CellPress

Chem Catalysis

Review

Synthesis of axially chiral compounds through catalytic asymmetric reactions of alkynes

Zhi-Xin Zhang,[1] Tong-Yi Zhai,[1] and Long-Wu Ye[1,2,*]

SUMMARY

Axially chiral compounds are a result of the nonplanar arrangement of four groups in pairs about a chirality axis. Axially chiral molecules not only exist in a range of bioactive compounds, but also are widely applied in chiral ligands and catalysts. With these wide-ranging utilities, the construction of axially chiral compounds is attracting more and more interest from chemists. Recent advances in this rapidly expanding field involving the synthesis of axially chiral compounds via catalytic asymmetric reaction of readily available alkynes are introduced in this review, including transition-metal-catalyzed and organocatalytic reactions. A discussion of the reaction scope, mechanistic insights, and synthetic applications of these catalytic asymmetric reactions of alkynes is presented. We hope that this review will provide timely illumination and beneficial guidance for organic chemists who are interested in this area, and we strongly anticipate continued development of the field in the future.

INTRODUCTION

Axially chiral compounds are a result of the nonplanar arrangement of four groups in pairs about a chirality axis (IUPAC).[1] The restricted rotation around a single bond is imperative in the formation of atropisomers. When the energy barrier to rotation is high enough, the atropisomers can be isolated. In 1922. Christie and Kenner discovered the atropisomerism of 2,6,2′,6′-tetrasubstituted biphenyl compounds,[2] which was the first discovery of axial chirality. Except for the classical (hetero)biaryl atropisomers, it has been reported that nonbiaryl compounds such as aryl-substituted amides, anilines, and styrene derivatives may show axial chirality (Scheme 1).[3]

Axial chirality exists in a range of bioactive compounds, such as vancomycin,[4] korupensamine A,[5] mastigophorene,[6] steganacin,[7] and eupoluphagin[8] (Scheme 2). Furthermore, axially chiral molecules are also widely applied in chiral ligands and catalysts (Scheme 3A). One of the most representative ligands is BINAP,[9] which is an axially chiral biphosphoric ligand and is an efficient ligand for transition-metal-catalyzed asymmetric reactions. Nowadays, various chiral reagents with axially chiral scaffolds, such as BINOL[10] and BINOL-derived chiral phosphoric acids (CPAs),[11] are substantially being used in catalytic asymmetric reactions. It is notable that axial chirality also plays a key role in material science (Scheme 3B).

With the wide-ranging utilities of axially chiral compounds, the construction of axially chiral compounds is attracting more and more interest from chemists.[1,12–16] There are three major approaches to synthesizing axially chiral molecules: (1) formation of axial bonds, (2) construction of aryl rings, and (3) functionalization of prochiral or racemic compounds to achieve desymmetrization or kinetic resolution. Alkynes, readily available precursors and known as valuable building blocks for organic

The bigger picture

Axial chirality exists in a wide range of important molecules, such as bioactive compounds, chiral ligands and catalysts, and optically pure materials. The atroposelective synthesis of axially chiral compounds has been well established over the past decades. As an important building block in organic synthesis, alkynes have been more and more widely used in the construction of atropisomers in the past two decades. This review summarizes the advances in the field of catalytic asymmetric synthesis of atropisomers from alkynes by highlighting the reaction scope, mechanistic insights, and synthetic applications. The current challenges and the future directions to accelerate this field to the next level are also provided.

synthesis, can undergo numerous useful transformations such as nucleophilic addition and cycloaddition. The transition-metal-catalyzed reactions of alkynes have been well developed during past decades,[17–24] and organocatalyzed reactions of alkynes have been achieved in recent years.[12,25,26] Despite these achievements involving alkynes, the catalytic asymmetric reactions of alkynes to construct atropisomers had not been reported before 2004. With the development of the synthesis of atropisomers, alkynes are being utilized more and more in atroposelective synthesis due to their unique characteristics.

In this review, we will discuss the progress achieved in the field of synthesis of axially chiral compounds via the catalytic asymmetric reaction of alkynes. This review involving catalytic atroposelective reactions of alkynes is divided into two major parts: (1) progress in transition-metal-catalyzed reactions and (2) progress in organocatalytic reactions.

TRANSITION-METAL-CATALYZED CONSTRUCTION OF AXIALLY CHIRAL COMPOUNDS FROM ALKYNES

Transition-metal-catalyzed reactions, as a powerful approach to numerous compounds, have a history of more than 100 years. Transition-metal-catalyzed construction of atropisomers via cross-coupling, C–H arylation, desymmetrization, and kinetic resolution has been well established. In 2004, the first transition-metal-catalyzed atroposelective synthesis of axially chiral compounds from alkynes was reported by Shibata et al.[27] In this section, we will introduce the transition-metal-catalyzed atroposelective reaction of alkynes since 2004.

[2+2+2] cycloaddition

Transition-metal-catalyzed [2+2+2] cycloaddition[28–30] is considered an efficient strategy for the synthesis of six-membered rings. Compared with other typical methods for the construction of substituted arenes, [2+2+2] cycloadditions are more atom-economic. Various compounds containing unsaturated bonds, such as alkynes, alkenes, and nitriles, have been employed as the substrates of [2+2+2] cycloaddition in the past decades. Of these reactions, [2+2+2] reactions involving alkynes have been well established.[29]

Enantioselective [2+2+2] cycloaddition of alkynes was first reported by Sato, Nishimata, and Mori.[31] They selected nickel(0) as the catalyst to construct isoindolines or isoquinolines bearing a chiral center via catalytic desymmetrization of triynes. Other examples of transition-metal-catalyzed [2+2+2] cycloadditions were reported several years later using nickel(0) or cobalt(0) as the catalyst.

In 2004, transition-metal-catalyzed atroposelective [2+2+2] cycloaddition was first reported by Shibata et al.,[27] and it created a trend in the construction of axially chiral compounds in the subsequent several years. In this section, we will introduce the synthesis of axially chiral compounds via [2+2+2] cycloaddition.

Construction of axially chiral biaryl compounds via [2+2+2] cyclotrimerization of alkynes

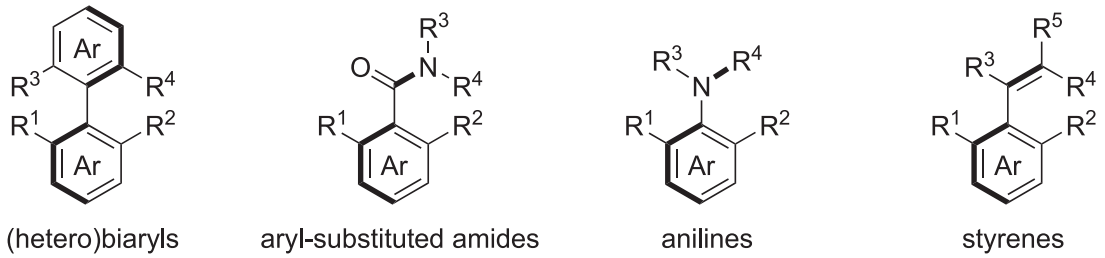
Alkyne [2+2+2] trimerization is a powerful strategy for the construction of phenyl rings,[28–30] but the reactions for the synthesis of axially chiral compounds via alkyne trimerization were not reported until 2004. The first transition-metal-catalyzed construction of axially chiral compounds via asymmetric [2+2+2] cycloaddition was achieved by Shibata and co-workers.[27] As shown in Scheme 4A, the authors employed 1,6-diyne **1** and symmetrical internal alkynes **2** as substrates. They

[1]Key Laboratory of Chemical Biology of Fujian Province, State Key Laboratory of Physical Chemistry of Solid Surfaces, College of Chemistry and Chemical Engineering, Xiamen University, Xiamen 361005, China

[2]State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China

*Correspondence: longwuye@xmu.edu.cn

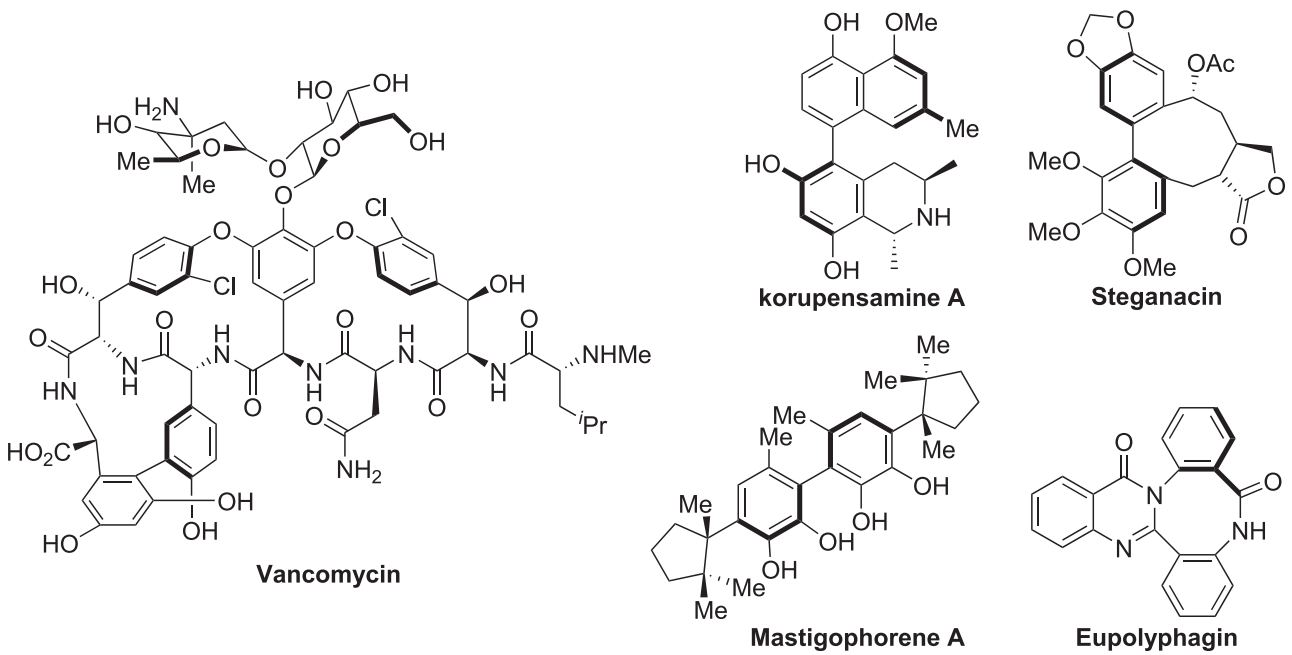
https://doi.org/10.1016/j.checat.2021.09.011



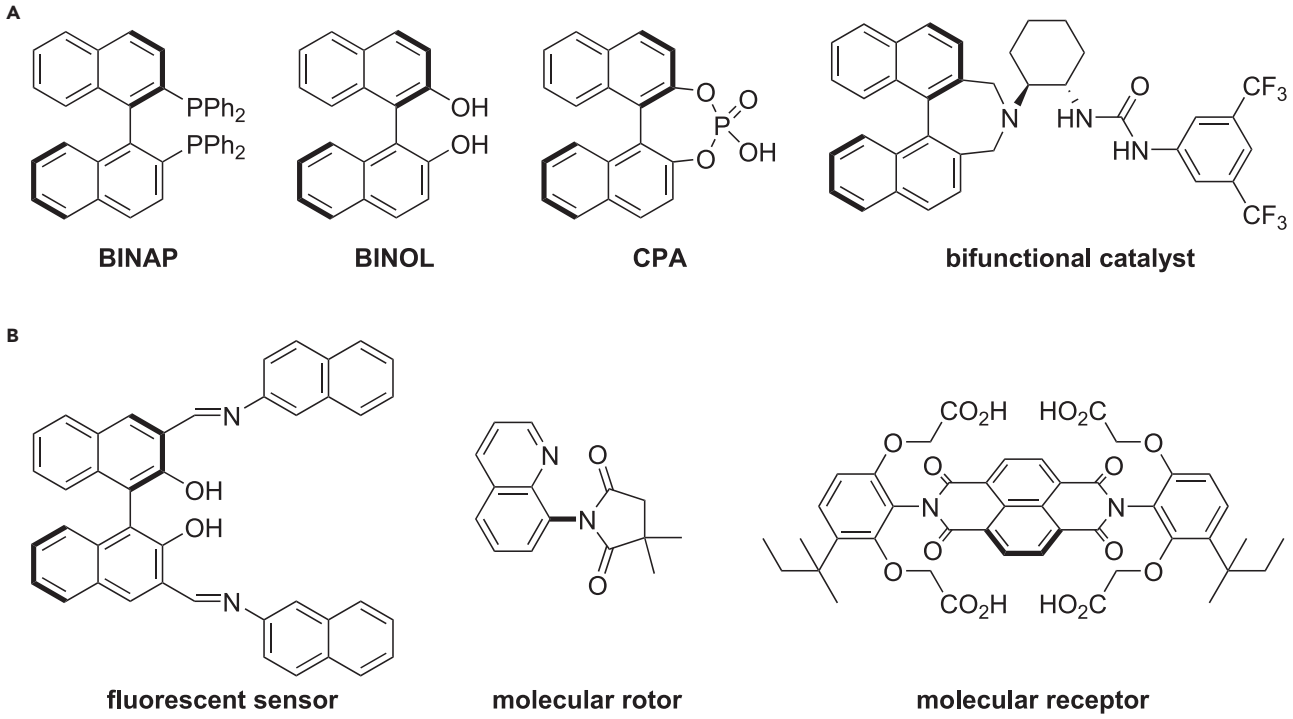
Scheme 1. Different types of axially chiral compounds

successfully synthesized axially chiral compounds **3** in the presence of an iridium catalyst. Various 1,6-diynes, including nitrogen or oxygen-bridged 1,6-diynes, and *ortho*-substituted phenyls or naphthyls substituted on the terminus of 1,6-diynes were well tolerated in this reaction. Different protected 2-butyne-1,4-diols as symmetrical internal alkynes could also achieve excellent results. In addition, the use of *cis*-olefin-tethered octa-1,7-diyne **4** with alkyne **2** under standard conditions, followed by oxidation by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), could lead to the formation of chiral ternaphthylene **6** in high enantioselectivity and diastereoselectivity (Scheme 4B).

Rhodium also shows high reactivity in [2+2+2] cycloaddition reactions for the synthesis of arenes.[32] Intermolecular cyclotrimerization of electron-efficient alkynes and terminal alkynes was reported by Tanaka et al. in 2003.[33] Based on the above results, Tanaka and co-workers devised a strategy for rhodium-catalyzed enantioselective cross-trimerization of unsymmetrical 1,6-diynes and alkynes in 2004.[34] Initially, they utilized terminal alkynes **8** as monoynes. The reaction generated two regioisomers, and the enantiomeric excesses (ees) of major products were moderate (Scheme 5A). Through further investigation, they discovered that using symmetrical



Scheme 2. Bioactive natural products with axial chirality



Scheme 3. Atropisomers in ligands, catalysts, and material science
(A) BINAP, BINOL, CPA, and a bifunctional catalyst.
(B) A fluorescent sensor, molecular rotor, and molecular receptor.

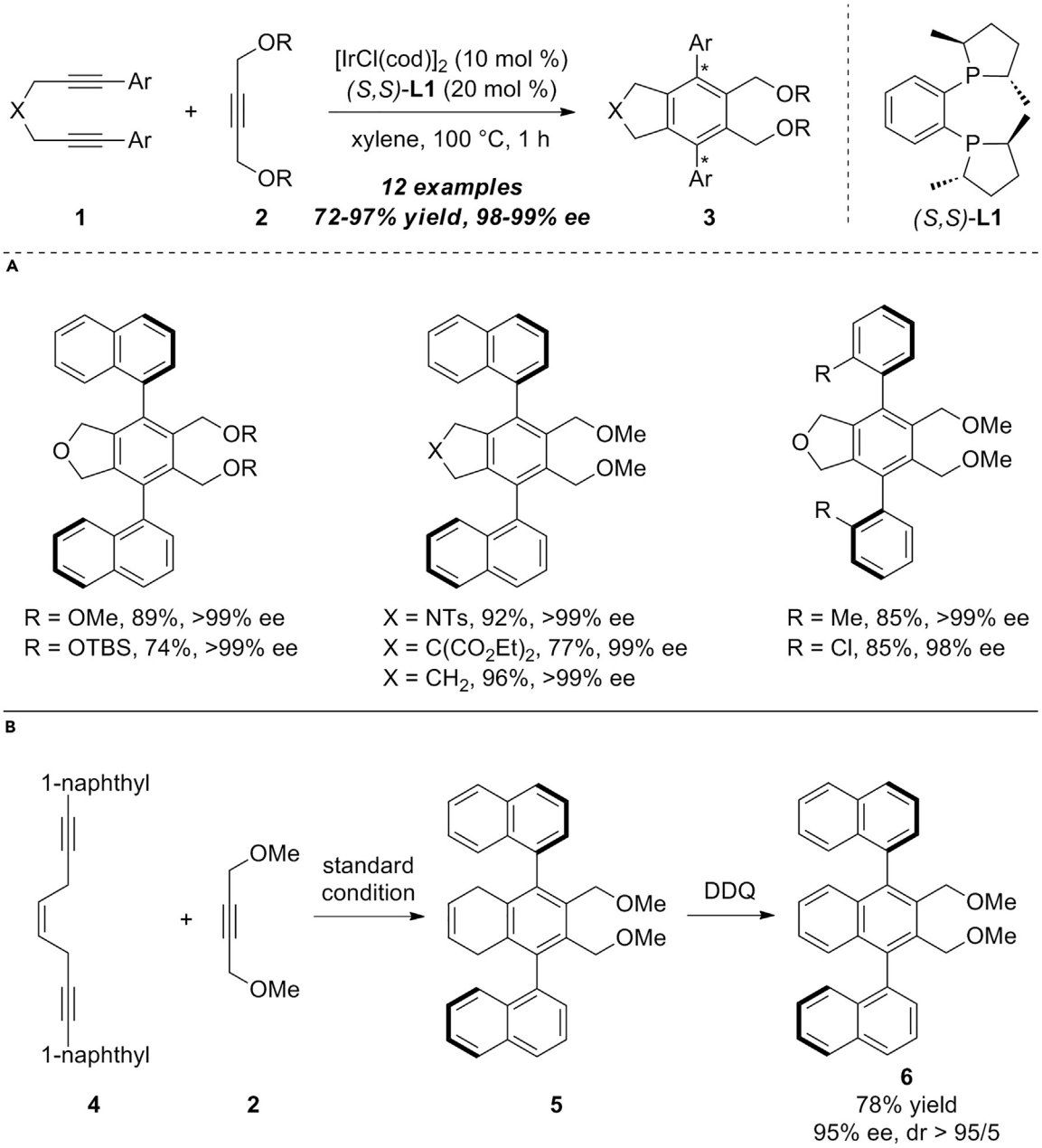
internal monoynes **2** could give only products **11** with good yields and high ees. Different Ar groups of **7** were well tolerated in this reaction, and it is worth noting that the hydroxyl group on monoynes **2** (R = H) could also be well tolerated in this reaction (Scheme 5B).

Compared with the above two examples involving catalytic [2+2+2] cycloaddition, carrying out complete intermolecular cyclotrimerization of two or three different alkynes will face greater challenges. In 2005, Tanaka and co-workers accomplished the construction of fully substituted phenyl rings via rhodium-catalyzed [2+2+2] reaction (Scheme 6).[35] A trimerization was performed with two molecules of electron-deficient dimethyl or diethyl acetylene dicarboxylate alkynes **13** and one molecule of internal alkynes **12**. When the R group on **12** was H or a methoxy group, the reaction could not give satisfying results, which means that the acetoxymethyl group on **12** is crucial. On the other hand, various aryl substitutes on **12**, including different phenyl groups bearing *ortho*-substituted groups and naphthyl, could be well tolerated in this reaction.

A plausible mechanism is shown in Scheme 7. The rhodium-ligand complex initially forms the rhodacyclopentadiene intermediate **15**, and this step is considered to be the chemo- and enantioselectivity-determining step. Intermediate **15** then generates complex **16** via the coordination of rhodium to alkyne **12a**. Finally, the insertion of alkyne and subsequent reductive elimination deliver product **14a** and regenerate the rhodium complex.

[2+2+2] cycloaddition of ynamides with diynes to construct axially chiral compounds containing C–N axes

Ynamides are a type of electron-rich alkyne with an amide group directly attached to the terminus of alkyne. Ynamides have been widely applied to various synthetic

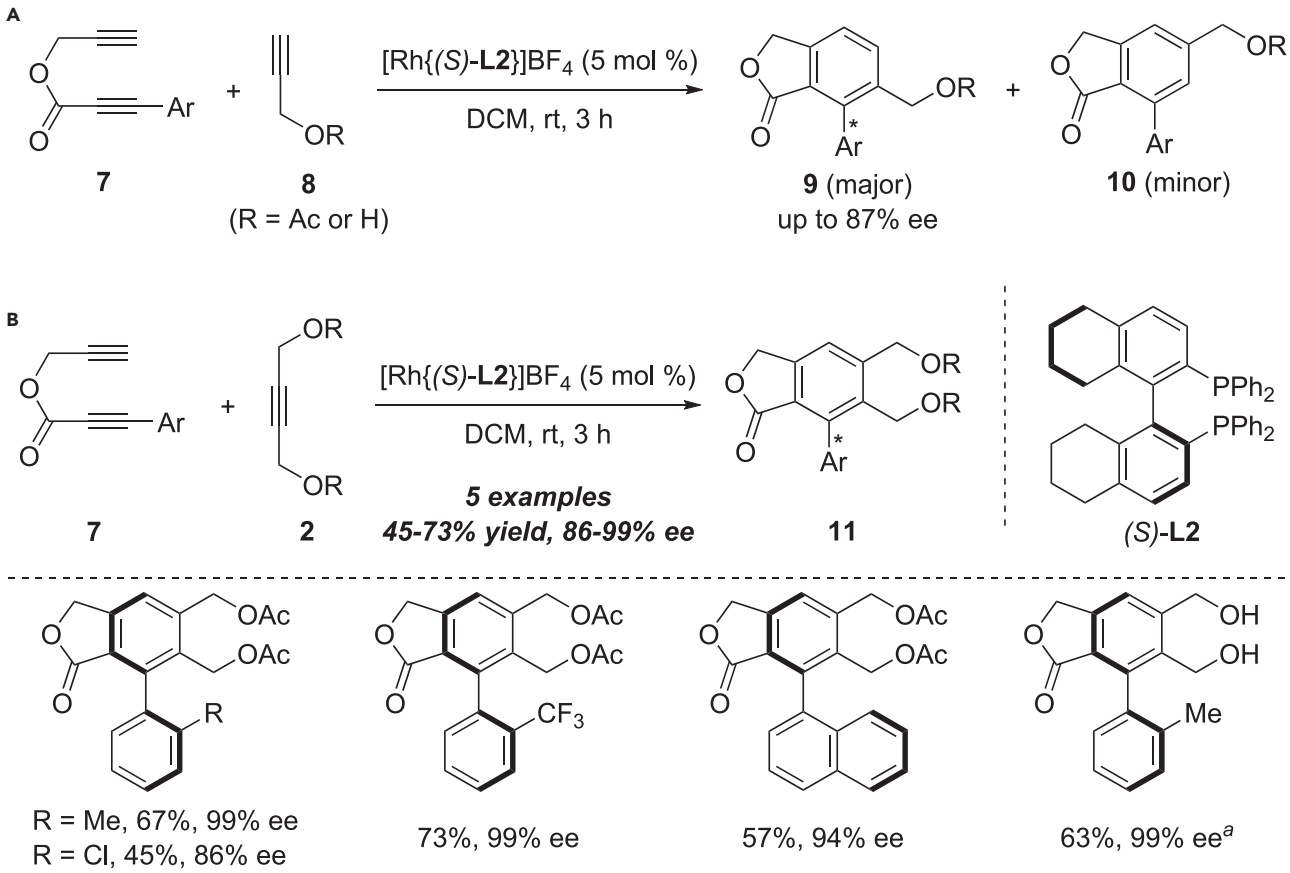


Scheme 4. Synthesis of axially chiral compounds via iridium-catalyzed [2+2+2] cycloaddition

(A) Selected examples.

(B) Synthesis of axially chiral ternaphthylene.

methodologies in the past decades.[36–44] In 2006, Tanaka and co-workers demonstrated a rhodium-catalyzed [2+2+2] cyclotrimerization of 1,6-diynes and trimethylsilylynamides.[45] As shown in Scheme 8, the authors utilized internal diynes **17** because terminal diynes formed homo [2+2+2] cycloadducts rapidly, and the desired anilides **19** with a C–N chiral axis were successfully constructed with high enantioselectivities. The formation of rhodacyclopentadiene and the subsequent coordination to the ynamide is considered to be the enantioselectivity-determining step, which is similar to the examples reported above.[34,35]



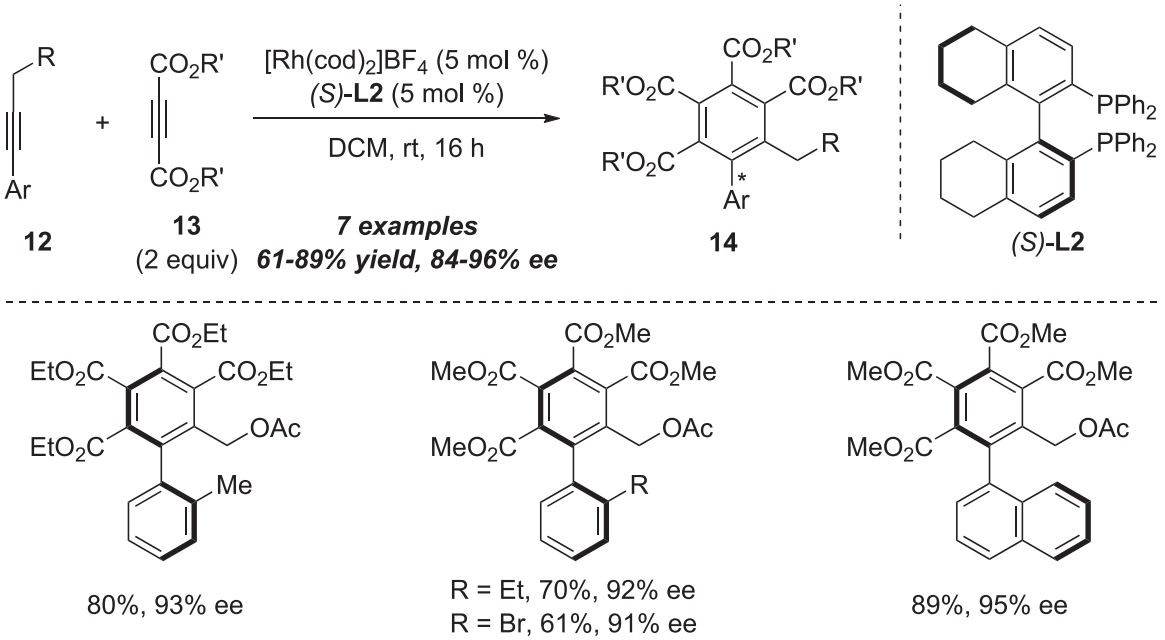
[a]THF was used as the solvent.

Scheme 5. Rhodium-catalyzed asymmetric [2+2+2] cycloaddition of monoynes and diynes
(A) Terminal alkynes.
(B) Internal monoynes.

By applying a similar strategy, Hsung and co-workers reported another [2+2+2] cyclotrimerization of 1,6-diynes and ynamides catalyzed by rhodium in 2007 (Scheme 9).[46] In this work, they introduced achiral ynamides **21** to furnish chiral *N,O*-biaryls. In the presence of a rhodium catalyst and optimized chiral ligand (*S*)-**L3**, ynamides **21** and internal 1,6-diynes **20** were efficiently converted into axially chiral products **22** with C–N and C–C axes simultaneously. Reaction scope studies showed that ynamides containing a *gem*-dimethyl group and bearing *ortho*-substituted aryl groups were compatible with this reaction.

Atroposelective [2+2+2] cycloadditions of alkynes with other unsaturated motifs

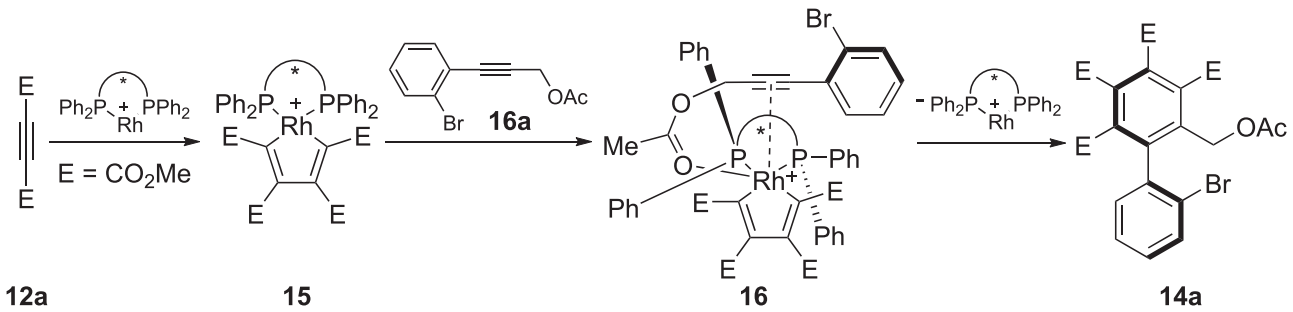
The [2+2+2] cycloaddition of alkynes with nitriles is a valuable method to synthesize a broad variety of substituted pyridines. The construction of pyridine derivatives via cobalt(I)-catalyzed [2+2+2] cycloaddition was reported in 2003.[47] In 2004, Heller and co-workers disclosed an intermolecular reaction between alkynes and nitriles,[48] which was performed with visible light in the presence of cobalt complex **C1** (Scheme 10). At first, the authors subjected monoynes and nitriles to this reaction, but unsatisfying results were obtained. After replacing monoynes with 2-methoxy-1-(1,7-octadiynyl)naphthalene **23**, the enantioselectivity and the yield of this reaction were significantly improved. Different nitriles were compatible with this reaction.



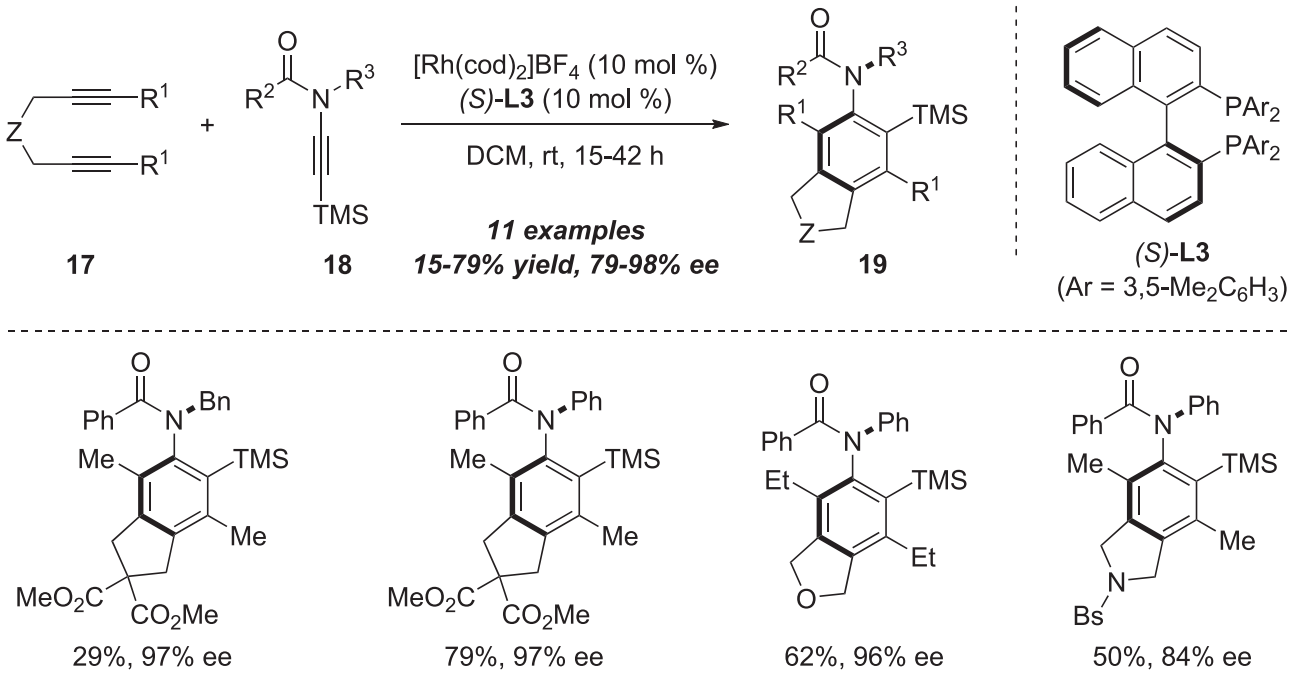
Scheme 6. Complete atroposelective intermolecular trimerization via rhodium catalysis

The proposed mechanism shows that cobaltacyclopentadiene **25** is first formed by the reaction of diyne **23** with Co complex **C1**. This step is considered to be the enantioselectivity-determining step. This species is then attacked by different nitriles to eventually furnish products **24**. Based on this hypothesis, the authors explained that the sterically and electronically different nitriles had little effect on the enantioselectivity.

Transition-metal-catalyzed [2+2+2] cycloaddition of alkynes with isocyanates is a useful tool to construct 2-pyridones. By applying this strategy, the synthesis of 2-pyridones was first reported by Yamazaki using a cobalt catalyst.[49] In 2005, Tanaka and his co-workers utilized this strategy to achieve Rh(I)-catalyzed enantioselective [2+2+2] cycloaddition to construct substituted 2-pyridones with a stereogenic axis (Scheme 11).[50] They first performed this reaction with terminal monoynes and isocyanates but failed to obtain satisfying results. Then they discovered that the reaction of isocyanates **27** with 1,6-diynes **26**, instead of terminal monoynes, proceeded smoothly to deliver the desired products **28** in high yields. In particular, excellent enantioselectivities were achieved when (*R*)-**L4** was employed as the chiral ligand. Both cyanates and alkynes bearing various substituents were well tolerated in this reaction.

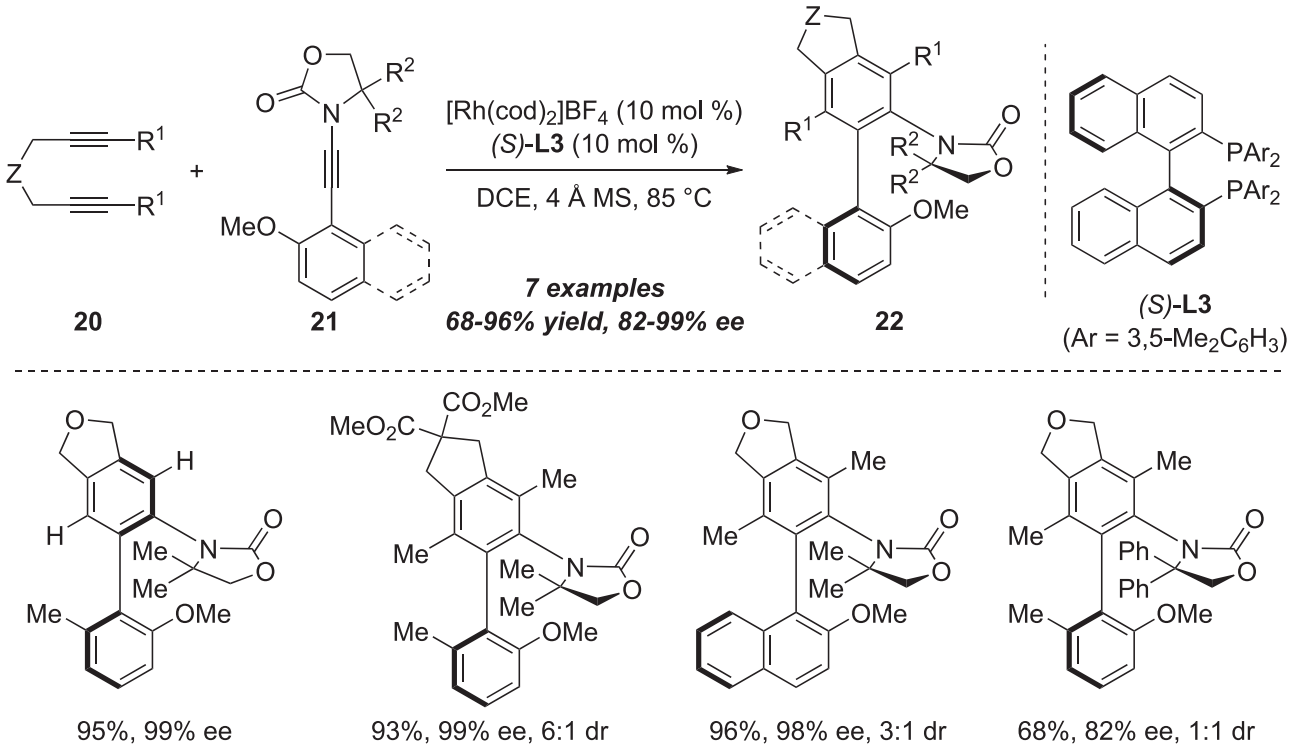


Scheme 7. Proposed mechanism of rhodium-catalyzed [2+2+2] cycloaddition of alkynes

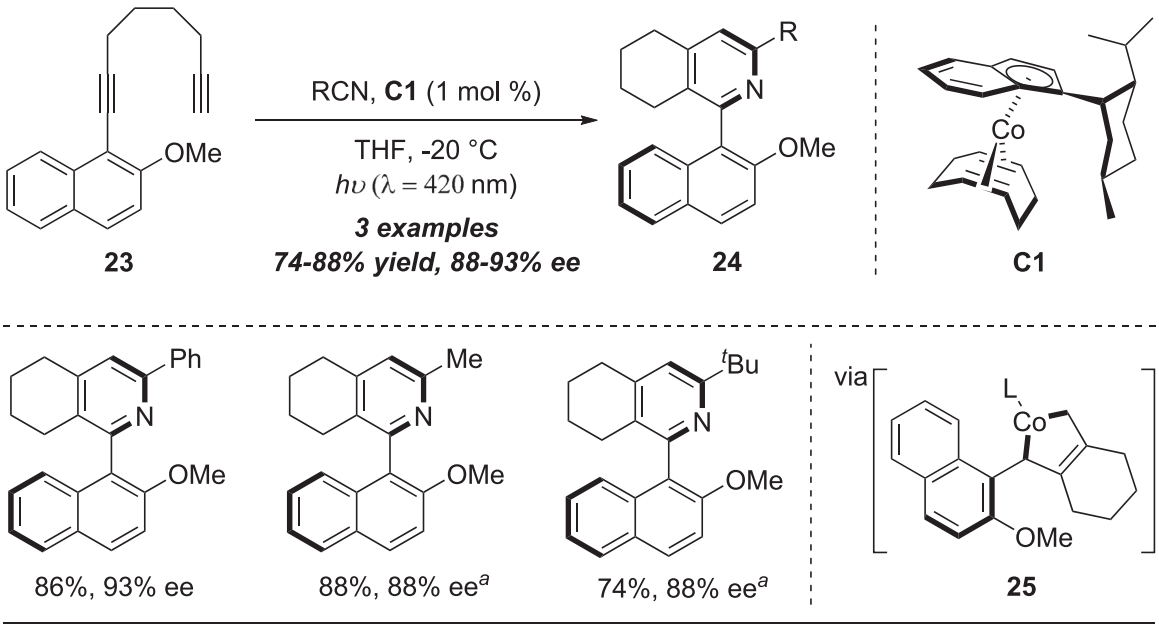


Scheme 8. Atroposelective [2+2+2] cycloaddition of diynes and ynamides to construct anilides with a stereogenic C–N axis

Except for the axially chiral compounds containing a σ bond, it is found that some spiro compounds also have stable axial chirality, and some of these spiro compounds have been widely used in chiral ligands.[51–53] The axially chiral spiro



Scheme 9. Synthesis of compounds containing two chiral axes via rhodium-catalyzed [2+2+2] cycloaddition of diynes and ynamides



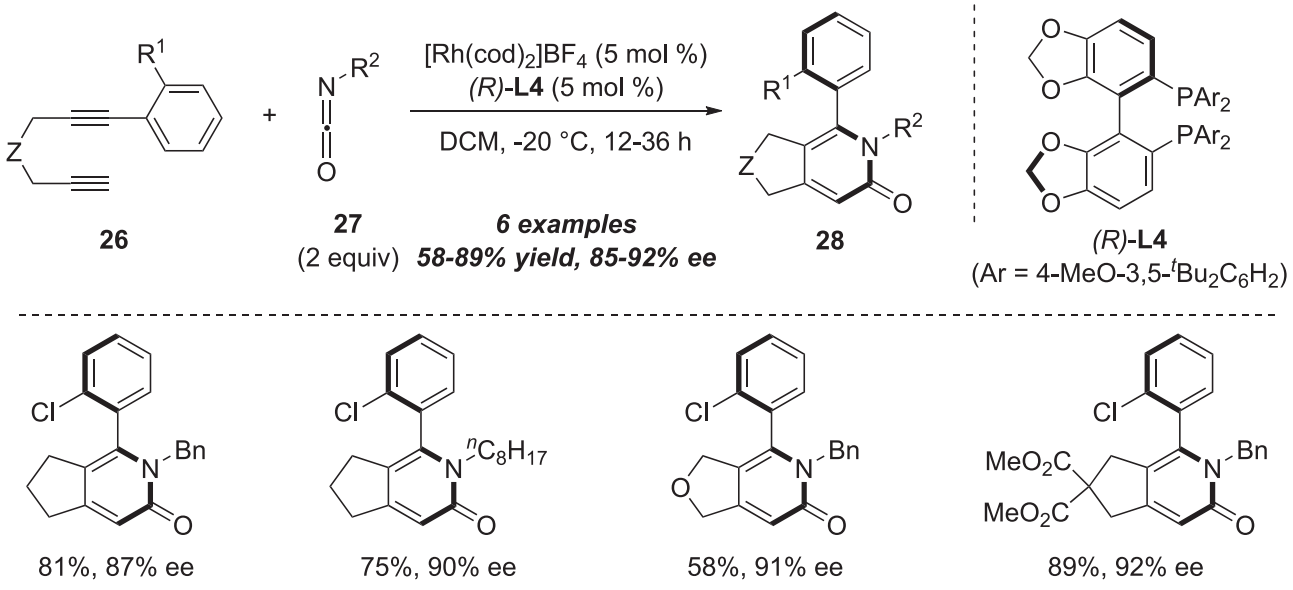
[a]The reaction was performed at 3 °C.

Scheme 10. Cobalt-catalyzed atroposelective [2+2+2] cycloaddition of alkynes and nitriles

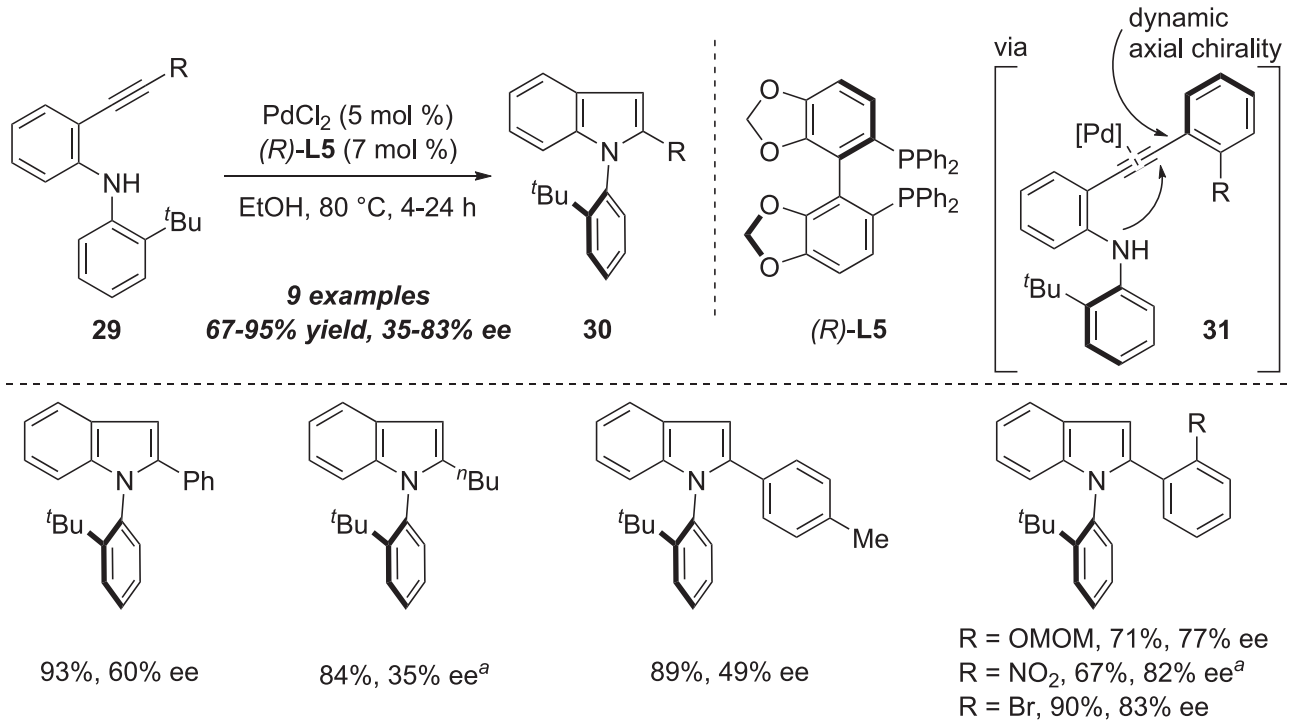
compounds can be constructed via [2+2+2] cycloaddition of appropriate substrates. For example, in 2007, Tanaka and co-workers synthesized a type of C_2-symmetric spirobipyridine through rhodium-catalyzed intramolecular double [2+2+2] cycloaddition of bis-diynenitriles.[54]

Synthesis of axially chiral compounds via cyclization of alkynes

Alkynes, on one hand, can be activated by transition metals and be attacked by various nucleophiles.[21–23,55–60] On the other hand, some transition metals can



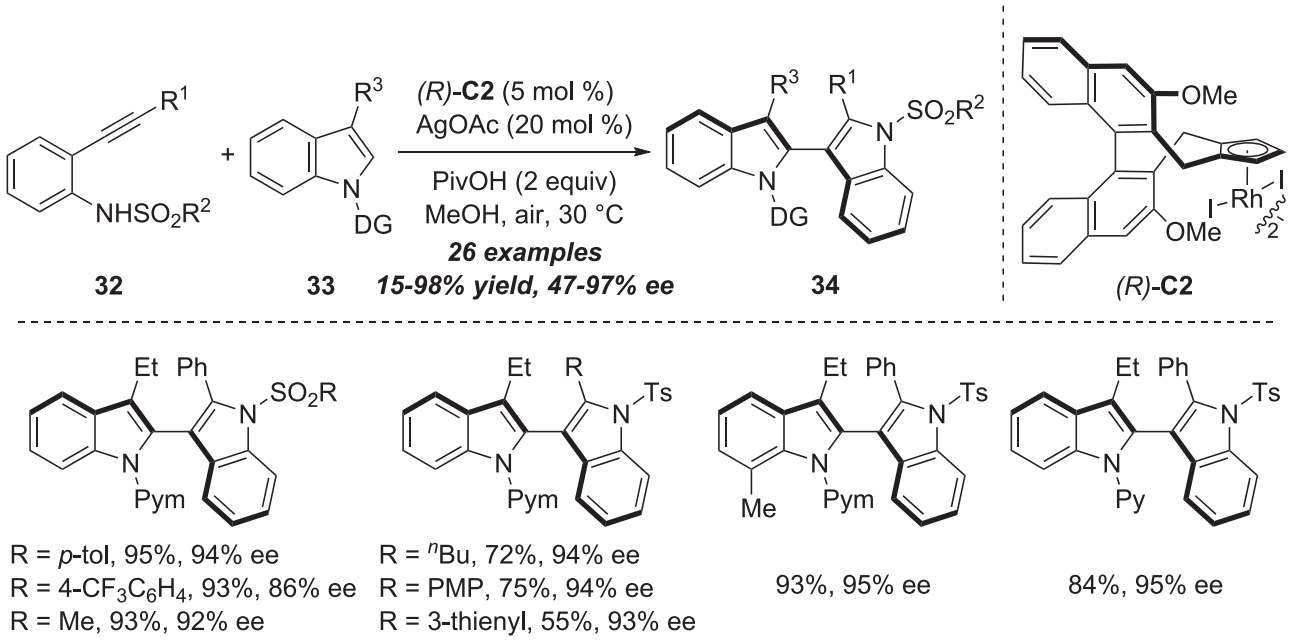
Scheme 11. Atroposelective [2+2+2] cycloaddition of alkynes and isocyanates



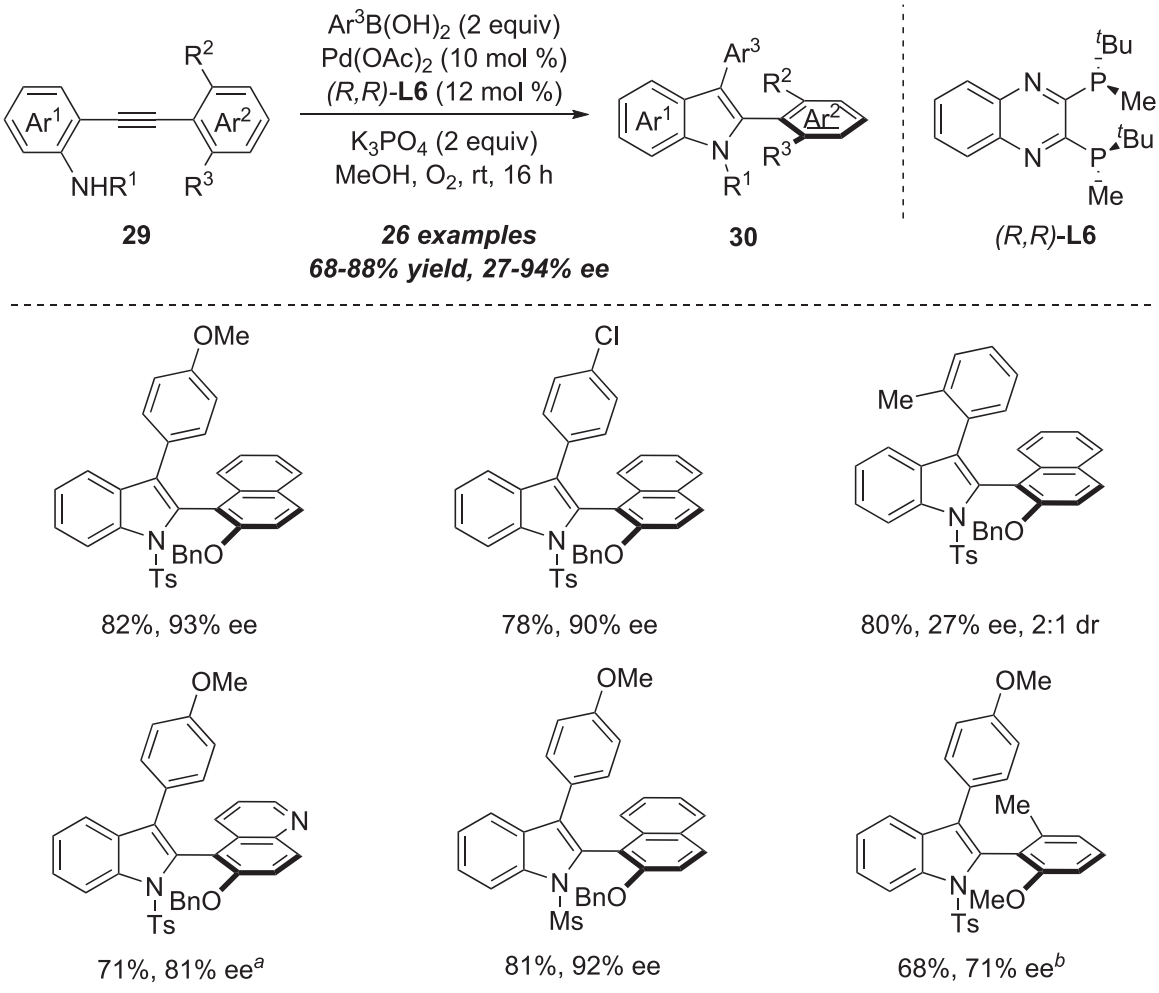
[a]5 mol % of AgOTf was added.

Scheme 12. Construction of indoles containing C–N axes via palladium-catalyzed intramolecular cyclization

undergo insertion into alkynes. Those two reaction pathways can lead to the cyclization of alkynes and deliver indoles, phenyls, and other rings. When the substrates bear an appropriate bulky group, the cyclization of alkynes may produce axially chiral compounds if the rotation around the axes is effectively restricted.



Scheme 13. Construction of biindoles via rhodium-catalyzed C–H activation and nucleophilic cyclization



[a]At 40 °C. [b]At 10 °C.

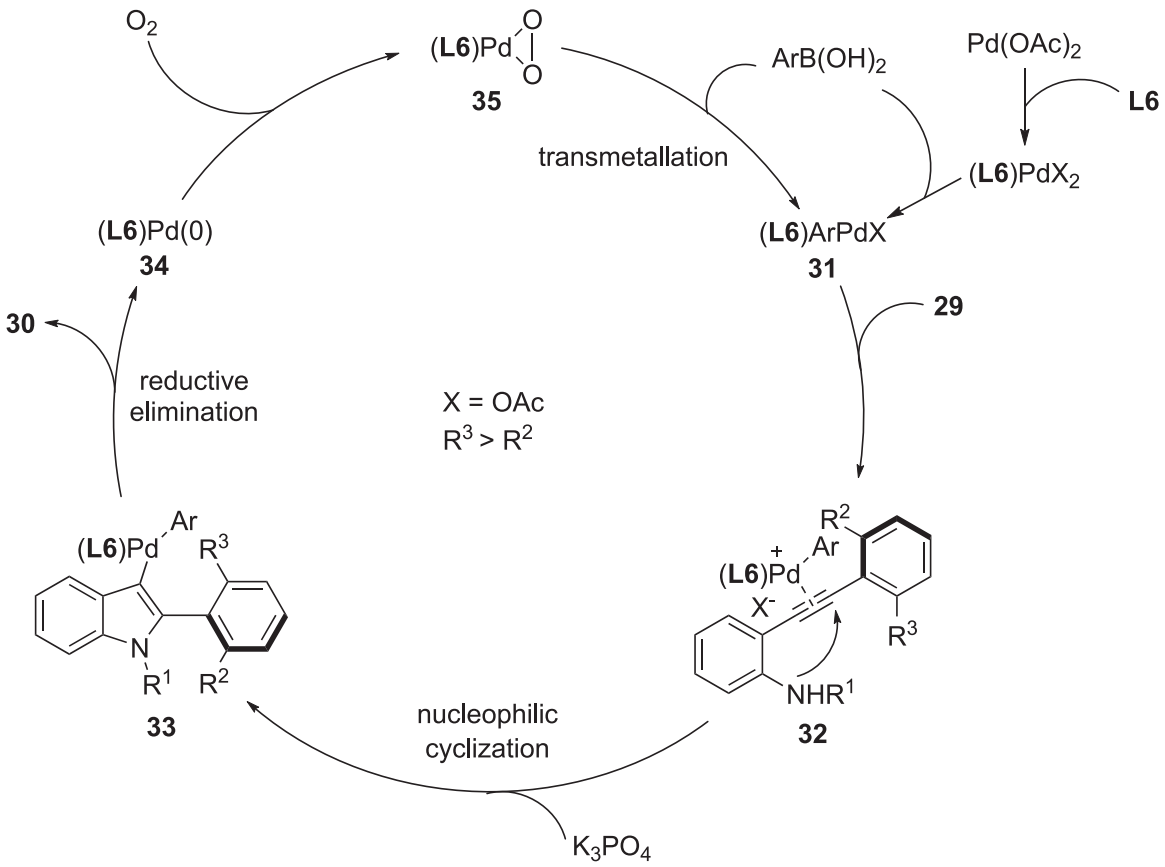
Scheme 14. Synthesis of axially chiral 2,3-disubstituted indoles via palladium-catalyzed enantioselective Cacchi reaction

In this section, we will summarize the construction of axially chiral compounds via transition-metal-catalyzed cyclization of alkynes.

Construction of axially chiral compounds via indole formation

In 2010, Kitagawa and his co-workers developed a protocol for the construction of indoles with N–C axial chirality via palladium-catalyzed hydroaminocyclization of 2-alkynylanilines.[61] As shown in Scheme 12, the 2-alkynylanilines **29** could undergo an enantioselective 5-*endo-dig* cyclization in the presence of a catalytic amount of palladium catalyst and chiral ligand, affording a range of axially chiral indoles **30** in high yields, and the highest ee value reaches 83%. The authors proposed that the dynamic chirality of the C–C bond between alkyne moiety and phenyl-group-bearing *ortho*-substituent contributed to the formation of axial chirality. In other words, the construction of an axially chiral N–C bond occurs in the step of cyclization. It is difficult to direct stereocontrol by the chiral palladium species due to its long distance to the N–C axis being constructed.

In 2019, Li and his co-workers reported an approach for the synthesis of axially chiral biindoles via rhodium(III)-catalyzed C–H activation and nucleophilic cyclization.[62] As

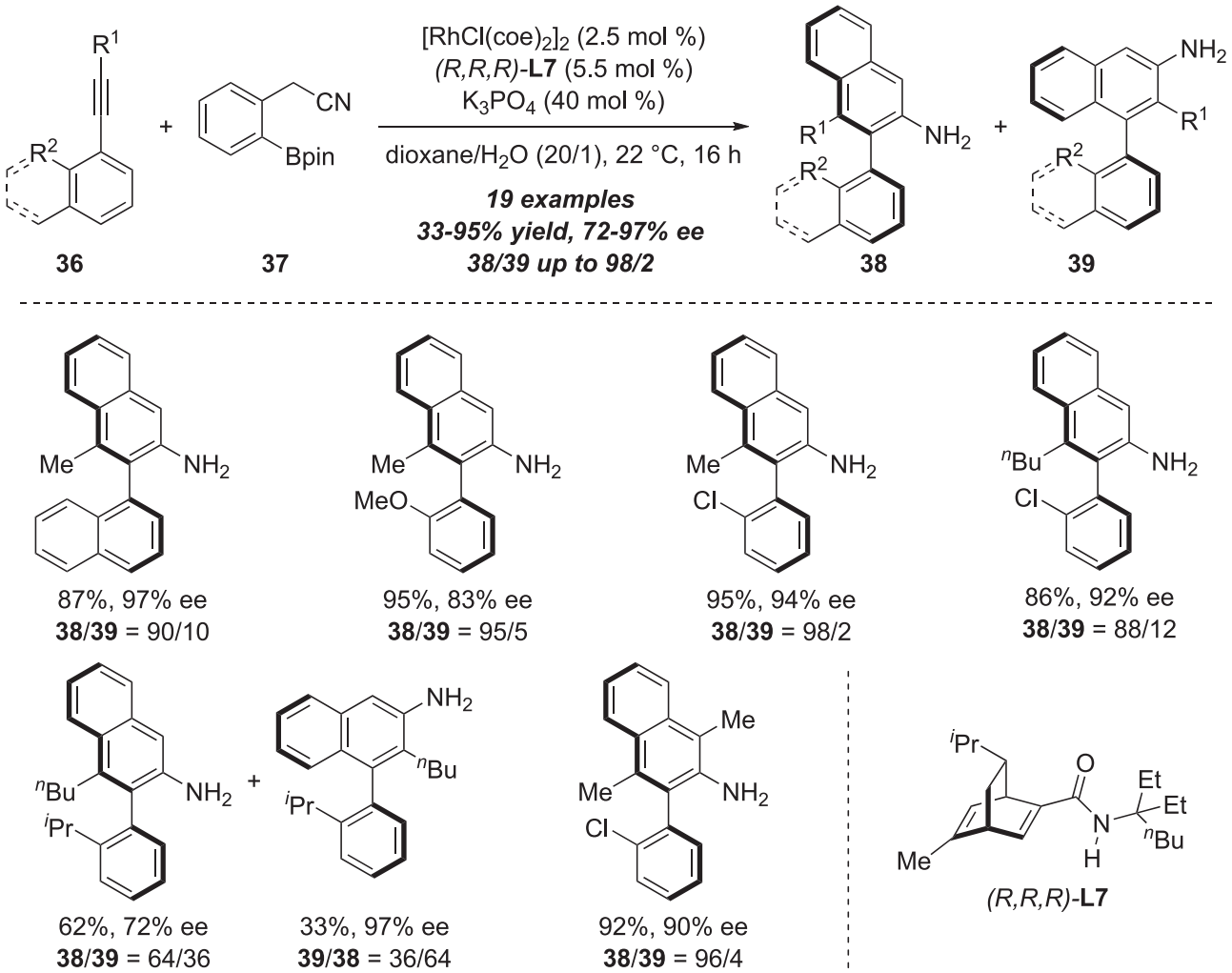


Scheme 15. Proposed mechanism for the palladium-catalyzed synthesis of 2,3-disubstituted indoles

shown in Scheme 13, the reaction occurred efficiently in the presence of rhodium catalyst **C2** and co-catalyst AgOAc with a stoichiometric amount of $Cu(OAc)_2$ and PivOH. The CpRh(III) catalyst would allow a merge of C–H activation and nucleophilic cyclization due to its high activity and Lewis acidity. A series of mechanistic studies revealed that this reaction pathway was likely through a pathway of initial cyclometallation of **33** and **C2** followed by alkyne cyclization to form a Rh(III) diaryl complex, eventually affording biindole products **34** via reductive elimination.

In 2020, Zhu and his co-workers disclosed a protocol for the synthesis of axially chiral 2,3-disubstituted indoles via a palladium-catalyzed enantioselective Cacchi reaction (Scheme 14).[63] Alkynes **29** could react smoothly with aryl boric acids in the presence of the palladium catalyst and optimized ligand under an atmosphere of oxygen, generating axially chiral products **30** in good to high yields and with excellent ee values. The substrate scope studies show that different aryl boronic acids bearing various groups were well tolerated in this reaction. The nature of the OR groups on the naphthyl ring attached to the terminus of alkynes was also compatible with this reaction.

A plausible mechanism is depicted in Scheme 15 based on the results of control experiments. The palladium complex first undergoes a transmetallation with aryl boric acid to afford ArPdLX species **31**. The coordination of **31** to **29** generates palladium complexes **32**, followed by nucleophilic cyclization and subsequent reductive elimination giving the desired products **30**. The palladium(0) species is oxidized into the palladium(II) peroxo complex by oxygen, which can form **31** with the aryl boric acid.

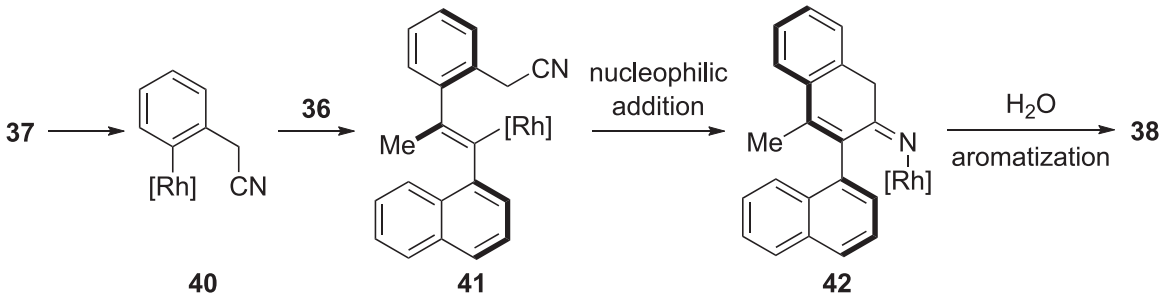


Scheme 16. Rhodium-catalyzed benzannulation of 1-arylalkynes and 2-(cyanomethyl)phenylboronates

Construction of axially chiral compounds via benzene ring formation

2-Boronophenyl acetonitriles could react with alkynes in the presence of a palladium catalyst to deliver substituted 2-naphthalenamines, which were reported by the Tsukamoto group.[64] Based on these reports, Hayashi and his co-worker developed a method to access axially chiral 2-aminobiaryls by rhodium-catalyzed benzannulation of 1-aryl alkynes and 2-(cyanomethyl)phenylboronates in 2018.[65] As shown in Scheme 16, the reaction proceeded smoothly at 22°C, affording major products **38** and minor products **39**, with high ratios of **38**/**39**. Various substituents on the terminus of alkynes and the naphthyl or *ortho* position of phenyl groups were well tolerated in this reaction.

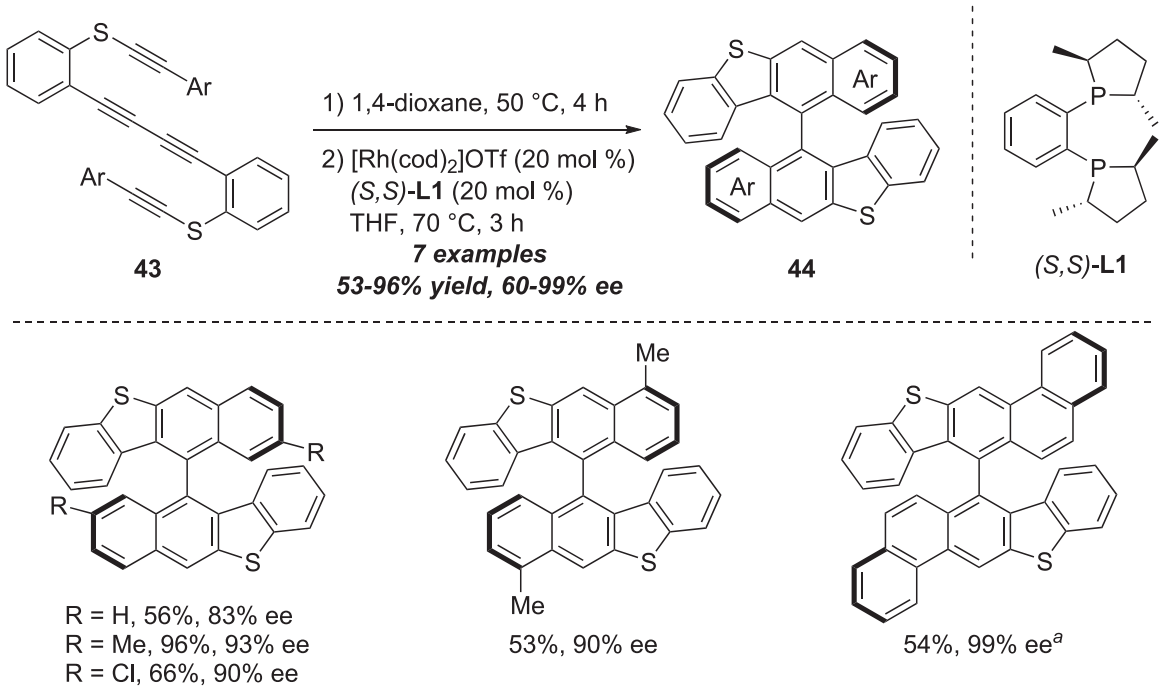
The proposed mechanism is shown in Scheme 17. The rhodium catalyst and chiral ligand first form a rhodium-ligand complex, which undergoes a transmetallation with **37** to afford **40**. The alkenyl-rhodium intermediate **41** is then formed via the addition of **40** to **36**, which subsequently generates **42** by stereoselective intramolecular addition to the cyano group. Finally, hydrolysis of the N-Rh bond and arylation deliver the main product **38**.



Scheme 17. Proposed mechanism for the palladium-catalyzed synthesis of axially chiral 2-aminobiaryls

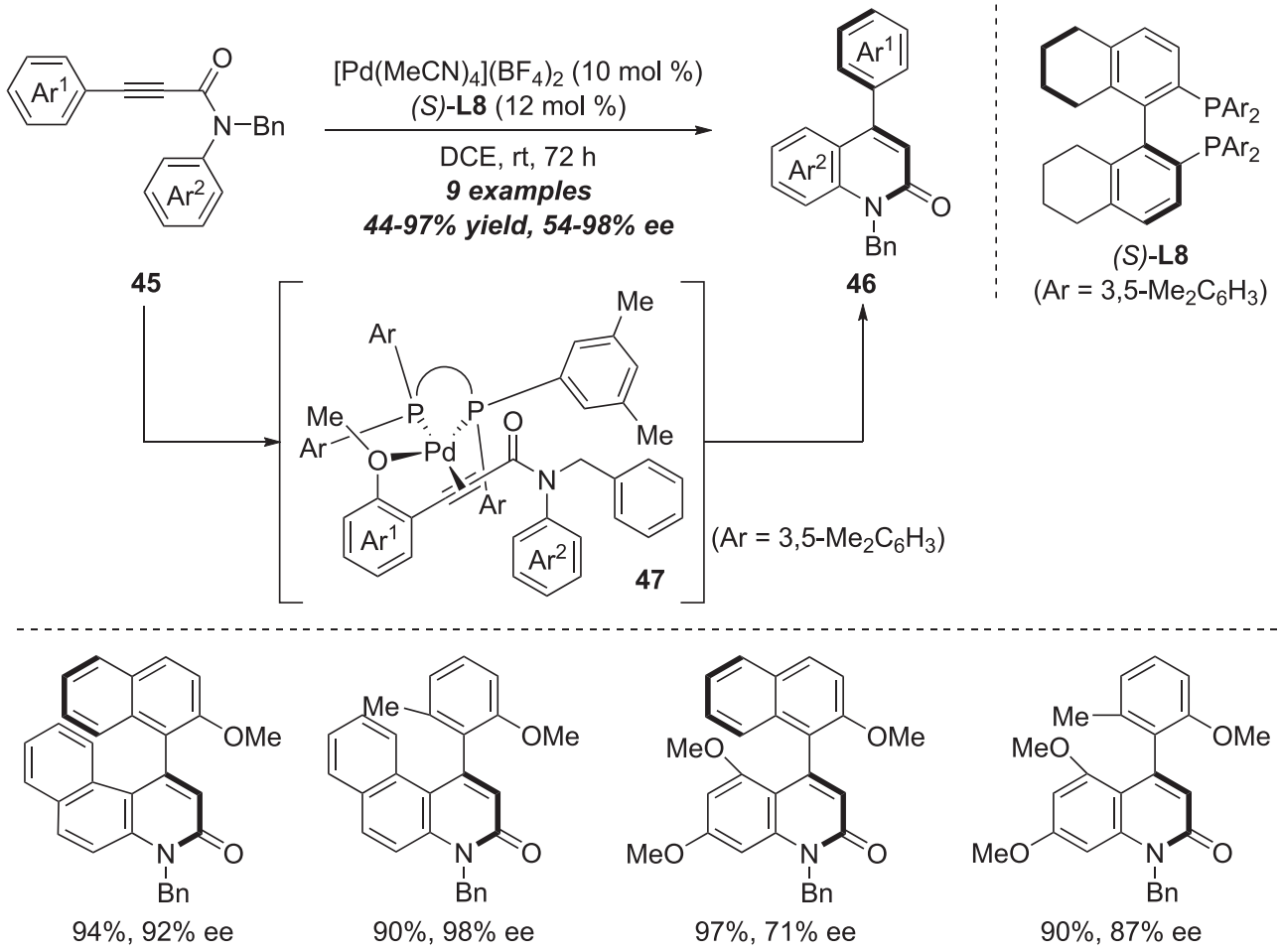
The dehydro-Diels-Alder (DDA) reaction is a type of Diels-Alder reaction involving alkynes in the substrate(s).[66,67] In particular, the intramolecular DDA reaction of alkynes with aromatic enynes is a useful approach to synthesize compounds containing multicyclic fused aromatic rings. Based on this background, in 2018, Shibata and co-workers reported a catalytic enantioselective intramolecular consecutive DDA reaction. After investigation of the intramolecular DDA reaction of tetraynes **43** (Scheme 18),[68] the authors disclosed that the tetraynes **43** would initially form a fused aryl ring via thermal DDA cyclization without any catalysts, followed by a rhodium-catalyzed enantioselective DDA reaction to construct the second fused aryl rings and eventually the axially chiral polycyclic products **44**.

The benzene ring can also be constructed via an insertion of an alkyne to a metal–C bond. By applying this strategy, the synthesis of axially chiral compounds can be achieved. For example, in 2020, Shibata and co-workers reported a



[a]The first reaction was conducted at 40 °C.

Scheme 18. Rhodium-catalyzed enantioselective DDA reaction of tetraynes



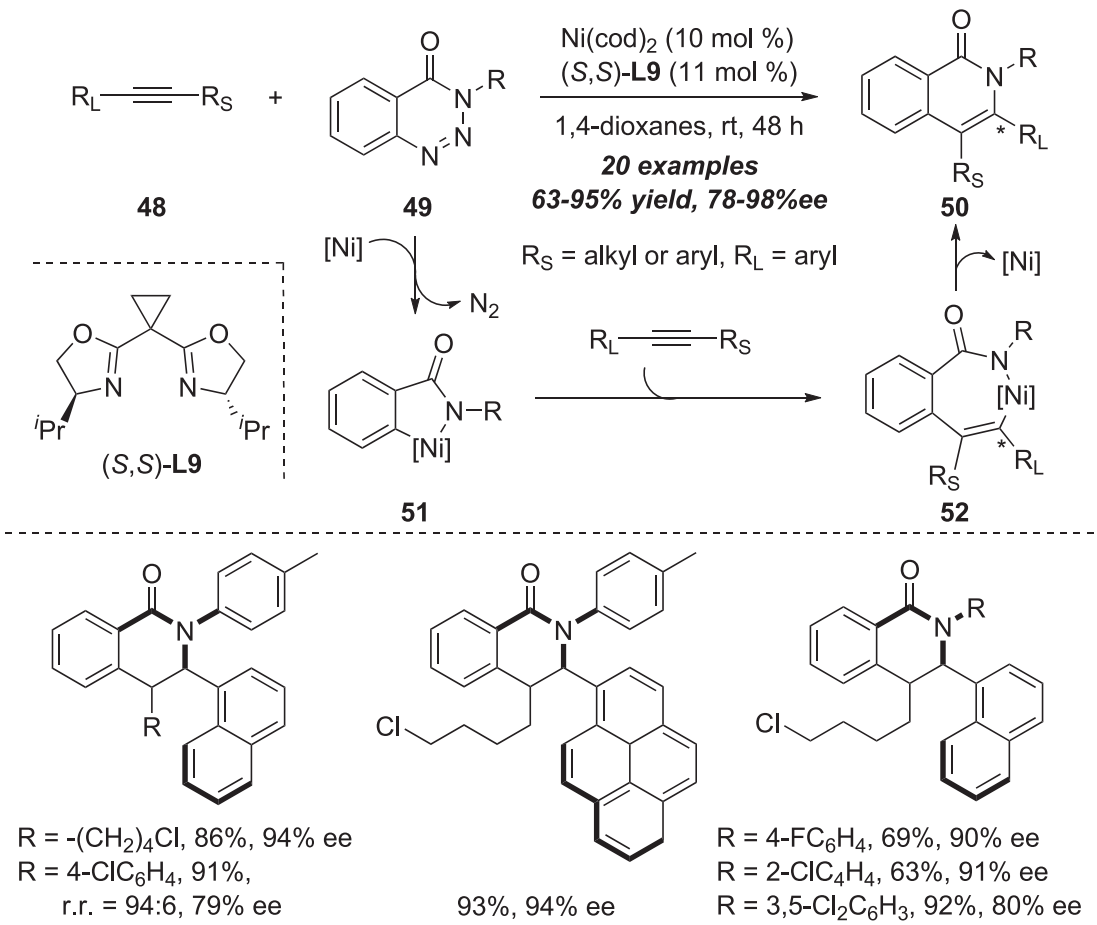
Scheme 19. Palladium-catalyzed atroposelective intramolecular hydroarylation of alkynes

rhodium-catalyzed regioselective and enantioselective C–C bond activation of biphenylenes to synthesize axially chiral polycyclic aromatic hydrocarbons.[69]

Construction of axially chiral compounds via the formation of other rings

Transition-metal-catalyzed intramolecular hydroarylation of alkynes has been considered an efficient method for the construction of fused aromatic compounds. It was first reported by Fujiwara and colleagues in 2000.[70] In 2011, Tanaka and his coworkers devised a strategy for palladium-catalyzed atroposelective intramolecular hydroarylation of alkynes.[71] As shown in Scheme 19, the treatment of 3-aryl propiolamides **45** with a palladium catalyst and optimized chiral ligand could afford the corresponding axially chiral 4-aryl 2-quinolinones **46**.

A plausible mechanism for the construction of **46** via enantioselective hydroarylation is proposed by the authors. A key intermediate **47** is formed through the chelation of alkynes and alkoxy groups by the palladium cation, which will induce the high reactivity of alkyne. The axial chirality of **46** is well controlled due to the avoidance of steric interaction between the benzyl group of **45** and the aryl group on the chiral ligand. By applying a similar strategy, a more efficient and active catalyst was developed by Alcarazo and colleagues.[72] The authors utilized a gold catalyst and



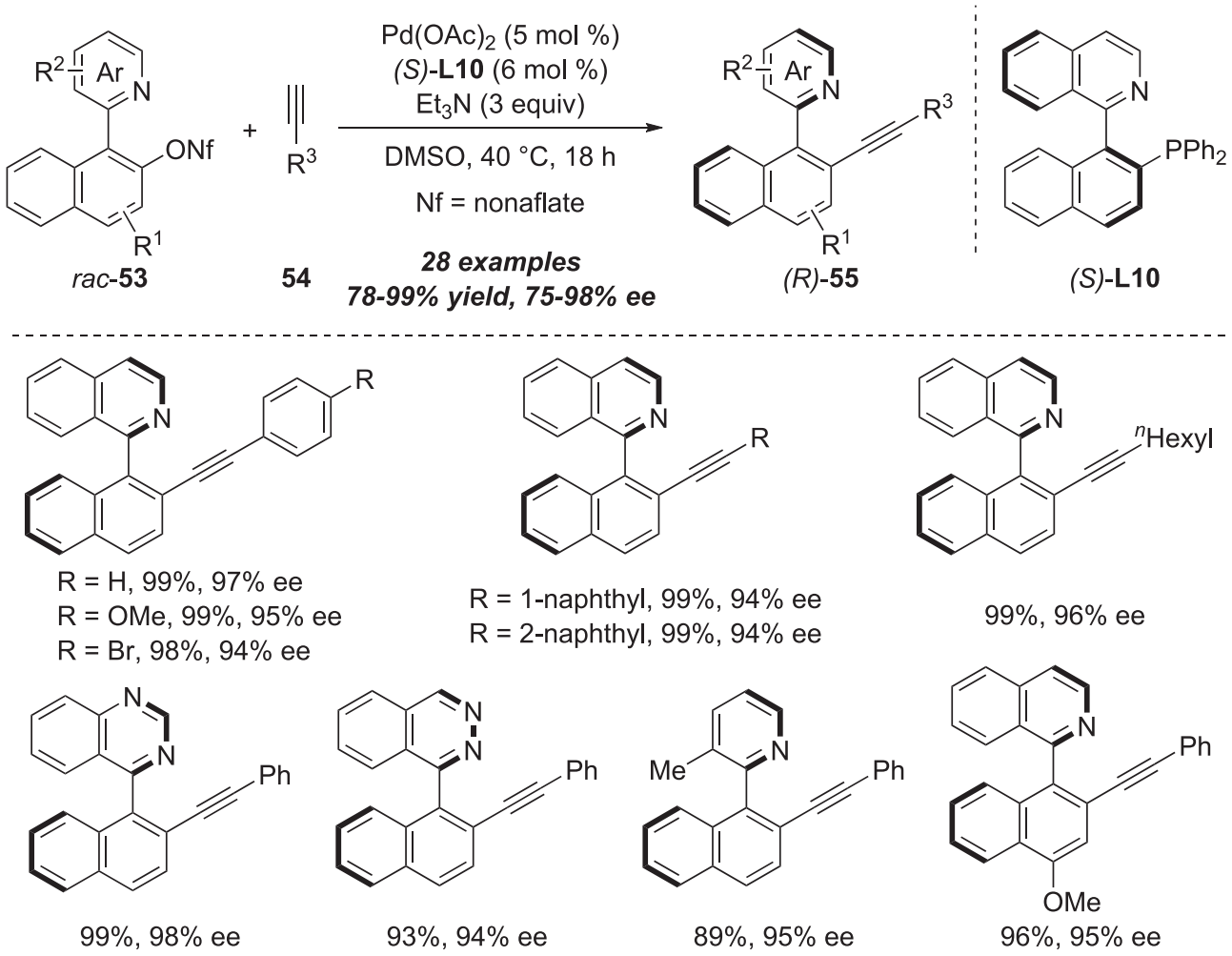
Scheme 20. Nickle-catalyzed denitrogenative transannulation to construct axially chiral isoquinolones

optimized chiral ligands to achieve the atroposelective synthesis of 1,1′-binaphthalene-2,3′-diols.

Triazole compounds are important building blocks for the synthesis of N-heterocyclic compounds. Transition-metal-catalyzed denitrogenative transannulation of triazole rings and alkynes has been well established.[73,74] In 2015, Liu and co-workers applied nickel-catalyzed denitrogenative transannulation to construct axially chiral isoquinolones from benzotriazin compounds **49** and internal alkynes **48**.[75] As shown in Scheme 20, the benzotriazin derivatives **49** first generate nickelacycle intermediates **51** *in situ* and then undergo a regioselective insertion of alkynes **48**. The isoquinolones **50** are finally formed via the reductive elimination of intermediates **52**. Different substituents on the terminus of alkynes and on the benzotriazin derivatives are well tolerated in this reaction.

Synthesis of axially chiral compounds via direct coupling with alkynes

There is a strategy for the construction of axially chiral compounds by asymmetric substitution on achiral or pseudoachiral biaryls. This type of reaction has been widely reported, and various substituents, such as aryl groups[76] and alkenes,[77] have been introduced into biaryl compounds to deliver axially chiral biaryls. In 2016, Lassaletta and co-workers demonstrated a protocol of dynamic kinetic asymmetric alkynylation to construct axially chiral heterobiaryl alkynes (Scheme 21).[78] Racemic biaryls **53**



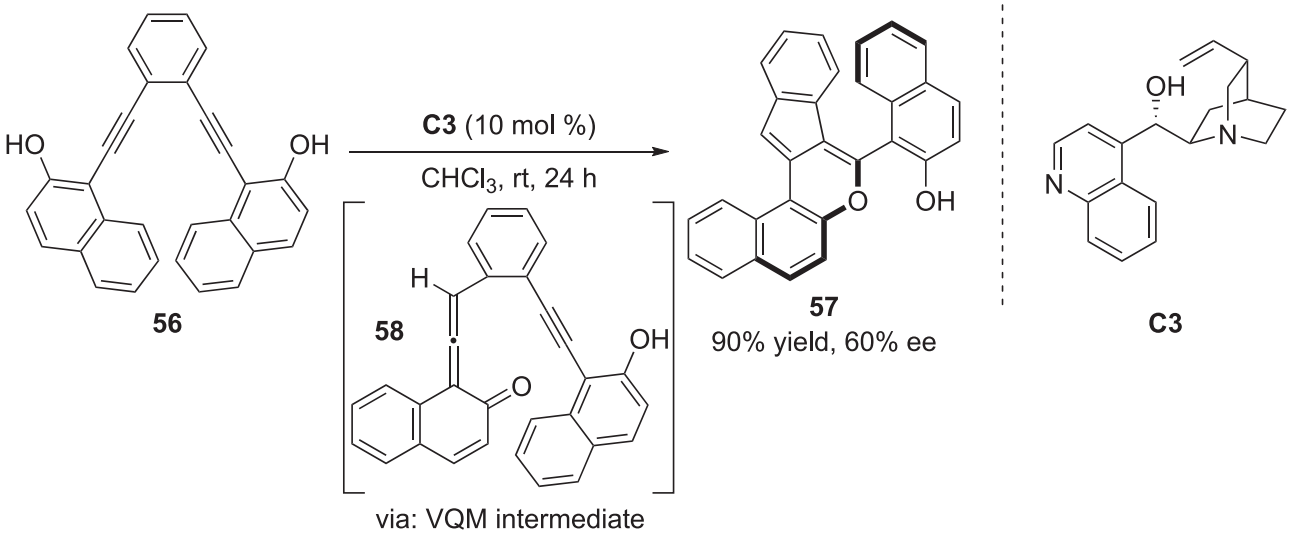
Scheme 21. Palladium-catalyzed dynamic kinetic asymmetric alkynylation

could react with terminal alkynes **54** in the presence of the palladium catalyst and the optimized chiral ligand. The use of various substituted alkynes could afford chiral alkynylation products **55** with high yields and excellent ee values. The *N*-heteroaryl group on biaryls **53** serves as a directing group. These biaryl compounds **53** are configurationally labile, which is the reason that dynamic kinetic asymmetric alkynylation could be achieved in this case.

ORGANOCATALYTIC CONSTRUCTION OF AXIALLY CHIRAL COMPOUNDS FROM ALKYNES

Organocatalysis has received tremendous interest over the past two decades, and numerous efficient synthetic methods have been developed. Compared with transition-metal catalysis, organocatalysis has the advantage of being cheaper and greener. While the research on the construction of axial compounds has focused on transition-metal catalysis in past decades, methodologies in the field of organocatalytic asymmetric construction of axially chiral compounds from alkynes have been more and more reported in recent years.

In this section, we will give an introduction to the construction of axially chiral compounds via the organocatalytic asymmetric reaction of alkynes.



Scheme 22. Organocatalytic asymmetric HDA cycloaddition of *o*-phenylenediyne-linked bis(arenol)s

Synthesis of axially chiral compounds via VQMs

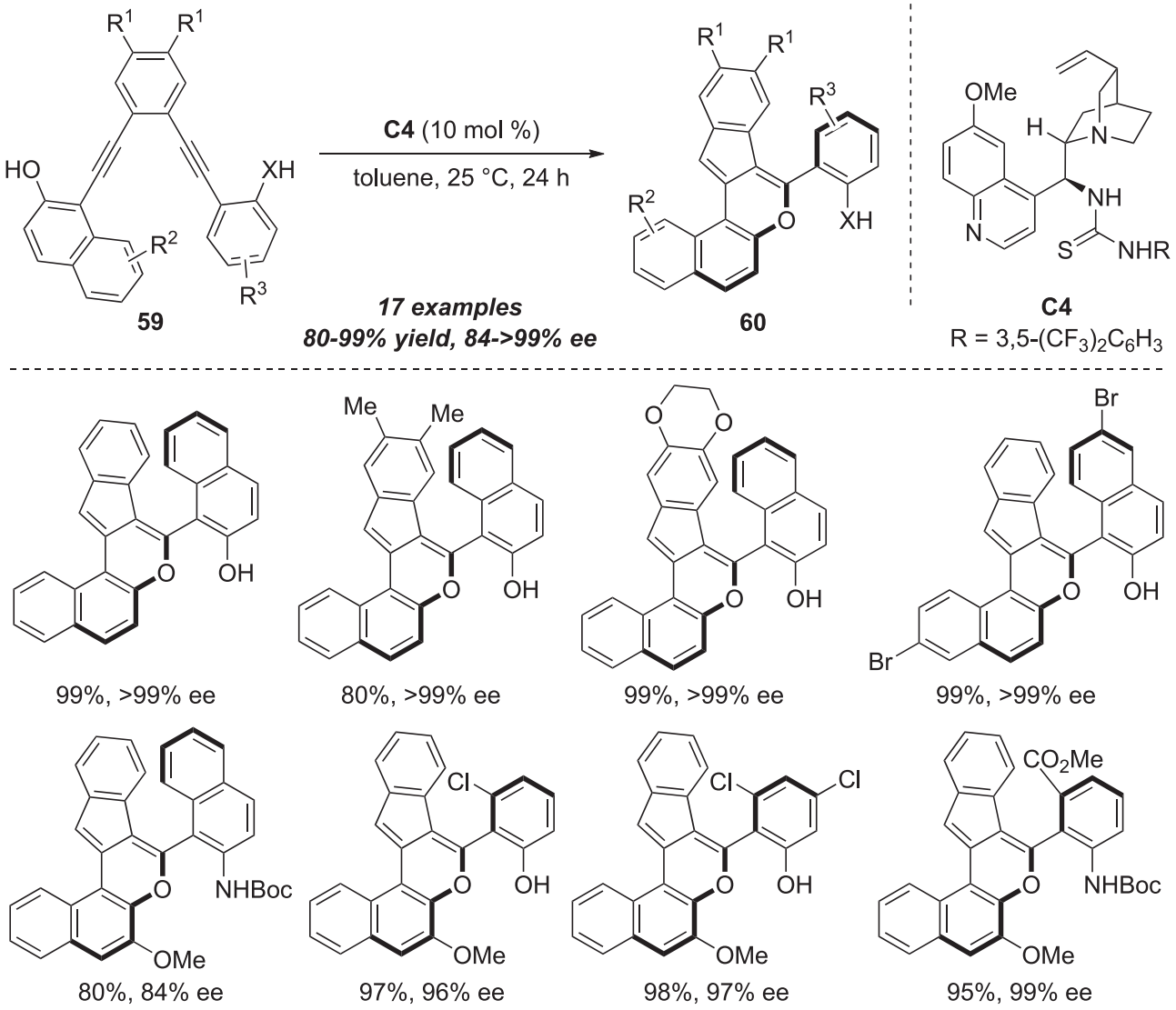
Vinylidene *o*-quinone methide (VQM) intermediates have received much attention due to their high reactivity and useful applications in organic synthesis.[79,80] VQM intermediates can be commonly generated from *ortho*-(phenylethynyl)phenols via a prototropic rearrangement under basic or acid conditions. In general, VQM intermediates show their electrophilicity on the vinylidene moiety, which benefits Michael addition to generate the substituted *ortho*-(phenylethenyl)phenols. In this section, we will summarize the construction of axially chiral compounds through VQMs.

Construction of axially chiral polycyclic compounds

In 2013, Irie and co-workers realized the first metal-free catalytic construction of indeno[1,2-*c*]chromenes from *o*-phenylenediyne-linked bis(arenol)s.[81] As shown in Scheme 22, the reaction proceeded smoothly in the presence of K_2CO_3 or Et_3N, furnishing the desired racemic products in high yields. They explained that the *o*-hydroxy naphthyl alkyne moiety might undergo a prototropic rearrangement to generate a VQM, which was considered as the key intermediate of this reaction. The VQM intermediate subsequently generates indeno[1,2-*c*]chromene via formal inverse-electron-demand hetero-Diels-Alder (HDA) cycloaddition. Of note, attempts to construct axially chiral indeno[1,2-*c*]chromenes by employing a chiral base catalyst **C3** gave only moderate enantioselectivities. The results of this reaction show the potential of organocatalytic asymmetric reactions of this type of alkynes.

On the basis of the above results, in 2018, Yan and co-workers utilized similar substrates and carried out further optimization of organocatalysts (Scheme 23).[82] They successfully constructed a variety of indeno[1,2-*c*]chromenes with high enantioselectivities by employing a quinine-derived thiourea catalyst **C4**. The reaction scope studies showed that various substituents on phenyl or naphthyl rings of substrates **59** were compatible with this reaction. Moreover, nonsymmetric diynes were also well tolerated in this reaction.

In 2019, Yan and co-workers reported an organocatalytic enantioselective synthesis of both helical and axial stereogenic compounds.[83] The bisquinine squaramide catalyst **C5** was selected as the organocatalyst. Various 2-ethynylnaphthol derivatives **61**



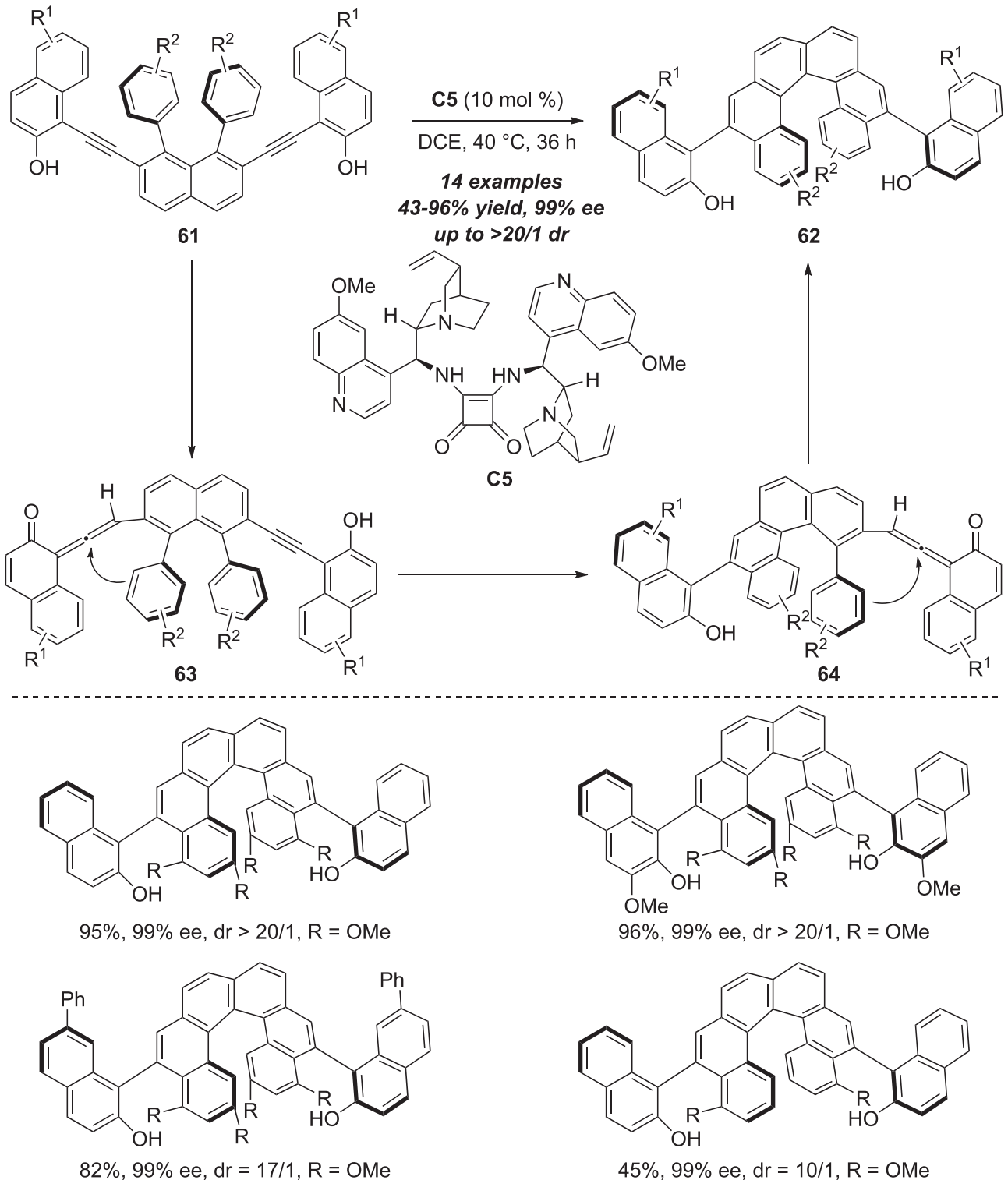
Scheme 23. Synthesis of axially chiral heterobiaryls via organocatalytic asymmetric intramolecular [4+2] cycloaddition

bearing different substituents on the naphthol moieties and the phenyl groups could afford the desired products **62** in high yields with excellent enantioselectivities and diastereoselectivities (Scheme 24).

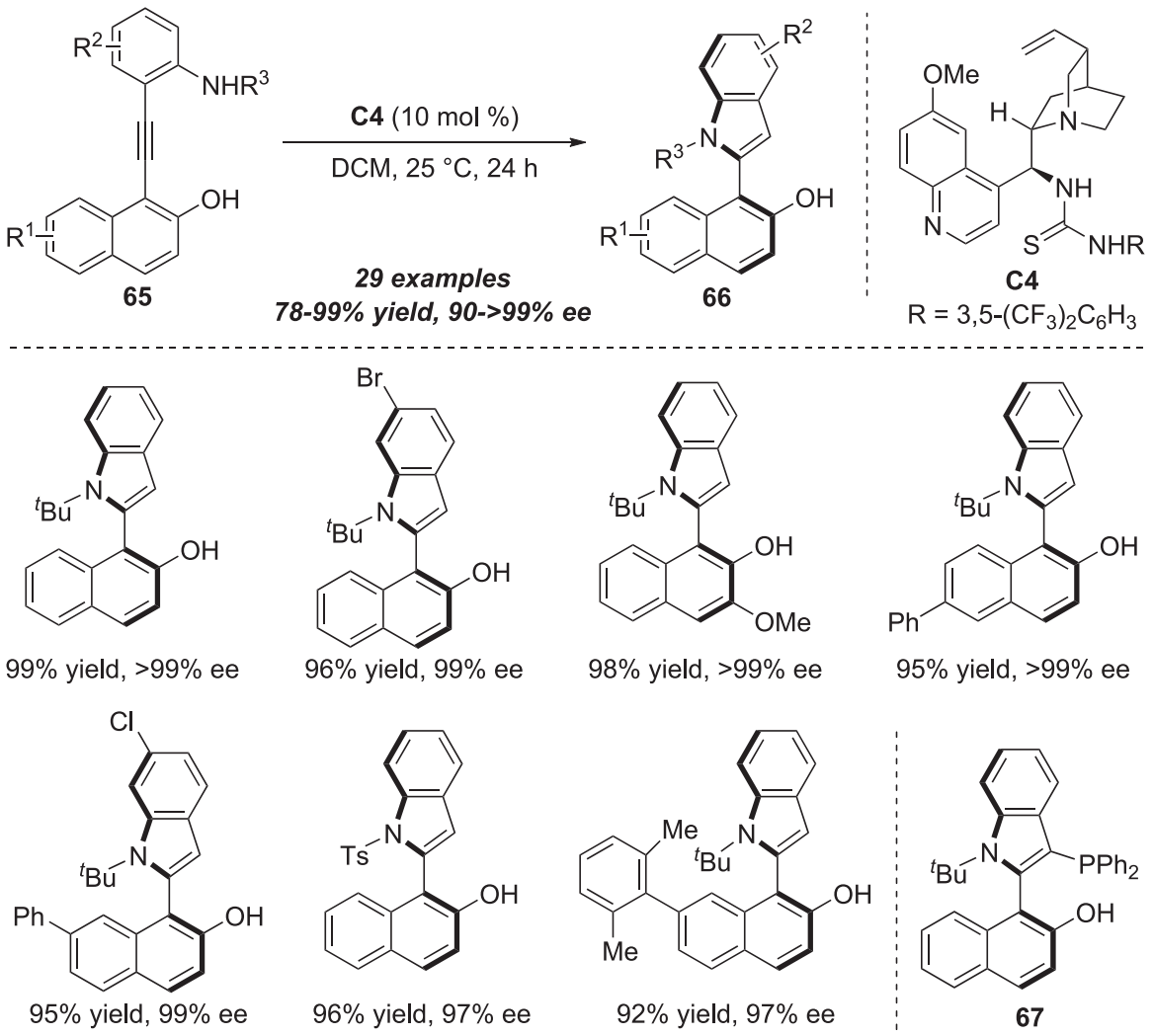
The authors envisioned that substrates **61** would furnish VQM intermediates **63** through a prototropic rearrangement (tautomerization). The following cyclization and tautomerization generate VQM intermediates **64** with a stereogenic axis. After the second cyclization, the compounds containing both chiral helicenes and stereogenic axes are finally obtained.

Construction of axially chiral biaryl compounds

In 2019, Yan and co-workers disclosed the synthesis of axially chiral naphthyl-C2-indoles via organocatalytic asymmetric annulation of *o*-alkynylanilines.[84] As shown in Scheme 25, the authors used the quinine-derived thiourea catalyst **C4** as the metal-free catalyst. *o*-alkynylanilines **65** could be transformed into VQM



Scheme 24. Organocatalytic asymmetric synthesis of both helical and axial stereogenic compounds



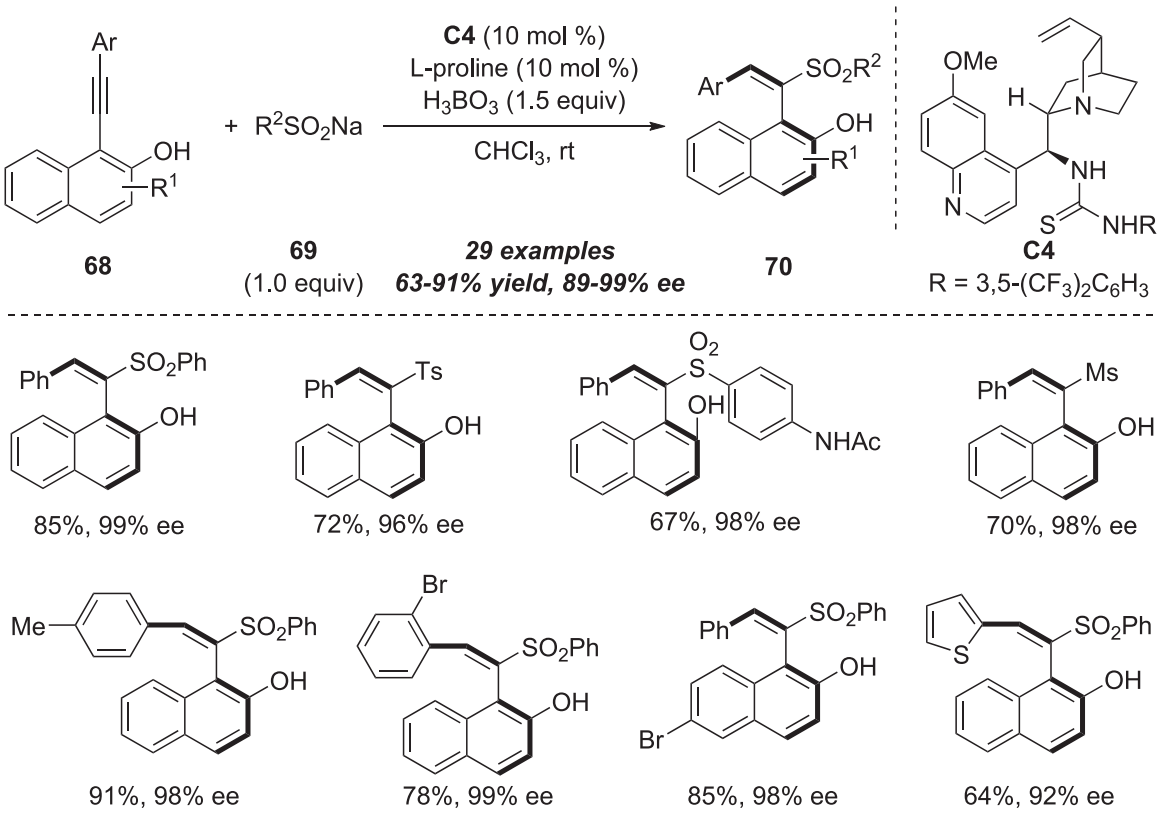
Scheme 25. Organocatalytic asymmetric annulation of *o*-alkynylanilines

intermediates followed by nucleophilic attack by the amino group, affording the final products **66** with high yields and excellent enantioselectivities. Remarkably, this reaction could be applied on a decagram scale and the products showed high tolerance toward racemization, which indicates their potential as precursors of chiral ligands or catalysts.

The authors applied monophosphine **67** derived from product **66** as an organocatalyst to the asymmetric aza-Baylis-Hillman reaction and [4+2] tandem cyclization, and both of these reactions occurred smoothly, indicating the potential of the utility of such a naphthyl-C2-indole skeleton.

Construction of axially chiral styrenes

In 2018, Yan and co-workers devised another interesting strategy for the construction of axially chiral sulfonestyrenes (Scheme 26).[85] The authors utilized a variety of substituted 1-ethynyl-2-naphthol derivatives **68**, and the desired axially chiral olefin products **70** could be obtained in high yields with excellent enantioselectivities in the presence of **C4**, L-proline, and boronic acid. Of note, the *E*/*Z* ratios of **70** are also satisfying.

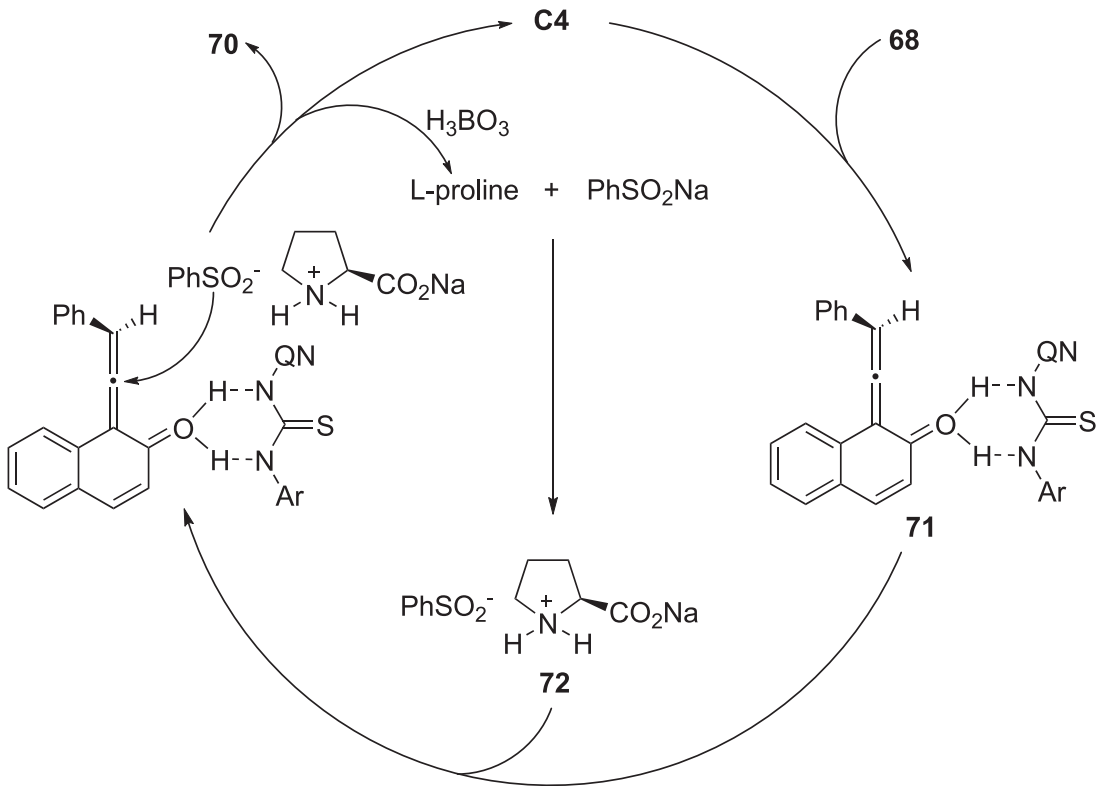


Scheme 26. Organocatalytic asymmetric synthesis of axially chiral sulfonestyrenes

According to the reaction pathway shown in Scheme 27 depicted by the authors, 1-ethynyl-2-naphthols **68** initially generate VQM intermediates **71** promoted by catalyst **C4** and form hydrogen bonds with the thiourea catalyst. L-proline and sodium sulfonate can furnish the sulfonate anion salt, which increases the reactivity of sodium sulfonate. After subsequent nucleophilic addition, axially chiral products **70** are eventually obtained. The authors assumed that boric acid may reactivate the proline due to its proton buffering property.

In 2018, Yan and co-workers reported an attractive organocatalytic construction of vicinal diaxial styrenes.[86] The authors selected *N*-iodosuccinimide (NIS) as the electrophile and aryl sulfonyl acid as the nucleophile. As shown in Scheme 28A, the reaction proceeded smoothly and delivered tetrasubstituted axial styrenes **74** with contiguous axes in high yields with excellent enantioselectivities and diastereoselectivities. Also, the authors introduced two sterically hindered substituents based on **73** skeletons. The racemic substrates **73** could produce tetrasubstituted axially chiral sulfonestyrenes **74** and unreacted chiral substrates **73** via kinetic resolution under the standard condition (Scheme 28B).

A plausible mechanism was proposed by the authors. Tautomerization of **73** occurs quickly, promoted by catalyst **C6**, and subsequently generates tetrasubstituted VQM intermediates **70** in the presence of NIS. The succinimide anion released from NIS can capture a proton from the sulfonyl acid and produce the sulfonate anion, which undergoes a nucleophilic addition to VQM to afford the final products **74**.

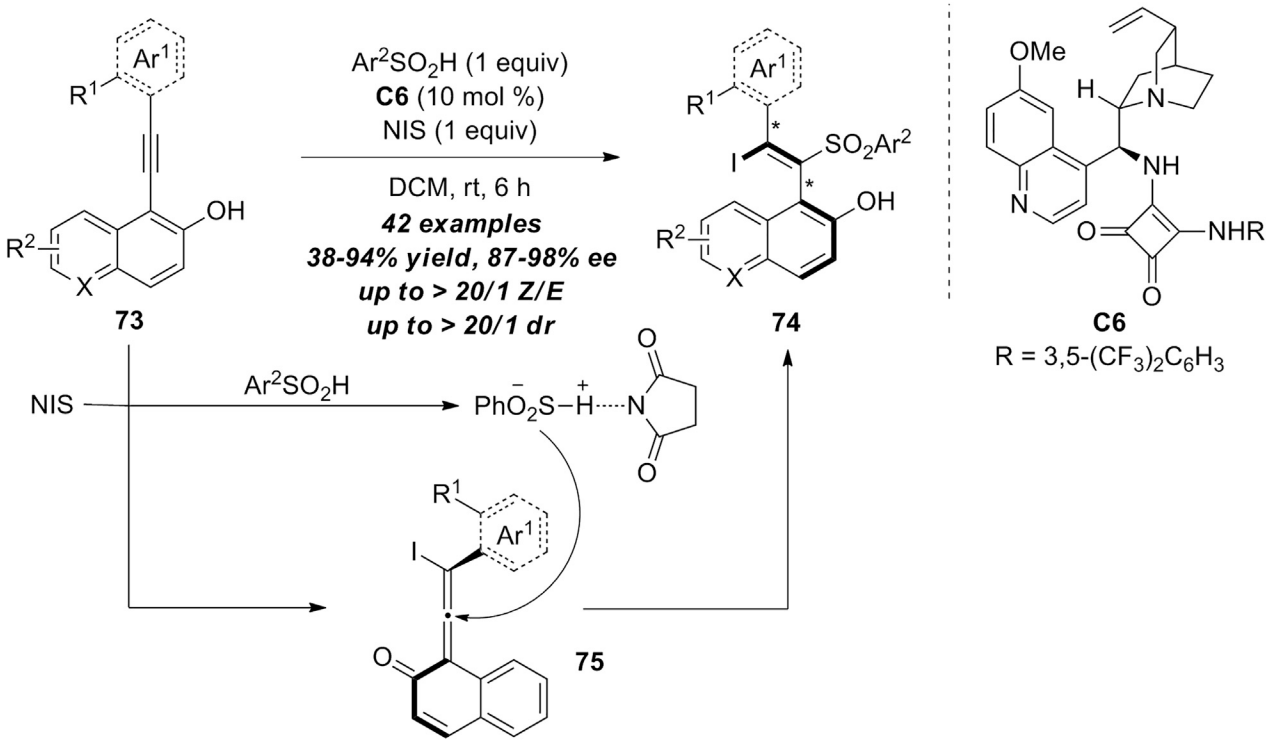


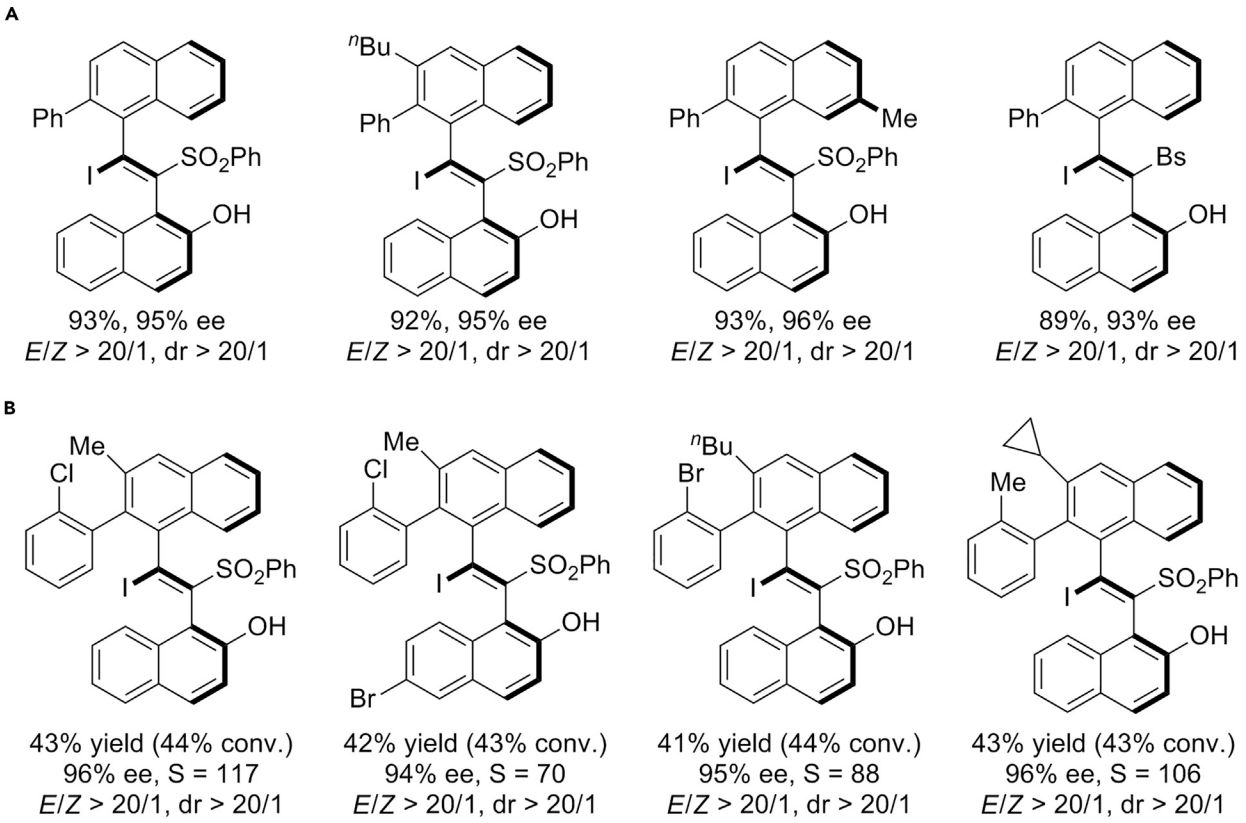
Scheme 27. Proposed mechanism for the synthesis of axially chiral sulfonestyrenes

In 2020, Zhao and co-workers developed a method for the synthesis of axially chiral amino sulfide vinyl arenes via organocatalytic cyclization (Scheme 29).[87] The authors utilized sulfide catalyst **C7** and achieved atroposelective electrophilic carbothiolation of alkynes **76**. The use of various substituents on two aromatic rings of **76**, and trifluoromethyl or substituted phenyl groups attached to the sulfur atom of **77**, could allow the formation of the desired products **78** in high yields with excellent enantioselectivities.

The possible pathway of this reaction is shown in Scheme 30. The intermediates **79** are first generated from the reaction of catalyst **C7** and sulfur reagents **77** in the presence of the Lewis acid trimethylsilyl trifluoromethanesulfonate (TMSOTf). Intermediates **79** will react with substrates **76** to afford thiirenium ion intermediates **80**. After the following tautomerization, intermediates **81** are furnished. Finally, an intramolecular hydroarylation on intermediates **81** gives the desired products **78**. The authors disclosed that amino groups on both catalyst and substrate protected by appropriate groups could form hydrogen bonds and lead to good enantioselectivities.

In 2019, Li and co-workers reported an organocatalytic asymmetric construction of axially chiral styrenes containing a stereogenic center.[88] As shown in Scheme 31, in the presence of catalyst **C5**, alkynes **82** could react with 5*H*-oxazol-ones **83** to give styrenes **84** in high yields with excellent ee values, diastereomeric ratio (dr) values, and *E*/*Z* ratios. The 5*H*-oxazolones act as nucleophiles and are activated by the cinchona alkaloid catalyst **C5** through deprotonation, thus affording the enolates, which undergo nucleophilic addition to VQM intermediates generated from **82**, furnishing the desired products **84**.

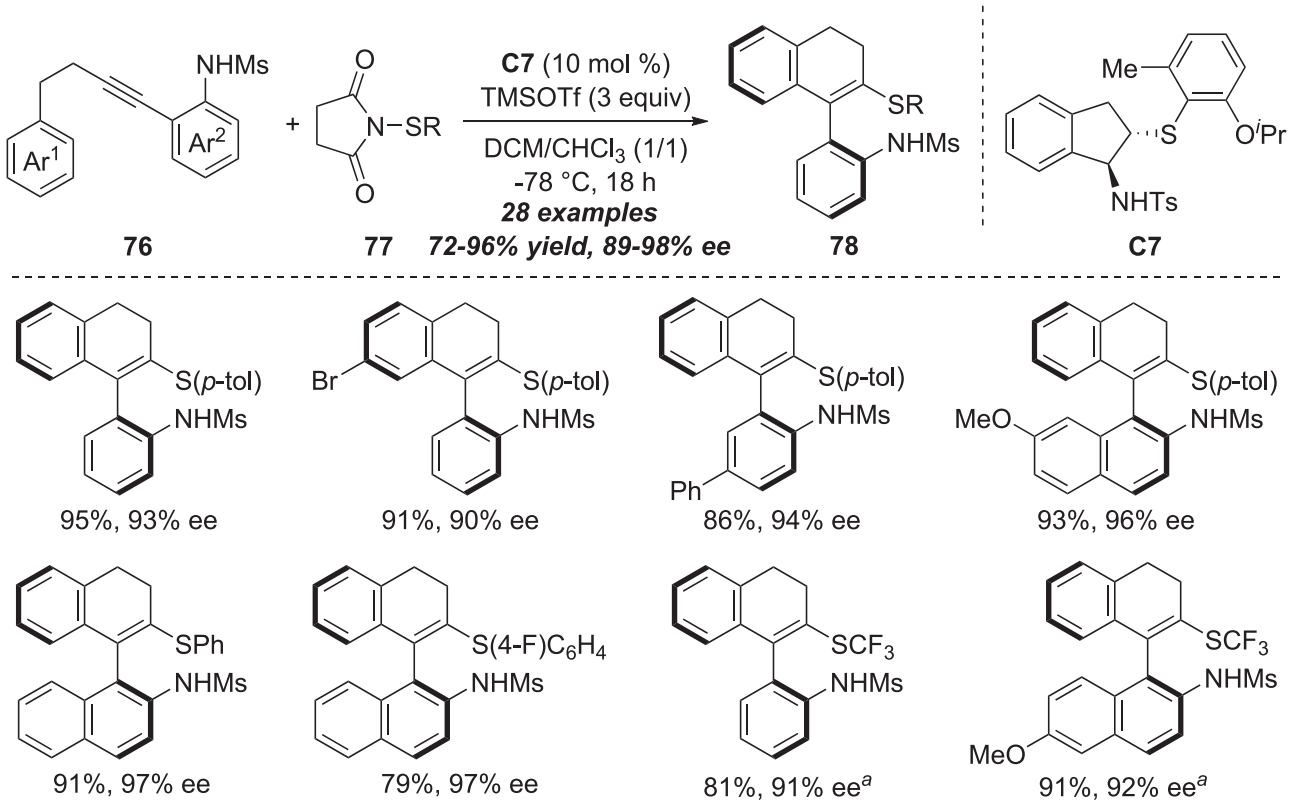




Scheme 28. Organocatalytic asymmetric construction of vicinal diaxial and triaxial styrenes

(A) Selected examples containing two stereogenic axes.

(B) Selected examples containing three stereogenic axes (kinetic resolution).



[a]*N*-CF_3S-saccharin was used.

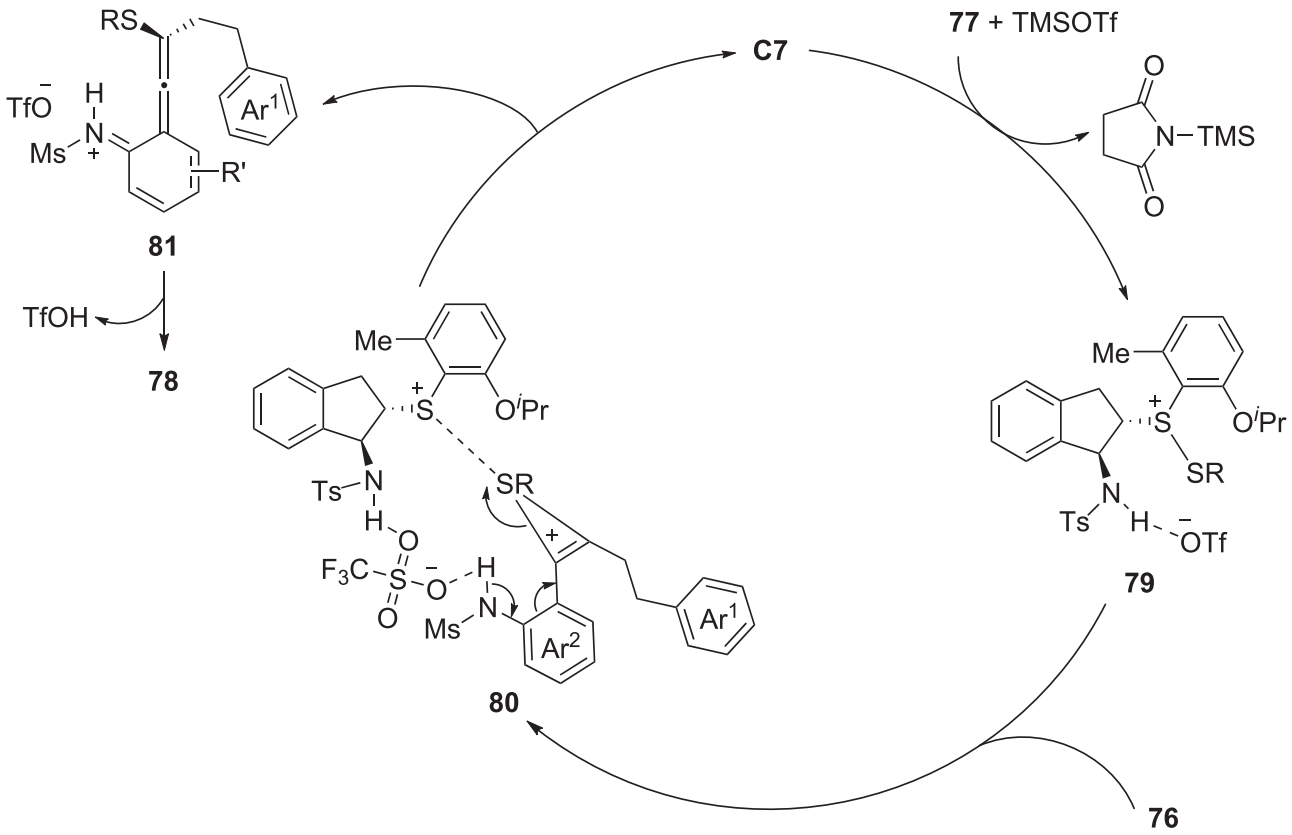
Scheme 29. Synthesis of axially chiral amino sulfide vinyl arenes via organocatalytic cyclization

In 2019, Tan and co-workers disclosed a CPA-catalyzed enantioselective synthesis of axially chiral 1,1′-(ethane-1,1-diyl)binaphthols (EBINOLs).[89] As shown in Scheme 32, the authors used 2-naphthols **85** and *o*-hydroxy or N-substituted amino arylethynylenes **86** as substrates, and the reaction proceeded smoothly in the presence of the CPA catalyst to deliver the corresponding products **87**. Different substituents on the *ortho* position of the ethynyl group of **85**, including the hydroxyl group, phenyl-substituted amino groups, and benzyl amino groups, could afford EBINOL derivatives **87** in high yields with excellent ee and dr values. Notably, the CPA **88** and chiral phosphine ligands **89** and **90** derived from EBINOLs performed well in some catalytic reactions, indicating the potential applications of EBINOLs.

According to the calculated free energy profile for the reaction, a plausible mechanism of this reaction is depicted in Scheme 33. Initially, the reaction of **86a** and **C10** forms a relatively stable intermediate **91**, and the subsequent concerted 1,5-H transfer generates intermediate **92** with axial chirality. Then, 2-naphthol undergoes a nucleophilic attack to produce intermediate **92**, which transfers the axial chirality from allene to alkene, furnishing intermediate **94**. Finally, intermediate **94** undergoes aromatization to afford the final product **87a** and regenerate the free catalyst.

Construction of axially chiral compounds via direct Michael-type addition

In 2017, Tan and co-workers reported an elegant protocol for organocatalytic asymmetric construction of axially chiral styrenes.[90] As shown in Scheme 34,



Scheme 30. Proposed mechanism for the synthesis of axially chiral amino sulfide vinyl arenes

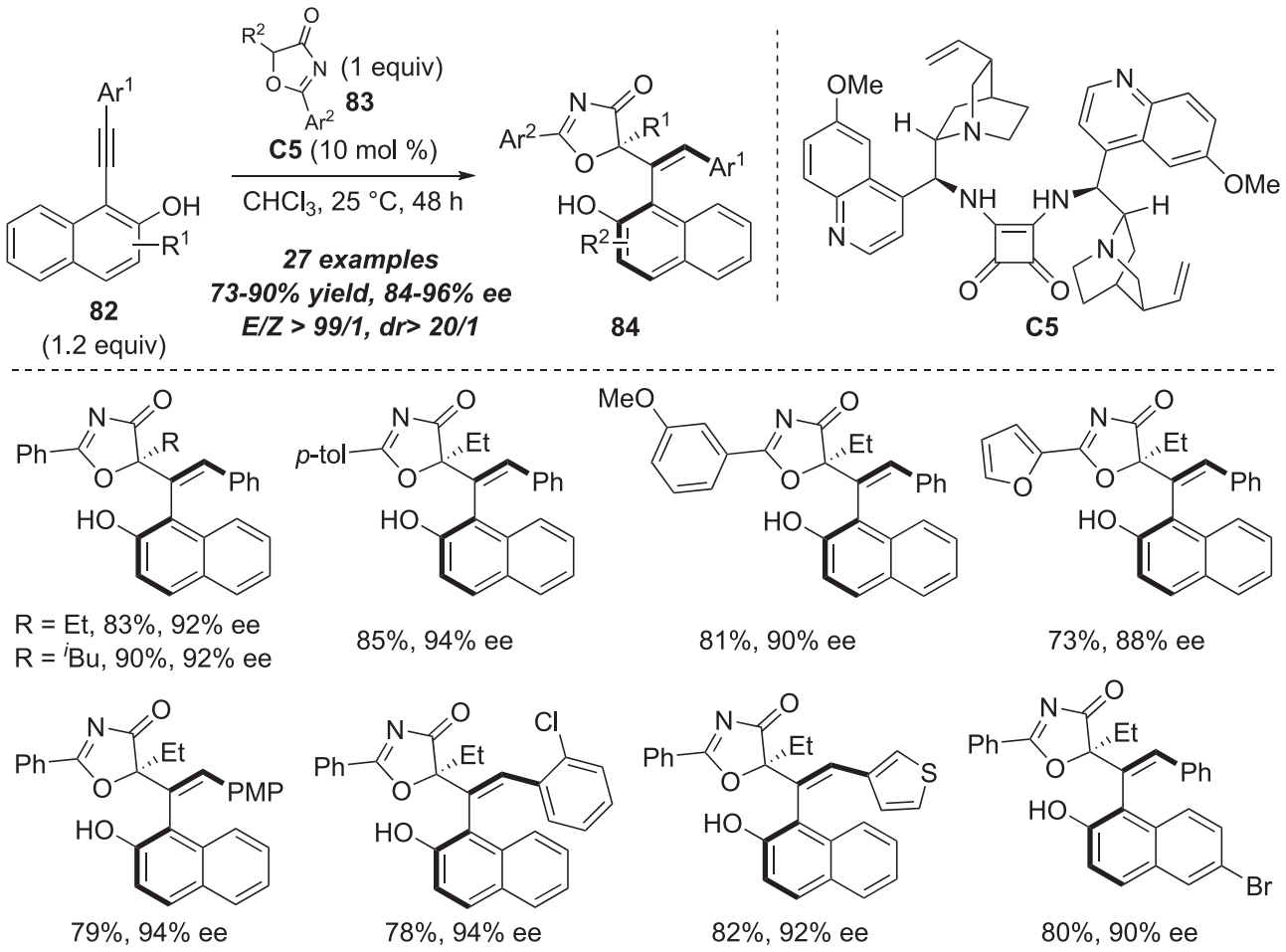
3-(4-bromobenzyl)pentane-2,4-diones or 2-benzylmalononitriles **95** could react with 2-substituted phenylpropiolaldehydes **96** in the presence of the secondary amine catalyst **C11**, giving products **97** in high, ee values, and *E*/*Z* ratios.

The proposed reaction mechanism is shown in Scheme 35. Alkynals **96** are initially converted into intermediates **98**, followed by the nucleophilic addition generating allenamine intermediates **99**. The formation of allenamines controls the axial chirality of products. Subsequently, the intermediates **99** are further converted into iminium intermediates **100** with efficient control of *E*/*Z* selectivity. Finally, the hydrolysis of intermediates **100** delivers products **97**.

By employing a similar strategy, in 2019, Yan and co-workers realized an organocatalytic atroposelective Michael addition of ynones with sulfone-type nucleophiles (Scheme 36).[91] The authors employed α-amido sulfones **102** and *ortho*-substituted ynones **101** as substrates. The reaction proceeded efficiently in the presence of the cinchona alkaloid catalyst, affording the corresponding sulfonyl styrenes **103** in good yields with excellent enantioselectivities.

Construction of axially chiral bridged biaryl compounds via NHC catalysis

Axially chiral bridged biaryls, which bear an additional linkage between the two arenes, are abundant in bioactive molecules.[6,7] However, the synthesis of these bridged biaryls generally requires multistep procedures. In 2019, Zhao and co-workers developed a strategy for the construction of axially chiral eight-membered lactone-bridged biaryls through N-heterocyclic carbene (NHC)-catalyzed cascaded



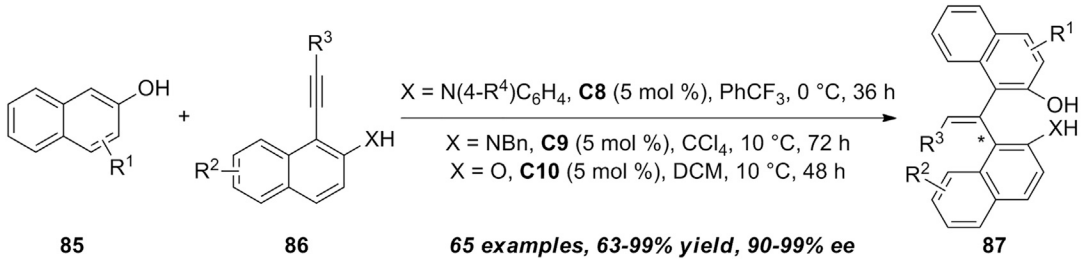
Scheme 31. Asymmetric construction of axially chiral styrenes containing stereogenic centers via organocatalysis

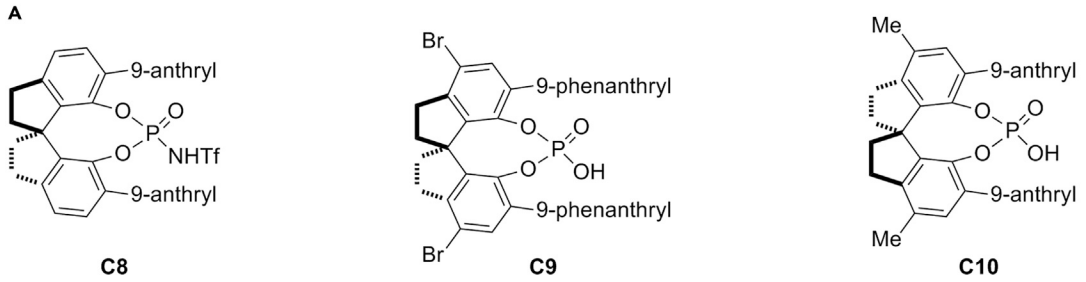
cyclization (Scheme 37).[92] A wide range of substituted propargylic alcohols **104** and enals **105** could be converted to the desired products **106** with both central and axial chirality with high yields, ee values, and dr values.

The proposed mechanism based on density functional theory (DFT) calculations is shown in Scheme 38. The NHC catalyst **C13** first reacts with **105** to form azolium enolates. Then, a propargylic substitution of azolium enolates generates allene intermediates **107**. Intermediates **107** can undergo two nucleophilic cyclizations to afford the final products **106** through intermediates **108** and **109**.

CONCLUSIONS

Axially chiral compounds are widely applied in the synthesis of bioactive molecules, drug discovery, and asymmetric reactions. Although alkyne moieties cannot be directly transformed into chiral centers, they can form alkenes or aryl rings with potential axial chirality through various types of reactions such as nucleophilic addition and cycloaddition. Atroposelective reactions of alkynes have received more and more attention and attempts at the construction of axially chiral compounds from alkynes have been made in recent years. For transition-metal catalysis, [2+2+2] cycloaddition was the main approach for the synthesis of





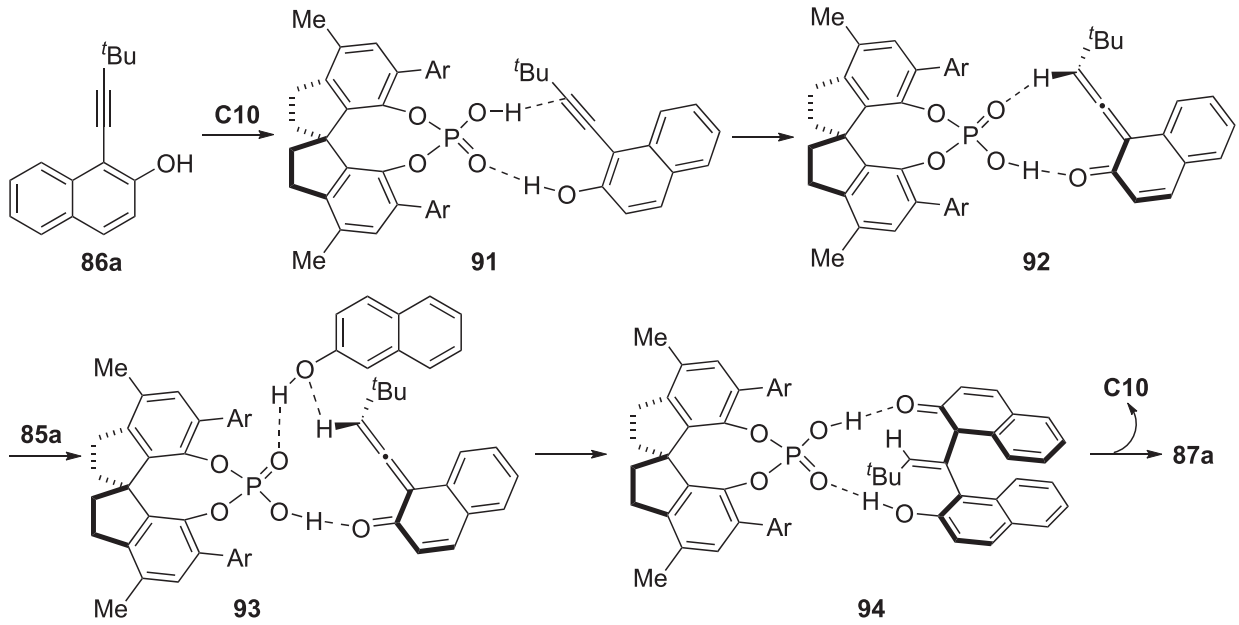
[a]Time: 12 h.

Scheme 32. CPA-catalyzed enantioselective synthesis of axially chiral EBINOLs

(A) The CPA catalysts **C8**–**C10**.

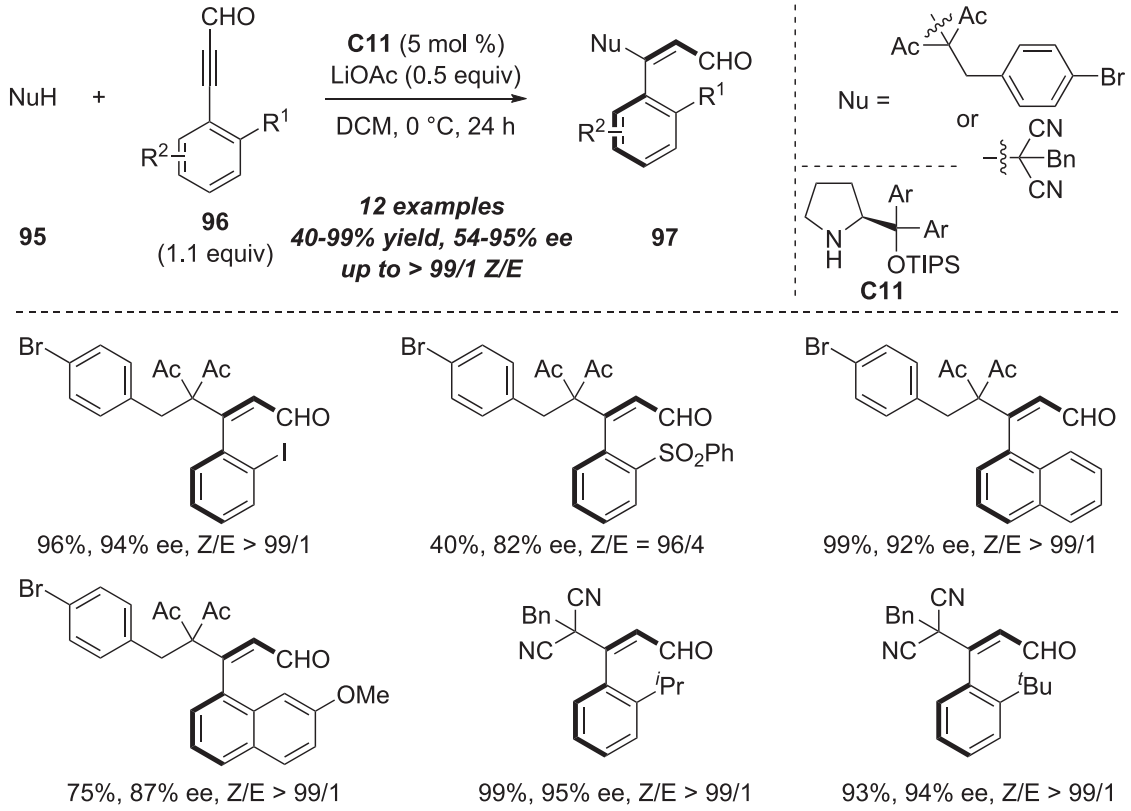
(B) Selected examples.

(C) CPA and phospheric ligands derived from **87**.

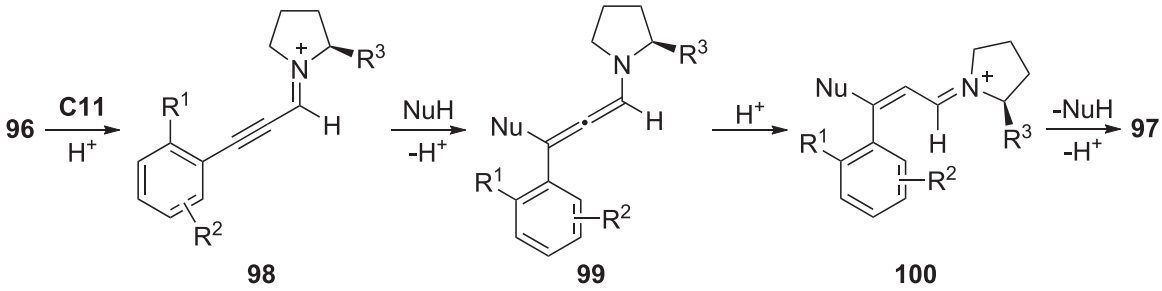


Scheme 33. Proposed mechanism for the CPA-catalyzed enantioselective synthesis of axially chiral EBINOLs

atropisomers from alkynes before 2010. In the past decade, other methodologies have been reported, including nucleophilic addition, insertion, and cross-coupling of alkynes. Transition-metal catalysis is an efficient catalytic model with low catalyst

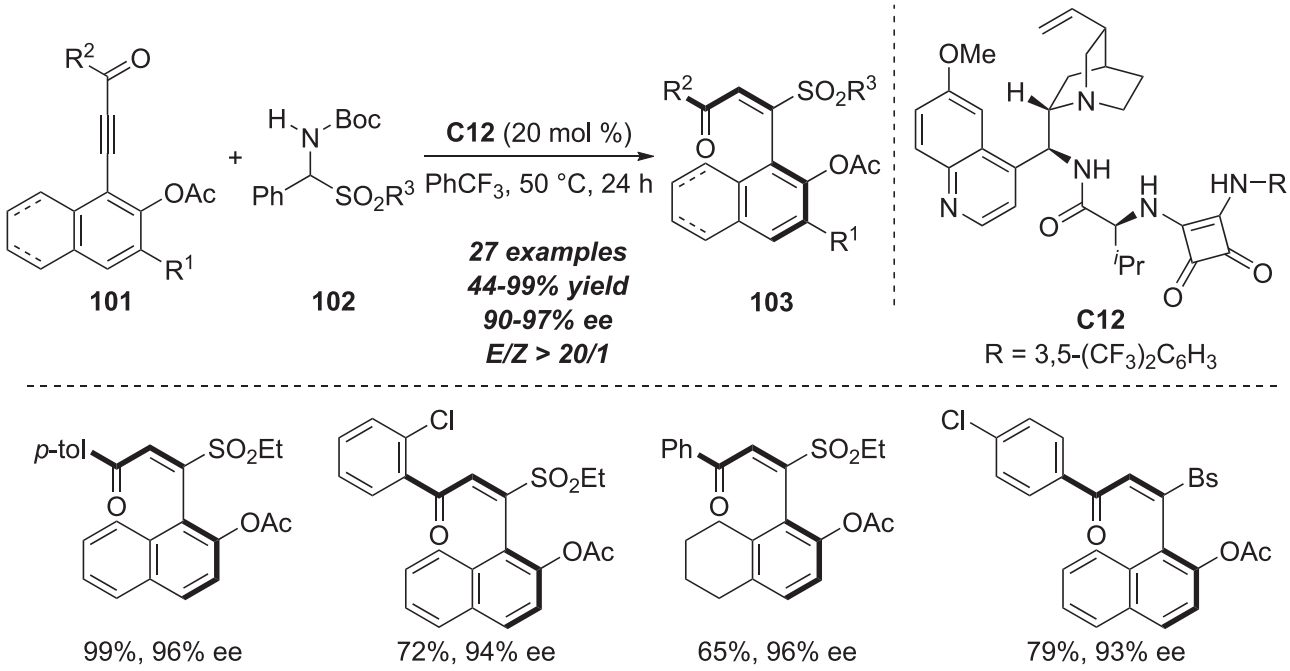


Scheme 34. Asymmetric construction of axially chiral styrenes via organocatalytic direct Michael-type addition

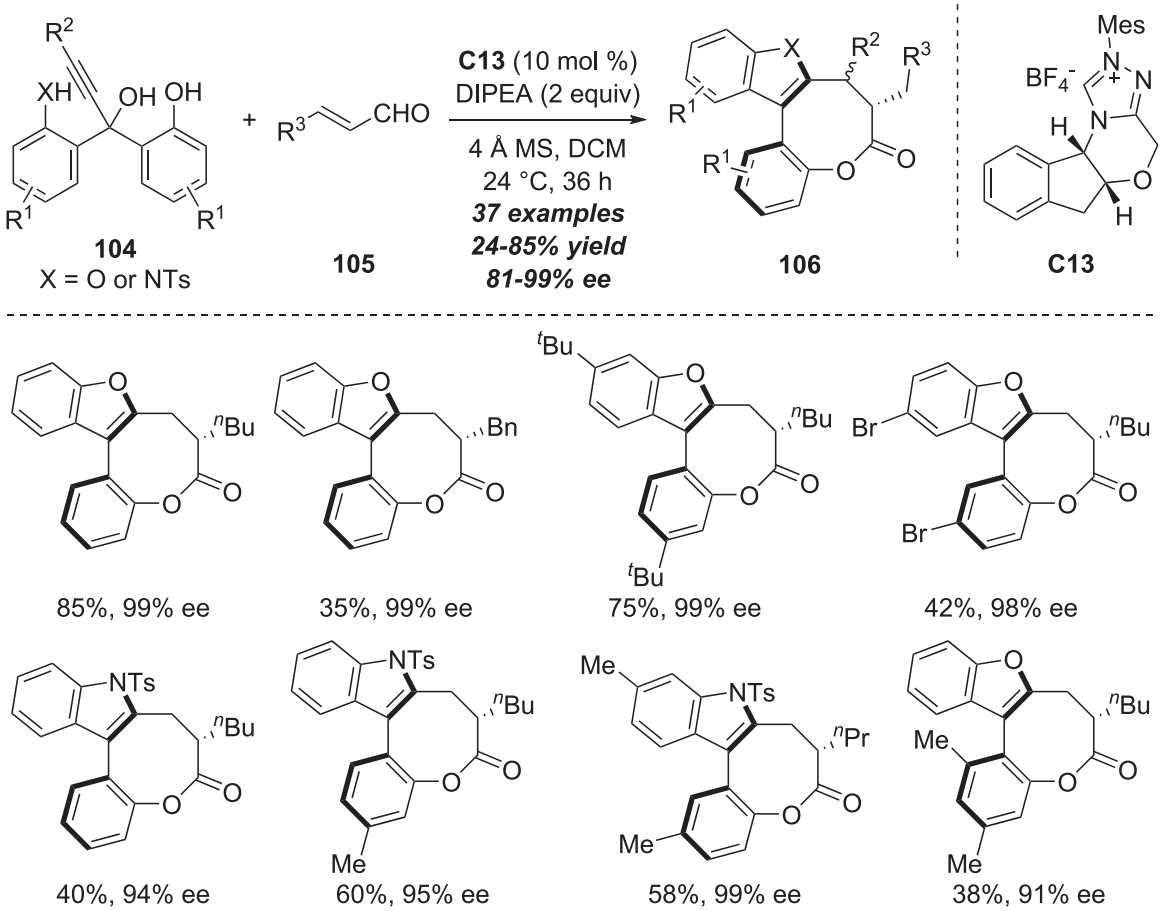


Scheme 35. Proposed mechanism for the organocatalytic Michael-type addition of phenylpropiolaldehydes

loading and short reaction time. However, some transition-metal-catalyzed reactions require high temperature, which is unfavorable for the construction of axially chiral compounds, since some atropisomers may racemize at high temperature. In addition, many metal catalysts are sensitive to air, which may limit their potential industrial application. Organocatalytic synthesis of atropisomers from alkynes has been widely reported in recent years. VQM intermediates are generally involved in these reactions. In addition, the organocatalytic direct Michael-type addition of alkynes to synthesize atropisomers is also well established. The organocatalysts utilized in these reactions include thioureas, amines, CPAs, and NHCs. The organocatalytic methodologies have developed rapidly in the past decade due to their inherent advantages. Compared with transition-metal-catalyzed reactions, organocatalytic reactions usually proceed smoothly under mild conditions with low temperature (room temperature or lower), and an open-air condition is allowed in organocatalytic reactions. The organocatalysts also possess the advantages of being cheaper and greener. Nevertheless, these organocatalytic reactions of alkynes still have several limitations. First, the reactions are feasible only for activated alkynes such as VQM precursors (*ortho*-hydroxy aryl ethynes) and alkynes



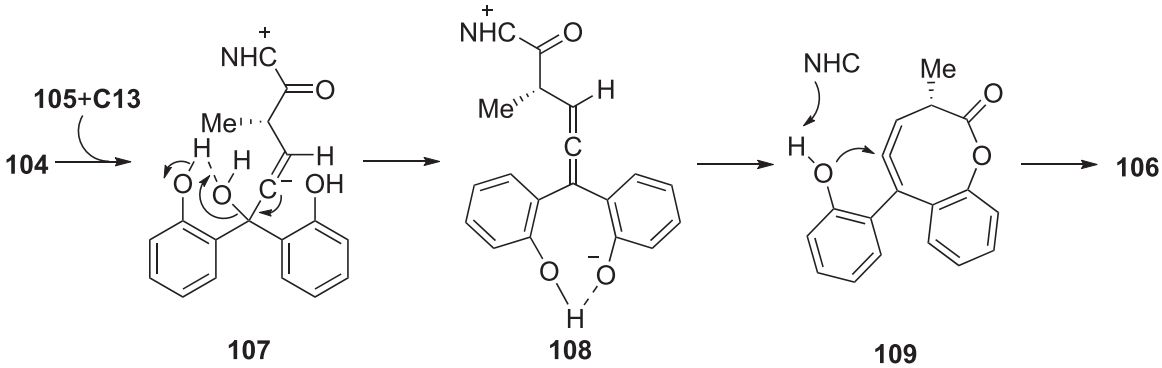
Scheme 36. Organocatalytic asymmetric Michael-type addition of ynones with sulfone-type nucleophiles



Scheme 37. NHC-catalyzed cascade cyclization to construct axially chiral bridged biaryls

attached with electron-withdrawing groups (EWGs). In other words, the organocatalytic reactions of inactivated alkynes to construct atropisomers are still challenging. Second, high catalyst loading is typically required.

Through the analysis of the field of atroposelective reactions based on alkynes, it is obvious that there remain some challenges in this field despite the significant achievements introduced in this review. Noble metals such as rhodium and palladium are widely utilized in transition-metal-catalyzed atroposelective reactions of



Scheme 38. Proposed mechanism for the synthesis of axially chiral bridged biaryls

alkynes, while the application of nonnoble metals, including copper, zinc, nickel, and cobalt, etc., in the atroposelective reactions of alkynes is rarely reported, although various other types of reactions of alkynes catalyzed by these nonnoble metals have been well established. In addition, compared with the well-developed atroposelective [2+2+2] cycloaddition of alkynes, the reports of atroposelective insertion and cross-coupling of alkynes catalyzed by transition metals are sporadic. For the organocatalytic atroposelective reactions of alkynes, these types of reactions usually require activated alkynes as substrates, and the utilization of inactivated alkynes is rarely reported. The most utilized organocatalysts in these types of reactions are thiourea and amine catalysts, while other organocatalysts, such as peptides, Brønsted acids, NHCs, phosphines, and phase-transfer catalysts, are relatively less employed. Moreover, enzymes, which are a type of newly developed efficient catalyst and perform well in a variety of catalytic reactions, are neglected in this field. In summary, it is urgent to improve catalytic atroposelective reactions of alkynes in several aspects, including the catalysts, reaction types, and universality of alkynes. We believe that these methodologies rarely reported will be gradually established with the development of axially chiral chemistry, and alkynes will further show their potential in the construction of axially chiral compounds in the future.

ACKNOWLEDGMENTS

We are grateful for financial support from MOST (2021YFC2100100), the National Natural Science Foundation of China (22125108, 92056104, and 21772161), the Natural Science Foundation of Fujian Province of China (2019J02001), President Research Funds from Xiamen University (20720210002), NFFTBS (J1310024), and PCSIRT.

AUTHOR CONTRIBUTIONS

Conceptualization, L.-W.Y.; writing – original draft, Z.-X.Z.; writing – review & editing, L.-W.Y. and T.-Y.Z.; supervision, L.-W.Y.

DECLARATION OF INTERESTS

The authors declare no competing interests.

REFERENCES

1. Kumarasamy, E., Raghunathan, R., Sibi, M.P., and Sivaguru, J. (2015). Nonbiaryl and heterobiaryl atropisomers: molecular templates with promise for atropselective chemical transformations. Chem. Rev. *115*, 11239–11300. https://doi.org/10.1021/acs.chemrev.5b00136.

2. Christie, G.H., and Kenner, J. (1922). LXXI.—the molecular configurations of polynuclear aromatic compounds. Part I. The resolution of γ-6:6′-dinitro- and 4:6:4′:6′-tetranitro-diphenic acids into optically active components. J. Chem. Soc. Trans. *121*, 614–620. https://doi.org/10.1039/CT9222100614.

3. Clayden, J. (1997). Non-biaryl atropisomers: new classes of chiral reagents, auxiliaries and ligands? Angew. Chem. Int. Ed. Engl. *36*, 949–951. https://doi.org/10.1002/anie.199709491.

4. McCormick, M.H., Stark, W.M., Pittenger, G.E., Pittenger, R.C., and McGuire, J.M. (1955). Vancomycin, a new antibiotic. new antibiotic. III. Preliminary clinical and laboratory studies. Antibiot. Annu. *3*, 606–611. pubmed.ncbi.nlm.nih.gov/13355338/.

5. Hallock, Y.F., Manfredi, K.P., Blunt, J.W., Cardellina, J.H., Schaffer, M., Gulden, K.P., Bringmann, G., Lee, A.Y., Clardy, J., Boyd, M.R., et al. (1994). Korupensamines A-D, novel antimalarial alkaloids from ancistrocladus korupensis. J. Org. Chem. *59*, 6349–6355. https://doi.org/10.1021/jo00100a042.

6. Bringmann, G., and Menche, D. (2001). Stereoselective total synthesis of axially chiral natural products via biaryl lactones. Acc. Chem. Res. *34*, 615–624. https://doi.org/10.1021/ar000106z.

7. Kupchan, S.M., Britton, R.W., Ziegler, M.F., Gilmore, C.J., Restivo, R.J., and Bryan, R.F. (1973). Steganacin and steganangin, novel antileukemic lignan lactones from Steganotaenia araliacea. J. Am. Chem. Soc. *95*, 1335–1336. https://doi.org/10.1021/ja00785a054.

8. Jiang, H.-L., Luo, X.-H., Wang, X.-Z., Yang, J.-L., Yao, X.-J., Crews, P., Valeriote, F.A., and Wu, Q.-X. (2012). New isocoumarins and alkaloid from Chinese insect medicine, Eupolyphaga sinensis Walker. Fitoterapia *83*, 1275–1280. https://doi.org/10.1016/j.fitote.2012.06.005.

9. Noyori, R., and Takaya, H. (1990). BINAP: an efficient chiral element for asymmetric catalysis. Acc. Chem. Res. *23*, 345–350. https://doi.org/10.1021/ar00178a005.

10. Brunel, J.M. (2007). BINOL: a versatile chiral reagent. Chem. Rev. *107*, PR1–PR45. https://doi.org/10.1021/cr078004a.

11. Yu, J., Shi, F., and Gong, L.-Z. (2011). Brønsted-acid-catalyzed asymmetric multicomponent reactions for the facile synthesis of highly enantioenriched structurally diverse nitrogenous heterocycles. Acc. Chem. Res. *44*, 1156–1171. https://doi.org/10.1021/ar2000343.

12. Wang, Y.-B., and Tan, B. (2018). Construction of axially chiral compounds via asymmetric organocatalysis. Acc. Chem. Res. *51*, 534–547. https://doi.org/10.1021/acs.accounts.7b00602.

13. Wencel-Delord, J., Panossian, A., Leroux, F.R., and Coloberta, F. (2015). Recent advances and new concepts for the synthesis of axially stereoenriched biaryls. Chem. Soc. Rev. *44*, 3418–3430. https://doi.org/10.1039/c5cs00012b.

14. Cheng, J.K., Xiang, S.-H., Li, S., Ye, L., and Tan, B. (2021). Recent advances in catalytic asymmetric construction of atropisomers. Chem. Rev. *121*, 4805–4902. https://doi.org/10.1021/acs.chemrev.0c01306.

15. Lassaletta, J.M. (2019). Atropisomerism and Axial Chirality (World Scientific).

16. Tan, B. (2021). Axially Chiral Compounds: Asymmetric Synthesis and Applications (Wiley-VCH).

17. Schore, N.E. (1988). Transition metal-mediated cycloaddition reactions of alkynes in organic synthesis. Chem. Rev. *88*, 1081–1119. https://doi.org/10.1021/cr00089a006.

18. Alonso, F., Beletskaya, I.P., and Yus, M. (2004). Transition-metal-catalyzed addition of heteroatom-hydrogen bonds to alkynes. Chem. Rev. *104*, 3079–3160. https://doi.org/10.1021/cr0201068.

19. Kotha, S., Brahmachary, E., and Lahiri, K. (2005). Transition metal catalyzed [2+2+2] cycloaddition and application in organic synthesis. Eur. J. Org. Chem. *2005*, 4741–4767. https://doi.org/10.1002/ejoc.200500411.

20. Jiménez-Núñez, E., and Echavarren, A.M. (2008). Gold-catalyzed cycloisomerizations of enynes: a mechanistic perspective. Chem. Rev. *108*, 3326–3350. https://doi.org/10.1021/cr0684319.

21. Tan, T.-D., Chen, Y.-B., Fan, X.-Y., and Ye, L.-W. (2019). Recent progress in the copper-catalyzed cascade cyclization involving intramolecular hydroamination of terminal alkynes. Synlett *30*, 2035–2040. https://doi.org/10.1055/s-0037-1611903.

22. Ye, L.-W., Zhu, X.-Q., Sahani, R.L., Xu, Y., Qian, P.-C., and Liu, R.-S. (2020). Nitrene transfer and carbene transfer in gold catalysis. Chem. Rev. *121*. https://doi.org/10.1021/acs.chemrev.0c00348.

23. Guo, J., Cheng, Z., Chen, J., Chen, X., and Lu, Z. (2021). Iron- and cobalt-catalyzed asymmetric hydrofunctionalization of alkenes and alkynes. Acc. Chem. Res. *54*, 2701–2716. https://doi.org/10.1021/acs.accounts.1c00212.

24. Li, J., He, D., Lin, Z., Wu, W., and Jiang, H. (2021). Recent advances in NHC-palladium catalysis for alkyne chemistry: versatile synthesis and applications. Org. Chem. Front. *8*, 3502–3524. https://doi.org/10.1039/D1QO00111F.

25. Salvio, R., Moliterno, M., and Bella, M. (2014). Alkynes in organocatalysis. Asian J. Org. Chem. *3*, 340–351. https://doi.org/10.1002/ajoc.201400021.

26. Sharma, A., Nagaraju, K., Rao, G.A., Gurubrahamam, R., and Chen, K. (2021). Asymmetric organocatalysis of activated alkynes and enynes. Asian J. Org. Chem. *10*, 1567–1579. https://doi.org/10.1002/ajoc.202100252.

27. Shibata, T., Fujimoto, T., Yokota, K., and Takagi, K. (2004). Iridium complex-catalyzed highly enantio- and diastereoselective [2+2+2] cycloaddition for the synthesis of axially chiral teraryl compounds. J. Am. Chem. Soc. *126*, 8382–8383. https://doi.org/10.1021/ja048131d.

28. Varela, J.A., and Saá, C. (2003). Construction of pyridine rings by metal-mediated [2+2+2] cycloaddition. Chem. Rev. *103*, 3787–3802. https://doi.org/10.1021/cr030677f.

29. Yamamoto, Y. (2005). Recent advances in intramolecular alkyne cyclotrimerization and its applications. Curr. Org. Chem. *9*, 503–519. https://doi.org/10.2174/1385272053544399.

30. Chopade, P.R., and Louie, J. (2006). [2+2+2] Cycloaddition reactions catalyzed by transition metal complexes. Adv. Synth. Catal. *348*, 2307–2327. https://doi.org/10.1002/adsc.200600325.

31. Sato, Y., Nishimata, T., and Mori, M. (1994). Asymmetric synthesis of isoindoline and isoquinoline derivatives using nickel(0)-catalyzed [2+2+2] cocyclization. J. Org. Chem. *59*, 6133–6135. https://doi.org/10.1021/jo00100a003.

32. Shibata, Y., and Tanaka, K. (2012). Rhodium-catalyzed [2+2+2] cycloaddition of alkynes for the synthesis of substituted benzenes: catalysts, reaction scope, and synthetic applications. Synthesis *44*, 323–350. https://doi.org/10.1055/s-0031-1289665.

33. Tanaka, K., and Shirasaka, K. (2003). Highly chemo- and regioselective intermolecular cyclotrimerization of alkynes catalyzed by cationic rhodium(I)/modified BINAP complexes. Org. Lett. *5*, 4697–4699. https://doi.org/10.1021/ol035963s.

34. Tanaka, K., Nishida, G., Wada, A., and Noguchi, K. (2004). Enantioselective synthesis of axially chiral phthalides through cationic [$Rh^{I}(H_8$-binap)]-catalyzed cross alkyne cyclotrimerization. Angew. Chem. Int. Ed. *43*, 6510–6512. https://doi.org/10.1002/anie.200461533.

35. Tanaka, K., Nishida, G., Ogino, M., Hirano, M., and Noguchi, K. (2005). Enantioselective synthesis of axially chiral biaryls through rhodium-catalyzed complete intermolecular cross-cyclotrimerization of internal alkynes. Org. Lett. *7*, 3119–3121. https://doi.org/10.1021/ol0511880.

36. DeKorver, K.A., Li, H., Lohse, A.G., Hayashi, R., Lu, Z., Zhang, Y., and Hsung, R.P. (2010). Ynamides: a modern functional group for the new millennium. Chem. Rev. *110*, 5064–5106. https://doi.org/10.1021/cr100003s.

37. Wang, X.-N., Yeom, H.-S., Fang, L.-C., He, S., Ma, Z.-X., Kedrowski, B.L., and Hsung, R.P. (2014). Ynamides in ring forming transformations. Acc. Chem. Res. *47*, 560–578. https://doi.org/10.1021/ar400193g.

38. Evano, G., Theunissen, C., and Lecomte, M. (2015). Ynamides: powerful and versatile reagents for chemical synthesis. Aldrichim. Acta *48*, 59–70.

39. Pan, F., Shu, C., and Ye, L.-W. (2016). Recent progress towards gold-catalyzed synthesis of N-containing tricyclic compounds based on ynamides. Org. Biomol. Chem. *14*, 9456–9465. https://doi.org/10.1039/C6OB01774F.

40. Zhou, B., Tan, T.-D., Zhu, X.-Q., Shang, M., and Ye, L.-W. (2019). Reversal of regioselectivity in ynamide chemistry. ACS Catal. *9*, 6393–6406. https://doi.org/10.1021/acscatal.9b01851.

41. Chen, Y.-B., Qian, P.-C., and Ye, L.-W. (2020). Brønsted acid-mediated reactions of ynamides. Chem. Soc. Rev. *49*, 8897–8909. https://doi.org/10.1039/d0cs00474j.

42. Hong, F.-L., and Ye, L.-W. (2020). Transition metal-catalyzed tandem reactions of ynamides for divergent N-heterocycle synthesis. Acc. Chem. Res. *53*, 2003–2019. https://doi.org/10.1021/acs.accounts.0c00417.

43. Tan, T.-D., Wang, Z.-S., Qian, P.-C., and Ye, L.-W. (2021). Radical reactions of ynamides. Small Methods *5*, 2000673. https://doi.org/10.1002/smtd.202000673.

44. Li, L., Luo, W.-F., and Ye, L.-W. (2021). Recent progress in the gold-catalyzed annulations of ynamides with isoxazole derivatives via α-Imino gold carbenes. Synlett *32*. https://doi.org/10.1055/a-1344-5998.

45. Tanaka, K., Takeishi, K., and Noguchi, K. (2006). Enantioselective synthesis of axially chiral anilides through rhodium-catalyzed [2+2+2] cycloaddition of 1,6-diynes with trimethylsilylynamides. J. Am. Chem. Soc. *128*, 4586–4587. https://doi.org/10.1021/ja060348f.

46. Oppenheimer, J., Hsung, R.P., Figueroa, R., and Johnson, W.L. (2007). Stereochemical control of both C−C and C−N axial chirality in the synthesis of chiral N,O-biaryls. Org. Lett. *9*, 3969–3972. https://doi.org/10.1021/ol701692m.

47. Heller, B., Sundermann, B., Fischer, C., You, J., Chen, W., Drexler, H.-J., Knochel, P., Bonrath, W., and Gutnov, A. (2003). Facile and racemization-free conversion of chiral nitriles into pyridine derivatives. J. Org. Chem. *68*, 9221–9225. https://doi.org/10.1021/jo030206t.

48. Gutnov, A., Heller, B., Fischer, C., Drexler, H.-J., Spannenberg, A., Sundermann, B., and Sundermann, C. (2004). Cobalt(I)-catalyzed asymmetric [2+2+2] cycloaddition of alkynes and nitriles: synthesis of enantiomerically enriched atropoisomers of 2-arylpyridines. Angew. Chem. Int. Ed. *43*, 3795–3797. https://doi.org/10.1002/anie.200454164.

49. Hong, P., and Yamazaki, H. (1977). Synthesis of 2-oxo- and 2-imino-1,2-dihydropyridines by cobalt-catalyzed cyclocotrimerization of acetylenes with isocyanates and carbodiimides. Tetrahedron Lett. *18*, 1333–1336. https://doi.org/10.1016/S0040-4039(01)93010-2.

50. Tanaka, K., Wada, A., and Noguchi, K. (2005). Rhodium-catalyzed chemo-, regio-, and enantioselective [2+2+2] cycloaddition of alkynes with isocyanates. Org. Lett. *7*, 4737–4739. https://doi.org/10.1021/ol052041b.

51. Chan, A.S.C., Hu, W., Pai, C.-C., Lau, C.-P., Jiang, Y., Mi, A., Yan, M., Sun, J., Lou, R., and Deng, J. (1997). Novel spiro phosphinite ligands and their application in homogeneous catalytic hydrogenation reactions. J. Am.

Chem. Soc. *119*, 9570–9571. https://doi.org/10.1021/ja970955q.

52. Zhu, S.-F., Xie, J.-B., Zhang, Y.-Z., Li, S., and Zhou, Q.-L. (2006). Well-defined chiral spiro iridium/phosphine–oxazoline cationic complexes for highly enantioselective hydrogenation of imines at ambient pressure. J. Am. Chem. Soc. *128*, 12886–12891. https://doi.org/10.1021/ja063444p.

53. Wakita, K., Arai, M.A., Kato, T., Shinohara, T., and Sasai, H. (2004). Spiro bis(isoxazole) as a new chiral ligand. Heterocycles *62*, 831–838. https://doi.org/10.3987/COM-03-S(P)60.

54. Wada, A., Noguchi, K., Hirano, M., and Tanaka, K. (2007). Enantioselective synthesis of C2-symmetric spirobipyridine ligands through cationic Rh(I)/modified-BINAP-catalyzed double [2+2+2] cycloaddition. Org. Lett. *9*, 1295–1298. https://doi.org/10.1021/ol070129e.

55. Zhang, L. (2014). A non-diazo approach to α-oxo gold carbenes via gold-catalyzed alkyne oxidation. Acc. Chem. Res. *47*, 877–888. https://doi.org/10.1021/ar400181x.

56. Huple, D.B., Ghorpade, S., and Liu, R.-S. (2016). Recent advances in gold-catalyzed N- and O-functionalizations of alkynes with nitrones, nitroso, nitro and nitroxy species. Adv. Synth. Catal. *358*, 1348–1367. https://doi.org/10.1002/adsc.201600018.

57. Zheng, Z., Wang, Z., Wang, Y., and Zhang, L. (2016). Au-catalysed oxidative cyclisation. Chem. Soc. Rev. *45*, 4448–4458. https://doi.org/10.1039/c5cs00887e.

58. Asiriaand, A.M., and Hashmi, A.S.K. (2016). Gold-catalysed reactions of diynes. Chem. Soc. Rev. *45*, 4471–4503. https://doi.org/10.1039/c6cs00023a.

59. Zhou, B., Li, L., and Ye, L.-W. (2016). Recent progress in the metal-free or nonnoble-metal-catalyzed oxidation of alkynes by using pyridine *N*-oxides as external oxidants. Synlett *27*, 493–497. https://doi.org/10.1055/s-0035-1560961.

60. Li, L., Tan, T.-D., Zhang, Y.-Q., Liu, X., and Ye, L.-W. (2017). Recent advances in transition-metal-catalyzed reactions of alkynes with isoxazoles. Org. Biomol. Chem. *15*, 8483–8492. https://doi.org/10.1039/c7ob01895a.

61. Ototake, N., Morimoto, Y., Mokuya, A., Fukaya, H., Shida, Y., and Kitagawa, O. (2010). Catalytic enantioselective synthesis of atropisomeric indoles with an N–C chiral axis. Chem. Eur. J. *16*, 6752–6755. https://doi.org/10.1002/chem.201000243.

62. Tian, M., Bai, D., Zheng, G., Chang, J., and Li, X. (2019). Rh(III)-catalyzed asymmetric synthesis of axially chiral biindolyls by merging C–H activation and nucleophilic cyclization. J. Am. Chem. Soc. *141*, 9527–9532. https://doi.org/10.1021/jacs.9b04711.

63. He, Y.-P., Wu, H., Wang, Q., and Zhu, J. (2020). Palladium-catalyzed enantioselective cacchi reaction: asymmetric synthesis of axially chiral 2,3-disubstituted indoles. Angew. Chem. Int. Ed. *59*, 2105–2109. https://doi.org/10.1002/anie.201914049.

64. Tsukamoto, H., Ikeda, T., and Doi, T. (2016). Palladium(II)-catalyzed annulation of alkynes with 2-(cyanomethyl)phenylboronates leading to 3,4-disubstituted 2-naphthalenamines. J. Org. Chem. *81*, 1733–1745. https://doi.org/10.1021/acs.joc.5b02378.

65. Xue, F., and Hayashi, T. (2018). Asymmetric synthesis of axially chiral 2-aminobiaryls by rhodium-catalyzed benzannulation of 1-arylalkynes with 2-(cyanomethyl) phenylboronates. Angew. Chem. Int. Ed. *57*, 10368–10372. https://doi.org/10.1002/anie.201806324.

66. Wessig, P., and Müller, G. (2008). The dehydro-Diels-Alder reaction. Chem. Rev. *108*, 2051–2063. https://doi.org/10.1021/cr0783986.

67. Li, W., Zhou, L., and Zhang, J. (2016). Recent progress in dehydro(genative) Diels-Alder reaction. Chem. Eur. J. *22*, 1558–1571. https://doi.org/10.1002/chem.201503571.

68. Shibata, T., Sekine, A., Mitake, A., and Kanyiva, K.S. (2018). Intramolecular consecutive dehydro-Diels-Alder reaction for the catalytic and enantioselective construction of axial chirality. Angew. Chem. Int. Ed. *57*, 15862–15865. https://doi.org/10.1002/anie.201810174.

69. Takano, H., Shiozawa, N., Imai, Y., Kanyiva, K.S., and Shibata, T. (2020). Catalytic enantioselective synthesis of axially chiral polycyclic aromatic hydrocarbons (PAHs) via regioselective C–C bond activation of biphenylenes. J. Am. Chem. Soc. *142*, 4714–4722. https://doi.org/10.1021/jacs.9b12205.

70. Jia, C., Piao, D., Oyamada, J., Lu, W., Kitamura, T., and Fujiwara, Y. (2000). Efficient activation of aromatic C–H bonds for addition to C–C multiple bonds. Science *287*, 1992–1995. https://doi.org/10.1126/science.287.5460.1992.

71. Shibuya, T., Shibata, Y., Noguchi, K., and Tanaka, K. (2011). Palladium-catalyzed enantioselective intramolecular hydroarylation of alkynes to form axially chiral 4-aryl 2-quinolinones. Angew. Chem. Int. Ed. *50*, 3963–3967. https://doi.org/10.1002/anie.201100152.

72. Zhang, J., Simon, M., Golz, C., and Alcarazo, M. (2020). Gold-catalyzed atroposelective synthesis of 1,1′-binaphthalene-2,3′-diols. Angew. Chem. Int. Ed. *59*, 5647–5650. https://doi.org/10.1002/anie.201915456.

73. Chuprakov, S., Hwang, F.W., and Gevorgyan, V. (2007). Rh-catalyzed transannulation of pyridotriazoles with alkynes and nitriles. Angew. Chem. Int. Ed. *46*, 4757–4759. https://doi.org/10.1002/anie.200700804.

74. Miura, T., Yamauchi, M., and Murakami, M. (2009). Nickel-catalysed denitrogenative alkyne insertion reactions of *N*-sulfonyl-1,2,3-triazoles. Chem. Commun. *2009*, 1470–1471. https://doi.org/10.1039/b819162j.

75. Fang, Z.-J., Zheng, S.-C., Guo, Z., Guo, J.-Y., Tan, B., and Liu, X.-Y. (2015). Asymmetric synthesis of axially chiral isoquinolones: nickel-catalyzed denitrogenative transannulation. Angew. Chem. Int. Ed. *54*, 9528–9532. https://doi.org/10.1002/anie.201503207.

76. Ros, A., Estepa, B., Ramírez-López, P., Álvarez, E., Fernández, R., and Lassaletta, J.M. (2013). Dynamic kinetic cross-coupling strategy for the asymmetric synthesis of axially chiral heterobiaryls. J. Am. Chem. Soc. *135*, 15730–15733. https://doi.org/10.1021/ja4087819.

77. Zheng, J., Cui, W.-J., Zheng, C., and You, S.-L. (2016). Synthesis and application of chiral spiro Cp ligands in rhodium-catalyzed asymmetric oxidative coupling of biaryl compounds with alkenes. J. Am. Chem. Soc. *138*, 5242–5245. https://doi.org/10.1021/jacs.6b02302.

78. Hornillos, V., Ros, A., Ramírez-López, P., Iglesias-Sigüenza, J., Fernández, R., and Lassaletta, J.M. (2016). Synthesis of axially chiral heterobiaryl alkynes via dynamic kinetic asymmetric alkynylation. Chem. Commun. *52*, 14121–14124. https://doi.org/10.1039/c6cc08997f.

79. Sachie, A., Masaki, F., Shota, B., Kazunobu, I., Katsuhiko, T., and Ryo, I. (2018). Vinylidene *ortho*-quinone methides: unique chiral reaction intermediates in catalytic asymmetric synthesis. Chimia *72*, 892–899. https://doi.org/10.2533/chimia.2018.892.

80. RoDriguez, J., and Bonne, D. (2019). Enantioselective organocatalytic activation of vinylidene-quinone methides (VQMs). Chem. Commun. *55*, 11168–11170. https://doi.org/10.1039/C9CC05097C.

81. Furusawa, M., Arita, K., Imahori, T., Igawa, K., Tomooka, K., and Irie, R. (2013). Base-catalyzed Schmittel cycloisomerization of *o*-phenylenediyne-linked bis(arenol)s to indeno [1,2-c]chromenes. Tetrahedron Lett. *54*, 7107–7110. https://doi.org/10.1016/j.tetlet.2013.10.080.

82. Liu, Y., Wu, X., Li, S., Xue, L., Shan, C., Zhao, Z., and Yan, H. (2018). Organocatalytic atroposelective intramolecular [4+2] cycloaddition: synthesis of axially chiral heterobiaryls. Angew. Chem. Int. Ed. *57*, 6491–6495. https://doi.org/10.1002/anie.201801824.

83. Jia, S., Li, S., Liu, Y., Qin, W., and Yan, H. (2019). Enantioselective control of both helical and axial stereogenic elements though an organocatalytic approach. Angew. Chem. Int. Ed. *58*, 18496–18501. https://doi.org/10.1002/anie.201909214.

84. Peng, L., Li, K., Xie, C., Li, S., Xu, D., Qin, W., and Yan, H. (2019). Organocatalytic asymmetric annulation of *ortho*-alkynylanilines: synthesis of axially chiral naphthyl-C2-indoles. Angew. Chem. Int. Ed. *58*, 17199–17204. https://doi.org/10.1002/anie.201908961.

85. Jia, S., Chen, Z., Zhang, N., Tan, Y., Liu, Y., Deng, J., and Yan, H. (2018). Organocatalytic enantioselective construction of axially chiral sulfone-containing styrenes. J. Am. Chem. Soc. *140*, 7056–7060. https://doi.org/10.1021/jacs.8b03211.

86. Tan, Y., Jia, S., Hu, F., Liu, Y., Peng, L., Li, D., and Yan, H. (2018). Enantioselective construction of vicinal diaxial styrenes and multiaxis system via organocatalysis. J. Am. Chem. Soc. *140*, 16893–16898. https://doi.org/10.1021/jacs.8b09893.

87. Liang, Y., Ji, J., Zhang, X., Jiang, Q., Luo, J., and Zhao, X. (2020). Enantioselective construction of axially chiral amino sulfide vinyl arenes by chiral sulfide-catalyzed electrophilic carbothiolation of alkynes. Angew. Chem. Int. Ed. *59*, 4959–4964. https://doi.org/10.1002/anie.201915470.

88. Huang, A., Zhang, L., Li, D., Liu, Y., Yan, H., and Li, W. (2019). Asymmetric one-pot construction of three stereogenic elements: chiral carbon center, stereoisomeric alkenes, and chirality of axial styrenes. Org. Lett. *21*, 95–99. https://doi.org/10.1021/acs.orglett.8b03492.

89. Wang, Y.-B., Yu, P., Zhou, Z.-P., Zhang, J., Wang, J., Luo, S.-H., Gu, Q.-S., Houk, K.N., and Tan, B. (2019). Rational design, enantioselective synthesis and catalytic applications of axially chiral EBINOLs. Nat. Catal. *2*, 504–513. https://doi.org/10.1038/s41929-019-0278-7.

90. Zheng, S.-C., Wu, S., Zhou, Q., Chung, L.W., Ye, L., and Tan, B. (2017). Organocatalytic atroposelective synthesis of axially chiral styrenes. Nat. Commun. *8*, 15238. https://doi.org/10.1038/ncomms15238.

91. Zhang, N., He, T., Liu, Y., Li, S., Tan, Y., Peng, L., Li, D., Shan, C., and Yan, H. (2019). Organocatalytic atropo- and *E/Z*-selective Michael addition reaction of ynones with α-amido sulfones as sulfone-type nucleophile. Org. Chem. Front. *6*, 451–455. https://doi.org/10.1039/C8QO01241E.

92. Lu, S., Ong, J.,-Y., Yang, H., Poh, S.B., Liew, X., Seow, C.S.D., Wong, M.W., and Zhao, Y. (2019). Diastereo- and atroposelective synthesis of bridged biaryls bearing an eight-membered lactone through an organocatalytic cascade. J. Am. Chem. Soc. *141*, 17062–17067. https://doi.org/10.1021/jacs.9b08510.