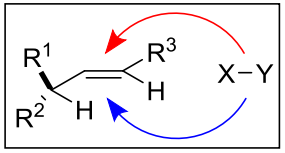
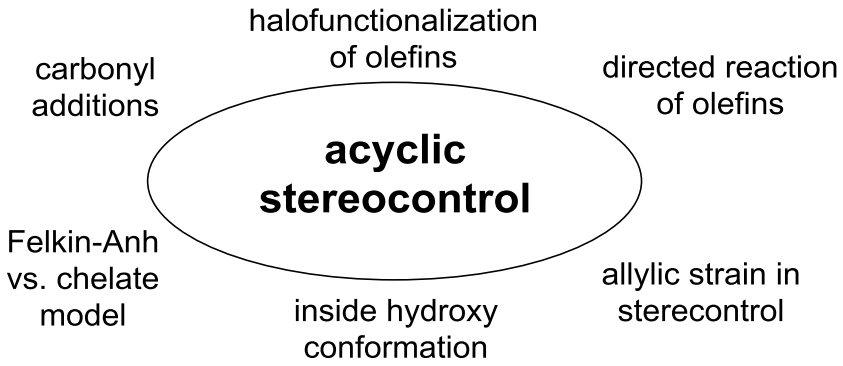
Acyclic Stereocontrol

Eugene E. Kwan, Christian M. Gampe



Scope of Lecture

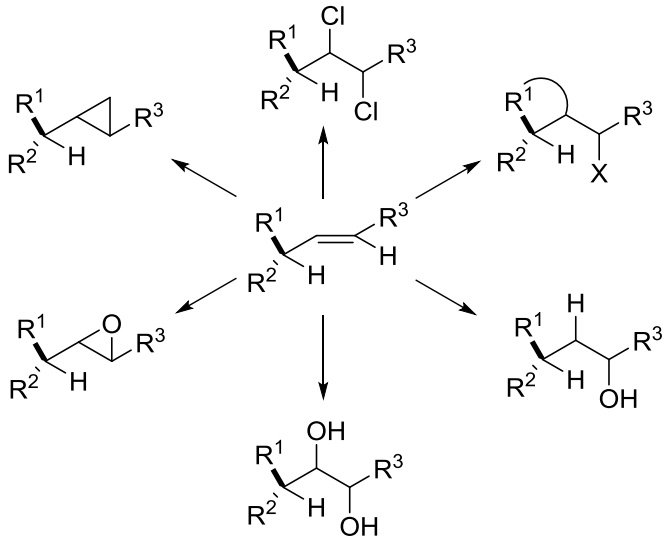


Helpful References

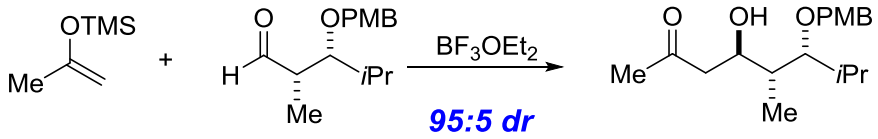
1. "Classics in Stereoselective Synthesis", E. M. Carreira, L. Kvaerno, Wiley-VCH **2010.**
2. "March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure", M. B. Smith, J. March, Wiley Interscience **2007.**
3. "Substrate Directable Reactions", A. H. Hoveyda, D. A. Evans, G. Fu, *Chem. Rev.* **1993**, *93*, 1307.
4. "Acyclic Stereocontrol Induced by Allylic Alkoxy Groups" J. K. Cha, N.-S. Kim, *Chem. Rev.* **1995,** *95,* 1761.
5. "Allylic 1,3-Strain as a Controlling Factor in Stereoselective Transformations", *Chem. Rev.* **1989,** *89,* 1841.
6. "Stereoselective Cyclopropanation Reactions" *Chem. Rev.* **2003,** *103,* 977.

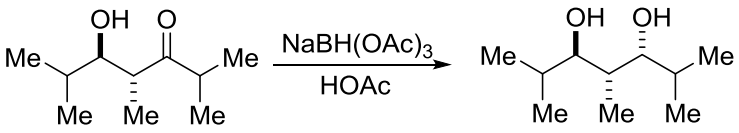
Key Questions

1. How do allylic and homoallylic steregenic centers influence the stereochemical outcome of these reactions?



2. How can we explain the following?

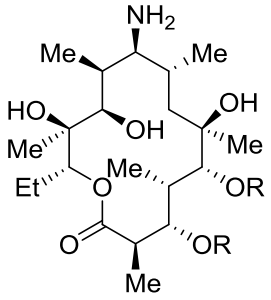




Lecture notes edited by Richard Liu

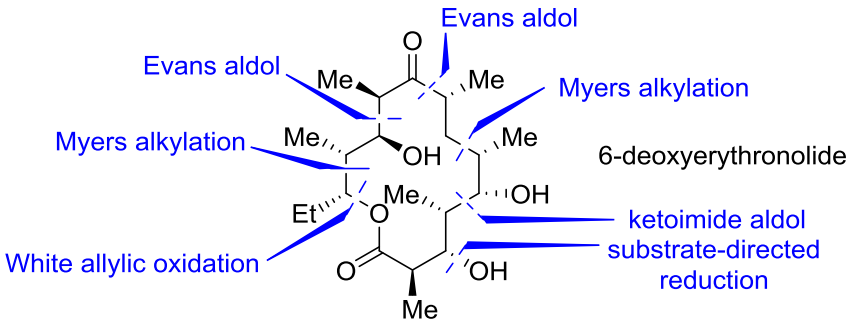
Acyclic Stereocontrol

Highly diastereoselective reactions controlled only by substrate stereochemistry have become an invaluable tool in organic synthesis. In 1965 before their prevalence, Woodward famously remarked that the total synthesis of the erythronolides, a family of macrocylic antiobiotic compounds, was "hopelessly complex" on account of its multiple contiguous stereocenters.



erythromycin

Only 34 years later, a recent synthesis of 6-deoxyerythronolide by the White group sets every stereocenter except one by acyclic stereocontrol, using reactions that have become standard in the field.

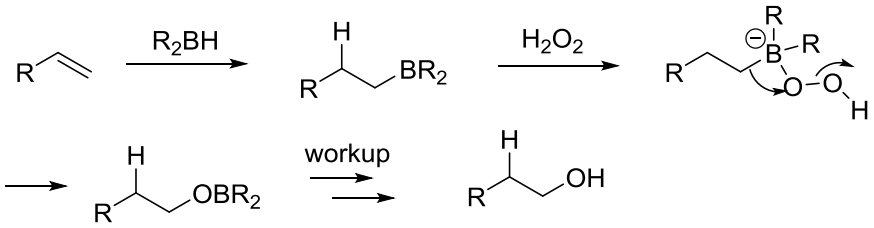


Nat. Chem. **2009** *1* 547

In this lecture, we will explore some reactions that proceed under substrate stereocontrol and some models for their selectivity based on principles of acyclic conformational analysis. Next lecture, we will discuss aldol-like reactions in more detail.

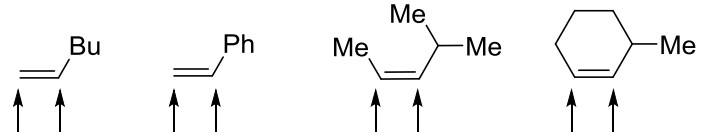
Hydroboration

Hydroboration used to be an important reaction for converting alkenes to alcohols. Nowadays, the intermediate organoboranes are highly useful in themselves and can participate in cross-couplings, addition-migration reactions and halogenations.



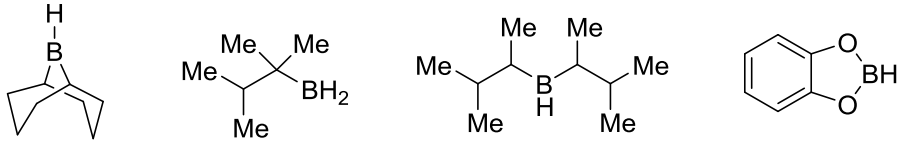
Sodium perborate oxidation/workup (milder alternative):
Kalbalka *JOC* **1989** *54* 5930

Regioselectivity is generally moderate with BH_3·THF, but good with bulkier reagents like 9-BBN:

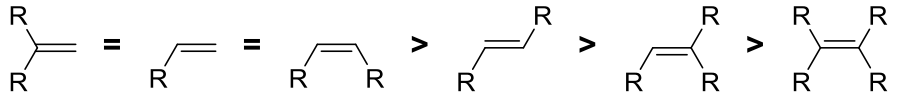


BH_3	94:6	81:19	57:43	50:50
9-BBN	99.9:0.1	98.5:1.5	98.8:0.2	80:20

Common hydroboration reagents:



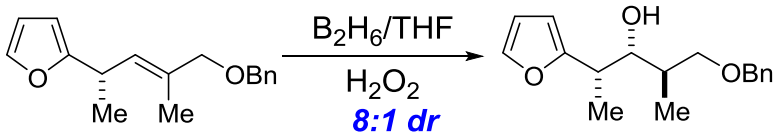
General trend of the rate of hydroboration:



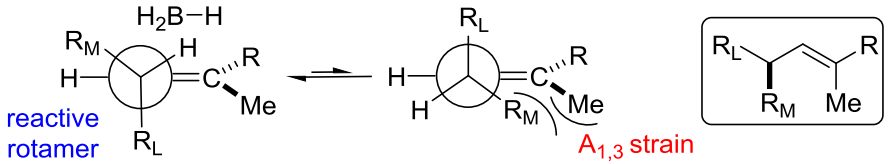
Hydroboration controlled by $A_{1,3}$ strain

Houk *Tetrahedron* **1984** *40* 2257

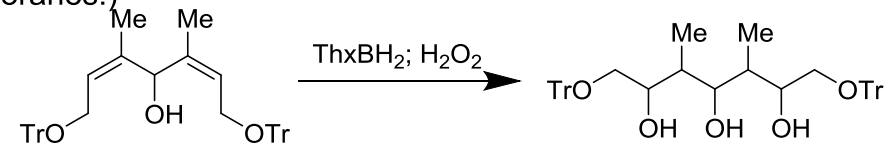
Consider this reaction in Kishi's Monensin synthesis *(JACS* **1979** *101,* 260; *JACS* **1979,** *101,* 262.)



This result can be rationalized by conformational analysis. The reactive conformation of the starting material is the one in which $A_{1,3}$ strain is minimized. BH_3 then approaches from the face opposite to the larger substituent.

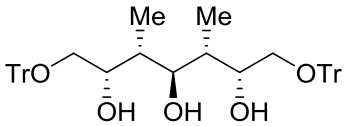


In this case the severe $A_{1,3}$ strain of the 1,1,2-trisubstitued olefin dictates the reactive conformation. What is your prediction for the stereochemistry of this reaction? (-OH does not direct normal boranes.)



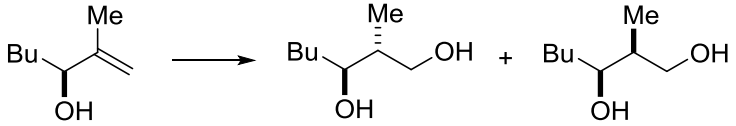
Still, W. C. *JACS* **1983** *105* 2487

We could do the conformational analysis again (you should), or we can just do this by analogy to the upper example. Pick an orientation for the central hydroxyl (let's say "up"). Now clearly the borane approaches from the top face of both olefins to give:



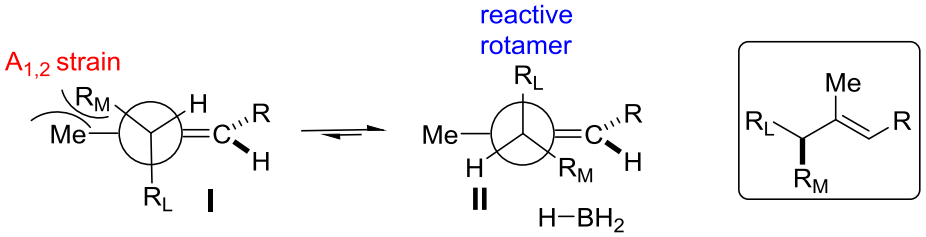
Hydroborations Controlled by $A_{1,2}$ Strain

Let's look at a 1,1-disubstituted olefin. Still has reported a study on the hydroboration of allylic alcohols (*JACS* **1983** *105* 2487). He notes that BH_3 displays only poor diastereoselectivity. However, if 9-BBN is used, good selectivities are obtained and the stereoinduction is reversed. So what is going on here? Again, a conformational analysis is revealing.



BH_3: d.r. 1:1.4
9-BBN: d.r. 11:1

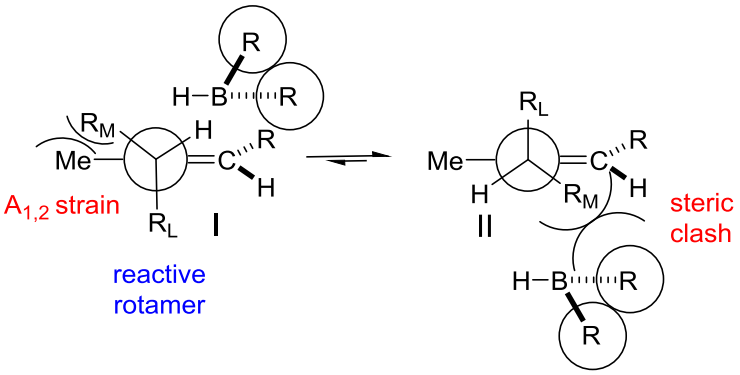
small boranes:



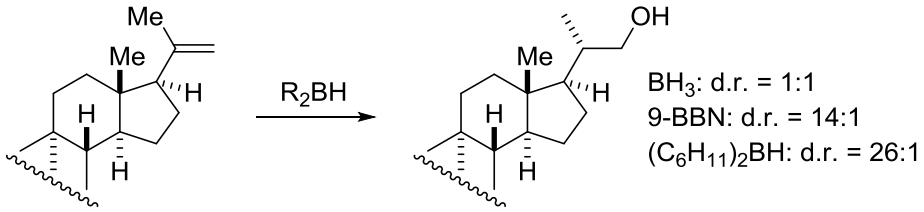
In *E*-1,1,2-trisubstituted olefins $A_{1,2}$ strain in conformer **I** will favor conformer **II.** A small borane reagent can now come in from either side and will have to pass either R_M or R_L, which explains the poor selectivity. *In general, selecting between R_M and R_L is always much more difficult than selecting between R_M and H.*

large boranes:

If large borane reagents are used conformer **II** will still be favored. However, severe steric clash between R_M and the borane will prevent the reaction with rotamer **II**. Instead, the less stable rotamer becomes the reactive one, reversing the observed selectivity.

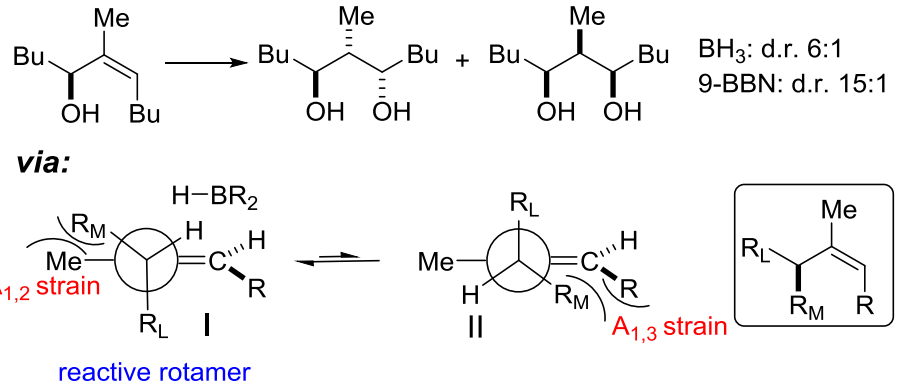


Another instructive example was reported by Midland (*JACS* **1983,** *105,* 3725):



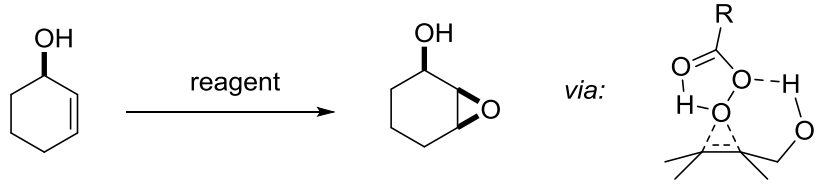
Competing $A_{1,3}$ and $A_{1,2}$ strain

In *Z*-1,1,2 substituted olefins both conformers **I** and **II** will suffer from $A_{1,2}$- and $A_{1,3}$-strain, respectively. The following experiment by Still shows that **$A_{1,3}$ strain dominates $A_{1,2}$ strain** and reactive conformer **I** is favored despite the $A_{1,2}$ energy. Note that the steric clash with bulky borane reagents favors **I** as well; both effects work in concert to give pronounced stereoinduction. (*JACS* **1983** *105* 2487)

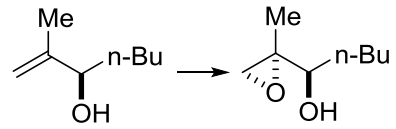


Directed Reactions: Epoxidation

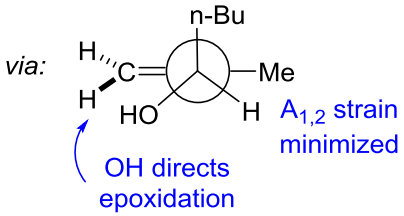
Thus far, the substrate controlled-selectivity we have discussed has relied on repulsive steric interactions. However, substrate control can also derive from attractive non-covalent interactions such as hydrogen-bonding or Lewis acid/base complexation. The resulting association of the substrate and reagent induces a conformational bias in the ground state that translates to highly organized transition states, and hence, high selectivity. Interestingly, the substrate-reagent interaction can also increase the rate of reaction as well. For example, in hydroxyl-directed peracid epoxidations, the carbonyl oxygen becomes more negatively charged in the transition state. As a result, hydrogen bonding is stronger in the transition state than the ground state, and the overall rate is faster (*J. Chem. Soc.* **1957** 1958; *Proc. Chem. Soc.* **1963** 159; *JACS* **1997** 119 3385).

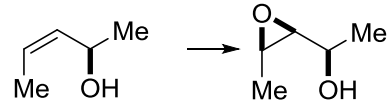


Sharpless carried out an instructive study of acyclic stereocontrol in the epoxidation of allylic alcohols. As you can see, we perform the same type of conformational analysis using allylic strain, but now the electrophile approaches from the hydroxyl side, rather than the least hindered side.

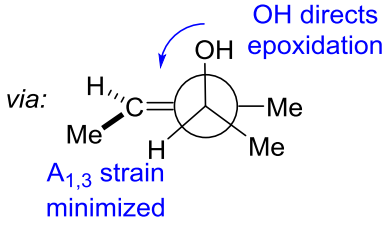


m-CPBA d.r. = 59:41
*t*BuOOH, $VO(acac)_2$ d.r. = 98:2

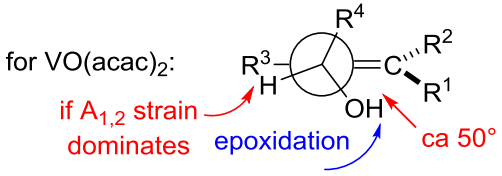


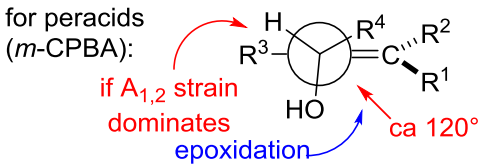


m-CPBA d.r. = 95:5
*t*BuOOH, $VO(acac)_2$ d.r. = 71:29



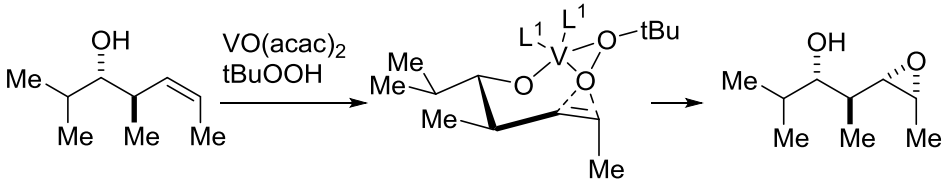
Sharpless model (*Aldrichimica Acta* **1979** 63):





Stereoinduction using *m*-CPBA is highest if the dihedral angle is around 120°. In contrast the V(V) species prefers to be directed by a hydroxy group that forms a dihedral angle of ca. 50°.

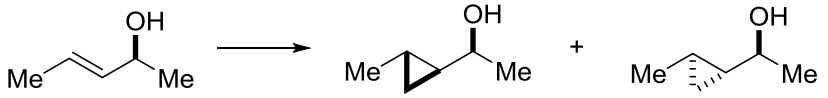
Homoallylic alcohols have as well been reported to react in highly diastereoselective epoxidation reactions. Direction of the metal reagent by the hydroxyl group in a cyclic transition structure was proposed, in which most substituents occupy the equatorial position (*JACS* **1981,** 7690).



Cyclopropanation

Directed cyclopropanation of allylic alcohols can also be quite stereoselective, but the mechanism is not as well understood.

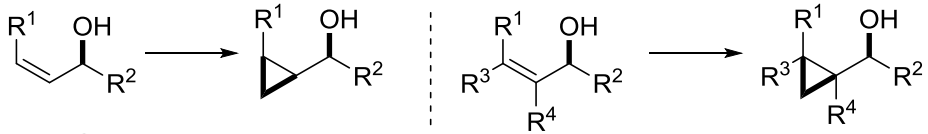
The cyclopropanation of ***E*-allylic alcohols** is highly dependant on the reaction conditions. Furukawa's conditions (Et_2Zn, CH_2I_2) generally give higher d.r. than the Simmons-Smith procedure or the samarium carbenoid.



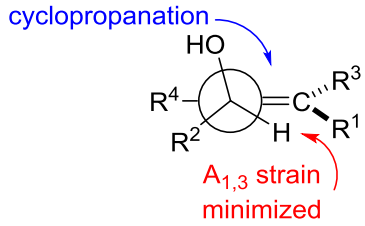
Zn/Cu, CH_2I_2, Et_2O	56:44
Et_2Zn, CH_2I_2, CH_2Cl_2	86:14
Sm(Hg), CH_2I_2, THF	25:74

The fact that samarium carbenoids often give complementary stereoinduction to zinc carbenoids is difficult to explain.

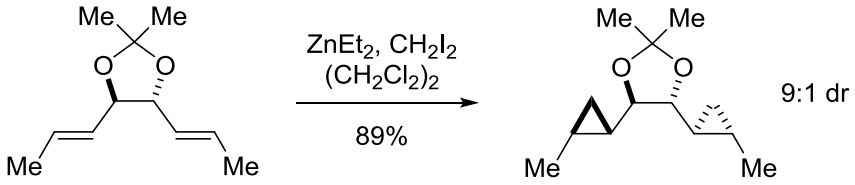
On the other hand, **Z-allylic alcohols** or trisubstituted olefins react under a variety of conditions to give the syn-products in good selectivities, usually >9:1.



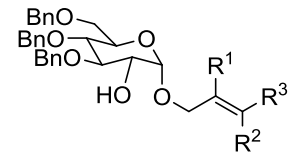
With a few exceptions, the directing effects of basic groups that do not reside on a stereogenic center is rather poor.



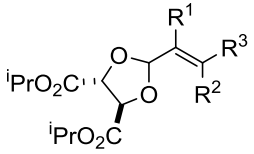
Since this directing effect relies on interaction with the metal center rather than hydrogen bonding, cyclopropanation is directed by many more Lewis basic functionalities than are useful for peroxide-promoted epoxidation. For instance, allylic silyl ethers and acetals can be viable directing groups.



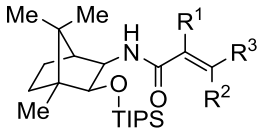
Numerous chiral auxiliaries have been developed. A selection of these auxiliaries is depicted below, for a good overview, see: *Chem. Rev.* **2003** 977.



Charette, *JACS* **1991** *113* 8166



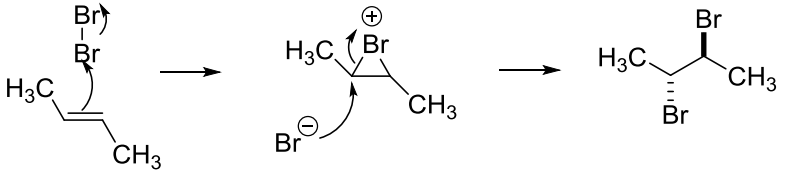
Yamamoto, *Tetrahedron* **1986** 6447



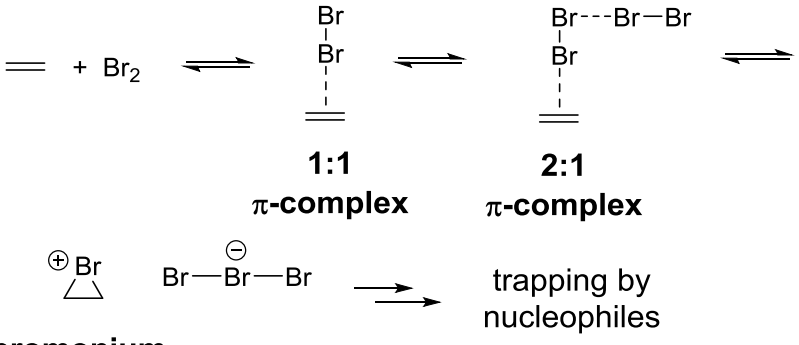
Imai, *JOC* **1990** 4986

Halofunctionalizations

We conclude our discussion of stereoselective olefin functionalization with a discussion of reactions that proceed through halonium ions. First, we will need some background. Typically, the bromination of an olefin is trans-selective. In 1937, Roberts proposed (*JACS* **1937** *59* 947) that bromonium ions are intermediates:



However, this picture is gravely lacking in mechanistic detail. It now appears that, like in hydroboration, π-complexes are often important intermediates. The exact mechanism depends also on the solvent. **In aprotic solvents:**

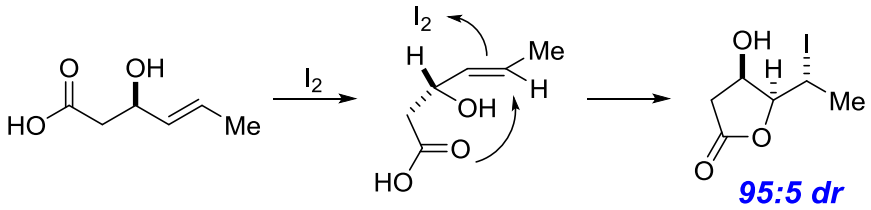


Chem. Eur. J. **2003** *9* 1037-1044.

(Complexes of 3:1 stoichiometry or higher are possible.) Nucleophiles can attack any of these intermediates, giving rise to very complex mechanistic behavior. These π-complexes were examined by Mulliken (Molecular Complexes, **1969**, Wiley Interscience).

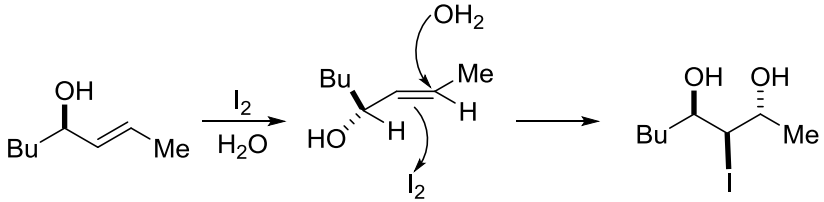
Chamberlin and Hehre have noted that the stereoselectivity of trapping reactions on allylic alcohol-derived bromonium ions depends on whether the nucleophile is internal or external (*JACS* **1983** *105* 5819; *JACS* **1987** *109* 672)!

With **internal nucleophiles**, the product seems to derive from a conformer in which the **allylic alcohol occupies the inside position**:



95:5 dr

With external nucleophiles, the product seems to derive from a conformer in which the **allylic alcohol occupies the normal, outside position:**

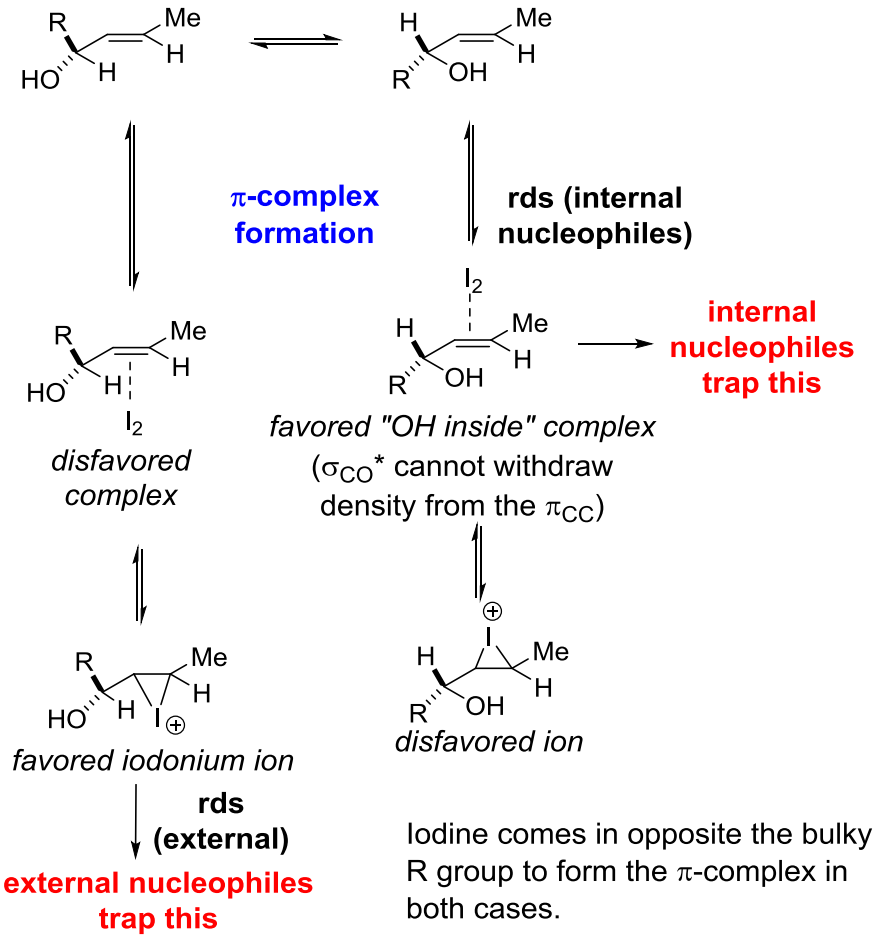


99:1 dr

This is rationalized by considering a *change in the rate-determining step*:

(1) when the nucleophile is internal, the more stable complex is trapped quickly.

(2) when the nucleophile is external, trapping is slow, and cannot occur directly via the π-complex, so the more iodonium is trapped.



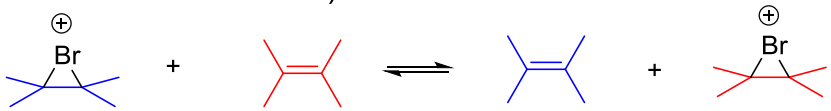
(3) the "OH inside" complex is favored becase I_2 does not compete with σ_{CO}* for the π_{CC} electron density.

(4) the left-hand iodonium ion is favored because the C-O inductively stabilizes the iodonium ion.

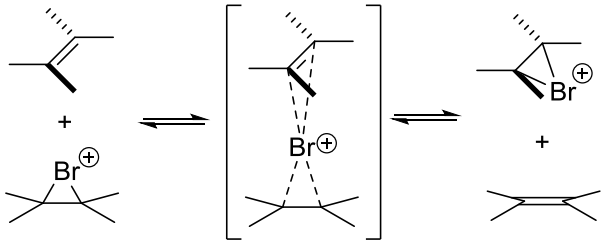
(5) evidently there is a considerable barrier to go from the π-complex to the iodonium ion (reactions in Et_2O)

Configurational Stability of Halonium Ions

Interestingly, one bromonium ion can exchange with another (Brown *ACR* **1997** *30* 131):



The barrier to exchange for Ad=Ad is very small and can be determined by NMR lineshape analysis. Apparently, there is an intermediate in this process:



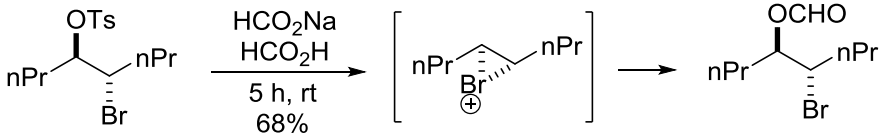
at -80 °C:

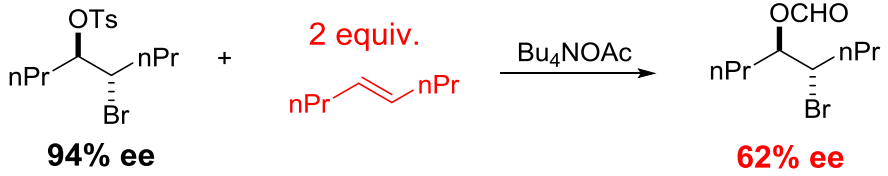
$\Delta H^{\ddagger}$ = 1.8 kcal/ mol

$\Delta S^{\ddagger}$ = -21 eu

The negative entropy of activation is to be expected from a highly organized bimolecular reaction of this type. Transfers from the Ad=Ad (Ad = 2-adamantylidene) bromonium ion to less hindered olefins like cyclohexene occur faster, but the rate of transfer between cyclohexene bromonium ions is unclear.

A very clever experiment by Denmark (*JACS* **2010** *132* 1232) shows that exchange definitely occurs for other olefins:





Carbonyl Additions

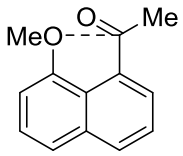
From Crystal Statics to Chemical Dynamics Bürgi, H.B.; Dunitz, J.D. *Acc. Chem. Res.* **1983**, *16*, 153-161.

Stereochemistry of Reaction Paths... Bürgi, H.B. *ACIE* **1975** *14* 460-473.

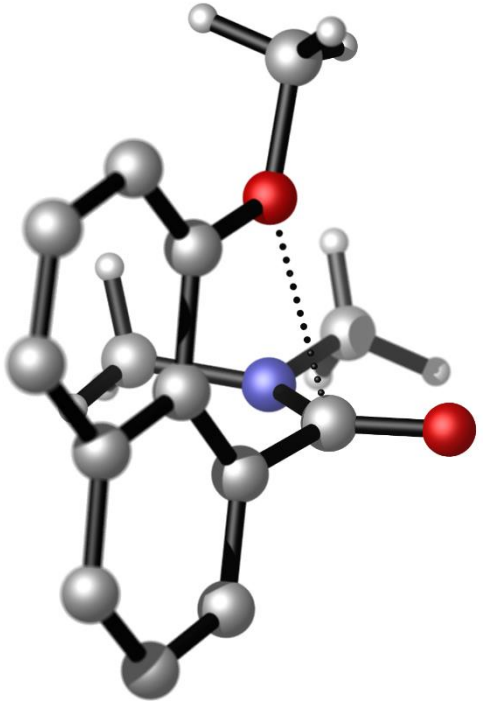
Q: What is the trajectory of attack of a nucleophile on a carbonyl group?

Unfortunately, there is no way to observe reactions as they occur (yet). The idea is to instead infer reaction trajectories from perturbations seen from crystal structures.

Case 1: 1,8-Disubstituted Naphthalenes

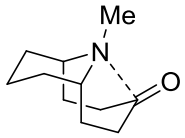


This is a highly strained system where the oxygen nucleophile is forced to be close to the ketone. The O-C=O angle in the crystal structures is 103°.

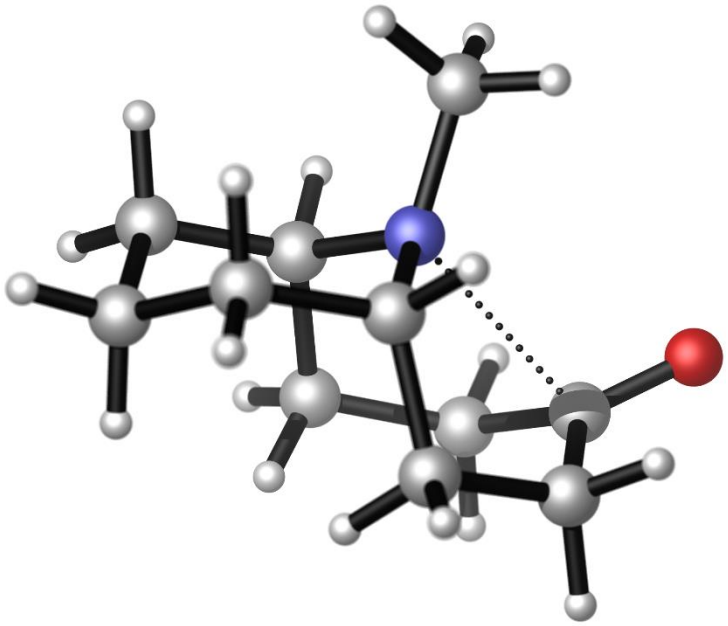


Note that the O-C distance is 2.60 A, which is in the ballpark for a typical transition state.

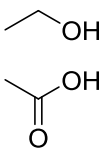
Case 2: Cyclic Aminoketones



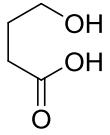
Here, the N-C distance is 2.47 A, which is a bit more advanced. The N-C=O angle is 111°.



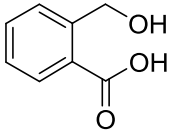
Bürgi argues (*JACS* **1972** *94* 5805) that the relative rate of lactonization in various hydroxyacids is increased in substrates for which the O-C=O bond angle is close to 100°.



1



79



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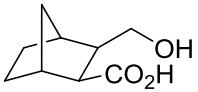
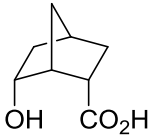


6633



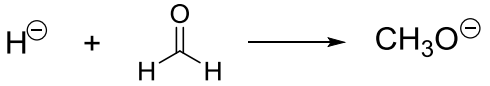
10^6

Of course, the structures shown above are not transition state energy maxima, but ground state energy minima because they are derived from crystals.

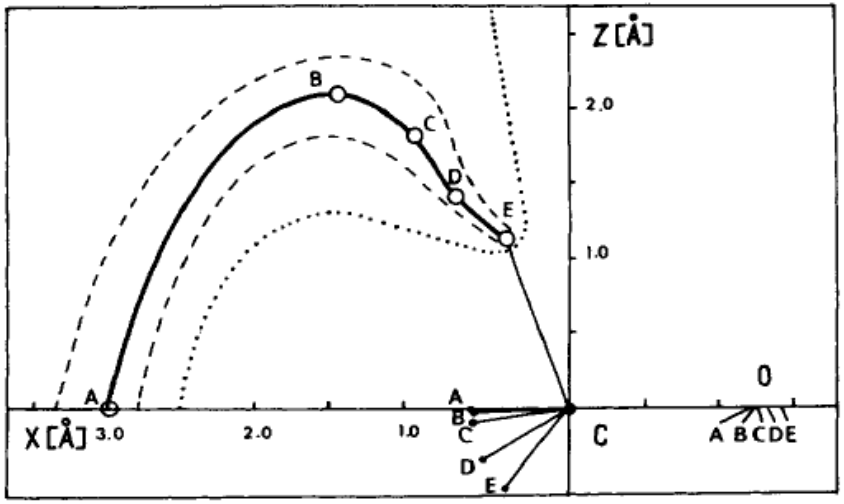
The Bürgi-Dunitz Trajectory

There are two approaches to this. In an ideal world, one could perform molecular dynamics simulations, where nucleophiles and electrophiles are initialized with random trajectories. The simulation would run, and one would examine the trajectories that lead to product and determine what their Nuc-C=O bond angles were. Unfortunately, with today's technology a picosecond's worth of simulation time correponds to about a week's worth of computer (wallclock) time, so this is entirely impractical. Another way to look at it is that most collisions do not actually result in a collisions; reactions are such rare events that one would have to run a huge number of trajectories to accurately sample anything.

A less ideal approach is to simply constrain the Nuc...C=O distance and measure the electronic energy. This has been done at a relatively crude level (roughly Hartree-Fock):



The "tightness" of the angle of attack depends on how far the hydride is from formaldehyde:



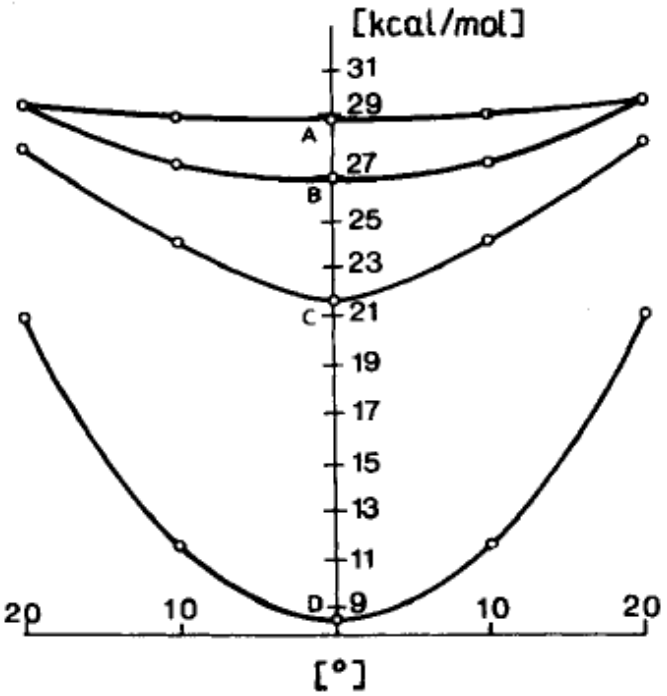
Thus, one should not think of a specific Bürgi-Dunitz *angle*, but rather a Bürgi-Dunitz *cone*:

(1) At large distances, the nucleophile and electrophile don't have a significant bonding interaction. The nucleophile approaches along the H-C(O)-H bisector, consistent with an electrostatic view.

(2) At medium distances, bond formation begins to develop and we are in the neighborhood of a transition state. Given the numbers here for C, which has a realistic TS bond forming distance of 2.0 A, we guess that the H-C=O angle must be between 110 and 130°.

(3) At close distances, we are essentially wiggling a H-C bond in a methoxide, and the curvature of the well simply reflects the normal modes of the product.

A: 3.0 A
B: 2.5 A
C: 2.0 A
D: 1.5 A
E: 1.12 A

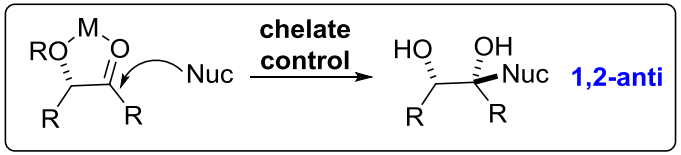


Chelate-Controlled Carbonyl Additions

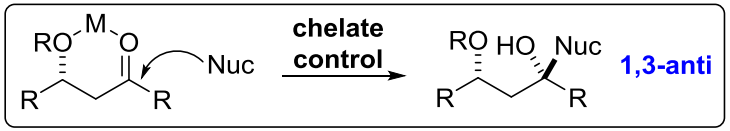
"...Aspects of Chelation-Controlled Carbonyl Additions"
Reetz, M.T. *Acc. Chem. Res.* **1993** *26* 462

These are the easiest diasteroselective carbonyl additions to understand. Asymmetric induction is possible from both α- and β-stereocenters; in both cases, a metal chelate is formed, and the nucleophile comes in anti to the stereocenter:

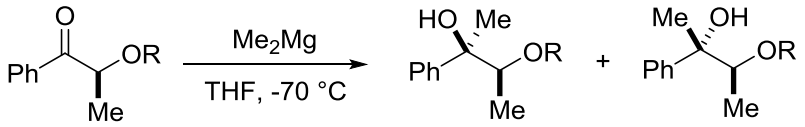
1,2-induction



1,3-induction



If this model is right, then changing the nature of the protecting group on oxygen should change the stereochemical outcome. Indeed, this is exatly what is found (Eliel, *JACS* **1992** *114* 1778):



chelate product

R=Me, **99:1**
R=TBS, **89:11**
R=TBDPS **68:32**

What is the evidence for this model, other than the stereochemistry? Just because a chelate is possible does not mean that it will speed up the reaction:

chelate speeds up reaction

ketone ⇌ **chelate** → **product**

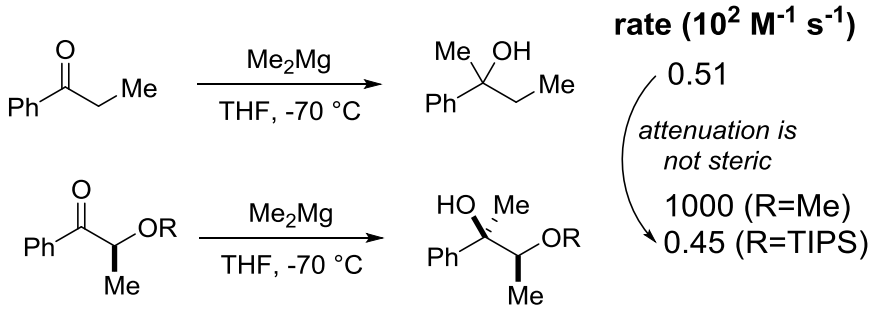
chelate slows down reaction

chelate ⇌ **ketone** → **product**

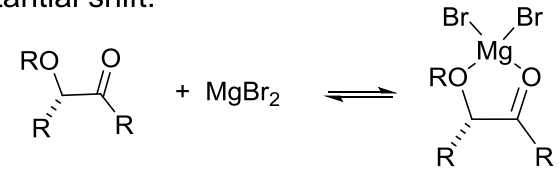
(1) If the chelate is just an unproductive side equilibrium, then it will just stabilize the ground state and slow down the reaction.

(2) Conversely, the chelate might just form in the transition state, lowering its energy and speeding up the reaction.

It is found that chelation *significantly accelerates* addition:



(3) α-Alkoxyketones and magnesium bromide do not visibly coordinate by NMR. This is expected, since THF is quite a good ligand for magnesium. However, in CD_2Cl_2, there is a substantial shift.



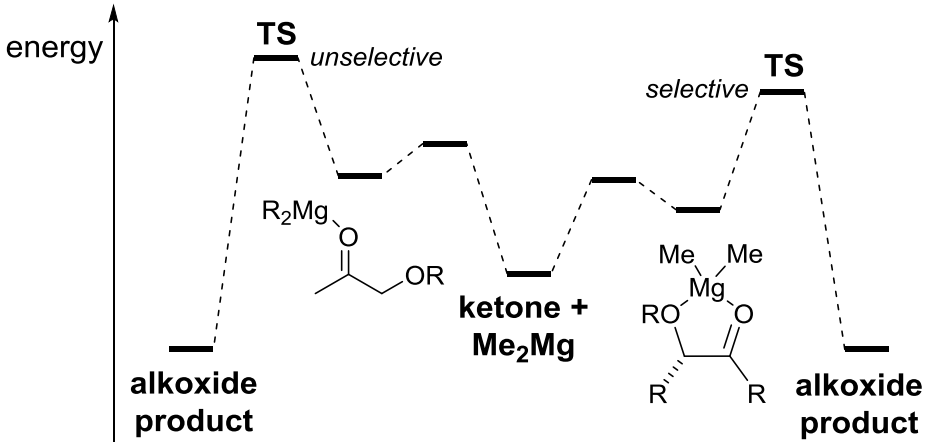
The extent of chelation in CD_2Cl_2 depends on the protecting group.

(4) The reaction is first order in ketone and Me_2Mg.

This means that the scenario is:

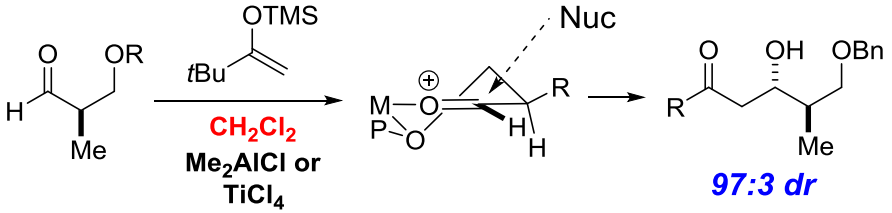
ketone ⇌ **chelate** → **product**

If we want to draw an energy diagram, we can can compare the competing chelated and unchelated transition states:



There is no differentiation between forming major and minor products on this diagram. Thus, we have to think of each transition state as really representing a pair of transition states, one for the major and one for the minor product.

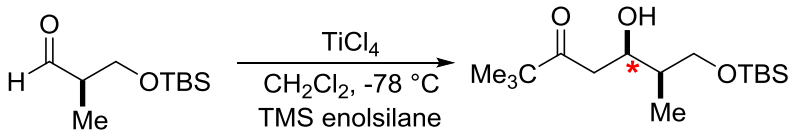
Interestingly, β-αlkoxy ketones do not seem to experience any rate acceleration. This is consistent with other literature precedents, which suggest that 5-membered chelates are more reactive than 6- membered chelates. However, 6-membered chelates do give high selectivity (Evans *JACS* **2001** *123* 10840):



Intrinsic vs Chelate Selectivity

Before analyzing the outcomes of these chelate-controlled additions in more detail, it is important to realize that there is an intrinsic selectivity that is being turned over when chelation occurs (Evans *JACS* **2001** *123* 10840):

"intrinsic selectivity"



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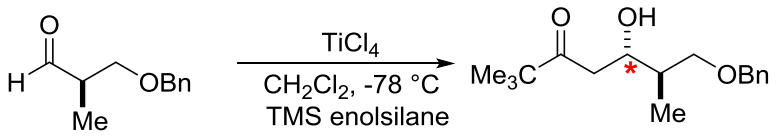
"Cram chelate selectivity"



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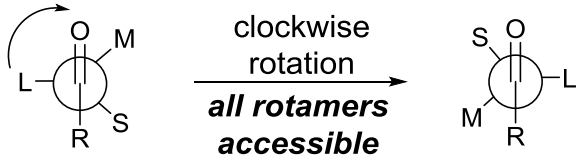
The idea here is that going from a bulky protecting group, TBS, to a less hindered, coordinating protecting group, Bn, gives chelate control. But ***where does the intrinsic selectivity come from?***

Felkin-Anh-Eisenstein Model

In the Felkin model, one assumes:

(1) all ground state rotamers are accessible (Curtin-Hammett)

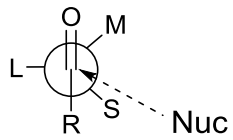


(2) the transition states are very early (exothermic reaction)

(3) both the major and minor transition states place the largest substituent anti to to the incoming nucleophile

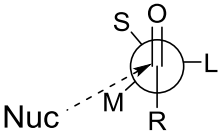
(4) the major transition state minimizes torsional interactions between the C-R bond in the front and the C-M group in the back (L=large, M=medium, S=small):

major TS



- L is opposite Nuc
- the torsional interaction between C-R and C-S is small
- also could imagine that S/Nuc interactions are small

minor TS



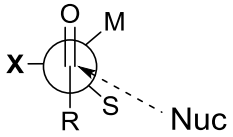
- L is still opposite Nuc
- the C-R/C-M interaction is bad
- so is the Nuc/M interaction

This model works for the vast majority of aldehydes and ketones and is generally accepted. However, it does seem to fail in some pathological cases, such as sterically unbiased ketones which are nonetheless slightly electronically biased.

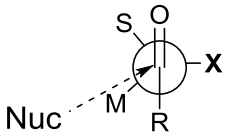
Effect of Electronegative Substituents

In the above analysis, it was tacitly assumed that all three substituents were alkyl; i.e., not electronically biased. Anh and Eisenstein showed that polar substituents X can take the place of the large group:

major TS



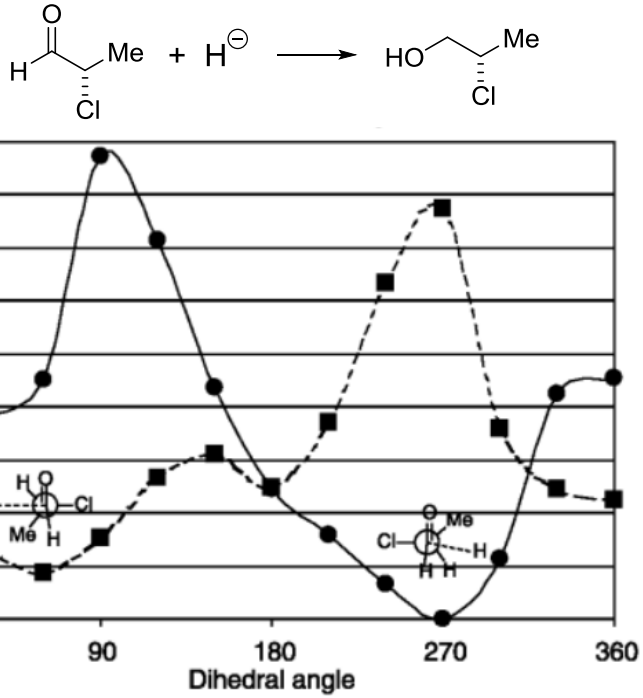
minor TS



Effect of Electronegative Substituents

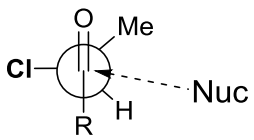
The work of Anh and Eisenstein (*Nouv J Chem* **1977** *1* 61) was seminal because it showed that computational chemistry could be a powerful tool for analyzing real problems in organic chemistry. Even though their work was, in today's terms, at a very crude level of theory (HF/STO-3G), it is telling that it gives the right predictions most of the time.

In their study, they analyzed the reduction of 2-chloropropanal with hydride. The distance between the hydride and the carbonyl carbon was fixed at 1.5 A, and the Cl-C-C=O dihedral angle was varied. Bachrach (page 303 of his book) has recomputed their results at a more modern (B3LYP/6=31++g(d)) level of theory:

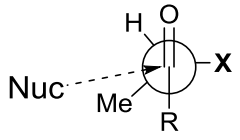


(1) The solid line (circles) represents configurations that lead to the major product; dashed (squares) lead to minor product.

(2) The minimum energy structures of the solid and dashed lines correspond to the rotamers depicted:



major TS



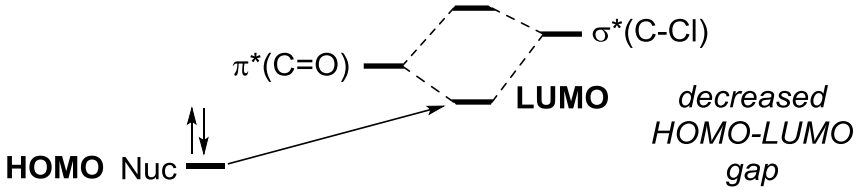
minor TS

(3) Notice that the nucleophile approaches at the Bürgi-Dunitz angle. Hydride is not a very realistic nucleophile, but the Bürgi-Dunitz constraint is still realized.

(4) ***Why does the C-X bond take the place of the large group?***

Explanation 1. Donation from the forming σ(C-Nuc) into the π*(C=O). However, this is a very early TS, so there is very little density in σ(C-Nuc); NBO analysis shows that this is not a very significant interaction.

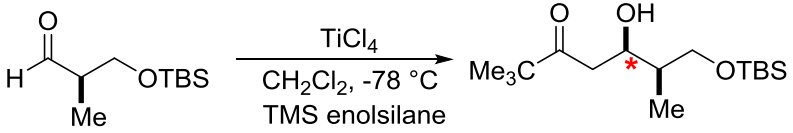
Explanation 2. The π*(C=O) and σ*(C-Cl) combine to form a better acceptor:



(5) The possibilities of asymmetric π* lobes (i.e., bigger on one diastereofacial surface) and electrostatic minimization (Cornforth model) have been examined.

Practice with Stereochemical Models

From a practical standpoint, what is the stereochemical outcome of a Felkin-controlled 1,2-addition? Let's analyze the reaction from before:



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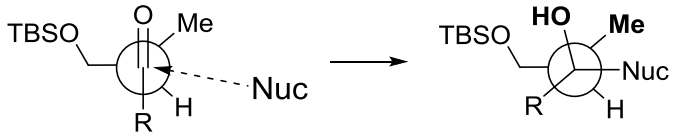
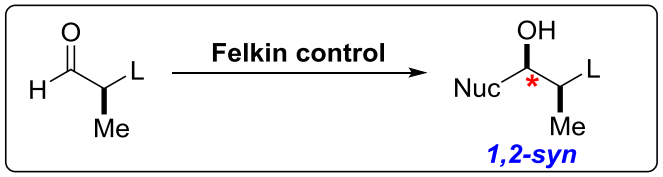
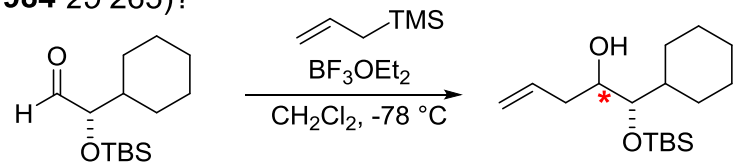
The major TS positions the large CH_2OTBS group anti to the nucleophile, which comes over the smallest group:



Notice that in the product, we have the R and the CH_2OTBS in the "zig-zag." So the Me and the OH are syn, as is observed. (If the R and CH_2OTBS weren't anti to each other, then we would need to rotate the Newman projection first.)



What is the expected Felkin product of this addition (Keck, *TL* **1984** *25* 265)?



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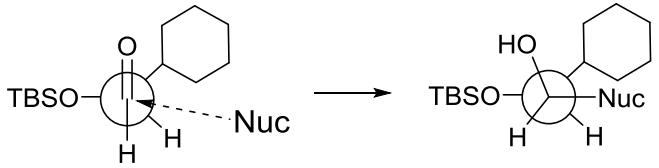
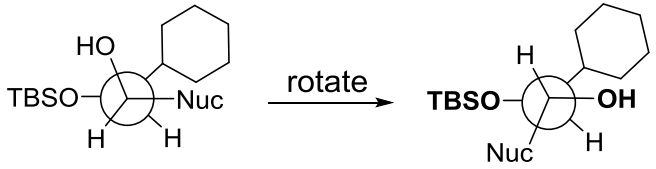
(When there's a polar group involved, we use the "**polar Felkin-Anh(-Eisenstein) model**.")

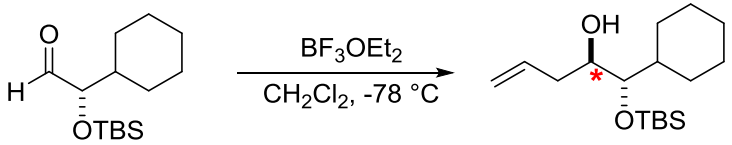
The OTBS takes the place of the large group (it is interesting that the electronegative substituent seems to override the bulkiness of the cyclohexyl group):



Notice that we need to have the allyl nucleophile and the cyclohexyl group anti to each other in the Newman projection to decide if the product is 1,2-syn or 1,2-anti:



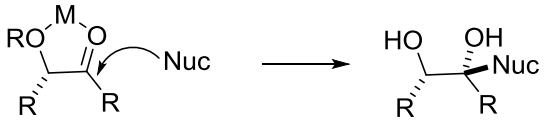
So the OH and the OTBS are **1,2-anti**:



95:5 dr

A Half-Chair Model for Chelate Control

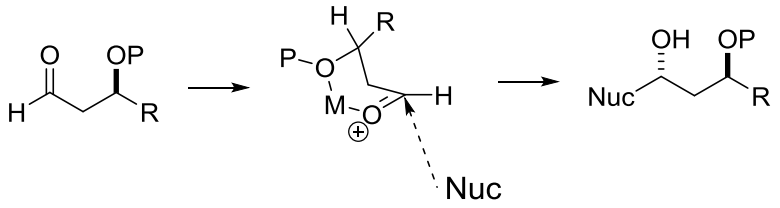
With 1,2-chelates, the nucleophile simply adds from the face opposite the α-substituent:



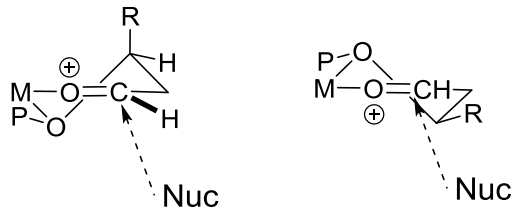
The kinetic data on this is unclear (Reetz, *ACR* **1993** *26* 462), and it is possible than nucleophile transfer can be either intra- or inter-molecular, depending on the situation. But this is still a useful model for predicting stereoselectivity.

For 1,3-chelate induction, a half chair model has been proposed by Evans (*JACS* **2001** *123* 10840). In some cases, a 2:1 bidentate chelate is observable in the ground state; in others, a monodentate 1:1 complex. So given the lack of kinetic data, it is unclear whether one can view all of these reactions as adding a nucleophile to a chelated complex. However, if one assumes this, then the performance of the stereochemical model is very good.

If one assumes a boat-like chelate, then the nucleophile comes in opposite the R group:



If it's a half-chair, the same prediction is obtained:

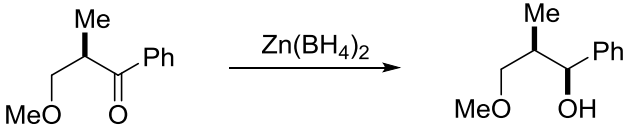


disfavored **favored**

As usual the Furst-Plattner rule dictates chair-axial opening. Interestingly, even if a *monodentate* carbonyl-Lewis acid complex is formed, the same outcome is observed. A polar 1,3-stereoinduction model predicts this (Evans *JACS* **1996** *118* 4322). We will discuss this in the next lecture.

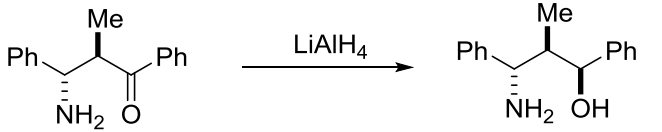
Directed Reductions

These are among the most useful of the chelate-controlled addition reactions. What happens in this reaction?



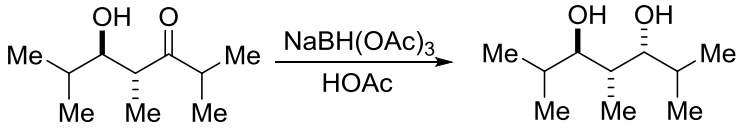
97:3 dr

Chelate control wins out over Felkin control. What is the stereochemical outcome of this reaction?

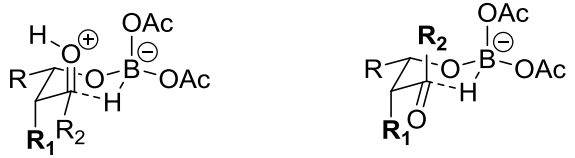


88:12 dr

Evans has also developed (*JACS* **1988** *110* 3560) reductions where chelation overrides Felkin selectivity:



98:2 dr



favored TS ***disfavored TS***

Note that 1,3-diaxial interactions are much worse on the top than on the bottom, where $\mathbf{R_1}$ is the only axial substituent. In contrast, when $\mathbf{R_2}$ is axial in the disfavored TS, it interacts with the acetate and axial hydrogen on the top face.