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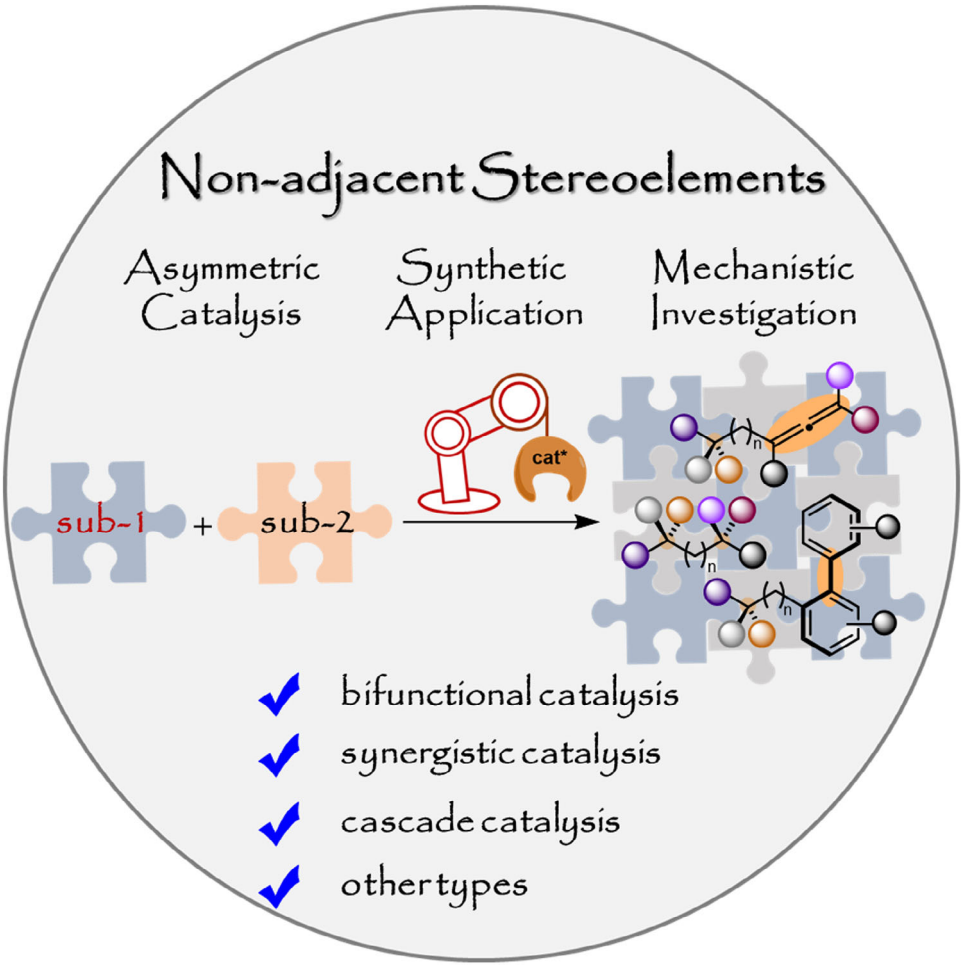
Asymmetric Synthesis

Catalytic Asymmetric Construction of Nonadjacent Stereoelements

*Chong-Lei Ji, Xi-Zhang Zou, and De-Wei Gao**

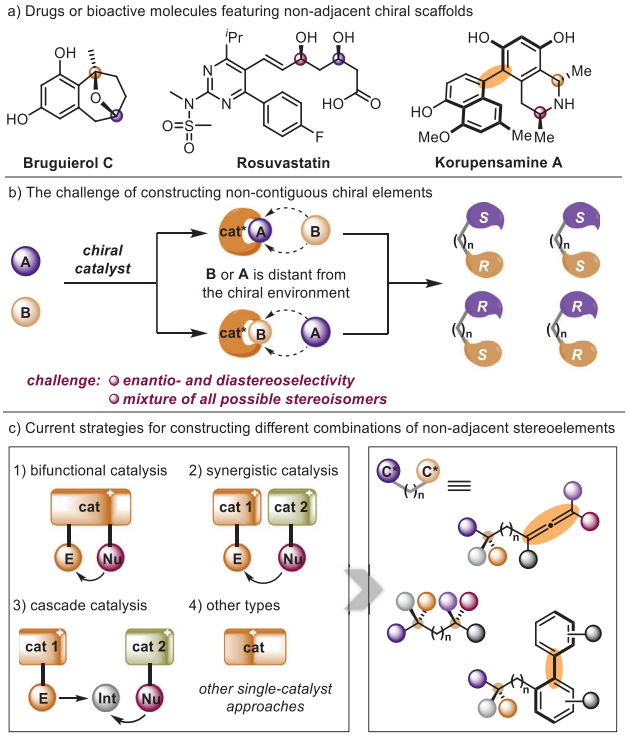


Abstract: Nonadjacent chiral scaffolds are privileged motifs in bioactive molecules and medicines, which have stimulated chemists' ingenuity in achieving the asymmetric construction of non-contiguous chiral elements directly. Current strategies include bifunctional catalysis, synergistic catalysis, cascade catalysis and others, enabling the production of a wide range of enantiomerically enriched compounds featuring different combinations of nonadjacent chirality, including multiple elements of central chirality, central and allenyl axial chirality, and central and biaryl axial chirality. As compared to the patterns of multiple nonadjacent elements of central chirality, the latter two are less frequently reported. This minireview aims to summarize the key developments in reaction design, mechanistic studies, and synthetic applications, with the goal of stimulating further exploration in this important area of asymmetric catalysis.

1. Introduction

Asymmetric catalysis has become a cornerstone of modern synthetic chemistry, enabling access to enantioenriched functional molecules that are crucial for applications in medicine and material science.[1–5] Most research has focused on constructing single and vicinal chiral elements,[6–13] with significant advances made in stereodivergent synthesis.[14–23] The prevalence of non-Tevicinal chirality in complex molecules has driven significant interest in their direct catalytic asymmetric construction (Scheme 1a).[24–29] However, developing methodologies for the catalytic asymmetric construction of 1,n-stereocenters ($n \geq 3$) and nonadjacent central and axial chiral elements remains a formidable challenge.[30–32] This difficulty primarily arises from the flexible transition state, which complicates the simultaneous and effective control of remote stereochemistry. Additionally, as the distance between stereogenic elements increases, achieving efficient asymmetric induction becomes increasingly challenging. The formation of multiple nonadjacent stereoelements can lead to at least four possible stereoisomers, further complicating selective synthesis (Scheme 1b).

Despite these inherent difficulties, ingenious catalytic strategies have emerged. The first approach relies on bifunctional catalysis,[33] where the catalyst activates reactants using different functional groups within the same catalyst, influencing both enantio- and diastereoselectivity through interactions with the substrates. Synergistic catalysis,[35–39] involving the concurrent activation of both a nucleophile and an electrophile using distinct catalysts, offers another powerful strategy. This approach allows for the stereodivergent synthesis of all four possible stereoisomers by judiciously combining two chiral catalysts. The third strategy is cascade catalysis,[40–46]



Scheme 1. Representative molecules possessing nonadjacent chirality, along with the main challenges as well as strategies to construct these chiral scaffolds.

wherein one reaction is catalyzed by one catalyst, followed by another independent transformation catalyzed by the same or a different catalyst. This enables precise control over enantio- and diastereoselectivity in the construction of non-contiguous chiral elements. Besides, other single-catalyst approaches (excluding bifunctional catalysis and domino cascade catalysis) for constructing diverse non-adjacent chiral scaffolds are also discussed. (Scheme 1c). These powerful catalytic strategies offer promising routes to diverse and valuable chiral scaffolds found in natural products and bioactive molecules.

Despite significant advances in the catalytic asymmetric synthesis of molecules featuring nonadjacent chiral elements over the past two decades, a comprehensive review integrating catalyst design, reaction development, mechanistic investigations, and synthetic applications remains lacking. The objective of this minireview is to discuss various approaches for the catalytic asymmetric construction of nonadjacent stereoelements. To guide readers through this topic, the reactions are categorized into four sections based on different strategies: 1) Bifunctional catalysis; 2) synergistic catalysis; 3) cascade catalysis; and 4) others. In each section, the catalytic strategy will be further divided into several subsections based on reaction mechanisms. The reaction design, key transformations, and relevant mechanistic insights will be highlighted, along with a critical assessment of current limitations in the field.

It is worth noting that although asymmetric cycloaddition reactions can be used to construct cyclic molecules with multiple stereocenters, which may include nonadjacent chiral centers, this area has already been well-reviewed.[47–54] Additionally, the introduction of non-contiguous chiral

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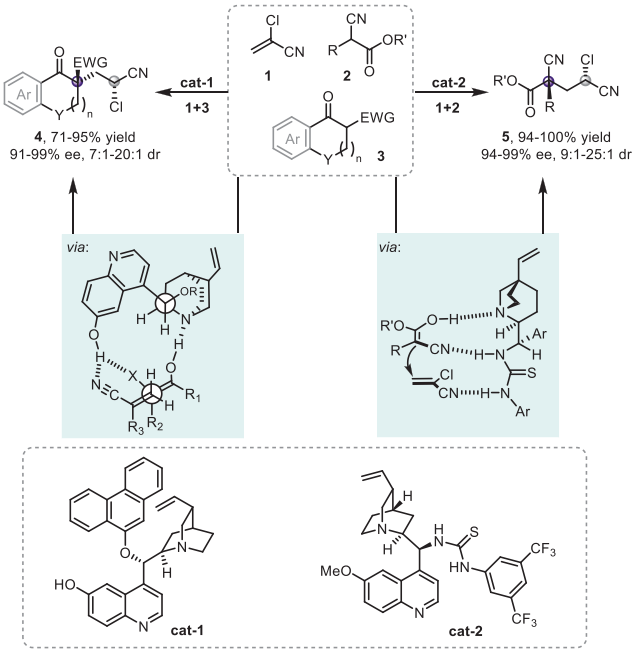
elements through kinetic resolution is beyond the scope of this minireview,[55–59] as the article emphasizes the direct construction of at least two non-contiguous chiral elements, whereas in kinetic resolution and some other reactions, one of the chiral elements is pre-existing.

2. Advances in Bifunctional Catalysis to Construct Nonadjacent Stereocenters

Highly enantio- and diastereoselective reactions that generate chiral products with multiple stereocenters in a single step are exceptionally valuable in synthetic chemistry. Bifunctional catalyst enables the simultaneous activation of different substrates through the functional groups within the catalyst. The resulting intermediates are positioned in a relatively rigid chiral environment, which regulates the stereoselectivity of the reaction. In this section, we provide detailed examples of constructing non-contiguous stereocenters, with an emphasis on discussing reaction mechanisms and stereoselective induction models driven by bifunctional catalysis. Based on the reaction mechanisms, these reactions can be categorized into three types, including chiral Brønsted base catalysis, chiral Brønsted acid catalysis, and phase transfer catalysis.

2.1. Constructing Nonadjacent Stereocenters Enabled by a Chiral Brønsted Base

The Deng group pioneered significant studies on the construction of 1,3-nonadjacent stereocenters by asymmetric tandem conjugate addition-protonation reactions. In 2006 and



Scheme 2. Asymmetric catalysis to construct nonadjacent stereocenters by cinchona alkaloids.[60,61]

2007, they began developing asymmetric Michael addition reactions, utilizing cinchona alkaloids (**cat-1** and **cat-2**) as bifunctional catalysts (Scheme 2).[60,61] These catalysts feature both hydrogen bond donor and acceptor units within the same molecule. When cyclic α-oxoesters or α-cyanoesters

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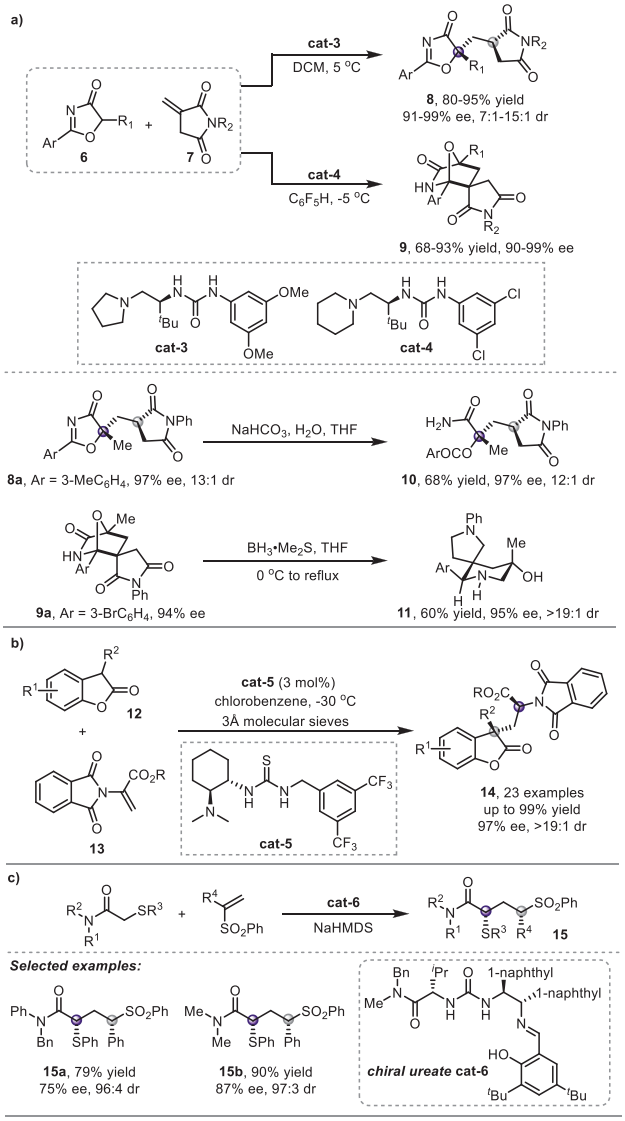
were reacted with α-chloroacrylonitrile in the presence of **cat-1**, the adducts **4** were obtained diastereoselectively. Conversely, using the 9-thiourea cinchona alkaloid **cat-2** as the organocatalyst led to the formation of adducts **5**. The proposed model suggests that a network of hydrogen-bonding interactions within a precisely controlled transition state governs this dual control. The catalyst (**cat-1**) facilitates the enantioselective approach of the trisubstituted carbon nucleophile to α-substituted Michael acceptor. The 6′-OH group and the C9 substituent of the cinchona alkaloid are hypothesized to create a chiral environment that influences the preferred orientation of the nucleophile, controlling the stereochemistry at the newly formed tertiary center. The catalyst (**cat-2)** could produce the diastereomer compared to the reaction with **cat-1**, starting from the same precursors. This switch in diastereoselectivity is proposed to result from a reversal during the nucleophilic addition step, where the putative enolic Michael donor approaches the Michael acceptor with its s_i face using **cat-2** as the catalyst. These studies represent pioneering research in the construction of nonadjacent stereocenters, offering valuable insights into the stereochemical models of chiral induction. Using a similar strategy, Palomo and Oiarbide achieved the construction of all-carbon tertiary/quaternary nonadjacent stereocenters through conjugate addition.[62]

An asymmetric organocatalytic reaction involving 5*H*-oxazol-4-ones and *N*-itaconimides was reported by Coote, Jiang, and coworkers.[63] The reaction outcome varied depending on the organocatalyst used (Scheme 3a). When **cat-3** was used in DCM as the solvent, the reaction afforded compounds **8** via Michael addition. In contrast, employing **cat-4** in C_6F_5H as the solvent led to the formation of bicyclic heterocycles **9** via a formal (4 + 2) annulation. Both reactions proceeded with good yields and enantioselectivity. The synthetic utility of this work was demonstrated by converting the Michael addition product **8a** into a benzoyl-protected α-tertiary alcohol using $NaHCO_3$ in THF, maintaining high enantioselectivity. Additionally, the [4 + 2] cycloaddition product **9a** was reduced using a borane-dimethyl sulfide complex, generating a spiro-piperidine-pyrrolidine derivative, which is particularly noteworthy due to its potential applications in pharmaceuticals.

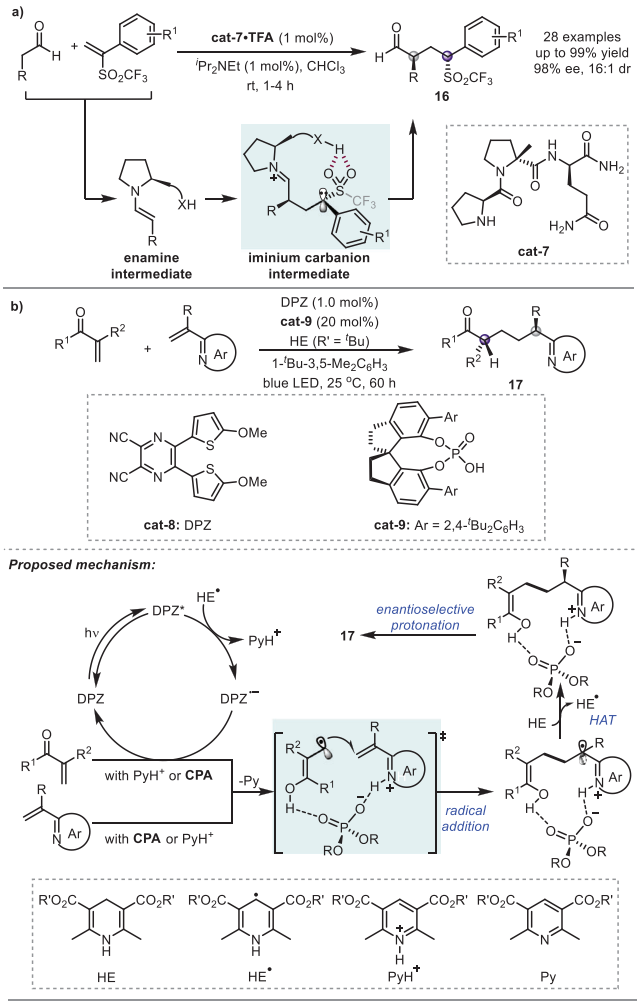
Benzofuran-2(3*H*)-ones **14** with quaternary stereogenic centers are significant in biological compounds and asymmetric synthesis. The construction of these compounds with nonadjacent stereogenic centers remains particularly challenging. In 2016, Cheng, Li, and coworkers employed novel bifunctional tertiary amine thiourea catalysts, which were designed using free-energy relationship (FER) analysis to predict their performance (Scheme 3b).[64] These catalysts were optimized by evaluating their steric and electronic properties, leading to high enantioselectivity and diastereoselectivity in the Michael addition of 3-substituted benzofuranones and alkyl 2-phthalimidoacrylates. The predictive model developed in the study showed a strong correlation between the experimental and predicted stereoselectivity outcomes, highlighting its reliability. The optimal catalyst, 3,5-bis(trifluoromethyl)benzyl-substituted tertiary amine thioureas (**cat-5**), demonstrating high yields and excellent stereoselectivity in the synthesis of



Scheme 3. a) Asymmetric Michael addition and formal [4 + 2] cycloaddition between 5*H*-oxazol-4-ones and *N*-itaconimides.[63] b) Asymmetric conjugate addition of benzofuran-2-ones to alkyl 2-phthalimidoacrylates.[64] c) Enantioselective addition of α-thioacetamides to α-substituted vinyl sulfones catalyzed by a chiral strong Brønsted base.[65]

α-amino acid derivatives containing nonadjacent stereogenic centers. The discovery suggests that combining steric and electronic parameters enables the rational design of highly effective catalysts.

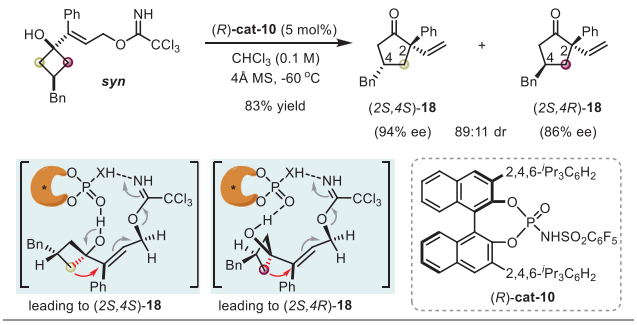
Recently, the Terada group applied a chiral strong Brønsted base to construct acyclic, 1,3-nonadjacent stereogenic centers (Scheme 3c).[65] They successfully addressed the limitations of existing methods by employing α-thioacetamides as less acidic pronucleophiles, along with a range of α-substituted vinyl sulfones and α-aryl acrylates as electrophiles. The key was the development of a chiral sodium ureate, which exhibits significantly higher basicity than conventional chiral catalysts. The sodium cation interacts with both the amide oxygen and the carbanion, stabilizing the



Scheme 4. a) Bifunctional catalysis enables access to triflones bearing nonadjacent stereogenic centers through radical strategy.[68] b) Asymmetric construction of azaarenes containing 1,4-stereocenters through radical strategy.[69]

intermediate in a chair-like structure and playing a crucial role in diastereoselective protonation.

The trifluoromethylsulfonyl (SO_2CF_3, triflyl) group is valuable in various fields such as therapeutics, catalysis, and material science due to its unique chemical properties.[66,67] Recently, Budinská and Wennemers developed a stereoselective method for the formation of γ-triflylaldehydes with two noncontiguous chiral centers using a chiral bifunctional peptide catalyst (Scheme 4a).[68] The catalyst's (**cat-7**) bifunctionality is key to achieving this dual control. The amine moiety of the peptide catalyst facilitates enamine formation with the aldehyde, activating it for conjugate addition to the α-aryl vinyl triflone. This step generates one stereogenic center, with the catalyst's steric environment favoring the preferential formation of one diastereisomer over the other. The second step involves the stereoselective protonation of the resulting triflyl carbanion intermediate. This carbanion is not simply a free anion, but is instead stabilized by negative hyperconjugation into the σ^* orbital of the S-CF_3 bond. This stabilization, combined with the planar geometry of the carbanion, affects



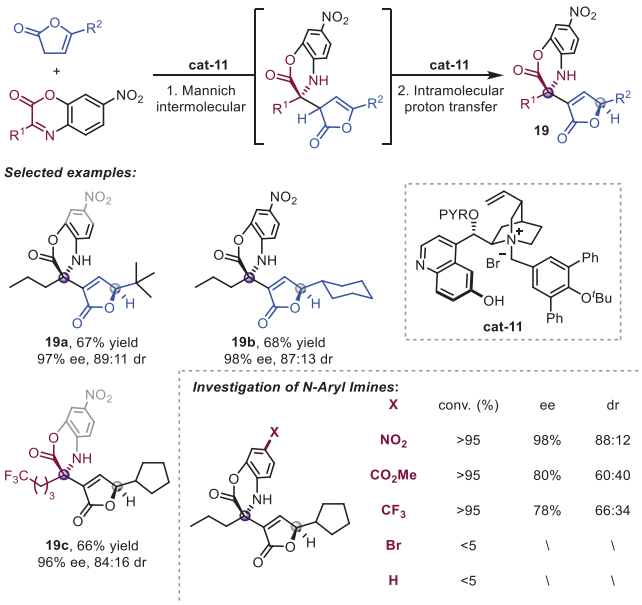
Scheme 5. Asymmetric construction of 1,3-steregenic centers by a chiral Brønsted acid.[71]

the accessibility of its two faces for protonation, thereby establishing the secondary stereocenter. This methodology enables the production of a diverse range of γ-triflylaldehydes with good diastereo- and enantioselectivity.

2.2. Constructing Nonadjacent Stereocenters Enabled by a Chiral Brønsted Acid

In 2021, Jiang, Cao and coworkers developed a novel and highly efficient reductive cross-coupling of olefins, providing a powerful tool for constructing 1,4-stereocenters in azaarene derivatives (Scheme 4b).[69] The key innovation of this method lies in the synergistic use of photoredox and chiral hydrogen-bonding catalysis. The versatility of this method was further demonstrated by its successful application to α-branched vinylazaarenes, enabling the formation of challenging 1,4-stereocenters. Mechanistic studies, including control experiments and density functional theory (DFT) calculations, suggest a tandem mechanism involving radical addition, enantioselective hydrogen atom transfer (HAT), and enantioselective protonation. This research not only broadens the synthetic toolbox for accessing chiral azaarene derivatives but also paves the way for further exploration of radical-based bifunctional catalysis for accessing nonvicinal stereocenters.

Inspired by an enantioselective formal [3 + 2] cycloaddition reaction between β,γ-epoxysulfones and imines catalyzed by a chiral Brønsted base,[70] Terada and coworkers developed a vinylogous Wagner–Meerwein rearrangement, a classic skeletal rearrangement reaction catalyzed by a chiral Brønsted acid (**cat-10**).[71] Central to this success is the use of a chiral *N*-triflyl phosphoramide catalyst, which effectively differentiates the prochiral faces of a key allylic intermediate. This intermediate, generated through activation of a trichloroacetimidate leaving group by the chiral acid, undergoes migration to produce the desired α-vinyl ketone product (Scheme 5). Mechanistic studies, employing deuterium-labeled and diastereomerically pure substrates, strongly support a concerted *anti*-S_N2' mechanism for the carbon migration step. The stereospecificity observed in the deuterium labeling experiment rules out stepwise S_N1' or ion-pair mechanisms. Further investigations using a substrate with a benzyl group at the 3-position of the cyclobutane ring identified the migrating carbon atom and demonstrated



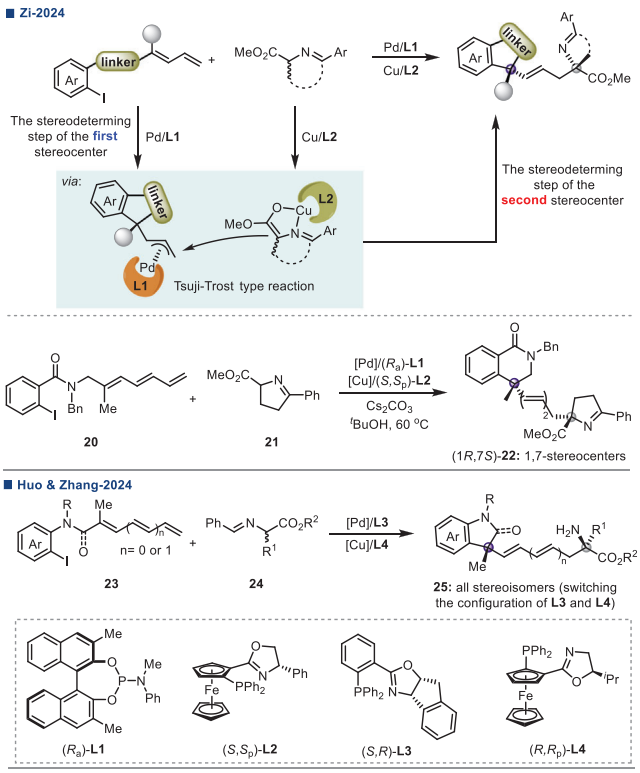
Scheme 6. Mannich-isomerization reactions enabled by a dual-functional betaine catalyst.[72]

a preference for the *s-cis* conformation of the C— O bond in the transition state. Notably, high enantioselectivity was maintained despite the reaction likely proceeding through different conformations, underscoring the effectiveness of the chiral catalyst in achieving precise stereochemical control.

2.3. Constructing Nonadjacent Stereocenters Enabled by Phase Transfer Catalyst

In 2022, the Deng group developed an organocatalytic approach for the asymmetric construction of 1,4-stereocenters through a tandem Mannich-isomerization reactions mediated by a single chiral betaine catalyst (**cat-11**) (Scheme 6).[72] This catalyst acts as a dual-functional catalyst, facilitating both the enantioselective intermolecular C—C bond formation and the subsequent stereoselective intramolecular 1,3-proton transfer reaction. This strategy effectively streamlined the synthesis of chiral amino butenolides, which are key structural motifs in various biologically active natural products. This tandem reaction demonstrated a broad substrate scope, showcasing its compatibility with a range of alkylated and aryl ketimines, as well as γ-substituted β,γ-unsaturated butenolides. Notably, the presence of a *para*-nitrophenyl group on the ketimine significantly enhanced the stereoselectivity of both the Mannich and isomerization reactions. The proposed catalytic cycle involved the interaction of the betaine catalyst with the imine, followed by deprotonation of the butenolide, leading to an asymmetric Mannich reaction. This resulted in the formation of an intermediate that undergoes stereoselective isomerization to generate the desired product.

Bifunctional catalysis offers an effective approach for constructing nonvicinal stereogenic centers. However, due to interactions, such as weak or covalent interactions between the substrate and the functional groups in the catalyst, the substrate is required to contain specific functional groups. This requirement limits the generality of the substrates and the scope of applicable reactions.



Scheme 7. Synergistic Pd/Cu-catalyzed stereodivergent construction of 1,5-and 1,7-nonadjacent stereocenters developed by Zi and Huo and Zhang independently.[73,74]

3. Advances in Synergistic Catalysis to Construct Nonadjacent Stereoelements

Synergistic catalysis, a powerful approach for reaction development, involves the use of two catalysts to activate both the nucleophile and electrophile.[35–39] In this process, the two catalysts each regulate a nonvicinal stereocenter, often offering a unique advantage in accessing all four possible stereoisomers. This section provides a comprehensive summary of the construction of nonvicinal stereoelements through synergistic catalysis, including metal/metal and metal/organocatalyst catalytic systems.

3.1. Constructing Nonadjacent Stereoelements by Pd/Cu or Pd/Co Synergistic Catalysis

The Zi group introduced a novel synergistic palladium/copper catalytic system for 1,4-difunctionalization of 1,3-dienes, leading to the stereodivergent construction of 1,5-nonadjacent quaternary stereocenters (Scheme 7a).[73] The key to this method lies in the independent control of stereochemistry at each newly formed stereocenter through the palladium and

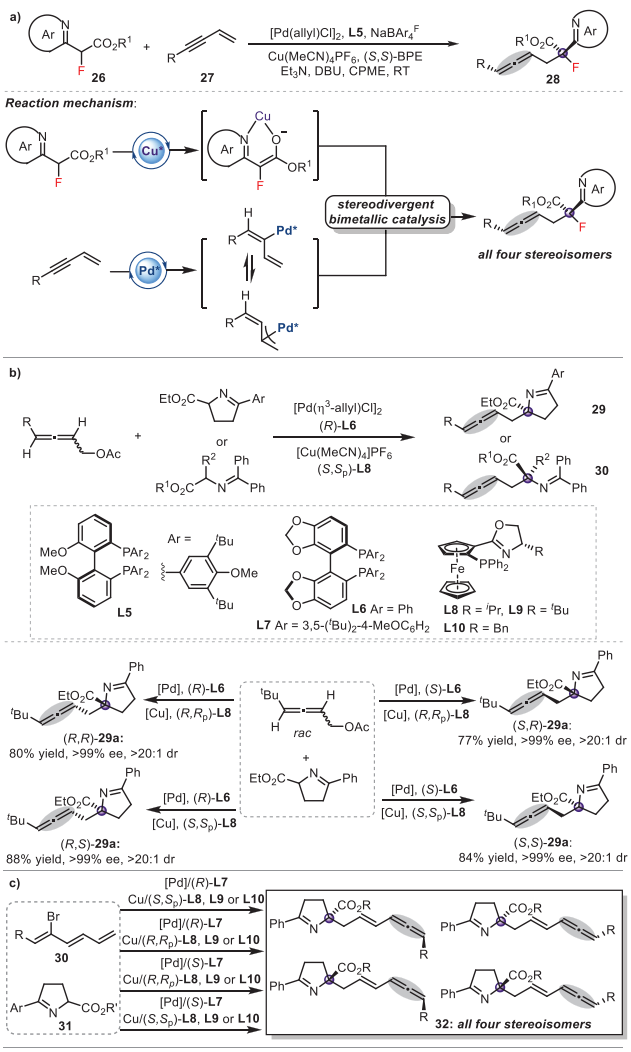
copper catalysts. By selecting the appropriate combination of chiral catalysts, all four diastereomers of the product can be efficiently generated. The authors demonstrated the broad substrate scopes of this reaction, highlighting its applicability to various 1,3-dienes and nucleophiles, including aryl ketimine esters and aldimine esters. Notably, 1,7-stereocenters were efficiently constructed when 1,3,5-triene was used as the substrate. Combined experimental and computational mechanistic studies reveal that the reaction proceeds via Heck/Tsuji–Trost type cascade reaction, elucidating the origin of C1 and C5 stereoselectivity, respectively. In the absence of the copper catalyst, the enantiomeric excess (ee) value of the product reached 93% when dimethyl malonate was used as the nucleophile. This indicated that the C1 enantioselectivity is governed by the palladium catalyst, further confirmed by a linear relationship between the ee values of ligand **L1** and product. Computational studies support that the C5 enantioselectivity depends on the copper catalyst.

At the same time, Zhang and Huo achieved an efficient Pd/Cu-cocatalyzed asymmetric Heck cascade reaction for the stereodivergent construction of 1,5- or 1,7-nonadjacent tetrasubstituted stereocenters using a similar strategy (Scheme 7b).[74] This method enables the efficient preparation of chiral molecules bearing two privileged scaffolds, oxindoles and non-natural α-amino acids, with good functional group tolerance. Importantly, the authors demonstrated the ability to access all four stereoisomers of the products by simply combining two chiral metal catalysts with different enantiomers. Mechanistic studies indicated that the configuration combinations of two ligands significantly influence the stereocontrol over the two remote stereocenters.

Allenes, characterized by their unique orthogonal cumulative π-systems, are highly valuable in synthetic chemistry due to their versatile reactivity and intrinsic chirality.[75–80] They find applications in various fields, including pharmaceuticals, advanced materials, as well as substrates for asymmetric transformations. Although allenes have been synthetically accessible since the late 19th century, there remains a continuous demand for new methods to produce enantiomerically pure allenes, driven by their significance in the synthesis of functional molecules.

In 2021, He and Lin developed a Pd/Cu synergistic catalytic system for the stereoselective synthesis of tertiary fluoride-tethered axial allenes containing quaternary carbon centers.[81]

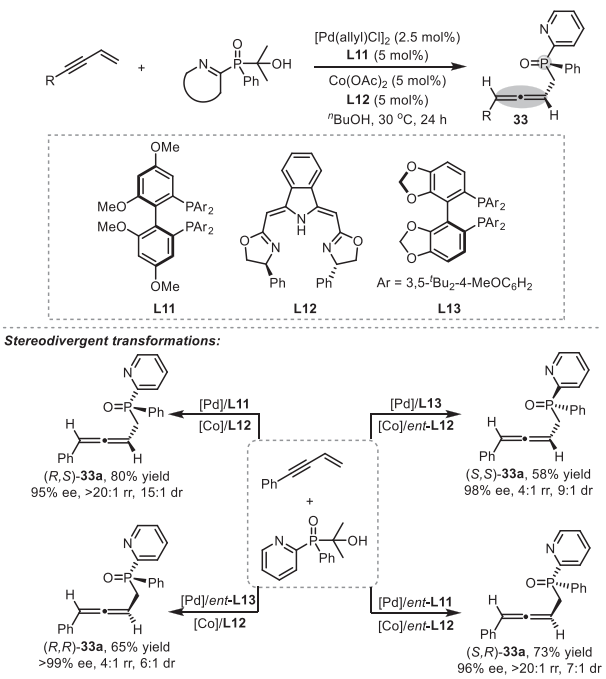
The process involves the formation of a palladium hydride species, which inserts into the enyne to generate an allylpalladium intermediate. Then this intermediate is captured by Cu-coordinated fluorinated enolate, followed by reductive elimination to afford the desired product **28** (Scheme 8a). This approach demonstrated robust yields and stereoselectivity across a broad substrate scope, underscoring its practical utility. Soon after, Zhang and Ma developed chiral Pd/Cu synergistic catalysis to construct axial allenes with nonadjacent central chirality (Scheme 8b).[82] This reaction was found to be highly compatible with diverse cyclic or acyclic imino esters derived from racemic amino acids. By switching the combinations of the two chiral catalysts, they achieved stereodivergent synthesis of 1,3-noncontiguous axial allenes



Scheme 8. a) Asymmetric hydrofunctionalization of conjugated enynes through synergistic catalysis.[81] b) Synergistic Pd/Cu-catalyzed dynamic kinetic asymmetric allenylation with racemic allenylic esters.[82] c) Synergistic Pd/Cu-catalyzed 1,5-double chiral inductions.[83]

with central chirality. Recently, the same groups reported a novel synergistic Pd/Cu-catalyzed 1,5-double chiral induction model for the asymmetric synthesis of chiral allenes bearing 1,5-nonadjacent chirality (Scheme 8c).[83] The cornerstone of this strategy is a C=C bond relay mechanism, which facilitates the transfer of chiral information from the Cu catalyst to the Pd catalyst. The authors demonstrated that all four possible stereoisomers of the target products can be obtained in a stereodivergent manner by simply changing the combination of two chiral catalysts with different configurations. Control experiments and DFT calculations revealed a novel mechanism involving 1,5-oxidative addition, contra-thermodynamic η^3-allyl palladium shift, and conjugate nucleophilic substitution. These processes are crucial in controlling reactivity as well as regio-, enantio-, and diastereoselectivity.

The He group developed an innovative Pd/Co dual-catalytic system that enables highly diastereo- and enantioselective hydrophosphinylation of a wide range of unsaturated carbon–carbon bonds, including allenes, conjugated

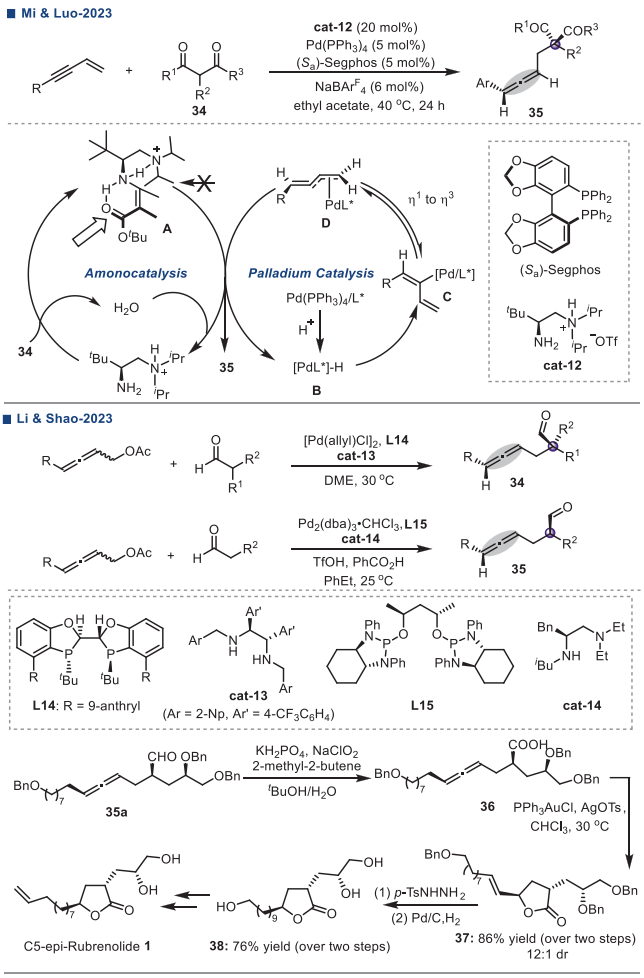


Scheme 9. Synergistic Pd/Co-catalyzed asymmetric hydrophosphinylation reactions of conjugated enynes.[84]

enynes, and 1,3-dienes (Scheme 9).[84] The key innovation depends on the use of a masked phosphinylating reagent, α-hydroxyalkylphosphonate. In combination with synergistic Pd/Co catalysis, it facilitates the formation of allyl motifs containing both a tertiary C- and P-stereocenter with remarkable stereocontrol. Expanding the scope of this methodology, the authors successfully achieved the diastereoselective hydrophosphinylation of 1,3-enynes, affording chiral allenes featuring a P-stereocenter and nonadjacent chiral axis with excellent stereocontrol. Notably, the authors demonstrated the versatility of their approach by achieving stereodivergent hydrophosphinylation, which allowed access to all four stereoisomers of the phosphorus-containing products through the selective use of different chiral ligands for each transition-metal catalyst. This work provides a highly efficient and versatile platform for constructing complex organophosphorus compounds.

3.2. Constructing Nonadjacent Stereoelements by Pd/Organocatalyst Synergistic Catalysis

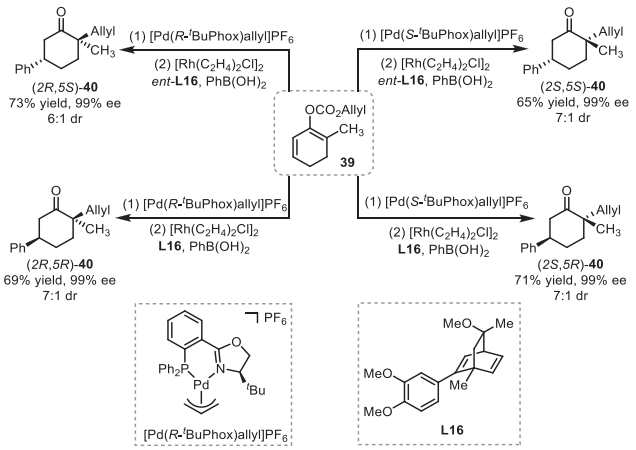
In 2023, Luo and Mi developed an innovative strategy for the asymmetric α-allylic allenylation of β-ketocarbonyls and aldehydes using a synergistic Pd/chiral primary amine catalytic system (Scheme 10a).[85] This dual catalytic system was compatible with a broad substrate scope, including various β-ketocarbonyls and aldehydes. The author proposed that the chiral primary amine interacts with the aldehyde or ketone moiety to form enamine intermediate **A**. Concurrently, the palladium hydride species **B** undergoes insertion into the enyne, forming *syn*-η^3-allylic palladium intermediate **D** via σ-π rearrangement from intermediate **C**. The π-allyl-palladium



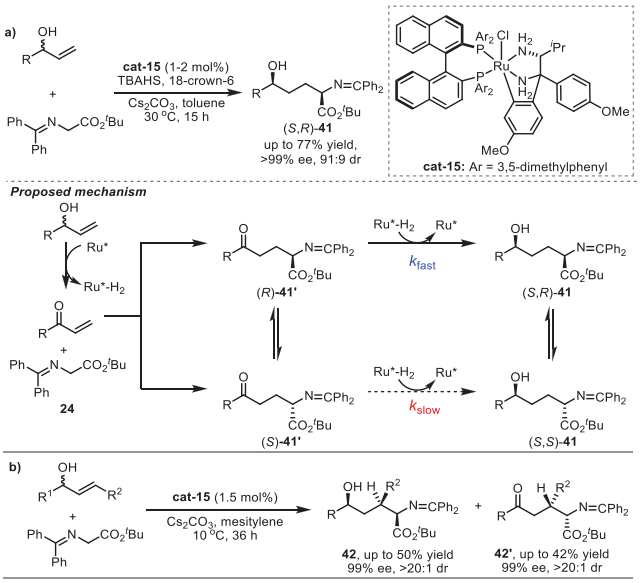
Scheme 10. Synergistic Pd/organo-catalytic system for the construction of chiral allenes with remote central stereocenters.[85,86]

is then captured by the enamine intermediate **A**. Finally, reductive elimination establishes both the all-carbon quaternary stereocenter and axial chirality of the allene. Notably, the use of $NaBAr^F_4$ as an additive and ethyl acetate as solvent was crucial for enhancing reaction efficiency and selectivity. At the same time, Shao and Li independently introduced a novel method for asymmetric allenylic substitution of aldehydes using a dual Pd/chiral amine catalytic system (Scheme 10b).[86] The substrate scope of this reaction is broad, encompassing diverse racemic allenylic acetates, branched aldehydes, and linear aldehydes, and it achieves high yields with excellent enantioselectivity and diastereoselectivity. The authors performed a series of transformations, including the formal synthesis of C5-epi-Rubrenolide **1**, which contains a γ-lactone core. This compound was constructed through gold-catalyzed cyclization reaction of **36** derived from **35a**, resulting in the conversion of axial chirality to central chirality.

The synergistic catalytic system provides an efficient approach for constructing noncontiguous chiral elements, particularly in the synthesis of chiral dienes with nonvicinal central chirality. However, the requirement of two catalysts to simultaneously activate different substrates, transfer reaction intermediates, and control two remote stereocenters during



Scheme 11. Sequential reactions through Pd-catalyzed asymmetric allylic alkylation followed by Rh-catalyzed 1,4-conjugate addition.[87]



Scheme 12. a) Ru-catalyzed asymmetric hydroalkylation of racemic allylic alcohols.[88] b) Transforming racemic compounds into two enantioenriched products via intermediate kinetic resolution.[89]

the reaction process, severely limits the range of compatible reaction systems. Currently, research primarily focuses on Pd/Cu synergistic catalytic systems, with limited examples of Pd/Co and Pd/chiral amine catalytic systems. Developing new compatible synergistic catalytic systems to enable the synthesis of chiral molecules with nonadjacent stereoelements is highly desirable.

4. Advances in Cascade Catalysis to Construct Nonadjacent Stereoelements

Cascade catalysis offers significant advantages in multistep synthesis with high selectivity and efficiency. Therefore, this strategy holds great promise for simplifying synthetic routes to deliver valuable and useful natural products. In this section, we will discuss cascade reactions based on the mode of operation, categorizing them into three types: (i) Pd/Rh sequential cascade catalysis, (ii) Ru-catalyzed domino cascade catalysis, and (iii) Ru/Cu relay cascade catalysis, in which different catalysts play distinct roles at each step to construct noncontiguous stereoelements.

4.1. Constructing Nonadjacent Stereocenters by Pd/Rh Sequential Cascade Catalysis

In 2021, the Lautens group developed Pd-catalyzed asymmetric allylic alkylation followed by Rh-catalyzed enantioselective 1,4-conjugate addition, starting from cyclic allyl enol carbonate **39** in a sequential procedure (Scheme 11).[87] An intriguing phenomenon of statistical amplification of enantioselectivity was observed, exceeding the enantioselectivity achievable by each asymmetric transformation when performed independently. This methodology demonstrated the ability to access all stereoisomers of the cyclic ketones from the same set of starting materials simply by varying the catalyst and ligand combinations. This achievement underscores the method's precision and versatility, offering a powerful tool for stereoselective synthesis in synthetic chemistry.

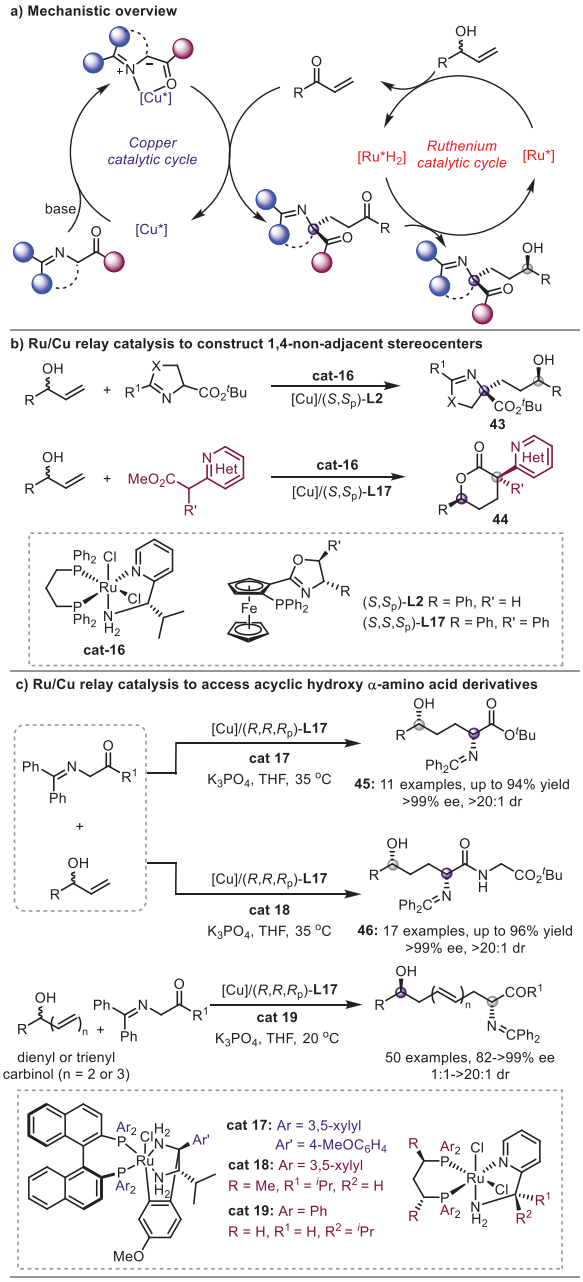
4.2. Constructing Nonadjacent Stereocenters by Ru-Catalyzed Domino Cascade Catalysis

In 2022, the Zhang group developed a novel asymmetric hydroalkylation of racemic secondary allylic alcohols catalyzed by a chiral ruthenium catalyst (**cat-15**), producing chiral amino acid derivatives **41** with 1,4-stereocenters (Scheme 12a).[88] This reaction proceeds via a borrowing hydrogen mechanism, where the allylic alcohol undergoes dehydrogenation to form an α,β-unsaturated ketone, which subsequently reacts with a glycine-derived Schiff base via Michael addition. The resulting ketone is subsequently reduced by the ruthenium hydride species, affording the desired product. Mechanistic studies revealed a dynamic kinetic asymmetric transformation process during the reduction step, where the chiral center in the ketone intermediate (*R*-**41′** and *S*-**41′**) continuously racemizes, facilitating the formation of the chiral center adjacent to the hydroxyl group (**41**). The phase transfer reagents (TBAHS and 18-crown-6) enhance the solubility of Cs_2CO_3, initiating the reversible protonation and deprotonation at the α-position of Schiff base. Later, the same group developed a similar method for transforming racemic compounds into two enantioenriched chiral products, termed "intermediate kinetic resolution" (IKR).[89] This approach focused on the kinetic resolution of reaction intermediates rather than the substrates themselves (Scheme 12b). This IKR strategy offers a promising alternative to traditional kinetic resolution methods, enabling the efficient transformation of racemic compounds into valuable enantioenriched products with 100% theoretical yield.

4.3. Constructing Nonadjacent Stereocenters by Ru/Cu Relay Cascade Catalysis

Considering the significance of multiple stereocenters in drug discovery and development, the Wang group developed a series of atom- and step-economical and redox-neutral cascade reactions by merging ruthenium-catalyzed asymmetric borrowing-hydrogen reaction with copper-catalyzed asymmetric Michael or 1,6-addition.[90–93] These approaches begin with Ru-catalyzed dehydrogenation of racemic allylic alcohol to form a vinyl ketone. The resulting ketone is then captured by an azomethine ylide through 1,4- or 1,6-addition, activated by chiral Lewis acid Cu catalysis. Subsequently, the ketone formed during the addition step is selectively reduced to generate valuable hydroxyesters featuring 1,n-nonadjacent stereocenters by in situ generated [Ru*H_2] species (Scheme 13a). Highly functionalized δ-hydroxyesters (**43**) and δ-valerolactones (**44**), bearing 1,4-nonadjacent stereocenters, were produced in good yields with high levels of diastereoselectivity and excellent enantioselectivity under mild reaction conditions (Scheme 13b). Furthermore, a variety of highly functionalized amino acid esters or peptides bearing 1,4-,1,6- or 1,8-nonadjacent stereogenic centers were prepared in high yields with excellent enantio- and diastereoselectivity (Scheme 13c).

As mentioned above, cascade catalysis is highly efficient in constructing nonadjacent chiral centers, especially remote 1,n-stereocenters ($n \geq 4$). However, it requires precise relay and control of intermediates generated during the reaction, which can lead to issues with catalyst compatibility. Therefore, the catalytic systems are quite limited, primarily focusing on Ru/Cu relay catalysis or Ru-catalyzed tandem catalysis.

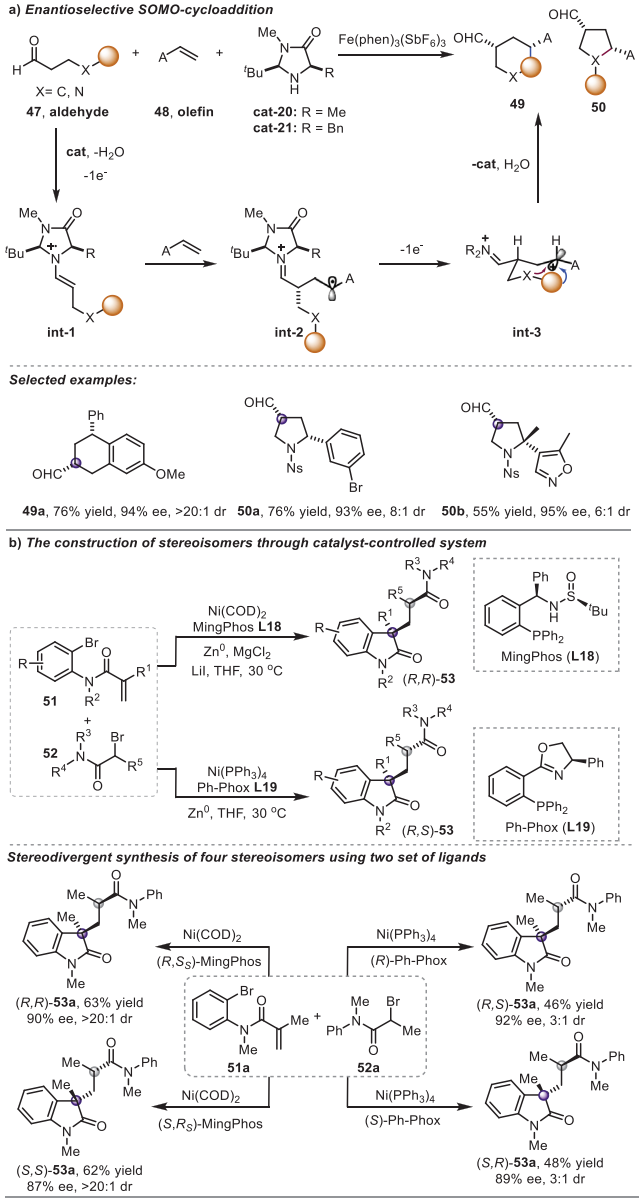


Scheme 13. Ru/Cu relay catalysis.[90–93]

5. Other Advances to Construct Nonadjacent Stereoelements

In this section, we will discuss other strategies for constructing noncontiguous chiral elements, including the formation of nonvicinal central chiral molecules, chiral dienes with central chirality, atropisomers possessing central chirality, and diaxially chiral compounds. It is important to note that all the works discussed in this section utilize a single organocatalyst or transition-metal catalyst, but do not involve bifunctional catalysis or domino cascade processes.

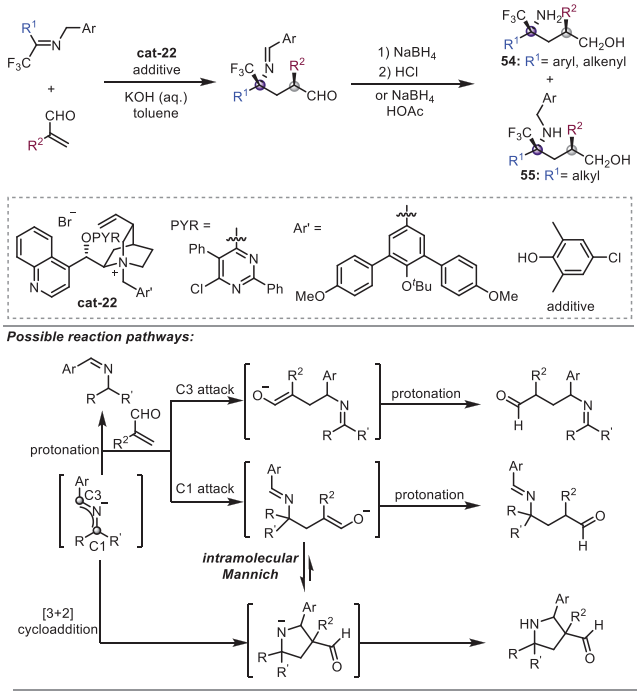
Inspired by the efficiency and predictability of the Diels–Alder reaction, MacMillan and coworkers employed the principles of singly occupied molecular orbital (SOMO) catalysis,[94,95] a mode of activation previously developed by his group.[96] The reaction proceeds through a radical-polar crossover mechanism, a distinctive feature of SOMO catalysis, which distinguishes it from traditional Diels–Alder reaction (Scheme 14a). The process initiates with the condensation of a chiral imidazolidinone catalyst (**cat-20** or **cat-21**) with aldehyde **47**, followed by oxidation by a tris(phenanthroline)iron(III) complex, forming a radical cation intermediate (**int-1**). This intermediate undergoes radical addition to generate intermediate **int-2**. Oxidative radical-polar crossover then furnishes the carbon-cation intermediate **int-3**, which is subsequently attacked by the nitrogen motif or an aromatic ring to produce the desired product **49** and **50**, respectively. In the generation of pyrrolidines, the enantioselectivity of the radical cation is governed by the chiral catalyst, setting the stage for stereoselective bond formation. The nature of the nitrogen-protecting group on the β-amino aldehyde significantly influences the diastereoselectivity of the reaction. When the nucleophile is changed to an aromatic ring, the carbocation undergoes intramolecular Friedel–Crafts alkylation with the pendant aromatic ring, forging six-membered ring and completing the cascade cycloaddition. The stereochemistry of the final



Scheme 14. Asymmetric construction of 1,3-nonadjacent stereocenters through radical strategies.[94,95,97]

product is controlled by both the initial enantioselective radical addition and the preference for a chair-like transition state during the cyclization step, where substituents favor equatorial positions. The new SOMO-catalyzed cycloaddition provides a powerful and efficient approach to access complex carbocyclic frameworks.

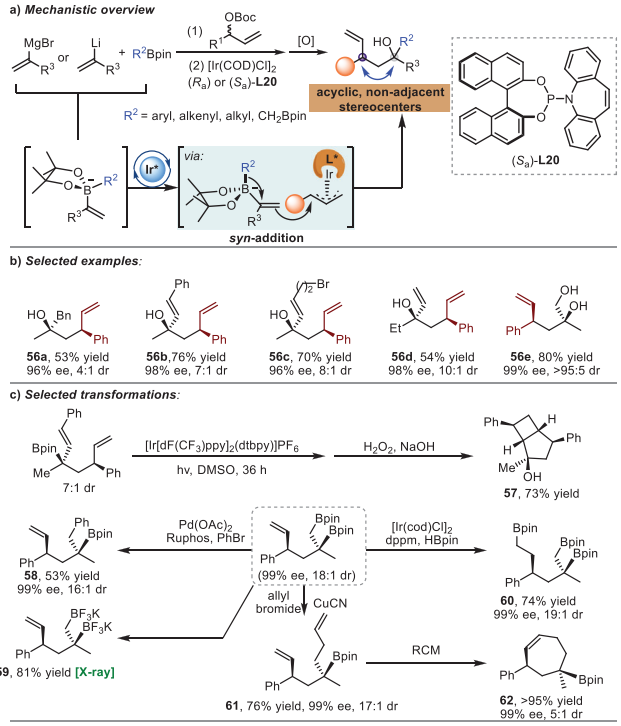
In 2024, Kong, Zhang, Wang and coworkers developed a reductive cyclization and cross-coupling strategy involving alkene-tethered aryl bromides **51** and α-bromoamides **52**.[97] Two ligands, MingPhos (**L18**) and Ph-Phox (**L19**), were crucial for the stereodivergent synthesis. By switching the absolute configuration of these two ligands, all four stereoisomeric products could be obtained from the same set of starting materials, thereby overcoming the traditional substrate-dependent diastereoselectivity (Scheme 14b).



Scheme 15. Asymmetric synthesis of chiral amines by a cinchonium-derived phase-transfer catalyst.[98]

In 2018, Deng and coworkers developed a catalytic system for the direct synthesis of chiral amines bearing 1,3-nonadjacent stereocenters (**54** or **55**).[98] A key challenge was steering the reaction away from undesired side reactions, such as [3 + 2] cycloaddition and isomerization, toward the formation of the desired product. The initial investigation employed a cinchonium salt catalyst (**cat-22**) to promote the deprotonation of *N*-benzyl imines, forming 2-aza-allyl anions, which then reacted with α-substituted enals. However, this approach resulted in a significant amount of [3 + 2] adduct as a side product. NMR studies revealed that the [3 + 2] adduct was formed via a stepwise conjugate addition-Mannich reaction pathway, with the conjugate addition being the rate-determining step. This insight highlights that controlling the chemoselectivity of the enolate intermediate, favoring protonation over intramolecular Mannich cyclization, is essential for achieving the desired tandem reaction. To address this, a phenolic proton donor was introduced into the reaction system. This additive was selected for its acidity, which was greater than that of water, to accelerate the protonation of the enolate while selectively favoring this process over other potential anionic intermediate pathways (Scheme 15). Notably, the reaction could be extended to simple aldimines, with the elimination of [3 + 2] adduct as a side product. This improvement is attributed to the absence of a tetra-substituted carbon center in the enolate intermediate, which is critical for the intramolecular Mannich reaction due to the Thorpe–Ingold effect.

Since 2021, Ready and our group have independently disclosed asymmetric 1,2-metalate shift reactions that utilize B-ate complexes prepared from aryl, alkenyl, alkyl boronates, or *gem*-diborylalkanes (Scheme 16).[99–105] This



Scheme 16. Iridium-catalyzed 1,2-metalate shift to construct 1,3-nonadjacent stereocenters.[101–105]

reaction proceeds through an enantioselective allylation step followed by a stereoselective 1,2-functional group rearrangement, producing two nonadjacent stereocenters in a single step. The broad scope was demonstrated with various boronates, organolithium reagents, Grignard reagents, and allylic carbonates including those bearing electron-donating and electron-withdrawing groups, heterocycles, and *ortho*-substituted aryl groups. The synthetic utility of the reaction was further showcased by the use of a 1,6-diene in a photocatalytic [2 + 2] cycloaddition, leading to the formation of a cyclobutane derivative **57**. We also explored the compatibility of a wide range of *gem*-diborylalkanes, including those with mono-substituents as well as cyclic *gem*-diborylalkanes, leading to the formation of 1,2-bis(boronates) with three to seven-membered rings.[106–110] The desired product underwent diverse late-stage functionlization (**58** to **62**), further demonstrating its synthetic utility.

The Lundgren group described the development of Rh-catalyzed enantioselective α,δ-difunctionalization of electron-deficient dienes (Scheme 17).[111] The reaction proceeds via a three-component coupling involving a diene, an aryl boronic acid, and an aldehyde, with a broad substrate scope. The key to success lies in the use of a chiral tetrafluorobenzobarrelene ligand (**L21**, Ph-tfb) with the Rh catalyst, which enables the selective δ-arylation of the diene followed by *Z*-selective trapping of the aldehyde by the Rh-allyl intermediate. They also demonstrated that the *Z*-homoallylic alcohol can be further functionalized to generate acyclic compounds with up to five stereocenters (**64** and **65**).

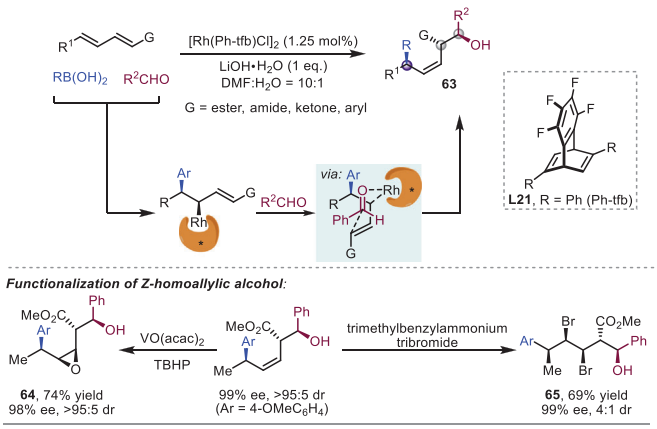
Palladium-catalyzed asymmetric allylic reactions have proved to be efficient for accessing chiral allenes. These reactions begin with oxidative addition of the racemic allene to form a cationic palladium-trimethylenemethane (TMM) complex. This complex undergoes an adynamic kinetic asymmetric transformations (DYKATs), ensuring the subsequent transformations. This step is crucial for achieving high enantioselectivity in the final product (Scheme 18a). The Trost group disclosed a study on the palladium-catalyzed asymmetric [3 + 2] cycloaddition reactions (eq 1),[112] enabling the successful synthesis of cyclopentanes, pyrrolidines as well as spirocycles with high levels of diastereo- and enantioselectivity. Later, the same group introduced a novel palladium-catalyzed asymmetric allylic alkylation (Pd-AAA) method for the selective functionalization of α-hydroxyketones (eq 2).[113] Using boronic acids as traceless templates, they successfully controlled the enolate geometry and prevented undesired *O*-alkylation. This strategy enabled the direct alkylation of unprotected α-hydroxyketones, offering a significant advantage over traditional methods that require protecting groups.

In 2023, Wang and coworkers reported palladium-catalyzed asymmetric allenylic alkylation reaction for the stereoselective construction of 1,3-stereogenic elements incorporating both axial and central chirality (eq 3).[114] Almost at the same time, Zhou and Yu developed palladium-catalyzed asymmetric allenylic alkylation for the stereoselective synthesis of chiral allenes possessing nonadjacent axial and two central chiral centers (eq 4).[115] This novel approach, which employs a retro-oxa-Michael addition strategy, provides a valuable tool for accessing a wide range of complex allenes with precise stereocontrol (Scheme 18b).

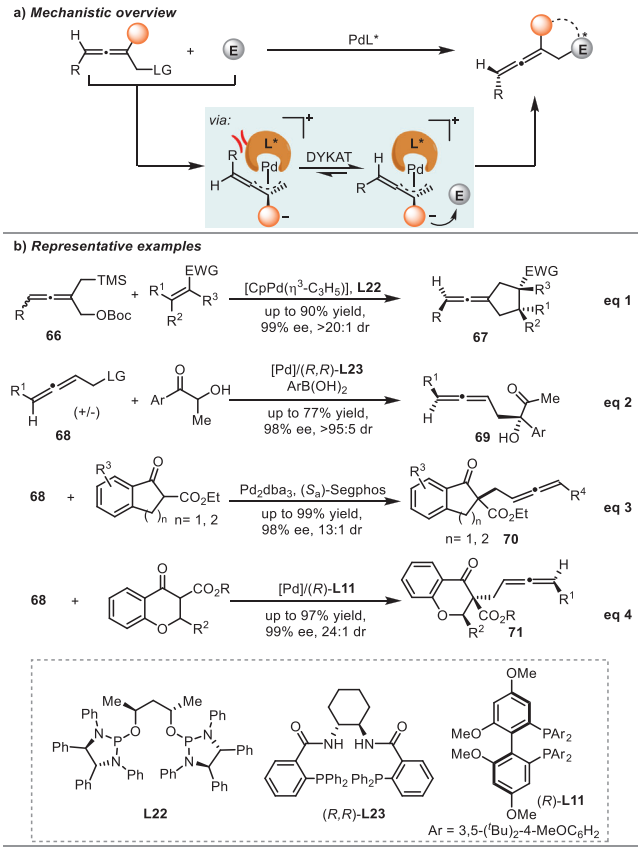
Atropisomers have garnered extensive attention in asymmetric synthesis due to their significant roles in natural products, chiral catalysis, and synthetic chemistry.[116–126] However, previous studies have primarily focused on the construction of molecules with single axial chirality or adjacent axial and central chirality, which is beyond the scope of the following discussion. The development of methods for constructing nonadjacent axial and central chiral elements has progressed slowly, significantly limiting the applications of this class of compounds and forming the central theme of the following discussion (Scheme 19). It should be noted that the construction of multiple chiral centers, including both complex vicinal and nonvicinal stereoelements, is not covered here due to space limitations and the detailed summaries provided in the previous review.[127–132]

In 2021, Xu and Cao developed a novel palladium-catalyzed asymmetric tandem reaction that combines C–C bond activation and Cacchi cyclization (Scheme 20a).[133] The proposed mechanism involves the initial oxidative addition of cyclobutanone to the palladium catalyst, followed by enantioselective β-carbon elimination to produce the key chiral σ-alkylpalladium intermediate. Subsequently, this intermediate undergoes intramolecular cyclization with 2-methoxynaphthalen-1-yl-substituted *o*-ethynylaniline, ultimately leading to axially chiral indoles through reductive elimination.

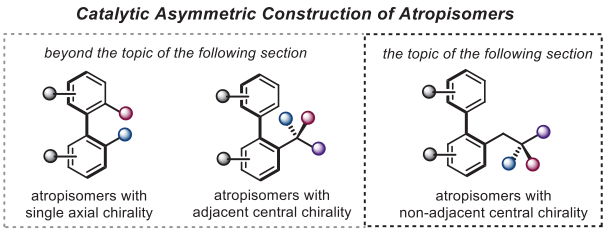
The Li group employed a highly enantioselective rhodium(III)-catalyzed [3 + 2] annulation reaction for the construction of axially and centrally chiral indenes



Scheme 17. Rh-catalyzed enantio-, diastereo-, and *Z*-selective α,δ-difunctionalization of electron-deficient dienes.[111]



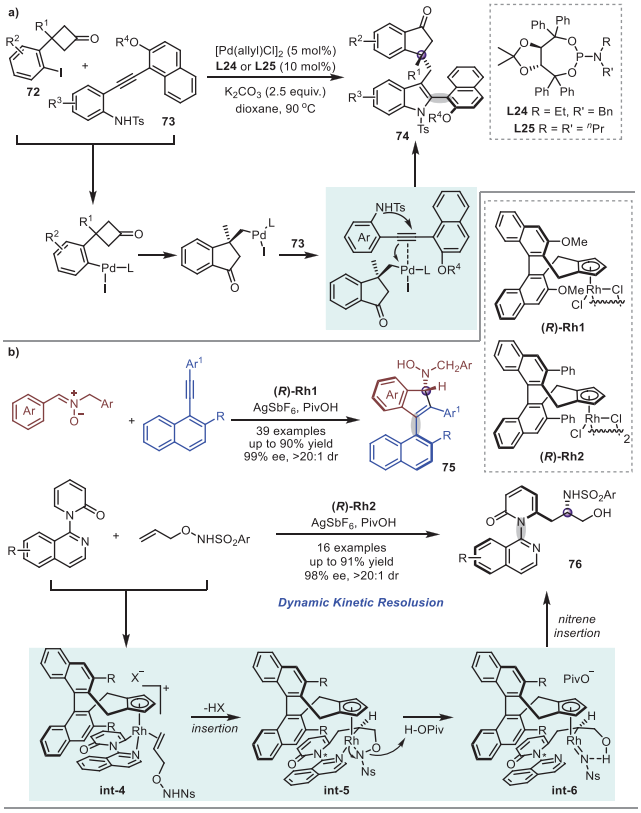
Scheme 18. Pd-catalyzed stereoselective synthesis of chiral allenes bearing nonadjacent axial and central chiral elements.[112–115]



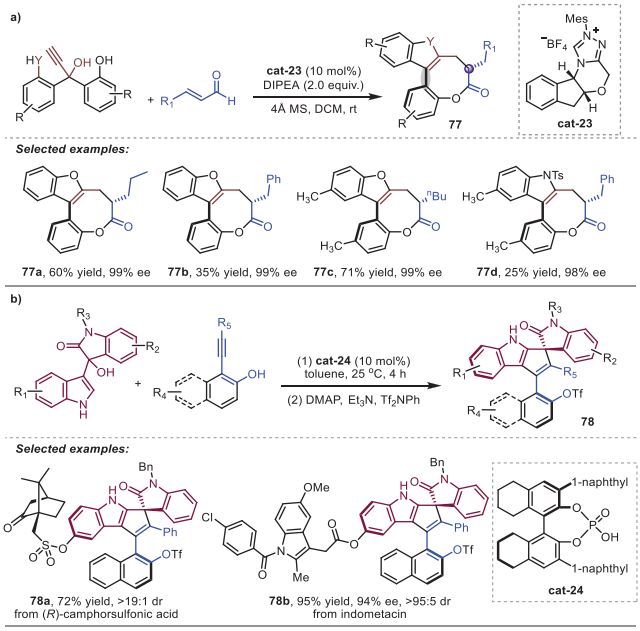
Scheme 19. Defining the scope of the following discussion on the catalytic asymmetric construction of atropisomers with nonadjacent central chirality.

and indenones (Scheme 20b).[134] This dual chirality arises from two distinct, catalyst-controlled migratory insertion steps. The mild reaction conditions employed are crucial for maintaining both high enantio- and diastereoselectivity. Additionally, they developed a novel bifunctional olefin, *N*-protected *O*-allylhydroxyamine, designed for the synthesis of chiral amino alcohols via asymmetric carboamidation in 2023 (Scheme 20c).[135] The proposed mechanism involves C–H activation to form a rhodacyclic intermediate, followed by migratory insertion to generate a chelation-stabilized (*S*)-configurated alkyl chiral intermediate (**int-5**). Subsequently, PivOH assists in forming a nitrene intermediate (**int-6**), which undergoes nitrene insertion and Rh-N protonation, ultimately furnishing the desired product **76**.

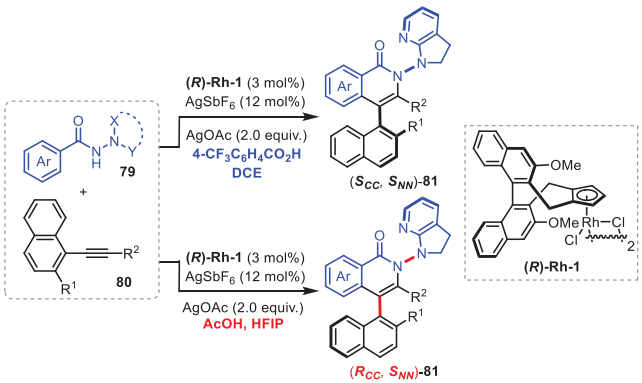
The Zhao group detailed a novel organocatalytic method for the diastereo- and atrop-enantioselective synthesis of bridged biaryls bearing eight-membered lactones (Scheme 21a).[136] This reaction proceeds through a propargylic substitution and two cascade cyclizations to deliver the desired products with central and axial chiral elements by employing *N*-heterocyclic carbene (NHC) catalysis. This work provides a highly efficient and stereoselective method for the synthesis of complex bridged biaryls. The broad substrate scope, high stereoselectivity, and mechanistic insights make this a valuable contribution to the field of asymmetric catalysis. Recently, Shi, Tan and Ni developed catalytic atroposelective synthesis of cyclopentenyl-[*b*]indoles, a novel class of alkene atropisomers possessing both axial and central chirality (Scheme 21b).[137] This method utilizes an unexpected catalytic asymmetric rearrangement reaction of 3-indolylmethanols, rather than the initially intended (3 + 2) cycloaddition with phenylacetylenes. This serendipitous discovery not only provides a new synthetic route to the desired cyclopentenyl-[*b*]indoles but also introduces the first catalytic enantioselective rearrangement reaction of 3-indolylmethanols. The synthetic utility of the resulting cyclopentenyl-[*b*]indoles is further highlighted through their



Scheme 20. a) Pd-catalyzed enantioselective tandem C—C bond activation/Cacchi reaction.[133] b) Rh-catalyzed asymmetric construction of axially and centrally chiral indenes and amino alcohols.[134,135]



Scheme 21. a) Organocatalyzed diastereo- and atroposelective synthesis of bridged biaryls.[136] b) Organocatalyzed synthesis of cyclopentenyl[*b*]indole motifs with axial and central chiral elements.[137]



Scheme 22. Rhodium-catalyzed enantioselective and diastereodivergent access to diaxially chiral heterocycles.[138]

subsequent transformations into various chiral molecules. Mechanistic studies provide insights into the role of the CPA catalyst and the importance of hydrogen bonding interactions in controlling both reactivity and enantioselectivity.

In 2023, Li, Huang, Wang and coworkers detailed a novel rhodium-catalyzed C—H activation strategy for the synthesis of diaxially chiral heterocycles with *N*—*N* axial chirality (Scheme 22).[138] The core of their approach involves the use of a bulky *N*—*N* containing directing group on a benzamide substrate, which facilitates C—H activation and provides steric hindrance crucial for controlling stereochemistry in the presence of chiral rhodium catalyst (**Rh-1**). By simply changing the solvent from 1,2-dichloroethane (DCE) to hexafluoroisopropanol (HFIP), they achieved complementary diastereoselectivity, obtaining different diastereisomers with high enantioselectivity. Mechanism studies revealed that HFIP solvent plays a dual role, acting as both a solvent and a ligand, influencing the sequence of elementary steps in the catalytic cycle. The ability to achieve diastereodivergence using a single catalyst opens exciting possibilities for the development of synthetic methodologies in asymmetric catalysis.

As mentioned above, progress has been made in constructing nonadjacent stereoelements using other strategies. Most of these approaches rely on a single catalyst to simultaneously control both enantio- and diastereoselectivity. In the construction of nonadjacent chiral centers, these reactions are primarily limited to the formation of 1,3- stereocenters. Studies on the synthesis of chiral allenes have been largely restricted to Pd-catalyzed Tsuji-Trost type reactions, while the preparation of atropisomers has predominantly focused on scaffolds featuring cyclic central chirality. However, these advances do not fully align with the potential applications of such compounds. Therefore, there is an urgent need to develop new catalytic systems that enable the construction of nonvicinal chiral elements with greater structural diversity.

6. Summary and Outlook

In this minireview, we discuss a series of strategies for the catalytic asymmetric construction of nonadjacent chiral elements, categorized into four main approaches:

bifunctional catalysis, synergistic catalysis, cascade catalysis, and other single-catalyst controlled methods. Bifunctional catalysis emphasizes the activation of substrates by different functional groups within the catalyst, regulating both enantio- and diastereoselectivity. Synergistic catalysis is exemplified by dual catalysts that control the stereoselectivity of nucleophiles and electrophiles separately, such as Pd/Cu, Pd/Co, and Pd/oraganocatalyst combinations for constructing 1,n-stereocenters, as well as extending to the generation of allenyl axial and central chiral elements. Cascade catalysis, which focuses on the construction of 1,4-, 1,6-, and 1,8-stereocenters, is exemplified by Pd/Rh sequential catalysis, Ru-catalyzed domino cascade catalysis, and Ru/Cu relay catalysis. Finally, the review discusses additional strategies utilizing single-catalyst approaches (excluding bifunctional catalysis and domino cascade catalysis) for constructing diverse nonadjacent stereoelements.

As a promising direction, current research primarily focuses on exploring various types of nonvicinal chiral elements through asymmetric catalysis. Although significant progress has been made, several limitations remain in this field: (1) Radical pathways to access nonadjacent chirality are still in their infancy; (2) most examples developed thus far have focused on central/central and central/axial chiral elements, while the development of other types of nonadjacent chirality, such as planar/central and helical/central chirality, remains underexplored; and (3) the construction of remote 1,n-stereocenters ($n \geq 5$) and the stereospecific applications of these compounds, particularly in the development of chiral bioactive molecules, require further attention. To address the limitations of these methodologies, more powerful and efficient strategies need to be developed. These could include, but are not limited to, the following: (1) Exploring catalytic methods for producing molecules with noncontiguous chirality, such as photoredox, electrochemical, and enzymatic catalytic systems, with an emphasis on reaction efficiency, waste reduction, and safer processes; (2) designing catalysts to precisely regulate the stereoselectivity of free radical pathways; and (3) leveraging advances in computing power, software, algorithms, and data availability to enable digital approaches for chemical design challenges. In particular, machine learning facilitates the rapid assessment of properties in diverse systems, accelerating the design and evaluation of catalysts for constructing nonvicinal chiral elements, including those with challenging quantum mechanical properties.

We hope that the insight provided in this minireview will inspire and accelerate advancements in constructing remote stereogenic elements, thereby expanding the synthesis of functional molecules for applications in material science and medicinal chemistry.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Keywords: Asymmetric catalysis · Axial chirality · Center chirality · Diastereoselectivity · Nonadjacent stereocenters

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Minireview

Asymmetric Synthesis

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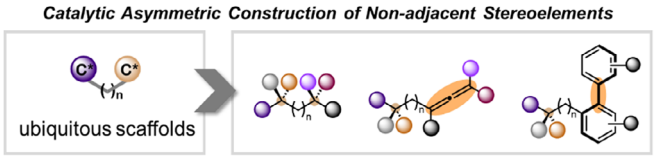
Catalytic Asymmetric Construction of Nonadjacent Stereoelements



This minireview highlights recent advances in the construction of non-adjacent stereogenic elements and summarizes the various strategies employed, including bifunctional catalysis, synergistic catalysis, cascade catalysis, and other approaches. The synthetic applications and mechanistic investigations are also discussed to facilitate understanding of this field.