

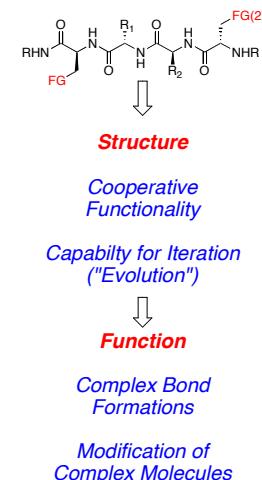
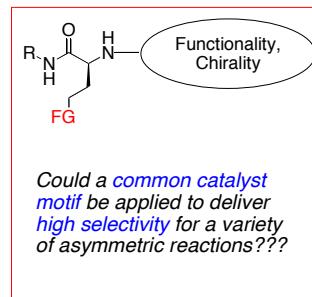
A "Biomimetic" Approach
to
Asymmetric Synthesis

Scott J. Miller
Yale University

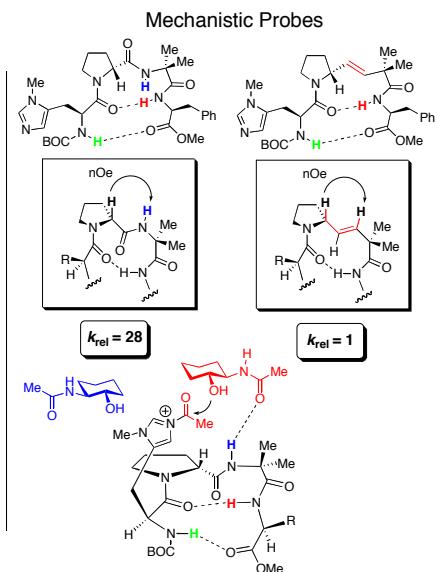
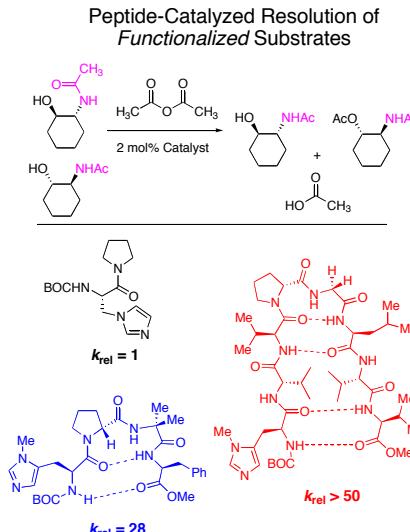
IASOC Conference, September 17, 2006

Some Elements of a "Biomimetic" Approach

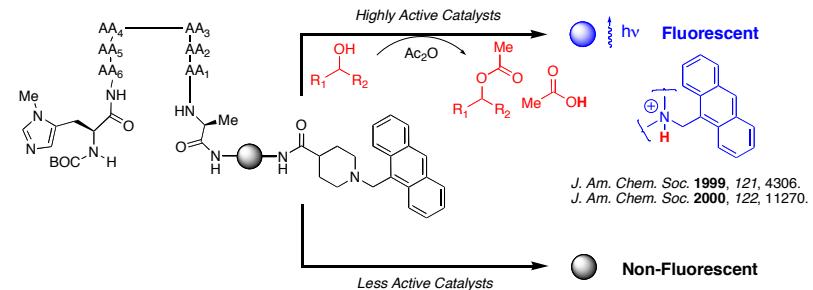
Thoughts Concerning the Apparatus of Biosynthesis



Enantioselectivity as a Model System



Diversity-Based Approach with a Reactivity-Based Assay



Split and Pool Library Features

14 Protected Amino Acid Monomers
D-Val, D-Phe, D-Pro, L-Ile, L-(O-t-Bu)-Tyr, L-(trt)-Gln
D-Ala, L-(trt)-Asn, Gly, Alb, L-(O-t-Bu)-Asp,
L-(BOC)-Irp, L-(trt)-His
D-(O-t-Bu)-Glu

Theoretical Diversity

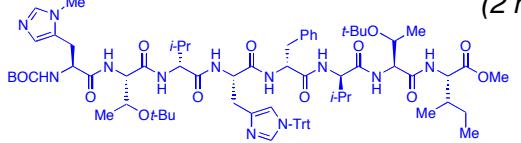
$14^6 = 7,529,536$ Possible Catalyst Candidates

Actual Diversity (5 g of 500 μm beads):

~100,000 Different Catalysts Represented

Kinetic Resolutions with Other Substrates and "Hit" Catalyst

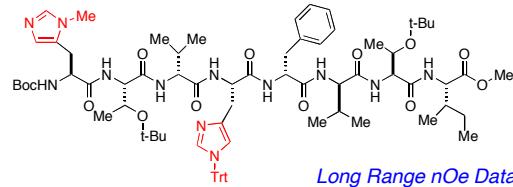
(2 mol%, -65 °C)



Racemic Substrate	Preferred Product Enantiomer	k_{rel}
		20
		>50
		16
		11

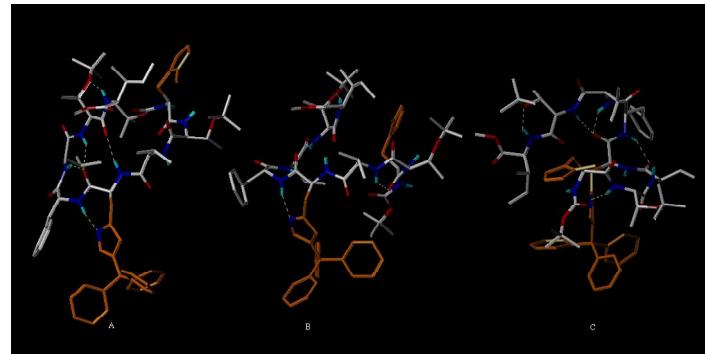
J. Am. Chem. Soc. 2001, 123, 6496-6502.

Three Dimensional Conformation of New Peptide Catalyst



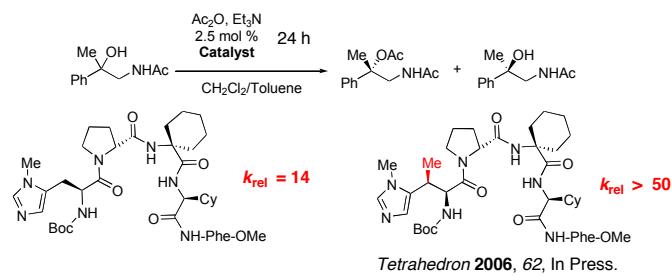
With:

Prof. Daniel O'Leary (Pomona College)
Prof. Wayne Steinmetz (Pomona College)
J. Am. Chem. Soc. 2004, 126, 6967-6971.

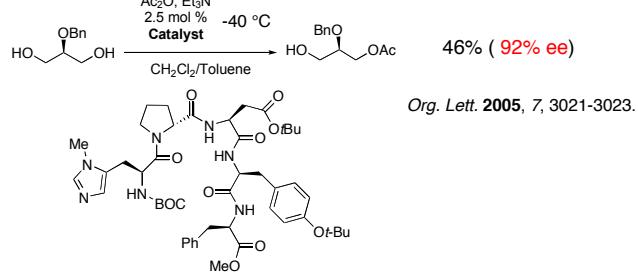


Can Catalysts be Found for Any Substrate?

Tertiary Alcohols



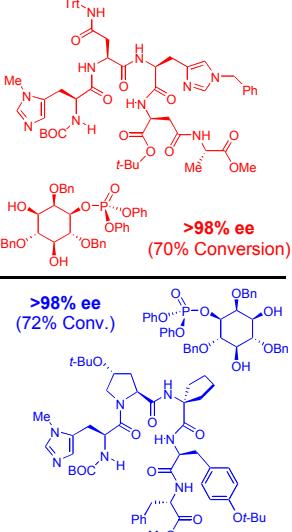
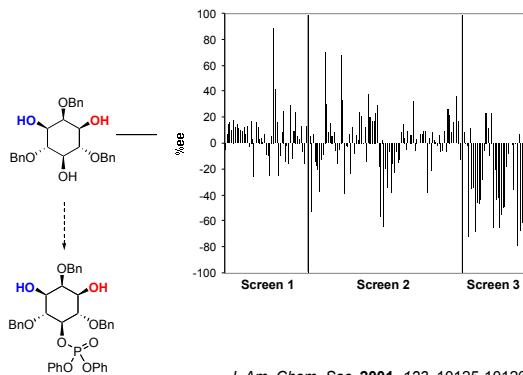
Primary Alcohols

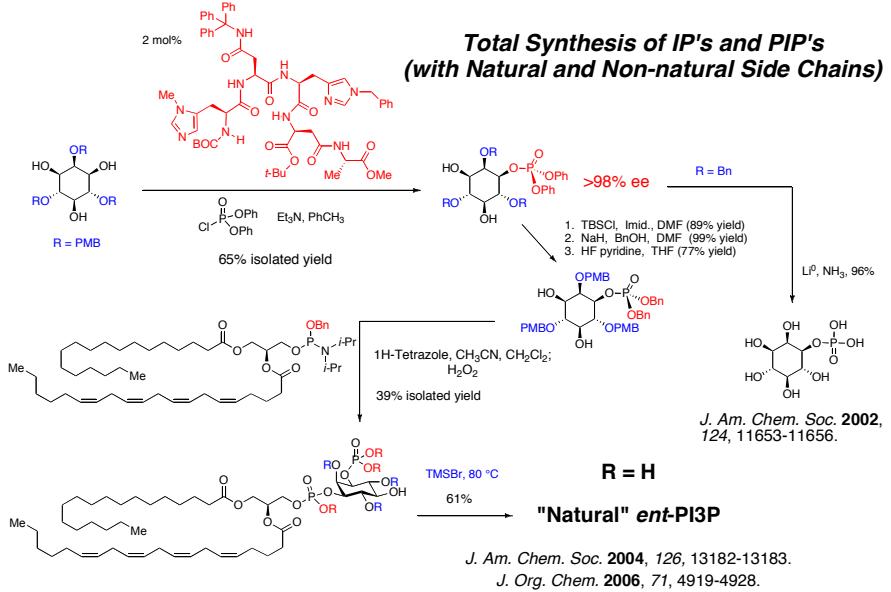


Desymmetrization via Phosphorylation Catalyst Screening

Resynthesis and Rescreening Data:

178 Peptide Screen: Unoptimized ee's



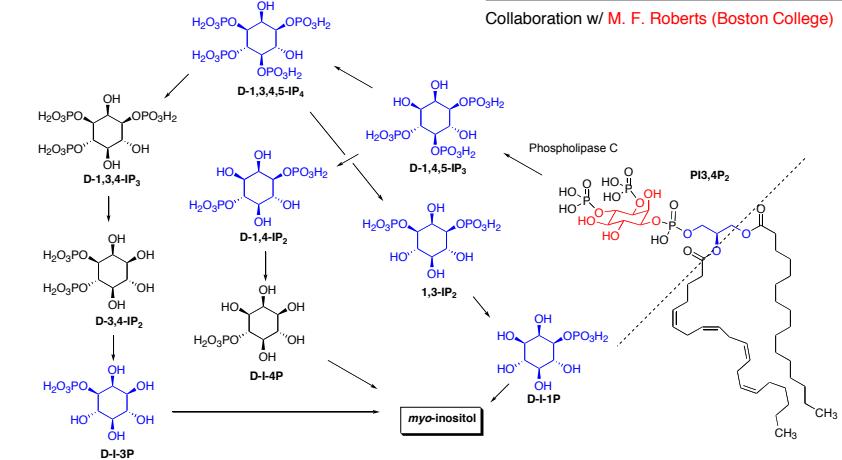


Can Streamlined Syntheses Elucidate Chemical Biological Questions?

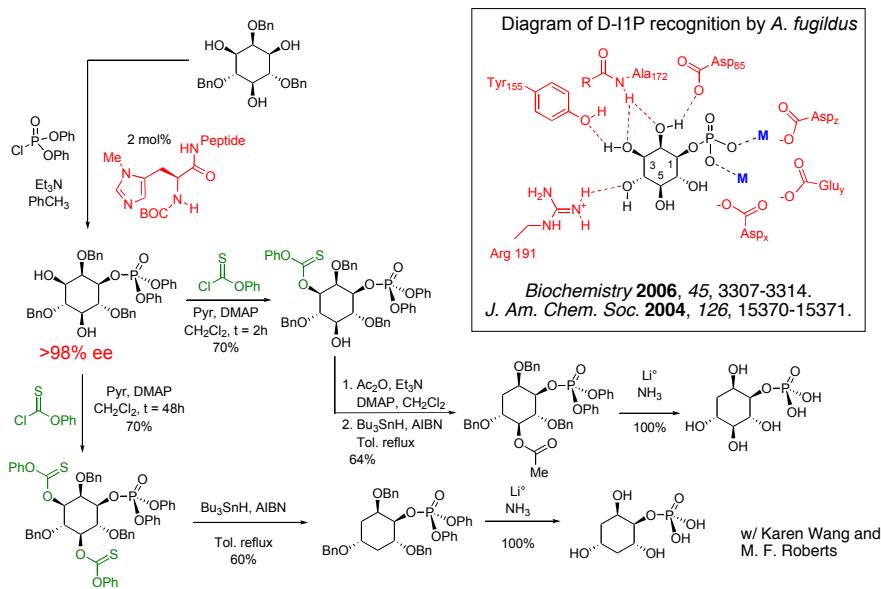
Inositol Phosphate-Based
Signal Transduction

Berridge, M.J.; Irvine, R.F. *Nature*, 1984, 312, 315-321

Collaboration w/ M. F. Roberts (Boston College)

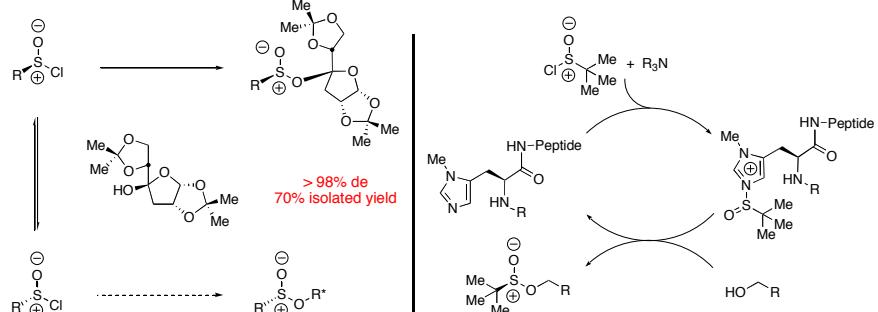


Synthesis of Deoxy-IP'S and Mechanistic Probes



Enantioselective Sulfinyl Transfer:

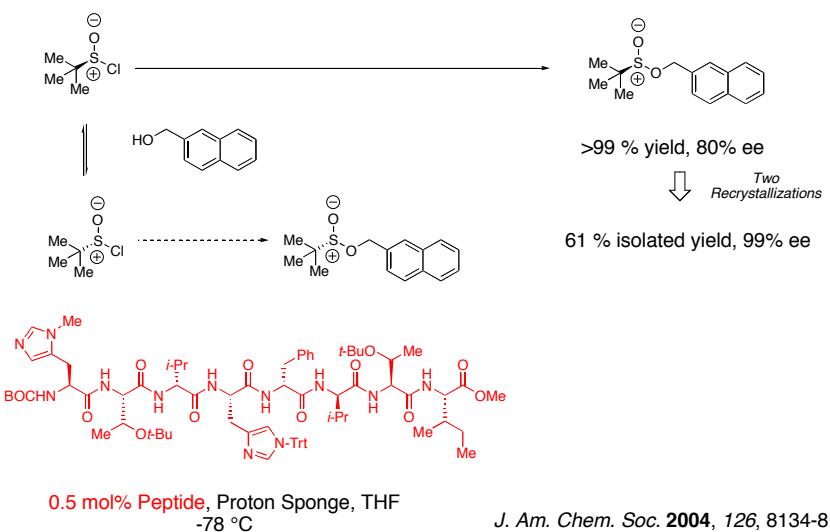
A Case of Dynamic Kinetic Resolution



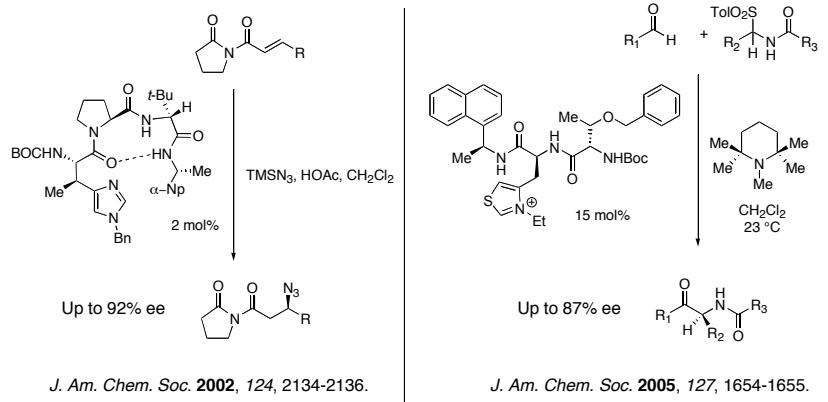
See:

Fernandez et al. *J. Am. Chem. Soc.* 2000, 122, 7598.

Enantioselective Sulfinyl Transfer: A Case of Dynamic Kinetic Resolution



Other Reactions - Other Mechanisms



Two-Catalyst Asymmetric Baylis-Hillman Reactions

