Kinetic Resolution of Alcohols Catalyzed by Tripeptides Containing the *N*-Alkylimidazole Substructure

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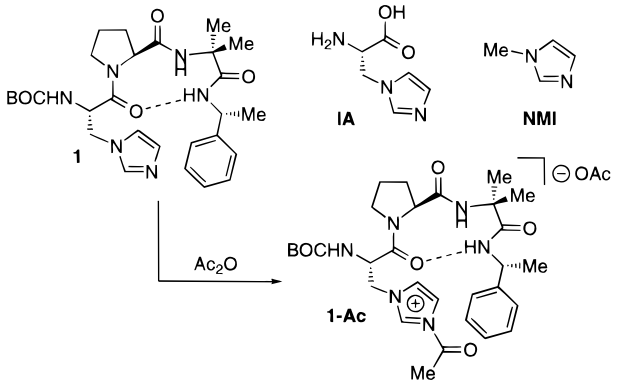
Peptide−substrate interactions frequently account for the specificity of enzymes. The combined effect of intermolecular hydrogen bonding, hydrophobic effects, electrostatics, and solvent reorganization is at the heart of the precise enzyme−substrate associations which lead to selectivity.[1] The application of these concepts to the design of small molecule catalysts promises to make the development of low-molecular-weight enzyme-like systems possible.[2] In this context, we are investigating synthetic peptides containing nonproteinogenic amino acids that impart catalytic activity with the ultimate goal of developing selective peptide-based catalysts for asymmetric synthesis. Herein we report the design and synthesis of new, functional peptides that catalyze the kinetic resolution of certain secondary alcohols.[3,4]

Our initial design focused on peptide **1** (Scheme 1), which contains 3-(1-imidazolyl)-(*S*)-alanine (**IA**) as the *N*-terminal amino acid.[5,6] Within **IA** is the *N*-methylimidazole (**NMI**) substructure, which is capable of catalyzing the acylation of secondary alcohols by acetic anhydride through a nucleophilic mechanism.[7] We felt that incorporation of **IA** into short, folded peptides would allow for the formation of an acyl imidazolium intermediate (e.g., **1-Ac**)[8] in proximity to the chiral environment created by the peptide backbone. In particular, we introduced **IA** into a predisposed β-turn structure defined by the proline-α-aminoisobutyric acid framework.[9] Incorporation of the C-terminal (*R*)-α-methylbenzylamide was intended to create the possibility for π-stacking of the charged acylimidazolium ion with the phenyl group of the catalyst (**1-Ac**).[4e,10]

Preliminary experiments were designed to demonstrate that substrate interactions with the peptide backbone were kinetically significant. Accordingly, we performed competition experiments between alcohols substituted with amides (which could participate in intermolecular transition state hydrogen bonding) and alcohols

Scheme 1



devoid of a second functional group (eq 1, Table 1). When 1 equiv of *trans*-2-(*N*-acetylamino)cyclohexan-1-ol (**2**), 1 equiv of aromatic alcohol **3**, and one equiv of acetic anhydride were treated with 0.05 equiv of **NMI,** the corresponding acetate esters **2-Ac** and **3-Ac** were each formed in equal quantities. However, when the identical experiment was conducted with β-turn catalyst **1** in place of **NMI**, **2-Ac** and **3-Ac** were observed in a 6:1 ratio. As a control, the reaction was conducted in the presence of tripeptide **4** which lacks the alkyl imidazole substructure. In this experiment, no products were detected (<2% by 400 MHz NMR spectroscopy), indicating that the **NMI** substructure is crucial for catalysis. One possible explanation for the preferential acylation of **2** relative to **3** in the presence of **1** could be the existence of a favorable transition state hydrogen bond between the amide of **2** and the peptide backbone of **1**. While alternative explanations cannot be ruled out at this time, the results substantively demonstrate the capacity of peptide architecture to perturb reaction selectivities.[11]

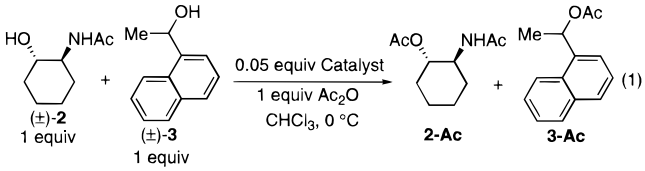


Table 1. Competitive Acylation Experiments between Alcohols **2** and **3**

Catalyst	Product Distribution **2-Ac**	**3-Ac**
NMI	1	1
1	6	1
4	No Reaction	

1, R = Im
4, R = Ph

We then turned our attention to issues of enantioselective catalysis (eq 2). Treatment of racemic *trans*-2-(*N*-acetylamino)-cyclohexan-1-ol (**2**, 10 equiv) with 1 equiv of acetic anhydride in the presence of 0.05 equiv of peptide **1** resulted in the formation of the corresponding amidoacetate **2-Ac** in 95% yield (relative to Ac_2O); the product exhibited an experimentally reproducible enantiomeric excess of 48% (k_{fast}/k_{slow} (S) = 3.0).[12] In contrast, the naphthyl-substituted alcohol **3** did not exhibit detectable enantioselectivity (S = 1) under analogous conditions and at

(1) For a recent compendium of pertinent reviews, see: Gellman, S. H., Ed.; *Chem. Rev.* **1997**, *97* (Chemical Reviews Thematic Issue on Molecular Recognition), 1231−1734.

(2) (a) Breslow, R. *Acc. Chem. Res.* **1995**, *28*, 146−153. (b) Murakami, Y.; Kikuchi, J.; Hiseada, Y.; Hayashida, O. *Chem. Rev.* **1996**, *96*, 721−758.

(3) The kinetic resolution of racemic alcohols is a powerful approach to the preparation of optically pure compounds. For a review of enzymatic approaches, see: Wong, C.-H.; Whitesides, G. M. *Enzymes in Synthetic Organic Chemistry*; Elsevier Science Ltd.: Oxford, 1994; Chapter 2.

(4) For previously reported chiral nucleophilic catalysts which effect kinetic resolution of racemic alcohols, see: (a) Vedejs, E.; Chen, X. *J. Am. Chem. Soc.* **1996**, *118*, 1809−1810. (b) Vedejs, E.; Daugulis, O.; Diver, S. T. *J. Org. Chem.* **1996**, *61*, 430−431. (c) Ruble, J. C.; Fu, G. C. J. *Org. Chem.* **1996**, *61*, 7230−7231. (d) Ruble, J. C.; Latham, H. A.; Fu, G. C. *J. Am. Chem. Soc.* **1997**, *119*, 1492−1493. (e) Kawabata, T.; Nagato, M.; Takasu, K.; Fuji, K. *J. Am. Chem. Soc.* **1997**, *119*, 3169−3170.

(5) For a synthesis of **IA**, see: (a) Tohodo, K.; Hamada, Y.; Shiori, T. *Synlett* **1994**, 247−249. (b) Arnold, L. D.; Kalantar, T. H.; Vederas, J. C. *J. Am. Chem. Soc.* **1985**, *107*, 7105−7109.

(6) Assembly of peptides followed conventional solution phase techniques. See the Supporting Information for details.

(7) (a) Guibe-Jampel, E.; Bram, G.; Vilkas, M. *Bull. Soc. Chim. Fr.* **1973**, 1021−1027. (b) Höfle, G.; Steglich, W.; Vorbrüggen, H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 569−583. (c) A general base-type mechanism cannot be excluded. See: Pandit, N. K.; Connors, K. A. *J. Pharm. Sci.* **1982**, *71*, 485−491.

(8) Rybachenko, V. I.; Chervinskii, A. Y.; Kapkan, L. M.; Semenova, R. G.; Titov, E. V. *Zh. Org. Khim.* **1976**, *12*, 240−241.

(9) Ravi, A.; Balaram, P. *Tetrahedron* **1984**, *40*, 2577−2583.

(10) Ma, J. C.; Dougherty, D. A. *Chem. Rev.* **1997**, *97*, 1303−1324.

(11) Hydrogen bonding has been implicated as a factor in determining the stereochemical course of stoichiometric acyl transfer reactions involving chiral acyl halides. See: Ishihara, K.; Kubota, M.; Yamamoto, H. *Synlett* **1994**, 611−614.

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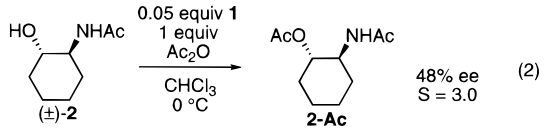
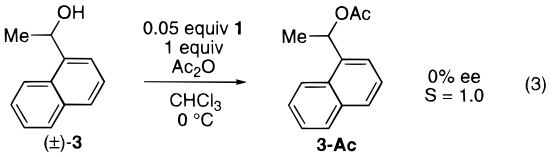


(2)

comparable conversion (eq 3). Thus, substrate **2**, which was



(3)

found to undergo preferential acylation in the competition experiment employing peptide **1**, exhibited an appreciable response to the chiral environment of the peptide. Substrate **3** was inert to chirality transfer.

Optimization studies revealed that solvents which favor hydrogen bonding lead to selectivity enhancement (Table 2). For example, optimum selectivities were obtained in nonpolar solvents that are not Lewis basic (entry 3 84% enantiomeric excess (ee) in toluene, $S = 12.6$; entry 4 12% ee in CH_3CN, $S = 1.3$). Protic media proved to have a deleterious effect on reaction selectivity as well, with a chloroform−*t*-BuOH medium leading to a completely nonselective reaction (entry 5).[13] It is important to note that these data do not distinguish between the significance of intramolecular or intermolecular hydrogen bonds. Nevertheless, they do reflect the potential for substantial k_{fast}/k_{slow} values to be obtained with relatively simple peptide systems.

Experiments employing different substrates have provided further data concerning catalyst−substrate interactions (Figure 1). When the optimized conditions were employed (Table 2, entry 3), cyclohexene derivative **5** exhibited a k_{fast}/k_{slow} ratio of 3.0 under the influence of peptide **1** (entry 1); cycloheptane derivative **6** also exhibited an appreciable k_{fast}/k_{slow} ratio of 4.6 under the same reaction conditions (entry 2). In contrast, acetate ester **7** (entry 3), isosteric with acetamide **2** but less Lewis basic and incapable of acting as a hydrogen bond donor through the ester, showed a greatly diminished k_{fast}/k_{slow} ratio of 1.4 under the reaction conditions. These data also point to transition state involvement of the amide of the substrate with the asymmetric functional group array provided by the catalyst backbone.

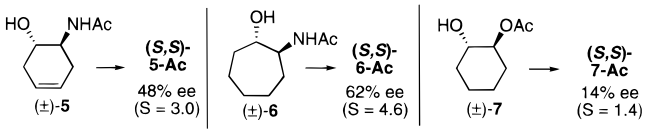
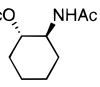


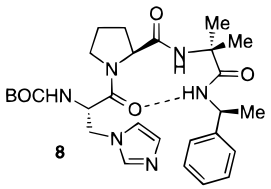
Figure 1. Influence of substrate structure on resolutions catalyzed by **1**.

We have now begun to investigate the consequences of peptide backbone conformation on reaction selectivities in detail. Gellman and co-workers have recently delineated the consequences of stereogenic center configuration on the propensity of given peptide sequences to form β-turns in a nonpolar medium.[14] We synthesized the epimeric β-turn catalyst **8** to evaluate the significance of the absolute configuration of the α-methylbenzamide moiety. Of note is the fact that whereas peptide **1** exists as essentially one conformation in $CDCl_3$ solution at 23 °C (>90% by 400 MHz ^{1}H NMR),[15] peptide **8** exists as 3:1 conformational mixture at the same temperature. Catalyst **8** was then studied for its ability to effect kinetic resolution of **2** under the optimized conditions. Peptide **8** proved to be a substantially less-selective catalyst than **1** under the optimized conditions, affording **2-Ac** with 53% ee ($S = 3.5$; cf. 84% ee, $S = 12.6$ with **1**). Additional studies are now underway to identify (i) the specific catalyst−substrate interactions that dictate selectivity and (ii) their relationship to catalytically active peptide conformations.[16]

Table 2. Influence of Solvent on the Kinetic Resolution of Hydroxyamide **2** Catalyzed by **1**

entry[a]	racemic starting material	major product	solvent temp (°C)	enantiomer ratio (ee)[c]	(S)[d]
1			CH_2Cl_2 0 °C	70:30 (40)	2.4
2			$CHCl_3$ 0 °C	74:26 (48)	3.0
3			$PhCH_3$[b] 0 °C	92:8 (84)	12.6
4			CH_3CN 0 °C	56:44 (12)	1.3
5			$CHCl_3$/*t*-BuOH 0 °C	1:1 (0)	1.0

[a] All reactions were performed with 10 equiv of racemic substrate, 1 equiv of acetic anhydride, and 0.05 equiv of catalyst **1**. Reactions proceeded to 90−100% yield based on Ac_2O. Yields were measured following silica gel chromatography. Absolute configurations were assigned by analogy to authentic materials. [b] A minimum amount of $CHCl_3$ was introduced initially to solubilize catalyst and starting alcohol. [c] Determined by chiral HPLC or GC analysis. [d] Calculated according to the method of Kagan (ref 12).



In summary, we have established that short peptides containing the synthetic amino acid **IA** are asymmetric catalysts for the kinetic resolution of functionalized racemic alcohols. The present data suggest that alcohols containing an amide functional group are substrates for the peptide catalyst and that transition state hydrogen bonding may play a role in enantiomer differentiation. Further studies toward the development of more general and highly selective peptide-based asymmetric catalysts are in progress. In addition, these studies should afford significant information on peptide−substrate interactions which are of general interest in the context of biological catalysis.

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Supporting Information Available: Characterization data for all compounds and experimental details for their preparation (9 pages). See any current masthead page for ordering information and Web access instructions.

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(12) *S* values were calculated according to the method of Kagan. See: Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249−330.

(13) Running the reaction to higher levels of conversion under these conditions leads to a decrease in selectivity. At 33% conversion, the product exhibits 60% ee ($S = 5.3$).

(14) For a detailed discussion of the influence of backbone stereochemical configuration on β-turn conformation, see: Haque, T. S.; Little, J. C.; Gellman, S. H. *J. Am. Chem. Soc.* **1996**, *118*, 6975−6985.

(15) Detailed conformational analyses employing NMR techniques are in progress. Peptides **1**, **4**, and **8** each exhibited IR stretches consistent with both C═O···H−N hydrogen bonds (<3400 cm^{-1}), and non-hydrogen-bonded N−H groups (>3400 cm^{-1}). At 0.002 M/CH_2Cl_2, **1**, 3427, 3365 cm^{-1}; **4**, 3421, 3358 cm^{-1}; **8**, 3421, 3364 cm^{-1}). For an interpretation of N−H stretches in CH_2Cl_2, see: (a) Gellman, S. H.; Dado, G. P.; Liang, G.-B.; Adams, B. R. *J. Am. Chem. Soc.* **1991**, *113*, 1164−1173. (b) Liang, G.−B.; Desper, J. M.; Gellman, S. H. *J. Am. Chem. Soc.* **1993**, *115*, 925−938. (c) Gardner, R. R.; Liang, G.-B.; Gellman, S. H. *J. Am. Chem. Soc.* **1995**, *117*, 3280−3281. (d) Rao, C. P.; Nagaraj, R.; Rao, C. N. R.; Balaram, P. *Biochemistry* **1980**, *19*, 425−431.

(16) Use of the unsubstituted pyrrolidine-derived amide of *N*-BOC-**IA** as a catalyst for the resolution of **2** afforded **2-Ac** without detectable enantioselectivity. Other derivatives of **IA** as well as other nucleophile-loaded amino acids are currently under study.