Is There a "Crams'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 (●).

Not Covered:
OsO₄ Dihydroxylations ([2 + 2] or [3 + 2] mechanism), reviewed recently. See ● Barrow, J. Seminar Notes, 1993, 235.

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, dithioketene acetals).
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)

-Joe Duffy
1/4/1994
Predictions from Computational Studies

Transition States (3-21G)

Ethylene vs. formaldehyde for CH₃Li addition.

- Ethylene has a shorter Nu-C bond length (less exothermic, later TS‡).
- Potentially higher diastereoselectivity for olefins than carbonyls.

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

| Structure | H°rel | 1.03 | 2.36 |


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.


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).

HOMO
LUMO

0° 30° 90°
The SN2' Reaction - Alkyl Substitution

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

Ketone equivalent

<table>
<thead>
<tr>
<th>R</th>
<th>R'M</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>Bu₂CuLi·ZnCl₂</td>
<td>78 : 22</td>
</tr>
<tr>
<td>Me₂CuLi·ZnCl₂</td>
<td>88 : 12</td>
<td></td>
</tr>
</tbody>
</table>

Added Lewis acid was required in all cases (RCu was unreactive, R₂CuLi gave only SN₂ products).

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

The \( S_{N2}' \) Reaction - Alkyl Substitution

Proposed transition state:

(E) Olefins

\[
\begin{align*}
\text{Felkin like TS}^\dagger & \quad \xrightarrow{\text{favored}} \\
\text{Anti Felkin like TS}^\dagger & \quad \xrightarrow{\text{distavored}} \\
\end{align*}
\]

Similar 4-centered TS\(^\dagger\) for Sia\(_2\)BH reduction of ketones favors anti-Cram product (opposite steric contraints on reagent).


(Z) Olefins

\[
\begin{align*}
\text{Felkin like TS}^\dagger & \quad \xrightarrow{\text{favored}} \\
\text{A-1,3 Strain TS}^\dagger & \quad \xrightarrow{\text{distavored}} \\
\end{align*}
\]

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

The \( S_{N2}' \) Reaction - Alkoxy Substitution

Felkin like TS\(^\dagger\)

\[
\begin{align*}
\text{For } Y = O & \quad \text{For } Y = \text{CHCH}_2X
\end{align*}
\]

Same ratios observed using \( \text{Bu}_2\text{Zn} / \text{cat CuBr-Me}_2\text{S} \), \( \text{BuCu-BF}_3 \), \( \text{BuTi(OiPr)}_3 / \text{cat CuBr-Me}_2\text{S} \), and \( \text{Bu}_2\text{Zn}+2\text{LiCl} / 2\text{ HMPA (no copper)} \).

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‡

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

(Z) Olefins

A-1,3 Strain TS‡

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


The Michael Reaction - Alkyl Substitution

(Felkin like TS‡)

For Y = O

For Y = CHCOR

(E) Olefins

"Cram"

"Chelate"

Lewis Acid

<table>
<thead>
<tr>
<th>Lewis Acid</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMS + TiCl₄</td>
<td>80 : 20</td>
</tr>
<tr>
<td>TMS + BF₃•OEt₂</td>
<td>80 : 20</td>
</tr>
<tr>
<td>MgBr•CuBr</td>
<td>80 : 20</td>
</tr>
</tbody>
</table>


(Z) Olefins

"Cram"

"Chelate"

<table>
<thead>
<tr>
<th>RM</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bu₂CuLi•BF₃</td>
<td>70 : 30</td>
</tr>
<tr>
<td>BuCu•BF₃</td>
<td>88 : 12</td>
</tr>
<tr>
<td>Me₂CuL₂•BF₃</td>
<td>87 : 13</td>
</tr>
</tbody>
</table>

**The Michael Reaction - Alkyl Substitution**

(Z) Olefins:

\[
\text{Bu}_2\text{CuLi} \rightarrow \text{BuCuLi} \rightarrow \text{MeCu}
\]

<table>
<thead>
<tr>
<th>RM</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bu\textsubscript{2}CuLi + BF\textsubscript{3}</td>
<td>30 : 70</td>
</tr>
<tr>
<td>BuCuLi + BF\textsubscript{3}</td>
<td>74 : 26</td>
</tr>
<tr>
<td>Me\textsubscript{2}CuLi + BF\textsubscript{3}</td>
<td>21 : 79</td>
</tr>
</tbody>
</table>

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

(E) Olefins:

"Felkin-like TS" 

"Electron transfer TS" 

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

(Z) Olefins:

"Felkin-like TS" 

"Electron transfer TS" (similar to product conformer)

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

**The "Michael" Reaction - Alkyl Substitution**

Disubstituted Olefins

\[
\text{Ph}_2\text{CuLi} \rightarrow \text{BuCuLi} \rightarrow \text{MeCu}
\]

<table>
<thead>
<tr>
<th>RM</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph\textsubscript{2}CuLi</td>
<td>12 : 88</td>
</tr>
<tr>
<td>Me\textsubscript{2}CuLi</td>
<td>32 : 68</td>
</tr>
<tr>
<td>MeCu</td>
<td>84 : 16</td>
</tr>
</tbody>
</table>

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

Disubstituted Olefins

\[
\text{PhCO}_2\text{Et} \rightarrow \text{MeCN}
\]

<table>
<thead>
<tr>
<th>RM</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me\textsubscript{2}CuLi</td>
<td>13 : 87</td>
</tr>
<tr>
<td>MeCu</td>
<td>23 : 77</td>
</tr>
<tr>
<td>MeCu</td>
<td>67 : 33</td>
</tr>
<tr>
<td>Me\textsubscript{2}CuLi</td>
<td>67 : 33</td>
</tr>
<tr>
<td>nBu\textsuperscript{•}Chex\textsuperscript{•}</td>
<td>83 : 17</td>
</tr>
<tr>
<td>Chex\textsuperscript{•}</td>
<td>87 : 13</td>
</tr>
<tr>
<td>tBu\textsuperscript{•}</td>
<td>93 : 7</td>
</tr>
</tbody>
</table>

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**

<table>
<thead>
<tr>
<th>E</th>
<th>E'</th>
<th>(E_{\text{red}}) vs SCE (V)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CN</td>
<td>CN</td>
<td>-1.52</td>
</tr>
<tr>
<td>CO(_2)Et</td>
<td>CN</td>
<td>-1.73</td>
</tr>
<tr>
<td>CO(_2)Et</td>
<td>CO(_2)Et</td>
<td>&gt;-2.0</td>
</tr>
</tbody>
</table>

Further claim: \(\text{R}_2\text{CuLi}\) is an electrophilic radical, with an attack angle < 90°.

Refuted by Morokuma: calculated TS\(^\dagger\) at UHF / 3-21G level:

\[
\text{CH}_3^+ \quad 115°
\]

Energy of complexation: -4.63 kcal/mol

Morokuma's proposed TS\(^\dagger\)

\[ \text{E}_{\text{rel}} 0.0 \]

\[ \text{E}_{\text{rel}} 1.44 \]

\[ \text{E}_{\text{rel}} 2.32 \]

Why does p-DNB shut down this mechanism?

---

**The Michael Reaction - Alkoxy Substitution**

A. Alkoxy substitution:

(E) Olefins

\[
\text{Me}\text{--}\text{CO}_2\text{Et} \rightarrow \text{Me}\text{--}\text{CO}_2\text{Et} + \text{Me}\text{--}\text{CO}_2\text{Et}
\]

"Cram" "Chelate"

<table>
<thead>
<tr>
<th>P</th>
<th>RM</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bn</td>
<td>(2-methallyl)(_2)CuLi</td>
<td>58 : 42</td>
</tr>
<tr>
<td>Bn</td>
<td>MeCu-BF(_3)</td>
<td>31 : 69</td>
</tr>
<tr>
<td>Bn</td>
<td>MeCu(CN)Li-BF(_3)</td>
<td>5 : 95</td>
</tr>
<tr>
<td>Bn</td>
<td>BuCu-BF(_3)</td>
<td>8 : 92</td>
</tr>
<tr>
<td>TBS</td>
<td>MeCu-BF(_3)</td>
<td>32 : 68</td>
</tr>
<tr>
<td>TBS</td>
<td>MeCu(BF(_3))</td>
<td>27 : 73</td>
</tr>
<tr>
<td>TBS</td>
<td>Me(_2)CuLi-BF(_3)</td>
<td>8 : 92</td>
</tr>
</tbody>
</table>


In the synthesis of Olivomycin A

\[
\text{Me} \quad \text{Bn} \quad \text{Me} \quad \text{Et}_2\text{O, Me}_2\text{S, THF}
\]

98 : 2

"Chelate"


---

The Michael Reaction - Alkoxy Substitution

**Chelate**

\[
\begin{align*}
\text{Me-}\text{CH=CH-CO-O}_{\text{Bn}} & \quad \text{R} \\
\text{R'} & \quad \text{TMS} \\
\text{TiCl}_4 & \quad \text{Me-}\text{CH=CH-CO-O}_{\text{Bn}} + \text{Me-}\text{CH=CH-CO-O}_{\text{Bn}}
\end{align*}
\]

**Cram**

<table>
<thead>
<tr>
<th>R</th>
<th>R'</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>H</td>
<td>88 : 12</td>
</tr>
<tr>
<td>Me</td>
<td>Me</td>
<td>80 : 20</td>
</tr>
<tr>
<td>Ph</td>
<td>H</td>
<td>89 : 11</td>
</tr>
</tbody>
</table>


In the synthesis of Leucomycin A₃

\[
\begin{align*}
\text{Bn-}\text{O}_{\text{Me}}-\text{CH=CH-CO}_{\text{Me}}_{\text{Me}} & \quad \text{R} \\
\text{O}_{\text{Me}} & \quad \text{TMS} \\
\text{Li-CuI} & \quad \text{Bn-}\text{O}_{\text{Me}}-\text{CH=CH-CO}_{\text{Me}}_{\text{Me}}
\end{align*}
\]

93 : 7


In the synthesis of β-lactams

\[
\begin{align*}
\text{Me-}\text{O}_{\text{Me}}-\text{CH=CH-CO}_{\text{Et}} & \quad \text{Ph} \\
\text{NH}_2 & \quad \text{R} \\
\text{neat, -50°C} & \quad \text{Me-}\text{O}_{\text{Me}}-\text{CH=CH-CO}_{\text{Et}}
\end{align*}
\]

*exclusively*


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.

\[
\begin{align*}
\text{E}_{\text{rel}} & \quad 0.0 \text{ kcal} \\
0.6 \text{ kcal} & \quad \text{vs.}
\end{align*}
\]

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.

**The Michael Reaction - Alkoxy Substitution**

Felkin like TS

(Z) Olefins

In the synthesis of 20/22

```
BuCu•BF3
MeCu•BF3
MeCu•BF3
Me2CuLi•BF3
Me2CuLi•BF3
```

**Non cuprate nucleophiles:**


In the synthesis of β-lactams


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

In the synthesis of Olivomycin A


- Yamamoto observes a turnover in selectivity based on olefin geometry, Roush does not!
**The Michael Reaction - Alkoxy Substitution**

**Bis-activated Olefins**

\[
\text{Me}^\text{CO}_2\text{Et} \quad \rightarrow \quad \text{Me}^\text{CO}_2\text{Et} + \text{Me}^\text{CO}_2\text{Et}
\]

"Cram" "Chelate"

<table>
<thead>
<tr>
<th>P</th>
<th>RM</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bn</td>
<td>(2-methallyl)_2CuLi</td>
<td>90 : 10</td>
</tr>
<tr>
<td>Bn</td>
<td>MeCu•BF(_3)</td>
<td>94 : 6</td>
</tr>
<tr>
<td>Bn</td>
<td>MeCu</td>
<td>89 : 11</td>
</tr>
<tr>
<td>Bn</td>
<td>BuCu•BF(_3)</td>
<td>95 : 5</td>
</tr>
<tr>
<td>TBS</td>
<td>MeCu•BF(_3)</td>
<td>84 : 16</td>
</tr>
<tr>
<td>TBS</td>
<td>MeCu(CN)Li</td>
<td>92 : 8</td>
</tr>
<tr>
<td>TBS</td>
<td>MeCu(CN)Li•BF(_3)</td>
<td>91 : 9</td>
</tr>
</tbody>
</table>

- Same facial preference as (Z) 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:**

"Cram" "Chelate"

Violates A-1,3 strain principles!

**Nucleophiles with Lewis acid (Heathcock proposal):**

"Chelate" "Cram"

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.

\[
\Delta E_{rel} \quad 0.0 \text{ kcal} \quad \text{vs.} \quad 4.07 \text{ kcal}
\]

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

---


Vinyl Sulfone Additions

**Carretero's proposal:**

<table>
<thead>
<tr>
<th>R</th>
<th>R'</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>Me</td>
<td>96 : 4</td>
</tr>
<tr>
<td>Me</td>
<td>tBu</td>
<td>&gt;98 : 2</td>
</tr>
<tr>
<td>iPr</td>
<td>Me</td>
<td>&gt;98 : 2</td>
</tr>
<tr>
<td>iPr</td>
<td>tBu</td>
<td>&gt;98 : 2</td>
</tr>
</tbody>
</table>

**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:**


CNO 11.1 1/12/94  11:10 AM
**Dithioketene Acetal Additions**

\[
\text{Me}^\text{Me} \quad \text{OH} \quad \text{S} \quad \text{S} \quad \text{THF/HMPA} \quad \text{2 RLi} \quad \rightarrow \quad \begin{array}{c}
\text{Me}^\text{Me} \quad \text{OH} \quad \text{S} \quad \text{S} \\
\text{Me}^\text{Me} \quad \text{OH} \quad \text{S} \quad \text{S}
\end{array}
\]

<table>
<thead>
<tr>
<th>R</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>100</td>
</tr>
<tr>
<td>Et</td>
<td>100</td>
</tr>
<tr>
<td>nBu</td>
<td>98</td>
</tr>
<tr>
<td>Ph</td>
<td>100</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>R</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>1</td>
</tr>
<tr>
<td>Et</td>
<td>4</td>
</tr>
<tr>
<td>nBu</td>
<td>1</td>
</tr>
<tr>
<td>Ph</td>
<td>0</td>
</tr>
</tbody>
</table>

**Vinyl Sulfone Additions**

Carretero's proposal:

\[
\text{Me} \quad \text{O} \quad \text{O} \quad \text{H} \quad \text{R} \quad \text{Li} \quad \text{H} \quad \text{R}
\]

Isobe's proposal:

\[
\text{Me} \quad \text{O} \quad \text{O} \quad \text{H} \quad \text{R} \quad \text{Li} \quad \text{H} \quad \text{R}
\]

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

Asymmetric variant:

\[
\text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me}
\]

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

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

α-Electron donating substituents:


Diels Alder Reactions - Alkoxy Substitution

R' AcO OAc OAc OAc

Toluene

Δ

only diastereomer (exo product!)

3:1 exo : 1 endo

Both "Chelate"


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.


[3 + 2] Additions

Proposed Mechanism: A genuine nucleophilic attack.


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

Claims silicon acetonide provides higher dipole, resulting in higher stereoselectivity.

Dipole model is similar to Kahn / Hehre proposal.

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

**[3 + 2] Additions - Alkyl Substitution**

Felkin like TS‡

B. Nitrile Oxide [3+2]

\[ \text{CH}_2\text{Cl}_2, \text{r.t.} \]

**[3 + 2] Additions - Alkoxy Substitution**

Felkin like TS‡

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


Both authors invoke the Felkin like transition state above.
[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.

\[
\begin{align*}
\text{E}_{\text{rel}} \text{ kcal} & \quad 0.0 \\
& \quad 0.8 \\
& \quad 1.1 \\
\end{align*}
\]

- Predicts Anti-Cram / Cram ratio of 68:32 at room temperature (observed 64:36).
- Larger R group affords higher diastereoselectivity.

2,3-Wittig Rearrangement

Felkin like TS$^\dagger$

(E) Olefins

\[
\text{BuLi} \quad -78^\circ C
\]

"Chelate"

Proposed:

(L) Olefins

(E) Olefins

(Z) Olefins

── Violates the Kahn / Hehre proposal.

Claisen Rearrangements

Claisen Rearrangements - The Aldol Analogy

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

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.

Evans, D. A.; Duffy, J. L. Unpublished results.
Again, anti-Felkin or inside alkoxy transition states are proposed.

Case 1: \( X=H, Y=O, R''=\text{Et} \)
Case 2: \( X=\text{Cl}, Y=S, R'=\text{iPr} \)

or

\((E)\) Olefin, methyl ketone enolate

\[
\begin{align*}
\text{Me} & \quad \text{MeC(OEt)}_3 \\
\text{OTHP} & \quad \text{cat RO}_2\text{H} \\
140^\circ\text{C} \\
\end{align*}
\]

"Cram" 33 : 67 "Anti-Cram"


Thioester Claisen

\[
\begin{align*}
R & \quad \text{O} & \quad \text{S} & \quad \text{Me} \\
\text{OTBS} & \quad \text{Cl} & \quad \text{Cl} \\
\end{align*}
\]

"Cram" "Anti-Cram"

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


Case 1: \( X=H, Y=O, R''=\text{Et} \)
Case 2: \( X=\text{Cl}, Y=S, R'=\text{iPr} \)

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

- Vinyl sulfone additions (E) and (Z)
- Michael additions (E) and (Z) except (Z) "charge transfer"
- [3 + 2] Nitrone additions (E)

**SN2' additions (E) and (Z)**

Michael addition (Z) "charge transfer"

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.

**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 = Rm for alkoxy substituted olefins.
- This disregards any electronic component, but predicts the correct product.