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Review

Synthetic strategies and mechanistic studies of axially chiral styrenes

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SUMMARY

Axially chiral molecules, as a distinct subclass of molecular chirality, exist in a series of biologically active compounds and are put to use extensively in chiral ligands and catalysts. Atropisomeric styrenes are an essential category of axially chiral compounds with constrained rotation of the C(vinyl)-C(aryl) single bond, in which the less rigid framework of styrenes normally induces instability with lower rotational barriers compared with biaryl atropisomers. While lacking attention for a long time, recent advances in this category of unique structures have expanded rapidly, and plenty of means have been developed for chemical preparation of styrenes exhibiting atropisomeric optical activity. In this review, we expound on the synthetic strategies and some corresponding mechanistic studies of axially chiral styrenes, aiming to give scientists who are interested in this topic inspiration and helpful advice.

THE BIGGER PICTURE

Atropisomeric styrenes are an essential category of axially chiral compounds with constrained rotation of the C(vinyl)-C(aryl) single bond, which attracts more and more attention as platform molecules convert into chiral ligands and catalysts. The recent past has witnessed rapid development of the strategy of synthesizing atropisomeric styrenes. The development of the method of synthesizing atropisomeric styrenes is summarized in this review by highlighting the mechanistic insights. Current challenges and the future orientations in this area are also supplied.

INTRODUCTION

Because of their abundance in bioactive substances, chiral chemical catalysts, and ligands, axially chiral compounds—their chirality arising from a stereogenic axis with severe sterically impeded rotation—have been drawing increasing interest from chemists.[1–7] First proposed by Maxwell and Adams[8] in 1930 and constructed by Mills and Dazeley in 1939[9] as well as by Kawabata et al.[10] in 1991, axially chiral styrenes, with a C(sp^2)-C(sp^2) chiral axis between the vinyl and aryl groups, have been rarely constructed because of their anticipated instability, which would impede their production and usage.[11,12] Desymmetrization of racemic styrenes to generate atropisomers is always accompanied by two dilemmas: first, the reactions have to be in progress under mild conditions to maintain the resulting products' enantiomeric purity with comparatively lower conformational stability; second, sensible modification of an appropriate interaction between racemic styrenes and catalysts, regardless of organometallic or small-organic-molecule catalytic systems. By emphasizing mechanistic insights into the reaction, we will address the advances made in the field of axially chiral styrene synthesis. As shown in Figure 1, four parts comprise this review of styrene catalytic asymmetric reactions: (1) desymmetrization of an existing C(sp2)-C(sp2) axis, (2) metal-catalyzed cross-coupling to construct a chiral C(aryl)-C(alkene) axis, (3) transformation from central chirality to axial chirality, and (4) alkyne-participated construction of axially chiral styrenes. Although some reviews related to axially chiral styrenes have been published,[13–15] this review is focused on mechanistic studies of axially chiral alkenes.

DESYMMETRIZATION OF AN EXISTING C(SP2)-C(SP2) AXIS

The last few years have witnessed great developments in the construction of atropisomeric styrenes by desymmetrization of an existing C(sp^2)-C(sp^2) axis through

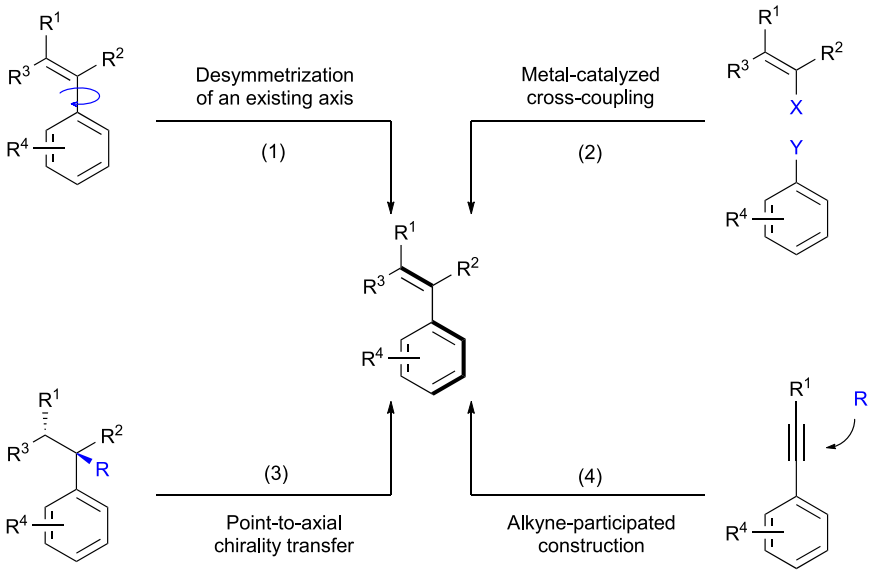

Figure 1. Strategies for enantioselective synthesis of axially chiral styrenes

functionalization of substrates. Several approaches based on desymmetrization of an existing C(sp2)-C(sp2) axis have evolved for construction of axially chiral styrenes.

Kinetic resolution for desymmetrization

To generate axially chiral arylcyclohexenes, in 2017, Jolliffe et al.[16] used a highly enantioselective cation-directed *O*-alkylation method. They treated racemic 1-aryl-2-tetralones with a quinidine-derived chiral ammonium salt under basic conditions with the assistance of an alkylating agent, which prompted atroposelective *O*-alkylation (Scheme 1). In the process of catalyst screening and assessing the scope of this reaction, they found that the free OH group, as a Brønsted acidic group in quinidine-derived phase-transfer catalyst 3, as well as the oxygen substituent in the 2′ position of substrate 1 play a momentous part in reactivity as well as selectivity. They opined that, under basic conditions, the chiral quinidine-derived ammonium counterion might differentiate between swiftly equilibrating atropisomeric enolate precursors, leading to a dynamic kinetic resolution (DKR) process for highly atroposelective *O*-alkylation. Additionally, this method provides a universal method for production of atropisomeric materials that are enantioenriched. In 2019, adopting a similar catalytic strategy, Wang et al.[17] reported a novel strategy to straightforwardly assemble atropisomeric multisubstituted alkenes via dazzling functional-group tolerance and enantioselectivities in enantioselective *N*-alkylation processes (Scheme 2). Based on this work, Hang et al.[18] reported a promotive method for atroposelective synthesis of isochromenone-indoles that is axially chiral, in which homophthalic anhydride-based indole derivatives serve as a novel class of indole-based platform molecules for DKR to synthesize a variety of axially chiral isochromenone-indoles with excellent high yields (Scheme 3).

In 2020, Ma et al.[19] accomplished an ingenious atroposelective method to obtain oxindole-based axially chiral styrenes with chiral-phosphoric-acid-catalyzed kinetic resolution, which provided two classes of oxindole-based axially chiral styrene derivatives with excellent diastereoselectivities and enantioselectivities in high-selectivity factors (Scheme 4). This strategy provides convenient access to simultaneously obtain oxindole-based axially chiral styrenes and bisamide derivatives with axial

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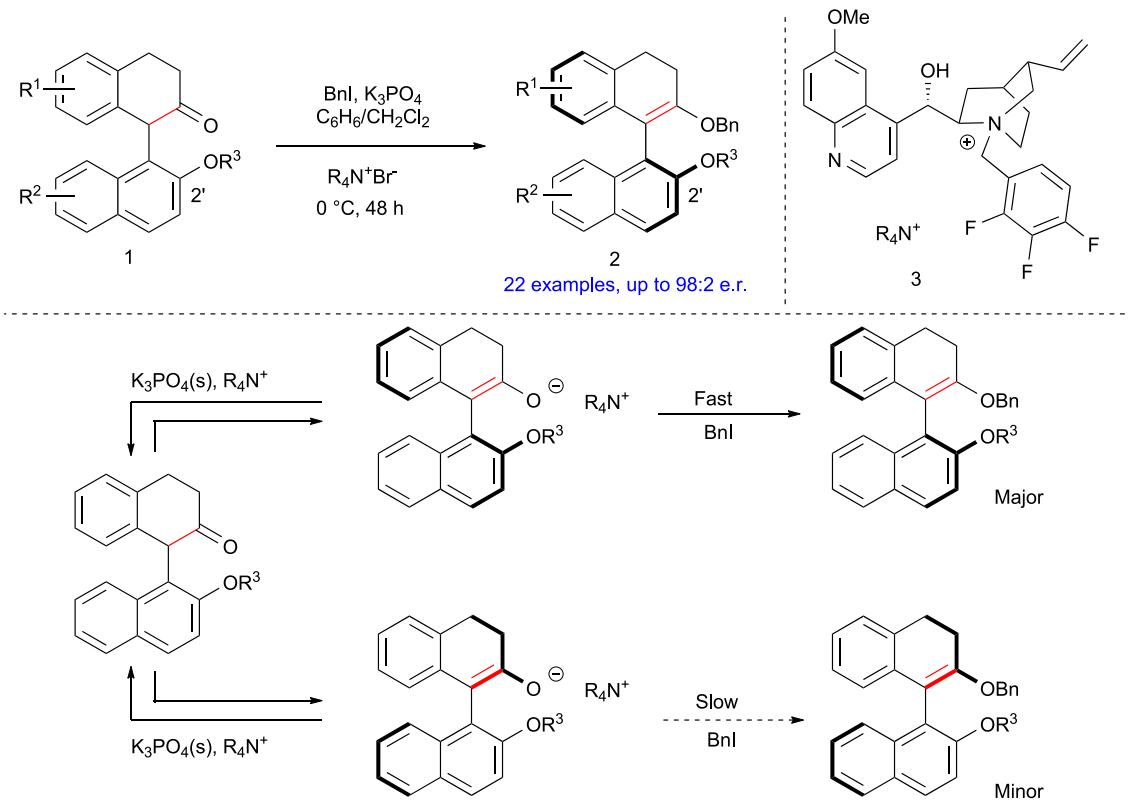
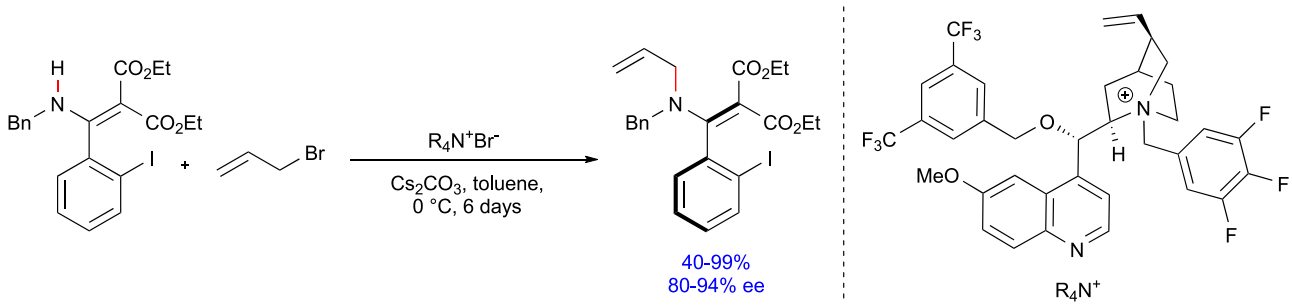


Scheme 1. Cation-directed *O*-alkylation method to construct axially chiral arylcyclohexenes

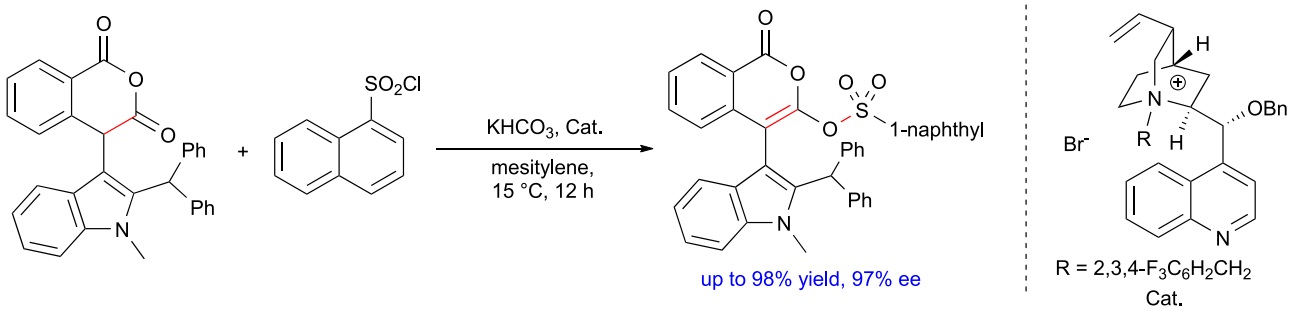
and central chirality. Further applications have proven the broad prospects of this class of oxindole-based axially chiral styrenes in asymmetric organocatalysis.[20–22]

In 2020, Li et al.[23] developed a pioneering palladium-catalyzed DKR method to synthesize atroposelective styrene organosilanes with C-H olefination and alkynylation. This strategy had two distinct DKR processes: first, atroposelective C-H functionalization produced axially chiral vinylsilanes or alkylsilanes, and second, further DKR C-H functionalization leads to *o*,*o*′-C-H multifunctional axially chiral organosilicon compounds with up to 99% ee (Scheme 5).

In 2021, Shao et al.[24] described a notable CPA-promoted asymmetric reductive amination reaction of 1-enal-substituted 2-naphthols for the structure of axially chiral



Scheme 2. A novel approach to assemble atropisomeric multisubstituted alkenes through enantioselective N-alkylation reactions



Scheme 3. Atroposelective synthesis of axially chiral isochromenone-indoles by homophthalic anhydride-based indole derivatives

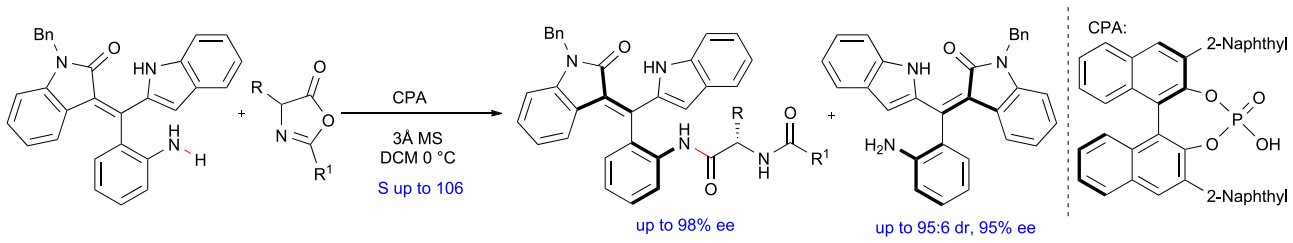
styrene architectures with a designed DKR method according to configurationally unstable 1-enal-substituted 2-naphthols. By performing a control experiment, they inferred that the free OH group at the naphthol moiety of 4 is in charge of the desired racemization of substrates via intermediate 6 to achieve successful DKR as well as a necessity to elaborate efficient enantiocontrol in the reaction through generating H-bond interactions with CPA. For the whole reaction process, the reaction is initiated with the condensation of 4 and aromatic amines 5, leading to mutually atropisomeric imine intermediates 7 and 8. The rapid interconversion between 7 and 8 proceeds via intermediate 6. Subsequently, because of the appropriate weak interaction differences between CPA and imine intermediates, 7 has a better consistency with a higher reaction rate, which affords products such as the major isomers (Scheme 6).

Palladium-catalyzed C-H functionalization for desymmetrization

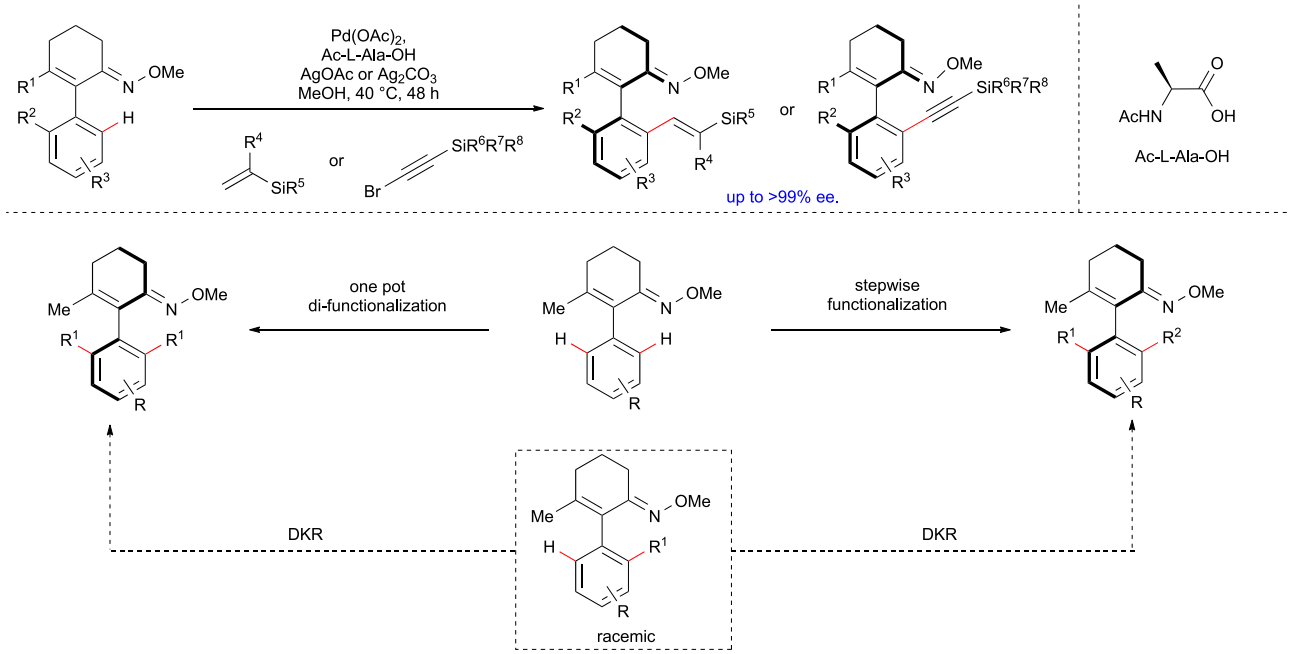
In the last few years, asymmetric palladium-catalyzed C-H functionalization has been greatly expanded in organic synthesis and sometimes used to synthesize atropisomeric styrenes accompanied by the dilemma that the reaction has to be conducted under mild conditions to preserve the resulting products' enantiomeric purity with relatively lower conformational stability.

In 2018, Sun et al.[25] reported inventive palladium-catalyzed enantioselective C-H olefination of 2-arylcyclohex-2-enone oxime ether with the assistance of ketoxime chelation to synthesize axially chiral styrenes with standout enantioselectivities under mild conditions, which employs ketoxime ether as an effectual directing group (Scheme 7).

Apart from direct introduction of imine as a directing group, in 2020, Song et al.[26] prominently reported efficient and applied Pd(II)-catalyzed atroposelective C-H olefination by utilizing a bulky amino amide as a transient chiral auxiliary to generate



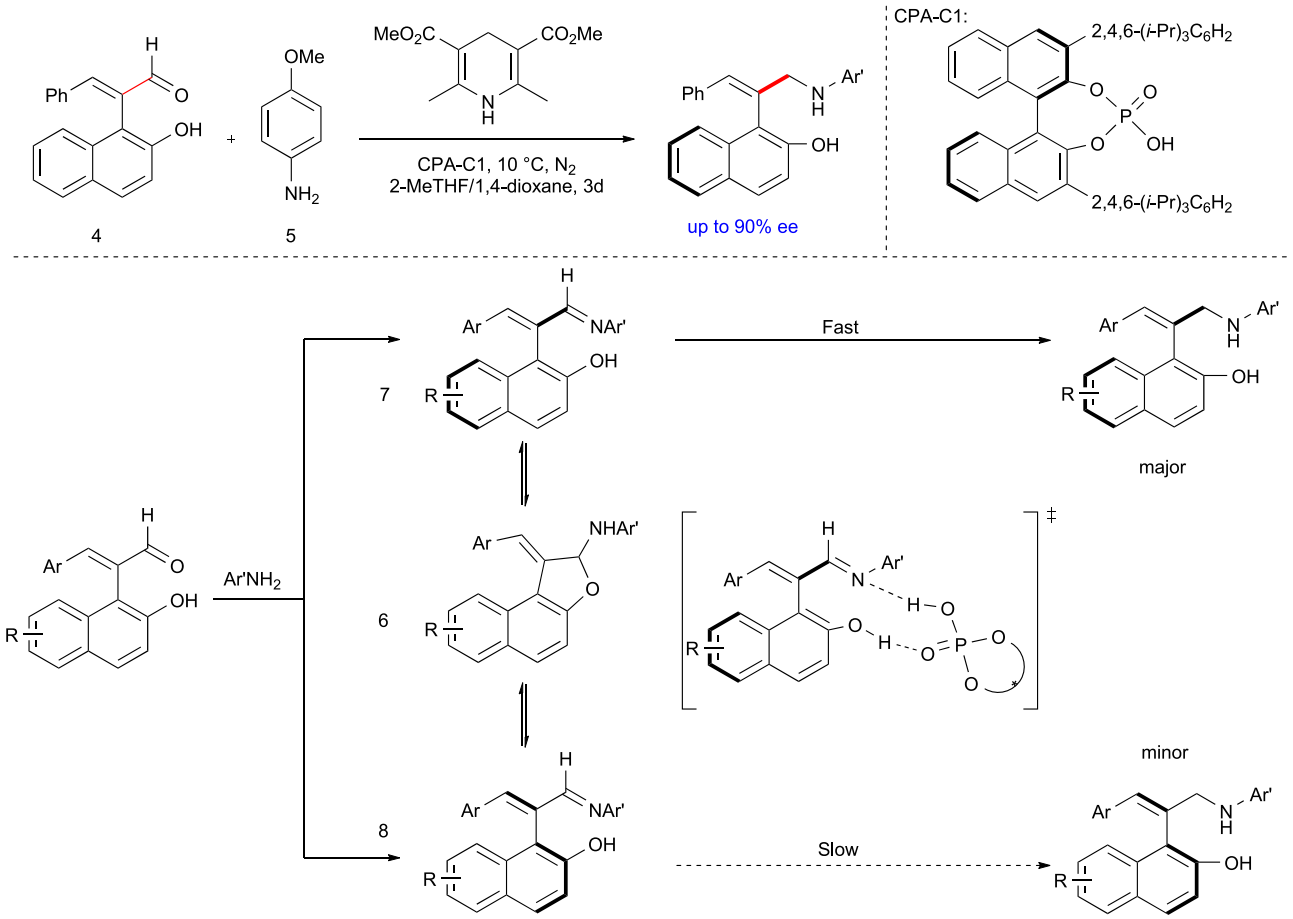
Scheme 4. An atroposelective method for oxindole-based axially chiral styrenes with CPA-catalyzed kinetic resolution



Scheme 5. Pd-catalyzed DKR method to synthesize atroposelective styrene organosilanes with C-H olefination and alkynylation

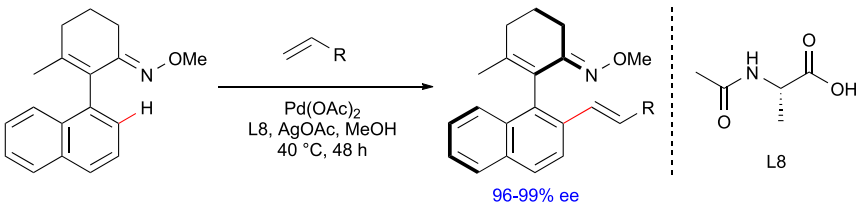
various axially chiral styrenes with excellent yields and enantioselectivity. To elucidate the reaction mechanism, the palladacycle intermediate 10 was isolated with a stoichiometric reaction of the preformed imine 9 and $Pd(OAc)_2$ in AcOD-*d*1, which was determined by single-crystal X-ray diffraction. The reaction catalyzed by intermediate 10 also led to the target product with good yield and slightly reduced enantioselectivity. Besides, the kinetic experiment declared that the C-H cleavage step is both the enantioselectivity and rate-determining step, and the deuterium-labeling experiments suggested that the C-H activation step is reversible (Scheme 8). In 2022, Shen et al.[27] described a similar Pd catalysis strategy to atroposelectively prepare aryl 1,3-dienes from readily available styrenes and olefins through an aldehyde-derived transient chiral auxiliary, which proceeds by enantioselective olefinic C-H alkenylation of styrenes via seven-membered endo-cyclometallation (Scheme 9). In the same year, Liu et al.[28] described creative Pd(II)-catalyzed C(alkenyl)-H alkenylation that was made possible by a transient directing group (TDG) strategy. This method takes advantage of reversible condensation between an alkenyl aldehyde substrate and an amino acid TDG to make coordination of the metal catalyst easier and produce a 1,3-diene with high regio- and E/Z selectivity. Using L-*tert*-leucine, the process allows synthesis of rarely studied enantioenriched atropoisomeric 2-aryl-substituted 1,3-dienes with good yield and outstanding atroposelectivity (Scheme 10).

In 2020, Jin et al.[29] developed a highly visionary atroposelective method via a Pd(II)-catalyzed C-H alkenylation and alkynylation to synthesize atroposelective styrenes with an open-chained alkene by applying L-pyroglutamic acid as the chiral ligand, where the pyridine group in 11 acts as the intramolecular directing group. For an in-depth exploration of the reaction mechanism, experimental and computational research was carried out to explain the atroposelective C-H alkenylation. The mechanistic experiment about the kinetic isotope effect (KIE) indicates that the C-H bond cleavage process might not be involved in a rate-determining step, which is mechanistically dissimilar from the reaction in Scheme 8. According to initial rate studies, a

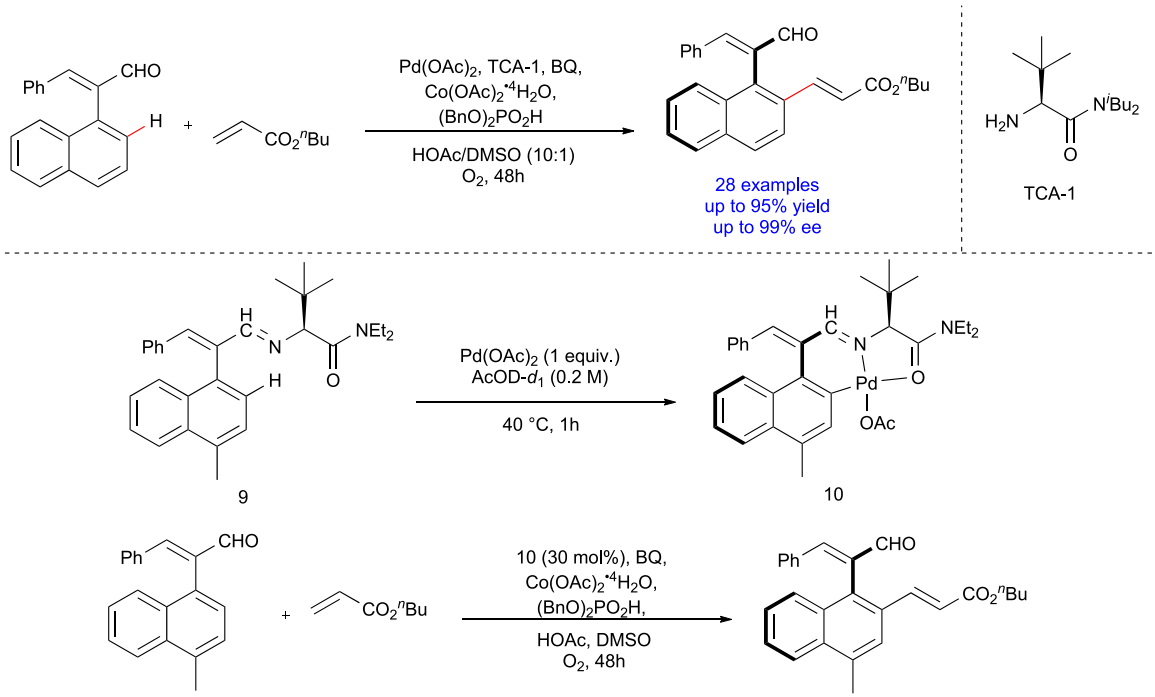


Scheme 6. CPA-promoted asymmetric reductive amination reaction of 2-naphthols for the structure of axially chiral styrene with a designed DKR

ligand deceleration effect (LDE) in this reaction was rationalized to facilitate high enantioselectivity by restraining the background reaction, in which L-pGlu-OH undergoes a highly favorable ligand exchange with $Pd(OAc)_2$ to obtain a chiral Pd(L-pGluO)(OAc)-type catalyst. This can explain the demand for an excess of chiral ligands to ensure that no isolated palladium acetate is present. Based on DFT calculations, the reaction relates to successive C-H bond activation, alkene insertion, and pyridine-assisted β-hydride transfer, in which the second step is a rate-determining step via TS2, which needs to overcome a barrier of 23.9 kcal/mol. The origin of chiral induction was also provided, where the major enantiomer's generation relates to reversible C-H bond activation via TS1 and later rate-determining alkene insertion via TS2. The C-H bond activation process, through TS3, suppresses the competitive



Scheme 7. Pd-catalyzed ketoxime-chelation-assisted enantioselective C-H olefination to synthesize atroposelective styrenes

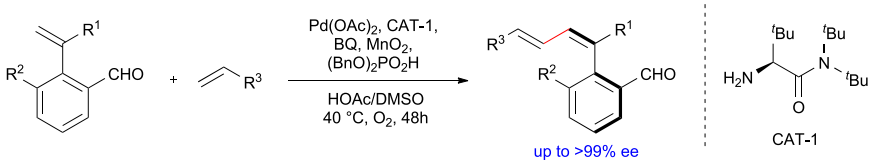


Scheme 8. Pd(II)-catalyzed atroposelective C-H olefination with the help of a bulky amino amide to construct axially chiral styrenes

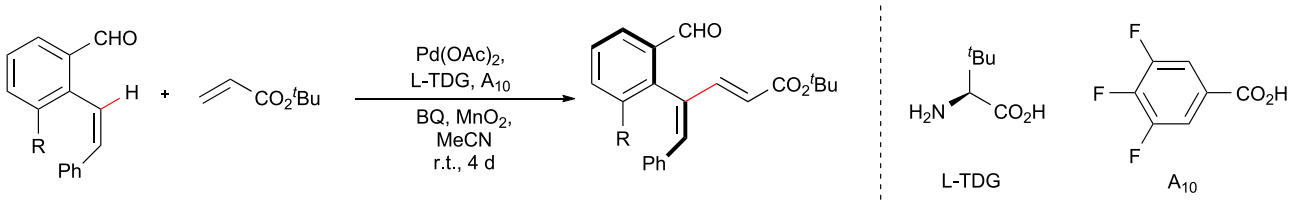
production of the minor enantiomer. The production of the main enantiomer is 4.5 kcal/mol more advantageous than that of the minor enantiomer when comparing the determining stages (TS2 vs. TS3), which attested to the brilliant enantioselectivities in experimental observations (Scheme 11).

Apart from the pyridine group in the olefin part of the styrene acting as a directing group, the carboxyl group can also play a role in weakly coordinated carboxylate-directed, palladium-catalyzed, atroposelective C-H functionalization to form carboxylic acids with axially chiral styrene skeleton. In 2021, Yang et al.[30,31] developed advanced palladium-catalyzed, atroposelective C-H arylation, olefination, and alkynylation of cinnamic acid derivatives for facile formation of axially chiral styrene-type carboxylic acids by a catalytic mechanism as in Scheme 11, which may be employed for a novel kind of chiral ligands or catalysts in asymmetric synthesis (Scheme 12).

Barring the directing group on the olefin part of styrene, which leads to C-H functionalization on the aryl, axially chiral styrene can also be formed by C-H activation of the olefin through the directing group on the aryl. In 2021, Jin et al.[32] developed a highly resourceful atroposelective strategy for atroposelective styrenes with a conjugated 1,3-diene skeleton through Pd(II)-catalyzed thioether-directed alkenyl C-H



Scheme 9. Pd catalysis to atroposelectively prepare aryl 1,3-dienes via an aldehyde-derived transient chiral auxiliary

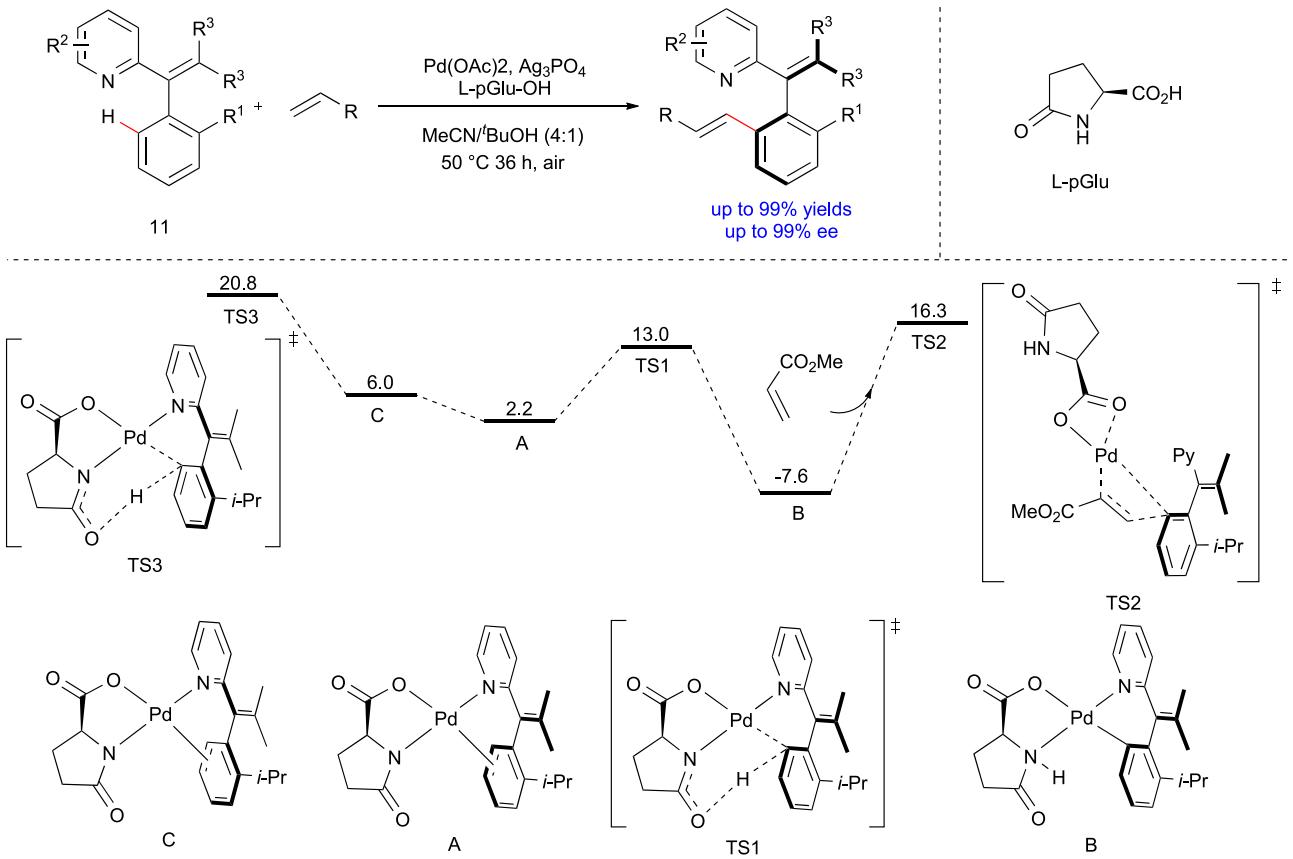


Scheme 10. Pd catalysis to atroposelectively prepare aryl 1,3-dienes with high regio- and E/Z selectivity

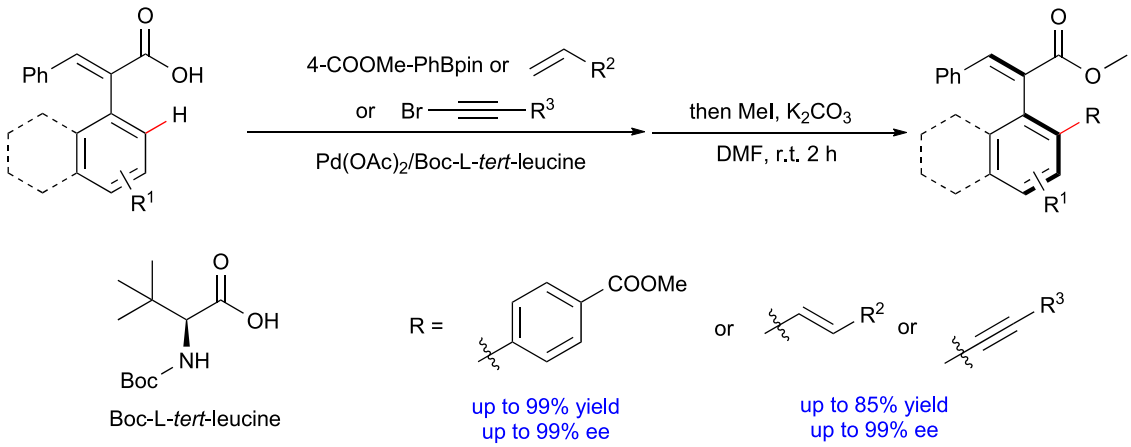
olefination (Scheme 13). In a Pd-catalyzed atroposelective cross-coupling reaction between olefins, developed by Dai et al.,[33] the tosylamide group can advantageously instruct stereospecific activation of the alkenyl C-H bond (Scheme 14).

METAL-CATALYZED CROSS-COUPLING TO CONSTRUCT A CHIRAL C(ARYL)-C(ALKENE) AXIS

Apart from desymmetrization of the existing axis to axially chiral styrene, in 2017, with the assistance of BoPhoz-type phosphine-aminophosphine ligands, Pan et al.[34] developed an innovative palladium-catalyzed asymmetric strategy to synthesize enone-based atropisomers by aryl boronic acid and 2-iodo-3-methylcyclohex-2enones, in which these cyclohexenone-based atropisomers are excellent candidates for use as platforms for synthesis of biaryl atropisomers with various *ortho* substituents (Scheme 15).

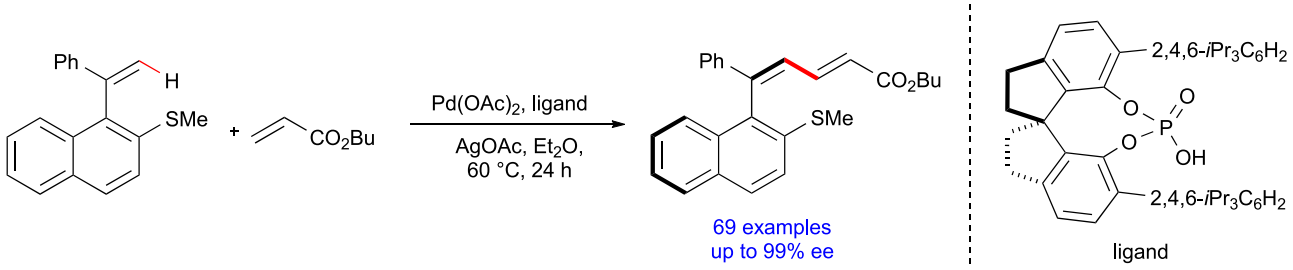


Scheme 11. Pd(II) catalysis C-H alkenylation and alkynylation strategy of axially chiral styrenes by using L-pyroglutamic acid

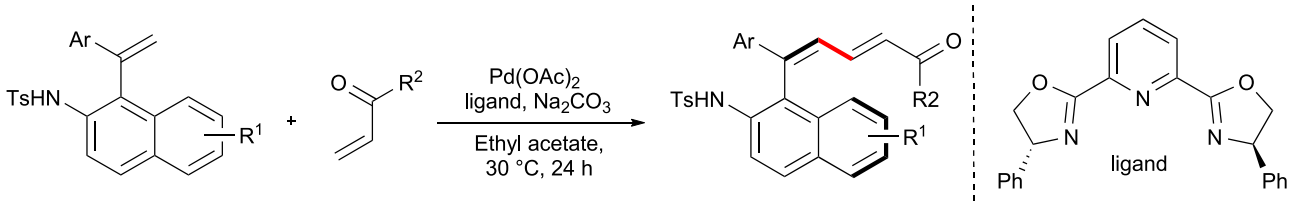


Scheme 12. Axially chiral styrene construction via atroposelective C-H arylation, olefination, and alkynylation of cinnamic acid derivatives catalyzed by Pd

Compared with arylcyclohexene-type axially chiral styrenes, as shown in Scheme 15, exclusion of cyclic alkene component requires voluminous and cumbersome substituents to furnish ample rigidity but weakening reactivity in palladium-catalyzed cross-coupling. Moreover, the more energetic conditions required to overcome steric hindrance are likely to ruin the axially chiral configurational stability of products, and addition of a base, illumination, or transition metal cation may facilitate interconversion of C=C geometry during creation of the chiral axis, resulting in a mixture of E/Z atropisomers. In response to these problems, in 2022, Qiu et al.[35] described promotive Pd-catalyzed asymmetric cross-coupling to generate axially chiral acyclic alkenes by *ortho*-substituted aryl halides and vinyl boronates. The triphenylsilyl-substituted ligand was proven to activate the reaction and control selectivity under mild conditions. Based on experimental findings and earlier studies, they came up with a mechanism where the chiral palladium complex formed by zero-valent palladium and ligand goes through oxidative addition accompanied by aryl bromide to generate intermediate 12 and then goes through ion exchange with K_3PO_4 to generate intermediate 13. Then the phosphate anion can promote vinyl boronate's transmetalation to the Pd center and obtain 14, which is in equilibrium with 15 through coordination exchange from the solvent molecule to the carbonyl oxygen of the ester group. In the end, as a stereo-determining step, reductive elimination liberates the cross-coupled product and revives the catalyst. According to observed stereochemical results, control experiments, and DFT calculations, they introduced a chiral induction model in which the reductive elimination transition states can be stabilized by π-d coordination between the Pd center and the phenyl ring of the triphenylsilyl group in the catalyst. The alkene component was nearer to the



Scheme 13. Pd(II) catalysis atroposelective strategy to form axially chiral styrenes by conjugated 1,3-diene

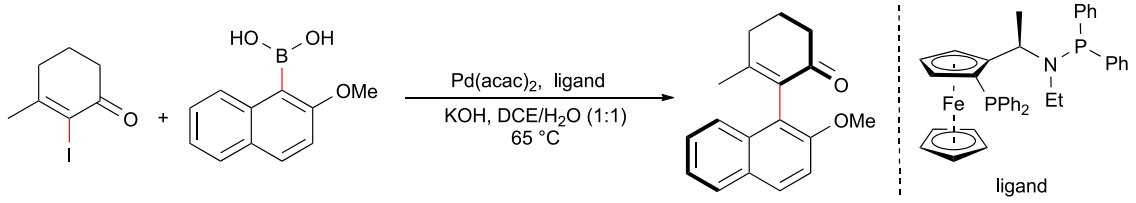


Scheme 14. Pd-catalyzed atroposelective cross-coupling reaction between olefins to synthesize axially chiral styrenes

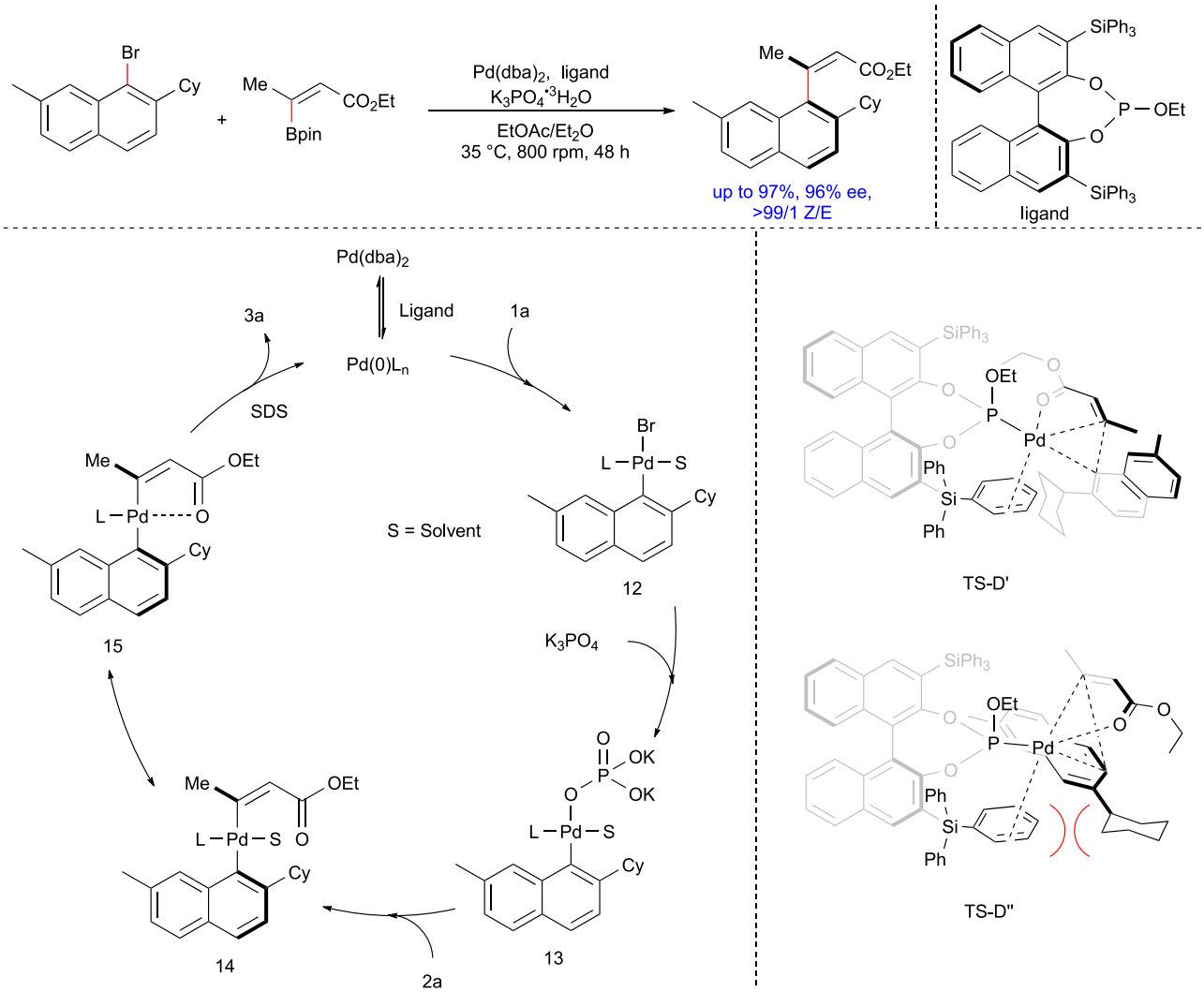
naphthalene ring and farther from the Pd center in the advantageous transition state TS-D′ than in the unfavored transition state TS-D″. Moreover, the triphenylsilyl moieties with steric bulk regulate the conformation of the 2-substituent on the naphthalene ring and alkene component to minimize steric hindrance, where the two triphenylsilyl groups are located distant from the cyclohexyl-substituted arene and methyl group and promote the more favored reductive elimination proceeding through TS-D′ with 2.2 kcal/mol relative Gibbs free energy vantage (Scheme 16).

In 2022, Li et al.[36] reported boosting atroposelective arylboration with alkynes, B_2pin_2, and aryl bromides catalyzed by Cu and Pd, providing a method to obtain tetrasubstituted axially chiral alkenylboronates with good Z/E selectivity, regiocontrol, and enantioselectivity. To attain a clear understanding of the mechanism, a range of evaluation experiments was performed, in which they found that the enantioselectivity of the product was dominated by the chirality of the Pd complex paired with the chiral ligand, and the reaction activity of the bimetallic Cu/Pd catalyst system was greater than that of the isolated Pd catalyst. Thus, they proposed a possible Cu/Pd dual catalytic cycle in which the intermediate 20 produced by the Cu-catalyzed borylcupration of the alkyne is β-boryl alkenylcopper. The electronic directing effect of an aryl group, which guides the copper moiety to add to the α position of the aryl group, controls the regioselectivity of unsymmetric aryl alkyl internal alkynes. Simultaneously, for the Pd catalytic cycle, aryl Pd(II) intermediate 21 is produced by oxidative addition of 18 to chiral L*Pd(0). Intermediate 22 is then produced by enantioselective transmetalation of intermediate 20 with intermediate 21, and the desired product 19 is then generated by further reductive elimination (Scheme 17).

In 2022, Li et al.[37] reported progressive Ni/pyridine-oxazoline-system-catalyzed alkynes, aryl iodides, and alkyl iodides participating in radical alternate reductive coupling to rapidly generate axially chiral styrene with high productivity and brilliant enantioselectivity (Scheme 18). To elucidate the mechanism and source of the enantio- and chemoselectivity, they performed EPR experiments and DFT calculations on the reaction, which showed that the catalytic cycle model with Ni(I)/Ni(III) is energetically more advantageous. Under reductive conditions, the Ni(I) generates *in situ* first and subsequently connects with ligand as well as Cl^- to form the initial, which then undergoes oxidative addition to form intermediate B with PhI via TS1 with 5.3 kcal/mol lower than that reacting with tBu-I. The subsequent step involved a highly

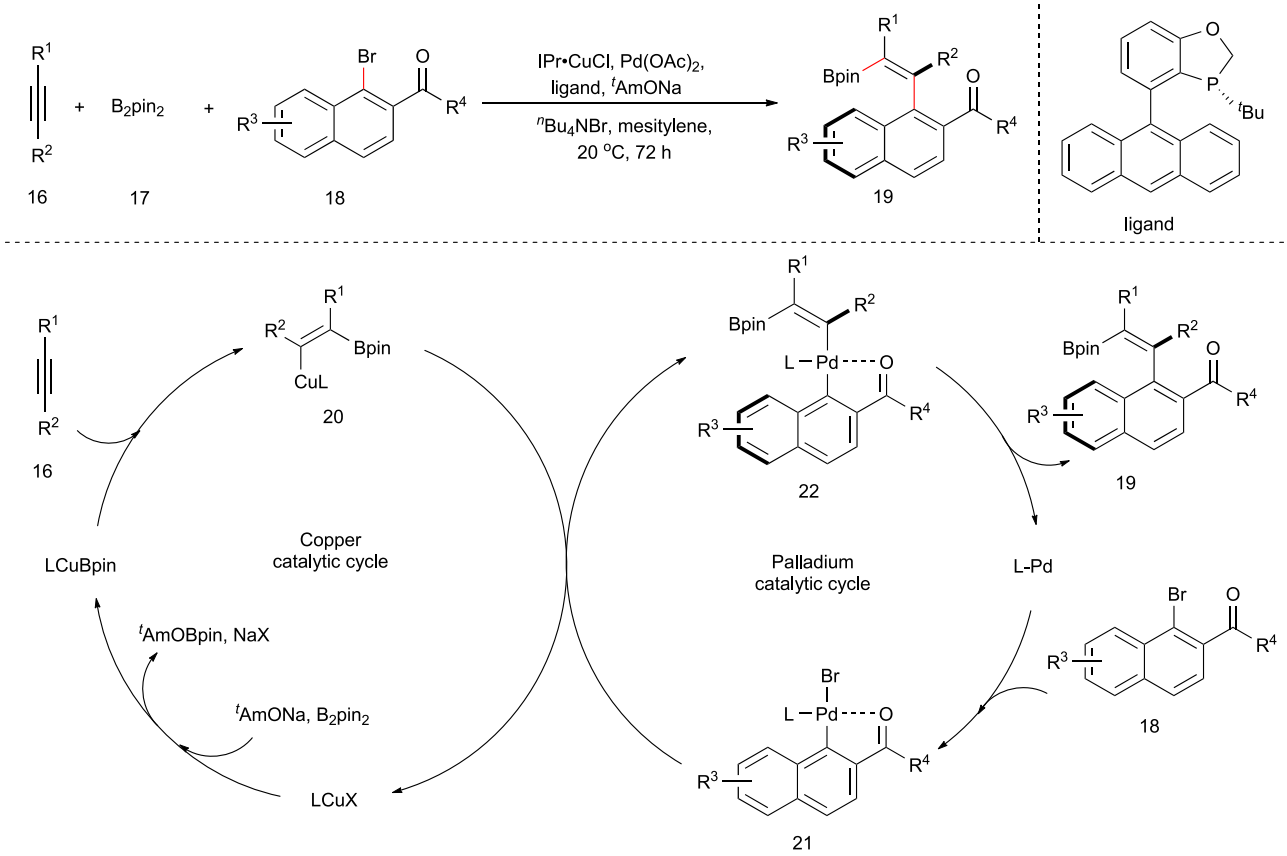


Scheme 15. Pd-catalyzed asymmetric synthesis of enone-based axially chiral styrenes with BoPhoz-type ligands



Scheme 16. Asymmetric cross-coupling with Pd is used to create axially chiral acyclic alkenes

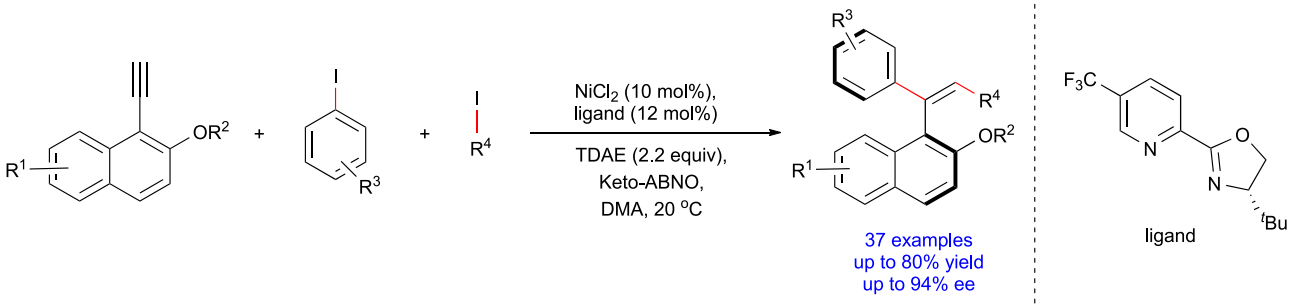
exergonic two-electron reduction of highly valent metal species B by TDAE to produce intermediate C. Subsequently, tBu-I reacted with C via TS2 with 0.4 kcal/mol lower than Ph-I to generate Ni(II) species, tBu· radical (E), and I^-. Then, the tBu· radical adds to the alkyne from two sides via TS3, creating G and G′, which can readily transition in configuration via TS4. Next, because of the energetic advantage, through TS5 and TS5′, respectively, Ni(II) species prefer to leave I^- to react with G and G′, where the stereochemical model of transition states demonstrates the steric hindrance of the phenyl group and the allene intermediate G attaching to the Ni center. Comparing the bond angle of the phenyl group ($N_{Oxazole}$-Ni-$C_{Ni\text{-}Ph}$) between Ph-Ni-I(II) (159.4°) species and TS5/TS5′, the torsion in TS5′ (124.3°) was much larger than that in TS5 (163.7°), which indicated that the steric hindrance in TS5 is slightly weaker than that in TS5′, making TS5′ energetically disfavored ($\Delta\Delta G‡$ = 2.0 kcal/mol), thus explaining the Sa configuration of the final product and matching the experimental results. The next step is highly exergonic reductive elimination of H via TS6 to create intermediate I. In the end, the Ni species was separated from I to produce the finished product J (Scheme 19).



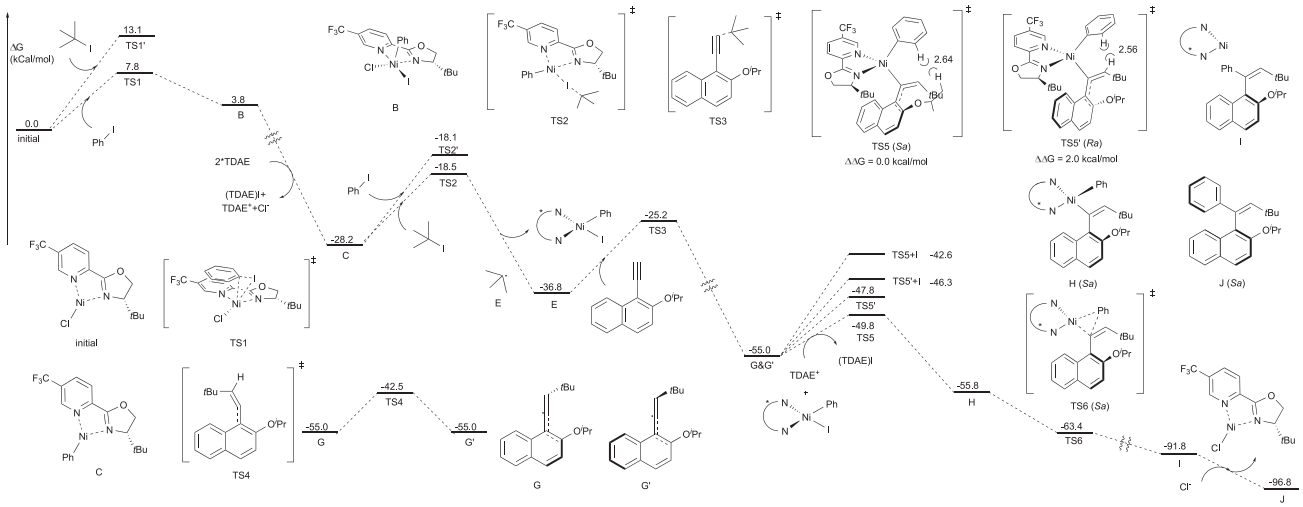
Scheme 17. Cu/Pd dual-catalysis-promoted atroposelective arylboration to access tetrasubstituted axially chiral alkenylboronates

TRANSFORMATION FROM CENTRAL CHIRALITY TO AXIAL CHIRALITY

Besides rotating the existing axis or constructing an axis between aryl and alkene, some strategies focus on transformation from central chirality to axial chirality. In 2001, Hattori et al.[38] showed an innovative 1,2 addition of the 2-methoxy-1-naphthylytterbium reagent to chiral tetralone 23-induced C centrochirality at the carbonyl carbon with complete stereoselectivity, giving carbinol 25. Although the carbinol existed as an equilibrium mixture of two conformational isomers, the C centrochirality was highly stereospecifically converted into the axial chirality of dihydrobinaphthalene 26 by preferential dehydration of conformer 28 (Scheme 20). Insufficient, the procedure needs to be combined with an efficient method for generation of enantiomerically pure 2-substituted 1-tetralones.

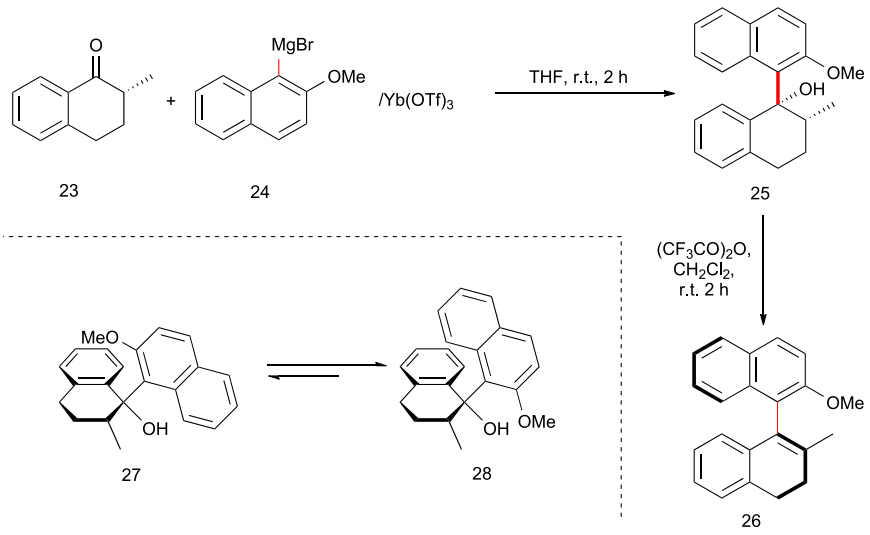


Scheme 18. Ni/pyridine-oxazoline-system-catalyzed three-component radical alternate reductive coupling to construct axially chiral styrene

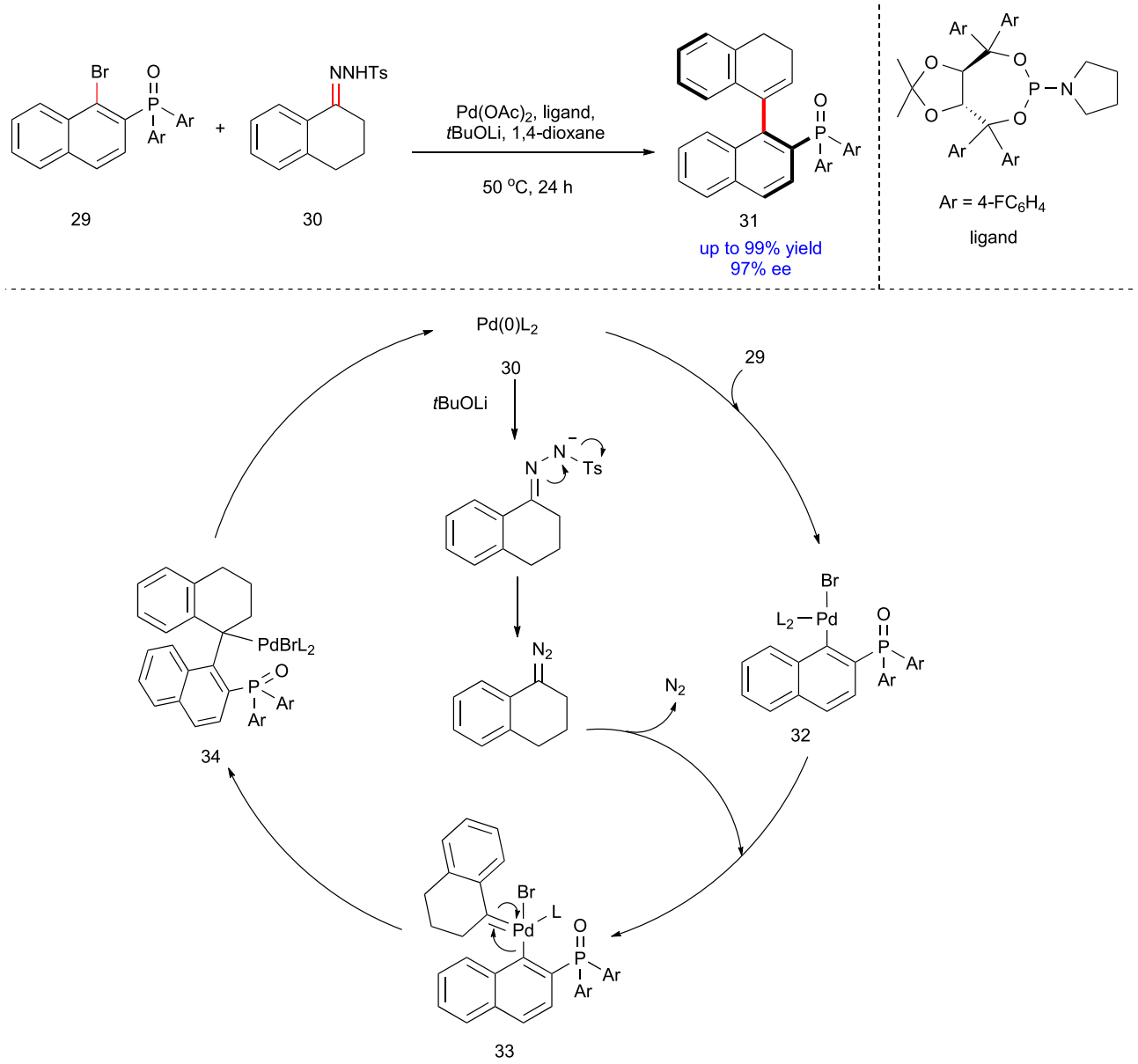


Scheme 19. DFT calculation on Ni/pyridine-oxazoline-system-catalyzed radical relayed reductive coupling

In 2016, Feng et al.[39] reported creative asymmetric synthesis using Pd from aryl bromides 29 and hydrazones 30, resulting in axially chiral 1-vinylnaphthalen-2-yl phosphine oxides 31, in which employment of carbene precursors as coupling partners enhances the tolerance of different functional groups as well as mellows the reaction conditions. With regard to the reaction mechanism, they tendered a catalytic cycle in that 29 would undergo oxidative addition with Pd(0) to give 32, which reacts with the diazo compound (generated *in situ* from hydrazones with the assistance of ^{t}BuOLi) to obtain the carbene-coordinated complex 33. Migration and insertion of 33 result in quaternary carbon intermediate 34 with central chirality containing a C-Pd bond. Subsequently, intermediate 34 goes through a β-hydride elimination and transforms to axially chiral styrene. According to a control reaction using diethyl phosphonate as a substrate resulting in 7% ee, they deemed that possibly the enantioselectivity is partially affected by the π-π interaction of the phenyl ring of the phosphine oxide in 29 with the tetrahydronaphthalene moiety of 30 in either intermediate 33 or 34



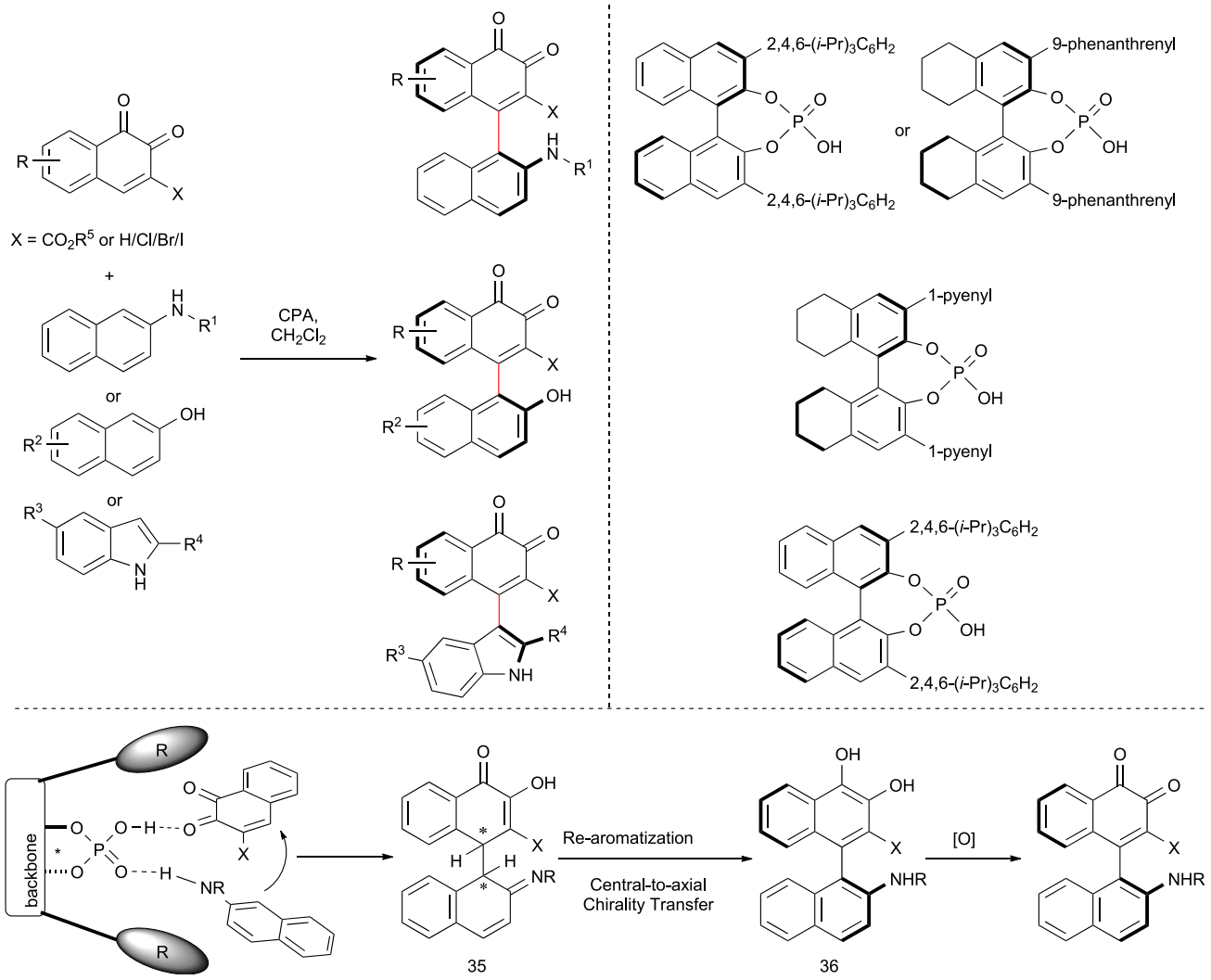
Scheme 20. 1,2-addition of 2-methoxy-1-naphthylytterbium to chiral tetralone induced C-centrochirality



Scheme 21. Pd-catalyzed asymmetric synthesis of axially chiral 1-vinylnaphthalen-2-yl phosphine oxides

(Scheme 21). In 2017, Wu et al.[40] reported a similar strategy, which can be exploited to generate vinyl arenes with alkyl-substituted phosphine oxides.

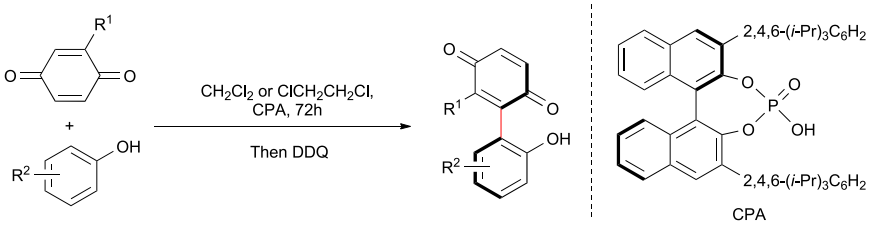
In 2019, Zhu et al.[41] reported a prominent bifunctional chiral phosphoric acid-catalyzed reaction to form axially chiral arylquinones by sequential asymmetric conjugate addition, central-to-axial chirality transfer, and oxidation, in which the *o*-naphthoquinone acts as the electrophile and the oxidant to react with three types of arylation counterparts (namely, 2-naphthylamines, 2-naphthols, and indoles) with good yields and enantioselectivities. Relying on the experimental results and previous reports, they proposed a possible reaction pathway where the chiral phosphoric acid first catalyzes two substrates to form intermediate 35 with two chiral centers by asymmetric conjugate addition. The following rearomatization with a central-to-axial chirality



Scheme 22. Construction of axially chiral arylquinones by bifunctional CPA-catalyzed asymmetric conjugate addition

conversion process gives an atropisomeric intermediate 36. Finally, oxidation by excessive *o*-quinone generated the excepted axially chiral arylquinone (Scheme 22). Later, in 2020, they[42] also reported a chiral phosphoric acid-catalyzed enantioselective structure of axially chiral (hetero)aryl-p-quinone frameworks with novel structure via assembly of p-quinones and naphthols or indoles by central-to-axial chirality conversion (Scheme 23).

In 2021, by separately utilizing cinnamyl carbonate analogs and naphthols as electrophiles and nucleophiles, Wang et al.[43] developed a pioneering tandem iridium catalysis strategy to synthesize axially chiral styrenes according to asymmetric allylic substitution isomerization (AASI). In this work, two independent iridium catalytic cycles, central-to-axial chirality stereospecific 1,3-hydride transfer and iridium-catalyzed asymmetric allylic substitution, were used to produce axially chiral styrenes *in situ*. The DFT research for the isomerization process showed that the central-to-axial chirality stereospecific 1,3-hydride transfer occurs via Ir-catalyzed benzylic C-H oxidative addition and reductive elimination, where the deprotonated hydroxyl



Scheme 23. CPA-catalyzed enantioselective construction of axially chiral (hetero)aryl-p-quinone frameworks

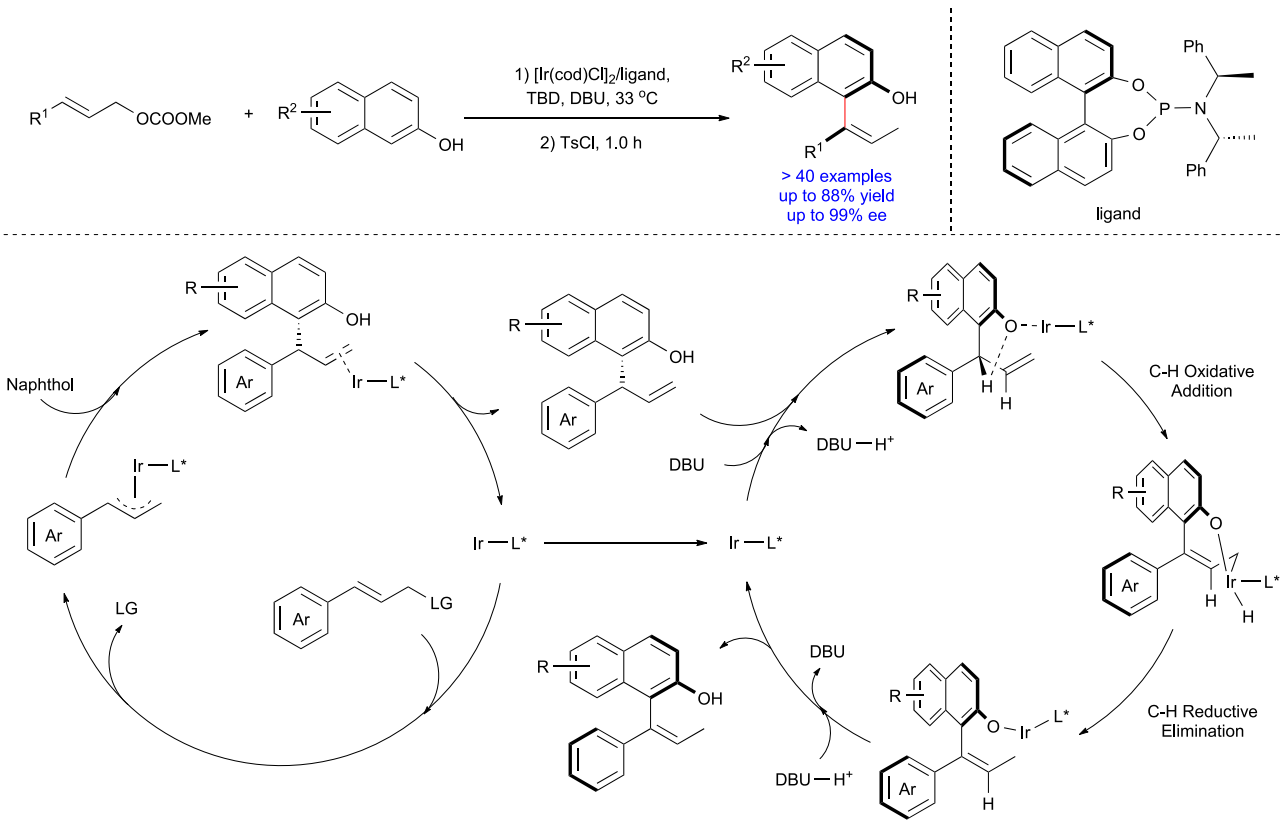
of naphthol coordinates with Ir(I) to prevent C(sp2)-C(sp2) axes from rotation (Scheme 24). Zhao et al.[44] reported similar work in the same year.

ALKYNE-PARTICIPATED CONSTRUCTION OF AXIALLY CHIRAL STYRENES

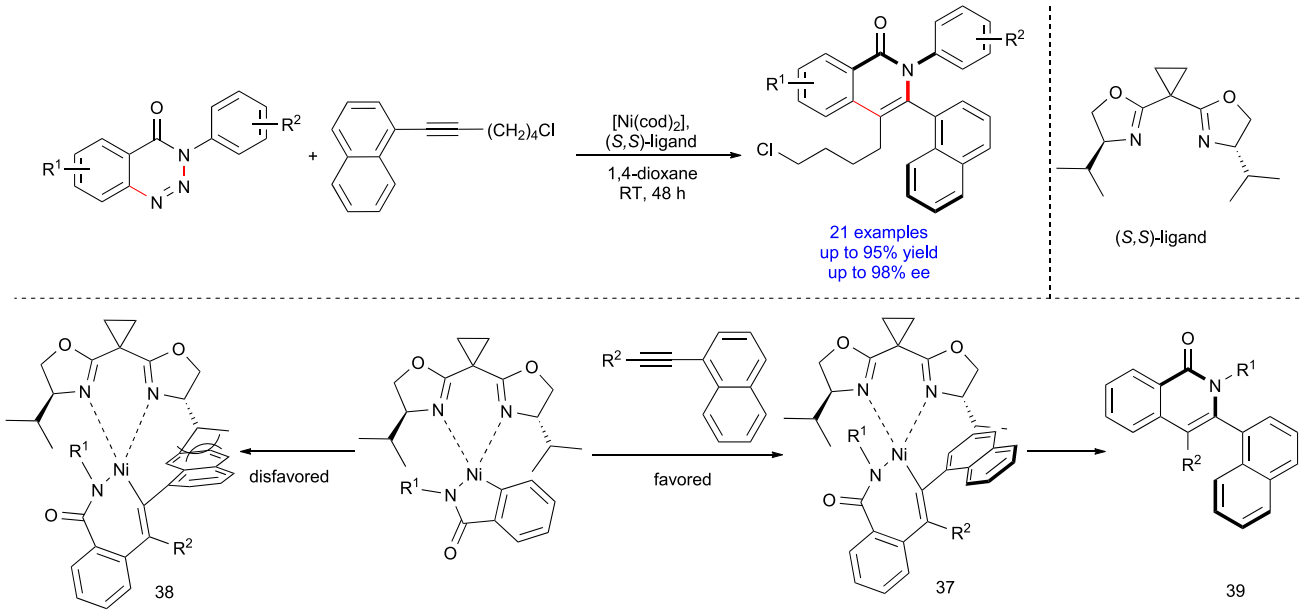
Alkynes, as an important type of synthetic block, are commonly applied in the asymmetric catalytic reaction. As for generation of axially chiral styrenes, three kinds of strategies are discussed in this section. Several approaches based on participation of alkynes have been exploited for construction of atropisomeric styrenes.

Metal-catalyzed migration insert of alkyne

In 2015, Fang et al.[45] described distinguished, highly regio- and enantioselective chiral nickel(0)/bis(oxazoline)-catalyzed denitrogenation transannulation of 1,2,3-benzotriazin-4(3*H*)-ones and bulky internal alkynes to synthesize a novel class of axially chiral



Scheme 24. Tandem Ir-catalyzed synthesis of axially chiral styrenes enabled by AASI

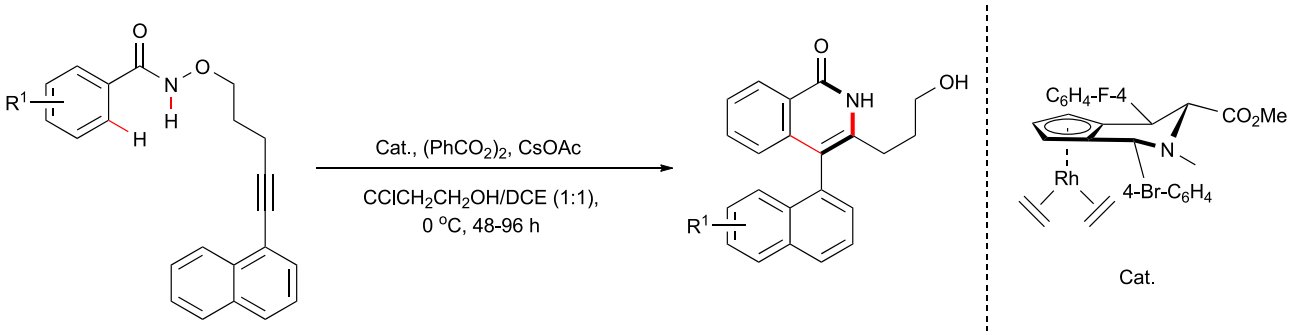


Scheme 25. Chiral nickel(0)/bis(oxazoline)-catalyzed denitrogenation transannulation to synthesize axially chiral isoquinolones

isoquinolones. They modeled the geometry of intermediates and characterized the transition states using DFT calculations to gain an understanding of the origin of the axial chirality, where steric hindrance among the naphthyl ring of the alkyne and the isopropyl group of the catalyst brings a 3.6 kcal/mol disadvantage to the transition state for formation of 38 rather than 37. This study supports the preference of the aR-configured product 39 with participation of (S, S)-L10 as the chiral ligand, and the axial chirality is probably determined by the reactant/chiral catalyst arrangement in the Ni(II) complex (Scheme 25). In 2016, Wang et al.[46] specially reported a mechanistic study using a control experiment as well as DFT calculations. The results reveal that the transformations proceeds via a sequential nitrogen extrusion, carbometalation, Ni-C bond insertion, and reductive elimination process. Furthermore, the calculated results show that high enantioselectivity is mainly resolved by the orientation difference of the naphthyl substituent to the chiral ligand between the two transition states of the key annulation step, which agrees with the previous study.

Encouraging rhodium(III)-catalyzed atroposelective synthesis of axially chiral 4-arylisoquinolones was reported by Shan et al.[47] 2018, with C-H bond activation and intramolecular annulation with excellent yields as well as enantioselectivity with chiral cyclopentadienyl ligands embodying a piperidine ring as a skeleton (Scheme 26). Inspired by previous work, as a continuation of their research on arenes' asymmetric C-H activation mediated by Rh(III), in 2020, Wang et al.[48] reported eminent Rh(III)-catalyzed C-H activation to synthesize atroposelective biaryl NH isoquinolones by benzamides and intermolecular [4+2] annulation with sterically hindered alkynes, in which alkyne insertion, which determines stereochemistry, undergoes a dynamic kinetic change in a redox-neutral annulation to establish the axial chirality. According to their mechanistic experiment, regio- and enantioselectivities were produced through steric interactions between the amide-directing group and the alkyne substrate (Scheme 27).

In 2019, Yang et al.[49] developed notable asymmetric synthesis of axial chiral vinylarenes featuring an oxindole moiety via sequential carbopalladation/C-H olefination



Scheme 26. Rh(III)-catalyzed C-H bond activation and intramolecular annulation method for synthesis of axially chiral 4-arylisoquinolones

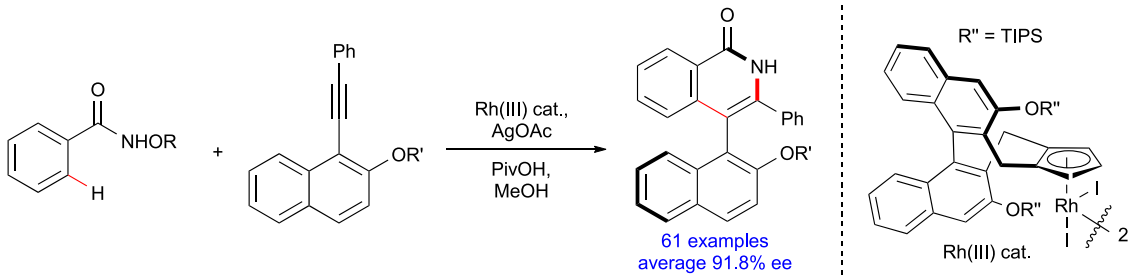
from readily available materials with palladium catalysis. Among them, tartaric acid-derived phosphoramidite ligands gave good yields and moderate enantioselectivity (Scheme 28).

Constructing axially chiral styrenes via a vinylidene *o*-quinone methide (VQM) intermediate

VQM, derived from 2-ethynylphenol derivatives and a highly active electrophilic intermediate, can be generated through prototropic rearrangement (tautomerization) of 2-(phenylethynyl)phenol under basic conditions and prefers to react with electron-rich substrates. Some reactions are reported to construct axially chiral styrenes by using this strategy, in which determination of axial chirality in styrenes usually counts on the chiral VQM intermediates.

In 2018, Jia et al.[50] reported a progressive highly enantioselective strategy to form axially chiral sulfone-containing styrene derivatives with chiral organocatalysis with excellent yields and enantioselectivities via a VQM intermediate. Based on control experiments, previous achievements, and DFT calculations, they came up with a plausible catalytic cycle where prototropic rearrangement of 2-ethynylphenol to produce the VQM intermediate is first aided by the quinuclidine base and hydrogen bonding of the thiourea catalyst. The allene moiety's absolute configuration was determined to be R. The DFT calculations showed that formation of S-isomer allene is unfavorable because of the strong repulsion between the benzene ring and vinyl-quinuclidinyl groups of the catalyst in a transition state to form an S configuration, which also weakened the hydrogen bond between the VQM intermediate and catalyst. Next, nucleophilic addition of the sulfinate anion activated by proline to the highly active VQM intermediate occurs, obtaining the axially chiral styrene product (Scheme 29). In the same year, they reported five other strategies to construct axially chiral styrenes via VQM intermediates with thiourea and squaramide catalysts, including an asymmetric Mannich reaction[51] and intramolecular [4+2] cycloaddition.[52] In addition, with Huang et al.,[53] they developed a reaction to form tetra-substituted axially chiral styrenes,[54] a kinetic resolution process for multiple contiguous axial chiral styrene systems,[54,55] as well as multiple stereoisomers bearing E/Z configurations, stereogenic carbon centers, and axially chiral styrenes. This systematic work about axially chiral styrenes brings extensive attention to synthetic chemists for a new addition to the axially chiral family.

Atroposelective assembly for synthesis of axially chiral heteroarylalkenes has only been reported recently and is still a mystery to chemists. This may be attributed to the substantial difficulties present in axially chiral alkene-heteroaryl scaffolds,

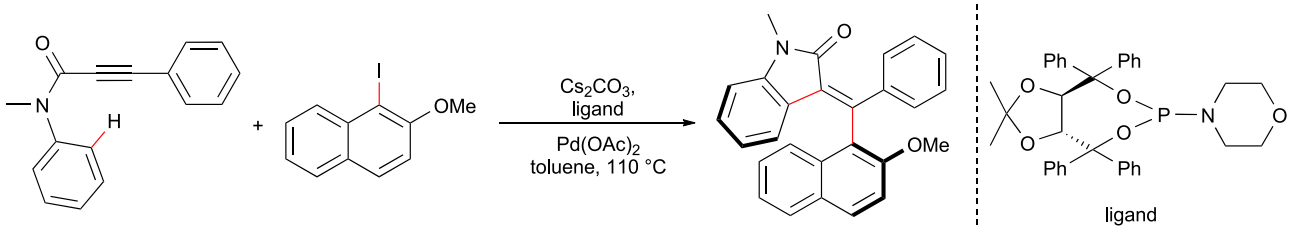


Scheme 27. Atroposelective synthesis of biaryl NH isoquinolones by Rh(III)-catalyzed C-H activation

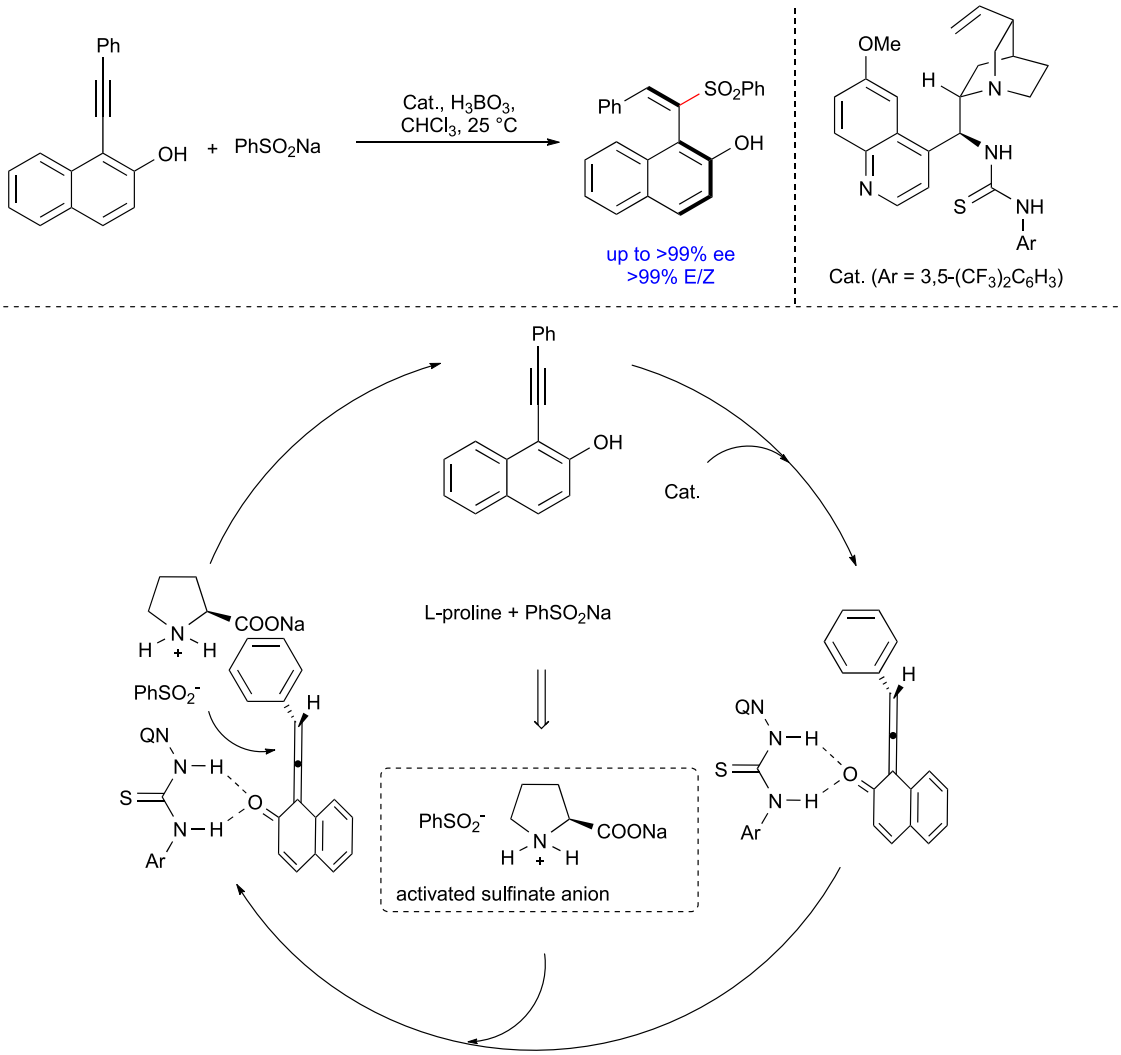
including their less stable conformation and lower rotational barrier, which are highly desired to be achieved. By using a catalytic enantioselective addition reaction of 3-alkynyl-2-indolylmethanols with bulky nucleophiles, α-amido sulfones were used as competent nucleophiles, and CPA served as an appropriate chiral catalyst for this addition reaction. Wang et al.[56] reported creative atroposelective construction of axially chiral alkene-indole scaffolds via an allene-iminium intermediate in 2021. This reaction creates a new class of axially chiral acyclic alkene-indoles while being the first catalytic enantioselective production of such frameworks (Scheme 30).

In 2019, Wang et al.[57] reported prominent effectual CPA-catalyzed asymmetric hydroarylation of alkynes to generate the chiral VQM intermediate through concerted 1,5-H transfer with excellent yields, enantioselectivities, and E/Z selectivity control, which means that activating alkyne by Brønsted acid yields good compatibility with several activating group types. DFT calculations showcased the reaction mechanism and the derivation of the enantioselectivity, in which the structural misfit of the substrate in the chiral pocket of the catalyst in the unfavorable transition structure causes the energy difference between the two transition structures of the corresponding isomers (Scheme 31).

In 2020, Liang et al.[58] devised a resourceful electrophilic carbothiolation method for axially chiral amino sulfides that is enantioselective, which is achieved by a Ts-protected bifunctional sulfide catalyst and Ms-protected *ortho*-alkynylaryl amines (Ts = tosyl; Ms = mesyl) via aza-vinylidene-quinone methide (aza-VQM) intermediates. Based on previous studies, they depicted a plausible reaction pathway, where catalyst 42 activates the electrophilic sulfur reagent to form intermediate 43 with a Lewis acid. When intermediate 43 combines with substrate 40, thiirenium ion intermediate 44 with an anion bridge formed from an acid is produced. The catalyst can then be renewed by further converting intermediate 44 to chiral azavinylidene-quinone methide (aza-VQM) intermediate 45. The intermediate 45 is hydroarylated intramolecularly after that, producing an axially chiral product. In the enantiocontrol via hydrogen bonding, the amino groups on the catalyst and substrate are both essential (Scheme 32).

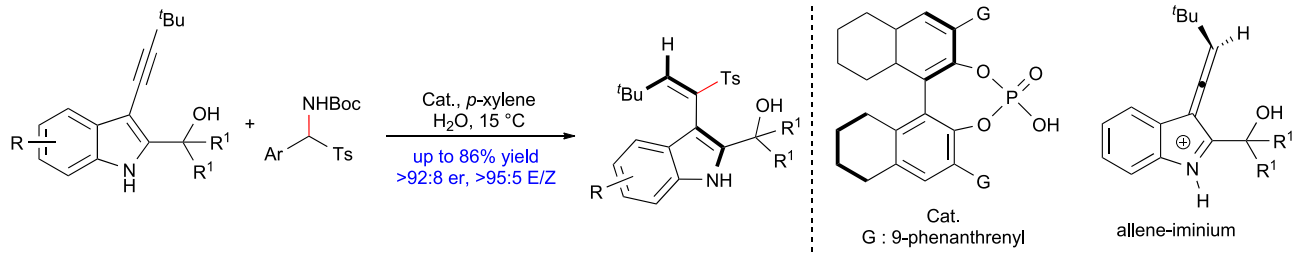


Scheme 28. Synthesis of axial chiral vinylarenes featuring an oxindole moiety via sequential carbopalladation/C-H olefination

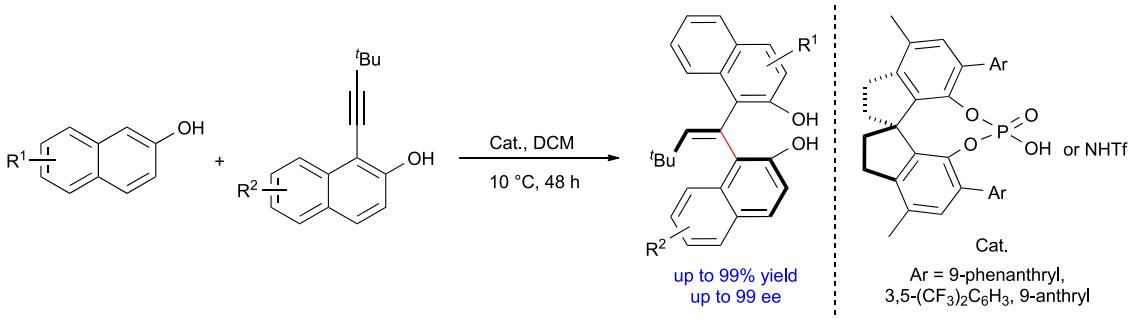


Scheme 29. Asymmetric organocatalysis is employed to synthesize axially chiral sulfone-containing styrene derivatives using a VQM intermediate

In 2020, Li et al.[59] reported a conspicuous peculiar construction of axially chiral naphthylamine heterocycle styrenes using concerted 1,5-H transfer to create a chiral aza-VQM intermediate via π-π interaction as well as a dual-H-bond-concerted control approach. Indoles and 4-hydroxycoumarins were successfully used to create an axially chiral framework with outstanding yields and enantioselectivities using *ortho*-alkynyl-naphthylamines as the electrophile. Based on the experimental outcome and

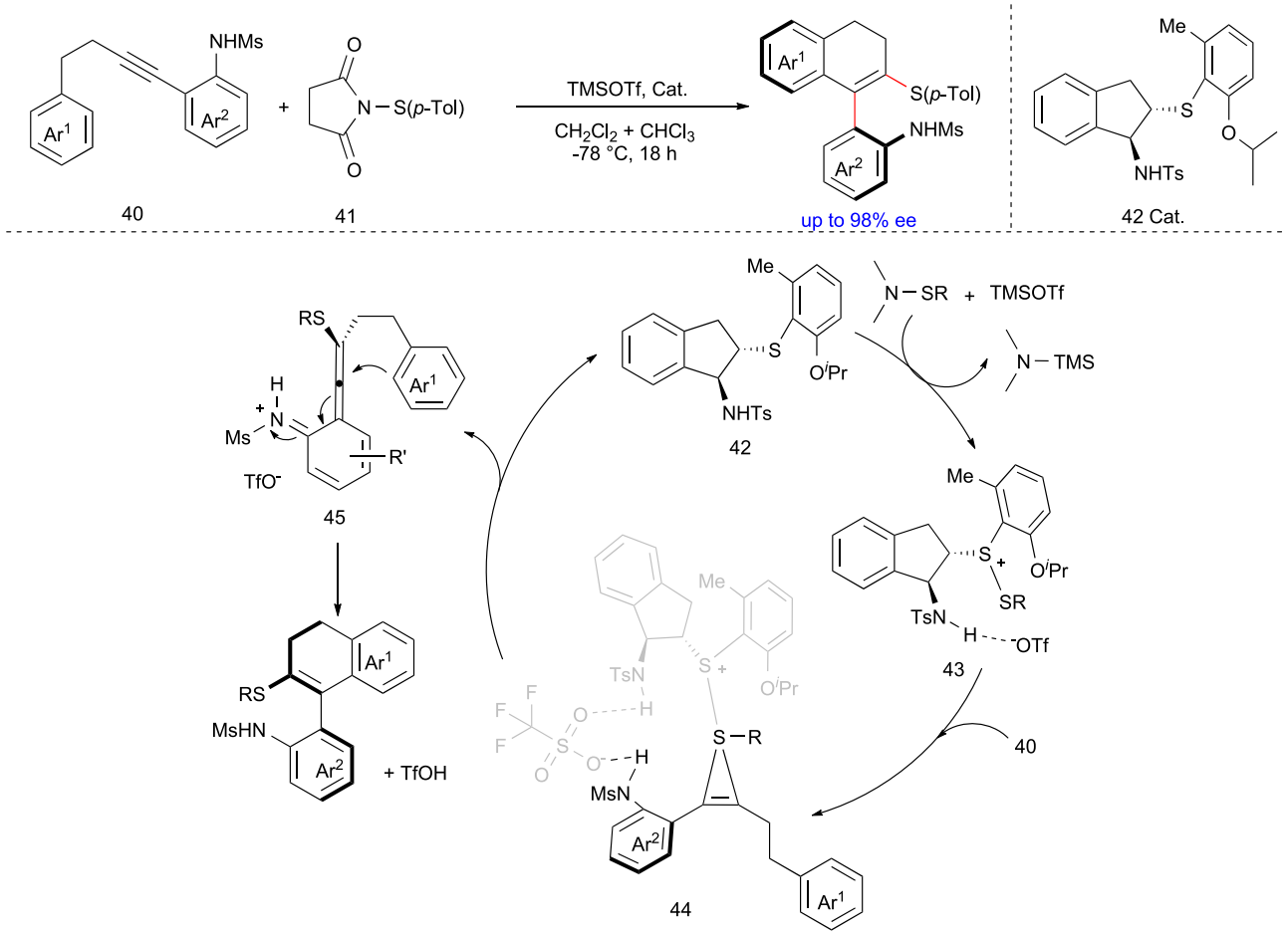


Scheme 30. Atroposelective construction of axially chiral alkene-indole scaffolds using the allene-iminium intermediate



Scheme 31. Alkynes are hydroarylated asymmetrically by CPA via coordinated 1,5-H transfer to create the intermediate chiral VQM

previous literature, a possible reaction mechanism was rendered in which catalyst 47 and alkyne 46 first form a comparatively stable complex 48 via dual-hydrogen-bonding interactions to ameliorate enantioselectivity steadiness. Then, to create chiral aza-VQM intermediate 49, the activated alkyne proceeds through a coordinated 1,5-H transfer, which also regulates the E/Z selectivity. Subsequently, in intermediate 50, the axial chirality is transferred from the allene to the alkene when the indole's C-3 adds to the allene from the side opposite the bulky group of the



Scheme 32. Construction of axially chiral amino sulfides by electrophilic carbothiolation of alkynes via aza-VQM intermediates

phosphoric acid, producing the matching Z isomer 51. Finally, 51 passes through aromatization to produce the finished product and replenish the catalyst (Scheme 33).

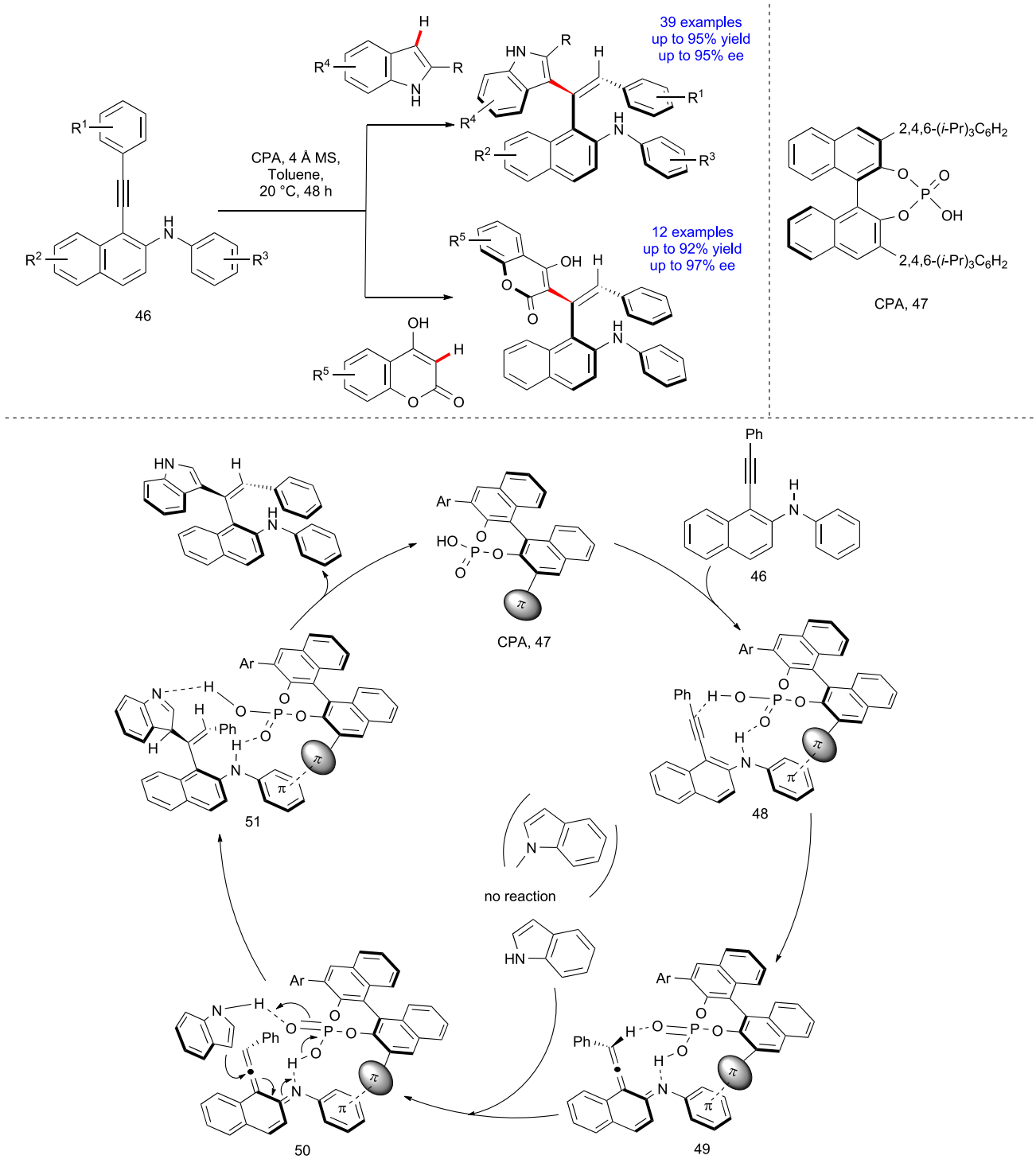
In 2021, Zhang et al.[60] reported a resourceful method to create C-4 alkenylated pyrazolone derivatives with various stereoelements, including E and Z configurations, stereogenic carbon centers, and axially chiral styrene elements, by adding pyrazolone through an asymmetric organocatalytic Michael reaction to *o*-alkynylnaphthol. The probable transition state model reveals that the reaction is promoted by chiral VQM produced *in situ* via hydrogen-bonding interaction between the organic catalyst and the substrate (Scheme 34).

In 2022, Zhang et al.[61] reported an advancing asymmetric free radical reaction of potassium alkyltrifluoroborates, potassium metabisulfite, and 1-(alkynyl)naphthalen-2-ols promoted by photo to access axially chiral styrenes that include sulfonyl by inserting sulfur dioxide with excellent enantioselectivity and good yield. Alkylsulfonyl radicals are produced *in situ* during the transformation, along with tandem enantioselective radical addition and a reduction of radical species (Scheme 35).

In 2022, Gou et al.[62] reported eminent CPA-catalyzed nucleophilic addition of 2-alkynylnaphthols to *o*-quinone methides or imines with the assistance of chiral all-carbon tetrasubstituted VQM intermediates, where the cycloaddition process can intramolecularly grab. Moreover, cycloaddition of alkynylnaphthols with *o*-quinone methides appears to comprise a [2+2] cycloaddition, 4π-electrocyclic ring opening, and 6π-electrocyclization, according to preliminary mechanistic investigations and DFT calculations. Sequential [2+4] cycloaddition and an auto-oxidation process were employed in the cycloaddition of alkynylnaphthols with imines (Scheme 36).

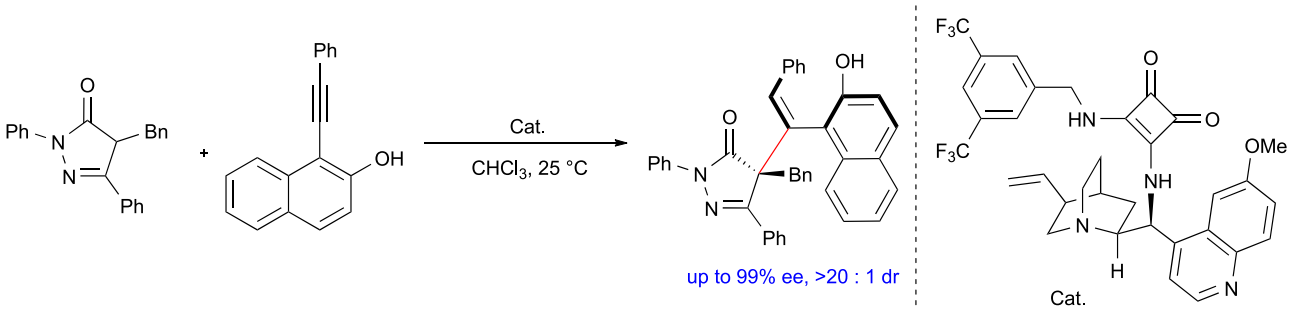
In 2022, Cai et al.[63] exploited distinctly regional atroposelective hydrophosphinylation of hydroxynaphthylalkynes with phosphine oxides co-catalyzed by Cu and CPAs to obtain axially chiral phosphorus-containing styrenes with excellent yields and enantioselectivities, where the innate low nucleophilicity of phosphorus compounds is overcome by incorporating VQM intermediates *in situ*. To explore the mechanism and the crucial roles that CPA and Cu cation play, they performed DFT calculations, where the CPA not only assists hydroxynaphthylalkynes in forming chiral (S)-VQM via 1,5-H transfer but tautomerizes phosphine oxide to hydroxydiphenylphosphane with a nucleophilic phosphorus center. As for $CuCl_2$, the Cu atom can bridge the hydroxydiphenylphosphane and CPA by coordination and promotes formation of a new hydrogen bond between the hydroxyl H atom in hydroxydiphenylphosphane with the oxygen atom on VQM, which lowers the transition state energy barrier. Moreover, generation of (S)-VQM is more advantageous than the R configuration, which derives from the distortion of dihedral angles between vinylidene and quinone in the structures of corresponding transition states (Scheme 37).

Regarding axially chiral heteroarylalkenes, catalytic asymmetric building has proven challenging for alkene-indole skeletons, which have recently drawn interest because of the distinct characteristics of the indole ring and indole-containing scaffolds. For instance, the rotational barrier of alkene-indole frameworks is exceedingly low as a result of the integration of an alkene group with a five-membered indole ring, leading to the exceptionally poor configurational stability of such skeletons. More crucially, there would still be a great deal of difficulty in controlling the (E/Z) selectivity and the enantioselectivity of the alkene-indole structures. To overcome these



Scheme 33. π-π interaction and dual H-bond concerted control strategy to construct axially chiral naphthylamine heterocycle styrenes through an aza-VQM intermediate

problems, Wang et al.[64] created an innovative new class of axially chiral aryl-alkene-indole frameworks in 2020, and the first catalytic asymmetric construction of such scaffolds was made possible by the strategy of organocatalytic (Z/E)-selective and



Scheme 34. Construction of C-4 alkenylated pyrazolone derivatives through the asymmetric organocatalytic Michael addition

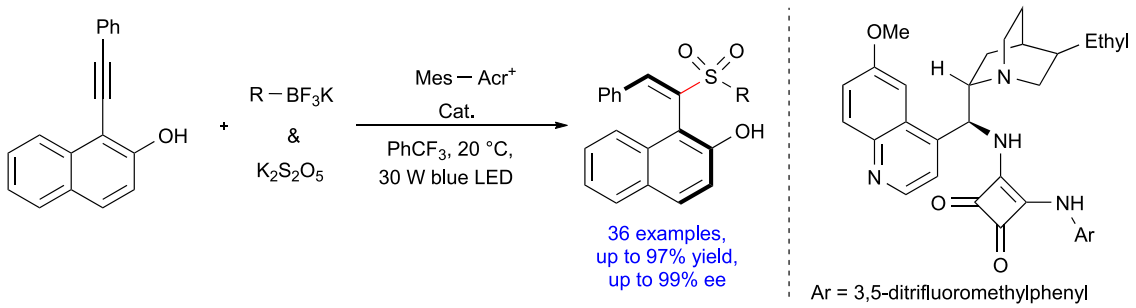
enantioselective (4+3) cyclization of 3-alkynyl-2-indolylmethanols with 2-naphthols. According to the control experiment and theoretical calculations, the OH group in substrates 53 and the NH group in substrates 52 may interact with CPA through hydrogen bonds and ion-pairing interactions. Moreover, the carbocation in intermediate 54 would be stabilized by the two aromatic groups at the benzylic position of 3-alkynyl-2-indolylmethanols (Scheme 38). In 2023, Wu et al.[65] reported the first Brønsted acid-catalyzed organocatalytic Nazarov-type cyclization of aryl-substituted 3-alkynyl-2-indolylmethanols with 2-naphthols. This resulted in efficient construction of a new class of axially chiral 3, 4-dihydrocyclopenta[*b*]indole scaffolds by switching the alkynyl terminal substituent from *t*-Bu to an aryl group, although the yield and atroposelectivity of the axially chiral product in this organocatalytic asymmetric version are not satisfactory (Scheme 39).

Other addition reactions for alkyne to construct axially chiral styrenes

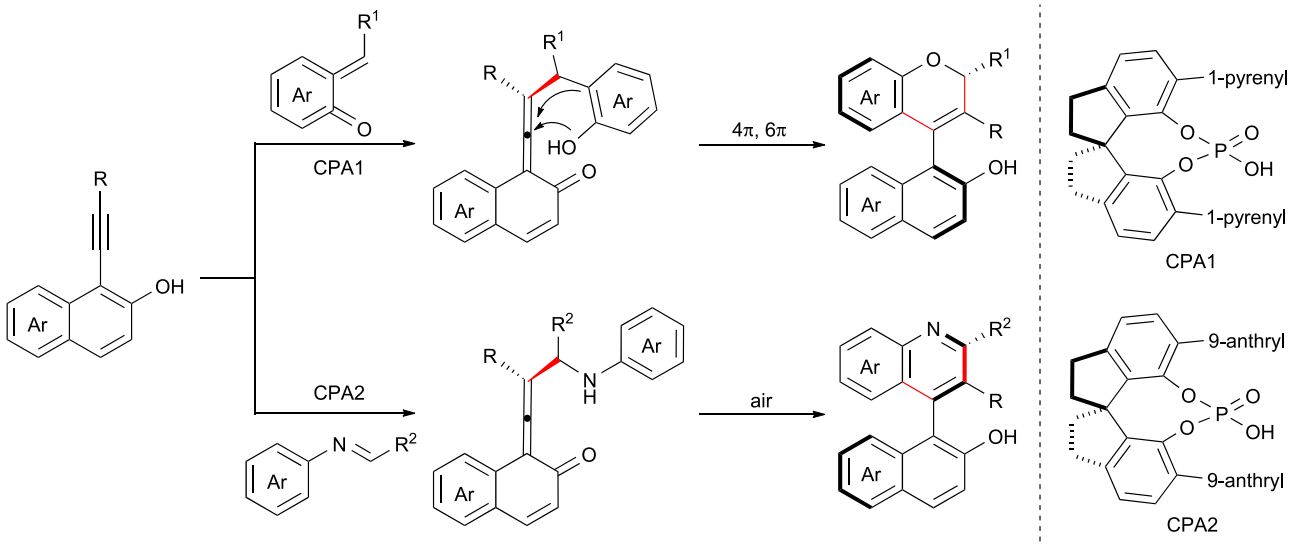
Apart from the addition reaction via VQM intermediates for alkynes, some other strategies are also practical to construct atroposelective styrenes.

In 2017, Zheng et al.[66] created an inventive direct Michael addition of substituted diones, ketone esters, and malononitrile to alkynals via an organocatalytic method to atroposelectively synthesize axially chiral styrene derivatives with excellent yields, enantioselectivities, and nearly total E/Z selectivities under benign reaction conditions because of activation of a secondary amine-catalyzed iminium (Scheme 40).

In 2019, Zhang et al.[67] developed a progressive straightforward approachable organocatalytic asymmetric Michael reaction of ynones with α-amido sulfones catalyzed by multiple-hydrogen-bonding *N*-squaramide originating from cinchona alkaloid to obtain sulfone-containing axially chiral styrenes with splendid stereoselectivity as well as practically total E/Z selectivity even at a high temperature (50°C). According



Scheme 35. Photo-induced free radical reaction to form sulfonyl-containing atropisomeric styrenes

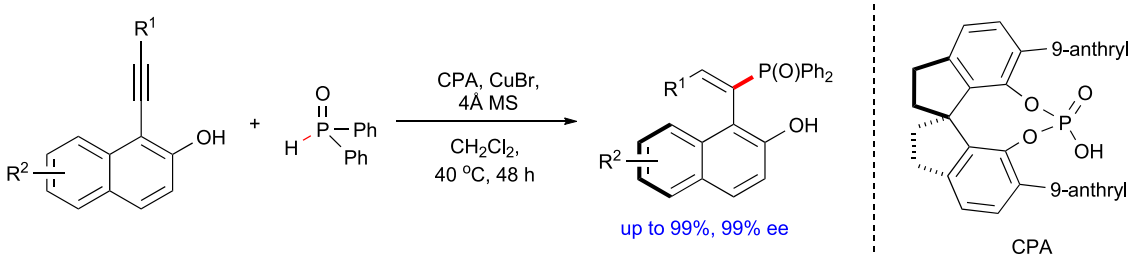


Scheme 36. CPA-catalyzed nucleophilic addition of 2-alkynylnaphthols via chiral all-carbon tetrasubstituted VQM intermediates

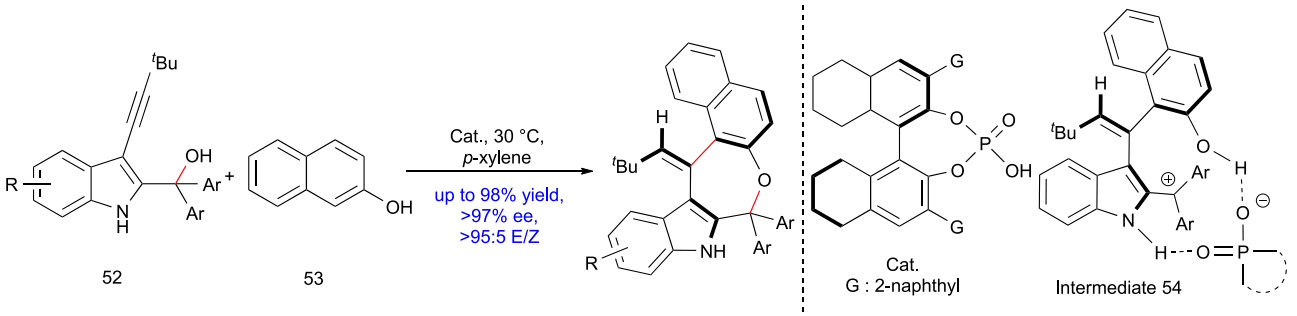
to control experiments, the rate-determining step is heavily impacted by creation of the sulfone anion with nucleophilic characteristics from α-amido sulfones (Scheme 41).

In 2022, Zhang et al.[68] developed novel single-step and efficient construction of 1,2-diaxially chiral triaryl α-pyranones with good stereoselectivity under benign circumstances by *N*-heterocyclic carbene organocatalytic asymmetric [3+3] annulation of well-designed alkynyl acylazolium precursors and enolizable sterically hindered 2-aryl ketones. DFT calculations have been carried out to investigate the intricate mechanism and derivation of the high diastereoselectivity and enantioselectivity in this [3+3] annulation process, which indicated that the NHC catalysis of 59, obtained by deprotonation of 58, catalyzed nucleophilic addition to 55 and initiates the whole process, followed by the leaving group going away to form intermediate 60. Next, the 56 would attack alkynyl with four stereoselective pathways, where the most energy-efficient pathway is to obtain the R, R configuration to form 61 because the weak interactions are more than others to lower the transition state energy barrier. Then, with the aid of $CsHCO_3$, 61 experiences a protonated [1,3]-hydrogen shift with the assistance of the base to form 62. Subsequently, in 62, the C-O bond forms, and the C-C bond breaks to form product 57 (Scheme 42).

Also in 2022, Ji et al.[69] described inventive atroposelective palladium-catalyzed hydrophosphination of various sterically hindered internal alkynes with a variety of



Scheme 37. Cu and CPA co-catalyzed atroposelective hydrophosphinylation of hydroxynaphthylalkynes to obtain axially chiral phosphorus-containing styrenes

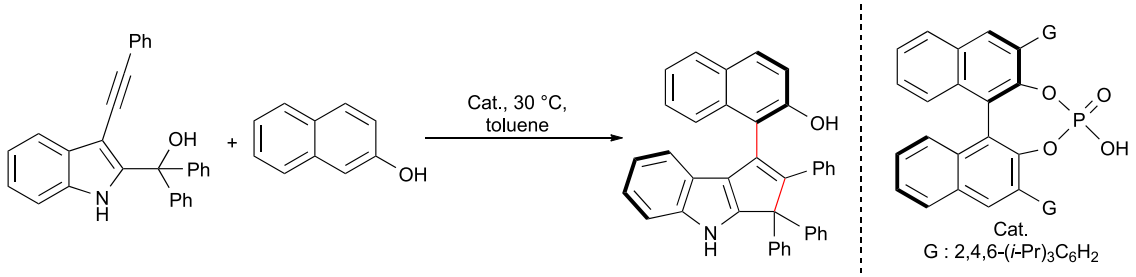


Scheme 38. CPA-catalyzed asymmetric construction of axially chiral aryl-alkene-indole frameworks

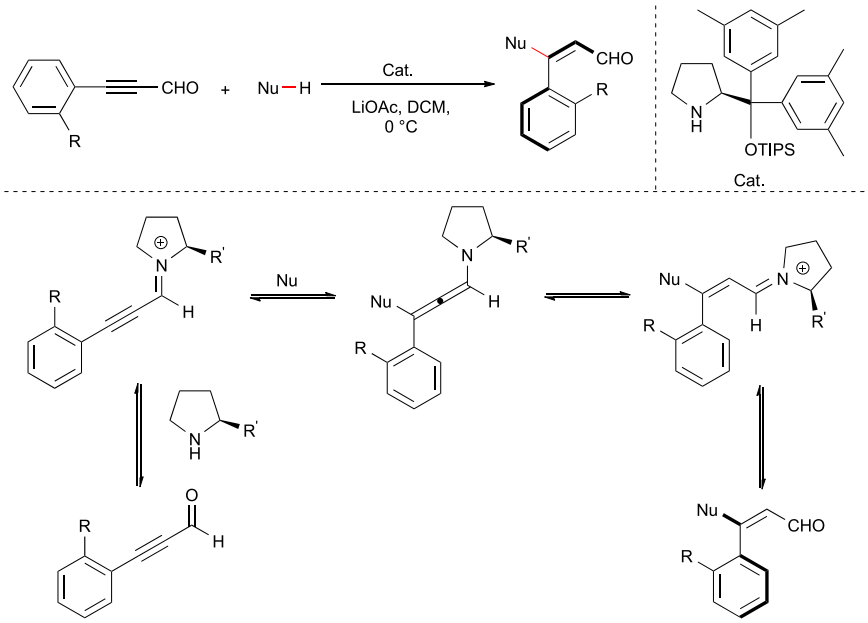
symmetrical and nonsymmetrical secondary phosphines to afford C-N axially chiral trisubstituted olefins (vinylphosphines) with excellent regioselectivity, Z/E selectivity, and enantioselectivity under mild reaction conditions. By combining hydrophosphination and dynamic kinetic transformation of the alkynes, the axial chirality was created. According to DFT calculations, the major route's transition state, where one of the PPh_2 group's phenyl rings forms a T-shaped orientation with the phenyl of the alkyne and the other phenyl group in the PPh_2 lies between the phenyl and indole rings, avoiding steric interactions, was found to have a lower free energy than the minor route by 7.5 kcal/mol, keeping the T's side chain away from the bulky alkylphosphino group (Scheme 43).

CONCLUSION AND OUTLOOK

Many natural products, bioactive substances, privileged chiral ligands, catalysts, synthetic building blocks, and pharmaceuticals have axial chirality, which is a vast family of chiral platforms. Compared with prevalent optically active biaryls that have been extensively studied, however, it is still daunting and challenging to establish atroposelective synthesis of axially chiral styrenes with a chiral axis between a simple alkene and an aromatic ring. The dilemma with synthesis of atropisomeric styrenes is mainly divided into two aspects, the first of which is control and maintenance of selectivity. As for axially chiral styrenes, the bonds around the open-chain C=C bond may undergo distortion to minimize steric repulsion, which leads to lower rotational barriers and reduced atropostability. Furthermore, their catalytic enantioselective synthesis is much more challenging than that of other axial chiral compounds because Z/E selectivity and atroposelectivity need to be taken into account and carefully managed jointly throughout the synthesis. The conflict between reactivity and atropostability is the second problem. To attain the necessary stiffness, the alkene component requires bulkier substituents, which would limit the reactivity and entail harsher conditions, possibly impairing the products' naturally poorer



Scheme 39. CPA-catalyzed organocatalytic Nazarov-type cyclization of axially chiral 3, 4-dihydrocyclopenta[*b*]indole scaffolds



Scheme 40. The organocatalytic method for atroposelective synthesis of axially chiral styrene derivatives according to direct Michael addition

configurational stability. Furthermore, the development of this crucial class of compounds would be hampered by the need for specialized substrates.

Over the past few years, a lot of work has been put into discovering novel methods for synthesizing stable axially chiral styrenes, including desymmetrization of an existing C(sp2)-C(sp2) axis, metal-catalyzed cross-coupling to construct a chiral C(aryl)-C(alkene) axis, transformation from central chirality to axial chirality, and alkyne-participated construction of axially chiral styrenes, which resulted in many novel styrene frameworks to be uniquely applied in asymmetric synthesis. However, concise and efficient strategies, especially for unrestrictive substrates to synthesize axially chiral styrenes with high enantioselectivity are still lacking. Moreover, the extensibility and subsequent application of synthesized axially chiral styrenes should also be explored in depth.

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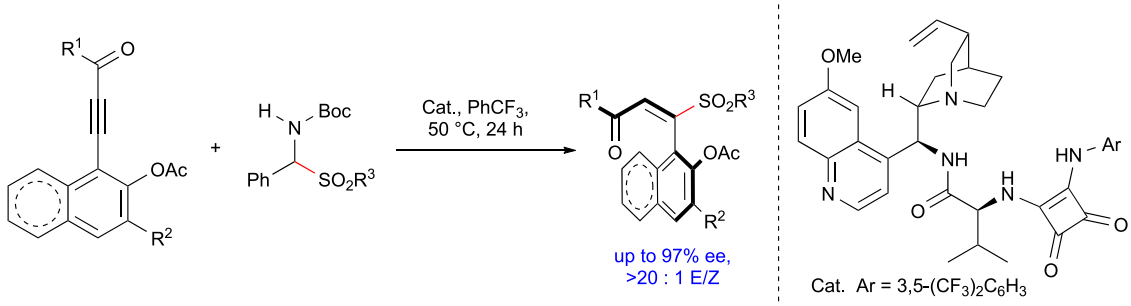
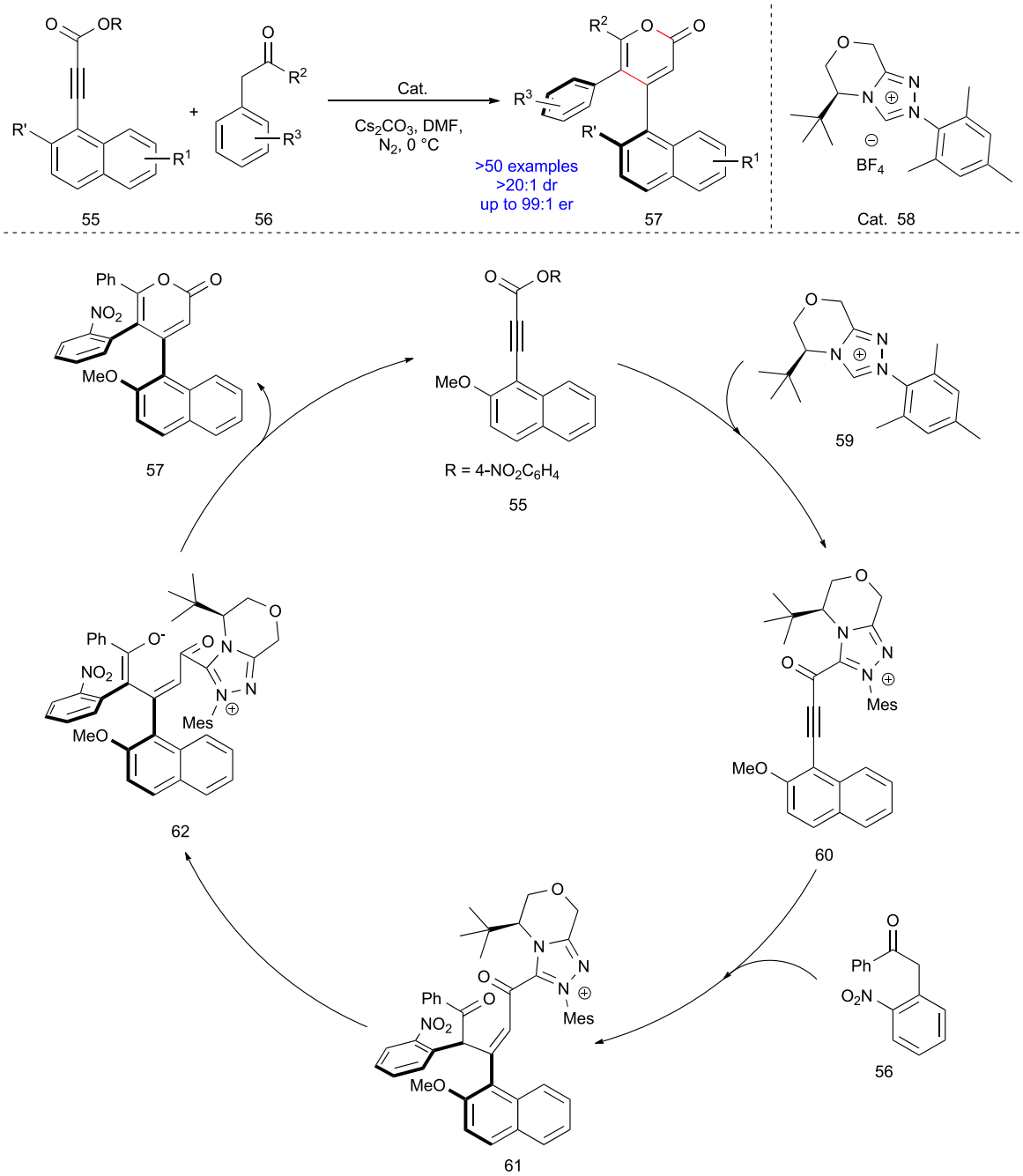


Scheme 41. A direct organocatalytic asymmetric Michael reaction of ynones to obtain sulfone-containing axially chiral styrenes



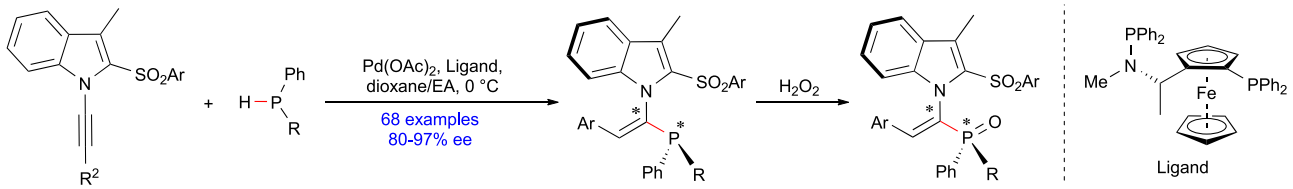
Scheme 42. Construction of 1,2-diaxially chiral triaryl α-pyranones by N-heterocyclic carbene organocatalytic asymmetric [3+3] annulation

AUTHOR CONTRIBUTIONS

Conceptualization, S.-Y.Z.; discussion, Q.-Z.L. and H.-Y.B.; writing – original draft, Z.-H.L.; writing – review & editing, S.-Y.Z. and Z.-H.L.; supervision, S.-Y.Z.

DECLARATION OF INTERESTS

The authors declare no competing interests.



Scheme 43. Pd-catalyzed atroposelective hydrophosphination of sterically hindered internal alkynes

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