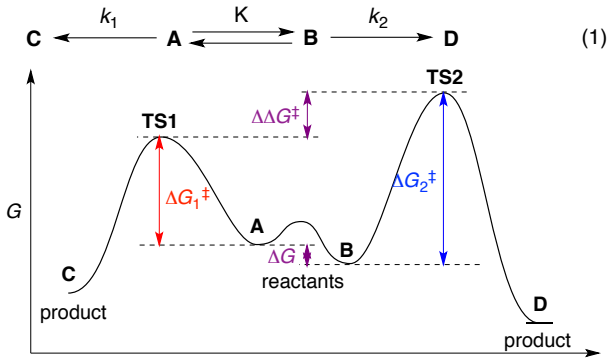
2. Stereocontrol in Organic Reactions

(1) Principles in selective organic reactions

(a) Curtin–Hammett principle

Selectivities are controlled by the relative energies of two transition states. The difference of reactants or products does not affect the selectivity.

- Curtin-Hammett principle is useful for considering selectivities of organic reactions, when the reaction forms different products (**C** and **D**) from two substrates (or intermediates) (**A** and **B**) in rapid equilibrium with one another (eq. 1).
- The selectivity, [**C**]/[**D**], is equal to $\exp(-\Delta\Delta G^{\ddagger}/RT)$. Therefore, the selectivity depends on only $\Delta\Delta G^{\ddagger}$, although $\Delta\Delta G^{\ddagger} = \Delta G_2^{\ddagger} - (\Delta G_1^{\ddagger} + \Delta G)$.
- Even if the reactant (or intermediate) **A** is less stable than **B**, product **C** would be the major product when **TS1** is more stable than **TS2**.
- Avoid to discuss the selectivity with the structures of reactants (or intermediates).



J. I. Seeman, *Chem. Rev.*, **1983**, *83*, 83.

(b) Hammond's postulate

If two states, as for example, a transition state and an unstable intermediate, occur consecutively during a reaction process and have nearly the same energy content, their interconversion will involve only a small reorganization of the molecular structure.

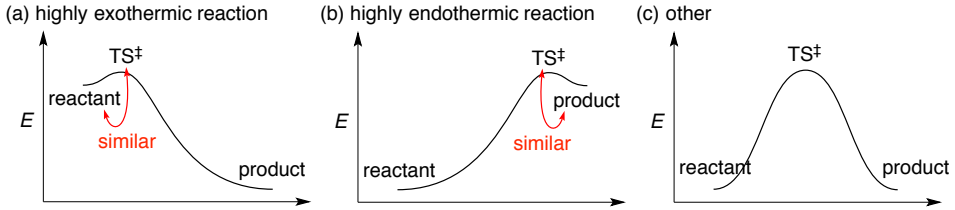
The postulate is useful for predicting the property of the transition state in highly exothermic or endothermic process (Figs a and b). Do not apply the postulate to the reactions, in which the reactant is similar in potential energy to the product (Fig c).

1) Highly exothermic reaction

- The energy diagram of a highly exothermic step (Fig a) indicates that the reactant reaches the transition state at early stage. Therefore, the transition state is similar in structure and energy to the reactant.
- Selectivities, including stereoselectivity, would be affected by the relative energy of each reactant (or its conformer).

2) Highly endothermic reaction

- The energy diagram of a highly endothermic step (Fig b) indicates that the reactant reaches the transition state at late stage. Therefore, the transition state is similar in structure and energy to the product.
- Selectivities, including stereoselectivity, would be affected by the relative energy of each possible product.



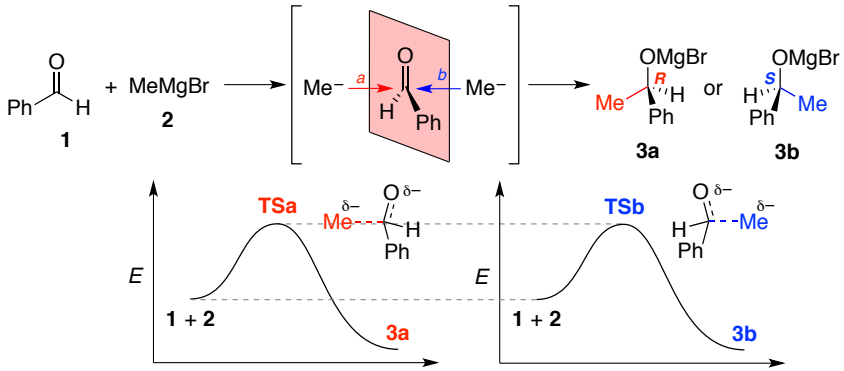
G. S. Hammond, *J. Am. Chem. Soc.*, **1955**, *77*, 334.
See also, J. E. Leffler, *Science*, **1953**, *117*, 340.

(2) Stereoselective reaction and prochirality

(a) Enantioselective reaction

1) Features

- Enantioselective reaction is the reaction that produces an optically active compound from an achiral or racemic starting material with an optically active reagent or catalyst.
- It is ordinary that an achiral compound is converted into a 1:1 mixture of *R*- and *S*-products, if the reaction creates a new chiral center. Both pathways leading to *R*- and *S*-products proceed through enantiomeric transition states, which have the same energy level each other.
- The optically active reagent or catalyst can discriminate the prochirality of the substrate.



- Commonly, the stereoselectivity in the enantioselective reaction, which is called enantioselectivity, is equivalent to the enantiomeric excess of the optically active product.
- There are two types of stereodiscrimination in enantioselective reaction. One involves the discrimination of enantiotopic faces; another involves that of enantiotopic groups.

2) Prochirality of achiral compounds

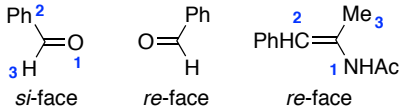
Enantiotopic face (*re*/*si*)

- In general, achiral unsaturated molecules have a symmetry plane involving the double bond. The plane has two faces. If the attack of a reagent on each face leads to forming different enantiomer, the face is called 'enantiotopic face'.
- Prochirality of enantiotopic face can be indicated with descriptor *re* or *si*. The prochirality is assigned as follows:

i) Determine the priority of the three substitutents on the atom, which will become a chiral center after the enantioselective reaction.

ii) View the face from above. The face is called *re*-face when the direction of $a \rightarrow b \rightarrow c$ is clockwise. Otherwise, the face is *si*-face.

$a \rightarrow b \rightarrow c$
clockwise ··· *re*-face
anticlockwise ··· *si*-face



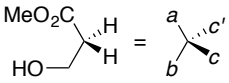
si-face *re*-face *re*-face

Enantiotopic group (or atom) (*pro-R*/*pro-S*)

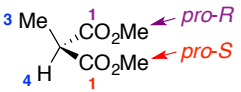
- When two equivalent groups (or atoms) are attached on a sp^3-hybridized carbon, the reaction occurring on one of the groups results in forming a new chiral center. Different enantiomers will be obtained from the reactions on each group. The two equivalent groups are called 'enantiotopic group'.
- Prochirality of enantiotopic group can be indicated with descriptor *pro-R* or *pro-S*. The prochirality is assigned as follows:

i) Determine the priority of the four substituents on the atom, which will become a chiral center after the enantioselective reaction. Here, one of the enantiotopic groups is tentatively assume to be dominant over another.

ii) Determine the *R*/*S* configuration with the above tentative priority. When the configuration is *R*, the prochirality of the substituent with higher priority is assigned to *pro-R*. Otherwise, the prochirality is *pro-S*.



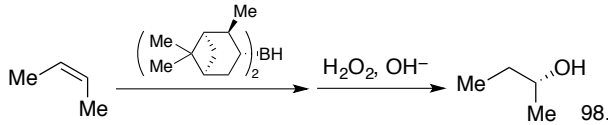
If $c > c'$, the tentative configuration is *S*.
The prochirality of *c* is *pro-S*.
The prochirality of *c'* is *pro-R*.

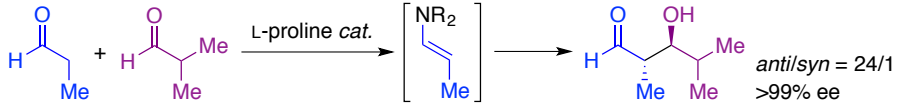


3) Discrimination of enantiotopic faces

- In most enantioselective reactions, a chiral reagent or catalyst discriminates two enantiotopic faces of the unsaturated bond in the substrate (or intermediate) to give the enantio-enriched product (See the figure in the left column).
- After the stereoselective reaction, no unreacted unsaturated bond remains in the resulting product. Therefore, the enantioselectivity of the reaction reflects the selection of the enantiotopic faces.

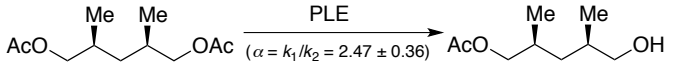
Examples



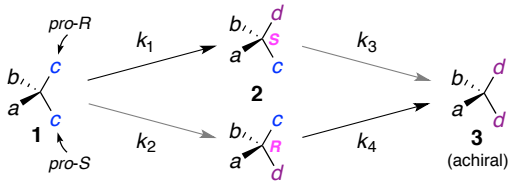


4) Differentiation of enantiotopic groups (or atoms)

- In some enantioselective reactions, a chiral reagent or catalyst discriminates two enantiotopic groups of a substrate to give an enantio-enriched product.
- After forming the chiral product, one of the enantiotopic groups remains in the product. The desired product will further react with the reagent, if the chiral reagent or catalyst exhibits low stereoselectivity. However, the overreaction may lead to increasing in the enantiomeric excess of the product. The enantiomeric excess of the product does not reflect the selection of the enantiotopic groups.



at 36% yield ··· 80% ee
at 15% yield ··· 95% ee



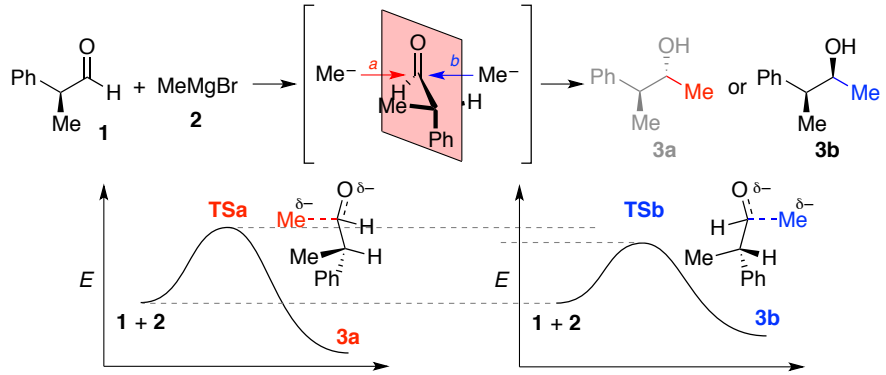
If the *pro-R*-*c* is more reactive than *pro-S*-*c* in **1**, (*S*)-**2** is obtained as the major product ($k_1 > k_2$).
The minor product (*R*)-**2** still has *pro-R*-*c*. The group *c* would be more reactive than *pro-S*-*c* remaining in (*S*)-**2**. Therefore, (*R*)-**2** would be easier to be converted into achiral **3** than (*S*)-**2** ($k_4 > k_3$).

C. J. Sih, *J. Am. Chem. Soc.* **1984**, *106*, 3695. See also, S. L. Schreiber, *J. Am. Chem. Soc.*, **1987**, *109*, 1525.

(b) Diastereoselective reaction

1) Properties

- Diastereoselective reaction produces a new chiral center on the substrate, which has a chiral center. The diastereoselectivity reflects the ratio of the diastereoisomeric products.
- The stereogenic center in the substrate can control the stereochemistry of the reaction (*i. e.* diastereoselectivity). Therefore, an achiral reagent can selectively produce a single diastereomer in diastereoselective reaction.



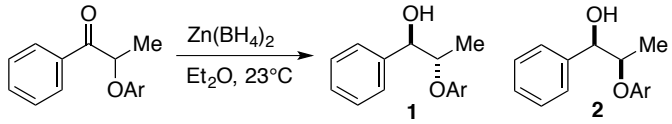
- The stereoselectivity in the diastereoselective reaction is often evaluated with diastereomeric excess (de, %), which is the difference between percentages of major and minor products, (de (%) = 100([major product] – [minor product])/([major product] + [minor product]).
- There are two manners of stereocontrol in diastereoselective reaction. One is the stereocontrol by the chirality of the substrate; another is that by the chirality of the reagent or catalyst.

How to predict the major product

- **By transition state**: In principle, the stereoselectivity is controlled by the difference in energy between favorable and unfavorable transition states. Comparing the two possible transition states is useful for predicting the major product. However, it is not easy to predict structure and energy of each transition state.
- **By structure of the chiral substrate:** The structure sometimes strongly relates to the stereoselectivity. When the reaction is known to proceed through early transition state (in Hammond postulate), the major product can be predicted with the steric hindrance imagined from the structure of the substrate.
- **By structures of the diastereomeric products (or intermediates):** The difference in thermodynamic stability between the possible diastereomeric products sometimes strongly relates to the stereoselectivity. When the reaction is known to proceed through late transition state (in Hammond postulate), the major product can be predicted with the thermodynamic stability of each possible product.

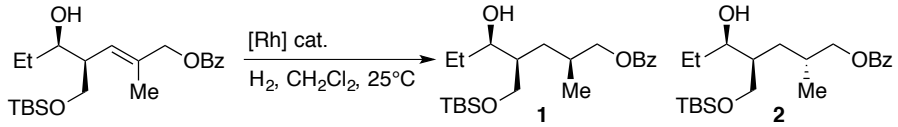
2) Substrate-controlled reaction

- In the substrate-controlled reaction, the stereochemistry of the substrate predominantly controls the stereoselectivity.
- All diastereoselective reactions are substrate-controlled reactions when they are conducted with an achiral reagent (or catalyst).



Ar = 2-$MeOC_6H_4$ **1**/**2** = >99/1
Ar = 2-(*t*-Bu)C_6H_4 **1**/**2** = <1/99

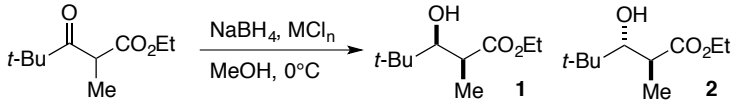
D. A. Nelson, *Tetrahedron Lett.* **1986**, *27*, 3091.



[Rh] = Rh(dppb)$^+$ **1**/**2** = 89/11
[Rh] = Rh[(*R*)-binap]$^+$ **1**/**2** = 97/3
[Rh] = Rh[(*S*)-binap]$^+$ **1**/**2** = 92/8

D. A. Evans, *Tetrahedron Lett.* **1985**, *26*, 6005.

- Choice of the achiral reagent may bring about reversal of the stereoselectivity. However, such a reaction should be treated as a substrate-contorolled reaction, because the interaction between the reagent and the substrate must strongly affect the stereoselectivity.



MCl_n = none **1**/**2** = 10/90
MCl_n = $MnCl_2$ **1**/**2** = 95/5

K. Oshima, K. Utimoto, *Tetrahedron*, **1993**, *49*, 11169.
(review) O. Reiser, *Chem. Rev.*, **1999**, *99*, 1191.

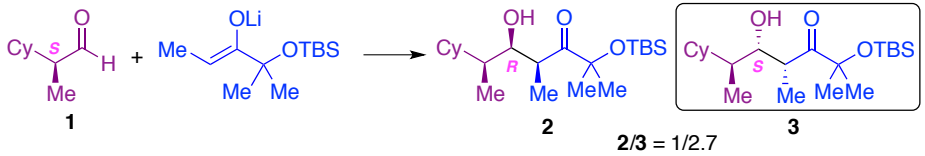
3) Double stereodifferentiation (review) S. Masamune, *Angew. Chem. Int. Ed. Engl.*, **1985**, *24*, 1.

- In the reaction between two chiral molecules, both of the substrates affect the stereoselectivity. The effect of the combination of two chiral molecules is called double strereodifferentiation.
- If the stereochemical effect of the chiral substrate is predominant over that of the reagent, the reaction should be categorized as substrate-controlled reaction.
- If the effect of the chiral reagent or catalyst is predominant over that of the substrate, the reaction should be categorized as a reagent-controlled reaction.
- When the chiral substrate and reagent (or catalyst) are comparable in the effect on

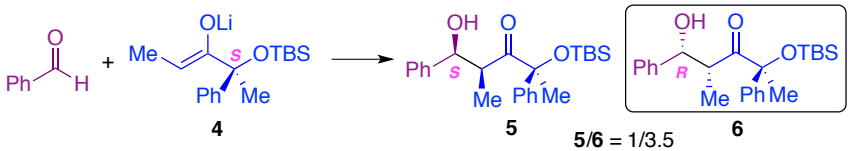
stereoselectivity, the direction of asymmetric induction arising from each compound should be carefully considered.

- Diastereoselectivity of the reaction would enhance, when the directions of both asymmetric induction are parallel. The combination of the substrate and reagent is called matched pair. If the directions are opposite each other, the stereochemical combination is called mismatched pair.

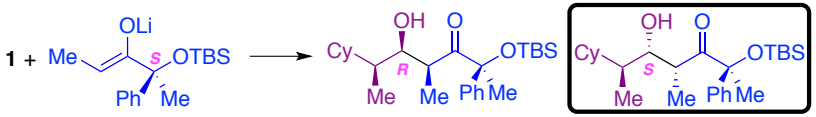
(Diasteleoselective aldol reaction controlled by chiral **aldehyde**)



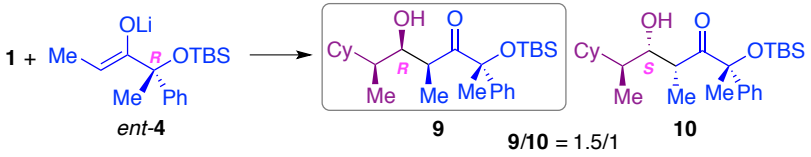
(Diasteleoselective aldol reaction controlled by chiral **enolate**)



(Aldol reaction with **matched pair**)



(Aldol reaction with **mismatched pair**)

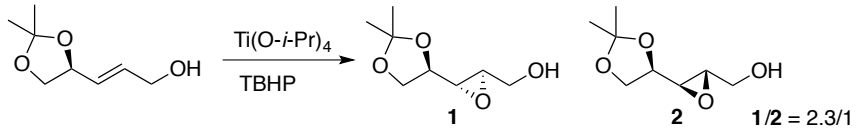


S. Masamune, *Angew. Chem. Int. Ed. Engl.*, **1980**, *19*, 557.

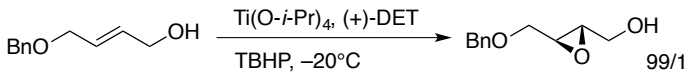
4) Reagent-controlled reaction

- In the reagent-controlled reactions, the stereochemistry of the reagent (or catalyst) predominantly affects the stereoselectivity of the reaction.
- A new chiral center possessing the desired configuration can be created on a chiral substrate independent of its stereochemistry by choosing the enantiomeric reagent (or catalyst).

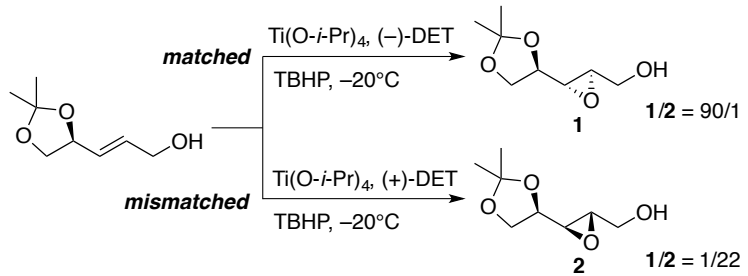
(Substrate-controlled epoxidation)



(Enantioselective epoxidation (Katsuki-Sharpless oxidation))



(Reagent-controlled epoxidation)

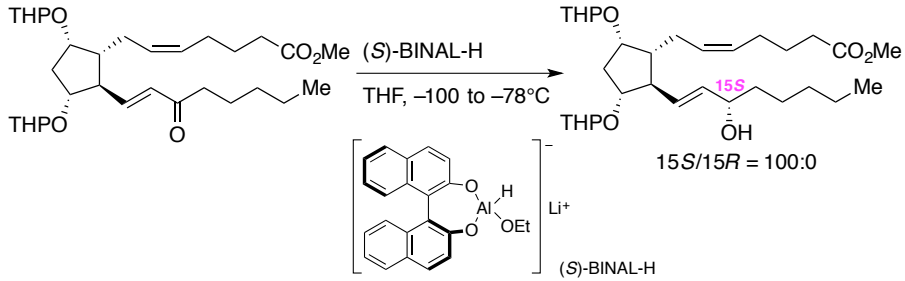


S. Masamune, K. B. Sharpless *J. Am. Chem. Soc.*, **1982**, *47*, 1373.
See also, S. Masamune, *Angew. Chem. Int. Ed. Engl.*, **1985**, *24*, 1.

(c) How to control stereochemistry

1) Chiral reagent

- In the reaction producing a chiral compound from an achiral substrate, the product may be obtained as an optically active form, if the reagent is modified with an enantiopure substituent.
- The optically active reagent is called chiral reagent.
- The reaction with the chiral reagent proceeds enantioselectively. The product does not contain the chiral substituent on the chiral reagent.
- Stoichiometric or excess amount of the chiral reagent is required to obtain the desired chiral product with high ee.



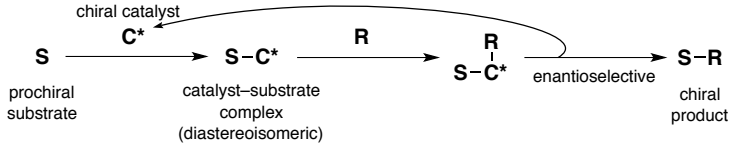
R. Noyori, *J. Am. Chem. Soc.*, **1979**, *101*, 3129; **1984**, *106*, 6709; **1984**, *106*, 6717.

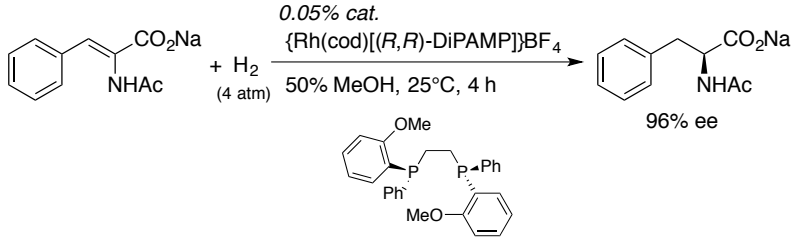
2) Chiral catalyst

- If the reaction proceeds through a catalyst, the chiral product may be obtained as an optically active form, if the catalyst is modified with an enantiopure substituent or compound.
- The optically active catalyst and the enantiopure ligand are called chiral catalyst and chiral ligand, respectively. The enantioselective reaction through a chiral catalyst is called catalytic asymmetric reaction.
- In the catalytic asymmetric reaction, a prochiral substrate (**S**) interacts with a chiral catalyst (**C***) to form a chiral intermediate (**S**–**C***), which is often called catalyst–substrate complex. The

complex reacts with another substrate (or reagent) (**R**) to form the desired product (**S**–**R**). The chiral catalyst is regenerated and then activates **S** again.

- The reagents employed in catalytic asymmetric reactions are achiral.



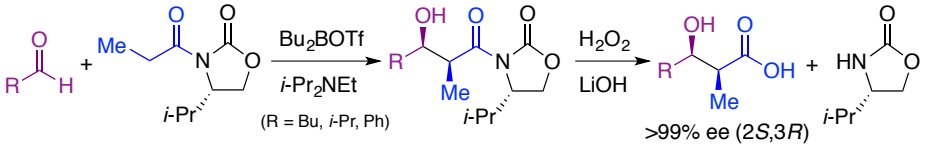


(*R*,*R*)-DiPAMP

W. S. Kowles, *J. Am. Chem. Soc.*, **1975**, *97*, 2567; *Acc. Chem. Res.* **1983**, *16*, 106.

3) Chiral auxiliary

- An achiral or racemic substrate can be modified with an enantiopure compound in order to obtain the enantio-enriched product, when it has a reactive functional group, *e.g.* carboxylate, alcohol, or amine. The enantiopure compound for the chiral modification is called chiral auxiliary.
- The chiral auxiliary can be removed with hydrolysis *etc.* after the desired stereoselective reaction. The used chiral auxiliary can be recycled.
- In this case, the substrate has the chiral center stemming from the auxiliary. Therefore, the stereoselective reaction involving the chiral auxiliary is not enantioselective reaction, but diastereoselective one.
- It is relatively easy to design the key intermediate involving the substrate and chiral auxiliary and to predict the stereochemistry of the product. Therefore, the stereoselective reaction using a chiral auxiliary is frequently used in organic synthesis as compared to other methods.



D. A. Evans, *J. Am. Chem. Soc.*, **1981**, *103*, 2127.

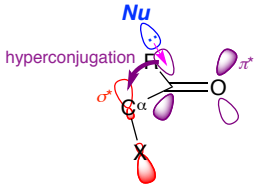
(3) Stereochemistry in the nucleophilic addition and reduction of carbonyl groups

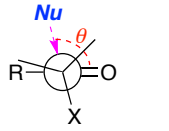
1) Acyclic 1,2-asymmetric induction

- Nowadays, the nucleophilic addition is believed to mostly proceed through the transition state proposed by Felkin and Ahn. However, several transition state models have been proposed and used for illustrating the stereochemistry of the nucleophilic addition. This section describes not only the Felkin-Ahn model but also the other transition state models.

Felkin–Ahn model

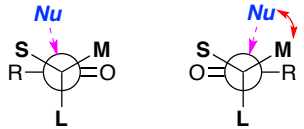
- In a nucleophilic addition, the nucleophile donates its lone pair to the π^* orbital of carbonyl group.
- In the transition state, the electrons shared between the nucleophile and π^* orbital conjugate the σ^* orbital of C^{α}–X bond.
- The hyperconjugation stabilizes the transition state.





Newman projection

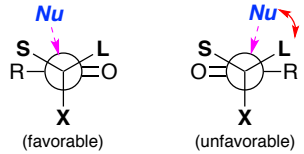
- In the transition state, the angle of ***Nu***–C–O (θ) is *ca.* 110°.
- If the carbonyl substrate has a chiral center on its α-carbon, the largest substituent (**L**) is located on the antiperiplanar position of ***Nu***.
- To avoid the steric hindrance to the attack of the nucleophile to the carbonyl, the middle (**M**) and smallest substituent (**S**) are respectively located by the carbonyl oxygen and carbonyl substituent R in the favorable transition state.



Felkin–Ahn model
(**L** > **M** > **S**)

polar-Felkin–Ahn model

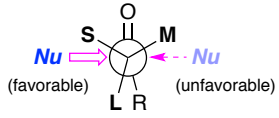
- In a C–X bond, the large electronegativity of X causes decrease in the energy level of its σ^* orbital. The effect enhances the ability to accept electrons through the hyperconjugation.
- Therefore, an additional rule is required for predicting or explaining the stereochemistry of the nucleophilic addition, when the electrophilic substrate has a polar substituent on its α-carbon of carbonyl group.
- The polar substituent **X**, *e.g.* OMe, Cl, *etc.*, prefers the antiperiplanar position of the nucleophile ***Nu*** in the Felkin-Ahn transition state.
- To avoid the steric hindrance to the attack of the nucleophile to the carbonyl, the large (**L**) and small substituent (**S**) are respectively located by the carbonyl oxygen and carbonyl substituent R in the favorable transition state.



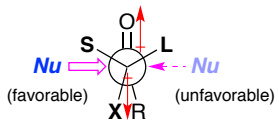
polar-Felkin–Ahn model
(**L** > **S**, **X** = polar substituent)

Cram's rule

- Cram's rule is an empirical method for predicting the stereochemistry of the nucleophilic addition.
- It is assumed that the largest substituent (**L**) prefers to stay in the eclipsed position of carbonyl substituent R.
- The nucleophile ***Nu*** attacks on the carbonyl carbon from the side of the smallest substituent **S**.
- In the case of ketone or aldehyde bearing a polar substituent **X**



Cram's rule

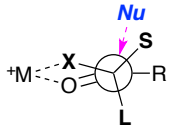


Conforth model

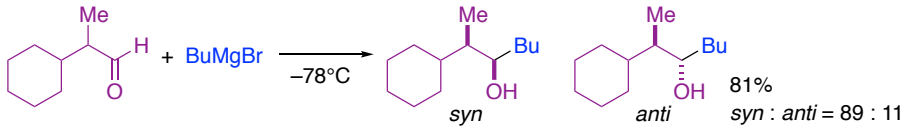
on the α-carbon, the polar substituent prefers to stay in the eclipsed position of carbonyl substituent R because of the dipole interaction between C=O and C^{α}–**X** (Cornforth model).

2) Chelation-controlled 1,2-asymmetric induction

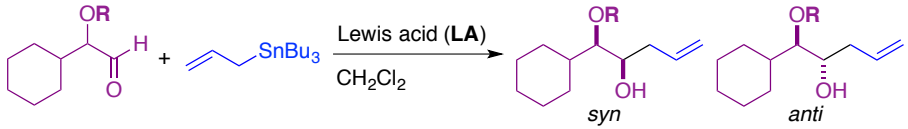
- Stereoselectivity in the nucleophilic addition is often controlled by a metal atom, when the substrate has a Lewis basic heteroatom (*e.g.* -OR) on its α-carbon and the metal atom has sufficient Lewis acidity.
- The heteroatom and the carbonyl oxygen interact with the metal atom to form a chelate complex as shown in the right figure. The coordination of carbonyl oxygen to metal enhances the reactivity of the substrate.
- The nucleophile ***Nu*** attacks on the carbonyl carbon from the side of the smaller substituent **S**.
- In general, the chelation-controlled reaction proceeds with the opposite stereoselectivity to the Felkin–Ahn-controlled reaction.



chelation model
(**L** > **S**, **X** = OR *etc.*)



H. Yamamoto, *J. Am. Chem. Soc.* **1988**, *110*, 3588.



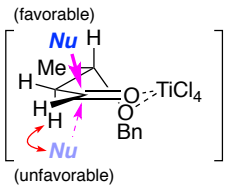
LA = BF_3•OEt_3, **R** = TBS — *syn* : *anti* = 9 : 91 (Felkin-controlled)
LA = BF_3•OEt_3, **R** = Bn — *syn* : *anti* = 39 : 61
LA = $MgBr_2$, **R** = TBS — *syn* : *anti* = 21 : 79
LA = $MgBr_2$, **R** = Bn — *syn* : *anti* = >250 : 1 (chelation-controlled)

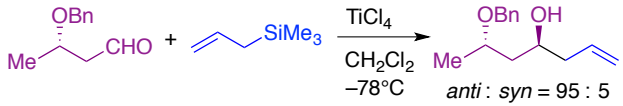
G. E. Keck, *Tetrahedron Lett.* **1984**, *25*, 265.

3) 1,3-Asymmetric induction

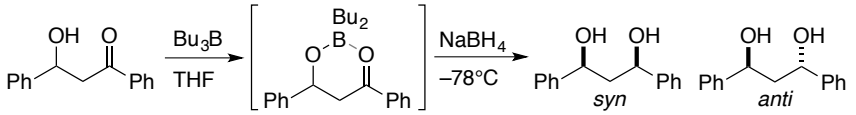
i) Chelation-controlled 1,3-asymmetric induction

- Stereoselectivity in the nucleophilic addition is sometimes controlled by the stereochemistry of the β-carbon of the substrate, which has a Lewis basic heteroatom on its β-carbon.
- The substrate readily forms a 6-membered chelate complex with a Lewis acid possessing multiple coordination sites (*e.g.* $TiCl_4$, $SnCl_4$) as shown in the right figure. The nucleophilic addition will occur from the chelate intermediate.
- The nucleophile ***Nu*** accesses the carbonyl carbon from above to avoid the steric interaction with the pseudo-axial proton at the α-position.





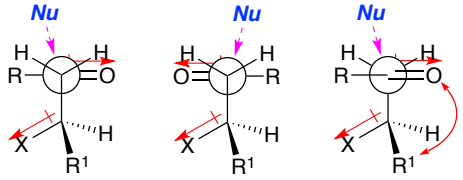
M. T. Reetz, *J. Am. Chem. Soc.* **1983**, *105*, 4833.

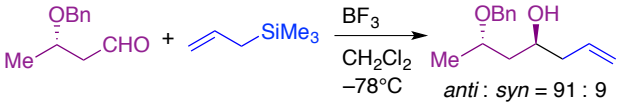


K. Narasaka, *Tetrahedron* **1984**, *40*, 2233.

ii) Non-chelation-controlled 1,3-asymmetric induction

- The nucleophilic addition (Sakurai-Hosomi reaction) provides the 1,3-*anti*-product with high diastereoselectivity when BF_3 is used as a promoter, although BF_3 cannot form the chelate intermediate.
- In the favorable transition state, substituent R^1 on the β-carbon would be located at the antiperiplanar position of the formyl group.
- The carbonyl double bond faces the opposite direction to the C–X bond to avoid the dipole repulsion.
- The nucleophile ***Nu*** attacks on the carbonyl carbon from the opposite side to the β-carbon.

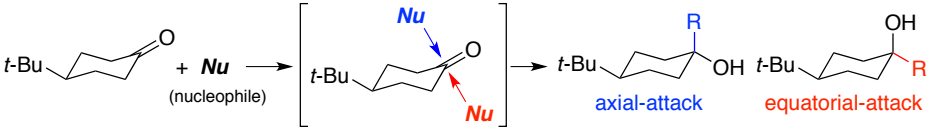




M. T. Reetz, *Tetrahedron Lett.* **1984**, *25*, 729. D. A. Evans, *Tetrahedron Lett.* **1994**, *35*, 8537.

4) Stereochemistry in the reaction of cyclohexanone

- The stereoselectivity of the nucleophilic addition of cyclohexanone is strongly affected by the substituent and/or the size of the nucleophile.
- Small nucleophiles prefer the axial attack in general. Large ones prefer the equatorial attack.



Nu = $LiAlH_4$ (R = H) — **90** : 10
Nu = Li(*s*-Bu)$_3$BH (L-selectride) (R = H) — 12 : **88**
Nu = MeLi (R = Me) — 21 : **79**
Nu = MeLi (with MAD) (R = Me) — **99** : 1

H. Yamamoto, *J. Am. Chem. Soc.* **1985**, *107*, 4573.

(4) Stereochemistry in the reaction of enolates

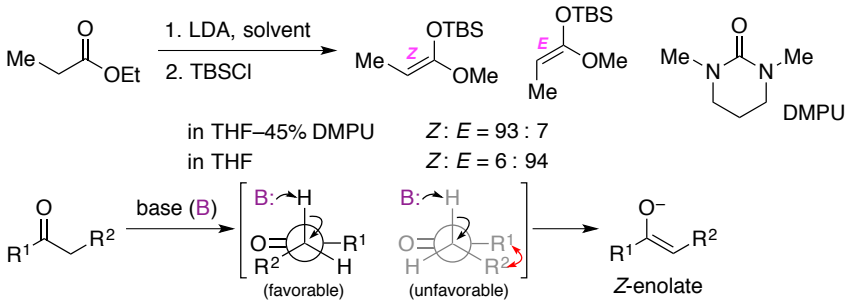
1) Stereochemistry in the formation of enolates

• Enolates are generated from carbonyl compounds through the deprotonation of the α-proton with a base. The enolates are possible to possess geometric isomerism. The stereochemistry can be controlled by metal and/or reaction conditions.

Lithium enolate

• The deprotonation often proceeds through the conformation in which a C_α–H bond is perpendicular to the carbonyl group, because the σ-orbital of the C–H bond is required to interact with π^*-orbital of the C=O bond in order to form the C=C bond in the resulting enolate.

• Repulsion between R^1 and R^2 in the carbonyl substrate controls the *E*/*Z* selectivity of the enolate.



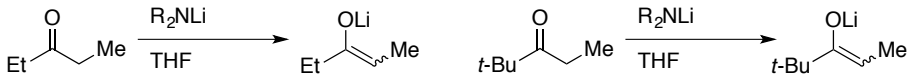
in THF–45% DMPU *Z* : *E* = 93 : 7

in THF *Z* : *E* = 6 : 94

R. E. Ireland, *J. Org. Chem.* **1991**, *56*, 650.

• The deprotonation is believed to proceed through Ireland's transition state model, when lithium dialkylamide was used as the base.

• Higher reaction temperature is advantageous to the formation of *E*-enolate. *Z*-Enolate may be kinetically preferable, and *E*-enolate may be thermodynamically preferable.



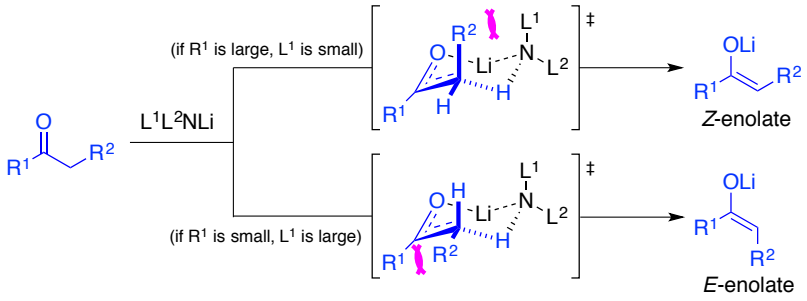
with (***t*-Bu**)(TMS)NLi at 23°C ***E*** : *Z* = 94 : 6

with **Ph**(TMS)NLi at –78°C *E* : ***Z*** = 7 : 93

with (***t*-Bu**)(TMS)NLi at 23°C *E* : ***Z*** = 11 : 89

with **Ph**(TMS)NLi at –78°C *E* : ***Z*** = 0 : 100

L. Xie, *J. Org. Chem.* **1997**, *62*, 7516.



R. E. Ireland, *J. Am. Chem. Soc.* **1976**, *98*, 2868.

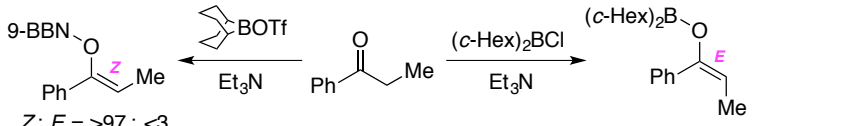
Soft enolization T. Mukaiyama, *Chem. Lett.* **1976**, 559: *Bull. Chem. Soc. Jpn.* **1980**, *53*, 174.

• Ketones and thioesters can be transformed into their enolates in the presence of a tertiary amine and a Lewis acid (soft enolization). The interaction between the carbonyl oxygen and the Lewis acid facilitates the deprotonation of the α-hydrogen.

• The soft enolization is useful for preparing boron, tin, silicon, titanium, magnesium enolates.

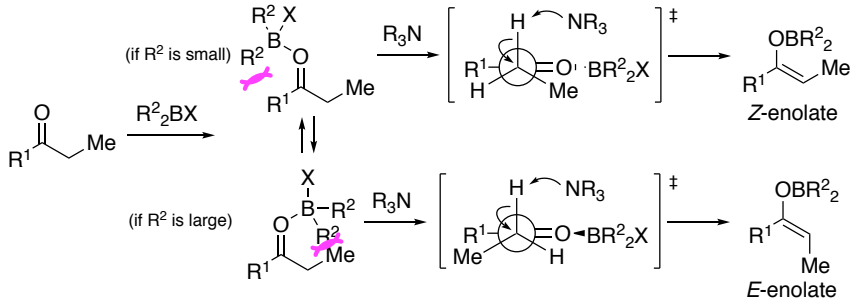
• Stereochemistry of the boron enolate can be controlled by choosing the boron Lewis acid. *Z*-Enolate will be selectively formed when two alkyl substituents on the boron atom are relatively small.

• Triflate or iodide is favorable for the formation of *Z*-enolate. Chloride is favorable for the formation of *E*-enolate.



Z : *E* = >97 : <3 *Z* : *E* = <3 : >97

H. C. Brown, *J. Org. Chem.* **1993**, *58*, 147.

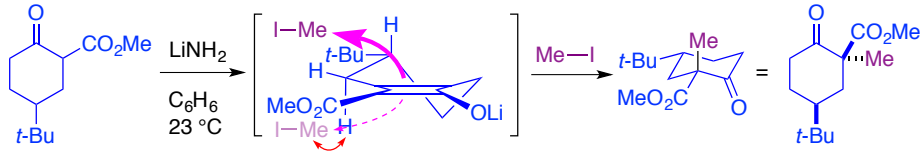


2) Stereochemistry in the reaction of chiral enolates with electrophiles

Cyclohexanone enolate

• The enolates of cyclohexanones take a half-chair conformation. The substituent on the cyclohexene ring prefers an equatorial position.

• An electrophile preferentially approaches the enolate from above in order to avoid the steric hindrance of the pseudo-axial proton.



M. E. Kuehne, *J. Org. Chem.* **1970**, *35*, 171.

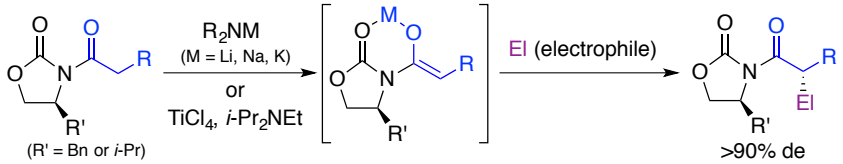
Evans's oxazolidinone

• Optically active oxazolidinones, which are readily prepared from β-amino alcohols and phosgene, are widely used as the chiral auxiliaries for carboxylate enolates.

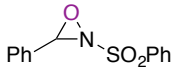
• In general, the *N*-acyloxazolidinone gives its *Z*-enolate through deprotonation.

• The carbonyl oxygen of the oxazolidinone can bond to the metal atom of the enolate. The chelation fixes the conformation of the enolates.

• Electrophiles preferentially approaches the enolate to avoid the steric hindrance of the substituent R.
• Various electrophiles are possible to react with the chiral enolate to give the optically active α-substituted carboxylates with high enantiomeric excesses.



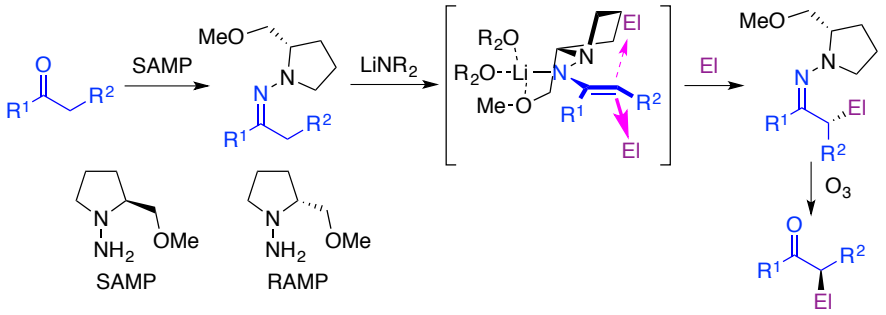
El:



(R–X) D. A. Evans, *J. Am. Chem. Soc.* **1982**, *104*, 1737; **1990**, *112*, 8215.
($ArSO_2N_3$) D. A. Evans, *J. Am. Chem. Soc.* **1990**, *112*, 4011.
(BocN=NBoc) D. A. Evans, *Tetrahedron* **1988**, *44*, 5525.
(Davis reagent) D. A. Evans, *J. Am. Chem. Soc.* **1985**, *107*, 4346.

Enders's hydrazone (SAMP/RAMP)

• SAMP and RAMP are prepared from (*S*)-proline and (*R*)-glutamic acid, respectively. These hydrazones can form chiral hydrazones with an achiral ketone or aldehyde.
• The hydrazones are readily deprotonated with lithium dialkylamides to give their azaenolates. Coordination of the methoxy group to lithium fixes the conformations of the azaenolates.
• Electrophiles react with the azaenolates from the same side of the MeO group to avoid the steric hindrance of the pyrrolidine ring.

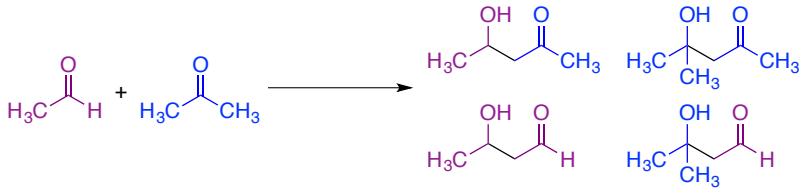


D. Enders, *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 549; (review) *Tetrahedron* **2002**, *58*, 2253.

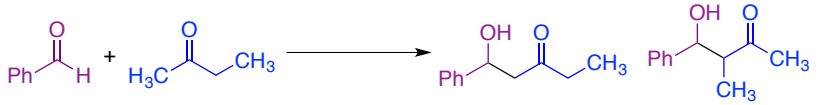
(5) Stereoselective aldol reaction

1) Problems in aldol reaction

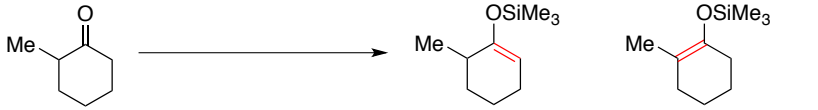
• Aldol reaction is the reaction of an enolate with an aldehyde or a ketone, giving β-hydroxy carbonyl compound (aldol).
• Chemoselectivity



• Regioselectivity in the formation of enolate



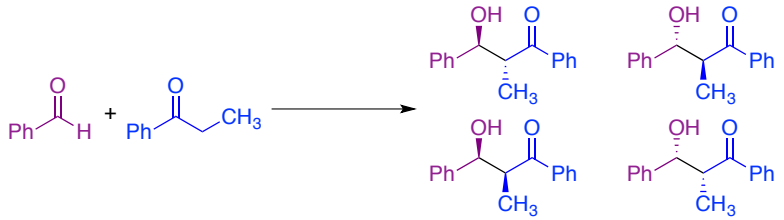
These problems are solved by preformed enolate. Formation of more substituted enolate is thermodynamically favored. Formation of less substituted enolate is kinetically favored.



(1) LDA, THF, –78°C (2) Me_3SiCl, –78°C to rt 99 : 1
Et_3N, Me_3SiCl, DMF, 130°C, 90 h 12 : 88

H. O. Hause, *J. Org. Chem.* **1969**, *34*, 2324. (modified method) 第 4 版 実験化学講座 24, p 154.

• Diastereo- and enantioselectivities (stereoselectivity)

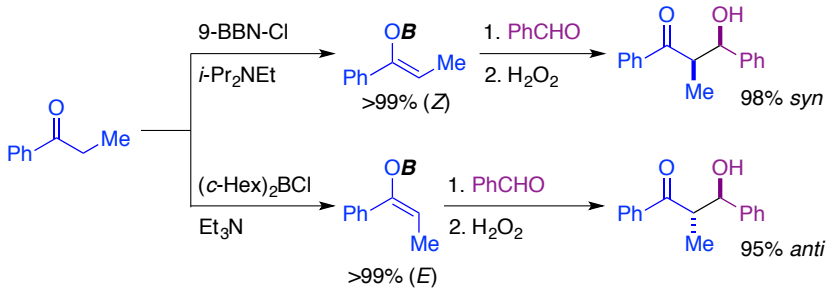


2) Stereocontrol of vicinal chiral centers of the aldol product

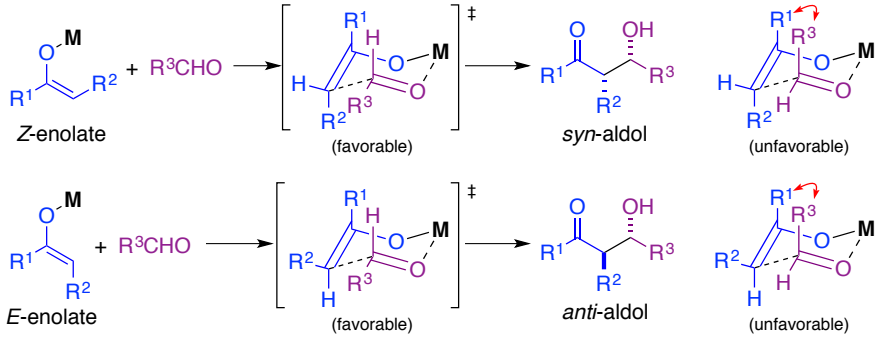
• In the aldol reactions of prochiral enolates with carbonyl compounds, the aldol products have vicinal chiral centers. The stereochemistry of the vicinal chiral centers is often controllable.

Aldol reactions through Zimmerman-Traxler transition state

• The electrophilic substrate is activated by the interaction between its carbonyl oxygen and the metal atom of enolate, when the enolate has a strong Lewis acidic metal. The complexation allows the intramolecular aldol reaction through 6-membered transition state (Zimmerman–Traxler transition state).
• In the aldol reactions through Zimmerman–Traxler transition state, *Z*-enolates selectively yield *syn*-product. *Anti*-aldols are preferentially obtained from *E*-enolates.



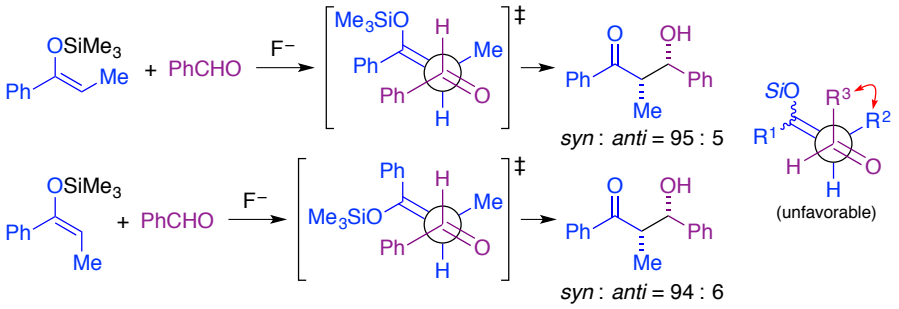
H. C. Brown, *J. Am. Chem. Soc.* **1989**, *111*, 3441.



H. E. Zimmerman, *J. Am. Chem. Soc.* **1956**, *79*, 1920.

Aldol reactions through open transition state model

- If the metal atom of enolate cannot interact with the carbonyl oxygen, their aldol reaction proceeds through the antiperiplanar transition state, in which the dipole of C=O is arrayed to avoid the repulsion of the dipole of C–OSi.
- Both of *E*- and *Z*-enolates selectively give the *syn*-aldol product, because the stereochemistry is mainly controlled by the steric repulsion between **R²** and **R³**.

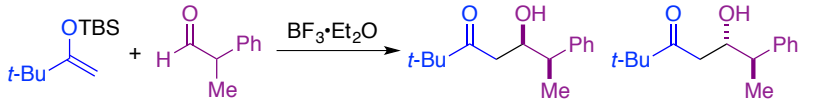


R. Noyori, *J. Am. Chem. Soc.* **1981**, *103*, 2106; **1983**, *105*, 1598.

3) Stereocontrol with the chiral center of the electrophilic substrate (aldehyde)

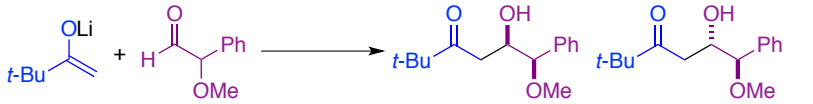
- In the aldol reactions of chiral α-substituted aldehydes, the stereochemistry is controlled by Felkin–Ahn or chelate model.

Felkin–Ahn-controlled aldol reaction



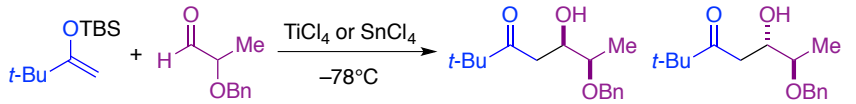
C. H. Heathcock, *J. Am. Chem. Soc.* **1983**, *105*, 1667.

Polar-Felkin–Ahn-controlled aldol reaction



C. H. Heathcock, *J. Am. Chem. Soc.* **1987**, *109*, 3353.

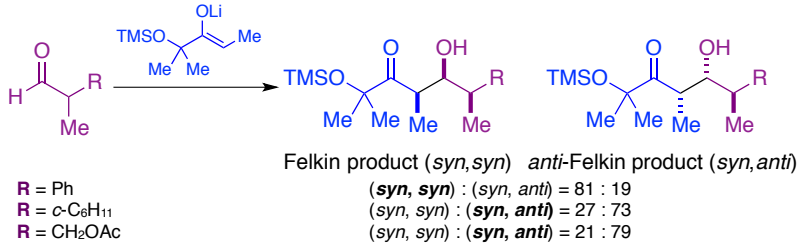
Chelation-controlled aldol reaction

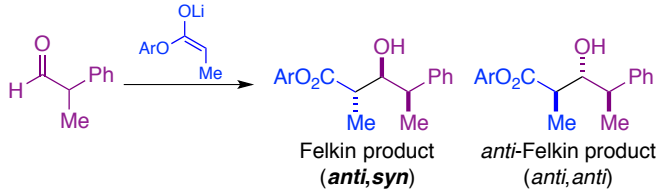


M. T. Reetz, *Tetrahedron Lett.* **1984**, *25*, 729.

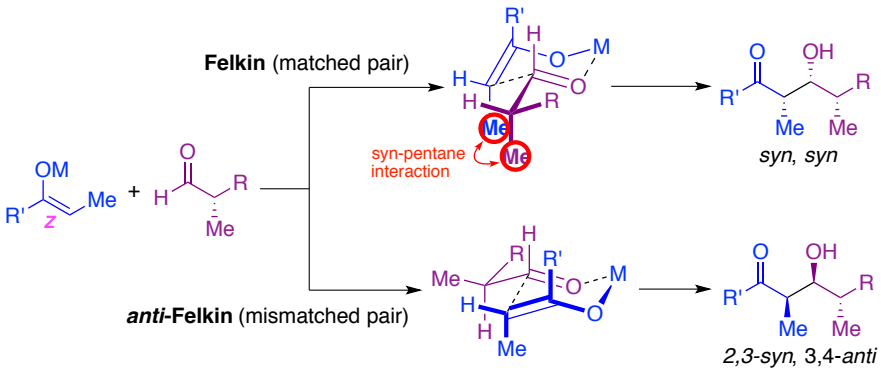
Double stereodifferentiation: Felkin–Ahn model and Zimmerman–Traxler model

- Reactions of *Z*- and *E*-enolates

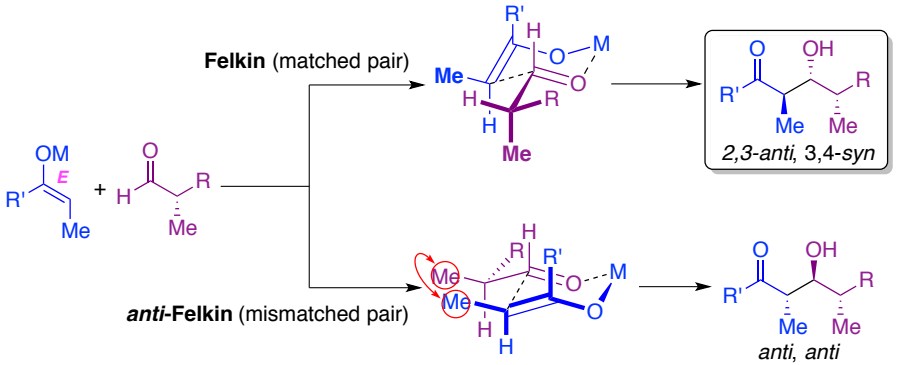




• In the aldol reaction of *Z*-enolate, the matched-pair transition state is unfavorable because of the syn-pentane interaction between the enolate α-substituent and the middle-sized α-substituent of aldehyde. Therefore, the stereoselectivity varies along with the substituent R of the aldehyde.



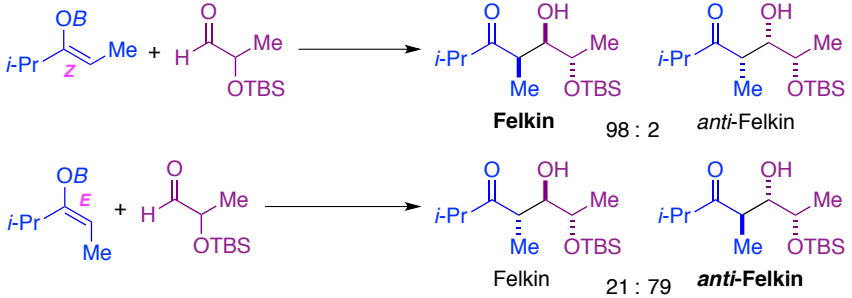
• In the aldol reaction of *E*-enolate, the matched-pair transition state is favorable. Therefore, the aldol reaction generally proceeds through Felkin-Ahn transition state to give (2,3-*anti*, 3,4-*syn*)-product with good selectivity.



W. Roush, *J. Org. Chem.* **1991**, *56*, 4151.

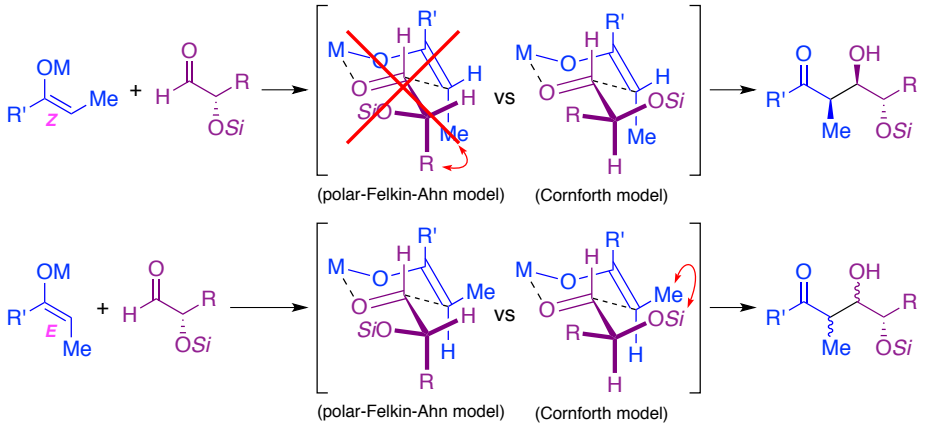
<u>Double stereodifferentiation: polar-Felkin–Ahn model vs Zimmerman–Traxler model</u>

• Reactions of *Z*- and *E*-enolates



• Chiral α-oxy-substituted aldehydes react with *Z*-enolates in high stereoselectivity. Meanwhile, the stereoselectivity is disturbed in the aldol reaction of *E*-enolate.

• Cornforth model is more plausible for the aldol reaction than Felkin-Ahn model.

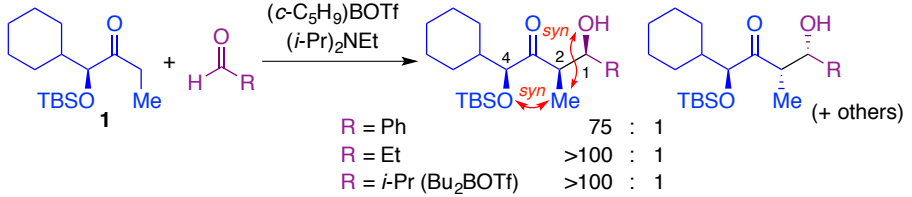


D. A. Evans, *Angew. Chem. Int. Ed.* **2003**, *42*, 1761.

4) Stereocontrol with the chiral center of the enolate substrate

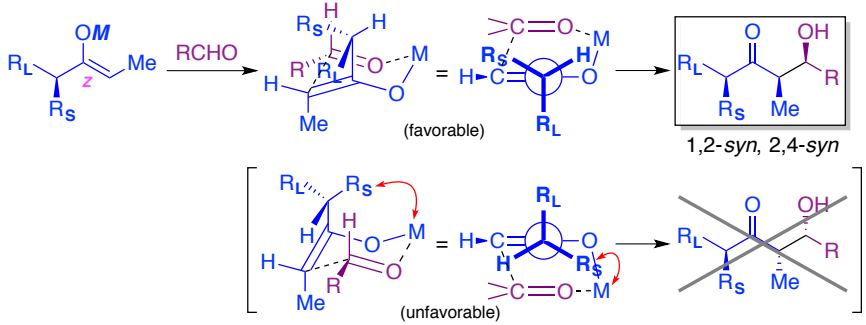
<u>Reaction of *Z*-enolate bearing a chiral center at its α-position</u>

• The *Z*-enolate of chiral ketone **1** reacts with an aldehyde to give the 1,2-*syn*-2,4-*syn* aldol product with high stereoselectivity.



R = Ph	75 : 1
R = Et	>100 : 1
R = *i*-Pr (Bu_2BOTf)	>100 : 1

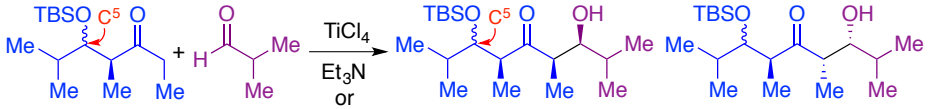
S. Masamune, *J. Am. Chem. Soc.* **1981**, *103*, 1566.



D. A. Evans, *J. Am. Chem. Soc.* **1991**, *113*, 1047.

• According to Evans, the large-sized substituent R_L on the α-carbon locates the antiperiplanar position of the forming bond to avoid the steric repulsion between R_L and the aldehyde. In the transition state, the middle-sized substituent R_S is oriented to the enolate C=C bond to escape the steric repulsion toward the enolate metal M.

• The chiral center of β-position scarcely affects the stereochemistry of the aldol reaction.

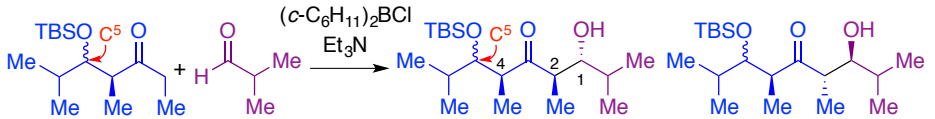


C5 ··· R 95 : 5
C5 ··· S 95 : 5

D. A. Evans, *J. Am. Chem. Soc.* **1991**, *113*, 1047.

Reaction of *E*-enolate bearing a chiral center at its α-position

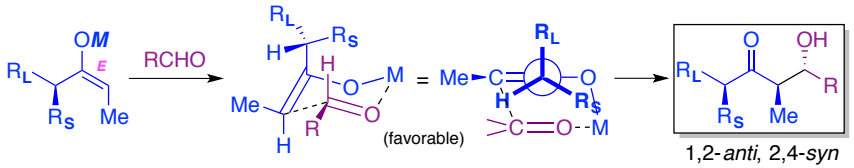
• The *E*-enolate of a chiral ketone **2** reacts with an aldehyde to give the 1,2-*anti*, 2,4-*syn* aldol product with high stereoselectivity.

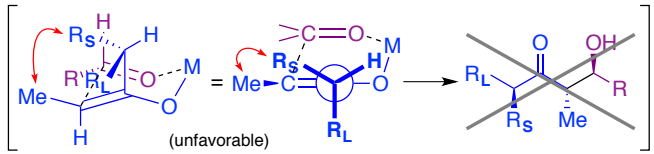


2

C5 ··· R 94 : 6
C5 ··· S 96 : 4

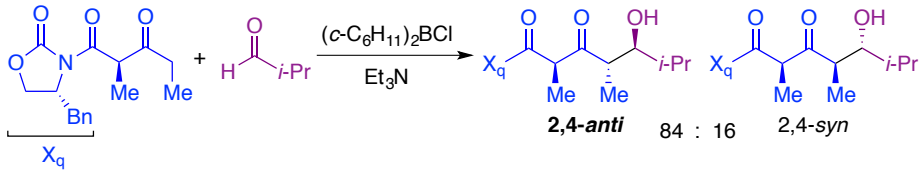
D. A. Evans, *Tetrahedron* **1992**, *48*, 2127.





see also, C. Gennari, I. Paterson, *Tetrahedron* **1993**, *49*, 685.

• Sometimes, the aldol reactions of *E*-enolate selectively gives 1,2-*anti*, 2,4-*anti* aldol product.



2,4-*anti* 84 : 16 2,4-*syn*

D. A. Evans, *Tetrahedron* **1992**, *48*, 2127.

5) Asymmetric aldol reaction of the enolate modified with a chiral auxiliary

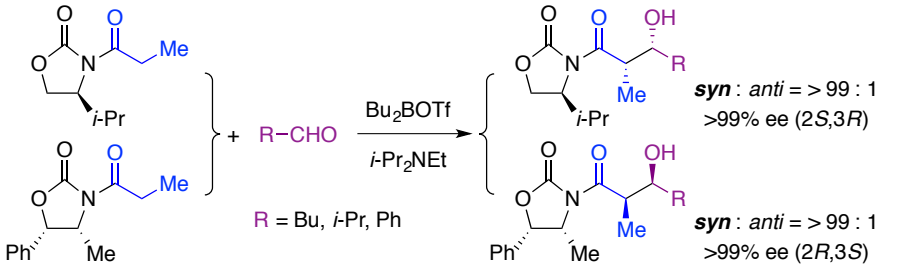
Syn-selective Evans asymmetric aldol reaction

• Chiral *N*-alkanoyloxazolidinones react aldehydes to give *syn*-aldol products with high stereoselectivities. Boron or titanium Lewis acid is commonly used for the enolization.

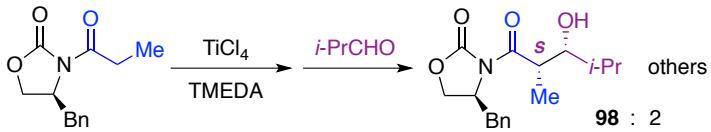
• In general, the alkanoyl group is converted to its *Z*-enolate, which react with an aldehyde through Zimmerman-Traxler transition state.

• It is noteworthy that the aldehyde preferentially reacts the *re*-face of the enolate bearing (4*S*)-oxazolidinone to give the (2*S*,3*R*) product. Other electrophiles, *e.g.* haloalkane, attack the *si*-face in general.

• When the oxazolidinone derived from (1*S*,2*R*)-norephedirine is used as the chiral auxiliary, the aldol reaction selectively gives the *syn*-(2*R*,3*S*)-aldol.

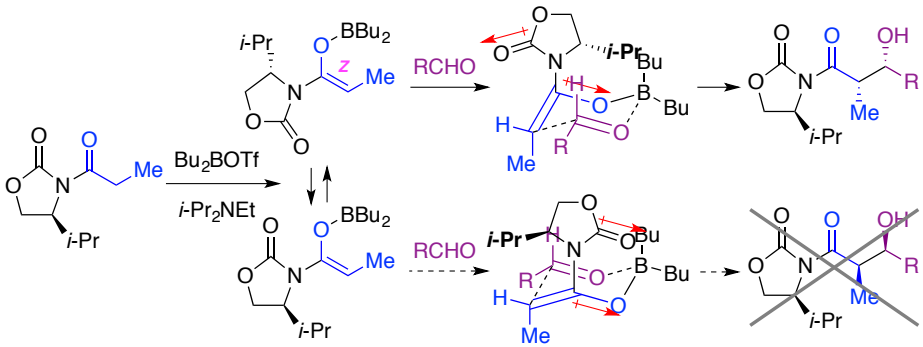


D. A. Evans, *J. Am. Chem. Soc.* **1980**, *113*, 1047.



D. A. Evans, *J. Am. Chem. Soc.* **1991**, *113*, 1047.

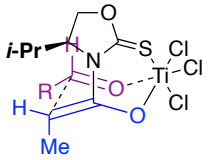
• Possible reaction pathways and transition states:

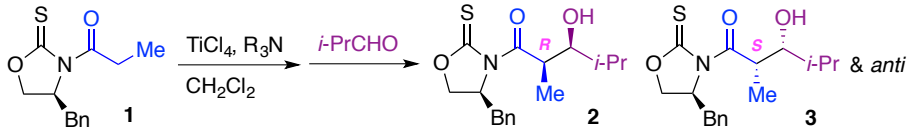


• In the transition state of the asymmetric aldol reaction, the carbonyl oxygen of the oxazolidinone is dissociated from the metal (B or Ti) of the enolate. The C=O of the chiral auxiliary is oriented to the antiperiplanar position of the C–O bond of enolate in order to cancel these dipoles.

• The aldehyde attacks the enolate to avoid the steric hindrance of the substituent of chiral oxazolidinone.

- In the titanium-mediated aldol reaction of *N*-alkanoyloxazolidinethione **1**, each stereoisomer of the *syn*-aldol product can be selectively prepared by choosing amine base and Lewis acid stoichiometry.
- The aldol reaction of **1** gives (2*S*)-aldol **2**, which corresponds to the Evans aldol product, when it is conducted with 2 eq. of $TiCl_4$ and 2.5 eq. of diamine, such as TMEDA or spartein.
- The antipode, **3**, is obtained from the reaction with 1 eq. of $TiCl_4$ and 1.1 eq. of monoamine, such as *i*-Pr_2NEt. The thiocarbonyl group forms a chelate with the titanium atom in the transition state.



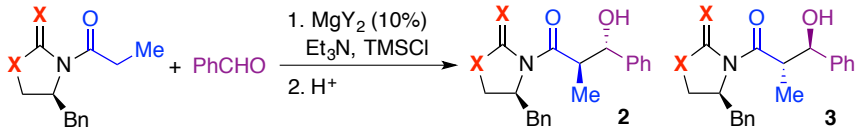


$TiCl_4$ (2 eq.), *i*-Pr_2NEt (1.1 eq.) **2** : **3** : *anti* = 95 : 0 : 5
$TiCl_4$ (1 eq.), (–)-spartein (2.5 eq.) **2** : **3** : *anti* = 2 : 97 : 1

M. T. Crimmins, *J. Am. Chem. Soc.* **1997**, *119*, 7883.
See also, E. R. Thornton, *J. Org. Chem.* **1991**, *56*, 2489.

<u>*Anti*-selective Evans asymmetric aldol reaction</u>

- The aldol reaction of *N*-alkanoyloxazolidinone is promoted in the presence of TMSCl by a magnesium(II) catalyst to give the *anti*-aldol product.
- The *N*-acyloxazolidinone **1a** is selectively converted into the aldol product **2** with 2*R*-configuration. Meanwhile, the *anti*-(2*S*)-aldol **3** is selectively obtained from the reaction of the thiazolidinethione **1b**.
- The *Z*-enolate is exclusively formed in the soft enolization with the magnesium Lewis acid. However, the magnesium-catalyzed aldol reaction selectively affords the *anti*-aldol products, because it proceeds through boat transition states.

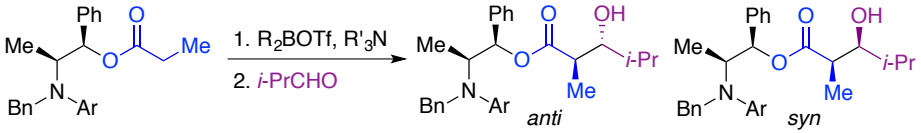


X = O (**1a**) $MgCl_2$ **2a** : **3a** (& others) = 32 : 1
X = S (**1b**) $MgBr_2$•Et_2O **2b** : **3b** (& others) = 1 : 19

(X = O) D. A. Evans, *J. Am. Chem. Soc.* **2002**, *124*, 392.
(X = S and PM3 study on TS) D. A. Evans, *Org. Lett.* **2002**, *4*, 1127.

<u>Abiko-Masamune chiral auxiliary</u>

- In contrast to imides, carboxylate esters is readily converted to *E*- and *Z*-enolates by choosing boron triflate and amine.
- *N*-(Arenesulfonyl)-*N*-benzylnorephedrines are sometimes employed as the chiral auxiliary for the asymmetric aldol reaction. It is noteworthy that the chiral auxiliary allows the selective formation of *E*-enolate and the *anti*-selective asymmetric aldol reaction. Bulky boron triflate (*c*-Hex)$_2$BOTf and small amine Et_3N is of choice for the *anti*-selective aldol reaction.
- The chiral auxiliary is possible to use for the *syn*-selective asymmetric aldol reaction. Use of small boron triflate and bulky amine allows the *syn*-selective aldol reaction.



Ar = Mes R = *c*-Hex, R'$_3$N = Et_3N ***anti*** : *syn* = >98 (96% de) : 2

Ar =  R = Bu, R'$_3$N = *i*-Pr_2NEt *anti* : ***syn*** = 6 : >94 (94% de)

(*anti*-selective) A. Abiko, S. Masamune, *J. Am. Chem. Soc.* **1997**, *119*, 2586.
(*syn*-selective) A. Abiko, S. Masamune, *Tetrahedron Lett.* **1998**, *39*, 1873.
A. Abiko, S. Masamune, *J. Org. Chem.* **2002**, *67*, 5250. (see also) 安孫子淳, 有機合成化学協会誌, **2003**, *61*, 24.