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Research Progress in Enantioselective Radical Desymmetrization Reactions

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Abstract

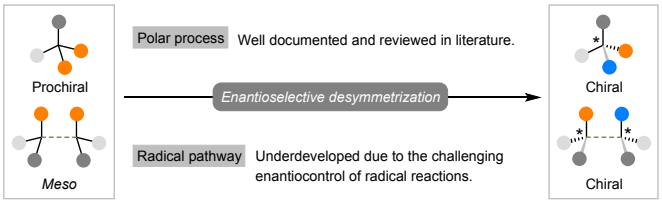
Enantioselective radical desymmetrization is a highly effective approach for rapidly creating enantioenriched molecules, introducing dramatically increased structural complexity from readily available prochiral or *meso* compound feedstocks. Two strategic modes have been developed for these reactions, which differ in the nature of the stereo-determining steps. The first category deals primarily with the stereoselective desymmetrization of closed-shell radical precursors or functional reagents, whereas the second category achieves desymmetrization by stereoselectively functionalizing open-shell radical species. This mini-review explores the research progress in this growing field, aiming to elucidate mechanistic scenarios related to stereochemical control. Additionally, it offers insights into the challenges and opportunities that lie ahead for further development.

Keywords

radical desymmetrization, enantioselective desymmetrization, radical functionalization, transition-metal catalysis, asymmetric catalysis

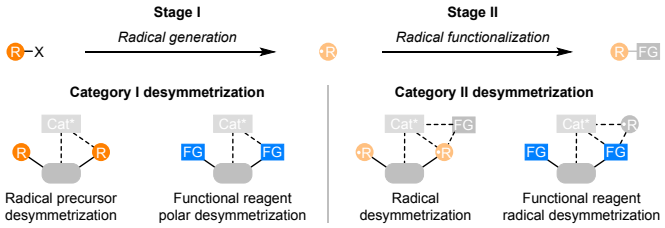
Introduction

Enantioselective desymmetrization of prochiral and *meso* compounds is an attractive and efficient method to produce single or multiple stereogenic centers in one synthetic step for constructing diverse enantioenriched molecules with enhanced structural complexity.[1–4] This strategy has proven practical in enantioselective total synthesis of natural products and bioactive compounds, particularly those that use readily available starting materials.[5,6] Enantioselective desymmetrization reactions are a synthetically superior alternative to kinetic resolutions, as they can theoretically tolerate all types of catalytic asymmetric transformations to convert achiral substrates into enantioenriched products with quantitative yields.[4] Considerable efforts have been directed towards catalytic enantioselective desymmetrization using various chiral catalysts, including enzymes,[7–9] metal complexes,[10,11] and organocatalysts.[12,13] Although significant advances have been made in enantioselective desymmetrization reactions proceeding through polar processes,[1–4,10–15] the development of their counterparts that involve a radical pathway has largely lagged behind. The lack of effective strategies to selectively control both the reactivity and enantioselectivity of radical transformations is the main issue (Scheme 1).[16] In recent years, the explosive emergence and development of enantioselective radical-involved reactions[17–20] has provided a mechanistically unique platform for achieving enantioselective radical desymmetrization reactions. This mini-review highlights the recent research progress in this field and also introduces relevant earlier achievements where appropriate. It should be noted that relevant enantioselective enzymatic desymmetrization reactions in organic synthesis have already been comprehensively reviewed[7] and will not be specifically discussed further in this review.



Scheme 1 *General discussion on enantioselective desymmetrization of prochiral and meso compounds.*

The development of enantioselective radical reactions has to surmount the inherently inevitable challenge that is to maintain competent covalent and/or non-covalent interactions effectively between chiral catalysts or reagents and stereotopic motifs embedded in substrates, especially in the presence of highly reactive radical species. In principle, enantioselective radical desymmetrization reactions can be largely classified into two strategic modes based on the stage where the stereo-determining step occurs (Scheme 2). The first category involves the desymmetrization of symmetric radical precursors or polar desymmetrization of functional reagents. Specifically, the stereo-determining activation of radical precursors or functional reagents occurs during the radical generation stage (stage I; Scheme 2, left). By contrast, reactions of the second category achieve desymmetrization through stereo-determining radical functionalization reactions. Accordingly, prochiral radicals or equivalents are first generated, which next engage in stereoselective desymmetrization of either themselves or functional reagents (stage II; Scheme 2, right). In other words, the first category of reactions hinges on the desymmetrization of closed-shell molecules while the second category deals with open-shell species. In this sense, these two reaction categories involve substantially distinct reactive species that pose different stereochemical challenges. This mini-review is organized based on these two categories, with particular emphasis on mechanistic insights into stereochemical modes. In addition, the current challenges and future perspectives in this area are also discussed.



Scheme 2 *Two strategic modes for achieving enantioselective radical desymmetrization reactions.*

Category I Desymmetrization via Asymmetric Radical Generation or Polar Manifolds

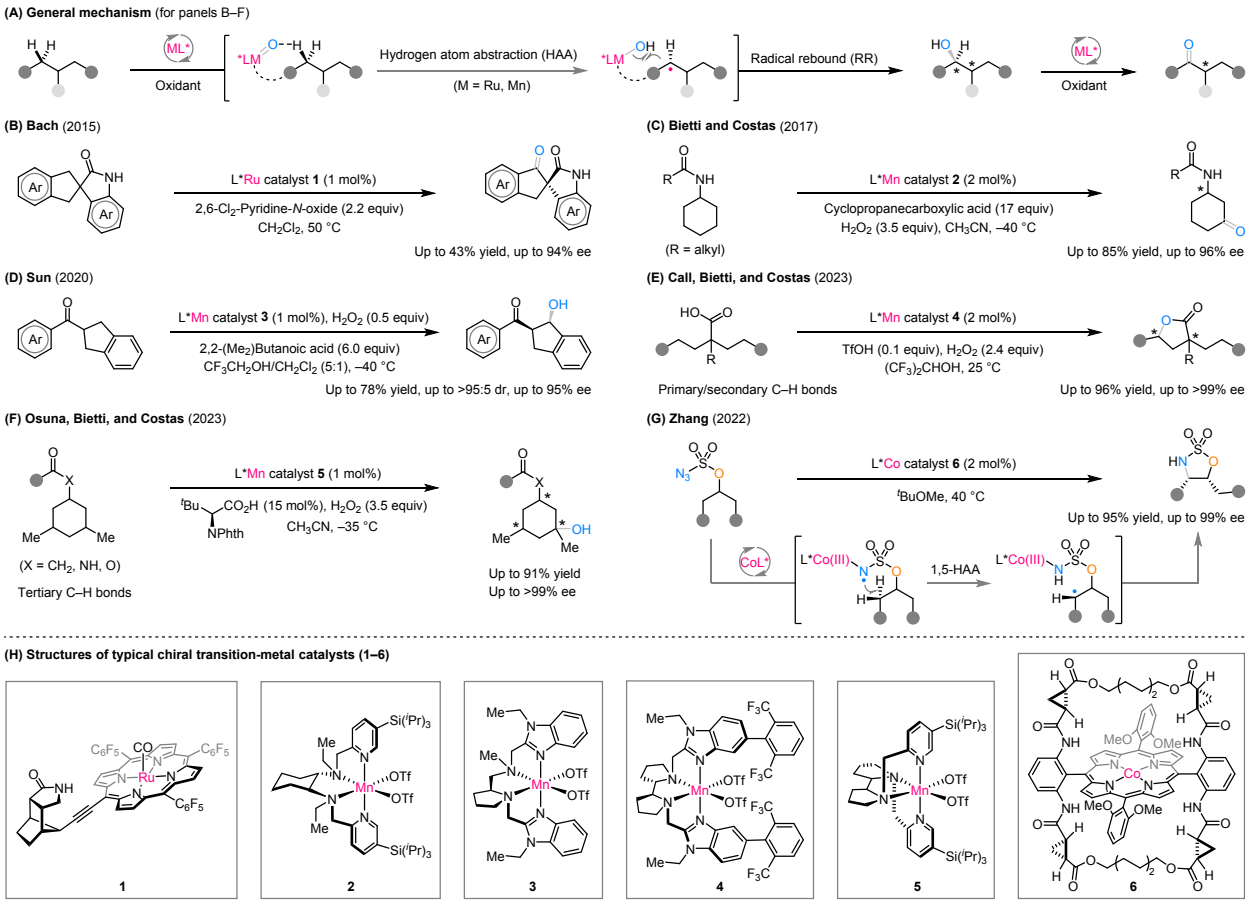
Desymmetrization via enantiotopic group-selective radical generation reactions

Catalysts or reagents are required for reactions in this category to interact effectively with enantiotopic groups of closed-shell prochiral or *meso* substrates for eliciting competent desymmetrization. This process breaks the overall molecular symmetry and involves the generation of radical species that would engage in further transformations. However, the comparable reactivities of the two enantiotopic groups within a single molecule can lead to unintended overreactions, posing a significant obstacle to achieving precise enantiocontrol for a given reaction. To enable improved reaction efficiency and enantioselectivity, it is important to carefully consider the appropriate choice of chiral catalysts, substrates, and reaction conditions. In this regard, several sophisticated methods have been successfully demonstrated to realize enantioselective desymmetrization through enantiotopic group-selective radical generation reactions. The following subsections will discuss these advances primarily based on the different closed-shell substrates employed.

Desymmetrization of enantiotopic C(sp^3)–H bonds

Enantioselective radical functionalization of C(sp^3)–H bonds is a highly efficient method for producing high-value chiral molecules, eliminating the need for prefunctionalization of starting materials.[21] It has been recognized that biomimetic chiral transition-metal complexes can serve as effective catalysts for achieving enantioselective desymmetrizing hydroxylation of prochiral methylene compounds in the presence of stoichiometric terminal oxidants.[22] Inspired by biological processes, these reactions mechanistically proceed via a desymmetrizing hydrogen atom abstraction (HAA) of the enantiotopic C–H bonds in substrates by a high-valent metal-oxo species, generating a hydroxometal intermediate and a conformationally constrained transient radical species, respectively. This is followed by a stereoretentive fast radical rebound (RR) process to yield the corresponding enantioenriched secondary alcohols.[23] Of particular note is that the target secondary alcohols may be overoxidized to ketones, which is often unavoidable and frequently observed (Scheme 3A). This has been demonstrated independently by the groups of Katsuki[24–27] and Murahashi[28,29] in the early cases of enantioselective oxidative desymmetrization reactions using chiral Mn- or Ru-salen complexes as catalysts. Nevertheless, the overoxidation process could enable the precise conversion of

prochiral substrates that contain two enantiotopic methylene groups into chiral ketones with nearby stereocenters located away from the reaction sites. In 2015, Bach and coworkers reported an enantioselective desymmetrizing ketonization of spirocyclic oxindoles using chiral Ru porphyrin catalyst **1** (Scheme 3B and 3H) with a remote lactam moiety and a pyridinium *N*-oxide oxidant.[30] Mechanistic studies suggested that the high enantiocontrol originated from a well-defined spatial relationship between the chiral catalyst and substrate molecule via hydrogen bonding. However, the desired chiral ketone products were isolated in low to moderate yields due to incomplete oxidation of *in situ*-formed alcohol intermediates. In 2018, Nam, Sun, and their colleagues described a similar enantioselective desymmetrizing ketonization of spirocyclic tetralones and indanones.[31] They employed a chiral tetradentate Mn catalyst **3** (Scheme 3H) and a stoichiometric amount of aqueous H_2O_2 as the terminal oxidant, resulting in the corresponding chiral spirocyclic ketones in good yields with high enantioselectivities. When the same chiral Mn catalytic system was applied to spirocyclic oxindole and quinolinone derivatives, however, both the desired chiral ketones and chiral secondary alcohol intermediates were obtained in moderate yields, respectively.[32] As for non-activated enantiotopic methylene groups, Bietti, Costas, and their colleagues discovered a highly regioselective and enantioselective desymmetrizing ketonization of *N*-(cyclohexyl)alkanamides with chiral Mn catalyst **2** (Scheme 3C and 3H) and H_2O_2 as the oxidant, leading to the exclusive synthesis of enantioenriched *N*-(3-oxocyclohexyl)alkanamides.[33] The success of this reaction relied on the introduction of bulky tri(isopropyl)silyl groups in the ligand to create a tight chiral cavity, as well as the assistance of an oxidant-resistant alkyl carboxylic acid as an ancillary ligand in defining the active site. However, the exceptional role of the basic amide moiety of substrates in determining regioselectivity and enantioselectivity has not yet been fully understood.



Scheme 3 *(A –H) Catalytic enantioselective radical desymmetrization of enantiotopic C(sp³) –H bonds.*

At the same time, efficient protocols have also been established to address the problem of undesired overoxidation in enantioselective radical desymmetrization of prochiral methylene compounds, which allow for the introduction of a chiral alcohol group at the reaction site in specific molecules. In 2020, Sun and coworkers discovered that highly diastereo- and enantioselective desymmetrizing hydroxylation of carbonyl group-substituted indane derivatives could be achieved using H_2O_2 as the oxidant and an alkyl carboxylic acid as the additive under the catalysis of chiral Mn complex **3** (Scheme 3D and 3H).[34] The choice of 2,2,2-trifluoroethanol as the reaction medium was crucial in preventing further oxidation of the resulting secondary alcohols, likely via forming hydrogen bonds with them to deactivate their α-C–H bonds toward HAA. High stereocontrol observed in this study was attributed to the proposed multiple hydrogen bonding interactions

between the Mn-oxo species, substrate, polyfluorinated alcohol, and carboxylic acid additive. In this regard, Bietti, Costas, and coworkers demonstrated that by carefully introducing a carboxylic acid moiety into the starting substrates, highly enantioselective desymmetrizing lactonization of adamantaneacetic acid[35] and α-amino acid derivatives[36] could be achieved using a similar chiral Mn catalyst and H_2O_2 reaction system. The use of a carboxylic acid moiety as a directing group to coordinate with the chiral catalyst, along with the employment of fluorinated alcohols as strong hydrogen bond donor solvents, ensured a rigid environment for excellent enantiocontrol and regiocontrol. Isotopic labeling experiments revealed that the oxygen atom on the chiral lactone ring originated competitively from both the carboxylic acid group and hydrogen peroxide.[35] This result suggested that the detailed radical rebound mechanism might be more complex than the schematic illustration of Scheme 3A.[23,37] In 2023, Call, Bietti, Costas, and coworkers extended the carboxylic acid-directed lactonization approach to enantioselective desymmetrization of non-activated primary and secondary C–H bonds by a sterically encumbered chiral Mn catalyst **4** (Scheme 3E and 3H).[38] As for tertiary C–H bonds, Osuna, Bietti, Costas, and coworkers recently reported a non-directed enantioselective desymmetrizing hydroxylation of functionalized cyclohexanes using chiral Mn catalyst **5** (Scheme 3F and 3H), providing enantioenriched tertiary alcohols with multiple stereocenters.[39] The addition of a chiral α-amino acid as a co-ligand was essential for achieving improved enantioselectivity and significant match-mismatch effects were observed using both enantiomers of catalyst **5**. Theoretical analysis unveiled that the enantiocontrol was governed by a synergistic interplay of weak interactions and structural complementarity between the substrate and chiral catalyst.

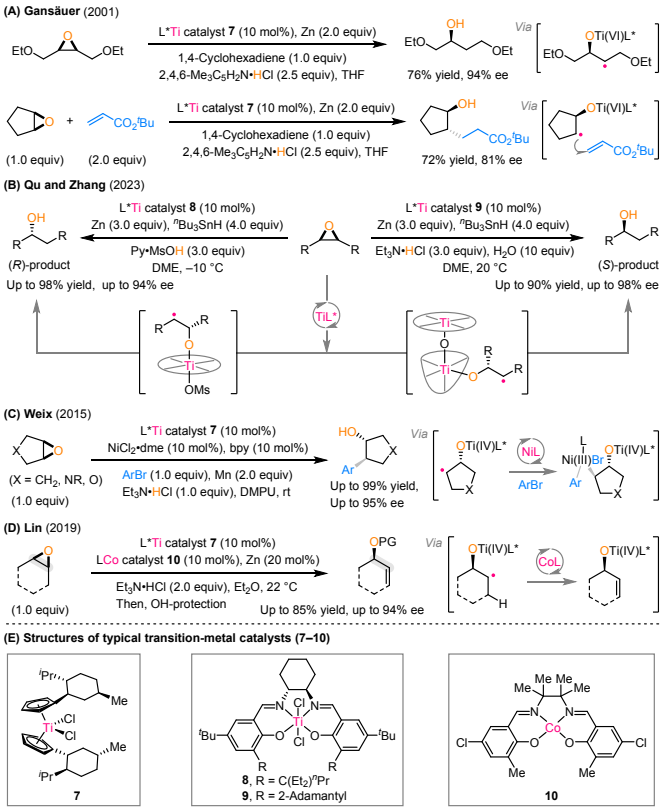
In addition to oxidation reactions, enantioselective desymmetrization of enantiotopic C–H bonds can also proceed through radical amination reactions. In this aspect, Zhang's group has designed a range of bridged chiral porphyrin ligands with a tunable cavity-like chiral environment for Co(II)-based metalloradical catalysis.[40] In 2022, Zhang and coworkers reported an enantioselective desymmetrizing amination reaction of enantiotopic C–H bonds in alkoxysulfonyl azides using chiral Co complex **6** (Scheme 3G and 3H) as the catalyst.[41]

The chiral Co(II) complex activated the azide substrates via homolytic fission to generate a Co(III)-stabilized aminyl radical, which underwent a sequential desymmetrizing enantiodifferentiative intramolecular 1,5-HAA and stereoselective radical substitution pathway, resulting in the formation of chiral cyclic sulfamidates in high yields with excellent diastereoselectivities and enantioselectivities.

Desymmetrization of *meso* epoxides

Meso epoxide derivatives are frequently used as the starting materials for developing enantioselective desymmetrization reactions. This is due to their high reactivity, which is a result of the inherent three-membered ring strains, as well as their ready availability from simple alkene precursors.[1,42] In addition, the well-polarized enantiotopic C–O bonds of epoxides are prone to undergo homolytic cleavage and generate an open-shell carbon-centered radical species when exposed to an oxophilic Ti(III) complex, which acts as a single-electron reducing reagent.[43] In this regard, the Gansäuer group has pioneered the use of a chiral titanocene catalyst, an analog of Ti(IV)-based complex **7** (Scheme 4E), to achieve catalytic enantioselective radical desymmetrization of *meso* epoxides.[44] In 2001, the same group reported the enantioselective desymmetrizing reductive ring-opening reactions of *meso* epoxides using 1,4-cyclohexadiene as a hydrogen atom donor (HAD) and chiral Ti catalyst **7** (Scheme 4A and 4E) in the absence or presence of acrylate, resulting in the formation of new C–H and C–C bonds.[45] The catalytic cycle was achieved by reducing the Ti(IV) precatalyst into a Ti(III) active species with a stoichiometric amount of Zn powder as the reductant in the presence of a weak acid additive, such as substituted pyridine hydrochloride.[46] The acid additive served as a proton source to facilitate the protonation of the final Ti(IV) alkoxide intermediate, releasing the chiral alcohol product and Ti(IV) precatalyst. Additionally, Gansäuer and coworkers also described a modification of this delicate reaction system utilizing a coupled catalytic cycle approach with rhodium hydride as the radical HAD.[47] In 2019, Gansäuer and coworkers extended the reaction conditions in a more sustainable manner by merging chiral titanocene catalysis with photoredox catalysis, dispensing with the need for stoichiometric acidic additives and metal reductants.[48] In 2023, Qu, Zhang, and coworkers developed a catalyst nuclearity-controlled

enantiodivergent reductive ring-opening desymmetrization of *meso* epoxides using chiral Ti catalysts **8** and **9** (Scheme 4B and 4E) with analogous stereogenic scaffolds.[49] Both antipodes of the chiral alcohol products were selectively obtained under the catalysis of mononuclear Ti(III) active species and their oxygen-bridged binuclear $Ti(III)_2O$ counterparts *in situ* generated with the aid of H_2O, respectively. Mechanistic investigations revealed that the divergent enantiocontrol originated from an enthalpy-controlled enantiodifferentiation mode in the mononuclear catalysis but an entropy-controlled one in the binuclear catalysis. However, detailed information regarding the large entropy contribution in the binuclear catalysis pathway remained elusive.



Scheme 4 *(A –E) Catalytic enantioselective radical desymmetrization of meso epoxides.*

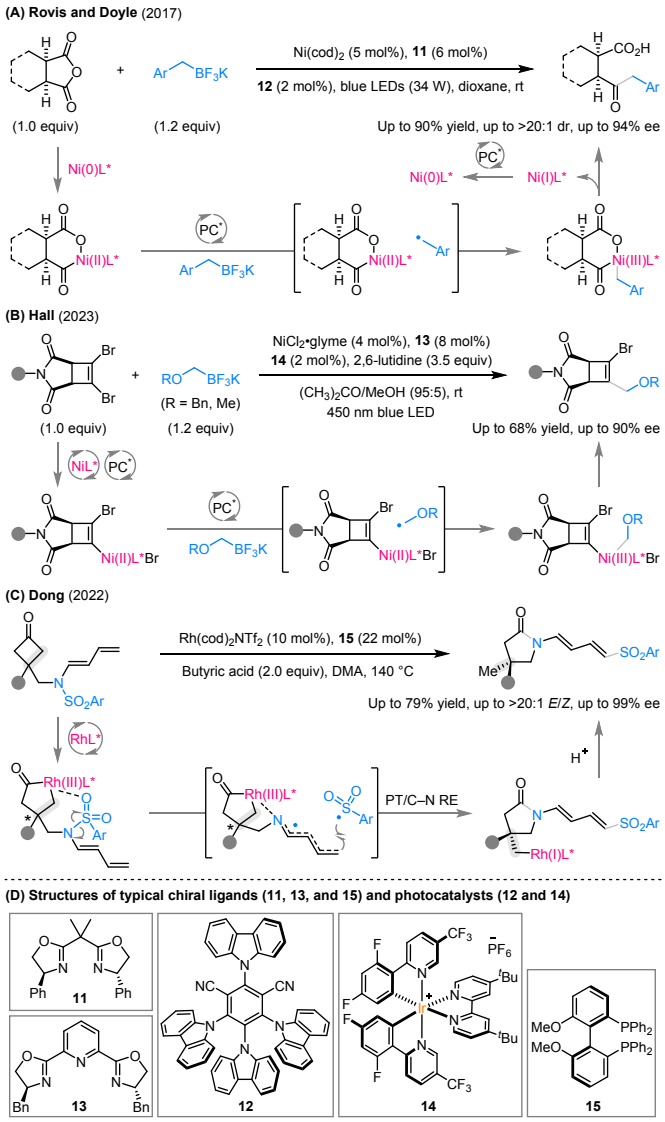
Research endeavors in this area have also significantly enriched the reaction scope. In 2015, Weix and coworkers developed a catalytic enantioselective desymmetrizing cross-coupling reaction of *meso* epoxides

with aryl bromides using dual-metal catalysis.[50] This reaction initially underwent the enantiodiscriminative desymmetrizing ring-opening of *meso* epoxides with chiral Ti complex **7** (Scheme 4C and 4E). In contrast to the aforementioned examples, which were selectively terminated by a hydrogen atom transfer process, the thus-generated chiral β-titanoxyl carbon-centered radical species was intercepted by an achiral Ni-complex-catalyzed stereoselective arylation reaction to produce the desired cross-coupling product. It is worth noting that both catalytic cycles benefited from the use of stoichiometric Mn powder reductants to generate the corresponding catalytic species. In addition, the dual-metal catalysis strategy has also been applied to enantioselective desymmetrizing isomerization of *meso* epoxides. In 2019, Lin and coworkers discovered that the enantioselective isomerization of *meso* epoxides, forging enantioenriched allylic alcohol derivatives, was achieved by combining chiral Ti catalyst **7** with an achiral Co catalyst **10** (Scheme 4D and 4E).[51] The achiral Co(II) complex facilitated the intermolecular HAA or ligand-assisted, proton-coupled electron transfer (PCET) process of the thus-generated chiral β-titanoxyl carbon-centered radical species to furnish the alkene moiety, as well as the subsequent alkoxide protonation to release the chiral allylic alcohol products. This reaction possesses a noteworthy feature: the resulting redox pair of Ti(IV) and Co(I) complexes reacted with each other to regenerate the corresponding Ti(III) and Co(II) active species and thus, only a catalytic amount of Zn powder was required as a reductant.

Desymmetrization via enantiotopic group-selective polar transformations

Reactions of this type share many of the stereochemical features of enantioselective polar desymmetrization reactions in terms of stereocontrol. In this aspect, by merging chiral Ni catalysis and photoredox catalysis, Rovis, Doyle, and coworkers disclosed an enantioselective radical desymmetrization of *meso cis*-anhydrides with benzyl trifluoroborates.[52] This reaction started with the enantiodetermining oxidative addition of a Ni(0) catalyst to *cis*-anhydrides with chiral bisoxazoline **11** (Scheme 5A and 5D) as the ligand, leading to the corresponding closed-shell chiral *cis*-Ni(II)-adduct. Under photoredox catalysis with achiral organic compound **12** (Scheme 5D) as the photocatalyst, benzyl trifluoroborate was transformed into a benzylic radical species.

The radical was then intercepted by the chiral *cis*-Ni(II)-adduct to generate a chiral Ni(III) intermediate, which underwent subsequent reductive elimination to give the enantioenriched alkyl keto-acid product. Interestingly, an epimerization event could occur on the chiral *cis*-Ni(II)-adduct, which delivered both the *cis* and *trans* diastereomers through a reversible decarbonylation and carbonylation pathway. This event was identified by increasing the Ni(0) catalyst loading while decreasing the photocatalyst loading. As such, this reaction presented an attractive potential to obtain either *cis* or *trans* chiral products from the identical *meso cis*-anhydride substrate, albeit with a relatively low diastereoselectivity at this stage.



Scheme 5 *(A –D) Catalytic enantioselective radical desymmetrization via enantiotopic group-selective polar transformations.*

This dual catalysis method was also suitable for developing enantioselective radical desymmetrizing cross-coupling of 1,2-dibromocyclobutene scaffolds. In 2023, Hall and coworkers reported the enantioselective desymmetrization of *meso* 1,2-dibromocyclobutene imides with alkyltrifluoroborates.[53] The reaction was achieved by a merge of chiral Ni catalysis using chiral pyridyl-bisoxazoline **13** as the ligand and photoredox catalysis using racemic Ir-based photocatalyst **14** (Scheme 5B and 5D), giving rise to chiral bromocyclobutenes in good yields and high enantioselectivities. Control experiments showed that the chiral ligand-controlled inhibition of a second coupling was important for this desymmetrization reaction. Mechanistically, the photoredox catalytic cycle initially generated the Ni(0) active species and alkyl radical species from the Ni(II) precatalyst and alkyltrifluoroborate salt, respectively. The enantiodetermining oxidative addition of the Ni(0) active species to the dibromide substrate produced a key closed-shell chiral Ni(II)-adduct, which then captured the alkyl radical to form a chiral Ni(III) intermediate. This intermediate underwent reductive elimination to yield the enantioenriched bromocyclobutene product. However, an alternative mechanistic scenario, in which the alkyl radical was trapped by the Ni(0) active species to form a chiral Ni(I)-adduct followed by enantiodetermining oxidative addition with the dibromide substrate to give the chiral Ni(III) intermediate, could not be excluded.[53]

Regarding other transition-metal catalysts, Dong and coworkers recently developed a Rh(I)-catalyzed enantioselective radical desymmetrization of cyclobutanones that contain a sulfonamide-tethered 1,3-diene moiety using chiral bisphosphine ligand **15** (Scheme 5C and 5D), thus enabling the catalytic enantioselective synthesis of chiral γ-lactams bearing an all-carbon quaternary stereocenter.[54] Both experimental and theoretical mechanistic studies indicated that this unusual reaction began with Rh(I)-mediated desymmetrizing oxidative addition into the prochiral cyclobutanone C–C bond, affording a closed-shell chiral Rh(III)

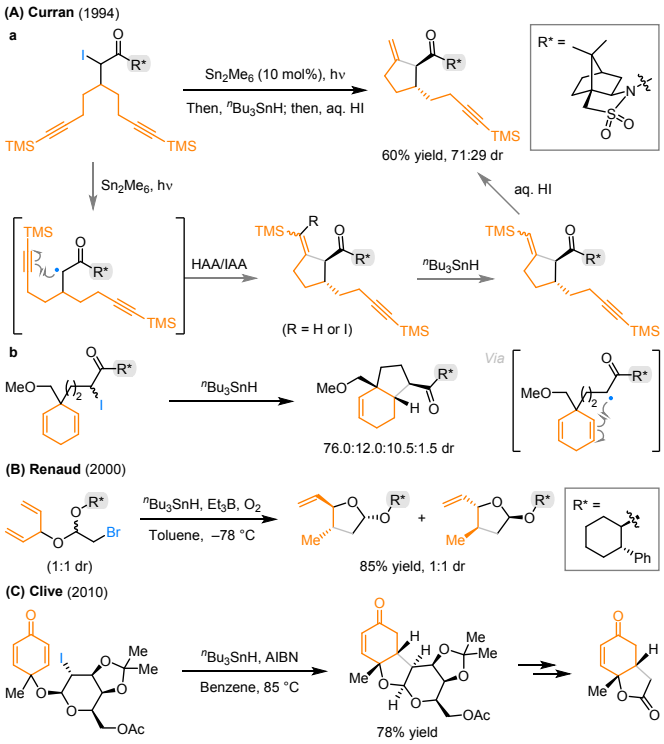
intermediate. Subsequent processes involved Rh(III)-triggered N–S bond homolytic cleavage and migration of the resulting sulfonyl radicals, followed by proton transfer (PT) and C–N bond reductive elimination (RE). The resulting chiral Rh(I) intermediate finally underwent protonation to release the chiral product.

Category II Desymmetrization via Asymmetric Radical Functionalization

Reactions in this category initially produce an open-shell radical species from either a stereoisomeric mixture of substrate molecules or an achiral radical precursor without touching the stereotopic groups to be desymmetrized. Then, the thus-generated radical species engages in desymmetrization through asymmetric radical functionalization reactions. Chiral auxiliary-controlled approaches have been established primarily in the early stages to achieve enantiocontrollable desymmetrizing radical transformations, although these reactions heavily relied on the stoichiometric chiral auxiliaries attached to the starting materials. Chiral reagent-driven enantioselective radical desymmetrization of prochiral substrates represents a complementary stoichiometric method for constructing chiral molecules with multiple stereocenters in both diastereoselective and enantioselective manners. It proves particularly useful when the deployed stoichiometric chiral reagents are readily available or can be recycled. In this context, catalytic asymmetric radical desymmetrization is a more practical and sustainable technique. Nevertheless, it poses significant challenges in developing efficient chiral catalytic systems for the stereocontrol of highly reactive open-shell radical species.[20] Conceptually, two different catalytic strategies have been developed to achieve asymmetric desymmetrizing radical functionalization reactions: (1) enantioselective radical formation followed by diastereotopic group-selective radical functionalization reactions, and (2) non-stereoselective radical generation followed by enantioselective radical functionalization. These tactics have been successfully demonstrated in the development of catalytic asymmetric radical desymmetrization reactions. The research progress in this aspect will be methodically described in the following subsections.

Chiral auxiliary-controlled desymmetrization reactions

This reaction type involves the generation of a radical from the starting substrate to produce a chiral open-shell intermediate. This intermediate then undergoes a diastereoselective desymmetrization process controlled by a substrate-bound chiral auxiliary to ensure the transfer of stereochemical information. In this vein, Curran and coworkers pioneered the introduction of chiral auxiliary-controlled desymmetrization reactions to realize asymmetric radical cyclization of α-carbonyl alkyl iodides, albeit with relatively moderate levels of diastereoselectivity (Scheme 6A).[55] Diynyl-substituted radical precursor underwent desymmetrizing radical cyclization using Oppolzer's camphor sultam[56] as a chiral auxiliary, giving rise to chiral cyclic product. This reaction was proceeded through sequential iodine atom abstraction (IAA) and 5-exo-dig radical cyclization, followed by a HAA or IAA process to produce a mixture of vinyl iodide/silane. The resulting mixture was then reductively deiodinated with tributyltin hydride and subsequent protodesilylation upon exposed to aqueous HI to yield the product. Cyclohexadienyl-substituted radical precursor also readily participated in the desymmetrizing radical cyclization, affording the corresponding chiral bicyclic product. Additionally, Renaud and coworkers reported asymmetric desymmetrizing radical cyclization of dienyl α-bromoacetal using a chiral cyclohexane moiety as an auxiliary (Scheme 6B).[57] The starting diastereomeric mixture of α-bromoacetals underwent Sn-triggered Ueno–Stork-type radical cyclization[58,59] to give the resulting chiral tetrahydrofuran derivatives in a completely diastereoselective manner. Further investigations showed that the acetal stereocenter solely dictated the stereochemistry of the radical cyclization.[60] Therefore, the use of an easily recoverable chiral auxiliary provided a practical method for the synthesis of enantiomerically pure cyclic products. In a related study, Clive and his colleague achieved the asymmetric desymmetrizing radical cyclization of α-iodoacetal bearing a cyclohexadienone moiety (Scheme 6C).[61] This reaction utilized a chiral galactal as an auxiliary to smoothly deliver the corresponding enantioenriched polycyclic product in good yield, which was transformed into chiral cyclohexenone fused γ-lactone upon further manipulations.

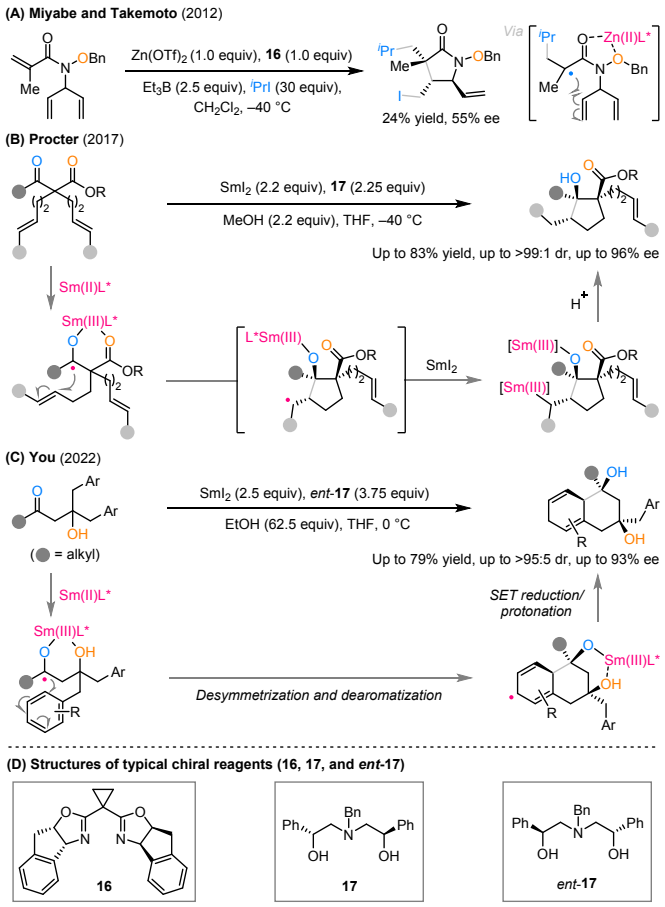


Scheme 6 *(A –C) Chiral auxiliary-controlled asymmetric radical desymmetrization reactions.*

Chiral reagent-driven desymmetrization reactions

Reactions of this kind have relied on a stoichiometric chiral reagent to effectively suppress uncatalyzed, non-stereoselective background reactions. Early preliminary attempts in this area include the α-ethyl camphorate-promoted Cu-catalyzed enantioselective oxidative desymmetrization of allylic C–H bonds by Denney and coworkers[62] and the chiral acylaminyl oxide-mediated enantioselective desymmetrizing oxidation of *meso* dihydrobenzoin by Perkins and his colleague.[63] In addition, Miyabe, Takemoto, and their colleague developed enantioselective desymmetrizing radical cascade cyclization of diene-tethered hydroxamate ester with isopropyl iodide using stoichiometric Zn(II) and bisoxazoline **16** (Scheme 7A and 7D) as the chiral mediator.[64] With triethylborane as a radical initiator, the nucleophilic isopropyl radical *in situ*-formed from isopropyl iodide initially reacted with the electron-deficient acryloyl moiety in the substrate, producing a carbonyl-stabilized open-shell intermediate. As an electrophilic radical,[65] this intermediate underwent radical addition-triggered

stereoselective desymmetrizing intramolecular 5-*exo*-*trig* cyclization. Subsequently, an intermolecular iodine atom-transfer process from isopropyl iodide to the resulting terminal radical occurred to afford the chiral cyclic product (Scheme 7A). The oxygen atoms in the hydroxamate ester group served as coordination sites with the chiral Lewis acid center, which was essential for the enantiocontrol of this reaction. The desired chiral γ-lactam, bearing three contiguous stereocenters, was forged in relatively low yield with moderate enantioselectivity.



Scheme 7 *(A –D) Chiral reagent-driven enantioselective radical desymmetrization reactions.*

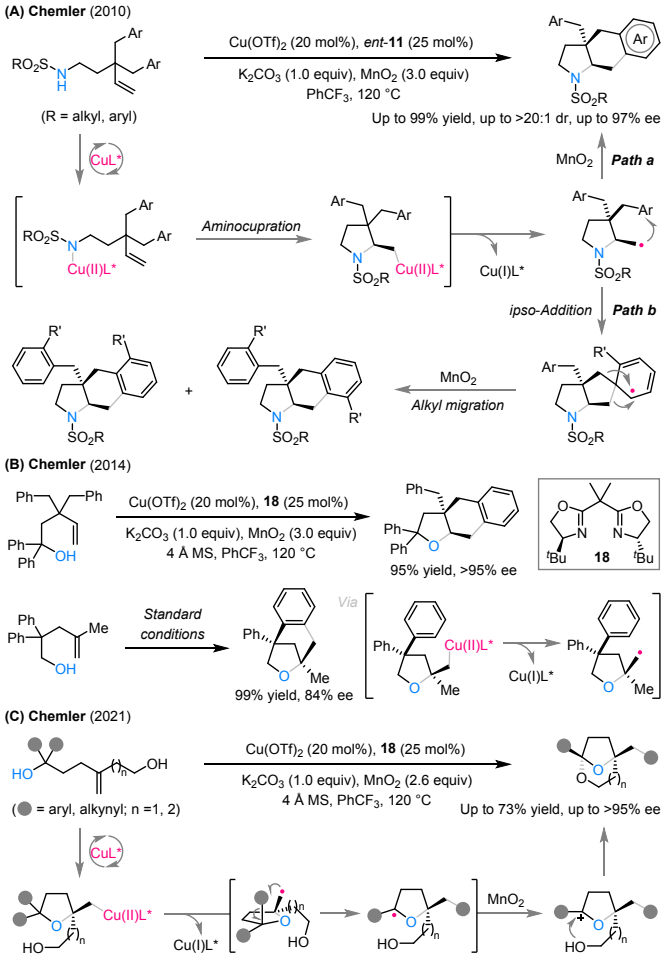
In 2017, Procter and coworkers made a significant breakthrough in this field with the discovery of highly diastereoselective and enantioselective desymmetrizing radical cyclization of dienyl β-ketoester (Scheme 7B).[66] They employed a stoichiometric chiral Sm(II) complex formed *in situ* from SmI_2 and a recyclable chiral tridentate

aminodiol **17** (Scheme 7B and 7D) as a chiral mediator, leading to the effective synthesis of enantioenriched carbocyclic products containing multiple stereocenters. The success of this reaction was ascribed to the creation of a nucleophilic samarium ketyl radical species through an SET process between the chiral Sm(II) complex and the substrate molecule. This allowed for a formal umpolung of the ketocarbonyl group, followed by cascade intramolecular radical cyclization, another SET process, and protonation, resulting in the formation of the chiral cyclic products. A stoichiometric amount of MeOH as an additive was found to be essential for enhancing both the efficiency and enantioselectivity, which probably played dual roles during the ketyl radical cyclization: (1) acting as a sacrificial proton donor, thus preserving the integrity of the chiral aminodiol ligand, and (2) binding to Sm(II) and/or Sm(III) species, thereby affecting the coordinative environment around the metal center to induce higher enantiocontrol.

Direct enantioselective dearomatization reactions are of great importance for accessing enantioenriched three-dimensional polycyclic molecules from the chemical space of planar aromatic compounds.[67] In 2022, You and coworkers reported a SmI_2-mediated enantioselective desymmetrizing reductive dearomatization reaction of bisbenzyl β-hydroxyketone using tridentate aminodiol *ent*-**17** (Scheme 7C and 7D) as a chiral ligand and a large excess of ethanol as an additive.[68] The dearomatized chiral polycyclic cyclohexa-1,4-diene derivatives were obtained in good yield with high diastereoselectivity and enantioselectivity. The *in situ*-formed chiral samarium ketyl radical species underwent intramolecular stereoselective cyclization onto one of the two aryl rings, generating a key desymmetrized open-shell intermediate through a conformationally restricted cyclic transition state. This was then followed by SET reduction and subsequent protonation to produce the chiral product. Control experiments showed that the loadings of the chiral reagent and alkyl alcohol additives played crucial roles in inhibiting unexpected side reactions, such as the direct reduction of the ketocarbonyl group and the retro-aldol reaction of the starting materials, to achieve satisfactory reaction efficiency.

Catalytic desymmetrization via diastereotopic group-selective radical functionalization

This reaction type comprises an initial catalytic enantioselective polar transformation, succeeded by radical generation and subsequent diastereotopic group-selective[69] radical functionalization, leading to formal desymmetrization. In this context, the Chemler group has pioneered the alkene nucleocupration strategy for developing enantioselective desymmetrizing intramolecular oxidative carboamination of diaryl-tethered terminal alkenamines. They employed a combination of $Cu(OTf)_2$ and chiral ligand *ent*-**11** (the enantiomer of bisoxazoline **11**, Scheme 5D) as the catalyst along with a stoichiometrically excess amount of MnO_2 as an oxidant, resulting in an attractive protocol to access chiral *cis* fused-polycyclic pyrrolidine derivative with high diastereoselectivity and enantioselectivity.[70] As shown in Scheme 8A, the success of this reaction depended on a key elementary mechanism step: Cu(II)-facilitated enantiodetermining intramolecular syn aminocupration of the terminal alkene moiety in alkenamines.[71] The resulting closed-shell chiral Cu(II) complex intermediate then underwent homolytic cleavage of the C–Cu bond, generating a reactive primary carbon-centered radical species. This species engaged in stereoselective desymmetrizing intramolecular addition to the proximal *cis*-aromatic ring and further underwent an oxidative aromatization process, resulting in the formation of the chiral product (Scheme 8A, path a). Noteworthy is that regioisomeric products were isolated when substrates with *ortho*-substituents or a *para*-CF_3 group were used.[70] The authors proposed that, in these cases, the radical species were prone to undergo *ipso*-addition of the aryl group to form a spirocyclic intermediate, followed by an alkyl migration process (Scheme 8A, path b), rather than a direct *ortho*-substitution pathway.



Scheme 8 *(A –C) Catalytic desymmetrization via diastereotopic group-selective radical functionalization.*

Building upon this strategic protocol, Chemler and coworkers also developed Cu-catalyzed enantioselective desymmetrizing intramolecular oxidative carboetherification of diaryl-tethered terminal alkenols, using bisoxazoline **18** (Scheme 8B) as a chiral ligand. This approach provides a facile synthesis of either *cis* fused- or bridged-polycyclic tetrahydrofuran derivatives, the outcome depending on the substitution patterns of aryl groups.[72] Mechanistic studies revealed that the enantiodetermining C–O bond formation proceeded through intramolecular *cis*-oxycupration of the alcohol-coordinated Cu(II) complex with the terminal alkene moiety. Subsequently, desymmetrizing C–C bond formation occurred via stereoselective intramolecular radical addition to the aryl group, followed by an oxidative aromatization process to complete the catalytic cycle.[73] In

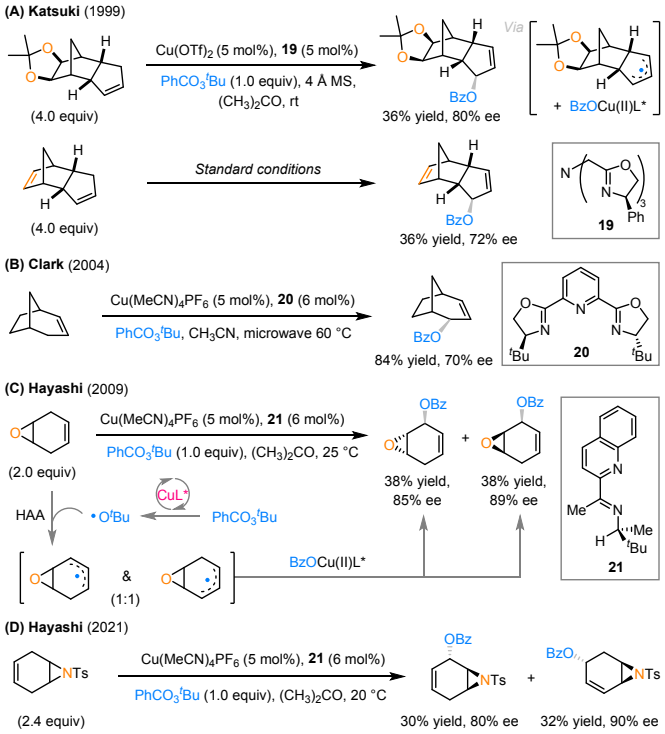
2020, Chemler and coworkers successfully established an aerobic approach for both the enantioselective intramolecular carboamination and carboetherification reactions by employing 10% oxygen in nitrogen as the oxidant instead of stoichiometric MnO_2, thus rendering these reactions more environmentally sustainable.[74] By integrating the enantiodetermining alkene oxycupration-triggered cyclization and a stereoselective desymmetrizing distal group migration process, Chemler and coworkers recently developed an elegant method to produce highly enantioenriched bridged-bicyclic ketals from acyclic 1,1-disubstituted alkenols with a pendent alcohol moiety (Scheme 8C).[75] This reaction was attributed to the formation of a primary carbon-centered radical species that underwent *ipso*-addition to an aryl group, followed by C–C bond cleavage and aryl group transfer. The resulting open-shell alkoxy-stabilized carbon-centered radical intermediate then engaged in sequential oxidation and ketalization, providing the chiral bridged-bicyclic ketal. Of note is that this radical-polar crossover reaction was also compatible with dialkynyl substituents, producing the corresponding chiral product in moderate yield with high enantioselectivity.

Catalytic desymmetrization by enantioselective radical functionalization

In the aforementioned examples, radical species were either absent in the stereo-determining steps or were under effective stereocontrol by tightly bound, preexisting stoichiometric stereocenters from an auxiliary, a reagent, or a preceding enantioselective polar transformation. By contrast, reactions falling into the current subsection lie on the delicate interactions between chiral catalysts and transient radical species formed *in situ* to achieve stereocontrolled radical functionalization. The typically low barriers of radical-mediated reactions often result in significant non-stereoselective background reactions. More importantly, they also preclude the appropriate energetic distribution of different stereoisomeric transition states necessary for achieving high enantioselectivity.[16] Accordingly, developing these desymmetrization reactions in a highly stereoselective manner proves to be particularly challenging. Early explorations toward this goal by Katsuki and his coworker revealed that racemic bridged-tricyclic alkenes underwent Cu-catalyzed enantioselective desymmetrizing Kharasch–Sosnovsky-type[76,77] allylic oxidation. This process utilized chiral trisoxazoline **19** (Scheme 9A) as a

ligand, resulting in chiral allylic esters in low yield with moderate to good enantioselectivity.[78] The low efficiency of this reaction was mainly due to the relatively low regioselectivity of the HAA step by *tert*-butoxy radicals. The *meso* π-allylic radical species thus generated were likely captured by Cu(II), and subsequent S_N2'-type reductive elimination delivered the oxidation products. A similar Cu-catalyzed enantioselective radical desymmetrization of racemic bridged-bicyclic alkene was also disclosed by Clark and coworkers with chiral pyridyl-bisoxazoline **20** (Scheme 9B) as a ligand, giving rise to the corresponding chiral allylic ester in good yield and moderate enantioselectivity.[79]

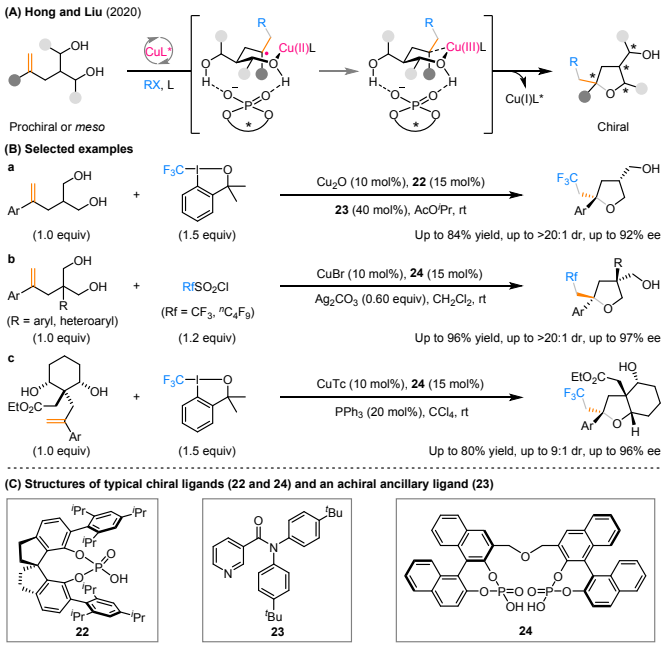
Relatedly, in 2009, Hayashi and coworkers reported a Cu-catalyzed enantioselective Kharasch–Sosnovsky-type oxidative desymmetrization reaction of allylic C–H bonds in *meso* epoxycyclohexene using chiral ligand **21** (Scheme 9C).[80] The initial intermolecular HAA of *meso* epoxycyclohexene by *tert*-butoxy radicals, formed *in situ*, generated a racemic mixture of allylic radical intermediates, which can be considered as formally symmetric. The desymmetrization of these intermediates was then achieved by coordination with chiral Cu(II) complexes and subsequent reductive elimination, producing a diastereoisomeric mixture of enantioenriched allylic benzoate derivatives. In 2021, the Hayashi group disclosed a similar enantioselective allylic oxidative desymmetrization reaction of *meso* azabicycloheptene using identical reaction conditions.[81] However, this reaction led to two enantioenriched regioisomeric products (Scheme 9D). In this case, while the radical pathway seems mechanistically reasonable for this desymmetrization reaction, it is important to note that an alternative mechanism involving the formation of diastereomeric allylic Cu(III) intermediates directly from the reaction of chiral peroxide Cu(I) complexes with the substrate could not be excluded.[81] Although the above examples clearly demonstrate the convenient access to complex molecules with multiple stereocenters via direct enantioselective desymmetrizing oxidation of C–H bonds, they all fall short due to unsatisfactory selectivity and limited substrate scope.



Scheme 9 *(A –D) Cu-Catalyzed enantioselective radical desymmetrization of enantiotopic allylic C –H bonds.*

In 2020, Hong, Liu, and their colleagues achieved a significant advancement in catalytic enantioselective radical desymmetrization of prochiral or *meso* alkene-tethered 1,3-diol with various radical precursors by utilizing Cu(I) and chiral phosphoric acid (CPA) cooperative catalysis (Scheme 10A).[82] An array of structurally diverse enantioenriched trifluoromethyl-substituted tetrahydrofurans was obtained in a highly diastereoselective and enantioselective manner from prochiral olefinic 1,3-diol and Togni's reagent in the presence of a cooperative catalytic system of Cu_2O and CPA **22**, with an achiral pyridine derivative **23** as a Lewis base additive (panel a of Scheme 10B; Scheme 10C). The chiral Cu(II) phosphate, formed *in situ* from an SET process between Cu(I)/CPA and radical precursors, readily associated with the subsequently generated alkyl radical species, thus providing a well-defined chiral microenvironment[83–87] for the following stereo-determining C–O bond formation step. Theoretical investigations showed that this step proceeded through stepwise heterolytic cleavage of the Cu–C bond and subsequent outer-sphere C–O bond formation. Both the hydrogen-bonding network with the CPA

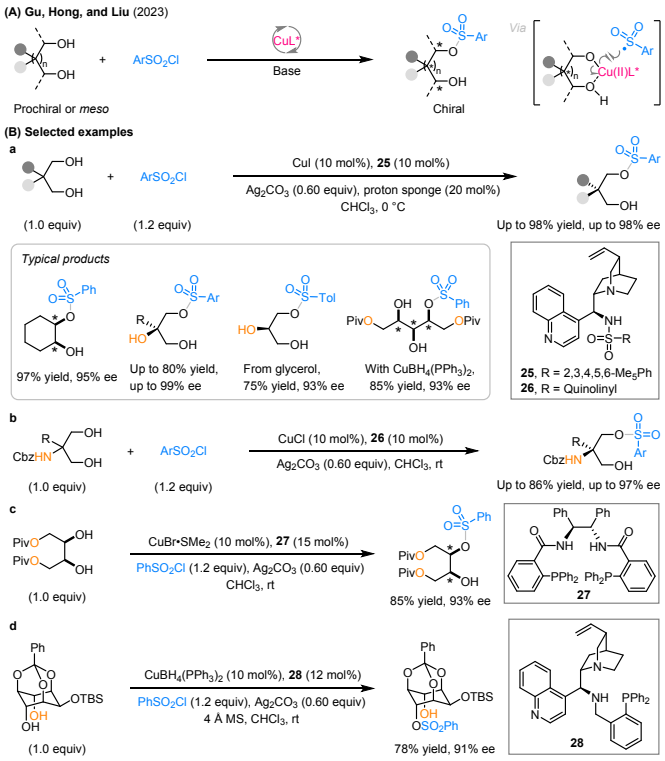
anion and the π–π stacking interactions with the pyridine moiety were beneficial in creating a compact chiral environment, thus leading to the remarkable differentiation of the four competing transition states with excellent stereocontrol. Accordingly, the Lewis base additive effectively served as a bridge to transfer the chirality of the CPA anion to the remote forming stereocenter.[82] Based on this catalytic mode, the authors also described the enantioselective radical desymmetrization of olefinic 1,3-diol bearing a quaternary stereocenter with perfluoroalkyl sulfonyl chloride as a radical precursor. In this case, chiral bisphosphoric acid **24** (panel b of Scheme 10B; Scheme 10C) was found to be optimal, while any Lewis base ancillary ligands were no longer required. In addition, Ag_2CO_3 was introduced as a scavenger of the *in situ* generated HCl by-product, which would otherwise result in racemic background reactions. As such, the corresponding chiral perfluoroalkylation products bearing two congested quaternary stereocenters were produced in good yield with high diastereoselectivity and enantioselectivity. For the enantioselective radical desymmetrization of *meso* olefinic 1,3-diol embedded on a cyclohexane skeleton, the use of chiral bisphosphoric acid **24** together with a catalytic amount of triphenylphosphine as a Lewis base ancillary ligand was crucial for achieving chiral fused bicyclic products with four stereocenters (panel c of Scheme 10B). Overall, this reaction provides a flexible platform for the rapid and effective generation of chiral building blocks with multiple contiguous stereocenters, particularly in the synthesis of complex chiral heterocyclic molecules.



Scheme 10 *(A –C) Catalytic enantioselective desymmetrizing functionalization of alkyl radicals via Cu(I)/chiral phosphoric acid (CPA) cooperative catalysis.*

Transition-metal-catalyzed enantioselective radical cross-coupling reactions of racemic alkyl halides with nucleophiles represent a powerful tool for rapidly assembling enantioenriched molecules. In this regard, Liu's research group has systematically developed a series of Cu catalysts featuring chiral multidentate anionic ligands. These ligands not only enhance the reducing capacity of Cu catalysts to facilitate radical generation under mild thermal conditions but also provide a rigid chiral environment for high enantiocontrol of radical functionalization. Accordingly, this constitutes a mechanistically distinctive strategy for catalytic enantioselective radical transformations.[88,89] Equipped with their developed chiral Cu catalysts, Liu and coworkers have made significant progress in Cu-catalyzed enantioselective radical carbon–carbon and carbon–heteroatom cross-coupling reactions, forging diverse chiral C–C,[90–96] C–N,[97–101] C–P,[102] and C–S bonds.[103] Nevertheless, the enantioselective heteroatom–heteroatom cross-coupling of heteroatomic (pseudo)halides with heteroatomic nucleophiles has remained yet largely underexplored,[104] probably due to the usually difficult

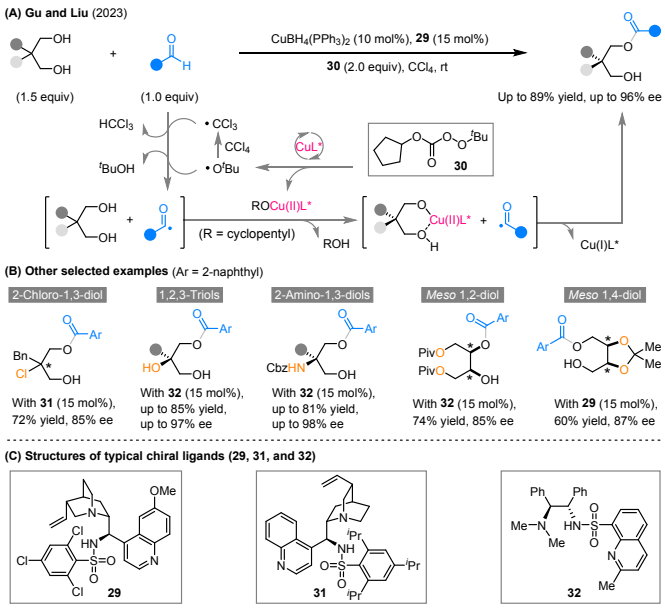
heteroatom–heteroatom reductive elimination. In 2023, Gu, Hong, Liu, and their colleagues unveiled a Cu-catalyzed enantioselective radical heteroatomic S–O cross-coupling reaction using a panel of chiral multidentate ligands **25**–**28** (Scheme 11).[105] This reaction led to the enantioselective radical desymmetrizing sulfonylation of prochiral or *meso* diols or triols with arylsulfonyl chlorides as readily available sulfonyl radical precursors. Both experimental and theoretical mechanistic studies supported that the enantiodetermining S–O bond formation proceeded through a single-electron reductive elimination pathway via an outer-sphere radical substitution-type open-shell singlet transition state (Scheme 11A). The exceptional enantiocontrol observed in the desymmetrizing radical sulfonylation reaction was attributed to the steric repulsion between the attacking sulfonyl radical and the ligand quinuclidine moiety in the transition state that led to the disfavored product enantiomer.[105] In addition, different chiral ligands **25**–**28** proved to be crucial for distinguishing otherwise similar C–O bonds in various molecular settings, possibly as a result of varied coordination modes of these substrates with copper catalysts (Scheme 11B). Accordingly, a large number of highly enantioenriched diol and polyol scaffolds with up to six stereocenters, including acyclic all-carbon quaternary and nitrogen- and oxygen-containing tetrasubstituted carbon stereocenters, were efficiently constructed. Notably, the reaction also provided a robust avenue for the conversion of biomass-derived feedstock glycerol into high-value-added chiral synthetic building blocks, and a long-sought solution to the chemically catalytic 4,6-desymmetrization of *myo*-inositol. These results thus highlighted the great potential of enantioselective radical heteroatomic cross-coupling as a general method for chiral heteroatom–heteroatom bond formation.



Scheme 11 *(A and B) Cu-Catalyzed enantioselective desymmetrizing heteroatomic S – O cross-coupling of sulfonyl radicals.*

Building on these promising results, Gu, Liu, and coworkers have expanded their research to explore additional applications of this catalytic system. Most recently, they successfully developed a Cu-catalyzed enantioselective desymmetrizing C–O cross-coupling of acyl radicals with prochiral or *meso* diol or triol (Scheme 12).[106] Although the generation of acyl radicals from aldehydes via an HAA process has been well investigated, the development of corresponding transition-metal-catalyzed enantioselective acyl radical functionalization has remained uncommon. This scarcity may be attributed, on one hand, to the relatively harsh conditions required for acyl radical generation, which can compromise enantiocontrol. On the other hand, the intrinsically high reactivity of σ-type acyl radicals poses a significant challenge for stereocontrol, especially over remote sites in the desymmetrization setting. Accordingly, the authors took advantage of the enhanced reducing power of their copper catalysts to accomplish efficient acyl radical generation under

ambient conditions. More importantly, they achieved excellent stereocontrol using a panel of multidentate ligands **29**, **31**, and **32** (Scheme 12C). Thus, a considerable range of aryl, heteroaryl, and alkyl aldehydes were all accommodated by the standard reaction conditions (Scheme 12B). Furthermore, this reaction was also suitable for prochiral 2-chloro-1,3-diol and *meso* primary 1,4-diol, both of which are challenging substrates for known desymmetrization methods. Mechanistic studies indicated that the Cu(I)/chiral anionic ligand catalytic system readily reduced peroxide **30** (Scheme 12A) to *tert*-butoxy radical,[86,87] which underwent either a direct or indirect HAA process with aldehyde to give the key acyl radical species. This species then underwent an enantioselective desymmetrization reaction with a chiral Cu(II)–alkoxide complex, giving rise to the desired chiral C–O cross-coupling product. Theoretical investigations suggested that the enantiodetermining C–O formation likely followed a radical-substitution type pathway.[106] This method is anticipated to encourage further efforts to develop enantioselective functionalization reactions of acyl radicals using chiral transition-metal catalysis.



Scheme 12 *(A –C) Cu-Catalyzed enantioselective desymmetrizing C –O cross-coupling of acyl radicals.*

Summary and Outlook

The recent integration of asymmetric catalysis and radical chemistry has significantly advanced the progress of enantioselective radical desymmetrization reactions. These represent elegant and effective approaches for the expeditious assembly of enantioenriched molecules with substantially elevated structural complexity from readily available prochiral or *meso* compound feedstocks. This mini-review provides an overview of this progress, highlighting both early explorations and recent advances. Two strategic modes have been developed, distinguished by where the stereo-determining event occurs. The first category emphasizes the stereo-determining desymmetrization of closed-shell radical precursors or functional reagents, while the second category centers on the stereoselective desymmetrizing functionalization of open-shell radical species. These remarkable achievements are of great significance, not only for advancing the long-standing challenging field of enantioselective radical chemistry but also for opening up unprecedented synthetic avenues to construct structurally diverse chiral molecules with multiple stereocenters that are often difficult to access by other alternative methods.

Although substantial efforts have been made in this research field, the development of enantioselective radical desymmetrization reactions is still in its early stages. There are several challenges and also opportunities for future development, including: (1) To ensure continuous advances in this field, it is highly desirable to rationally design new catalytic systems and gain a fundamental mechanistic understanding. This is particularly crucial in developing earth-abundant first-row transition-metal catalysis with good SET ability. The competent interactions between transition metals and alkyl radical species have proven to be crucial for controlling chemo-, regio-, and stereoselectivities and for inhibiting undesired background reactions.[89] The integration of transition-metal catalysis with photoredox catalysis[48,52,53] and dual-metal catalysis[50,51] has shown promising potential directions. In addition, the incorporation of conceptually designed chiral anionic ligands in copper catalysis[82,105,106] has provided a complementary strategy to enhance the versatility and effectiveness of this field. (2) Further efforts are required to expand the scope of prochiral or *meso* starting materials and radical

precursors, enhancing the power and generality of enantioselective radical desymmetrization reactions. Of particular note is that the enantioselective desymmetrizing functionalization of unactivated alkyl radicals has remained to be developed.[82] Classical biomimetic catalysis[30,33,34] and chiral titanocene chemistry[45,49] have arguably been restricted by the availability of viable substrate variants. As for the nucleocupration pathway,[70,72,75] the intermolecular aminocupration and oxycupration reactions continue to pose significant challenges. (3) Despite the application of several representative methods,[39,57,105,106] the great potential of enantioselective radical desymmetrization reactions for the synthesis of bioactive molecules and natural products has not been sufficiently investigated. Therefore, this mini-review aims to provide a panoramic overview of research progress, challenges, and opportunities for potential researchers. We tentatively conclude that further exploration will foster sustainable growth in this burgeoning field.

Conflict of Interest

The authors declare no competing interests.

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