

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 π^* 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:

OsO₄ Dihydroxylations ([2 + 2] or [3 + 2] mechanism), reviewed recently.
See ● Barrow, J. *Seminar Notes*, **1993**, 235.

Predictions from Computational Studies

Transition States (3-21G)

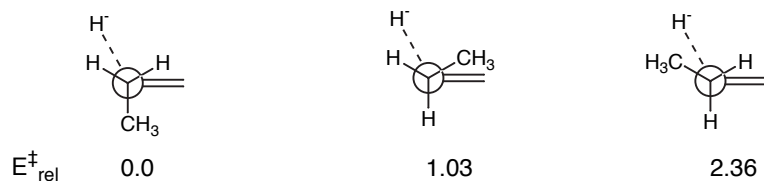
Ethylene vs. formaldehyde for CH_3Li addition.

Ethylene vs. formaldehyde for LiH addition.

- Ethylene has a shorter Nu-C bond length (less exothermic, later 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.

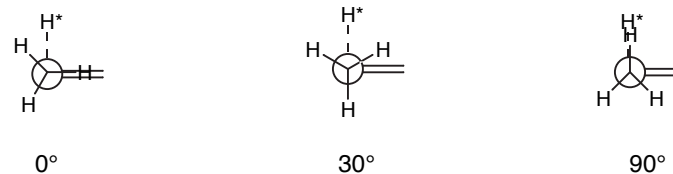
"Felkin-Like" Steric Analysis (STO-3G)



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

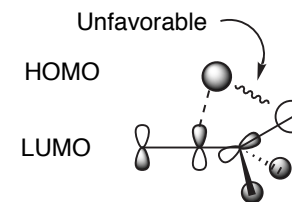
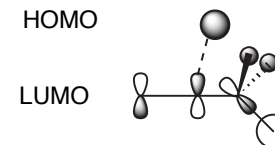
Predictions from Computational Studies

Transition state assumption: Attack angle of 90° , 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."

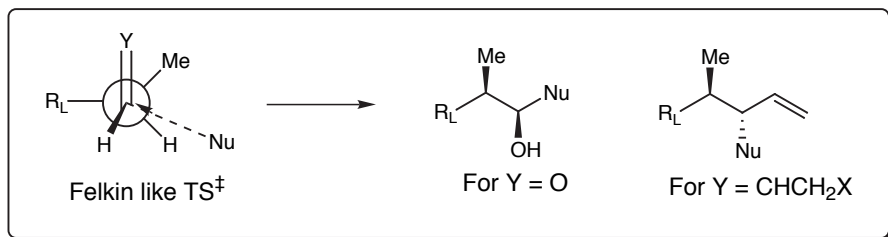


□ FMO aspects are somewhat vague.

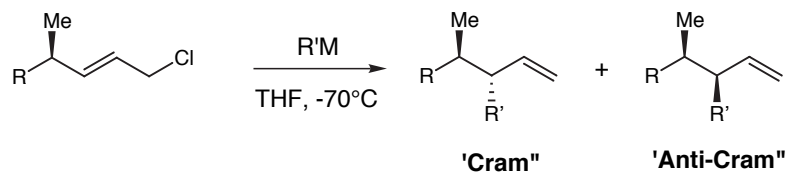
□ Avoid eclipsing interactions in the transition state.

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

The S_N2' Reaction - Alkyl Substitution



(E) - olefins



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

¹ Catalytic CuI•2LiCl added

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

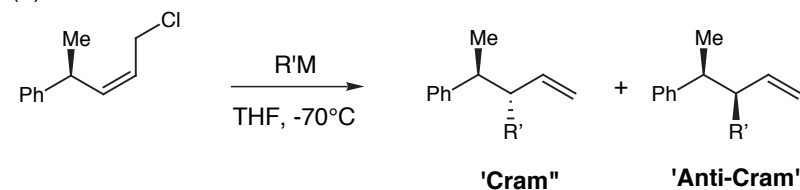
□ Added Lewis acid was required in all cases (RCu was unreactive, R₂CuLi gave only S_N2 products).

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

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

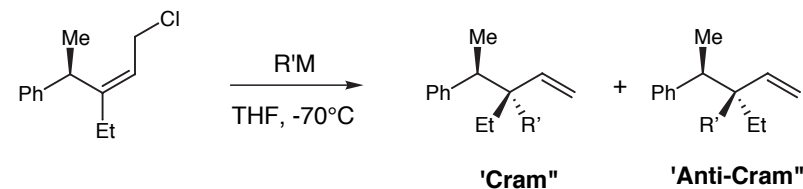
The S_N2' Reaction - Alkyl Substitution

(Z) - olefins



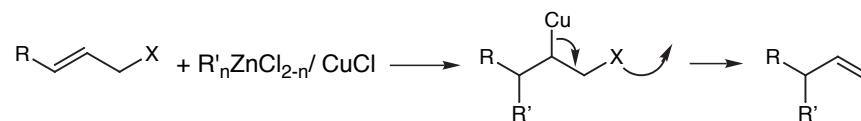
| R'M | Ratio | |
|--|-------|------|
| Bu ₂ CuLi•ZnCl ₂ | 78 | : 22 |
| Me ₂ CuLi•ZnCl ₂ | 88 | : 12 |

Ketone equivalent



| R'M | Ratio | |
|--|-------|-----|
| Bu ₂ CuLi•ZnCl ₂ | 100 | : 0 |
| Me ₂ CuLi•ZnCl ₂ | 100 | : 0 |

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



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

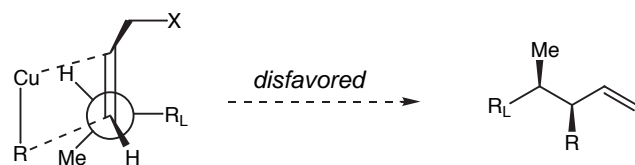
The S_N2' Reaction - Alkyl Substitution

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



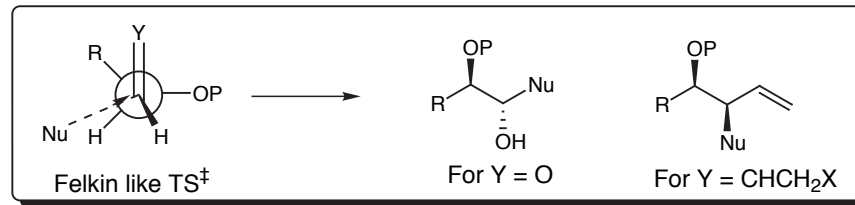
Felkin like TS^\ddagger



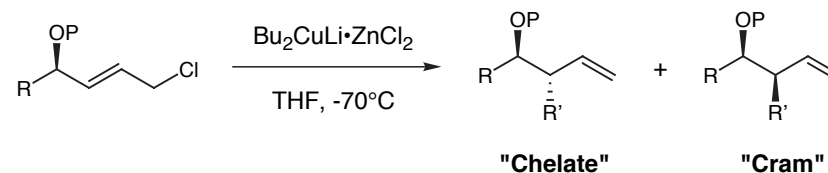
A-1,3 Strain TS^\ddagger

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

The S_N2' Reaction - Alkoxy Substitution



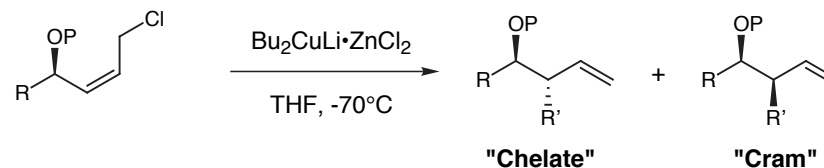
(E) olefins



| 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



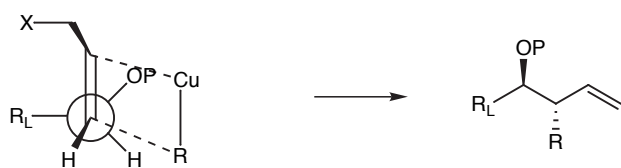
| R | P | Ratio | |
|-----|-----|-------|------|
| iPr | Bn | 90 | : 10 |
| tBu | MOM | 40 | : 60 |

- 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_N2' Reaction - Alkoxy Substitution

Proposed transition state:

(E) Olefins



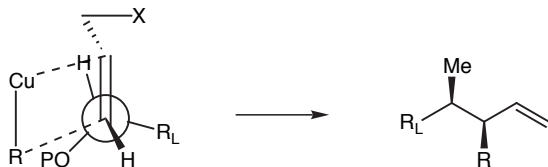
Chelate like TS^\ddagger

- No anchimeric assistance from OR (since OTIPS gives 100 : 0).
- Could be based on sterics as concluded from dialkyl cases ($OP = R_m$).
- 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

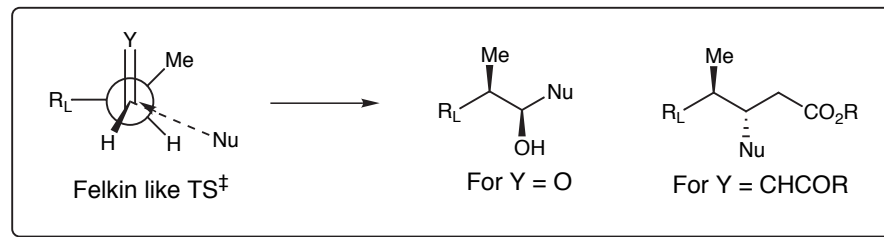


A-1,3 Strain TS^\ddagger

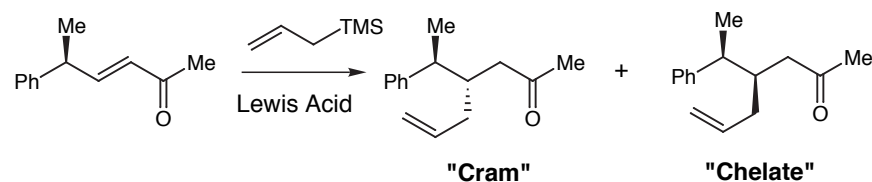
- A-1,3 Strain may diminish stereoselectivity for (Z) olefins.
- Larger R_L prefers A-1,3 model more.

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

The Michael Reaction - Alkyl Substitution

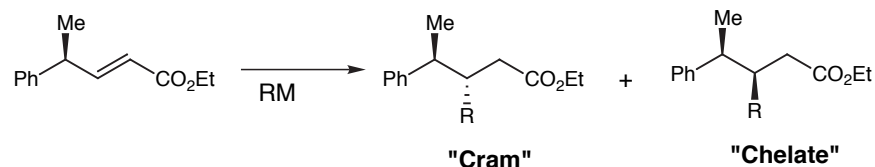


(E) Olefins



| Lewis Acid | Ratio | |
|--------------------------|-------|------|
| TMS + $TiCl_4$ | 80 | : 20 |
| TMS + $BF_3 \cdot OEt_2$ | 80 | : 20 |
| $MgBr \cdot CuBr$ | 80 | : 20 |

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

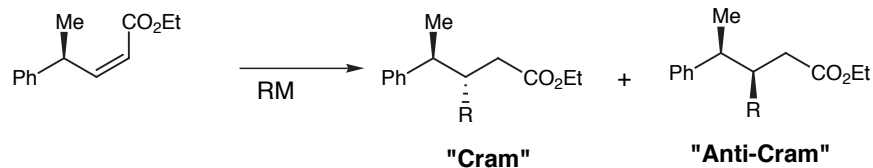


| RM | Ratio | |
|-------------------------|-------|------|
| $Bu_2CuLi \cdot BF_3$ | 70 | : 30 |
| $BuCu \cdot BF_3$ | 88 | : 12 |
| $Me_3CuLi_2 \cdot BF_3$ | 87 | : 13 |

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

The Michael Reaction - Alkyl Substitution

(Z) Olefins

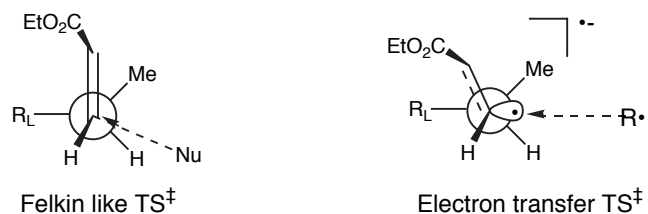


| RM | Ratio | |
|--|-------|------|
| Bu ₂ CuLi•BF ₃ | 30 | : 70 |
| BuCu•BF ₃ | 74 | : 26 |
| Me ₃ CuLi ₂ •BF ₃ | 21 | : 79 |

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

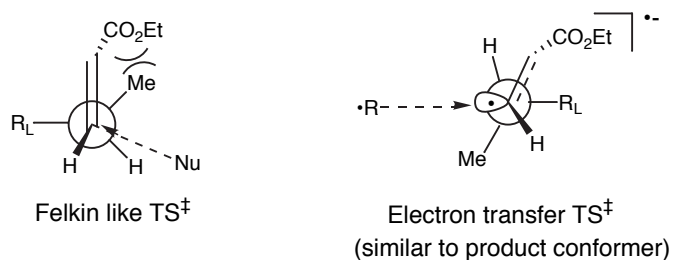
Yamamoto's hypothesis: organocopper species react as a nucleophile, cuprates via initial electron transfer, affording a semi-pyramidalized transition state.

(E) Olefins:



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

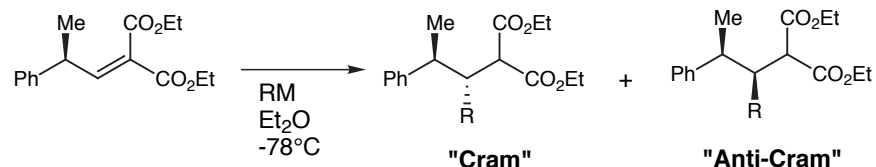
(Z) Olefins:



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

The "Michael" Reaction - Alkyl Substitution

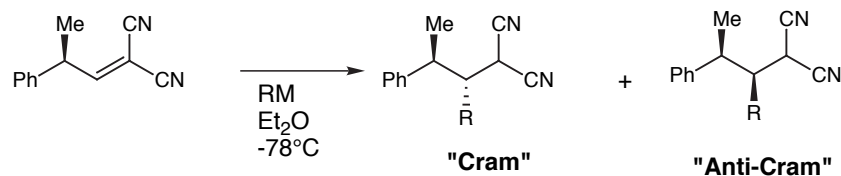
Disubstituted Olefins



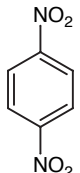
| RM | Ratio | |
|----------------------|-------|------|
| Ph ₂ CuLi | 12 | : 88 |
| Me ₂ CuLi | 32 | : 68 |
| MeCu | 84 | : 16 |

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

Disubstituted Olefins



| RM | Ratio | |
|----------------------|-------|------|
| Me ₂ CuLi | 13 | : 87 |
| MeCu | 23 | : 77 |
| MeCu | 67 | : 33 |
| Me ₂ 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.

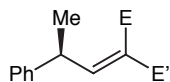
The "Michael" Reaction

Yamamoto's next generation hypothesis:

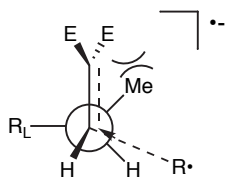
All reactions of dinitriles proceed via the electron transfer mechanism.

Substrate Reduction Potentials

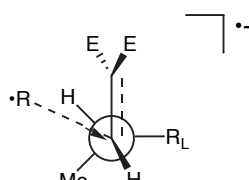
| E | E' | E_{red} vs SCE (V) |
|--------------------|--------------------|----------------------|
| CN | CN | -1.52 |
| CO ₂ Et | CN | -1.73 |
| CO ₂ Et | CO ₂ Et | >-2.0 |



Further claim: R₂CuLi is an electrophilic radical, with an attack angle < 90°.

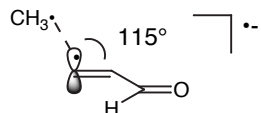


Felkin like TS[‡]
attack angle >90°



Electrophilic radical TS[‡]
attack angle <90°

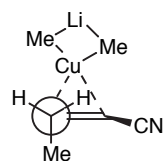
Refuted by Morokuma: calculated TS[‡] at UHF / 3-21G level:



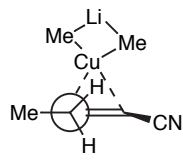
Same as for CH₃[•]

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

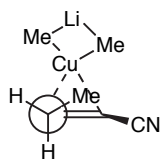
Energy of complexation: -4.63 kcal / mol



E_{rel} 0.0

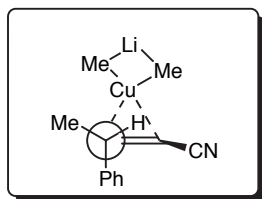


1.44



2.32

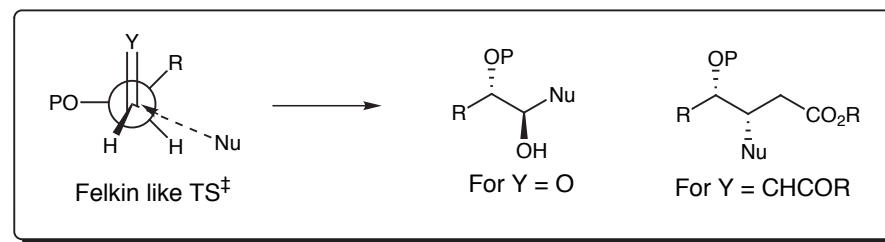
Morokuma's proposed TS[‡]



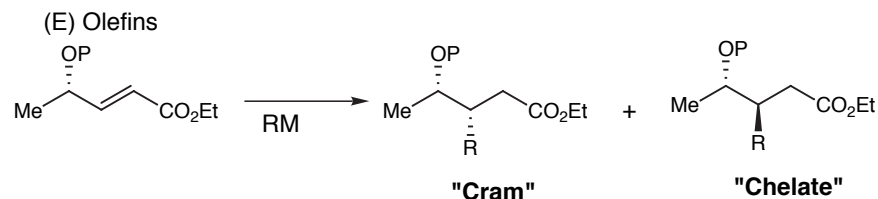
□ Why does p-DNB shut down this mechanism?

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

The Michael Reaction - Alkoxy Substitution



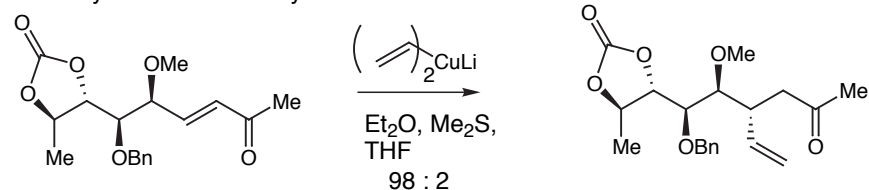
A. Alkoxy substitution:



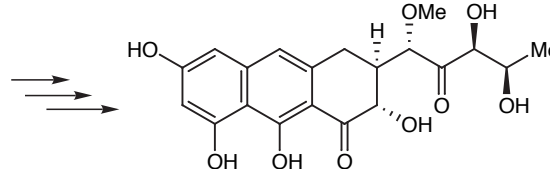
| P | RM | Ratio | |
|-----|--|-------|------|
| Bn | (2-methylallyl) ₂ CuLi | 58 | : 42 |
| Bn | MeCu•BF ₃ | 31 | : 69 |
| Bn | MeCu(CN)Li•BF ₃ | 5 | : 95 |
| Bn | BuCu•BF ₃ | 8 | : 92 |
| TBS | MeCu•BF ₃ | 32 | : 68 |
| TBS | Me ₂ CuLi•BF ₃ | 27 | : 73 |
| TBS | Me ₂ Cu(CN)Li ₂ •BF ₃ | 8 | : 92 |

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

In the synthesis of Olivomycin A

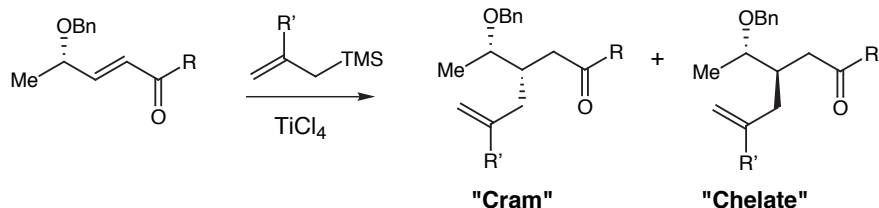


"Chelate"



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

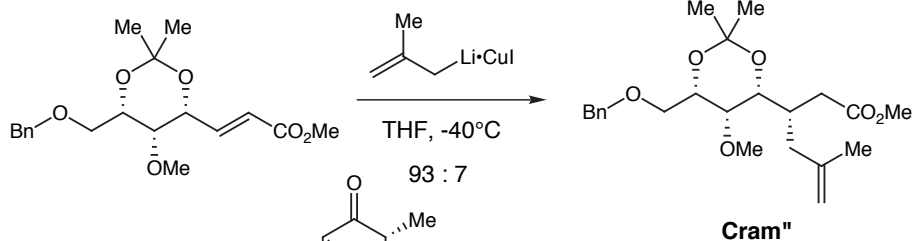
The Michael Reaction - Alkoxy Substitution



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

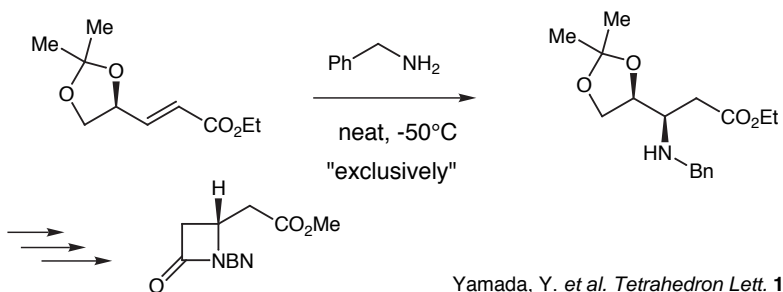
Heathcock, C. H. *et al. J. Org. Chem. Soc.* **1984**, 49, 4214.

In the synthesis of Leucomycin A₃



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

In the synthesis of β -lactams



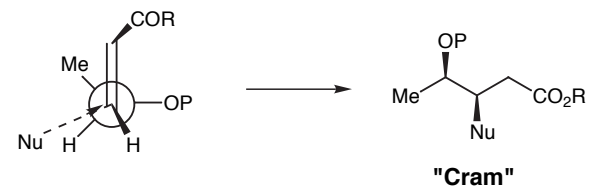
Yamada, Y. *et al. Tetrahedron Lett.* **1983**, 24, 3009.

The Michael Reaction - Alkoxy Substitution

Observations on (E) olefins

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

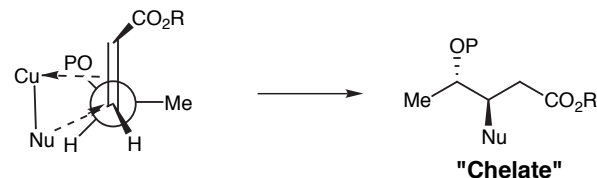
Heathcock's proposal:



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

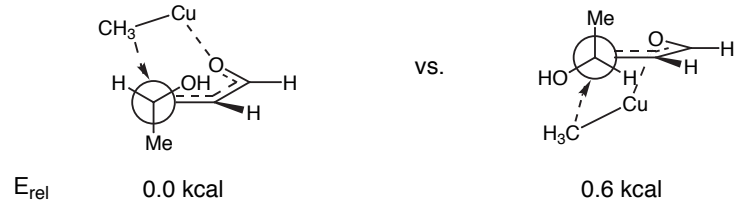
*** Note that figure 2 is incorrect in Heathcock publication, read text carefully***

Yamamoto's revised next generation proposal:



π - Complex involves electrophilic attack, governed by the "inside alkoxy effect."

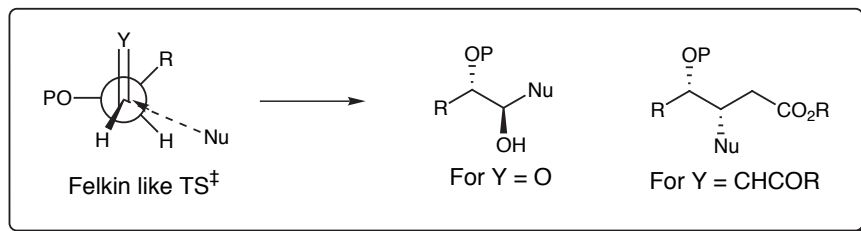
Computational support: Transition structures located at RHF / 3-21G.



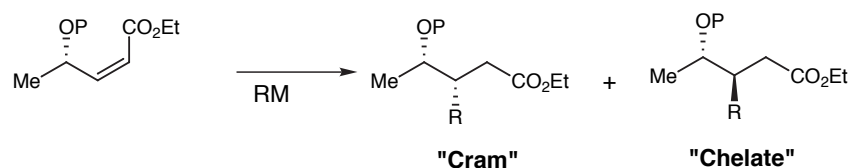
Electron donor should be antiperiplanar, electron acceptor should be out of conjugation. The two computed transition structures predict a ratio of 73 : 27 for MeCu additions at r.t., Yamamoto found 69 : 31.

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

The Michael Reaction - Alkoxy Substitution



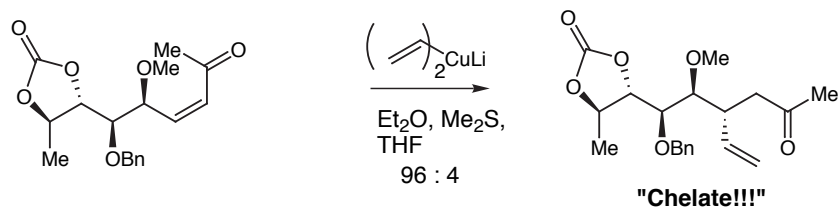
(Z) Olefins



| P | RM | Ratio | |
|-----|--|-------|------|
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| Bn | MeCu·BF ₃ | 78 | : 22 |
| Bn | MeCu(CN)Li·BF ₃ | 74 | : 26 |
| Bn | BuCu·BF ₃ | 78 | : 22 |
| TBS | MeCu·BF ₃ | 86 | : 14 |
| TBS | Me ₂ CuLi·BF ₃ | 87 | : 13 |
| TBS | Me ₂ Cu(CN)Li ₂ ·BF ₃ | 83 | : 17 |

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

In the synthesis of Olivomycin A

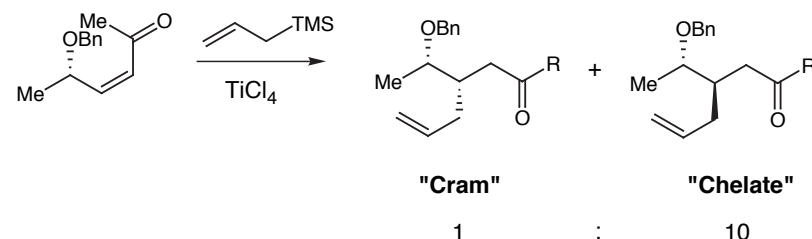


Roush, W. R. *et al J. Am. Chem. Soc.* **1989**, 111, 2984.

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

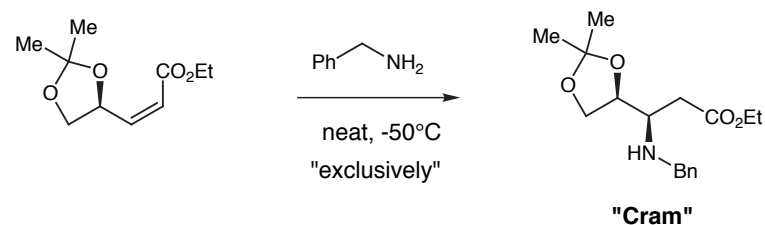
The Michael Reaction - Alkoxy Substitution

Non cuprate nucleophiles:



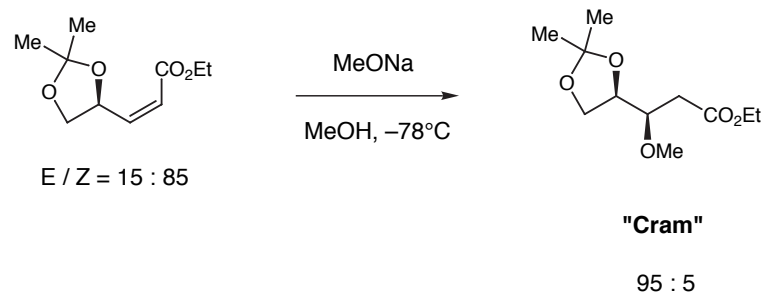
Heathcock, C. H. *et al J. Org. Chem. Soc.* **1984**, 49, 4214.

In the synthesis of β-lactams



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

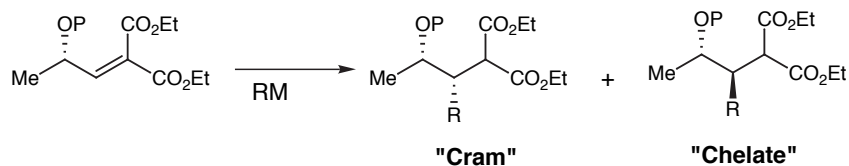
□ Heathcock observes a turnover in selectivity based on olefin geometry, Yamada does not.



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) ₂ CuLi | 90 : 10 |
| Bn | MeCu•BF ₃ | 94 : 6 |
| Bn | MeCu | 89 : 11 |
| Bn | BuCu•BF ₃ | 95 : 5 |
| TBS | MeCu•BF ₃ | 84 : 16 |
| TBS | MeCu(CN)Li | 92 : 8 |
| TBS | MeCu(CN)Li•BF ₃ | 91 : 9 |

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

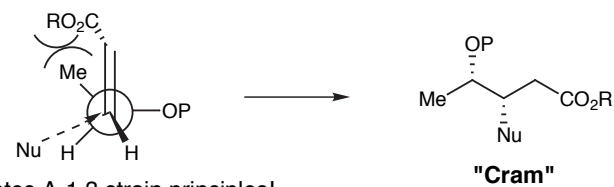
□ Same facial preference as (Z) olefins.

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.

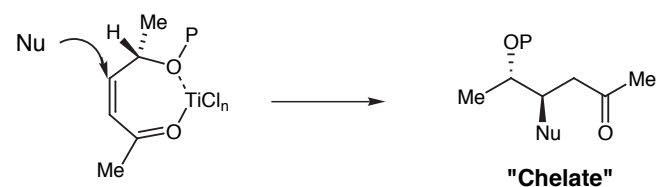
The Michael Reaction - Alkoxy Substitution

Nucleophiles without Lewis acid:

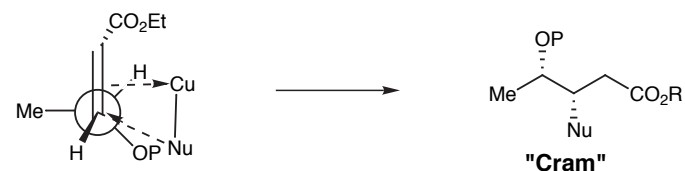


Violates A-1,3 strain principles!

Nucleophiles with Lewis acid (Heathcock proposal):

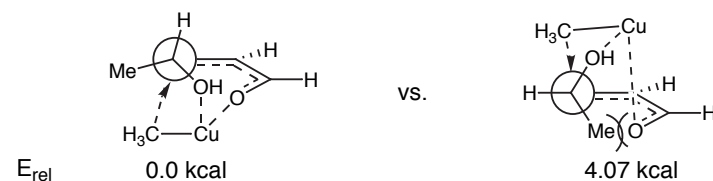


Organocuprate addition:



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

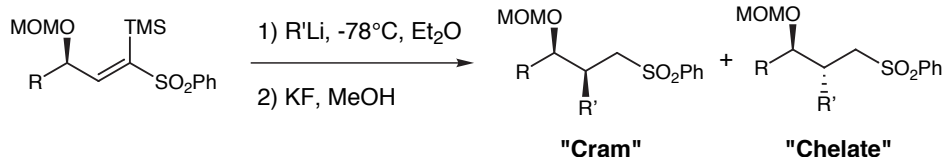
Computational support: Transition structures located at RHF / 3-21G, found same diastereofacial preference, but from a different rotamer.



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

(E) Vinyl sulfones:

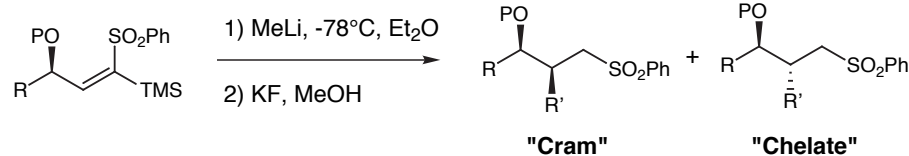
Vinyl Sulfone Additions



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

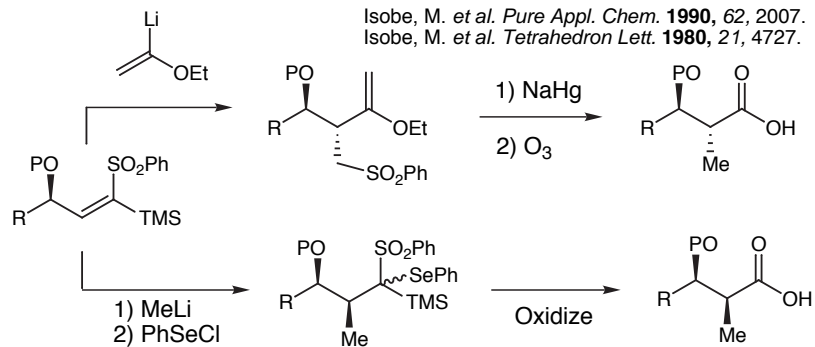
Carretero, J. C. et al. *Tetrahedron Lett.* **1991**, 32, 1385.

(Z) Vinyl sulfones:



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

Utility:

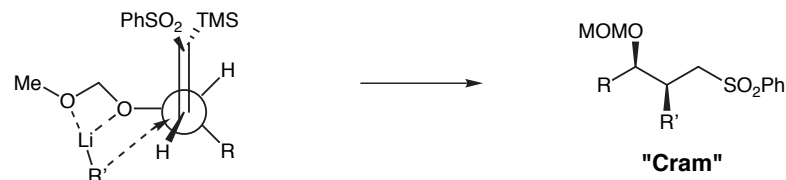


Isobe, M. et al. *Pure Appl. Chem.* **1990**, 62, 2007.
Isobe, M. et al. *Tetrahedron Lett.* **1980**, 21, 4727.

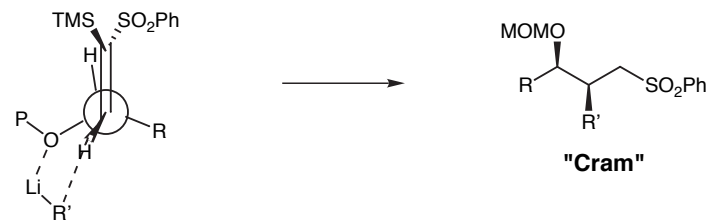
● Isobe, M. et al. *Tetrahedron*, **1986**, 42, 2863.

Vinyl Sulfone Additions

Carretero's proposal:



Isobe's proposal:



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

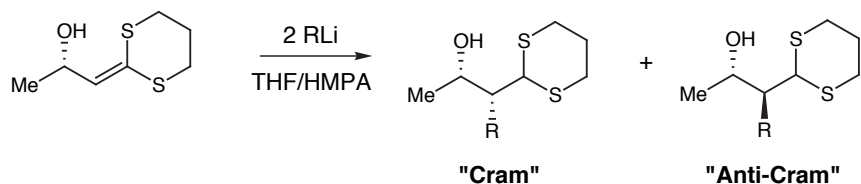
□ Same diastereofacial selectivity is observed with P = TBS!

Asymmetric variant:

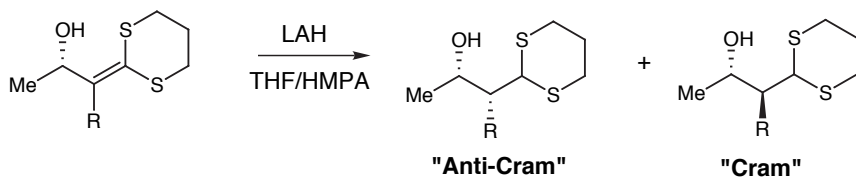


Isobe, M. et al. *Tetrahedron Lett.* **1988**, 29, 4773.

Dithioketene Acetal Additions

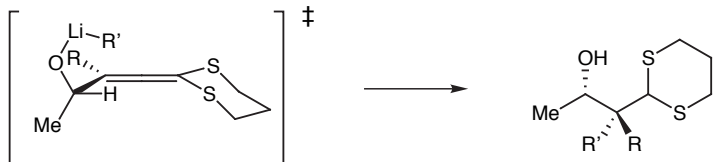


| R | Ratio | | |
|-----|-------|---|---|
| Me | 100 | : | 0 |
| Et | 100 | : | 0 |
| nBu | 98 | : | 2 |
| Ph | 100 | : | 0 |



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

Transition state proposal:

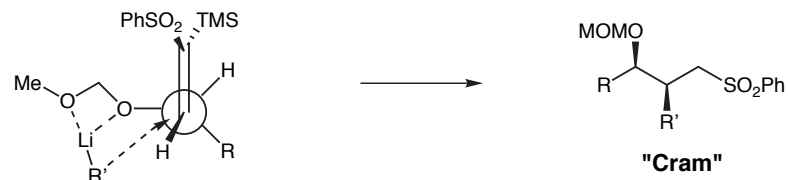


- Governed by A-1,3 interactions with directed nucleophilic attack.
- OTBS protected substrate decomposed, the role of chelation was not further tested.

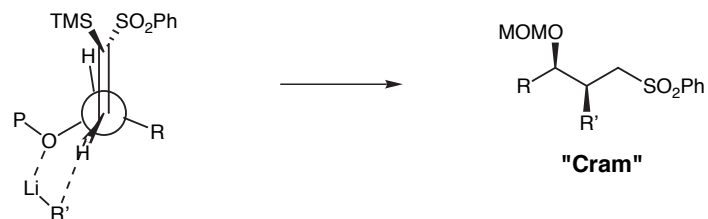
Fujisawa, T. *et al. Tetrahedron Lett.* **1989**, 30, 977.

Vinyl Sulfone Additions

Carretero's proposal:

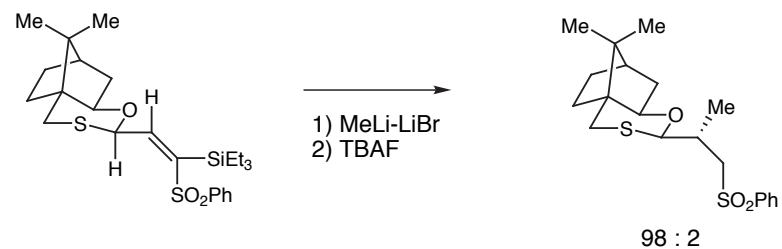


Isobe's proposal:



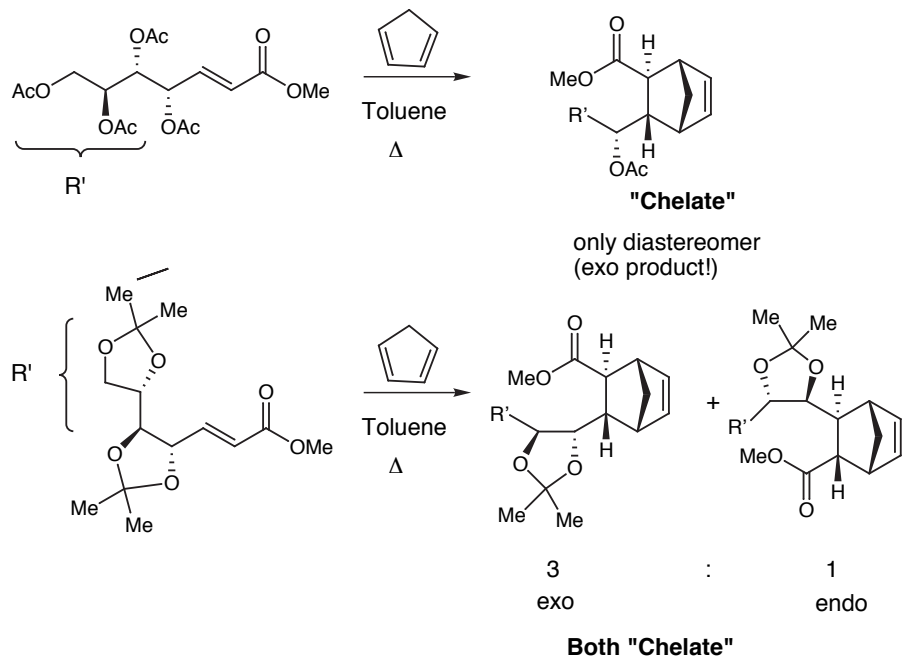
- Both are similar, except Isobe recognizes the importance of A-1,3 strain.
- Same diastereofacial selectivity is observed with P = TBS!

Asymmetric variant:



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

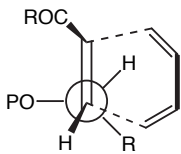
Diels Alder Reactions - Alkoxy Substitution



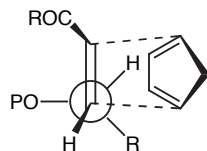
Horton, D. *et al. J. Chem. Soc. Chem. Comm.* **1981**, 88.

□ Anti Cram dienophile diastereoface is preferred in each case.

Similar proposal for each:



Franck

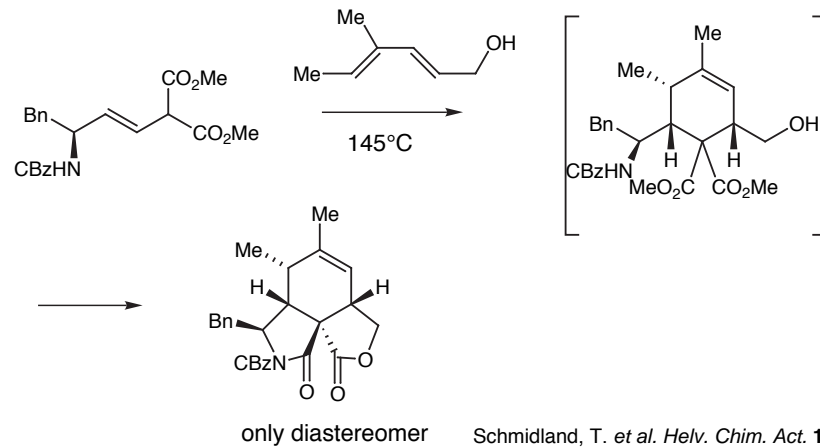


Horton

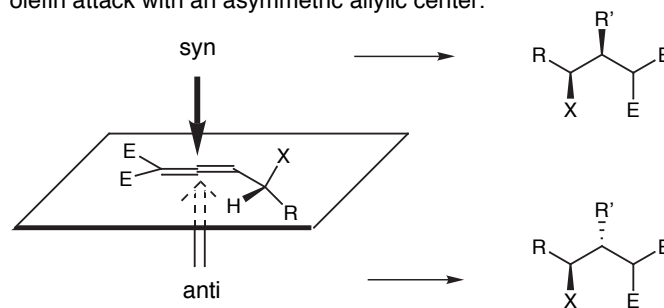
(no explanation for exo preference)

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.



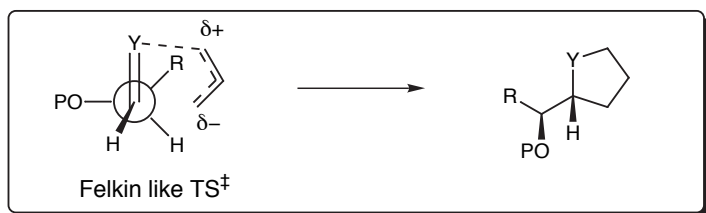
| X | Electrophile | Nucleophile |
|---------------|--------------|-------------|
| Electron Rich | Syn | Anti |
| Electron Poor | Anti | Syn |

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

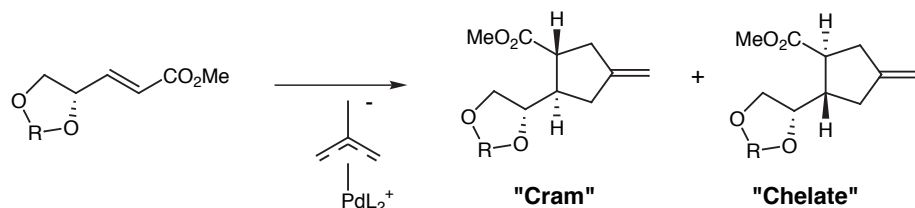
□ Makes no account for (E) vs (Z) olefins.

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

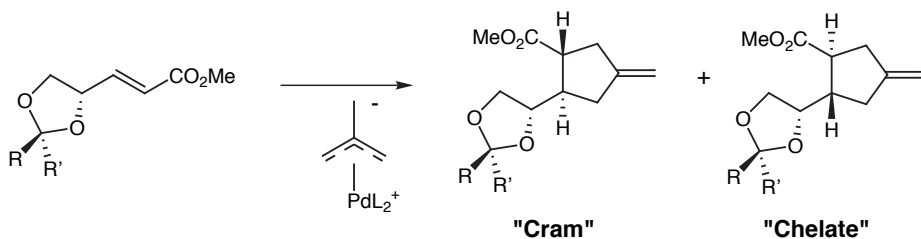
[3 + 2] Additions



A. Palladium catalyzed [3+2]



| R | Ratio | |
|----------------------------------|-------|------|
| C(CH ₃) ₂ | 75 | : 25 |
| Si(tBu) ₂ | 88 | : 12 |



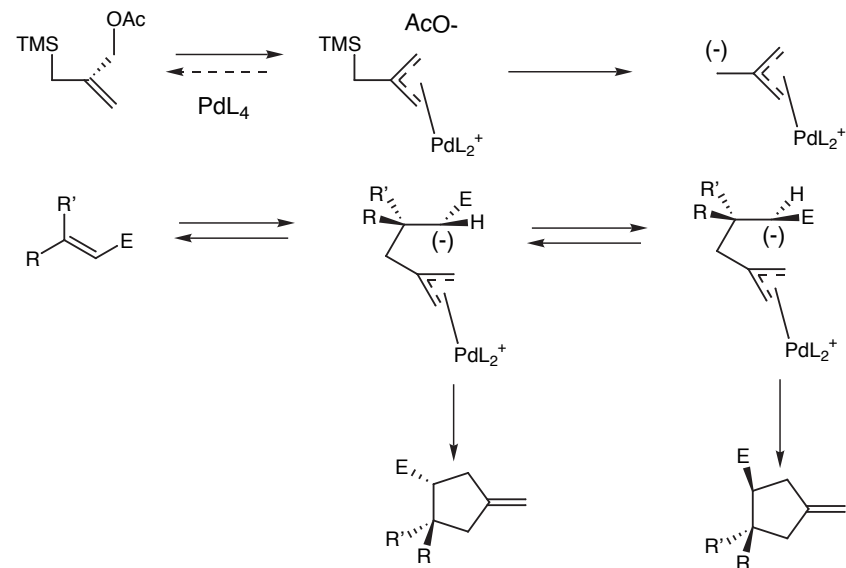
| R | R' | Ratio | |
|-----|-----|-------|------|
| BOM | H | 72 | : 28 |
| H | BOM | 72 | : 28 |

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

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

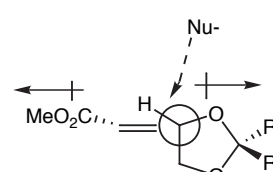
[3 + 2] Additions

Proposed Mechanism: A genuine nucleophilic attack.

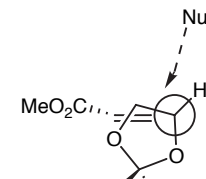


□ Reactions of (E) olefins are stereospecific, (Z) olefins are not (with recovery of isomerized starting material).

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



Dipole Model



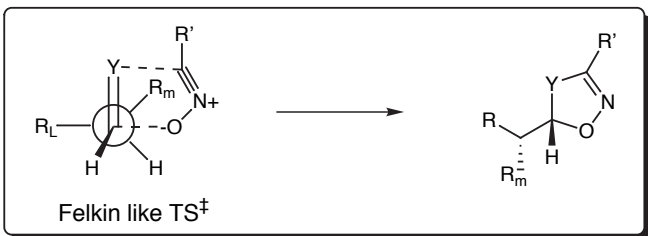
Felkin Model

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

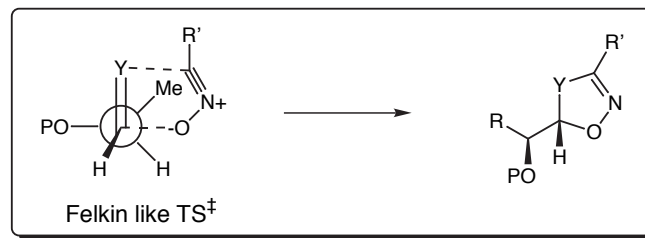
□ Claims silicon acetone provides higher dipole, resulting in higher stereoselectivity.

□ Dipole model is similar to Kahn / Hehre proposal.

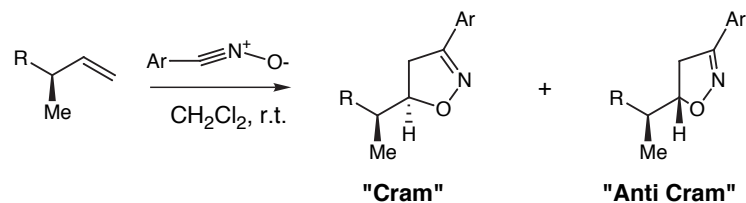
[3 + 2] Additions - Alkyl Substitution



[3 + 2] Additions - Alkoxy Substitution



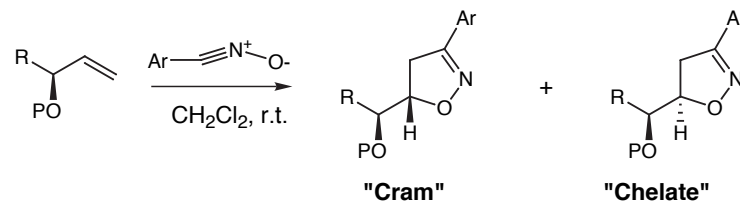
B. Nitrile Oxide [3+2]



| 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.

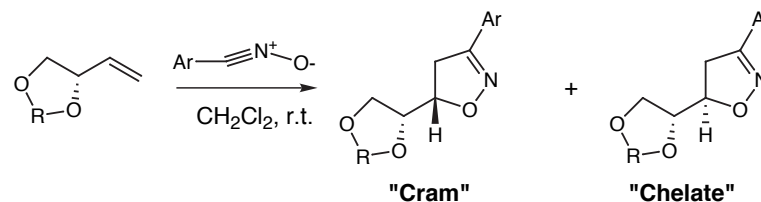
□ Both authors invoke the Felkin like transition state above.



| 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



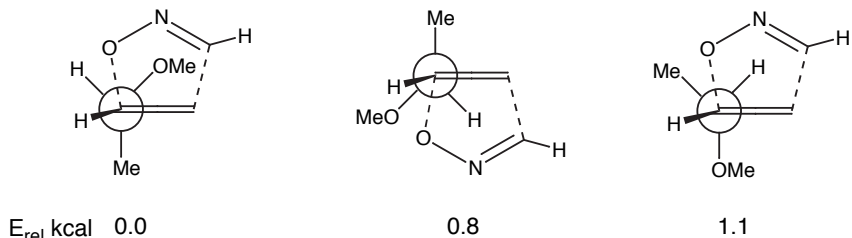
| R | Ratio | |
|--------------------|-------|------|
| C(Me) ₂ | 15 | : 85 |
| Chex | 19 | : 81 |
| C=O | 18 | : 82 |

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.

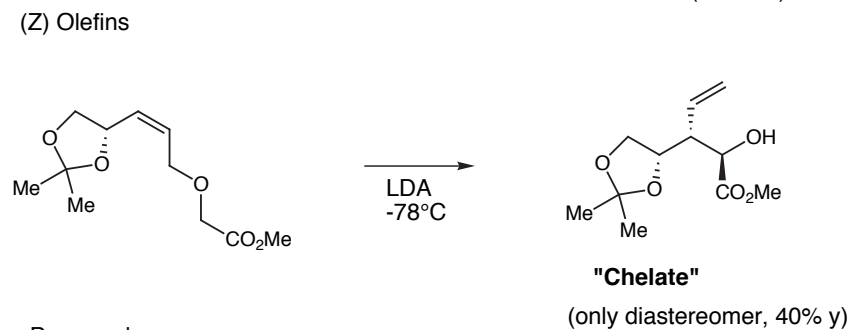
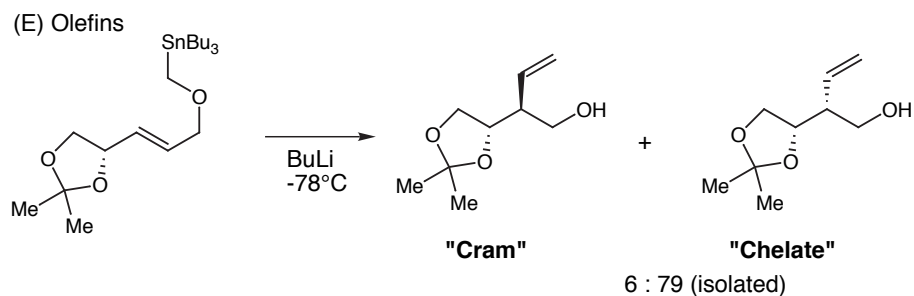
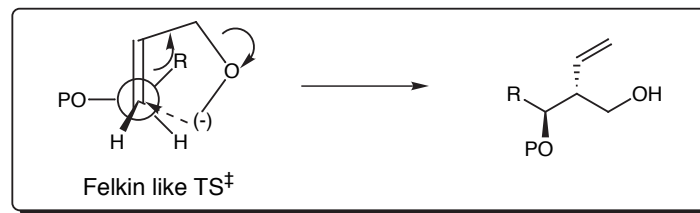
Computational evidence: Base transition structure (propene) was found at the 3-21G level, then the substituted rotamers were minimized by MM2, with single point energy calculations at STO-3G.



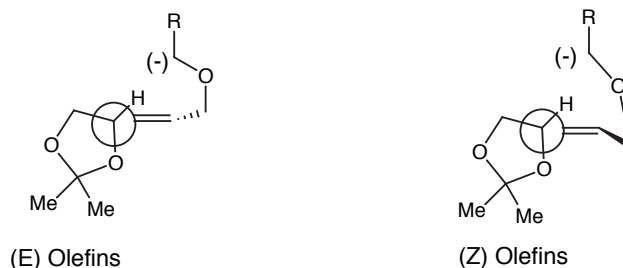
☐ Predicts Anti-Cram / Cram ratio of 68:32 at room temperature (observed 64:36).

☐ Larger R group affords higher diastereoselectivity.

2,3-Wittig Rearrangement



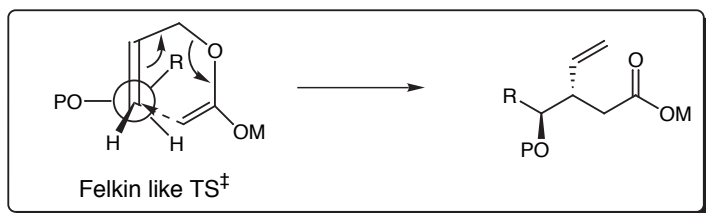
Proposed:



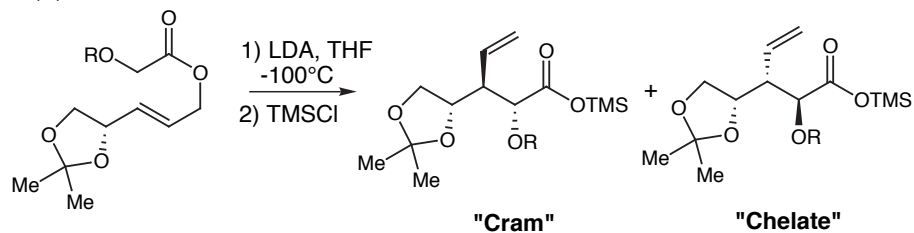
☐ Violates the Kahn / Hehre proposal.

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

Claisen Rearrangements

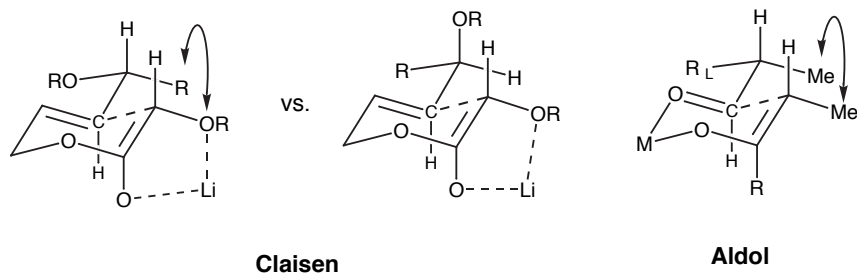


(E) Olefins



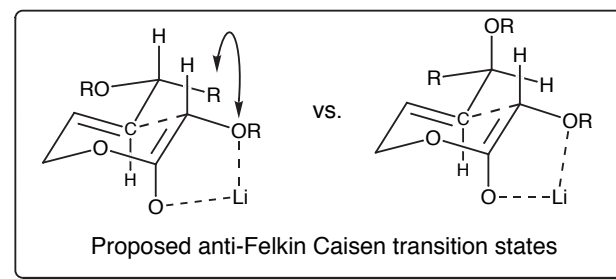
| R | Ratio | |
|-----|-------|------|
| Me | 19 | : 81 |
| MOM | 20 | : 80 |
| BOM | 19 | : 81 |

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

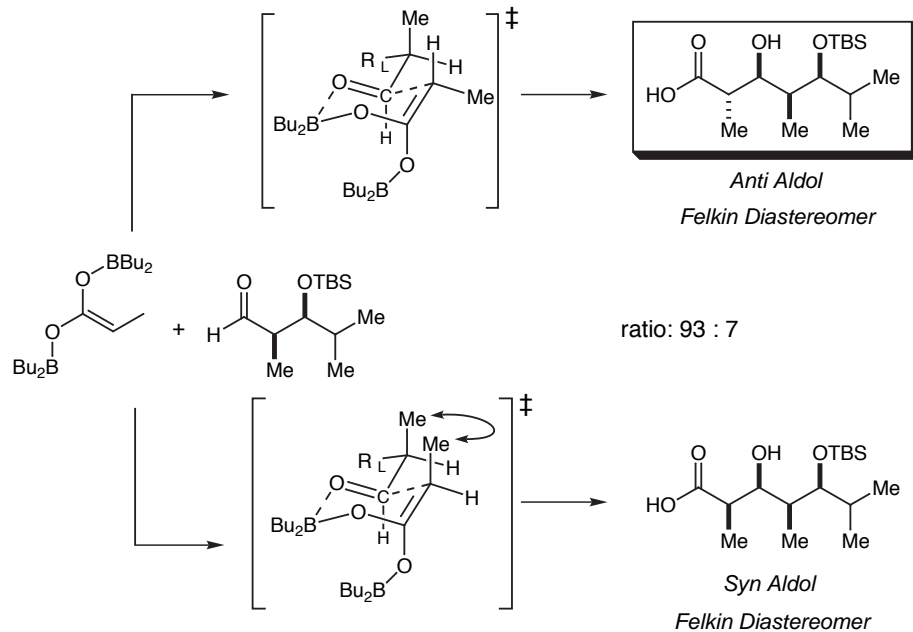


- ❑ The Claisen (Z) enolate is analogous to the aldol (E) enolate.
- ❑ This [3,3] sigmatropic rearrangement is isoelectronic with the aldol reaction.
- ❑ The inside alkoxy transition state avoids the syn-pentane interaction, but should only apply to electrophilic additions.
- ❑ Violates Kahn / Hehre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

Claisen Rearrangements - The Aldol Analogy



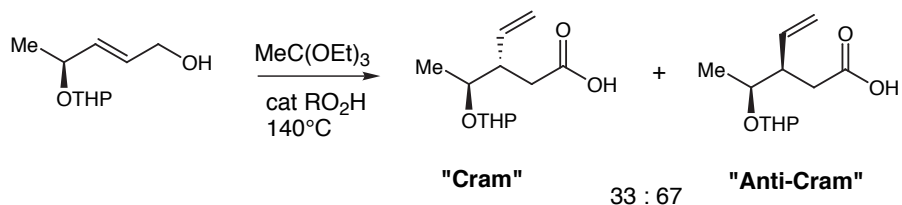
- ❑ Geometrically and electronically analogous to the acid diolate aldol reaction, which exhibits an exceptional Felkin diastereo-preference.



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

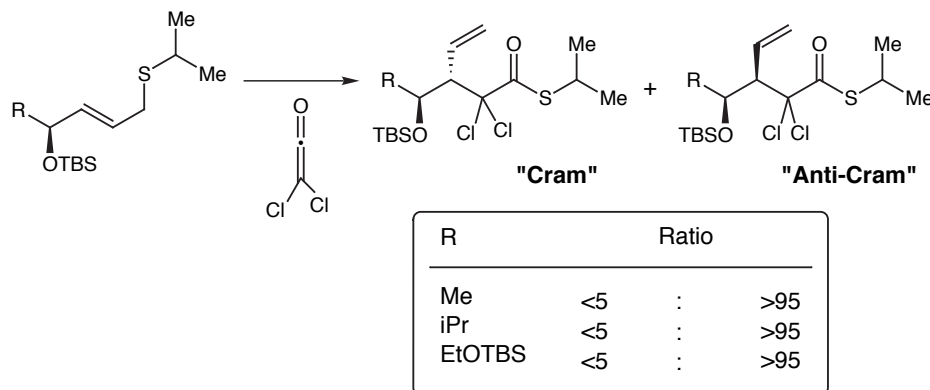
Claisen Rearrangements

(E) Olefin, methyl ketone enolate

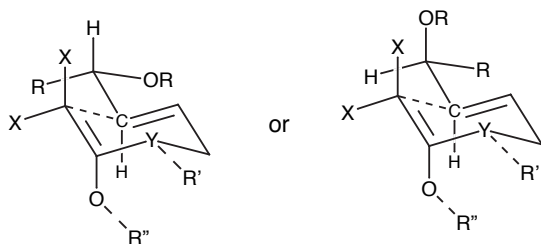


Takano, S. et al. *Tetrahedron Lett.* **1985**, 26, 865

Thioester Claisen



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

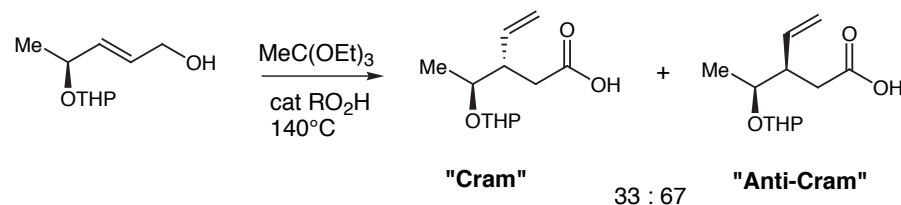


Case 1: X=H, Y=O, R'=Et
Case 2: X=Cl, Y=S, R'=iPr

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

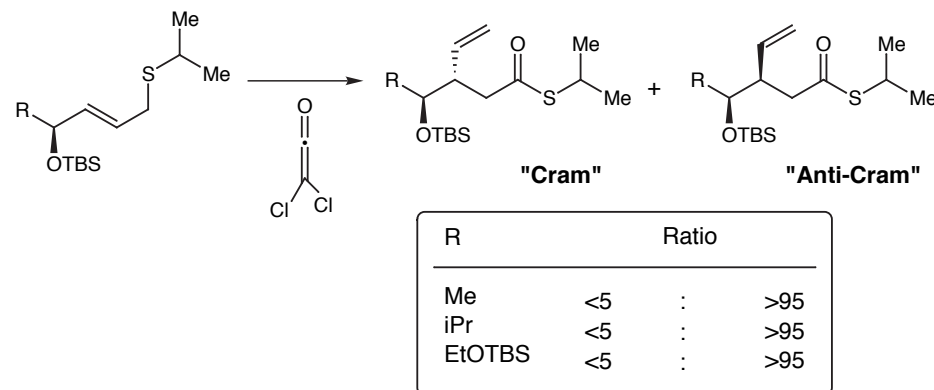
Claisen Rearrangements

(E) Olefin, methyl ketone enolate

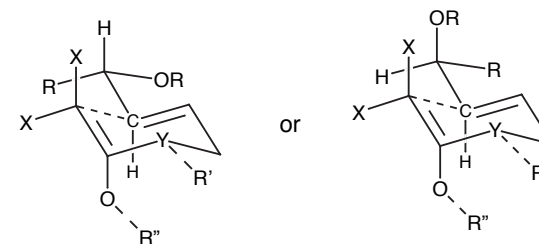


Takano, S. et al. *Tetrahedron Lett.* **1985**, 26, 865

Thioester Claisen



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



Case 1: X=H, Y=O, R'=Et
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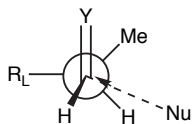
Conclusions???

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

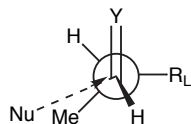
However, application of Cram's rules in the following way predicts the favored product for everything except Michael additions:

- ☞ 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"

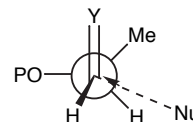
[3 + 2] Nitron additions (E)

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

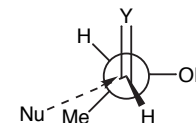
☐ In no case does attack of the preferred A-1,3 strain conformer predominate.

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"

S_N2' additions (E) and (Z)

Diels Alder reactions

[3 + 2] Pd - C(CH₂)₃ additions

[3 + 2] Nitron additions

[2,3] Wittig rearrangements

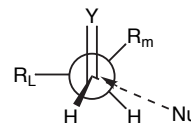
Claisen rearrangements

Michael additions (Z)
"charge transfer"

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

☐ All cycloadditions follow the Cram Chelate rule.

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_m for alkoxy substituted olefins.

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

● J. Leighton, private communication.