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Transition-metal-catalyzed atroposelective synthesis of axially chiral styrenes

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Axially chiral styrenes, a type of atropisomer analogous to biaryls, have attracted great interest because of their unique presence in natural products and asymmetric catalysis. Since 2016, a number of methodologies have been developed for the atroposelective construction of these chiral skeletons, involving both transition metal catalysis and organocatalysis. In this feature article, we aim to provide a comprehensive understanding of recent advances in the asymmetric synthesis of axially chiral styrenes catalyzed by transition metals, integrating scattered work with different catalytic systems together. This feature article is cataloged into five sections according to the strategies, including asymmetric coupling, enantioselective C–H activation, central-to-axial chirality transfer, asymmetric alkyne functionalization, and atroposelective [2+2+2] cycloaddition.

1. Introduction

Axial chirality, which originates from the inconvenient rotation of a chiral axis restricted by nearby steric hindrance groups,[1] is widely present in functional molecules among biochemistry, material science and so on,[2] as well as privileged chiral ligands in asymmetric catalysis.[3] Among all the axially chiral structures, most of them possess a rotation-restricted axis located between two aromatic moieties, known as biaryl atropisomers, such as BINOL, BINAP and so on, which were initially represented by Christie and Kenner in 1922.[4] Owing to the importance of this structural motif, the catalytic atroposelective construction of axially chiral (hetero)biaryls has been intensively developed since the 1980s.[5]

When one of the aryls is replaced by an alkene, the corresponding chiral compounds bearing a rotation-restricted axis between the simple alkene and an (hetero)aromatic ring are so-called axially chiral styrenes, and necessary steric hindrance to inhibit the rotation of the chiral axis is provided by two bulky substituents on the vinyl and another one or two steric groups on the aryl. This structure was first hypothesized by the Adams group during the study of axially chiral diphenyls in 1928,[6] and

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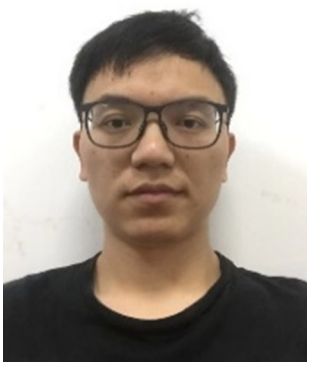
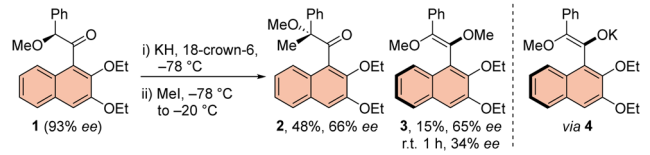


Tao Zhou

Tao Zhou was born in 1989 Hubei, China. He received a BSc degree (2012) in Shandong University and PhD (2017) from Nankai University under the supervision of Prof. Bai-Quan Wang. Then he worked as a postdoctoral fellow in the group of Prof. Bing-Feng Shi in Zhejiang University. And then he was promoted to associate professor in 2021. His current research interests are focused on transition-metal catalyzed asymmetric C–H activation.



Scheme 1 Pioneering work of asymmetric synthesis of axially chiral styrenes.

quickly certified with the resolution of 2-(2,4-di-methylpent-2-en-3-yl)-*N*,*N*,*N*-trimethylbenzenaminium iodide by the Mills group in 1939[7] and also with 3-(3-bromo-2,4,6-trimethylphenyl)-3-chloro-2-methylacrylic acid by Adams and co-workers in 1940.[8] During the 1940s, the Adams group further systematically explored the synthesis, resolution, and atropostability of axially chiral styrenes.[9] However, in sharp contrast, the axially chiral styrenes have been rarely studied with respect to asymmetric synthesis and applications until 2016. That is, for the sake of obtaining excellent atroposelectivity, axially chiral styrenes must possess sufficient steric hindrance, which is quite struggle to be achieved. Compared with biaryl compounds, axially chiral styrenes are more flexible, resulting in the reduction of the rotational barrier for racemization.[10] Meanwhile, protocols for the synthesis of sterically bulky tri- or tetra-substituted alkenes which own enough rotational hindrance are rather rare. Therefore, it is apparently more challenging to control the enantioselectivity when synthesizing axially chiral styrenes.

In 1991, Fuji and co-workers fortuitously obtained axially chiral styrene *via* a central-to-axial chirality transfer (Scheme 1).[11] When treating naphthyl ketone **1** (93% ee) with KH and then MeI, the desired *C*-alkylation product **2** was successfully gained. Interestingly, the *O*-alkylation by-product **3**, an axially chiral styrene with low atropostability, has also been isolated in 65% ee, certifying the existence of chirality memorization in chiral enolate **4**. Using the same strategy, the Baker group accomplished the asymmetric construction of axially chiral 1-(3′-indenyl)naphthalene in 1996,[12]

Bing-Feng Shi

Bing-Feng Shi was born in Shandong, China. He received his BS degree from Nankai University in 2001 and a PhD degree from the Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences under the guidance of Professor Biao Yu in 2006. Following time as a postdoctoral fellow at the University of California, San Diego (2006–2007), he moved to The Scripps Research Institute working with Professor Jin-Quan Yu as a research associate. In 2010, he joined the Department of Chemistry at Zhejiang University as a professor. His research focus is transition metal-catalyzed C–H functionalization and its application in the synthesis of biologically important small molecules.

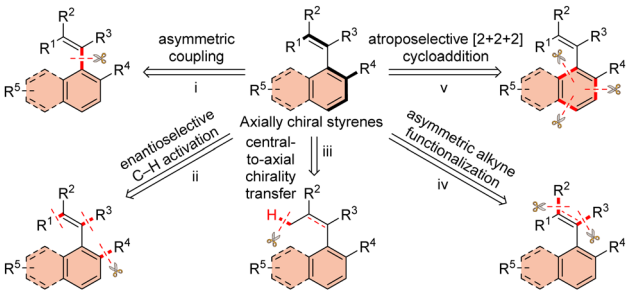


Fig. 1 Strategies for transition-metal-catalyzed asymmetric synthesis of axially chiral styrenes.

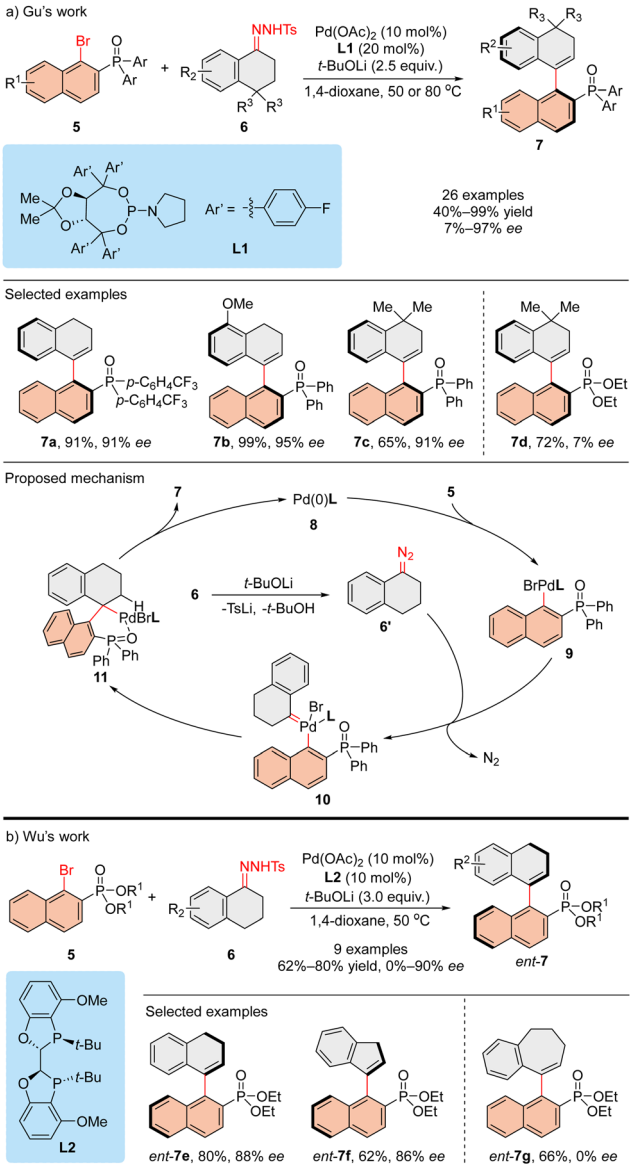
while Hattori, Miyano and co-workers also gained chiral 3,4-dihydro-1,1′-binaphthalene *via* stereospecific dehydration in 2001.[13] Subsequently, with axially chiral olefins as key intermediates, the Suzuki group achieved the asymmetric total synthesis of TAN-1085 in 2009.[14] Nevertheless, these previous studies still strongly rely on pre-installed stoichiometric chiral auxiliaries.

In recent years, with the dramatic progress of asymmetric catalysis, a number of methods for the atroposelective synthesis of axially chiral styrenes have been developed, involving both transition metal catalysis[15] and organocatalysis.[16] In comparison with well summarized organocatalyzed atroposelective synthesis of axially chiral olefins, advancements *via* transition metal catalysis have not been comprehensively summarized. We thus aim to provide a comprehensive understanding of recent advances in the asymmetric synthesis of axially chiral styrenes catalyzed by transition metals, mainly discussing mechanism and strategies rather than scattered reactions. This feature article covers all of the literature in related fields until June 2023, and is cataloged into five sections according to different strategies that have been employed *via* transition metal catalysis, including asymmetric coupling, enantioselective C–H activation, central-to-axial chirality transfer, asymmetric alkyne functionalization, and atroposelective [2+2+2] cycloaddition (Fig. 1).

2. Asymmetric C–C coupling strategy

In the synthesis of axially chiral biaryls, the simplest thought is to atroposelectively couple the two arenes together.[17] In this strategy, the C(vinyl)–C(aryl) axes are mainly formed during the atroposelective reductive elimination or β-H elimination, Furthermore, a weak coordination group at the ortho position of the C(vinyl)–C(aryl) axes is usually momentous for the enantiocontrol.

In 2016, applying this strategy, the Gu group reported the first catalytic enantioselective construction of chiral aryl olefins (Scheme 2a).[18] With a double bond located in a six-membered ring which enhanced the rigidity and atropostability of the structure, several diarylphosphine oxides bearing both electron-rich and -deficient substituents were gained. The indispensability of the diarylphosphoryl group may indicate that a π–π interaction could exist between the phenyl rings of the phosphine oxides **5** and arenes on TADDOL-based ligand **L1**, affecting partially the reaction enantioselectivity, as the ee value declined to 7% when



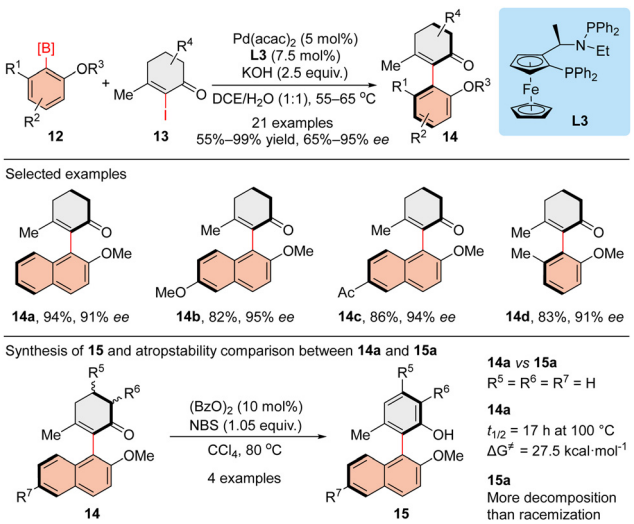
Scheme 2 Construction of axially chiral aryl olefins *via* Pd-catalyzed oxidative addition/carbene insertion.

diethylphosphonate **5d** was used. A plausible catalytic mechanism was presented. Starting by the oxidative addition of Pd(0) **8** with phosphine oxides **5**, the Pd(II) intermediate **9** reacts with diazo compound **6′** which is generated *in situ* when treating hydrazone **6** with *t*-BuOLi. A migration/insertion of Pd(IV) complex **10** then takes place, affording intermediate **11** bearing a quaternary carbon center. Through a further atroposelective β-H elimination, the final product **7** is yielded with regeneration of Pd(0) complex **8**. Additionally, the axially chiral phosphine oxides **7** could be reduced by $LiAlH_4$ to form a new class of chiral phosphine ligands, and could also be further aromatization by DDQ oxidation to form biaryl atropisomers when R^3 = H.

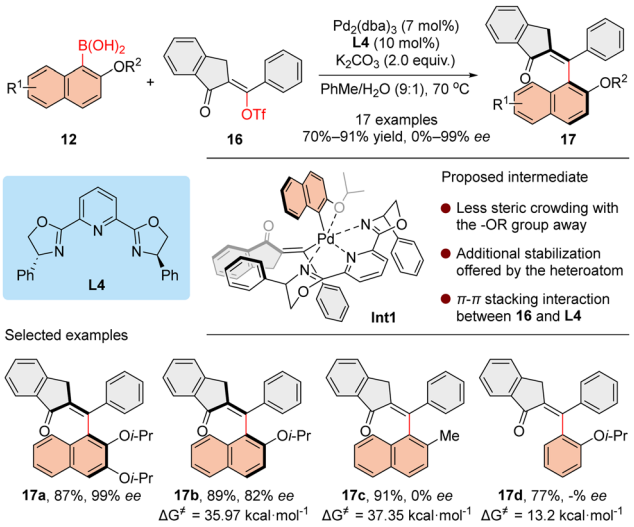
Shortly after, Wu and co-workers solved the scope limitation of dialkylphosphonates in the Gu's catalytic system smoothly (Scheme 2b).[19] Assisted by *ortho*-OMe-substituted BI-BOP ligand **L2**, a similar transformation was established. It is worth pointing out that the *N*-tosylhydrazone with a double bond enclosed in a five-membered ring was also tolerated (*ent*-**7f**), while the product with a seven-membered ring was obtained without any enantiomeric excess (*ent*-**7g**), which may be due to the more flexibility for a seven-membered cyclic skeleton.

Palladium-catalyzed Suzuki, Kumada, Negishi or Hiyama cross-coupling is quite powerful in the synthesis of axially chiral compounds.[20] In 2017, the Gu group employed this reaction for the enantioselective synthesis of styrene atropisomers *via* Suzuki–Miyaura cross-coupling with alkenyl iodides (Scheme 3).[21] In the presence of both central and planar chiral BoPhoz-based ligand **L3**, the target compounds could be acquired in up to 95% ee, and both naphthyl (**14a–14c**) and *ortho*-Me substrates (**14d**) were tolerated. The obtained 2-aryl-cyclohexenones were embellished into many kinds of compounds, such as 2-naphthylphenol **15**, quinone, carbazole and other biaryl atropisomers, without obvious loss of enantiomeric purity. Moreover, the racemization barriers of **14a** and **15a** have also been investigated. The half-life of **14a** was about 17 h at 100 °C with $\Delta G^{\ddagger}$ around 27.5 kcal mol^{-1} for racemization. While heating the 2-naphthylphenol **15a** at the same temperature for 48 h, more decomposition was observed than racemization with only 1% reduction of ee value. Determined by X-ray single crystal diffraction, a torsion angle of 20.6° was observed between the methyl group and carbonyl group in **14a**, exhibiting its more flexibility than biaryl **15a**.

In 2021, Ramasastry and co-workers achieved the catalytic asymmetric synthesis of diarylmethylidene indanones **17** with naphthyl boronic acids **12** and enol triflates **16** (Scheme 4).[22] When screening the reaction conditions, a tremendous decrease of ee value was observed when replacing the phenyl in bisoxazoline **L4** with a bulkier i-Pr group. Meanwhile, the ee value diminished to 64% when the *tert*-butoxy group was used and even became racemic for the *ortho*-methyl substituted compound **17c**, despite of which the rotational barrier was



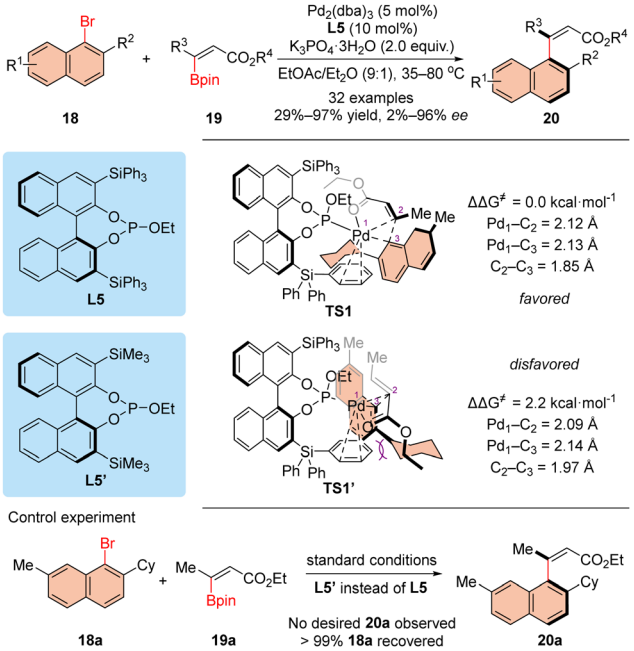
Scheme 3 Pd-Catalyzed asymmetric Suzuki–Miyaura cross-coupling for construction of 2-aryl cyclohex-2-enone.



Scheme 4 Pd-Catalyzed asymmetric Suzuki–Miyaura cross-coupling for the construction of diarylmethylidene indanones.

higher than that of iso-propoxy substituted **17b** (37.35 kcal mol^{-1} *vs.* 35.97 kcal mol^{-1}, calculated by DFT). When the naphthyl ring was replaced by a phenyl group, the corresponding product **17d** bearing a flexible C–C axis with insufficient atropostability was formed, which was unable to be resolved by chiral stationary phase HPLC at room temperature. Based on these results, a probable intermediate **Int1** has been proposed, involving a weak coordination between Pd and the iso-propoxy group in **12** as well as a π–π interaction between ligand **L4** and substrate **16.**

Later in 2022, Tan, Zhang, Yu and co-workers also reported an atroposelective construction of open-chain aryl-alkene



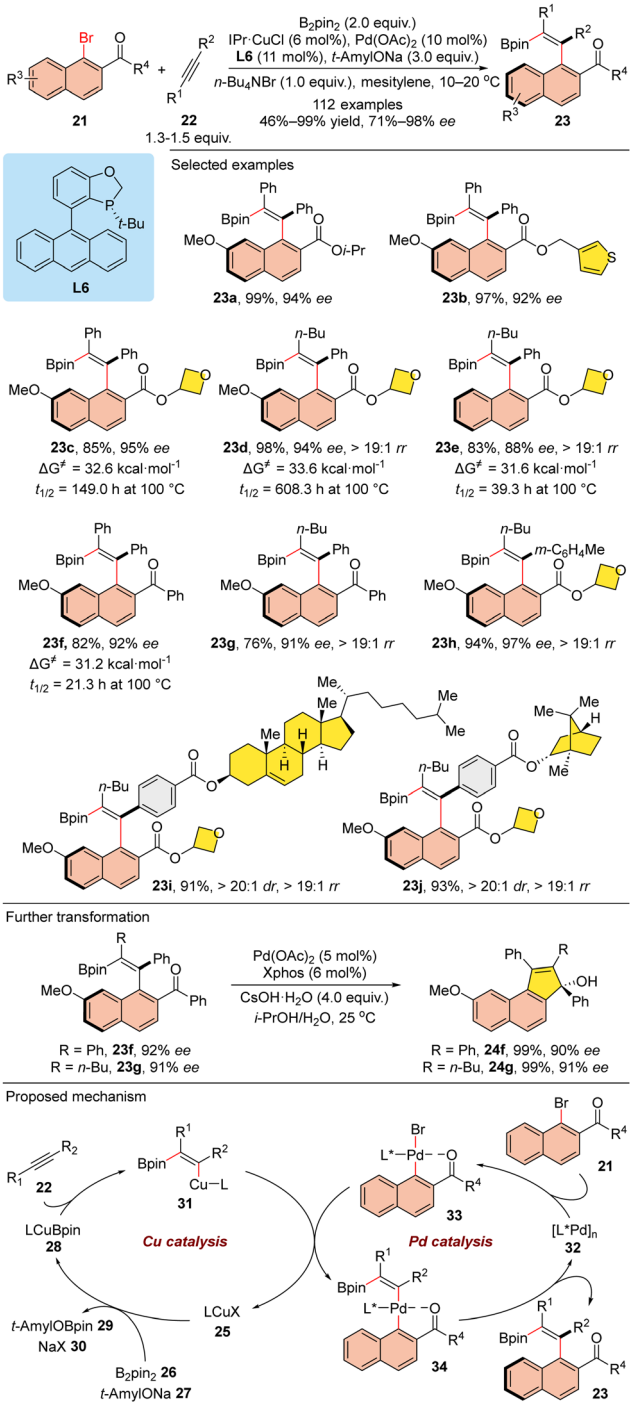
Scheme 5 Pd-Catalyzed asymmetric Suzuki–Miyaura cross-coupling for the construction of chiral open-chain styrenes.

atropisomers *via* enantioselective Suzuki–Miyaura cross-coupling (Scheme 5).[23] With the absence of weak coordination from the *ortho*-ether group and π–π stacking from the aryl rings on the substrates, it becomes more difficult to control atroposelectivity. A beneficial correlation was observed between enantioselectivity and the steric bulk of C2-/C7-substituted naphthalene halides. With further modifications of the ligands, phosphite ester **L5** was determined as an optimal ligand, providing a broad scope of substrates with both electron-donating and -withdrawing groups at different positions. Based on the DFT studies and experimental observations, the π–d coordination between palladium and the triphenylsilyl group was regard as a momentous issue in reductive elimination, offering a 2.2 kcal mol^{-1} difference of relative free energy between **TS1′** and more favored transition state **TS1**. The existence of π–d coordination was further corroborated by two main control experiments: addition of 10 equivalents of toluene adversely influenced the yield, which had a π–d coordination competition with the triphenylsilyl group; and when 3,3′-trimethylsilyl-substituted phosphite ester **L5′** was used as the ligand, no desired product **20a** was observed.

Recently, the Song group achieved the arylboronation of alkynes enabled by Cu/Pd dual catalysis (Scheme 6).[24] Various axially chiral alkenylboronates **23** were gained in up to 99% yield with 98% ee, and several natural product-derived substrates were also tolerated (**23i** and **23j**). For unsymmetric alkynes, the corresponding products (**23d**, **23e** and **23g–j**) were obtained in excellent regioselectivities. When the *ortho* weak coordination group was replaced with a ketone, the transformation could still take place smoothly with slightly lower ee value (**23f** and **23g**). Meanwhile, in all cases, only *syn*-arylboronation compounds were detected, implying the complete *E*-selectivities. The rotational barriers of **23c–f** were determined as 32.6 kcal mol^{-1}, 33.6 kcal mol^{-1}, 31.6 kcal mol^{-1} and 31.2 kcal mol^{-1} with racemization experiments in i-PrOH at 100 °C respectively. The results showed that the axis in the product bearing an ester group was stabler than the aryl ketone substituted one (**23c** *vs.* **23f**). Furthermore, the methoxy group at the 7-position also contributed greatly to the atropostability of the C–C axis (**23d** *vs.* **23e**). A series of transformations were operated on Bpin and ester groups, extremely enriching the scope of axially chiral styrenes. Moreover, the axial chirality could be transferred into *C*-central chirality with a mild erosion of enantiomeric purity *via* Pd-catalyzed C–C coupling. Confirmed by further mechanistic experiments, a thorough understanding of this Cu/Pd combined catalysis system was acquired. Promoted by *t*-AmylONa, a transmetalation between NHC-Cu **25** and B_2pin_2 **26** occurs, followed by *syn*-addition with alkynes **22.** Then the chiral Pd(II) complex **34** is formed *via* another transmetalation, further generating axially chiral alkenylboronate **23** through atroposelective reductive elimination.

3. Enantioselective C–H activation strategy

In the past few decades, directed transition-metal-catalyzed asymmetric C–H functionalization has been dramatically



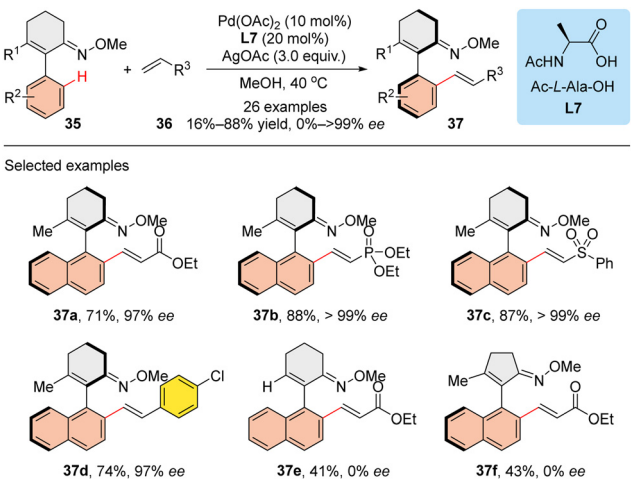
Scheme 6 Atroposelective synthesis of axially chiral alkenylboronates enabled by Cu/Pd combined catalysis.

developed,[25] bringing a powerful method for synthesizing structurally complicated chiral molecules.[26] For the construction of C(vinyl)–C(aryl) axes, the C–H activation process *via* dynamic kinetic resolution is always the enantio-determining step. Several palladium(II)-catalyzed enantioselective olefinations, alkynylations and arylations have been developed using this strategy.

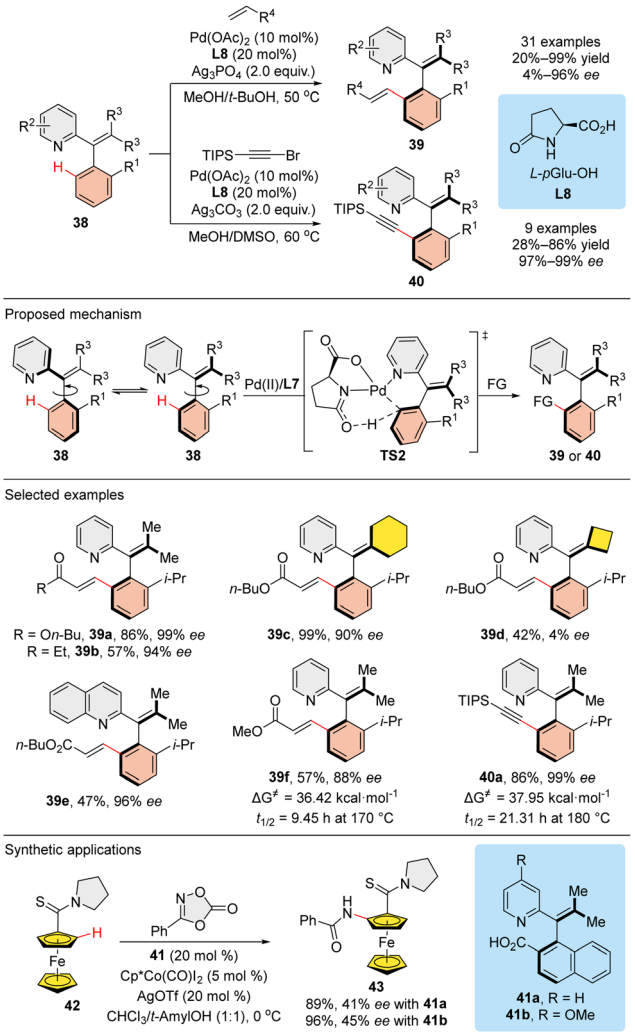
As an important catalytic system in Pd-catalyzed asymmetric C–H functionalizations, Pd/MPAA catalysis has blossomed rapidly[27] since the pioneering work accomplished by the Yu group in 2008.[28] In 2018, Xu, Cui and co-workers reported a palladium/acetyl-L-alanine catalyzed enantioselective C–H olefination with 96% to >99% ee directed by *N*-methoxy ketoxime (Scheme 7).[29] Manifold olefins were tolerated smoothly, including acrylates (**37a**), vinyl ketones, vinyl sulfones (**37b**), vinyl phosphonates (**37c**) and vinyl benzenes (**37d**). When the olefinic methyl group was replaced by a H atom or the double bond was located in a five-membered ring instead, racemic products **37e** and **37f** were derived, which may be probably due to their lower rotation-resisting barriers. Sequently, when replacing the coupling reagents to alkenyl silanes or silyl alkynyl bromides, the Xu group extended this protocol in the construction of styrene-derivated axially chiral organosilanes with the same ligand **L7** *via* alkenylation or alkynylation directed by *N*-methoxy ketoxime as well.[30]

Controlled by L-pyroglutamic acid **L8**, our group orchestrated the Pd-catalyzed atroposelective C–H alkenylation and alkynylation in 2020 (Scheme 8).[31] Confirmed by DFT calculations, unlike the conventional Pd/MPAA systems, with the axis rotating freely in **38**, enantioselectivity was operated mainly owing to the ideal match between chiral induction and axial conformation rather than steric hindrance during the reversible C–H activation *via* transition state **TS2**. Compared with pyridine-directed **39a** with 86% yield and 99% ee, the quinoline could also be used as the directing group, affording the target product **39e** in moderate yield with a slightly lower enantioselectivity. The cyclobutyl substituted compound **39d** was obtained in lower yields with only 4% ee, which may be caused by its insufficient rotational barrier. The racemization barriers of olefination product **39f** and alkynylation product **40a** were measured at 170 °C and 180 °C as 36.42 kcal mol^{-1} and 37.95 kcal mol^{-1} in i-PrOH respectively, implying dramatic stabilities of the C(vinyl)–C(aryl) axes. Chiral carboxylic acids **41a** and **41b**, transformed *via* double bond cleavage, were a capable ligand in the Cp*Co-catalyzed enantioselective C–H amidation of ferrocene.[32]

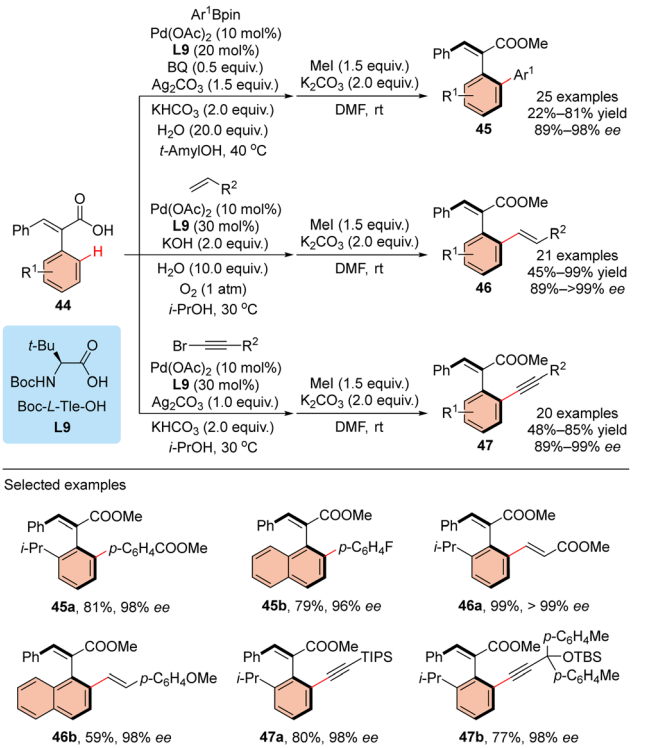
Later in 2021, the Wang group adjacently realized the asymmetric synthesis of axially chiral styrenes *via* C–H arylation,



Scheme 7 Pd-Catalyzed enantioselective C–H olefination enabled by Ac-L-Ala-OH.



Scheme 8 Pd-Catalyzed enantioselective C–H olefination and alkynylation enabled by L-*p*Glu-OH.

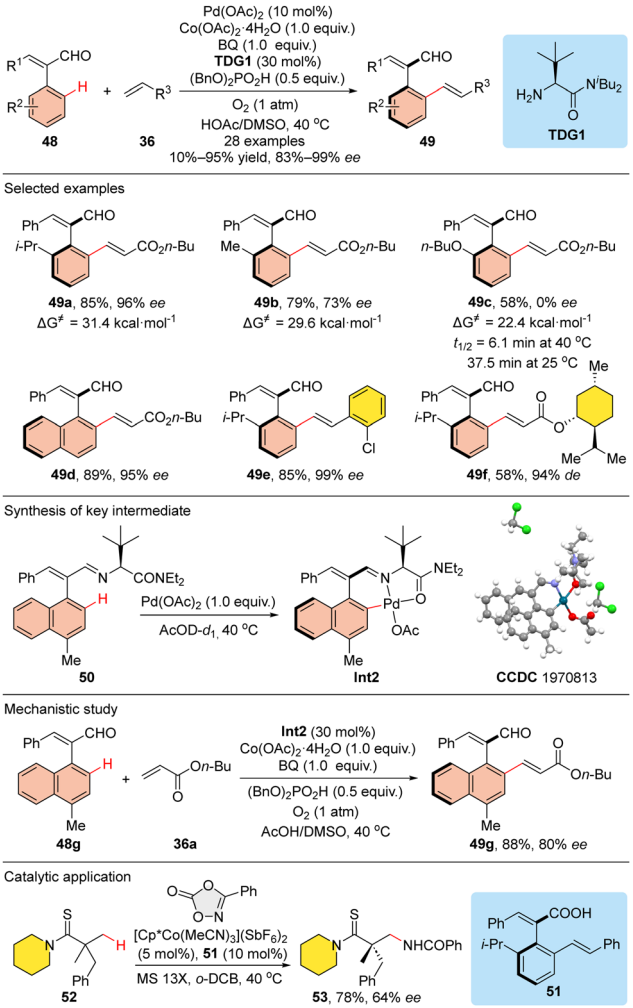


Scheme 9 Pd-Catalyzed enantioselective C–H arylation, olefination and alkynylation enabled by Boc-L-Tle-OH.

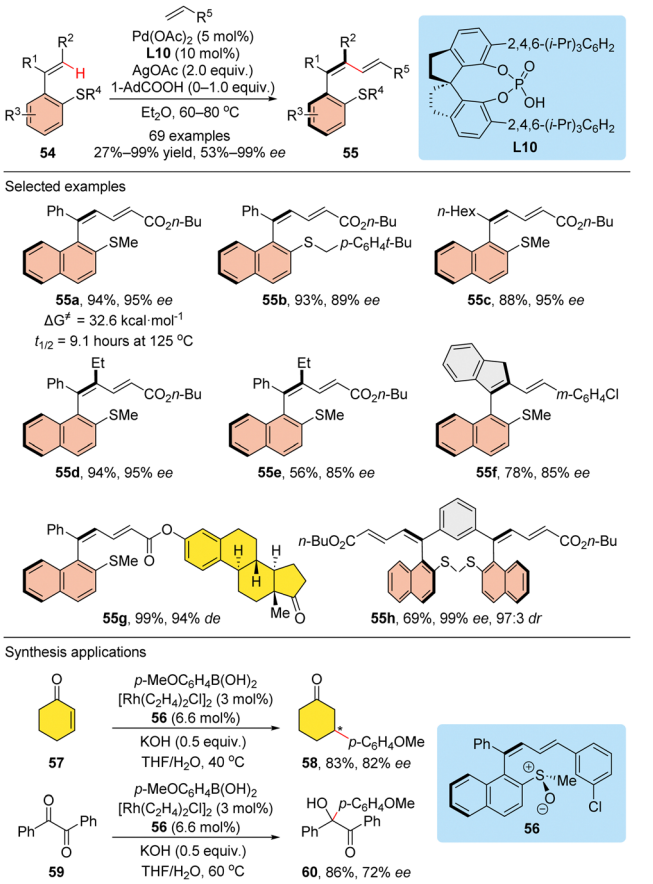
alkenylation or alkynylation catalyzed by palladium(II) in combination with *N*-Boc-protected *tert*-leucine **L9**, yielding the corresponding esters with further methylation (Scheme 9).[33] Compared with strong coordination the directing group including *N*-methoxy ketoxime and pyridine mentioned above, carboxyl is a relatively weak directing group, increasing the difficulty of the corresponding transformation. With extensive optimization of the conditions, all these three conversions were conducted successfully under mild conditions with broad substrate scopes, expending the multiformity of such styrene-type chiral carboxylic acids.

The chiral transient directing group (*c*TDG) elegantly obviated the installation and removal of external directing groups for asymmetric C–H functionalization.[34] Applying this strategy, our group actualized the atroposelective synthesis of open-chain axially chiral styrenes *via* dynamic kinetic resolution (Scheme 10).[35] Similar to our previous works in the construction of axially chiral biaryl compounds,[36] the alkenyl aldehyde was employed for dehydration condensation with *tert*-leucine-derived amino amide **TDG1**, forming a transient directing group *in situ*. Adscititious DMSO may serve as a ligand to stabilize the Pd intermediate, as only trace product was detected without DMSO. Rotational barriers of **49a**, **49b** and **49c** were figured out by DFT calculations, indicating that smaller substituents have significantly lower rotational barriers. In particular for **49c** bearing a *n*-BuO group, its half-life period was only 6.1 min at the reaction temperature (40 °C), which is extremely effortless to racemize during the reaction. Meanwhile, the key chiral palladacycle intermediate **Int2** was isolated and characterized by X-ray single crystal diffraction from preprepared imine **50**, which could catalyze the reaction of **48g** and **36a** in good yield with slightly reduced enantioselectivity. These experiments clarified that C–H cleavage is the enantioselectivity determining step commanded by the dynamic bonded chiral transient directing group. In addition, the axially chiral product was derivatized into chiral carboxylic acid **51** *via* Pinnick oxidation, which was also a serviceable ligand in Cp*Co(III) catalyzed asymmetric C(sp^3)–H amidation.[37]

Apart from aryl C–H activation/functionalization, alkenyl C–H activation is another pathway for the generation of axially chiral styrenes. On account of multiple side reactions and the conformational complexity of olefins, asymmetric alkenyl C–H activation is more challenging, and thus remains underexplored until 2021.[38] Based on previous achievements on palladium-catalyzed enantioselective C–H functionalization in combination with chiral phosphoric acid,[39] a thioether-directed olefinic C–H alkenylation was demonstrated by our group, producing various axially chiral aryl 1,3-dienes with entire *Z*-selectivities in excellent yields and enantiomeric excess (Scheme 11).[40] The 3,3′-bulky hindrance of spiro phosphoric acid was crucial for excellent enantioselectivity, as the ee value



Scheme 10 Pd-Catalyzed enantioselective C–H olefination based on the chiral transient directing strategy.



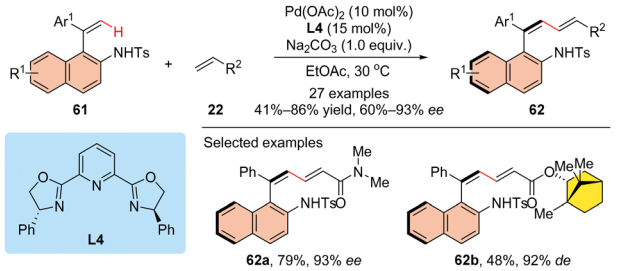
Scheme 11 Palladium-catalyzed enantioselective alkenyl C–H olefination assisted by bulky spiro phosphoric acid.

declined remarkably from 95% to only 10% when using the simplest spiro phosphoric acid instead of 3,3′-(2,4,6-(i-Pr)$_3$-C$_6$H$_2$)$_2$ substituted ligand **L10**. A series of novel C_2-symmetrical styrenes bearing two stereogenic axes, such as **55h**, were manufactured in up to 99% ee and 97 : 3 dr under faintly modified conditions. By further oxidation with stoichiometric *m*-CPBA at −78 °C, the corresponding chiral sulfoxide olefin such as **56** was obtained, which could be used as the chiral ligand in the rhodium-catalyzed asymmetric additions of arylboronic acid to cyclohexanone or α-diketones.[41] Besides, the same conversion directed by a tosylamine group was also accomplished by the Xu group using bisoxazoline pyridine **L4** as a chiral ligand in early 2022, in which both dimethylacrylamides and multiple acrylates were compatible (Scheme 12).[42]

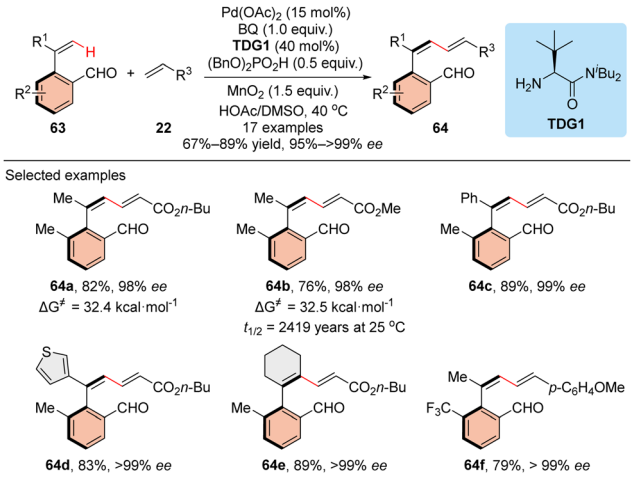
In 2022, Zhang, Zhong and co-workers also proceeded with an enantioselective alkenyl C–H olefination enabled by a chiral transient directing group (Scheme 13).[43] Axially chiral conjugated aryl 1,3-dienes were formed with excellent atroposelectivities and regioselectivities *via* a seven-membered *endo*-palladacycle, while no competing aryl C–H olefination product was observed in this protocol. Heteroaromatic alkene **64d** and cyclic olefin **64e** were also applicative. Moreover, the rotational barriers of **64a** and **64b** were measured as 32.4 kcal mol^{-1} and 32.5 kcal mol^{-1} by DFT calculations respectively, illustrating distinguished atropostability with a half-life over 2000 years at ambient temperature.

Almost simultaneously, with the steric hindrance group moved to the β-position, Engle, Liu and co-workers realized olefinic α-C–H alkenylation facilitated by the chiral transient directing group **TDG2** (Scheme 14a).[44] Stoichiometric 3,4,5-C$_6$H$_2$F$_3$COOH was necessary for C–H activation as a concerted metalation deprotonation (CMD) process. Notably, all the α-C–H alkenylation dienes were acquired with 99% ee at least. In the presence of pyridine, the chiral six-membered *exo*-palladacycle was isolated as a mixture of *Z*/*E*-stereoisomers, and the *Z*-isomer assembled from glycine was confirmed by X-ray single crystal diffraction ulteriorly. The mechanistic experiments also pointed out that when glycine acted as the transient directing group instead of *tert*-leucine **TDG2**, the *Z*/*E*-isomerization of the C–C double bond was quite a bit easier.

Meanwhile, Zhang, Zhong and co-workers also accomplished the same olefinic α-C–H alkenylation under similar conditions (Scheme 14b).[45] Both acrylates and acrylamides with various substituents including even chiral natural product fragments were well tolerated. Evaluated by DFT calculations, the rotational



Scheme 12 Palladium-catalyzed enantioselective alkenyl C–H olefination assisted by bisoxazoline pyridine.



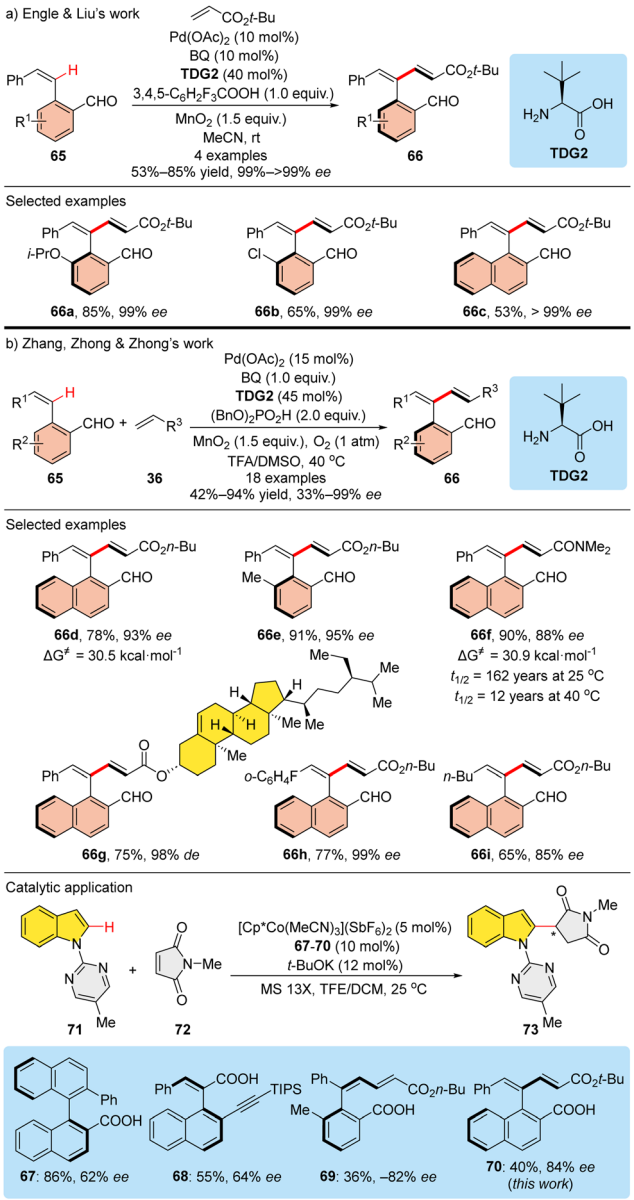
Scheme 13 Palladium-catalyzed enantioselective alkenyl β-C–H olefination based on the chiral transient directing strategy.

barriers of **66d** and **66f** were determined as 30.5 kcal mol^{-1} and 30.9 kcal mol^{-1} with a half-life over 100 years at room temperature. Several axially chiral carboxylic acids were synthesized *via* Pinnick oxidation, and then were examined in the Cp*Co(III)-catalyzed alkylation compared with other chiral carboxylic acids developed previously.[46]

4. Central-to-axial chirality transfer strategy

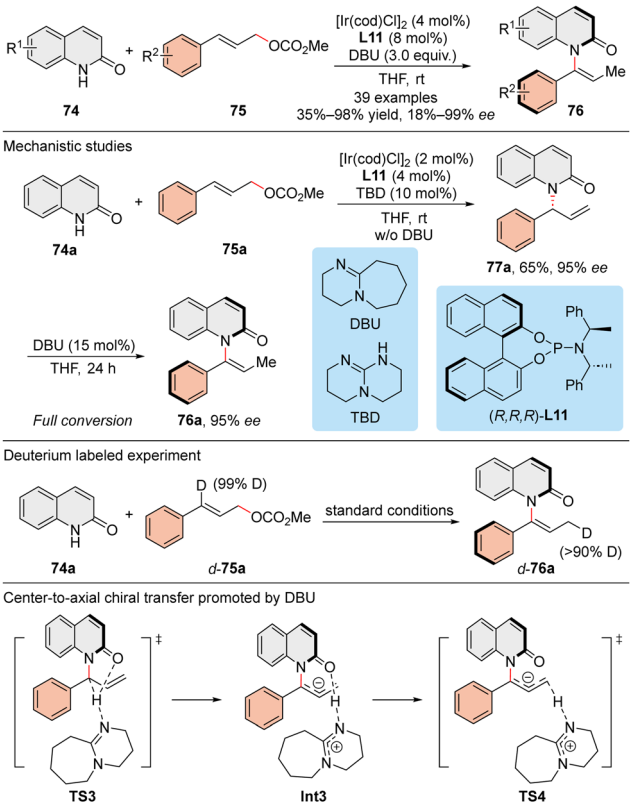
With the mechanism revealed by Paton in 2018,[47] organocatalyzed [1,3]-H transfer has evolved as a powerful method in the stereospecific isomerization of allylic compounds.[48] Stimulated by the organocatalysis approaches, several works about iridium(I)-catalyzed atroposelective synthesis of axially chiral styrenes have been reported. A tertiary carbon stereocenter precursor is formed *via* asymmetric allylation, followed by an enantiospecific [1,3]-proton transfer or [1,3]-hydride transfer to achieve chirality transfer from central to axial. Hence, this strategy was also referred to as the asymmetric allylic substitution–isomerization (AASI) strategy.

In 2020, He, Liu and co-workers achieved the asymmetric synthesis of axially chiral styrenes *via* iridium(I)-catalyzed

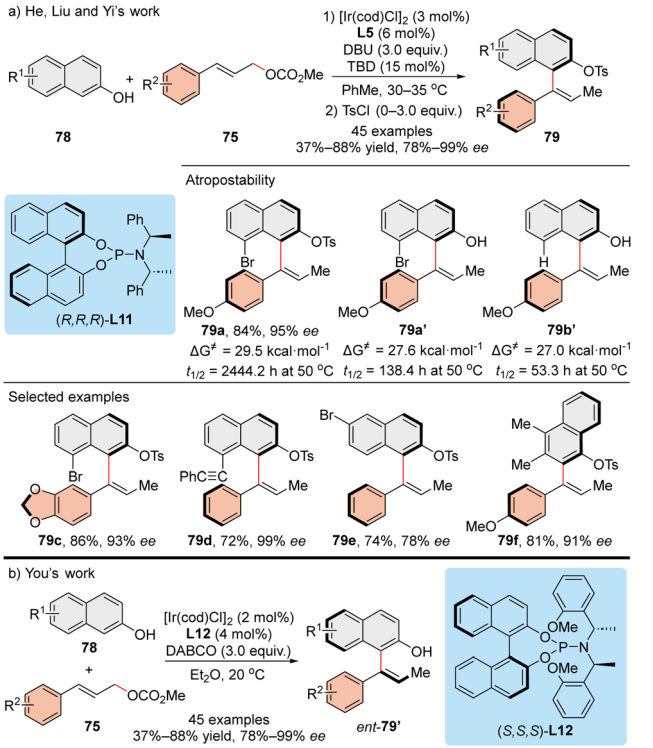


Scheme 14 Palladium-catalyzed enantioselective alkenyl α-C–H olefination based on the chiral transient directing strategy.

asymmetric C–N coupling followed by an *in situ* central-to-axial chirality transfer (Scheme 15).[49] Most of the products were obtained in >90% ee and >20 : 1 *Z*/*E*, exhibiting the robustness of this one-pot protocol. In fact, the enantioenriched allylic precursor **77a** could be isolated in 65% yield and 95% ee when TBD was used instead of DBU, which subsequently enantiospecifically isomerized into **76a** promoted by DBU with full conversion. When deuterium labelling substrate d-**75a** was reacted under standard conditions, the target product d-**76a** was received with >90% deuterium transfer. Meanwhile, verified by DFT calculations, the ion pair **Int3** for suprafacial [1,3]-proton transfer was proposed, and a hydrogen-bond interaction has been discovered in transition state **TS3** of DBU-cooperated deprotonation.



Scheme 15 Iridium/DBU-catalyzed asymmetric synthesis of C–N axially chiral alkenyl indoles *via* [1,3]-proton transfer.

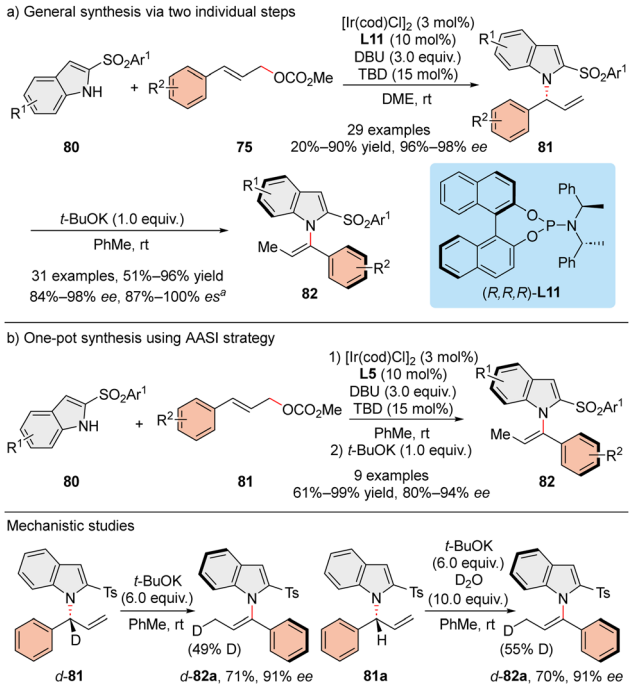


Scheme 16 Asymmetric synthesis of C–C axially chiral styrenes *via* iridium-catalyzed [1,3]-hydride transfer.

Shortly after, the He and Liu group extended this asymmetric allylic substitution-isomerization (AASI) strategy to the construction of C–C axially chiral styrenes (Scheme 16a).[50] In efforts to enhance the atropostability, the hydroxy group was further protected by *p*-methylbenzenesulfonyl (29.5 kcal mol^{-1} for **79a** *vs.* 27.6 kcal mol^{-1} for **79a′**) in most instances, and the steric hindrance of the bromine atom at C8 position of naphthol also contributed to the restricted rotation about the C–C axes (27.6 kcal mol^{-1} for **79a′** *vs.* 27.0 kcal mol^{-1} for **79b′**). A series of 2-naphthols and allylic carbonates bearing both electron-rich and -deficient substituents were compatible, giving the desired products in good to excellent enantioselectivities. Pre-protected naphthols such as 2-methoxynaphthalene could not undergo this reaction, which may disrupt the coordination of phenolic hydroxyl groups with iridium or hydrogen-bond interactions in transition states. Nevertheless, different from DBU-promoted [1,3]-proton transfer in their previous work, this reaction may operate *via* an Ir-catalyzed [1,3]-hydride transfer instead, which has been clarified by control experiments and DFT calculations. A similar conversion has also been achieved in moderate to good enantioselectivity by You and co-workers using a similar ligand **L12** (Scheme 16b).[51] Further mechanism studies supported that iridium and organic base DBU are both essential in the central-to-axial chirality transfer.

In 2022, the atroposelective synthesis of C–N axially chiral alkenyl indoles was also achieved by He, Liu and co-workers (Scheme 17).[52] Depending on reaction time, the enantioenriched C–N coupling allylic compounds **81** bearing a *C*-stereo center were isolated in 96–98% ee, followed by a potassium *tert*-butoxide-mediated isomerization to give vinylindoles **82** in up to 100% es (Scheme 17a). Moreover, vinylindoles **82** were directly generated in analogous yields and enantioselectivities by one-pot reaction (Scheme 17b). An intramolecular π–π stacking interaction was observed between Ar^1 on the sulfonyl group and the R^2-substituted phenyl group, strengthening the atropostability of products **82**. Proved by deuterium-labelling experiments, the isomerization proceeded *via* both intra- and intermolecular [1,3]-proton transfer. KIE studies suggested that the benzylic C–H cleavage was the rate-determining step in isomerization. Based on their previous work,[49,50,53] the author thought that H-bonding interactions with a sulfonyl group might be vital for enantiospecific [1,3]-proton transfer.

With the AASI strategy, the He group further orchestrated the asymmetric construction of axially chiral B,N-heterocycles *via* two individual steps (Scheme 18).[54] Numerous allylic C–N cross-coupling products **84** were synthesized smoothly with **L13** promoted by LiHMDS for deprotonation of the N–H group. Unfortunately, since **85a** only has a 6.58 h short half-life under room temperature ($\Delta G^{\ddagger}$ = 23.62 kcal mol^{-1}), when the base-mediated stereospecific isomerization of **84a** (R^4 = R^5 = R^6 = H) was tested, an arresting ee erosion of **85a** appeared, and racemic product **85a** was detected when reacting for 48 h. Aiming to increase the atropostability,[55] B,N-heterocycles bearing an *ortho*-substituent arene on the B atom were used for stereospecific isomerization, which provides sufficient steric



Scheme 17 Asymmetric synthesis of C–N axially chiral alkenyl indoles with intramolecular π–π stacking interactions. *a*: es = ee_{82}/ee_{81} × 100%.

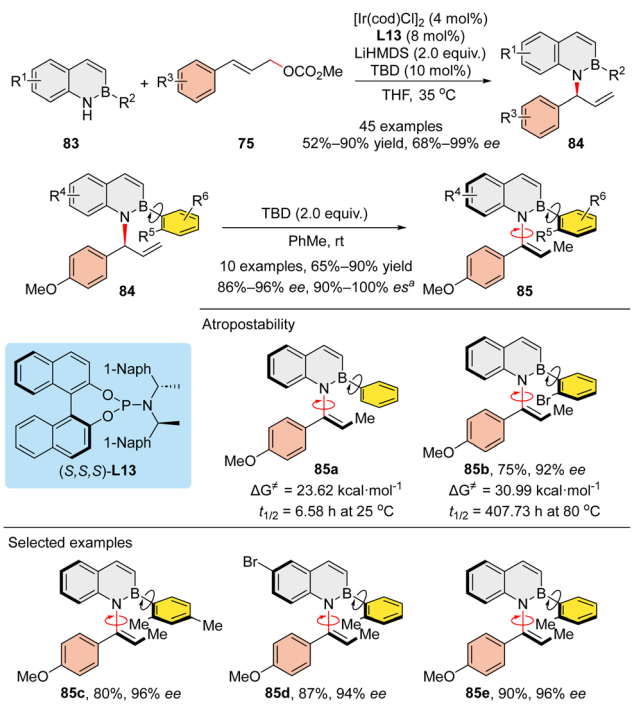
hindrance without weak coordination. Stable biaxial compounds were generated *via* [1,3]-proton transfer in up to 100% es, such as **85b** ($t_{1/2}$ = 407.73 h at 80 °C), in which the B–C axes existed as the main conformers under thermodynamic control. Further control experiments and DFT calculations revealed that the N–⋯ interaction was notable in *C*-stereo central to N–C axial chirality transfer through isomerization.

5. Asymmetric alkyne functionalization strategy

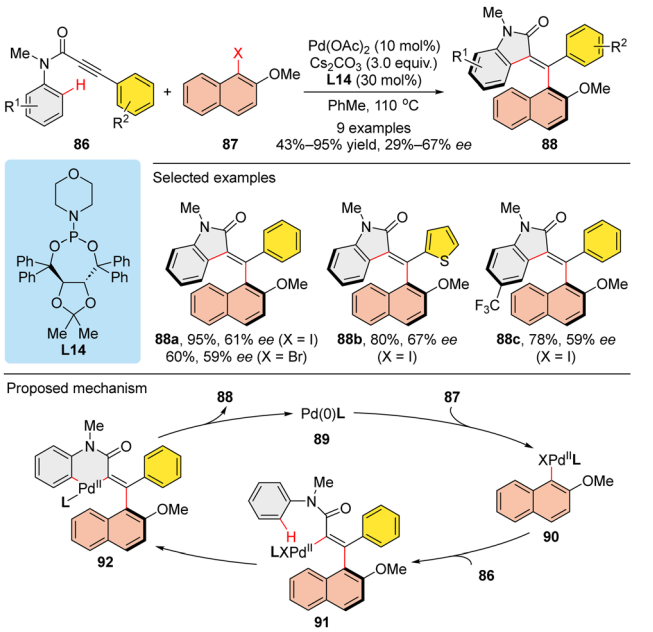
As an efficient and straightforward technique in chemo-, regio- and stereoselective synthesis of tri- or tetrasubstituted olefins, functionalization of alkynes has magnetized great attention from chemists.[56] Furthermore, the chiral C(vinyl)–C(aryl) axes could also be gained through the metal-catalyzed atroposelective functionalization of alkynes.

In 2019, Liu, Mao and co-workers employed this strategy in the synthesis of oxindole-derived axially chiral styrenes **88** *via* tandem carbopalladation/C–H olefination enabled by TADDOL-type ligand **L14** (Scheme 19).[57] A plausible catalytic cycle was proposed, starting with oxidative addition of **87**. After the alkyne coordinated with Pd(II) complex **90**, a carbopalladation occurs, which might be the enantio-determining step in this protocol. Then intramolecular C–H activated palladacycle **92** is generated, giving oxindole **88** *via* further reductive elimination. A weak coordination may exist between the methoxy group in **87** and Pd atom during the formation of the C–C axis. For atropostability of the C–C axis, no racemization was observed with the toluene solution of product **88a** heated at 110 °C for 10 h.

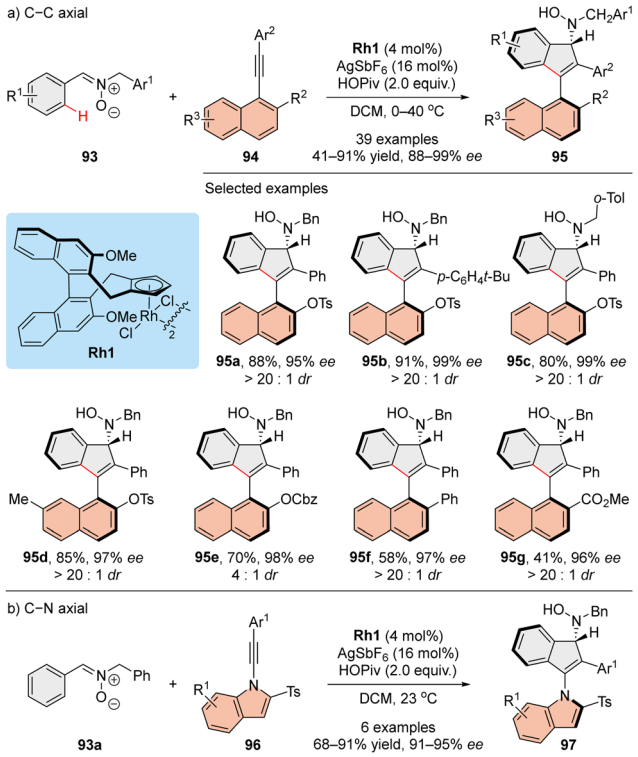
Utilizing chiral $Cp^{X}Rh(III)$ catalysts,[58] which were initially developed by Rovis[59] and Cramer,[60] respectively, the Li group constructed quite a few both axially and centrally chiral aryl indenes *via* asymmetric [3+2] annulation of alkynes in 2021 (Scheme 20).[61] Attributed to the efficient chirality control model, the products bearing a C–C (**95**) or C–N (**97**) axis and a carbon



Scheme 18 Asymmetric synthesis of biaxially chiral B,N-hetero styrenes using the AASI strategy. *a*: es = ee_{85}/ee_{84} × 100%.



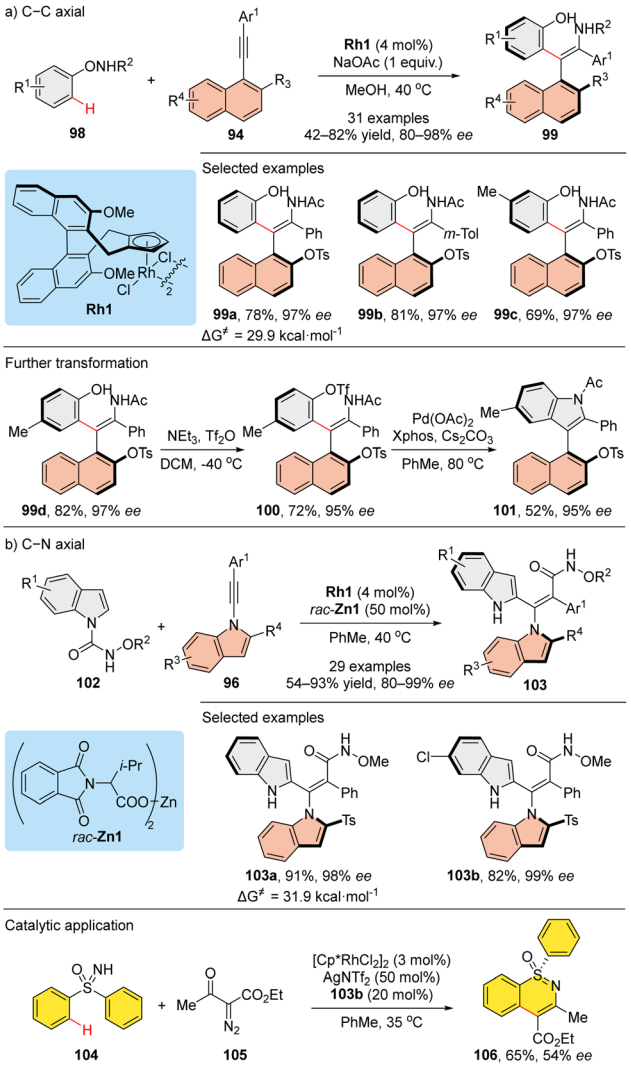
Scheme 19 Asymmetric synthesis of oxindole-derived axially chiral styrenes *via* tandem carbopalladation/C–H olefination.



Scheme 20 Synthesis of both axially and centrally chiral styrenes *via* $Cp^{X}Rh(III)$-catalyzed asymmetric C–H alkenylation.

center were both generally produced in excellent enantio- and diastereoselectivities, which could be further oxidated to axially chiral indanone and nitrone or reduced to deoxygenated indenamine under mild conditions with little erosion of ee. The KIE experiments and DFT calculations identified that the C–H cleavage is the rate-determining step, and the enantio-deciding alkyne migratory insertion ensures the axis as *S*-configuration, followed by a *Re*-selective 1,2-addition of nitrone.

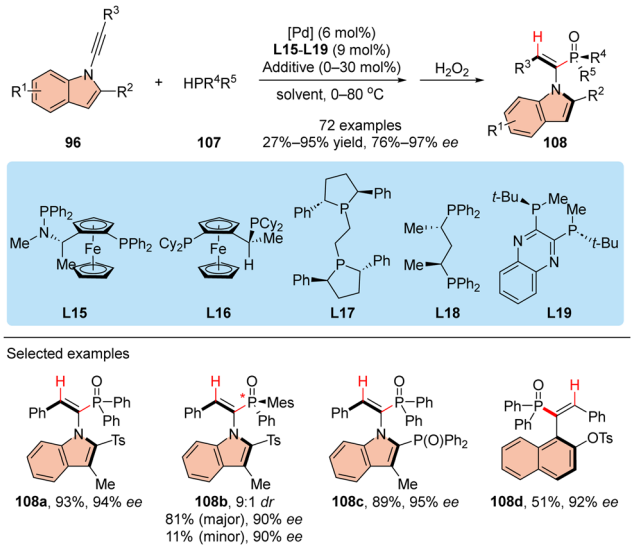
Soon afterwards, Li, Wang and co-workers reported another atroposelective synthesis of axially chiral styrenes *via* $Cp^{X}Rh(III)$-catalyzed asymmetric C–H alkenylation (Scheme 21).[62] At the beginning of the reaction, a rhodacycle intermediate is manufactured *via* a carboxylate cooperated C–H activation from phenoxyacetamides **98** or aminocarbonylindoles **102**, followed by a regio- and enantioselective alkyne insertion elaborated by steric hindrance between the substrates and chiral Cp^{X} ligand. Then migration of the directing group takes place through N–O oxidation addition (for **98**) or β-N-elimination (for **102**), and the target tetrasubstituted alkenes **99** bearing a C–C axis or **103** bearing a C–N axis are obtained with further protonation. Racemization barriers of representative compounds **99a** and **103a** were measured in anisole at 100 °C, indicating that indole-derived olefin **103a** possesses quite a bit higher atropostability ($\Delta G^{\ddagger}$ = 31.9 kcal mol^{-1}) than styrene **99a** ($\Delta G^{\ddagger}$ = 29.9 kcal mol^{-1}). The fluorescence emission properties of **99d** were surveyed, and the indole-derived Weinreb amide **103b** could act as a chiral ligand in the Cp*Rh(III)-catalyzed asymmetric [4+2] annulation of sulfoximine with α-diazo acetyl acetate.[63] Very recently, the



Scheme 21 Synthesis of chiral styrenes with either C–C or C–N axis *via* $Cp^{X}Rh(III)$-catalyzed asymmetric C–H alkenylation.

construction of axially chiral trisubstituted olefins was also achieved by the same group, which is more challenging in view of their much lower racemization barriers compared with tetrasubstituted alkenes.[64]

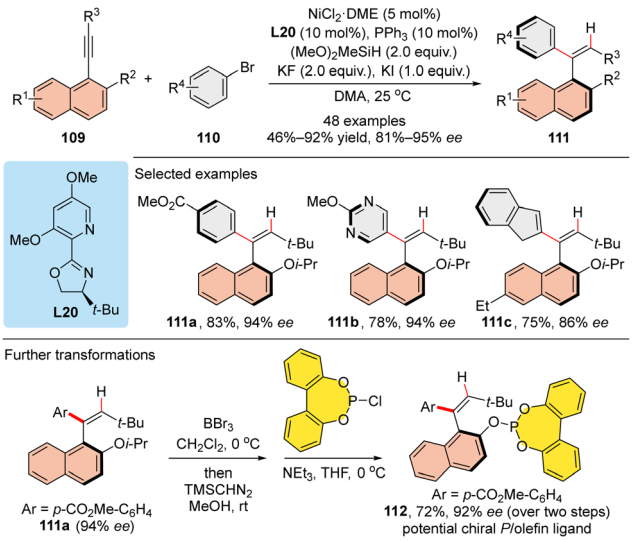
Notably, pioneered by Tan[65] and Yan[66] in organocatalysis, hydrofunctionalization of sterically hindered alkynes is also a widely used methodology in the asymmetric synthesis of axially chiral styrenes. For transition metal catalysis, Li, Wang and co-workers applied this strategy in the construction of axially chiral olefins *via* palladium-catalyzed regio- and enantioselective hydrophosphination of bulky internal alkynes in 2022 (Scheme 22).[67] A variety of trisubstituted C–N or C–C axially chiral alkenes were yielded in up to 97% ee with four corresponding ligands **L15-L19** under slightly modified conditions. It was also worth mentioning that both C–N axial and *P*-central chirality in **108b**-like compounds were commendably regulated with both good enantio- and diastereoselectivities (up to 93% ee and 10 : 1 dr). Deuterium-labelling experiments explored that the generation of **108** from the phosphopalladation intermediate



Scheme 22 Asymmetric synthesis of C–N or C–C axially chiral styrenes *via* hydrophosphination of alkynes.

passed through both protonolysis and σ-bond metathesis. Furthermore, the reaction could be strongly inhibited by excessive HPR^4R^5 **107** (10 equiv.), while negligible inhibition was observed by unoxidized phosphine products **108.**

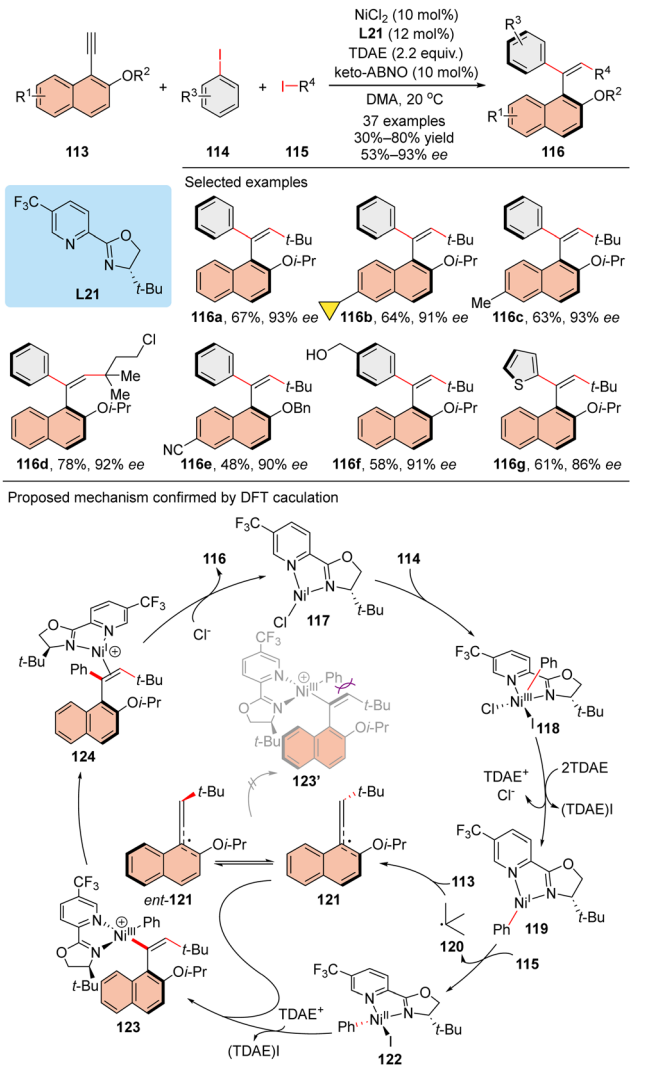
In March 2023, Zhu, Wang and co-workers reported the asymmetric synthesis of C–C axially chiral styrenes *via* NiH-catalyzed hydroarylation of alkynes (Scheme 23).[68] Diverse alkynes **109** and arylbromides **110** were tolerated in this conversion, even involving heteroaromatic bromides such as pyrimidine (**111b**), pyridine and thiophene. Extended atroposelective hydroalkenylation was also materialized smoothly, producing the corresponding 1,3-diene **111c** in 75% yield and 86% ee. The alkoxy group was quite momentous to the reactivity and enantioselectivity as well, which may offer a weak coordination



Scheme 23 Asymmetric synthesis of C–C axially chiral styrenes *via* NiH-catalyzed hydroarylation of alkynes.

with the Ni catalyst. Additionally, the obtained products could be converted into a *P*/olefin bidentate ligand **112** within two single steps. Referring to their previous work,[69] the mechanism might be assumed through NiH-catalyzed hydronickelization of alkynes, oxidative addition of arylbromides, then reductive elimination, and forming products **111** eventually.

Radical-involved atroposelective bifunctionalization of alkynes for the construction of axially chiral styrenes was also realized by the Zhang group in 2022 (Scheme 24).[70,71] Assisted by pyridoxazolin **L21**, multifarious C–C axially chiral styrenes bearing both electron-donating and electron-withdrawing groups at various positions were obtained *via* Ni-catalyzed three component radical coupling. For deep insight into the detailed mechanism, DFT calculations were performed on the basis of evidence supplied by electron paramagnetic resonance (EPR) experiments. Starting with the *in situ* formation of Ni(I)/PyrOx complex **117**, an oxidant addition takes place, and an aromatic nickel(I) complex **119** is generated through two single electron



Scheme 24 Asymmetric synthesis of C–C axially chiral styrenes *via* Ni-catalyzed radical-involved bifunctionalization of alkynes.

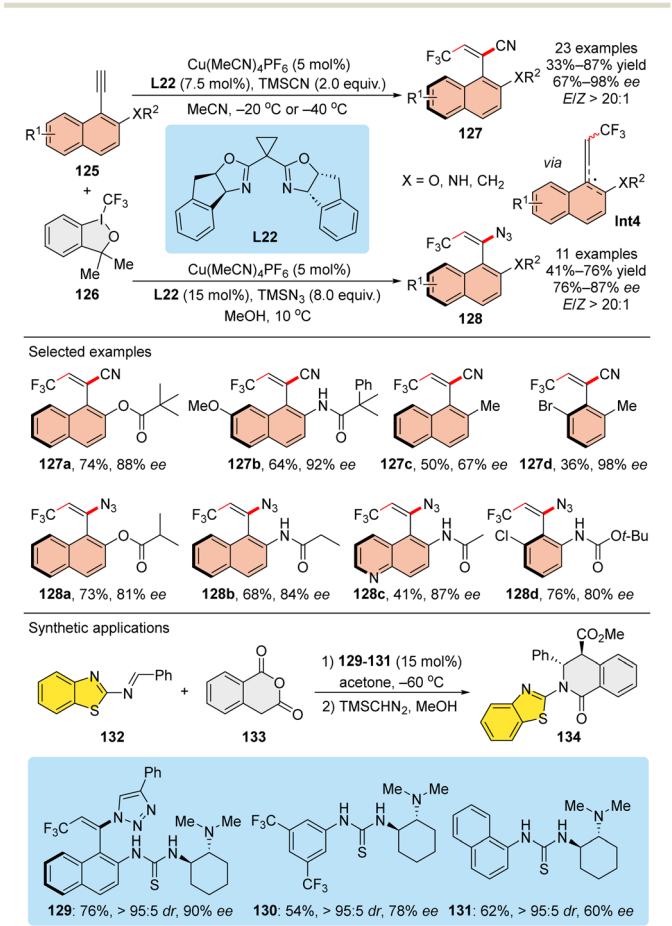
reduction processes. A *tert*-butyl radical **120** is formed by radical reduction with tertiary iodide **115**, followed by a single electron addition with terminal alkyne **113**. It should be pointed out that only tertiary iodides **115** were a suitable reagent for this transformation because of the stability of the corresponding radical. A pair of enantiomers was present as **121** and *ent*-**121**, which could convert to each other easily. Intermediate **121** is captured by Ni(II) complex **122** in view of configuration matching, determining the atroposelectivity of the C–C axis. With ensuing reductive elimination and coordination dissociation, the target molecule **116** is yielded successfully, and the Ni(I) complex **117** is regenerated at the same time.

Copper-catalyzed asymmetric radical coupling was a powerful strategy to access the bifunctionalization of unsaturated C–C bonds.[72] Very recently, on the foundation of their previously developed Cu-catalyzed asymmetric radical functionalization reactions,[73] the Liu group demonstrated the synthesis of axially chiral styrenes **127** through atroposelective functionalization of vinyl radicals formed from terminal alkynes (Scheme 25).[74] *Via* an analogous enantiocontrol process with Zhang's work mentioned above, both cyanation and azidation were carried on with **Int4**, which was acquired from radical trifluoromethylation of alkynes **125** bearing acyloxy (X = O), acylamino (X = NH) or alkyl (X = CH_2) groups. Compound **128b** was further decorated into **129**, which was a more efficient organocatalyst in asymmetric [4+2] cycloaddition of **132** and **133** compared with traditional thioureas **130** and **131**.[75]

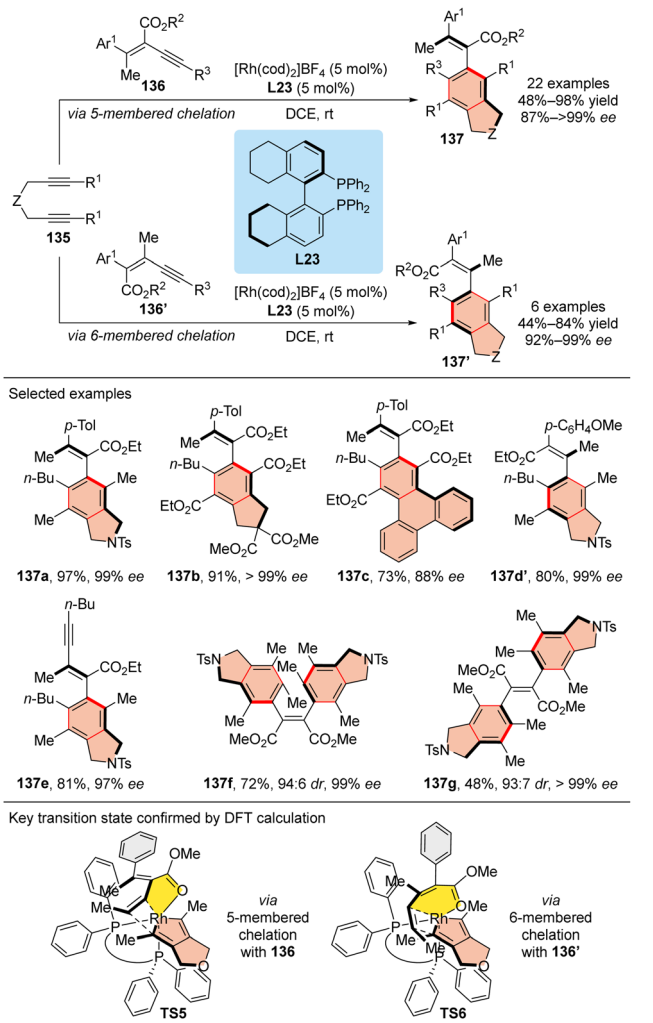
6. Atroposelective [2+2+2] cycloaddition strategy

Transition-metal-catalyzed [2+2+2] cycloaddition occupies an indispensable status in the asymmetric synthesis of chiral biaryls.[76] Unlike other strategies discussed above, the aromatic ring was constructed asymmetrically from scratch. A 5-membered metallacycle intermediate is generated with cycloaddition of diynes, followed by atroposelective migratory insertion with another alkyne molecule.

In 2022, aided with H_8-BINAP **L23**, Tanaka, Nagashima and co-workers realized the asymmetric synthesis of axially chiral styrenes *via* a cationic Rh(I)-catalyzed [2+2+2] cycloaddition with 1,6- or 1,7-diynes **135** (Scheme 26).[77] Two isomers of 1,3-enyne carboxylic esters **136** and **136′** were tolerated, giving the



Scheme 25 Asymmetric synthesis of C–C axially chiral styrenes *via* Cu-catalyzed radical-involved bifunctionalization of alkynes.



Scheme 26 Asymmetric synthesis of C–C axially chiral styrenes *via* Rh-catalyzed [2+2+2] cycloaddition.

corresponding products **137** or **137′** with opposite enantioselectivities. A perfect chemoselectivity was shown as only **137e** was generated with no **137e′** detected when ethyl (*Z*)-2-(hex-1-yn-1-yl)-3-methylnon-2-en-4-ynoate was used, illustrating that the five-membered chelation pathway is more favorable than the six-membered one. Both C_2 symmetric *cis*- and *trans*-stilbenes **137f** and **137g** bearing two chiral axes were also obtained in excellent enantioselectivities and good diastereoselectivities. Moreover, on the foundation of the experimental results, key transition states **TS5** and **TS6** in alkyne migratory insertion were interpreted with DFT calculations, and this process was recognized as the chemo- and enantiocontrol step.

7. Conclusion and outlook

In this feature article, we have summarized recent advancements in the transition-metal-catalyzed asymmetric synthesis of axially chiral styrenes, categorizing these reports with different strategies. However, though a range of vinyl aryl skeletons have been constructed, it's still highly demanded to discover new classes of catalytic systems for the concise and efficient synthesis of diverse atropisomeric styrene compounds. Meanwhile, the majority of recent achievements rely on directing groups or assisted weak coordinating groups at the *ortho*-position of the C–C or C–N axes to benefit the enantioselectivity, which limited the original design of novel axially chiral styrenes. Thus, to develop several transformations without the assistance of *ortho*-coordinating groups is also significant. More importantly, compared with biaryl atropisomers, the applications of axially chiral styrenes have lagged far behind. It is immensely urgent to further develop useful chiral ligands in asymmetric catalysis based on this scaffold or seek unique properties in pharmacochemistry, agrochemistry and other related areas. We hope that this feature article will bring a more comprehensive understanding and some insights with connections between each work, contributing to the innovation of this emerging field.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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