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Asymmetric Catalysis Mediated by Synthetic Peptides, Version 2.0: Expansion of Scope and Mechanisms

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Abstract

Low molecular weight synthetic peptides have been demonstrated to be effective catalysts for an increasingly wide array of asymmetric transformations. In many cases, these peptide-based catalysts have enabled novel multifunctional substrate activation modes and unprecedented selectivity manifolds. These features, along with their ease of preparation, modular and tunable structures, and often biomimetic attributes make peptides well-suited as chiral catalysts, and of broad interest. Many examples of peptide-catalyzed asymmetric reactions have appeared in the literature since the last survey of this broad field in *Chemical Reviews* (*Chem. Rev.* **2007**, *107*, 5759–5812). The overarching goal of this new review is to provide a comprehensive account of the numerous advances in the field. As a corollary to this goal, we survey the many different types of catalytic reactions, ranging from acylation to C–C bond formation, in which peptides been successfully employed. In so doing, we devote significant discussion to the structural and mechanistic aspects of these reactions that are perhaps specific to peptide-based catalysts and their interactions with substrates and/or reagents.

Graphical Abstract

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1. Introduction

Mimicry of biological systems has spawned an enormous amount of research. Under the banner of “biomimetic chemistry,” scientists have synthesized countless compounds that resemble biological molecules in some way, reproducing aspects of both structure and function.¹ Function itself may be considered from several perspectives. On the one hand, a small molecule that mimics a partner in a binding event, such as a protein-protein interaction,² constitutes a significant achievement in molecular design at the interface of chemistry and biology, with a particular emphasis on thermodynamics. On the other hand, mimicking bond-forming reactions is a parallel thrust, and expands the challenge to include the kinetic details of the respective transition states.³

In this latter context, low molecular weight peptides have played a significant role in terms of both establishing new fundamental concepts and contributing useful catalysts for powerful, important, and often challenging reactions. While the study of peptide-based catalysis may well have begun in search of analogies between synthetic catalysts and enzymes,⁴ it quickly became clear that many of the mechanistic features underlying effective catalysis by small molecules and enzymes were similar. For example, the reliance on noncovalent interactions is now a theme throughout the field of asymmetric catalysis, and is one that is routinely identified in studies of both small molecule catalysts and enzymes.⁵ The search for peptide-based catalysts in the context of synthetically useful transformations has also created synergy with the broad field of organic synthesis.⁶

The exploration of peptide catalysis has also provided particular opportunities for heuristic comparison to enzymes, given the shared reliance on amino acid sequences to deliver folded, three-dimensional structures and arrays of cooperative functional groups for substrate activation.^{7,8} These synthetic peptides have provided taut springboards for the investigation of conformationally dynamic—if not “flexible”—catalysts, which are now ever more under study.⁹ Moreover, peptide catalysts have both enabled novel, multifunctional substrate activation modes and addressed selectivity challenges in unique stereochemical contexts, spanning point, axial, and conformation-dependent chirality. In the process, numerous peptides have now been shown to be effective catalysts for an increasingly wide array of important asymmetric transformations from the perspective of synthetic utility, including many that are not extant in biochemistry. These attributes, along with their ease of preparation, tunable structures, and often biomimetic characteristics, have made peptides well-suited as chiral catalysts and contributed to the growing interest in their application. Indeed, features of oligopeptides now routinely appear in partially peptidic, and even non-peptidic, catalyst designs of very broad mechanistic and functional scope. Examples abound in organocatalytic systems,^{10–12} as well as in organometallic chemistry, wherein the peptidic functionalities serve as ligands on transition metal complexes.¹³

Many highly creative and synthetically useful examples of peptide-catalyzed asymmetric reactions have appeared in the literature since our group's first *Chemical Reviews* article on the subject.⁸ The overarching goal of this new review—thirteen years later—is to provide as comprehensive an accounting of the numerous advances in the field as is possible. As a corollary to this goal, we survey the many different types of asymmetric reactions, ranging from C–C bond forming reactions to halogenation, in which peptides have been successfully employed. In so doing, we devote significant discussion to the structural and mechanistic aspects of these reactions that perhaps began as specific to peptide-based catalysts and their interactions with substrates and/or reagents, but which are now appearing more broadly in many other catalytic scaffolds. Our goal has been to compliment the other, more focused reviews of peptide-based catalysts that have recently appeared.^{14–16}

Because of the explosive growth in the field, boundary conditions are necessary in order to limit this review to a tractable length. Although many exemplary reactions catalyzed by single amino acids and their derivatives have been reported to date, we intend to focus primarily on oligopeptides consisting of 2–20 amino acids, where both secondary structure and multifunctional activation modes likely contribute to selective catalysis. In select cases, we do opt to discuss amino acid-catalyzed reactions, when the discussion illuminates an instructive concept. Additionally, since we have recently reviewed the topic of site-selective functionalization of complex molecules,^{17,18} this current review focuses solely on catalytic, enantioselective reactions mediated by synthetic peptides. Our literature survey endeavors to span the years of 2007–2019.

2. Oxidation

The most common asymmetric oxidation mediated by peptides prior to 2007, and overall one of the most well studied peptide-catalyzed reactions, was the Juliá–Colonna epoxidation (Section 2.1.1). Since then, numerous additional reports improving both the efficiency of the

transformation and studying the mechanism have been disclosed. Additionally, a substantial amount of recent work has focused on the development of new and more powerful peptide-based catalysts for epoxidations based on aspartyl (Asp) peracids (Section 2.1.2) and dioxiranes (Section 2.1.3). Numerous other reports highlighted that the sequences of these Asp-based catalysts could be reprogrammed to facilitate Baeyer–Villiger oxidations (Section 2.2), Trp oxidations, and *N*-oxidation of pyridines (Section 2.3.1). Finally, various reports have also highlighted the utility of other peptides as catalysts for oxidations of alcohols (Section 2.3.2) and carbonyl α -positions (Section 2.3.3).

2.1. Epoxidation

2.1.1. Juliá–Colonna Epoxidation.—Since its initial development in the 1980s, few peptide catalyzed reactions have received as much attention as the Juliá–Colonna epoxidation.^{19,20} A subclass of Weitz–Scheffer epoxidation, Juliá–Colonna reactions involve the nucleophilic epoxidation of electron-deficient olefins with aqueous hydrogen peroxide in the presence of both base and a poly(amino acid) catalyst (Figure 1a). In lieu of traditional stepwise peptide synthesis, these catalysts are normally synthesized through polymerization in the presence of an initiator amine and a sufficient amount of *N*-carboxyanhydride derived from the desired amino acid (Figure 1b). The epoxidation reactions are traditionally performed in a triphasic mixture consisting of both water and organic solvent, along with solid-supported peptide catalysts.

Analysis of the reaction mechanism in epoxidations of chalcone derivatives (**2.1**)—the most common substrate for this transformation—reveals a complicated picture (Figure 1c).^{21,22} Beginning either with stereopure **2.1** or a mixture of both *Z*- and *E*-alkenes, nucleophilic addition of peroxide occurs, possibly with assistance from the peptide catalyst. While reversible, the facial specificity of this addition is enantiodetermining for the β -position. The C–C bond adjacent to the peroxy group in the resulting intermediate can freely rotate to facilitate orbital overlap of the peroxy species with either face of the enolate π -bond, leading to either diastereomer of epoxide **2.2**. Diastereoselectivity is hence determined by the orientation of this dihedral angle. In assessing how peptides can control the selectivity in both of these critical steps, the most common catalysts are purported to adopt α -helical conformations, such as poly(Leu) peptides.^{21,23} In this structure, the four *N*-terminal NH groups are not engaged in intrachain, helix-forming H-bonds and thus make excellent handles for H-bond donation to substrates. A putative model containing the critical noncovalent interactions associated with the peptide (red) and between the peptide and substrates (blue), was proposed to account for the observed enantioselectivity (Figure 1d).

Given the high enantioselectivity afforded by these peptides, numerous reports since 2007 have focused on advancing this system through (1) improvement over the often challenging triphasic (water/organic/solid) reaction conditions, (2) further development of more selective catalysts, (3) expansion of substrate scope, and (4) mechanistic analysis.

One aspect of the Juliá–Colonna epoxidation that has been the subject of extensive study is catalyst design. A complication of the earlier conditions for this reaction is that the peptide catalysts often formed a voluminous gel upon workup, making extractions difficult and

impeding reuse. A workaround for this issue has been to synthesize solid-supported polypeptides, which are easier to separate.

In continuing to make more powerful catalysts that (1) have a lower molecular weight and (2) are easier to reuse, Yang, Tang, and co-workers applied concepts from phase transfer catalysis toward these epoxidations.²⁴ Efforts in phase transfer catalysis have previously been undertaken with regards to the Juliá–Colonna epoxidation, specifically in the use of additives to increase the concentration of peroxide in the organic layer.²⁵ Building on this approach, the authors synthesized poly(Leu) peptides with an imidazolium-containing initiator to form peptide **2.3a** (Figure 2a). When comparing this catalyst to the poly(Leu) peptide synthesized with *n*-butylamine as an initiator (**2.3b**) in the epoxidation of **2.1**, imidazolium-containing **2.3a** provided epoxide **2.2** in substantially higher yield and enantioselectivity (Figure 2b). Furthermore, catalysts were easily re-isolated from reactions, and reusable with minimal perturbation to enantioselectivity. Reaction times even decreased after the first reaction with a batch of catalysts.

While helical polypeptides have dominated the field of Juliá–Colonna epoxidation since its inception, limited work has focused on incorporating other peptide structural elements within this framework. Kudo and co-workers had previously developed peptide catalysts for transfer hydrogenations (see Section 3.1) consisting of a Pro-containing β -turn attached to a poly(Leu) chain supported on resin. The *N*-terminal Pro-residue operates *via* iminium catalysis to activate enals toward reduction with Hantzsch ester, while the β -turn provides a good chiral environment for asymmetric induction. The poly(Leu) chain was later added to increase the hydrophobicity of the catalyst for reactions in aqueous media. However, given the known efficacy of poly(Leu)-based peptides in epoxidation reactions, the authors further studied their catalysts in this context.²⁶ Specifically, the aqueous epoxidation of enals *via* iminium catalysis was examined, which is similar, yet mechanistically distinct, from the classic Juliá–Colonna epoxidation of enones. Commencing with a previously developed catalyst for transfer hydrogenation, peptide **2.6a** was found to afford epoxide **2.5** in a good er of 14:86, albeit with low conversion (Figure 3a, entry 1). Removing the first *N*-terminal Pro residue and replacing the α -aminoisobutyric acid (Aib) residue with 1-aminocyclohexane carboxylic acid (Achc, **2.6b**) enabled an increase in conversion to 77% with similar enantioselectivity (entry 2). Deletion of the two Trp-containing residues resulted in reduction of the observed er to 79:21, indicating these positions play an essential role in enantioinduction (entry 3). Given the importance of these positions, the authors postulated that the inclusion of very bulky pyrenylalanine (Ala(1-Pyn)) might increase the enantioselectivity, and indeed catalysts **2.6d** and **2.6e** provided **2.5** in up to 97:3 er (entries 4–5). Finally, the α -helical forming poly(Leu) chain on the *C*-terminus was confirmed to be important for catalyst activity, as variation in this sequence resulted in lower ers and conversions.

Given the success in the context of asymmetric epoxidation of enals, Kudo and co-workers next applied their system toward the oxidation of enones (Figure 3b).²⁷ In this case, secondary amines are too sterically hindered to activate ketones *via* iminium catalysis, so the authors turned to primary amine-based catalysts.²⁸ Specifically, given the observed effect of the aromatic residues near the *N*-terminus in epoxidations of **2.4**, the authors designed new

catalysts with *N*-terminal aromatic residues (**2.7a** & **2.7b**). Either Trp or Ala(1-Pyn) residues were appended to a Pro for structural rigidity, followed by a 3_{10} -helix forming Leu-Leu-Aib repeating sequence. While Trp-containing **2.7a** provided epoxide **2.2** in low conversion and er, Ala(1-Pyn)-containing **2.7b** afforded **2.2** with 90:10 er and 60% conversion. Strikingly, the absolute stereochemistry of **2.2** is reversed compared to reactions mediated by poly(Leu) catalysts, despite both containing only L-amino acids.

Further efforts to render peptide catalysts more easily separable from reaction mixtures were accomplished by Segarra and co-workers, who reported the immobilization of poly(Leu)-containing peptides on hydrotalcite (Figure 4).²⁹ Synthetic polypeptides were immobilized in less than 30 min under ultrasonic conditions. These nanohybrid materials did not require any pre-activation time, provided rapid and selective epoxidations, and were easily reutilized in subsequent reactions without change in activity.

In addition to solid-supported catalysts, recent work has focused on the development of *de novo* solution-phase peptides with a variety of intriguing design features.

Given the hypothesis that Juliá-Colonna catalysts predominantly exist as helices, Kurihara and co-workers attempted to stabilize this secondary structure by stapling the peptide backbone (Figure 5).^{30–32} Intrachain stapling between residues positioned adjacent to each other within a helical scaffold, such as the *i* and *i*+4 positions, has been shown to stabilize that conformation.³³ As such, allylated L/D-Ser derivatives were incorporated into short peptide chains (**2.8**) and subjected to ring-closing metathesis and subsequent olefin hydrogenation to access all four diastereomers of stapled peptide **2.9** (Figure 5a). Spectroscopic analysis of these peptides was performed to assess the different structures of the unstapled (**2.8**) and stapled (**2.9**) variants of each stereoisomer. Overall, seven of the eight peptides were observed to adopt 3_{10} -helical conformations, indicating that stapling did not affect the structures of three of the four diastereomers of **2.8**. However, stapling of 3_{10} -helical (**3R,7R**)-**2.8** altered the conformation of (**3R,7R**)-**2.9** to an α -helix, an observation later confirmed by X-ray crystallography. Intriguingly, when applying all eight of these peptide catalysts (**2.8** & **2.9**) toward the epoxidation of **2.1a**, α -helical (**3R,7R**)-**2.9** was the lone stapled peptide that provided **2.2a** in substantially higher er compared to the uncyclized catalyst (**3R,7R**)-**2.8**. This catalyst also achieved the highest overall er (Figure 5b, entries 7 & 8). This study highlights how even subtle changes to peptide or helical type can have a substantial impact on catalyst selectivity.

Alternatively, Tanaka and co-workers chose to stabilize α -helical conformations by including α,α -disubstituted residues in a poly(Leu) peptide.³⁴ Residues such as the cycloleucine (Cle) derivatives in Figure 6a are known to induce the formation of α -helices within (Leu-Leu-Xaa) units. While myriad peptides were synthesized and assayed in the epoxidation of **2.1**, general trends are presented here. Peptide length was shown to have a significant effect on selectivity, as the er rose from 66:34 to 99:1 by increasing the length of catalyst from six residues in **2.10a** to twelve in **2.10c** (entries 1–3). Furthermore, most *N*-terminal Boc-containing peptides provided low ers (entries 4 & 5). Finally, the choice of α,α -disubstituted residue had a significant effect on selectivity. Compared to catalysts **2.10** and **2.11**, peptides of the **2.12** set, which contain the (*S*)-3-methoxy Cle residue, provided

high er even at unoptimized lengths and with Boc groups (entries 6–9). Crystallographic analysis of high performing peptide **2.10c** revealed an α -helix (Figure 6b). Further evidence that this conformation appears to be important for achieving high enantioselectivity in Juliá–Colonna epoxidations.

In contrast to larger, helical forming peptides, Voyer and co-workers explored the use much smaller cyclic dipeptides (Figure 7).³⁵ Known for a variety of other asymmetric transformations, these minimal peptides have never been applied toward epoxidation.³⁶ Despite the substantial reduction in size compared to the helical polypeptides, diketopiperazine **2.13a** was able to achieve 85:15 er in the epoxidation of **2.1**. The relative stereochemistry of the dipeptide was essential for enantioselectivity, as **2.13c** provided racemic product. Furthermore, a linear dipeptide variant (**2.14**) only achieved epoxidations in 58:42 er, implying that cyclization was required for high catalytic activity. While conversions were generally low in reactions performed in hexanes, they could be accelerated in protic solvents, albeit at expense of enantioselectivity.

While the effects of variations to peptide catalysts have been studied extensively, one challenge still facing Juliá–Colonna epoxidations is the paucity of methods for the fast and controllable synthesis of longer helical peptides.

Leigh and co-workers addressed this issue in their report on alternative, faster strategies for the construction of poly(amino acid) chains.³⁷ Central to their approach was a rotaxane-based molecular machine appended with a short peptide chain (Figure 8a).³⁸ The macrocycle is threaded onto a mono-dispersed oligomeric track, on which are attached various amino acid phenyl esters. As the rotaxane moves along the linear chain, it collects all residues blocking its path and incorporates them onto the growing peptide chain. As such, a one-barrier [2]rotaxane (**2.15**) was synthesized (Figure 8b). The ring was appended with a protected trimer sequence (Cys-Gly-Gly) on which to grow the peptide. This ring (blue) was blocked on one side by a phenyl ester (green) on the linear chain (black), which contains the next amino acid building block to incorporate onto the rotaxane ring. Attached to the linear chain is a polymer precursor containing the leucine building blocks, and this was synthesized via copolymerization with styrene and *p*-leucyloxystyrene (purple). On average, the molecular machines contained approximately 52 styrene units, and 6 Leu units.

To facilitate chain-walking peptide synthesis, **2.15** was treated with triethylamine at 65 °C in DMF (Figure 8b). The reaction proceeds first *via* native chemical ligation onto a Cys appended to the rotaxane (red), followed by transfer to the *N*-terminal amino acid. After reacting with the phenyl ester, the rotaxane ring can walk over the unprotected phenol. Upon reacting with all the phenyl esters, macrocycle-containing peptide **2.16** is eventually released from the linear chain, which contains on average 6.5 Leu residues incorporated (Figure 8c). Alternatively, as a control, the peptide synthesis was performed without the molecular machine, with a mimic of the barrier leucine phenyl ester, and only 2.9 couplings were performed under similar conditions, highlighting the importance of the constrained rotaxane as a driving force for chain elongation (Figure 8d). In applying these catalysts toward the epoxidation of **2.1b**, catalyst **2.16** was found to provide minimal levels of enantioselectivity (Figure 8e). The Cys in **2.16** was found to oxidize to a sulfonic acid under the reaction

conditions, and this is hypothesized to disrupt the α -helical structure of the peptide. Peptide **2.16** was subjected to reductive radical desulfurization to produce **2.17**, which provided epoxide **2.2b** in an er of 96:4. Molecular machines hence could be a useful method for the synthesis of polypeptide catalysts.

Hernández and co-workers explored alternative techniques to accomplish polymerization using a combination of enzymatic catalysis with the aid of mechanochemical synthesis (Figure 9a).³⁹ Proteases have previously been shown to function as efficient amino acid polymerization catalysts in solution. However, issues of oligopeptide solubility often limit the degree of polymerization (DP) due to intermediate product precipitation.⁴⁰ A workaround that the authors explored in this study was to facilitate chain growth with ball milling (Figure 9b). This type of milling involves the grinding of solid reagents in a rotating cylindrical tube containing one or numerous freely moving balls, and its utility in synthesis has recently gained traction.⁴¹ Under near solvent-free conditions, a combination of powdered protease papain and sodium carbonate was found to mediate the polymerization of various amino acids with good chain lengths (Figure 9a). Notably, the protein is stable to this mechanochemical technique. After optimization of conditions with Phe **2.18a**, 99% yield of peptide could be obtained with a DP of 8.0 using hydrated sodium carbonate under planetary ball milling conditions (entry 1). Switching to anhydrous base resulted in erosion of both yield and DP, and this observation was made for Leu **2.18b** as well (entries 2–3). While water did not play as great a role in governing the polymerization yields for small residues, such as Gly **2.18c**, the DP was substantially lowered with anhydrous base (entries 4–5). The authors hypothesize that the addition of water could create a hydrophobic pocket that attracts the amino acid residues closer to the enzyme active site (Figure 9c). This effect is more pronounced for more lipophilic residues such as Phe and Leu as opposed to Gly. Performing epoxidations on **2.1** with enzymatically and mechanosynthesized **2.18a** resulted in excellent yields and enantioselectivities (Figure 9d).

Finally, to combat the normal limitation of performing Juliá–Colonna epoxidations under triphasic conditions (water/organics/solid-supported catalyst), Voyer and co-workers developed purely aqueous conditions (Figure 10a).⁴² The pH of the medium plays an important role in both er and yield. Yields are normally higher under more basic conditions, albeit at the expense of enantioselectivity (entries 1–3). At pH 8, when the catalytic loading was increased to 10 mol%, yields as high as 97% could be achieved (entry 4). Given that H-bonding interactions are often disrupted in pure water, the authors proposed that a hydrophobic effect between **2.1** and catalyst may be required to obtain enantioselectivity in this reaction setup. MD simulations revealed that the sidechains of poly(Leu) peptide **2.20** could form a hydrophobic pocket adjacent to the α -helix (Figure 10b). Lipophilic chalcones are presumed to bind to the catalyst in these chiral clefts.

2.1.2. Aspartyl Peracid-Based Epoxidations.—Orthogonal to the use of poly(Leu) catalysts for nucleophilic Juliá–Colonna epoxidations of chalcone derivatives, our group sought to develop a complementary peptide-based catalytic system functioning by an alternative electrophilic epoxidation mechanism.⁴³ While Juliá–Colonna epoxidations rely on stereocontrolled nucleophilic additions of peroxides to electron-deficient olefins, our initial approach centered on the generation of a transient, catalytically-active peracid species

(**C**, Figure 11a), mirroring the widely used peracid oxidants, such as *m*-CPBA.⁴⁴ We envisioned that this peracid could be formed *via* carbodiimide activation of an aspartic acid residue in the presence of 30% aqueous H₂O₂. There were many potential challenges associated with this catalytic approach, including (1) depletion of DIC due to interception by other compounds and (2) formation of off-cycle diacyl compounds (**C'**). To combat these issues, DMAP was added to accelerate both acyl transfer of **B** to **C** and the breakdown of diacyl peroxide **C'** to peracid **C**.⁴⁵ Under these conditions, Asp-containing peptides were able to epoxidize allylic carbamates **2.21** with high conversions to **2.22** (Figure 1b). Substrate **2.21** was chosen specifically to facilitate noncovalent interactions between the catalyst and substrate. Evaluation of a minimal library of peptide catalysts led to tripeptide **2.23**, which provided up to 96:4 er in epoxidations of **2.21**.

To study the nature of the putative H-bonding interactions between **2.21** and peptide **2.23**, the catalyst was subjected to various point mutations in which key H-bond donors and acceptors were deleted (Figure 11c).⁴⁶ Tripeptide **2.23** was proposed to adopt a type II β -turn,⁴⁷ and it was crucial to this study that this overall secondary structural motif remained largely unaltered despite significant functional changes. It was hypothesized that the *N*-terminal Boc group of **2.23** could be deleted without affecting catalyst structure since it was not expected to be involved in intramolecular H-bonding. Indeed, catalyst **2.24** afforded epoxide **2.22a** with similar levels of enantioselectivity as parent catalyst **2.23**, albeit with lower conversion. A greater challenge was how to appropriately substitute the loop region amide for a non-H-bonding functional group, since it is such an integral part of the β -turn backbone structure. One approach for the isosteric replacement of amide bonds is using alkenes.⁴⁸ Alkene-containing peptide **2.25** was found to give significantly lower enantioselectivity than **2.23**. However, further structural analysis revealed that **2.25** exhibited substantially more conformational flexibility than **2.23**. While unfunctionalized alkenes may not be capable of fully mimicking characteristics of the polarized nature of amides, fluoroalkenes were proposed to serve this purpose.⁴⁹ Indeed, peptide **2.26** was shown to primarily adopt a single conformation in solution that is quite similar to that of **2.23**. While fluoroalkene-containing **2.26** provided **2.22a** with lower er than parent catalyst **2.23**, its efficacy was vastly improved over alkene-containing catalyst **2.25**. Within the type II β -turn framework, it is possible that the *i*+1 C=O of the loop amide is essential for H-bonding with the carbamate of **2.21a** (Figure 11d). The structural similarity between **2.23** and **2.26** could imply that the C–F bond of **2.26** is a competent, yet significantly inferior, H-bond acceptor.

These results highlight the utility of peptide-based catalysts biased toward β -turn conformations, as their programmable secondary structures could allow for selective reactions with many different substrate classes. However, while the modular peptide framework and the availability of amino acids provides nearly limitless potential for the discovery of unique catalyst sequences and structures, the rapid discovery of high-performing catalysts that are matched with specific substrates can be challenging. Analogous to the field of enzyme-mediated transformations, it is often difficult to predict the folded secondary structures of specific peptide sequences⁵⁰ and which peptide structures will provide high levels of selectivity for particular transformations or substrates.⁵¹

Building upon precedent in combinatorial catalyst library screening,^{52,53} our group sought to develop an analogous high-throughput method for the discovery of competent oxidation catalysts.⁵⁴ We envisioned that this approach could facilitate the identification and optimization of catalyst sequences for enantioselective transformations of small molecules (*e.g.*, **2.21a**), as well site-selective modifications of more complex molecules like farnesol (**2.27**, Figure 12a).^{55,56} Specifically, a one-bead-one-catalyst (OBOC) screening platform was chosen, as it had previously been effective in developing highly selective, peptide-based acylation catalysts.⁵⁷

The workflow for OBOC synthesis, screening, and identification of hit sequences is presented in Figure 12b, which follows a split-and-pool method.⁵⁸ Beginning with resin-bound precursors having an appropriate linker, individual beads can be split into various reaction vessels and coupled to various amino acid residues. To generate diversity, these beads are then pooled together, followed by random splitting and further coupling. In the simple example presented in Figure 12b, with two coupling steps each with three unique amino acids, nine theoretical dipeptides are possible. Moreover, this method offers control over the identities of amino acids at each position. For example, if a Pro residue was proposed to be essential at *i*+1, all beads could be programmed to contain a Pro or Pro-like derivative at that position. After synthesizing large arrays of on-bead peptide libraries, each bead can be manually sorted into individual reaction vessels and screened for activity using GC or HPLC to assess conversion and enantioselectivity. High-performing catalysts can then be sequenced *via* partial Edman degradation-mass spectrometry.⁵⁹ As such, it is essential that all amino acids utilized in the synthesis of the library have different molecular weights in order to discriminate between mass fragments. Upon identification of hit sequences, the peptides are resynthesized and evaluated in solution. It is often the case that peptide-based catalysts perform notably better in solution, implying that the solid-support can interfere in enantioinduction. This means that even small increases in selectivity observed on-bead are often amplified in solution.⁶⁰ As a proof of concept, an on-bead library of catalysts for the epoxidation of **2.21a** was synthesized and screened using the OBOC method.⁵⁴ Of the 512 peptide sequences synthesized, the highest performing catalyst (Boc-Asp-Pro-D-Val-Tyr(*t*-Bu)-linker-bead) was quite similar in structure to peptide **2.23** that was previously developed for the for epoxidation of **2.21a**,⁴³ differing only at the *i*+3 position.

Having validated the OBOC peptide library screening platform, we next sought to expand its utility in more challenging reaction paradigms, such as the site-selective epoxidation of complex molecules.^{55,56} Farnesol (**2.27**) contains three different alkenes that are expected to exhibit similar reactivity patterns. Because the only notable difference between these olefins is their relative distance from the terminal alcohol, it is particularly difficult to achieve the differentiation required for site-selective modification. In nature, enzymes often overcome site-selectivity issues by taking advantage of well-defined binding pockets to interact with substrates in a precisely controlled manner.⁶¹ For example, squalene epoxidase is able to selectively oxidize one alkene of the three chemically distinct alkenes in squalene.⁶² This catalyst-controlled site-selectivity has been a challenging paradigm to translate to small molecule catalysts.¹⁷ Our group has held that peptide catalysis may offer a solution, as diverse peptide sequences could tune the reactivity and selectivity of a conserved catalytic

residue through the formation of specific secondary structures and precise noncovalent interactions with complex substrates.

Inspired by the selectivity exhibited by squalene epoxidase,^{62,63} our group sought to apply aspartic acid-containing peptides toward the site-selective epoxidation of farnesol (Figure 13a).⁵⁵ While *m*-CPBA delivered an unselective mixture of epoxide products (Figure 13b, entry 1), initial screening revealed that peptide **2.31** selectively targets the 2,3-alkene to provide **2.28** in a 4:1:1 ratio over 6,7-epoxide **2.29** and 10,11-epoxide **2.30** (entry 2). A peptide library biased toward sequence **2.31** was synthesized using the OB OC method by coupling approximately 50% of the beads with the parent residue at each position. From this library, peptide **2.32** was discovered, which exhibited an increased 2,3-selectivity of 8.2:1.0:1.3 (entry 3). The Pro-Asn(Trt) diad was retained from parent sequence **2.31**, highlighting its importance to selectivity. A second library now biased toward **2.32** led to the identification of two even more selective catalysts, **2.33a** and **2.34a** (entries 4–5). Upon validation of these on-bead sequences in solution, their site-selectivities increased to >100:1:1 (entries 6–7). We hypothesized that highly site-selective catalysts might also be highly enantioselective, since the best catalysts would presumably form specific networks of noncovalent interactions with substrates. Indeed, catalyst **2.34b** was able to perform the site-selective epoxidation at the 2,3-position of farnesol with an er of 93:7 (entry 7). Further study of this peptide revealed that it was a highly selective in the epoxidation of allylic alcohols, providing high levels of enantioselectivity over a range of substrates **2.35** (Figure 13c). The alcohol was hypothesized to serve as a directing group for the functional group-rich backbone of the peptide, facilitating reaction at the adjacent alkene.

Up to this point, peptides appeared to favor alcohol-directed 2,3-epoxidations of farnesol. However, our group sought to identify different peptide-based catalysts that could selectively deliver the other farnesyl epoxides **2.29** and **2.30**.⁵⁶ An initial hint of selectivity in favor of the 6,7-alkene came with catalyst **2.37b** (Figure 13d, entry 8). Based on this initial hit, three subsequent libraries of extended peptide sequences were synthesized, and the data were presented in the ternary plots shown in Figure 13d. These plots represent the relative ratios of the 2,3-, 6,7-, and 10,11-epoxide products. 6,7-Selective catalysts appear closer to the top vertex of the graph. The first library produced mostly non-selective catalysts or peptides that still favored 2,3-epoxidation (plot 1), though it did generate a high performing catalyst with a Thr(Bn) residue at the *i*+2 position. Two subsequent biased libraries (plots 2 and 3) revealed hit catalyst **2.37b**, which provided a 1.0:8.6:1.1 ratio of products favoring 6,7-epoxide **2.29** upon validation in solution (entry 9). It is noteworthy that this rapid enhancement of 6,7-selectivity was enabled by on-bead library screening based on a lead sequence with very modest positional selectivity (**2.37a**).

In order to determine the origins of catalyst-controlled selectivity, NMR studies (in CDCl₃) were performed to assess the solution structures of peptides **2.34b**⁶⁴ and **2.37b**.⁵⁶ Structural analysis of peptides can often be challenging due to their inherent conformational flexibility. One approach to overcome this issue is to use a combination of NMR and computational methods to predict an ensemble of possible structures, thereby modeling catalyst dynamics in solution. Two-dimensional ROESY spectra were recorded, and the through-space contacts were assigned, integrated, and used to calculate inter-proton distances. These NMR-derived

distances were then used as restraints to calculate the most plausible structures.⁶⁵ Both peptides were found to adopt multiple conformations in solution, but key structural features of these ensembles emerged. While the termini of **2.34b** were quite flexible in solution, a central N-H(*i*+5)•••O=C(*i*-3) γ -turn H-bond was retained in most structures (Figure 14a). A key N-H(*i*+3)•••O=C(*i*) β -turn H-bond dominated the structures of **2.37b** (Figure 14b). Because numerous, discrete conformations of **2.34b** were consistent with the NMR data, it was difficult to propose one particular active conformer. However, since this peptide is highly selective for 2,3-epoxidation of **2.27**, it likely interacts with the adjacent allylic alcohol *via* H-bonding (Figure 14c). On the other hand, given the more consistent β -turn conformation of **2.37b**, it is plausible that the allylic alcohol binds much further away from the aspartyl peracid, possibly through H-bonds with N-H(*i*-2) and the sidechain of Thr(Bn), placing the 6,7-alkene in closer proximity to the peracid (Figure 14d). While elucidation of the exact catalytically active conformation of minimal peptides remains challenging, NMR and computational tools exist that enable ensembles of potential structures to be considered.

Given the effectiveness of Asp-containing peptides for both enantio- and site-selective epoxidations, this catalytic strategy has been applied in the total synthesis of natural products.^{66,67} While oxidized indoles are a prodigious class of natural products, efforts to effect catalyst-controlled, enantioselective indole oxidations have suffered from complications associated with chemoselectivity and the propensity for product rearrangement. To address these issues, our group applied Asp-based peptides toward selective synthesis of 3-hydroxy-indolenines in collaboration with the Movassaghi Group.⁶⁶ We hypothesized that, upon initial epoxidation of indole **2.38** with aspartyl peracids, subsequent rearrangement would result in **2.39** (Figure 15a). Upon optimization of reaction conditions, evaluation of a small library of Asp-containing catalysts resulted in the discovery of pentapeptide **2.40**, which afforded a wide-range of 3-hydroxy-indolenines **2.39** with *er* values up to 95:5. Having developed a highly efficient catalyst, we turned our attention toward substrates **2.41** as a means to address issues of site- and diastereoselectivity (Figure 15b), which can become quite important in the context of total synthesis and complex molecule functionalization. While reactions in the presence of an achiral carboxylic acid revealed a subtle substrate-controlled selectivity favoring the (*R*)-stereochemistry of the oxidized indole (69:31 *dr*), peptide **2.40** enhanced this selectivity to 92:8 *dr* (entries 1–2). Interestingly, using *ent*-**2.40** provided a mismatched case and negligible diastereoselectivity (entry 3).

Similar selective indole oxidations were pursued in the total synthesis of citrinalin B and cyclopiamine B by a team of researchers led by the Sarpong Group.⁶⁷ Cyclopiamine B (**2.43**) could be accessed through an indole-to-spirooxindole rearrangement of **2.44**, which itself could arise from indole **2.45** (Figure 16a). When oxaziridines (**2.49–2.51**) were utilized to oxidize the C3 position of indole **2.45**, the desired alcohol diastereomer **2.46** was not obtained as the major product, suggesting that the inherent facial selectivity of O-atom delivery favors diastereomer **2.47** (Figure 6b). Rearranged spirocycle **2.48** was also formed, though unfortunately this compound was epimeric to the desired spirocycle **2.43**. These results spurred a campaign to develop reagents or catalysts that could overturn this inherent selectivity. Asp-containing peptides were particularly promising given that the acetamide of

2.45 could function as a directing group to enable oxidation from the desired face of the molecule. Indeed, following evaluation of a focused catalyst library, peptide **2.52** was found to provide the desired oxidized indole **2.46** in 83% yield. Unfortunately, further rearrangement of **2.46** to the desired spirooxindole was not observed, as pseudooxindole **2.53** was the isolated product. In the end, a different synthetic route was pursued, which did not require the peptide-controlled indole oxidation to access cyclopamine B.

2.1.3. Trifluoromethyl Ketone-Derived Dioxiranes for Epoxidations.—

In addition to peracids, dioxiranes have also been successfully employed as O-atom transfer catalysts in selective epoxidation reactions. In particular, Shi and co-workers developed fructose-based ketone **2.54**, which can be converted into a dioxirane upon treatment with mild oxidants *in situ* (Figure 17a).⁶⁸ This dioxirane is a highly effective epoxidizing agent known for delivering high levels of enantioselectivity over a broad range of substrates. As such, our group sought to investigate whether transient dioxiranes could be generated within a peptidic framework and used to effect enantioselective olefin epoxidation reactions.⁶⁹ Trifluoromethyl ketone-containing **2.55** was chosen as the catalytically active motif, as these electron deficient ketones have been shown to form highly reactive dioxirane species under mild conditions.⁷⁰ Chiral ketone **2.55** could be prepared in a short synthetic sequence starting with a chiral oxazolidinone and subsequently attached to peptide sequences using established amide coupling methods. A focused library of catalysts was evaluated in the epoxidation of **2.56** to **2.57** using hydrogen peroxide as the stoichiometric oxidant (Figure 17b). Peptide **2.58a** emerged as the lead catalyst, affording up to 91:9 er over a range of unfunctionalized olefin substrates with no additional H-bonding functionality.

Further optimization of the catalytic residue was pursued, specifically targeting aryl trifluoromethyl ketones like **2.59**.⁷¹ This class of compounds could allow for additional tuning of the ketone electronic *via* modification of the arene *para*-position, such as with fluorine.⁷² Synthesis of the aryl ketone monomer could be accomplished in a short sequence, originating from serine-like derivatives. Incorporation of a methyl group at the α -position of **2.59** was required, given that traditional protected amino acid residue could cyclize onto the ketone and deactivate the catalyst. Elongated peptide catalyst containing **2.59** provided a range of epoxidized products with excellent levels of conversion, albeit with low enantioselectivities. More decisive secondary interactions with the substrates will be needed in future generations of catalysts.

2.2. Baeyer–Villiger Oxidation

While epoxidation has received significant attention in the field of asymmetric catalysis, asymmetric Baeyer–Villiger (BV) oxidations have traditionally been more difficult to accomplish.⁷³ Enantioselectivity in epoxidation reactions is achieved *via* discrimination of the enantiotopic alkene faces, which is a fairly common selectivity paradigm in asymmetric catalysis. However, the situation is markedly different in BV oxidations of symmetrical ketones. Following initial addition of the peroxide/peracid nucleophile to form the Criegee intermediate, enantioselectivity is determined solely by the dihedral angle of the C–C–O–O bond, which dictates which C–C bond will migrate (Figure 18a).⁷⁴ This type of catalyst-

control over a single torsion is quite challenging to achieve. However, numerous catalysts have recently emerged that overcome this inherent obstacle.

Building on previous peptide-mediated epoxidations with Asp-containing peptides, our group sought to expand the utility of these catalysts into BV oxidations (Figure 18b). Owing to the similarities between the catalytically active Asp-derived peracid and *m*-CPBA, which is known to exhibit diverse patterns of reactivity, it seemed plausible that Asp-containing peptides might also function through alternative mechanistic paradigms.⁷⁵ In this sense, BV oxidations would also require the peracid as a key moiety in the catalytic cycle, but it would need to function as a nucleophilic oxidant, in contrast to its role in alkene epoxidations, providing an excellent testing ground for the versatility of these peptides.

Our group set out to apply these aspartyl peracids to BV oxidations (Figure 19),⁷⁵ shortly after the initial epoxidation was reported.⁴³ Unfortunately, the previously optimized conditions for epoxidation provided only low conversions to lactone **2.61a** (13%, Figure 19a). It was hypothesized that a slow rate of addition of peracid **C** to the ketone substrate slowed the reaction, allowing the peracid species to dimerize and form off-cycle diacyl peroxide **C'** (Figure 19c). When the DIC was introduced slowly to limit the amount of excess peracid species, yields were increased to 76%. At this stage, it was hypothesized that increasing the acidity of the catalyst could have an advantageous effect on reaction rates. Indeed, pentafluorobenzoic acid catalyst **2.63** ($pK_a = 1.74$) outcompeted **2.62** ($pK_a \approx 4.4$) in the BV oxidation of **2.60b** to lactone **2.61b** using batch-wise delivery of DIC (Figure 19b). However, despite the low reactivity of Asp-derived catalyst **2.62**, it remained plausible that incorporation of this monomer into an extended peptide sequence would enhance reaction rates *via* multifunctional substrate activation. Indeed, evaluation of Boc-Asp-Pro-D-Val-Val-(*R*)- α -Mba (Mba = methylbenzylamine) with substrate **2.60b** ($R^1 = \text{Ph}$, $R^2 = \text{OH}$) under the slow addition protocol provided product with 70:30 er, a promising start for future studies.

In choosing a new substrate class to maximize peptide/substrate interactions, compounds like **2.64**, which contain an amide directing group at the 3-position, were evaluated in peptide-catalyzed BV reactions (Figure 20).⁶⁰ In these kinetic resolutions, the relative rates of reaction for each ketone enantiomer determine the ultimate enantioselectivity of the product, and migration of either adjacent C–C bond now creates an opportunity to control regioselectivity. Typically, the most electron-rich bond migrates. However, it is plausible that catalyst control could reverse the inherent migratory aptitude through precise control of the C–C–O–O dihedral angle.

Initially, incorporation of Asp into various peptide sequences that were selective in epoxidations and other reactions were not effective in BV oxidations of **2.64**. As such, a library of on-bead catalysts was synthesized using the OBOC method (see Section 2.1.2, Figure 12). The library was biased to have a Pro residue at the *i*+1 position, as we have observed that this design element is essential for enantioinduction in many cases with substantial variation to the remainder of the sequence (Figure 21a). Ketone substrate **2.64a** was initially used in catalyst screening, as its 2-naphthyl chromophore facilitated reaction analysis. Evaluation of the catalyst library led to the identification of peptide **2.68b**, the

resin-cleaved variant of **2.68a**, which mediated the BV kinetic resolution of **2.64a** to lactone **2.65a** with a k_{rel} of 1.7, a promising starting point for subsequent optimization.

This catalyst was next tested on parent substrate **2.64b** (Figure 21b). The inherent preference for migration of this substrate in oxidations with *m*-CPBA is the normal migratory mode by a 7.9:1 ratio (entry 1). Alternatively, catalyst **2.68b** provided *reversed* product **2.66b**, in a 1:3.4 ratio and 91:9 er (entry 2). This catalyst-controlled overturning of the preferred migratory aptitude was further enhanced with minimal peptide optimization. Epimeric catalyst **2.68c** delivered **2.66b** in 1:12 ratio and 96:4 er (entry 3). Alteration of the 3-amido group of **2.64** revealed a continued preference for the reversed migration product using catalyst **2.68c** (Figure 21c); **2.66e** was isolated in <1:100 ratio. Using *m*-CPBA, **2.64f** was converted to normal product **2.65f** in >100:1. Catalyst **2.68c** was able to reduce this large migratory preference to 2.3:1 with an er of 99:1.

On-bead screening has been extremely valuable for the identification and optimization of highly selective catalysts for a variety of oxidation reactions, including epoxidation and BV oxidation. Many of these catalysts, including **2.68c**, possessed never-before-studied sequences. As such, it was unclear at the outset what secondary structural attributes, if any, peptide **2.68c** would exhibit under the reaction conditions. The solution structure of **2.68c** was examined using NMR spectroscopy.⁷⁶ Through-space NOE contacts were used to generate distance restraints for structural calculations in CNS to generate an ensemble of structures,⁶⁵ the lowest energy of which was subjected to DFT optimization (Figure 22). Two critical H-bonds were found in the ground state structure of **2.68c**: (1) a seven-membered ring N–H(Tyr)•••O=C(D-Pro) H-bond indicative of a γ -turn, and (2) an H-bond between the sidechain N–H of Lys and its backbone carbonyl. Furthermore, it is apparent that the active Asp sidechain is nearby the Lys residue in space. Moreover, NMR structural analyses of 1:1 mixtures of peptide **2.68c** with (1) a mismatched substrate enantiomer (*S,R*)-**2.64e** and (2) the favored product (*R,S*)-**2.66e** revealed subtle, yet noticeable, differences between these complexes and the structure of **2.68c** alone. More telling is that the structures of the two complexes themselves were extremely similar. By comparison, the 1:1 mixture of **2.68c** and matched substrate (*R,S*)-**2.64e** elicited significant changes in the catalyst structure. Most notably, the Lys sidechain was displaced from its ground-state H-bond with the backbone carbonyl. It is possible that this reorganization facilitates substrate docking or perhaps the substrate induces this change to a more catalytically active conformation. Overall, these data illuminate the precise nature of the noncovalent interactions between matched substrates and peptide **2.68c**.

While BV oxidation catalyst **2.68c** and epoxidation catalyst **2.34b** share the same catalytic Asp residue, the reactive peracid intermediate functions as a nucleophile in the former case and an electrophile in the latter (Figure 23a). The tuning of a conserved reactive species for diverse transformations is a hallmark of enzymatic catalysis,⁷⁷ which is normally accomplished through evolutionary alteration to the proteins' three-dimensional structure. Our group wondered whether the distinct sequences of peptides **2.68c** and **2.34b** could control aspartyl peracid reactivity toward complex substrates in which epoxidation *and* BV oxidation are viable reaction pathways.⁷⁸ Substrate *trans*-**2.69**, which contains a 3-amidocyclohexanone motif for BV oxidation and an allylic alcohol for epoxidation, was

chosen to explore these questions (Figure 23b). Potential oxidation products include the lactones from normal (**2.70**) and reversed (**2.71**) migration, two mono-epoxide diastereomers (**2.72** & **2.73**), and numerous over-oxidation products. Reactions in the presence of *m*-CPBA produced an unselective mixture of products with a slight preference for epoxides **2.72** and **2.73** (1:1 ratio) over lactones **2.70** and **2.71** (entry 1). The preferred BV migratory aptitude favored the normal lactone over the reversed in a 2.9:1 ratio. On the other hand, epoxidation catalyst **2.34b** provided substantial rate enhancement for its matched epoxide product **2.72** in >100:1:1 chemoselectivity and >99:1 diastereoselectivity (entry 2). The BV oxidation catalyst **2.68c** was initially found to give low selectivity in the reaction of *trans*-**2.69**, suggesting that the catalyst was mismatched with the enantiomer of **2.69** that was synthesized. However, peptide *ent*-**2.68c** was found to provide good conversion to a mixture of products favoring lactones **2.70** and **2.71** in a 12.5:1 ratio over epoxides **2.72** and **2.73** (entry 3). The catalyst also overturned the inherent migratory preference of the substrate in favor of reversed lactone **2.71** in >50:1 ratio. Interestingly, a larger amount of water was found to be productive for BV selectivity, potentially by disrupting the H-bonding interactions between the catalyst and the allylic alcohol that might direct epoxidation (Figure 23c), as with peptide **2.34b** (Figure 23d). Overall, this study further demonstrated the concept that minimal peptides can tune the reactivity of a shared catalytic residue through precise outer-sphere interactions with substrates, with control over not only stereochemical issues, but also through divergent functional group selection.

The utility of Asp-containing peptides was further explored in BV oxidations of ketone substrates that were not addressed by catalyst **2.68c**. Unfunctionalized ketone substrate **2.74** was of particular interest, as the absence of any obvious H-bonding functionality would require the development of complementary catalyst scaffolds. In collaboration with the Anslyn Group, we pursued on-bead peptide screening to address this challenge, and two moderately selective catalysts were discovered (**2.76a** & **2.77a**, Figure 24a).⁷⁹ These two catalysts provided opposite absolute configurations of product **2.75**, even though each contained only L-amino acids. In order to model putative catalyst–substrate interactions, exact stereochemical assignments of these products were required. One avenue for obtaining this information is using circular dichroism (CD). To facilitate the determination of absolute configuration using CD, it would be desirable to incorporate the products into zinc(II) complexes. Upon methanolysis of **2.75** to alcohol **2.78**, TREN-like ligands were added to facilitate dynamic assembly of zinc(II) complexes, such as **2.79** (Figure 24b). These complexes exhibit characteristic Cotton effects, in which the intensity of the CD signal varies linearly with the ee of the appended alcohol. Furthermore, the sign of the signal correlates with either the *M* or *P* helical twist of the pyridine ligands around the zinc center, which is governed by the absolute configuration of the chiral alcohol. We expected that this method would not only be effective at assessing the absolute stereochemical configuration of products, but also as an alternative, rapid assay for the evaluation of catalyst selectivity. Catalysts discovered in the on-bead assay were re-synthesized in solution and screened in the BV oxidation of **2.74**. The resulting lactone products **2.75** were then assayed for er using traditional HPLC methods. Lactones **2.75** were subsequently ring-opened, converted to Zn-complexes **2.79**, and assayed for er using CD. The measurements recorded using both methods were quite close over a range of high and low performing catalysts, and

measurements by CD reduced the time cost from ~30 min by HPLC to a few seconds per sample. Furthermore, the absolute configuration of products of both **2.76b** and **2.77b** were determined by CD to be (2*R*,6*S*) and (2*S*,6*R*), respectively. It appears that the identity of the *i*-2 position is essential for this inversion of enantioselectivity, as catalysts with Leu produced products with the (2*R*,6*S*) configuration, whereas catalysts incorporating Ser(*t*-Bu) at this position favor (2*S*,6*R*)-**2.75**. Further development of this CD assay is currently underway, including studies on the nature of the pyridine ligands utilized to form the zinc complexes.⁸⁰

While most of the advances in peptide-mediated BV oxidation have relied on aspartyl peracids, new classes of Brønsted acid catalysts have recently emerged to provide an alternative approach. BINOL-derived chiral phosphoric acids (CPAs), which are well known to mediate a wide variety of transformations,^{81,82} have recently been extended toward BV oxidation.⁸³ Unlike Asp-containing peptides, which react *via* a transiently generated peracid to enable asymmetric BV oxidations, CPAs function through a Brønsted acid catalytic mechanism to activate ketones for outer-sphere attack by hydrogen peroxide and subsequently facilitate selective bond migration of the Criegee intermediate (Figure 25).⁸⁴ Inspired by this complementary mechanistic paradigm, our group set out to develop a new class of peptide-based BV oxidation catalysts based using phosphothreonine (pThr) as a Brønsted acidic residue.⁸⁵ These pThr-containing peptides (*i.e.*, phosphopeptides) had been previously demonstrated in enantioselective reduction chemistry (see Section 3),^{86,87} and we hoped to expand this approach into the realm of oxidation.

The phosphopeptide strategy was tested in the BV oxidation of cyclobutanones **2.80**, which contain a pendent directing group to facilitate catalyst–substrate interactions, using aqueous hydrogen peroxide as the oxidant (Figure 26a).⁸⁵ Evaluation of various pThr-containing catalysts led to the discovery that an additional directing group installed at the *i*+3 position of the peptide, namely an acetyl-protected L-diaminopropionic acid (Dap) residue (**2.82**), was highly advantageous for enantioselectivity. This effect was especially pronounced for substrates containing H-bond donor functionality (*e.g.*, **2.80a–e**), as Dap(Ac)-containing **2.82** provided lactones **2.81** with higher yields and *ee*s than Phe-containing **2.83**. On the other hand, substrates lacking a pendent H-bond donor group (*e.g.*, **2.80f–h**) were processed more effectively by catalyst **2.83**. NMR structural studies of peptides **2.82** and **2.83** revealed that both catalysts adopt a β -hairpin structure in solution. Since the enhanced selectivities exhibited by the Dap(Ac)-containing catalyst do not stem from the formation of a unique secondary structure, it is plausible that the primary function of this residue is to nucleate additional noncovalent interactions with the substrate. These observations led to a proposed model for enantioinduction, wherein the phosphoric acid moiety of pThr engages with the Criegee intermediate while the Dap(Ac) side chain H-bonds with the substrate directing group (Figure 26b).

The high degree of specificity in the interactions between peptide **2.82** and its substrates was further probed using cyclobutanone **2.84**, in which the carbamate directing group is installed at the *meta*-position (Figure 26c). While Phe-containing peptide **2.83** processes **2.84** with moderate *ee* on par with what was measured for **2.80a** (79:21 *vs.* 66:34), Dap(Ac)-containing **2.82** provides lactone **2.85** with the opposite absolute stereochemistry relative to

2.80a (94:6 vs. 13:87 er). These data show that it is possible to observe enantiodivergence without altering a single stereocenter in the peptide catalysts, as Dap(Ac) and Phe are both L-amino acids. It is also striking that peptide **2.82** can process such similar substrates with highly enantiodivergent outcomes solely based on the position of a remote directing group. These phenomena speak to the central challenge of asymmetric BV oxidations, as catalysts must be able to control subtle torsional angle differences within the Criegee intermediate to produce enantiomeric products (Figure 20). Minimal peptide catalysts appear capable of addressing these challenges through the construction of precise noncovalent interactions with substrates.

In an analogous approach, Imada and co-workers employed isoalloxazines inspired by flavin-dependent monooxygenase enzymes to enable biomimetic oxidation reactions (Figure 27a).⁸⁸ FAD functions as a cofactor in numerous classes of oxidations *in vivo*, often through the generation of a hydroperoxyflavin with molecular oxygen (C, Figure 27b).⁸⁹ By embedding isoalloxazine units at the *N*-termini of short peptide-sequences, the authors were able to harness FAD-like reactivity in a synthetic context. Potential peptide sequences to be appended to the isoalloxazine were evaluated using DFT computations, which led to the incorporation of Pro at the *i*+1 position in order to favor a γ -turn structure and thereby orient the peptide scaffold nearby the catalytically active moiety. Acidic functionality was also incorporated at the *i*+3 position to interact with the intermediate peroxy species. Polymer-supported peptide **2.86** was found to be competent in both sulfide and BV oxidations. In oxidations of sulfide **2.87** to sulfoxide **2.88**, catalyst **2.86** was utilized in tandem with oxygen and hydrazine, the latter of which functions as the terminal reductant for catalyst regeneration (Figures 2.27b–c). Inclusion of hydrazine is thought to activate the peroxy species toward nucleophilic attack by the sulfide through H-bonding (Figure 27b). This hypothesis was corroborated through the generation of a Hammett plot, which suggested that electron-rich sulfides were more reactive (Figure 27c). Peptide **2.86** was also able to mediate the BV oxidation of **2.89** using Zn as the terminal reductant (Figure 27d). In these competition experiments, oxidants such as *m*-CPBA inherently favored sulfide oxidation while **2.86** showed exceptional chemoselectivity for BV oxidation (Figure 27e). This chemoselectivity is possibly due to H-bonding between the *i*+3 carboxylic acid and the peroxy species to enhance its nucleophilicity (Figure 27b). Hence, subtle variation of reaction conditions enables access to distinct reaction mechanisms of a conserved hydroperoxyflavin species. Although no enantioselectivity was reported in these particular oxidation reactions, this novel flavin-containing peptide catalyst platform opens the door for future development of asymmetric reactions.

2.3. Additional Oxidations

Beyond epoxidation and BV reactions, peptide-based catalysts have also been developed to mediate a number of other oxidative transformations, including the *N*-oxidation of pyridines (Section 2.3.1), alcohol oxidations (Section 2.3.2), and α -functionalization reactions (Section 2.3.3).

2.3.1. N-Oxidation of Pyridines.—Asp-Containing peptides have been shown to function as powerful catalysts for various asymmetric transformations. The ease of

generating the active aspartyl peracid moiety *in situ* has enabled peptides containing this catalytic residue to be applied in epoxidations (Section 2.1.2)⁴³ and Baeyer–Villiger oxidations (Section 2.2).⁷⁵ Notably, the aspartyl peracid can be encoded to function as either a nucleophilic or an electrophilic oxidant by tuning the peptide sequence in which it is embedded.⁷⁸ This renders the aspartyl peracid moiety highly general and capable of diverse reactivity.

Given the range of reported peracid-mediated oxidations, our group sought to program the Asp-containing peptides for new reactions, specifically in the construction of decorated, chiral pyridines (Figure 28). While these heterocycles are ubiquitous in natural product and drug scaffolds, methods for their enantioselective syntheses remain challenging.⁹⁰ One common strategy for functionalizing pyridines uses *N*-oxidation to generate an electrophilic pyridine *N*-oxide species that is highly activated toward nucleophilic addition reactions. In 1983, the Sharpless Group demonstrated that Ti-based complexes can catalyze the kinetic resolution of tertiary amines via *N*-oxidation.⁹¹ Building upon these precedents, our group envisioned a scenario wherein Asp-containing peptides could oxidize pyridines to the corresponding *N*-oxides through the aspartyl peracid scheme.⁹² Complex substrates exhibiting multiple conformations or containing various oxidizable functionality would pose issues of site- and stereoselectivity that could serve as a testing ground for this new paradigm in catalyst-controlled selective oxidations.

Bis(pyridine) **2.91a** was chosen as a test system for enantioselective *N*-oxidation, as it contains a prochiral pivalamide directing group to maximize the potential for noncovalent interaction with the catalyst (Figure 29a).⁹² Effective desymmetrization of **2.91a** would require remote asymmetric induction in order to differentiate the enantiotopic pyridines that are separated from each other and the prochiral center by great distances. Various peptides were evaluated in the desymmetrization of **2.91a** that derived from either a combinatorial OBOC library or rationally designed β -turn-biased sequences. Both approaches yielded initial hit results, providing pyridine mono-*N*-oxide **2.92a** in as high as 74:26 er, and β -turn-containing peptide **2.94** was chosen for further study. Most mutations of the *i*+1, *i*+2, and *i*+3 positions of **2.94** resulted in lower observed selectivities. Catalysts with an additional residue at the *i*-1 position were substantially more selective, and the best catalyst, phenylglycine (Phg)-containing **2.95**, provided **2.92a** with an er of 86:14. This catalyst was tolerant of variable substitution at the C6 position of **2.91**, delivering the corresponding products **2.92** with up to 99:1 er (Figure 29b). Although **2.95** was also able to address substrates with C5-functionality, C2-substitution led to racemic products.

Upon developing an enantioselective *N*-oxidation catalyst, we sought to examine its potential in the synthesis of medically relevant derivatives. Loratadine is the active ingredient in the antihistamine Claritin®, which exists in rapid equilibrium between two enantiomeric, helically chiral conformations.⁹³ This scenario provided the possibility for a peptide-catalyzed dynamic kinetic resolution (DKR) if *N*-oxidation were to effectively inhibit racemization. As such, peptide **2.94** was indeed able to effectively convert loratadine derivative **2.91c**, in which urea directing group was incorporated in place of the native ethyl carbamate, to *N*-oxide **2.92c** in 45% yield and 95:5 er (Figure 29c). Additionally, varenicline, the active ingredient in smoking cessation aid Chantix®, contains a symmetrical

quinoxaline ring,⁹⁴ which we hypothesized to be an excellent candidate for a peptide mediated desymmetrization. While oxidations of this more electron deficient heterocycle were slower, varenicline derivative **2.91d** was successfully transformed into *N*-oxide **2.92d** in 95:5 er and 61% yield (Figure 29d). Finally, to showcase the broad synthetic utility of enantiopure *N*-oxidized pyridines, a variety of nucleophiles were added to bis(pyridine) **2.92** under previously reported conditions.⁹⁵ Stereoretentive amination, etherification, thioetherification, and sulfonamidation reactions were straightforward, highlighting the power of this platform in the site- and stereoselective functionalization of medicinally relevant *N*-heterocycles.

2.3.2. Alcohol Oxidation.—A common strategy for the development of new asymmetric catalysts is to embed a known reactive species into a chiral backbone. Ward, Kirshenbaum, and co-workers sought to generate a chiral variant of the known oxidant, TEMPO,⁹⁶ by embedding the persistent radical species within an oligopeptide framework. The authors studied whether the incorporation of TEMPO into these foldamers, or oligopeptide sequences of non-proteinogenic amino acids that are known to adopt specific secondary structures, would produce a new class of oxidation catalyst.⁹⁷ Specifically, they chose to investigate peptoids derived from *N*-substituted glycine residues that are known to exhibit helical structures in which the helix sense is controlled by the absolute configuration of the phenethylamine substituents (Figure 30a).⁹⁸ A library of peptoid-based TEMPO catalysts was synthesized and screened in the oxidative kinetic resolution of compound **2.100**, given the well documented activity of TEMPO as a general oxidant for secondary alcohols (Figure 30b). In the presence of external peptoid **2.98**, TEMPO-derivative **2.97** provided negligible selectivities. However, TEMPO-embedded catalyst **2.99** was notably more effective, giving a k_{rel} of 4.6 in the kinetic resolution of **2.100**. Further catalyst screening revealed that it was preferable to embed the TEMPO motif at the *N*-terminus of the peptoid, as selectivities were eroded upon moving the TEMPO moiety into the center of the sequence. Analysis of the structure of **2.99** revealed that the steric environment near TEMPO is quite hindered, leaving a small cleft accessible for substrate binding.

2.3.3. α -Functionalization of Aldehydes.—Alternatively, Kudo and co-workers focused on controlling the reactivity of TEMPO through the addition of external peptide catalysts.^{99–101} They specifically targeted α -oxyaminations of aldehydes,¹⁰² which has previously been reported with TEMPO in the presence of chiral imidazolidinone catalysts.¹⁰³ Upon condensation of the imidazolinone onto the aldehyde, single-electron oxidation of the incipient enamine resulted in formation of a planar radical cation, which can undergo enantioselective C–O bond formation with TEMPO. The Kudo Group sought to develop a variant of this reaction with a new class of Pro-containing peptides in aqueous conditions.

The use of Pro as a catalytic residue for the activation of substrates is among the critical advances in the field of organocatalysis.¹¹ Specifically, Pro and other chiral secondary amines are able to condense onto aldehydes and ketones, activating the carbonyl compounds as either (1) iminium ions for stereocontrolled nucleophilic attack or (2) enamines for stereoselective addition to electrophiles. Pro-containing peptides have featured prominently in these reaction paradigms through the years.^{14,15}

The Kudo group has pioneered the development of Pro-containing catalysts like **2.104** for a variety of reactions in aqueous conditions.¹⁶ Peptide **2.104** contains both a β -turn element (D-Pro-Aib-Trp) known to bolster asymmetric induction and a poly(Leu) chain to provide a hydrophobic environment for attracting organic substrates when water is used as a solvent. First developed in 2009 for reductions (Section 3.1),¹⁰⁴ the authors sought to expand the catalysts' utility into enamine-type activation mechanisms, such as α -oxidation (Figure 31a). Indeed, conditions were developed utilizing both Fe(II)¹⁰⁰ and Cu(I) salts¹⁰¹ to facilitate SET from the activated enamines, with molecular oxygen as the terminal oxidant. Selectivities of up to 97:3 er were achieved.

Upon developing efficient conditions for α -oxidations in water, Kudo and co-workers further optimized the reaction conditions with environmentally friendly reagents.¹⁰¹ Laccase is a copper-containing oxidase enzyme that has emerged as a potential candidate for diverse applications in synthetic chemistry.¹⁰⁵ However, it has yet to be reported within the context of aldehyde α -functionalization. Given the excellent activities afforded by peptide **2.104** in aqueous conditions, laccase appeared to be suitably matched for use with an enzymatic cocatalyst in water (Figure 31b). Following optimization of the reaction conditions, two products predominated the reaction mixtures, aldehyde **2.105** and over-oxidized carboxylic acid **2.106**. It was found that the product distribution could be controlled by the addition of a nonionic surfactant, Tween 80. The presence of Tween 80 resulted in an acceleration of the aldehyde to carboxylic acid oxidation by laccase. Overall, this method demonstrates the possibility of dual catalysis using short peptides and enzymes together to achieve highly selective α -oxidations of aldehydes with up to 96:4 er.

Enamine activation by Pro-based peptide catalysts have also been reported in α -amination reactions of aldehydes **2.107** using azodicarboxylate **2.108** (Figure 32).^{106,107} Kudo and co-workers further explored the utility of recyclable, on-bead peptides for the formation of amino alcohols **2.109**.¹⁰⁸ While Pro alone linked to the resin produced only a moderate er of 19:81 (entry 1), extending the peptide chain to include a β -turn forming motif (D-Pro-Aib-Xaa) provided higher enantioselectivities favoring the opposite enantiomer (entries 2–4). Indeed, catalyst **2.110** delivered **2.109** in 96:4 er (entry 4). The absolute sense of asymmetric induction is controlled by the configuration of the *N*-terminal Pro residue; using the L-Pro variant of **2.110** provides **2.109** in 5:95 er favoring the opposite enantiomer compared to **2.110**. While recycling the freebase of catalyst **2.110** resulted in a reduction in yields, the TFA salt of **2.110** could be reused up to 10 times with minimal perturbation to product yields and ers.

Expanding upon the use of solid-supported peptides as catalysts for α -functionalizations of aldehydes, Fülöp and co-workers developed a continuous-flow type process to produce α -aminated products in a high-throughput manner (Figure 33).¹⁰⁹ A library of minimal peptide catalysts containing Pro at the *N*-terminus and a variety of carboxylic acid-containing residues embedded into the sequences were evaluated in the α -oxidation of aldehyde **2.111** with azodicarboxylate **2.112**. Peptide **2.115** was able to provide amino alcohols **2.114** with high er values both in batch and flow reaction setups. Upon optimization of the flow parameters, including flow rate, residence time of reactants with the catalyst bed, reagent concentrations, and pressure, a highly efficient protocol was developed, allowing for the

formation of **2.113** in up to 99:1 er on gram-scale. The immobilized peptide column was found to be durable, with no signs of decrease in er or efficiency even after 20 consecutive hours of use.

3. Reduction

Prior to 2007, peptide-based catalysts had been demonstrated only sporadically in asymmetric reductions of various functional groups. Among the earliest contributions were electrochemical reductions, wherein polypeptide-coated electrodes were employed to enable asymmetric induction during electron transfer events.^{110–113} Since then, numerous advances have been made in the application of both solution-phase and resin-supported peptide catalysts toward the reductions of ketones, imines, quinolines, and conjugated alkenes, often with high levels of enantiocontrol. In particular, three classes of peptides have emerged as excellent platforms for such processes, including (1) amine-containing peptides *via* iminium catalysis, (2) phosphothreonine (pThr)-containing peptides for Brønsted acid catalysis, and (3) various peptide-based ligands in metal-based reduction systems (Section 11.2).

3.1. Transfer Hydrogenation

Proline is one of the most robust and versatile catalytic residues for peptide-based asymmetric catalysis.¹¹ In particular, Pro-containing peptides are well known to form chiral iminium ions following condensation onto aldehydes, which can then be intercepted by a variety of nucleophiles with enantiofacial selectivity governed by the peptide catalyst. Building on the seminal advances from the MacMillan¹¹⁴ and List¹¹⁵ Groups, which revealed that secondary amine catalysts could enable enantioselective reductions of enals with Hantzsch ester (HEH) *via* iminium catalysis, Kudo and co-workers reported an aqueous, peptide-catalyzed variant in 2008 (Figure 34).¹¹⁶ Peptide-mediated reductions with HEH are a fascinating class of reactions, as both reaction partners are biomimetic in nature—peptide-based catalysts are often modeled on certain features of enzymes, while the dihydropyridine-based reductant mimics one of nature's most prolific redox cofactors, NAD(P)H.¹¹⁷

In that context, the authors began with the reduction of enal **3.1** to aldehyde **3.2** in THF/H₂O (1:2 v/v) solvent mixtures using resin-bound, Pro-containing peptide catalysts (Figure 34a).¹¹⁶ However, Pro alone did not provide meaningful levels of conversion to **3.2**.¹¹⁸ The authors posited that the incorporation of a hydrophobic environment near the Pro residue would be required to attract the lipophilic substrate and reductant to catalyst binding pocket. A key aspect of this design principle was to employ peptide-based catalysts in which the *N*-terminal, catalytically active Pro residue was linked to the resin through a helical poly(Leu) chain. While catalysts with short poly(Leu) domains delivered **3.2** in 21% conversion and 54:46 er (entry 1), reactivity and selectivity was enhanced to 63% conversion and 62:38 er upon increasing the average length to ~25.4 Leu units (entry 2)—sufficiently long to form a stable, helical secondary structure. Although this design feature seemed to address the issue of low reactivity, product enantioselectivities were still quite low. As such, peptide **3.3** was devised, in which a β -turn inducing sequence, D-Pro-Aib-(Xaa)₂, was inserted between the catalytic Pro residue and poly(Leu) chain.¹¹⁹ Using this catalyst, **3.2** was formed in 75%

conversion and with 96:4 er (entry 3), suggesting that the β -turn motif is able to provide excellent levels of asymmetric induction. To highlight putative hydrophobic effects exhibited by this catalyst, decreasing the amount of water to 2:1 THF/H₂O resulted in only 13% conversion to **3.2** using peptide **3.3**. A variety of enals **3.1** were addressed by the catalyst, except for sterically hindered compounds, such as *ortho*-chloro-containing **3.1d** (Figure 34b).

Having developed highly enantioselective enal reductions using peptide **3.3**, Kudo and co-workers next probed whether these Pro-containing catalysts could be applied toward more complex substrates, such as $\alpha,\beta,\gamma,\delta$ -unsaturated aldehyde **3.4** (Figure 35).¹²⁰ In addition to enantioselectivity, substrates like **3.4** pose inherent challenges in regioselectivity, namely the control of initial 1,4-reduction to deliver γ,δ -unsaturated aldehyde **3.5** over 1,6-reduction that could afford achiral α,β -unsaturated **3.6** or saturated aldehyde **3.7**. Utilizing pyrrolidine as a simple achiral standard, 76% of 1,4-addition product **3.5** was obtained (entry 1). However, catalyst **3.3** predominantly gave 1,6-addition products **3.6** and **3.7**, an example of catalyst-controlled reversal of inherent regioselectivity (entry 2). In that scenario, peptide **3.3** delivered **3.7** in 94:6 er. Further optimization of the β -turn-inducing sequence revealed that electron-rich Trp residues enhanced the er of **3.7** to up to 99:1 (entry 3), and variation of the *i*+2 position from Aib to Achc increased conversion to this product to 87% (entries 4). Truncation of the α -helical poly(Leu) sequence from 25 to 6 residues resulted in increased conversion and enantioselectivity, revealing peptide **3.8** as the optimal catalyst (entry 5), which was found to be effective over a range of substrates.

Kudo and co-workers further applied these Pro-containing catalysts in the kinetic resolution of planar-chiral ferrocene complexes *via* asymmetric reduction of racemic, enal-containing **3.9** (Figure 36a).¹²¹ While β -turn-containing catalysts lacking an appended hydrophobic chain provided (*R_p*)-**3.10** with a modest *k_{rel}* of 2.3 (entry 1), incorporation of a (Leu-Leu-Aib)₂ unit increased the *k_{rel}* to 4.0 (entry 2). Unlike previous catalysts, such as **3.3** (Figure 34) and **3.8** (Figure 35), which relied on an α -helical polyleucine chain, the (Leu-Leu-Aib)₂ motif is believed to form a 3₁₀ helix. Further optimization of this catalyst revealed that alterations to the *i*+4 position played an essential role in selectivity, with methyl-protected homoserine (Hse(Me)) increasing the *k_{rel}* to 11.7 (**3.11**, entry 3). While the effect of this residue is not entirely understood, the β -turn is thought to position Hse(Me) adjacent to the catalyst-bound substrate. This orientation potentially facilitates secondary interactions between the iminium cation and the oxygen lone pairs of Hse(Me), which may inhibit particular approach trajectories of the HEH reductant (Figure 36a). This methodology was further expanded to address symmetrical, bis(enal)-containing ferrocene compounds, such as **3.12** (Figure 36b).¹²² In this case, both mono-reduced **3.13** and the product of intramolecular cyclization (**3.14**) were possible. The choice of an acidic additive proved essential to controlling the product ratio. Using **3.11** as the catalyst with substoichiometric HCl as the additive, **3.13** was obtained with 87:13 er in a 99:1 ratio over **3.14** (entry 1). Using two equivalents of benzoic acid instead, peptide **3.11** now favored **3.14** in a 73:27 ratio, with products **3.13** and **3.14** being isolated with 97:3 er and 93:7 er, respectively (entry 2).

In a complementary approach to iminium activation by Pro-containing catalysts, Brønsted acid catalysts have also been reported to mediate Hantzsch ester-based reductions. In 2004, the Akiyama¹²³ and Terada¹²⁴ Groups independently reported the development of a new BINOL-derived chiral phosphoric acid (CPA). CPAs are now considered privileged catalysts, and they have since been reported to mediate a vast array of transformations,⁸² including reductions.^{125–128} However, efforts to develop alternative catalyst architectures have been slow. The C_2 -symmetry of the CPA scaffold has been proposed to be essential for effective catalysis, as this property makes tautomerization of the phosphoric acid proton between the two phosphate oxygens degenerate, which would otherwise provide distinct diastereomeric species with potentially different catalytic activities.

In pursuit of an alternative to the archetypal CPA scaffold, our group postulated that short-sequence peptides could serve as a new family of chiral Brønsted acid catalysts. In this case, catalyst rigidity would perhaps not be necessary, as noncovalent interactions between the flexible peptide backbone and substrates could enable high degrees of selectivity. Moreover, the modularity and tunability of the peptide sequence would enable the development of catalysts with highly diverse structures and functions. Our first forays into this realm began in 2015, when we identified and developed pThr as a catalytic residue that could be easily embedded into peptidic scaffolds to enable Brønsted acid catalytic activation modes (Figure 37a).⁸⁶ Although pThr is a well-known product of post-translational modification that is central to the regulation of cell function, it has never been reported as part of a catalytic apparatus in nature.¹²⁹

Our efforts to develop enantioselective pThr-based catalysts began with studies on the HEH-mediated transfer hydrogenation of quinolines (Figure 37b).⁸⁶ While minimally substituted quinolines were reduced with high conversions, no enantioselectivity was observed. However, incorporation of a directing group handle on the quinoline C8-position (*e.g.*, **3.17**), which was presumed to facilitate noncovalent interactions between catalyst and substrate, greatly improved the efficacy of the peptide-mediated reduction to tetrahydroquinoline **3.18**. Evaluation of a small library of peptides containing an *N*-terminal pThr residue revealed that a central D-Pro-Acpc dyad (Acpc = 1-aminocyclopropane carboxylic acid) at the *i*+1 and *i*+2 positions was critical for obtaining high levels of selectivity. Further optimization of the *i*+3 residue led to the identification of Met-containing phosphopeptide **3.16** (Figure 37a), which mediated the transfer hydrogenation of 8-aminoquinolines **3.17** in good yields and up to 94:6 er (Figure 37b). These selectivities were comparable to those afforded by a known BINOL-derived CPA, (*R*)-TRIP (**3.15**, Figure 37a). NMR studies showed that, despite the increased flexibility of peptide-based catalyst **3.16** as compared to **3.15**, high selectivities could be achieved through: (1) the incorporation of critical secondary structural elements into the peptide, in this case a β -turn motif that is stabilized by a 10-membered ring N-H(*i*+3)•••O(*i*) H-bond, and (2) secondary interactions between the catalyst and substrate directing group, specifically the 8-amino group of **3.17** (Figure 37b). These results demonstrate the difference between pThr-peptides and BINOL-derived CPAs, which achieve selectivity through distinct activation mechanisms.

Given the high selectivities achieved by both BINOL-derived and pThr-based CPAs despite their significant differences in design and mechanism, our group sought to further probe the

activities of these catalysts in more complex transformations. For example, the reduction of bis(quinoline) **3.19** would pose interesting selectivity challenges, as two sequential transfer hydrogenations can occur on one substrate (Figure 38a).¹³⁰ Following initial formation of both enantiomers of mono-reduced **3.20**, further reduction can result in a mixture of both chiral (**3.21**) and *meso* (**3.22**) products. The use of two chirality-generating steps in tandem is a strategy for enhancing the enantioselectivity of the overall process, as governed by Horeau's Principle.¹³¹ Under ideal conditions, with the assumption that the catalyst reduces **3.19** to **3.20** and **3.20** to **3.21** with the same levels of selectivity, the final er of doubly reduced **3.21** can be predicted by squaring the er of the first reduction.

Applying pThr-containing catalyst **3.16** to the reduction of **3.19**, mono-reduced **3.20** was produced with 67:33 er ($s_1 = 2.0$, Figure 38a, entry 1),¹³⁰ notably lower than previously observed for the reduction of quinoline **3.17** (Figure 37b). Based on this result, the theoretical er of the di-reduced product is 81:19 ($s_1^2 = 4.1$), yet catalyst **3.16** produced **3.21** with 95:5 er ($s_2 = 19$). This result indicates that **3.16** is substantially more selective in the second reduction step than in the first. Alternatively, BINOL-derived catalyst *ent*-**3.15** performed the first reduction with 86:14 er, yet only produced di-reduced **3.21** with 87:13 er (entry 2), implying this catalyst is matched preferably in the first reduction.

Given the complementarity of catalysts *ent*-**3.15** and **3.16**, reductions of **3.19** were performed in the presence of both catalysts in one pot, with the expectation that each catalyst would selectively facilitate its matched step. Indeed, using the catalysts together, both **3.20** and **3.21** were produced with high enantioselectivities of 83:17 er and 94:6 er, respectively, which is comparable with the values each catalyst was able to achieve separately (entry 3). These observations suggest that both catalysts indeed exerted control over their matched steps (Figure 38b). To further test this hypothesis, catalyst *ent*-**3.15** was substituted with (*R*)-TRIP (**3.15**) in these one-pot reactions (entry 4). While **3.15** maintained control over the first step with the opposite sense of enantioinduction, delivering (*R*)-**3.20** in 28:72 er, peptide **3.16** produced (*S,S*)-**3.21** as the major di-reduced product, reversing the absolute stereochemistry for the product of the second step (63:37 er). This phenomenon is a rare instance of two co-catalysts with the same catalytic motif (a phosphoric acid) acting in tandem in a one-pot process. By appending different chiral scaffolds to a phosphoric acid (*e.g.*, BINOLs *vs.* peptides), each catalyst is matched for a different substrate—BINOL-derived CPAs for bis-quinoline **3.19** and peptide-based CPAs for mono-reduced **3.20**. These results speak to the potential complementarity of BINOL-derived and peptide-based CPAs in complex settings, including situations where they might be employed *in situ* and in one-pot.

While divergent *selectivities* were observed between different CPA catalysts for reductions, our group had also developed π -methylhistidine (Pmh)-based catalysts that exhibit distinct *reactivity* profiles based solely on the appended peptide sequence.¹³⁰ In 1999, Pmh-containing peptide **3.23** was shown to mediate the kinetic resolution of racemic amino alcohol **3.25** *via* acylation with acetic anhydride (Figure 39a).^{132–134} Additionally, Pmh-containing peptide **3.24** was found to selectively phosphorylate *myo*-inositol derivative **3.26** at the 1-hydroxyl group.^{135,136} In analogy to the concept explored using CPAs to perform the reductions of bis(quinoline) **3.21** (Figure 38), we had shown that whether each of these

catalysts **3.23** and **3.24** could perform their matched reactions when all the reagents and catalysts were added together in one pot (Figure 39b).¹³⁰ Inclusion of both substrates **3.25** and **3.26**, acylation and phosphorylation reagents, and catalysts **3.23** and **3.24** in one reaction could result in myriad of mono- and poly-acylated and phosphorylated products and the corresponding stereoisomers. Despite this complexity, the acylated amino alcohol **3.27** and phosphorylated inositol derivative **3.28** were the primary products of this reaction, and each was formed with good enantioselectivity. The only other significant product observed was **3.29**, in which the unreactive enantiomer of **3.25** was phosphorylated. These results demonstrated the sequence-dependent reactivity Pmh-containing peptides **3.23** and **3.24** for acylation and phosphorylation of targeted substrates and foreshadowed our more recent findings with CPAs. This peptide-encoded reactivity is presumably the result of precise outer-sphere interactions between the peptides and their substrates.

3.2. Reductive Amination

The utility of pThr-embedded peptides for HEH-mediated reductions was further explored in the reductive amination of 3-amidocyclohexanones **3.30** with *p*-anisidine (Figure 40a).⁸⁷ Both the *cis*- and *trans*-isomers of amine product **3.31** were possible in this case, providing enantio- and diastereoselectivity challenges for the peptide-based catalysts to address. Upon confirming the inherent *trans*-selectivity of the reaction with achiral diphenyl phosphate as the catalyst (DPP, 69:31 dr, entry 1), peptide **3.16**, the lead catalyst for quinoline reduction,⁸⁶ was evaluated in this new context. Unfortunately, **3.16** gave nearly racemic products (entry 2). Extensive screening of the peptide sequence revealed that bulky, L-amino acids at the *i*+2 position, such as Val, provided *cis*-**3.31** with up to 83:17 er (entry 3). However, further increases in enantioselectivity were difficult to achieve.

Given that the protected pThr monomer alone was able to provide fair levels of enantioselectivity in *cis*-**3.31** (75:25 er, entry 4), we suspected that changes to the catalytic residue could have a more substantial impact on catalyst selectivities. Indeed, changing the *N*-terminal protecting group from Fmoc to the more electron-rich *p*-methoxybenzamide and further tailoring the peptide sequence led to the identification of **3.32**, which produced *cis*-**3.31** in 93:7 er (entries 5–6). Peptide **3.32** was also modestly more *cis*-selective than DPP (51:49 vs. 69:31 dr, entries 6 vs. 1). NMR studies revealed that the electron-rich benzamide enabled the formation of a 10-membered ring N–H(*i*+2)•••O(*i*–1) H-bond, defining a β -turn that is shifted over one residue with respect to the secondary structure of peptide **3.16**. Alternatively, BINOL-derived CPA *ent*-**3.15** yielded higher dr and er for *trans*-**3.31** (entry 7). This complementarity was further investigated using kinetic studies (Figure 40b). While *ent*-**3.15** operates *via* a kinetic resolution regime, in which the (*S*)-enantiomer of **3.30** reacts more rapidly and with higher selectivity than the other; peptide **3.32** performs a parallel kinetic resolution, in which both enantiomers are converted to different products with high selectivity in each—(*R*)-**3.30** to *cis*-**3.31** and (*S*)-**3.30** to *trans*-**3.31**.

The complementarity of peptide-based Brønsted acid catalysts compared to BINOL-derived CPAs is further explored in Section 11

4. Group Transfer

Group transfer reactions, such as phosphorylation and acylation, are not only key steps in biosynthetic and regulatory pathways *in vivo*, but they are also highly useful and often strategic transformations in synthetic chemistry. As such, a wide variety of catalytic group transfer methods have been developed through the years, many of which take advantage of Lewis basic activation modes. In the context of polyfunctional molecules, selective group transfer reactions can provide direct access to functionalized targets without recourse to protecting group manipulations. While this sort of selective transformation is routine for enzymes, it presents a greater challenge for small molecule catalysts. Drawing upon inspiration from nature's group transfer catalysts, synthetic peptide catalysts have been developed for asymmetric group transfer reactions in recent years, including phosphorylation (Section 4.1), sulfonylation (Section 4.2), carbamoylation (Section 4.3), and acylation (Section 4.4). Many of these reactions rely on a Pmh residue embedded within the peptide framework to enable Lewis base catalytic pathways. However, catalytic residues based on tetrazoles and pyridines have also been developed. The advent of these new catalytic systems has also been coupled to mechanistic studies using experimental and computational techniques.

4.1. Phosphorylation

Protein phosphorylation is the most common post-translational modification, which is crucial for regulating protein function.^{137,138} In nature, histidine-dependent kinases utilize an active site His residue to mediate phosphorylation events *via* Lewis base catalysis. Inspired by the reactivity and selectivity exhibited by various kinases, small peptides have been designed and developed to catalyze phosphate group transfer reactions of both natural and synthetic small molecule substrates, as well as complex natural products.¹⁷ Similar to histidine-dependent kinases, these biomimetic peptide catalysts typically rely on Pmh as the catalytically active residue. However, alternative reaction strategies have also been developed utilizing tetrazolylalanine (Atz).

In 2001, our group first demonstrated that short-sequence Pmh-embedded peptides could catalyze asymmetric phosphorylation reactions. Using either peptide **4.3**¹³⁵ or β -turn-biased **4.4**,¹³⁹ *myo*-inositol derivative **4.1** could be desymmetrized to afford either **4.2** (65% yield, >98% ee) or *ent*-**4.2** (56% yield, >98% ee) with excellent levels of enantioselectivity (Figure 41a). Though both peptides contain the same absolute configuration of the catalytically active Pmh residue, **4.3** and **4.4** provide enantiodivergent outcomes in this phosphorylation reaction, likely due to their different secondary structures. These early studies indicated that peptide-catalysts are well-suited for the enantioselective synthesis of biologically relevant inositol monophosphates.

Among the monophosphates of inositol, phosphatidylinositol-5-phosphate (PI5P) has gained attention for its role in regulating cellular processes.¹⁴⁰ However, investigations of PI5P had been limited, perhaps due to a lack of biological or synthetic availability. To address this challenge, our group developed a rapid and efficient total synthesis of PI5P derivative **4.5** using our previously developed strategy for the desymmetrization *myo*-inositol **4.1** (Figure 41a).¹⁴¹ We began with a large-scale synthesis of **4.2** using peptide **4.3** to catalyze the

enantioselective phosphorylation. This material was then converted to PI5P derivative **4.5** in 21% yield from **4.2** over 8 synthetic steps (Figure 41b). Alternatively, peptide **4.4** could be employed to synthesize *ent*-**4.2**, which was ultimately converted into *ent*-**4.5**, the total synthesis of which had not been previously reported. Facile access to **4.5** and *ent*-**4.5** enabled further studies of the biological roles that these inositol monophosphates play. Moreover, the rapid and efficient total synthesis of PI5P analogs highlights the utility of Pmh-embedded peptide catalysts both for asymmetric phosphate group transfer and in target-oriented synthesis.

A similar strategy was applied to the syntheses of L,L- and L,D-di-*myo*-inositol-1,1'-phosphate (DIP, **4.6**), which has been identified as a major intracellular solute in several hyperthermophiles, acting as a stabilizer of enzyme activity under high temperature conditions (Figure 42).¹⁴² The stereochemical configuration of naturally occurring DIP has been an ongoing topic of discussion in the literature, as there have been reports implicating both chiral L,L-**4.6** and *meso* L,D-**4.6** isomers.^{143–145} Given our previous use of Pmh-containing peptides for the desymmetrization of *myo*-inositol derivative **4.1**, we proposed that peptides like **4.3** and **4.4** could be used to synthesize both DIP isomers selectively. Access to both diastereomers of **4.6** could help to shed light on the question of which isomer is indeed the naturally occurring one.

Starting from *ent*-**4.2**, which was synthesized using peptide **4.4** according to the conditions reported in Figure 41a, **4.7** can be accessed in 73% yield over 3 steps. Efforts were then directed toward identifying reaction conditions to promote the selective coupling of **4.7** with **4.1** (Figure 43). Achiral nucleophilic catalysts, such as NMI, established the degree of inherent substrate control during the formation of DIP adducts L,D-**4.8** and L,L-**4.8** in a 4:1 ratio (entry 1). Using peptide **4.4**, a modest reversal of the intrinsic selectivity was observed, favoring L,L-**4.8** in a 1:1.25 ratio (entry 2). Upon evaluating 20 other catalysts, peptides **4.9** and **4.10** were identified as highly selective for L,D-**4.8** (13:1) and L,L-**4.8** (1:2.5), respectively (entries 3 & 4). Although Figure 43 reports the product ratio as the relative amounts of L,D-**4.8** and L,L-**4.8**, this reaction is actually more stereochemically complex. A diastereomeric mixture of phosphoryl chlorides—which are epimeric at the stereogenic P-center—is prepared *in situ* from **4.7** and then coupled with **4.1** to afford the desired products. This further highlights the challenges associated with reaction optimization and perhaps makes the results achieved by peptides **4.9** and **4.10** all the more remarkable.

With each individual isomer of **4.8** in hand, these compounds were globally deprotected to form the sodium salts of L,D- and L,L-**4.6** (Figure 42). The differential biological activity of each isomer was then assessed.¹⁴² Thermal stability studies indicated that the sodium salts of both L,L-**4.6** and L,D-**4.6** were similarly effective. In most cases, biological targets are tuned to interact with a specific isomer of a substrate. However, this scenario represents a potentially unusual example in which there is virtually no specificity for one DIP isomer over the other.

At this point, the peptide-catalyzed desymmetrizing phosphorylation of *myo*-inositol derivative **4.1** had been well established as a reliable method to differentiate the enantiotopic alcohols at the 1- and 3-positions.¹³⁹ However, efforts to use a peptide-based strategy to

discriminate between the enantiotopic 4- and 6-hydroxyls in analogous *myo*-inositol derivative **4.11** had remained an unmet challenge (Figure 44); over 150 Pmh-containing peptides were screened to no avail. In 2010, our group reported a related approach to address the desymmetrization of **4.11** that capitalizes on the known ability of tetrazoles to mediate phosphoramidite transfer reactions.¹⁴⁶ Whereas Pmh-containing peptides mediate the transfer of P(V) groups through an activated phosphorylimidazolium intermediate (Figure 44a), we proposed that Atz would mediate P(III) group transfer chemistry, possibly providing access to an alternate mechanistic pathway that would enable the desymmetrization of **4.11** (Figure 44b). This mechanism would begin with protonation of the phosphoramidite reagent by Atz and subsequent displacement of the amine ligand to afford an active tetrazolylated phosphoramidite intermediate **A** for P(III) group transfer to **4.11**. In this scenario, an amine scavenger is required to facilitate catalyst turnover.

As such, Atz was synthesized from β -cyanoalanine and tributyltin azide *via* a [3+2] cycloaddition and subsequently incorporated into a library of peptides using conventional coupling methods. These Atz-containing peptides were screened in the desymmetrization of **4.11** in the presence of dibenzyl-*N,N*-diethylphosphoramidite using 10 Å molecular sieves to scavenge diethylamine. A workup with aqueous hydrogen peroxide was used to convert initially formed phosphite **4.12** to the corresponding phosphate **4.13**. Evaluation of the peptide library led to the identification of **4.15**, which delivered **4.13** in 71% yield and 85:15 er. Notably, **4.15** shares several constituent amino acids with highly selective P(V)-transfer catalyst **4.4**, namely the *tert*-butyl-protected hydroxyproline (Hyp) residue at *i*+1 and the *C*-terminal diad of benzylic residues. When ($\pm$)-**4.13** was subjected to the **4.15**-catalyzed phosphorylation conditions, a significant k_{rel} of 34.5 was measured *en route* to the bis(phosphate) byproduct, suggesting that secondary kinetic resolution contributes, at least in part, to the observed er in the desymmetrization reaction.

We were able to leverage this observation to our advantage in order to obtain highly enriched **4.13** to be used in the enantioselective total synthesis of *D*-*myo*-inositol-6-phosphate **4.14** (Figure 45). Following initial desymmetrization of **4.11**, enantioenriched **4.13** (85:15 er) was re-subjected to the peptide **4.15**-catalyzed phosphoramidite transfer conditions on gram-scale. Following oxidative workup, monophosphate **4.13** was isolated in 52% yield and >98:2 er, as the minor enantiomer was selectively converted into the symmetrical bis(phosphate). Monophosphate **4.13** was then globally deprotected *via* dissolving metal reduction to yield **4.14**, a biologically relevant phosphorylated metabolite, in nearly quantitative yield.

4.2. Sulfonylation

Although Pmh-containing peptides had been used to mediate a number of group transfer reactions with alcohols, such as phosphorylation (Section 4.1) and acylation (Section 4.4), the selective transfer of sulfur-based groups was less thoroughly explored and limited to sulfinylation.¹⁴⁷ To address this, our group developed a method for the peptide-catalyzed, enantioselective sulfonylation of *meso*-1,3-diols (Figure 46).¹⁴⁸ Reaction optimization was performed using the familiar *myo*-inositol derivative **4.1** as the substrate. Among the sulfonylating reagents assessed, *p*-nitrobenzenesulfonyl chloride (*p*-NsCl) was found to be

optimal. Using sodium bicarbonate as the base, no racemic background reaction was detected in the absence of a catalyst, yet good conversion to mono-sulfonylated inositol **4.16** was observed under Pmh catalysis. Thus, a series of peptide-based catalysts were evaluated for their ability to desymmetrize **4.1** *via* Pmh-mediated sulfonylation. Pentapeptide **4.4**, which was previously identified as highly enantioselective in the desymmetrizing phosphorylation of **4.1** (Figure 41),¹³⁹ delivered **4.16** with a modest er of 67.5:32.5. After screening several Pmh-containing catalysts, tetrapeptide **4.18**, which shares the same β -turn-inducing Hyp(*t*-Bu)-Cle sequence (Cle = cycloleucine) as pentapeptide **4.4**, was identified as the lead catalyst, providing **4.16** in 76% yield and 97:3 er. Among the 10 substrates examined under these conditions, those based on the inositol framework were processed by **4.18** with excellent yields and enantioselectivities, while *cis*-cyclohexane-1,3-diol led to racemic product. Glycerols were also effective substrates, and the degree of enantioselectivity observed was dependent on the relative stereochemistry of the substituents. Taken together, these data suggest that **4.16** is better able to differentiate the enantiotopic hydroxyl groups in *meso*-1,3-diol substrates with certain conformational preferences.

Although sulfonylation catalyst **4.18** and phosphorylation catalyst **4.4** share similar sequences, these peptides interact with *myo*-inositol **4.1** in unexpectedly different ways (Figure 46). When **4.1** was subjected to the phosphorylation conditions with peptide **4.4**, phosphoryl group transfer occurred selectively at the 3-hydroxyl, affording *ent*-**4.2** in >99:1 er. Conversely, under the **4.18**-catalyzed sulfonylation conditions, the hydroxyl group at the 1-position was selectively sulfonylated to provide **4.16** in 97:3 er. However, when *ent*-**4.2** and **4.16** were subsequently subjected to the sulfonylation and phosphorylation conditions, respectively, both species converge to the same enantiomer of mono-phosphorylated, mono-sulfonylated **4.17** as confirmed by HPLC retention times. These data show that **4.4** and **4.18** indeed target enantiotopic hydroxyl groups of **4.1** despite their sequence homology, suggesting that these two peptides operate *via* disparate catalytic activation modes. While it is tempting to conclude that this stems from differences in secondary structure, it is also possible that mechanistic changes as a function of the electrophile, stoichiometric base, or solvent give rise to this unexpected enantiodivergence. As is so often the case with peptide-based catalysts, seemingly minor differences in sequence and reaction conditions can lead to large perturbations in reactivity and selectivity.

4.3. Carbamoylation

In addition to group transfer reactions of alcohols, Pmh-containing peptide catalysts have also been used to mediate the enantioselective carbamoylation of formamides and thioformamides **4.19** as an entry into chiral secondary amine derivatives **4.20** (Figure 47).¹⁴⁹ Chiral amine building blocks are highly valuable in synthetic chemistry. However, the ability to use group transfer kinetic resolutions to access chiral amines has presented a longstanding challenge to the field. Prior to this work, non-enzymatic approaches using small molecule catalysts under mild conditions were fairly limited.^{150–154} Since then, however, several methods have been developed for the synthesis of optically enriched amines employing small molecule catalysts.¹⁵⁵ Combining the benefits of enzymatic and small molecule catalysis, our group sought to employ Pmh-containing peptides to catalyze the kinetic

resolution of (thio)formamides **4.19** *via* selective Boc group transfer from di-*tert*-butyldicarbonate (Boc₂O). The Pmh-containing peptide was anticipated to initially transfer a Boc group to the (thio)carbonyl group of **4.19**. This kinetically more favorable *O*- or *S*-acylated intermediate **I** would subsequently rearrange to deliver the more thermodynamically stable imide **4.20**. Enantioenriched **4.20** could then be selectively deprotected to deliver chiral amine building blocks.

Catalyst optimization led to the discovery of β -hairpin-biased peptide **4.21**, which yielded formamide **4.19a** with an *s*-factor of 9.6 at 37% conversion (Figure 47, entry 1). We hypothesized that thioformamides would be more reactive both toward initial *S*-acylation and subsequent *S*-to-*N* acyl shift. Indeed, thioformamide **4.19b** substantially was processed by **4.21** with an *s*-factor of 12.8 at 51% conversion (entry 2). When examining the reaction scope of thioformamides, electron rich aryl substituents promoted higher *s*-factors than electron poor ones, as exemplified by **4.19c** and **4.19d**, respectively (entries 3 & 4). The largest *s*-factor was obtained with the highly electron rich thioformamide **4.19c**, with an *s*-factor of 43.7. *N*-Heterocycle-containing **4.19e** was also tolerated under the reaction conditions, albeit with a reduced *s*-factor of 5.6 (entry 5). In this case, it is possible that the pyridine moiety of **4.19e** catalyzes a competing Boc group transfer process that erodes the selectivity, though different interactions with peptide **4.21** are also possible.

We further demonstrated the utility of these enantioenriched thioformamide products for the synthesis of chiral amine building blocks (Figure 48). Cleavage of the Boc group from **4.20b** using trifluoroacetic acid, followed by *S*-to-*O* exchange led to the formation of formamide **4.20a** in 82% yield. Additionally, Boc-protected **4.22** could be accessed in 81% yield *via* oxidative hydrolysis of the thioformamide group. These results further highlight the ability of Pmh-containing peptides to deliver synthetically useful products that are difficult to access by other means.

4.4 Acylation

Since the initial reports on the use of Pmh-containing peptides for the enantioselective acylation of amino alcohols,^{6,132} the scope of acylation reactions amenable to Pmh-embedded peptide catalysis has grown significantly. While the earliest studies of peptide-catalyzed asymmetric acylation reactions were discussed in our previous review,⁴ this Section reports on the more recent advances in this area that amount to a significant expansion of scope and mechanistic understanding.

In collaboration with Merck in 2006, we reported the first example of a peptide-catalyzed remote desymmetrization reaction.^{156,157} Prior to this report, remote asymmetric induction was often thought to require enzymes in order to differentiate enantiotopic groups separated by great distances.¹⁵⁸ However, Pmh-containing peptide **4.25** was able to desymmetrize diarylmethane bis(phenol) **4.23a** to mono-acylated **4.24a** in 80% yield and 97.5:2.5 er (Figure 49). In the context of this pharmaceutically relevant scaffold,¹⁵⁹ peptide **4.25** was able to discriminate between enantiotopic hydroxyl groups that are separated from one another by nearly a full nanometer (9.9 Å) and from the pro-stereogenic center by 5.8 Å.

While examining the scope of this remote desymmetrization reaction, a trend between the steric demand of the prochiral substituent of **4.23** and the enantioselectivity was observed. In collaboration with the Sigman Group, we employed physical organic tools to investigate the factors that govern selectivity in this peptide-catalyzed reaction.¹⁶⁰ Linear free-energy relationships were used to correlate the observed enantioselectivity ($G^\ddagger$) with various steric parameters, including Sternhell interference energies (Figure 49).¹⁶¹ A steep linear dependence on the steric demand of the prochiral substituent was identified, with bulky substituents, such as *tert*-butyl, delivering the best enantioselectivities. It was reasoned that bulky substituents could give rise to conformational preferences, such as differences in the propeller-like twisting of the diarylmethane scaffold, that might enable the discrimination of the enantiotopic arenes. In a follow-up study, the Sigman Group was able to further elaborate on the source of selectivity in this reaction using multidimensional parameterization techniques.^{162,163} In this study, the authors were able to identify correlations between the measured enantioselectivity and DFT-computed vibrational frequencies of the arene rings of **4.23**. These new data suggested that peptide **4.25** is sensitive to both steric and electronic substituent effects in diarylmethane **4.23**.

In addition to the early reports from our group, highly significant contributions in the arena of Pmh-containing peptide-mediated acylation reactions have been made by the Schreiner Group in recent years.^{164–166} Unique to the Pmh-containing peptides developed by Schreiner and co-workers is the presence of the non-proteinogenic amino acid γ -aminoadamantanecarboxylic acid (^AGly, Figure 50). This residue can be synthesized in one step from the corresponding carboxylic acid *via* direct C–H bond amidation using acetonitrile as the nitrogen nucleophile.¹⁶⁷ Incorporation of this rigid, hydrophobic residue was designed to diminish catalyst self-association (*e.g.*, dimerization or folding), enable low catalyst loadings, and facilitate solubility in nonpolar organic solvents.

Using this class of peptide catalysts, Schreiner and co-workers first pursued the kinetic resolution of simple *trans*-cycloalkane-1,2-diols **4.26** *via* acylation (Figure 50), a reaction which had posed significant challenges for methodology development at the time, even with enzymatic catalysts.^{164,166} After evaluating several lipophilic amino acids at the *i*+2 position, ultimately **4.28**, bearing cyclohexylalanine (Cha), was selected as the lead catalyst. In toluene as solvent with a mere 1 mol% catalyst loading, **4.28** was able to achieve excellent selectivities in the acylation of *trans*-1,2-diols **4.26** with ring sizes ranging from 5–8 members (entries 1–4). While six- (**4.26b**), seven- (**4.26c**), and eight-membered rings (**4.26d**) were highly selective in this transformation with *s*-factors > 50 (entries 2–4), *trans*-cyclopentane-1,2-diol **4.26a** was the exception, which was only modestly selective with an *s*-factor of 8 (entry 1). Low selectivity with this substrate is likely due to the need for minimal amounts of dichloromethane co-solvent to overcome the poor solubility of **4.26a** in toluene, and the selectivity was found to be quite sensitive to the reaction medium. Though linear diols were also examined, peptide **4.28** achieved significantly higher levels of selectivity with cyclic diols.¹⁶⁶

The authors turned to computations in order to shed light on the origins of enantioselectivity in the kinetic resolution of **4.26** with peptide **4.28**.¹⁶⁴ Molecular dynamics simulations (MMFF) were used to search for low energy conformations of the active *N*-acylimidazolium

intermediate of **4.28**. Regardless of the starting geometry, all of the lowest-energy conformers placed the *i*+2 cyclohexylalanine (Cha) residue in close proximity to the acylimidazolium moiety (Figure 51). The authors used the low-energy conformations of acylated **4.28** to propose a transition state model, which evokes an H-bond between the carbonyl of the *i*+2 residue with the nonreacting diol and hydrophobic interactions between Cha and the cycloalkane of **4.26** to induce high selectivity in favor of the experimentally observed (–)-enantiomer of **4.27**. This model was further supported by NMR studies performed by Thiele and co-workers.¹⁶⁸ Examination of peptide **4.28** alone using NOE- and residual dipolar coupling (RDC)-based methods revealed an ensemble of four major conformers, which resemble the “pocket-like” structure shown in Figure 51. Upon addition of (–)-**4.27b**, intermolecular NOE contacts between the substrate and catalyst could be detected using advanced NMR methods, including a pure shift EASY ROESY experiment developed by the authors. Notably, NOE contacts between the cyclohexyl groups of the substrate and peptide were observed (blue arrow, Figure 51), which further supports the importance of hydrophobic interactions for achieving high enantioselectivity in this reaction.

In a subsequent computational study by Sunoj and co-workers, the mechanism of the peptide **4.28**-catalyzed acylation of *trans*- (**4.26b**) and *cis*-cyclohexane-1,2-diols (**4.29a**) was examined in more depth.¹⁶⁹ Although *cis*-diols were not reported in Schreiner's original paper,¹⁶⁴ the authors studied this substrate class computationally. For geometry optimizations, the most crucial parts of the reacting system—the diol and acylated Pmh residue—were described using density functional theory (B3LYP/6-31G*), while the peptide backbone was treated as a lower layer using the semiempirical PM3 method. When considering the mechanism of these acylation reactions, a complex between acylated **4.28** and the diol substrate is first formed, and then stereoselective acyl group transfer occurs within this chiral environment. Thus, the inclusion complex between different stereoisomers of the diols (either **4.26b** or **4.29a**) and acylated-peptide (**4.28**) was first examined (Figure 52). The lowest-energy complex for *trans*-diol **4.26b** leading to a (1*R*, 2*R*)-configuration (**Complex I**)—the observed enantiomer of the product—shows a stabilizing H-bonding interaction between the carbonyl of the *i*+2 Cha residue and the nonreacting hydroxyl group of **4.26b**. This type of interaction was in agreement with the model proposed by Schreiner and co-workers (Figure 51).¹⁶⁴ While **Complex I**, leading to (1*R*, 2*R*)-**4.27b**, was most stable for *trans*-**4.26b**, **Complex II** with a (1*R*, 2*S*)-orientation was the most preferred for *cis*-**4.29a**. This reinforces the notion of a proclivity toward selective chiral recognition of each diol by the peptide, which produces the desired chiral environment for enantioselective acyl group transfer.

Next, the transition states (TSs) for the acyl group transfer step were identified.¹⁶⁹ The two lowest-energy transition states of each enantiomer of *trans*-diol **4.26b** with acylated peptide **4.28** are shown in Figure 53. As anticipated, **TS 4.1** with the (1*R*, 2*R*)-enantiomer of **4.26b** is the lowest conformer, which leads to the experimentally observed product **4.27b**.¹⁶⁴ Comparing the geometrical features of **TS 4.1** and **TS 4.2** further emphasizes the crucial role of the stabilizing H-bond between the nonreacting hydroxyl of **4.26b** and the *i*+2 carbonyl of peptide **4.28**. The distances between the acyl group and the Pmh nitrogen and diol oxygen also suggest a product-like TS for this acyl transfer reaction. Across the various TSs for this

step, the conformation of the peptide, particularly the orientation of cyclohexyl group of the Cha residue, exhibited significant deviations (*e.g.*, **TS 4.1** vs. **TS 4.2**, Figure 53). The effects of the peptide conformation and noncovalent interactions between the acylated-peptide and diol culminate in a significant energy separation between the diastereomeric acyl transfer TSs to render this acylation selective for the *trans*-(1*R*,2*R*)-**4.26b**. Although the stereochemical outcome was correctly predicted, the calculated enantiomeric excess of **4.27b** (>99% ee) was significantly higher than the experimental outcome (Figure 50, entry 2).

For the desymmetrizing acylation of *cis*-diol **4.29a**, this computational method predicted that the (1*R*,2*S*)-enantiomer would give the lowest-energy TS, with a $G^\ddagger$ of 4.3 kcal/mol between the diastereomeric TSs.¹⁶⁹ Such a large energy difference indicates that peptide **4.28** should also be able to acylate *cis*-1,2-diols **4.29**, affording (1*R*,2*S*)-**4.30**. Overall, this in-depth computational study of the kinetic resolution of *trans*- and *cis*-1,2-diols further highlights the bifunctional nature of Pmh-based catalysts, which not only serve as nucleophilic catalysts, but also govern selectivity through peptide secondary structure, noncovalent interactions, and chiral recognition.

Fulfilling the computational predictions by Sunoj and co-workers,¹⁶⁹ the desymmetrization of *meso*, *cis*-1,2-diols (**4.29**) using the same peptide (**4.28**) was later developed by Schreiner and co-workers.¹⁷⁰ The reaction conditions used for the kinetic resolution of *trans*-diols **4.26** (Figure 50) translated well to *cis*-diols **4.29**, with only minor optimization required.

Although exogenous base is not required in this reaction, the inclusion of 5.3 equivalents of *N,N*-diisopropylethylamine (DIPEA) lead to significantly faster reaction rates and increased selectivity; the molar equivalency of acetic anhydride was adjusted to match that of the base. Under these conditions, peptide **4.28** successfully desymmetrized *meso*-vicinal diols **4.29** (Figure 54), achieving up to 94:6 er with **4.29a** at –40 °C (entry 1). Further cooling the reaction mixture to –55 °C increased the enantioselectivity of **4.30a** to 95:5 er but decreased the yield to 61%. Both cyclic and linear *meso* diols provided >90:10 er, with the exception of *meso*-hydrobenzoin **4.29e** (entry 5) and heteroatom-containing diol **4.29f** (entry 6).

The ability to achieve high enantioselectivity with *meso*-diols **4.29** is challenging, due in part to the intramolecular acyl group migration that can occur in **4.30**, which effectively racemizes the product. Indeed, the authors noted that partial racemization of **4.30** was detected upon reaction workup. To combat this problem, a subsequent oxidation of the remaining alcohol was developed to convert **4.30** into α -hydroxyketones **4.31** (Figure 55).¹⁷⁰ After exploring various oxidants, TEMPO and *m*-CPBA were selected as co-oxidants for *in situ* oxidation of stereochemically labile **4.30a** to afford **4.31a** in 70% yield and 94:6 er. This protocol was applied to several other *meso*-1,2-diols **4.29** without significant perturbation to the enantioselectivity after oxidation.

This one-pot enantioselective acylation/oxidation protocol was later advanced to use a single multicatalyst to perform both the enantioselective acylation and subsequent alcohol oxidation (Figure 56a).¹⁷¹ This represents the first report of an organocatalytic, enantioselective tandem reaction mediated by a single catalyst containing orthogonal catalytic moieties. Several multicatalysts were synthesized and evaluated, varying the

location of the TEMPO moiety relative to the Pmh residue. The best results were obtained using peptide **4.32**, whose structure and sequence most closely resemble **4.28**, which was previously optimized for acyl transfer.^{164,170} An overlay of the lowest-energy conformations of the two acylated catalysts **4.28** and **4.32** obtained using molecular force-field analysis highlights their structural similarities (Figure 56b).

A comparison between both approaches for the acylation/oxidation of *meso*-diols, which proceed either by concurrent tandem desymmetrization/oxidation accomplished with multicatalyst **4.32** (blue) or peptide **4.28**-catalyzed desymmetrization followed by one-pot TEMPO oxidation (red; Figure 57).^{170,171} With most substrates, yields and selectivities were slightly reduced using multicatalyst **4.32**. However, using **4.29b**, higher enantioselectivity was achieved (87:13 er) with peptide **4.32** rather than with the two-step approach using **4.28** followed by TEMPO (82:18 er, entry 2). The incorporation of the TEMPO moiety within the peptide sequence increased the oxidation activity as compared to TEMPO alone. This is reflected in the milder oxidation conditions employed when using multicatalyst **4.32**. In this way, the multicatalyst approach offers some benefit over the two-step route to access **4.31**. This proof-of-principle study demonstrates the first organocatalytic multicatalyst reaction using short oligopeptides with two orthogonal catalytic moieties. The Schreiner Group has since developed several other peptidic multicatalyst systems that are discussed below.

In addition to performing *acetylation* of *trans*-1,2-diols **4.26** using acetic anhydride, the Schreiner Group developed a Steglich-type protocol, which relies on the use of a carboxylic acids rather than anhydrides (Figure 58).¹⁷² Using carboxylic acids is often advantageous, as some anhydrides may be unstable or not readily available. In the presence of DIC, the carboxylic acid can be converted into an *O*-acyl isourea intermediate, which can then further react to form a symmetrical anhydride. A Lewis basic catalyst can then deliver this acyl group to kinetically resolve *trans*-1,2-diols such as **4.26b**. By using a Pmh-embedded peptide catalyst, this report represents the first enantioselective Steglich-type esterification of alcohols.

Peptide **4.28**, which had been optimized for acylation with acetic anhydride,¹⁶⁴ delivered monoacetylated **4.27b** in higher conversion (55 %) and selectivity (83% ee) using acetic *acid* rather than acetic *anhydride* (Figure 58, entry 1 vs. Figure 50, entry 2). Using diol **4.26b**, 10 carboxylic acids were examined, selected examples of which are shown in Figure 58. *s*-Factors >50 were achieved for the kinetic resolution of *trans*-cyclohexane-1,2-diol **4.26b** with propionic and phenylacetic acids, as well (entries 2 & 3). Sterically hindered acids, such as *tert*-butyl and adamantane carboxylic acids, resulted in significantly lower *s*-factors (entries 4 & 5). Overall, this Pmh-mediated Steglich esterification strategy greatly improves the scope of this method from simple acetylation to general acylation.

Schreiner and co-workers expanded this method for enantioselective acyl group transfer to diol **4.26** by developing conditions for the oxidative esterification of aldehydes (Figure 59).¹⁷³ Using aldehydes is advantageous given that these compounds are typically more soluble in organic solvents, easier to purify, and more reactive than anhydrides. In this approach, an aldehyde can be activated by a sacrificial carboxylic acid and subsequently oxidized to form a mixed anhydride *in situ*. This species can then be selectively transferred to the diol *via*

Pmh-containing peptide catalysis, analogously to the previously reported methods. Conditions optimization was first performed using TEMPO as the oxidation catalyst and peptide **4.28** to mediate the selective acyl group transfer. Various carboxylic acids were evaluated to determine the ideal aldehyde activator for *in situ* anhydride formation. 4-Nitrobenzoic acid was found to be optimal for both conversion into and enantioselectivity of monoacylated **4.27be**. This two-catalyst method was applied to various *trans*-cycloalkane-1,2-diols **4.26** and aldehydes, achieving up to 81% ee of **4.26** and 88% ee of mono-acylated product **4.27** (*s*-factor = 39).

With conditions optimized using a two-step approach, peptidic multicatalyst **4.32** was employed in the one-pot, tandem, enantioselective oxidative esterification of **4.26b**. Though the yields were comparable, the enantioselectivities obtained for **4.26b** (73% ee) and **4.27be** (73% ee; *s*-factor = 14) were slightly lower than with the two-step protocol. By enabling the use of aldehydes over anhydrides, Schreiner and co-workers further expanded the scope of peptide-mediated acyl transfer to *trans*-1,2-diols **4.26** and demonstrated the power of peptidic multicatalysts to perform two different transformations with a single peptide.

In 2015, the protocol for the tandem oxidative esterification reaction of *trans*-1,2-diols **4.26** with multicatalyst **4.32** was further improved to use *alcohols* as acyl synthons (Figure 60).¹⁷⁴ Alcohols are superior acyl equivalents to anhydrides, acids, and aldehydes owing to their high stability and commercial accessibility. Similar to their strategy using aldehydes,¹⁷³ Schreiner and co-workers proposed that multicatalyst **4.32** could be used to first oxidize the alcohol *in situ* to the corresponding carboxylic acid with its TEMPO moiety along with co-oxidant *m*-CPBA. The acid could then be activated with DIC to provide a mixed anhydride that could then be transferred to various *trans*-1,2-diols **4.26** *via* the Pmh-residue of **4.32**. Using this three-step, one-pot strategy with multicatalyst **4.32**, higher yields and selectivities were obtained for recovered diols **4.26** and mono-acylated products **4.27** compared to the two-step procedure starting with aldehydes (Figure 59). Figure 60 shows a selection of the substrate scope, achieving up to 97% ee for **4.26** and 87% ee for **4.27**. Alcohols with smaller steric bulk proved most successful in this transformation (*e.g.*, **4.27b** *vs.* **4.27be** *vs.* **4.27bf**). The ring size of the diol did not significantly affect enantioselectivity (**4.26b** *vs.* **4.26d**), and the use of acyclic diols, such as **4.26e**, was also possible with this route.

Instead of employing *trans*-1,2-diols **4.26** as the starting material for enantioselective acylation, Schreiner and co-workers developed a method to generate the requisite diol *in situ* starting from simple alkenes using a one-pot multicatalyst approach (Figure 61).¹⁷⁵ This strategy relies on a sequence of catalytic epoxidation, epoxide-opening with water as the nucleophile, and kinetic resolution of the resulting racemic diol *via* enantioselective, peptide-catalyzed acylation. While streamlined, some challenges associated with this strategy included competitive catalyst oxidation, or interference of epoxide side products in the following steps. Therefore, each step in this sequence was optimized separately. Beginning with *meso*-epoxides **4.33**, the last two steps of this sequence were examined using peptide-based multicatalyst **4.34** in a one-pot reaction. This peptidic salt combines the ability of sulfuric acid to catalyze the racemic epoxide opening *via* Brønsted acid catalysis with that of the Pmh residue to serve as a nucleophilic catalyst for enantioselective acylation.

Peptide **4.34**—the bisulfate salt analog of the highly efficient acylation catalyst **4.28**¹⁶⁴—was found to be an efficient catalyst for both the racemic epoxide opening with water and the subsequent enantioselective acyl group transfer, providing *s*-factors of up to 48 (entries 1–4). Moreover, this reaction can be scaled up to 1 mmol with minimal perturbations to selectivity (entry 2).

With a two-step strategy in hand, Schreiner and co-workers were then able to extend this system to the desired three-step, one-pot reaction beginning with alkenes (Figure 62).¹⁷⁵ Several multicatalysts containing β -aspartate for epoxidation⁴³ and Pmh for enantioselective acylation were synthesized, varying the spacer length between the two catalytic moieties. Multicatalyst **4.35** was identified as the lead catalyst for epoxidation and enantioselective acylation. Under the optimized conditions, hydrazine bisulfate was found to be the lead Brønsted acid catalyst for epoxide opening. Several alkenes were transformed into diol **4.26** *in situ*, then kinetically resolved to the mono-acylated product **4.27** with *s*-values of up to 26.

The mechanism of this one-pot, three-step transformation catalyzed by **4.35** was later investigated using electrospray ionization mass spectrometry in a collaboration between the Schreiner and Schrader Groups (Figure 63).¹⁷⁶ The initial epoxidation of cyclohexene **4.34** with multicatalyst **4.35** was examined first. During this step, DIC activates the β -aspartate residue *via* *O*-acyl isourea intermediate **I**, which can either release diisopropyl urea and water to produce anhydride **II** or rearrange to the off-cycle *N*-acylurea **III**. Intermediate **II** can further react with hydrogen peroxide to give the catalytically active peracid **IV**, which can convert cyclohexene **4.34** to cyclohexene oxide **4.33b**. A potential side product of the incorporation of hydrogen peroxide is catalyst oxidation to form **V**. Due to the short lifetime of some of the reactive intermediates, an online microflow reactor and MS methods were used to identify and study these species in detail.

Using these techniques, species **I–V** were identified as intermediates of the epoxidation of **4.34** (Figure 63). While rearrangement product **III** was observed, the molecular ion was present in such a low level that it was deemed fairly irrelevant to catalysis. Under multicatalysis conditions with **4.35**, only 35% of mono-acetylated **4.27b** was obtained when starting from cyclohexene (Figure 62), yet when starting from epoxide **4.33b** with catalyst **4.34**, 57% yield of **4.27b** was obtained (Figure 61).¹⁷⁵ The diminished activity of multicatalyst **4.35** was suspected to be caused by oxidation of the peptide. Indeed, intermediate **V**, in which the Pmh-moiety has been oxidized, was identified *via* MSⁿ experiments.

The next catalytic step investigated was the enantioselective acylation of racemic diol **4.26** (Figure 64).¹⁷⁶ To simulate the one-pot reaction conditions, **4.35** was subjected to both acetic anhydride and hydrogen peroxide. It was found that not only the Pmh catalytic moiety is activated by acetic anhydride, but also the β -aspartate residue, providing the catalytically active intermediate **VI**, confirmed *via* high resolution MSⁿ experiments. Under the one-pot conditions, several other species were detected, including **II** and **VII**, all of which may influence the enantioselectivity of acyl transfer. This hypothesis is rooted in the observation that **4.35** provides lower selectivities as compared to the originally developed acylation catalyst **4.28**.^{164,175} Overall, the use of high-resolution mass spectroscopy was valuable for

the identification of ephemeral reaction intermediates and potentially deleterious side products found in these one-pot tandem epoxidation/epoxide opening/ acylation reactions.

In addition to the many contributions from the Schreiner Group, Qu and co-workers were able to modify previously reported Pmh-containing peptide **4.38a** for the enantioselective acylation of amino alcohols **4.36** (Figure 65).¹⁷⁷ In our original report, tetrapeptide **4.38a** was able to catalyze the kinetic resolution of ($\pm$)-**4.36**, affording enantioenriched (1*S*,2*S*)-**4.36** in 98% ee and acetylated product **4.37** in 73% ee, with a k_{rel} of 28 (entry 1).¹³² High selectivity in this transformation can be attributed, in part, to the β -hairpin conformation of **4.38a**. Chen and Qu hypothesized that incorporation of a thioamide—in which the carbonyl oxygen of the *i*+1 Pro residue is replaced with sulfur—in peptide **4.38a** might improve the enantioselectivity of this kinetic resolution. Thioamide replacement in peptides can give rise to several consequences, such as increased acidity of the thioamide N–H, increased rotational barrier about the peptide C–N bond, and decreased conformational flexibility of the surrounding residues.^{178–183} Incorporation of a thioamide at the *i*+2 position or a sulfonamide at the *N*-terminus was expected to strengthen the intramolecular H-bonds reinforcing the β -hairpin secondary structure. Alternatively, a thioamide could be inserted at the *i*+1 or *i*+2 positions. The substrate was proposed to interact with **4.38a** *via* H-bonding with the *i*+2 amide N–H. Modification of this position to a thioamide could improve the H-bond donor ability of the peptide, and thereby improve the enantioselectivity.

Thus, Qu and co-workers synthesized several derivatives of peptide **4.38** varying the location of the thioamide modification.¹⁷⁷ The kinetic resolution of ($\pm$)-**4.36** with peptide **4.38b**, containing a thioamide substitution at the *i*+2 position, resulted in a diminished k_{rel} of 23 (Figure 61, entry 2). However, incorporation of the thioamide at *i*+1 (**4.38c**) resulted in a significant enhancement in selectivity, with k_{rel} reaching 63 (entry 3). Tetrapeptides modified at the *N*-terminus (**4.38d–f**) gave higher selectivity than that of **4.38a**, with an upward trend from Ms to Ns to Ts (entries 3–5). Combining the benefits of the *N*-terminal Ts-protecting group and the *i*+1 thioamide, peptide **4.38g** provided the highest selectivity in this reaction, with a k_{rel} of 109 using only 0.2 equivalents of DIPEA (entry 6). Using peptide **4.38g**, 8 additional 1,2-amino alcohols were examined, with **4.36** providing the highest selectivity. The secondary structures of modified peptides **4.38** were studied using NMR and FT-IR techniques. Examination of the NHs of lead peptide **4.38g** by FT-IR indicated a tight first interstrand H-bond, suggesting that incorporation of the thioamide at *i*+1 position promotes a more rigid β -hairpin conformation. Though Ns-containing **4.38e** bears the most acidic N–H, which is often correlated with strong interstrand H-bonds, it did not provide the highest stereoselectivities in this asymmetric acyl transfer reaction. This may support the notion that some degree of flexibility is an important feature for asymmetric peptide catalysis and also highlights that acidity and H-bond strength are not always correlated in a simple way.¹⁸⁴

Mechanistic studies on the peptide-mediated kinetic resolution of ($\pm$)-**4.36** have also been reported by the Liao, Santoro, and Himo Groups using DFT calculations (Figure 66).¹³⁴ The reaction was treated as proceeding through two sequential steps: (1) acylation of peptide **4.38a** with acetic anhydride to form intermediate **I** *via* **TS 4.3**, and (2) acyl transfer from **I** to **4.36** with a concerted proton transfer from **4.36** to the acetate ion (**TS 4.4**). The authors

focused on modeling the second step of the reaction with tetrapeptide **4.38a**, as this is the process that confers asymmetric induction. Even with the assumption that the peptide adopts a stable β -hairpin structure, the Pmh-residue can still freely rotate about bonds A, B, and C of intermediate **I**, generating numerous conformations to consider in **TS 4.4**. Among the conformations of **I**, the *re*- and *si*-face attack of **I** by **4.36**, and each enantiomer of **4.36**, 48 distinct transition states were considered, each of which was optimized using DFT with the B3LYP functional.

The 48 transition states were categorized into three groups depending on the interaction mode between peptide intermediate **I**, amino alcohol **4.36**, and the acetate ion. The lowest energy conformation of each mode of **TS 4.4** with experimentally favored (1*R*,2*R*)-**4.36** is depicted in Figure 67. In **TS 4.4A**, the N–H of the *i*+2 Aib residue of **I** forms an H-bond to the carbonyl of the **4.36** acetamide. Alternatively, the Aib N–H of **I** can H-bond with the acetate ion (**TS 4.4B**). In **TS 4.4C**, no H-bond is formed between the peptide backbone and **4.36**. All of the TSs show the acetamide N–H of **4.36** H-bonding with the carbonyl of the acetylated Pmh-residue in **I**. Overall, the lowest energy TS leading to the favored (1*R*, 2*R*)-enantiomer of **4.37** is **TS 4.4A**, in which the peptide backbone H-bonds to the acetamide carbonyl of **4.3**, in accordance with, but expanding in detail and precision, the model that we originally proposed.¹⁸⁵

The lowest-energy diastereomeric TSs leading to each enantiomer of **4.37** are shown in Figure 68.¹³⁴ As described by the authors, the favored enantiomer of **4.37** engages in noncovalent interactions with **4.38a** as represented in **TS 4.4A** (Figure 68a). Alternatively, the lowest energy TS leading to disfavored (1*S*, 2*S*)-**4.37** proceeds *via* **TS 4.4B** (Figure 68b), in which the N–H of the *i*+2 residue H-bonds to the acetate anion. This indicates that mode **A** of **TS 4.4** offers a more stabilizing network of noncovalent interactions. Experimental studies show the relative acylation rate of each enantiomer to be 28 (Figure 61, entry 1),¹³² which converts to 2.0 kcal/mol. Therefore, the calculations ($\Delta G^\ddagger = 2.6$ kcal/mol) are in reasonable agreement with the experimental findings.

Another type of acylation reaction is the Dakin–West (DW) reaction, which was first disclosed in 1928 as a method to access α -acylamido ketones, such as **4.40**, from α -amino acids, such as, **4.39** (Figure 69).^{186,187} In the presence of a base at elevated temperatures, carbon dioxide is evolved from **4.39 en route** to the α -acylamido ketone product, providing a thermodynamic driving force for this multistep process. Though several advances have been made to this reaction since 1928,¹⁸⁸ it was not rendered asymmetric until 2016, when Schreiner and co-workers reported the first enantioselective DW reaction using Pmh-containing peptide catalysts.¹⁸⁹

The authors envisioned that a Pmh-containing peptide catalyst could serve multiple roles along the putative DW reaction pathway (Figure 69).¹⁸⁹ Amino acid **4.39** is first converted to the mixed anhydride, followed by cyclodehydration to oxazolone intermediate **I**. Subsequent acetylation of **I** affords oxazole **II**, which can undergo a Steglich rearrangement to form α -acyl oxazolone intermediate **III**. Alternatively, enolate formation and subsequent *C*-acetylation of **I** can also produce **III** directly. Acid mediated ring-opening of **III** affords β -ketoacid **IV**, which undergoes decarboxylation to form enolate **V**. Enantioselective

protonation of **V** produces α -acylamido ketone **4.40**. Performing the DW reaction enantioselectively is particularly challenging, as it requires a stereoselective proton transfer in the presence of stoichiometric acid within a rather complex multistep reaction framework. Moreover, the Pmh-catalyst would be required to serve a dual role as a Lewis base for acyl transfer and Brønsted base in the decarboxylative protonation step.

When screening reaction conditions, the authors found that addition of *N,N'*-dicyclohexylcarbodiimide (DCC) improved the reaction by (1) facilitating cyclization to **I**, (2) acting as an auxiliary base in the deprotonation steps, and (3) promoting the conversion of the acetic acid byproduct back into the anhydride. Importantly, the byproduct formed from using DCC—dicyclohexyl urea (DCU)—cannot act as a base in the final decarboxylation step and thereby minimizing racemic background reactivity. Peptide **4.41** was identified as the lead catalyst for this transformation. The strikingly better performance of tripeptide **4.41** in the asymmetric DW reaction compared to that of tetrapeptide **4.28**—which was successfully employed in previous acyl group transfer reactions¹⁶⁵—may be a result of the location of the Pmh moiety as *C*-terminal residue in this case, leading to more efficient association with **4.39**. With peptide **4.41**, 10 α -amino acids **4.39** were examined in this transformation, achieving up to 58% ee in the ketone products **4.40**. Some products could be recrystallized up to 84% ee.

Schreiner and co-workers also investigated the mechanism of this reaction using DFT calculations.¹⁸⁹ The exact nature of the decarboxylative step is not clear, however, asymmetric induction is believed to stem from the deprotonation of **IV**, release of carbon dioxide, and subsequent enantioselective protonation of enolate **V**. Possible complexes between enolate **V** and protonated peptide **4.41** were therefore computed. The lowest-energy complex, shown in Figure 70, reveals the close proximity (1.94 Å) of the α -carbon of **V** to the protonated Pmh residue. This computed complex leads to the observed (*S*)-enantiomer, which is favored by 2.1 kcal/mol over the complex leading to the (*R*)-product. The observed selectivity may result from shielding of one face of enolate **V** by its own sidechain and the Cha residue of **4.41**, inhibiting non-selective protonation by acetic acid in solution. Comparing various substrates, the higher selectivity observed for *N*-acyl amino acids bearing aliphatic sidechains (*e.g.*, **4.39**) likely originates from attractive dispersion interactions between the Cha residue of catalyst **4.41** and the side chain of enolate **V**.¹⁹⁰

In addition to Pmh-containing catalysts, advances have been made in asymmetric acylation using peptides bearing pyridine derivatives as the catalytic residue.¹⁶⁵ The 4-dimethylaminopyridine (DMAP)-^{191,192} and pyrrolidinopyridine (PPY)-type^{193,194} catalysts have found wide use as nucleophilic catalysts for acyl group transfer reactions in organic synthesis. Combining the modularity of peptides with the robustness of DMAP as a catalyst, Mandai, Suga and co-workers developed a robust synthetic strategy to synthesize peptide-tethered DMAPs **4.43** from aldehyde **4.42** and α -amino acids using an Ugi multicomponent reaction (Figure 71).¹⁹⁵ Using this strategy, diastereomerically pure peptides **4.43a** and **4.43b** were obtained in 51 and 37% yield, respectively. Peptides **4.43** were then examined as chiral catalysts in the asymmetric Steglich rearrangement of acyloxyindoles **4.44** to oxindoles **4.45**.¹⁹⁶

Impressively, all 13 acyloxyindoles **4.44** examined were processed by peptides **4.43** with exceptional yields of >98% and enantioselectivities of >92:8 er (Figure 72).¹⁹⁶ For the majority of substrates, Val-containing catalyst **4.43a** tended to provide higher selectivities than the corresponding *tert*-leucine (Tle)-containing catalyst **4.43b**. Acyloxyindoles **4.44a–d** proceeded efficiently, achieving 92:8 to 99:1 er of the desired products (entries 1–4). Additionally, 3-aryl-(entry 5) or 3-heteroaryl-substituted oxindoles (entry 6) gave equally excellent enantioselectivities. Mechanistically, the Steglich rearrangement is believed to proceed through the formation of an ion-pair between the pyridinium cation of peptide **4.43** and the oxindole enolate derived from **4.44**, followed by C–C bond formation to give the *C*-acyl oxindole **4.55**. TSs to C–C bond formation for the ion-pair complex between acylated **4.43b** and the enolate of **4.44b** were calculated using DFT at the B3LYP/6-31G(d) level of theory. Schematic representations of the lowest energy TSs that deliver (*R*)- and (*S*)-**4.45b** are shown in Figure 73. (*R*)-TS **4.5** may be disfavored due to destabilizing steric repulsion between the *tert*-butyl of the Boc group in **4.43b** and the phenylene group of **4.44b**. The energy difference between the two transition states ($\Delta G^\ddagger$) was calculated to be 2.99 kcal/mol, which is consistent with the experimentally obtained enantioselectivity of 99:1 er (Figure 72, entry 2).

Using another type of pyridine-containing peptide, Kawabata and co-workers employed PPY-embedded, *C*₂-symmetric catalysts to promote the desymmetrization of *meso*-diols *via* acylation (Figure 74).¹⁹⁷ The desymmetrization of *meso*-diols **4.29** through acylation had been well-studied by Schreiner and co-workers using Pmh-containing peptides,¹⁶⁵ providing a standard to which this new catalyst archetype may be compared. Various *C*₂-symmetric, chiral PPY-based peptides **4.46** were prepared from 5-oxo-Pro in several synthetic steps (Figure 74a)^{197,198} and subsequently evaluated in the enantioselective desymmetrization of **4.29a** with isobutyric anhydride (Figure 74b). Chiral catalysts containing aromatic residues, such as L- (**4.46a**) or D-Trp (**4.46b**) and L- (**4.46c**) or D-(2-naphthyl)alanine (2-Nal, **4.46d**) were first synthesized and tested (entries 1–4). Peptide **4.46a** had proven to be a highly efficient catalyst in the regioselective acylation of glucopyranoses.¹⁹⁸ As such, it was the first peptide to be employed in this system, delivering mono-acylated **4.30ab** in 85% and 73% ee (entry 1). In screening the other aromatic catalysts, the highest selectivity was achieved with D-2-Nal-containing **4.46d**, affording **4.30ab** in 77% yield and 83% ee (entry 4). The absolute configuration of **4.30ab** was unaffected by the configuration of the amino acid residue, though the extent of the enantioselectivity was indeed impacted (entries 1 vs. 2 & 3 vs. 4). Aliphatic residues, such as Val (**4.46e**) and Leu (**4.46f**) were also examined (entries 5 & 6), but neither was as selective as **4.46d**, though Leu-containing **4.46f** was quite similar overall. Lastly, achiral pendent groups were assessed, including Gly-containing **4.46g** and *N*-hexyl **4.46h** (entries 7 & 8). Interestingly, **4.46h** delivered **4.30ab** in 75% yield and 87% ee, suggesting that pendent residues with chiral sidechains were not necessary for selectivity in the context of these *C*₂-symmetric PPY-based catalysts.

With optimal catalyst **4.46h** in hand, reaction conditions such as solvent, temperature, time, equivalents of anhydride, and catalyst loading were investigated.¹⁹⁷ Lowering the reaction temperature to –40 °C, **4.30ab** was produced in 92% yield and 88% ee after 24 h (Figure 74, entry 9). The highest selectivity of 98% ee was achieved by increasing the equivalents of

collidine (entry 10). The increased ee of mono-acylated **4.30ab** is associated with an attendant increase in the amount of diacylated material, eroding the yield to 59%. This suggests that the ee of **4.30ab** is amplified to some degree by a secondary kinetic resolution *en route* to the symmetrical diacylated byproduct. To confirm this suspicion, racemic **4.30ab** was subjected to the reaction conditions, affording (1*R*,2*S*)- **4.31ab** in 67% ee with an *s*-factor of 7.7. The authors proposed two potential stereochemical models for the **4.46**-catalyzed acylation of **4.29a** (Figure 75). In one model, the amide carbonyls of **4.46** formed H-bonds with the non-reacting alcohol of **4.29a**. The other model invokes the opposite antipode of H-bonding between **4.46** and **4.29a**, wherein the amide N–H of **4.46** engages with the non-reacting alcohol of **4.29a**. Indeed, when the amide of **4.46h** is methylated or replaced with an ester linkage, **4.30ab** is produced in only 13% ee. Though the authors prefer the former model, both transition state assemblies remain possible.

Another variant of PPY-containing peptide catalysts based on general scaffold **4.49** was developed by Hunter and co-workers for the enantioselective acylation of racemic *sec*-alcohols **4.47** with isobutyric anhydride (Figure 76).¹⁹⁹ Molecular modeling was used as a tool to facilitate catalyst optimization for the kinetic resolution of alcohol **4.47a** *via* acylation. The first PPY-catalyst tested contained a Leu-Trp-OMe sidechain (**4.49a**). The Trp residue was incorporated in an attempt to engage **4.47a** in π -stacking interactions with the *N*-acylated pyridinium intermediate, as shown in model **4.50**. This was hypothesized to encourage facial discrimination of the pyridine ring as a means of achieving asymmetric induction in the acyl group transfer. A Leu residue was added upstream of Trp to improve catalyst solubility and further facilitate discrimination of one of the pyridine faces. Using **4.49a** as an initial catalyst for enantioselective acylation, a low, yet nonnegligible, *s*-value of 5.3 was measured (entry 1).

Computational modeling of the *N*-acyl intermediate **4.50** was then employed to identify potential structural elements for improvement. An initial set of 1,000 conformers of **4.50a** were generated and optimized using molecular mechanics (MMFF94). A subset of the 100 lowest-energy conformers were then further optimized *via* quantum mechanical methods (HF-3c). From these 100 structures, the 10 lowest-energy conformers were refined using DFT calculations (B3LYP-D3(BJ)/def2-SVP), and the lowest-energy conformer identified is shown in Figure 77a. In this structure, the peptide chain curves underneath the pyridinium ring, favoring attack of alcohol **4.47** from the opposite *re*-face. A potential H-bond is also observed between the indole N–H of Trp and the carbonyl of the catalytic residue (2.335 Å). The aromatic pyridinium and Trp sidechain appear too far apart to for a stabilizing π -stacking interaction. NMR studies further supported the calculated structure.

Based on the computed structure, the authors decided to extend the catalyst from a di- to tripeptide. Thus, peptides **4.49b** and **4.49c** were synthesized and evaluated in the kinetic resolution of **4.47a** (Figure 76, entries 2 & 3). Unfortunately, the *s*-values for these tripeptides were even lower than those of dipeptide **4.49a**. Once again, Hunter and co-workers turned to modeling for a solution. The optimized structure of **4.50a** also indicated that functionalization of the indole ring of Trp could be a fruitful avenue. Before synthesizing a new catalyst, the structure of **4.50d** was calculated using the same method as

described previously. The lowest energy conformer of **4.50d** is shown in Figure 77b. As noted with **4.50a**, the peptide chain once again coils underneath the pyridinium ring. However, with **4.50d**, the *N*-acyl group is in an *s-cis* conformation, which was shown to be a more favorable orientation. Most notably, introduction of the Boc group into the dipeptide resulted in a shift of the Trp indole ring to lay more in-line with the pyridinium ring. In this configuration of **4.50d**, a π -stacking interaction between Trp and the pyridinium ring should be possible.

Given the promising results of modeling **4.50d**, peptide **4.49d** was synthesized and tested in the enantioselective acylation of **4.47a**, achieving the highest *s*-factor yet of 8.1 (Figure 76, entry 4). With dipeptide **4.49d** in hand, the reaction was performed with several other *sec*-alcohols **4.47** (Figure 78). 1-Phenylethanol **4.47b** achieved a slightly higher *s*-factor of 8.9 compared to 1-(2-naphthyl)ethanol **4.47a**. Increased steric bulk on the aryl ring by inclusion of methyl groups, as in **4.47c**, resulted in the highest overall *s*-value of 10.8 (entry 2). Electron-donating groups, such as *para*-methoxy in **4.47d** (entry 3), were preferred over electron-withdrawing substituents, like *para*-nitro in **4.47e** (entry 4). A preference for electron-donating substituents also supports the importance of π -stacking interactions governing selectivity, with increased electron density in the arene of **4.47** favoring a tighter association with the electron-deficient pyridinium ring of **4.50**.

5. Nucleophilic Additions to Carbonyls & Epoxides

The addition of nucleophiles to carbonyls and epoxides are two of the most fundamental and useful transformations in organic synthesis. Countless asymmetric carbonyl addition and epoxide-opening methodologies have been reported to date,²⁰⁰ and peptide-based catalysts have played an important role in the development of this area. This Section summarizes the recent reports of peptide-catalyzed 1,2-additions to aldehydes (Sections 5.1 & 5.2) and esters (Section 5.3), wherein the nucleophiles are simple, commercially available reagents. Reactions of enols and enolates are reserved for subsequent sections (Sections 6–8). A peptide-catalyzed *meso*-epoxide opening is also summarized in Section 5.4.

5.1. Hydro- & Silylcyanation of Aldehydes.

One of the earliest contributions to the field of peptide catalysis dates to 1981, when Inoue and co-workers reported the enantioselective hydrocyanation of benzaldehydes catalyzed by a cyclic dipeptide, or diketopiperazine.³⁶ As one of the first highly selective, organocatalytic transformations,²⁰¹ this reaction triggered a cascade of excellent new applications and mechanistic studies through the early 2000s, which was covered extensively in our previous review.⁴ However, the mechanistic picture has undergone continuous exploration and enhancement in recent years. Below, Section 5.1.1 updates the mechanistic model for this important transformation, and Section 5.1.2. summarizes an alternate peptide-catalyzed strategy for the 1,2-addition of cyanide to benzaldehydes.

5.1.1. Hydrocyanation of Aldehydes.—Under the conditions originally reported by Inoue, *cyclo*[L-Phe-L-His] **5.3** catalyzes the highly enantioselective hydrocyanation of benzaldehyde **5.1a** to the corresponding cyanohydrin **5.2a** in 97% yield and 97% ee (Figure

79).²⁰² High levels of selectivity are only possible in this reaction with nonpolar solvents, such as toluene, making these reactions heterogeneous. Moreover, Danda and co-workers reported the observation of enantioselective autoinduction, in which the ee values increased with higher conversion to the (*R*)-product.²⁰³ The stoichiometry of **5.3** to (*R*)-**5.2a** in the active catalyst was found to be approximately 1:1. Kinetic analyses showed that the reaction is second-order in **5.3**, suggesting that the catalytically active species is dimeric in solution.^{203,204} Three limiting models have been proposed for this transformation (**A–C**, Figure 79), none of which are consistent with all of the data. Model **C** notably employs a catalytic dimer, in which one imidazole activates **5.1a** as an H-bond donor, while the other delivers the nucleophile.²⁰⁵

In this context, Houk and co-workers performed a computational study in 2009 aimed at providing a unified mechanistic picture of the **5.3**-catalyzed asymmetric hydrocyanation reaction.²⁰⁶ Their study began with an assessment of achiral model systems consisting of imidazole(s), hydrogen cyanide, and methanol was intended to approximate the incorporation of product **5.2a** into the active catalyst. Three preliminary DFT findings informed their initial model: (1) in the presence of two methanol molecules, the barrier for isomerization of H–CN to CN–H was only about 1 kcal/mol in the gas phase; (2) imidazolium was determined a more effective H-bond donor for aldehyde activation than the peptidic core of **5.3**; and (3) transition states with a 2:2:1 stoichiometry of imidazole/methanol/HCN were lower in energy. Together, these data led to **TS1** (Figure 80), which was the lowest energy transition state located in an assessment of multiple possibilities with different ratios of methanol and HCN.

To account for the dimeric nature of the active catalyst, the authors used MM simulations to search for low-energy dimer conformations beginning from three initial arrangements—one head-to-head and two different head-to-tail—the outputs of which were optimized using DFT. All three converged to head-to-tail dimer **D1** as the global minimum (Figure 80), in which the two **5.3** amides are engaged in reciprocal N–H•••O H-bonds and the imidazole sidechains H-bond with one another and the peptide core. To derive transition states for the enantioselective hydrocyanation of **5.1a**, features of both **TS1** and **D1** were combined, replacing a methanol equivalent with (*R*)-**5.2a** to account for the known product complexation, and the resulting structures were optimized to transition states at –20 °C. The result was **TS2** and **TS3**, wherein one imidazole activates **5.1a** through H-bonding while the other imidazolium delivers the cyanide nucleophile (Figure 80). **TS2**, which leads to the experimentally observed (*R*)-cyanohydrin, is favored over (*S*)-selective **TS3** by 1.8 kcal/mol, in good agreement with the observed enantioselectivity ($\Delta G^\ddagger = 2.1$ kcal/mol). This stabilization predominantly results from an extended edge-to-face π -interaction network involving the Phe sidechain of **5.3** and the phenyl groups of both **5.1a** and (*R*)-**5.2a**. These interactions are largely absent in (*S*)-selective **TS3**.

Danda and co-workers reported that adding catalytic quantities of (*R*)-**5.2a** to the reaction results in constant, high levels of selectivity over the course of the reaction, whereas asymmetric autoinduction is observed when the opposite enantiomer is included.²⁰³ The authors re-optimized the transition states including (*S*)-**5.2a** as the additive and found that (*R*)-selective **TS4** and (*S*)-selective **TS5** now only differ by 1.1 kcal/mol, resulting in

reduced selectivity (Figure 81). Additionally, **TS4** was found to be about 1 kcal/mol higher in energy than **TS2** due to differences in the π -interaction network. Thus, the (*R*)-**5.2a**•**5.3** complex is expected to outcompete the (*S*)-complex, which is consistent with Danda's observations.

Taken together, these computational data provide a more unified model for enantioinduction in this important, peptide-catalyzed reaction. Thematically, these studies reinforce that excellent catalytic activity is made possible by the ability of peptide **5.3** to engage in productive noncovalent interactions with its substrate.

5.1.2. Silylcyanation of Aldehydes.—An alternate peptide-catalyzed method for the cyanation of aldehydes was reported in 2012 by Kudo and co-workers.²⁰⁷ Drawing inspiration from the Juliá-Colonna epoxidation (see Section 2.1),²⁶ their strategy was to employ helical polypeptides to mediate the enantioselective cyanosilylation of benzaldehyde **5.1a** to TMS-protected cyanohydrin **5.4a** (Figure 82). Catalyst platform **5.5** was designed as a PEG-PS-supported poly(L-Leu) sequence, which is known to adopt an α -helical conformation once a critical chain length is met. The authors chose to use a solid support for ease of synthesis and handling and to facilitate solubility. Moreover, much like in the Juliá-Colonna epoxidation, a free *N*-terminus was proposed to be crucial to catalysis in this cyanosilylation reaction.

An investigation of catalysts **5.5** with varying poly(L-Leu) chain lengths revealed the importance of the helical structure to both reactivity and selectivity (Figure 82). Short sequence peptides ($n < 5$) provided reasonable conversions to **5.4a** with very low levels of ee. Of particular note, a single resin-bound Leu residue provides racemic product **5.4a**, suggesting that the point chirality of this amino acid alone is unable to induce asymmetry. Low, yet measurable ee values were obtained with chain lengths of 10–20 Leu residues, but the highest observed enantioselectivities required longer poly(Leu) sequences ($n > 35$). Using 40-mer **5.5**, TMS-protected cyanohydrin **5.4a** was obtained in 90% conversion and 51% ee. Poly(L-Leu) sequences were uniquely suited to this reaction, as poly(L-Ala) and poly(L-Glu(Bn)) provided reasonable conversion with low ee values. The authors used TFA-salt **5.6** and dimethylamine **5.7** as control peptides to probe the effect of the *N*-terminus. Both peptides exhibit low reactivity and selectivity compared to **5.5**, suggesting that a free amino group is required to achieve tractable levels of enantioselectivity.

A key difference between this poly(Leu)-catalyzed aldehyde cyanosilylation and the classical Juliá-Colonna epoxidation is that, in this reaction, good conversion can be achieved independent of the chain length, while useful ee values are only possible with longer sequences. The opposite is true in the Juliá-Colonna reaction; good enantioselectivity can be achieved with only a few amino acids, but increasing the chain length increases yields.²⁰⁸ This is likely a manifestation of the different reaction mechanisms and modes of asymmetric induction.

Lowering the reaction temperature to $-20\text{ }^{\circ}\text{C}$, peptide **5.5** was able to deliver **5.4a** in quantitative conversion and 62% ee (compared to 90% conversion and 51% ee at ambient temperature). These conditions were then used to investigate the substrate scope of this

reaction (Figure 83). On preparative scale, isolated yields and enantioselectivities of **5.4** were recorded following hydrolysis of the TMS ether and subsequent *O*-acetylation. Peptide **5.5** addressed a modest scope of benzaldehydes **5.1** using 1.2–2.0 equivalents with good yields and ee values ranging from 31–62%.

5.2. Organozinc Additions to Aldehydes.

Since the 1990s, short sequence peptides have been widely applied as chiral ligands for various asymmetric organometallic additions to carbonyl compounds.^{209,210} An archetypal scaffold for these ligands is a dipeptide sequence capped on the *N*-terminus with a Schiff base moiety for metal chelation. Originally reported by Inoue and co-workers for the Ti-catalyzed, asymmetric hydrocyanation of aldehydes,²¹¹ the impactful expansion of this general ligand framework was pioneered by Hoveyda, Snapper, and co-workers throughout the 2000s, which led to the development of highly enantioselective organometallic 1,2-^{212–214} and 1,4-addition^{215,216} reactions. These methodologies helped to establish the dipeptide-based ligand as a reliable and robust means of achieving asymmetric induction in challenging scenarios.

Building off of this body of work, Park and co-workers reported a peptide-catalyzed method for the enantioselective alkylation of aldehydes with dimethylzinc.²¹⁷ Their strategy was to optimize a dipeptide scaffold—without an *N*-terminal Schiff base—that is able to chelate to and activate dimethylzinc for addition to prochiral aldehydes, such as **5.8**, providing access to enantioenriched secondary alcohols **5.9** (Figure 84). All of the peptides examined adhered to the general sequence R₂-Xaa-Pro-OMe (**5.10**), in which the *N*-terminus was either mono- or dialkylated. The catalyst library was evaluated in the addition of dimethylzinc to benzaldehyde **5.8a** in toluene at ambient temperature.

When Xaa was D-Phg, the degree of alkylation at *N*-terminus had an interesting effect on enantioselectivity (Figure 84, entries 1–3). While the monobenzyl amine variant delivered **5.9a** in 35% yield and 53:47 er (entry 1), *N*-benzyl-*N*-methyl amine gave a notable boost in yield to 85% with equal and opposite enantioselectivity (entry 2). However, the dibenzylamine-containing peptide returned **5.9a** in 85% yield and 88:12 er, restoring (and amplifying) the sense of asymmetric induction (entry 3). These data suggest that the reaction is quite sensitive to *N*-terminal substitution. The effect of the *C*-terminal ester was probed next (entries 3–6), and selectivity was found to decrease significantly with increasing steric bulk of the ester substituent. The *tert*-butyl ester also provided an enantiodivergent outcome (entry 6). Ligands containing D-Phe (entry 7) and D-Ala (entry 8) as the *N*-terminal residue were modestly less selective than the D-Phg variant (entry 3), but the Gly variant delivered nearly racemic product (entry 9). Epimerizing the *N*-terminal residue to L-Ala improved the er to 92:8 at the expense of some yield (entry 10), and L-Leu was similarly reactive but less selective (entry 11). Benzyl-protected L-Asp was found to be optimal at this position, providing **5.9a** in 90% yield and 94:6 er (entry 12). The yield and er could be further improved by modification of the *N*-terminal dibenzylamine (entries 13–15), with bulky 3,5-di-*tert*-butylbenzyl variant **5.10a** delivering the product in 95% yield and 97:3 er (entry 15).

Having identified **5.10a** as the leading ligand, the authors proceeded to examine the substrate scope for this transformation. Peptide **5.10a** was effective in the dimethylzinc addition to various benzaldehydes **5.8**, providing secondary alcohols (*S*)-**5.9** in 65–94% yield and 94:6 to 96:4 er (Figure 85). The authors also demonstrated that excellent yield and er could be obtained with only 5 mol% catalyst loading (entry 2).

5.3. Ester Hydrolysis & Alcoholysis

Lipases are an important class of hydrolytic enzymes that have been widely employed in asymmetric synthesis,²¹⁸ even on industrial scale.²¹⁹ These enzymes often leverage a catalytic triad of Ser, His, and Asp residues that are precisely oriented in the active site to enable the rapid and highly selective hydrolysis and alcoholysis of esters.^{220,221} This mechanistic framework has inspired efforts to develop synthetic, small molecule catalysts that expand upon the native activity and substrate scope of lipases. Peptide-based catalysts are well-suited for these goals due to their ability to fold into well-defined secondary structures, wherein catalytically active residues are oriented in close proximity to one another and to H-bond donor/acceptor groups of the peptide backbone. This Section summarizes recent campaigns to design peptide-based catalysts that mimic lipase activity.

5.3.1. Solvolysis of Formylphenyl Esters.—In 2016, Kudo and co-workers devised a strategy to develop synthetic catalysts with lipase-like hydrolytic activity.²²² They envisioned a scenario in which a bifunctional oligopeptide containing catalytic Pro and His residues could mediate the hydrolysis of formylphenyl esters **5.11** to the corresponding carboxylic acid **5.12** and 4-formylphenol (Figure 86). Building upon their previous work in Michael addition chemistry (see Section 7.2), they proposed that the *N*-terminal Pro residue could potentially engage ester **5.11** through the reversible formation of an iminium ion intermediate. This intermediate would subsequently be hydrolyzed by the *C*-terminal His residue *via* either a Lewis base or Brønsted base activation mechanism.

This mechanistic hypothesis was investigated using resin-bound peptides in which the active His and Pro residues were interspersed with a β -turn biased sequence of three amino acids.²²³ The catalytic pentapeptide was attached to the ambiphilic resin through a helical linker. Following some initial optimization, the authors identified peptide **5.14**, which was able to catalyze the hydrolysis of **5.11** in 38% conversion (Figure 86). The precise spacing of the Pro and His residues was found to be important, as peptide **5.15**, in which the Pro and His are one-residue closer together, was notably less active. Moreover, substituting out the Tyr residue of **5.14** proved modestly detrimental to catalysis. For example, Trp-containing **5.16** delivered carboxylic acid **5.12** in 27% conversion. Lacking a His residue, peptide **5.17** was significantly less reactive, providing only 15% conversion to the products. Including 20 mol % of imidazole along with **5.17** provided no advantage over the reaction catalyzed by imidazole alone, suggesting that the peptide-based catalyst requires both the Pro and His residues in order to meaningfully accelerate the reaction. Additionally, the 4-cyano variant of ester **5.12** exhibited low reactivity, providing evidence in support of the putative iminium ion intermediate. Replacing the water co-solvent with methanol resulted in increased reactivity, as peptide **5.14** delivered methyl ester **5.13** in 80% conversion.

Recognizing the lipases are principally used for hydrolytic kinetic resolutions of esters, the authors sought to demonstrate the viability of their approach in the kinetic resolution of 2-formylphenyl ester **5.18** (Figure 87). Preliminary results using catalyst **5.14** under the methanolytic conditions led to a very modestly selective kinetic resolution, in which methyl ester **5.19** was formed in 74% conversion and 7% ee, with **5.18** being enriched to 11% ee. These initial results establish proof-of-principle that alcoholic reactions can be mediated by small molecule peptide catalysts and set the stage for further optimization.

5.3.2. Ring-Opening DKR of Oxazolones.—Oxazol-5(4*H*)-ones, such as **5.20**, are versatile synthetic building blocks due to their multifaceted reactivity profiles that provide access to a variety of useful heterocyclic frameworks.²²⁴ These cyclodehydrated amino acid derivatives have anomalously acidic α -C–H bonds ($pK_a \sim 9$), which is due to aromatic stabilization of the oxazole enolate conjugate base (**5.21**, Figure 88). This elevated acidity allows for rapid, autocatalytic racemization in solution, making oxazolones **5.20** prime candidates for ring-opening dynamic kinetic resolution (DKR) reactions, a process that provides access to enantioenriched α -amino acid derivatives **5.22**. Various catalyst types have been employed in alcoholic DKRs of oxazolones, ranging from transition metal complexes²²⁵ and organocatalysts^{226,227} to lipase enzymes.²²⁸ Peptide-based catalysts have also been developed for this purpose.

In one of the earlier examples of an oxazolone ring-opening DKR, Hua and co-workers reported that diketopiperazine **5.3**, the lead catalyst in Inoue's benzaldehyde hydrocyanation methodology (see Section 5.1),³⁶ was also able to catalyze the conversion of racemic oxazolone **5.20a** to protected Phe-derivative **5.22a** (Figure 89).²²⁹ In the absence of any chiral additive, **5.3** provided only very low levels of enantioinduction in this reaction. Based on mechanistic studies of the **5.3**-catalyzed hydrocyanation of benzaldehyde suggesting that the active catalyst could be a complex of **5.3** and cyanohydrin **5.2**,²⁰³ the authors postulated that a chiral additive might enhance the selectivity of **5.3** in the ring-opening reaction of **5.20a**. Indeed, using 2 equivalents of diisopropyl-L-tartrate as an additive, **5.3** delivered (*S*)-**5.22a** in quantitative conversion and 27–39% ee depending on the nature of the alcohol nucleophile. While only modestly selective, this study provided a foothold for future developments.

In 2014, our group reported a highly selective methanolytic DKR of oxazolones **5.20** catalyzed by tertiary amine-containing tetrapeptides.²³⁰ The catalyst library was designed around general scaffold **5.23**, in which a β -dimethylaminoalanine (Dmaa) residue is embedded at the *N*-terminus of a well-defined β -turn secondary structure (Figure 90). This general arrangement provided the possibility for a multifunctional activation mechanism, wherein the tertiary amine side chain of Dmaa engages and selectively delivers methanol to one enantiomer of ($\pm$)-**5.20**, while the peptide backbone stabilizes charge buildup on the substrate through noncovalent interactions.

The library consisted of 14 Dmaa-containing peptides biased toward a type II' β -turn by incorporation of a central D-Pro-Xaa sequence motif (*e.g.*, **5.23**, Figure 90).²²³ These catalysts were evaluated in the ring-opening DKR of oxazolone **5.20a** in the presence of 5 equivalents of methanol. Peptide **5.23a**, which possesses an archetypal D-Pro-Aib β -turn

sequence and a Phe residue at the *i*+3 position, delivered **5.22a** in 37% conversion and 67:33 er. Changing the *C*-terminal cap to a dimethyl amide in **5.23b** led to a modest improvement in conversion to 47% and a notable boost in selectivity to 74:26 er. This is possibly due to the increased H-bond acceptor ability of the amide relative to the ester, making the 14-membered ring β -hairpin H-bond more favorable. In an assessment of the effect of the *i*+2 residue, 2-aminoindane-2-carboxamide (Aic)-containing **5.23f** stood out as significantly more reactive and selective than the other variants (**5.23b–e**), providing **5.22a** in 84% conversion and 93:7 er. Exchanging the *i*+3 Phe with D-Phe in **5.23g** only slightly eroded the yield and er, and an evaluation of other *i*+3 residues (**5.23f–l**) led to the identification of Ser(Bn)-containing **5.23k**, which delivered **5.22a** in 97% conversion and 96:4 er. In an attempt to further strengthen the β -hairpin H-bond, different *N*-terminal protecting groups were assessed (**5.23l–n**), but none were as effective as Boc. Lastly, peptide **5.24**, in which the Dmaa residue is replaced with Leu—its *C*-isostere—did not catalyze the methanolysis reaction.

A sequence truncation study was performed to examine the effect of the lead catalyst's residues on the reactivity and selectivity observed in the methanolysis of **5.20a** (Figure 91). Compared to tetrapeptide **5.23k**, tripeptides **5.25** were notably less reactive and selective. However, secondary amide-containing **5.25b** was significantly more reactive and selective than its tertiary amide counterpart **5.25a**, providing **5.22a** in 62% conversion and 86:14 er—a value on par with some of the less selective tetrapeptides. This perhaps speaks to the importance of the 10-membered ring β -turn H-bond to catalysis, as **5.25a** is able to nucleate that interaction while **5.25a** cannot. Dipeptides **5.26** provided only modestly enantioenriched product in low conversion, while Dmaa monomer **5.27** was essentially inactive. It is noteworthy that **5.27** provides very low levels of selectivity in favor of the opposite enantiomer of **5.22a**, suggesting that the secondary structure of higher-order peptides overturns the inherent preference of the catalytic monomer.

Peptide **5.23k** was able to address a scope of oxazolones **5.20** bearing variable substitution at the α -position (Figure 92). Benzylic and heterobenzylic substrates (entries 1–7) were processed by **5.23k** with excellent yields (78–93%) and ers (88:12 to 98:2). Electron rich benzylic oxazolones (entry 6) were more selective than their electron-poor congeners (entry 7). Compared to **5.20a** (entry 1), benzhydryl substitution led to only a modest decrease in selectivity to 90:10 er with a significant drop in yield to 19% (entry 8), while homologating the side chain by one methylene unit led to decreases in both yield and er (entry 9). Ester substitution at the β -position was well tolerated (entry 10), but branched alkyl substrates were generally less reactive and selective benzylic ones (entries 11–12). Yields and er values decreased with increasing substitution at both the β - (entry 11 vs. 13) and γ -positions (entry 12 vs. 14).

Based on the peptide-optimization data, substrate trends, and preliminary mechanistic experiments, a self-consistent stereochemical model was proposed that accounts for the observed absolute configuration of methyl esters **5.22** (Figure 93). In this model, the Dmaa sidechain of **5.23k** delivers methanol to selectively to the *re*-face of (*S*)-**5.20a**, as the peptide stabilizes the transition state leading to the zwitterionic tetrahedral intermediate through

charge-stabilizing H-bonds. Putative edge-to-face π -stacking between the oxazolone α -substituent and the *i*+2 Aic residue perhaps accounts for the catalyst's preference for benzylic substrates. The convergence of these noncovalent interactions to both activate the nucleophile and stabilize the intermediate is reminiscent of enzymatic oxyanion holes.²³¹ In that sense, **5.23k** is proposed to operate through a biomimetic mechanism.

5.4 *meso*-Epoxide Opening

Asymmetric ring-opening reactions of epoxides are valuable methodologies that provide access to chiral, enantioenriched alcohol derivatives, which themselves are important synthetic building blocks. These methods generally fall into two strategic categories: (1) kinetic resolutions of racemic epoxides, or (2) enantioselective ring-openings of *meso*-epoxides.²³² Many examples of each strategy have been reported to date that implement a variety of catalyst types and architectures. While peptide-based catalysts have track record in epoxidation (see Section 2.1), peptide-mediated epoxide opening reactions have only recently been developed.

In 2014, Chimni and co-workers reported a peptide-catalyzed, asymmetric ring-opening reaction of *meso*-stilbene oxides **5.28** with *N*-phenylpiperazine **5.29** to access chiral amino alcohols **5.30** (Figure 94).²³³ The general catalyst design centered on short, β -turn forming sequences capped with an *N*-terminal thiourea moiety. In that way, the authors intended to capitalize on the demonstrated ability of thioureas to activate electrophiles through H-bonding interactions,²³⁴ as well as the folded secondary structures of peptides to provide a robust chiral environment for asymmetric induction. They proposed a model wherein the *N*-terminal thiourea engages the epoxide, while the peptide scaffold activates the amine nucleophile *via* H-bonding with backbone carbonyls (X in Figure 94).

The authors evaluated a modest library of peptides biased toward β -turn conformations by incorporation of either L-Pro-D-Pro^{15,235} or D-Pro-Gly²³⁶ turn motifs. The former sequence emerged as the front-runner, and optimization of the *i* residue led to the identification of thiourea-embedded tripeptide **5.31a**, which delivered amino alcohol **5.30** (Ar = Ph) in 89% yield and 79% ee (entry 1, Figure 95). Peptide **5.31a** effectively catalyzed the ring-opening of a small scope of stilbene oxides **5.28** using piperazine **5.29**. Compared to the parent substrate (entry 1), substitution of Cl or Br at the *meta*-position of the phenyl rings was tolerated in terms of yield, but selectivity decreased notably to 50–52% ee (entries 2 & 3). Substitution at the *ortho*-position of the aryl groups in **5.28** was not tolerated (entry 4), nor was nitro group incorporation anywhere on the phenyl ring (entries 5–7). The authors attribute this to competitive binding of the nitro group by the thiourea of **5.31a**. Piperidine, *N*-methyl piperazine, *N*-benzyl piperazine were also poorly selective in this reaction, providing the corresponding amino alcohol product in <10% ee.

A series of epimeric catalysts were assessed under the standard epoxide-opening conditions in order to examine the effect of each stereogenic center of peptide **5.31a** on the observed enantioselectivity (Figure 96). Compared to the lead catalyst, converting the *C*-terminal residue from D-Pro to L-Pro in **5.31b** led to a notable decrease in ee from 79% to 22% (entry 1 *vs.* 2), suggesting that this Pro residue plays a role in the selective transition state. Peptide

5.31c, in which the central Pro residue is epimerized from D to L, gave a somewhat less drastic drop in ee to 33%. Notably, the Phe-epimer **5.31d** was found to deliver **5.30a** in 52% ee favoring the opposite enantiomer, which suggests that the configuration of the *N*-terminal Phe residue largely controls the selectivity in this reaction. These data show that the various diastereomers of **5.31** form different secondary structures that exhibit different degrees of selectivity in the epoxide opening.

6. Aldol Reaction

The aldol reaction is a powerful C–C bond-forming process, and when it is performed with control of regio-, diastereo-, and enantioselectivity, it is able to streamline the synthesis of complex molecules. Historically, asymmetric aldol reactions relied on the use of stoichiometric chiral reagents or auxiliaries. Although many of these are reliable approaches, they often require additional synthetic steps to install or remove the chiral control elements and generate stoichiometric byproducts. Therefore, catalytic variants of this powerful transformation have undergone intense development. More recently, a large body of literature on catalytic asymmetric aldol reactions employing metal-based or organocatalysts have been reported.²³⁷ Among them, the Pro-catalyzed aldol reaction is best connected to peptide-based catalysis.²³⁸ Despite the many advances in this area, certain challenges still remain unmet, such as reducing catalyst loading, increasing catalytic efficiency, improving stoichiometry of substrates, and expanding the substrate scope. To address these issues, there has been efforts to develop new peptide-based catalysts for asymmetric aldol reactions.

Many peptide-based catalysts for aldol reactions can be generally categorized into two different classes (Figure 97). In the most common design, Pro—a venerable catalyst for the aldol reaction in its own right—is positioned at the *N*-terminus of a peptidic scaffold, availing its free pyrrolidine moiety for condensation onto aldehydes and ketones. While extensively studied, mechanistic analyses of the Pro-catalyzed aldol will not be considered here, as the focus is on more elaborated peptide-catalyzed processes.^{239–243} The other major class of catalysts is inspired by type I aldolase, an enzyme that catalyzes aldol reaction *in vivo* using a catalytically-active Lys residue in the active site.²⁴⁴ These catalysts typically bear a free primary amino group at the *N*-terminus. Both of these catalyst classes are designed to engage their substrates *via* enamine catalysis. As detailed below, the modular nature of peptides provides easy access to diverse Pro- and aldolase-like catalysts with tunable lengths, secondary structures, and functional groups, which together can be exploited to engage in precise noncovalent interactions with substrates. These characteristics provide opportunities to tailor and expand the scope of the aldol reaction. Additionally, replacement of the α -carboxylate group of simple Pro-based catalysts, for example, with peptide backbones is a means of suppressing known potential off-cycle processes, such as formation of oxazolidinones.²⁴¹

The focus of this Section is to present a comprehensive overview of amine-containing peptide catalysts for asymmetric aldol reactions. In lieu of presenting a detailed substrate scope for each catalyst, pertinent issues in catalyst concepts and design are discussed. For those reactions catalyzed by a single amino acid or its derivatives, prior reviews provide the necessary insight.^{237,238}

6.1. Enantio- & Diastereoselective Aldol Reactions Using Amine-Based Peptide Catalysts

To assist in the discovery of new peptide catalysts, highly electrophilic acceptors, such as 4-nitrobenzaldehyde, and simple donors, such as acetone and cyclohexanone, that are often used in large excess, have been employed as benchmark substrates. The new catalysts that have been developed in recent years are structurally quite diverse, as their designs were inspired by various attributes including known amino acid sequences in enzymes, protein secondary structures, and solid-supported materials. All of these peptides were found to be effective catalysts for asymmetric aldol reactions between 4-nitrobenzaldehyde and acetone (Figure 99) and cyclohexanone (Figure 100) with varying degrees of reactivity and selectivity. For diastereoselective aldol reactions, most peptide catalysts are selective for the *anti*-diastereomer, much like in the corresponding Pro-catalyzed reactions.

Inspired by enzymes, many catalyst designs are centered on the ability of peptides to form defined secondary structures or stable geometries. The β -turn is a common secondary structure found within proteins⁴⁷ that has proven particularly fruitful in achieving asymmetric induction.²⁴⁵ Da and co-workers used the β -turn secondary structure as a key feature in the design of their catalyst that bears an *N*-terminal primary amine.²⁴⁶ After evaluation of multiple tetrapeptides, peptide **6.1** was identified as the lead catalyst (Figure 99a). Incorporation of the central D-Pro-Gly sequence was intended to bias the structure toward a β -turn conformation, which was supported by CD and NOESY NMR structural studies in methanol, the solvent for the reaction. Additionally, truncation studies of peptide **6.1** revealed that the corresponding di- and tripeptides were far less selective catalysts, delivering the aldol product in < 31% ee. It is likely that the shorter peptides do not form a stable β -turn under the reaction conditions, especially in H-bond competitive solvents, like methanol. Furthermore, the authors identified that the presence of a *C*-terminal carboxylic acid is crucial for obtaining high levels of enantioselectivity. Although high catalyst loadings were used (20 mol% of **6.1** and 40 mol% of benzoic acid co-catalyst), the product was obtained in 58% yield and 95% ee. The same catalyst worked fairly well using cyclohexanone as the nucleophile (Figure 100a). Interestingly, the *syn*-diastereomer was modestly favored (64:36 dr for *syn*) using **6.1**, which provided the aldol product in 87% total yield and 86% ee in the major *syn*-diastereomer. The minor *anti*-diastereomer was also formed with a moderate ee of 51%.

Using a more biomimetic approach, Rahman and co-workers designed a peptide catalyst for asymmetric aldol reactions based on the active sites of aldo-keto reductases (AKRs, PDB = 1VBJ), which bear a conserved Lys residue (Figure 98).²⁴⁷ Although enzymes often achieve high selectivities under mild reaction conditions, they often suffer from limitations in scope. To address this issue, the authors targeted peptide-based catalysts as a means of emulating the activity of AKRs in a more tunable catalytic scaffold. Initially, two 18-mers (**6.2a** & **6.2b**) and one 16-mer (**6.2c**) were evaluated in the reaction of 4-nitrobenzaldehyde with cyclohexanone in aqueous media (entries 1–3). Using **6.2a**, the aldol product was isolated in 88% yield with an exceptional dr of 99:1 and moderate enantioselectivity of 63% ee (entry 1). Significant improvements to both yield (95%) and enantioselectivity (86% ee) were observed when **6.2b** was employed as the catalyst (entry 2). On the other hand, peptide **6.2c** showed diminished yield (67%) and enantioselectivity (39% ee) compared to the 18-mers

(entry 3). Following truncation studies and an investigation into the importance of a free Lys residue, octapeptide **6.2d** bearing an *N*-terminal Pro residue was discovered. This catalyst afforded the highest observed yield (97%) and stereoselectivity (90:10 dr for *anti*, 97% ee) of the catalysts examined (entry 4; also shown in Figure 100a). Furthermore, **6.2d** provided high yield (97%) and good enantioselectivity (77%) in the aldol reaction with acetone (Figure 99a). The reusability of **6.2d** was also demonstrated by recovering and reusing this catalyst up to 10 times (83% yield, 76% ee *vs.* entry 4).

Additionally, there have been many efforts to use non-proteinogenic amino acids to promote a rigid secondary structure in peptide-based catalysts. Reiser and co-workers integrated conformationally restricted β -amino acids, specifically β -aminocyclopropylcarboxylic acid (β -Acc), into short peptide sequences in order to stabilize turn-like secondary structures.^{248,249} As such, β -Acc was incorporated into either the central or terminal positions of various *N*-terminal Pro-containing peptides. For the reaction between acetone and 4-nitrobenzaldehyde, catalyst **6.3a**, which contains β -Acc as the *C*-terminal residue, gave the aldol product in 86% yield and 88% ee (Figure 99a). In an aqueous media, peptide **6.3b**, a constitutional isomer of **6.3a** in which the β -Acc residue was moved to the central position of the tripeptide, delivered the aldol product in 75% yield and 6:1 dr favoring the *anti*-diastereomer (Figure 100a). Both diastereomers were isolated with excellent levels of enantioselectivity (95% ee for *anti* & 99% ee for *syn*).

Illa, Branchadell, Ortuño, and co-workers synthesized short peptides bearing a central *cis*-cyclobutane γ -amino acid (*cis*- γ -Cbaa), which is derived from (–)-verbenone.^{250,251} As observed in their previous study on *cis*- γ -Cbaa-containing foldamers, these catalysts (*e.g.* **6.4**) are designed to form a seven-membered N–H(*i*+1)•••O(*i*+1) H-bond across the central cyclobutane framework (Figure 99a).²⁵² The intramolecular H-bond contributes to the high rigidity of the peptide catalyst, which is supported by NMR and computational studies. Upon examination of various diastereomers of *cis*- γ -Cbaa-bearing peptides in the benchmark acetone aldol reaction, peptide **6.4** emerged as the lead catalyst, providing the aldol product in 97% yield and 76% ee in only 2 hours (Figure 99a).²⁵³ For the reaction with cyclohexanone, peptide **6.4** was found to be notably less selective. In this case, the aldol product was obtained in 99% and modest selectivity (2:1 dr favoring *anti*, 58% ee, Figure 100a). However, the catalyst was ineffective towards electron-rich 4-methoxybenzaldehyde and gave no conversion.

Calmès and co-workers also sought to use conformationally restricted residues to nucleate turn structures in peptide-based catalysts.²⁵⁴ The authors incorporated a conformationally constrained 2-aminobicyclo[2.2.2]octane carboxylic acid (Aboc) residue into short peptide sequences. This bicyclic amino acid was prepared previously by the authors using an asymmetric Diels–Alder reaction,²⁵⁵ and it was demonstrated to induce a β -turn secondary structure when embedded at the central position of a tripeptide sequence.²⁵⁶ Using Aboc residues, the authors prepared a number of di- and tripeptides bearing *N*-terminal Pro residues for enamine catalysis. In general, tripeptides with heterochirality were more efficient than their corresponding homochiral diastereomers. With 5 mol% of the lead catalyst **6.5**, the aldol product between acetone and 4-nitrobenzaldehyde was obtained in 86% yield and 87% ee (Figure 99a). As they hypothesized, an X-ray crystal structure of **6.5**

revealed a β -turn conformation, wherein the *N*-terminal pyrrolidine and the *C*-terminal carboxylate groups were in close proximity, possibly interacting through H-bonding. The authors reasoned that this geometric arrangement of the two termini of the peptide allows for selectivity in the peptide-catalyzed aldol reaction.

Solid-phase peptide synthesis (SPPS) is a powerful and practical way of preparing peptides, and as such there are number of reports detailing the development of solid-supported peptide-based catalysts. This approach offers a number of advantages, including ease of synthesis and catalyst recycling. Such benefits represent an atom-economical, effective solution to the recurring requirement of high catalyst loadings in peptide-catalyzed aldol reactions.

Fülöp and co-workers developed a highly recyclable, solid-supported peptide-catalyzed continuous flow (CF) process. Inspired by Wennemers' tripeptidic aldol reaction catalyst,²⁵⁷ the authors synthesized **6.6** on TentaGel® resin *via* SPPS, which they directly immobilized onto a CF cartridge, obviating the need for any purification steps (Figure 99b).²⁵⁸ With the benchmark substrates, this CF method can generate the aldol product in quantitative conversion with 80% ee, and the catalyst cartridge can be recycled up to 20 times while retaining efficiency and selectivity. Such CF process could be a useful tool for large-scale and sustainable catalytic reactions.

Gruttadauria and co-workers also utilized Wennemers' previously reported aldol catalyst **6.7** in developing recyclable materials.²⁵⁹ The peptide catalyst (H-Pro-Pro-Asp-NH₂) was adsorbed onto the surface of silica gel functionalized with 1,2-dimethyl-imidazolium salts (Figure 99b). In the first use of the supported catalyst in the aldol reaction of 4-nitrobenzaldehyde and acetone, the β -hydroxyketone product was obtained in 99% yield and 86% ee, comparable results to those obtained under homogeneous conditions. However, both yield and enantioselectivity diminished over the course of a few subsequent runs with the recycled catalysts (38% yield, 83% ee).

Ordered mesoporous silicas (OMSs) can be covalently functionalized with large biomolecules, including enzymes.²⁶⁰ Utilizing known trialkoxysilane chemistry that functionalizes OMSs, Mehdi, Subra, and co-workers developed a method for synthesizing hybrid peptide-OMS materials.²⁶¹ They installed a trialkoxysilane group onto the *C*-terminus of Wennemers' aldol catalyst **6.7** *via* a urea linker (Figure 99b), and this peptide-silane building block was used to directly graft a non-functionalized silica matrix to give the hybrid peptide-OMS catalyst **6.8**. Following a brief optimization of the reaction conditions, this hybrid bioorganic material proved to be a highly selective catalyst, providing the aldol product in >95% ee, albeit with lower reactivity (59% yield) than in the corresponding homogeneous system.²⁵⁷ The hybrid peptide-OMS could be recovered from the reaction mixture by a simple filtration step. However, the use of recycled OMS in aldol reaction was not demonstrated.

Wang and co-workers developed a silica-supported, non-canonical diproline catalyst **6.9**, which gave high yield (82%) and enantioselectivity (96% ee) in the aldol reaction between acetone and benzaldehyde (Figure 99b).²⁶² With cyclohexanone as the substrate, **6.9** also

delivered the aldol product in high yield (98%) and with good diastereo- (60:40 dr favoring *anti*) and enantioselectivity (90% ee) in the major diastereomer (Figure 100b). Other catalysts containing a range of Pro units were examined, but they were less selective than the dipeptide catalyst **6.9**. It was demonstrated that this catalyst can be recycled up to 5 times while preserving the observed yield and enantioselectivity.

Furthermore, Canivet and co-workers demonstrated the first example of functionalizing metal-organic-frameworks (MOFs) with peptides using microwave-assisted amide bond formation.²⁶³ First, MOFs bearing 2-aminoterephthalates were coupled to the *C*-terminus of the desired peptide sequence. Then the *N*-terminal Boc protecting group is removed under microwave/thermal conditions to afford the functionalized MOFs **6.10** (Figure 99b). As a proof-of-concept, the MOFs were employed as catalysts for the aldol reaction between 4-nitrobenzaldehyde and acetone. Despite the low enantioselectivity of 17% ee, the product was obtained in near quantitative yield.

Gruttadauria and coworkers utilized a thiol-ene coupling reaction between mercaptomethyl functionalized polystyrene resin and a styrene-containing dipeptide to prepare solid-supported aldol catalyst **6.26** (Figure 100b).²⁶⁴ The desired peptide sequence was synthesized using a *trans*-4-styrenyl-Hyp. After the evaluation of various dipeptides and stereoisomers, the supported catalyst bearing a Hyp-D-Phe sequence gave the highest yield (97%), diastereoselectivity (91:9 dr favoring *anti*), and enantioselectivity (86% ee for *anti*) in the aldol reaction between cyclohexanone and 4-nitrobenzaldehyde under aqueous conditions. It was shown that the catalyst can be reused four times with reproducible results. Also, an electron-rich aromatic aldehyde underwent the **6.26**-catalyzed aldol reaction to give the corresponding product in high diastereo- and enantioselectivity (Figure 101b).

To date, the majority of new peptide-based catalysts for aldol reactions are two or three residues in length. Since a carboxylic acid moiety of an amino acid—Pro in many cases—can be easily modified through well-established amide bond forming methods, large libraries of diverse catalysts can be accessed (Figures 6.2c & 6.3c).

Li and co-workers showed that globally unprotected dipeptide **6.11** (H- Pro-Trp-OH) can be used to catalyze the aldol reaction of simple ketones with various aldehydes in water.²⁶⁵ Due to the aqueous media, the presence of a surfactant (*e.g.*, SDS) was proven to be essential for reactivity, as only trace product was observed when the reagent was omitted. A high yield of 94% and a good enantioselectivity of 58% ee were obtained in the reaction of 4-nitrobenzaldehyde with acetone (Figure 99c). For aldol reaction with cyclohexanone, corresponding aldol product was obtained in 93% yield, 90:10 dr in favor of the *anti*-isomer, and 97% ee (Figure 100c). This peptide-based catalyst was able to address a range of aldehyde substrates, including electron-rich aromatic (Figure 101b) and aliphatic aldehydes (Figure 103b), and it was also effective using an unsymmetrical aliphatic ketone (Figure 109). In many cases, the aldol products were obtained with enantioselectivities of up to 97% ee.

Organocatalyzed asymmetric aldol reactions often require high catalyst loadings—typically 10–30 mol%—in order to achieve synthetically useful levels of enantioselectivity. However,

Zhang, Wang and co-workers reported that dipeptide catalyst **6.12** is an effective catalyst at only 1 mol% loading.²⁶⁶ Under the optimized conditions, peptide **6.12** delivered the aldol product of 4-nitrobenzaldehyde and acetone in 80% yield and 45% ee (Figure 99c). During the course of catalyst optimization, it was found that the (*R*)- α -methylbenzyl amide *C*-terminal cap was crucial for enantioselectivity, as peptides having the (*S*)-variant or an achiral amide group led to lower enantioselectivity in the product. Moreover, the authors discovered that performing the reaction in brine was also key to success. When the reaction was performed in water, the enantioselectivity decreased significantly to 7.5% ee. The authors proposed that this observation may be due to the previously reported “salting-out” effect.^{267–269} The authors further demonstrated that this catalytic system was highly effective for both electron-deficient and electron-rich benzaldehydes. In the aldol reaction between 4-nitrobenzaldehyde and cyclohexanone, **6.12** afforded the product in 82% yield and 96:4 dr in favor of the *anti*-isomer, which was enriched to 88% ee (Figure 100c). The reactions between an electron-rich benzaldehyde and acetone (Figure 101a) or cyclohexanone (Figure 101b) also provided impressive yields and good selectivities using peptide **6.12** (see Section 6.2).

In an alternate catalyst design strategy, Rahman and co-workers prepared tripeptides containing residues with polar sidechains (Tyr, Glu, or His) in order to exploit their ability to engage in H-bonding interactions with substrates.²⁷⁰ Evaluating their library, they identified His-bearing catalyst **6.13**, which gave the aldol product of 4-nitrobenzaldehyde and acetone in 98% yield and 52% ee (Figure 99c). High stereoselectivities were observed in the reaction with cyclohexanone under the same conditions, in which the product was isolated in 98% yield, 95:5 dr favoring the *anti*-product, and 94% ee (Figure 100c). The authors speculate that aldehyde may be activated by the imidazole *via* H-bonding in the aldol transition state.

Andreu and co-workers showed that simple dipeptide **6.14** (as the TFA salt) can catalyze highly selective acetone aldol reactions (up to 86% ee) when used in combination with co-catalytic zinc or sodium acetate (Figure 99c).²⁷¹ Deprotonation of **6.14**•TFA by the acetate base is thought to reveal the active amine catalyst. Furthermore, it is proposed that those metal cations could act as Lewis acids to activate aldehydes toward aldol addition of the enamine nucleophile. These metal cations were shown to greatly enhance conversion relative to the corresponding reactions lacking them.

In 2009, Chandrasekhar and co-workers discovered that dipeptide **6.15** is an effective catalyst for the acetone aldol reaction, providing the β -hydroxyketone product in 91% yield and 82% ee (Figure 99c).²⁷² While the *C*- and *N*-termini were unprotected, the lead catalyst employed a TBS-ether on the Thr sidechain. Despite using different conditions and being reported by different authors, peptides **6.14** and **6.15**—both of which possess the same stereodiad of L-Pro-D-Xaa—are remarkably consistent in terms of their efficacy and selectivity in the benchmark acetone aldol reaction.

By comparison, Al-Momani has explored an alternative catalytic design based upon sidechain functionalized Hyp residues.²⁷³ Catalyst **6.16**, in which a Val residue is coupled to the γ -hydroxyl group of Hyp, was identified as the lead catalyst, providing the acetone aldol product in 98% conversion and 80% ee (Figure 99c). Although there is no experimental

support, it is speculated that enamine formation occurs at the secondary amine site rather than at the primary amine of the pendent Val ester.

Moutevelis-Minakakis and co-workers developed *C*-terminal pyrrolidinone-containing peptide **6.17**,²⁷⁴ in which the lactam motif was derived from glutamic acid.²⁷⁵ When the catalyst was employed in asymmetric aldol reactions with acetone using co-catalytic 4-nitrobenzoic acid, the product was obtained in 58% yield and 89% ee (Figure 99c). Higher yields and selectivities were observed in the corresponding cyclohexanone aldol reaction, in which **6.17** delivered the product in 92% yield favoring the *anti*-diastereomer in 93:7 dr and 93% ee (Figure 100c).

Upon examination of various *N*-terminal Pro-based dipeptide catalysts, the Peng Group found that it was important to fine-tune the sidechain sterics of the second residue.²⁷⁶ For instance, Ala-containing peptide **6.27** gave the best selectivity in the cyclohexanone aldol reaction (Figure 100c, 98:2 dr favoring *anti*, 93% ee), whereas residues with bulkier sidechains, such as Val, Leu, and Ile, delivered to lower ee values (79%, 83%, and 90% ee, respectively). Interestingly, when Gly was incorporated at the second residue, only trace amount product was observed. Furthermore, both electron-rich and electron-poor substituents on the *C*-terminal aniline resulted in lower yields and selectivities.

In addition to α -amino acids, β -amino acids have been utilized in the design of peptide-based catalysts. Nisco and co-workers prepared and examined various Pro- β^3 -amino ester catalysts for diastereo- and enantioselective aldol reactions under aqueous conditions.²⁷⁷ The authors found that peptide **6.28**, which possesses a β^3 -Trp-OMe residue with a free indole sidechain, gave the best results in the aldol reaction of 4-nitrobenzaldehyde and cyclohexanone, providing the product in >99% yield, 94:6 dr favoring *anti*, and 90% ee (Figure 100c). A π - π interaction might play a role in organizing the transition state.

The Kokotos Group has developed numerous highly selective peptides to date, including **6.18** and **6.19** (Figures 6.2c & 6.3c) and **6.29** (Figure 100c).^{278–280} These catalysts all possess an *N*-terminal Pro residue for enamine catalysis but vary with respect to their lengths and residue composition. Using both acetone and cyclohexanone as a substrate with 4-nitrobenzaldehyde, these catalysts work well in an aqueous media to generate the corresponding aldol products in up to quantitative yield with stereoselectivities up to 94:6 dr favoring *anti* and 95% ee.

One common strategy used to enhance the efficiency of peptide-based catalysts is to increase the acidity of its amide N–H bonds. It is often proposed that this modification will enable stronger H-bonding interactions between the aldehyde substrate and the peptide backbone, which can effectively increase the electrophilicity of the aldehyde partner.

For example, Kokotos and co-workers showed that the presence of a *C*-terminal methanesulfonamide group in dipeptide **6.20** greatly improved the enantioselectivity of the aldol reaction between 4-nitrobenzaldehyde and acetone from 34% ee to 77% ee (Figure 99c).²⁸¹ The authors proposed that the increase in the enantioselectivity can be attributed to the increased H-bond donor ability of the *C*-terminal residue. Upon further optimization of the reaction temperature, the aldol product was obtained in 49% yield with 87% ee.

Zhang and co-workers identified Val-Val-based dipeptide **6.21** as a catalyst for asymmetric aldol reactions.²⁸² Using 10 mol% of 2,4-dinitrophenol as a co-catalyst, they observed that peptides bearing a C-terminal 3-nitroaniline group exhibited increased stereocontrol. Although low enantioselectivity was observed in the acetone aldol (Figure 99c), the reaction with cyclohexanone was highly selective, providing the aldol product in 84% yield, 98:2 dr favoring *anti*, and 95% ee (Figure 100c).

Compared to the corresponding native amide-based peptides, the thioamide-containing catalyst **6.22** developed by Li and co-workers gave higher yield (72% vs. 59%) and enantioselectivity (85% vs. 35%) in the direct aldol reaction of 4-nitrobenzaldehyde with acetone (Figure 99c).²⁸³ Thioamides are stronger H-bond donors than the corresponding amides. As such, Pro thioamide-containing peptide **6.22** is thought to be a more effective catalyst due to its enhanced ability to activate the aldehyde reaction partner through H-bonding,¹⁸⁰ although additional mechanistic studies are required. Notably, reduction of the C-terminal methyl ester of **6.22** to a primary alcohol led to a further increase in enantioselectivity to 95% ee (not shown).

High Speed Ball-Milling (HSBM) has been utilized as an environmentally friendly, mechanochemical tool for performing asymmetric aldol reactions under solvent-free conditions. This area was pioneered by the Bolm Group in 2007 in the context of Pro catalysis.²⁸⁴ Using a related mechanochemical technique, Juaristi and co-workers have found that a series of dipeptides **6.23–6.25** (Figure 99c) can also be used to catalyze asymmetric aldol reactions with good yields (50–82%) and enantioselectivities (34–69% ee).^{285–287} For the catalysts bearing aromatic sidechains (*e.g.*, **6.23** & **6.24**), the authors have speculated that noncovalent π - π interactions between the aromatic motif and the aromatic aldehyde could contribute to the high enantioselectivities observed. In comparison to the reactions with acetone under ball-milling conditions, catalysts **6.23–6.25** and **6.30** mediated highly diastereoselective aldol reactions with cyclohexanone as the donor, delivering the aldol products in up to 98% yield, 98:2 dr favoring *anti*, and >98% ee (Figure 100c). Much like in the solution phase reactions, *anti*-diastereoselectivity was also observed under these solvent-free conditions.^{286–288}

Self-assembled fibrillar networks of organic molecules play important roles in the localization of reactants within cellular environments.²⁸⁹ Inspired by such supramolecular phenomena, Ashkenasy, Escuder, and co-workers developed a short peptide **6.31**, which possesses a long alkyl chain at the C-terminus, that was shown to self-assemble into high aspect ratio aggregates and hydrogels.²⁹⁰ They observed that these aggregates are able to catalyze the aldol reaction of 4-nitrobenzaldehyde with cyclohexanone in aqueous media, providing the product in high yield (>99% conversion), 86:14 dr favoring *anti*, and 76% ee (Figure 100c), whereas non-aggregated analogues gave notably diminished reactivity (32% yield). The authors proposed that the long, hydrophobic alkyl chain of the catalyst may function as a surfactant to help solubilize substrates in the aqueous media. Moreover, the authors also used **6.31** to catalyze the self-aldol reaction of TBDPS-protected 2-hydroxyacetaldehyde to afford a tetrose derivative in 84% yield, 90:10 dr favoring *anti*, and 82% ee (not shown).

Using a similar self-assembly approach, Alves and co-workers designed an amphiphilic tripeptide catalyst **6.32**, which possesses Arg and Trp residues for hydrophilicity and a *C*-terminal *n*-hexadecyl chain for lipophilicity.²⁹¹ This peptide was reported to catalyze the cyclohexanone aldol reaction in excellent yield and 92:8 dr favoring the *anti*-isomer with 85% ee (Figure 100c). Various imaging techniques (small-angle X-ray scattering and cryo-TEM), as well as molecular dynamics simulations, supported the hypothesis that **6.32** forms micelles under the aqueous reaction conditions. The same research group later demonstrated that oligopeptide **6.33** can self-assemble in an aqueous medium, and this supramolecular assembly can mediate the cyclohexanone aldol reaction with moderate yield (42% conversion) and good stereoselectivity (86:14 dr favoring *anti*, 85% ee).²⁹²

6.2. Expansion of Substrate Scope

In addition to 4-nitrobenzaldehyde, other electron-deficient aromatic aldehydes, such as those functionalized with halogen, nitrile, and trifluoromethyl substituents, are used in the vast majority of peptide-catalyzed asymmetric aldol reactions. This is presumably due to their greater electrophilicity and increased propensity toward nucleophilic addition. In comparison, only a handful of examples using electron-rich aromatic and aliphatic aldehydes have been reported to date. The peptide-based catalysts that are able to address these more challenging aldol substrates are presented below in Figures 101 and 103, respectively. Additional examples of peptide-catalyzed aldol reactions employing aldehydes other than benzaldehyde and its simple derivatives are also presented below.

Zhang and Wang showed that peptide **6.12** effectively catalyzed aldol reactions using 3,4,5-trimethoxybenzaldehyde as the electrophile.²⁶⁶ Using only 1 mol% of **6.12** under mild conditions, the acetone aldol product was obtained in 78% yield and 47% ee (Figure 101a), comparable to the results obtained with 4-nitrobenzaldehyde (see Figure 99c). Peptide **6.12** was similarly reactive and slightly more selective in the corresponding reaction with cyclohexanone, delivering the product in 80% yield favoring the *anti*-diastereomer in 89:11 dr and 66% ee (Figure 101b).

The reduced reactivity of electron-rich benzaldehydes has also been observed under continuous flow and ball-milling conditions. Although Fülöp's solid-supported peptide catalyst **6.6** was proven to be highly recyclable and robust in aldol reactions with 4-nitrobenzaldehyde (see Figure 99b), the corresponding reaction with 2-methoxybenzaldehyde was significantly lower yielding, providing only 37% yield of the aldol product in 76% ee (Figure 101a).²⁵⁸ Similarly, Gruttadauria's recyclable polystyrene resin-supported catalyst **6.26** was also less reactive with 3-methoxybenzaldehyde and cyclohexanone, as the product was obtained in only 34% yield favoring the *anti*-diastereomer in 93:7 dr and 93% ee (Figure 101b).²⁶⁴ Moreover, under solvent-free HSBM conditions, peptide catalyst **6.30** afforded only 7% yield of the product in the aldol reaction between 4-methoxybenzaldehyde and cyclohexanone (Figure 101b).²⁸⁸ Despite the very low yield, a good selectivity was observed, as the product was obtained in 91:9 dr favoring the *anti*-isomer and 84% ee. Yet, in other HSBM methods with different peptide catalysts, such as **6.23** and **6.24**, much improved yields of 62–64% were observed, complimented by good *anti*-selectivities of 84:16–96:4 dr and enantioselectivities up to 57% ee (Figure 101b).

^{285,286} However, these ee values are significantly lower than those measured for the reaction with 4-nitrobenzaldehyde (see **Figures 6.2c & 6.3c**)

Spawning from the continuous efforts to expand the scope of peptide-catalyzed, asymmetric aldol reactions, a few peptides have been reported that provide both high yields and stereoselectivities with electron-rich benzaldehyde substrates. For example, Li's dipeptide **6.11** was an effective catalyst for the aldol reaction of 4-methoxybenzaldehyde and cyclohexanone, affording 67% yield of the *anti*-product in 95:5 dr and 83% ee, although long reaction times were required (Figure 101b).²⁶⁵ Perhaps some of the most stereoselective examples were reported by the Rahman Group. The His-bearing tripeptide **6.13** worked quite well with 4-methoxybenzaldehyde, delivering the product in 60% yield, 99:1 dr favoring the *anti*-isomer, and 87% ee.²⁷⁰ Moreover, their enzyme-inspired catalyst **6.2d**, a globally unprotected heptapeptide, essentially afforded a single stereoisomer in the aldol reaction between 4-methoxybenzaldehyde and only 1.2 equivalents of cyclohexanone as the *anti*-product was isolated in 65% yield, 99:1 dr and 95% ee (Figure 101b).²⁴⁷

Inspired by dehydratases, Da and co-workers devised a complementary method for generating enantioenriched aldol products *via* dehydrative kinetic resolution of racemic β -hydroxyketones (Figure 102).²⁹³ Interestingly, the authors found that peptide **6.1**, the optimal catalyst from their asymmetric aldol reaction (see Figure 99a), was also the most effective in this context. As mentioned above, catalytic aldol reactions of electron-rich aldehydes often give low yields and enantioselectivities. On the other hand, dehydrative kinetic resolutions were particularly effective for these electron-rich substrates. For example, the *ortho*-methoxy substituted ($\pm$)-**6.34** undergoes **6.1**-catalyzed dehydration with an *s* factor of 21.2 to provide the enantioenriched **6.34** in 45% isolated yield and 91% ee (Figure 102a). Enone byproduct (*E*)-**6.35** was also isolated as a single geometric isomer in 48% yield. Based on preliminary studies, the authors proposed a mechanism that requires both termini of **6.1** to be unprotected, enabling a bifunctional activation mechanism; the Pro condenses onto the ketone to first form imine **I** *en route* to enamine **II**, which subsequently dehydrates to leave α,β -unsaturated imine **III** (Figure 102b). Rehydration and cleavage from the peptide generates **6.35** and turns over the catalyst.

Examples of peptide-catalyzed direct aldol reactions with aliphatic aldehydes are scarce (Figure 103). Alkyl aldehydes are often problematic substrates due to their propensity to undergo self- or cross-aldol reactions. To combat this issue, aldehydes that are non-enolizable or would lead to less reactive enamine intermediates have been used. Commonly, α,α -disubstituted aldehydes are employed. Peptides with rigid conformations, such as **6.3a** and **6.4**, have been shown fairly effective as catalysts for the asymmetric aldol reaction between cyclohexanecarbaldehyde and acetone, providing the β -hydroxyketone product in 57% and 50% yield and 82% ee and 64% ee, respectively (Figure 103a).^{248,253} In 2009, Chandrasekhar and co-workers used simple dipeptide **6.15** to catalyze the same aldol reaction to give a fairly high yield of 80% and a good selectivity of 75% ee (Figure 103a).²⁷²

iso-Butyraldehyde has been also used as an electrophile in asymmetric aldol reactions, and a handful of peptide-based catalysts have been used to mediate its reaction with acetone and/or cyclohexanone with varying degrees of efficacy. Notably, Bartók and co-workers

developed peptide **6.36**, which gave 94% ee using acetone as the donor substrate (Figure 103b) and 98:2 dr (*anti*) and 95% ee using cyclohexanone (Figure 103c), albeit with <30% yield in each case.²⁹⁴ The authors observed effects of catalyst-lengths on enantiodivergence, which is described in Section 6.3 below (Figure 114). Moutevelis-Minakakis and co-workers also applied their *C*-terminal pyrrolidinone-containing peptide **6.17** in an asymmetric aldol reaction of *iso*-butyraldehyde with acetone (Figure 103b).²⁷⁴ However, the desired aldol product was produced in only 4% yield and 44% ee. Using cyclohexanone as the donor, a similarly low yield of 10% yield was obtained, but the product was formed in >98:2 dr favoring the *anti*-isomer in 97% ee (Figure 103c).

Beyond using traditional aldehydes as substrates, Kudo and co-workers have focused on expanding the scope of these asymmetric aldol reactions by employing masked or unconventional acceptors. Employing acetals, the authors developed the first enantioselective, successive acid- and base-catalyzed reactions in a single reaction vessel using resin-bound peptide catalysts to mediate the process (Figure 104).²⁹⁵ This method builds upon their first report of a polymer-supported peptide catalyst for asymmetric aldol reactions performed under aqueous conditions.¹¹⁸ Using commercially available Amberlite IR-120 resin (H⁺ form) in tandem with PEG-PS-bound tripeptide **6.3**, acetal **6.37** was hydrolyzed to 2-nitrobenzaldehyde, which then underwent a **6.39**-catalyzed aldol reaction with acetone to afford β -hydroxyketone **6.38** in one-pot, 89% NMR yield, and 73% ee. The authors demonstrated the reusability of the resin-supported catalyst, which can be easily separated from the reaction mixture by filtration and subsequently regenerated by drying. Even after six uses, the catalytic activity of **6.39** was largely retained.

Kudo and co-workers also used resin-bound peptide-based catalysts to explore a tandem oxidation/direct aldol strategy, which could improve reaction outcomes for chemically unstable aldehydes and for those that are only commercially available in the alcohol oxidation state (Figure 105).²⁹⁶ Using a similar strategy to their previous report,²⁹⁵ the authors developed two resin-supported catalysts to mediate each step of the process. Together with a Cu(I) catalyst, TEMPO-derived peptide **6.41** would mediate the oxidation of benzylic alcohol **6.40** to the corresponding benzaldehyde.²⁹⁷ Pre-treatment of **6.41** with a Cu(I) salt and 2,2'-bipyridine ligand was necessary to achieve suitable yields in the oxidation step. A Pro-containing peptide would then catalyze the direct aldol reaction between 2-nitrobenzaldehyde and acetone *via* enamine catalysis to provide β -hydroxyketone **6.38**. Modest optimization of their previously reported PEG-PS-bound tripeptide led to **6.42**—the sidechain-protected variant of **6.39** (Figure 104)—which was found to be a more active catalyst under the reaction conditions. Employing the pre-adsorption method, the one-pot, tandem oxidation/aldol sequence was performed under the optimized reaction conditions to afford **6.38** in 78% yield and 87% ee (Figure 105), a marked improvement in selectivity over the previous report.²⁹⁵ This system also lends itself to catalyst recycling, as peptide **6.42** maintained its activity over eight cycles. TEMPO-containing **6.41** was removed *via* filtration after the alcohol oxidation to prevent decomposition of the aldol catalyst. Peptide **6.42** was then added to the reaction mixture along with EDTA to deactivate any remaining Cu species.

Using previously identified peptide **6.39** (Figure 104) and its enantiomer (*ent*-**6.39**), Kudo and co-workers developed a strategy for the kinetic resolution of racemic ansa cyclophanes (*i.e.*, cyclophanes with an aliphatic bridge) *via* a sequential aldol/retro-aldol process (Figure 106).²⁹⁸ Planar-chiral cyclophanes have been used as sources of chirality in asymmetric catalysis and in the synthesis of functional materials.^{299,300} However, limited methods for the enantioselective synthesis of ansa cyclophanes have been reported, presumably due to the flexibility of the aliphatic bridge.³⁰¹ Peptide catalysis proved a viable solution to this unmet challenge. Each step of the tandem process was optimized individually. The initial aldol reaction of ansa cyclophane **6.43** with acetone catalyzed by **6.39** selectively delivered β -hydroxyketone (S_p , S)-**6.44** in 93:7 dr and 67% ee, enriching starting material **6.43** to 19% ee (entry 1). The ansa chain was hypothesized to block *si*-face attack that would produce the (R_p)-isomer about the planar-chiral cyclophane. This aldol product with two elements of chirality—a chiral plane and a chiral center—could then be resolved itself *via* a retro-aldol reaction catalyzed by *ent*-**6.39**, in which minor aldol product (R_p , S)-**6.44** was preferentially converted back into the starting aldehyde, thus increasing the enantiopurity of both (S_p , S)-**6.44** and **6.43**. Using this two-step kinetic resolution strategy, aldol product (S_p , S)-**6.44** was successfully obtained in 37% yield and with an enhanced ee of 82%; aldehyde **6.43** was also recovered in 38% yield and 46% ee, and the minor diastereomer (R_p , S)-**6.44** was produced in 4% yield and 95% ee (entry 2). The reusability of the resin-supported peptide catalysts was tested, and the selectivity was found to diminish only slightly after two reuses (entry 3). Substrates with an ansa chain of 8 residues and sulfur-linkages were also tested in this reaction, yielding similar results (entries 4 & 5).

Various ketones have been also used as acceptors in peptide-catalyzed direct aldol reactions (Figure 107). Reiser and co-workers demonstrated that β -Acc-containing tripeptide **6.3b** catalyzed the Robinson Annulation of **6.45** to the Wieland–Miescher ketone (**6.46**) in 88% yield and 92% ee (Figure 107a).²⁴⁸ These results are comparable to the best-known examples in the literature.³⁰²

Intermolecular direct aldol reactions of more electron deficient ketones are also known. Kohari and co-workers reported the asymmetric direct aldol reaction of isatins like **6.47** with acetone to afford functionalized products **6.48** (Figure 107b).³⁰³ Upon evaluation of various tripeptide catalysts, it was apparent that both a D-configured residue and a free carboxylic acid at the C-terminus were essential for achieving high levels of enantioselectivity. Using peptide catalyst **6.49**, in which the catalytically active Pro and D-Ala are interspersed with a Gly residue, β -hydroxyketone **6.48** was obtained in 92% yield and 94% ee. Moreover, Moutevelis-Minakakis and co-workers also utilized an electron-deficient ketone, trifluoroacetophenone **6.50**, which delivered **6.51** in 63% yield and 70% ee using pyrrolidinone-containing catalyst *epi*-**6.17** (Figure 107c).²⁷⁴ Interestingly, this peptide is the C-terminal epimer of the catalyst that provided optimal results in the aldol reactions of 4-nitrobenzaldehyde (see Figure 99c) and *iso*-butyraldehyde (Figure 103c) with acetone.

6.3. Stereo- & Site-Divergence in Asymmetric Aldol Reactions

As the diversity of peptide-based catalyst libraries continues to increase, hints of the next directions that could expand the scope of the asymmetric aldol reaction beyond benchmark

substrates are beginning to emerge. For example, when using an unsymmetrical aliphatic ketone as an aldol nucleophile, an additional level of control must be considered due to the presence of multiple enolizable sites that could lead to a mixture of β -hydroxyketone products (Figure 108). Fully catalyst-controlled site-, diastereo-, and enantioselectivity are goals that are clearly becoming within reach.

Divergence in site-selectivity has been observed in asymmetric aldol reactions using different catalytic conditions (Figure 109). For instance, in the aldol reaction between 4-nitrobenzaldehyde and methyl *iso*-butyl ketone, Li and co-workers observed complete branch site-selectivity when dipeptide **6.11** was used as the catalyst. Despite the long reaction time of 180 h, **6.11** delivered branched product **6.52a** in 67% yield, 95:5 dr favoring *anti*, and 83% ee for the major diastereomer.²⁶⁵ However, in the same reaction, Da's β -turn-biased peptide **6.1** solely produced the linear isomer with a high 93% ee, albeit in only 24% yield after 240 h.²⁴⁶ In addition to differences in secondary structure, peptides **6.11** and **6.1** differ in the degree of substitution on the catalytically active amine: **6.11** employs the secondary amine of its *N*-terminal Pro, while **6.1** uses an *N*-terminal primary amine of Val. As such, these data show that it is possible to achieve site-divergence by modifying the catalyst sequence. In that sense, the modularity of peptide-based catalysts relative to other organocatalytic scaffolds is particularly beneficial.

In another example, Peng observed that both branched and linear β -hydroxyketone products were formed in the peptide **6.27**-catalyzed aldol reaction between 4-nitrobenzaldehyde and 2-butanone (Figure 110).²⁷⁶ Branched product **6.53a** was obtained in 54% yield, 90:10 dr in favor of the *anti*-isomer (96% ee), while linear product **6.53b** was formed in only 36% yield and with 53% ee. On the other hand, using 2-pentanone as the nucleophile, which is only a single methylene unit longer than 2-butanone, only linear product **6.54b** was formed in 69% yield and 39% ee. No branched product **6.54a** was observed in this reaction. The authors speculated that two enolizable sites on the ketone substrates could lead to two different chair-like transition states, wherein the size of the ketone substituents would affect the degree of site-selectivity. Although this may explain the apparent substrate-controlled site-selectivity observed for this particular catalytic system, the examples from Figure 109 may suggest that such selectivity could also be achieved in a catalyst-controlled manner.

Diastereoselective direct aldol reactions that operate *via* enamine-catalysis have often been shown to favor the *anti*-diastereomer as the major product. Indeed, most of the peptide-based catalysts discussed in Section 6.2 above were *anti*-selective (see Figures 100, 101, & 103). However, it is sometimes possible to achieve catalyst-controlled diastereodivergence as a function of catalyst structure. For example, in the aldol reaction of 4-nitrobenzaldehyde with 2-hydroxyacetone, β -turn-containing peptide **6.1** gave **6.55** in quantitative yield, 74:26 dr favoring *anti*, and 87% ee in the major diastereomer (Figure 111).²⁴⁶ The use of co-catalytic (*S*)-BINOL was found to be beneficial for catalysis, but nearly identical diastereo- and enantioselectivities were obtained using either enantiomer of BINOL. Notably, replacement of the BINOL additive with benzoic acid switched the sense of diastereoselectivity to slightly favor the *syn*-diastereomer in 58:42 dr. By comparison, Tomasini and co-workers observed significant *syn*-selectivity in the same reaction under the control of peptide catalyst **6.56** (Figure 111).³⁰⁴ In this case, *syn*-**6.55** was obtained in 98% yield, 83:17 dr, and 88%

ee. Interestingly, only branched products were observed in these reactions. Again, catalysts **6.1** and **6.56** differ in their structures and in the nature of the catalytically active amine, both of which could give rise to the observed preferences in diastereoselectivity.

Enantiodivergence has also been observed in peptide-mediated aldol reactions. Messerer and Wennemers discovered a unique reversal in the enantioselectivity of a peptide-catalyzed aldol reaction solely by changing the reaction medium (Figure 112).³⁰⁵ β -Turn-biased tripeptide **6.58** was previously identified as an effective catalyst for direct aldol reactions.^{257,306} To improve the solubility of **6.58**, peptide **6.59** was synthesized, which bears a long-chain *N*-alkyl amide rather than a primary amide. This peptide produced comparable results to **6.58** in the original aldol reaction, indicating that the alkyl chain did not affect the catalytic properties, only the solubility. The catalytic properties of **6.59** were assessed in the aldol reaction between cyclohexanone and 4-nitrobenzaldehyde (Figure 112). Although the aldol product was generally obtained in 1:2 dr favoring the *anti*-isomer, the solvent had a remarkable effect on observed enantioselectivity. In the absence of water, both DMSO and methanol solvents resulted in the formation of (*R,S*)-**6.57** in 55% and 58% ee, respectively (entries 1 & 4). However, adding of as little as 2.5 vol% of water to DMSO resulted in a reversal in the absolute configuration of the product, favoring (*S,R*)-**6.57** in 42% ee (entry 2). Larger quantities of water increased the enantioselectivity up to 69% ee with 10% water in DMSO (entry 3). This trend was also observed in methanol solvent; as the amount of water increased, the enantioselectivity of (*S,R*)-**6.57** increased up to 20% ee (entries 5 & 6).

To gain a better understanding of the source of this enantiodivergence, the authors recorded CD spectra of **6.59** in methanol, water, and mixtures of the two solvents (Figure 113). The spectra of **6.59** revealed remarkable conformational differences in methanol as compared to water, suggesting that the switch in the enantioselectivity of this aldol reaction is due to a conformational change from one β -turn conformation to another that has the opposite twist sense.

Bartók and co-workers also noted an interesting case of enantiodivergence when using solid-supported di- versus tri-peptides as catalysts in asymmetric aldol reactions (Figure 114).²⁹⁴ In all the reactions examined, dipeptide **6.36**, which is bound to polystyrene resin through a methyl benzhydryl amine (MBHA) linker, delivered the (*R*)-configured aldol product (entries 1 & 3). However, under otherwise identical reaction conditions, tripeptide **6.60** reliably favored the (*S*)-aldol product (entries 2 & 4). Imidazole was included as a co-catalyst in these reactions to suppress the formation of side-products, and it was shown not to influence the stereochemical outcomes. To determine whether the resins had any effect on the enantioselectivity outcomes, the same reactions of 4-nitrobenzaldehyde and acetone were performed using solution-phase variants of **6.36** (Pro-Glu-NH₂) and **6.60** (Pro-Pro-Glu-NH₂). These soluble catalysts provided the (*R*)-product in 32% ee (25% conversion) and the (*S*)-product in 42% ee (5% conversion), respectively (compare to entries 1 & 2). These data suggest that the MBHA linker and resin may exert some influence over the reactivity and selectivity of the aldol reaction. In order to better understand the source of enantiodivergence in these peptide-catalyzed reactions, DFT calculations were performed on the enamine intermediates, which were modeled using related aldol catalysts, H-Pro-Asp-MHBA and H-Pro-Pro-Asp-MBHA. The relative energies of the diastereomeric enamine-

aldehyde adducts were compared. With respect to tripeptide **6.60**, formation of the (*S*)-enantiomer was favored by 0.52 kcal/mol. However, dipeptide **6.36** favored the (*R*)-enantiomer by 0.82 kcal/mol.

Taken together, all of these reports show that peptide catalysis is a viable approach for controlling stereochemical outcomes in many direct aldol reactions. Initially discovered in now straightforward reactions, the venerable Pro-catalyzed transformation is expanding into ever more complicated situations.

7. Conjugate Addition

The prowess of enamine catalysis for the aldol reaction (Section 6) has now also been demonstrated explosively in reactions involving conjugate addition. In the mechanism proposed by List and Houk for Pro catalysis, proton transfer between the carboxylic acid moiety of the catalyst and the substrate is critical for nucleating catalyst–substrate interactions.^{307,308} In this regard, peptide-based catalysts have proven particularly well-suited for engaging conjugate acceptor substrates, as the increase in distance between the *C*-terminal carboxylic acid and *N*-terminal Pro residue provides space to accommodate the additional two atoms present in conjugate acceptor substrates (Figure 115). This Section summarizes recent advances in peptide-catalyzed conjugate addition reactions, with a particular emphasis on catalyst structural and mechanistic features. Additions of aldehyde- and ketone-derived nucleophiles into activated olefin acceptors (Section 7.1) is treated separately from the conjugate addition of other *C*-based nucleophiles, such as indoles and nitronates (Section 7.2).

7.1. Conjugate Additions of Aldehydes & Ketones to Activated Olefin Acceptors

Recognizing the increased distance requirements of 1,4- relative to 1,2-additions, Wennemers and co-workers hypothesized that β -turn-biased tripeptides, which had previously been shown to be effective catalysts for asymmetric aldol reactions,²⁵⁷ might also be well suited for conjugate addition reactions (Figure 116).³⁰⁹ Molecular modeling indicated that approximately 3 Å of additional space between the secondary amine and carboxylic acid moieties is present in the lowest-energy structure of tripeptide **7.4** (H-Pro-Pro-Asp-NH₂, Figure 116a) compared to the Pro monomer (Figure 116b), which could accommodate the extra two atoms present in conjugate acceptors. Peptide-catalyzed conjugate addition reactions of aldehydes into nitroolefins had previously been demonstrated and was thus selected as a model reaction.⁴ Indeed, these tripeptides proved highly effective in the reactions of aldehydes **7.1** with nitroolefins **7.2**, providing γ -nitroaldehyde products **7.3** in excellent yields, diastereoselectivities, and enantioselectivities at catalyst loadings as low as 1 mol% (Figure 116c). Of the four possible diastereomers **7.4–7.7** (entries 1–4), it was found that the D-Pro-Pro-Asp stereotriad of **7.7** was the most selective, providing *syn*-**7.3** in 25:1 dr and 97:3 er (entry 4). It is notable that related chiral amine catalysts typically require catalyst loadings of 10–20 mol% in order to achieve similar results. Studies of the primary sequence revealed that while the *N*-terminal Pro stereogenic center controls the enantioselectivity, the remaining stereocenters on the catalyst must be matched in order to achieve high catalytic performance.

Following this initial study, the Wennemers Group investigated conjugate additions of aldehydes **7.1** into terminal nitroolefins **7.8** to provide γ -nitroaldehydes **7.9**, which in turn could be converted into monosubstituted γ^2 -amino acids (Figure 117).³¹⁰ The previously identified peptide **7.7** was found to be an effective catalyst for this transformation, as well. However, significant rate enhancement and increases in the observed enantioselectivity were observed by simply exchanging the *C*-terminal Asp residue for a Glu residue, which bears an additional methylene (**7.10**, entry 2). While such conjugate addition reactions are often plagued by the formation of homoaldol side-reactivity, this byproduct was not observed using catalyst **7.10**. Additionally, only a minimal excess (1.5 equiv) of aldehyde relative to nitroolefin was required to achieve high levels of reactivity. With slightly higher catalyst loadings (3 mol%), substrates with bulky substituents were tolerated, such as isopropyl and *tert*-butyl groups.

A more in-depth interrogation of the *C*-terminal residue in the peptide-catalyzed conjugate addition of **7.11** into **7.12** revealed that the enantioselectivity of the reaction was relatively insensitive to the identity of the *C*-terminal functional group (Figure 118, entries 1–3).³¹¹ Conversely, when the identity of the sidechain carboxylate was altered to an amide (entry 4), significant reductions in both conversion and enantioselectivity were observed, suggesting that this carboxylic acid plays a critical role in substrate coordination and orientation. While the insertion of an additional methylene unit to obtain Glu from Asp was found to be beneficial to both yield and selectivity (entry 5), addition of a third methylene within the sidechain residue decreased the observed selectivity (entry 6).

Moreover, the effect of water on the reactivity of this system was assessed by comparing “standard” and “dry” reaction conditions, in which water had been rigorously excluded (Figure 119a).³¹² It was found that reaction times could be substantially shortened under the dry conditions (entries 1 vs. 2). Additionally, at longer reaction times, substantially lower catalyst loadings could be used (0.1 mol%) with only a minor drop in enantioselectivity (entry 3). Studies of the fundamental steps revealed that, at higher concentrations, the reaction displays a zero-order dependence with respect to butanal **7.11**, indicating a steady state is reached between the aldehyde and the catalyst, presumably to form an enamine intermediate (Figure 119b, green line). This suggests that enamine formation is not rate-determining. When using the dry conditions (red line), this steady state is reached at a lower concentration. When additional water is intentionally included (blue line), the steady state is never reached. Kinetic studies revealed that reactions conducted under the anhydrous conditions proceeded rapidly, while reactions with added water were relatively sluggish (Figure 119c).

While an enamine mechanism for this transformation is widely accepted, it had not been unambiguously determined for peptide catalyzed reactions. The groups of Wennemers and Pfaltz employed ESI-MS in order to rigorously investigate the presence of an enamine intermediate, (Figure 120).³¹³ According to the principle of microscopic reversibility, if the C–C bond-forming step was rate-determining, then the related C–C bond cleavage step of the reverse reaction should be governed by the same transition states. As such, the difference in energy between transition states should be the same, which governs the enantioselectivity of a transformation. The reverse C–C bond cleavage step requires the addition of peptide to

form an iminium ion. Therefore, if the forward reaction proceeds through an iminium/enamine mechanism, the enantioselectivity of both the forward and the reverse process should be equal. By using a mixture of quasi-enantiomeric substrates **7.14** that vary at the 4-position of the aryl ring, enantioselectivity can be measured rapidly by quantitative MS analysis. Indeed, the mass distribution between enamine **7.16a** and **7.16b** reflected the measured ee values for the forward transformation catalyzed by peptide **7.10**. The performance of related catalysts that lack an acidic group (*e.g.*, **7.17**), suggest that C–C bond formation is only rate determining in cases where rapid protonation is facilitated by an optimally positioned acidic group.

The Wennemers Group has also demonstrated that the ability to synthesize peptides on-resin allows for the facile development of immobilized catalysts, which can be recycled multiple times.³¹⁴ In principle, organic catalysts are particularly attractive when immobilized, as they tend to be moisture and air stable. These peptide-based catalysts for conjugate addition reactions have been shown to be highly effective when immobilized on solid support, allowing for the isolation of conjugate addition products in high yield and stereoselectivity after simple filtration of the catalyst and removal of volatiles (Figure 121a). In this system, catalysts were able to be recycled at least 30 times without diminished reactivity or selectivity (Figure 121b). Similarly, immobilized peptide catalysts have also been successfully employed in flow reaction setups.³¹⁵

Additionally, Wennemers and co-workers have also explored the behavior of these trimeric catalysts under aqueous reaction conditions.³¹⁶ When lead catalyst **7.10** was appended with long alkyl chains at the C-terminus and on the Pro sidechain, peptide catalysts **7.18** and **7.19**, respectively, were found to form emulsions in aqueous media due to the hydrophobic effect (Figure 122). Despite the negative effect of water in these conjugate additions (*vide supra*), these emulsions were found to efficiently catalyze the conjugate addition of **7.1** into **7.2** with catalyst loadings as low as 3 mol% (entries 2 & 3). Catalysts lacking these modifications did not emulsify in aqueous media, and diminished catalytic efficiency was observed as a result (entry 1). The rate of reactivity for these transformations was found to depend not only on the reactivity of the nitroolefin, but also on the ability of the peptide to effectively form an emulsion in water.

Encouraged by these promising results, the Wennemers Group further expanded their studies to include conjugate additions of α,β -disubstituted nitroolefins **7.20** (Figure 123a), which have historically proven to be particularly challenging substrates.³¹⁷ The presence of α -substitution not only provides additional steric hindrance, but it also distorts the planarity between the aryl β -substituent and the double bond, hampering conjugation and deactivating the substrate toward 1,4-addition. Furthermore, the formation of an additional stereogenic center in these reactions must be controlled in order to achieve a highly selective transformation. After examining several variations of parent catalyst **7.10**, peptides **7.22** and **7.23** were identified as particularly effective. These peptides contain a Pro-Pro sequence instead of the D-Pro-Pro motif that had proven effective in the previously studied reactions. It is notable that of the four possible diastereomers of γ -nitroolefin **7.21** (without considering their enantiomers), significantly different distributions are observed when catalysts **7.22** and **7.23** are employed as opposed to pyrrolidine or Pro (Figure 123b, entries 3 & 4 vs. 1 & 2).

In fact, upon examining the distribution of **7.21a** and **7.21c**, which are epimers at the α -position, opposite epimers are favored in the case of peptide- *versus* non-peptide-catalyzed reactions, indicating that the protonation step is also under catalyst control. It is also notable that catalysts **7.22** and **7.23** favor the same product diastereomer (**7.21a**) despite having different stereotriads; **7.23** has the opposite configuration at the *C*-terminal residue.

Despite great successes in the conjugate addition of aldehydes into α,β -disubstituted nitroolefins, sterically congested β,β -disubstituted nitroolefins, such as **7.24**, proved to be more challenging initially (Figure 124).³¹⁸ Evaluation of the previously explored peptides resulted in low conversions to the desired product **7.25** and produced large amounts of the undesired homoaldol product (entry 1). It was found that substituting out the *C*-terminal carboxylic acid and amide of peptide **7.10** with aryl groups dramatically increased conversion (entries 2 & 3). This observation was in contrast to earlier studies, which had identified that carboxylic acid functionality as critical for selective catalysis. Additionally, new solvent conditions were required for high reactivity, with *tert*-butanol ultimately emerging as the optimal solvent (entry 4). Under these conditions, peptide **7.27** afforded γ -nitroaldehyde **7.25**, which possesses an all-carbon quaternary stereocenter, in 96% conversion, 6:1 dr, and 94% ee. Further mechanistic studies of this reaction are presented below.

Seeking to expand the scope of peptide-catalyzed, asymmetric conjugate additions, the Wennemers Group examined the addition of acetophenone and related ketones **7.28** to dicyanoolefins **7.29** (Figure 125).³¹⁹ Under the optimized conditions, catalyst **7.10** was found to be effective without the need for further catalyst optimization, despite the well-known challenges in iminium ion formation between secondary amines and ketones. In order to overcome low reactivity, however, 20 mol% of the catalyst was used, and an excess of ketone **7.28** (5.0 equiv) was required. Under these conditions, **7.10** delivered ketones **7.30** in up to 90% yield and 88:12 er.

The Wennemers Group reasoned that, given the highly tunable nature of peptide scaffolds and their previous successes in their studies of related conjugate additions, maleimide (**7.32**) could also serve as a potential conjugate acceptor (Figure 126).³²⁰ After screening previously reported peptides with limited success (Figure 126a, entries 1 & 2), it was found that the incorporation of additional amide functionalities at the *C*-terminus (entries 3 & 4) proved to be effective in promoting both reactivity and enantioselectivity in the reaction of aldehydes **7.31** with **7.32**. Lead catalyst **7.35** delivered the succinimide product **7.33** in 93% conversion, 86:14 dr, and 98% ee under the optimized conditions. It was proposed that H-bonding, rather than protonation, is critical for accelerating the C–C bond forming pathway. In fact, when maleimide **7.36** (which lacks an H-bond donor) was subjected to the reaction conditions, the product was obtained with high enantioselectivity, but in low yield (Figure 126b), which suggests an H-bonding interaction with the maleimide helps to increase reactivity.

While many of the lead peptides identified over the course of these studies contain a D-Pro-Pro motif, subtle differences in the *C*-termini led to drastically different catalytic performances. In order to gain insight into how structural differences between the peptides

might impact catalytic function, X-ray crystal structures of peptides **7.7**, **7.27**, and **7.35** were obtained and analyzed (Figure 127a).³²¹ An overlay of these structures reveals that they adopt relatively similar conformations with respect to the D-Pro-Pro turn motif, with some variation being observed in the ring pucker of the *i*+1 Pro residue (Figure 127b). A significant difference between these three peptides, however, is the presence or absence of an intramolecular H-bond between the *C*- and *N*-termini. This H-bond, or lack thereof, was dependent on the identity of the *C*-terminal residue. While all three peptides adopt a similar β -turn structure in the solid state, the turn conformations do vary as a result of this *C*- to *N*-terminal interaction. Additionally, the presence of an $n \rightarrow \pi^*$ interaction³²² between the *C*-terminal D-Pro carbonyl and the adjacent Pro carbonyl (Figure 127c) is present in peptides **7.7** and **7.27** as evidenced by Bürgi–Dunitz trajectories ($95^\circ < \theta < 125^\circ$) and significantly shortened O_{i-1} to C_i distances. This interaction is not present in **7.35**, which instead is engaged in an intramolecular H-bond between the *C*-terminal amide and *N*-terminal Pro. While these studies provide valuable insight into the conformation of peptide catalysts, it was recognized that more in-depth studies of the solution-phase structure of the peptides would be required for understanding catalytically relevant species.

The $n \rightarrow \pi^*$ interaction present in the crystal structures of **7.7** and **7.27** has been the study of several solution-phase studies by the Wennemers Group. This interaction is of particular interest, as it has been shown to influence the *trans/cis* equilibrium ($K_{t/c}$) of Pro amides and to impact the structures of peptides and proteins.^{323,324} In light of this, Wennemers and co-workers hypothesized that such interactions may influence the catalytic performance of tripeptide-based catalysts. Accordingly, peptides with different *i*+1 Pro analogs of various ring sizes were examined for their *trans/cis* ratio in solution (Figure 128).³²⁵ NMR analysis was used to measure $K_{t/c}$, which was found to be highly correlated with enantioselectivity in the addition of aldehyde **7.11** to nitroolefin **7.12**. It is noteworthy that, upon examining different solvent mixtures, peptides **7.38**, **7.10**, and **7.39** exhibited different *trans/cis* ratios, and the catalyst that displayed the highest $K_{t/c}$ would vary depending on the medium. However, the enantioselectivity consistently displayed a linear relationship with the percentage of peptide adopting the *trans* conformation. It was confirmed that the $K_{t/c}$ of the unfunctionalized peptide is correlated with the $K_{t/c}$ of the reactive enamine intermediate **7.10-En** that is relevant to catalysis. This trend was found to be true for conjugate addition reactions involving maleimides as well.

Substituents on the pyrrolidine ring of the *i*+1 Pro have also been shown to affect the *trans/cis* ratio in peptide catalysts.³²⁶ 4*R*-Substituted pyrrolidine rings typically favor the *C γ -exo* ring pucker, in contrast to unsubstituted pyrrolidine rings, which favor the *C γ -endo* ring pucker. Accordingly, peptides with this pyrrolidine substitution adopt a β -turn conformation that lacks the stabilizing $n \rightarrow \pi^*$ interaction that is present in other peptides. Lower selectivity is observed in reactions catalyzed by these peptides, which is consistent with previous studies on *trans/cis* ratios (Figure 129, entries 2 & 3 vs. 1). In contrast, 4*S*-substituted pyrrolidine rings, which favor the *C γ -endo* ring pucker have an inverse relationship to $K_{t/c}$. It is proposed that the substituent points directly towards the cavity of the catalyst and overrides the selectivity afforded by the higher *trans/cis* ratio (entries 4–6).

Additional studies had identified that *trans/cis* ratios are influenced not only by an $n \rightarrow \pi^*$ interaction, but also by the net dipole moment of the peptide molecule (Figure 130).³²⁷ DFT calculations revealed that the Boltzmann-averaged dipole moment of model compound **7.42**, which contains a *C*-terminal dimethylamide, is significantly higher for the *cis* conformation than that of the *trans* (μ). This is in stark contrast to methyl esters **7.41**, in which both amide isomers have very similar dipole moments. As such, the variability in $K_{t/c}$ as a function of solvent polarity is much greater for amide **7.42**, wherein the *trans* conformer is greatly favored in non-polar solvents, such as chloroform and dioxane. NMR analysis of peptide **7.7**, which also contains a dialkylamide motif adjacent to the *N*-terminal Pro residue (*i.e.*, the *i*+1 Pro), in DMSO-*d*₆ and a 9:1 mixture of CDCl₃/CD₃OD revealed that a greater *trans/cis* ratio is indeed observed in the more non-polar solvent mixture. Reactions conducted in these solvents reflected this difference in the enantioselectivity of the reaction.

In order to assess the potential structures of catalytically relevant species, detailed NMR studies were conducted on peptide catalyst **7.10**, providing insight into the structure in solution, which is not apparent from previous studies analyzing crystal structures.³²⁸ Using a combination of HSQC, ROESY, TOCSY, DQF-COSY, and HMBC methods, the solution phase structure of peptide **7.10** was found to be consistent with a type I β -turn (Figure 131a).⁴⁷ Notably, several changes were observed in the NOE interactions of enamine derivative **7.10-En**, wherein some interactions were notably stronger or weaker, suggesting a relaxation of the β -turn structure (Figure 131b). When explored computationally, it was found that the lowest energy structures of both **7.10** and **7.10-En** showed significant overlap in the backbone suggesting a β -turn (Figure 131c). However, four conformations were found to exist within 2 kcal/mol of this ground state for **7.10-En**, suggesting a highly flexible structure (Figure 131d). The noted shifts in NOE interactions were in good agreement when these four structures were considered. It was proposed that upon formation of the enamine, a stabilizing H-bonding interaction with the *C*-terminal carboxylate is weakened, greatly increasing flexibility, which could help accommodate the incoming nitroolefin.

Taking these mechanistic studies into account, the Wennemers Group proposed the following catalytic cycle (Figure 132). The ground state of the catalyst primarily adopts a type I β -turn (**7.43**), which undergoes reversible condensation with an aldehyde substrate. The resulting enamine **7.44** has increased structural flexibility that may assist in accepting a nitroolefin during the rate-determining C–C bond-forming step. Nitronate intermediate **7.45** is then rapidly protonated by an appropriately positioned acidic group before releasing the product through hydrolysis of iminium ion **7.46**.

While venerable peptide coupling protocols have enabled the rapid synthesis of peptide-based catalysts,³²⁹ other strategies have emerged for the synthesis of diverse peptide scaffolds. For instance, the groups of Orru and Paixao have demonstrated that 4-component Ugi reactions can be employed to generate tripeptide catalysts similar to those explored by Wennemers and co-workers (Figure 133a).³³⁰ In several publications, Orru recognized that peptide **7.49** resembled trimeric peptides that Wennemers had previously disclosed. When employed as a catalyst in the same asymmetric addition of aldehyde **7.47** to nitroolefins **7.2**, high enantioselectivity was observed in γ -nitroaldehyde **7.48** (Figure 133b). Paixao and co-workers further utilized a 4-component Ugi reaction to generate various structurally diverse

trimeric peptides.³³¹ Upon assessing 13 different catalysts in the reaction between **7.1** and **7.2**, peptides **7.50** and **7.51** emerged as reasonably selective catalysts (Figure 133c). A conformational search of both catalysts using Monte Carlo molecular mechanics revealed that 673 conformations of **7.50** existed within 5 kcal/mol of one another. In contrast, **7.51** exhibited only 162 conformations that were within 5 kcal/mol. Computationally optimized structures of the **7.51** enamine revealed that the cyclohexyl group provides significant shielding on one face of this intermediate. Ultimately, **7.51** was found to be the more selective catalyst, providing **7.3** in up to 93% yield, 97:3 dr, and 98% ee in a series of conjugate addition reactions. In later studies, Paixao demonstrated that immobilized versions of these peptides could be easily formed by using silicon appended substrates and demonstrated the efficacy of these catalysts in flow chemistry setups.³³²

Lecouvey and co-workers explored trimeric peptide scaffolds that contain a phosphonic acid on the *C*-terminal residue as catalysts in the asymmetric conjugate addition of aldehydes **7.1** into nitroolefins **7.2** (Figure 134).³³³ Due to the multiple potential protonation states of the catalyst, it was envisioned that enamine formation could be favored without the introduction of external base to deprotonate the *N*-terminal Pro residue. Reactivity and selectivity were found to be influenced by the protonation state of the catalyst. Fully protonated peptide **7.52** was ineffective as a catalyst, while fully deprotonated **7.53** delivered full conversion in 24 h, providing **7.3** in 85:15 dr and 87:13 er. Mono deprotonated **7.54**, however, was notably more reactive and selective. Using this catalyst, full conversion was achieved within 20 h, and **7.3** was obtained in 91:9 dr and 93:7 er. These catalysts were found to be easily recyclable through aqueous extraction and could be reused up to 10 times with only a slight decrease in enantioselectivity. Intriguingly, the opposite enantiomer of the product was obtained compared to what Wennemers and co-workers observed, presumably as a function of the phosphonic *versus* the carboxylic acid functional group on the *C*-terminal residue sidechain.

Tsogoeva and co-workers had previously demonstrated that short peptides were capable of catalyzing conjugate addition reactions between enone substrates and nitroalkanes.³³⁴ Expanding upon these results, they demonstrated that dipeptide H-Pro-Phe-OH can catalyze the conjugate addition reactions of ketones **7.55** to nitroolefins **7.2** under completely aqueous conditions (Figure 135).³³⁵ Judicious choice of base was required in order to achieve high reactivity, with NaOH ultimately emerging as the optimal choice. It was proposed that H-bonding between the Pro carbonyl and water increases the acidity of the corresponding amide proton enough for it to act as a H-bond donor to the nitroolefin.

In light of the contributions to the field of nitroolefin conjugate additions by the Wennemers Group, Piarulli and co-workers studied whether diketopiperazines could function in a similar capacity in the reaction of aldehyde **7.11** with nitroolefin **7.12** (Figure 136).³³⁶ A series of diastereomeric diketopiperazines **7.57–7.60** were synthesized in order to explore the stereochemical relationships within the catalyst. Intriguingly, the catalytic behavior of **7.57** was matched with **7.59**, both of which have an appended D-Pro residue, whereas those appended with L-Pro demonstrated lower selectivity. This trend was found to be true across multiple substrates.

7.2. Conjugate Additions of Nucleophiles to Unsaturated Aldehydes & Ketones

Substantial contributions have been made by Kudo and co-workers in the area of peptide-catalyzed conjugate additions by exploiting many of the same design strategies featured in their studies of aqueous oxidations and transfer hydrogenations (see Sections 2 & 3). Catalysts explored for these transformations typically involved: (1) a β -turn region, which provides a robust chiral environment suitable for asymmetric catalysis; (2) an α -helical region, which provides a hydrophobic pocket in aqueous media and has been shown to greatly enhance reaction rates; and (3) a solid support resin. These strategies were found to be highly transferable and effective in accelerating the Friedel–Crafts-type alkylations of indoles under fully aqueous conditions (Figure 137).³³⁷ In fact, reactions conducted in the absence of water, with THF as the sole solvent, failed to provide any product. The authors proposed that rate acceleration is achieved by enhanced hydrophobic interactions between the peptide and its substrates as a consequence of the aqueous media. Fine-tuning of the β -turn region of **7.64** revealed that the stereocenters of the two Trp residues had a large impact on enantioselectivity in the reaction between enal **7.61** and indole **7.62**, and that an L-Trp-L-Trp stereochemical array was required for optimal enantioselectivity (Figure 137a, entries 1–3). Using catalyst **7.64a**, alkylated indole **7.63** was obtained in 85% yield and 88% ee (entry 1), while ee values <45% were obtained with D-Trp-containing peptides **7.64b** and **7.64c**. Furthermore, it was observed that a poly(Leu) linker sequence had a high propensity to form an α -helical structure. Consistent with their hypothesis, the hydrophobic pocket formed in this region was required for both high reactivity and enantioselectivity (entries 4–7). Upon further examination, peptide **7.64f**, which contains a related Leu-Leu-Aib triad that promotes a 3_{10} -helix rather than an α -helix further enhances selectivity, provided **7.63** in 92% conversion and 91% ee (entry 7).³³⁸ Techniques such as IR, ROESY, and CD confirmed the helicity of such structures in aqueous media. Taking advantage of the compatibility of catalyst **7.64f** with water, a one-pot sequential alkylation, oxidation sequence was realized, wherein the oxidation was facilitated by the oxidizing enzyme, laccase.³³⁹ This synthetic sequence was enabled by the viability of peptides in aqueous media.

Catalyst **7.64f** also proved competent in the asymmetric conjugate addition of nitromethane (**7.67**) into β,β -disubstituted α,β -unsaturated aldehydes **7.66**, although low yields were observed in reactions conducted in H₂O (Figure 138a, entry 1).³⁴⁰ Upon examining related solvent mixtures (entries 2–5), it was found that mixtures of methanol and water were optimal (entry 5) relative to reactions conducted in methanol alone (entry 4). This suggests that hydrophobic interactions were crucial for the efficacy of this transformation, as well. Under these conditions, **7.64f** delivered γ -nitroaldehyde **7.68a** in 47% yield and 91% ee (entry 5). The hydrophobic helical region was shown to affect both conversion and enantioselectivity (entry 5 vs. 6), and reactivity could be enhanced by using α -helical, poly(Leu)-containing peptide **7.69**, which provided **7.68a** in 54% yield and 96% ee. This result stands in contrast to the authors' previous work on the Friedel–Crafts reaction, wherein the 3_{10} -helical linkers were found to be superior catalysts. Under the optimized conditions, a variety of substrates containing all-carbon quaternary centers could be synthesized with high levels of enantioselectivity (Figure 138b).

While peptides such as **7.64f** and **7.69** are effective catalysts for conjugate additions into *enals*, which easily form iminium ions upon condensation with secondary amines, Kudo and co-workers anticipated that catalysts with primary amine-containing catalytic residues would be better suited for *enone* substrates (Figure 139).²⁸ A series of resin-bound catalysts containing various unprotected *N*-terminal residues were assessed in the addition of nitromethane (**7.67**) into enones **7.70** (entries 1–5). Ultimately, peptide **7.75**, which contains an *N*-terminal diad of Trp residues and a 3_{10} -helix-promoting linker region, was identified as the lead catalyst, as it afforded product **7.71** in 93% yield and 91% ee (entry 4). Notably, peptide **7.76**, which contains an α -helical linker, was ineffective as a catalyst (entry 5).

Similar to the enantioselective reduction of $\alpha,\beta,\gamma,\delta$ -unsaturated aldehydes *via* transfer hydrogenation previously reported (Section 3.1),¹²⁰ the Kudo Group demonstrated that selectivity could also be imparted in the related conjugate addition of 2-naphthalenethiol (**7.78**) into $\alpha,\beta,\gamma,\delta$ -unsaturated aldehydes **7.77** (Figure 140).³⁴¹ When imidazolidinone catalyst **7.80** was employed, product **7.79**, which is obtained from two sequential 1,6- and 1,4-conjugate additions, was formed as a nearly racemic mixture for each possible diastereomer. The authors examined peptide **7.64f** due to its successful application in previous conjugate addition reactions (*vide supra*). Indeed, when **7.64f** was employed, the ratio of the three possible products greatly favors **7.79c**, with modest enantioselectivity detected for both possible diastereomers. The identity of the counter ion was found to greatly influence conversion in this reaction. Moreover, resin-bound **7.64f** could be recycled three times with essentially no decrease in catalytic performance.

During their investigations into the kinetic resolution of metallocenes **7.81** *via* transfer hydrogenation (Section 3.1), Kudo and co-workers also explored conjugate additions of nitromethane (Figure 141).¹²² Using peptide **7.83**—the same catalyst that was used to catalyze the transfer hydrogenation of **7.81**—a high k_{rel} was observed, providing the conjugate addition product (R_p)-**7.82** in >99:1 dr and 95% ee (Figure 141a). However, this catalyst proved ill-suited in catalyzing the related conjugate addition of nitromethane into [2.2] paracyclophane derivatives **7.84** (Figure 141b). The authors reasoned that a less sterically hindered catalyst lacking a β -turn-region and containing a primary amine as opposed to a secondary amine might be more suitable in this transformation, as the catalyst must engage a relatively hindered ketone rather than an aldehyde. After screening a variety of *N*-terminal residues, it was found that residues with linear sidechains generally performed well, such as Hse(Me). Additionally, the 3_{10} -helix-inducing triad of Leu-Leu-Aib was crucial for promoting reactivity. Ultimately, the desired kinetic resolution was achieved with a k_{rel} of 39 using peptide **7.86**, which delivered (S_p,R)-**7.85** in 41% yield and 90% ee; the starting material was also recovered in 53% yield and 63% ee. It was proposed that H-bonding between the amide backbone and the nucleophile helps to direct reactivity.

In addition to reactions in aqueous media, several transformations have also been reported in completely organic solvents, such as the conjugate addition of vinyl boronic acids **7.88** into α,β -unsaturated aldehydes **7.87** (Figure 142).³⁴² In analogy to previous studies, the presence of a helical motif linking the solid support to the catalytically active Pro residue was found to be important for reactivity and selectivity compared to simple monomers and dimers (entries 1 & 2 *vs.* 3 & 4). It was found that helices comprised of Leu and Ala residues were

most effective in this particular transformation (entries 3 & 4). It is noteworthy that Leu and Ala are the amino acid monomers with the highest helical propensity, and that sequences containing other residues performed notably worse in the conjugate addition reaction. Peptide **7.91** delivered hemiacetal **7.90** in 99% conversion and 91% ee. NMR titration experiments, as well as IR studies, confirmed the helical conformation of peptide **7.91** in solution.

Although diverse peptide libraries can be rapidly synthesized on solid support *via* split and pool methods, analysis of hundreds of reactions can become rate-limiting for project progress. Our Group and the Wennemers Groups had previously addressed this issue by using strategies involving (1) fluorescent reporter molecules attached to substrates or (2) reactions in which the substrate is covalently bound to the peptide catalyst.^{343,344} However, these strategies were incompatible with the conjugate addition reactions studied by the Kudo Group, and a new approach was required in order to accelerate the screening process. Recognizing that the fundamental steps of Pro-catalyzed conjugate additions involve the formation of an iminium ion, Kudo and co-workers reasoned that reduction of this intermediate would produce a resin bound conjugate addition product (Figure 143a).³⁴⁵ Using dye-modified malonate **7.92** as conjugate addition substrate, this strategy could be used to covalently append a dye molecule to a catalytically active peptide. Upon washing away excess dye, beads that remained colored would identify peptides with high reactivity, and presumably high enantioselectivity, which would help to prioritize reactions for sequencing by mass spectroscopic techniques. Initial screening efforts focused on introducing diversity at the fourth and fifth positions in order to keep the helical and β -turn regions intact (Figure 143b). Both Trp-Trp and Phe-His motifs were found with a high frequency using this approach. It was determined that the conjugate addition of a His sidechain at the fifth position was highly reversible, and could contribute to an increase in the ratio of the enal taken up by the resin (Figure 143c). Catalysts containing this His residue typically demonstrated higher rates of reactivity in addition to increased enantioselectivity. A more in-depth screen that included the helical region of identified peptides **7.101** and **7.102**, which despite sharing a similar *N*-terminal residue, afford opposite enantiomers of the product (Figure 143d).³⁴⁶ Both peptides contain a His residue at the seventh residue. These new peptides were found to be even more effective in entrapping substrate onto the resin, possibly *via* the mechanism described in Figure 143c.

8. Other C–C Bond-Forming Reactions

Reactions that form C–C bonds are at the very heart of synthetic and biological chemistry, and a plethora of methods have been developed to forge these highly important bonds with control over stereochemical outcomes. Asymmetric C–C bond-forming reactions permeate multiple sections of this Review. Thus far, classical additions of *C*-centered nucleophiles into carbonyl compounds have been discussed (Section 5), as well as aldol (Section 6) and Michael addition reactions (Section 7). Moreover, more modern photochemical and transition metal-catalyzed methods for C–C bond formation will be treated in subsequent sections (Sections 9 & 11, respectively). This Section is dedicated to the other asymmetric, peptide-catalyzed C–C bond-forming reactions that do not easily fit into the other categories, such as cyclopropanation (Section 8.1), Morita–Baylis–Hillman (Section 8.2), and Rauhut–

Currier reactions (Section 8.3). These are also very powerful transformations that have been widely utilized in organic synthesis through the years. Recent examples of peptide-catalyzed asymmetric variants of these important C–C bond-forming reactions are discussed below with a particular emphasis on mechanistic study, which has received significant attention over the past decade.

8.1. Cyclopropanation

Despite being the most strained cycloalkane ring-system, cyclopropanes are widely found in natural products and pharmaceuticals, and they also serve as useful synthetic intermediates for subsequent transformations.^{347–350} Thus, the development of stereoselective methods for the construction of cyclopropanes is of particular interest and value to the field. One of the most widely used methods for constructing three-membered carbocycles is the Simmons–Smith cyclopropanation, in which a Zn species inserts into diiodomethane to form a reactive organozinc carbenoid capable of converting alkenes into cyclopropanes.^{351,352} Asymmetric variants of the Simmons–Smith reaction that utilize chiral auxiliaries, reagents, or catalysts typically rely on the presence of a directing group in the alkene substrate. Coordination of a heteroatom in the alkene substrate to the Zn reagent not only enhances the reaction rate, but also improves stereocontrol. Therefore, prior to 1998, there were only two reports of an enantioselective cyclopropanation of *unfunctionalized* olefins, achieving <4% ee.^{353,354} However, using a chiral alcohol to coordinate to the organozinc species, Shi and co-workers were able to cyclopropanate an unfunctionalized olefin with 51% ee.³⁵⁵

This method was later improved using dipeptide **8.3a** to mediate the asymmetric Simmons–Smith type cyclopropanation of styrene **8.1** (Figure 144).³⁵⁶ By adding ethyl methoxyacetate (EMA) as an achiral additive, this reaction was rendered catalytic, decreasing the loading of **8.3a** from 1.25 equivalents to 25 mol%.³⁵⁷ Under these conditions **8.3a** delivered the cyclopropane **8.2** in 87% yield and 89% ee. In a subsequent study, Shi and co-workers explored the mechanism of this peptide-catalyzed transformation with **8.1**.³⁵⁸ In contrast to the optimized catalyst **8.3a**, no conversion was observed using *N*-methylated dipeptide **8.3b**. This suggested that the free N–H of **8.3a** is crucial for reactivity in this cyclopropanation reaction. The authors probed the mechanism further by subjecting peptide **8.3a** to the cyclopropanation reaction conditions sequentially and characterizing the intermediates (Figure 145). Initial treatment of **8.3a** with diethylzinc evolves ethane gas and generates intermediate **I**, in which Zn coordinates to both the amide nitrogen and the carbonyl oxygen of the Val residue. This intermediate can then react with diiodomethane at lower temperatures to afford carbenoid intermediate **II**. The structures of these intermediates were assigned using NMR data coupled with an X-ray crystal structure of a related dipeptide.

The cyclopropanation of **8.1** was then tested using peptide-zinc complex **II**, which had been synthesized according to Figure 145. After 24 h, complex **II** had only delivered 7% conversion of **8.1** into **8.2**, although with 83% ee. Upon adding one equivalent of Zn(CH₂I)₂ to **II**, conversion into **8.2** was fully restored to 89%, and the ee increased to 90%. This result suggests that Zn(CH₂I)₂ is necessary for catalyst turnover. One hypothesis for the role of Zn(CH₂I)₂ is that it may decompose to ZnI₂, which has been demonstrated to facilitate cyclopropanation in other systems.^{359–361}

Taking all of these mechanistic results together, the authors proposed two possible catalytic cycles (Figure 146). Once intermediate **II** is generated by deprotonation with diethylzinc and subsequent halogen exchange with diiodomethane, it can be activated by XZnI to form either complex **III** or **IV**. If intermediate **III** is produced (blue cycle), this species can cyclopropanate **8.1** directly to form olefin **8.2** and intermediate **IV**. Transmetalation with $\text{Zn}(\text{CH}_2\text{I}_2)$ regenerates **III**, closing the catalytic cycle. Alternatively, intermediate **IV** can act as a chiral Lewis acid to activate XZnCH_2I , forming **V** (red cycle). This species can then cyclopropanate **8.1** to regenerate intermediate **IV**. Overall, this study sheds light on the interactions between dipeptides and organozinc reagents that ultimately give rise to a highly enantioselective cyclopropanation reaction.

Following the earlier works of MacMillan,^{362,363} Arvidsson,³⁶⁴ and Ye,³⁶⁵ Kudo and coworkers sought to use resin-supported, *N*-terminal Pro-containing peptides to catalyze the asymmetric cyclopropanation of α,β -unsaturated aldehydes **8.4** with sulfur ylides (Figure 147).³⁶⁶ This strategy invokes an iminium catalytic activation mechanism to produce 1,2,3-trisubstituted cyclopropanes bearing three contiguous stereogenic centers. Cinnamaldehyde **8.4a** was used as a model substrate for screening. Although chloroform was initially tested as the reaction medium, it was found that the reaction rate could be significantly accelerated (3 vs. 24 h) using aqueous conditions ($\text{THF}/\text{H}_2\text{O}$, 2:1). Furthermore, this solvent system enabled *in situ* generation of the requisite sulfur ylide using sodium bicarbonate as the base rather than pre-forming the ylide, which tends to be unstable.

The authors then evaluated several resin-supported peptides **8.8** as secondary amine catalysts for the cyclopropanation of **8.4a** with an acetophenone-derived sulfonium ion (Figure 147). These peptides were designed to include both a β -turn motif, induced by incorporation of a central D-Pro-Aib sequence, and a helical section linker. The authors proposed that the β -turn motif is crucial for controlling enantioselectivity, while the hydrophobic helical portion could stabilize the peptide in the aqueous reaction medium.³³⁸ The *i*-3 and *i*-4 residues, which were hypothesized to be important for noncovalent interactions with aldehyde **8.4**, were first examined pairwise. It was found that residues containing a hydroxyl group, such as Ser and Hse, gave promising diastereoselectivities (entries 1 & 2). When the *i*-4 residue was replaced with Trp, both the diastereo- and enantioselectivity decreased significantly (entry 3). However, incorporation of Trp at *i*-3 provided a boost in selectivity (entry 4). With Trp at *i*-3, the position of the oxygen atom and the length of the chain at the *i*-4 position was then assessed (entries 4–7). It was found that Ser(Me)-containing **8.8e** gave the best overall stereoselectivity, providing 92% conversion to **8.5a** in 93:5:2 dr and 99% ee (entry 5). While the role of the sidechain ether functionality has not been fully elucidated, the authors propose an attractive interaction between the ether O-atom and the sulfonium salt, which may increase the selectivity for three-membered ring formation *via* transition state stabilization.

With peptide **8.8e** in hand, various α,β -unsaturated aldehydes **8.4** were investigated in this reaction (Figure 148, entries 1–5). Both electron-rich and electron-poor α,β -unsaturated aryl aldehydes consistently afforded **8.5** in high yields (>84%), diastereoselectivities (>94:3:3), and enantioselectivities (99%). The reusability of the resin-supported catalyst was also examined with enal **8.4e**. No significant decrease in catalytic activity was observed up

through the fifth reuse of the catalyst, in which yield decreased slightly from 87% to 83%, yet enantioselectivity of **8.5e** remained constant at 99% ee (entry 5).

8.2. Morita–Baylis–Hillman Reaction

Since its discovery over 50 years ago, the asymmetric Morita–Baylis–Hillman (MBH) reaction has become a useful method for forging C–C bonds with control over the newly formed alcohol- or amine-bearing stereogenic center.³⁶⁷ Broadly defined, MBH reactions operate under Lewis base catalytic mechanisms, often employing tertiary amine- or phosphine-based catalysts to mediate the coupling of an α,β -unsaturated carbonyl compound with an aldehyde or imine. The nucleophilic catalysts are thought to undergo 1,4-addition with the α,β -unsaturated substrate, activating it as a transient enolate equivalent for addition into the aldehyde or imine electrophile. Proton transfer and conjugate elimination then restores the catalyst to its active form.

When considering the reaction between allenates **8.9** and imines **8.10**, two possible reaction pathways lead to two different types of products (Figure 149). Using a chiral phosphine catalyst, an asymmetric formal [3+2] cycloaddition can occur between **8.9** and **8.10** to generate dihydropyrroles **8.13**.^{368–370} Alternatively, **8.9** and **8.10** can react in a classical aza-MBH fashion to yield allenates **8.11**. Employing a chiral phosphine catalyst, Lu and co-workers had previously indicated the imine *N*-substituent on **8.10** could influence the product distribution, with tosylates favoring **8.13** and carbamates preferentially proceeding through the MBH reaction.³⁷¹ When coupling allenates **8.9** with enones, our group observed that the product distribution could be affected by catalyst type.³⁷² In this system, phosphines preferred to catalyze the formal cycloaddition, while amines tended to favor the aza-MBH reaction. Therefore, our group hypothesized that peptidic amine catalysts could offer complementary reactivity to the phosphine catalysts previously employed for the coupling of **8.9** and **8.10**.³⁷³ This strategy would provide access to enantioenriched allenic amines **8.11**, representing the first enantioselective aza-MBH reaction of its class.

Reaction optimization included both tertiary amine and phosphine catalysts to mediate the coupling of allenate **8.9a** with imine **8.10a** (Figure 150).³⁷³ Using triphenyl phosphine led to 57% isolated yield of the aza-MBH product **8.11aa** (entry 1). However, *N*-heterocyclic catalysts, such as DMAP and protected Pmh monomer only afforded trace product (entries 2 & 3). Pyridine and the protected 3-pyridylalanine (3-Pal) monomer, however, proved to be quite effective catalysts for this transformation, forming **8.11aa** in 75% and 71% yield, respectively (entries 4 & 5).

With promising levels of conversion using Pal, a library of Pal-embedded peptides designed to adopt β -turn secondary structures was synthesized, as this motif had proven to be highly effective in peptide-catalyzed asymmetric transformations previously (entries 6–10). The library was biased by strategic incorporation of a central Pro-Aib sequence motif, which is known to induce β -turn conformations in solution.²²³ While peptide **8.12a**, which contains a Pro residue at the *i*+1 position, gave detectable enantioenrichment in **8.11aa** (56:44 er, entry 6), D-Pro-containing **8.12b** provided a significant increase in enantioselectivity to 78:22 er (entry 7). Using peptide **8.12b**, the *N*-protecting group of imines **8.10** was then evaluated.

Exchanging ethoxycarbonyl group of **8.10a** for a benzyl group (**8.10b**) fully ablated reactivity (entry 8). However, *N*-benzoylated imine **8.10c** proved to be more reactive and selective than carbamate **8.10a**, affording **8.11ac** in 94% yield and 84:16 er (entry 9). Exchanging the *C*-terminal protecting group of the peptide from a methyl ester in **8.12b** to a dimethyl amide in **8.12c** resulted in a further increase in er to 92:8 (entry 10).

With catalyst **8.12c** in hand, the substrate scope was examined for this aza-MBH reaction (Figure 151). With benzyl allenolate **8.9a**, aryl imines with electron donating substituents at both the *ortho*- (**8.10d**) and *para*- (**8.10e**) positions were well tolerated (entries 1 & 2). Moreover, **8.11ae** could be recrystallized up to 98.5:1.5 er without significant loss in yield (entry 2). Imines with halide substitution on the arene, such as **8.10f**, were marginally less effective in terms of yield and enantioselectivity (entry 3). Once again, recrystallization could be used to increase enantioselectivity of **8.11af** to 96.5:3.5 er. Allenolate **8.9b** was also a highly effective coupling partner with imine **8.10c**, with optimal yields and selectivity obtained at 0 °C (entries 4 vs. 5). Under these enhanced reaction conditions, a more expansive substrate scope was examined, (entries 5–9). Once again, electron rich-aryl imines **8.10e** and **8.10g** were processed with high enantioselectivities of 92.5:7.5 er (entries 6 & 7). Naphthyl-substituted imine **8.10h** was also coupled with **8.9b** to deliver **8.11bh** in 66% yield with 92:8 er (entry 8). Aliphatic imines, such as **8.10i**, were also tolerated in this reaction, albeit with reduced yield and enantioselectivity (42% yield, 80.5:19.5 er; entry 9).

In a subsequent report, our group performed an in-depth mechanistic study of this peptide-catalyzed aza-MBH reaction using various kinetics experiments.³⁷⁴ A series of initial rate studies revealed that the reaction between **8.9a** and **8.10c** is first order in both allenolate and peptide **8.12c** and zero order with respect to the imine. Compared to other MBH and aza-MBH reactions, the kinetic order of the imine **8.10c** in this peptide-catalyzed reaction is unusual.³⁶⁷ This may be attributed to the possibility that the rates were measured at catalyst saturation in imine, though that concentration would have to be lower than NMR titration experiments suggested. We then sought to identify the rate determining step (RDS). Comparing allenolate **8.9a** to its α -deuterated variant, a small KIE of 1.08 was measured, suggesting that proton transfer is likely not rate-determining, also in contrast to previously studied aza-MB reactions.³⁶⁷ Since the kinetic data indicated that imine **8.10c** is not involved in the RDS, catalyst addition to allenolate **8.9a** was proposed to be rate determining in this case. To further establish if this mechanism is unique to the peptide-catalyzed reaction, analogous kinetics experiments were performed using pyridine as the catalyst rather than **8.12c**. In this case, a nearly identical allenolate KIE was observed ($k_H/k_D = 1.03$). However, the pyridine-catalyzed reaction was significantly slower than the **8.12c**-catalyzed variant, suggesting that the peptide is better suited to activate the allenolate for coupling with the imine. Based on these data, a mechanism for this transformation was proposed (Figure 152). First, the Lewis basic pyridine moiety of the peptide adds into allenolate **8.9** at the β -position to form zwitterionic intermediate **I** in what may be the RDS. Intermediate **I** then reacts with imine **8.10** to yield intermediate **II** through the formation of a C–C bond. Proton transfer gives enolate intermediate **III**, which undergoes elimination *via* an E1cB mechanism to release the peptide-based catalyst and deliver product **8.11**.

In 2014, our group extended this Pal-containing peptide-catalyzed aza-MBH reaction to the coupling of allenates **8.14** with *N*-acylimines **8.10** to deliver products **8.15** that possess two different stereochemical elements—a stereogenic center and an axis of chirality (Figure 153).³⁷⁵ Adding to both the challenge and intrigue of this transformation, the peptide-based catalyst must be able to exert control over both stereogenic elements in order to achieve a highly selective process. Initially, the previously identified catalyst **8.12c** and conditions were tested in the reaction of chiral, racemic allenate **8.14a**.³⁷³ Under these conditions, **8.15ac** was produced in 67% yield, with modest diastereo- and enantioselectivities of 1:1.2 dr and 38.5:61.5 er (entry 1). An additional site for H-bonding between allene **8.14** and the peptide was added in an effort to enhance selectivity. Indeed, using anilide-substituted allenate **8.14b**, 85% of **8.15bc** was isolated in just 1 h with an improved dr of 1:2.7 (entry 2). Replacing the amide of **8.14b** with an ester, as in **8.14c**, eroded the dr to 1:1.2, further supporting the importance of an H-bond donor at this position (entry 3).

Using allene **8.14b** with imine **8.10c**, analogs of peptide **8.12c** were examined (Figure 153, entries 4–6). A matched and mismatched case of stereochemistry at the *i*+1 and *i*+3 positions was observed. With L-Pro at *i*+1 and D-Phe at *i*+3 (**8.12d**), diastereoselectivity decreased even further to 1:1.1 dr (entry 4). However, employing peptide **8.12e**, which contains D-configured residues at both *i*+1 and *i*+3, **8.15bc** was obtained in 1:3.0 dr and 22:78 er (entry 5). Exchange of the *C*-terminal protecting group of the peptide from a methyl ester to a dimethylamide in **8.12f** provided a slight boost in dr to 1:3.4 with the same level of enantioselectivity (entry 6). Having achieved substantial dr and er in this transformation using peptide **8.12f**, the effects of altering the allenic ester substituent of **8.14** were then investigated. Exchange of the phenyl ester for aliphatic groups improved dr, with the bulkier isopropyl ester **8.14e** giving the highest dr of 1:6.2 (entries 7 & 8). With respect to the imine, sterically bulkier carbamate **8.10j** further improved the dr to 1:12 (entry 9).

Several additional peptides were examined in the aza-MBH reaction between **8.14e** and **8.10j** in pursuit of higher enantioselectivity values. Ultimately, tetrapeptide **8.12g**, bearing a *trans*-4-hydroxy-L-proline (Hyp) residue at *i*+1 and 2-aminoindane-2-carboxylic acid (Aic) at *i*+2, delivered **8.15ej** in 92% yield, 1:16 dr, and 88:12 er (Figure 154, entry 1). Electron-donating substituents on the imine aryl ring had a negligible effect on selectivity, while electron-deficient aryl imine **8.10k** provided marginally decreased selectivities of 1:10 dr and 85.5:14.5 er (entry 2). Tetrasubstituted allene **8.15ek** could be recrystallized up to 98:2 er. This aza-MBH reaction was reasonably sensitive to substitution at the γ -position of allene **8.14**, as **8.14f** required a longer reaction time to isolate **8.15fj** in 70% yield with reduced dr of 1:11 and er of 71.5:28.5 (entry 3). The reaction between allenic thioester **8.14g** and Cbz-protected imine **8.10l** was also examined, producing **8.15gl** in 90% yield, 1:42 dr, and 94:6 er (entry 4). Increased steric bulk at the γ -position of thioester **8.13h** also resulted in a significant loss of both reactivity and selectivity, producing **8.15hm** in 58% yield with 1:5.8 dr and 75.5:24.5 er (entry 5).

Several kinetics experiments were performed to elucidate the mechanism of this interesting aza-MBH variant.³⁷⁵ We first sought to define the role of the peptide as either a Brønsted or Lewis base catalyst. Hydrogen/deuterium-exchange studies were performed with a

representative allenolate using D₂O or MeOD-*d*₄ as the deuterium source in the presence of various bases. The rates of H/D-exchange with inorganic bases, such as potassium carbonate and potassium hydroxide, under phase-transfer conditions were orders of magnitude greater than with any tertiary amine bases examined. Of the amine bases, the rate of exchange with peptide **8.12g** was significantly faster than pyridine, quinuclidine, and triethylamine, all of which are expected to be more basic than **8.12g** from a *pK_a* standpoint. These data suggest that different bases may operate *via* alternate catalytic mechanisms. Additional kinetics studies were conducted to determine the RDS of this peptide-catalyzed transformation. The reaction was found to be first order in both allenolate **8.14e** and peptide **8.12g**. The rate dependence on imine **8.10j** was very small at synthetically relevant concentrations and could be interpreted as close to zero order, consistent with imine saturation. Again, no primary KIE was observed for the proton transfer step. These results mirror those obtained in our previous study (Figure 152),³⁷⁴ which support catalyst addition to the allenolate as the RDS.

These studies culminated in the proposed mechanism depicted in Figure 155, in which peptide **8.12g** acts as a Lewis base catalyst. First, **8.12g** adds into (±)-**8.14e** to form zwitterionic intermediate **I**, which may exist in several isomeric forms (*e.g.*, **IA** & **IB**). Interconversion of these intermediates effectively ablates the axial chirality of allenolate **8.14e**. While this step may be rate-determining, it is most likely not stereodetermining. Imine **8.10j** can then react with intermediate **I** to form intermediate **II**, thus establishing the α-amine stereocenter. At least four isomers of intermediate **II** (**A–D**) may exist, with catalyst control over the distribution of these species. Subsequent α-proton transfer followed by catalyst elimination defines the chiral axis of **8.15ej** and determines the dr.

NMR experiments were performed in order to shed light on the mode of activation in this peptide-catalyzed reaction. Spectra recorded of peptide **8.12g** alone show multiple signatures of a β-turn secondary structure. However, addition of 1 equivalent of allenolate **8.14e** under otherwise identical conditions produced several changes in the ¹H-NMR resonances of **8.12g**, consistent with the formation of a ground state complex. Taking these data into consideration, a potential binding model was constructed (Figure 156). In intermediate **I**, the peptide (gray) is proposed to maintain a β-turn secondary structure while H-bonding to the N–H of allene **8.14e** through the C-terminal carbonyl. Allenes lacking this N–H generally resulted in low selectivity. As such, we believe this moiety is crucial for effective catalyst–substrate docking and orientation. The *i*-2 N–H of the peptide may also form an H-bond with *N*-acylimine **8.10j**, facilitating stereoselective C–C bond formation.

8.3. Rauhut–Currier Reactions

Related to the MBH reaction, the Rauhut–Currier (RC) reaction—also termed the vinylogous MBH—involves the coupling of two α,β-unsaturated carbonyl compounds under Lewis base catalysis to deliver dicarbonyl products through the formation of a C–C bond between the α- and β-positions of the Michael acceptor substrates. While it was first disclosed in 1963, it was not until 2007 that an RC reaction was rendered asymmetric.^{376,377}

Though Cys is an exceedingly common nucleophilic catalyst for biochemical reactions *in vivo* owing to the nucleophilicity of the sidechain thiol, this proteinogenic residue had not

yet been utilized in small molecule Lewis base catalysis for synthetically relevant transformations. In 2007, our group reported the first enantioselective RC reaction that was enabled by Cys catalysis (Figure 157a).^{378,379} We chose to investigate this process in the context of the cycloisomerization of bis(enone) **8.16** to carbocycle **8.17**, and while Cys-containing peptides were initially targeted, it was found that protected Cys monomer **8.18** was quite reactive and selective on its own. Following careful optimization of the reaction parameters (*e.g.*, base, solvent, temperature, & additives), stoichiometric **8.18** was able to deliver **8.17** in 70% yield and 95% ee using potassium *tert*-butoxide as the base in a solvent mixture of water and acetonitrile at –40 °C. Using 20 mol% of **8.18**, the cycloisomerization of **8.16** proceeded in 75% yield and 92% ee, but decreasing the loading further led to a steep decline in the reaction yields. Several additional bis(enone) substrates were examined, affording carbocyclic products in 54–73% yield and 67–95% ee at 100 mol% loading of **8.18**.

Following reaction optimization, mechanistic aspects of this Cys-catalyzed transformation were explored in order to shed light on the nature of asymmetric induction. To frame these studies, a plausible catalytic cycle was proposed (Figure 158). The Cys catalyst **8.18** is first deprotonated to generate thiolate **I**, which reversibly adds into **8.16** to deliver intermediate **II**. This covalent catalyst–substrate adduct subsequently undergoes an intramolecular Michael addition to afford **III**. Irreversible proton transfer and subsequent catalyst elimination yields **8.17** and regenerates active thiolate **I**. Two observations informed this mechanistic proposal. First, when 18-crown-6 was included in the reaction, the reaction was very sluggish and cyclic enone **8.17** was not the major product, but rather a deconjugated isomer of **8.17** predominated. This suggested that potassium ion was important in the selective reaction pathway. Second, when the reaction was run to low conversion, **8.18** delivered **8.17** in 29% yield and 95% ee, but the remainder of the mass balance consisted of five diastereomers of the protonated form of intermediate **III**. When this covalent complex was oxidized to the sulfone and eliminated under irreversible conditions, **8.17** was obtained in only 40% ee. This suggested that the proton transfer and catalyst elimination steps are both rate- and stereodetermining. Based on these data, a stereochemical model was proposed (Figure 157b). Important for achieving high levels of enantioselectivity could be a stabilizing potassium ion chelate between the carbonyl of the *N*-acyl protecting group of **8.18** and the enolate of intermediate **III**.

Houk and co-workers then probed the reaction mechanism further using DFT calculations.³⁸⁰ The computational data supported that deprotonation/thiolate elimination is rate determining, and it proceeds through an E1cB mechanism. This process is comprised of two steps: (1) α -deprotonation and (2) catalyst extrusion to form **8.17** and regenerate thiolate **I** (Figure 158). Since catalyst elimination can only occur when the Cys moiety is in an axial orientation, the number of reasonable stereoisomers of **III** was reduced from eight to four. Regardless of the stereoisomer, the deprotonation step was found to have a higher activation barrier than the subsequent catalyst elimination step, consistent with an E1cB mechanism. During reaction optimization, it became apparent that the catalyst was sensitive to the equivalents of water added and the nature of the base employed. Therefore, the effects of the counterion and water on this E1cB process were studied computationally.

Transition states with zero, one, or two water molecules and either potassium, sodium, or no counteranion were optimized. A synergistic effect between the potassium counterion and the presence of water was identified, and the lowest energy transition states for the α -deprotonation step were obtained when two water molecules and one potassium cation were included (Figure 159); one water was proposed to stabilize the hydroxide anion that deprotonates **III** at the α -position, and the other could interact with the enolate. The potassium cation was found to orient the hydroxide anion proximally to the site of deprotonation. **TS II**, which leads to the experimentally observed (*S*)-enantiomer of **8.17**, was favored by about 0.8 kcal/mol (79.5:20.5 er). Experimentally, the addition of one equivalent of water at room temperature resulted in 71:29 er, and three equivalents led to 78.5:21.5, quite similar to the computed energy difference.³⁷⁹ Houk and co-workers propose that **TS II** may be favored due to the pre-organization of the potassium cation and the hydroxide anion and the more favorable, planar orientation of cysteine.

The enantioselective, cysteine-catalyzed RC reaction was also applied in the asymmetric total synthesis of Sch-642305 (**8.21**, Figure 160),³⁸¹ which has been shown to exhibit promising anti-HIV activity.³⁸² As noted previously, Cys residues within enzymes are known to catalyze a number of biological reactions, but an enzymatic, cysteine-mediated RC reaction had not yet been identified. However, we wondered if a cysteine-dependent enzyme might be capable of mediating the ring contraction of **8.19** to **8.20 en route** to **8.21**. Thus, we proposed a Cys-catalyzed ring contraction process as a quasi-biomimetic strategy to rapidly access natural product **8.21**.

Macrocycle **8.19** was synthesized in order to study the key Cys-mediated RC reaction (Figure 160). Tributyl phosphine was initially employed as a catalyst, affording **8.20** in 80% yield and >30:1 dr. This implied that the substrate may indeed govern selectivity in this transformation. Reaction optimization with Cys **8.18** culminated in the delivery of **8.20** in 66% yield. Under the same conditions, yet with *ent*-**8.18** as the catalyst, the desired product was not detected. These results imply that a matched/mismatched situation exists between **8.19** and catalyst **8.18**. Moreover, when achiral isobutyl thiol was used as a putative catalyst, the RC reaction product **8.20** was not obtained. Instead, a mixture of thiol conjugate addition products was observed, suggesting that **8.18** is uniquely apt as an RC catalyst in this context.

With compound **8.20** in hand, natural product **8.21** could be accessed in 21% yield over five steps. Additionally, **8.20** could be funneled to *epi*-**8.21** in 43% yield over 3 steps. These compounds, along with other structural analogs, were tested against HIV-1 in MT-2 human T-cells. Notably, natural product **8.21** exhibited significantly higher activity (IC_{50} = 0.75 μ M) than the four other analogs tested.

The stereochemical dependence of this RC reaction stimulated an experiment to determine whether **8.20** could be produced *via catalyst*- rather than *substrate*-control. Thus, macrocycle **8.23**, lacking any stereogenic centers, was tested in this RC reaction with catalyst **8.18** (Figure 161). After 24 h with 7.5 equivalents of exogenous base, **8.24** was produced in 25% yield and 82.5:17.5 er. Studies aimed at further improving these results are currently ongoing.

9. Photochemical Radical Reactions

Photochemical reactions often involve high-energy free radical intermediates, which are difficult to control using catalytic asymmetric approaches.^{383,384} While many advances have been made on this front, peptide catalysis remained largely unexplored. This may have been due to perceived challenges associated with their conformational flexibility, which might amplify the already daunting task of asymmetric induction with radical species. Moreover, the noncovalent interactions that peptides typically exploit to organize transition states in selective reactions may have been anticipated to be weak or inoperative with neutral, open-shell intermediates. Despite these liabilities, highly enantioselective photochemical reactions utilizing peptide-based catalysts have indeed been demonstrated in recent years.

Two of these methodologies were enabled by the strategic use of cysteine as a catalytic residue. Enzymes are known to use active-site cysteine residues to mediate both polar and radical transformations *in vivo*.^{385,386} Cysteine proteases are an example of the former, which use nucleophilic cysteine thiolates to catalyze amide bond hydrolysis.³⁸⁵ On the other hand, ribonucleotide reductases enlist cysteine residues in the active site as HAT catalysts that assist in the deoxygenation of ribonucleotides to deoxyribonucleotides.³⁸⁷ Following the initial report of cysteine as a nucleophilic catalyst for asymmetric Rauhut–Currier reactions (Section 8.3),^{378,379} our group became interested in targeting the radical reactivity of cysteine-containing peptides. This catalytic platform was first assessed in the context of covalent thiyl radical catalysis (Section 9.1) and was later explored in enantioselective HAT chemistry governed by putative noncovalent interactions (Section 9.2).

A third recent strategy for peptide-catalyzed radical chemistry employs peptidic ligands on rare-earth metals to induce asymmetry in a dual photoredox-/Lewis acid-catalyzed [2+2] cycloaddition (Section 9.3). Among the various “privileged chiral scaffolds” examined,³⁸⁸ peptide-based ligands were uniquely effective in promoting this transformation.

9.1. Vinylcyclopropane Ring-Opening/Cycloadditions

Although the reactivity patterns of thiyl radicals have been extensively studied in a host of synthetically useful transformations (*e.g.* HAT, additions to C=C bonds, etc.), very few examples of asymmetric, thiyl-catalyzed reactions exist to date.^{389,390} Early examples reported by Roberts and co-workers used sugar-derived thiols as chiral, polarity-reversal HAT catalysts³⁹¹ for modestly enantioselective alkene hydrosilylation chemistry.^{392,393} In 2014, Maruoka and co-workers reported an asymmetric vinyl cyclopropane (VCP) ring-opening/cycloaddition cascade reaction catalyzed by chiral thiophenols.³⁹⁴ In this process, the chiral thiyl was presumed to directly engage the substrate in covalent catalysis, implementing a steric blocking strategy to deliver elaborated cyclopentane products with excellent diastereo- and enantioselectivities. Given the demonstrated thiyl radical reactivity of cysteines *in vivo*,³⁸⁶ as well as the challenges associated with the synthesis and diversification of chiral thiophenol-based organocatalysts, a peptide-mediated process seemed a viable extension.

Our group explored the VCP ring-opening/cycloaddition cascade reaction as a means to probe the hitherto unprecedented radical reactivity of cysteine in asymmetric catalysis.³⁹⁵ The overall strategy was to employ disulfide-bridged peptide dimers as thiyl radical precursors that would enable the formal radical cycloaddition of VCPs **9.1** and acceptor olefins **9.2** to yield cyclopentane derivatives **9.3** with high levels of selectivity (Figure 162). Mechanistically, UV-photoexcitation of the cysteine disulfide (*i.e.*, cystine) homolytically cleaves the S–S bond, providing two equivalents of active thiyl radical catalyst. The thiyl then adds to the C=C bond of **9.1**, resulting in covalent complex **I** following rapid cyclopropane ring-opening. Addition of electron-deficient radical **I** to alkene **9.2** results in heteroatom-stabilized radical intermediate **II**. Subsequent 5-*exo*-trig cyclization and catalyst elimination delivers **9.3** with diastereo- and enantioselectivity governed by interactions between the peptide and its covalently bound substrate.

Preliminary results showed that the diester VCP **9.1a** used by Matsubara and co-workers was an ineffective substrate in peptide-catalyzed reactions (Figure 163). Multiple cystine-containing peptides were examined, and while good reactivity was often observed, the reactions were not enantioselective. However, the analogous diamide VCP **9.1b** was modestly selective under the influence of cystine-containing peptides. Using β -turn-biased peptide **9.4**, *tert*-butyl vinyl ether **9.2**, and exposure to UV light, diamide **9.1b** was converted to a nearly 1:1 mixture of *cis*- and *trans*-**9.3b**, with the *cis*-isomer being enriched to 38:62 er.

Catalyst optimization was carried out for the reaction of VCP **9.1c** with *tert*-butyl vinyl ether under continuous UV irradiation (Figure 164). Known catalyst scaffolds **9.4** and **9.5** were not selective in this context, suggesting that these legacy structural motifs were not effectively engaging the diamide substrate. Reasoning that the spin density of key intermediates **I** and/or **II** (Figure 162) was distal to the peptide, scaffold **9.6** was conceived, wherein the *i*+1 Pro residue is functionalized at the γ -position in an attempt to extend the chiral pocket and improve asymmetric induction. Indeed, peptide **9.6a** delivered **9.3c** in quantitative conversion and notably improved er for both diastereomers—80:20 er for the major *trans* isomer and 57:43 for the minor *cis* isomer.

Modification of the Pro γ -substituent provided another accessible handle for catalyst optimization (Figure 165). While the pivalamide led to further improvements in er for both diastereomers (**9.6b**), both tosyl- (**9.6c**) and phenyl urea-protected amines (**9.6d**) were significantly inferior catalysts. γ -Arylated derivatives were similarly poor in the reaction of **9.1c** with *tert*-butyl vinyl ether (**9.6e–g**). A Hammett analysis of various γ -benzamide-containing peptides showed that enantioselectivity was not sensitive to electronic perturbations. However, er did correlate with the steric size of the γ -amine protecting group. Bulky amide groups provided the requisite boost in enantioselectivity, and peptide **9.6h** was chosen as the lead catalyst, providing the major *trans*-**9.3c** in 90:10 er and minor *cis*-**9.3c** in 75:25 er.

Peptide **9.6h** was found to address a reasonable scope with respect to both VCPs **9.1** and acceptor olefins **9.2** (Figure 166). Diastereoselectivity was found to be intrinsic to each VCP substrate, and the major *trans* diastereomer was always formed with higher levels of enantioselectivity. In general, electron-deficient amides were more selective in the reaction

(entries 3 & 6–9 vs. entries 1 & 4–5). This provides some evidence in support of H-bonding between the VCP substrate and the catalyst. With regard to the acceptor olefin, only electron-rich alkenes were converted to the corresponding cyclopentane products **9.3d–i** with good to excellent er values.

A model was proposed for the **9.6**-catalyzed ring-opening/cycloaddition cascade reaction of VCP **9.1c** (Figure 167). In the model, an amide N–H of the VCP substrate engages in an H-bond with the *i*+1 carbonyl of peptide **9.6h**. The combination of this key noncovalent interaction with the steric blocking effect of the Pro γ -substituent requires that radical addition to the acceptor olefin occur from opposite side, such that the *t*-butoxy group is oriented away from the γ -substituent. This putative arrangement is consistent with the absolute configuration of *trans*-**9.3** as determined by X-ray crystallography.

9.2. Photoredox Deracemization

An underexplored avenue for asymmetric synthesis is *deracemization*, or the direct conversion of a racemate into a single enantiomer of the same compound (Figure 168).³⁹⁶ This process may occur, in principle, when a chiral catalyst converts each enantiomer of the starting material into a common, achiral intermediate at different rates, enriching the reaction mixture in the slow-reacting isomer. Subsequent non-selective back-reactions from the achiral intermediate can then return both enantiomers of the starting material, which reenter the cycle. As these steps are repeated iteratively, the reaction mixture may become enriched in one enantiomer, such that synthetically useful ee values can be obtained. Seminal examples by Turner, Toste, and Zhou implement sequential redox steps to achieve deracemization.^{397–399}

Although conceptually quite straight forward, fundamental challenges associated with deracemization methodologies have contributed to their relative scarcity in the literature. First, the conversion of a two-state racemate to a one-state (*i.e.*, enantiopure) system makes these processes thermodynamically uphill ($\Delta G^\circ = +0.42$ kcal/mol). From a kinetic standpoint, the elementary steps that destroy and create stereochemistry must occur through distinct mechanisms in order to observe deracemization. If these steps are microscopic reverses of one another, then an equilibrium mixture—that is, a racemate—is inevitable. Chemoselectivity is also a critical challenge in deracemization, as the reagents that effect the stereoablative and stereogenic steps are often incompatible (*e.g.*, oxidants and reductants).

In collaboration with the Knowles Group, we recently reported a light-driven deracemization method for the direct optical enrichment of cyclic urea substrates **9.7** (Figure 169).⁴⁰⁰ The conversion of ($\pm$)-**9.7** to enantioenriched (**R**)-**9.7** is jointly mediated by an Ir(III)-based photosensitizer, a chiral BINOL-derived Brønsted base, and a cysteine-containing peptide as an HAT catalyst. Together, these three catalysts act to break and reform the stereogenic α -C–H bond of the substrate in a sequence of electron-transfer (ET), proton transfer (PT), and HAT steps. This process is driven solely by the absorption of visible photons and uses no stoichiometric reagents and produces no waste byproducts.

The proposed deracemization mechanism begins with non-selective single-electron oxidation of ($\pm$)-**9.7** by the excited state of the Ir(III) photoredox catalyst,⁴⁰¹ which then provides both enantiomers of radical cation **9.7⁺** in an equal ratio (Figure 170). These reactive intermediates are then kinetically resolved *via* enantioselective deprotonation by the chiral phosphate base, delivering achiral α -amino radical **9.8**. This PT step is proposed to enrich the reaction mixture in the slower reacting enantiomer (**R**)-**9.7⁺**, which reverts to (**R**)-**9.7** through charge recombination with the reduced Ir(II) state of the photocatalyst. Enantioselective HAT catalyzed by a cysteine-containing peptide then converts **9.8** into either (**R**)- or (**S**)-**9.7** depending on the sense asymmetric induction. In the matched case, the peptide-catalyzed HAT forms (**R**)-**9.7**, causing the reaction mixture to further enrich in that isomer. The resulting peptidic thiol is then reduced and protonated to restore the three catalytic components to their active states. Unlike other reported deracemization methods,^{397–399,402} this process involves two mechanistically distinct, enantioselective steps—PT that ablates chirality and HAT that re-establishes it. This provides the unique opportunity to observe multiplicative enantioselectivity outcomes, wherein the observed er is the product of the individual ers of both the PT and HAT steps ($er_{obs} = er_{PT} \cdot er_{HAT}$). Within this framework, two modestly selective steps could give rise to a highly selective overall transformation.

Optimization of this deracemization process began with a separate evaluation of each enantioselective step using amide-functionalized urea ($\pm$)-**9.7a** as the model substrate and [Ir(dF(CF₃)ppy)₂(bpy)]PF₆ as the photocatalyst (Figure 171). Pyrene-substituted BINOL phosphate **9.9** emerged from base screening as the most selective PT catalyst. Using thiophenol as an achiral HAT catalyst, **9.9** was able to deracemize **9.7a** in 84% recovered yield and 79:21 er (entry 1). Addition of molecular sieves improved both the yield and selectivity, providing (**R**)-**9.7a** in 92% yield and 86:14 er (entry 2).

Cysteine-containing peptides were then evaluated as HAT catalysts using an achiral phosphate as the base (Figure 171). While protected cystine returned **9.7a** in 92% yield and 47:53 er (entry 3), disulfide-bridged tetrapeptide **9.10a**, which was biased toward a β -hairpin conformation with its central D-Pro-Aic sequence, provided a modest boost in selectivity to 59:41 er in favor of the opposite enantiomer (entry 4). This suggests that the secondary structure of **9.10a** can overturn the inherent enantioselectivity of the catalytically active HAT residue. Substituting the methyl ester for a dimethyl amide C-terminal cap in **9.10b** resulted in a notable increase in selectivity (entry 5), as did reducing disulfide **9.10b** to the corresponding thiol **9.10c** (entry 6). Changing the $\dot{i}+3$ residue from Phe in **9.10c** to Gly in **9.10d** led to an increase in er at the expense of some yield (entry 7). However, peptide **9.10e**, which contained Acpc and Phg (phenylglycine) residues at the $\dot{i}+2$ and $\dot{i}+3$ positions, respectively, deracemized **9.7a** in 97% yield and 78:22 er (entry 8). Interestingly, selectivity was significantly reduced with epimeric, D-Phg-containing **9.10f** (entry 9). The selectivity of **9.10e** was slightly better when molecular sieves were included (entry 10).

Using both catalysts **9.9** and **9.10e** under the optimized conditions, urea **9.7a** was returned in 96% yield and 93:7 er (Figure 171, entry 11), proving that two modestly selective catalysts can, together, perform a highly effective deracemization in the proposed mechanistic

framework. However, the theoretical er based on the product of er_{PT} (entry 2) and er_{HAT} (entry 10) is 96:4 er, slightly higher than what was observed experimentally (entry 11). It was reasoned that the thiyl radical of peptide **9.10e** could induce some degree of racemization *via* HAT from the α -C–H bond of (**R**)-**9.7a**. This adventitious side reactivity was suppressed by addition of 50 mol% triphenylmethane as an H-atom buffer, and the theoretical er of 96:4 er was obtained (entry 12). Using 5 mol% of **9.9** and **9.10e** and 25 mol % of triphenylmethane, **9.7a** was effectively deracemized in 96% isolated yield and 96:4 er (entry 13).

Together, phosphate **9.9** and peptide **9.10e** were able to effectively deracemize an array of urea substrates with variable substitution on both the core and pendent amide functionality (Figure 172). Various α -amino substituents (**9.7a–e**) and urea *N*-substituents (**9.7f–h**) were accommodated by the dual catalyst system with excellent yields and ers. Likewise, perturbations to the pendent secondary amide led to only minor changes in yield and er (**9.7i–n**). However, tertiary amide **9.7o** was significantly less selective. Investigating each of the enantioselective steps separately, peptide **9.10e** was found to process **9.7o** with 77:23 er, while phosphate **9.9** returned only 58:42 er. This indicates that the secondary amide moiety is crucial in the enantioselective PT step. Assessed separately, the enantioselective HAT step was relatively invariant across all substrates, suggesting that **9.10e** effectively associates with the urea core and likely induces asymmetry through stabilizing noncovalent interactions along the HAT reaction coordinate. Based on previous data, it is possible that the *i*+2 amide N–H of **9.10e** forms an H-bond with the urea carbonyl of **9.7** in the selective transition state.

In addition to providing the proof-of-principle for this light-driven, dually enantioselective deracemization process, this study provided a proving ground for Cys-containing peptides as selective HAT catalysts. Examples of enantioselective HAT reactions are quite rare,^{383,403} possibly owing to the inherent difficulty of controlling the trajectory of H-atom delivery to a reactive intermediate. Peptide-based catalysts have proven to be a viable solution and may be particularly useful as this area is likely to expand.

9.3. Photoredox [2+2] Cycloadditions

In 2014, Yoon and co-workers reported a photochemical [2+2] cycloaddition of enones **9.11** and **9.12** to decorated cyclobutanes **9.13** employing a dual photoredox/Lewis acid catalytic strategy (Figure 173).⁴⁰⁴ Previous works by the Yoon group showed that Lewis acid coordination to enones can enable single-electron reduction events that are otherwise unfavorable.^{405,406} In this study, the authors sought to investigate the possibility of enantioselective, intermolecular [2+2] photocycloadditions by including a chiral ligand for the Lewis acid catalyst. The proposed catalytic cycle begins with photoexcitation of a Ru(II)-based photocatalyst to its triplet excited state.⁴⁰¹ Oxidative quenching of the excited-state Ru(II) species by a tertiary amine generates a reduced Ru(I) species and the amine radical cation. Alone, the Ru(I) species ($E^\circ = -1.3$ V *vs.* SCE) is insufficient to reduce enone **9.11** ($E^\circ = -1.4$ V *vs.* SCE) to the corresponding radical anion. However, Lewis acid coordination to **9.11** makes this SET step feasible, resulting in radical intermediate **9.14**, which subsequently undergoes a formal [2+2] cycloaddition with **9.12** and one-electron oxidation to form cyclobutanes **9.13**.

Their studies began with an evaluation of chiral ligands that have proven highly selective in a host of different reactions through the years (Figure 174).³⁸⁸ A preliminary evaluation of different Lewis acids revealed that lanthanide triflates were the most effective in the photocycloaddition of **9.11a** and methyl vinyl ketone **9.12a** using 5 mol% of Ru(bpy)₃Cl₂ as the photocatalyst. In the absence of a chiral ligand, Gd(OTf)₃ provided cyclobutane **9.13a** in 32% yield as a 3:1 mixture of 1,2-*trans*- and *cis*-diastereomers (entry 1). BINOL **9.15** (entry 2), TADDOL **9.16** (entry 3), and PyBOX **9.17** (entry 4) were ineffective ligands for this transformation, providing yields and drs that were no better than without ligand. However, dipeptide **9.18** delivered the [2+2]-cycloadduct in 56% yield and 6:1 dr favoring *trans*-**9.13a**, which was enriched to 21% ee (entry 5). These Schiff base-functionalized dipeptides were reported in the 2000s by Hoveyda and co-workers, who found them to be highly selective in a variety of enantioselective organometallic reactions (see Section 5.2).

This result spurred a combinatorial screen of dipeptide sequences, which led to Pro-containing **9.19** that gave 43% yield of *trans*-**9.13a** (>10:1 dr) in 56% ee (entry 6). Substituting Eu(OTf)₃ as the Lewis acid provided a noteworthy boost in ee to 78% at the expense of dr (entry 7). Increasing the equivalents of **9.12a** and reducing the loadings of Eu(OTf)₃ and **9.19** led to a significant improvements in yield, dr, and ee (entry 8), and -20 °C provided the highest observed ee of 92% (entry 9). Control experiments showed that the reaction completely shuts down in the absence of light, photocatalyst, Lewis acid, and DIPEA base. Moreover, enantioselectivity is independent of Eu(OTf)₃/**9.19** loading, suggesting the absence of a racemic background reaction.⁴⁰⁸

Interestingly, diastereodivergence was observed using peptide **9.20**, in which the imine functionality is reduced to an amine. Even though this modification occurs to an achiral portion of the catalyst scaffold, the selectivity switches to favor *cis*-**9.13a** (1:4.5) in 95% ee, even at ambient temperature (entry 10). This result possibly points to a change in the ligand conformation that overrides the intrinsic *trans*-selectivity of the transformation.

The substrate scope of the dual photoredox- and Lewis acid-catalyzed [2+2] cycloaddition was evaluated with both ligands **9.19** and **9.20** (Figure 175). The scope was found to be general for both *trans*-selective **9.19** and *cis*-selective **9.20**. Various aryl ketones were well-tolerated by both peptidic ligands (entries 1–8), as were substitutions at the enone β-position (entries 1 & 9–11). Overall, yields and ee values tended to be modestly improved with peptide **9.20**, whereas dr values were generally higher with imine-containing **9.19**.

10. Halogenation

A wide variety of asymmetric halogenation methodologies have been developed over the past three decades, ranging from α-halogenations of carbonyl compounds^{409,410} and olefin halofunctionalizations^{411,412} to dihalogenation reactions of allylic alcohols.⁴¹³ In recent years, the application of peptide-based catalysts in this area has led to a significant expansion of scope and mechanistic understanding. Not only have peptides been employed as catalysts for venerable halolactonization reactions (Section 10.3), but they have also enabled novel asymmetric S_EAr chemistries that presented interesting selectivity challenges.

Of particular note is the ability of these peptidic catalysts to achieve remote asymmetric induction in compounds where the pro-stereogenic element is distal from the reaction site (Sections 10.1 & 10.2).²⁴⁵ In this Section, we summarize the recent peptide-catalyzed, asymmetric bromination methods with a particular emphasis on the specific attributes of peptide-based catalysts that make them well-suited to address intriguing stereochemical problems.

10.1. Atroposelective Electrophilic Aromatic Bromination

Previous examples of asymmetric S_EAr methods largely follow a mechanistic paradigm wherein an arene nucleophile adds into a prochiral electrophile, with enantiofacial discrimination governed by the catalyst–electrophile complex.^{414–416} However, the rapidly growing interest in enantiopure atropisomers—compounds that exhibit axial chirality by virtue of hindered rotation about a single bond—for natural products,⁴¹⁷ pharmaceuticals,⁴¹⁸ and catalysis,^{81,419} provided an impetus for the development of direct *atroposelective* S_EAr reactions.

In that regard, our group envisaged a scenario in which one enantiomer of a chiral, rapidly racemizing biaryl phenol (*e.g.*, **10.1**) could undergo selective electrophilic aromatic bromination *via* preferential interaction with a peptide-based catalyst (Figure 176). This would enable the DKR of **10.1** if the following criteria are met: (1) racemization of **10.1** is fast relative to S_EAr ; (2) the product is configurationally stable under the reaction conditions; and (3) the peptide-based catalyst is able to engage in remote asymmetric induction, as the phenol group is distal from the axis of chirality. Mono-*ortho*-substituted biaryls, such as **10.1**, are known to have low enantiomerization barriers ($\Delta G^\ddagger \sim 7$ kcal/mol), which all but ensured rapid racemization under the reaction conditions. However, we anticipated that two *ortho*-bromination events would be necessary to lock the configuration of the product. In order to meet this requirement and also avoid complicated mixtures of poly-brominated product isomers, we decided to pursue the tribromination of **10.1**. The biaryl tribromide products (*e.g.*, **10.2**) were expected to have enantiomerization barriers exceeding 30 kcal/mol, which is sufficiently high to avoid *in situ* racemization. Lastly, we hypothesized that incorporation of a suitable directing group on the opposite ring (X, Figure 176) would facilitate multidentate interactions with the peptide catalyst and provide a more robust handle for enantio-discrimination in the stereodetermining transition state.

Using this general DKR strategy, our group has been able to develop highly atroposelective, peptide-catalyzed bromination reactions of biaryl (Section 10.1.1), non-biaryl (Section 10.1.2 & 10.1.3), and heterobiaryl (Section 10.1.4) atropisomers. Unique peptide catalysts were optimized for each substrate class, and multifunctional binding and activation mechanisms were proposed to be crucial for achieving high levels of enantioselectivity in each case. Moreover, the tribrominated products are able to be regioselectively functionalized using robust cross-coupling protocols to access high value derivatives that often have drug-like properties.

Prior to this body of work, most reported examples of catalytic, atroposelective methods took advantage of transition metal-mediated cross-coupling reactions to forge biaryl C–C bonds with stereocontrol over the nascent axis.⁴²⁰ However, a conceptually similar DKR

strategy had been developed by Bringmann and co-workers, which involved the atroposelective ring opening of biaryl lactones with various chiral nucleophiles.⁴²¹ These strained lactones racemize rapidly due to ground state destabilization, but the ring-opened products are configurationally stable *ortho*-tetrasubstituted biaryls, which are especially difficult to access using asymmetric cross-coupling methods. Since then, catalytic versions of this reaction have recently been reported.⁴²² A single catalytic, atroposelective DKR example had been reported by Murai and co-workers prior to our initial report.⁴²³ This method employed a chiral Rh(I)-complex to effect a C–H/olefin coupling *via* a modestly atroposelective C–H activation event. These pioneering studies informed many aspects of our atroposelective DKR platform.

10.1.1. Atroposelective Bromination of Biaryls.—In 2010, our group successfully implemented the atroposelective DKR strategy in the peptide-catalyzed bromination of biaryls **10.1** (Figure 177).⁴²⁴ Our catalyst design was centered around an *N*-terminal, tertiary amine-containing catalytic residue, β -dimethylaminoalanine (Dmaa), which was intended to nucleate complexation with **10.1** through H-bonding/ion pairing interactions. Indeed, high levels of selectivity were only observed when the directing group on scaffold **10.1** was a carboxylic acid; pendent ester, amide, and nitro groups resulted in poor to modest enantioinduction. Tripeptide **10.3** emerged from sequence optimization studies as the lead catalyst. Under the optimized reaction conditions employing *N*-bromophthalimide (NBP) as the brominating reagent and acetone as a polar additive, **10.3** was able to address a reasonable scope of biaryls **10.1** with variable substitution on the benzoic acid moiety. Tribromides **10.2** were isolated in up to 85% yield and 97:3 er (entries 1–9). Even a pyrrole-containing substrate was selectively brominated by **10.3** in 77% yield and 85:15 er when four equivalents of NBP were used (entry 10). The absolute configuration of the product was assigned as (*aR*) for tribromide **10.2a** (R = H) using single crystal X-ray crystallography.

A series of control reactions were performed in order to glean which elements of tripeptide **10.3** were essential for catalysis (Figure 178). In the absence of a catalyst, background bromination of **10.1a** was slower and non-selective; only 15% of **10.2a** was isolated after 18 hours, with the remainder of the mass balance consisting of mono- and dibrominated isomers. The yield of **10.2a** improved to 31% when 10 mol% of DIPEA was employed as a mimic of the Brønsted basic Dmaa residue. However, a boost to 91% yield was observed using catalytic ($\pm$)-Boc-Val-NMe₂ to simulate the *C*-terminus of **10.3**. Taken together, these data suggest that the *C*-terminal D-Val residue of **10.3** contributes more substantially to bromination catalysis, perhaps through bromonium ion delivery by the tertiary amide moiety. Lewis basic carbonyl-type functionality are known to accelerate halogenation reactions in other contexts.⁴²⁵

Based on all of the data, we proposed a self-consistent binding and activation model was proposed that accounts for the observed absolute configuration of product **10.2** (Figure 179). Proton transfer from **10.1a** to **10.3** allows for ion pairing/H-bonding between the carboxylate of **10.1a** and the Dmaa residue of **10.3**. This salt bridge formation may nucleate additional multidentate H-bonding interactions between the backbone amides of **10.3** and the phenol moiety **10.1a**. This possibly leaves the *C*-terminal tertiary amide of **10.3** available for

bromonium ion transfer, though no direct evidence for such an interaction has been obtained to date. In collaboration with the Johnson Group, we used cryogenic infrared spectroscopy⁴²⁶ to study the nature of the ground state **10.3**•**10.1a** complex.⁴²⁷ The results of this study were quite consistent with the proposed model.

To demonstrate the synthetic utility of these tribrominated products, we showed that protected tribromides **10.4** can undergo sequential cross-coupling reactions with no erosion of configurational integrity (Figure 180).⁴²⁸ This “A-B-C” coupling strategy capitalizes on the steric and electronic differentiation of each individual bromide to enable regioselective functionalization. The A-coupling selectively targets the bromide *para* to the chiral axis to provide C–C-, C–N-, C–O-, and C–H-coupled products **10.5** in 45–70% yield. Next, the B-coupling allows for the functionalization of the bromide *para* to the methoxy group, delivering derivatives **10.6** in 37–65% yield. The final C–Coupling functionalizes the most sterically encumbered bromide to provide tris-functionalized products **10.7** in 70–80% yield under slightly more forcing conditions. Differentiated pentaaryls are accessible in virtually enantiopure form (99:1 er) using this strategy.

10.1.2. Atroposelective Bromination of Tertiary Benzamides.—Our group expanded the general atroposelective DKR strategy to include non-biaryl atropisomers with our 2013 report of the peptide-catalyzed, asymmetric bromination of tertiary benzamides **10.8** (Figure 181).⁴²⁹ Axially chiral benzamide motifs have appeared frequently in pharmaceutical compounds exhibiting a range of biochemical functions.^{418,430,431} In-depth studies by Mannschreck,⁴³² Clayden,⁴³³ and others on the atropisomeric properties of benzamides like **10.8** and **10.9** provided crucial insight into the challenges associated with the atroposelective bromination of these compounds. Namely, the amide *N*-substituents would have to be sufficiently large so as to ensure the configurational stability of the tribromide products **10.9**. We hypothesized that this would also provide the added benefit of minimizing background tertiary amide-catalyzed bromination. Preliminary results showed that the *N,N*-diisopropyl benzamide motif indeed provided improved yields and selectivities over the corresponding piperidinyl and piperazinyl benzamides in the peptide-catalyzed bromination reaction.

Sequence optimization led to the discovery of Dmaa-containing tetrapeptide **10.10** as the lead catalyst for this transformation. Using 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) as the brominating reagent, **10.10** delivered tribromide **10.9a** (R = H) in 89% yield and 94:6 er favoring the (a*S*)-configuration (Figure 181, entry 1). The secondary structure of **10.10** was biased toward a type II' β -hairpin by incorporation of the central D-Pro-Aib sequence, a feature that proved to be important for selectivity in the bromination of **10.8**. Interestingly, this same sequence (*i.e.*, Boc-Xaa-D-Pro-Aib-Phe-OMe) emerged as highly effective in a variety of mechanistically distinct reactions.^{4,6}

Peptide **10.10** selectively brominated a variety of substituted benzamides **10.8** under the optimized conditions. Variable substitution at the 4- and 5-positions was well-tolerated (Figure 181, entries 2–7), while *ortho*-substituents presented a more complicated scenario. At the 6-position, methyl substitution was processed selectively by **10.10** (entry 8), whereas a pre-installed bromide completely ablated the selectivity (entry 9). The observed disparity

is possibly due to differences in the enantiomerization barriers; the *ortho*-bromides are expected to decrease the rate of racemization relative to *ortho*-methyl groups due to their increased demand,¹⁶¹ which would decrease the efficacy of the DKR. On the other hand, neither methyl nor bromide substituents were tolerated at the 2-position (entries 10–11). A possible rationale for this observation was gleaned from LC/MS analyses of crude, low-conversion reaction mixtures (Figure 182). In the absence of a catalyst and when 10 mol% of triethylamine was employed, monobromination of **10.8a** at both the 4- and 6-positions was observed at low conversion, leading to monobromides **10.11a** and **10.12a**, respectively, in a ratio favoring **10.12a**. However, only **10.13a** was observed in the presence of **10.10**, suggesting that the peptide selectively brominates **10.8a** at the 2-position. These data suggest that **10.10** overturns the inherent regioselectivity of the reaction by promoting monobromination at the most sterically encumbered position. Moreover, if the first bromination is stereodetermining, then 2-substituted benzamides are expected to provide poor selectivities in the **10.10**-catalyzed reaction, which is consistent with the substrate data (Figure 181, entries 10–11).

Based on NMR studies of the ground state catalyst-substrate complex, we proposed a model for binding and enantioinduction that involves multi-point docking between **10.10** and **10.8a** (Figure 183). H-Bonding between the tertiary amine of **10.10** and the phenol of **10.8a** is presumed to nucleate catalyst-substrate association and activate the phenol ring toward S_EAr by making it more phenolate-like. An additional H-bonding interaction between the substrate and the N–H of the *i*+2 Aib residue holds **10.8a** in the (*aS*)-configuration with the 2-position oriented toward the peptide scaffold. If one of the Lewis basic amides of **10.10** indeed delivers bromenium to **10.8a**, then this model is also consistent with the predicted site of stereodetermining monobromination.

Given the apparent pharmaceutical importance of this class of compounds, we next demonstrated that tribromides **10.9** could be regioselectively derivatized *en route* to functional, drug-like molecules (Figure 184a).⁴³⁴ Selective cross-coupling of the *para*-bromide provided monofunctionalized compounds **10.14** in 61–80% yield and with little to no erosion of er ($G^\ddagger \sim 28$ kcal/mol). *ortho*-Lithiation of the 2-bromide followed by electrophile trapping led to products **10.15** in good yields and up to 99:1 er following recrystallization. The utility of these derivatives was demonstrated by utilizing phosphine **10.15a** as a chiral ligand for a Pd-catalyzed, enantioselective Tsuji–Trost-type allylation (Figure 184b). Remarkably, **10.16** was converted into allylated malonate **10.17** in 93% yield and 96:4 er.

As an extension of this methodology, we next pursued the atroposelective bromination of benzamides such as **10.18** that possess two stereogenic axes—one defined by the C_{Ar}–C(O) bond (red) and the other about the N–C(O) bond of the differentially *N,N*-disubstituted amide (blue, Figure 185).⁴³⁵ Tribromination of **10.18** has the potential to deliver up to four stereoisomers of **10.19**. We hypothesized that, if both axes were configurationally stable following tribromination, it may be possible to optimize a unique, peptide-based catalyst that would provide selective access to each diastereomeric product and enable the fully catalyst-controlled, stereodivergent synthesis of **10.19**.

We began by importing the optimized conditions (Figure 181) from the bromination of benzamides **10.8** into this system. In the absence of a catalyst, bromination of **10.18** initially provided a 40:60 *trans/cis* mixture of ($\pm$)-**10.19** which slowly equilibrated to 76:24 over 72 hours at ambient temperature. DFT computations confirmed that, while the barrier to rotation about the C_{Ar}–C(O) axis is sufficiently high as to be configurationally locked following tribromination, rotation about the amide N–C(O) axis is accessible, albeit slow, at ambient temperature. Under the control of tetrapeptide **10.10**, tribromide **10.19** was initially obtained with a similar *trans/cis* ratio of 43:57, but each amide isomer was processed with different enantioselectivity; *cis*-**10.19** was processed by **10.10** with an er of 88:12 favoring the (a*S*)-isomer, while *trans*-**10.19** was characterized by a lower er value of 66:34. However, this kinetically controlled mixture of diastereomers **10.19** changed over time as the *trans/cis* ratio converged on its equilibrium value of 76:24. Over the 72 hour equilibration period, the er of *trans*-**10.19** spontaneously increased to 79:21 as the er of *cis*-**10.19** eroded to the same value. These findings marked a rare example of spontaneous enantioenrichment, which was made possible by the ability of peptide **10.10** to differentially process the amide isomers of benzamide **10.18**.

10.1.3. Atroposelective Bromination of Amido-Tropolones.—Murelli and co-workers recently reported the atroposelective bromination of amide-substituted α -hydroxytropolone derivative **10.20** (Figure 186).⁴³⁶ α -Hydroxytropolones are potent inhibitors of several medicinally relevant metalloenzymes,⁴³⁷ including HIV reverse transcriptase RNase H, a promising target for the development of HIV therapeutics.⁴³⁸ Like the analogous benzamides, amido-tropolones such as **10.20** are axially chiral about the C_{Ar}–C(O) bond. However, these compounds are expected to exhibit higher enantiomerization barriers owing to the wider internal bond angles of the seven-membered tropolone ring that exacerbate strain in the coplanar rotational transition state. DFT calculations show that amido-tropolone **10.20** has an enantiomerization barrier of 16.9 kcal/mol *versus* 13.0 kcal/mol for benzamide **10.21**, which corresponds to roughly a 750-fold difference in half-life. This effect is even more pronounced in the monobromide products; tropolone **10.22** has an enantiomerization barrier of 31.2 kcal/mol *versus* 24.2 kcal/mol in benzamide **10.23**—a 160,000-fold difference in rotational half-life. Binding simulations suggest that some α -hydroxytropolone derivatives preferentially dock with the RNase H domain of HIV RT in a single atropisomeric form.⁴³⁹ Therefore, the development of single-enantiomer α -hydroxytropolone-based drugs could lead to enhanced potency and selectivity for an array of metalloenzyme targets.

In order to test this hypothesis, the authors developed a peptide-catalyzed bromination of **10.20**, providing access to configurationally stable monobromide **10.22**.⁴³⁶ Following assessment of a series of Dmaa-containing peptide catalysts with sequences biased toward type II' β -turns, tetrapeptide **10.24** was identified as the lead catalyst, providing **10.22** in 50% yield and 75:25 er. Enantioselectivity was proposed to originate from binding and activation in analogy to that of complex **10.10**•**10.8a** (Figure 183), wherein the Dmaa residue engages with the free O–H of **10.20** while the peptide backbone H-bonds with the amide group. Moreover, selective monobromination of **10.20** was possible in this case due to the electronically deactivated nature of the tropolone ring, which may also contribute to the

overall lower reactivity observed in this system. While preliminary, this result proves that the peptide-catalyzed DKR strategy is viable for synthesizing enantioenriched α -hydroxytropolone derivatives bearing a functional handle for additional modification and SAR study. Further optimization of this transformation is currently underway in the Murelli Group.

10.1.4. Atroposelective Bromination of 3-Arylquinazolinones.—In 2015, our group reported the atroposelective bromination of 3-arylquinazolin-4(3*H*)-ones (e.g., **10.25**), a class of heterobiaryl compounds that exhibit axial chirality about the anilide N–C_{Ar} bond.⁴⁴⁰ The atropisomeric quinazolinone nucleus is an important pharmacophore that frequently appears in a range of biologically active molecules, from recreational hallucinogens to anti-cancer drugs.⁴⁴¹ Many such 3-arylquinazolinone-based drugs are known to engage in enantiomer-specific binding with their biological targets, and access to single enantiomer compounds could enable the development of more potent and/or selective drugs. In that vein, we envisioned that peptide-catalyzed, atroposelective bromination could be an effective means of accessing enantiopure 3-arylquinazolinone tribromides that are primed for late-stage derivatization and SAR study.

Our investigations began with the optimization of a peptide-based catalyst for the atroposelective conversion of quinazolinone **10.25a** into tribromide product **10.26a** using NBS as the brominating agent (Figure 187). Under these conditions, product yields were always near-quantitative, and so enantioselectivity was used as the sole determinant for catalyst selection. Examination of an initial library of 21 Dmaa-containing tetrapeptides **10.27**, all of which were biased toward a type II' β -hairpin geometry by incorporating a central D-Pro-Xaa sequence element, revealed several interesting trends, including a particularly striking effect of the *i*+2 residue. Comparing a homologous series of *i*+2 variants (Figure 187, blue), we observed that Acpc-containing **10.27h** delivered **10.26a** in 88:12 er, significantly higher than the Aib- (**10.27c**, 70:30 er), Cle- (**10.27g**, 70:30 er), L-Phe- (**10.27i**, 70:30 er), and Aic-containing (**10.27j**, 61:39 er) homologs. This effect was tentatively attributed to a beneficial effect of the wider *i*+2 main-chain angle (τ_{i+2}) of Acpc-containing **10.27h** relative to the more acute values expected in the other homologs. Having identified a suitable *i*+2 residue, the catalyst sequence was fine-tuned by modification of the *i*+3 residue. Alkyl-substituted residues were found to be more selective than Phe- or Gly-derivatives, and we ultimately arrived at Leu-containing peptide **10.27q** as the lead catalyst (Figure 187, red), which provided **10.26a** in 92:8 er. Further sequence optimization did not lead to noticeable improvements in selectivity.

Seeking further understanding of the structural attributes that contribute to high selectivity, a truncation study was performed, wherein residues were sequentially removed from the C-terminus of lead peptide **10.27q** (Figure 188). For tripeptides **10.28**, while methyl ester **10.28a** and dimethylamide **10.28b** provided modest selectivities in the bromination of quinazolinone **10.25a** under the screening conditions, *N*-methyl amide **10.28c** remained a viable catalyst, furnishing **10.26a** in 82:18 er. This observation was attributed to the ability of **10.28c** to maintain a β -turn secondary structure through the formation of the crucial N–H(*i*+3)•••O(*i*) H-bond. A similar trend was observed in the dipeptides **10.29** following

truncation of the Acpc residue. Only *N*-methyl amide **10.29c** provided any significant selectivity (71:29 er), while methyl ester **10.29a** and dimethyl amide **10.29b** both delivered nearly racemic product. Thus, having an N–H bond at the *i*+2 position available for H-bonding with the substrate is likely important for selective catalysis, although formation of a γ -turn secondary structure *via* an N–H(*i*+2)•••O(*i*) H-bond could also contribute to the elevated selectivity of dipeptide **10.29c**. Interestingly, Dmaa-monomer **10.30** provides modest selectivity (46:54 er) in favor of the opposite enantiomer, suggesting that secondary structural attributes overturn the inherent selectivity of the catalytically active residue.

DFT computations showed that the enantiomerization barrier of **10.25a** is 19 kcal/mol, which corresponds to a half-life of approximately seven seconds at ambient temperature. Compared to the other substrates we have examined in the context of atroposelective bromination, namely biaryls **10.1** ($G^\ddagger \approx 7$ kcal/mol) and benzamides **10.8** ($G^\ddagger \approx 10$ kcal/mol), these quinazolinones are expected to racemize significantly slower, likely as a consequence of the shorter N–C_{Ar} bond defining the chiral axis. Thus, we reasoned that slow delivery of NBS could result in higher levels of enantioselectivity by permitting more complete re-racemization of **10.25a** on the extremely rapid bromination time scale, thereby enabling a more efficient DKR. Indeed, syringe pump addition of NBS over three hours in the presence of peptide **10.27q** led to an energetically significant boost in the er of **10.26a** from 92:8 to 97:3 er (Figure 189, entry 1). X-Ray crystallography showed that **10.27q** delivered **10.26a** in the (a*S*)-absolute configuration.

Under the optimized reaction conditions, tetrapeptide **10.27q** was found to address a reasonably broad scope of quinazolinones **10.25** (Figure 189). Alkyl substitution at the 2-position of **10.25** was well tolerated (entries 1–5), as were electronically diverse substituents on the benzo moiety (entries 8–9). Additionally, substrates containing methyl and chloro substituents at the *meta*- and *para*-positions (relative to the chiral axis) of the phenol ring were also processed by **10.27q** with high levels of enantioselectivity (entries 10–13). In fact, *para*-methyl **10.26** was isolated in 92% yield and 99:1 er (entry 13). However, three of the substrates examined performed rather poorly in the atroposelective bromination reaction (entries 6, 7, and 14). While the 2-trifluoromethyl group of **10.25b** was presumed to negatively influence catalyst-substrate assembly *via* unfavorable electrostatic interactions, the other two substrates likely underperformed due to rotational barrier-related issues. For example, the preinstalled *ortho*-fluoro substituent of **10.25c** was proposed to significantly reduce the racemization rate of this substrate, thereby precluding it from effective DKR. Indeed, **10.26c** was formed in 84% yield and only 56:44 er (entry 14), and DFT computations determined the enantiomerization barrier of **10.25c** to be over 26 kcal/mol. However, when the reaction with **10.25c** is run to low conversion using only 0.5 equivalents of NBS, **10.26c** can be isolated in 14% yield and 93:7 er, suggesting that compounds like these are suitable kinetic resolution substrates.

Mechanistically, low-conversion LC/MS studies revealed that peptide **10.27q** overturns the inherent regioselectivity of the enantiodetermining step by promoting monobromination at the *ortho*-position, as was observed in the bromination of benzamides **10.8**. Monobromination at the least sterically encumbered *para*-position is observed in

triethylamine-catalyzed reaction. Moreover, due to the inherently high N-C_{Ar} rotational barriers of the quinazolinone system, the *ortho*-monobromide of **10.25a** was able to be isolated with 98:2 er. This unambiguously demonstrates that *ortho*-monobromination is the enantiodetermining step in the **10.27q**-catalyzed reaction.

NMR complexation experiments were also performed in order to study catalyst-substrate association in solution. Relative to their individual spectra acquired under identical conditions, the ¹H-NMR spectrum of a 1:1 mixture of **10.25a** and **10.27q** showed a number of chemical shift perturbations consistent with intermolecular association. For example, the N-H(*i*+2) resonance shifted downfield by over 1 ppm, suggesting that this amide engages the substrate in H-bonding, likely with the carbonyl group of the quinazolinone core structure. NOESY experiments also revealed a number of intermolecular NOEs between **10.25a** and **10.27q**, a relatively uncommon finding for systems involving weak association (Figure 190). The distances ascribed to the NOEs allowed for the development of a precise, self-consistent binding and activation model (**10.27q**•**10.25a** complex) that predicts the site of enantiodetermining monobromination, as well as the observed (*aS*) product configuration. Again, association is likely nucleated by H-bonding between the phenol of **10.25a** and the Dmaa sidechain of **10.27q**, with backbone H-bonding from the N-H(*i*+2) further stabilizing the complex.

Due to the pharmaceutical relevance of these compounds, we also demonstrated that tribromides **10.26** could be regioselectively derivatized to access functionalized quinazolinones (Figure 191). Selective removal of the least sterically encumbered bromides could be achieved by careful hydrogenation of **10.26a**, providing monobromide **10.31** with no erosion of er. DFT computations showed that **10.31** is configurationally stable with an enantiomerization barrier of over 35 kcal/mol. Suzuki–Miyaura cross-coupling of **10.31** delivered arylated derivatives **10.32** in 83–95% yield and with no enantioerosion. Alternatively, selective Buchwald–Hartwig amination targeted the *para*-bromide of **10.26a**, furnishing amines **10.33** in 60–75% yield and in 96:4 er.

A follow-up study on the peptide-catalyzed quinazolinone bromination reported an expansion of the catalyst library in search of additional information on the relationship between structure and function.⁴⁴² Interestingly, although *C*-terminal methyl esters were previously found to be inferior to dimethyl amides in the lower-selectivity regime (Figure 187, **10.27a–c**), peptide **10.34a**—the methyl ester variant of the original lead catalyst (**10.27q**)—was found to be a more reactive and selective catalyst (Figure 192, entries 1 *vs.* 2). Under the screening conditions, **10.34a** delivered **10.26a** in 95:5 er, even at only 1 mol% loading (entry 2). Recourse to the slow addition protocol provided a modest boost in selectivity to 97:3 er at 1 mol% of **10.34a**. The origin of this increased catalyst efficacy by methyl ester substitution is currently uncertain, but the effect only manifests with Acpc at the *i*+2 position.

Another effect that is seemingly unique to Acpc-containing peptides was identified that involves the substitution of L-Pro for D-Pro within an otherwise homologous sequence (Figure 192, entries 2–7). Epimerization of the catalyst in that way is expected to invert the turn sense from a so-called “mirror image β-turn” (*e.g.*, type II') to a canonical β-turn (*e.g.*,

type II).^{47,223} We have often found previously that catalyst epimerization at the *i*+1 position results in selectivity favoring the opposite enantiomer with a significant reduction in the absolute er value.⁴ Such is the case here for the Aib- and Aic-containing peptides. The change from D-Pro-Aib (**10.34b**) to L-Pro-Aib (*epi*-**10.34b**) produced a drop in selectivity from 68:32 er to 45:55 er (entries 4 vs. 5). The change from D-Pro-Aic (**10.34c**) to L-Pro-Aic (*epi*-**10.34c**) followed suit (entries 6 vs. 7). However, the *epi*-**10.34a** maintained a high level of enantioselectivity in the opposite direction (11:89 er) relative to the D-Pro-Acpc-variant **10.34a** (entry 2 vs. 3). This result may suggest that absolute enantiocontrol is largely dictated by the turn sense with relatively minor contribution from the flanking residues. Using the optimized slow addition protocol, peptide *epi*-**10.34a** delivers *ent*-**10.26a** in 78% yield and 9:91 er. This degree of enantiodivergence is notable and unprecedented for an epimeric catalyst.

In that same follow-up study, some preliminary structural data was reported for the lead quinazolinone bromination catalysts (**10.27q** and **10.34a**).⁴⁴² Three discrete conformations of **10.27q** were observed in the solid state by X-ray crystallography (Figure 193). One crystal structure showed two conformations within the same asymmetric unit, both of which were characterized as type II' β -hairpins based on the ϕ and ψ dihedral angles of the central two residues (*i.e.*, the loop region)⁴⁷ and presence of 10-membered N-H(*i*+3)•••O(*i*) and 14-membered N-H(*i*)•••O(*i*+3) intramolecular H-bonds (**I** and **II**). This was the designed secondary structure for the initial quinazolinone bromination catalyst library (see Figure 187). The primary difference between conformers **I** and **II** is the degree of backbone bending. An unexpected secondary structure was observed in a separate crystallographic sample of **10.27q**. Conformer **III** also possessed the 10-membered ring N-H(*i*+3)•••O(*i*) β -turn H-bond observed in the designed conformers, but its loop region amide was inverted relative to **I** and **II**, allowing for a second 10-membered N-H(*i*+2)•••O(Boc) H-bond. This sequential double turn structure renders **III** prehelical in nature, with the central ϕ and ψ dihedrals resembling those of a type I' β -turn.⁴⁷ Interestingly, peptide **10.34a**, which was found to be more active and selective than **10.27q**, reliably adopted the prehelical conformation in the solid state. These unanticipated findings prompted an NMR study of these two peptides in solution. Two-dimensional NOESY spectra were acquired for each under identical conditions, and the cross-peak volumes were converted into distance restraints for structure simulations. The NOEs tabulated for **10.27q** satisfied both the hairpin and prehelical geometries, and as such the simulated structure was intermediate between the two. However, peptide **10.34a** predominantly adopted the prehelical type I' β -turn conformation. Taken together, these results suggest that the most selective quinazolinone bromination catalysts can adopt multiple conformations, including secondary structures that were not designed at the outset.

In order to glean more information about the conformations accessible to these tetrapeptides and better understand how structure affects catalysis, we conducted an in-depth structural investigation of the bromination catalyst library.⁵⁰ X-Ray crystal structures of 35 different peptides were obtained, giving rise to 53 total peptide conformations due to the occurrence of symmetry-independent molecules and polymorphs for multiple cases. Various structural parameters of these peptides were analyzed, including backbone dihedrals, side chain

dihedrals, and H-bond geometries, among others, in search of information that might be relevant to catalyst design and function. In general, the peptides were found to be quite structurally diverse for a library that was biased toward a particular β -turn conformation. This structural diversity in the solid state often translated to solution phase dynamics, as many of the peptides showed NOE signatures of multiple limiting conformations, including type II' β -hairpins like **I** and **II**, prehelical type I' β -turns like **III**, and γ -turns. In many cases, the designed conformation was not predominant in solution.

One noteworthy aspect of this study came from the investigation of homologous $i+2$ variants of sequence **10.34** (Figure 194). While all of the catalysts were designed to adopt type II' β -hairpins by incorporating a central D-Pro-Xaa sequence (where Xaa is a symmetrically disubstituted residue), only Aib-containing **10.34b** exhibited this conformation in the solid state. All of the other members of this series (**10.34a,c–g**) existed in the unexpected type I' prehelical conformation with very little backbone deviation. Most of the variation between these structures occurred at the C-termini and the $i+3$ sidechains (see structural overlay). Both high- and low-selectivity catalysts adopted the prehelical secondary structure in the solid state, and given the high degree of backbone similarity, it was unclear what factors might make certain sequences more selective, namely Acpc-containing **10.34a** and Gly-containing **10.34g**.

A possible explanation emerged in the form of a linear correlation between the enantioselectivity measured in the peptide-catalyzed bromination of quinazolinone **10.25a** and the main-chain angle of the catalyst $i+2$ residue (τ_{i+2} , Figure 195). While this feature was not designed into the catalyst library at the outset, the data showed that catalysts with wider τ_{i+2} values tend to be more selective. In proteins, turn residues with wide τ values often have relaxed torsional energy profiles, making their respective secondary structures more structurally flexible.⁴⁴³ In that light, these data hinted at the possibility that the most selective quinazolinone bromination catalysts are also conformationally dynamic.⁹

Evidence in support of this hypothesis was obtained from solution-phase NMR studies of the same homologous $i+2$ series.⁵⁰ Analysis of the NOESY spectra of peptides **10.34a–g** revealed that most of the peptides were conformationally dynamic in solution, as determined by the presence of NOE signatures of two or more secondary structural archetypes (*e.g.*, β -hairpin, prehelical β -turn, and γ -turn). The exception was **10.34b**. This low-selectivity catalyst only showed NOEs consistent with the designed β -hairpin, mirroring the solid-state observations (Figure 196). In contrast, highly selective catalysts like **10.34a** and **10.34g** predominantly adopted the prehelical conformation in solution, while also equilibrating between multiple minor secondary structures.

The situation was different in the presence of quinazolinone substrates **10.25**. When lead catalyst **10.27q** was treated with an equimolar amount of **10.25a**, its solution conformation changed from predominantly prehelical to the β -hairpin.⁵⁰ However, when **10.27q** was treated with an equivalent of quinazolinone **10.25b**—a poorly performing substrate (see Figure 189)—the degree of change was notably less. In collaboration with the Jorgensen Group, high level molecular dynamics (MD) simulations were performed to model these NMR spectroscopic observations.⁴⁴⁴ Over the course of a 1600 ns simulation in explicit

benzene solvent, **10.27q** alone was found to exhibit the prehelical conformation 75% of time, while the remaining 25% consisted of the β -hairpin and other conformers (Figure 197a). Upon treatment with selective substrate **10.25a**, the conformation of the peptide catalyst flipped to favor the β -hairpin 75% of the time. In contrast, the conformational landscape in the presence of **10.25b** favored a hairpin-like conformation only 51% of the time. In both cases, the lowest energy binding modes very closely resembled the proposed model shown in Figure 190; the complex with **10.25b**, however, was notably more dissociated than that of **10.25a** (Figure 197b). These data seemed to imply that selective bromination substrates induce a more substantial conformational change than do less-selective ones in a manner analogous to conformational selection in enzymatic catalysis.

While these NMR titration studies generated valuable information on the ground state catalyst-substrate complex, the findings do not necessarily provide a readout on the stereodetermining transition state of the peptide-catalyzed quinazolinone bromination reaction. Following the identification of the τ_{i+2} correlation shown in Figure 195, we engaged in a collaboration with the Sigman Group to utilize multidimensional reaction analysis¹⁶³ to identify catalyst parameters relevant to asymmetric induction.⁴⁴⁵ Features of both limiting catalyst conformations—the type II' β -hairpin and the prehelical type I' β -turn—correlated well with the measured enantioselectivity ($\% ee$) in the bromination of quinazolinone **10.25a** (Figure 198). For the type II' β -turns, the infrared stretching frequency and intensity of the loop region amide C=O and N–H bonds, respectively, likely read out on the importance of this amide in nucleating an H-bonding interaction with the quinazolinone substrate. For the prehelical conformers, τ_{i+2} emerged as an important parameter, as well as the 10-membered β -turn H-bond strength measured through natural bond order (NBO) analysis. The Sterimol parameter L of the $i+3$ sidechain was found to be important in both models, suggesting that the steric effect of this residue is common to both peptide conformations. Ultimately, these findings imply that the enantioselectivity observed in the bromination of quinazolinones **10.25** may derive from a transition state ensemble wherein the catalyst interacts with the substrate from multiple conformational states.

Taken together, this body of work on the atroposelective bromination of biaryls (Section 10.1.1), tertiary benzamides (Section 10.1.2), amido-tropolones (Section 10.1.3), and 3-arylquinazolinones (Section 10.1.4) has provided a viable and robust strategy for the synthesis of enantioenriched atropisomers. The tribromide products of these transformations are of significant value in medicinal chemistry due to the drug-like properties of the core atropisomeric structures and their demonstrated elaboration using reliable cross-coupling methods. Moreover, these works have contributed significantly to the fundamental understanding of peptide-catalyzed transformations and the degree to which concepts imported from structural biology can be reliably exploited to achieve selectivity in small-molecule catalysis.

10.2. Desymmetrizing Bromination of Diarylmethylamido Bis(phenols)

In the atroposelective bromination reactions reviewed in Section 10.1, the peptide-based catalysts were able to impart enantioselectivity by effectively differentiating the enantiomeric orientations of a *meta*-phenol ring. While the crucial phenol OH group is

some extent, the primary source of asymmetric induction is indeed enantiotopic arene differentiation.

During the course of catalyst optimization, an interesting case of enantiodivergence was noted (Figure 201). Whereas Acpc-containing **10.38** delivered monobromide **10.36a** in 69% NMR yield and 95:5 er, its Aib homologue **10.10**—the lead catalyst discovered for the atroposelective benzamide bromination discussed in Section 10.1.2—provided 46% yield modestly favoring the opposite enantiomer in 42:58 er (entry 1). Moreover, the degree of enantiodivergence was found to be substrate dependent, with $\Delta G^\ddagger$ values ranging from 1.10–1.86 kcal/mol contingent upon nature of the amide substituents R and R' (entries 2–5). Enantiodivergent outcomes in asymmetric catalysis are uncommon for non-enantiomeric catalysts. This case is particularly striking, because the two catalysts in question only differ by a 2 amu-perturbation at an achiral residue. As such, the observed enantiodivergence most likely stemmed from differences in the secondary structures of **10.38** and **10.10** and how those structures interact with **10.35**.

A possible clue for this intriguing effect came from analysis of X-ray crystal structures of the catalyst library. As in the atroposelective quinazolinone bromination discussed in Section 10.1.4, a linear correlation between the measured ee of monobromide **10.36a** and the main-chain angle of the catalyst $i+2$ residue (τ_{i+2}) was observed (Figure 202). Again, catalysts with wide τ_{i+2} values delivered the highest ees, while values closer to tetrahedral (109.5°) gave modestly inverted selectivities. Based on the structural analyses we performed previously,⁵⁰ wide-angle Acpc-containing catalysts like **10.38** were expected to primarily adopt prehelical type I' β -turn structures in solution, while the narrower Aib-containing congeners like **10.10** were more likely to exist as type II' β -hairpins (see Figure 193). A major difference between these two conformations is that the loop region amide is flipped, or oppositely oriented, which could give rise to the observed enantiodivergence.

Based on these concepts, we proposed models wherein diarylmethylamido bis(phenol) **10.35** interacts with peptide **10.38** from its likely prehelical conformation and with **10.10** from its β -hairpin structure (Figure 203). In both models, a key intermolecular H-bond between the tertiary amine of the catalyst Dmaa residue and a phenol O–H of **10.35** is proposed to activate the substrate toward S_EAr . However, the oppositely oriented loop amides of **10.38** and **10.10** are proposed to invert the binding orientation of **10.35** through differential interaction with either antipode of the central pivalamide moiety.

This method provides access to highly enantioenriched diarylmethylamido bis(phenol) monobromides (*e.g.*, **10.36**) that can be reliably diversified using known cross-coupling protocols. A similar system was recently reported by Lewis and co-workers that employs a halogenase enzyme to enantioselectively chlorinate a diarylmethane bis(aniline) substrate with excellent levels of selectivity.⁴⁵⁰ On the other hand, the achievements of this study were made possible by the remarkable ability of a small molecule peptide to effectively differentiate enantiotopic phenols separated by long distances.

10.3 Asymmetric Bromolactonization

Halofunctionalization reactions of alkenes have been well established in the literature for over a century. These reactions typically proceed through the formation of a bridged haliranium ion followed by trapping with nucleophiles, allowing for the 1,2-difunctionalization of the olefin starting material.^{411,412,425} In many cases, formation of the haliranium ion intermediate renders these reactions stereospecific, making them quite valuable in organic synthesis. Olefin halolactonization, in particular, has found wide use as a reliable approach for the formation of lactone products that can be subsequently derivatized *via* displacement of the adjacent halide.⁴⁵¹ However, catalytic asymmetric variants have been difficult to realize through the years.⁴¹¹ This is due, in part, to the challenge associated with olefin-to-olefin haliranium ion transfer, which ultimately leads to product racemization if the rate is competitive with that of nucleophilic addition. In this context, Borhan and co-workers became interested in developing asymmetric halolactonization methods. In 2010, they developed an enantioselective chlorolactonization protocol that employs a cinchona alkaloid-derived organocatalyst to mediate halenium ion transfer.⁴⁵² This method provided the desired chlorolactone products in good yields and enantioselectivities up to 90% ee. The group soon expanded this methodology to address allylic amide substrates for the asymmetric synthesis of oxazoline and dihydrooxazine heterocycles depending on the cyclization mode.⁴⁵³

Building upon these works, the Borhan Group later pursued an alternative approach to catalytic, asymmetric halolactonization that would take advantage of hypervalent iodine(III) species generated *in situ* to mediate halenium ion transfer.⁴⁵⁴ The authors chose to investigate this strategy in the bromolactonization of 4-arylpenicillenic acid **10.40** to the corresponding bromolactone **10.41** (Figure 204). They proposed to embed an *ortho*-iodobenzamide moiety within a peptide scaffold, which would oxidatively cyclize to form a bromoiodinane intermediate upon exposure to NBS. The peptidic bromoiodinane would then serve as a bromenium transfer catalyst. This concept was based on the known ability of simple *ortho*-iodobenzamides to accelerate non-stereoselective bromolactonization reactions *via* the bromoiodinane intermediate.⁴⁵⁵ By incorporating the iodoarene moiety within a well-defined peptidic framework, this process could be rendered asymmetric.

The authors chose to investigate the bromolactonization of **10.40** using peptide-based catalysts adhering to three structural archetypes: (1) linear di- and tripeptides **10.42**, (2) pentapeptides **10.43** biased toward β -turns by incorporation of a central Pro-D-Xaa sequence, and (3) symmetrically substituted **10.44** (Figure 205).⁴⁵⁴ While scaffolds **10.42** and **10.43** place the catalytically active moiety at the *N*-terminus of the peptides, the aryl iodide is centrally located on **10.44**. The authors screened their catalyst library on microscale (50 μ mol) and only used ee values as the basis for peptide evaluation. In total, the authors investigated a library of nearly 40 peptides. All of the 29 peptides **10.42** provided full conversion to bromolactone **10.41**, and appreciable selectivity was only observed for tripeptides where R = *t*-Bu. The most selective catalyst of the set was *tert*-leucine-trimer **10.42a**, which provided **10.41** in 14% ee under the screening conditions. The four β -turns **10.43** examined gave no appreciable selectivity, with 5% maximum ee observed. No selectivity was observed with any of the three symmetrical aryl iodides **10.44**. Further

sequence optimization did not yield further improvements. However, **10.41** could be obtained in quantitative conversion and up to 24% ee using 111 mol% of tripeptide **10.42a**. The authors reasoned that this low “ceiling enantioselectivity” could be due to the high background rate and/or a low equilibrium population of the catalytically active bromoiodinane species.

While this approach ultimately did not deliver synthetically useful levels of ee in the bromolactonization of pentenoic acid **10.40**, this study presented a novel and interesting approach to asymmetric halolactonization at a time where few examples of this type of transformation were reported. Since then, much progress has been made in this realm, but no further attempts using peptide-based catalyst scaffolds have been made.

11. Transition Metal- & Lewis Acid-Peptide Complexes in Asymmetric Catalysis

While enzymes have long been considered ideal catalysts with respect to the near perfect levels of chemo-, site-, and enantioselectivity that they are able to impart on their substrates, a number of valuable transition metal-catalyzed reactions exist solely within the realm of synthetic chemistry, including but not limited to hydroformylation, olefin metathesis, and cross-coupling among others. Conversely, while ligand design for transition metal catalysis has enabled a plethora of powerful transformations, enantioselectivity can be hard to achieve for particular reaction classes or substrates, in particular those that contain functional groups that may bind to metal centers. Additionally, many ligand classes are difficult to derivatize, which often makes the tailoring of ligands for desired reactivity and selectivity outcomes quite challenging. The use of artificial metalloenzymes, wherein transition metal complexes are incorporated into the active site of an enzyme, has emerged as an extremely powerful solution.^{13,456–459} Additional approaches, however, are needed to combine the broad reactivity of organometallic complexes with the exquisite selectivity of enzymes. A strategy which has emerged at the interface between these two fields is the design of short peptide-based ligands, which can direct reactivity through noncovalent interactions with the substrate. The modular nature of peptide synthesis provides access to large amounts of chemical space, enabling the rapid generation of ligand derivatives. Elegant early applications of peptidic ligands in transition metal-catalyzed reactions include the pioneering work of Hoveyda, Snapper, and co-workers,^{214–216,460} Gilbertson and co-workers,⁴⁶¹ as well as the resin-bound phosphine catalysts developed by Landis.⁴⁶² This Section will specifically focus on the most recent advances in this area. Similarly, significant progress has been made in the application of single amino acid ligands in transition metal-catalyzed processes, such as the Cu-catalyzed cross-coupling reactions developed by Ma and co-workers⁴⁶³ and the C–H functionalization reactions reported by the Yu Group.⁴⁶⁴ In this Section, however, we have elected to focus only on examples employing ligands of two or more residues. Such peptide-based ligand systems have made significant recent contributions in several synthetically useful reaction classes, including allylation (Section 11.1), hydrogenation (Section 11.2), oxidation (Section 11.3), Lewis acid-catalyzed reactions (Section 11.4), Rh carbenoid-mediated insertions and cyclopropanations (Section 11.5), and cross-coupling (Section 11.6).

11.1. Allylation

The most common strategy for developing peptide-based ligands for transition metal catalysts is to incorporate a motif designed to coordinate the transition metal within the peptide sequence. In this scenario, the metal-ligating group directly interacts with the transition metal center, while the remainder of the peptide scaffold provides a (1) chiral environment for asymmetric induction through its secondary structure and (2) functional handles for orienting substrates through noncovalent interactions.

Many efforts have focused on exploring decorated phosphine ligands with peptide-based backbones. Seminal publications from Gilbertson and co-workers demonstrated that bidentate phosphine ligands, such as **11.3**, could be applied as ligands in palladium-catalyzed asymmetric allylation reactions (Figure 206).⁴⁶⁵ This study employed SPPS in order to rapidly generate and assess 96 on-bead catalysts in the allylation of **11.1** with dimethylmalonate. It was found that catalysts with sequences that were expected to disrupt the designed β -turn conformation provided allylic malonate **11.2** with lower ee values, suggesting that peptide secondary structure played a role in governing the enantioselectivity of this transformation. Further examination revealed that α,α -disubstituted residues at the $i+2$ position, such as Aib, were detrimental to selectivity. While these types of residues are often strategically incorporated at the $i+2$ to favor β -turn formation,²²³ in this case they introduce steric bulk oriented toward the coordinated Pd, which was detrimental for catalysis. Ultimately, Pro-D-Val-containing bis(phosphine) **11.4** was identified as the lead ligand, providing **11.2** in 75% ee. This pioneering work laid the foundation for much of the research discussed in this Section by demonstrating the modularity and efficacy of peptides as ligands for transition metals.

More recently, Meldal and co-workers explored the benefits of modular peptide ligand synthesis in the context of Pd-catalyzed allylation reactions of malonate **11.5** and allylic acetate **11.6** (Figure 207).⁴⁶⁶ Recognizing that *P,S*-ligands had been previously shown to be effective in these types of reactions, a series of Cys(*t*-Bu)-containing peptides **11.8** was synthesized, in which a phosphine moiety was appended to the amide backbone adjacent to the thioether in an arrangement that was intended to favor chelation of Pd. Surprisingly, the configuration of allylic malonate **11.7** was found to invert not only when L-Cys(*t*-Bu) was replaced with D-Cys(*t*-Bu) (entries 1 & 2 vs. 3 & 4), but also when the number of methylene groups between the phosphine and amide backbone was changed (entries 1–4 vs. 5–8). This changes the palladacycle formed from a six-membered to a seven-membered ring. The complete reversal of enantioselectivity as the result of an additional methylene is challenging to predict *a priori* and emphasizes how rapid screening methods can lead to the discovery of efficient catalysts and unanticipated reactivity and selectivity outcomes. The most selective catalyst **11.8** for this reaction, which possesses D-Cys and L-Phe moieties, delivered **11.7** in 60% ee (entry 3).

11.2. Hydrogenation

The self-assembly of subunits through complementary noncovalent interactions is an important process in nature that not only governs receptor–substrate association and protein

folding, but it also enables the formation of macromolecular assemblies that are critical in biological catalysis. Inspired by this, Breit and co-workers have extensively explored the utility of spontaneous molecular assembly as a means for rapidly generating catalysts for asymmetric transformations. Their initial efforts were focused on developing peptide-based mimics of PlanePhos, a cyclophane-derived, planar-chiral phosphine ligand (Figure 208).⁴⁶⁷ While bidentate PlanePhos is a powerful ligand class, members of this family often require multistep syntheses.⁴⁶⁸ An alternative strategy would be to design a simple monodentate phosphite ligand that could be programmed to self-assemble into a π -stacked complex similar to that of PlanePhos in the presence of a transition metal (Figure 208a). Peptide chains appended to the arenes could serve this function, as their functional group-rich nature makes them strong candidates to facilitate ligand assembly through precise H-bonding networks.

Upon treatment of ligands **11.9** and **11.10**, which contain both a BINOL-phosphite element and a peptide chain attached to the arene, with either *cis*-[Cl₂Pt(cod)] or [Rh(cod)₂]BF₄, the desired homodimeric helical complexes formed.⁴⁶⁷ The structure of the Pt complex of **11.10** and its helical tail was confirmed by X-ray crystallography. However, NMR analysis revealed that while the arene stacking was stable in solution, H-bonding between peptide chains appeared to be dynamic. As a control, a Rh complex with ligand **11.11** that lacks the potential to self-assemble through H-bonding, was synthesized and evaluated. The three Rh complexes derived from ligands **11.9**, **11.10**, and **11.11** were next evaluated in the hydrogenation of α,β -unsaturated esters **11.12** (Figure 208b). The absolute configuration of products **11.13** was determined by the BINOL-phosphite moiety of the ligand. For **11.12a** and **11.12b**, the (*S*)-BINOL-derived catalyst led to (*R*)-**11.13a,b** (entries 1 & 4), while the (*R*)-BINOL catalyst diastereomer delivered (*S*)-**11.13a,b** selectively (entries 2–3 & 5–6). In the case of **11.12c**, the (*S*)-BINOL catalyst provided the (*S*)-product **11.13c** (entry 7), and the (*R*)-catalyst provided the (*R*)-product (entries 8 & 9). While subtle, the peptide chain does appear to be matched stereochemically with the (*R*)-BINOL-phosphite, as absolute enantioselectivities are higher for all substrates **11.12** with ligand **11.10** than **11.9**. Intriguingly, catalyst **11.11**, which does not have a peptide chain to anchor the ligand self-assembly, still provides excellent levels of enantioselectivity for all substrates and is most selective for **11.12c** (entry 9).

Breit and co-workers further expanded upon this concept of self-assembly to probe the viability of developing heterodimeric ligands capable of spontaneously constructing β -sheets (Figure 209a).⁴⁶⁹ This phenomenon is not only of interest to the synthetic community as a means of generating PlanePhos mimics, but it is also relevant to the independent study of protein self-assembly in nature.⁴⁷⁰ As such, two classes of phosphine ligands, C-terminal peptidyl ligands (L_C, **11.17–11.20**) and N-terminal peptidyl ligands (L_N, **11.21–11.23**), were chosen that contained complementary amide functionality for matched H-bonding (Figure 209b). NMR and MS studies revealed that when L_C and L_N were added together without metal, they did not form a complex. However, upon addition of *cis*-[PtCl₂(cod)] to a 1:1 mixture of both ligand classes, a coordination complex was observed to form. Despite the statistical probability of a 50:25:25 mixture of heterodimeric complex to the two homodimeric complexes, heterodimer formation predominated in almost every case owing

to the matched inter-peptide H-bonding. Further NMR and DFT studies confirmed the existence of the proposed β -sheet, with a non-traditional H-bond between the *ortho*-aryl C–H of L_C and the pyridine of L_N (Figure 209a). When these catalysts were applied in the hydroformylation of styrene **11.14**, homodimeric complexes of both L_C ligand **11.17** and L_N ligand **11.22** were found to exert excellent control over the ratio of linear (L) and branched (B) products **11.15** and **11.16** (entries 1 & 2). However, the major branched aldehyde **11.15** was nearly racemic in both cases. Conversely, the heterodimeric complexes were notably more enantioselective at the expense of B/L ratio (entries 3–6). For example, the heterodimeric complex between **11.18** and **11.22** was found to deliver branched **11.15** in 87:13 B/L and 36% ee (entry 4).

In light of these publications from the Breit Group, Kirin and co-workers noted that the proposed interactions between the L_C and L_N ligands formed two 10-membered ring H-bonds, which is analogous to β -turn motifs (Figure 210).⁴⁷¹ The effect of inter-strand H-bonding on ferrocene helicity had been previously studied by Herrick and co-workers,^{472,473} and it was found that the inter-strand H-bonding pattern within the sidechain is propagated through a “backdoor effect” to determine the helical chirality of the stacked aromatic rings (Figure 210a). The helical configuration of these ligands in turn governs the major product enantiomer observed in the hydrogenation of dehydroalanine derivative **11.12** (Figure 210b). In this way, remote chiral information is relayed to enforce the stereochemical outcome of the reaction.

Keeping this mode of asymmetric induction in mind, a series of Rh catalysts were synthesized containing monodentate arylphosphine ligands similar to those explored by Breit,⁴⁶⁷ but with several key differences (Figure 210a). Initial studies focused on ligands containing *para*-arene substitution, which would render the system insensitive to 180° rotations about a single ligand. In combination with pendent L-amino acids, these *para*-substituted ligands induced *P*-helical chirality and ultimately provided the (*R*)-enantiomer of **11.13**. Trimeric peptides with C-terminal amides were employed in order to maximize H-bonding interaction between strands (Figure 210c). Following optimization, peptide **11.24** was determined to be the premier ligand, affording **11.13** in >98% yield with 68% ee. In subsequent studies, the authors found that through incorporating additional H-bonding residues at the 3- and 5-positions of the phosphine ligand (*e.g.*, **11.25**), an increased number of H-bonding interactions could be promoted, further increasing enantioselectivity of **11.13** to 84% ee.⁴⁷⁴ It was generally observed that smaller peptide chains resulted in higher levels of enantioselectivity, while phosphine ligands containing longer peptide chains were less selective. Ultimately, peptide **11.25**, which contains two Ala residues, was found to be the optimal ligand for the hydrogenation of **11.12**. Consistent with their proposed model for “backdoor induction,” the observed (*S*)-enantiomer of the product was opposite to that observed with 4-substituted ligands, despite the fact that amino acids with the same sense of chirality were used in both cases. Finally, bidentate phosphines that were connected by various carbon-based linkers were explored (*e.g.*, **11.26–11.28**).⁴⁷⁵ It was found that as the rigidity of the linker increased, a concomitant increase in the enantioselectivity was generally observed, with **11.28** providing (*R*)-**11.13** in >98% yield and 81% ee. It was

proposed that this increased linker rigidity promoted H-bonding interactions between the two Ala residues, leading to a greater chirality transfer to the metal site.

In a similar way, the Neumann Group has taken advantage of the propensity of ambiphilic, anionic peptides, such as **11.29** and **11.30**, to self-assemble upon treatment with cationic transition metal species (Figure 211).^{476,477} These peptides have been shown to self-assemble in water *via* coordination of the *N*-terminal phosphonate functionality with Ti(IV) to form macrocyclic complexes (Figure 211a). By incorporating a large number of hydrophobic residues, a porous material is formed with many chiral, hydrophobic pockets that are sequester organic reagents. This strategy was found to be highly effective for incorporating an achiral Ru complex into the chiral pocket, generating an molecular assembly capable of catalyzing the asymmetric hydrogenation of ketones, such as **11.31**, to secondary alcohols, such as **11.32** (Figure 211b).⁴⁷⁷ In general, it was found that enantioselectivity correlated with the degree of hydrophobicity of the catalyst (entries 1–3), with Phg-containing **11.29** providing **11.32** in 70% ee when coupled with tetraphenyl Ru-complex **c** (entry 3). The same trend was observed with Leu-containing peptide **11.30** (entries 4–6), but the degree of enantioselectivity was generally lower. The authors also demonstrated that these peptide assemblies were able to encapsulate Mn-salen complexes to form chiral catalysts for the asymmetric epoxidation of styrenes **11.33** (Figure 211c).⁴⁷⁶ Peptide **11.29** effectively coordinated the Mn complex to generate assembly **11.29d**, which delivered epoxides **11.34** and diols **11.35** in good yields and enantioselectivities over a modest scope (entries 1–4). In general, diols **11.35** were obtained with higher ee values.

In addition to the design of catalytic phosphine and phosphonate complexes that self-assemble, naturally occurring peptidic architectures have also been explored. For instance, a peptidic natural product, gramicidin S, adopts a β -hairpin conformation by virtue of its cyclic structure (Figure 212).^{478,479} Additionally, the two ornithine (Orn) residues orient their sidechains on the same face of the macrocycle, providing handles for functionalization with transition metal-coordinating groups. Using this parent scaffold, several peptidic arylphosphine ligands **11.36–11.39** were synthesized and examined in the asymmetric hydrogenation of dehydroalanine **11.12a**. While, gramicidin-based ligands with *ortho*-arylphosphine (**11.36**) and alkylphosphine (**11.39**) linkages were inactive (entries 1 & 4), those with *meta*- (**11.37**) and *para*-linkages (**11.38**) to the Orn sidechains delivered **11.13a** with modest enantioselectivities (entries 2 & 3). Intriguingly, ligands **11.37** and **11.38** were observed to be enantiodivergent, affording opposite enantiomers of **11.13a** despite the fact that they contain identical stereoconfigurations. It was speculated that shortening the distance between the phosphine and the amide backbone may increase the enantioselectivity of the reaction by placing the metal center closer to the chiral information of gramicidin S.

11.3. Oxidation

Asp-containing peptides have found wide utility in peracid-mediated oxidations in recent years (Section 2.2).^{43,78} Based on this body of work, Costas and co-workers envisioned a complementary application of carboxylate-embedded peptides as ligands for organometallic oxidations (Figure 213).⁴⁸⁰ Fe-PDP complexes were first developed by White and co-workers in 2007 as highly selective C–H oxidation catalysts in the presence of hydrogen

peroxide and acetic acid.⁴⁸¹ The Costas Group later reported the more electron-rich Fe-PDP^{NMe2} complexes that were able to catalyze the epoxidations of enones with high levels of stereoselectivity.⁴⁸² The authors hypothesized that carboxylate-containing peptides may serve as competent ligands for Fe-PDP, such that the selectivity afforded by the complex could be tuned *via* outer-sphere interactions rather than inner-sphere coordination (Figure 213a).⁴⁸⁰ This concept is fundamentally similar to how the selectivity of enzymatic Fe complexes is altered by virtue of the surrounding amino acid residues. It was found that when Fe-PDP^{NMe2} was paired with peptide **11.42**, which contains a central D-Pro-Pro β -turn motif and a free C-terminus, high levels of selectivity could be achieved in the epoxidation of styrenes **11.40** *via* the carboxylate-coordinated Fe complex (Figure 213b). Epoxides **11.41** were obtained in up to 84% yield and 96:4 er under these conditions. While enantioselectivity was found to be governed by the configuration of the Fe-PDP^{NMe2} complex, the chirality of the peptide needed to be matched in order to ensure high levels of selectivity. Control experiments using acetic acid as a simple carboxylate ligand indicated that high selectivity is a function of not only the chiral metal center, but of the more remote stereocenters present on the peptide ligand **11.42** as well (Figure 213c).

11.4. Lewis Acid Catalysis

Multiple strategies have recently emerged for using peptides as chiral ligands in Lewis-acid catalyzed reactions. For example, Roelfes and co-workers took advantage of the secondary structural motifs present in bovine pancreatic polypeptide (bPP) to design a peptide-based ligand capable of coordinating Cu (Figure 214).⁴⁸³ The sequence of bPP is only 36 amino acids long, and its structure is comprised of a type II helix (residues 1–8), a β -turn (residues 9–12), and an α -helix (residues 13–31). These proteins naturally dimerize in water due to hydrophobic interactions to form an antiparallel homodimer (Figure 214a). It was thought that substitution of Tyr7 (shown as “N” in Figure 214a) for a Cu-coordinating residue, such as His or Pal, would be ideal, since this residue is found at the dimer interface such that a bidentate Cu complex could be formed upon dimerization *via* coordination with the “N” residue on both peptides. The authors therefore synthesized and designed a series of bPP mutants **11.43–11.47**, in which Tyr7 is replaced with His, 4-Pal, & 3-Pal (Figure 214b). These ligands were then evaluated in Lewis acid-catalyzed reactions of enones **11.48** and **11.49** using Cu(II) salts (Figure 214c). In the Diels–Alder reaction of **11.48** with cyclopentadiene, peptide **11.45**—the direct 3-Pal analog of bPP—delivered cycloadduct **11.50** in 73% conversion and 83% ee (entry 3). Peptide **11.46**, in which the Asp10 residue is replaced with a Glu, was also found to be effective, providing **11.50** in quantitative conversion and 80% ee (entry 4). The His- and 4-Pal-containing peptides **11.43** and **11.44** were unselective in this transformation (entries 1 & 2), as was the triple bPP mutant **11.47** (entry 5). In the Cu-catalyzed conjugate addition of dimethylmalonate into **11.49**, peptides **11.45** and **11.46** were again found to be selective, delivering the **11.51** in 66% and 86% ee, respectively, at good levels of conversion (entries 6 & 7). In this case, however, triple mutant **11.47** was similarly effective to **11.45**. These data show that the identity of the coordinating residue has a profound impact on the selectivity of the peptidic Cu complex. In addition to providing a chiral environment for asymmetric induction, the dimerized peptides greatly accelerated reaction rates due to the effective increase in the concentration of reagents sequestered in the hydrophobic cavities.

Herrmann and co-workers also examined the potential for small peptides to serve as chiral ligands in similar Lewis acid-catalyzed reactions (Figure 215).⁴⁸⁴ They reasoned that focusing on shorter peptide sequences would be generally more tractable than larger protein domains, facilitating the synthesis of small ligand libraries that could be evaluated in the Cu-catalyzed Diels-Alder reaction of enones **11.48**. Inspired by the widespread occurrence of disulfide bridges in proteins and their influence on secondary structure, a series of cyclic peptides containing disulfide bridged Cys residues at the *C*- and *N*-termini were synthesized in order to enforce a rigid conformation within the peptide. These peptides could then ligate Cu(II) either *via* the free amine *N*-terminus or a His side-chain. While initial library screening identified selective His containing catalysts, ultimately **11.52** was found to be most selective, providing cycloadduct **11.50** in 85% ee. An Ala scan experiment was performed, wherein each individual residue is mutated to Ala in order to assess the contribution of each residue to selective catalysis. Surprisingly, the only mutation that significantly affected the reaction outcome was that of the achiral Gly residue just upstream of the *N*-terminal Cys; when this Gly was substituted for Ala, racemic **11.50** resulted. All of the other Ala variants provided only minor perturbations to the 85% ee result with **11.52**. While these results are potentially consistent with *N*-terminal coordination of Cu(II), the exact site of binding was not rigorously determined. Truncation studies ultimately led to the identification of hexapeptides **11.53** and **11.54** as highly selective catalysts, which delivered **11.50** in 94% and 96% ee, respectively. Control experiments with linear variants of **11.53** and **11.54** showed no selectivity, confirming the efficacy of the cyclic structures. The scope of these ligands was then investigated in related Diels-Alder and Friedel-Crafts reactions (Figure 216). The authors focused on reactions of α,β -unsaturated 2-acylimidazole **11.55** rather than pyridine-containing **11.48** due to the challenges associated with removing pyridyl auxiliaries. Ligands **11.53** and **11.54** proved to be quite effective in both of these transformations, providing cycloadducts **11.56** in up to 99% conversion, 96:4 *endo/exo* ratio, and 99% ee (Figure 216a) and Friedel-Crafts products **11.57** in up to 99% conversion and 86% ee (Figure 216b).

A potentially powerful approach to the design of peptide-ligated transition metal catalysts is to take advantage of the natural metal binding domains found in enzymes. Human Ctr-1 is a membrane protein of 190 amino acids that serves as a Cu transporter. Within this protein, a short sequence of eight residues called Mets7 was known to bind well to Cu(I) and Pt(II).⁴⁸⁵ Recognizing this, Rimoldi and co-workers examined the efficacy of Mets7-Cu complexes as Lewis acid catalysts for Henry (nitroaldol) reactions of benzaldehyde **11.58** with nitromethane **11.59** (Figure 217).⁴⁸⁶ Native peptide **11.61a** was found to adopt two major conformations using MD simulations, both of which were consistent with β -turn motifs (Figure 217b). However, this sequence exhibited a high degree of flexibility, and cluster analysis predicted that only 57% of the population would adopt either of these β -turn conformations at a given time. This structural heterogeneity may have resulted in lower levels of enantioselectivity in the Henry reaction, as the product was isolated in only 48% ee using **11.61a** as the ligand. Recognizing that a more rigid structure may be better suited for asymmetric catalysis, modified peptide **11.61b** was proposed, which possesses a nonnative β -turn-promoting motif consisting of a functionalized piperidine linked to a Pro residue that was expected to render the structure more rigid. Indeed, MD simulations predicted 91% of

the population of **11.61b** to occupy the two major β -turn conformations, and this ligand showed notable improvements in enantioselectivity, providing the nitroaldol product **11.60** in 75% ee at similar conversion.

11.5. Rhodium Carbenoid-Mediated Insertions & Cyclopropanations

The Ball Group has recognized that dirhodium tetracarboxylates are attractive transition metal complexes for incorporation into peptide scaffolds (Figure 218). Not only have they been shown to catalyze myriad carbenoid insertion reactions in water, but they have been found to be stable to carboxylate exchange in water at pH < 7.⁴⁸⁷ Previous work from the Ball Group had demonstrated that Rh(II) could be bound to peptides through Asp sidechains. These Rh-peptide catalysts were capable of site-selective carbenoid insertion reactions on complex peptide substrates.⁴⁸⁸ Emboldened by these successes, the authors began to explore the efficacy of Rh-peptide catalysts in asymmetric insertion reactions of small molecule substrates.⁴⁸⁹ Using the Si–H insertion of dimethylphenylsilane into methyl α -diazophenylacetates **11.62** as a model reaction (Figure 218a), they assessed a series of peptides containing either Glu or Asp at the *i* and *i*+4 positions so that both carboxylate functional groups would be displayed on the same face of the helical secondary structure (Figure 218b). Moreover, either monomeric or dimeric catalysts with respect to the peptide ligands were accessible from Rh-tetraacetate species. As such, monomer **11.64a**, parallel dimer **11.64b**, and anti-parallel dimer **11.64c** were synthesized by complexation of peptide **11.64** with dirhodium tetraacetate. Evaluated in the silane insertion reaction of **11.62**, the three Rh-peptide complexes exhibited different levels of enantioselectivity. Notably, anti-parallel dimer **11.64c** was significantly more selective than the monomer and parallel isomer, providing silane product **11.63** in 45% ee. During ligand optimization, it was found that the anti-parallel isomer generally afforded higher levels of enantioselectivity than the other isomer across all 22 peptide sequences assessed. Modifications at residues adjacent to the Asp residues were particularly influential on the observed selectivity, presumably due to their proximity to the metal center. Ultimately, peptide **11.65** emerged from optimization as the lead ligand, providing silanes **11.63** in up to 97% yield and 99% ee. CD experiments confirmed that a helical conformation is achieved upon complexation with the dirhodium species.

While the parallel and anti-parallel isomers of the Rh-peptide dimers proved to be readily separable by chromatographic methods, identification proved to be more challenging, as both isomers showed similar NMR signatures, even at low temperatures, in many cases. Pyrene Excimer Fluorescence is a distance-sensitive technique that has been used as a tool in the study of peptide assembly. In this technique, fluorescence is only detected in situations where pyrene functionalities are in close proximity to one another, such that a π -stacking exciplex can be formed. In the context of dimeric Rh-peptide complexes, only the parallel configuration should exhibit fluorescence (Figure 219a). Given that the two isomers do not interconvert, even under forcing conditions, this technique was employed to unambiguously determine the orientation of isolated peptides.⁴⁹⁰ The superior performance of the anti-parallel peptide in carbenoid insertion reactions (Figure 218) is intriguing from the standpoint of molecular symmetry. While both dimeric isomers are C_2 -symmetric, the axis

symmetry of anti-parallel **11.65-Pyr** passes through both Rh atoms such that the metal centers are non-equivalent, allowing for multiple sites of catalysis (Figure 219b).

Ball and co-workers have also applied similar Rh-peptide complexes in the asymmetric cyclopropanation of styrene derivatives (Figure 220).⁴⁹¹ In order to accelerate the discovery of selective ligand sequences, a small library of peptides was synthesized on-bead (Figure 220a). Because it is challenging to synthesize dimeric peptide complexes on solid support, the authors elected to evaluate monomeric Rh-peptide complexes on-bead wherein two acetate ligands replaced a second peptide, and assumed that the selectivity of an optimized mono-peptide ligand would be improved upon conversion into a dimer complex with two peptides. However, while several dimeric peptides outperformed their monomeric, on-bead counterparts, no direct correlation was observed. Moreover, some peptides that had performed poorly on-bead demonstrated high enantioselectivities as the dimer complexes, suggesting that some viable candidates had been excluded using this method. However, the majority of unoptimized sequences were not effective catalysts. Following optimization, complex **11.68** was identified, which catalyzed the cyclopropanation of styrenes with α -diazophenylacetates **11.66** to deliver **11.67** in up to 95% yield and 95% ee over a modest scope (Figure 220b). Intriguingly, complex **11.69** also emerged from this screening strategy, delivering *ent*-**11.67** in up to 94% yield and 97% ee. Peptides **11.68** and **11.69** are not enantiomers of one another, and yet they deliver enantiodivergent outcomes. Because these peptides are both comprised of only L-residues and differ only at residues flanking the active ligand motifs, it is possible that enantiodivergence stems from differences in secondary structure.

In light of these results, the Ball Group next sought to develop monomeric Rh-peptide scaffolds that showed comparable reactivity and selectivity to the previously reported dimers and that would allow for on-bead screening of catalysts (Figure 220).⁴⁹² A contributing factor to the poor performance of monomeric Rh-peptide complexes is the lack of symmetry, which leaves the two Rh atoms in chemically unique environments, each of which can catalyze the reaction with different levels of selectivity. In order to address this, the Ball and co-workers evaluated a library of peptides which contained adjacent His residues that could potentially coordinate to an exposed axial site of the Rh complex (Figure 221a). This was hypothesized to inactivate a less selective site of catalysis, which could improve the selectivity of the overall transformation. Following optimization, peptide ligand **11.70** was identified (Figure 221b), which was found to be highly reactive and selective in the cyclopropanation of alkenes **11.71** with α -diazophenylacetates **11.66**, providing cyclopropanes **11.72** in up to 99% yield and 99% ee over a modest scope (Figure 221c). In contrast to the previously optimized catalysts, this new His-containing peptide only showed high enantioselectivity as an on-bead catalyst as opposed to in solution. It was shown that axial binding of the His residue disrupts the helical structure of the peptide, which enables additional intermolecular His–Rh interactions with the more active Rh atom instead (Figure 221a). While intermolecular His–Rh coordination keeps the helical structure intact, this results in the aggregation of the peptide catalysts, decreasing the enantioselectivity of the reaction. Conversely, on-bead catalysts have a limited ability to engage in intermolecular interactions, and do not aggregate. Ultimately, this strategy simultaneously simplified

catalyst synthesis by removing the requirement to separate parallel and anti-parallel dimer isomers and enabled the rapid on-bead screening of catalysts, which led to the identification of more selective catalysts for this known cyclopropanation reaction.

Section 11.6. Cross-Coupling

While examples of asymmetric cross-coupling are increasingly common in the literature, most reported examples involve bond formation directly at the newly formed stereogenic element.^{493–495} In contrast, cross-coupling reactions that establish chirality in the broader context of the molecule, as is the case of desymmetrization reactions, are relatively rare. In such transformations, chiral information needs to be relayed between the site of bond formation and the remote stereogenic element. This problem is further exacerbated when the catalyst is required to discriminate between remote enantiotopic sites, as is the case in desymmetrization reactions. Our group has recently detailed several reports wherein diarylmethine substrates, such as **11.73**, are desymmetrized *via* Cu-catalyzed cross-coupling reactions to form C–C,⁴⁹⁶ C–O,⁴⁹⁷ and C–N bonds (Figure 222).⁴⁹⁸ Key to the success of these coupling reactions was the development of peptide-based ligands containing an *N*-terminal tetramethylguanidinylated Asp residue (TMG-Asp), which is linked to the peptide scaffold through its sidechain. This active ligand moiety is proposed to form a 5-membered *N,O*-chelate with the Cu(I) catalyst that facilitates bond formation.

The TMG-Asp ligand moiety was originally developed for the cross-coupling of **11.73** with malonate nucleophiles to deliver C–C coupled products **11.74** (Figure 222).⁴⁹⁶ In order to relay stereochemical information between the prochiral center of **11.73** and the site of bond formation, additional recognition elements were required. It was hypothesized that a catalyst capable of interfacing with both termini of the substrate would enable close catalyst–substrate interactions and assist in the discrimination of the remote enantiotopic aryl bromides. The presence of a *C*-terminal carboxylate in peptide-based ligand **11.77** was found to improve enantioselectivity significantly. This carboxylate moiety was initially thought to interact with the distal site of **11.73** in a salt bridging interaction with the deprotonated trifluoroacetamide. In order to probe this hypothesis, a series of kinetic resolution experiments were performed on racemic substrates **11.80** (Figure 223). While racemic diarylmethine **11.80a**, which lacks one of the aryl bromides, was processed with a moderate k_{rel} of 5.3, compound **11.80b** lacking a trifluoroacetamide gave a high k_{rel} of 11.3, suggesting that the proposed salt bridging interaction was not operative in the selective desymmetrization pathway. Moreover, compound **11.80c**, which lacks both bromide and trifluoroacetamide substituents on the distal arene, was also processed with a high k_{rel} of 10.3. To compliment these findings, substrates lacking aryl functionality altogether, such as **11.80d** and **11.80e**, afforded low k_{rel} values. Taken together, these data suggest that the aryl group itself, rather than any substituent, was required for strong catalyst–substrate interactions with peptide **11.77**. As such, we ultimately proposed that the *C*-terminal carboxylate of the peptide interacted with the distal unfunctionalized terminus of the substrate through a cation- π interaction that is not possible with substrates **11.80d** and **11.80e**.

During subsequent studies examining C–O bond formation using phenol nucleophiles to deliver diarylethers **11.75**, stereochemical relationships within the peptide ligand were more rigorously explored (Figure 222). Although tetrapeptide **11.78**—which contains four different residues—was found to be optimal with respect to yield and enantioselectivity, only the stereocenters at the *i* and *i*+1 positions were found to impact catalytic performance to a significant degree. Additionally, the *i* position was shown to be stereodetermining, as inverting this chiral center resulted in *ent*-**11.75**. In contrast, substitutions at other positions provided nearly identical results in most cases to those observed when **11.78** was employed. Using peptide ligand **11.78**, a broad scope of diarylethers **11.75** could be accessed in up to 71% yield and 99:1 er. Notably, *ortho*-substituted phenols, a challenging class of substrates in other cross coupling methodologies, were viable nucleophiles in this Cu-peptide-mediated reaction. Furthermore, phenol substrates bearing benzylic alcohols as well as indole functionality were well tolerated, with exclusive coupling at the phenolic oxygen.

While exploring the viability of nitrogen-based nucleophiles in the desymmetrization of **11.73**, it was found that both anilines and amines afforded the desired *N*-arylated product. However, due to the high nucleophilicity of the resulting diarylamine product, partial cyclization would occur for many substrates, affording the corresponding benzimidazoles **11.76** (Figure 222). As such, we elected to expose the crude reaction mixtures to acidic conditions in order to fully drive cyclization to completion. Under the optimized reaction conditions, a variety of anilines with diverse electronics and substitution patterns were found to be well tolerated by the newly optimized ligand **11.79**, providing benzimidazoles **11.76** in up to 71% yield and >99:1 er. Similarly, benzylic, primary, and secondary amines were also found to be effective coupling partners. Intriguingly, upon acid-mediated cyclodehydration of the intermediate diarylaniline species containing sufficiently bulky *ortho* functionality, a chiral axis was formed as a result of hindered bond rotation about the C–N bond. We questioned if this process could be performed under catalyst control to selectively set an additional element of chirality within the same scaffold. Several pThr-containing peptide catalysts (see Section 3) were evaluated in the atroposelective cyclodehydration of diarylaniline **11.82** to benzimidazole **11.83** (Figure 224a). Peptide **11.84** emerged as highly selective for this transformation, providing **11.83** in 99% conversion and 96:4 er (entry 1). The configuration of the pThr β -stereocenter and the nature of the β -turn loop region was found to have influence the sense of asymmetric induction, as allothreonine-containing peptide **11.85** delivered *ent*-**11.83** in 99% conversion and 17:83 er (entry 2). When this strategy was applied to enantioenriched diarylmethine **11.86**, both diastereomers of product could be accessed with high diastereo- and enantioselectivity, under complete catalyst control (Figure 224b).

12. Conclusion & Outlook

Peptide-based catalysts now encompass many classes and have been applied to numerous reaction types. It seems inevitable that the field will continue to record impressive successes as this approach to catalysis is implemented in increasingly complicated reaction classes and substrate types. As a result, while opportunities for expansion seem easy to anticipate, it is more challenging to extract the broader lessons that these peptides may teach. For example,

are we moving closer to an era in which it may be possible to design effective peptidic catalysts from first principles, or will a reliance on integrated design and screening approaches persist well into the future? The use of modern physical organic tools presents exciting opportunities to push the field toward a deeper understanding and, eventually, explicit molecular design.^{499,500} Yet, it also seems likely that at least some stochastic aspect of the catalyst discovery process will persist. In this sense, we are reminded of the evolutionary history of enzymes. While convergence on a finite number of protein folds supports catalysis of reactions in far greater number,⁷⁷ it is also true that the nuances of catalyst variation within enzyme classes can be very great, and of course evolvable to the desires of humans directing evolution.⁵³ Very likely, peptide-based catalysts—and maybe all classes of catalysts—will be subject to the same opportunities for convergence on a finite number of powerful scaffolds. However, adaptability to applications in the essentially infinite diversity presented by chemical space⁵⁰¹ will continue to generate more catalysts for application-specific settings. In this sense, it is well to conclude on an optimistic note, celebrating the achievements of highly effective catalysts, including some that are privileged,³⁸⁸ while welcoming ever more catalysts into a less exclusive, but no less special club.

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Alex J. Chinn began his chemical career at The College of William and Mary, where he received a B.S. in Chemistry. He went on to obtain a Ph.D. in chemistry from Yale University in 2019 under the guidance of Professor Scott J. Miller. While at Yale, his research focused on the design of peptide-based ligands and their application in asymmetric cross-coupling reactions. He is currently conducting postdoctoral research at Princeton University with Professor Abigail G. Doyle.

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Byoungmoo Kim received a B.Sc. in Biochemistry at the University of Waterloo, Canada, in 2008 and a Ph.D. in organic chemistry under the supervision of Professor Vy M. Dong at the University of Toronto and partly at the University of California, Irvine in 2014. In the Dong Group, he developed new stereoselective methods using rhodium catalysts. He then undertook a postdoctoral position in Professor Scott J. Miller's research group at Yale University (2014–2019), where he developed new, chiral, peptidic ligands and discovered unique stereochemical phenomena. In the Fall of 2019, he started his independent career as an assistant professor in the Department of Chemistry at Clemson University. His group is interested in developing new synthetic methods for biomacromolecule functionalization.

Scott J. Miller is from Buffalo, NY. He received his B.A. (1989), M.A. (1989), and Ph.D. (1994) from Harvard University, working with Professor David Evans as an NSF Predoctoral Fellow. He was an NSF Postdoctoral Fellow at the California Institute of Technology with Robert Grubbs before joining the faculty at Boston College in 1996. Since 2006, he has been on the faculty at Yale University.

AMINO ACID RESIDUE ABBREVIATIONS

Aboc	2-aminobicyclo[2.2.2]octane carboxylic acid
Acbc	1-aminocyclobutane carboxylic acid
Acc	β -aminocyclopropylcarboxylic acid
Achc	1-aminocyclohexane carboxylic acid
Acpc	1-aminocyclopropane carboxylic acid
^AGly	γ -aminoadamantanecarboxylic acid
Aic	2-aminoindane carboxylic acid
Ala	alanine
Ala(1-Pyn)	1-pyrenylalanine
Arg	arginine

Asn	asparagine
Asp	aspartic acid
Atz	tetrazolylylalanine
Cbaa	cyclobutane γ -amino acid
Cha	cyclohexylalanine
Chg	cyclohexylglycine
Cle	cycloleucine
Cys	cysteine
(Cys)₂	cystine
Dap	diaminopropionic acid
Dmaa	dimethylaminoalanine
Gln	glutamine
Glu	glutamic acid
Gly	glycine
His	histidine
Hse	homoserine
Hyp	hydroxyproline
Ile	isoleucine
Leu	leucine
Lys	lysine
α-Mba	α -methylbenzylamine
Met	methionine
Nal	naphthylalanine
Orn	ornithine
3-Pal	3-pyridylalanine
Phe	phenylalanine
Phg	phenylglycine
Pip	pipecolic acid
Pmh	π -methylhistidine

Pro	proline
pThr	phosphothreonine
Ser	serine
Thr	threonine
Tle	<i>tert</i> -leucine
TMG-Asp	tetramethylguanidinylated aspartic acid
Trp	tryptophan
Tyr	tyrosine
Val	valine.

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Figure 1.

(a) Juliá-Colonna epoxidation. (b) Synthesis of polypeptides by polymerization with *N*-carboxyanhydrides. (c) Analysis of reaction mechanism and intermediates. (d) Proposed model for stereoselectivity.²¹

• *n*-BuNH₂ is normally used as initiator

• insoluble, powdery, & recyclable catalyst

entry ^a	catalyst	time (h)	yield (%)	er
1	2.3a	2	96	98:2
2	<i>n</i> -BuNH ₂ -poly(Leu) (2.3b)	54	66	81:19

^a Substrate **2.1a**, with R₁ = R₂ = Ph, was used for catalyst optimization.

Figure 2.

(a) Synthesis of imidazolium-containing poly(Leu) catalyst. (b) Epoxidation reactions.²⁴

Figure 3.

(a) Epoxidations of enals mediated by Pro-containing peptides with both β-turn and α-helix design elements. **(b)** Epoxidations of enones mediated by free *N*-terminal arene-containing residues.^{26,27}

- Mg-Al hydrotalcites can immobilize poly(Leu) peptides.
- Immobilization can be performed in H_2O in 30 min under ultrasonic treatment.
- Catalysts require no pre-activation, can be filtered, & are reusable.

Figure 4.

Juliá-Colonna epoxidations mediated by poly(Leu) peptide immobilized on hydrotalcite.²⁹

Figure 5.

(a) Stapling of short peptides in order to stabilize helical conformations. **(b)** Epoxidations utilizing stapled and unstapled peptides.³⁰

Figure 6.

(a) Epoxidation with peptide containing helical forming cyclic residues. **(b)** Crystal structure of peptide **2.10c**. Adapted with permission from ref. 34. Copyright 2010 American Chemical Society.

Figure 7.
 Juliá-Colonna epoxidations mediated by cyclic dipeptides.³⁵

Figure 8.

(a) Cartoon depicting the synthesis of a polypeptide with a rotaxane-based molecular machine. (b) Synthesis of a poly(Leu) peptide with a rotaxane-based molecular machine. (c & d) The degree of polymerization (DP) with and without the molecular machine approach. (e) Epoxidations mediated by the rotaxane-based poly(Leu) catalysts. Adapted with permission from ref. 37. Copyright 2017 Nature Publishing Group.

Figure 9.

(a) Polymerization of amino acids mediated by the protease papain utilizing mechanosynthesis. **(b)** Cartoon representation of simple ball milling. **(c)** Water is beneficial for many lipophilic amino acids, indicating that a hydrophobic effect could be operative. **(d)** Epoxidations with mechanosynthesized peptides.³⁹

^a Using **2.1a**, where R¹ = R² = Ph. ^b 10 mol% peptide.

Figure 10.

(a) Juliá–Colonna epoxidations in pure water. **(b)** Mechanistic model centered on a hydrophobic cavity formed from the Leu sidechains of the α -helix. Adapted with permission from ref. 42. Copyright 2017 Royal Society of Chemistry.

Figure 11.

(a) Putative catalytic cycle for the generation of electrophilic aspartyl peracid species. (b) Epoxidation of **2.21** with aspartyl peracid-based peptides. (c) Functional analysis of catalyst **2.23** through synthesis of peptidomimetic analogues. (d) Hypothesized transition state for enantioselective epoxidations.^{43,46}

Figure 12.

(a) The prediction of peptide sequences that are matched to perform selective chemistry on new substrates remains challenging. (b) Split-and-pool one-bead-one-catalyst library synthesis, screening, and identification.⁵⁴

Figure 13.

(a) The epoxidation of farnesol **2.27** could provide up to six epoxide products, posing challenges in site-selectivity and enantioselectivity. (b) Biased libraries for selective 2,3-epoxidation revealed hit catalyst **2.34b**. (c) Peptide **2.34b** can function as a highly selective catalyst in the epoxidation of numerous allylic olefins. (d) Evolution of a 6,7-selective farnesol epoxidation catalyst.^{55,56} Ternary plots show the positional selectivity, with 6,7-selective catalysts toward the top. Reproduced with permission from ref. 56. Copyright 2014 American Chemical Society.

Figure 14.

(a) NMR and computational structural analysis of peptide **2.34b**. Adapted with permission from ref. 64. Copyright 2014 Royal Society of Chemistry. **(b)** NMR-constrained computational structural analysis of peptide **2.37b**. Reproduced with permission from ref. 56. Copyright 2014 American Chemical Society. **(c)** Proposed model for the 2,3-selective epoxidation of farnesol with **2.34b**. **(d)** Proposed model for the 6,7-selective epoxidation of farnesol with **2.37b**.

Figure 15.

(a) Enantioselective peptide-based oxidations of achiral indole **2.38**. (b) Diastereo- and site-selective oxidations of indole **2.41** with peptides.⁶⁶

Figure 16.

(a) Initial retrosynthesis of **2.43** proceeded through a key, diastereoselective indole oxidation of **2.45**. (b) Catalyst **2.52** overturned the inherent substrate-derived selectivity and provided **2.46**, *syn* to the acetamide motif. (c) Rearrangement of **2.45** provided pseudoindoxyl **2.53**, instead of the desired spirooxindole **2.43**.⁶⁷

Figure 17.

(a) Dioxirane-based epoxidation catalysts. (b) Epoxidation of **2.56** with trifluoromethyl ketone-containing peptide catalysts.^{69,71}

Figure 18.

(a) The mechanism of Baeyer–Villiger (BV) oxidation: nucleophilic addition of the peracid species followed by 1,2-migration of an adjacent C–C bond. (b) A conserved, peptide-based aspartyl peracid catalyst could function as both a nucleophile in BV oxidations and as an electrophile in epoxidations.⁷⁵

Figure 19.

(a) BV oxidations with monomeric Asp catalyst. (b) BV oxidations with perfluorinated benzoic acid. (c) Mechanism of BV oxidation, with key off-cycle intermediate inhibiting higher conversions.⁷⁵

Figure 20.

Mechanistic analysis of kinetic resolution of **2.64** *via* BV oxidation. In this case, rotation of the peracid dihedral results in the formation of regioisomeric products.⁶⁰

Figure 21.

(a) On-bead screening of Asp-containing peptide catalysts for the BV oxidation of **2.66**. (b) Solution-phase screening of hit Asp peptides for the BV oxidation of **2.64a**. (c) Selected substrate scope entries highlights the general tendency of **2.68c** to reverse the inherent migratory aptitude.⁶⁰

Figure 22.

(a) Ground state structure of **2.68c**. (b) Structure of **2.68c** with an equimolar amount of **(R,S)-2.64e** Adapted with permission from ref. 76. Copyright 2016 American Chemical Society.

Figure 23.

(a) Asp-containing peptide catalysts for BV oxidation and epoxidation. (b) Dual substrate *trans*-2.69, containing both a 3-amidocyclohexanone motif for BV oxidation and an allylic alcohol for epoxidation. While achiral catalysts provide limited selectivity, catalysts 2.68c and 2.34b facilitated their matched reactivities. (c) Model for selective BV oxidation with *ent*-2.68c. (d) Model for selective epoxidation with 2.34b.⁷⁸

Figure 24.

(a) On-bead peptide library screening for the BV oxidation of **2.74** revealing two peptides that give opposite senses of asymmetric induction. **(b)** Coordination of chiral, ring opened products to zinc(II) pyridyl complexes for analysis of absolute stereochemistry and enantioselectivity by CD.⁸⁰

Figure 25.

Putative mechanism of BV oxidation with CPAs, which activate the ketone and Criegee intermediate via outer-sphere interactions.

Figure 26.

(a) Phosphopeptides as catalysts for the BV oxidation of cyclobutanones **2.80** with aqueous H_2O_2 . A key Dap(Ac) residue at the *i*+3 position facilitates noncovalent interactions with the substrate. (c) Reversal in the sense of asymmetric induction upon switching from an *ortho*-(**2.80**) to a *meta*-directing group (**2.84**).⁸⁵

Figure 27.

(a) Flavin-embedded peptides as oxidation catalysts, with a specifically designed secondary point of contact at the $i+3$ position for further intra- and intermolecular interactions. **(b)** Proposed mechanistic cycle for flavin-based oxidations. **(c)** Flavin catalyzed sulfide oxidation. **(d)** Flavin catalyzed BV oxidation. **(e)** Competition experiment revealed that flavin-based peptides are more matched to facilitate BV oxidation than sulfide oxidation.⁸⁸

Figure 28.

Asymmetric reactions mediated by aspartyl peracid-based peptides: epoxidations, BV oxidations, and most recently, *N*-oxidations of pyridines.

Figure 29.

(a) Desymmetrization of bis(pyridine) **2.91a** to the corresponding mono-*N*-oxide **2.92a** catalyzed by Asp-containing peptide **2.95**. **(b)** Optimal conditions and selected substrates for the **2.95**-catalyzed desymmetrizing *N*-oxidation. **(c)** Enantioselective synthesis of loratadine derivative **2.91c**, which freely interconverts between two helically chiral conformations and is locked upon **2.94**-catalyzed *N*-oxidation. **(d)** Desymmetrizing *N*-oxidation of varenicline catalyzed by **2.94**. **(e)** The *N*-oxidized bis(pyridine)s could be further functionalized with retention of enantiopurity.⁹²

Figure 30.

(a) Incorporation of a TEMPO catalyst into a helix-forming peptoid sequence. (b) Examination of peptoid-based catalysts in oxidative kinetic resolutions of secondary alcohols.⁹⁷

Figure 31.

(a) Pro-mediated α -oxidation of aldehydes with TEMPO. **(b)** Combination of peptide-based catalyst and enzymatic oxidant.^{99–101}

entry	peptide	yield (%)	er
1	H-Pro-	93	19:81
2	H-D-Pro-Aib-	92	86:14
3	H-D-Pro-Aib-Ala-	99	89:11
4	H-D-Pro-Aib-Ser-Ser- (2.110)	99	96:4
5	H-Pro-Aib-Ser-Ser-	86	5:95

Figure 32.

Development of a resin-bound, Pro-based peptide catalyst for the α -amination of aldehydes.

Figure 33.

Development of a flow process, featuring solid-supported proline-containing peptides, for α -amination of aldehydes.¹⁰⁹

entry ^a	peptide	conv (%)	er
1	H-Pro-(Leu) _{7,5}	21	54:46
2	H-Pro-(Leu) _{25,4}	63	62:38
3	H-Pro-D-Pro-Aib-(Trp) ₂ -(Leu) _{25,4} (3.3)	75	96:4
4 ^b	H-Pro-D-Pro-Aib-(Trp) ₂ -(Leu) _{25,4} (3.3)	13	96:4

^a Optimized using **3.1a**, where R = Ph. ^b THF/H₂O (2:1).

= -HN-CH₂-CH₂-PEG-PS

Figure 34.

(a) Reduction of enals **3.1** with HEH using proline-containing peptide catalysts. Catalysts required a β -turn motif to achieve high selectivity, as well as a hydrophobic poly(Leu) chain to give high conversion. (b) Selected substrate scope entries.^{116,119}

entry	catalyst	conv (%)	3.5/3.6/3.7	er (3.5)	er (3.7)
1		12	76:0:24	n/a	n/a
2	H-Pro-D-Pro-Aib-(Trp) ₂ -(Leu) _{25,4} - (3.3)	52	11:36:53	76:24	94:6
3	H-Pro-D-Pro-Aib-[Trp(5-OMe) ₂](Leu) _{29,9} -	32	16:50:34	88:12	99:1
4	H-Pro-D-Pro-Ahc-[Trp(5-OMe) ₂](Leu) _{29,9} -	98	13:0:87	79:21	98:2
5	H-Pro-D-Pro-Ahc-[Trp(5-OMe) ₂](Leu) ₆ - (3.8)	99	10:0:90	89:11	>99:1

= -HN-CH₂-CH₂-PEG-PS

Trp(5-OMe) =

Figure 35.

Enantio- and regioselective reduction of α,β,γ,δ-unsaturated aldehyde **3.4** with Pro-containing catalysts.¹²⁰

Figure 36.

(a) Kinetic resolution of enal-containing ferrocene complexes with Pro-based peptide catalysts. **(b)** Desymmetrization of bis(enal) containing ferrocene complexes.^{121,122}

Figure 37.

(a) Two complementary classes of chiral phosphoric acid (CPA) catalysts: BINOL-derived (**3.15**) and peptide-based (**3.16**) CPAs. **(b)** The transfer hydrogenation of 8-aminoquinolines with pThr-based catalysts.⁸⁶

Figure 38.

(a) Reduction of bis(quinoline) **3.19** with both BINOL-derived CPA *ent*-**3.15** and peptide-based CPA **3.16**. **(b)** Overview of this process when both catalysts are added together.

Catalyst *ent*-**3.15** is matched for the first reduction, while catalyst **3.16** is matched for the second.¹³⁰

entry ^a	catalyst	<i>er</i> (<i>trans</i>)	<i>er</i> (<i>cis</i>)	<i>dr</i> (<i>trans/cis</i>)
1	diphenyl phosphate (DPP)	n/a	n/a	69:31
2	Fmoc-pThr(Bn)-D-Pro-Acp-Met-OMe (3.16)	51:49	51:49	78:22
3	Fmoc-pThr(Bn)-D-Pro-Val-Leu-OMe	70:30	83:17	58:43
4	Fmoc-pThr(Bn)-NMe ₂	66:34	75:25	52:48
5	<i>p</i> -MeO-Bz-pThr(Bn)-D-Pro-Val-Leu-OMe	73:27	91:9	51:49
6	<i>p</i> -MeO-Bz-pThr(Bn)-D-Pro-Val-Ser(<i>t</i> -Bu)-OMe (3.32)	76:25	93:7	52:48
7	(<i>S</i>)-TRIP (<i>ent</i> - 3.15)	71:29	38:62	79:21

^a Optimized using substrate **3.30a**, where R = C(O)Bn.

Figure 40.

(a) Reductive amination of 3-amidocyclohexanones **3.30**. (b) Kinetic analysis and proposed transition state of the reaction.⁸⁷

Figure 41.

(a) Desymmetrization of *myo*-inositol derivative **4.1** using Pmh-containing peptides **4.3** or **4.4** to provide each enantiomer of monophosphate **4.2** with high levels of enantioselectivity.^{135,139} **(b)** This strategy was employed in the total synthesis of PI5P-DiC8 **4.5**.¹⁴¹

Figure 42.

Two diastereomers of di-*myo*-inositol-1,1'-phosphate (DIP; **4.6**).¹⁴²

entry	catalyst	L,D-/L,L-4.8
1	<i>N</i> -methylimidazole (NMI)	4:1
2	Boc- <i>Pmh</i> -Asn(Trt)-His(Bn)-Asp(<i>t</i> -Bu)-Ala-OMe (4.4)	1:1.25
3	Boc- <i>D-Pmh</i> -Pro-Aib-Trp(Boc)-Phe-OMe (4.9)	13:1
4	Boc- <i>Pmh</i> -D-Pro-Aib-D-Phe-D-Phe-OMe (4.10)	1:2.5

Figure 43.

Examination of catalysts for the selective synthesis of both L,L- and L,D-di-*myo*-inositol-1,1'-phosphate derivatives **4.8**.¹⁴²

(a) P(V) Transfer **(b) P(III) Transfer** **Figure 44.**

Mechanism of (a) Pmh-based catalysis of P(V) transfer vs. (b) Atz-containing peptide catalysis of P(III) transfer.¹⁴⁶

Figure 45.

Peptide **4.15**-catalyzed P(III) group transfer to *myo*-inositol derivative **4.11** followed by kinetic resolution of **4.13** and subsequent deprotection to afford highly enantioenriched D-*myo*-inositol-4-phosphate **4.14** on gram scale. Conditions: (a) NH_3 , Na, -78°C ; (b) DOWEX 50WX8-500, $\text{C}_6\text{H}_{11}\text{NH}_2$.¹⁴⁶

Figure 46. Comparison between Pmh-peptide catalyzed sulfonylation and phosphorylation.¹⁴⁸

entry	X	Ar	R	4.19	conv. (%)	s-factor
1 ^a	O	Ph	Me	a	37	9.6
2	S	Ph	Me	b	51	12.8
3	S	3,5-OMePh	Me	c	52	43.7
4	S	3-BrPh	Me	d	52	12.5
5	S	3-OMePh	2-pyridine	e	53	5.6

^a Reaction performed for 36 h.

Figure 47.

Peptide **4.21**-catalyzed kinetic resolution of (thio)formamides (±)-**4.19**.¹⁴⁹

Figure 48.
Derivatization of thioformamide **4.20b**.¹⁴⁹

Figure 49.

Peptide-catalyzed remote desymmetrization of bis(phenol) **4.23**, noting the correlation between the observed enantioselectivity and the steric demand of the substituent R.¹⁶⁰

entry	<i>n</i>	time (h)	conv. (%)	ee (%) (+)-4.26	ee (%) (-)-4.27	<i>s</i> -factor
1 ^a	1 (4.26a)	9	63	84	49	8
2	2 (4.26b)	4	37	>99	78	>50
3	3 (4.26c)	5	41	>99	79	>50
4	4 (4.26d)	5	44	>99	85	>50

^a 2 mol% catalyst loading.

Figure 50.

Kinetic resolution of *trans*-cycloalkane-1,2-diols **4.26** with tetrapeptide **4.28**.¹⁶⁴

Figure 51.

Model for the enantioselective acylation of *trans*-cycloalkane-1,2-diols **4.26** in the chiral “pocket” of acylated peptide **4.28**. Hydrogens are omitted for clarity. Adapted with permission from ref. 164. Copyright 2011 Wiley.

Figure 52.

Lowest-energy computed complexes between acylated-peptide **4.28** and *trans*-(1*R*,2*R*)-**4.26b** (**Complex I**, left) and *cis*-(1*R*,2*S*)-**4.29a** (**Complex II**, right). Computations were performed at the B3LYP/6-31G*//ONIOM2(B3LYP/6-31*:PM3) level of theory.¹⁶⁹

Figure 53.

Two lowest-energy transition states for acyl transfer from **4.28** to *trans*-diol **4.26b** leading to each enantiomer of **4.27b**. Only select hydrogens are shown for clarity. Lighter gray and darker colored shadings, respectively, represent the lower (PM3) and higher (B3LYP) layers in the ONIOM2 partitioning. Adapted with permission from ref. 169. Copyright 2009 American Chemical Society.

entry	substrate	time (h)	yield (%)	er
1	 4.29a	48	81	94:6
2	 4.29b	7	89	90:10
3	 4.29c	22	97	92:8
4	 4.29d	24	85	92:8
5 ^a	 4.29e	5	45	69:31
6 ^a	 4.29f	2	78	73:27

^a 2 mol% catalyst loading.

Figure 54.

Desymmetrization of *meso*, *cis*-Diols **4.29** using peptide **4.28**.¹⁷⁰

Figure 55. Peptide **4.28**-catalyzed acyl transfer followed by *in situ* oxidation to produce configurationally stable **4.31a**.¹⁷⁰

Figure 56.

(a) Peptidic multicatalyst **4.32** designed from the sequence of lead catalyst **4.28** for asymmetric acyl-transfer. (b) An overlay (molecular force-field analysis) of both acylated-peptides is shown below. Adapted with permission from ref. 171. Copyright 2011 Wiley.

multicatalysis					
desymmetrization then oxidation					
		multicatalysis		desymm. then ox.	
entry	substrate	yield (%)	er	yield (%)	er
1	 4.29a	70	88:12	70	94:6
2	 4.29b	60	87:13	69	82:18
3	 4.29c	83	91:9	97	97:3
4	 4.29d	49	83:17	42	91:9

Figure 57.

Concurrent tandem desymmetrization/oxidation of *meso*-diols **4.29** using multicatalyst **4.32**¹⁷¹ as compared to a two-step approach with peptide **4.28**.¹⁷⁰

entry	R	time (h)	conv. (%)	ee (%) (S,S)-4.26b	ee (%) (R,R)-4.27bx	s-factor
1	Me (4.27b)	15	55	>99	83	>50
2	<i>i</i> -Pr (4.27ba)	24	54	>99	85	>50
3	Bz (4.46bb)	2	57	>99	75	>50
4 ^a	<i>t</i> -Bu (4.46bc)	48	4	4	86	14
5 ^a	Ad (4.46bd)	48	60	85	57	9

^a 2 equiv DIC used.

Figure 58.

Acylation of *trans*-cyclohexane-1,2-diol **4.26b** peptide **4.28**-catalyzed Steglich esterification.¹⁷²

Figure 59.

Kinetic resolution of (±)-4.26b via oxidative esterification of aldehydes.¹⁷³

Figure 60.

Kinetic resolution of *trans*-diols (**4.26**) using various alcohols as acyl synthons with peptidic multicatalyst **4.32**.¹⁷⁴

entry	epoxide	conv. (%)	ee (%) (<i>S,S</i>)- 4.26	ee (%) (<i>R,R</i>)- 4.27	s-factor
1		4.33a 71	78	32	4
2 ^a		4.33b 57	>99 (>99)	74 (65)	48 (33)
3		4.33c 58	>99	70	40
4		4.33d 68	>99	48	19

^a Values in parentheses were obtained when performing the reaction on a 1 mmol scale.

Figure 61.

Peptide salt **4.34**-catalyzed epoxide opening to *trans*-1,2-diols **4.26** and subsequent kinetic resolution *via* acylation.¹⁷⁵

Figure 62.

Epoxidation, ring-opening, and subsequent acylation mediated by peptide **4.35** and hydrazine bisulfate leading to enantioenriched mono-acylated diol **4.27b** and *trans*-diol **4.26b** from alkene **4.34**.¹⁷⁵

Figure 63.
Catalytic cycle for the epoxidation of cyclohexene (4.34) with multicatalyst 4.35.¹⁷⁶

Figure 64.

Activation of Pmh- and β -Asp residues in multicalyst **4.35** for acylation of ($\pm$)-**4.26**.¹⁷⁶

entry	peptide				conv. (%)	ee (%)		k_{rel}
	X	Y	R	4.38		(1S, 2S)-4.36	(1R, 2R)-4.37	
1	O	O	Boc	a	58	98	73	28
1	O	S	Boc	b	51	83	80	23
2	S	O	Boc	c	50	90	91	63
3	O	O	Ms	d	50	82	83	27
4	O	O	Ns	e	50	84	85	32
5	O	O	Ts	f	49	85	88	44
6 ^a	S	O	Ts	g	50	93	94	109

^a 0.2 equiv DIPEA used in this reaction.

Figure 65.

Kinetic resolution of **(±)-4.36** with various β -hairpin-biased tetrapeptides **4.38**.¹⁷⁷

Figure 66.

General reaction mechanism for the acylation of (±)-4.36 catalyzed by peptide 4.38a.¹³⁴

Figure 67. Lowest-energy transition states for the three interaction modes of intermediate **I** with (1*R*, 2*R*)-**4.36**.¹³⁴

Figure 68.

Lowest-energy transition states of (a) TS 4.4 with (1*R*, 2*R*)-4.36 and (b) (1*S*, 2*S*)-4.36.

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Figure 69.

Proposed mechanism of the peptide **4.41**-catalyzed Dakin–West reaction of (±)-**4.39**.¹⁸⁹

Figure 70. B3LYP-D3 (BJ)/6-31+G(d,p) optimized structures representing the lowest-energy complex of protonated peptide **4.41** with enolate **V**. Key noncovalent interactions are highlighted. Reproduced with permission from ref. 189. Copyright 2016 Wiley.

Figure 71.

Synthesis of diastereomerically pure DMAP derivatives **4.43** via a one-pot, Ugi multicomponent reaction.¹⁹⁵

entry	R	with 4.43a		with 4.43b	
		yield (%)	er	yield (%)	er
1	Me (4.44a)	>98	92:8	>98	95:5
2	Bn (4.44b)	>98	99:1	>98	93:7
3	CH ₂ CH ₂ NHCO ₂ Me (4.44c)	>98	92:8	>98	93:7
4	CH ₂ CN (4.44d)	>98	99:1	>98	98.5:1.5
5	Ph (4.44e)	>98	92:8	>98	95:5
6	2-thiofuran (4.44f)	>98	99:1	>98	93:7

Figure 72.

Enantioselective Steglich rearrangement of various *O*-acylated oxindole derivatives **4.44** using catalysts **4.43a** or **4.43b**.¹⁹⁶

Figure 73. Schematic models of the energetically favorable transition states leading to (*S*)- and (*R*)-**4.45b**.¹⁹⁶

^a This reaction was run for at $-40\text{ }^{\circ}\text{C}$ for 24 h. ^b 1.6 equiv of $(i\text{-PrCO})_2\text{O}$ and 1.7 equiv of collidine were used, and the reaction was run for 14 h.

Figure 74.

(a) Synthesis of chiral, C_2 -symmetric PPY catalysts **4.46** for (b) the asymmetric desymmetrization of *meso*-diol **4.29**.¹⁹⁷

Figure 75.

Two possible models for the transition state assembly in the asymmetric acylation of **4.29a** catalyzed by **4.46h**.¹⁹⁷

entry	peptide	conv. (%)	ee (%) 4.47	ee (%) 4.48	s-factor
1	PPY-Leu-Trp-OMe (4.49a)	34	31	59	5.3
2	PPY-Leu-Trp-Trp-OMe (4.49b)	51	22	21	1.9
3	PPY-Leu-Trp-Leu-OMe (4.49c)	6	3	53	3.3
4	PPY-Leu-Trp(Boc)-OMe (4.49d)	50	63	62	8.1

Figure 76.

The kinetic resolution of racemic *sec*-alcohol **4.47a** catalyzed by PPY-containing peptides **4.49**.¹⁹⁹

Figure 77.

Lowest-energy conformers of (a) **4.50a** and (b) **4.50d**. Adapted with permission from ref. 199. Copyright 2016 Royal Society of Chemistry.

entry	R	conv. (%)	ee (%) 4.47	ee (%) 4.48	s-factor
1	H (4.47b)	42	50	69	8.9
2	2,4,6-trimethyl (4.47c)	44	57	72	10.8
3	4-OMe (4.47d)	30	29	68	7.0
4	4-NO ₂ (4.47e)	36	14	25	1.9

Figure 78.

Kinetic resolution of various racemic *sec*-alcohols **4.47** catalyzed by peptide **4.49d**.¹⁹⁹

Figure 79.

Asymmetric hydrocyanation of benzaldehyde **5.1a** to cyanohydrin **5.2a** catalyzed by diketopiperazine **5.3** originally reported by Inoue and co-workers.^{36,202} Three limiting models for asymmetric induction (**A**, **B**, & **C**) have been proposed.

Figure 80.

Computed structures of **TS1** and **D1** led to the transition state models **TS2** and **TS3**, which provide a basis for stereoselectivity in the **5.3**-catalyzed hydrocyanation of benzaldehyde **5.1a**. B3LYP/6-31G* geometries and energies reported. Adapted in part with permission from reference 206. Copyright 2009 American Chemical Society.

Figure 81.

Computed structures of **TS4** and **TS5**. B3LYP/6-31* geometries and energies reported.

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5.1a**5.4a**

<i>n</i>	conversion (%)	ee (%)
0	75	<1
1	84	<1
4	85	5
9	88	16
19	91	31
39	90	51

10% conversion, 37% ee

31% conversion, 12% ee

Figure 82.

Optimization of the asymmetric cyanosilylation of benzaldehydes catalyzed by resin-bound helical polypeptides **5.5**.²⁰⁷

entry	aldehyde	equiv TMS-CN	yield (%) ^a	ee (%)
1		1.2	77	62
2		2.0	81	55
3		2.0	84	48
4		1.2	84	31
5		2.0	91	31

^a Isolated yield after hydrolysis of the silyl ether followed by *O*-acetylation.

Figure 83.

Scope of the **5.5**-catalyzed asymmetric cyanosilylation of benzaldehydes **5.1**.²⁰⁷

entry	R ¹	R ²	R ³	R ⁴	yield (%)	er
1	Bn	H	Ph (<i>R</i>)	Me	35	53:47
2	Bn	Me	Ph (<i>R</i>)	Me	85	47:53
3	Bn	Bn	Ph (<i>R</i>)	Me	85	88:12
4	Bn	Bn	Ph (<i>R</i>)	Bn	77	88:12
5	Bn	Bn	Ph (<i>R</i>)	<i>i</i> -Pr	85	74:26
6	Bn	Bn	Ph (<i>R</i>)	<i>t</i> -Bu	85	44:56
7	Bn	Bn	Bn (<i>R</i>)	Me	79	81:19
8	Bn	Bn	Me (<i>R</i>)	Me	81	80:20
9	Bn	Bn	H	Me	82	51:49
10	Bn	Bn	Me (<i>S</i>)	Me	72	92:8
11	Bn	Bn	<i>i</i> -Bu (<i>S</i>)	Me	73	86:14
12	Bn	Bn	CH ₂ CO ₂ Bn (<i>S</i>)	Me	90	94:6
13	Ar = 3,5-Me ₂ Ph				94	96:4
14	Ar = 3,5-(MeO) ₂ Ph				92	96:4
15	5.10a Ar = 3,5-(<i>t</i> -Bu) ₂ Ph				95	97:3

Figure 84.

Optimization of a dipeptide-based ligand for the asymmetric addition of dimethylzinc to benzaldehyde **5.8a**.²¹⁷

entry	R	yield (%)	er
1	4-BrPh	94	96:4
2*	4-CNPh	91	96:4
3	4-NO ₂ Ph	88	94:6
4	4-MePh	83	96:4
5	1-naphthyl	74	96:4
6	2-naphthyl	65	95:5
7	3-BrPh	88	96:4

* 5 mol% catalyst loading.

Figure 85.

Scope of the **5.10a**-catalyzed, asymmetric organozinc addition to benzaldehydes **5.8**.²¹⁷

2:1 co-solvent	catalyst	conversion (%)
THF/H ₂ O	5.14	38
THF/H ₂ O	5.15	15
THF/H ₂ O	5.16	27
THF/H ₂ O	5.17	15
THF/H ₂ O	imidazole	16
THF/H ₂ O	imidazole + 5.17	14
MeOH/THF	5.14	80

Figure 86.

Development and optimization of a resin-bound, bifunctional peptide catalyst for the hydrolysis of formylphenyl esters **5.11**.²²²

Figure 87.
Preliminary results for a hydrolytic kinetic resolution.²²²

Figure 88. Peptide-catalyzed, alcoholytic ring-opening DKR of oxazol-5(4*H*)-ones **5.20**.

R	conversion (%)	ee (%)
Me	>99	27
Et	>99	39
<i>n</i> -Bu	>99	35

Figure 89.Diketopiperazine-catalyzed, alcoholic ring-opening DKR of oxazolone **5.20a**.²²⁹

peptide	<i>i</i>	<i>i</i> +1	<i>i</i> +2	<i>i</i> +3	conversion (%)	er
5.23a	Boc-Dmaa	D-Pro	Aib	Phe-OMe	37	67:33
5.23b	Boc-Dmaa	D-Pro	Aib	Phe-NMe ₂	47	76:24
5.23c	Boc-Dmaa	D-Pro	Cle	Phe-NMe ₂	55	79:21
5.23d	Boc-Dmaa	D-Pro	Acpc	Phe-NMe ₂	37	75:25
5.23e	Boc-Dmaa	D-Pro	Phe	Phe-NMe ₂	50	78:22
5.23f	Boc-Dmaa	D-Pro	Aic	Phe-NMe ₂	84	93:7
5.23g	Boc-Dmaa	D-Pro	Aic	D-Phe-NMe ₂	75	91:9
5.23h	Boc-Dmaa	D-Pro	Aic	Gly-NMe ₂	62	89:11
5.23i	Boc-Dmaa	D-Pro	Aic	Abu-NMe ₂	94	96:4
5.23j	Boc-Dmaa	D-Pro	Aic	Cys(Me)-NMe ₂	97	95:5
5.23k	Boc-Dmaa	D-Pro	Aic	Ser(Bn)-NMe ₂	97	96:4
5.23l	Boc-Dmaa	D-Pro	Aic	Leu-NMe ₂	70	91:9
5.23m	Ac-Dmaa	D-Pro	Aic	Leu-NMe ₂	51	87:13
5.23n	Ts-Dmaa	D-Pro	Aic	Leu-NMe ₂	31	84:16
5.24	Boc-Leu	D-Pro	Aic	Cys(Me)-NMe ₂	0	N/D

Figure 90.

Optimization of a β -turn biased peptide catalyst for the methanolytic ring-opening DKR of oxazol-5(4*H*)-one **5.20a**.²³⁰

Figure 91.

Sequence truncation study showing the effect of each residue on the reactivity and selectivity in the methanolytic DKR of **5.20a** under the conditions described in Figure 90.²³⁰

entry	R	time (h)	conversion (%) ^a	yield (%) ^b	er
1	Bn	24	90	86	96:4
2	(2-furyl)CH ₂	26	99	78	96:4
3	(2-thienyl)CH ₂	24	95	84	97:3
4	(1-naphthyl)CH ₂	25	93	84	93:7
5	(3-indolyl)CH ₂	26	99	93	98:2
6	(4- <i>t</i> -BuOPh)CH ₂	45	92	78	93:7
7	(4-NO ₂ Ph)CH ₂	30	94	88	88:12
8	Ph ₂ CH	48	26	19	90:10
9	PhCH ₂ CH ₂	48	50	47	81:19
10	MeO ₂ CCH ₂	25	99	79	90:10
11 ^c	<i>i</i> -Bu	48	60	58	93:7
12 ^c	<i>i</i> -Pr	48	30	27	83:17
13 ^c	neopentyl	69	46	33	80:20
14 ^c	<i>t</i> -Bu	62	9	5	71:29

^a Conversion measured by crude ¹H-NMR analysis. ^b Isolated yield after chromatography.

^c 5.0 equiv MeOH.

Figure 92.

Scope of the methanolytic DKR of oxazolones **5.20** catalyzed by **5.23k**.²³⁰

5.23k·(*S*)-5.20a complex

Figure 93.

Stereochemical model for the **5.23k**-catalyzed methanolysis of (*S*)-**5.20a**.²³⁰

Figure 94.
Thiourea-derived peptide catalysts for the asymmetric ring-opening of *meso*-stilbene oxides.
233

entry	Ar	yield (%)	ee (%)
1	Ph	89	79
2	3-ClPh	86	52
3	3-BrPh	83	50
4	2-ClPh	trace	N/D
5	4-NO ₂ Ph	trace	N/D
6	3-NO ₂ Ph	trace	N/D
7	2-NO ₂ Ph	trace	N/D

Figure 95. Asymmetric ring-opening of stilbene oxides **5.28** with piperazine **5.29** catalyzed by thiourea-functionalized peptide **5.31a**.²³³

entry	peptide	sequence	yield (%)	ee (%)
1	5.31a	Thiourea-L-Phe-L-Pro-D-Pro-OMe	79	-79
2	5.31b	Thiourea-L-Phe-L-Pro-L-Pro-OMe	82	-22
3	5.31c	Thiourea-L-Phe-D-Pro-D-Pro-OMe	81	-32
4	5.31d	Thiourea-D-Phe-L-Pro-D-Pro-OMe	81	+52

Figure 96.Effect of catalyst epimerization and the observation of enantiodivergence.²³³

Figure 97:
Inspirations for the design of amine-based peptide catalysts.

entry	peptide	yield (%)	dr (%)	ee (%)
1	PEAGAIASGVPELFVKLH (6.2a)	88	99:1	63
2	PHAGAIASGVPELFVKLH (6.2b)	95	95:5	86
3	AGAIASGVPELFVKLH (6.2c)	67	97:3	39
4	PELFVKLH (6.2d)	97	90:10	97

Figure 98:
Aldol reaction catalyzed by aldo-keto reductase mimics.²⁴⁷

Figure 99:

Peptide catalysts for the asymmetric aldol reaction between 4-nitrobenzaldehyde and acetone: **(a)** Enzyme/protein-inspired or geometrically constrained peptide catalysts; **(b)** Solid-supported catalysts; and **(c)** various di/tri-peptide catalysts.

Figure 100:

Peptide catalysts for the asymmetric aldol reaction between 4-nitrobenzaldehyde and cyclohexanone: **(a)** Enzyme/protein-inspired or geometrically constrained peptide catalysts; **(b)** Solid-supported catalysts; **(c)** Various di/tri-peptide catalysts.

Figure 101:

Peptide catalysts for the asymmetric aldol reaction between electron-rich benzaldehydes and (a) acetone and (b) cyclohexanone.

Figure 102:
(a) Dehydrative kinetic resolution of hydroxy ketones (b) Proposed catalytic cycle.²⁹³

Figure 103:

Peptide catalysts for the asymmetric aldol reaction between **(a)** cyclohexanecarboxaldehyde and acetone, **(b)** *iso*-butyraldehyde and acetone, and **(c)** *iso*-butyraldehyde and cyclohexanone.

Figure 104:

One-pot tandem aldol reaction using solid-supported acid and base catalysts showcasing the reusability of the catalysts.²⁹⁵

Figure 105:

One-pot, tandem oxidation/aldol reaction using resin-supported catalysts that may be reused up to eight times.²⁹⁶

entry	X	n	6.43		(S _p ,S)-6.4		(R _p ,S)-6.4	
			ee (%)	yield (%)	ee (%)	yield (%)	ee (%)	yield (%)
1 ^a	O	9	19	76	69 (93:7 dr)	—	—	—
2	O	9	46	38	82	37	95	4
3 ^b	O	9	42	39	77	41	94	7
4	O	8	40	41	83	36	93	6
5	S	8	31	57	83	31	92	4

^a Only the aldol reaction was performed (24 h). ^b Second reuse of peptide catalysts.

Figure 106:

Kinetic resolution of ansa cyclophanes by aldol and retro-aldol reactions.²⁹⁸

Figure 107:
Peptide-catalyzed asymmetric aldol reactions using various ketone acceptors.

Figure 108:
Potential future directions for catalytic direct aldol reactions.

Figure 109:
Divergence in site-selective, asymmetric aldol reactions catalyzed by short peptides.^{265,246}

Figure 110: Substrate-influenced site-selectivity in asymmetric aldol reaction.²⁷⁶

Figure 111:
Divergence of diastereoselectivity in peptide-catalyzed, asymmetric aldol reactions.^{246,304}

entry	solvent	yield (%)	<i>syn/anti</i>	ee (%)	abs. config.
1	DMSO	98	1:3.5	55	(<i>R,S</i>)
2	DMSO + 2.5% H ₂ O	96	1:1.5	42	(<i>S,R</i>)
3	DMSO + 10% H ₂ O	95	1:2.0	69	(<i>S,R</i>)
4	MeOH	93	1:2.5	58	(<i>R,S</i>)
5	MeOH + 2.5% H ₂ O	94	1:1.5	9	(<i>S,R</i>)
6	MeOH + 10% H ₂ O	97	1:1.5	20	(<i>S,R</i>)

Figure 112:

Aldol reaction between cyclohexanone and 4-nitrobenzaldehyde showcasing a reversal in enantioselectivity with **6.46** in different solvents.³⁰⁵

Figure 113:
CD spectra of **6.59** in methanol (blue), 10% H₂O in methanol (red), 50% H₂O in methanol (green), and water (orange). Reproduced with permission from ref. 305. Copyright 2011 Thieme.

entry	R ¹	peptide	conv. (%)	ee (%)	abs. config.
1	2-NO ₂ Ph	6.36	55	52	(<i>R</i>)
2	2-NO ₂ Ph	6.60	77	39	(<i>S</i>)
3	<i>i</i> -Pr	6.36	28	94	(<i>R</i>)
4	<i>i</i> -Pr	6.60	31	50	(<i>S</i>)

Figure 114:
Aldol reactions catalyzed by di- and tripeptides that provide enantiodivergent outcomes.²⁶²

1,2-addition reaction

- proton transfer with substrate is facilitated by carboxylic acid

1,4-addition reaction

- additional space between amide & acid helps accommodate new substrates

Figure 115.

Pro-catalyzed 1,2-addition reaction (*i.e.*, aldol) compared to a peptide-catalyzed 1,4-addition reactions.

Figure 116.

Lowest-energy conformations of (a) H-Pro-OH and (b) H-Pro-Pro-Asp-NH₂ (7.4) calculated using MacroModel 8.0. (c) Peptide-catalyzed conjugate addition of aldehydes 7.1 into nitroolefins 7.2, which is proposed to proceed through an enamine intermediate and is assisted by judicious placement of a protic sidechain. Reproduced in part with permission from ref. 309. Copyright 2008 Wiley.

entry ^a	peptide	conc. (M)	t (h)	ee (%)	conv. (%)
1	H-D-Pro-Pro-Asp-NH ₂ (7.7)	0.1	50	90	85
2	H-D-Pro-Pro-Glu-NH ₂ (7.10)	0.1	15	>95	>95

^a For catalyst optimization, R = Bn.

Figure 117.

Conjugate addition of aldehydes **7.1** into nitroolefins **7.8** lacking substitution at the β -position.³¹⁰

Figure 118.

Optimization of the *C*-terminal residue of tripeptides in the asymmetric conjugate addition of aldehydes into nitroolefins.³¹¹

entry	7.10 (mol%)	ratio 7.11:7.12	conditions	t (h)	syn/anti	ee (%)	conv. (%)
1	1	1:1.5	standard	7	98:2	97	>95
2	1	1:1.5	dry	3	97:3	97	>95
3	0.1	1:1.5	dry	48	94:6	97	~90

Figure 119.

(a) Conjugate additions between *n*-butanal **7.11** and nitrostyrene **7.12** under different conditions. Under the “dry” conditions, anhydrous reagents and solvents were used in contrast to the standard conditions. (b) Initial rates vs. concentration of **7.11** under various conditions in the conjugate addition of **7.11** to **7.12** (green = standard conditions, red = anhydrous conditions, and blue = 10 mol% excess of water). (c) Influence of water on rates of product formation. Reproduced in part with permission from ref. 312. Copyright 2010 American Chemical Society.

- equimolar mixture of quasienantiomers
- ratio of **a** to **b** determined by mass spec analysis
- distribution of enamine products (back reaction of conjugate addition) should match enantioselectivity (forward reaction) if enamine mechanism is at play by virtue of microscopic reversibility of transitions states

Quasienantiomeric Substrates		Selected Catalysts Assessed	
7.14a	7.14b		
		peptide	er 7.16a:7.16b
		7.10 , R ¹ = OH, R ² = NH ₂	73:27 73:27
		7.17 , R ¹ = NHC ₁₂ H ₂₅ , R ² = OMe	74:26 84:16

Figure 120.

Strategy for verifying an enamine mechanism by employing an ESI-MS study of the reverse-reaction using mass-labeled quasi-enantiomeric conjugate addition products.³¹³

Figure 121.

(a) Strategy for conducting reactions with tripeptide catalysts suspended on resin. **(b)** Performance of the proposed strategy in the asymmetric conjugate addition of aldehyde **7.11** into nitroolefin **7.12**. Reproduced in part with permission from ref. 314. Copyright 2011 Wiley.

entry ^a	peptide	t (h)	dr	ee (%)	conv. (%)
1	7.10	96	97:3	73	28
2	7.18	8	98:2	91	>95
3	7.19	19	97:3	80	>95

^a For catalyst/solvent optimization, R¹ = Et, R² = Ph.

Figure 122.

Application of tripeptide catalysts with added alkyl chains (*e.g.*, **7.18** & **7.19**) to promote micelle formation in asymmetric conjugate addition reactions under aqueous conditions.³¹⁶

entry	catalyst	dr ratio (a:b:c:d)	ee of 7.21a (%)	conv. (%)
1	pyrrolidine	22:18:40:20	—	—
2	H-Pro-OH	32:16:36:16	31	>95
3	H-Pro-Pro-D-Glu-OH (7.22)	84:10:5:1	99	100
4	H-Pro-Pro-Asn-OH (7.23)	82:12:4:2	99	100

Figure 123.

(a) Conjugate addition of aldehydes **7.1** to nitroolefins **7.20** bearing both α - and β -substitution catalyzed by peptides **7.22** and **7.23**. (b) Influence of catalysts on the distribution of diastereomers **7.21a–d** in the conjugate addition of aldehyde **7.11** into nitroolefin **7.20a** bearing both α - and β -substitution. Both peptide catalysts **7.22** and **7.23** substantially alter the intrinsic diastereomeric preference.³¹⁷

entry ^a	catalyst	R ²	R ³	solvent	conv. (%)	dr	ee (%)
1	7.10	CONH ₂	CH ₂ CO ₂ H	<i>i</i> -PrOH	50	4.0:1	75
2	7.26	CO ₂ Me	Ph	<i>i</i> -PrOH	86	3.6:1	85
3 ^b	7.27	Ph	4-Me-C ₆ H ₆	<i>i</i> -PrOH	78	4.6:1	90
4 ^b	7.27	Ph	4-Me-C ₆ H ₆	<i>t</i> -BuOH	96	6.0:1	94

^a For catalyst/solvent optimization, R¹ = Et, Ar = 4-F-C₆H₄.

^b C-terminal residue is used as a diastereomeric mixture. Enantiopure variants did not improve yields.

Figure 124.

Optimization of tripeptides for the conjugate addition of aldehydes **7.1** into sterically hindered β,β-disubstituted nitroolefins **7.24** to generate an all-carbon quaternary stereogenic center.³¹⁸

Figure 125.

Conjugate addition of acetophenone into dicyanoolefins catalyzed by a tripeptide **7.10** containing a secondary amine.³¹⁹

Figure 126.

(a) Optimization of tripeptide-based catalysts for the asymmetric conjugate addition of aldehydes **7.31** into maleimide **7.32**. **(b)** Low-yielding conjugate addition into *N*-phenyl protected maleimide.³²⁰

Figure 127.

(a) Crystal structures of three optimized catalysts for conjugate addition reactions with various olefin acceptors. **(b)** Overlay of the three crystal structures for **7.7** (green), **7.27** (orange), and **7.35** (yellow) with H-atoms and TFA counterion removed for clarity. **(c)** The $n \rightarrow \pi^*$ interactions suggested by the distance between the carbonyl O and the adjacent carbonyl C, as well as the approximation of the Bürgi–Dunitz angle. Reproduced in part with permission from ref. 321. Copyright 2011 Wiley.

entry	peptide	<i>n</i>	$K_{t/c}$	dr	ee (%)	conv. (%)
1	7.38	1	10	26:1	92	>95
2	7.10	2	46	35:1	97	>95
3	7.39	3	71	50:1	99	>95

entry	catalyst	$K_{\text{trans/cis}}$		
		d ⁶ -DMSO	CDCl ₃	CDCl ₃ /CD ₃ OH (9:1)
1	7.10	2.7	36	46
2	7.10-En	2.6	15	20

Figure 128.

(a) Influence of ring size on the *trans/cis* ratio for the amide bond of the central Pro residue and its relation to enantioselectivity in the conjugate addition reactions. (b) $K_{t/c}$ values for catalyst **7.10** and its enamine form **7.10-En** in different solvents.³²⁵

with **4R-7.40**

entry	X	$K_{t/c}$		ee (%)	yield (%)
1	H	46	35:1	97	>95
2	OH	36	25:1	95	>95
3	N ₃	30	24:1	95	>95

with **4S-7.40**

entry	X	$K_{t/c}$	dr	ee (%)	yield (%)
4	OH	>50	17:1	93	>95
5	H	46	35:1	97	>95
6	N ₃	20	29:1	99	>95

Figure 129.

Effects of substitution on the ring pucker of the $i+1$ Pro residue and its influence on enantioinduction in the asymmetric conjugate additions of aldehydes **7.11** into nitroolefins **7.12**.³²⁶

Figure 130.

(a) $K_{trans/cis}$ values for **7.41** and **7.42** in various solvents. (b) Computed Boltzmann-averaged dipole moments of *trans* and *cis* conformers for compounds **7.34** and **7.35**. (c) Solvent influence on *trans/cis* ratios of peptide **7.7** and its effect of enantioselectivity. Ratios were determined by NMR analysis in DMSO- d_6 and a 9:1 mixture of CDCl₃:CD₃OD. Reproduced in part from with permission from ref. 327. Copyright 2015. Royal Society of Chemistry.

Figure 131.

(a) Selected NOE, $^3J_{H,H}$ coupling, and $^3J_{C,H}$ coupling interactions for catalyst **7.10**. (b) Variations in NOE interactions between **7.10** and **7.10-En**. (c) Overlay of lowest energy DFT structures **7.10** (blue) and **7.10-En** (green) (d) Overlay of four calculated structures within 2 kcal/mol of lowest energy structure of **7.10-En**. Reproduced in part from with permission from ref. 328. Copyright 2018 American Chemical Society.

Figure 132.

Proposed catalytic cycle for the peptide-catalyzed, asymmetric conjugate addition of aldehydes to nitroolefins considering all previous mechanistic studies.³²⁸

Figure 133.

(a) Strategy for the synthesis of diverse peptide catalysts scaffolds *via* a four-component Ugi reaction. (b) Asymmetric conjugate addition of aldehyde **7.47** into nitroolefin **7.2** catalyzed by peptide **7.49**.³³⁰ (c) Diversity oriented approach pursued by Paixao and co-workers to develop catalysts for asymmetric conjugate addition reactions and a comparison of the number of low energy conformations of peptides **7.50** and **7.51**. Reproduced in part from with permission from ref. 331. Copyright 2013 American Chemical Society.

13 Examples

• up to 99% yield, 95:5 dr, & 93:7 er

7.52

No reaction*

7.53

24 h to full conversion*

85:15 dr

87:13 er

7.54

20 h to full conversion*

91:9 dr

93:7 er

* R¹ = Me, R² = Ph

Figure 134.

Asymmetric conjugate addition of aldehydes **7.1** to nitroolefins **7.2** catalyzed by tripeptides bearing a bifunctional phosphonic acid moiety at the C-terminal residue.³³³

entry ^a	additive (mol%)	ee (%)	dr (%)	yield (%)
1	none	--	--	0
2	NaOH (30 mol%)	68	95:5	90
3	AcOH (30 mol%)	--	--	0
4	LiOH (30 mol%)	67	94:6	80
5	KOH (30 mol%)	44	94:6	75
6	Li ₂ CO ₃ (30 mol%)	54	93:7	71

^a For reaction optimization, **7.55** = cyclohexanone and R³ = Ph.

Figure 135.

Asymmetric conjugate addition of aldehydes **7.1** into nitroolefins **7.2** catalyzed by H-Pro-Phe-OH under aqueous conditions.³³⁵

Figure 136.

Asymmetric conjugate addition of aldehydes into nitroolefins catalyzed by bifunctional diketopiperazine.³³⁶

β-turn region optimization^a

entry	peptide	Trp-Trp	yield (%)	ee (%)
1	7.64a	Trp-Trp	85	88
2	7.64b	D-Trp-Trp	81	43
3	7.64c	Trp-D-Trp	87	41

^a Reactions conducted in a 1:2 THF/H₂O mixture, helical region = (Leu)_{28.3}.

helical region optimization^b

entry	peptide	(AA) _n	conv. (%)	ee (%)
4	7.64a	(Leu) _{28.3}	63	86
5	7.64d	—	20	22
6	7.64e	Leu-Leu-Aib	84	82
7	7.64f	(Leu-Leu-Aib) ₂	92	91

^b Reactions conducted in H₂O, turn region = Trp-Trp.

Figure 137.

(a) Peptide-catalyzed asymmetric Friedel–Crafts-type addition of indole **7.62** into unsaturated aldehydes **7.62** in aqueous media.³³⁸ (b) One-pot sequential Friedel–Crafts-type alkylation and oxidation catalyzed by **7.64f** and laccase.³³⁹

Figure 138.

(a) Catalyst and solvent optimization for the conjugate addition of nitromethane (7.67) to unsaturated aldehyde 7.66a. (b) Asymmetric conjugate addition of nitromethane 7.67 into β,β -disubstituted α,β -unsaturated aldehydes 7.66 catalyzed by peptide 7.69 in aqueous media.³⁴⁰

entry ^a	peptide	conversion (%)	ee (%)
1	H-(Leu-Leu-Aib) ₂ (7.72)	99	52
2	H-Trp-(Leu-Leu-Aib) ₂ (7.73)	96	80
3	H-Trp-Trp-(Leu-Leu-Aib) ₂ (7.74)	87	88
4	H-Trp-Trp-(Leu-Leu-Aib) ₃ (7.55)	93	91
5	H-Trp-Trp-(Leu) ₆ (7.76)	39	7

^a For optimization, R¹ = Me, R² = 4-NO₂.

Figure 139.

Asymmetric conjugate addition of nitromethane (**7.67**) into α,β -unsaturated ketones **7.70** catalyzed by peptides containing unprotected *N*-termini.²⁸

catalyst	ratio of a:b:c	dr of c ^a	ee of c diastereomers (%)	conv. (%)
7.80	1:17:82	60:40	3, 2	82
7.64f	6:3:91	58:42	73, 58	76

^a The relative stereochemistry of the diastereomers was not determined.

Figure 140.

Asymmetric conjugate addition of 2-naphthalenethiol **7.78** into α,β,γ -unsaturated aldehydes **7.77**.³⁴¹

Figure 141.

(a) Kinetic resolution of metallocene complexes *via* peptide **7.83**-catalyzed conjugate addition of nitromethane into α,β -unsaturated aldehydes **7.81**. (b) Kinetic resolution of paracyclophane derivatives **7.84** *via* peptide **7.86**-catalyzed conjugate addition.¹²²

entry	peptide	conversion (%)	ee (%)
1	H-Pro	72	7
2	H-D-Pro-Aib	72	-18
3	H-Pro-D-Pro-Aib-(Leu) ₄ (7.90)	99	77
4	H-Pro-D-Pro-Aib-(Ala) ₅ (7.91)	99	91

Figure 142.

Asymmetric conjugate addition of boronic acids **7.88** into γ -hydroxy- α,β -unsaturated aldehydes **7.87**.³⁴²

Figure 143.

(a) Strategy for the visualization and identification of strongly active catalysts *via* immobilization of dye molecules to on-bead peptide catalysts. This facilitates rapid screening of peptide catalysts for the conjugate addition of malonate nucleophiles, such as **7.92**, into α,β -unsaturated aldehyde like **7.61**. **(b)** Selected enantioselectivity values for high performing catalysts in the reaction of aldehyde **7.61** with dimethyl malonate (**7.93**). **(c)** Optimized conditions for asymmetric conjugate addition of **7.99** into enals **7.98** and proposed model for the efficacy of His residues at the 5th position. **(d)** Catalysts identified

after further screening that demonstrate divergent enantioselectivity in the reaction of **7.61** with **7.93**.

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Figure 144. Dipeptide **8.3**-catalyzed cyclopropanation of **8.1** to afford **8.2**.^{357,358}

Figure 145.

Treatment of dipeptide **8.3a** with diethylzinc followed by diiodomethane.³⁵⁸

Figure 146. Two potential mechanisms for the dipeptide **8.3a**-catalyzed cyclopropanation of **8.1**.³⁵⁸

entry	peptide			conv. (%)	8.5a/8.6a/8.7a	ee 8.5a (%)
	AA ₁	AA ₂	8.8			
1	Ser	Ser	a	97	83:11:6	90
2	Hse	Hse	b	80	85:9:6	95
3	Hse	Trp	c	51	63:18:19	81
4	Trp	Hse	d	84	89:9:2	99
5	Trp	Ser(OMe)	e	92	93:5:2	99
6	Trp	Hse(OMe)	f	82	85:11:4	96
7	Trp	Met	g	95	81:13:6	95

Figure 147.

Peptide catalyst optimization for the cyclopropanation of α,β -unsaturated aromatic aldehyde **8.4a**.³⁶⁶

entry	R	8.5/8.6/8.7	yield (%) 8.5	ee (%) 8.5
1	2-NO ₂ (8.4a)	96:2:2	84	99
2	4-CF ₃ (8.4b)	95:3:2	84	99
3	4-Br (8.4c)	95:3:2	88	99
4	H (8.4d)	94:3:3	87	99
5 ^a	4-OMe (8.4e)	95:2:3	87(83)	99(99)

^a Values in parentheses were obtained after the 5th reuse of **8.8e**.

Figure 148.

Selected substrate scope for the asymmetric cyclopropanation of **8.4** using peptide **8.8e**.³⁶⁶

Figure 149.

Two potential modes of reactivity in the Lewis base-catalyzed reactions of allenates **8.9** and imines **8.10**.³⁷³

entry	R	catalyst	yield (%)	er
1	CO ₂ Et (8.11aa)	PPh ₃	57	—
2	CO ₂ Et (8.11aa)	DMAP	trace	—
3	CO ₂ Et (8.11aa)	Boc- 3-Pmh -OMe	trace	—
4	CO ₂ Et (8.11aa)	pyridine	75	—
5	CO ₂ Et (8.11aa)	Boc- 3-Pal -OMe	71	50:50
6	CO ₂ Et (8.11aa)	Boc- 3-Pal -Pro-Aib-Phe-OMe (8.12a)	57	56:44
7	CO ₂ Et (8.11aa)	Boc- 3-Pal -D-Pro-Aib-Phe-OMe (8.12b)	86	78:22
8	Bn (8.11ab)	Boc- 3-Pal -D-Pro-Aib-Phe-OMe (8.12b)	NR	—
9	Bz (8.11ac)	Boc- 3-Pal -D-Pro-Aib-Phe-OMe (8.12b)	94	84:16
10	Bz (8.11ac)	Boc- 3-Pal -D-Pro-Aib-Phe-NMe ₂ (8.12c)	80	92:8

Figure 150. Catalyst optimization for the aza-MBH reaction of allenoate **8.9a** and imine **8.10**.³⁷³

entry	R ¹	R ²	8.11	yield (%) ^a	er ^a
1	Bn	2-MeOPh	ad	79	90.5:9.5
2	Bn	4-MeOPh	ae	88 (81)	92:8 (98.5:1.5)
3	Bn	4-BrPh	af	56 (46)	88.5:11.5 (96.5:3.5)
4	Ph	Ph	bc	48	86.5:13.5
5 ^b	Ph	Ph	bc	64	94.5:5.5
6 ^b	Ph	4-MeOPh	be	49	92.5:7.5
7 ^b	Ph	4- <i>t</i> -BuPh	bg	55	92.5:7.5
8 ^b	Ph	1-Nal	bh	66	92:8
9 ^b	Ph	<i>i</i> -Pr	bi	42	80.5:19.5

^a Parenthetical values were obtained from the mother liquor after the racemate crystallized out. ^b Performed at 0 °C for 1 h.

Figure 151.

Scope of the peptide-catalyzed aza-MBH reaction between allenolates **8.9** and imines **8.10**.³⁷³

Figure 152.
Proposed mechanism for the peptide-catalyzed aza-MBH reaction.³⁷⁴

entry	R ¹	R ²	R ³	peptide	yield (%)	dr	er ^a
1 ^b	Ph	Ph (8.14a)	Ph (8.10c)	Boc- Pal -D-Pro-Aib-Phe-NMe ₂ (8.12c)	67	1:1.2	38.5:61.5
2	NHPh	Ph (8.14b)	Ph (8.10c)	Boc- Pal -D-Pro-Aib-Phe-NMe ₂ (8.12c)	85	1:2.7	39:61
3 ^c	OEt	Ph (8.14c)	Ph (8.10c)	Boc- Pal -D-Pro-Aib-Phe-NMe ₂ (8.12c)	87	1:1.2	ND
4	NHPh	Ph (8.14b)	Ph (8.10c)	Boc- Pal -Pro-Aib-D-Phe-OMe (8.12d)	76	1:1.1	ND
5	NHPh	Ph (8.14b)	Ph (8.10c)	Boc- Pal -D-Pro-Aib-D-Phe-OMe (8.12e)	80	1:3.0	22:78
6	NHPh	Ph (8.14b)	Ph (8.10c)	Boc- Pal -D-Pro-Aib-D-Phe-NMe ₂ (8.12f)	71	1:3.4	22:78
7 ^c	NHPh	Me (8.14d)	Ph (8.10c)	Boc- Pal -D-Pro-Aib-D-Phe-NMe ₂ (8.12f)	>95	1:5.0	21:79
8 ^c	NHPh	<i>i</i> -Pr (8.14e)	Ph (8.10c)	Boc- Pal -D-Pro-Aib-D-Phe-NMe ₂ (8.12f)	93	1:6.2	22:78
9 ^c	NHPh	<i>i</i> -Pr (8.14e)	<i>O</i> <i>t</i> -Bu (8.10j)	Boc- Pal -D-Pro-Aib-D-Phe-NMe ₂ (8.12f)	78	1:12	27:73

^a The er reported is for the major diastereomer of **8.15**. ^b 30 mol% catalyst loading and 23 h. ^c 8 h.

Figure 153.

Optimization of the peptide **8.12**-catalyzed coupling of allenates (±)-**8.14** with imines **8.10**.³⁷⁵

entry	R ¹	R ²	R ³	Ar	8.15	time (h)	yield (%)	dr	er ^a
1	Me	O <i>i</i> -Pr	Boc	Ph	ej	24	91	1:16	88:12
2	Me	O <i>i</i> -Pr	Boc	4-BrPh	ek	24	95	1:10	85.5:14.5 (98:2)
3	Et	O <i>i</i> -Pr	Boc	Ph	fj	120	70	1:11	71.5:28.5
4 ^b	Me	S <i>i</i> -Pr	Cbz	2-MePh	gl	15	90	1:42	94:6
5	<i>i</i> -Bu	S <i>i</i> -Pr	Cbz	Ph	hm	96	58	1:5.8	75.5:24.5

^a The er is reported is for the major diastereomer. Values in parentheses are for after recrystallization. ^b Reaction was performed at -20 °C.

Figure 154.

Selected scope for the peptide **8.12g**-catalyzed coupling of allenates **8.14** and imines **8.10**.³⁷⁵

Figure 155.

Proposed mechanism for the peptide **8.12g**-catalyzed aza-MBH reaction of allenolate **8.14e** and imine **8.10j**.³⁷⁵

Figure 156.
Speculative binding model for the addition reaction between intermediate **I** and imine **8.10j** leading to intermediate **II**.³⁷⁵

Figure 157.

(a) Cys-catalyzed, intramolecular Rauhut–Currier reaction of bis(enone) **8.16** and (b) proposed model for selectivity.^{378,379}

Figure 158. Proposed mechanism for the Cys-catalyzed intramolecular RC reaction.^{378,379}

Figure 159.

Optimized transition states for the α -deprotonation step of the E1cB process for (1*S*, 2*R*, 3*S*) and (1*R*, 2*S*, 3*R*) enantiomers of intermediate **III** including potassium counterion and two explicit water molecules. Distances and angles are denoted in Å and degrees, respectively. Adapted with permission from ref. 380. Copyright 2013 Wiley.

Figure 160.

Substrate controlled Cys-catalyzed RC ring contraction leading to Sch-642305 (**8.21**) and *epi*-Sch-642305 (*epi*-**8.21**).³⁸¹

Figure 161.

Catalyst **8.18**-controlled enantioselective RC ring contraction of **8.23**.³⁸¹

Figure 162.

General strategy and mechanistic proposal for the peptide-catalyzed VCP ring-opening/cycloaddition cascade enabled by cysteine thiyl radicals.³⁹⁵

Figure 163. Initial results establishing proof-of-principle with amide-functionalized VCPs **9.1**.³⁹⁵

Figure 164.

Peptide optimization for the VCP ring-opening/cycloaddition cascade reaction. Scaffold **9.6** led to significant improvements in enantioselectivity compared to the other archetypal peptides **9.4** and **9.5**.³⁹⁵

Figure 165.

Modulation of the *i*+1 Pro γ -substituent led to the identification of lead catalyst **9.6h**.

Results are presented for the reaction of VCP **9.1c** under the conditions described in Figure 164.³⁹⁵

VCP Scope

entry	R	solvent	yield (%)	dr (<i>trans:cis</i>)	er (<i>trans</i>)	er (<i>cis</i>)
1	NHBn	THF	70	40:60	83:17	72:28
2	4-CF ₃ Ph	THF	82	77:23	88:12	76:24
3	4-CF ₃ Ph	hexanes/THF	84	79:21	90:10	75:25
4	4-MeOPh	THF	79	68:32	85:15	75:25
5	4- <i>t</i> -BuPh	hexanes/THF	32	68:32	86:14	75:25
6	Ph	hexanes/THF	77	73:27	90:10	79:21
7	4-SF ₅ Ph	hexanes/THF	83	80:20	90:10	76:24
8	3-Br-4-CF ₃ Ph	hexanes/THF	81	82:18	90:10	73:27
9	3,5-(CF ₃) ₂ Ph	hexanes/THF	94	82:18	90:10	73:27

Olefin Acceptor Scope Ar = 4-CF₃Ph **Figure 166.**Substrate scope of the **9.6h**-catalyzed VCP ring-opening/cycloaddition cascade reaction.³⁹⁵

9.6–9.1c Covalent Complex

Figure 167.

Proposed model for the 9.6-catalyzed VCP ring opening/cycloaddition cascade reaction.³⁹⁵

Figure 168.

General conception of and challenges associated with cyclic deracemization strategies.³⁹⁶

Figure 169.

Deracemization of cyclic ureas **9.7** jointly mediated by an Ir(III)-based photocatalyst, a chiral Brønsted base, and a cysteine-containing peptide catalyst.⁴⁰⁰

Figure 170.

Proposed mechanism for the deracemization of urea **9.7**. The cysteine containing peptide-based catalyst would mediate the enantioselective HAT step.⁴⁰⁰

entry	Brønsted base	HAT co-catalyst	additive	yield (%)	er
1	9.9	PhSH	none	84	79:21
2	9.9	PhSH	MS	92	86:14
3	Bu ₄ N ⁺ (PhO) ₂ P(O)O ⁻	(Boc-Cys-OMe) ₂	none	92	47:53
4	Bu ₄ N ⁺ (PhO) ₂ P(O)O ⁻	9.10a	none	99	59:41
5	Bu ₄ N ⁺ (PhO) ₂ P(O)O ⁻	9.10b	none	93	68:32
6	Bu ₄ N ⁺ (PhO) ₂ P(O)O ⁻	9.10c	none	97	70:30
7	Bu ₄ N ⁺ (PhO) ₂ P(O)O ⁻	9.10d	none	90	72:28
8	Bu ₄ N ⁺ (PhO) ₂ P(O)O ⁻	9.10e	none	97	78:22
9	Bu ₄ N ⁺ (PhO) ₂ P(O)O ⁻	9.10f	none	99	59:41
10	Bu ₄ N ⁺ (PhO) ₂ P(O)O ⁻	9.10e	MS	96	79:21
11	9.9	9.10e	MS	96	93:7
12	9.9	9.10e	50 mol% Ph ₃ CH, MS	85	96:4
13	5 mol% 9.9	5 mol% 9.10e	25 mol% Ph ₃ CH, MS	96	96:4

9.10a (Boc-Cys-D-Pro-Aic-Phe-OMe)₂
9.10b (Boc-Cys-D-Pro-Aic-Phe-NMe₂)₂
9.10c Boc-Cys-D-Pro-Aic-Phe-NMe₂
9.10d Boc-Cys-D-Pro-Aic-Gly-NMe₂
9.10e Boc-Cys-D-Pro-Acpc-Phg-NMe₂
9.10f Boc-Cys-D-Pro-Acpc-D-Phg-NMe₂

Figure 171.

Optimization of the light-driven deracemization of urea **9.7**. The enantioselective PT and HAT steps were mediated by chiral BINOL-derived phosphate **9.9** and cysteine-containing tetrapeptides **9.10**, respectively.⁴⁰⁰

Figure 172.

Scope of the light-driven deracemization of urea **9.7**. Entries marked with an asterisk (*) indicate a 12 h reaction time.⁴⁰⁰

Figure 173.

Dual catalytic strategy for the photochemical [2+2] cycloaddition of enones **9.11** and **9.12** to deliver substituted cyclobutanes **9.13** with high levels of diastereo- and enantioselectivity.⁴⁰⁴

Figure 174.

Optimization of the Lewis acid and chiral ligand led to the identification of peptides **9.18** and **9.19**, which provided diastereodivergent results in the [2+2] cycloaddition of **9.11a** with **9.12a**.⁴⁰⁴

entry	R ¹	R ²	with peptide 9.19 (−20 °C)			with peptide 9.20 (rt)		
			yield (%)	dr	ee _{trans} (%)	yield (%)	dr	ee _{cis} (%)
1	Ph	Me	71	7:1	92	78	1:4.5	95
2	4-ClPh	Me	65	7:1	90	79	1:3.5	95
3	4-BrPh	Me	69	5.5:1	90	65	1:3.5	95
4	4-MeOPh	Me	54	6:1	86	74	1:2.5	90
5	3-MeOPh	Me	66	2.5:1	91	80	1:2	90
6	2-FPh	Me	70	7:1	93	—	—	—
7	2-naphthyl	Me	62	3:1	89	64	1:3	84
8	2-furyl	Me	72	8:1	93	70	1:2	86
9	Ph	Et	68	4:1	91	—	—	—
10	Ph	CH ₂ OBn	52	4:1	90	80	1:2.5	97
11	Ph	<i>i</i> -Pr	34	3:1	88	67	1:3.5	94

Figure 175.

Scope of the dual catalytic [2+2] photocycloaddition of enones **9.11** and **9.12a** using both peptides **9.19** and **9.20**.⁴⁰⁴

Figure 176.DKR of biaryl compounds *via* atroposelective electrophilic aromatic bromination.

entry	R	yield (%)	er
1	H	80	97.0:3.0
2	4-NO ₂	85	97.0:3.0
3	5-NO ₂	75	96.5:3.5
4	4-OMe	80	94.0:6.0
5	5-OMe	70	96.0:4.0
6	4-F	65	96.5:3.5
7	5-F	70	97.0:3.0
8	3-Me	85	87.0:13.0
9	4,5-OCH ₂ O	70	95.0:5.0
10 ^a		77	85.0:15.0

^a 4.0 equiv NBP.

Figure 177.

Tripeptide **10.3**-catalyzed atroposelective bromination of biaryls **10.1**.⁴²⁴

Figure 178.

Racemic control reactions to investigate the elements of peptide **10.3** that are crucial for catalysis.⁴²⁴

Figure 179.

Proposed binding and activation model for the **10.3**-catalyzed bromination of **10.1a**.^{424,427}

Figure 180.

Sequential "A-B-C" cross-coupling of **10.4** enables the synthesis of highly functionalized derivatives **10.7**. **Conditions:** (a) 1 equiv aryl MIDA-boronate, 10 mol% $\text{Pd}(\text{PPh}_3)_4$, 8 equiv K_3PO_4 , THF/ H_2O (5:1, 0.1 M), 65 °C, 14 h; (b) 1 equiv benzylamine, 10 mol% $\text{Pd}(\text{OAc})_2$, 20 mol% *rac*-BINAP, PhMe (0.1 M), 100 °C, 18 h; (c) 1.2 equiv phenol, 10 mol% $\text{Pd}(\text{OAc})_2$, 13 mol% *t*-Bu₂XPhos, 2 equiv K_3PO_4 , PhMe (0.3 M), 100 °C, 14 h; (d) 1 equiv NaBH_4 , 5 mol% $\text{Pd}(\text{OAc})_2$, 5.5 mol% *rac*-BINAP, 1.5 equiv TMEDA, THF (0.25 M), 50 °C, 14 h; (e) 1 equiv aryl MIDA-boronate, 10 mol% $\text{Pd}_2(\text{dba})_3$, 10 mol% (*S*)-BINAP, 8 equiv K_3PO_4 , THF/ H_2O (4:1, 0.1 M), 65 °C, 14 h; (f) 1 equiv aryl boronic acid, 5 mol% $\text{Pd}(\text{PPh}_3)_4$, THF/2 M aq. Na_2CO_3 (2:1, 0.1 M), 100 °C, μw irradiation, 1 h.⁴²⁸

Figure 181.

Peptide **10.10**-catalyzed, atroposelective bromination of tertiary benzamides **10.8**.⁴²⁹

Figure 182.

LC/MS studies of reaction mixtures at low conversion under various catalytic conditions.⁴²⁹

Figure 183.

Binding and activation of benzamide **10.8a** by peptide **10.10**.⁴²⁹

Figure 184.

(a) Regioselective derivatization of tribromides **10.9** using a cross-coupling/*ortho*-lithiation sequence. **Conditions:** (a) 1 equiv phenyl boronic acid, 5 mol% Pd(PPh₃)₄, 8 equiv K₃PO₄, THF/H₂O (5:1, 0.1 M), 50 °C, 20 h; (b) 1.05 equiv NaBH₄, 5 mol% Pd(OAc)₂, 5.5 mol% *rac*-BINAP, 1.5 equiv TMEDA, THF (0.25 M), 50 °C, 17 h; (c) 1 atm CO, 10 mol% Pd(OAc)₂, 10 mol% Xant-Phos, 10 equiv Et₃N, MeOH (0.05 M), 60 °C, 16 h; (d) 1.1 equiv aniline, 5 mol% Pd₂(dba)₃, 10 mol% Xant-Phos, 2.5 equiv NaO*t*-Bu, THF (0.25 M), 50 °C, 3.5 h; (e) 1.1 equiv *n*-BuLi, THF (0.1 M), −78 °C; then 1.2 equiv (i) (MeS)₂, (ii) Ph₂P–Cl, or (iii) Ph₂C=O, 10 min. (b) Implementation of the derivatized product **10.15** as a chiral ligand in enantioselective Tsuji–Trost-type allylation.⁴³⁴

Product (**10.19**) Ratios Over Time at 25 °C^a

time	2 h	10 h	24 h	72 h
<i>trans/cis</i>	43:57	54:46	68:32	76:24
<i>er</i> _{<i>trans</i>} (<i>S</i> : <i>R</i>)	66:34	72:28	77:23	79:21
<i>er</i> _{<i>cis</i>} (<i>S</i> : <i>R</i>)	88:12	86:14	84:16	79:21

^a Without catalyst, the *trans/cis* ratio changes from 40:60 to 76:24 over 50 h.**Figure 185.**

Spontaneous enantioenrichment following **10.10**-catalyzed bromination of two-axis substrate **10.18**.⁴³⁵

Figure 186.

Peptide **10.22**-catalyzed bromination of tropolone **10.20**. Compared to the corresponding benzamides, amido-tropolones have notably higher rotational barriers.⁴³⁶

Figure 187. Optimization of a peptide-based catalyst for the atroposelective bromination of 3-arylquinazolinone **10.25a**, highlighting the effect of the *i*+2 residue.⁴⁴⁰

Figure 188.

Sequence truncation reveals the structural attributes key for selectivity in the bromination of quinazolinone **10.25a** under the conditions described in Figure 187.⁴⁴⁰

Figure 189. Peptide **10.27q**-catalyzed, atroposelective bromination of quinazolinones **10.25**.⁴⁴⁰

Figure 190.

A model for binding and activation of quinazolinone **10.25a** by peptide **10.27q** was proposed on the basis of NMR complexation experiments (10 mM in C_6D_6 , 25 °C, 600 MHz), which revealed a number of intermolecular NOEs.⁴⁴⁰

Figure 191.

Regioselective derivatization of tribromides **10.26a** using cross-coupling methodologies.

Conditions: (a) 1 atm H₂, 10 mass% Pd/C, MeOH (0.02 M), 12 h, 0 °C. (b) 2.0 equiv Ar–B(OH)₂, 10 mol% Pd₂(dba)₃, 20 mol% P(*t*-Bu)(Cy)₂•HBF₄, 4.0 equiv K₃PO₄, THF/H₂O (3:1, 0.1 M), 45 °C, 24 h. (c) 2.0 equiv NHR₂, 10 mol% Pd₂(dba)₃, 20 mol% *rac*-BINAP, 1.4 equiv NaO*t*-Bu, PhMe (0.1 M), 80 °C, 18 h.⁴⁴⁰

entry	catalyst	<i>i</i> +1	<i>i</i> +2	er
1	10.27q	D-Pro	Acpc	92:8
2	10.34a	D-Pro	Acpc	95:5 ^a
3	epi-10.34a	L-Pro	Acpc	11:89
4	10.34b	D-Pro	Aib	68:32
5	epi-10.34b	L-Pro	Aib	45:55
6	10.34c	D-Pro	Aic	61:39
7	epi-10.34c	L-Pro	Aic	44:56

^a 95:5 er is also observed at only 1 mol% loading.

Figure 192.

Expansion of the catalyst library for the peptide-catalyzed bromination of quinazolinone **10.25a**.⁴⁴²

Figure 193.

The three conformations of peptide **10.27q** observed by X-ray crystallography. The X-ray structure of peptide **10.34a** overlays closely with conformer **III**.⁴⁴²

Figure 194.

X-Ray crystal structures of the homologous $i+2$ variants of sequence **10.34**. All but **10.34b** adopted the unexpected prehelical conformation, including the most selective quinazolinone bromination catalysts. Enantioselectivity data are for the bromination of quinazolinone **10.25a** to tribromide **10.26a** under the conditions reported in Figure 192.⁵⁰

Figure 195.

Correlation between enantioselectivity (ee) and catalyst τ_{i+2} . The homologous catalysts highlighted in Figure 194 are indicated on the plot. Enantioselectivity data are for the bromination of quinazolinone **10.25a** to tribromide **10.26a** under the conditions reported in Figure 192.⁵⁰

Figure 196.

NOESY correlation diagrams for highly selective catalyst **10.34a** and less selective catalyst **10.34b**.⁵⁰

Figure 197.

(a) Conformational landscape of peptide **10.27q** alone and in the presence of 1.0 equiv of quinazolinone substrates **10.25a** and **10.25b**. (b) Lowest-energy binding modes showing key intermolecular interactions.⁴⁴⁴

type II' β -turns

- $i+1$ C=O stretching frequency
- intensity of $i+2$ N-H stretch
- steric size of $i+3$ substituent

$$\Delta\Delta G^\ddagger = 0.77 + 0.34(\nu_{\text{C=O},i+1}) + 0.18(i_{\text{N-H},i+2}) + 0.13(L_{i+3})$$

type I' β -turns

- $i+2$ main-chain angle
- orbital coefficients of β -turn H-bond
- size of $i+3$ substituent

$$\Delta\Delta G^\ddagger = 0.77 + 0.38(\tau_{i+2}) - 0.16(\text{NBO}_{\text{H-Bond}}) + 0.13(L_{i+3})$$

Figure 198.

Multidimensional parameterization data shows that features of both limiting catalyst conformations correlate well with the observed enantioselectivity in the bromination of quinazolinone **10.25a**.⁴⁴⁵

Figure 199.
General strategy for the desymmetrizing bromination of diarylmethylamido bis(phenol)s **10.35**.⁴⁴⁸

entry	catalyst	10.35a:10.36a:10.37a ^a	er 10.36a
1	10.38	0:69:31 (66%)	95:5
2	10.39	59:35:4	52:48
3	Et ₃ N	19:43:19 ^b	nd
4	none	74:26:0	nd

^a Product ratios were determined by ¹H-NMR analysis of crude reaction mixtures relative to an internal standard prior to methylation. Values in parentheses are for isolated yields. ^b Byproducts were observed. nd = not determined

Figure 200.

Results from the peptide-catalyzed desymmetrizing bromination of **10.35a** demonstrating the importance of the Dmaa residue for selective catalysis.⁴⁴⁸

entry	R ¹	R ²	with peptide 10.38		with peptide 10.10		$\Delta(\Delta\Delta G^\ddagger)$ (kcal/mol)
			10.35:36:37	er	10.35:36:37	er	
1	Me	Ph	0:69:31	95:5	7:46:47	42:58	1.45
2	Me	4-MeOPh	0:56:44	97:3	3:71:26	33:67	1.86
3	Me	4-BrPh	5:59:36	92:8	57:40:3	49:51	1.10
4	<i>i</i> -Pr	Ph	1:68:31	94:6	7:57:36	49:51	1.24
5	Me	OMe	7:55:39	83:17	10:50:40	26:74	1.17

Figure 201.

Enantiodivergence between catalysts **10.38** and **10.10** in the bromination of diarylmethylamido bis(phenols) **10.35**.⁴⁴⁸

Figure 202.

A plot of ee vs. catalyst τ_{i+2} revealed a linear correlation for the desymmetrizing bromination of **10.35a** under the conditions reported in Figure 201.⁴⁴⁸

Figure 203.

Differences in the solution conformations of **10.38** and **10.10** could possibly give rise to inverted binding and activation modes.⁴⁴⁸

Figure 204.

The general strategy for the peptide-catalyzed bromolactonization of pentenoic acid **10.40** to bromolactone **10.41** takes advantage of a bromoiodinane generated *in situ* to transfer bromonium ion to the olefin.⁴⁵⁴

Figure 205.

Key results from the evaluation of peptide scaffolds **10.42**, **10.43**, and **10.44** in the bromolactonization of pentenoic acid **10.40**.⁴⁵⁴

Figure 206. Asymmetric Pd-catalyzed allylation of dimethylmalonate with **11.1** using peptide-based phosphine ligands **11.3** and **11.4**.⁴⁶⁵

Figure 207.

Application of peptide-based *P,S*-ligands **11.8** in the Pd-catalyzed allylation of malonate **11.5** with allylic acetate **11.6**. Modular peptide synthesis enabled the assessment of many distinct stereochemical arrays.⁴⁶⁶

Figure 208.

(a) Development of a peptide based "SupraPhanePhos" ligand. **(b)** Catalyst evaluation in the hydrogenation of α,β -unsaturated esters **11.12**.⁴⁶⁷

Figure 209.

(a) Asymmetric hydroformylation of styrene **11.14** mediated by heterodimeric β -sheet-like self-assembled Rh complexes. **(b)** Design of various carbon linked (L_C) and nitrogen linked (L_N) ligands.⁴⁶⁹

Figure 210.

(a) Influence of peptide H-bonding patterns on the helical chirality of supramolecular phosphine structures. **(b)** Asymmetric, Rh-catalyzed hydrogenation of dehydroalanine **11.12** to afford **11.13**. **(c)** Optimized ligand scaffolds that have been applied in the hydrogenation of **11.12**.^{471,474,475}

Figure 211.

(a) Design strategy for the encapsulation of achiral catalysts in homochiral, peptide-based Ti-phosphonate assemblies in aqueous environments. (b) Asymmetric hydrogenation of acetophenone **11.31** catalyzed by achiral Ru complexes encapsulated by **11.29** and **11.30**.⁴⁷⁷ (c) Asymmetric epoxidation/ring-opening of styrenes **11.33** catalyzed an achiral Mn-salen complex encapsulated by **11.29**.⁴⁷⁶

Figure 212.

Application of bidentate phosphine ligands **11.36–11.39** derived from gramicidin S in the asymmetric hydrogenation of dehydroalanine **11.12a**.^{478,479}

Figure 213.

(a) Design of carboxylate-containing peptide ligands for Fe-based catalysts. (b) Asymmetric epoxidation of styrenes **11.40** mediated by Fe-PDP^{NMe₂} and peptide ligand **11.42**. (c) A comparison of enantioselectivity when acetic acid is used compared to peptide **11.42**.⁴⁸⁰

^aendo/exo >95:5 in all cases

Figure 214.

(a) Molmol representation of monomeric bPP and its dimerization driven by hydrophobic interactions. N represents a site for the introduction of a Cu-coordinating residue at the hydrophobic interface between the two monomers. (b) A comparison of ligand sequences and their relative positions in the secondary structure of bPP. (c) Asymmetric Diels-Alder and conjugate addition reactions of enones **11.48** and **11.49** catalyzed by Cu-bPP complexes in water. Reproduced in part with permission from ref. 483. Copyright 2009 Wiley.

Figure 215.

Optimization of Cu-coordinating peptides **11.52–11.54** in the asymmetric Diels–Alder reaction of enone **11.48**. Ala scan and truncation experiments were used to study the peptides.⁴⁸⁴ MOPS = 3-(*N*-morpholino)propanesulfonic acid buffer.

Figure 216.

Application of peptides **11.53** and **11.54** in (a) asymmetric Diels–Alder reactions and (b) asymmetric Friedel–Crafts-like conjugate addition reactions of enones **11.55**.⁴⁸⁴

Figure 217.

(a) Henry reaction of benzaldehyde **11.58** with nitromethane **11.59** used to study the application of peptides derived from the Crt-1 Mets7 motif. (b) The unmodified structure of Crt-1 Mets7 (**11.61a**) that naturally binds Cu and modified scaffold **11.61b**, which is more conformationally rigid.⁴⁸⁶

Figure 218.

(a) Asymmetric Si-H insertion reaction of α -diazoacetates **11.62** with dimethylphenylsilane catalyzed by helical Rh-peptide complexes. **(b)** A comparison of the performance of monomeric Rh-peptide **11.64a**, parallel dimeric complex **11.64b**, and anti-parallel dimer **11.64c** in the reaction of **11.62** with dimethylphenylsilane. **(c)** Peptide **11.65** was ultimately identified as the lead catalyst.⁴⁸⁹

Figure 219.

Catalyst **11.65** with appended pyrenes. While the (a) parallel isomer **11.65-Pyr** that displays detectable fluorescence, (b) anti-parallel isomer **11.65-Pyr** is not able to form an exciplex.

490

Figure 220.

(a) Synthesis and screening of monomeric catalysts “on-bead” in order to rapidly identify selective sequences. (b) Application of optimized dimeric catalysts **11.68** and **11.69** in the asymmetric cyclopropanation of styrenes with α -diazophenylacetate **11.66**, wherein divergent enantioselectivity is observed between the two peptides.⁴⁹¹

Figure 221.

(a) Disruption of helicity and inactivation of one Rh-site *via* His coordination to an adjacent axial position on Rh. **(b)** Optimized peptide **11.70** for cyclopropanation that was identified from on-bead screening of monomeric Rh-peptide complexes. **(c)** Asymmetric cyclopropanation of olefins **11.71** with α -diazo phenylacetates **11.66** catalyzed by resin-supported tripodal Rh-peptide complex **11.70**.⁴⁹²

Figure 222.

Desymmetrization of diarylmethine **11.73** via Cu-catalyzed C–C, C–O, and C–N cross-coupling reactions.^{496–498} Reactivity was enabled by peptide-based ligands containing TMG-Asp residues at the *N*-terminus, which are proposed to form a 5-membered metallocycle with the Cu(I) catalyst.

Figure 223.

Kinetic resolutions of racemic substrates **11.80** informed a self-consistent model for catalyst–substrate interactions for the transformation depicted in Figure 222.⁴⁹⁶

(a)

entry	peptide	conv. (%)	er
1	Fmoc-pThr-D-Pro-Acpc-Chg-NMe ₂ (11.84)	99	96:4
2	Fmoc- <i>allo</i> -pThr-D-Pro-Aib-Phe-NMe ₂ (11.85)	99	17:83

(b)

Figure 224.

(a) Atroposelective cyclodehydration of trifluoroacetamides **11.82** to benzimidazoles **11.83** catalyzed by pThr-containing peptides. (b) Catalyst-controlled diastereoselective cyclodehydration of enantioenriched **11.86**.⁴⁹⁸