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In Search of Peptide-Based Catalysts for Asymmetric Organic Synthesis

SCOTT J. MILLER*
Department of Chemistry, Merkert Chemistry Center, Boston College, Chestnut Hill, Massachusetts 02467
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ABSTRACT
The discovery of short peptide sequences that function as asymmetric catalysts for a variety of reactions is documented. The evolution of the project from an exercise in rational design to an endeavor that combines combinatorial screening with various mechanism-based experiments is presented. The specific development of catalysts for enantioselective acylation, phosphorylation, conjugate addition, and Morita−Baylis−Hillman reactions is described.

Introduction

The fields of organic synthesis and enzymology have a curious intersection. In one arena, organic synthesis is concerned with natural product synthesis, and of course the synthesis of other biologically active molecules. Within the field, both target- and diversity-oriented syntheses have benefited greatly from advances in the understanding of enzyme-mediated biosynthesis, and indeed biomimetic synthesis may even be a field in itself.[1,2] Catalytic processes also have a tremendous impact on synthesis. The catalysts that are routinely employed span a staggering molecular weight range. At one extreme, enzymatic catalysts are applied with great success in syntheses.[3] At the other end of the molecular weight spectrum, man-made, small-molecule catalysts have also recorded many successes.[4] Whether the catalysts are composed of transition metal complexes or simple organic molecules, the degree to which a small molecule can exert "catalyst control" over a given reaction coordinate seems to me equally impressive in comparison to enzymes.

To what extent have developments at the various ends of the catalyst molecular weight spectrum fueled discovery in the respective fields? The scope of inquiry under the umbrella of "biomimetic chemistry" has been incredibly wide,[5] and the goal of catalysts designed to mimic various qualities of enzymes has resulted in a rich literature.[6] Furthermore, many laboratories have explored simple organic molecules,[7] including simple amino acids and small peptides,[8] as catalysts for organic reactions. Among these examples is the remarkable scope of chemistry catalyzed by the single amino acid proline.[9] Likewise, synthetic methods inspired by multicomponent biocatalytic assembly lines represent an exciting frontier.[10]

It is probably a legitimate debate to question the extent to which these "minimal" systems reflect, reproduce, or indeed mimic the behavior of biomolecules. As my laboratory initiated research, among our questions was the enduring one: How does the primary sequence of a peptide dictate a catalytic function? While the scientific community has moved closer to an answer over the years, I am not sure that the chemistry I will describe has necessarily contributed to this understanding. But, on the other hand, we have been fortunate to discover some interesting catalysts that raise provocative questions and that present mechanistic puzzles. We have discovered some active and selective catalysts for synthetically useful reactions. Perhaps more curiously, we have begun an interrogation of sequence space in short peptides that may lead to some lessons about the minimal requirements for bifunctional rate acceleration, stereochemical information transfer, and the peptide-catalyzed assembly of complexity. Such lessons, once learned, could indeed lead to accelerated catalyst discovery for organic synthesis. The same lessons might also suggest what is special about certain peptide sequences, secondary structures, and side-chain orientations. It is possible, but perhaps too hopeful, to propose that the lessons learned might indeed inform us about the inner workings of the peptide substructures within the many fascinating proteins found in nature.[11]

Results and Discussion

Acyl Transfer. Our studies began in the midst of the expanding field of small-molecule-catalyzed asymmetric acylation.[12] The development of chiral nucleophiles as asymmetric catalysts for acyl transfer had been examined in classic work but was also gaining momentum with the development of chiral 4-substituted pyridines[13] and phosphines,[14] both strategies that have fluorished since. Our initial studies asked: Could a peptide-embedded nucleophile catalyze a highly selective asymmetric acylation? While we were tempted to examine rigid structures, it seemed equally provocative to ask whether there would be sufficient preorganization in a short, acyclic peptide such that significant catalyst−substrate interactions could result. Very quickly, we recognized that we were really looking for bifunctional catalysis, a phenomenon often considered a hallmark of biological catalysis.[15]

The first generation catalysts were designed to contain a nucleophilic substructure (e.g., a 4-*N*,*N*-dimethylaminopyridine (DMAP) analogue, or a 1-substituted imidazole).[16] The goal was to embed the nucleophile in a peptide sequence that would have a propensity to turn the catalytically active residue toward the functional groups displayed by the peptide backbone and side chains (i.e., structure **1**). The notion is reminiscent of the "convergent functional group" concept.[17] Histidine and its analogues (e.g., **2a** and **2b**) present themselves as obvious candidates to serve as the nucleophilic residue,

Scott J. Miller was born in Buffalo, NY. He received his B.A. and Ph.D. degrees from Harvard University under the guidance of David A. Evans. Following postdoctoral studies with Robert H. Grubbs at Caltech, he joined the faculty at Boston College in 1996, where he is currently a Professor of Chemistry. His research interests are in organic synthesis, catalysis, and chemical biology.

* E-mail address: scott.miller.1@bc.edu.

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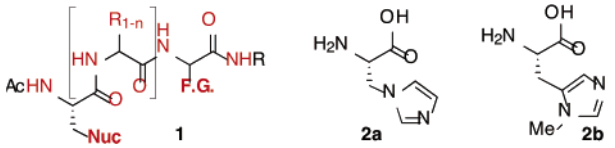
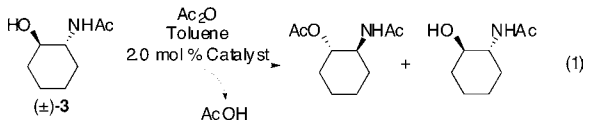


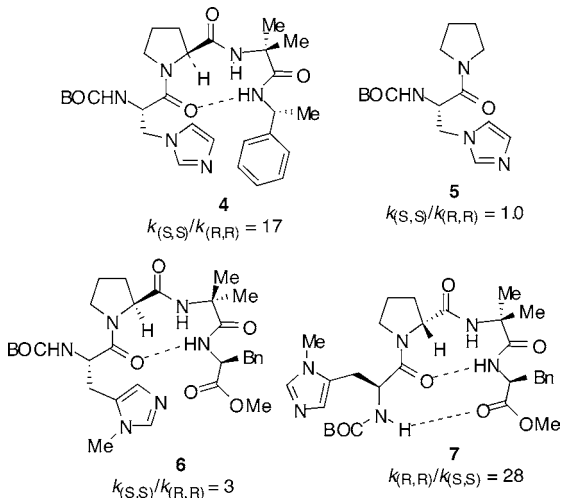
in part due to their analogy to biological systems and also their ready availability.

Since the stereogenic center of **2a** or **2b** is remote from the nucleophilic nitrogen, we anticipated that a "folded" secondary structure would be necessary for relay of stereochemical information during catalysis. Thus, we selected the β-turn as the initial platform for design. Next, we selected a test reaction. We chose the kinetic resolution of *trans*-1,2-acetamidocyclohexanol (**3**, eq 1), speculating



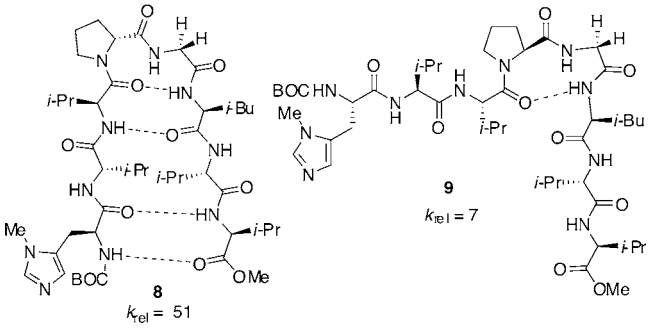
that the presence of a substrate amide would heighten affinity between catalyst and substrate through hydrogen bonding. The choice was fortuitous in two ways: first, we were able to observe decently selective catalysis on this basis early in the project; second, and perhaps more important, the choice made the first generation catalysts highly substrate-specific. While initially a limitation, the result presented a tremendous stimulus to pursue more aggressive approaches.

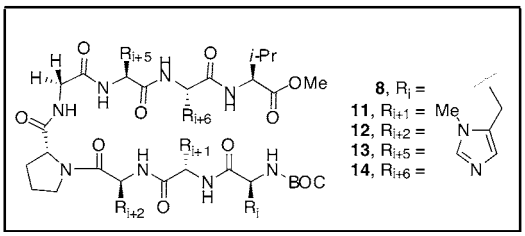
The initial kinetic resolutions provided some positive feedback. Catalyst **4**, with amino acid **2a** incorporated into



the L-Pro-Aib (Aib, α-aminoisobutyric acid) dipeptide sequence gave, under optimized conditions in a nonpolar solvent, a selectivity factor (k_{rel}) of 17.[18] Control catalysts that lacked secondary structure (e.g., **5**) afforded no detectable selectivity. A particularly intriguing result came from the comparison of peptides **6** and **7**.[19] Foreshadowed by outstanding work in the study of peptide folding preferences,[20] the two catalysts exhibit strikingly different conformations *and* strikingly different reactivity. Whereas catalyst **6** contains an L-Pro residue in the $i + 1$ position, catalyst **7** contains the D-Pro epimer at $i + 1$. The former catalyst exhibits only a modest k_{rel} for eq 1, affording k_{rel} = 3; but, catalyst **7**—different only by one stereogenic center—offers a substantially higher k_{rel} of 28 for the same reaction. In addition, the two catalysts exhibit a preference for the reaction of *opposite enantiomers*. The enantiodivergent behavior of the two catalysts turned out to be a phenomenon we would observe frequently as our studies of catalytic peptides continued.[21]

Mechanistic investigations of catalysts **6** and **7** led to the hypothesis that enhancement of the catalyst secondary structure (i.e., rigidity) led to increased selectivity. The hypothesis stimulated us to synthesize octapeptide catalysts biased to form β-hairpins. Since the D-Pro-Gly sequence had been a well-documented biasing element,[22] we prepared catalysts **8**—**14**.[23] Indeed, β-hairpin **8** affords



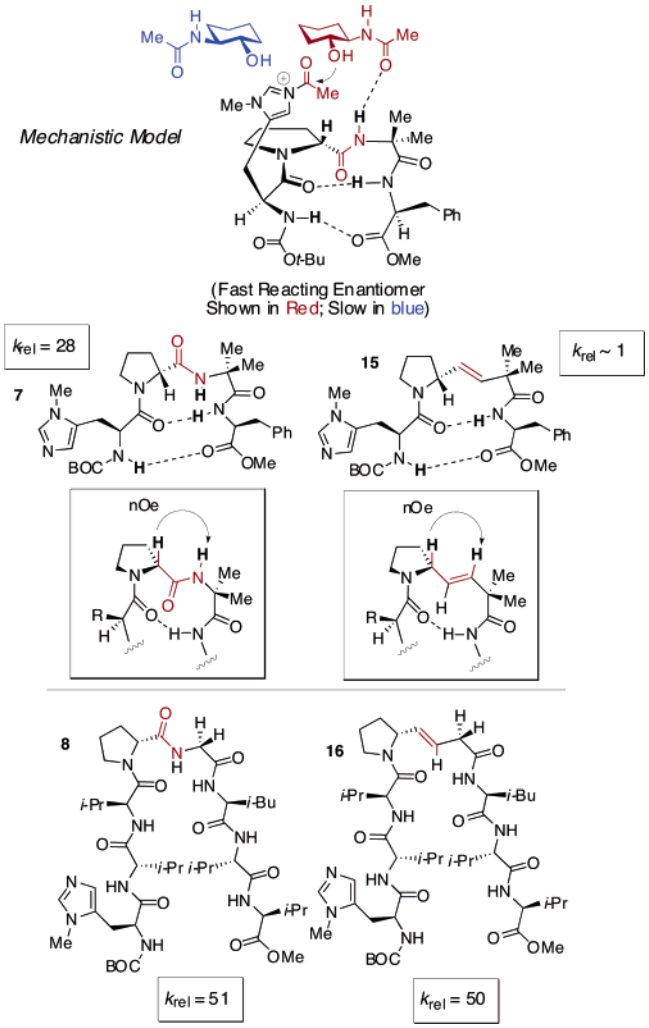


k_{rel} > 50 (for eq 1), whereas peptide **9** (with L-Pro) is structurally much less well-defined and substantially less selective (k_{rel} = 7).[24] Furthermore, peptides **11**—**14**, with the nucleophilic residue moved out of the *N*-terminal position and around the hairpin, provided a fascinating structure—activity relationship, "SAR", but a uniformly less selective set of catalysts for the amidocycloalkanol kinetic resolutions (k_{rel} = 2—14, eq 1).

With catalysts of high selectivity on hand, albeit for a limited set of substrates, we became increasingly interested in the mechanistic basis of the enantioselectivity. We had three types of data upon which to build a mechanistic proposal. First, kinetics experiments had shown that, under the appropriate conditions, the reactions were first-order in both alcohol and catalyst. Second, for the most selective catalysts, we had NMR data that delineated the intramolecular hydrogen bonding networks and several key nuclear Overhauser enhancements (nOe's). Third, we had a collection of "structure—selectivity relationships" that allowed us to correlate the structure of the catalyst to the identity of the fast reacting enantiomer. These observations taken together led to a mechanistic hypothesis, shown in Scheme 1 for the tetrapeptide **7**.

Indeed, the data are consistent with the acylation reaction occurring concomitantly with a catalyst—sub-

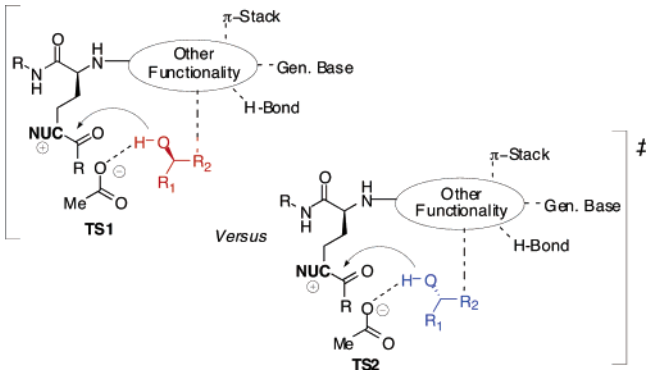
Scheme 1



strate hydrogen bond between the acetamide and the Pro-Aib amide. The model led to the design of an experimental probe to test the significance of the contact. The medicinal chemist's tool of the dipeptide alkene isostere seemed well-suited to evaluate the kinetic significance of the interaction.[25] We therefore made catalyst **15**, analogous to catalyst **7**, except for the exchange of the key amide for an alkene.[26] Solution NMR studies suggested a conformation for **15** that was analogous to **7**. Yet, consistent with the mechanistic model for stereoselectivity, the enantioselection observed with **7** nearly disappeared with catalyst **15**. Perhaps more importantly, the absolute catalytic activity of **15** was a fraction of that exhibited by **7**, also consistent with our mechanistic proposition. Clearly, the D-Pro-Aib linkage in **7** is of great significance to its enantioselective behavior. By contrast, the alkene isostere **16**, intended to probe octapeptide **8**, provided a similarly revealing result. In this case, both catalyst **8** and **16** afford $k_{rel} \approx 50$ for the key reaction, suggesting that the D-Pro-Gly linkage of **8** plays a purely structural role.

While we were excited by the results we had gained, we were simultaneously confronting the fact that the catalysts were uniquely suited to substrates armed with acetamides. In fact, attempted kinetic resolutions of unfunctionalized racemic alcohols with these catalysts

Scheme 2



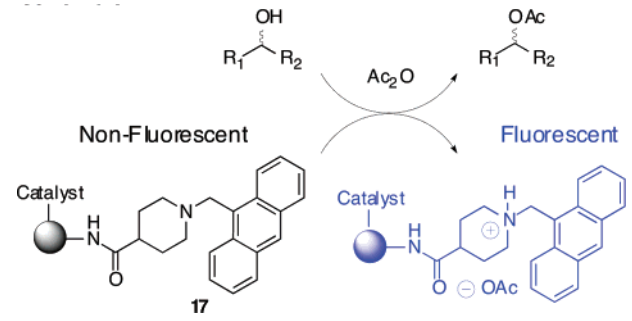
yield only nonselective reactions. To generalize the approach, we embarked upon a different experimental course.

A Combinatorial Assay. One of the most intriguing observations we faced as our data sets expanded was a correlation between those catalysts that were simultaneously very active and selective. Once again, we were drawn to ideas articulated by those studying biomimetic processes. To the extent that bifunctional catalysis is a hallmark of biological catalysis, could stereoselectivity be a hallmark of bifunctional catalysis?[27] The prospect seems possible, although it is certainly plausible that one could find highly active catalysts that exhibit no stereoselectivity. The experiment we set up to probe this question was essentially an adventure in statistics. If, for example, one could make and screen thousands of catalysts for reactions, with what frequency would the bifunctional rate acceleration be coupled to the transfer of stereochemical information? As shown in Scheme 2, transition state organization in a bifunctional mode would require that a bidentate catalyst–substrate ensemble would, by definition, present diastereomeric assemblies of different energy for enantiomeric substrates. With what frequency would these ensembles be separated by synthetically useful energy differences? How often would they be very close in energy? We required an experiment to begin to reveal the answer.

Since peptide-based diversity would allow rapid generation of hundreds of thousands of unique catalysts to screen, the main challenge was the development of an assay to inform on the attributes of the individual library members.[28] Clearly, serial chiral HPLC or GC was not practical if we were serious about evaluating thousands of catalysts. (A typical assay to separate enantiomers of substrate for a single experiment requires multiple minutes, at least.) However, we felt that it could be quite powerful to limit the detailed screening (i.e., chiral HPLC or GC) to those catalysts that exhibited very high overall catalytic activity–indeed, those peptides that offered catalytic rates that were substantially higher than a simple alkyl imidazole. These, presumably, are the most likely candidates for exhibition of bifunctional catalysis.

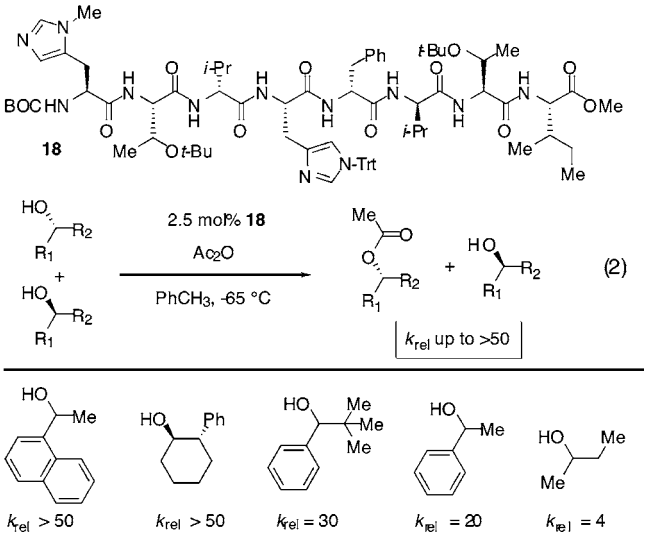
The assay we developed is based on the concept of proton-activated fluorescence.[29] Acyl transfers of acetic anhydride afford not only the ester but also an equivalent

Scheme 3



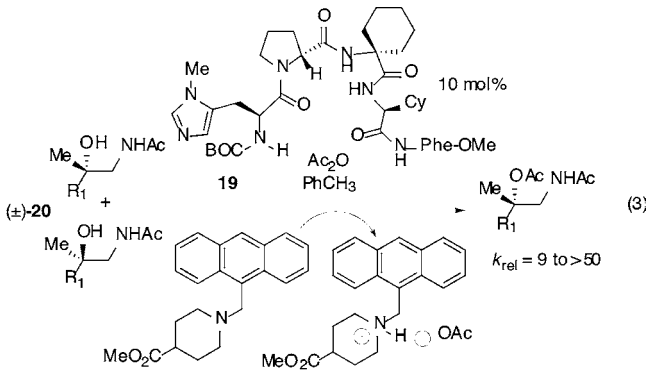
of acetic acid on a per turnover basis (Scheme 3). As such, we felt that incorporation of a proton-activated fluorophore (such as aminomethylanthracene, **17**)[30] as a constituent of each bead-bound catalyst in a library would provide a real-time readout of catalytic activity. With screens of pooled beads performed under a fluorescence microscope, the brightest beads correlate to those carrying the most active catalysts.[31] We therefore synthesized and screened a sensor-functionalized peptide library. To achieve a significant diversity, we relied on the power of split-pool synthesis.[32]

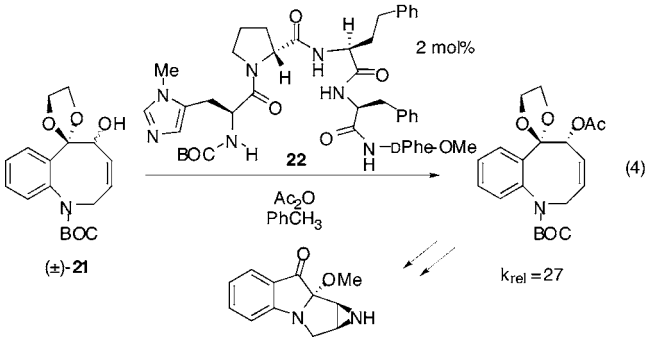
The technique proved effective for the selection of peptides that exhibited high activity in the acylation of a prototype unfunctionalized alcohol, *sec*-phenylethanol. Furthermore, the most active of the beads also exhibited appreciable k_{rel} values, with the best exhibiting a $k_{rel} = 8$ under optimized conditions. Since all of the peptides we had made previously provided nonselective catalysis for unfunctionalized alcohols, we now felt that we had a "hit." To optimize the hit, we made a new split-pool library that was biased to reflect the hit sequence.[33] From this library came a remarkable sequence, peptide **18**, that provides



substantial k_{rel} values for a relatively diverse set of alcohols (eq 2)—all of which share the common feature that an acetamide moiety is absent.[34]

Simultaneously, we hoped to apply the catalysts to a wide array of problems in synthesis. For example, we applied the proton-activated fluorophore method to a parallel enantiomer assay that revealed pentapeptide **19**, a catalyst for kinetic resolution of a number of tertiary alcohols ([±-**20**], eq 3).[35] Tertiary alcohols are a particularly

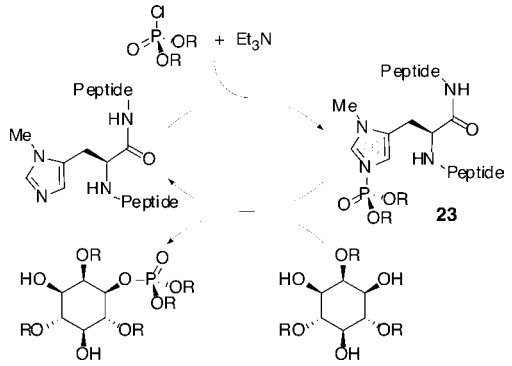




resilient class for asymmetric acylation catalysis, and in fact, even enzymatic examples are rare.[36] Also, in an effort to apply the discovery protocols to reactions of significance in the often case-specific realm of target-oriented synthesis, we discovered a catalyst for a key reaction in an approach to mitomycin C (eq 4).[37] Given that tertiary alcohol **20** and mitocene precursor **21** are of such different structure, it is perhaps not surprising that different peptide-based catalysts (**19** vs **22**) were found for their respective kinetic resolutions. In the absence of a predictive model that would enable a priori selection of an optimal catalyst–substrate pair, the development of a rapid discovery protocol may be a useful tool. Looking to the future, we hope to develop a sufficiently large database of catalyst-selectivity profiles such that both predictive models and detailed insights into the factors that control selectivity may be extracted.

Phosphoryl Transfer and Site-Selective Catalysis. Given that we had observed substantial stereoselectivity in kinetic resolution and that, in some cases, the selectivity could be due to multidentate interactions between catalysts and substrates, we sought to extend the reaction scope to include "site-selective" and "regioselective" processes. We were particularly excited about the challenge given that precedent for carrying out catalyst-controlled variants of these processes was not extensive. Furthermore, in terms of site-selective functionalization of polyols, the state-of-the-art seemed to be in the hands of the enzymatic catalysts,[38] so we were eager to test small peptides in this context. Finally, given that nucleophilic catalysis could be applied not only to acyl transfer but to

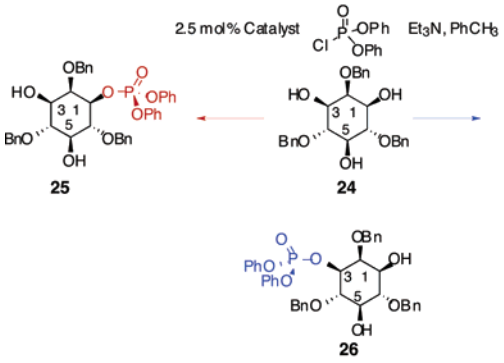
Scheme 4



other types of group transfers, we targeted asymmetric phosphorylation in the context of inositol phosphate synthesis as an initial testing ground. As shown in Scheme 4, the same family of catalysts that we had applied to acylation would now be screened for phosphoryl transfer. The intermediacy of phosphoryl histidine residues (**23**) would also provide an intriguing analogy to the histidine-dependent kinases,[39] themselves masters of site-selective chemistry.

We have recently reviewed our progress in this area,[40,41] so the highlights only will be described here. Our initial studies endeavored to compare small focused libraries of peptides that might be considered biased toward β-turns against those that were essentially random. For the β-turn family, we simply collected samples of our previously prepared L-Pro and D-Pro containing peptides. For the random sequences, we applied a randomization algorithm to deliver the unbiased sequences.[42] Of particular note, both libraries turned out to be quite fertile in the sense that moderately selective catalysts for the desymmetrization of triol **24** (eq 5) were well-represented in each set (Figure 1). Similarly, the libraries contained sequences that were nearly equally apt to favor the formation of D-I-1P product, **25**, as they were to produce the enantiomeric D-I-3P, **26**. From the screens, pentapeptide **27** was identified that provided phosphate **25** in >98% ee (70% conversion); pentapeptide **28** was found to provide the enantiomer **26** with equally high selectivity at comparable conversion (Scheme 5). These catalytic reactions enabled efficient syntheses of the enantiomeric D-I-1P and D-I-3P in good overall yield.

The conformations of the two selective phosphorylation catalysts, as well as the mechanisms of their enantio-



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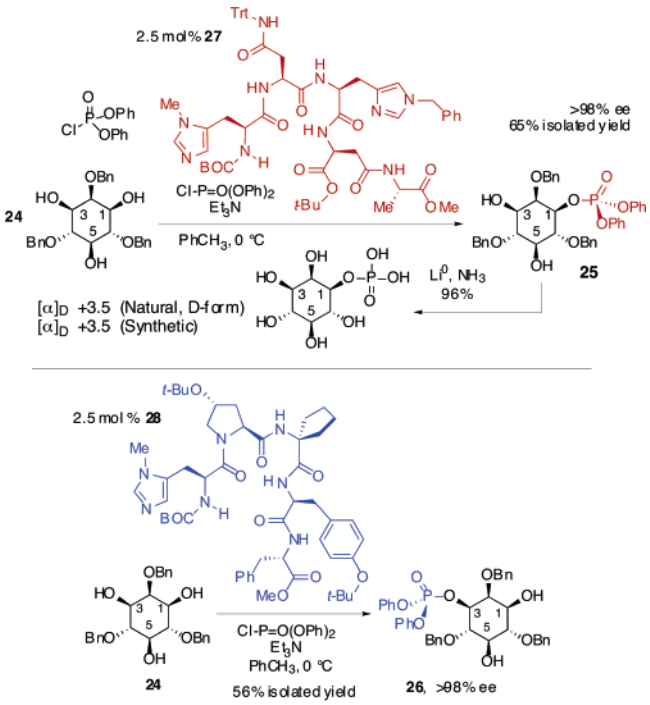
divergent catalysis, are now topics of investigation. We are particularly keen to elucidate their mechanisms considering the provocative observation that while one peptide (**28**) derived from the "biased β-turn" library, the alternative peptide (**27**) was conceived by the randomization algorithm.

Scheme 5



From the synthetic standpoint, one key result of the phosphorylation screens is that enantioselective catalysis

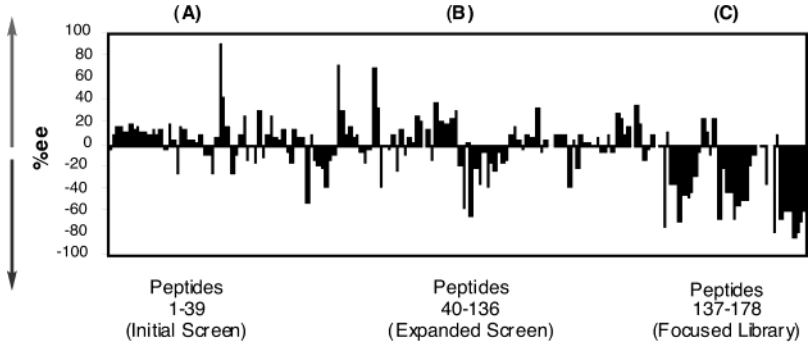
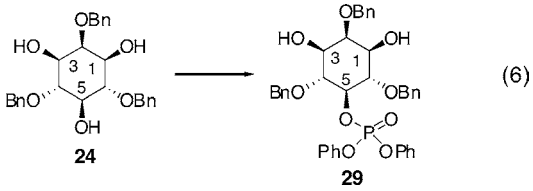


FIGURE 1. Screening data for enantioselective phosphorylation of triol **24**. Screens were performed at 25 °C, and reactions were run to ~70% conversion.

was more readily achieved than "site-selective catalysis." That is, the phosphorylation of the 5-hydroxyl group of **24**, to deliver the achiral product **29** (eq 6), was observed



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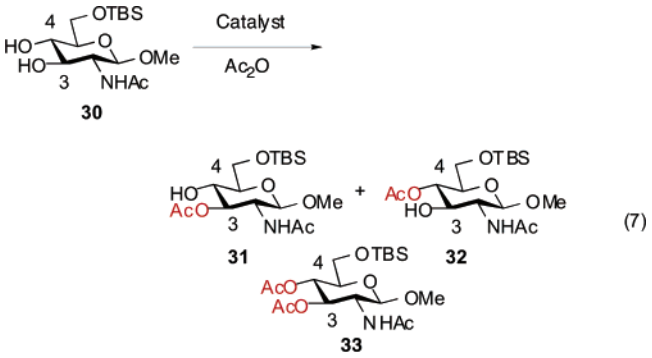
in only trace amounts under the conditions of the screen. The sluggish rate of formation of **29** reflects the lower inherent reactivity of the 5-position in comparison to the more reactive enantiotopic 1- and 3-positions. As such, more highly active and discriminatory catalysts await discovery to meet this challenge in site selection.

To begin our studies in this area, we examined the ability of peptide-based acylation catalysts to perturb kinetic selectivity in the site-selective modification of simple carbohydrates.[43] For example, acylation of *N*-acetyl glucosamine derivative **30** reveals that *N*-methyl imidazole (NMI) as a catalyst provides a 2.3:1 kinetic distribution of monoacetates **31** and **32** (eq 7). Screening a random set



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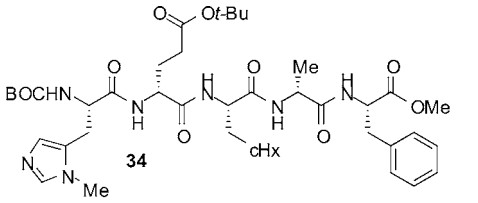
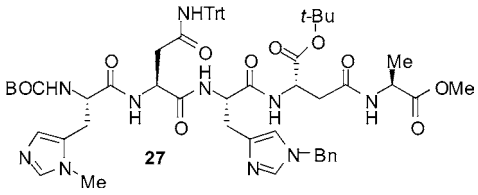
of 150 peptides with the goal of finding peptides that could

Table 1. "Hit" Catalysts for Deviation from NMI Derived from the Initial Peptide Library[a]

catalyst	**31**	**32**	**33**	total conversion
NMI	50	22	28	86
34	97	3	0	88
27	53	47	0	80

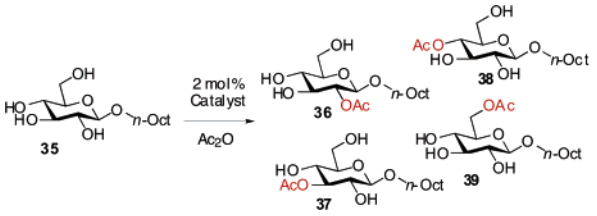
[a] 2 mol % catalyst, $PhCH_3$, 25 °C, 15 h.





select in a quantitative fashion for either monoacetate provided encouraging results (Table 1). Peptide-catalyst **34** provides high kinetic selectivity for monoacetate **31** (97:3). Identification of a catalyst that reverses the selectivity to provide monoacetate **32** did not result from the limited catalyst set that we screened. However, catalyst **27** (identical to one of the highly selective phosphorylation catalysts) does provide a hint at reversal of regioselection delivering the two distinct monoacetates in a nearly 1:1 ratio.

A more dramatic result was obtained by screening a 36-member library in the site-selective modification of glucoside **35** (eq 8). In this case, NMI provides a mixture



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of monoacetates, primary acetate **39** appearing as the predominant product. In contrast, peptide **40** provides a substantial deviation from NMI, delivering secondary acetate **38** as the major product (Table 2). In nearly all of the cases we examined, the overall conversion with the peptide-based catalysts is greater than that observed with NMI, reflecting the higher activity of the catalysts in these reactions.[44]

While this aspect of the project is in its infancy, we are hopeful that we will be able to develop a database of catalysts with corresponding activity and selectivity profiles. Additional data may lead to predictive models that could assist in the selective modification of complex polyols, leading to production of analogues.

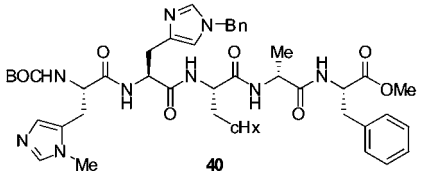
Conjugate Addition. As our research into peptide-catalyzed group transfers unfolded, we aspired to generalize the chemistry to include other types of bond constructions. In particular, we wondered whether the same sets of catalysts that were effective for acylation and phosphorylation might be sufficiently general to catalyze enantioselective conjugate additions and C−C bond forming reactions. In this context, we examined conjugate addition of azide ion to α,β-unsaturated imides, a reaction that would deliver β-amino acid synthons (eq 9).[45]

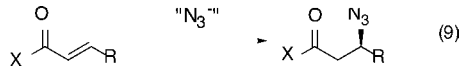
Asymmetric catalytic methods for asymmetric β-amino acid syntheses are highlighted by metal-based methods,[46]

Table 2. "Hit" Catalysts for Deviation from NMI Derived from the Peptide Library[a]

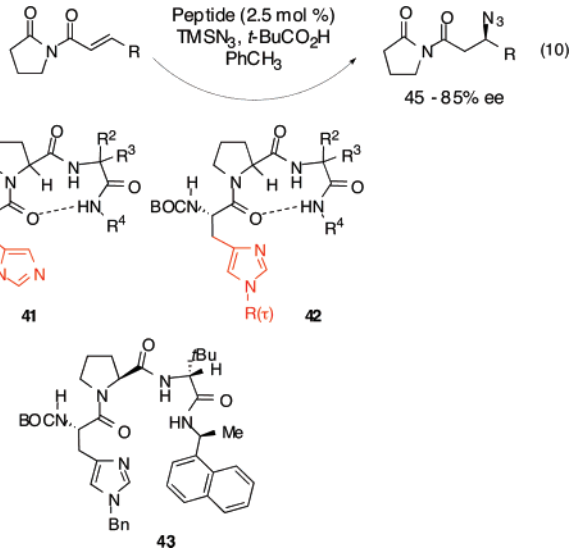
catalyst	**36**	**37**	**38**	**39**	total conversion
NMI	0	20	16	64	14
40	9	11	58	22	100

[a] 2 mol % catalyst, $PhCH_3/CH_2Cl_2$, 0 °C, 15 h.



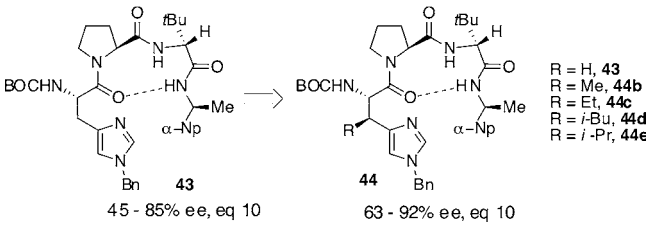


including the elegant Al-salen catalyzed delivery of azide by the Jacobsen laboratory.[47] Our studies were also inspired by the classic work of Wynberg on cinchona-alkaloid-catalyzed asymmetric thiol addition to enones.[48] By analogy, we developed a mild set of amine-catalyzed reaction conditions that avoided the use of stock solutions of HN_3.[49] In the process, we determined that simple histidine analogues would indeed catalyze conjugate addition of azide. Of note, π-methylated histidine-derived catalysts (i.e., catalyst family **41**, analogous to effective

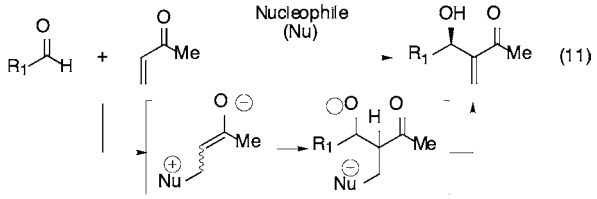


peptide catalysts for acylation and phosphorylation) were nonselective for the synthesis of the optically enriched azido-imides. On the other hand, insertion of τ-alkylated histidine (i.e., **42**) led to improvements. Catalyst **43** allowed the observation of ee's from 45% to 85% for several β-substituted acroyl imides (eq 10) and represented a lead for further optimization.[50]

Throughout the project, we have been alert to the fact that the highest selectivities have been observed with acyclic, "open chain" catalysts. While we have not completed an exhaustive study of *cyclic* peptide catalysts, those we have made on an ad hoc basis to compare to acyclic analogues have always led to inferior selectivities. The observations are reminiscent of what biological chemists have described as enzymatic "breathing,"[51] reflecting the need for enzymes to alter conformations as the catalysis proceeds through a dynamic reaction coordinate. Nevertheless, the azidation catalysts provided an opportunity to examine a strategy for conformational restriction that was not based on covalent macrocyclization. Rather, specific substitution at the β-position of histidine, targeted at dihedral angle restriction,[52] appears to be an effective strategy for biasing catalysts toward reactive and selective conformations, without over-engineering the design with macrocyclization. Indeed, catalysts related to **44** provide substantive improvements in the selectivities for these conjugate additions (up to 92% ee).[53]

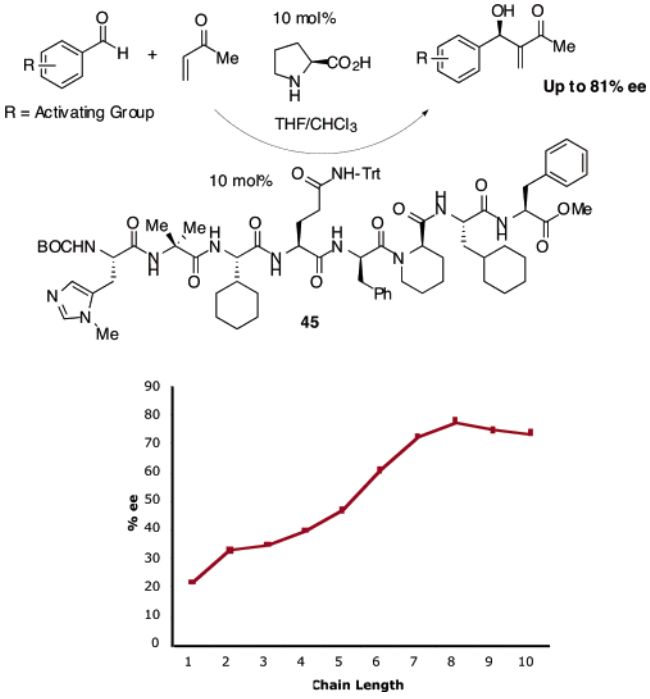


Asymmetric C−C Bond Formation. The privileged catalyst concept is one that is emerging and inspiring chemists to test fully the synthetic versatility of particular catalyst families.[54] In the context of the histidine-dependent peptide catalysts, we had demonstrated a modicum of success in several nucleophile- and general base-catalyzed processes. In an effort to extend the scope of the histidine-based catalysts to reactions where a C−C bond is formed enantioselectively, we turned our attention to the Morita−Baylis−Hillman (MBH) reaction of ketones (eq 11).[55]

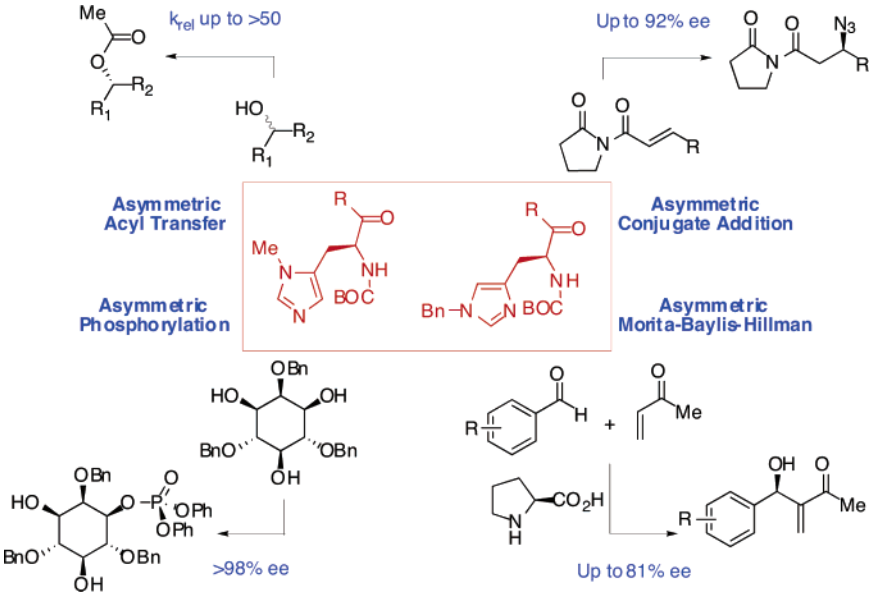


Since the MBH reaction is a prototype nucleophile-catalyzed process, we were initially disappointed to find that the catalysts we had on hand were ineffective in terms of both rate and selectivity. In analogy to the work of Shi,[56] however, we found that the use of proline as a cocatalyst actually provided a dramatic rate acceleration and state-of-the-art ee's for the methyl vinyl ketone variant of the process. As shown in Scheme 6, screening a limited set of

Scheme 6



Scheme 7



catalysts of varying chain lengths, we found that octapeptides (e.g., **45** in combination with L-Pro) with the *N*-terminal Pmh residue afforded optimum selectivity (up to 81% ee for activated aldehydes).[57] Of note, shorter peptide chain lengths led to lower selectivity; in contrast, a selectivity plateau was observed in the 7-mer to 10-mer range. The result is certainly at risk for overinterpretation. That is, we have not yet screened comprehensive libraries of peptides at each chain length. It is perhaps of note, however, that within the confines of small (~12 member) sets of peptides of a given length, this study converged on a dual catalyst system that resulted in the highest ee's reported to date for the simple MVK-based MBH reaction.

Perhaps of greater significance for the future is the observation of a tunable additive effect based on the cocatalysis by a simple amino acid and readily accessible peptides. The documentation of significant stereochemical consequences in this context necessitates the incorporation of cocatalysts as a key dimension in future diversity-based screens.[58] As is so often the case in chemistry research, we now look back with yearning over the past results and wonder what the additive effects are in the arenas described above. At present, such effects remain unknown and challenge us to improve the protocols for multidimensional parameter screening in the development of catalytic processes.

Conclusions

It is difficult to draw unifying conclusions from the data presented herein. That said, the project has been inspiring in that the interplay of physical organic hypotheses and screening has led to catalysts for a number of disparate bond constructions of varying degrees of utility in synthesis (Scheme 7). Particularly exciting to us is the opportunity to elucidate the basis of the stereoselectivities with catalysts whose discovery lies outside of the conception of detailed transition state models.

Perhaps equally perplexing is the opportunity to probe peptide sequence space for the dominant motifs that lead to control of the rate and stereochemical course of reactions. It is tempting to speculate that there may be a practically infinite set of structural motifs that lead to highly active and selective catalysis for various reactions. On the other hand, in nature, evolution has converged on a strikingly small fraction of structural space for the assembly of functional proteins.[11] Could it be that probing sequence space in small peptides will lead to a similar convergence on certain structural motifs? If so, how many are there? Do they bear any structural relationship to active sites in naturally occurring enzymes, present or extinct? Can the rules be extracted to assist in the development of practical catalysts? The answers to these questions appear to be elusive at present, and they are among the uncertainties inspiring us to explore this area further.

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