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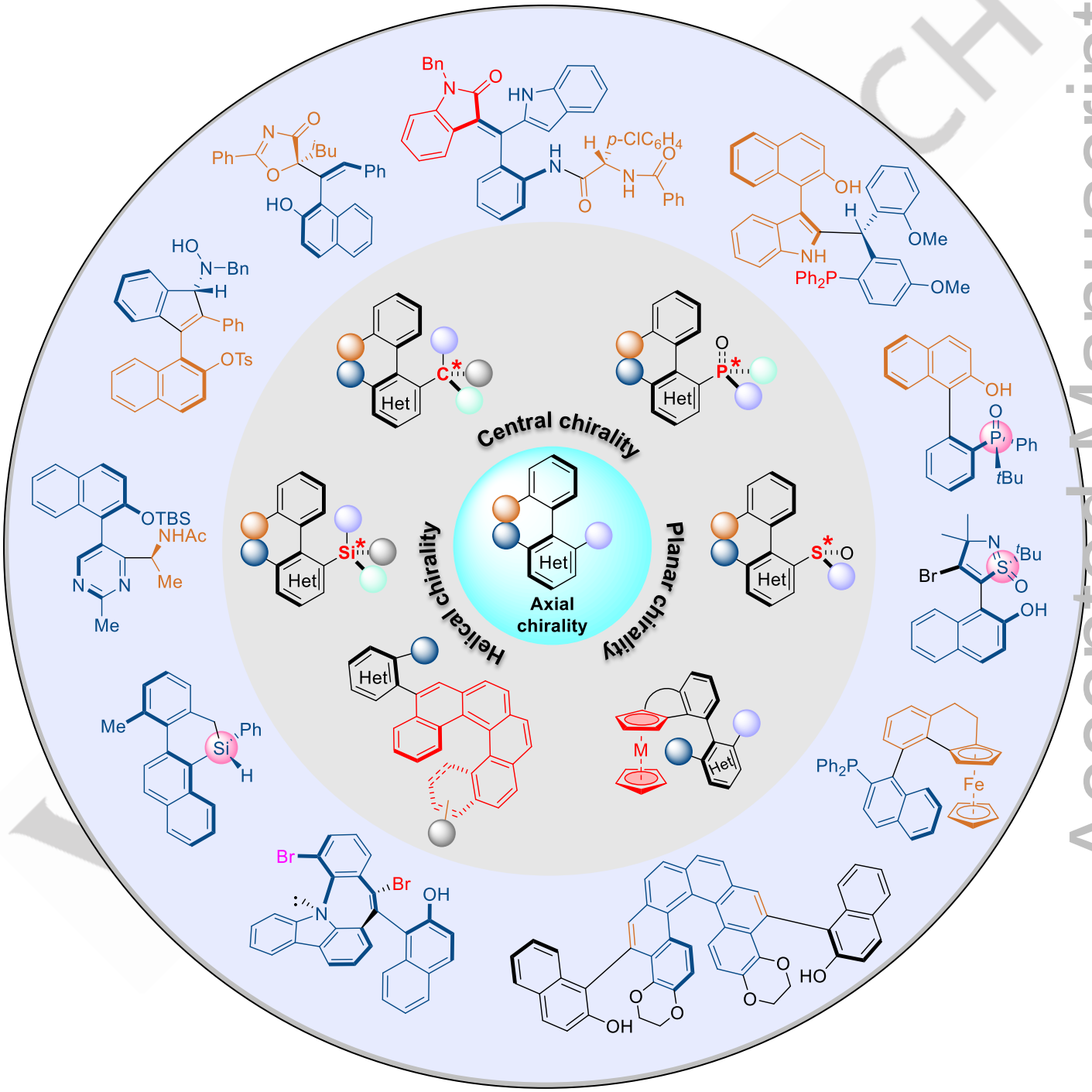
REVIEW

Catalytic Asymmetric Synthesis of Atropisomers Bearing Multiple Chiral Elements: An Emerging Field

Hong-Hao Zhang,*[a] Tian-Zhen Li,[a] Si-Jia Liu,[a] and Feng Shi*[a,b,c]



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REVIEW

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Abstract: With the rapid development of asymmetric catalysis, the demand for the enantioselective synthesis of complex and diverse molecules with different chiral elements is increasing. Owing to the unique features of atropisomerism, the catalytic asymmetric synthesis of atropisomers has attracted a considerable interest from the chemical science community. In particular, introducing additional chiral elements, such as carbon centered chirality, heteroatomic chirality, planar chirality, and helical chirality, into atropisomers provides an opportunity to incorporate new properties into axially chiral compounds, thus expanding the potential applications of atropisomers. Thus, it is important to perform catalytic asymmetric transformations to synthesize atropisomers bearing multiple chiral elements. In spite of challenges in such transformations, in recent years, chemists have devised powerful strategies under asymmetric organocatalysis or metal catalysis, synthesizing a wide range of enantioenriched atropisomers bearing multiple chiral elements. Therefore, the catalytic asymmetric synthesis of atropisomers bearing multiple chiral elements has become an emerging field. This review summarizes the rapid progress in this field and indicates challenges, thereby promoting this field to a new horizon.

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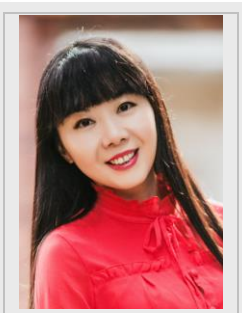
Feng Shi received her Ph.D. degree from Soochow University and worked as a visiting scholar at Nanyang Technological University. She started her independent career from 2013 and was appointed to a Full Professor in 2015. Her research field is chiral indole chemistry, which focuses on catalytic asymmetric synthesis of enantioenriched indole derivatives. She has published over 130 research papers in international peer-reviewed journals. She is a recipient of the "National Science Fund for Distinguished Young Scholars in China".



1. Introduction

Chirality is a fundamental property of nature,[1] and it has various types, which include central chirality (carbon chirality and heteroatom chirality), axial chirality, planar chirality, and helical chirality (**Figure 1a**). The enantioselective synthesis of chiral molecules via asymmetric catalysis has become one of the most important and fast-growing fields in modern organic synthesis.[2] With the rapid development of this field, the demand for the enantioselective synthesis of complex and diverse molecules with different chiral elements is increasing. In particular, over the past decade, the catalytic asymmetric synthesis of atropisomers, one class of axially chiral molecules, has attracted a considerable interest from the chemical science community[3] because of the unique features of atropisomerism.[4] Despite substantial advances in the catalytic asymmetric synthesis of atropisomers, the development of effective strategies to expand their structural diversity is required. Introducing additional chiral elements in atropisomers provides an opportunity to incorporate new properties into axially chiral compounds, thus expanding their potential applications.[5] For instance, various axially chiral catalysts and ligands with carbon- or heteroatom-stereogenic centers represent unique catalytic activity in asymmetric catalysis (**Figure 1b**).[6] Therefore, it is very important to perform catalytic asymmetric transformations to synthesize atropisomers bearing multiple chiral elements.

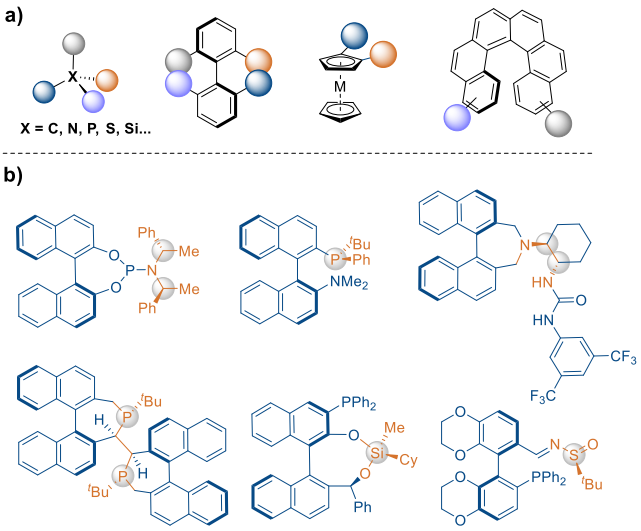


Figure 1. a) Common chiral elements. b) Representative axially chiral catalysts and ligands bearing other chiral elements.

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However, such transformations involve considerable challenges, i.e., simultaneously generating axial chirality and other chiral elements in one step and controlling diastereoselectivity and enantioselectivity during the generation of multiple chiral elements. To address these challenges, in recent years, chemists have devised powerful strategies, e.g., dynamic kinetic resolution (DKR), kinetic resolution (KR), *de novo* ring formation and desymmetrization under asymmetric organocatalysis or metal catalysis, thus synthesizing numerous enantioenriched atropisomers bearing multiple chiral elements. The structures of synthesized atropisomers bearing multiple chiral elements can be classified into atropisomers with C-stereogenic centers, heteroatom (S, P, and Si)-stereogenic centers, planar chirality, and helical chirality (**Figure 2**).

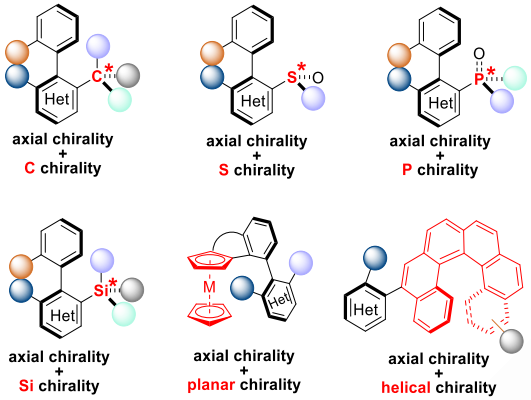


Figure 2. Structures of atropisomers bearing multiple chiral elements.

Therefore, the catalytic asymmetric synthesis of atropisomers bearing multiple chiral elements has become an emerging field. To promote the rapid development of this field, a timely summary, highlight, and outlook on this topic are highly desired. Therefore, this review summarizes the rapid progress in this field and provides some insights into future developments. Diastereoselective transformations of chiral substrates[5c] are not included in this review. Moreover, this review includes different types of chiral elements introduced in atropisomers, including carbon-stereogenic centers, heteroatom-stereogenic centers, and other chiral elements.

2. Atropisomers with C-Stereogenic Centers

The catalytic asymmetric synthesis of atropisomers with C-stereogenic centers has enhanced rapidly in recent years, which constitute a majority of this emerging field. Mostly, synthesized atropisomers bearing C-stereogenic centers are aryl-based atropisomers, which can be classified into aryl atropisomers and heteroaryl atropisomers bearing a C–C or C–N axis. In subdivisions, synthesized aryl atropisomers with C-stereogenic centers include nonbiaryl atropisomers, biaryl atropisomers, and heteroaryl atropisomers. Recently, although the catalytic asymmetric synthesis of nonbiaryl C−N atropisomers[3c,f,7], medium-sized bridged axially chiral biaryls[8] and heteroaryl atropisomers[9] has been well summarized, a summarization on the catalytic asymmetric synthesis of such atropisomers bearing other chiral elements has not appeared yet. In this section, we focus on introducing the catalytic asymmetric synthesis of atropisomers bearing C-stereogenic centers.

2.1. Nonbiaryl Atropisomers with C-Stereogenic Centers

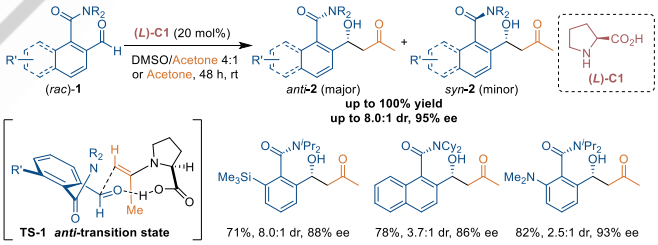
When one of the pivoting groups around the stereogenic axis is not an aromatic ring, such atropisomers are defined as nonbiaryl atropisomers. Currently, nonbiaryl atropisomers with C-stereogenic centers can be divided into nonbiaryl C−C atropisomers and nonbiaryl C−N atropisomers.

2.1.1 Nonbiaryl C−C Atropisomers with C-Stereogenic Centers

This section covers asymmetric synthesis of nonbiaryl C−C atropisomers bearing carbon-stereogenic centers, including C(carbonyl)−C(aryl) and C(alkenyl)−C(aryl) atropisomers, through organocatalytic approaches and metal-catalyzed approaches.

2.1.1.1. Organocatalytic Asymmetric Approaches

The organocatalytic asymmetric synthesis of atropisomers bearing multiple chiral elements was first performed in 2004 by Walsh and coworkers, who realized the DKR of atropisomeric amides **1** via *L*-proline **C1** catalyzed aldol condensation with acetone.[10] Using this approach, *anti*-isomers **2** bearing the axial chirality of aryl amide and a C-stereogenic center were obtained in high diastereo- and enantioselectivities (**Scheme 1**). This study provided an early example of the catalytic asymmetric synthesis of atropisomers bearing multiple chiral elements, which addressed the challenge of simultaneously controlling axial and central chirality in one step.



Scheme 1. The first catalytic asymmetric synthesis of atropisomers bearing multiple chiral elements.

In spite of this early report, the field of organocatalytic asymmetric synthesis of atropisomers bearing multiple chiral elements did not develop rapidly until recently, which might be ascribed to a considerable increase in interest in atropisomers and the rapid development of asymmetric catalysis. Recently, Jiang and coworkers successfully employed pyrrolylanilines **4** as electron-rich heterocycles to undergo asymmetric cascade cyclization with amide naphthaldehyde **3** in the presence of CPA **C2**, affording axially chiral arylamides **5** bearing a C-stereogenic center in high enantio- and diastereoselectivities (**Scheme 2**).[11] This reaction proceeded via an imine formation, followed by an intramolecular Mannich reaction. Therefore, this study provided a useful strategy for synthesizing axially chiral amides with a C-stereogenic center.

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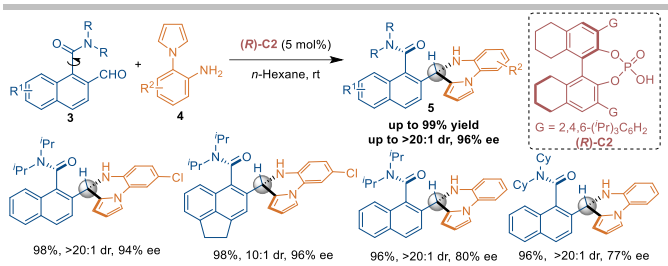
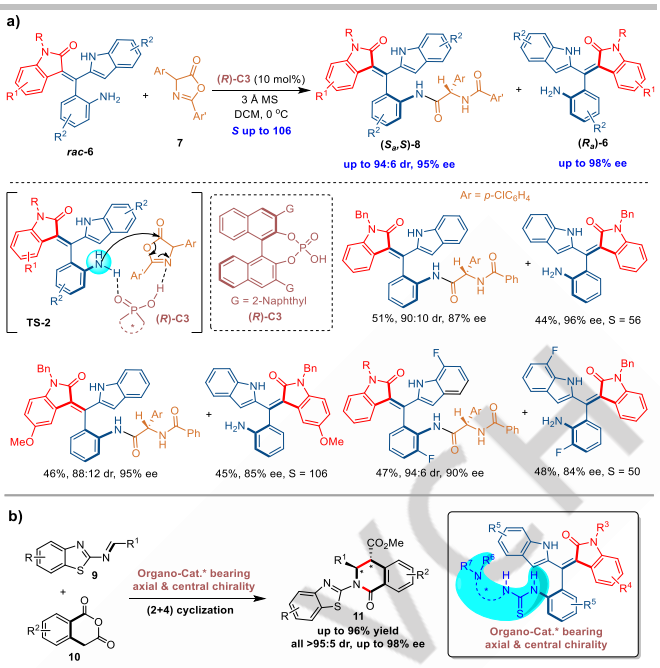


Scheme 2. Synthesis of axially chiral aryl amides with a C-stereogenic center.

Another essential branch of nonbiaryl C−C atropisomers is C(alkenyl)−C(aryl) system, which was first disclosed and investigated by Adams in the 1940s.[12] The low rotation barrier between two aryl-olefin enantiomers thwarted the development of this trend. When another chiral element was imported into this system, it's more difficult to construct this scaffold stereoselectively. In recent years, a representative example on the catalytic asymmetric synthesis of nonbiaryl C(alkenyl)−C(aryl) atropisomers with C-stereogenic centers was reported in 2020 by Shi's group.[13a] They employed organocatalytic KR as a powerful strategy for the atroposelective synthesis of oxindole-based axially chiral styrenes as a class of nonbiaryl C−C atropisomers. As shown in **Scheme 3a**, they applied racemic oxindole-based styrenes ***rac*-6** as platform molecules to the asymmetric ring-opening reaction of azalactones **7** under the catalysis of chiral phosphoric acid (CPA) **(*R*)-C3**, which underwent a KR pathway to produce two types of oxindole-based axially chiral styrene derivatives **(R_a)-6** and **(S_a,*S*)-8** with high selectivity factors (*S* up to 106). Notably, bisamide derivatives **(S_a,*S*)-8** bearing both axial and central chirality were obtained with good diastereoselectivities (up to 94:6 dr) and excellent enantioselectivities (up to 98% ee). In the plausible activation model, i.e., **TS-2**, CPA activated two substrates via hydrogen-bonding interactions, thus simultaneously controlling axial and central chirality. Later, the same group designed a new class of axially chiral styrene-based organocatalysts (Organo-Cat.*) bearing axial and central chirality, which enabled the diastereo- and enantioselective (2 + 4) cyclization of 2-benzothiazolimines **9** with homophthalic anhydrides **10** (**Scheme 3b**),[13b,c] demonstrating the potential of the class of organocatalysts in asymmetric catalysis.



Scheme 3. a) Synthesis of oxindole-based styrenes bearing multiple chiral elements. b) The application of axially chiral styrene-based organocatalysts in asymmetric catalysis.

Recently, vinylidene *ortho*-quinone methide (VQM) has emerged as an efficient and powerful intermediate for organocatalytic asymmetric synthesis of axially chiral styrenes.[14] A highly electrophilic VQM intermediate is easily attacked by nucleophiles. Thus, the selection of racemic nucleophiles to attack the VQM intermediate would lead to axially chiral styrenes with additional C-stereogenic centers. Based on this strategy, in 2019, Li's group used racemic 5*H*-oxazol-4-ones **13** as nucleophiles to react with alkynylnaphthols **12**, i.e., the precursors of VQMs, under the catalysis of chiral squaramide **C4**, affording axial chiral styrenes **14** with a C-stereogenic center in excellent stereoselectivities (**Scheme 4a**).[15] They suggested a possible activation mode, which involved a *Re*-face selective Michael addition of enolate to VQM (**Scheme 4b**). Based on the similar strategy, Wang and coworkers used racemic pyrazolone as a nucleophile and synthesized axial chiral styrenes with a C-stereogenic center.[16] Moreover, Li, Hong and coworkers synthesized spiroketal-based lactones bearing axial and central chirality via an organocatalytic asymmetric intramolecular cascade cyclization of VQM derivatives.[17]

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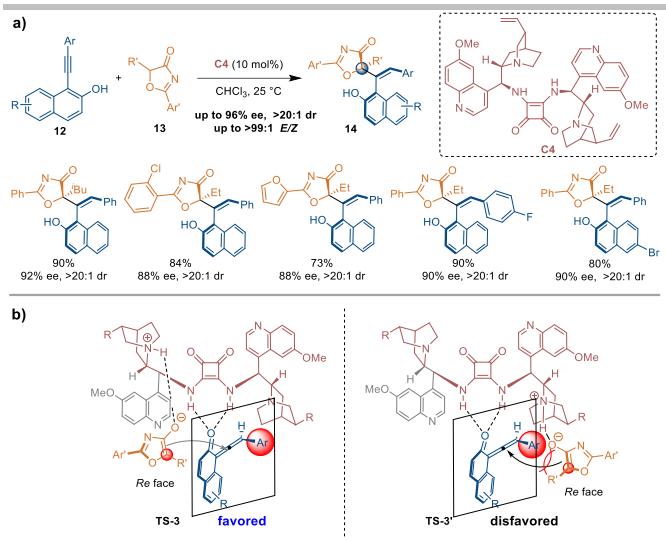
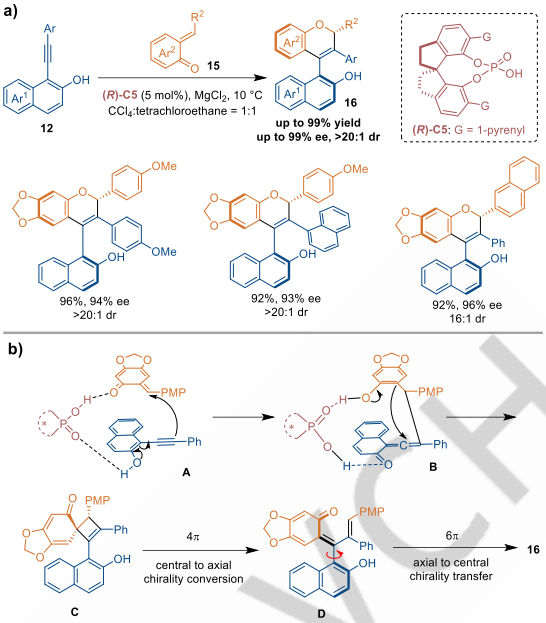


Scheme 4. a) Synthesis of axially chiral styrenes with a C-stereogenic center. b) Proposed transition state.

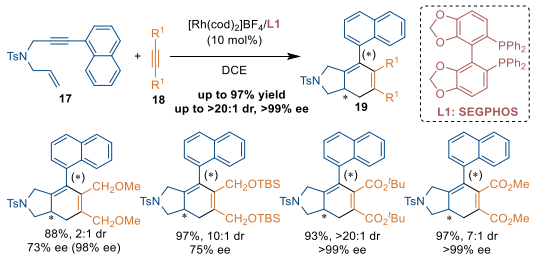
In 2022, Zhou's group developed a CPA-catalyzed cycloaddition of alkynylnaphthols **12** with *o*-quinone methides **15** via all-carbon tetrasubstituted VQMs (Scheme **5a**).[18] New alkenyl-aryl/heteroaryl atropisomers **16** bearing a center chirality were synthesized in excellent diastereo- and enantioselectivities. Control experiments revealed that OH group of **12** is vital to these transformations, and CPA activated both substrates via dual hydrogen bonding. Mechanistically (**Scheme 5b**), alkynylnaphthol **12** first attacked the *o*-quinone methides **15** to form all-carbon tetrasubstituted VQM **B**. Under the activation of CPA, an intramolecular nucleophilic addition of VQM resulted in a chiral spirocyclic intermediate **C**, which underwent a 4π-electrocyclic ring opening to form intermediate **D** and realized the central-to-axial chirality conversion.[19] Finally, the oxa-6π electrocyclization of **D** resulted in naphthyl-2*H*-chromenes **16** bearing axial and central chirality. This class of atropisomers **16** with C-stereogenic centers could be transformed into chiral phosphine ligands, which exhibited moderate-to-good catalytic activity in the Pd-catalyzed asymmetric allylation reaction.



Scheme 5. a) Synthesis of atropisomers **13** bearing axial and central chirality. b) Proposed reaction mechanism.

2.1.1.2. Metal-Catalyzed Asymmetric Approaches

An early example of metal-catalyzed enantioselective synthesis of atropisomers containing a C(alkenyl)−C(aryl) axial chirality and central chirality was reported in 2008 by Endo and coworkers, who explored a Rh/SEGPHOS complex-catalyzed [2 + 2 + 2] cycloaddition of nitrogen-tethered enyne **17** and alkynes **18**, affording bicyclic cyclohexa-1,3-dienes **19** with both axial and central chirality in excellent diastereo- and enantioselectivities (**Scheme 6**).[20]



Scheme 6. Synthesis of nonbiaryl atropisomers with both axial and central chirality via Rh-catalyzed [2 + 2 + 2] cycloaddition.

In addition to aryl amides and styrene derivatives, axially chiral indenes belong to an important class of nonbiaryl C−C atropisomers with C-stereogenic centers. In 2021, Li's group established a Rh-catalyzed annulation reaction of nitrones **20** with sterically hindered aryl/heteroaryl alkynes **21**, affording axially chiral indenes **22** with a C-stereogenic center with excellent enantio- and diastereoselectivities (**Scheme 7a**).[21] In the suggested reaction pathway (**Scheme 7b**), after *O*-directed C−H activation of nitrone **20**, intermediates **E** underwent migratory insertion with alkyne **21**, producing the alkenyl intermediate **F** with a (*S*) chiral axis. Subsequently, the *Re*-face selective migratory insertion of **F** resulted in the (*S*) carbon-stereogenic center.

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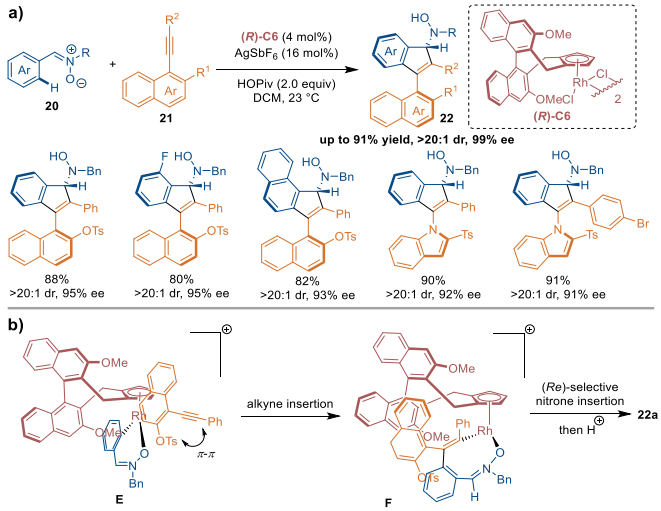
Therefore, herein, the axial chirality and central chirality were generated in two distinct stereo-determining steps of migratory insertions, which provided an excellent example of stereo-control in constructing scaffolds with both axial and central chirality.



Scheme 7. a) Synthesis of axially chiral indenes with a C-stereogenic center. b) Proposed transition state.

2.1.2 Nonbiaryl C−N Atropisomers with C-Stereogenic Centers

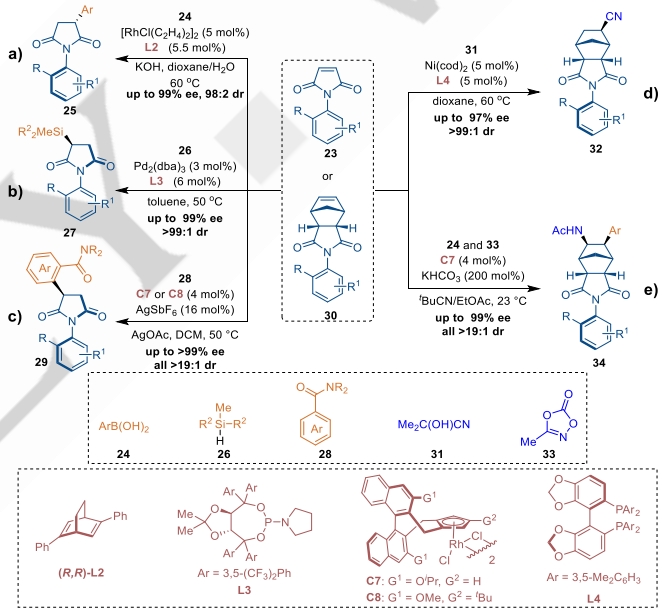
By comparison, stereoselective construction of nonbiaryl C−N atropisomers with C-stereogenic centers developed much better than nonbiaryl C−C atropisomers.[3c,f,7] Various synthetic strategies have been developed for catalytic asymmetric synthesis of nonbiaryl C−N atropisomers with C-stereogenic centers, such as enantioselective desymmetrization of prochiral substrates, kinetic resolution and dynamic kinetic resolution of racemic substrates, atroposelective *N*-annulation and so on. So, this section is classified by the different strategies for catalytic asymmetric synthesis of nonbiaryl C−N atropisomers with carbon-stereogenic centers.

2.1.2.1. Desymmetrization of *N*-aryl Maleimides and Their Analogs

Among various synthetic strategies, enantioselective desymmetrization of *N*-aryl maleimides represents a direct approach to access C–N atropisomers. Both organocatalytic approaches and metal-catalyzed approaches have been well used in this field.

Metal-Catalyzed Asymmetric Approaches. A pioneering work on transition-metal-catalyzed desymmetrization of *N*-aryl maleimides was first reported by Hayashi and coworkers in 2007.[22] Through a Rh-catalyzed asymmetric 1,4-addition of phenylboronic acids **24** to maleimides **23**, *N*-aryl succinimides **25** with a C–N axis and a C-stereogenic center could be obtained with excellent enantio- and diastereoselectivities (**Scheme 8a**). Recently, significant progresses have been made in this field. In 2020, Xu and coworkers developed a Pd-catalyzed asymmetric hydrosilylation of maleimides **23**, giving a series of C–N axially chiral silyl succinimides **27** bearing a C-stereogenic center with high diastereo- and enantioselectivities (**Scheme 8b**).[23] More recently, using *N*-arylmaleimides **23** as the alkylating reagent, Li and coworkers realized a Rh-catalyzed enantioselective C–H alkylation of benzamides to give *N*-aryl succinimides **29** bearing both axial and central chirality (**Scheme 8c**).[24]

Some *N*-arylmaleimide analogs, such as Diels-Alder reaction-derived maleimide adducts, can also be employed as prochiral substrates for the desymmetrization strategy to construct C–N axial chirality. In 2021, Cheng, Fang, and coworkers realized desymmetrization of *N*-aryl 5-norbornene-endocis-2,3-dicarboximides **30** via a nickel-catalyzed enantioselective hydrocyanation, leading to the generation of *N*-aryl succinimides **32** bearing five contiguous stereogenic centers and one remote C–N axis with excellent diastereo- and enantioselectivities (**Scheme 8d**).[25] Very recently, Li and coworkers accomplished a Rh-catalyzed three-component asymmetric carboamidation of prochiral *N*-aryl maleimide analogs **30** with aryl boronic acid **24** and dioxazolones **33** (**Scheme 8e**), affording products **34** bearing both central chirality and C-N axial chirality.[26]



Scheme 8. Synthesis of nonbiaryl C−N atropisomers with C-stereogenic centers via transition-metal-catalyzed desymmetrization of *N*-aryl maleimides.

Non-redox metal ions serving as Lewis acids have also been well used in the desymmetrization strategy. For example, using chiral *N*,*N*'-dioxide-Sc(III) complex as a catalyst, Feng and coworkers accomplished catalytic asymmetric Michael addition/desymmetrization of *N*-aryl maleimides **23** with unprotected 3-substituted-2-oxindoles **35**, constructing both central chirality and C–N axial chirality with excellent diastereo- and enantioselectivities (**Scheme 9a**).[27] In addition, metal-catalyzed asymmetric 1,3-dipolar cycloadditions is one of the most efficient strategies for desymmetrization of *N*-arylmaleimides. In 2016, Wang and coworkers developed a desymmetrization of *N*-arylmaleimide **23** via Ag(I)-catalyzed 1,3-dipolar cycloaddition with azomethine ylides generated in situ from imino esters **37** (**Scheme 9b**).[28] Using this strategy, Yuan, Han, and coworkers developed Cu-catalyzed desymmetrizative 1,3-dipolar cycloaddition of *N*-arylmaleimide **23** with *N*-2,2,2-

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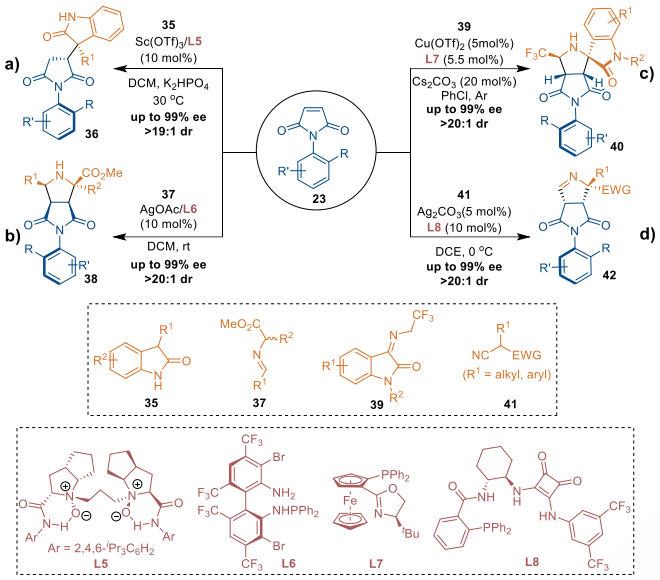
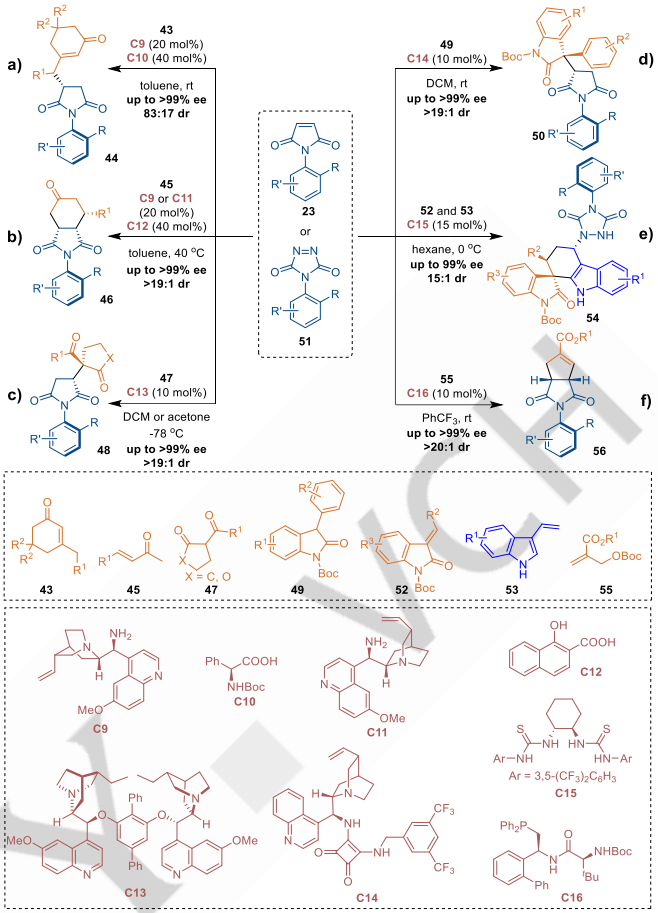
trifluoroethylisatin ketimines **39** (**Scheme 9c**).[29] Independently, Liao, Qian, and coworkers reported Ag-catalyzed desymmetrizative (3 + 2) cycloaddition of *N*-Aryl caleimides **23** with activated isocyanides **41** (**Scheme 9d**).[30] By these approaches, chiral products **38**, **40**, **42** bearing a C-N axis were synthesized with overall high stereoselectivities.



Scheme 9. Synthesis of nonbiaryl C−N atropisomers with C-stereogenic centers via chiral Lewis acid-catalyzed desymmetrization of *N*-aryl maleimides.

Organocatalytic Asymmetric Approaches. The first organocatalytic desymmetrization of *N*-aryl maleimides was reported by Bencivenni and coworkers in 2014 (**Scheme 10a**).[31] Using the combination of quinine **C9** with chiral cocatalyst **C10**, the desymmetrizative vinylogous Michael addition of 3-substituted cyclohexenones **43** to *N*-arylmaleimides **23** led to the synthesis of C−N axially chiral succinimides **44** with two adjacent stereocenters with moderate diastereoselectivities and excellent enantioselectivities. Later, the same group applied this desymmetrization strategy in formal Diels−Alder reaction with enones **45** to generate atropisomers **46** (**Scheme 10b**).[32] Furthermore, this group extended the desymmetrizative Michael addition of *N*-aryl maleimides **23** to other carbon nucleophiles **47** and **49**, which offered succinimides **48** and **50** bearing contiguous stereogenic centers and one C–N axis with excellent diastereo- and enantioselectivities (**Scheme 10c-d**).[33,34] In 2018, Tan and coworkers devised an asymmetric three-component ene reaction involving 4-aryl-1,2,4-triazole-3,5-diones **51** (*N*-aryl maleimide analogs) to synthesize spirooxindole-urazoles **54** bearing both a chiral C-N axis and carbon stereocenters (**Scheme 10e**).[35] Recently, Wang, Lin, and coworkers developed an organocatalytic desymmetrizative (3 + 2) annulation of MBH carbonates **55** with *N*-aryl maleimides **23** to give nonbiaryl C−N atropisomers **56** with C-stereogenic centers in good results (**Scheme 10f**).[36]



Scheme 10. Synthesis of nonbiaryl C−N atropisomers with C-stereogenic centers via organocatalytic desymmetrization of *N*-aryl maleimides.

It is a great challenge in asymmetric catalysis to control multiple chiral centers simultaneously. This is particularly true for the construction of chiral frameworks bearing multiple non-adjacent chiral elements. Very recently, a representative example on the catalytic asymmetric synthesis of axially chiral phthalimides with up to four stereogenic centers and two remote chiral axes was reported by Amatore, Constantieux, and coworkers (**Scheme 11a**).[37] Initially, they designed a chiral NHC-catalyzed desymmetrizative formal (4 + 2) oxidative annulation of *N*-aryl maleimides **23** with enals **57**. Unexpectedly, enals **57** reacted with two equivalents of *N*-aryl maleimide **23** to afford *bis*-succinimides **58** bearing six stereogenic elements including four carbon stereocenters and two remote Csp^2–N stereogenic axes with excellent diastereo- and enantioselectivities. In the suggested reaction pathway, the initial addition of chiral NHC to enals **57** led to the formation of the Breslow intermediates **G**, which are subsequently converted to azolium dienolates **H** via oxidation. Then, intermediates **H** attacked prochiral maleimides **1** to form intermediates **I**, which underwent an intramolecular cyclization to generate enantioenriched cyclohexanones **J** as key intermediates and regenerated the active catalyst. Finally, intermediates **J** performed conjugate addition with another molecule of maleimides **23** to give the observed *bis*-succinimides **58**, rather than oxidation to yield the anticipated phenols **58'** (**Scheme 11b**).

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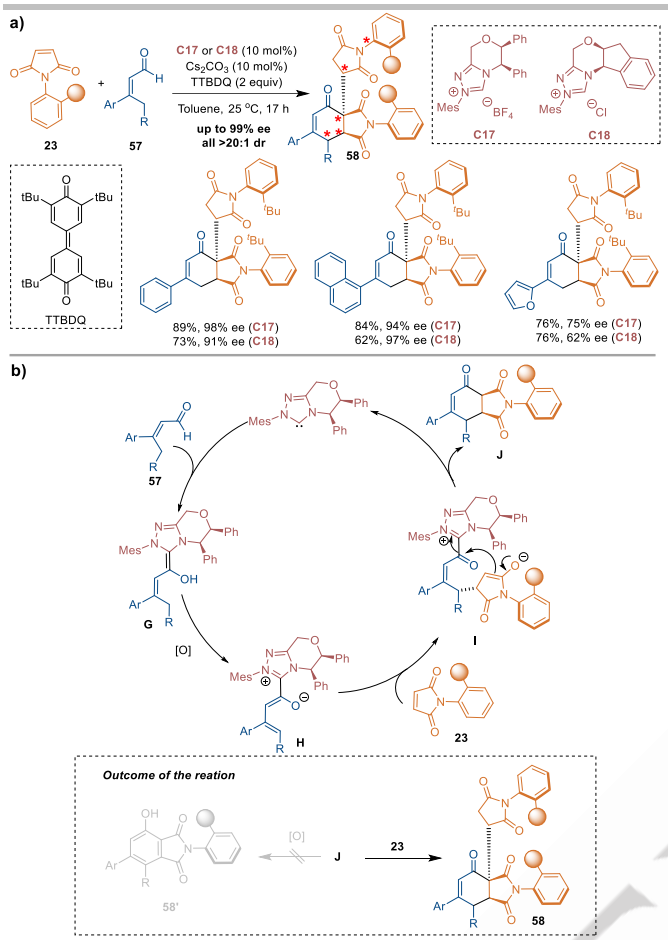
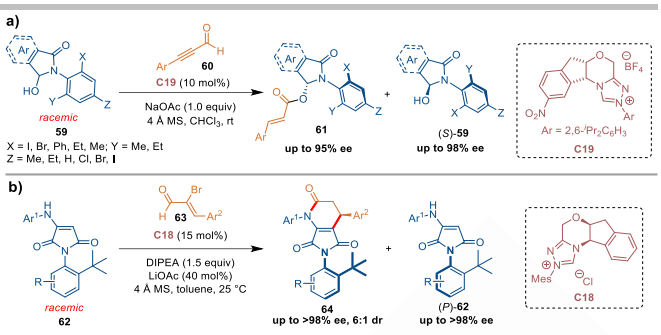


Scheme 11. a) Atroposelective synthesis of axially chiral phthalimides bearing multiple stereogenic centers. b) Proposed reaction mechanism.

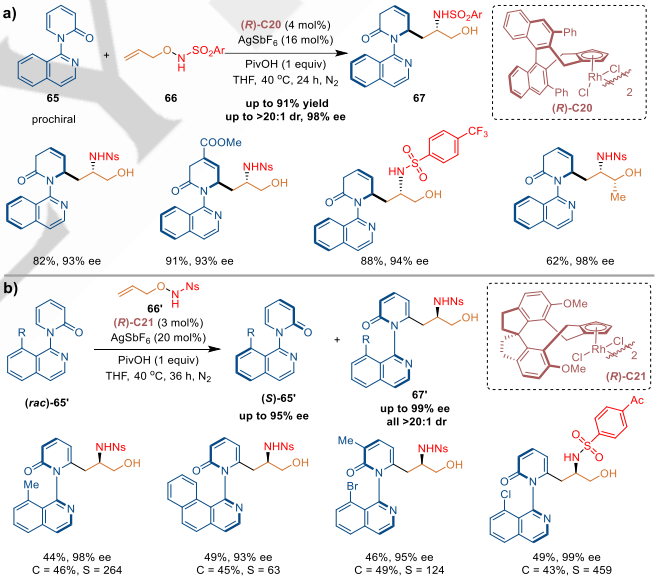
2.1.2.2. Kinetic Resolution and Dynamic Kinetic Resolution of Racemic Substrates

Kinetic resolution of racemic substrates is an efficient synthetic strategy for C–N atropisomers with C-stereogenic centers. In 2018, Wang and coworkers reported a kinetic resolution of racemic aza-hemiacetals **59** through an enantioselective NHC-catalyzed acylation (**Scheme 12a**).[38] Through this KR process, acylated products **61** with both C–N axial chirality and central chirality were formed with excellent enantioselectivities. Later, Biju and coworkers developed a kinetic resolution of *N*-aryl aminomaleimides **62** via an NHC-catalyzed asymmetric (3 + 3) annulation with 2-bromoenals **63**, giving rise to products **64** in good diastereo- and enantioselectivities (**Scheme 12b**).[39]



Scheme 12. Synthesis of C–N atropisomers with C-stereogenic centers via KR.

Recently, Li and coworkers designed *N*-protected *O*-allylhydroxyamines **66** as bifunctional olefins for Rh-catalyzed asymmetric 1,2-carboamidation with arenes **65** to access axially and centrally chiral amino alcohols **67**.[40] Interestingly, 2-pyridones **65** bearing an C8-unsubstituted *N*-isoquinolyl directing group underwent a DKR process (**Scheme 13a**), while 2-pyridones **65'** bearing a bulky C8-substituted isoquinolyl directing group underwent a KR process (**Scheme 13b**). This is because the existence of C8-substituents makes prochiral substrates **65** become racemic substrates **65'** with stable axial chirality.



Scheme 13. Synthesis of C–N atropisomers with C-stereogenic centers via KR and DKR.

2.1.2.3 Other Catalytic Atroposelective Approaches

Some other catalytic atroposelective approaches, such as N-H functionalization and *N*-annulation, have been developed for the synthesis of nonbiaryl C−N atropisomers with C-stereogenic centers.

In early 2000s, Pd-catalyzed *N*-allylation of achiral N–H anilides was applied by the groups of Taguchi[41] and Curran[42] independently for the asymmetric construction C–N axial chirality. However, catalytic asymmetric synthesis of C–N atropisomers with C-stereogenic centers remained elusive until very recently. Jiang's group developed a Pd-catalyzed atroposelective

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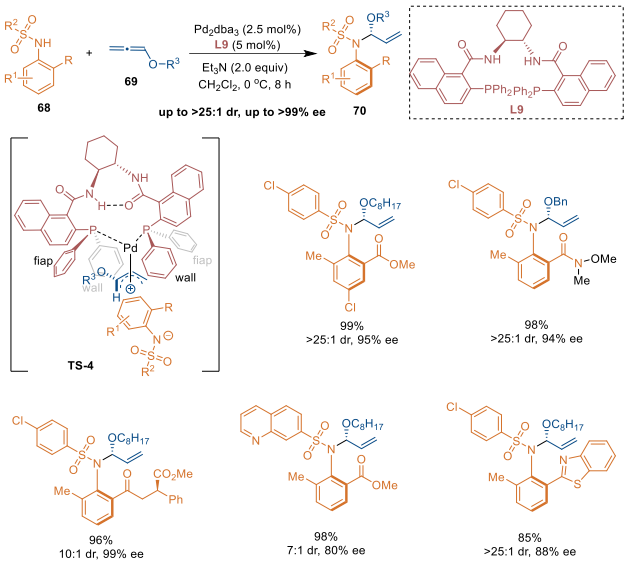
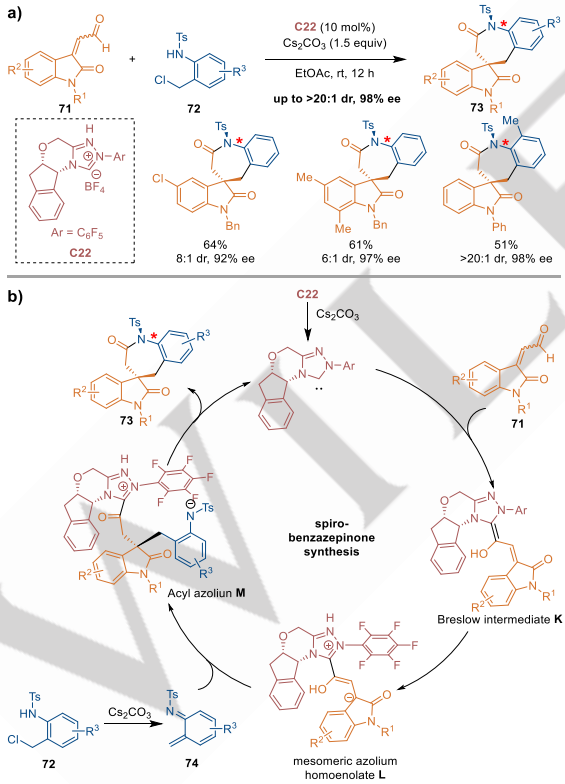
hydroamination of allenes **69**, affording a series of axially chiral sulfonamides **70** bearing a central chirality with high enantio-, diastereo-, and regioselectivities (**Scheme 14**).[43]



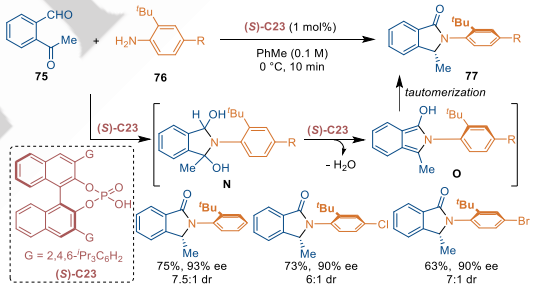
Scheme 14. Synthesis of axially chiral sulfonamides with C-stereogenic centers via atroposelective hydroamination of allenes.



Scheme 15. a) Atroposelective synthesis of spirobenzazepinones with C-stereogenic centers. b) Proposed reaction mechanism.

Medium-sized chiral *N*-heterocycles are important pharmacophores that are widely present in bioactive compounds.[44] So, it is highly desirable to realize the efficient synthesis of such compounds. In 2016, Enders and coworkers developed an NHC-catalyzed formal (3 + 4) annulation of isatin-derived enals **71** with aza-*o*-quinone methides formed in situ from *N*-(*ortho*-chloromethyl)aryl amides **72**. By this approach, seven-membered heterocyclic spirobenzazepinones **73** bearing a C–N axis and a quaternary all-carbon stereocenter were formed with moderate to high diastereoselectivities and excellent enantioselectivities (**Scheme 15**).[45] The key steps of the reaction include the formation of mesomeric azolium homoenolate **L**, conjugate addition of **L** to aza-*o*-quinone methide **74**, followed by an intramolecular cyclization of intermediate acyl azolium to afford the desired products **73**. Control experiments indicated that both carbonyl and *N*-tosyl groups were essential to generate the atropisomerism in the structure of products **73**.

In 2017, Seidel and coworkers disclosed a catalytic asymmetric *N*-annulation of anilines **76** with 2-acylbenzaldehydes **75**. In the presence of CPA **C23**, a highly efficient biomimetic condensation between 2-substituted anilines **76** and 2-acylbenzaldehydes **75** led to the atroposelective construction of C–N axially chiral *N*-arylisoindolinones **77** bearing a central chirality (**Scheme 16**).[46] Mechanistically, this reaction proceeded through the formation of cyclic bis-hemiaminal **N**, followed by sequential dehydration and tautomerization, wherein the tautomerization of **O** to **77** was the key enantiodetermining step. Very recently, Duan, Qi, and coworkers achieved the synthesis of axially chiral dihydropyridones bearing a central chirality through an NHC-catalyzed atroposelective (3 + 3) annulation of enals with 2-aminomaleate derivatives.[47]



Scheme 16. Atroposelective synthesis of isoindolinones with C-stereogenic centers.

2.2. Biaryl Atropisomers with C-Stereogenic Centers

Among different atropisomers, biaryls are the most common frameworks, so the catalytic asymmetric synthesis of biaryl atropisomers have been intensively investigated in the past decades. Nevertheless, the catalytic asymmetric construction of biaryl atropisomers with C-stereogenic centers are relatively limited, which mainly include catalytic atroposelective synthesis of medium-sized bridged biaryls and other biaryl atropisomers with C-stereogenic centers.

2.2.1. Medium-Sized Bridged Biaryls with C-Stereogenic Centers

The medium-sized bridged biaryls, which bear an additional linkage between the two arenes, belong to one of the essential classes of axially chiral biaryls. Their unique conformational

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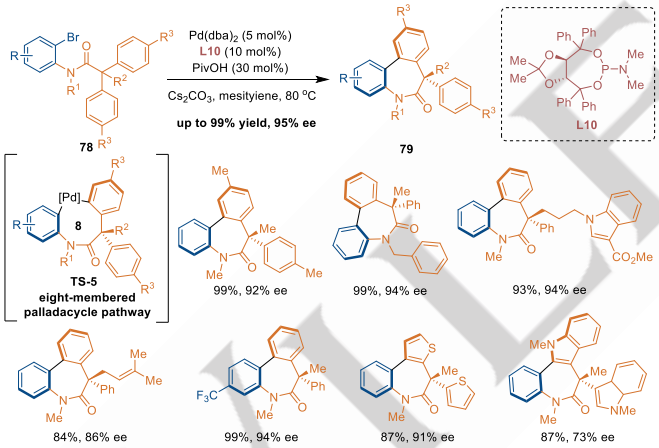
features arising from the restricted rotation around the pivotal bond make them able to be resolved as atropisomers. Introducing a stereogenic center on the bridging cycle may improve the rigidity and enforce the bridged structure to acquire the desired conformation at the biaryl chiral axis by a central-to-axial chirality conversion[19] process. In this section, the recent research progresses on the catalytic asymmetric synthesis of axially chiral medium-sized bridged biaryls with C-stereogenic centers are highlighted according to the synthetic strategies: (1) construction of medium-sized bridged biaryls; (2) functionalization of medium-sized bridged biaryls.

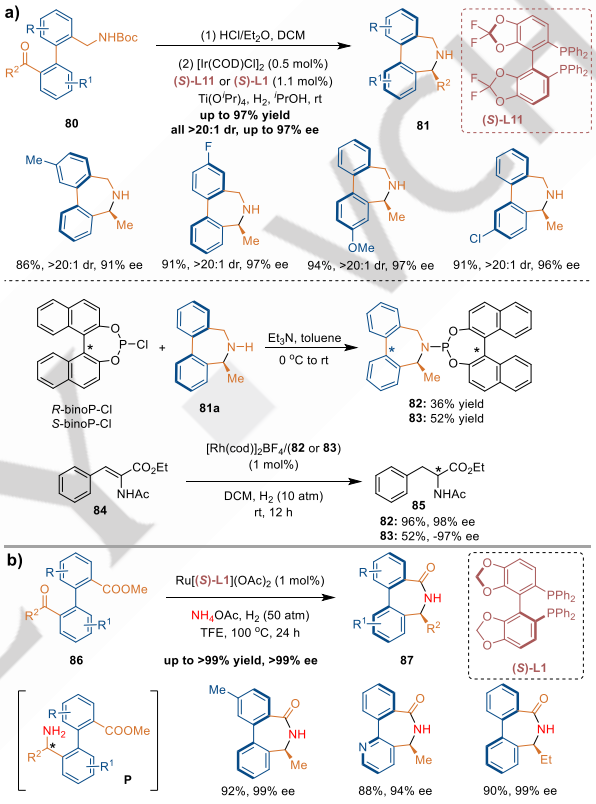
2.2.1.1. Construction of Medium-Sized Bridged Biaryls

Metal-Catalyzed Asymmetric Approaches. Transition-metal-catalyzed intramolecular aryl-aryl coupling reaction has been recognized as a powerful and straightforward protocol to construct axial chiral bridged biaryls. In 2013, Cramer and coworkers disclosed a Pd-catalyzed intramolecular asymmetric C–H arylation of aryl bromides **78**. Using a TADDOL-derived chiral monophosphoramidite ligand **L10**, the C−H activation went through a rare eight-membered palladacycle intermediate (**Scheme 17**).[48] A series of seven-membered aza-heterocyclic bridged biaryls **79** possessing a quaternary stereocenter were afforded with moderate to good enantioselectivity. Notably, only one single diastereomer was observed, which indicated that the introduction of C-stereogenic center could improve rotational barrier of the bridged biaryl.



Scheme 17. Synthesis of seven-membered aza-heterocyclic bridged biaryls bearing a quaternary stereocenter via Pd-catalyzed asymmetric C–H arylation.

In 2019, Yin, Zhang, and coworkers described a Ir-catalyzed intramolecular asymmetric cyclization of biaryl aminoketones **80** (**Scheme 18a**).[49] This approach proceeded through a one-pot *N*-Boc deprotection, followed by a Ir-catalyzed intramolecular asymmetric reductive amination. Using DifluorPhos **L11** or SegPhos **L1** as a ligand, Ti(O^{i}Pr)$_4$ as an additive, a series of dibenz[*c*,*e*]azepines **81** possessing both central and axial chirality could be obtained with excellent enantio- and diastereoselectivities. In addition, the resultant dibenz[*c*,*e*]azepines could transform into chiral monodentate phosphorus ligands **82** and **83**. The application of these chiral monodentate phosphorus ligands in Rh-catalyzed asymmetric hydrogenation of α-dehydroamino acid derivative **84** led to the desired product **85** with an excellent enantioselectivity, which demonstrated the potential of this kind of scaffold with multiple chiral elements in developing new chiral ligands. Shortly after, Chen, Fan, and coworkers reported a Ru-catalyzed direct asymmetric hydrogenation of dibenzo[*c*,*e*]azepines.[50] Later, Yin, Zhang, and coworkers designed a Ru-catalyzed asymmetric reductive amination (ARA)/ringclosing cascade reaction for enantioselective synthesis of biaryl-bridged NH lactams **87** (**Scheme 18b**).[51] Compared to their previous work,[49] this transformation avoided inconvenient preparation and isolation of amine substrates **P**.



Scheme 18. Enantioselective synthesis of biaryl-bridged NH lactams with C-stereogenic centers.

In 2021, Luo, Zhu, and coworkers applied cyclic carbopalladation−carbonylation (CCC) tandem reactions to atroposelective construction of medium-sized bridged biaryls (**Scheme 19**).[52] To address the considerable challenges in this medium-sized ring formation, such as competing carbonylation and β-H elimination of δ-alkylpalladium intermediate, they designed iodo-substituted biphenyl acrylamide as substrates **88**. Using anilines **89**, alcohols, or phenols **90** as nucleophiles, this Pd-catalyzed 7-*exo*-tig CCC cascade reaction delivered a diverse array of axially chiral seven-membered aza-heterocyclic bridged biaryls **91** or **92** bearing a C-stereogenic center with excellent diastereo- and enantioselectivities.

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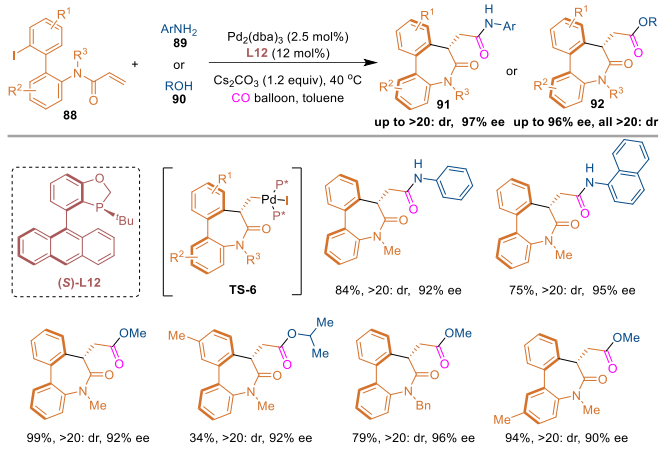
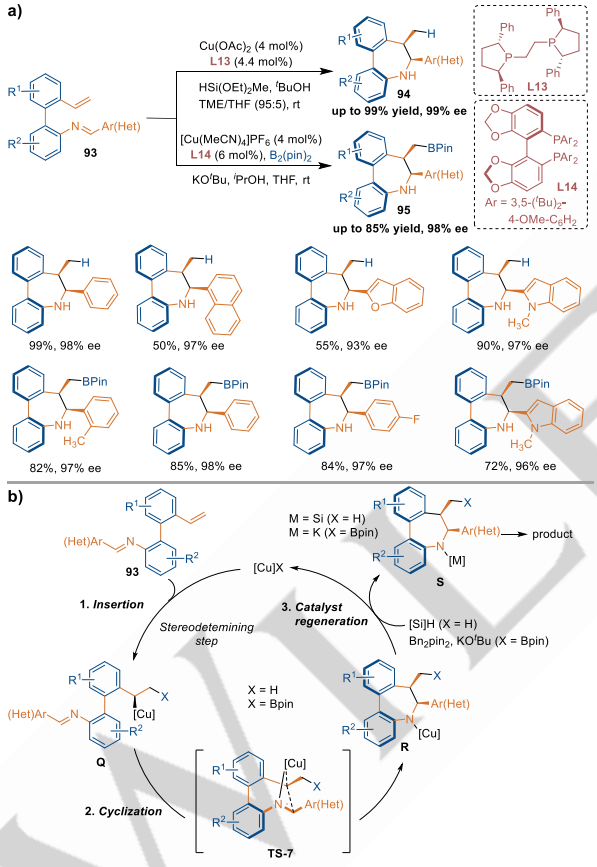


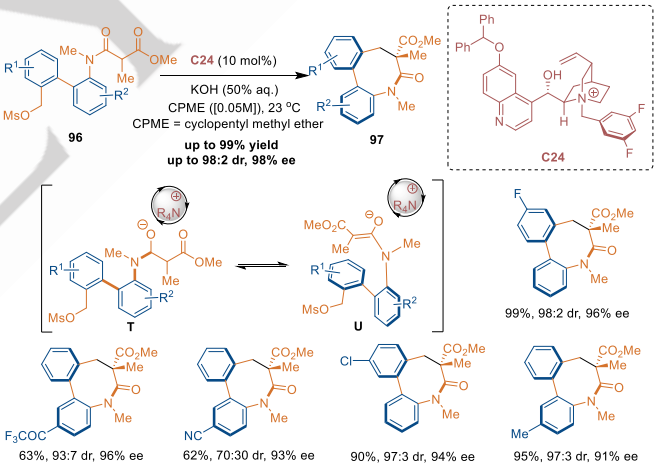
Scheme 19. Atroposelective construction of medium-sized bridged biaryls with C-stereogenic centers via Pd-catalyzed cascade reaction.



Scheme 20. a) Atroposelective synthesis of dibenzo[*b*,*d*]azepines bearing C-stereogenic centers via Cu-catalyzed reductive or borylative cyclization. b) Proposed reaction mechanism.

In 2021, Hornillos and coworkers designed 2'-vinylbiaryl-2-imines **93** for Cu-catalyzed asymmetric intramolecular reductive or borylative cyclization, which afforded enantioenriched dibenzo[*b*,*d*]azepine derivatives **94** and **95** bearing a stereogenic axis and two contiguous stereogenic centers in moderate to high yields with excellent diastereo- and enantioselectivities (**Scheme 20a**).[53] Mechanistically, the insertion of active copper species into substrates **93** provided intermediates **Q**. Then, with the coordination of the imine nitrogen, intermediates **Q** underwent a *cis*-selective cyclization through transition state **TS-7** to form intermediates **R**. Finally, intermediates **R** reacted with silane or borane reagent to give the desired products **94** or **95** and regenerate the catalyst (**Scheme 20b**).

Organocatalytic Asymmetric Approaches. No breakthrough has been made in the field of organocatalytic asymmetric construction of medium-sized bridged axially chiral biaryls until recently.[54] This is because converting racemic substrates bearing multiple stereochemical features directly into an enantioenriched products with diastereo- and enantiocontrol is very challenging. Smithet and coworkers confronted this challenge by realizing an enantioconvergent intramolecular cyclization of biaryl anilides (**Scheme 21**).[54a] In the presence of a base and a quinidine-derived ammonium salt **C24** as a phase-transfer catalyst, racemic biaryl anilides **96**, a complex mixture of enantiomers and diastereoisomeric conformers, could be converted into axially chiral eight-membered lactams **97** with C-stereogenic center in a diastereo- and enantioselective manner. In the plausible mechanism, the formation of enolates **U** ablated the stereogenic center and significantly reduced the rotational barrier in the anilide substrates, which led to rapid and reversible configurational and conformational equilibration. Then, the enolates **U** underwent a diastereo- and enantioselective cyclization under the activation and control of chiral ammonium counterion to deliver the medium-ring lactams **97**.



Scheme 21. Enantioconvergent synthesis of axially chiral eight-membered lactams with C-stereogenic centers.

2.2.1.2. Functionalization of Medium-Sized Bridged Biaryls

During the prior studies on Pd-catalyzed (5+2) annulation of *o*-arylanilines with alkynes,[55] Luan and coworkers found that weakly acidic silica gel could realize enamine-imine tautomerization. Based on this observation, they performed studies on the catalytic enantioselective tautomerization of dibenzo[*b*,*d*]azepines **98** (**Scheme 22**).[56] Under the catalysis of chiral phosphoric acid **C25**, an asymmetric tautomerization proceeded efficiently and stereoselectively, offering a series of seven-membered imine products **99** bearing both axial and central chirality in good yields with excellent enantio- and diastereoselectivities. A plausible mechanism was proposed, in

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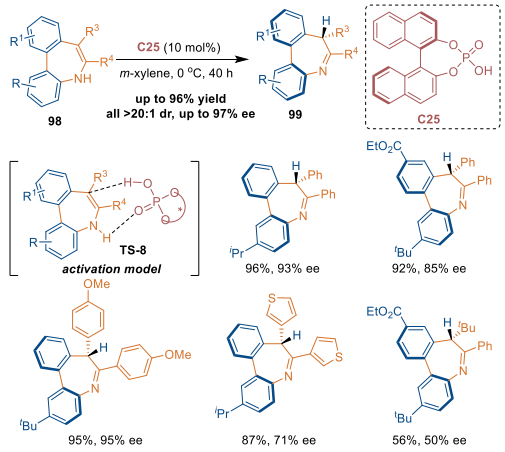
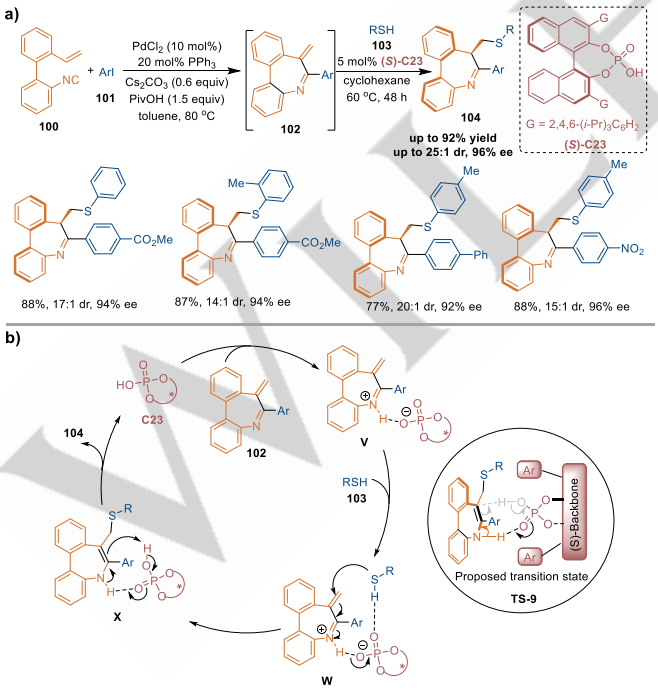
which the hydrogen bond between phosphoryl oxygen of CPA **C25** and NH group of enamines was the key for this reaction.



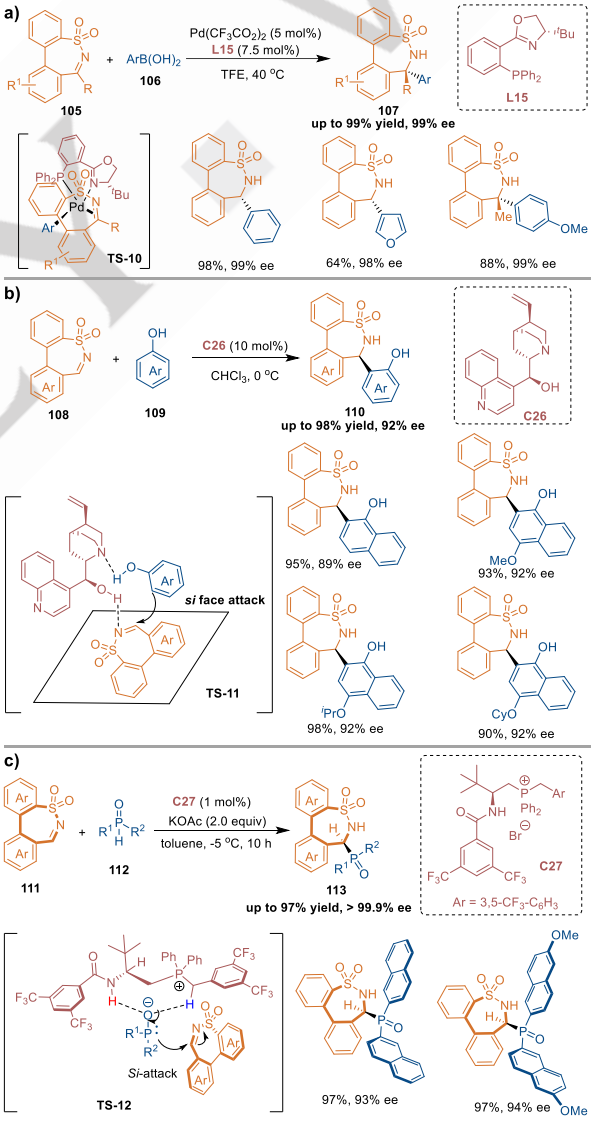
Scheme 22. Synthesis of axially chiral seven-membered bridged biaryls with C-stereogenic centers via tautomerization of metastable enamines.

Recently, Zhao, Zhu, and coworkers designed α,β-unsaturated cyclic imines for the asymmetric synthesis of dibenzo[*b*,*d*]azepines (**Scheme 23**).[57] In the presence of CPA **C23**, 7-methylene-6-aryl-7*H*-dibenzo-[*b*,*d*]azepines **102** synthesized from Pd-catalyzed imidoylative Heck cyclization underwent a sulfa-Michael addition reaction, followed by enantioselective protonation reaction, delivering desired products **104** bearing both axial and central chirality with excellent diastereo- and enantioselectivities.



Scheme 23. a) Atroposelective synthesis of dibenzo[*b*,*d*]azepines with C-stereogenic centers. b) Proposed reaction mechanism.

Seven-membered cyclic *N*-sulfonylimine have emerged as versatile substrates for asymmetric synthesis of seven-membered benzosultams with diverse bioactivities. In 2019, Zhou and coworkers established a Pd-catalyzed asymmetric arylation of seven-membered cyclic *N*-sulfonylimines **105** with arylboronic acids **106** (**Scheme 24a**).[58] Both aldimines and ketimines could undergo this transformation, providing the corresponding axially chiral ε-sultams **107** containing a C-stereogenic center with excellent diastereo- and enantioselectivities. In the same year, using cinchona alkaloid **C26** as a bifunctional organocatalyst, they applied cyclic *N*-sulfonylimines **108** to asymmetric aza-Friedel-Crafts reaction of naphthols **109** (**Scheme 24b**).[59] The cinchona alkaloid **C26** formed double hydrogen bonds with both imines and naphthols to promote this reaction. In 2021, Wang and coworkers developed a phosphonium salt **C27** catalyzed enantioselective hydrophosphonylation of seven-membered cyclic *N*-sulfonylimines **111** (**Scheme 24c**).[60] Using chiral phosphonium salt **C27** as phase transfer catalyst, a series of axially chiral phosphorus-containing ε-sultams **113** were obtained in high yields with excellent enantioselectivities. In addition, the mild reaction conditions, low catalyst loading, and scaled-up reactions demonstrated the utility of this protocol.



Scheme 24. Atroposelective synthesis of bridged biaryls with C-stereogenic centers through asymmetric functionalization of cyclic *N*-sulfonylimines.

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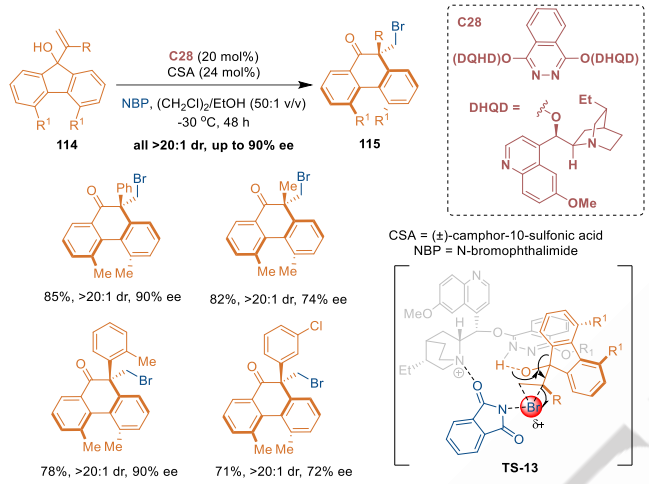
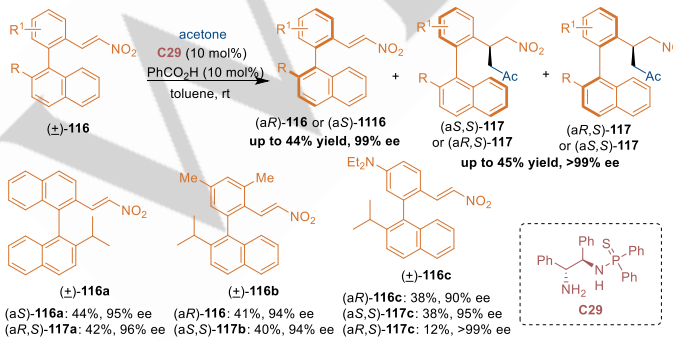
2.2.2. Other Biaryl Atropisomers with C-Stereogenic Centers

The construction of axially chiral six-membered bridged biaryls is more challenging than medium-sized bridged biaryls for the lower configurational stability, and usually requires two *ortho*-substituents.[8] in 2017, Yeung and coworkers developed an organocatalytic dynamic kinetic resolution-semipinacol rearrangement to access axially chiral six-membered bridged biaryls **115** (**Scheme 25**).[61] Using $(DHQD)_2PHAL$ **C28** as the organocatalyst, *N*-bromophthalimide (NBP) as halogen sources, (±)-camphor-10-sulfonic acid (CSA) as an additive, the dynamic kinetic resolution of **114** introduced an axial chirality together with a quaternary stereocenter with excellent diastereo- and enantioselectivities.



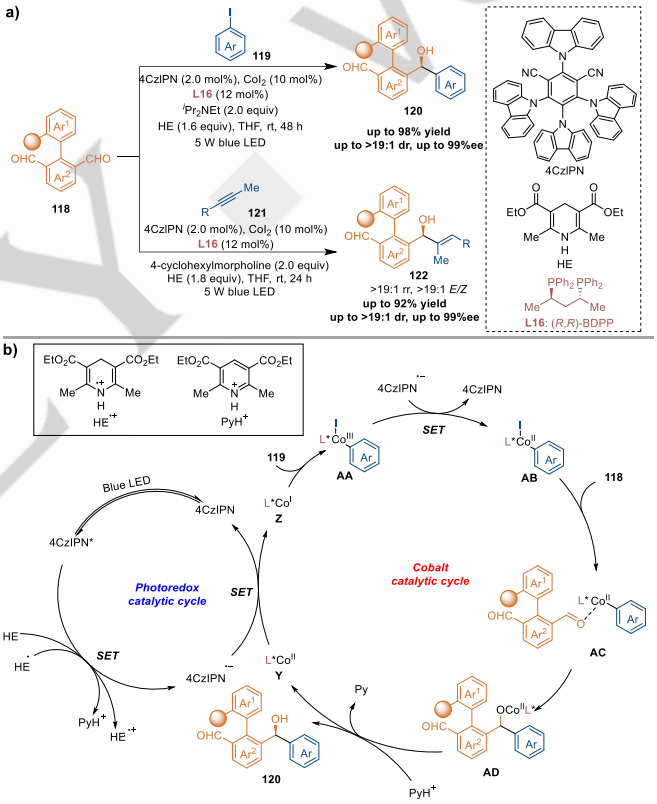
Scheme 25. Atroposelective synthesis of biaryls with C-stereogenic centers via organocatalytic DKR-semipinacol rearrangement.

In 2019, Li, Zhou, and coworkers established a kinetic resolution of axially chiral 2-nitrovinyl biaryls via bifunctional thiophosphinamide **C29** catalyzed Michael addition of acetone to racemic 2-nitrovinyl biaryls **116** (**Scheme 26**).[62] By this protocol, products **117** bearing both central and axial chirality and the recovered axially chiral 2-nitrovinyl biaryls **116** could be obtained with high enantioselectivities.



Scheme 26. Atroposelective synthesis of biaryls with C-stereogenic centers via KR of 2-nitrovinyl biaryls.

Recently, merging photoredox catalysis with transition-metal catalysis, termed metallaphotoredox catalysis by MacMillan and coworkers has become a popular strategy for expanding the synthetic utility of visible-light photocatalysis and provides a potential solution to stereoselective control of photochemistry.[63] Using this strategy, Xiao, Cheng and coworkers described a Co/photoredox cocatalyzed asymmetric reductive coupling of prochiral biaryl dialdehydes **118** with aryl iodides **119** or alkynes **121** (**Scheme 27a**).[64] Through this desymmerization strategy, a series of axially and centrally chiral alcohols **120** and **122** could be obtained in good yields with excellent diastereo- and enantioselectivities. In the proposed mechanism (**Scheme 27b**), the reductive quenching process of the photoexcited 4CzIPN* by Hantzsch ester (HE) led to $4CzIPN^{\bullet-}$, which produced Co(II) complex **Y** to the low-valent Co(I) species **Z**. Then, oxidative addition of aryl iodides **119** to Co(I) species **Z** generated aryl Co(III) **AA**. The single-electron reduction of **AA** by $4CzIPN^{\bullet-}$ afforded aryl Co(II) **AB**, which underwent a Grignard-type addition to aldehydes **118** and followed by protonation, thus delivering products **120** and regenerating the Co(II) species **Y**.



Scheme 27. a) Synthesis of biaryls with C-stereogenic centers via photoredox/Co cocatalyzed desymmetrization of prochiral biaryl dialdehydes. b) Proposed reaction mechanism.

Nearly at the same time, Qian, Liao, and coworkers developed an Ag/**L**-catalyzed desymmetric (3 + 2) cycloaddition of prochiral biaryl dialdehydes **1** with activated isocyanides **2** to access a series of biaryl aldehydes **3** bearing a stereogenic C–C axis and two adjacent stereogenic carbon centers (**Scheme 28**).[65]

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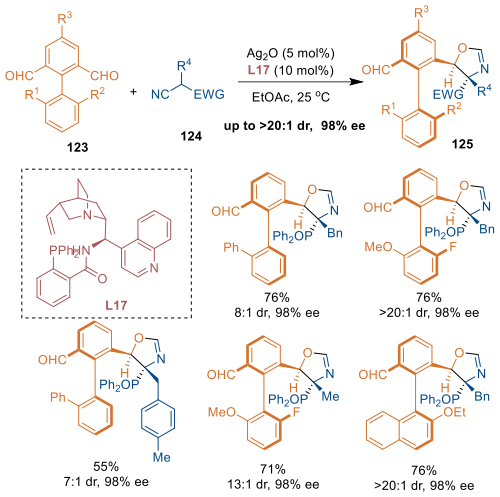
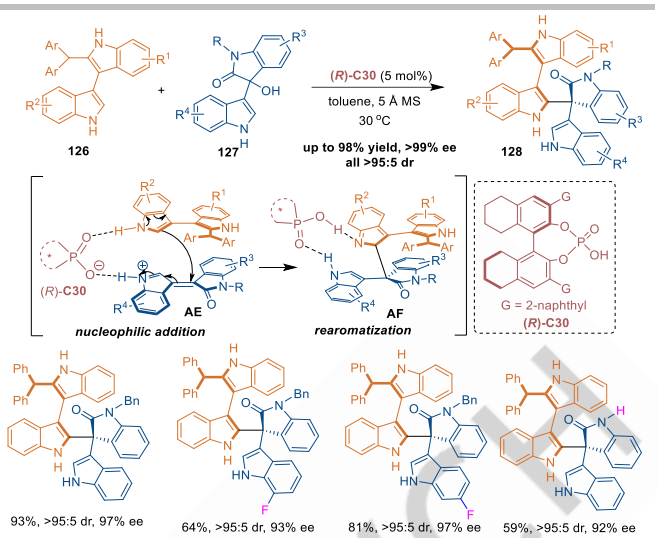


Scheme 28. Atroposelective synthesis of biaryls bearing both axial and central chirality via desymmetric (3 + 2) cycloaddition.

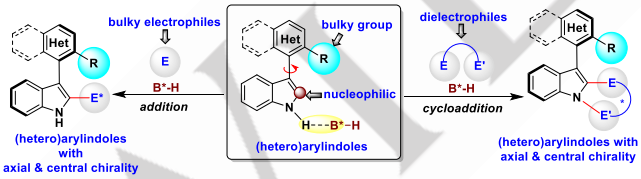


Scheme 30. Synthesis of 3,3'-bisindoles bearing axial and central chirality.

2.3. Heteroaryl Atropisomers with C-Stereogenic Center

2.3.1. Organocatalytic Asymmetric Approaches

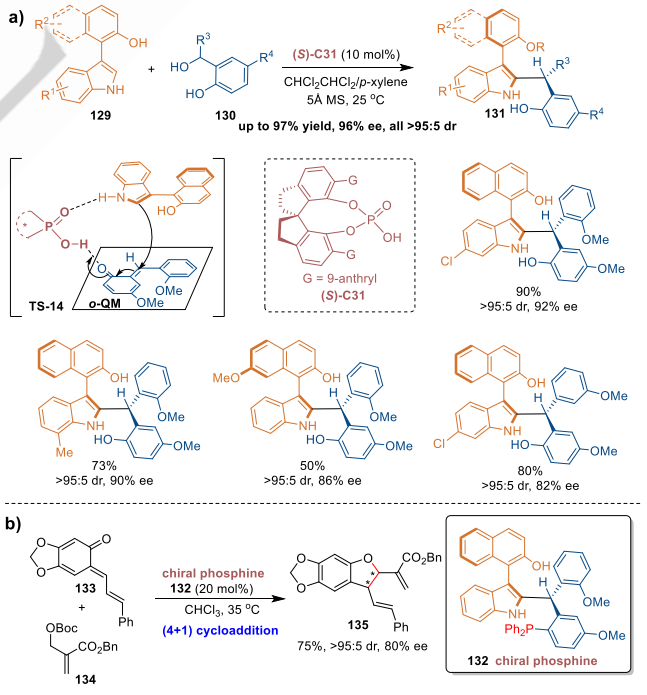
In recent years, the catalytic asymmetric synthesis of heteroaryl atropisomers has garnered a considerable interest from the chemical science community.[9,66] In particular, the catalytic asymmetric construction of axially chiral indole-based scaffolds has become an emerging field.[9,67] Consequently, the catalytic asymmetric synthesis of indole-based atropisomers with multiple chiral elements has become an important target. To achieve this target, Shi's group designed (hetero)arylindoles as platform molecules,[68] which have unique features, such as possessing bulky group, nucleophilic and activation sites (**Scheme 29**), thus exhibiting the capability of undergoing addition and cycloaddition reactions via the DKR process under the catalysis of the chiral Brønsted acid (B*-H).



Scheme 29. Design of (hetero)arylindoles as platform molecules for the synthesis indole-based atropisomers with multiple chiral elements.

Based on this strategy, in 2019, Shi's group applied 3,3'-bisindoles **126** as platform molecules in the addition reaction with 3-indolylmethanols **127** as bulky electrophiles in the presence of CPA (*R*)-**C8**,[69] affording axially chiral 3,3'-bisindoles **128** bearing a quaternary stereogenic center (**Scheme 30**). In the proposed reaction pathway, under the activation of (*R*)-**C8**, 3,3'-bisindoles **126** reacted with vinyliminium intermediates **AE** via nucleophilic addition and rearomatization to produce products **128**. This study demonstrates the first highly atroposelective synthesis of axially chiral 3,3'-bisindoles.

Later, the same group applied the DKR strategy for the synthesis of 3-arylindole atropisomers **131** with a C-stereogenic center using 3-arylindoles **129** as platform molecules and *o*-hydroxybenzyl alcohols **130** as bulky electrophiles via the formation of *o*-QM intermediates (**Scheme 31a**).[70] More importantly, this class of 3-arylindoles bearing multiple chiral elements could be transformed into chiral phosphines **132** (**Scheme 31b**), which exhibited promising catalytic activity in the (4 + 1) cycloaddition of *o*-QM **133** with Morita−Baylis−Hillman (MBH) carbonate **134**.



Scheme 31. a) Synthesis of 3-arylindoles bearing axial and central chirality. b) The application of axially chiral 3-arylindole-based organocatalyst in asymmetric catalysis.

In the aforementioned two approaches, alcohols such as 3-indolylmethanols **127** and *o*-hydroxybenzyl alcohols **130** were used as bulky electrophiles. Moreover, imines can serve as bulky

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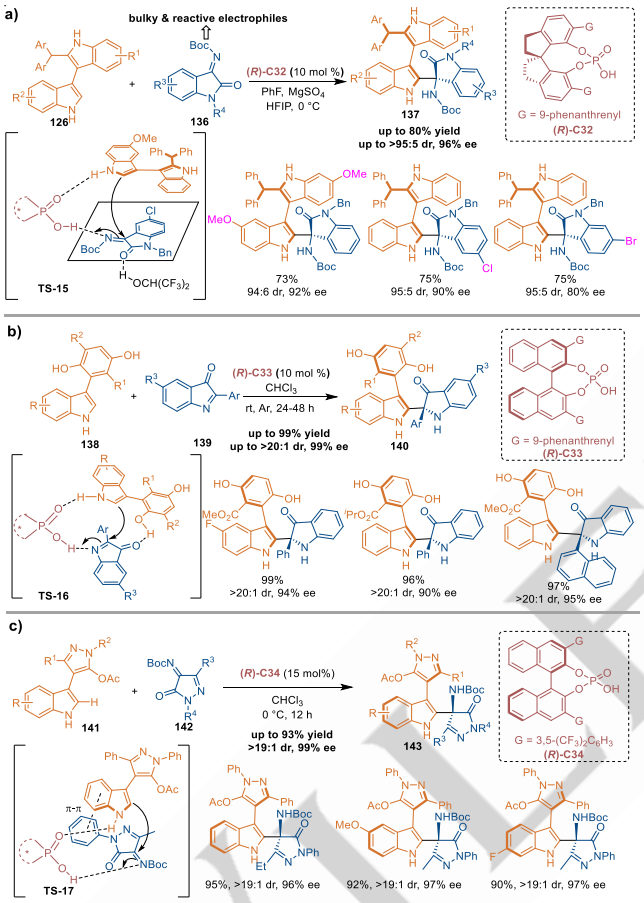
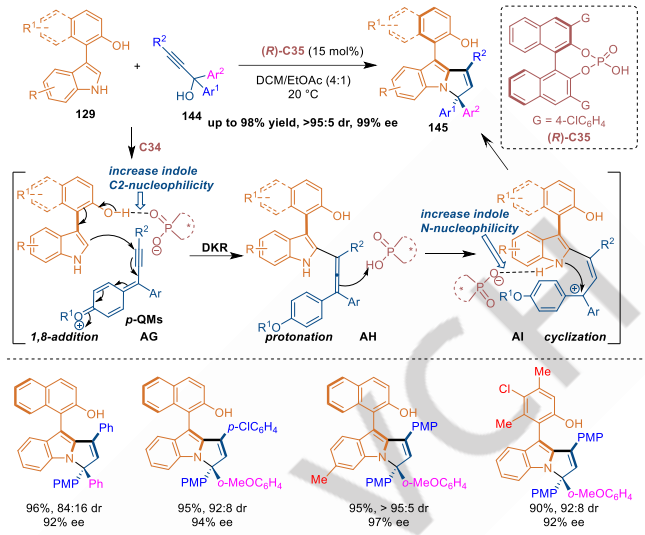
electrophiles in addition reactions with (hetero)arylindoles platform molecules. For example, in 2020, Shi's group employed isatin-derived imines **136** in the synthesis of axially chiral 3,3'-bisindoles **137** bearing a quaternary stereogenic center (**Scheme 32a**).[71] Fu and coworkers used 2-aryl-3*H*-indol-3-ones **139** as electrophiles to synthesize 3-arylindole atropisomers **140** with a C-stereogenic center (**Scheme 32b**).[72] Additionally, Zhan, Huang, and coworkers designed 3,4'-indole-pyrazolyl acetate **141** as heteroarylindoles to undergo an asymmetric Mannich reaction with imine **142**, affording 3-pyrazolyl indoles **143** with axial and central chirality (**Scheme 32c**).[73]



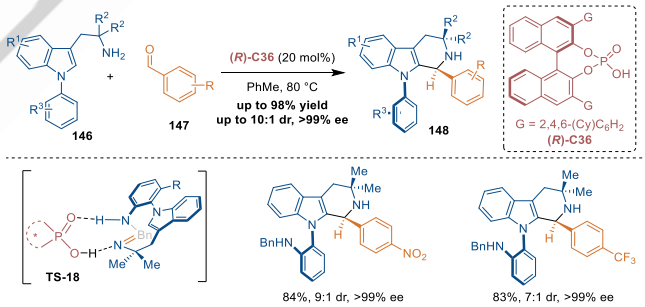
Scheme 32. Synthesis of (hetero)arylindoles bearing axial and central chirality using imines as electrophiles.

Besides addition reactions, (hetero)arylindoles can undergo cycloadditions using the C2 and NH nucleophilicity of the indole ring, thereby deriving another strategy for the synthesis of (hetero)arylindoles bearing axial and central chirality. A recent example was established by Shi's group, who designed CPA-catalyzed asymmetric (2 + 3) cycloadditions of 3-arylindoles **129** with propargylic alcohols **144** as 1,3-dielectrophiles for constructing axially chiral aryl-pyrroloindole scaffolds **145** (**Scheme 33**).[74] Moreover, when racemic propargylic alcohols **144** possess different Ar^1 and Ar^2 groups, axially chiral aryl-pyrroloindoles **145** bearing a quaternary stereogenic center were obtained in excellent diastereo- and atroposelectivities. DFT calculations supported a DKR process for this reaction, wherein an enantioselective 1,8-addition between **129** and *p*-QM intermediates *in situ* generated from **144** was the key step. Later, the same group[75] and Li's group[76] applied this strategy to synthesize other aryl-pyrroloindole derivatives bearing axial and central chirality using isoindolinone-based propargylic alcohols as 1,3-dielectrophiles.



Scheme 33. Synthesis of aryl-pyrroloindoles with axial and central chirality.

In addition to 3-(hetero)arylindoles, *N*-arylindoles can be used as competent substrates for the synthesis of indole derivatives with axial and central chirality. In 2021, Kwon and coworkers developed a DKR reaction of *N*-arylindoles **146** via a CPA **C36**-catalyzed Pictet–Spengler reaction (**Scheme 34**).[77] When aromatic aldehydes **147** were used, a C-stereogenic center was installed in the axially chiral *N*-arylindole scaffolds **148** with a moderate diastereoselectivity.



Scheme 34. Synthesis of *N*-arylindole atropisomers with C-stereogenic centers.

The combination of asymmetric organocatalysis with photoredox catalysis has proven to be a powerful tool for constructing enantioenriched scaffolds under mild and environmentally benign conditions.[78] Recently, Xiao's group used this synergistic catalytic strategy for the synthesis of 5-arylpyrimidine atropisomers with C-stereogenic centers (**Scheme 13**).[79] Based on photoredox and the CPA co-catalyzed asymmetric Minisci reaction of 5-arylpyrimidines **149**, 5-arylpyrimidines **151** bearing axial and central chirality were generated in excellent diastereo- and enantioselectivities. In the suggested reaction mechanism, the key transition state involved a regio- and enantioselective addition of pyrimidine with a radical intermediate under the activation of CPA via hydrogen bonds. Most approaches for the catalytic asymmetric synthesis of atropisomers were based on ionic protocols, whereas radical-

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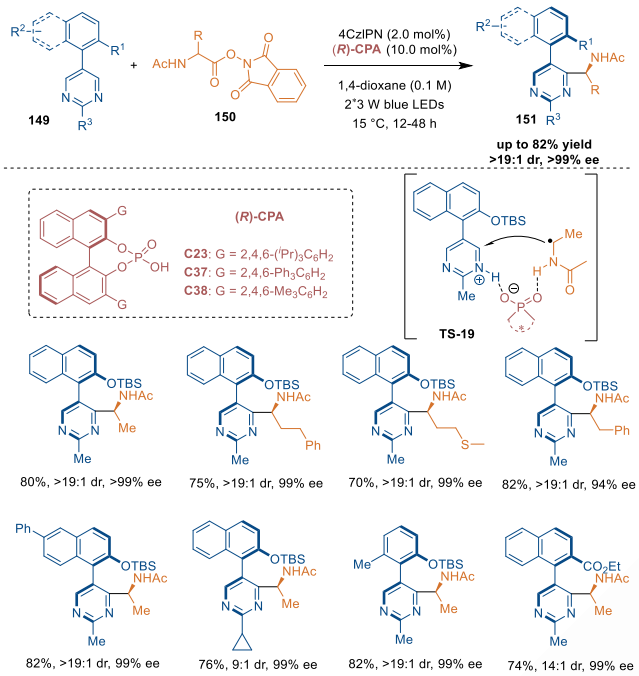
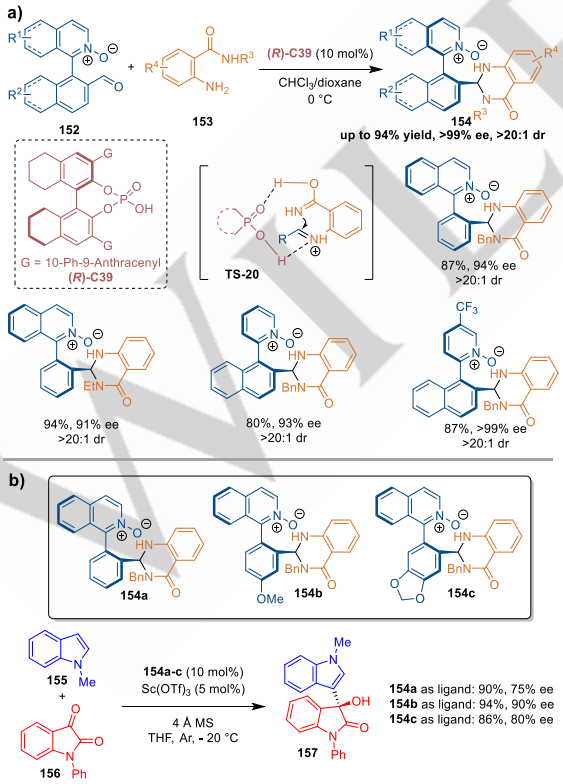
based protocols were hardly reported. Thus, this study proposed an intriguing and highly valuable strategy for synthesizing enantioeniched atropisomers, which opened a new avenue for catalytic asymmetric synthesizing atropisomers bearing multiple chiral elements.



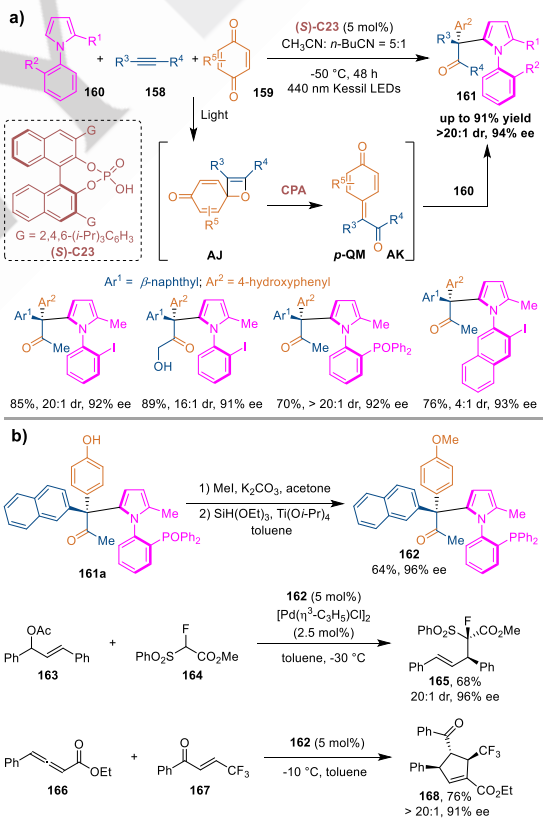
Scheme 35. Synthesis of 5-arylpyrimidine atropisomers with C-stereogenic centers.



Scheme 36. a) Synthesis of heterobiaryl *N*-oxides bearing axial and central chirality. b) The applications of chiral heterobiaryl *N*-oxides.

Very recently, Wang's group accomplished the synthesis of axially chiral heterobiaryl *N*-oxides **154** bearing a C-stereogenic center via the CPA (*R*)-**C39**-catalyzed annulation reaction of heterobiaryl aldehydes **152** with aminobenzamides **153** via the DKR process (**Scheme 36a**).[80] Axially chiral heterobiaryl *N*-oxides **154a–c** could be applied as chiral ligands to the Lewis-acid-catalyzed 1,2-addition of indoles **155** to isatins **156**, which demonstrated the practical utility of this kind of heterobiaryl *N*-oxides (**Scheme 36b**).

Very recently, Lu and coworkers developed a light-induced CPA-catalyzed one-pot, three-component oxo-diarylation reaction (**Scheme 37a**).[81] Using readily available unactivated alkynes **158** as substrates, a range of C−N axially chiral arylpyrroles **161** featuring an all-carbon quaternary stereogenic center were prepared with excellent diastereo- and enantioselectivities. Mechanistic studies suggested that the key steps of the reaction includeed the formation of spiro-oxetene intermediate **AJ** via light-induced regioselective Paternò-Büchi (2 + 2) reaction, ring-opening of oxetane to form *p*-quinone methide (*p*-QM) intermediate **AK**, followed by the nucleophilic addition of *N*-arylpyrrole **160** to *p*-QMs (**Scheme xa**). Notably, chiral product **161a** could be efficiently transformed into an axially and centrally chiral phosphine **162**, which was used as an efficient chiral ligand in Pd-catalyzed allylic substitution reaction or chiral phosphine catalyst for asymmetric (3 + 2) annulation.



Scheme 37. a) Synthesis of axially chiral *N*-arylpyrroles with a C-stereogenic center. b) The applications of chiral *N*-arylpyrroles.

In addition to the catalytic asymmetric transformations of hetero-biaryls, the heteroarene formation is also a robust strategy for the synthesis of heteroaryl atropisomers with multiple chiral elements. In 2019, Zhao and coworkers described NHC **C39**

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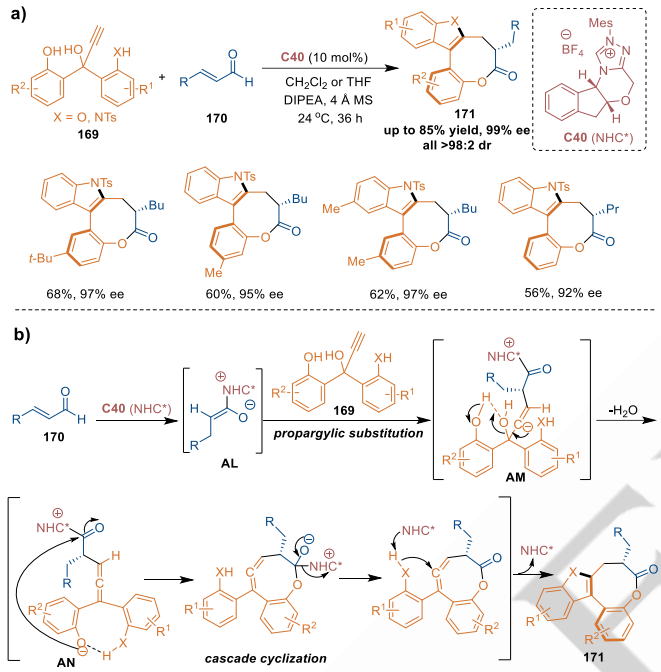
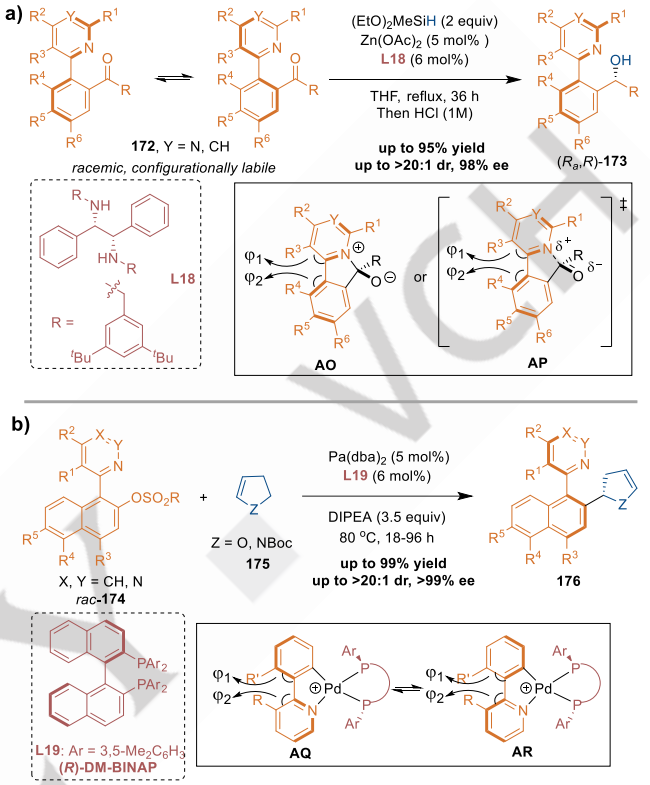
catalyzed asymmetric aromatizations for the construction of benzofuran/indole-derived bridged biaryls bearing an eight-membered lactone **171** (**Scheme 38a**).[82] Notably, these novel scaffolds containing both axial and central chirality could be generated with excellent diastereoselectivities. Based on the DFT calculations, a plausible mechanism is proposed (**Scheme 38b**). The in-situ generated azolium enolates **AL** underwent an enantioselective propargylic substitution to form intermediates **AM**. Then, a facile dehydration of **AM** generated allene intermediates **AN**, which proceeded an intramolecular acylation followed by an NHC-promoted intramolecular nucleophilic addition to give the final bridged biaryl products **171**.



Scheme 38. a) Construction of benzofuran/indole-derived bridged biaryls bearing both axial and central chirality. b) Proposed reaction mechanism.

2.3.2. Metal-Catalyzed Asymmetric Approaches

As a complementary method of asymmetric organocatalysis, asymmetric metal catalysis also showed its power in the synthesis of heterobiaryls bearing axial and central chirality. In 2018, Lassaletta and coworkers realized the synthesis of heterobiaryls **173** based on the Zn-catalyzed asymmetric hydrosilylation of heterobiaryl ketones **172** via a DKR process (**Scheme 39a**).[83] This DKR process relies on a weak Lewis acid−base interaction between the heterocyclic N atom and ketone carbonyl group, which can widen the angles φ_1 and φ_2 in five-membered cyclic intermediates **AO** or **AP**. This class of heterobiaryls **173** could be used as precursors for chiral ligands and organocatalysts. Later, the same group developed a Pd-catalyzed asymmetric Heck reaction of heterobiaryl sulfonates **174** by using (*R*)-DM-BINAP **L19** as the ligand, which enabled the coupling with 2,3-dihydrofuran or *N*-Boc protected 2,3-dihydropyrrole **175** to give heterobiaryls **176** bearing axial and central chirality (**Scheme 39b**).[84a] The widening of angles φ_1 and φ_2 in oxidative addition intermediates **AQ** and **AR** resulted in the labilization of the stereogenic axis, which is the key for the DKR process. This study demonstrated the applicability of metal-catalyzed asymmetric arene functionalization in the synthesis of atropisomers with multiple chiral elements. Very recently, they applied DKR strategy in asymmetric synthesis of quinoline-derived atropisomers and indole-based sulfenylated heterobiaryls bearing central and axial chirality.[84b,c]



Scheme 39. Synthesis of heterobiaryls bearing axial and central chirality based on metal-catalyzed functionalization.

The transition-metal-catalyzed asymmetric C–H functionalization of racemic heterobiaryls plays an important role in the synthesis of heterobiaryls bearing axial and central chirality. In 2020, Lassaletta and coworkers developed a direct enantioselective C−H functionalization of heterobiaryls **177** with vinyl ethers **178** or bicycloalkenes **180** using *in situ* formed Ir/**L20** or Ir/**L21** complex as the catalyst, which generated heterobiaryls **61** and **63** with axial and central chirality (**Scheme 40a**).[85] In 2022, Ackermann's group accomplished the Ru-catalyzed C−H activation of *N*-isoquinoline indole **182** with terminal alkenes **183** to produce *N*-heteroarylindoles **184** bearing central and axial chirality (**Scheme 40b**).[86] In the proposed mechanism, the ruthenium complex **AS** was generated by the reaction of $[RuCl_2(p\text{-cymene})]_2$, $AgPF_6$ and **L22**. Then, **AS** and **182a** underwent C−H ruthenation to produce the ruthenium species **AT**. Subsequently, alkene **183a** coordination generates intermediate **AU**, which underwent ligand-assisted migratory insertion to produce intermediate **AV**. Finally, the proto-demetalation of **AV** with **L22** leads to product **184a**. This study demonstrated metal-catalyzed asymmetric C−H functionalization for the synthesis of atropisomers with C-stereogenic centers.

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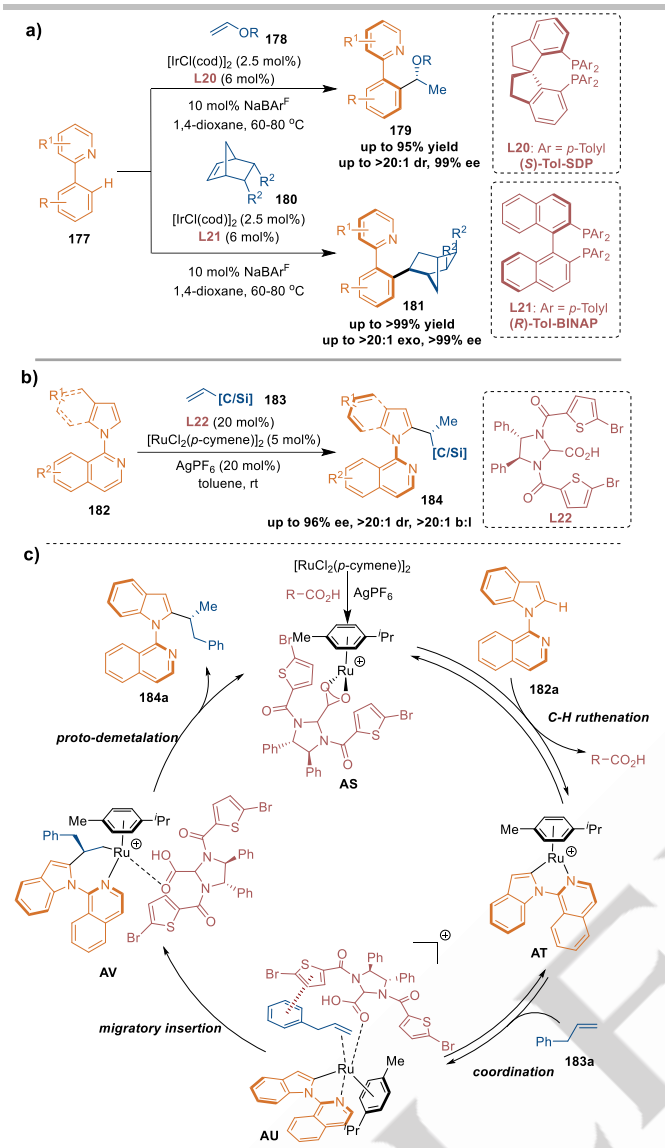
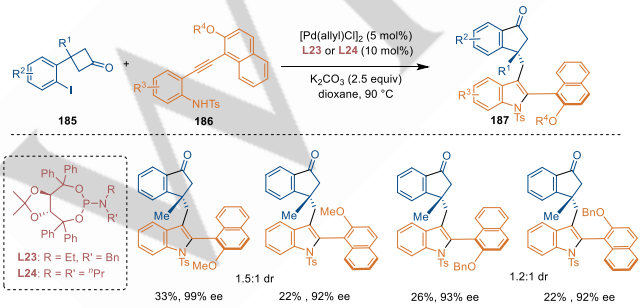


Scheme 40. a,b) Synthesis of heterobiaryls bearing axial and central chirality via metal-catalyzed C−H functionalization. c) Proposed reaction mechanism.



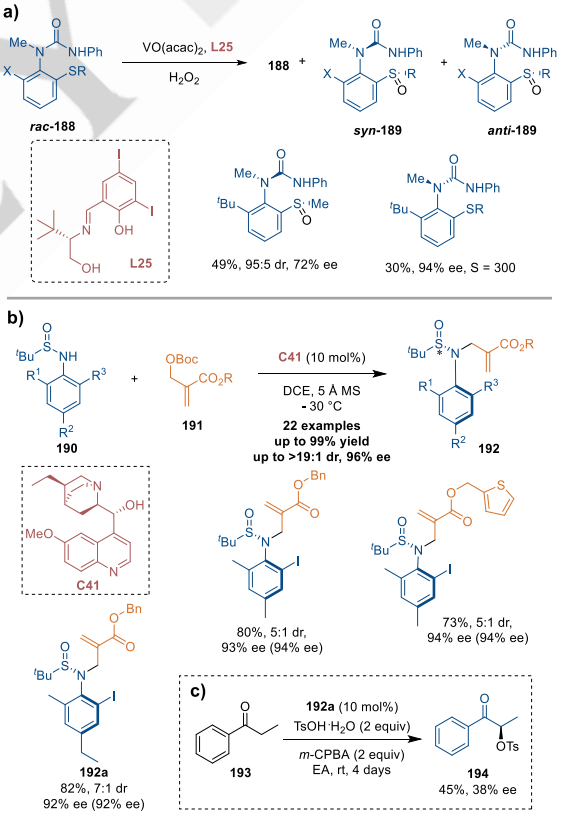
Scheme 41. Synthesis of heterobiaryls with axial and central chirality by metal-catalyzed *de novo* ring formation.

Apart from metal-catalyzed functionalization of preformed racemic heterobiaryls, metal-catalyzed *de novo* ring formation can be applied for synthesizing heterobiaryls with axial and central chirality. For example, in 2021, based on the Cacchi reaction, Xu's group established a Pd-catalyzed cascade reaction between cyclobutanones **185** and *ortho*-ethynylanilines **186**, providing indanone-substituted axially chiral indoles **187** with a C-stereogenic center (**Scheme 41**).[87] This reaction is very efficient because two C−C bonds and one C−N bond were formed with simultaneous generation of one all-carbon quaternary stereogenic center during the reaction pathway.

3. Atropisomers with Heteroatom-Stereogenic Centers

3.1. Atropisomers with S-Stereogenic Centers

An early example of the catalytic asymmetric synthesis of atropisomers with S-stereogenic centers was reported in 2009 by Clayden and coworkers, who used the oxidative KR of sulfanyl ureas *rac*-**188** in the presence of vanadium/**L25**, leading to atropisomeric *N*,*N*′-diaryl urea **189** with a S-stereogenic center (**Scheme 42a**).[88] However, no significant progress has been made in this field until recently. In 2021, Li and coworkers developed a hydroquinine-**C41**-catalyzed asymmetric allylic alkylation reaction of *N*-aryl *tert*-butylsulfinamides **190** with MBH adducts **191** (**Scheme 42b**),[89] enabling the synthesis of axial chiral sulfinamides **192** bearing a S-stereogenic center. In addition, a preliminary application of chiral sulfinamide **192a** as a chiral hypervalent iodine catalyst in the asymmetric α-sulfonyl-oxylation of ketone **193** demonstrated the potential of this kind of sulfinamide scaffold (**Scheme 42c**).



Scheme 42. a,b) Synthesis of atropisomers with S-stereogenic centers. c) The applications of axial chiral sulfinamides in stereoselective synthesis.

A representative work was established in 2022 by Yan's group, who realized the catalytic asymmetric construction of axially chiral *N*,*S*-1,2-azole scaffold bearing a S-stereogenic center (**Scheme 43**).[90] In the presence of organocatalyst **C42** and *N*-bromophthalimide (NBP), a modified VQM precursor *rac*-**195** underwent a KR process to produce axially chiral naphthyl-isothiazole *S*-oxides **196** and recover chiral sulfinamides **195** with

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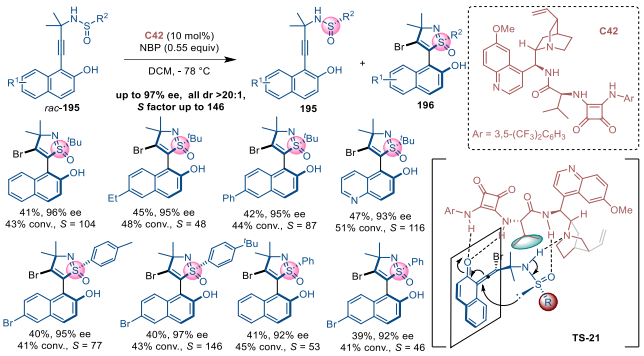
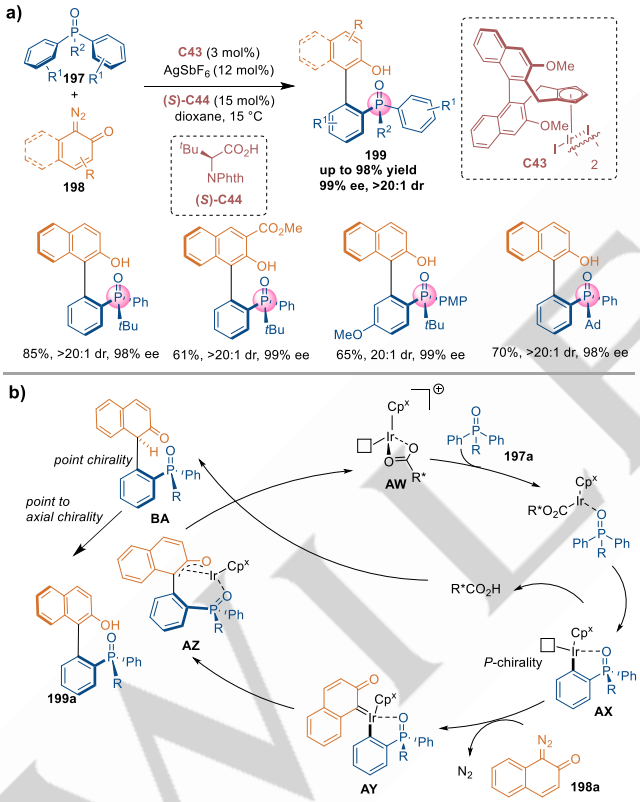
high *S* factors. Notably, this work simultaneously controlled the atroposelective installation of a stereogenic axis and the formation of a chiral heterocyclic ring.



Scheme 43. Synthesis of axially chiral *N*,*S*-1,2-azoles bearing a S-stereogenic center.

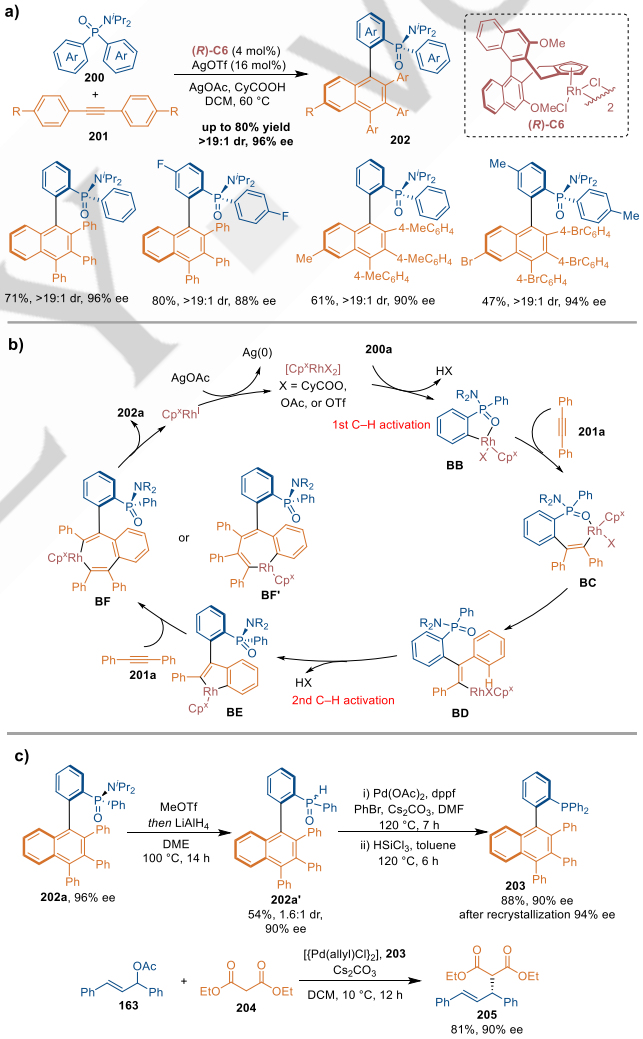
3.2. Atropisomers with P-Stereogenic Centers



Scheme 44. a) Synthesis of biaryl atropisomers with P-stereogenic centers via Ir(III)-catalyzed C–H arylation. b) Proposed reaction mechanism.

The catalytic enantioselective synthesis of atropisomers with P-stereogenic centers has not been reported until recently. In 2018, Cramer's group accomplished chiral Ir(III) complex **C43** and phthaloyl tertleucine **C44** co-catalyzed enantioselective C–H arylation of phosphine oxides **197** with *o*-quinone diazides **198**, allowing the synthesis of biaryl-based phosphine oxides **199** bearing axial and P-chirality (**Scheme 44a**).[91] In the possible reaction pathway (**Scheme 44b**), intermediate **AX** bearing a P-chirality was generated from the desymmetrization of prochiral **197a** via enantioselective *ortho*-directed C-H activation. Then, **AX** trapped *o*-quinone diazide **198a** to form intermediate **BA**, which underwent aromatization to produce product **199a**. The enantiospecific reduction of products **199** resulted in monodentate chiral phosphines, which could be used as ligands in asymmetric catalysis.

In 2021, Li's group reported a stereoselective Rh(III)-catalyzed cascade reaction based on two C–H functionalization events with diarylacetylenes for the synthesis of biaryls **202** bearing P-chirality and axial chirality (**Scheme 45a**).[92] The suggested reaction pathway (**Scheme 45b**) involved the formation of rhodacyclic intermediates **BB** to **BE** and the second alkyne insertion into **BE** to produce **BF** or **BF'**, which underwent C–C reductive elimination to release product **202a**. The product could be transformed into chiral phosphorus ligand **203**, which was applied to Pd-catalyzed asymmetric allylic alkylation (**Scheme 45c**). Moreover, Duan and coworkers reported a related transformation catalyzed by Cp*Ir to access axially chiral phosphine oxides with P-stereogenic centers.[93]



Scheme 45. a) Synthesis of biaryl atropisomers with P-stereogenic centers via Rh(III) catalyzed C–H functionalization cascade. b) Proposed reaction mechanism. c) Product transformations and applications

In 2022, Li's group realized the catalytic asymmetric synthesis of *N*-alkenylindole atropisomers via the Pd-catalyzed asymmetric hydrophosphination of internal alkynes **206** with nonsymmetric secondary phosphines **207** (**Scheme 22**).[94] When **L26** was used as the chiral ligand, axially chiral *N*-alkenylindoles **208** bearing a P-stereogenic center were synthesized in high

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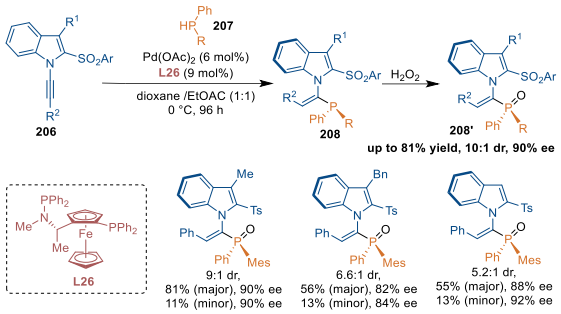
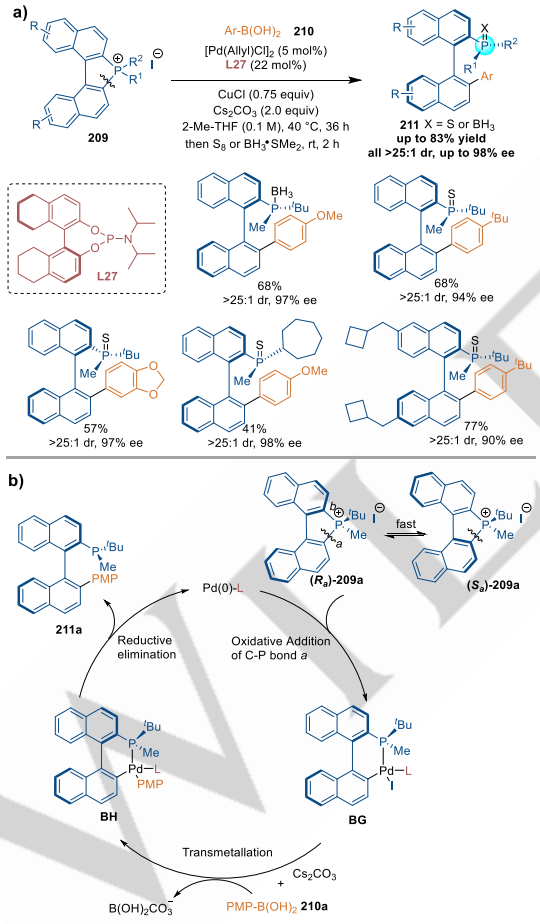
diastereo- and enantioselectivities. This study demonstrated the first case of synthesizing axially chiral alkenylindoles with multiple chiral elements, which possess potential applications in asymmetric catalysis as chiral ligands due to the existence of alkenyl and phosphine functional groups in such structures.



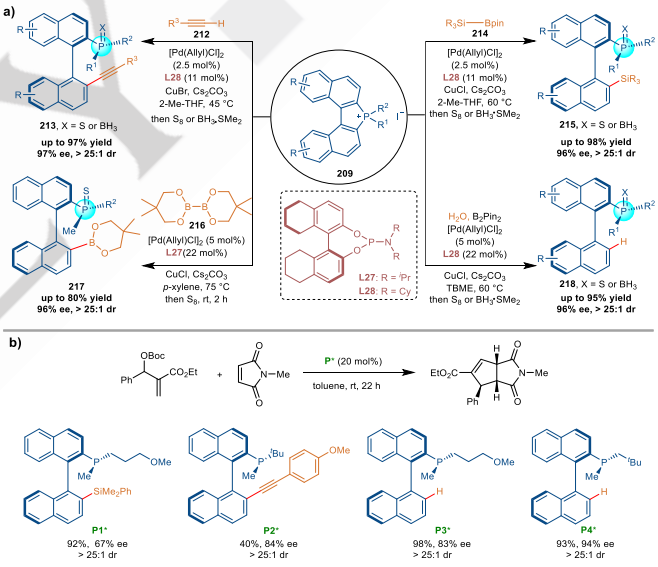
Scheme 46. Synthesis of *N*-alkenylindole atropisomers with P-stereogenic centers.



Scheme 47. a) Synthesis of biaryl atropisomers containing a P-stereogenic center via the Pd-catalyzed activation of the C–P bond. b) Proposed reaction mechanism.

Recently, Li, Yu, and coworkers used the Pd-catalyzed stereoselective cleavage of the C–P bond to synthesize biaryl atropisomers **211** containing a P-stereogenic center (**Scheme 47a**).[95] This protocol enabled the creation of a P-stereogenic center and stereogenic axis in one step with excellent diastereo- and enantioselectivities. In the proposed mechanism (**Scheme 47b**), the oxidative addition of Pd(0) to phosphonium salts **209** led to the C–P bond cleavage and formation of chiral biaryl intermediate **BG**. Then, **BG** underwent transmetalation with aryl boronic acid **210a** to generate Pd(II) intermediate **BH**, which underwent reductive elimination to afford product **211a**. This study demonstrated the application of torsional-strain-promoted ring-opening reactions[4b] in catalytic asymmetric synthesis of atropisomers containing P-stereogenic centers.

In their following studies, the same group extended their protocol to the catalytic asymmetric synthesis of other biaryl atropisomers containing a P-stereogenic center with a range of coupling partners, such as alkynes **212**, R_3Si-Bpin **214**, diboron esters **216**, and hydride source (H_2O/B_2pin_2), affording various enantioenriched structurally diverse chiral monodentate biaryl phosphines with excellent diastereo- and enantioselectivities (**Scheme 48a**).[96] These chiral monodentate biaryl phosphines could be directly used as chiral catalysts in asymmetric (3 + 2) annulation of MBH carbonate with *N*-methylmaleimide to give chiral functionalized bicyclic imide with excellent diastereo- and enantioselectivities. These results indicated the great potential of this class of chiral biaryl phosphines in the development of valuable chiral ligands and organocatalysts (**Scheme 48b**).



Scheme 48. a) Synthesis of biaryl atropisomers containing a P-stereogenic center and their application in asymmetric catalysis. b) The applications of chiral biaryl phosphines.

3.3. Atropisomers with Si-Stereogenic Centers

The catalytic asymmetric synthesis of atropisomers with Si-stereogenic centers has scarcely been reported until recently. In 2021, as a continuation of their efforts in synthesizing biaryl atropisomers via the strategy of torsional-strain-promoted ring-opening reactions,[4b] Gu's group realized the synthesis of axially chiral binaphthyl silanols **221** with a Si-stereogenic center via the asymmetric ring opening/acylation of silafluorenes **219** in the presence of Rh/**L29** (**Scheme 49a**).[97] In the suggested mechanism (**Scheme 49b**), the oxidative addition of Rh catalyst **BI** to **219** cleaved the Si–C bond and resulted in rhodacycle **BJ**,

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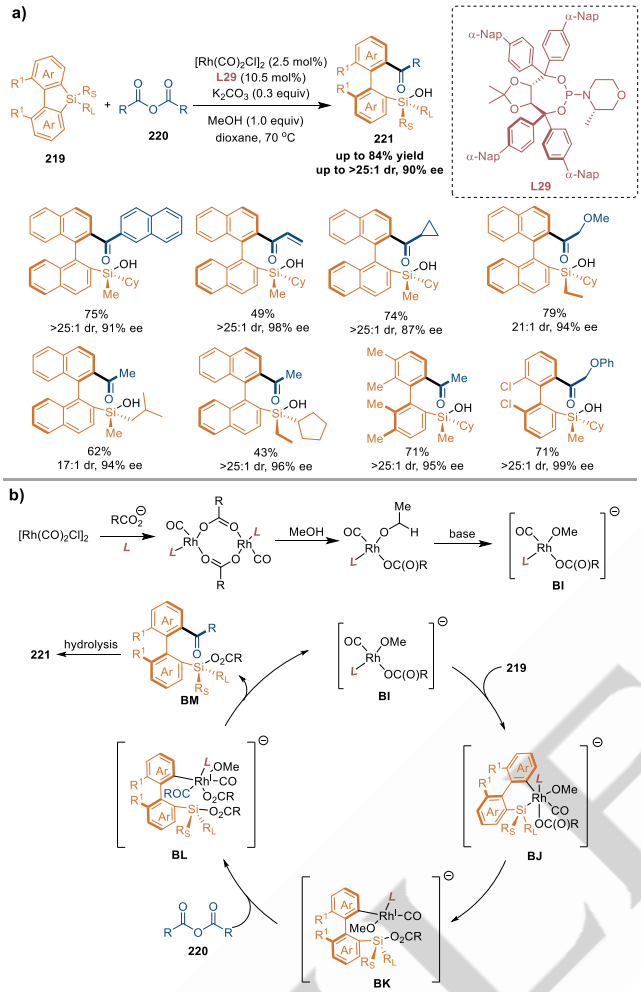
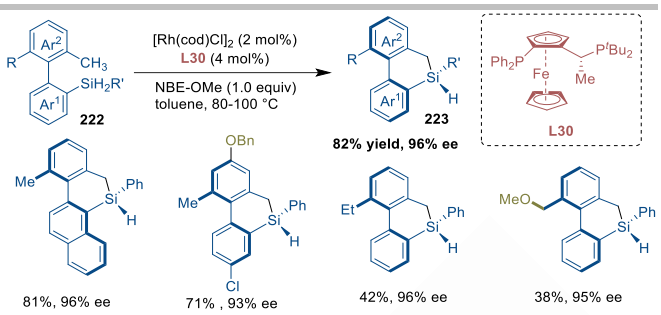
which underwent reductive elimination to generate complex **BK**. Then, the second oxidative addition of **BK** to acid anhydride **220**, followed by reductive elimination and hydrolysis led to the final product **221**. This study provided a useful strategy for the catalytic asymmetric synthesis of atropisomers containing Si-stereogenic centers.



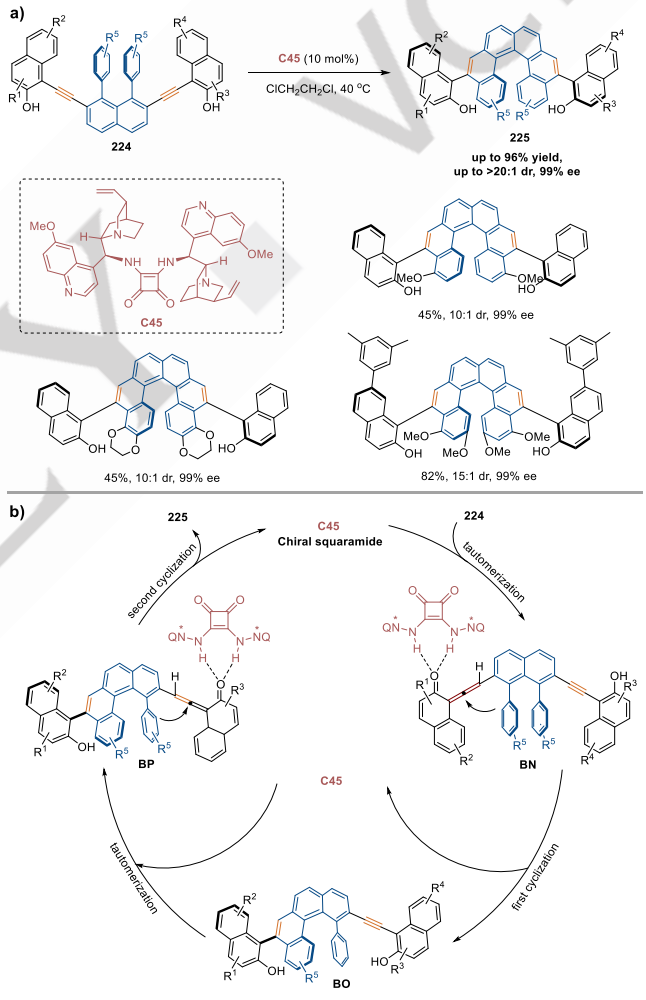
Scheme 49. a) Synthesis of atropisomers with Si-stereogenic centers via the Rh-catalyzed ring opening of silafluorenes. b) Proposed reaction mechanism.

Meanwhile, He and coworkers developed enantioselective Rh-catalyzed enantioselective intramolecular dehydrogenative C(sp^3)-H silylation of **222** for the synthesis of axially chiral six member–bridged biaryls **223** with a Si-stereogenic center (**Scheme 50**).[98] Moreover, a novel silicon central-to-axial chirality relay phenomenon was discovered, and the longer C–Si bond and larger atomic radius of Si resulted in the configurational stability of biaryl atropisomers. This study provided a unique class of six-member-bridged biaryl atropisomers bearing a Si-stereogenic center, which might find their applications in chiroptical materials.



Scheme 50. Synthesis of atropisomers with Si-stereogenic centers via Rh-catalyzed intramolecular dehydrogenative C(sp^3)–H silylation.

4. Atropisomers with Other Chiral Elements



Scheme 51. a) Synthesis of atropisomers with helical chirality. b) Proposed reaction mechanism.

In addition to atropisomers with carbon- or heteroatom-stereogenic centers, atropisomers bearing other chiral elements, such as helical chirality and planar chirality, have recently been synthesized via asymmetric catalysis. The catalytic asymmetric synthesis of chiral helicenes is highly desirable but full of challenges.[99] To address this challenging task, in 2019, Yan's group employed the VQM chemistry in the catalytic

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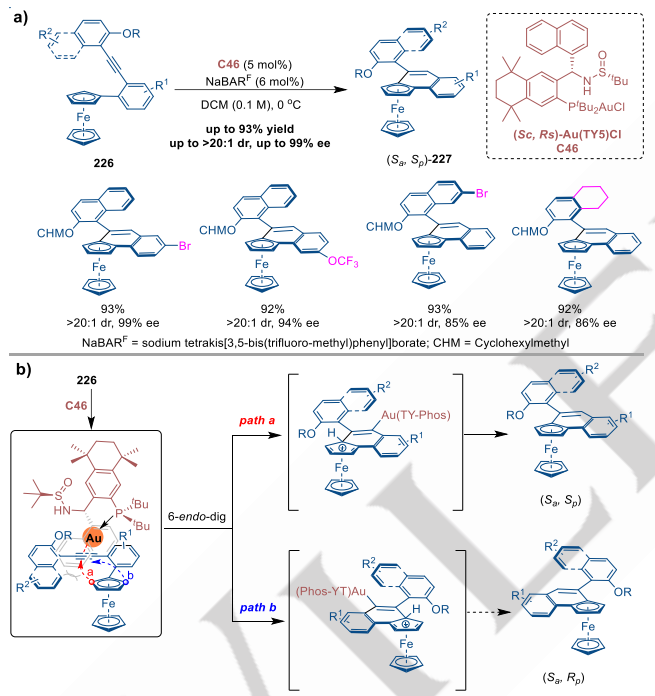
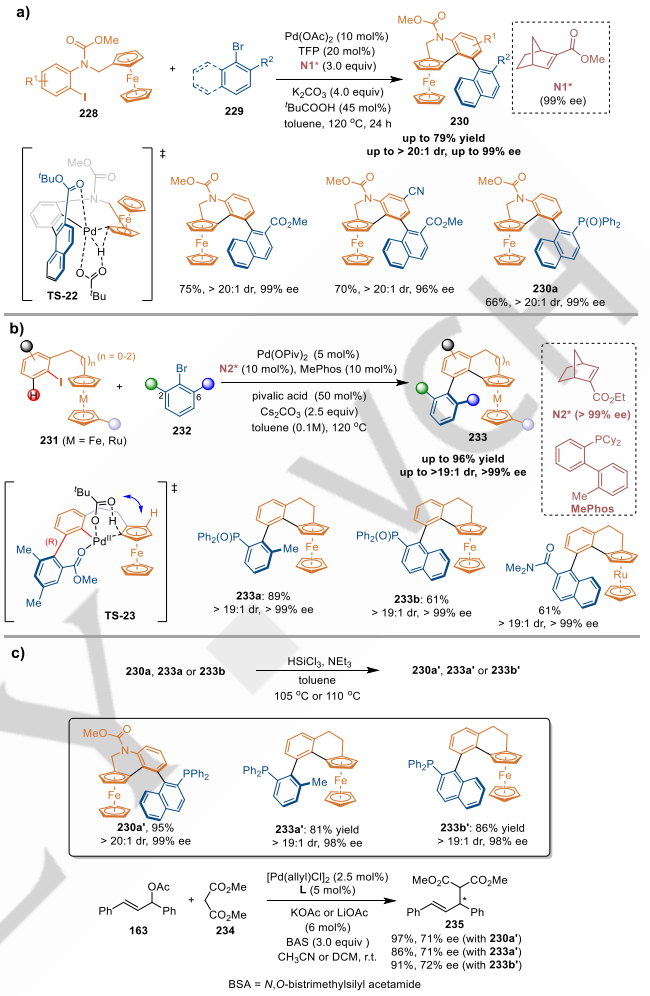
enantioselective synthesis of chiral helicenes **225** containing stereogenic axes (**Scheme 51**).[100] Under the catalysis of the bisquinine squaramide organocatalyst **C22**, the precisely designed substrates **224** facilitated cyclizations twice via VQM intermediates, thus affording products **225** bearing helical and axial stereogenic elements with excellent enantio- and diastereoselectivities. This study represents a rare example of catalytic asymmetric construction of complex scaffolds bearing both helical chirality and axial chirality.

The first catalytic asymmetric synthesis of atropisomers with planar chirality was accomplished in 2021 by Zhang's group, who considered the cationic gold-catalyzed asymmetric intramolecular hydroarylation of *ortho*-alkynylaryl ferrocenes derivatives **226** (**Scheme 52a**).[101] Under the catalysis of the chiral Au catalyst **C46**, the hydroarylation reaction enabled the simultaneous construction of axial and planar chirality with excellent enantio- and diastereoselectivities. A catalytic chirality-induced model was proposed (**Scheme 52b**), wherein the naphthyl group of the ligand shielded the *Re* face of the alkyne and alkoxy groups; therefore, the *Si* face attack of ferrocene resulted in the (S_p)-planar chirality.



Scheme 52. a) Synthesis of atropisomers with planar chirality via Au-catalyzed hydroarylation. b) Proposed reaction mechanism.

In recent years, Pd/norbornene (NBE)-based cooperatively catalyzed Catellani-type reaction has become a valuable multicomponent strategy for the synthesis of polysubstituted arenes.[102] Using this strategy, Liang's group[103] (**Scheme 53a**) and Zhou's group[104] (**Scheme 53b**) independently realized the synthesis of ferrocene derivatives bearing axial and planar chirality. Under Pd/NBE cooperative catalysis, *ortho*-ferrocene-tethered aryl iodides **228** or **231** and aryl bromides **229** or **232** underwent a Catellani reaction, followed by selective C−H functionalization to obtain ferrocenes **230** or **233** bearing axial and planar chirality with excellent enantio- and diastereoselectivities. The reduction of some products led to chiral phosphines **230a'**, **233a'** and **233b'**, which were used as ligands for Pd-catalyzed asymmetric allylic alkylation (**Scheme 53c**), demonstrating the potential applications of these types of scaffolds with multiple chiral elements in asymmetric catalysis.



Scheme 53. a,b) Synthesis of atropisomers with planar chirality via axial-to-planar diastereo-induction. c) The applications of products in asymmetric catalysis.

Yan's group reported the catalytic asymmetric synthesis of atropisomers bearing more than two chiral elements in 2021. They demonstrated organocatalytic intramolecular electrophilic aromatic substitution with an *in situ* generated chiral VQM intermediate (**Scheme 54a**).[105] Under the activation of bifunctional catalysts **C47** via hydrogen-bonding interaction, a chiral azepine skeleton **237** bearing four types of stereogenic elements (C–C, C–N axial chiralties, nitrogen chiral center, and saddle-shaped conformation) was constructed with excellent diastereo- and enantioselectivity. The suggested reaction mechanism (**Scheme 54b**) involved the generation of intermediates **BQ** and a chiral-brominated VQM intermediate **BR**, which underwent intramolecular electrophilic aromatic substitution via **BS** to generate product **237** with multiple chiral elements. This reaction exhibited the power of asymmetric organocatalysis[3a,4c,106] in constructing atropisomeric scaffolds bearing multiple chiral elements.

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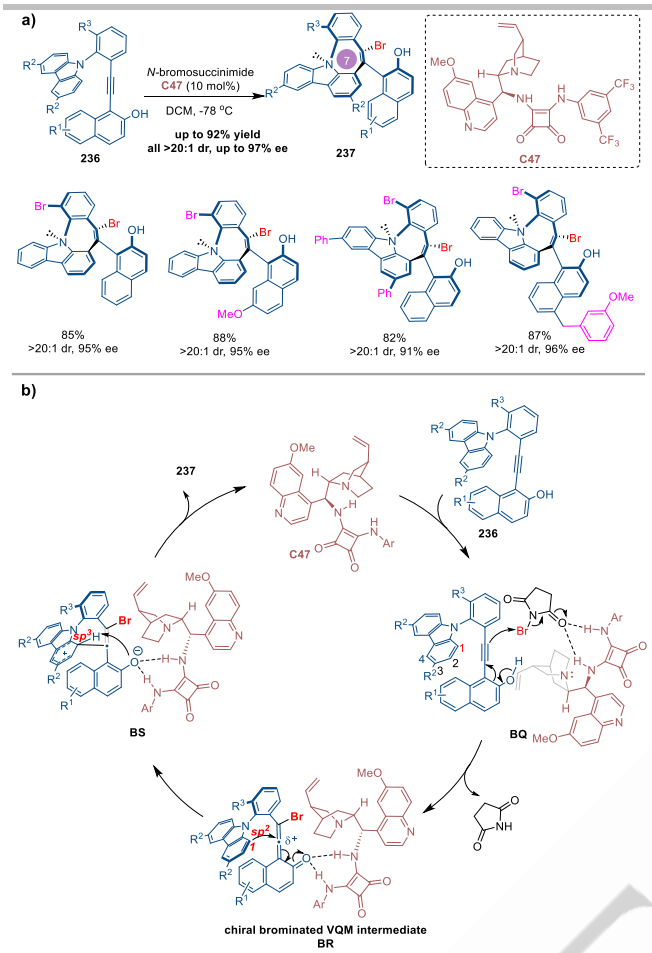

Scheme 54. a) Construction of an azepine skeleton bearing multiple chiral elements. b) Proposed reaction mechanism.

5. Summary and Outlook

In this review, we summarize the rapid advances in the catalytic asymmetric synthesis of atropisomers bearing multiple chiral elements, such as those with C-stereogenic centers, heteroatom-stereogenic centers, helical chirality, planar chirality, and other chiral elements. Evidently, the catalytic asymmetric synthesis of atropisomers bearing multiple chiral elements has become an emerging field. Although rapid developments have been achieved, a few challenging issues still exist in this field. For example, a majority of synthesized atropisomers bear C-stereogenic centers, whereas atropisomers bearing heteroatom-stereogenic center only occupy a small number. Moreover, the catalytic asymmetric synthesis of atropisomers with helical chirality, planar chirality, and other chiral elements is sporadically reported. These outcomes might be ascribed to the difficulty in constructing heteroatom, helical, and planar chirality and controlling the enantioselectivity of these chiral elements. Therefore, there is a considerable demand for developing new strategies (design new substrates and reactions) and robust catalytic modes for synthesizing atropisomers bearing heteroatom-stereogenic centers, helical chirality, planar chirality, and so on. Additionally, the applications of atropisomers bearing multiple chiral elements in asymmetric catalysis, organic synthesis, medicinal chemistry, and materials science are limited. Multiple chiral elements can lead to the introduction of unique properties and improvements in this class of atropisomers, which have potential applications in different areas. Thus, it is highly valuable to perform in-depth investigation of the properties and applications of this class of atropisomers, specifically the interaction among different chiral elements within one molecule. With the persistent efforts of chemists, these challenging issues can be addressed and the emerging field of the catalytic asymmetric synthesis of atropisomers bearing multiple chiral elements will flourish to a new horizon.

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Keywords: asymmetric catalysis • atropisomer • axial chirality • multiple chirality • helical chirality • planar chirality

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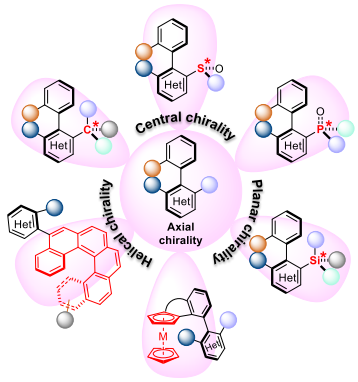

The catalytic asymmetric synthesis of atropisomers bearing multiple chiral elements has recently become an emerging research field. Chemists have devised metal-catalyzed or organocatalytic asymmetric reactions for accessing atropisomers with multiple chiral elements, such as those with center chirality, planar chirality, and helical chirality. This review summarizes the rapid developments in this field and indicated the remaining challenges.