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Perspective

Reducing Challenges in Organic Synthesis with Stereoselective Hydrogenation and Tandem Catalysis

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ABSTRACT: Tandem catalysis enables the rapid construction of complex architectures from simple building blocks. This Perspective shares our interest in combining stereoselective hydrogenation with transformations such as isomerization, oxidation, and epimerization to solve diverse challenges. We highlight the use of tandem hydrogenation for preparing complex natural products from simple prochiral building blocks and present tandem catalysis involving transfer hydrogenation and dynamic kinetic resolution. Finally, we underline recent breakthroughs and opportunities for asymmetric hydrogenation.

INTRODUCTION

Once an academic curiosity, asymmetric hydrogenation (AH) now stands among the most robust and industrially relevant strategies to construct chiral centers with high selectivity, atom economy, low cost, and minimal waste.[1−8] The 2001 Nobel Prize in chemistry was awarded to Knowles, Noyori, and Sharpless for inventing the field of enantioselective catalysis by achieving early examples of both hydrogenation and epoxidation or dihydroxylation.[9−11] Today, AH enables large-scale manufacturing. Monsanto's synthesis of levodoa (L-DOPA) used a Rh(I)−DiPAMP catalyst and revolutionized industrial production standards (Figure 1).[1] Syngenta's

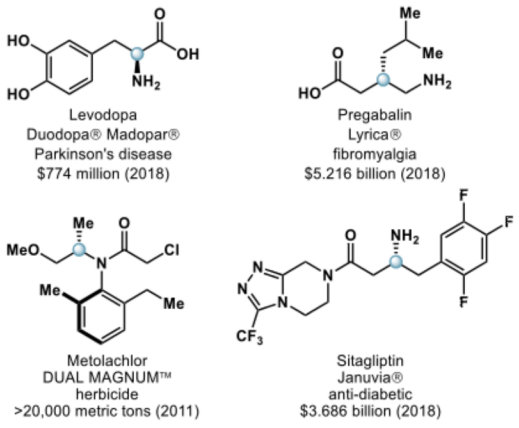

Figure 1. Impacts of hydrogenation on the chemical industries.

commercial synthesis of the herbicide metolachlor features a chiral Ir(I)−diphosphine complex, with an impressive 2,000,000 turnover number (TON) and 400,000 h^{-1} turnover frequency (TOF).[12,13] Pfizer developed a large-scale synthesis of the fibromyalgia drug pregabalin, whereas Merck reduced an unprotected enamine in the commercial synthesis of sitagliptin, an anti-diabetic.[14−18]

Inspired by its broad applicability, our laboratory has focused on developing cascade and tandem processes that feature hydrogenation. Herein, we give our perspective on breakthroughs in this research area while emphasizing our own contributions. First, we highlight cascade hydrogenations to target natural products, with selected examples from other laboratories to provide context for our studies on cyclic peptides. In the second part, we show ways in which hydrogenation can be merged with other mechanisms via tandem catalysis. Lastly, we share our outlook on the future of the field by highlighting areas for further discovery.

CASCADE HYDROGENATION

Cascade transformations represent an attractive strategy to rapidly build complexity in the target-oriented synthesis of complex natural products. Despite their diverse biosynthetic pathways, a wide array of natural products can be addressed by asymmetric reduction. Herein, we highlight how cascade hydrogenations have been applied in the synthesis of terpenes, polyketides, peptides, and alkaloids.

Terpenes and Polyketides. Two of the largest and most complex natural product families are terpenes and polyketides. Despite vast structural diversity, the biosynthetic pathways for each family have similar origins: they both arise from simple chains of repeating units. For terpenes, this unit is derived from isoprene.[19,20] For polyketides, this unit is derived from acetate and propionate fragments.[21,22] As a result of further modifications, terpenes and polyketides bear intricate stereochemical structures. Thus, these natural products present formidable synthetic challenges, and many strategies have been

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embarked upon to streamline their synthesis. These processes include radical poly-cyclizations, consecutive Michael additions, and pericyclic cascades.[23,24] The use of hydrogenation for this purpose, however, has been underdeveloped, largely due to the difficulty of reducing unactivated, non-directed, and/or sterically hindered tri- and tetra-substituted olefins.[25−32] Early reports by Kagan and Buchwald centered around chiral titanocene and zirconocene complexes, respectively.[33−35] These highly electrophilic complexes overcome the low reactivity of tetra-substituted olefins; however, low stability, large catalyst loadings, and high pressure have prevented these methods from becoming more mainstream. Alternatively, Ir catalysis has shown effectiveness for the AH of unfunctionalized and sterically hindered substrates that have been largely unreactive with traditional Rh- and Ru-based complexes. In 1998, Pfaltz developed this technology using a cationic Ir−BAr^F complex bearing a chiral phosphinooxazoline (PHOX) ligand.[36] In this report, several tri- and tetra-substituted styrene and stilbene derivatives were hydrogenated in up to 98% *ee*. Since this pioneering work, numerous reports have emerged showcasing the power of chiral variants of Crabtree's catalyst for the AH of unfunctionalized and sterically hindered olefins.

With this catalyst design breakthrough, Pfaltz achieved the synthesis of γ-tocotrienol, a component of vitamin E, through the cascade hydrogenation of the poly-unsaturated precursor γ-tocotrienyl acetate. A model system employing cyclohexyl butene **1** was successfully hydrogenated to cyclohexylbutane **2** in 92% *ee* using a cationic Ir complex containing the pyridine-based P,N ligand **L1** (Figure 2).[37] The purely alkyl substrate is

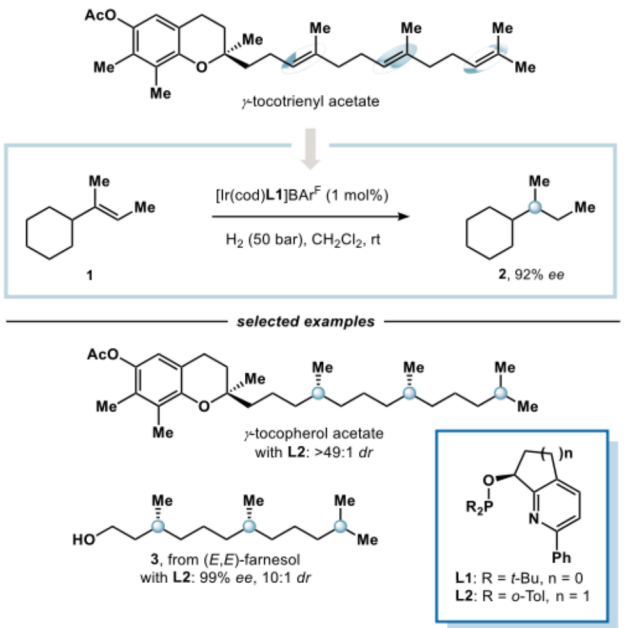

Figure 2. AH of unfunctionalized tri-substituted olefins for the global reduction of γ-tocotrienyl acetate and *E*,*E*-farnesol.

void of directing groups and aromatic rings that have the potential to assist with binding of the olefin to the catalyst. These conditions were extended to the triple hydrogenation of γ-tocotrienyl acetate to γ-tocopherol acetate in >49:1 *dr* using **L2**. Additionally, (*E*,*E*)-farnesol was reduced to compound **3** in 99% *ee* and 10:1 *dr*.[26,28] These advancements showcase the potential of cascade AH for the synthesis of complex terpenoids.

Two factors explain the greater reactivity of cationic Ir catalysis toward the AH of hindered unactivated olefins: (1) oxidation state and (2) steric hindrance. Experimental studies and DFT calculations reported by Burgess, Andersson, and Bayer elucidated a mechanism involving an Ir(I) double oxidative addition to two molecules of H_2. This transformation leads to an Ir(V) complex which is higher in oxidation state, and thus more electrophilic, than the Rh(III) intermediates generated by variants of Wilkinson's catalyst. Furthermore, the resulting seven-coordinate $L_2Ir(V)H_4$−olefin complex, with its four small hydride ligands, is less sterically hindered than the corresponding $L_2XRh(III)H_2$−olefin complexes.[38−44]

More recently, this technology has been developed for the AH of terpenoid and polyketide precursors. Burgess outlined chiral variants of Crabtree's catalyst for the stereocontrolled synthesis of commonly found natural product fragments (termed chirons) that lack strongly coordinating directing groups and with adjacent stereocenters. These studies have produced predictable stereochemical outcomes for mostly *single* olefin reductions; however, the *double* hydrogenation of allylic diene **4** was accomplished to provide alcohol **5** in 83% yield (Figure 3).[29,45] The diastereoselectivity is catalyst

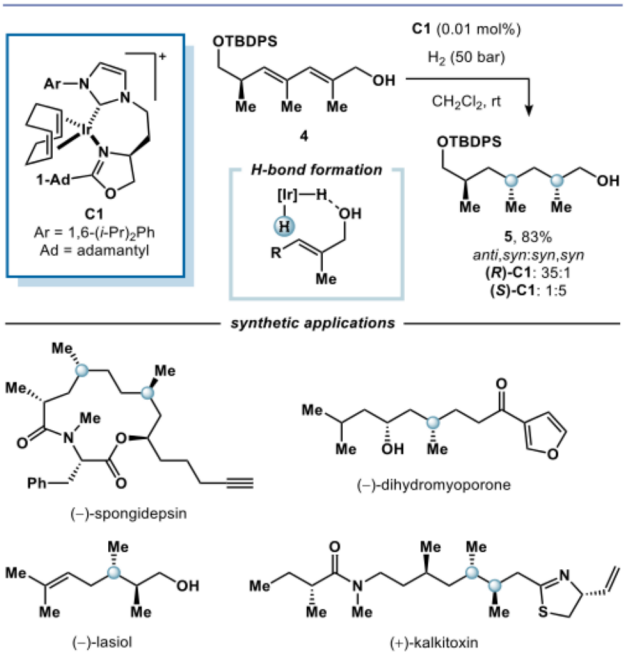

Figure 3. Ir-catalyzed AH of allylic dienes for the synthesis of polyketide chirons.

controlled, giving 35:1 preference for the *anti*,*syn* isomer over the *syn*,*syn* isomer with the matched (*R*)-**C1** substrate pair. The selectivity is reversed for the mismatched pair albeit to a lesser degree. This lowering of selectivity is attributed to substrate influences involving the minimization of 1,3-allylic strain, *syn*-pentane interactions, and the promotion of facial selectivity governed by conformational bias of nearby stereocenters. In addition, modulation of the ligand can affect the acidity of the resulting Ir−H intermediates, which leads to the formation of byproducts from acid-labile substrates. Carbene ligands (such as the one found in **C1**) and other σ-donor ligands give more electron-rich metal centers, which can alter

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the acidity of intermediate complexes. In this manner, the catalyst might act as an H-bond donor in the presence of acceptor functional groups such as alcohols. These findings are supported by DFT calculations and deuterium labeling studies.[41] Nonetheless, this strategy has been applied to the synthesis of natural products such as (−)-spongidepsin, (−)-dihydromyoporone, (−)-lasiol, and (+)-kalkitoxin.[46,47] Altogether, these findings are a promising step forward in the application of cascade hydrogenation for the synthesis of complex terpenes and polyketides.

Peptides. Dehydroamino acid derivatives have been the historic models for testing homogeneous AH. An early report from Kagan showed the double hydrogenation of a bis-dehydro-dipeptide **6** to the bis-phenylalanine-dipeptide **7** (Figure 4).[48] Using a cationic Rh catalyst and (*R*,*R*)-DiPAMP (**L3**), dipeptide **7** was formed in excellent enantio- and diastereoselectivity. This early example demonstrated the potential for cascade hydrogenation via catalyst control.

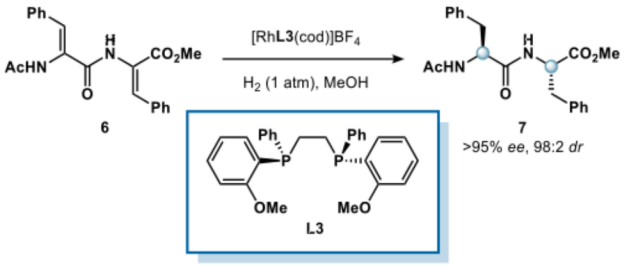
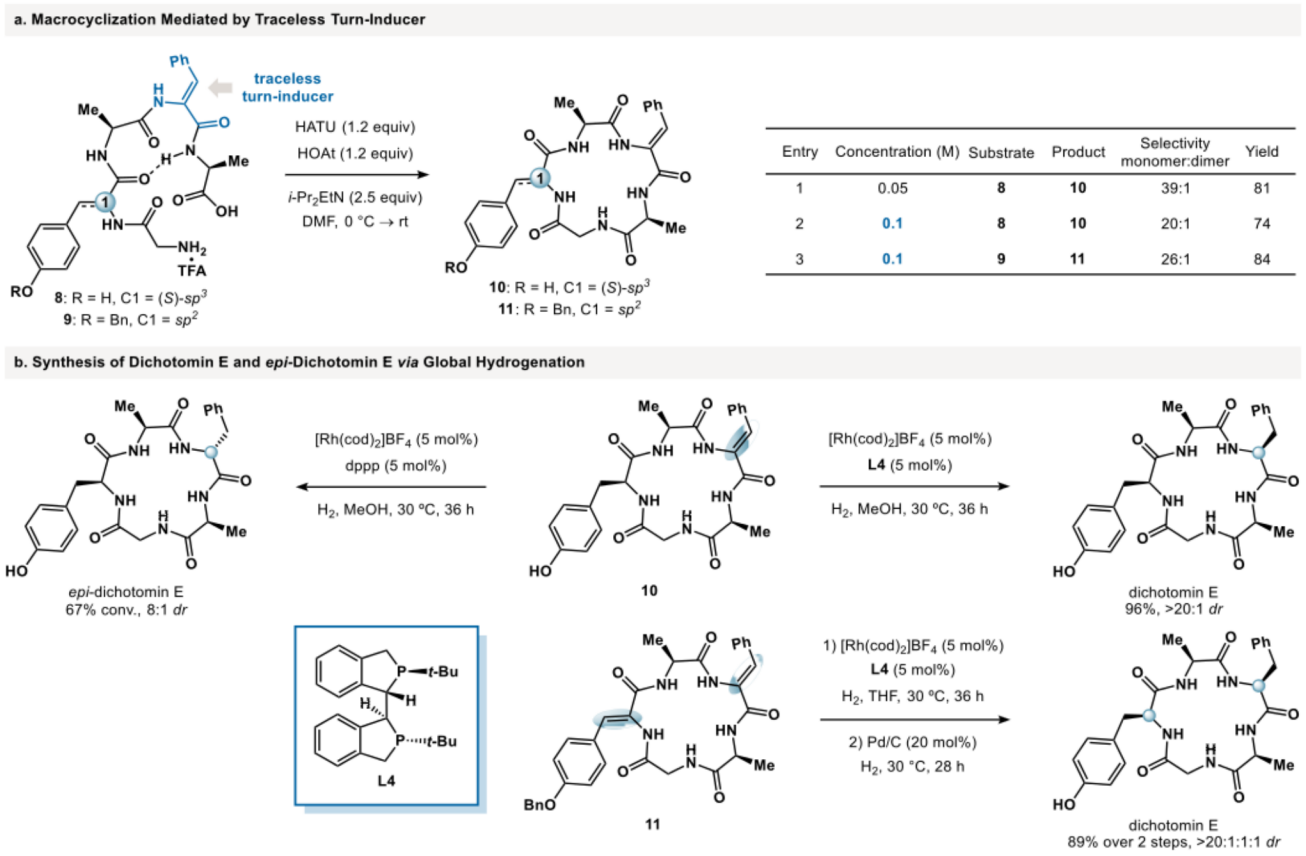


Figure 4. AH of a bis-dehydro-dipeptide with Rh catalyst.

There has been a growing interest in strategies for accessing cyclic peptides. In contrast to their linear counterparts, these more constrained structures provide enhanced metabolic stability and can act as mimics of protein−protein interactions, properties that enhance their potential as therapeutics, such as immunosuppressants and antibiotics.[49−53] Traditionally, cyclic peptides are made by the macrolactamization of their saturated and enantiopure linear counterparts; however, this strategy poses a challenge when applied to medium sized cyclic peptides.[54,55] Oftentimes, dimerization and C-terminal epimerization become competitive side reactions which require dilute concentrations to avoid.[56]

Our group reported the hydrogenation of unsaturated cyclic peptides as a strategy for the total synthesis of dichotomin E. The synthesis was accomplished using dehydroamino acids as traceless turn inducers for macrocyclization.[57] Dehydrophenylalanine has been studied for its ability to modulate the backbone conformation of small peptides by inducing folded structures such as compounds **8** and **9** (Figure 5a).[58−63] Due to the imposed α-turn, observable by NMR analysis and molecular modeling, the N- and C-termini are prearranged for macrocyclization to the cyclic peptides **10** and **11**. These were obtained in high yield, excellent monomer selectivity, and at 100 times the concentration of previously reported methods.[64] The diastereoselective conversion of **10** to either dichotomin E or its epimer could be controlled by the ligand. Using 1,3-



Entry	Concentration (M)	Substrate	Product	Selectivity monomer:dimer	Yield
1	0.05	**8**	**10**	39:1	81
2	**0.1**	**8**	**10**	20:1	74
3	**0.1**	**9**	**11**	26:1	84

Figure 5. (a) Macrocyclization studies with dehydro amino acids as traceless turn inducers at high concentrations. (b) Ligand-controlled diastereoselectivity in the global hydrogenation of dehydro cyclic peptides for the synthesis of dichotomin E and *epi*-dichotomin E.

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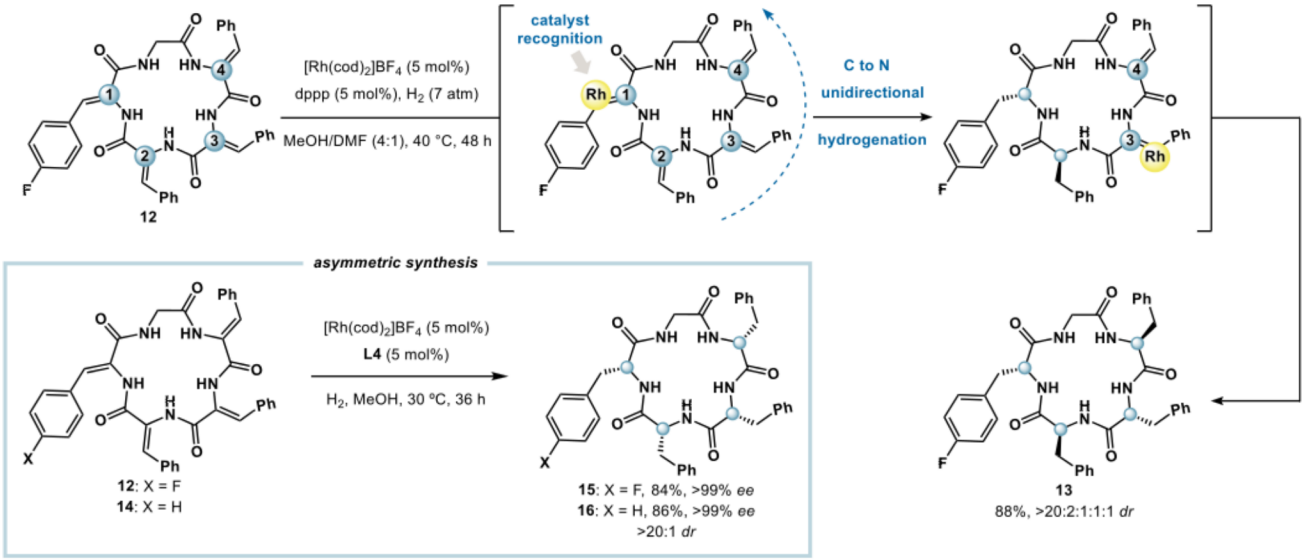

Figure 6. Unidirectional AH of poly-unsaturated cyclic peptides through catalyst binding via substrate recognition.

bis(diphenylphosphino)propane (dppp), the epimer of dichotomin E was formed in 8:1 *dr*; however, (*S*,*S*′,*R*,*R*′)-DuanPhos (**L4**) gave the proper natural product stereochemistry in >20:1 *dr* (Figure 5b). In addition, **L4** was able to achieve the global hydrogenation of bis-dehydro cyclic peptide **11**, furnishing dichotomin E as a single diastereomer.

Following these results, we reported a unidirectional cascade hydrogenation of fully unsaturated cyclic peptides. Compound **12** was fully reduced to the saturated cyclic peptide **13** with complete diastereocontrol using a cationic Rh catalyst precursor and dppp as the ligand (Figure 6).[65] The (±)-cyclic D,L-α-peptides, such as **13**, have been used to treat Gram-negative and Gram-positive bacteria.[66,67] In contrast, the synthesis of **13** from **12** was accomplished using heterogeneous catalysis with Pd/C. This process was non-selective and gave a mixture of all eight diastereomers. The Rh-catalyzed process sets four stereocenters in a unique mechanism involving a C-to-N unidirectional hydrogenation via catalyst−substrate recognition. The mechanism involves dissociation and re-association as opposed to a processional pathway whereby the catalyst remains bound to the substrate. The Rh catalyst first binds to the prochiral olefin of C1, enabled by the flexibility of the adjacent glycine residue. As each reduction occurs, the adjacent olefin becomes more flexible and is reduced in sequence with high *anti*-diastereoselectivity. This sequential unidirectional mechanism was supported by time-point ^{19}F NMR and mass spectrometry studies as well as conformational analysis using computational models. Furthermore, single enantiomers of cyclic peptides **15** and **16** can be obtained from **12** and **14**, respectively, with the use of **L4** as a chiral ligand. This stereoselective sequential hydrogenation through catalyst−peptide recognition is reminiscent of the substrate specificity exercised by enzymatic processes as well as gene regulation through ribosome−codon binding. It is an inspiring design highlighting the possibility of molecular recognition in organic synthesis. Subsequent to our work, Ding has reported the use of Ir-catalyzed AH of cyclic dipeptides using a similar processive hydrogenation strategy.[68] Collectively, these studies outline a route to cyclic peptides from oxidized achiral building blocks.

Alkaloids. With an array of biological activities from anti-microbial to anti-cancer, alkaloids comprise a large class of structurally diverse natural products.[69,70] Their most distinguishing feature is the presence of a basic nitrogen atom that often poses synthetic challenges. Heteroarene reduction by cascade hydrogenation has shown potential for piecing together these intricate frameworks from achiral substrates.[71−76] Multiple stereocenters can be generated in one step by global reduction of a simple, highly oxidized aromatic substrate. This strategy has had an impact on the production of fine chemicals, with large multi-thousand-ton scale industrial processes developed. It poses an attractive and direct route to rapidly construct complex motifs from simple prochiral substrates.

The difficulties of this strategy are seen in its prerequisites. Namely, the limitations of arene functionalization arise largely from the added kinetic barrier for de-aromatization which is not present in other reductively labile functional groups, such as alkenes and ketones. This disparity requires a level of reactivity to overcome issues of chemoselectivity. For strongly stabilized rings, such as benzene derivatives, few catalysts are able to overcome the activation barrier for de-aromatization, resulting in adverse side reactions such as hydro-defunctionalization.[74]

Despite these challenges, recent years have seen breakthroughs in arene hydrogenation. For example, Glorius has reported the hydrogenation of fluorinated benzenes and pyridines. The Rh-CAAC complex **C2** (CAAC = cyclic-alkyl-amino-carbene) was found to circumvent the issue of hydrodefluorination and shortcut the *cis*-selective synthesis of polyfluorinated cycloalkanes and piperidines (Figure 7).[77−81] The high bond dissociation energy and strong dipole moment of the C−F bond along with the relatively small fluorine atom have allowed industrial scientists to fine-tune the properties (such as polarity and acidity) of fine chemicals.[82−85] Compounds **17** and **18** were obtained as single diastereomers, cutting previously 12- and 6-step syntheses, respectively, down to a single step. This strategy gives access to two important design features used in medicinal chemistry. Piperidine **18** has since been commercialized on a large scale (Sigma-Aldrich

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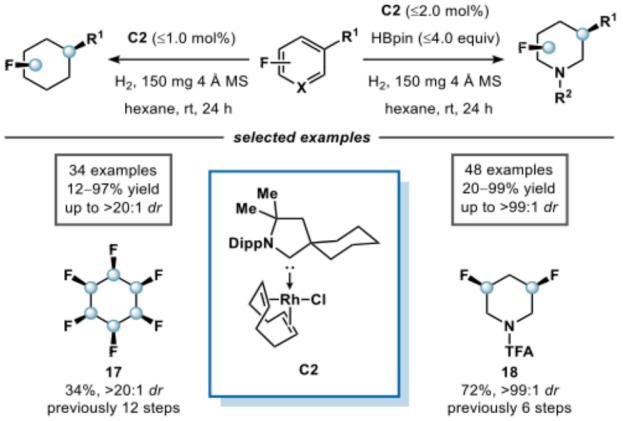

Figure 7. Hydrogenation of per-fluorinated benzenes and piperidines. Dipp = 2,6-diisopropylphenyl.

product no. 903817). Catalyst **C2** has also been used for the hydrogenation of numerous other functionalized arenes (such as aryl ketones, silanes, and boronate esters), giving access to building blocks for pharmaceutical and polymer chemistry.[86−91] The highly electron-donating CAAC ligand creates an electron-rich metal center. Therefore, arene binding is favorable due to strong back-donation into its anti-bonding π orbitals.[92,93] More recently, Glorius reversed the selectivity from the traditional *cis*-relative stereochemistry to *trans* by using a heterogeneous Pd catalyst and *para*-substituted phenols. This method was applied to the synthesis of the mucolytic agent ambroxol.[94]

AH methods have been developed for approximately three dozen heteroarenes, with quinolines, quinoxalines, indoles, and isoquinolines being the most common.[71−76] General strategies employ chiral auxiliaries, organocatalysis, and transition metal catalysis, the latter being the most frequently used, with many recent applications to the synthesis of complex alkaloids. For example, Zhao used a hydrogen-borrowing approach (*vide infra*) to effect an asymmetric reductive amination cascade for the synthesis of tetrahydroquinolines.[95] Similarly, Fan reported a tandem process involving an AH and intramolecular reductive amination of quinolines and quinoxalines **19** to produce complex tricyclic ring systems using a Ru catalyst and a chiral amino-sulfonamide ligand (Figure 8).[96] Each of the 46 examples provided the desired products with exquisite enantio- and diastereoselectivities. A challenge for this method is the chemoselective reduction of the heteroarene **19** and tetra-substituted iminium intermediate **20** over the ketone to provide product **21** over the byproduct **22**. This method was employed in the total synthesis of (+)-gephyrotoxin, where intermediate **24** was formed from **23** with excellent enantio- and diastereoselectivity.

Over the past four decades since their discovery, the bis-tetrahydroisoquinoline alkaloids have drawn interest for their potent anti-cancer activity.[97,98] Natural products such as (−)-jorumycin and (−)-jorunnamycin A contain pentacyclic scaffolds with highly oxygenated outer rings A and E as well as a pro-iminium ion motif that provides a covalent attachment to DNA resulting in cell death (Figure 9).[98] Although the mechanism of action of these alkaloids has been elucidated, drug development efforts for determining structure−activity relationships (SARs) have been largely understudied. Previous synthetic approaches to (−)-jorumycin and (−)-jorunnamycin

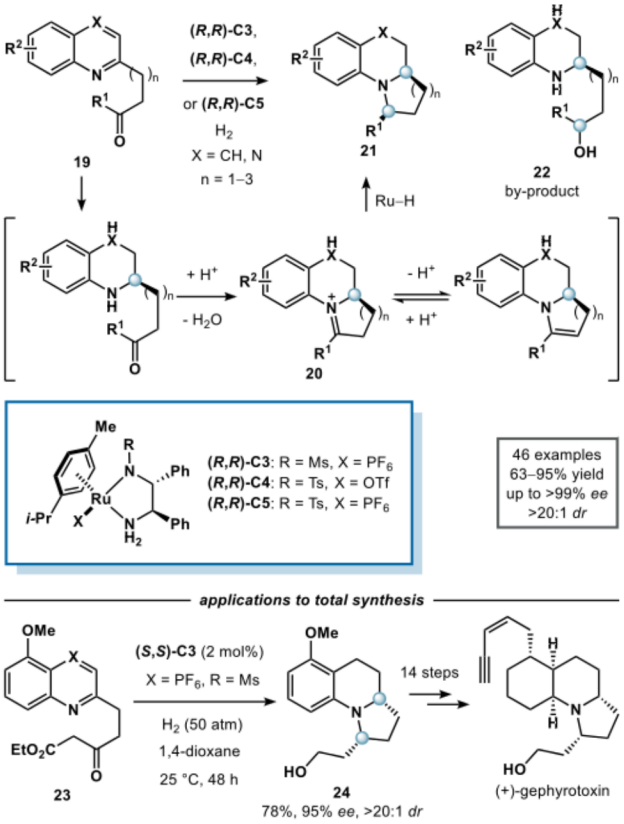

Figure 8. Tandem arene AH/reductive amination for the synthesis of tricyclic nitrogen heterocycles and applications to total synthesis.

A have not been flexible to broad diversification and are therefore not amenable to extensive biological investigations.

Recently, Stoltz sidestepped the common Pictet−Spengler-ase biomimetic approach to report an elegant synthesis of (−)-jorumycin and (−)-jorunnamycin A. Therein, the key step involved a cascade hydrogenation cyclization of a highly oxidized achiral common intermediate, **25**.[99] Inspired by O-directed imine hydrogenation for the industrial synthesis of metolachlor (Figure 1),[12,13] treatment of **25** with $[Ir(cod)Cl]_2$ and **L5** under an H_2 atmosphere afforded the desired pentacyclic natural product scaffold **28** in excellent yield and enantioselectivity and as a single diastereomer. The reaction is believed to proceed through the initial reduction of ring B, assisted by the appended hydroxy methylene to intermediate **26**. The conformational rigidity of **26** allows for the selective hydrogenation of ring D from the more accessible bottom face, leading to intermediate **27**. Finally, lactamization of **27** provides **28**, which was subsequently converted to (−)-jorumycin and (−)-jorunnamycin A in 16 and 15 total linear steps, respectively. Through these studies, the Stoltz group expanded the SAR analysis through the synthesis of previously inaccessible analogues to probe the importance of the oxygenation of rings A and E on the biological activity. Thus, the cascade hydrogenation of **25** arose from a strategic disconnection to introduce four equivalents of H_2, generate four stereocenters from an achiral substrate, and provide the natural product scaffold in a single step.

There are several examples of de-aromative cascade hydrogenation strategies being used for the synthesis of therapeutics in addition to the ones discussed above. For

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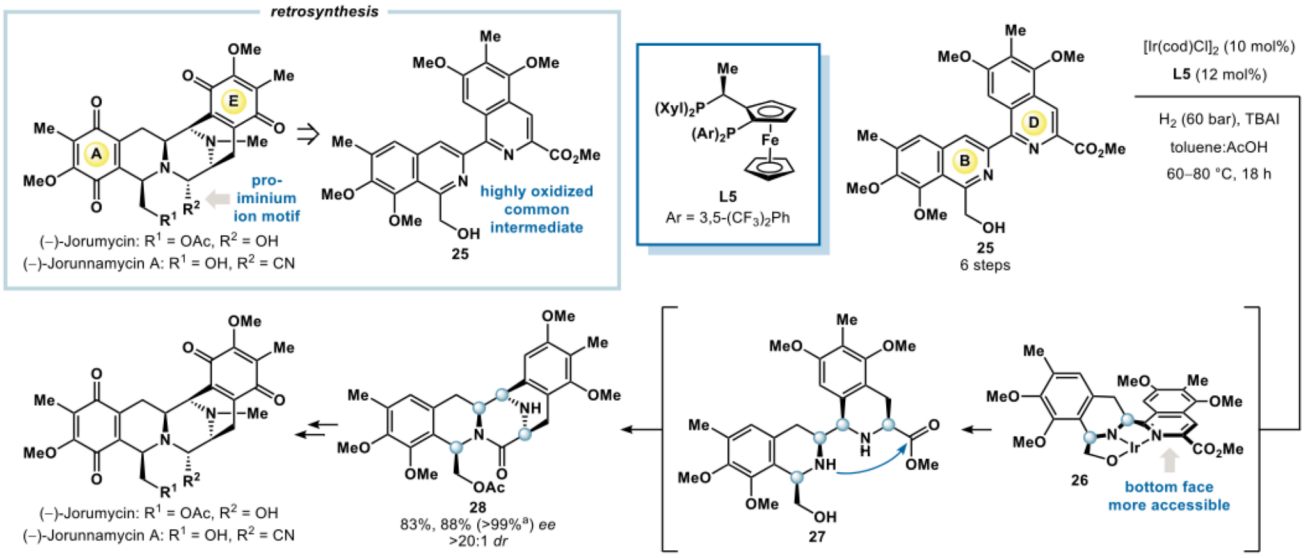

Figure 9. Total synthesis of (−)-jorumycin and (−)-jorunnamycin A via an AH cascade of a highly oxidized intermediate. [a]After one recrystallization.

instance, a concise multi-kilogram synthesis of an intermediate en route to the anti-diabetic active pharmaceutical ingredient (API) **29** was reported by Boehringer Ingelheim Pharmaceuticals. This strategy featured an asymmetric fused-piperidine hydrogenation to install the two stereocenters in a seven-step synthesis (Figure 10).[100] Zhou and co-workers have developed

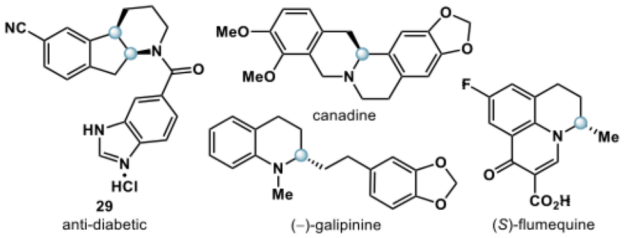

Figure 10. Applications of cascade AH of arenes in total synthesis.

an Ir-catalyzed AH of quinolines that has been applied for the synthesis of (−)-galipinine as well as the antibiotic (*S*)-flumequine.[101] Additionally, Tong and co-workers have demonstrated an asymmetric synthesis of canadine using this de-aromative hydrogenation strategy.[102] The field of de-aromative cascade hydrogenation has grown significantly in recent years. More efficient methods are continually being developed and promise a bright future for this impactful field.

As a whole, cascade hydrogenations have become attractive strategies for the rapid installation of molecular complexity in a single step, giving rise to numerous natural products and biologically relevant scaffolds from simple building blocks. The coupling of oxidized prochiral building blocks and subsequent global asymmetric reduction is emerging as a modernized approach for the synthesis of complex natural products and fine chemicals. This technology introduces multiple complex stereocenters in a single transformation while improving step and atom economies and showing great potential for use in the chemical industries.

TANDEM CATALYSIS

In tandem catalysis, two or more mechanistically distinct transformations can be performed in one pot with either one (auto tandem catalysis) or multiple (orthogonal tandem catalysis) catalysts.[103−105] Such transformations save time and money by improving step economy, lowering production costs, and generating less waste. Orthogonal tandem catalysis has been used by Brookhart and Goldman in alkane metathesis. Here, a dual Ir dehydrogenation/hydrogenation catalyst and a cross olefin metathesis catalyst stitch together low-molecular-weight *n*-hexane to *n*-decane with highly controlled molecular weight distribution and selectivity for linear alkanes.[106,107] Because alkanes comprise the major components of petroleum, this strategy could greatly impact the fuel industry. As oil reserves diminish, the world may rely on manufacturing procedures such as the Brookhart−Goldman method and the Fischer−Tropsch process, which involves the reductive oligomerization of CO and H_2.[108−110] On the flip side, auto tandem catalysis has been used with AH to promote cascade reductions (*vide supra*) as well as mechanistically distinct transformations. In this way, reactions such as oxidations, isomerizations, and rearrangements can be merged with hydrogenation to effect unique transformations. Numerous AHs feature the use of hydrogen-transfer reagents and dynamic kinetic resolution (DKR). Herein, we provide brief historical perspectives followed by our group's interest in merging hydrogenation with tandem catalysis.

Transfer Hydrogenation. While enzymes use cofactors (e.g., NADH, NADPH, and $FADH_2$), chemists exploit reagents (e.g., isopropanol, Hantzsch esters, and formic acid) as the hydrogen source for AH. These inexpensive and readily available hydride-transfer reagents provide a convenient and safe alternative to pressurized H_2. The earliest knowledge of transfer hydrogenation dates back to 1903, when Knoevenagel showed the disproportionation of dimethyl 1,4-dihydroterephthalate using Pd black.[111] Subsequent improvements in catalyst preparations broadened the scope and applications of *heterogeneous* transfer hydrogenation.[112,113] The first examples of *homogeneous* transfer hydrogenation catalysts were devel-

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oped by Bailar, who used Pd or Pt complexes and methanol to hydrogenate unsaturated fatty acid esters.[114] Henbest and Blum were the first to report homogeneous Ir and Ru complexes, respectively, for the transfer hydrogenation of α,β-unsaturated ketones.[115−117]

The first asymmetric transfer hydrogenation (ATH) was achieved by Noyori. The Noyori catalyst consists of a Ru arene complex containing a chiral amino sulfonamide ligand (**L6**) and has been used for the ATH of aryl ketones to secondary alcohols with high enantiocontrol and without directing groups (Figure 11).[10,118,119] Subsequent reports use base-free

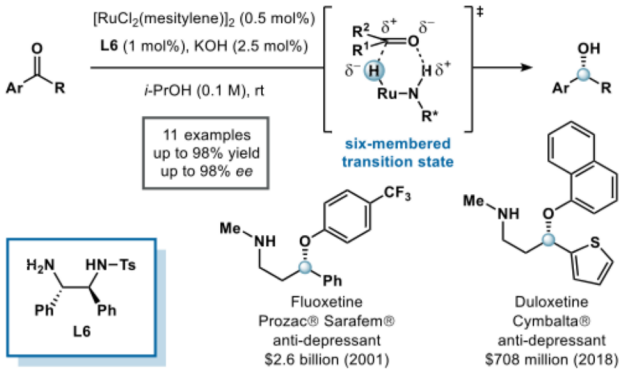

Figure 11. ATH of aryl ketones with a bifunctional Ru catalyst.

conditions and proceed with exceedingly low catalyst loadings (0.001 mol%), high TON (in some cases on the order of 10^6), and high TOF.[120] Theoretical and experimental analysis revealed a bifunctional mechanism whereby simultaneous delivery of the Rh−H hydride and N−H proton proceeds through a six-membered pericyclic transition state through hydrogen bonding to the ligand rather than coordinating directly to the metal center. Ketone hydrogenations such as these have seen many applications to the synthesis of pharmaceutically relevant compounds, including the anti-depressant drugs fluoxetine and duloxetine.[121,122]

Since this discovery, much progress has been made in developing alternative catalysts and expanded variants of ATH.[123−126] Our laboratory leveraged transfer hydrogenation to tackle three distinct challenges: (1) enantioselective ketone hydroacylation, (2) diastereoselective amination, and (3) semi-reduction of allenes.

The γ-butyrolactone scaffold occurs in over 15 000 natural products and biologically active compounds and is a useful synthetic intermediate. Our research group has used Rh-catalyzed hydroacylations to target chiral lactones.[127−129] During these early studies, we found success with substrates bearing coordinating heteroatoms or rigid backbones; however, these Rh catalysts failed to cyclize 1,4-keto aldehydes to generate γ-butyrolactones efficiently (Figure 12a). Decarbonylation was a common decomposition pathway for these conformationally flexible substrates. Tishchenko-type cyclizations of related 1,5-keto aldehydes had been reported using SmI_2 and chiral alcohols or mercaptans as auxiliaries to promote enantioinduction.[130] Additionally, Krische and co-workers have used ATH conditions to effect the hydroacylation of alkynes and 1,3-dienes with alcohols.[131−133] Inspired by these studies, we achieved an enantioselective intramolecular hydroacylation of keto alcohols using a Noyori ATH catalyst (Figure 12b).[134] The reduction proceeds via

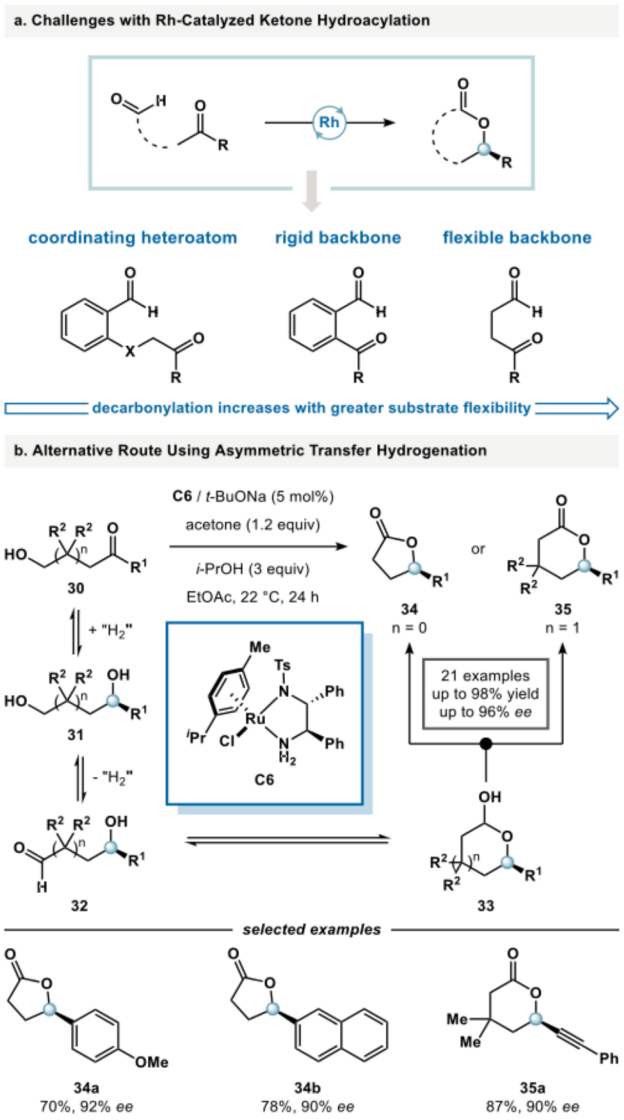

Figure 12. (a) Intramolecular ketone hydroacylation becomes more challenging as backbone flexibility increases. (b) Alternative route to γ-butyrolactones with flexible backbones via ATH.

reversible asymmetric hydride transfer from isopropanol to the alcohol substrate **30** to give diol **31**. This is followed by reversible hydride transfer from the primary alcohol of diol **31** to acetone, giving hydroxy aldehyde **32**. Finally, the acetal isomer **33**, which is in equilibrium with **32**, undergoes *irreversible* hydride transfer to give lactones **34** and **35** in up to 98% isolated yield and up to 96% *ee*. The transformation gives much higher enantioselectivity for the electron-rich substrate **34a** (92% *ee*) than for Noyori's hydrogenation of the analogous *p*-methoxyacetophenone (72% *ee*).[118] This result along with deuterium labeling studies indicates that the ATH of ketone **30** is rate-limiting. The protocol works well for other π-aromatic substrates such as **34b** and for the synthesis of six-membered lactones such as **35a**, despite the greater ring strain.

A kinetic profile revealed a rate dependence on the equivalents of acetone and a process that was autocatalytic with respect to the isopropanol byproduct. Addition of three equivalents of isopropanol significantly increased the rate and reduced the induction period. This behavior was attributed to

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an isopropanol-promoted formation of the Ru hydride; however, a delicate balance of equivalencies was required for success. Too much isopropanol led to over-reduced tetrahydrofuran products, whereas too much acetone led to catalyst inhibition.

A number of methods have since been reported for the synthesis of γ-butyrolactones that follow a hydrogenation strategy. Ogiwara has reported a lactonization of γ-keto acids using catalytic $GaCl_3$ and $PhSiH_3$ as a hydride-transfer reagent.[135] This Lewis acid-catalyzed process is free of transition metals and provides good yields for a number of aryl-substituted γ-keto acids. Other reports by Zhan and Zhou have used chiral Ru and Ir complexes, respectively, to effect similar hydrogenation/lactonization of γ-keto acids with high enantioselectivities.[136,137] Lastly, enzymatic approaches have also been reported. Gotor and Borowiecki have demonstrated stereodivergent enzyme-catalyzed AH/cyclizations of γ-keto esters, giving both enantiomers of the corresponding lactone, depending upon the enzyme chosen.[138,139] Collectively, these reports demonstrate clever design of hydrogenation conditions to solve synthetic challenges.

Polyoxygenated stereocenters are common fragments of polyketides. Stereoselective strategies for the synthesis of these molecules have relied upon chiral auxiliaries and organometallic nucleophiles.[140] These approaches, however, require complicated multi-step substrate synthesis and stoichiometric reagents. To bypass these disadvantages, Krische reported an alternative C−C bond-forming transfer hydrogenation using a chiral Ir complex and **L7** to combine alcohol dehydrogenation with carbonyl allylation (Figure 13).[141,142] Alcohol dehydrogenation forms an aldehyde which then undergoes asymmetric allylation. This process can be iterated for the asymmetric synthesis of polyoxygenated motifs. For instance, the total synthesis of (+)-roxaticin was accomplished in 20 steps from 1,3-propanediol. Seven hydroxy stereocenters were formed by Ir-catalyzed C−C bond-forming hydrogenation without the need for chiral auxiliaries or complex pre-activated substrates.

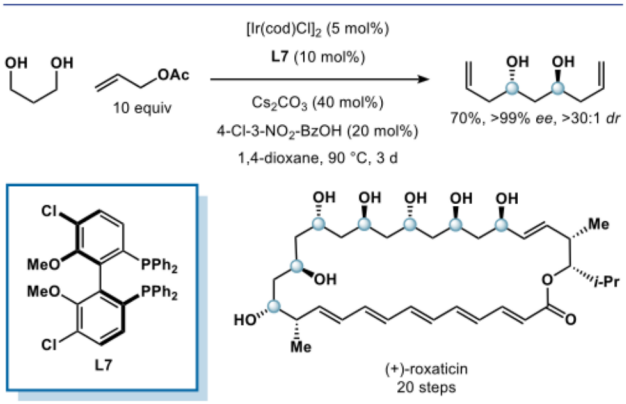

Figure 13. Synthesis of polyoxygenated polyketide motifs via a tandem transfer hydrogenation/allylation process and application to the total synthesis of (+)-roxaticin.

Our laboratory was interested in developing a direct conversion of racemic alcohols to enantioenriched amines. Historically, this required a multi-step process consisting of oxidation, imine formation, and finally, reduction. Advancements in ATH, however, have allowed for the borrowing of hydrogen from racemic alcohols followed by transfer of this H_2 equivalent back to an *in situ*-generated imine. This redox-neutral process converts alcohols directly to enantioenriched amines by avoiding stoichiometric reagents and producing water as the sole byproduct.[143] Zhao reported the first asymmetric variants by using a chiral Ir complex bearing an amino sulfonamide ligand capable of producing acyclic amines in high yields and enantioselectivities.[144] This transformation was limited to the synthesis of chiral anilines. As a complementary approach, in collaboration with the Guan lab, we reported the conversion of racemic secondary alcohols to sulfinamides.[145] Using the chiral Ru P,N,P-type pincer catalyst Ru-Macho and Ellman's auxiliary, a diastereoselective amination of racemic secondary alcohols to sulfinamides was realized (Figure 14). Oxidation of **39** with Ru-Macho to ketone **40** and subsequent condensation to sulfinylimine **41** were followed by hydrogenation by Ru(H_2)-Macho to form the desired α-chiral sulfinamide **42** and water. This transformation was demonstrated on 16 examples with excellent diastereoselectivities and a few notable limitations. Yields were diminished for substrates such as **42a** which lack an α-methyl substituent for R^1 or R^2. Moreover, the outcome is sensitive to sterics, where similar sized β-substituents afford lower diastereoselectivities (**42b**) and no reactivity is observed with bulky groups (**42c**).

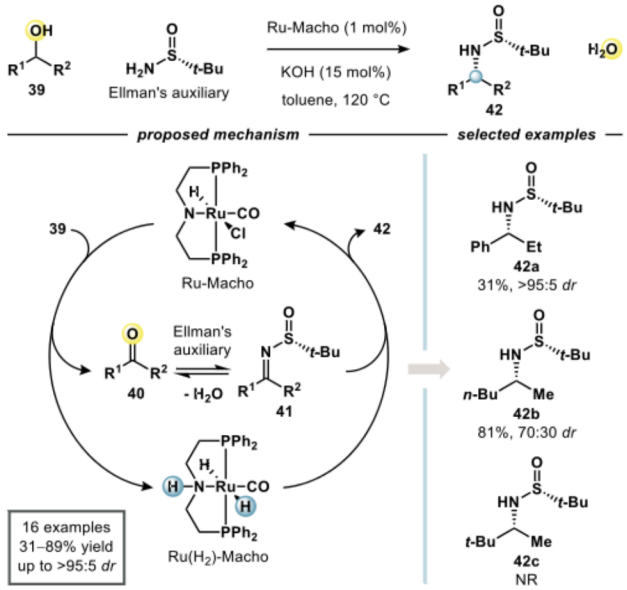

Figure 14. Diastereoselective hydroamination of racemic secondary alcohols via borrowing hydrogen.

Subsequent to our studies, there have been a number of breakthroughs. Related strategies for borrowing hydrogen have used first-row transition metals such as Fe, Co, and Ni for hydroaminations, nitrile reductions, and C−C bond formations.[146−149] Mutti and Turner have reported a dual enzyme-catalyzed hydrogen-borrowing strategy for the enantioselective amination of racemic alcohols.[150] This environmentally benign protocol uses ammonium as the nitrogen source to provide direct access to primary amines. In addition, a transition-metal-free procedure was reported by Wang, detailing the diastereoselective Meerwein−Ponndorf−Verley-type reduction of imines using Ellman's auxiliary and sodium hydroxide. The diastereoselectivity is believed to arise via a chelated transition state whereby a Na ion directs the hydride transfer from an alkoxide to the C atom of an *in situ*-generated imine. The

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transformation slows down with increased concentration of 15-crown-5, a known sequester of Na ions, indicating support for the proposed mechanism.[151]

Biomimetic reductions using natural sources of hydrogen are an attractive feature of transfer hydrogenation. Naturally occurring C−H stereocenters are installed by enzymes such as oxidoreductases using hydride donor cofactors such as NADH and NADPH.[152] MacMillan reported a biomimetic enantioselective hydrogenation of α,β-unsaturated aldehydes using an organocatalyst, chiral amine co-catalyst, and Hantzsch ester as the hydrogen source.[153] Other reports by MacMillan and List used chiral phosphoric acid catalysts and Hantzsch esters in a counterion-directed approach.[154−157]

We sought to use Hantzsch esters in the Rh-catalyzed asymmetric semi-reduction of allenes. This approach would generate compounds **43** with allylic stereocenters, which are traditionally made by the substitution of pre-formed allylic leaving groups with organometallic reagents (Figure 15a).[158] Overcoming issues with chemo- and regioselectivity is a challenge for allene reductions. Previous reports have shown that the less substituted double bond tends to be reduced over the more substituted ones, giving rise to internal olefins,[159−161] whereas methods that reduce the more substituted alkene were limited to mono-substituted allenes.[162,163] Over-reduction to the saturated alkane can also compete, as well as isomerization to 1,3-dienes. Therefore, we sought to identify a catalyst capable of promoting semi-reduction over isomerization.

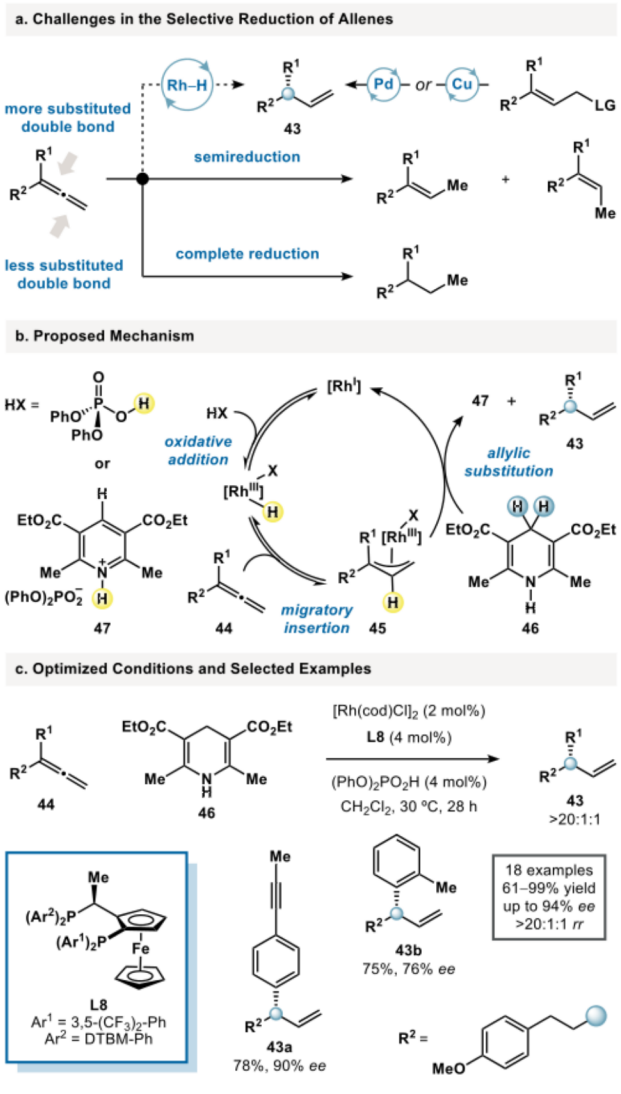

Figure 15. (a) Current and proposed methods for the reduction of allenes. (b) Proposed mechanism involves Rh(III)−π-allyl intermediate. (c) Conditions along with selected examples.

The hydrofunctionalization of allenes through the generation of metal allyl complexes has become an emerging atom-economical technology for the construction of allylic stereocenters.[164−171] Mechanistically, we proposed that Rh(I) oxidative addition to a Brønsted acid would generate a Rh(III)-H (Figure 15b). After insertion of allene **44** and formation of the Rh allyl complex **45**, allylic substitution with Hantzsch ester **46** generates product **43** and pyridinium **47**. Labeling experiments showed complete transfer of deuterium from the *para* position of **46** to the chiral tertiary C−H bond of **43**. Additional deuterium labeling studies suggested that pyridinium **47** may participate in the oxidative addition step. The conditions provided excellent yields, enantioselectivities, and regioselectivities for allylic tertiary stereocenters using the chiral Josiphos ligand **L8** (Figure 15c). Although 1-aryl-1-propynes are known to undergo isomerization in the presence of Rh(III)−H,[172−177] compound **43a** was formed as the major product, leaving the alkyne untouched. Sterically hindered substrates, however, pose limitations on the enantioselectivity; compound **43b** was obtained with a lower 76% *ee*. Regardless, this method demonstrates a promising tool for generating allylic tertiary stereocenters.

Tandem reactions involving ATH have provided significant contributions to the field of AH. Biomimetic approaches allow for work-around strategies to address common challenges in many areas of synthesis. Future innovations in this area can be coupled with more sustainable catalysts to provide greener solutions for modern technologies.

Dynamic Kinetic Resolution. In contrast to kinetic resolution, DKR allows full conversion of both enantiomers of a racemic mixture to an enantioenriched product by way of rapid epimerization. A classic example of a DKR is Noyori's hydrogenation of racemic α-substituted β-keto esters **48** to generate β-hydroxy esters bearing two contiguous stereocenters (Figure 16a). The (*S*,*R*)-**49** isomer is obtained out of four possible stereoisomers with excellent enantio- and diastereocontrol. Quantitative analysis of the process revealed k_S and k_{rac} to be 15 and 92 times faster than k_R, respectively.[178] The diastereoselectivity was found to be dependent upon the solvent. When the reduction is conducted in methanol, the diastereoselectivity of (*S*,*R*)-**49** and (*R*,*R*)-**49** is reduced from 99:1 to 1:1. This is due to a smaller disparity between k_S and k_R. The Noyori DKR-AH of β-keto esters enables the industrial synthesis and commercialization of the carbapenem core, which can be found in Merck's multi-million-dollar antibiotic ertapenem.[179,180]

Non-directed ketone hydrogenation using DKR to construct vicinal stereocenters has also been demonstrated. Early reports by Noyori showed the reduction of 2-isopropylcyclohexanone to one of four stereoisomers of 2-isopropylcyclohexanol using **C7** to give 93% *ee* and 99.8:0.2 *dr* (Figure 16b).[181] The diastereoselectivity can be rationalized by considering steric interactions in the transition states. The catalyst approach from one face places the isopropyl group in a pseudo-equatorial conformation on the opposite side (**TS1**), whereas approach

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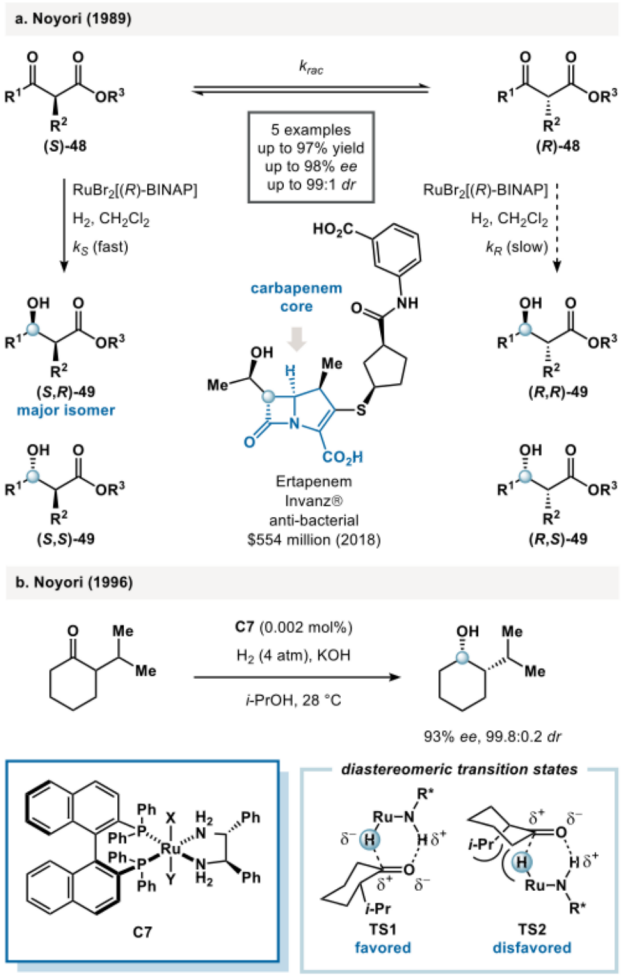

Figure 16. (a) Noyori's pioneering DKR-AH of β-keto esters. (b) Noyori's DKR-AH of simple cyclic ketones.

from the same side causes a disfavored steric interaction between the catalyst and the α-substituent (**TS2**). The favored transition state, **TS1**, gives rise to the *cis* relative stereochemistry observed in the product.

Since Noyori's pioneering work, DKR-AH has become an expanding area of research. In a recent example, Zhou used spiro diphosphine ligands for the reduction of aldehydes and ketones bearing α-stereocenters.[182−186] Johnson reported the enantioselective merging of an ATH lactonization with DKR for the reduction of β-substituted α-keto esters to form densely functionalized γ-butyrolactones (Figure 17).[187] Using a newly designed Ru catalyst and the chiral amino sulfonamide ligand **L9**, efficient access to three contiguous stereocenters of trisubstituted γ-butyrolactones was obtained with high enantioselectivity and remarkable diastereocontrol from easily accessible starting materials. This dynamic reduction leads to diastereoselective formation of α- and β-stereocenters, and the nascent α-hydroxy group undergoes lactonization to an appended methyl ester, generating the third stereocenter.

Asymmetric reductive aminations using DKR-AH provides access to β-chiral amines and β-amino alcohols. Zhao pioneered hydrogen-borrowing strategies for the direct conversion of alcohols to amines with water as the sole byproduct.[95,144,188,189] The first asymmetric DKR variants by Zhao featured a chiral Ir complex (**C9**) and a chiral phosphoric

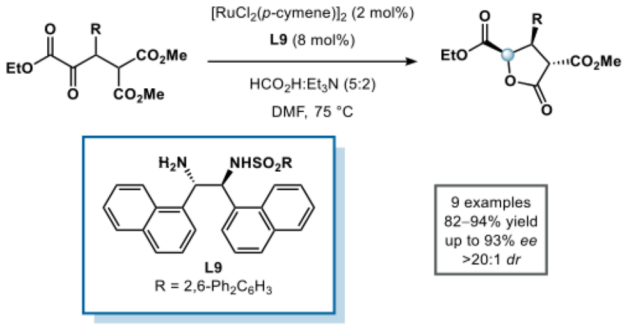

Figure 17. Johnson's synthesis of γ-butyrolactones bearing three contiguous stereocenters via DKR-ATH of α-keto esters.

acid co-catalyst (**C8**) as a cooperative pair (Figure 18).[188] Here, secondary alcohols bearing α-stereocenters comprised of

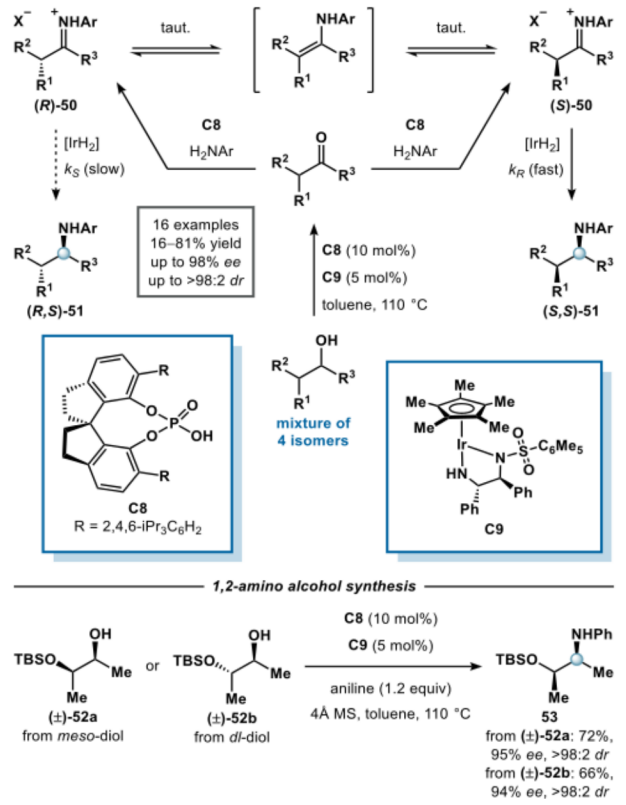

Figure 18. Hydrogen-borrowing strategy for the dynamic AH of racemic secondary alcohols to chiral amines bearing vicinal stereocenters.

all four stereoisomers were oxidized to the corresponding ketones and epimerized by enamine formation, assisted by the acid co-catalyst. In addition to differentiating between (*S*)-**50** and (*R*)-**50**, the catalyst must also distinguish between the enantiotopic faces of each imine to control the diastereo- and enantioselectivity. The synthesis of chiral acyclic amines (*S,S*)-**51** containing vicinal stereocenters was accomplished with excellent stereoselectivities for up to 16 examples. Furthermore, all four stereoisomers of **52** converged to a single isomer of β-amino alcohol **53** with comparable yields and stereoselectivities. Traditional asymmetric routes to β-amino alcohols can become arduous multi-step processes if not derived from

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natural chiral pool sources such as the canonical amino acids. These developments demonstrate the power of DKR-AH as a viable route to traditionally difficult-to-access motifs.

Sigmatropic rearrangements represent a pathway for racemization that is unique from the epimerization of carbonyl α-stereocenters.[190−192] For instance, the Mislow−Evans [2,3]-sigmatropic rearrangement of allylic sulfoxides passes through an intermediate sulfenate ester, resulting in epimerization of a sulfur stereocenter (Figure 19).[192] Considering the value of

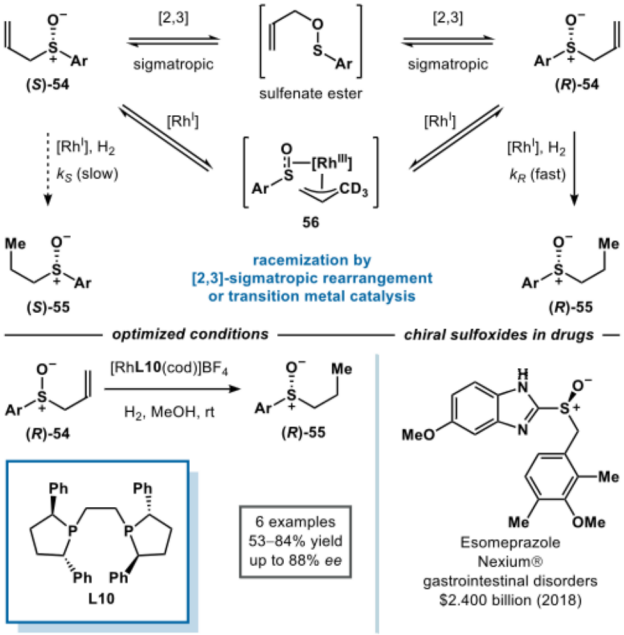

Figure 19. Dynamic AH of sulfoxides via auto tandem catalysis.

chiral sulfoxides in medicines (esomeprazole, modafinil, dexlansoprazole, and pantoprazole) and ligands,[193−198] we sought to access enantiopure sulfoxides via DKR. Previous asymmetric routes to chiral sulfoxides primarily relied upon *oxidative* strategies. In contrast, we imagined a complementary asymmetric *reductive* method. Using a Rh catalyst, successful hydrogenation of (*R*)-**54** over (*S*)-**54** was achieved in moderate yields and enantioselectivities to give saturated sulfoxides (*R*)-**55**.[199] Kinetic studies demonstrated an enhancement of racemization by a factor of 33 when the reaction was performed in MeOH and in the presence of [Rh**L10**(cod)]BF_4. Computational analysis and deuterium labeling studies support an auto tandem catalytic process whereby the rate of epimerization is accelerated by the Rh catalyst through oxidative addition and formation of the π-allyl complex **56**. Polar protic solvents are critical for this Rh-catalyzed rearrangement; rate enhancement was not observed in a non-polar medium (i.e., toluene:CH_2Cl_2). Following this report, Vidal-Ferran demonstrated a Rh-catalyzed hydrogenative kinetic resolution of vinyl sulfoxides.[200] These reports provide mutual reaction toolbox contributions for the reductive synthesis of sulfoxide stereocenters.

Tandem hydrogenations involving DKR have become an expanding technology. The ability to access a product with a single stereoconfiguration out of multiple possible stereoisomers is a powerful tool with broad applications for the synthesis of biologically relevant motifs. The usage of novel modes of epimerization is sure to lead to further discoveries in the field of AH.

■ FUTURE PROSPECTS

The future of AH will hinge upon the design of cheaper, greener, and more sustainable catalysts. Within this framework, we highlight recent advancements in two general categories: (1) chemocatalysis and (2) biocatalysis. We imagine opportunities for further catalyst improvements through the design of ligands that can control the reactivity of more earth-abundant metals. We also envision metal-free alternative strategies. In addition, enzyme-catalyzed processes will play an ever increasing and competitive role.

Chemocatalysis. The greatest feats of AH are due almost exclusively to the design of catalysts involving the late second- and third-row transition metals. However, interest in sustainability has ushered a search for more environmentally friendly methods to address critical challenges of the modern era. Recent advancements have identified (1) earth-abundant first-row transition metals, (2) novel ligand design, and (3) metal-free catalysts as viable paths. Herein, we highlight notable developments in these areas.

AH methods using Fe, Co, and Ni would be more sustainable and cost-effective alternatives to the use of their second- and third-row counterparts. Early catalysts derived from first-row metals often suffered from poor functional group tolerance and issues with stability owing to a lower HOMO/LUMO gap compared to second- and third-row metals. Morris developed an Fe-catalyzed ATH using the so-called FeATHer complexes. These Fe(II) catalysts bear tetradentate P,N,N,P ligands and have been shown to hydrogenate ketones and imines with up to >99% *ee*.[201,202] Ligand design was key to discovering highly active Fe complexes with catalytic TOFs (>200 s^{-1} at 28 °C and TON up to 6100) comparable, or even superior, to those obtained with precious metal catalysts (analogous Ru-P,N,N,P complexes give a TOF of 92 s^{-1} at 60 °C).[203] These FeATHer complexes and others have been used for the ATH of numerous other groups such as imines and nitriles.[204−206]

Methods of AH catalyzed by Co and Ni have surged in popularity in recent years. Pfaltz reported an early example of a Co-catalyzed hydrogenation using borohydrides as the reductant; however, this method was limited in scope and was poorly selective.[207] Recent modifications have been reported by Chirik using Co catalysis.[208−211] Here, the high-throughput screening (HTS) of 216 bidentate ligands led to the 200 g scale AH of **57** to give 97% yield and 98.2% *ee* of the anti-convulsant drug levetiracetam (Keppra) used to treat epilepsy (Figure 20).[210] Zn dust was employed as a mild activator, along with $CoCl_2$ and **L12** at incredibly low catalyst loadings of 0.08 mol%. Deuterium studies support a pathway involving the homolytic cleavage of H_2. This report is analogous to studies from Kagan and Knowles on the Rh-catalyzed hydrogenation of dehydroamino acids and computational studies from Zhou on Ir-catalyzed systems.[212−214] A complementary and patented procedure with Rh requires much higher catalyst loadings and a less environmentally friendly solvent (CH_2Cl_2 as compared to MeOH).[215] Alongside these studies, Chirik has disclosed the AH of α,β-unsaturated carboxylic acids using both Co and Ni.[211,216] Contrary to Co-catalyzed hydrogenation, the Ni-catalyzed method involves heterolytic cleavage of H_2 analogous to the Ru-catalyzed mechanism. Co has also been used for the AH of

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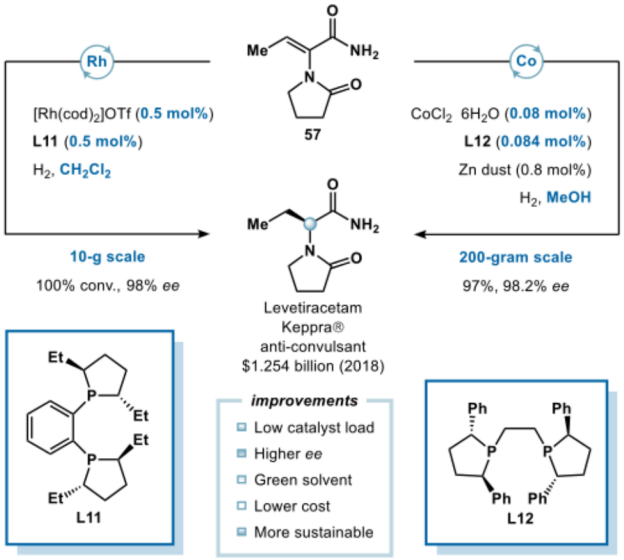

Figure 20. Co-catalyzed AH for the synthesis of levetiracetam.

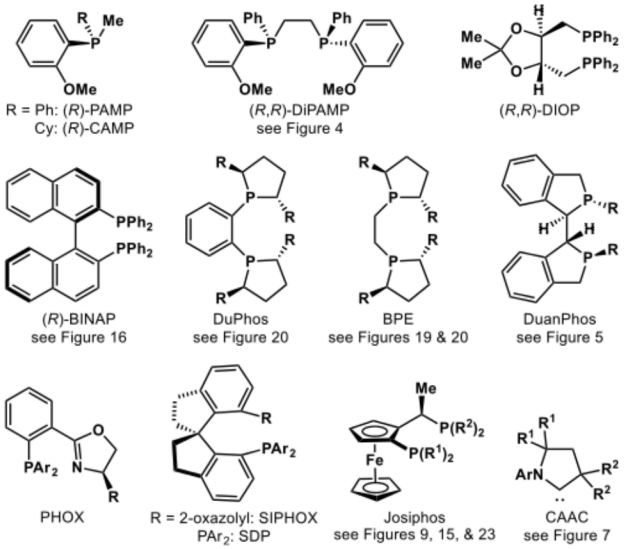

Figure 21. Ligand diversity in stereoselective hydrogenation.

1,1-diboryl olefins, whereas Ni has been used for the AH of *N*-sulfonyl imines and dehydroamino acid derivatives.[217−219] Evidenced by these reports, first-row transition metals are taking the lead for the modernization of AH.

When considering the future of AH, one would be remiss to ignore the most important design element: the ligand. While the options for *metals* are discretely limited to the periodic table, the options for *ligands* are seemingly endless and provide a toolbox for the stereoelectronic fine-tuning of metal centers. After more than 50 years, accurate stereochemical predictions with computational models remain a challenge.[220] This is because the energy difference for achieving 95% *ee* is comparable to the energy of the C−C bond rotation of ethane (~2 kcal·mol^{-1}). Therefore, ligand design has been partly a guessing game governed often by trial and error rather than rationale. Regardless, major achievements have led to innumerable highly selective and modular ligand classes that have expanded the scope of accessible chiral motifs. A detailed review of ligands is beyond the scope of this Perspective; however, highlights here will demonstrate the importance of ligands on the future of AH.

The discoveries of homogeneous Rh-centered hydrogenation catalysts by Wilkinson and methods for preparing enantioenriched phosphines by Horner and Mislow enabled Knowles to report the first asymmetric transition-metal-catalyzed reaction in 1968, wherein a Rh catalyst bearing (−)-methyl-propyl-phenyl-phosphine was used to reduce α-phenylacrylic acid in 15% *ee*.[221] The earliest ligand designs targeted monodentate phosphines with chirality centered at the P atom. Ligands such as PAMP and CAMP (Figure 21) could hydrogenate *N*-acyl-dehydrophenylalanine in 58% *ee* and 88% *ee*, respectively. At his 2001 Nobel lecture, Knowles recounted the following about the significance of these results:[9]

> *"It all seems too easy and simple, but this was the first time ever that anyone had obtained enzyme-like selectivity with a man-made catalyst! ... I don't think that even we were emotionally equipped to realize what we had done. Here, with this simplest of molecules [CAMP], we had solved one of the toughest synthetic problems. For the past hundred years, it had been almost axiomatic among chemists that only nature's enzymes could ever do this job."*

Following these discoveries, C_2-symmetric bidentate bisphosphines were found to greatly impact the enantioselectivity of AH. Some ligands include DIOP by Kagan[222] (1971) which introduced backbone chirality, DiPAMP by Knowles[9,223,224] (1977) which gave L-DOPA in 95% *ee* (Figure 1), and BINAP by Noyori[10,225−227] (1980) which demonstrated the potential for axial chirality. Each of these pushed structural boundaries and expanded the scope of AH. Subsequently, rigid electron-rich ligands such as DuPhos and BPE by Burk[228,229] (1991) as well as DuanPhos by Zhang[220,230] (2007) were highly modular and gave increased TON at lower catalyst loadings. The C_2-symmetric ligands improve selectivity by reducing the number of geometrically unique transition states and providing identical steric environments from each face of the complex.

The ligand toolbox for AH continues to grow with greater structural diversity. Some bidentate P,N ligands include PHOX by Pfaltz[231−233] (1998) for the AH of unfunctionalized and sterically hindered olefins and SIPHOX by Zhou[234−236] (2006) for the AH of ketones and imines. The spiro SDP series by Zhou (2003), when complexed to Ru, can hydrogenate simple ketones with up to 99.5% *ee*.[237,238] Ferrocene backbones such as the C_1-symmetric planar chiral Josiphos by Togni from Solvias (1990) provide exceedingly high TON and TOF for the AH of olefins, carbonyls, and imines.[239,240] Additionally, carbene-based ligands such as CAAC by Bertrand[75,241] (2005) have been used for the hydrogenation of aromatic rings. These represent just a few examples of the immense ligand arsenal available for asymmetric metal-catalyzed processes.

Efforts to streamline transition-metal catalysis into safer, more robust, and cost-effective strategies could greatly improve industrial applications. With virtually infinite possible ligand

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scaffolds, manually fine-tuning the stereoelectronics of metal centers can be arduous, and screening countless ligands is a nearly impossible task. Time is valuable, and HTS technologies have alleviated the period to evaluate hundreds (or even hundred-thousands) of conditions from months or even years to just days.[242,243] The use of *in silico* techniques to expedite ligand design has become the "holy grail" for the advancement of asymmetric catalysis.[244] Computational strategies have shown promise in recent years for predicting stereochemical outcomes.[245−252] One example employs the quantum-guided molecular mechanics (Q2MM) model developed by Wiest. Here, Q2MM computes transition-state force fields used for analysis of conformational ensembles to predict stereoselectivity by Boltzmann distribution averaging. This has been used to predict stereochemical outcomes of Rh- and Ru-catalyzed hydrogenations.[65,253−255] In fact, the mean unsigned error for the Ru-catalyzed AH model is 0.65 kcal·mol^{-1}, which is within the range required to accurately identify a highly stereoselective transformation.[255] Here, predictions of 98% *ee* would result in experimental values within a range of 2%. In addition, machine learning (ML) technology has had major impacts across many fields, including AH. Sunoj demonstrated the use of a random forest ML algorithm to predict stereochemical outcomes of AH. Analysis of catalyst−substrate molecular parameters across 368 known binaphthyl catalyst families led to a root-mean-square error (rmse) of 8.4 ± 1.8 for the prediction of enantiomeric excess compared to experimental values.[256] This method was an improvement to conventional ML approaches such as extreme gradient boosting (rmse = 9.6 ± 1.9) and convolutional neural networks (rmse = 11.6 ± 2.8). Despite early success, *in silico* design has not become widely available, due in part to limited computing power as well as insufficient accessibility to and specialized knowledge by average synthetic chemists. Regardless, as computer technology advances rapidly, new possibilities in computational methods will continue to thrive.

Along with *in silico* design, continuous-flow processes have shown promise in recent years. Commercial reactors such as the H-Cube by ThalesNano have become popular for safe and convenient small-scale hydrogenations up to 100 bar.[257] Moreover, Kobayashi has reported a heterogeneous AH of 20 enamides and dehydroamino acids in >95% yield and >95% *ee*.[258] A chiral Rh-QuinoxP* catalyst was immobilized by a heteropoly-acid/amine-functionalized mesoporous silica composite through acid−base electrostatic interactions and remained active for up to 90 h without any detectable leaching into the crude mixture. Furthermore, the AH of three API intermediates showed the feasibility of this method for the synthesis of drug candidates. Another example by Vincent used an enzyme-modified nanotube for the AH of ketones with excellent enantioselectivities.[259] Scientists at Eli Lilly have developed a pressurized flow reactor for the 144 kg scale hydrogenation of an API intermediate in 99% *ee*.[260] The process included liquid−liquid extraction, solvent exchange distillation, and crystallization steps while using equipment that fits inside common laboratory fume hoods. Additionally, scientists at AstraZeneca have used AH flow technology with a solid-supported Rh catalyst for the kg-scale synthesis of an API intermediate in 98% yield, >99% *ee*, and with <1 ppm Rh content.[261] Compared to batch protocols, continuous flow provides simplified workups, greater efficiencies, and improved safety profiles, leading to a more sustainable, robust, and cost-effective option for industrial scale-up efforts.

There are a number of promising metal-free alternatives to AH. An incipient strategy developed by Stephan demonstrates the activation of H_2 by non-metal catalysts coined frustrated Lewis pairs (FLPs) (Figure 22a).[262−265] FLPs arise from

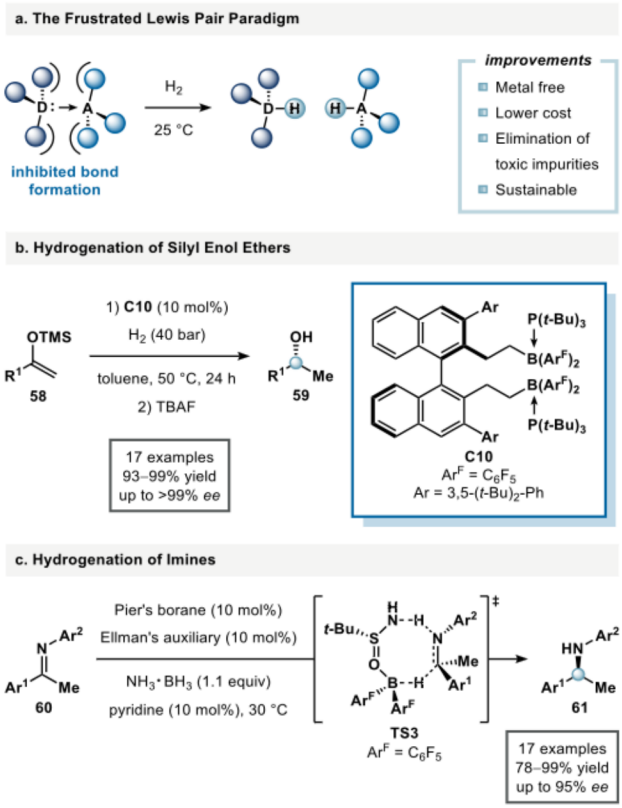

Figure 22. (a) FLP paradigm and its potential impacts. (b) Formal AH of ketones using silyl enol ethers and an axially chiral bis-FLP catalyst. (c) AH of imines with chiral bimolecular FLP catalyst via an eight-membered transition state.

electron donor−acceptor pairs in which dative bond formation is impeded by factors such as sterics. This obstruction results in a dissociative equilibrium favoring the free acid and base. Chiral variants of FLP catalysts have been developed.[266−271] Du reported the AH of silyl enol ethers **58** to enantioenriched alcohols **59** using the axially chiral bis-FLP catalyst **C10** as a formal asymmetric reduction of ketones (Figure 22b).[268] This was applied to 17 substrates in high yields and excellent enantioselectivities. In addition, Du has developed an FLP-ATH of imines **60** to enantioenriched amines **61** using a bimolecular catalyst consisting of Pier's borane ($HB(C_6F_5)_2$) and Ellman's auxiliary (Figure 22c).[271] Experimental and computational studies indicate an eight-membered transition state (**TS3**) upon binding with **60**. The FLP catalyst is regenerated by hydrogen transfer from ammonia borane and is the first highly enantioselective example using this hydrogen source. Collectively, these developments show promise for the discovery of metal-free catalysts. Further developments of processes such as this could impact industry by lowering costs, eliminating toxic metal impurities from drug intermediates, and improving sustainability.

Electrochemical hydrogenations provide another avenue for further development. Transfer hydrogenations using ammonium have shown success for the reduction of heterocycles and

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olefins.[272−274] Asymmetric electrochemical transformations have been developed in recent decades.[275] An early method by Osa used modified Raney Ni powder electrodes with tartaric acid for the AH of ketones.[276] Although poorly selective, this example demonstrated that electrodes modified with chiral agents could be a platform for electrochemical AH. The low enantioselectivity of this system was attributed to poor distribution of the chiral tartaric acid across the electrode. Subsequent methods used chiral polymer-coated[277] (such as a poly-L-valine graphite cathode), transition-metal-complexed[278−280] (Rh and Pd), or alkaloid-doped[281−287] (yohimbine, strychnine, and cinchonidine) electrodes for the AH of olefins and carbonyl derivatives with low to moderate stereoselectivities. Enzyme-catalyzed electrochemical reductions have also been reported. Tischer demonstrated the ATH of sodium α-methylcinnamate in 95% yield and 95% *ee* using an enolate reductase and NADH.[288] Methyl viologen acts as a mediator between the cathode and the reduction of NAD^+ to regenerate NADH. Similarly, Yoneyama reported the AH of ketones via an alcohol dehydrogenase giving >99% *ee* in most cases.[289] Yoneyama also demonstrated the asymmetric imino hydrogenation of pyruvic acid using a D-amino acid oxidase-modified glassy carbon electrode and an electron mediator to give D-alanine in >99% yield and >99% *ee*.[290] Schmid reported the ATH of 3-methylcyclohexanone in 96% *dr* using an alcohol dehydrogenase, NADH, and a Rh complexed cathodic mediator.[291] These investigations provide a way forward for the development of more robust asymmetric electrochemical hydrogenations.

Biocatalysis. In contrast to chemocatalysis, biocatalysis has leapt to the forefront of modern chemistry. The revolutionary technique known as directed evolution has allowed for the discovery of enzymes with novel non-natural functions.[292−301] This technology continues to replace traditional methods of organic synthesis, and the 2018 Nobel Prize in Chemistry was awarded to Arnold for her pioneering work.[301] In addition, recent advancements in the use of enzymes for the synthesis of complex biologically active molecules have had enormous impacts on medicinal chemistry and industrial syntheses.[302−305] There are several advantages to using biocatalysts. (1) They are renewable and biodegradable, which could positively impact long-term cost and sustainability. (2) They tend to be more environmentally benign and less toxic than heavy metals. (3) Their specificity and selectivity can be evolved to suit a specific substrate by eliminating arduous substrate syntheses and screening of reaction parameters.

This technology has been applied to industrial processes. A notable example is Merck's synthesis of the anti-diabetic drug sitagliptin. The original process involved an asymmetric chemocatalyzed hydrogenation of the unprotected enamine **64**, which was derived from the pro-sitagliptin β-keto amide intermediate **63** (Figure 23).[16,17] This route provided Januvia in 95% *ee*; however, it suffered from unsatisfactory enantioselectivity, necessitated high pressures of H_2 (250 psi), and required rigorous purification at the expense of yield due to residual Rh contamination. Using a clever combination of *in silico* design and biocatalyst engineering followed by directed evolution, scientists at Merck were able to evolve a transaminase that was highly active for ketone **64**.[18] Since the reaction conditions were much different from those that enzymes experience in nature, the challenges with this historic development were multi-dimensional. Namely, the chemical process had to be iteratively optimized in tandem with each newly evolved enzyme to obtain variants both increasingly more tolerant of the reaction conditions (such as reagent concentrations, solvent solubility, and temperature) and that could provide the desired product with >99.9% *ee*. Ultimately, all of these prerequisites were met, and sitagliptin was obtained in >99.95% *ee* without a trace of the enantiomer. Improvements from the chemocatalyzed process included (1) an increase in overall yield and productivity, (2) a decrease in waste and manufacturing cost, and (3) overall milder conditions under ambient pressure without the use of toxic heavy metals.

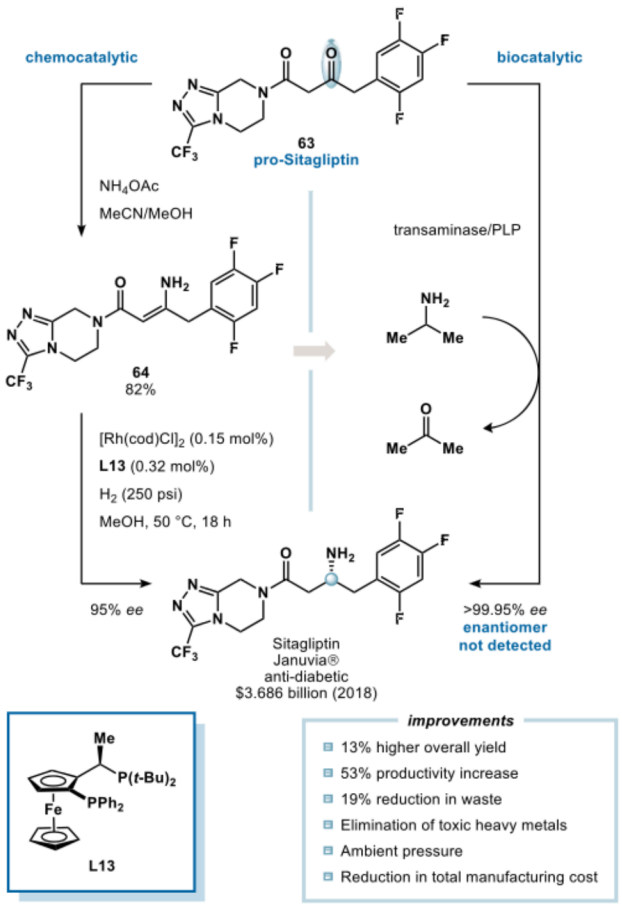

Figure 23. Evolution of sitagliptin synthesis from chemocatalysis to biocatalysis.

■ CONCLUSIONS

From humble beginnings as an academic curiosity to use in large-scale industrial manufacturing, AH has revolutionized the construction of chiral centers. Its continual relevance hinges upon mechanistic understanding, catalyst evolution, and innovative applications. When combined, these form a synergistic connection that has sustained AH as the state-of-the-art among modern transformations.

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Notes

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