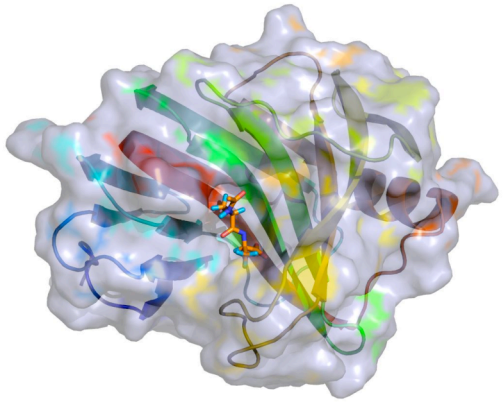
Biomimetic Chemistry

Artificial Enzymes, Molecular Recognition, & Bioinspired Reactivity

David Nagib

MacMillan Group Meeting
10.31.07



Key References

Cram, D., *Angew. Chem. Int. Ed. Engl.,* **1988**, 27, 1009
Rebek, J., *Science*, **1987**, *235*, 1478
Breslow, R., Dong, S., *Chem. Rev*. **1998**, *98*, 1997
McMurry, J., Begley, T., *The Organic Chemistry of Biological Pathways*, **2005**

Biomimetic Chemistry

a method of scientific inquiry that involves mimicking the laws of nature to create new synthetic compounds

a laboratory *procedure* designed to imitate a natural chemical process

- Biomimetic synthesis
- Natural product synthesis
- Asymmetric catalysis
- Reaction methodology

a *compound* that mimics a biological material in its structure or function

- Natural products
- Medicinal chemistry targets
- Molecular recognition hosts
- Artificial enzymes
- Photovoltaic cells
- Hydrogen fuel cells
- Redox metals

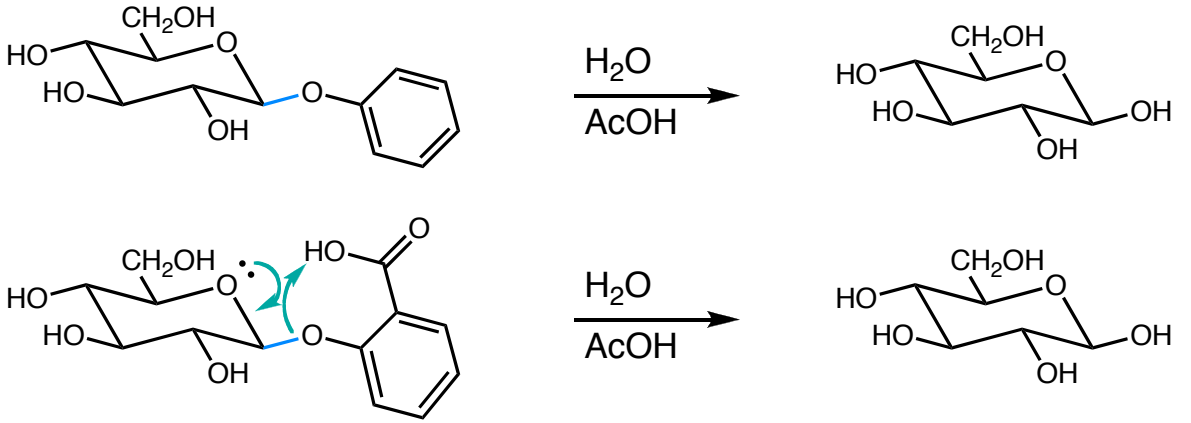
Ronald Breslow

"In biomimetic chemistry, we take what we have observed in nature and apply its principles to the invention of novel synthetic compounds that can achieve the same goals … As an analogy, we did not simply make larger versions of birds when we invented airplanes, but we did take the idea of the wing from nature, and then used the aerodynamic principles in our own way to build a jumbo jet."

-- R. Breslow

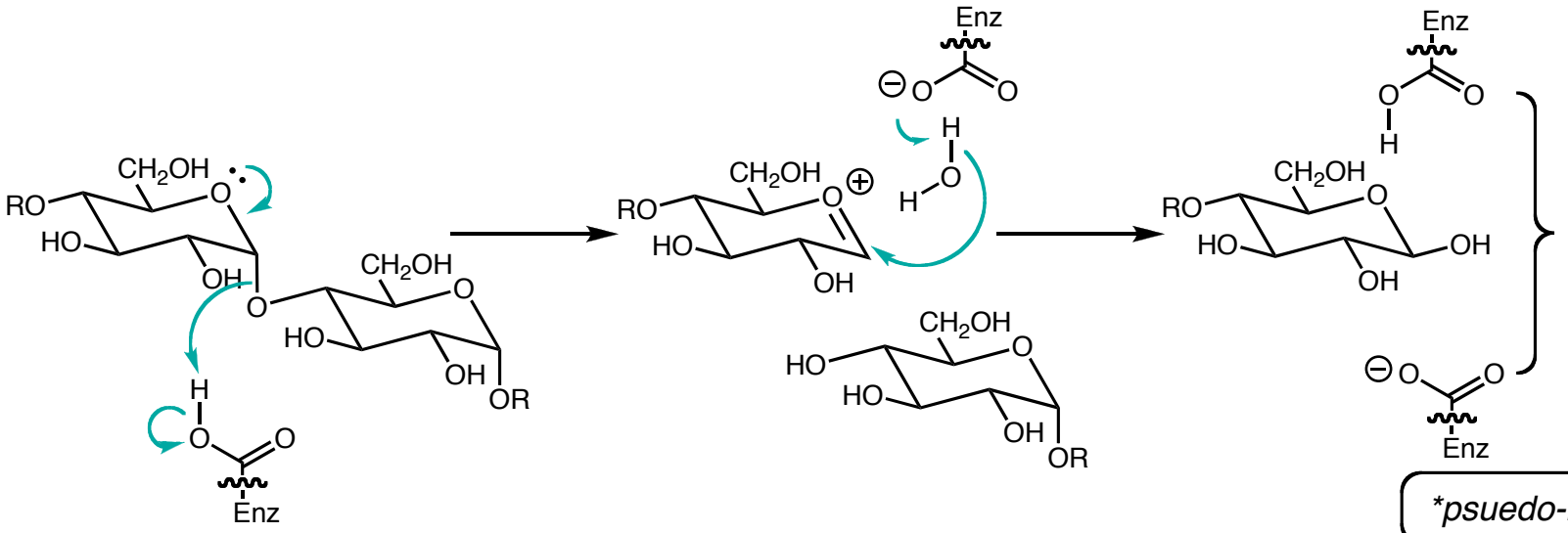
Exploring Nature's Optimized Reactions

- Hydrolysis of a glycoside bond



**Induced proximity effect*

- Glycosidase-catalyzed hydrolysis of a glycoside bond

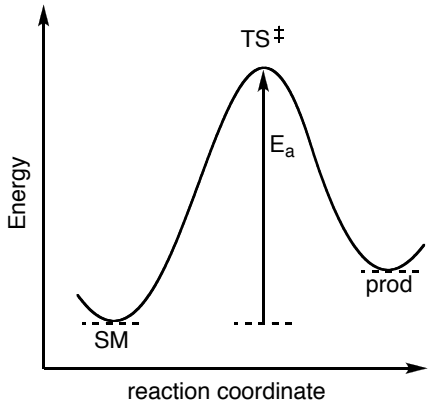


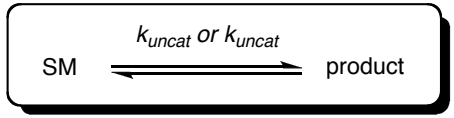
**psuedo-intramolecularity*

Rye, C., Withers, S., *Curr. Opin. In Chem. Biol.*, **2000**, *4*, 573

Fundamentals of Catalysis

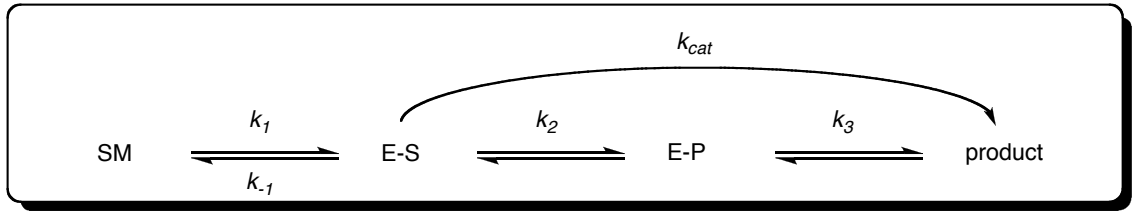
- Energy diagram explanation





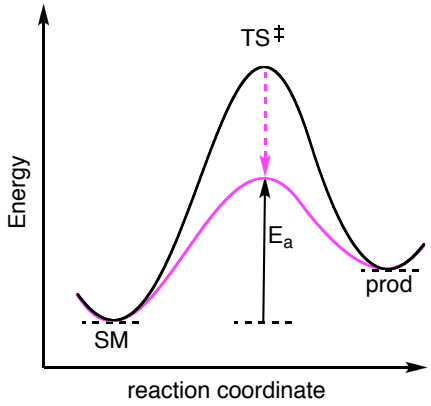
*Catalysis - reaction rate acceleration (k_{cat} > k_{uncat}) via decrease in E_a

Enzyme catalyzed reaction



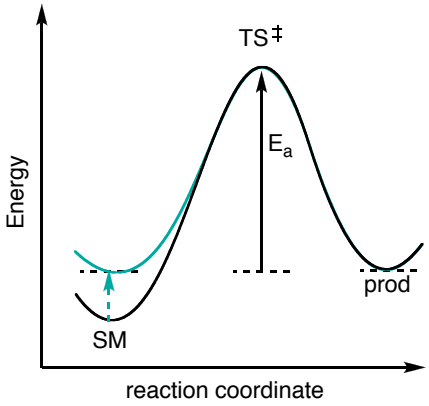
- Varying methods of enabling catalysis

transition state stabilization

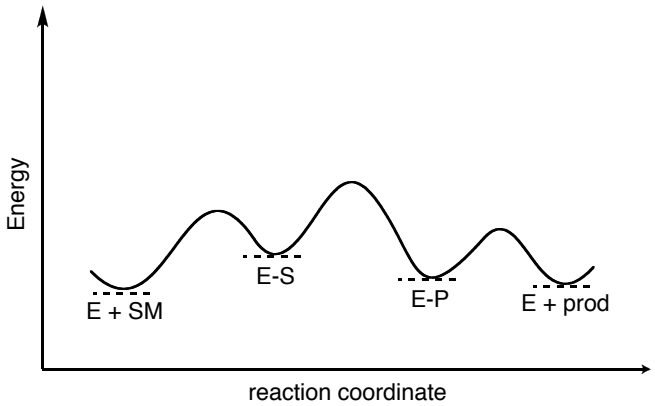


+

ground state destabilization



Enzyme catalysis

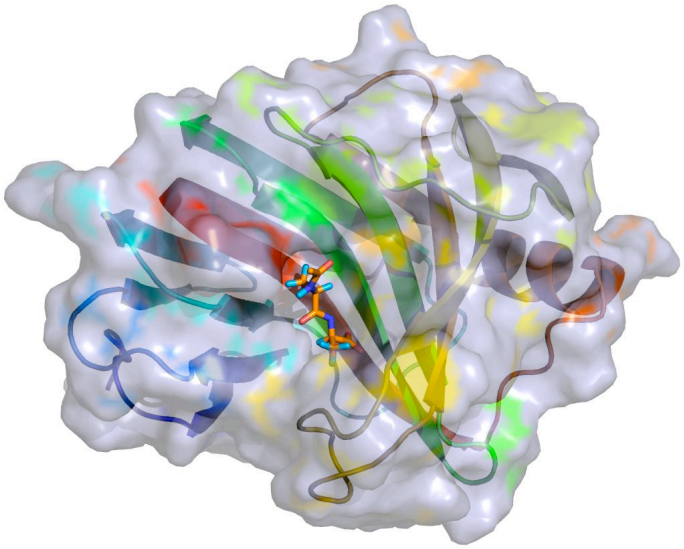


Enzymes often stabilize a TS by binding to it as much as 10^{12} times more tightly than to the SM or product

Enzyme Catalysis

- Factors that influence TS stabilization

Non-covalent electrostatic interactions
Hydrogen bonding
ion pairing
π-acid to π-base (cation-π)
metal-ligand binding
van der Waals attractions
hydrophobic stabilization
solvent reorganization



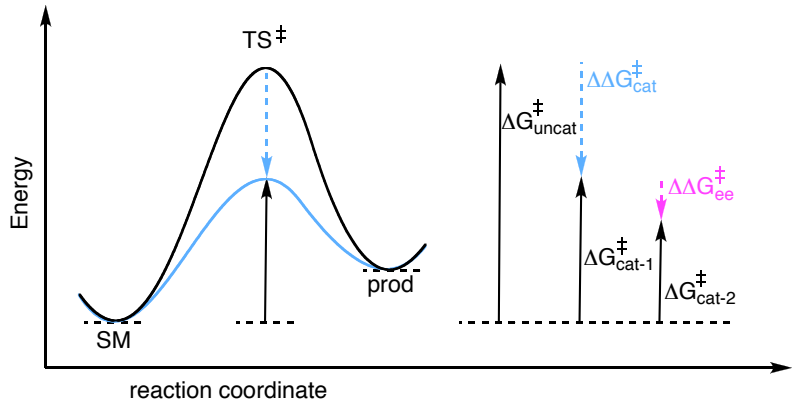
**Aggregate of these weak interactions (< 5-10 kcal/mol) can sum up to a larger stabilizing effect*

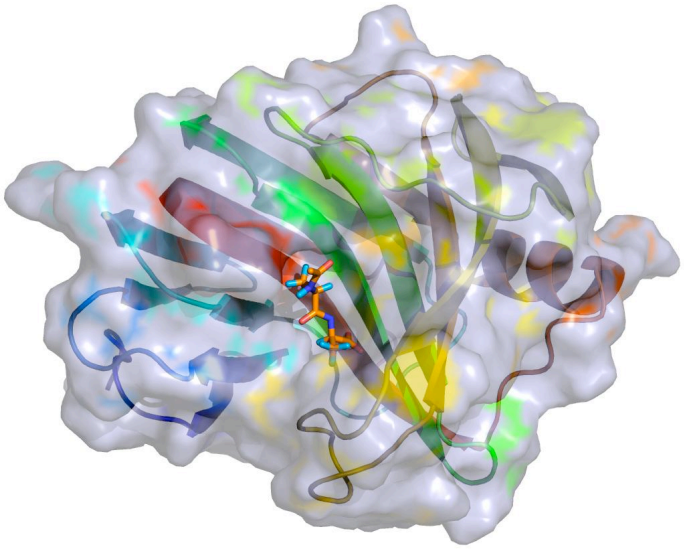
- Chemical transformations facilitated by enzymes

class	catalyzed transformation
oxidoreductases	oxidations and reductions
transferases	transfer of a group from one substrate to another
hydrolases	hydrolysis reactions of esters, amides, and related substrates
lyases	the elimination or addition of small molecules such as H_2O
isomerases	isomerizations (i.e. racemizations)
ligases	bonding together of 2 molecules (often via hydrolysis of ATP)

Selectivity in Catalysis

- $\Delta\Delta G^{\ddagger}$ represents the difference in reaction pathway





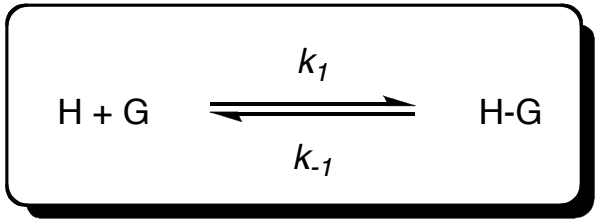
A small $\Delta\Delta G^{\ddagger}$ can still result in a large ratio between products because of this relationship: $\Delta G = -RT\ln K$

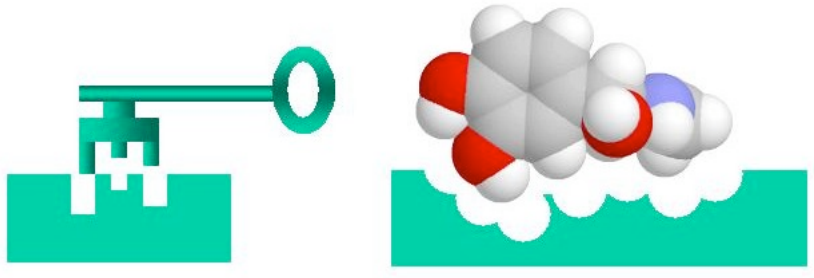
- Product ratios calculated at selected temperatures

$\Delta\Delta G^{\ddagger}$	0ºC	r.t.
0.5 kcal	2.5:1	2.3:1
1.0 kcal	6.3:1	5.4:1
2.0 kcal	40:1	30:1
3.0 kcal	250:1 (99.6%)	200:1 (99.5%)
1.4 kcal		10:1
1.8 kcal		20:1
2.7 kcal		100:1

Molecular Recognition

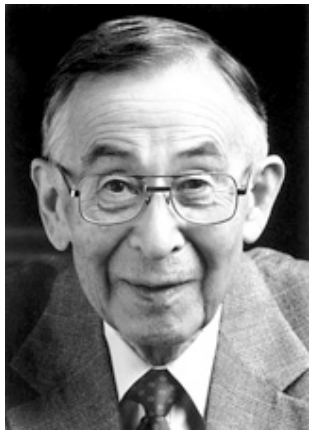
- Host-Guest Interactions





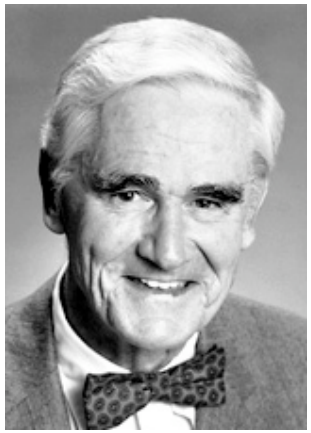
In analogy to a lock and key, enzymes exhibit their stabilizing forces by very specific association between itself (the host) and a *complementary* substrate (a guest).

"For their development and use of molecules with structure-specific interactions of high selectivity," especially as it pertained to artificially replicating this mechanism, the 1987 Nobel prize in chemistry was bestowed to the following researchers.



Charles Pedersen

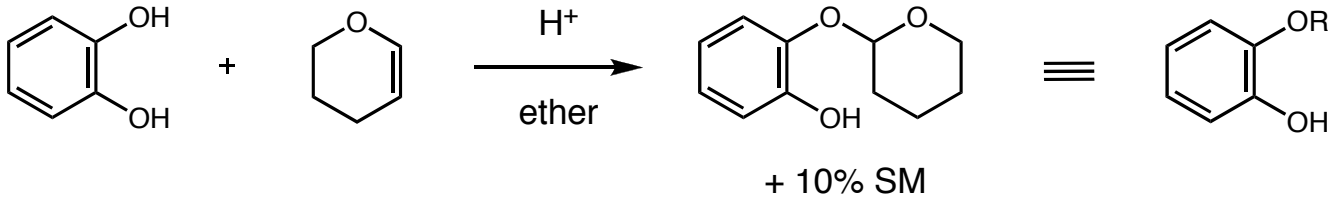
Jean-Marie Lehn

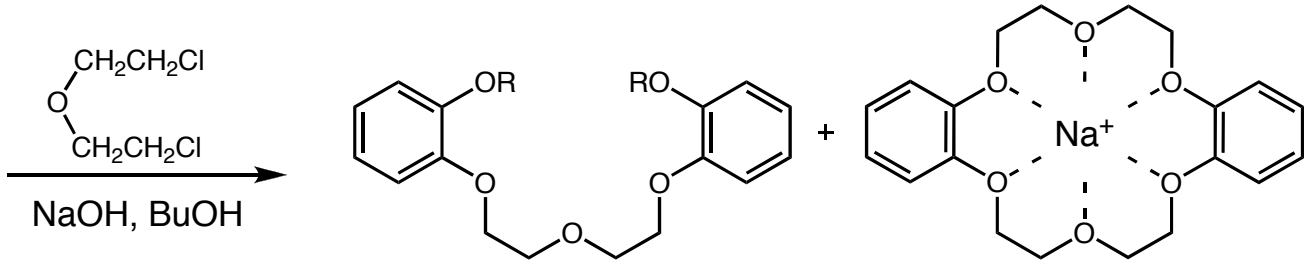


Donald Cram

Crown ethers

- Pedersen's serendipitous discovery of spontaneous complexation to alkali metals

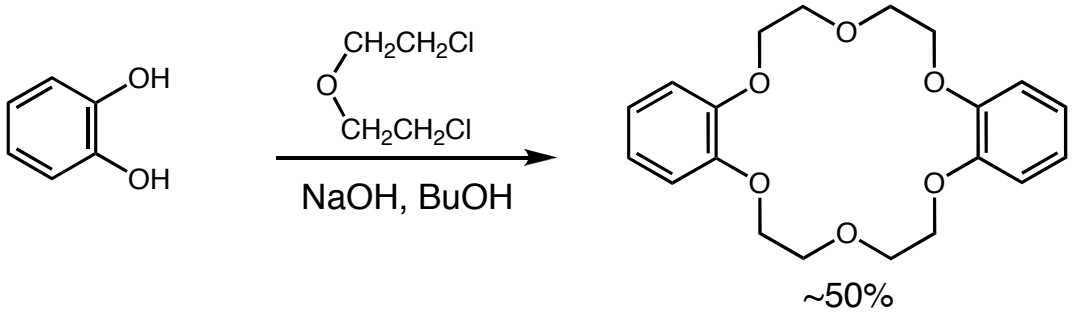




desired vanadium-chelating ligand
major component, oily residue

<1% - crystalline solid

- Resultant facile synthesis of dozens of crown ethers

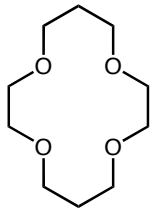


~50%

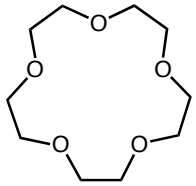
Pedersen, C. *JACS*, **1967**, *89*, 2495
Pedersen, C. *Nobel lecture*, December 8, 1987

Properties of Crown Ethers

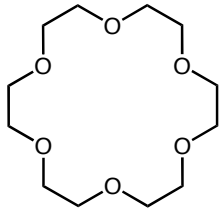
- Elucidation of cation solvation properties and applications



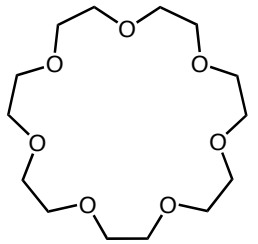
14-crown-4



15-crown-5



18-crown-6



21-crown-7

Ionic Diameters and Host Cavity Sizes (Å)

cation	Ionic diameter[a]	Polyether ring	Hole size[b]
Li^+	1.36	14-crown-4	1.2 - 1.5
Na^+	1.94	15-crown-5	1.7 - 2.2
K^+	2.66	18-crown-6	2.6 - 3.2
Rb^+	2.94	21-crown-7	3.4 - 4.3
Cs^+	3.34		
NH_4^+	2.86		
Ag^+	2.52		

[a] Crystal diameter. [b] Pedersen & CPK models

Optimum ring size
for solvation of cations:

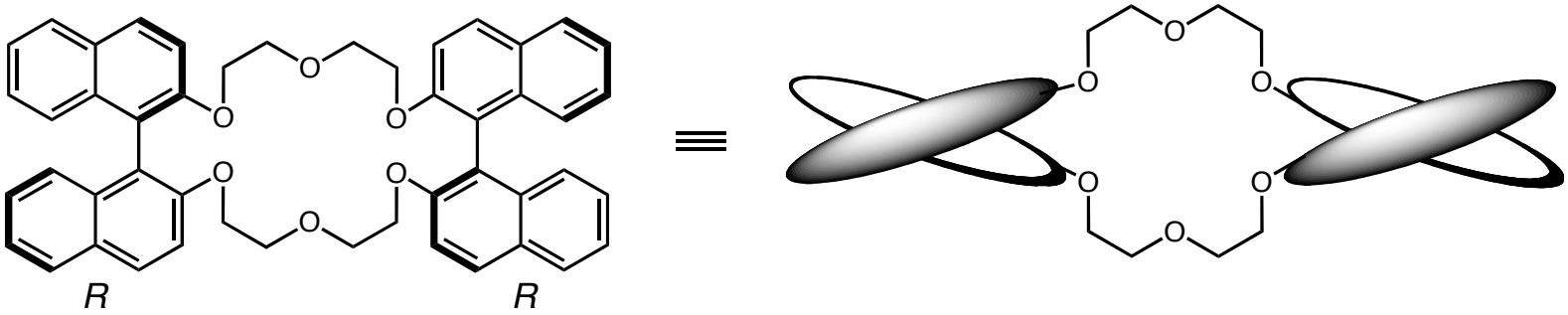
Na^+ : 15 - 18
K^+ : 18
Cs^+ : 18 - 21

*Important for investigating the function of certain antibiotics on ion channels within the cell membrane

Frensdorff, H. *JACS*, **1971**, *93*, 600
Pedersen, C.; Frensdorff, H. *Angew. Chem. Int. Ed.*, **1972**, *11*, 16
Izatt, R., Rytting, H., Nelson, D., Haymore, B., Christensen, J., *Science*, **1969**, *164*, 443

Chiral Crown Ethers

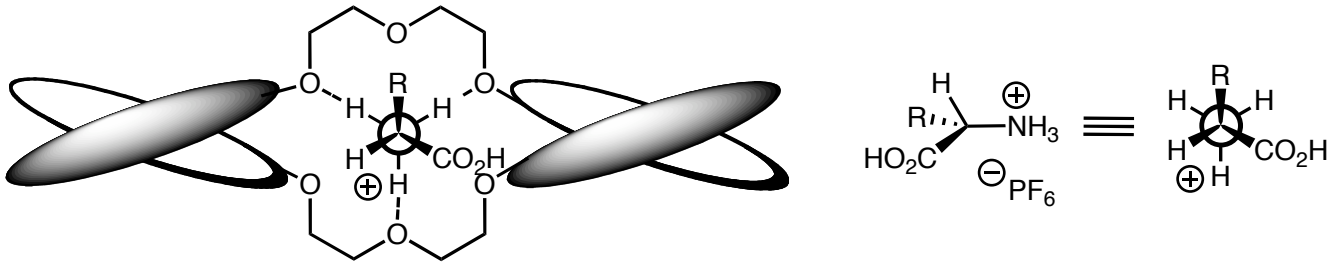
- Designing asymmetric host molecules to distinguish between enantiomers



C_2 symmetric host

By employing C_2 symmetric binapthyls, Cram was able to develop classes of crown ether hosts that could resolve racemic ammonium salts and amino acids

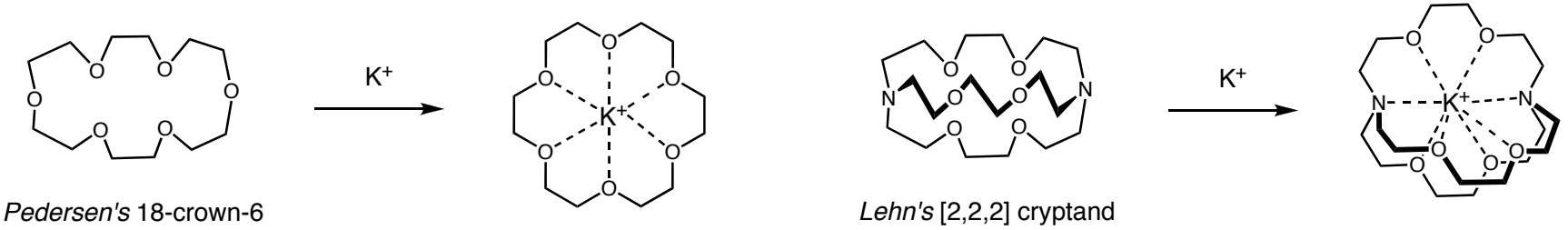
- Amino acids could then be resolved within these *meso*-hosts by means of a defined sense of stereoinduction



Cram, D., Cram, J., *Science*, **1974**, *183*, 803

Conformational Analysis of Crown Ethers

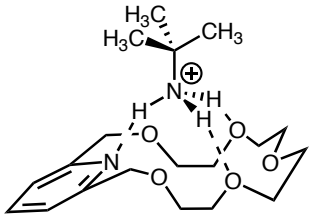
- Crystal structures of the *crown ethers* and *cryptands* show that they contain neither cavities nor convergently arranged binding sites in their uncomplexed states



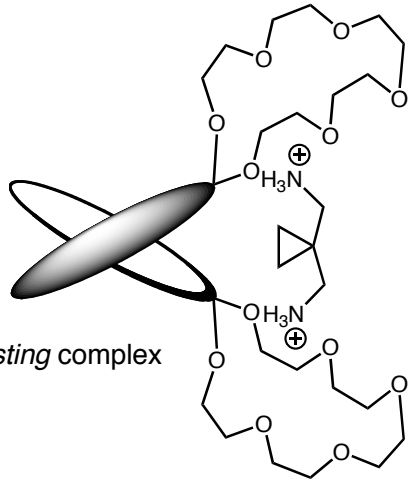
Pedersen's 18-crown-6

Lehn's [2,2,2] cryptand

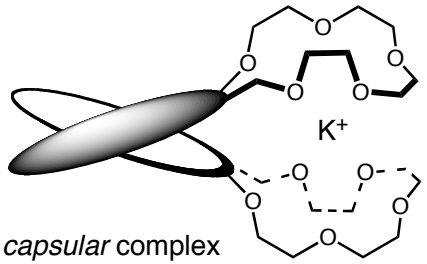
- Additionally, these host-guest complexes are not planar as typically drawn, but rather can exist in any of the following conformations, depending on the host and guests involved.



perching complex



nesting complex



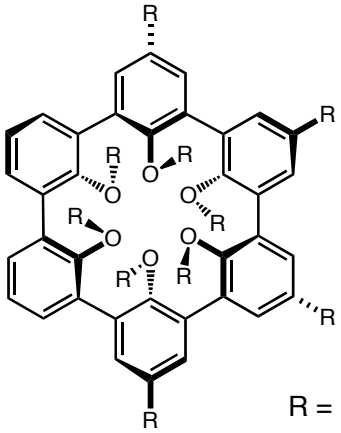
capsular complex

Dietrich, B., Lehn, J., Sauvage, J. *Tetrahedron Lett.*, **1969**, *10*, 2885

Cram, D., *Angew. Chem. Int. Ed. Engl.*, **1988**, *27*, 1009

Principles of Preorganization

- Cram's proposed host, targeted as a result of CPK molecular models



Cram's spherand

24 lone pair electrons shielded from solvation by 6 aryl & 6 methyl groups

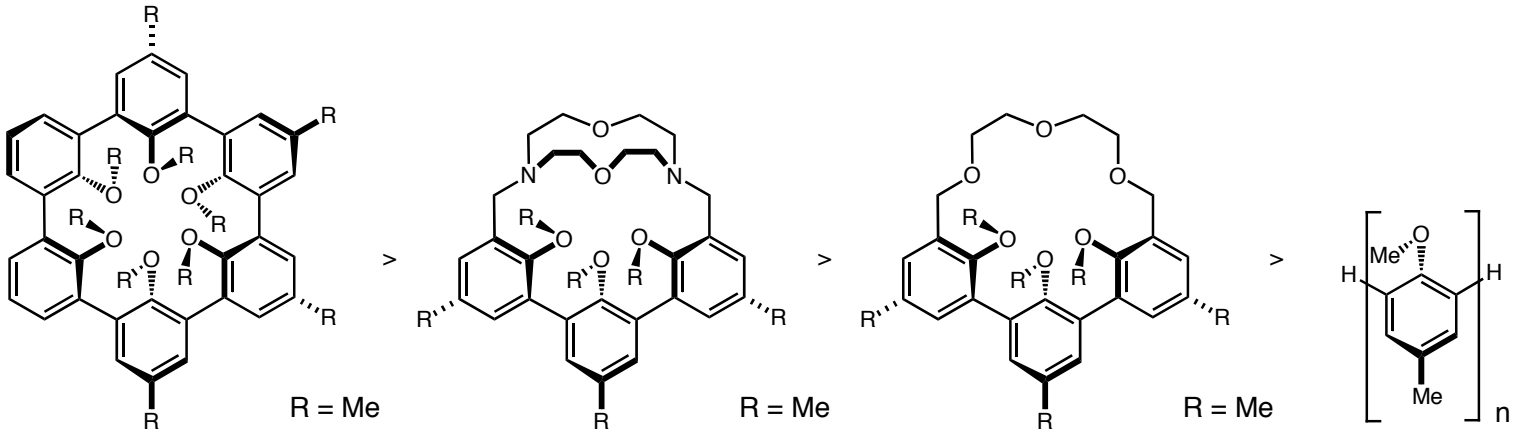
$K^A/K^{A'}$ values for binding to alkali metal picrates:

$Li^+/Na^+ > 600$

$Na^+/K^+ > 10^{10}$

Unlike the crown and cryptand structures, this fairly rigid molecule was completely organized for complexation during *synthesis*, rather than *complexation*, and thus exhibits significantly higher $-\Delta G^o$ values for binding.

- As the host becomes less preorganized, there is a corresponding decrease in binding ability



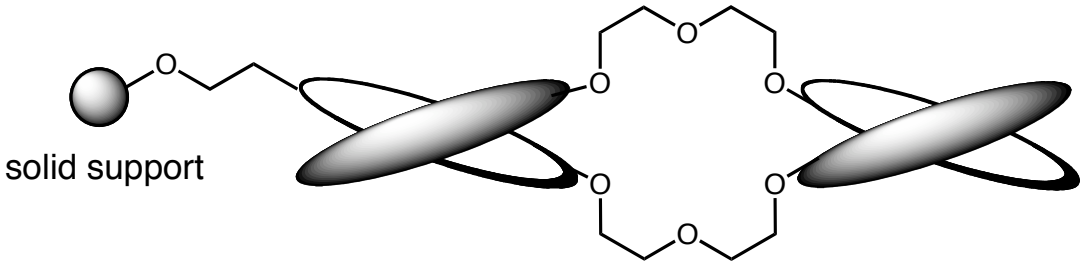
spherand > cryptashperand > hemispherand > podand

The difference in $-\Delta G^o$ values for spherand & the linear podand binding to Li^+ is >17kcal/mol, or a difference in K of a factor of 10^{12}

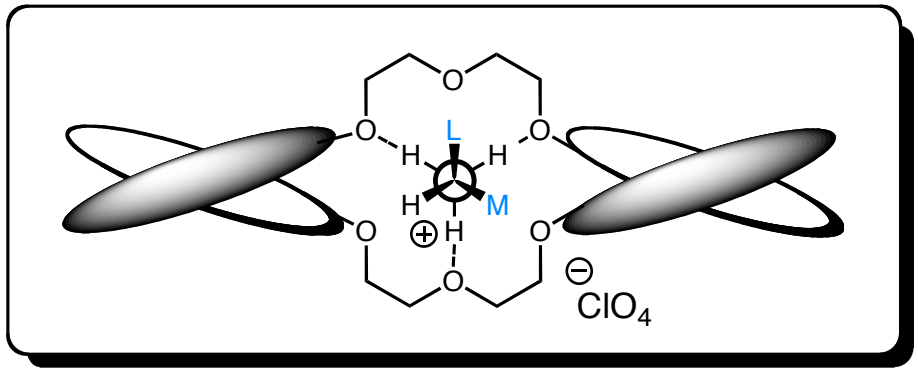
Cram, D., *Angew. Chem. Int. Ed. Engl.*, **1988**, *27*, 1009

Immediate Practical Applications

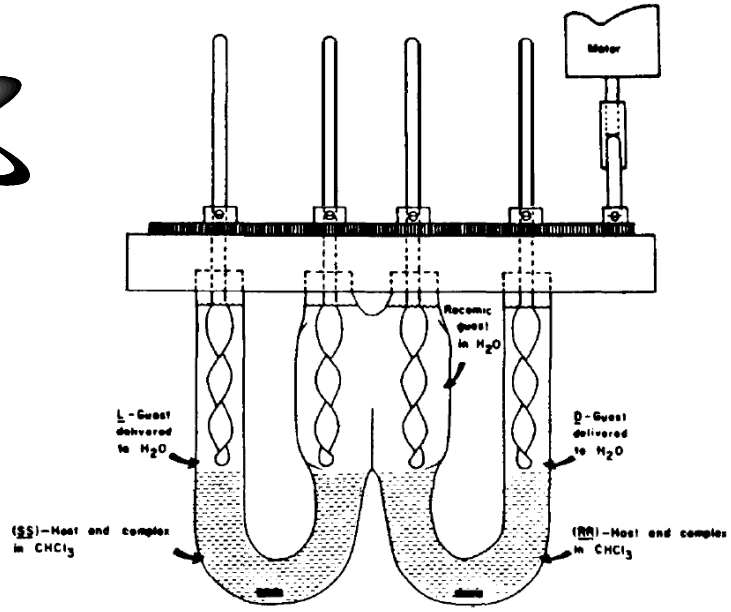
- The ability to efficiently resolve amino acid enantiomers quickly led to the invention of numerous applications



Early “chiral column”



Thanks to this defined rupric for selectivity, the scope of these processes could include a wide variety of amino acids

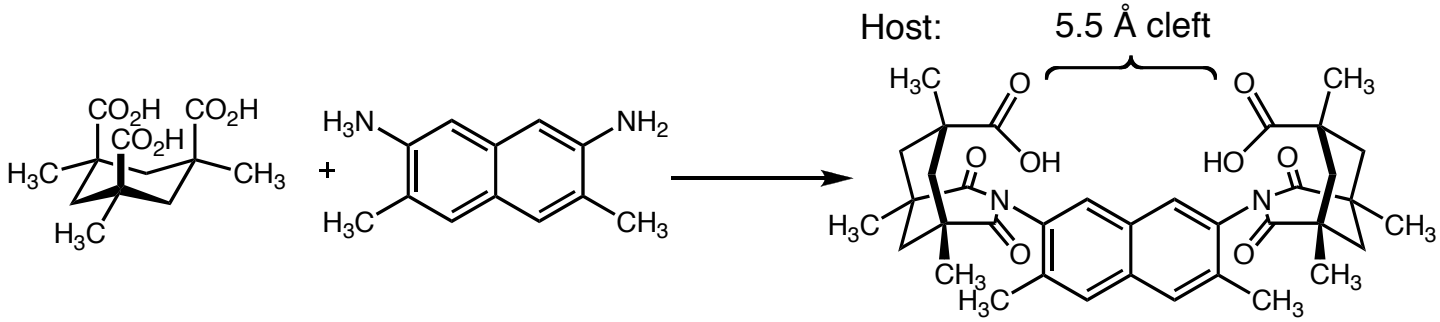


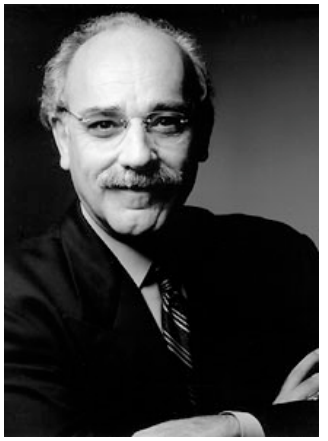
Enantiomer resolving machine

Cram, D., *Angew. Chem. Int. Ed. Engl.*, **1988**, *27*, 1009

Designing Simpler Hosts

- Rebek employed Kemp's Triacid as a readily available H-bonding source

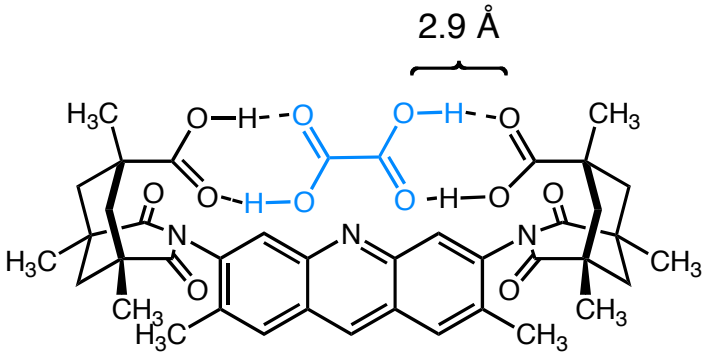




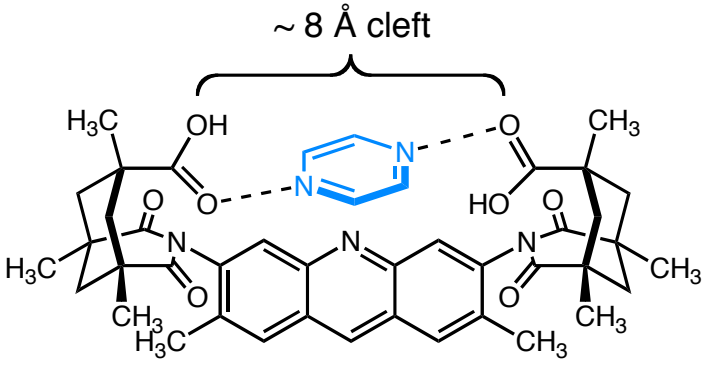
Julius Rebek, Jr.

Guests: alcohols, amines

- By varying the aryl linker, the cleft size could be manipulated so as to accommodate (and resolve) a wide variety of substrates from solutions



The greatly reduced H-bonding distance between host and picric acid guest was determined by x-ray crystallography and is quite comparable to covalent bond distances



Compared to:

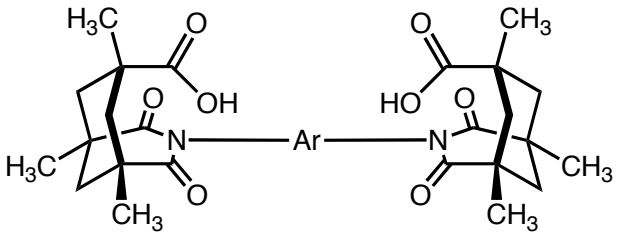
C-C: 1.54 Å
C-O: 1.2 Å

Rebek, J., *Science*, **1987**, *235*, 1478

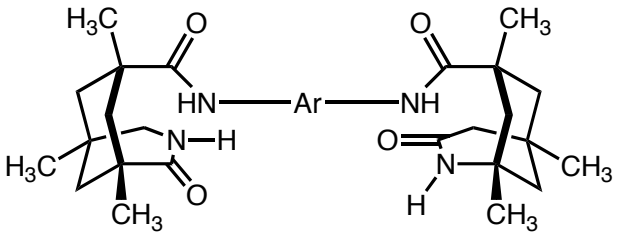
Simpler Asymmetric Hosts

- Modifying the host linker and installing a new H-bond motif allowed for chiral recognition

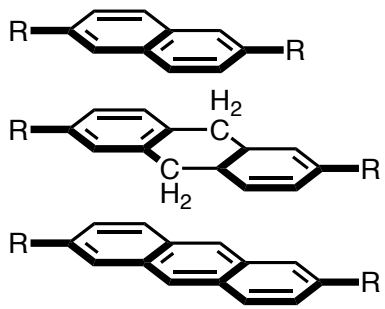
1st Generation: Imido linkage



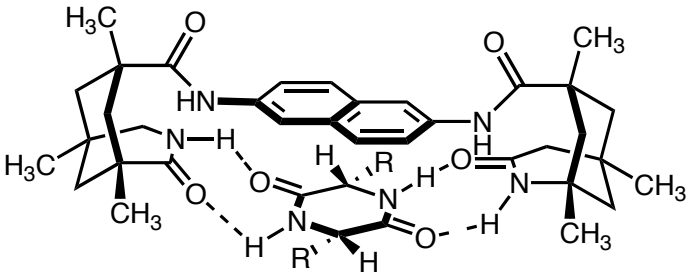
2nd Generation: Amide linkage



Ar =



- These molecular clefts afforded high resolutions of diketopiperazines as guests binding to the host lactam



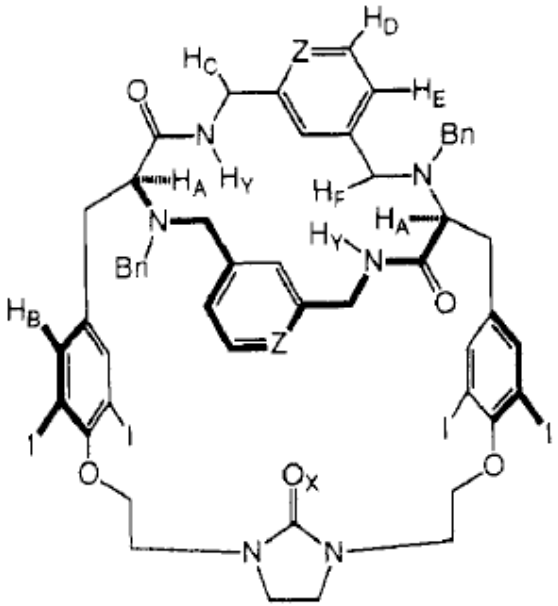
up to 100-fold enantiomeric resolution ($\Delta G \sim 2.5$ kcal/mol)
for recognition of cycl-(L-leucyl-L-leucine)

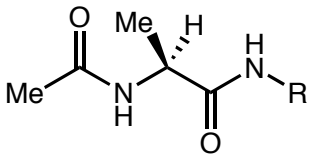
Cooperative H-bonds (*bi-functional binding*)
in an asymmetric environment

Jeong, K., Muehldorf, A., Rebek, J., *JACS*, **1990**, *112*, 6144

Vancomycin Mimic

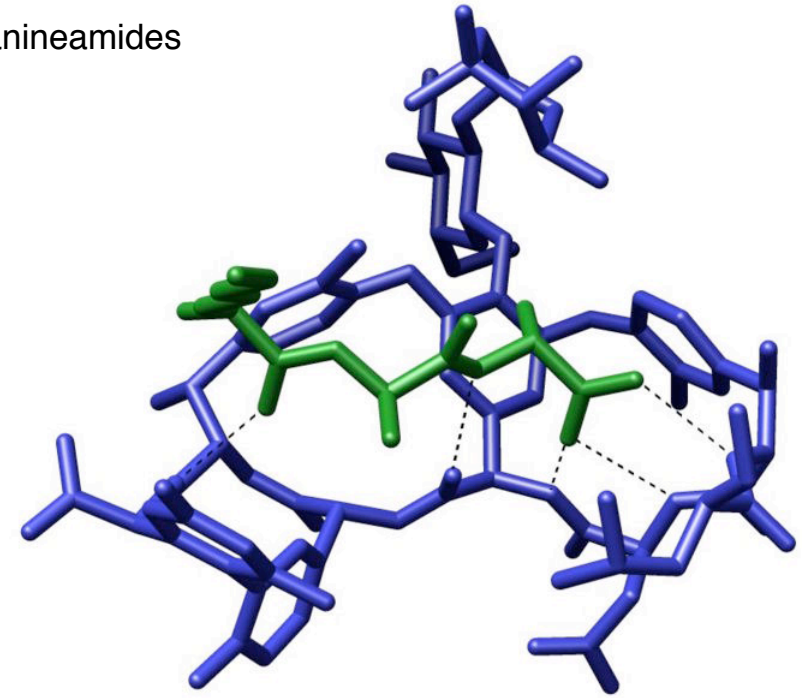
- Starting from L-tyrosine, Still synthesized a chiral host molecule that could bind enantioselectively to acyclic alanine dipeptides





acetyl-L-alanineamides

W. Clark Still

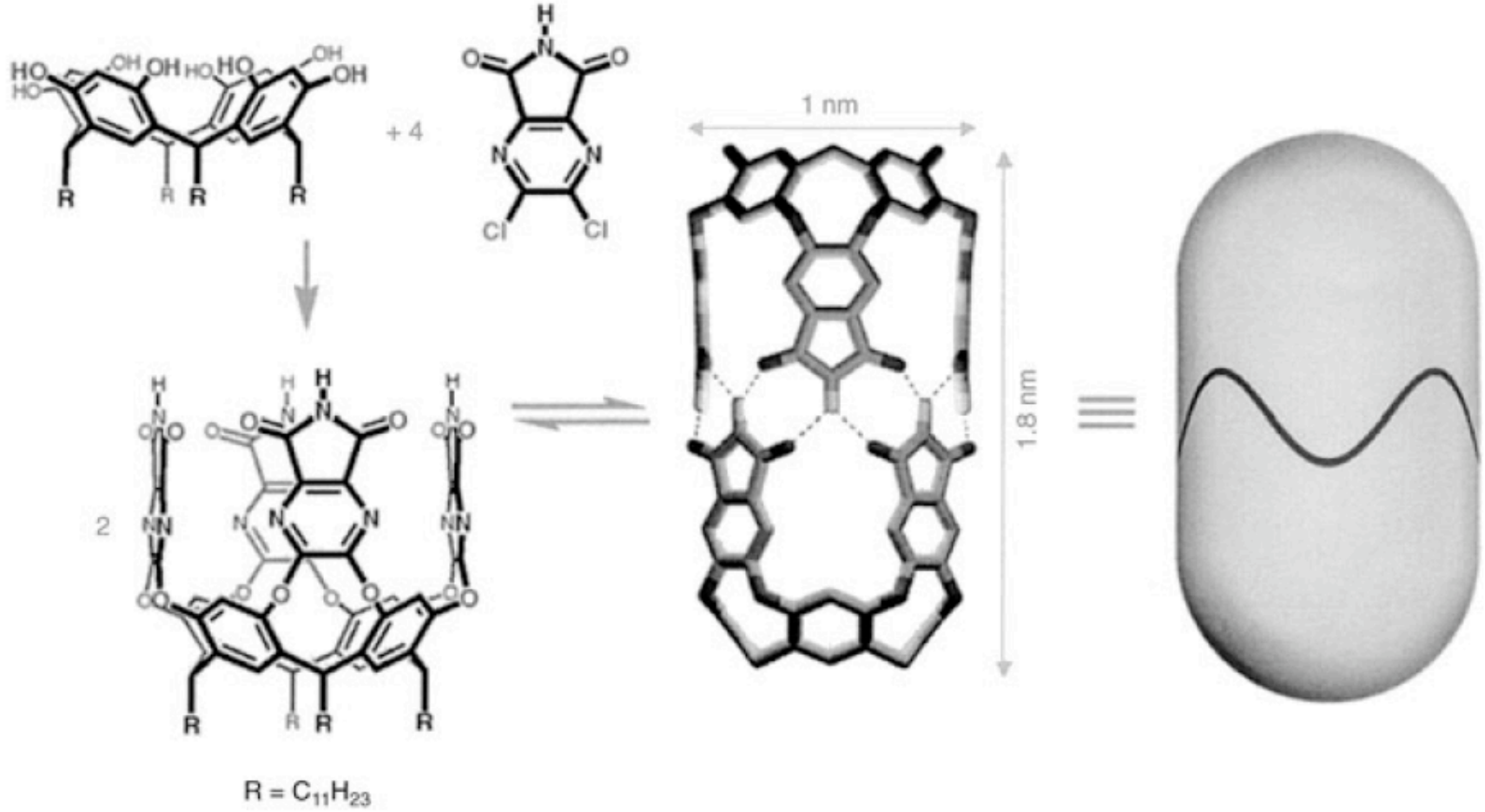


Showcasing modern model calcluations technology, Still and coworkers were able to optimize this host from initial enantioselections of 20-40% ee to ~70% ee

Liu, R., Sanderson, P., Still, W., *J. Org. Chem.,* **1990**, *55*, 5184

Encapsulation Era

- Advances in predictive modeling technology as well as 2D NMR techniques have propelled progress in this area far beyond the days of mere molecular recognition



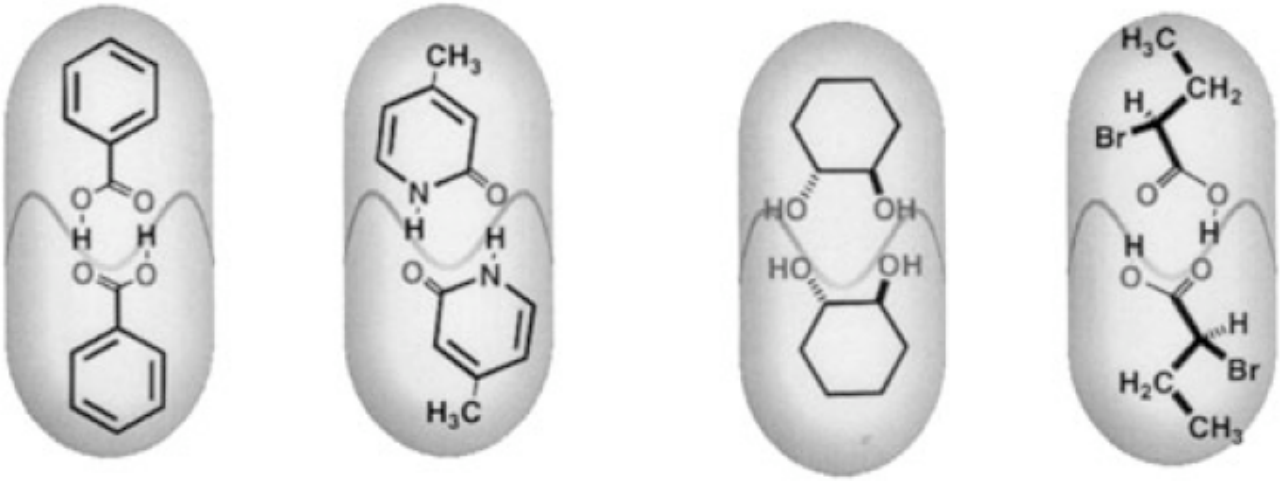
By employing arrays of purposefully positioned H-bond donors and acceptors, researchers have been able to “synthesize” the large, self-assembling structures (>400 Å)

Rebek, J., *Angew. Chem. Int. Ed. Engl.*, **2005**, *44*, 2068

Frontiers of Encapsulation Era

- These self-assembling capsules employ the same non-covalent interactions to bring together multiple guest molecules within these hosts

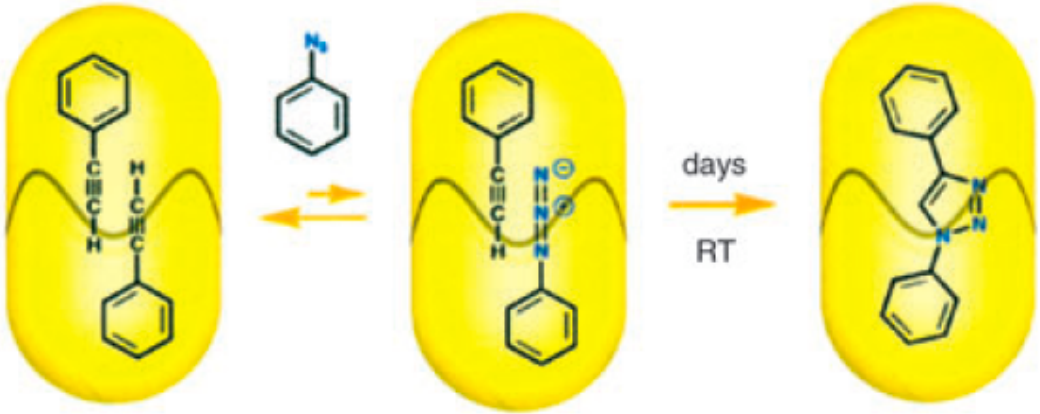
H-bond dimers



chiral spaces

- When complementary guests assemble together within a capsule, accellerated reactivity can occurr in a similar manner to the induced proximity effect created within an enzyme

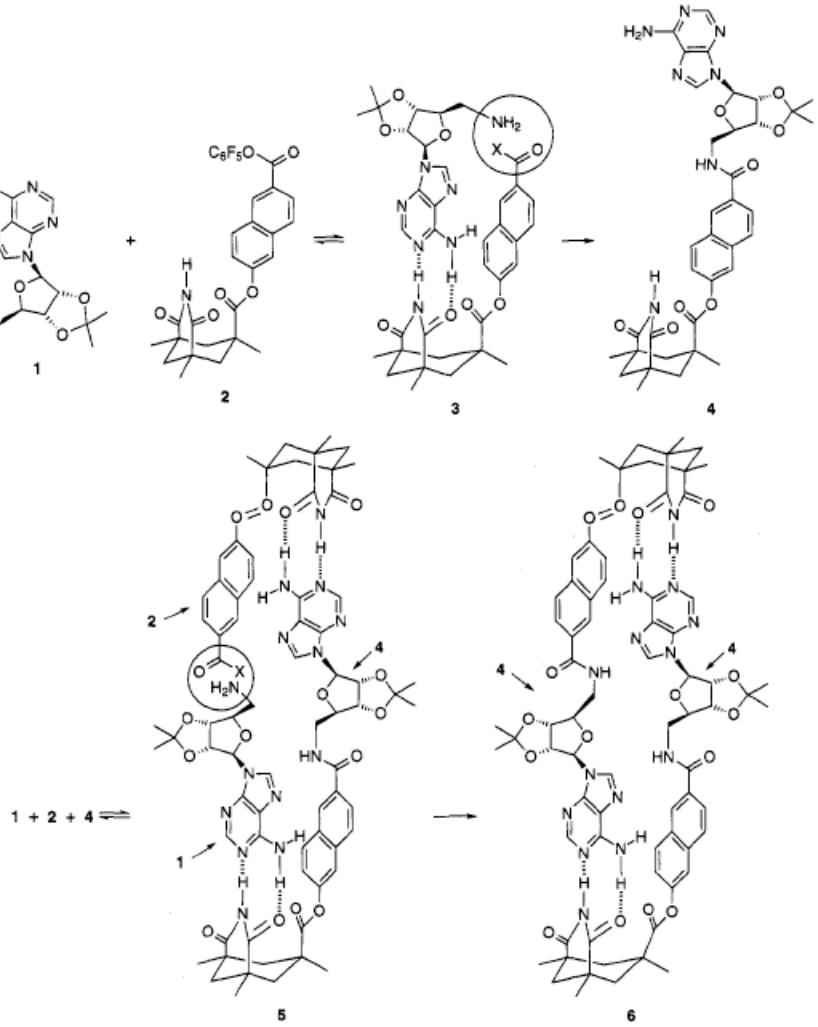
Click chemistry

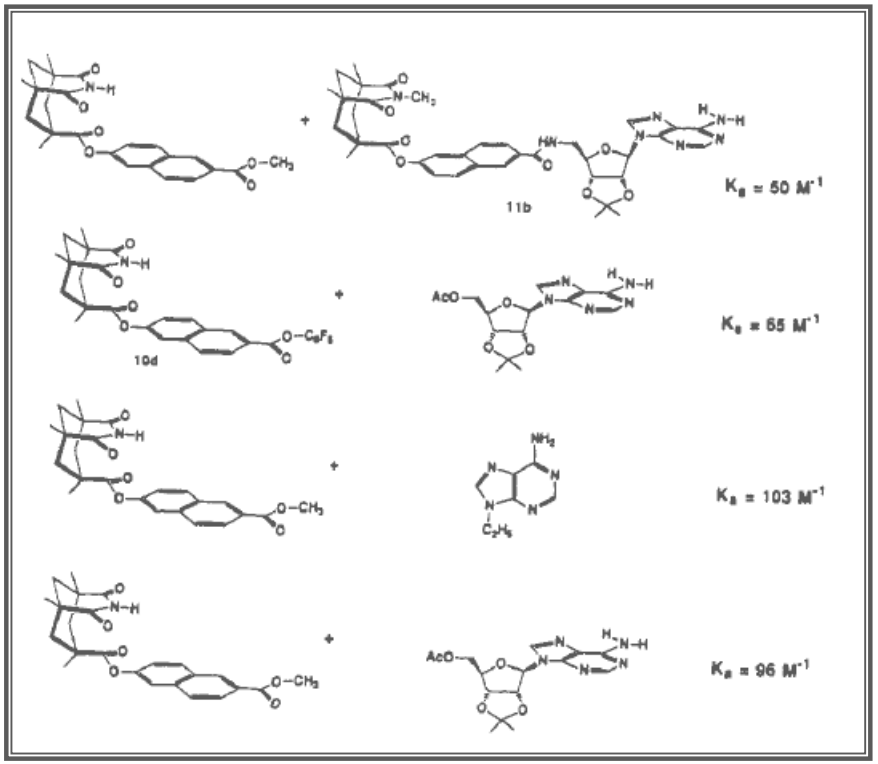


Rebek, J., *Angew. Chem. Int. Ed. Engl.*, **2005**, *44*, 2068

Mimicking Life: Self-replication

- After synthesizing a Kemp's acid template containing adenosine spacers, Rebek observed significant rate enhancement and proposed a mechanism involving the first synthetic, self-replicating system



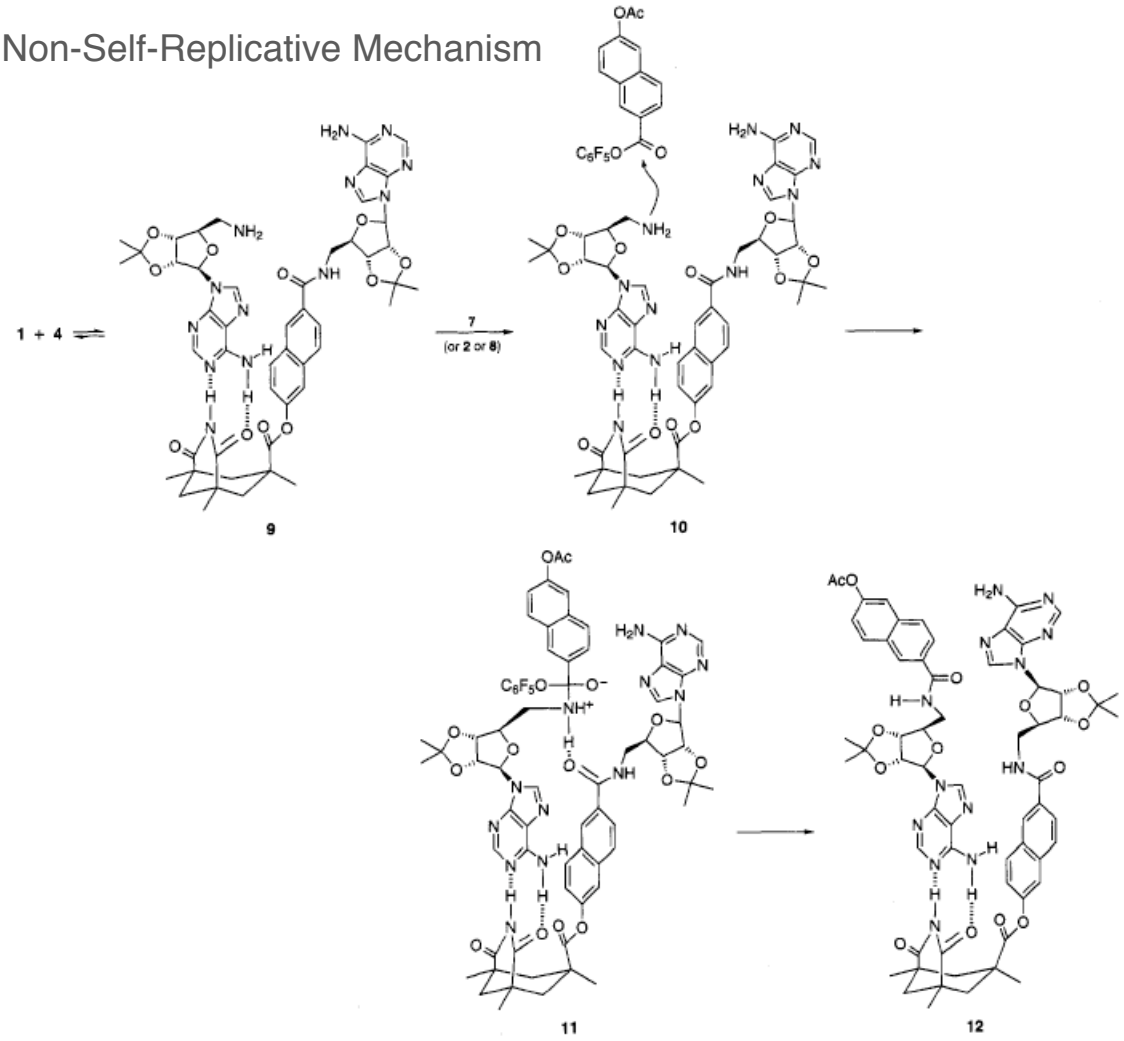


Nowick, J., Feng, Q., Tjivikua, T.,Ballester, P., Rebek, J., *JACS,* **1991**, *113*, 8831

Self-replication refuted?

- In a controversial series of articles, Rebek and Menger disputed the nature of the proposed mechanism of this allegedly, self-replicating system

Menger's Non-Self-Replicative Mechanism

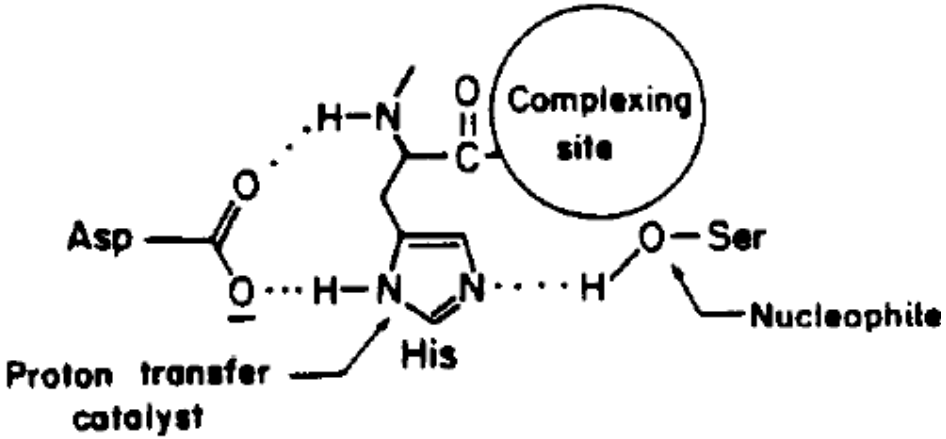


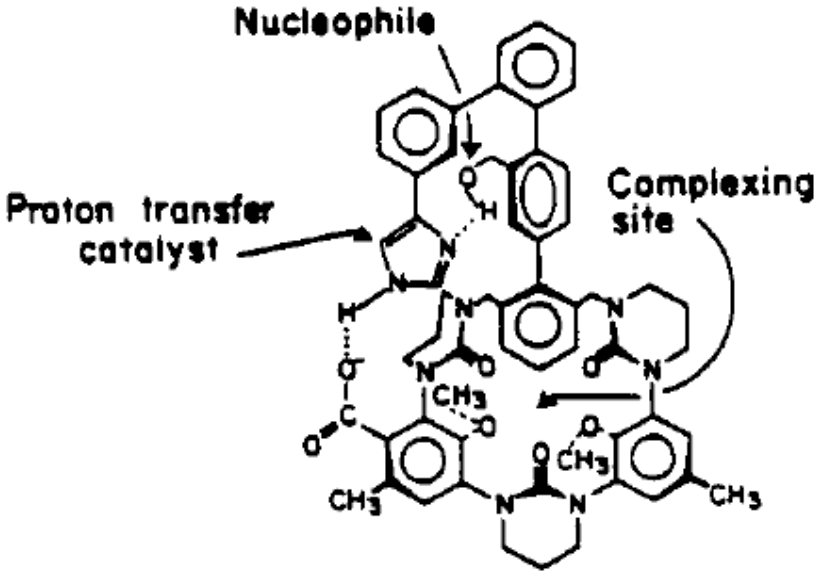
Menger, F., Eliseev, A., Khanjin, N., Sherrod, M., *JOC,* **1995**, *60*, 2850

Catalytic Triad Mimics

- Early attempt to mimic the cooperative catalysis exhibited in nature within the serine proteases

Active site of chymotrypsin combines a binding pocket, nuclepholic hydroxyl, imidazole, and carboxyl group in a preorganized array of H-bonded amino acids





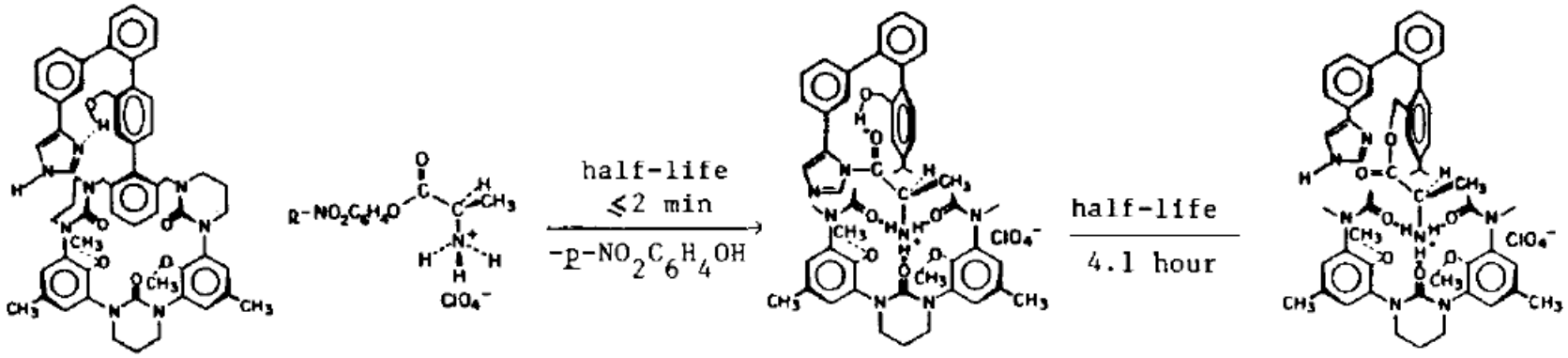
proposed enzyme mimic
after nearly a decade, a 30 step synthesis of a related analog was achieved

Few scientists acquainted with the chemistry of biological systems at the molecular level can avoid being inspired. Evolution has produced chemical compounds exquisitely organized to accomplish the most complicated and delicate of tasks. Many organic chemists viewing crystal structures of enzymes … must dream of designing and synthesizing simpler organic compounds that imitate working features of these naturally occurring compounds. -- Donald Cram

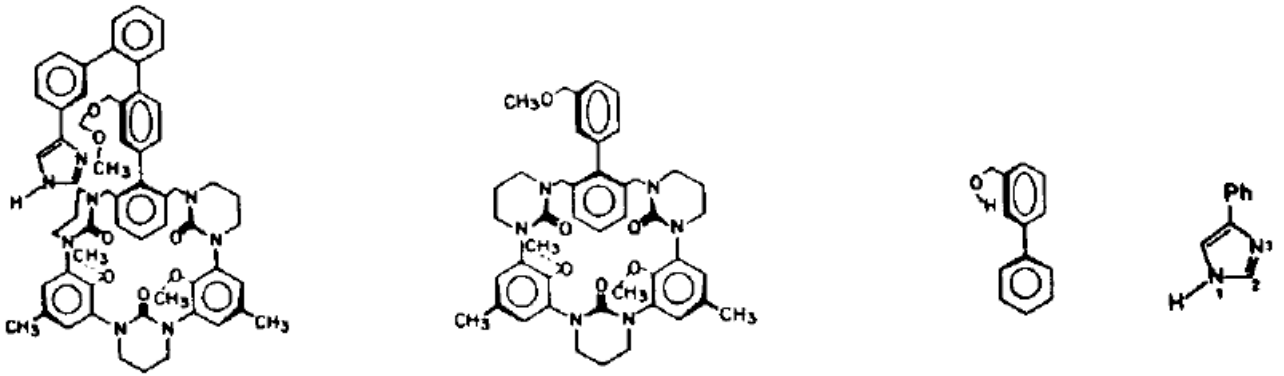
Cram, D., *Angew. Chem. Int. Ed. Engl.*, **1988**, *27*, 1009

Synthetic Catalytic Triads

- Artificial serine protease mimic exhibited significantly increased reaction kinetics for transacylation



- These kinetics correlated well with those of model systems including only some components of the triad



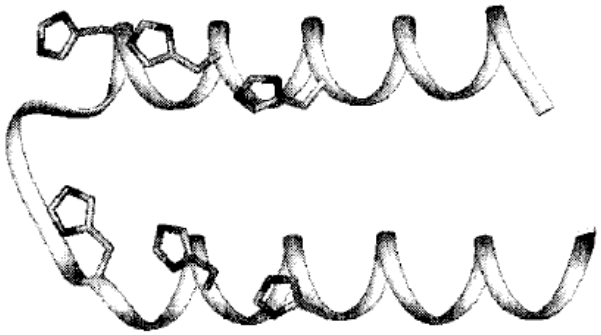
k_{rel}	10^{11} (10^5 if complexation is factored out)	10	1

Cram, D., *Angew. Chem. Int. Ed. Engl.*, **1988**, *27*, 1009

Asymmetric Enzyme Mimics

- In order to fully mimic the chiral nature of naturally occuring catalytic triads, Baltzer synthesized de Novo 42 residue proteins with purposefully positioned histidines within the substrate binding site

Lars Baltzer

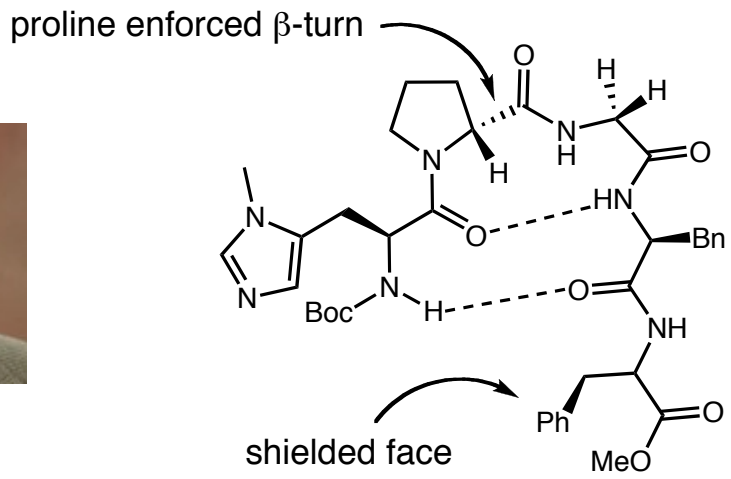


De Novo protein-catalyzed hydrolysis of esters are 230 times faster than catalysis via 4-methyl-imidazole alone

Broo, K., Nilsson, H., Nilsson, J., Baltzer, L., *JACS*, **1998**, *120*, 10287

- Hypothesizing that the immediate binding pocket was the only necessary structural feature, Miller showed that low molecular weight peptide chains of merely 5 amino acids could effect high enantioselectivity

Scott Miller



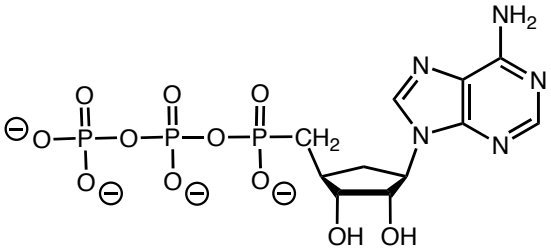
Catalytic, enantioselective

- acylations
- phosphorylations
- sulfinylations
- azidations
- Morita-Baylis-Hillman

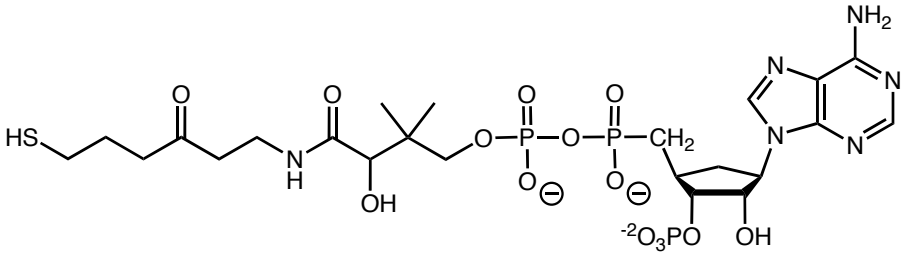
France, S., Guerin, D., Miller, S., Lectka, T., *Chem. Rev.*, **2003**, *103*, 2985

Coenzymes: Nature's Catalytic sites

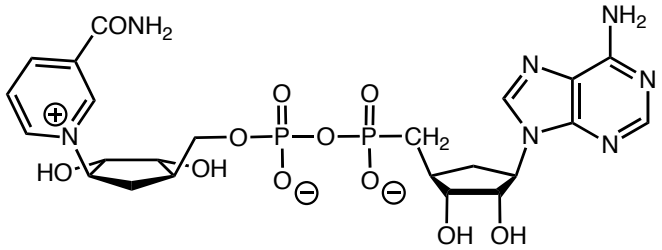
- A survey of some common coenzymes and their reactivities



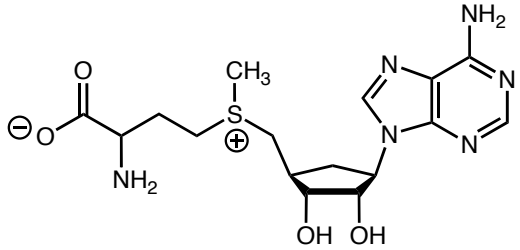
Adenosine triphosphate, ATP (phosphorylation)



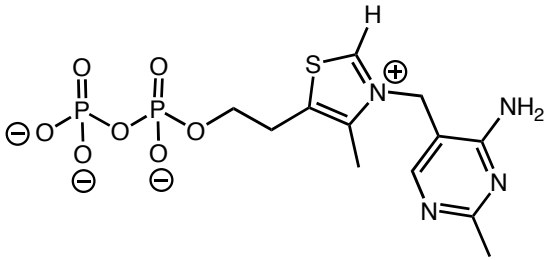
Coenzyme A (acyl transfer)



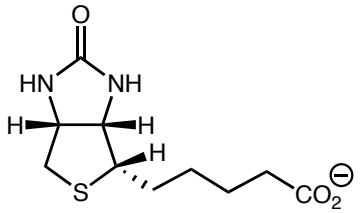
Nicotinamide adenine dinucleotide, NAD+ (oxidation-reduction)



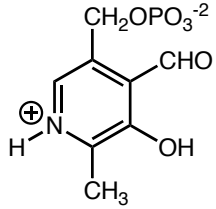
S-Adenosylmethionine, SAM (methyl transfer)



Thiamine diphosphate, TPP (decarboxylation)



Biotin (carboxylation)

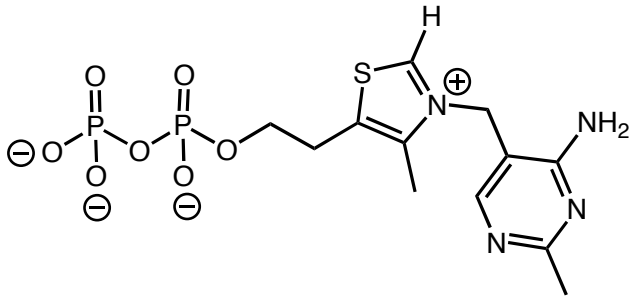


Pyridoxal phosphate (amino acid metabolism)

McMurry, J., Begley, T., *The Organic Chemistry of Biological Pathways*, 2005

Thiamine Diphosphate

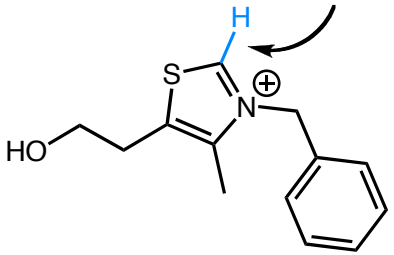
- By investigating numerous catalytic analogs, Breslow determined the key reactive ylid of TPP



thiamine diphosphate (TPP)

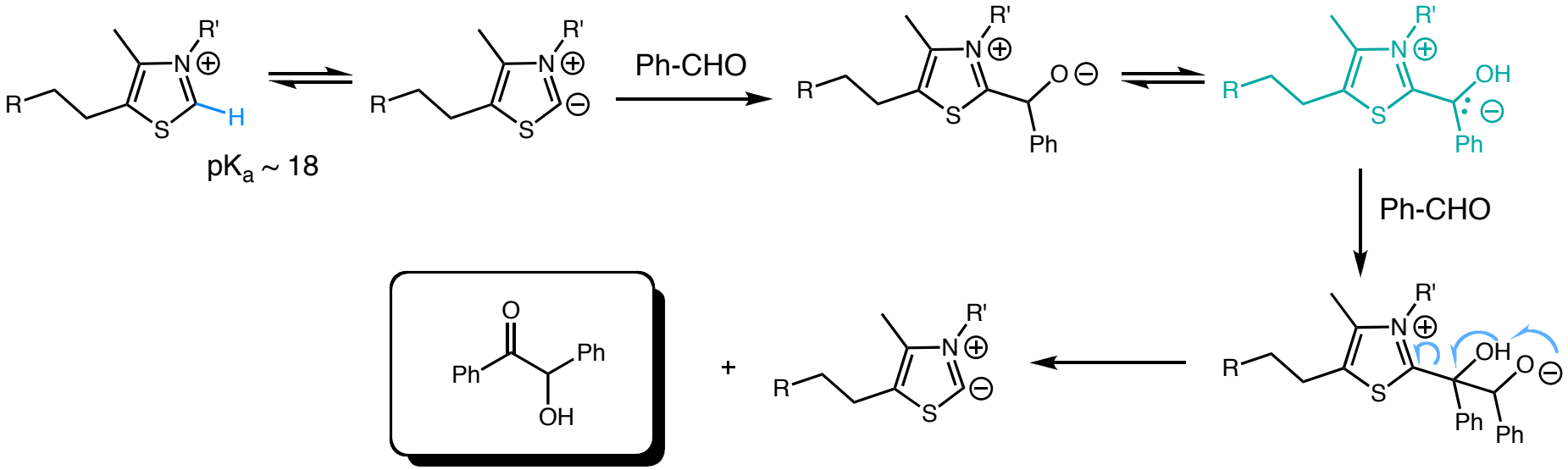
- pyruvate additions
- acyloin condensations

exchanges rapidly with D_2O



Breslow's thiamine analog

- This discovery then made possible elucidation of the TPP-catalyzed benzoin condensation mechanism

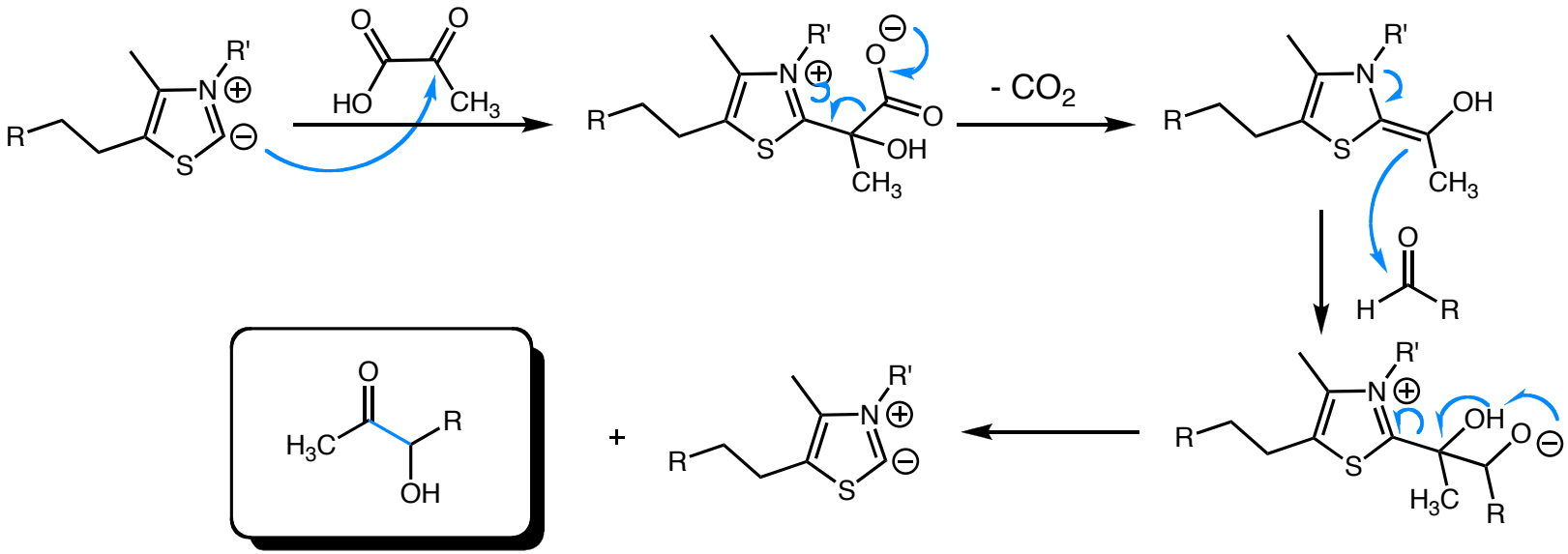


The highlighted acyl anion, or *Breslow intermediate*, is a staple of all TPP-catalyzed reactions in nature

Breslow, R. *JACS*, **1958**, *80*, 3719

Further Investigations of TPP

- By analogy, the mechanism of pyruvate addition via ylid-stabilized decarboxylation to acetaldehyde and attack on the resultant enolate was also elucidated.



One of nature's key
C-C bond forming reactions

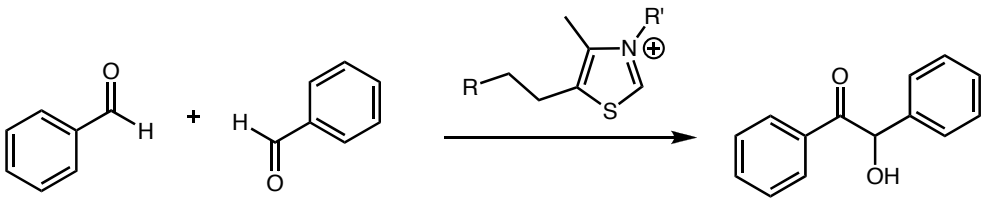
In elucidating such enzymatic mechanisms, chemistry complements biology with a molecular understanding of processes happening within the cell while also adding to her own repertoire of catalytic reactivity

Breslow, R. *JACS*, **1958**, *80*, 3719

McMurry, J., Begley, T., *The Organic Chemistry of Biological Pathways*, 2005

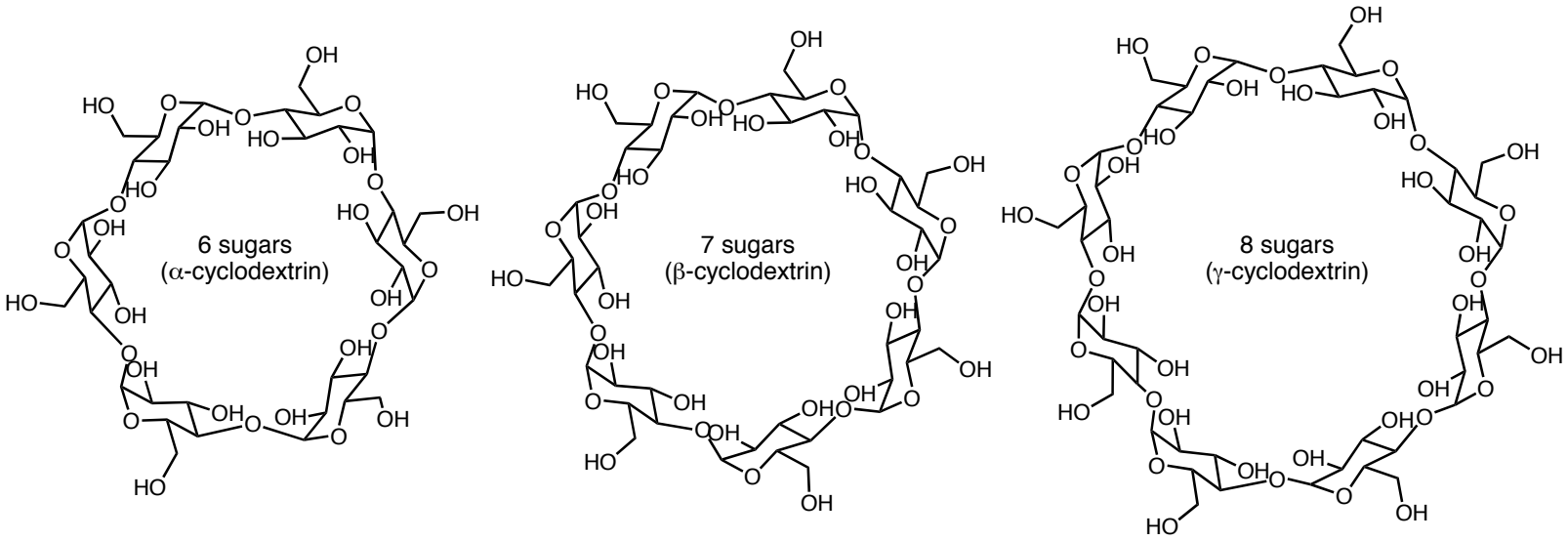
Enhancing Thiamin Catalysis

- By securing the non-reactive side chain of thiamin to a host, Breslow was able to accelerate the rate of reaction for the benzoin condensation



catalyst	k_{rel}
R=OH, R'=Et	1
R=β-CD, R'=Et	2
R=γ-CD, R'=Et	9
R=OH, R'=Bn	20
R=β-CD, R'=Bn	50
R=γ-CD, R'=Bn	150

- The structures of the cyclodextrin (CD) hosts are depicted below

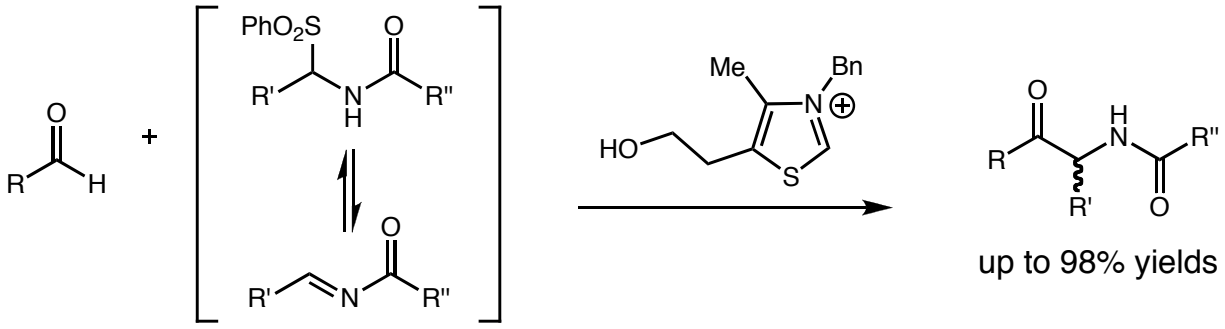


Rate acceleration by the larger γ-cyclodextrin ring is associated with this host's ability to create a larger hydrophobic environment for the benzoin reaction to occur

Breslow, R., Kool, E., *Tetraheron Lett.*, **1988**, *29*, 1635

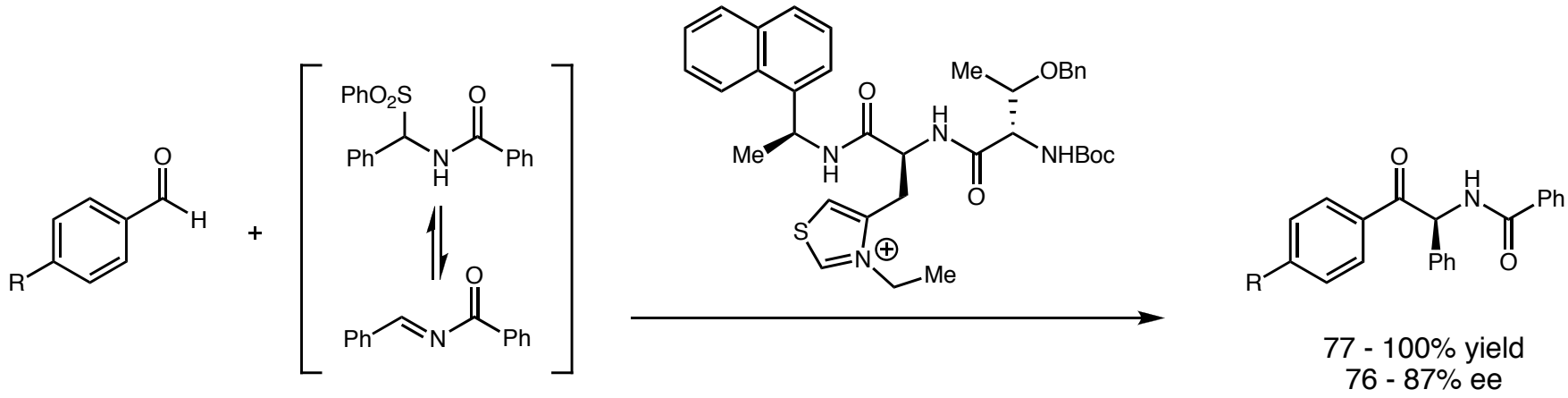
Asymmetric Thiamin Catalysis

- In analogy to the benzoin condensation and Stetter reaction, Merck was able to develop a thiazolium mediated reaction between acylimines and thiazolium-stabilized acyl anions



Murry, J., Frantz, D., Soheili, A., Tillyer, R., Grabowski, E., Reider, P., *JACS*, **2001**, *123*, 9696

- By securing a thiazolium derived amino acid onto a chiral host such as a peptide backbone, Miller was able to expand on these methodologies further to effect an enantioselective aldehyde-imine coupling



Stereoinduction is postulated to arise during the H-bond-stabilized transition state, which is defined by the geometry of the chiral peptide backbone

Mennen, S., Gipson, J., Kim, Y., Miller, S., *JACS*, **2005**, *127*, 1654

Conclusion

- Enzymatic catalysis is an aggregate of weak, non-covalent interactions that sum to a larger stabilizing effect
- These electrostatic forces consist of fundamental interactions that we already know and understand
- It is possible to devise simple (and complex) systems to imitate the stabilizing forces of enzymes
- High enantioselectivity requires only small differentiation in $\Delta\Delta G^{\ddagger}$ among competing pathways
- Chemical investigations of biological systems can offer unique insights into their mechanistic understanding
- Nature has optimized her synthetic toolbox over eons and we would do well to try to imitate her