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Review

Axially chiral alkenes: Atroposelective synthesis and applications

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ABSTRACT

Axial chirality is historically epitomized by biaryl compounds containing rotationally impeded aryl-aryl linkage. As the field of atroposelective catalysis advances, the synthesis and application of less common scaffolds such as alkenes have now come to the fore. The manifestation of axial chirality in aryl alkenes was hypothesized in 1928 and the first resolution was achieved nearly a decade later. However, catalytic asymmetric construction of axially chiral open-chain alkenes appeared only in 2017 which ushered in a renewed focus on these structures. In principle, axially chiral alkenes possess an alkene group tethered at one end of the stereogenic axis, which greatly reduces the overall rigidity. To date, atropisomers with C (vinyl)-C (aryl) and C (vinyl)-heteroatom bond have been reported. Considering the rapid growth in the synthesis and synthetic utility of axially chiral open-chain alkenes, this review intends to provide a historical overview and discusses these new developments. It is hope that this timely discussion would motivate continued growth of this nascent field.

1. Introduction

Exactly 100 years ago in 1922, Christie and Kenner resolved 2,6,2′,6′-tetrasubstituted biphenyl acids [1], which verified for the first time the existence of axial chirality in biphenyl compounds. At present, the emblematic axially chiral compounds are allenes and biaryls which feature a non-planar arrangement of four groups in pair about a chirality axis. Axial chirality exists widely in natural products and bioactive molecules, such as Vancomycin [2], Korupensamine A [3], Mastigophorene [4], Marinopyrrole [5] and Steganacin [6]. Despite this early disclosure, it was not until several decades later that the success of BINAP (2,2′-bis(diphenylphosphino)-1,1′-binaphthyl) ligand in catalytic enantioselective hydrogenation [7] captured the imagination of the organic chemistry community on axial chirality in 1980s. It follows that the research on the synthesis and application of atropisomeric compounds has been promoting the rapid growth of asymmetric synthetic chemistry. In particular, numerous efficient ligands and catalysts were designed on the basis of biaryl structures with high stereochemical stability (Fig. 1) [8–12].

As the field evolves, nonbiaryl compounds such as benzamides, imides, lactams, anilines, and styrenes bearing sufficiently large steric groups have been reported to show axial chirality as well (Fig. 2). According to the rotation axis, the atropisomers could be encompassed into C–C atropisomers, C–N atropisomers and so on [13]. In fact not long after the discovery of axially chiral biaryl compounds, Hyde and Adams reasoned that if the hindered rotation was simply due to the space occupied by the interfering groups, appropriately substituted aryl alkenes could be resolved as well [14,15]. This hypothesis was not corroborated until Mills and co-workers resolved 2-(2,4-dimethylpent-2-en-3-yl)-*N*,*N*,*N*-trimethylbenzenaminium iodide into optical isomers in 1939 [16]. This early precedent did not attract proper attention to asymmetric construction of axially chiral alkenes and their application in organic synthesis until 2017, which is in contrary to the rapid development of (hetero)biaryl atropisomers since 1980s. One primary reason could be the challenge to obtain aryl alkenes with stable rotation axis due to their much lower rotational barrier [12,17].

Systematic method development to construct axially chiral open-chain alkenes commenced with the pioneering work of Tan and co-workers in 2017 [17]. This first catalytic enantioselective synthesis of axially chiral open-chain alkenes was accomplished by aminocatalytic Michael addition of alkynes and initiated considerable interests in the synthetic community. In the ensuing years, an outpour of reports emerged featuring the preparation of axially chiral alkenes *via* (i) asymmetric functionalization of aryl alkynes with pre-installed bulky *ortho*-substituents, (ii) asymmetric aryl or alkenyl C–H functionalization of aryl-alkene derivatives, or (iii) asymmetric cross-coupling to form

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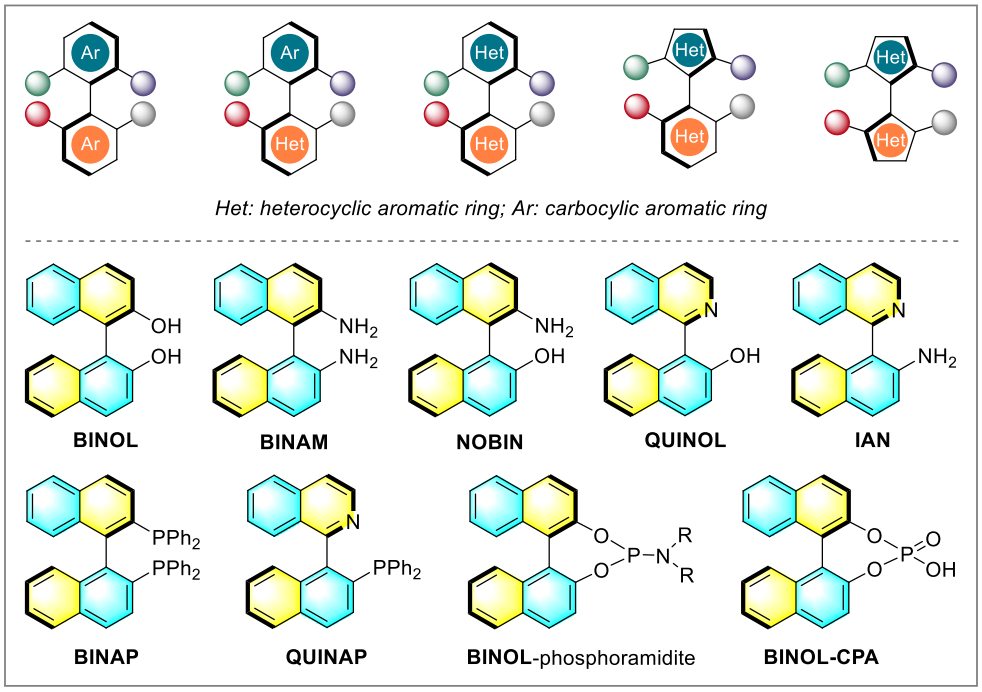


Fig. 1. Axially chiral biaryl frameworks and representative ligands and catalysts.

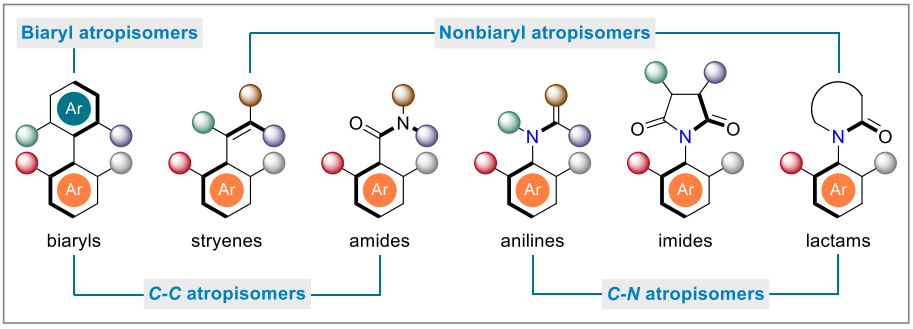


Fig. 2. Classification of atropisomers.

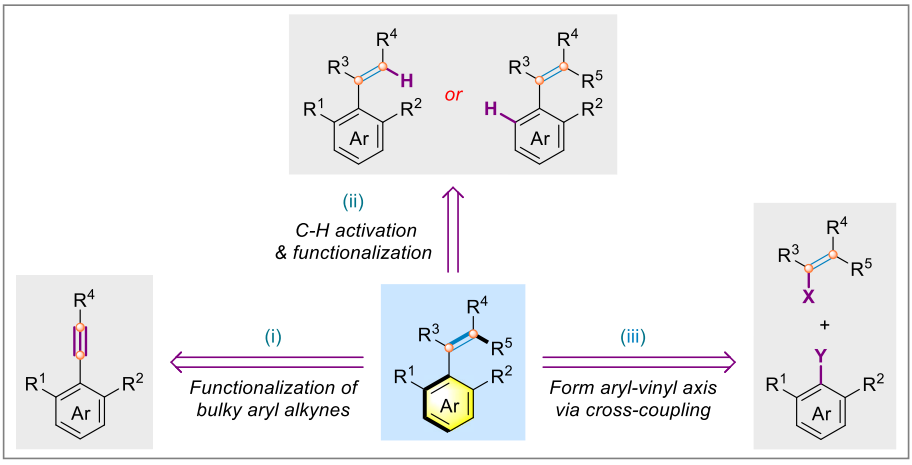


Fig. 3. Main strategies to construct axially chiral alkenes.

aryl-vinyl axis (Fig. 3). These new axially chiral skeletons allowed the design of novel ligands and catalysts, revealing some elegant applications even though they are yet to be investigated as thoroughly as their biaryl congeners.

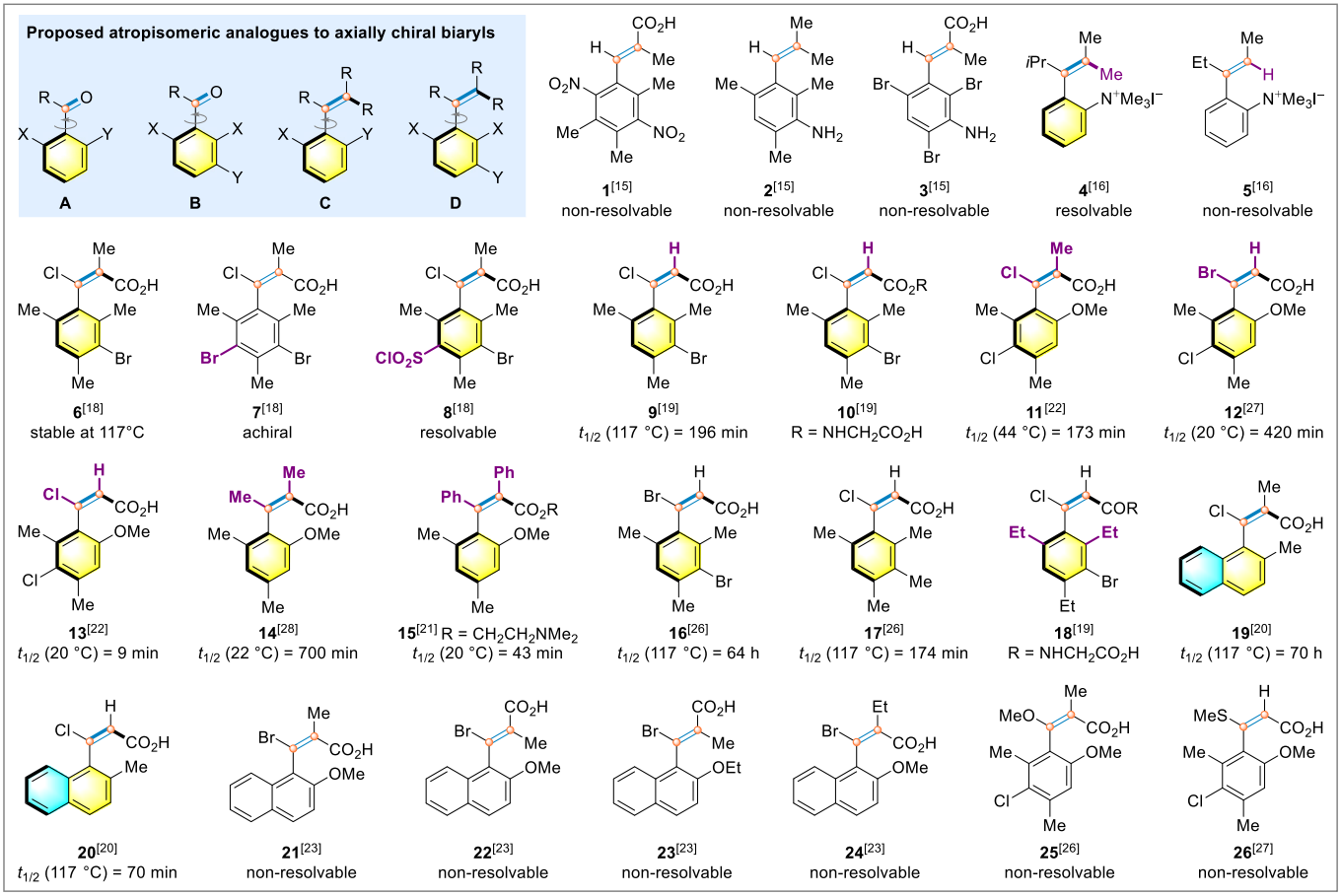


Fig. 4. Possible atropisomeric analogues, resolution of axially chiral alkenes and structure-stability studies.

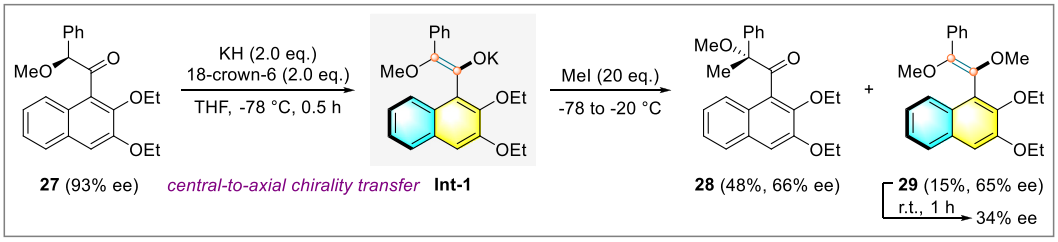
In view of the establishment of alkene-type atropoisomers and promising utilities demonstrated, this review intends to provide a systematic summary of research in axially chiral acyclic alkenes. After a historical overview on early studies, the evolvement of synthetic strategies will be discussed followed by their applications in catalytic asymmetric synthesis. Considering the structural difference of cyclic alkene atropisomers such as those with an arene connecting to indene or dihydronaphthalene as well as their resemblance to biaryl analogues, their detailed synthetic preparation is outside the focus of this review.

2. Preliminary research before 2017

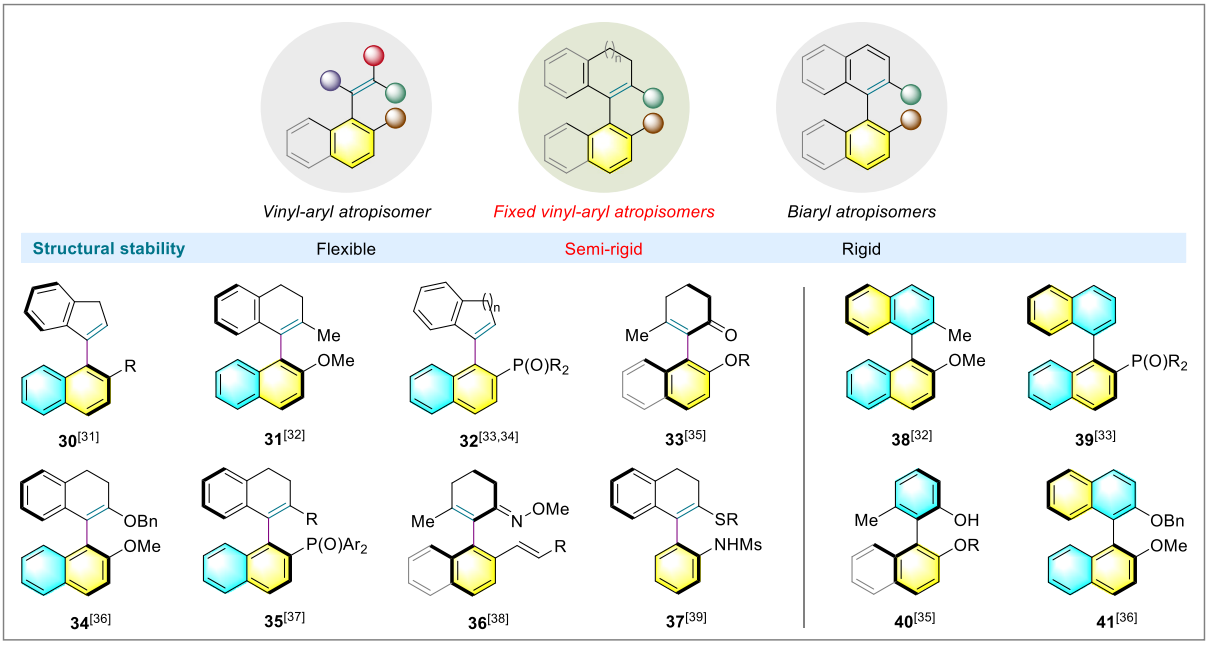
The resolution of 6,6′-dinitro-2,2′-diphenic acid and 4,4′,6,6′-tetranitro-2,2′-diphenic acid with brucine by Christie and Kenner [1] signified the first observation of molecular asymmetry resulting from impeded free rotation of single bond between the aryl rings, although this defining factor of chirality was unclear at that time. Based on the assumption that steric hindrance was the sole decisive element in conferring the chirality of biphenyl derivatives, Hyde and Adams considered the possibility of bulky aryl ketones (Fig. 4, **A** and **B**) and alkenes (**C** and **D**) exhibiting asymmetry in 1928 [14]. Subsequently when Adams and co-workers attempted to resolve aryl alkenes **1**–**3**, the effort was unfruitful due to the small size of hydrogen atom as α-substituent (Fig. 4) [15]. In 1939, Mills and Dazele substantiated Adams' original hypothesis about stable styrene atropisomers with their successful resolution of 2-(2,4-dimethylpent-2-en-3-yl)-*N*,*N*,*N*-trimethylbenzenaminium iodide (**4**) with bromocamphorsulphonic acid [16]. The replacement of dimethylisopropylvinyl group by methylethylvinyl group rendered olefin **5** non-resolvable, indicating that steric hindrance was the prime contributor to restricted rotation for observed chirality. In the following year, Adams and co-workers reported on the preparation and resolution of *β*-chloro-*β*-(2,4,6-trimethyl-3-bromophenyl)-*α*-methylacrylic acid (**6**) [18]. By comparing achiral bromination product **7** and chiral chlorosulfonyl-substituted compound **8**, an unsymmetrical substitution on the aryl ring was found mandatory to yield molecular chirality. Adams then investigated a series of bulky aryl olefins to elucidate the relationship between the steric properties of the molecules and their stability to rotation by comparing the half-lives (Fig. 4, compounds **9**–**26**) [19–28]. While these works constitute a pivotal groundwork in the synthesis of axially chiral olefins, the asymmetric synthesis has remained unattained for half a century since the restricted rotation of these molecules was first observed.

In 1991, Kawabata, Yahiro and Fuji [29] reported alkylation reaction of chiral carbonyl compounds containing a carbon stereogenic center at the *α*-position (Scheme 1). By treating enantioenriched ketones **27** with potassium hydride and alkyl halide, the conversion to *α*-alkyl compound **28** occurred with two-step chirality transfer in moderate efficiency. Intriguingly, the procurement of axially chiral olefin **29** as a byproduct from *O*-alkylation of **Int-1** gave the direct evidence on the central-to-axial chirality transfer. The rapid HPLC analysis revealed that the chiral axis in **29** was configurationally unstable, where the enantiomeric excess (ee) reduced to 34% from 65% at room temperature (r.t.) after 1 h.

Due to the more flexible structural feature, obtaining stable axially chiral olefins faces paramount challenge compared to biaryl atropisomers. A workaround strategy is to enclose the double bond of olefin within a five- or six-membered ring for increased rigidity and to confer a degree of structural resemblance to biaryls [30]. In 1996, Baker reported on the first synthesis of chiral aryl-indenes **30** (Scheme 2) with the double bond fixed in a five-membered ring *via* alkene isomerization *with* point-to-axial chirality transfer [31]. Also through chirality transfer,



Scheme 1. Chirality transfer in enantioselective alkylation of chiral aryl ketones.



Scheme 2. Asymmetric synthesis of axially chiral styrenes with double bond fixed in 5- or 6-membered ring and their applications in synthesis of biaryl atropisomers.

Hattori and Miyano devised stereospecific dehydration for the access of **31** [32]. A palladium-catalyzed cross-coupling of aryl bromides and *N*-tosyl hydrazones was first disclosed by Gu in 2016 [33] followed by Wu [34] to access axially chiral cyclic alkenes **32**. In 2017 Gu further accessed 2-aryl cyclohex-2-enones **33** by employing an enantioselective cross-coupling of 2-iodo-3-methylcyclohex-2-enones with arylboronic acids [35]. Besides the asymmetric construction of stereogenic axis by coupling reactions, functionalization of scaffolds with preformed alkene-aryl bond provides an alternative synthetic access. In this regard, Smith [36] envisioned the organocatalytic synthesis of atropisomeric olefins **34** *via* chiral cation-directed *O*-alkylation of racemic 1-aryl-2-tetralones in 2017. Gu and Fu [37] established a visible light-accelerated stereospecific C–H arylation of vinyl arenes with diaryliodonium salts (**35**) while Cui and Xu [38] envisioned an enantioselective palladium-catalyzed C–H olefination of 2-aryl cyclohex-2-enones (**36**). Through chiral sulfide-catalyzed electrophilic carbothiolation of activated alkynes, Zhao [39] accomplished the construction of axially chiral amino sulfide vinyl arenes (**37**). These atropisomerically enriched 1, 2-dihydronaphthalenes could undergo ready conversion into biaryl atropisomers (**38**–**41**) through facile 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)-mediated oxidation/aromatization.

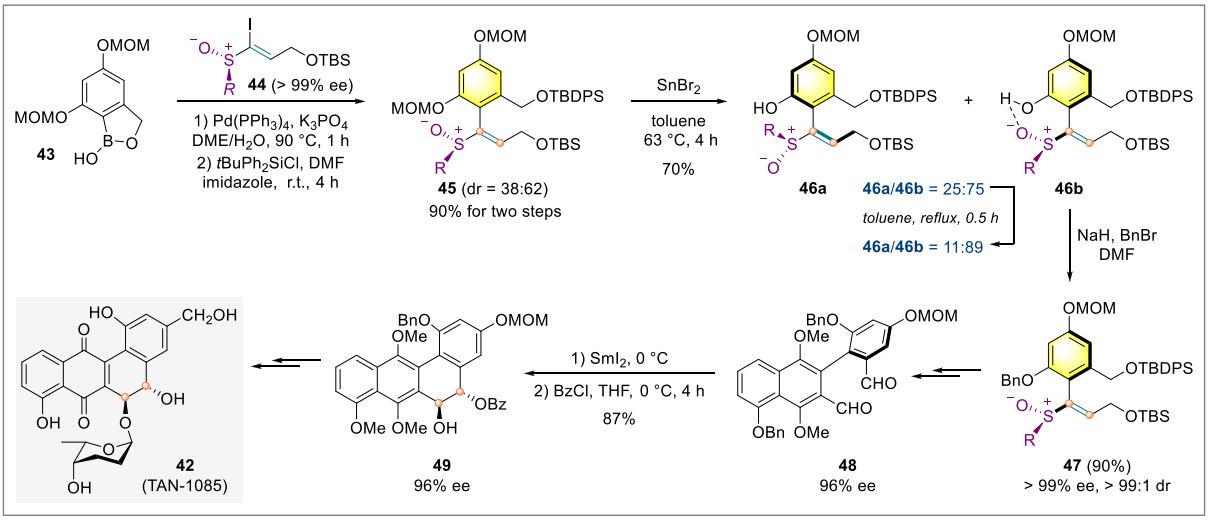
Inspired by Adams' preliminary research on axially chiral alkene, Suzuki designed a stereochemical relay strategy [40] to fulfill the asymmetric total synthesis of the antibiotic TAN-1085 (**42**) in 2009 (Scheme 3). With sulfoxide as a chiral auxiliary, a palladium-catalyzed asymmetric Suzuki-Miyaura coupling gave two inseparable diastereomers of aryl alkenes (**45**) bearing both chiral axis and *S*-stereogenic center in 38:62 ratio. Diastereoselectivity improved to 25:75 upon liberation of free hydroxy group *ortho* to the axis, permitting the separation of resulting diastereomers (**46a** and **46b**) by chromatography. Chiral alkene **47** gave rise to atropisomeric biaryl (**48**) after several chemical conversions. A subsequent stereospecific pinacol cyclization then yielded tetracyclic diol **49** which eventually led to TAN-1085 after additional several steps. Chirality transfer was embodied in conversion of **43** to **45** (central-to-axial), **47** to **48** (axial-to-axial), and **48** to **49** (axial-to-central). Similar strategy was adopted to synthesize C_2-symmetric paracyclophanes with diastereoselective Suzuki-Miyaura coupling as one key step [41].

3. Catalytic atroposelective synthesis of axially chiral alkenes

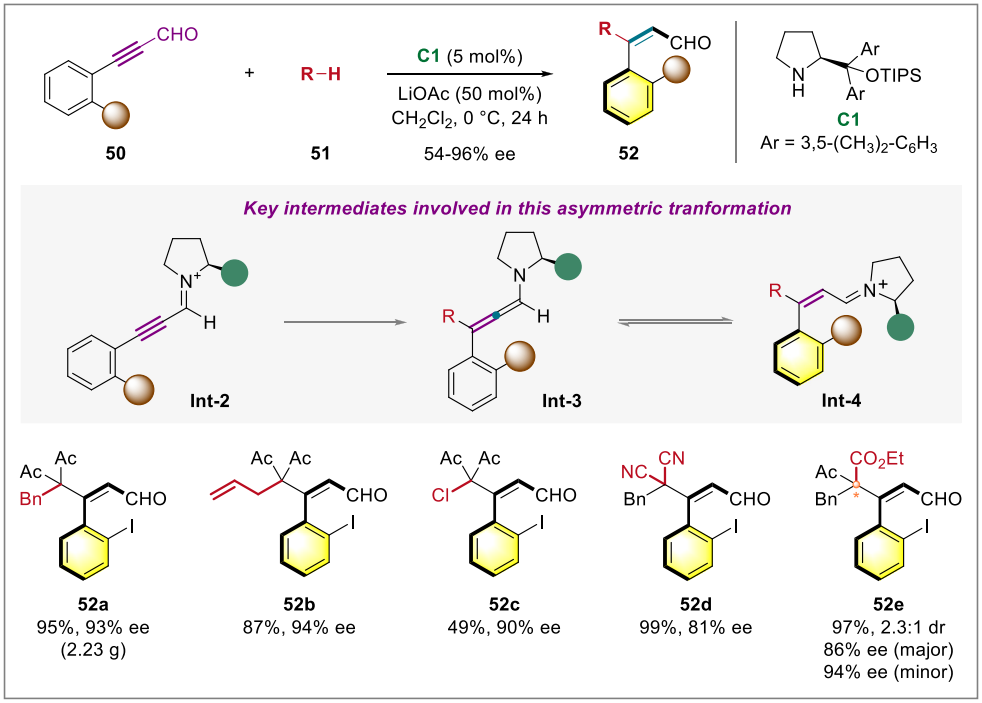
Despite the inherent stability issue imposed by the low rigidity of aryl alkenes leading to conspicuous absence of relevant report for a prolonged period, broadened understanding of axial chirality coupled with rapid development of transition metal catalysis and organocatalysis have progressively surmounted this synthetic barrier. In 2017, Tan's findings [17] on the asymmetric construction of axially chiral acyclic olefins by Michael addition to functionalized alkynes originated a proliferation of studies on the atroposelective synthesis of this compound class, which will be discussed in this section.

3.1. Construction of axially chiral alkenes via asymmetric functionalization of alkynes

Addition reaction of alkynes represents one of the most powerful methods to construct functionalized alkenes. On account of the



Scheme 3. Asymmetric total synthesis of TAN-1085 (**42**) *via* stereochemical relay strategy.

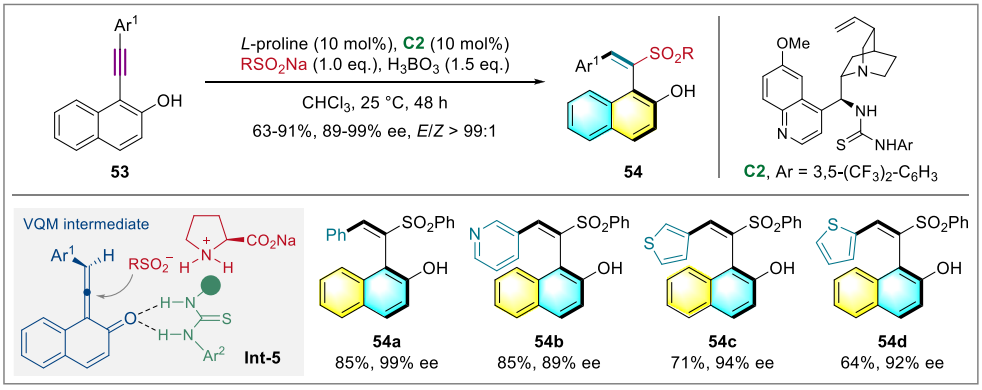


Scheme 4. Chiral secondary amine catalyzed stereoselective Michael addition to alkynyl aldehydes.

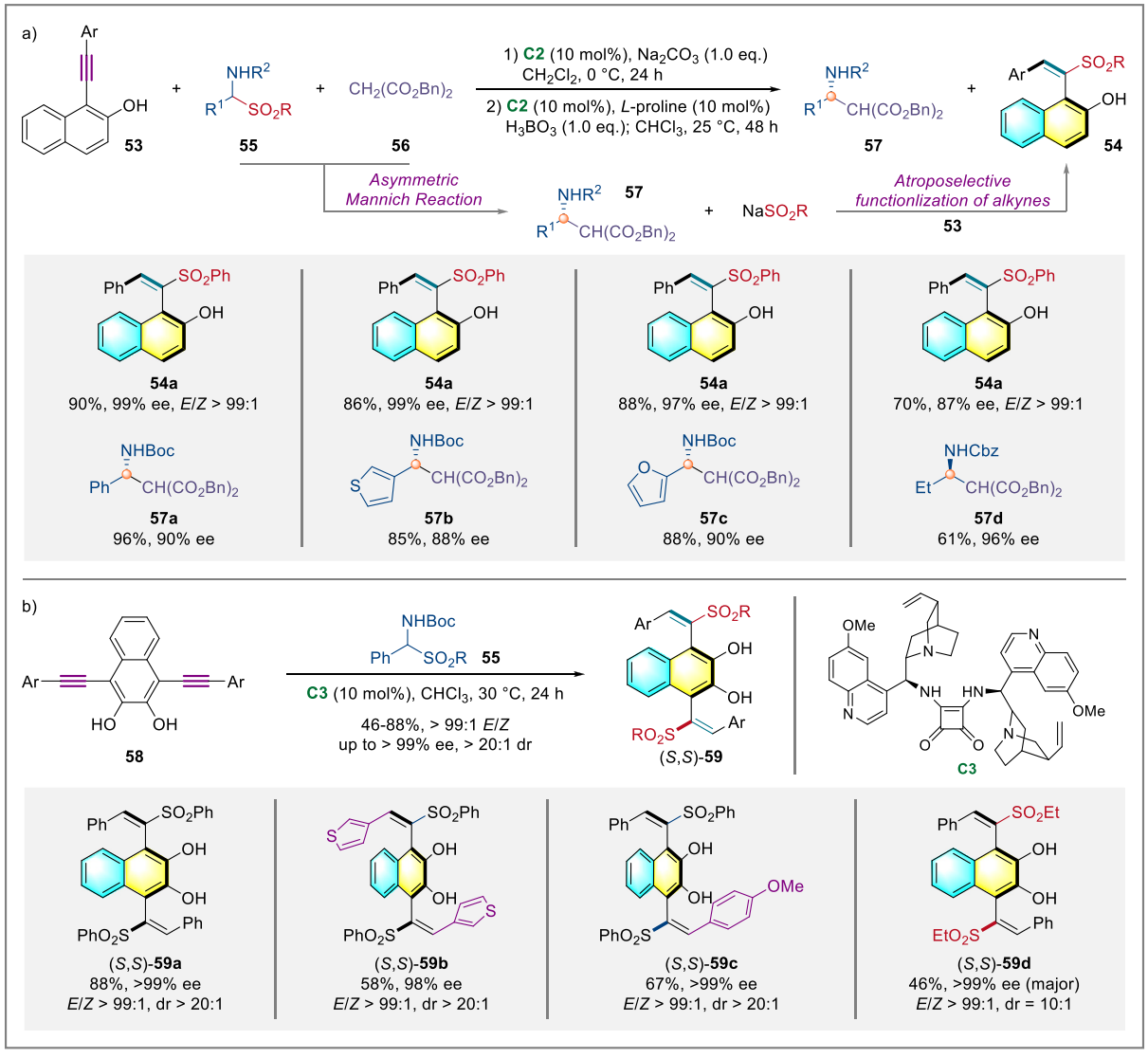
phenomenal growth experienced by asymmetric organocatalysis since the beginning of 21st century, novel activation modes have been developed including aldehyde activation by secondary amine. This enabled numerous stereoselective transformations such as Aldol reaction, Mannich reaction, Michael addition to alkenes and so on. These elegant works stimulated Tan's pursuit of chiral pyrrole derivative (**C1**) to catalyze the first asymmetric Michael addition to alkynyl aldehydes (**50**) to reach axially chiral alkenes (**52**) (Scheme 4) [17].

The mechanistic postulation involves initial activation of alkynyl aldehydes by catalyst **C1** to form iminium **Int-2** which possesses enhanced reactivity towards asymmetric nucleophilic addition (Scheme 4). Chiral intermediate **Int-3** then isomerizes into axially chiral iminium **Int-4** followed by hydrolysis to liberate the final product and catalyst. The reaction exhibits excellent substrate universality and ready translation to gram scale. Furthermore, the chiral cinnamaldehyde products could undergo diverse functional group transformations, reinforcing the synthetic utility of this protocol. Following this pioneer research, Yan [42] reported the asymmetric Michael addition reaction of ynones catalyzed by cinchona alkaloid-derived *N*-squaramide catalyst with *α*-amido sulfones as nucleophile to synthesize axially chiral sulfone-containing alkenes in excellent stereoselectivity in 2019.

Besides ynones, Yan [43] demonstrated that 1-(aryl-ethynyl)-naphthalen-2-ols (**53**) could undergo functionalization by sodium sulfinates to yield sulfone-containing alkenes (**54**) where chiral vinylidene *ortho*-quinone methide (VQM) species is generated from prototropic rearrangement of **53** catalyzed by quinuclidine base and aided by hydrogen bonding of the bifunctional thiourea catalyst **C2** (Scheme 5). The solubility and reactivity of sulfinate salts were improved *via* the formation of quaternary ammonium salt *with L*-proline. Subsequently, a formal nucleophilic addition of this activated sulfinate anion to the chiral VQM intermediate (**Int-5**) yields the sulfone-containing alkenes with excellent stereoselectivity. Aside from a variety of aryl, alkyl and cyclopropyl



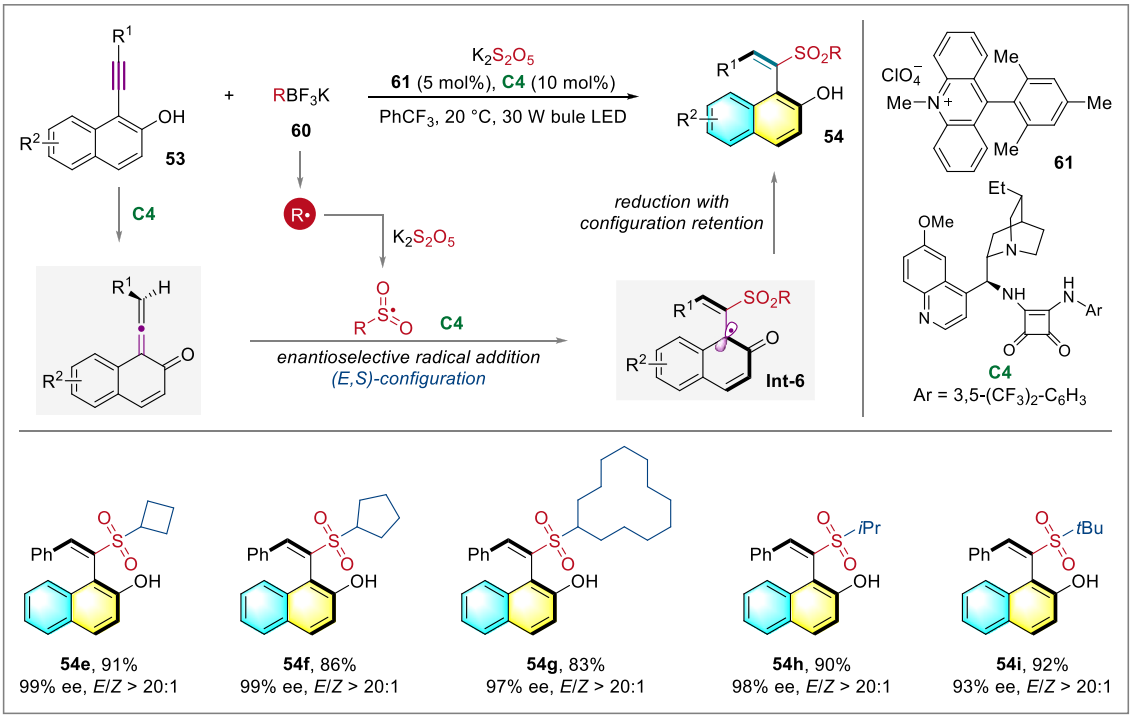
Scheme 5. Synthesis of axially chiral sulfone-containing alkenes *via* VQM intermediates.



Scheme 6. Synthesis of axially chiral sulfone-containing alkenes with α-amido sulfones as nucleophiles.

sulfinates, heteroarenes such as thiophene and pyridine connecting to alkyne (**54b**-**54d**) were tolerated under these conditions.

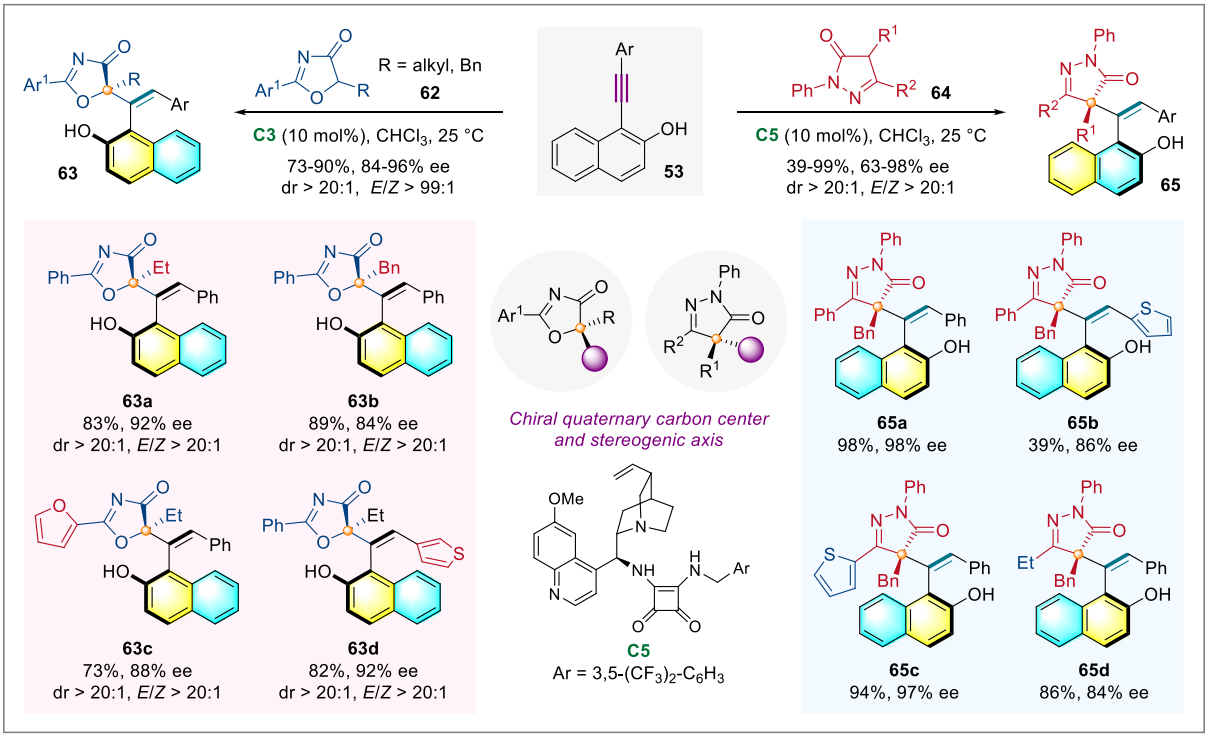
Building on this study, Yan extended the approach to access axially chiral alkenes **54** and chiral β-amino acid derivatives **57** from alkynes **53** and α-amido sulfones **55** in a single step (Scheme 6a) [44]. In the presence of cinchona alkaloid-based thiourea catalyst **C2**, α-amido sulfones (**55**) were used as the imine for asymmetric Mannich reaction and as the nucleophilic sulfinates for atroposelective alkyne functionalization, resulting in 100% atom efficiency. This reaction overcame the low atom economy associated with the use of α-amido sulfones in asymmetric Mannich reaction as precursors of imines to synthesize chiral amines where the sulfone groups are usually wasted in the form of sulfinates.



Scheme 7. Synthesis of axially chiral alkenes *via* radical addition to VQMs.

Later, Yan also described the stereoselective construction of axially chiral 1,4-distyrene 2,3-naphthalene diols (**59**) bearing two rotation axes by using quinine-derived squaramide catalyst **C3** (Scheme 6b) [45].

Aside from the nucleophilic addition to VQM intermediates developed by Yan et al., Wu and co-workers recently finished the first enantioselective radical addition to alkynes to access the axially chiral sulfone-containing alkenes **54** (Scheme 7) [46]. Potassium alkyltrifluoroborates **60** were employed as alkyl radical precursors under photoredox conditions and $K_2S_2O_5$ was used as sulfur dioxide surrogate. A sulfonyl radical is generated from insertion of the resulting alkyl radical into sulfur dioxide. In the presence of chiral quinine-derived squaramide catalyst **C4**, the chiral VQM is selectively formed in *R* configuration from 1-alkynylnaphthalen-2-ol **53**, followed by an asymmetric radical addition of the sulfonyl radical to provide the axially chiral



Scheme 8. Synthesis of axially chiral alkenes with multiple stereochemical elements.

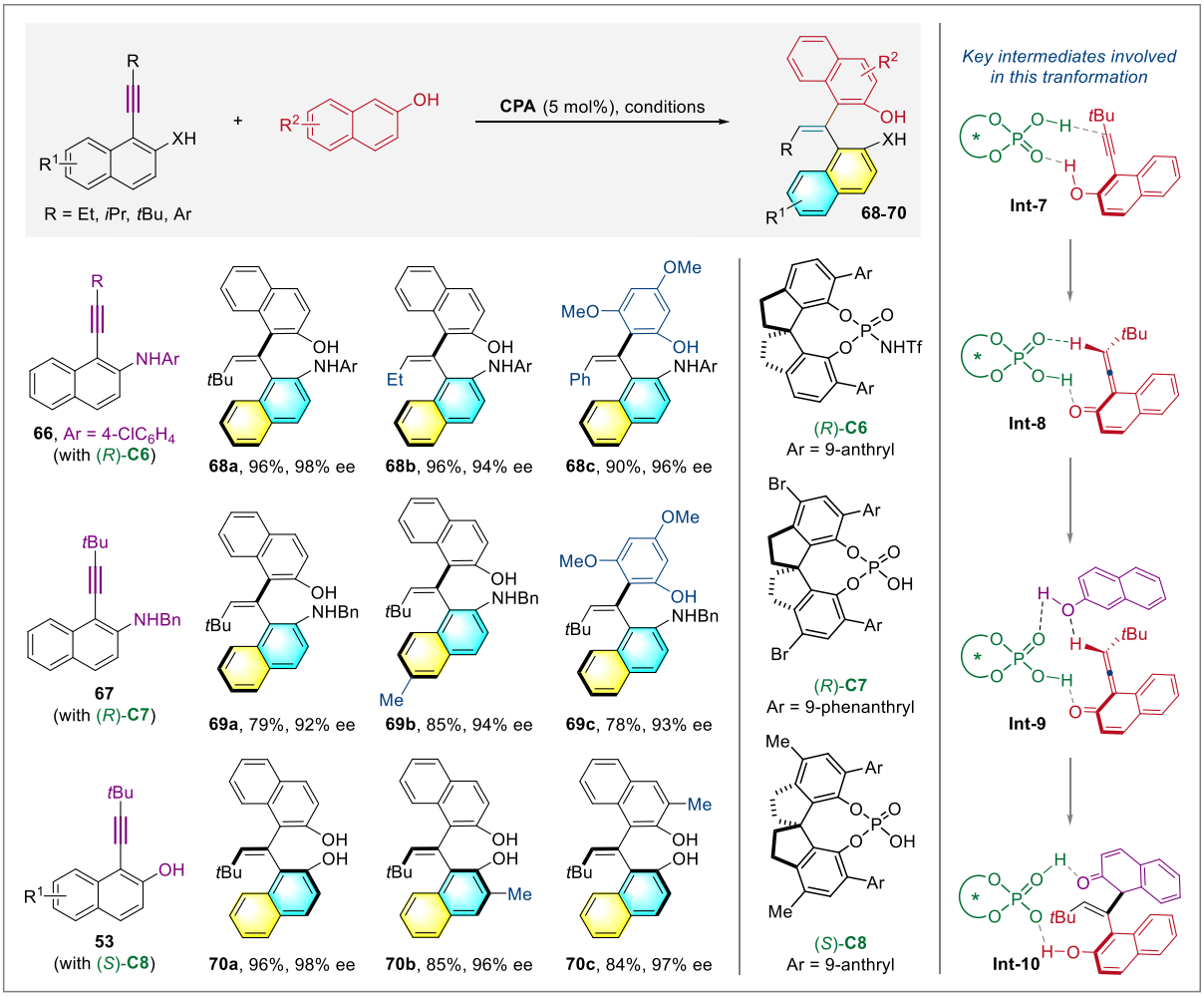
radical intermediate **Int-6** in (*E,S*)-configuration. Finally, a photoinduced single electron transfer (SET) reduction and aromatization of **Int-6** occurs with retention of configuration under the catalysis of **C4**. Axially chiral (*S,E*)-1-(1-(alkylsulfonyl)-2-arylvinyl)-naphthalen-2-ols (**54**) were obtained in good yields with excellent enantio- and regioselectivities.

By leveraging the versatility of enantioselective prototropic rearrangement of 1-(aryl-ethynyl)-naphthalen-2-ols (**53**) catalyzed by chiral organocatalysts, a series of atropisomers bearing multiple stereogenic elements were constructed by Yan [47] in 2019 and Wang [48] more recently (Scheme 8). Racemic *5H*-oxazol-4-ones (**62**) and pyrazolones (**64**) could be activated by the tertiary amine of the cinchona alkaloid through deprotonation to form the nucleophilic enolate, which undergoes Michael addition to the *in-situ* generated chiral VQM intermediate from the *Re* face. Diverse axially chiral alkenes with chiral center and axis were afforded with excellent *E/Z* selectivity, diastereoselectivity, and enantioselectivity.

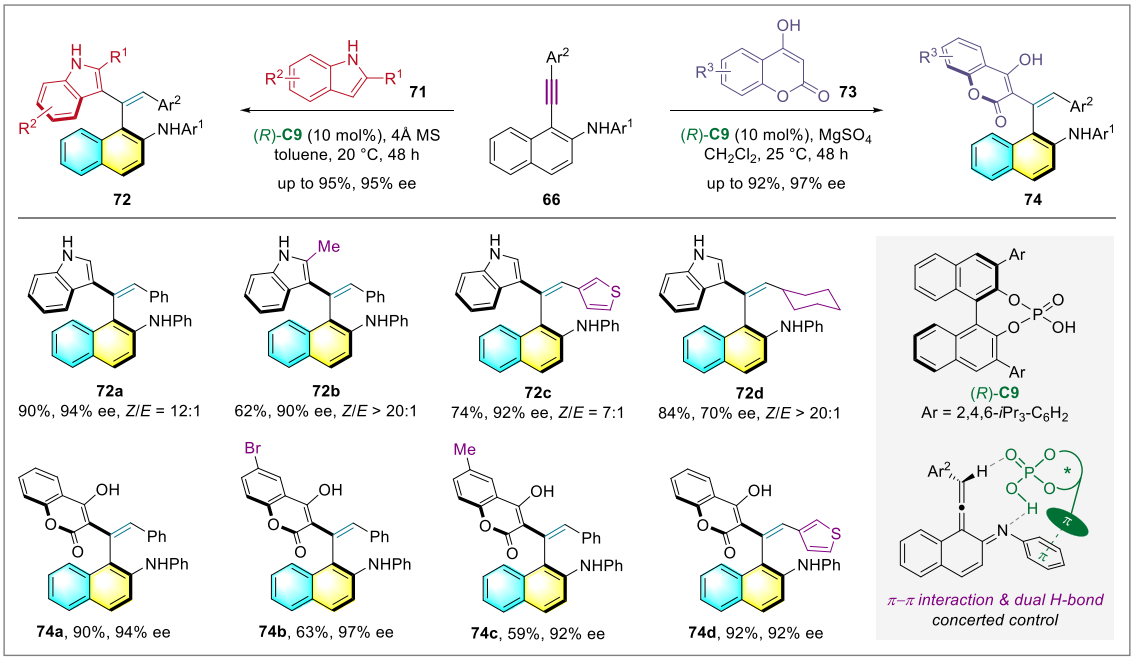
In addition to cinchona alkaloid-based bifunctional catalysts, chiral phosphoric acid (CPA) was found to catalyze stereoselective generation of VQM intermediates *via* 1,5-proton shift of alkyne. Based on their findings on CPA-catalyzed construction of biaryl atropisomers by arylation with 2-naphthols [49], in 2019 Tan's group devised CPA-catalyzed stereoselective Michael addition using 2-naphthols as nucleophiles *via* chiral VQM intermediates [50] (Scheme 9). This protocol furnished 1,1'-(ethene-1,1-diyl)-binaphthols (EBINOLs) in high efficiency and excellent stereoselectivity. The CPAs smoothly promoted the atroposelective hydroarylation of 2-alkynyl anilines (**66** and **67**) with nucleophilic 2-naphthols to form the EBINOL analogues (**68** and **69**) *via* aza-VQM intermediates. As a collaborative work with Houk who performed the density functional theory (DFT) calculations, a possible reaction mechanism was proposed: the chiral Brønsted acid **C8** serves as a bifunctional catalyst to convert **53a** into chiral VQM (**Int-8**) *via* a concerted 1,5-H transfer mechanism. This process determines the enantioselectivity and a chirality transfer forms the final EBINOL product.

This CPA catalytic strategy was extended by Zhang to heterocycles in the following year (Scheme 10) [51]. Indoles (**71**) and 4-hydroxycoumarins (**73**) performed as heteroaryl nucleophiles to form heterocycle-substituted axially chiral alkene derivatives (**72** and **74**). As expected, both the *N*-aryl group and the *N*–H bond of *ortho*-alkynyl-naphthylamines (**66**) had a significant impact on the yield and stereoselectivity. Hence, they postulated that the stereoselectivity is controlled synergistically by π-π interaction and dual H-bonds of the catalyst. The gram-scale synthesis and derivatization verified the application potential of this reaction.

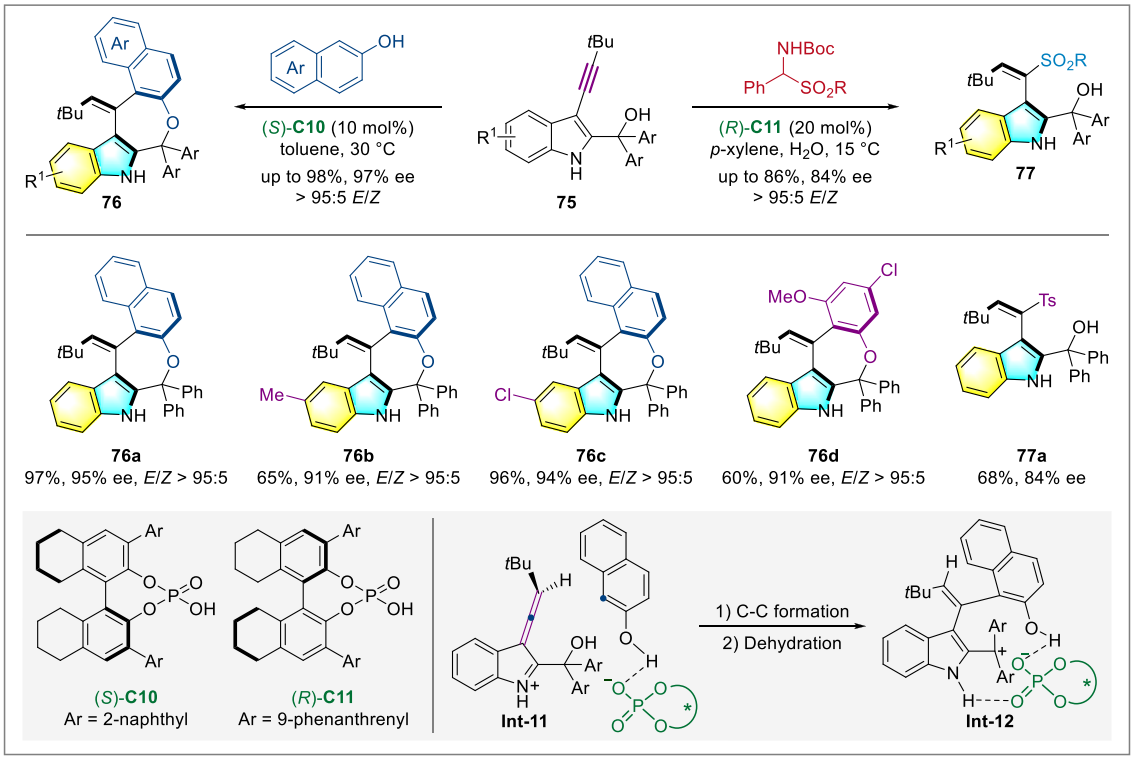
To further enrich the library of axially chiral vinyl arenes, Shi designed axially chiral alkene-indole frameworks [52] in 2020 and assembled them through organocatalytic enantioselective (4 + 3) cyclization of 3-alkynyl-2-indolylmethanols (**75**) with 2-naphthols or phenols (Scheme 11). After a chiral CPA-mediated generation of allene-iminium **Int-11** from 3-alkynyl-2-indolylmethanol, the CPA anion further guides the nucleophilic addition of 2-naphthol followed by dehydration to provide carbocation intermediate **Int-12**. Finally, an intramolecular nucleophilic addition by the hydroxyl group gives axially chiral (4 + 3) cyclization product **76**. This strategy underpinned the atroposelective synthesis of acyclic alkene-indoles **77** developed by the same group [53].



Scheme 9. Atroposelective construction of axially chiral EBNIOLs and derivatives.



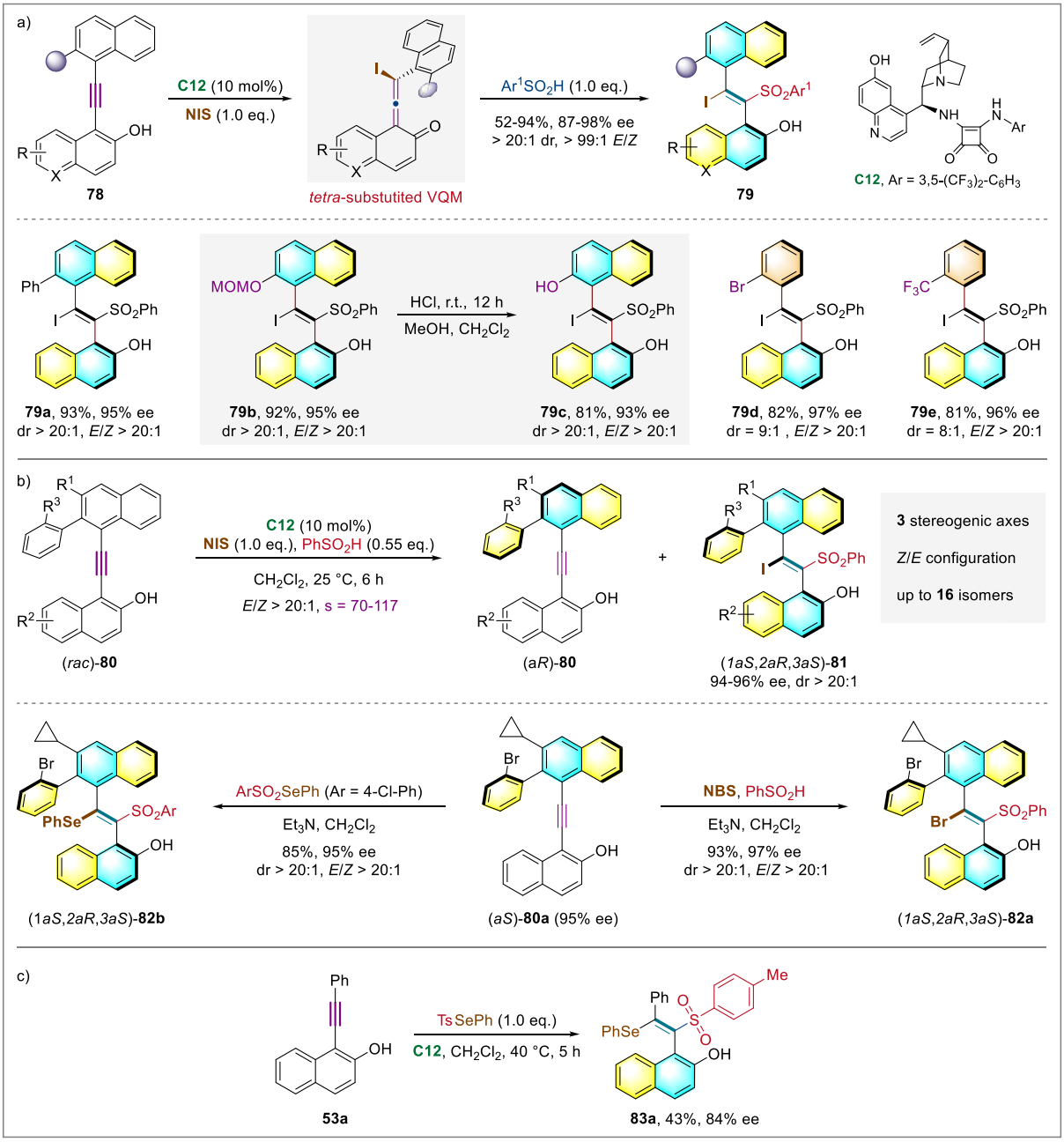
Scheme 10. CPA catalyzed asymmetric hydroarylation of 2-alkynyl anilines with heterocycles.



Scheme 11. CPAs catalyzed asymmetric construction of axially chiral alkene-indole scaffolds.

With α-amido sulfones as nucleophiles, the new class of axially chiral acyclic alkenes **77** were achieved in high yields, excellent (*E*/*Z*)-selectivities and moderate to good enantioselectivities.

Despite the robustness of enantioselective tautomerization to generate tri-substituted VQM intermediates, the products were limited to axially chiral tri-substituted alkenes. To overcome the mechanistic and structural limitation, the formation of tetra-substituted VQM [54] that would lead to alkyne difunctionalization was designed by incorporating suitable electrophile that could be trapped during prototropic rearrangement (Scheme 12a). This resulted in formation of vicinal diaxial styrenes **79** in high yields and stereoselectivities based on Michael addition to this chiral VQM. When racemic 1-(naphthyl-ethynyl)-naphthalen-2-ols bearing a rotationally impeded biaryl axis (**80**) were treated in the presence of *N*-iodosuccinimide (NIS) and phenylsulfinic acid, kinetic resolution occurred and formed tetra-substituted axially chiral alkenes **81** with three consecutive stereogenic axes in excellent *ee* and *dr* (Scheme 12b). The selective factor was up to 117. The authors further demonstrated the applicability of other electrophiles, which added



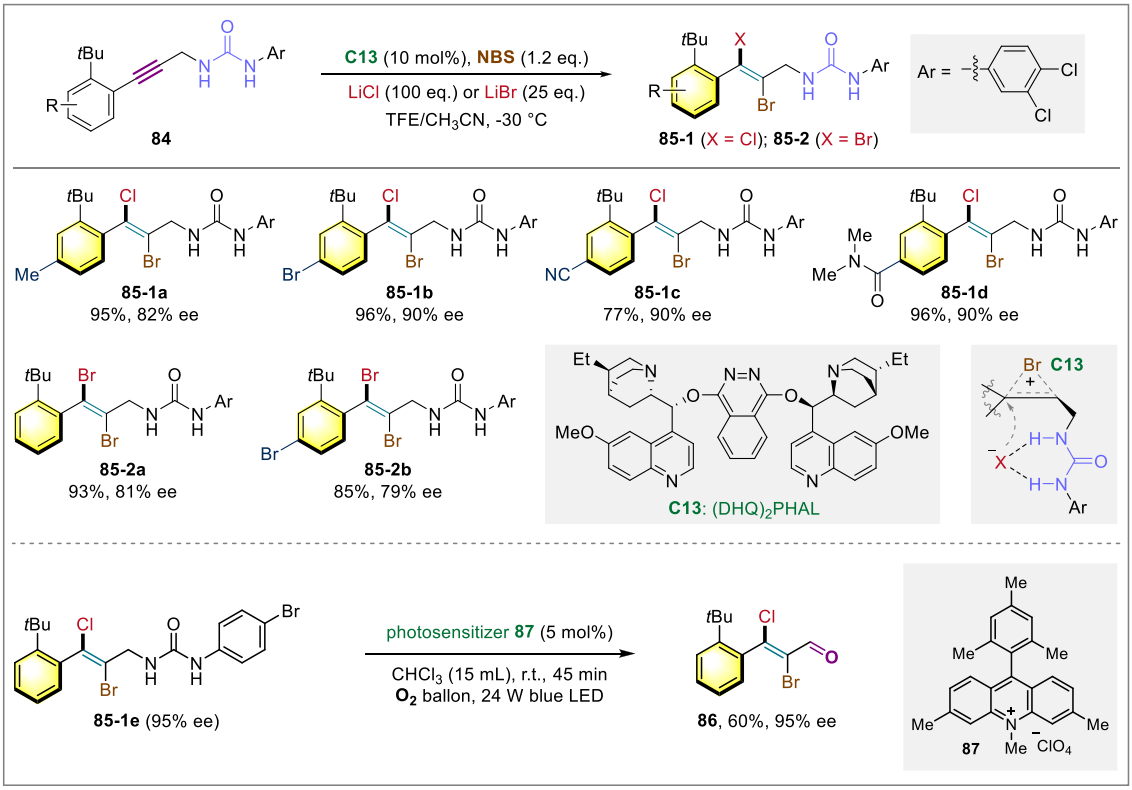
Scheme 12. Organocatalytic enantioselective construction of styrenes *via* tetrasubstituted VQMs.

successfully onto enantioenriched biaryl **80a** and generated multiaxis alkenes **82** without employing additional chiral source.

On the other hand, Qin reported on selenosulfonylation of alkynes to access tetra-substituted alkenes **83a** [55] in the following year (Scheme 12c). In preliminary exploration of catalytic asymmetric transformation by using cinchona alkaloid-derived *N*-squaramide **C12**, axially chiral tetra-substituted alkene (**83a**) could be obtained in moderate yield (43%) with good enantioselectivity (84% ee).

These reports illustrated the strategic efficiency to access axially chiral alkenes from asymmetric functionalization of alkynes. Inspired by the well-studied asymmetric dehalogenation reactions of alkenes, Tan's team envisioned the more challenging catalytic dihalogenation reaction of alkynes to construct new atropisomeric alkene scaffolds. The lower electrophilic reactivity of alkynes and generation of unstable prochiral omnium species dramatically increase the difficulty of selectivity control. To this end, they designed a urea directing group on alkynes that could anchor the halide and thus circumvented the regioselectivity issue (Scheme 13) [56]. The use of readily available *N*-bromosuccinimide (NBS) combined with alkali metal halides (LiCl or LiBr) as halogenating reagents was another hallmark of this strategy. On top of the excellent efficiency and stereoselectivity in providing an array of axially chiral dihalogenated alkenes **85**, methyl, bromine, cyano, ester and amide were compatible functionalities in this reaction. This directing group could be readily cleaved, giving rise to α,β-unsaturated aldehyde (**86**) in moderate yield with undiminished eantiopurity. Gram-scale synthesis and the facility with which urea group could be cleaved highlighted the synthetic utility of this method.

While organocatalytic functionalization of alkynes usually involves *trans* addition, Li [57] recently devised an approach to *cis* addition products *via* rhodium-catalyzed C–H activation and directing group migration (Scheme 14a). The coupling of *N*-phenoxyacetamides **88** with 1-alkynylnaphthalenes **89** afforded tetrasubstituted enamides **90** in



Scheme 13. Catalytic stereoselective dihalogenation of alkynes.

excellent enantioselectivity under the catalysis of chiral rhodium catalyst. The broad scope in terms of both *N*-phenoxyacetamides and 1-alkynylnaphthalenes indicated the excellent functional group compatibility (**90a**-**90e**). The same catalyst enabled the asymmetric coupling of *N*-aminocarbonylindoles **91** with 1-alkynylindoles **92**, delivering acrylamides **93** defined by a chiral *C* (olefinic)-*N* axis (Scheme 14b). A catalytic amount of racemic phthalimide-based zinc carboxylate (**Zn1**) was vital to enhance the efficiency and enantioselectivity and the authors verified that enantioselectivity control was independent of the configuration of additive. A plausible mechanism involving C–H bond activation and directing group migration was proposed based on control experiments and DFT calculations (Scheme 14c).

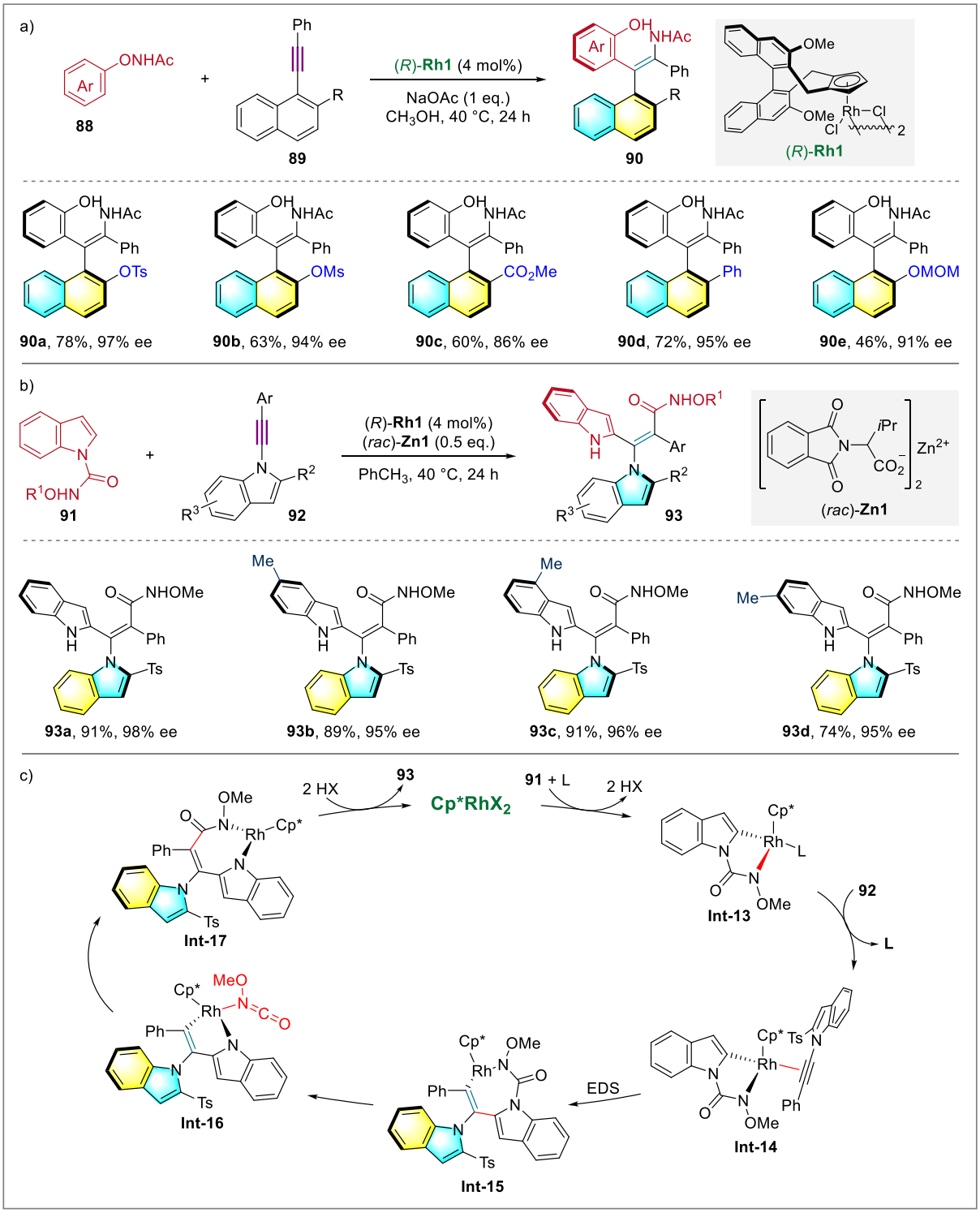
3.2. Construction of axially chiral alkenes via transition-metal-catalyzed asymmetric C–H functionalization of aryl alkenes

Besides the catalytic atroposelective functionalization of aryl alkynes, transition-metal-catalyzed asymmetric C–H activation and functionalization of aryl alkenes provides alternative avenues to access axially chiral alkenes. This metal catalytic approach has proven utility in establishing a rapid access to biaryl atropisomers, which typically involves restricting the free rotation by introducing a large substituent at the *ortho*-position of the preformed axis. As an extension of their research on atroposelective construction of biaryl atropisomers, Shi realized the first palladium-catalyzed asymmetric synthesis of axially chiral alkenes through transient chiral auxiliary (TCA)-enabled C–H activation and olefination (Scheme 15) [58]. Condensation of aldehyde with *tert*-leucine-derived amino amide (**L1**) generates imine (**Int-18**) to act as directing group for the C–H activation. Control experiments showed that removal of benzoquinone (**97**) would significantly reduce the yield and other additives had obvious influence on the yield and selectivity. Acrylaldehydes with alkyl substituent (**96b** and **96c**) were transformed in much lower efficiency as compared to aryl-substituted analogues (**96a**). As with most other cases, sterically bulky substituents at the *ortho*-position were necessary to ensure configurational stability and enantiocontrol (**96d**-**96g**).

The same group also described another palladium-catalyzed asymmetric C–H alkenylation and alkynylation of alkenes bearing pyridine as directing group and used inexpensive L-pyroglutamic acid (**L2**) as the chiral ligand (Scheme 16) [59]. On alkenylation (**99**) and alkynylation (**101**), the free rotation about the vinyl-aryl axis in substrates (**98**) is hindered by the introduced steric congestion. Aside from various acrylates, acrolein, vinyl ketone, acrylamide, alkenyl phosphate and 4-methoxystyrene were also compatible with the alkenylation reaction, affording enantioenriched axially chiral alkenes in good yields. In general, alkynylation with TIPS-protected alkynyl bromide proceeded with better enantiocontrol than the alkenylation. The atropisomeric alkenylated and alkynylated products could be subjected to downstream chemical derivatization with conserved enantiomeric excess.

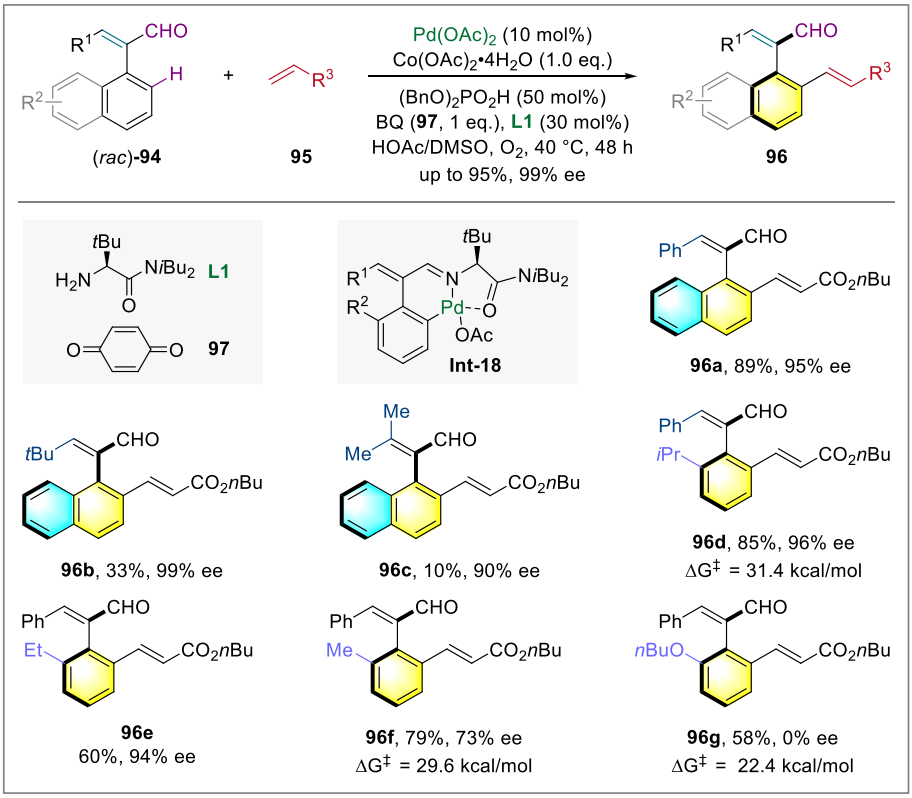
The emergence of chiral carboxylic acids (CCAs) as powerful ligands in asymmetric C–H functionalization has driven the design and synthesis of axially chiral carboxylic acids. Beginning from readily available racemic cinnamic acid derivatives (**102**), Wang recently reported the Pd-catalyzed atroposelective C–H arylation (**104**) [60], alkenylation (**106**) [60] and alkynylation (**108**) [61] to streamline the access of CCAs based on axially chiral alkene skeletons (Scheme 17). The carboxyl group which functions as key motif of CCA ligands serves the role of directing group. The CCAs obtained by this one-step transformation showed chirality induction properties in Co-catalyzed enantioselective C (sp^3)-H amidation reaction and 1,4-addition reaction.

Compared to aryl C–H activation, asymmetric vinyl C–H functionalization is usually associated with complicated side reaction caused by the

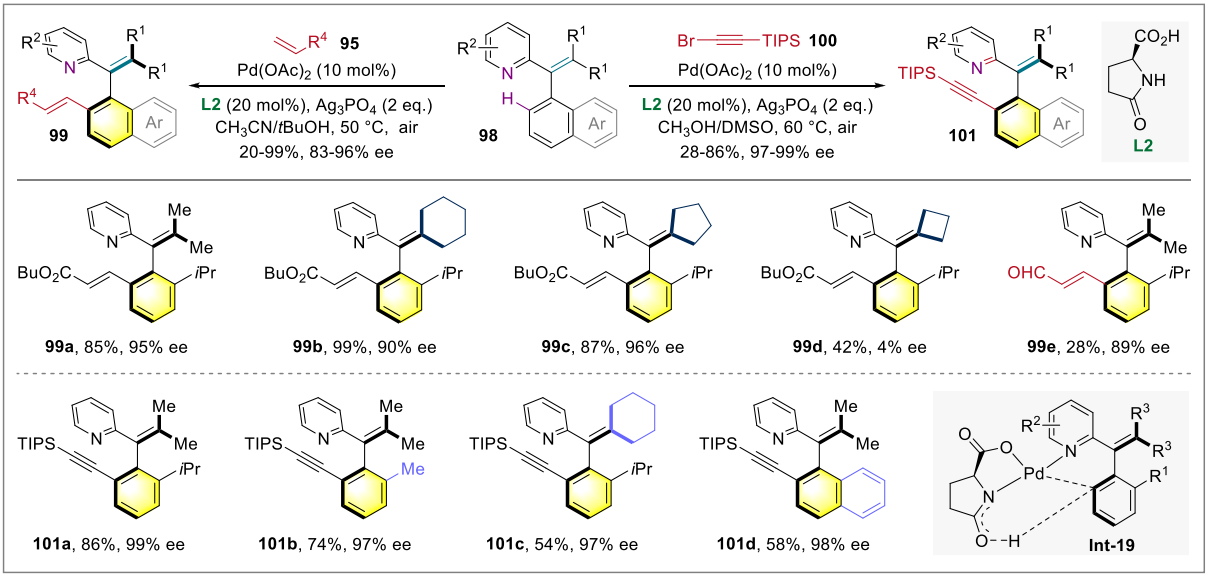


Scheme 14. Synthesis of axially chiral alkenes *via* C–H bond activation and directing group migration.

double bond. In envisioning the assembly of axially chiral styrenes bearing multi-substituted conjugated 1,3-diene, additional layer of complexity could stem from *E/Z* isomerization besides enantiocontrol. Building on their research on palladium-catalyzed aryl C–H activation, Shi recently disclosed the first atroposelective construction of axially chiral aryl dienes by way of asymmetric vinyl C–H olefination (Scheme 18a) [62]. The thioether group on aryl alkenes **110** serves as the directing group and an unusual six-membered palladacycle is implicated in determining the *Z/E* configuration of resulting dienes. The enantioselectivity was found to vary with the steric size of thioether directing groups where a larger steric repulsion with ligand could negatively affect selectivity control. Employment of spiro phosphoric acid (SPA, **C14**) could provide aryl dienes **111** in most optimal yield, enantioselectivity and complete *Z*-selectivity. Besides trisubstituted alkenes, these



Scheme 15. Synthesis of axially chiral alkenes *via* TCA-enabled C–H activation/olefination.

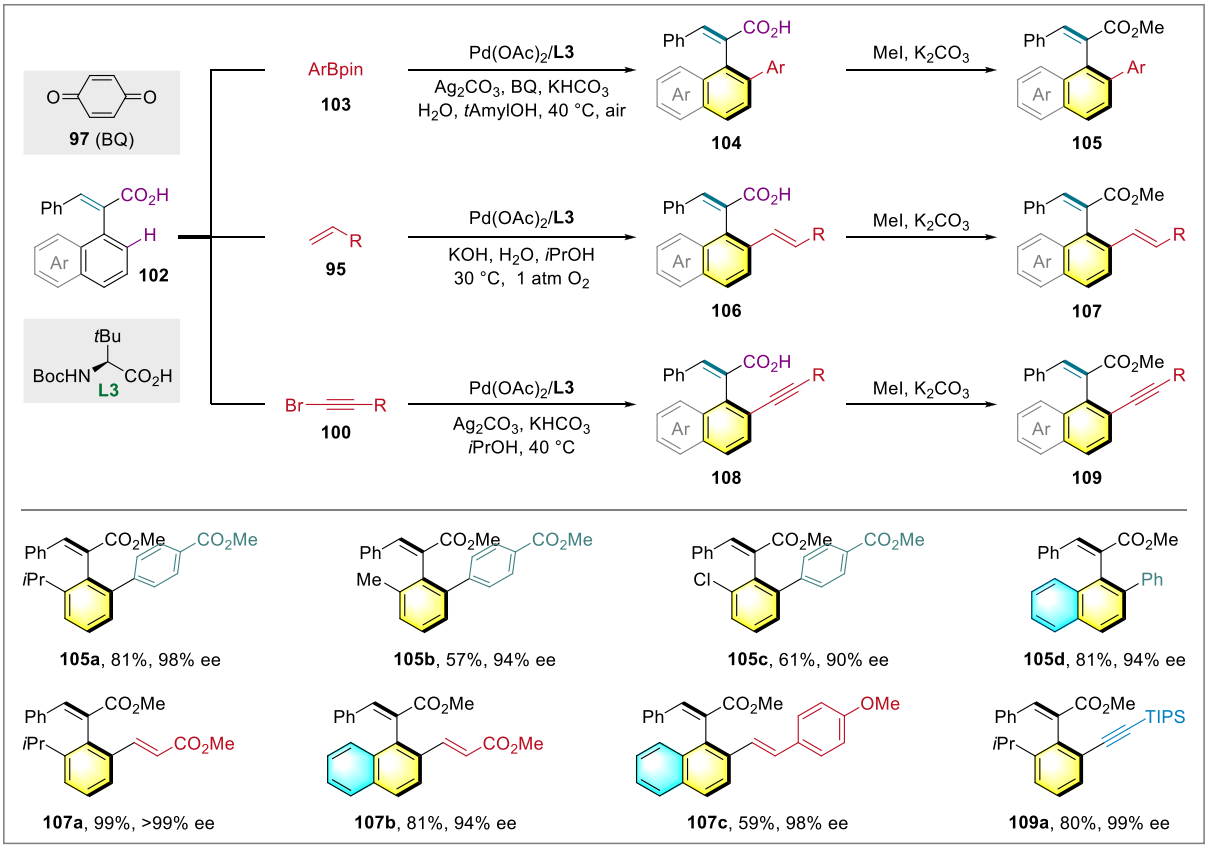


Scheme 16. Pyridine directed asymmetric C–H functionalization for the synthesis of axially chiral alkenes.

conditions enabled also the delivery of chiral tetrasubstituted alkenes (**111c-111e**). The wide substrate scope greatly increased the utility of this reaction: a variety of alkenes including acrylates, styrenes, acrylamide, acrolein, vinyl ketone and alkenes derived from the drug molecules or natural products were suitable coupling partners. Furthermore, the synthesis of atropisomers with two stereogenic styrene-type axes (**113**) could also be accomplished *via* this asymmetric vinyl C–H olefination (Scheme 18b). Very recently, another palladium-catalyzed atroposelective vinyl C–H olefination to access axially chiral conjugated dienes was reported by Xu and coworkers [63]. In this work, tosylamine group at the *ortho*-site of the rotation axis served as the directing group, which played a similar role to thioether group in Shi's work.

3.3. *Construction of axially chiral alkenes via atroposelective formation of vinyl-aryl rotation axis and other strategies*

Beyond the strategy involving stereoselective C–H functionalization to introduce bulky groups at neighboring positions to restrain the free rotation of a preformed axis, transition metal-catalyzed cross-coupling constitutes another efficient method to forge and control the stereogenic



Scheme 17. Chiral carboxylic acids as ligands for diverse asymmetric C–H functionalizations.

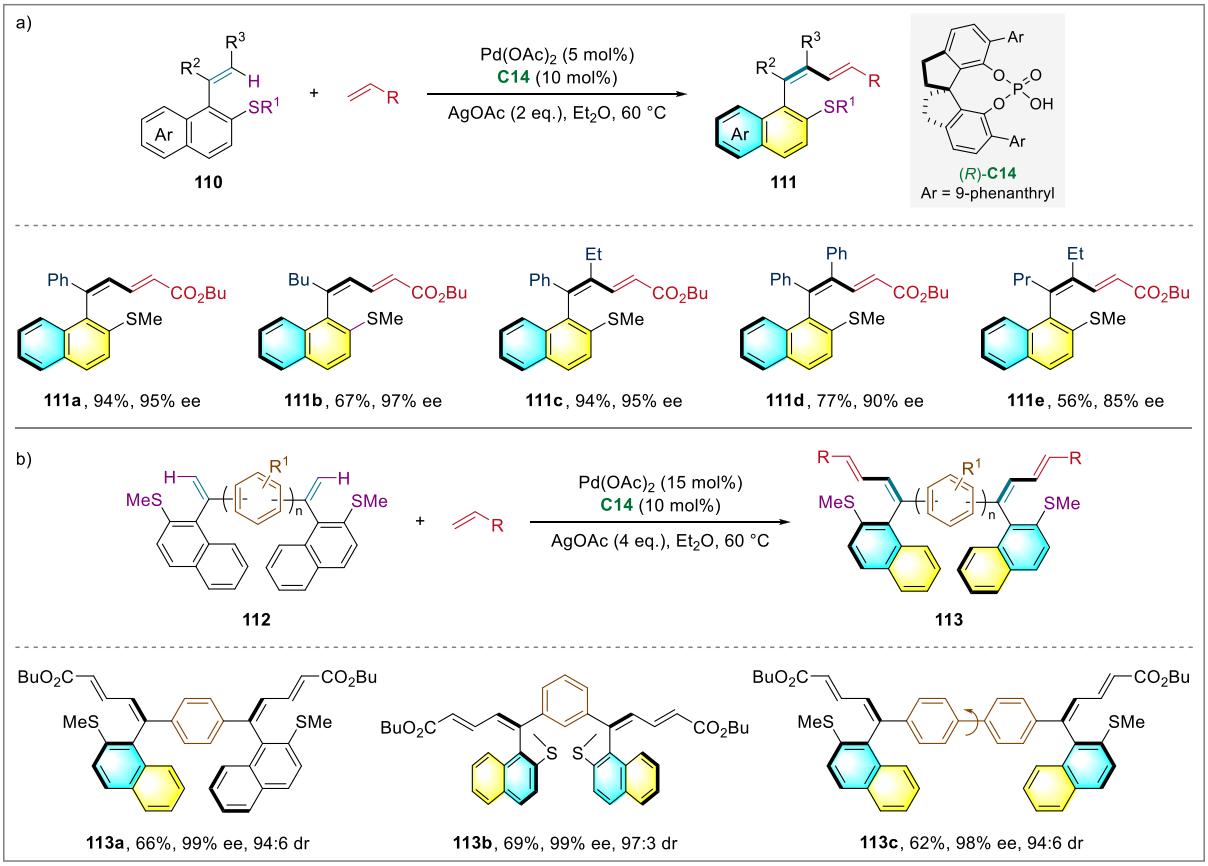
(hetero)biaryl linkage. Alkene atropisomers were difficult to access through this strategy considering the generally high temperatures required in such coupling reactions. Poor enantiocontrol and loss of chirality could result, which is particularly pronounced for axially chiral alkenes with low atropostability.

In this regard, Liu cleverly explored a Pd-catalyzed cross-coupling reaction to form vinyl-aryl axis of atropisomeric acyclic alkenes [64]. The axially chiral alkenes **116** were obtained in good to excellent yields (up to 95%) with moderate enantioselectivities from 1-iodo-2-methoxynaphthalenes (**115**) and *N*-methyl-*N*,3-diphenylpropiolamides (**114**) under the catalysis of palladium acetate and chiral phosphoramidite **L4** (Scheme 19). While a switch to naphthyl bromide substrate could adversely affect the product yield but barely the selectivity, both reactivity and selectivity changed according to the aryl substituent of **114**. The reaction initiates with oxidative addition of Pd (0) to naphthyl halide, followed by the atroposelectivity-determining insertion of the C≡C triple bond to give the axially chiral **Int-20**. An intramolecular C–H activation thus forms the six-membered palladacycle **Int-21**, which delivers axially chiral alkenes **116** after reductive elimination.

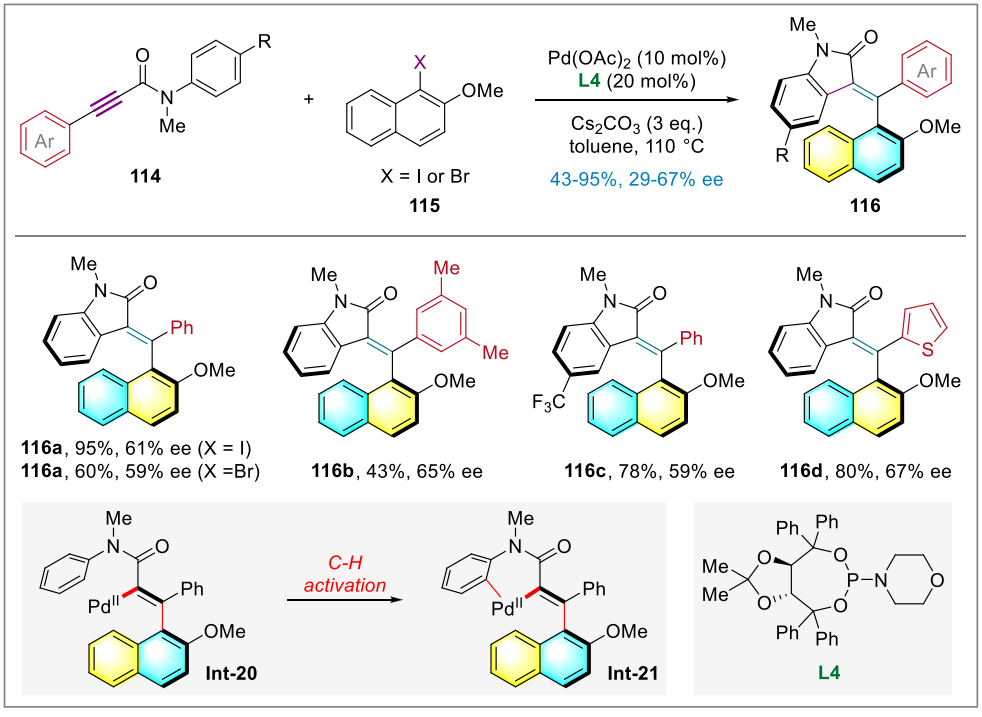
In another development, a highly atroposelective formation of *C* (aryl)-*C* (alkenyl) bond was realized by He and Liu in 2020. In this transformation, an asymmetric allylic substitution (AAS) of 2-quinolinol (**118**) is first catalyzed by iridium and chiral BINOL-based phosphoramidite **L5** to form a chiral *C* (sp3)-*N* bond [65] (Scheme 20). Excellent central-to-axial transfer of chirality ensues through an organic base-promoted *1,3*-proton transfer to generate alkenes with chiral *C* (sp2)-*N* axis (**119**) in good to excellent yields as well as excellent enantioselectivities. This asymmetric allylic substitution-isomerization (AASI) strategy was also used to construct axially chiral naphthyl alkenes (**121**) from cinnamyl carbonate (**117**) as electrophiles and naphthols (**120**) as nucleophiles [66] in excellent yields and high enantioselectivities. Based on the control experiments and DFT calculations, two independent iridium catalytic cycles were proposed. The first iridium catalytic cycle for this protocol is identical to the one implicated in the construction of enamides **119**, in which the chiral *C* (sp3)-*C* (sp2) bond is formed to give point-chiral compound **Int-22**. Instead of *1,3*-proton transfer, here an iridium-catalyzed olefin isomerization operates to effect the central-to-axial chirality transfer. In this stereospecific 1,3-hydride transfer, a benzylic C–H oxidative addition to Ir forms the axially chiral intermediate **Int-24**, followed by C–H reductive elimination.

Diversely, Ramasastry recently reported the atroposelective Suzuki-Miyaura cross-coupling reaction of *β*-keto enol triflates (**122**) with 1-naphthyl boronic acids (**123**) catalyzed by palladium in the presence of chiral bisoxazoline (BOX)-type ligand **L6** (Scheme 21). Various axially chiral (*Z*)-diarylmethylidene indanones (**124**) were obtained with moderate to good enantioselectivities [67]. Comparing alkenes **124a**-**124c**, *ortho*-substituent other than alkoxy groups on boronic acids had little influence on product yield but could markedly diminish the enantioselectivity. From the comparable rotational barriers and atropostabilities between **124b** and **124c**, steric factor should not be the main reason behind the ablated selectivity. Instead, an oxygen-containing substituent plays important role in enantioinduction.

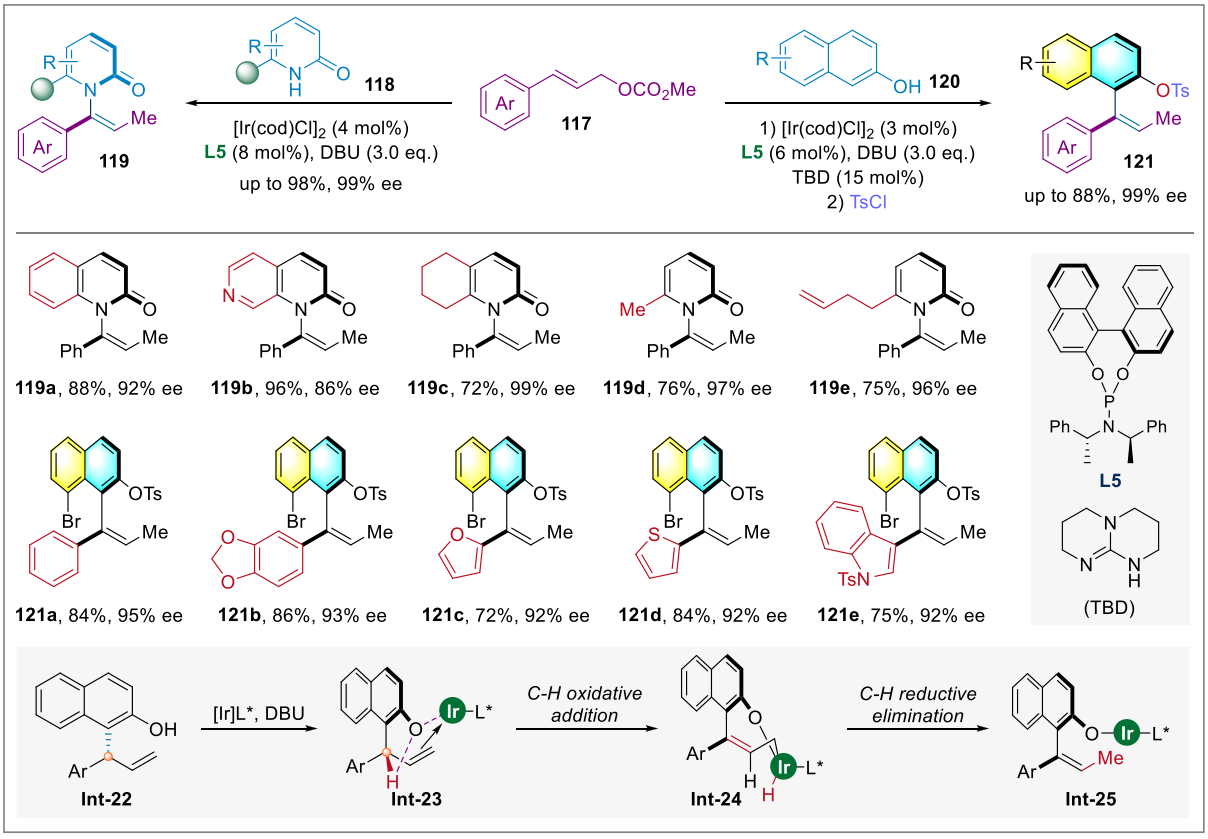
Besides metal-catalyzed C–H activation and cross-coupling strategies covered in previous sections, organocatalysis contributes several other synthetic methodologies for axially chiral alkenes. In 2019, Tan's group developed an atroposelective N-alkylation reaction [68] of enamine-type aryl alkenes **125** catalyzed by cinchonine-based chiral phase-transfer catalyst (PTC) **C15** (Scheme 22). Different alkylation reagents such as



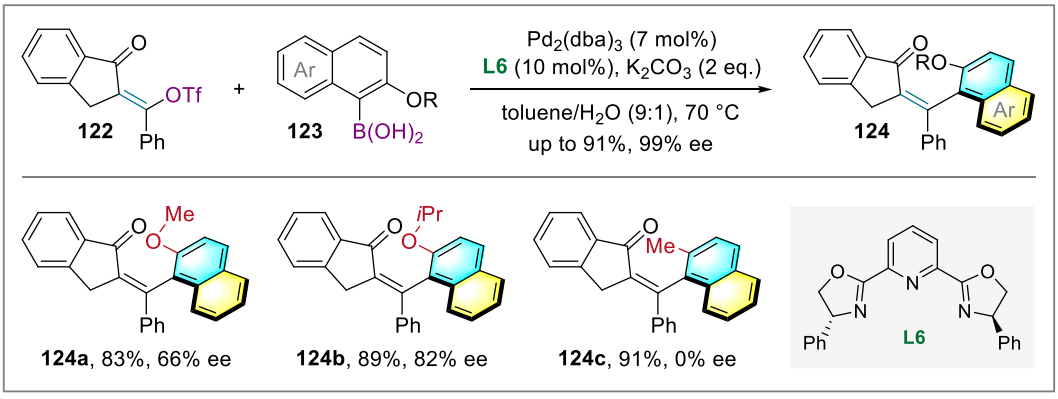
Scheme 18. Atroposelective synthesis of axially chiral aryl conjugated dienes *via* alkenyl C–H olefination.



Scheme 19. Palladium catalyzed asymmetric tandem carbopalladation/C–H olefination to form the vinyl-aryl axis.



Scheme 20. Atroposelective construction of axially chiral alkenes *via* asymmetric allylic substitution and central-to-axial chirality transfer.

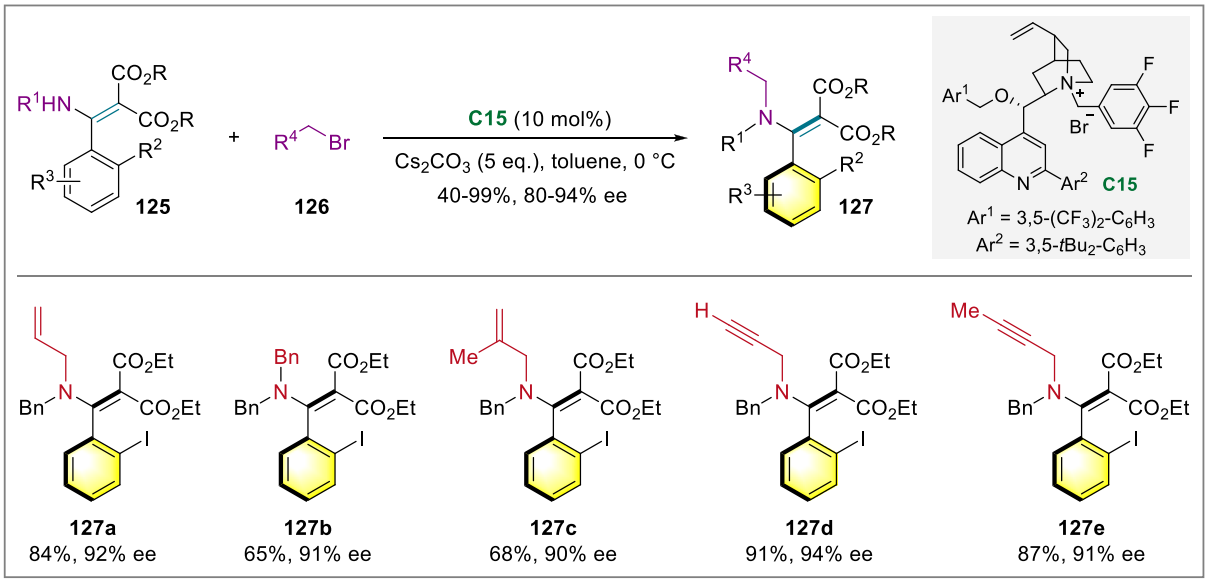


Scheme 21. Construction of axially chiral alkenes *via* enantioselective Suzuki-Miyaura reaction.

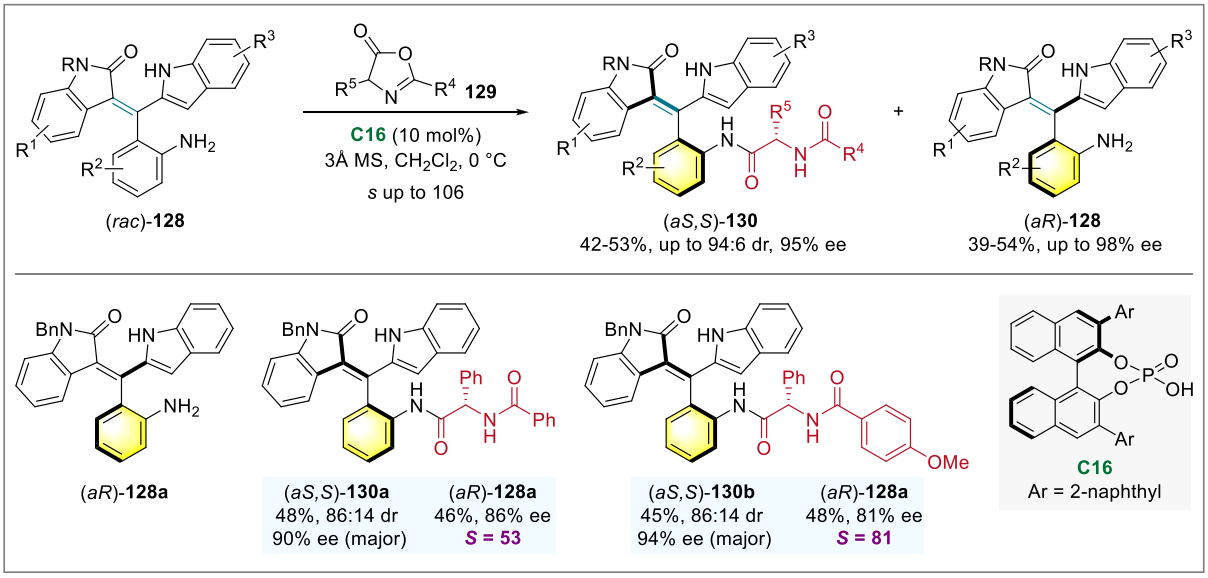
benzyl, allyl and propargyl bromides were applicable to yield densely functionalized alkenes **127** in enantioenriched form. The diverse functionalities enabled a range of follow-up transformations to access other atropisomers *via* chirality transfer.

In Shi's 2020 report, the racemic oxindole-based alkenes with an aryl amine motif (**128**) underwent KR in reaction with azalactones (**129**) to construct oxindole-based axially chiral alkenes with selectivity factor up to 106 (Scheme 23) [69]. In the presence of CPA catalyst **C16**, one of the enantiomers reacted to form enantioenriched bisamides **130** featuring both axial and central chirality. Consequently, two types of oxindole-based axially chiral alkenes could be obtained in a single step with excellent diastereoselectivities and enantioselectivities (up to 98% ee and 94:6 dr). The unreacted enantioenriched materials (*aR*)-**128** bore amino group as versatile reaction handle for derivatization into other axially chiral molecules.

Also through atroposelective synthetic modification of preformed aryl alkenes, Shao and Cheng designed the atroposelective reductive amination of 1-enal-2-naphthols **131** to construct chiral allylamines bearing vinyl-aryl axis in the presence of CPA catalyst (Scheme 24) [70]. This reaction exhibited a broad substrate scope and good stereoselectivity under mild reaction conditions. The control experiments indicated that the free hydroxyl group (OH) played a decisive role in enantiocontrol, presumably through hydrogen bonding interactions with CPA catalyst. This observation and literature report served as the basis for their proposed mechanism. Firstly, **131** condenses with aromatic amines **132** to give racemic imine intermediates (**Int-26** and *ent*-**Int-26**), which



Scheme 22. Construction of axially chiral alkenes *via* atroposelective N-alkylation enabled by chiral phase-transfer catalyst (PTC) .



Scheme 23. Atroposelective construction of oxindole-based axially chiral alkenes *via* CPA-catalyzed kinetic resolution.

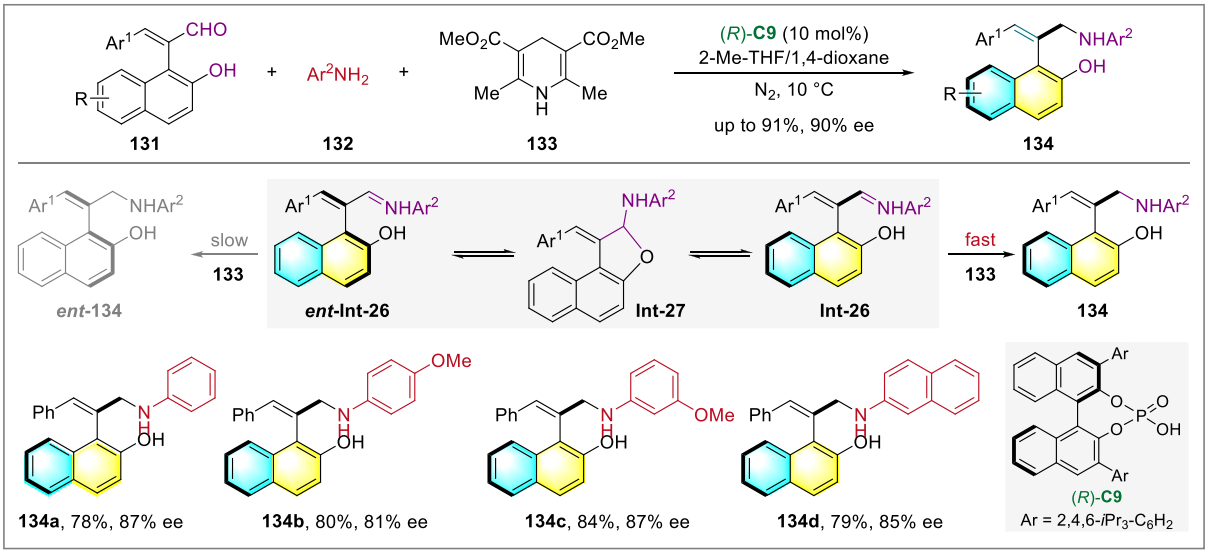
could interconvert *via* a five-membered cyclic *N,O*-acetals (**Int-27**). Finally, dynamic kinetic resolution is achieved during CPA-catalyzed transfer hydrogenation of **Int-26** with Hantzsch ester **133**.

4. Synthetic applications of axially chiral alkenes

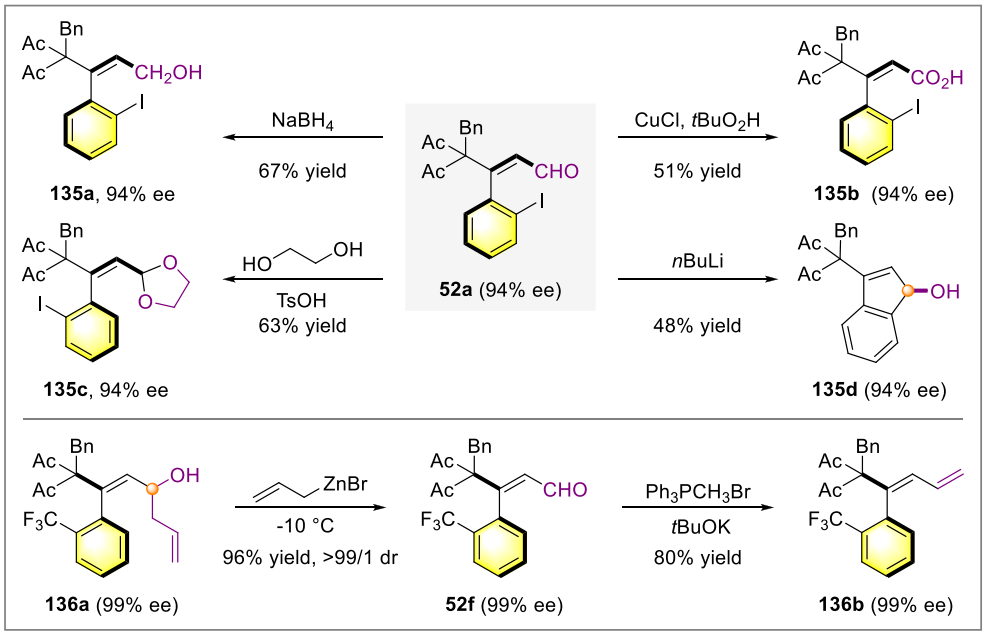
The well-defined spatial orientation of functionalities on an axially chiral scaffold presents unique advantage for application as catalysts and ligands. Indeed, functional molecules based on biaryl derivatives undergird the revolution and development of asymmetric synthesis in the past decades. While exploration of axially chiral alkenes has historically taken a backseat to the biaryl counterparts, the recent development in methodology development facilitates the studies of their various synthetic roles. Aside from being used as an intermediate to relay chiral information in the total synthesis of antibiotic TAN-1085 [40], synthetic potential and catalytic role of axially chiral alkenes remained virtually unexplored. With the appearance of effective synthetic strategies, exploring the application of this new class of chiral molecules has become increasingly relevant.

In Tan's pioneering work in 2017 [17], the aldehyde functionality on resulting axially chiral cinnamaldehyde analogue **52** could be reduced to alcohol (**135a**), oxidized to carboxylic acid to give CCA (**135b**) or condensed with glycol (**135c**) (Scheme 25). By treatment with *n*-butyllithium, chiral *1H*-inden-1-ol **135d** was obtained with same enantiopurity *via* axial-to-central chirality transfer. Furthermore, axially chiral diene **136b** was obtained from analogue **52f** in excellent ee following a Wittig reaction. The same analogue (**52f**) gave rise to alkene **136a** displaying a chiral axis and a chiral center in excellent yield with perfect stereoselectivities on treatment with allyl zinc bromide. These transformations illustrated the synthetic opportunities offered by this new scaffold to access various axially chiral molecules.

On the other hand, Yan demonstrated that on hydroxyl protection of axially chiral sulfone-containing alkene **54a**, the highly enantioenriched triflate **137a** could exhibit a range of cross-coupling reactivity and



Scheme 24. Atroposelective construction of axially chiral alkenes *via* CPA-catalyzed reductive amination.

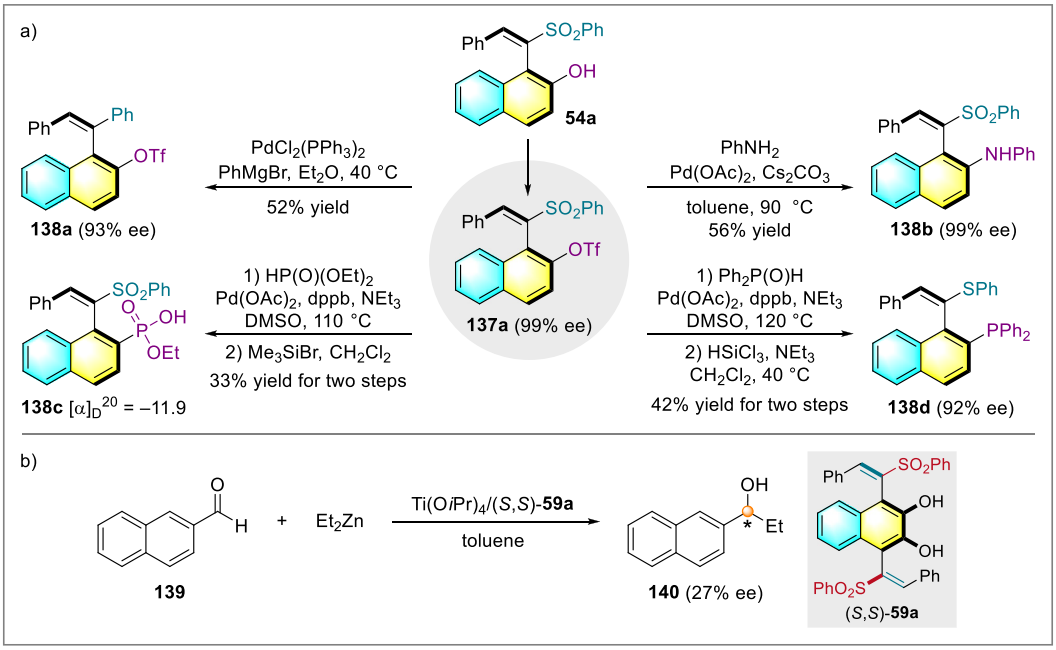


Scheme 25. Derivatization of axially chiral cinnamaldehyde analogues.

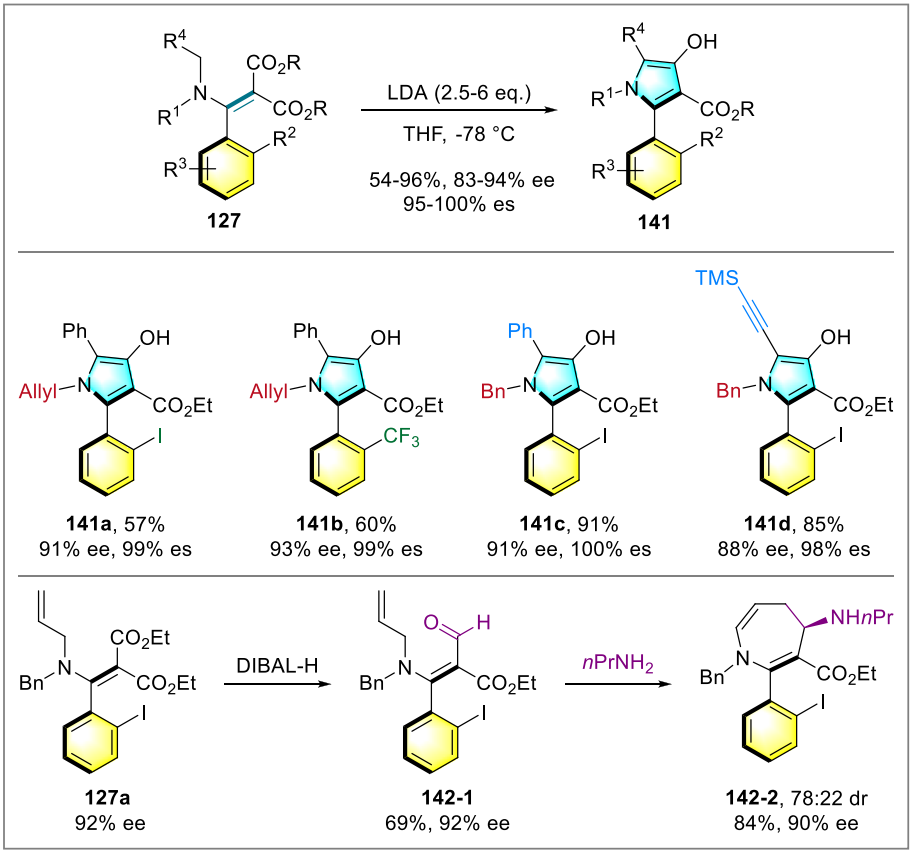
readily formed analogues **138a**-**138d** *via* C–C, C–N or C–P bond formation (Scheme 26) [43]. Among these, phosphonic acid ester **138c** and sulfide **138d** represented a potential organocatalyst and S/P ligand respectively. In their other work on construction of chiral 1,4-distyrene 2, 3-naphthalene diols (**59**) bearing two rotation axes [45], Yan used the chiral diol as ligand for the enantioselective addition of diethylzinc to naphthalene formaldehyde. Despite the poor enantioselectivity (27% ee for **140**), this signified the first exploration of the stereoinduction capability of axially chiral alkenes.

Variously, Tan's team showed that axially chiral aryl enamine **127** obtained from chiral PTC-catalyzed atroposelective N-alkylation could undergo lithium diisopropylamide (LDA)-mediated cyclization to afford axially chiral 2-arylpyrroles (**141**) with preserved enantiomeric excess (Scheme 27) [68]. In particular, fully substituted chiral 2-arylpyrroles were obtained which were usually difficult to prepare by traditional strategies. In addition, one of the two ester groups on alkene **127a** could be selectively reduced to an aldehyde group. By a sequential reaction with amine, potentially bioactive 2-arylazepine (**142–2**) was formed in enantioenriched form.

Also in the same year of 2019, Tan introduced new phosphonamidites (**143a, b**) and phosphoric acid (**145**) based on atropisomeric EBINOL skeleton (Scheme 28a and b) [50]. When compared in asymmetric reduction of enamide (**146, 148**) (Scheme 28c) as well as 1,4-addition of nitro alkene (**150**) and chalcone (**152**) (Scheme 28d), phosphonamidite **143a** or **143b** provided better yields and enantiocontrol than analogues derived from BINOL (**L7** and **L8**) and SPINOL (**L9** and **L10**). Similarly when evaluated in a Mannich reaction as chiral catalyst (Scheme 28e), chiral phosphoric acid **145** performed much better than the BINOL or



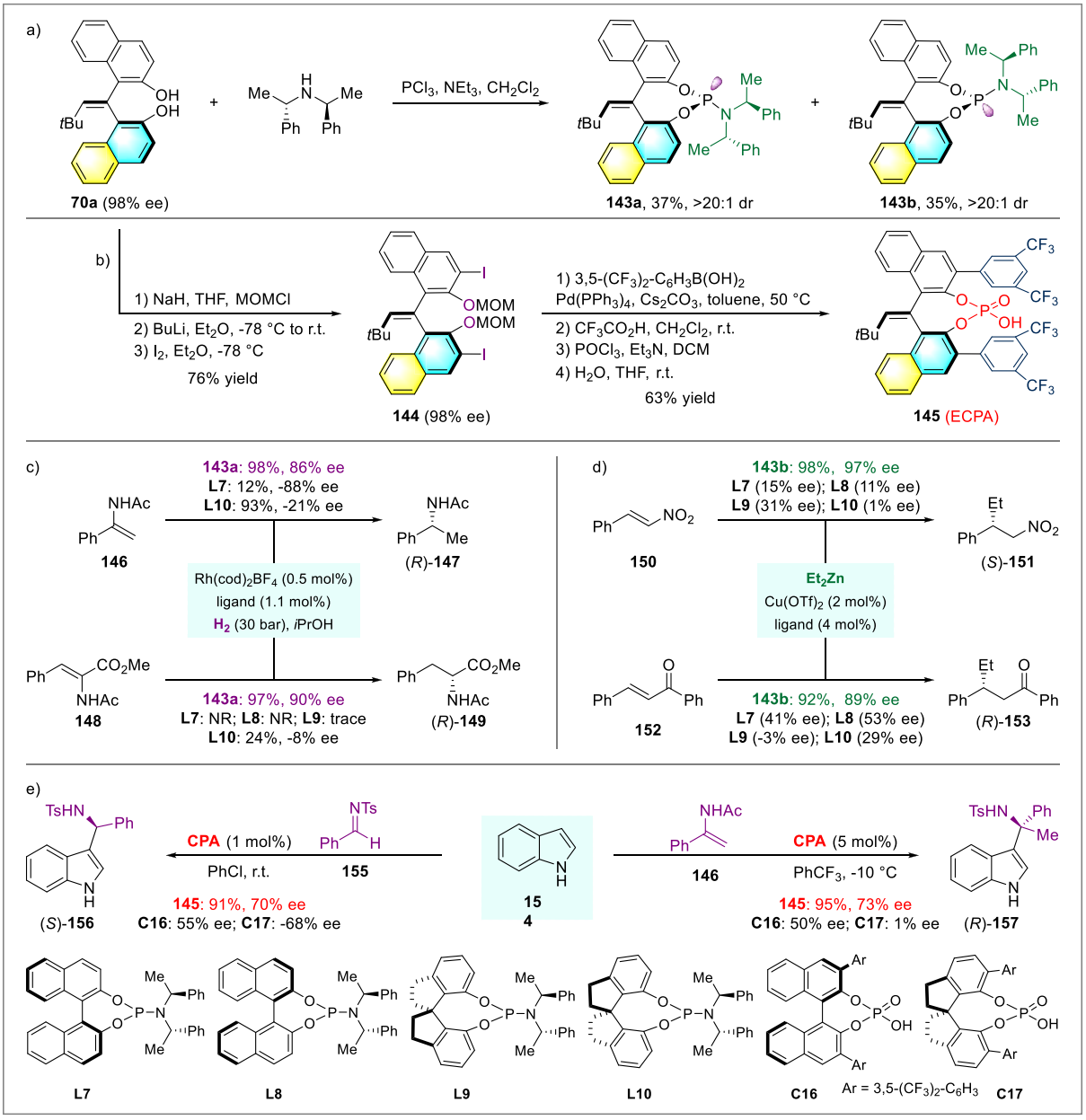
Scheme 26. Derivatization and application of axially chiral sulfone-containing alkenes.



Scheme 27. Derivatization of axially chiral aryl enamines.

SPINOL analogues albeit the moderate enantioselectivities. These results hinted at the great application potential of EBINOL framework in asymmetric catalysis.

In Shi's 2020 disclosure of pyridine-directed palladium-catalyzed atroposelective aryl C–H olefination and alkynylation [59], the authors included several examples on the elaboration of axially chiral alkene product **99a** with excellent stereoretention. The pyridine directing moiety could be oxidized to *N*-oxide pyridine derivative **158** with *m*-CPBA (Scheme 29). Alternatively, selective oxidative cleavage of the less hindered alkene leading to chiral carboxylic acid **159** could take place with



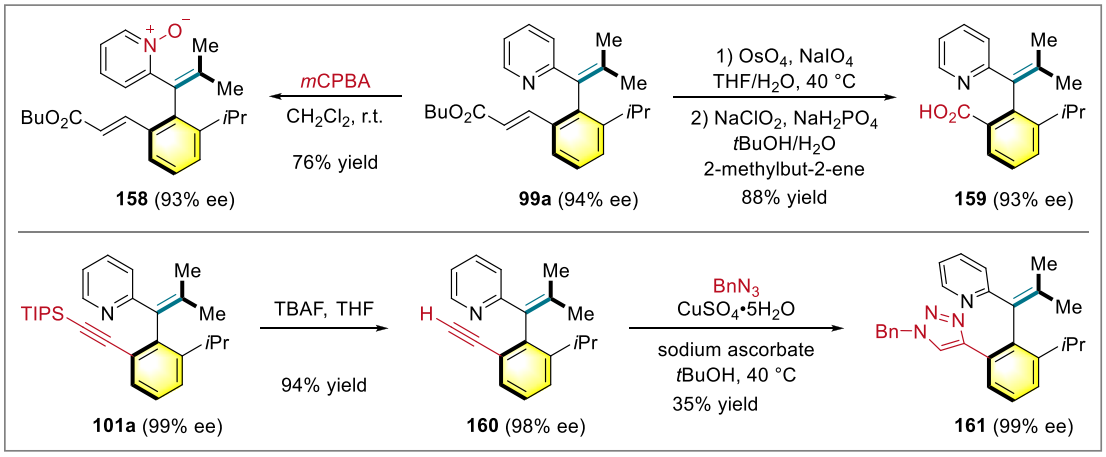
Scheme 28. Synthesis and application of chiral phosphonamidites (**143**) and CPA (**145**) based on EBINIOL skeleton.

high yield. By deprotection with tetrabutylammonium fluoride (TBAF), the terminal alkyne **160** released efficiently was amenable to a copper-catalyzed click reaction with benzyl azide to give axially chiral triazole **161**. While this step observed a moderate yield, the enantiopurity was not compromised.

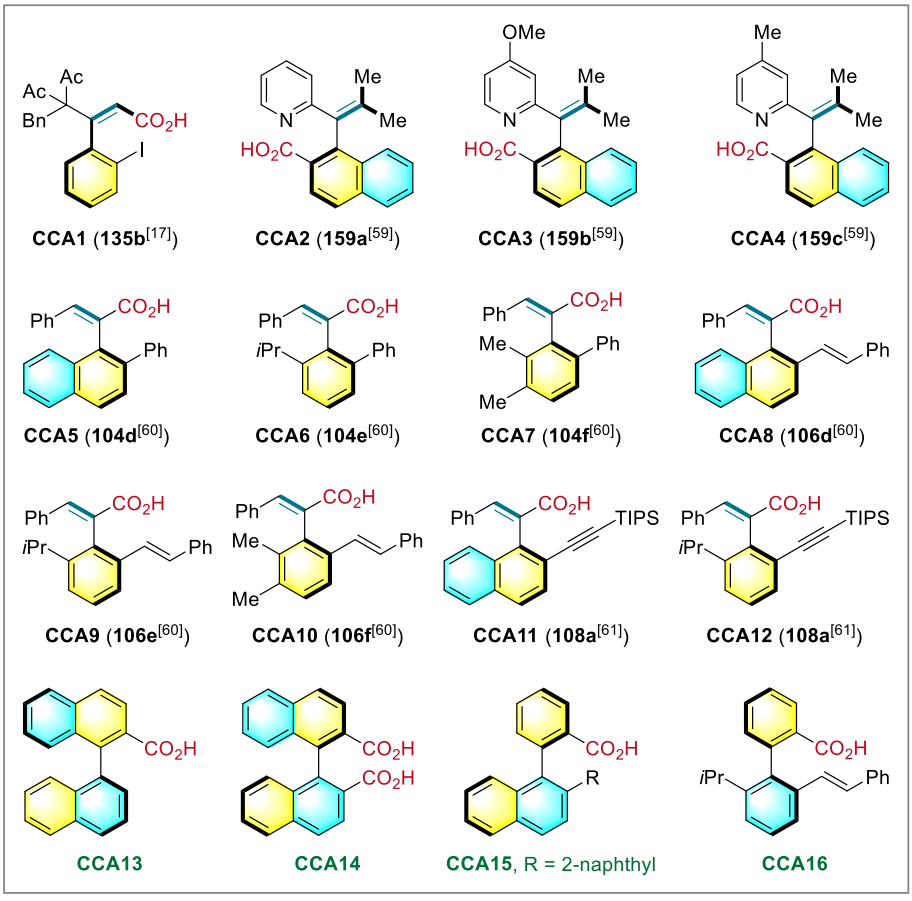
Aside from being widely used organocatalysts, chiral carboxylic acids (CCAs) show high activity as chiral ligands in many important transition metal-catalyzed asymmetric C–H activation reactions. From 2017 following the first report on constructing axially chiral open-chain alkenes, various CCAs were synthesized based on these novel atropisomers (Scheme 30, **CCA1-12**) and were employed as chiral ligands in C–H functionalization chemistry.

Shi [59] first evaluated the efficacy of CCAs in Co(III)-catalyzed enantioselective C–H amination of ferrocene in 2020 (Scheme 31a). With **CCA2** and **CCA3**, the related amination product **164** could be obtained in good yields (89–96%) and moderate enantioselectivities (41–45% ee). Compared to the biaryl analogues (**CCA13–15**), this seminal study informed the potential or even the superiority of axially chiral alkenes in selectivity control of certain asymmetric reactions. In related research on Co-catalyzed asymmetric C–H activation and functionalization reported by Shi [58] and Wang [60,61] (Scheme 31b and c), similar results were observed. While there is room for improvement, these preliminary studies showcased the promising use of axially chiral styrene-type CCAs.

In their 2021 report on Pd(II)-catalyzed thioether-directed alkenyl C–H olefination, the Shi group disclosed the formation of new chiral S-olefin ligands (**170**) embodying alkene axial chirality and *S*-stereogenic center *via* oxidation of axially chiral diene products (**111**) (Scheme 32a) [62]. When examined in Rh-catalyzed asymmetric conjugate addition or 1,2-addition reaction of aryl boronic acid **172** (Scheme 32b and c), the anticipated products were generated smoothly with moderate to good enantioselectivities (up to 82% ee for *β*-aryl ketone **173**).



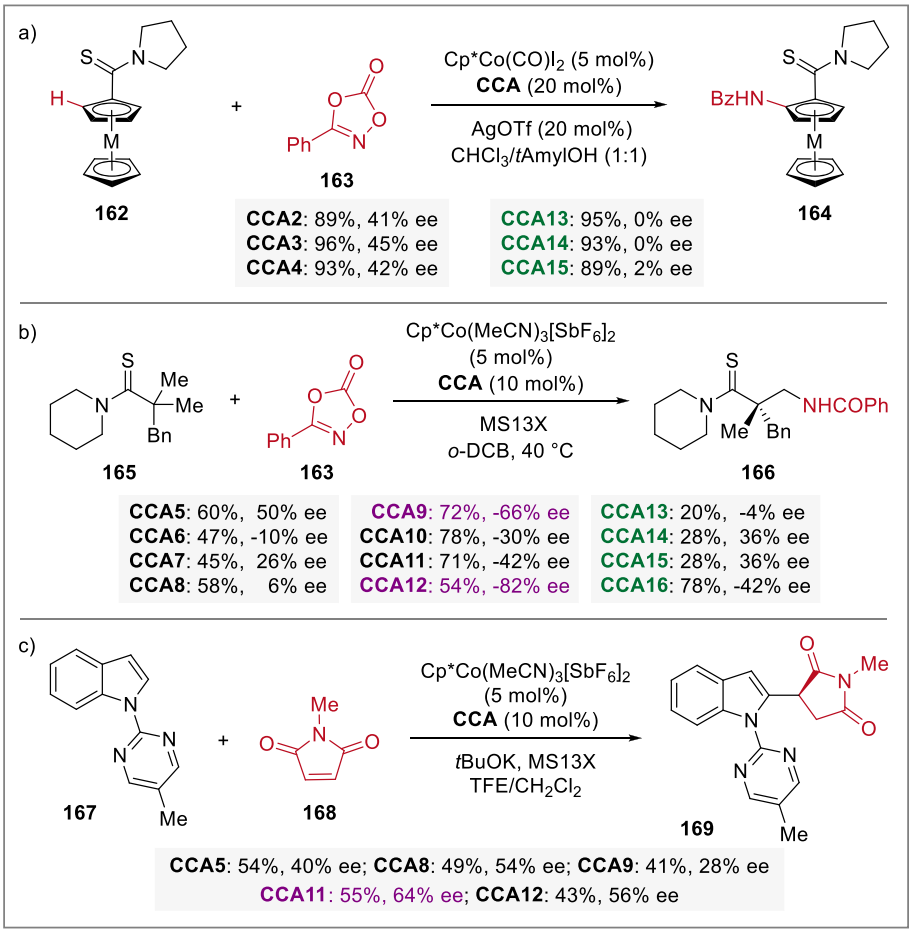
Scheme 29. Derivatization of axially chiral alkenes obtained *via* pyridine-directed C–H activation and functionalization.



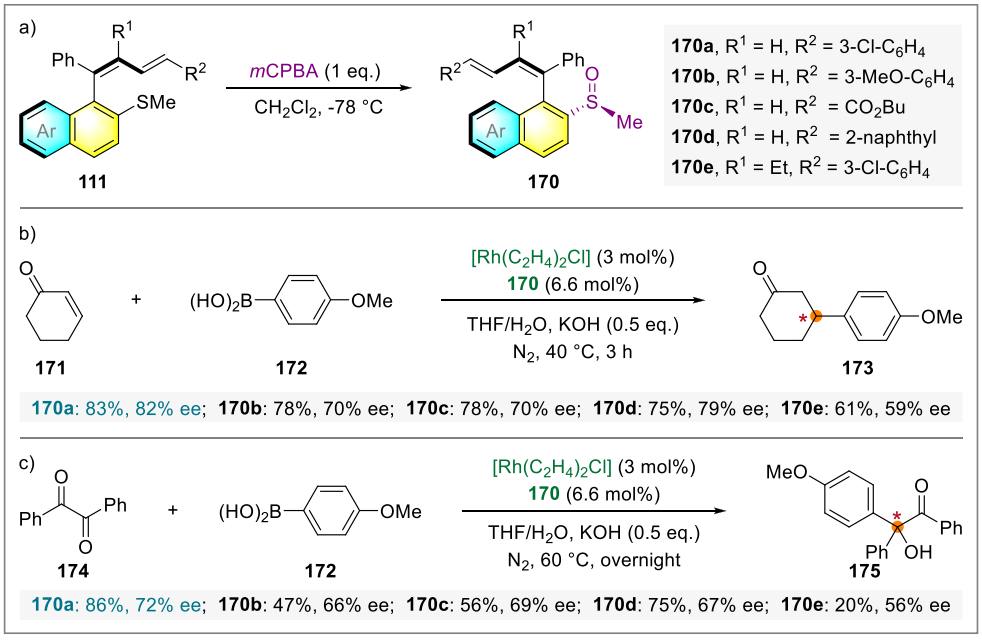
Scheme 30. Summary of chiral carboxylic acids (CCAs) based on axially chiral alkene skeleton and representative biaryl analogues.

In conjunction with Li's more recent report on the synthesis of axially chiral *N*-vinyl indole-based carboxamides (**93**) [57], they have additionally tested these compounds as additives in $[Cp^*RhCl_2]_2$-catalyzed annulative coupling of diphenylsulfoximine (**176**) with α-diazo acetyl acetate (**177**) (Scheme 33). This desymmetrization reaction provided sulfoximine **178** in moderate yields and stereoselectivities (32–54% ee). The importance of *N–H* group in establishing the stereochemical control was verified in a control reaction using N-protected indole, which resulted in ablated product enantioselectivity.

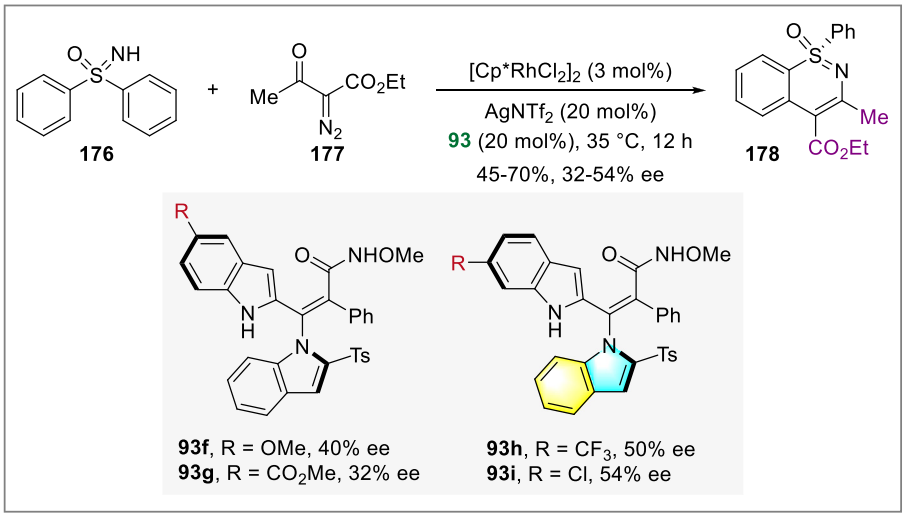
Else_com_jmstpress_logoThe new class of axially chiral oxindole-based alkenes derived by Shi using CPA-catalyzed kinetic resolution in 2020 [69] served also as useful catalyst precursors. As a versatile reaction handle, the amine moiety allowed smooth elaboration into bifunctional catalysts (Scheme 34, **179**–**181**). For instance, thiourea-amine **181a** bearing a chiral cyclohexane-1,2-diamine motif was found to efficiently catalyze the asymmetric (4 + 2) annulation of *ortho*-quinone methide (**182**) with malononitrile (**183**) with 90% yield and 91% ee. It was verified from the control experiments conducted with thioureas



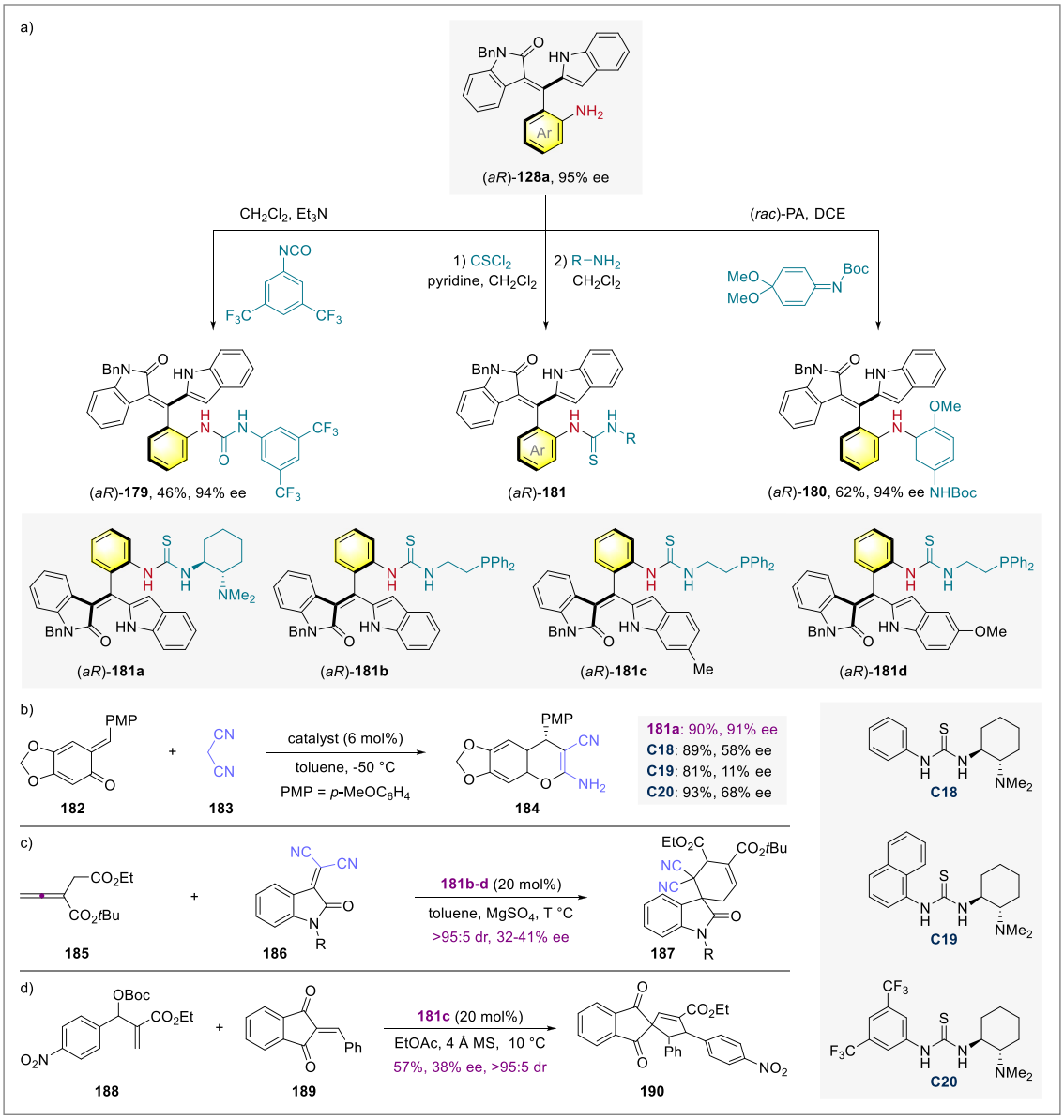
Scheme 31. Application of CCAs derived from axially chiral alkenes in asymmetric C–H functionalization.



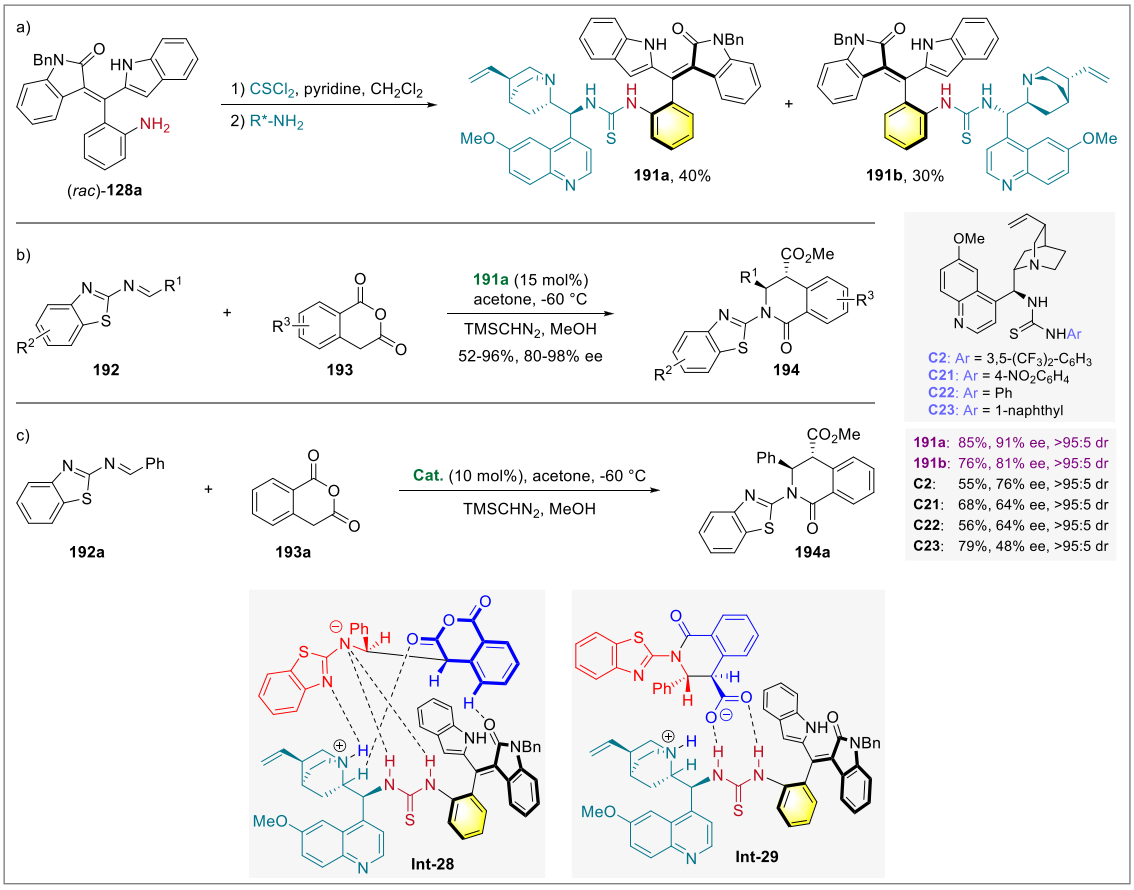
Scheme 32. Applications of novel chiral *S*-olefin ligands in Rh-catalyzed asymmetric addition reactions.



Scheme 33. Applications of axially chiral *N*-vinyl indole in Rh-catalyzed coupling reaction.



Scheme 34. Preliminary applications of axially chiral alkene-based bifunctional organocatalysts.



Scheme 35. Applications of axially chiral alkene-based organo-bifunctional catalysts in catalytic asymmetric (2 + 4) cyclization reactions.

(**C18**–**20**) bearing the same chiral amine motif that the axially chiral framework gave major contribution in the observed enantioselectivity. Thiourea-diphenylphosphines (**181b-d**) were also evaluated for (4 + 2) annulation of allene ester **185** with isatin-derived alkenes **186** as well as (3 + 2) annulation of Morita-Baylis-Hillman carbonate **188** with ninhydrin-derived alkene **189**. The suboptimal reaction enantioselectivities nevertheless offered a glimpse of the potential of oxindole-based thiourea-amines in stereochemical control.

Building on this exploratory study, the same group conducted a focused research on the catalytic performance of rationally designed styrene-based thiourea-tertiary amine catalysts [71]. The catalyst library was modularly assembled *via* sequential reactions of racemic oxindole-based axially chiral aryl amines (**128**) with thiophosgene and commercial chiral amines (Scheme 35). The quinine-derived thiourea **191a** exhibited excellent efficiency and stereocontrol competence in the asymmetric (2 + 4) cyclization of 2-benzothiazolimine (**192**) with homophthalic anhydride (**193**). Aside from control reactions that supported the effect of axially chiral skeleton on stereoselectivity, theoretical calculations gave insights into the origin of reactivity and enantioselectivity. DFT calculations indicated that the 2-benzothiazolimine **192a** and the anion of homophthalic anhydride **193a** could be activated by this new organocatalyst by forming multiple hydrogen bonds. The chiral intermediate **Int-28** is generated *via* a diastereo- and enantioselective addition reaction, which is likely the rate-limiting and enantioselectivity-determining step. **Int-29** is then generated through an intramolecular cyclization, followed by esterification to yield the product. Compared to common thiourea-amine catalyst, the axially chiral oxindole-based styrene moiety could form additional three hydrogen bonds with both reactants in the transition state leading to **Int-28**. The latter provides a pocket-like chiral environment from intramolecular H-bond of indole and oxindole rings. Collectively, the lower free energy barrier and better differentiation of the two competing transition states give rise to the observed higher catalytic activity and enantioselectivity.

5. Summary and outlook

The evolution of axially chiral alkenes has experienced a slow start owing to their higher structural flexibility. The expanding knowledge on atroposelective synthesis provides the foundation for the more challenging synthesis of axially chiral acyclic alkenes. Following the first report on a catalytic enantioselective construction in 2017, more than 30 papers have been reported by 15 research groups in the span of approximately four years. At the same time, the applications of these newly designed atropisomeric frameworks have seen promising success. Despite this progress, the field is only at an early stage of development and multiple hurdles remained to be cleared. A foremost challenge is the expansion of structural variability given that most reported frameworks feature a chiral vinyl-aryl axis and only a single report showed the construction of *C* (sp2)-*N* axis. Expanding the current synthetic options with increased efficiency and practical utility is another significant task to encourage investigations into their utility. In particular, the design of catalysts and ligands based on these frameworks will be a highly worthwhile pursuit. The success of birayl congeners and results from preliminary studies are indicative of the fascinating opportunities forthcoming.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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