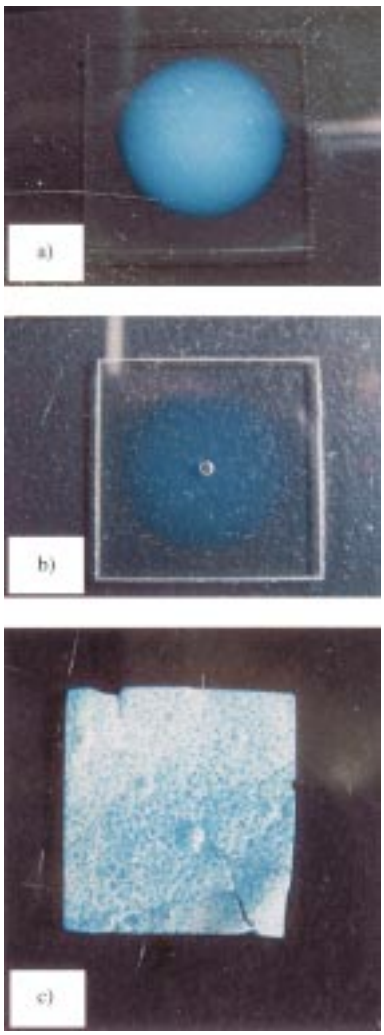

Figure 3. TEM photographs of a) a solution of the microspheres in MMA; b) locking film MP-L; c) a swollen film of cross-linked SV2 which exhibits a lamellar morphology in benzene.

interplanar spacing, and θ is the glancing angle between the incident light and the diffracting crystal planes. n is defined by Equation (2):

$$n = n_A\phi_A + n_B\phi_B + n_C\phi_C \quad (2)$$

where ϕ is the volume fraction of each component and subscripts A, B, and C indicate the three phase-separated components, namely, the P4VP core, PS shell, and PMMA matrix, respectively. The Bragg spacing d_1 is related to the cell edge a_c of the cubic lattice and the nearest neighbor distance (D_S) of the spheres [Eqs. (3), (4)]:

$$D_S = (\sqrt{3}/2)a_c = \left(\sqrt{3/2}\right)d_1 \quad \text{for BCC} \quad (3)$$

$$D_S = (1/\sqrt{2})a_c = \left(\sqrt{3/2}\right)d_1 \quad \text{for FCC} \quad (4)$$

The interplanar spacings of superstructures can be controlled by changing the monomer concentration and the type of cubic lattices. The work here demonstrates a method for preparing polymeric superstructures composed of nanoscopic cubic lattices. These materials can be used for light modulation in tunable diffracting and transmitting optical devices. We are investigating the diffraction behavior of the polymeric superstructure films with a near-IR spectrophotometer.

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Incorporation of Peptide Isosteres into Enantioselective Peptide-Based Catalysts as Mechanistic Probes**

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The discovery of small-molecule mimics of enzymes has been a longstanding objective at the interface of bioorganic chemistry and organic synthesis.[1] We have been studying small peptide catalysts within this context because they offer great opportunities for structural variation (i.e., diversity).[2, 3] Furthermore, they offer a direct analogy to enzymes because such catalysts are composed entirely of the same fundamental building blocks, amino acid subunits. As such, we have been interested in determining the mechanistic basis for the enantioselectivities that such catalysts afford.[4, 5]

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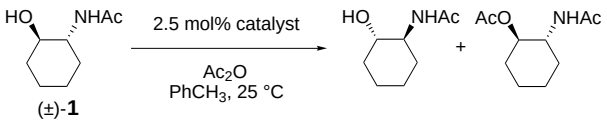
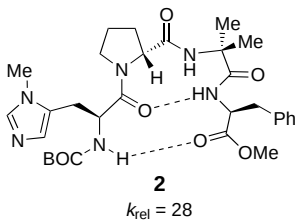
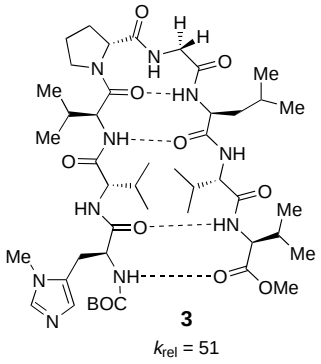
In particular, we have found that substantial selectivity factors (k_{rel} values) can be obtained for the kinetic resolution of substrates such as **1** (Scheme 1).[6, 7] Tetrapeptide **2** catalyzes the kinetic resolution with a k_{rel} value of 28; octapeptide catalyst **3** accomplishes this resolution with $k_{rel} > 50$. The resolutions are more effective with substrates like **1**, which contain an acetamide functional group, than with unfunctionalized substrates.[2] Furthermore, previously reported kinetic studies have revealed (for catalyst **3**) that the reaction appears to be first order in both substrate **1** and catalyst **3**. Given the role of the substrate amide, and the stereochemical identity of the fast and slow reacting enantiomers, we sought to develop a structural model that would account for the sense and degree of enantiospecificity observed with each catalyst.

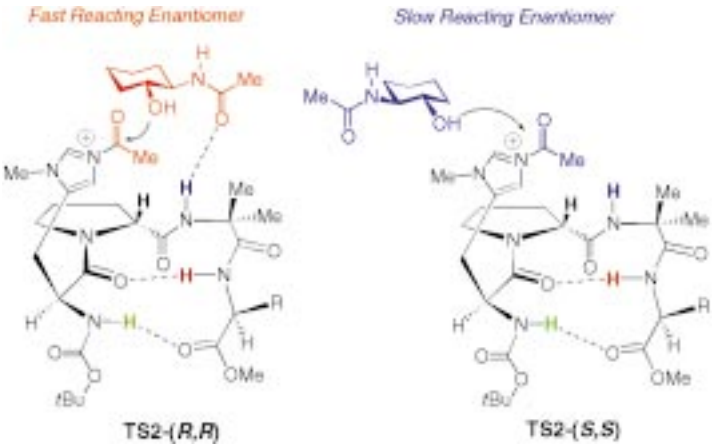


Scheme 1. Kinetic resolution of **1**.





The development of our mechanistic model began with a determination of the solution conformation of catalyst **2**. Two-dimensional NMR spectroscopic techniques (COSY, ROESY), in combination with solvent titrations of the peptide hydrogen bonding network,[8] revealed that peptide **2** possesses the two intramolecular hydrogen bonds illustrated in Figure 1. Furthermore, the Aib N–H (Aib = α-amino isobutyric acid) and the prolyl C_α-H atoms exhibit a significant NOE (Figure 1).[9] The kinetic resolution of **1** with catalyst **2** leads to a situation where (*R*,*R*)-**1** is the fast reacting enantiomer.[10] Such enantiospecificity is consistent with a transition state that could involve the two-point contact shown in structure **TS2-(*R*,*R*)**. It is plausible that the first contact involves the hydroxy group of **1** attacking the acyl imidazolium ion;[11] the second could involve a hydrogen bond between the substrate and the D-Pro-Aib amide group that serves as the hydrogen bond donor. Consistent with transition state stabilization, reactions of the functionalized substrates (e.g. **1**) are substantially faster than those that lack secondary amides. Furthermore, (*S*,*S*)-**1** cannot readily achieve an analogous two-point contact without a conformational change in either the substrate, catalyst, or both species (cf. **TS2-(*S*,*S*)**).



We required an experiment to test this hypothesis. One possibility that seemed to offer an unambiguous interpretation involved the synthesis and evaluation of so-called olefin isosteres.[12] Such compounds are important in the peptidomimetic arena owing to their propensity to adopt conformations that can be nearly superimposable on their parent peptide. The key advantages of olefin isosteres as mechanistic probes are the potentially identical conformations, but total absence of the polar amide functional group that could participate in a key intermolecular interaction with substrate. Compound **4**[13] thus emerged as a potential mechanistic probe for the behavior of **2**.

With catalyst **4** in hand, we set out to establish that its conformation is similar to peptide **2**. The same NMR spectroscopic experiments that had been applied to **2** were carried out with **4**, and indeed the ground-state solution conformations appear similar (Figure 2). The D-Pro C_α-H exhibits a substantial NOE interaction with the alkene proton of **4** that is analogous to the Aib-NH of **2**. Furthermore, titrations of the hydrogen bonding network suggest that both the BOC-NH (BOC = *tert*-butoxycarbonyl) and the Phe-NH (Phe = phenylalanine) hydrogen atoms are involved in intramolecular hydrogen bonds.[14]

Most notable is the performance of isostere **4** in kinetic resolutions in comparison with peptide **2**. Whereas peptide **2** effects kinetic resolution with a k_{rel} value of 28, isostere **4** provides no enantioselectivity

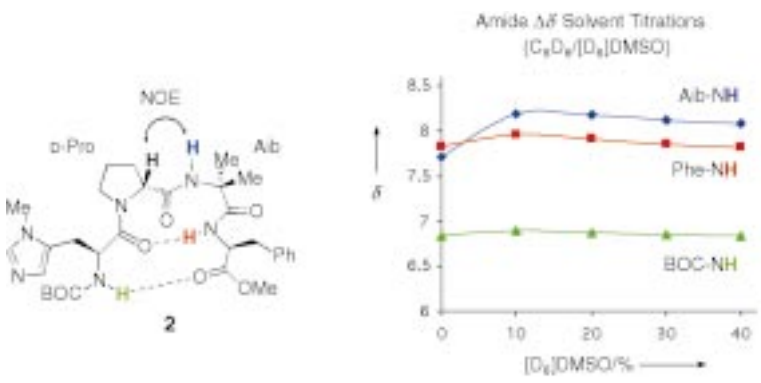


Figure 1. ^{1}H NMR data for peptide **2**.

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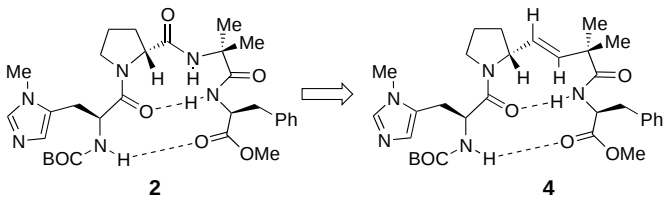


Scheme 2. Compound **4**, a potential mechanistic probe for the behavior of **2**.

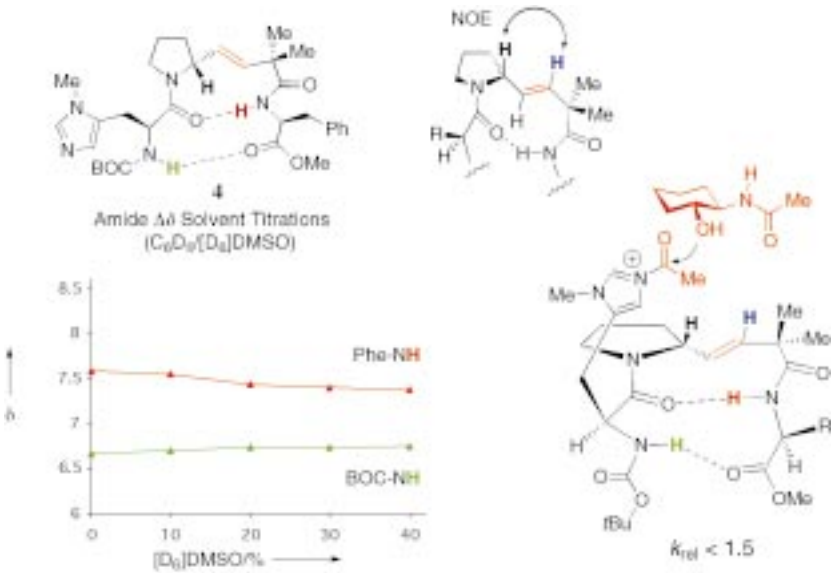


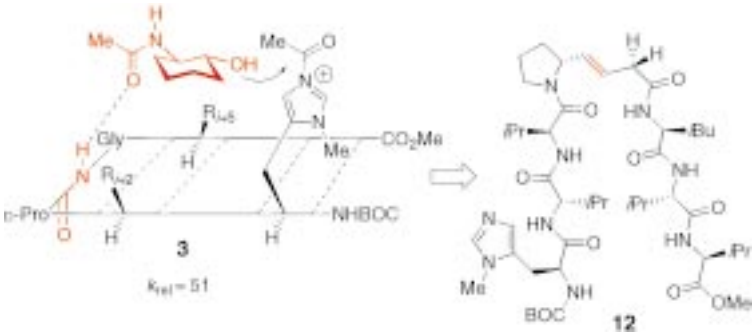
Figure 2. ^{1}H NMR data for peptide **4**.

($k_{rel} < 1.5$), despite possessing a very similar conformation. Catalyst **4** also mediates a much slower reaction relative to that catalyzed by **2**. This observation is consistent with a critical role for the D-Pro-Aib amide of peptide **2**.

We wished to show that these results were not specific to substrate **1** (Table 1). Peptide **2** provides a k_{rel} value of 17 and 6 for the seven- (**10**) and five-membered (**11**) homologs of **1**, respectively. Isostere **4** is completely ineffective in terms of asymmetric induction with these other substrates ($k_{rel} < 1.5$), demonstrating that the D-Pro-Aib amide is critical for these substrates as well.

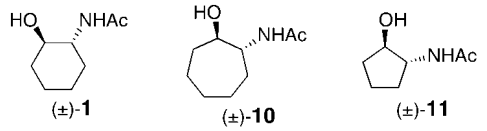
With some evidence supporting the pivotal role of the prolyl amide for the asymmetric catalysis achieved with tetrapeptide **2**, we then turned our attention to the octapeptide **3**. Octapeptides are substantially more complicated than tetrapeptides; the derivation of a structural hypothesis for enantioselectivity is therefore more difficult. Nevertheless, as shown in Scheme 3, we were once again intrigued by the potential role of the prolyl (D-Pro-Aib) amide in orchestrating the observed enantiospecificity. Although this site is more remote from the nucleophilic histidine residue at the N-terminus, it appeared from molecular models that the distance between the two functional groups could actually be optimal. Isostere **12** is thus an appropriate catalyst to test this hypothesis.

The synthesis of octapeptide isostere **12** is analogous to that of tetrapeptide **4** (see Supporting Information). Preliminary ^{1}H NMR spectroscopic experiments were conducted with catalysts **3** and **12**, and the results point to similar conformations. Both catalysts afford well-defined ^{1}H NMR spectra in homogeneous $CDCl_3$ solution. Peptides **3** and **12** also afford NOE signals and amide NH titration data that are consistent with a Type II′ conformation at the turn of the corresponding β-hairpins.[15–17]



Scheme 3. Potential interaction of **1** with octapeptide **3**. Isostere **12** is an appropriate model to study the role of the prolyl amide.

Table 1. Selectivities for various substrates in kinetic resolutions with peptide catalysts.[a]



Entry	Catalyst	Racemic substrate	Conversion	$k(R,R)/k(S,S)$
1	**2**	**1**	49%	28
2	**2**	**10**	51%	17
3	**2**	**11**	56%	6
4	**4**	**1**	50%	< 1.5
5	**4**	**10**	52%	< 1.5
6	**4**	**11**	50%	< 1.5

[a] The reactions were conducted with 1–2 mol% catalyst (5.9 mM in substrate, toluene solvent) at 25 °C. Conversions and enantioselectivities were measured by chiral GLC (Chiraldex GTA).

The comparison of peptide **3** and isostere **12** in a catalytic setting provides a striking result. Whereas replacement of the prolyl amide with an apolar alkene in the tetrapeptide series (**2** → **4**) eradicates enantioselectivity, suggesting the site of a key catalyst–substrate contact, in the octapeptide series (**3** → **12**) the two catalysts afford nearly identical selectivity (Table 2). For the six-membered ring **1**, octapeptide **3** affords a k_{rel} value of 51 (Table 2, entry 1). With isostere **12**, the resolution proceeds with $k_{rel} = 50$ (Table 2, entry 4). These nearly identical results suggest that the two catalysts may share substantial mechanistic similarity with respect to the enantioselectivity-determining steps. Furthermore, these data strongly refute the proposition that the D-Pro-Gly amide group of **3** is a key transition state contact for the reaction of substrate **1**.

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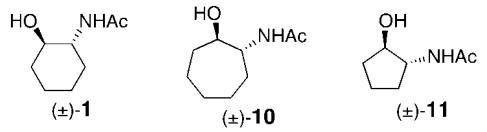
Table 2. Selectivities for various substrates in kinetic resolutions with peptide catalysts.[a]



Entry	Catalyst	Racemic substrate	Conversion	$k(R,R)/k(S,S)$
1	**3**	**1**	50%	51
2	**3**	**10**	45%	15
3	**3**	**11**	49%	27
4	**12**	**1**	53%	50
5	**12**	**10**	47%	31
6	**12**	**11**	53%	26

[a] The reactions were conducted with 1–2 mol% catalyst (5.9 mM in substrate, toluene solvent) at 25 °C. Conversions and enantioselectivities were measured by chiral GLC (Chiraldex GTA).

Once again, we found that these observations are mirrored with other substrates in this class (Table 2). Whereas catalyst **3** affords a $k_{rel} = 27$ for five-membered ring **11**, isostere **12** affords a nearly identical k_{rel} of 26 (Table 2, entries 3 and 6). For seven-membered ring **10**, catalyst **3** affords $k_{rel} = 15$; isostere **12** is actually more selective for this substrate, affording $k_{rel} = 31$ (Table 2, entries 2 and 5). These results underscore both the functional similarity of octapeptide **3** and isostere **12**, and the greater complexity in analyzing the octapeptide system. If there is a unique contact between the amides of substrates such as **1** and peptide **3**, it appears not to be at the D-Pro-Gly linkage.

In summary, we report an approach to probing the mechanisms by which peptide-based enantioselective catalysts function. Relying on conformational analogies between such catalysts and their derived alkene isosteres, we have uncovered a specific, kinetically significant amide in a tetrapeptide system. Applying the same approach to a highly selective octapeptide system, we have excluded the central amide of a β-hairpin as the kinetically significant binding site. Additional studies along these lines should provide further mechanistic insight into the inner workings of peptide-based catalysts and, potentially, their more complex enzymatic counterparts.

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Ion-Pair Recognition by Nucleoside Self-Assembly: Guanosine Hexadecamers Bind Cations and Anions**

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Ion-pair recognition calls for receptors with separate cation and anion binding sites. Ditopic hosts typically have these discrete binding sites built into their covalent frameworks.[1, 2] A more efficient approach might be to use noncovalent interactions to build the ion-pair receptor from multiple components.[3] Below, we describe a prime example of how

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