

HIGHLIGHTS OF THE GPCR HETEROCYCLIC TEMPLATES + WITH K. SEUTNER

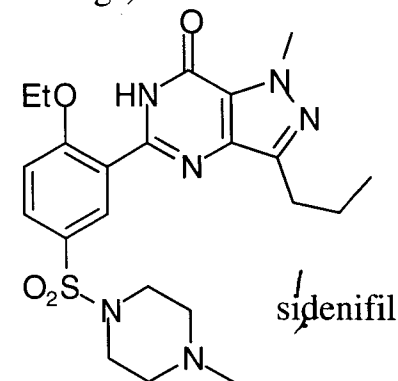
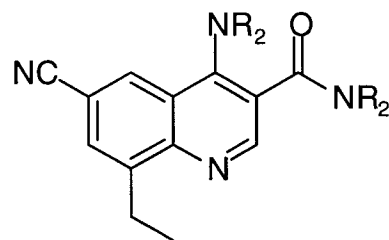
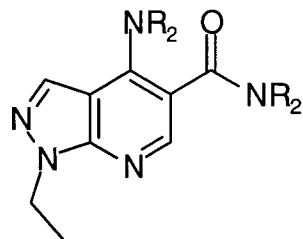
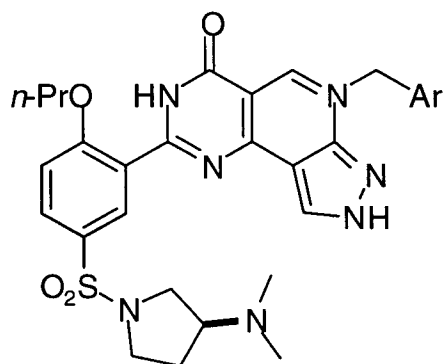
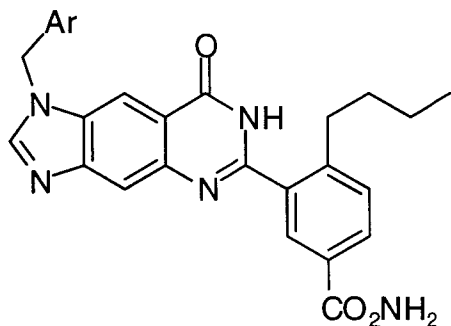
COMPOUNDS 2101 214601

John Macor, Bristol Myers Squibb

The Discovery of Multiple Heterocyclic Templates Producing Sub-Nanomolar PDE5 Inhibitors
(Viagra analogs)

- sildenafil (Pfizer) has poor selectivity for other PDE enzymes which are involved in the regulation of cyclic GMP

- BMS analogs:

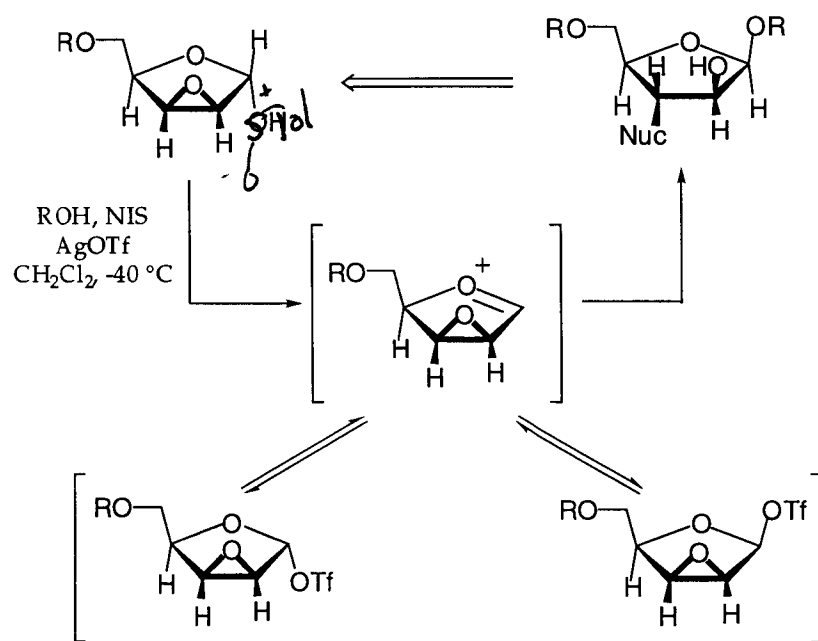
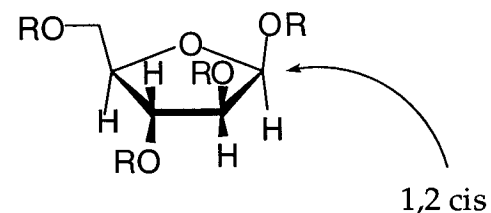


- Most lead compounds show moderate to good selectivity and the activities are comparable to sildenafil

Todd Lowery, Ohio State University

Highly Stereoselective Glycosylations via 2,3-anhydrosugar derivatives

- 1,2 trans linkages are 'easy' due to protecting group participation
- 1,2 cis linkages are 'hard' to control

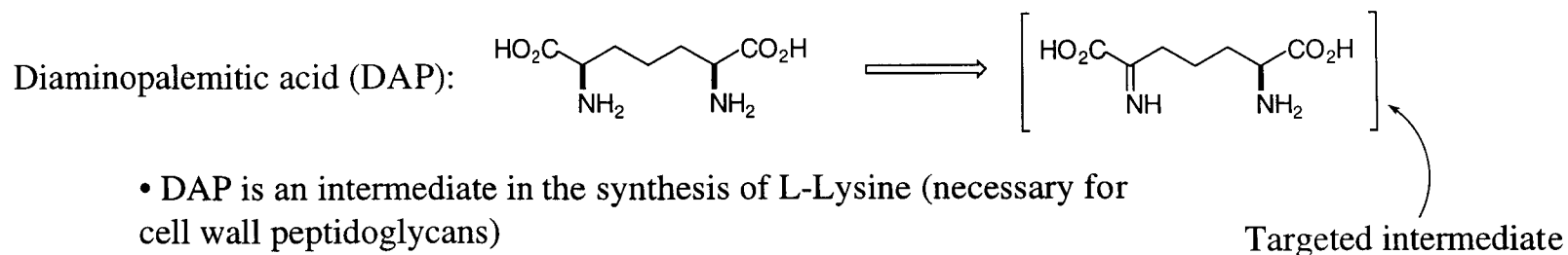


α -triflate is preferred

- Glycosyl acceptor approaches from the same face as the epoxide
- α/β configuration depends on the epoxide configuration
- epoxide is opened by glycosyl acceptor in some cases
- moderate regioselectivity selectivity ($\sim 3/1$) in separate epoxide opening

John Vederas, University of Alberta

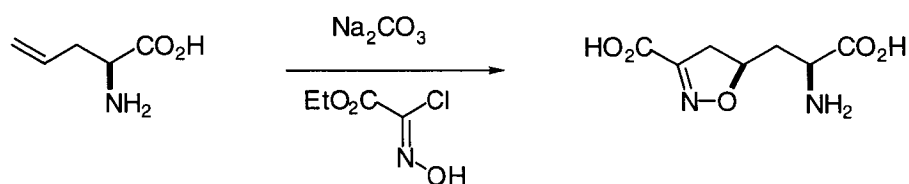
Heterocyclic Amino Acids as Inhibitors of the Diaminopimelate Pathway to L-Lysine



- DAP is an intermediate in the synthesis of L-Lysine (necessary for cell wall peptidoglycans)

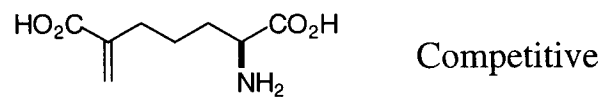
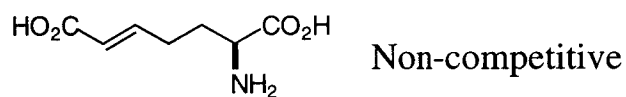
- The enzymes involved are not found in mammalian cells

Nitrile oxide [3+2]:

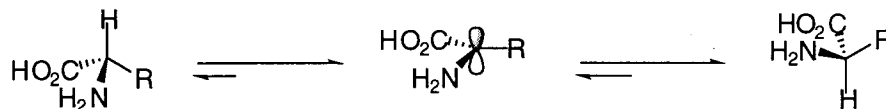


Compound is not competitive with DAP
-binds in a different manner (wrong end)

Others:

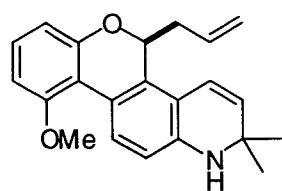


- Also investigates DAP epimerase:



Yi-Yin Ku, Abbott Laboratories

Asymmetric Synthesis of A-240610 via Atropisomeric Control of Axial Chirality

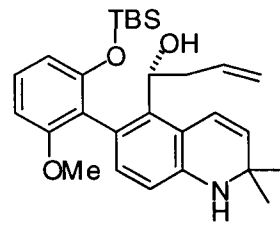
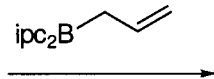
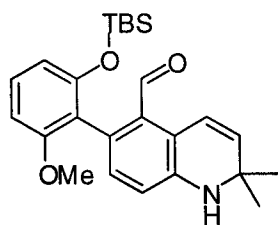


Lead compound for steroidal receptor (for anti-inflammatory agent)

Med. Chem.

Suzuki coupling, Sn-allylation, separation of enantiomers

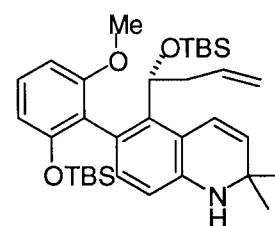
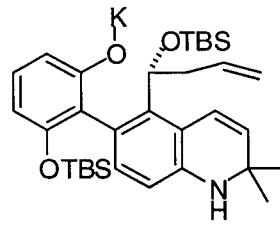
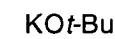
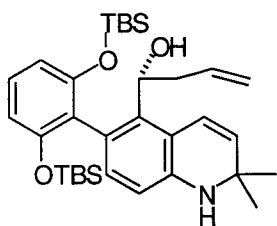
Process:



90% de (1/1 atropisomer)

Could cyclize only one isomer, the other eliminated

Solution:



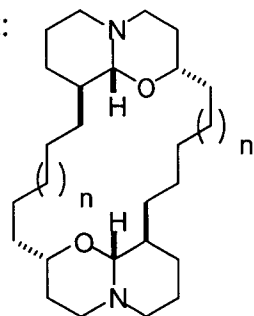
1) Deprotect

2) Cyclize

A-240610

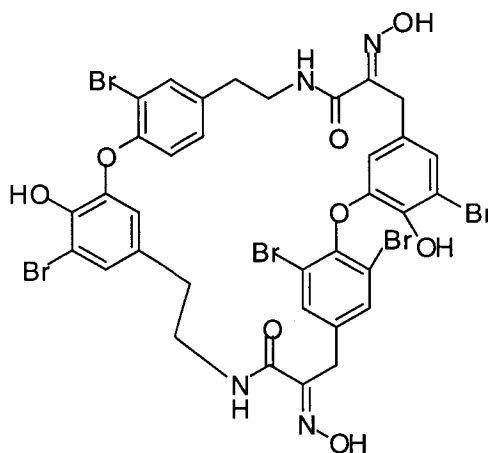
Tadeusz Molinski, University of California, Davis
Marine-Derived Heterocycles: Nature Drives Discovery

Ca^{2+}
 Ca^{2+} channel antagonist:



- 2,9-Bisoxaquinolizidines
- wide number isolated differing in conf. and chain length
- compounds bind to ion channel not to the corresponding receptor

Ca^{2+}
 Ca^{2+} channel agonist:

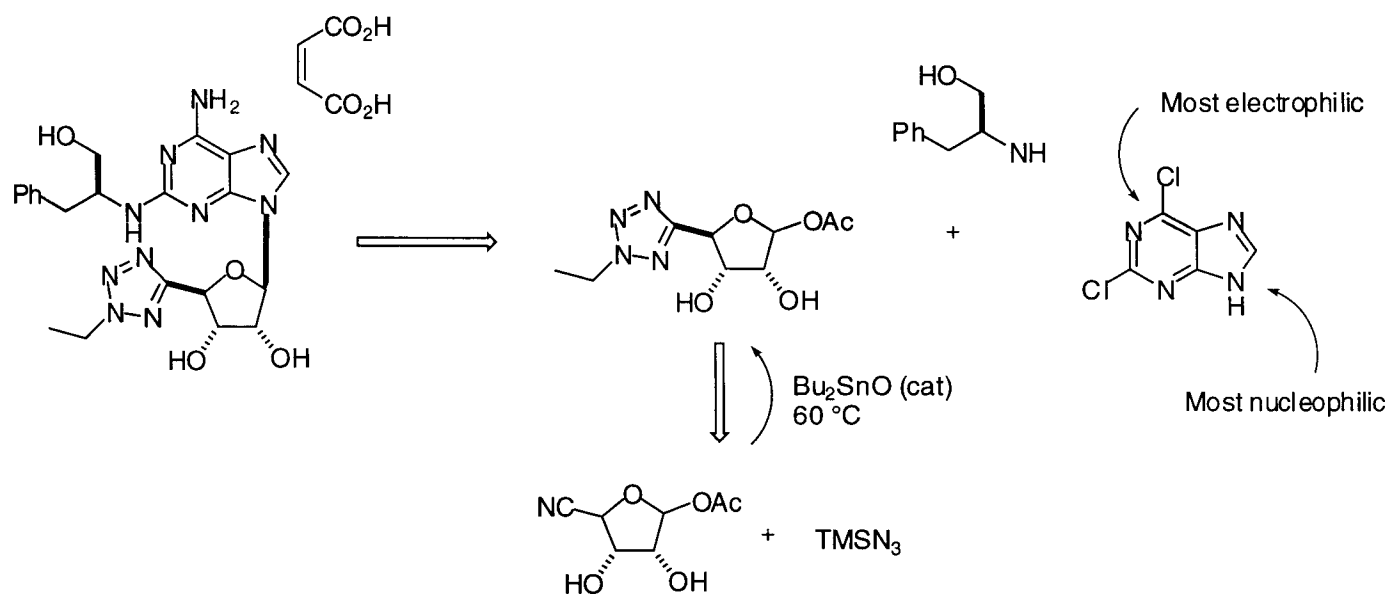


- Bastadin 5

Thomas Roper, GlaxoWellcome

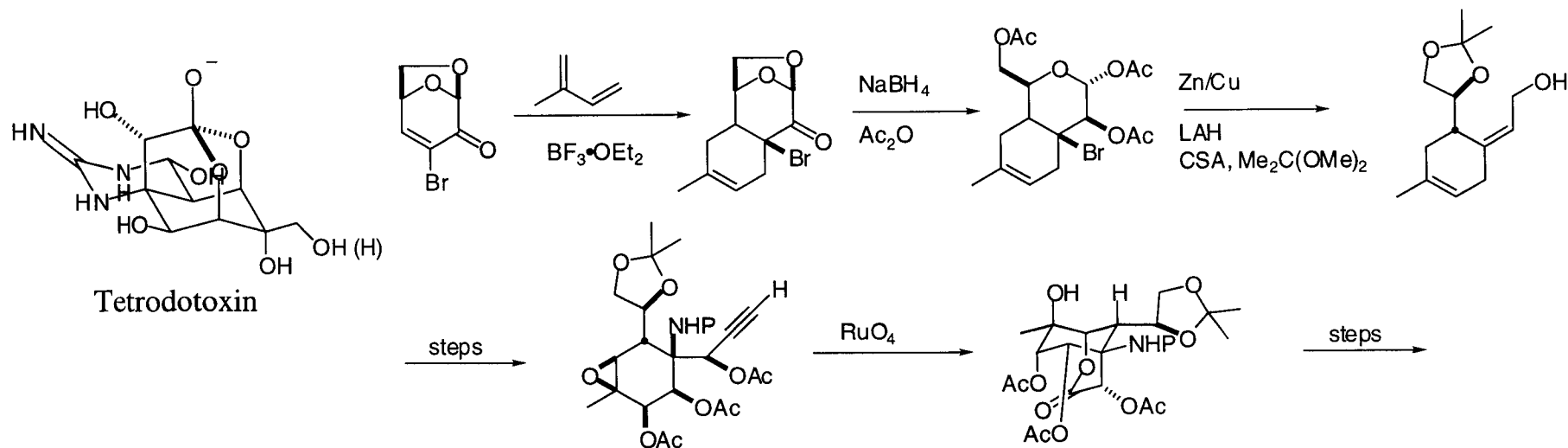
Convergent Synthesis of Adenosine A2a Agonists: New Approaches to 2-Alkylaminoadenosines

Adenosine-PA maleate - powerful anti-inflammatory agent



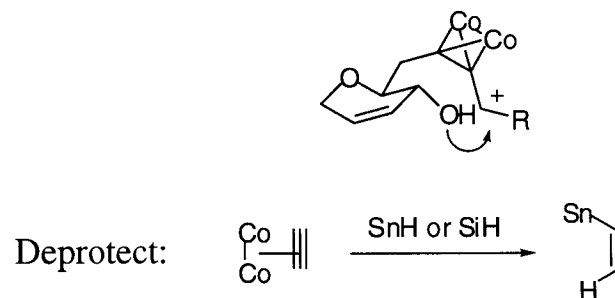
Minoru Isobe, Nagoya University

Synthesis of Marine Toxins



Ciguatoxin -fused polycyclic ethers

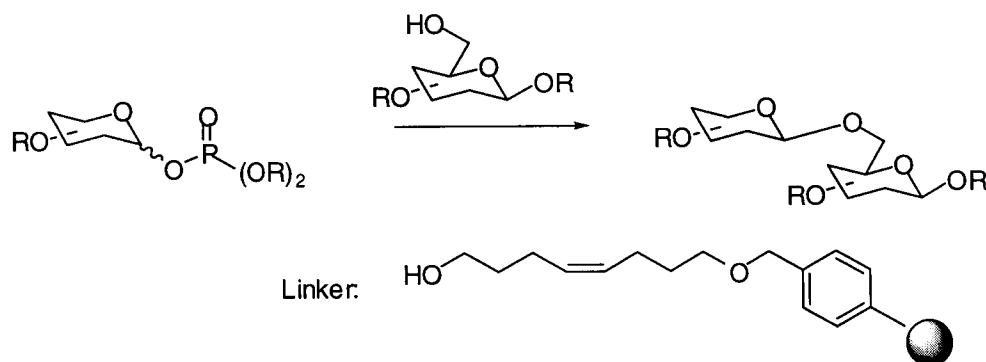
- Uses Nigishi coupling two couple two halves
- For medium size rings, uses Co-Co group to protect/ bend alkyne to improve closure



Peter Seeberger, MIT

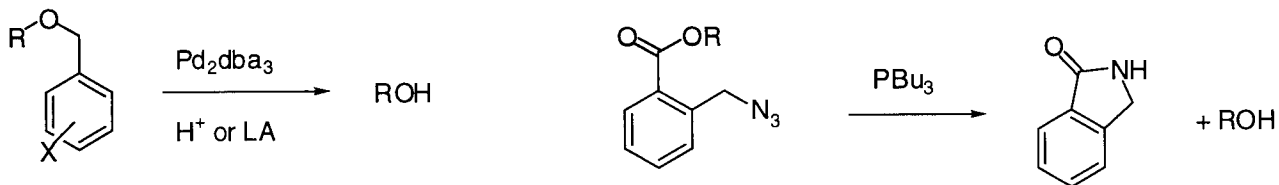
Automated Synthesis of Oligosaccharides and Glycosaminoglycans

- Linking glycosyl acceptor to solid phase allows excess donor, higher yields



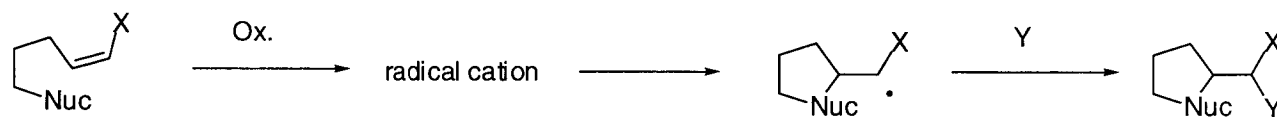
Can cleave linker via Olefin Cross Metathesis

- Interesting protecting groups:

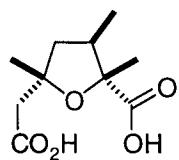


Kevin Moeller, Washington University

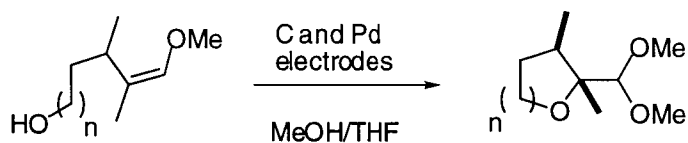
Reversing the Polarity of Enolate Equivalents: Developing an Efficient Route to (+)-Nemorensic Acid



Towards:



Acid group associated with necine



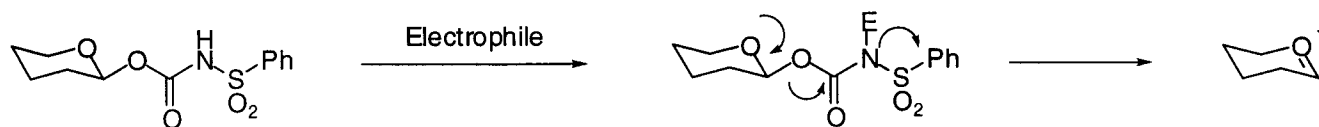
- Good yield when $n = 1, 2$
- No product when $n = 3$
- ~3/1 selectivity with $n = 1$ (1/1 with $n = 2$)

Enol configuration is unimportant as the radical cation is not conformationally stable

Laura Kiessling, University of Wisconsin, Madison
Synthesis of Functional Oligosaccharides and Glycoproteins

- Synthesis of oligosaccharides crosslinked by Ring Opening Metathesis
- The proximity of activators brings cellular receptors in close proximity
- Polymerized activators provide larger responses than unpolymerized activators at the same conc.
 - There is an additive effect of bringing receptors together
 - Can tune polymerization to achieve optimal spacing

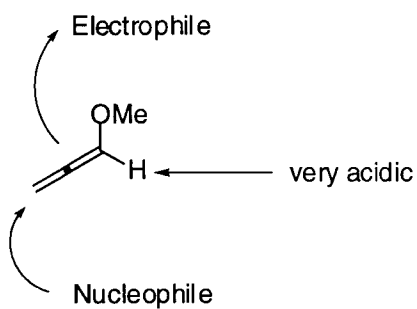
Advances to safety-catch activator:



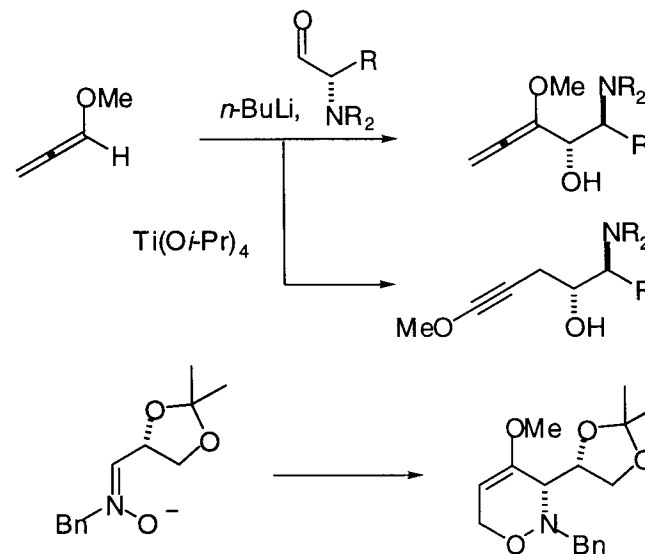
W/o E - low reactivity
W/ Me - mod reactivity
W/ CH_2CN - mod reactivity
W/ Allyl - high reactivity

Hans Reissig, Free University of Berlin

Stereoselective Synthesis of Heterocycles via Metallated Alkoxyallenes



- Versatile reagent for heterocyclic synthesis



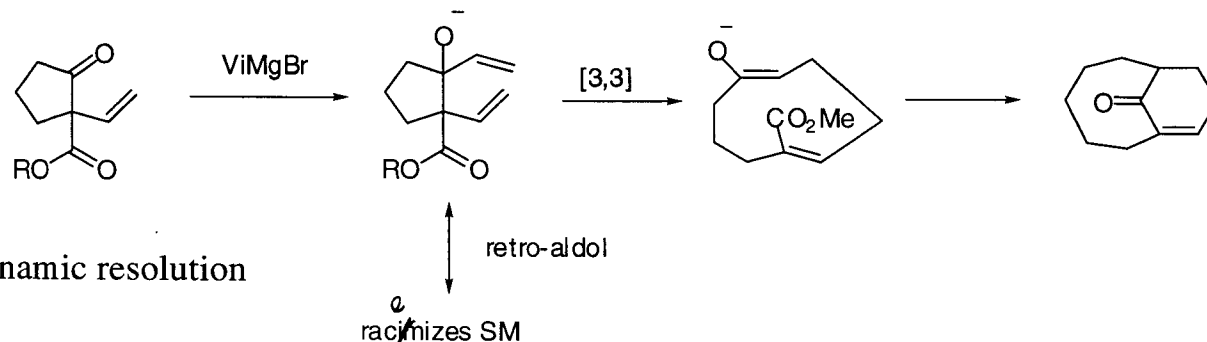
- Choice of metal determines α vs γ reaction
- Can also add to nitrones, imines

- Chiral allenes do not give good differentiation in addition reactions
- Needs to use a chiral auxilliary (sugar based in place of OMe)

Matthew Shair, Harvard University

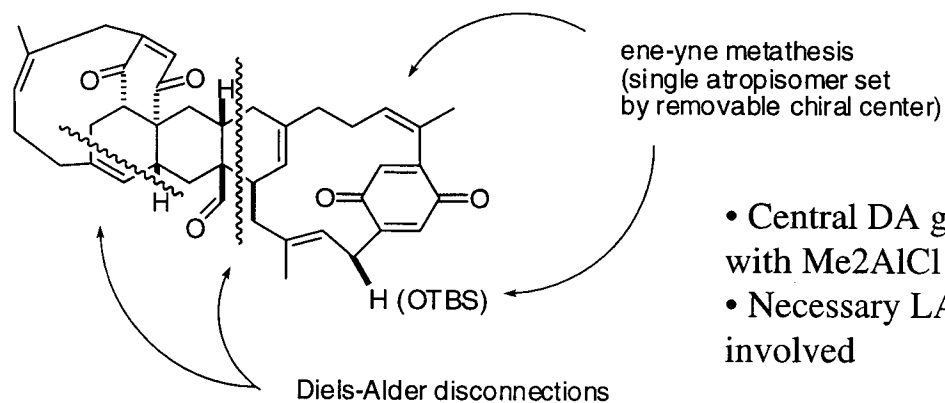
From Target-Oriented Synthesis to Diversity-Oriented Synthesis and Their Use in Exploring Cell Biology

Work towards the CP molecules:



Retro-aldol may allow for dynamic resolution

Lingithorone A:



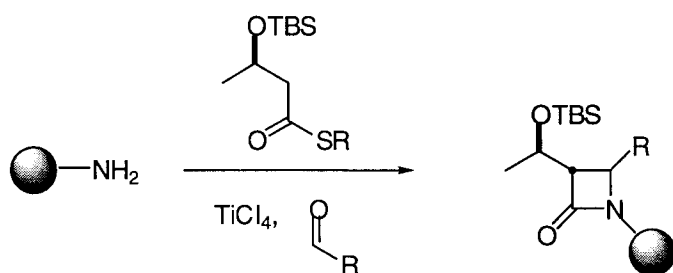
- Central DA goes with 3/1 selectivity (facial) with Me₂AlCl
- Necessary LA suggest Diels-Alderase may be involved

Divergent synthesis: Combi-chem based on the core structure of know natural product (for other uses)

Franco Cozzi, University of Milan

Poly(ethylene glycol)-supported Synthesis of Heterocycles and Chiral Heterocyclic Ligands and Catalysts

- PEG support:
- Soluable polymer support
 - Has low loading - can add dendridic linkers for inreased loadings



Selectivity is maintained on the polymer support

Can also use as supports for:

- Ammonium salts
- bisoxazoline ligands
- proline based catalysts

Eric Jacobsen, Harvard University

Target-Oriented Synthesis Based on Asymmetric Catalytic Methods

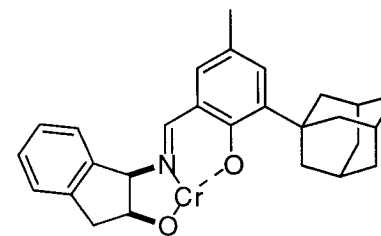
New salen ligands for hetero-Diels-Alder:



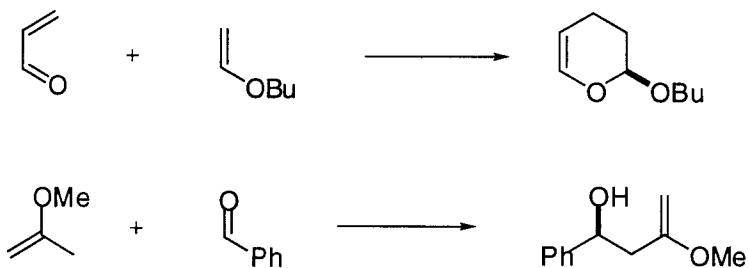
Does not work with: RCH_2CHO

- Suggests there is single point binding on the aldehyde
- Kinetics show 1st order in diene, catalyst
- Catalyst is dimer in solid state but no non-linear effect (only homochiral dimer)

Best Ligand:

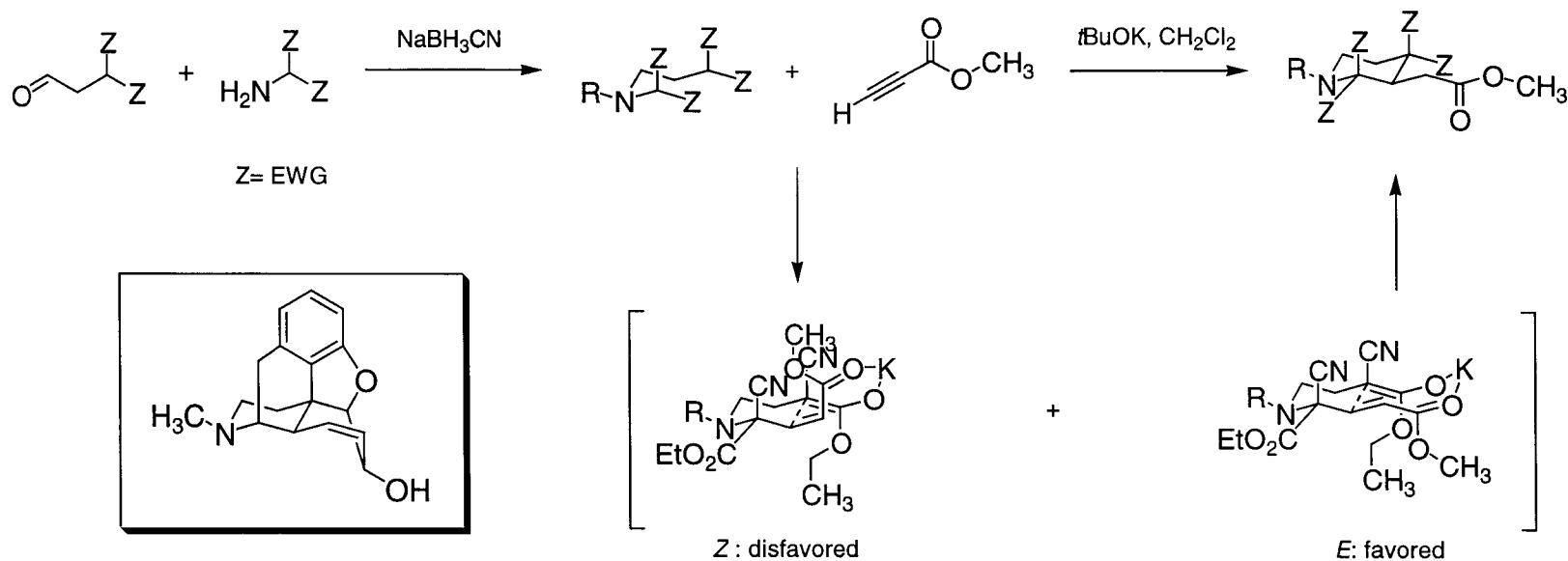


Catalyst also works well with inverse demand D-A and ene reactions



Dr. Robert Grossman, University of Kentucky

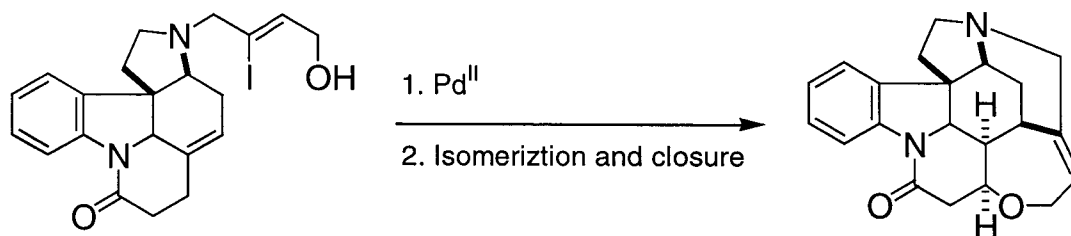
[5 + 1] Annulation Route to Highly Substituted and Functionalized Piperidines: A Heterocycle-Forming Double Michael Reaction



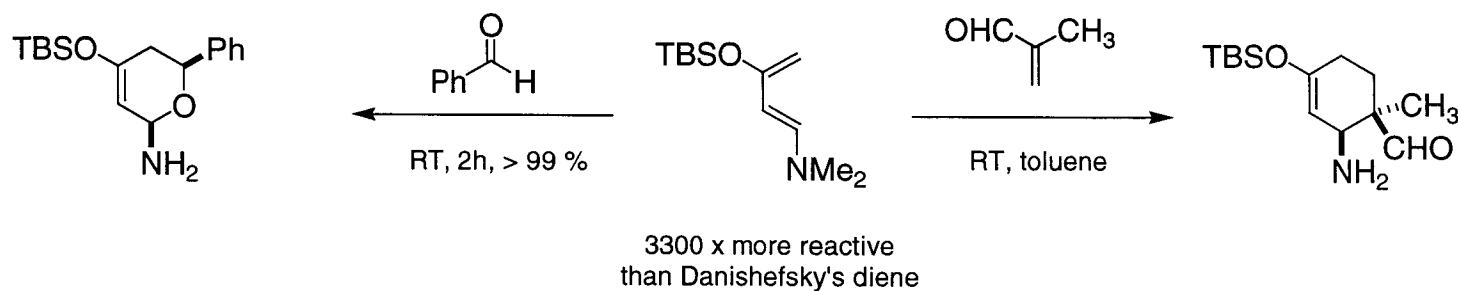
- Annulation is typically high yielding and shows high diastereoselectivity for the equatorially disposed acetate group.
- The observed selectivity appears to be a kinetic process controlled by the initial conjugate addition to the propiolate.
- It has been shown that this first addition occurs through the carbon proximal to the nitrogen atom.
- The highly substituted piperidine core can be further functionalized into a number of groups:
 - Reduction of the cyanide to an amine
 - Lactamization or Dieckmann condensation

Viresh Rawal, University of Chicago

New Methods and Strategies for the Stereocontrolled Asymmetric Synthesis of Indole Alkaloids

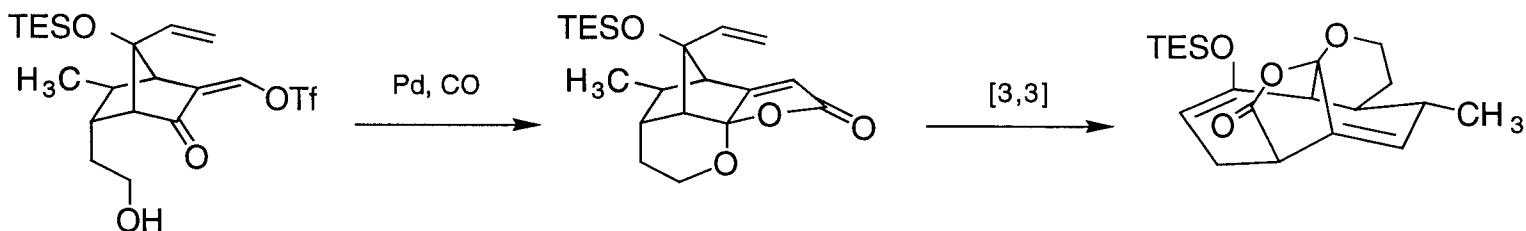


- This strategy avoids the traditionally used organometallic addition, which adds numerous steps.

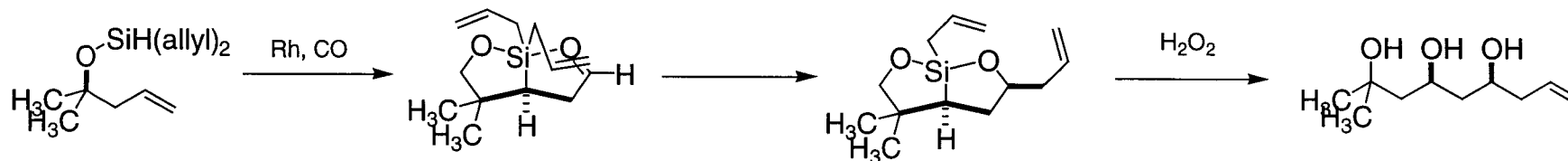


- This powerful diene allows for a variety of Diels-Alder type processes to occur under mild conditions.
- Application of asymmetric catalysis using Cr(III)-salen complexes allows for highly enantioselectivity, >89% yield and >95% ee (see *J. Am. Chem Soc.* **2000**, 122, 7843).
- This strategy has also been applied to alkaloid synthesis, especially the *Aspidosperma* family.

James Leighton, Columbia University
Strained Silacycles in Organic Synthesis

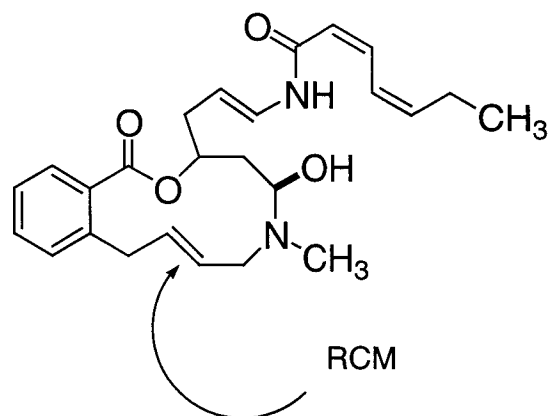


- Strain relief plays a major role in driving this sigmatropic rearrangement en route to the CP skeleton.



- This intermolecular silyl formylation / allylation sequence allows for rapid access to polyols.
- Strain relief Lewis acidity accounts for the activation of the aldehyde by the carbon-bound silicon.

Gunda Georg, University of Kansas
Synthesis and Evaluation of Novel Heterocyclic Anticancer Agents



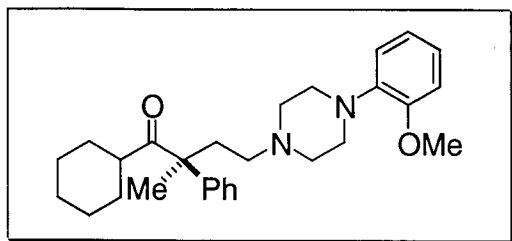
Salicylihalamide A

potent toxin with activity against melanoma

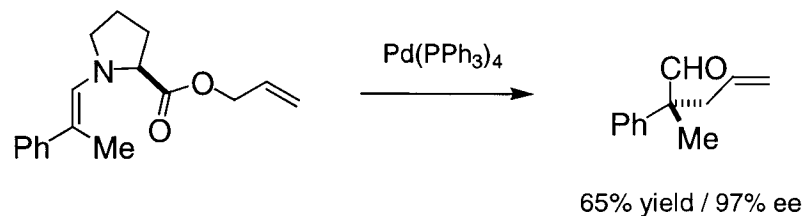
- While the RCM works very well, late stage formation of the enamine has prevented completion of the synthesis.
- A novel method for removal of ruthenium containing impurities:
 - Stir with SiO₂ in DMSO then filter

Tony Zhang, Eli Lilly

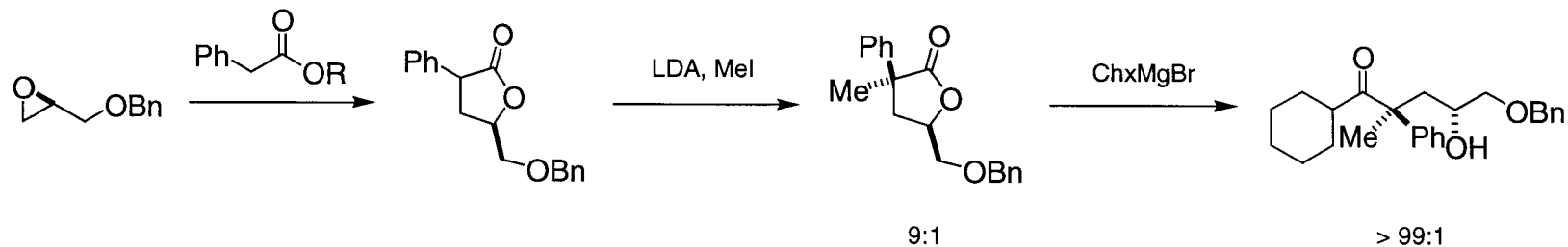
Selective Synthesis of Heterocycles for the Process Development of 5HT_{1a} Antagonists



Medicinal Chemistry Route:

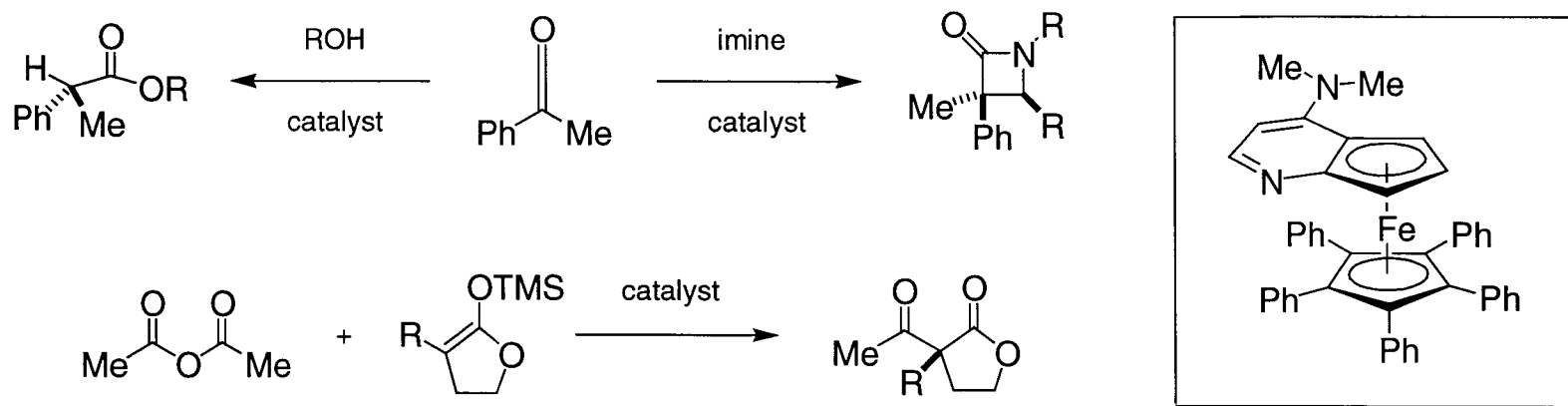


Process Route:



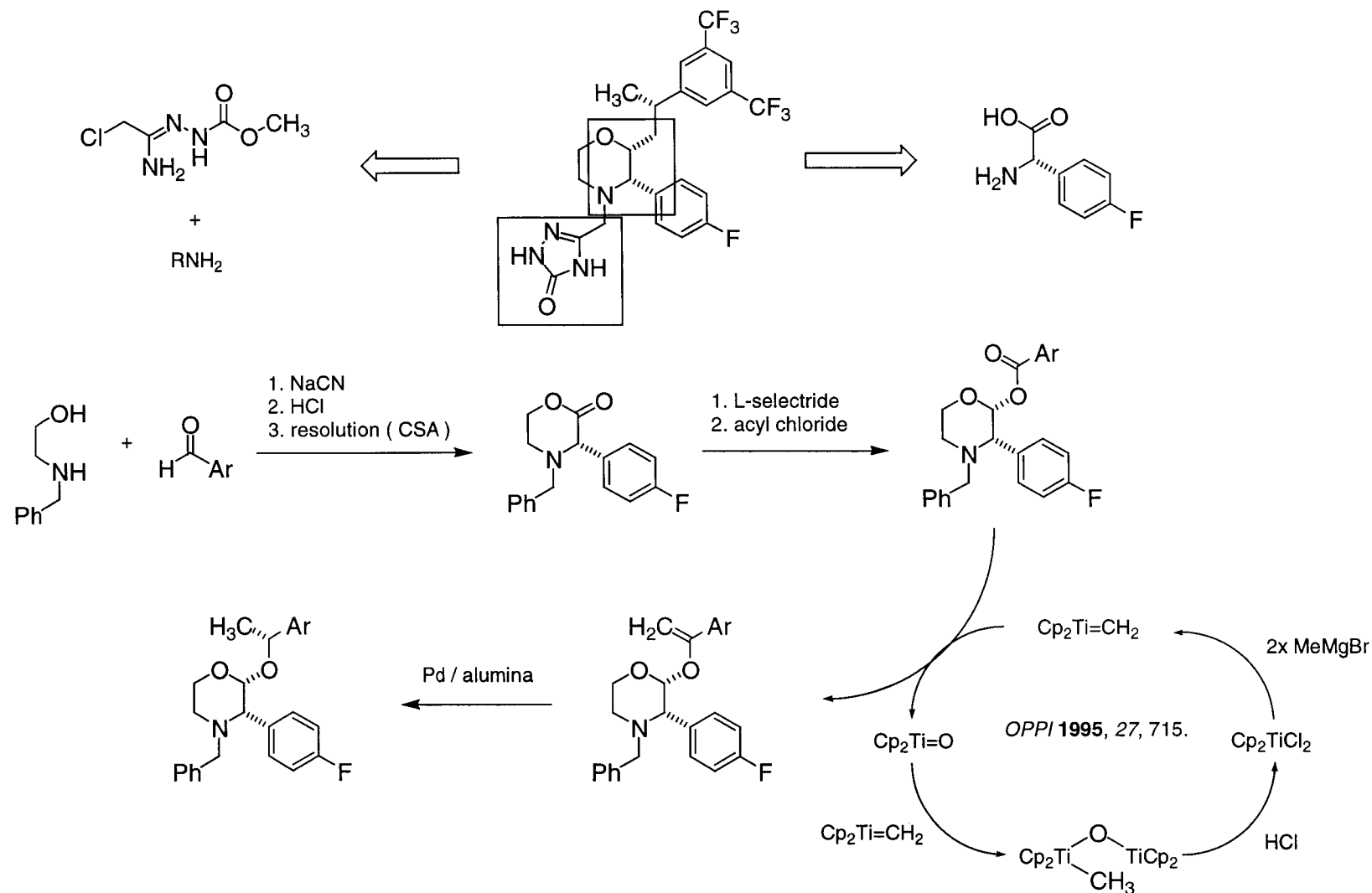
- Several routes were examined towards generating the stereocenter in this molecule:
 - Enzymatic resolution
 - Palladium catalyzed enolate arylation
- The process route was successful since during the Grignard addition to the lactone, only the major diastereomer reacts.

Greg Fu, Massachusetts Institute of Technology
Asymmetric Catalysis with "Planar-Chiral" Heterocycles

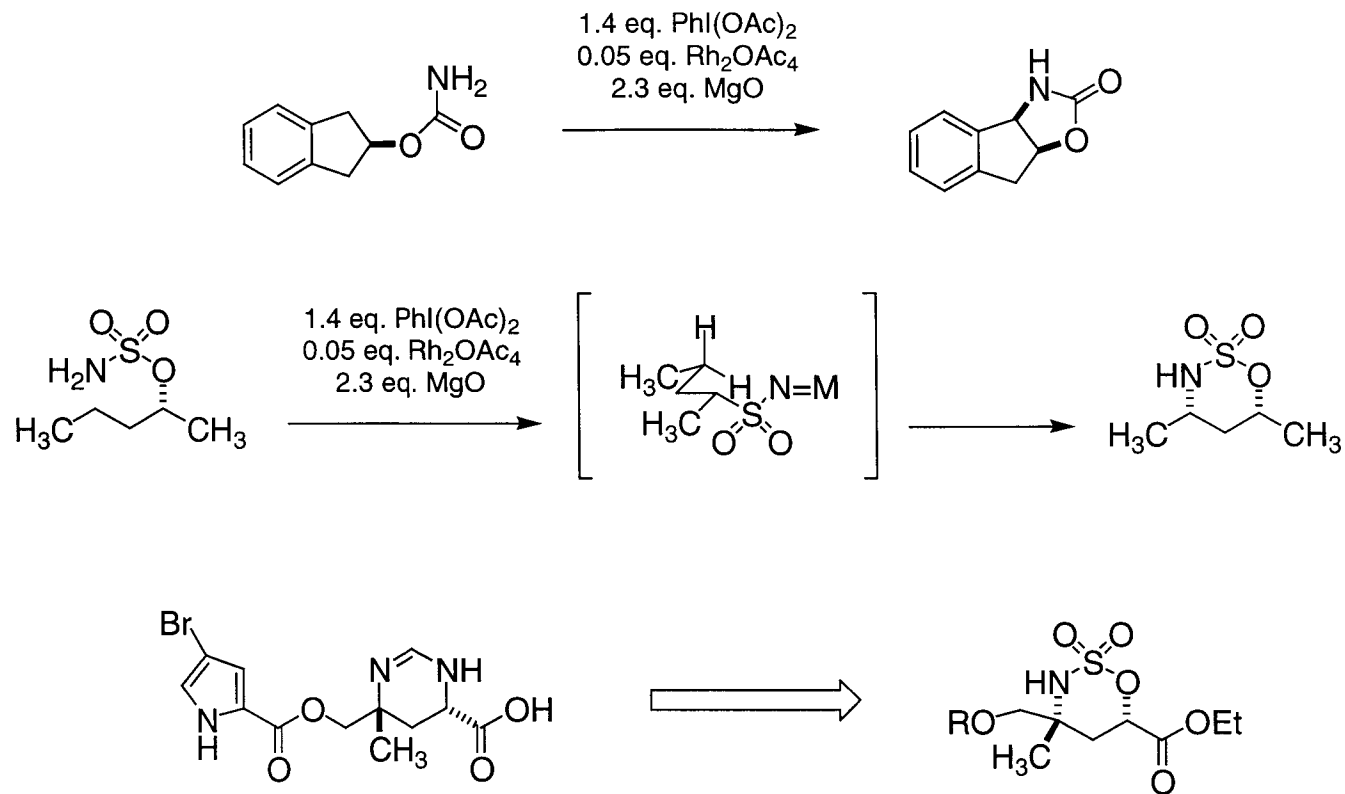


- Planar chiral heterocycles have proven themselves as powerful, asymmetric Lewis base catalysts:
 - Resolution of alcohols and amines
 - Ketene reactions: protonation and beta-lactam formation
 - Epoxide openings
- In most cases, attack of the nucleophile on the catalyst-reagent complex is rate determining.

James McNamara, Merck
Asymmetric Syntheses of an NK-1 Receptor Antagonist

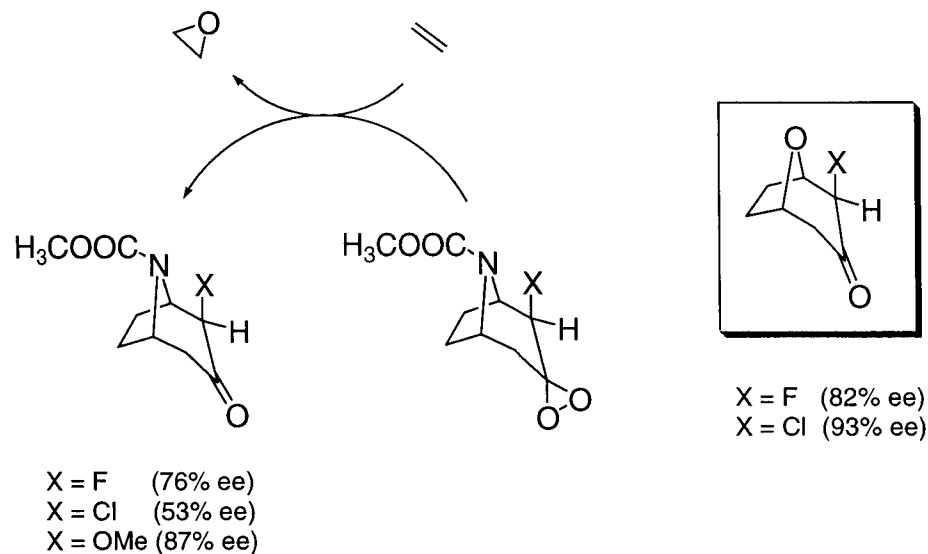


Justin Du Bois, Stanford University
Catalytic Insertion Reactions for the Amination of C-H Bonds

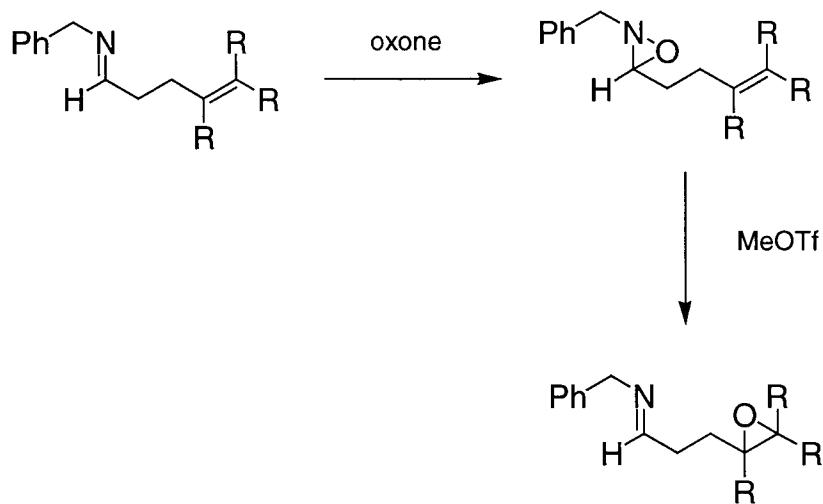


- Reaction proceeds through a metal nitrene complex.
- Sulfur containing linker holds great synthetic potential due to ease of removal.
- Also, the geometry of the sulfoxide linker favors formation of a 6 member ring over a 5 membered ring.

Alan Armstrong, Imperial College
Asymmetric Heteroatom Transfer from Small-Ring Heterocycles

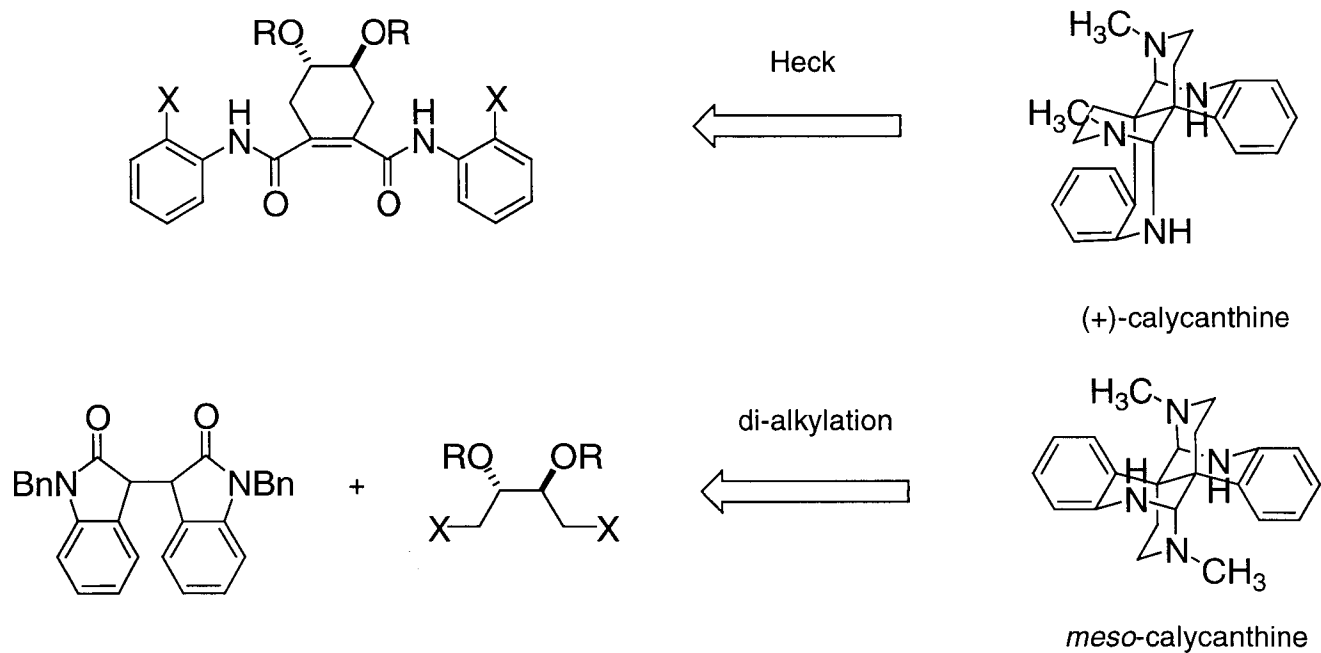


- Installation of the alpha heteroatom serves a dual purpose: stabilization of the catalyst against BV oxidation, introduction of an enhanced chiral environment.
- Still, despite an extensive empirical survey only 93% ee could be obtained.



- Oxaziridines seemed promising based on literature precedent.
- Early success in the realm of intramolecular transfer has promise for an asymmetric, auxiliary based methodology.

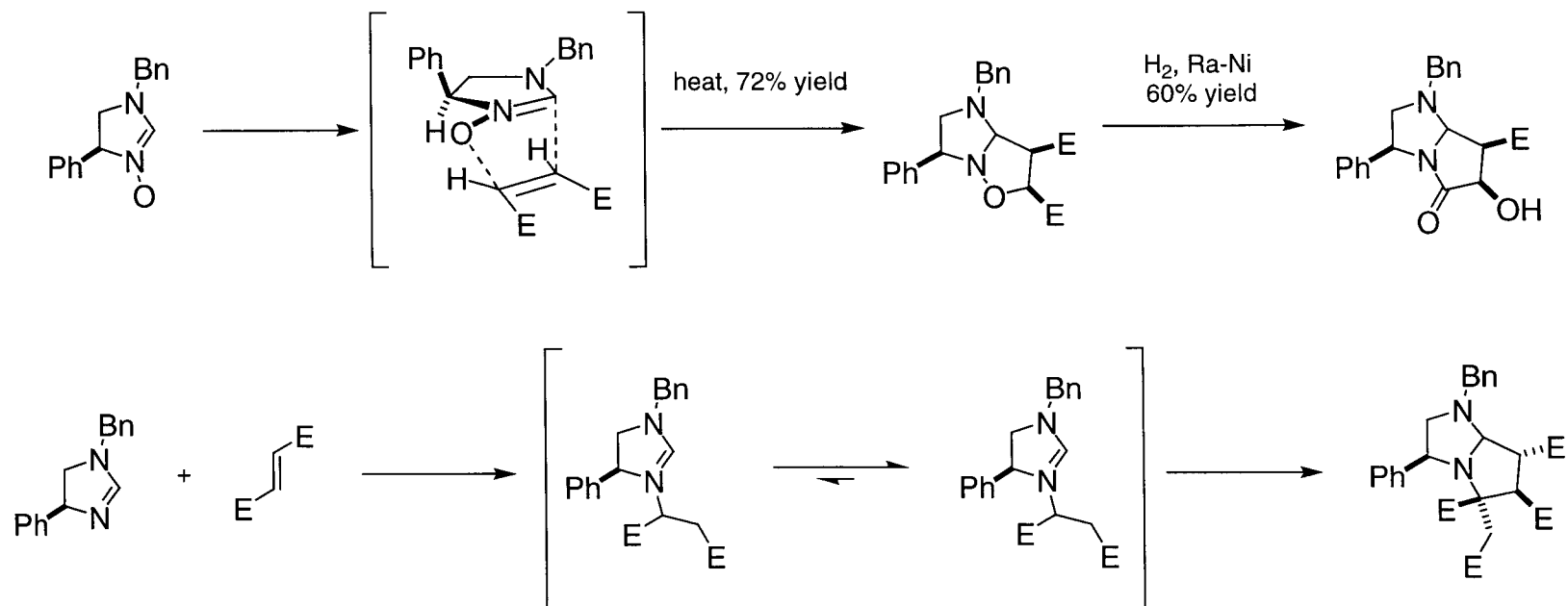
Larry Overman, University of California, Irvine
Recent Studies in Alkaloid Total Synthesis



- Overman has developed two distinct strategies for formation of vicinal quaternary centers.
- Both strategies rely on installation of two control stereocenters.
- However, the conformation of the final structure plays a major role in determining the overall selectivity of the synthesis.

Ray C. F. Jones, Loughborough University

Ringing the Changes: Expected and Unexpected Annulations of Imidazolines



- Reaction of the imidazole based dipole yields the *anti* product with high diastereoselectivity.
- Both oxygenated and carbon containing dipoles work well.
- The formation of the di-addition product is facile when good Micheal acceptors are employed.

Albert Eschenmoser, ETH-Zürich/Scripps

Chemical Etiology of Nucleic Acid Structure: Strategy and Recent Results

- The criterion for good DNA base pairing known: the energy of the C=O bond is 30 kcal/mol less than the corresponding C=N bond. Hence the amide form of the base pair exists rather than the enamine form.
- Can similar criterion be found for the structure of the nucleic acid backbone?

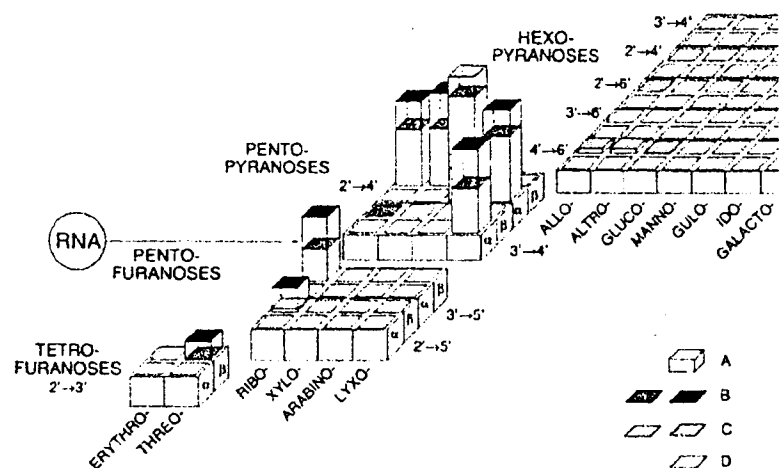
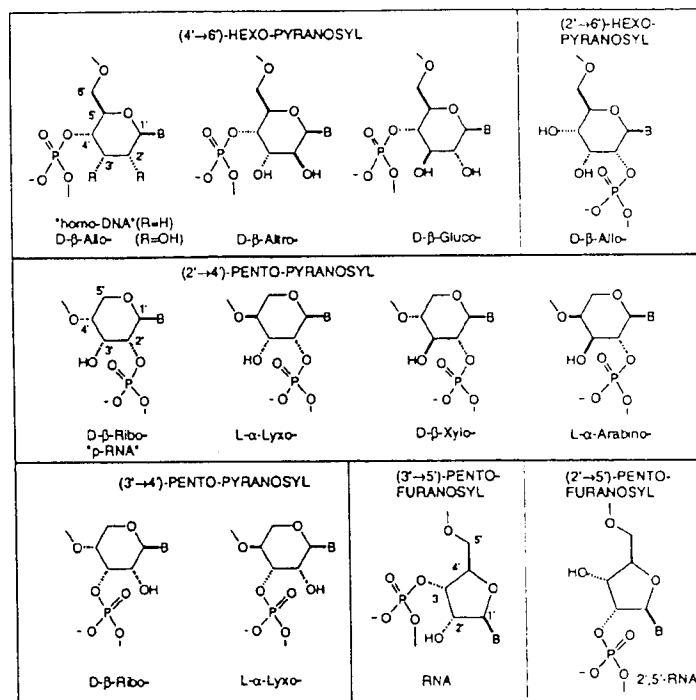


Fig. 5. Pairing-strength landscape of hexose-, pentose-, and tetrose-derived oligonucleotide systems, showing the range of the constitutional and configurational diversity of (potentially natural) alternatives of the RNA structure and giving T_m values of duplexes $A_8 \cdot T_8$ (red level) and $A_{12} \cdot T_{12}$ (black level) investigated in the ETH and TSRI laboratories. For conditions, see the caption of Fig. 3. (A) Column height unit is 10°C above 0°C (see also Fig. 3); (B) observed T_m values; (C) estimated T_m values, purple for $A_8 \cdot T_8$ and gray for $A_{12} \cdot T_{12}$; and (D) not investigated. Data are as follows: hexopyranosyl series (37), pentopyranosyl series (36, 38, 39), pentofuranosyl series (48), and tetrofuranosyl series (47).



- Ribose is not unique in its ability to pair or form anti-parallel strands. Certain structures (alpha 2,4 arabino pentose) even have higher melting temperatures than natural structures.