

Introduction:

- Ca. 325 publications from the Corey group in *Tetrahedron Letters* at the time of this seminar
- Only one paper in which Professor Corey is not first author; there must be a story there....
- To keep in mind: *T.L.* was 'supplanted' (subjectively, of course) only recently by *Org. Lett.*; in its day, it was the premier journal for brief notes/ communications in organic chemistry
- *T.L.* appears to have served as a virtual 'public notebook' for the Corey group; also functioned to dispel criticism and engage debate

Scope:

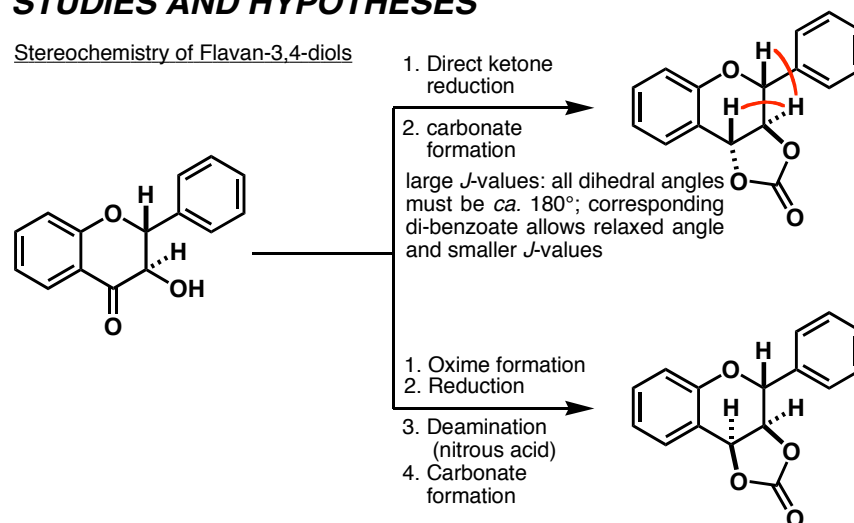
- To narrow subject matter and bolster coverage of new material, some (large) research programs were excised:
 - Lactacystin *et al* have been covered in previous group seminars
 - Prostaglandins and leukotrienes are covered extensively in *Logic*
 - Most analogical syntheses have been excluded
 - The oxazaborolidine program (even just from T.L.!) would comprise its own seminar; only choice topics have been included
- These 'classics' will include well-known and esoteric (to some of us) matter, but hopefully both will be illuminated by discussion

Organization:

- STUDIES AND FORMULATION OF HYPOTHESES/THEORIES
- REAGENTS: PG, PGM, FGI
- STRATEGIES: MOSTLY FGI AND EQUIVALENCIES
- SPECIFIC TGT SYNTHESIS

STUDIES AND HYPOTHESES

Stereochemistry of Flavan-3,4-diols

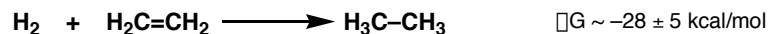


• 'The power of NMR as a tool in stereochemical analysis is vividly illustrated by this example in which a single measurement defines clearly the interrelationship of three asymmetric centers.'

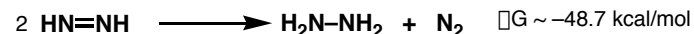
• 'The formation of a cyclic carbonate by the *trans*-3,4-diol indicates that the production of such derivatives can no longer be diagnostic for a *cis*-configuration.'

Chemistry of Diimide. Some New Systems for the Hydrogenation of Multiple Bonds

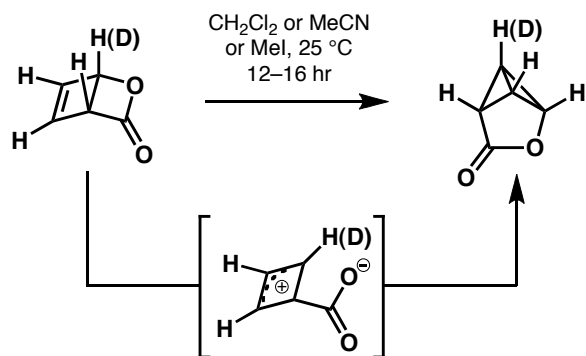
'In our view it seemed rather unlikely that hydrazine itself was the principle reducing species... the hitherto elusive and very unstable substance diimide appeared to be an outstanding candidate for this function.'



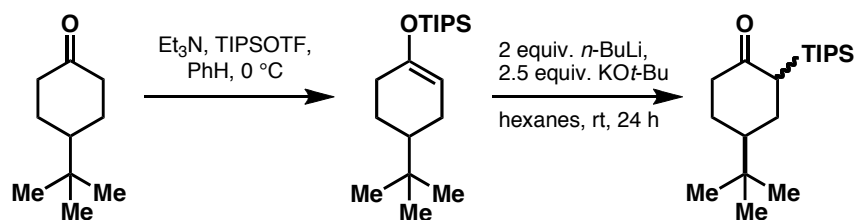
- Oxidizer is necessary with hydrazine
- Slow without heavy metal ions; rapid with cupric ion (instantaneous when $[\text{Cu}] \geq 1 \text{ mM}$)
- Reactive intermediate undergoes divertive self-destruction
- Azodiformate reaction is first-order and general acid catalyzed
- '...the intermediacy of diimide seems inescapable with its ultimate fate being sealed by a capacity to function both as a hydrogen acceptor and as a powerful hydrogen donor.'



Tricyclo[2^{3,6}.1.1.0]pyran-2-one

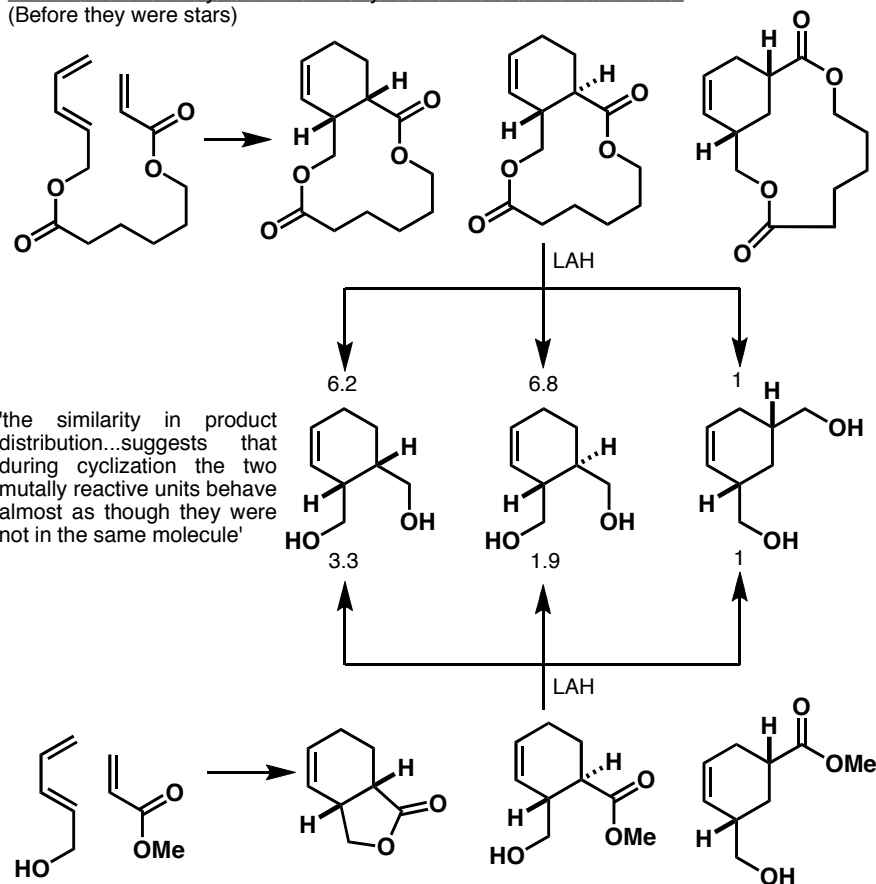


The 1,3-O-C Silyl Rearrangement of Silyl Enol Ether Anions -
Synthesis of β -Silyl Ketones



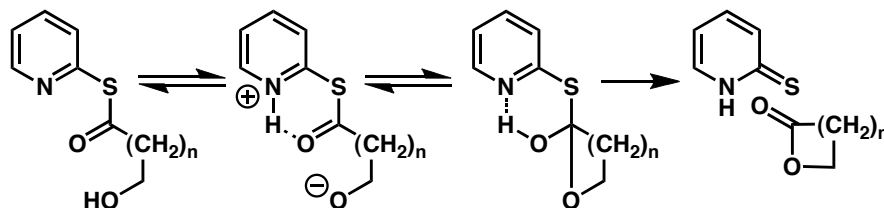
- Does not work with TMS (cleavage by BuLi)
- Silyl group migrates preferentially to the less hindered carbon
- Allylic deprotonation operative (not vinylic); allylic protons necessary
- Lower yields with unhindered, open chain silyl enol ethers
- Strictly intramolecular; crossover experiments confirm this

Formation of Macrocyclic Structures by use of the Diels-Alder Reaction
(Before they were stars)

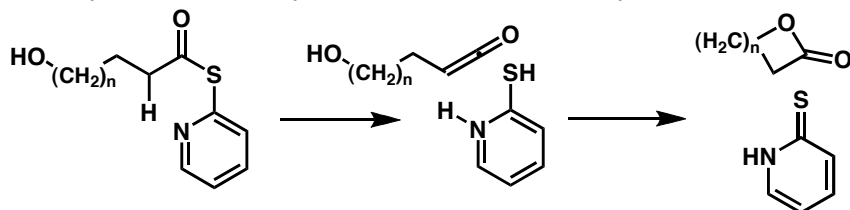


'the similarity in product distribution...suggests that during cyclization the two mutually reactive units behave almost as though they were not in the same molecule'

Mechanistic Studies on the Double Activation Method for the Synthesis of Macrocyclic Lactones



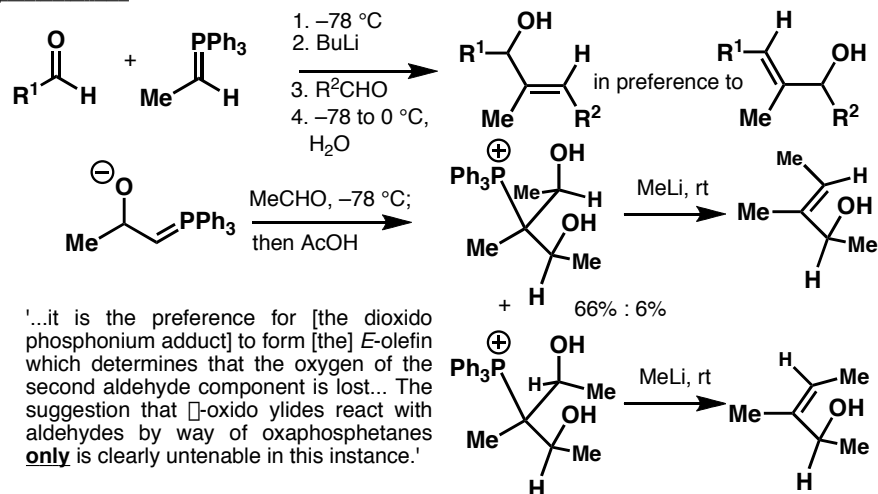
- Rate of lactonization not increased by acid or base; absence of base or acid catalysis
- 4-Pyridinethiol esters do not react!
- Phenylthiol esters do not cyclize with or without added tertiary amine



- O-deuterated alcohol failed to afford any β -deuterated lactone product
- Rate of lactonization was 13.6 ± 0.09 slower than for non-deuterated alcohol; no KIE is predicted for rate-limiting ketene formation
- Lactonization still occurs for α,β -dimethylated acids

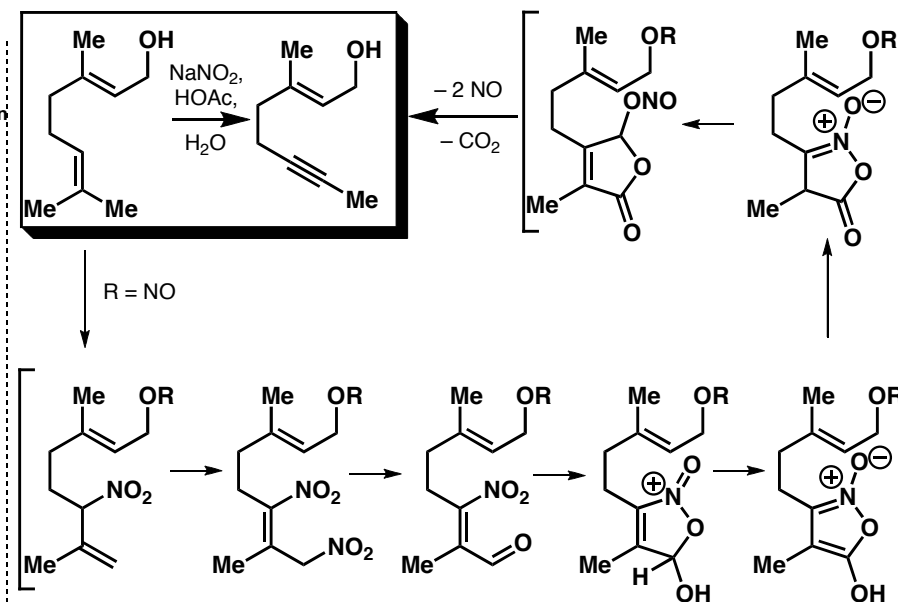
'A clear experimental distinction between the two looms as an unusually formidable problem.'

On the Origin of Stereo- and Position Selectivity in the Synthesis of Allylic Alcohols from α -Oxido Ylides

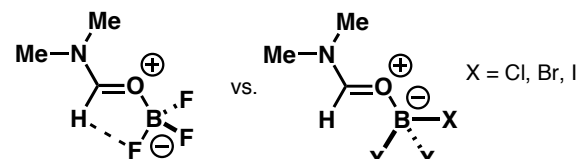


'...it is the preference for [the dioxido phosphonium adduct] to form [the *E*-olefin which determines that the oxygen of the second aldehyde component is lost... The suggestion that α -oxido ylides react with aldehydes by way of oxaphosphetanes **only** is clearly untenable in this instance.'

Mechanism of the Nitrous Acid-Induced Dealkylation of Trisubstituted (Terminal Isopropylidene) Olefins to Form Acetylenes



A Hypothesis For Conformational Restriction in Complexes of Formyl Compounds with Boron Lewis Acids. Experimental Evidence for Formyl CH--O and CH--F Hydrogen Bonds.



- Hydrogen bonding is expected to decrease in the order of F>Cl>Br>I
- The distance H--F is 2.67 Å, well within the combined van der Waals radii (2.67 Å)
- An anomeric effect between the uncoordinated O-lone pair and the B-X σ^* causing planarity would be expected to decrease B-I>B-Br>B-Cl>B-F, the opposite seen.

Reagents

Oxidations

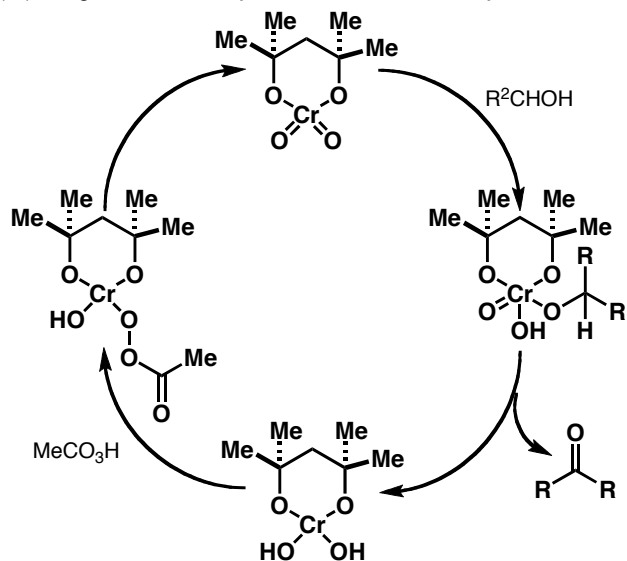
Pyridinium Chlorochromate: An Efficient Reagent for Oxidation of Primary and Secondary Alcohols to Carbonyl Compounds

- Readily available (now commercial), shelf stable, exhibits wide substrate capability and high efficiency
- Can be removed with filtration through Florisil with diethyl ether eluent
- Can be buffered with NaOAc
- Mild acidity can be used to advantage (one step citronellol \rightarrow pulegone synthesis)

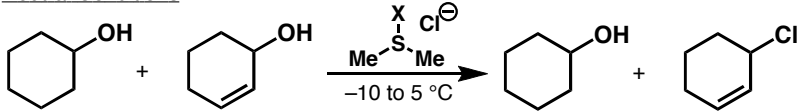
Useful Procedures for the Oxidation of Alcohols Involving Pyridinium Dichromate in Aprotic Media

- Solves the problem of PCC acidity
- Good replacement for the Collins reagent, which suffers from inconvenient preparation and requires large (6–10 equiv.) excess
- Admittedly not entirely novel: probably present in Sarett and Cornforth oxidations
- Oxidizes non-allylic alcohols to the corresponding acids under very mild conditions

A New Cr(VI) Reagent for the catalytic oxidation of Secondary Alcohols to Ketones



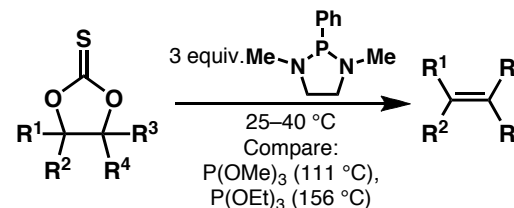
A Method for Selective Conversion of Allylic and Benzylic Alcohols to Halides Under Neutral Conditions



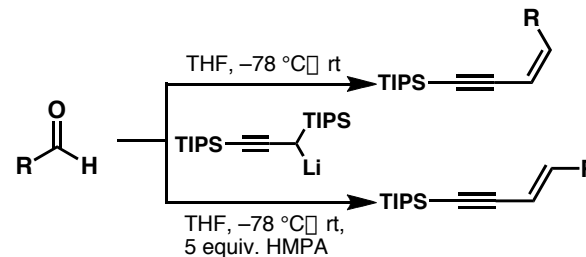
FGTs

A Mild Procedure for the Conversion of 1,2-Diols to Olefins

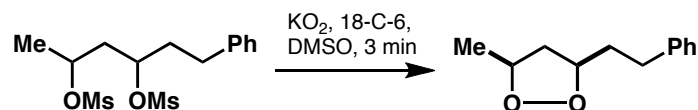
- Improvement to Corey-Winter Olefination



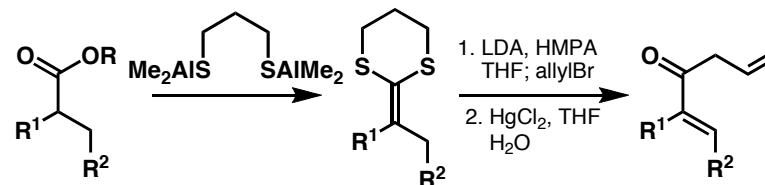
Useful Synthetic Reagents Derived from 1-Triisopropylsilylpropyne and 1,3-Bis-[Triisopropylsilyl]propyne. Direct, Stereoselective Synthesis of Either Z or E Enynes



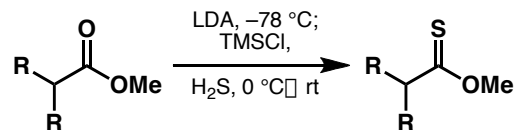
Superoxide Ion as a Synthetically Useful Oxygen Nucleophile



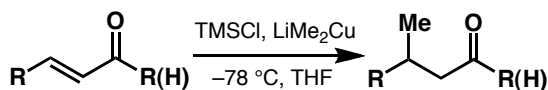
Bis(Dimethylaluminum) 1,3-Propandithiolate—A Useful Reagent in the Conversion of Esters to Unsaturated Aldehydes and Ketones



Convenient Synthesis of O-alkyl Thioesters from Esters

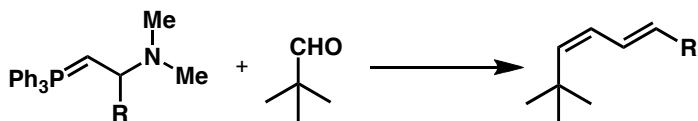


The Reactions of Combined Organocuprate–Chlorotrimethylsilane Reagents With Conjugated Carbonyl Compounds



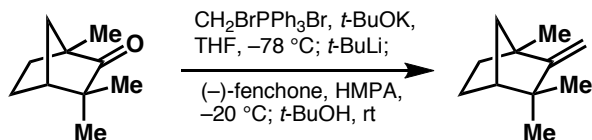
- Improves yields and 1,4 selectivity, often significantly
- Adding substrate into a mixture of TMSCl and cuprate does wonders for aldehydes

Highly Reactive Equivalents of Allylidetriphenylphosphoranes for the Stereospecific Synthesis of 1,3-Dienes by cis-olefination of Hindered Aldehydes

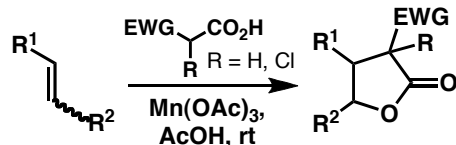


- Far superior to allyl or croyl ylides for reaction with hindered aldehydes

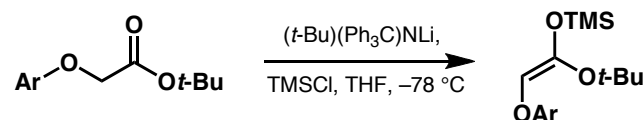
Activation of Methylene triphenyl phosphorane by Reaction with *t*-Butyl or *sec*-Butyllithium



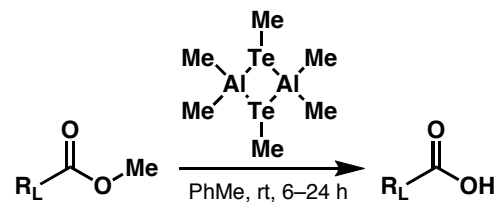
Carbolactonization of Olefins Under Mild Conditions by Cyanoacetic and Malonic Acids Promoted by Manganese (III) Acetate



Sterically Shielded Secondary *N*-tritylamines and *N*-tritylamide Bases, Readily Available and Useful Synthetic Reagents



Dimethylaluminum Methyltellurate, a New Reagent for the Cleavage of Hindered Methyl Esters Under Exceptionally Mild Conditions by a Novel Mechanism



Protecting Group Chemistry

MEM: $R-O-(CH_2)_2-O-CH_2-CH_2-O-Me$ Formed by treating RONA or ROLi with MEMCl in THF or DME at 0 °C OR by refluxing ROH with MEM(NEt₃)Cl in MeCN

Stable to nucleophiles and bases; stable to mild acid (TsOH, MeOH, rt or 3:1 AcOH:H₂O, 35 °C), but cleaved readily with ZnBr₂ or TiCl₄.

Can be converted into cyanomethyl ethers by the action of Nagata's reagent.

MTM: $R-O-CH_2-S-Me$

Stable to nucleophiles and bases; stable to mild acid (4:1 AcOH:H₂O, 45 °C, 1h; or 3:2:1 THF:AcOH:H₂O, 40 °C, 8h), but cleaved readily with HgCl₂ or AgNO₃.

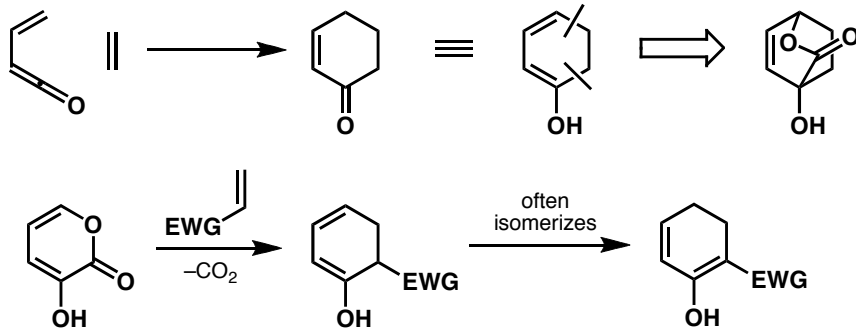
TBSOTf, TIPSOTf: Useful reagents for the silylation of hindered or unreactive alcohols, or for the silylation of reverse-phase silica support columns.

DBD-ketals: $R-O-CH_2-CH(Br)-CH_2-O-R$ Formed from the easily prepared 2,2-dibromo-1,3 propanediol by refluxing with the carbonyl in benzene with catalytic TsOH. Cleaved with Zn/Ag couple in THF at room temperature

Orthoesters: $R-O-CH_2-CH_2-O-Me$ 1. RCOCl 2. BF₃·Et₂O

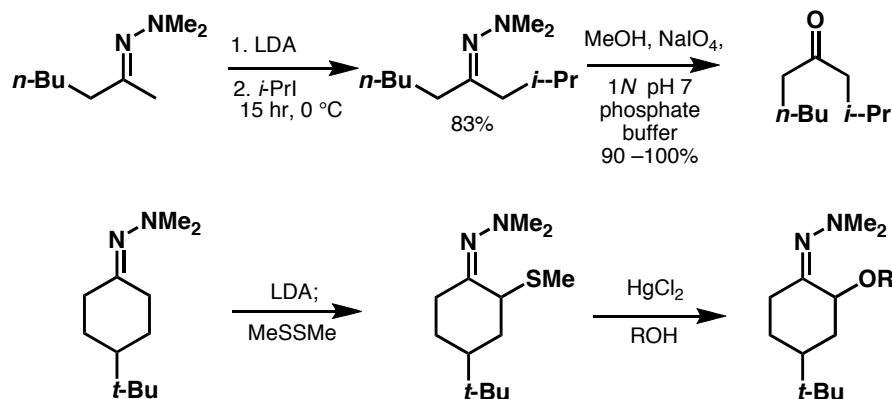
Equivalencies

3-Hydroxy-2-Pyrone as a Vinylketene Equivalent for the Synthesis of Dihydrophenols and Cyclohexenones



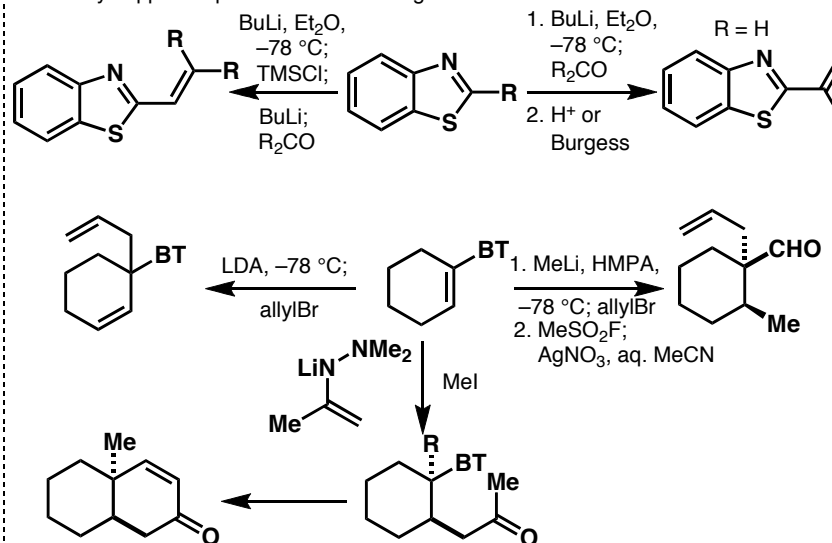
DIMETHYLHYDRAZONES

- Metallated enehydrazines have greater stability than their carbonyl equivalents
- Do not suffer from side condensation reactions
- Exhibit greater reactivity towards halides, epoxides, and carbonyl compounds
- May support a negative OR positive charge at α -carbon
- Form only monoalkylated products



Benzothiazoles

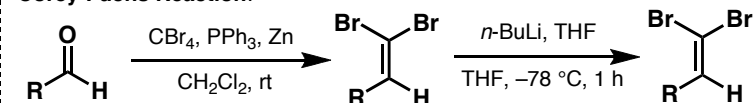
- Formyl anion equivalents
- Exhibit broad range synthetic applications
- When unsaturated, they act as 1,4 acceptors, not 1,2 (contrast enals)
- May support deprotonation at the ring carbon or an attached carbon



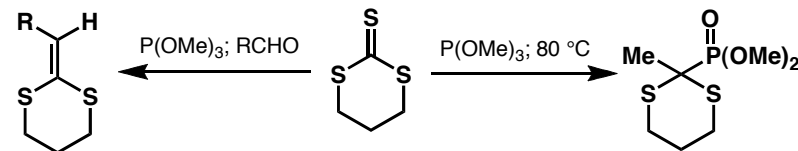
Functional Group Transformations

A Synthetic Method for Formyl \rightarrow Ethynyl Conversion

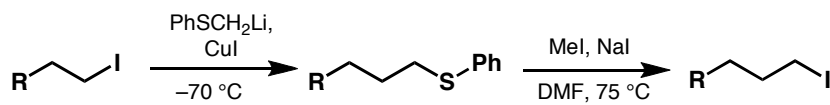
Corey-Fuchs Reaction:



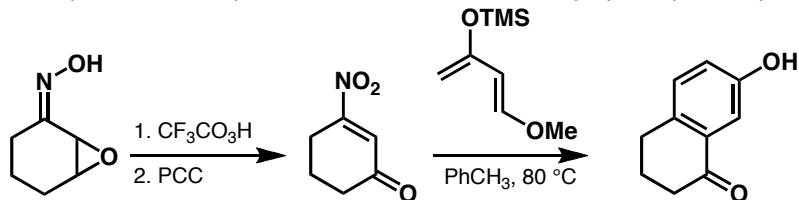
Generation of Phosphite Ylides from Trithiocarbonates and Trimethyl Phosphite and their Application to the Extension of Carbon Chains



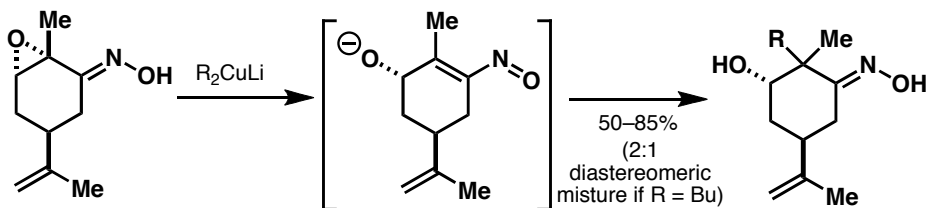
A Synthetic Method for the Homologation of Primary Halides



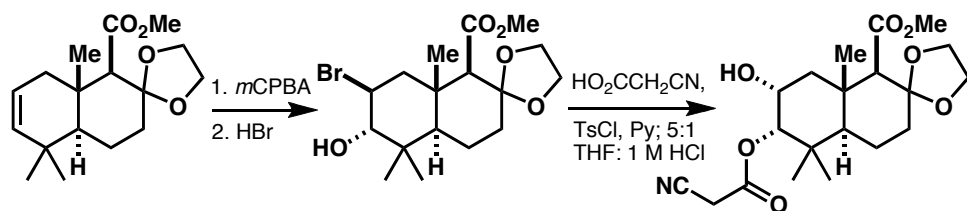
3-Nitrocycloalkenones, Synthesis and Use as Reverse Affinity Cycloalkynone Equivalents



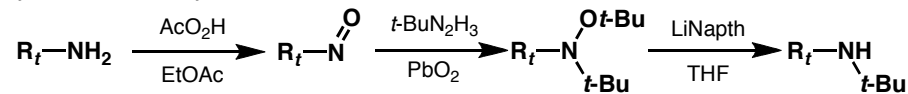
A Novel α -Alkylation of α,β -Epoxy Ketones



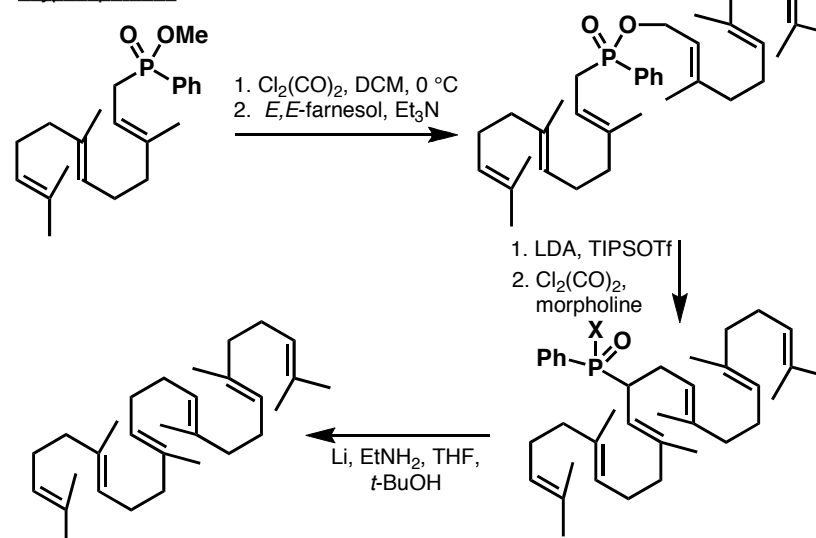
A New Method for Stereospecific *cis*-Hydroxylation of Olefins



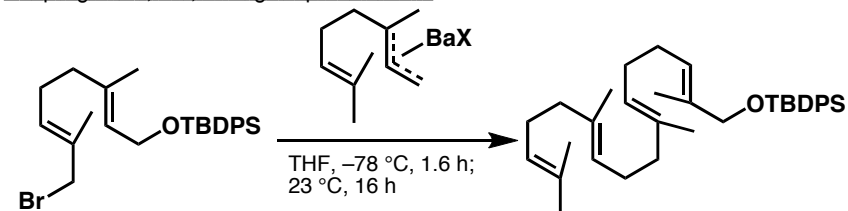
Synthesis of Di-*t*-alkylamines



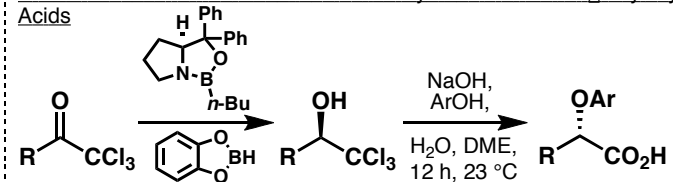
Carbon-Carbon Bond Formation by $\text{O} \rightarrow \text{C}$ Rearrangement of Allylidene-oxyphosphoranes



A Simple Synthetic Process for the Elaboration of Oligoprenols by Stereospecific Coupling of Di-, Tri-, or Oligoisoprenoid Units

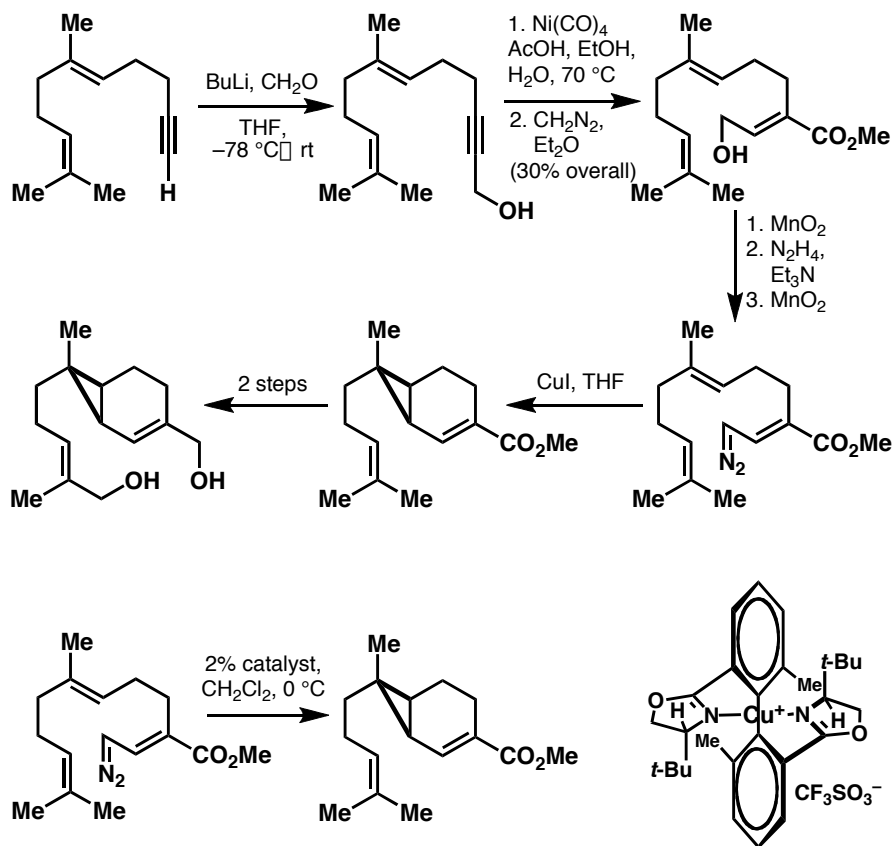


A New Process for the Enantioselective Synthesis of Chiral α -Aryloxy and α -Hydroxy Acids

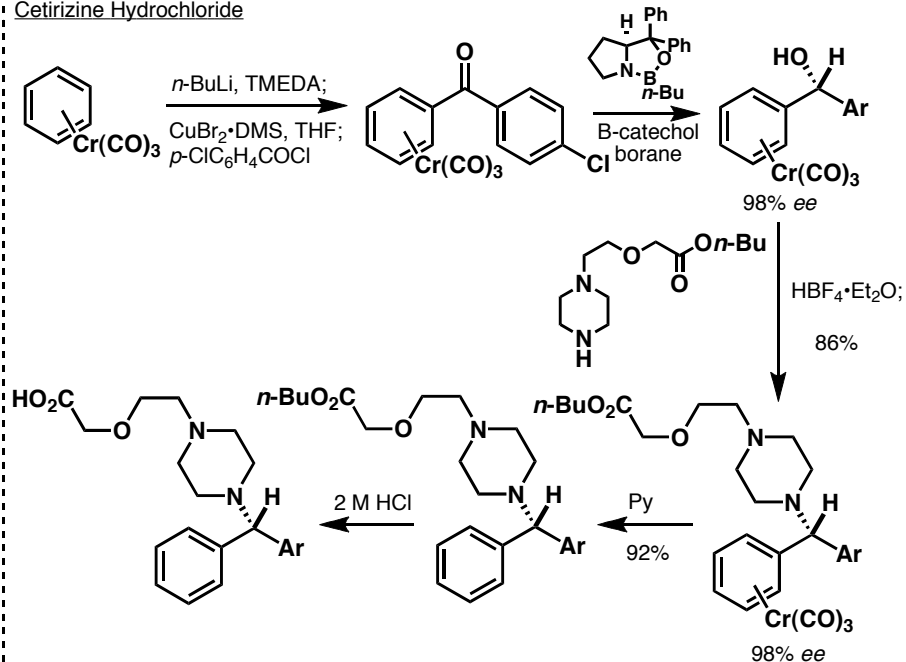


TGT Synthesis

A Simple Synthetic Route to *dl*-Sirenin



Catalytic Enantioselective Synthesis of the Second Generation Histamine Antagonist
Cetirizine Hydrochloride



Efficient Enantioselective Syntheses of Chloramphenicol and (*D*)-*threo* and (*D*)-*erythro*-
sphingosine

