

ORGANIC CHEMISTRY

Stereochemical editing logic powered by the epimerization of unactivated tertiary stereocenters

Yu-An Zhang[†], Vignesh Palani[†], Alexander E. Seim, Yong Wang, Kathleen J. Wang, Alison E. Wendlandt*

The stereoselective synthesis of complex targets requires the precise orchestration of chemical transformations that simultaneously establish the connectivity and spatial orientation of desired bonds. In this work, we describe a complementary paradigm for the synthesis of chiral molecules and their isomers, which tunes the three-dimensional structure of a molecule at a late stage. Key to the success of this strategy is the development of a mild and highly general photocatalytic method composed of decatungstate polyanion and disulfide cocatalysts, which enable the interconversion of unactivated tertiary stereogenic centers that were previously configurationally fixed. We showcase the versatility of this method—and the implementation of stereoediting logic—by the rapid construction of chiral scaffolds that would be challenging to access using existing tools and by the late-stage stereoediting of complex targets.

Stereochemistry plays a defining role in the chemical and physical properties of chiral molecules (*1*). Specific stereoisomers (enantiomers and diastereomers) frequently exhibit distinct interactions with chiral receptors (e.g., enzymes and proteins), giving rise to critical pharmacokinetic and pharmacodynamic differences (Fig. 1A) (2–4). Equally notable changes in the chemical and physical characteristics of diastereomers have been leveraged in the design of catalysts and functional materials (5, 6). However, because the influences of altering a single stereocenter within a complex molecule (and within bimolecular interactions) are rarely intuitive, such isomer effects are typically discovered empirically. Comprehensive synthetic access to the full complement of stereoisomers is thus essential for structure-function studies seeking to assess desirable properties of chiral organic molecules.

The construction of stereochemically well-defined complex organic molecules remains a central challenge in organic synthesis and catalysis. Stereoselective synthetic sequences often revolve around a small number of highly general and highly selective chemical reactions or seek to leverage enantiopure, chiral pool-derived starting materials to reliably establish the desired stereocenter(s). Consequently, selective access to some stereocenters and stereochemical patterns remains more challenging than access to others, and access to distinct stereoisomers frequently requires *de novo* synthesis of each target—often from specific starting materials or through complementary synthetic strategies. For example, a highly selective reduction of drimene (**1**) to 8 α (H)-drimane (**2a**) was achieved using conventional hydrogenation conditions, whereas access to the 8 β (H) epimer (**2b**) from the same interme-

diate required route redesign through an alternative, multistep sequence (Fig. 1B) (7).

A deceptively simple alternative would be the direct editing of chiral products to adjust their relative stereochemistry in a late-stage setting. In contrast to conventional stereoselective synthetic strategies, this stereochemical editing approach would enable a fundamentally different synthetic logic, allowing bond connectivity to be decoupled from the intrinsic stereoselectivity of the bond formation step(s). In principle, stereoediting logic would do several things: (i) enable challenging chiral target molecules to be prepared through unconventional and/or unselective retrons, (ii) provide a strategy to override strong substrate control effects within complex settings, and (iii) present new opportunities for late-stage diversification. Here, we report the realization of these goals, enabled by the identification of a highly general, broadly functional group-tolerant catalytic method to interconvert unactivated methine stereogenic centers.

The revision of stereogenic centers is routinely integrated into synthetic design but frequently requires multiple chemical steps and the use of stoichiometric redox or acid-base pairs. The direct, catalytic interconversion of stereocenters featuring acidic C–H bonds (e.g., α -carbonyl) is well established, and recent efforts have identified innovative strategies to control isomer distributions (8, 9). We and others have sought to expand the scope of stereoediting tools to allow for the revision of conventionally static stereocenters, leveraging radical reactions that selectively target homolytically weak C–H bonds adjacent to secondary alcohols (10–14) or other heteroatoms (15–18) and transiently electronically activated positions (19, 20). In spite of these substantial advances, the selective interconversion of stereocenters having strong, hydridic C–H bonds—such as unactivated tertiary methines—remains an unsolved problem. Lim-

ited reaction scope, poor functional group compatibility, long reaction times, use of super-stoichiometric reagent, and/or complex side-product profiles limit the application of existing tools using photoexcited ketone (21), HgBr₂ (22), azidyl radical (23), and transition metal-based (24, 25) reagents. The lack of general and efficient methods targeting unactivated tertiary stereocenters has limited the broad exploration of stereoediting logic in organic synthesis (Fig. 1C).

We selected *cis*-cyclobutane **3a**, which does not undergo efficient isomerization to the trans isomer using established conditions, as a model substrate to explore the epimerization of unactivated methine stereocenters. Combs-Walker and Hill have previously reported the epimerization of *cis*-decalin to *trans*-decalin using a decatungstate (DT) polyanion photocatalyst; however, the formation of **3b** was prohibitively slow using these conditions (Fig. 2B, black trace) (26). On the basis of our experience with cocatalytic systems composed of distinct H atom acceptor and donor reagents, we examined the effect of thiol and disulfide additives on isomerization efficiency (see the supplementary materials for full optimization details). Enhanced reaction rate was observed in the presence of latent H atom donors, such as bis(4-chlorophenyl) disulfide (Fig. 2B, red trace) (12, 13, 27, 28). Optimal reaction conditions using catalytic quantities of DT, disulfide, and base in MeCN/H₂O reached a final equilibrium after 4 hours at room temperature under 390-nm light-emitting diode (LED) irradiation (Fig. 2B, blue trace), allowing for the isolation of **3b** in 82% yield.

We applied these conditions to a suite of substrates featuring representative tertiary stereogenic centers to systematically assess the reactivity and selectivity of the method across diverse synthetic settings. In addition to 1,2-disubstituted cyclobutane **3a**, cyclopentane and cyclohexane congeners also react to form trans isomers **4b** and **5b**. We evaluated the effect of substitution pattern using a series of dimethylcyclohexanes (**6a** to **8a**) as substrates: *cis*-1,2- and *cis*-1,4-dimethylcyclohexanes reacted to form the corresponding trans isomers, whereas *trans*-1,3-dimethylcyclohexane reacted to preferentially form the cis isomer.

We next assessed substituent effects using a series of 1-methylcyclohexanols bearing 4-methyl- (**9a**), 4-*n*-pentyl- (**10a**), 4-isopropyl- (**11a**), 4-phenyl- (**12a**), and 4-*tert*-butyl- (**13a**) substituents. This series revealed the feasibility of isomerizing methine stereocenters bearing larger substituents, such as phenyl and isopropyl groups, although the reaction of **13a** (bearing a *tert*-butyl substituent) was prohibitively slow (10% yield after 24 hours). Based on the preferential isomerization of substrates **3a** to **8a** to form lower-energy isomers, we initially anticipated this series to strongly favor

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, MA 02139, USA.

*Corresponding author. Email: awendlan@mit.edu

[†]These authors contributed equally to this work.

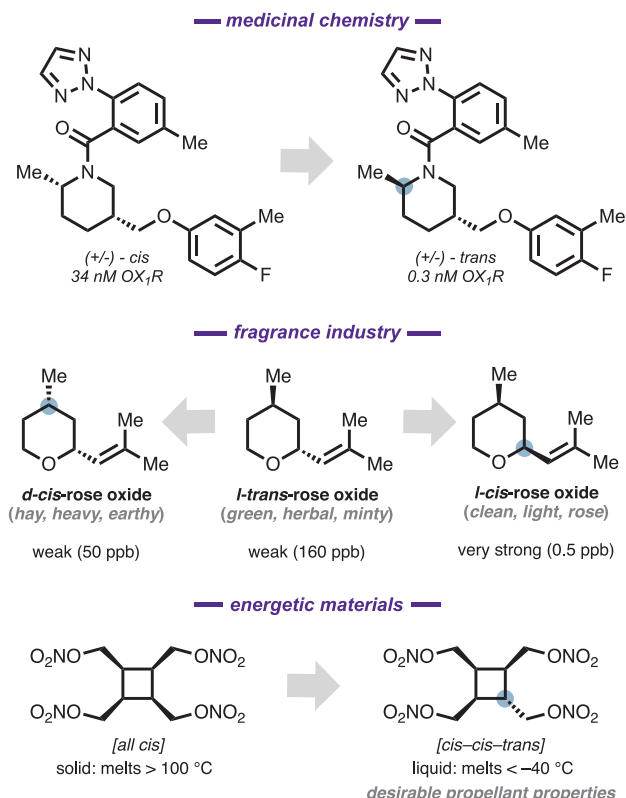
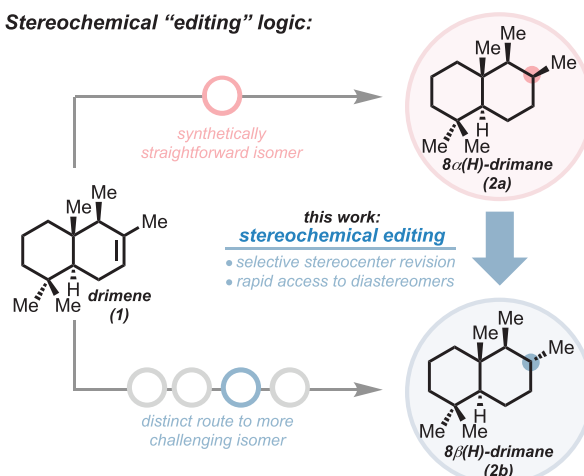
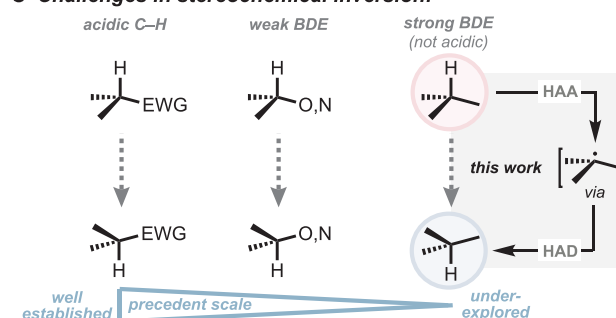
A Importance of relative stereochemistry in organic chemistry:**B Stereochemical “editing” logic:****C Challenges in stereochemical inversion:**

Fig. 1. Overview of stereochemical editing logic. (A) Diastereomers have distinct chemical and physical properties. ppb, parts per billion. (B) Illustration of a stereochemical inversion strategy in multistep synthesis. (C) Established and underexplored areas for stereoediting tools (3, 4, 5). BDE, bond-dissociation energy; EWG, electron withdrawing group; HAA, H atom abstraction; HAD, H atom donation.

formation of the corresponding trans isomers. However, final equilibrium product ratios up to 1:1 trans:cis were obtained starting from either cis- or trans-configured isomers, allowing for the isolation of higher-energy cis isomers **9b** to **12b** in 24 to 47% yields starting from the corresponding trans starting materials **9a** to **12a**. A similarly contra-thermodynamic final product ratio was obtained from the reaction of *trans*-1,2-methylaminocyclohexane **14a**, which equilibrated to a 2:1 cis:trans mixture, despite a 2.1 kcal/mol calculated thermochemical bias favoring the trans isomer (see the supplementary materials). Collectively, these data support the formation of a stereochemical photostationary state distinct from the thermodynamic product ratio, although the lower-energy isomer is frequently preferentially formed.

The reaction of **14a** was also carried out under deuterium isotope exchange conditions to identify the position(s) of C–H bond scission. No D incorporation was detected adjacent to the –NH₂Boc group (see the supplementary materials), implicating selective epimerization of the electron-rich α -methyl C–H bond, where D incorporation was observed. Similarly, the reaction of isomethone (+)-**15a** led to the formation of (+)-menthone **15b** in 78% yield;

again, no D incorporation was detected at the electronically deactivated α -carbonyl methine. The selective isomerization of electron-rich C–H bonds in the presence of electronically deactivated and/or more sterically encumbered positions also allows the isomerization of (+)-isomenthol derivatives **16a** and **17a** to react to form (+)-menthyl acetate congeners (**16b** and **17b**) without racemization. Finally, cis-fused bicyclic substrates, including decalin (**18a** and **19a**) and lactam and lactone congeners (**20a** to **22a**) reacted to form the corresponding trans-fused rings. These findings were readily translated into more complex polycyclic systems, allowing for the conversion of cis-fused AB ring of steroid (+)-**23a** to trans-fused (+)-**23b**.

We next sought to explore the strategic implications of this DT-mediated stereochemical editing method in more challenging synthetic settings. We focused our efforts on a series of retron-based strategies to explore the integration of this method into (retro)synthetic logic.

Expanding stereochemical outcomes accessible using versatile stereospecific reactions

Pericyclic reactions—such as the Diels–Alder (DA) reaction—are powerful complexity-generating

transformations that have been broadly implemented in the synthesis of polysubstituted cyclic small molecule and natural product targets. Like all stereospecific reactions, the DA reaction offers fixed stereochemical outcomes dictated by the configuration of the starting diene and dienophile isomers. In cases where the desired product configuration is mismatched with the intrinsic reaction specificity—or where the requisite well-defined diene or dienophile isomers are challenging to access—these intrinsic features of the DA reaction restrict its implementation.

We envisioned that the combination of DA and stereoediting reactions might expand the scope of stereochemical outcomes accessible using DA logic to provide rapid access to otherwise challenging scaffolds (Fig. 3). We first examined a series of DA reactions between cyclohexenones and 1,3-butadiene derivatives, which conventionally exclusively afford products with *cis*-decalin skeletons (Fig. 3A). Efforts to construct α -substituted *trans*-decalin products through a similar DA retron have met with limited success, requiring prefunctionalized dienophiles and multiple posttransformation steps (29). By contrast, our stereoediting method transforms the cis-configured adducts to

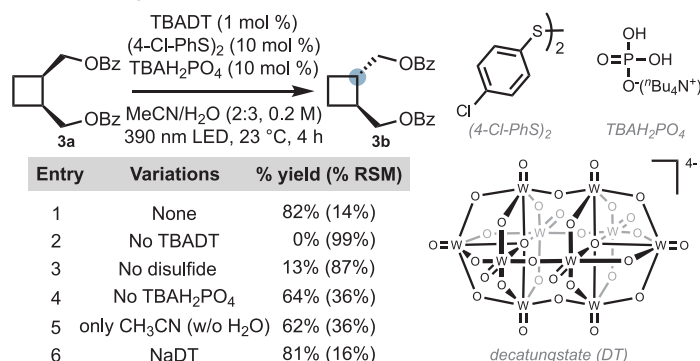
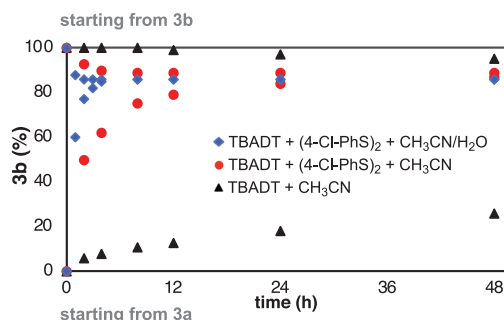
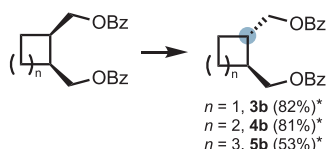
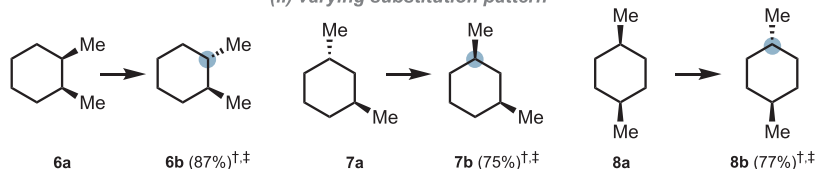
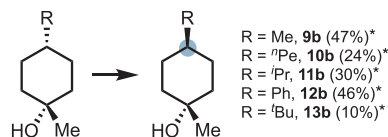
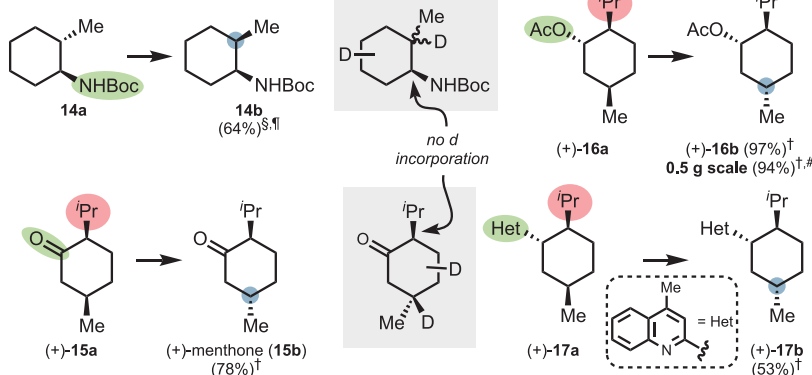
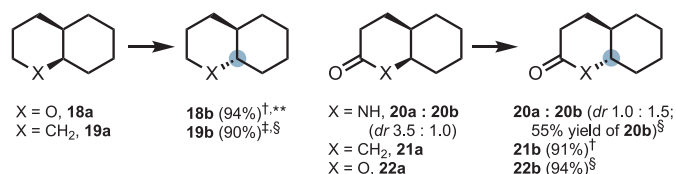
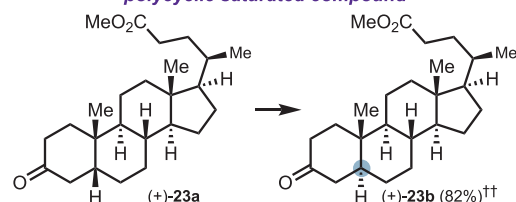
A Reaction optimization**B Timecourse data****C Preliminary synthetic scope: monocyclic saturated compounds****(i) ring strain effects****(ii) varying substitution pattern****(iii) substituent effects****(iv) site-selective HAA/HAD****fused bicyclic saturated compounds****polycyclic saturated compound**

Fig. 2. Reaction optimization and preliminary substrate scope. (A) Reaction optimization. RSM, recovered starting material; dr, diastereomeric ratio. (B) Time-course data highlighting difference in rate of the reaction. (C) Preliminary synthetic scope. Reactions were performed on 0.1- to 0.5-mmol scale with 1 mol % DT with either N^(t)Bu₄⁺ counterions (TBADT) or Na⁺ counterions (NaDT), 10 mol % (4-ClPhS)₂, and 10 mol % TBAH₂PO₄ or NaH₂PO₄•H₂O under 390-nm LED irradiation at 23 °C in MeCN (0.2 M) or MeCN/H₂O (v/v 4:1 or 2:3, 0.2 M) for 24 hours. Isolated yields are the average of two runs. *Reaction was performed with 1 mol % TBADT, 10 mol % (4-ClPhS)₂, and 10 mol % TBAH₂PO₄ in MeCN/H₂O (v/v 2:3). †Reaction was performed with 1 mol % TBADT, 10 mol % (4-ClPhS)₂, and 10 mol %

and 10 mol % TBAH₂PO₄ in MeCN/H₂O (v/v 4:1). ‡Yield was determined by gas chromatography (GC) analysis with nitrobenzene as an external standard. §Reaction was performed with 1 mol % TBADT, 10 mol % (4-ClPhS)₂, and 10 mol % TBAH₂PO₄ in MeCN. ¶No D incorporation was observed adjacent to the carbamate group. See the supplementary materials for full experimental details. #Reaction was performed on 2.5-mmol scale (single run). **Given yield is the proton nuclear magnetic resonance (¹H NMR) yield determined with nitrobenzene as an external standard. The isolated yield was 54% because of the volatility of **18b**. ††Reaction was performed with 1 mol % NaDT, 10 mol % (4-ClPhS)₂, and 10 mol % NaH₂PO₄•H₂O in MeCN.

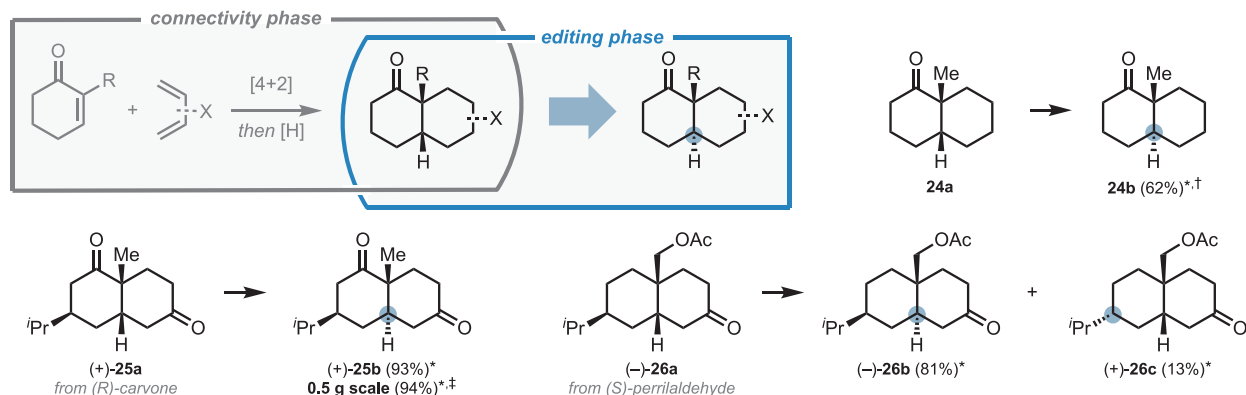
trans isomers in a single step. For example, bicyclic ketone **24a**, which was prepared readily from 2-methyl cyclohexanone and 1,3-butadiene, was isomerized into *trans*-decalin **24b** in 62% yield along with 14% recovered **24a** after

24 hours. (After 48 hours, no remaining **24a** was detected; however, the yield of desired **24b** was reduced slightly to 57%. See the supplementary materials.) Dione (+)-**25a**—derived from (*R*)-carvone—reacted to form

(+)-**25b** in >90% yield on a 0.5-g scale. (S)-Perrilaldehyde-derived ketone (–)-**26a** was converted to (–)-**26b** in 81% yield along with the minor epimer (+)-**26c** in 13% yield. These examples showcase the utility of stereoeediting

Expanding stereospecific reaction outcomes: Diels-Alder retron

A Inversion of stereocenters defined by dienophile component



B Inversion of stereocenters defined by diene component

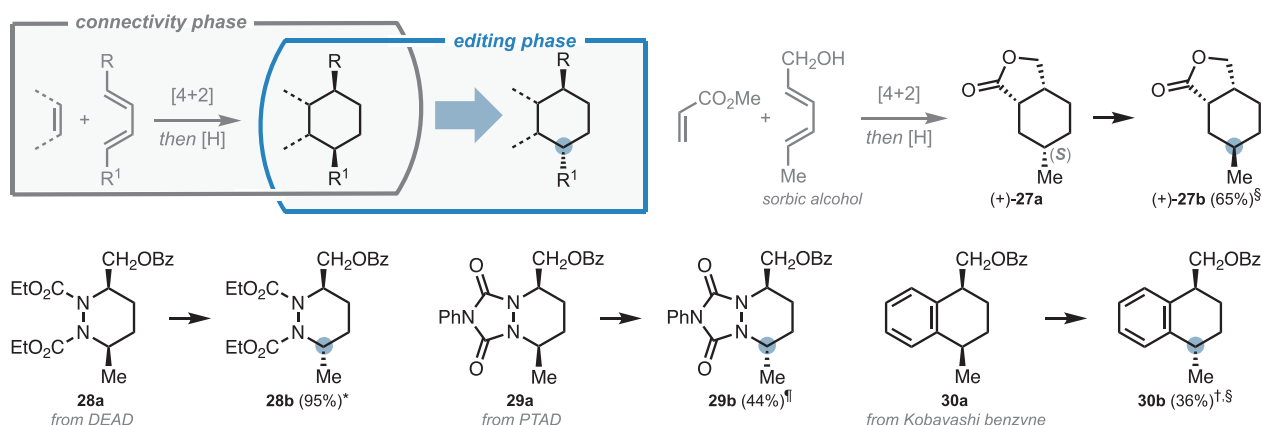


Fig. 3. Strategic application of stereocenter editing to DA cycloadducts.

(A) Stereochemical configuration dictated by the parent dienophile conformer. (B) Stereochemical configuration dictated by the parent diene conformer. Reactions were performed on 0.1- to 0.5-mmol scale with 1 mol % DT with either $N^t\text{Bu}_4^+$ counterions (TBADT) or Na^+ counterions (NaDT), 10 mol % (4-CIPhS)₂, and 10 mol % TBAH_2PO_4 or $\text{NaH}_2\text{PO}_4 \cdot \text{H}_2\text{O}$ under 390-nm LED irradiation at 23°C in MeCN (0.2 M) or MeCN/H₂O (v/v 4:1 or 2:3, 0.2 M) for 24 hours. Isolated yields are the average of two runs. See the

supplementary materials for full experimental details. *Reaction was performed with 1 mol % TBADT, 10 mol % (4-CIPhS)₂, and 10 mol % TBAH_2PO_4 in MeCN/H₂O (v/v 2:3). †Number in parentheses denotes ¹H NMR yield with nitrobenzene as an external standard. ‡Reaction was performed on 2.3-mmol scale (single run). §Reaction was performed with 1 mol % TBADT, 10 mol % (4-CIPhS)₂, and 10 mol % TBAH_2PO_4 in MeCN/H₂O (v/v 4:1). ¶Reaction was performed with 1 mol % TBADT, 10 mol % (4-CIPhS)₂, and 10 mol % TBAH_2PO_4 in MeCN.

methods in bridging DA logic to access *trans*-decalin synthons and further provide a strategy for efficient entry into a previously undisclosed array of chiral building blocks.

We next applied this logic to a different type of DA scaffold accessed using 1,4-disubstituted dienes (Fig. 3B). These cycloadditions produce two exocyclic stereogenic centers with configurations defined by the geometry of the diene component. For example, the reaction of sorbic alcohol [(2*E*,4*E*)-hexa-2,4-dien-1-ol] with methyl acrylate forms 1,4-*cis* lactone (+)-27a selectively. When (+)-27a was subjected to stereoediting conditions, methyl epimer (+)-27b was obtained in 65% yield. A direct DA approach to form 1,4-*trans* adducts, such as (+)-27b, would require the use of the corresponding (*E*,*Z*) dienes, which are generally regarded as poorer substrates for DA reaction; in this specific

case, [(2*E*,4*Z*)-hexa-2,4-dien-1-ol] is also substantially less accessible than the sorbate-derived alcohol. Notably, enantioenriched (+)-27a was converted into (+)-27b without racemization, revealing that no epimerization occurred at the bicyclic juncture. DA adducts (28a to 30a) that arose from various dienophiles, such as azodicarboxylate, triazole-dione, and benzyne, all reacted to give the corresponding epimerized products (28b to 30b) in synthetically useful yields, illustrating the broad functional group compatibility of the method and the broad applicability of this approach.

Overtuning substrate-controlled selectivities

The presence of an existing stereogenic center can present substantial challenges for the selective formation of additional stereocenters

in a molecule. In cases strongly governed by so-called substrate control, efforts to achieve complementary stereochemical outcomes through tuning the reagent or catalyst may meet with limited success. We explored opportunities to use stereoediting to upgrade or overturn substrate-controlled selectivities, using representative examples obtained through the hydrogenation retron (Fig. 4A). For example, *cis*-methylproline (–)-31a is obtained selectively (6:1 31a:31b) from the corresponding precursor *exo*-methylene using a conventional hydrogenation protocol. The reaction of this mixture under epimerization conditions resulted in the isolation of *cis*-epimer (–)-31b in 57% yield, with no detectable erosion of enantiomeric excess (see the supplementary materials). Treatment of (–)-31a under base-mediated epimerization conditions would, in principle, afford

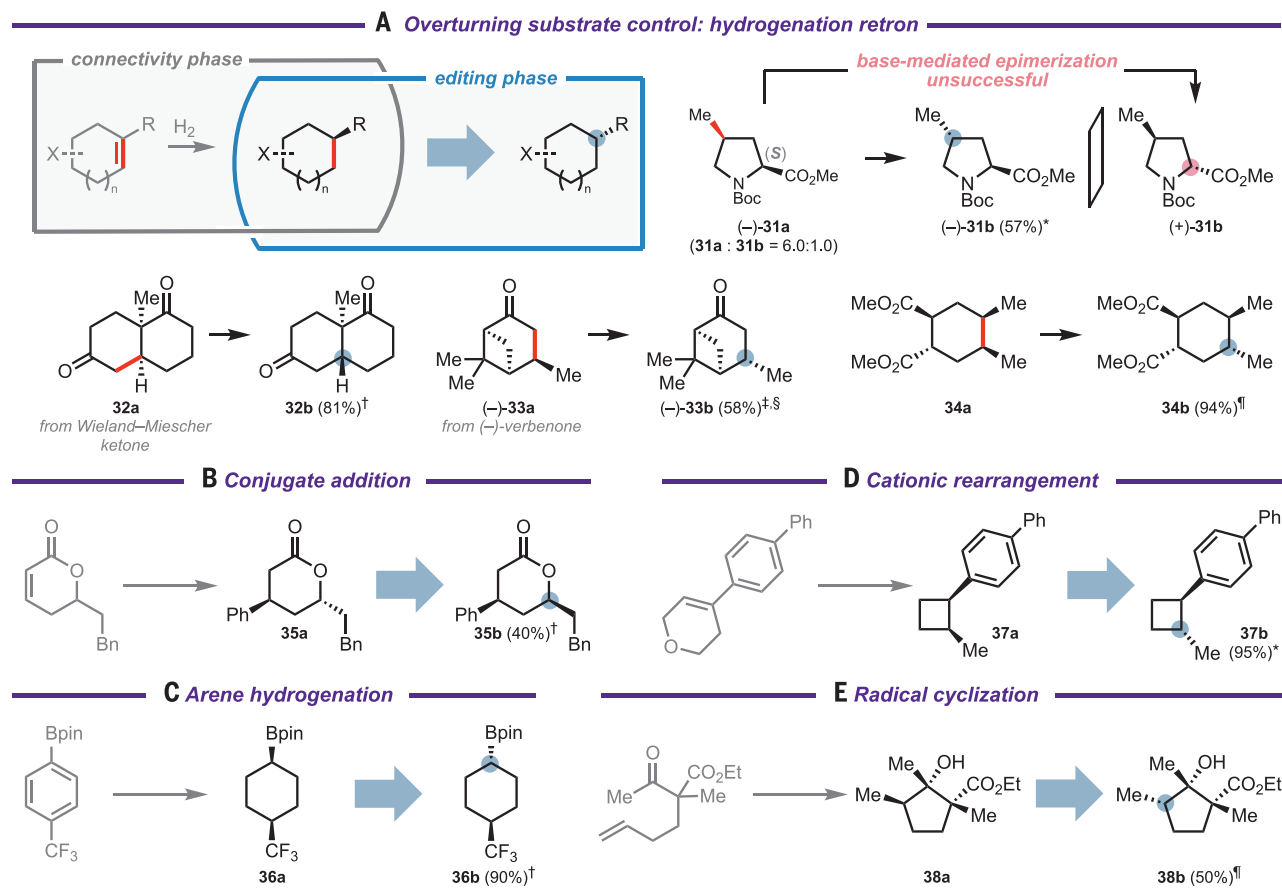


Fig. 4. Strategic application of stereocenter editing in diverse synthetic settings. (A to E) Stereocenter editing of hydrogenation (A), conjugate addition (B), arene hydrogenation (C), cationic rearrangement (D), and radical cyclization products (E). Reactions were performed on 0.2- to 0.5-mmol scale with 1 mol % DT with either $N^t\text{Bu}_4^+$ counterions (TBADT) or Na^+ counterions (NaDT), 10 mol % (4-ClPhS)₂, and 10 mol % TBAH_2PO_4 or $\text{NaH}_2\text{PO}_4 \cdot \text{H}_2\text{O}$ under 390-nm LED irradiation at 23°C in MeCN (0.2 M) or MeCN/H₂O (v/v 4:1 or 2:3, 0.2 M) for 24 hours. Isolated yields are the average of two runs. See the supplementary

materials for full experimental details. *Reaction was performed with 1 mol % TBADT, 10 mol % (4-ClPhS)₂, and 10 mol % TBAH_2PO_4 in MeCN. †Reaction was performed with 1 mol % NaDT, 10 mol % (4-ClPhS)₂, and 10 mol % $\text{NaH}_2\text{PO}_4 \cdot \text{H}_2\text{O}$ in MeCN. ‡Reaction was performed with 1 mol % TBADT, 10 mol % (4-ClPhS)₂, and 10 mol % TBAH_2PO_4 in MeCN/H₂O (v/v 2:3). §Number in parentheses denotes ¹H NMR yield with nitrobenzene as an external standard. ¶Reaction was performed with 1 mol % TBADT, 10 mol % (4-ClPhS)₂, and 10 mol % TBAH_2PO_4 in MeCN/H₂O (v/v 4:1).

(+)-**31b**; however, our efforts to promote this isomerization were unsuccessful, illustrating the difficulty of obtaining the trans isomer in this system while also showcasing the complementary chemoselectivity preferences of the DT-based conditions. Likewise, hydrogenation of Wieland-Miescher ketone and (–)-verbenone followed by epimerization afford the corresponding trans isomers **32b** and (–)-**33b** in 81 and 58% yields, respectively. Diester **34a**—obtained from syn-selective hydrogenation of the precursor alkene—also reacted under DT conditions to form trans isomer **34b** in 94% yield.

This stereocenter editing approach was also applied to a suite of other (retro)synthetic scenarios. A 1,4-conjugate addition forms trans-configured lactone **35a**, which reacted under epimerization conditions to form cis isomer **35b** in 40% yield (Fig. 4B). Exhaustive reduction of 1,4-disubstituted arene formed *cis*-boronate ester

36a; reaction of this substrate under standard conditions resulted in 90% yield of trans isomer **36b** (Fig. 4C). Cationic ring contraction to form **37a** (Fig. 4D) and radical cyclization to form **38a** (Fig. 4E) both occurred with excellent levels of diastereoselectivity. In both cases, epimerization under standard conditions resulted in the formation of the more synthetically intractable trans diastereomers **37b** (90% yield) and **38b** (50% yield). The latter two examples illustrate the potential application of epimerization for the revision of stereocenters generated in reactions that proceed through highly reactive intermediates that are intrinsically challenging to control.

Tools for late-stage diversification and to expand the chiral pool

In most synthetic applications, high yields and selectivities for a single reaction product are

desired. However, in some cases, access to several different isomers may be advantageous—for example, when the starting materials are abundantly available and where both products are potentially useful. Likewise, in other contexts, the formation of even small quantities of an isomer may be valuable, such as to access—and validate—a diastereomer that is extremely challenging to make so as to justify a targeted synthesis campaign.

We thus sought to explore whether a stereocenter editing approach could be leveraged to provide access to unnatural antipodes of a desired target starting from abundant, but incorrectly configured, chiral pool precursors. We obtained enantiopure 3-methylcyclohexanone from the naturally occurring (*R*)-pulegone through a retro-aldol reaction (Fig. 5A). A subsequent Reformatsky reaction resulted in the formation of a 1.3:1 mixture of diastereomers (–)-**39a** and (–)-**40a** as single enantiomers,

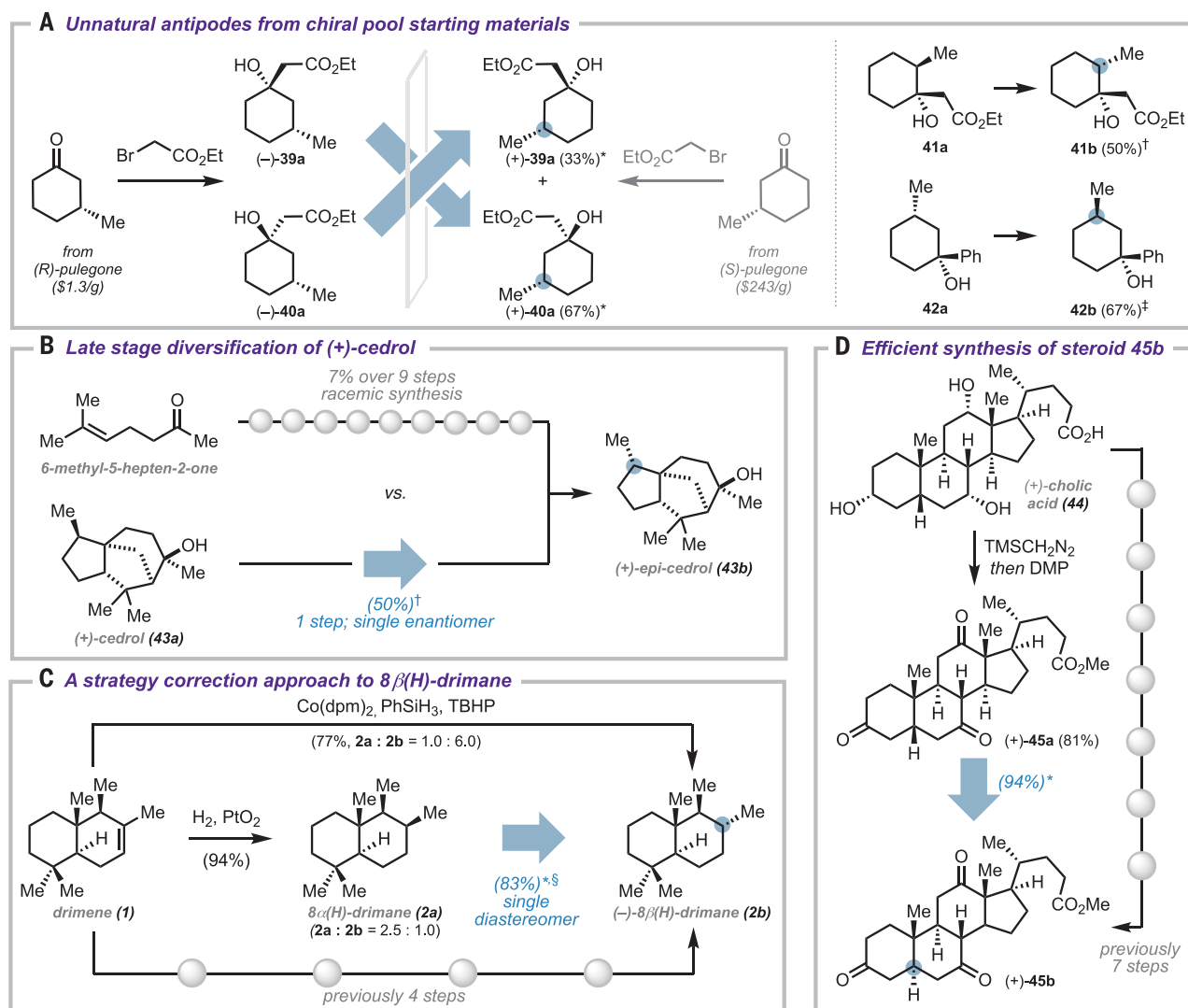


Fig. 5. Integration of stereocenter editing tools in late-stage and total synthesis applications. (A) Access to unnatural antipodes from chiral pool starting materials. (B) Semisynthetic approach to access (+)-*epi*-cedrol. (C) A strategy correction approach to 8β(H)-drimane. (D) Synthesis of steroid **45b**. Reactions were performed on 0.2- to 0.5-mmol scale with 1 mol % DT with either N^{(t)Bu}₄⁺ counterions (TBADT) or Na⁺ counterions (NaDT), 10 mol % (4-CiPhS)₂, and 10 mol % TBAH₂PO₄ or NaH₂PO₄•H₂O under 390-nm LED irradiation at 23°C in MeCN (0.2 M)

or MeCN/H₂O (v/v 4:1 or 2:3, 0.2 M) for 24 hours. Isolated yields are the average of two runs. See the supplementary materials for full experimental details. *Reaction was performed with 1 mol % NaDT, 10 mol % (4-CiPhS)₂, and 10 mol % NaH₂PO₄•H₂O in MeCN. †Reaction was performed with 1 mol % TBADT, 10 mol % (4-CiPhS)₂, and 10 mol % TBAH₂PO₄ in MeCN/H₂O (v/v 4:1). ‡Reaction was performed with 1 mol % TBADT, 10 mol % (4-CiPhS)₂, and 10 mol % TBAH₂PO₄ in MeCN/H₂O (v/v 2:3). §Reaction was performed in acetone instead of MeCN as the solvent.

respectively, which were readily separated by routine silica gel chromatography. Each diastereomer was then independently subjected to the epimerization conditions, which allowed for the isolation of another diastereomer having the opposite absolute stereochemistry [i.e., (–)-**39a** converted to (+)-**40a**, and (–)-**40a** converted to (+)-**39a**]. Overall, this strategy enables access to enantiopure diastereomers corresponding to the unnatural enantiomer of (S)-pulegone, which is more challenging to obtain, and illustrates the potential to use selective isomerization tools to expand the scope of chiral building blocks that can be obtained from the chiral pool. In principle, this strat-

egy can extend to other 1,2-addition products with varying substitution patterns when commenced from enantiomerically pure starting materials (see also **41a** and **42a**).

We next examined the application of stereoediting as a late-stage diversification strategy. Cedrol is an important fragrance compound, and molecules that contain the cedrane scaffold have shown activity in diverse biological settings (30, 31). Studies of structurally related C-7 cedrane epimers have not yet been reported. One factor that may have constrained advancement in this direction is the difficulty in accessing cedrane analogs: To date, the only reported synthesis of C-7-*epi*-cedrol (**43b**) was

completed in a racemic form, in 7% yield over nine steps (32). Using stereoediting conditions, enantiopure (+)-**43b** was obtained from commercially available (+)-cedrol (**43a**) in a single step in 50% yield (Fig. 5B).

Integrating stereoediting into the logic of multistep synthesis

Finally, we sought to integrate this stereocenter editing tool within the logic of multistep organic synthesis (33). The efficient assembly of complex organic molecules requires the precise orchestration of connectivity- and selectivity-generating bond formation steps; unexpected selectivity outcomes encountered along the way

can require the global revision or iteration of the overall synthetic design. For example, in the total synthesis of petroleum biomarker (–)-8 β (H)-drimane (**2b**) by González-Sierra *et al.*, hydrogenation of drimene (**1**) with Adam's catalyst afforded the undesired isomer **2a** as the major product; a four-step workaround was devised to obtain pure (–)-**2b** (7). This case represents a typical dilemma encountered by synthetic chemists: Strategic innovation was required because of undesired diastereoselective outcomes. This limitation was later addressed by Iwasaki and co-workers, who developed an elegant, mechanistically distinct Co-mediated radical reduction method to provide access to the desired trans isomer (–)-**2b** (6:1 diastereomeric ratio) (34). In our study, the stereoediting method offers a complementary approach to resolving this situation without requiring (i) revision of the optimal route or (ii) the development of novel chemical methods to achieve the desired transformation by direct revision of the undesired chiral center. This strategy correction approach upgrades the mixture of drimane (**2a** and **2b**) resulting from the original hydrogenation directly to (–)-8 β (H)-drimane (**2b**) in 83% yield with no remaining **2a** detected (Fig. 5C).

The same logic can be applied in the synthesis of allocholate derivative (+)-**45b**, which shares a common scaffold with various bioactive compounds and has found application in supramolecular systems (35, 36). Starting from (+)-cholic acid (**44**), a one-pot esterification-oxidation sequence afforded trione (+)-**45a** in 81% yield. The ensuing stereoediting step converted the cis-fused AB ring junction of (+)-**45a** to trans-fused (+)-**45b** in 94% yield (Fig. 5D). Overall, this route reflects an efficient two-step synthesis of (+)-**45b** from (+)-**44**, where previously reported efforts for the same purpose have required seven steps (37).

The stereoediting method reported here enables the selective isomerization of completely unactivated tertiary stereocenters, providing

efficient one-step access to distinct stereoisomers in diverse synthetic settings. This tool adds to a growing suite of stereoediting methods capable of independently tuning the three-dimensional structure of complex chiral molecules and unlocks a fundamentally distinct (retro)synthetic strategy. We further illustrate how stereoediting logic can be used to amplify the versatility of powerful existing transformations, streamline the synthesis of complex chiral targets, and expand access to previously undiscovered chiral pool building blocks and natural product analogs.

REFERENCES AND NOTES

- E. L. Eliel, S. H. Wilen, *Stereochemistry of Organic Compounds* (Wiley, 1994).
- J.-K. Jiang, M. Shen, C. J. Thomas, M. B. Boxer, *Curr. Top. Med. Chem.* **11**, 800–809 (2011).
- P. J. Coleman *et al.*, *ChemMedChem* **7**, 415–424 (2012).
- T. Yamamoto, H. Matsuda, Y. Utsumi, T. Hagiwara, T. Kanisawa, *Tetrahedron Lett.* **43**, 9077–9080 (2002).
- L. M. Barton *et al.*, *J. Am. Chem. Soc.* **141**, 12531–12535 (2019).
- G. W. Coates, *Chem. Rev.* **100**, 1223–1252 (2000).
- M. González-Sierra, M. de los Angeles Laborde, E. A. Rúveda, *Synth. Commun.* **17**, 431–441 (1987).
- C. Zhang *et al.*, *J. Am. Chem. Soc.* **143**, 13393–13400 (2021).
- M. Huang, L. Zhang, T. Pan, S. Luo, *Science* **375**, 869–874 (2022).
- Y. Wang, H. M. Carder, A. E. Wendlandt, *Nature* **578**, 403–408 (2020).
- Y.-A. Zhang, X. Gu, A. E. Wendlandt, *J. Am. Chem. Soc.* **144**, 599–605 (2022).
- C. J. Oswood, D. W. C. MacMillan, *J. Am. Chem. Soc.* **144**, 93–98 (2022).
- H. M. Carder, Y. Wang, A. E. Wendlandt, *J. Am. Chem. Soc.* **144**, 11870–11877 (2022).
- H.-S. Dang, B. P. Roberts, *Tetrahedron Lett.* **41**, 8595–8599 (2000).
- N. Y. Shin, J. M. Ryss, X. Zhang, S. J. Miller, R. R. Knowles, *Science* **366**, 364–369 (2019).
- J. Großkopf *et al.*, *J. Am. Chem. Soc.* **143**, 21241–21245 (2021).
- M. M. Walker *et al.*, *J. Am. Chem. Soc.* **142**, 8194–8202 (2020).
- A. M. Kazerouni *et al.*, *ACS Catal.* **12**, 7798–7803 (2022).
- J. S. DeHovitz *et al.*, *Science* **369**, 1113–1118 (2020).
- L. Saudan, J. Quintaine, "Isomerization Reactions," US Patent Application 20220041536A1 (2022).
- R. G. Salomon, J. K. Kochi, *Tetrahedron Lett.* **14**, 4387–4390 (1973).
- M. Gorodetsky, Y. Mazur, *J. Am. Chem. Soc.* **90**, 6540–6541 (1968).
- Y. Wang *et al.*, *J. Am. Chem. Soc.* **140**, 9678–9684 (2018).
- X. Zeng *et al.*, *J. Org. Chem.* **71**, 8864–8875 (2006).
- R. L. Augustine, J. A. Caputo, *J. Am. Chem. Soc.* **86**, 2751–2752 (1964).
- L. A. Combs-Walker, C. L. Hill, *J. Am. Chem. Soc.* **114**, 938–946 (1992).
- J. Dong *et al.*, *Chem. Sci.* **11**, 1026–1031 (2019).
- Y. Kuang *et al.*, *Chem. Sci.* **11**, 8912–8918 (2020).
- J. H. Lee, Y. Zhang, S. J. Danishefsky, *J. Am. Chem. Soc.* **132**, 14330–14333 (2010).
- K.-F. Chang *et al.*, *J. Nat. Prod.* **83**, 3021–3029 (2020).
- Y.-M. Zhang *et al.*, *J. Agric. Food Chem.* **69**, 5332–5343 (2021).
- E. G. Breitholle, A. G. Fallis, *J. Org. Chem.* **43**, 1964–1968 (1978).
- J. F. Hoskin, E. J. Sorensen, *J. Am. Chem. Soc.* **144**, 14042–14046 (2022).
- K. Iwasaki, K. K. Wan, A. Oppedisano, S. W. M. Crossley, R. A. Shenvi, *J. Am. Chem. Soc.* **136**, 1300–1303 (2014).
- J. C. Judkins *et al.*, *Angew. Chem. Int. Ed.* **53**, 2110–2113 (2014).
- V. Mancino *et al.*, *Org. Biomol. Chem.* **19**, 5403–5412 (2021).
- K. M. Bhattacharai *et al.*, *Chem. Commun.* **2006**, 2335–2337 (2006).

ACKNOWLEDGMENTS

The authors thank S. McMinn (Merck) for separation of cedrol epimers, X. Gu (MIT) for preliminary computational data, S. Feng (MIT) and J. L. Knippel (MIT) for supercritical fluid chromatography data collection, T. Pinto (MIT) for chiral high-performance liquid chromatography, and Z. Wickens (University of Wisconsin–Madison) for helpful discussions. **Funding:** Support for this work was provided by the National Institutes of Health (GM146248). **Author contributions:** All authors contributed to the design of the project. Y.-A.Z. and V.P. carried out the main experimental work, mechanistic studies, and data analysis. A.E.S., Y.W., and K.J.W. conducted preliminary studies. A.E.W. directed the research. A.E.W., V.P., and Y.-A.Z. drafted the manuscript, which was approved by all authors. **Competing interests:** The authors declare no competing interests. **Data and materials availability:** All data are available in the manuscript or the supplementary materials. **License information:** Copyright © 2022 the authors, some rights reserved; exclusive licensee American Association for the Advancement of Science. No claim to original US government works. <https://www.science.org/about/science-licenses-journal-article-reuse>

SUPPLEMENTARY MATERIALS

science.org/doi/10.1126/science.add6852
Materials and Methods
Figs. S1 to S44
Tables S1 to S5
NMR Spectra
References (38–90)

Submitted 30 June 2022; accepted 30 September 2022
10.1126/science.add6852