ORGANIC CHEMISTRY

Static to inducibly dynamic stereocontrol: The convergent use of racemic β-substituted ketones

Jacob S. DeHovitz*, Yong Yao Loh*, Jacob A. Kautzky, Kazunori Nagao, Andrew J. Meichan, Motoshi Yamauchi, David W. C. MacMillan†, Todd K. Hyster†

The synthesis of stereochemically complex molecules in the pharmaceutical and agrochemical industries requires precise control over each distinct stereocenter, a feat that can be challenging and time consuming using traditional asymmetric synthesis. Although stereoconvergent processes have the potential to streamline and simplify synthetic routes, they are currently limited by a narrow scope of inducibly dynamic stereocenters that can be readily epimerized. Here, we report the use of photoredox catalysis to enable the racemization of traditionally static, unreactive stereocenters through the intermediacy of prochiral radical species. This technology was applied in conjunction with biocatalysts such as ketoreductases and aminotransferases to realize stereoconvergent syntheses of stereodefined γ-substituted alcohols and amines from β-substituted ketones.

The concept of static stereocenters is a fundamental principle that underpins the induction, application, and teaching of stereochemistry. The vast majority of stereocenters are considered to be inherently static (i.e., once formed, they are stable toward racemization or epimerization) (Fig. 1A, left). As a result, the configuration of a stereocenter is generally thought to be intrinsically coupled to the step in which it was forged, requiring each bond-forming step to also bear the burden of possessing high levels of kinetic stereocontrol. This approach to structural complexity has been adopted universally (*1*–*6*); however, alternative strategies wherein bond formation and stereochemical induction are decoupled could prove to be both powerful and complementary.

Whereas most of the stereocenters in organic chemistry are classified as static, a small cadre of structural motifs are amenable to stereochemical interconversion (or stereoablation) under prescribed reaction conditions. These inducibly dynamic centers typically incorporate (i) acidic C–H bonds that can undergo reversible deprotonation in the presence of an appropriate base (e.g., α-carbonyl C–H bonds); (ii) α-heteroatom C–H bonds (such as α-hydroxy or α-amino) that can readily participate in hydrogen atom transfer (Fig. 1A, right); and (iii) C–heteroatom bonds that can undergo reversible formation via 1,2- or 1,4-addition (e.g., acetals or β-amino carbonyls) (*7*).

Although dynamic stereochemistry might seem antithetical to the objective of a multistep stereoselective synthesis, there have been a number of well-established strategies that elegantly exploit the capacity for stereogenic racemization or epimerization (Fig. 1A, right). In particular, out-of-equilibrium processes, such as the uphill olefin isomerization shown by Weaver and colleagues (*8*) and the deracemizations detailed by Turner and colleagues (*9*) and Knowles, Miller, and colleagues (*10*), as well as a litany of dynamic kinetic resolutions (DKRs) have successfully used dynamic stereocontrol over the past two decades (*11*–*13*). Among these strategies, DKRs rely on the rapid interconversion of substrate enantiomers, in combination with stereoselective bond formation, to transform racemic substrates into enantio- and diastereomerically pure products (Fig. 1A, right). Such a stereoconvergent approach can substantially simplify the steps required for complex molecule synthesis by effectively decoupling bond formation from stereoinduction, as racemic intermediates can be converted to stereochemically pure final products.

Dynamic kinetic resolutions are nonetheless currently restricted to substrates that incorporate traditionally inducibly dynamic stereocenters, which constitutes a serious limitation given that most stereogenic centers in organic chemistry are static. With this in mind, we sought to determine whether it might be feasible to develop catalytic approaches that would render traditionally static stereocenters dynamic under mild conditions. In particular, we were interested in combining such racemization protocols with the exquisite stereoselectivity of enzymes toward molecules with static distal stereocenters (*14*) (Fig. 1B, right). Here, we describe such an advance, wherein we apply photoredox catalysis to racemize traditionally static β-keto stereocenters while successfully merging this protocol with biocatalysis to achieve a dynamic kinetic resolution.

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Photoredox catalysis has emerged as an enabling platform for regioselective C–H functionalization through the generation and harnessing of reactive carbon-centered radical intermediates toward a variety of synthetically useful bond-forming reactions (*15*–*17*). The power of photoredox catalysis is highlighted by its activation of conventionally inert, remote C–H bonds, enabling the functionalization of C–H bonds at β-carbonyl (*18*), β-amino (*19*), and other unactivated aliphatic C–H moieties (*20*) (Fig. 1B, left). On this basis, we questioned whether we could leverage the photoredox-catalyzed generation of these planar, prochiral radicals as a stereoablative tool for traditionally static stereocenters. Subsequent nonstereospecific trapping of these carbon-centered radical species by a suitable hydrogen atom transfer (HAT) catalyst could then enable the racemization of static stereocenters via the reversible cleavage and formation of C–H bonds, allowing the use of substrates with remote, unactivated, static C–H stereocenters in stereoconvergent processes.

Specifically, we postulated that the direct β-functionalization of saturated cyclic ketones via the merger of photoredox and organocatalysis could serve as a framework for a method toward the racemization of β-keto stereocenters through the intermediacy of a key 5π e^- β-enaminyl radical species (Fig. 1C) (*18*). In contrast to the well-precedented DKRs of α-substituted ketones (*11*), DKRs of β-substituted ketones have remained underdeveloped owing to a lack of general methods for the racemization of static β-keto stereocenters. By applying the proposed photoredox racemization protocol in conjunction with a ketoreductase-catalyzed kinetic resolution, we aimed to achieve a broadly applicable dynamic reductive kinetic resolution of β-substituted ketones to furnish stereodefined γ-substituted alcohols as products. A crucial design element of this DKR strategy is the inability of alcohol products to form the key β-enaminyl radical intermediate, thereby precluding the product from undergoing racemization after its formation.

A proposed mechanism for this photoredox- and enzyme-catalyzed DKR of β-substituted ketones is outlined in Fig. 2A. For demonstration purposes, we have depicted the racemization process as the conversion of (*S*)-**1** to the faster reacting active enantiomer (*R*)-**1**. This begins through the condensation of (*S*)-**1** with amine catalyst **2** to form stereodefined enamine (*S*)-**3** in situ. At the same time, photoexcitation of photocatalyst [Ir(dF(CF_3)ppy)$_2$(dtbbpy)](PF_6) (**4**) would generate the highly oxidizing excited state *Ir(III) (**5**) (half-wave reduction potential $E_{1/2}^{red}$ [$*Ir^{III}/Ir^{II}$] = +1.21 V versus the saturated calomel electrode (SCE) in MeCN) (*21*). This species can then oxidize enamine (*S*)-**3** (half-peak potential E_p [$\mathbf{3}/\mathbf{3}^{\bullet+}$] = +0.36 V versus

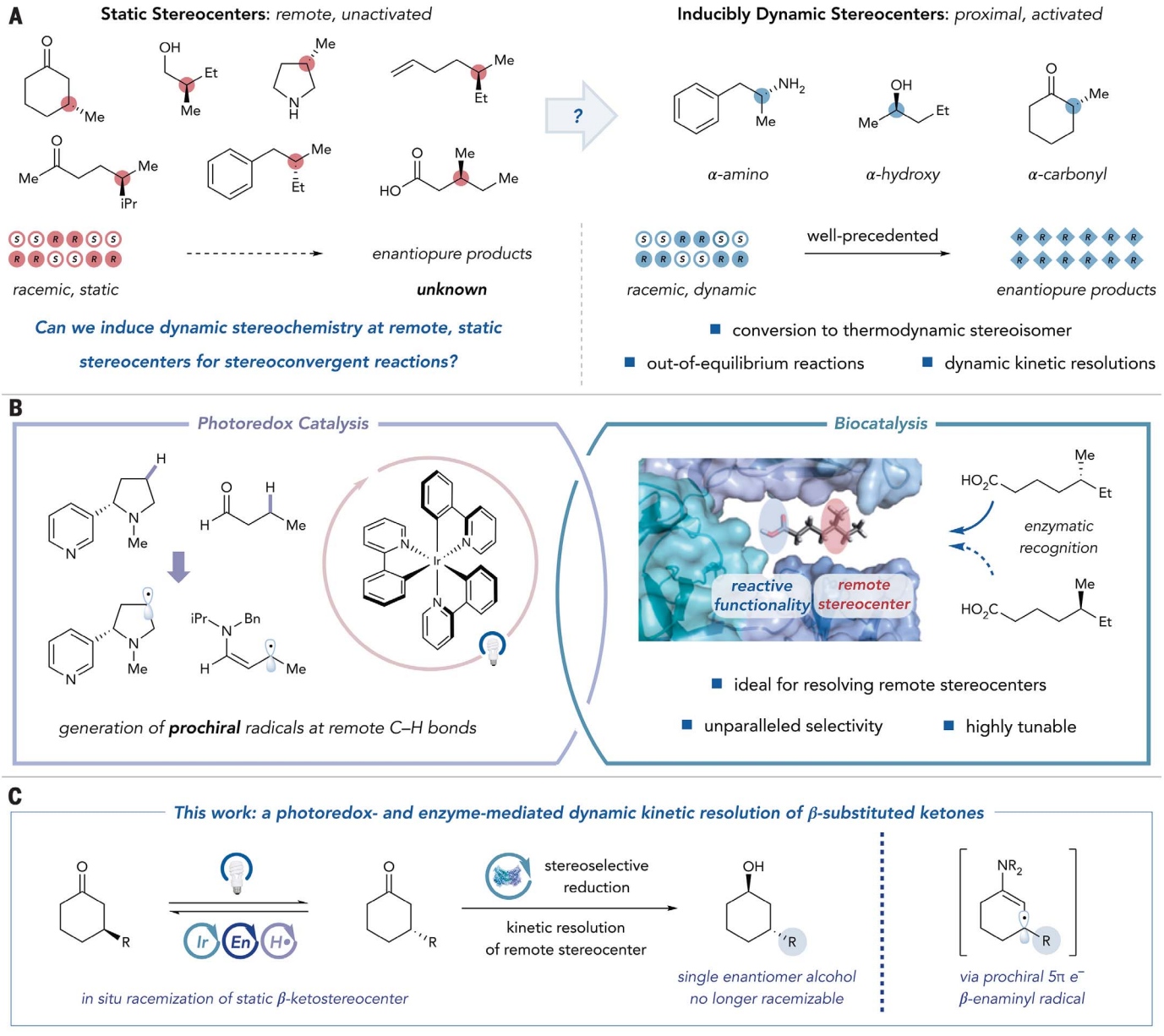

Fig. 1. Inducing dynamic stereochemistry for asymmetric synthesis. (**A**) Static stereocenters versus inducibly dynamic stereocenters. Red circles (filled and unfilled) indicate substrates containing static stereocenters. Blue circles (filled and unfilled) indicate substrates containing inducibly dynamic stereocenters. Blue diamonds indicate products formed from stereoconvergent reactions. *R* and *S* indicate the stereochemistry of compounds. (**B**) Combination of photoredox catalysis and biocatalysis for stereoconvergent reactions. (**C**) Proposed photoredox- and enzyme-catalyzed dynamic kinetic resolution. Me, methyl; Et, ethyl; iPr, isopropyl; Bn, benzyl; En, enamine; H•, hydrogen atom transfer.

SCE in MeCN) (*22*) to give reduced Ir(II) species (**6**) and enaminyl radical cation **7**. Subsequent allylic deprotonation of **7**, due to an increase in acidity of the allylic C–H bond, can then provide the nucleophilic 5π e^- β-enaminyl radical **8** (*23*). The formation of this key prochiral radical intermediate ablates the stereochemistry at the β-carbon, and subsequent polarity-matched HAT can occur between **8** and electrophilic thiol catalyst **9** [cyclohexene allylic C–H bond dissociation energy (BDE) = 83.2 kcal mol^{-1} (*24*), thiophenol S–H BDE = 76.9 kcal mol^{-1} (*25*)]. We expect this HAT event to be nonstereoselective, resulting in the gradual racemization of the stereocenter, with the formation of the opposite enantiomer of the enamine [(*R*)-**3**] occurring only 50% of the time. The photoredox and HAT catalytic cycles can then converge in a single-electron transfer (SET) event between **6** and thiyl radical **10**, regenerating ground-state photocatalyst **4** and forming thiolate **11**, which regenerates thiol catalyst **9** upon protonation [$E_{1/2}^{red}$ [Ir^{III}/Ir^{II}] = −1.37 V versus SCE in MeCN (*21*), $E_{1/2}^{red}$ [$PhS^{\bullet}/PhS^-$] = −0.06 V versus SCE in MeCN] (*26*). Finally, enamine (*R*)-**3** undergoes hydrolysis to furnish the active enantiomer of the ketone (*R*)-**1**. Concurrent with this racemization process, the ketoreductase-catalyzed stereoselective reduction of (*R*)-**1** is constantly occurring to furnish enantiopure alcohol **12** as product, using cofactor NADPH (the reduced form of nicotinamide adenine dinucleotide phosphate) as the hydride source. The reaction can then be rendered catalytic in NADPH via the use of an exogenous terminal reductant. Depending on

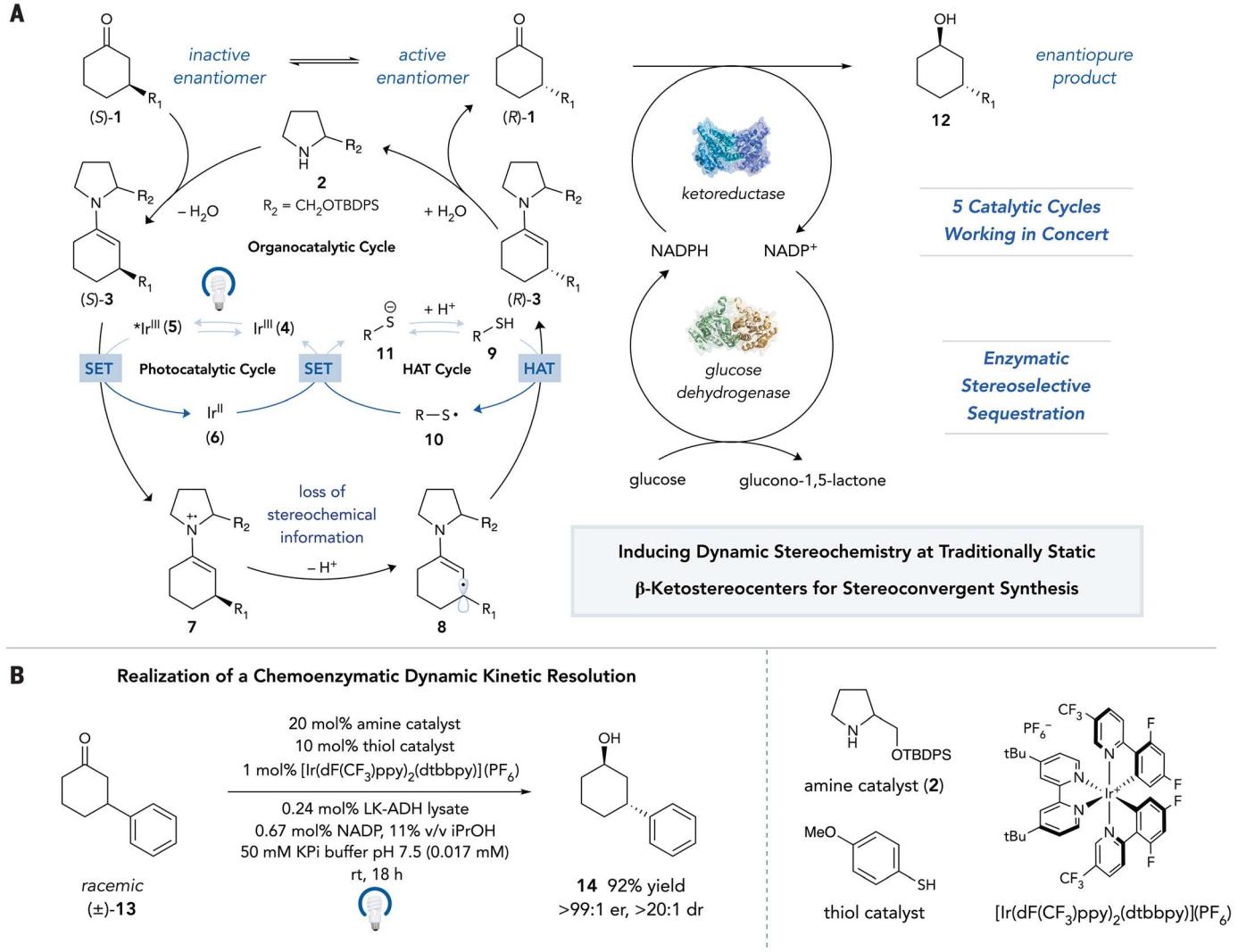

Fig. 2. Proposed mechanism and preliminary studies. (**A**) Proposed mechanism for the photoredox- and enzyme-catalyzed dynamic kinetic resolution of β-substituted ketones. For the purposes of demonstration, the racemization process is depicted as the conversion of (*S*)-**1** to the faster-reacting active enantiomer (*R*)-**1**. (**B**) Successful combination of photoredox and enzyme catalysis to realize a dynamic kinetic resolution. TBDPS, *tert*-butyldiphenylsilyl; tBu, *tert*-butyl; NADPH, reduced nicotinamide adenine dinucleotide phosphate; $dF(CF_3)ppy$, 2-(2,4-difluorophenyl)-5-(trifluoromethyl)pyridine; dtbbpy, 4,4′-di-*tert*-butyl-2,2′-bipyridine; LK-ADH, *Lactobacillus kefir* alcohol dehydrogenase [Protein Data Bank (PDB) ID 4RF2]; glucose dehydrogenase (PDB ID 1GCO); KPi, potassium phosphate; iPrOH, isopropyl alcohol; mM, millimolar; rt, room temperature; h, hours; er, enantiomeric ratio; dr, diastereomeric ratio.

the ketoreductase employed, either the combination of glucose dehydrogenase (GDH) with glucose (as shown) or excess alcoholic cosolvents, such as isopropanol, can be used. This demonstration of five catalytic cycles working in concert highlights the compatibility of enzymatic stereoselective sequestration with organocatalysis and the radical generation capabilities of photoredox catalysis (*27*–*30*), facilitating the engagement of traditionally static β-ketostereocenters in a stereoconvergent protocol.

We began our investigations into the proposed chemoenzymatic DKR of β-substituted ketone substrates by first examining the racemization of (*R*)-3-phenylcyclohexanone [(*R*)-**13**] (see supplementary materials for more details). After evaluating a variety of photocatalysts, amine catalysts, thiol catalysts, and solvents, we observed that the use of $[Ir(dF(CF_3)ppy)_2(dtbbpy)](PF_6)$ as photocatalyst, racemic 2-(((*tert*-butyldiphenylsilyl)-oxy) methyl)pyrrolidine as amine catalyst and 4-methoxythiolphenol as HAT catalyst facilitated efficient racemization after 4 hours of irradiation with visible light [98:2 to 60:40 enantiomeric ratio (er)] in the enzyme-compatible solvent system of isopropanol and phosphate buffer (1:8 ratio) (see supplementary materials). The hydrophobicity of the amine catalyst used was critical for efficient racemization owing to the well-precedented facile hydrolysis of the catalytically generated enamine species under predominantly aqueous conditions (*31*). In addition, preliminary studies also indicated the efficacy of the hydrophobic amine catalyst in mitigating enzymatic deactivation (see supplementary materials). Concurrent with the optimization of the racemization protocol, we also examined the ketoreductase-catalyzed kinetic resolution of racemic 3-phenylcyclohexanone [(±)-**13**] (see supplementary materials for more details). We found that wild-type *Lactobacillus kefir* alcohol dehydrogenase (LK-ADH) was able to successfully kinetically resolve 3-phenylcyclohexanone, giving alcohol **14** with excellent enantio- and diastereoselectivity [51% yield, 99:1 er, and 10:1 diastereomeric ratio (dr)]. With these promising results in hand, we proceeded to combine the racemization and the kinetic resolution

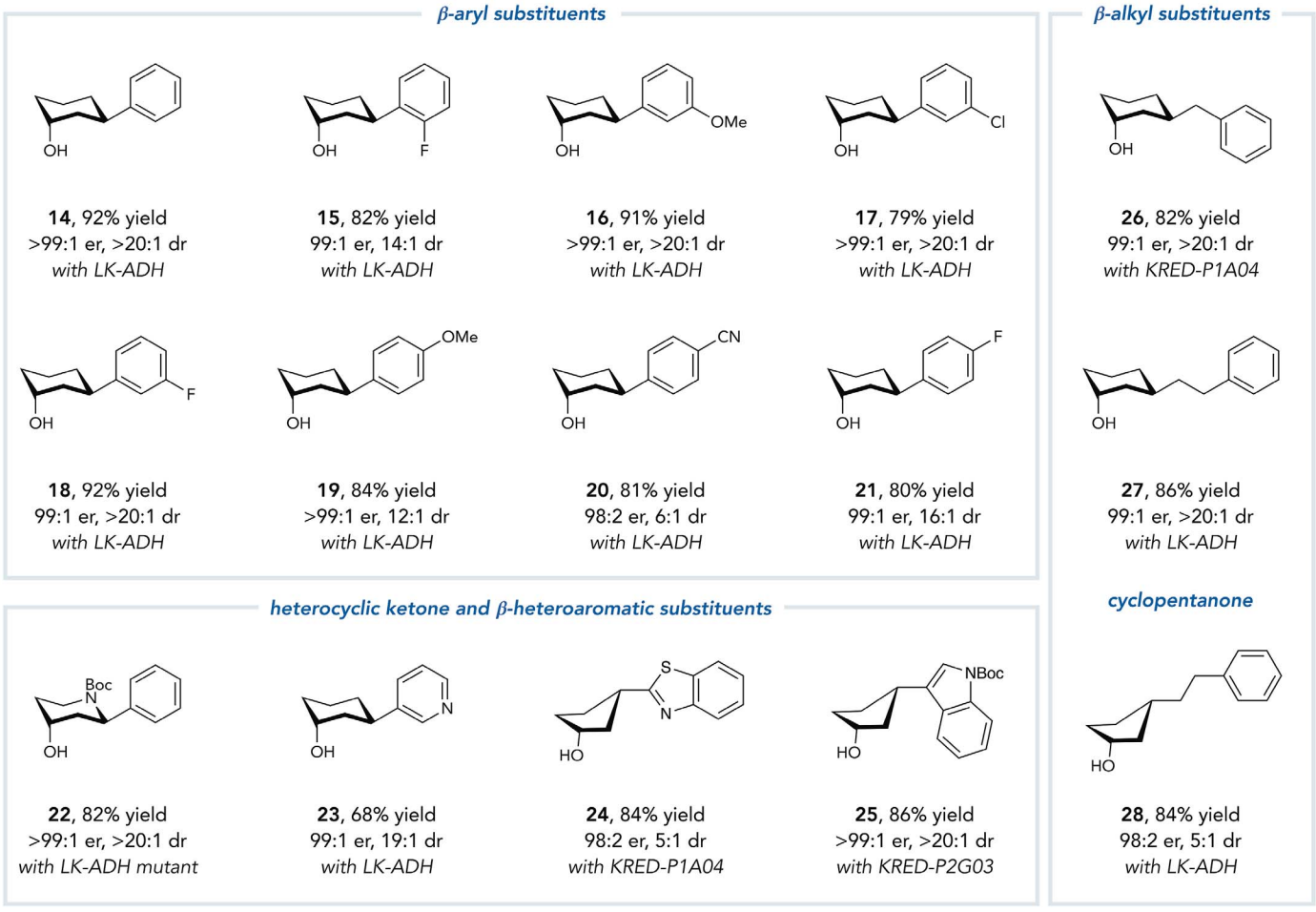

Fig. 3. Scope of dynamic kinetic resolution of β-substituted ketones. See supplementary materials for specific reaction details. Boc, *tert*-butyloxycarbonyl; KRED, ketoreductase.

to realize our desired DKR of β-substituted ketones (Fig. 2B). Upon subjecting (±)-**13** to our photoredox- and enzyme-catalyzed protocol, alcohol **14** was obtained in 92% yield, >99:1 er, and >20:1 dr.

Next, we set out to explore the scope of our DKR protocol (Fig. 3). Given the privileged status of ketoreductases in biocatalysis, we developed a library of 32 nicotinamide-dependent ketoreductases from both commercial sources and from in-house heterologous expression in *Escherichia coli*. Using this library, we were able to quickly identify the appropriate enzymes required for effective kinetic resolutions of a range of substrates. These hits were subsequently combined with our photoredox-catalyzed racemization protocol and translated into DKRs. We found that our racemization protocol was compatible with the different enzymes identified from the kinetic resolution screens, which speaks to the protocol's general biocompatibility.

A range of differentially substituted β-phenylcyclohexanones were found to be excellent substrates and were successfully converted into their corresponding γ-substituted alcohols in good yields and selectivities. Substitution at the ortho position with fluorine was well tolerated (**15**; 82% yield, 99:1 er, 14:1 dr), as were electronically diverse meta- (**16** to **18**; 79 to 92% yield, >99:1 er, >20:1 dr) and para-substituents (**19** to **21**; 80 to 84% yield, 98:2 to >99:1 er, 6:1 to 16:1 dr). Heterocyclic ketones such as piperidones also performed well in this reaction (**22**; 82% yield, >99:1 er, >20:1 dr), while β-heteroaromatic substituents such as pyridines, benzothiazoles, and indoles were good substrates as well (**23** to **25**; 68 to 86% yield, 98:2 to >99:1 er, 5:1 to >20:1 dr). Additionally, β-alkyl substituents such as benzyl and phenethyl also worked well in the DKR (**26** to **28**; 82 to 86% yield, 98:2 to 99:1 er, 5:1 to >20:1 dr). Finally, across these examples, cyclopentanones were demonstrated to be excellent substrates for this protocol (**24**, **25**, and **28**; 84 to 86% yield, 98:2 to >99:1 er, 5:1 to >20:1 dr).

To demonstrate the utility of our DKR in a pharmaceutical drug development setting, we applied it to the synthesis of LNP023, a complement factor B inhibitor recently reported by Novartis (*32*) (Fig. 4A). By subjecting racemic piperidone **29** to our DKR protocol, we were able to obtain alcohol **30** in 85% yield, >99:1 er, and >20:1 dr, shortening the synthesis of LNP023 by two steps, in addition to avoiding the need for two chiral resolutions, drastically simplifying the synthetic sequence.

Beyond streamlining the synthesis of a single enantiomer of a molecule, inducibly dynamic stereocenters also enable stereodivergent synthesis. By allowing molecules to be synthesized racemically and delaying the incorporation of stereochemical information, different stereoisomers of a desired product can be accessed simply by changing the selectivity sense of the chiral catalyst, avoiding the need for independent synthetic approaches (*33*). To showcase the viability of such an approach, we were able to identify three enzymes from our 32-enzyme library that enabled us to access the three remaining stereoisomers of **14** in good

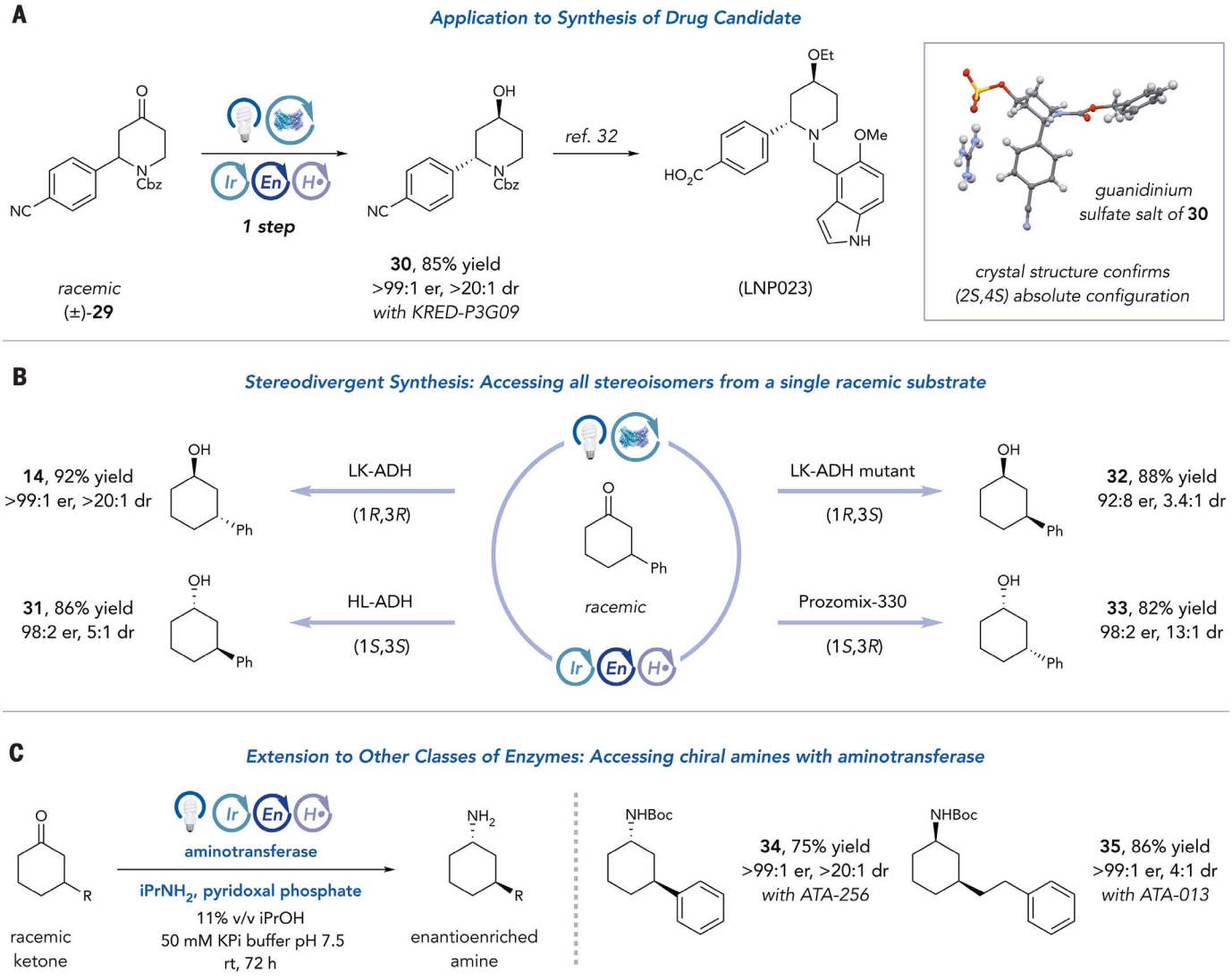

Fig. 4. Further applications of racemization protocol. (**A**) Simplification of synthetic routes to drug candidates. (**B**) Stereodivergent synthesis. (**C**) Extension to other classes of enzymes. Amine products were isolated after a Boc-protection workup. Cbz, benzyloxycarbonyl; HL-ADH, horse liver alcohol dehydrogenase; ATA, amine transaminase.

enantioselectivity and moderate diastereoselectivity (**31** to **33**; 82 to 88% yield, 92:8 to 98:2 er, 3.4:1 to 13:1 dr) (Fig. 4B).

As a final test of the generality and biocompatibility of our racemization protocol, we explored the feasibility of extending our scope to other classes of enzymes beyond ketoreductases and products beyond enantioenriched γ-substituted alcohols. In principle, any enzyme class that alters the carbonyl functional group to prevent enamine formation with the product should be compatible with our racemization strategy. To this end, we identified aminotransferases ATA-256 and ATA-013 to be capable of kinetically resolving 3-phenylcyclohexanone and 3-phenethylcyclohexanone, respectively. By combining these kinetic resolutions with our racemization protocol, we were able to successfully demonstrate the synthesis of enantioenriched amines **34** (75% yield, >99:1 er, >20:1 dr) and **35** (86% yield, >99:1 er, 4:1 dr) via a chemoenzymatic DKR protocol. We anticipate that this powerful platform for racemization will continue to challenge conventional definitions of static and dynamic stereocenters, enabling the development of additional stereoconvergent processes.

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ACKNOWLEDGMENTS

We thank Codexis and Prozomix for providing transaminases and ketoreductases, respectively. We also thank V. Bacauanu, B. X. Li, and D. K. Kim for their assistance with the preparation of this manuscript, and P. Jeffery for assistance with x-ray structure determination. **Funding:** Research reported in this publication was supported by BioLEC, an Energy Frontier Research Center funded by the U.S. Department of Energy, Office of Science, under award DE-SC0019370, and the Princeton Catalysis Initiative. The authors also acknowledge funding from Merck, Bristol-Myers Squibb (BMS), Eli Lilly, Genentech, Pfizer, and Johnson & Johnson. T.K.H. is supported by a Searle Scholars Award (SSP-2017-1741), a Sloan Research Fellowship, and the ACS-PRF. J.S.D. and Y.Y.L. are supported by BMS graduate fellowships. Y.Y.L. is also supported by an A*STAR graduate fellowship. J.A.K. is supported by a NSF GRFP (DGE 1656466) predoctoral fellowship. K.N. is supported by a JSPS overseas postdoctoral fellowship. M.Y. received funding from Daiichi Sankyo Co., Ltd. **Author contributions:** T.K.H. and D.W.C.M. conceived of the work. All authors designed the experiments. J.S.D., Y.Y.L., J.A.K., K.N., A.J.M., and M.Y. performed and analyzed the experiments. T.K.H., D.W.C.M., J.S.D., Y.Y.L., and J.A.K. prepared the manuscript. **Competing interests:** The authors declare no conflicts of interest. **Data and materials availability:** Commercial enzymes used are available from Codexis [single enzyme batches as well as screening kits such as the Codex Ketoreductase (KRED) Screening Kit and Codex Amine Transaminase (ATA) Screening Kit] and Prozomix [PRO-kREDy-to-go(001-384) Screening Kit]. Crystallographic parameters for the guanidinium sulfate salt of compound **30** are available free of charge from the Cambridge Crystallographic Data Centre under CCDC 2005332. Other data are available in the supplementary materials.

SUPPLEMENTARY MATERIALS

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Materials and Methods
Supplementary Text
Figs. S1 to S7
Tables S1 and S2
HPLC Traces
X-ray Crystallography Data
NMR Spectra
References (*37*–*57*)

25 May 2020; accepted 7 July 2020
10.1126/science.abc9909

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Science **369** (6507), 1113-1118.
DOI: 10.1126/science.abc9909

Expanding the kinetic resolution purview

Dynamic kinetic resolution (DKR) is a powerful method to transform a pair of mirror-image reactants into just one of the two possible mirror-image products. The key is to find a means of rapidly interconverting the reactants while one of them is being more efficiently funneled to product. DeHovitz *et al.* report cooperative application of organocatalysis, photoredox catalysis, and enzymatic catalysis to achieve DKR of β-substituted ketones into chiral alcohols. This β position has typically been considered too configurationally stable for a DKR approach.

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