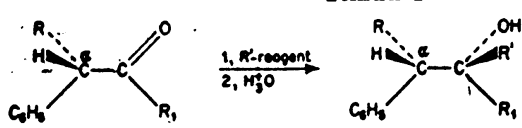


# Organometallics - Carbonyl Additions

It is a capital mistake to theorise before one has data. Insensibly, one begins to twist facts to suit theories, instead of theories to suit facts.

(Sherlock Holmes, A Scandal in Bohemia)



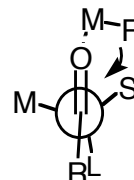
On  $\alpha$ -C,  $C_6H_5 \gg R \gg H$   
in order of decreasing effective bulk

Run no.	R	R <sub>1</sub>	Reagent	Config. product rule predicts <sup>a</sup>	Balance of isomers found	
					erythro	threo
1	CH <sub>3</sub>	H	CH <sub>3</sub> MgI	erythro	2	1
2	CH <sub>3</sub>	CH <sub>3</sub>	LiAlH <sub>4</sub>	threo	1	2.5
3	C <sub>2</sub> H <sub>5</sub>	H	CH <sub>3</sub> MgI	erythro	2.5	1
4	C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub>	LiAlH <sub>4</sub>	threo	1	3
5	CH <sub>3</sub>	H	C <sub>6</sub> H <sub>5</sub> MgBr	erythro	3	1
6	CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>	LiAlH <sub>4</sub>	threo	1	2
7	CH <sub>3</sub>	H	C <sub>6</sub> H <sub>5</sub> MgBr	threo	1	>4
8	CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	LiAlH <sub>4</sub>	erythro	≥4	1
9 <sup>b</sup>	CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	Na·EtOH	erythro	erythro predominates	

## Cram's Rule

- Cram, D. J.; Elhafez, F. A. A. *J. Am. Chem. Soc.* **1952**, *74*, 5828; *J. Am. Chem. Soc.* **1959**, *81*, 2748.

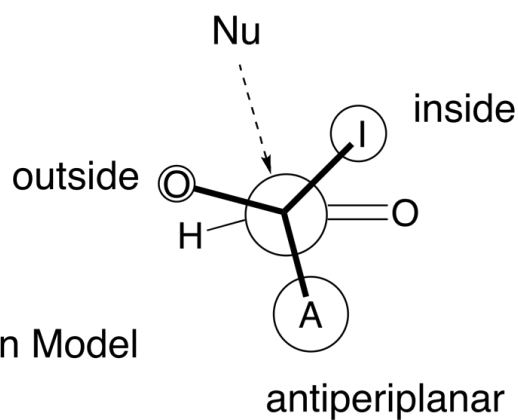
In this model, Cram proposed that complexation of the metal to the carbonyl oxygen rendered it the bulkiest group in the molecule, thus forcing it in between the two least bulky substituents at the  $\alpha$ -carbon. Attack would occur from the side of the smallest substituent.



This model correctly predicted the major diastereomer of most asymmetric additions, with the notable exception of Grignard additions to  $\alpha$ -chloro ketones. **Cornforth** proposed a model where the halogen plays the role of the large substituent, so that the C=O and C-Cl dipoles are opposed.

The predictive value of Cram's rule notwithstanding, the rationale was speculative, and as spectroscopic methods developed, it was called into question.

In 1968, Felkin noted that the Cram as well as the Karabatsos models failed to account for the outcome of nucleophilic additions to cyclohexanones, and do not explain the effect of the R substituent on the selectivity (*Tetrahedron Lett.* **1968**, 2199).



Felkin-Ahn Model

Substituents are usually ordered according to their effective size if steric hindrance is the selectivity-determining factor. For electronic effects, consider:

**Anh-Eisenstein:** The strongest  $e^-$ -withdrawing group favors the anti position,  $\sigma \rightarrow \sigma^*$

**Felkin/Karabatsos/Houk:** Torsional strain

**Klein/Burgess-Liotta:** Orbital distortion

**Cieplak:** The most powerful  $e^-$ -donating group favors the anti position,  $\sigma^* \leftarrow \sigma$

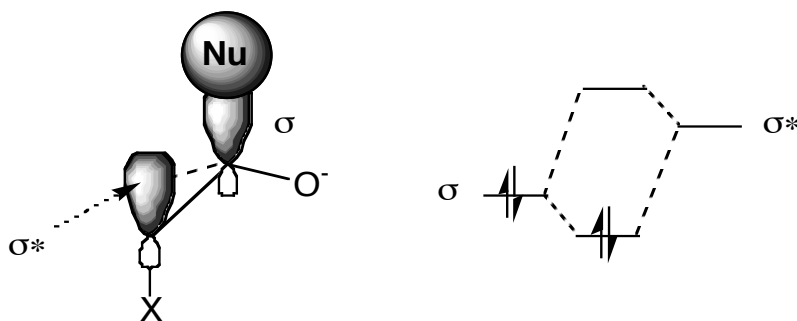
**Paddon-Row/Houk:** Electrostatic effects

**Anh and Eisenstein** also addressed the issue which substituent would assume the role of the large group anti to the incoming nucleophile. A simple rule was offered (*Nouv. J. Chim.* **1977**, *1*, 61): the substituents should be ordered according to the energies of the antibonding  $\sigma^*$  orbitals. The preferred anti substituent will be that one having the lowest lying  $\sigma^*$  orbital. This rule also explains the  $\alpha$ -chloro ketone anomaly, since the  $\sigma^*$  for the carbon-chlorine bond is lower than a carbon-carbon bond.

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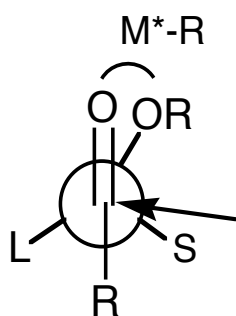
### Anh-Eisenstein (polar Felkin model)

→ attack is anti to a substituent with a low  $\sigma^*$  ( $\sigma \rightarrow \sigma^*$  donation)



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### Cram-Chelate

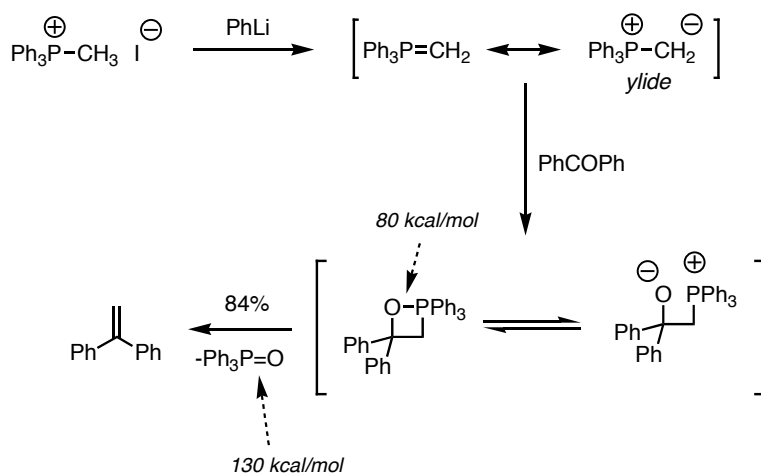


# -Synthetic Applications of alpha-Heteroatom-stabilized carbanions:

## - Alkene Synthesis

### Wittig Reaction(s)

First report: 1953, Wittig and Geissler, *Liebigs Ann.* **1953**, 580, 44.  
(Nobel Prize in Chemistry in 1979)



### Wittig Chain Extension

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



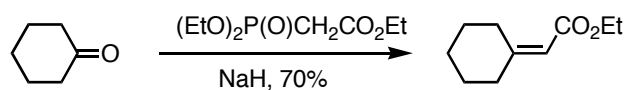
### (Z)-Selective Wittig Reactions

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

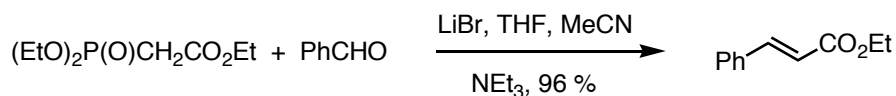


## Horner-Wadsworth-Emmons

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

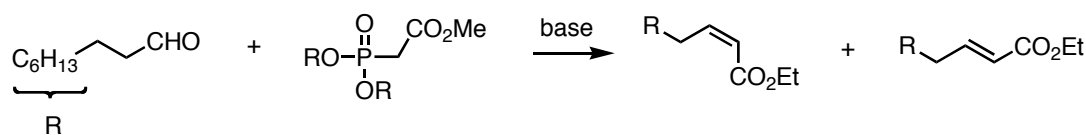


$(\text{EtO})_2\text{P(O)CH}_2\text{R}$ , R = Ph or R =  $\text{CO}_2\text{Et}$ ; with R = alkyl: slow reaction! (The reaction stops at betaine, and no alkene is produced).



Preparation: Arbuzov rearrangement:  $(\text{EtO})_3\text{P} + \text{BrCH}_2\text{CO}_2\text{Et}$

Advantage: Byproduct phosphate is water-soluble.



$\text{KOBu}^t/\text{THF}$	R = Me	2 : 5
$\text{KN}(\text{TMS})_2/\text{THF}/18\text{-C-6}$	R = Me	8 : 1
$\text{PhCH}_2\text{N}^+\text{Me}_3 \text{HO}^-/\text{THF}$	R = $\text{CH}_2\text{CF}_3$	7 : 1
$\text{K}_2\text{CO}_3/18\text{-C-6}/\text{toluene}$	R = $\text{CH}_2\text{CF}_3$	6 : 1
$\text{KN}(\text{TMS})_2/\text{THF}/18\text{-C-6}$	R = $\text{CH}_2\text{CF}_3$	12 : 1

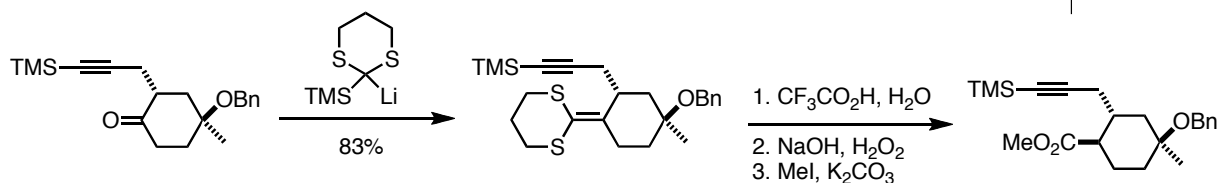
**Still-Wittig conditions** THL 1983, 24, 4405

The electron-withdrawing effect of the  $\text{OCH}_2\text{CF}_3$  substituents decreases the lifetime of the oxaphosphetane sufficiently to restrict any thermodynamic equilibration to the *trans* compound.

# The Peterson Olefination



Wulff, W. D.; Su, J.; Tang, P.-C.; Xu, Y.-C. *Synthesis* **1999**, 415.



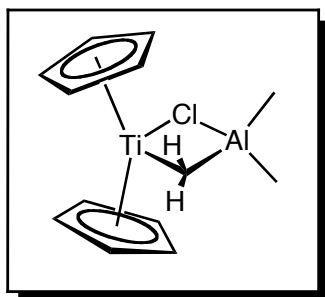
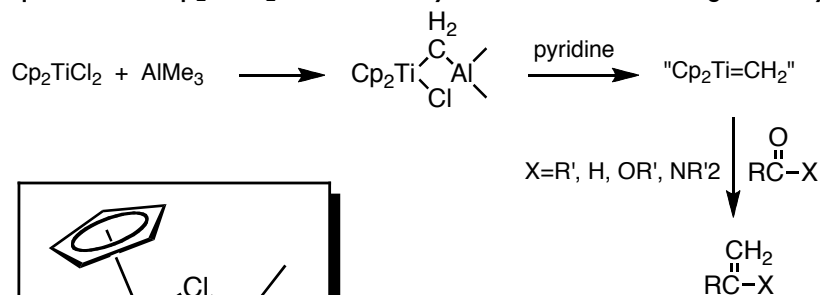
Patil, P. A.; Snieckus, V. *THL* **1998**, 39, 1325.

# Tebbe Reagents

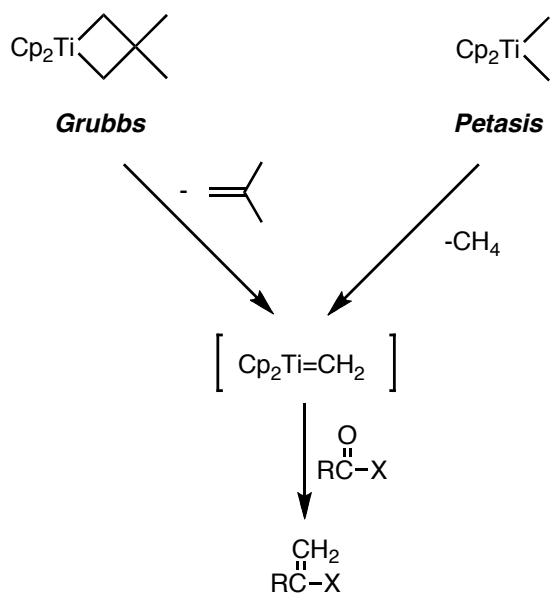


"Fischer" late transition metal carbene complexes are electrophilic, whereas the "Schrock" early transition metal carbene complexes have nucleophilic character. They are formed by metals in high oxidation states with strong donor ligands such as alkyl or cyclopentadienyl, and no acceptor ligands. These complexes have often Wittig-reagent-like reactivity, like ylides.

One of the most extensively studied nucleophilic carbene complexes is **Tebbe's reagent**, obtained by the reaction of  $\text{AlMe}_3$  and  $\text{Cp}_2\text{TiCl}_2$ . In the presence of pyridine, this complex is synthetically equivalent to  $\text{Cp}_2\text{Ti=CH}_2$ , and it is very effective in converting carbonyl groups to methylenes.



In addition to the Tebbe reagent, a titanacyclobutane reported by Grubbs and the Petasis reagent are available for efficient methylenations. In both cases, the methyldene complex is believed to be the reactive agent.



Gentle heating of Cp<sub>2</sub>TiMe<sub>2</sub>, generated by the simple treatment of titanocene dichloride with MeLi, "activates" the Petasis reagent. In some cases, it has advantages over Tebbe's reagent. For example, the spiro lactone shown below fragmented with Tebbe's reagent, while Cp<sub>2</sub>TiMe<sub>2</sub> cleanly methylenated it. In addition, benzylidene (PhCH=), and TMSCH= can be transferred.

However, none of these three routes to titanium-carbene complexes proved to be general for the preparation of substituted derivatives, and the use of these reagents in synthesis is essentially limited to the transfer of a methylene unit.