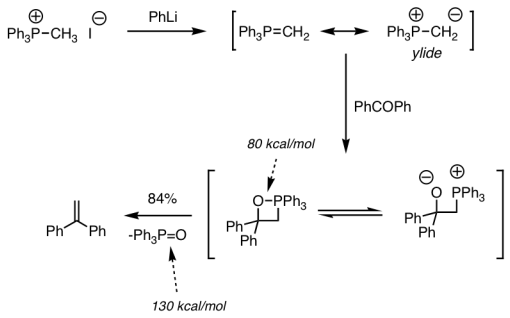
I. Basic Principles

I-I. Wittig Reaction

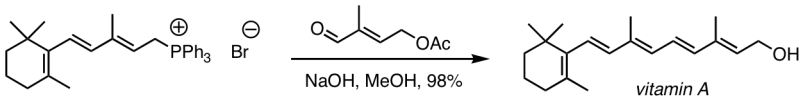
1. The Wittig Reaction

Reviews:
- Nicolaou, K. C.; Härter, M. W.; Gunzner, J. L.; Nadin, A. *Liebigs Ann./Recueil* **1997**, 1283.
- Vedejs, E.; Peterson, M. J. *Top. Stereochem.* **1994**, *21*, 1-157.
- Bestmann, H. J.; Zimmerman, R. In *Comprehensive Organic Synthesis*; B. M. Trost and I. Fleming, Ed.; Pergamon Press: Oxford, 1991; Vol. 6; pp 171.
- Schlosser, *Top. Stereochem.* **1970**, *5*, 1.

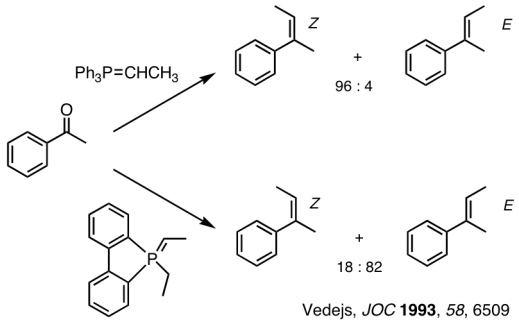
First report: 1953, Wittig and Geissler, *Liebigs Ann.* **1953**, *580*, 44.



Industrial preparation of Vitamin A (BASF, 1956)



Reagent control of *Z*/*E*-selectivity:



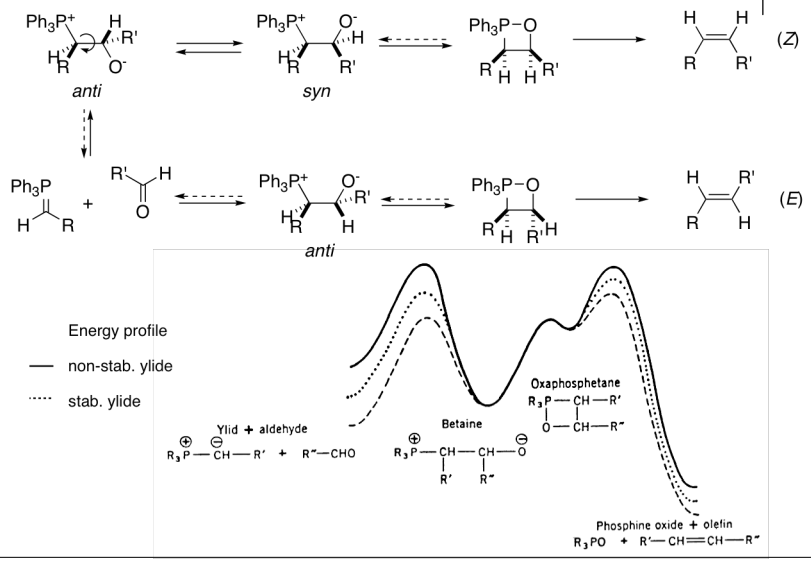
Vedejs, *JOC* **1993**, *58*, 6509

Over much of its history, the Wittig reaction has been described as a stepwise ionic process. The hypothetical betaine intermediates were never observed, but lithium halide adducts could be isolated in some of the early Wittig experiments. The newest hypothesis attributes stereoselectivity to a combination of steric effects and varying degrees of rehybridization at phosphorous in the formation of the covalent oxaphosphetane.

Wittig Mechanisms

Ref.: Vedejs, E.; Peterson, M. J. *Top. Stereochem.* **1994**, *21*, 1-157.

A. Stepwise, ionic process (betaine mechanism):



Evidence *against* this mechanism started to accumulate in the late 1960's. First, the solvent dependence of the Wittig reaction did not concur with a charged intermediate, the betaine. Also, it was found that the oxaphosphetane was actually more stable than the putative betaine. Experimental and theoretical insights can be summarized as follows:

1. Under salt-free, aprotic conditions, ylides Ph_3P=CHR (R=alkyl, alkenyl, phenyl) react with aldehydes to produce the oxaphosphetane directly via four-centered transition states.

2. The Z:E ratio of alkenes corresponds to the cis-trans ratio of oxaphosphetanes in typical reactions (kinetic control). This is true of nonstabilized ylides as well as carbonyl-stabilized ylides, although there are exceptions.

3. The oxaphosphetane decomposes by a syn-cycloreversion process to the alkene.

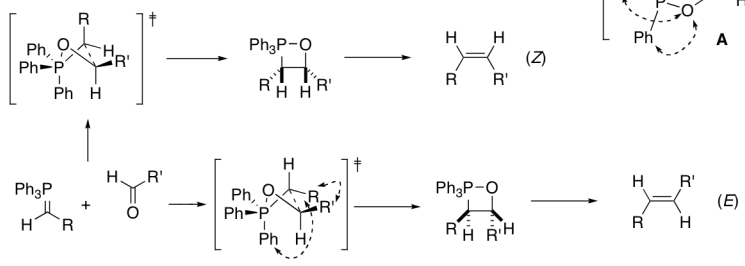
4. There are no zwitterionic or diradical intermediates having significant lifetimes.

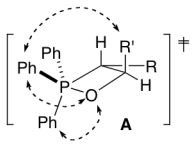
5. Betaines are energetically uphill compared to reactants as well as to oxaphosphetanes.

Accordingly, since the stereochemistry of the alkene product appears to be established in the TS leading to the oxaphosphetane, we need a new mechanism to explain the observed Z:E ratios that depend on the level of stabilization (charge delocalization) of the ylide. The Wittig reaction must involve a mechanism other than the betaine pathway. A synchronous cycloaddition process is consistent with the available evidence (Vedejs, *J. Am. Chem. Soc.* **1990**, *112*, 3905).

Ref.: Vedejs, E.; Peterson, M. J. *Top. Stereochem.* **1994**, *21*, 1-157.

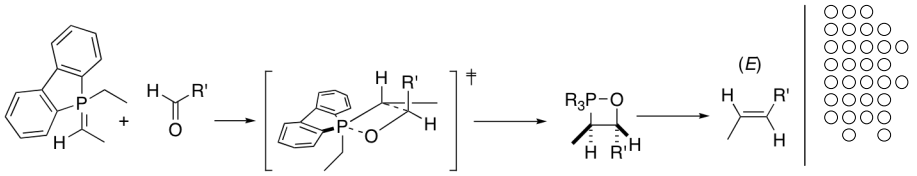
B. Four-center transition state analysis according to Vedejs:



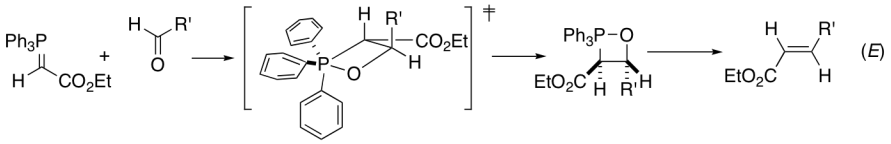


Planar transition states **A**, resembling oxaphosphetanes, are destabilized by the gauche interaction between the developing P-O bond with two phosphorus ligands and by a 1,3-interaction between the aldehyde substituent and the nearby phosphorus ligand. The 1,3-interactions can be reduced by puckering the four-membered ring. Here the cis- is favored over the trans-TS because of smaller 1,2-interactions between the ylide R substituent with R' (gauche interactions) and the eclipsing strain between R and the adjacent phosphorus Ph substituent.

If the phosphine rings are constrained as in the non-stabilized ylide shown below, the role of 1,3-interactions is reduced especially since the third phosphorus ligand (ethyl) is compact. There is little steric advantage for a puckered geometry, even though the TS is relatively early, and the TS geometry resembles a planar oxaphosphetane. The trans-selective pathway is favored because 1,2-interactions are now dominant.

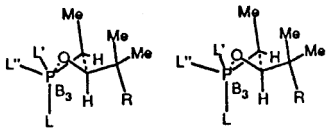


In the stabilized ylide case, increased P-O bonding in the (later) TS favors a more nearly planar four-center transition state geometry. Since phosphorus is closer to a trigonal bipyramidal geometry, the 1,3-interactions are relieved and 1,2-interactions control selectivity. The normal thermodynamic advantage for the trans-disubstituted oxaphosphetane is felt in the product-like TS, and the (E)-alkene is the major product. Because the TS is relatively rigid, the result is not much affected by changes in the phosphorus ligands, in contrast to the nonstabilized ylide reactions.

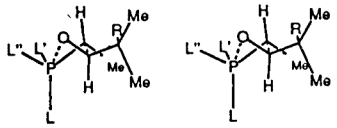


Stereo plot files (Vedejs, E., *J. Am. Chem. Soc.* **1988**, *110*, 3948, use stereo viewer):

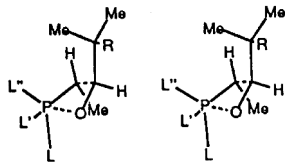
a) The cis-selective TS has a puckered ring and the aldehyde substituent in a pseudoequatorial orientation as far as possible from the phosphorus ligands.



b) The trans-selective variation is less stable because α-CH3 and tertiary alkyl are nearly in the same pseudoequatorial plane. If the transition state were late, this interaction would be reduced because of the phosphorous hybridization changes. This is why the final product is always more stable as the trans-disubstituted oxaphosphetane.



c) The trans-selective planar transition state reduces the gauche interaction but involves increased interactions with L", the nearby phenyl substituent at the partially rehybridized phosphorus. Again, in a later transition state when phosphorus rehybridization from sp^3 to dsp^3 (trigonal bipyramidal) has proceeded, these interactions will be reduced.

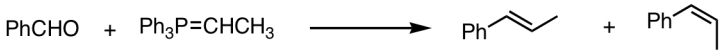


The variation in Wittig reaction stereochemistry is attributed to dominant kinetic control in nearly all cases. Formation of cis or trans oxaphosphetanes is the decisive step, and this occurs by an asynchronous cycloaddition. An interplay of 1,2- and 1,3-steric interactions decides which diastereomeric oxaphosphetane will be favored. It is important to recall, however, that oxaphosphetanes are rapidly cleaved by lithium halides to give betaine adducts.

For theoretical calculations that are in basic agreement with this analysis, see: Yamataka, H.; Nagase, S. *J. Am. Chem. Soc.* **1998**, *120*, 7530.

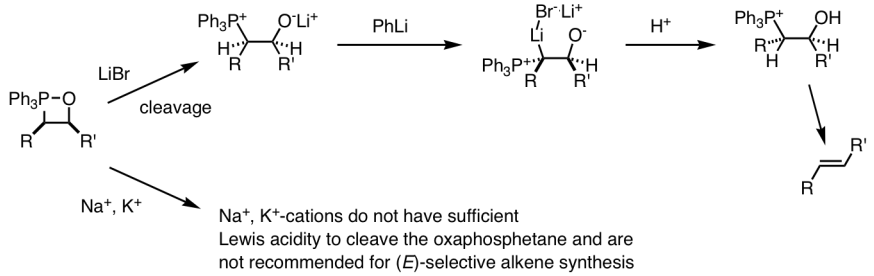
Schlosser Modification

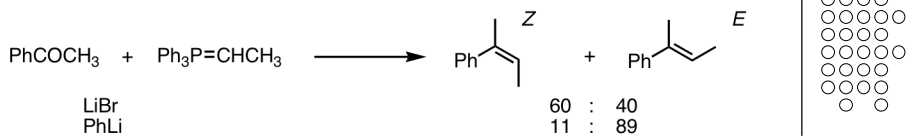
Li^+ catalyzes oxaphosphetane opening (stabilizes betaine)
→ excess salt promotes equilibration and formation of the (*E*)-alkene.



salt free	10 :	90
LiI	42 :	58

To avoid decrease in the (*Z*)-selectivity, standard Wittig reactions should be conducted with as low salt concentration as possible.
Subsequent addition of PhLi - Schlosser modification:

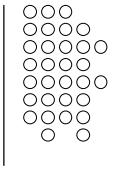




Wittig Chain Extension

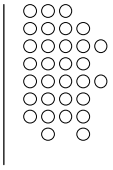
Danishefsky, S. J. et al. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2801. Synthesis of epothilone A.

(Z)-Selective Wittig Reactions



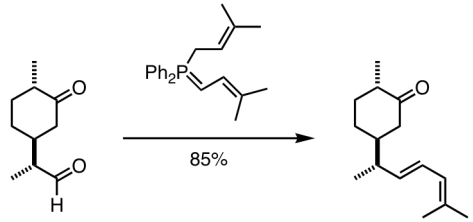
Corey, E. J.; Weinshenker, N. M.; Schaaf, T. K.; Huber, W. *J. Am. Chem. Soc.* **1969**, *91*, 5675.

Martin, T.; Soler, M. A.; Betancort, J. M.; Martin, V. S. *J. Org. Chem.* **1997**, 62, 1570.



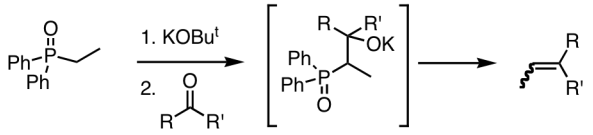
(*E*)-Selective Wittig-Vedejs Olefination

Corey, E. J.; Lazerwith, S. E., "A direct and efficient stereocontrolled synthetic route to the pseudopterosins, potent marine antiinflammatory agents." *J. Am. Chem. Soc.* **1998**, *120*, 12777.

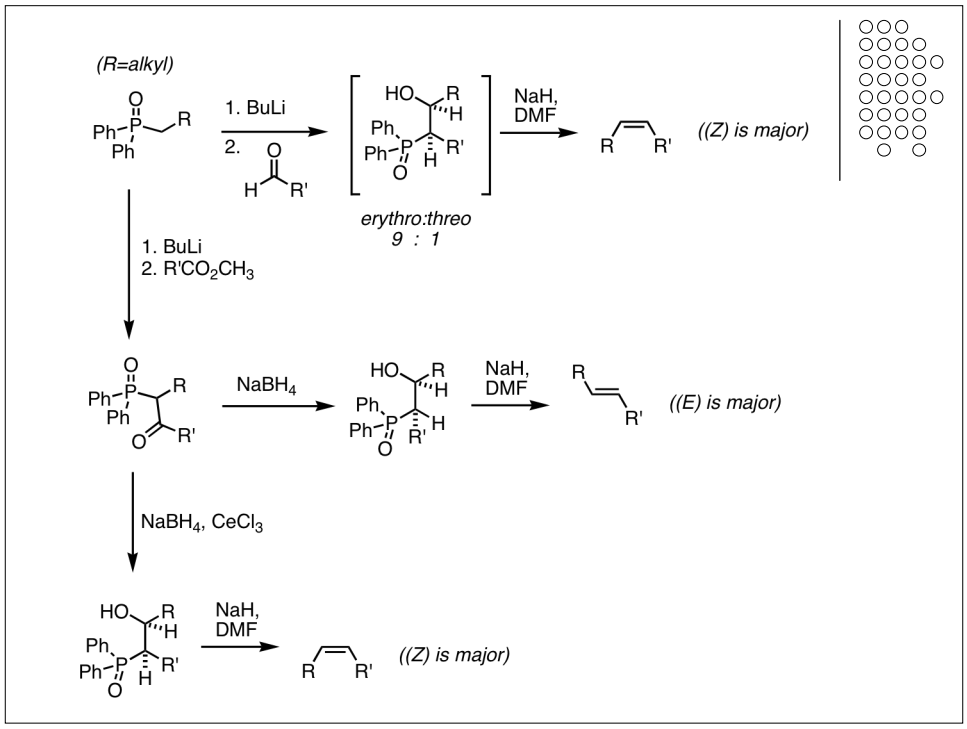


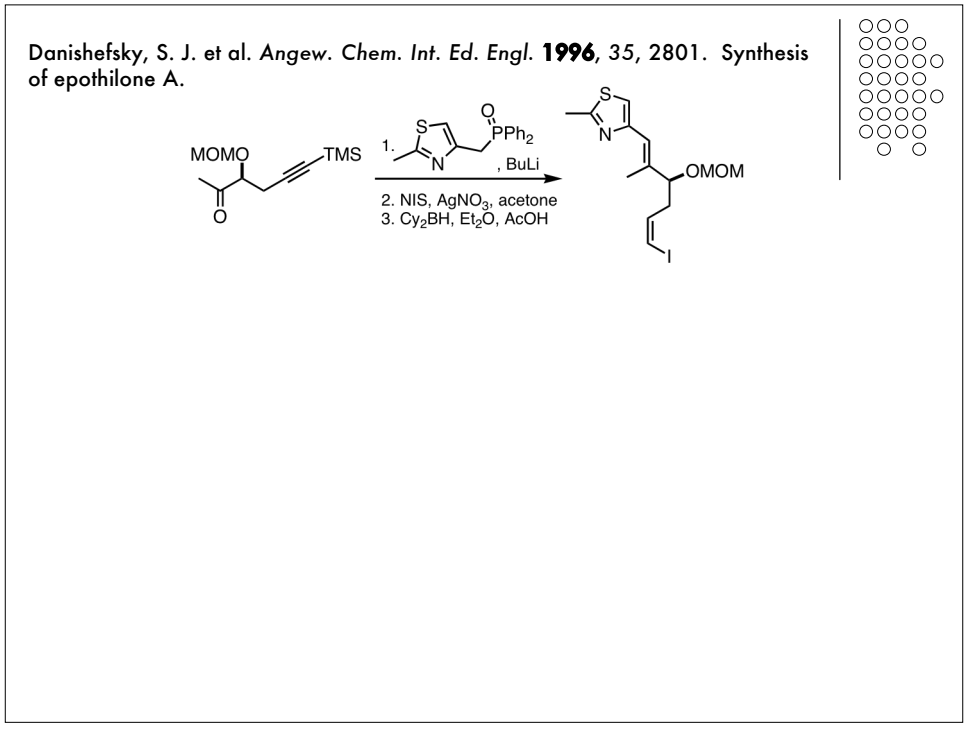
Horner Wittig Olefination

In 1958, Horner and co-workers described the use of phosphine oxides in Wittig-type reactions. This modification allows for the removal of phosphorous as a water-soluble side product. If a potassium base was used to generate the phosphine oxide anion, the reaction with a carbonyl compound proceeded as in the Wittig reaction to give an alkene:



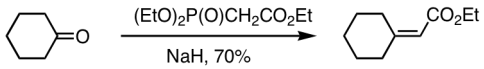
If a lithium base was used, the intermediate β-hydroxyphosphine oxide could be isolated and transformed into the alkene in a subsequent step.


(R=alkyl)
1. BuLi
2.
NaH, DMF
((Z) is major)
erythro:threo
9 : 1
1. BuLi
2. R'CO2CH3
NaBH4
NaH, DMF
((E) is major)
NaBH4, CeCl3
NaH, DMF
((Z) is major)


Danishefsky, S. J. et al. Angew. Chem. Int. Ed. Engl. 1996, 35, 2801. Synthesis of epothilone A.
MOMO
TMS
1.
, BuLi
2. NIS, AgNO3, acetone
3. Cy2BH, Et2O, AcOH
OMOM

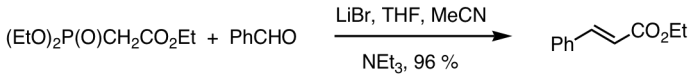
Horner-Wadsworth-Emmons

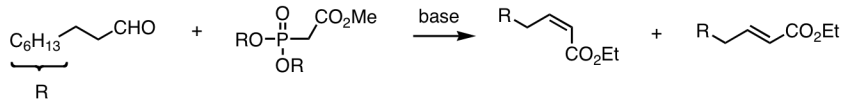
In 1961, Wadsworth and Emmons described the increased reactivity of phosphonate-stabilized carbanions with a-electron-withdrawing substituents.



$(EtO)_2P(O)CH_2R$, R = Ph or R = CO_2Et; with R = alkyl: slow reaction! (The reaction stops at betaine, and no alkene is produced).

Preparation: Arbuzov rearrangement: $(EtO)_3P$ + $BrCH_2CO_2Et$
Advantage: Byproduct phosphate is water-soluble.



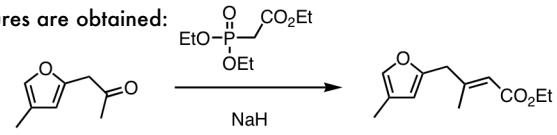


$KOBu^t$/THF	R = Me	2 : 5
$KN(TMS)_2$/THF/18-C-6	R = Me	8 : 1
$PhCH_2N^+Me_3$ HO^-/THF	R = CH_2CF_3	7 : 1
K_2CO_3/18-C-6/toluene	R = CH_2CF_3	6 : 1
$KN(TMS)_2$/THF/18-C-6	R = CH_2CF_3	12 : 1

Still-Wittig conditions THL **1983**, *24*, 4405

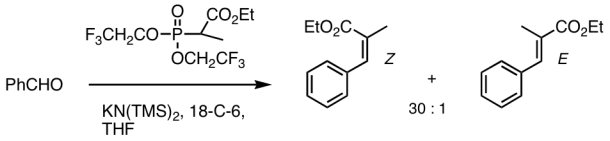
The electron-withdrawing effect of the OCH_2CF_3 substituents decreases the lifetime of the oxaphosphetane sufficiently to restrict any thermodynamic equilibration to the *trans* compound.

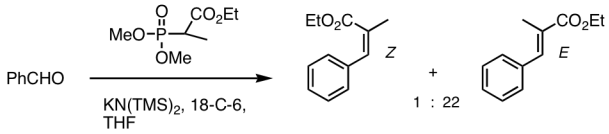
For trisubstituted alkenes, often mixtures are obtained:



(*E*) : (*Z*) = 3 : 1

But:

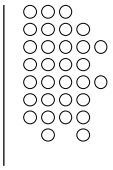




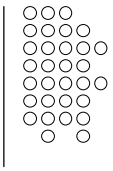
Corey, E. J.; Weinshenker, N. M.; Schaaf, T. K.; Huber, W. *J. Am. Chem. Soc.* **1969**, *91*, 5675.

Ali, S. M.; Georg, G. I. *Tetrahedron Lett.* **1997**, *38*, 1703.

Wipf, P.; Kim, H. Y. *J. Org. Chem.* **1993**, *58*, 5592. Isolation of the acid (rather than the usual ester) avoids deprotection and double bond isomerization during saponification.



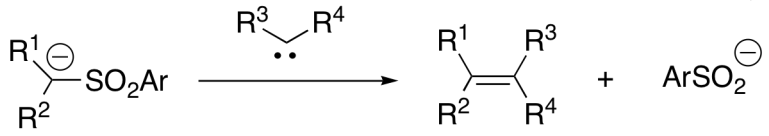
Sowinski, J. A.; Toogood, P. L. *Tetrahedron Lett.* **1995**, *36*, 67.



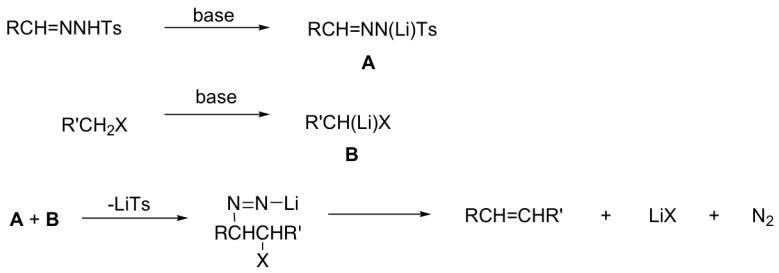
Intramolecular Horner-Emmons Cyclization

Williams, D. R.; Werner, K. M.; Feng, B. *Tetrahedron Lett.* **1997**, *38*, 6825.
Rhizoxin synthesis.

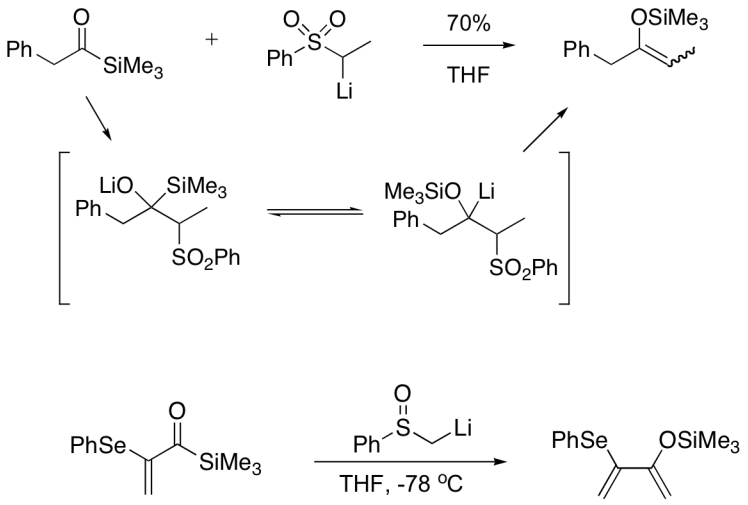
2. Olefin Synthesis from Sulfones and Carbenoids (Julia)



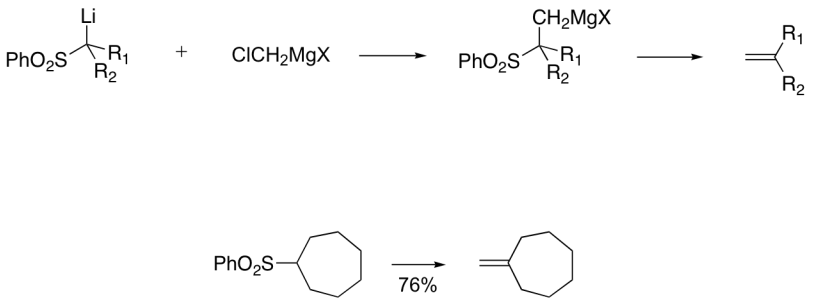
Vedejs, E.; Dolphin, J. M.; Stolle, W. T., "A new olefin synthesis: Condensation of aldehyde tosylhydrazones with stabilized carbanions." *J. Am. Chem. Soc.* **1979**, *101*, 249-251.



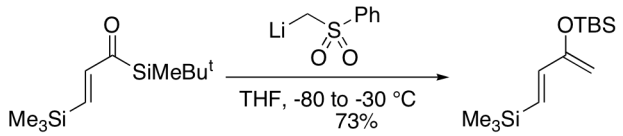
Reich, H. J.; Rusek, J. J.; Olson, R. E., "Silyl ketone chemistry. A new regiospecific route to silyl enol ethers." *J. Am. Chem. Soc.* **1979**, *101*, 2225-2227.



De Lima, C.; Julia, M.; Verpeaux, J. N., "Reaction of α-sulfonyl carbanions with electrophilic monohalocarbenoids: A new Wittig-like formation of alkenes." *Synlett* **1992**, 133-134.



Silylenolether Formation (Reich's Protocol; Takeda, K.; Sakumara, K.; Yoshii, E. *Tetrahedron Lett.* **1997**, *38*, 3257.



3. Olefin Synthesis from Sulfones and Aldehydes (Kociensky-Julia)

Lafontaine, J. A.; Provencal, D. P.; Gardelli, C.; Leahy, J. W. *Tetrahedron Lett.* **1999**, *49*, 4145