Advanced Functional Group Transformations and Reactions

C-X where X is an heteroatom (N,O,halogen)

C=C (double bonds)

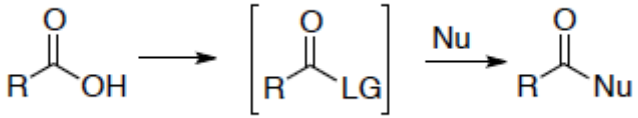
C-C (single bonds)

Amides and esters are two of the most fundamental and significant functional groups in chemistry, biochemistry, and materials science.
Therefore, many dehydrocondensing reagents for synthesizing amide and ester bonds from carboxylic acids and amines or alcohols have been developed over the past century. March 20, 2014

(1) Montalbetti, C. A. G. N.; Falque, V. *Tetrahedron* **2005**, 61, 10827− 1 0852.
(2) El-Faham, A.; Albericio, F. *Chem. Rev.* **2011**, 111, 6557− 6 602.
(3) Pattabiraman, V. R.; Bode, J. W. *Nature* **2011**, 480, 471− 4 79.

Dehydration reactions

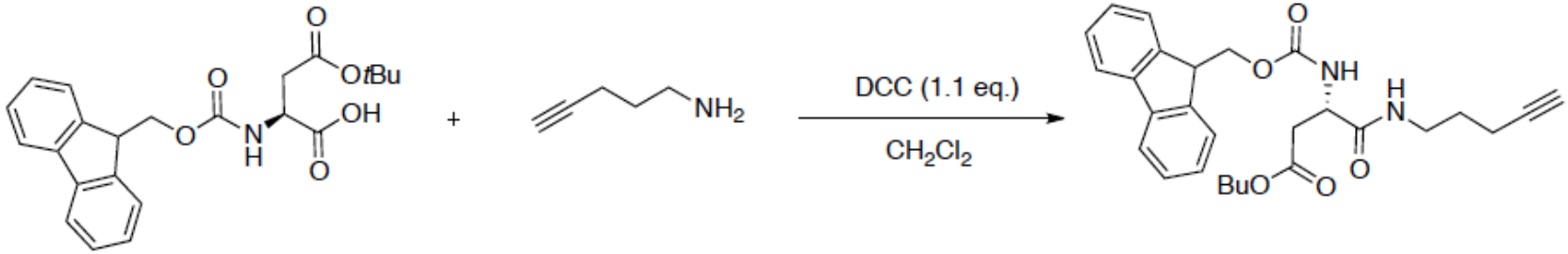
In the following some examples for activation of carboxylic acids towards nucleophiles are discussed:

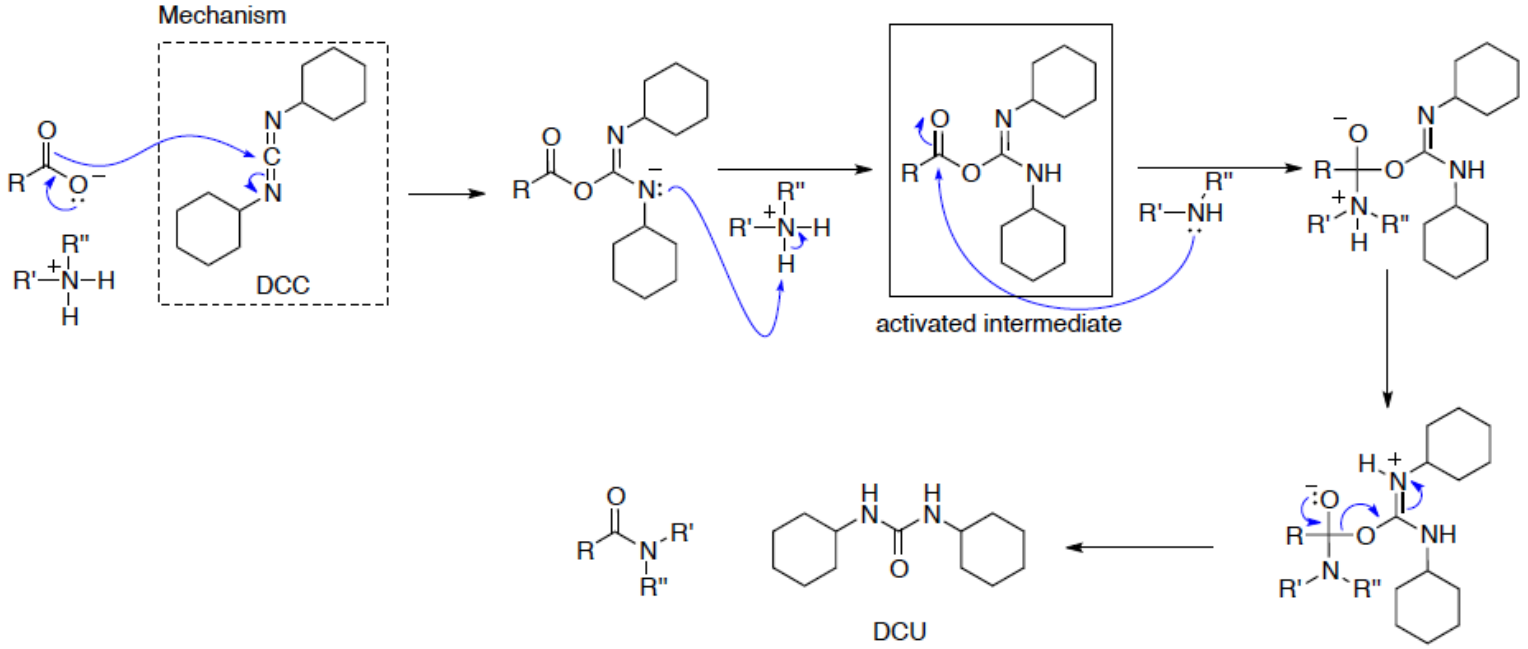


Nu: Oxygen and nitrogen nucleophiles

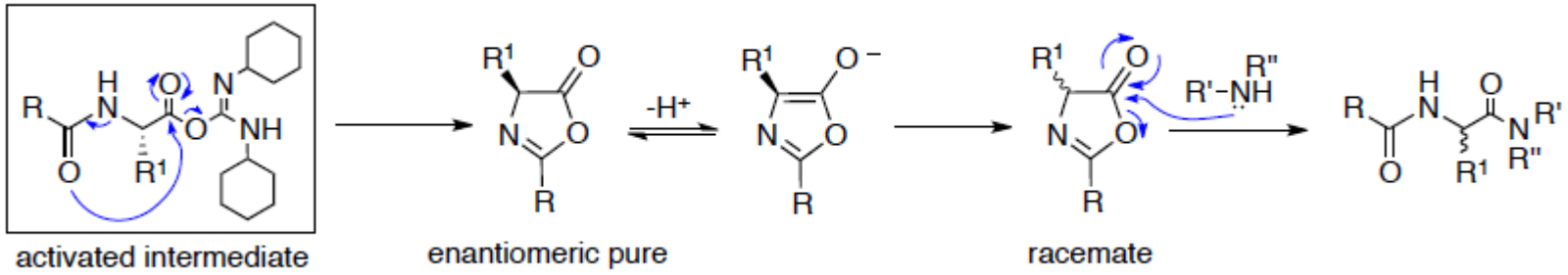
DCC amide couplings

Carboxylic acids are relatively unreactive with nucleophiles due high lying LUMO and bad leaving group (OH). A solution is the use of reagents which selectively activate a carboxyl group towards nucleophilic substitution. Carbodiimides such as *N,N'*-dicyclohexylcarbodiimide (DCC) are frequently used for amide and ester bond formation. As a driving force for the reaction serves the formation of urea (DCU).

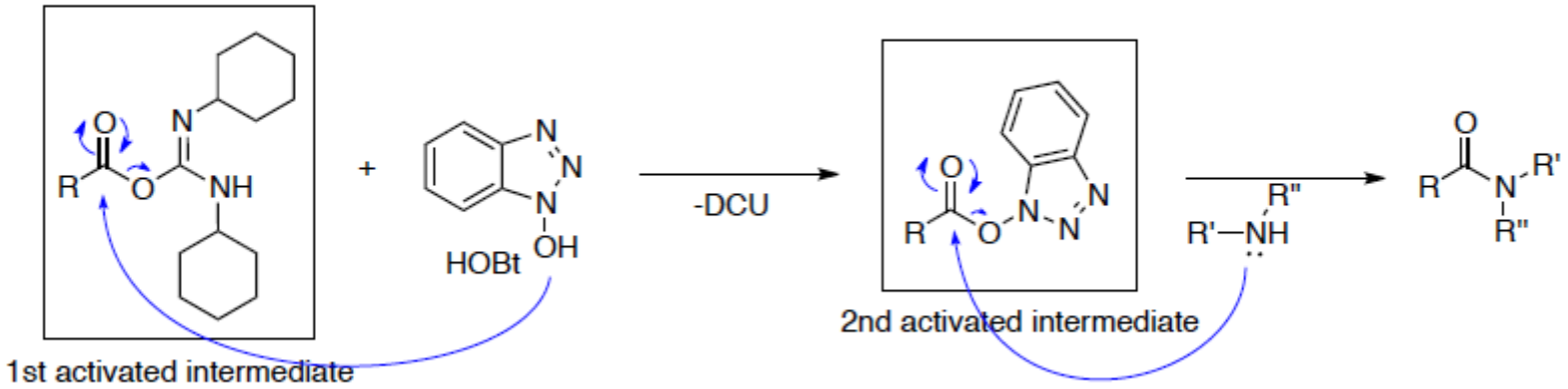




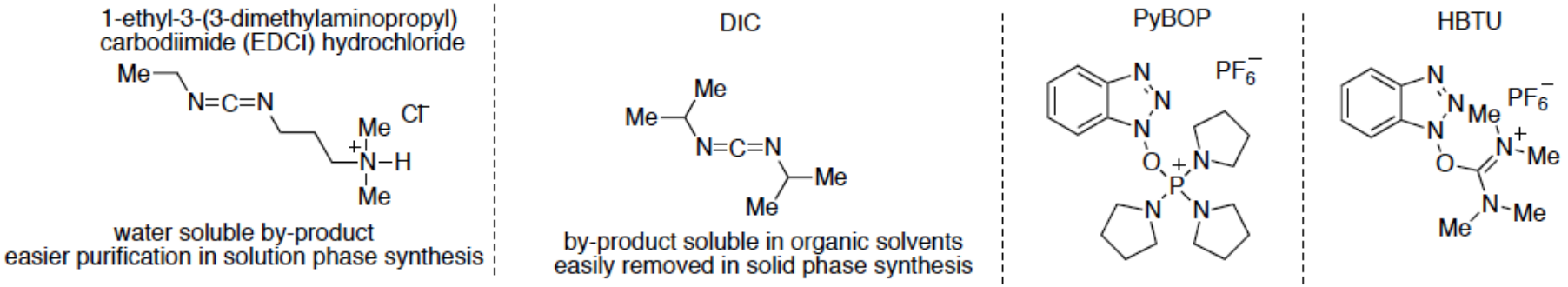
However, in the case of peptide synthesis the activation can leads to racemization of stereocenter at α-C position during the reaction.



Therefore reagents as HOBt, HBTU etc. were introduced as co-coupling agents. They react faster with the activated intermediate than the racemization at α-C position occurs.

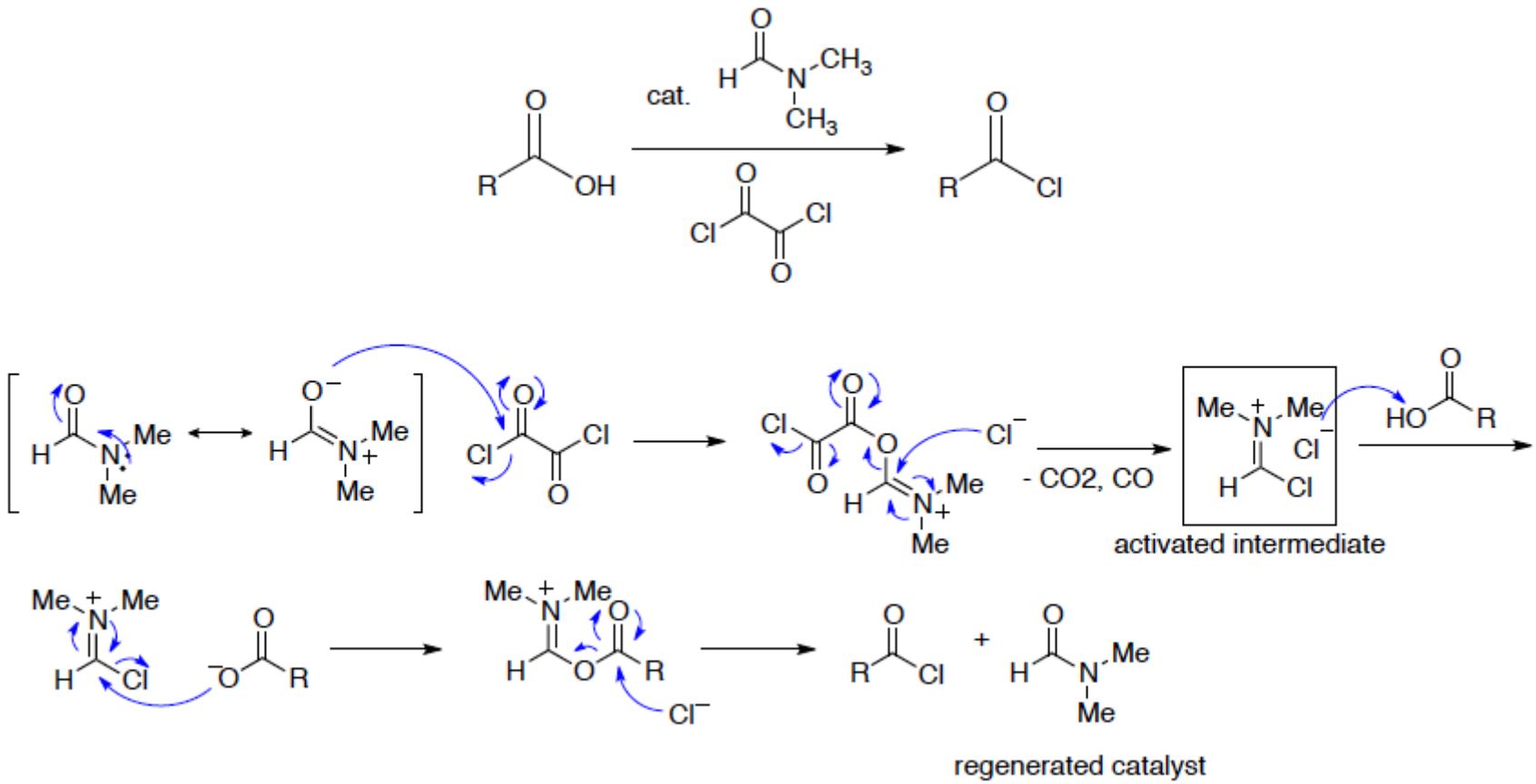


Other coupling agents frequently used:

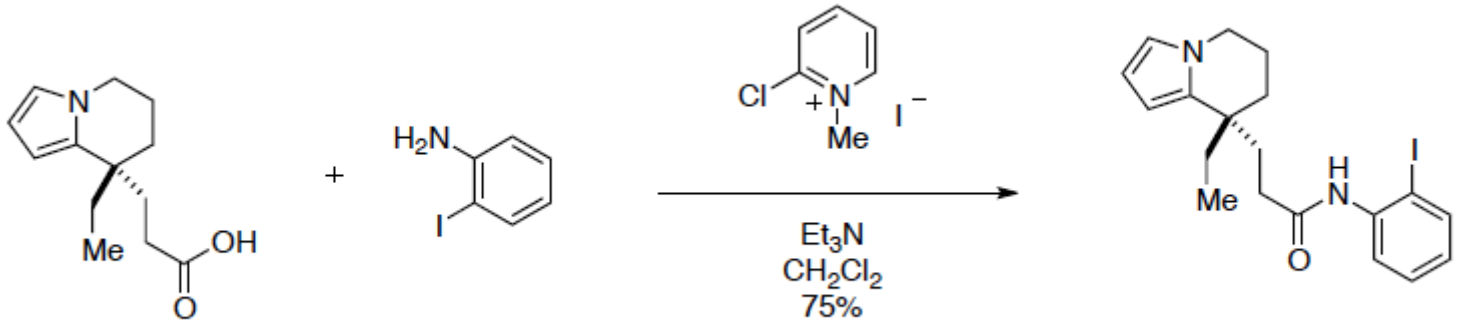


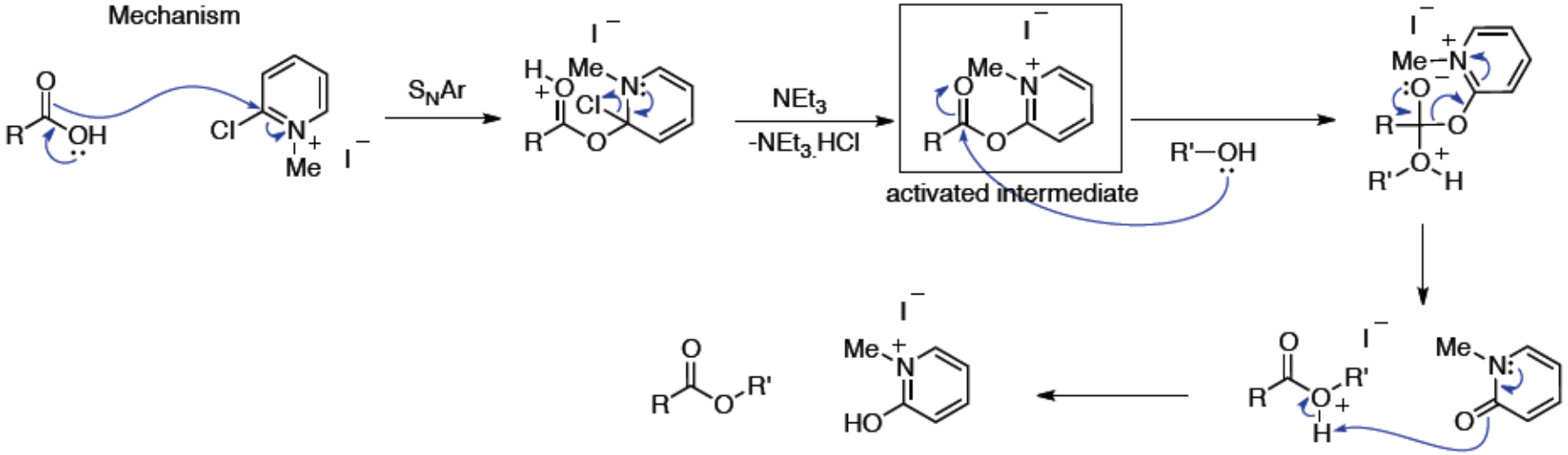
Acid chloride using DMF/oxalyl chloride

The standard way to activate a carboxyl group is to convert it in to an acid chloride. The oxygen of the carboxyl group is a very weak nucleophile and therefore does not react with oxalyl chloride. Readily after addition of catalytic amount of DMF a reactive intermediate formed which is electrophilic enough to react with the carboxyl group.



Mukaiyama coupling (2-chloromethylpyridinium iodide)





Macrolactonization

The cyclization reactions are highly dependent on two types of energy: enthalpy and entropy. Ease of ring formation is dependent on the size of the cycle to be formed. For small and medium size rings (4, 5 and 6- membered) cyclization is favored due to the higher enthalpy over entropy. For the 8 to 13 membered rings the entropy is higher than ethalpy and therefore they are the hardest to form.

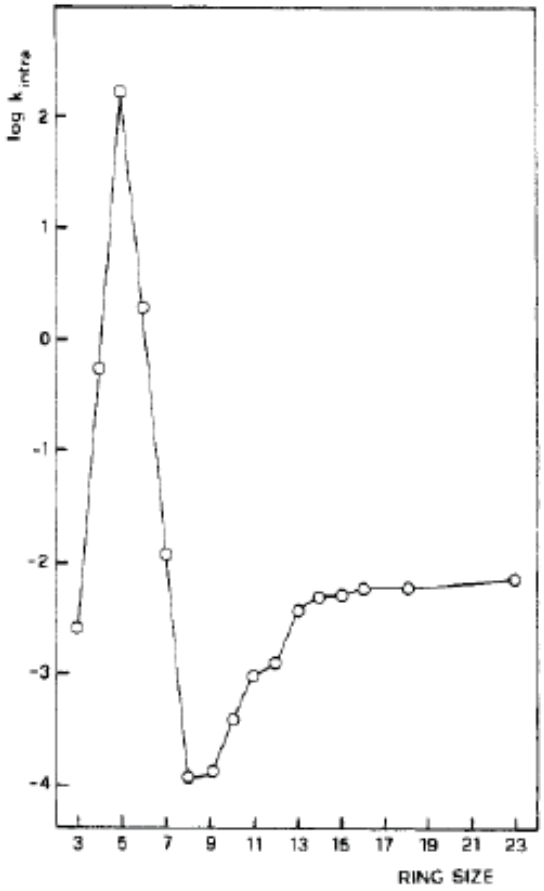
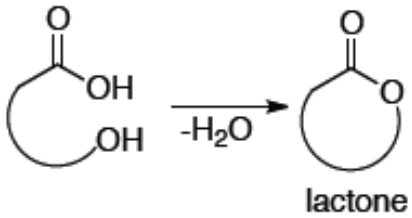
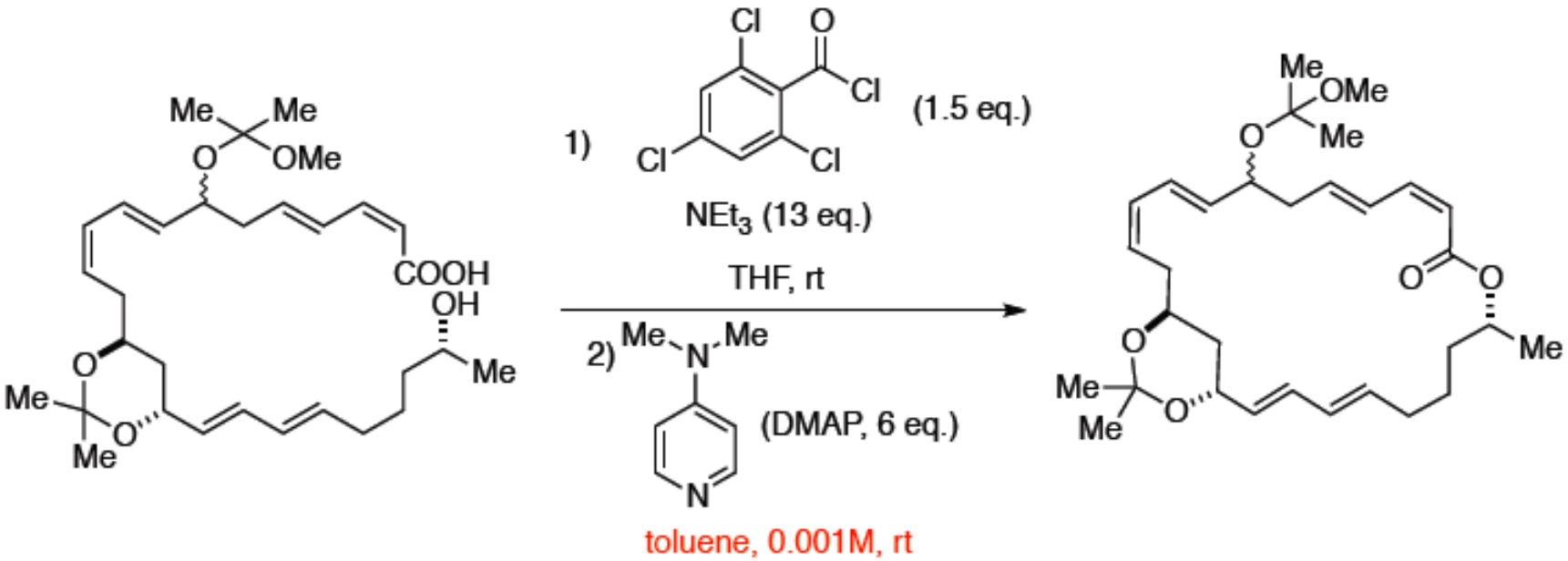


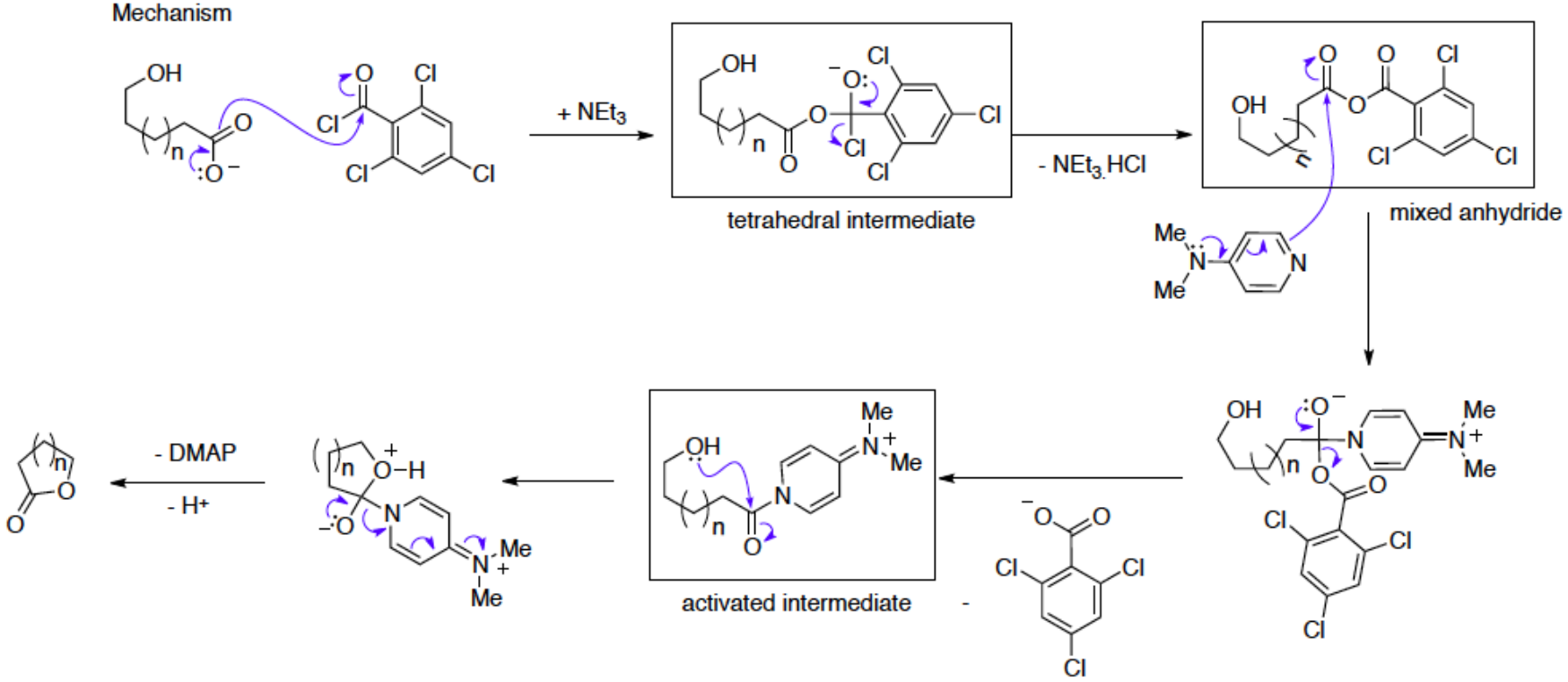
Figure 1. Reactivity profile for lactone formation (eq 4a).

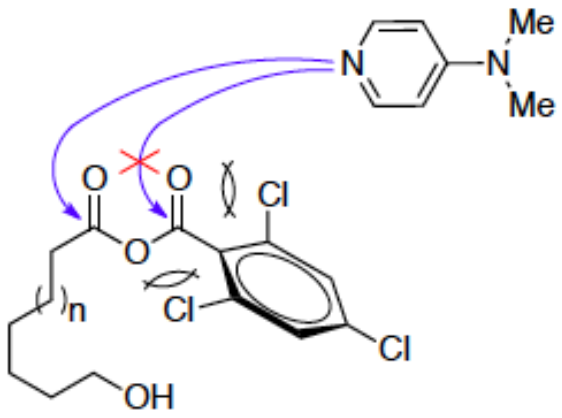


The Yamaguchi macrolactonization is a powerful method to form macrolactones.
Its exceptionally high reaction rate allow the reaction to be conducted at very high dilution, avoiding intermolecular couplings and by-products.
2,4,6-trichlorobenzoyl chloride (the Yamaguchi reagent) forms a mixed anhydride with a carboxylate, activates more the electrophilic carbon of the carboxyl group for a nucleophilic attack.



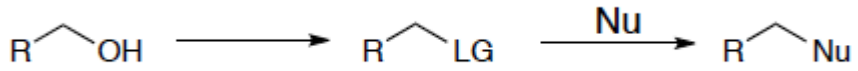
Mechanism


+ NEt3
tetrahedral intermediate
- NEt3.HCl
mixed anhydride
activated intermediate
-
- DMAP
- H+

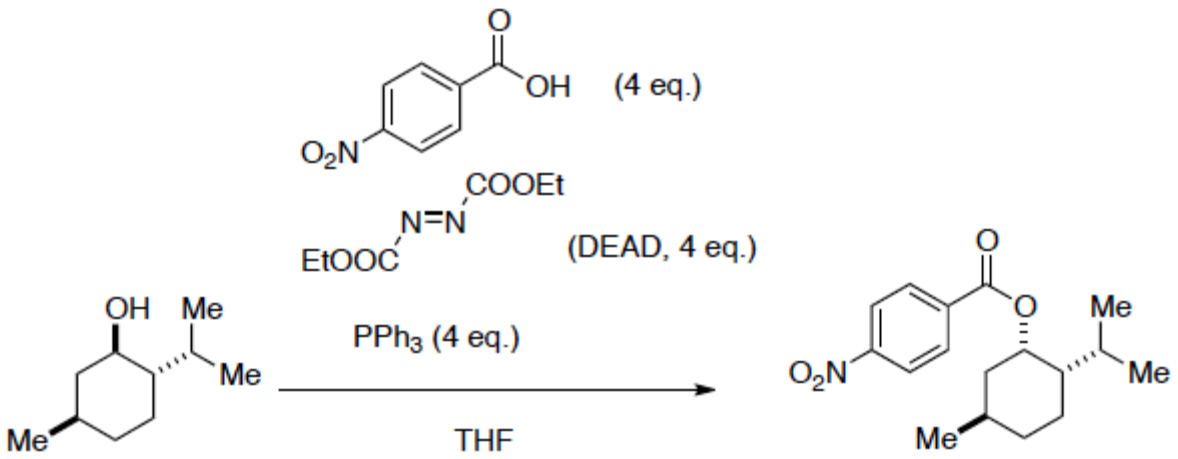


Mitsunobu Reactions

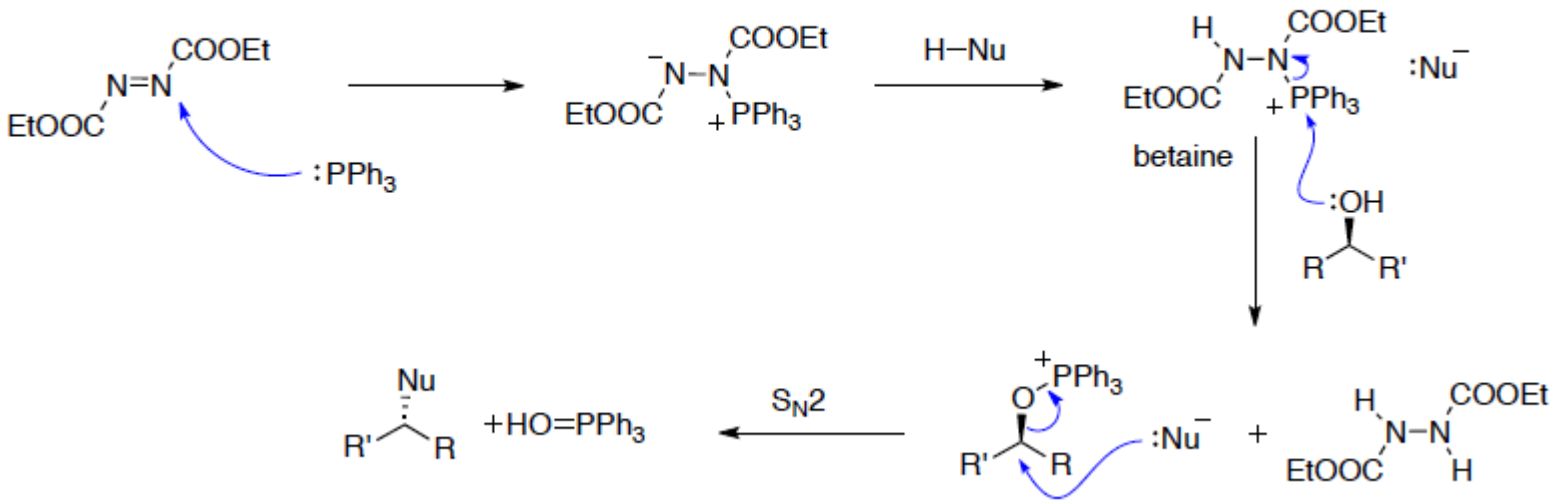
Activation of alcohols towards nucleophiles:



The Mitsunobu reaction is a modern SN2 reaction on alcohols involving in-situ activation using phosphorus chemistry.

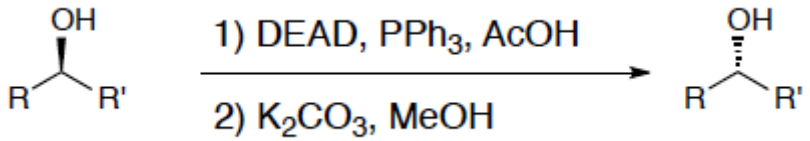


Mechanism

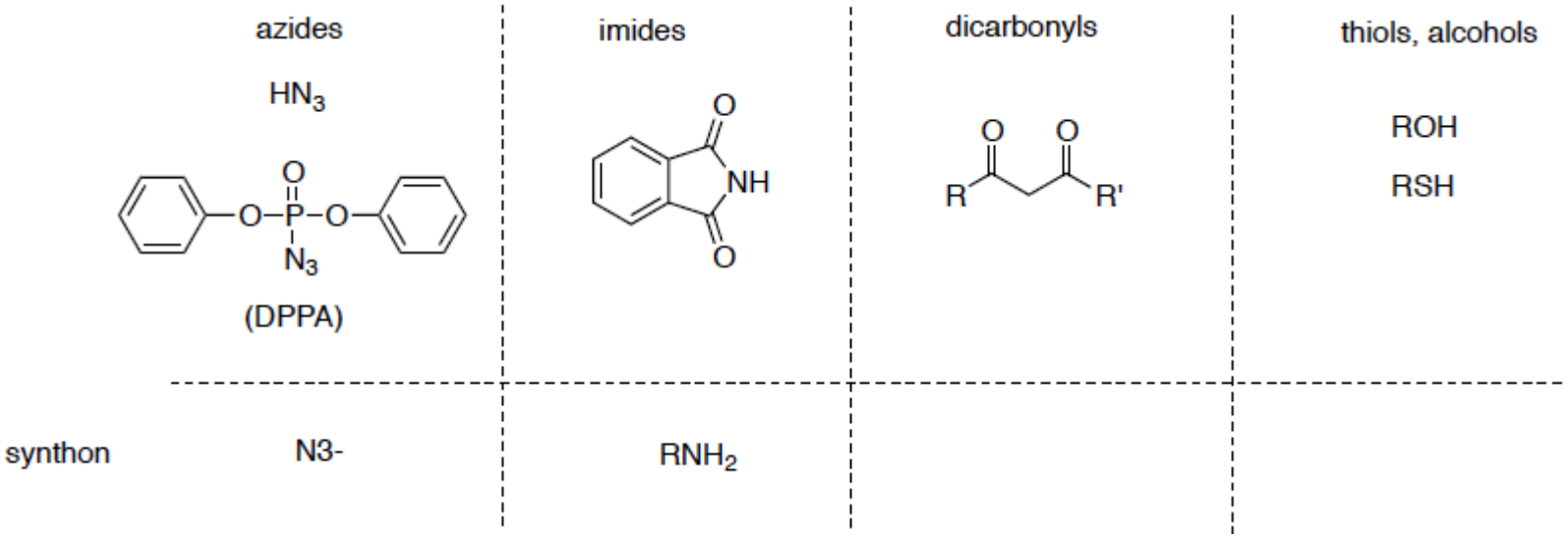


The pKa value of the NuH plays very important role, which is deprotonated by the betaine. If the proton of NuH is not acidic enough, the reaction does not occur. The pKa values are preferably below 11, which cover a broad spectrum of different types of nucleophiles, e.g. carboxylic acids, indoles, heterocycles and thiols. The driving force of the reaction is the formation of triphenylphosphine oxide (P=O bond 110 kcal/mol).

The alcohol undergoes a complete inversion of configuration. When a carboxylic acid is used as nucleophile, the resulting ester can be hydrolyzed yielding the starting material **with inversion of configuration**.

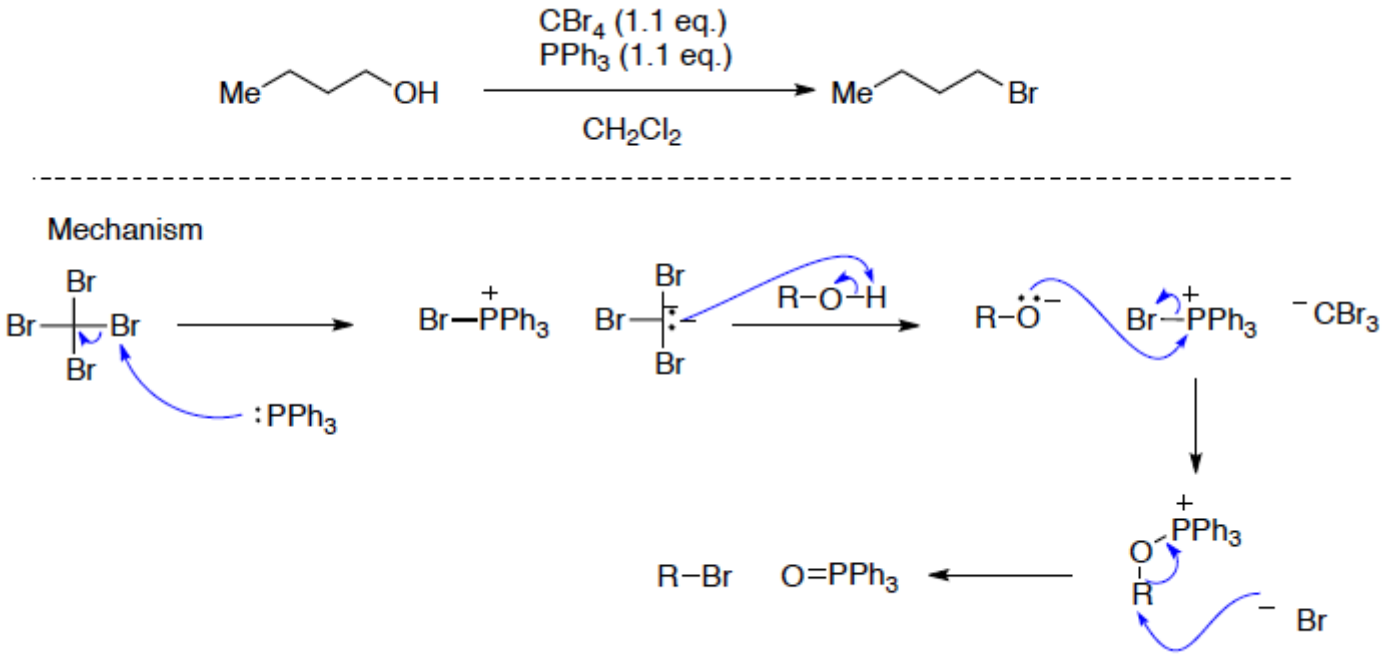


Other possible nucleophiles:



DPPA serves as an azide group (N3-) transfer reagent. Phthalimide is a masked primary amine which is used in Gabriel synthesis of primary amines.

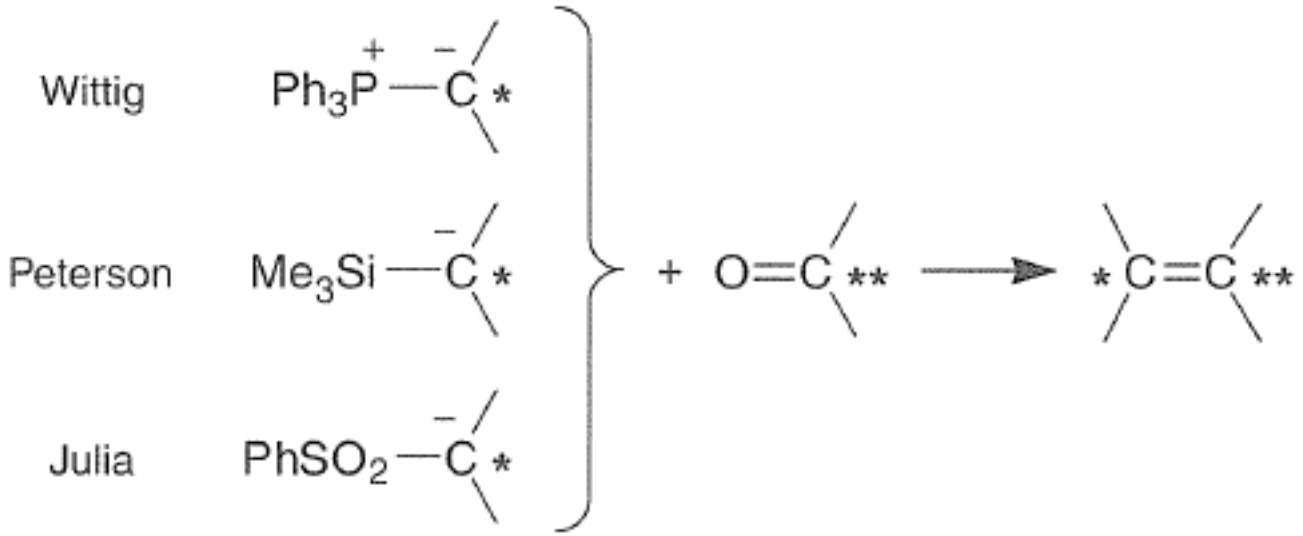
A related reaction is the **Appel reaction**, in which an alcohol is substituted by a halogen. The driving force of the Appel reaction is the formation of P-O double bond (P=O 110 kcals/mol).



C=C (double bonds)

Olefination Reactions

The olefination is one of the most powerful tools for the construction of double bonds and has found wide application in natural product synthesis as well in the pharmaceutical industry for the manufacture of drugs.



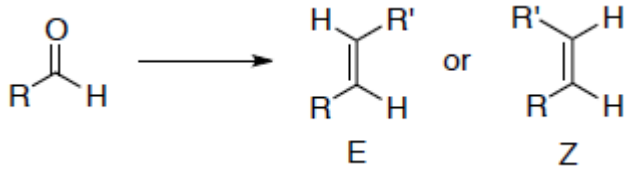
The prime utility of the Olefination reaction lies in the ease with which the reaction occurs under mild conditions and that no ambiguity exists concerning the location of the double bond in the product.

A drawback of the olefination reaction is its susceptibilitoy steric hindrance. Whereas aldehydes usually give high yield of alkenes, ketones often react less satisfactorily.

The synthesis of tetrasubstituted alkenes via the Olefination reaction is problematic.

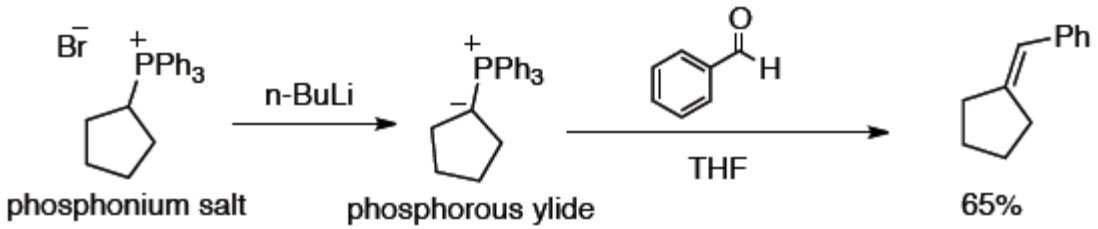
Phosphorous Ylide Chemistry

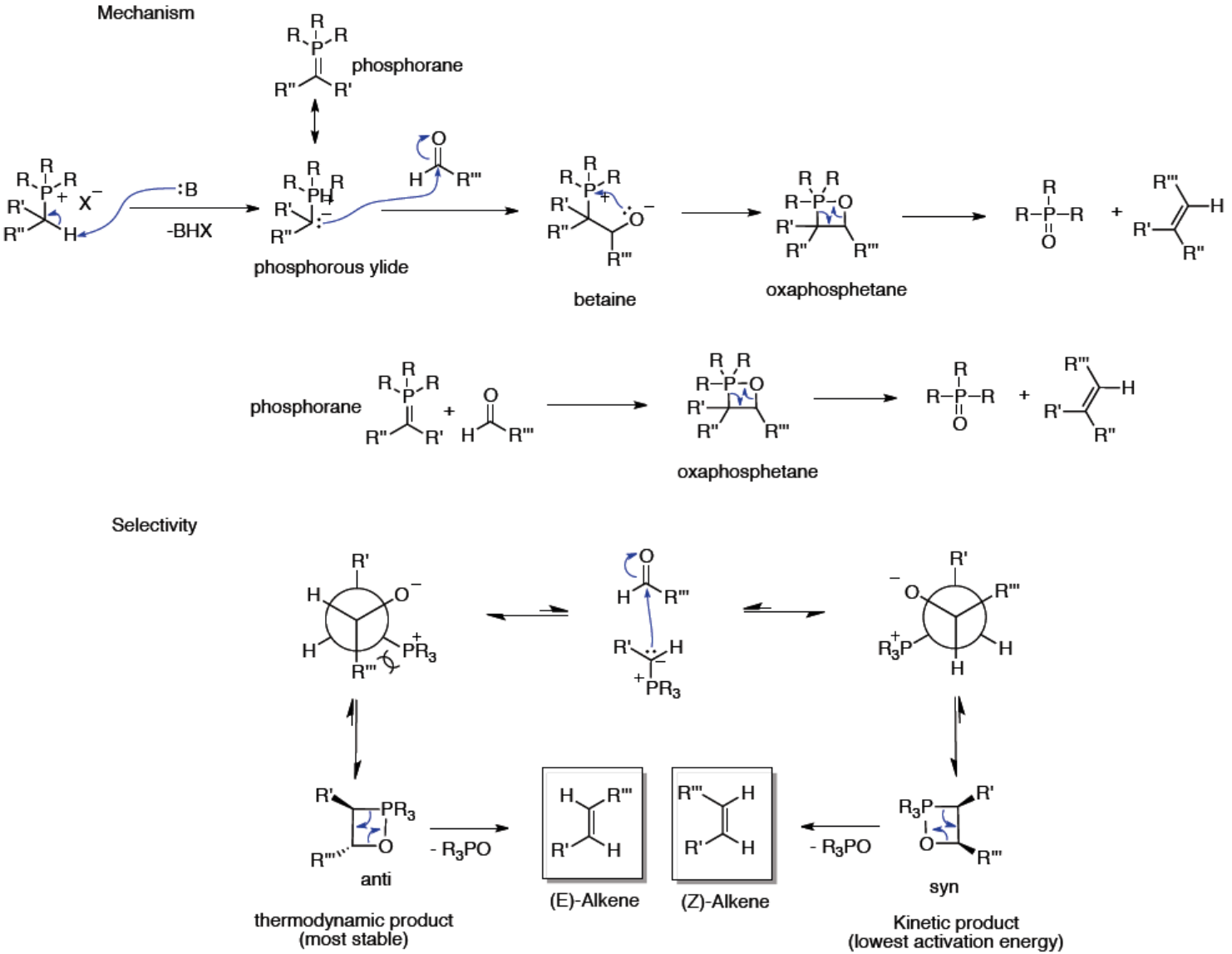
Transformation of aldehydes to olefins:



Wittig Reaction

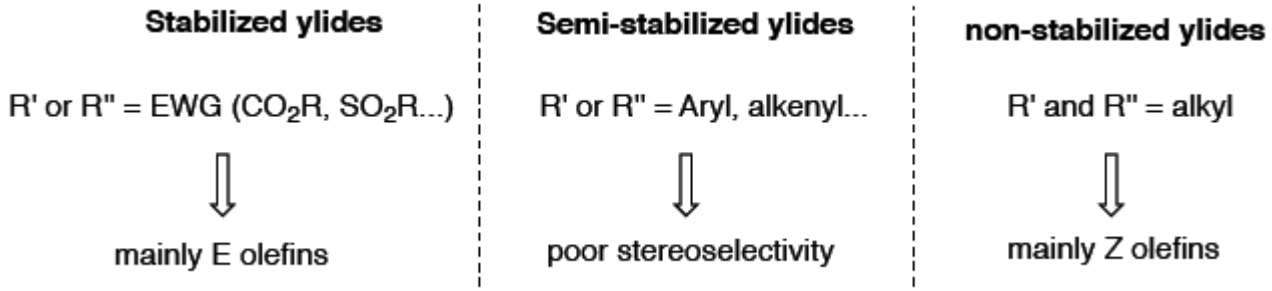
The Wittig reaction is a powerful method for the formation of alkenes, involving a phosphorous ylide (formed by deprotonation of a phosphonium salt with a base) and an aldehyde or a ketone.





The four-membered intermediate, an oxaphosphetane, which is formed via [2+2] or stepwise mechanism from phosphorous ylide and an aldehyde , undergoes **retro**-[2+2] ringopening, forming corresponding akene and phosphorous oxide as a by-product.

There are 3 different types of ylides, depending on the nature of the R' and R'' substituents:

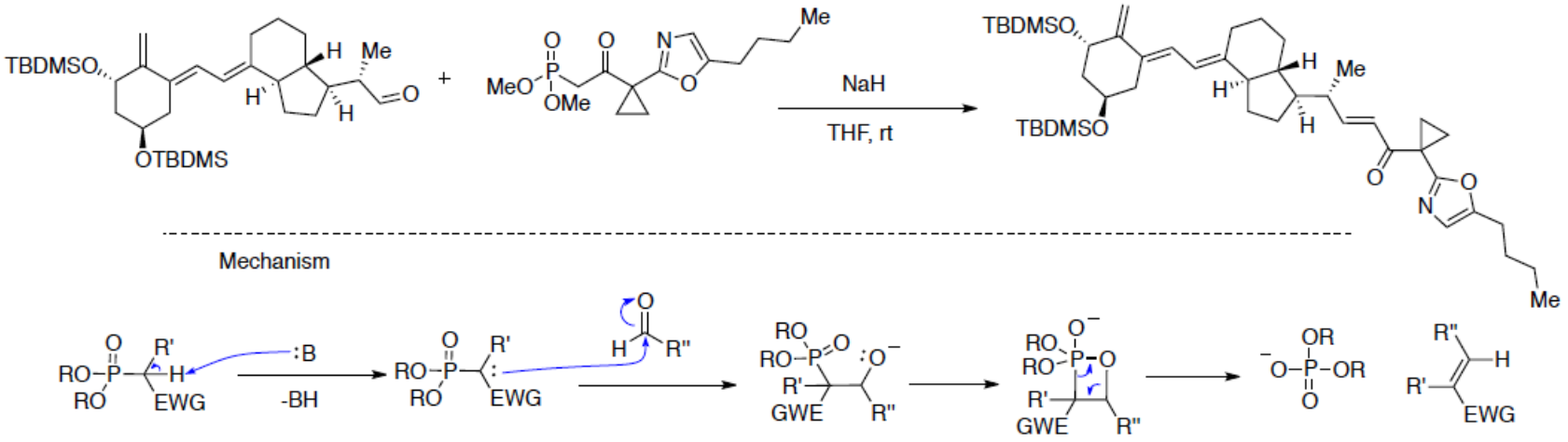


In the case of stabilized ylides, oxaphosphetane formation is **reversible** and equilibrates to the most stable structure (*anti*), affording mainly the *E* olefin (reaction under **thermodynamic control**).

In the case of non-stabilized ylides, the oxaphosphetane formation is **irreversible**, the *syn* oxaphosphetane is formed preferentially, affording mainly the *Z* olefin (reaction under **kinetic control**).

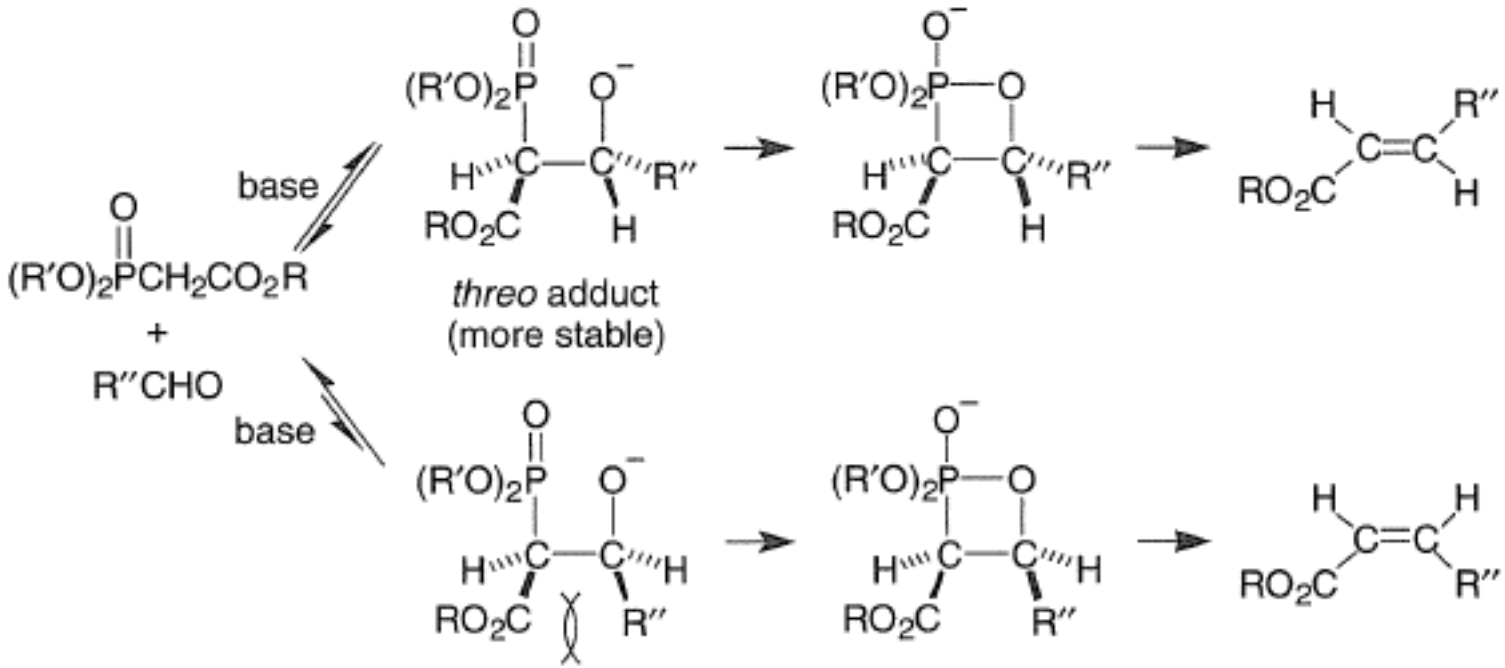
Horner-Wadsworth-Emmons reaction (HWE)

The HWE reaction is a modification of the Wittig reaction affording α,β-unsaturated carbonyls with mainly *E* selectivity.



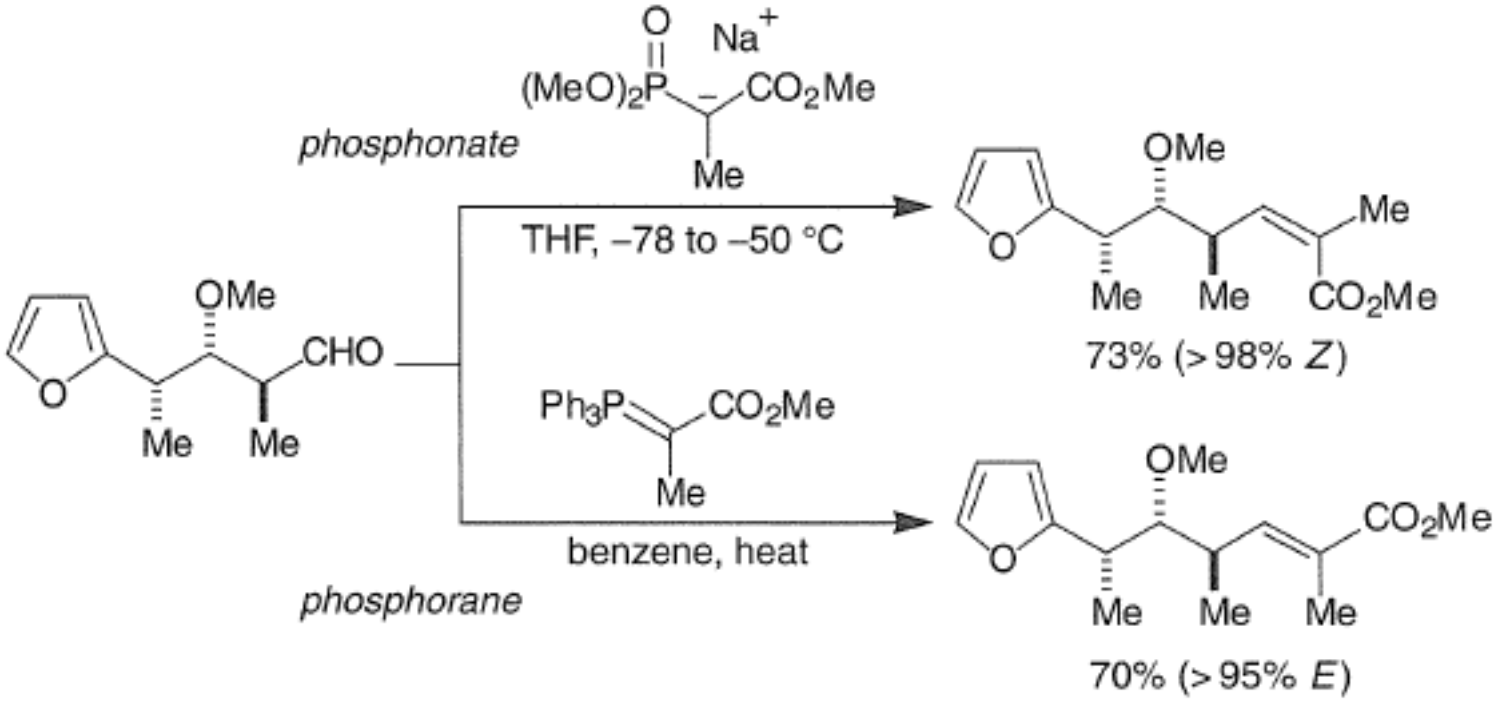
If R'=H, betaines and oxaphosphetanes intermediates equilibrate to the most stable *anti* oxaphosphetane, yielding mainly *E* alkenes (see the Wittig reaction mechanism).

The *(E)*- and (Z)-selectivity in HWE reactions is determined by a combination of the stereoselectivity in the initial carbon-carbon bond formation and the reversibility of the intermediate adducts.
The (E)-selectivity has been explained by the formation of the thermodynamically more stable threo-adduct, which then decomposes via the oxaphosphetane inter mediate to the E-olefin.

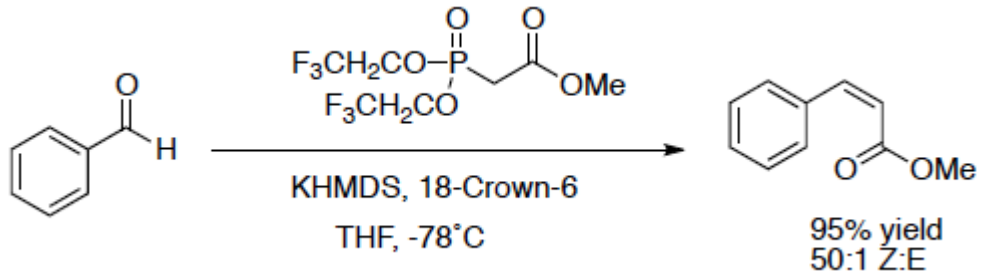


The HWE olefination offers several advantages over the Wittig reaction using stabilized ylides:

- Phosphonate carbanions are more nucleophilic than phosphonium ylides. Thus, they can be used in condensations with ketones as well as with aldehydes under mild conditions.
- Separation of the olefin product from the water-soluble phosphate ester by-product formed from phosphonates circumvents the problem often encountered in removing Ph3P = 0 .
- Reaction conditions are available for the preparation of alkenes enriched in either the (E)- or the Z-isomer

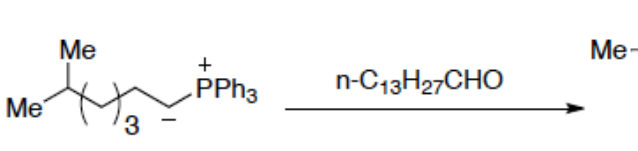


Still and Gennari have introduced a modification of this reaction using phosphonate with EWG under strongly dissociating conditions affording nearly exclusively *Z* alkenes.

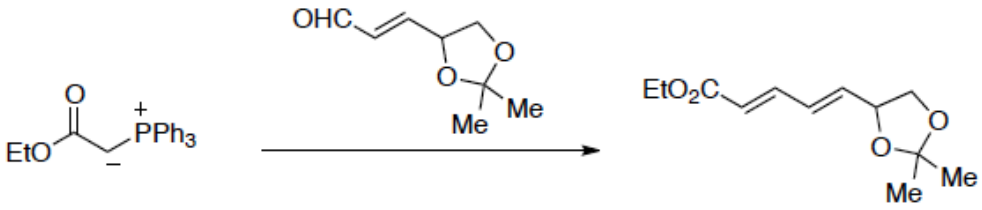


EWG on the phosphonate accelerates elimination relatively to isomerization.

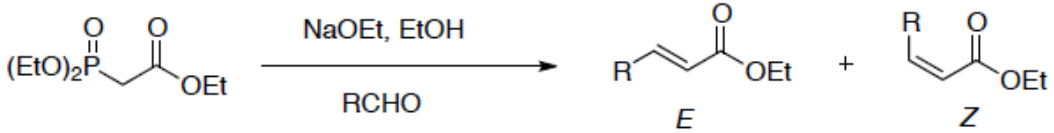
Examples



91% Yield, all Z



96% Yield, all E

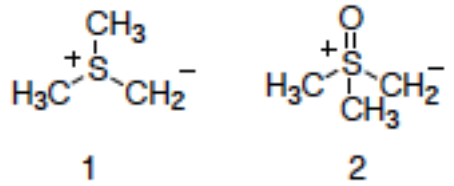


Aldehyde	*Ratio (E:Z)*
PhCHO	98 : 2
n-PrCHO	95 : 5
i-PrCHO	84 : 16

Sulfur Ylide Chemistry

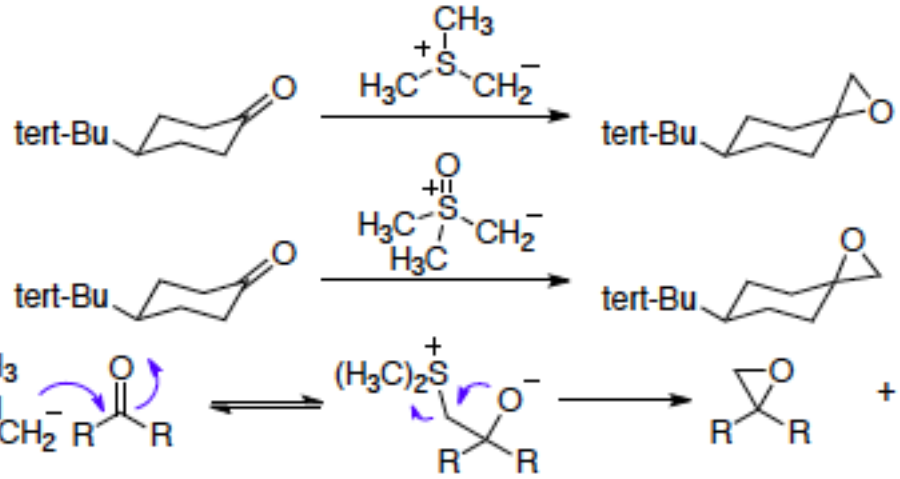
Transformation of ketones and aldehydes into 3-membered rings:

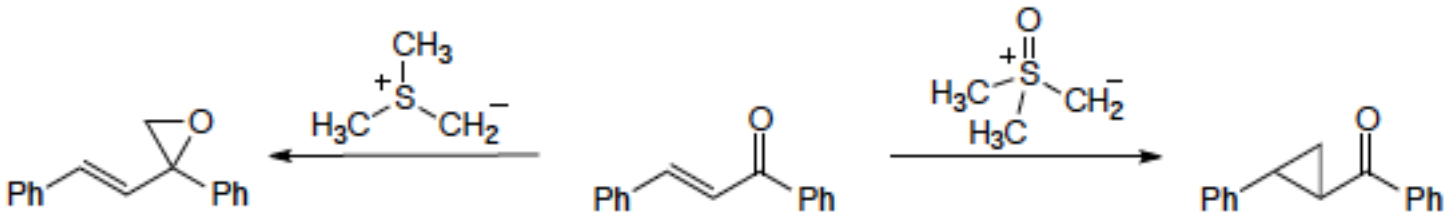
Two of the most widely used reagents are dimethylsulfonium methylide (1) and dimethylsulfoxonium methylide (2).
2 is more stable than 1. Addition of 2 to carbonyls is reversible.

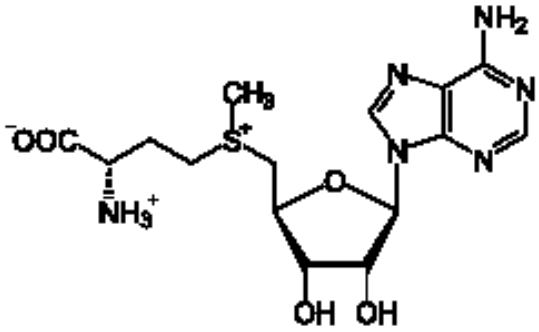


1

2







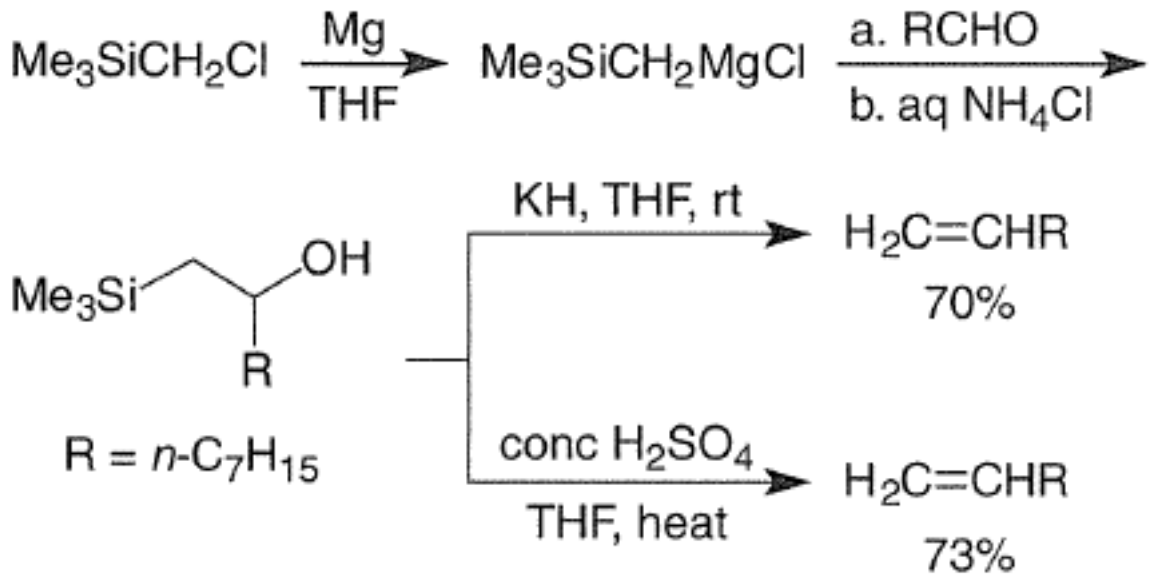
S-adenosil metionina (SAM)
Active Methyl Donor

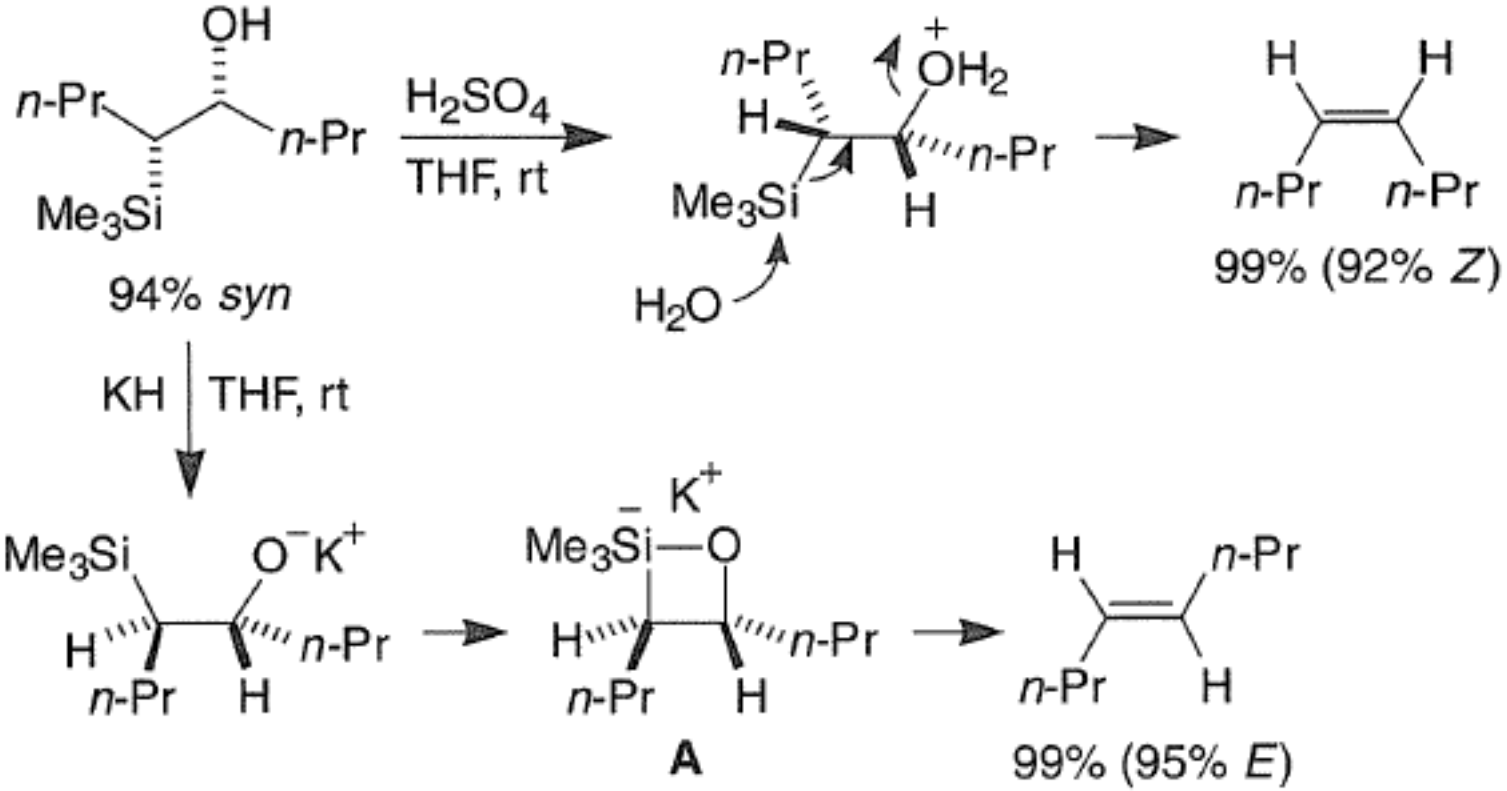
Go back to Olefination……

Peterson Olefination

The Peterson olefination is a connective alkene synthesis and represents a useful alternative to the Wittig reaction.

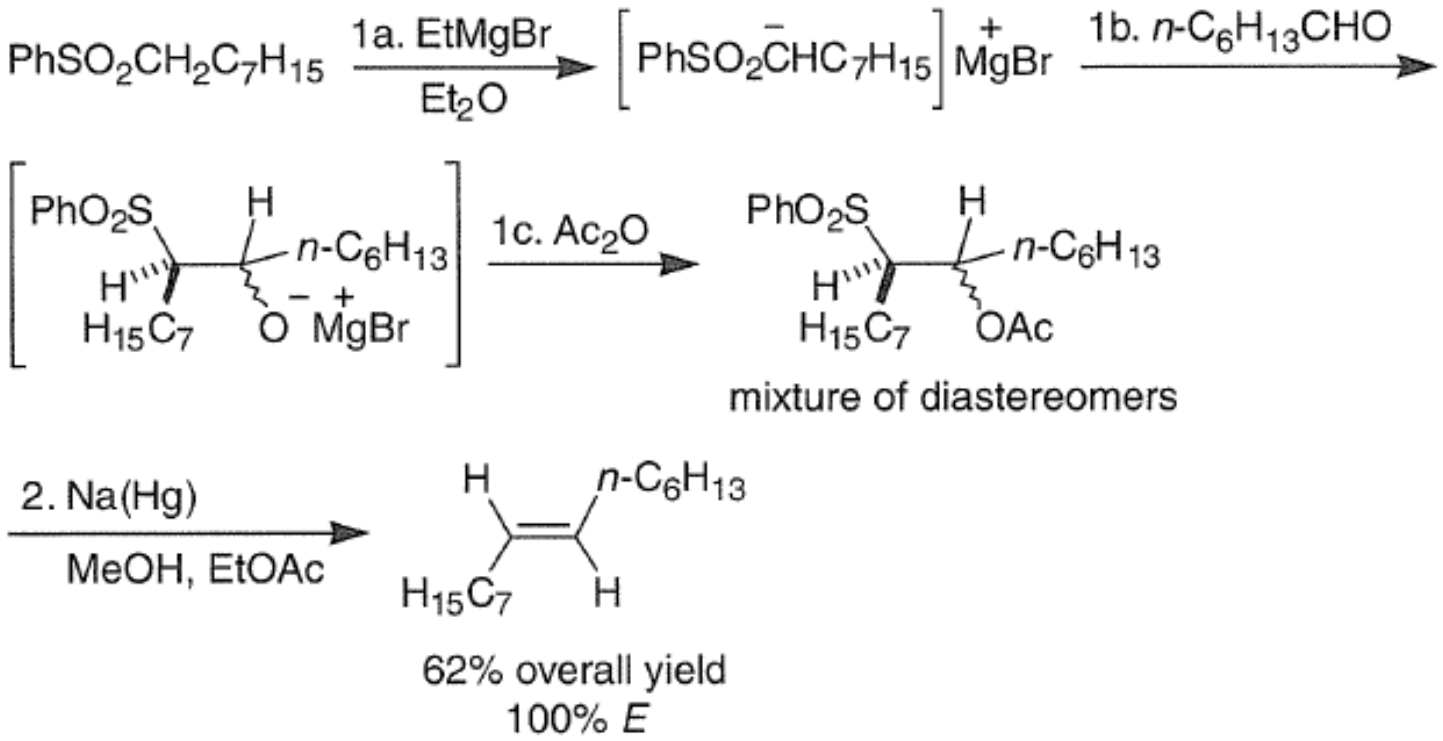
This olefination method is especially valuable for the preparation of terminal and exo-cyclic double bonds and for the methylenation of hindered ketones where the Wittig reaction is problematic.



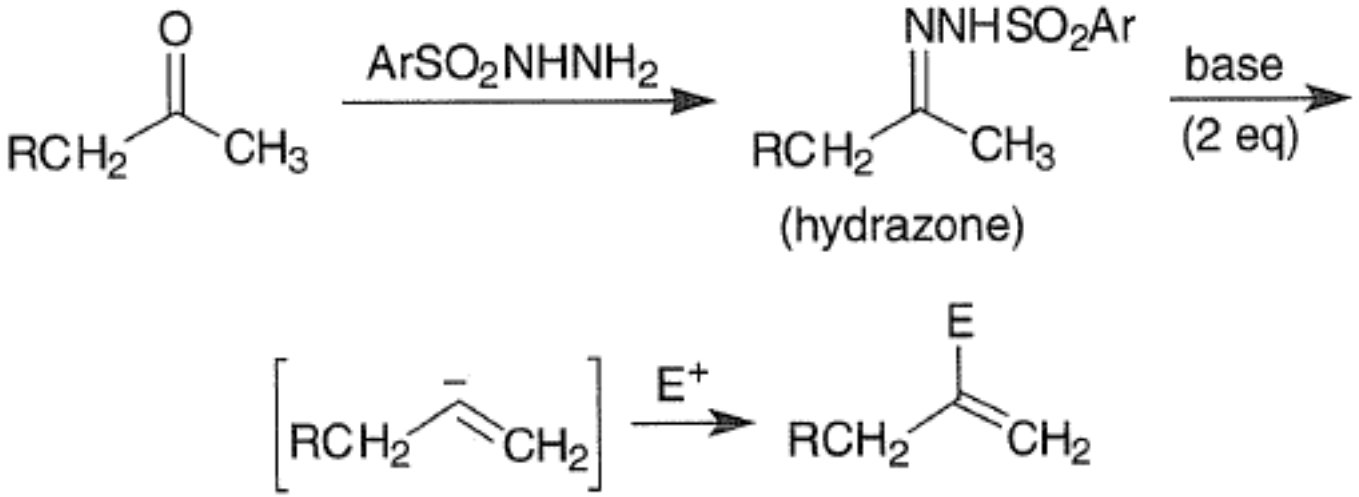

OH
n-Pr
n-Pr
Me3Si
94% syn
H2SO4
THF, rt
n-Pr
+OH2
H
n-Pr
Me3Si
H
H2O
H
H
n-Pr
n-Pr
99% (92% Z)
KH
THF, rt
Me3Si
O−K+
H
n-Pr
n-Pr
H
K+
Me3Si—O
H
n-Pr
n-Pr
H
A
H
n-Pr
n-Pr
H
99% (95% E)

Julia Olefination

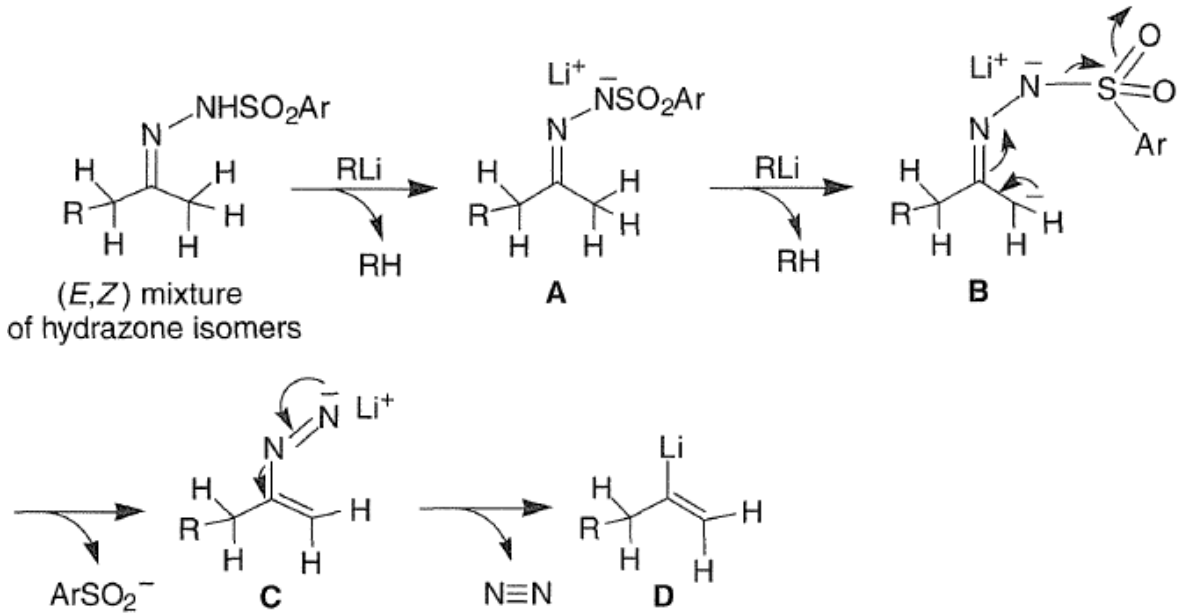
The Julia olefination reaction is highly regioselective and (E)-stereoselective,



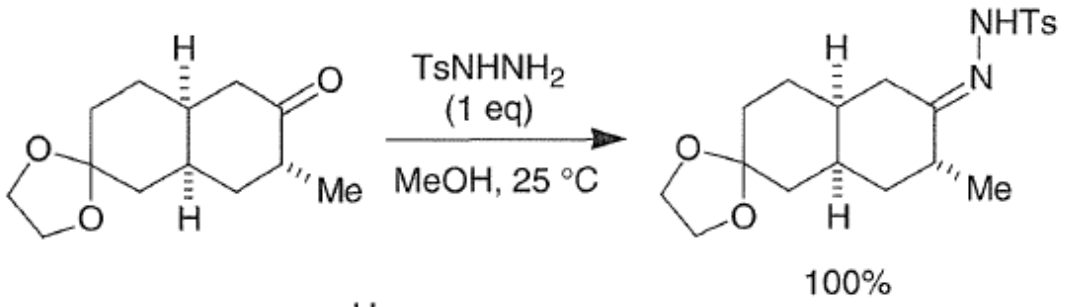
The **Shapiro** Reaction

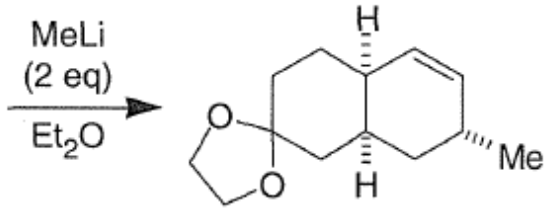


Mechanism

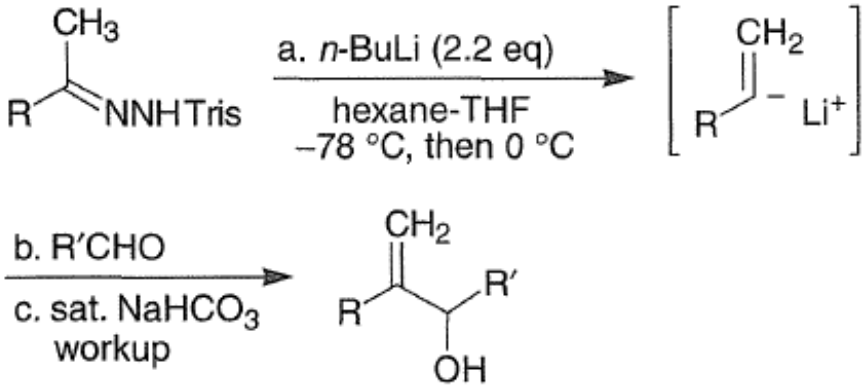


Examples

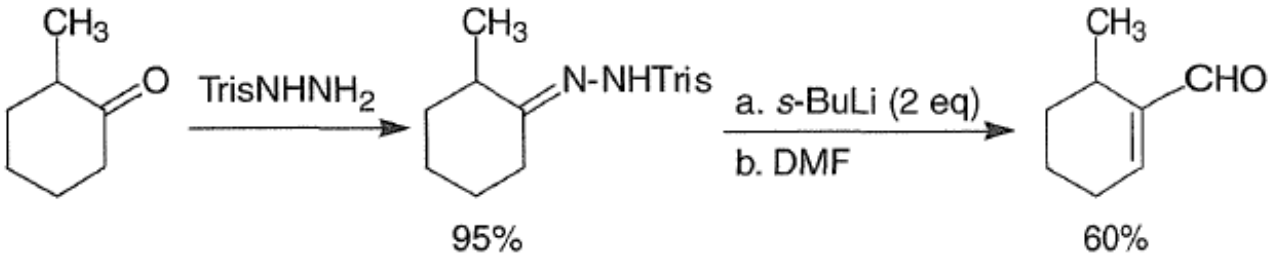




> 80% overall



90%; R = *i*-Pr, R′= *n*-C_6H_{13}



95% 60%

C-C (single bonds)

1,3-dicarbonyl and related compounds

(Alkylation, Conjugate Addition-Michael-Type Reactions, The Knoevenagel Condensation)

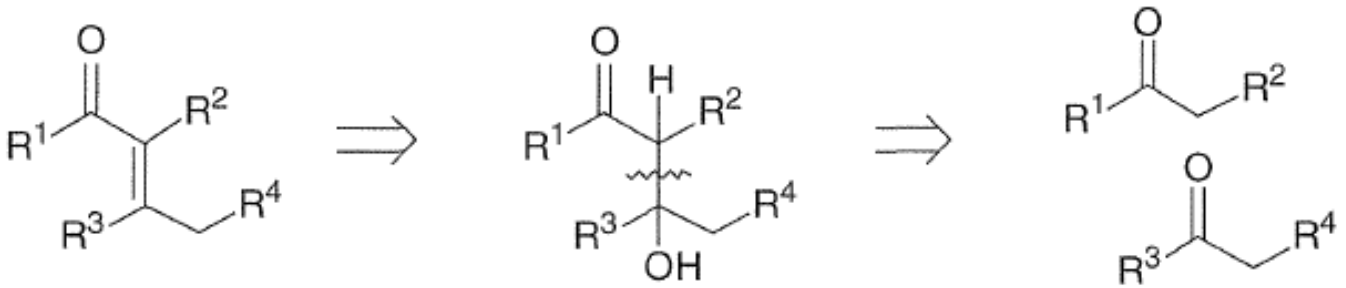
Ester

(Acylation i.e. Claisen Condensation and Alkylation)

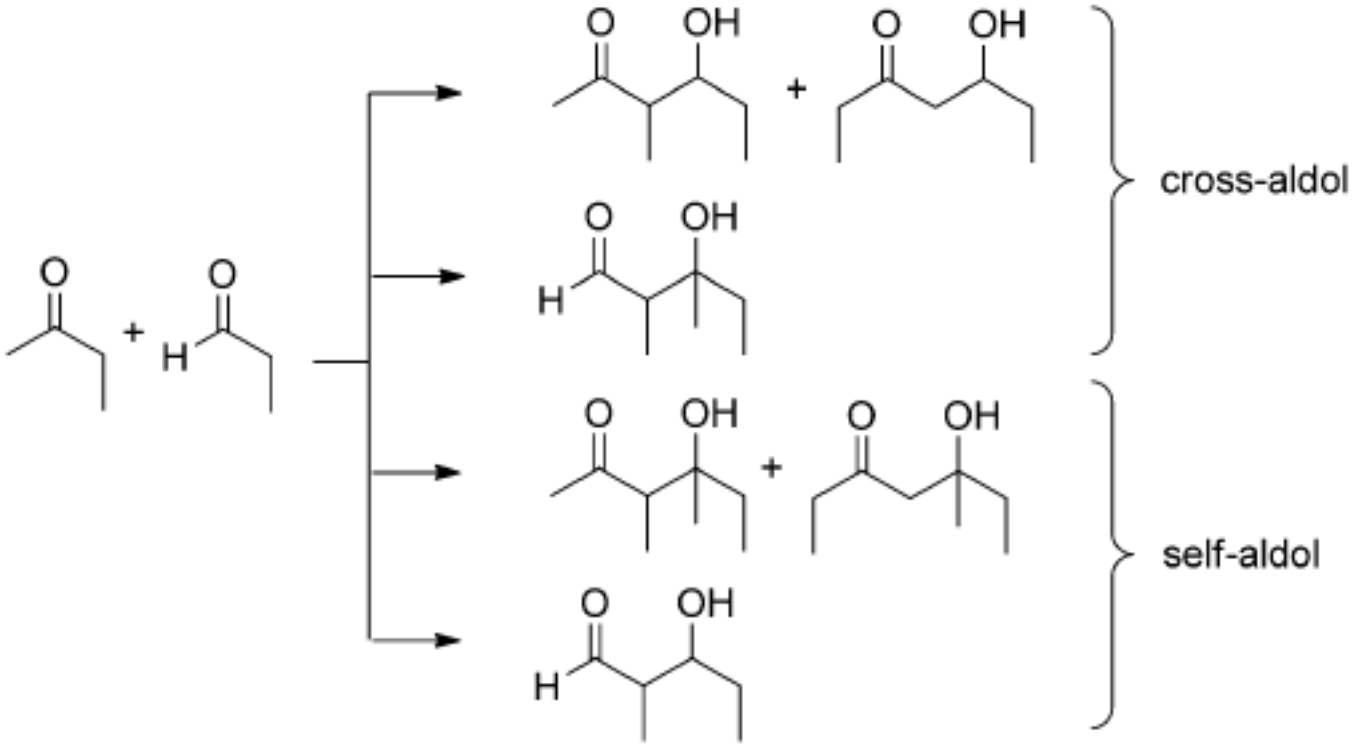
Ketone

(acylation and alkylation reaction, aldol reaction and its enamines alternatives but also Mannich reaction)

The aldol reaction is one of the most useful methods for the construction of carbon-carbon bonds. The products of aldol reactions are either β-hydroxy carbonyl compounds or, after dehydration, α, β -unsaturated carbonyl compounds.
The aldol reaction is useful not only for making C-C bonds, but also for providing two functional groups, the C=O and a β -OH, which can be further elaborated.
The intramolecular aldol condensation is a powerful tool for obtaining five- and six-member rings, think to the Robinson annulation

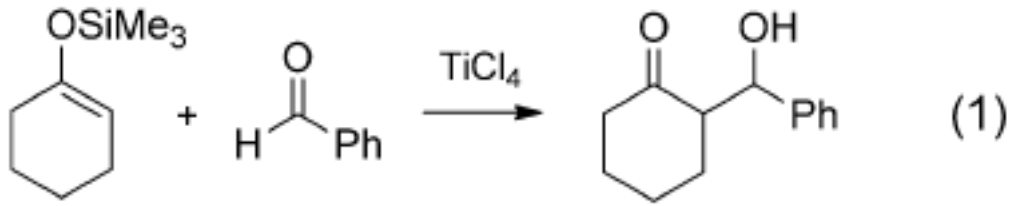


R^1, R^2, R^3, R^4 = H, alkyl, or aryl



Therefore, it was a significant challenge to selectively synthesize one desired stereodefined aldol product out of the many possible alternative aldol products. These situations lead to a strong demand to develop a convenient, efficient, and controlled method for directed cross-aldol reactions.

1973



Mukaiyama (1973)

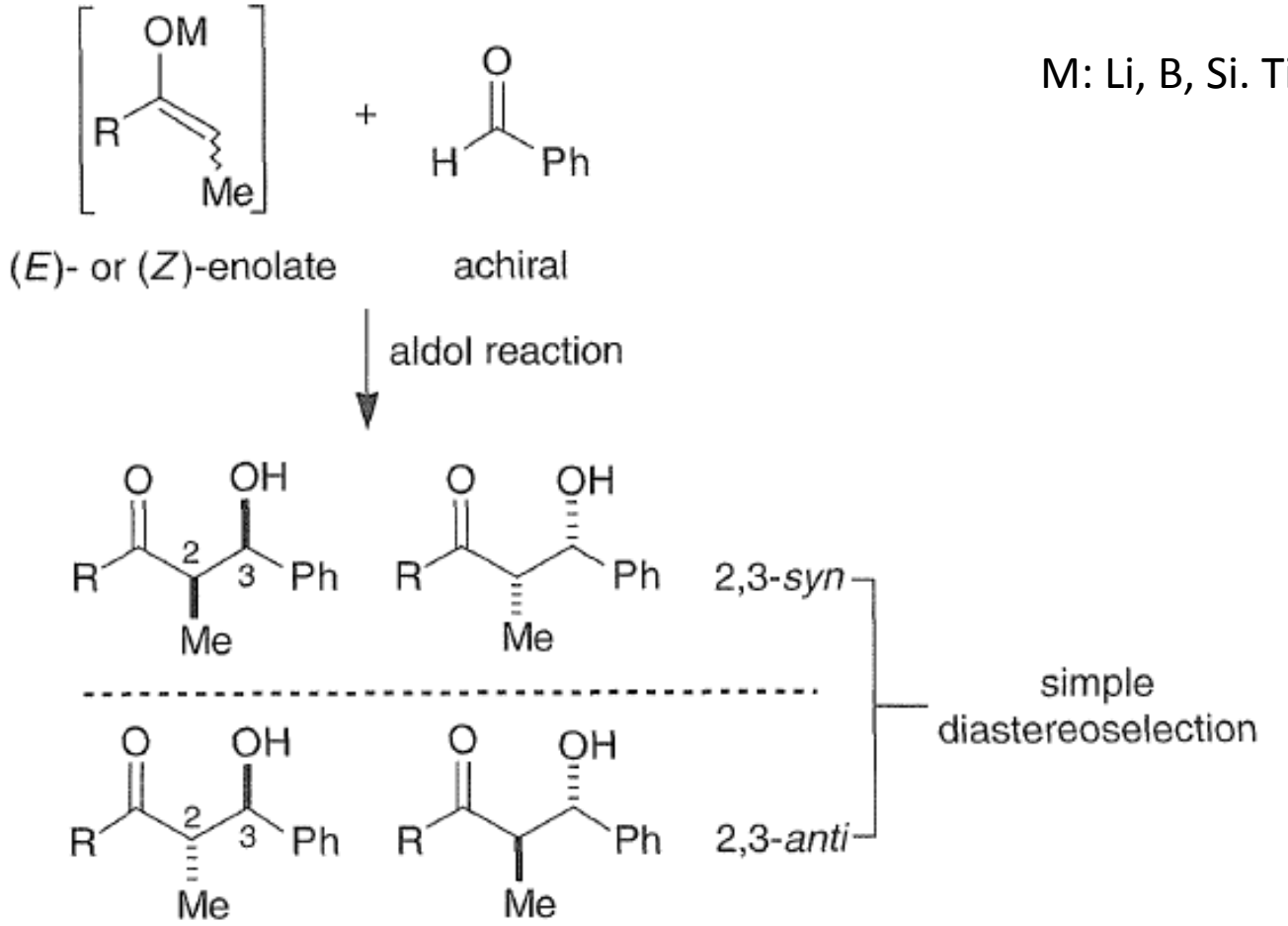
it was also 1973 when House first reported a directed cross-aldol reaction via lithium enolates.

One proceeding under **acidic** conditions and the other under **basic** conditions

In particular, the Mukaiyama aldol reaction provided a leading example in which aldehydes (or ketones) are activated by a Lewis acid in the presence of a carbon nucleophile.
Activation of a carbonyl group by a Lewis acid facilitates attack of a nucleophile and thus a carbon–carbon bond is formed under acidic conditions.

Stereoselective **Aldol** Reactions'

Simple diastereoselection

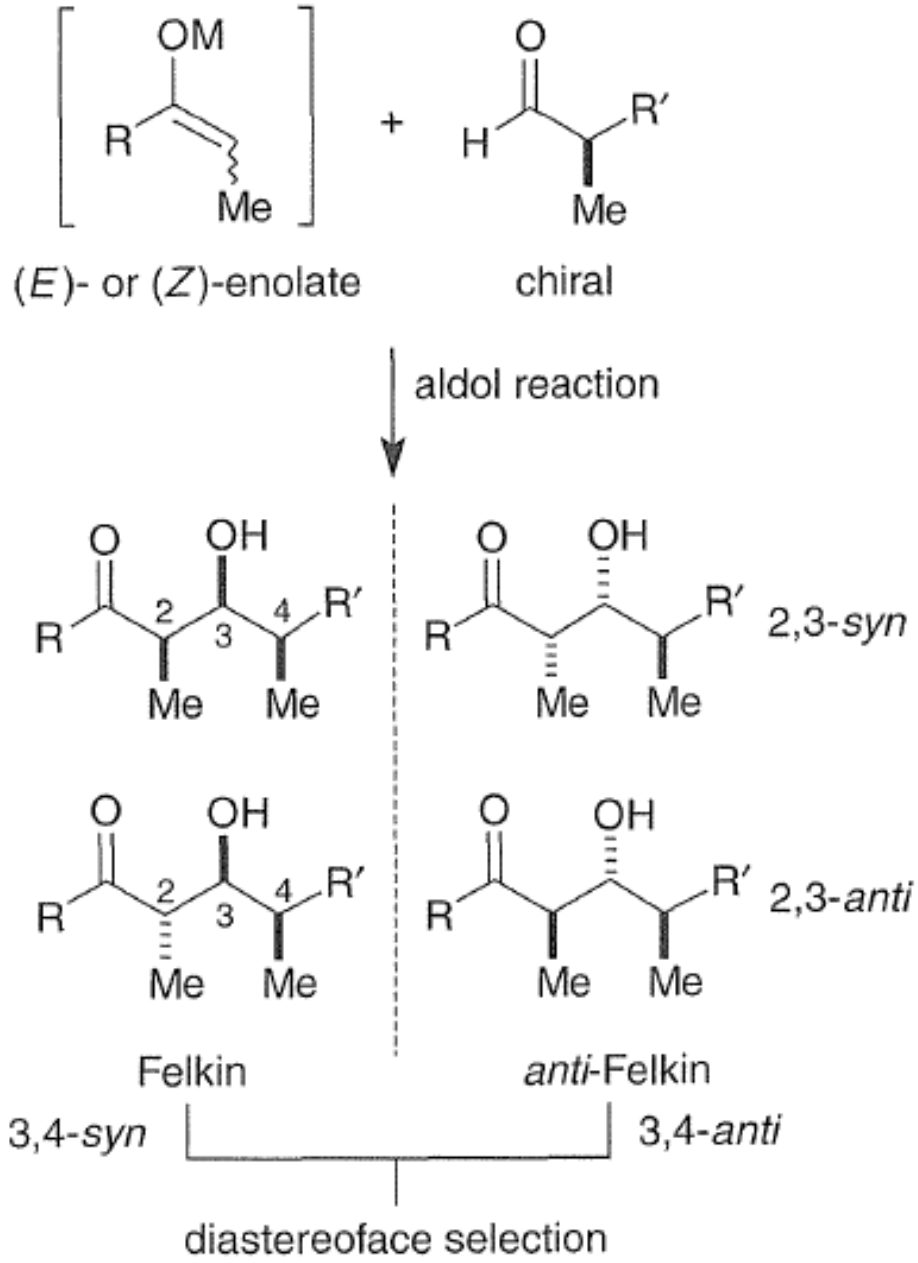


M: Li, B, Si. Ti, Sn

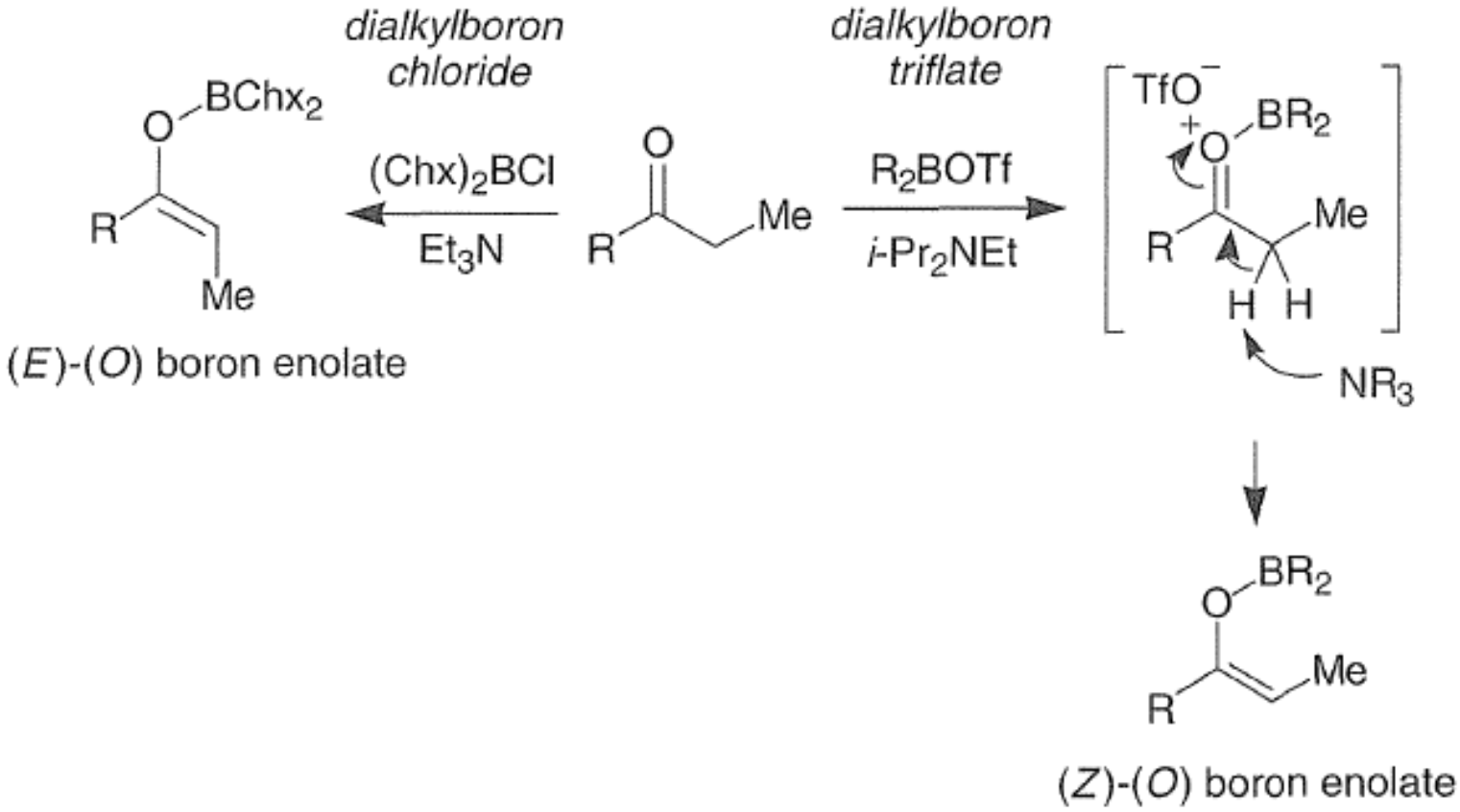
Controlled by: a) The configuration of the enolate ion, (E)-vs. Z-enolate.

b) The orientation of the enolate and aldehyde in the transition state of the aldol reaction, "open" transition state vs. the ordered, chelate-controlled transition state

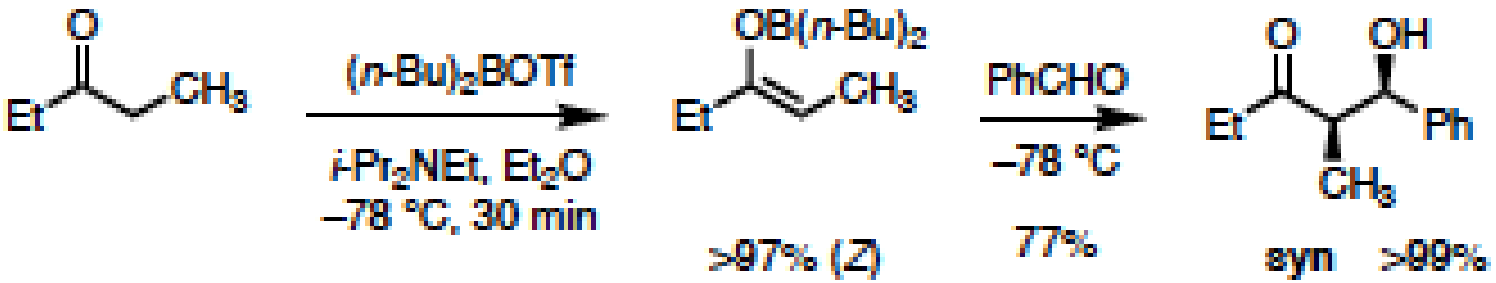
diastereoface selection

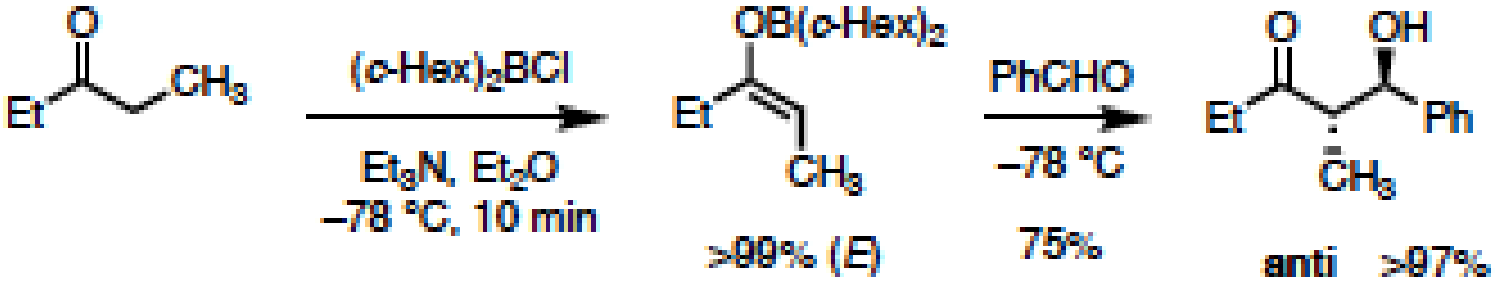


Although stereoselective formation of enolates from acyclic ketones with bases such as LDA is rather difficult, stereodefined boron enolates are more readily accessible



In analogous fashion, titanium, silicon and tin enolates are formed by the reaction of enolizable ketones with a tertiary amine and $TiCl_4$, Me_3SICl or $SnOTf_2$, respectively. The reactions of titanium enolates are highly selective and comparable to boron enolates in aldol condensations.





BTf------> Z ------> syn

BCl------> E ------> anti

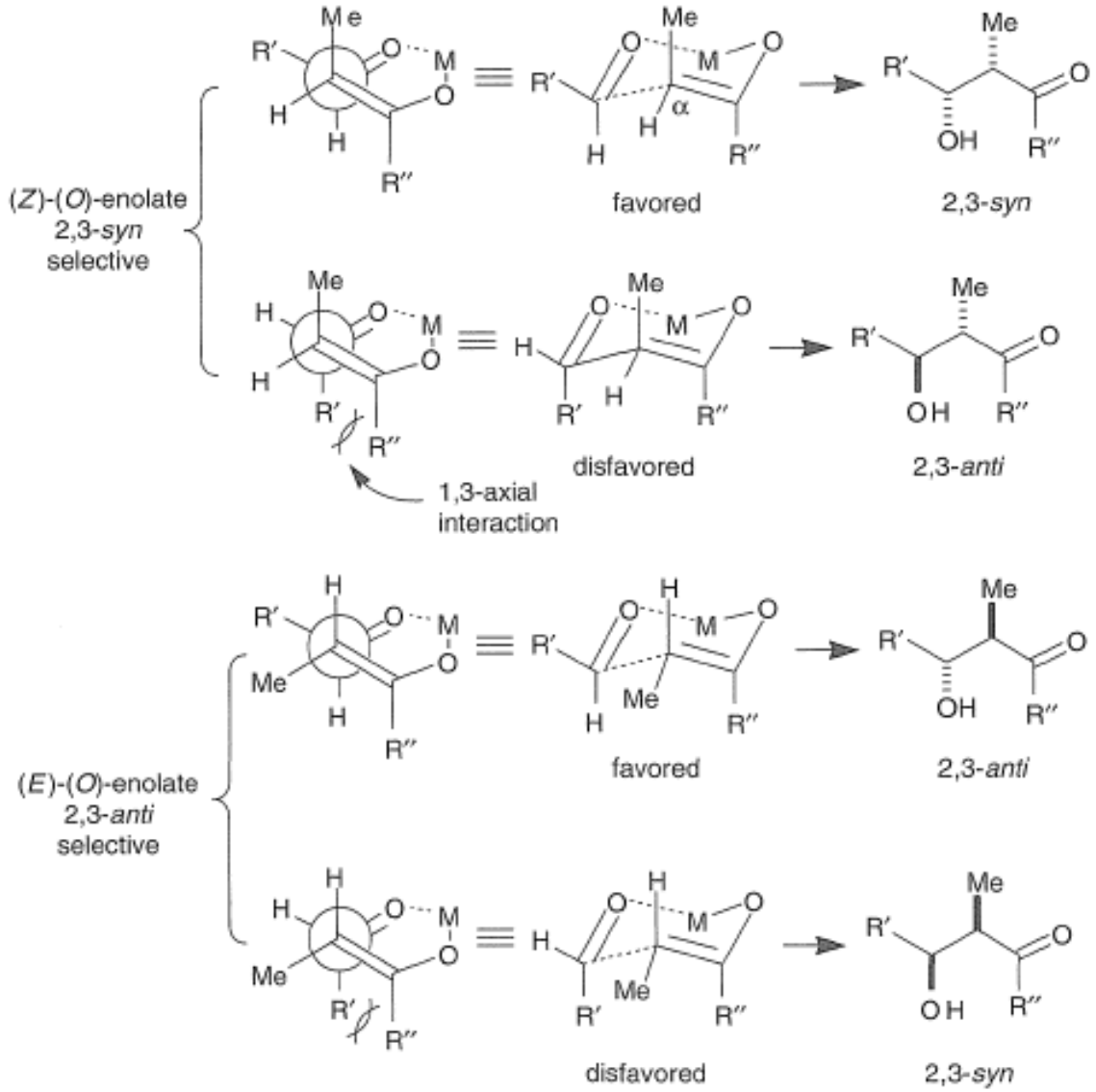
• Dialkylboron triflates typically afford (Z)-boron enolates, with little sensitivity toward the amine used or the steric requirements of the alkyl groups on the boron reagent.

• In the case of dialkylboron chlorides the geometry of the the product enolates is much more sensitive to variations in the amine and the alkyl groups on boron.

• The combination of (c-Hex)2BCl and Et3N provides the (E)-boron enolate preferentially.

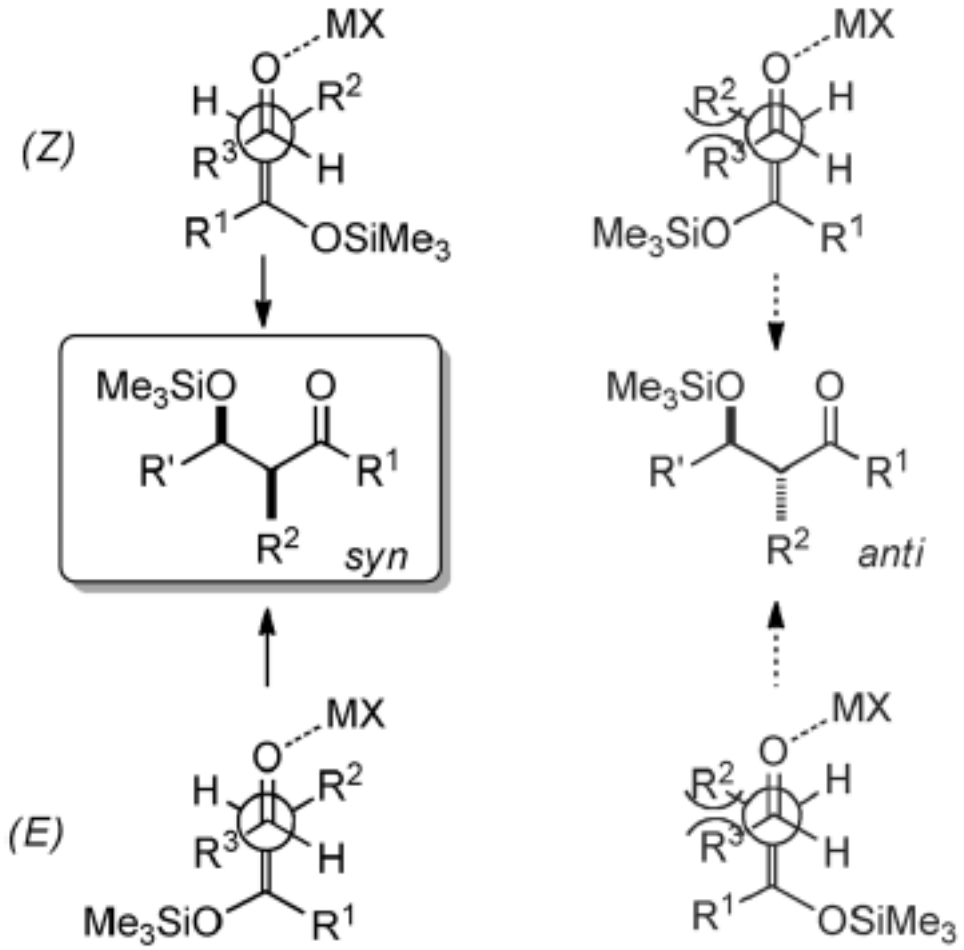
Simple Diastereoselection - *Syn-Anti*

Zimmerman-Traxler (1957) transition state model for (Z) and (E)-enolates

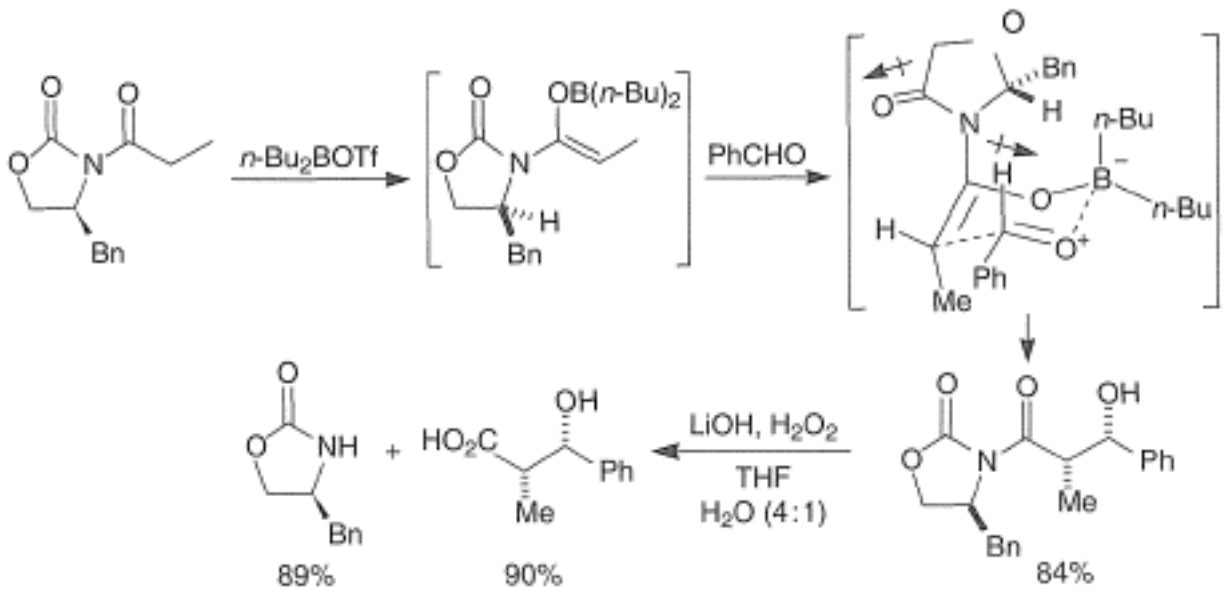


can be highly metal dependent; Only boron, reliably follow the indicated pathways.

Note: If the aldol reaction is catalyzed by Lewis acids such as BF3, or TiCl4, the addition reaction will proceed via an acyclic transition state (Mukaiyama aldol).

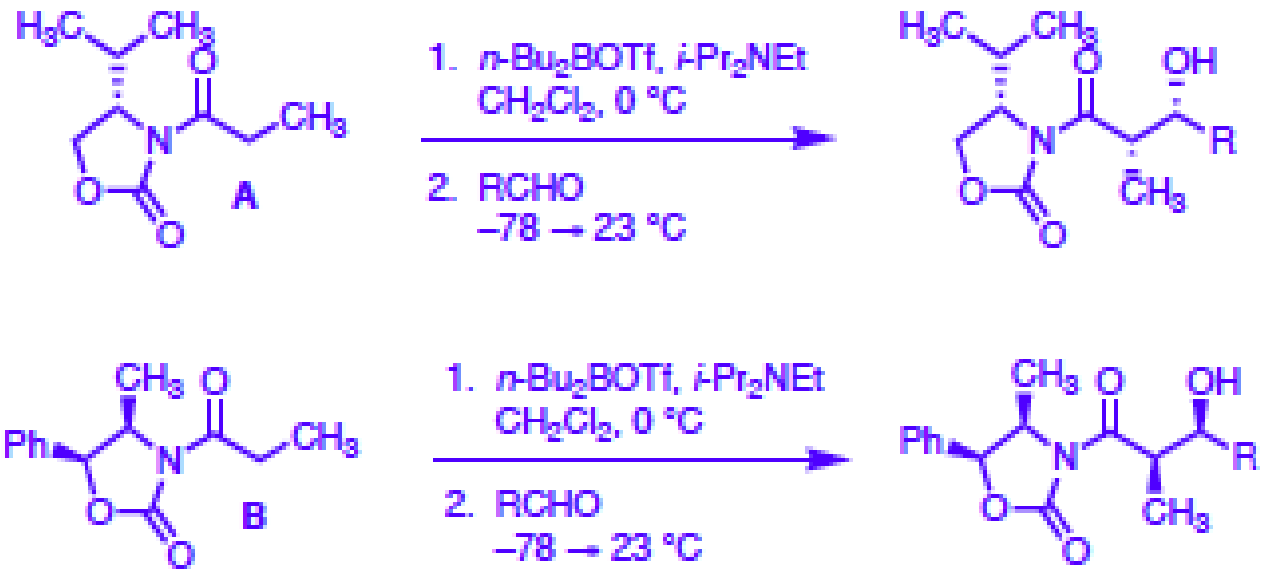


Enantioselective aldol Reaction (EVANS)



(MeO)MeNH gives the corresponding Weinreb amide.
DIBAL-H or with Grignard gives aldehyde or ketone, respectively.
LiBH4, affords the corresponding alcohol in good yield

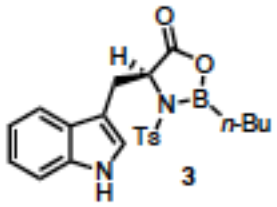
The oxazolidinone auxiliary group can also be used to direct the stereochemical outcome to favor anti-selective aldol reactions by diverting the reaction to an open transition state using Lewis acid conditions ($MgCl_2$, TMSCl, and Et_3N). anti

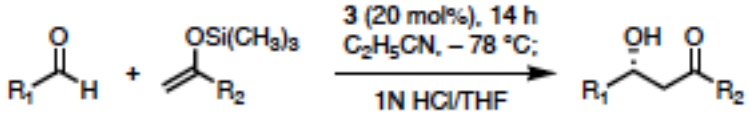


imide	aldehyde	diastereomeric[a] ratio	yield
A	$(CH_3)_2CHCHO$	497:1	78
B	$(CH_3)_2CHCHO$	<1:500	91
A	n-C_4H_9CHO	141:1	75
B	n-C_4H_9CHO	<1:500	95
A	C_6H_5CHO	>500:1	88
B	C_6H_5CHO	<1:500	89

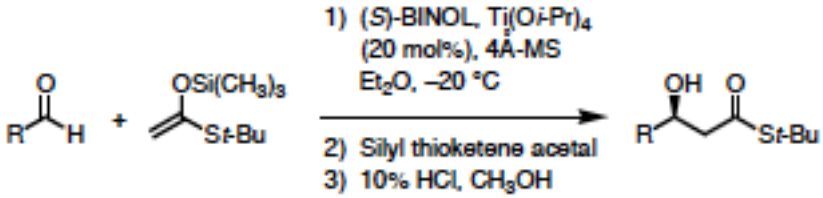
[a]Ratio of major syn product to minor syn product.

The big challenge Catalytic and Enantioselective





R_1	R_2	yield (%)	ee (%)
Ph	C_6H_5	82	89
c-C_6H_{11}	C_6H_5	67	93
2-furyl	C_6H_5	100	92
c-C_6H_{11}	*n*-C_4H_9	56	86



aldehyde	yield (%)	ee (%)
PhCHO	90	97
$PhCH_2CH_2CHO$	80	97
furylCHO	88	>98
c-$C_6H_{11}CHO$	70	89
$PhCH_2OCH_2CHO$	82	>98

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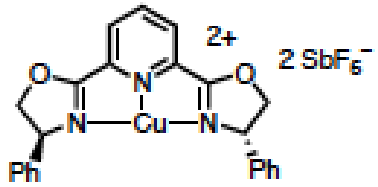
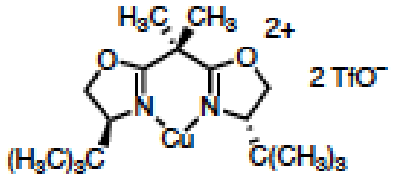
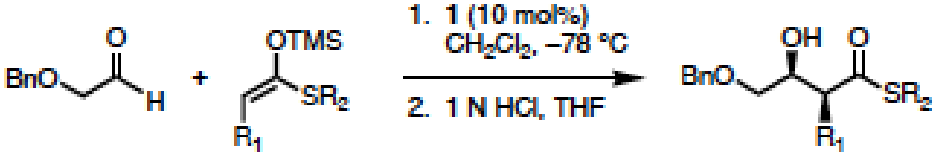


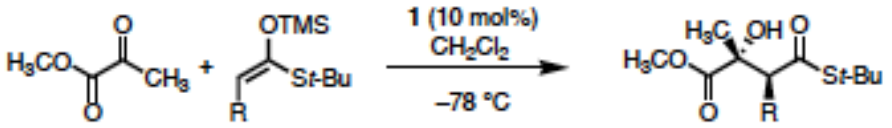
1



2

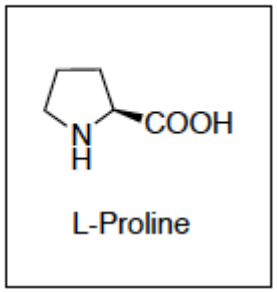


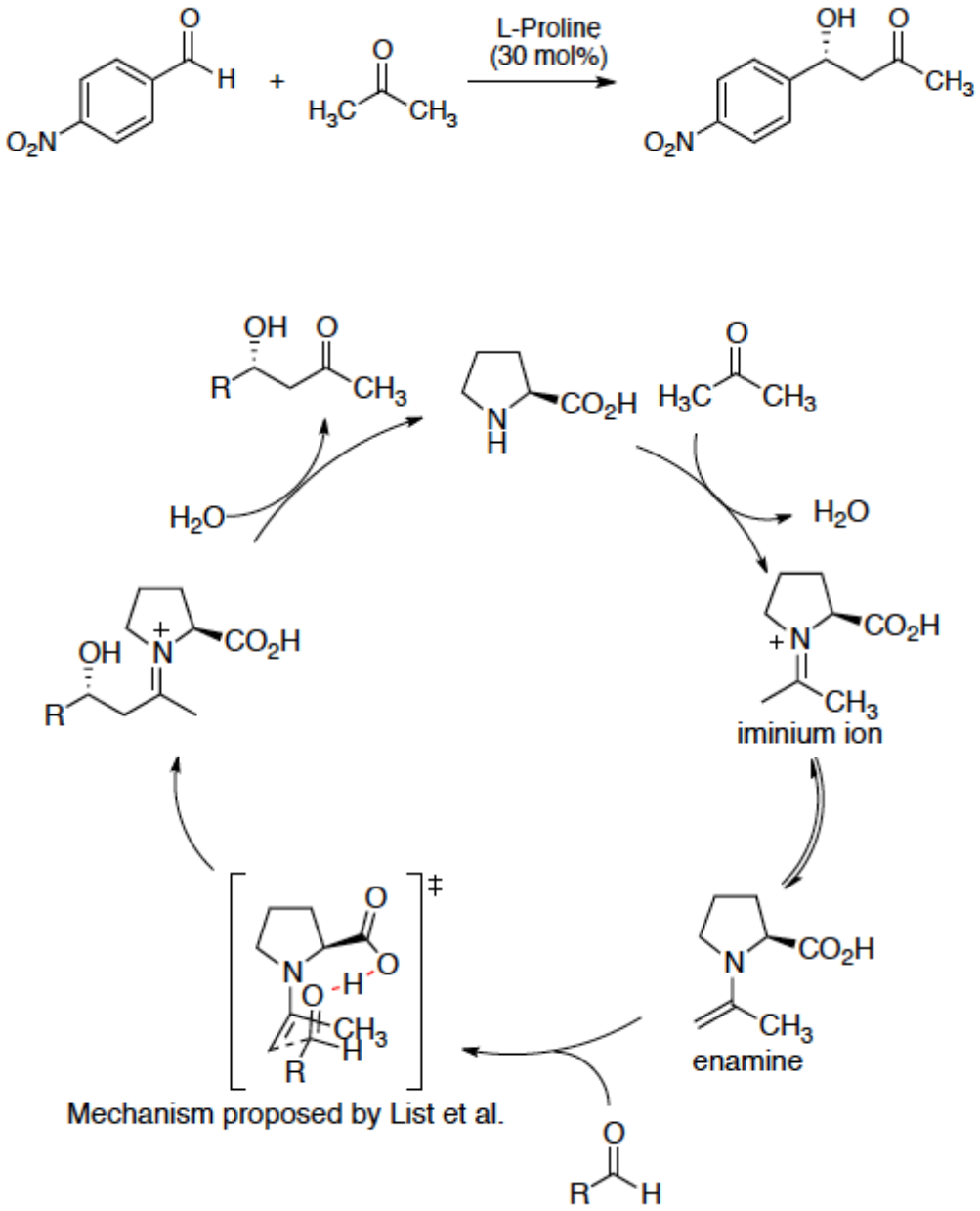
R_1	R_2	enol silane geometry	time (h)	T (°C)	syn:anti	%ee	yield (%)
H	*t*-Bu	–	24	–78	–	99	99
CH_3	Et	(*Z*)	4	–78	97:3	97	90
CH_3	Et	(*E*)	1d	–50	86:14	85	48
i-Bu	Et	(*Z*)	2d	–50	95:5	95	85



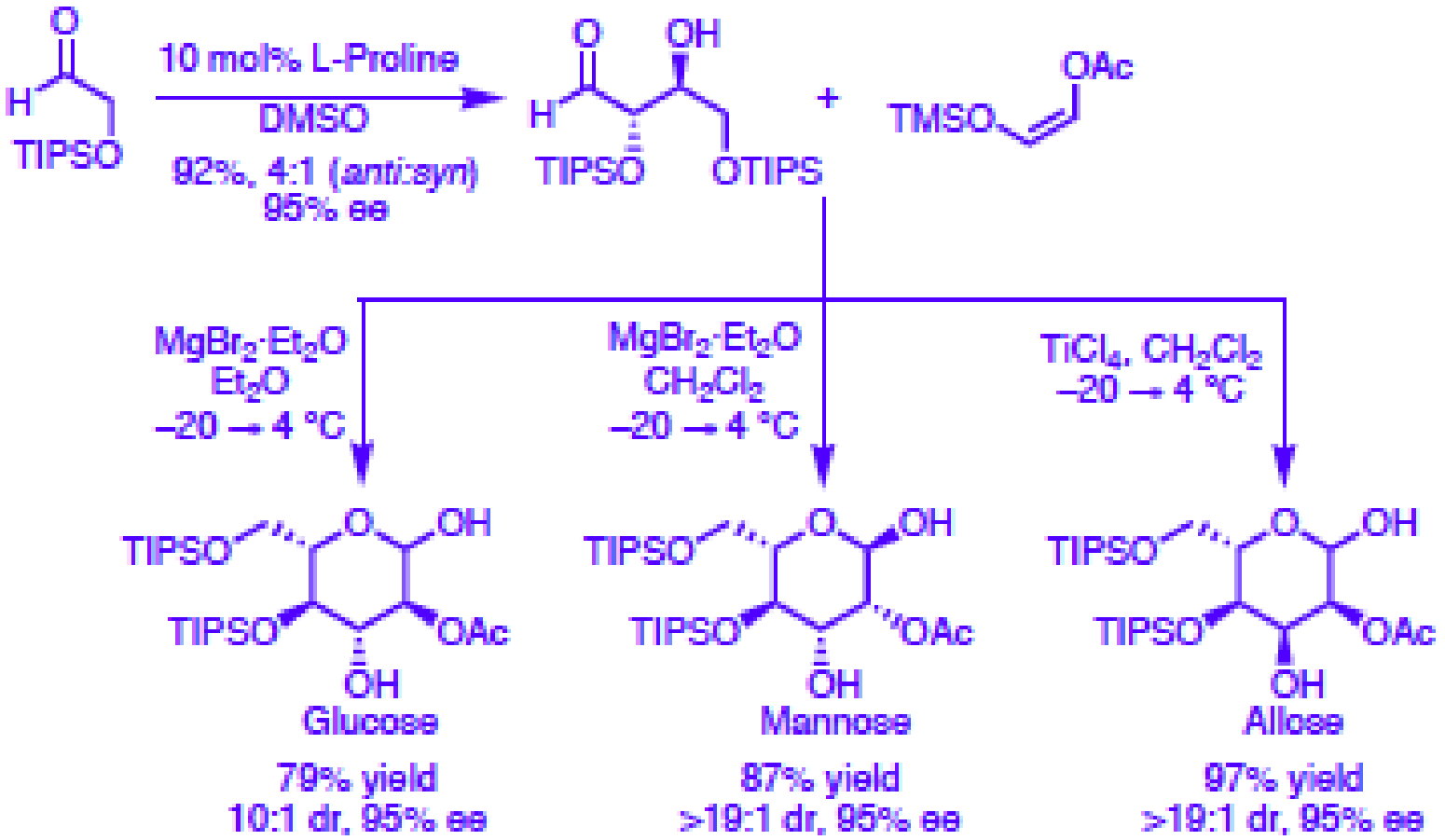
R = CH_3, Et, *i*-Bu
81-94%
≥96% ee
≥98:2 anti:syn

2000


COOH
N
H
L-Proline


L-Proline
(30 mol%)
OH
O
CH3
O2N
H3C
CH3
CO2H
H2O
iminium ion
enamine
Mechanism proposed by List et al.

- The aldol products from α-oxyaldehydes can be further elaborated as part of a two-step synthesis of carbohydrates.



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