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Perspective

Recent applications of axially chiral skeletons in asymmetric catalysis

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THE BIGGER PICTURE Catalysis using axially chiral molecules is advancing from empirical screening toward rational design. By establishing precise structure-performance relationships, this strategy facilitates the creation of tailored catalysts for specific synthetic challenges, markedly enhancing efficiency and extending the frontiers of viable chemical transformations. In parallel, the field is transitioning from isolated catalytic regimes to cooperative catalytic systems, where the central challenge resides in reconciling catalyst compatibility with other components while preserving rigorous enantiocontrol over reactive intermediates. Surmounting this bottleneck promises to unlock novel paradigms for stereochemical control of radicals and inert bond activation, thereby broadening the horizon of accessible synthetic pathways. Looking ahead, as laboratory methodologies continue to mature, the overarching imperative is to translate these powerful platforms into tangible industrial productivity for the scalable synthesis of high-value chiral molecules, ultimately fulfilling their transformative practical potential.

SUMMARY

Axially chiral skeletons provide a molecular foundation for constructing chiral environments in asymmetric catalysis by leveraging their rigid conformational architectures and tunable electronic properties. This perspective systematically elucidates the applications of such skeletons, from metal ligands to organocatalysts, through representative case studies. In metal catalysis, coordination with diverse metal centers enables efficient asymmetric induction. In organocatalysis, mechanisms such as hydrogen bonding and ion pairing allow direct substrate activation and stereochemical control. Notably, their applications in cooperative catalysis and photo-/electrocatalysis have led to breakthroughs in stereodiscrimination of highly reactive intermediates, expanding the frontiers of asymmetric synthesis. Future developments in this field will focus on function-oriented catalyst design, innovations in photo-/electrocatalytic systems, and industrial translation, thereby providing sustained driving force for the precise construction of complex chiral molecules.

INTRODUCTION

Axially chiral skeletons have demonstrated significant value in the field of asymmetric synthesis due to their unique structural rigidity, exceptional stereoinduction capabilities, and flexible synthetic tunability. These frameworks provide chemists with a molecular platform that combines stability with adjustability, serving as a core foundation for developing novel asymmetric catalytic methodologies. The integration of their rigid three-dimensional structures with well-defined chiral environments ensures the maintenance of stable spatial configurations during reactions, offering a structural guarantee for precise enantioselective control.

Axially chiral skeletons exhibit high structural modifiability. By introducing various functional groups in the peri-axial regions or modifying the aryl ring substitutions, fine-tuning of catalyst performance can be achieved to meet diverse synthetic requirements. In catalytic asymmetric synthesis, these skeletons have become essential building blocks for constructing various chiral ligands and catalysts. Specifically, the introduction of coordinating groups into the scaffold enables the development of biaryl and heteroaryl ligands, while structural modifications of the framework can yield spirocyclic or novel axially chiral scaffold ligands. Depending on the types of coordinating elements and the spatial arrangement of coordination sites, these ligands can coordinate with various metal centers, further leading to their participation in multiple pivotal catalytic reactions. On the other hand, by introducing functional groups capable of interacting with substrates, hydrogen-bonding

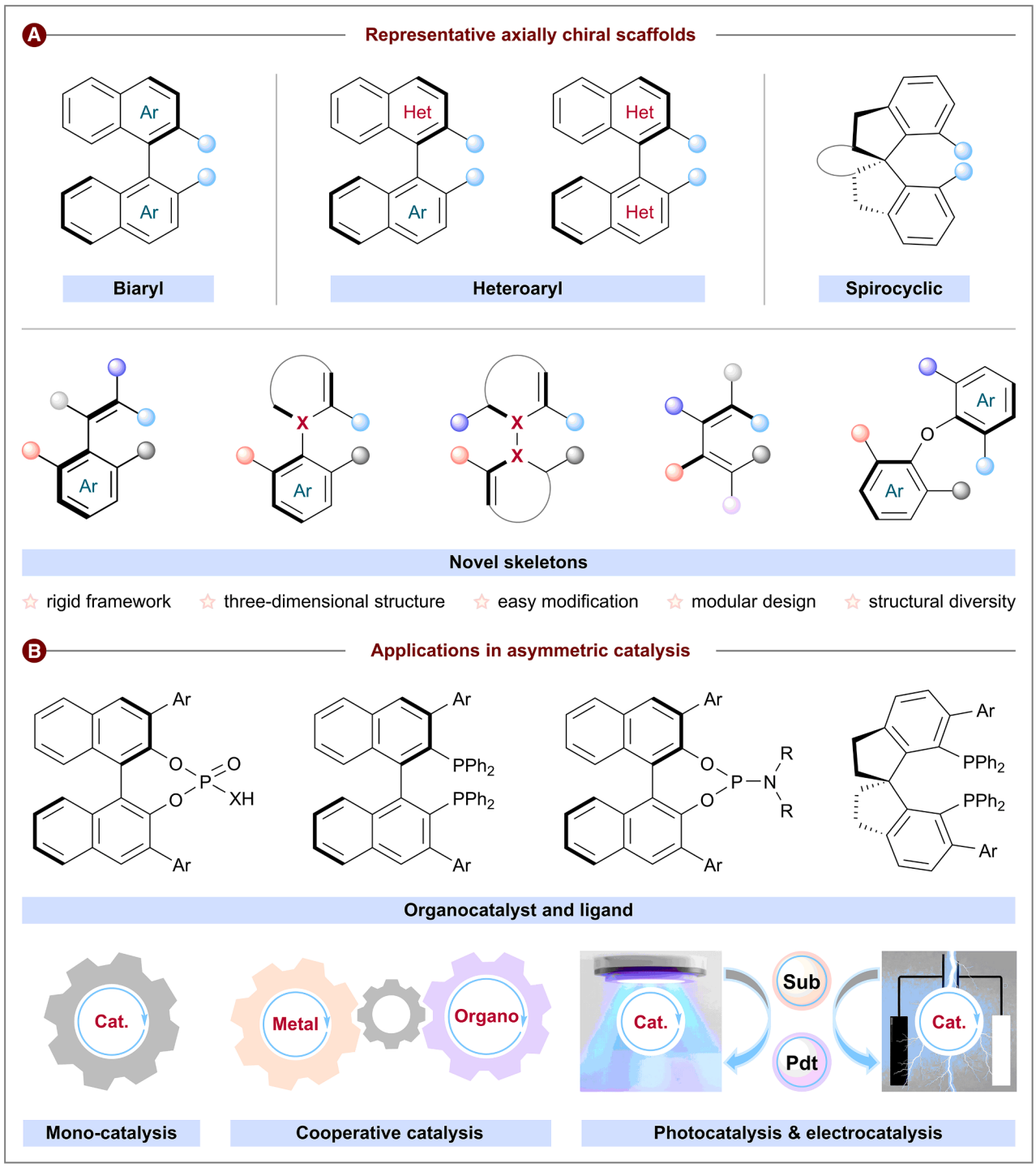


Figure 1. Structural characteristics and application of axially chiral skeletons

(A) Representative axially chiral scaffolds.

(B) Applications in asymmetric catalysis.

catalysts, ion-pair catalysts, and nucleophilic/electrophilic catalysts can be constructed. These are applicable to different reaction mechanisms and enable efficient control over reaction enantioselectivity (Figure 1A).

Furthermore, axially chiral skeletons provide an ideal platform for achieving synergy between metal catalysis and organocatalysis. By integrating these two catalytic modes, it is possible to overcome the limitations of single catalytic

systems, activate traditionally inert substrates, and leverage synergistic effects to achieve more efficient enantiocontrol. In both emerging photocatalytic and electrocatalytic systems, axially chiral skeletons also demonstrate excellent compatibility and effectively control reaction stereoselectivity. This capability transcends the constraints of traditional methodologies, opening up new frontiers for the efficient and sustainable construction of chiral molecules (Figure 1B).

In-depth research and widespread application of axially chiral skeletons have significantly advanced the efficient and precise synthesis of chiral pharmaceuticals, natural products, and functional materials. This has solidified their central role in modern synthetic chemistry and continues to inject new momentum into the field of asymmetric catalysis. This perspective will systematically elucidate the design strategies and catalytic mechanisms of axially chiral compounds from viewpoints such as structural scaffolds and modes of action, analyze their structure-activity relationships through representative case studies, and provide an outlook on future development directions.

APPLICATIONS OF AXIALLY CHIRAL SKELETONS IN LIGANDS

Axially chiral biaryl ligands

In the field of enantioselective catalysis, the use of chiral metal complexes is a highly versatile and flexible strategy. The success of this approach largely depends on ligand design: ligands must possess appropriate functional groups and specific substituents to precisely modulate the spatial and electronic environment around the metal center. Among various designs, C_2-symmetric ligands with axial chirality have found widespread applications, and 2,2′-dihydroxy-1,1′-binaphthyl (BINOL) and its derivatives represent an important class of molecules that coordinate with oxophilic metals. The BINOL framework itself is readily amenable to chemical modification, allowing for simultaneous adjustment of both steric hindrance and electronic properties at the metal center. Since Noyori's pioneering work in 1979,[1] BINOL as a ligand has primarily been studied in coordination with oxophilic metals (Ti, Zr, Al, and Ga). The metal centers in such complexes exhibit Lewis acidity and can serve as catalytic active sites to interact with atoms such as N and O, thereby activating imines, carbonyls, and ethers (Figure 2A).[2–5]

In recent years, the Shi group has extended the application of BINOL ligands from traditional oxophilic metals to transition-metal catalysis, carrying out a series of studies in enantioselective C-H activation with cost-effective BINOL ligands. For instance, in 2019, by employing 3,3′-difluoro-BINOL (**L1**) to enhance both ligand acidity and stereocontrol, Shi and colleagues realized the first enantioselective alkynylation of unactivated methylene C(sp^3)-H bonds (panel a).[6] Subsequently, this strategy was applied to economical nickel and copper catalytic systems.[7,8] Recently, Maji and co-workers introduced a novel bifunctional catalyst system that merges an iridium center with a Lewis acid. Capitalizing on the strong affinity of the BINOL ligand for the Lewis acid and incorporating a bipyridine moiety into its side chain, this system delivered remote, highly regioselective, and enantioselective *meta*-C(sp^2)-H borylation of α,α-diarylcarboxamides (**3**). These developments underscore the utility of BINOL as a versatile chiral ligand in diverse C-H functionalization reactions (panel b).[9]

N,N ligands[10] and N,O ligands[11,12] derived from axially chiral [1,1'-binaphthalene]-2,2'-diamine (BINAM) and 2'-amino-[1,1'-binaphthalen]-2-ol (NOBIN) are also representative axially chiral biaryl ligands (Figure 2B). In 2022, the Gulías group reported the first use of a novel chiral ligand derived from N-acylated NOBIN (**L3**, NOBINAc) in palladium-catalyzed enantioselective C-H activation and cycloaddition. This ligand cleverly merges the axial chirality of a binaphthyl framework with the bidentate coordination of a mono-N-protected amino acid (MPAA), markedly surpassing traditional MPAAs and permitting the efficient assembly of chiral 2-benzazepines (**6**) with enantioselectivities of up to 97% (panel c).[13] The following year, the Ma group described a copper-catalyzed asymmetric arylation of α-alkyl-substituted cyanoacetates (**7**) with (hetero)aryl iodides. By employing (*S*)-NOBIN-embodied picolinamide (**L4**), the reaction constructs an all-carbon quaternary stereocenter decorated with multiple convertible functional groups (panel d).[14] These ligands skillfully blend the conformational rigidity of a biaryl scaffold with the coordination and hydrogen-bonding capabilities of functional groups (such as amide and phenolic hydroxyl), delivering stereocontrol effects that are difficult to replicate with traditional point-chiral ligands. Such advances underscore the immense potential and design versatility of axially chiral ligands in complex asymmetric catalysis.

Axially chiral phosphine ligands remain among the most widely employed frameworks in this category. Building on the landmark breakthrough of 2,2'-bis(diphenylphosphanyl)-1,1'-binaphthalene (BINAP), the field has continued to evolve through the continual design of new, increasingly effective axially chiral phosphine ligands (Figure 2C).[15–19] These ligands demonstrate remarkable capability in stereochemical induction. In 2015, the Buchwald group disclosed copper-catalyzed hydroamination of alkynes (**10**). Within a single catalytic system, simple modulation of alcohol additives allows precise control over the reaction pathway, delivering highly enantioselective hydroamination or reductive hydroamination at will. Central to this strategy is the ability of ligand **L5** to precisely manipulate key copper intermediates, establishing a chiral environment while directing the reaction pathway through synergistic interactions with proton sources. This study demonstrates that axially chiral ligands govern both chemoselectivity and chirality induction, establishing a new paradigm for the precise control of complex transformations (panel 2e).[20] In 2023, the Zhang group reported a new class of axially chiral biphenyl diphosphine ligands, Em n-BridgePhos (**L6**). Installation of a flexible ether chain bridge at the 5,5′-positions of the biphenyl skeleton, in place of previously used rigid carbon linkers, dramatically expanded and finely tuned the dihedral angle of the biphenyl moiety in the ligand-rhodium complex, thereby addressing the challenge of highly enantioselective hydrogenation via desymmetrization of prochiral α-acetamido-1,3-indanedione (**13**). The study confirmed a positive correlation between the increase in this dihedral angle and the enhancement of catalytic performance (panel 2f).[21] Monodentate phosphine and phosphoramidite ligands likewise occupy important niches. Phipps used **sSPhos**

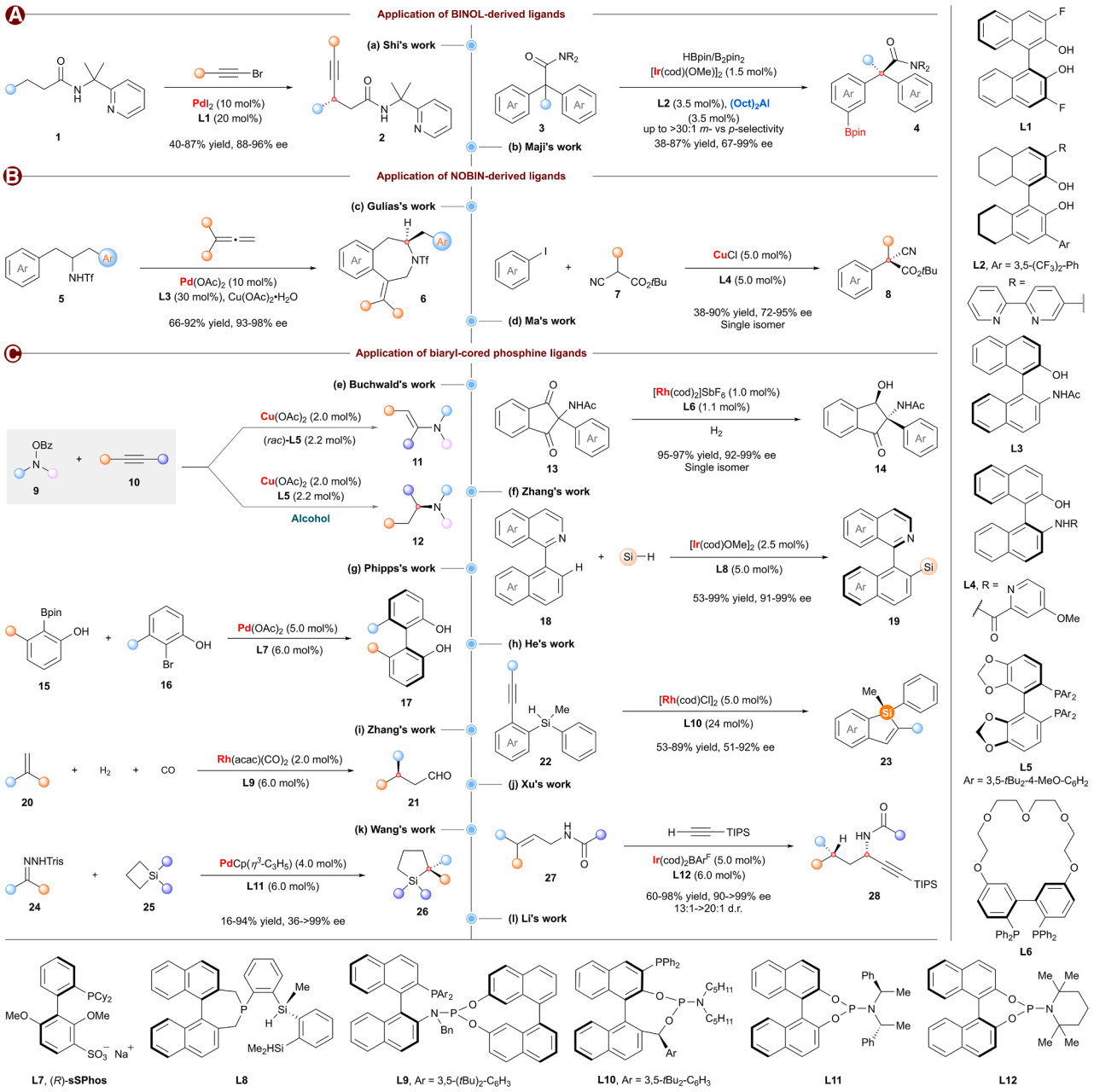


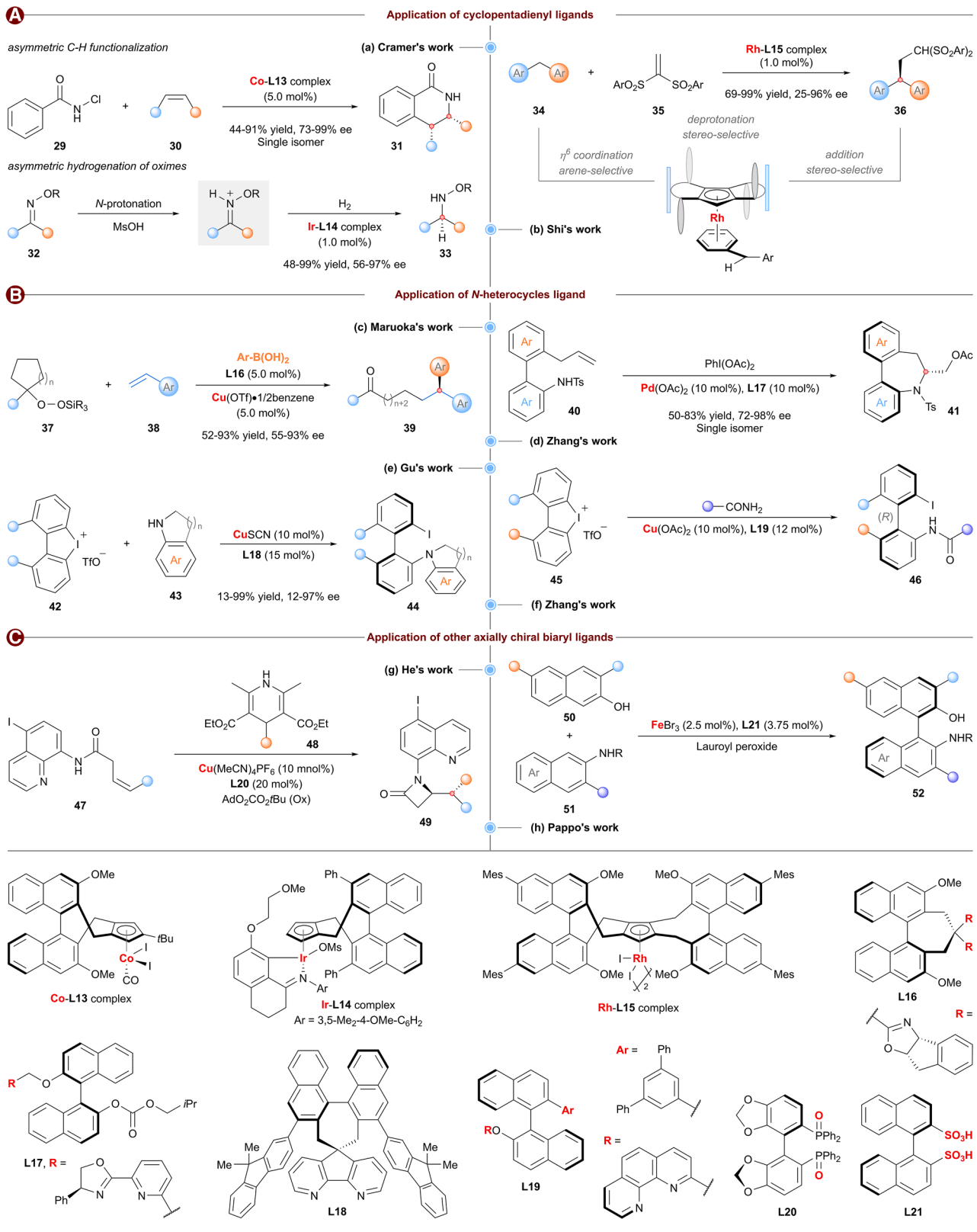
Figure 2. Representative applications of axially chiral biaryl ligands (part 1)

(A) Application of BINOL-derived ligands.

(B) Application of NOBIN-derived ligands.

(C) Application of biaryl-cored phosphine ligands.

(**L7**, sulfonated phosphine ligand), a chiral ligand whose axial chirality was revealed through sulfonation. The sulfonate group facilitates enantiocontrol via non-covalent interactions, such as hydrogen bonding, with phenolic substrates, allowing the direct and modular synthesis of axially chiral 2,2′-biphenol compounds (**17**) (panel 2g).[22] The He group devised a novel chiral PSiSi ligand (**L8**) for iridium-catalyzed atroposelective intermolecular C-H silylation of 2-arylisoquinolines (**18**). Key to this advance is the pincer-type scaffold bearing two Si-H units, which generates a crucial multi-coordinated active species with iridium and thereby exerts precise control over the reactions' chemo-, regio-, and stereoselectivity (panel 2h).[23] In 2018, the Zhang group tackled the long-standing challenge of asymmetric hydroformylation of unfunctionalized 1,1-disubstituted alkenes (**20**) through rational ligand design, creating a novel class of hybrid phosphorus ligands (**L9**) that delivered highly enantioselective



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anti-Markovnikov hydroformylation (panel 2i).[24] Recently, the Xu group described a rhodium-catalyzed dynamic kinetic asymmetric intramolecular hydrosilylation. Using the hybrid phosphine-phosphoramidite ligand SiMOS-Phos (**L10**), which features an axial chirality and a stereocenter, they efficiently converted racemic hydrosilanes (**22**) bearing "silicon-centered" chirality into silicon-stereogenic benzosiloles (**23**) in high yields and with excellent enantiocontrol (panel 2j).[25] Furthermore, an efficient palladium-catalyzed carbene insertion into carbon-silicon bonds. With a phosphoramidite ligand, asymmetric carbene insertion into the Si-C bonds of silacyclobutanes (**25**) furnished silacyclopentanes (**26**) bearing a tri- or tetra-substituted stereocenter in high yields and with excellent enantioselectivity (panel 2k).[26] The ligand has also demonstrated exceptional performance in the Li group's "directing relay" strategy. The work accomplishes 1,3-hydrofunctionalization of unactivated trisubstituted alkenes (**27**) through a three-step catalytic cycle: first, an amide directing group guides the iridium catalyst to activate the C-H bond, forming a π-allyliridium intermediate; next, under ligand control, a hydrogen atom selectively migrates to the γ-position; and finally, an alkyne undergoes regio- and stereoselective addition to the *in situ*-generated alkene, efficiently constructing chiral amines (**28**) containing non-adjacent stereocenters. The system permits stereodivergent synthesis of all four stereoisomers by modulating the ligand and substrate configuration, fully showcasing the precise control capability of phosphoramidite ligands in complex transformations (panel 2l).[27]

A class of C_2-symmetric axially chiral cyclopentadienyl ligands, featuring a unique "sidewall-and-backwall" design, creates a precise steric environment for Rh(III)-catalyzed asymmetric functionalization of C(sp^2)-H bonds, thereby effectively directing enantioselectivity (Figure 3A). This system ingeniously utilizes stable, easily handled Rh(I)-ethylene complexes as precatalysts, which undergo *in situ* oxidation under reaction conditions to generate highly active Rh(III) catalytic species. This strategy has been successfully applied to various transformations, including C-H allylation, carbene insertion, and the construction of axially chiral frameworks, demonstrating excellent enantioselectivity and functional group compatibility.[28] In 2019, the Cramer group extended this system to cobalt-catalyzed asymmetric C-H functionalization. The cobalt catalytic system exhibits excellent enantioselectivity and high regioselectivity, outperforming known rhodium(III)-based systems. Even challenging substrates such as alkyl alkenes (**30**) are well compatible with this system.[29] The following year, they successfully expanded the application scope of this class of ligands through an innovative dual-ligand cooperative catalysis strategy, achieving the challenging asymmetric hydrogenation of oxime compounds (**32**). This catalytic system ingeniously combines an axially chiral Cp ligand with an achiral aryl imine ligand coordinated to an iridium center, forming a structurally rigid cationic cyclometalated Ir(III) complex (Ir-**L14** complex). This design not only precisely controls the stereoselectivity of the hydrogenation process through steric effects but also enables the efficient synthesis of *N*-alkoxy hydroxylamine compounds (**33**) while maintaining N-O bond stability, successfully overcoming the synthetic challenge of balancing the low reactivity of oxime substrates with functional group stability (panel 3a).[30] The Hou group further applied this catalytic system to the scandium-catalyzed asymmetric [3+2] annulation of aldimines with alkenes in 2023. The reaction proceeds via ortho C(sp^2)-H activation, efficiently constructing multisubstituted chiral 1-aminoindanes with high stereoselectivity.[31] In 2024, Shi and co-workers developed a chiral bis(binaphthyl) cyclopentadienyl ligand (Rh-**L15** complex) for achieving rhodium(III)-catalyzed desymmetrization of diarylmethane (**34**) C(sp^3)-H bonds. Unlike previous methods relying on directing groups such as amides or isoquinolines, the key innovation of this study lies in the selective η^6-coordination with one aromatic ring to differentiate between the two similar aryl groups in diarylmethane. To accomplish this, the designed ligand features a "two-petal" chiral pocket that effectively fixes the conformation of the coordinated arene, enabling high enantioselectivity control at the remote benzylic position. This work provides a novel strategy for remote stereocontrol and significantly advances the development of chiral Cp ligands in the field of asymmetric C-H functionalization (panel 3b).[32]

Incorporating nitrogen-containing heterocycles with coordinating ability, such as oxazolines, pyridines, and phenanthrolines, into axially chiral biaryl scaffolds has spawned a series of high-performing ligands (Figure 3B). A copper-catalyzed asymmetric three-component radical relay coupling was disclosed by Maruoka and co-workers in 2020, built on a novel chiral binaphthyl-bis(oxazoline) hybrid ligand (**L16**). This transformation harnesses alkylsilyl peroxides (**37**) as alkyl radical sources and couples vinylarenes (**38**) with arylboronic acids in a highly enantioselective fashion, thereby providing a rapid entry to bioactive chiral 1,1-diarylalkane frameworks (**39**) (panel c).[33] By 2025, the Zhang group had devised a binaphthyl-enhanced pyridine-oxazoline ligand (**L17**), which permitted a highly enantioselective palladium-catalyzed intramolecular 7-exo aminoacetoxylation of unactivated biaryl alkenes (**40**) (panel d).[34] Planar atropochiral bipyridine ligands (**L18**, Y-BiPy) rooted in a chiral binaphthyl scaffold were subsequently introduced by Gu and co-workers. In the copper-catalyzed asymmetric ring-opening of cyclic diaryliodonium salts (**42**) with secondary amines (**43**), this ligand system delivered outstanding results and overcame the poor compatibility and limited stereoselectivity that plagued earlier methods (panel e).[35] A different design logic was pursued by the Zhang group, who embedded phenanthroline into an axially chiral backbone. Judicious tuning of the substituents gave conformationally switchable axially chiral phenanthroline-copper catalysts (**L19**) that promote both highly enantioselective ring-opening alkynylation and amination of cyclic diaryliodonium salts (**45**). These results illuminate the critical role of conformational flexibility

Figure 3. Representative applications of axially chiral biaryl ligands (part 2)

(A) Application of cyclopentadienyl ligands.

(B) Application of N-heterocycles ligand.

(C) Application of other axially chiral biaryl ligands.

in accommodating diverse nucleophilic reaction pathways (panel f).[36]

Besides the aforementioned ligands, in 2021, He and co-workers described a copper-catalyzed enantioselective alkylamination of unactivated internal alkenes (**47**). The method employs an amide-linked aminoquinoline as the directing group and 4-alkyl Hantzsch esters (**48**) as the alkyl radical donors. A biaryl diphosphine oxide (**L20**), serving as the chiral ligand for the first time, delivered highly enantioselective addition of alkyl radicals to the alkene (panel g).[37] In 2022, Pappo and colleagues devised a novel chiral disulfonate iron complex inspired by multi-coordinated $FeCl_3$. Exchanging chloride ions for the chiral bis-anionic ligand BINSA (**L21**) simultaneously installs chirality and preserves multiple coordination sites. Under mild conditions, this catalyst efficiently mediates the asymmetric oxidative cross-coupling between 2-naphthols (**50**) and 2-aminonaphthalene (**51**) derivatives (panel h).[38] Furthermore, chiral phosphoric acid (CPA) and its derivatives are also widely used as ligands in transition-metal-catalyzed reactions, which will not be discussed in detail here.[39]

Axially chiral heteroaryl ligands

While traditional C_2-symmetric biaryl ligands can effectively dictate enantioselectivity, the interactions between the two donor atoms and the metal in the key transition-metal complex intermediates may differ. Therefore, ligand design has gradually shifted toward a desymmetrization strategy, which involves independently modulating different donor atoms to align with the specific requirements of each stage in the catalytic cycle. The most common approach is to retain the π-acceptor functionality of the phosphorus atom while introducing a second donor atom such as nitrogen, realizing differentiated regulation of the electronic and steric properties at the coordination sites and constructing P,N-type hybrid ligands (Figure 4A). Representative ligands like 1-(2-(diphenylphosphanyl)naphthalen-1-yl)isoquinoline (**QUINAP**) and its derivatives, through precise adjustment of heterocyclic basicity and non-covalent interactions, have demonstrated outstanding performance in important asymmetric reactions such as hydroboration and amination. This highlights the significant value of this strategy in enhancing both the functional adaptability of ligands and catalytic efficiency (panel a).[40]

Parallel to the ligand classes described above, axially chiral heteroaryl scaffolds have continued to expand their reach in asymmetric catalysis, yielding remarkable recent advances. A copper catalytic system centered on StackPhos P,N ligands was introduced by Aponick and co-workers in 2024. It realizes the first enantioselective addition of nitrones (**53**) to alkynes (**54**), opening an efficient route to chiral propargylic *N*-hydroxyamines (**55**). Key challenges tackled by this methodology include the inherently low reactivity of nitrones, their propensity for undesired side reactions, and the difficulty of securing enantiocontrol. Later that year, the same copper/StackPhos platform was applied to the enantioselective dearomatization of pyrazines (**56**), delivering efficient and highly selective di-functionalization to furnish a single diastereomer of 2,3-disubstituted dihydropyrazine (**57**). These products serve as intermediates en route to chiral piperazines and C_1-symmetric 1,2-diamine bioactive molecules (panel b).[41,42] In a separate development, the Zheng group devised a family of C_4-symmetric axially chiral porphyrin ligands (**L24**) in 2024. The resulting iridium catalysts permit highly enantioselective carbene C(sp^3)-H insertion reactions. A notable feature of this system is that both regioisomeric iridium complexes direct the formation of the same major enantiomer, suggesting that stereocontrol stems primarily from the chiral environment cast by the porphyrin over both faces of the metal plane, rather than from exchangeable axial ligands.[43] Exploiting this property, the group extended the catalytic platform the following year to the enantioselective alkylation of primary C(sp^3)-H bonds in N-methyl tertiary amines (**61**), thereby circumventing the traditional reliance on deactivating or blocking groups (panel c).[44] This catalyst also exhibited excellent performance in the highly selective cyclopropanation of alkenes.[45]

Moving further into fully heteroaromatic architectures, the complete substitution of the naphthalene rings by heterocycles gives rise to axially chiral biheteroaromatic diphosphine ligands (Figure 4B). This structural alteration concurrently modulates both electronic properties and stereochemical microenvironments (panel d). In benchmark transformations such as hydrogenation and carbon-carbon bond formation, these ligands exhibit superior enantiocontrol relative to conventional BINAPs, substantially broadening the chiral ligand repertoire and furnishing a more powerful platform for molecular design.[46] Zhou and co-workers unveiled a palladium-catalyzed enantioselective C-H functionalization that relies on a novel axially chiral 2,2′-bipyridine ligand (**L25**). Using α-aryl-α-diazoacetates (**64**) as carbene precursors, the reaction site-selectively functionalizes the C3 position of indoles (**63**), marking the first successful deployment of an axially chiral bipyridine ligand in palladium-catalyzed carbene migratory insertion (panel e).[47] The Brückner group devised an atroposelective dibromination driven by ''point-to-axial'' asymmetric induction, which delivered stereodivergent synthesis of enantiomerically enriched 2,2′-biindolyl diphosphine ligands (**L26**). In palladium-catalyzed asymmetric allylations and ruthenium-catalyzed asymmetric hydrogenations, the resulting ligands exhibited excellent enantioselectivities, surpassing the classical BINAP ligand for selected substrates (panel f).[48]

Axially chiral spirocyclic ligands

Beyond biaryl and biheteroaryl systems, axially chiral spirocyclic scaffolds form a privileged ligand class. Their rigid three-dimensional architectures create stable chiral pockets that resist conformational change. Installing coordinating atoms or functional groups onto this platform yields well-defined complexes with metals such as Rh, Ru, and Pd, enabling excellent stereocontrol in asymmetric hydrogenation, cyclization, and coupling. Spiro and biaryl ligands play complementary roles: biaryl ligands offer broad reactivity via synthetic maturity and electronic tunability, while spiro ligands provide uniquely rigid and stable chiral environments for transformations demanding strict catalyst conformations. Together, they expand the asymmetric synthesis toolbox with versatile, reaction-specific design options.

Building on the inherent rigidity of spirocyclic frameworks, two principal strategies guide their further modification and functionalization. The first incorporates coordinating functional groups into the backbone or merges different donor atoms to

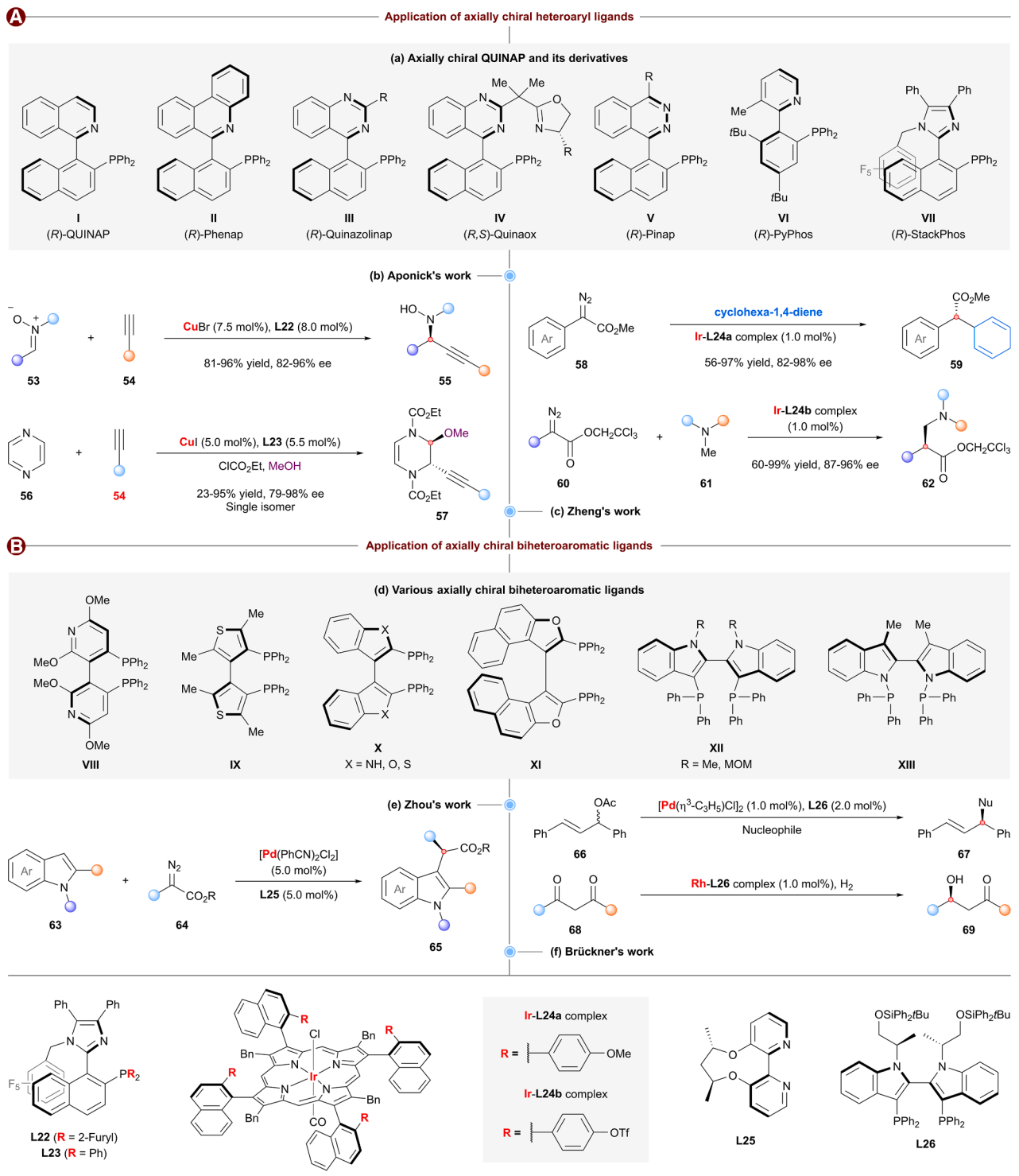

Figure 4. Representative applications of axially chiral heteroaryl ligands

(A) Application of axially chiral heteroaryl ligands.

(B) Application of axially chiral biheteroaromatic ligands.

assemble bifunctional ligands. The second reshapes the spiro core itself by varying ring size and the identity of the aromatic rings, thereby tuning catalytic performance. As novel spiro backbones continue to appear, ligand design and application in this area remain a vigorously progressing field.[49]

Capitalizing on their unique spatial and electronic properties, the first strategy installs coordinating functional groups onto classical axially chiral spiro skeletons to secure exceptional chiral recognition and control (Figure 5A). In 2020, Lassaletta and co-workers described an iridium-catalyzed asymmetric hydroarylation of electron-rich olefins with heterobiaryl (**70**) in which spiro diphosphine ligands (**L27**) delivered excellent performance for acyclic vinyl ethers, affording products with high regio-, diastereo-, and enantioselectivities (panel a).[50] The Zhou group introduced tridentate spirocyclic phosphine-amine-phosphine (**SpiroPNP**) iridium catalysts (**L28**) that tackle the enantioselective hydrogenation of dialkyl ketones (**72**) by overcoming the chiral recognition challenge posed by structurally similar alkyl groups (panel b).[51] A nickel-catalyzed stereoselective multicomponent coupling was devised by Xiao and colleagues for the one-step assembly of polyketide motifs (**76**). Merging an aldehyde, a diene (**75**), and a boronic acid, the transformation simultaneously forges two C-C bonds, controls olefin geometry, and sets two contiguous sp^3 stereocenters with high selectivity. Central to this success is a chiral spiro phosphine-oxazoline ligand (**L29**) that exerts precise chemo-, regio-, and stereocontrol through dual CH-π interactions (panel c).[52]

Spiro phosphoramidite ligands have likewise exhibited outstanding capabilities. In 2024, the Song group disclosed a cavity-size modulation strategy to direct regiodivergent and enantioselective ring expansion of benzosilacyclobutenes with internal alkynes (**77**). Two structurally distinct phosphoramidites steer the reaction through different activation pathways as a function of cavity size. The spiro-based ligand (**L30**) selectively activates the Si-C(sp^2) bond (panel d).[53] Extending this platform, Song subsequently described a nickel-catalyzed asymmetric arylboration of 1,3-cyclohexadiene with aryl iodides (**79**) and bis(pinacolato)diboron. The method effectively suppresses competing Miyaura borylation and Heck reactions, favoring the thermodynamically disfavored 1,4-cis-disubstituted borylated cyclohexene products with excellent regio-, enantio-, and diastereoselectivities (panel e).[54]

Furthermore, spirochiral cyclopentadienyl ligands have also proven capable of enantiocontrol in rhodium-catalyzed asymmetric C-H functionalization reactions. Whereas the construction of axially chiral aryl isoquinolines via C-X functionalization of 1-aryl isoquinolines is relatively mature, You and co-workers recently unveiled a conceptually distinct approach. Using a chiral spiro CpRh(III) catalyst (Rh-**L32** complex), they realized a rhodium-catalyzed asymmetric annulation that builds the isoquinoline ring *de novo* from aromatic imines (**81**) and alkynes through C-H activation (panel f).[55] The Li group constructed two asymmetric rhodium-catalyzed systems around a chiral spiro Cp ligand. In one, *N*-protected *O*-allylhydroxyamines were designed as bifunctional olefin reagents bearing both an amidation unit and a directing group, thereby mediating enantioselective carboamidation with arenes to furnish chiral amino alcohols (**84**) (panel g).[56] On the other hand, the same ligand was tailored for the enantiodivergent construction of C-N axial chirality in isoquinolones via a [3+3] annulation between *N*-alkoxy benzamides (**85**) and imidoyl sulfoxonium ylides (**86**). A striking solvent-controlled enantiodivergence is observed: in CH_2Cl_2, one enantiomer forms with up to 99% ee, whereas switching to HFIP with a Lewis acid produces the opposite enantiomer with up to 91% ee (panel h).[57]

Complementing the installation of coordinating groups on classical spiro skeletons, direct modification of the spiro backbone itself has also witnessed remarkable progress (Figure 5B). Key strategies involve appending substituents to the saturated linker and replacing the phenyl rings with alternative aromatic units. Such modifications fine-tune steric and electronic properties, opening avenues for tackling challenging stereoselective transformations. The spiroketal-based diphosphine (**SKP**) ligands introduced by the Ding group exemplify the modification of the saturated linker. In 2014, this ligand was deployed in the palladium-catalyzed allylic amination of racemic MBH adducts (**88**) with aromatic amines, furnishing β-aryl amino acid esters (**89**) with high efficiency and excellent enantio- and regioselectivities. Mechanistic studies revealed that the **SKP** ligand (**L34**) plays a distinct bifunctional role in the catalytic cycle: one phosphorus atom serves as a Lewis base, forming a C-P σ-bond with the terminal carbon of the MBH adduct, while the other phosphorus atom coordinates to palladium, generating a stable metal-active species. This approach elegantly merges organocatalysis with transition-metal catalysis, establishing a potent synergistic mechanism (panel i).[58] Subsequently, the group prepared monodentate phosphoramidite and tridentate phosphorus-aminopyridine ligands from the same cyclohexyl-fused spirobiindane core. These ligands exhibited catalytic performance on par with classic spirobiindane-based systems in asymmetric hydrogenation, hydroacylation, and [2+2] cycloaddition.[59] In 2018, the Nagorny group disclosed a readily accessible, structurally tunable C_2-symmetric spiroketal-based scaffold that gave access to a family of chiral ligands. The resulting ligands (**L35**) performed excellently across a range of transition-metal-catalyzed asymmetric transformations (panel j).[60] That same year, the Zhang group devised an oxa-spirocyclic scaffold and derived a tridentate ligand, **L36**, which was applied to the iridium-catalyzed asymmetric hydrogenation of Bringmann's lactones (**92**). Using molecular hydrogen as the reductant under mild conditions, this method efficiently afforded axially chiral biaryl diols (**93**) in up to 99% yield with >99% ee (panel k).[61] In 2020, the Wang group unveiled the first synthesis of a chiral spirosilabiindane scaffold through rhodium-catalyzed asymmetric double hydrosilylation. The enantiopure spirosilabiindane diol (SPSiOL) served as a new chiral building block for the monodentate phosphoramidite ligand SPSiPhos (**L37**), which imparted excellent enantioselectivity in rhodium-catalyzed hydrogenations. Notably, in palladium-catalyzed intramolecular carboamination, SPSiPhos surpassed its carbon-centered spirocyclic counterparts and allowed the reaction to run at room temperature.[62] Building on this scaffold, the group later introduced the C_2-symmetric bisoxazoline ligand SPSiBox (**L38**) and employed it in copper-catalyzed asymmetric carbene insertion into Ge-H and Si-H bonds. Mechanistic investigations indicated that the long C-Si

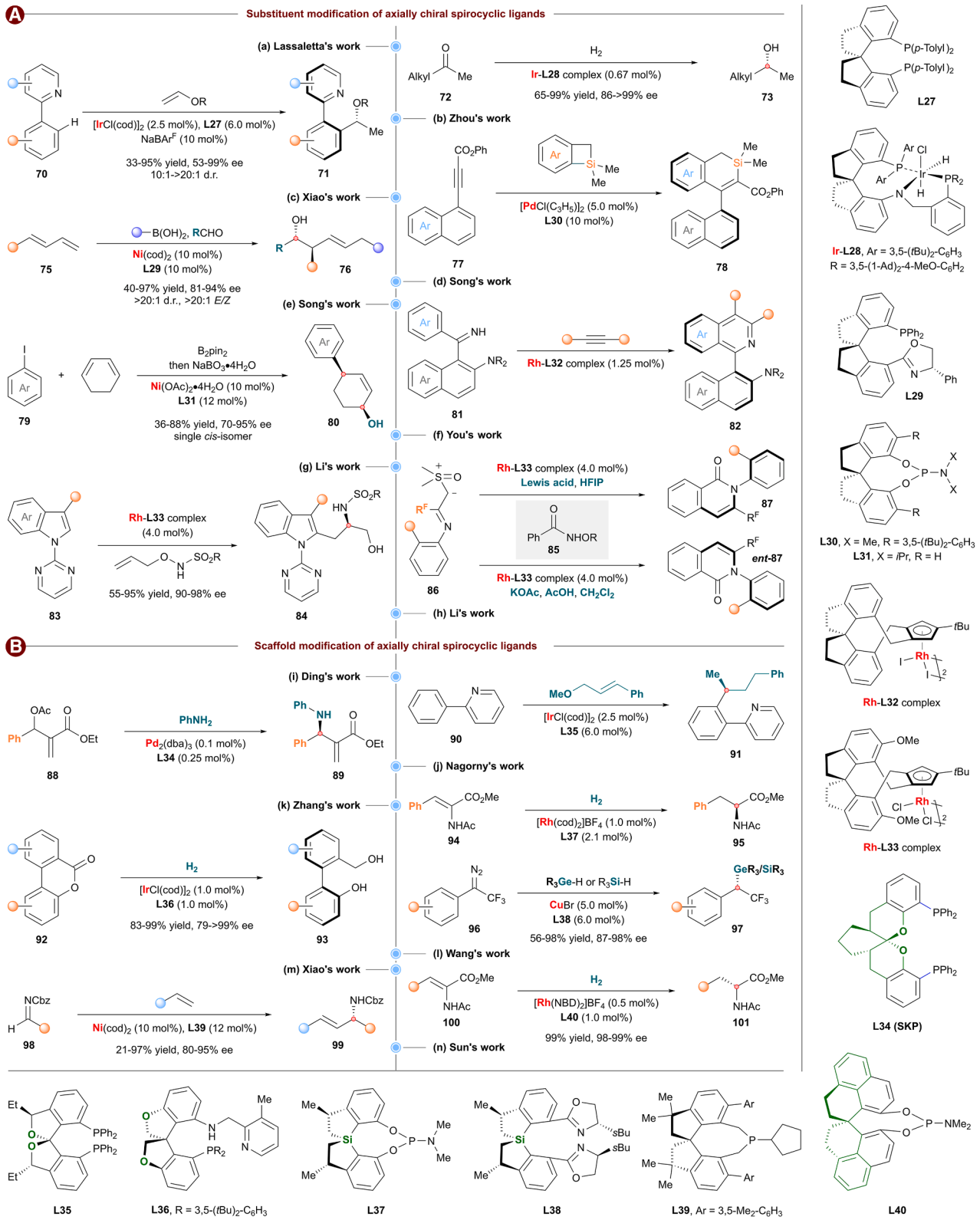

Figure 5. Representative applications of axially chiral spirocyclic ligands

(A) Substituent modification of axially chiral spirocyclic ligands.

(B) Scaffold modification of axially chiral spirocyclic ligands.

bonds and conformational flexibility of the SPSiBox backbone generate a "tunable chiral pocket" that accommodates the differing atomic radii and bond lengths of Ge and Si, a feature essential for securing high enantiocontrol (panel l).[63] The Xiao group developed a new family of C_2-symmetric, electron-rich chiral spiro monophosphine ligands (**L39**) built on a tetramethyl-1,1′-spirobiindane core. These ligands facilitate the nickel-catalyzed direct asymmetric addition of styrenes to aldimines (**98**), providing a highly enantioselective route to chiral allylic amines (**99**) (panel m).[64] More recently, the Sun group and the Tan group independently introduced a structural elaboration strategy that incorporates aromatic units such as 2-naphthol, 2-naphthylamine, and indole into the spirocyclic framework, generating a series of novel chiral ligands and catalysts. In 2021, Sun and co-workers combined the structural merits of BINOL and 2,2',3,3'-tetrahydro-1,1'-spirobi[indene]-7,7'-diol (SPINOL). Starting from commercially available 7-hydroxy-1-naphthaldehyde and employing established spirocyclization protocols, they completed the first efficient synthesis of enantiopure 2,2′,3,3′-tetrahydro-1,1′-spirobi[phenalene]-9,9′-diol (SPHENOL) on a gram scale. In various asymmetric reactions, SPHENOL-derived ligands and catalysts outperformed their BINOL and SPINOL counterparts, delivering superior catalytic activity and enantioselectivity. Structural studies traced this enhancement to a larger dihedral angle and a longer O-O distance in SPHENOL, which augment rigidity and spatial recognition, thereby tightening stereocontrol. For example, using enantiopure SPHENOL to prepare a phosphoramidite ligand (**L40**) for the rhodium-catalyzed asymmetric hydrogenation of enamides (**100**) afforded the corresponding α-amino ester (**101**) in quantitative yields and nearly enantiopure form (panel n).[65] By 2025, the group had further expanded structural diversity by incorporating indole, 2-naphthylamine, and related units into the spirocyclic framework, constructing novel scaffolds such as spiro bisindole (SPINDOLE), 2,2′,3,3′-tetrahydro-1,1′-spirobi-[phenalene]-9,9′-diamine (SPHENAM), and 9′-amino-2,2′,3,3′-tetrahydro-1,1′-spirobi[phenalen]-9-ol (NOSPHEN). The continual emergence of such chiral spirocyclic scaffolds has vastly enriched the structural diversity of chiral catalysts, holding great promise for advancing asymmetric catalytic synthesis.[66–70]

Novel axially chiral skeleton ligands

Beyond modifying existing skeletons, the pursuit of novel axially chiral frameworks has also flourished, offering alternative platforms for ligand and catalyst design. One prominent class consists of axially chiral aryl-alkenes (Figure 6A). In 2018, Yan disclosed an organocatalytic route to axially chiral 1,4-distyryl-2,3-naphthalene diols. When the enantioenriched diol was tested as a ligand (**L41**) in the addition of diethylzinc to an aldehyde (**102**), the enantiocontrol proved modest, yet the study highlighted the scaffold's potential as a chiral template (panel a).[71] In 2019, the Tan group introduced the axially chiral aryl-alkene scaffold EBINOL (1,1′-(ethene-1,1-diyl)binaphthol), distinguished by its non-C_2-symmetric architecture. This design creates a flexible and spatially differentiated chiral pocket that outperformed conventional scaffolds across the reactions examined. Notably, the phosphoramidite diastereomers derived from EBINOL (**L42** and **L43**) exhibit complementary catalytic preferences, one specializing in Rh(I) hydrogenation and the other in Cu(II) conjugate addition, exemplifying a "one scaffold, multiple functions" paradigm that balances generality with specificity (panel b).[72] In 2020, the Shi group devised a Pd-catalyzed asymmetric C-H olefination to access axially chiral aryl-alkenes. The products could be readily converted into chiral carboxylic acids (**L44**) and subsequently served as ligands in Co(III)-catalyzed enantioselective C(sp^3)-H amidation.[73] Later, the same group employed a Pd(II)-catalyzed, thioether-directed alkenyl C-H olefination to construct axially chiral aryl-alkenes bearing a conjugated 1,3-diene skeleton with high efficiency and enantioselectivity. Subsequent oxidation furnished chiral sulfoxide derivatives with strong diastereocontrol, which acted as chiral sulfur-olefin ligands (**L45**) in Rh-catalyzed asymmetric addition (panel c).[74] Recently, the Yu group disclosed the first Ni-catalyzed enantioselective carbo-carboxylation of alkynes with CO_2, providing axially chiral aryl-alkene carboxylic acids. To demonstrate the importance of the obtained aryl alkene carboxylic acids, they tested the catalytic activity of **L46**, which also functions as a chiral carboxylic acid ligand, in the Co-catalyzed asymmetric C-H activation of indoles (**112**) with maleimides (panel d).[75]

Shifting from carbon to heteroatom-linked atropisomerism, C-N and N-N axially chiral compounds represent another rapidly expanding family of frameworks (Figure 6B), alongside C-B axially chiral skeletons that also function as phosphine ligands.[76–79] To date, phosphine ligands built on these scaffolds have been primarily applied in palladium-catalyzed allylic substitution reactions (panel e).[80–85] A significant expansion of these scaffolds' utility came in 2022, when a Rh(III)-catalyzed C-H activation/directing group migration strategy was devised by the Li group to furnish C-N axially chiral acrylamides with high efficiency. These compounds served as chiral additives in a rhodium-catalyzed C-H activation/annulation between sulfoximine (**116**) and diazo compounds (**117**), where effective stereochemical induction was observed.[86] Extending this concept, the same group disclosed in 2024 an enantioselective Buchwald-Hartwig coupling protocol for the direct assembly of C-N axially chiral compounds. The products proved versatile: they could be converted into chiral carboxylic acids or amides to act as additives in C-H activation, or further elaborated into novel chiral phosphine ligands (**L48**). These phosphine ligands displayed catalytic activity in the ruthenium-catalyzed asymmetric addition of phenylboronic acid to aromatic aldehydes (**119**) (panel f).[87] A conceptually distinct approach was introduced by the Kwong group in 2022 with a new class of phosphine ligands featuring C-N axial chirality. The ligand (**L49**) overcame the previous restriction on reaction types for such frameworks and excelled in highly enantioselective Suzuki-Miyaura cross-couplings, delivering tetra-ortho-substituted biaryls with remarkable efficiency. Central to this performance is a carbazole core that permits dynamic interconversion between Pd-N and Pd-π coordination, facilitating a "Pd-arene-walking" process during catalysis. This unique mechanism substantially relieves steric congestion, enabling smooth coupling of bulky substrates. Additionally, a strategically placed 2,6-dimethoxyphenyl unit engages in transient secondary hydrogen bonding with the boronic acid, further tightening enantiocontrol (panel g).[88] Most recently, the Liu group prepared a family of C_2-symmetric N-N atropisomeric diphosphine ligands (**L50**). These ligands

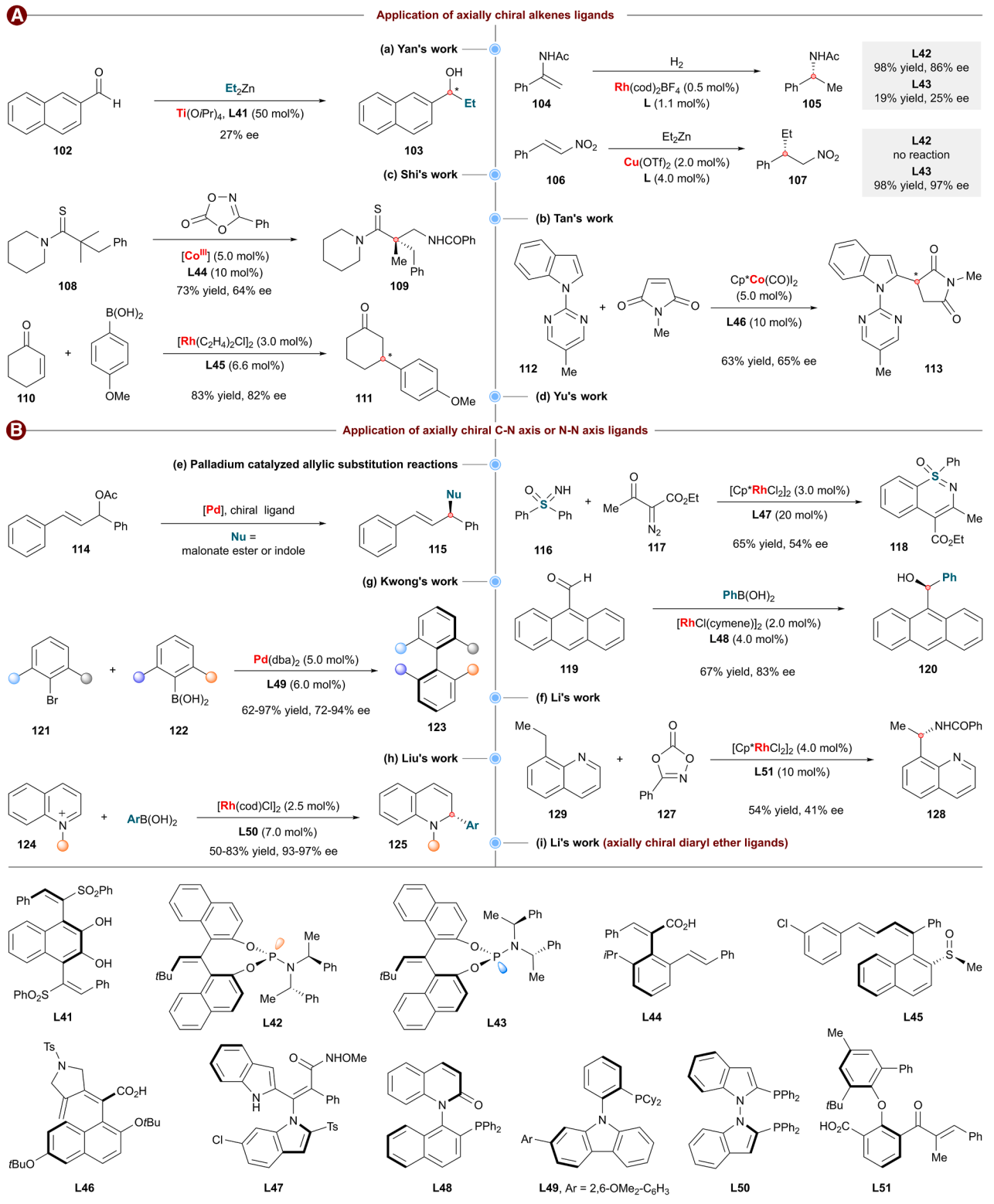

Figure 6. Representative applications of novel axially chiral scaffold ligands

(A) Application of axially chiral alkenes ligands.

(B) Application of axially chiral C-N axis or N-N axis ligands.

exhibited outstanding stereodirecting ability across a range of transition-metal-catalyzed asymmetric transformations (Rh, Pd, Ir, and Ru), including dearomative arylation of pyridinium and quinolinium salts (**124**) and dearomative cyclization of indoles, affording chiral products in high yields with excellent enantioselectivities. Significantly, in the asymmetric hydrogenation of quinolines and ethyl benzoylacetates, they matched or even surpassed the performance of classical BINAP (panel h).[89]

Axially chiral diaryl ethers represent another emerging class of atropisomeric scaffolds.[90,91] Their potential as chiral precursors was first demonstrated by the Zeng group in 2023, who converted them into phosphine ligands for palladium-catalyzed asymmetric allylation reaction, albeit with moderate enantioselectivity.[92,93] In 2024, the Li group transformed their axially chiral diaryl ether product into a chiral carboxylic acid (**L51**), which was then used as a chiral additive in ruthenium-catalyzed C(sp^3)-H amination, again affording the desired products with moderate enantioselectivity (panel i).[94]

APPLICATIONS OF AXIALLY CHIRAL SKELETONS IN ORGANOCATALYSTS

Axial chirality has also found fertile ground in organocatalysis, where axially chiral scaffolds form the core of small-molecule chiral catalysts. The central strategy exploits their rigid and stable chiral microenvironment to activate substrates and dictate transition-state stereochemistry through non-covalent or covalent interactions. These metal-free pathways circumvent issues of precious-metal residues while offering distinct advantages in atom economy and environmental compatibility, thereby serving as a complementary green synthesis tool that occupies a prominent place in modern synthetic methodology.[95]

Axially chiral hydrogen-bonding catalysts

Within this organocatalytic domain, asymmetric hydrogen-bonding catalysis has emerged as a particularly powerful strategy. It relies on directional non-covalent interactions between hydrogen-bond donors (e.g., [thio]ureas and squaramides) and electronegative acceptor sites on substrates (Figure 7). This specific binding plays a dual role: it lowers the activation barrier and positions the substrate in a well-defined spatial orientation dictated by the catalyst's chiral architecture. Axially chiral scaffolds offer unique advantages in this setting, accommodating a wide range of hydrogen-bond donors. The attendant bifunctional catalytic strategy has since become a cornerstone of modern enantioselective organocatalysis (panel a).[96–102]

The urea (thiourea) group functions as a potent hydrogen-bond donor. By activating substrates through dual hydrogen bonding, it has emerged as a privileged motif in hydrogen-bonding catalysis. The classic Takemoto catalyst, for example, uses a central chiral scaffold to achieve bifunctional catalysis through the synergistic action of a thiourea and a tertiary amine. In 2005, the Wang group pioneered the integration of an axially chiral scaffold with thiourea and tertiary amine units. This design furnished highly enantioselective MBH reactions between cyclohexenone and aldehydes, opening new avenues for multifunctional synergistic catalysis.[103] Subsequently, the Barbas group extended this concept to trifunctional catalysts (**C1**) by introducing primary amine groups. These catalysts orchestrated complex domino Michael-Aldol reactions to afford bispirooxindole frameworks (**131**) bearing three quaternary stereocenters, underscoring the capacity of axially chiral thiourea catalysts to assemble highly complex chiral molecules (panel b).[104] Other functional groups, such as alcohols, guanidines, or carboxylic acids, can also activate substrates via hydrogen bonding when incorporated into chiral catalysts. Although most such catalysts rely on centrally chiral scaffolds, numerous examples attest to the excellent enantioselectivity achievable with axially chiral systems. In 2005, the Rawal group first applied axially chiral 1,1′-biaryl-2,2'-dimethanol (BAMOL) to hydrogen-bonding-catalyzed asymmetric hetero-Diels-Alder reactions. Here, the two hydroxyl groups activate aldehydes (**133**) through intermolecular hydrogen bonds. Compared with earlier chiral diols such as TADDOL ((+)-4,5-bis[hydroxy(diphenyl)methyl]-2,2-dimethyl-1,3-dioxolane), the axially chiral skeleton of BAMOL both broadened the substrate scope and dramatically improved stereoselectivity (panel c).[105] The planar symmetry of the guanidine moiety poses a major challenge for its development as a chiral catalyst. Conventional solutions have focused on ring systems with central chirality. Terada group, however, reported a distinct strategy: introducing axially chiral binaphthyl skeleton. By placing aryl substituents at the 3,3′-positions (**C3**), this design effectively disrupts the guanidine's symmetry plane, creating a well-defined and tunable chiral pocket. This innovation successfully enabled the highly asymmetric 1,4-addition of 1,3-dicarbonyl compounds (**135**) to conjugated nitroalkenes (**136**) (panel d).[106] The Ishihara group employed axially chiral 1,1′-binaphthyl-2,2′-disulfonic acid (**C4**, BINSA) as a strong chiral acid core, which was dynamically combined *in situ* with tunable achiral 2,6-diarylpyridine bases. This afforded a class of dynamic acid-base composite salt catalysts whose spatial and electronic properties can be flexibly tuned by simply modifying the base component—an approach that permits precise optimization of both reactivity and enantioselectivity (panel e).[107] Finally, the Maruoka group achieved a highly asymmetric arylation of enecarbamates (**141**) with quinone imine ketals (**142**) using an axially chiral dicarboxylic acid (**C5**) to electrophilically activate the latter. The transformation proceeds via a stereocontrolled nucleophilic addition followed by intramolecular aromatization, delivering the chiral α-amino-β-aryl ether (**143**) in a single step with high yield and excellent stereoselectivity (panel f).[108]

CPAs constitute a prototypical class of hydrogen-bonding catalysts built upon axially chiral scaffolds. A key feature of CPAs is their dual-functional activation mode: the P-OH group functions as a Brønsted acid (hydrogen-bond donor), while the P=O oxygen serves as a strong hydrogen-bond acceptor (Lewis base). This arrangement allows for the simultaneous activation of both electrophiles and nucleophiles, orienting them in a fixed spatial arrangement to deliver high enantioselectivity. In 2004, Akiyama[109] and Terada[110] independently reported CPA catalysts derived from BINOL—a landmark achievement that pioneered the field of chiral Brønsted acid (CBA) catalysis. These catalysts have since become workhorses in asymmetric organic synthesis.

In recent years, CPA catalysts have proven indispensable for addressing synthetic challenges and constructing

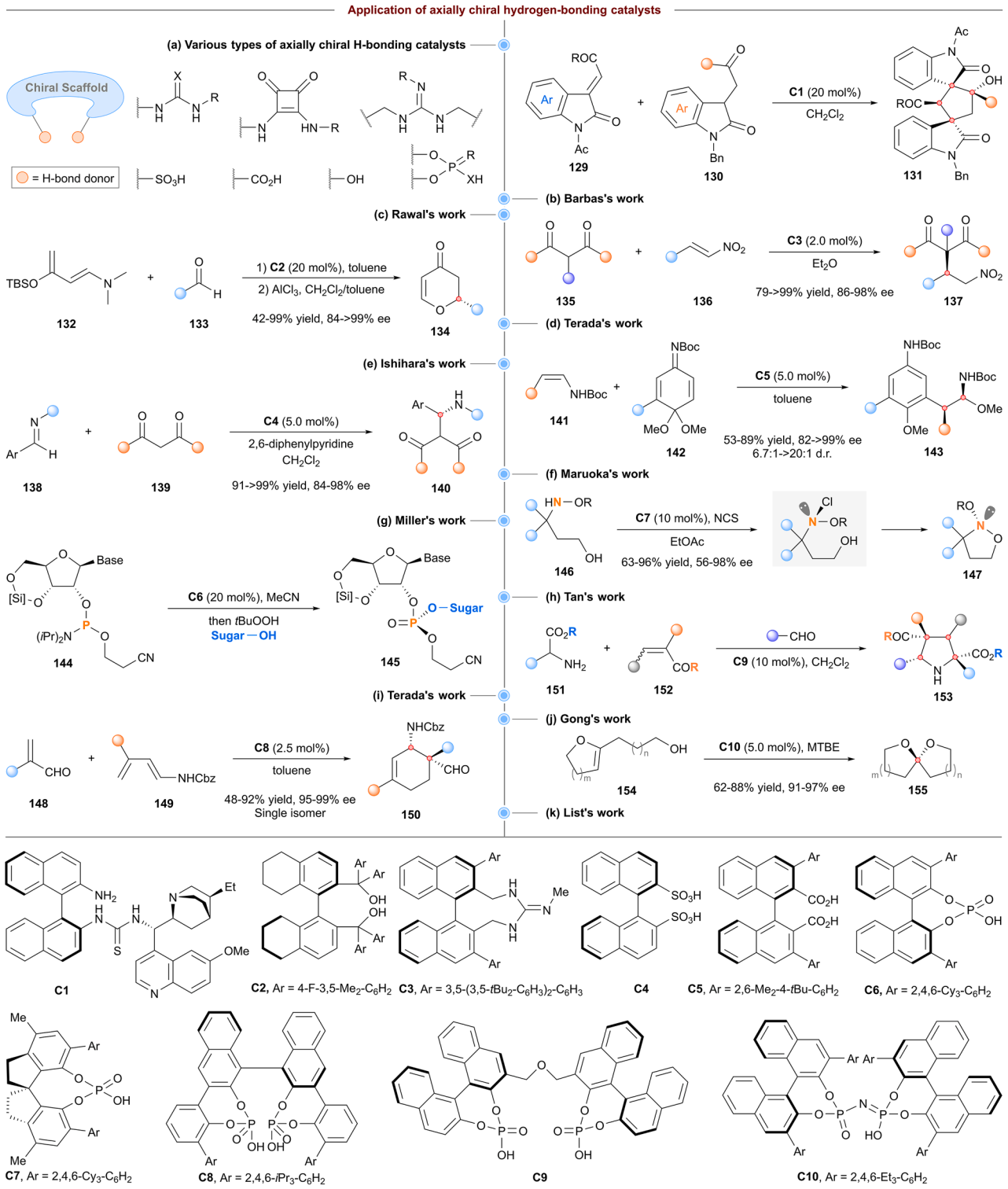

Figure 7. Representative applications of axially chiral hydrogen-bonding catalysts

high-value chiral molecules. In 2021, the Miller group employed a CPA catalyst to achieve precise stereocontrol of phosphorus stereocenters during phosphoramidite transfer. This method enabled the efficient, highly enantioselective synthesis of immunologically important phosphorus-chiral dinucleotides (**145**) without the need for stoichiometric activators or chiral auxiliaries.

The approach uses two structurally distinct CPA catalysts to selectively access each of the two phosphorus stereoisomers. Notably, the catalyst based on the C_2-symmetric BINOL skeleton exhibited remarkable advantages: it completely reversed the inherent stereoselectivity of the substrate and demonstrated the broad applicability and precise control capability of this catalytic framework in the synthesis of complex nucleotides (panel g).[111] The Tan group has achieved notable success in asymmetric synthesis using CPA catalysts. Recently, they addressed a long-standing challenge: the stereocontrol of configurationally unstable pyramidal nitrogen chirality. Through a stereoselective chlorination reaction, a transient *N*-chirogenic intermediate was generated and subsequently captured via intramolecular cyclization, enabling the efficient construction of nitrogen stereocenters (**147**). This strategy, which further enhances configurational stability by incorporating cyclic side chains, is also applicable to the synthesis of chiral *N*-chloroaziridines (panel h).[112]

In addition to monomeric Brønsted acids, the Terada group reported a chiral bis-phosphoric acid (**C8**) bearing a new chiral scaffold with triple axial chirality assisted by intramolecular hydrogen bonding in 2011. The resulting bis-phosphoric acid catalyst exhibited excellent performance in the Diels-Alder reaction of α,β-unsaturated aldehydes (**148**) with 1-*N*-acylamino-1,3-butadienes (**149**) (panel i).[113] In the same year, a new class of binaphthol-derived bis-phosphoric acid (**C9**) organocatalysts was reported by Gong and co-workers. These catalysts enabled the first highly enantioselective 1,3-dipolar cycloaddition of azomethine ylides with various electron-deficient dipolarophiles. The azomethine ylides were generated *in situ* from a wide range of aldehydes and α-amino esters (**151**). The study further revealed that the linker connecting the two BINOL units significantly influenced catalyst performance. The oxygen-linked bis-phosphoric acid catalyst exhibited the best reactivity and stereoselectivity (panel j).[114] In 2012, the List group designed a catalyst (**C10**) based on a C_2-symmetric imidodiphosphoric acid framework, achieved by linking two CBA units. This catalyst features a highly confined chiral microenvironment: its active site is surrounded by sterically bulky groups that form an enzyme-like pocket, enabling the first highly enantioselective spiroacetalization (panel k).[115] Derived from this design, a further developed analog, the chiral imidodiphosphorimidate (IDPi), has since delivered excellent enantioselective control across a range of asymmetric reactions.

The development of novel axially chiral scaffolds has brought various innovative catalytic systems into asymmetric synthesis. The Tan group deployed EBINOL-derived CPAs in the asymmetric addition of indole imines/enamines, where their performance significantly surpassed that of classic BINOL- and SPINOL-based catalysts.[72] The Shi group developed a new class of axially chiral styrene-based thiourea-tertiary amine organocatalysts. Through a concise route, they installed thiourea-tertiary amine functional groups onto an axially chiral styrene scaffold, furnishing catalysts that bear multiple stereogenic centers and activating motifs (hydrogen-bond donors/bases). These catalysts promoted a chemo-, diastereo-, and enantioselective [2+4] cyclization of 2-benzothiazolimines with homophthalic anhydrides, delivering benzothiazole-based chiral frameworks in high yield with excellent stereoselectivity.[116] The Sun group leveraged its self-developed chiral spirocyclic phosphoric acid catalyst to realize the first catalytic enantioselective type II intramolecular [5+2] cycloaddition of oxidopyrylium ylides, efficiently assembling bridged-ring molecules that contain an *anti*-Bredt bridgehead double bond.[117]

Axially chiral ion-pairing catalysts

The stereochemical control of charged species remains a major challenge in asymmetric synthesis, and ion-pair catalysis has emerged as a powerful solution to this problem. This strategy exploits electrostatic attractions between the catalyst and substrate to create tight ion pairs, which allow chirality to be transferred to the reactive site. Axially chiral frameworks serve as effective catalyst cores that deliver precise stereocontrol through ion-pair interactions. Such catalysts have found broad application in both phase-transfer catalysis and counterion-directed catalysis. Their mechanisms generally fall into two categories: one involves direct ion-pair formation with a chiral charged catalyst, while the other relies on non-covalent association between a chiral neutral catalyst and an existing ion pair. Both approaches prove effective in establishing asymmetric induction.[118,119]

A representative example of direct chiral cation catalysis involves chiral quaternary ammonium salts. In early studies, the structural diversity of these catalysts remained largely limited to cinchona alkaloid derivatives. In 1999, the Maruoka group first combined an axially chiral skeleton with a quaternary ammonium center, designing a class of C_2-symmetric phase-transfer catalysts.[120] Subsequent work demonstrated that such axially chiral quaternary ammonium catalysts possess outstanding enantioselective control across various asymmetric reactions (Figure 8A). In 2013, the Maruoka group accomplished the first highly enantioselective synthesis of tetra-substituted chiral allenes (**158**), thereby addressing a long-standing selectivity challenge in this field. The success of this strategy rested on rational substrate design, which allowed smooth γ-deprotonation under phase-transfer conditions to generate a delocalized cumulenolate active intermediate. Meanwhile, precise structural fine-tuning of the catalyst skeleton enabled accurate regulation of enantioselectivity, diastereoselectivity, and regioselectivity (panel a).[121] In 2015, Smith and co-workers further expanded the applicability of such catalysts by realizing a highly enantio- and diastereoselective 5-endo-trig cyclization under asymmetric phase-transfer conditions, efficiently constructing complex indane frameworks (**160**) bearing all-carbon quaternary stereocenters (panel b).[122] Similarly, axially chiral quaternary phosphonium salts are also applicable to asymmetric phase-transfer catalysis reactions.[123,124]

Chiral anion direct catalysis employs axially CBA anions as the enantiocontrol element, representing an asymmetric catalytic strategy in which the anion participates directly (Figure 8B). In a recent representative work, Tan and co-workers reported the direct activation and enantioselective bromination of inert alkene C(sp^2)-H bonds using CPA catalysis (**C13**), forging configurationally stable acyclic axially chiral 1,3-dienes (**162**). The mechanism proceeds via a potassium phosphate salt generated from CPA in the presence of potassium carbonate. This salt undergoes ion

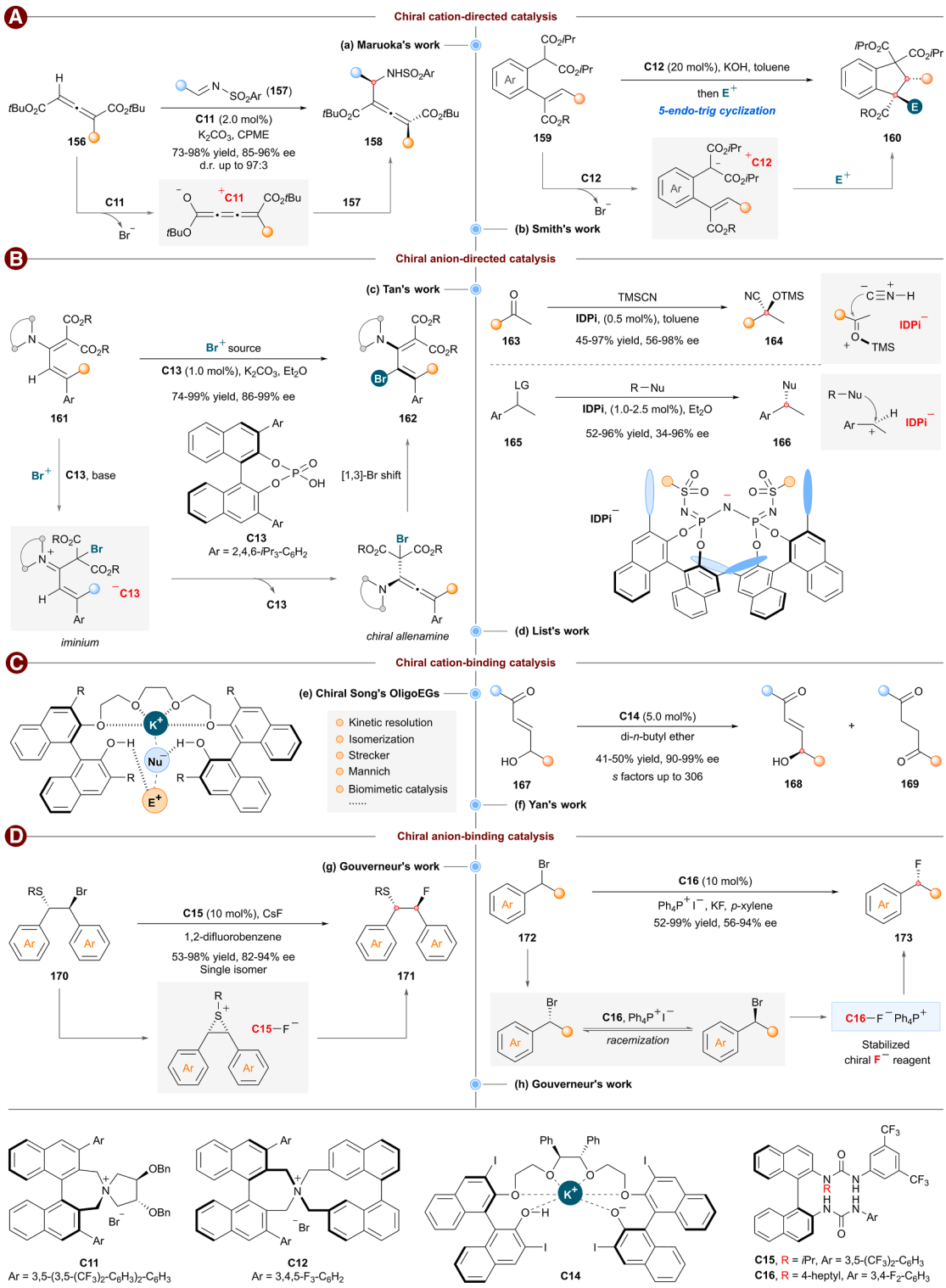

Figure 8. Representative applications of axially chiral scaffolds in ion-pair catalysis

(A) Chiral cation-directed catalysis.

(B) Chiral anion-directed catalysis.

(C) Chiral cation-binding catalysis.

(D) Chiral anion-binding catalysis.

exchange with the brominating reagent to form a tight chiral ion pair. Guided by this ion pair, the bromonium ion preferentially attacks the β-carbon of the enamine, triggering its conversion into an iminium ion and thereby markedly increasing the acidity of the target C–H bond. Because the entire reaction system resides within a chiral environment, the subsequent deprotonation step becomes confined to a specific spatial orientation, leading to a key chiral allenamine intermediate. Finally, an intramolecular [1,3]-bromine migration delivers the target product with high enantioselectivity (panel c).[125] In 2022, List and co-workers introduced a highly acidic, structurally confined IDPi catalyst that overcame a long-standing hurdle: differentiating between methyl and ethyl groups in small ketones such as 2-butanone. The catalyst promoted exceptionally efficient cyanosilylation. During the process, IDPi and TMSCN (trimethylsilyl cyanide) generate an active species *in situ*, converting the ketone into a silyloxycarbenium ion that is paired with a chiral anion. Hydrogen isocyanide is then precisely guided within the chiral cavity to execute an enantioselective attack on this intermediate, furnishing outstanding chiral outcomes.[126] In 2023, the same group extended this concept to tame unstable secondary benzylic cations, thereby delivering a catalytic asymmetric S_N1 reaction. The chiral anion derived from IDPi forms a tight, long-lived ion pair with the carbocation, suppressing deprotonation and other side reactions while providing a precise chiral environment for nucleophilic attack and allowing highly enantioselective construction of C-O, C-N, and C-C bonds (panel d).[127]

In addition to direct catalysis by chiral charged catalysts, another class of neutral catalysts can control selectivity by associating with ion-pair intermediates through non-covalent interactions (Figure 8C). A notable illustration of cation-binding catalysis is BINOL-based oligoethylene glycols (**oligoEGs**) developed by the Song group. By disrupting the cyclic framework of crown ethers, the ether oxygen atoms serve as Lewis bases to coordinate cations, whereas the terminal hydroxyl groups activate electrophiles via hydrogen bonding or modulate anion reactivity, thus realizing synergistic catalysis. This catalyst family exhibits an exceptionally broad reaction scope, including kinetic resolution, enantioselective protonation, Mannich reaction, and tandem cyclization. The utility of this system extends well beyond fluorides to various other alkali metal salts, including cyanides and phthalimide salts. The success of this system stems from a self-assembled, highly confined chiral cage formed *in situ* between the catalyst and the alkali metal salt. This chiral cage facilitates concurrent activation of reactants and efficient transmission of stereochemical information through synergistic cation-binding and hydrogen-bonding interactions. Noteworthily, its mechanism even mimics the allosteric regulation behavior observed in natural enzymes (panel e).[128] For instance, in 2019, the Yan group successfully applied this catalyst to the highly efficient kinetic resolution of racemic allylic alcohols (**167**). The strategy involved deprotonation of one phenolic hydroxyl group on BINOL to form a stable alkoxide species, whose structure was stabilized by a potassium ion, while the remaining phenolic hydroxyl group acted as a hydrogen-bond donor. This design constituted a bifunctional Brønsted base catalyst (**C14**). Mechanistic investigations indicated that deprotonation of the allylic C-H bond represents the rate-determining step, and the hydrogen-bonding interaction between the catalyst and the substrate plays a pivotal role in stereocontrol (panel f).[129]

In 2018, the Gouverneur group disclosed a significant advance in the application of axially chiral urea-based catalysts (**C15** and **C16**), constituting an important use of axial chirality in anion-binding catalysis (Figure 8D). They pioneered a novel strategy termed "hydrogen-bonding phase-transfer catalysis (HB-PTC)." This work tackled a long-standing issue: simple inorganic salts such as cesium fluoride (CsF) exhibit extremely poor solubility in organic solvents, which hinders their utility in enantioselective catalysis. At the core of this strategy was a chiral bis-urea catalyst (**C15**) based on a BINAM scaffold. This catalyst forms a tridentate "urea-fluoride" complex with fluoride ions through multiple hydrogen bonds, rendering the complex soluble in organic solvents. This design ingeniously merges the phase transfer of fluoride ions with chiral reaction control into a single operation. The research team successfully introduced this catalytic system in the asymmetric fluorination of racemic β-bromo sulfides (**170**), efficiently constructing valuable chiral β-fluoro sulfides (**171**) with high selectivity (panel g).[130] However, the aforementioned HB-PTC strategy suffers from systemic limitations. Its implementation depends heavily on "onium-type" electrophiles (such as episulfonium or aziridinium ions generated through substrate pre-design or *in situ* activation), with stereochemical information conveyed primarily via desymmetrization of these intermediates. To overcome this fundamental constraint, the same group unveiled "synergistic HB-PTC" in 2025. The key breakthrough lies in incorporating a second component, a structurally matched inorganic onium salt as a co-catalyst, which works synergistically with the original chiral bis-urea hydrogen-bond donor (**C16**) to form a well-defined, dynamically stable ternary "urea-onium-fluoride" complex with KF. This design decouples the essential phase-transfer function from the substrate structure and integrates it into the catalytic system itself. Consequently, the scope of catalytic fluorination has expanded for the first time from limited onium-type substrates to structurally diverse racemic alkyl halides (such as benzyl bromides (**172**)), permitting highly enantioconvergent fluorination. This strategy also successfully suppresses elimination side reactions induced by the strong basicity of fluoride ions, thereby boosting the reaction's chemoselectivity (panel h).[131]

Axially chiral nucleophilic catalysts

Nucleophilic catalysts comprise a class of catalysts that act as nucleophiles (electron-rich species), accelerating chemical reactions by donating electron pairs to form reversible covalent bonds with electrophilic centers (e.g., carbonyl carbons) in substrate molecules, thereby generating highly reactive intermediates. Compared with purely non-covalent catalysis, the formation of covalent bonds more effectively lowers reaction energy barriers and activates inert substrates. The covalent linkage between catalyst and substrate yields a more rigid transition state, which in turn enables more efficient and reliable chiral induction. This approach also permits the generation of intermediates with novel reactivity, allowing transformations that are difficult to realize through non-covalent catalysis. When an axially chiral framework transitions from merely serving as a "scaffold" for non-covalent interactions to reversibly forming

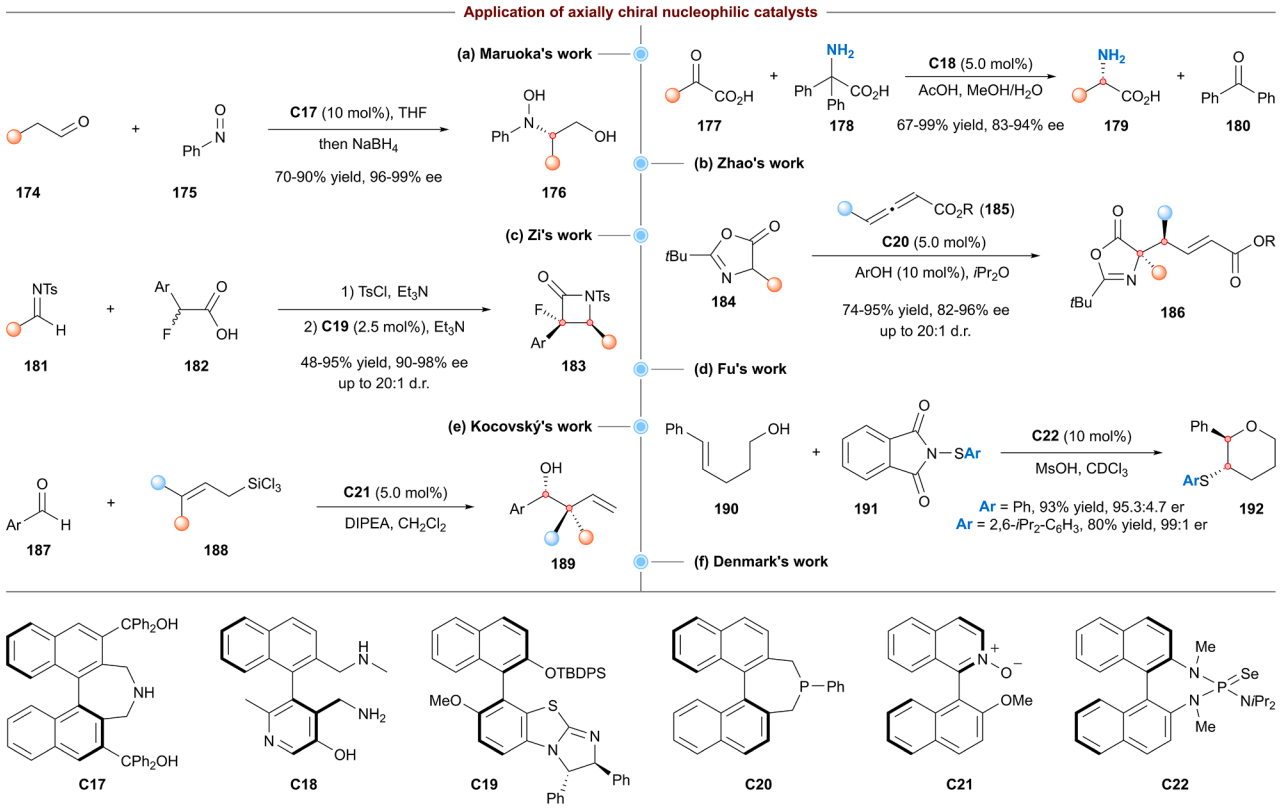

Figure 9. Representative applications of axially chiral nucleophilic catalysts

covalent bonds with substrates via its own nucleophilic sites, this strategy markedly expands the applicability and catalytic capability of axially chiral catalysts (Figure 9).

Chiral amine catalysis represents a classic nucleophilic catalytic strategy. Generally, it involves the formation of a reactive enamine intermediate between the catalyst's amino group and the substrate's carbonyl group, which drives the reaction forward and permits precise control over stereoselectivity. The Maruoka group pioneered the introduction of an axial chirality into catalyst design, developing a novel class of chiral secondary amine catalysts (**C17**) that efficiently delivered direct and highly enantioselective hydroxyamination of aldehydes (**174**) with nitrosobenzene (**175**). Driven by a multifaceted synergistic mechanism, the catalyst uses its secondary amine site to covalently activate the aldehyde and generate an enamine, while a hydroxyl side chain on the scaffold non-covalently orients and activates nitrosobenzene through hydrogen bonding. This integration of covalent activation, non-covalent orientation, and stereocontrol furnishes the reaction with both high enantio- and regioselectivity (panel a).[132] In 2016, inspired by the mechanism of transaminases, the Zhao group designed a class of axially chiral pyridoxamine catalysts (**C18**) featuring an amine group introduced into the side chain of a biaryl scaffold. This design enabled highly efficient and enantioselective biomimetic transamination of α-keto acids (**177**). Upon forming a Schiff base intermediate with the α-keto acid, the catalyst employs its side-chain amine as an intramolecular base to accelerate the rate-limiting 1,3-proton transfer, markedly boosting catalytic activity. Simultaneously, hydrogen bonding between the side chain and the substrate's carboxyl group cooperatively governs the stereoselectivity of the proton-transfer step (panel b).[133] Similarly employing nitrogen atoms in axially chiral frameworks as nucleophilic sites are chiral DMAP derivatives and benzotetramisole (BTM) catalysts. However, while existing catalysts predominantly derive their chirality from central or planar chirality, derivatives based on axially chiral skeletons remain scarcely explored. Recently, Zi and colleagues developed a novel class of axially chiral BTM (**C19**, AxBTM) catalysts that innovatively integrate the conventional BTM unit with a tunable biphenyl-based axially chiral scaffold. Based on this design, the group successfully accomplished the efficient asymmetric synthesis of *cis*-diaryl β-lactams (**183**) containing fluorinated quaternary stereocenters, permitting the precise construction of these high-value molecules with excellent enantioselectivity and diastereoselectivity (panel c).[134]

In nucleophilic catalytic systems, phosphorus and oxygen atoms serve as crucial activation centers alongside nitrogen. Axially chiral phosphines function not only as excellent chiral ligands but also directly as nucleophilic catalysts through modulation of the electronic and steric properties of substituents on the phosphorus atom. This capability permits efficient promotion of various transformations, including asymmetric MBH reactions, as well as [3+2] and [4+2] cyclizations.[135–137] For instance, in 2015, the Fu group employed a phosphine-catalyzed, doubly

stereoconvergent γ-addition reaction to couple racemic heterocycles (**184**) with allenoates (**185**), achieving high enantioselectivity and diastereoselectivity. This approach enabled the synthesis of protected α,α-disubstituted α-amino acid derivatives (**186**) bearing two adjacent stereogenic centers (panel d).[138] On the other hand, axially chiral isoquinoline *N*-oxide derivatives exemplify an oxygen-centered nucleophilic catalysis strategy. In 2008, the Kočovský group accomplished the asymmetric allylation of aromatic aldehydes (**187**) with allyltrichlorosilanes (**188**) using QUINOX (**C21**, 1-(2-(diphenylphosphanyl)naphthalen-1-yl)isoquinoline 2-oxide), an axially chiral isoquinoline *N*-oxide, as the catalyst. The reaction proceeds through a neutral, octahedral silicon transition state (panel e).[139] However, constrained by the strong affinity of oxygen for silicon, current applications of such catalysts remain largely limited to reaction systems that employ silicon-based reagents to deliver excellent enantioselective control.

In 2013, Denmark and co-workers first disclosed a chiral selenophosphoramide catalyst (**C22**) based on a BINAM scaffold. This Lewis base reacts with sulfur-transfer reagents to generate a key sulfenylated selenophosphoramide active species, which subsequently reacts with alkenes (**190**) to form chiral thiiranium ion intermediates. The final products are obtained via backside nucleophilic attack on these intermediates.[140,141] In 2014, the same research group conducted more in-depth investigations into this system and successfully isolated and characterized the crystal structure of the active species. Guided by a thorough understanding of its spatial configuration, they rationally designed more sterically hindered sulfenylating agents (such as 2,6-diisopropylphenyl derivatives), thereby improving the enantioselectivity of the asymmetric sulfenofunctionalization of alkenes from 95.3:4.7 to 99:1 e.r. (panel f).[142] The sulfenylated selenophosphoramide active species was subsequently applied to a broad range of other reaction types.[143–145] In 2022, the Chen group demonstrated that replacing selenium with sulfur in this catalyst also permits analogous catalytic reactions.[146]

Axially chiral electrophilic catalysts

Axially chiral electrophilic catalysts offer a complementary pathway to nucleophilic catalysis for asymmetric synthesis (Figure 10). Their design primarily relies on incorporating electron-deficient centers into the catalyst structure. For example, chiral aldehydes can react directly with amines to generate chiral iminium ion intermediates, while chiral hypervalent iodine reagents undergo pre-oxidation to form highly reactive iodonium species. These activated intermediates, possessing well-defined chiral environments, permit precise enantiocontrol through their rigid scaffolds. A prominent example of this design is the axially chiral pyridoxal-based catalysts (**C23**) developed by the Zhao group. This system accomplishes carbonyl catalysis via *N*-quaternized chiral pyridoxal, efficiently promoting the reaction of *tert*-butyl glycinate (**193**) with various imines (**194**) to synthesize valuable α,β-diamino acid esters (**195**). Mechanistically, the catalyst activates the α-position of *tert*-butyl glycinate through formation of an aldimine intermediate and a delocalized carbanion, while the pendant β-hydroxyamide moiety cooperatively stabilizes the imine substrate via hydrogen bonding, thereby attaining high stereoselectivity (panel a).[147] Subsequently, this catalytic system has been employed for asymmetric α-C(sp^3)-H addition of benzylamines to aldehydes, enantioselective allylic alkylation of α-amino esters, and asymmetric aldol reaction of glycine, among other transformations.[148–150] In the same year, the Guo group developed a chiral aldehyde catalyst (**C24**) based on BINOL, achieving a direct asymmetric conjugate addition-cyclization cascade between glycine esters (**196**) and α,β-unsaturated ketones (**197**). Similar to the catalyst in Zhao's work, this system also exhibits a bifunctional role: the aldehyde group forms an imine with the glycinate to activate the α-carbon, while the adjacent hydroxyl group participates in proton transfer via hydrogen bonding, lowering the energy barrier and synergistically delivering high stereoselectivity control (panel b).[151] Using this catalyst, Guo and co-workers have made significant contributions to the asymmetric α-functionalization of primary amines.[152]

Axially chiral ketones and iminium salt catalysts exhibit excellent enantiocontrol in asymmetric alkene oxidation.[153] In 2023, the Tan group applied axially chiral ketone catalysis (**C25**) to the enantioselective oxidation of isoquinoline nitrogen atoms, providing an efficient method for the kinetic resolution and dynamic kinetic transformation of axially chiral QUINAPO (**199**) and its analogs. The ketone catalyst, in combination with oxone, forms a chiral dioxirane intermediate (**C25-O**) *in situ*, which subsequently governs the enantioselectivity during the nitrogen oxidation process. This research has established a streamlined synthetic route, offering a practical new approach for preparing axially chiral N,P-ligands while markedly expanding the application scope of ketone catalysis in heteroatom asymmetric oxidation (panel c).[154]

Similarly, chiral iodine catalysts play an indispensable role in numerous other asymmetric oxidation reactions by forming key hypervalent iodine intermediates.[155] In 2010, the Ishihara group pioneered a chiral ammonium hypoiodite/iodate catalysis strategy, accomplishing for the first time the highly enantioselective oxidative cycloetherification of ketophenols (**201**) with hydrogen peroxide. This method readily forges biologically active chiral benzofuran scaffolds (**202**). The core innovation lies in using readily available chiral quaternary ammonium iodide salts (**C26**) as pre-catalysts, which react with H_2O_2 *in situ* to generate the active chiral hypoiodite/iodate ion pair. This strategy dispenses with stoichiometric and unstable hypervalent iodine reagents, establishing a new cooperative catalysis mode based on "inorganic iodine/chiral cation." It provides a novel approach for designing green and economical heterocycle synthesis and oxidation catalysis (panel d).[156] For the more challenging asymmetric construction of six-membered chroman scaffolds, the same group successfully addressed the critical issue of facile deactivation of the hypoiodite active species into triiodide by introducing potassium carbonate as a basic additive. This establishes a dynamic equilibrium that permits the reversible regeneration of hypoiodite from triiodide. This optimization reduced the catalyst loading to 0.5 mol%, substantially enhancing both catalytic efficiency and system stability.[157]

Alternatively, Du and colleagues reported in 2013 a strategy that employs chiral dienes (**C27**) as "ligands" to combine *in situ* with the borane catalyst $HB(C_6F_5)_2$, forming chiral frustrated Lewis pairs (FLPs) capable of asymmetric hydrogenation of

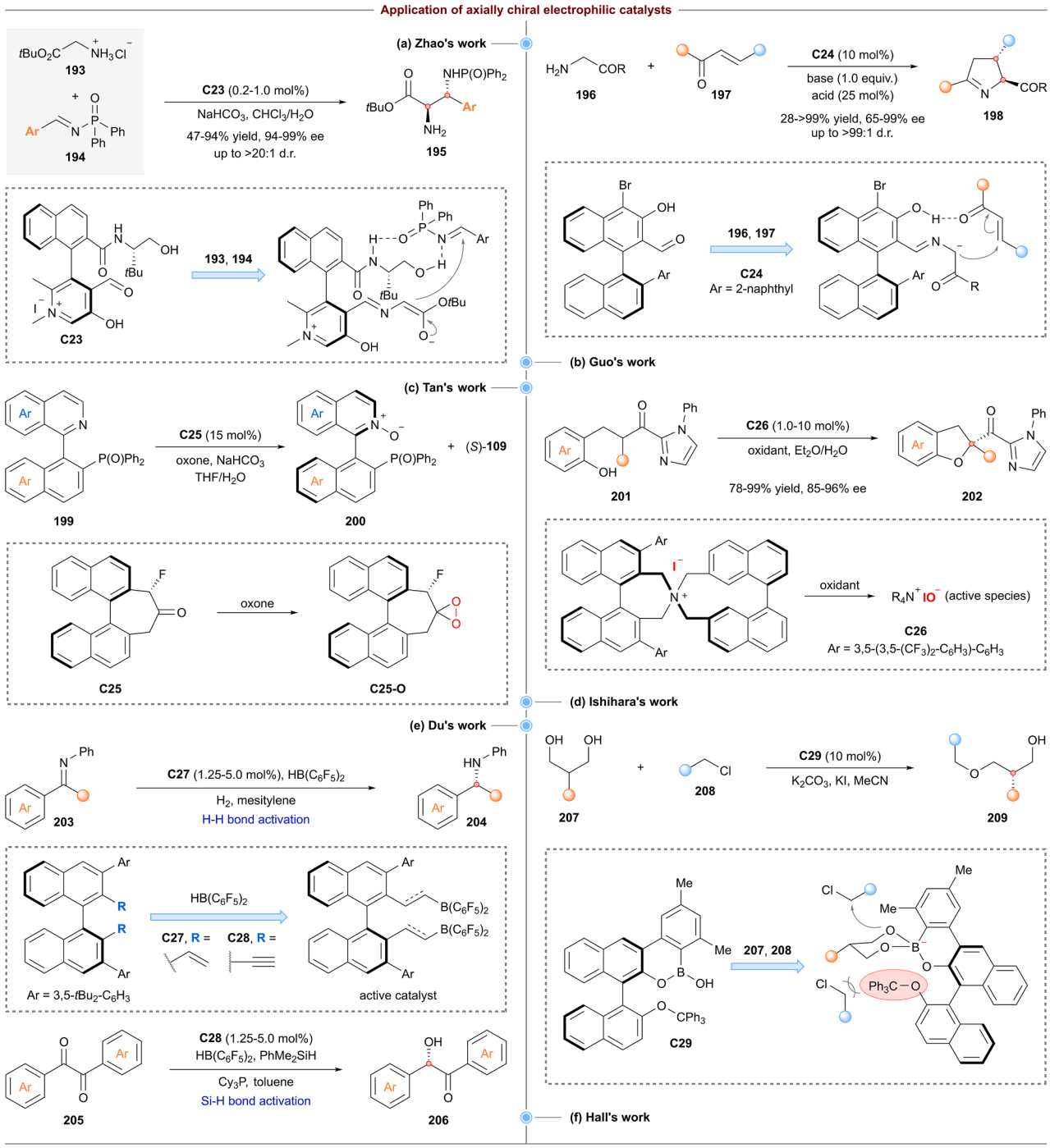

Figure 10. Representative applications of axially chiral electrophilic catalysts

imines (**203**). This system accommodated a variety of aromatic and several alkyl imine substrates, affording chiral amine products (**204**) in high yields with excellent enantioselectivity.[158] In 2016, the same group accomplished the highly efficient asymmetric reduction of 1,2-dicarbonyl compounds (**205**) by generating a chiral alkenylborane *in situ* from a chiral diyne (**C28**) and $HB(C_6F_5)_2$, which subsequently formed an FLP catalyst together with tricyclohexylphosphine (panel e).[159] Similarly, the axially chiral cyclic borane catalyst featuring a binaphthyl scaffold, designed by Oestreich group, exhibits an analogous catalytic effect.[160,161] Additionally, the Hall group devised a stable chiral hemiboronic acid catalyst (**C29**) based on the BINOL scaffold. This catalyst accomplishes highly enantioselective desymmetrization *O*-alkylation of 2-aryl-1,3-propanediol (**207**).

Through the formation of a six-membered anionic boronate complex with the substrate and utilization of a bulky trityl ether group to shield one hydroxyl group, the catalyst differentiates and selectively activates the two enantiotopic hydroxyl groups (panel f).[162]

APPLICATIONS IN ASYMMETRIC ORGANO/TRANSITION-METAL COMBINED CATALYSIS

Asymmetric organo/transition metal combined catalysis (AOMC) merges the respective strengths of metal catalysis and organocatalysis. Metal catalysis activates a broader range of chemical bonds, whereas organocatalysis excels in diversifying functional groups and delivering highly enantioselective transformations. Their combination permits simultaneous activation and reorganization of multiple chemical bonds through synergistic or relay mechanisms, thereby opening new reaction pathways. AOMC centers on pairing compatible chiral transition-metal complexes with small-molecule organocatalysts that function synergistically within a single system. This pairing efficiently converts achiral or racemic substrates into single enantiomers while overcoming limitations in reactivity and selectivity. The strategy operates through three main modes: cooperative catalysis, relay catalysis, and sequential catalysis. In summary, AOMC surpasses the constraints of single systems by integrating dual catalytic modes, activating inert chemical bonds, and attaining precise stereochemical control.[39,163–168] The following section will systematically showcase the specific applications of axially chiral skeletons in AOMC systems through representative cases (Figure 11).

In 2007, the Toste group introduced the ''chiral counterion catalysis'' concept by merging gold catalysts with CPA (**C13**), opening a fresh avenue in asymmetric catalysis. Departing from conventional strategies that tether chiral ligands covalently to the metal center, this approach relies on chiral phosphate anions (**C13-Ag**) to form tight ion pairs with cationic metal catalysts such as gold(I), imparting enantiocontrol through non-covalent interactions. This strategy also exhibits remarkable compatibility and synergistic potential. For demanding substrates where chiral ligands alone or counterions alone are insufficient to yield high enantioselectivity, pairing a chiral ligand with a chiral counterion as a ''matched pair'' constructs a more discriminating chiral environment that markedly strengthens stereochemical control. The pronounced boost in enantioselectivity observed in the hydrocarboxylation reaction attests to the power of this synergistic principle (panel a).[169] The following year, Matsunaga and Yoshino demonstrated that chiral organic anions could effectively govern the enantioselectivity of Cp*Rh(III)-catalyzed C-H functionalization even without chiral Cp ligands.[170]

In 2021, the Hu group designed a ternary cooperative catalytic system (achiral Pd/Rh complexes with a CPA), which for the first time drove a three-component asymmetric allylic alkylation reaction involving α-diazo carbonyl (**214**), allyl carbonates (**215**), and alcohols (**216**). The innovation of this strategy lies in an unprecedented S_N1-type interception mechanism: the palladium catalyst generates an electrophilic π-allylpalladium intermediate, while the rhodium catalyst facilitates the formation of an oxonium ylide that subsequently transforms into a nucleophilic enol intermediate. These two highly reactive, transient species then undergo convergent assembly, thereby providing efficient and highly enantioselective one-step construction of challenging chiral α,α-disubstituted ketones (**217**). Owing to its large bite angle, the Xantphos ligand markedly increases the electrophilicity of the π-allylpalladium species. Enantiocontrol originates from the chiral phosphate anion, which creates a precise chiral environment by forming a tight ion pair with the cationic palladium species and engaging in hydrogen-bonding interactions with the enol intermediate. Beyond offering a concise platform for constructing all-carbon quaternary stereocenters, this work also yields deep mechanistic insight into the power of multicatalyst synergistic catalysis (panel b).[171] A follow-up study in 2022 by the Echavarren group introduced an ''H-bonded counterion-directed catalysis'' strategy, extending the scope of chiral anion methods from traditional gold-catalyzed allene reactions to the more demanding alkyne reactions. The key innovation of this design is the introduction of hydrogen-bond donors onto the ligand (**LAu**Cl), which serves a dual purpose: first, displacing the chiral anion from the gold center via hydrogen bonding to free up coordination sites for alkyne (**218**) activation, and second, precisely positioning the chiral anion near the reaction center for efficient chirality transfer (panel c).[172]

Building on previous work, Zhao and co-workers in 2023 devised a direct enantioconvergent amination strategy based on a ''borrowing hydrogen'' mechanism. Through synergistic catalysis between a chiral iridium complex and a CPA, this system couples racemic secondary alcohols (**220**) with aliphatic primary amines (**221**) with high efficiency and selectivity. The reaction operates via a redox-neutral catalytic cycle, converting inexpensive and readily available feedstocks into valuable chiral aliphatic secondary amines (**222**) in one step without requiring additional stoichiometric oxidants or reductants. Prior borrowing hydrogen-catalyzed aminations had typically been confined to highly reactive aromatic amines or protected amine substrates. Aliphatic primary amines, by contrast, have long presented a dual challenge: low reaction efficiency and poor enantiocontrol. These difficulties stem from their strong basicity, relatively weaker nucleophilicity, and the high reactivity yet poor stability of the resulting imine intermediates, which are prone to side reactions such as overalkylation.[167] The synergistic effect of the dual catalytic system here overcomes these barriers, enhancing the reactivity of aliphatic amines while delivering excellent enantioselectivity. Notably, the method tolerates a broad range of substrates, offering a practical catalytic solution to entrenched selectivity challenges in this transformation (panel d).[173]

Recently, the Zi group devised a palladium/Lewis base (**C32**) synergistic catalytic system that constructs fluorinated quaternary stereocenters (**225**) within acyclic systems with high efficiency and selectivity. By harnessing the synergistic interplay between axially chiral Lewis bases and palladium catalysts, this system addresses two persistent challenges: the low reactivity and pronounced steric hindrance of fluorinated nucleophiles while simultaneously securing precise control over both enantio- and diastereoselectivity. Judicious pairing of Pd/AxBTM combinations bearing complementary stereoconfigurations unlocks stereodivergent synthesis, providing

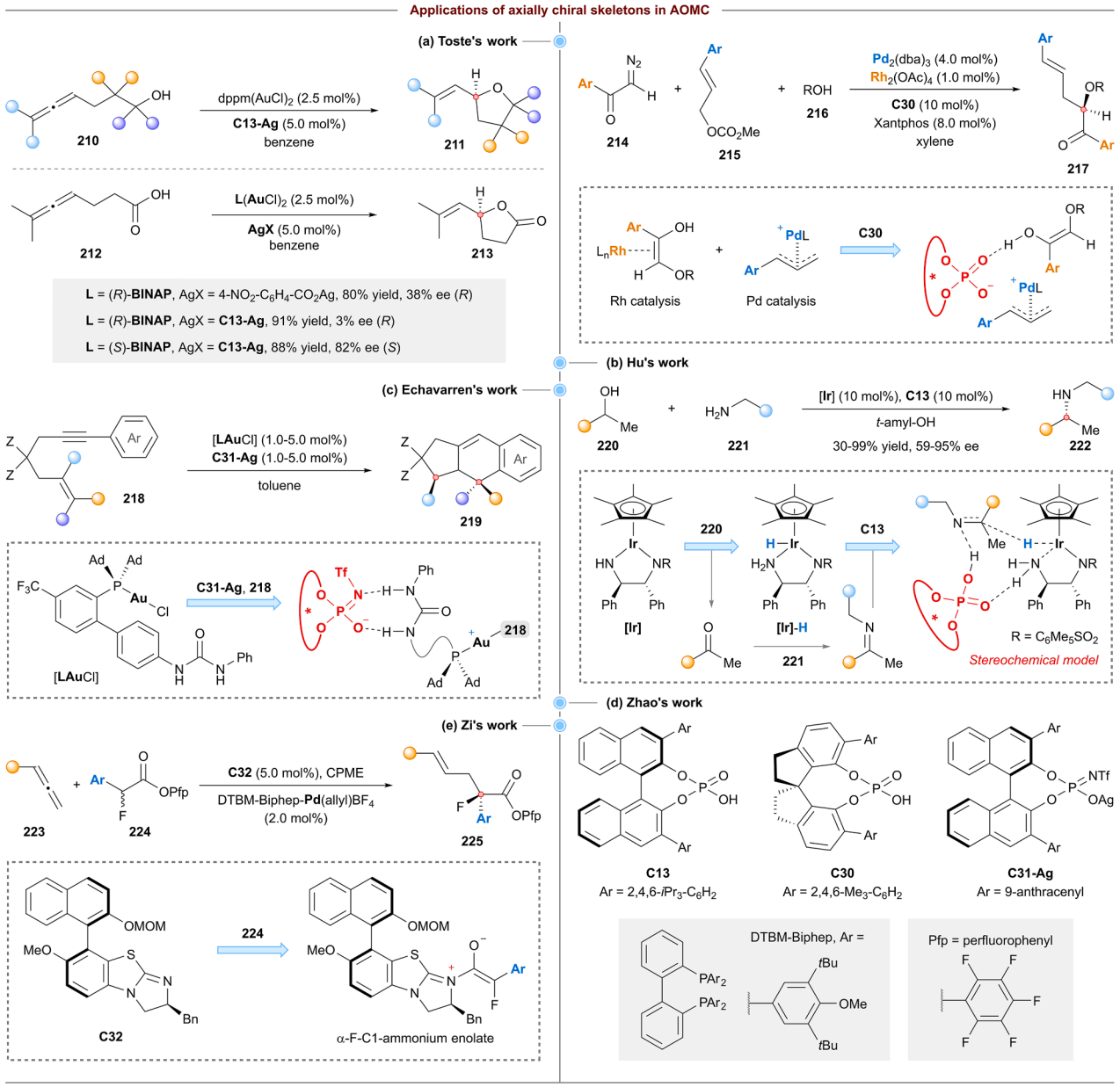

Figure 11. Representative applications of axially chiral skeletons in AOMC

programmable access to all four stereoisomers of fluorinated vicinal stereocenters (panel e).[174]

APPLICATIONS OF AXIALLY CHIRAL SKELETONS IN PHOTOCATALYSIS/ELECTROCATALYSIS

In the emerging fields of photocatalysis and electrocatalysis, axially chiral scaffolds increasingly display unique structural advantages and functional value. Traditional methods often suffer from narrow substrate scope or low chiral induction efficiency. By contrast, axially chiral scaffolds permit various highly selective transformations under photocatalytic or electrocatalytic conditions, including asymmetric hydrogen transfer, cross-coupling, and radical reactions. This approach overcomes many bottlenecks inherent in previous stereocontrol strategies and lays the groundwork for developing more efficient and sustainable asymmetric synthesis methods, driving chiral science into broader application domains (Figure 12).[175–179]

In 2016, Fu and Peters introduced the first visible light-induced enantioconvergent C-N cross-coupling reaction. This work employs earth-abundant copper as a single metal catalyst that functions simultaneously as both a photocatalyst and a chiral catalyst under mild visible light conditions. The system couples racemic tertiary alkyl chlorides (**226**) with amines (**227**) with

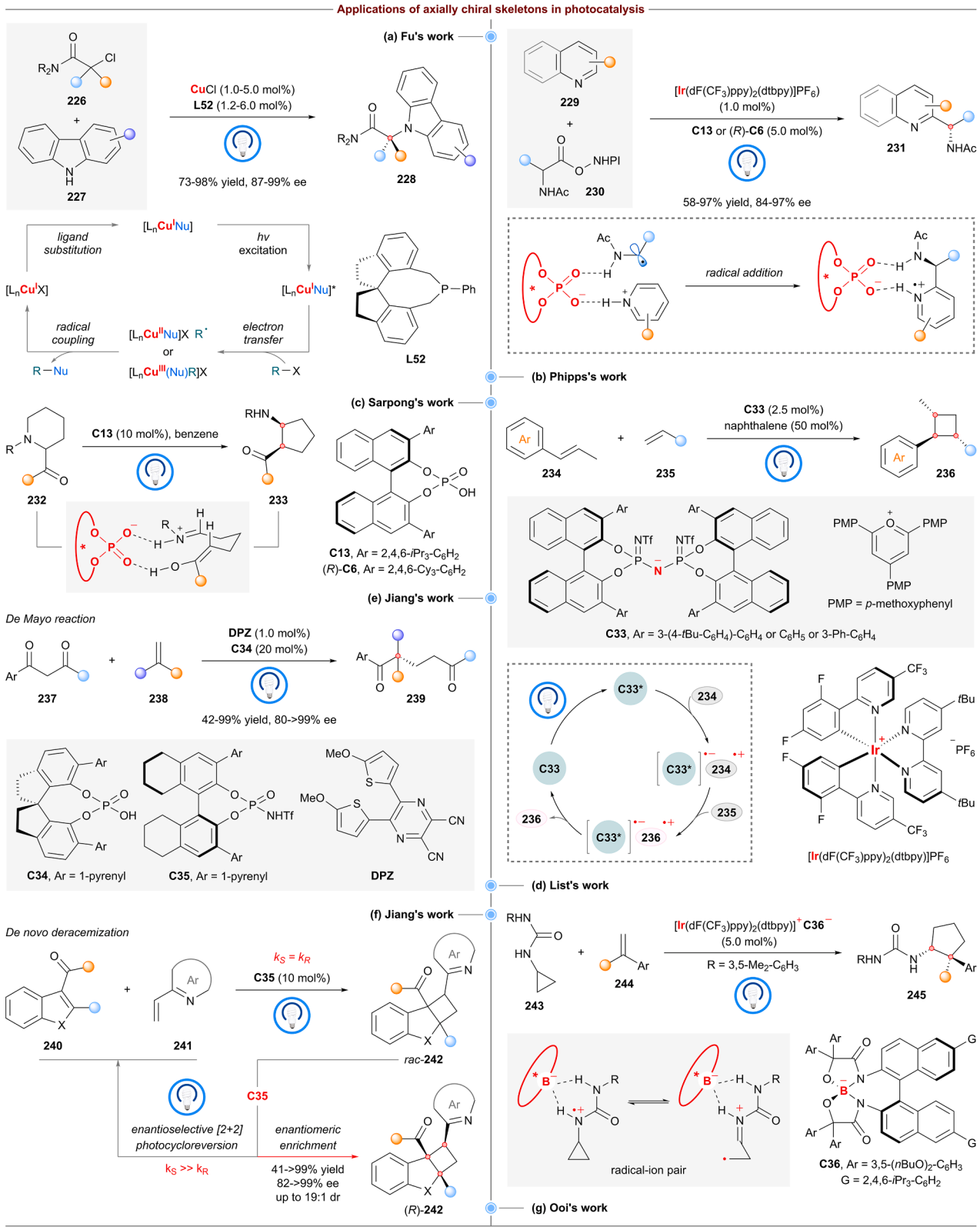

Figure 12. Representative applications of axially chiral skeletons in photocatalysis

high efficiency and enantioselectivity. By leveraging radical intermediates, this strategy overcomes traditional efficiency and selectivity barriers associated with constructing tertiary carbon stereocenters, realizing an ''enantioconvergent'' transformation from racemic starting materials to a single enantiomeric product. The axially chiral spirocyclic ligand (**L52**) cooperates with the copper center to provide effective stereocontrol for the radical coupling (panel a).[180]

Since its introduction in the 1960s, the Minisci reaction has served as a key method for modifying basic nitrogen-containing heterocycles. In 2018, the Phipps group addressed a long-standing challenge in Minisci-type enantiocontrol by merging photoredox catalysis with CPA. Amino acid-derived redox-active esters (**230**) serve as prochiral radical precursors. Under visible light irradiation, they undergo selective C2 functionalization of heterocycles (**229**) to forge stereogenic centers. The CPA (**C13** or (*R*)-**C6**) fulfills a dual role: activating the substrate and imparting enantioselectivity through hydrogen bonding, while the photoredox catalyst precisely governs radical generation and electron transfer (panel b).[181] In 2021, instead of using pre-synthesized redox-active esters, the same group employed readily available linear amides as radical precursors. Through a hydrogen atom transfer (HAT) process, the α-C-H bond of the amide undergoes direct activation to generate an α-aminoalkyl radical, successfully realizing formal oxidative cross-coupling between two C-H bonds of heteroarenes and amides.[182]

In 2021, Sarpong and co-workers developed a visible light-mediated ring contraction strategy for saturated heterocycles (**233**). This method directly restructures the core of various heterocyclic frameworks such as piperidine and morpholine (**232**). The key to this reaction is the Norrish Type II process. Upon photoexcitation, the α-acylated substrate undergoes 1,5-hydrogen atom transfer to generate a diradical intermediate, followed by C-N bond cleavage. The resulting imine enol intermediate then undergoes intramolecular Mannich cyclization, ultimately converting into cyclopentane derivatives bearing a β-aminoketone structure in high yield. This photoreaction system shows good compatibility with CPA catalysts, permitting stereocontrol in the final cyclization step and preliminarily demonstrating the potential of axially chiral catalysts in such photocatalytic skeletal editing applications.[183] Building on this foundation, subsequent in-depth research has rendered highly enantioselective control of this reaction possible with a CPA (panel c).[184] Contemporaneously, the Scheidt group accomplished an analogous transformation by employing a phosphorus-based reagent to activate carboxylic acids through *in situ* conversion to acyl phosphonates.[185]

Traditional asymmetric photoredox catalysis typically employs a dual-cycle strategy combining a ''photoredox cycle'' and a ''chiral catalytic cycle.'' The List group proposed a novel alternative in 2023 termed ''asymmetric counteranion-directed photoredox catalysis.'' Unlike traditional complex systems, this approach uses a confined chiral IDPi anion as the stereocontrol source. This anion forms a chiral ion pair with cationic photoredox catalysts (**C33**), permitting efficient enantiocontrol within a single photoredox cycle. The group demonstrated this concept in the intermolecular [2+2] cycloaddition of styrenes (**235**) with *trans* anethole derivatives (**234**). Remarkably, when the same IDPi anion was paired with various structurally distinct cationic photocatalysts, including pyrylium salts, acridinium salts, and ruthenium complexes, and irradiated at different wavelengths, the reaction consistently delivered the same high enantioselectivity. This finding directly proves that the stereocontrol originates from the anion itself, highlighting the generality and core advantage of this strategy (panel d).[186] 2 years later, the same group extended this strategy to an organocatalytic cyclopropanation, delivering the first highly enantioselective cyclopropanation of unactivated alkenes.[187]

The Jiang group has also conducted extensive research in the field of photoredox catalysis using CPAs. In 2024, they devised a dual catalytic system based on ''sensitization-initiated electron transfer'' for an asymmetric photocatalytic formal de Mayo reaction. This system uses dicyanopyrazine (**DPZ**) as the photosensitizer, working in synergy with a pyrene-functionalized CPA (**C35**). Through an excitation mechanism involving two photons and a Dexter energy transfer process, a pyrene radical anion with exceptionally strong reducing power is generated *in situ*, overcoming the thermodynamic limitations of traditional photocatalysis. This strategy merges efficient redox processes with precise stereocontrol. The CPA not only guides enantioselectivity via hydrogen bonding, but its pyrene moiety also acts as a co-sensitization center, ensuring that all key steps occur within the chiral environment. This work surpasses the reliance on the capabilities of a single photosensitizer, opening a new direction for developing challenging asymmetric photocatalytic reactions previously considered ''thermodynamically forbidden'' (panel e).[188] In the same year, the group also introduced a photochemical strategy termed ''*de novo* deracemization synthesis'' for constructing cyclobutane derivatives (**242**) bearing multiple stereocenters with high efficiency and enantioselectivity. Under light irradiation, these simple and readily available substrates undergo a reversible [2+2] photocycloaddition and photocycloreversion process, enabling dynamic kinetic resolution and deracemization. The key to this approach is the utilization of a CPA catalyst (**C35**) containing a pyrenyl group. This catalyst binds to the cyclobutane intermediate via hydrogen bonding, inducing a red shift effect that lowers the excitation energy. It also permits kinetic differentiation between the two enantiomers during the photocycloreversion step, thereby driving the reaction toward the enrichment of a single enantiomer (panel f).[189]

In addition to CPAs, the Ooi group introduced a visible light-induced, highly enantioselective, and diastereoselective [3+2] cycloaddition reaction. This work uses urea simultaneously as both a redox-active group and an anion-binding directing group. Employing an iridium complex chiral borate ion pair ([**Ir**(dF(CF$_3$)ppy)$_2$(dtbpy)]$^+$**C36**$^-$) as the photocatalyst, the team successfully realized the asymmetric cyclization of *N*-cyclopropylurea (**243**) with α-alkylstyrenes (**244**). The key to success is the pre-association of the urea group in the substrate with the chiral borate anion in the catalyst via hydrogen bonding, forming a supramolecular assembly. Upon light irradiation, the excited iridium cation undergoes single-electron transfer from the cyclopropylurea, forming a radical cation pair. This intermediate subsequently undergoes cycloaddition with the alkene within the stereochemical environment imparted by the closely associated chiral anion, thereby forging an aminocyclopentane skeleton

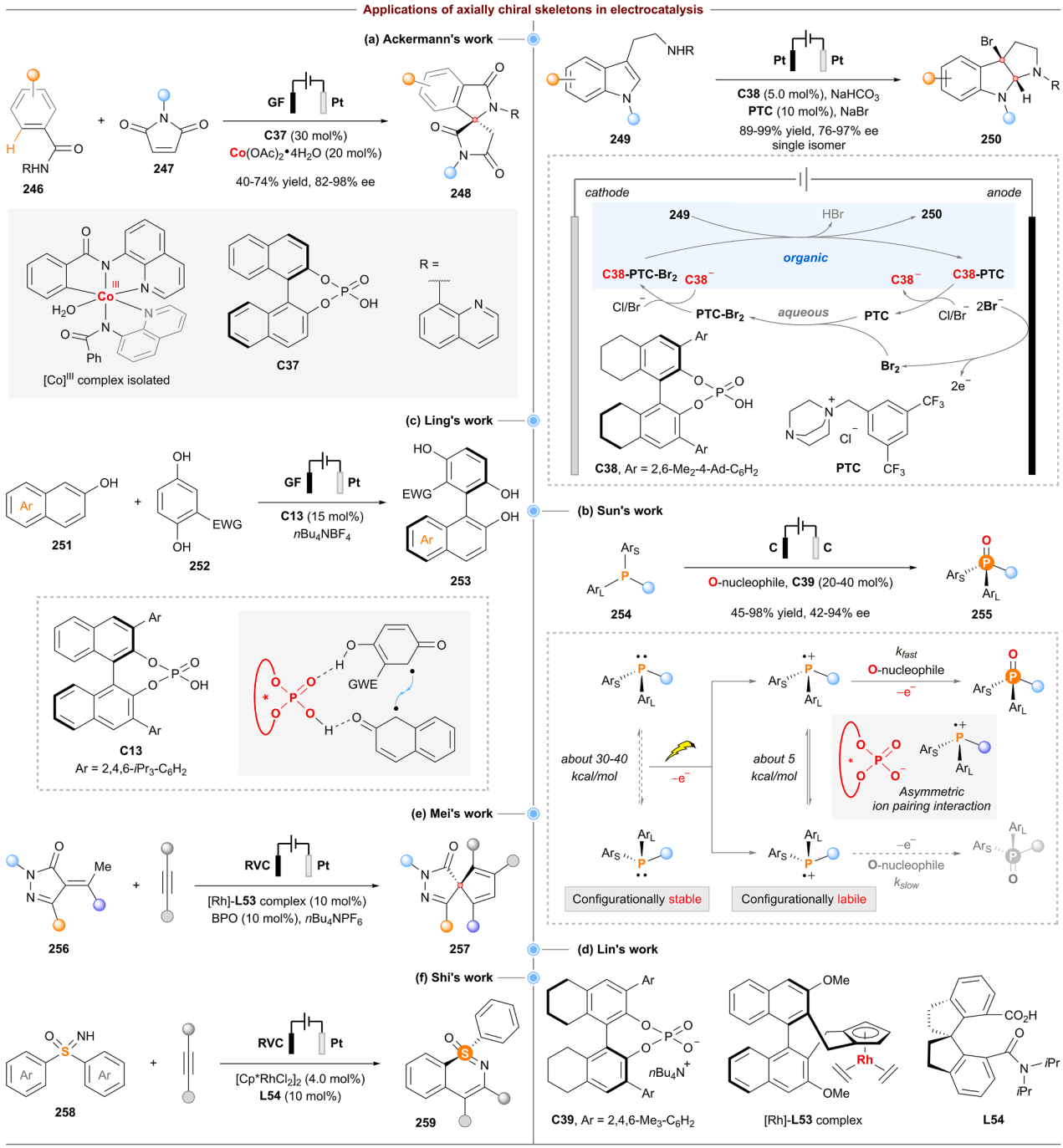

Figure 13. Representative applications of axially chiral skeletons in electrocatalysis

(**245**) bearing contiguous tertiary and quaternary stereocenters with high selectivity (panel g).[190]

The significance of axially chiral skeletons extends from photocatalysis to electrocatalysis (Figure 13). In 2023, the Ackermann group devised a sustainable enantioselective electrocatalytic strategy. This approach uses an inexpensive cobalt catalyst to replace precious metals, drives aryl (**246**) C-H activation via anodic oxidation, and couples this process with the cathodic hydrogen evolution reaction (HER), offering a green synthesis where hydrogen is the only byproduct. In this system, a CPA (**C37**) serves as the key ligand, directly coordinating to the cobalt center to construct a chiral environment, thereby precisely guiding the enantioselective C-H activation and cyclization of prochiral substrates (panel a).[191]

In 2023, the Sun group devised an electricity-driven asymmetric bromocyclization through the synergistic effect of chiral phosphate anions (**C38**) and phase-transfer catalysis (**PTC**). This study features a biphasic system that overcomes interference from electrolytes and polar solvents on weak ion-pair interactions. The pathway proceeds as follows: anodic oxidation of NaBr generates Br_2, which then combines with a phase-transfer catalyst to form a cationic species. This cation migrates to the interface of the two phases, where it undergoes anion exchange with chiral phosphate anions, forming a lipid-soluble ion pair, **C38-PTC-Br$_2$**, which transfers into the organic phase. There, this ion pair precisely induces highly enantioselective bromocyclization of the substrate. The addition of $NaHCO_3$ to the system was critical for maintaining alkalinity and suppressing Br_2 decomposition. This strategy offers a new design approach for electrochemical asymmetric catalysis, particularly for processes that depend on weak interactions (panel b).[192]

The Ling group developed an organo-electro-catalyzed strategy for the highly enantioselective synthesis of non-C_2-symmetric biaryldiols (**253**). Under mild electrochemical conditions, this method uses direct dehydrogenative cross-coupling of two phenolic derivatives, affording the product with up to 95% yield and 97% ee. The reaction process proceeds as follows: the two phenol substrates (**251** and **252**) undergo sequential oxidation at the anode to generate phenoxyl radicals, which then isomerize. Subsequently, under the hydrogen bonding control of **C13**, an asymmetric biradical cross-coupling takes place. The resulting centrally chiral intermediate undergoes dynamic transformation, ultimately constructing the axially chiral biaryldiol skeleton. This approach avoids over oxidation and overcomes the limitations of traditional nucleophilic addition pathways, offering a new strategy for the green and precise synthesis of axially chiral molecules (panel c).[193] The group also accomplished the asymmetric coupling between indoles and *p*-aminophenol using an analogous strategy.[194]

Recently, the Lin group developed an electrochemical strategy based on chiral supporting electrolytes (**C39**), realizing the dynamic kinetic resolution of trivalent phosphines (**254**) and producing phosphine oxides (**255**) with high enantiopurity. Traditional methods often require stoichiometric chiral alcohols and hazardous reagents while offering limited enantioselectivity. By contrast, this strategy uses electrochemical single-electron oxidation of racemic phosphines to generate highly configurationally unstable phosphoniumyl radical cations. These cations form tight ion pairs with chiral phosphate anions at the electrode interface, permitting precise enantiocontrol during the nucleophilic attack step. This work offers an innovative approach to direct asymmetric electrosynthesis without external chiral catalysts, demonstrating good synthetic applicability and reaction sustainability (panel d).[195] In the same year, the Jiang group accomplished a similar transformation using photocatalysis in combination with a CPA.[196]

In addition to CPAs, axially chiral ligands also find applications in asymmetric electrocatalysis, where electrical current primarily serves as a green oxidant. The Mei group developed an electrochemically driven rhodium ([Rh]-**L53** complex)-catalyzed enantioselective C-H/alkyne annulation strategy, which efficiently synthesizes spiropyrazolone-type compounds (**257**). In this reaction, electrical current replaces stoichiometric oxidants, enabling the oxidative dehydrogenative spiroannulation between α-arylidene pyrazolones (**256**) and alkynes. Anodic oxidation promotes the key reductive elimination step in the catalytic cycle, thereby efficiently driving the reaction under mild conditions (panel e).[197]

The Shi group developed an electrochemical enantioselective C-H alkyne annulation strategy based on cooperative catalysis between an achiral Rh(III) complex and a chiral carboxylic acid (**L54**). Using electrical current as the oxidant, the reaction performs selective annulation between sulfoximines (**258**) and alkynes, producing a series of biologically active chiral 1,2 benzothiazines (**259**). This method avoids the high temperatures required by conventional stoichiometric metal oxidants and eliminates potential competition between their anions and chiral ligands for coordination. Enantiocontrol originates from a spirocyclic chiral carboxylic acid ligand through synergistic non-covalent interactions, including dynamic coordination and hydrogen bonding (panel f).[198]

Conclusion and outlook

Axially chiral skeletons have become indispensable in asymmetric catalysis due to their unique spatial configurations, finely tunable electronic properties, and exceptional structural diversity. From classical biaryl frameworks to rigid spirocyclic skeletons, from heteroaromatic architectures to newly emerging axially chiral systems, these molecules perform with distinction across metal complex catalysis, organocatalysis, and multimode cooperative systems. Early representatives such as BINOL and BINAP established the fundamental design principles for chiral ligands. Spirocyclic skeletons later elevated stereocontrol precision and catalyst stability through their remarkable conformational rigidity. More recently, heteroaromatic, aryl alkene, and C-N axially chiral systems have expanded the synthetic "chiral toolbox," broadening reaction scope through diverse coordination modes and electronic effects. Beyond their role as ligands, axially chiral skeletons also serve as organocatalysts. Through non-covalent interactions such as hydrogen bonding, ion pairing, and π-stacking, they fine-tune stereochemistry with precision. Through covalent interactions, they construct unique chiral microenvironments across both nucleophilic and electrophilic pathways. Their application has extended from classical hydrogenation and cycloaddition to cutting-edge domains, including enantioselective C-H functionalization, radical stereocontrol, and molecular skeleton editing. Remarkably, in the emerging arenas of photocatalysis and electrocatalysis, axially chiral catalysts enable effective stereocontrol over highly reactive radical intermediates, circumventing conventional thermodynamic and kinetic barriers. This progress resolves a persistent challenge, namely enantiocontrol in radical chemistry, and heralds a new paradigm: multimode synergistic, green, and precise synthesis.

Future research will focus on deeper mechanistic understanding and function-oriented precision design. Advances in computation and characterization are illuminating transition-state interactions, shifting catalyst development from empirical screening to rational design. For any challenging reaction, mechanistic insight enables strategic installation of functional groups for directional non-covalent interactions. The emergence of

novel skeletons offers a richer structural palette, while AI coupled with high-throughput screening promises a shift from trial to rational prediction, accelerating catalyst discovery.

Under photo- or electrochemical conditions, axially chiral molecules act as both ligands and catalysts, enabling selective control over reactive intermediates. The central challenge is achieving precise stereochemical control while managing energy input. Promising strategies include designing redox- or photoactive axially chiral catalysts and developing chiral electrolytes or chirally modified electrodes to maintain a persistent chiral microenvironment. This integrated approach elegantly links energy input to asymmetric synthesis.

To bridge lab research and industrial synthesis, axially chiral catalysis must advance toward green, practical development. Priorities include recyclable, low-loading systems, which require efficient synthetic methods to rapidly construct diverse molecular libraries, reducing cost and step count. Catalyst recovery can be achieved via immobilization on polymers, magnetic nanoparticles, or MOFs (metal-organic framework). Process innovations such as continuous flow chemistry enable precise, low-cost, high-efficiency synthesis. Through full-chain optimization, axially chiral catalysis can address the large-scale green synthesis of pharmaceutical intermediates and functional materials.

In summary, research on axially chiral skeletons is entering a new phase defined by precision design, intelligent technologies, and interdisciplinary integration. Future development will emphasize modular and intelligent chiral catalytic platforms. Through deep integration of artificial intelligence predictions and sustainable processes, axially chiral catalytic systems can deliver precise, programmable synthesis of complex functional molecules. This advancement will propel chiral science from the laboratory to industrial production, overcoming persistent bottlenecks in constructing high-value chiral molecules for pharmaceuticals, materials, and other critical fields.

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AUTHOR CONTRIBUTIONS

Conceptualization, B.T. and J.W.; writing – original draft, P.-Y.J., S.W., S.-H.X., and B.T. All authors were involved in the discussion and review of the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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