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Perspective

Foldamer Catalysis

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ABSTRACT: The extraordinary rate accelerations and control of reactivity exhibited by enzymes have long inspired efforts to develop synthetic catalysts. Foldamers, which are oligomers with a strong tendency to adopt a specific conformation, represent unique platforms for efforts to harness principles of enzyme function for catalyst design. Well-defined helical structures that have been identified in several foldamer families can serve as scaffolds for the predictable spatial arrangement of functional groups. The chirality of these helices offers a basis for asymmetric catalysis. Thus, foldamer-based approaches to catalyst development represent an attractive alternative to well-developed strategies involving small molecules or conventional peptides.

1. INTRODUCTION

The remarkable selectivities and rate accelerations achieved by natural enzymes result from evolutionary selection over billions of years.[1] These enzymes show chemists how effective catalysis can be, establishing benchmarks for efforts to develop non-biological catalysts.[2] High-resolution enzyme structures can inspire new design strategies in synthetic systems.[3] Contemporary efforts to build from these biological precedents are limited, however, because human designs cannot yet mimic the ability of a folded polypeptide to envelope a substrate (or substrates) within a pocket that precisely orients multiple functional groups while maintaining flexibility. Nevertheless, significant progress has been made by using synthetically malleable molecular frameworks to arrange functional group sets in a manner that promotes catalysis.[4]

Enzymatic catalysis often depends on the positioning of an array of functional groups within an active site. Protein catalysis has inspired many efforts to use small molecules to display sets of two or even three functional groups in a manner that allows coordinated action on a substrate or set of substrates.[4] Significant successes have been recorded, but such efforts collectively highlight limitations of small-molecule frameworks. For example, cinchona alkaloids have provided the basis for a wide variety of useful catalysts, involving, for example, conjugate additions, Mannich reactions, and cyanation reactions.[5] However, the rigid skeletons of these alkaloids are generated by biosynthetic machinery and not easy to modify, which means that the chemist must be shrewd to find reactions that can be catalyzed by functional group arrangements accessible with these skeletons.

In contrast to the non-periodic backbones of rigid, polycyclic molecules, peptides offer a modular backbone from which a variety of reactive groups can be displayed. Miller and co-workers have pioneered the use of β-turn peptidic catalysts for enantioselective and site-selective catalysis.[4d] Reactivity control is often achieved through catalyst−substrate non-covalent interactions, which is reminiscent of substrate engagement among enzymes.[4d,6] Jacobsen and co-workers have elegantly shown that oligomeric catalysts, typically containing a urea or thiourea group for hydrogen bonding with substrates, are valuable catalysts for a plethora of asymmetric processes, including glycosylations, S_N1 substitutions, and Pictet−Spengler reactions.[7] Wennemers et al. have provided other relevant examples.[8] Peptides and other oligomers are amenable to the generation of large groups of candidates that can be screened for desired catalytic activities.[9]

Most α-amino acid residues are inherently flexible, a feature that can work against catalytic efficacy. Peptide flexibility can be modulated, however, in several ways, including (1) use of constrained residues, such as proline or non-proteinogenic analogues; (2) strategic combination of L and D residues; and (3) use of nonpolar solvents, which allow internal H-bonds to drive folding. Many significant advances in asymmetric catalysis and in site-specific modification of complex substrates have been achieved with catalysts composed entirely or primarily of α-amino acid residues.[4d,6]

As interest in late-stage modification of polyfunctional molecules grows, it will be necessary to develop catalysts that contain not only a catalytic group or set of catalytic groups that provides the desired reactivity, but also ancillary functionality to control the location within the substrate at which the catalytic component operates. Numerous catalyst−substrate interactions may be necessary to achieve differentiation among sites that have similar inherent reactivity within a complex substrate.[10] In particularly challenging cases, specific modes of catalyst−substrate engagement will be required to overcome intrinsic reactivity trends among potential modification sites within a substrate. Work from the groups of Miller, Jacobsen, and others, in which easily

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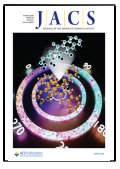

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modified peptidic or other oligomeric backbones were used to develop catalysts that manifest regio- and/or enantiocontrol,[11−13] has inspired our interest in trying to harness novel foldamer secondary structures. The continuously expanding collection of foldamer scaffolds broadens the ways in which sets of functional groups can be arranged in space to promote catalysis (Figure 1).

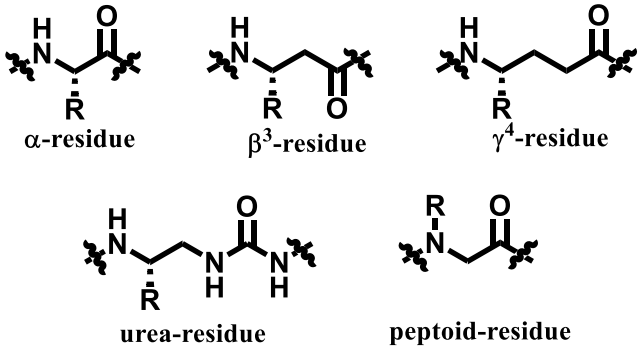

Figure 1. Selected natural and non-natural subunits found in foldamer backbones. R = generic side-chain group.

2. FOLDAMERS

"Foldamers" are oligomers or polymers that are strongly disposed to adopt specific conformations.[14] Interest in synthetic foldamers was inspired by the recognition that biology relies heavily on well-folded oligomers and polymers for catalysis and other sophisticated molecular tasks. Polypeptides and polyribonucleotides are the "biofoldamers", and the substantial differences between proteins and RNA at the backbone level have motivated chemists to survey non-biological backbones for discrete folding behavior. As conformational preferences have been elucidated for various types of unnatural backbones, it has been possible to endow these scaffolds with specific functions.[15] Here we review efforts to develop foldamers that catalyze reactions. The number of studies in this area has been modest so far, but the accomplishments to date suggest great potential for further development, particularly if chemists who specialize in solving synthetic problems are motivated to take up these non-traditional tools.

Most well-characterized foldamer scaffolds that are currently known adopt helical secondary structure.[15] In some cases, these helices can be engineered to undergo self-assembly, typically based on a hydrophobic driving force, which requires aqueous solution.[16] Intermolecular helix association could be a prelude to formation of helix-bundle tertiary structure, but progress toward foldamer tertiary structure has been limited, perhaps because of the technical challenges associated with constructing long oligomers. Therefore, efforts to devise foldamers that catalyze reactions have so far mostly been focused at the level of secondary structure, helices in particular. It should be noted that progress in the better-developed field of conventional peptide catalysis has been largely focused on relatively short oligo-α-peptides that adopt hairpin or helix conformations.[4d,6,8b]

The relationship between subunit identity and helix geometry is well-established for several types of synthetic foldamers. This knowledge allows a chemist to design linear sequences that will bring a specific pair of side-chain functional groups into proximity upon helical folding (Figure 2). Proteins, of course, offer a much broader range of possibilities in terms

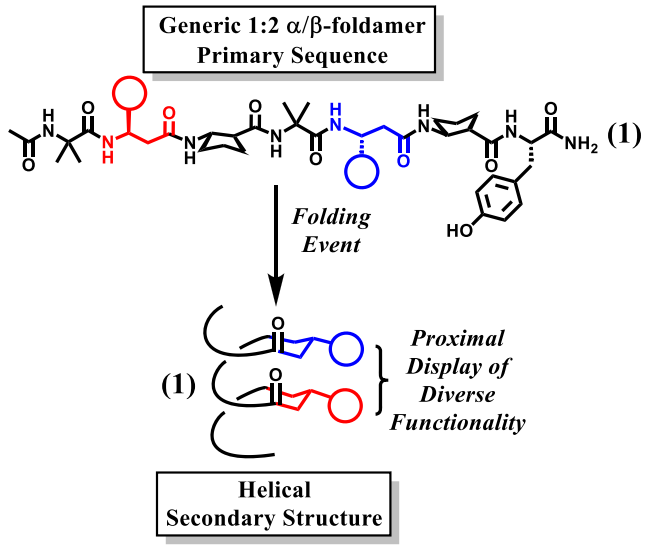

Figure 2. Primary sequence of generic 1:2 α/β-peptide foldamer (**1**), and cartoon depiction of the helical secondary structure that results in the alignment of functional groups from a common helical face.

of the number of catalytic groups that can be arranged and the geometric relationships that can be accessed among those groups. However, despite important advances, the dream of purely rational design of protein catalysts has not yet been realized. As an alternative, directed evolution and selection, sometimes with computational guidance, have proven effective at generating novel protein catalysts for diverse reactions, as demonstrated by creative contributions from the groups of Arnold, Baker, Hilvert, and others.[17−19] Considering foldamer secondary structures in the context of contemporary protein catalyst design suggests that the constraints of the foldamer systems (side chains and substrates remain largely solvent-exposed, and available side-chain arrangements are limited) are balanced by an advantage relative to proteins: foldamers can be engineered to display predictable secondary structures that are very stable at short lengths. These systems allow the chemist to achieve predetermined spatial arrangements of reactive groups, selected from a wide variety of possibilities, based on sequence-level design. As the range of well-characterized foldamer secondary structures grows, the opportunities for catalyst development will expand. Recent studies from the groups of Nicewicz, Miyake, and Kwon have highlighted the importance of understanding molecular shape in photocatalyst development and seem to suggest a new avenue for foldamer application.[20−22]

Potential benefits of foldamer-based design strategies can be illustrated by comparing α- and β-amino acid residues as building blocks. The familiar α-helix (pure α residue backbone) has ~3.6 residues per turn; therefore, residue pairs with $i,i+3$ or $i,i+4$ spacing will be approximately aligned along one side of an α-helix.[23] Use of other subunits provides access to helices with different structural parameters, which enables the designer to explore three-dimensional arrangements of a functional group diad that cannot be achieved with a conventional peptide. For example, β-amino acid oligomers (β-peptides) comprised entirely of β^3 residues adopt a helix with approximately three residues per turn ("14-helix", because

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the characteristic H-bonds involve 14-atom rings).[24] The 14-helix allows a closer angular alignment of an appropriately spaced pair of side chains (i,i+3) than can be achieved with an α-helix. This β-peptide helix brings the two side chains closer to one another in space, because the 14-helix has a rise of ~4.5 A per turn, while the α-helix has a rise of ~5.4 A per turn.

In addition to differences in diad geometry, changes at the backbone level can allow alteration of other important structural parameters. For example, a β-peptide comprised entirely of β^3 residues has only a modest propensity to fold because this type of residue is quite flexible.[24b] However, β-peptide 14-helix stability can be substantially enhanced by incorporating preorganized subunits derived from *trans*-2-aminocyclohexanecarboxylic acid (ACHC).[24a] Short β-peptides containing ACHC residues appear to be fully helical in aqueous solution,[25] a feat that is impossible to achieve for an α-helix without side-chain cross-linking. This distinction between the familiar α-helix and the β-peptide 14-helix illustrates a benefit offered by foldamer backbones: the degree of folding propensity can be modulated over a much wider range among β-peptides than is readily accessible among conventional peptides. Ramifications of this β-peptide feature in terms of catalysis are discussed below.

Not only can a specific helical conformation be stabilized by appropriate subunit preorganization, as illustrated by the impact of ACHC incorporation into 14-helical β-peptides, but also the nature of the helix can be altered by choice of subunit. Among β-peptides, replacing the six-membered ring constraint with a five-membered ring constraint, provided by *trans*-2-aminocyclopentanecarboxylic acid (ACPC), leads to formation of the 12-helix, which has ~2.5 residues per turn and a rise of ~5.4 A per turn (Figure 3).[26]

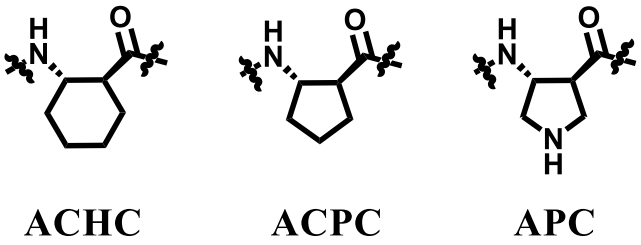

Figure 3. Representative five- and six-membered ring-constrained β-amino acid residues.

In addition, the β-peptide 12- and 14-helices vary in the directionality of their H-bonds (C=O(i)−H−N(i+3) in the former vs C=O(i)−H−N(i+2) in the latter). These two helices represent distinct scaffolds for display of functional group sets that might collectively display catalytic activity; each helix provides access to different (and therefore complementary) spatial arrangements of a given reactive group cluster. The ability to fine-tune functional group display through subunit identity and conformational preorganization may be useful in terms of asymmetric catalysis, where only a few kcal/mol difference between diastereomeric transition states can lead to substantial asymmetric induction.

Pushing beyond α-amino acid subunits in the quest for new foldamers offers an opportunity to explore heterogeneous backbones, a dimension of variation that has no parallel among the biological foldamers. Thus, for example, α- and β-amino acids can be combined to generate α/β-peptides with diverse patterns of α and β residues along the backbone, a dimension of sequence variation that is distinct from the more familiar variation that involves only side chains. A range of helical secondary structures has been identified among α/β-peptides with different proportions and arrangements of α and β subunits.[27] In general, these helices are stabilized by use of ACPC. As discussed below, the superfamily of ACPC-containing foldamers provides a fertile basis for catalyst discovery.

The preceding paragraphs have focused on foldamers containing β-amino acid residues because this group is particularly well characterized, but comparable possibilities emerge as more extended amino acids and related subunits are employed for foldamer construction. Thus, for example, several helical secondary structures have been identified among oligomers containing γ-amino acids, including γ-peptides, α/γ-peptides, β/γ-peptides, and $\alpha/\beta/\gamma$-peptides.[28] Fundamental structural studies have begun to provide a basis for γ-peptide catalyst development, as described below.

3. CARBON−CARBON BOND CHEMISTRY

The controlled formation or cleavage of carbon−carbon bonds is of central importance in metabolism and in synthetic organic chemistry. Both types of reaction have been explored in the context of foldamer catalysis.

In one of the earliest examples, Hilvert et al. showed that a β-peptide decamer could serve as an effective catalyst for the retro-aldol reaction of 4-phenyl-4-hydroxy-2-oxobutyrate in aqueous buffer (Figure 4).[29] This effort was inspired by earlier

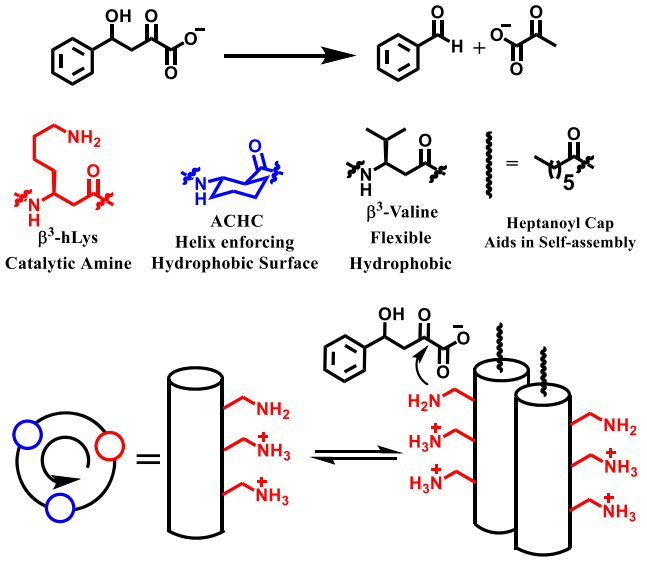

Figure 4. β-Peptide-catalyzed retro-aldol reaction. Cartoon depiction of helical wheel with ACHC and β^3-hLys residues clustered on respective helical faces.

work with designed lysine-containing α-peptides that adopt an α-helical conformation and display retro-aldol catalysis.[30,31] The catalytic mechanism appears to involve imine formation between the keto group of the substrate and a lysine side chain, the latter in the amino rather than ammonium form. The β-peptide designs featured β^3-homolysine (β^3-hLys) as the source of the catalytic group.

The most effective β-peptide featured the repeating sequence triad ACHC-ACHC-β^3-hLys, which generates a

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globally amphiphilic 14-helix with nonpolar cyclohexyl side chains dominating two-thirds of the circumference and a stripe of amine/ammonium side chains on the opposite side of the helical cylinder. The ACHC residues fulfill two roles, stabilizing the helical secondary structure and providing a composite hydrophobic surface that drives self-assembly in aqueous solution. Both features proved to be important for maximizing catalysis. A sequence isomer in which the β^3-hLys and ACHC residues were distributed around the entire helix circumference did not self-assemble and was a poor catalyst of the retro-aldol reaction. An analogue of the most effective β-peptide in which all of the preorganized ACHC residues were replaced by flexible but hydrophobic β^3-hVal residues was an inferior catalyst. It was proposed that self-assembly enhances catalysis by bringing positive charges near one another, thereby lowering the pK_a of at least one side-chain ammonium group.

Guichard et al. have characterized urea-based foldamers that form a helix with ~2.5 residues per turn.[32] This helix is stabilized by bifurcated H-bonds between each backbone carbonyl and both N−H groups of the urea group at position i +2. Palomo, Guichard, and co-workers have shown that oligourea **2** catalyzes the enantioselective addition of malonates to nitro-olefins (Figure 5A).[33]

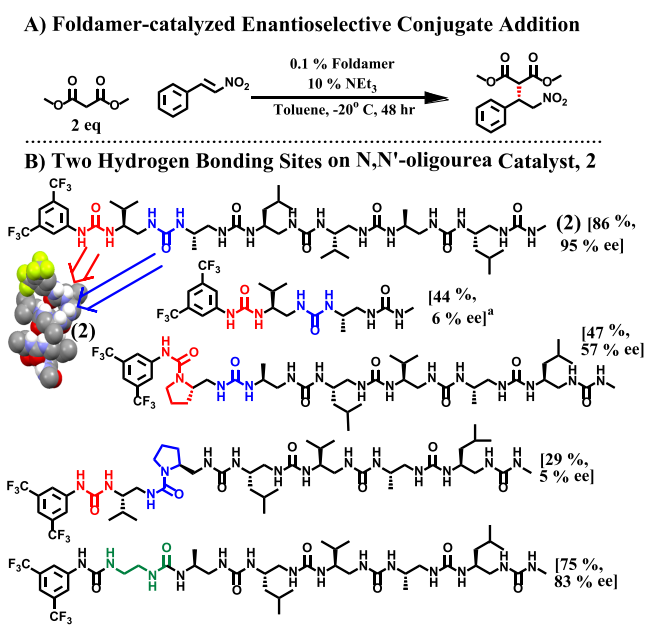

Figure 5. (A) Foldamer-catalyzed, enantioselective conjugate addition. (B) Selected *N,N′*-oligoureas for catalyst structure−activity relationship. Crystal structure of **2**. [a]Reaction run at room temperature. Hydrogen-bonding (or disrupted hydrogen-bonding) sites are highlighted in red and blue. Unsubstituted urea subunit in green. Crystal structure: black, carbon; red, oxygen; white, hydrogen; blue, nitrogen; green, fluorine. Only N−H hydrogens are shown.

Useful reactivity and high enantioselectivity (up to 99% ee) were achieved at extremely low catalyst loading (0.1 mol% urea oligomer, along with 10 mol% Et_3N), a significant feat in comparison to traditional organocatalytic loadings (10−20 mol %).[34] Helix formation generates two neighboring urea groups at the N-terminus, both of which are double H-bond donor sites. The authors propose that this NH-rich site is responsible for substrate recognition and activation.

Because they harness an active site involving the helical oligourea backbone rather than functional groups provided by side chains, the urea-based foldamers of Palomo, Guichard, et al. are reminiscent of the α-helical peptides employed in the Juliá-Colonna epoxidation.[35] This enone epoxidation is catalyzed by polyleucine, and the array of amide NH groups aligned at the N-terminus of the α-helix is proposed to be the site of substrate binding and activation. Roberts et al. have shown that poly-β^3-hLeu has comparable catalytic capabilities.[36]

Nitro-olefins are highly reactive electrophiles, and these molecules can be considered "privileged substrates" in the organocatalysis community because conjugate additions to nitro-olefins have been so widely studied.[37] Wennemers et al. have shown that the tri-α-peptide D-Pro-Pro-Glu-NH_2 (**3**) is an excellent catalyst for aldehyde additions to nitro-olefins (Figure 6A).[38]

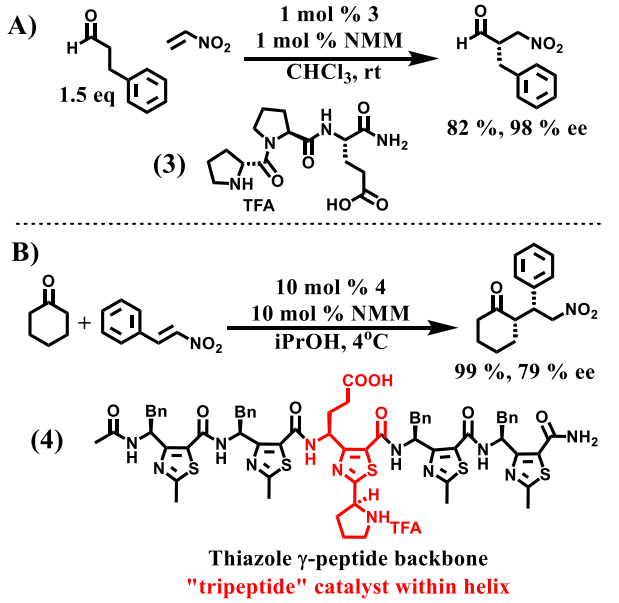

Figure 6. Conjugate additions to nitro-olefins catalyzed by (A) tri-α-peptide D-Pro-Pro-Glu-NH_2 and (B) thiazole-based γ-peptide. TFA = trifluoroacetic acid.

Recently, this group systematically evaluated the effect of replacing α residues with β homologues; only the Glu residue could be substituted without loss of reactivity or stereoselectivity.[39] Figueiredo, Maillard, et al. have reported that helical γ-peptides (**4**) containing thiazole-based subunits catalyze the stereospecific conjugate addition of ketones to nitro-olefins.[40] In this system, the two reactive groups required for bifunctional catalysis, a pyrrolidine and a carboxylic acid, are located within a single γ residue (Figure 6B). However, the authors demonstrated that yield and stereoselectivity increased modestly as the foldamer in which that γ residue was embedded grew longer, suggesting that the helical secondary structure is beneficial in terms of reaction outcome.

Price, Michaelis et al. have developed helical α-peptides that serve as bifunctional catalysts of enantioselective Diels−Alder and indole alkylation reactions.[41] These catalysts can be considered "foldamers" because they feature non-proteinogenic residues not only to provide catalytic functionality (an imidazolidinone and a thiourea, projecting from side chains) but also to promote a helical conformation (Aib residues). The Diels−Alder reaction between 2-butenal and a carbamate-

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functionalized diene occurred with high yield and enantioselectivity with a peptide catalyst (5) (Figure 7A). The

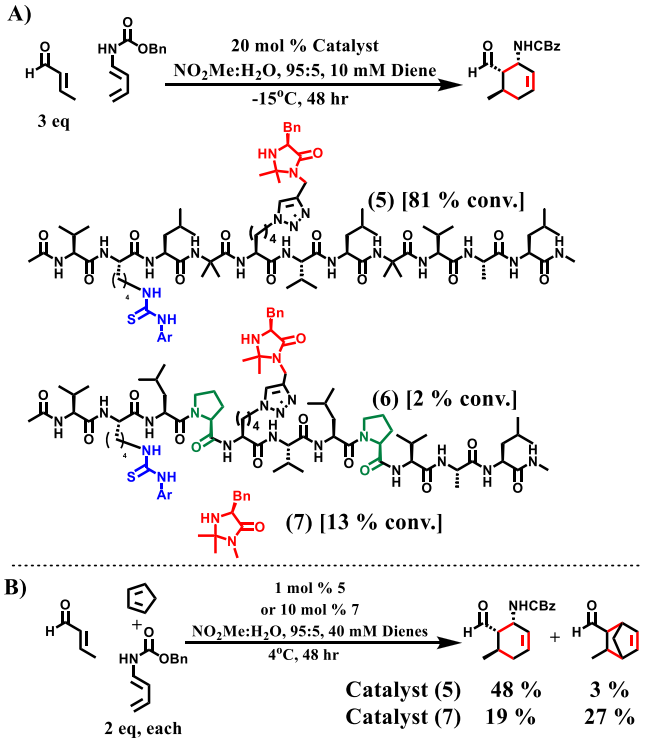

Figure 7. (A) Peptide-catalyzed Diels–Alder reaction. (B) Diene competition experiments comparing bifunctional peptide catalyst (5) and imidazolidinone (7).

imidazolidinone was intended to provide electrophilic activation for 2-butenal (via iminium formation).[42] The thiourea was positioned to be approximately aligned with the imidazolidinone upon helix formation;[4e,f] H-bonds from the thiourea to the carbamate carbonyl were intended to hold the diene near the iminium dienophile.

Control studies supported the authors' bifunctional catalysis hypothesis. For example, insertion of proline residues, expected to disrupt helical folding, led to a loss of catalysis (6). Another control experiment involved competition between two dienes, one bearing a carbamate, which can H-bond to the thiourea, and the other (cyclopentadiene) lacking an H-bonding site (Figure 7B). With a simple imidazolidinone catalyst (7), cyclopentadiene was modestly preferred over the carbamate-bearing diene, but the Diels–Alder reaction catalyzed by the bifunctional peptide showed a strong selectivity for the carbamate-bearing diene.

The use of Aib to stabilize helix formation in the work of Price, Michaelis, et al. is reminiscent of very clever work from Clayden et al. involving Aib-rich α-peptides.[43] This group has shown that stereochemical information, as provided in an sp^3 stereocenter at one end of the peptide, can be transmitted across 60 bonds contained in a locally achiral Aib-rich segment, to influence the stereochemical outcome of a carbon–carbon bond-forming reaction that generates a new sp^3 stereocenter at the other end of the peptide (Figure 8). This remarkable achievement reflects the influence on helix screw sense exerted by terminal stereogenic centers.

Matile et al. have reported an extremely elegant use of foldamer design to test the intriguing hypothesis that electron-

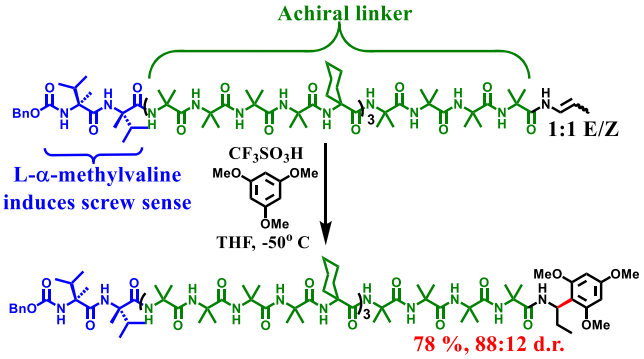

Figure 8. Asymmetric induction over 60 bonds.

deficient π-systems can control reactivity outcomes via their interactions with anionic intermediates. Specifically, this group developed a series of foldamers that promote face-to-face stacking of naphthalenediimide (NI) units. Catalysis was manifested in terms of chemoselectivity in reactions involving a malonic acid half thioester and a nitro-olefin. By incrementally varying foldamer length, and thereby the number of stacked NI units, Matile and co-workers were able to develop incisive support for the operation of long-range, synergistic anion-π catalysis (Figure 9),[44] which favors the conjugate addition

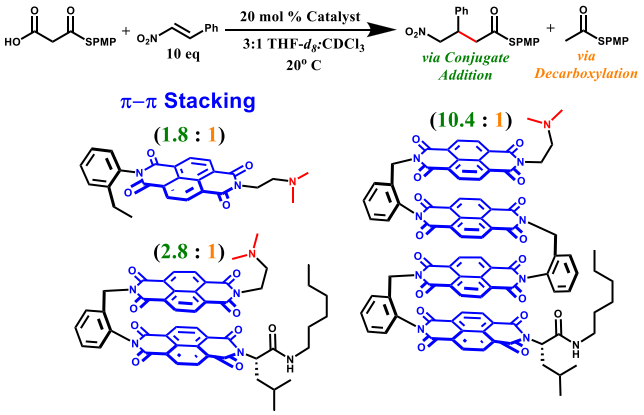

Figure 9. Synergistic anion-π catalysis via π-stacked foldamers leads to chemoselective conjugate addition, as manifested in the ratio of conjugate addition product to decarboxylation product. PMP = *p*-methoxyphenyl.

pathway over decarboxylation. Preference for conjugate addition increases as the NI stack grows longer. The ability to tune and enhance anion binding via foldamer elongation demonstrated in this work offers interesting opportunities for future studies involving anion-abstraction catalysis.[45]

Recent work in our laboratory has focused on bifunctional catalysis of aldol reactions by foldamer helices bearing amine diads. In the first phase of these studies, we employed a well-known type of selective crossed aldol condensation, in which formaldehyde is the obligate electrophile, to probe the different diad geometries that could be achieved across a superfamily of ACPC-based β- and α/β-peptides.[46] The crossed aldol reaction provided an assay for judging which backbone and sequential spacing enabled the most effective coordination between the two side-chain amino groups.

These experiments built upon an extensive literature on amine catalysis of aldol and related reactions.[4a,47] In particular,

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we were inspired by mechanistic analysis by Erkkilä and Pihko of pyrrolidine-catalyzed crossed aldol reactions involving formaldehyde. These researchers demonstrated second-order catalysis by pyrrolidine and concluded that both reactants are activated.[48] Specifically, formaldehyde is activated as an electrophile (iminium) by one pyrrolidine molecule, and the other aldehyde is activated as a nucleophile (enamine) by the other pyrrolidine molecule. The cyclopentane-based β residue ACPC can be replaced by pyrrolidine-based analogue APC (Figure 3) while retaining helical propensity.[49] Therefore, the mechanistic insights from Erkkilä and Pihko led us to hypothesize that foldamers containing two properly spaced APC residues would be effective catalysts of the crossed aldol reaction.

We evaluated this hypothesis by examining three series of APC-containing foldamers, one with a pure β residue backbone, one with a 1:1 alternation of α and β residues, and one with a 1:2 alternation of α and β residues. Each backbone had well-established conformational behavior, and we could be confident that examining bis-APC sequence variants for all three backbones would, collectively, explore a variety of spatial arrangements of the pyrrolidine units.

Our experimental design is illustrated for two of the backbones (pure β and 1:2 α:β) in Figure 10. We compared

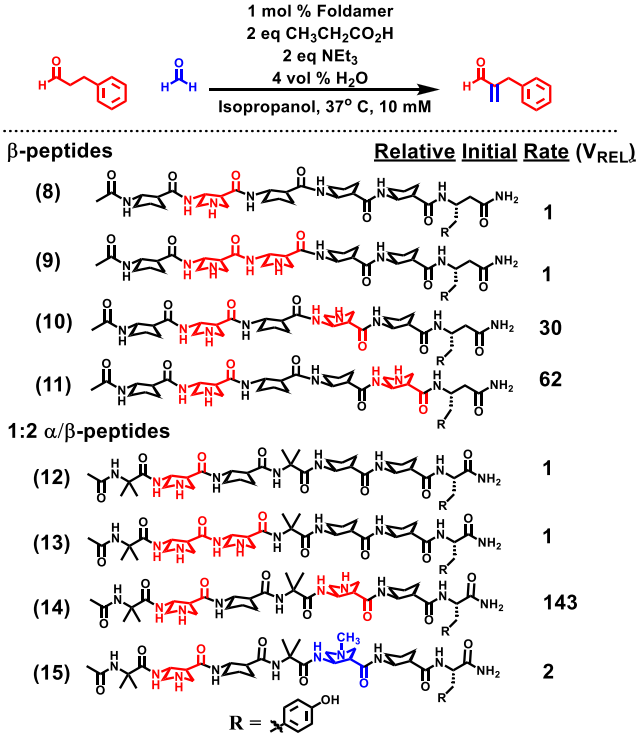

Figure 10. Evaluation of β- and 1:2 α/β-peptide amine diad geometries for the crossed aldol reaction.

relative initial rates of the crossed aldol condensation involving hydrocinnamaldehyde as nucleophile among foldamers with a common backbone. In each case, the initial rate was normalized to that observed for the foldamer bearing a single APC residue (**8** or **12**). In both series, placing the two APC residues adjacent in sequence (**9** or **13**) caused no increase in initial rate

These outcomes were expected, because helix formation causes the pyrrolidine nitrogen atoms to splay apart when the APC residues are adjacent in sequence. Further separation along the sequence allows the two pyrrolidine rings to approach alignment in the helical conformation. Thus, for the pure β backbone, which forms the 12-helix, with ~2.5 residues per turn, *i*,*i*+2 spacing (**10**) causes the pyrrolidines to be a little less that one turn apart, while *i*,*i*+3 spacing (**11**) causes them to be a little more than one turn apart. Both arrangements lead to a significant increase in initial rate of the crossed aldol reaction. The most substantial initial rate enhancement was observed in the 1:2 α/β series, when the pyrrolidines had *i*,*i*+3 spacing (**14**). This foldamer backbone forms a helix with ~3 residues per turn, and this sequential spacing should cause nearly perfect angular alignment of the pyrrolidine rings.

Mechanistic studies provided strong support for our hypothesis that α/β-peptide **14** acts as a bifunctional catalyst of the crossed aldol reaction, covalently activating formaldehyde as the iminium and hydrocinnamaldehyde as the enamine. For example, replacing one secondary amine with a tertiary amine (**15**) largely abolished the rate enhancement relative to mono-APC reference foldamer **12**, as predicted by this hypothesis. In addition, catalysis was shown to be first-order in terms of foldamer **14**.

The activity manifested by α/β-peptide **14** is significant in terms of the young field of foldamer catalysis, but this activity is not useful in a practical sense. If one needed to prepare the enal product generated from hydrocinnamaldehyde and formaldehyde, one would use pyrrolidine rather than synthesizing **14**. However, the identification of **14** as a bifunctional catalyst led us to wonder how this foldamer system might be used to achieve catalytic reactivity that was not readily accessible with simple amines. These considerations led us to explore intramolecular aldol reactions intended to form medium-sized rings.

Exploratory studies with dialdehyde **16** revealed that bis-APC foldamer **14** caused very little reaction.[50] However, when we examined analogue **17**, in which the catalytic diad has been altered to feature a primary amine in addition to a secondary amine, dialdehyde **16** was induced to form cyclodimers and cyclotrimers, containing 16- and 24-membered rings (another possible product, cyclo-octene-1-aldehyde, was not detected) (Figure 11). This unexpected outcome was intriguing because large carbocycles can be challenging to prepare, and because there was no way to predict that altering the composition of the catalytic diad would so profoundly affect reactivity. Control reactions with a 1:1 combination of pyrrolidine and *n*-

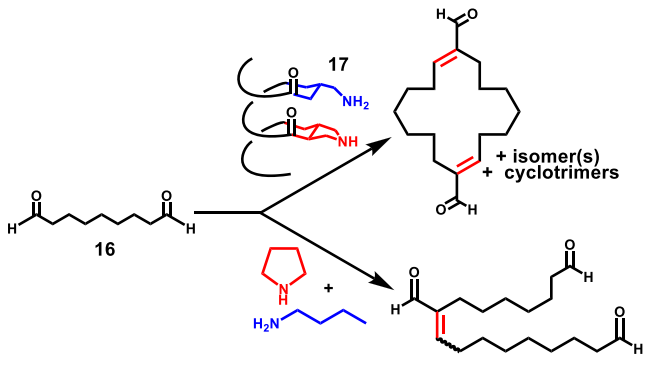

Figure 11. Foldamer-catalyzed cyclodimerization of dialdehyde **16**, and small-molecule control reaction.

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butylamine provided very little product, which demonstrated that the foldamer catalyst displays activity distinct from that of smaller and more conventional catalysts.

We turned to longer dialdehydes to evaluate the effects of ring size on catalytic efficacy of macrocyclizations. Good yields could be achieved for 14-, 16-, and 18-membered ring formation, but 12-membered ring formation in this series was accompanied by significant cyclodimerization. We speculate that ring strain associated with medium-sized rings (conventionally identified as those containing 8−11 atoms) makes it hard to effect their closure.[51] The observed catalysis of larger ring formation is attributed to a templation effect of the foldamer, which forms transient covalent intermediates (iminium and enamine) with both ends of a long-chain dialdehyde and facilitates ring-closing bond formation (Figure 12A).

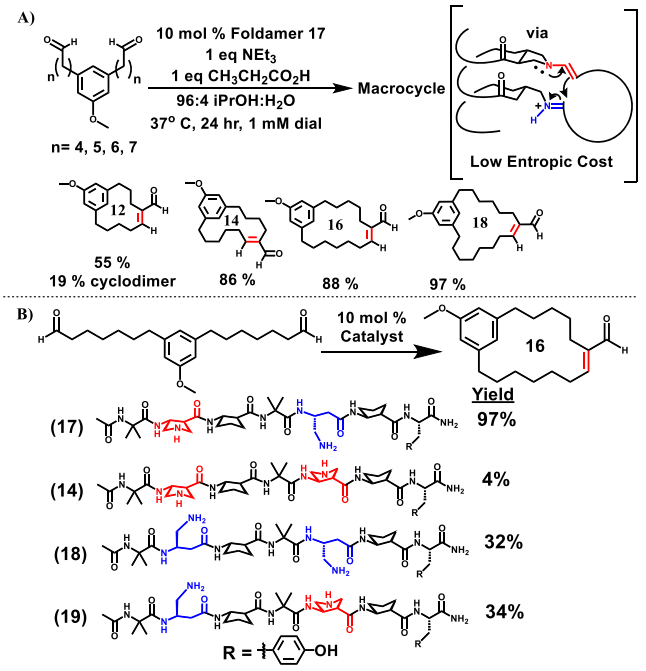

Figure 12. (A) Foldamer-templated macrocyclization of dialdehydes. (B) Effects of varying diad identity on catalysis.

The unimolecular cyclization to form a 16-membered ring enal provided the basis for exploring the impact of foldamer structure on reaction outcome (Figure 12B). Consistent with results from the crossed aldol study, we found that the *i*,*i*+3 spacing of the two amino groups is required for efficient macrocyclization. A diad comprised of two secondary amines was almost completely ineffective (**14**), and the yield was poor when the diad comprised two primary amines (**18**). Swapping the positions of the secondary and primary amines within the sequence caused a substantial decline in macrocycle yield (**19**), which shows that catalysis is very sensitive to the spatial arrangement of the two catalytic groups.

To illustrate the utility of this new type of macrocyclization reaction, we used foldamer **17** in the synthesis of the natural product robustol, which contains a 22-membered ring (Figure 13).[52] The cyclization step produced two regio-isomeric enals, because the starting dialdehyde was unsymmetrical. Subjecting this mixture to decarbonylation followed by hydrogenation

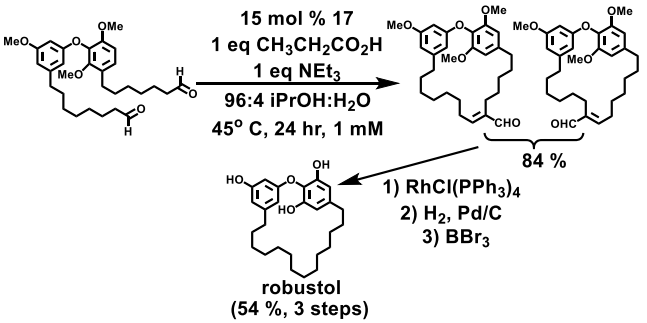

Figure 13. Total synthesis of robustol via foldamer-catalyzed macrocyclization.

provided a single product, which could then be converted to robustol.

4. OTHER REACTIONS

One of the earliest examples of foldamer catalysis featured the peptoid backbone. Peptoids are *N*-alkyl-glycine oligomers; therefore, the backbone contains only tertiary amide groups.[53] Because the peptoid backbone lacks H-bond donors, avoidance of steric repulsion plays a major role in determining secondary structure, although other non-covalent interactions contribute.[54]

Mayaan, Ward, and Kirshenbaum explored the oxidative kinetic resolution of racemic 1-phenyl-ethanol with peptoids bearing a nitroxyl group derived from TEMPO (Figure 14).[55,56] The peptoid subunits contained a stereogenic center

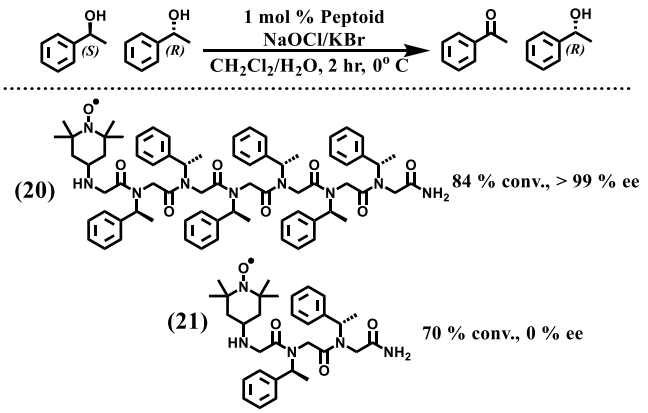

Figure 14. Oxidative kinetic resolution via peptoid catalysis.

in the side chain. Peptoids in this class had earlier been shown to adopt a helical conformation. When the nitroxyl group was placed on a peptoid heptamer (**20**), a kinetic resolution was observed (after 84% of the starting alcohol had been consumed, the remaining alcohol displayed 99% ee). The presence of the peptoid helix was important, because a peptoid dimer linked to the nitroxyl group (**21**), did not achieve any kinetic resolution of the alcohol enantiomers.

Reactions of activated ester substrates have been popular subjects for enzyme-mimetic catalysis studies. Substantial rate accelerations have been achieved for the transesterification of vinyl trifluoroacetate to methyl trifluoroacetate with "spiroligomers" that display rigid but readily diversifiable backbones. This family of oligomers with controlled shapes has been developed by Schafmeister et al. In collaboration with the Houk group, Schafmeister and colleagues designed a "spirolig-

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ozyme" that adopts a curved shape and projects three reactive groups from the concave surface (Figure 15A).[57]

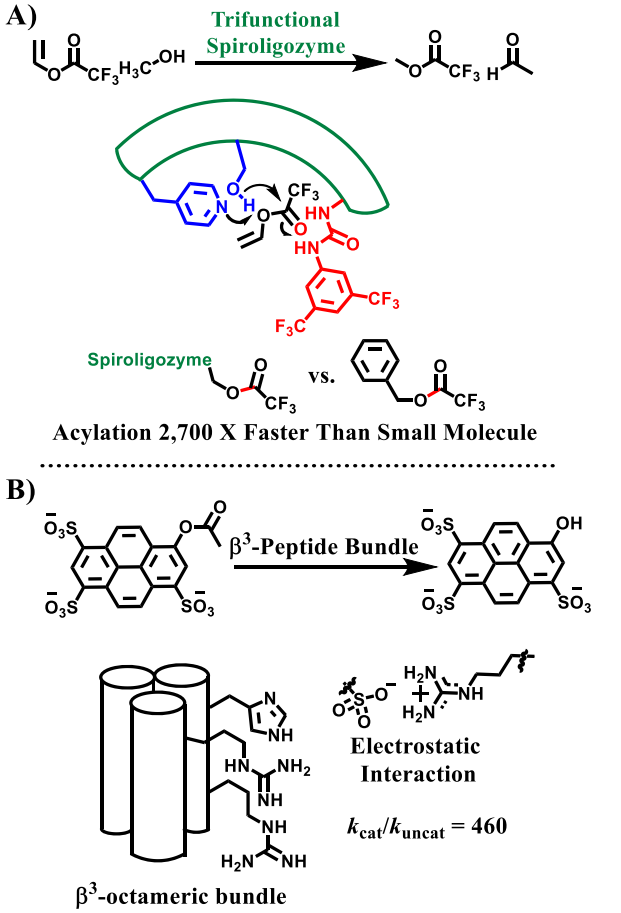

Figure 15. (A) Spiroligozyme0accelerated acylation/transesterification. (B) Activated ester hydrolysis catalyzed by a self-assembling β-peptide.

The transacylation reaction proceeds through an acyl-spiroligozyme intermediate that is reminiscent of the covalent intermediates formed by serine proteases. In subsequent work, this group developed a spiroligomer that catalyzes a Claisen rearrangement.[58]

Schepartz et al. have developed self-assembling β-peptides that catalyze the hydrolysis of 8-acetoxypyrene-1,3,6-trisulfonate (Figure 15B).[59] Unlike the β-peptides mentioned above that catalyze a retro-aldol reaction, the β-peptides of Schepartz et al. form discrete helix-bundles in aqueous solution. Catalysis was promoted by engineering a high positive charge density on the β-peptides, to attract the anionic substrate. The α-amino acid residue histidine was incorporated into these designs to provide a side-chain imidazole group that is critical for catalysis.

5. RECENT LESSONS FROM CONVENTIONAL PEPTIDES

As noted above, pioneering accomplishments from Miller et al. and other groups have demonstrated the catalytic prowess that can be elicited from relatively short peptides containing exclusively α residues, and these precedents have helped to inspire the foldamer-based efforts discussed above.[4d,6,8,9,38,39] Here we highlight recent advances with conventional peptide catalysts that suggest potentially productive paths for future foldamer-based studies.

Foldamers that adopt defined tertiary structure remain elusive, but combining two or more secondary structural motifs into a single catalyst scaffold represents an interesting alternative. Kudo et al. have taken this approach among α-peptides by linking a β-turn segment with a helical segment to develop a catalyst for regio- and enantioselective reductions of $\alpha,\beta,\gamma,\delta$-unsaturated aldehydes mediated by a dihydropyridine reagent (Figure 16).[60] Resin-supported catalyst **22** utilizes a

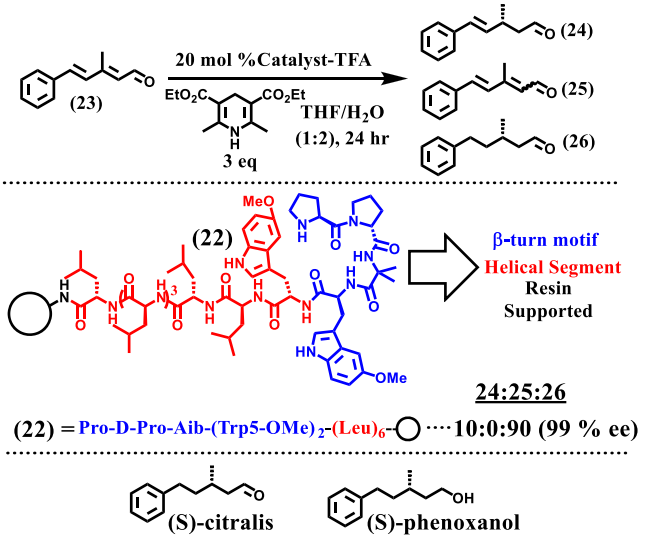

Figure 16. Regio- and enantioselective reduction of $\alpha,\beta,\gamma,\delta$-unsaturated aldehydes.

proline residue for iminium activation of unsaturated aldehyde **23**, and the tandem turn/helix motif provides an asymmetric environment for the reduction. Control peptides that lacked either the turn or helix segment resulted in decreased regio- and enantioselectivity. The catalyst-controlled reduction was utilized in the enantioselective synthesis of (*S*)-citralis and (*S*)-phenoxanol, from *E*/*Z*-$\alpha,\beta,\gamma,\delta$-unsaturated aldehyde **23**.

Foldamers containing tandem helical and turn motifs may offer an avenue toward catalysts that begin to surround their substrates in an enzyme-like manner. This approach could lead to foldamers that contain elements intended to engage substrates in ways that guide the operation of the reactive groups. An alternative approach to this challenge that does not require creation of an authentic tertiary structure is suggested by remarkable work of Huc et al.[61] This group developed aromatic oligoamides with large internal cavities that could be modified with H-bonding groups in a site-specific manner to generate substrate-selective carbohydrate binders. Placement of reactive groups on the cavity walls could lead to catalysis.

Most examples of foldamer catalysis have employed organic functionality to engage substrates ("organocatalysis"), but foldamer scaffolds could be powerful tools in the context of metal-mediated catalysis. The ability of chiral foldamer backbones to project metal-ligating groups in specific geometric orientations might support asymmetric catalysis. Ball et al. have provided an elegant conventional peptide example with peptide **27**, which adopts an α-helical conformation and aligns two side-chain carboxylates, from Asp residues with $i,i+4$ spacing, for multidentate coordination to a dirhodium core. Two peptide ligands, oriented antiparallel to one another,

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provide a complete coordination sphere of four carboxylates. The resulting complex, **28**, catalyzes enantioselective carbenoid insertion into Si–H bonds (Figure 17).[62,63]

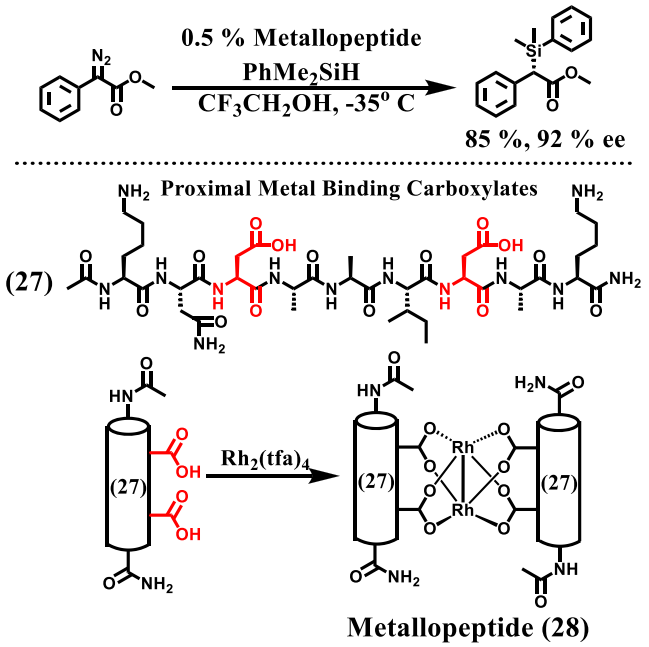

Figure 17. Metallopeptide-catalyzed enantioselective carbenoid insertion into Si–H bonds.

Mechanistic studies identified side chains near the coordinated metal ions as important for enantioselectivity. The modularity of these α-peptide ligands makes them attractive for optimizing asymmetric catalysis, since many alternative side chains, natural or unnatural, could be employed. Foldamers based on unnatural backbones would offer comparable benefits as metal ion ligands and offer side-chain arrangements complementary to those accessible with α-peptides.

Substrate activation via reversible covalent bonding is an attractive strategy for catalysis because key bond-forming steps can be rendered intramolecular in this way.[64] The entropic benefit of this approach can lead to accelerated rates relative to comparable intermolecular reactions. Several of the foldamer-based catalysts described above rely on amines for reversible covalent activation of substrates, such as aldehydes or ketones, but other modes of covalent activation should be fruitful as well.

Ghadiri et al. demonstrated the ability of a quaternary structure formed by peptides that adopt a specific secondary structure, an α-helical coiled-coil dimer, to serve as a basis for catalyst development. This system promoted diketopiperazine formation from thioester derivatives of α-amino acids via cysteine-based substrate anchoring (Figure 18).[65]

The coiled-coil dimer (**29**) was suggested to mimic a nonribosomal peptide synthetase in the juxtaposition of two cysteine side chains, each of which can capture a substrate (**30**) via transthiolesterification (**31**). Subsequent C–N bond formation was accelerated by the proximity of the two acyl-Cys units, as well as the nearby histidine residues, which may have a general base function. Cyclization generates the diketopiperazine by detaching the substrate, thus turning over the catalyst. In this example, formation of a transient

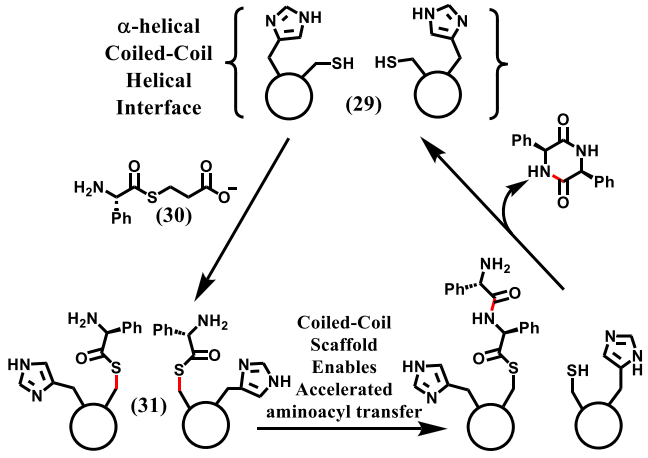

Figure 18. Diketopiperazine formation catalyzed by an α-helical coiled-coil.

thioester on the catalytic peptide does not significantly alter acyl group reactivity, relative to the thioester substrate, which contrasts with the activating effects of enamine or iminium intermediate formation in examples discussed above. Nevertheless, the benefit of bringing two thioesters together, as accomplished by quaternary structure formation, is clearly established in this example, which raises the possibility that foldamer quaternary structures might be harnessed for catalyst development.[66] It is noteworthy that cysteine itself has been used as a catalyst for enantioselective Rauhut–Currier reactions,[67] which suggests other ways to use cysteine or other thiol-bearing subunits in foldamer catalysis.

Additional inspiration can be found in very creative work from Arora et al. that has resulted in redox-active multifunctional catalysts of peptide bond formation from N-protected α-amino acid substrates.[68] This chemistry is compatible with conventional solid-phase synthesis and sets a standard toward which future foldamer catalysis efforts can strive.

6. PERSPECTIVE

The work summarized above suggests that foldamers offer a unique approach for development of new catalysts that are complementary to those accessible from small-molecule frameworks or conventional peptide scaffolds. Stable secondary structures established for diverse foldamer backbones expand the geometries available for orienting sets of reactive side chains in a manner that promotes multifunctional catalysis. As the folding "rules" for new foldamer systems are elucidated, the range of possible side-chain arrangements will grow. The inherently modular nature of foldamers at the covalent level, a feature shared with conventional peptides, facilitates the exploration of new geometries for side-chain clusters and new identities of the side chains in those clusters.

One potentially productive new path under examination in our group involves the creation of foldamer-based photocatalysts for organic transformations. Photocatalytic methods have exerted a profound effect on organic synthesis over the past decade, enabling a wide range of transformations to be driven by visible light.[69] Developments in this field can be hindered, however, by the fact that the excited states of many popular photocatalytic moieties are too short-lived to support efficient Dexter energy transfer or single-electron transfer, which results in low quantum yields.[70] We hypothesize that a properly chosen foldamer scaffold might allow efficient energy

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or electron transfer by enforcing proximity between a photocatalytic moiety and a substrate (Figure 19). Ultimately, juxtaposing photoactive and substrate-binding functionality along a foldamer backbone might enable catalysis of stereoselective and/or chemoselective reactions.

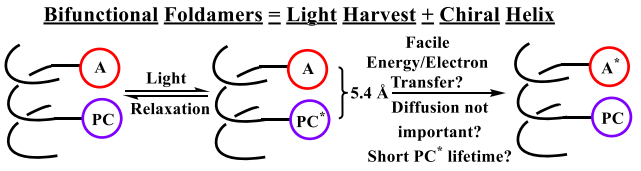

Figure 19. Cartoon depiction of efficient energy or electron transfer from an excited-state photocatalytic unit to a foldamer-bound ground-state acceptor. A = acceptor, PC = photocatalyst.

Foldamers enable programmable variation of side-chain display, which supports applications that span molecular recognition,[15,71] medicine,[15,72] and catalysis. Here we have highlighted foldamers that facilitate organic reactions and display desirable features such as stereoselectivity or templation of macrocycle formation. We speculate that future efforts will support the hypothesis that foldamers, collectively, provide a very diverse set of possibilities for orienting specific sets of functional groups to achieve catalytic goals.

As with many efforts to develop new catalysts, foldamer-based approaches are ultimately inspired by the extraordinary properties of enzymes and ribozymes that have been elicited by natural evolutionary processes. In this regard, it is noteworthy that laboratory-based evolution has been harnessed by Holliger et al. to generate "xeno nucleic acid" oligomers, which could be viewed as RNA-inspired foldamers, that display remarkable catalytic prowess.[73] In addition to the conceptual foundation provided by biopolymer catalysts, experimental work directed toward foldamer catalyst development benefits from the many impressive accomplishments of organic chemists who employ small molecules or conventional peptides as the basis for catalyst design or discovery.

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Notes

The authors declare no competing financial interest.

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