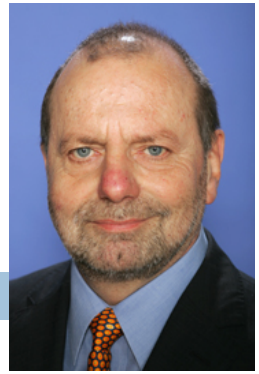
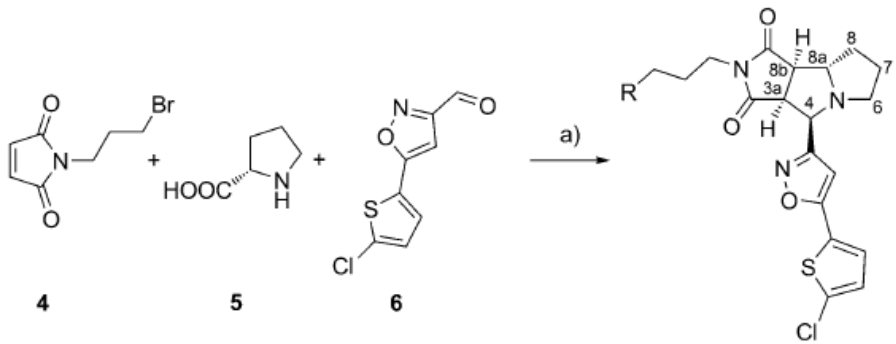
NATIONAL ORGANIC SYMPOSIUM 2013

SEATTLE, WA
JUNE 23-27, 2013

David Kornfilt

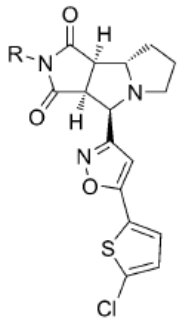
Diederich – Factor Xa Inhibitors





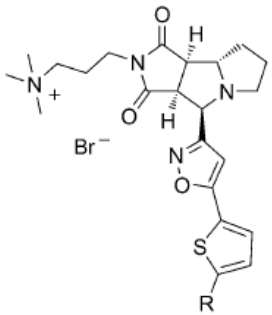
Two major active pockets. Size of group plays primary role in determining K_i

Compound	R	K_i / nM
(±)-**8**	H_2N	9800
(±)-**9**	N H	911
(±)-**10**	N	56
(±)-**1**	N+ Br−	9



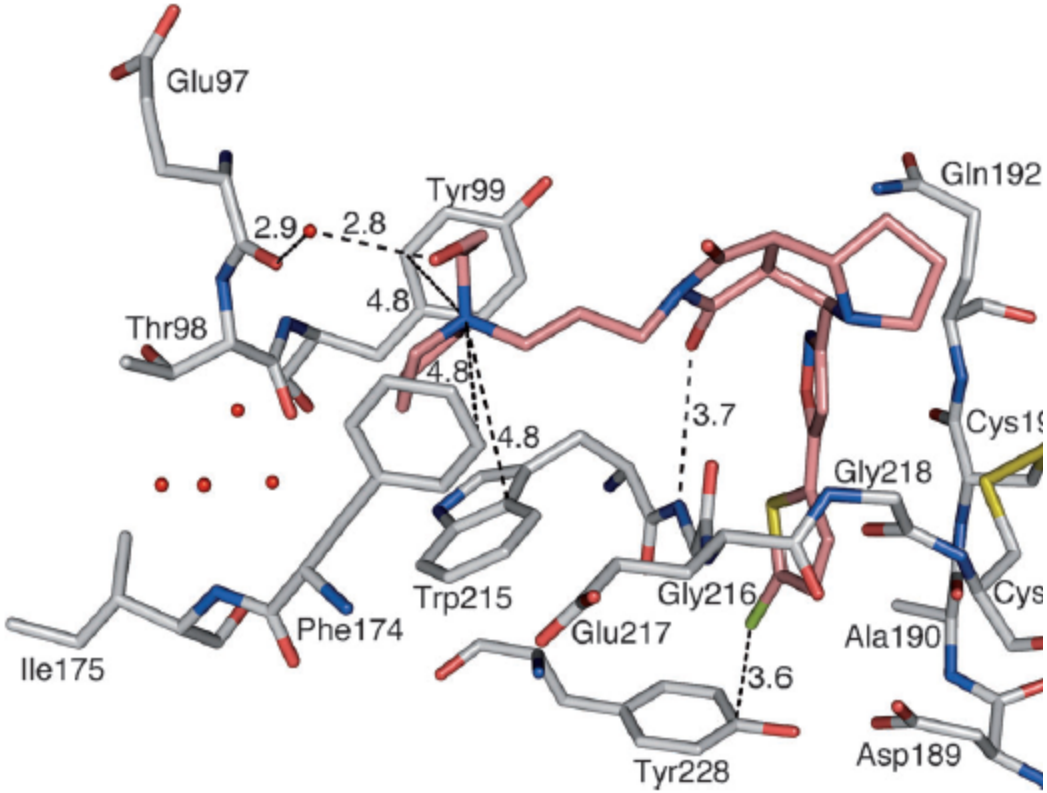
Compound	R	K_i / nM
(±)-**11**		10300
(±)-**12**		1400
(±)-**13**		750
(±)-**2**		550

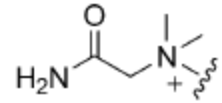
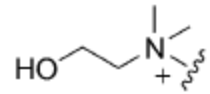
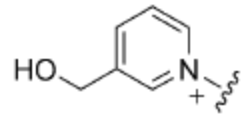
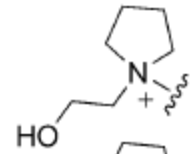
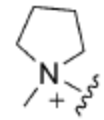
Compound	R	K_i / nM
(±)-**15**	H	612
(+)-**16**	OMe	509
(–)-**16**	OMe	3540
(±)-**17**	F	48
(±)-**1**	Cl	9
(±)-**18**	Br	6
(±)-**19**	I	47



Increased steric bulk excludes water from a hydrophobic pocket

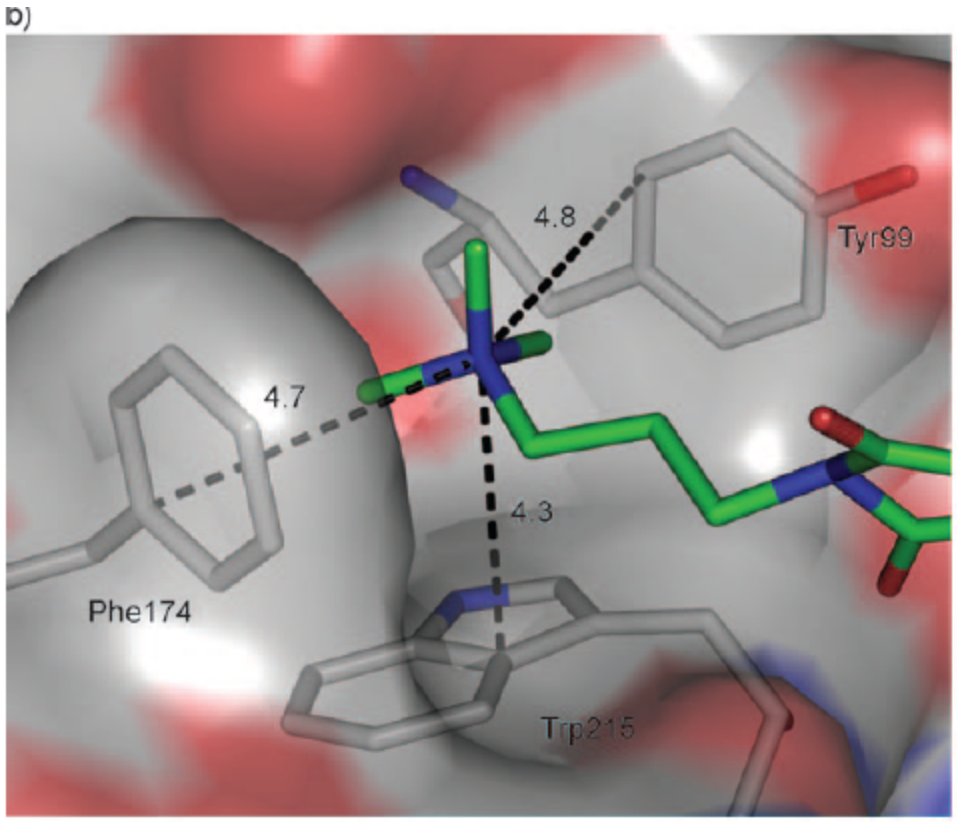
Factor Xa Active Site



Compound	R	K_i / nM
(±)-**22**		26
(±)-**23**		14
(±)-**24**		76
(±)-**25**		2
(±)-**26**		5

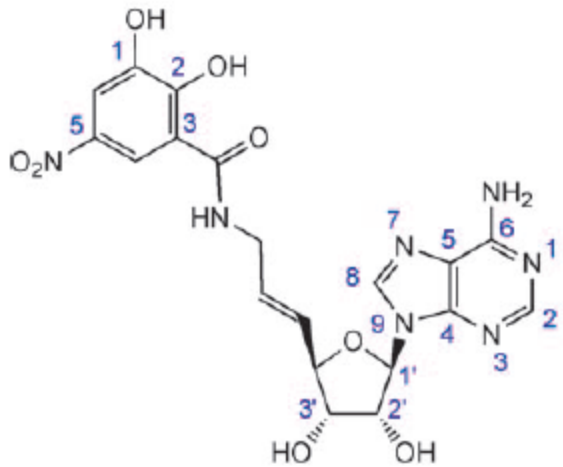
Water replacement primary reason behind entropy-driven binding.

Factor Xa Inhibitors

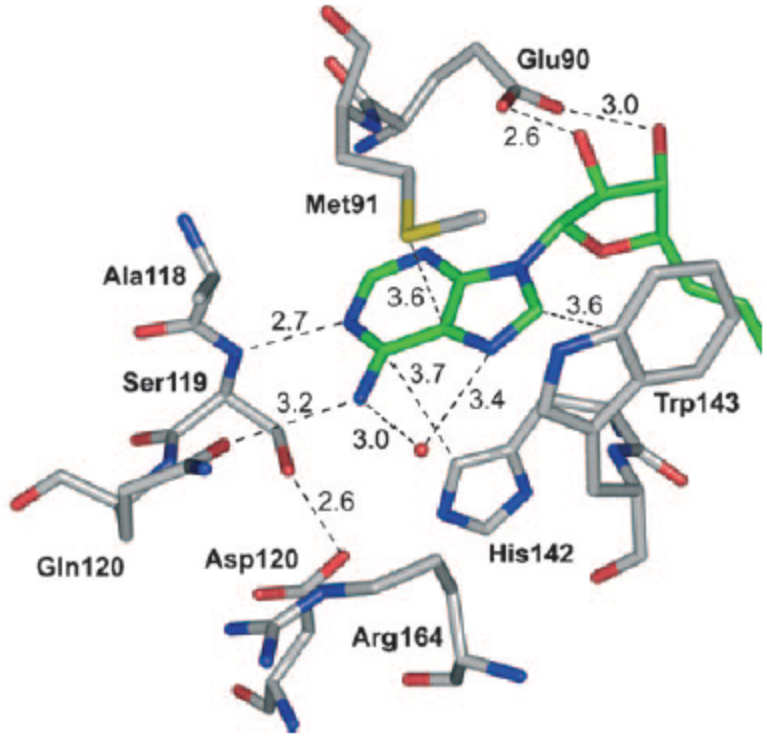


Ammonium ion occupies an aromatic pocket and engages in cation-π binding.

Two Case Studies: COMT and TGT



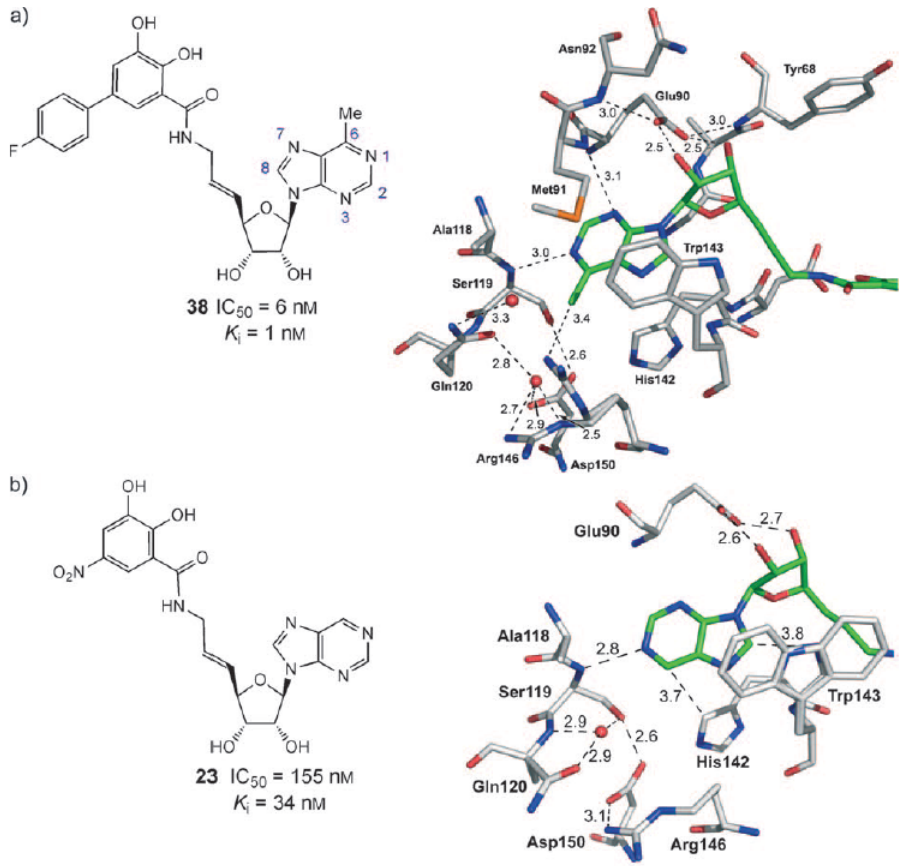
1 IC_{50} = 9 nM
K_i = 2 nM

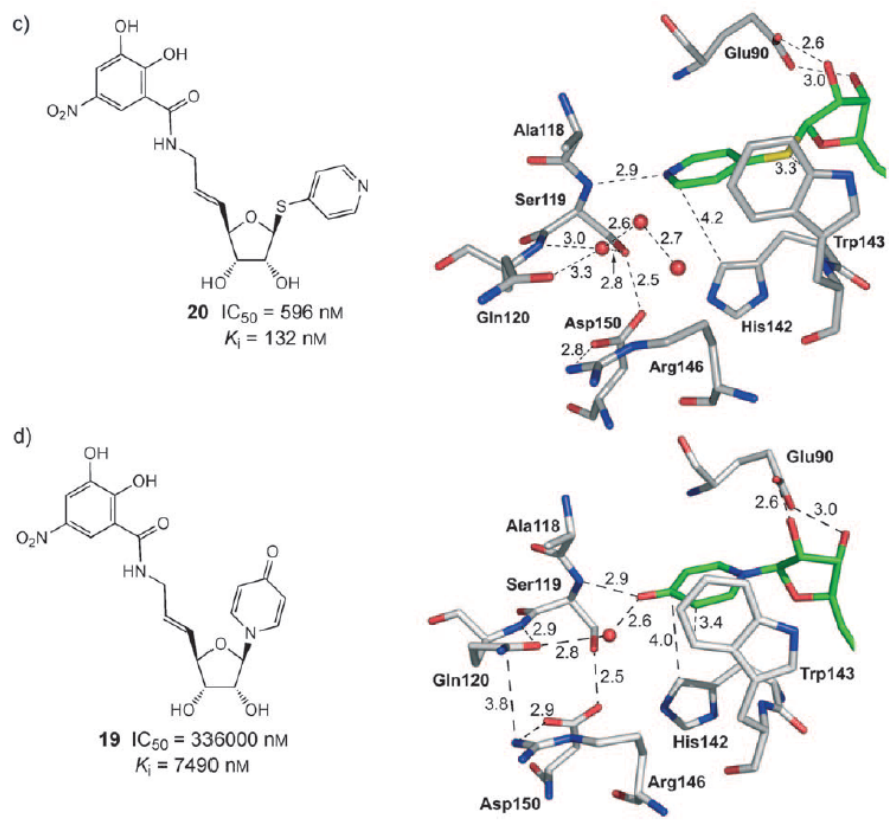


Catechol O-methyl Transferase.

Start off with known inhibitor 1.

COMT Inhibitors

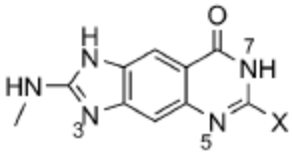




Exclusion of water results in 30-fold increase in binding affinity

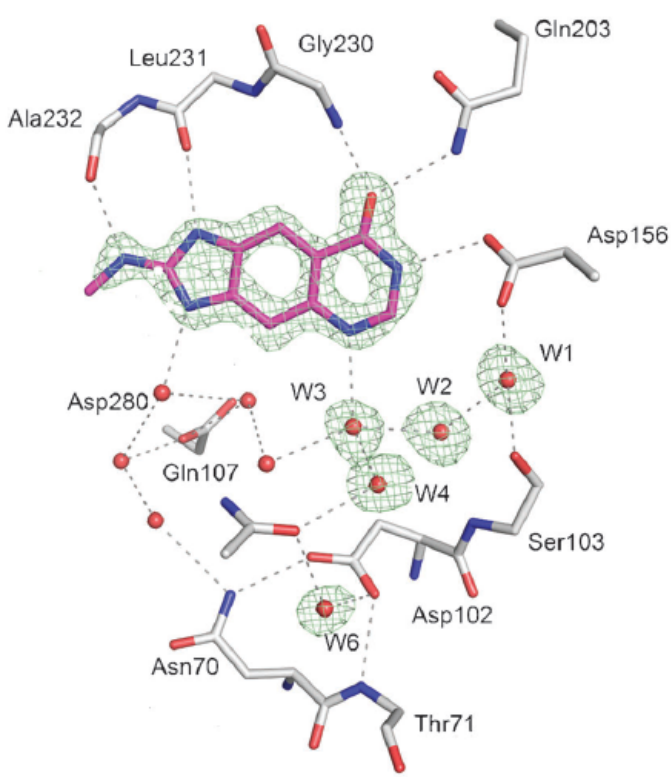
Void space of pyridone results in poor ligand efficiency

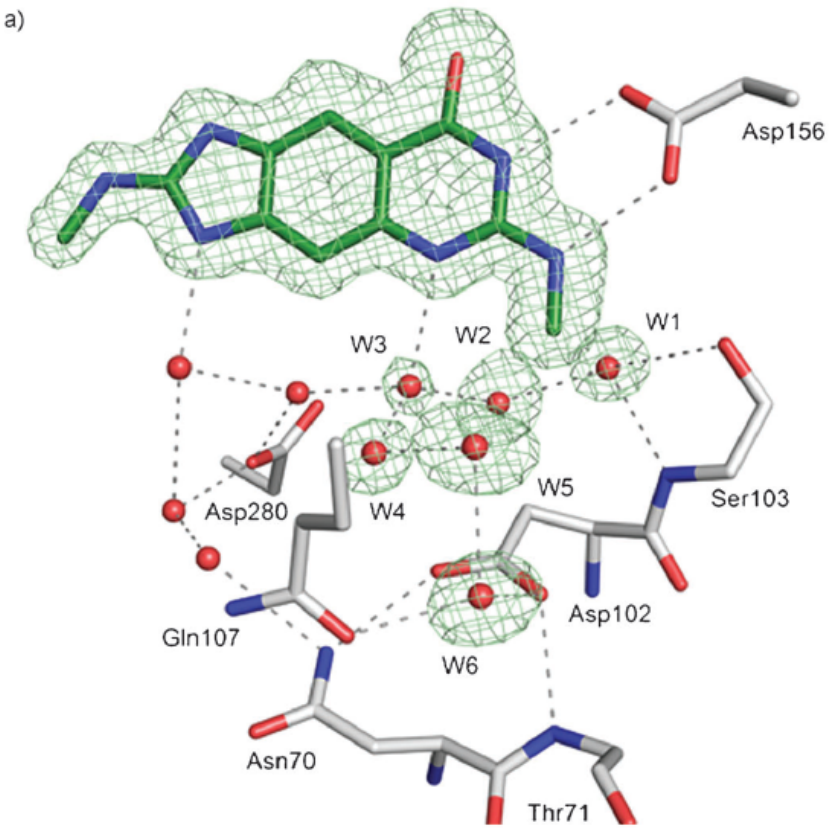
TGT Inhibitors



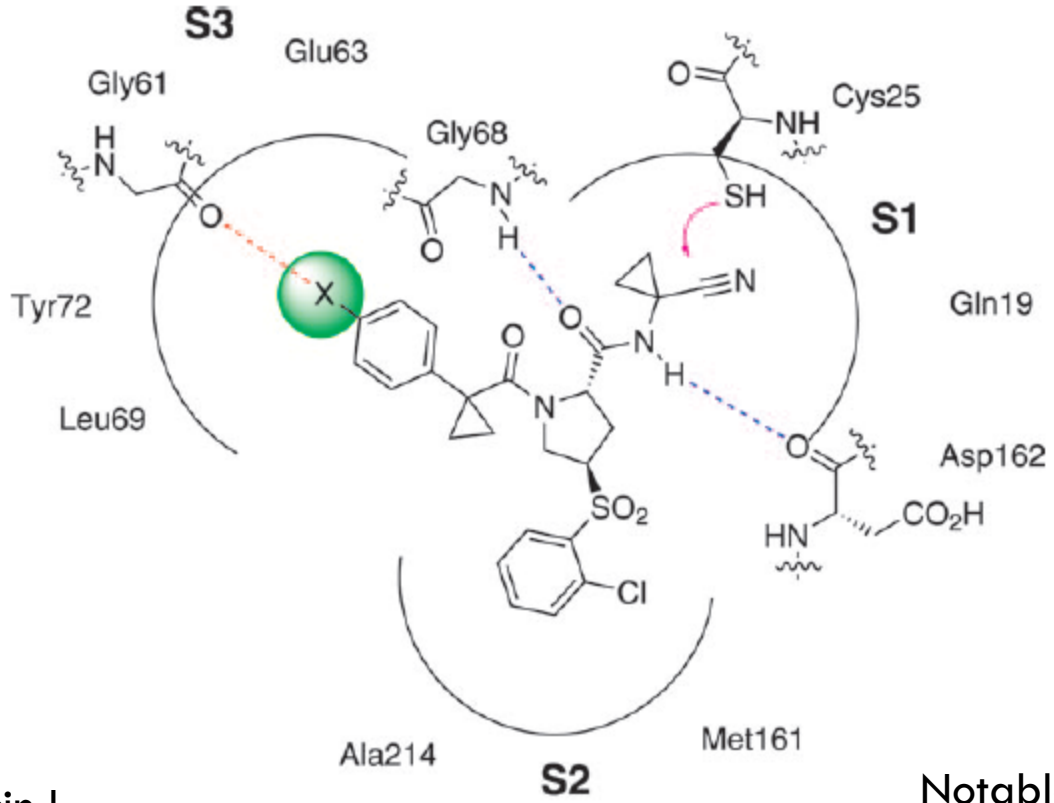
19 a	NH_2	58 ± 36[12]
8 a	H	6500 ± 2900
11 a	NHMe	28050 ± 11970
11 b	NHEt	40830 ± 4270

Water displacement leads to 100x stronger binding.





Halogen Bonding hCatL inhibitors

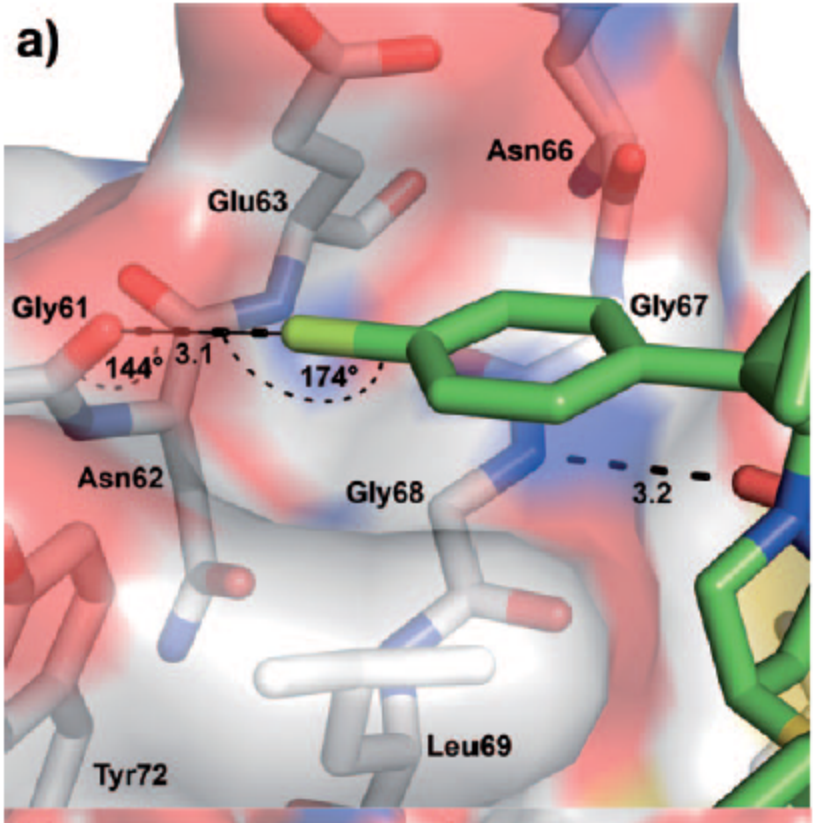


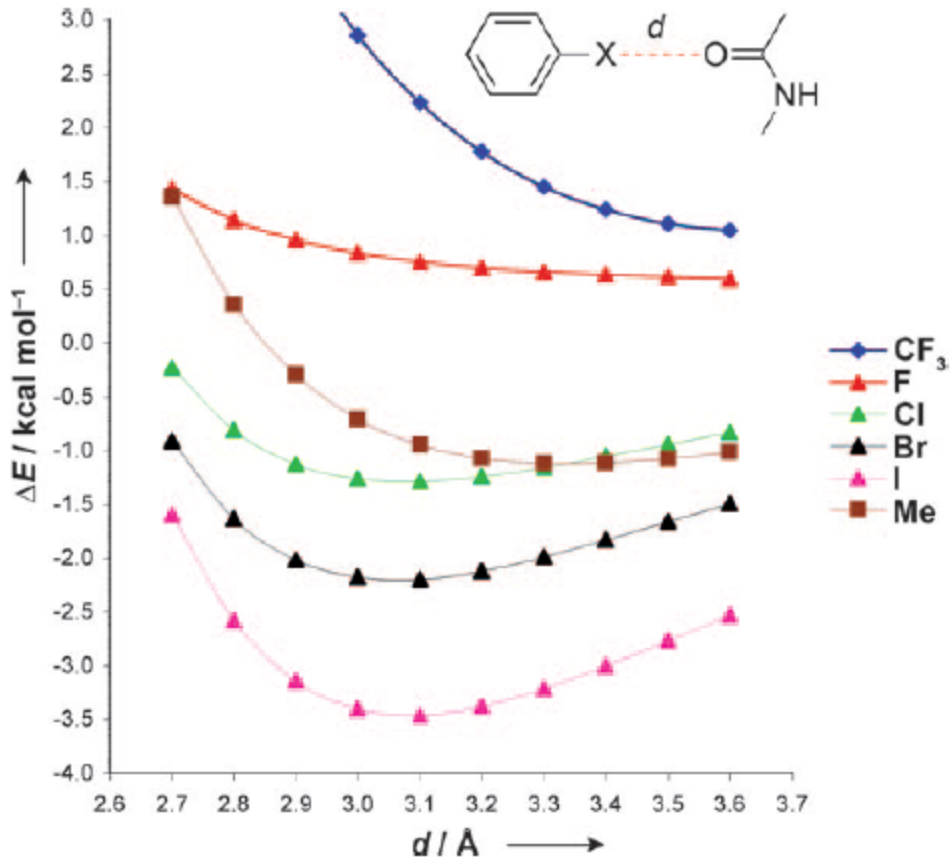
X = H: (–)-**1** IC_{50} = 0.29 μM
X = Cl: (–)-**22** IC_{50} = 0.022 μM

Human Cathepsin L

Notable because ligand has head-on C-O-X alignment with active site

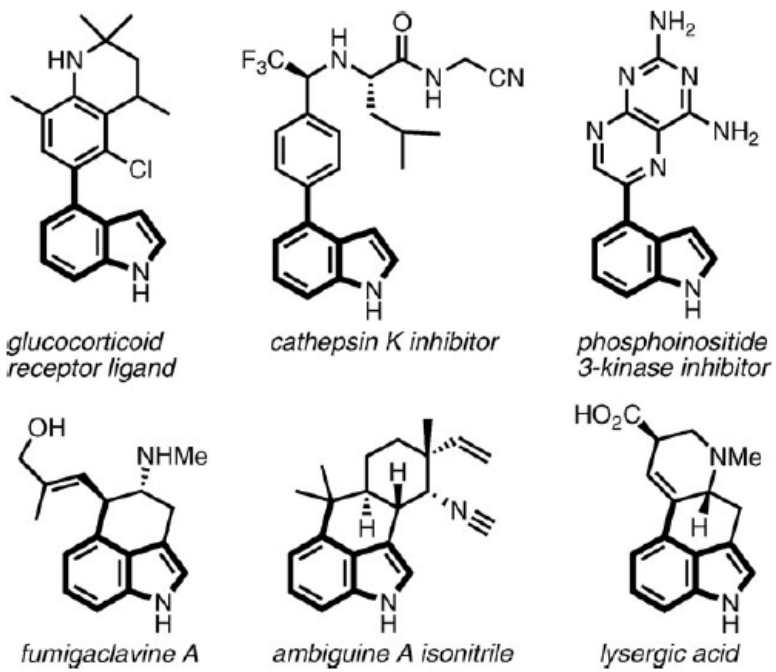
Halogen Bonding

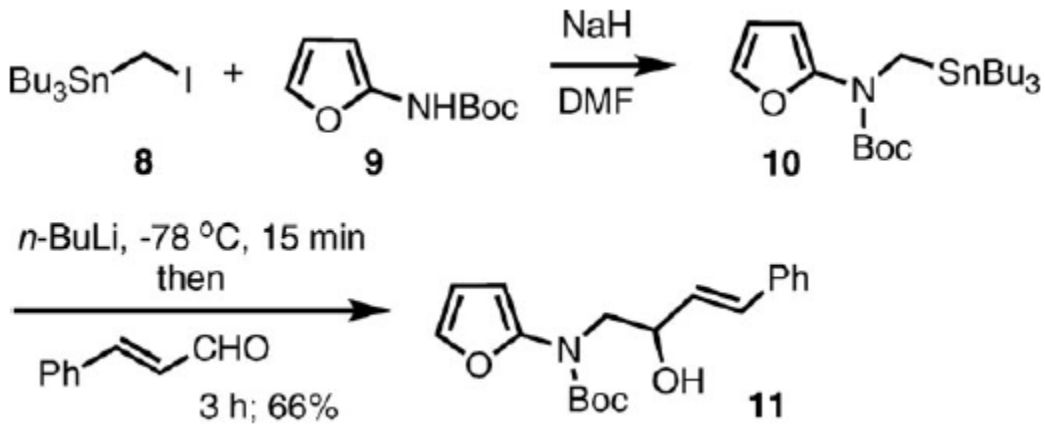




Strength of C-X-O bond: I > Br > Cl >> F
Studied computationally.

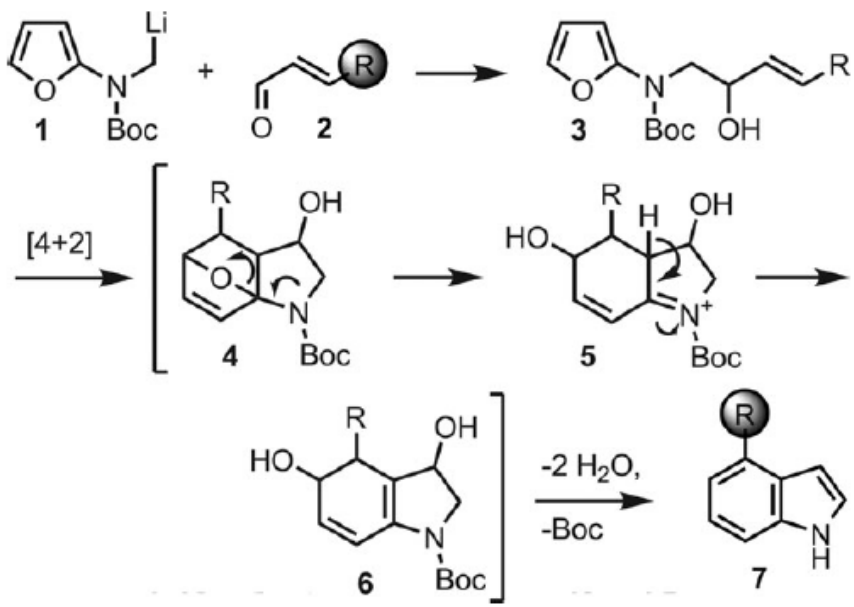
Wipf – 5- and 4-substituted Indoles

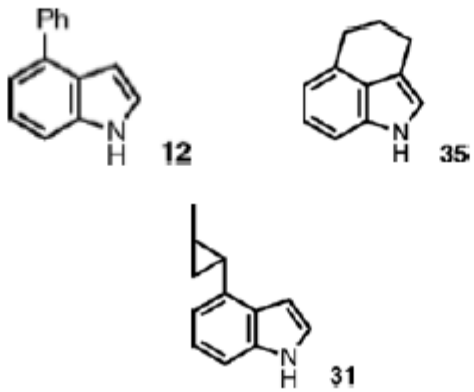




Use of tin-lithium exchange to form highly reactive organolithiums.
Precursor 11 is set up to do a intramolecular Diels-Alder reaction

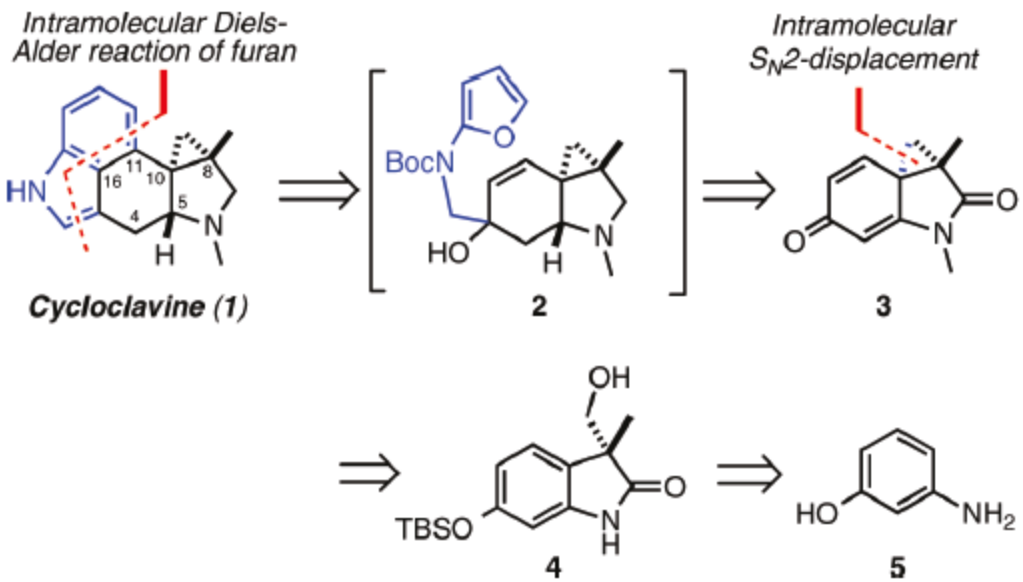
IMDA Indole Synthesis





A wide variety of indoles could be accessed.
Downside : 180-220 °C, MW

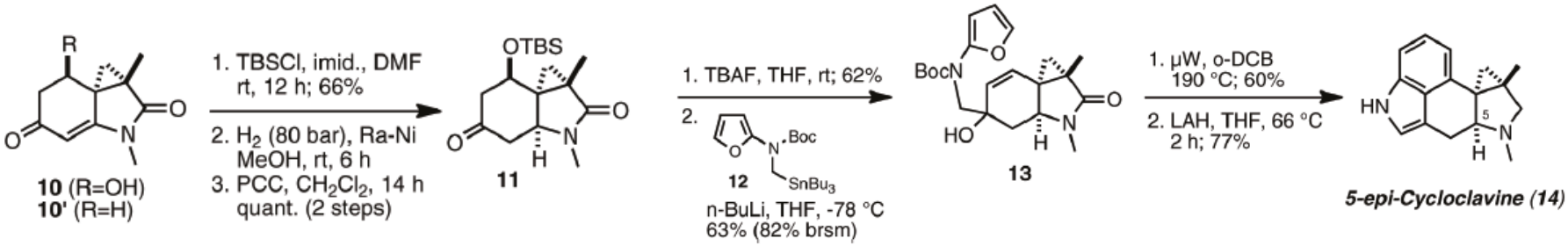
Synthesis of Cycloclavine



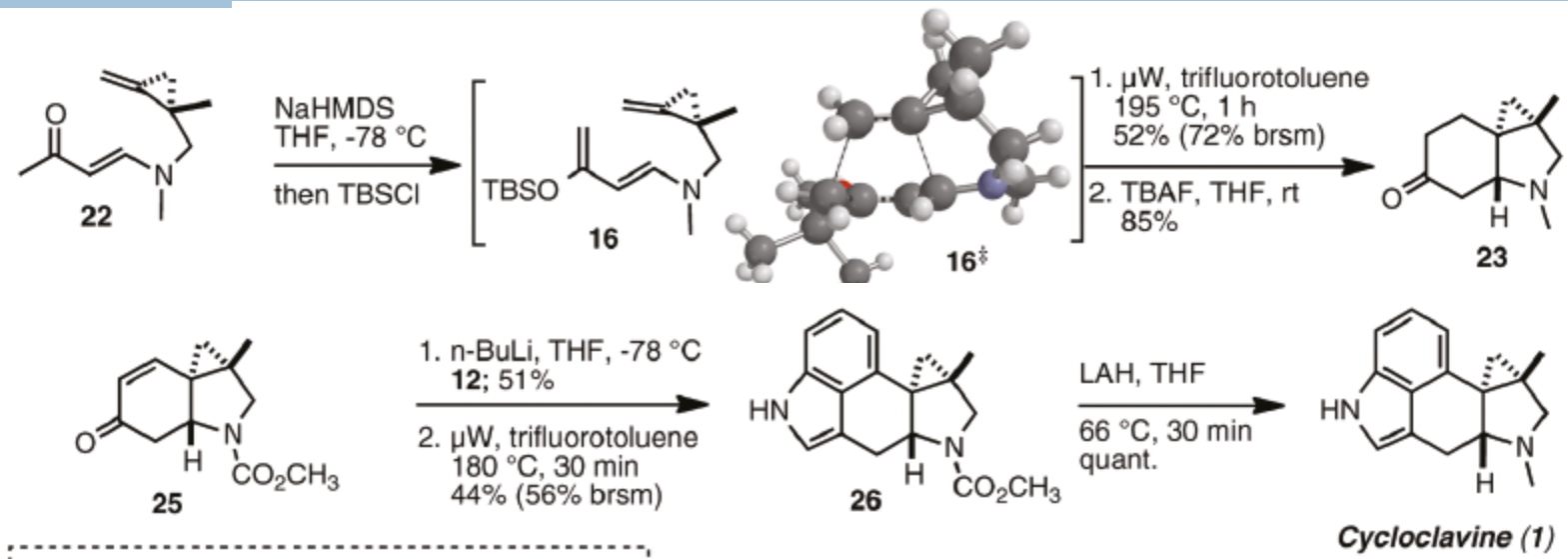
Ergot alkaloids, known for their medicinal and hallucinogenic properties

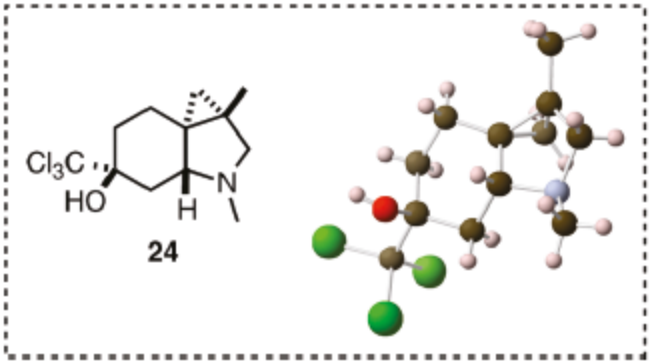
Hydrogenation of **10** led to undesired epimer at **11**

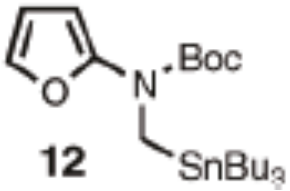
Furan-IMDA viable route to cycloclavine



2nd / 3rd Generation Approach





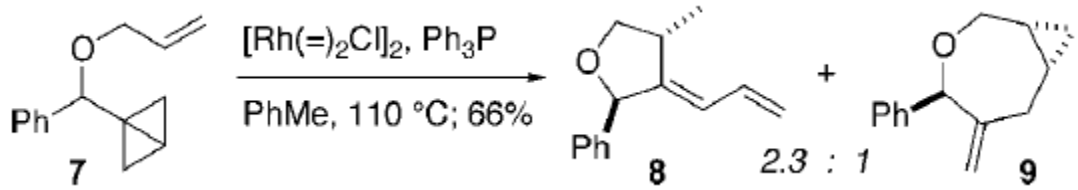


Use of a second DA to form the perhydroindole **23.**

Stereochemistry unambiguously established through $CHCl_3$ adduct crystal.

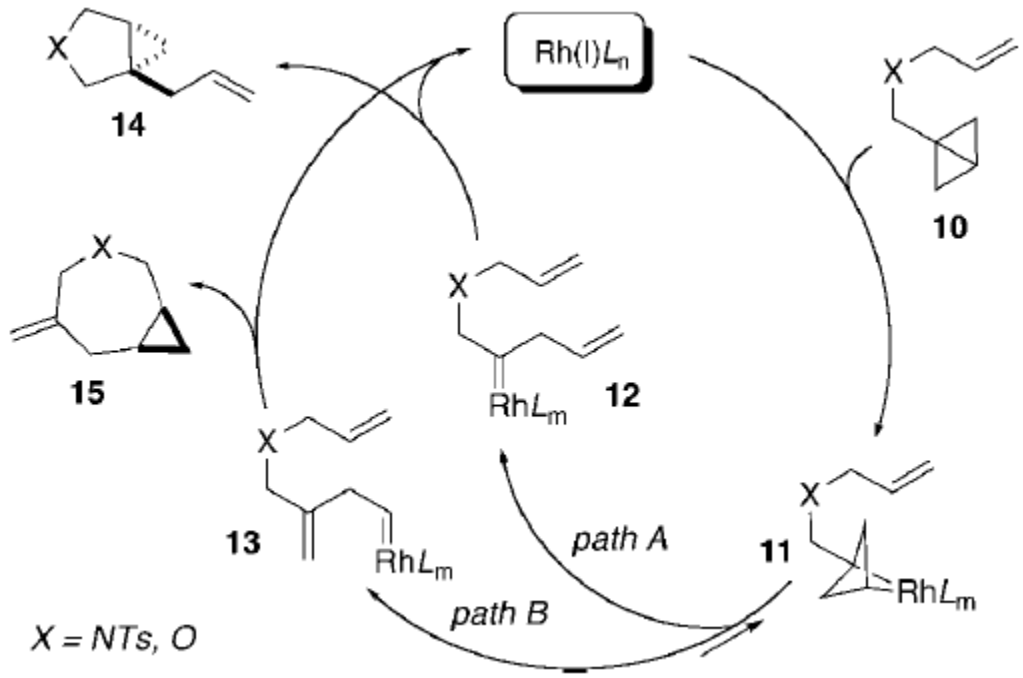
Addition of tin reagent **12** leads to correct precursor **26**

Isomerizations of Bicyclobutanes

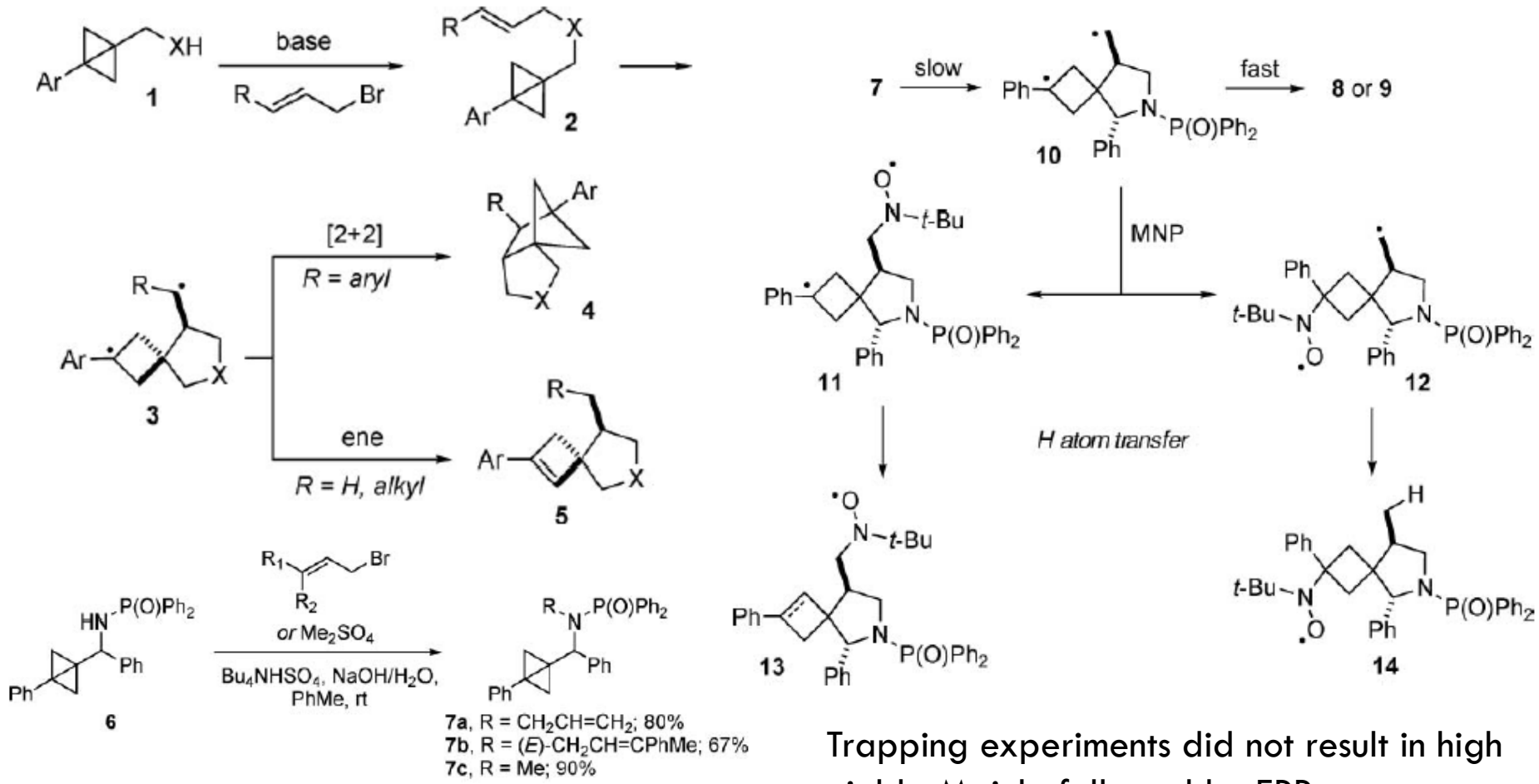


Bicyclobutanes have ca. 64 kcal/mol strain energy

Can control constitutional selectivity based on Rh source/Ligand



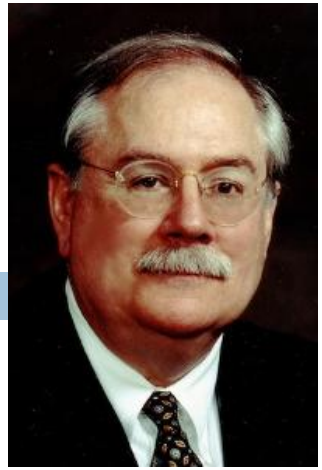
Non-metallic Opening of Bicyclobutanes

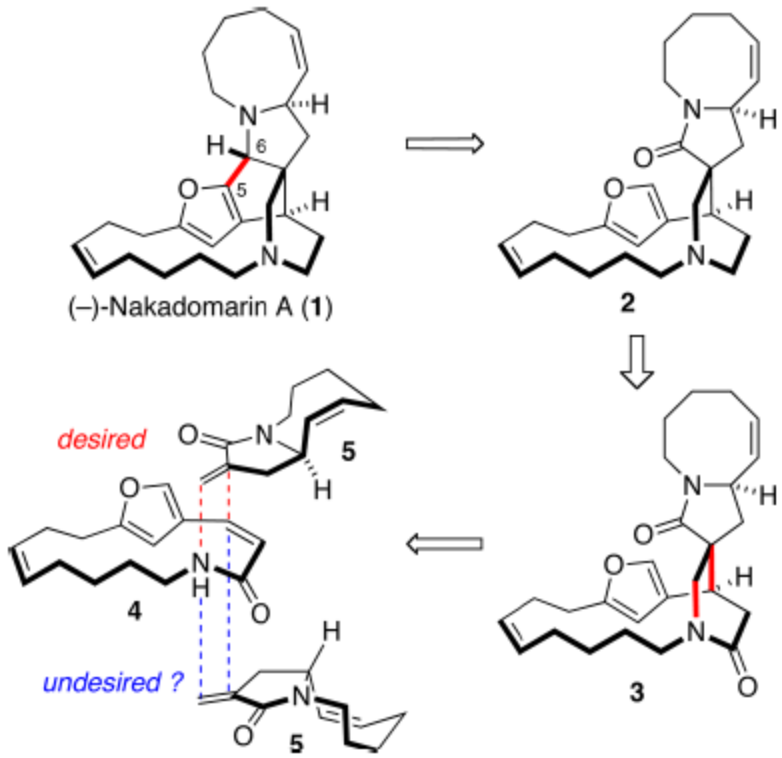


Stability of radical 3 is proposed to result in bifurcated pathways.

Trapping experiments did not result in high yields. Mainly followed by EPR spectroscopy/ modeling.

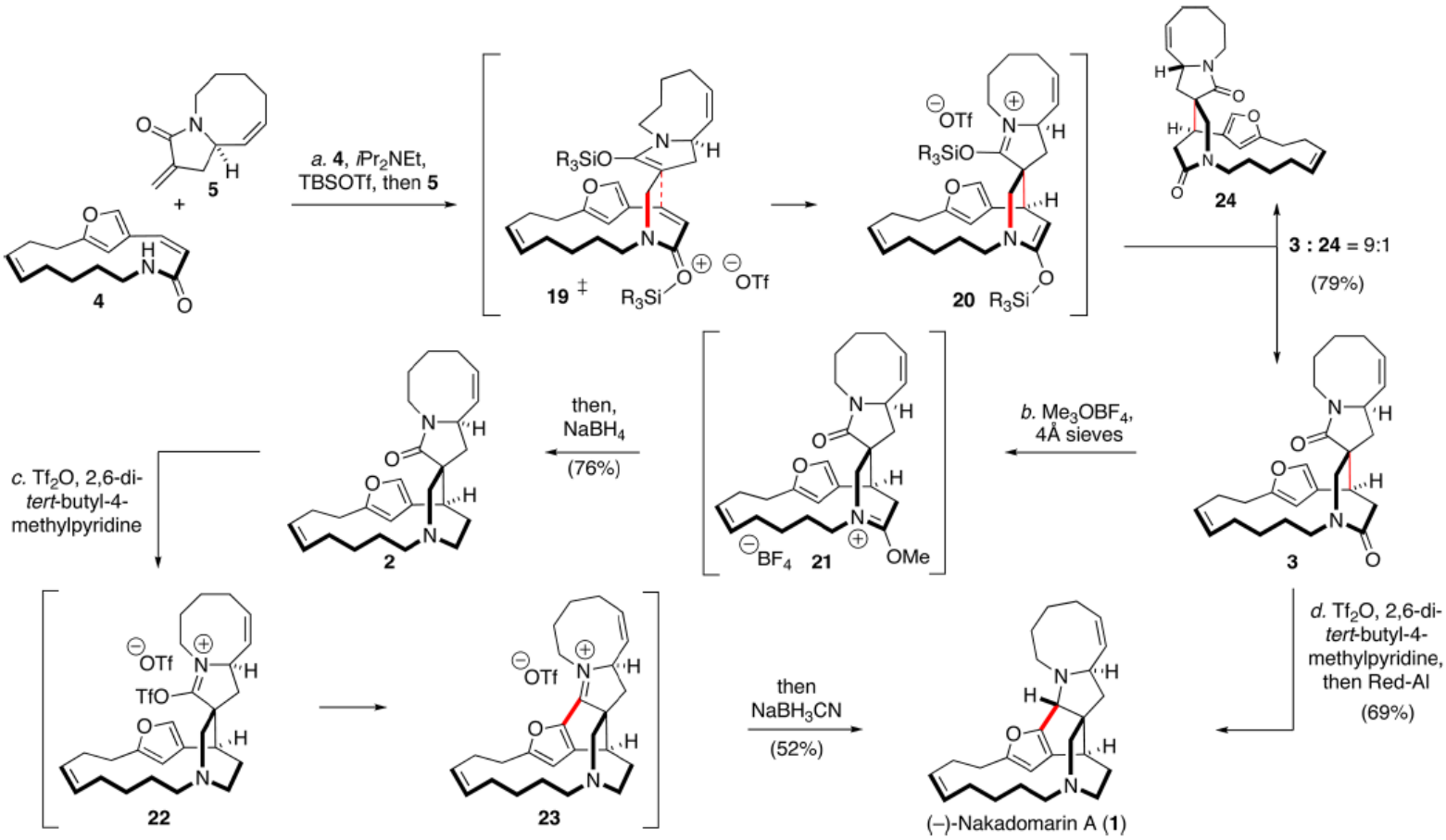
Evans – Stereochemical Course of Michael Additions





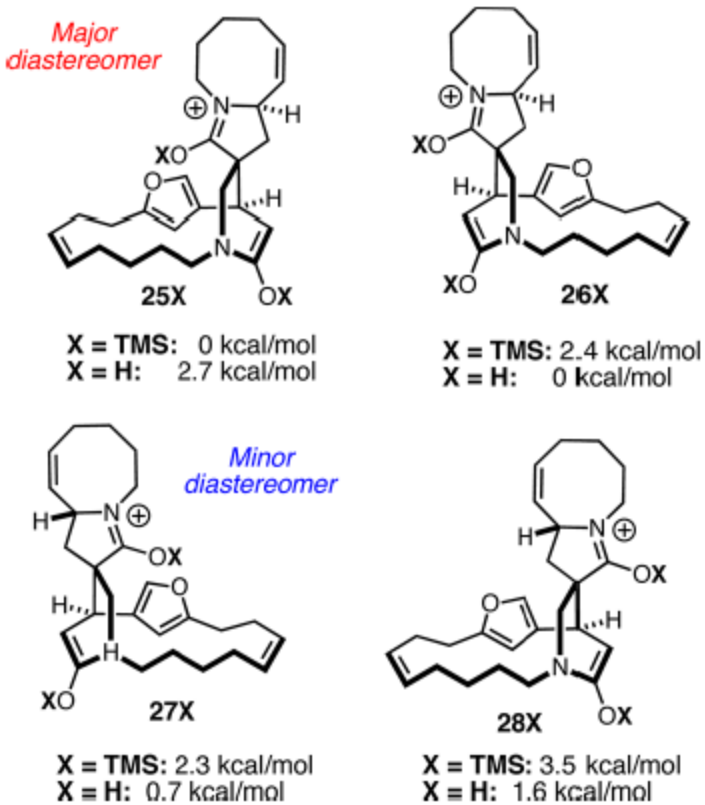
Stereochemical course of inter- and intramolecular Michael additions.
Manzamine family, with wide-ranging biological activity.

A Stereoselective Intermolecular Michael Reaction



Isolated minor isomer comes from attack on the concave face of **4.**

Where does the diastereoselection come from?

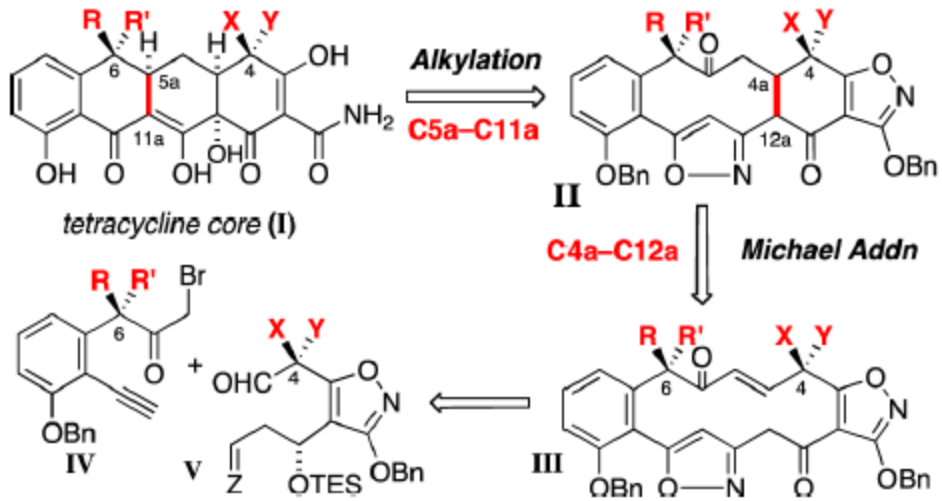


Computational studies indicate that dipole-dipole repulsions play only a modest role.

Major contributor to selectivity is the silyl group.

TMS/TBS difference leads to calculations understating the importance of the silyl group on the stereochemical outcome.

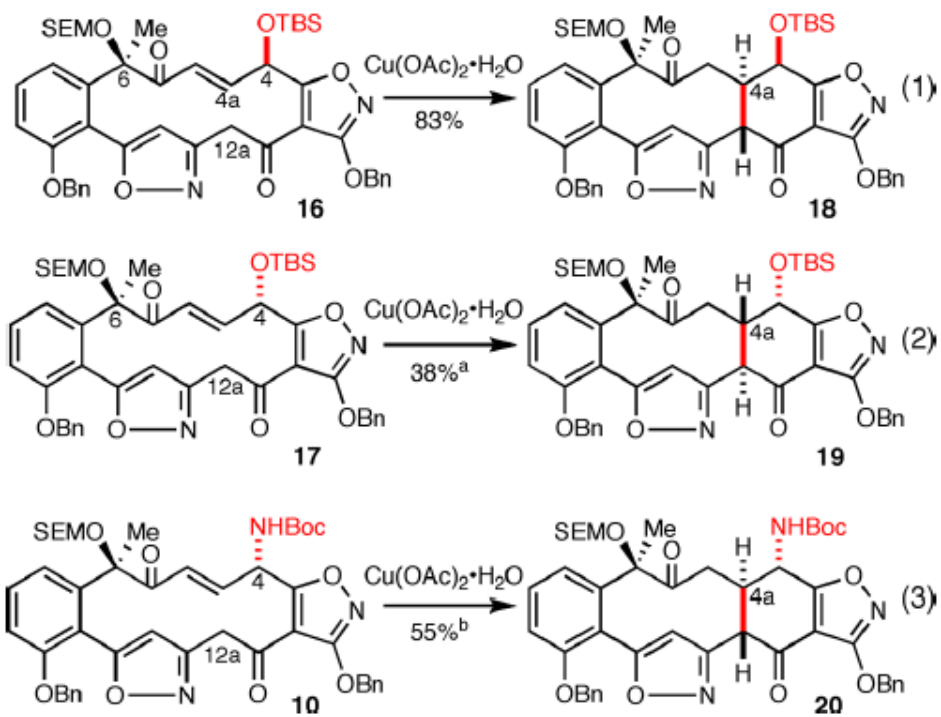
Transannular Michael Towards Tetracyclines

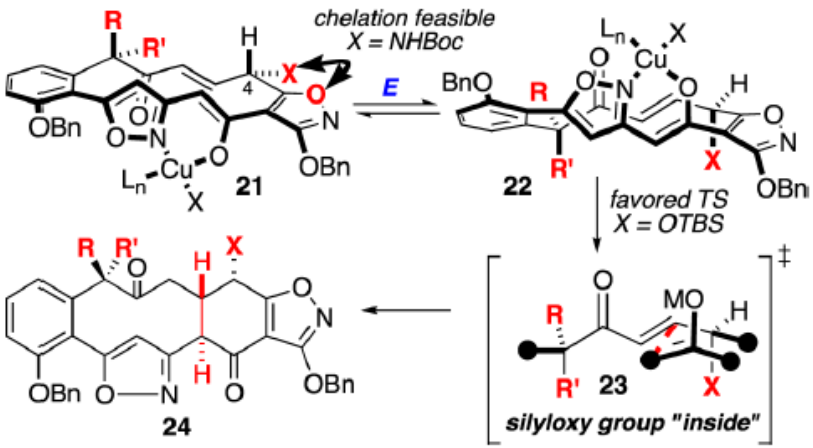


Tetracyclines : Major class of antibiotics. Treatment of choice for UTIs, chlamydia, anthrax, bubonic plague.

Michael addition followed by transannular aldol to form C4-C12 and C5-C11 linkages.

Stereochemistry of Transannular Michael



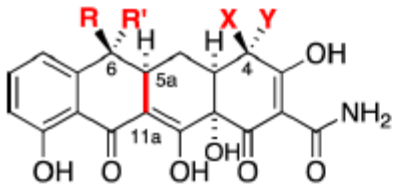


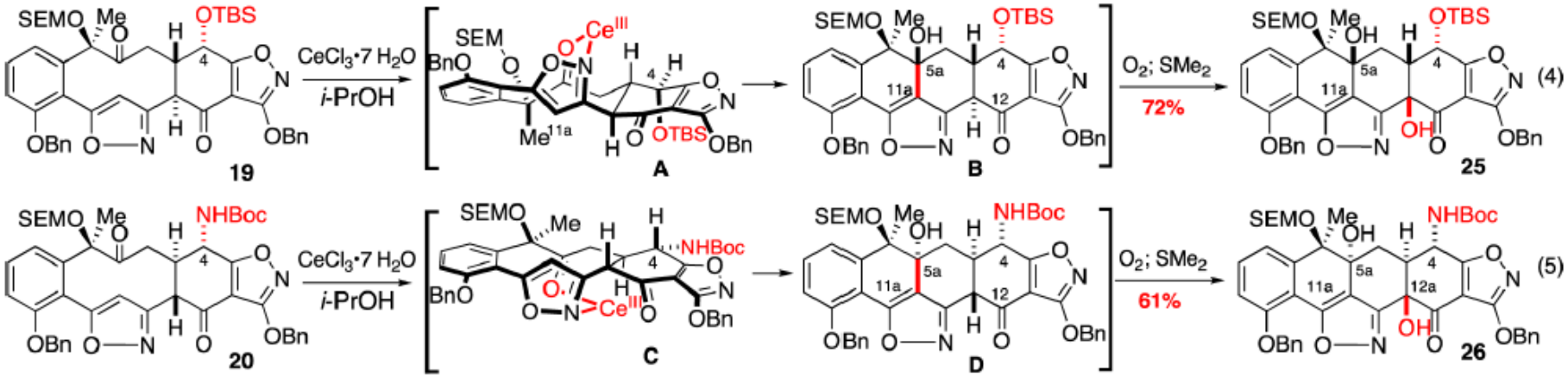
Silyl group prefers axial position!

NHBoc instead of silyl group reverses the selectivity, possibly due to chelation.

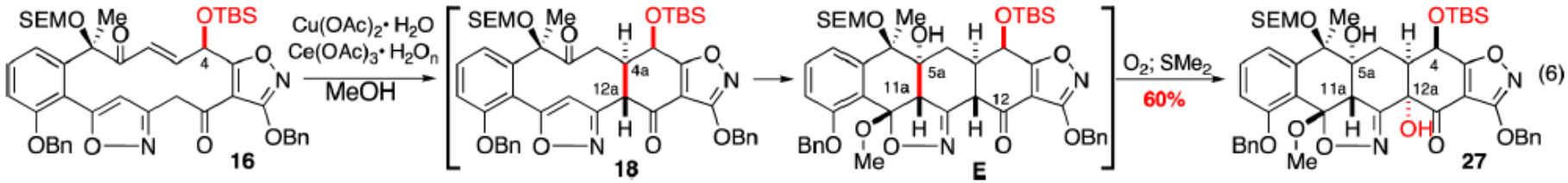
No good explanation yet as to why.

Single Pot Double-Michael Reac



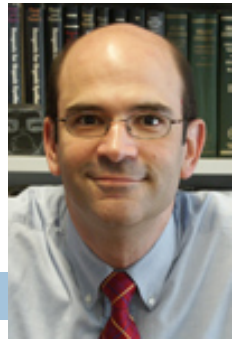


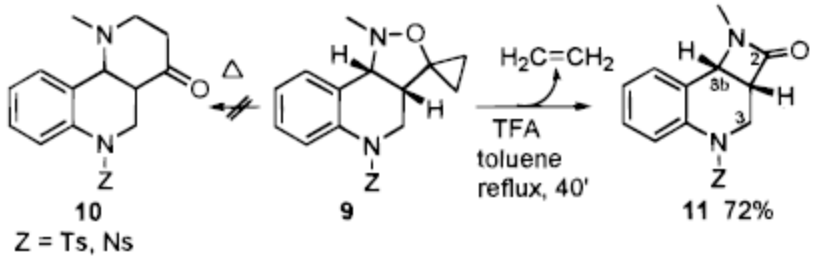
Cerium chloride to promote the transannular aldol reaction.

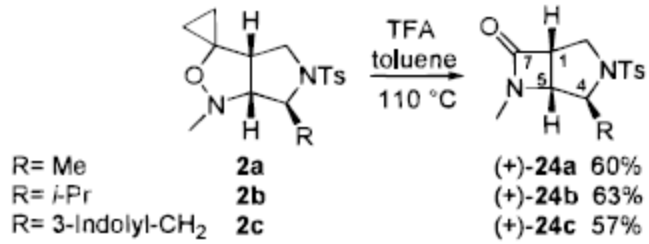


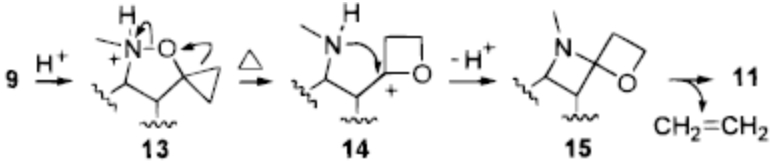
In a one pot procedure, MeOH captures the oxocarbenium ion formed in the transannular aldol.

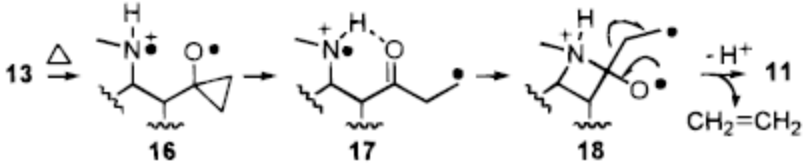
Carreira – Synthesis of Small Rings



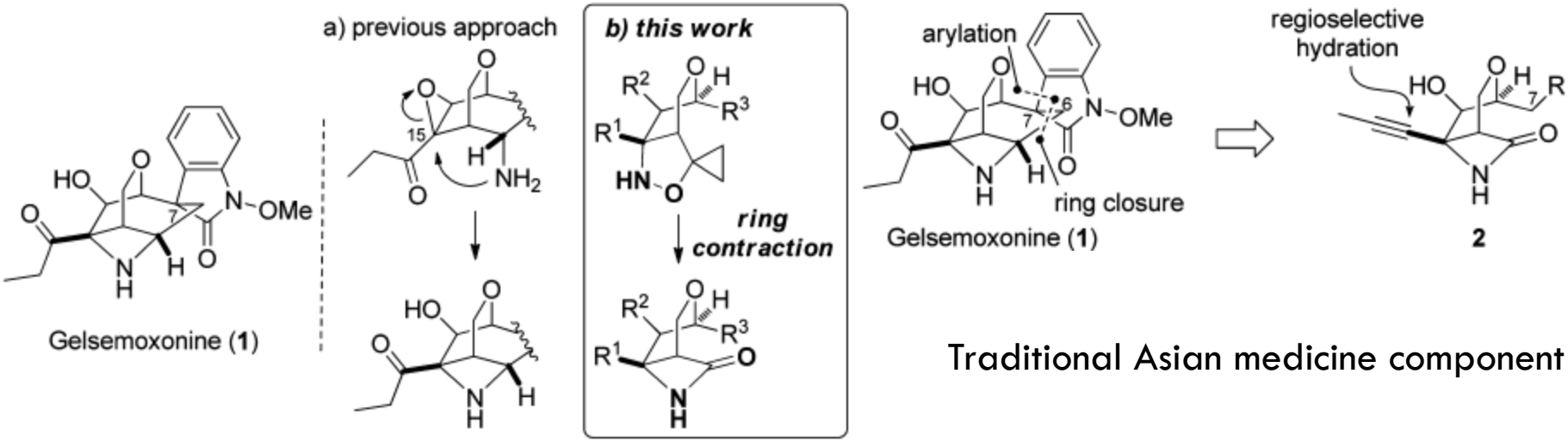






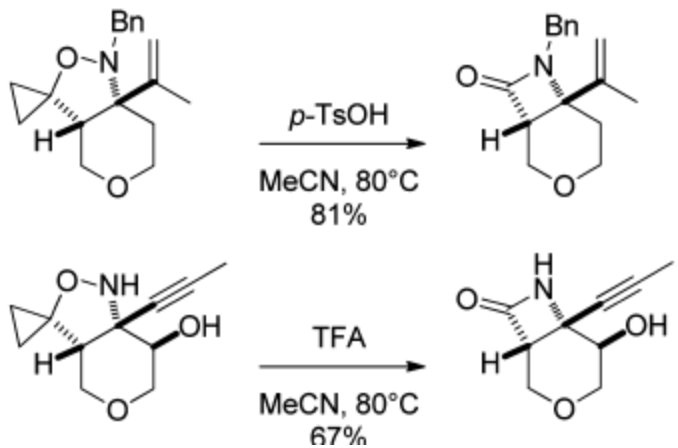


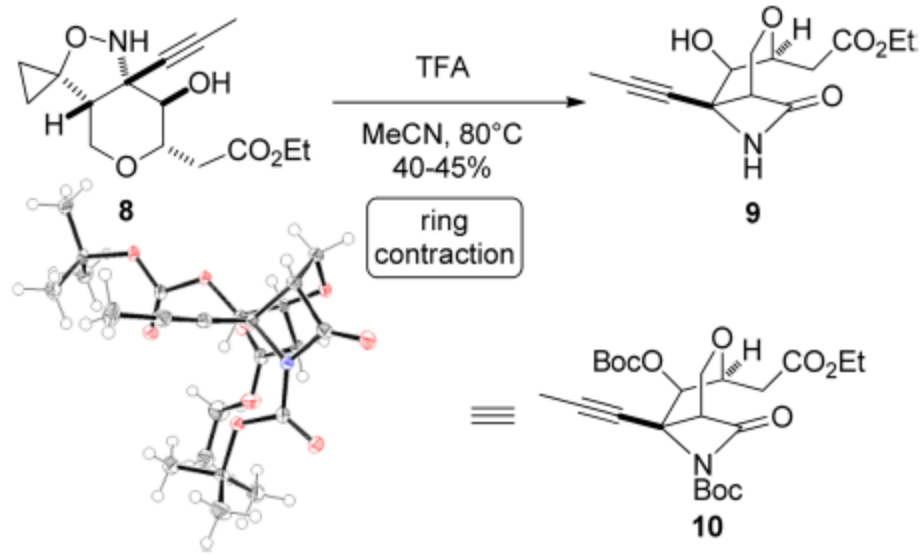
Many pathways proposed. Potentially a carbene type intermediate.



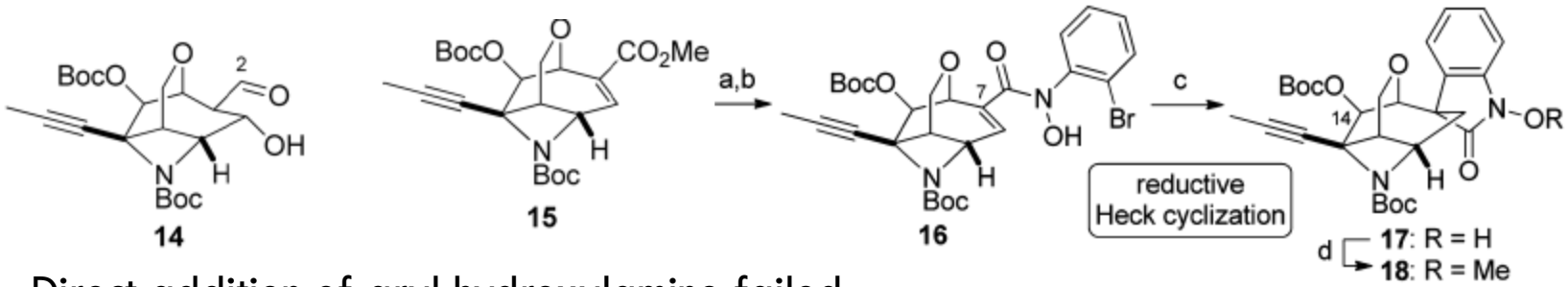
Traditional Asian medicine component

Total Synthesis of Gelsemoxonine



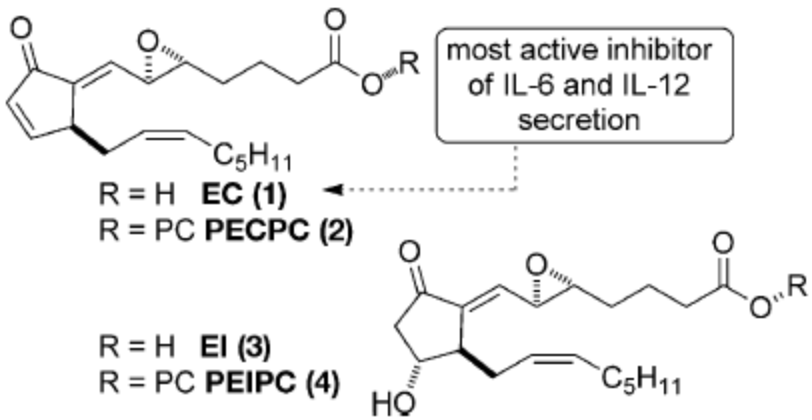


Studies on model system and actual precursor were successful.

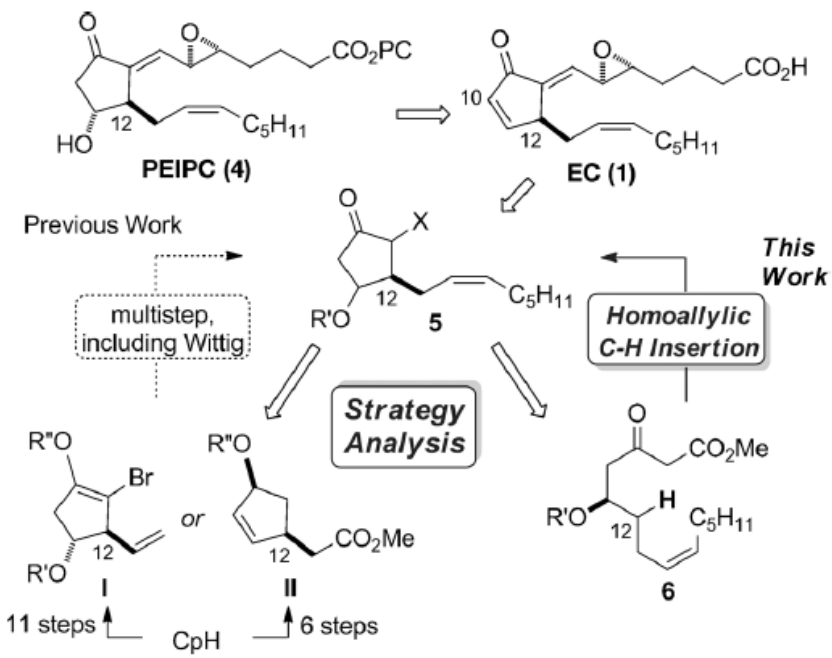


Direct addition of aryl hydroxylamine failed.
Cannot generate enolate of **14**.
Reductive Heck to form **17**.

Synthesis of Epoxyisoprostanes

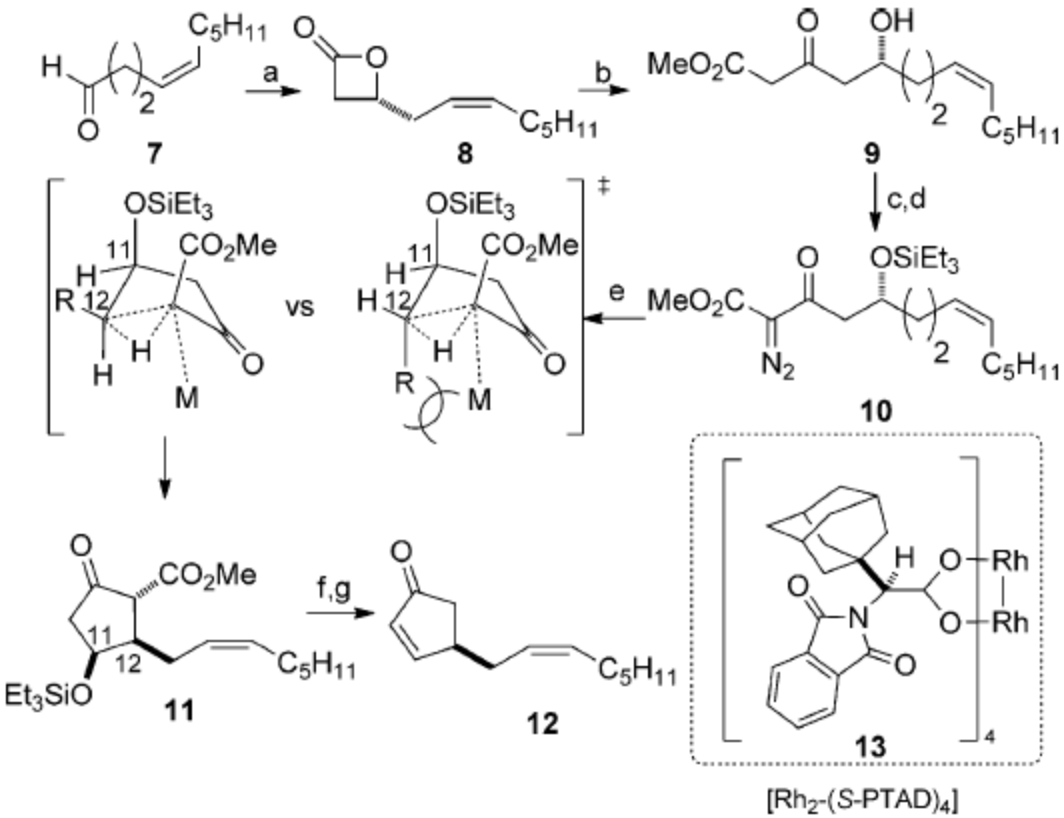


Human derived natural products.
Major control factors for inflammation.
May also play a big role in obesity by controlling fat cell distribution.



Extremely sensitive (<5 min half-life in aqueous solutions.)

Synthesis of Cyclopentenone Moiety

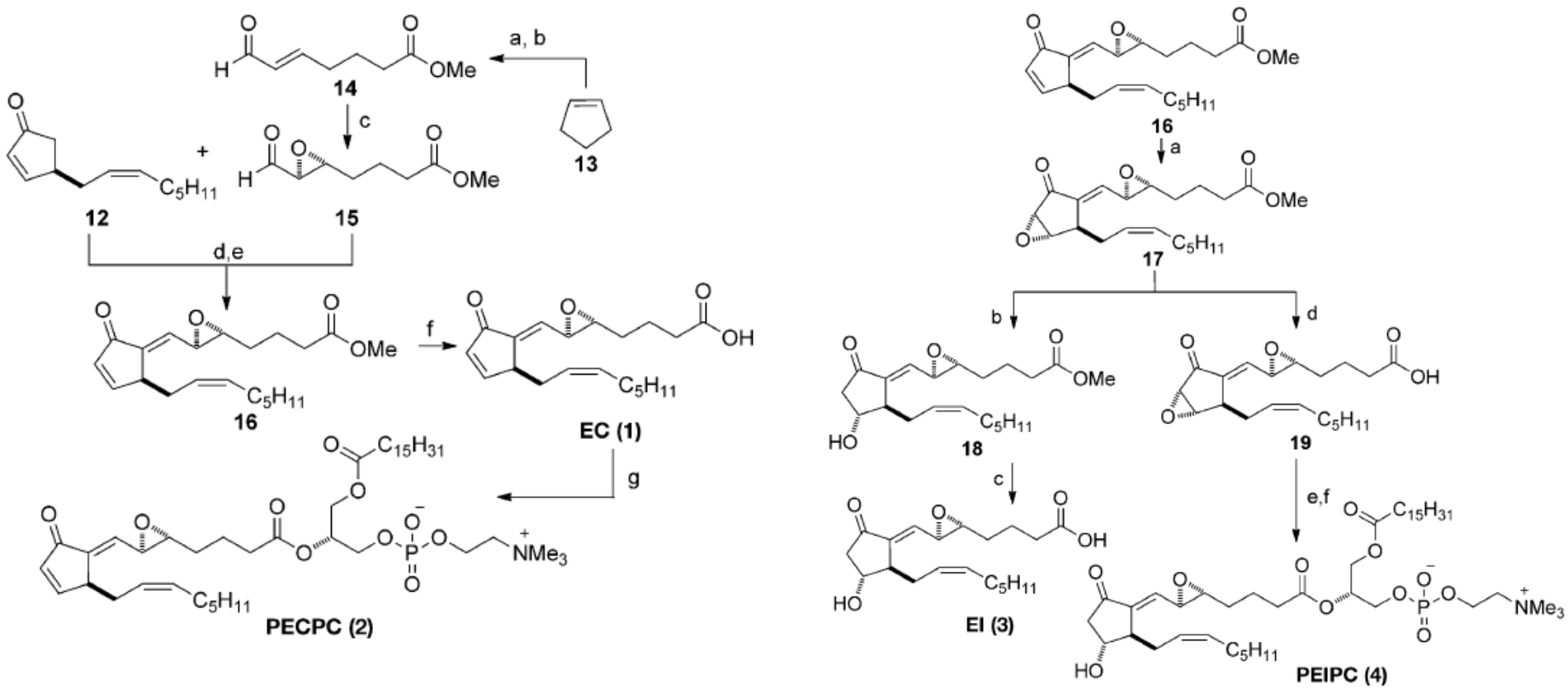


Ketene addition with TMS-quinidine to form **8.**

DuBois Catalyst
to form cyclopentanone ring.

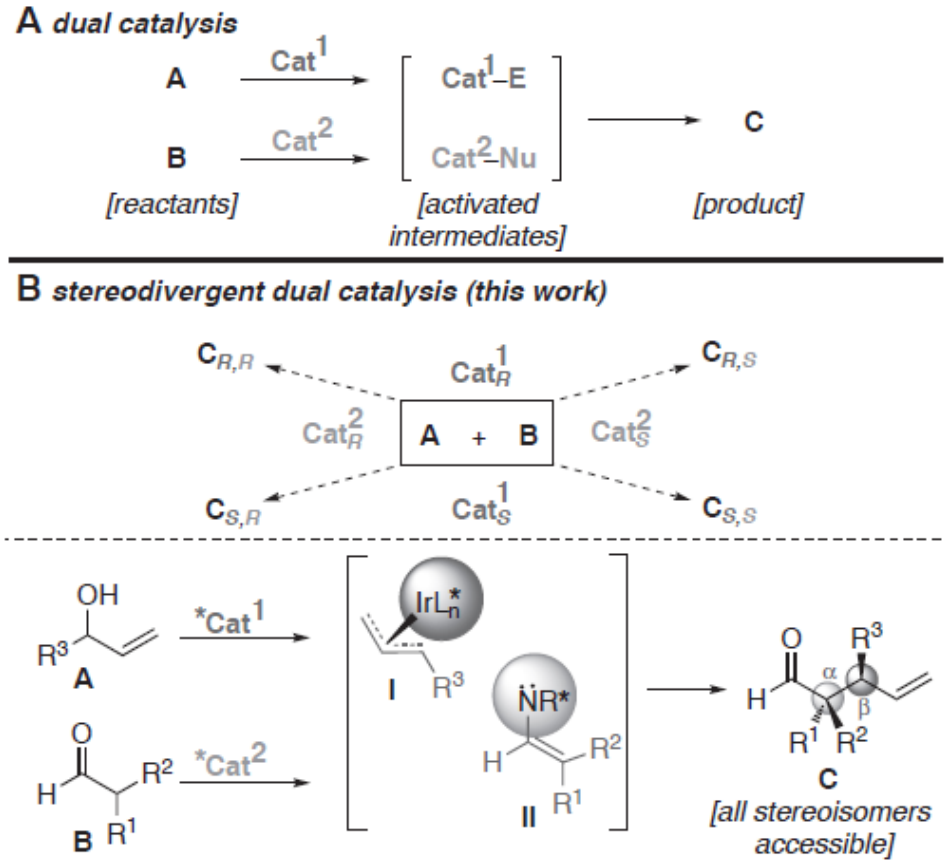
12 is a key intermediate for both PEIPC and PECPC

Synthesis of PECPC and PEIPC



Tedious purification due to presence of phosphocholine. Can easily convert to other arachnidoic acid derivatives. (ex. PEIPC->PECPC $t_{1/2}$ is 3 min at pH 7.4)

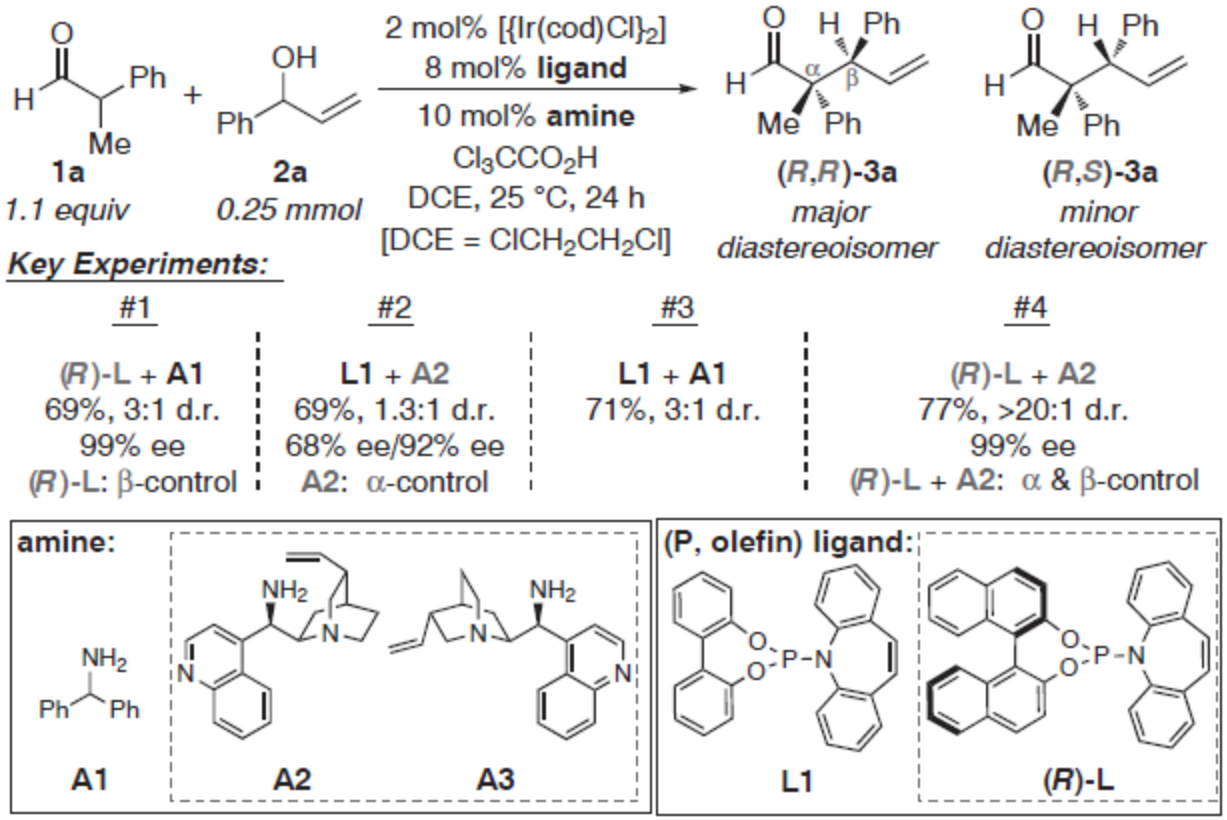
Divergent Catalysis



Two independent catalysts, each of them responsible for a single stereocenter.

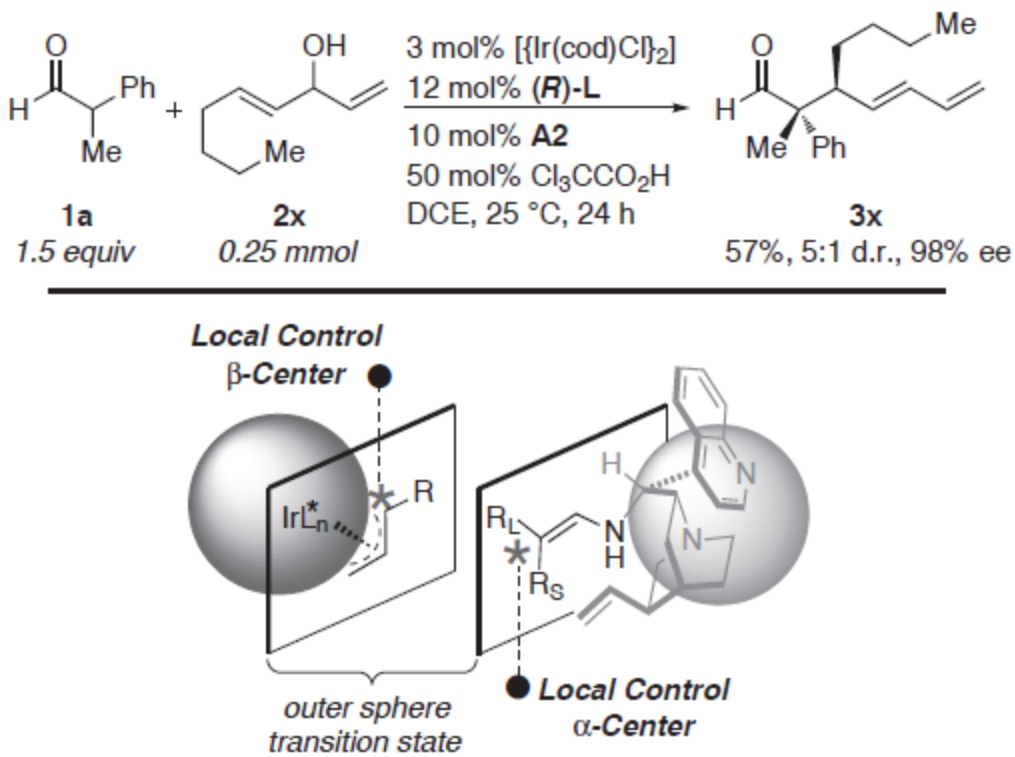
All four diastereomers of desired product can be made.

Key to Selectivity is lack of Cross-Reactivity



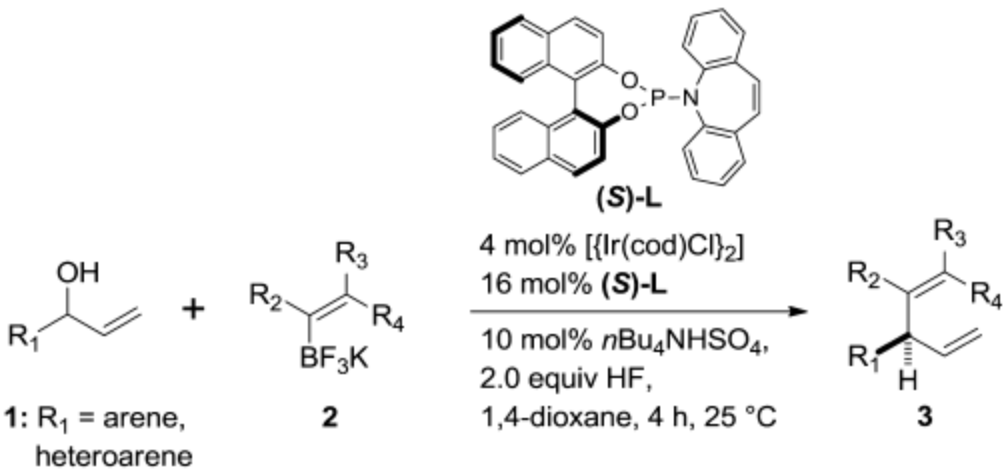
Iridium catalyst only interacts with allylic alcohol.
Cinchona-derived catalyst only interacts with aldehyde.

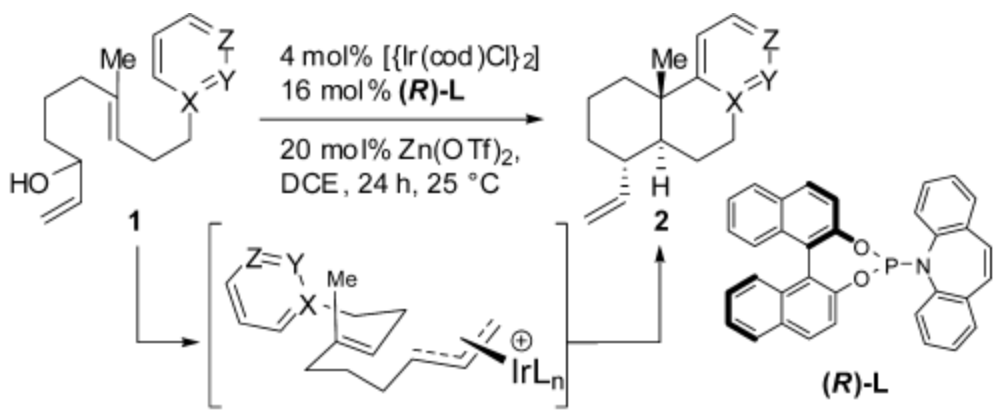
Proposed Mode of Action



Possible to form highly congested stereocenters with good selectivity.
Desymmetrization reactions also possible.
Independent steric hindrance mechanism.

Enantioselective Allylic Vinylation





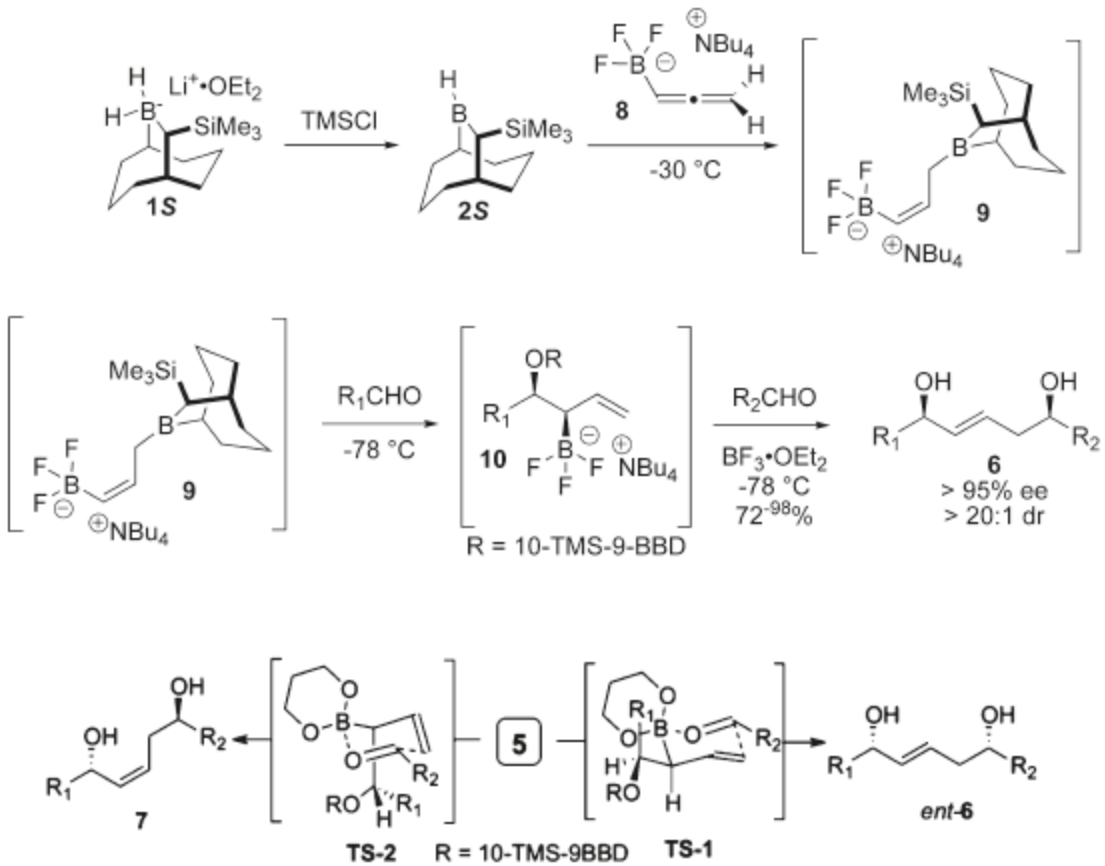
Vinylations proven difficult so far.

Key is use of ammonium bisulfate as a phase transfer source of acid.

Slow release of BF_3K salt

Cationic-type polyene cyclizations possible.

Roush – Boron Mediated Asymmetric Allylations



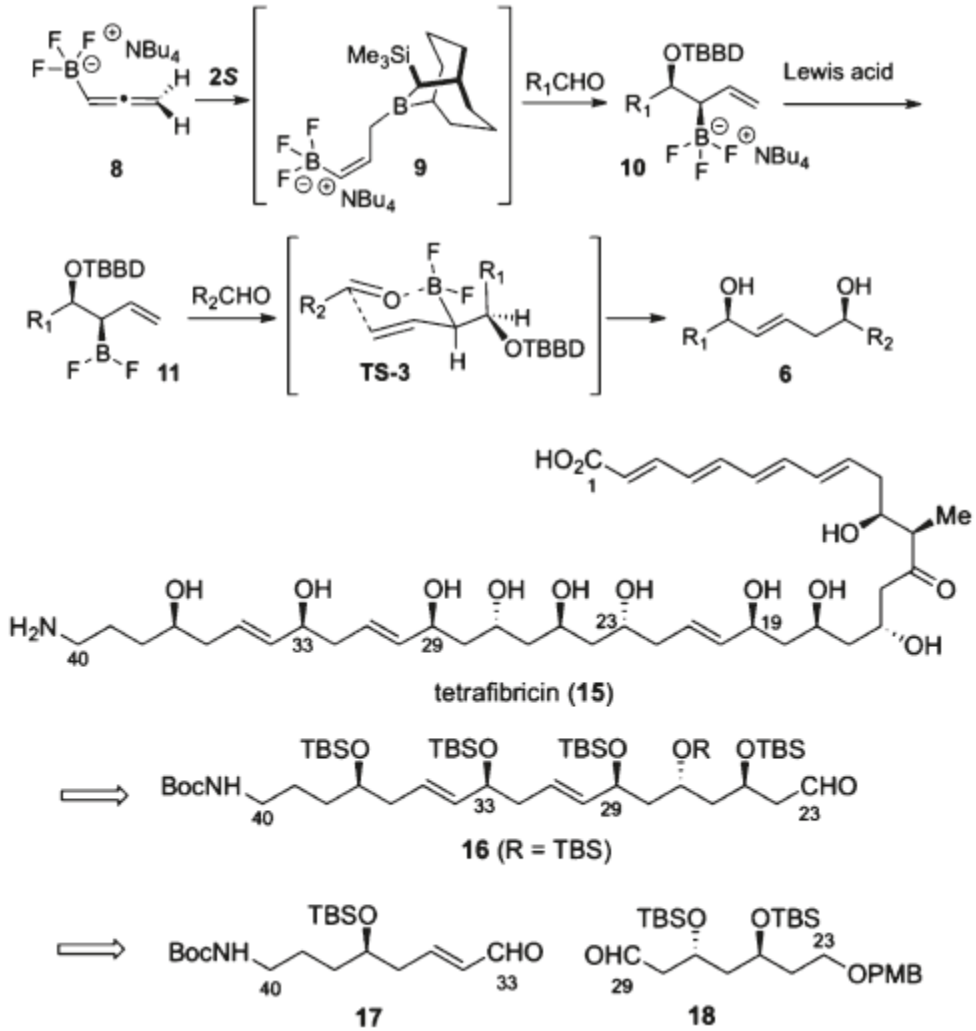
Start off with Soderquist borane **1S**

Bifunctional due to presence of BF_3K salt.

High diastereoselectivity for formation of 2-ene-1,5-diols.

Changing to 1,3-propanediolylborane leads to opposite enantiomer.

Synthesis of Tetrafibricin

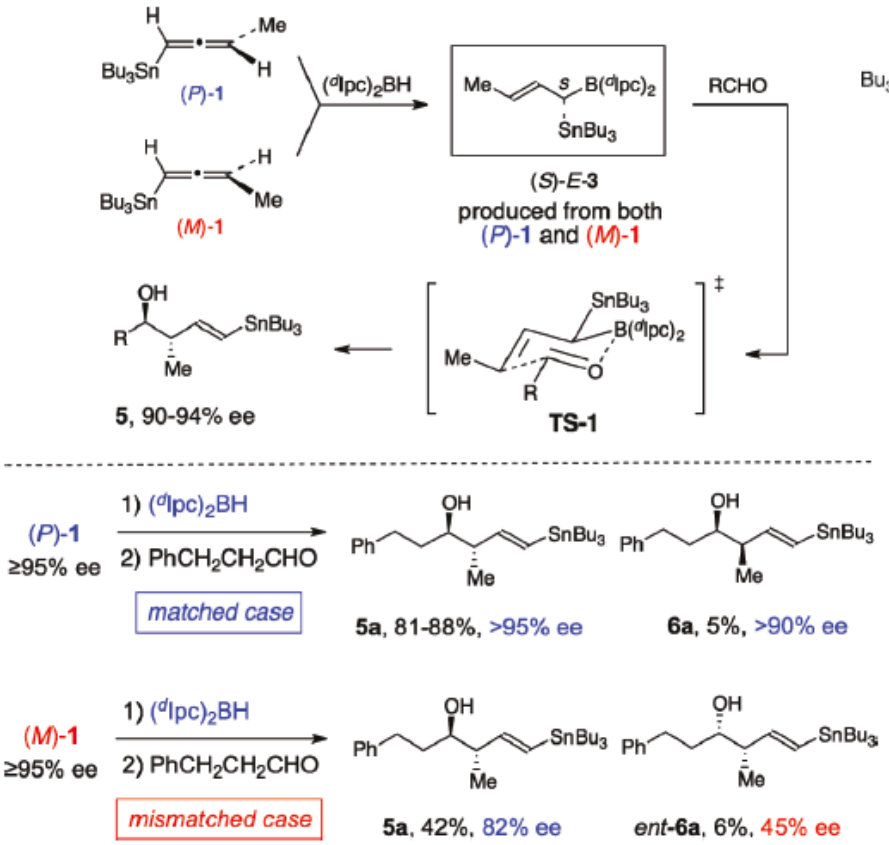


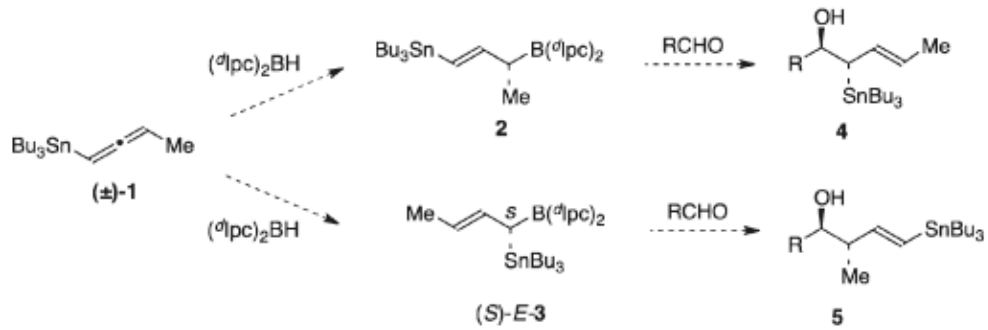
Second generation approach to preparing syn-diols.

Central fragment of the natural product tetrafibricin synthesized through this methodology.

C33-C29 disconnect.

Stereoconvergent Borylation of Allenes



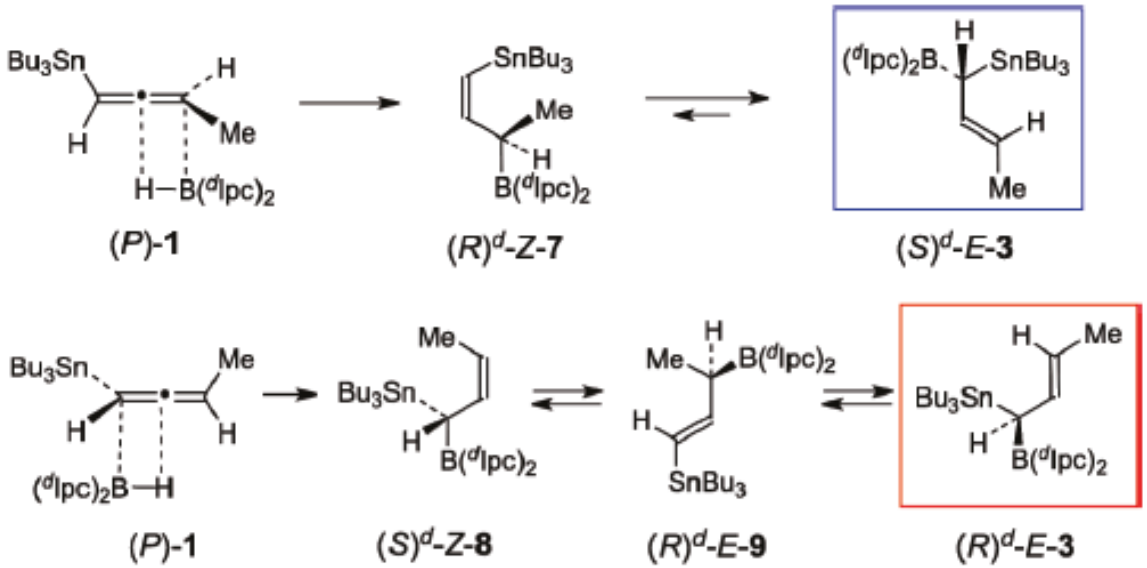


Bifunctional reagents derived from allenylstannanes – hard to prepare enantiopure.

Observed same product from both allene enantiomers.

Key experiment showed significant matched/mismatched effects.

Matched Case

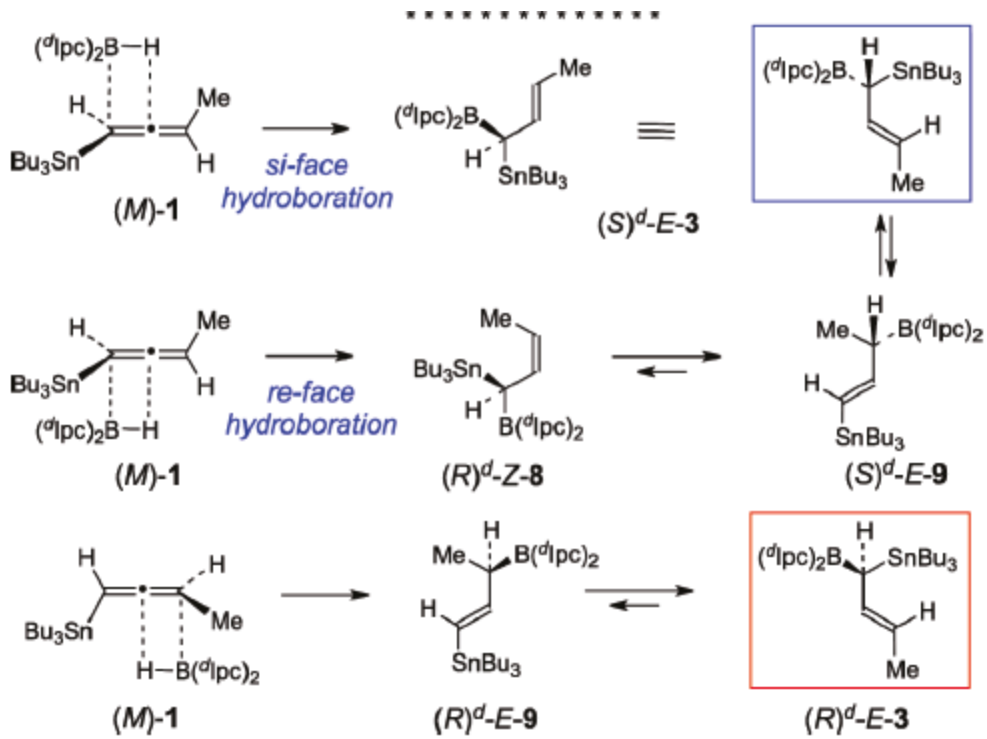


In matched case, (P)-**1** is selectively borylated at the distal double bond.

Boratropic shift to form (S)-**3**

(S)-**3** and (R)-**3** are diastereomers because of absolute configuration of Ipc group.

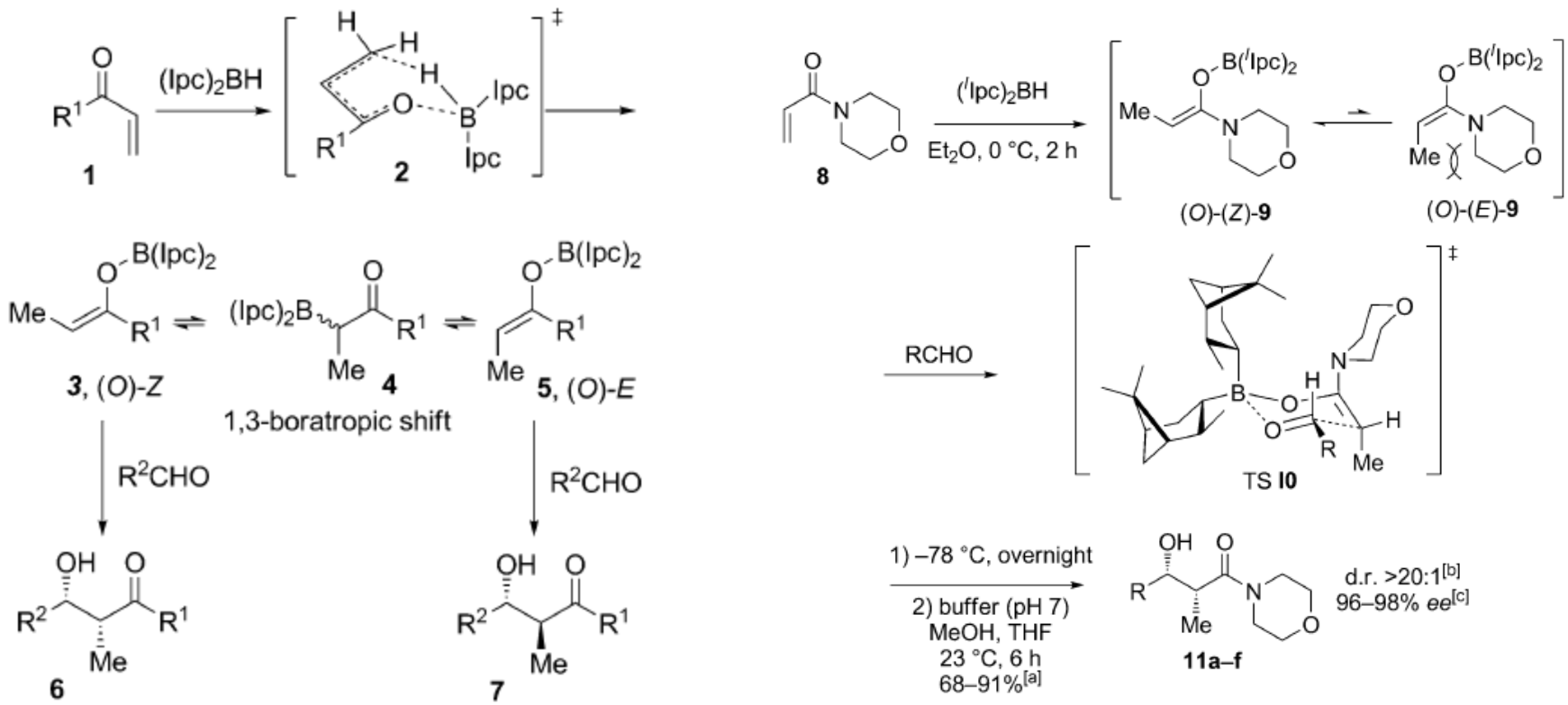
Mismatched Case



In mismatched case, proximal hydroboration of double bond leads to formation of (S)-**3**

Overall double asymmetric selection to give enantioconvergent borylation of allenes -> racemic allenes can be used as precursors.

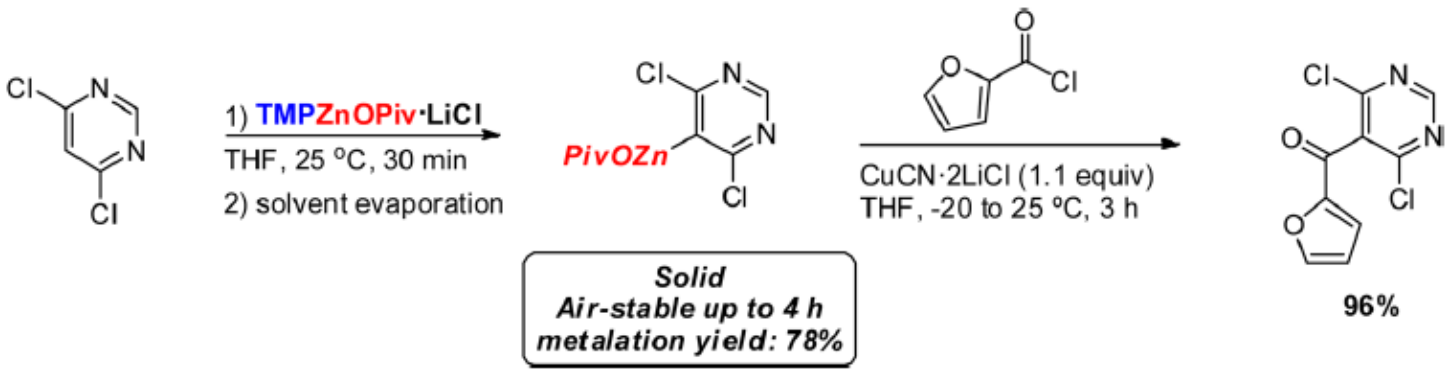
Boron Acrylamide-derived Enolates

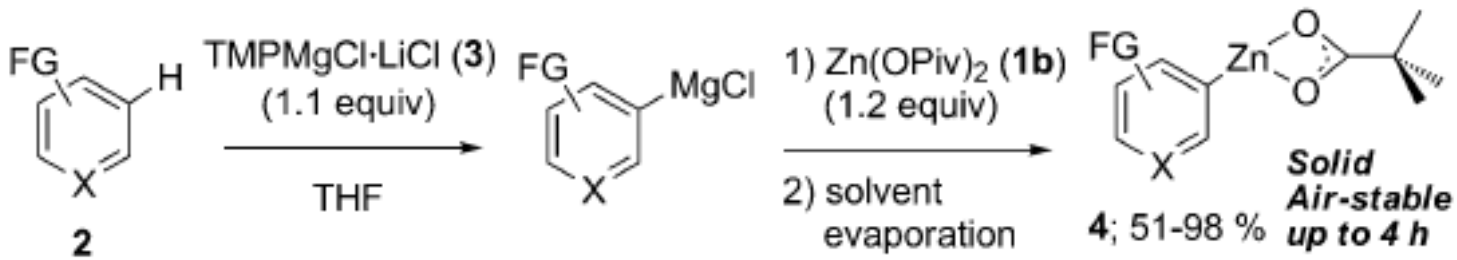


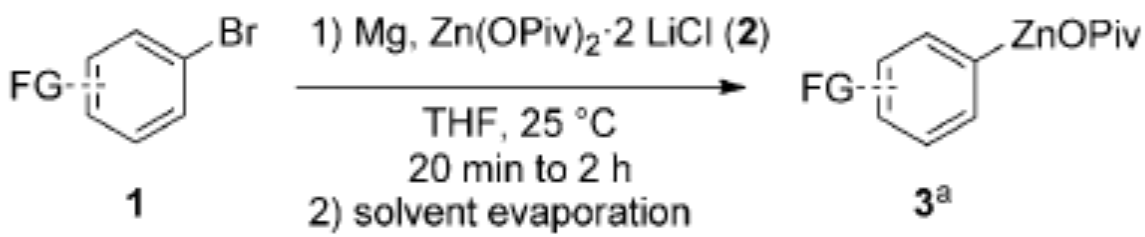
Enolate alkylations are done a million times over- this is really cheap.

Mol quantities for <$1. α,α-Disubstituted enolates give quaternary alkylation products.

Knochel – Air Stable Arylzinc Reage

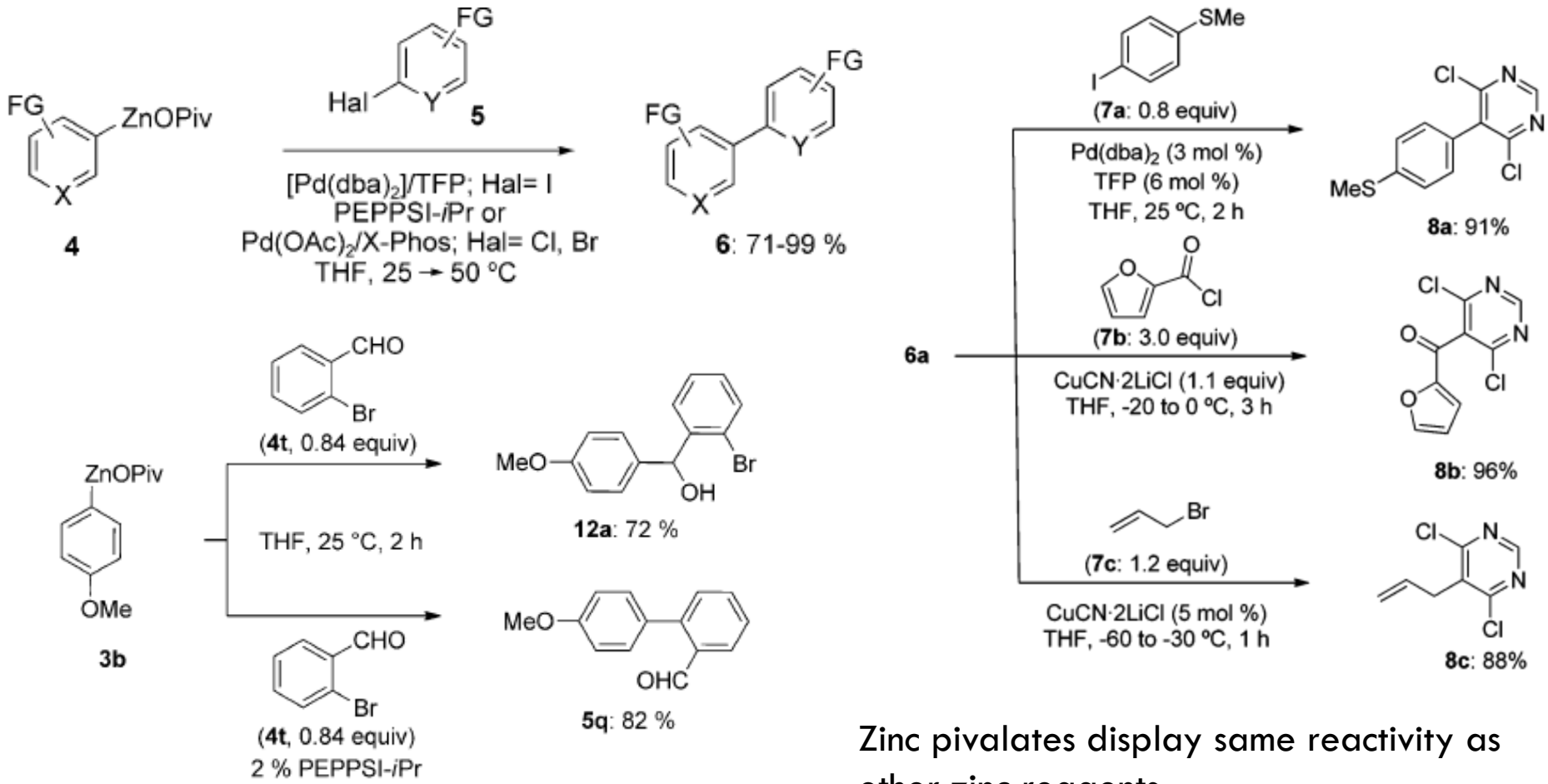






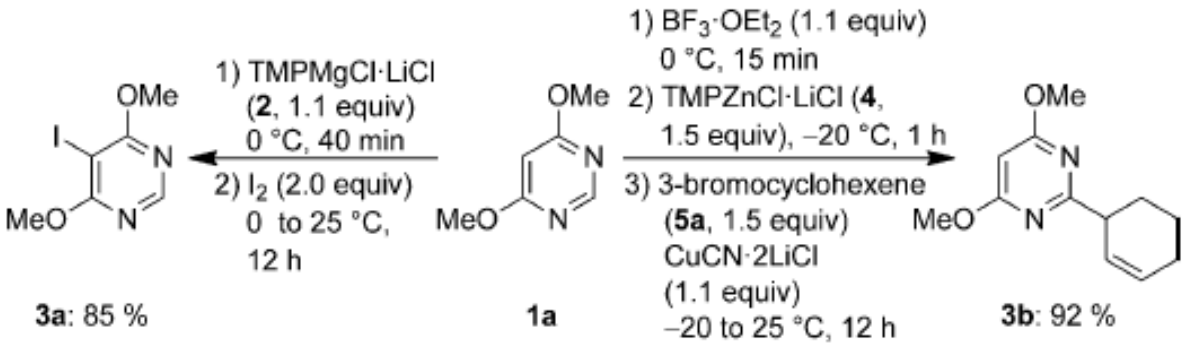
Zinc pivalates are semi-stable to atmosphere and engage in Negishi couplings.

Reactions of Aryl Zinc Pivalates

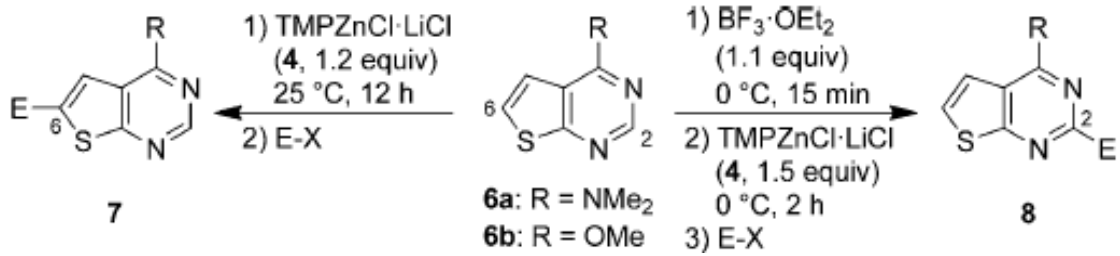


Zinc pivalates display same reactivity as other zinc reagents.
Highly FG compatible.

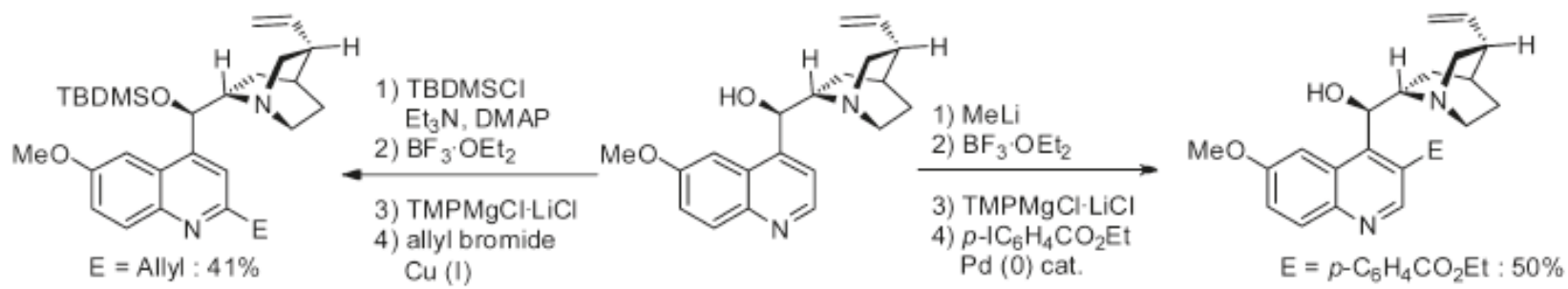
Site selective Metalations of Pyrimidines



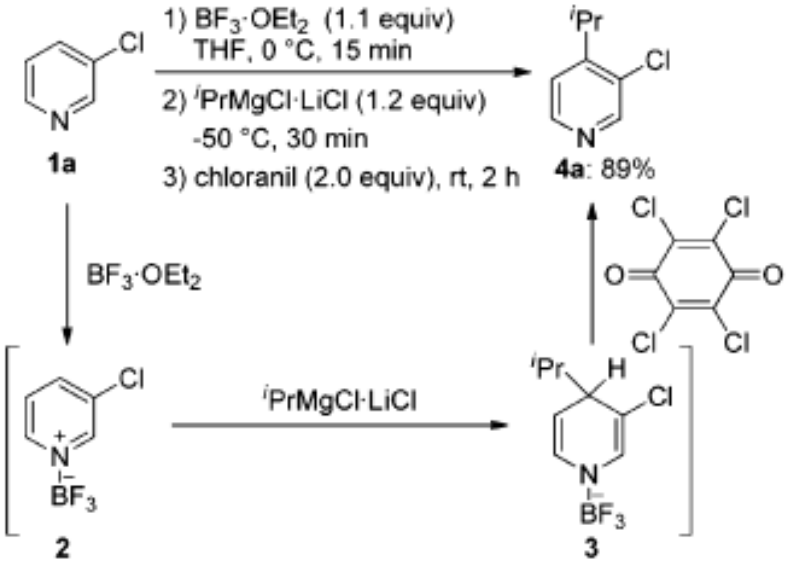
More reactive position is 5 position.
BF3-capping changes electronics to access alternative metalation sites.



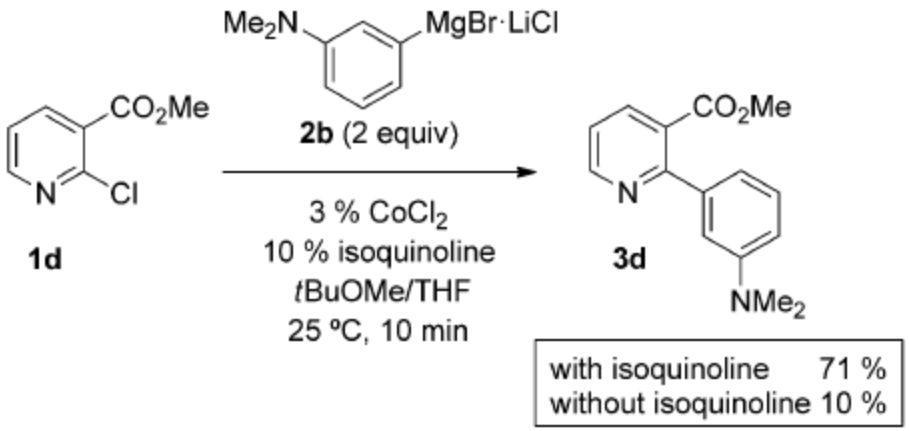
Wide variety of heterocycles amenable towards this type of blocking.



New Reactions of Chloropyridines



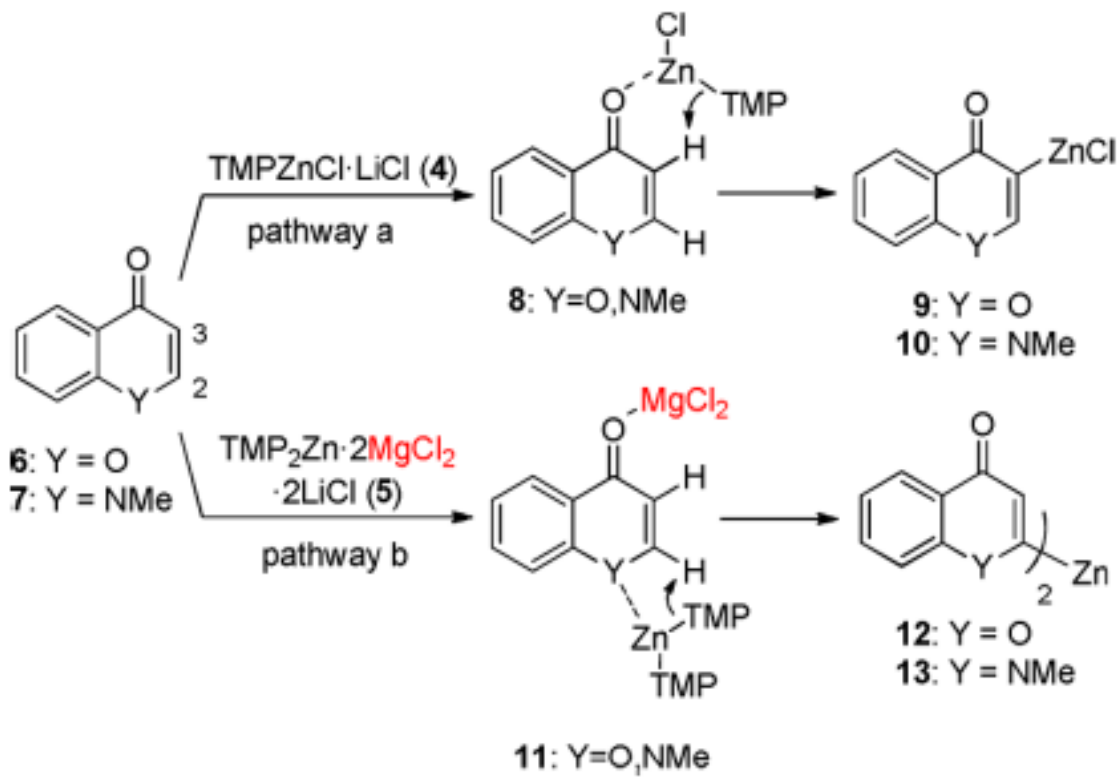
Direct addition into electron-poor pyridines.



Fe- or Co- catalyzed cross-coupling of arylmagnesium reagents.

Isoquinoline necessary to prevent homocoupling.

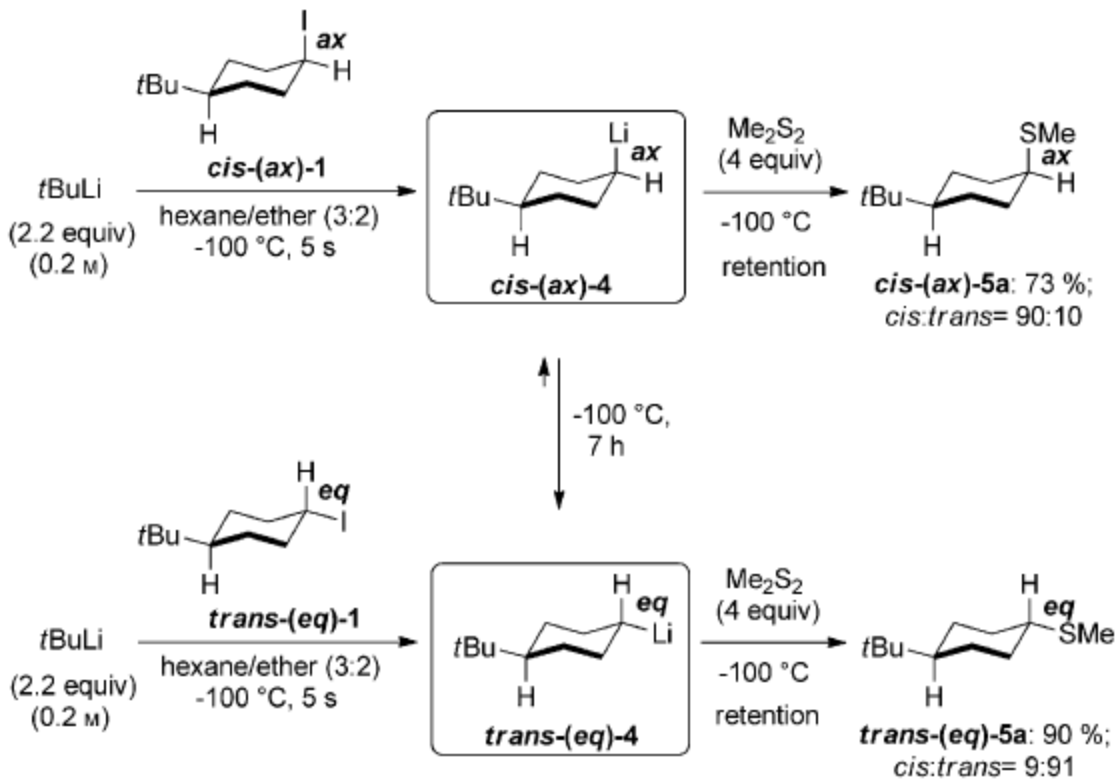
Site Selective Metalation of Flavones



Presence of Mg salts alters site selectivity of deprotonation.

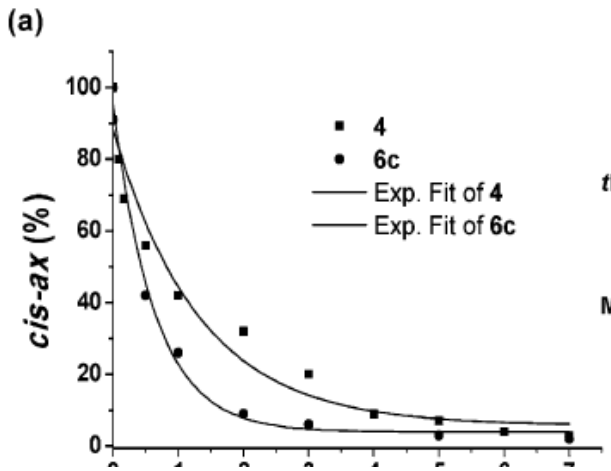
Can be used to functionalize chromones and chromone analogs – widely used in med. chem.

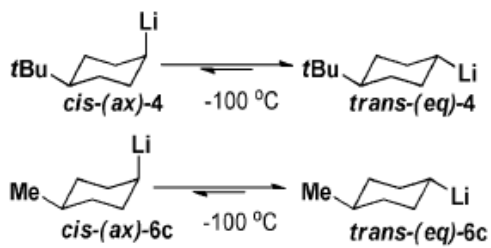
Configurationally Stable Secondary Alkyllithiums



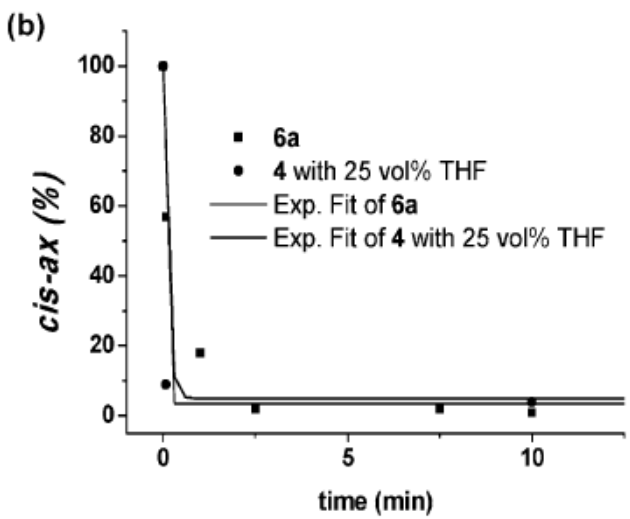
Alkyllithiums generally configurationally unstable. However, inversion can be suppressed at very low temp.

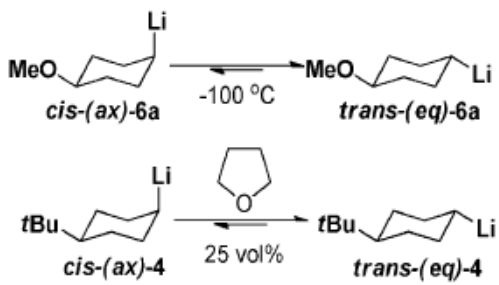
Isomerizations of Secondary Alkyllithiums



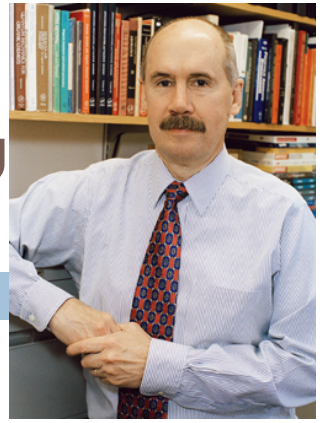


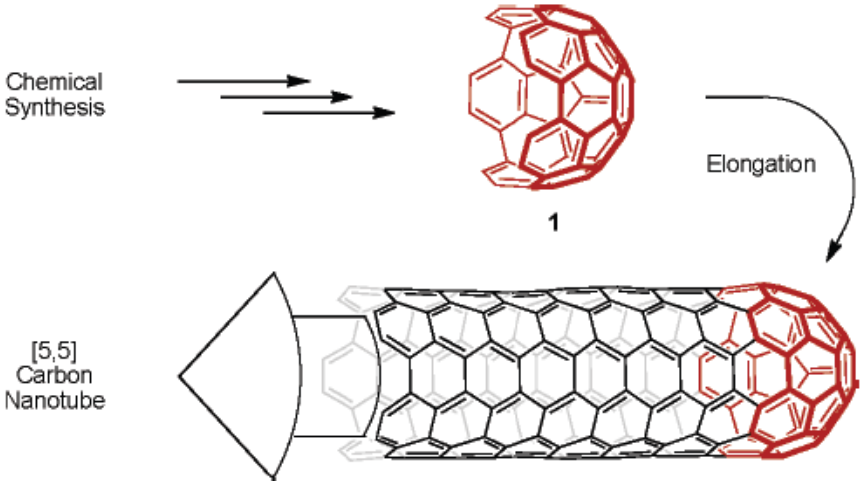
Presence of THF leads to increased isomerization rates

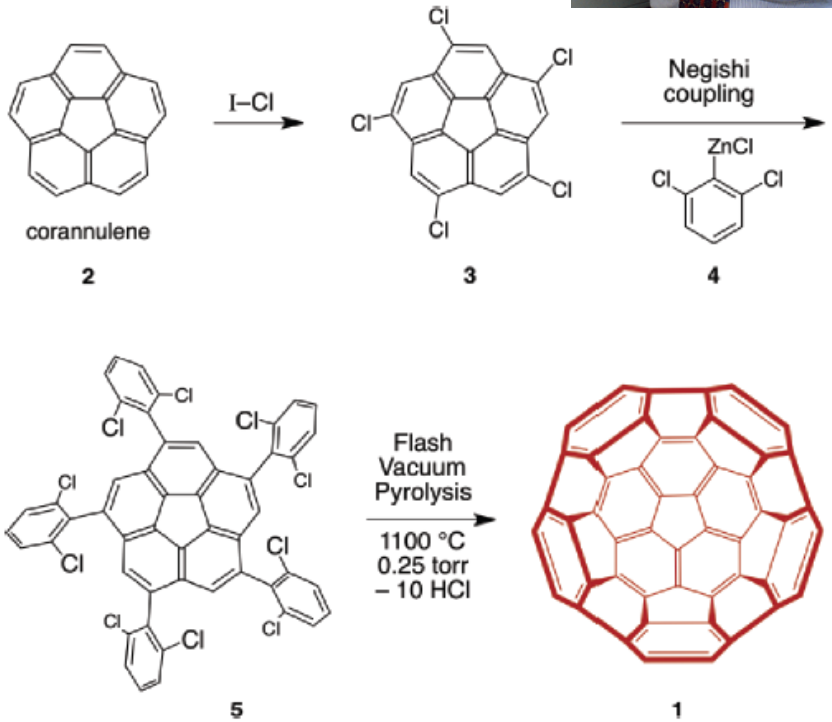




Scott – Synthesis of Carbon Nanotu







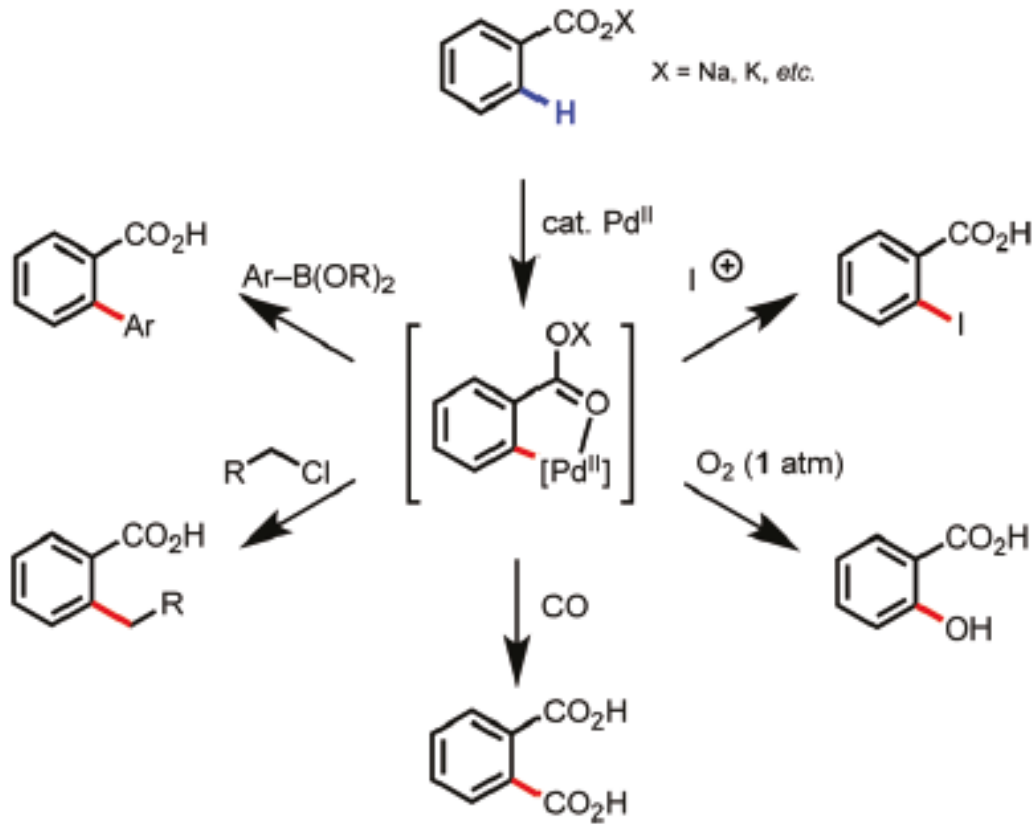
Synthesis of 5,5 carbon nanotubes.

Mainly involving corannulenes.

Use of nitroethylene for DA in growth region.

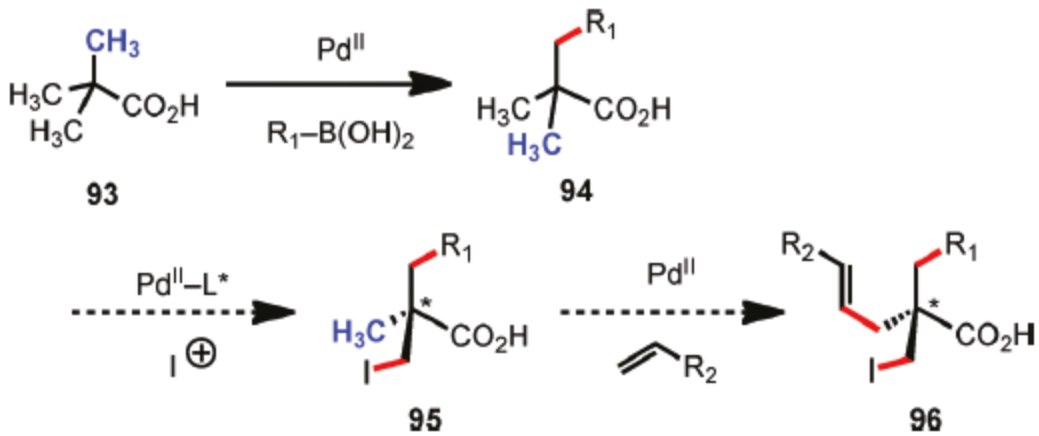
No major progress since UIUC visit.

Yu – Difficult C-H Activations



Weak coordination to Pd leads to highly reactive intermediates.
Many functionalizations possible.

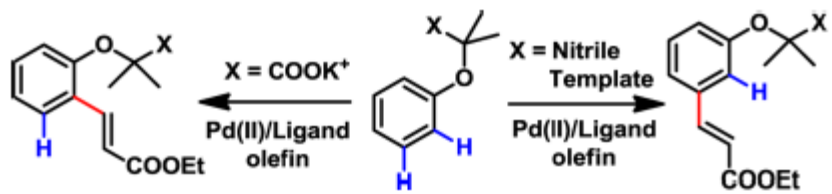
Carboxylate-Assisted C-H activation

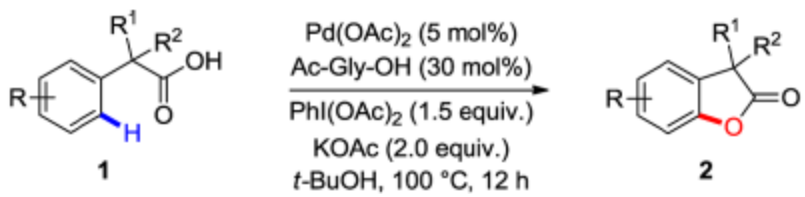


Ideal scenario:
Start with aliphatic acid (cheap)
Generate highly functionalized, enantioenriched products.

Major advance: use of carboxylate anions -
Just-right combination of coordination and reactivity.

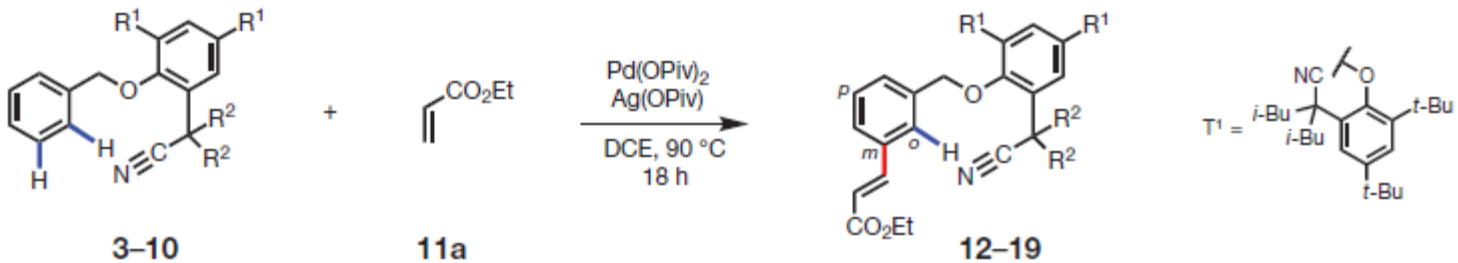
A Unified Approach

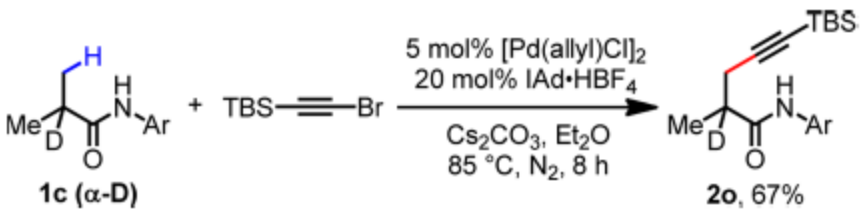




Phenoxyacetic acids are found in lots of drug molecules.

Direct functionalization for SAR studies.

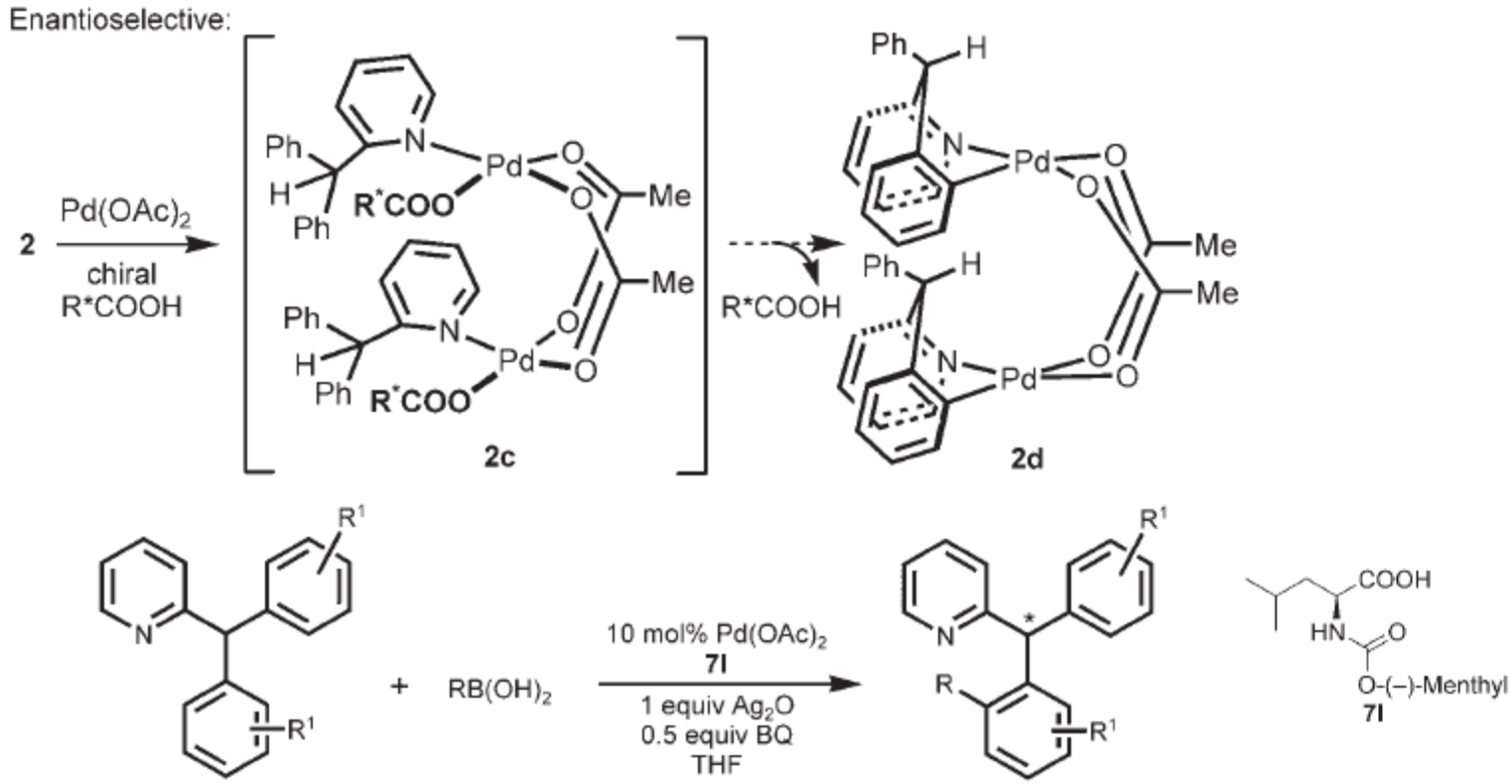




E-poor (Ar -4-$CF_3C_6F_4$) amides can engage in C-H activation.

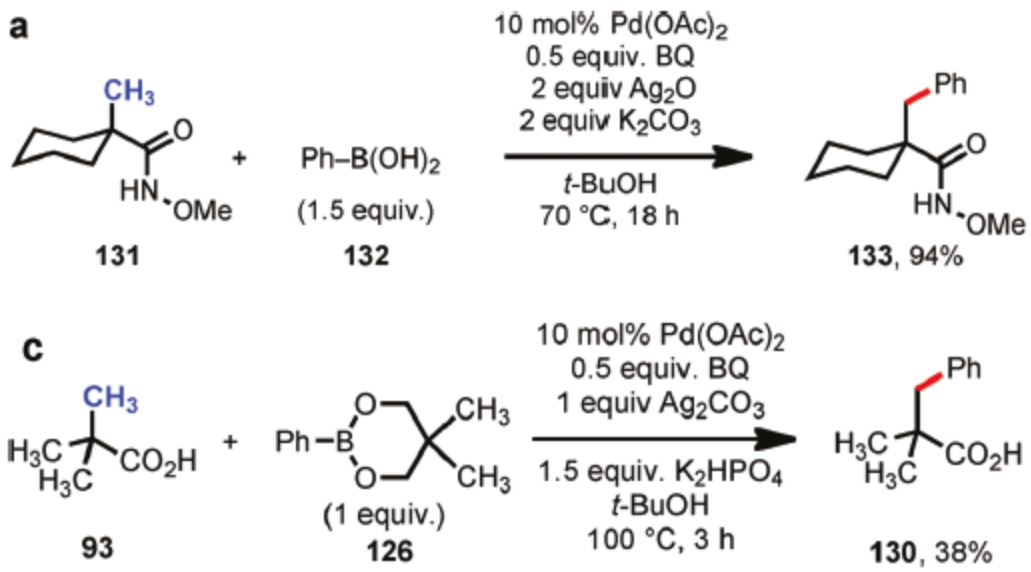
m-functionalization through U-turn chemistry.

Resolution of meso-arenes



Amino-acid derived chiral acids for desymmetrization of meso compounds.
69:31 e.r. for functionalization of 2-isopropylpyridine.

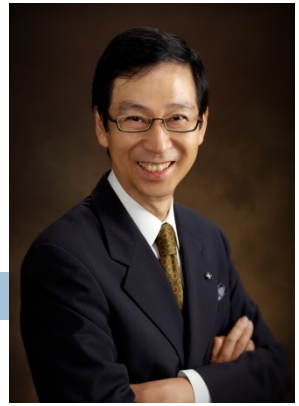
Direct sp3 C-H activation

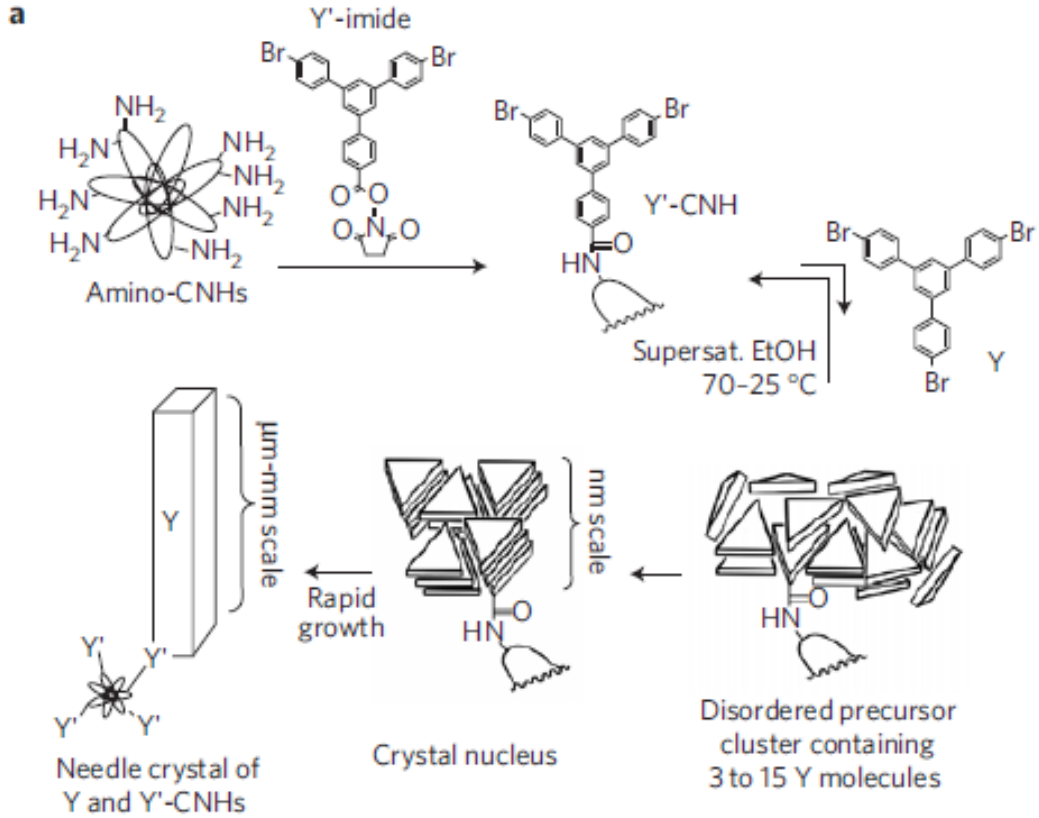


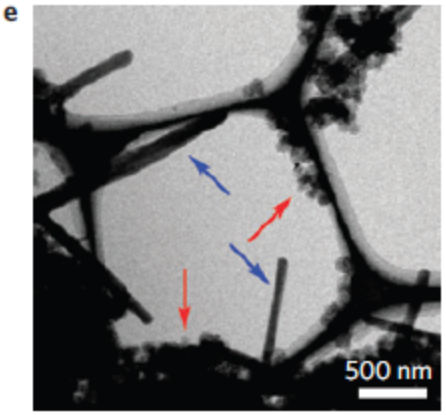
Single functionalization possible when Me-group is differentiated.

Generally overfunctionalization for t-butyl group (mostly difunctionalized).

Nakamura – SMRT-TEM

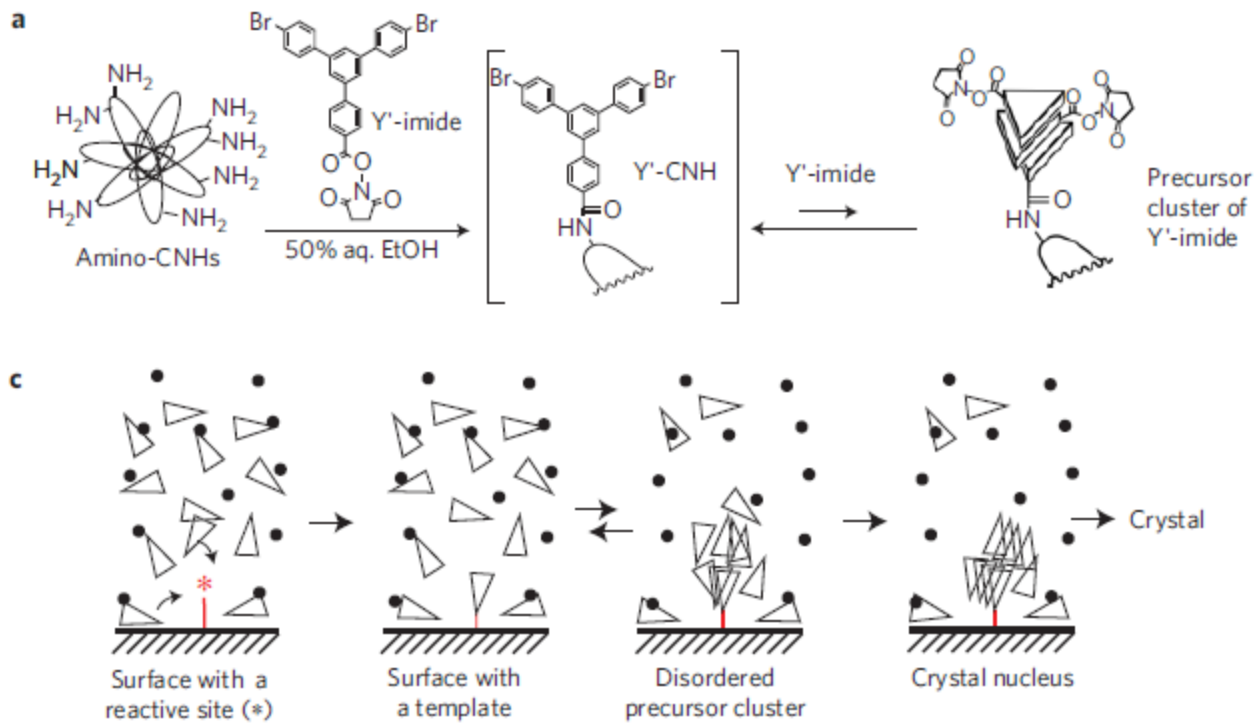






Study of crystallization kinetics and initiation through TEM.
Templating approach.

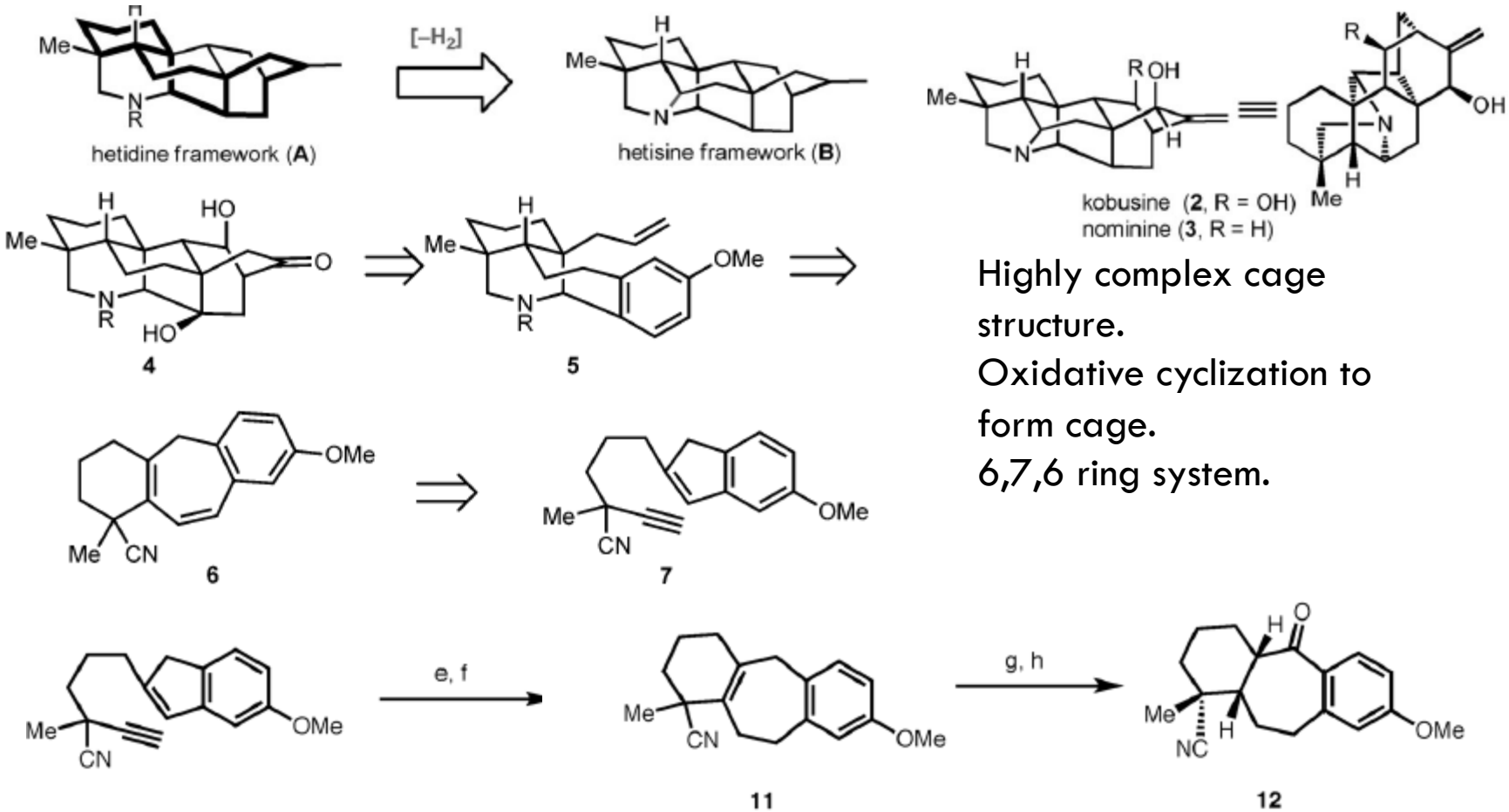
Crystal Nucleation and Growth



Heterogenous templated crystallization initiates similarly to homologous crystallization

2D->3D transition is critical.

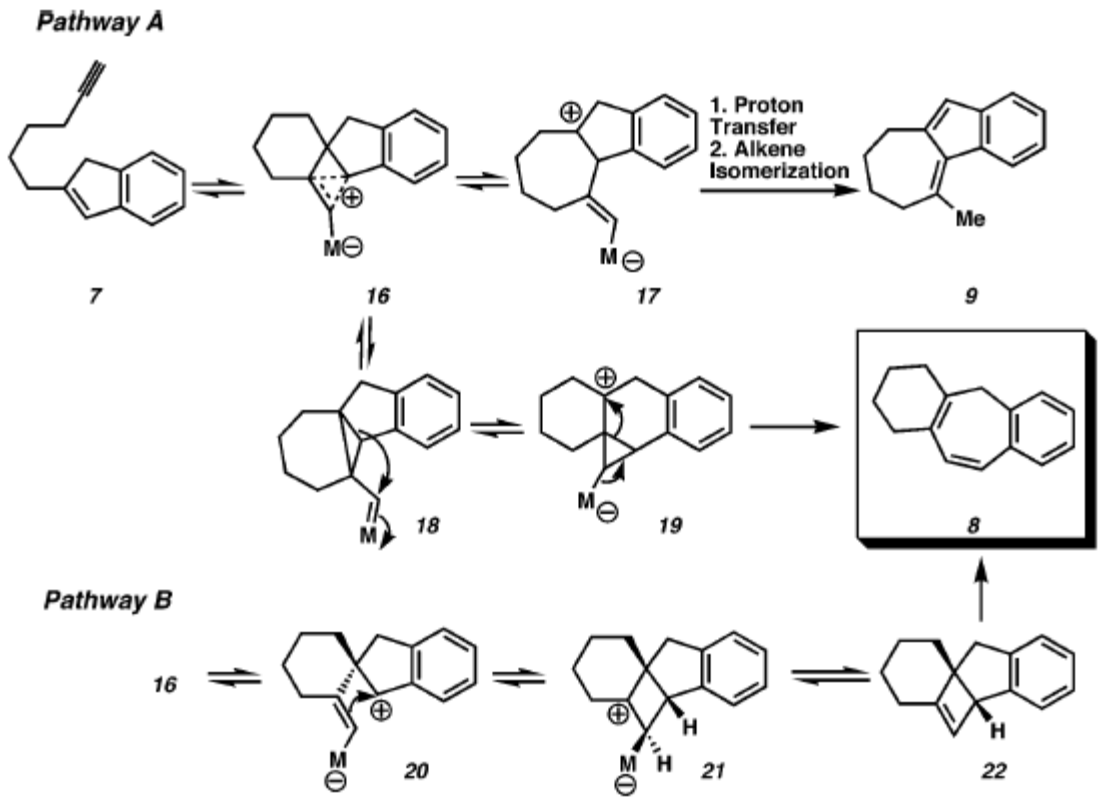
Sarpong – Hetidine Alkaloids



Highly complex cage structure.
Oxidative cyclization to form cage.
6,7,6 ring system.

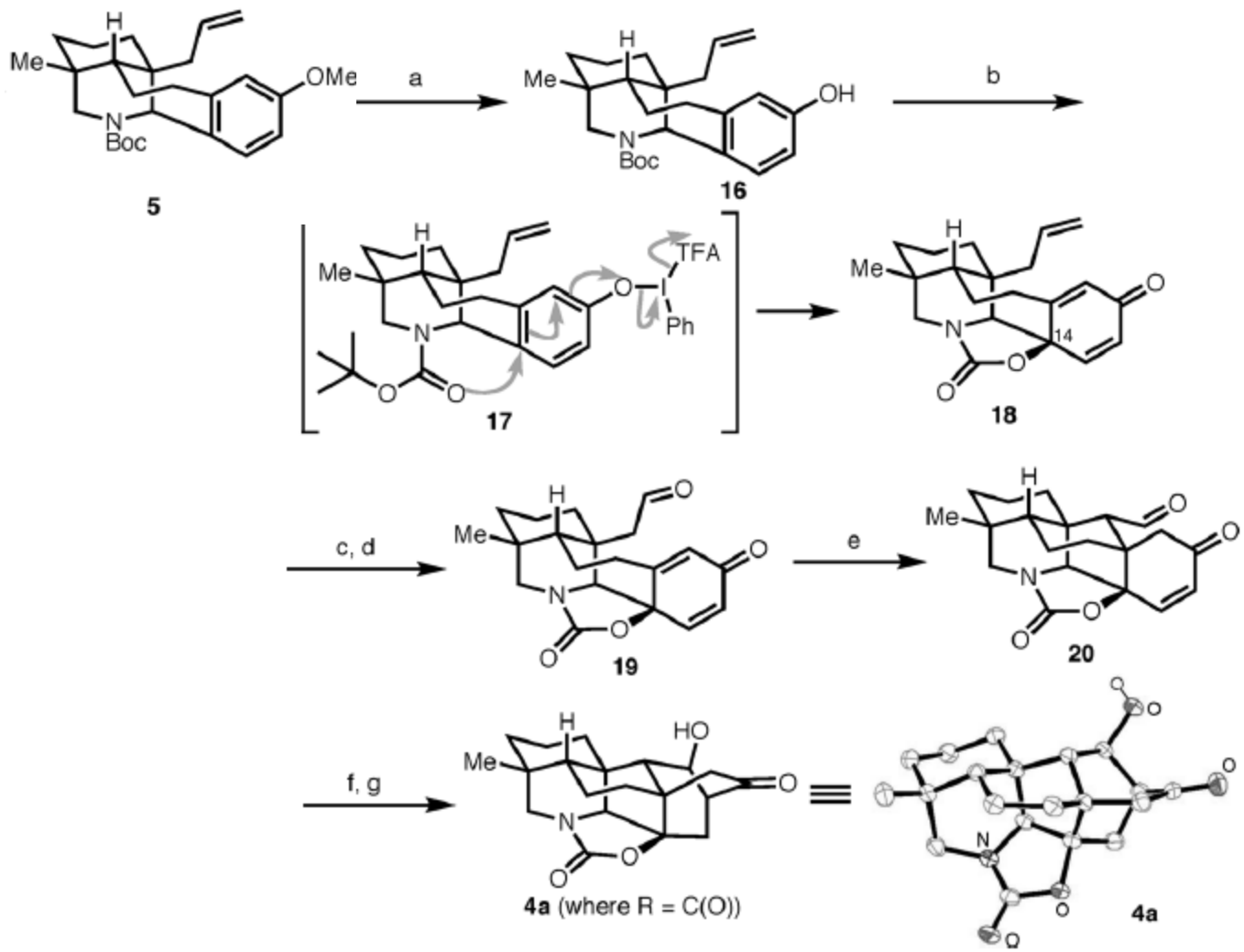
GaI_3-catalyzed cycloisomerization reaction to form key intermediate **11**

Mechanism of Ga-catalyzed cyclization



Did not mention which pathway is believed to dominate.

Synthesis of Advanced Intermediates

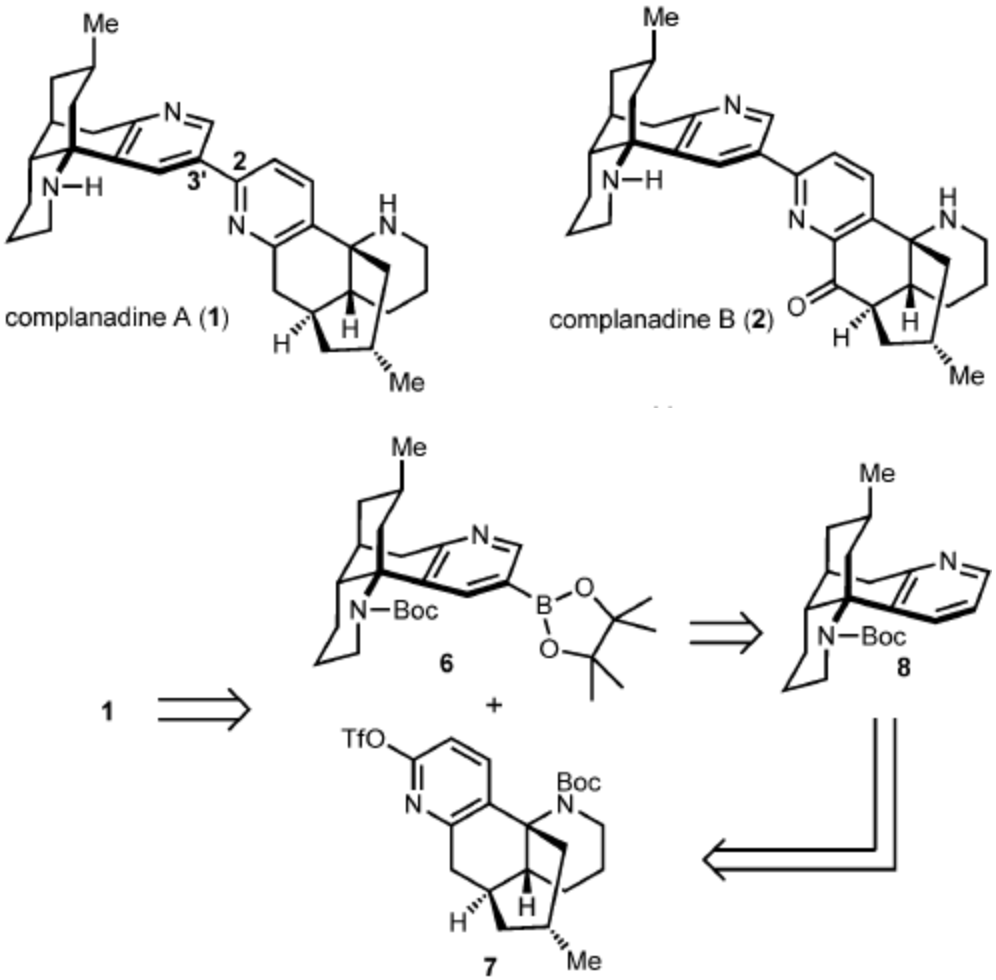


Many problems stitching the cage structure together.

Finally oxidative cyclization worked.

Still have not made final compound.

Complanadines

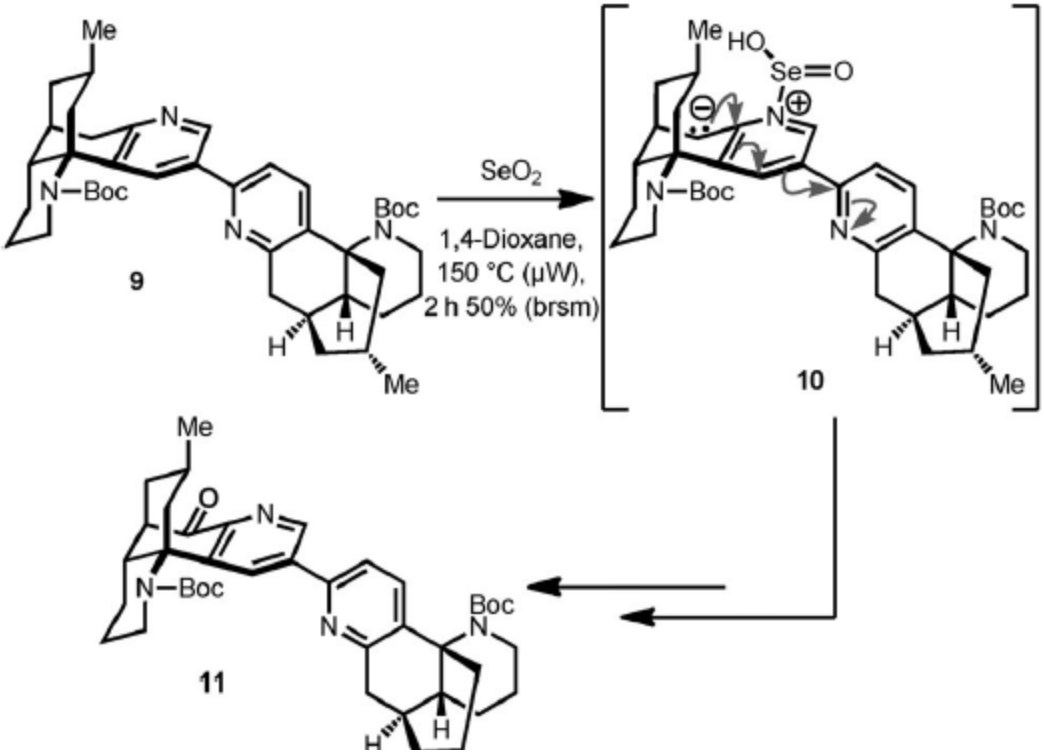


Dimers of lycopodium alkaloids.

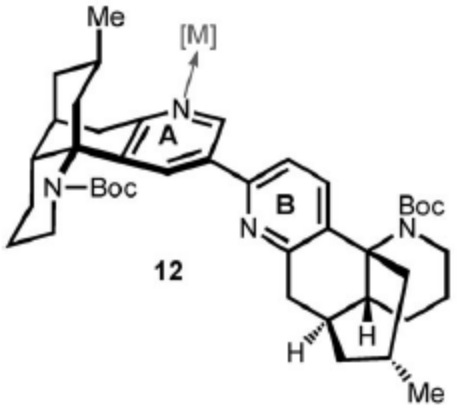
Pseudosymmetric.

Proposed biological dimerization.

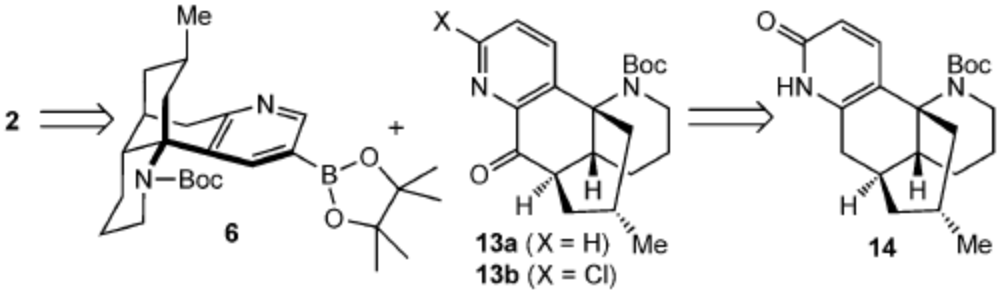
Synthesis of Complanadine B



Attempts to oxidize the eastern half failed.

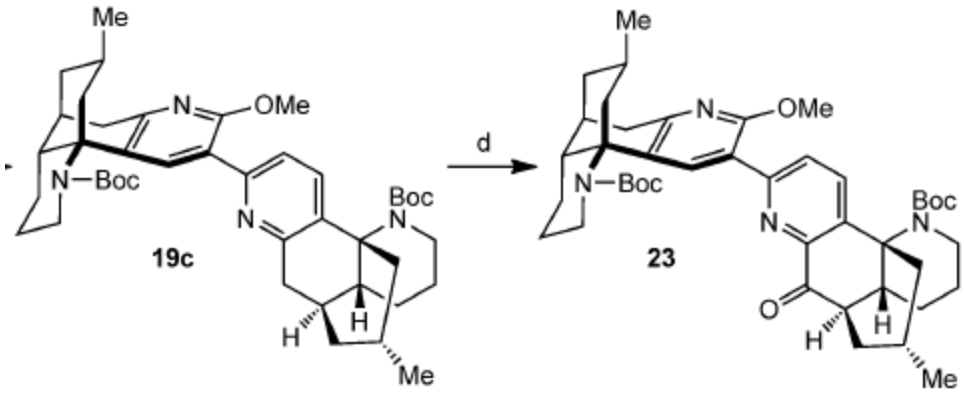


Dative interaction
'Protection' of pyridine A nitrogen atom



Reroute necessary.
How to attenuate reactivity of pyridine?

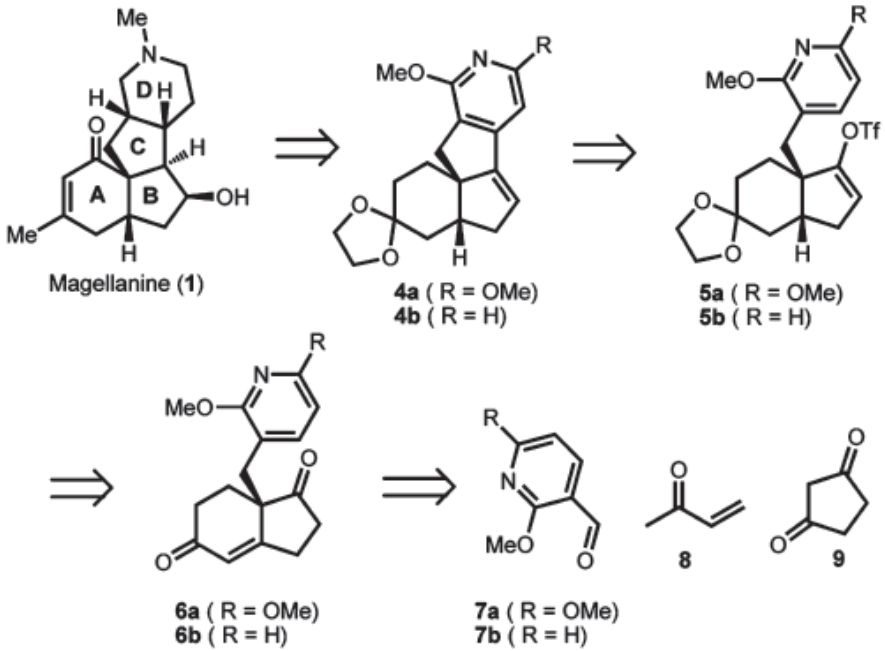
Attenuated Reactivity of 2-Methoxypyridines



E-poor methoxypyridine does not readily coordinate.

Clean oxidation of eastern half under identical conditions.

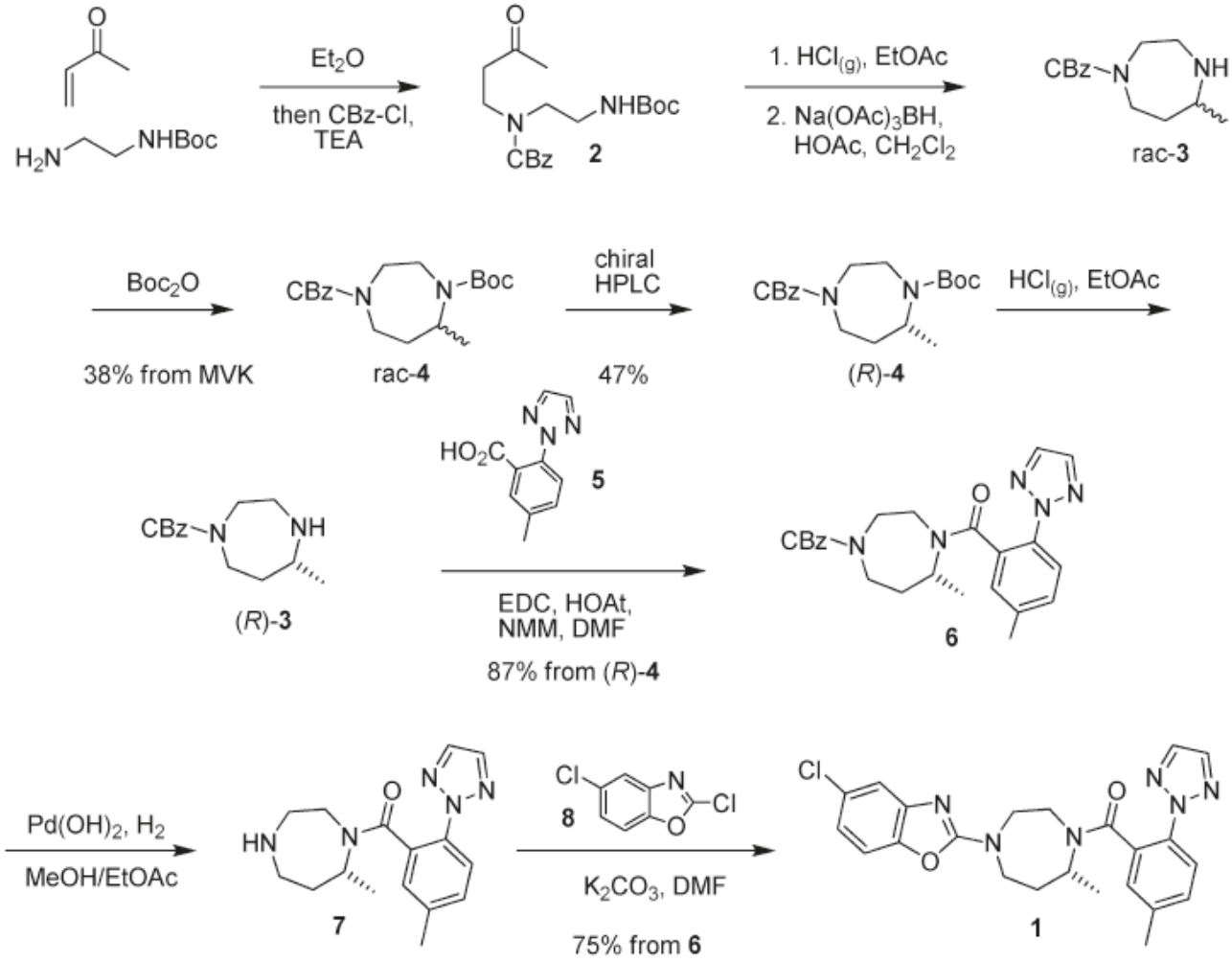
Tedious demethoxylation.



Reactions of attenuated pyridines applied to the synthesis of magellanine.

Again, total synthesis not complete yet.

Coleman – Synthesis of Suvorexant

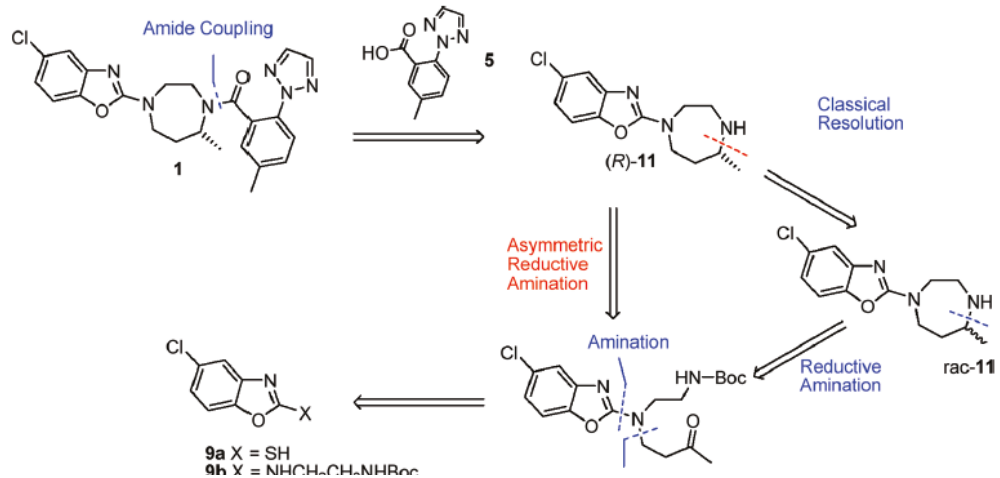


Suvorexant
New sleep aid

Orexin receptor mediated activity.

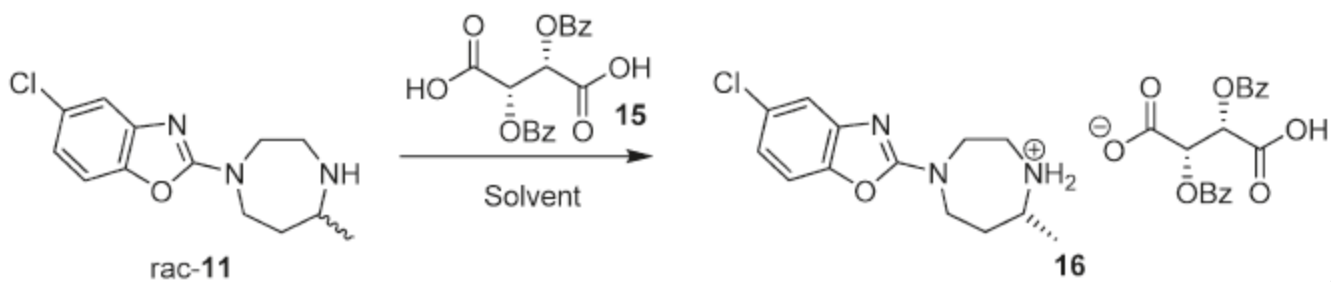
Initial med. chem. route relied on HPLC separation of isomers.

Process Chem Route

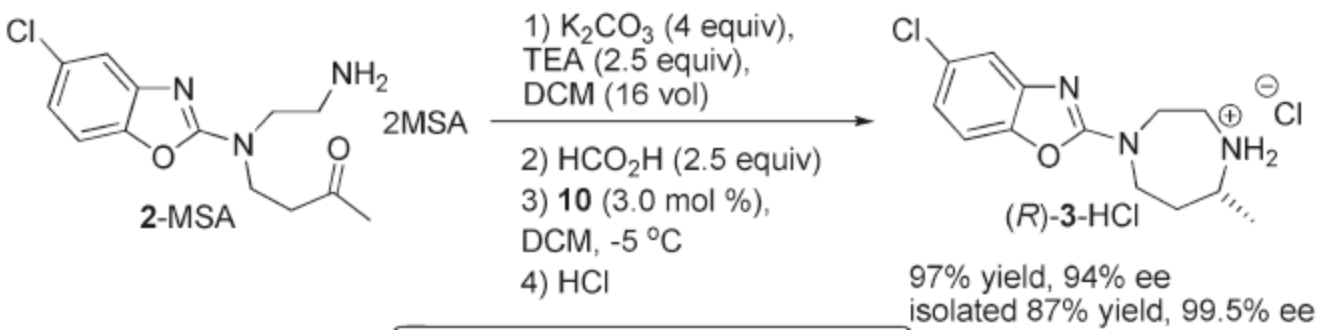


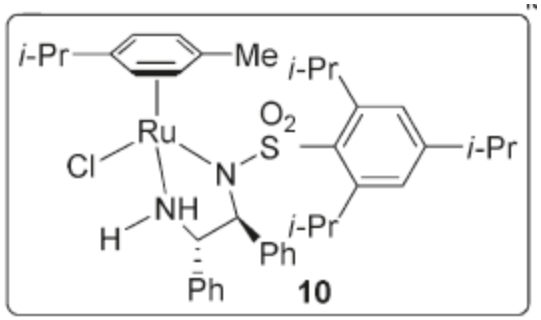
5, 9b synthesized separately.
Highly convergent synthesis.

Classical resolution proved problematic.
Isolated a 2:1 salt that is racemic.

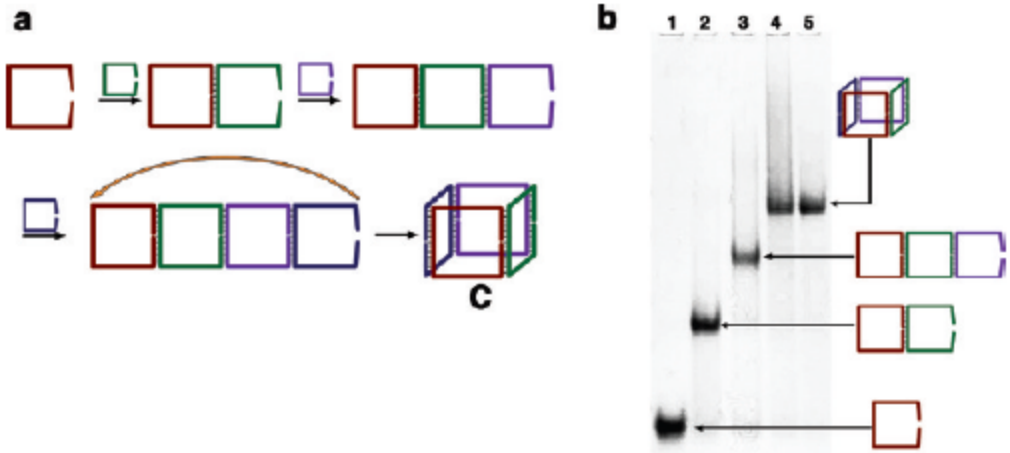


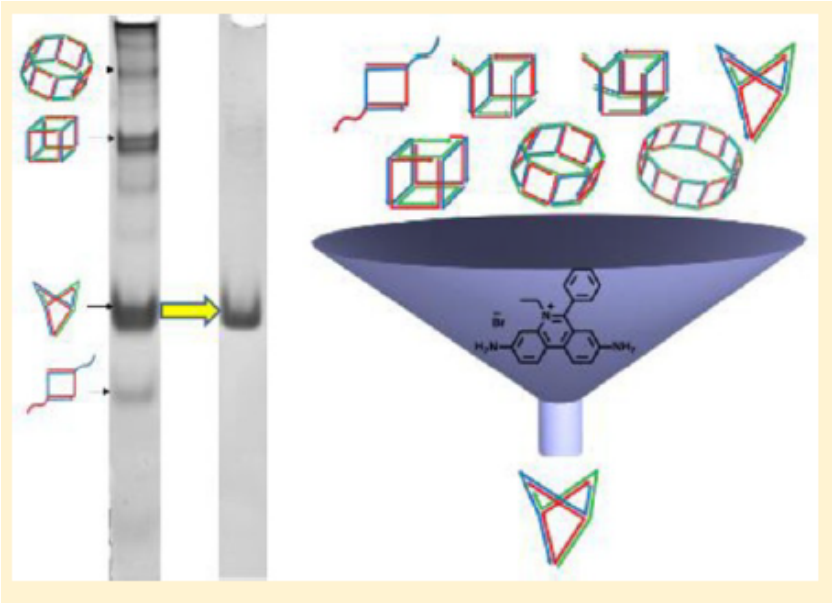
Solution: asymmetric reductive amination





Sleiman – 3-D DNA Cages





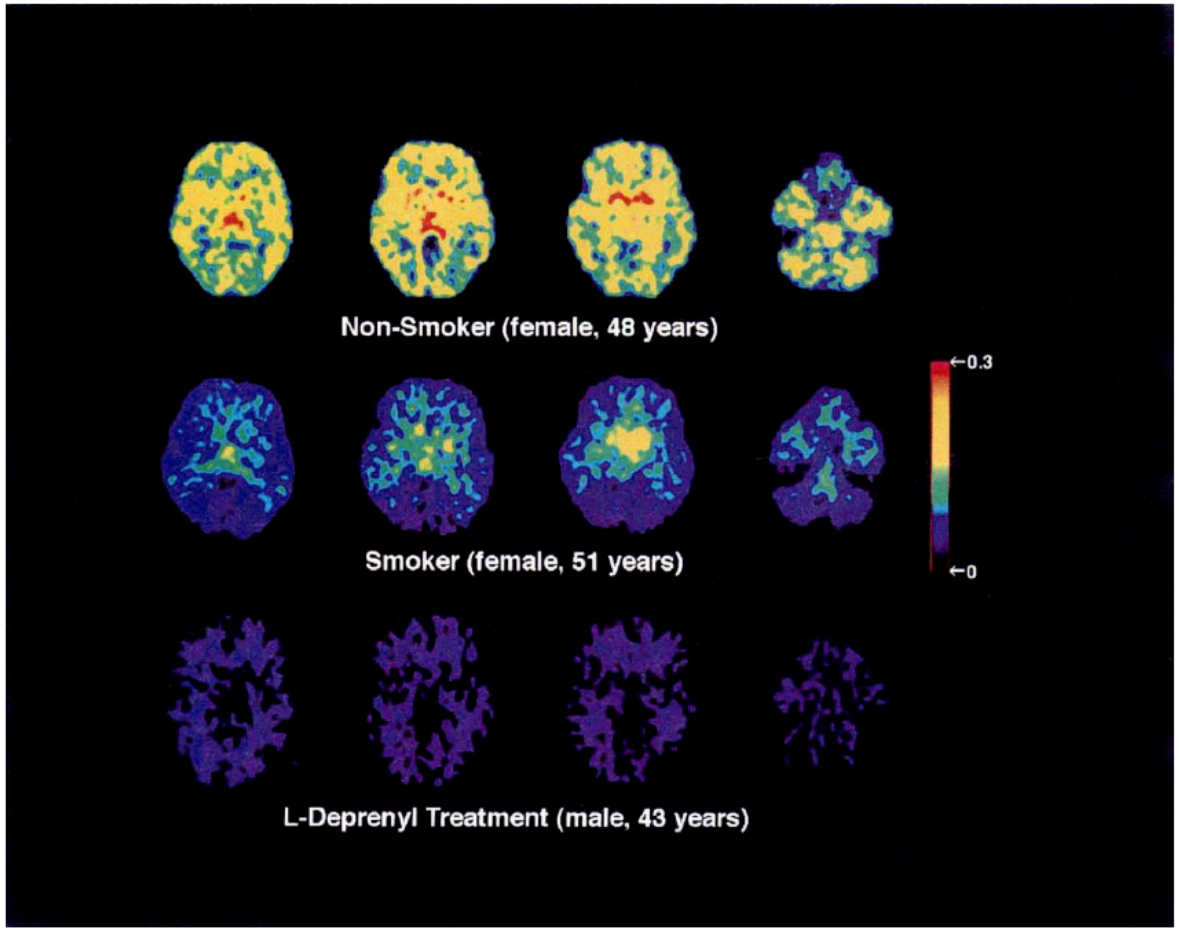
Templated design.

Appropriate use of ss-DNA strands leads to high control over annealing process.

Good control over 3D architecture.

Currently being evaluated as delivery vehicles for various small molecules.

Fowler – Monoamineoxidases in Brains of Smokers.

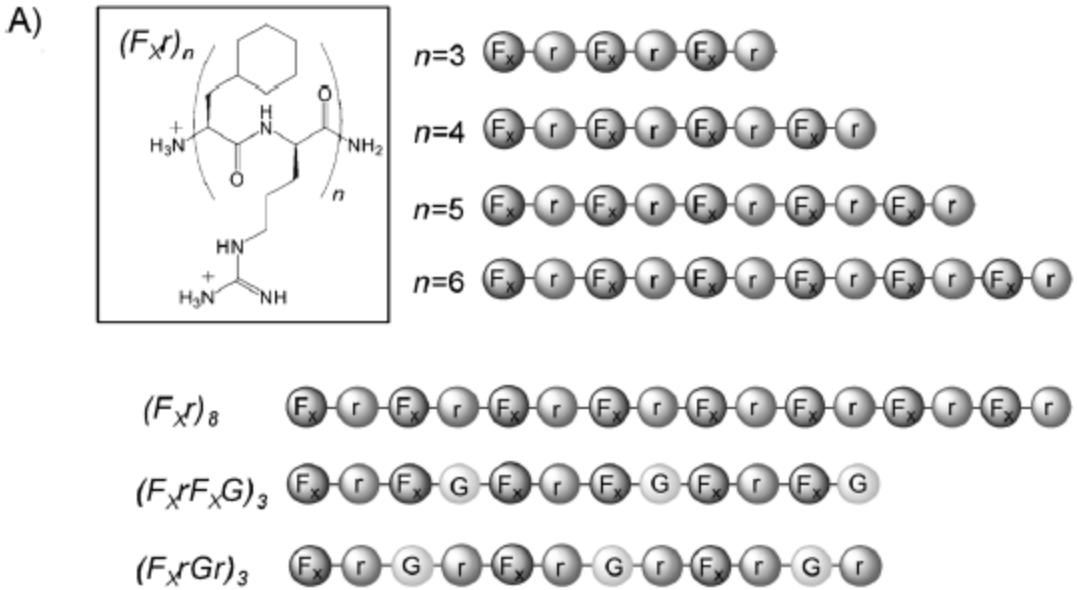


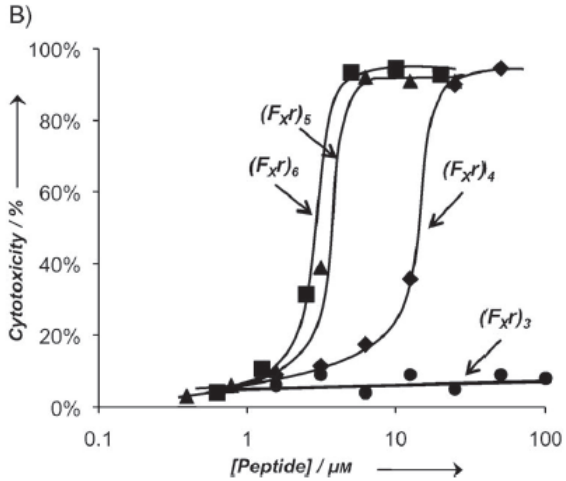
18F PET spectroscopical Study of MOA-A and MOA-B in brains of smokers.

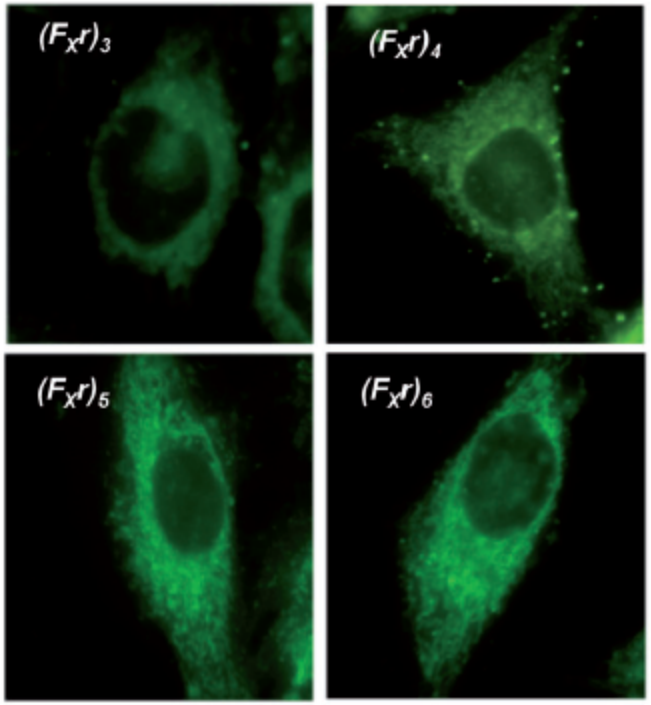
Highly biological talk, little synthesis.

Appears to be mostly unpublished work.

Kelley – Mitochondrial Targeting of Drugs



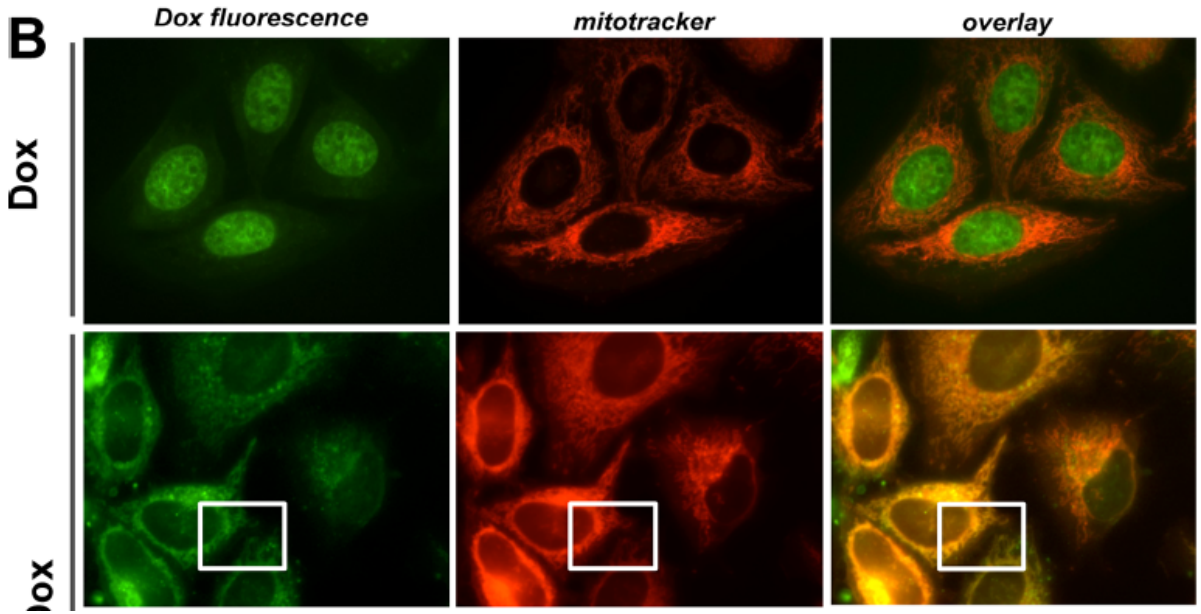


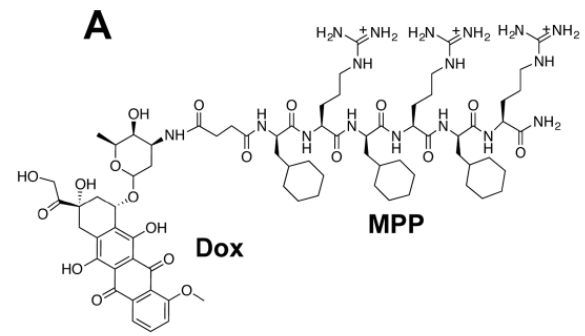


Appropriately spaced positive charges lead to high mitochondrial localization.

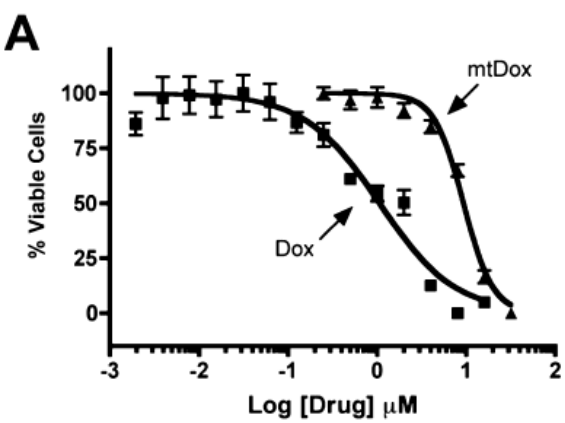
Can be used as a signal peptide for small molecule deilvery.

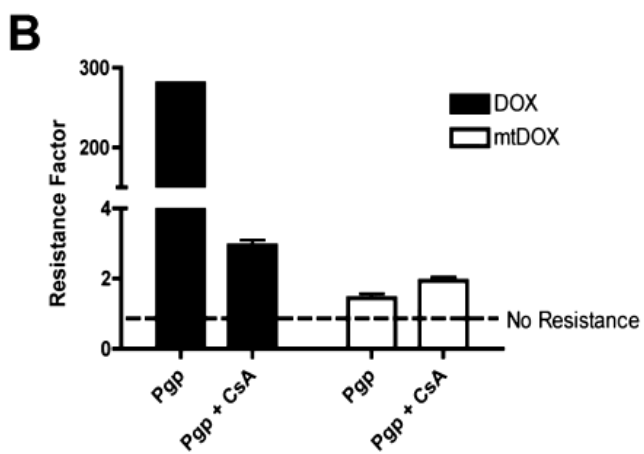
Mt-Targeted Dox





Mitochondrial targeted Dox shows increased activity.

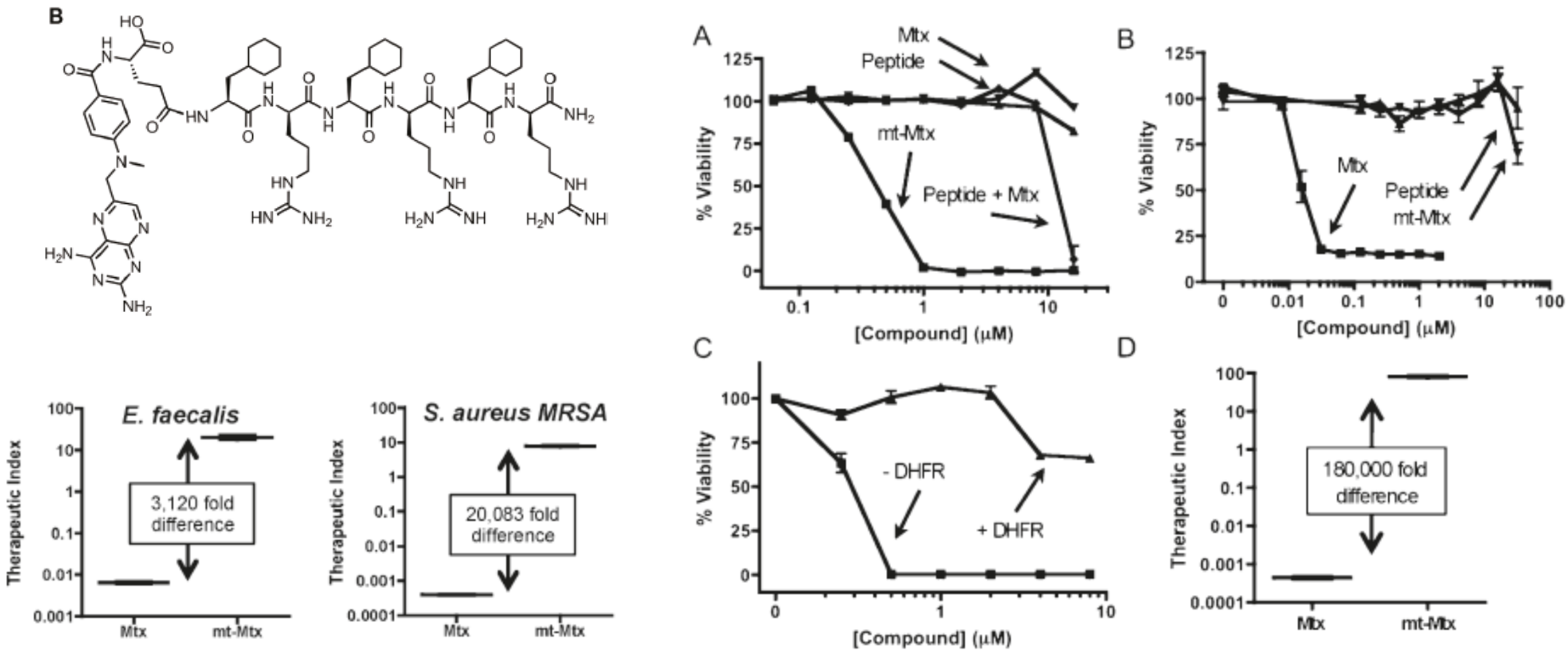




Known mechanisms of Dox resistance are not effective against mtDox

Method of action does not change (controls).

Mt-Targeted Methotrexate



DHFR inhibitor methotrexate.

Targeted towards bacteria cells. Increased localization – much lower concentrations needed for MIC.

Therapeutic index window increased 1000x-200000x.

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David Evans Lecture can be found at the ACS organic division website.

History of the NOS: Fenlon, Myers, J. Org. Chem. 2013, 78, 5817—5831