Light-driven deracemization enabled by excited-state electron transfer

Nick Y. Shin1, Jonathan M. Ryss2, Xin Zhang3, Scott J. Miller2*, Robert R. Knowles1*

Deracemization is an attractive strategy for asymmetric synthesis, but intrinsic energetic challenges have limited its development. Here, we report a deracemization method in which amine derivatives undergo spontaneous optical enrichment upon exposure to visible light in the presence of three distinct molecular catalysts. Initiated by an excited-state iridium chromophore, this reaction proceeds through a sequence of favorable electron, proton, and hydrogen-atom transfer steps that serve to break and reform a stereogenic C–H bond. The enantioselectivity in these reactions is jointly determined by two independent stereoselective steps that occur in sequence within the catalytic cycle, giving rise to a composite selectivity that is higher than that of either step individually. These reactions represent a distinct approach to creating out-of-equilibrium product distributions between substrate enantiomers using excited-state redox events.

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nentioselective reactions are essential to the pharmaceutical, agrochemical, and fine chemical industries, providing access to products enriched in just one of two mirror-image geometries. Conventional enantioselective methods either transform achiral starting materials into chiral products or rely on kinetic resolutions to differentially transform the stereoisomers of chiral reactants. Both approaches have been the subject of extensive interest and development (1). By contrast, methods for achieving selective deracemization—wherein a racemic mixture of a given compound is wholly transformed into a single enantiomer of the same molecule—are rare, despite their conceptual simplicity and potential practical benefits (Fig. 1A) (2–4). Two factors complicate the development of deracemization methods. First, the conversion of a racemic mixture into a single enantiomer is unfavorable on thermodynamic grounds because of an attendant decrease in entropy. Although this effect is small (ΔG° = +0.42 kcal/mol at 298 K), it requires that an additional source of energy be supplied to drive the reaction forward. The second challenge is kinetic in nature and relates to the principle of microscopic reversibility (5). As enantiomers are equal in energy by definition, any series of elementary steps along a single potential surface that converts (S) to (R) will be equally facile in the reverse direction that transforms (R) to (S). In the absence of an exogenous driving force, this necessarily results in an equilibrium (racemic) distribution of products. Accordingly, effective deracermizations require both an input of energy to impart reaction directionality and distinct mechanisms for the elementary steps that respectively create and destroy stereochemistry.

Seminal examples from Turner, Toste, Zhou, and others have demonstrated that these requirements can be met through sequential redox transformations fueled by chemically compatible (or phase separated) oxidants and reductants, wherein the oxidation and reduction reactions occur independently and in parallel (6–8). Although effective, this approach can be challenging to generalize and requires that two stoichiometric reagents be consumed each time a molecule of substrate is processed. Excited-state reactions can also satisfy these key mechanistic requirements. Because they occur across two distinct potential energy surfaces, photochemical transformations are not subject to detailed balance and can provide access to non-Boltzmann product distributions—a benefit that underlies the success of many classical photoisomerization reactions (9, 10). Moreover, from a practical perspective, such processes require no chemical reagents, produce no stoichiometric waste, and consume nothing but photons. Bach et al. very recently reported groundbreaking examples of photo-driven deracermizations of allenenes and cyclopropylquinolones using a chiral photosensitizer that exhibits different energy-transfer efficiencies for the two substrate enantiomers, resulting in high levels of optical enrichment (Fig. 1C) (11, 12). These and other photoisomerizations are generally understood to proceed through the electronic excited states of the substrates themselves, which strategically defines a substrate-specific paradigm (13–15).

We present here a complementary platform for light-driven deracermizations based on the use of excited-state redox events (Fig. 1B). These electron transfer–based approaches provide an alternative mechanism for driving reactions in opposition to a thermodynamic gradient yet are likely applicable to a wider range of substrates and reaction types than direct excitation or energy transfer–based approaches. We have previously shown that excited-state redox events can be used to drive out-of-equilibrium reactions, such as intermolecular olefin hydroaminations and the isomerization of cyclic alcohols to linear ketones, wherein the reaction products are higher in energy than the starting materials (16, 17). Here, we extend these studies and describe a method for the light-driven deracemization of cyclic ureas mediated by a ternary catalyst system comprising an Ir(III)−based photoredox catalyst, a 1,1′-bi-2-naphthol (BINOL)−derived chiral phosphate base, and a cysteine-containing peptide H−atom donor (Fig. 1D). This process occurs through a series of favorable electron, proton, and H−atom transfer events that serve to break and reform a stereogenic C−H bond. The extent of optical enrichment in these reactions is jointly determined by two independent enantioselective steps that proceed in sequence within the catalytic cycle. This results in an unusual (and beneficial) outcome in which two modestly stereoselective steps together result in an observed selectivity that is higher than that of either individual step. The discovery, optimization, scope, and a preliminary mechanistic model for this process are presented herein.

We first observed deracemization behavior serendipitously while attempting to develop an asymmetric variant of a previously reported hydroamination reaction mediated by an Ir(III)−based photoredox catalyst, a dialkyl phosphate base, and an aryl thiol H−atom donor under visible light irradiation (Fig. 2A) (18). We found that the use of chiral BINOL phosphates as Bronsted bases was effective in this chemistry and resulted in a modest amount of enantioselectivity. However, a course studies unexpectedly revealed that the urea product 1b was initially formed as a racemate but became slightly optically enriched during the course of the reaction. In subsequent control reactions, we subjected racemic 1b to the reaction conditions and observed significant optical enrichment with near-complete material recovery, indicating that a light-driven deracemization pathway was operative. Similarly, when enantiopure (S)−1b was subjected to identical conditions using an achiral phosphate base, racemization of the stereogenic C−H bond was observed.

On the basis of this discovery, we postulated that the excited state of the Ir photocatalyst reversibly oxidizes the racemic urea substrate to form a mixture of transient (and enantio- meric) arene radical cations (Fig. 2B). The stereogenic C−H bond in the resulting substrate radical cation is markedly acidified and can be deprotonated by the phosphate base to form a neutral α-amino radical (19, 20). However, as both the radical cation and the Bronsted base

1Department of Chemistry, Princeton University, Princeton, NJ 08544, USA. 2Department of Chemistry, Yale University, New Haven, CT 06520, USA.

*Corresponding author. Email: rknowles@princeton.edu (R.R.K.); scott.miller@yale.edu (S.J.M.)
are chiral, this process serves to kinetically resolve the enantiomeric radical cations, with the fast-reacting (R)-enantiomer undergoing proton transfer while the slower-reacting (S)-enantiomer is converted back to the urea starting material by charge recombination with the reduced Ir(II) state of the photocatalyst. In this way, the reaction becomes enriched in the slower-reacting (S)-enantiomer. After proton transfer, the resulting α-amino radical intermediate can be reduced by H-atom transfer with the achiral aryl thiol cocatalyst to return the closed-shell urea in a nonselective process. A proton-coupled electron transfer (PCET) event among the reduced Ir(II) complex, thiyl, and the protonated base could then return the active forms of all three catalysts.

If operational, this mechanism suggests that the two steps that create and destroy stereoselectivity in these reactions—proton transfer and H-atom transfer—operate independently of one another and are mediated by two independent catalysts. Accordingly, when both the proton-transfer and H-atom transfer catalysts are chiral, both elementary steps can potentially be rendered enantioselective, resulting in an unusual circumstance in which the observed stereoselectivity should be the product of the enantiomeric ratios for each of the two enantioselective steps (er \text{obs} = er_{PT} \cdot er_{HAT}).

To evaluate this hypothesis, we elected to further study the deracemization of N-aryl-substituted cyclic ureas. Preliminary studies demonstrated that a pendant amide H-bond donor group is crucial for obtaining high selectivities in the enantioselective deprotonation step using the chiral phosphate bases (vide infra), prompting us to evaluate the deracemization of urea 2a as a model substrate (Fig. 3A). A small collection of BINOL-derived phosphate bases were explored with [Ir(dF(CF3)ppy)2(bpy)]PF6 (Ir) and an achiral thiophenol H-atom donor catalyst in tetrahydrofuran under irradiation with blue light-emitting diodes (LEDs) at room temperature. Although a BINOL-derived phosphate with 1-adamantyl groups (3a) gave essentially racemic product, an analogous catalyst bearing phenyl groups gave an improved er of 69:31 (3b) (entries 1 and 2). We hypothesized...
that there might be a stabilizing π-cation interaction between the oxidized substrate radical cation and the aryl substituents of chiral phosphate, prompting us to examine catalysts bearing more expansive aryl substituents (entries 3 to 5). The addition of molecular sieves further improved the selectivity to 86:14 er (entry 6). We then investigated cysteine-based oligopeptides as enantioselective H-atom-transfer catalysts. Although cysteine residues are known to mediate H-atom–transfer reactions in a variety of biological contexts, they have only occasionally been explored for use in small-molecule asymmetric catalysis, and their study for catalytic asymmetric H-atom transfer (HAT).

We then investigated cysteine-based oligopeptides as enantioselective H-atom-transfer catalysts. Although cysteine residues are known to mediate H-atom–transfer reactions in a variety of biological contexts, they have only occasionally been explored for use in small-molecule asymmetric catalysis, and their study for catalytic asymmetric H-atom transfer is not yet reported (22–25). A small library of tetrapeptide disulfides (which are in equilibrium with their free thiol form under the reaction conditions) were initially screened with a catalytic amount of achiral tetrabutylammonium diphenylphosphinate base, providing a lead result of 68:32 er with peptide 4b (entries 7 to 9). The corresponding thiol 4c gave a slightly improved er of 70:30 (entry 10). Variations at the i+2 and i+3 positions demonstrated that cysteine-embedded tetrapeptide with phenylglycine as the C-terminal residue showed improved yield, leading to 4e with 78:22 er and good yield (entries 11 and 12). The use of molecular sieves slightly improved the selectivity to 79:21 er (entry 13). With optimized chiral phosphate 3e and chiral thiol 4e in hand, our mechanistic hypothesis predicted that reactions mediated by the stereochemically matched pair of catalysts should result in an observed er of 96:4 (86:14 • 79:21 = 96:4) (26).

With these optimized deracemization conditions in hand, we found that a variety of structural changes in the urea substrate could be accommodated (Fig. 3B). Alkyl substituents of varying steric demand could be tolerated at the stereogenic carbon with uniformly good levels of enantioselectivity (2a to 2e). Substitution of the distal urea nitrogen with the free N–H amide, benzyl, or isopropyl groups also provided the desired deracemized products with high levels of stereoselectivity (2f to 2h). Structural changes on the acyclic amide moiety were also tolerated, as was a benzamide derivative (2i to 2n). However, an N,N-dimethyl amide variant demonstrated a noticeable decrease in the er (2o). Upon reaching the steady-state level of optical enrichment, all of the substrates studied here (2a to 2o) can be recovered in nearly quantitative yield.

Numerous observations are consistent with the mechanistic proposal outlined above (Fig. 4A). Steady-state Stern–Volmer quenching studies and time-correlated single-photon counting experiments revealed that electron transfer between the urea substrate (E1/2 = 0.91 V versus Fc+/Fc in MeCN; fig. S1) and the excited state of Ir (*Eg2 = 0.94 V versus Fc+/Fc in MeCN) (28) is kinetically rapid (the rate constants for electron transfer events [kET]) for (R)-2a and (S)-2a are 9.0(8) × 108 M−1s−1.

Fig. 2. Discovery of light-driven deracemization (A) Initial observations. Ir is racemic in all experiments. (B) Postulated mechanism.
The subsequent proton transfer, H-atom transfer, and PCET steps are also thermodynamically favorable (fig. S3). These findings reinforce the notion that, as all the elementary steps proceeding from *Ir are exergonic, the observed product distributions are kinetically controlled and fully decoupled from the energetic difference between the racemic starting material and the optically enriched product. The steady-state er is achieved within only 1.5 hours, and no degradation of either yield or er was observed upon extended reaction times, suggesting that the system establishes a stable nonequilibrium state (Fig. 4B). The quantum yield of this process was measured to be 4.8(3)% (fig. S5) (29). We also found that catalyst-controlled stereoconversion from optically pure (S)-2a to (R)-2a could be achieved under the optimized condition with excellent er and reaction efficiency (Fig. 4C).

To investigate the generality of proposed synergistic stereoselectivity between the two chiral catalysts, the enantioselectivity of each catalyst was explored individually for a selected set of substrates (Table 1). First, substrates were subjected to deracemization with chiral base 3e and thiophenol as an achiral H-atom transfer catalyst, providing a measure of the selectivity in the H-atom transfer step. Although substitution of the urea backbone led to small variations, the enantioselectivity in the HAT step is similar for all substrates with or without the pendant amide group. When the stereochemically matched forms of both chiral catalysts were used [e.g., the phosphate selectively ablates the (S) enantiomer and the thiol preferentially decreased the er (entries 11 and 12), which supports a potential interaction between the distal amide N–H bond and the phosphate base during the asymmetric proton-transfer step. The same substrates were then deracemized with cysteine-embedded peptide 4e and tetrabutylammonium diphenylphosphate as an achiral Brønsted base catalyst, providing a measure of the selectivity in the H-atom transfer step. Although substitution of the urea backbone led to small variations, the enantioselectivity in the HAT step is similar for all substrates with or without the pendant amide group. When the stereochemically matched forms of both chiral catalysts were used [e.g., the phosphate selectively ablates the (S) enantiomer and the thiol preferentially...
**Fig. 4. Preliminary mechanistic studies.** (A) Free-energy profile of light-driven deracemization from rac-2a to (R)-2a. Details are included in the supplementary materials (fig. S3). (B) Time-course studies for deracemization of rac-2a to (R)-2a. (C) Selective stereoinversion of (S)-2a to (R)-2a.

**Table 1. Studies on synergistic enantioselectivity of each chiral catalyst and synergistic stereoselectivity.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Experimental er (erPT), chiral base only</th>
<th>Experimental er (erHAT), chiral thiol only</th>
<th>Predicted er (erPT × erHAT)</th>
<th>Experimental er (erobs), chiral base + chiral thiol</th>
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<tbody>
<tr>
<td>1</td>
<td>2a</td>
<td>86:14</td>
<td>79:21</td>
<td>96:4</td>
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<tr>
<td>2</td>
<td>2a</td>
<td>86:14</td>
<td>21:79 (ent-4e)</td>
<td>62:38</td>
<td>53:47</td>
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<tr>
<td>3</td>
<td>2b</td>
<td>77:23</td>
<td>85:15</td>
<td>95:5</td>
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<tr>
<td>4</td>
<td>2d</td>
<td>80:20</td>
<td>76:24</td>
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<tr>
<td>7</td>
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<td>76:24</td>
<td>74:26</td>
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</table>

Reaction conditions: 2 mol % Ir, 10 mol % 3e, 10 mol % PhSH, MS, THF, blue LEDs, 25°C, 4 hours (column 3). 2 mol % Ir, 10 mol % NBu4+(PhO)2P(O)O−, 10 mol % 4e (or ent-4e), 50 mol % Ph3CH, MS, THF, blue LEDs, 25°C, 4 hours (column 6). The reaction yields in all cases are >90%. Detailed experimental results are included in the supplementary materials (table S7). erPT, proton-transfer er; erHAT, H-atom–transfer er; erobs, observed er.
reforms the (R) enantiomer], the resultant enantiomer matched the predicted value closely matched the predicted value in all cases. Similarly, the combination of mismatched thiol ent-4c with base 3e provided diminished de for 2a, indicating conflicting stereochemical preferences wherein the deprotonation and HAT events both favor the (S) enantiomer (entry 2). These observations are consistent with the proposed mechanism and highlight the synergistic role of the two chiral catalysts in this transformation.

We anticipate that the mechanistic features underlying this work are general and may be adapted to a wide variety of other light-driven transformations to provide nonequilibrium product distributions in a catalyst-controlled fashion.

REFERENCES AND NOTES

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Charging through the looking glass
Asymmetric catalysis is a commonly applied technique to prepare just one of two mirror-image products in a chemical reaction. But what if you already have the compound you want, stuck in a mixture of left- and right-handed enantiomers? Shin et al. now show that light-induced electron transfer can trigger a favorable succession of proton and hydrogen-atom transfer steps, both of which are susceptible to biasing by catalysts, to preferentially convert a mixture of cyclic urea enantiomers into just one (see the Perspective by Wendlandt).

Science, this issue p. 364; see also p. 304

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