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Enantioselective Catalytic Hydrofunctionalization: Chalcogen Additions to Alkenes

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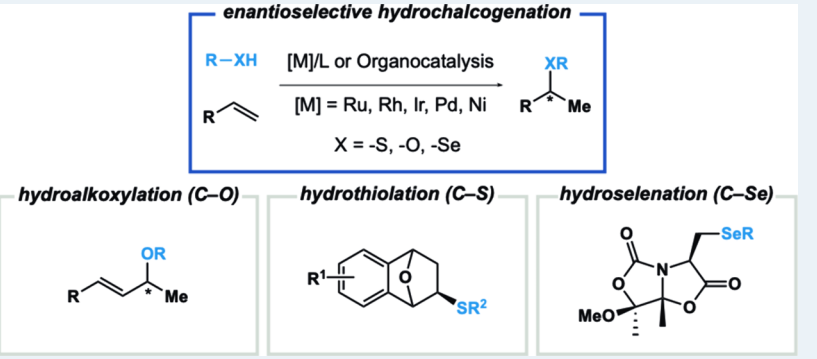

ABSTRACT: Hydrofunctionalization represents an efficient and atom-economical method for constructing carbon-chalcogen bonds from alkenes or alkynes. To date, numerous examples of hydrochalcogenation reactions have been developed, enabling the synthesis of compounds with carbon-chalcogen bonds. These advancements not only broaden the scope of synthetic chemistry but also provide valuable tools for further research and development in related fields. This perspective surveys the key advances in intermolecular asymmetric hydrooxygenation, hydrothiolation, and hydroselenation of alkenes. We organize our discussion by nucleophile type and alkene class (olefins, dienes, allenes), examining mechanistic insights and synthetic trends.

KEYWORDS: *hydrofunctionalization, catalysis, chalcogenation, olefins, enantioselectivity*

1. INTRODUCTION

The catalytic formation of carbon-chalcogen bonds (C−O, C−S, or C−Se) has emerged as a powerful strategy for synthesizing chiral molecules found in natural products, pharmaceuticals, and materials.[1−6] While the hydrofunctionalization of C−C π-bonds using nitrogen nucleophiles is more developed, the corresponding chalcogen nucleophiles have historically lagged due to challenges such as catalyst poisoning and poor stereocontrol.[6,7] Recent advances in transition metal and organocatalysis have begun to overcome these barriers, enabling highly regio- and enantioselective additions of chalcogen-based nucleophiles to alkenes. We focus on intermolecular reactions and summarize the literature from the original breakthrough to the most recent findings, classifying them by nucleophile and alkene class (Figure 1).

Across alkene classes, successful enantioselective hydrochalcogenation has depended strongly on both substrate activation and the mechanistic pathway employed. It is important to note that the term "olefins" encompasses a diverse range of reactivity profiles, including strained bicyclic alkenes, electronically activated vinyl ethers, simple α-olefins, and styrenes. These substrates differ substantially in their tendencies toward metal insertion, π-allyl formation, or carbocation stabilization, and therefore often require distinct catalytic strategies to achieve high levels of regio- and enantioselectivity. Electronically activated π-systems such as allenes and conjugated dienes frequently enable high selectivity through π-allyl or outer-sphere nucleophilic attack manifolds, whereas unactivated alkenes often suffer from poor facial discrimination and reversible insertion processes. For sulfur and selenium nucleophiles in particular, strong metal coordination and background reactivity remain dominant failure modes, necessitating alternative electrophilic activation strategies or carefully engineered ligand environments. These recurring mechanistic themes underpin both the successes and limitations of current asymmetric hydrochalcogenation methods and provide a framework for understanding progress across nucleophile classes.

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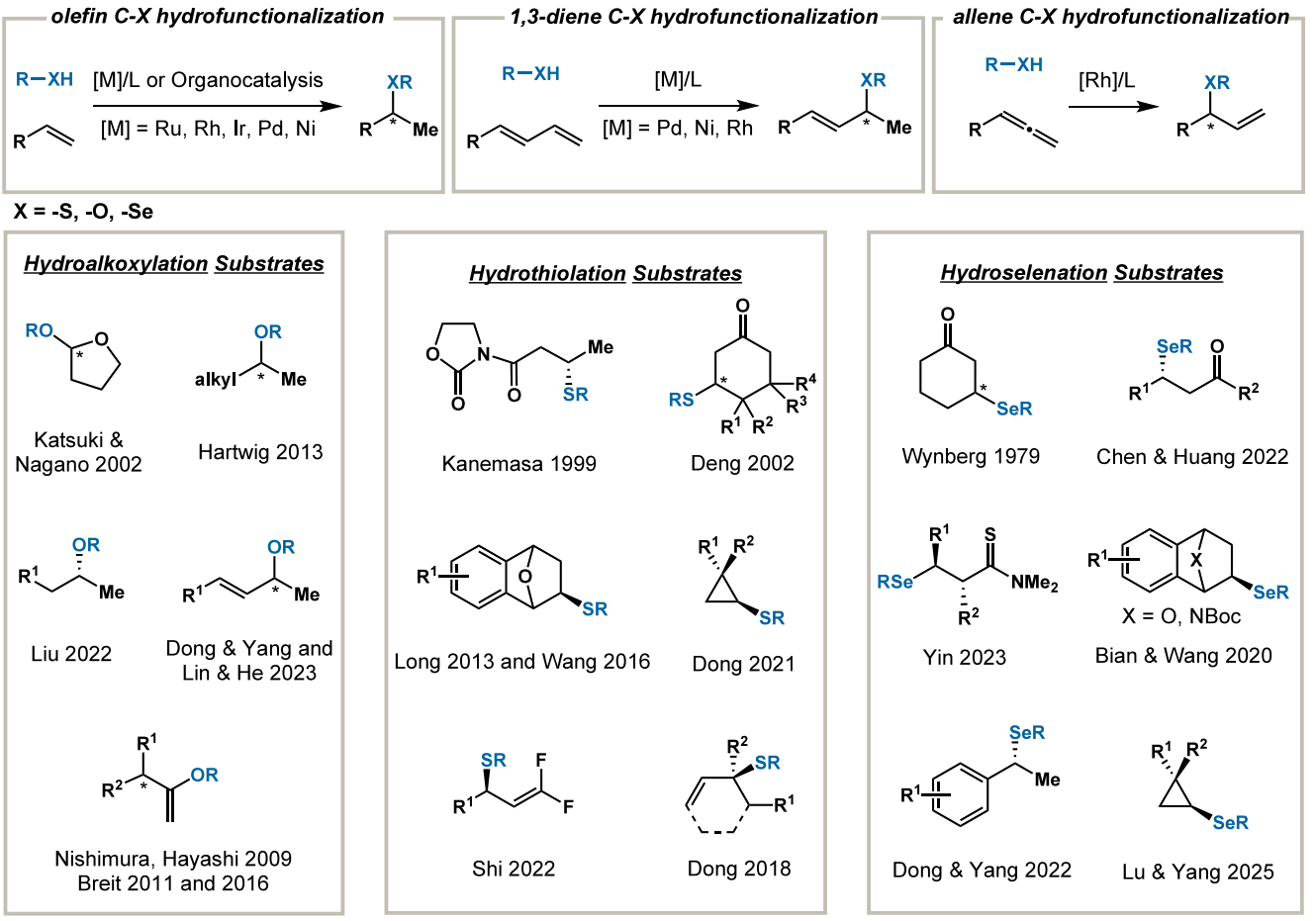

Figure 1. Overview of enantioselective transformations triggered by carbon-chalcogen activation and substrates featured in this account.

2. INTERMOLECULAR ASYMMETRIC HYDROOXYGENATION

2.1. Hydrooxygenation of Olefins

The enantioselective hydrooxygenation of alkenes offers a direct and atom-economical route to chiral ethers and esters, with broad relevance in pharmaceuticals. A seminal example was reported by Katsuki and Nagano in 2002, who demonstrated the hydroalkoxylation of dihydrofuran using a chiral Ru(II)-salen complex (Figure 2).[8] The transformation proceeded in excellent yield (up to 100%) and enantiomeric ratio (99:1 *er*), via a π-Lewis acid activation mechanism. A distinguishing aspect being, the Ru(II) precursor is photooxidized in situ to the catalytically active Ru(III) catalyst by the release of nitrous oxide upon irradiation.[9]

Achieving high enantioselectivity in the hydrochalcogenation of unactivated alkenes has remained a significant challenge. In a 2013 study, the Hartwig group developed an Ir-catalyzed hydroaroxylation of aliphatic alkenes with phenols, affording the corresponding ethers in 16–80% yield and up to 80:20 *er* (Figure 3).[10] Mechanistically, the transformation proceeds through a turnover-limiting oxymetallation step, that generates an alkoxy-hydrido Ir(III) species. This intermediate evolves to an 18-electron Ir(III) allyl hydride resting state, which lies off the catalytic cycle and undergoes C–H bond-forming reductive elimination to release the olefin and form an Ir(I) complex that lies on catalytic cycle prior to product formation. The modest enantioselectivity observed highlights the inherent challenge of facial discrimination in unactivated aliphatic alkenes without strong substrate–ligand interactions. More recently, the List group (2018) reported a Brønsted acid-catalyzed hydroalkoxylation of styrene with benzyl alcohol, achieving 77.5:22.5 *er*.[11] While this study examined a

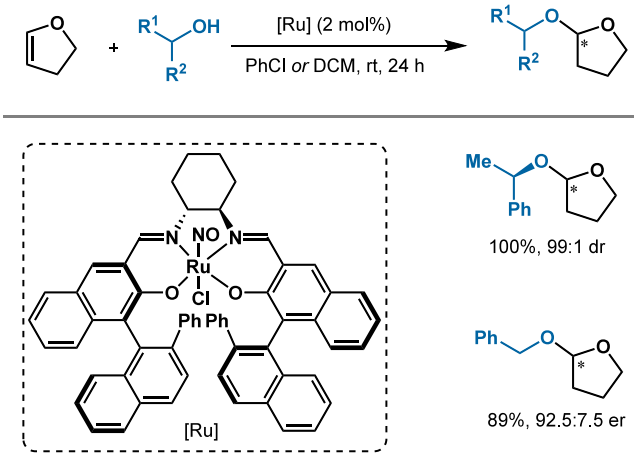

Figure 2. Ru-catalyzed asymmetric hydroalkoxylation of dihydrofuran.

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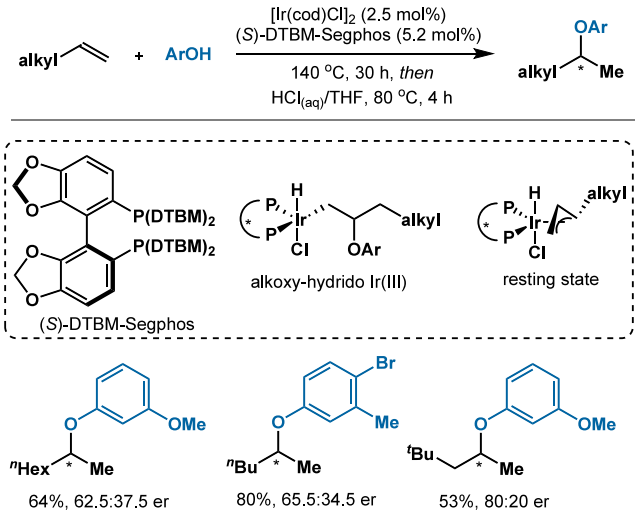

Figure 3. Ir-catalyzed asymmetric hydroaroxylation of unactivated alkenes.

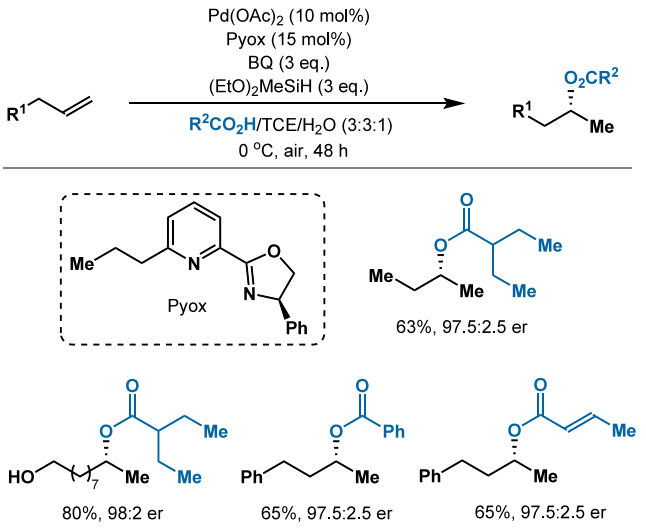

Figure 4. Pd-catalyzed asymmetric hydrooxygenation of unactivated alkenes.

single intermolecular substrate pair, it represents a significant breakthrough for aryl-substituted alkenes by demonstrating that strong chiral Brønsted acid activation can effectively organize olefin-nucleophile ion pairs to achieve enantioselective C−O bond formation without transition metals.

Recently, Liu and co-workers developed a novel Pd(II)-catalyzed enantioselective Markovnikov hydrooxygenation of unactivated terminal alkenes with carboxylic acids (Figure 4).[12] The $(EtO)_2MeSiH$/BQ redox system proved critical for achieving both high stereoselectivity and reactivity. In this system, an alkylpalladium(II) intermediate formed during the enantioselective oxypalladation step, is selectively reduced by the silane to furnish the product. This methodology enabled the synthesis of a broad range of optically pure alcohol esters with excellent enantioselectivities (95:5 to 99:1 *er*).

2.2. Hydrooxygenation of 1,3-Dienes

Conjugated dienes are abundant feedstock chemicals and versatile building blocks. Hydrochalcogenation of dienes provides direct access to allylic compounds, yet regiocontrol remains difficult due to the presence of multiple C−C double bonds in the conjugated diene. In 2019, Tran and Mazet reported the reactivity of intermolecular hydroalkoxylation to unsymmetrical 1,3-dienes with alcohols.[14] Their Ni-catalyzed method exhibited excellent branched regioselectivity. To achieve asymmetric hydroalkoxylation, they conducted a rapid screening of various chiral ligands and identified one that provided a chiral allylic ether formed in 24% conversion with 87:13 *er* after 6 h. However, extending the reaction to 24 h led to reduced enantioselectivity (74:26 *er*), which was attributed to the reversible nature of the reaction.

Sauthier and co-workers reported a nickel (Ni)-catalyzed asymmetric hydroalkoxylation of butadiene with ethanol using chiral diphosphate ligands in 2021 (Figure 5).[13] The desired ether product was obtained in high yields with 88.5:11.5 *er*. They observed that shorter reaction times resulted in higher enantiomeric excess, while prolonged reaction times led to racemization and isomerization.

In 2023, our group developed an enantioselective Ni-catalyzed hydroalkoxylation of dienes (Figure 6A).[15] Chiral allylic ether building blocks can be synthesized from petroleum feedstocks and readily available dienes with high regio- and enantioselectivity under solvent-free conditions. Unlike previous hydroalkoxylation reactions performed in solvents, the use of solvent-free conditions in this study effectively inhibits the reversibility and leads to high enantioselectivity. This method demonstrates good compatibility with a wide range of alcohols and bearing various functionalities such as phenyl, chloro, and trimethylsilyl groups, a feature attributed to the outer-sphere nucleophilic attack pathway that minimizes competitive coordination and suppresses reversibility. The solvent-free conditions further shift the equilibrium toward product formation, enhancing enantioselectivity. In the same year, He and co-workers also demonstrated a similar hydroalkoxylation reaction by using Pd/P,N-ligand, which afforded allylic ethers in 40–88% yields and up to 96:4 *er* (Figure 6B).[16] In addition, by using aryl-derived oxime, they successfully achieved corresponding hydration and hydroaminoxylation (Figure 7).

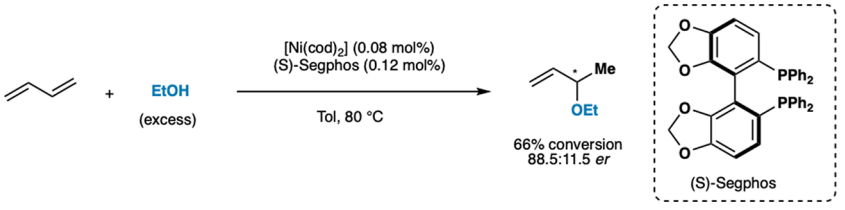

Figure 5. Ni-catalyzed asymmetric hydroalkoxylation of butadiene.

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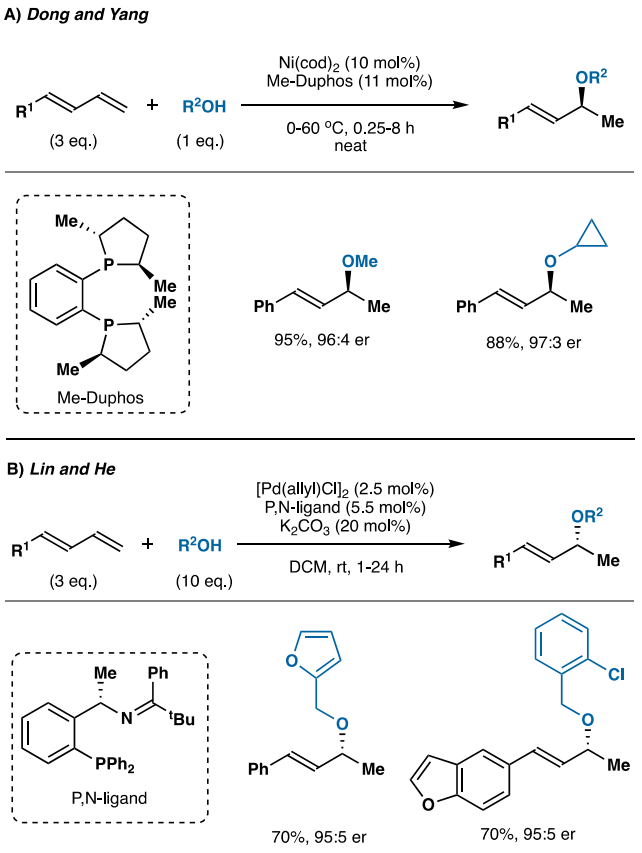

Figure 6. Ni- and Pd-catalyzed asymmetric hydroalkoxylation of 1,3-dienes. (A) Ni-catalyzed conditions reported by Dong and Yang. (B) Pd-catalyzed conditions reported by Lin and He.

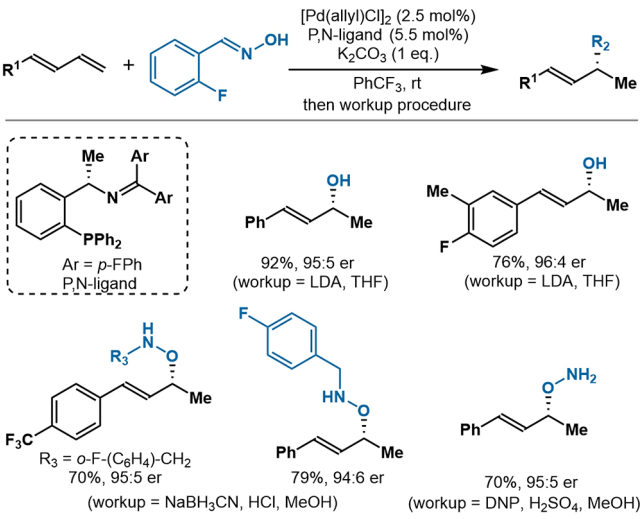

Figure 7. Pd-catalyzed asymmetric hydration and hydroaminoxylation of 1,3-dienes.

Notably, both mechanistic studies support an outer-sphere nucleophilic attack mode. The success of these systems underscores the importance of outer-sphere nucleophilic attack pathways in minimizing catalyst inhibition and suppressing reversibility, both of which are central to maintaining high enantioselectivity in diene hydrochalcogenation.

2.3. Hydrooxygenation of Allenes

Nishimura and co-workers reported an intermolecular hydroalkoxylation using Rh/(*R*)-DTBM-Segphos to catalyze the addition of phenols to diphenylphosphinylallenes in 2009 (Figure 8).[17] This method delivered vinyl ethers in 51–92% yields and 90:10 to 97:3 *er* via a π-allylrhodium intermediate, which releases product via a protonation process. However, reactivity was highly dependent on the presence of diphenylphosphoryl groups, limiting the generality. This requirement highlights the continued reliance on substrate activation strategies to achieve efficient and selective hydrooxygenation, underscoring the difficulty of engaging unbiased allenes under asymmetric conditions. Subsequent studies extended this reactivity to oxygen-substituted allenes, enabling concise access to bioactive motifs and the synthesis of various natural products with high enantioselectivity.[18−23]

In 2016, the Breit group developed a Rh(I)/diphenyl phosphoric acid-catalyzed hydroalkoxylation of a wide range of substrates, affording branched allylic ethers with up to 76% yield

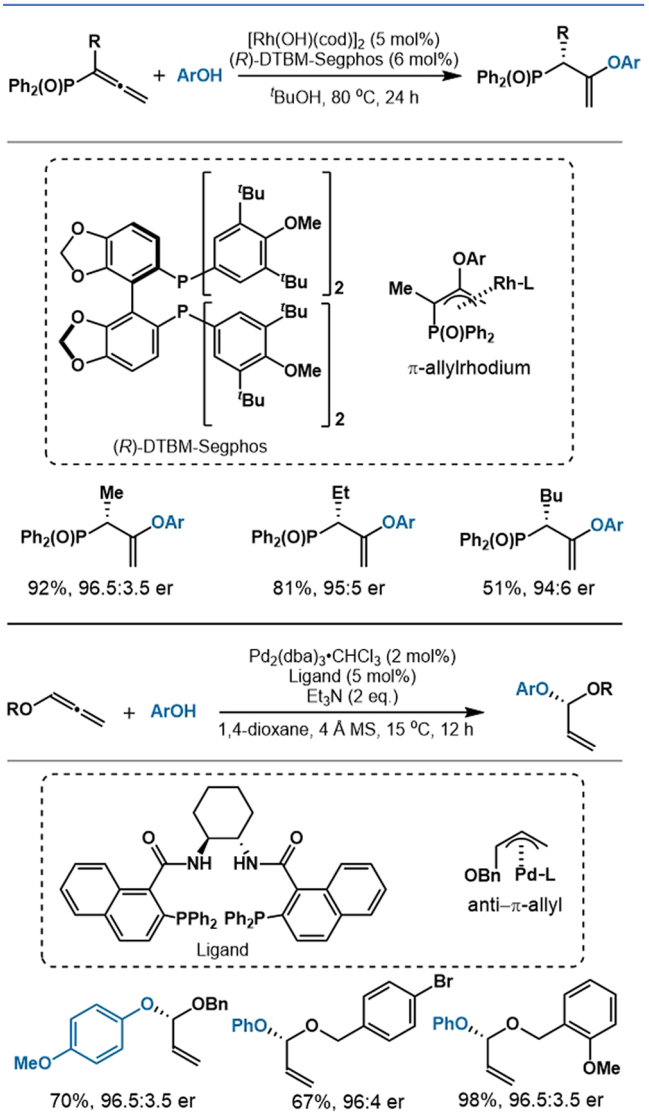

Figure 8. Metal-catalyzed asymmetric hydroalkoxylation of diphenylphosphinylallenes and oxygen-substituted allenes.

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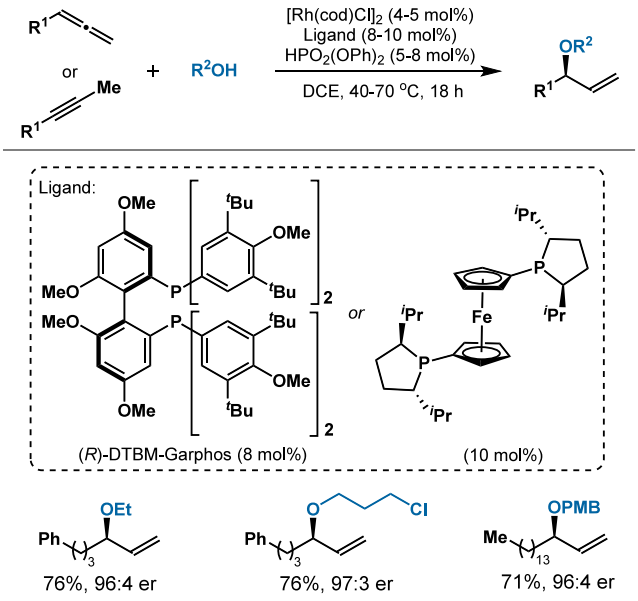

Figure 9. Rh-catalyzed asymmetric hydroalkoxylation of allenes.

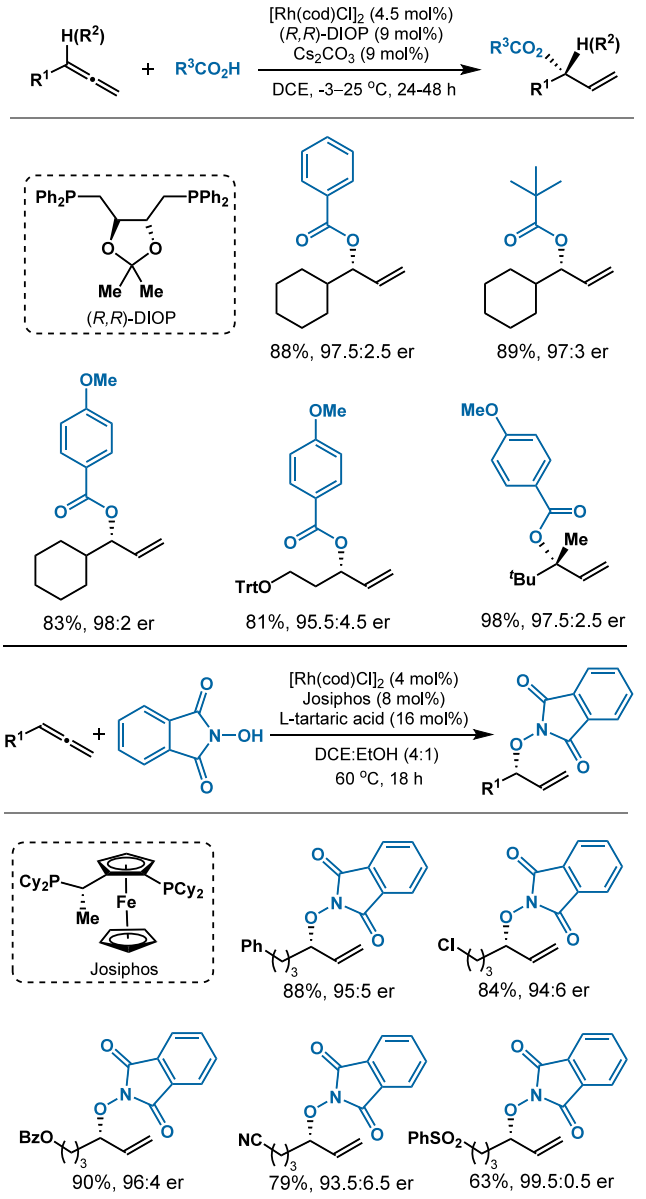

Figure 10. Rh-catalyzed asymmetric hydrooxygenation of allenes.

and 97:3 *er* (Figure 9).[24] The authors further demonstrated compatibility with alkynes, which undergo an in situ catalytic isomerization to the corresponding allenes prior to hydrofunctionalization.

Complementary strategies were also explored by the same group in 2011, introducing a Rh(I)/(*R*,*R*)-DIOP catalyzed enantioselective hydroacyloxylation of allenes or alkynes, yielding chiral ethers (Figure 10).[25] Subsequent applications of this method to the synthesis of various macrocyclic scaffolds and key intermediates for natural product synthesis demonstrated its robustness and versatility.[26−31] In addition, as a complement to *O*-nucleophiles, they utilized *N*-hydroxyphthalimide for the hydrooxygenation of allenes via a Rh(I)/Josiphos catalytic system in 2018. This approach led to the formation of chiral allylic alcohols in up to 96% yield and 98:2 *er*.[32]

Despite these advantages, enantioselective hydrooxygenation of alkenes remains comparatively underdeveloped, particularly for unactivated olefins. Many successful systems rely on electronically activated substrates such as allenes, conjugated dienes, or heteroatom-substituted alkenes, while general methods for simple aliphatic alkenes remain scarce. Reversibility in π-allyl or metal-alkyl intermediates can erode enantioselectivity, as observed in several diene systems, underscoring the challenge of controlling both regio- and stereoselectivity under mild conditions. In addition, catalyst systems often require carefully tuned ligand environments or redox partners, limiting operational simplicity. Continued development of robust catalysts capable of engaging unactivated substrates with high selectivity remains a key opportunity in this area.

3. INTERMOLECULAR ASYMMETRIC HYDROTHIOLATIONS

The asymmetric hydrothiolation of alkenes offers a direct method to construct C−S bonds, which are prevalent in biologically active compounds, natural products, and materials. In contrast to oxygen nucleophiles, sulfur nucleophiles introduce pronounced challenges in asymmetric hydrofunctionalization due to strong metal−sulfur coordination and rapid background reactivity. As a result, conjugate additions to activated Michael acceptors have emerged as the most reliable enantioselective C−S bond-forming strategies, whereas direct hydrothiolation of unbiased alkenes has required carefully engineered ligand environments, counterion control, or electrophilic activation pathways. These divergent mechanistic solutions highlight the central role of catalyst design in overcoming sulfur-induced deactivation while maintaining stereocontrol.

3.1. Hydrothiolation of Olefins

The enantioselective conjugate Michael addition of *S*-nucleophiles to electron-deficient olefins is a highly effective method for synthesizing optically active chiral organosulfur compounds, which have broad applications in organic and medicinal chemistry.[33,34] In 1977, Wynberg's group achieved the first enantioselective sulfa-Michael addition reaction (SMA) of cyclic enones

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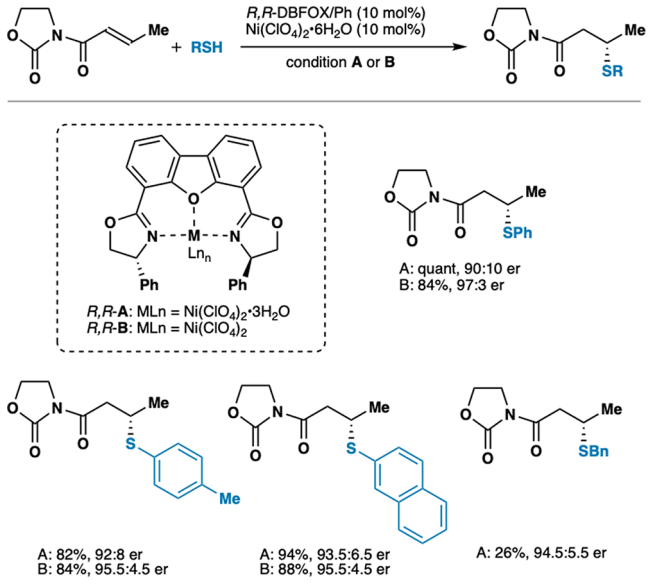

Figure 11. Ni-catalyzed asymmetric hydrothiolations of *N*-substituted α,β-unsaturated ketones.

and thiols using cinchona alkaloids, producing the desired β-thio ketones with modest enantioselectivities (53:47 to 72.5:27.5 *er*).[33] This was later improved in 1981 with quinine catalyst, which afforded β-sulfanyl ketones in up to 81:19 *er*.[35] In 1999, Kanemasa et al. developed a highly enantioselective hydrothiolation of 3-(2-alkenoyl)–2-oxazolidinone catalyzed by a Ni complex (Figure 11).[36] This provided the foundation for future Lewis acid-catalyzed systems of similar substrates, offering alternative approaches for the efficient synthesis of chiral sulfides.[37−43]

Deng and co-workers introduced the first highly enantioselective organocatalyzed method for sulfa-Michael addition using a $(DHQD)_2PYR$ catalyst in 2002 (Figure 12).[44] This method transformed a series of cyclic enones to the corresponding chiral sulfides with great reactivity and enantioselectivity. Over the following 20 years, a variety of Lewis acid-catalyzed[45−53] and organocatalyzed[54−67] hydrothiolations were further developed, offering high yields and enantioselectivities.

Long and co-workers described an Ir(I)/(*S*)-BINAP catalyzed addition reaction of N-substituted azabenzonorbornadienes with thiols in 2013.[68] Acting as a Lewis acid, the iridium catalyst can promote the addition reaction giving yields up to 90%. However, low enantioselectivities were obtained, likely reflecting insufficient substrate organization within the chiral pocket and competitive thiol coordination to the metal center, which can erode asymmetric induction. After this, Wang's group (2016) reported a similar method for the asymmetric addition of thiophenols to oxabenzonorbornadienes, giving exo-ring addition product in yields up to 96% and enantiomeric ratios as high as 99:1 (Figure 13).[69]

In 2021, our group developed a Rh-catalyzed hydrothiolation of cyclopropenes, enabling divergent formation of cyclopropyl or allylic sulfides through bisphosphine ligand-controlled selectivity (Figure 14).[70] The divergent selectivity arises from ligand-controlled partitioning of a common cyclopropyl-Rh(III) intermediate. Electron-rich Josiphos ligands favor direct reductive elimination to give cyclopropyl sulfides. In contrast, demanding atropisomeric ligands, such as DTBM-BINAP, promote

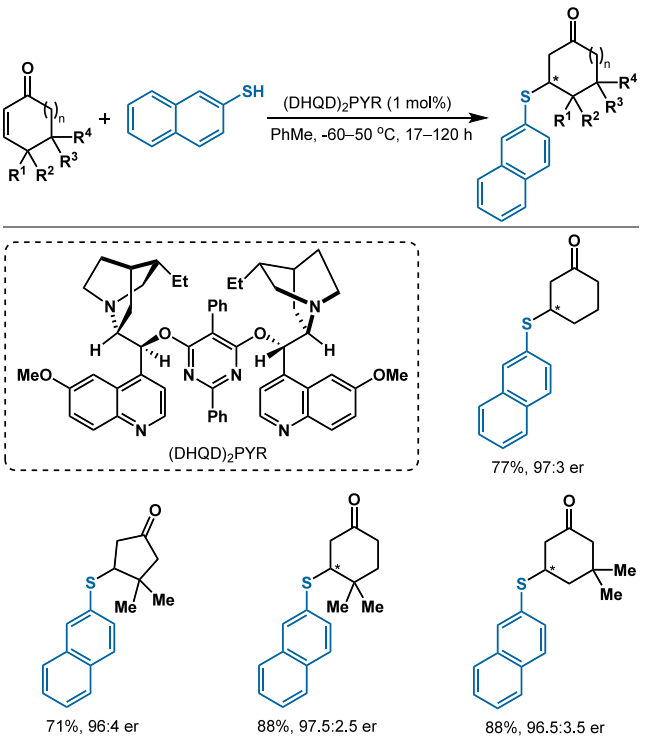

Figure 12. Organocatalyzed sulfa-Michael addition reaction.

ß-carbon elimination and enable ring opening to generate allylic sulfides. This study illustrates how subtle modulation of ligand electronics and sterics can redirect organometallic intermediates toward distinct enantioselective manifolds.

Zhao and co-workers developed an asymmetric hydrothiolation of unactivated cyclic or acyclic alkenes via an electrophilic pathway in 2022 (Figure 15).[71] The reaction was catalyzed by chalcogenide in the presence of electrophilic sulfur reagents and silanes, leading to the formation of chiral sulfides in 68–83% yield and 93.5:6.5 to 98.5:1.5 *er*. Mechanistically, the superior construction of a chiral thiiranium ion intermediate plays a crucial role in the reaction's enantioselectivity. This electrophilic activation strategy effectively bypasses catalyst deactivation by free thiols while enabling precise chiral control over ring opening, offering a powerful alternative to traditional metal−thiolate pathways.

The Zi group demonstrated a Pd-catalyzed hydrosulfonylation of styrenes with sodium sulfonates in 2023. This method provides rapid access to chiral benzylic sulfones in high yields (74–83%) with up to 98:2 *er* in the presence of a Brønsted acid (Figure 16).[72] Mechanistic studies revealed that the reaction involves a pseudo-allylic substitution of an η^3-benzylic-Pd species, which is derived from the stereoselective migratory insertion of Pd−H into the styrenes, followed by isomerization of an σ-benzylic-Pd species.

3.2. Hydrothiolation of Dienes

Hydrothiolation of 1,3-dienes has also seen notable developments. The He group initially demonstrated a hydrothiolation of 1,3-dienes with excellent 3,4-Markovnikov selectivity in 2007, though they did not achieve enantioselective control.[73] The first enantioselective 1,2-Markovnikov hydrothiolation of 1,3-dienes was reported by our group in 2018.[74] This method, using a Rh-catalyzed system, can generate either secondary or

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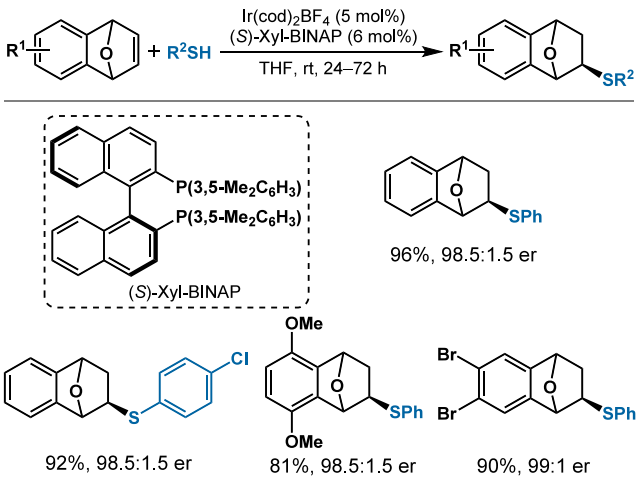

Figure 13. Ir-catalyzed hydrothiolation of heterobicyclic alkenes.

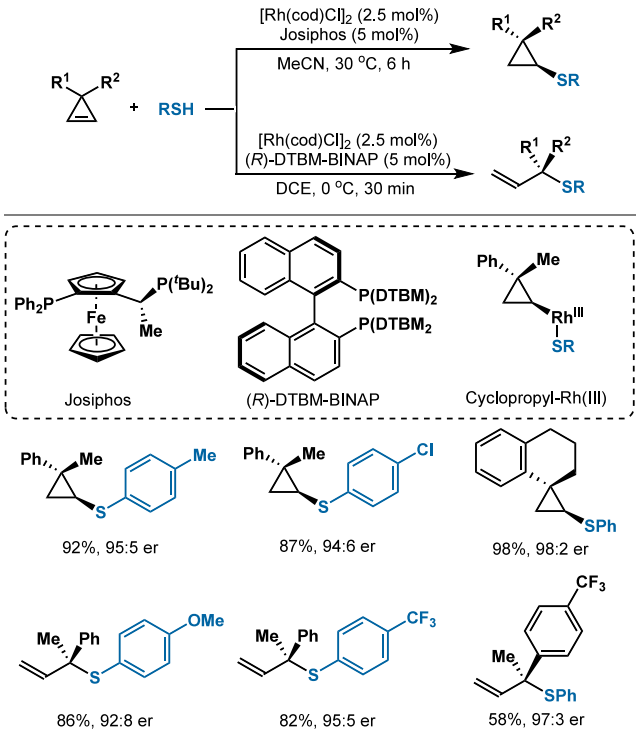

Figure 14. Rh-catalyzed asymmetric hydrothiolation of cyclopropenes.

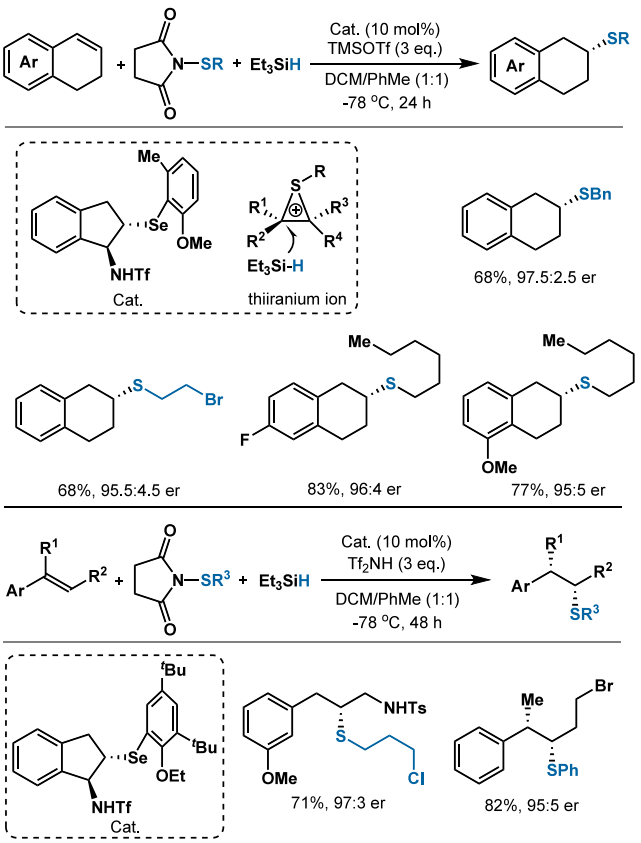

Figure 15. Chalcogenide-catalyzed asymmetric hydrothiolation of cyclic or acyclic alkenes.

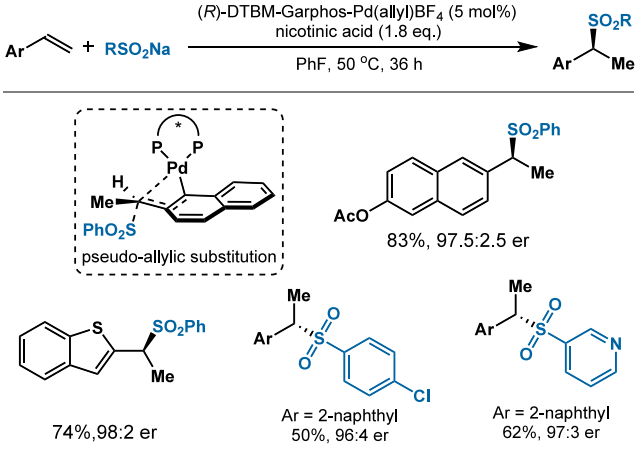

Figure 16. Pd-catalyzed asymmetric hydrosulfonylation of styrenes.

tertiary allylic sulfides with yields of up to 95% and as high as 99:1 *er* (Figure 17). The reaction is compatible with heteroarene, hydroxyl, carboxyl, amino and ester groups, in addition to aliphatic and aromatic thiols, coupled with a catalyst loading that can be as low as 0.1 mol %.

In the following year, we further investigated the regioselectivity of the catalytic hydrothiolation of 1,3-dienes.[75] We achieved high regioselectivities for the synthesis of either allylic or homoallylic sulfides by selecting different counterions associated with the Rh center. Allylic sulfides were obtained using non-coordinating counterions such as SbF_6^-, which permit η^4-diene coordination to Rh complexes, as illustrated in Figure 16. Conversely, homoallylic sulfides were produced using coordinating counterions such as Cl^-, which facilitate η^2-diene coordination to Rh complexes. These studies demonstrate how non-covalent ion pairing and coordination geometry can be leveraged to modulate alkene binding modes and dictate regio- and enantioselectivity, providing a general design principle for controlling complex hydrofunctionalization manifolds.

Chiral sulfones are widely used in pharmaceutical chemistry. In 2020, the Zi group developed a regio- and enantio-selective hydrosulfonylation of 1,3-dienes catalyzed by Pd/(*R*)-DTBM-Segphos for synthesizing chiral allylic sulfones (Figure 18A).[76]

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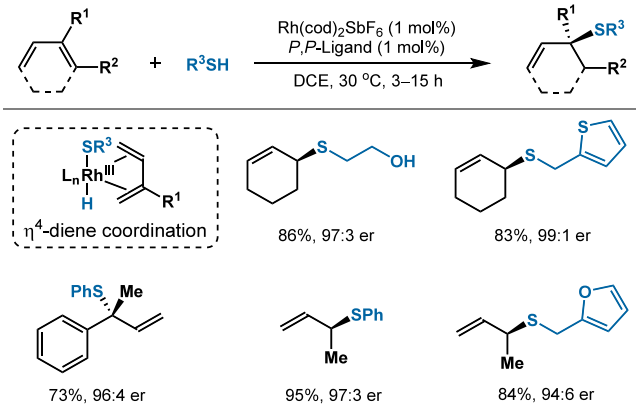

Figure 17. Rh-catalyzed asymmetric hydrothiolation of 1,3-dienes.

Mechanistic studies revealed that the steric repulsion between the tert-butyl group of DTBM-Segphos and the olefinic C−H of the substrate plays a crucial role in controlling the enantioselectivity. Several months later, the Zhou group reported a Pd-catalyzed asymmetric hydrosulfonylation of 1,3-dienes with sulfonyl hydrazides (Figure 18B).[77] They achieved a highly regio- and enantioselective conversion using a monodentate chiral spiro phosphoramidite ligand. Mechanistically, the chiral allylic sulfone product was formed through the generation of an allyl hydrazine intermediate and its subsequent rearrangement.

3.3. Hydrothiolation of Allenes

In 2009, Hayashi and co-workers described a Rh/(*R*)-DTBM-Segphos catalyzed hydrothiolation of diphenylphosphinylallenes to produce two examples of vinylthioethers with 90.5:9.5 and 87.5:12.5 *er*, respectively.[17] In 2022, two geminal or 1,1-difluoro substituted allenes attracted substantial research interest. The Shi group used a Rh catalyst and bidentate ligand to achieve the hydrothiolation of *gem*-difluoroallenes, giving a variety of substituted difluoroethenes and difluoropropenes with excellent regioselectivity, chemoselectivity and enantioselectivity (Figure 19).[78]

In the same year, Halimehjani and Breit reported the hydrothiolation of terminal allenes with thioacids using Rh/DIOP as the catalyst, achieving chiral branched allylic thioesters with high regioselectivity and up to 96:4 *er* (Figure 20).[79] This method demonstrated a broad tolerance for a variety of functional groups in both allenes and thioacids.

In 2024, the Aponick group reported the hydrothiolation of terminal allenes with sodium sulfonates using Rh and the C_1-symmetric *P*,*N*-ligand (R_{ax},*S*,*S*)-StackPhim as the catalyst, rapidly achieving chiral branched allylic sulfones with both high regioselectivity and enantioselectivity (>20:1, up to 98.5:1.5 *er*) (Figure 21).[80] This operationally simple method demonstrated a wide scope of functional groups in both alkyl or aryl-substituted allenes and sodium sulfonates.

Although asymmetric hydrothiolation has seen substantial growth, sulfur nucleophiles continue to present intrinsic challenges due to their strong coordination ability and tendency to deactivate metal catalysts. Many highly enantioselective systems rely on activated Michael acceptors or electrophilic pathways rather than direct addition to unactivated alkenes, highlighting the limited generality of current approaches. In transition-metal catalysis, achieving high selectivity often requires finely balanced ligand and counterion effects, and competing side reactions such as isomerization or over-addition can complicate reaction

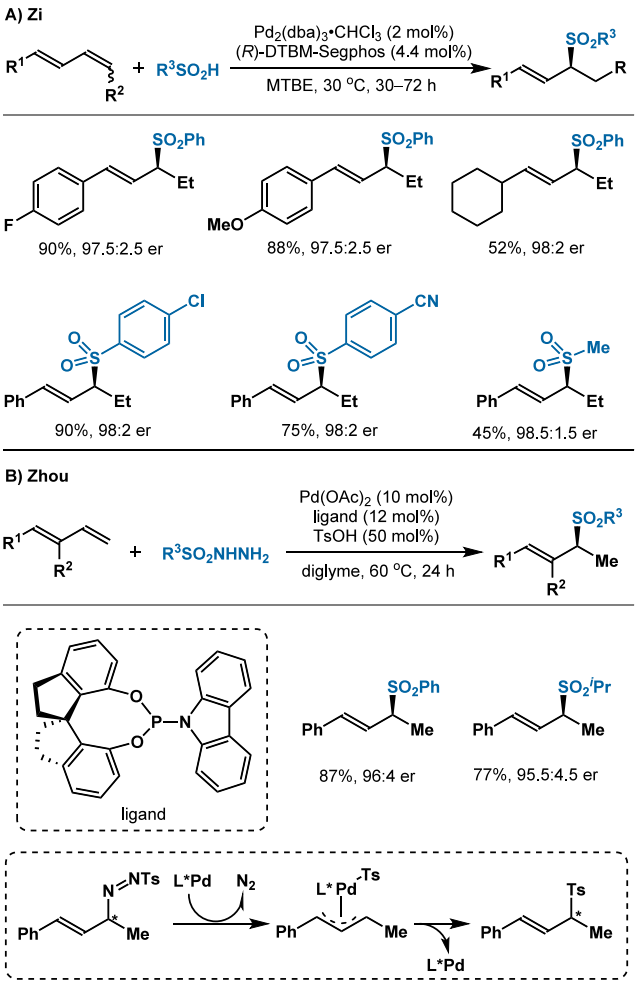

Figure 18. Pd-catalyzed asymmetric hydrosulfonylation of 1,3-dienes. (A) Reaction developed by Zi. (B) Reaction and proposed mechanism reported by Zhou.

outcomes. Furthermore, broad substrate scope across diverse alkene classes remains uncommon within a single catalytic platform. Future progress will benefit from catalyst designs that can tolerate sulfur coordination while maintaining high regio- and enantiocontrol under practical conditions.

4. INTERMOLECULAR ASYMMETRIC HYDROSELENATION

Although selenium-containing compounds are less commonly encountered in bioactive molecules than their oxygen and sulfur analogs, selenium has attracted increasing attention due to its unique reactivity and utility in synthetic and medicinal chemistry. Selenium plays a critical role as a micronutrient in the metabolic cycle of natural organisms. At present, 25 selenoproteins, containing selenocysteine (SeCys) residues at their active sites, are known in humans with roles in antioxidative pathways, selenium transport, maintaining intracellular redox status and in thyroid hormone production, amongst other functions.[81−84] Moreover, in synthetic chemistry, selenium also functions as unique active sites on catalysts and ligands, but the development of atom-economic hydroselenation reactions has remained limited. Hydroselenation shares many of the

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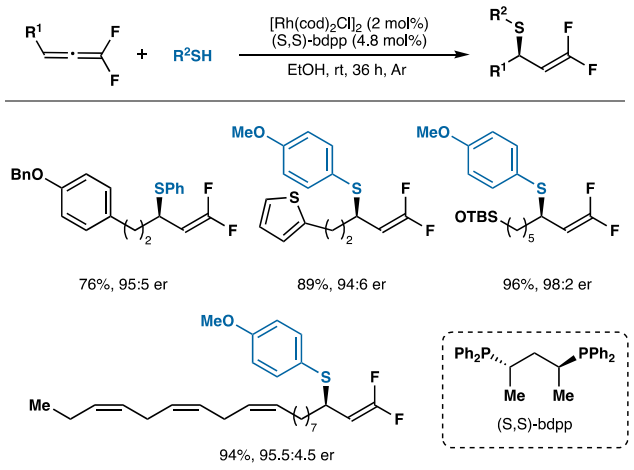

Figure 19. Rh-catalyzed asymmetric hydrothiolation of *gem*-difluoroallenes.

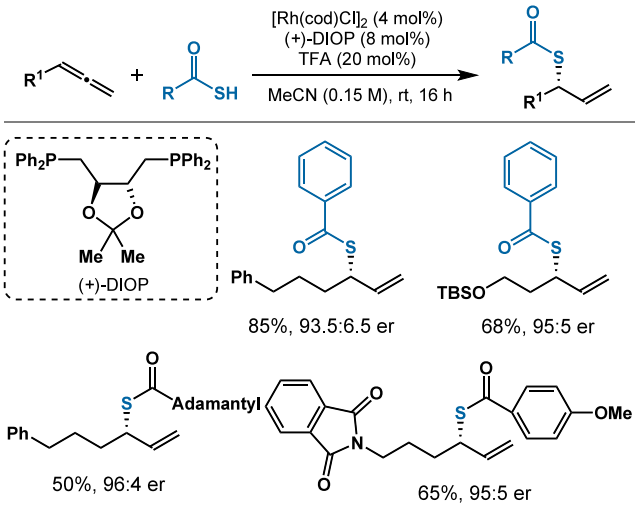

Figure 20. Rh-catalyzed asymmetric hydrothiolation of allenes with thioacids.

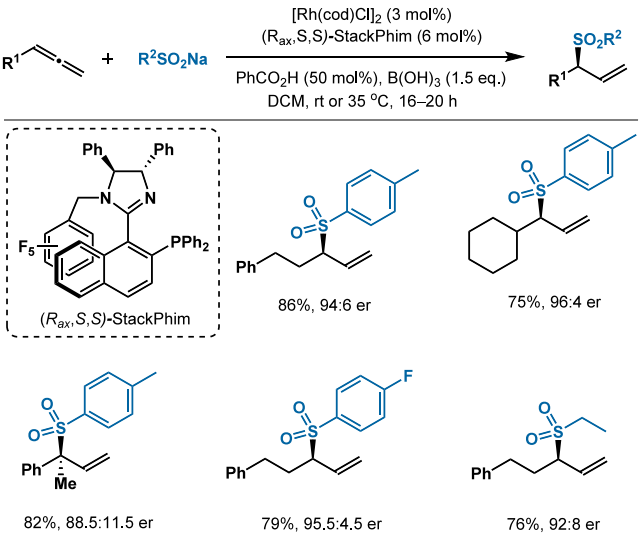

Figure 21. Rh-catalyzed asymmetric hydrosulfonylation of allenes with sodium sulfonates.

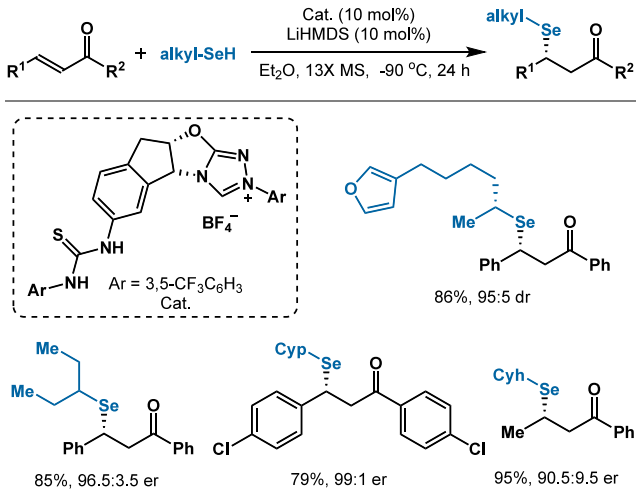

Figure 22. Bifunctional *N*-heterocyclic carbene (NHC)/thiourea-catalyzed asymmetric hydroselenization of α,β-unsaturated compounds.

coordination and reversibility challenges encountered in sulfur chemistry but is further complicated by the heightened nucleophilicity and lower pK_a of selenols. Consequently, early successes have largely relied on activated π-systems or bifunctional catalytic strategies designed to suppress nonselective background addition. Overall there has been limited development of asymmetric hydroselenations relative to oxygen- and sulfur-based systems, despite the synthetic and biological importance of organoselenium compounds. Only recently have metal-hydride and orthogonal activation pathways enabled selective engagement of relatively unactivated alkenes.

The first example of asymmetric hydroselenation was reported by Wynberg and Pluim in 1979, in which the reaction utilized (−)-cinchonidine to achieve the asymmetric addition of selenols to cyclohexenols, resulting in quantitative yields and up to 73.5:26.5 *er*.[85] In 2022, Huang and co-workers reported an enantioselective hydroselenation of α,β-unsaturated compounds using a chiral bifunctional *N*-heterocyclic carbene (NHC)/thiourea catalyst (Figure 22).[86] This new catalyst overcomes the issue of reversibility due to the high nucleophilicity and leaving group ability of selenols, which was the main challenge plaguing the development of asymmetric seleno-Michael addition reactions.[87−90] Using their method, alkyl selenols were efficiently converted into chiral selenides with excellent enantioselectivity (87.5:12.5 to 99:1 *er*). The cooperative bifunctional activation mode simultaneously organizes the electrophile and nucleophile while minimizing free selenolate concentration, thereby suppressing nonselective background reactions that had previously plagued asymmetric seleno-Michael additions.

The Yin group disclosed copper(I)-catalyzed asymmetric hydroselenation of α-substituted α,β-unsaturated thioamides with selenols in 2023 (Figure 23).[91] This reaction tolerates broad substrate scopes (including alkyl selenols), and offers chiral selenides with high to great enantioselectivity (up to 99.5:0.5 *er*). A [Cu-(R,R_P)-TANIAPHOS]-SePh species is well characterized by its ^{77}Se NMR spectra. Furthermore, a {[Cu-(R)-TOL-BINAP]-SePh}$_2$ species is characterized by X-ray

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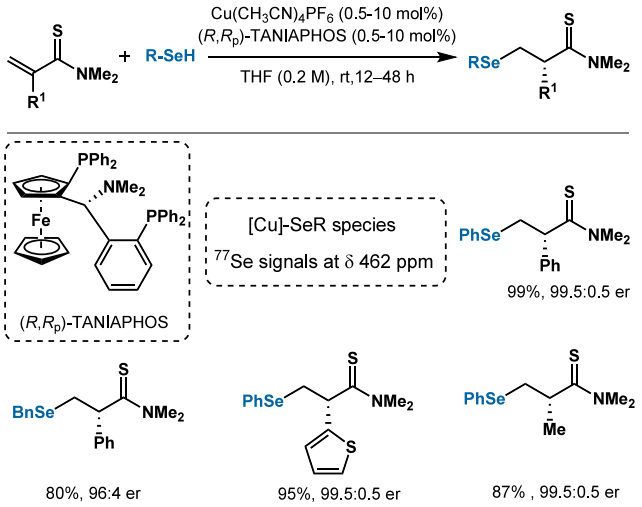

Figure 23. Cu-catalyzed asymmetric hydroselenation of α-substituted α,β-unsaturated thioamides.

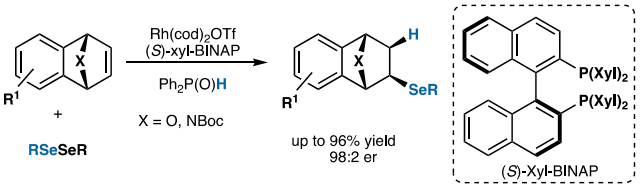

Figure 24. Rh-catalyzed asymmetric hydroselenation of heterobicyclic alkenes.

crystallography, which proves the formation of Cu−Se bond in this reaction. The direct observation of Cu−Se intermediates provides rare mechanistic evidence for controlled selenolate transfer in asymmetric catalysis, illustrating how stabilized metal−selenium bonds can be harnessed productively rather than leading to catalyst deactivation.

Bian and co-workers achieved Rh-catalyzed asymmetric formal hydroselenation of heterobicyclic C−C π bonds (Figure 24).[92] Under mild reaction conditions, this approach enabled the synthesis of selenol-incorporated adducts with excellent enantioselectivities (80:20 to 98.5:1.5 *er*) and high yields (up to 96%) across a diverse range of heterobicyclic alkenes. This strategy effectively addressed the challenges posed by selenium poisoning of rhodium and competitive self-promoted hydroselenation. As a result, this methodology has expanded the scope of asymmetric hydroselenation to include nonpolar olefins.

Our group demonstrated the first enantioselective hydroselenation of styrenes catalyzed by Rh/MeO-BIPHEP in 2022 (Figure 25).[93] Organoselenium building blocks were accessed with selectivity for the branched isomer. The high regio- and enantiocontrol observed in this system (>20:1 *rr* and 98:2 *er*) stems from a well-defined Rh-hydride insertion pathway, wherein migratory insertion into the alkene precedes stereodetermining C−Se bond formation. The ability to control hydride delivery and suppress background selenol addition is central to achieving selective functionalization of relatively unreactive styrenes. This work demonstrates that carefully engineered hydride-mediated pathways can overcome the intrinsic reactivity mismatch between selenols and unactivated alkenes, offering

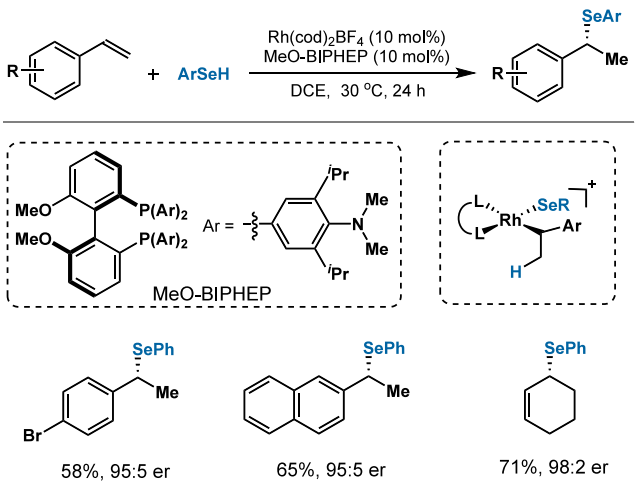

Figure 25. Rh-catalyzed asymmetric hydroselenation of styrenes.

a generalizable strategy for suppressing uncontrolled background addition while enabling high stereocontrol.

Our group recently demonstrated a catalyst-controlled divergent hydroselenation of cyclopropenes to obtain formation of cyclopropyl or allylic selenides (Figure 26).[94] The divergent reactivity is proposed to arise from the selection of metal catalyst. Rh(I)-catalysis activates selenols through an oxidative addition pathway to facilitate an enantioselective ring-retentive hydroselenation. Conversely, through Cu(I)-catalysis, cyclopropene is initially activated and promotes the ring-opening hydroselenation to form vinylselenides. Overall, while asymmetric hydroselenation lags behind its oxygen and sulfur counterparts, these examples demonstrate the increasing viability and versatility in using selenium nucleophiles. This catalyst-controlled divergence

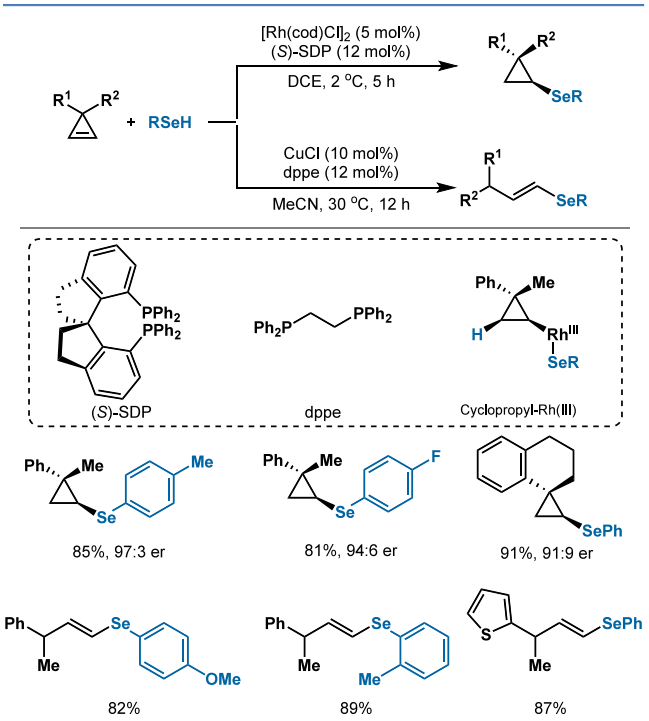

Figure 26. Transition-metal-catalyst controlled divergent hydroselenation of cyclopropenes.

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highlights how selective activation of either the nucleophile or the strained alkene can dictate distinct reaction manifolds, providing a blueprint for expanding asymmetric hydroselenation through orthogonal mechanistic pathways.

Overall, while asymmetric hydroselenation has made notable progress in recent years, it remains less mature than its oxygen and sulfur counterparts. The high nucleophilicity and strong metal-binding ability of selenols frequently lead to catalyst deactivation and reaction reversibility, which have historically limited substrate scope and stereocontrol. Most successful examples have focused on activated π-systems or carefully engineered catalytic pathways to suppress background reactions. Expanding these transformations to simple, unactivated alkenes with broad functional group tolerance remains a significant challenge. Continued innovation in catalyst design and mechanistic control will be essential to fully realize the synthetic potential of selenium-based hydrofunctionalization.

5. CONCLUSIONS AND OUTLOOK

Over the past two decades, remarkable progress has been made in developing intermolecular enantioselective hydrofunctionalization strategies using chalcogen nucleophiles. These advances have enabled the construction of C−O, C−S, or C−Se with high regio- and enantioselectivity across a variety of alkene classes, including olefins, 1,3-dienes, and allenes. The diversity of catalytic platforms, ranging from Brønsted acids catalysis to ligand-controlled transition-metal systems, underscores the creativity and mechanistic sophistication achieved in this area. Many recent successes have been driven by precise control over key intermediates such as π-allyl complexes, metal−hydride species, and electrophilic chalcogen-activated adducts.

Despite this progress, chalcogen-based hydrofunctionalization remains less mature than its nitrogen counterpart, particularly for electronically unbiased alkenes.[6,7] Persistent challenges include reversibility of metal−alkyl or allylic intermediates that erodes enantioselectivity, strong coordination of sulfur and selenium nucleophiles that leads to catalyst deactivation, and limited generality across substrate classes within single catalytic platforms. Addressing these challenges will likely require catalyst architectures capable of simultaneously controlling reactivity and suppressing nonproductive binding events.

Mechanistically guided strategies are likely to play a central role in future advances. Ligand frameworks that enforce defined alkene binding geometries while incorporating hemilabile or sterically shielding elements may mitigate chalcogen coordination without sacrificing activity. Pathways that leverage controlled hydride delivery, outer-sphere nucleophilic attack, or cooperative Brønsted acid/transition-metal catalysis may offer promising routes to overcome reversibility and background reactivity. Furthermore, orthogonal activation modes that selectively engage either the nucleophile or the alkene, as demonstrated in divergent catalytic systems, provide a blueprint for expanding reactivity while maintaining high stereocontrol.

As interest in chalcogen-containing molecules continues to grow across pharmaceutical, biological, and materials science, so too does the need for modular, stereoselective methods to build these bonds. We anticipate that continued integration of mechanistic insight with catalyst design will enable the development of next-generation hydrofunctionalization strategies capable of engaging unactivated substrates with high selectivity. Ultimately, such advances will not only expand the synthetic utility of Group 16 nucleophiles but also deepen fundamental understanding of asymmetric catalysis at reactive π-systems.

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Notes

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