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Nonenzymatic peptide-based catalytic asymmetric phosphorylation of inositol derivatives

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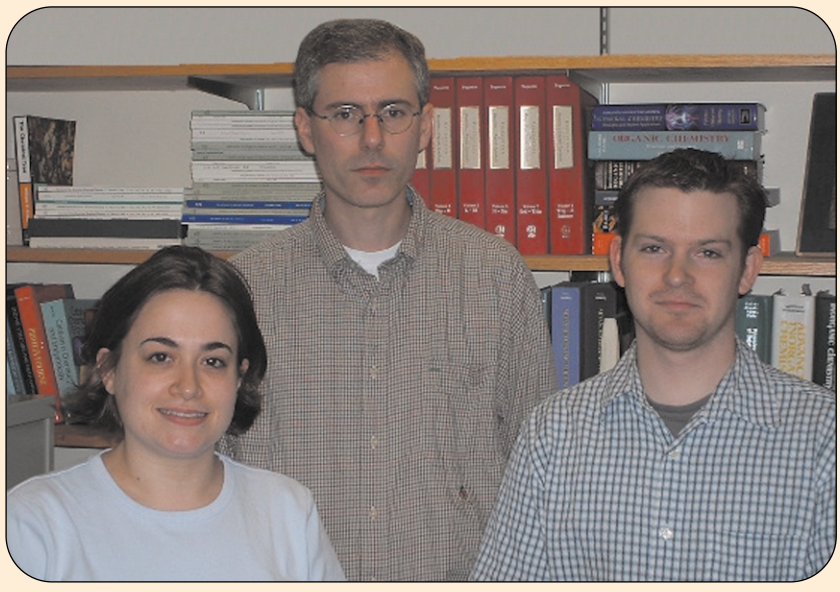
The ability to use small peptides as catalysts for asymmetric phosphorylation provides opportunities for rapid syntheses of phosphate-containing compounds and natural products. This short review outlines the genesis of this concept and its reduction to practice in the context of concise syntheses of the enantiomeric D-I-1P and D-I-3P targets. The implications for the development of additional site-selective catalysts are discussed.

The field of enantioselective catalysis has blossomed in recent years due to the concerted efforts of numerous workers in a variety of areas.[1] Catalysts ranging from small molecules (both metal-based and metal-free) to enzymes,[2] across a huge molecular weight spectrum, are having a dramatic impact on the way stereochemically complex molecules are synthesized. In addition to highly enabling methodology, these studies set the stage for the elucidation of new insights into chemical reactivity, providing an exciting frontier in mechanistic chemistry. As investigators have aimed to accelerate both the discovery process, and also the accumulation of data for mechanistic analysis, the field has also benefited from, and stimulated, advances in high throughput synthesis and screening science.[3]

In comparing enzymatic asymmetric catalysts to small molecule catalysts, one is struck, at present, by one of the major differences between the two major classes. Whereas both families have recorded remarkable achievements, enzymes maintain an advantage over small molecule catalysts in the realm of 'site-selective' catalysis.[4] Man-made catalysts have been discovered that mediate various bond-forming processes with excellent degrees of stereocontrol; yet, examples where a small molecule catalyst can direct a particular bond forming process to a particular functional group in the presence of several similar functional groups (*i.e.*, more than two) are less common.[5]



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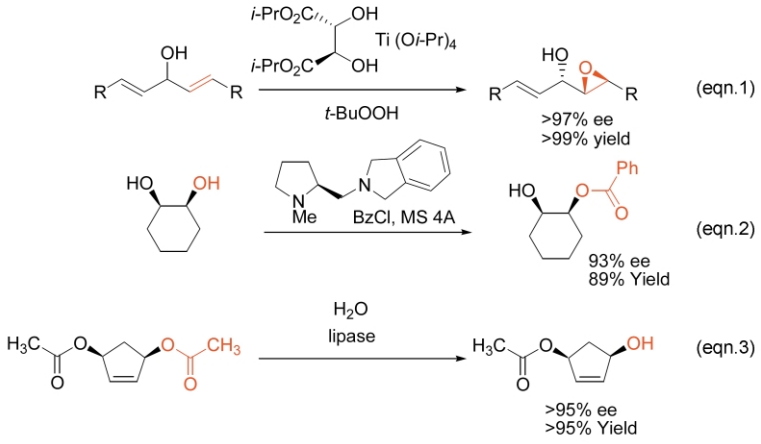
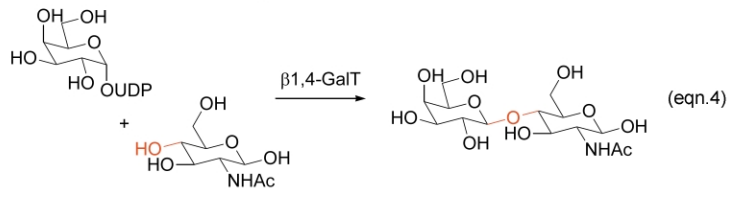
Powerful desymmetrization reactions have been developed,[6] wherein the symmetry plane in a *meso* compound is removed by a site-selective functionalization reaction (*e.g.*, the Sharpless asymmetric epoxidation effects chain terminus differentiation, eqn. 1; [7] diol desymmetrization may be accomplished with a diamine catalyst, eqn. 2).[8] In contrast, enzymes are known that not only carry out desymmetrization reactions of *meso* compounds (*e.g.*, *meso* diester hydrolysis, eqn. 3),[9] but also highly impressive site-selective functionalizations of polyol structures such as carbohydrates where symmetry is often minimal (*e.g.*, site-selective glycosylation, eqn. 4).[10] It is, perhaps, the absence of generalizable catalysts in this last category that has created such a dependence on the use of protective group strategies in complex polyhydroxylated target-oriented synthesis.

Several Desymmetrization Reactions



Prototype Site-Selective Reaction



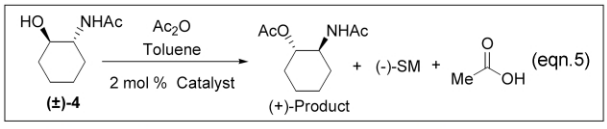
In examining the possible strategies one might pursue to achieve a generalizable platform for the development of site-selective catalysts, we began a program of study that we hoped would enable the achievements of both enzymatic and small-molecule asymmetric catalysis to merge. Inspired by enzymes, we sought to develop catalysts that would bring to bear many of the physical organic attributes of enzymes: the ability to adopt conformationally well defined functional group arrays for bifunctional (or even multifunctional) catalysis, as well as the presence of functional groups that would allow for catalyst-substrate interactions that could include hydrogen bonds, electrostatic interactions, covalent catalysis, hydrophobic and π-stacking effects. Yet, we hoped to present these advantages in the context of small molecules in the hopes of discovering 'simple' systems that would be amenable to high precision physical organic mechanistic analysis. In retrospect, it is our view at present that these initial considerations were quite naïve. Reproducing even a fraction of an enzyme's attributes is nontrivial. Similarly, very little has emerged from our work on small molecules that appears to be mechanistically simple. Nevertheless, the exploration of small peptides (≲8 residue sequences) has proven to be a fertile ground for discovery of enantioselective catalysts, and the stage is now set for further study of site-selective catalysis.

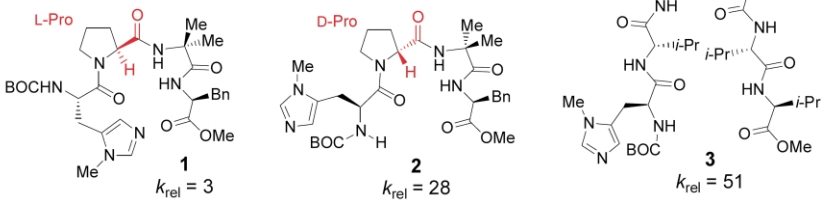
Our studies of asymmetric phosphorylation began with some experience in our laboratory with other peptide-catalyzed reactions. When we began our studies, there were several inspiring examples in the literature of amino acid and peptide-catalyzed reactions.[11] Among them are the impressive hydrocyanation of aldehydes and imines,[12] the Juliá-epoxidation of chalcones,[13] the ever-expanding repertoire of proline-catalyzed reactions,[14] in addition to others. Our initial studies addressed the use of short, β-turn and β-sheet type structures to catalyze asymmetric acylation reactions. Designed peptides such as **1**, **2** and **3** proved to be increasingly selective in the catalytic kinetic resolution of functionalized substrates such as **4** (eqn. 5).[15]

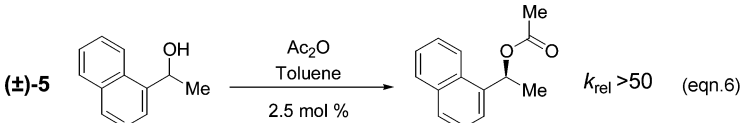
In contrast, peptides **1**–**3** were nonselective in attempted kinetic resolutions of substrates like **5**, implying that hydrogen bonding interactions were likely involved in stereochemistry determining events. In order to achieve enantioselective acylation catalysts for substrates such as **5**, we turned to combinatorial screening methods.[16] These studies led to peptides like **6** that were indeed effective for the kinetic resolution of alcohols across a broad structural scope (eqn. 6).[17]

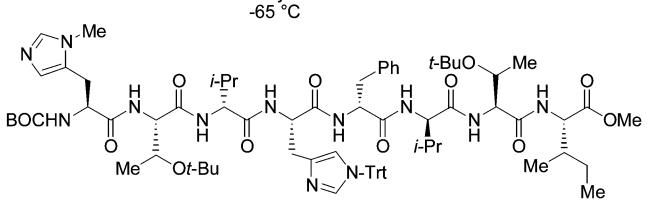
In parallel, we pursued peptide-catalyzed conjugate addition reactions and found that peptide **7** was effective for conjugate addition of azide to enoate derivatives affording the corresponding β-azido carbonyl compounds (eqn. 7).[18] A significant finding in this study was that the incorporation of dihedral angle-restricted versions of histidine was an important element for catalyst optimization.[19]

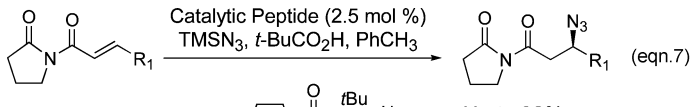
All of our studies pointed to the possibility that low molecular weight peptides could indeed bring with them sufficient stereochemical information to catalyze highly enantioselective transformations. With this in mind, we began our investigation of site-selective catalysis. We chose to explore enantioselective phosphorylation of *myo*-inositol (or more likely, an appropriate derivative) as a testing ground for several reasons.[20] First, we anticipated that the 'ideal' synthesis of D-*myo*-inositol-1-phosphate (**8**, R=H; Scheme 1), in one step from *myo*-inositol, would represent a tremendous challenge for small molecule site-selective catalysis.[21] In the unprotected form, *myo*-inositol presents six stereochemically unique hydroxyl groups. Second, we felt that a mechanistic analogy between the acylation catalysis we had been studying and catalytic phosphorylation could be designed such that we could explore the same catalysts in this new arena. That is, we were sold on exploring the paradigm of nucleophilic catalysis. Third, we were intrigued by the potentially biomimetic nature of our approach.[22] That is, if indeed we could

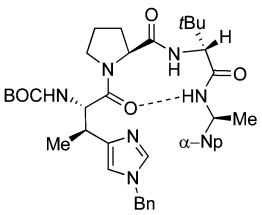








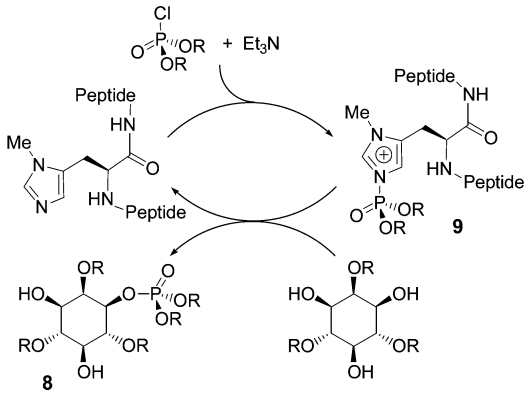




achieve catalysts that proceeded through the catalytic cycle shown in Scheme 1, phosphorylated histidyl peptides such as **9** would present a possible analogy to the phosphohistidine intermediates thought to play a key role in the function of the histidine-dependent kinases that provide exquisite site-selectivity in natural systems.[23]

Our studies then commenced with the evaluation of several peptide libraries we had prepared in our laboratory. Because most of our previous work had centered on evaluating peptides in organic solvents, we immediately encountered the first limitation of our approach – that we would need to convert *myo*-inositol to the *meso* tribenzyl derivative **10** (Fig. 1) to work in a solvent appropriate for the hydrophobic peptides we had on hand. Nevertheless, substrate **10** still provided an important testing ground for site-selective modification, presenting three stereochemically unique sites within a *meso* structure. While the details and rationale for the screens have been described in detail previously, in this Focus format we will simply discuss the highlights and the implications for site-selective catalysis. Strikingly, as shown in Fig. 1 (eqn. 8), the screens revealed that a very fertile area of diversity space was represented by the peptides we chose. Desymmetrization of substrate **10** was a readily achieved objective, highlighted by the discovery of two peptides, **11** and **12** (Scheme 2), that afforded each enantiomer of the product (**10-1P** or **10-3P**) with essentially total enantioselectivity at approximately 70% conversion.[24] Of particular note was the fact that nonenantiomeric peptides afford high degrees of enantioselectivity in the enantiodivergent sense.[25]

An especially noteworthy observation in the screening experiments was the absence of a significant rate of reaction for the catalytic phosphorylation of the 5-position of the inositol (*i.e.*, **10-5P**).[26] While selective production of compound **10-5P** would have converted one *meso* compound to another *meso* compound, the absence of its formation points to one of the major challenges we now face as we enter into expanded studies of site-selective catalysis. Indeed, carbohydrate chemists have known all along that regioselectivity is a particularly challenging objective since the competing functional groups do not present equivalent reactivity. The desymmetrization of **10** presents the challenge of selectively functionalizing the enantiotopic 1- or 3-positions of *myo*-inositol. In a sense, the desymmetrization experiment, while certainly nontrivial, presents the even-handed challenge of functionalizing *two hydroxyl groups of equivalent reactivity in the absence of a chiral catalyst.* For the goal of site-selective phosphorylation of the regiotopic 5-position, even more potent discriminatory catalysts will be required as we endeavor not only to clear the hurdle of enantiotopic environments, but also the



Scheme 1 Enantioselective phosphorylation of *myo*-inositol.

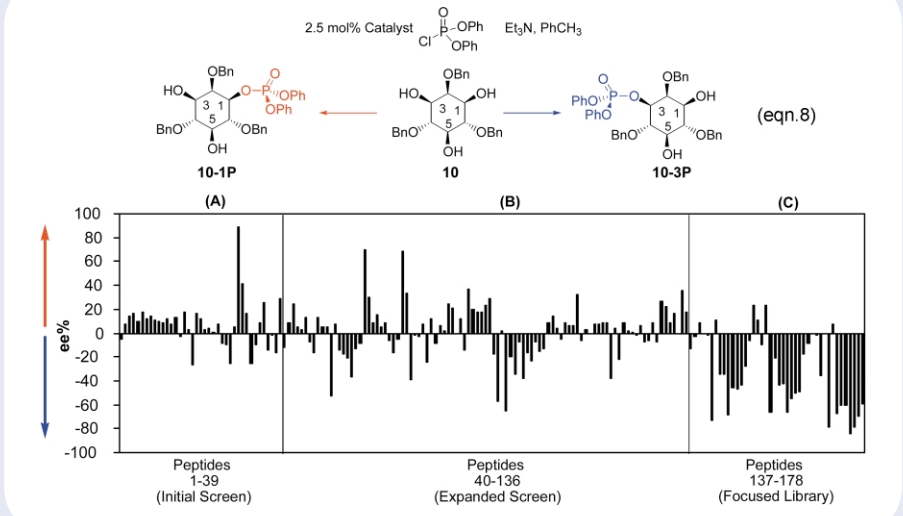
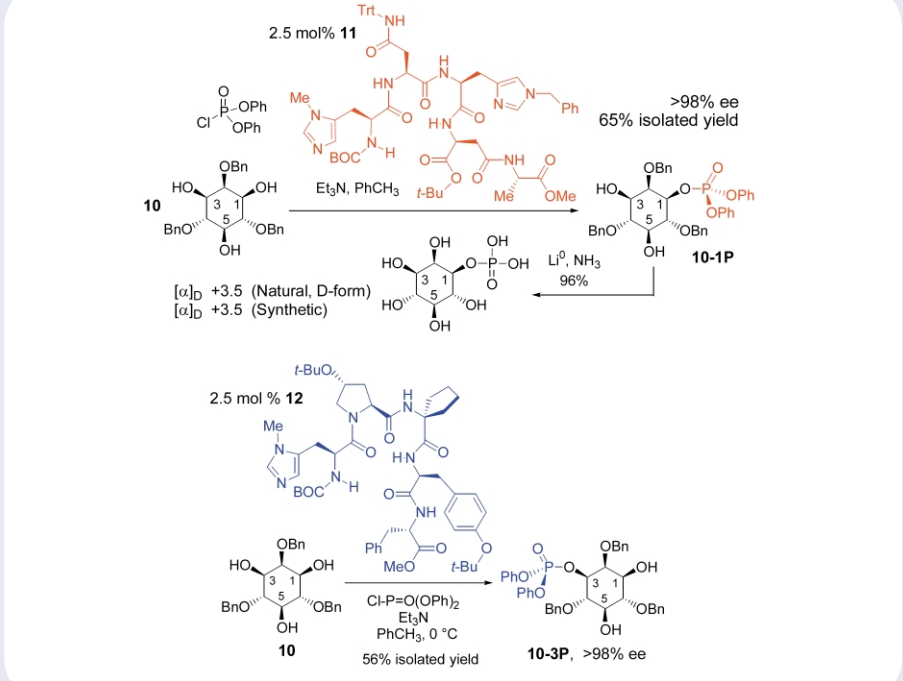


Fig. 1 Screening data for enantioselective phosphorylation of triol **10**. Reactions were run to ~70% conv.



Scheme 2 Desymmetrization of **10** to the enantiomeric phosphates **10-1P** and **10-3P**.

additional energetic barrier associated with functional groups of reduced inherent reactivity.

Future developments in this field will likely benefit from the continued role of combinatorial screens. One of the advantages of these approaches is the plethora of interesting data that emerges. But, one of the major challenges we now face is the development of a mechanistic understanding of the catalysts we have discovered. Analysis of the data, in combination with mechanistic studies, may lead to additional catalyst families that are effective for the selective derivatization of polyfunctional molecules within the inositol class, and hopefully beyond. These objectives are topics of continuing investigation in our laboratory.

Acknowledgement

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