

## Is There a "Cram's Rule" for Olefins?

### Part A: C=C Nucleophile Additions

#### Reviews:

-This may be it.

-Cited papers with particularly elaborate / insightful discussion will be marked with a dot (●).

-Joe Duffy  
1 / 4 / 1994

## Nucleophilic Olefin Additions?!

Any reaction which proceeds through electron donation (pair or radical) into the  $\pi^*$  orbital of the olefin in the transition state.

#### Scope:

1.  $S_N2'$  Displacements
2. Michael additions
3. Additions to activated olefins (vinyl nitriles, vinyl sulfones, dithioacetals).
4. Diels Alder reactions (chiral dienophile)
5. [3 + 2] Dipolar additions (chiral dipolarophile)
6. Claisen and related [3,3] rearrangements (chiral allylic moiety)
7. Wittig [2,3] rearrangements (chiral allylic moiety)

#### Not Covered:

OsO<sub>4</sub> Dihydroxylations ([2 + 2] or [3 + 2] mechanism), reviewed recently.  
See ● Barrow, J. *Seminar Notes*, **1993**, 235.

## Predictions from Computational Studies

### Transition States (3-21G)

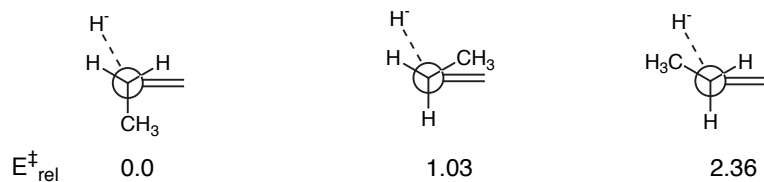
Ethylene vs. formaldehyde for  $\text{CH}_3\text{Li}$  addition.

Ethylene vs. formaldehyde for  $\text{LiH}$  addition.

- Ethylene has a shorter Nu-C bond length (less exothermic, later  $\text{TS}^\ddagger$ ).
- Potentially higher diastereoselectivity for olefins than carbonyls.

Houk, K. N. Von R. Schleyer, P. *J. Am. Chem. Soc.* **1985**, 107, 2821, and 5560.

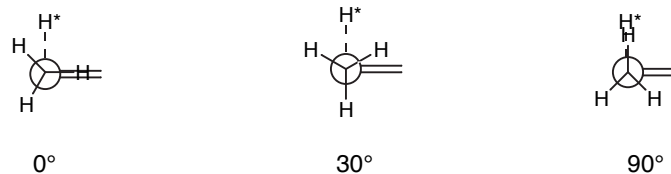
### "Felkin-Like" Steric Analysis (STO-3G)



Houk, K. N. *et al.*, *J. Am. Chem. Soc.* **1982**, 104, 7162

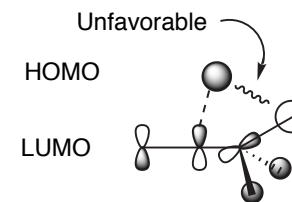
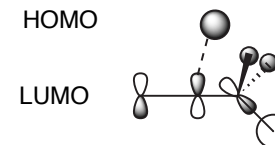
## Predictions from Computational Studies

Transition state assumption: Attack angle of  $90^\circ$ , 2 Å, relative energies calculated at STO-3G (verified with single point calculations at MP2/4-31G level).



### Houk's Rule:

"The tendency for staggering of vicinal bonds with respect to partially formed bonds is greater than for fully formed bonds."

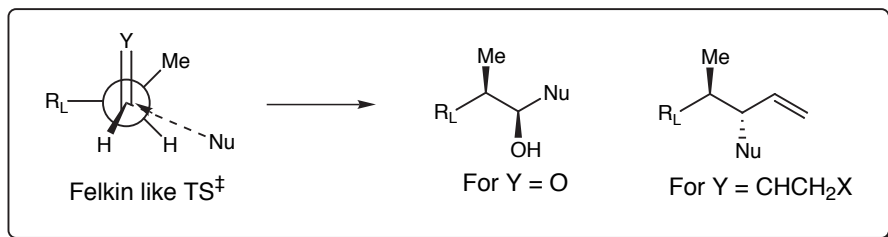


□ FMO aspects are somewhat vague.

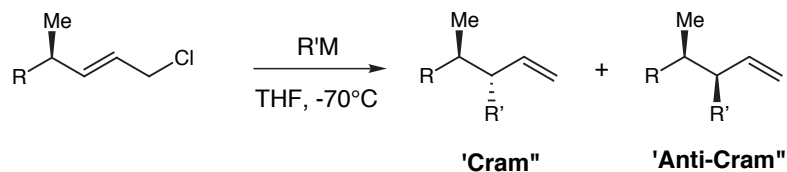
□ Avoid eclipsing interactions in the transition state.

Houk, K. N. *et al.* *J. Am. Chem. Soc.* **1981**, 103, 2438.

### The S<sub>N</sub>2' Reaction - Alkyl Substitution



(E) - olefins



R	R'M	Ratio	
Ph	Bu <sub>2</sub> Zn•2LiCl	89	: 11
Ph	Bu <sub>2</sub> CuLi•ZnCl <sub>2</sub>	95	: 5
Ph	Bu <sub>2</sub> Ti(OiPr) <sub>3</sub> Li <sup>1</sup>	95	: 5
Ph	BuCu•BF <sub>3</sub>	96	: 4
Ph	Me <sub>2</sub> CuLi•ZnCl <sub>2</sub>	95	: 5
Chex	Bu <sub>2</sub> CuLi•ZnCl <sub>2</sub>	100	: 0
Chex	Me <sub>2</sub> CuLi•ZnCl <sub>2</sub>	100	: 0
***Analogous Carbonyl Additions*** <sup>2</sup>			
Ph	MeMgI	67	: 33
Chex	BuMgI	66	: 34

<sup>1</sup> Catalytic CuI•2LiCl added

<sup>2</sup> Cram, D. J. *et al.* *J. Am. Chem. Soc.* **1952**, *74*, 5828; Cram, D. J. *et al.*, *J. Am. Chem. Soc.* **1953**, *75*, 6005.

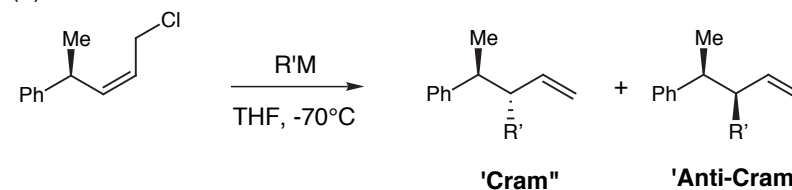
□ Added Lewis acid was required in all cases (RCu was unreactive, R<sub>2</sub>CuLi gave only S<sub>N</sub>2 products).

□ (E) olefins afford higher diastereofacial selectivity than carbonyls with the same sense of induction

● Nakamura, E. *et al.* *J. Org. Chem.* **1993**, *58*, 5121.

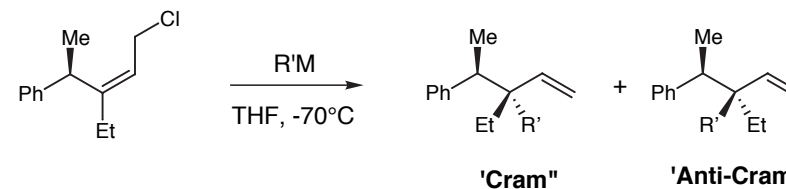
### The S<sub>N</sub>2' Reaction - Alkyl Substitution

(Z) - olefins



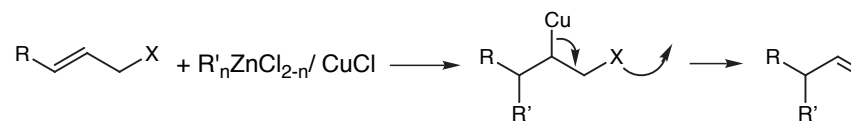
R'M	Ratio	
Bu <sub>2</sub> CuLi•ZnCl <sub>2</sub>	78	: 22
Me <sub>2</sub> CuLi•ZnCl <sub>2</sub>	88	: 12

Ketone equivalent



R'M	Ratio	
Bu <sub>2</sub> CuLi•ZnCl <sub>2</sub>	100	: 0
Me <sub>2</sub> CuLi•ZnCl <sub>2</sub>	100	: 0

□ Proposed Mechanism: Nucleophilic attack of the R group, not the Cu(I) to Cu(III).

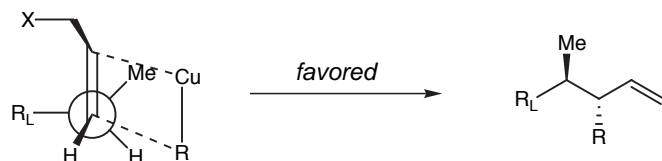


*J. Am. Chem. Soc.* **1990**, *112*, 8042

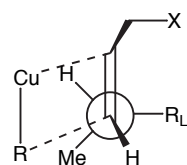
## The $S_N2'$ Reaction - Alkyl Substitution

Proposed transition state:

(E) Olefins



Felkin like  $TS^\ddagger$



Anti Felkin like  $TS^\ddagger$

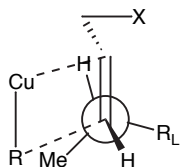
- Similar 4-centered  $TS^\ddagger$  for  $Sia_2BH$  reduction of ketones favors anti-Cram product (opposite steric constraints on reagent).

Midland, M. *et al.* *J. Am. Chem. Soc.* **1983**, *105*, 3725.  
Houk, K. N. *et al.* *J. Am. Chem. Soc.* **1982**, *104*, 7162.

(Z) Olefins



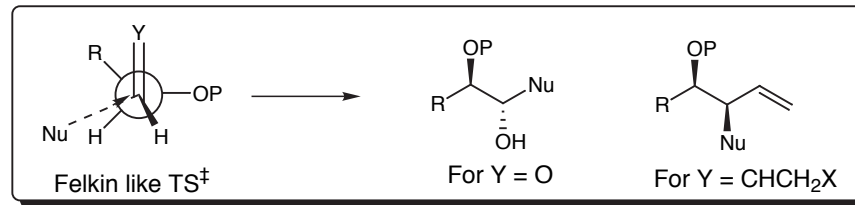
Felkin like  $TS^\ddagger$



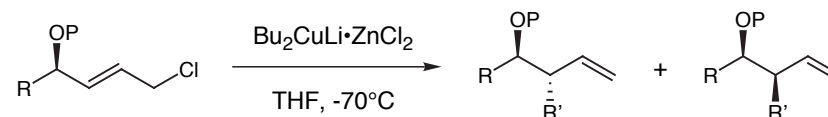
A-1,3 Strain  $TS^\ddagger$

- A-1,3 Strain may diminish stereoselectivity for (Z) Olefins.

## The $S_N2'$ Reaction - Alkoxy Substitution



(E) olefins



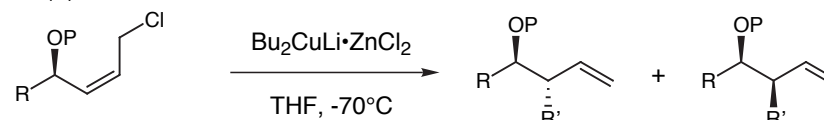
"Chelate"

"Cram"

R	P	Ratio	
Me	MOM	65	: 35
iPr	Bn	100	: 0
iPr	MOM	100	: 0
iPr	TIPS	100	: 0
tBu	MOM	100	: 0

- Same ratios observed using  $Bu_2Zn$  / cat  $CuBr \cdot Me_2S$ ,  $BuCu \cdot BF_3$ ,  $BuTi(OiPr)_3$  / cat  $CuBr \cdot Me_2S$ , and  $Bu_2Zn \cdot 2LiCl$  / 2 HMPA (no copper).

(Z) olefins



"Chelate"

"Cram"

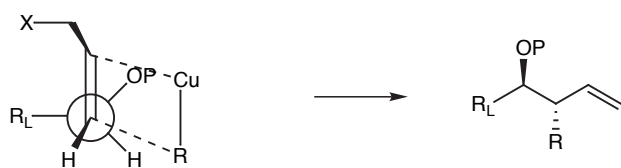
R	P	Ratio	
iPr	Bn	90	: 10
tBu	MOM	40	: 60

- The "chelation control" product predominates in the absence of chelation!
- The ratio is enhanced by larger "R" for (E) olefins, decreased by larger "R" for (Z) olefins.

## The S<sub>N</sub>2' Reaction - Alkoxy Substitution

Proposed transition state:

(E) Olefins



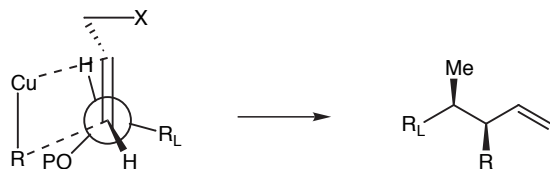
Chelate like TS<sup>‡</sup>

- No anchimeric assistance from OR (since OTIPS gives 100 : 0).
- Could be based on sterics as concluded from dialkyl cases (OP = R<sub>m</sub>).
- Could be a definitive case of Houk's "inside alkoxy effect" which applies to electrophilic additions.



Houk, K. N. *et al. J. Am. Chem. Soc.* **1984**, 106, 3880.

(Z) Olefins

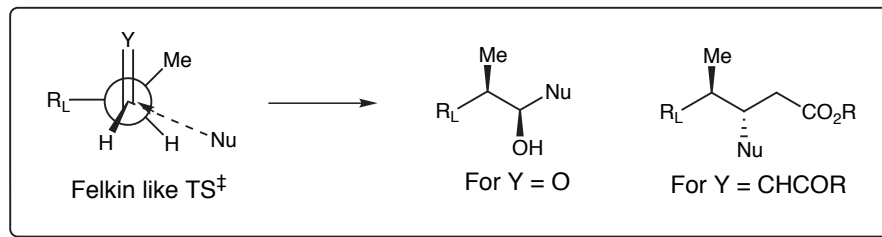


A-1,3 Strain TS<sup>‡</sup>

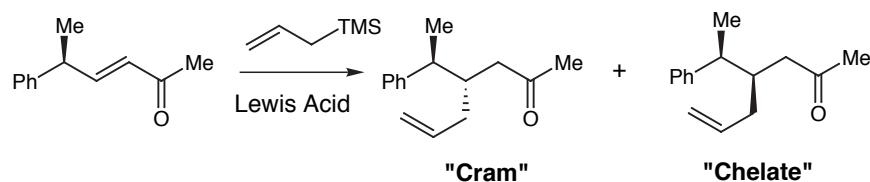
- A-1,3 Strain may diminish stereoselectivity for (Z) olefins.
- Larger R<sub>L</sub> prefers A-1,3 model more.

● Nakamura, E. *et al. J. Org. Chem. Soc.* **1993**, 58, 5121.

## The Michael Reaction - Alkyl Substitution

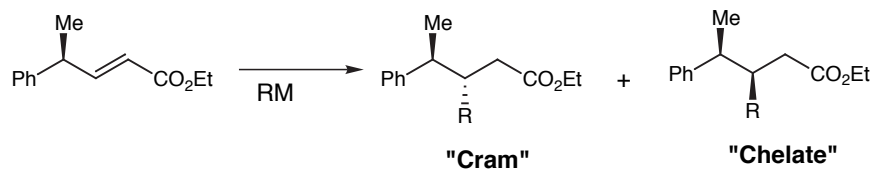


(E) Olefins



Lewis Acid	Ratio	
TMS + TiCl <sub>4</sub>	80	: 20
TMS + BF <sub>3</sub> ·OEt <sub>2</sub>	80	: 20
MgBr·CuBr	80	: 20

Heathcock, C. H. *et al. J. Org. Chem.* **1984**, 49, 4214.

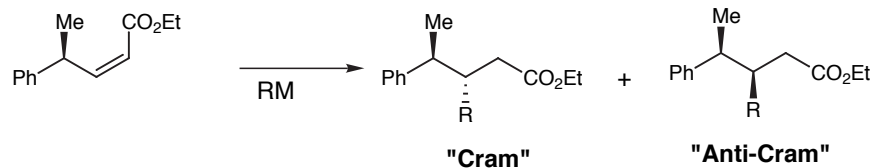


RM	Ratio	
Bu <sub>2</sub> CuLi·BF <sub>3</sub>	70	: 30
BuCu·BF <sub>3</sub>	88	: 12
Me <sub>3</sub> CuLi <sub>2</sub> ·BF <sub>3</sub>	87	: 13

Yamamoto, Y. *et al. J. Chem. Soc. Chem. Comm.* **1987**, 1572.

### The Michael Reaction - Alkyl Substitution

(Z) Olefins

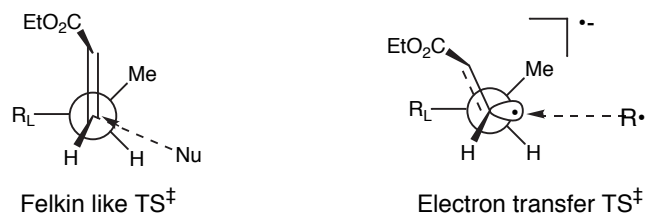


RM	Ratio	
Bu <sub>2</sub> CuLi•BF <sub>3</sub>	30	: 70
BuCu•BF <sub>3</sub>	74	: 26
Me <sub>3</sub> CuLi <sub>2</sub> •BF <sub>3</sub>	21	: 79

Yamamoto, Y, et al. *J. Chem. Soc. Chem. Comm.* **1987**, 1572.

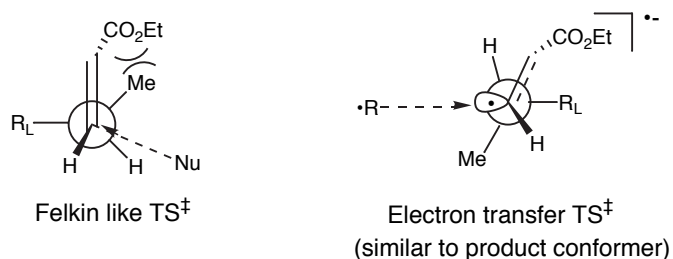
Yamamoto's hypothesis: organocopper species react as a nucleophile, cuprates via initial electron transfer, affording a semi-pyramidalized transition state.

(E) Olefins:



□ Both the Felkin and electron transfer models predict the same product for (E) olefins.

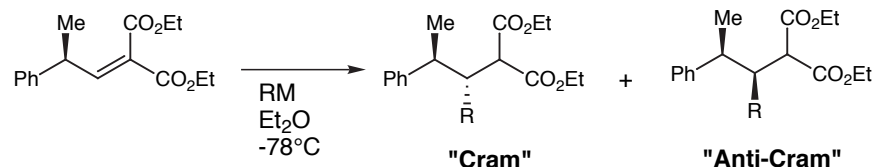
(Z) Olefins:



□ Felkin model violates A-1,3 strain for (Z) olefins.

### The "Michael" Reaction - Alkyl Substitution

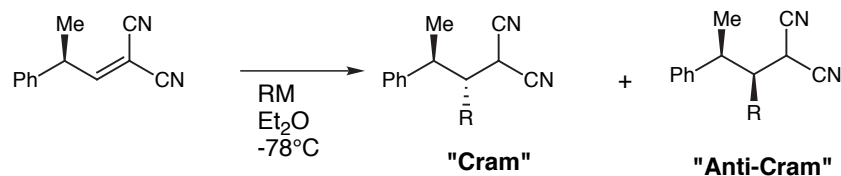
Disubstituted Olefins



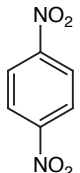
RM	Ratio	
Ph <sub>2</sub> CuLi	12	: 88
Me <sub>2</sub> CuLi	32	: 68
MeCu	84	: 16

□ Similar results to (Z) olefins, reagent based turnover is observed.

Disubstituted Olefins



RM	Ratio	
Me <sub>2</sub> CuLi	13	: 87
MeCu	23	: 77
MeCu	67	: 33
Me <sub>2</sub> CuLi	67	: 33
nBu•	83	: 17
Chex•	87	: 13
tBu•	93	: 7

Added 1 eq.  RI + Zn/CuI

● Yamamoto, Y. et al. *J. Am. Chem. Soc.* **1988**, 110, 617.  
Geise, B. et al. *Synlett* **1992**, 441.

□ Organocopper and cuprate reagents both give anti Cram diastereofacial selectivity.

□ Diastereofacial selectivity for both can be reversed with an electron acceptor.

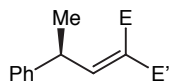
## The "Michael" Reaction

Yamamoto's next generation hypothesis:

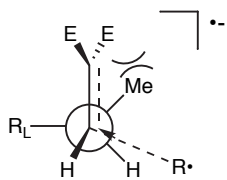
All reactions of dinitriles proceed via the electron transfer mechanism.

Substrate Reduction Potentials

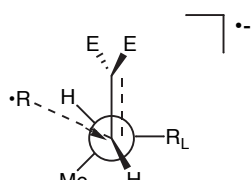
E	E'	$E_{red}$ vs SCE (V)
CN	CN	-1.52
CO <sub>2</sub> Et	CN	-1.73
CO <sub>2</sub> Et	CO <sub>2</sub> Et	>-2.0



Further claim: R<sub>2</sub>CuLi is an electrophilic radical, with an attack angle < 90°.

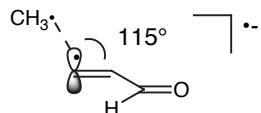


Felkin like TS<sup>‡</sup>  
attack angle >90°



Electrophilic radical TS<sup>‡</sup>  
attack angle <90°

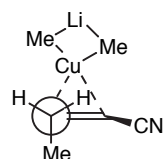
Refuted by Morokuma: calculated TS<sup>‡</sup> at UHF / 3-21G level:



Same as for CH<sub>3</sub><sup>-</sup>

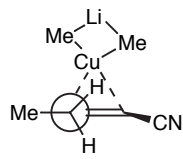
However, copper may form the electrophilic π - complex at <90° which prefers "inside" hydrogen.

Energy of complexation: -4.63 kcal / mol

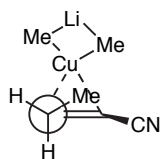


E<sub>rel</sub>

0.0

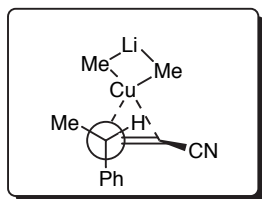


1.44



2.32

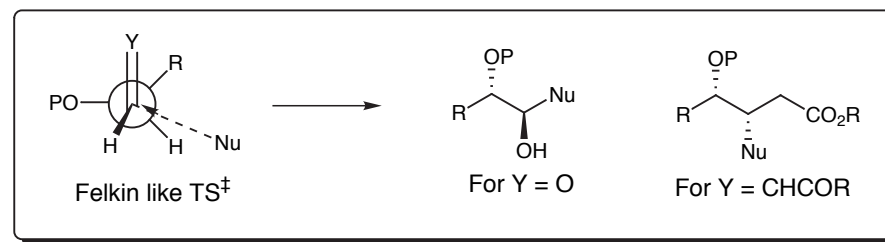
Morokuma's proposed TS<sup>‡</sup>



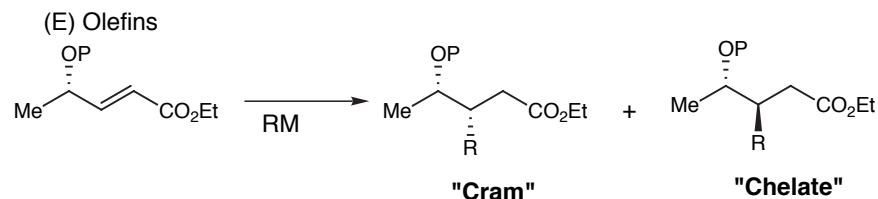
□ Why does p-DNB shut down this mechanism?

Morokuma, K. *et al. J. Chem. Soc. Chem. Comm.* **1989**, 1884.

## The Michael Reaction - Alkoxy Substitution



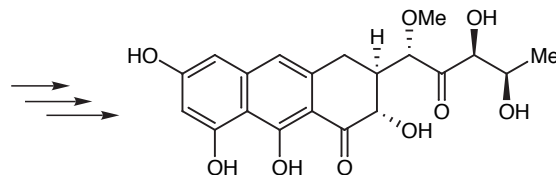
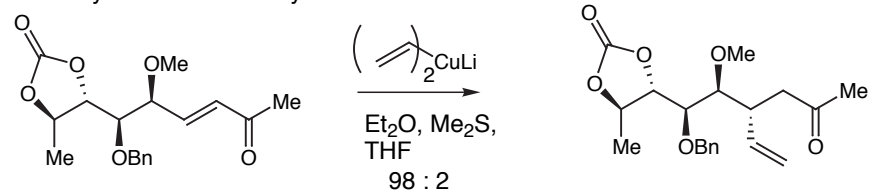
A. Alkoxy substitution:



P	RM	Ratio	
Bn	(2-methylallyl) <sub>2</sub> CuLi	58	: 42
Bn	MeCu•BF <sub>3</sub>	31	: 69
Bn	MeCu(CN)Li•BF <sub>3</sub>	5	: 95
Bn	BuCu•BF <sub>3</sub>	8	: 92
TBS	MeCu•BF <sub>3</sub>	32	: 68
TBS	Me <sub>2</sub> CuLi•BF <sub>3</sub>	27	: 73
TBS	Me <sub>2</sub> Cu(CN)Li <sub>2</sub> •BF <sub>3</sub>	8	: 92

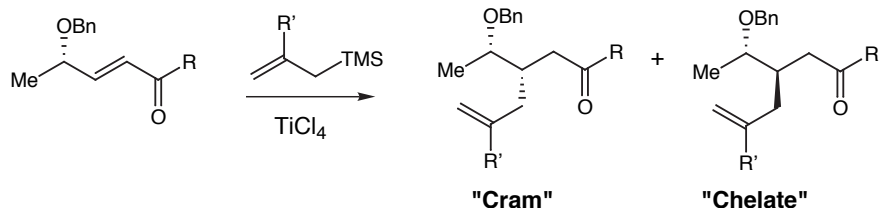
● Yamamoto, Y. *et al. J. Am. Chem. Soc.* **1992**, 114, 7652.

In the synthesis of Olivomycin A



Roush, W. R. *et al. J. Am. Chem. Soc.* **1989**, 111, 2984.

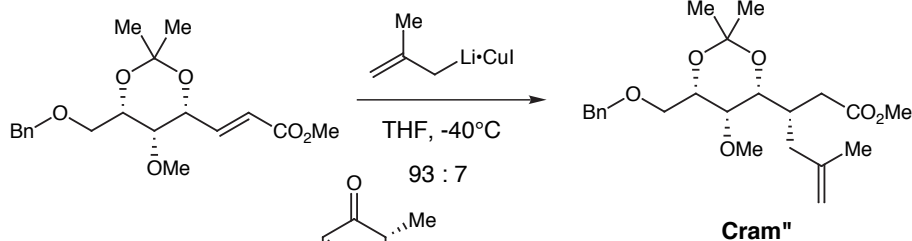
## The Michael Reaction - Alkoxy Substitution



R	R'	Ratio
Me	H	88 : 12
Me	Me	80 : 20
Ph	H	89 : 11

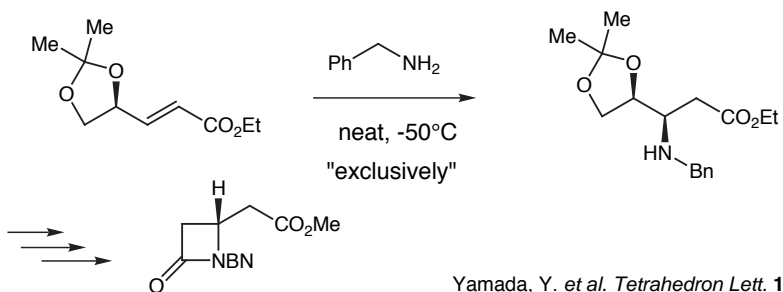
Heathcock, C. H. *et al. J. Org. Chem. Soc.* **1984**, 49, 4214.

In the synthesis of Leucomycin A<sub>3</sub>



Nicolaou, K. C., *et al. J. Am. Chem. Soc.* **1981**, 103, 1224.

In the synthesis of  $\beta$ -lactams



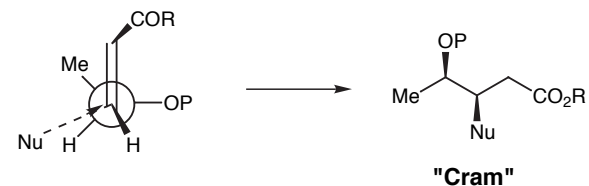
Yamada, Y. *et al. Tetrahedron Lett.* **1983**, 24, 3009.

## The Michael Reaction - Alkoxy Substitution

### Observations on (E) olefins

- Anti Cram ("chelate") diastereomer is favored for cuprates.
- Cram diastereomer is favored for other nucleophiles.

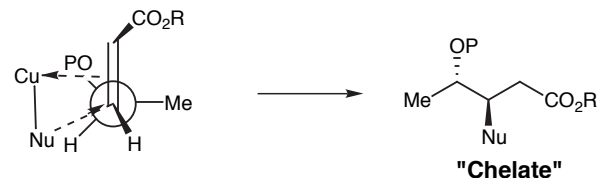
Heathcock's proposal:



"The stereostructures of the major isomers produced...are those predicted by the application of Felkin's model (Figure 2)."

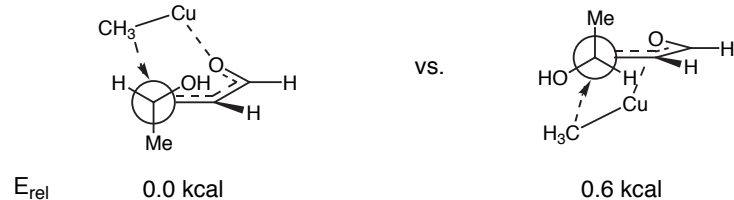
\*\*\* Note that figure 2 is incorrect in Heathcock publication, read text carefully\*\*\*

Yamamoto's revised next generation proposal:



$\pi$  - Complex involves electrophilic attack, governed by the "inside alkoxy effect."

Computational support: Transition structures located at RHF / 3-21G.

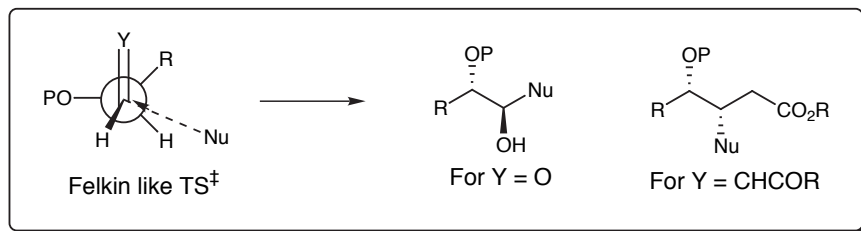


Electron donor should be antiperiplanar, electron acceptor should be out of conjugation. The two computed transition structures predict a ratio of 73 : 27 for MeCu additions at r.t., Yamamoto found 69 : 31.

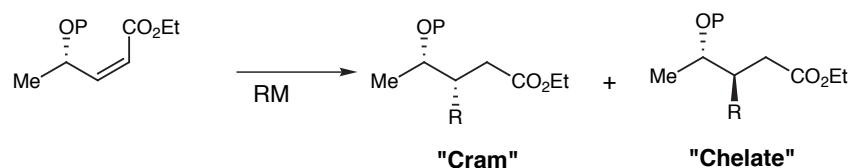
Morokuma, K. *et al. J. Am. Chem. Soc.* **1989**, 111, 6524.



## The Michael Reaction - Alkoxy Substitution



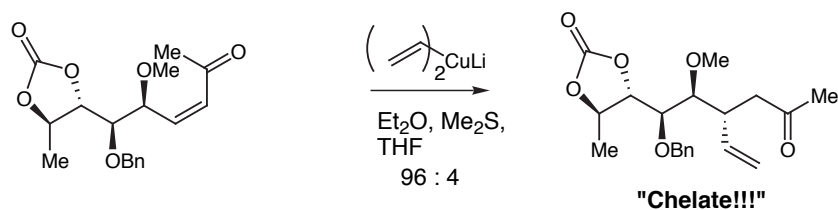
(Z) Olefins



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Bn	MeCu·BF <sub>3</sub>	78	: 22
Bn	MeCu(CN)Li·BF <sub>3</sub>	74	: 26
Bn	BuCu·BF <sub>3</sub>	78	: 22
TBS	MeCu·BF <sub>3</sub>	86	: 14
TBS	Me <sub>2</sub> CuLi·BF <sub>3</sub>	87	: 13
TBS	Me <sub>2</sub> Cu(CN)Li <sub>2</sub> ·BF <sub>3</sub>	83	: 17

● Yamamoto, Y. *et al J. Am. Chem. Soc.* **1992**, 114, 7652.

In the synthesis of Olivomycin A

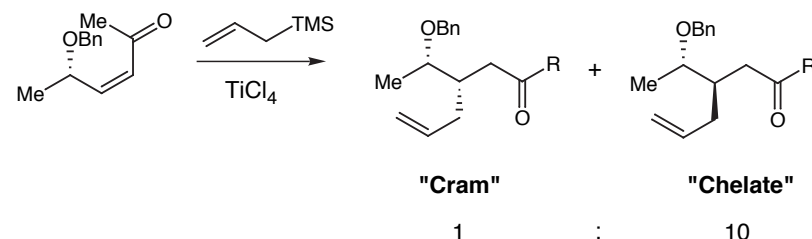


Roush, W. R. *et al J. Am. Chem. Soc.* **1989**, 111, 2984.

□ Yamamoto observes a turnover in selectivity based on olefin geometry, Roush does not!

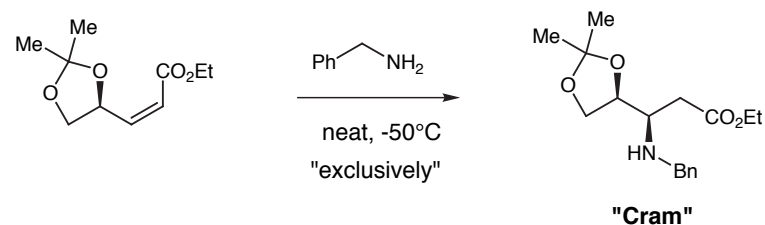
## The Michael Reaction - Alkoxy Substitution

Non cuprate nucleophiles:



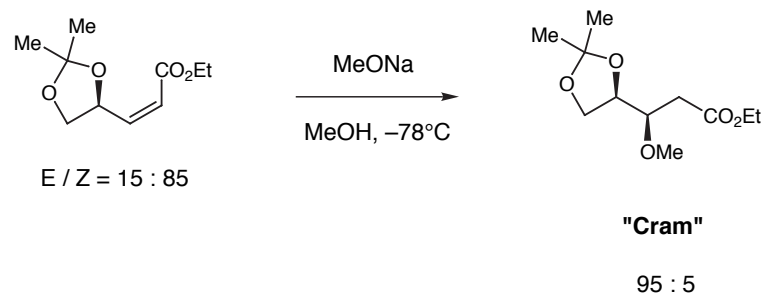
Heathcock, C. H. *et al J. Org. Chem. Soc.* **1984**, 49, 4214.

In the synthesis of β-lactams



Yamada, Y. *et al Tetrahedron Lett.* **1983**, 24, 3009.

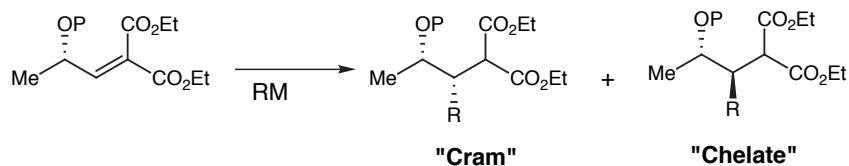
□ Heathcock observes a turnover in selectivity based on olefin geometry, Yamada does not.



Mulzer, J. *et al Angew. Chem. Int. Ed. Eng.* **1984**, 23, 704.

## The Michael Reaction - Alkoxy Substitution

Bis-activated Olefins



P	RM	Ratio	
Bn	(2-methylallyl) <sub>2</sub> CuLi	90	: 10
Bn	MeCu•BF <sub>3</sub>	94	: 6
Bn	MeCu	89	: 11
Bn	BuCu•BF <sub>3</sub>	95	: 5
TBS	MeCu•BF <sub>3</sub>	84	: 16
TBS	MeCu(CN)Li	92	: 8
TBS	MeCu(CN)Li•BF <sub>3</sub>	91	: 9

● Yamamoto, Y. *et al J. Am. Chem. Soc.* **1992**, *114*, 7652.

□ Same facial preference as (Z) olefins.

### Observations on (Z) and Bis-activated Olefins

- Cram product favored for copper-based additions (except Roush case which remains unexplained).
- Anti-Cram (or "chelate") product favored for non-copper nucleophiles with added Lewis acid.
- Cram product favored for non-copper nucleophiles without added Lewis acid.

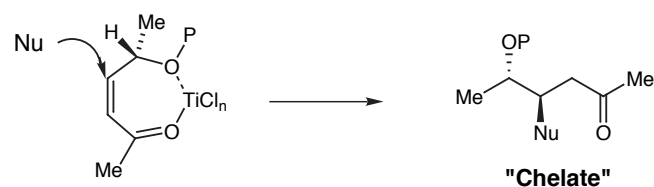
## The Michael Reaction - Alkoxy Substitution

Nucleophiles without Lewis acid:

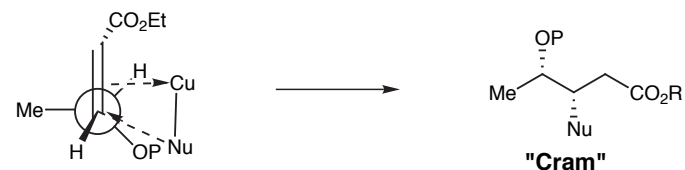


Violates A-1,3 strain principles!

Nucleophiles with Lewis acid (Heathcock proposal):

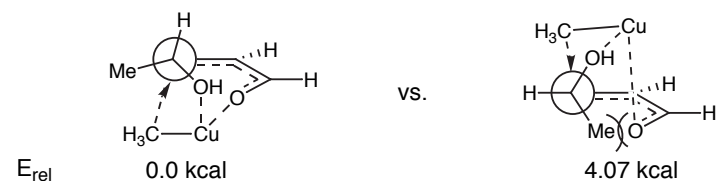


Organocuprate addition:



A-1,3 strain forces OP to the outside position.

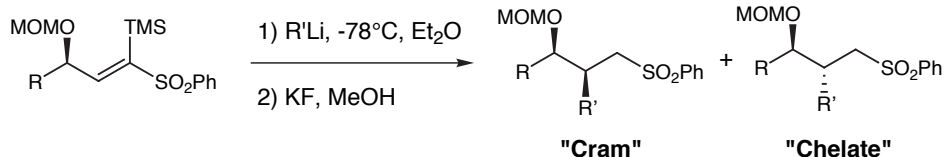
Computational support: Transition structures located at RHF / 3-21G, found same diastereofacial preference, but from a different rotamer.



Morokuma, K. *et al J. Am. Chem. Soc.* **1989**, *111*, 6524.

(E) Vinyl sulfones:

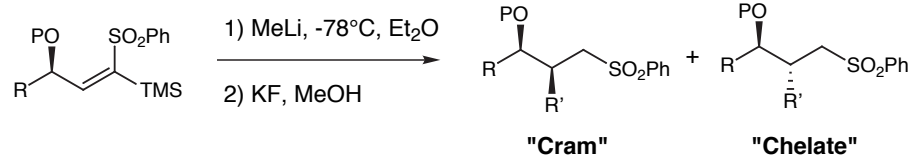
### Vinyl Sulfone Additions



R	R'	Ratio
Me	Me	96 : 4
Me	tBu	>98 : <2
iPr	Me	>98 : <2
iPr	tBu	>98 : <2

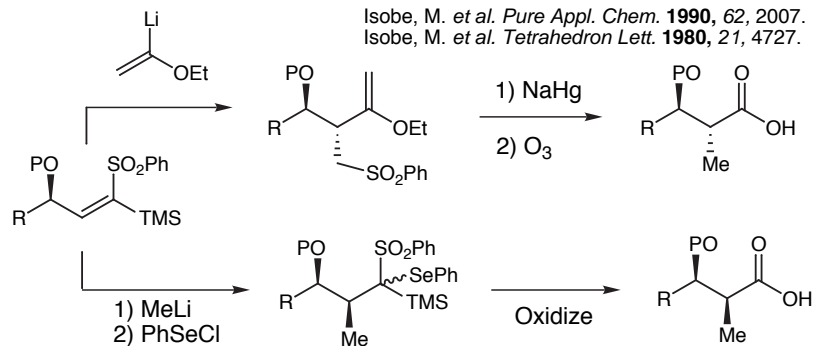
Carretero, J. C. et al. *Tetrahedron Lett.* **1991**, 32, 1385.

(Z) Vinyl sulfones:



R	P	Ratio
iPr	MOM	"only"
CH <sub>2</sub> Bn	MEM	97 : 3
CH <sub>2</sub> Bn	H	>99 : <1
CH <sub>2</sub> Bn	TBS	95 : 5

Utility:

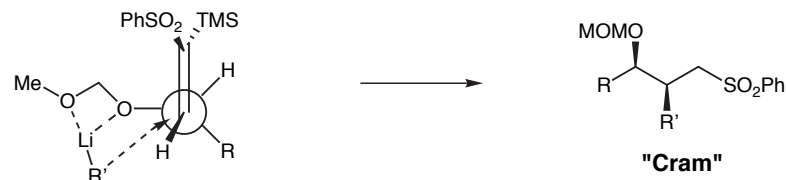


Isobe, M. et al. *Pure Appl. Chem.* **1990**, 62, 2007.  
Isobe, M. et al. *Tetrahedron Lett.* **1980**, 21, 4727.

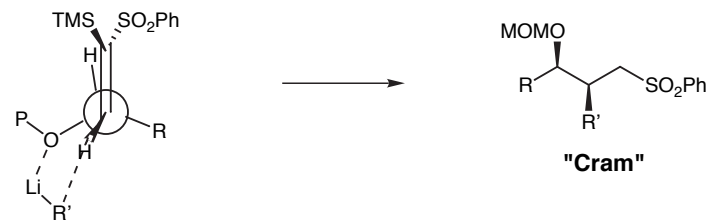
● Isobe, M. et al. *Tetrahedron*, **1986**, 42, 2863.

### Vinyl Sulfone Additions

Carretero's proposal:



Isobe's proposal:



□ Both are similar, except Isobe recognizes the importance of A-1,3 strain.

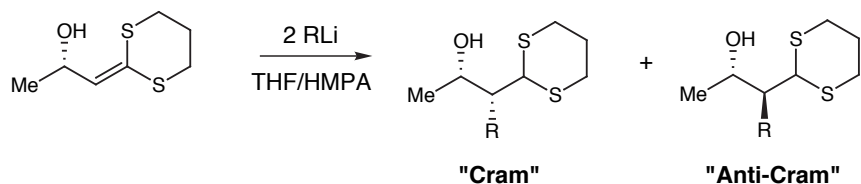
□ Same diastereofacial selectivity is observed with P = TBS!

Asymmetric variant:

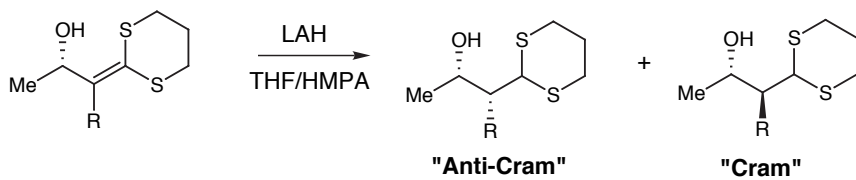


Isobe, M. et al. *Tetrahedron Lett.* **1988**, 29, 4773.

### Dithioketene Acetal Additions

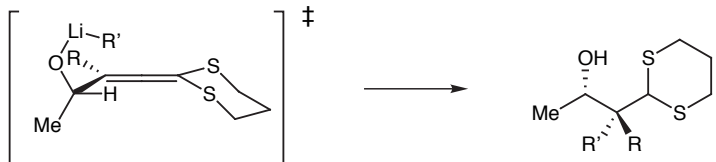


R	Ratio		
Me	100	:	0
Et	100	:	0
nBu	98	:	2
Ph	100	:	0



R	Ratio		
Me	1	:	99
Et	4	:	96
nBu	1	:	99
Ph	0	:	100

Transition state proposal:

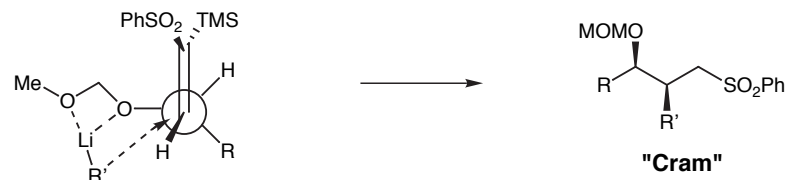


- Governed by A-1,3 interactions with directed nucleophilic attack.
- OTBS protected substrate decomposed, the role of chelation was not further tested.

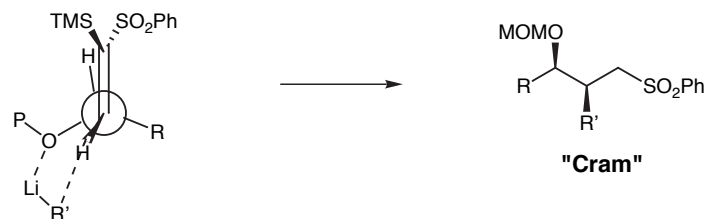
Fujisawa, T. *et al. Tetrahedron Lett.* **1989**, 30, 977.

### Vinyl Sulfone Additions

Carretero's proposal:

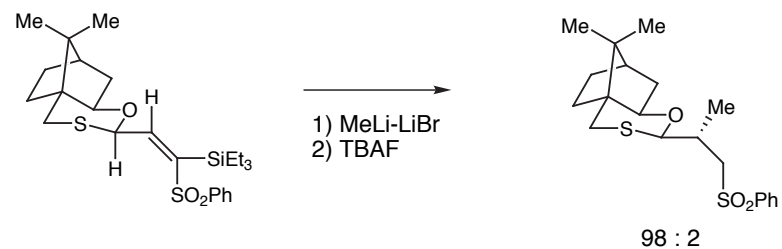


Isobe's proposal:



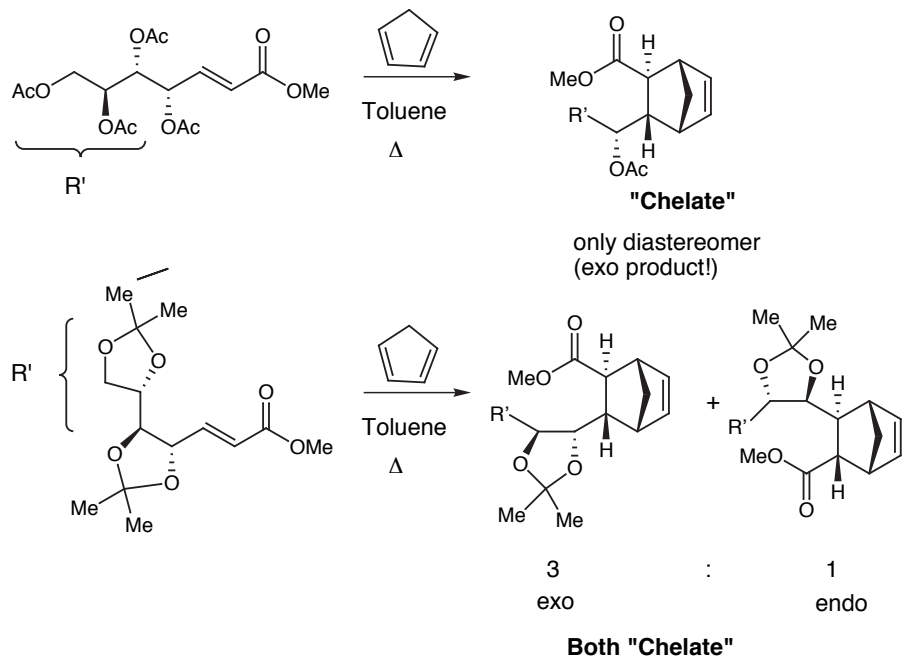
- Both are similar, except Isobe recognizes the importance of A-1,3 strain.
- Same diastereofacial selectivity is observed with P = TBS!

Asymmetric variant:



Isobe, M. *et al. Tetrahedron Lett.* **1988**, 29, 4773.

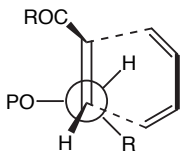
## Diels Alder Reactions - Alkoxy Substitution



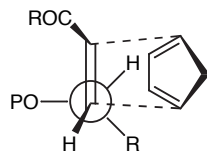
Horton, D. *et al. J. Chem. Soc. Chem. Comm.* **1981**, 88.

□ Anti Cram dienophile diastereoface is preferred in each case.

Similar proposal for each:



Franck

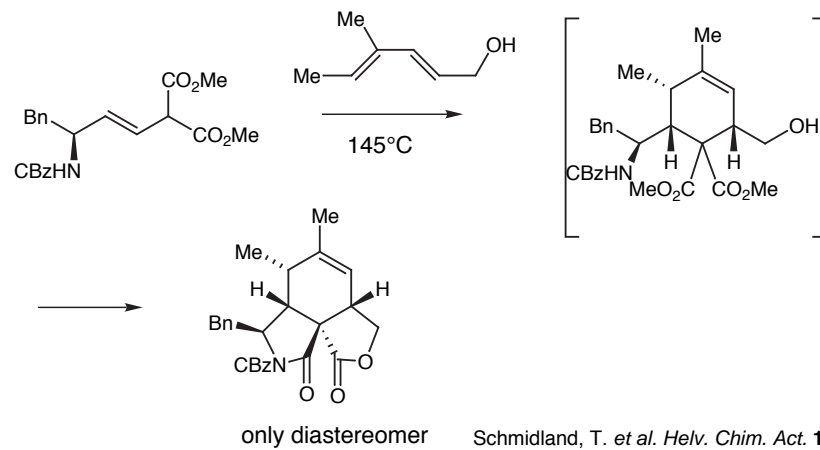


Horton

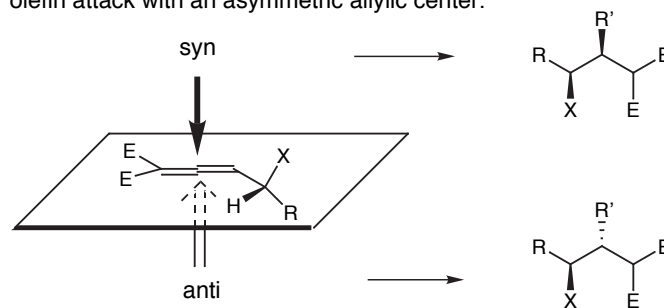
(no explanation for exo preference)

## Diels Alder Reactions - Amine Substitution

α-Electron donating substituents:



Hehre's Proposal: The Diels Alder results are expanded into a general rule for olefin attack with an asymmetric allylic center.



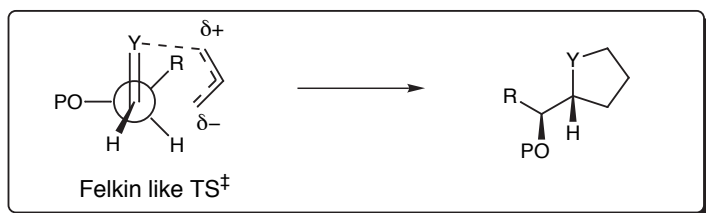
X	Electrophile	Nucleophile
Electron Rich	Syn	Anti
Electron Poor	Anti	Syn

□ This theory works well for all reactions covered except Michael additions.

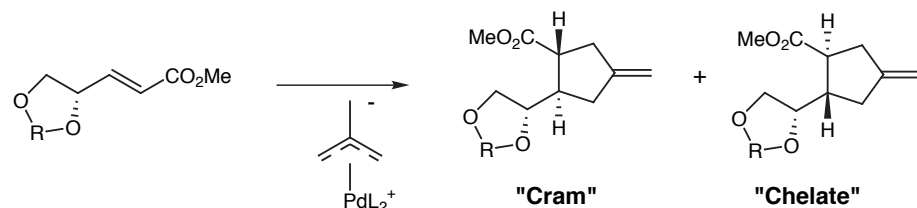
□ Makes no account for (E) vs (Z) olefins.

● Hehre, W. J., Kahn, S. D. *J. Am. Chem. Soc.* **1987**, 109, 663.

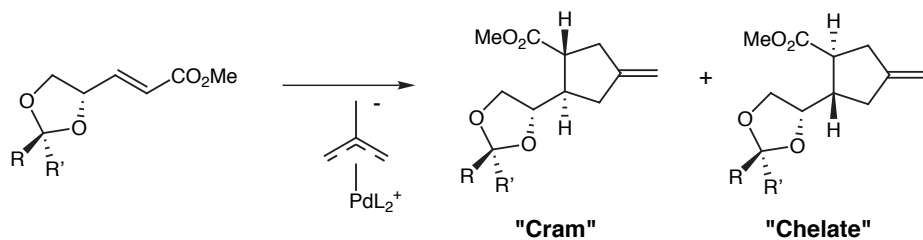
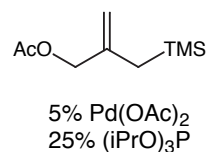
### [3 + 2] Additions



#### A. Palladium catalyzed [3+2]



R	Ratio	
C(CH <sub>3</sub> ) <sub>2</sub>	75	: 25
Si(tBu) <sub>2</sub>	88	: 12



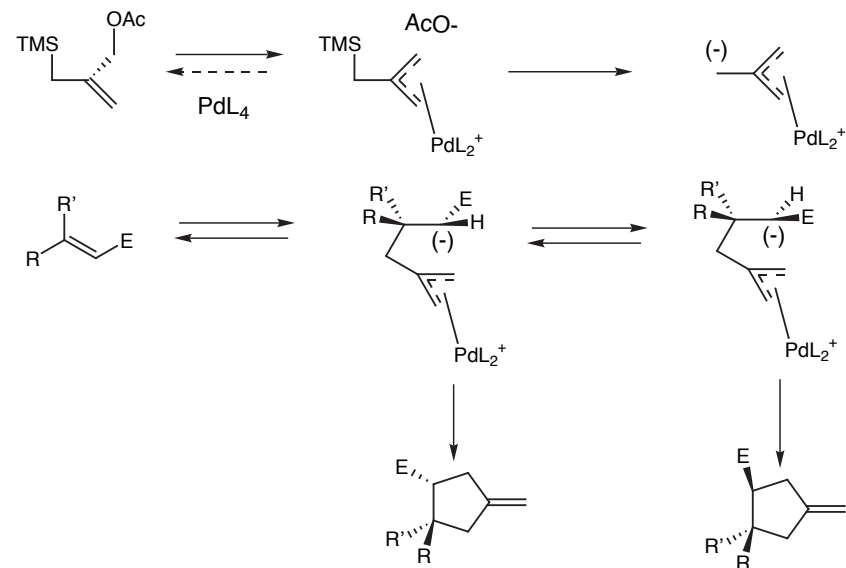
R	R'	Ratio	
BOM	H	72	: 28
H	BOM	72	: 28

□ The steric environment of the protecting group is not a factor.

Trost, B. M. *et al. Tetrahedron Lett.* **1985**, 26, 6313.

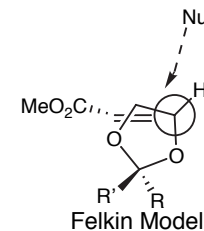
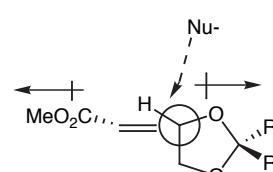
### [3 + 2] Additions

Proposed Mechanism: A genuine nucleophilic attack.



□ Reactions of (E) olefins are stereospecific, (Z) olefins are not (with recovery of isomerized starting material).

Trost, B. M. *et al. J. Am. Chem. Soc.* **1983**, 105, 2315.  
Trost, B. M. *et al. J. Am. Chem. Soc.* **1983**, 105, 2326.

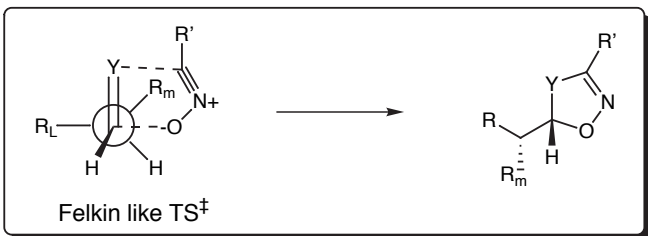


□ Trost claims the reaction is governed by the molecular dipole, not Felkin, based on independence of sterics of R and R'.

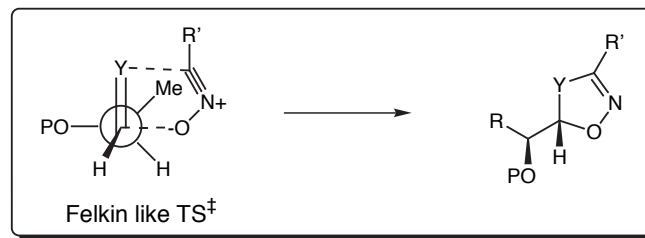
□ Claims silicon acetone provides higher dipole, resulting in higher stereoselectivity.

□ Dipole model is similar to Kahn / Hehre proposal.

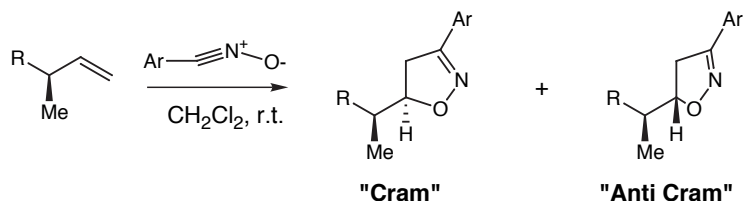
[3 + 2] Additions - Alkyl Substitution



[3 + 2] Additions - Alkoxy Substitution



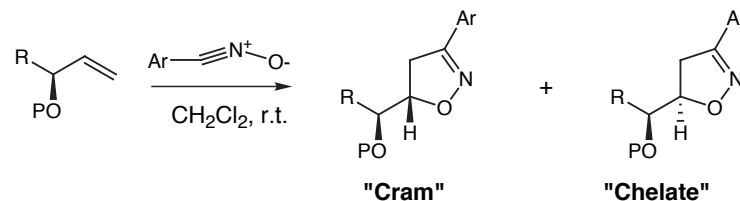
B. Nitrile Oxide [3+2]



R	Ratio	
Ph	59	: 41
iPr	65	: 35
tBu	77	: 23
TMS	60	: 40

Houk, K. N. *et al.* *J. Am. Chem. Soc.* **1986**, 108, 2754  
 Curran, D. P. *et al.* *Synthesis* **1986**, 312.

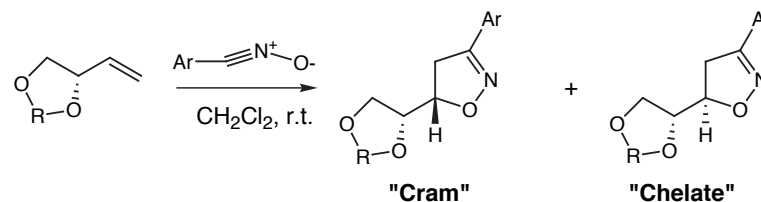
□ Both authors invoke the Felkin like transition state above.



R	P	Ratio	
Me	Me	36	: 64
Me	TMS	29	: 71
Me	TBS	28	: 72
tBu	Me	<5	: >95
tBu	TMS	<5	: >95

Greater dependence  
 on the size of "R" than  
 of "P."

- Houk, K. N. *et al.*, *J. Am. Chem. Soc.* **1984**, 106, 3880
- Houk, K. N. *et al.*, *J. Am. Chem. Soc.* **1986**, 108, 2754
- Kozikowski, A. P. *et al.*, *J. Org. Chem.* **1984**, 49, 2762



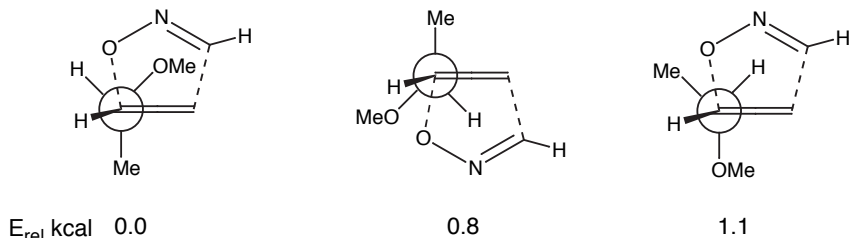
R	Ratio	
C(Me) <sub>2</sub>	15	: 85
Chex	19	: 81
C=O	18	: 82

Kozikowski, A. P. *et al.* *J. Am. Chem. Soc.* **1982**, 104, 5788  
 Houk, K. N. *et al.* *J. Am. Chem. Soc.* **1984**, 106, 3880.

## [3 + 2] Additions - Alkoxy Substitution

Houk claims the additions are more electrophilic in nature, and conform to the "inside alkoxy effect" rule.

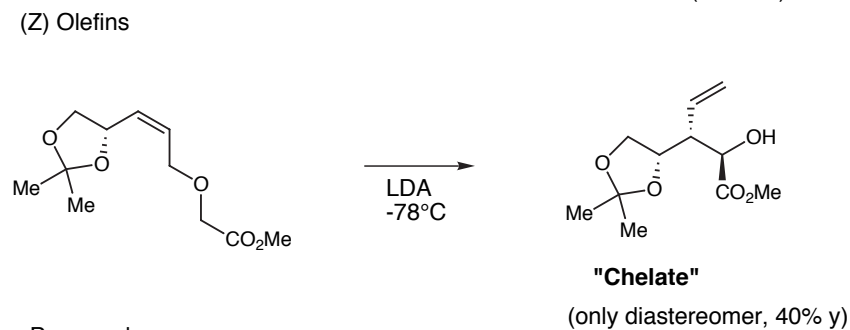
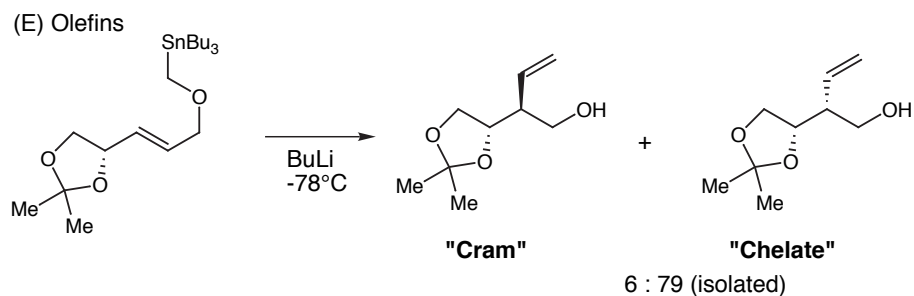
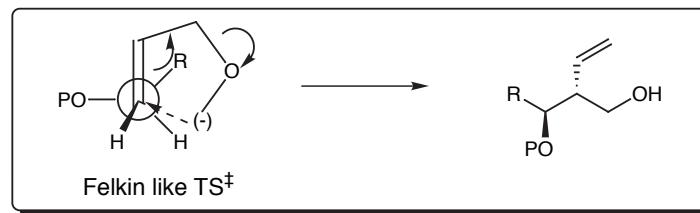
Computational evidence: Base transition structure (propene) was found at the 3-21G level, then the substituted rotamers were minimized by MM2, with single point energy calculations at STO-3G.



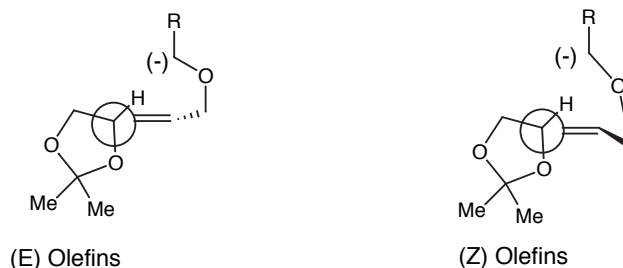
☐ Predicts Anti-Cram / Cram ratio of 68:32 at room temperature (observed 64:36).

☐ Larger R group affords higher diastereoselectivity.

## 2,3-Wittig Rearrangement



Proposed:

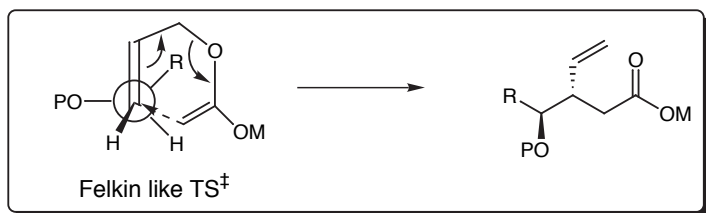


☐ Violates the Kahn / Hehre proposal.

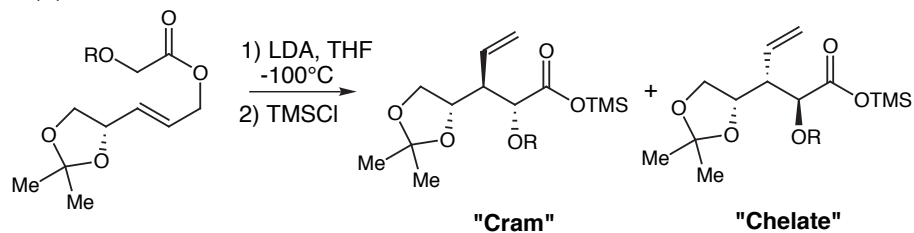
Bruckner, R. *et al*, *Angew. Chem. Int. Ed. Eng.* **1988**, 27, 278.



## Claisen Rearrangements

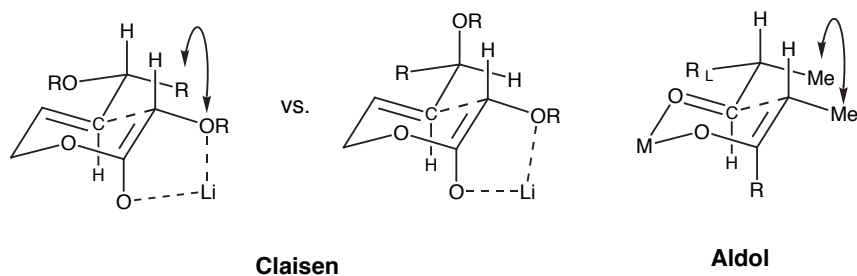


(E) Olefins



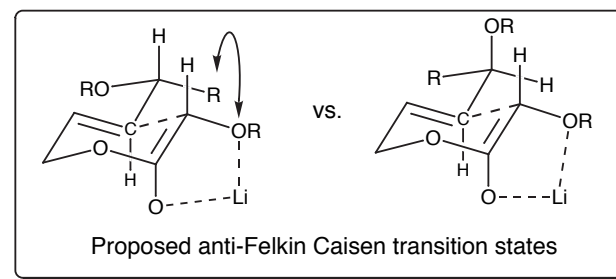
R	Ratio	
Me	19	: 81
MOM	20	: 80
BOM	19	: 81

Cha, J. K. *et al. Tetrahedron Lett.* **1984**, 25, 5263

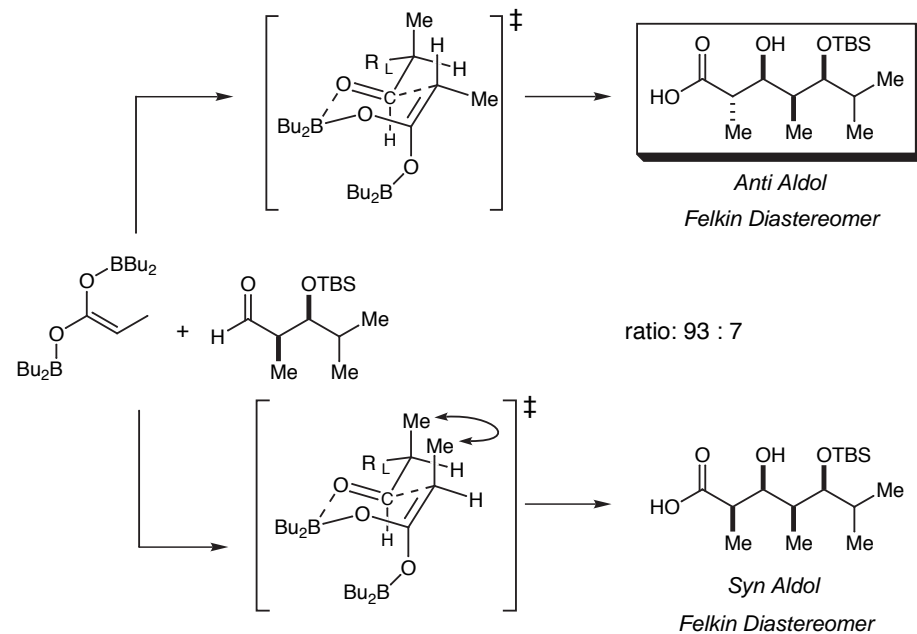


- ❑ The Claisen (Z) enolate is analogous to the aldol (E) enolate.
- ❑ This [3,3] sigmatropic rearrangement is isoelectronic with the aldol reaction.
- ❑ The inside alkoxy transition state avoids the syn-pentane interaction, but should only apply to electrophilic additions.
- ❑ Violates Kahn / Hehre proposal. ● Dart, M., private communication.

## Claisen Rearrangements - The Aldol Analogy



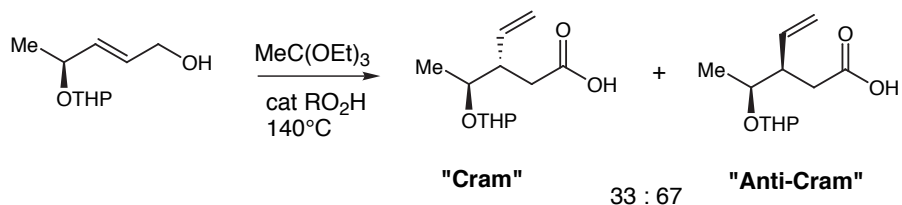
- ❑ Geometrically and electronically analogous to the acid diolate aldol reaction, which exhibits an exceptional Felkin diastereo-preference.



Evans, D. A.; Duffy, J. L. Unpublished results.

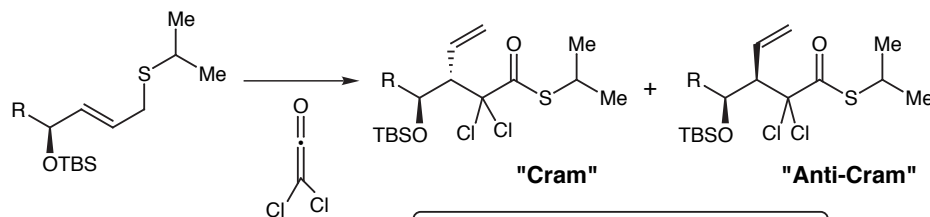
## Claisen Rearrangements

(E) Olefin, methyl ketone enolate



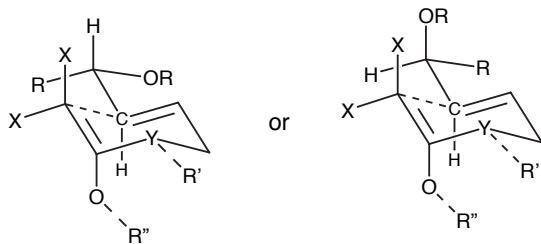
Takano, S. et al. *Tetrahedron Lett.* **1985**, 26, 865

Thioester Claisen



R	Ratio		
Me	<5	:	>95
iPr	<5	:	>95
EtOTBS	<5	:	>95

Ernst, B.; Bellus, D. et al. *Angew Chem. Int. Ed. Eng.* **1991**, 30, 1465.

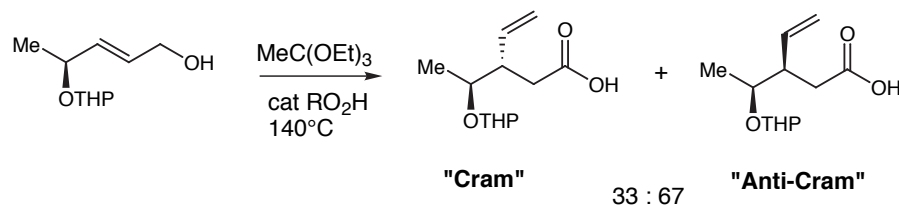


Case 1: X=H, Y=O, R'=Et  
Case 2: X=Cl, Y=S, R'=iPr

□ Again, anti-Felkin or inside alkoxy transition states are proposed.

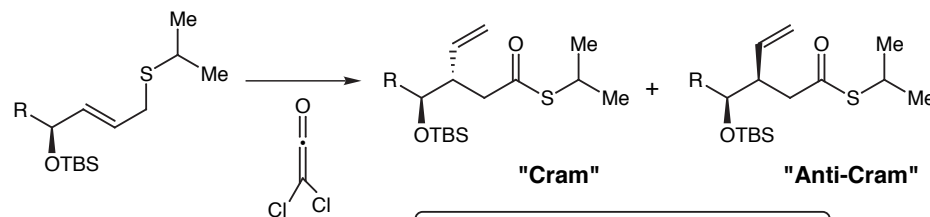
## Claisen Rearrangements

(E) Olefin, methyl ketone enolate



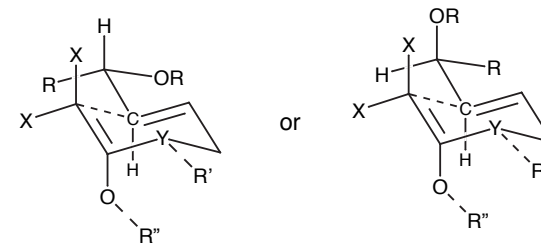
Takano, S. et al. *Tetrahedron Lett.* **1985**, 26, 865

Thioester Claisen



R	Ratio		
Me	<5	:	>95
iPr	<5	:	>95
EtOTBS	<5	:	>95

Ernst, B.; Bellus, D. et al. *Angew Chem. Int. Ed. Eng.* **1991**, 30, 1465.



Case 1: X=H, Y=O, R'=Et  
Case 2: X=Cl, Y=S, R'=iPr

□ Again, anti-Felkin or inside alkoxy transition states are proposed.

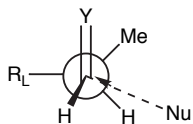
## Conclusions???

Is there a "Cram's Rule" for nucleophilic attack of olefins? **NO...**

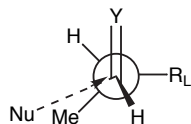
However, application of Cram's rules in the following way predicts the favored product for everything except Michael additions:

- ☞ Alkyl substituted olefins follow the Cram Steric rule.
- ☞ Alkoxy substituted olefins follow the Cram Chelate rule.

### Alkyl-Substituted Additions



Cram Diastereoface



Anti-Cram Diastereoface  
(A-1,3 Diastereoface)

$S_N2'$  additions (E) and (Z)

Michael additions (E) and (Z)  
except (Z) "charge transfer"

[3 + 2] Nitron additions (E)

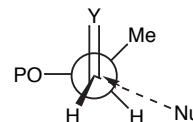
☐ In the absence of "charge transfer" mechanisms, Cram's rule generally applies for nucleophiles and nucleophilic radicals.

☐ In no case does attack of the preferred A-1,3 strain conformer predominate.

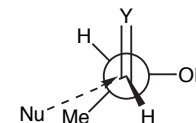
Michael addition (Z)  
"charge transfer"

## Conclusions???

### Alkoxy-Substituted Additions



Cram Diastereoface



Anti-Cram Diastereoface  
(Chelation Diastereoface)

Vinyl sulfone additions  
(E) and (Z)

Michael additions (E) and (Z)  
except (Z) "charge transfer"

☐ Michael - type additions follow Cram's (Felkin's) rule.

☐ All cycloadditions follow the Cram Chelate rule.

$S_N2'$  additions (E) and (Z)

Diels Alder reactions

[3 + 2] Pd - C(CH<sub>2</sub>)<sub>3</sub> additions

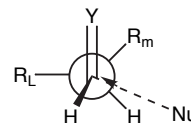
[3 + 2] Nitron additions

[2,3] Wittig rearrangements

Claisen rearrangements

Michael additions (Z)  
"charge transfer"

**Note added in proof:** A model was suggested which would explain all of the results presented (except Michael additions):



☐ Nucleophilic attack on olefins always follows Cram's steric rule, where OP = R<sub>m</sub> for alkoxy substituted olefins.

☐ This disregards any electronic component, but predicts the correct product.

● J. Leighton, private communication.