CJC Chinese Journal of Chemistry 中国化学 - An International Journal

For submission: https://mc.manuscriptcentral.com/cjoc
For published articles: https://onlinelibrary.wiley.com/journal/16147065

Recent Advances

Cite this paper: *Chin. J. Chem.* **2024**, *42*, 3414—3428. **DOI: 10.1002/cjoc.202400296**

Reduction of Tertiary Carbon Radicals via Asymmetric Hydrogen Atom Transfer (AHAT)†

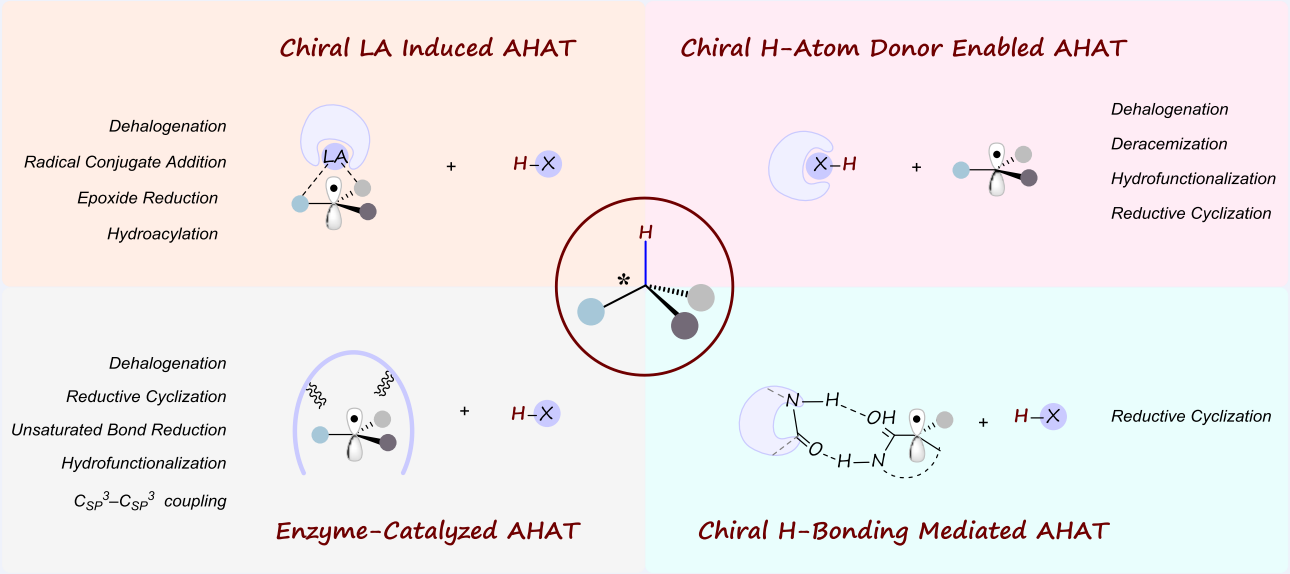
Xue Han and Chuan He*

Shenzhen Grubbs Institute and Department of Chemistry, Guangdong Provincial Key Laboratory of Catalysis, Southern University of Science and Technology, Shenzhen, Guangdong 518055, China

Keywords

AHAT | Radical reactions | Asymmetric synthesis | Enantioselective radical reactions | Hydrogen atom transfer | Chirality | Reduction | Synthetic methods

Comprehensive Summary



In the past two decades, the development of asymmetric radical reactions has achieved tremendous progress, which has emerged as a powerful tool for the synthesis of chiral molecules in synthetic chemistry. Among the diverse array of radical processes, the transfer of hydrogen atoms to tertiary carbon radicals offers the potential for constructing chiral tertiary carbon centers in a stereoselective fashion. Notwithstanding the challenges associated with the reactive and evanescent nature of radical species, the use of chiral reagents or mediators has enabled the stereocontrol of the asymmetric hydrogen atom transfer (**AHAT**), which provides novel avenues for advancing the field of asymmetric synthesis.

*E-mail: hec@sustech.edu.cn

† Dedicated to the Special Issue of Emerging Investigators in 2024.

Key Scientists

Osamu Hoshino, Science University of Tokyo
Chiral Lewis acid mediated enantioselective dehalogenation with Bu_3SnH

Fumie Sato, Tokyo Institute of Technology
Chiral Lewis acid mediated enantioselective radical conjugate addition

Dennis P. Curran, University of Pittsburgh
Chiral stannane hydride enabled enantioselective dehalogenation

1995

1996

Mukund P. Sibi, North Dakota State University
Various auxiliary-assisted chiral Lewis acid mediated enantioselective radical reactions

Carl H. Schiesser, University of Melbourne
Various chiral H-atom donors enabled enantioselective dehalogenation

Brian P. Roberts, University College London
Chiral thiol catalyst enabled enantioselective radical-chain hydrosilylation of alkenes

2001

1999

1998

Thorsten Bach, Technische Universität Mu¨nchen
Chiral reagent mediated enantioselective reductive cyclization via H-bonding interaction

Todd K. Hyster, Princeton University
Enzyme-photo-coupled catalysis enabled enantioselective radical reactions

Robert R. Knowles, Princeton University
Cysteine-based oligopeptides enabled enantioselective radical reactions

2004

2016

2019

Huimin Zhao, University of Illinois at Urbana-Champaign
Enzyme-photo-coupled catalysis intermolecular radical hydrofunctionalization reactions

2020

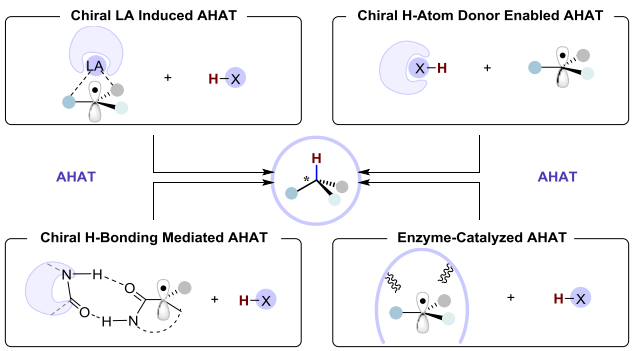
Stories to be Continued

Contents

1. Introduction

Radical chemistry has attracted considerable interest and made significant advancements during the past decades.[1-3] In particular, the evolution of asymmetric radical reactions has become a hot topic in modern synthetic chemistry, which represents one of the most efficient methods for the synthesis of a variety of chiral molecules.[4-6] As an eminent sub-type reaction in this field, hydrogen atom transfer (HAT), referring to the transfer of a hydrogen atom from an H-transfer agent to a radical species, typically allows a functional group interconversion from an alkyl halide to an alkane, serving as a powerful reduction method.[7-9] These HAT reactions usually feature excellent functional group tolerance and high efficiency, and the transfer of hydrogen atoms to tertiary carbon radicals offers the potential for the construction of tertiary carbon-stereogenic centers. Despite the appeal of the asymmetric hydrogen atom transfer (**AHAT**) process, the control of enantioselectivity is inherently challenging due to the high reactivity and low barrier of radical species. To tackle the challenges encountered, a series of strategies have been developed to steer the interaction between the chiral agents or mediators and prochiral tertiary carbon radical species, allowing effective **AHAT** reactions. In this review, we aim to highlight and discuss breakthroughs and recent advances in the **AHAT** processes. According to the different strategies, four sections are presented in detail (Scheme 1), including 1) chiral Lewis acid complexes induced **AHAT**; 2) chiral hydrogen-bonding mediated **AHAT**; 3) chiral hydrogen-atom donor enabled **AHAT**; and 4) enzyme-catalyzed **AHAT**. We hope that this review will showcase the great potential of **AHAT** in asymmetric synthesis and inspire further developments in this emerging field.

Scheme 1 Four strategies enabled AHAT



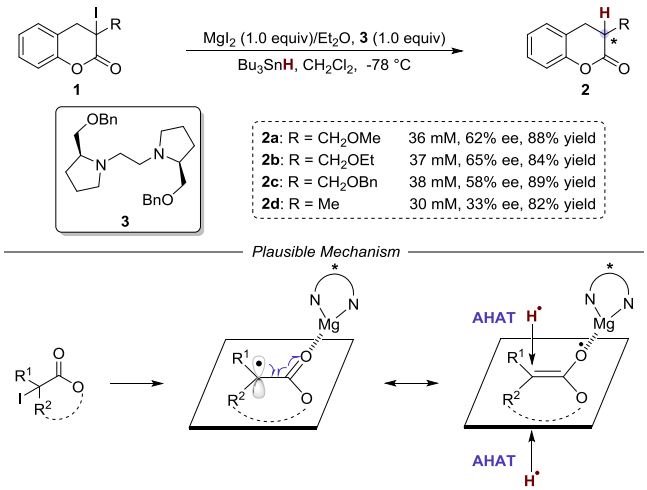
2. Chiral Lewis Acid Induced AHAT

Taking advantage of the seminal research on chiral auxiliary chemistry, a handful of enantioselective radical processes were developed by the chiral Lewis acid-induced **AHAT**. Various chiral Lewis acid complexes can be used to bind to specific substrates and determine the enantioselective hydrogen atom transfer approach.

2.1. Dehalogenation

The earliest asymmetric radical reaction induced by a chiral Lewis acid dated back to 1995, when Hoshino *et al*. reported the reduction of an α-alkyl-α-iododihydrocoumarins **1** in the presence of magnesium iodide (1.0 equivalent) with a chiral diamine **3** (1.0 equivalent) (Scheme 2).[10-11] A tertiary carbon radical is generated at the α-position of the carbonyl group, potentially leading to the formation of an enol tautomer. Assisted by the chiral Lewis acid complex, the hydrogen atom that originated from Bu_3SnH approaches the tertiary carbon radical from distinct directions delivering enantioselective products **2** with up to 65% ee (enantiomeric excess). It is noteworthy that the ee value of this asymmetric reduction reaction depends on the concentration of the substrate **1**. Under diluted conditions, lower enantioselectivity was observed possibly due to the uncomplexed enol radical with the chiral Lewis acid, which fails to provide a chiral environment during the HAT process. Poor ee was observed in the reaction with a bulky triphenyltin hydride, and tris(trimethylsilyl)-silane failed to yield the desired product.

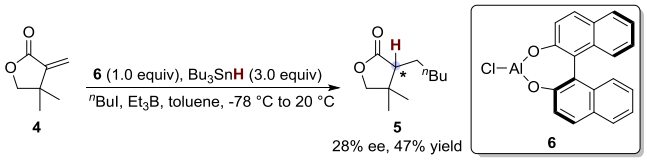
Scheme 2 Enantioselective reduction of α-iodolactone



2.2. Radical conjugate addition

Another pioneering exploration of chiral Lewis acid-induced asymmetric radical reaction was reported by Sato *et al*. in 1995. They developed a radical conjugate addition reaction of α-methylenebutyrolactone **4** with butyl radical, followed by a chiral aluminum complex **6** (1.0 equivalent) induced **AHAT** process (Scheme 3).[12] The initial attempt obtained 28% ee and 47% yield for product **5**, providing valuable insights for subsequent related studies.

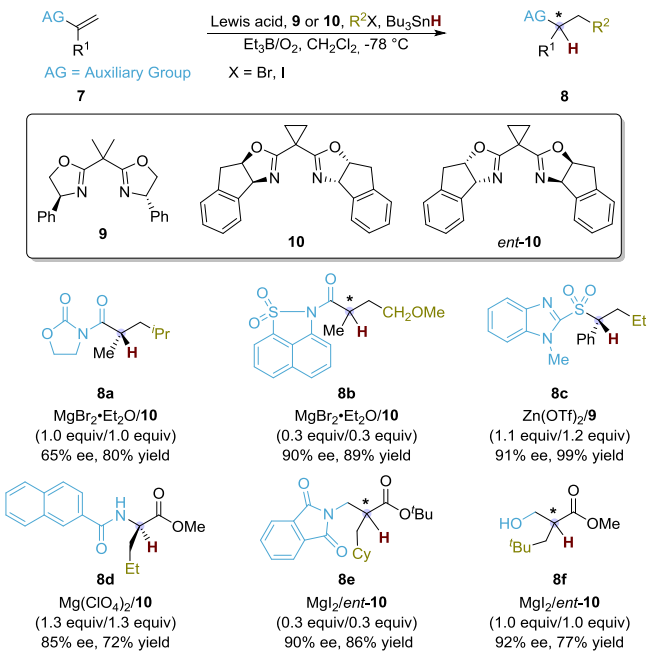
Scheme 3 Asymmetric radical conjugate addition of α-methylenebutyrolactone



In 1996, Sibi and Porter *et al*. reported a significant advancement in the chiral Lewis acid-mediated asymmetric radical reac-

tion, in which an oxazolidinone auxiliary was equipped in the acyclic substrate to coordinate with the chiral Lewis acid for controlling the enantioselectivity of the radical conjugate addition reaction.[13] Later, by using the oxazolidinone-steered strategy, they further realized a conjugate addition of an isopropyl radical to an α-methacrylate derivative, followed by an **AHAT** process, giving access to product **8a** in an 80% yield with 65% ee in the presence of 1.0 equivalent of $MgBr_2$•Et_2O and 1.0 equivalent of chiral bisoxazoline **10** (Scheme 4).[14] In addition to oxazolidinone moiety, variants of auxiliaries are employed for investigating the radical conjugate addition reactions via **AHAT** mediated by chiral Lewis acids. A naphthosultam-template **8b** exhibited enhanced enantioselectivity (90% ee) in the presence of a 30 mol% $MgBr_2$•Et_2O with a 30 mol% chiral bisoxazoline **10**. When a stoichiometric amount $Zn(OTf)_2$/**9** was used to coordinate with the benzimidazolyl sulfonyl auxiliary, substrate **7c** could undergo an **AHAT** process with 91% ee reported by the Toru group.[15] Meanwhile, the enantioselective radical conjugate addition reaction was also utilized for the construction of chiral amino acid derivatives. By using the auxiliary-assisted chiral Lewis acid-induced strategy, Sibi *et al*. demonstrated the preparation of diverse amino acid derivatives **8d**, **8e** and 3-hydroxy ester product **8f** with excellent ee.[16-18]

Scheme 4 Auxiliary-assisted asymmetric radical conjugate addition reactions

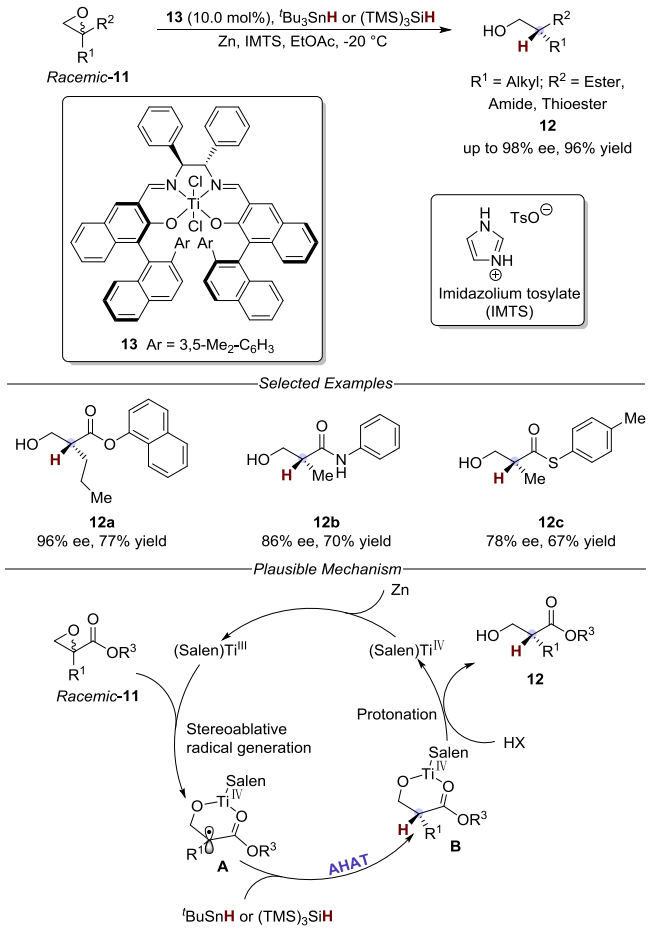


2.3. Epoxide reduction

Typically, enantioselectivity decreases with lower loading of chiral Lewis acid in **AHAT**, because the extraneous radical applied for carbon radical generation is not correlated with the chiral Lewis acid used for enantiocontrol of the HAT. A diminished ability to discriminate in reactivity between chiral Lewis acid-activated substrates and non-activated ones leads to the generation of non-complexed radical intermediates to undermine the essential enantioselectivity.

In 2022, Zhang *et al*. showcased a chiral Ti/salen-catalyzed redox strategy to address this challenge. This approach establishes a direct correlation between the generation of epoxy radical intermediate and the enantioselective control of catalytic **AHAT** mediated by the 10 mol% chiral Lewis acid complex **13** (Scheme 5).[19] The reaction affords glycidic esters, thioesters, and amides **12** that exhibit a wide range of scope and high enantioselectivities (up to 98% ee, 96% yield). A plausible mechanism is proposed that the redox-active (salen)Ti^{III} coordinates to the epoxide **11** and induces homolytic cleavage of the more substituted C—O bond to produce prochiral tertiary carbon radical **A** through a SET (single-electron transfer) from the reductive Ti^{III} center to epoxide **11**. Then, the radical intermediate **A** undergoes the key **AHAT** with ^{t}BuSnH or $(TMS)_3SiH$, and forms a chiral tertiary carbon center. Further protonation of **B** with acid results in the release of (salen)Ti^{IV}. Finally, the catalytic cycle is closed by reducing Ti^{IV} to regenerate the reductive Ti^{III} species with zinc. Key to the success is the smooth generation of radicals, facilitated by the driving force from the release of the ring strain in epoxide. Moreover, the formation of strong titanium-oxygen bond plays a pivotal role in ensuring the coordination needed for subsequent **AHAT**.

Scheme 5 Chiral Ti/salen-catalyzed AHAT reaction

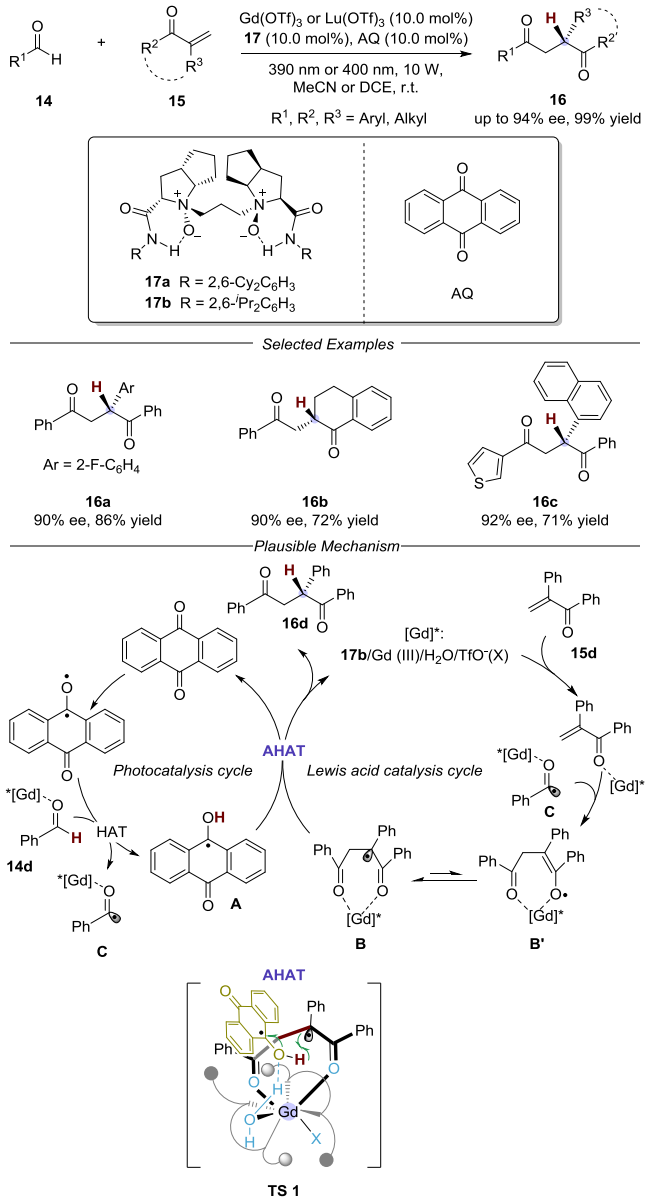


2.4. Hydroacylation

Hydrogen atom transfer can terminate tertiary carbon radicals to achieve an enantioselective hydroacylation reaction. Feng *et al*. reported that in the presence of the photocatalyst anthraquinone (AQ) and a 10 mol% chiral $Gd(OTf)_3$/*N*,*N*′-dioxide **17** complex, the acyl radical formed by a HAT reaction of aldehyde **14** adds to α,β-unsaturated carbonyl compounds **15**, achieving up to 94% ee in the formation of 2-substituted 1,4-diketones **16** (Scheme 6).[20] The proposed mechanism entails the coordination of aldehyde **14d** and conjugated enone **15d** with Gd*/**17b**, accompanied by additional H_2O and −OTf ligands. Initially, AQ generates the triplet-state photocatalyst AQ* under light, which abstracts hydrogen atom from the chiral Lewis acid-activated aldehyde **14d**. This produces the semiquinone-type intermediate **A** and the Gd(III)-bonded benzoyl radical **C**. Subsequently, the radical **C** undergoes conjugate addition with the chiral Lewis acid-activated enone compound **15d** to form the tertiary carbon radical intermediate **B**,

which binds to Gd(III) in a bidentate manner. Finally, the **AHAT** occurs between the semiquinone radical **A** and the tertiary carbon radical **B**, which mainly determines the enantioselectivity of the hydroacylation, resulting in the desired optically active product **16d** upon catalyst release. The possible transition state of the **AHAT** process involves the semiquinone radical intermediate **A** using hydrogen bonds with water to attack the *Si* face of radical **B**, encountering minimal steric hindrance, leading to the *R*-configuration observed in product **16d**.

Scheme 6 Chiral $Gd(OTf)_3$/*N*,*N*′-dioxide-catalyzed enantioselective hydroacylation



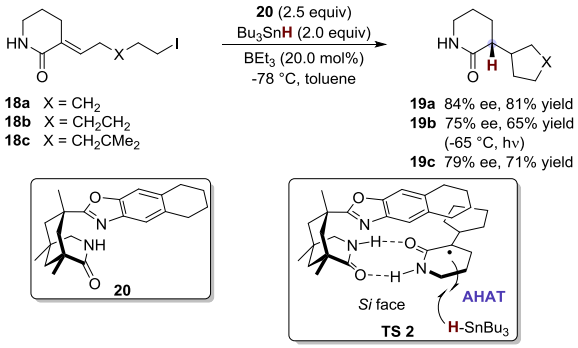
3. Chiral Hydrogen-Bonding Mediated AHAT

Unlike the chiral Lewis acid-induced **AHAT**, which achieves enantioselectivity control through dative bond coordination, a distinct strategy for creating a chiral environment through non-coordinative hydrogen bonding also allows for the discrimination of the enantiotopic faces of tertiary carbon radicals, thereby enabling **AHAT**.

3.1. Reductive cyclization

In 2004, Bach *et al*. prepared a chiral reagent **20** bearing an amide moiety, which could be employed to interact with the lactam substrate **18** via a hydrogen-bonding interaction (Scheme 7).[21] After a typical intramolecular radical cyclization of the iodide **18**, the generated prochiral radical in the α-position of the carbonyl group is terminated by extracting a hydrogen atom from Bu_3SnH on the *Si* face, while the *Re* face is shielded by the tetrahydronaphthyl residue. This process leads to the formation of the cyclized product **19** with up to 84% ee. Notably, enantioselectivity enhancement can be realized by addressing three factors: 1) employing lower temperature; 2) minimizing the usage of initiator BEt_3; and 3) increasing the dosage of the chiral reagent **20**.

Scheme 7 H-bonding facilitated enantioselective cyclization



In addition to the aforementioned **AHAT** process, it is worth noting that an alternative pathway exists in which tertiary carbon radicals can undergo a single-electron transfer (SET) process, followed by enantioselective protonation with chiral hydrogen-bonding catalysis.[22-25]

4. Chiral H-Atom Donor Enabled AHAT

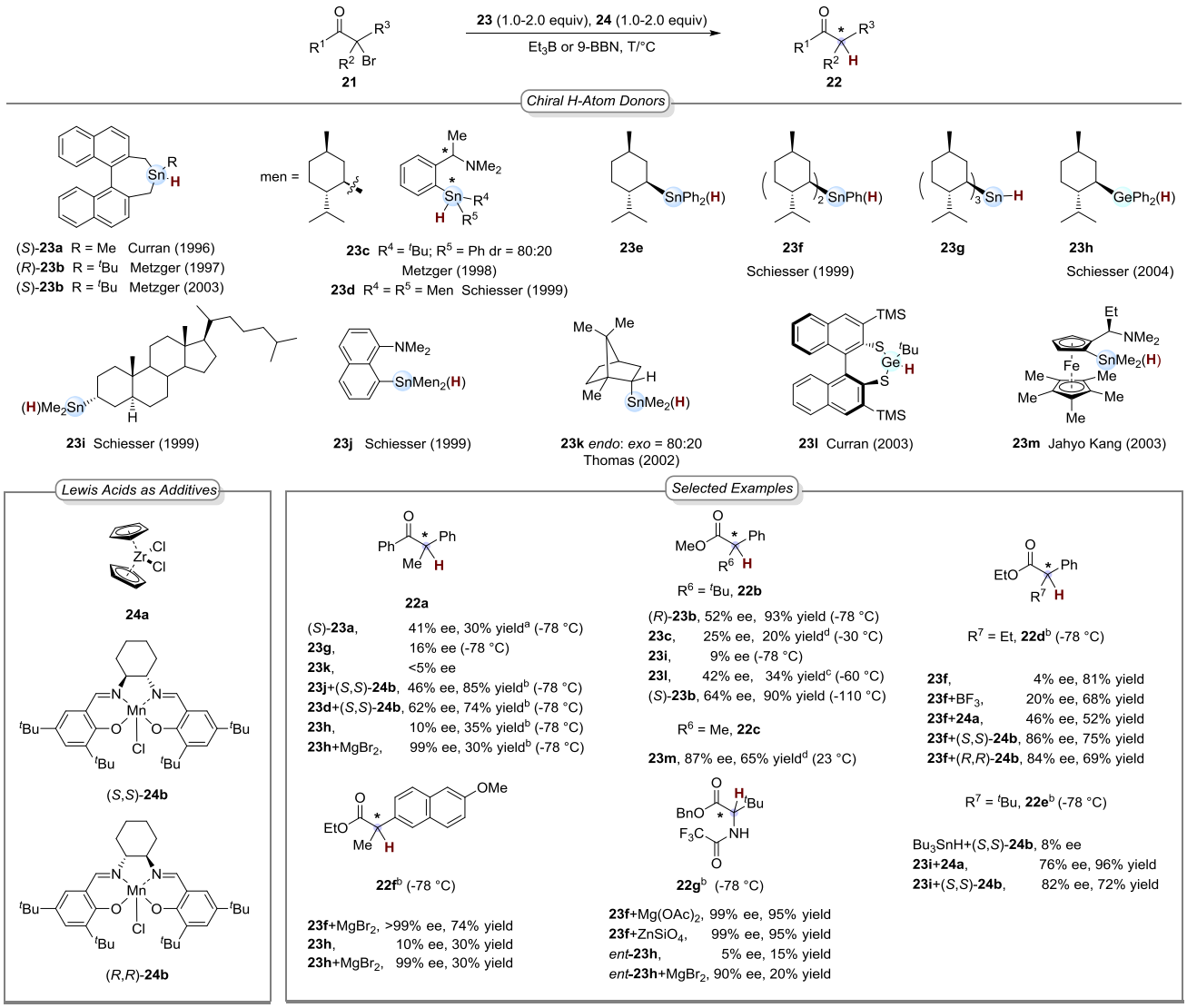
Besides the aforementioned two **AHAT** strategies involving the H-atom transfer from achiral reductants to chiral source complexed radicals, the HAT process from chiral hydrogen atom donors to radicals is also feasible to create the carbon-stereogenic centers selectively. The capacity of the chiral H-atom donor can discern between the enantiotopic faces of a radical in diastereomeric transition states, and induce stereocontrol relying on steric differentiation of groups adjacent to the transferred hydrogen atom. The utilization of stoichiometric quantities of chiral tin hydrides and germanes in halide abstraction reaction is typically required for achieving optimal reaction efficiency, while the chiral thiols, serving as the polarity-reversal catalysts, can be applied to various types of radical reactions.

In 1979, the Ohno group initiated the study of using chiral nicotinamide for ketone reduction, which achieved a significant 68% ee in the resulting alcohol.[26] Later, Tanner *et al*. investigated the mechanism of this reaction and proposed that it proceeds through a free radical pathway.[27]

4.1. Dehalogenation

In 1996, Curran and Nanni pioneered the utilization of a H-atom donor tin hydride (*S*)-**23a** featuring an axially chiral binaphthyl group, which was employed in the dehalogenative **AHAT** reaction to produce product **22a** with 41% ee (Scheme 8).[28] Calculations evaluated the structure of a similar chiral tin hydride (*R*)-**23b** with *tert*-butyl substitution bearing an identical C_2-symmetric binaphthyl, which maintains a rigid conformation in relation to the stannepine ring reported by the Metzger group.[29] The speculated transition state for H-transfer, is characterized by a linear arrangement of donor, hydrogen, and acceptor atoms (Sn···H···C). The reduction of α-bromoester by (*R*)-**23b** afforded a product **22b** with 52% ee.

Scheme 8 Chiral H-atom donors enabled asymmetric dehalogenation reactions



[a] Determined by HPLC; [b] GC Conversion; [c] By ^{1}H NMR analysis; [d] Conversion.

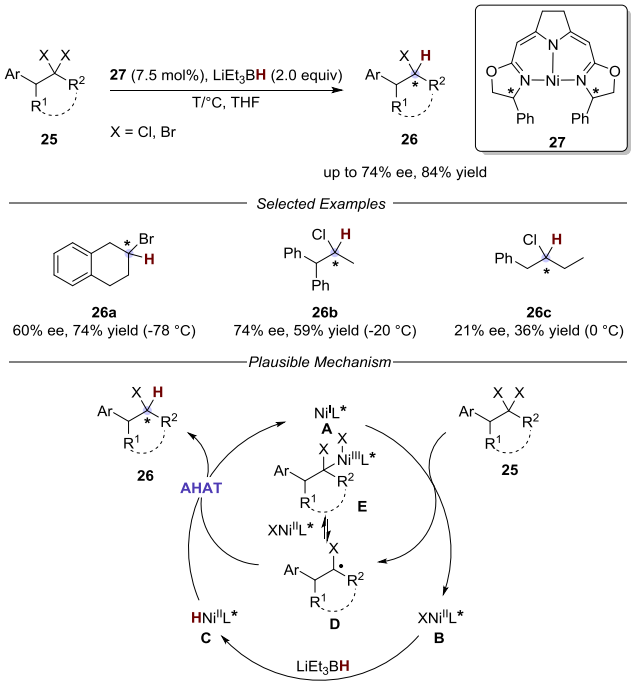
In 1998, Metzger *et al*. proposed incorporating a chiral 2-[(1-dimethylaminoalkyl)phenyl] motif into the tin hydride.[30] The reduction carried out with a mixture of **23c** having an 80∶20 diastereomeric ratio resulted in the product **22b** with 25% ee. Next, Schiesser *et al*. were prompted to explore the efficacy of a series of menthyl-substituted tin hydrides **23e—23g** in the dehalogenative **AHAT** reactions. However, they found that only a 16% ee was obtained for **22a** when **23g** was used as the H-atom donor.[31] Considering the transition state distance of approximately 3.5 Å between tin and carbon center during the hydrogen transfer process, the steric influence of menthyl substitution on tin appears insufficient for recognizing the enantiotopic faces. In addition, stannanes **23i** derived from steroids[32] and bicyclo[2.2.1]hept-2-ylstannanes **23k** derived from camphor[33] were also tested in the radical reduction reactions. The products **22b** and **22a**, were obtained with 9% ee and less than 5% ee, respectively. In 2003, Curran and Gualtieri prepared a stable chiral organogermane **23l** derived from a C_2-symmetric dithiol,[34-35] which provided the reduction product **22b** with 42% ee. Meanwhile, Jahyo Kang *et al*. designed a planar chiral metallocene tin hydride **23m**, which allowed the dehalogenative **AHAT** reaction with an impressive 87% ee for **22c**.[36]

Notably, the incorporation of Lewis acid significantly enhanced the enantioselectivity of the chiral H-atom donor tin hydride enabled asymmetric reduction reactions.[37-42] For example, the addition of BF_3 led to a rise in ee of **22d** from 4% to 20% in the presence of **23f**. After increasing the steric hindrance of the Lewis acid, a result of 46% ee was obtained using **24a**, while employing Lewis acid (*S*,*S*)-**24b** led to a substantial ee of 86%.[37] A similar result was also observed with the use of (*R*,*R*)-**24b**. The enhancement in ee is ascribed to a substantial increase in steric hindrance on the ester side, presumably arising from the coordination process of the carbonyl moiety with the Lewis acids. Although Lewis acids remarkably contribute to enhancing ee in the reaction, chirality transfer may still originate from the chiral H-atom donor tin hydride. When achiral tin hydride was employed in the reaction with the use of (*S*,*S*)-**24b**, only 8% ee of **22e** was observed. In contrast, using (*S*,*S*)-**24b** and **24a** in the presence of chiral tin hydride **23i** resulted in excellent ee, suggesting the chirality in tin hydride is more important than that in the Lewis acid. Furthermore, a wide cross-section of magnesium as Lewis acid additives was used for the reduction, and the product **22f** was obtained with 99% ee. In addition, the preparation of chiral amino acids (**22g**) could also be facilitated by utilizing this **AHAT** strategy.[40] It is likely that the formation of coordinated dimers is facilitated by the inclusion of magnesium salts, wherein one ester unit contributes the necessary steric hindrance for achieving high selectivity in the reduction of the other unit. Next, germane **23h** was aimed to replace tin hydride reagents.[42] When no additives were used, the products (**22a**, **22f**, **22g**) exhibited low ee. However, upon the

addition of magnesium bromide, the enantioselectivity increased significantly, albeit without the increase in the yield.

In contrast to the stereoselective induction mode of dehalogenation reduction by stoichiometric chiral H-atom donors, the chiral nickel(I)/nickel(II) hydride system allows for catalytic enantioselective hydrodehalogenation of prochiral geminal dihalogenides, yielding products **26** with moderate to good enantioselectivities (Scheme 9).[43] The catalytic cycle begins with the initial interaction between nickel(I) complex **A** and substrates **25**, forming halogenido complex **B** and tertiary carbon radicals **D**, which may rapidly equilibrate with a metal-stabilized form **E**. Subsequently, the radicals are transformed by **AHAT** via the hydrido nickel complex **C**, yielding the catalytic reaction products **26** and simultaneously regenerating nickel(I) complex **A**.

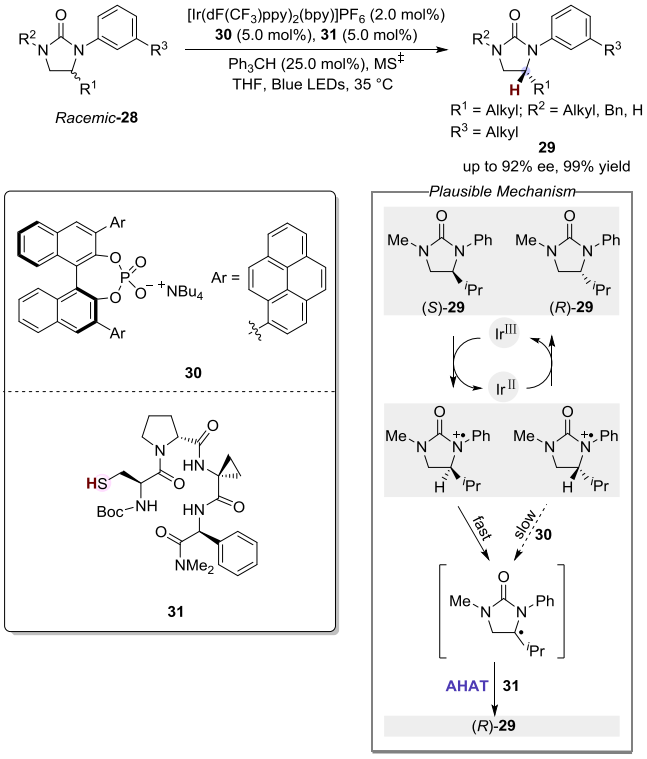
Scheme 9 Chiral nickel(I)/nickel(II) hydride-catalyzed enantioselective hydrodehalogenation



4.2. Deracemization

In 2019, Knowles *et al*. reported a light-driven deracemization of urea derivatives, which provided enantioenriched products **29** with up to 92% ee. The method comprised three distinct catalysts: an Ir(III)-based photoredox catalyst, a chiral phosphate base **30** derived from 1,1'-bi-2-naphthol (BINOL), and notably, a 5 mol% cysteine-containing peptide thiol **31** serving as the H-atom donor. The proposed mechanism is depicted in Scheme 10.[44] The racemic urea substrate **28** is reversibly oxidized by the excited state of the iridium photocatalyst, generating a mixture of transient radical cations, which enhances the acidity of the adjacent C—H bond, thereby facilitating the deprotonation process by the chiral phosphate base **30** and leading to the formation of a neutral α-amino radical. The kinetic resolution of enantiomeric radical cations is achieved in this process, where the fast-reacting (*S*)-enantiomer undergoes proton transfer, whereas the slower-reacting (*R*)-enantiomer reverts to the initial urea by charge recombination with the reduced Ir(II) state of the photocatalyst. Thus, the reaction becomes enriched in the slower-reacting (*R*)-enantiomer. After proton transfer, the resulting α-amino radical intermediate undergoes selective reduction via H-atom transfer with the chiral thiol cocatalyst, leading to the regeneration of the closed-shell urea. Through a proton-coupled electron transfer (PCET) event involving the reduced Ir(II) complex, thiyl, and the protonated base, the active forms of all three catalysts can be returned. In these reactions, enantioselectivity is determined by the proton-transfer and H-atom transfer steps sequentially within the catalytic cycle. The pendant amide H-bond donor group of the substrate plays a pivotal role in achieving good selectivities during the enantioselective deprotonation step using chiral phosphate bases.

Scheme 10 Light-driven deracemization of ureas

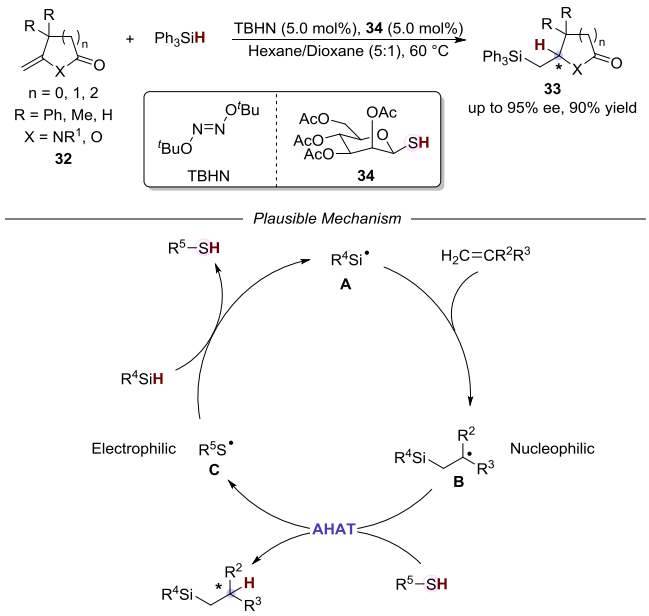


4.3. Hydrofunctionalization of alkenes

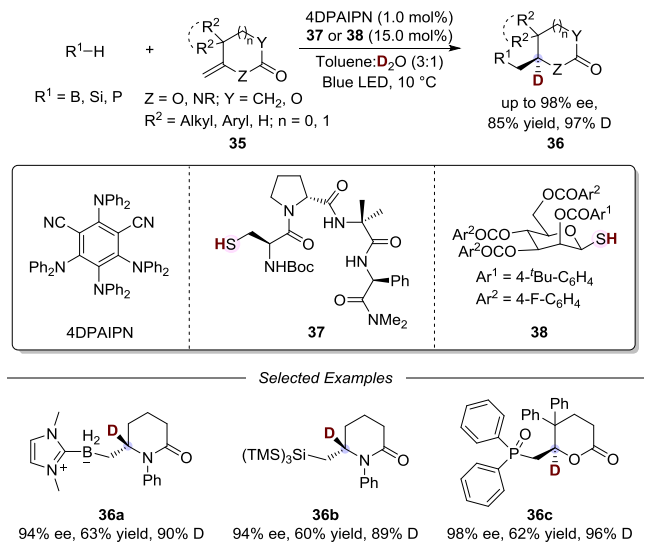
In addition to chiral tin and germanium hydrides acting as H-atom donors, chiral thiols have been developed to function as polarity-reversal catalysts, enabling the radical-chain hydrosilylation of olefins in conjunction with silane. The abstraction of electron-rich hydrogen from silane by the nucleophilic alkyl radical **B**, formed by the addition of the silyl radical **A** to the alkene, is unfavorable. The thiol catalyst featuring electron-deficient hydrogen, facilitates the HAT process of the β-silylalkyl radical **B**. If the thiol catalyst is optically active, the HAT process could be enantioselective. On the basis of the design, Roberts *et al.* reported a radical-chain hydrosilylation reaction employing a 5 mol% β-mannose thiol catalyst **34**, which resulted in the hydrosilylation product **33** with 95% ee when both R substituents are phenyl groups (Scheme 11).[45-49] The effectiveness of polarity-reversal catalysts is attributed to the relatively high electrophilicity of the thiyl radical facilitating the H-abstraction from hydrosilane, and the enhanced strength of the S—H bond due to the presence of multiple electronegative oxygen atoms.

In 2022, the Ye group reported a series of photocatalyst and peptide- or sugar-derived thiol catalysts (**37**, **38**) enabled deuteroboration, deuterosilylation, and deuterophosphinoylation of exocyclic olefins when D_2O was used as the deuterium source, which furnishes a wide range of deuterated products **36** with high enantioselectivities (up to 98%) (Scheme 12).[50-51] The process starts with the visible-light-induced photoexcitation of the photocatalyst (PC) producing the excited state PC*, which oxidizes the thiol catalyst into an electrophilic thiol radical species **A** along with the formation of the reduced state ($PC^{\bullet-}$) under a synergistic PCET in the presence of D_2O. Then, a hydridic R^1—H (R^1 = B, Si or P) bond of the

Scheme 11 Asymmetric hydrosilylation using chiral thiol catalyst



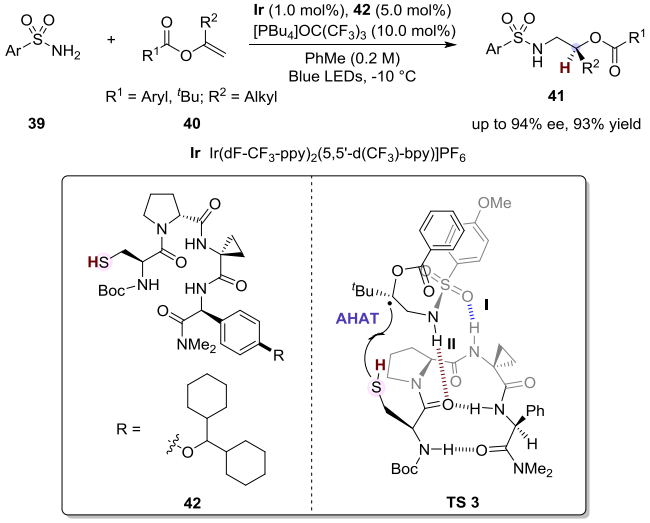
Scheme 12 Radical deuteration using peptide- or sugar-derived thiol catalyst



substrate undergoes a HAT event with the thiol radical to result in a radical species **B**. The latter, in combination with an alkene, forms a nucleophilic carbon center radical species **C**. According to the polarity matching effect, it is advantageous for nucleophilic tertiary alkyl radical **C** to abstract a deuterium atom from the electrophilic thiol radical. This radical **C** undergoes an asymmetric deuterium atom transfer (**ADAT**) process with the *in situ*-generated deuterated chiral thiol (R*SD), transferring the required deuterium to produce the deuterated product **36** and regenerate the thiol radical. Finally, the radical anion state ($PC^{\bullet-}$) undergoes a SET process with the thiol radical, thereby regenerating the photocatalyst and deuterated thiol after protonation. Density functional theory (DFT) calculations reveal that the stereoselectivity for the **ADAT** process originates from hydrogen-bonding interactions between the heteroatoms in the radical adduct and the peptidic thiol backbone. Additionally, a pronounced C—H···π interaction is observed between the phenyl ring of the radical adduct and the proline on the *Si* face of the transition state.

In 2023, a peptide organocatalyst **42** (5 mol%) is investigated to conduct a light-driven hydroamination of enol esters **40** with sulfonamides **39** reported by Knowles *et al*. This method enabled hydrofunctionalization beyond exocyclic olefins via **AHAT**, wherein the addition of sulfonamides **39** to the terminal position of the double bond from enol esters **40** results in the formation of a tertiary radical. The polarity matching effect favors the abstraction of a hydrogen atom from electrophilic thiol radicals by these nucleophilic tertiary alkyl radicals, generating 23 protected β-amino-alcohol products **41** with excellent enantioselectivities (up to 94% ee) (Scheme 13).[52] It is worth mentioning that the enol ester moiety on the substrate plays a crucial role in attaining favorable levels of enantioselectivity. It was found that substituting R with a dicyclohexylmethyl group significantly improves enantioselectivity through the systematic adjustments at each position of the tetrapeptide thiol structure. This enhancement is attributed to the stabilizing force caused by the non-covalent interactions (NCIs) between the cyclohexyl group of **42** and the aromatic ring on the substrate, aligning with the occurrence of London dispersion interaction. The presence of cyclohexyl groups consequently leads to a diminished barrier for the major HAT transition state by the interaction. When analyzing the origin of enantioselectivity in the reaction (using R as an H atom), it is found that a primary hydrogen bond linkage exists between the sulfonamide oxygen and N–H_{Acpc} (**I**), and this is complemented by a secondary hydrogen bond interaction connecting the sulfonamide N–H with the carbonyl of the Cys residue (**II**). Additionally, an intramolecular π–π stacking interaction is observed between the aromatic rings of the benzoate and benzenesulfonamide groups for the prochiral carbon-centered radical species. The conclusions are derived from experimental and computational studies, indicating that substrate recognition and enantioinduction are influenced by London dispersion interactions, hydrogen-bonding interactions, and π–π stacking.

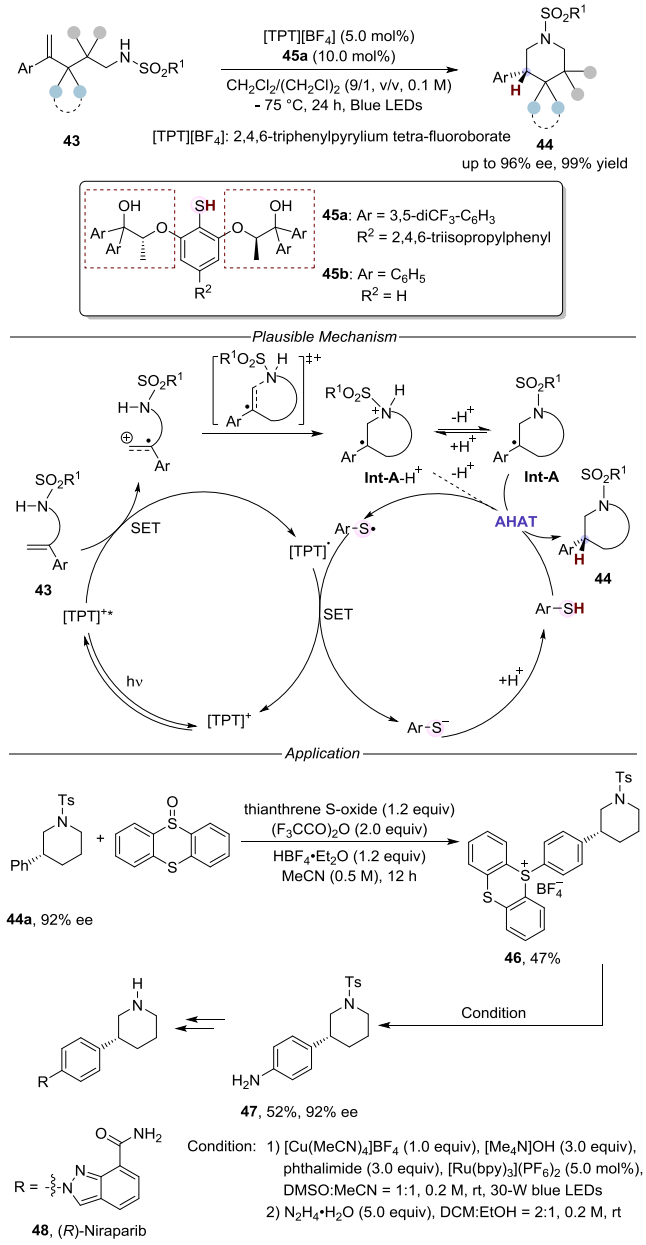
Scheme 13 Tetrapeptide thiol-catalyzed hydroamination



Peptide- or sugar-derived thiol catalysts have been proven as powerful chiral H-atom donors in **AHAT**. Currently, chiral C_2-sym-

metric arylthiol catalysts **45a**, derived from available enantiomeric lactate ester and 2,6-dialkoxy-substituted thiophenol skeleton, can serve as effective chiral H-atom donors for achieving **AHAT**. The Dong group introduced 10 mol% chiral C_2-symmetric arylthiol catalyst **45a** featuring a more congested chiral pocket to realize an anti-Markovnikov alkene enantioselective hydroamination–cyclization, obtaining a variety of pharmaceutically significant 3-substituted piperidines **44** with moderate to high enantioselectivities (Scheme 14).[53] Notably, the attachment of the aryl group with arylthiol catalyst **45** to the 1,2,2-trisubstituted ethylene glycol monoether pendants and R^2 is essential for achieving efficient enantiocontrol and high catalytic activity. The proposed mechanism involved a 5 mol% photoredox catalyst $[TPT]^+$ that generates an excited state $[TPT]^{+}$* under light irradiation, which oxidizes α-substituted styrene **43** to the alkene cation radical intermediate via a SET process. Subsequently, the addition of a tosyl-substituted amido group to the alkene cation radical occurs, resulting in the formation of **Int-A**-H^+. The chiral thiol catalyst **45b** transfers a hydrogen atom from the *N*-tosyl amido group of **Int-A**-H^+ to the benzyl-substituted C-3 site of the piperidine ring to offer **44**, undergoing a polarity-matched HAT event to produce arylthiol radical. Computational studies indicate that this process overcomes a significantly higher free-energy barrier compared to **Int-A**. Finally, the $[TPT]^{\bullet}$ undergoes a SET process with the arylthiol radical, thereby regenerating the photocatalyst and arylthiol after protonation. Remarkably, in the geometry-optimized transition states, both chiral ethylene glycol monoether pendants adopted the gauche conformation, stabilized by hydrogen-bonding interactions between the hydroxy group and the etheric oxygen atom, which facilitated the effective distal transfer of stereochemical information during the enantioselectivity-determining HAT process. Additionally, chiral 3-aryl-substituted piperidine **44a** is demonstrated to be valuable in the formal synthesis of Niraparib **48** with excellent enantioselectivity.

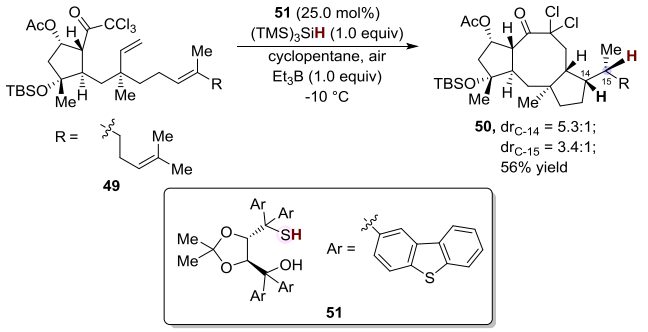
Scheme 14 Chiral C_2-symmetric arylthiol-catalyzed anti-Markovnikov hydroamination



4.4. Reductive cyclization

Notably, the chiral thiol-catalyzed **AHAT** reaction has also been applied in natural product synthesis. For example, a TADDOL-derived (a,a,a',a'-tetraaryl-2,2-disubstituted 1,3-dioxolane-4,5-dimethanol) thiol catalyst **51** enables the control of the diastereoselective reductive radical cyclization of intermediate **50** in the total synthesis of the natural product (–)-6-*epi*-ophiobolin N (Scheme 15).[54]

Scheme 15 Reductive radical cyclization using chiral thiol catalyst

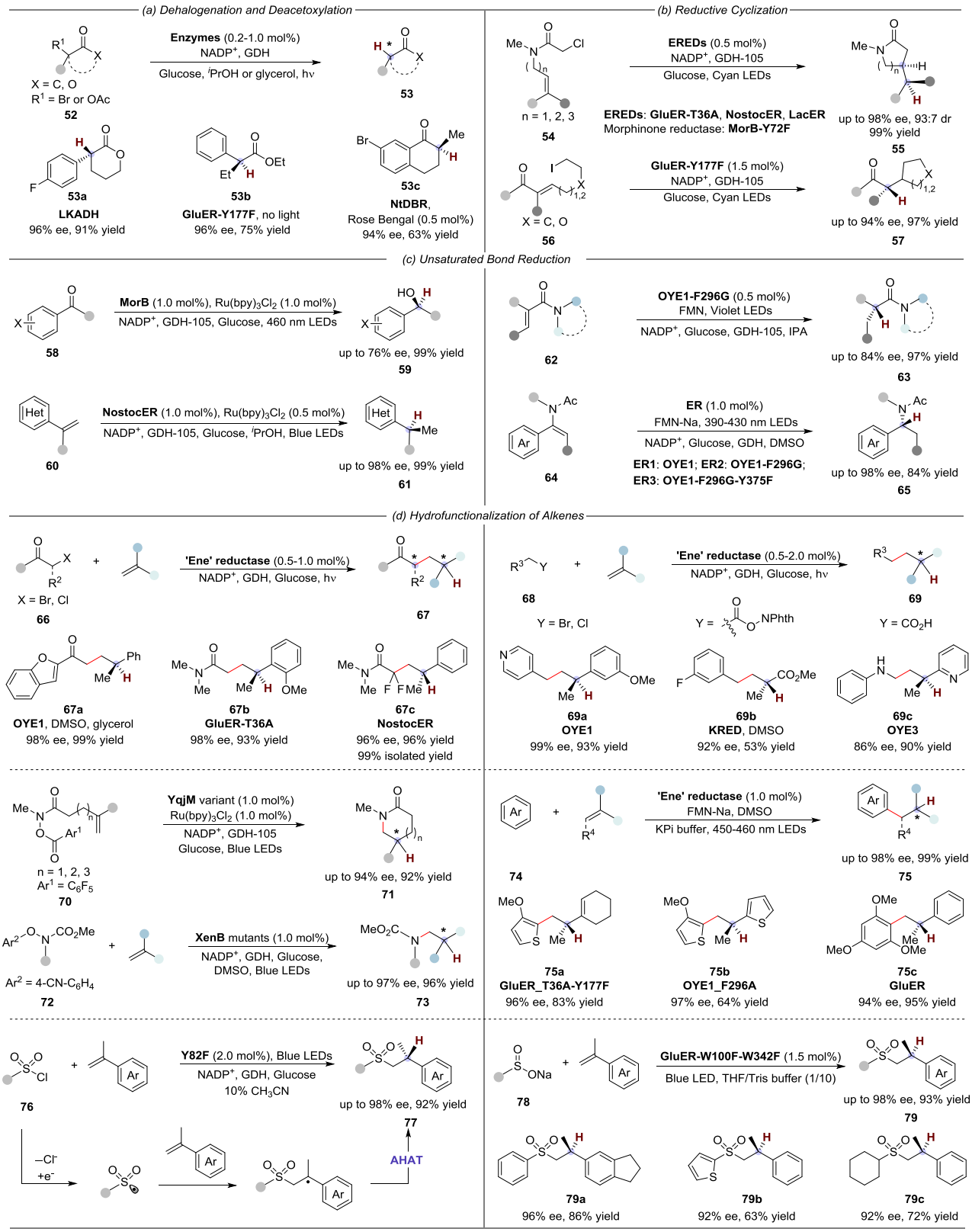


5. Enzyme-Catalyzed AHAT

The development of novel chiral chemical reagents and catalysts is central to asymmetric synthesis. In recent years, the rapid evolution of biocatalysis has emerged as a powerful and efficient method for the synthesis of various chiral molecules. In particular, enzymatic catalysis is steadily revealing its distinctive advantages in asymmetric radical chemistry.

In 2016, Hyster *et al*. pioneered the introduction of enzymatic catalysis into **AHAT**. Under visible light irradiation, the nicotinamide-dependent ketoreductases (**KRED**s) are employed as radical initiators for the dehalogenation of cyclic lactones (Scheme 16a).[55] Electron transfer occurs through a donor-acceptor (EDA) complex, formed exclusively within the active site of **KRED**, utilizing NADH and NADPH (the reduced forms of nicotinamide adenine nucleotide and nicotinamide adenine dinucleotide phosphate) as the potent single-electron reductant and hydrogen atom source. The **LKADH** (0.25 mol%) dehydrogenase of the bacterium Lactobacillus kefiri led to the formation of the (*R*)-enantiomer with the reduced product **53a** (96% ee). Building on this research, Flavin-dependent 'ene'-reductases (**ERED**s) have been identified in mediating the dehalogenation of acyclic ester. The mechanism entails electron transfer from flavin hydroquinone (FMN_{hq}), serving as a proficient single-electron reductant to electronically activate substrates. Additionally, flavin semiquinone (FMN_{sq}) plays a pivotal role as the hydrogen atom source, and the enzyme contributes to the chirality. Notably, visible light irradiation is not needed here. The ee of the dehalogenation product **53b** from α-bromoester can reach up to 96% in the presence of a 0.75 mol% **GluER-Y177F** (an **ERED** from *G. oxydans* variant).[56] Later, a photo-

Scheme 16 Enzyme-catalyzed AHAT reactions



redox system was incorporated into double-bond reductase catalysis for the enantioselective deacetoxylation of heteroarenes and dehalogenation of α-bromoamides and α-bromolactones that were completely unreactive with EDA complex and NADPH. When nicotinamide-dependent double-bond reductases from *Nicotiana tabacum* (**NtDBR**, 1 mol%) were used, the product of deacetoxylation **53c** was obtained with 94% ee.[57] The method would attenuate the reduction potential of the substrate that binds the protein via hydrogen-bonding interactions, facilitating electron transfer. The meticulous selection of a photocatalyst ensures that radical formation occurs exclusively within the chiral environment of the active site to prevent racemic background reactions between the photocatalyst and the substrate in solution.

Under light-induced conditions, the EDA complex formed between the electron-deficient α-chloroamides and the reduced flavin cofactor within the active site of **ERED**, undergoes initial

single-electron transfer. This process facilitates asymmetric radical cyclization of α-chloroamides **54** by the **ERED**s family (**GluER-T36A**, **NostocER** and **LacER**) and Morphinone reductase (**MorB-Y72F**) catalysts, giving access to the five-membered γ-lactam product **55** with an impressive ee of up to 98% (Scheme 16b).[58] Similarly, the use of a variant from Gluconobacter (**GluER-Y177F**, 1.5 mol%) allows for the reaction of unactivated alkyl iodides, which are more challenging to reduce and possess lower electron affinity. The generated nucleophilic radicals undergo intramolecular Michael cyclization, resulting in the synthesis of chiral esters, amides, and lactones **57**.[59]

Furthermore, with the synergistic catalysis of the photoredox catalyst and the morphinone reductase from *P. putida* (**MorB**, 1 mol%), the reduction of aromatic ketones to alcohols **59** is achieved (Scheme 16c).[60] Notably, the hydrogen required for this transformation originates from flavin, contributing to an ee of up to 76%. The asymmetric reduction of vinyl heteroarenes **60** is achieved by **ERED** from *N. punctiforme* (**NostocER**, 1 mol%) through the catalytic action of this strategy.[61] The need for achieving high enantioselectivity levels is demonstrated by control experiments, highlighting the essential role of flavin binding to the protein active site. Subsequently, the excited state hydroquinone enables electron transfer via photoinduced electron transfer (PET) upon direct excitation of the flavin cofactor (**OYE1-F296G**, 0.5 mol%) to reduce α,β-unsaturated amides **62**. This proceeds through **AHAT** from FMNsqH, yielding products **63** with up to 97% yield and 84% ee.[62] Similarly, the single-electron reduction through direct visible-light excitation of the hydroquinone state of the flavin cofactor enhances the reducing capacity of ene-reductases. This achieves the reduction of enamides **64** to chiral amines **65** with up to 98% ee.[63]

In 2020, the Zhao group disclosed an intermolecular hydroalkylation between α-halo ketones and alkenes mediated by 'ene' reductase (**ER**) (Scheme 16d).[64] This reaction obtained γ-chiral carbonyl product **67a** with an impressive 98% ee when 1 mol% **OYE1** (an Old Yellow Enzyme from *Saccharomyces cerevisiae*) was used as the catalyst, in which the tyrosine residue facilitated the direct donation of a hydrogen atom to the prochiral radical, leading to the (*S)*-configuration of **67a**. After the HAT process, the resulting *O*-centered radical of tyrosine abstracts hydrogen atom primarily from flavin mononucleotide semiquinone ($FMNH^{\bullet}$) or from the active protons of amino acid residues or solvents. The Hyster group further proceeded to achieve an intermolecular hydroalkylation between α-chloroamide and alkene, leading to the formation of enantioenriched γ-stereoisomeric amide **67b** with 98% ee.[65] Regarding **GluER-T36A**, radical termination almost exclusively occurred through **AHAT** from FMNsq. Notably, α,α-difluorochloroamide is tolerated in the process and affords product **67c** in a high yield and enantioselectivity by the use of 1 mol% **NostocER**.

Unlike conventional carbonyl-containing halogenated substrates, the nitrogen atom of bromomethyl pyridine establishes a similar hydrogen bond interaction with the **ER**, which facilitates substrate recognition and activation. Thus, the addition of azaarene to α-methyl styrene through HAT can modulate the enantioselectivity of the remote carbon center, constructing the corresponding γ-stereocenter product **69a** (99% ee) by using 1 mol% **OYE1**.[66-67] The HAT process serves as both the rate-determining and enantio-determining steps. Hydrogen atoms may originate from FMNsq. The importance of achieving such remarkable stereoselectivities is underscored by the hydrogen-bonding and steric effects of the critical amino acid residues. In addition, a different kind of radical precursor derived from *N*-(acyloxy)phthalimides to react with electron-deficient alkenes catalyzed by **KRED**s (using cell-free lysate (K3) or lyophilizate of **KRED**s) was reported by the Zhao group, giving access to α-carbonyl stereocenter product **69b** (92% ee).[68] The hydrogen atoms are entirely derived from NADPH generated *in situ*. Notably, the enantioselectivity of this reaction might not be determined by the HAT step; instead, it is influenced by the conformation of the bound alkene substrate. Moreover, an exogenous $Ru(bpy)_3^{2+}$ cofactor with 1 mol% **OYE3** facilitates the redox-neutral decarboxylative coupling of amino acids with vinylpyridines, achieving **69c** in a 90% yield and 86% ee.[69] The determination of stereoselectivity is attributed to the HAT step rather than the formation of the C—C bonds.

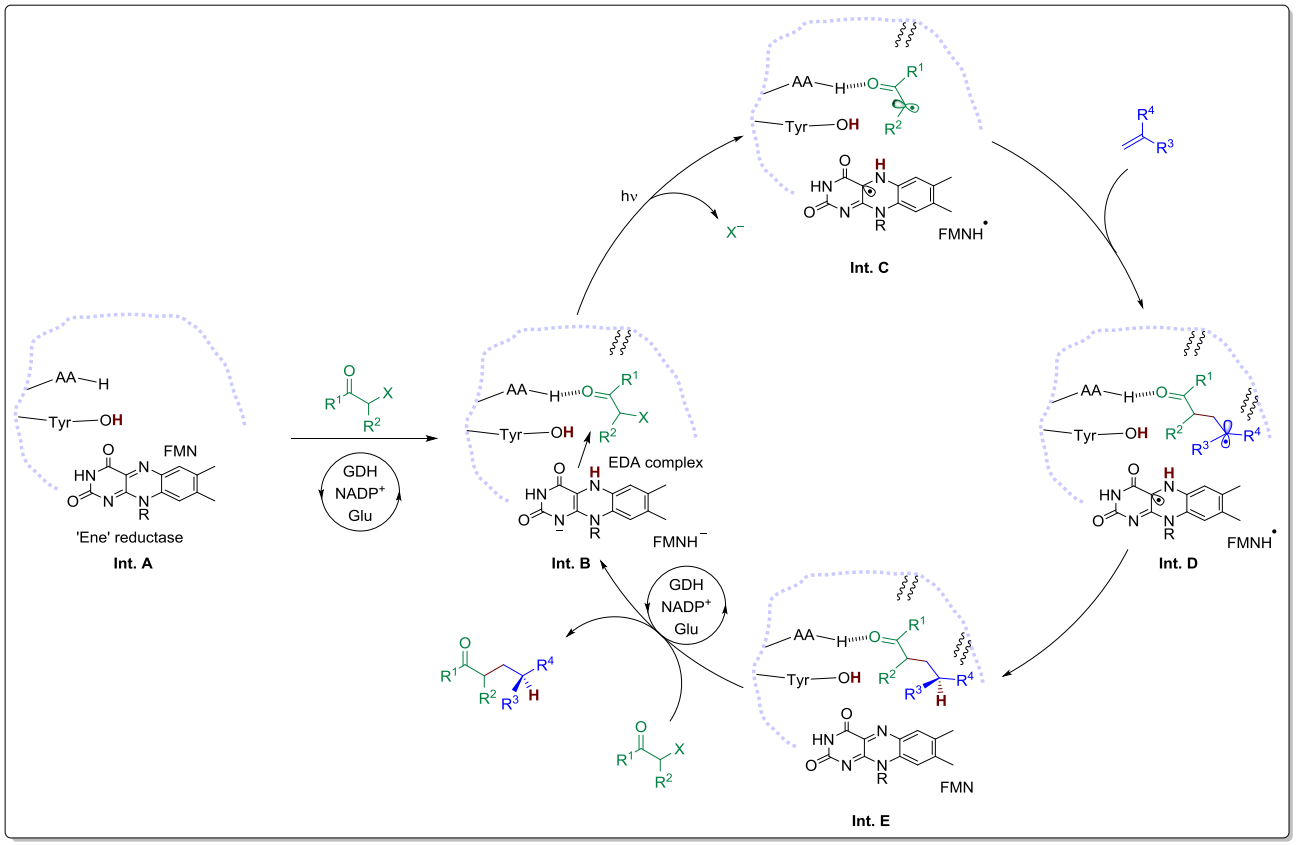
Besides the aforementioned hydroalkylations, several hydroamination reactions have also been demonstrated by enzymatic catalysis with high efficiency. Hyster *et al*. demonstrated the use of stable hydroxamic esters **70** as radical precursors to enable the intramolecular hydroamination synergistically catalyzed by the $Ru(bpy)_3Cl_2$ and **YqjM-*R*** (an **ERED**s from Bacillus subtilis), which afforded 5-*exo*, 6-*endo*, 7-*endo*, 8-*endo* products **71** with up to 94% ee.[70] The enantio-determining step in these reactions is identified as the formation of the C—N bond. In addition, the Zhao group reported that nitrogen-containing substrates **72** bearing phenolate leaving groups could react with terminal alkenes in the presence of 1 mol% **XenB** (from *Pseudomonas putida*), which allowed for an intermolecular hydroamination reaction giving product **73** with 97% ee.[71] This process effectively addresses the challenge of nitrogen radicals being quenched by hydrogen atoms. The hydrogen atoms are derived from $FMNH^{\bullet}$ in this reaction, and the enantioselectivity arises from the C—N bond formation rather than HAT.

In 2023, the intermolecular hydroarylation of alkenes with electron-rich arenes is also accomplished by visible-light-excited **ERED**s, which terminate tertiary carbon radicals via HAT from FMNsq.[72] Under different types of **ER** catalyzed conditions, a wide range of products **75** were obtained with up to 98% ee in the hydroarylation process. Notably, the enantioselectivity is mainly determined by the C—C coupling step.

The photoenzymatic strategy can be extended to asymmetric hydrosulfonylation. Sulfonyl chloride **76** serves as a precursor, with photoexcited flavin-independent enzymes (2 mol% **Y82F**) generating sulfonyl radicals, which are captured by alkenes within the enzyme's binding pockets. Following the **AHAT** termination from tyrosine, chiral sulfone scaffolds **77** are formed.[73] Additionally, the Ye group reported enantioselective hydrosulfonylation achieved through an oxidation-initiated photoenzymatic strategy for sodium sulfinates **78** to produce sulfonyl radicals. This employs a novel mutant of Gluconobacter ene-reductase (1.5 mol% **GluER-W100F-W342F**). The corresponding product **79** is obtained with up to 98% ee and 93% yield through a tyrosine-mediated **AHAT** process.[74] This approach eliminates the need to add a ternary mixture to regenerate a cofactor turnover system, thereby streamlining the reaction setup. Moreover, it avoids the formation of EDA complexes with substrates, expanding the range of usable sulfonyl radical precursors and olefins.

From a mechanistic point of view, a selected catalytic cycle for the enzyme-catalyzed hydroalkylation reaction[64] was outlined in Scheme 17. A simplified mode of **ER** is shown as intermediate A (**Int. A**), which contains FMN as a redox-active center and features the active-site residues asparagine and histidine as hydrogen-bonding donors, as well as tyrosine as a proton donor. Firstly, GDH facilitates the conversion of $NADP^+$ into its reduced form NADPH, along with inducing the oxidation of glucose to gluconic acid. The *in-situ* produced NADPH transfers the hydride to **ER** and generates $FMNH^-$. Through hydrogen bonding interactions with the His/Asn residues, the α-halo carbonyl compound is bound to the active site of the enzyme, forming an EDA complex **Int. B** with the adjacent $FMNH^-$, which is excited by visible light to trigger the single electron transfer process. Concurrent release of the halo anion X^- leads to the formation of **Int. C** containing the $FMNH^{\bullet}$ and the α-carbonyl carbon-centred radical, addition of which to the alkene delivers the prochiral radical **Int. D**. After stereocontrolled HAT, the enzyme-associated product is produced together with the quinone FMN to form **Int. E**. Finally, product-substrate

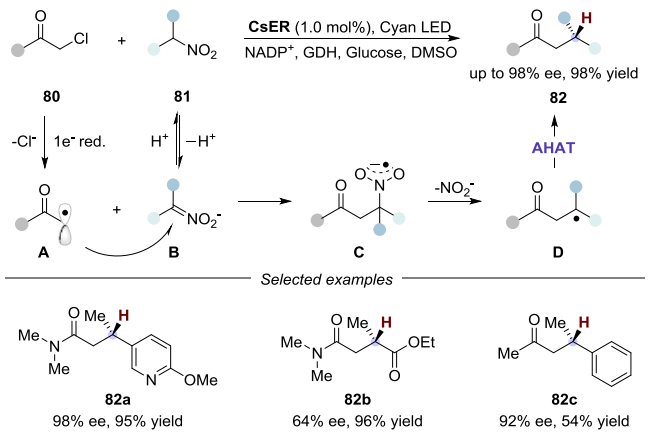
Scheme 17 The proposed catalytic cycle of enzyme-catalyzed hydroalkylation



exchange, as well as the regeneration of $FMNH^-$ through the GDH/$NADP^+$/glucose system completes the catalytic cycle.

Besides terminating the tertiary carbon radical formed by functional group additions to the double bond, **AHAT** also terminates the tertiary carbon radical arising from the C_{SP}^3–C_{SP}^3 cross-coupling reaction (Scheme 18).[75] Hyster *et al.* reported that through the formation of protein-templated charge-transfer (CT) complexes between the protein and the alkyl halide, flavin-dependent **ERED**s (1 mol% **CsER**) can selectively reduce the alkyl halide **80** to generate the alkyl radical **A**, without affecting nitroalkane **81**. The alkyl radical **A** undergoes C_{SP}^3–C_{SP}^3 nucleophilic coupling with *in situ*-generated nitronates, forming a C–C bond and the nitro radical anion **C**. This process culminates in the collapse to form nitrite and the alkyl radical **D**, with the reaction concluding via HAT from FMNsq, producing the cross-coupled product **82** with up to 98% ee.

Scheme 18 Enzyme-catalyzed asymmetric C_{SP}^3–C_{SP}^3 cross-electrophile coupling



6. Summary and Outlook

In summary, this review highlights the substantial progress achieved in the construction of tertiary carbon-stereogenic centers via **AHAT**. Four asymmetric strategies are discussed in detail allowing the enantioselective radical reactions, including 1) the coordination of chiral Lewis acid with substrate to generate a chiral environment; 2) the use of chiral hydrogen-bonding reagent to discriminate the enantiotopic faces; 3) the chiral hydrogen atom donor to control HAT process; and 4) the creation of a chiral cavity environment for radical via enzyme catalysis. These effective strategies serve to circumvent background reactions, thereby achieving high enantiocontrol in various asymmetric radical reactions, which open up new avenues for the synthesis of chiral drug molecules and natural products containing tertiary carbon-stereogenic centers.

Despite significant achievements in this field, several challenges remain unresolved. For instance, 1) the catalytic version of chiral Lewis acid-mediated **AHAT** is rare. Therefore, the development of novel efficient chiral Lewis acid catalysts, that could bind with the native functionality of the substrates creating a precise chiral pocket for **AHAT** is highly demanded. 2) The chiral hydrogen atom donor-catalyzed halide abstraction reaction has not been achieved. The high toxicity of chiral tin reagents and the insufficient reactivity of chiral germanium reagents highlight the need to search for new efficient hydrogen atom donor reagents. The readily available and low-toxic chiral hydrosilanes may have great potential as good candidates for the next generation of chiral hydrogen atom donors. 3) The substrate scope of enzyme-catalyzed **AHAT** is limited, and the development of new types of reactions with broad scope is highly demanded.

Acknowledgement

We are grateful for financial support from the National Natural Science Foundation of China (22122102, 22271134), Guangdong Provincial Key Laboratory of Catalysis (No. 2020B121201002), Guangdong Pearl River Talent Program (2019QN01Y628), Shenzhen Science and Technology Innovation Committee (RCJC20221008092723013, JCYJ20230807093104009).

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Manuscript received: May 22, 2024
Manuscript revised: June 27, 2024
Manuscript accepted: July 2, 2024
Version of record online: September 18, 2024

Left to Right: Xue Han, Chuan He

Xue Han (left) received her Ph.D. from Lanzhou University (China) under the supervision of Prof. Yongqiang Tu (2017—2022), where her research focused on asymmetric nitrogen insertion reactions. Then she joined the Southern University of Science and Technology (China) as a postdoctoral researcher under the supervision of Prof. Chuan He. Her current research interests mainly focus on the application of chiral monohydrosilane compounds.

Chuan He received his BS degree in Chemistry from Wuhan University (China) in 2008, after which he studied for a Ph.D. at the same university under the supervision of Prof. Aiwen Lei. In 2013, he joined Prof. Matthew Gaunt's group as a postdoctoral researcher and Marie Curie Research Fellow at the University of Cambridge (UK). In 2018, he started his independent research career at the Southern University of Science and Technology (China). His current research interests include: chiral organosilicon chemistry; chiral organoboron chemistry; electrocatalytic heteroatom chemistry; chiral organic functional materials.