

# Olefin Synthesis

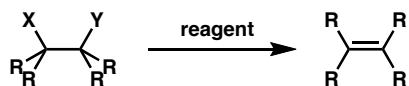
Chem 6352  
Jeremy May

-Plethora of references in the literature on olefin synthesis: see Larock 2<sup>nd</sup> ed. p. 215-562

-These can be categorized by reaction type:

-Or categorized by the olefinic product:

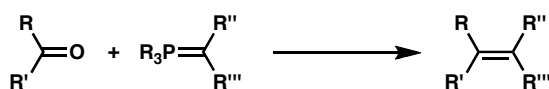
Elimination Reactions - Larock p. 251-315



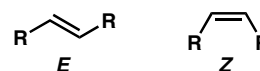
Terminal Olefins (see other handout)



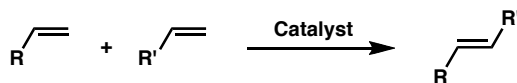
Wittig-type Reactions - Larock p. 327-350



1,2-Disubstituted Olefins



Metathesis Reactions - Grubbs group



Tri & Tetrasubstituted olefins (see other handout)

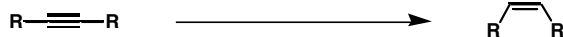


*Note: these are much more difficult because of E/Z issues!*

## 1,2-Disubstituted Olefins

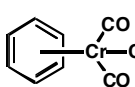
•Z-olefins

-From Acetylenes: by reduction

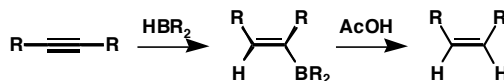


I Lindar's Catalyst, H<sub>2</sub>  
Pd/BaSO<sub>4</sub>, Quinoline (partially poisons catalyst)

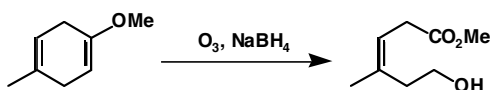
II Diimide reduction  
H-N=N-H

III  , H<sub>2</sub> (JOC 1985, 30, 1147)

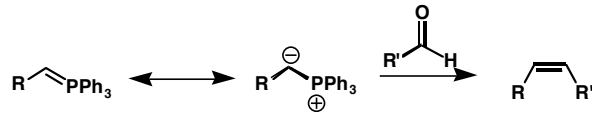
IV Hydroboration/Acidic Quench



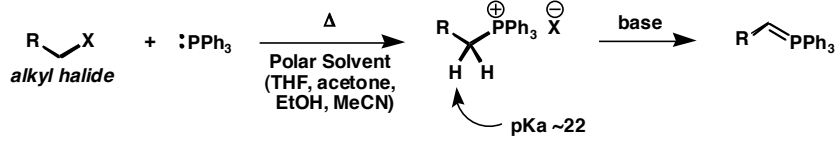
-From Rings:



-From Wittig Reaction:



preparation of ylide:

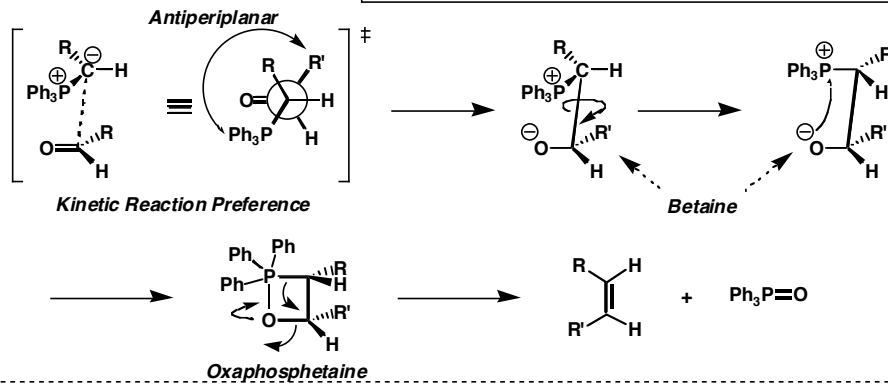


mechanism of the Wittig reaction:

Chem. Rev. 1989, 863  
JACS 1989, 6861  
JACS 1981, 2823

Vedejs

Base: *n*BuLi, LDA, KHMDS, NaHMDS, LiHMDS, *t*BuOK, S<sup>-</sup>, etc.  
(DMSO, NaH)



-Salt Effect:

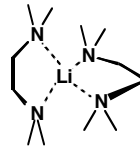


Activation of the carbonyl by a Lewis acidic salt can increase the reaction rate and lower the selectivity. Also, it leads to a more open transition state (ie. there are fewer steric effects).

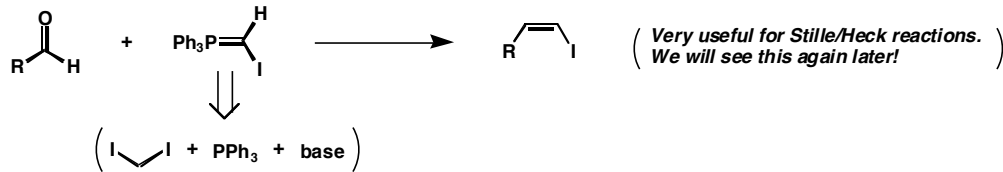
-To counter the effect:

Additives: HMPA, TMEDA → these break up and sequester lithium ions

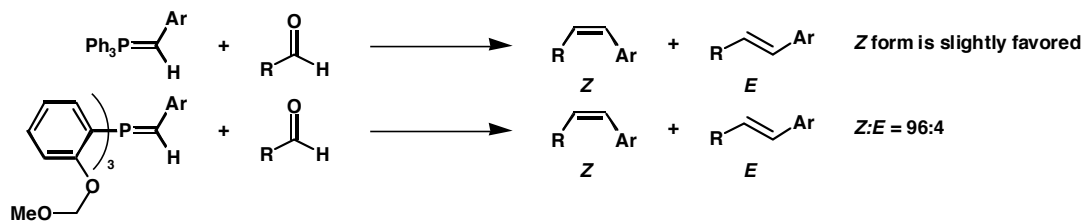
Freeze/filter salts: becomes difficult preparatively.



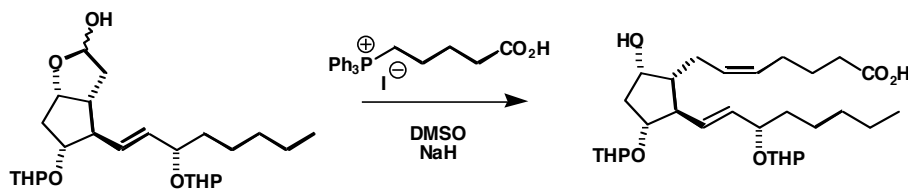
-Examples: (Stork TL 1989, 30, 2173)



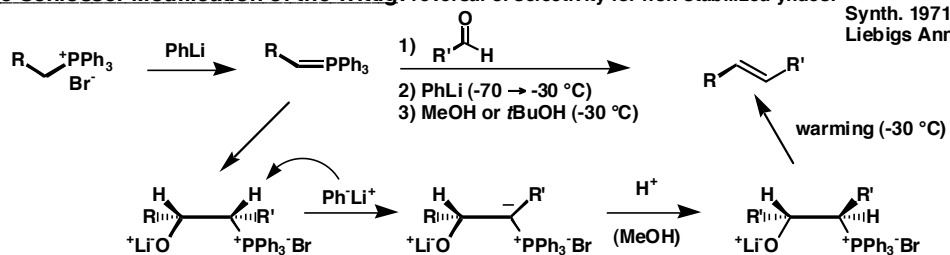
-Phosphine effect: Synlett 1990, 605



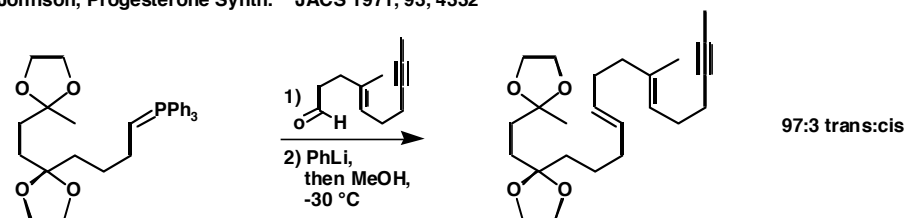
-The Reaction of Lactols: (Corey, JACS 1969, 91, 5675)



The Schlosser Modification of the Wittig: reversal of selectivity for non-stabilized ylides. ACIEE 1966, 5, 126  
Synth. 1971, 29  
Liebigs Ann. 1967, 708, 35

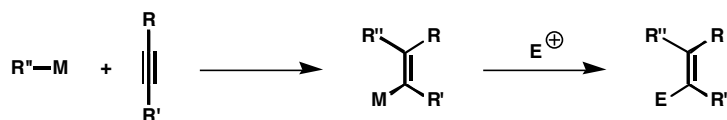


W. S. Johnson, Progesterone Synth. JACS 1971, 93, 4332

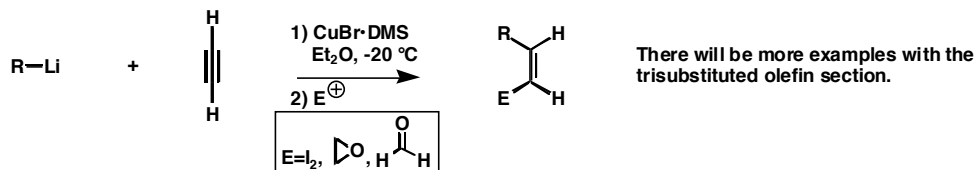


More Z-olefin formation:

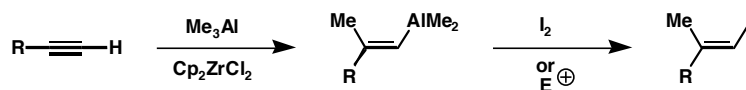
-Carbometallation:



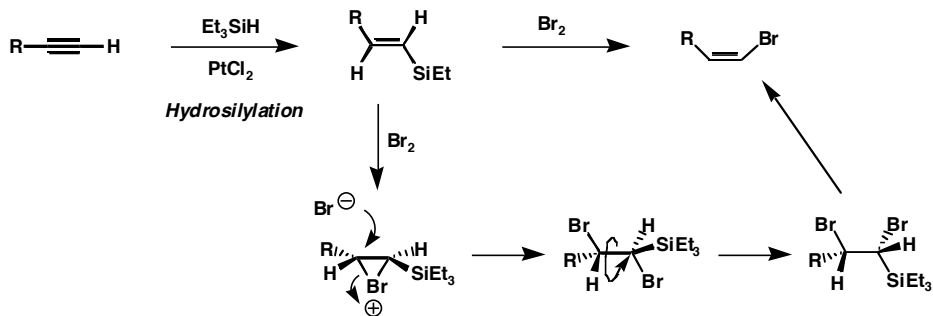
-Copper/Magnesium:



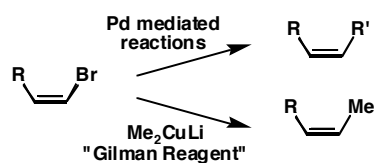
-Zirconium/Aluminum:



**-Hydrometalation/Halogenation:**

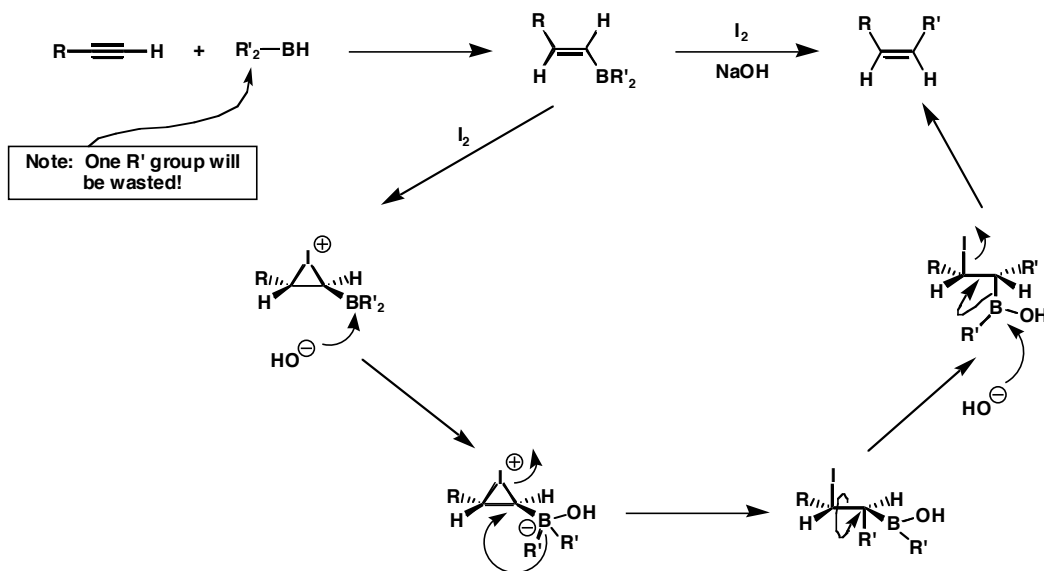


Further reaction of the vinyl bromide:



Note: treatment with I<sub>2</sub> gives R-CH=CH-I.

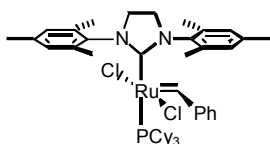
**-Hydroboration/Alkyl transfer:**



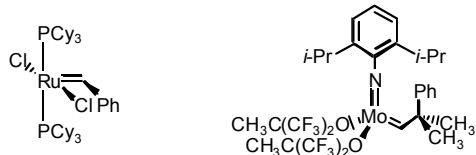
• **E-olefins:** 1,2-disubstituted olefins continued

From Olefins: Olefin Metathesis

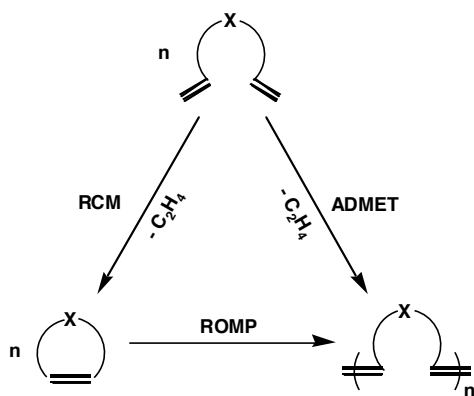
Grubbs Acc. Chem. Res. 2000, 34, 18



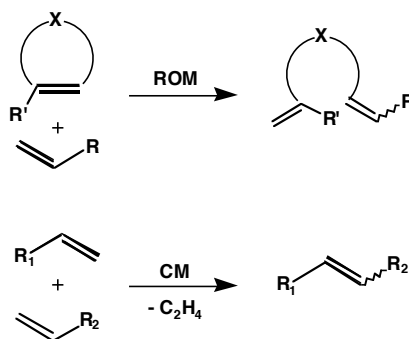
Schrock JACS 990, 112, 3875



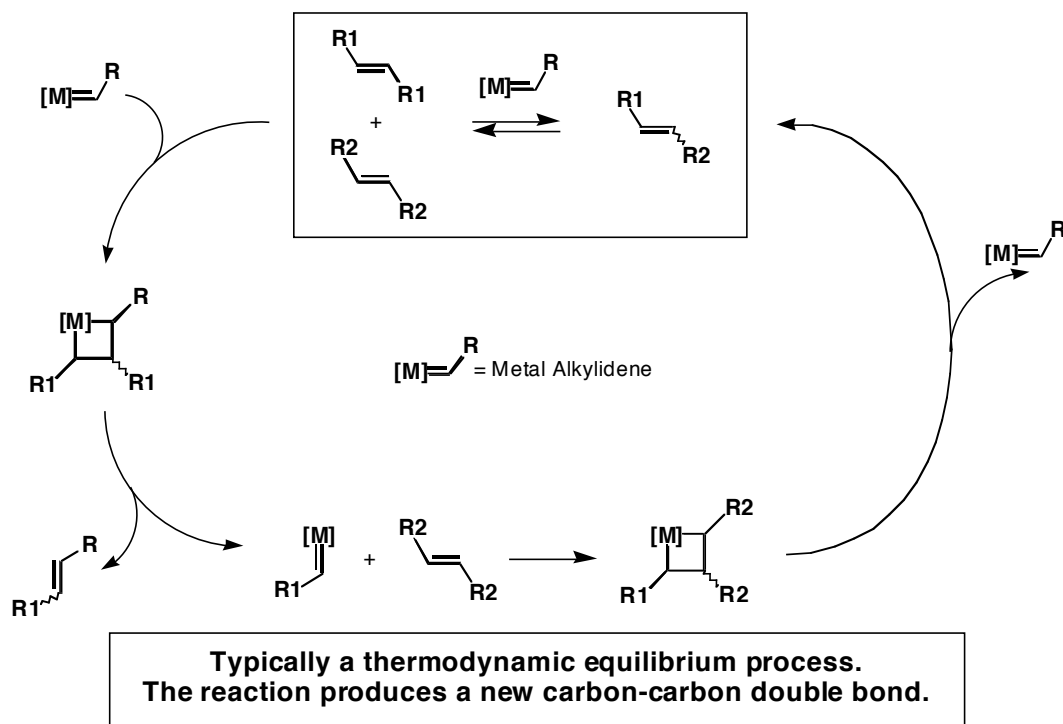
**Diene Metathesis Reactions**



**Terminal Olefin Intermolecular Reactions**

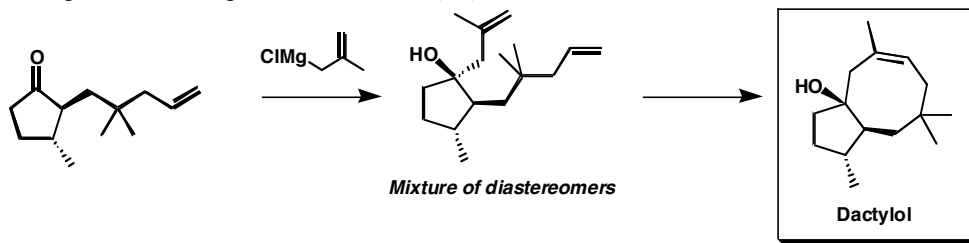


-**Mechanism of Olefin Metathesis:**

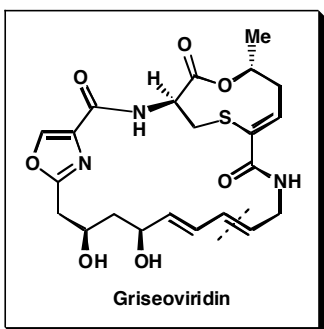


**Examples:**

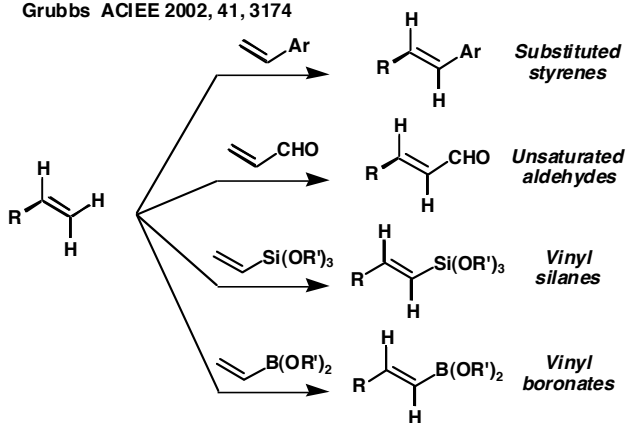
Ring closing for medium rings: Furstner JOC 1996, 61, 8746



Macrocyclic formation:  
Meyers ACIEE 2000, 9, 1664



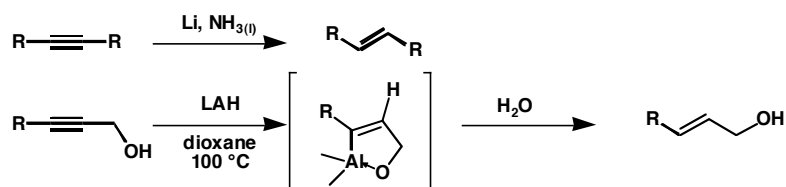
Cross Metathesis:  
Grubbs ACIEE 2002, 41, 3174



*Olefin Categorizing for Selective Cross Metathesis*

Olefin type	1	2	3
<b>Type 1</b> (fast homodimerization)	Terminal olefins, 1° allylic alcohols, esters Allylboronate esters, Allylic halides Styrenes (no large ortho substit.) Allyl phosphonates, phosphine oxides, sulfides, protected amines	Terminal olefin Allylsilanes 1° allylic alcohols, ethers, esters Allylboronate esters Allylhalides	Terminal olefins Allylsilanes
<b>Type 2</b> (slow homodimerization)	Styrenes (large ortho substit.) Acrylate esters, amides, acids, aldehydes, and vinylketones 2° allylic alcohols Unprotected 3° allylic alcohols Vinyl epoxides Perfluorinated alkane olefins	Styrene 2° allylic alcohols Vinyl dioxolanes Vinyl boronates	Styrene Allylstannanes
<b>Type 3</b> (no homodimerization)	1,1-Disubstituted olefins Vinylphosphonates Phenyl Vinyl Sulfone 4° allylic carbons (all alkyl substituents) 3° allylic alcohols (protected)	Vinylsiloxanes	Tertiary allylamines Acrylonitrile
<b>Type 4</b> (spectators to CM)	Vinyl nitro olefins Trisubstituted allylic alcohols (protected)	1,1-disubstituted olefins Disubstit. α,β-unsaturated carbonyls 4° allylic carbon containing olefins Perfluorinated alkane olefins 3° allylamines (protected)	1,1-disubstituted olefins

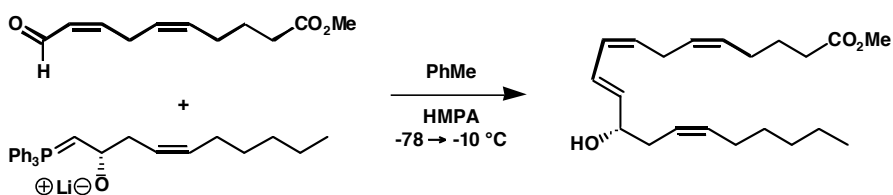
**From Acetylenes:**



**From Aldehydes:**

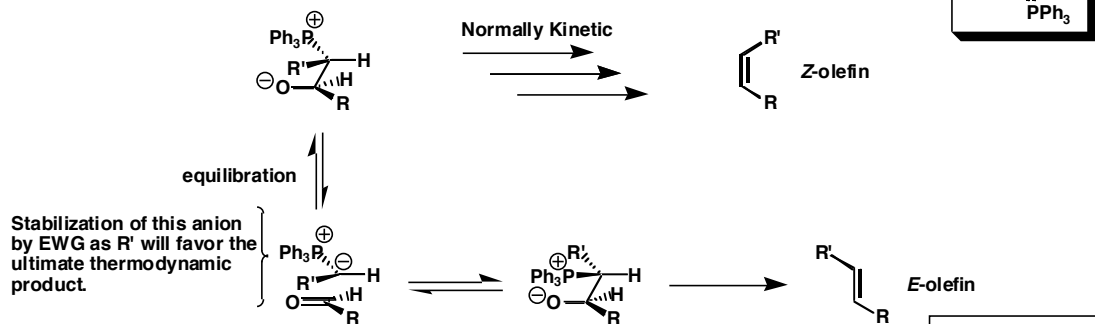
**Wittig Reaction: Modifications to give *E*-selectivity**  
 -Internal basic group promotes *E*-selectivity

JACS 1978, 100, 1942  
 Corey Ch. 11 - Prostanoids  
 Ch. 12 - Leukotrienes & Eicosanoids  
 Nicolaou ACIEE 1991, 30, 1100

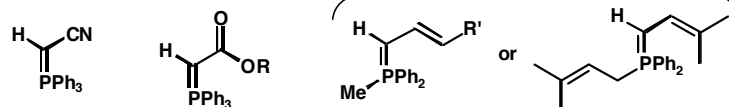


**-Electron Withdrawing Group (EWG) on Wittig Reagent:**

Consider the mechanism:

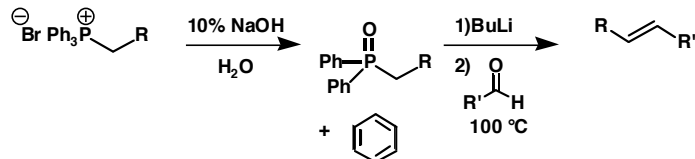


Examples:



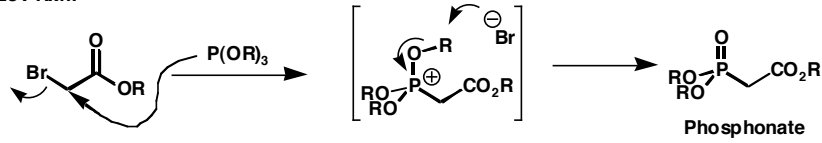
Vedejs  
 JOC 1984, 49, 210  
 Synth. 1988, 911  
 Corey and Lazerwith  
 JACS 1998, 12777

also: Phosphine oxides: S. Warren JCSPT1 1985, 2307 (Horner)

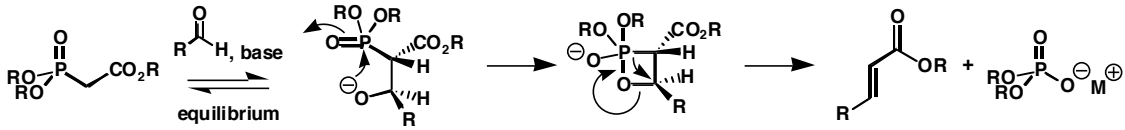


**-Horner-Emmons-Wadsworth Modification**

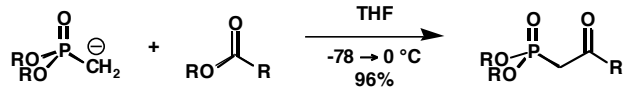
Arbuzov Rxn:



HEW Rxn:

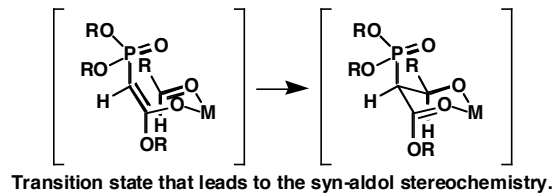
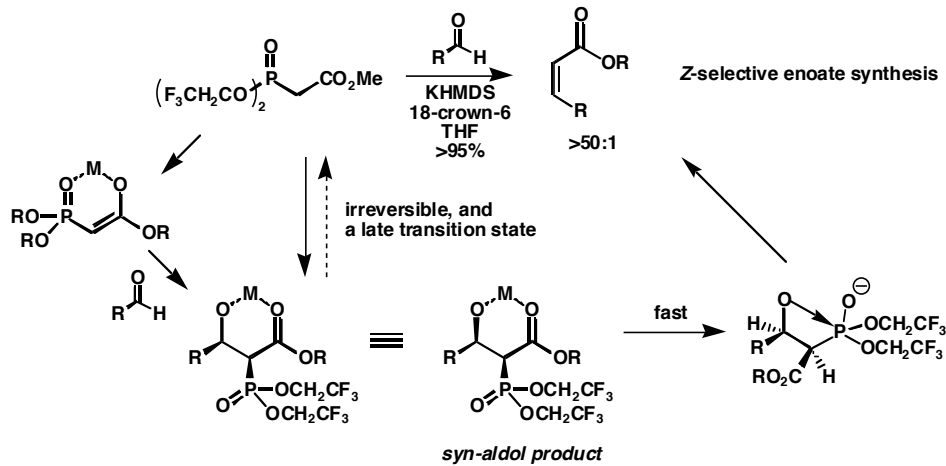


Also:



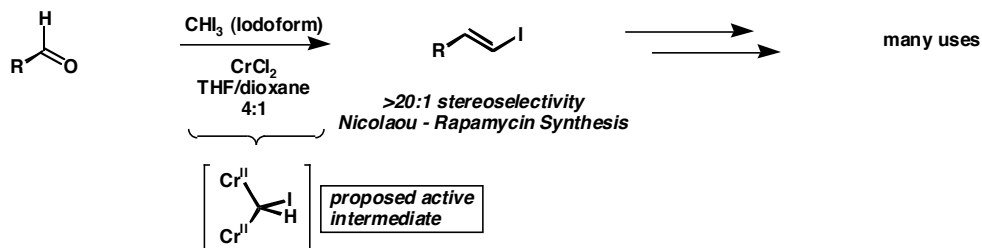
see Nicolaou amphotericin synthesis in [Classics of Total Synthesis](#) (many other examples).

**-Still Modification of the HEW reaction: TL 1983, 24, 4405**

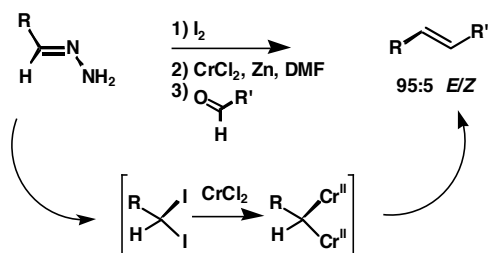




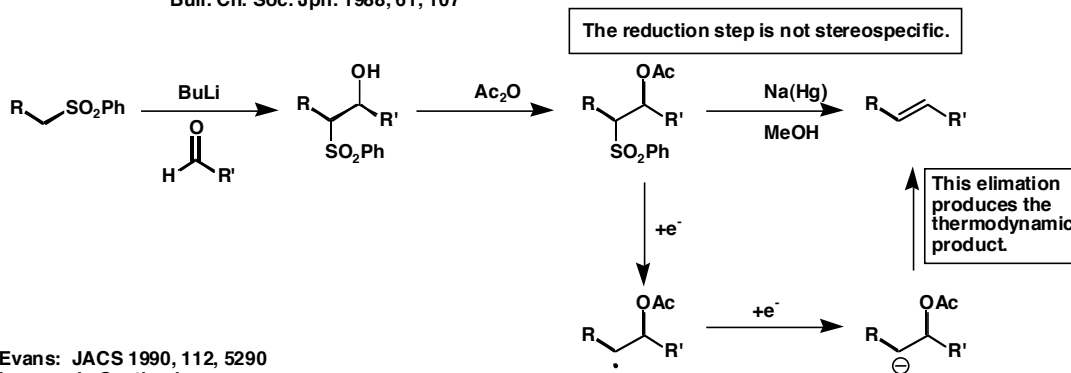
-Takai Reaction: JACS 1986, 108, 6048  
JACS 1987, 109, 951



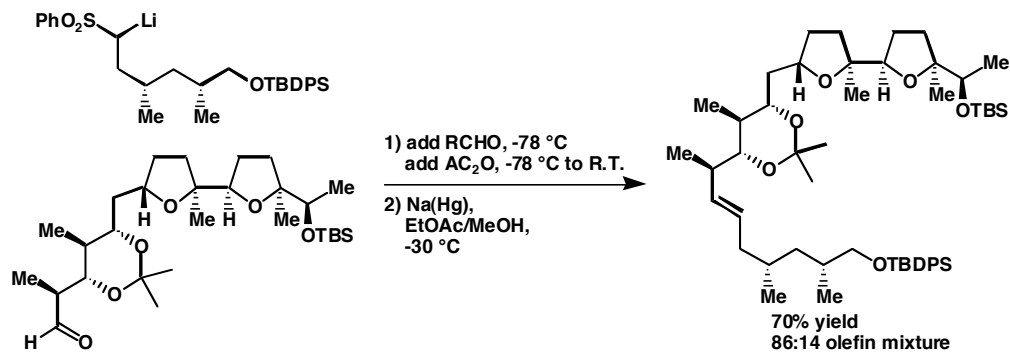
Also:



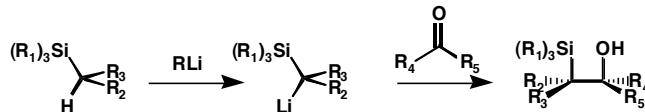
-Julia Olefination: Phosphorus & Sulfur 1985, 24, 97  
JCSPK1 1978, 834  
Bull. Ch. Soc. Jpn. 1988, 61, 107



Evans: JACS 1990, 112, 5290  
Ionomycin Synthesis



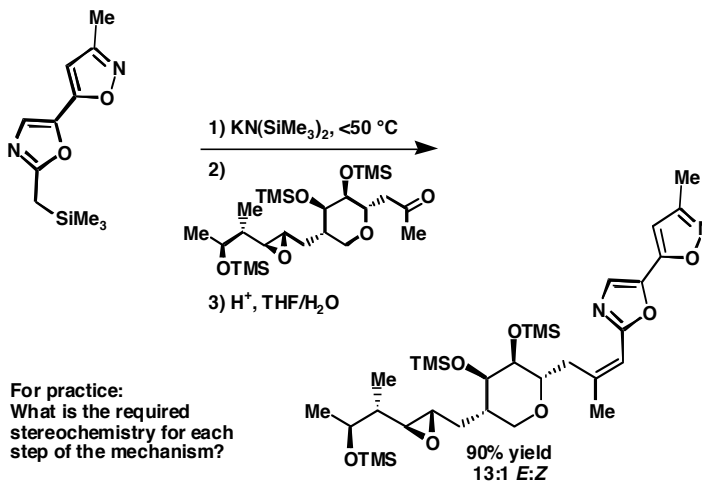
**-Peterson Olefination:**



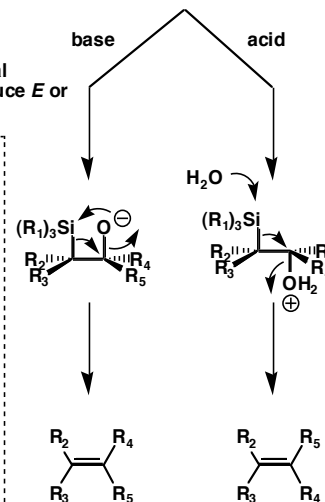
Peterson: JOC 1968, 33, 780  
Ager: Synth 1984, 384

Conditions control the stereospecificity of the elimination reaction, but the initial stereochemistry of the addition to the carbonyl must also be controlled to produce *E* or *Z* olefins specifically.

Tetrahedron 1994, 50, 6643



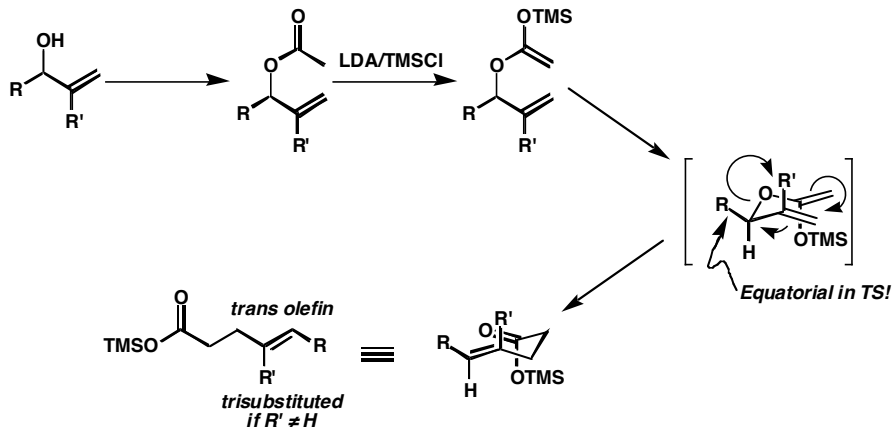
For practice:  
What is the required stereochemistry for each step of the mechanism?



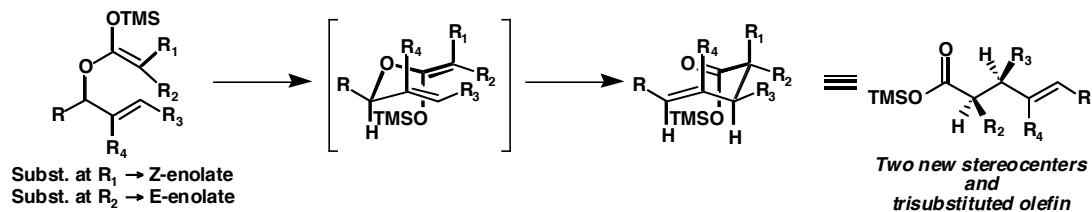
**Claisen Rearrangement:** (more at the end)

Ireland-Claisen: very powerful reaction

Recall: Enolate geometry arguments  
•Esters + LDA → *E*-enolates  
•Esters + LDA + (HMPA or DMPU) → *Z*-enolates



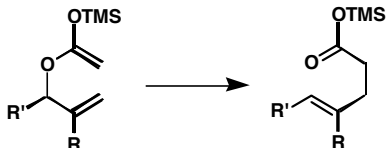
Of Note:



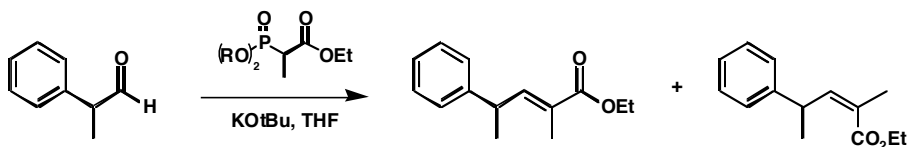
## Trisubstituted Olefins



- I | 2,3 and 3,3 rearrangements (eg Wittig, Claisen, Cope, etc.)  
In fact 3,3 rearrangements are among the best methods.



- II | Wittig Rxns: Typically not very selective (if R' and R'' are different).  
some examples with stabilized reagents: Kishi  
TL 1981, 37, 3873  
JACS 1979, 101, 259



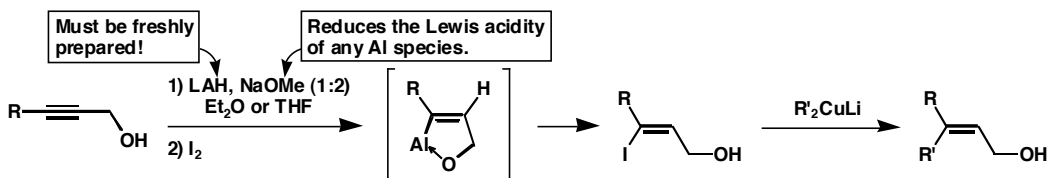
R=	Me	95 : 5
	<i>i</i> Pr	5 : 95
	CH <sub>2</sub> CF <sub>3</sub>	1 : 50

- III | From acetylenes by metalation reactions

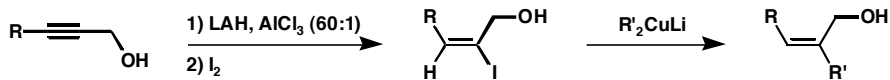
## Acetylenes/Propargylic alcohols

-With aluminum reagents:

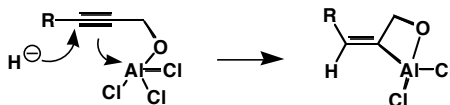
Corey:  
JACS 1967, 89, 4245  
JACS 1970, 92, 6314  
JACS 1968, 90, 5618



-if there is a small amount of Lewis acid present:

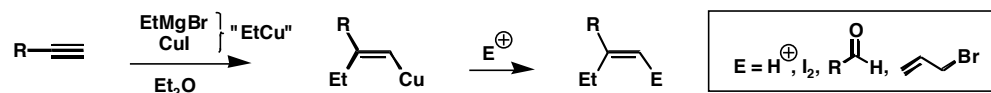


Maybe ???

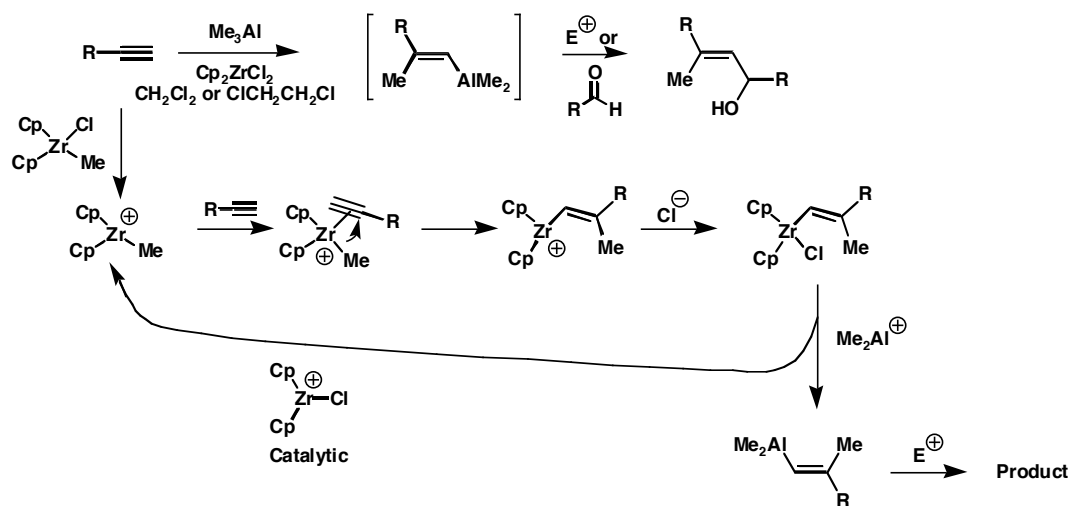


-With organocopper reagents:

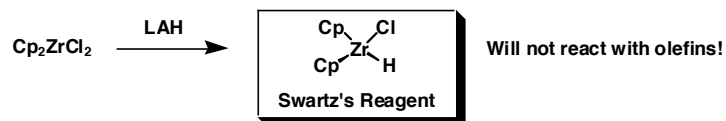
terminal acetylenes: Org. Synth. VII 236-240



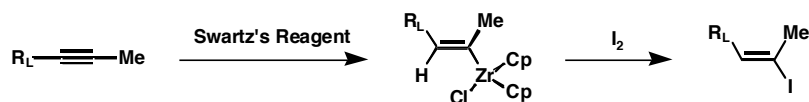
Negishi Protocol: JOC 1980, 45, 2526  
JACS 1981, 103, 1276  
JACS 1981, 103, 4985



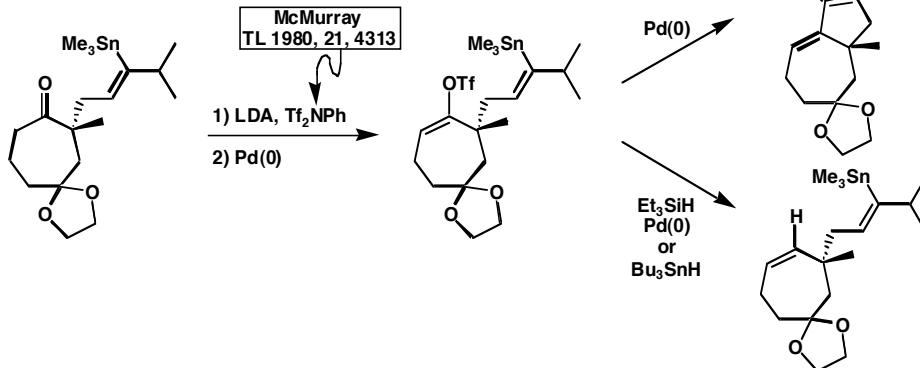
-Schwartz Hydrozirconation Reaction: TL 1987, 28, 3895  
Jeffrey Swartz (Princeton) TL 1990, 31, 7257



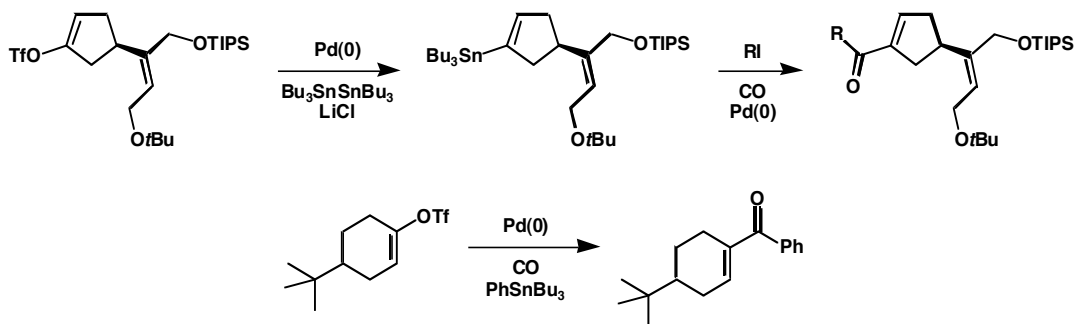
(Hydroboration is not as selective between olefins and alkynes.)



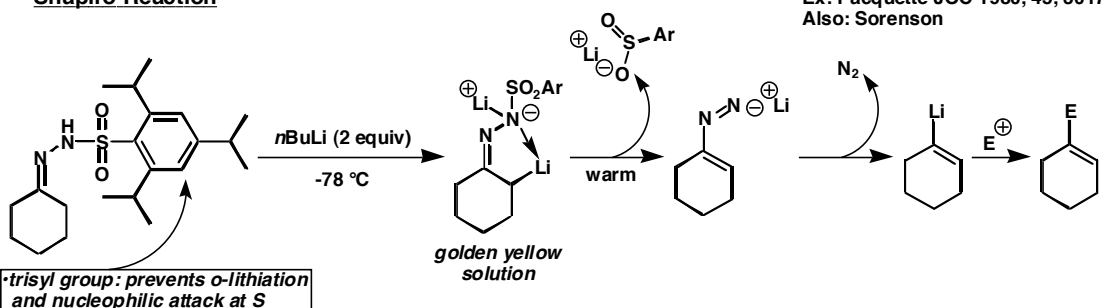
**Enol Triflates:** JOC 1986, 3405



Also: JACS 1993, 115, 9293

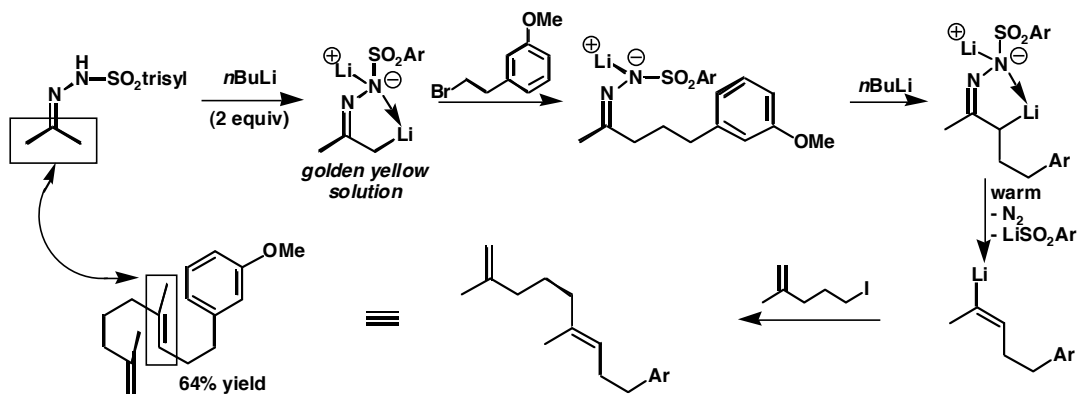


**Shapiro Reaction**



-Also acyclic examples:

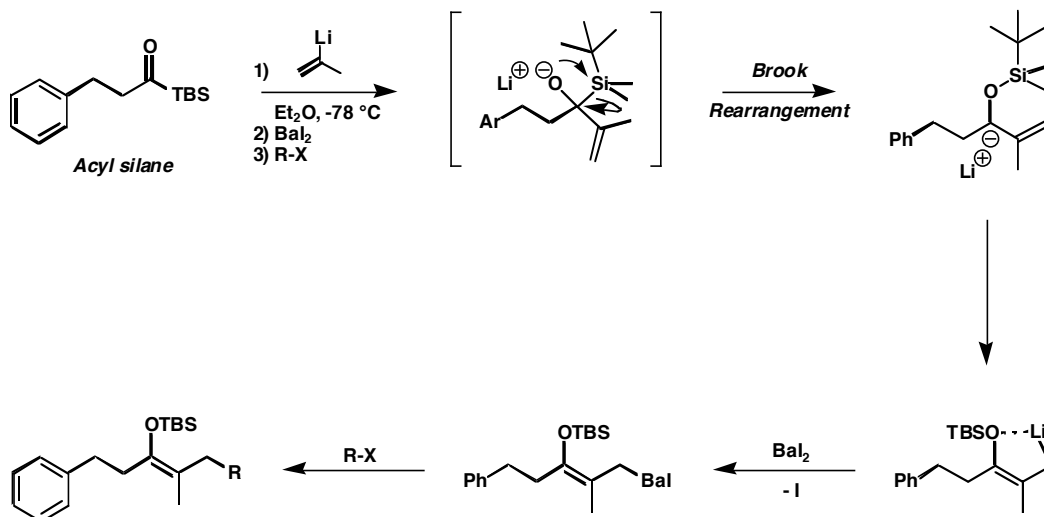
TL 1997, 38, 8915 } Corey and Roberts  
TL 1997, 38, 8919 }



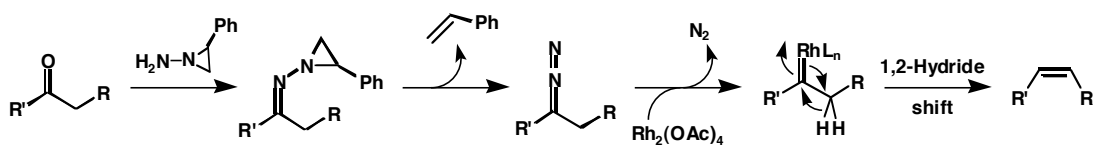
## Tetrasubstituted Olefins

-Z-enol Silyl Ethers:

Corey  $\left\{ \begin{array}{l} \text{TL 1997, 38, 5771} \\ \text{JACS 1996, 118, 8765} \end{array} \right.$



## Applications of Olefin Synthesis: The Bamford-Stevens Reaction

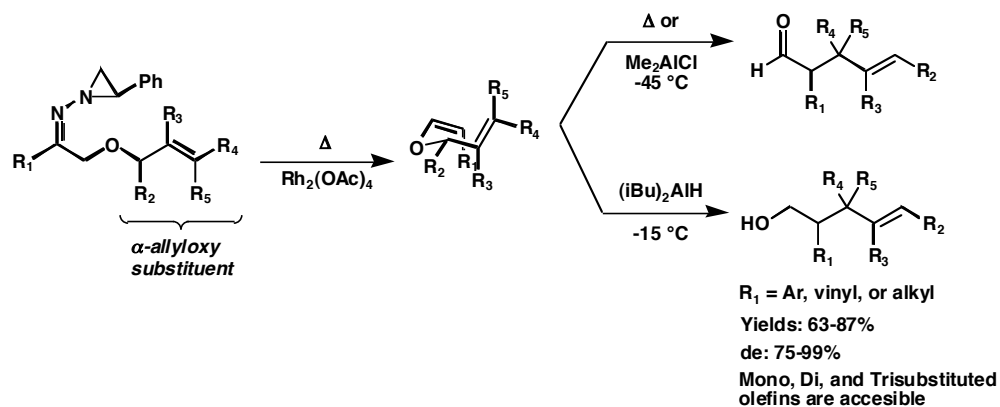


Results in the lab: Can this reaction be made more powerful?

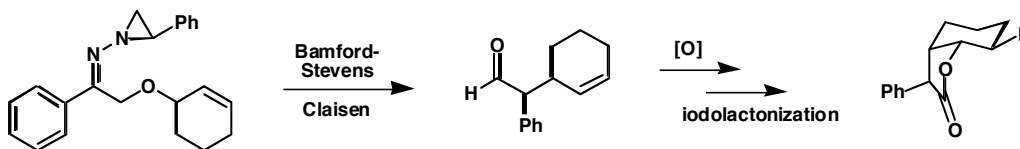
entry	Substrate	Product	Yield	Z:E
1			70	1:0
2			81	1:0
3			63	1:0
4			69	1:0

JACS 2002, 124, 12426

**Coupling of the Bamford-Stevens reaction to a Claisen Reaction**

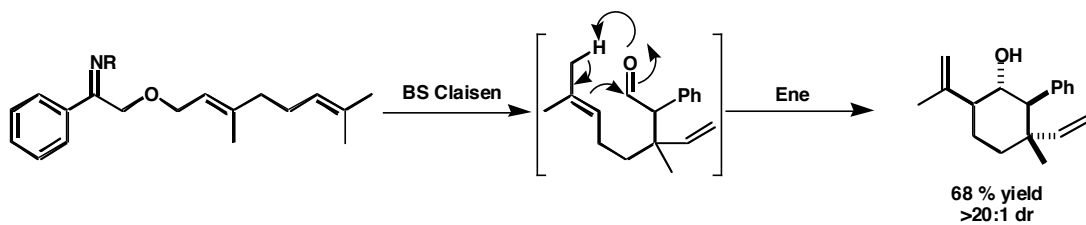


As seen previously, aldehydes offer access to many transformations:



**Coupling of the Bamford-Stevens Claisen to the Cope and Ene Reactions:**

**Bamford-Stevens/Claisen/Ene**



**Bamford-Stevens/Claisen/Cope**

