Light empowers *contra*-thermodynamic stereochemical editing

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Creating, preserving, and manipulating the stereochemistry of organic compounds has long been a cornerstone of modern organic synthetic chemistry, and the synthetic routes are typically designed according to stereoselectivity-determining step that is known as stereochemical logic. As an alternative strategic platform, stereochemical editing, wherein the chiral- or geometry-defining events are decupled from the main scaffold or complexity-forming steps, has the potential for late-stage flexibility in generating isomers from a single compound. However, under many instances, the desired stereochemical editing processes are *contra*-thermodynamic on ground states and thus unfavorable. Recent research has begun to leverage photocatalysis to yield many potentially generalizable concepts to empower *contra*-thermodynamic stereochemical editing by providing approach to irreversible elementary steps via excited electronic states and/or by introducing thermochemical biases. A broad range of synthetically valuable *contra*-thermodynamic stereochemical editing processes were thus invented, including deracemization of racemic chiral molecules, positional alkene isomerization, and dynamic epimerization of sugars and diols. In this review, we highlight how an understanding of the mechanisms of visible-light photocatalysis and of the general reactivity patterns of the photogenerated radical intermediates has been engineered to develop these concepts.

1. Introduction

Chemists have already reported more than 100 million molecular compounds and are capable of synthesizing any possible structure. Explicitly, without solving selectivity issues, no type of chemistry is of sufficiently efficiency. There is also an issue of another type, and even more challenging to tackle: construction of stereoisomers at will with minimum possible expenditure. The stereochemistry that deals with the spatial arrangements of atoms and groups in a molecule is critical to many aspects of chemistry and biology, as the isomers can often demonstrate distinctly different properties, reactivity modes, and chemical or biological functions[1]. Not surprisingly, the development of methods toward creating, preserving, and manipulating the stereochemistry of organic compounds has long been a cornerstone of modern organic and medical chemistry[2]. As the majority of the stereochemical elements is typically derived from bond-forming steps, excellent levels of kinetically selective substrate- or catalyst-promoted stereocontrol are usually required. Therefore, in strategies using

'stereochemical logic', wherein retrosynthetic route is designed based on a key stereoselectivity-determining step, stereochemistry considerations often dictate the choice of suitable retron and starting materials (Figure 1A)[3,4]. In contrast, "stereochemical editing" provides an alternative strategy for construction of stereochemistry, wherein the stereochemistry-defining events are decoupled from the main connectivity- and complexity-forming steps, thus enabling late-stage flexibility in forming diverse isomers from stereoadaptive compounds (Fig. 1B). Specifically, if mechanistically diverse, robust and selective strategies can be identified to alter stereochemistry when functional groups are installed, the scope of synthetic methods available to access desired product would be significantly expanded. Despite remarkable progress in the area of catalytic science, however, there are still very few mild and efficient catalytic methods for direct stereochemical editing, particularly in the context of contra-thermodynamic versions. Taking deracemization for example that represents one of the most common stereochemical editing methods for obtaining single enantiomers of the same molecules, the process is unfavorable on thermodynamic grounds due to an attendant decrease in entropy[5]. As a result, despite the small effect ($\Delta G°$=+0.42 kcal/mol at 298 K), it still requires additional energy input to compensate the thermodynamic bias. Furthermore, this method is also constrained by the kinetic in nature and the principle of microscopic reversibility[6]. As (*R*) and (*S*) enantiomers are equal in energy, any elementary step or equilibrium process based on the same potential surface that transforms (*R*) to (*S*) will be equally efficient in converting (*S*) back to (*R*) in the absence of any exogenous driving force.

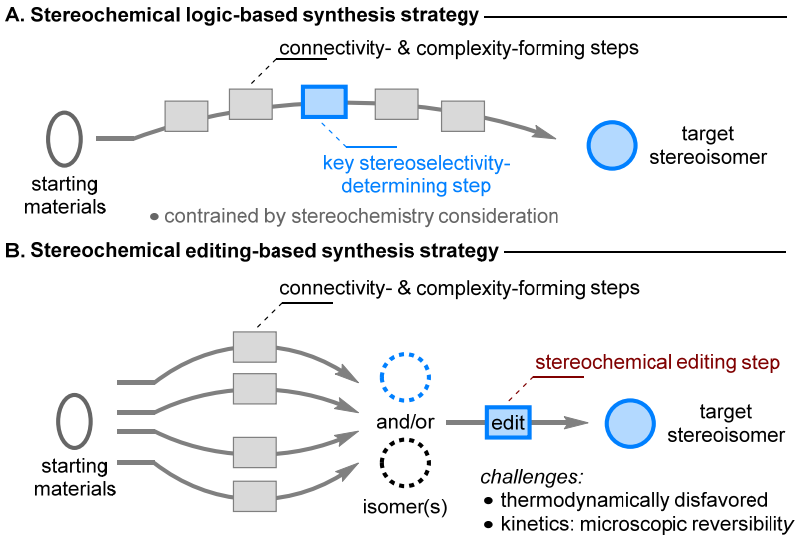

Fig. 1. Stereoselective synthesis by stereochemical logic or by stereochemical editing. (**A**) Synthetic route based on stereochemical logic. (**B**) Synthetic route based on stereochemical editing.

Over the past decade, organic synthetic chemistry has witnessed a broadening of its horizons by the flourishing field of visible-light photocatalysis[7]. This tool has been frequently exploited by chemists to carry out controlled generation of diverse reactive species and thermally difficult transformations. The strategic advantages of this catalytic method can be attributed to the chemical ambivalence of the photocatalysts, displayed by their flexibility to switch between triplet energy transfer (EnT), oxidative

or reductive single-electron-transfer (SET), and hydrogen-atom-transfer (HAT) processes depending on the reaction conditions (Fig. 2A). Notably, photochemical processes have been long known among a few exceptions to the microscopic balance, because forward and reverse steps might progress along distinct potential energy surfaces[8]. For example, photochemical isomerization of alkenes by triplet excited state, wherein the selective absorption of light by (*E*)-alkenes can lead to enrichment of the relevant less thermodynamically stable (*Z*)-alkenes, represents a prominent example[9]. Therefore, visible-light photocatalytic processes are well-suited to empower *contra*-thermodynamic stereochemical editing by providing approach to irreversible elementary steps via excited electronic states and/or by introducing thermochemical biases that allow endergonic product formation. Recently, the unique visible-light photocatalysis has been utilized by many research groups to carry out a range of selective *contra*-thermodynamic stereochemical editing processes with chiral photocatalyst alone or by merger of achiral photocatalyst with other chiral catalysts; representative reaction classes include deracemization of racemization of chiral compounds, positional alkene isomerization, and dynamic epimerization of diols (Fig. 2B). In this review, we highlight how an understanding of the mechanistic features of photocatalytic activation and reactivity patterns of the photogenerated intermediates has enabled the development of this diverse suite of *contra*-thermodynamic stereochemical editing.

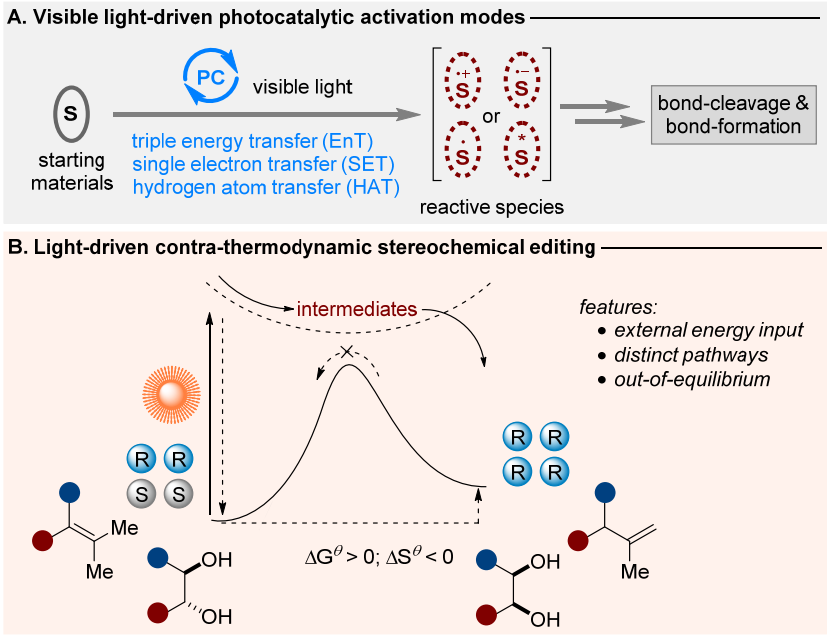

Fig. 2. Visible-light photocatalytic activation modes and application to *contra*-thermodynamic stereochemical editing. (**A**) Typical photocatalytic activation modes. (**B**) Visible-light-driven *contra*-thermodynamic stereochemical editing.

2. Light-driven photocatalytic deracemization

For most chiral drug molecules, very often, only one enantiomer has the desired biological activity, whereas the other enantiomer might produce unwanted or even

detrimental effect[10]. As a consequence, efficient synthesis of single enantiomers is essential for both pharmaceutical and chemical industries. Despite many impressive advances in enantioselective synthesis, in many cases, the production and unselective synthesis of racemates is sometimes unavoidable or less expensive than the selective synthesis of single enantiomer. Kinetic resolution and dynamic kinetic resolution are frequently used to obtain enantiomerically enriched chiral compounds from racemates. However, these classical methods can reach only a maximum 50% yield or afford chemically modified products. In contrast, catalytic direct deracemization of racemic chiral compounds represents an ideal approach for converting a racemate into a single enantiomer, but such a process is entropically disfavored and cannot be carried out by a traditional catalyst under thermal conditions. When forward and reverse steps are engineered to proceed by distinct mechanisms via a common prochiral intermediates, highly selective deracemization might be achieved. Visible light-driven photocatalysis is potentially ideal for this task since light not only provides the energy input, but also enable different potential energy surfaces for the forward and reverse transformations, thus overcoming the microscopic reversibility. Although envisioned for over half century[11], photocatalytic deracemization reactions generally demonstrated low enantioselectivity until recently[12].

2.1 Based on triplet energy transfer

Despite the energetic degeneracy of enantiomers **M** and *ent*-**M**, a photochemical equilibrium in favor of single enantiomer, **M** or *ent*-**M**, is in principle potentially feasible, when interacted selectively with a suitable chiral photocatalyst under sensitization. Building on their continued interest in enantioselective triplet-sensitized reactions[13], the Bach group presented a novel concept of light-driven triplet sensitization for deracemization (Fig. 3A)[14]. Specifically, chiral compounds that exist exclusively as enantiomers **M** and *ent*-**M** in the ground state might be directly deracemized through selective triplet energy transfer from a chiral photosensitizer. As a proof of this concept, Bach and co-workers explored challenging but useful axially chiral allenes as a model, and achieved for the first time a highly efficient visible-light-driven catalytic deracemization of axially chiral allene lactams *rac*-**1** with their previously developed chiral thioxanthone **2** (2.5 mol%) as the photosensitizer[15]. This seemingly impossible but apparently irreversible photochemical reaction enabled generation of a range of single enantiomers (*R*)-**1** from the corresponding racemic mixture with good yields and excellent enantioselectivity (17 examples, 89-97% ee). On the basis of a series of mechanism studies and DFT calculations, a simplified sketch for this deracemization is also proposed to illustrate the mode of action. For example, the chiral photocatalyst **PS-1** can distinguish between two enantiomers (*S*)-**1a** and (*R*)-**1a** by a non-valent two-point hydrogen-bonding interaction. Moreover, the interaction of photocatalyst **PS-1** with (*S*)-**1a** is much stronger than its with (*R*)-**1a** as shown by the calculated distance between the carbonyl carbon atom of the thioxanthone and the terminal carbon atom of the allene moiety. As a result, more efficient triplet energy transfer from photocatalyst **PS-1** to (*S*)-**1a** occurs to enable its racemization via a 1,3-diradical intermediate **A**, thus enriching the enantiomer (*R*)-**1a**. This working model

was also supported by the fact that complete inversion of (*S*)-**1a** (95% ee) into (*R*)-**1a** (96% ee) was observed under otherwise same reaction conditions.

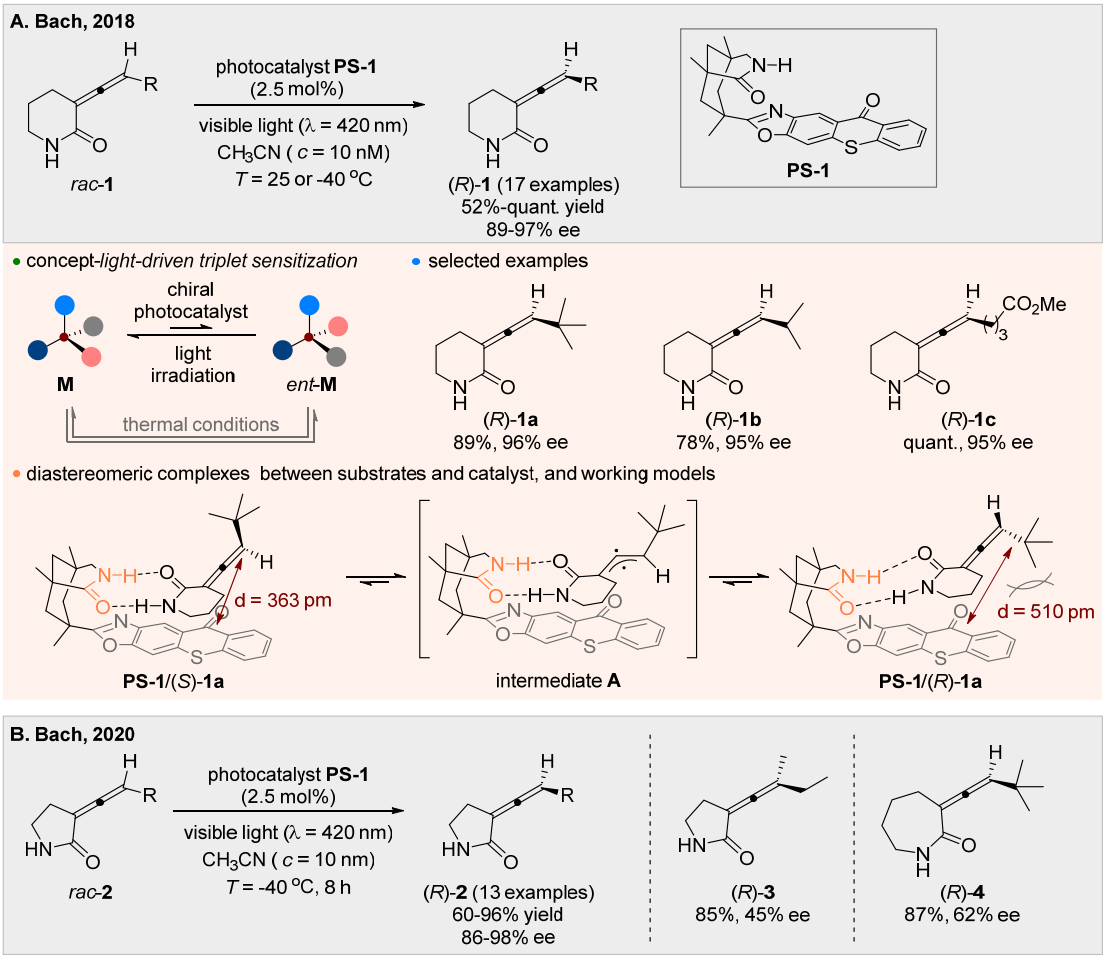

Fig. 3. Visible-light-driven photocatalytic deracemization of axially chiral allenes by triplet sensitization.

Though this type of new reaction might be limited by the requirement of hydrogen-bonding templates in both substrate and photosensitizer, it opened up a fresh avenue in catalytic direct deracemization. Shortly after, the same group successfully extended the scope of this strategy to the deracemization of trisubstituted allenes *rac*-**2** bearing a 3-(1'-alkenylidene)-pyrrolidin-2-one motif using chiral triplet sensitizer **PS-1** as the catalyst under similar conditions (13 examples, 86-98% ee) (Fig. 3B)[16a]. Impressively, even sterically demanding tetrasubstituted allene (*R*)-**3** (45% ee) and a seven-membered 3-(1'-alkenylidene)-azepan-2-one (*R*)-**4** (62% ee) can also be enriched though with moderate enantioselectivity. Efficient conversion of the axial chirality of the allenes into center chirality by routine manipulations such as Diels-Alder and bromination reactions also highlights the potential of this method. Notably, the visible-light-driven triplet sensitization by photosensitizer **PS-1** could be further applied to deracemization of primary acyclic 2,4-disubstituted 2,3-butadienamides to enantioenriched products[16b]. Several chiral sulfoxides bearing a lactam hydrogen-bonding site were subsequently proven to be also amenable to a sensitized deracemization (up to 55% ee), when using

similar chiral xanthone as a photocatalyst[16c].

The idea of employing chiral sensitizer-based triplet energy transfer to execute enantioselective photochemical isomerization of cyclopropanes was first presented by Hammond in 1960s[17]. Despite being potentially useful, little attention has been paid to such a reaction class in the following decades mainly because of low efficiency and dearth of suitable chiral photosensitizers[11b]. Based on the successful application of a novel class of chiral thioxanthone and xanthone as triplet sensitizers in deracemization of lactam-containing axially chiral allenes, Bach and co-workers continued to extend this strategy to the deracemization of 3-cyclopropylquinones *rac*-**6** using thioxanthone *ent*-**PS-1** as the chiral photosensitizer (Fig. 4A)[18]. Notably, 3-cyclopropylquinones *rac*-**6** could also be photochemically formed in situ from 3-allyl-substituted quinolones **5** via a triplet-sensitized di-π-methane rearrangement reaction under light irradiation[19]. Thus, they developed an efficient, one-pot procedure for converting an array of 3-allyl-substituted quinolones **5** into the corresponding chiral 3-cyclopropylquinones (*R*)-**6** upon irradiation with visible light (λ = 420 nm) (9 examples, 88-96% yield, 32-55% ee). Though the enantioselectivities of products remained modest, the action mode appeared to be remarkable. Control experiments confirmed that the observed enantioselectivity was not dictated by the initial cyclopropane formation, but was the consequence of subsequent photochemical cyclopropane deracemization. Studies on the association behavior of (*S*)-**6a** and (*R*)-**6a** toward photosensitizer *ent*-**PS-1** showed that (*S*)-**6a** binds to *ent*-**PS-1** more strongly than the major enantiomer (*R*)-**6a**. As a result, intramolecular sensitization within the complex *ent*-**PS-1**/(*S*)-**6a** is faster than within the counterpart *ent*-**PS-1**/(*R*)-**6a**, thus resulting in enrichment of (*R*)-**6a**. Interestingly, in contrast to the previous work on deracemization of allenes[14], DFT calculations disclosed that the distances between the thioxanthone carbonyl group and quinolone double bond are not distinctly different, suggesting no obvious kinetic preference during the sensitization. Therefore, the moderate enantioselectivity can be partially attributed to the fact that the 1,3-diradical intermediate **B** favors the formation the minor (*S*)-**6a** owing to the geometric constraints, while the deracemization process shows a preference for the major enantiomer (*R*)-**6a**.

Building on the underlying principle for the deracemization process of *rac*-**6**, soon thereafter, Bach and co-workers further developed a highly enantioselective photochemical deracemization of two classes of spirocyclopropyl oxindoles, 2,2-dichloro and 2,2-dialkyl-substituted compounds (*rac*-**7** and *rac*-**8**) (Fig. 4B)[20]. Using thioxanthone **PS-1** and xanthone **PS-2** as ideal chiral photosensitizers under irradiation of visible light (λ = 420 nm) and near-UV light (λ = 366 nm) respectively, the corresponding differently substituted chiral spirocyclopropyl oxindoles (*R*)-**7** and (*R*)-**8** were obtained with good yields (65-98%) and significantly improved enantioselectivity (50-85% ee). Notably, in this work, the postulated 1,3-diradical intermediate has also been detected experimentally. Based on combined studies involving NMR titration, transient absorption spectroscopy, and DFT calculations, three mechanistic contributions were identified to co-work favorably for high enantioselectivity, including the difference in binding strength among substrate and sensitizer, the smaller distance in the complex of the minor enantiomer, and the lifetime

of the prochiral 1,3-diradical intermediate.

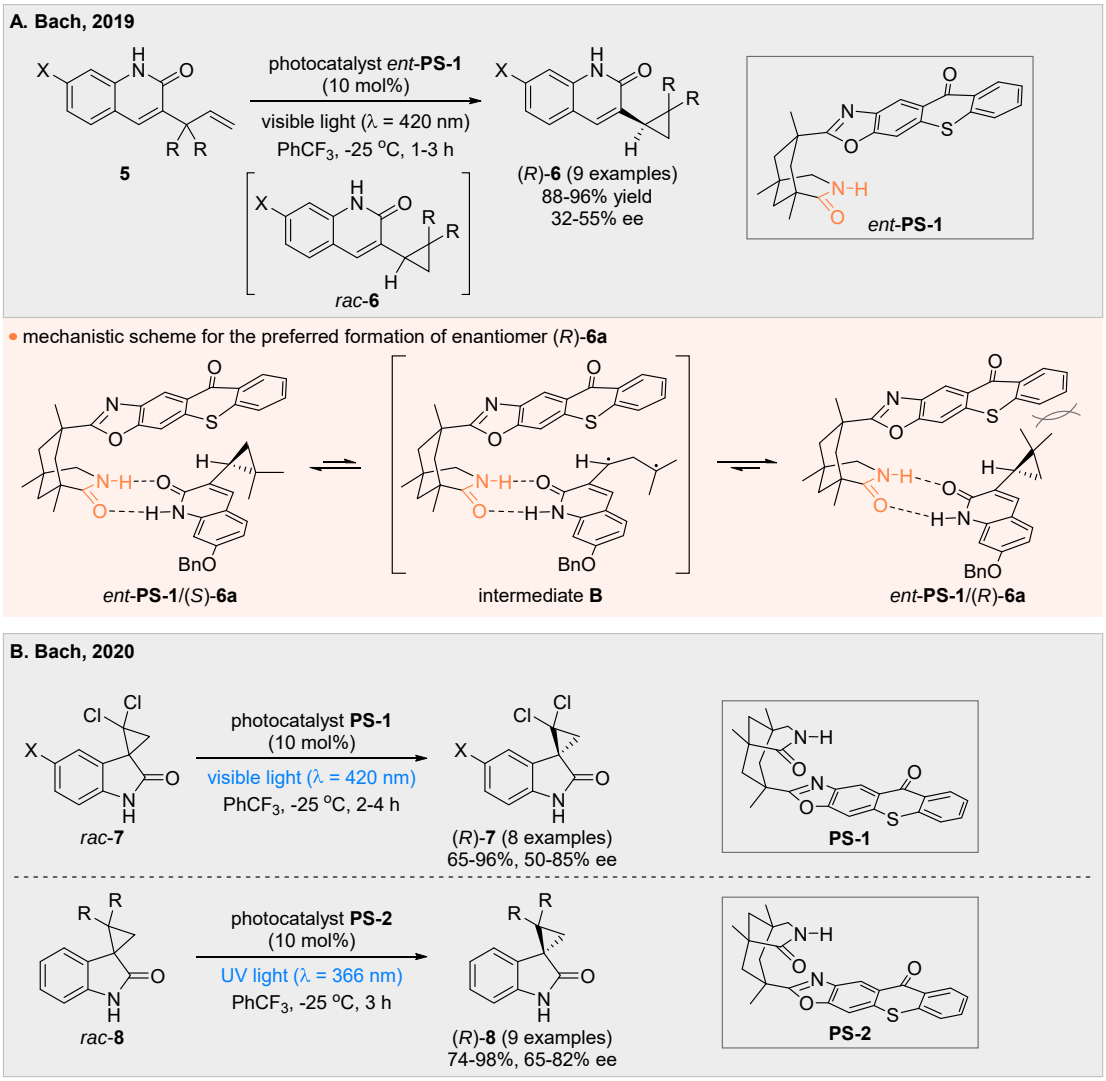

Fig. 4. Visible-light-driven deracemization of centrally chiral cyclopropanes by triplet-sensitization. (**A**) Construction of 3-cyclopropylquinolones by deracemization. (**B**) Deracemization of spirocyclopropyl oxindoles.

As mentioned above, a range of seminal works by Bach have demonstrated the robustness of chiral thioxanthone and xanthone photocatalysts in triplet energy transfer-enabled deracemization[14,16,20]. The inherent working modes rely non-covalent two-point hydrogen bonding interaction for enantiomer recognition. However, in certain realistic scenario, such binding situation might not be as perfect as expected and other parameters may significantly influence the selectivity. To overcome these limitations, merger of the mode of triplet energy transfer with other catalytic tactics might provide a new platform for the expansion of the profile of substrates[21]. Given the ready availability of their racemates, catalytic deracemization of α-branched aldehydes is arguably the most straightforward and atom-economical strategy for the construction of enantiopure α-tertiary carbonyl compounds, which are versatile synthetic building blocks in making pharmaceuticals. However, the inherent issues associated with deracemization and the lability of the α-carbonyl stereocenter render this process

complicated and fiddly. Recently, a novel strategy of photochemical *E*/*Z* isomerization of enamine developed by the Luo group has made it as simple as turning on a light, when using simple chiral aminocatalyst and readily available photocatalyst (Fig. 5)[22]. Conceptually, it was proposed that a matched pair of chiral aminocatalyst and one enantiomer of chiral aldehyde would stereospecifically form an enamine of certain configuration (*E* or *Z*), and the *E*/*Z* distribution of the in situ-formed enamine might be perturbed by triplet energy transfer-mediated photoisomerization. Despite extensive exploration of visible-light-driven *E* to *Z* isomerization of alkenes, such a process of catalytically formed transient intermediate has yet to be reported[23]. After extensive investigation into the combination of aminocatalyst and photosensitizer, Luo and co-workers realized this idea in deracemization of 2-phenylpropionaldehyde *rac*-**9a** by combination of primary-tertiary amine (*S*)-**10**/$HNTf_2$ and $Ir(ppy)_3$ in the presence of benzoic acid as an additive under visible-light irradiation (λ = 400 nm), leading to enrichment of (*R*)-**9a**. Notably, control experiments with both optically pure (*S*)- and (*R*)-**9a** give rise to (*R*)-selectivity, which confirms the light being the main driving force, while racemization was observed in these cases without light irradiation. The process accommodated a wide range of 2-(hetero)arylpropanals and proceeded efficiently to give the corresponding (*R*)-enantiomers with excellent enantioselectivity. In the case of substrate bearing both ketone and aldehyde functionality, the deracemization exclusively occurred at the α-carbon of the aldehyde and ketone remained intact. However, this approach is not suitable for aldehydes other than 2-arylacetaldehyde and α-branched ketones. Facile conversion of products into nonsteroidal *anti*-inflammatory pharmaceuticals such as (*R*)-Ibuprofen **10a** and (*R*)-Flurbiprofen **10b** without erosion of enantiopurity also highlights the potential of this protocol.

Mechanism studies including photodynamic equilibrium, enamine formation process, and DFT calculations indeed proved the photochemical enamine isomerization pathway. At the ground state, chiral primary aminocatalyst (*S*)-**10** stereochemically matched with (*S*)-**9a** to generate dominant *E*-enamine. Since the steric hindrance in the *Z*-enamine led to deconjugation of the β-enaminyl aromatic group, *E*-enamine could be preferentially excited over *Z*-enamine, which is also supported by their vertical excitation energies (S_0 to T_1, 71.8 vs 74.6 kcal/mol). As a result, visible-light-driven triplet sensitization promoted rapid and continuous photodynamic isomerization of *E*-enamine to its disfavored *Z*-isomer, which ultimately underwent facile selective protonation to give mismatched enantiomer (*R*)-**9a**. Obviously, the transient enamine acts as a shuttle between *S*-α-branched aldehyde and *R*-α-branched aldehyde interconversion. Despite some limitations in the substrate class, this work provides an elegant solution to the important and very challenging problem in catalytic deracemization of α-tertiary aldehydes. There is little double that this strategy will be adopted by other chemists and will inspire additional development in this area.

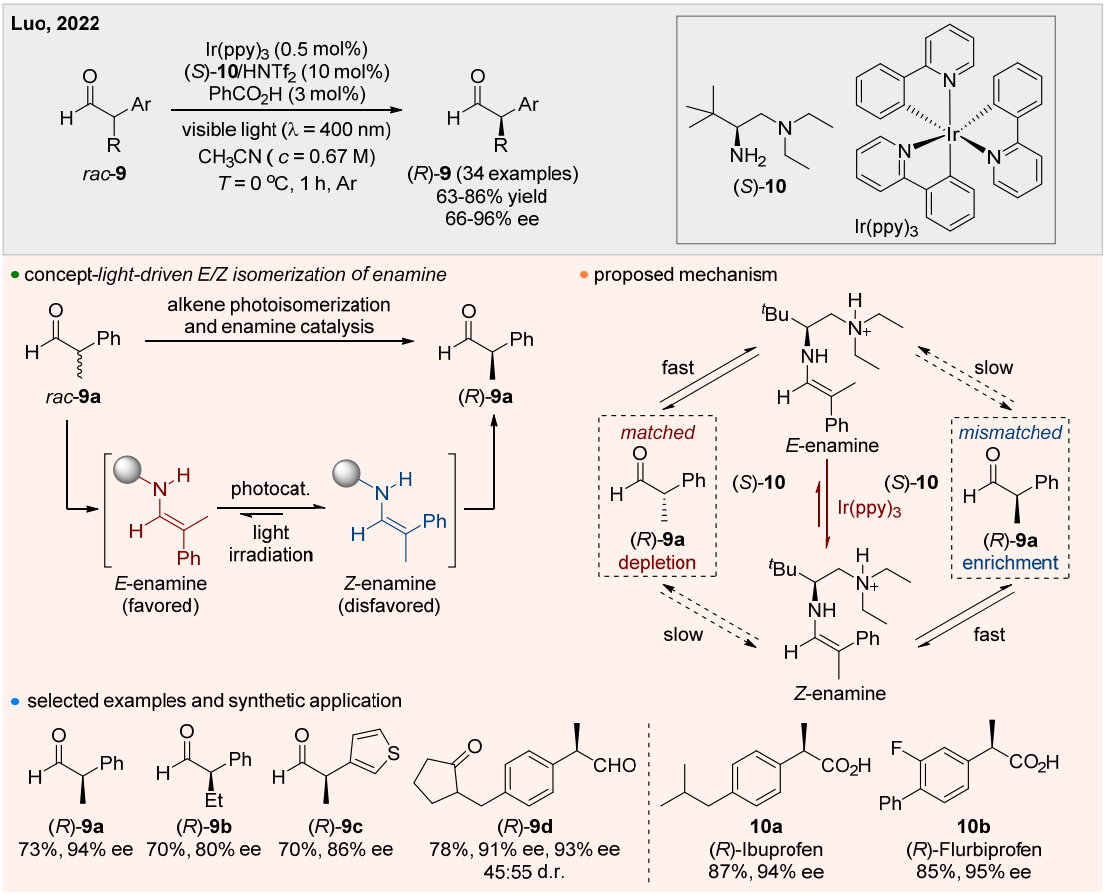

Fig. 5. Visible-light-driven deracemization of α-branched aldehydes by triplet-sensitization of enamines.

2.2 Visible light-driven single electron transfer-triggered deracemization

Visible-light-driven triplet sensitization-enabled deracemizations rely on different energy-transfer efficiency for two substrate enantiomers or two in-situ-formed isomers, which thus results in preferential formation of certain electronic excited states. However, such inherent mode strategically determines substrate-specific paradigm. Reductive or oxidative single electron transfer (SET) between photocatalysts and substrates is another major activation mode for generation of highly reactive radical species in photochemical reactions. In principle, these SET-mediated excitation-state reactions might also meet the key mechanistic requirements for deracemization as these transformations proceed across two distinct potential energy surfaces.

Drawing inspiration from their previous out-of-equilibrium intermolecular alkene hydroamination[24], Knowles et al. envisioned that visible-light-driven SET-based methods would likely provide a complementary platform for deracemization of a wider range of substrates (Fig. 6). To show proof of concept, Knowles, Miller and co-workers in 2019 reported a groundbreaking example of visible-light-driven deracemization of cyclic ureas via a sequential single electron transfer (SET), proton transfer (PT), and hydrogen atom transfer (HAT) process[25]. A ternary catalyst system consisting of an Ir(III)-based photocatalyst ($[Ir(dF(CF_3)ppy)_2(bpy)]PF_6$), and two chiral organocatalysts, 1,1'-bi-2-naphthol (BINOL)-derived phosphate base **12** and peptide-

based thiol **13** enabled excellent levels of optical enrichment in the presence of molecular sieves and triphenylmethane (25 mol%) as additional HAT donor. Detailed control experiments and DFT computational studies confirmed that the deracemization reaction proceeded through a series of selective SET, PT, and HAT events, rendering cleavage and reformation of a stereogenic N-α-C-H bond. The racemic urea substrate firstly underwent reversible SET-oxidation of by the exited state Ir-photocatalyst to form chiral radical cations (*S*)-**11A** and (*R*)-**11A**, which can then be kinetically resolved by selective deprotonation in the presence of chiral phosphate **12**. Namely, faster-deprotonation of (*S*)-radical cation (*S*)-**11A** allowed its facile conversion to the prochiral radical **int-A**, while stereochemically mismatched (*R*)-radical cation was converted back to the (*R*)-urea substrate through charge recombination with the reduced form of photocatalyst Ir(II), enriching the once-racemic starting mixture in the (*R*)-**11**. Next, prochiral radical **int-A** reacted with chiral thiol **13** in an enantioselective HAT manner, this time kinetically favoring the formation of the (*R*)-enantiomer, further increasing the optical purity of the (*R*)-**11**. Finally, SET and PT occurred among the reduced Ir(II) species, thiyl radical, and the protonated base returned the original forms of all three catalysts. Remarkably, the synergistic effect of chiral catalysts **12** or **13** is critical to the excellent enantioselectivity as urea products with obviously diminished levels of enantioselectivity were obtained when either of them was replaced with an achiral one. The standard catalytic system also allowed complete conversion of (*S*)-**11A** into (*R*)-**11A**, further supporting the proposed working model. A wide variety of ureas with a pendant amide H-bond donor group on the *N*-aryl moiety could be well accommodated, and the steady-state enantioselectivity was achieved efficiently, with the corresponding (*R*)-**11** being recovered in nearly quantitative yield. Notably, compared to the traditional sequential redox-driven transformations that necessitate stoichiometric amounts of oxidants and reductants[26], the whole reaction is a redox-neutral process and consumes only photons. Although the scope of reaction is currently limited to proof-of-concept ureas, it is undoubtedly possible to expand this strategy to the deracemization of other important classes of chiral compounds with structural similarity to ureas.

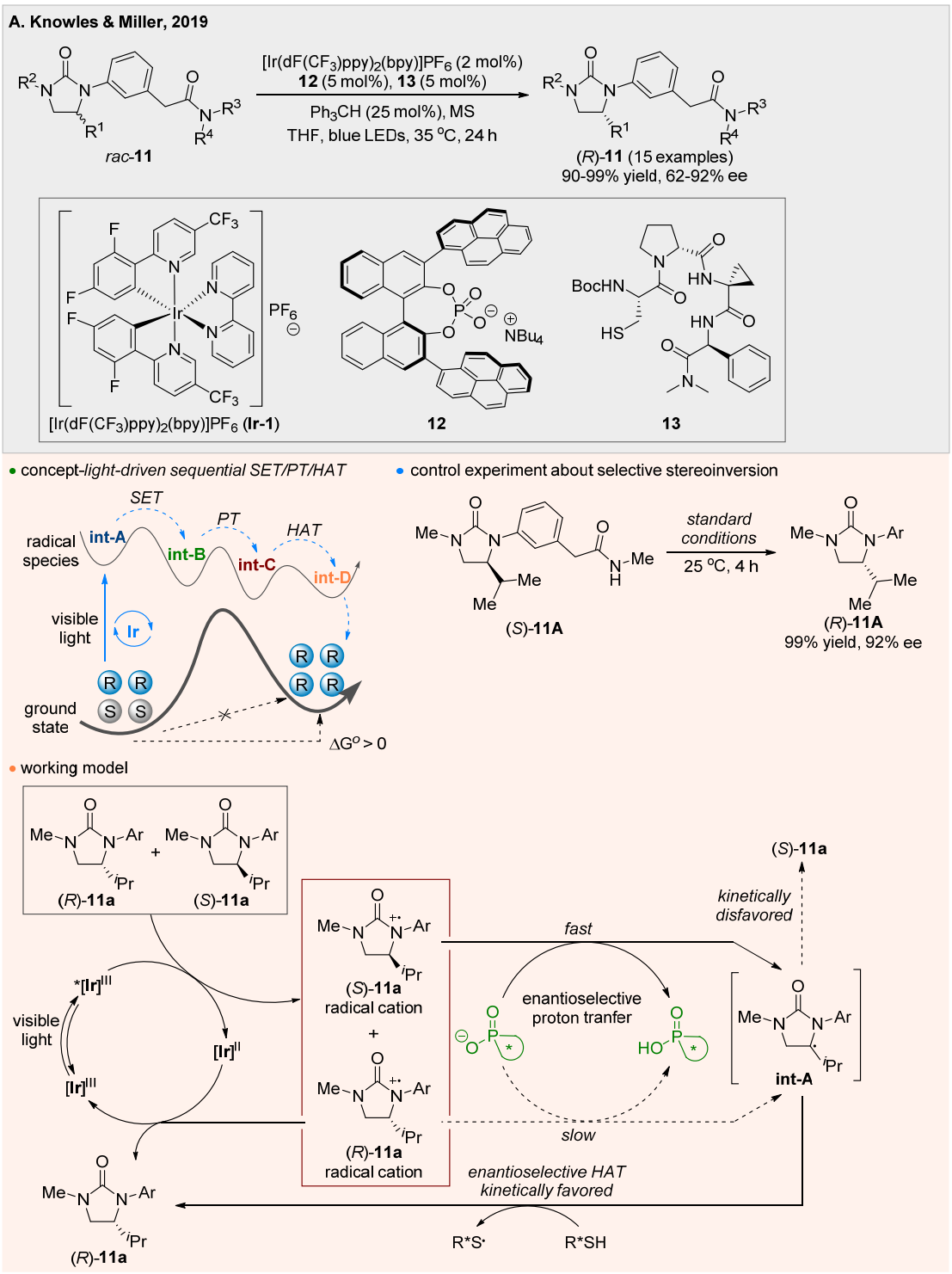

Fig. 6. Visible-light-driven Deracemization of ureas by sequential electron, proton, and hydrogen-atom transfer.

Catalytic deracemization of α-branched ketones is an attractive but challenging task[27]. Building on the well-established enantioselective enolate protonation-mediated deracemization, Meggers and Chen recently envisioned that a successful one-pot catalytic deracemization of carbonyl compounds might be achieved if enolate formation could be divided into two elementary steps to overcome microscopic reversibility (Fig.

7)[28]. Specifically, photoinduced SET-reduction allowed generation of ketyl intermediate and subsequent HAT (lose of hydrogen), thus leading to net deprotonation. As such, deprotonation and protonation of carbonyl compounds would proceed through different potential surfaces, therefore enabling enrichment of one enantiomer. Based on this conceptually simple strategy of visible-light-driven photoredox deprotonation and enantioselective protonation, the groups of Meggers and Chen reported the first example of highly efficient catalytic α-deracemization of pyridylketones *rac*-**14** with stereocenters at the α-position in a single reaction using a combination of a chiral-at-metal rhodium **Λ-RhInd**[29] as a photocatalyst and *N*-phenylpiperidine as an HAT reagent under blue light irradiation. The pyridyl moiety not only serves a chelator for coordinating with photoactive **Λ-RhInd** complex, but also could stabilize the ketyl intermediate due to its electron-withdrawing nature. Generally, the reaction shows good functional group tolerance and diverse structural modifications could be well accommodated, though moderate enantioselectivity was observed in the case of pyridylketone with stereocenter connecting to two aliphatic side chains.

Mechanistic experiments and DFT computations provide solid evidences in supporting the design plan and proposed reaction pathway. Initial bidentate coordination of the racemic pyridylketone *rac*-**14** to chiral catalyst **Λ-RhInd** generates complex **14-I** as a mixture of two diastereomers, (*R*)-**14-I** and (*S*)-**14-I**. However, DFT calculations revealed that (*R*)-**14-I** is 2.9 kcal/mol higher in free energy than (*S*)-**14-I**, which means that the less stable (*R*)-**14-I** can readily undergo ligand exchange with another molecule of (*S*)-**14** to form (*S*)-**14-I**. Then, photoexcitation of the photoactive (*S*)-**14-I** to its triplet state **14-^{3}I**, followed by SET from *N*-phenylpiperidine to afford the ketyl radical **14-^{2}II** and amine radical cation. An HAT from the α-position of **14-^{2}II** to amine radical cation furnished enolate **14-^{1}III** and a protonated amine, which transferred a proton to the enolate **14-^{1}III** in diastereoselective manner to afford Rh-bound pyridylketone (*R*)-**14-I** as a single stereoisomer. Release of pyridylketone (*R*)-**14-I** generates free catalyst **Λ-RhInd** for the next catalytic cycle. Collectively, key to success of this approach relies on two enantioselectivity filters originating from chiral catalyst **Λ-RhInd**; namely, selective enolate protonation favorability of (*S*)-**14-I** over (*R*)-**14-I** ensuring product inhibition by (*R*)-**14-I** does not occur. Over time, (*R*)-**14-I** was enriched in the reaction mixture. Remarkably, the chiral rhodium catalyst plays a bifunctional role as photoredox catalyst and chiral Lewis acid, while tertiary amine serve triple functions as SET donor, HAT acceptor and proton donor in a single catalytic cycle. Considering numerous methods exist for installing substituents into the α-position of carbonyl compounds and easy follow-up chemistry about the pyridylketone moiety, this single catalyst-based deracemization strategy provides a blueprint for other deracemizations of carbonyl compounds.

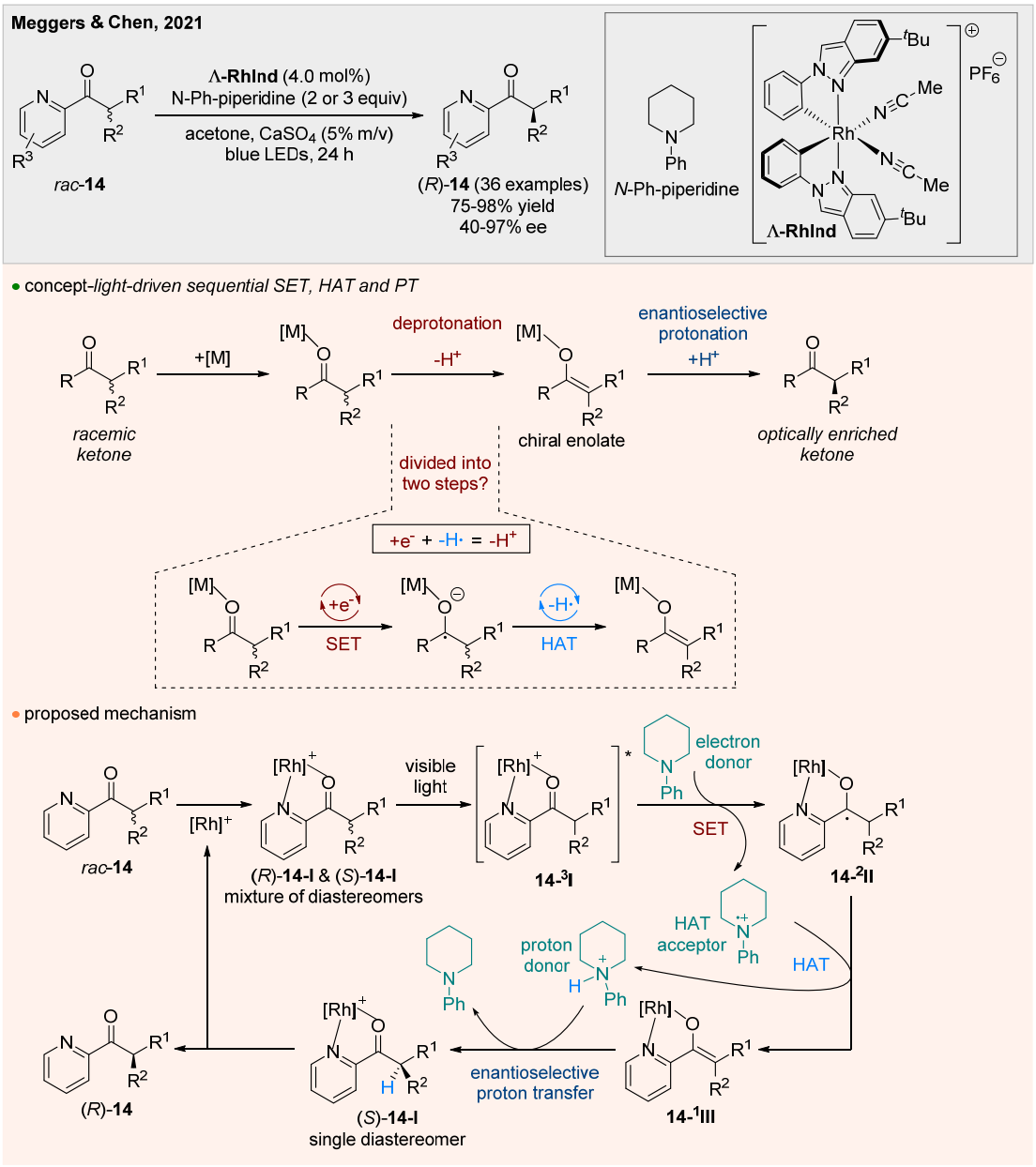

Fig. 7. Deracemization of pyridylketones by electron, hydrogen-atom and proton transfer.

2.3 Based on hydrogen atom transfer (HAT)

It is well established that photoexcited benzophenones are capable of abstracting hydrogen atoms from sp^3-hybridized carbon centers[30]. Building on the chiral thioxanthone or xanthone catalyzed triplet energy transfer-based photochemical deracemization[14,15,16], Bach and co-workers presented a new concept for photochemical deracemization, wherein a suitable chiral diarylketone that also has two-point hydrogen bond site might discriminate between two enantiomers of amino acid derivatives to render selective reversible HAT (Fig. 8). Specifically, though the two enantiomers **I** and *ent*-**I** of certain amino acid derivative can under undergo interconversion via prochiral radical intermediate **II** by reversible HAT, use of chiral HAT catalyst might retard or block the HAT form to the chiral photocatalyst. As such, enantiomer **I** would be

enriched, and ideally with 100% ee. Bach et al. translated this idea into reality by developing the first example of photochemical deracemization of pharmaceutically useful 5-substituted 3-phenylimidazolidine-2,4-diones (hydantoins) by using their previously developed benzophenone **PS-3**[31] as a chiral organic photocatalyst under irradiation at λ = 366 nm. DFT calculations on the ground-state configurations of two complexes (*S*)-**15a**/**PS-3** and (*R*)-**15a**/**PS-3** revealed that, within (*S*)-**15a**/**PS-3**, the distance between the carbonyl oxygen atom and α-hydrogen atom is only 264 pm. As a result, upon irradiation, an HAT event should occur more easily in complex (*S*)-**15a**/**PS-3** than in (*R*)-**15**/**PS-3**. Control experiments and H/D scrambling also supported that back HAT of (*S*)-**15a**-derived prochiral proceeded through an intermolecular process, leading to racemization of (*S*)-**15a**. Over time, **(*R*)-15a** would prevail, enabling the conversion of the racemic mixtures into a single enantiomer. Interestingly, in contrast to Knowles and Miller's method[25], in this approach, no additive was required to server as hydrogen atom shuttle in the back HAT process. This deracemization worked efficiently with a range of hydantoin derivatives bearing alkyl and benzyl substituents at the sp^3-hybridized carbon center, and enantioselectivity excess can generally reach a plateau after 13 h (27 examples, 69%-quant., 80-99% ee). Given the readily availability and biological importance of the racemic hydantoins[32], as well as the simplicity of the procedure, this conceptually new method complements the toolbox for both medicinal and synthetic chemists. Extension to use of visible light as source can be expected upon further structural modification of photocatalyst of such type.

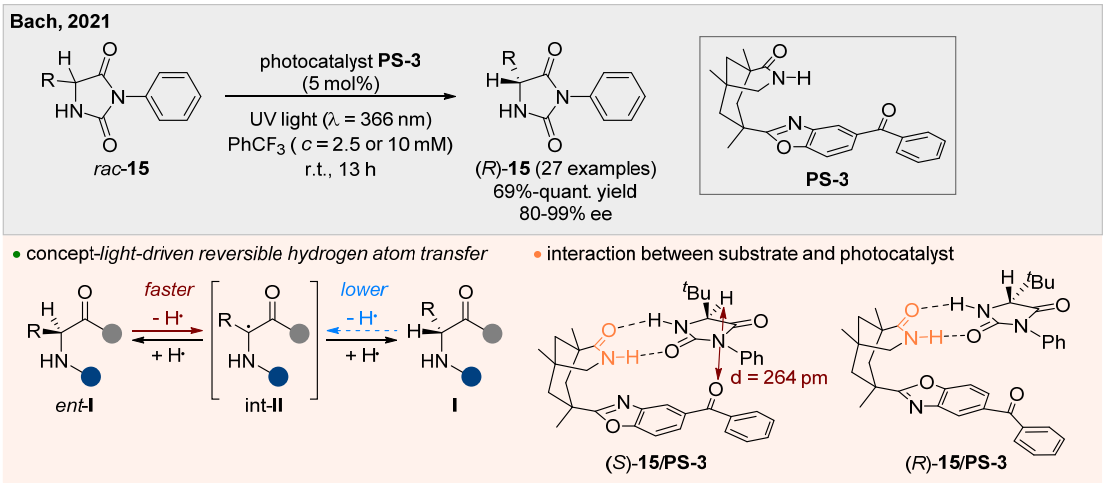

Fig. 8. Deracemization of hydantoins by light-driven reversible hydrogen atom transfer.

Asymmetric transition metal catalysis and biocatalysis[33] have been established as two reliable methods for construction of diverse chiral compounds from simple, readily available starting materials. Because of the good compatibility of photocatalysis[34], the combination of powerful redox- and bond-formation transformations of photocatalysis with the catalytic power and excellent enantioselectivities of transition metal catalysts and enzymes in functional group interconversions, also constitutes an emerging field for deracemization of racemic chiral compounds. For instance, the Hu group disclosed an interesting visible-light-driven one-pot deracemization of secondary alcohols by a

sequential irreversible photochemical dehydrogenation and an enantioselective thermal hydrogenation, using a combination of Ni-modified cadmium sulphide and Noyori's Ru-based chiral hydrogenation catalyst[35]. Recenlty, Glueck, Winkler, and co-workers reported a concurrent photocatalytic oxidation and biocatalytic reduction procedure for cyclic deracemization[36]. In this one-pot protocol, an unselective visible-light-driven protochlorophyllide-catalyzed sulfide oxidation was coupled with an enantioselective sulfoxide reduction catalyzed by (*S*)-selective methionine sulfoxide reductases, providing access to valuable optically pure sulfoxides.

3. Catalytic *contra*-thermodynamic positional alkene isomerization

Given the ubiquity of feedstock alkenes in many disciplines and their versatile downstream synthetic applications, the development of stereocontrolled methods for construction and manipulation of olefines have long been a major topic of research in synthetic chemistry. Strategies to achieve the geometric adjustment or positional relocation of pre-existing alkenes via external stimuli complement the existing arsenal of *de novo* olefination methods and are being intensively pursued[9,37]. However, thermal direct catalytic approaches can only convert less stable alkenes to the more stable isomers, and such equilibrium populations are thus significantly dominated by their thermodynamic stabilities. Alternatively, recent mechanistic understanding of photochemical reactions and advances in the light-emitting diode (LED) technology have enabled design and conception of visible-light-driven *contra*-thermodynamic positional and geometric isomerization of alkenes. As a recent review article by Gilmour focused on geometric isomerization of alkenes[9c], only recent strategies about *contra*-thermodynamic positional isomerization of alkenes were discussed.

In nature's structure-function continuum, prenyl motifs are a ubiquitous class of biological regulators, and synthetic methods for introduction of this venerable scaffold are essential. Building on the seminal reports by Pete on enantioselective photodeconjugation of α,β-unsaturated esters[38], Gilmour and Morack recently envisioned that chromophore augmentation and visible-light irradiation would provide a general and mild method for deconjugative isomerization-based prenylation (Fig. 9)[39]. Conceptually, the sequential input of energy from light is critical to this *contra*-thermodynamic process. Initially, visible-light irradiation of aryl ketone **16** facilitated its geometric *E* to *Z* isomerization of the alkene moiety to intermediate **16-I**, wherein the methine proton is positioned in close proximity to the carbonyl group. Then, such a structural preorganization would promote intramolecular hydrogen atom transfer (HAT) upon another irradiation to form transient dienol **16-II**, which could undergo irreversibly protonation to form the desired deconjugated product. In principle, addition of suitable chiral hydrogen bond catalyst would enable an enantioselective version by engagement in the final reprotonation step. Based on this design plan, Gilmour and Morack achieved a visible-light-driven deconjugative isomerization of activated alkenes bearing an aryl ketone antenna as chromophore through a sequential geometric isomerization/ HAT/protonation process. This mild protocol tolerated a wide range of acyclic and cyclic substrates to afford the corresponding products with generally good yields, though ones with electron-withdrawing groups proved more challenging.

Detailed mechanistic studies also supported the proposed concept and an overall slightly endergonic process (ΔG = 0.6 kcal/mol). It was also established that the final re-protonation is the rate-determining step. These investigations thus guided development of an enantiodivergent variant of this process using inexpensive chiral pool quai-enantiomers, quinine **18** and quinidine **19** by temperature.

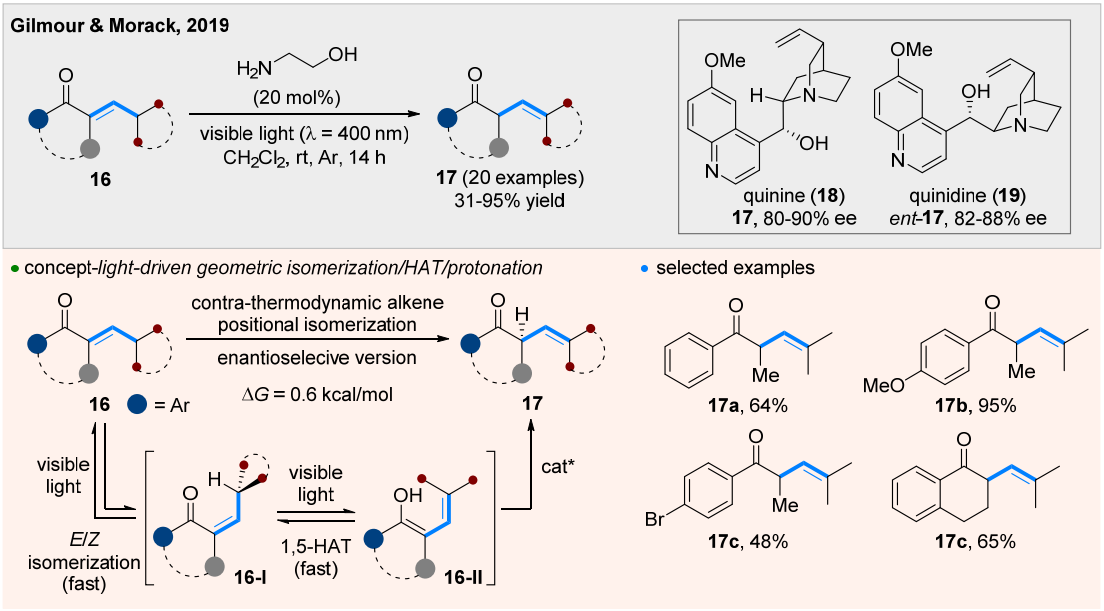

Fig. 9. Visible-light-driven deconjugative positional isomerization of activated alkenes.

Building on the dual photoredox and chromium catalyzed allylation of aldehydes from Glorius[40] and Kanai[41], as well as the protodemetalation activity mode of allylchromium(III)[42], the Knowles group recently developed a novel strategy of visible-light-driven allylmetallation and protodemetallation for *contra*-thermodynamic positional isomerization of alkenes (Fig. 10A)[43]. Specifically, electron-rich alkene **20** can be first oxidized to a transient alkene radical cation **20-A** by the photoexcited catalyst. The acidity of the allylic C-H bonds in such radical cation is markedly strengthened, rendering favorable deprotonation to afford an allylic radical **20-B** in the presence of Brønsted base. The relatively stabilized radical **20-B** is captured by a Cr(II) catalyst go generate an allylchromium(III) complex **20-C**. Notably, formation of such type of complex by synergistic photoredox and chromium catalysis has been well explored by Glorius and Kanai[40,41]. Then, if a suitable proton donor can intercept the allylchromium complex, a regioselective protodemetallation would occur at the more sterically hindered internal carbon of allylchromium(III) complex **20-C** via an S_E2' process, thus giving rise to the less substituted alkene isomer **21**. Ultimately, an SET from the reduced state of the photocatalyst to the resulting Cr(III) results in regeneration of ground state photocatalyst and Cr(II) catalyst. As the more substituted and more thermodynamically stable alkene isomers might be more easily oxidized than the less substituted alkene products, an appropriated selected photocatalyst with suitable oxidation potential window would differentiate these isomers, thus leading to accumulation of less-substituted and less-thermodynamically stable alkenes that were

inert to further SET-oxidation. Guided by this design plan, Knowles identified that catalytic systems comprising of Ir-based photocatalyst and $CrCl_2$ or $CrCl_3$ and MeOH as proton source showed exceptional selectivity and efficiency, with a broad substrate range of alkene classes being well accommodated, including enol ethers, enamides, styrenes, 1,3-dienes, as well as tetrasubstituted alkyl olefins.

At the same time, the group of Wendlandt independently reported that alternative catalytic system consisting of $Na_4W_{10}O_{32}$ (NaDT), Co(dmgH)(dmgH$_2$)Br$_2$ (Co(III)−H), and 2,4,6-triisopropylbenzene disulfide (TripS$_2$) also promoted *contra*-thermodynamic internal-to-terminal olefin isomerization (Fig. 10B)[44]. Interestingly, in sharp contrast to previous energy-transfer or SET-based deconjugation that have some intrinsic scope limitations[38,43], key to success of this reaction relied on visible-light-driven HAT/allylmetallation/biomolecular homolytic substitution (S_H2') process. Notably, both HAT event and allylcobaloxime complex formation that are influenced by steric- rather than purely electronic-factors, contribute to the overall terminal-selective alkene formation. As such, this protocol demonstrates an exceptionally broad substrate scope.

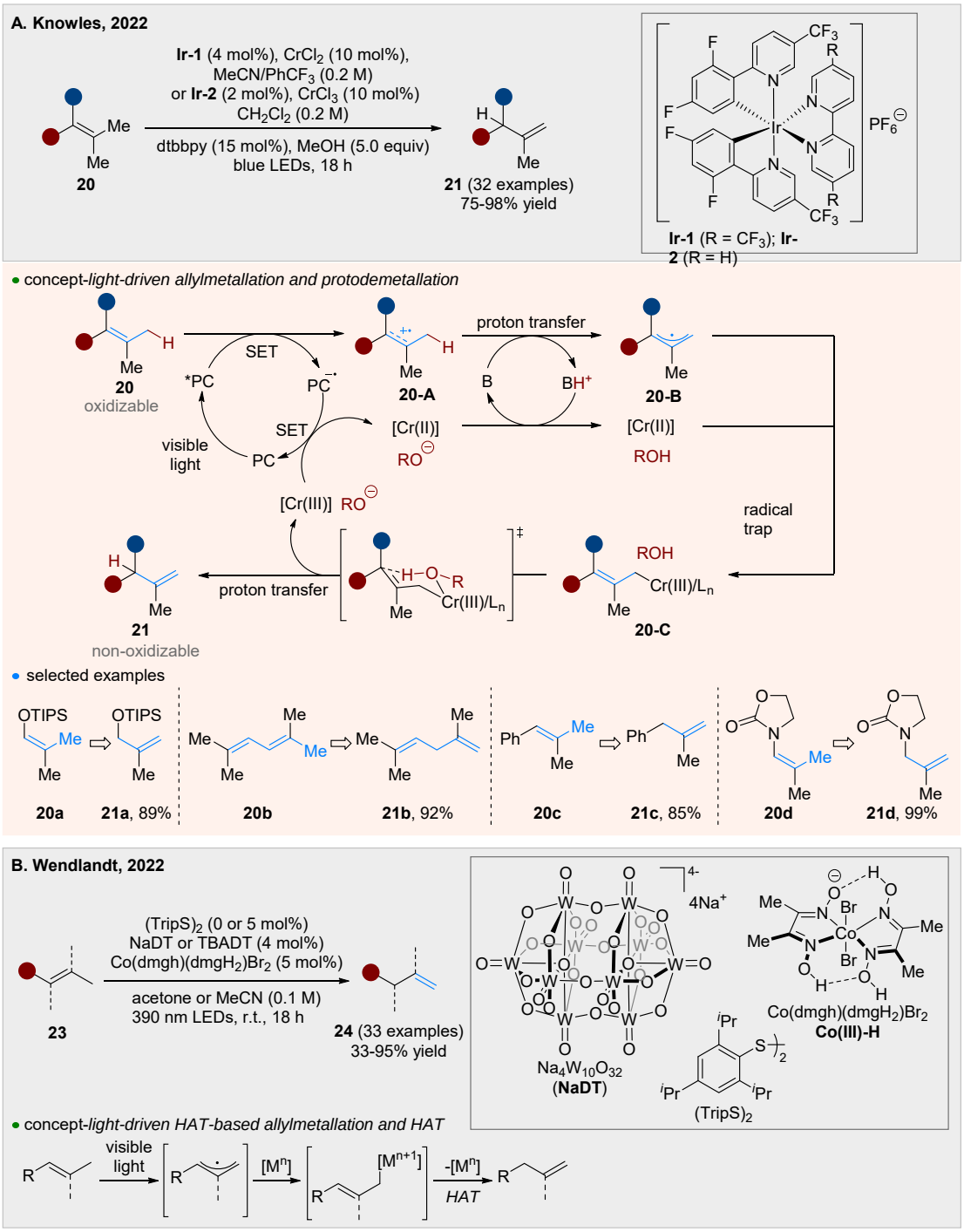

Fig. 10. Visible-light-driven *contra*-thermodynamic positional isomerization of alkenes. (**A**) SET-triggered catalytic positional alkene isomerization. (**B**) HAT-triggered catalytic positional alkene isomerization.

4. Dynamic epimerization of sugars and diols

Biomass precursors provide abundant natural sources for a small library of carbohydrates, however, numerous biologically important so-called rare sugars are not directly available from the natural sources[45]. Multistep chemical and enzymatic isomerizations were typically required to access these rare distinct monosaccharides, but often suffered from the issues of low selectivity and efficiency caused by the

intrinsic reversible polar enolization mechanisms.

Drawing the inspiration from the biosynthesis of neomycin B from neomycin C that was enabled by an HAT/re-delivery of hydrogen atom cycle[46], Wendlandt envisioned that, if a new strategy could allow homolytic C-H bond cleavage and re-formation to proceed by distinct mechanisms, a kinetically controlled direct radical epimerization of biomass-derived carbohydrates to less table rare sugar isomers might be viable, with efficiency and selectivity exceeding these obtained in the classic equilibrium-controlled chemical and enzymatic isomerization processes. Thus, Wendlandt and co-workers has established the conceptual feasibility of *contra*-thermodynamic radical isomerization of biomass-derived precursors to rare sugar isomers by a strategy of visible-light-driven sequential HAT and HAT process (Fig. 11)[47]. Photochemical conditions employing 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene (4-CzIPN) as an organic photoredox catalyst, quinuclidine as a hydrogen atom abstractor, and adamantane thiol as a hydrogen atom donor in the presence of tetrabutylammonium *p*-chlorobenzoate as a base proved to be effective for a wide range of biomass-derived monosaccharides. Minimally protected and unprotected monosaccharides as well as oligosaccharides and glycans were well accommodated. Detailed studies on the individual elementary steps and control experiments support the kinetically controlled pathway that involves two sequential HAT steps. First, the quinuclidinium radical cation that was generated from quinuclidine by SET-oxidation was able to mediate an irreversible HAT step to generate sugar radical. Then, thiol co-catalyst engages in the subsequent irreversible diastereoselective HAT to the initially formed sugar radical to afford the final isomerized product. A switch from this kinetic to thermodynamic control in epimerization is also possible by use of suitable HAT catalyst. For instance, Wendlandt and co-workers reported that, upon 456 nm LED irradiation, a catalyst system consisting of $[Ir(dF(CF_3)ppy)_2(dtbpy)]PF_6$ as a photocatalyst and Ph_3SiSH (30 mol%) as an HAT catalyst in the presence of DABCO (10 mol%) as a base promoted direct and selective isomerization of a broad range of *cis*-1,2-diols to their *trans*-diequatorial-1,2-diols[48]. Key to the success of this process relied on a reversible HAT event mediated by silanethiyl radical.

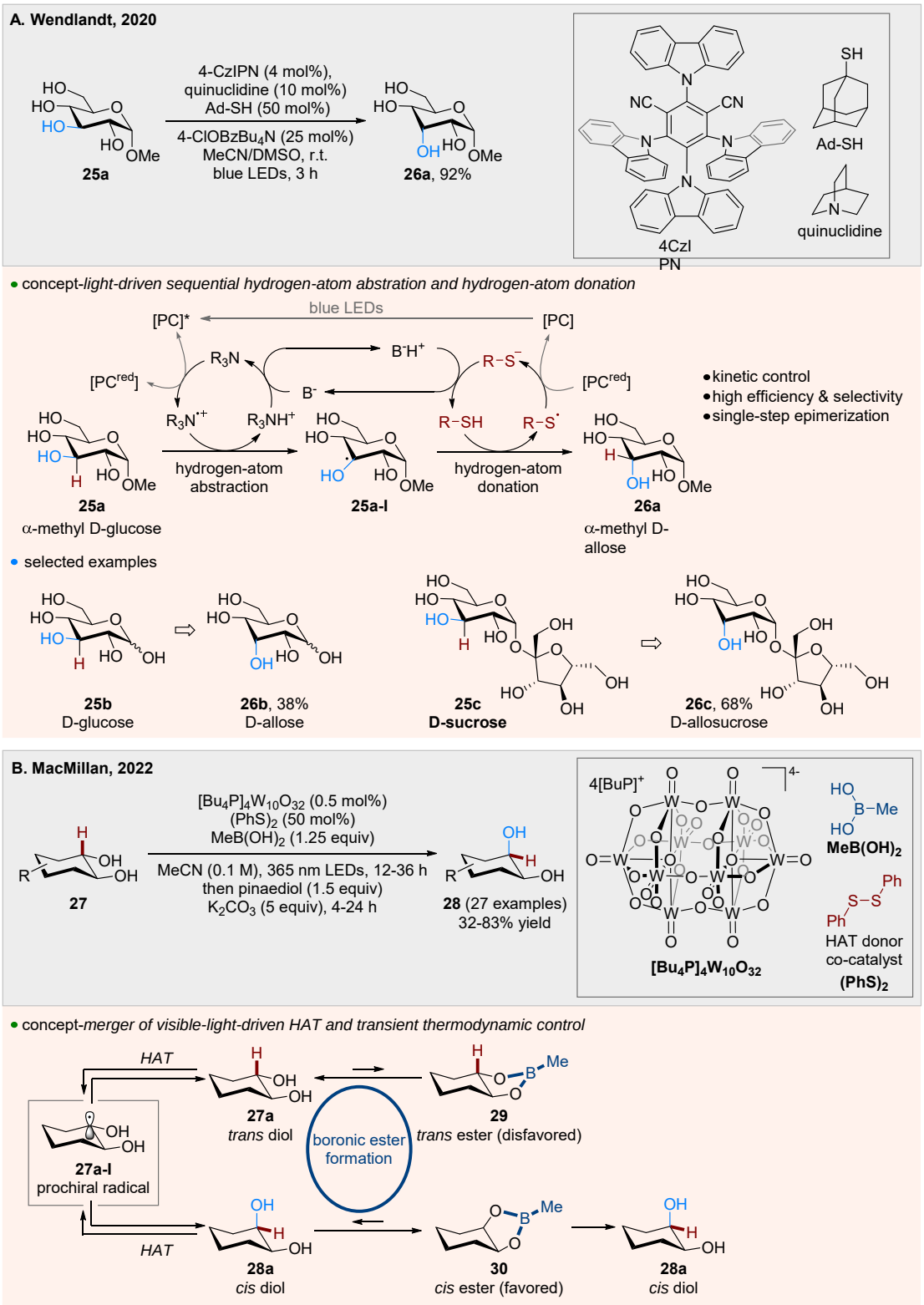

Fig. 11. Visible-light-driven epimerization of sugars and diols. (**A**) Selective epimerization of saccharides and glycans. (**B**) Selective dynamic epimerization of cyclic *trans*-diols to less stable *cis*-diols.

In sharp contrast to Wendlandt's strategy based on single HAT catalyst-promoted preferential formation of more stable *trans*-diols[48], at the same time, the MacMillan group independently reported a novel strategy involving merger of visible-light-driven

hydrogen atom transfer and boronic acid-mediated transient thermodynamic control enabled selective uphill epimerization of cyclic *trans*-diols to the less stable *cis*-diols (Fig. 11B)[49]. As *cis* diols react more readily with boronic acids to form boronic esters than their *trans* counterparts, it was conceived that the relative stability of *cis* and *trans* diol isomers might be inverted. As such, *cis* diol of mixture isomers, which were generated by repeated reversible HAT-based racemization of alcohol stereocenters, will be captured by boronic acids, resulting dynamic equilibration. This design plan was translated into reality, when employing a combination of $(PBu_4)_4W_{10}O_{32}$ (0.5 mol%) as an HAT photocatalyst, $(PhS)_2$ as an HAT donor, and $MeB(OH)_2$ (1.25 equiv) as chelating additive under irradiation of 365 nm LEDs. A range of cyclic *trans* 1,2- and 1,3-diols as well as polyols could be epimerized to the corresponding less stable *cis* products. Notably, this strategy has also enabled the divergent epimerization of a single sugar isomer. This transient thermodynamic control as a concept provides a more generally applicable platform for selective edition of the stereochemistry of organic molecules.

5. Conclusion and outlook

Stereoselective synthesis has long been a cornerstone of synthetic chemistry, and benefits greatly from the advances in intellectually adjacent catalytic disciplines such as transition metal catalysis, organocatalysis, and biocatalysis. Stereoselective logic-wherein the synthetic routes are designed according to stereoselectivity-determining step-has thus been predominantly used for construction of molecules of desired stereochemistry and chemical space. By contrast, stereochemical editing, wherein the chiral- or geometry-defining events are decupled from the main scaffold or complexity-forming steps, has the potential to have a substantial impact on the field of stereoselective synthesis, enabling late-stage flexibility in generating isomers from a single compound. Under many instances, however, the desired stereochemical editing processes are *contra*-thermodynamic on ground states and thus unfavorable. The growing recognition of operationally simple visible-light-driven photochemical reactions and good compatibility between photocatalysis and other catalytic modes are bringing us to this goal-*contra*-thermodynamic stereochemical editing.

Recent research in visible-light photocatalysis have yielded many generalizable concepts to empower *contra*-thermodynamic stereochemical editing by providing approach to irreversible elementary steps via excited electronic states and/or by introducing thermochemical biases that allow endergonic product formation. Strategic exploration of photocatalytic activation modes, triplet energy transfer (EnT), oxidative or reductive single-electron-transfer (SET), and hydrogen-atom-transfer (HAT), and merger of these activation modes with other catalytic methods allowed achievement of a diverse range of *contra*-thermodynamic stereochemical editing processes, including deracemization of racemic chiral molecules, positional alkene isomerization, and dynamic epimerization of sugars and diols. These works and mechanistic features establish several conceptual frameworks through which the reaction classes are anticipated to be expanded. In the coming years, visible-light-driven *contra*-thermodynamic stereochemical editing will certainly also have extensive impact in

organic synthesis and pharmaceutical industry.

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