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Catalytic enantioselective synthesis of axially chiral allenes

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ABSTRACT

The conventional procedures for preparing optically active axially chiral allenes generally require stoichiometric chiral sources as either substrates or reagents. On the other hand, examples of *catalytic asymmetric synthesis of axially chiral allenes* are rare and it is a relatively underdeveloped area in synthetic organic chemistry. In this review article, various methods for preparing enantiomerically enriched axially chiral allenes using substoichiometric chiral sources are surveyed. Some reactions with stoichiometric but recoverable chiral sources are also mentioned. Most of the asymmetric reactions in these categories are transition-metal-catalyzed reactions, and there are a few examples of organocatalytic reactions. In addition, some enzymatic/microbial systems are also known.

Contents

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1. Introduction

Allenes (1,2-propadiene derivatives) are an important class of compounds and have gained increasing attraction as interesting building blocks in synthetic organic chemistry.[1,2] Allenes are characterized by two cumulated carbon–carbon double bonds, and their characteristic reactivity as well as unique steric properties originates in the propadienyl structures. As depicted in Figure 1, proper substitution induces axial chirality in allenic compounds. However, the potential of applying axially chiral allenes as chiral synthons has been retarded by limited accessibility of enantiomerically enriched compounds.[3] Most of the reported methods for preparing scalemic axially chiral allenes require stoichiometric chiral sources as either substrates or reagents. Representative examples include chirality transfer from optically active centrally chiral propargyl compounds and resolution of racemic allenes. Several more efficient approaches, that is, *catalytic enantioselective synthesis* of axially chiral allenes, have been recently developed. In this article, the enantioselective preparation of axially chiral allenes under asymmetric catalysis is surveyed. Coverage of this review article is the reactions with *substoichiometric* or *recoverable* chiral sources, and thus diastereoinduction of allenic axial chirality or chirality transfer from stereogenic centers to allenic chiral axes will be excluded.

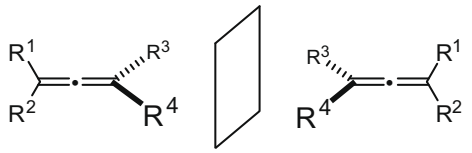


Figure 1. Enantiomeric pair of axially chiral allene.

2. Axial chirality in allenes

The two C=C bonds in a propadiene unit are perpendicular to each other, and the four atoms/substituents in an allenic framework are arranged in an elongated tetrahedral fashion. Therefore, a substituted allene becomes chiral if $R^1 \neq R^2$ and $R^3 \neq R^4$ (Fig. 1). Whereas the rotation barrier of the allenic C=C=C axis is generally high (about 46 kcal/mol for 1,3-dialkylallenes),[4] enantiomeric pairs of axially chiral allenes can be separable as persistent isomers under usual conditions. The possible existence of two enantiomeric forms in a properly substituted allene was predicted by van't Hoff as early as 1875.[5] Experimental confirmation of van't Hoff's prediction was realized 60 years later by two independent research groups (Fig. 2). In 1935, Maitland and Mills reported the preparation of optically active 1,3-di(α-naphthyl)-1,3-diphenylallene **1** by asymmetric dehydration of the corresponding allylic alcohol in the presence of catalytic *d*- or *l*-camphorsulfonic acid.[6]

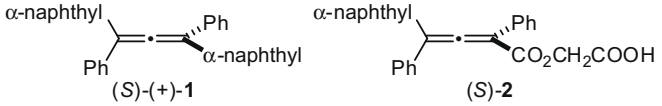


Figure 2. The first isolated scalemic axially chiral allenes.

It is worthy of note that one of the first optically active axially chiral allenes was obtained by catalytic asymmetric synthesis albeit with low enantioselectivity (see Section 4.1 for details). In the same year, resolution of the racemic allenic carboxylic acid **2** was achieved by Kohler, Walker, and Tishler using brucine as a resolving reagent.[7]

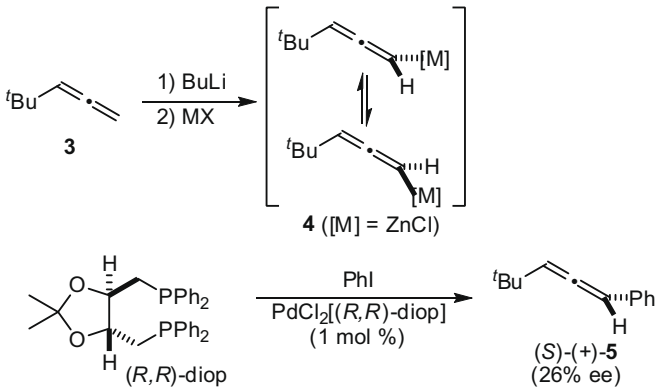
3. Transition-metal-catalyzed reactions

Enantioselective organic transformations catalyzed by chiral transition-metal species are arguably the most active area in modern asymmetric synthesis. Catalytic asymmetric syntheses are desirable processes from an atom-economical point of view. For applying the same tactics in the enantioselective preparation of axially chiral allenes, setup of suitable reaction systems, that is, formation of axially chiral allenic compounds starting with achiral (or prochiral) precursors in the presence of substoichiometric transition-metal catalysts, is indispensable (Sections 3.1 and 3.2). Another approach in this category is the use of chiral transition-metal catalysts in enantiomer-differentiating reactions (kinetic resolutions) of racemic allenes. Several examples of effective kinetic resolutions of the racemic axially chiral allenes have been developed to date (Section 3.3).

3.1. Enantioselective synthesis by substitution

3.1.1. Palladium-catalyzed cross-coupling of metalated terminal allenes

The first example of transition-metal-catalyzed asymmetric synthesis of axially chiral allenes was reported by Elsevier in 1989 (Scheme 1).[8] Lithiation of 4,4-dimethyl-1,2-pentadiene **3** takes place highly regioselectively at the terminal position, and various metalated allenes **4** are generated in situ from the lithiated species by appropriate metal exchange. The metalated allenes **4** undergo the cross-coupling reaction with iodobenzene in the presence of a palladium species coordinated with a chiral ligand to give an axially chiral allene **5** with modest enantioselectivity. Among the chiral ligands examined, the bidentate bisphosphine (*R*,*R*)-diop shows the highest enantioselectivity for the reaction with the chlorozinc species ([M] = ZnCl in **4**) giving (*S*)-**5** of 26% ee. For the reactions with the chloromagnesium ([M] = MgCl) or the copper ([M] = Cu) nucleophile, a reversal of the configuration in the allenic

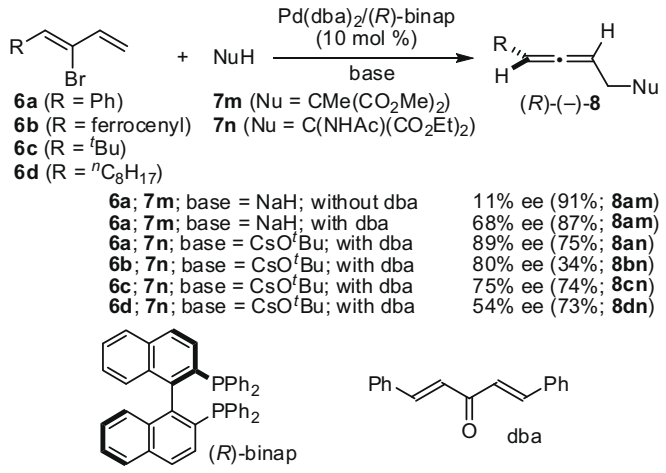


Scheme 1. Pd-catalyzed cross-coupling of metalated allenes.

product is observed, and (*R*)-(−)-**5** of low enantiopurity (3–10% ee) is obtained using the same Pd/(*R*,*R*)-diop catalyst. Although the metalated allenes **4** are axially chiral in principle, the two enantiomers are in rapid equilibrium.[9] And thus, enantioselective substitution is realized.

3.1.2. Palladium-catalyzed S_N2' substitution of 2-bromo-1,3-dienes

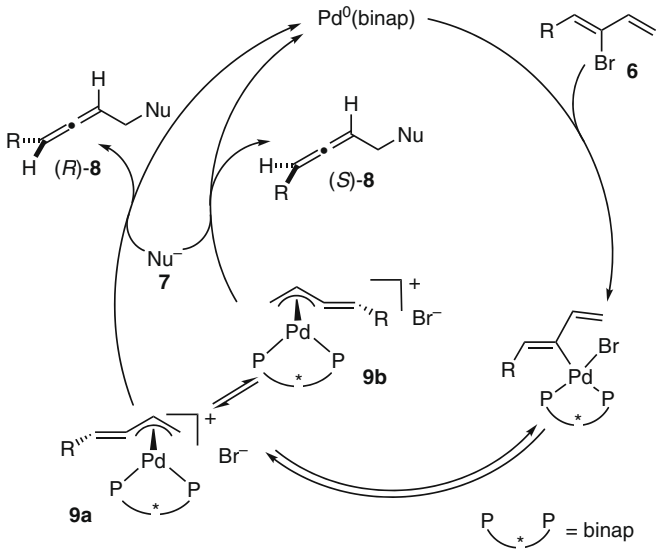
In 2000, our group reported that a formal S_N2' substitution of easily accessible 2-bromo-1,3-butadiene derivatives **6** with an appropriate soft nucleophile **7** was brought about in the presence of a catalytic Pd/bisphosphine complex.[10] While the substrates **6** of this transformation are achiral dienes, the reaction products **8** can be axially chiral allenes with proper substitution. Consequently, this reaction is an ideal prototype for catalytic asymmetric synthesis of axially chiral allenes (Scheme 2). Indeed, highly enantioselective preparation of various allenic compounds **8** is achieved in up to 89% ee (for **8an**) by the use of a Pd/(*R*)-binap catalyst. It is found that the presence of catalytic dibenzalacetone (dba) plays a vital role in the high enantioselectivity of the asymmetric reaction.[11a] For the reaction between **6a** and **7m**, the enantioselectivity is only 11% ee without dba and 68% ee with dba.



Scheme 2. Pd-catalyzed substitution of 2-bromo-1,3-dienes with soft nucleophiles.

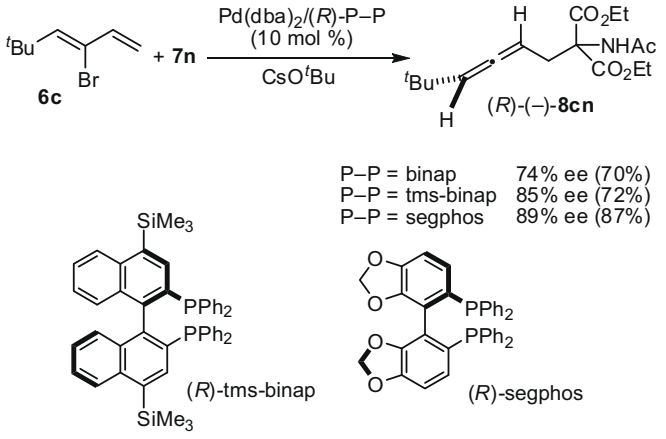
The catalytic cycle of the present asymmetric reaction is depicted in Scheme 3. With the chiral phosphine 'binap' on the palladium center, a key intermediate, (*exo*-alkylidene-π-allyl)palladium species,[12] exists as an equilibrium mixture of the two diastereoisomers **9a** and **9b**. Each diastereomeric palladium intermediate gives either (*S*)- or (*R*)-allene **8** by the reaction with nucleophile **7**. In this reaction scheme, the enantioselectivity of the allene formation is controlled by two factors: one is the relative reactivity (toward **7**) between **9a** and **9b**, and the other is equilibrium (including the exchange rate) between the two diastereomeric intermediates. If the exchange rate between **9a** and **9b** is *very* slow, the ee value of **8** is controlled by the relative abundance of the initially formed two diastereomers, even though there is a sufficient difference in the relative reactivity between **9a** and **9b** toward **7**.[11a]

The NMR studies on the solution behavior of the isolated (*exo*-benzylidene-π-allyl)palladium species reveal that the coexistent dba accelerates the epimerization in **9** (equilibrium between **9a** and **9b**) ca. 12–25 times faster, which is probably a main factor of the unique positive effect of dba on the enantioselectivity of the asymmetric synthesis of **8**.



Scheme 3. Catalytic cycle of Pd-catalyzed asymmetric synthesis of allenes **8** from 2-bromo-1,3-dienes **6** and nucleophile **7**.

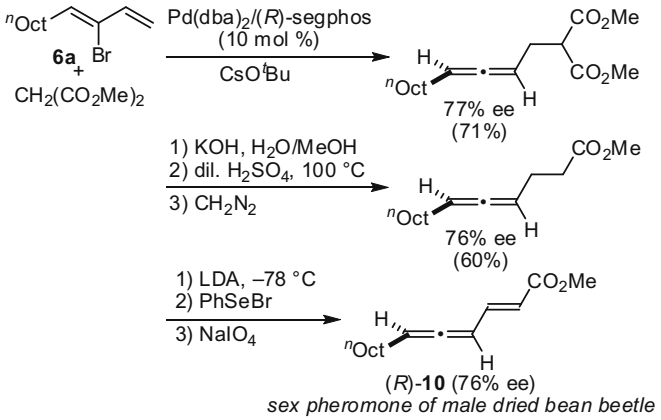
In the Pd-catalyzed asymmetric reaction between **6** and **7** giving the axially chiral allenes **8**, atropisomeric biaryl-based chiral bisphosphines show good enantioselectivity. It is found that tms-binap[11b] and segphos[11c,d] exhibit better performance than binap. An example of comparison between the three chiral ligands is shown in Scheme 4 for the reaction of **6c** with **7n**.



Scheme 4. Comparison between binap, tms-binap, and segphos in Pd-catalyzed allene synthesis.

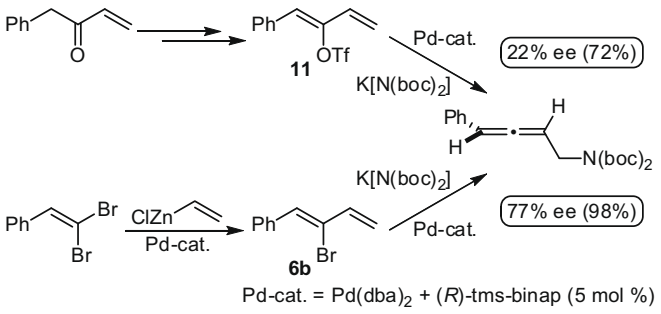
The Pd-catalyzed asymmetric S_N2' substitution is utilized for the formal total synthesis of a naturally occurring axially chiral allene, methyl (*R*,*E*)-tetradeca-2,4,5-trienoate (*R*)-**10**, which is the sex attractant of the male dried bean beetle (Scheme 5).[11d] The unique axial chirality in the pheromone is induced by the palladium-catalyzed asymmetric reaction, and the synthetic pheromone is obtained in 76% ee, which is practically the comparable enantiomeric purity as in the sample extracted from the natural source.

As in the case of bromodienes **6**, 1,3-dien-2-yl triflates **11**, which are easily prepared from the corresponding alkenylketones, are reactive substrates for the Pd-catalyzed reactions with the soft nucleophiles producing various functionalized allenes **8** in high yields. In the asymmetric reactions catalyzed by Pd/(*R*)-tms-binap,



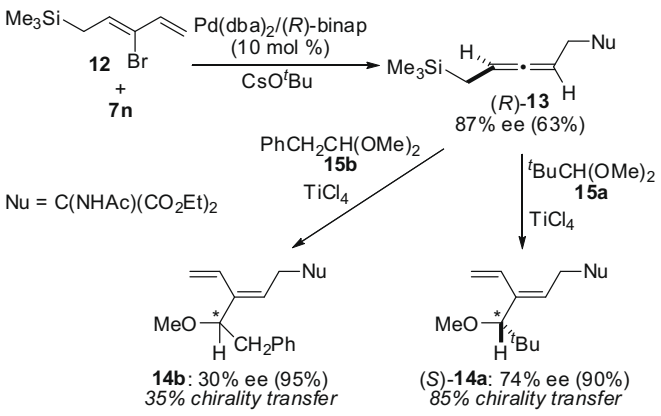
Scheme 5. Formal total synthesis of sex pheromone of male dried bean beetle.

however, the allenic product from **11** shows lower enantiomeric purity than that from **6** (Scheme 6).[11b,13]



Scheme 6. Comparison between dienyl triflate and bromodiene in Pd-catalyzed asymmetric allene synthesis.

The axially chiral (allenylmethyl)silanes **13** are prepared from (3-bromopenta-2,4-dienyl)trimethylsilane **12** by the Pd-catalyzed asymmetric reaction with the soft nucleophiles **7** with up to 88% enantioselectivity. The (allenylmethyl)silanes obtained have a function as chiral synthons, which transfer their axial chirality into newly generated stereogenic centers in the 1,3-dienyl products **14** by the desilylative S_E2' reaction with appropriate electrophiles (Scheme 7).[11c] The 1,3-dienyl products **14** have (*E*)-geometry



Scheme 7. Pd-catalyzed asymmetric synthesis of axially chiral (allenylmethyl)silanes and their application in axial-to-central chirality transfer in S_E2' reactions.

exclusively. The efficiency of the axial-to-central chirality transfer in the S_E2' reaction is highly dependent on the steric characteristics of the proelectrophiles **15**. The reaction of (*R*)-**13** (87% ee) with an electrophile generated from pivalaldehyde dimethyl acetal (**15a**) and $TiCl_4$ gives 90% yield of **14a**, which is an (*S*)-isomer of 74% ee (85% chirality transfer). On the other hand, an analogous reaction between (*R*)-**13** (87% ee) and **15b** affords the 1,3-diene **14b** of only 30% ee (35% chirality transfer).

Although allenes have recently gained much attention as synthetic intermediates, their applications in organic synthesis are still relatively unexplored compared to those of alkenes and alkynes. These situations can be attributed to their limited availability as well as the complicated stereoselectivity issues to be controlled in the organic transformations of allenes. Among internal allenes, endocyclic allenes possess a characteristic topological property: the carbon chains connecting the two allenic termini could effectively shield one side of the allenic skeletons. This might direct allenic reactions with incoming molecules onto the unencumbered faces. Therefore, the endocyclic allenes have potential for being unique synthons in stereoselective transformations (Fig. 3).

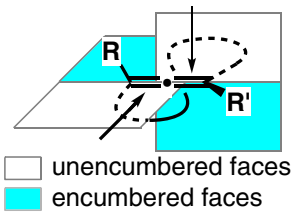
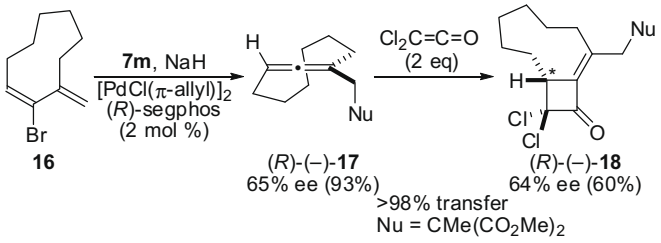


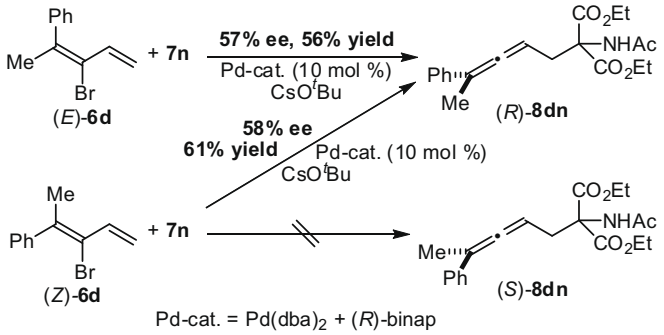
Figure 3. Steric properties of endocyclic allenes.

The reaction of (*E*)-2-bromo-3-*exo*-methylenecyclononene **16** with **7m** proceeds in the presence of the Pd/(*R*)-segphos catalyst (2 mol %) to give an axially chiral endocyclic allene (*R*)-**17** in moderate enantioselectivity of 65% ee (93% yield). Subsequent [2+2]cycloaddition of the enantiomerically enriched (*R*)-**17** with dichloroketene affords (*R*)-(–)-**18** in 64% ee and 60% yield. The chirality transfer of the reaction is estimated to be >98% (Scheme 8). The cycloaddition product **18** is obtained as a single isomer. The stereoselectivity of this transformation indicates that the cyclic structure in **17** directs the reacting ketene from the unencumbered face as expected (see, Fig. 3).[14] Indeed, the [2+2]cycloaddition between an analogous acyclic allene and dichloroketene gives the products as a mixture of four structural isomers.



Scheme 8. Pd-catalyzed asymmetric synthesis of endocyclic allene and its application to [2+2]cycloaddition with dichloroketene.

The structural difference between (*E*)- and (*Z*)-isomers of the bromodiene substrate **6d** shows no influence in the (alkylidene-π-allyl)palladium-mediated asymmetric allene synthesis. A reaction of (*E*)-**6d** with **7n**/CsO^{t}Bu at 30 °C in the presence of a Pd(dba)$_2$/(*R*)-binap catalyst gives an axially chiral allene (*R*)-**8dn** of 57% ee in 56% yield (Scheme 9). On the assumption that there is no dynamic processes exchanging the Ph- and the Me-substitu-

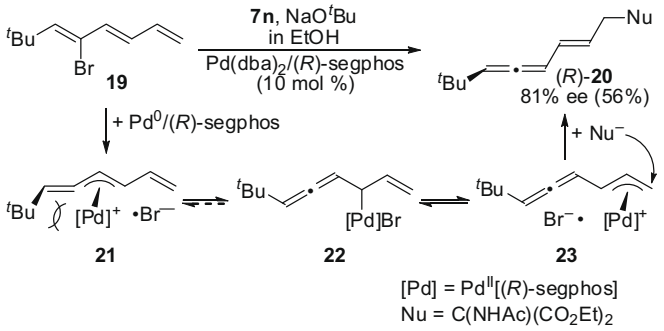


Scheme 9. Comparison between (*E*)- and (*Z*)-bromodienes in Pd-catalyzed asymmetric allene synthesis.

ents of **6d** in the Pd-intermediates, the reaction of (*Z*)-**6d** with **7n**/CsO^{t}Bu catalyzed by Pd/(*R*)-binap should form (*S*)-**8dn**, in which the relative positions of the Ph- and the Me-groups on the allenic terminal carbon are reversed compared with the allenic product from (*E*)-**6d**. However, the product from (*Z*)-**6d** is also (*R*)-**8dn** with nearly identical enantiopurity (58% ee, 61% yield).[12]

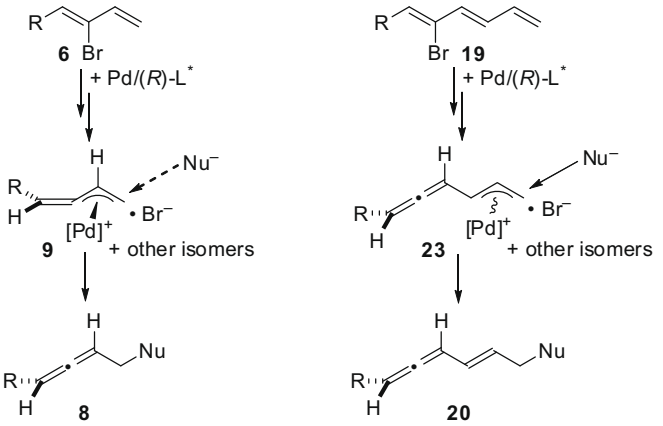
3.1.3. Palladium-catalyzed S_N2'' substitution of 2-bromo-1,3,5-trienes

A reaction of 5-bromo-7,7-dimethylocta-1,3,5-triene **19** with **7n**/NaO^{t}Bu is catalyzed by a palladium species generated from Pd(dba)$_2$ and (*R*)-segphos to give the conjugated vinylallene **20** selectively. The reaction is a formal S_N2'' process and proceeds via an (alkylidene-π-allyl)palladium intermediate **21** and (allenyl-π-allyl)palladium intermediate **23**. A dynamic process involving the two palladium intermediates plays important roles in determining the selectivity of the Pd-catalyzed reaction, and the vinylallene **20** forms as a sole organic product in the reaction shown in Scheme 10. Under the reaction conditions shown in Scheme 10, the axially chiral vinylallene (*R*)-**20** of 81% ee is obtained in 56% yield starting with the achiral substrate **19**.[15]



Scheme 10. Pd-catalyzed S_N2'' substitution of 2-bromo-1,3,5-triene with soft nucleophile.

A comparison between the two asymmetric processes for producing axially chiral allenes, which show that one is with the bromodienes **6** (Scheme 2) and the other is with the bromotrienes **19** (Scheme 10), is illustrated in Scheme 11. In the reaction of the bromodiene **6**, the configuration of the axially chiral allene is determined by nucleophilic attack of Nu$^-$ to an alkylidene-π-allylpalladium intermediate **9** (Scheme 11, left). In the reaction of the bromotriene **19**, however, the local allenic configuration is already fixed prior to the nucleophilic attack of Nu$^-$ to an allenyl-π-allylpalladium intermediate **23**.

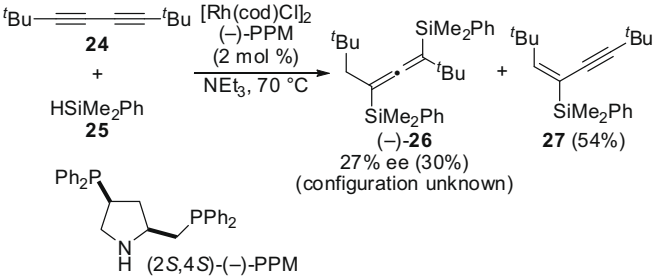


Scheme 11. Comparison between two asymmetric reactions for preparing axially chiral allenes.

3.2. Enantioselective synthesis by addition

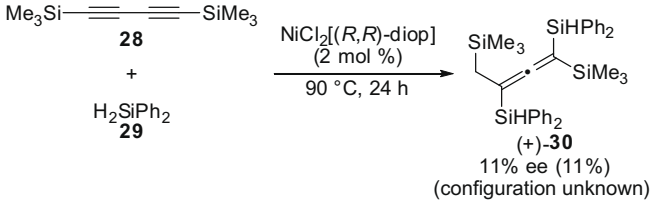
3.2.1. Rhodium- or Nickel-catalyzed double hydrosilylation of conjugated diynes

Catalytic asymmetric synthesis of axially chiral allenes was achieved by double hydrosilylation of 1,3-butadiynes **24** with HSiMe$_2$Ph **25** using a chiral rhodium species generated in situ from [Rh(cod)Cl]$_2$ and (2*S*,4*S*)-(−)-PPM. It is found that the presence of a small amount of NEt$_3$ increases enantioselectivity. Under the optimized conditions, the highest ee value of 27% is observed in the asymmetric reaction. However, the chemical yield of the axially chiral allene **26** is only 30%, and an undesirable single hydrosilylation product **27** is obtained in 54% (Scheme 12). The enyne **27** is not an intermediate of the double hydrosilylation, because treatment of **27** with **25** under the same reaction conditions does not yield **26**.[16]



Scheme 12. Rhodium-catalyzed asymmetric double hydrosilylation of diyne.

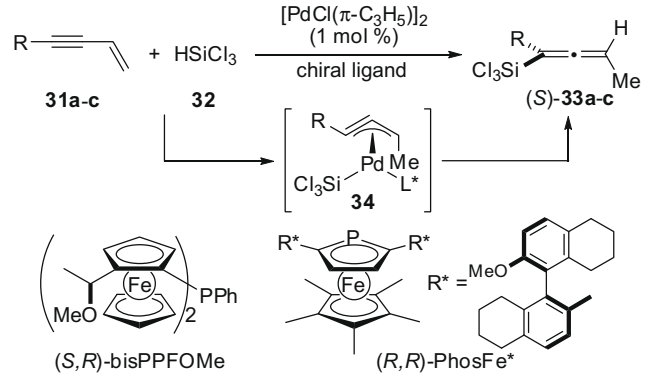
For the reaction between the diyne **28** and diphenylsilane **29**, NiCl$_2$[(−)-diop] was examined and the axially chiral allene (+)-**30** was obtained in 11% ee albeit in low yield (Scheme 13).[16b]



Scheme 13. Nickel-catalyzed asymmetric double hydrosilylation of diyne.

3.2.2. Palladium-catalyzed 1,4-hydrosilylation of conjugated enynes

In 2001, palladium-catalyzed asymmetric hydrosilylation of 4-substituted-but-1-en-3-ynes **31** with trichlorosilane **32** was reported by Hayashi et al.[17a] A monodentate bulky chiral phosphine, (*S*,*R*)-bisPPFOMe, is found to be effective for the asymmetric synthesis of the axially chiral allenylsilanes (*S*)-**33**, and up to 90% enantioselectivity is achieved (Scheme 14). The hydrosilylation of **31** is proposed to proceed through a catalytic cycle involving hydropalladation of the double bond in **31**, forming a π-propargyl(silyl)palladium intermediate **34**. The bulky substituent at the 4-position in **31** is essential for retarding the hydropalladation at the alkyne moiety in **31**. Indeed, the reaction of $^{n}C_6H_{13}$–C≡C–CH=CH_2 gives a complex mixture of the hydrosilylation products that consist of less than 20% of the allenylsilane. More recently, Ogasawara and Hayashi applied a monodentate chiral phosphaferrocene, (*R*,*R*)-PhosFe*, in the same asymmetric reaction. It shows much better performance giving (*R*)-**33a** in higher yield (82%) and with better enantioselectivity (92% ee). The sterically demanding η^5-C_5Me_5 moiety in (*R*,*R*)-PhosFe* is important for the high performance of the chiral ligand. The use of an analogous phosphaferrocene with η^5-C_5H_5 gives (*R*)-**33a** of 41% ee in 57% yield.[17b] The allenyl(trichloro)silanes **33** obtained are allowed to react with benzaldehyde to give the corresponding homopropargyl alcohols transferring their axial chirality into newly formed stereogenic centers.



R in 31	conditions	yield (%)	%ee (config)
^{t}Bu (**31a**)	0 °C, 160 h, bisPPFOMe	37 (**33a**)	90 (*S*)
^{t}Bu (**31a**)	0 °C, 72 h, PhosFe*	82 (**33a**)	92 (*R*)
mesityl (**31b**)	20 °C, 64 h, bisPPFOMe	90 (**33b**)	77 (*S*)
$SiMe_2{}^{t}$Bu (**31c**)	20 °C, 160 h, bisPPFOMe	40 (**33c**)	68 (*S*)

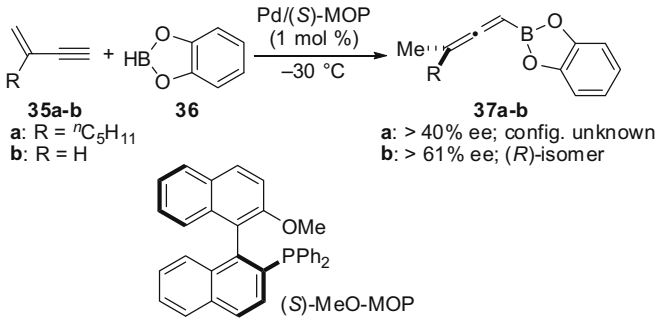
Scheme 14. Palladium-catalyzed asymmetric 1,4-hydrosilylation of conjugated enynes.

3.2.3. Palladium-catalyzed 1,4-hydroboration of conjugated enynes

The Pd-catalyzed asymmetric hydroboration of conjugated enynes **35** with catecholborane **36** was reported in 1993.[18a] A chiral monodentate phosphine (*S*)-MeO-MOP is used as a chiral ligand for the palladium catalyst, and the axially chiral allenylboranes **37** are obtained in up to 61% ee (Scheme 15). Enantioselectivity of the asymmetric hydroboration is estimated from the enantiopurity of the homopropargyl alcohols, which are obtained from the axially chiral allenylboranes and benzaldehyde via an S_E2' pathway.

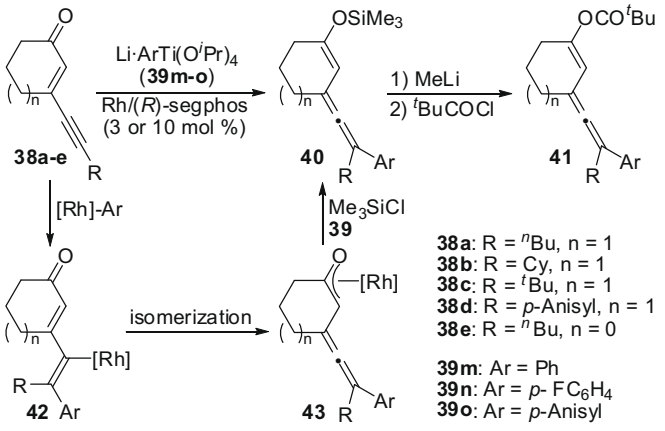
3.2.4. Rhodium-catalyzed 1,6-addition of aryltitanates to conjugated ynenones

The addition of aryltitanate reagents Li·ArTi(O^{i}Pr)$_4$ **39** to 3-alkynyl-2-en-1-ones **38** in the presence of Me_3SiCl and a catalytic Rh(I)/



Scheme 15. Palladium-catalyzed asymmetric 1,4-hydroboration of conjugated enynes.[18b]

(*R*)-segphos complex proceeds in a 1,6-addition fashion to give a high yield of axially chiral allenylalkenyl silyl enol ethers **40** with up to 93% ee (Scheme 16).[19] Because the silyl ethers **40** are not stable enough for chiral HPLC analyses, they are converted into the corresponding pivalate esters **41** by a successive treatment with MeLi/^{t}BuCOCl. The use of **39** and Me_3SiCl at the same time is important for the present reaction, and no 1,6-addition products are detected without Me_3SiCl. Because the spontaneous non-catalyzed 1,6-addition process (even though this was slow) is competing with the Rh-catalyzed process, the use of a relatively large amount (~10 mol %) of the catalyst results in a slightly higher enantioselectivity. The 1,6-addition is considered to proceed through an initial insertion of the C–C triple bond in **38** into the Rh–Ar bond giving **42**, which isomerizes into the thermodynamically more stable oxa-π-allylrhodium intermediate **43**. At this isomerization, the stereochemical outcome of the asymmetric 1,6-addition should be determined. The final step is the silylation and transmetalation of **43**, giving **40,** and regeneration of the aryl-rhodium intermediate.



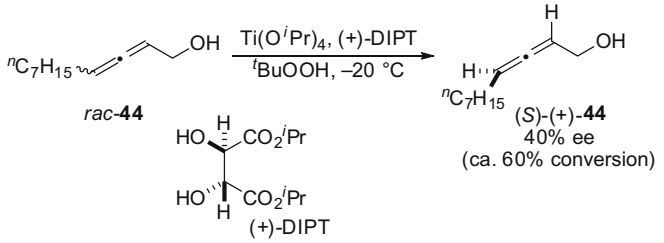
ynenone **38**	Li·ArTi(O^{i}Pr)$_4$ **39**	Rh-cat.	yield of **40**	%ee of **41**
38a	**39m**	3 mol %	>99%	90
38a	**39m**	10 mol %	>99%	92
38a	**39n**	10 mol %	>99%	91
38a	**39o**	10 mol %	>99%	93
38b	**39o**	10 mol %	>99%	80
38c	**39m**	10 mol %	61%	26
38d	**39m**	10 mol %	56%	75
38e	**39m**	3 mol %	>99%	70

Scheme 16. Rhodium-catalyzed 1,6-addition of aryltitanates to conjugated ynenones.

3.3. Kinetic resolution of racemic allenes

3.3.1. Titanium-catalyzed oxidation of (allenyl)methanol

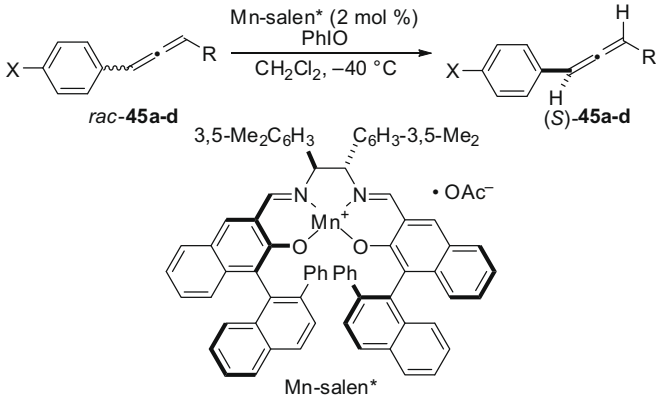
A single example of the titanium-catalyzed kinetic resolution of a racemic allenic alcohol was described briefly in 1983.[20] Oxidation of racemic **44** under the well-known Sharpless oxidation conditions, that is, with $Ti(O^iPr)_4$, (+)-diisopropyl tartrate [(+)-DIPT], and ^{t}BuOOH, provides optically active (*S*)-(+)-**44** of 40% ee; however, the relative reaction rate between the two enantiomers of **44** is not very large (Scheme 17).



Scheme 17. Kinetic resolution of racemic allenic alcohol by Ti-catalyzed Sharpless oxidation.

3.3.2. Manganese-catalyzed oxidation of arylallenes

In 1998, Katsuki et al. demonstrated the kinetic resolution of racemic allenes **45** by way of an enantiomer-differentiating manganese-catalyzed oxidation (Scheme 18).[21] Treatment of *rac*-**45** with 1 equiv of PhIO and 2 mol % of the Mn-salen* complex in the presence of 4-phenylpyridine N-oxide results in partial asymmetric oxidation, which leads to the recovery of enantioenriched allenes (*S*)-**45**. The relative reaction rates between the two enantiomeric allenes reach to as high as 23 in **45c**.

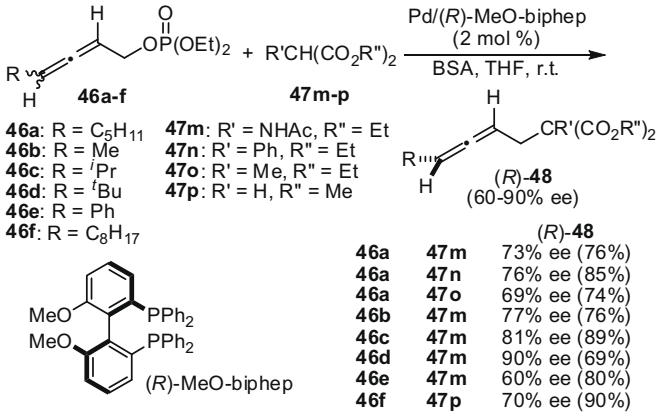


45 (X, R)	conv. (%)	recovered **45**	k_{rel}
a (H, Me)	45.5	60% ee	10
b (H, Ph)	59.5	96.3% ee	19±1
c (H, *p*-ClC$_6$H$_4$)	59.7	98.7% ee	23±1
d (Me, *p*-MeC$_6$H$_4$)	77.8	97.3% ee	6±1

Scheme 18. Kinetic resolution of racemic 1,3-disubstituted allenes by Mn-salen*-catalyzed asymmetric oxidation.

3.3.3. Palladium-catalyzed dynamic kinetic resolution of racemic allenylmethyl esters

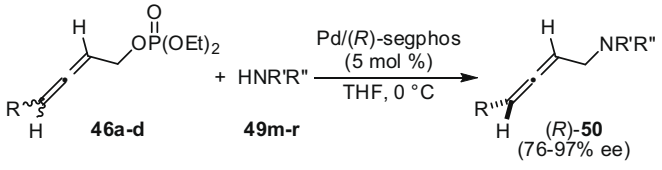
Preparation of optically active (allenylmethyl)malonate derivatives (*R*)-**48** by palladium-catalyzed asymmetric alkylation of racemic allenylmethyl phosphates **46** with an appropriate malonate-derived pronucleophile **47** was reported by Imada, Murahashi, et al. in 2002 (Scheme 19).[22a] Oxidative addition of the phosphate **46** to a Pd(0) species produces an (*exo*-alkylidene-π-allyl)palladium intermediate, which is isostructural to the intermediate **9** in Scheme 3, and thus the modes of enantioinduction in the two reactions shown in Schemes 2 and 19 should be the same. Due to the dynamic process (epimerization) of this intermediate (see Scheme 3), effective asymmetric induction becomes possible even with more than 50% conversion of the substrates (dynamic kinetic resolution in a broader sense). By the use of (*R*)-MeO-biphen as a chiral ligand and *N*,*O*-bis(trimethylsilyl)acetamide (BSA) as a base, the highest enantioselectivity of 90% ee is achieved for the reaction between **46d** and **47m**.



		(*R*)-**48**
46a	**47m**	73% ee (76%)
46a	**47n**	76% ee (85%)
46a	**47o**	69% ee (74%)
46b	**47m**	77% ee (76%)
46c	**47m**	81% ee (89%)
46d	**47m**	90% ee (69%)
46e	**47m**	60% ee (80%)
46f	**47p**	70% ee (90%)

Scheme 19. Pd-catalyzed dynamic kinetic resolution of racemic allenylmethyl phosphates with malonate-based carbon nucleophiles.

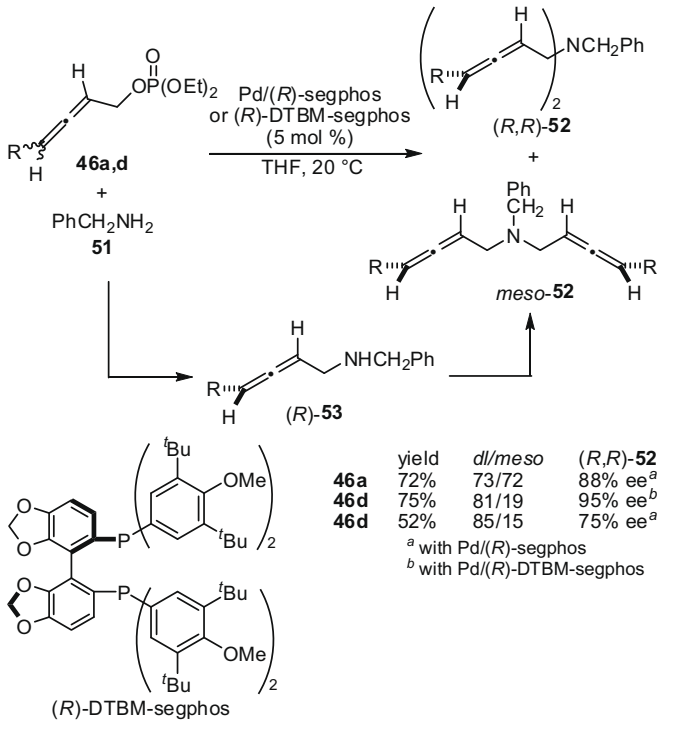
The same authors report that a variety of nitrogen nucleophiles, such as secondary amines **49m–n,** hydroxyamine **49o**, imides **49p–q**, and sulfonamide **49r**, can be applied to preparation of axially chiral (allenylmethyl)amine derivatives **50** by the analogous Pd-catalyzed asymmetric reaction of the phosphate substrates **46**. For the asymmetric amination, (*R*)-segphos is a chiral ligand of choice and shows excellent enantioselectivity of up to 97% ee (Scheme 20).[22b] The mechanistic studies reveal that (*R*)-**46a** is consumed 4.1–4.2 times faster than the (*S*)-congener under the present conditions.



		(*R*)-**50**
46a	**49m**	84% ee (72%)
46a	**49n**	91% ee (56%)
46a	**49o**	76% ee (59%)
46a	**49p**	97% ee (77%)
46a	**49q**	83% ee (64%)
46a	**49r**	80% ee (26%)
46c	**49p**	82% ee (85%)
46d	**49p**	87% ee (51%)

Scheme 20. Pd-catalyzed dynamic kinetic resolution of racemic allenylmethyl phosphates with nitrogen nucleophiles.

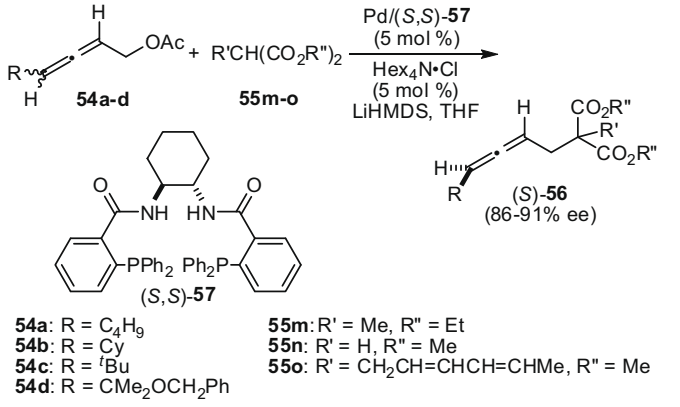
Sequential double asymmetric allenylmethylation is achieved by the use of benzylamine **51** as a nitrogen nucleophile for the similar Pd-catalyzed reactions (Scheme 21).[22c] In the presence of 5 mol % of Pd/(*R*)-segphos or Pd/(*R*)-DTBM-segphos, the reactions take place as a two-step process via an initial formation of a mono(allenylmethyl)amine (*R*)-**53**, which subsequently undergoes



Scheme 21. Pd-catalyzed sequential asymmetric double allenylmethylation of benzylamine with allenylmethyl phosphates.

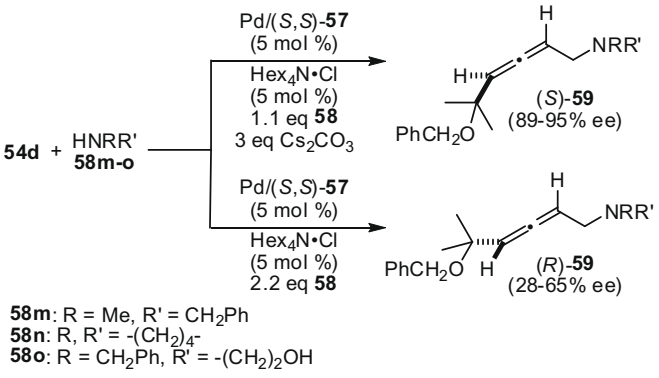
the second Pd-catalyzed allenylmethylation to afford a mixture of the chiral (*R*,*R*)-**52** and the mesomeric (*R*,*S*)-**52** with good diastereoselectivity. The axially chiral allenic moiety in (*R*)-**53** shows negligible influence on the second allenylmethylation, because the chiral element in (*R*)-**53** is located in a sufficiently remote position from the electrophilic nitrogen center. The highest enantioselectivity of 95% ee is achieved for the reaction of **46d** using a Pd/(*R*)-DTBM-segphos catalyst with a diastereoselectivity of *dl*/*meso* = 85/15.

In 2005, Trost et al. demonstrated that racemic allenylmethyl acetates **54** could be used in an analogous dynamic kinetic resolution catalyzed by a palladium species coordinated with the chiral ligand (*S*,*S*)-**57** giving scalemic axially chiral allenes with excellent enantioselectivity.[23] Under the optimized conditions, the malonate-derived pronucleophiles **55** afford the allenes in 86-91% ee (Scheme 22).



Scheme 22. Pd-catalyzed dynamic kinetic resolution of racemic allenylmethyl acetates with malonate-derived pronucleophiles.

In the Pd-catalyzed dynamic kinetic resolution of **54d** with amines **58**, the unique influence of the base on the enantioselectivity is observed (Scheme 23). Axially chiral (allenylmethyl)amines **59** of (*S*)-configuration are obtained with high enantioselectivities (89–95% ee) by employing 1.1 equiv of the amine and an excess of Cs_2CO_3. On the other hand, with the identical Pd/(*S*,*S*)-**57** catalyst system and twofold excess of the amine result in the formation of the opposite enantiomer (*R*)-**59** with lower enantiomeric excess (28–65% ee).

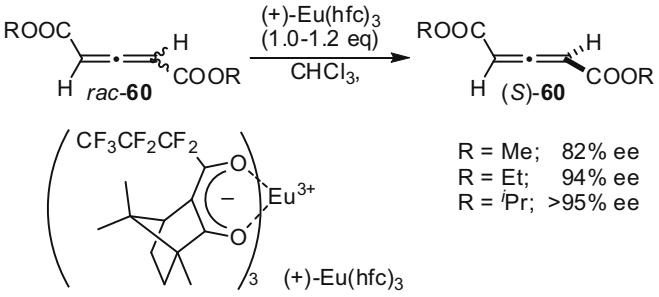


Scheme 23. Pd-catalyzed dynamic kinetic resolution of racemic allenylmethyl acetates with amines.

3.4. Deracemization of racemic allenes

3.4.1. Europium-mediated deracemization

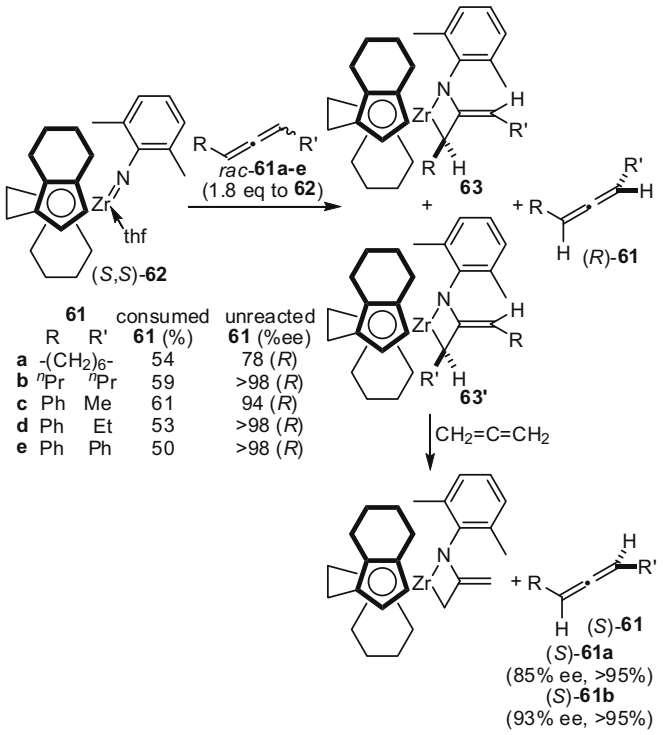
Interaction of various racemic dialkyl penta-2,3-dienedioates **60** with stoichiometric (+)-Eu(hfc)$_3$ in chloroform promotes deracemization of the axially chiral allenes to give (*S*)-**60** of high enantiomeric purity (Scheme 24).[24] The deracemization is characteristic of the europium reagent, and analogous rare-earth complexes, such as (+)-Pr(hfc)$_3$, (+)-Er(hfc)$_3$, or (+)-Yb(hfc)$_3$, do not promote the deracemization.



Scheme 24. Eu-mediated deracemization of dialkyl penta-2,3-dienedioates.

3.4.2. Zirconium-mediated kinetic resolution and deracemization

In 2000, Andersen, Bergman, et al. reported that a planar-chiral zirconocene-imide species, (ebthi)Zr(=NHAr)(thf) **62**, possessed an excellent ability to discriminate two enantiomers of axially chiral allenes.[25] Addition of racemic 1,3-diphenylallene **61a** (1.8 equiv to Zr) to a benzene solution of (*S*,*S*)-**62** at 23 °C results in consumption of 50% of **61a**. The unreacted **61a** is highly enriched in the (*R*)-enantiomer, which was >98% ee (Scheme 25). The kinetic resolution (enantioselective capture) by (*S*,*S*)-**62** can be applied to other racemic 1,3-disubstituted axially chiral allenes with excellent selectivity. The bulky nature of the *N*-aryl substituent in **62** is

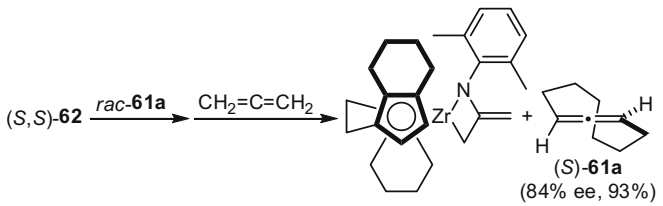


61	R	R'	consumed 61 (%)	unreacted 61 (%ee)
a	-(CH2)6-		54	78 (R)
b	nPr	nPr	59	>98 (R)
c	Ph	Me	61	94 (R)
d	Ph	Et	53	>98 (R)
e	Ph	Ph	50	>98 (R)

Scheme 25. Zr-mediated kinetic resolution of 1,3-disubstituted allenes.

important for the high enantioselectivity. An analogous Zr-species with the *N*-(*p*-tolyl) imide group is substantially less selective than **62**. Treatment of the Zr-allene complexes **63** and **63′** with excess $CH_2{=}C{=}CH_2$ promotes retro-cycloaddition to regenerate the faster reacting allenic enantiomer of high enantiopurity.

It was found that **62** is capable of deracemizing racemic **61** to enrich one of the enantiomers selectively.[25] As shown in Scheme 26, reaction between (*S*,*S*)-**62** and *rac*-**61a**, followed by treatment of the mixture produced with $CH_2{=}C{=}CH_2$, affords (*S*)-**61a** of 84% ee in 93% yield.

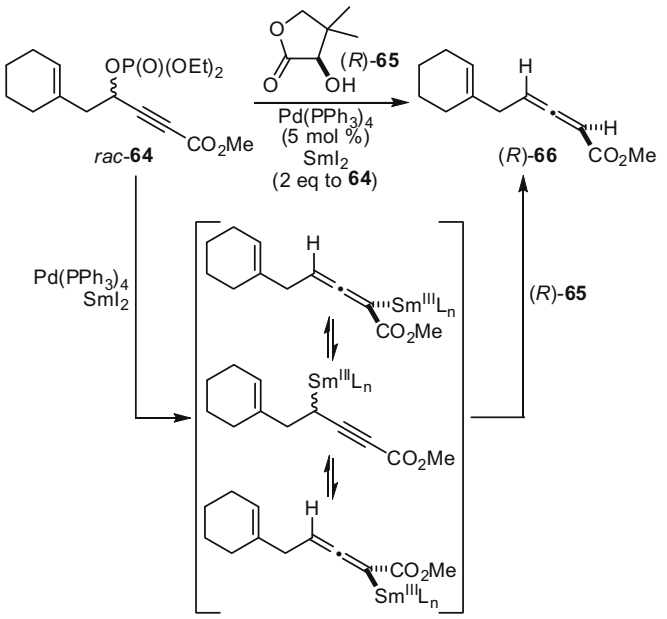


Scheme 26. Zr-mediated deracemization of 1,3-disubstituted allenes.

3.5. Transition-metal-catalyzed asymmetric synthesis with recyclable chiral sources

3.5.1. Dynamic kinetic protonation of racemic allenylsamarium species generated under palladium catalysis

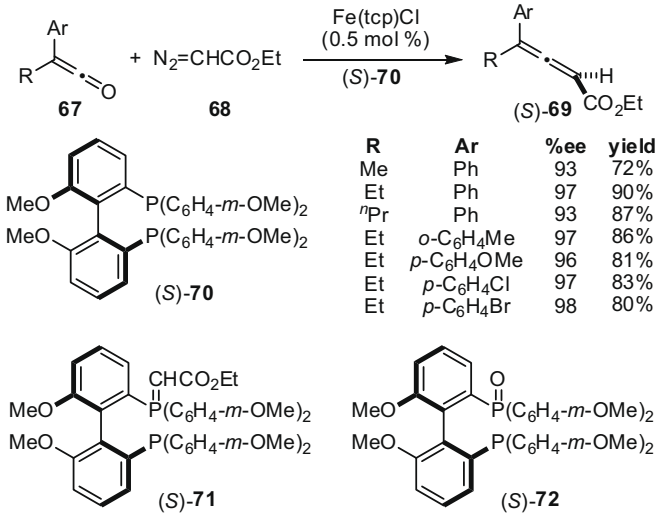
A reaction of a racemic propargyl phosphate **64** with (*R*)-pantolactone **65** in the presence of catalytic $Pd(PPh_3)_4$ (5 mol %) and stoichiometric SmI_2 (2 equiv to **64**) affords an allenic ester (*R*)-**66** in ⩾95% ee (68% yield).[26] The reaction proceeds via initial formation of organosamarium species, which are an equilibrated mixture of enantiomeric allenylsamarium species, and enantioselective protonation of one of the two allenylsamarium intermediate by **65** gives **66** of high enantiomeric purity (Scheme 27).



Scheme 27. Dynamic kinetic protonation with catalytic Pd, SmI_2, and (*R*)-pantolactone.

3.5.2. Iron-catalyzed asymmetric olefination of ketenes

Olefination of various ketenes **67** with ethyl diazoacetate **68** takes place in the presence of catalytic tetra(*p*-chlorophenyl)porphyrin iron(III) chloride (Fe(tcp)Cl; 0.5 mol %) and stoichiometric (*S*)-**70** with excellent enantioselectivity to give axially chiral allenylcarboxylates (*S*)-**69** in 93–98% ee in good yields (Scheme 28).[27] A probable intermediate of the asymmetric reaction is the chiral Wittig-monoylide (*S*)-**71**. The monophosphine oxide (*S*)-**72** is recovered from the reaction mixture in 83% yield, which can be reused after reduction to (*S*)-**70**.



R	Ar	%ee	yield
Me	Ph	93	72%
Et	Ph	97	90%
nPr	Ph	93	87%
Et	o-C6H4Me	97	86%
Et	p-C6H4OMe	96	81%
Et	p-C6H4Cl	97	83%
Et	p-C6H4Br	98	80%

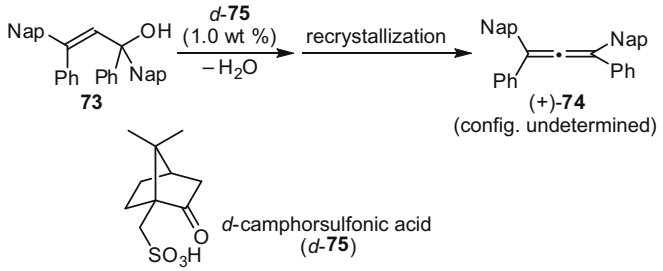
Scheme 28. Fe-catalyzed asymmetric olefination of ketenes.

4. Organocatalytic reactions

Development of 'asymmetric organocatalysts' is a recent trend in asymmetric synthesis. Quite surprisingly, the first isolation of an optically active axially chiral allene was achieved by the use of an organocatalyst in 1935, although the term 'organocatalyst' did not exist at that time. Up to now, only two organocatalytic systems have been applied in an asymmetric synthesis of axially chiral allenes.

4.1. Camphorsulfonic acid-catalyzed enantioselective dehydration of an allylic alcohol

In 1935, Maitland and Mills described the first isolation of an optically active axially chiral allene **74** to prove the van't Hoff prediction.[6a] The asymmetric synthesis was attained by enantioselective dehydration of the racemic allylalcohol **73** in the presence of catalytic camphorsulfonic acid **75**. Although the degree of initial asymmetric induction in the dehydration reaction is low (estimated to be ca. 4–5% ee),[6b] the preferred enantiomer can be enriched to an enantiomerically pure form by repeated recrystallization because the racemic and the single enantiomeric forms of **74** show quite different crystallinity/solubility (Scheme 29). While (+)-**74** is obtained using *d*-**75**, *l*-**75** affords (−)-**74** preferentially.

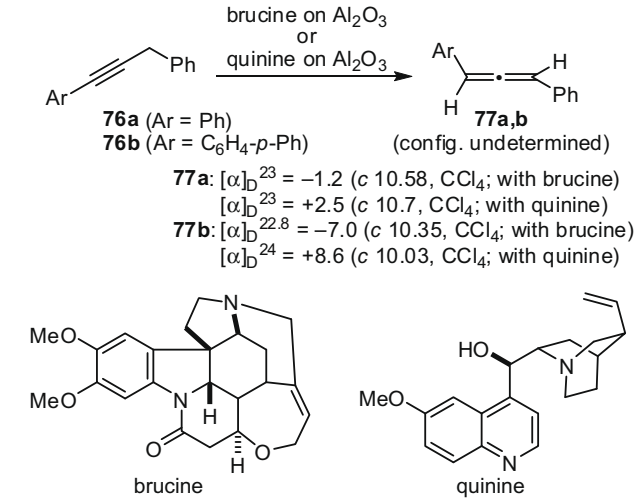


Scheme 29. Camphorsulfonic acid-catalyzed enantioselective dehydration of an allylic alcohol.

4.2. Base-promoted alkyne-to-allene 1,3-prototropic rearrangement

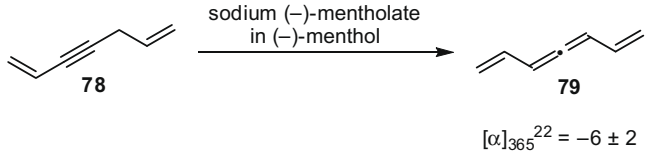
Base-promoted isomerization of 3-aryl- or 3-alkenylpropargyl compounds to the thermodynamically more stable allenic compounds via 1,3-prototropic rearrangement is facilitated in the presence of appropriate catalysts.

Asymmetric rearrangement of 1,3-diphenylpropyne **76a** and 1-(*p*-biphenyl)-3-phenyl-1-propyne **76b** to the corresponding allenes **77** is accomplished by adsorbing the acetylenic compounds on columns of neutral alumina, which is impregnated with brucine or quinine (Scheme 30).[28] The products with the brucine-impregnated columns are levorotatory, and the maximum specific rotation values are −1.2 for **77a** and −7.0 for **77b**, respectively. With quinine-impregnated columns, dextrorotatory products are obtained with maximum specific rotation of +2.5 for **77a** and +8.6 for **77b**, respectively. Attempts to isolate a pure enantiomer are unsuccessful although it is possible to increase the specific rotation slightly by fractional crystallization.



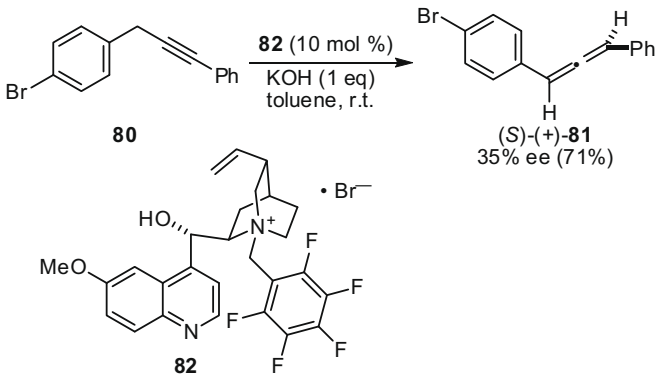
Scheme 30. Asymmetric alkyne-to-allene isomerization on alkaloid-impregnated alumina.

As shown in Scheme 31, isomerization of hepta-1,6-dien-3-yne **78** is promoted by sodium (−)-mentholate in (−)-menthol to give the levorotatory divinylallene **79** ($[\alpha]_{365}^{20} = -6 \pm 2$).[29]



Scheme 31. Asymmetric isomerization of hepta-1,6-dien-3-yne into divinylallene by sodium (−)-mentholate.

Isomerization of an alkyne **80** is facilitated by the chiral quaternary ammonium salt **82** to give an optically active allene (*S*)-(+)-**81** of 35% ee in 71% yield under the PTC conditions (Scheme 32).[30]

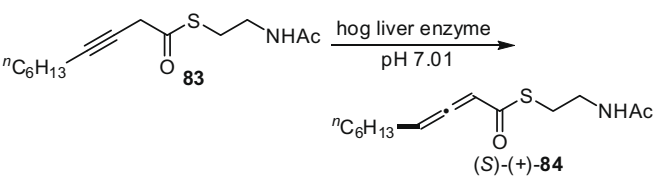


Scheme 32. Asymmetric alkyne-to-allene isomerization by a chiral phase-transfer catalyst.

5. Enzymatic/microbial reactions

5.1. Enzyme-promoted alkyne-to-allene 1,3-prototropic rearrangement

A hog liver enzyme is found to catalyze the conversion of 3-decynoyl-*N*-acetylcysteamine **83** to 2,3-decadienoyl-*N*-acetylcysteamine **84** cleanly (Scheme 33).[31a] The allenic compound obtained, of which absolute configuration is determined to be (*S*),[31b] is optically active with $[\alpha]_D^{25} = +55$ (*c* 1.33, CH_2Cl_2), but its enantiomeric purity is not reported.

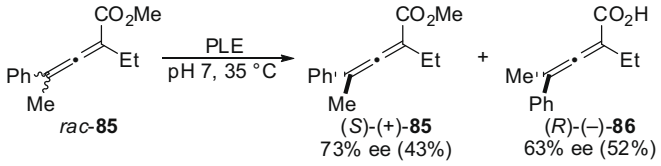


Scheme 33. Hog liver enzyme-promoted isomerization of 3-decynoyl-*N*-acetylcysteamine to 2,3-decadienoyl-*N*-acetylcysteamine.

5.2. Kinetic resolution of racemic allenes

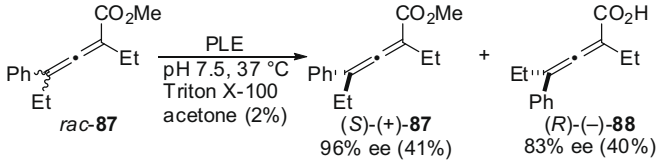
5.2.1. Enantioselective hydrolysis of racemic allenic esters

In 1986, Jones et al. reported that pig liver esterase (PLE) promoted the hydrolysis of variously substituted racemic methyl allenylcarboxylates with predictable enantiomeric selectivity.[32] The enantioselectivity is generally higher for the highly substituted substrates. A persubstituted allenic ester **85** (73% ee, 42% yield) and the corresponding carboxylic acid **86** (63% ee, 52% yield) are obtained in the example shown in Scheme 34.



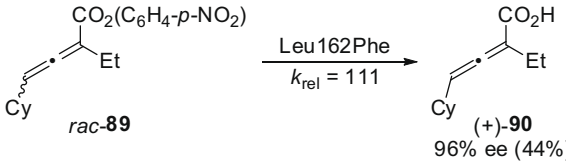
Scheme 34. Pig liver esterase-catalyzed hydrolysis of racemic methyl allenylcarboxylates.

In 1999, Pietzxch et al. further optimized the conditions of the above-mentioned reaction. The k_{rel} value for the kinetic resolution shown in Scheme 35 is as high as 60.[33]



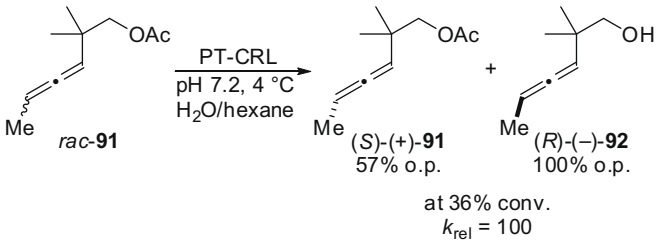
Scheme 35. Pig liver esterase-catalyzed hydrolysis of racemic methyl allenylcarboxylates under optimized conditions.

Reetz and Bäckvall described that directed evolution of *Pseudomonas aeruginosa* lipase by the use of combinatorial active-site saturation test (CAST) criteria provided a highly enantioselective mutant (Leu162Phe) for hydrolytic kinetic resolution of an axially chiral allene, *p*-nitrophenyl 4-cyclohexyl-2-methylbuta-2,3-dienoate **89**.[34] The observed k_{rel} values are up to 111 for the reaction (Scheme 36).



Scheme 36. Hydrolytic kinetic resolution of allenic ester with mutant (Leu162Phe) from *Pseudomonas aeruginosa* lipase.

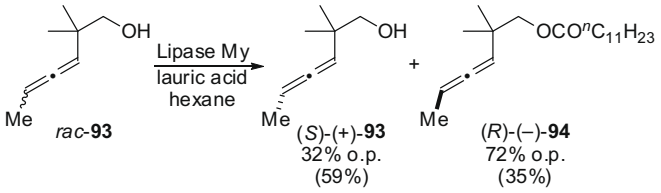
The strategy of hydrolytic kinetic resolution can be applied to esters of allenic alcohols as well.[35] The propan-2-ol-treated lipase from *Candida rugosa* (PT-CRL) shows excellent enantioselectivity for hydrolysis of *rac*-**91** to give an enantiomerically pure axially chiral allenic alcohol (*R*)-(−)-**92** (Scheme 37).



Scheme 37. Lipase-catalyzed kinetic resolution of ester of allenic alcohol.

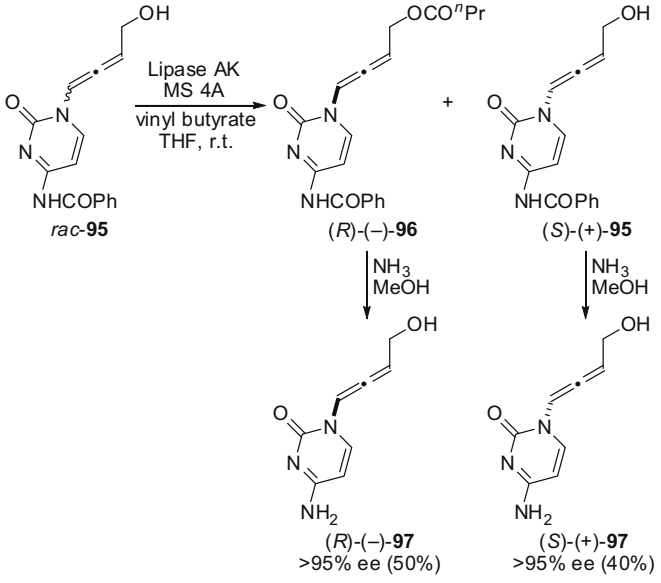
5.2.2. Enantioselective esterification of allenic alcohols

Lipase My, which is from the yeast *Candida cylindracea*, is effective for the kinetic resolution of racemic axially chiral allenic alcohols via their partial esterification with lauric acid in hexane (Scheme 38).[36] The preferentially transformed alcohols do not always have the same relative configuration.



Scheme 38. Kinetic resolution of racemic allenic alcohol by lipase-catalyzed partial esterification with lauric acid.

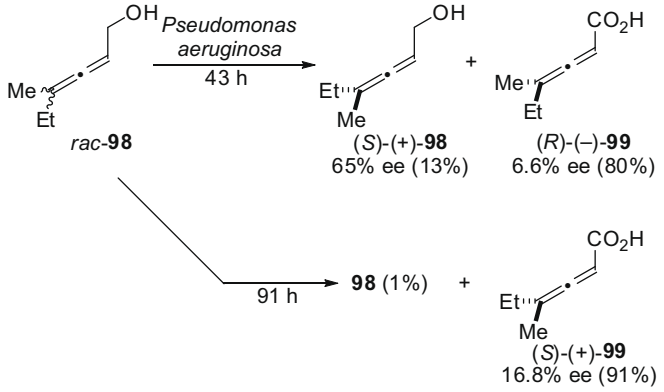
Lipase-catalyzed esterification of racemic cytallene derivatives with vinyl butyrate or vinyl acetate proceeds with various enantioselectivities.[37] Under the optimized conditions, the kinetic resolution of (±)-N^4-benzoylcytallene **95** can be attained with excellent enantioselectivity, and both enantiomers of cytallene **97** can be obtained in greater than 95% ee, which are further purified to >99% ee by single recrystallizations (Scheme 39).



Scheme 39. Lipase-catalyzed kinetic resolution of (±)-N^4-benzoylcytallene by esterification with vinyl butyrate.

5.2.3. Microbial enantioselective oxidation of allenic alcohols

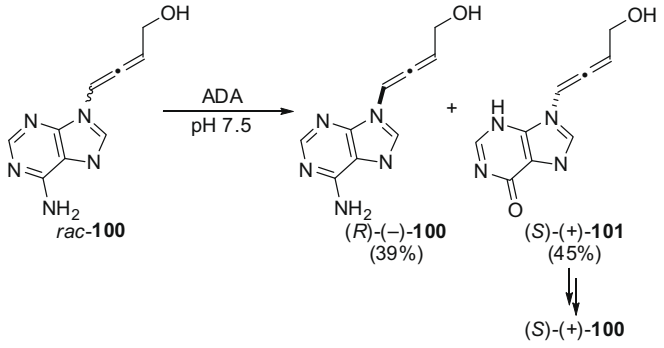
A bacterial strain, *P. aeruginosa* (ATCC 17504), oxidizes diversely substituted primary α-allenic alcohols to the corresponding carboxylic acids with modest enantioselectivity.[38] The (*R*)-isomer of **98** is oxidized faster than the antipode to enrich (*S*)-(+)-**98** in the remaining alcohol. The absolute configuration of the oxidized product **99** is varied depending on reaction time. These observations can be attributed to preferential degradation of (*R*)-(−)-**99** in the reaction mixture (Scheme 40).



Scheme 40. Enantioselective microbial oxidation of allenic alcohols.

5.2.4. Enantioselective deamination of racemic adenallene

Racemic adenallene **100** is subjected to deamination with adenosine deaminase (ADA) from calf intestine to give (−)-**100** and (+)-hypoxallene **101** in 39% and 45% yields, respectively. Both compounds are obtained in essentially enantiomerically pure forms after a single recrystallization (Scheme 41). The latter compound can be converted to (+)-**100** with retention of the enantiomeric purity.[39]



Scheme 41. Preparation of (*R*)- and (*S*)-adenallene by ADA-catalyzed deaminative kinetic resolution.

6. Conclusions

In spite of the increasing importance of allenic compounds in modern synthetic organic chemistry, application of their axially chiral congeners has been very limited. The situation can be attributed to a lack of proper methods of supplying enantiomerically enriched compounds. As surveyed in this article, 'catalytic enantioselective synthesis of axially chiral allenes' is still a relatively new and underrepresented area of synthetic organic chemistry. Although some interesting reactions have been developed in the last decade, additional examples are clearly desirable, which would certainly enhance synthetic usefulness of allenic compounds.

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