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Advances in photocatalytic deracemization of sp^3-hybridized chiral centers *via* hydrogen atom transfer

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ABSTRACT

The enantioselective separation of racemate, particularly those containing C(sp^3)-H bonds knowns for their high bond dissociation energies and significant polarity, presents a significant challenge in pharmaceutical synthesis. Recent advances have witnessed the fusion of photocatalysis with hydrogen atom transfer (HAT) methodologies, marking a notable trend in synthesis of chiral molecules. This technique uses the excitation of a catalyst to activate substrates, enabling the selective isomerization of chiral centers containing C(sp^3) configurations. This process distinctively facilitates the direct activation of the C(sp^3)-H bond in targeted reagents. This review systematically discusses the photocatalytic isomerization of various chiral molecule featuring C(sp^3)-H centers, capable of undergoing deracemization through two primary HAT mechanisms: direct and indirect pathways. From the perspective of synthetic organic chemistry, this field has progressed towards the development of isomerization strategies for molecules that incorporate an activating group at the α-position adjacent to the C(sp^3) chiral center. Moreover, it covers methodologies applicable to molecules characterized by specific C-C and C-S bond configurations. The integration of photocatalysis with HAT technology thus provides valuable strategies for the synthesis of enantiopure compounds with enhanced selectivity and efficiency.

1. Introduction

Enantiomerically pure molecules play a crucial role in biology and medicine, driving advancements in asymmetric catalytic techniques [1]. Traditionally, the separation of racemic mixtures through kinetic methods has been the most widely employed approach for the large-scale preparation of enantiomerically pure compounds with sp^3 chiral centers [2]. However, this method is limited by a theoretical maximum yield of 50%, resulting in significant material wastage. Recent research has aimed to overcome this limitation by developing strategies to directly convert racemates into single enantiomers. These strategies include dynamic kinetic resolution [3], dynamic kinetic asymmetric transformation [4,5], and deracemization processes [6]. Despite the fact that dynamic kinetic resolution and dynamic kinetic asymmetric transformation can achieve 100% yield in theory, these methods often result in chemically modified products different from the starting racemates. Deracemization process also has the potential to achieve a theoretical yield of 100%, particularly when the target product shares the same molecular structure as the starting material, which eliminates the need for complex post-processing steps [7]. The exceptional atom economy and practical efficiency of these innovative techniques have garnered significant interest, notably within the pharmaceutical and manufacturing industries [8].

In the absence of external forces, deracemization involves two opposing reactions that share the same reaction pathway. This process has two primary disadvantages: First, deracemization is inherently an endergonic process characterized by a decrease in entropy [9]; Second, in accordance with the principle of microscopic reversibility, the forward and reverse reactions of a chiral catalyst cycle are identical [10]. Consequently, without the intervention of external chemical or physical forces, the enantiomeric enrichment of substrates cannot be controlled. More importantly, conventional methods of deracemization, which usually require the introduction of a heat source or the addition of a strong base to complete, are not possible for the sp^3 tertiary carbon chiral center without neighboring activating groups [11,12]. Because for sp^3 chiral centers containing a carbon-hydrogen bond: particularly challenging is the high bond energy ($BDE_{C\text{-}H}$, ~85–105 kcal/mol) [13] and low polarization of C–H single bonds [14], which complicates the achievement of enantiomer enrichment *via* reversible cleavage and reformation of stereocenters—a problem that has not yet been effectively addressed (Fig. 1a). For example, Wang *et al.* report

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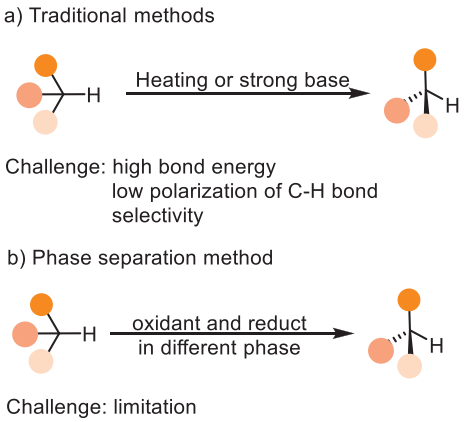

Fig. 1. Traditional synthetic method toward chiral molecule containing tertiary C(sp^3) center.

the first synthetically useful protocol for the epimerization of tertiary carbons *via* reversible radical cleavage of unactivated C(sp^3)-H bonds with hypervalent iodine reagent benziodoxole azide [15]. Inevitably, they used hypervalent iodine, a strong oxidizing substance to achieve the isomerization of cyclohexane, which make the practical industrial application very difficult.

A common strategy for disrupting and restoring chirality at stereocenters involves the sequential use of oxidation and reduction reactions. However, a major challenge in redox-driven deracemization is the tendency for oxidants and reductants to be prematurely neutralized within a single reactor, a process that is typically favored both thermodynamically and kinetically (Fig. 1b). The initial breakthrough in this area occurred in 1965 with the introduction of biocatalysis, which utilized enzymes' compartmentalization to control the redox process [16]. This approach utilizes phase separation to prevent the premature neutralization of oxidizing and reducing agents by dispersing them in separate compartments. Despite its effectiveness, this method is limited in its applicability to other types of reactions. Therefore, there is a need to develop new, milder methods for achieving deracemization, particularly in cases involving non-activated C(sp^3) centers.

Catalytic C–H bond cleavage and formation in combination with an HAT reagent appear to be an ideal approach. For chiral molecules containing C(sp^3)-H, isomerization often necessitates the cleavage of the C–H bond to generate carbon radicals followed by C–H bond reorganization. Previous studies have primarily generated carbon radicals by converting the C–H bond into the more cleavable C-Z (C-I, C-Br, C-Se, C-Te, *etc.*) or by cleaving the N–O bond in Barton esters (Fig. 2a) [17]. However, molecules with chiral centers are often challenging to control during bond transitions, and direct C–H bond cleavage appears to more efficient and convenient approach. Nevertheless, the high polarity of C(sp^3)-H has led to a prolonged period of stagnation, and the few reported instances of direct cleavage of C(sp^3)-H typically require high-energy reagents, such as the strong oxidant azide [15].

Photocatalysis is an excellent solution due to the ability of photocatalysts (PCs) to activate substrates through various mechanisms including single electron transfer (SET) and energy transfer (ET) of the excited PCs [18]. At the same time, hydrogen atom transfer (HAT) emerged as an efficient mechanism for transporting H, garnering attention in the deracemization field. In the process of C–H bond cleavage and recombination in chiral molecules containing C(sp^3)-H bond, photocatalytic reactions typically involve two HAT pathways, direct HAT [19] and indirect HAT [20]. Direct HAT is often more limited, with only a few species of photocatalysts known to induce this process. The photocatalyst, usually a specific structure like a ketone or polymetallic oxonate, can bind to racemic

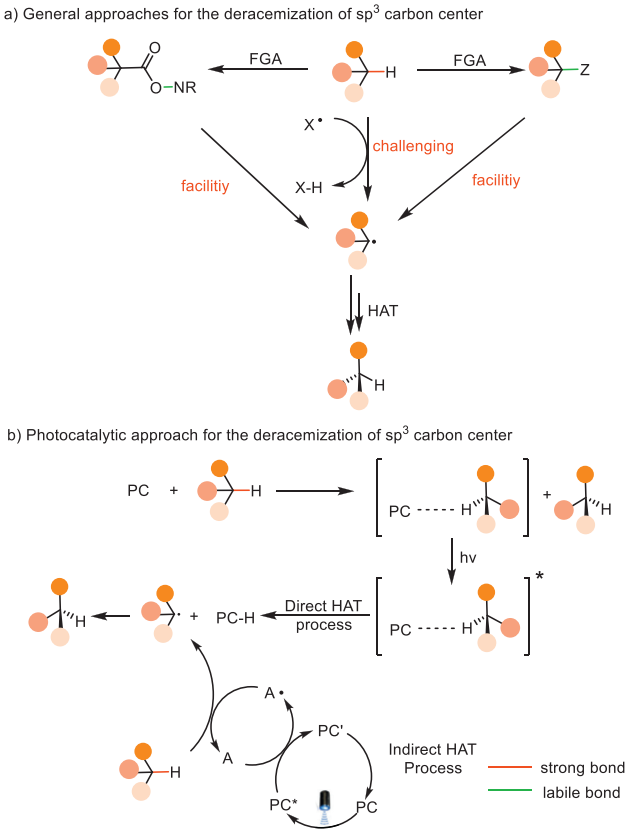

Fig. 2. (a) General approaches for the deracemization of sp^3-hybridized chiral center. FGA = functional group addition, X= hydrogen atom abstraction agent. (b) photocatalytic approach for the deracemization of sp^3-hybridized chiral center. A = hydrogen-transfer reagent.

substrate through hydrogen bonding. Upon light excitation, an energy transfer occurs between the photocatalyst and the racemic substrate, significantly reducing the bonding energy of C(sp^3)-H in the racemic substrate. This allows hydrogen in the racemic substrate to easily transfer to the photocatalyst, generating a carbon free radical (Fig. 2b). On the other hand, the photocatalytic indirect HAT process is more conventional, requiring the addition of a hydrogen-transfer reagent. When excited by light, the photocatalyst undergoes electron transfer with the HAT reagent to form a radical intermediate, which captures the hydrogen in the racemic substrate to form the carbon radical. Then the carbon radical will undergo C–H bonding recombination to form a sp^3 chiral center (Fig. 2b). Compared to other methods, the photocatalytic deracemization process combined with a HAT process eliminates the need to convert C–H bonds to C-Z bonds, which is more atomically economical, and also avoids the use of strong oxidizing agents.

This field has begun to attract much attention in recent years and a large number of reports have appeared [21,22]. Many organic compounds can be photocatalyzed to achieve C–H activation, which in turn leads to the deracemization of racemate containing C(sp^3)-H. Several comprehensive reviews have already discussed the photocatalytic racemization reactions, categorizing them based on the interaction between the photosensitizer and the substrate [23] or the types of substrate involved [24]. Within this contest, HAT plays a crucial role in achieving photocatalytic racemization, particularly for chiral substrates containing C(sp^3)-H bonds. However, recent summaries focusing on this aspect are lacking. Therefore, this review aims to present the deracemization of racemate containing C(sp^3)-H bonds based on different substrate types, utilizing either direct or indirect HAT processes. We hope that

our brief summary will provide new insights and inspire breakthroughs in this field.

2. Deracemization of C(sp^3)-H bonds

The presence of sp^3 hybridized chiral centers is crucial for the synthesis of biopharmaceutical intermediates [25]. However, the inherent low reactivity of these centers has historically impeded progress in this domain. Recent advancements have demonstrated that integrating photocatalysis with HAT technology facilitates the deracemization of various substrates containing C(sp^3)-H bonds. This approach has significantly expanded the possibilities of racemate deracemization. Accordingly, this section of the review will be organized based on the substrate type incorporating the C(sp^3)-H bond.

2.1. Direct HAT process

Aromatic ketones have long been recognized for their ability to absorb hydrogen atoms upon exposure to light [26]. Integrating this phenomenon with the deracemization of racemate containing C(sp^3)-H bonds has led to the development of an approach that harnesses the synergistic potential of photocatalysis and the HAT process. This approach has been elucidated through a series of case studies. Additionally, polymetallic oxonates have proven to be effective HAT reagents. Similar to aromatic ketones, these oxonates offer a feasible pathway for the deracemization of racemate featuring C(sp^3)-H bonds.

In one instance, Großkopf and colleagues have reported an alternative deracemization strategy employing photochemical means for 5-substituted 3-phenylimidazolidine-2,4-diones (hydantoins, **2**), achieving 69%-quantitative yields and 80%–99% *ee* (Fig. 3a) [27]. The proposed mechanism involves benzophenone as a chiral organocatalyst capable of hydrogen bonding and discriminating between enantiomers (Fig. 3b). Theoretical calculations indicate that the complex [**1**·*ent*–**2a**] can adopt a ground-state conformation with the carbonyl oxygen atom just 264pm away from the hydrogen atom at the stereogenic center, enabling a direct HAT upon excitation, unlike complex [**1**·**2a**], where the critical hydrogen atom is on the opposite, inaccessible side of the hydantoin ring.

The chiral benzophenone catalyst has enabled the photochemical deracemization of racemic 3-substituted oxindoles to enantiomerically pure or enriched materials (up to 99% *ee*) under

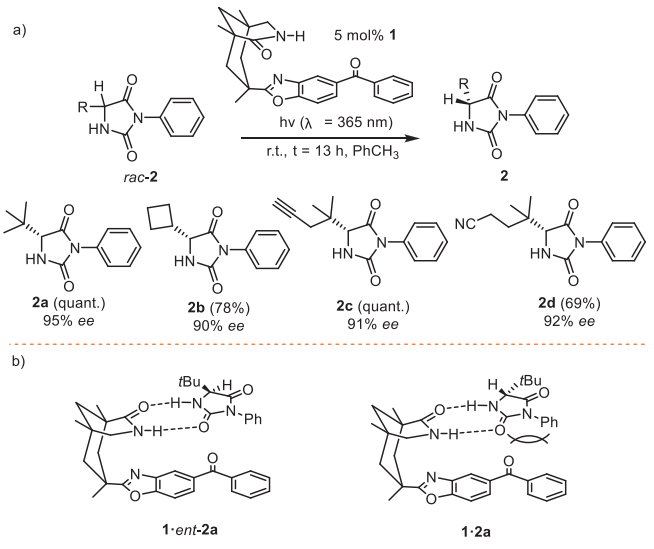

Fig. 3. (a) Photocatalytic deracemization of hydantoins by chiral ketone. (b) Proposed noncovalent interaction between photocatalyst and substrate.

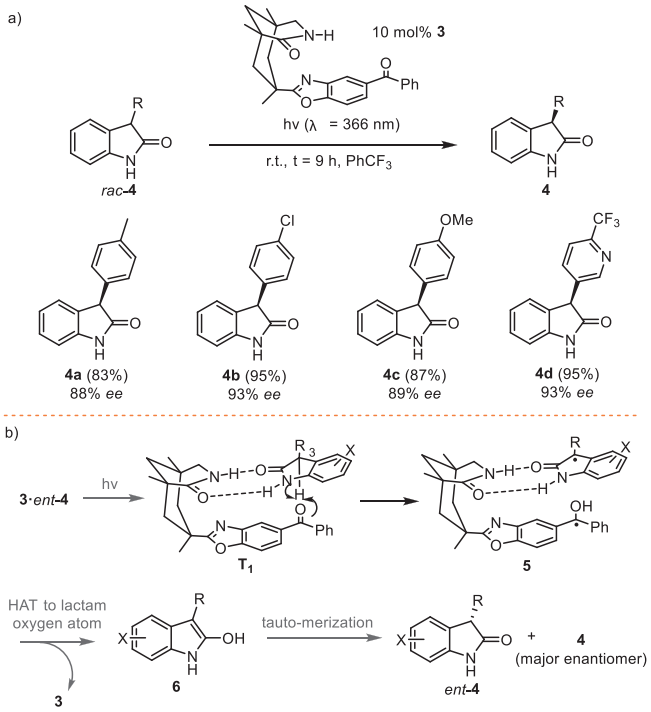

Fig. 4. (a) Photocatalyzed deracemization of oxindoles with benzophenone catalyst. (b) Proposed mechanism.

366 nm light irradiation (Fig. 4a) [28]. In contrast to prior instances utilizing precious metal photocatalysts, this method employs a chiral benzophenone as catalyst. The process enables precise modification of the stereogenic center containing C(sp^3)-H. The proposed mechanism involves the chiral catalyst **3** selectively inducing direct HAT from the oxindole enantiomer *ent*–**4** within a hydrogen-bonded complex [**3**·*ent*–**4**] (Fig. 4b). Following excitation and intersystem crossing to the triplet state T_1, the benzophenone's carbonyl group abstracts the hydrogen atom at the C3 position of compound **4**, generating two carbon-centered radicals within the complex **5**. Unlike in hydantoins where the transferred hydrogen is directed to an oxygen atom not involved in hydrogen bonding [29], in oxindoles, the hydrogen atom is either returned unselectively to the carbon atom or, more likely, to the hydrogen-bonded lactam oxygen atom. The latter pathway would result in the formation of intermediate **6**, which is expected to tautomerize, yielding a statistical mixture of oxindoles *ent*–**4** and **4**. Due to the inaccessibility of the C3-position hydrogen atom in **4** within a hypothetical complex [**3**·**4**], the enrichment of this enantiomer occurs while the *ent*–**4** enantiomer is recycled back into the photocatalytic cycle.

In addition to aromatic ketones, direct HAT can also occur with polymetallic oxonate. MacMillan and co-workers have reported a selective epimerization of cyclic-diols through direct HAT photocatalysis, paired with boronic acid-mediated transient thermodynamic control (Fig. 5a) [30]. This strategy favors the formation of the less stable *cis* isomers over the typically favored trans configurations. With the optimized conditions established, the researchers explored the scope of the reaction, finding that various cyclic 1,2-*trans*-diols were effective substrates, furnishing the *cis*-diol with commendable yield and selectivity. Further studies extended to 1,3-diol substrates, anticipating that the epimerization would favor the diol isomer capable of stabilizing the most stable bicyclic boronic ester, in line with their mechanistic hypothesis. Mechanistic investigations have elucidated that the dynamic HAT between the decatungstate anion and diol leads to an equilibrium mixture of *trans*-**7** and *cis*-**8** diol isomers (Fig. 5b). Within this sys-

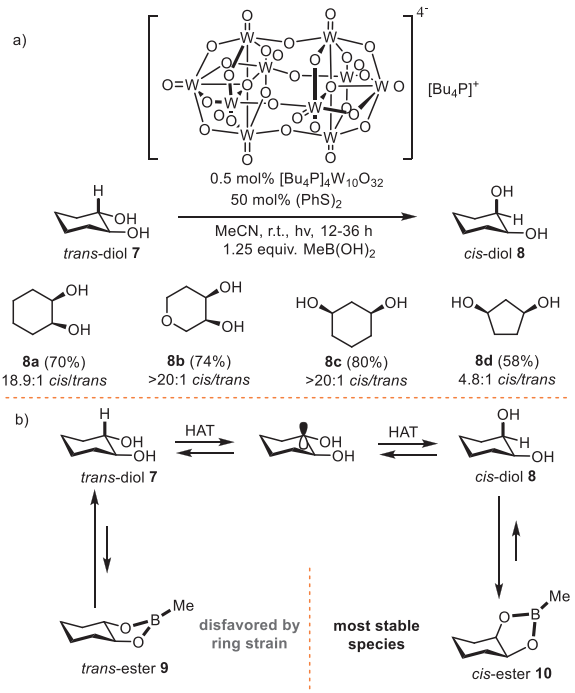

Fig. 5. (a) Epimerization of 1,2-diols and 1,3-diols by the decatungstate anion. (b) Proposed mechanism.

tem, methylboronic acid preferentially reacts with the *cis*-diol to yield the stable *cis*-boronic acid ester **10**. Conversely, the synthesis of the *trans*-boronic acid ester **9** is impeded by ring strain, rendering it a less favored product. Additionally, the formation of these boronic esters is reversible, allowing for the conversion of any *trans*-boronic ester **9** back to its corresponding *trans*-diol **7**. By reaching thermodynamic equilibrium and employing a simple hydrolysis step, the selective synthesis of the thermodynamically less stable *cis*-diol diastereoisomers from the more stable *trans* counterparts can be achieved without the need for additional reagents.

In the context of decalin epimerization, Combs-Walker and Hill demonstrated the conversion of *cis*-decalin to *trans*-decalin using a decatungstate (DT) polyanion photocatalyst [31]. However, the formation of the desired *trans*-decalin product was notably slow under these conditions. In a complementary approach, Zhang *et al.* delineate a novel paradigm for synthesizing these chiral molecules (Fig. 6) [32]. By applying these conditions to a range of substrates (**11a**-**11c**), the reactivity and selectivity of the method were assessed across various compounds containing tertiary stereogenic carbon centers. The breakthrough of this strategy lies in the development of a mild and highly direct HAT synergistic photocatalytic system, comprising decatungstate polyanion and disulfide cocatalysts. This system enables the interconversion of previously unalterable tertiary stereogenic centers. The flexibility of the method is underscored by its ability to rapidly construct intricate chiral scaffolds and facilitate late-stage stereoediting of complex molecules.

2.2. Indirect HAT process

In the photocatalytic process, the generation of free radicals or radical ions is a common phenomenon. Molecules containing oxygen and nitrogen, which possess lone pairs of electrons, are particularly prone to participating in electron transfer reactions [33-35]. In these reactions, the C(sp^3)-H bond located at the α position is preferentially targeted by HAT agents. This interaction often leads to subsequent isomerization of the molecule. Numerous compounds featuring nitrogen and oxygen atoms have been effectively isomerized through these indirect HAT mechanisms.

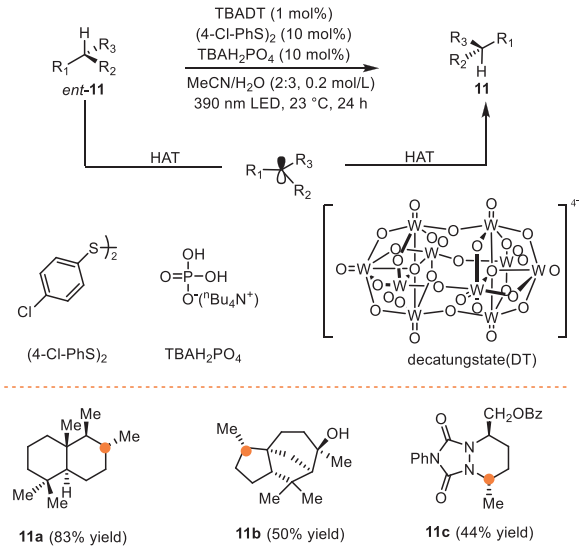

Fig. 6. Photocatalytic deracemization of decalin using a decatungstate polyanion photocatalyst.

Shin and colleagues conducted pioneering research introducing a deracemization method wherein urea derivatives **12** undergo spontaneous optical enrichment when exposed to visible light in the presence of three distinct molecular catalysts (Fig. 7a) [36]. This method achieves excellent yields and selectivity across a variety of substrates. The proposed mechanism involves the excited state of an iridium-based photocatalyst, which reversibly oxidizes the racemic urea, generating a mixture of transient nitrogen radical cations (Fig. 7b). In these cations, the steric environment around the C(sp^3)-H bond significantly acidifies it, enabling protonation by a chiral phosphonate base to form a carbon radical. The chiral nature of both the radical cation and the phosphonate base leads to a kinetic resolution of the enantiomeric radical cations. This process favors the faster-reacting (*R*)-enantiomer for proton transfer, while the slower-reacting (*S*)-enantiomer undergoes charge recombination with the reduced state of Ir(II), returning it to the urea precursor. Consequently, this selective reactivity enriches the (*S*)-enantiomer in the product mixture.

Shen and coworkers reported the photocatalyzed epimerization of morpholines and piperazines through a reversible HAT process (Fig. 8a) [37]. This methodology provides an efficient method to modulate the stereochemical configurations of these saturated aza-heterocycles, which are commonly found in pharmaceutical compounds. A variety of morpholine derivatives, including those with electron-deficient and electron-rich substituents on the aromatic moiety, were found to be effective substrates, yielding anti stereoisomers with high yields and diastereoselectivities. Piperazines, despite being less stable, were similarly epimerized to the more stable anti products with comparable efficiency and selectivity. A mechanistic pathway is supported by experimental data (Fig. 8b), suggesting that the excited state of a photocatalyst is quenched by an *in situ* generated thiol anion, followed by a reversible HAT between a thiyl radical and the saturated aza-heterocycle.

In a similar vein, Kazerouni developed a photoredox-mediated HAT approach for the epimerization of δ-lactams (Fig. 9a) [38]. This method facilitates the preferential formation of the more stable anti diastereomers from the less thermodynamically favorable syn isomers. A mechanistic model (Fig. 9b) consistent with the observed results involves the initial excitation of an Ir^{III} photocatalyst to its $^*Ir^{III}$ state, followed by reduction *via* a TIPS-S anion to yield a TIPS thiyl radical. The subsequent equilibration of lactams **17a**-

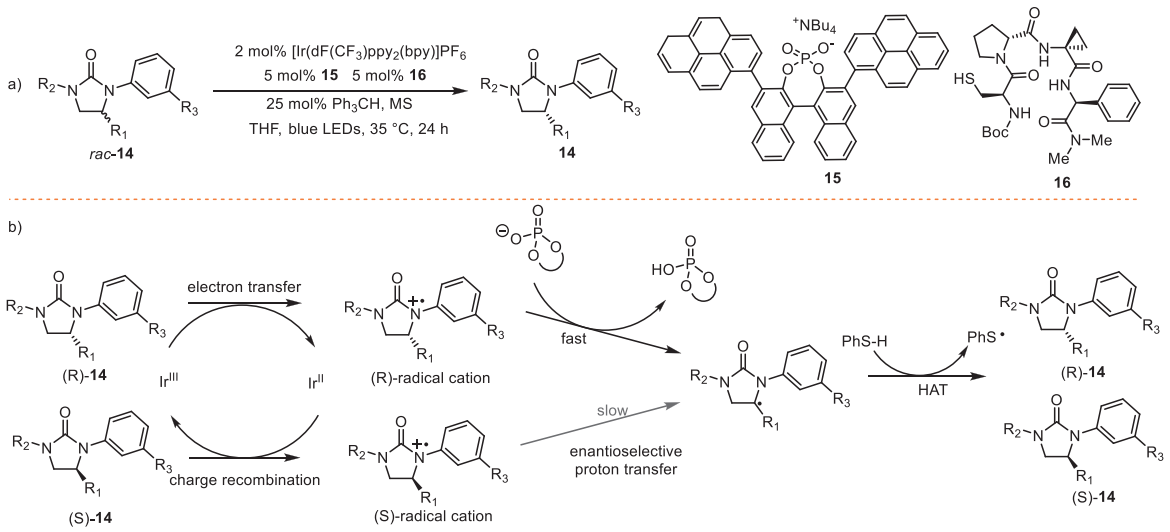

Fig. 7. (a) Light-driven deracemization of amine derivatives. (b) Proposed mechanism.

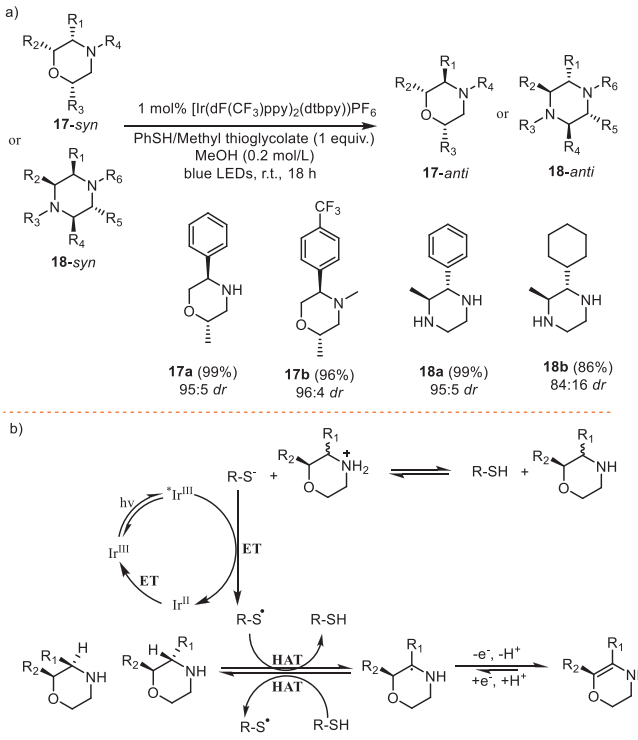

Fig. 8. (a) Epimerization of morpholines and piperazines. (b) Proposed mechanism.

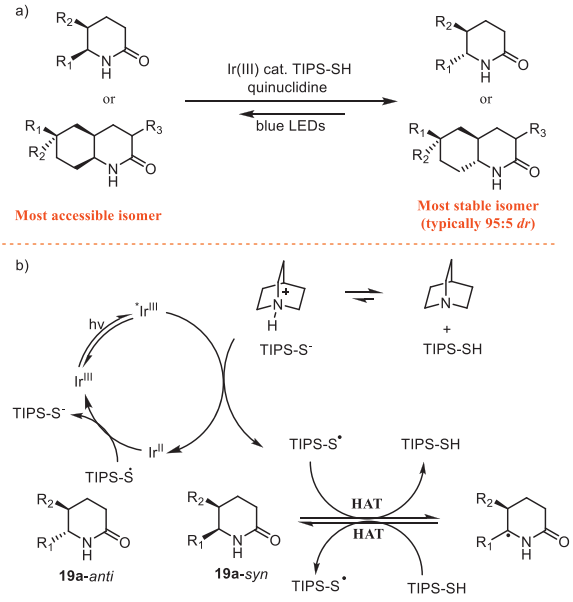

Fig. 9. (a) Photocatalytic epimerization of lactams. (b) Proposed mechanism.

syn/anti is achieved through reversible polarity-matched HAT with the TIPS thiyl radical. The photocatalytic cycle is completed by an electron transfer from Ir^{II} to the thiyl radical or possibly to the TIPS disulfide formed by radical recombination, regenerating the ground state Ir^{III} catalyst.

Furthermore, Shen and coworkers introduced a combined photocatalytic and HAT strategy for the light-mediated epimerization of accessible piperidines, affording the more stable diastereomer with high selectivity (Fig. 10a) [38]. The proposed mechanism, corroborated by mechanistic experiments, involves the excitation of an iridium(III) photocatalyst to generate the highly oxidizing $^*Ir^{III}$ state, which is then reduced by an *in situ* produced thiophenolate. Most of the hydrogen atom abstraction agents involved in the HAT process are electrophilic radicals (*e.g.*, thiophenyl radical). According to the principle of polarity matching [39–41], these electrophilic radicals are more prone to reacting with electron-rich R-H (R = C, Si, B, *etc.*) bonds as well as partially electroneutral alkyl C-H bonds, resulting in the formation of nucleophilic radicals. Consequently, the ensuing thiophenyl radical engages in reversible polarity-matched HAT with piperidines **18a**-*syn/anti*, leading to the formation of an α-amino radical **19** and PhSH. A HAT between this α-amino radical and PhSH regenerates the piperidines alongside the thiophenyl radical. The photocatalytic cycle is completed by an electron transfer from Ir^{II} to the thiophenyl radical or to PhSSPh, restoring the ground state Ir^{III} (Fig. 10b).

Gu and coworkers have introduced a photoredox-neutral catalysis platform, enabling efficient and modular enrichment of α-amino esters and derivatives (Fig. 11a) [42]. The optimized reaction conditions facilitated a broad substrate scope evaluation, resulting in deracemization products with up to 90% to quantitative yields and 90% to 95% *ee*. The conceptual underpinning of this methodology is the overcoming of poor atom and step economy through redox-neutral photocatalysis. The proposed reaction mechanism in-

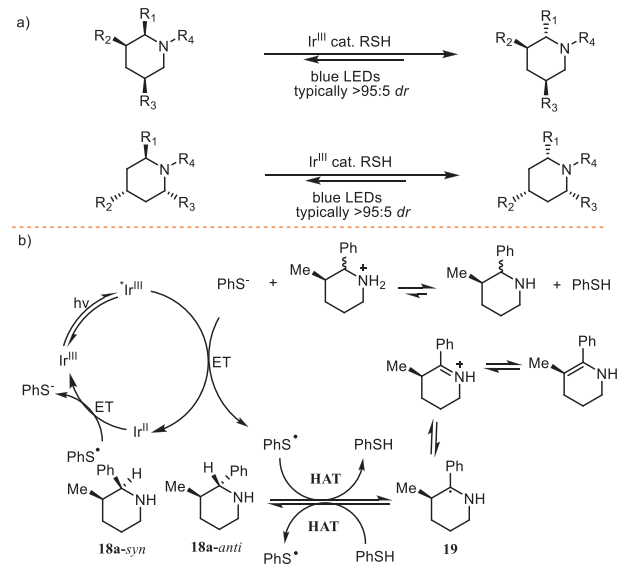

Fig. 10. (a) Photocatalytic epimerization of piperidines. (b) Proposed mechanism.

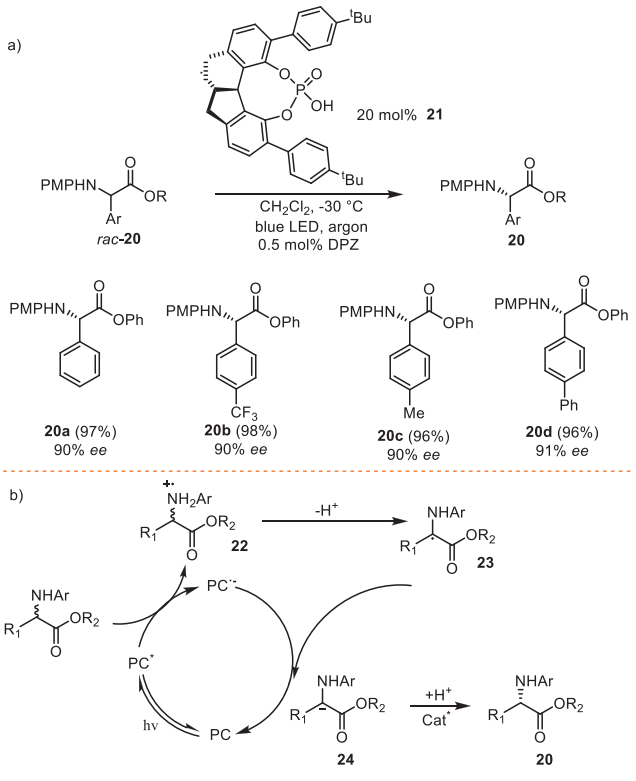

Fig. 11. (a) Photocatalytic deracemization of α-aryl amino esters. (b) Proposed mechanism.

volves single-electron oxidation of the N atom of amino ester by the activated photosensitizer *PC, creating amine cation radicals **22**. These radicals **22** then undergo further transformations to generate radical intermediates **23**, and the photocatalytic cycle is completed by the reduction of these intermediates, leading to anionic species **24** and the final product **20** (Fig. 11b).

The α-position adjacent to carbonyl groups is known for its acidic character, which has been harnessed to achieve the deracemization of sp^3 carbon centers, thereby establishing a sophisticated and versatile strategy [43]. Zhang and co-workers have extended this concept by reporting a catalytic deracemization of α-stereocentric ketones through a process of deprotonation followed by enantioselective reprotonation, yielding a range of substrates with high yields (75%–98%) and enantioselectivities (40%–96%) (Fig. 12a) [44]. Fig. 12b outlines the proposed mechanism for the visible-light-driven deracemization of α-stereocenters in pyridyl ketones. The catalytic cycle initiates with the racemic pyridyl ketone coordinating bidentately to the enantiomerically pure rhodium catalyst, forming complex **27** as a mixture of diastereomers, (*R*)–**27** and (*S*)–**27**. Photoexcitation to the triplet state **28**, and subsequent single-electron transfer from the tertiary amine led to the formation of the rhodium ketyl radical complex **29**. HAT from the α-position of ketyl to the amine radical cation results in the rhodium enolate **30** and protonated amine. A diastereoselective proton transfer then regenerates the rhodium-coordinated ketone **27** as a singular stereoisomer. The release of the ketone from the complex allows for the continuation of the catalytic cycle.

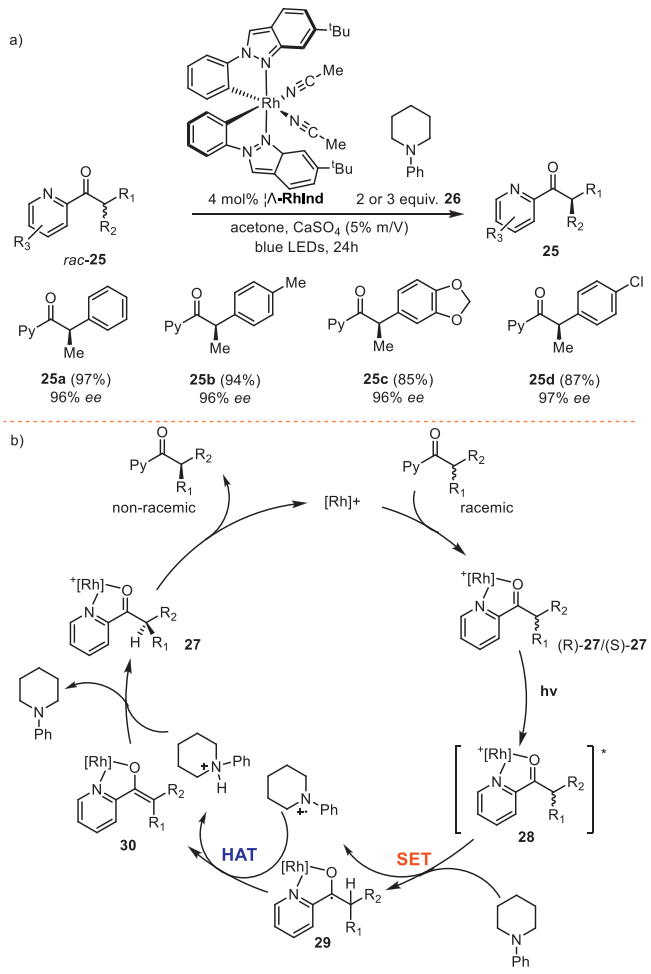

Fig. 12. (a) Photocatalytic deracemization of α-stereocentric ketones. (b) Proposed mechanism.

Chen and colleagues have reported the use of a biphasic system comprising a toluene/aqueous cyclodextrin emulsion to modulate the balance between the Hantzsch ester as a HAT agent and an electron acceptor (Fig. 13) [45]. This elegantly designed redox deracemization cascade, initiated by a photocatalyzed oxidation and followed by a chiral phosphoric acid-catalyzed reduction, proceeds out-of-equilibrium and directly affords enantiomerically pure indolines and tetrahydroquinolines. The underlying photoredox mechanism involves a SET pathway, commencing with the formation of an excited *Ir state, followed by reductive quenching to $Ir^{\bullet -}$, which facilitates radical anion transfer for photocatalyst regeneration. During this cycle, *rac*-**31a** is converted *via* SET to a N-radical

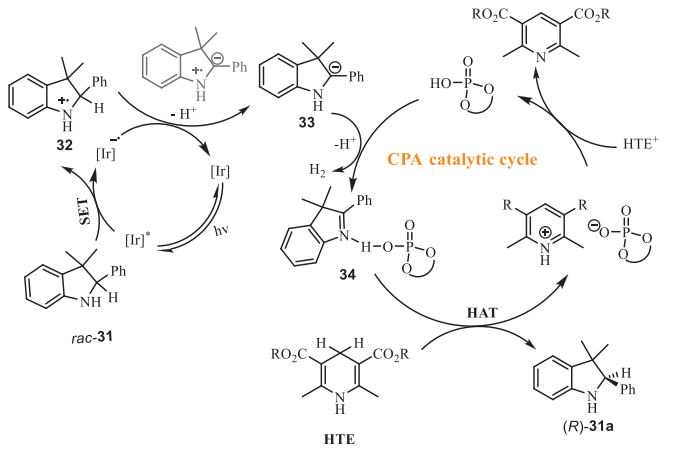

Fig. 13. Proposed reaction pathway for the light-driven deracemization.

cation **32**, which is subsequently reduced by $Ir^{\bullet-}$, accompanied by proton loss, forming a benzylic carbanion. In the chiral phosphoric acid (CPA) catalytic cycle, protonation of **33** by CPA initially yields a chiral ion pair **34**, which, upon H-atom transfer from HTE, delivers the chiral product (*R*)–**31a**. The catalytic cycle is completed with the regeneration of the chiral phosphoric acid upon the release of the final oxidative adduct of HTE through an HTE/HTE$^{\bullet}$ to HTE$^{\bullet+}$/HTE^{+} pathway [46,47].

2.3. Photocatalytic deracemization through other approaches

Although photocatalytic deracemization combined with hydrogen atom transfer (HAT) is relatively straightforward to implement and widely accepted, successful examples of this approach remain limited. In this section, we also aim to briefly introduce alternative methods capable of isomerizing C(sp^3)-H-containing chiral molecules. Several other techniques, including C-C bond cleavage and reorganization, photocatalytic redox reactions, and carbonyl groups activation, are discussed to provide readers with a comprehensive overview of the field.

2.3.1. C-C bond cleavage and reorganization

Zuo and colleagues have developed a photochemically-driven protocol for deracemization that harnesses a single chiral catalyst to facilitate two distinct mechanistic steps: C-C bond cleavage and formation (Fig. 14a) [48]. This dual functionality significantly enhances stereoinduction, resulting in high stereoselectivity. The protocol leverages the photocatalytic properties of a common Lewis acidic Ti(IV) catalyst, which is complexed with either chiral phosphoric acid or bisoxazoline ligands. Notably, racemic alcohols with adjacent and fully substituted stereogenic centers are efficiently transformed into their enantioenriched counterparts with pronounced selectivity. Moreover, the protocol extends beyond cyclic structures, as evidenced by the successful deracemization of acyclic alcohols, particularly 1,2-diaryl aminoalcohols, which are essential scaffolds for chiral ligand synthesis. Mechanistic investigations reveal that asymmetric ligand-to-metal charge transfer (LMCT) catalysts can selectively coordinate with one of two conformations present in racemic alcohols. This selective coordination leads to the formation of a diastereomeric metal oxide complex with one conformation, resulting in enantioselective C-C bond cleavage. Although the cleavage itself may not be induced asymmetrically, the subsequent steps are critical for stereoselectivity. The simultaneous generation of carbonyl fragments and transient carbon-centered radicals sets the stage for one-electron reduction and enantioselective addition, thereby reconstructing the

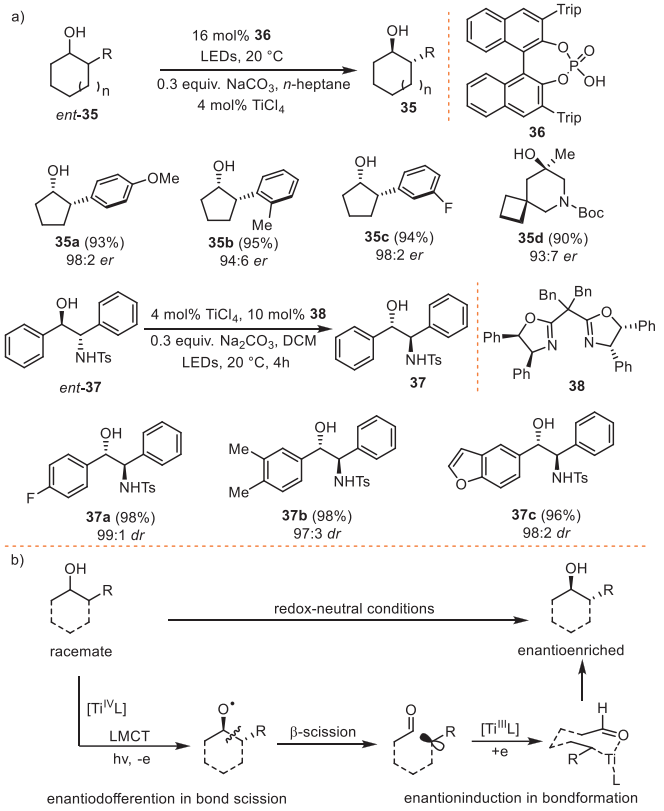

Fig. 14. (a) Photocatalytic deracemization of cycloalkanols and acyclic alcohols by LMCT process. (b) Proposed mechanism.

steric C-C bond. This reformation is further facilitated by the generation of low-valent chiral metal complexes during the photoexcitation process, as depicted in Fig. 14b.

Cyclopropanes, with their distinctive three-membered ring structures, play a crucial role in facilitating C-C bond cleavage and reorganization. Taking advantage of this characteristic, researchers have successfully achieved isomerization of cyclopropanes using chiral reagents. The group led by Gilmour has introduced a novel method that leverages brief photochemical reactions followed by enantioselective transformations of cyclopropyl ketones. They demonstrated that chiral Al-salen complexes **40**, with well-characterized photophysical properties, facilitate efficient photochemical deracemization of cyclopropyl ketones, with enantiomeric ratios (*er*) up to 98:2 [49]. According to Fig. 15, both high yields and levels of enantioselectivity were typically observed.

In conjunction with these experimental results, a comprehensive computational study was performed to delve into the deracemization mechanism (Fig. 16). It was revealed that the substrate, upon forming a complex with the aluminum catalyst *via* Lewis acid/base interactions, readily absorbs visible light to reach an excited state **41**. This state is characterized by significant charge-transfer due to electron migration from the ligand to the carbonyl group of the ketone, forming intermediate **42**. The presence of free charge in the π^* orbital of the carbonyl group in intermediate **42** renders it susceptible to ring-opening reactions, leading to intermediate **43**. This is followed by highly enantioselective ring-closing reactions in the presence of chiral salen ligands, favoring the formation of (*S*)-enantiomers.

The development of effective hydrogen-bonding templates and catalysts has demonstrated that the challenge of insufficient enantioface differentiation can be surmounted [50–52]. The breakthrough came in 2009 with the disclosure of the first triplet-sensitized, highly enantioselective reaction [53]. More recently,

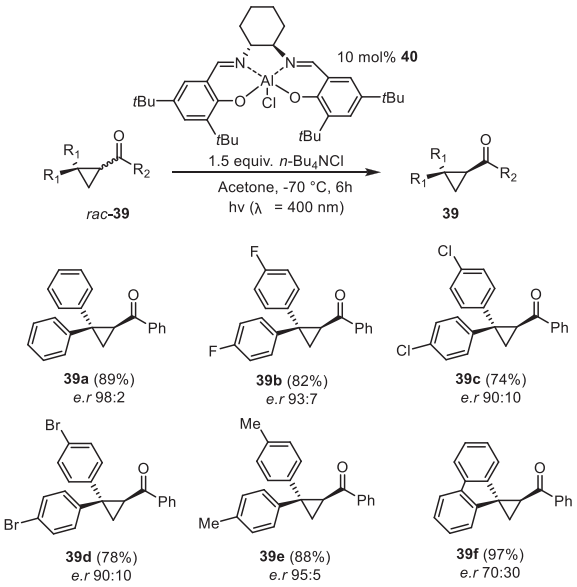

Fig. 15. Investigation of the deracemization of cyclopropyl ketones.

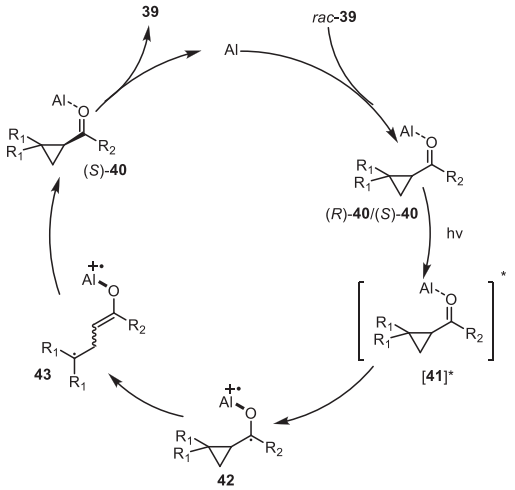

Fig. 16. Proposed mechanism of deracemization of cyclopropanes.

Tröster and colleagues have shown that cyclopropanes can undergo triplet-sensitized deracemization using a chiral thioxanthone sensitizer (Fig. 17) [54]. Their initial experiments focused on an asymmetric [2+ 2] photocycloaddition reaction facilitated by energy transfer [53,55]. They achieved the enantioselective di-π-methane rearrangement of 3-allyl substituted quinolone **44** under visible light irradiation. Remarkably, the product **44** was analyzed by chiral HPLC and found to possess an *ee* greater than 99%, indicating that both enantiomers of product **44** can react with **45**. In this instance, the differing rates of reaction appear to be attributable to disparate sensitization rates; specifically, the minor enantiomer is preferentially sensitized relative to the major enantiomer. This ultimately leads to the accumulation of products **44**.

Li and colleagues have explored the photocatalyzed deracemization of spirocyclopropyl oxindoles [56]. Utilizing chiral thioxanthone or xanthone photosensitizers furnished with a lactam hydrogen bonding site enabled the deracemization of various substituted spirocyclopropyl oxindoles, achieving yields of 65%–98% and *ee* of 50%–85% across 17 examples (Fig. 18a). To elucidate the mechanism of this reaction, the team determined the binding constants of the enantiomers *ent*–**47a** and **47a** to sensitizer **48** *via* NMR titration. Surprisingly, they discovered only a slight binding

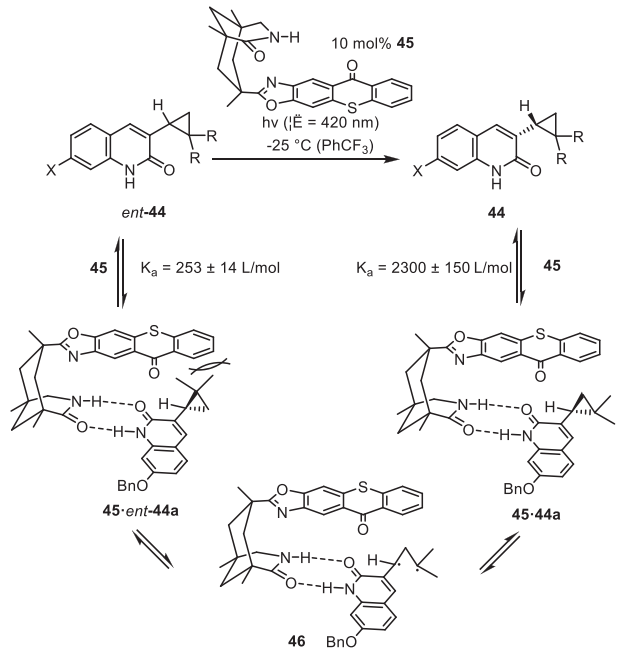

Fig. 17. Thioxanthone photocatalyzed deracemization of 3-allyl quinolones through energy transfer process.

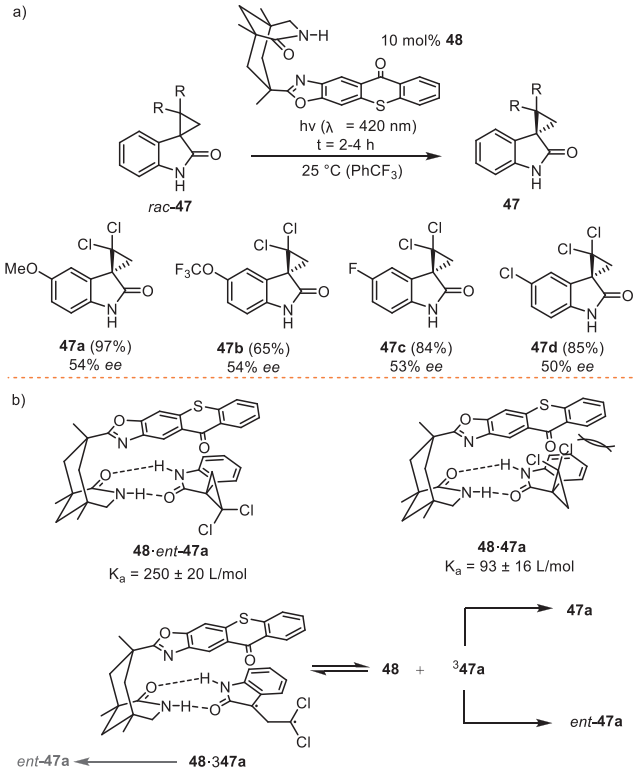

Fig. 18. (a) Deracemization of dichloro-substituted spirocyclopropyl oxindoles by chiral thioxanthone. (b) Proposed mechanism.

preference for *ent*–**47a**. Additionally, they noted that the steric influence of the thioxanthone framework should favor the cyclization to *ent*–**47a**. Thus, achieving cyclization without any steric bias, which would result in a racemic mixture of **47a** and *ent*–**47a**, is preferred (Fig. 18b).

An enantioselective approach mediated by visible light for the synthesis of axially chiral alkenes is presented by Knowles and

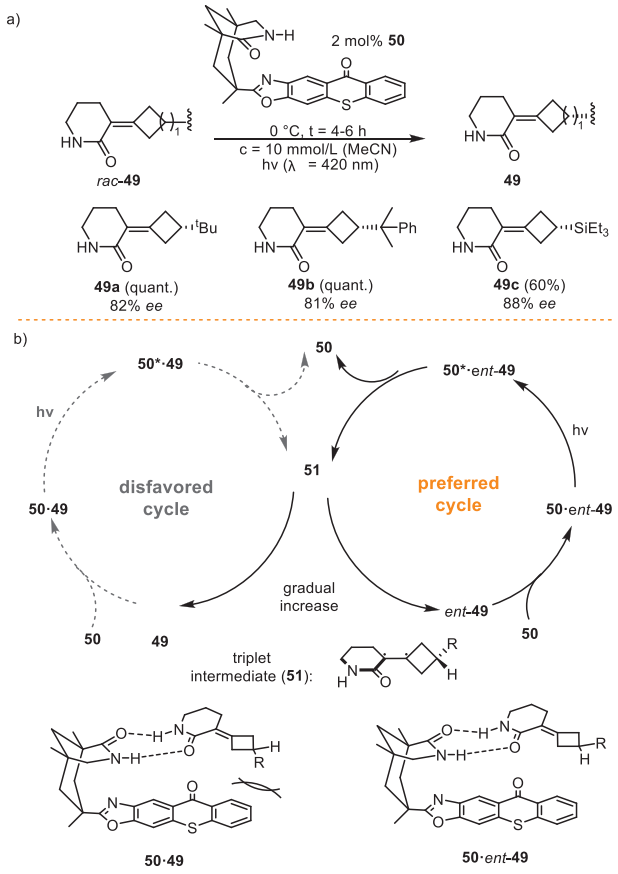

Fig. 19. (a) Photochemical deracemization of alkylidenecyclobutanes and cyclopentanes catalyzed by chiral sensitizer. (b) Proposed mechanism.

co-works (Fig. 19a). This method begins with a racemic mixture from which a predominant alkene enantiomer is selectively obtained. This selectivity is attributed to the triplet energy transfer from a chiral photosensitizer **50** that functions catalytically. A modest catalyst loading of 2 mol% is sufficient to achieve consistently high enantioselectivities and yields across 16 examples, with conversions 51%-quant. and *ee* ranging from 81% to 96% [57]. Given the extensive research on the enantioselective synthesis of alkylidenecyclohexanes [58–62], this study concentrates on the corresponding cyclobutene- and cyclopentane-derivatives.

Mechanistic and theoretical investigations have probed the interactions between the photosensitizer thioxanthone **50** and the enantiomers of alkene **49** and its mirror isomer, *ent*–**49** (Fig. 19b). The formation of 1:1 complexes is at the core of the proposed mechanism, which posits two catalytic cycles—one for each enantiomer. The preferential cycle leads to an accumulation of *ent*–**49**, culminating in a photostationary state [63]. This preferential sensitization of *ent*–**49** is attributed to the more favorable formation of complex **50**·*ent*–**49** over **50**·**49**.

2.3.2. Photocatalytic redox reactions

Alcohols represent a ubiquitous class of compounds with the α-position C-H bond often exploited for racemization due to its pronounced activity. Anyway, the ease with which alcohols can be oxidized to aldehydes or ketones and then reduced to alcohols has prompted interest in oxygen-containing chiral molecules. Zhang and colleagues have introduced a heterogeneous photocatalytic deracemization method for secondary benzylic alcohols (Fig. 20a), which serve as pivotal synthetic intermediates and products across various industries [64]. The scope of this method encompasses a broad range of arylalkyl alcohols, with those bearing electron-

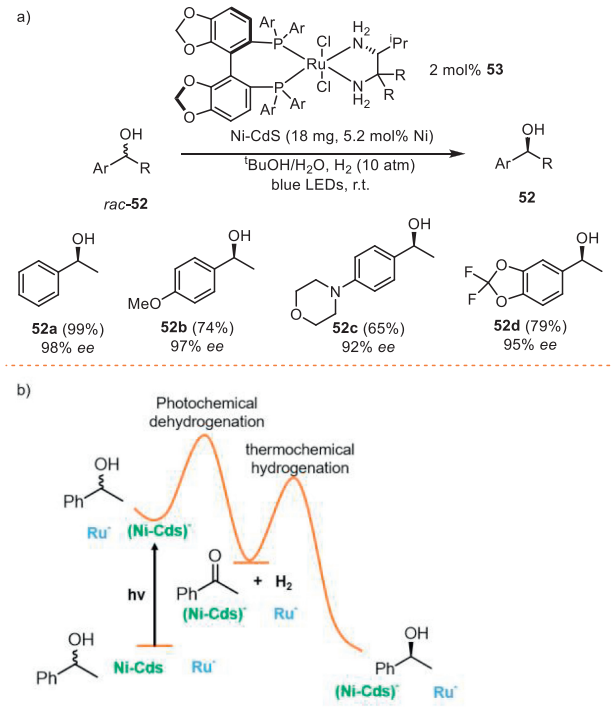

Fig. 20. (a) Photocatalytic deracemization of secondary alcohols. (b) Proposed mechanism.

donating groups at the 4- or 3-positions on the aryl ring achieving high yields and *ee*. It is noteworthy that different substrates exhibit disparate reaction rates, necessitating tailored optimization of reaction times and solvent ratios.

The underlying mechanism is conjectured to involve dehydrogenation within the excited state of Ni-CdS (Fig. 20b). Illumination induces the formation of electron-hole pairs in CdS, with the holes oxidizing an alcohol to a ketone, likely *via* proton-coupled electron transfer, while the electrons reduce protons to hydrogen at Ni sites [65–68]. Although dehydrogenation of an alcohol is endothermic, light excitation tips the balance in favor of this reaction. Conversely, the exothermic hydrogenation of the resultant ketone does not proceed on Ni-CdS due to a substantial kinetic barrier. However, in the presence of a chiral hydrogenation Ru catalyst **53**, the process ensues, yielding an enantiomerically enriched alcohol. The synergy of Ni-CdS and Ru catalyst appears to meet the kinetic prerequisites for an effective deracemization system.

2.3.3. Carbonyl groups activation

Ketones can undergo enol interconversion because they contain carbonyl groups. Using photocatalysis, the kinetic splitting of two enols with different configurations results in a ketone with a single configuration. This method is very delicate and is only effective for compounds that can undergo enol interconversion classes. Huang and colleagues have developed a photochemical *E/Z* isomerization strategy for the deracemization of α-branched aldehydes using simple amino catalysts and photosensitizers (Fig. 21a) [69]. This approach employs a multicatalytic system with the non-chiral photocatalyst $Ir(ppy)_3$ serving as a triplet sensitizer and a chiral amino organocatalyst, rather than relying on chiral photocatalysts. This method has been applied to a broad range of α-aryl aldehydes with various functional groups, yielding the deracemized, enantioenriched aldehydes with high efficiency (up to 96% *ee*). Similarly, they have conducted mechanistic studies in Fig. 21b. In the ground state, the stereochemically favored (*E*)-configured enamine is continuously converted to the less favored *Z*-isomer *via* photocatalytic energy transfer. Facially selective protonation of the (*Z*)-enamine

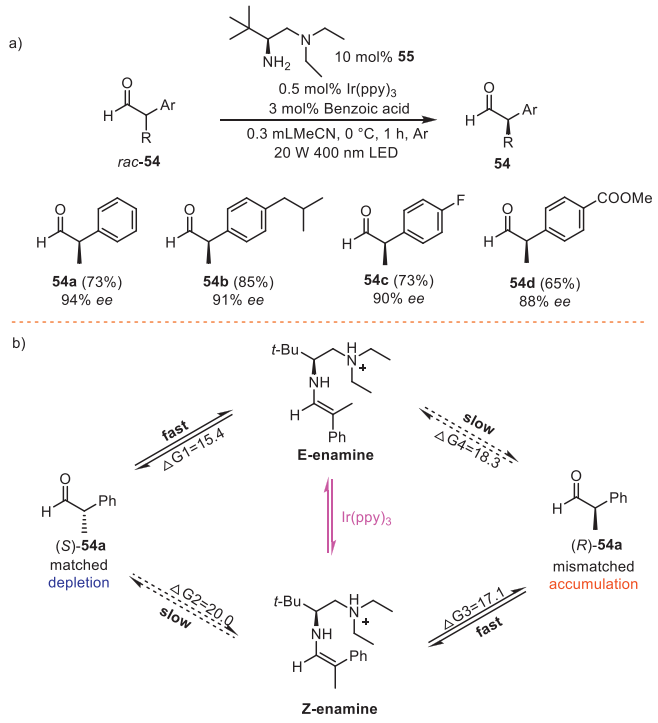

Fig. 21. (a) Photocatalytic deracemization of α-branched aldehydes. (b) Proposed mechanism.

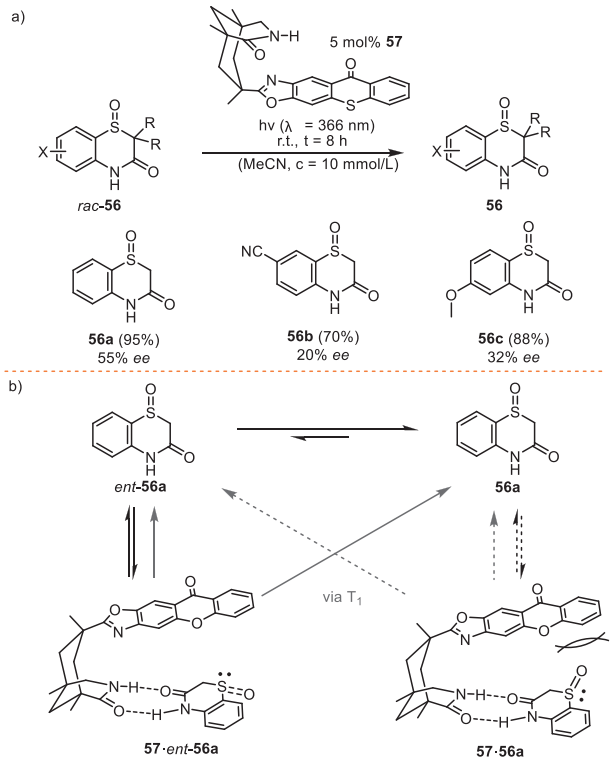

Fig. 22. (a) Deracemization of sulfoxides by chiral xanthone. (b) Proposed mechanism.

then produces the mismatched enantiomer, perpetuating the consumption of the matched enantiomer and accumulation of the mismatched one, thus enabling effective deracemization.

3. Photocatalytic deracemization of sulfoxides

Chiral molecules featuring C(sp^3)-H bonds are ubiquitous in natural products and pharmaceuticals, yet those containing sp^3 hybridized chiral centers other than carbon, such as sulfur, are equally important. Traditional activation strategies involving HAT are not applicable for the isomerization of chiral molecules lacking C-H bonds. Consequently, researchers have ingeniously utilized photocatalysis to facilitate the isomerization of these compounds. This method effectively circumvents the need for HAT by exploiting light-driven processes to manipulate the stereochemistry of molecules containing diverse bond types.

Sulfoxides that possess two distinct substituents exhibit chirality and can be isolated as enantiomerically pure substances, a feature attributable to the configurational stability of their stereogenic sulfur centers [70]. While enantioselective oxidation is commonly employed to obtain enantiomerically enriched sulfoxides [71–73], there is a recognition that racemic sulfoxides could be selectively transformed into a single enantiomer through photochemical deracemization. In a study conducted by Laura *et al.*, a chiral xanthone derivative, characterized by the 1,5,7-trimethyl-3-azabicyclo[3.3.1]nonan-2-one framework **57**, was employed as a catalyst in 5 mol% concentration to induce the deracemization of racemic benzothiazinone-1-oxides **56** in an acetonitrile medium (Fig. 22a) [74]. This technique successfully achieved the deracemization of five different substrates, with the products attaining *ee* of up to 55%. Specifically, the deracemization of the substrate *rac*-**56a** resulted in the predominance of the enantiomer **56a**. This finding indicates that the triplet energy transfer process was more effective for the enantiomer *ent*–**56a**. It is inferred that *ent*–**56a** exhibited a more favorable interaction with the catalyst, positioning its chromophore in closer proximity to the xanthone. Such an arrangement enhances the efficiency of the energy transfer necessary for deracemization (Fig. 22b).

4. Conclusion and outlook

The review of recent advancements reveals several clear trends in the deracemization of tertiary C(sp^3) chiral centers, with a particular emphasis on the innovative integration of photocatalysis and HAT technologies. This combination has proven effective in cleaving the robust and polar C(sp^3)-H bonds, facilitating the isomerization of a diverse range of substrates. Despite these advances, several challenges remain:

(1) The majority of chiral molecules amenable to these techniques still contain activating groups such as amino, hydroxyl, or carbonyl functionalities adjacent to the tertiary carbon center. These groups facilitate the activation of the C(sp^3) chiral centers, enhancing reaction efficiency. However, the isomerization of chiral centers lacking such activating groups remains a significant challenge, underscoring a critical area for future research.

(2) Direct HAT processes are advantageous due to their simplicity, not requiring additional reagents and thereby simplifying the reaction setup. However, the range of photocatalysts effective in direct HAT is currently limited to aromatic ketones and polymetallic oxides. Aromatic ketones often necessitate specific functional group interactions and excessive catalyst loading, complicating purification efforts. Conversely, polymetallic oxides, such as those involving the decatungstate anion, are effective in smaller quantities but require ultraviolet light and are thus less versatile.

(3) Indirect HAT processes mitigate some limitations of direct HAT by allowing a broader range of photocatalyst options. However, these reactions typically require more additives, which can detract from the attractiveness of the method due to increased complexity and potential impurity issues.

(4) There are fewer examples of light and HAT co-catalysis, and still many are based on redox processes. In addition, when heteroatoms are involved, there are few reactions that undergo the HAT mechanism because the chiral centers do not contain hydrogen (*e.g.*, sulfoxides, chiral molecules containing C–C bonds). This is an area where further improvement is needed.

In conclusion, while significant progress has been made in the field of chiral center isomerization *via* photocatalysis and HAT, the work presented thus far only scratches the surface of potential developments. A breakthrough is anticipated with the development of novel photocatalysts capable of facilitating direct HAT under visible light irradiation conditions. Such a catalyst would ideally activate tertiary chiral C-centers without the need for activating groups, simplifying the process and easing subsequent purification steps. Concurrently, advancements in related equipment, such as photoreactors and continuous flow systems, are necessary to keep pace with scientific developments. These innovations could substantially accelerate the development of deracemization processes, with profound implications for the pharmaceutical and materials sciences industries.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Yuan Liu: Writing – original draft, Investigation, Conceptualization. **Zhu Yin:** Writing – original draft, Data curation. **Xintuo Yang:** Writing – review & editing. **Jiajia Cheng:** Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization.

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