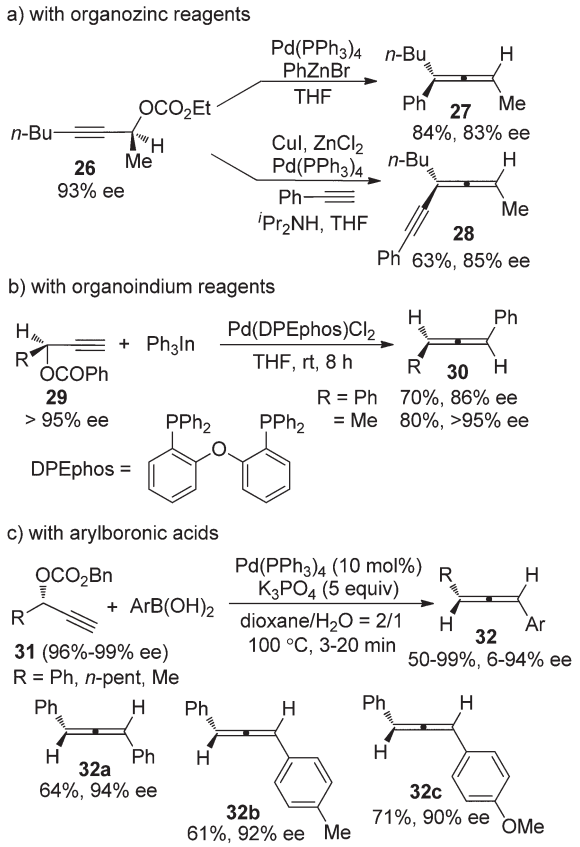
While Cu-catalyzed chirality transfer of enantioenriched propargylic alcohol derivatives with Grignard reagents to synthesize axially chiral allenes has met with considerable success, an asymmetric variant of this reaction is yet to be realized. A major breakthrough in this area was made by Alexakis *et al.* in 2012.[14] By employing the chiral ligand **L1** developed in their own group, chloroallenes **23** were obtained in high yields with exclusive regioselectivity and moderate to good enantioselectivity from 1,1-dichloropropargylic compound **22** and alkyl Grignard reagents (Scheme 7). Notably, the chloroallene products could be easily transformed into trisubstituted allenes **24** or terminal alkynes **25** with a propargylic quaternary carbon center without appreciable loss of enantiopurity in the presence of aryl or alkyl Grignard reagents, respectively.



Scheme 7 Catalytic asymmetric synthesis of chloroallenes from 1,1-dichloropropargylic compounds.

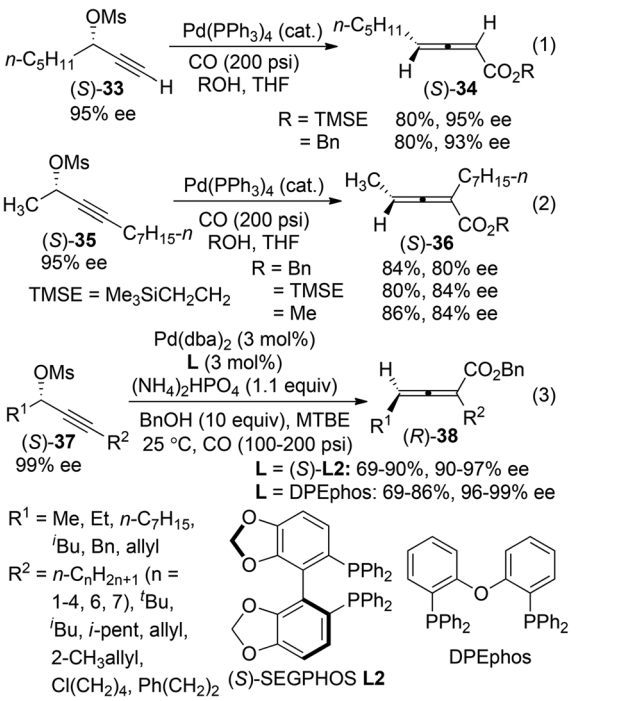
2.1.2 Palladium-catalyzed transformations. Palladium-catalyzed coupling reaction of propargylic compounds with various nucleophiles is another straightforward approach for the synthesis of allenes.[4] However, deterioration of enantiopurity was also often observed in the chirality transfer process, as demonstrated in the reactions where organozinc[15a] or organoindium[15b] reagents or arylboronic acids[15c] were utilized as the coupling

partner of propargylic electrophiles (Scheme 8). For example, in the reactions of propargylic carbonates **31** with arylboronic acids, only three products **32a–c** were obtained with ≥90% ee, while the other arylboronic acids or alkyl-substituted propargylic carbonates all gave products with low efficiency of chirality transfer (c, Scheme 8). Isomerization between η^1-propargyl and η^1-allenylpalladium intermediates, which were generated from oxidative addition of the propargylic electrophiles with Pd(0), was believed to be responsible for the loss of optical activity. Thus, while loss of enantiopurity was observed in both Cu- and Pd-catalyzed transformations, the reason behind is different as a result of the different mechanisms of these reactions.



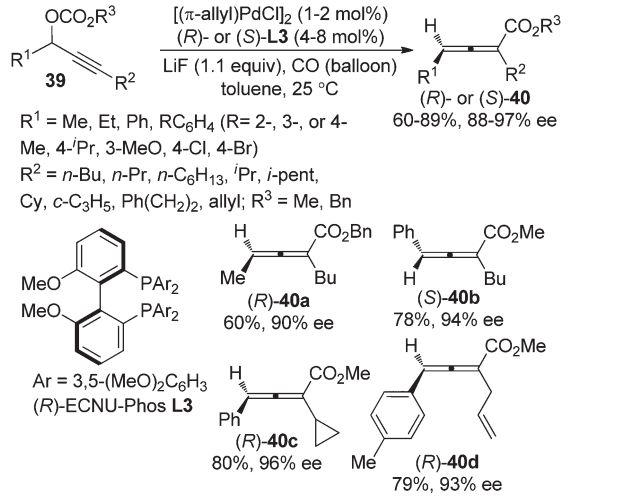
Scheme 8 Chirality transfer of propargylic electrophiles with a variety of organometallic reagents.

2,3-Allenoates are versatile building blocks in organic synthesis due to the synthetic potentials of the ester functionality.[3h] One of the most widely used methods for the synthesis of axially chiral 2,3-allenoates is based on Pd-catalyzed carbonylation reactions of optically active propargylic alcohol derivatives under a carbon monoxide atmosphere.[4] In Pd-catalyzed carbonylation reactions of optically active propargylic mesylates reported by Marshall *et al.*,[16] retention of enantiomeric purity was observed in the case of terminal alkyne (*S*)-**33** (eqn (1), Scheme 9). In contrast, an obvious loss of enantiopurity was encountered when internal alkyne derivative (*S*)-**35** was utilized (eqn (2), Scheme 9). To address such a concern referring to the internal C–C triple bond, two modified procedures were recently developed, in which biphosphine ligand (*S*)-SEGPHOS **L2** or DPEphos was applied to minimize racemization during the chirality transfer process of the internal propargyl mesylates (*S*)-**37** (eqn (3), Scheme 9).[17]



Scheme 9 Synthesis of axially chiral 2,3-allenoates *via* carbonylation reactions of propargylic mesylates.

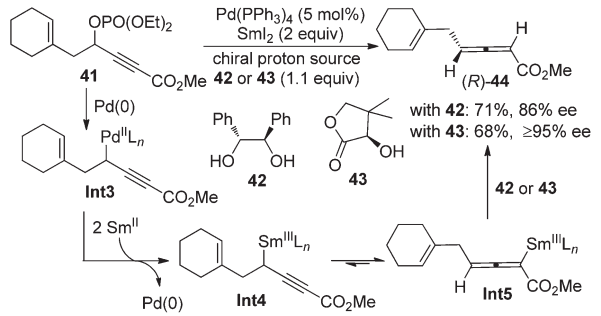
Very recently, we further developed a highly enantioselective protocol for the synthesis of 2,3-allenoates **40** directly from racemic propargylic carbonates **39** by utilizing the newly developed biphenyl biphosphine ligand (*R*)- or (*S*)-ECNU-Phos **L3** (Scheme 10).[18] The 3,5-dimethoxy substituents on the phenyl group linked to the phosphorus atom (Ar) may provide the



Scheme 10 Catalytic asymmetric synthesis of 2,3-allenoates from racemic propargylic carbonates.

required steric and electronic environments for achieving a high enantioselectivity at room temperature, which is of critical importance for this type of reaction due to the temperature-sensitive nature of electron-deficient axially chiral allenes. However, terminal propargylic carbonates (R^2 = H) are not compatible with this procedure and further efforts are needed.

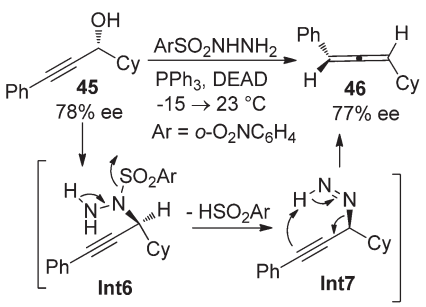
Besides the chirality transfer approach and asymmetric catalysis, 2,3-allenoates may also be prepared by the enantioselective protonation using a stoichiometric amount of chiral reagents. Mikami *et al.* reported that in the presence of chiral proton source **42** or **43**, allenylsamarium(III) intermediates **Int5** generated from the corresponding palladium species **Int3** could be asymmetrically protodemetallated to afford axially chiral allene (*R*)-**44** in practical yields with a reasonably high enantiopurity (Scheme 11).[19] However, the generality of this approach has not been explored, as only a single example was reported.



Scheme 11 Synthesis of 2,3-allenoates using stoichiometric amounts of chiral proton sources.

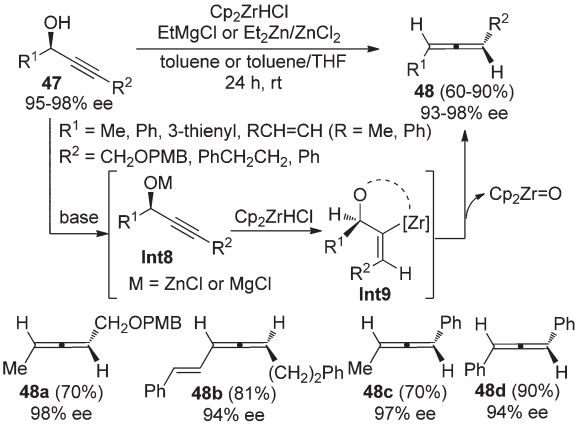
2.2 From propargylic alcohols

While the aforementioned methodologies all rely on the transformations of propargylic alcohol derivatives with a suitable leaving group, propargylic alcohols themselves have also been utilized to prepare allenes. Myers *et al.* reported such an example by using enantioenriched propargylic alcohol **45** (78% ee) with *o*-nitrobenzenesulfonylhydrazine to give axially chiral allene **46** with complete retention of enantiopurity (Scheme 12).[20] The reaction is believed to proceed *via* the formation of propargylic hydrazine intermediate **Int6** followed by intramolecular [1,5]-H transfer.



Scheme 12 Chirality transfer of propargylic alcohol in the presence of *o*-nitrobenzenesulfonylhydrazine.

Ready and co-workers demonstrated an alternative approach to achieve this goal (Scheme 13).[21] With EtMgCl or the combination of Et_2Zn and $ZnCl_2$ as the base, highly enantioenriched propargylic alcohols **47** were converted to the corresponding disubstituted allenes in good yields and with high stereochemical purity in the presence of the Schwartz reagent (Cp_2ZrHCl). Strict *syn*-hydrozirconation followed by *syn*-elimination of Cp_2ZrO accounts for the high efficiency of the chirality transfer process.



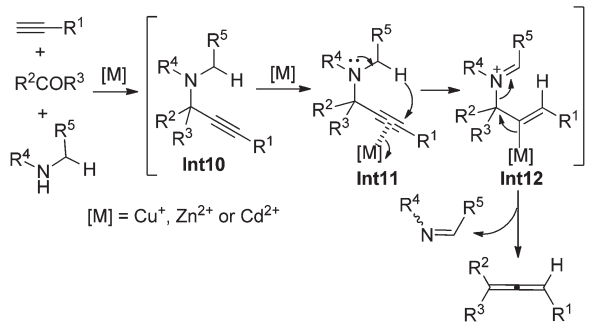
Scheme 13 Chirality transfer of propargylic alcohols in the presence of the Schwartz reagent.

3. From terminal alkynes, aldehydes, and amines – allenylation of terminal alkynes (ATA) reaction

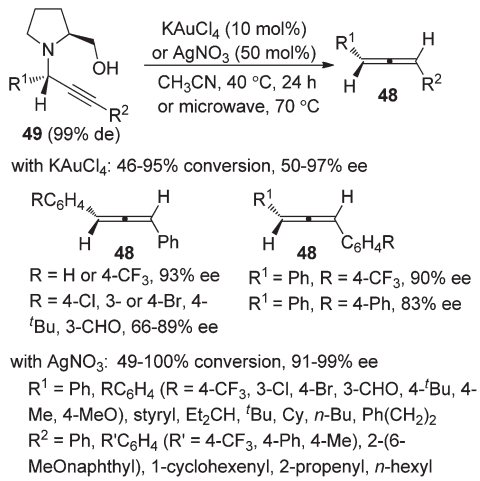
3.1 Chiral amine approach

In 1979, Crabbé *et al.* developed an efficient synthesis of monosubstituted allenes directly from terminal alkynes in the presence of paraformaldehyde and diisopropylamine, albeit with low yields and a limited scope only workable with paraformaldehyde.[22] We have later modified this procedure for higher yields with CuI and Cy_2NH[23a] and established efficient ZnI_2- or CdI_2-mediated synthesis of 1,3-disubstituted[23b] or 1,1,3-trisubstituted[23c] allenes from terminal alkynes and aldehydes or ketones in the presence of secondary amines. The ATA reaction is believed to proceed *via* an initial formation of propargylic amine intermediate **Int10** followed by metal-mediated intramolecular [1,5]-H shift and β-elimination (Scheme 14).[22,23]

It should be noted that Che and co-workers developed the Au(III)-catalyzed[24a] or Ag(I)-mediated[24b] enantioselective synthesis of axially chiral allenes from enantioenriched propargylic amines **49** (Scheme 15), which, in turn, were prepared *via* Au(III) salen complex-catalyzed three-component coupling reactions of terminal alkynes, aldehydes, and chiral prolinol.[24c] Although the Au(III)-catalyzed approach is confined to 1,3-diarylallenes and electron-poor propargylic amines, the efficiency of the chirality transfer process is generally good in the Ag(I)-mediated protocol. However, the conversions in both cases are unsatisfactory as most of the substrates failed to reach full conversion under the reaction conditions.

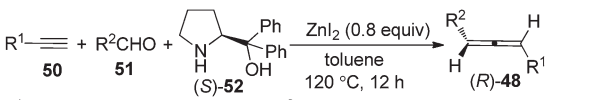


Scheme 14 A possible mechanism of the ATA reaction.



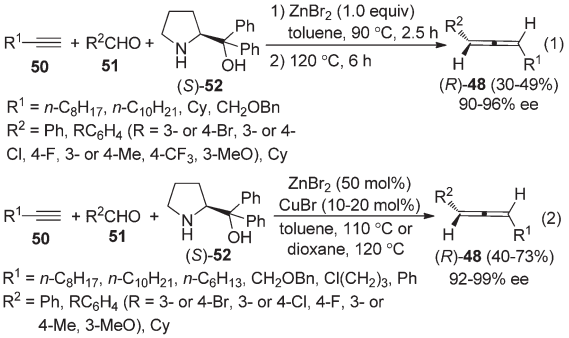
Scheme 15 Au(III)- or Ag(I)-promoted synthesis of axially chiral allenes from enantioenriched propargylic amines.

As the ZnI_2-mediated protocol for aldehydes[23b] makes enantioselective synthesis of 1,3-disubstituted allenes possible by utilizing chiral amines as well as chiral ligands, we turned our attention to the enantioselective allenylation of terminal alkynes (EATA) *via* such an approach. Thus, a "chiral amine" approach was developed using commercially available and inexpensive (*S*)- or (*R*)-α,α-diphenylprolinol **52** as the chiral amine (Scheme 16).[25,26] However, extensive studies showed that the scope of the reaction was quite limited as only terminal alkyne **50a** with a sterically bulky group and aliphatic aldehydes are suitable substrates; simple alkynes such as **50b** with a less sterically bulky alkyl group and propargyl alcohols such as **50c** with a free hydroxyl group all gave very poor results.[25]



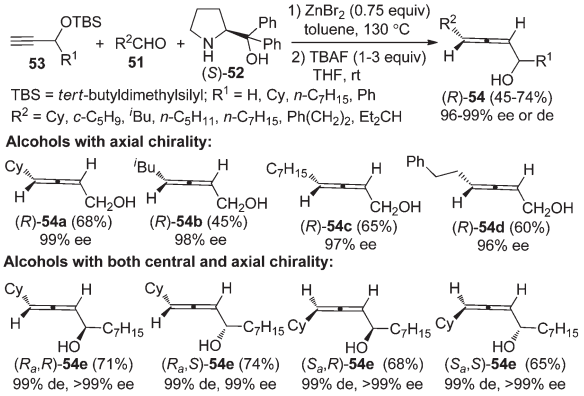
Scheme 16 Initial observations on the chiral amine approach.

Thus, a "two-stage" procedure for the reactions of simple terminal alkynes with aromatic or aliphatic aldehydes was established to give the allene products with excellent enantioselectivity; however, the yields are still quite low (eqn (1), Scheme 17).[26a] Although Periasamy *et al.* recently reported the synthesis of axially chiral allenes from simple non-functionalized terminal alkynes using α,α-diphenylprolinol **52**,[27a] we have not been able to reproduce their results in terms of ee and yield: the calibrated specific optical rotations of the same allenes with similar ee values from our study and the data in their report are different.[26a] To further improve the yield and enantioselectivity as well as broaden the scope of this reaction, a Cu^+/Zn^{2+} bimetallic approach was developed, providing axially chiral allenes (*R*)-**48** in somewhat higher yields with excellent enantioselectivity (eqn (2), Scheme 17).[26b] However, heteroaromatic and α,β-unsaturated aldehydes are still incompatible substrates for the reaction. Control experiments revealed that CuBr is responsible for the efficient formation of the propargylic amine intermediate while both CuBr and $ZnBr_2$ play crucial roles in the propargylic amine-to-allene transformation.



Scheme 17 Synthesis of simple axially chiral allenes *via* the chiral amine approach.

α-Allenols with axial chiralities are valuable building blocks in organic synthesis due to the synthetic potential of the hydroxyl group.[12] The reactions of TBS-protected propargyl alcohol **53** (R^1 = H) with various aliphatic aldehydes afforded primary α-allenols such as (*R*)-**54a–d** in practical yields with excellent enantioselectivity after deprotection of the TBS group (Scheme 18).[26c] Synthesis of α-allenols with both central and

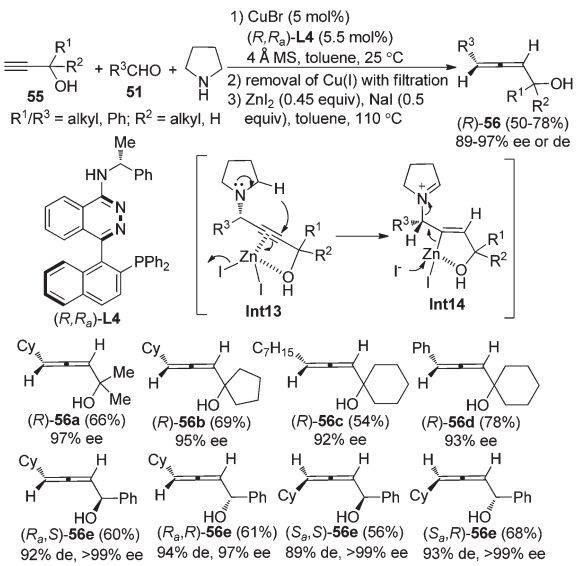


Scheme 18 Synthesis of axially chiral α-allenols *via* the chiral amine approach.

axial chiralities is challenging. Notably, all of the four diastereoisomers of secondary α-allenols **54e** could be highly stereoselectively prepared simply by adjusting the absolute configurations of the central chiralities in the TBS-protected secondary propargylic alcohols **53** and α,α-diphenylprolinol **52**. Control experiments revealed that the TBS group is acting not only as a protecting group but also as a steric-dictating group for the excellent enantioselectivity. However, this reaction is currently not applicable to aromatic and α,β-unsaturated aldehydes.

3.2 Chiral ligand approach

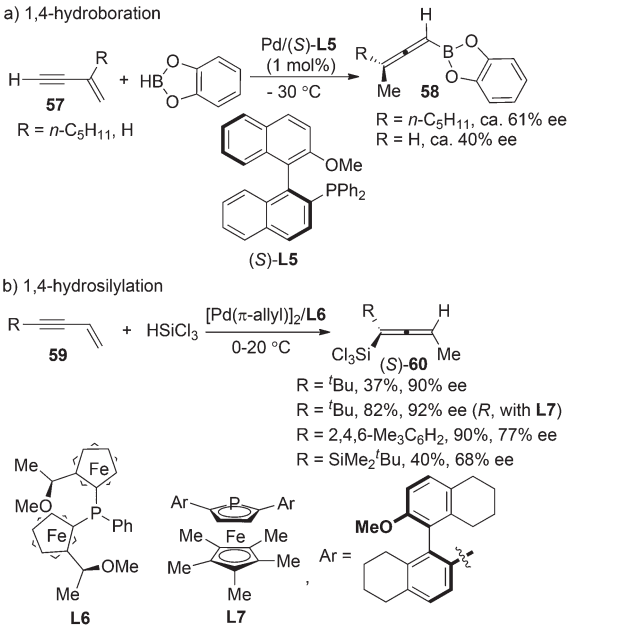
Furthermore, a "chiral ligand" approach was developed to give axially chiral allenes, especially highly useful α-allenols, in decent yields with excellent enantio- or diastereoselectivity from terminal alkynes, aldehydes, and pyrrolidine by applying the chiral ligand (R,R_a)-PINAP **L4** (Scheme 19).[25] Again, by simply changing the central chirality of secondary propargylic alcohols **55** and axial chirality of the chiral ligand, all of the four diastereoisomers of the secondary α-allenols **56e** could be highly stereoselectively prepared. The free hydroxyl group in the terminal alkynes **55** proved to be crucial both for the yield and enantioselectivity of the reaction, which may be explained by its coordination with Cu^{+} and/or Zn^{2+} in the first and the second step of this transformation. However, primary propargylic alcohol is not compatible with this procedure, probably resulting from the lack of effective coordination of the hydroxyl group with Zn^{2+}. Nevertheless, the corresponding primary α-allenols may be easily prepared through the "chiral amine" approach (Scheme 18). When ZnI_2 was replaced with $KAuCl_4$ [24a] or $AgNO_3$,[24b] only trace amounts of allenol products were detected, suggesting that matching reactivity between substrates and metal salts is crucial for the transformation of propargylic amine to the functionalized allene. Further efforts to design a more practical "one-pot" procedure are in progress in this group.



Scheme 19 Synthesis of axially chiral secondary and tertiary α-allenols *via* the chiral ligand approach.

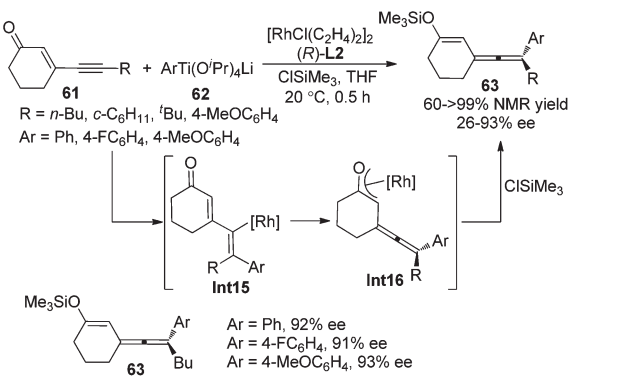
4. From conjugated enynes

Pd-catalyzed asymmetric 1,4-addition of hydroborane[28a] or hydrosilane[28b,c] to conjugated enynes has been established by Hayashi *et al.* as a very promising strategy for the synthesis of axially chiral allenylboranes or allenylsilanes, which are valuable propynylating reagents in asymmetric synthesis. However, the enantioselectivities were moderate in most cases; the substrate scope also proved to be very limited (Scheme 20).



Scheme 20 Pd-catalyzed 1,4-hydroboration of conjugated enynes.

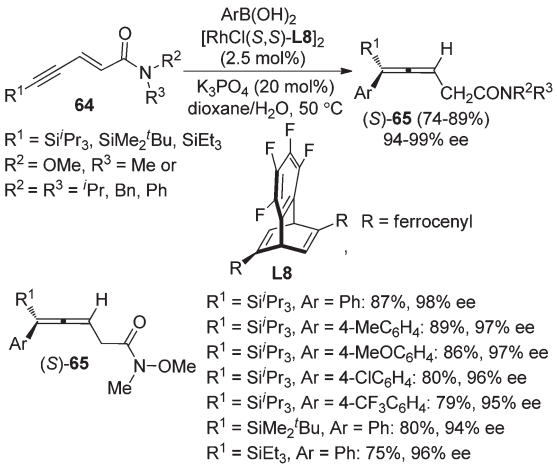
Following these previous studies, the same group developed a Rh-catalyzed asymmetric 1,6-addition of aryltitanates **62** to conjugated enynones **61** to give axially chiral allenylalkenyl silyl enol ethers **63** in the presence of chiral ligand (R)-SEGPHOS **L2** and chlorotrimethylsilane (Scheme 21).[28d] While >90% ee of the products were observed when the terminal substituent (R) is an *n*-butyl group, only moderate enantio-



Scheme 21 Rh-catalyzed asymmetric 1,6-addition of aryltitanates to conjugated enynones.

selectivity was obtained in other cases. A mechanism involving carborhodation, enantioselective isomerization, silylation and transmetallation was proposed for the reaction.

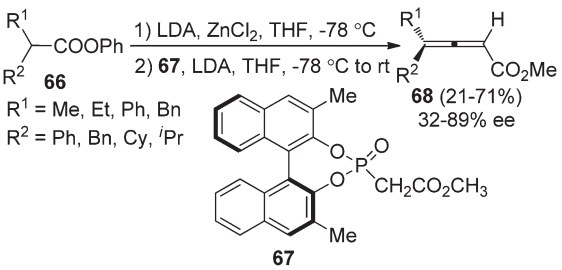
Recently, Hayashi and co-workers further developed a Rh/chiral diene complex-catalyzed enantioselective approach for the synthesis of allenylsilanes **65** with 94–99% ee *via* the 1,6-addition of arylboronic acids to enynamides **64** (Scheme 22).[28e] Both the ferrocenyl group of the chiral diene ligand **L8** and bulky silyl substituent of the alkyne were found to be critical for achieving high regio- and enantioselectivity.



Scheme 22 Rh-catalyzed asymmetric 1,6-addition of arylboronic acids to enynamides.

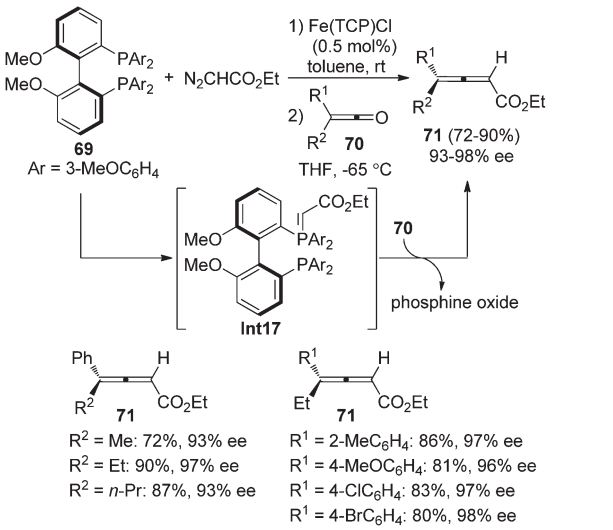
5. From ketenes

Olefination of ketenes with ylides is also an efficient approach to synthesize allenes.[4] Thus, in the presence of a chiral ylide, axially chiral allenes may be accessible. Bestmann[29a] and Musierowicz[29b] *et al.* made pioneering contributions in this area, although the 2,3-allenoates thus obtained exhibited a low optical activity. Tanaka and co-workers showed that chiral ylide derived from BINOL-based phosphinate ester **67** reacted with the *in situ* generated ketenes to afford 4,4-disubstituted 2,3-allenoates **68** in 21–71% yield with 32–89% ee (Scheme 23).[30]



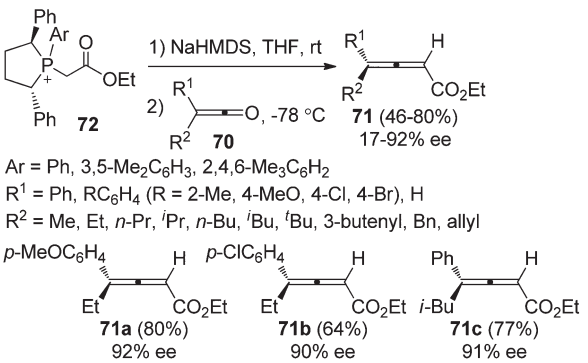
Scheme 23 Olefination of ketenes with BINOL-based chiral ylide.

Tang and co-workers reported an iron-porphyrin complex-catalyzed olefination of ketenes **70** with diazoacetate, furnishing 4,4-disubstituted 2,3-allenoates **71** in good yields with excellent enantioselectivity, albeit the substrate scope was somewhat limited (Scheme 24).[31a] It is worth noting that the chiral phosphine oxide by-product could be easily recycled *via* reduction. Although diphosphine **69** was utilized, control experiment revealed that the reaction proceeded *via* monoylide **Int17**.



Scheme 24 Fe-catalyzed olefination of ketenes with diazoacetate.

Tang *et al.* further developed pseudo-C_2-symmetric monoylides **72** for the synthesis of optically active 2,3-allenoates. The scope of ketenes was expanded; however, the enantioselectivities were generally moderate with only three products **71a–c** being obtained with ≥90% ee (Scheme 25).[31b,c]

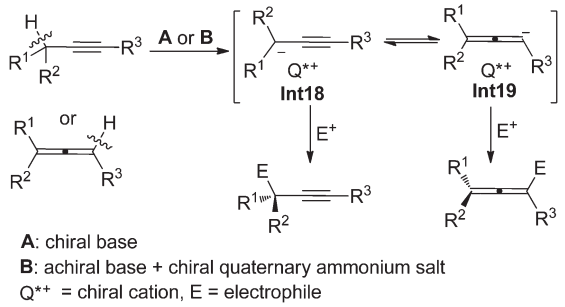


Scheme 25 Olefination of ketenes with pseudo-C_2-symmetric ylides.

6. From propargyl/1,2-allenyl anion intermediates

In the presence of a chiral base or an achiral base combined with a chiral quaternary ammonium salt, properly substituted propargylic compounds or allenes would be deprotonated to afford propargyl/1,2-allenyl anion intermediates **Int18**/**Int19**

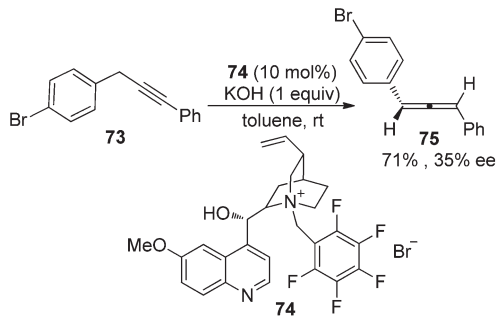
with a chiral cation, which may react with electrophiles enantioselectively to furnish propargylic compounds with a central chirality and/or allenes with an axial chirality depending on the substituents of substrates and the type of electrophiles (Scheme 26).



Scheme 26 Two strategies for the generation of propargyl/1,2-allenyl anion intermediates with a chiral cation.

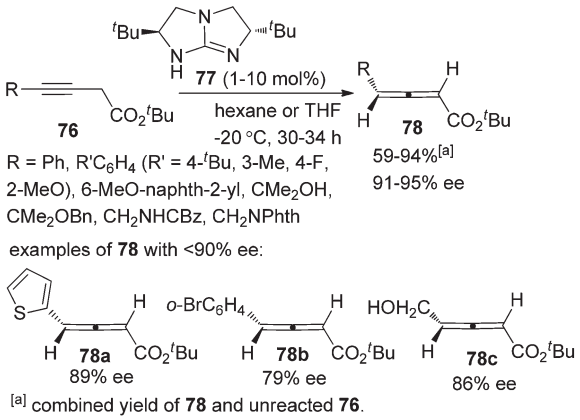
6.1 Alkyne isomerization

In the first place, base-promoted isomerization of alkynes has long been recognized as another straightforward protocol to allenes;[4] however, catalytic asymmetric approaches have rarely been reported.[32] In 2000, Arai and Shioiri *et al.* reported a single example of asymmetric isomerization of 1,3-diaryalkyne **73** to axially chiral allene **75** in the presence of phase-transfer catalyst **74** with a low enantioselectivity (Scheme 27).[33]

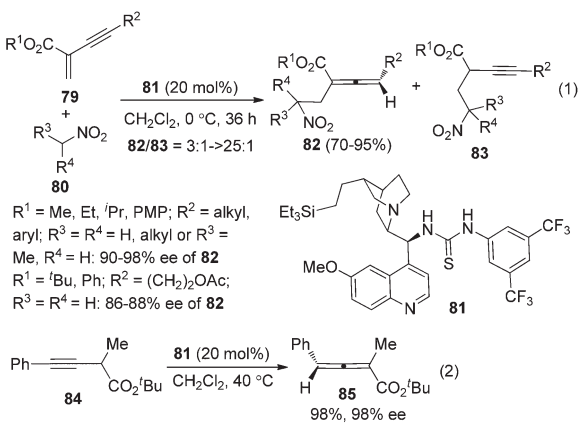


Scheme 27 Alkyne isomerization in the presence of a chiral phase-transfer catalyst.

In 2009, Huang and Tan *et al.* demonstrated that guanidine **77** was a highly enantioselective catalyst for the isomerization of 3-alkynoates **76** to disubstituted 2,3-allenoates **78** (Scheme 28).[34] The bulky *tert*-butyl in the ester group is crucial for the reaction to proceed in high enantioselectivity. While 91–95% ee was obtained for most of the substrates, relatively lower enantioselectivities were observed when the terminal substituent (R) is a 2-thienyl, *o*-BrC_6H_4, or CH_2OH group. A flaw in this procedure is that the reaction cannot reach full conversion even after extending the reaction time, which makes the isolation of pure 2,3-allenoates **78** problematic due to the similar polarity of the unreacted 3-alkynoates. Besides, the reactivity of 2-substituted 3-alkynoate has not been demonstrated, although it might be useful for the synthesis of trisubstituted 2,3-allenoates. This limitation has been nicely addressed very recently by Zhang and Sun,[35] who developed a tandem conjugate addition/isomerization sequence from activated enynes **79** and nitroalkanes **80** using the newly developed cinchona-based thiourea catalyst **81**, resulting in trisubstituted 2,3-allenoates **82** in high yields with excellent enantioselectivity, albeit in some cases contaminated with a minor amount of alkynoate intermediates **83**, which can be further isomerized to the corresponding 2,3-allenoates under the same reaction conditions (eqn (1), Scheme 29). To further demonstrate the generality of thiourea **81** as an isomerization catalyst, the authors also realized the highly enantioselective isomerization of racemic alkynoate **84** to trisubstituted 2,3-allenoate **85** in 98% yield with 98% ee (eqn (2), Scheme 29).



Scheme 28 Guanidine-catalyzed isomerization of 3-alkynoates to disubstituted 2,3-allenoates.

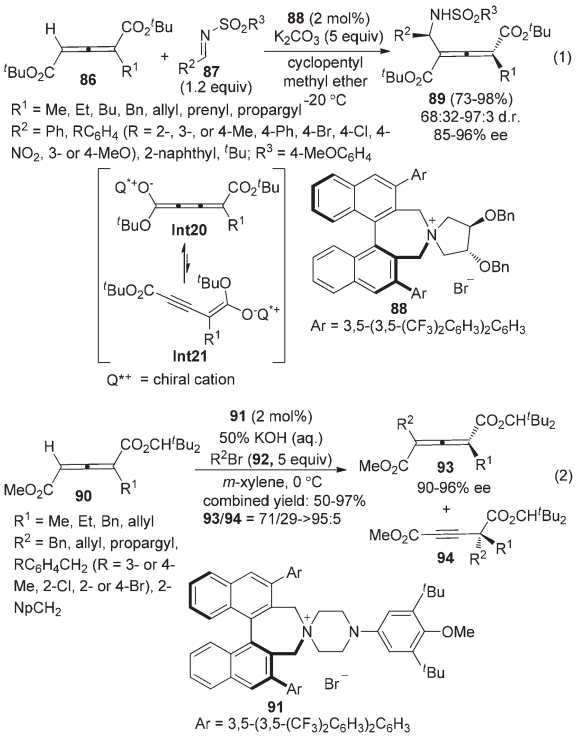


Scheme 29 Cinchona-based thiourea-catalyzed asymmetric synthesis of trisubstituted 2,3-allenoates.

6.2 Electrophilic addition and substitution of 1-alkylallene-1,3-dicarboxylates

Although considerable progress has been made in the enantioselective synthesis of di- or trisubstituted allenes in the past few decades, such a synthesis of tetrasubstituted allenes has

rarely been explored.[4] Recently, Maruoka and co-workers reported a phase-transfer-catalyzed approach for the generation of axially chiral tetrasubstituted allenes from 1-alkylallene-1,3-dicarboxylates **86** or **90** and *N*-arylsulfonyl imines **87** or alkyl bromides **92** (Scheme 30).[36] Chiral cumulenolate **Int20** and α-alkynyl enolate **Int21** generated *in situ* from 1-alkylallene-1,3-dicarboxylates in the presence of a chiral quaternary ammonium salt under basic conditions were acting as the nucleophiles. Interestingly, when *N*-arylsulfonyl imines **87** were utilized as the electrophile, tetrasubstituted allenes **89** were obtained as a single regioisomer with 68/32–97/3 dr and 85–96% ee in the presence of phase-transfer catalyst **88** (eqn (1), Scheme 30). In contrast, with alkyl bromides **92** as the electrophile under the catalysis of chiral quaternary ammonium salt **91**, poorer regioselectivities were observed: both tetrasubstituted allenes **93** (90–96% ee) and alkynes **94** were obtained with the ratio of **93**/**94** ranging from 71/29 to >95/5 (eqn (2), Scheme 30).

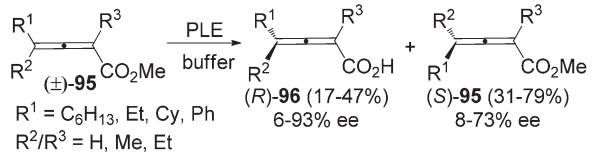


Scheme 30 Electrophilic addition and substitution reactions of 1-alkylallene-1,3-dicarboxylates.

7. From racemic allenes

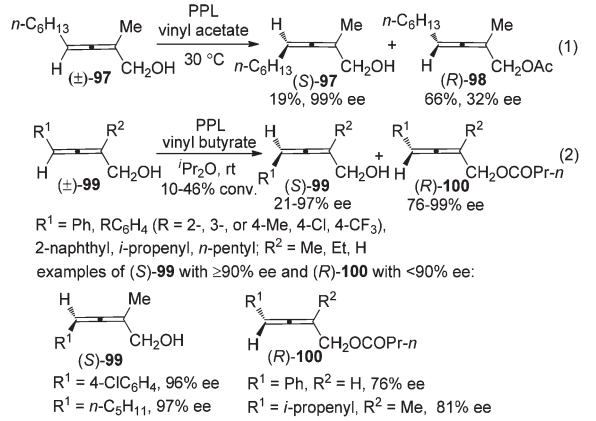
7.1 Kinetic resolution or desymmetrization

7.1.1 Kinetic resolution or desymmetrization using enzyme. Resolution of racemic allenes with inexpensive enzyme is another approach to obtain axially chiral allenes. However, a lack of generality is the common problem of this method. Jones *et al.* found that optically active 2,3-allenoic acids **96** could be accessed *via* hydrolysis of racemic 2,3-allenoates **95** in the presence of PLE. However, only two substrates (R^1 = Ph, R^2 = R^3 = Me or Et) afforded the corresponding 2,3-allenoic acids with >90% ee (Scheme 31).[37]



Scheme 31 PLE-catalyzed hydrolysis of 2,3-allenoates. PLE = pig liver esterase.

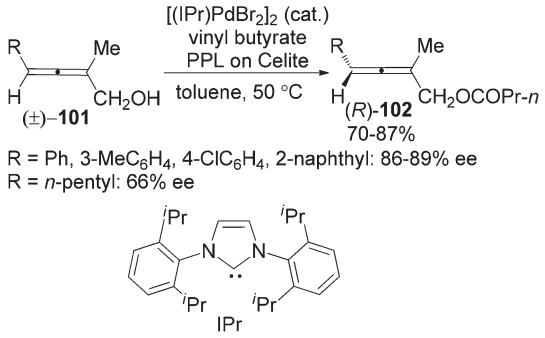
For 2-substituted axially chiral 2,3-allenols, this group found that PPL is an optimal enzyme for the resolution of this type of substrates; for example, trisubstituted 2,3-allenol (*S*)-**97** was obtained with 99% ee, albeit in low yield (eqn (1), Scheme 32).[38] Bäckvall *et al.* studied the kinetic resolution of this type of allenols using vinyl butyrate as the acyl donor and found that 4-aryl substituted allenols were resolved more efficiently than 4-alkyl substituted ones, affording the corresponding allenyl esters (*R*)-**100** with excellent enantioselectivity. A substituent at 2-position is required as when R^2 is hydrogen, a low reaction rate and selectivity were observed (eqn (2), Scheme 32).[39a]



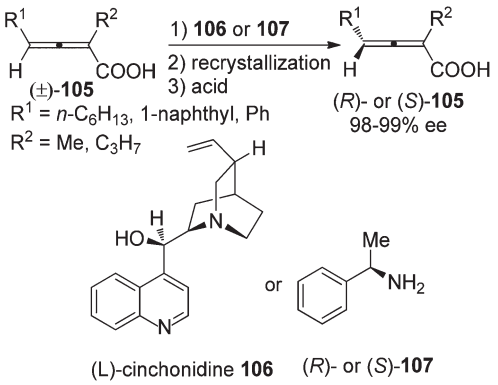
Scheme 32 Resolution of 2-substituted 2,3-allenols with PPL. PPL = porcine pancreatic lipase.

Following this study, the same group developed a dynamic kinetic resolution (DKR) of trisubstituted 2,3-allenols **101** by combining enzymatic dynamic kinetic resolution with Pd-catalyzed *in situ* racemization of allenes, providing allenyl butyrates **102** in 70–87% yields with 86–89% ee for aryl substrates and 66% ee when R is an *n*-pentyl group (Scheme 33).[39b] However, the substrate scope was very limited as only 2-methyl substituted substrates are applicable. The N-heterocyclic carbene (IPr) was found to be the optimal ligand for ensuring a faster racemization of the chiral allene moiety in the allenol than the allenyl ester, which is of critical importance for the DKR process.

Enzymatic desymmetrization of prochiral allenes is another way for the preparation of axially chiral allenes, which may also overcome the intrinsic yield limitation (≤50%) encountered in the traditional kinetic resolution. Deska and co-

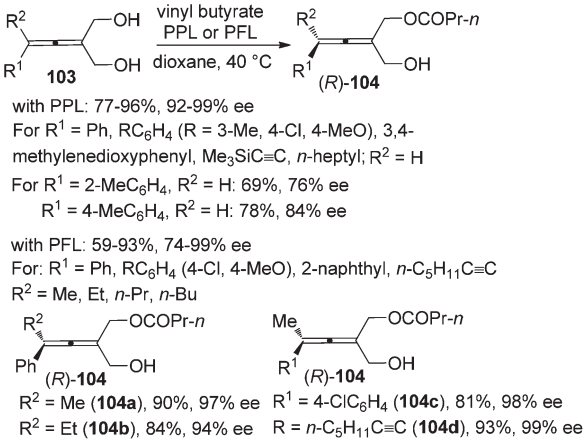


Scheme 33 Dynamic kinetic resolution of trisubstituted 2,3-allenols.



Scheme 35 Resolution of 2,3-allenoic acids with chiral amines.

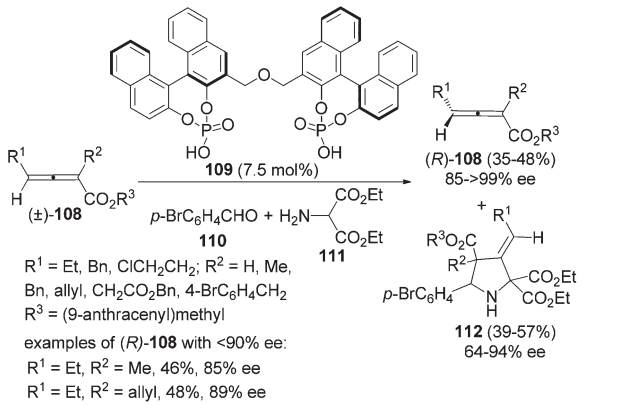
workers demonstrated that porcine pancreatic lipase (PPL) is an excellent biocatalyst for the desymmetrization of trisubstituted prochiral allenic diols **103**, producing 2,3-allenols with an extra ester group **104** in moderate to high yields with excellent enantioselectivity except when R^1 is a 2-MeC_6H_4 or 4-MeC_6H_4 group (Scheme 34).[40a] For the tetrasubstituted substrates, the authors revealed that the lipase from *Pseudomonas fluorescens* (PFL) is a more effective catalyst in terms of reaction rate and selectivity and tetrasubstituted 2,3-allenols **104a–d** were obtained with >90% ee.[40b]



Scheme 34 Enzymatic desymmetrization of prochiral allenic diols. PFL = *Pseudomonas fluorescens* lipase.

7.1.2 Kinetic resolution using other chiral reagents. In the presence of a readily available and inexpensive chiral amine such as L-cinchonidine **106** or methylbenzylamine **107**, racemic 2,3-allenoic acids **105** were classically resolved to afford the corresponding axially chiral ones with 98–99% ee after recrystallization and acidification of the acid–base salts with very low efficiency and limited scope (Scheme 35).[41]

Besides enzyme and chiral amine, organocatalysts such as bisphosphoric acid **109** can also be applied to the kinetic resolution of racemic 2,3-allenoates in the presence of aldehyde **110** and amine **111**: optically active 2,3-allenoates **108** and 1,3-dipolar cycloaddition products 3-methylenepyrrolidine derivatives **112** were obtained in 35–48% yield with 85–99% ee and in 39–57% yield with 64–94% ee, respectively (Scheme 36).[42] However, this reaction may not be applied to aryl-substituted substrates.

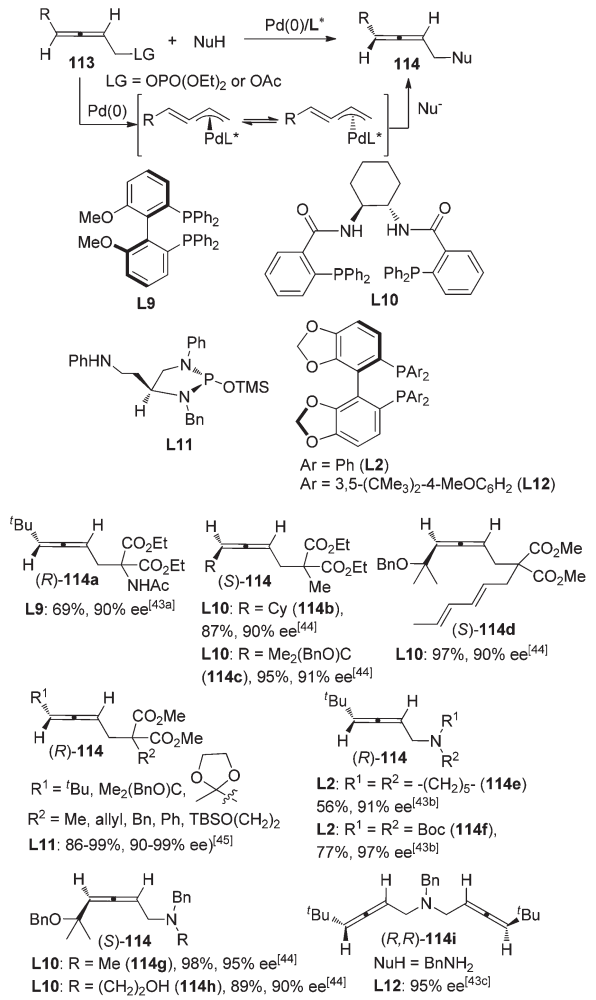


Scheme 36 Kinetic resolution of racemic 2,3-allenoates *via* organocatalysis.

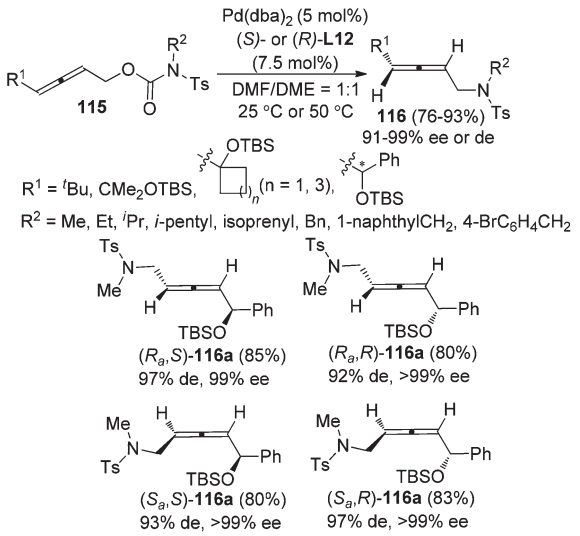
7.2 Pd-catalyzed nucleophilic allenylation reactions

Pd-catalyzed asymmetric synthesis of axially chiral allenes with a nucleophilic functionality from 2,3-allenyl phosphates or carboxylates **113** in the presence of a chiral ligand and a nucleophile such as amine or malonate derivative has been extensively studied by Imada,[43] Murahashi,[43a,b] Naota,[43b,c] Trost,[44] and Hamada[45] *et al.* since 2002, leading to functionalized allenes **114** in practical yield with moderate to good enantiopurity. Allene products with high enantiopurity (≥90% ee) are shown in Scheme 37. This part of the work has been well summarized by Ogasawara in 2009[4e] and thus will not be discussed in detail here. However, it should be noted that a sterically bulky substituent on the allene moiety is generally required for achieving a high level of enantioselectivity. In addition, the scope of nucleophiles also awaits further expansion.

While previous studies have focused on intramolecular reactions, an enantioselective synthesis of axially chiral allenyl amines **116** *via* "intramolecular" decarboxylative amination of allenyl *N*-tosylcarbamates **115** was recently developed by our group (Scheme 38).[46] The chiral ligand (*S*)- or (*R*)-**L12** imparted



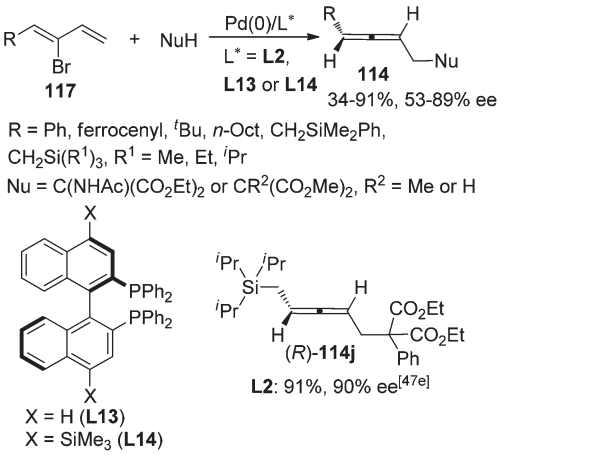
Scheme 37 Pd-catalyzed asymmetric synthesis of axially chiral allenes from 2,3-allenyl phosphates or carboxylates.



Scheme 38 Pd-catalyzed synthesis of axially chiral allenyl amines *via* decarboxylative amination.

remarkable enantio- and diastereoselectivity under Pd catalysis. However, as observed in previous studies, a sterically bulky substituent on the allene moiety (R^1) is required in order to achieve high enantioselectivity.

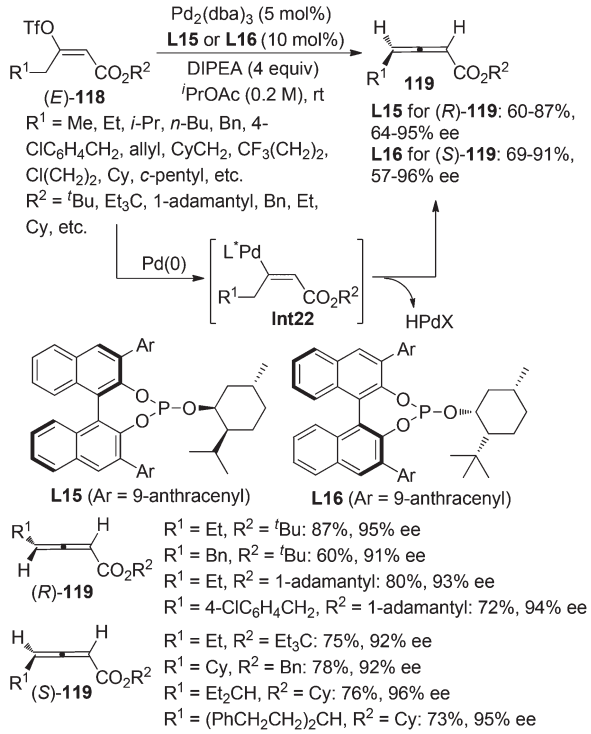
Besides 2,3-allenyl phosphates or carboxylates **113**, 2-bromo-1,3-dienes **117** have also been utilized by Hayashi,[47a,c] Takahashi,[47d,e] and Ogasawara[47] *et al.* to synthesize functionalized axially chiral allenes in a similar manner, although the enantioselectivities were generally lower than using 2,3-allenyl phosphates or carboxylates **113** as the starting material and only one product (*R*)-**114j** was obtained with high enantiopurity (≥90% ee) (Scheme 39).



Scheme 39 Pd-catalyzed asymmetric synthesis of axially chiral allenes from 2-bromo-1,3-dienes.

8. From enol triflates *via* β-hydride elimination

While β-hydride elimination of alkyl palladium species is commonly observed in the traditional Heck reaction,[48a] β-hydride elimination of vinyl palladium species has rarely been observed[49] as it was considered to be an energetically unfavorable process,[48] albeit formation of allene intermediate *via* β-hydride elimination has been proposed in several transformations.[50] However, Miura and co-workers reported that trisubstituted allenes could be prepared *via* the Pd-catalyzed coupling reactions of dialkylacetylenes with aryl bromides, which was believed to proceed *via* β-hydride elimination of vinyl palladium intermediate under a very high temperature (130 °C).[49a] Very recently, Frantz and co-workers realized such a concept by developing a Pd-catalyzed asymmetric β-hydride elimination for the synthesis of axially chiral 2,3-allenoates **119** from (*E*)-enol triflates **118** in the presence of the newly developed chiral phosphite ligand **L15** or **L16** (Scheme 40).[51a] In sharp contrast with the aforementioned work of Miura *et al.*,[49a] the current reaction may be carried out at room temperature, which may explain why further hydropalladation of



Scheme 40 Pd-catalyzed asymmetric synthesis of 2,3-allenoates from (*E*)-enol triflates.

the allene products delivering 1,3-dienes in the authors' previous study[51b] was inhibited in this catalytic system. In addition, low temperature is required to avoid *in situ* racemization of the electron-deficient chiral allene products. A limitation is that aryl-substituted 2,3-allenoate may not be accessible *via* this procedure. Besides, trisubstituted 2,3-allenoates were obtained with low conversion and enantioselectivity from the corresponding fully substituted (*E*)-enol triflates.

9. Conclusions and perspectives

Despite the substantial advances that have been made so far, enantioselective approaches to obtain axially chiral allenes are still just at the very early stage and thus of high current interest, especially in the area of asymmetric catalysis: developing chiral ligands of new skeletons or modifying known privileged ligands for catalytic enantioselective synthesis of allenes would undoubtedly be one of the most active areas as many reactions that were once considered as impossible or formidable are now realized with the aid of novel chiral ligands.

Secondly, although the first synthesized axially chiral allene **3** was prepared *via* organocatalysis (Scheme 1), this area remains largely underdeveloped and may be worth exploring as many types of chiral organocatalysts are readily available nowadays. The chiral base-catalyzed isomerization reactions (section 6.1), for example, still suffer from limited substrate scope and more general approaches are highly sought after. In addition, propargylic compounds have only been used in isomerization reactions to date; a more desirable and challenging goal is to access tri- or tetrasubstituted allenes in the presence of an external electrophile (Scheme 26).

Thirdly, as β-hydride elimination of vinyl palladium species has been proven to be feasible for the synthesis of both racemic and enantioenriched allenes, further efforts to establish more protocols with broader substrate scope and better reactivity and enantioselectivity should be a promising area. In addition to palladium, other transition metals such as rhodium and iridium may also be considered for such a β-hydride elimination strategy. Other types of β-elimination will also be applied.

Last but not least, completely new approaches to obtain allenes will be highly expected. Overall, given the rapid development of allene chemistry and the widespread utility of axially chiral allenes, chemists around the world will surely spare no efforts to overcome the challenges in the next few decades. The efforts to obtain axially chiral allenes have already been initiated.

Acknowledgements

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