Stereochemical Control of Polyketides through Asymmetric Aldol Reaction

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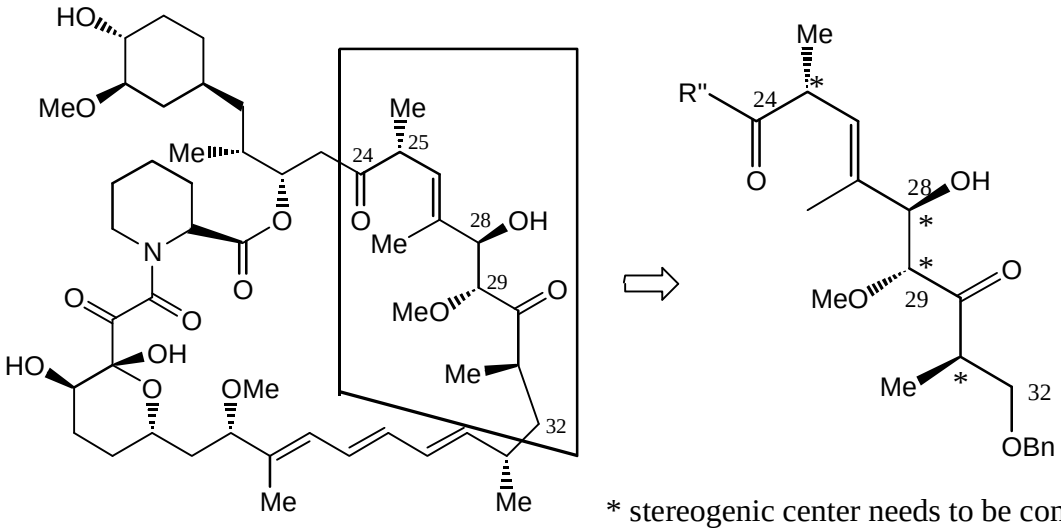
(ABSTRACT)

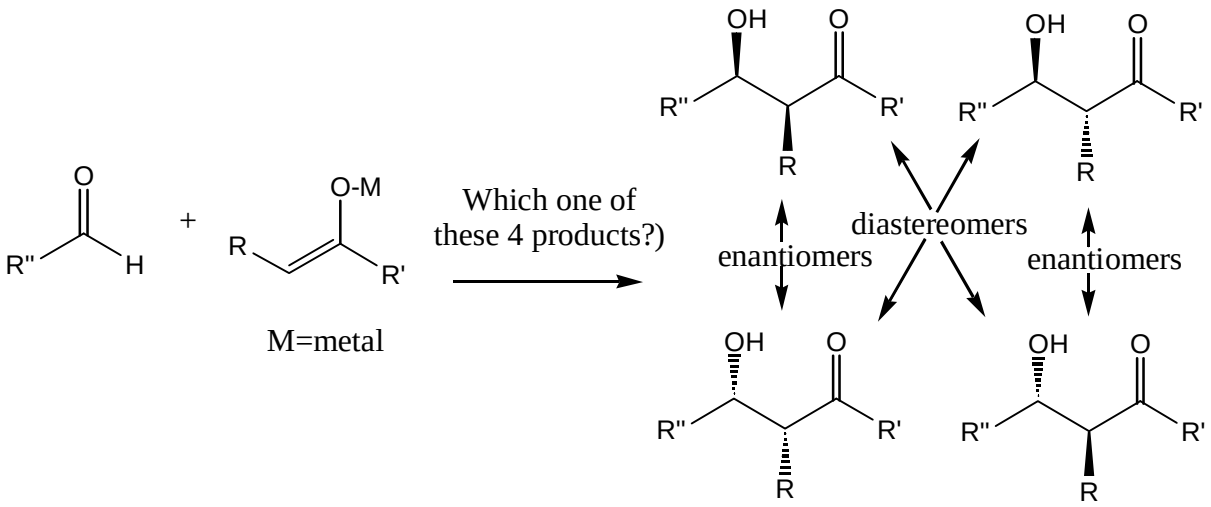
Polyketides are a group of complex natural products that can inhibit the growth of bacteria, viruses, fungi, and tumor cells. Most polyketides are very difficult to extract from bacteria. Therefore, numerous syntheses of polyketide-related synthons have been attempted.



An example of complex polyketide - Rapamycin

However, controlling the stereochemistry of the polyketide poses the most challenging task for researchers. The aim of this report is to discuss control of the stereochemistry of the polyketide-related synthons in asymmetric aldol reactions. Several important methodologies for stereochemical control in the aldol reaction exist. The first approach is to control the enolate geometry and the aldehyde (or ketone) geometry. The

second approach is to use a chiral auxiliary and chiral ligands. The third approach is to use a chiral catalyst, which is the most efficient method if the catalyst operates with complete efficiency. Proposed transition states are also described to explain the resulting stereochemistry of the aldol adduct.



The Asymmetric Aldol Reaction

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Chapter One. Introduction

The asymmetric aldol reaction is one of the most powerful reactions for stereoselective carbon-carbon bond formation in organic synthesis.[1] Specifically, the aldol reaction between the metal enolate and the aldehyde or ketone is widely used for constructing polyketide-derived natural products.[2] Two examples of polyketides are the C-1 to C-11 portion of the antibiotic lonomycin A[3] (Figure 1) and the C-24 to C-32 portion of rapamycin (Figure 2).[4]

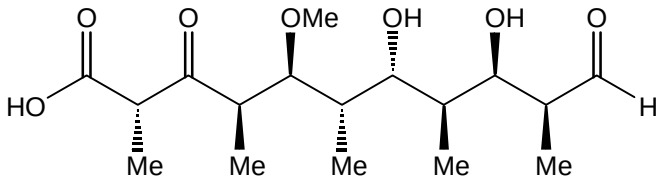

Figure 1. Lonomycin A C-1- C-11 Synthon

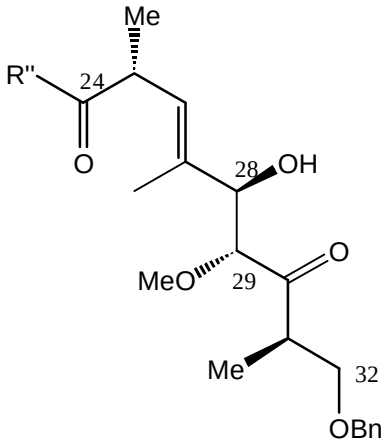

Figure 2. C-24 - C-32 of Rapamycin

[1]Heathcock, C. H.; *Asymmetric Aldol Condensations*, **1984**, 177-183.
[2] Evans, D. A.; Rieger, D. L.; Bilodeau, M. T.; Urpi, F.; *J. Am. Chem. Soc*. **1991**, 113, 1047-1049.
[3] Evans, D. A.; Clark, J. S.; Metternich, R.; Novack, V. J.; Sheppard, G. S.; *J. Am. Chem. Soc*. **1990**, 112, 866-868.
[4] Paterson, I.; Tillyer, R. D.; *J. Org. Chem*. **1993**, 58, 4182-4184.

The polyketides are a group of natural products that have numerous important biological activities. They are often used in clinical practice as antibiotic, antiviral, antifungal, and immunosuppressive reagents.[5] Most polyketides are difficult to isolate from bacteria, and extracted quantities are usually low.[6] Because of the high demand for polyketides in clinical use and low supply of polyketides in the market, the prices of polyketides are high. As a result, numerous syntheses of polyketide-related synthons have been attempted. However, the synthesis of polyketides is still a very challenging and tedious task. Synthesizing the shortest polyketide may require as many as twenty steps, and each step usually involves the formation of two new chiral centers, the stereochemistry of the aldol adduct must be controlled very carefully.

The basic skeleton of the polyketides is depicted in Figures 1 and 2. Generally, the skeleton of the polyketide has alternating hydroxy (or alkoxy) groups and methyl groups (or hydrogen). The hydroxy group usually comes from the electrophilic aldehyde or ketone, and the α-carbon substituents (R = methyl, ethyl, etc.) are derived from the enolates of asymmetric aldol reactions (Scheme 1). Since different types of α-carbon substituents in the enolate can be used in the aldol reactions, many variations of polyketides are possible. This method provides a flexible and versatile way to synthesize polyketides with different substituents and varied lengths. However, the creation of the two chiral centers in this process is a difficult aspect of the asymmetric aldol reaction to control.

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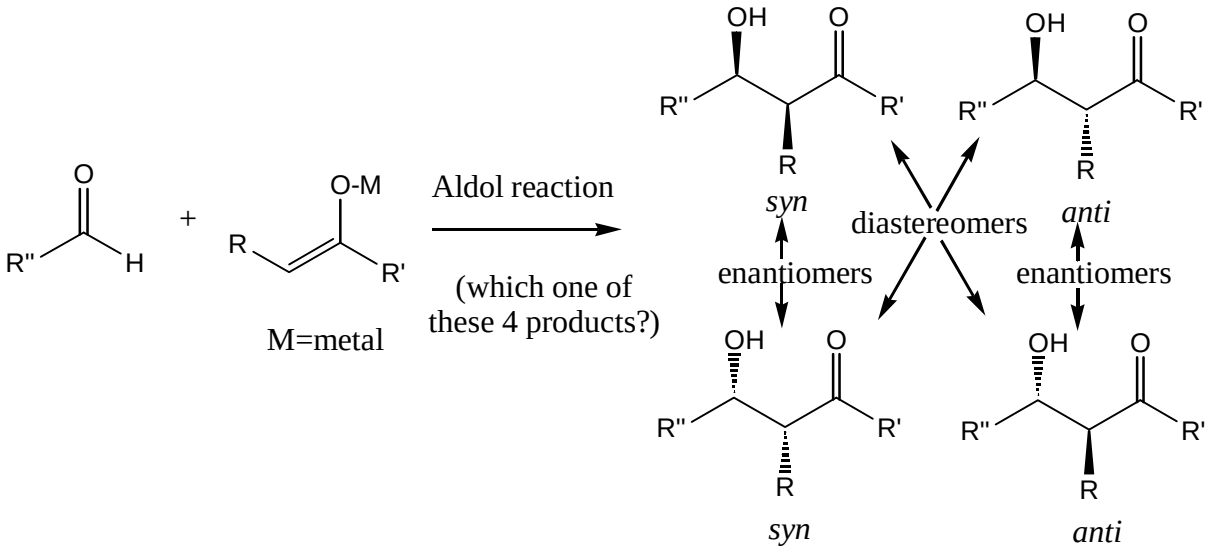
[5] Nakayama, I. Macrolides in Clinical Practice. In *Macrolide Antibiotics: Chemistry, Biology and Practice*, 1st ed.; Omura, S. Ed.; Academic Press, Inc.: New York, **1984**; 262-298.
[6] (a) Katz, L.; *Chem. Rev*. **1997**, 97, 2557. (b) Hopwood, D. A.*; Chem. Rev*. **1997**, 97, 2465.

The stereochemistry of the two new chiral centers generated by the aldol reaction has been studied for more than a decade from both synthetic and mechanistic points of view (Scheme 1).[7] This report explores different methodologies used to control the stereoselectivity in the creation of the two new chiral centers.

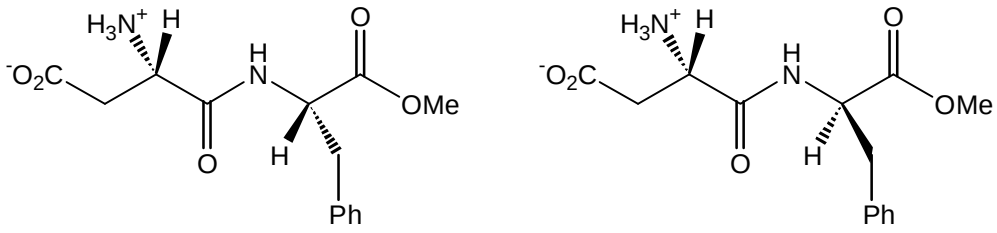
Scheme 1



Before going into the methodological discussion, it is important to note the stereochemical nomenclature of the aldol adducts as depicted in Scheme 1. If the hydroxy and the R group of an adduct are pointing to the same side, either front or back, it is described as a "syn" aldol adduct. However, if the hydroxy and the R group are pointing to opposite sides, then the adduct is described as an "anti" aldol adduct. In this report, we are going to develop models that can be used to predict which of the stereoisomers above are selectively formed as the major aldol adduct.

[7] Proctor, G.; Asymmetric Synthesis, **1996**, 69-70.

As mentioned earlier, controlling the stereochemistry in the aldol reaction is by far the most important factor in drug design and synthesis. Most biologically active compounds possess one or more chiral centers, and the enantiomers (or diastereomers) are likely to differ in biological activity.[8] Usually, only one enantiomer (or diastereomer) is active, and the other one is either not active or causes serious side effects. For example, the (S,S) form of the food additive Aspartame is an artificial sweetner, whereas the (S,R) form tastes very bitter (Figure 3).[9] Therefore, controlling the stereochemistry at each chiral center in the asymmetric aldol reaction is very important.



Aspartame (S,S),
an artificial sweetner

Aspartame (S,R),
tastes bitter

Figure 3. Aspartame (S,S) and Aspartame (S,R).

One might assume that achieving excellent stereochemical control in an aldol reaction would be a very tedious task, but the use of several strategies can dramatically optimize the stereoselectivity of the aldol reaction. Some of the strategies include controlling the E or Z enolate geometry, and choosing the appropriate reagent, Lewis acid, chiral auxiliary, chiral reagent, or chiral catalyst. These factors can have a large effect on

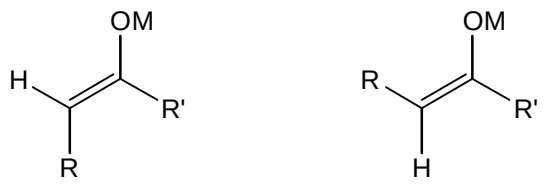
[8] Ariens, E. J.; *Chirality in Drug Design and Synthesis*. **1990**, 29-43.
[9] Stephenson, G. R.; *Advanced Asymmetric Synthesis*. **1996**, 7-8.

the stereoselectivity of the reaction. Of all the aforementioned methodologies, chiral catalysis is the most active research area currently, because only a small catalytic amount of catalyst is required to achieve stereoselective formation of a stoichiometric amount of product.[10] In addition, the use of chiral catalysts can also dramatically reduce the costs, making the cost of stereoselectively producing a product affordable. Because of the effectiveness and versatility of chiral catalysis, this report will spend a significant amount of time on the discussion of chiral catalysis of the aldol reaction in Chapter Four.

[10] Proctor, G.; *Asymmetric Synthesis*. **1996**, 12-13.

Chapter Two. Enolate Geometry & Aldehyde Geometry

The stereochemistry of the enolate, either E or Z (Figure 4), plays an important role



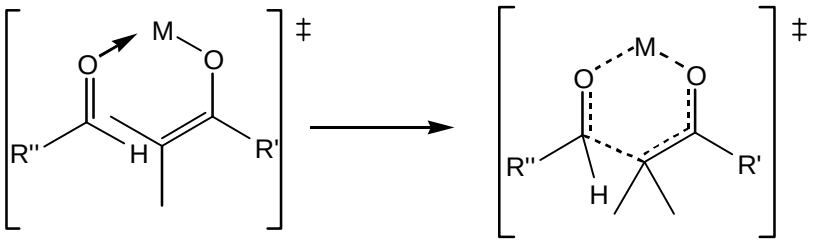
(E)-Enolate (Z)-Enolate

Figure 4. (E) and (Z) enolates

in the stereoselectivity of aldol reactions.[11] Atom M, which is usually a transition metal, can be either aluminum, boron, magnesium, tin, lithium, titanium, copper(I), copper(II), zinc, or silver(I).[12] The metal functions as a Lewis acid and is important for coordination to the aldehyde (or ketone). Furthermore, researchers believe that the metal complexes with the aldehyde, and causes the enolate to approach the aldehyde through a transition state model known as the "Zimmerman-Traxler" transition state.[13] The "Zimmerman-Traxler" transition state has fewer degrees of freedom than the open transition state. The Zimmerman-Traxler transition state is also widely known as the "closed transition state" (Scheme 2) for asymmetric aldol reactions. In this report, the term "Zimmerman-Traxler transition state" and "closed transition state" are used interchangeably.

[11] Roush, W. R.; *J. Org. Chem*. **1991**, 56, 4151-4153.
[12] Santelli, M.; Pons, J-M.; *Lewis Acids and Selectivity in Organic Synthesis*. **1995**, 91-105.
[13] Zimmerman, H.; Traxler, M.; *J. Am. Chem. Soc*. **1957**, 79, 1920.

Scheme 2



Enolate complexes with aldehyde

Zimmerman-Traxler (closed) transition state

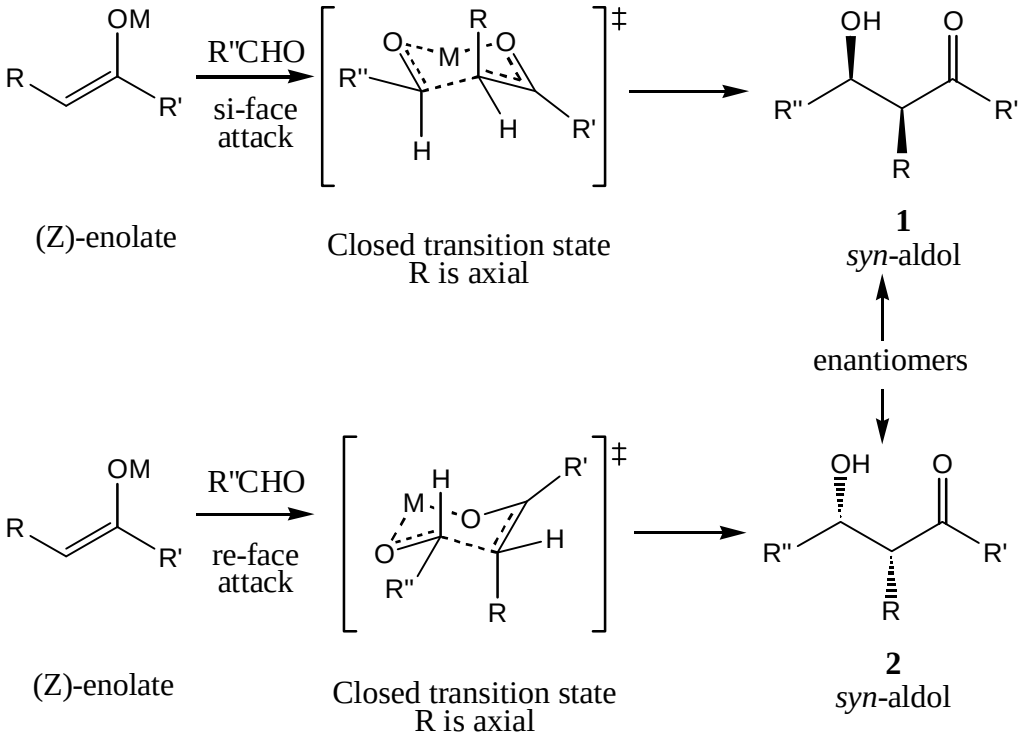
In this model, the closed transition state is analogous to the six-membered chair conformation of cyclohexane. However, there is a difference between the six-membered chair conformer of cyclohexane and this proposed closed transition state. In a chair form of cyclohexane, all the bonds are equal in length, but this is not the case in the closed transition state. There are heteroatoms such as oxygen atoms and the metal atom in the closed transition state to effect the bond order and bond length. Besides, a closed transition state has partially formed and broken bonds. Nevertheless, the closed transition state is still a good model as it predicts the stereoselectivity of the aldol reaction. According to this closed transition state scheme, the (E)-enolates give an anti-aldol adduct, and the (Z)-enolates give a syn-aldol adduct.[14]

For the syn-aldol adduct, how the aldehyde (or ketone) approaches the enolate in the closed transition state determines whether the hydroxy group and the R group are pointing out the plane or pointing into the plane. If the aldehyde approaches from the "back" side of the enolate (i.e.: si-face attack), then the syn-aldol adduct **1** is favored (Scheme 3). On the other hand, if the aldehyde (or ketone) approaches from the "front"

[14] (a) Procter, G.; *Asymmetric Synthesis*. **1996,** 72-74. (b) Atkinson, R. S.; *Stereoselective Synthesis*. **1995**, 217-228.

side of the enolate (i.e.: re-face attack), then the syn-aldol adduct **2** is favored (Scheme 3). Notice in Scheme 3 the R group is in the axial position, which gives the correct prediction for the syn-aldol adducts from the (Z)-enolate.[14,15]

Scheme 3

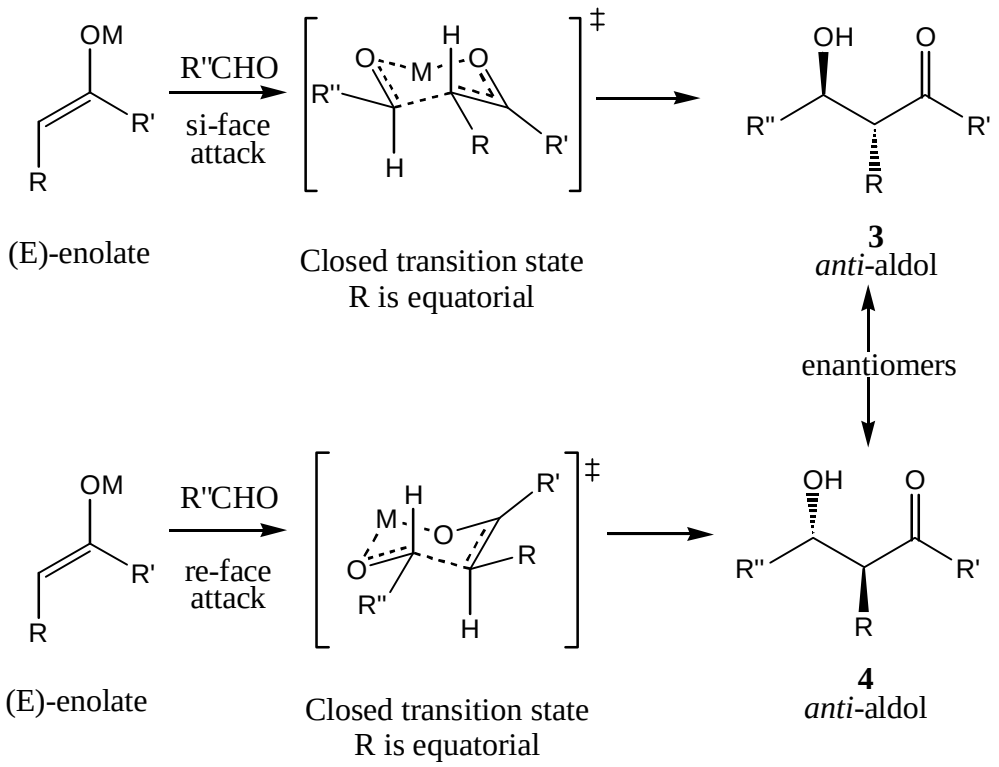


For the anti-aldol adduct, whether the hydroxy group is pointing out the plane and the R group is pointing into the plane or the reverse orientations also depends on how the aldehyde (or ketone) approaches the enolate in the closed transition state. From Scheme 4, when the aldehyde approaches from the "back" side of the enolate (i.e.: si-face attack), the

[15] (a) Paterson, I.; Lister, M. A.; McClure, C. K.*; Tetrahedron Letters*. **1986**, 27, 4787-4788. (b) Gennari, C.; Hewkin, C. T.; Molinari, F.; Bernardi, A. C.; Goodman, J. M.; Paterson, I.*; J. Org. Chem*. **1992**, 57, 5173-5174. (c) Corey, E. J.; Lee, D. H.; *Tetrahedron Letters*. **1993**, 34, 1737-1738.

anti-aldol adduct **3** is favored. However, if the aldehyde approaches from the “front” side of the enolate (i.e.: re-face attack), then the anti-aldol adduct **4** is favored. In this case, the R group is in the equatorial position. Again, the closed transition state predicts the correct anti-aldol adducts from the (E)-enolate.[14,15,16]

Scheme 4



It is clear that the enolate geometry controls the stereochemistry of the aldol reaction. As a result, one must control the enolate geometry very carefully from the beginning. From Scheme 3 and Scheme 4, increased bulkiness of group R' favors the (Z)-

[16] Majewski, M.; Gleave, D. M.; *Tetrahedron Letters*. **1989**, 30, 5681-5683.

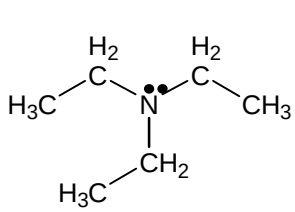
enolate because of the destabilizing steric interaction between R and R' for the (E)-enolate. The bulkiness of R' is very important in asymmetric aldol reactions because it can actually "block" one face of the enolate. Therefore, good stereoselection can be achieved. The R' group can be used as a chiral auxiliary to control the creation of the two stereocenters of the aldol adduct. In fact, this is one of the most widely used methods to control the stereoselectivity of aldol reactions, and there is a detailed discussion of this important methodology in the next chapter.

Among the metals that are most widely used for chelation in aldol reactions are boron and titanium. Boron reagents such as R_2BOTf, R_2BX[17] (R= alkyl, X= halogens), and 9-BBNOTf[18] are commonly used. Titanium reagents such as $TiCl_4$,[19] $Ti(OiPr)_4$,[20] and the catalyst of BINOL-Ti[21] are also common. These "sterically hindered" metal reagents, with the exception of BINOL-Ti, are believed to coordinate the enolate and the aldehyde (or ketone), which results in the blocking of one face of the enolate. As a result, good stereocontrol is achieved. This is known as chiral ligands methodology. This methodology is very similar to the auxiliary methodology, but it has one more advantage. It does not require adding and removing the auxiliary group for the aldol reaction. This advantage dramatically reduces the number of steps in the synthesis, and usually increases the overall yield. In addition, researchers take another challenging step. They try to use only a catalytic amount of the metal reagent (< 10-mole %) for asymmetric aldol reactions, such as the use of the BINOL-Ti complex mentioned earlier. This method is known as chiral

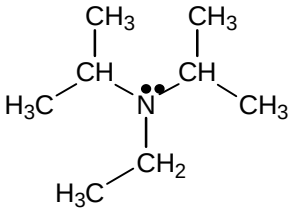
[17] Brown, H. C.; Ganesan, K.; *J. Org. Chem*. **1993**, 58, 7162-7167.
[18] Masamune, S.; Choy, W.; Kerdesky, F. A. J; Imperiali, B.; *J. Am. Chem. Soc*. **1981**, 103, 1567-1568.
[19] Evans, D. A.; Urpi, F.; Somers, T. C.; Clark, J. S.; Bilodeau, M. T.; *J. Am. Chem. Soc*. **1990**, 112, 8215-8216.
[20] Carreira, E. M.; Singer, R. A.; Lee, W.; *J. Am. Chem. Soc*. **1994**, 116, 8837-8838.
[21] Delas, C.; Szymoniak, J.; Lefranc, H.; Moise, C.; *Tetrahedron Letters*. **1999**, 40, 1121-1122.

catalysis, and it is still being actively developed nowadays. But, unfortunately, there are only a few catalysts that can produce good stereoselectivity in aldol reactions.

The bulkiness of the amine base used to trap the leaving group (e.g.: X = halogens, triflate, etc.) of the metal reagent had a significant effect on enolate geometry (Scheme 5). Brown and coworkers discovered that the boron mediated (E)-enolates were optimized by using a smaller amine base such as triethylamine (Figure 5) in a non-polar solvent, whereas the boron mediated (Z)-enolates were optimized by using a bulkier amine base such as N,N-diisopropylethylamine (Figure 5) in a more polar solvent.[17] Similarly, Evans



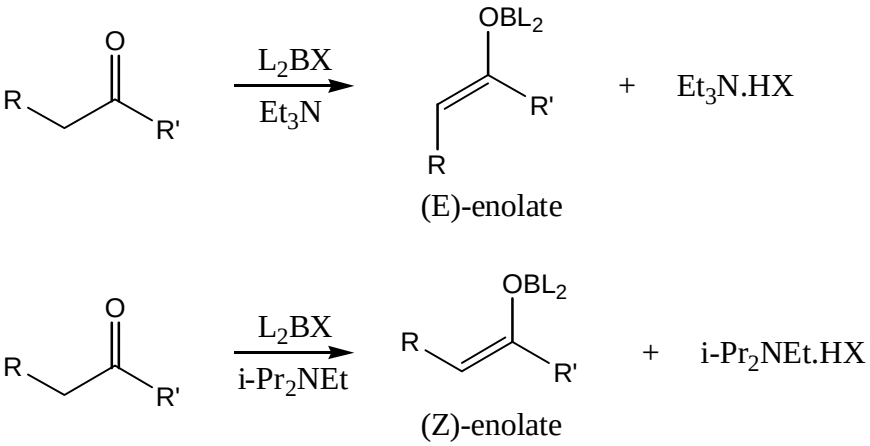
Triethylamine (Et_3N)



N,N-disopropylethylamine ($i\text{-}Pr_2NEt$)

Figure 5. Triethylamine and N,N-diisopropylethylamine

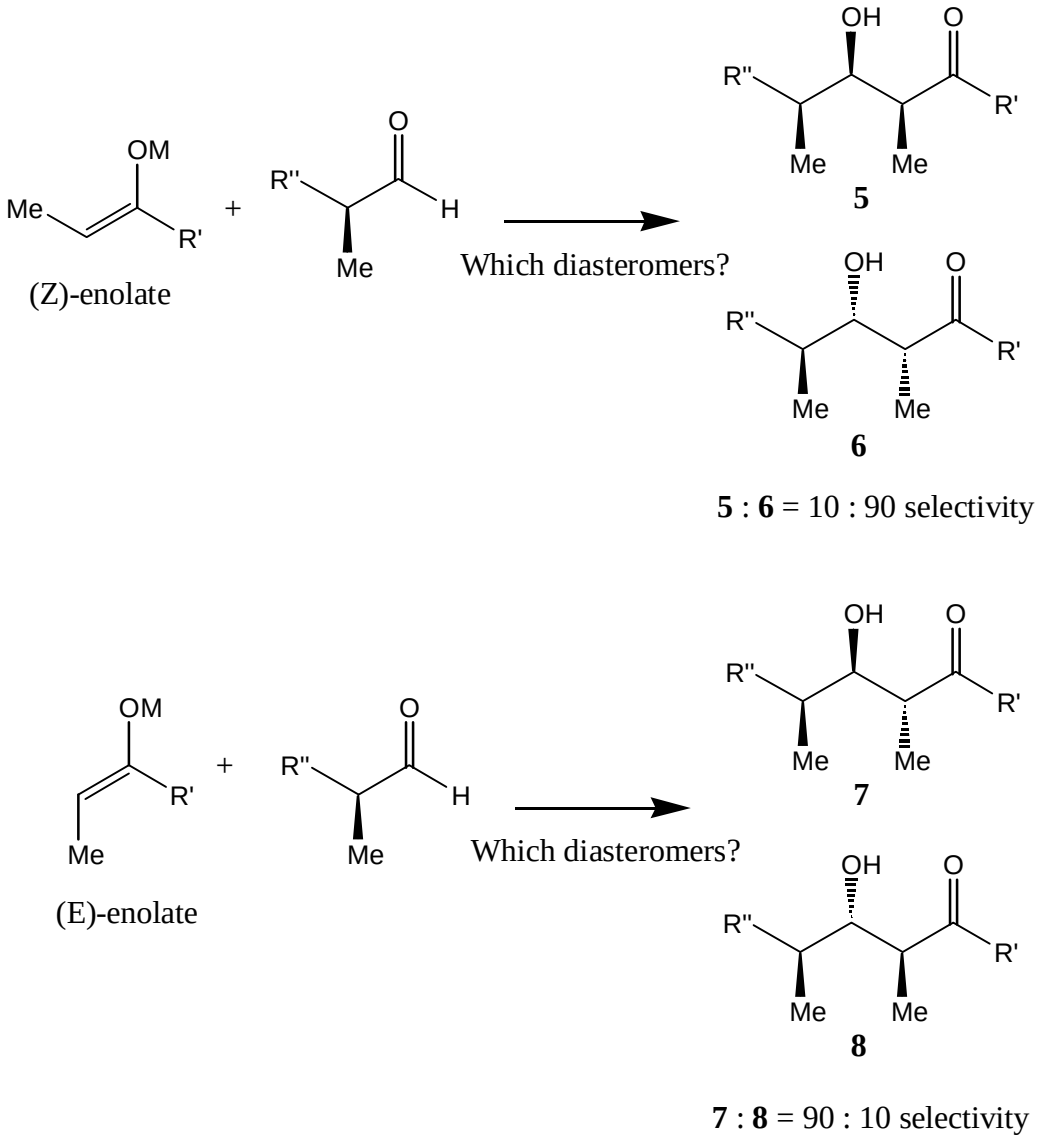
Scheme 5



and coworkers determined that the titanium-mediated (Z)-enolates were slightly more favored using N,N-diisopropylethylamine rather than triethylamine.[2] The effects of other parameters, such as temperature and the order of addition of substrates, were negligible.

In this chapter, the importance of the enolate geometry for good stereoselection is discussed. But what is the role of the aldehyde (or ketone) geometry in stereoselectivity? From the Zimmerman-Traxler transition state model as depicted in Scheme 2, the generic R" of the aldehyde is noted to have a significant effect on stereoselection in the aldol reaction. Specifically, the use of the α-methyl chiral aldehyde is a good example to explain the diastereoselectivity of the aldol reaction. In the following discussion, the R" represents any large bulky or sterically hindered group which is adjacent to the α-methyl chiral center of the aldehyde (Scheme 6). From Scheme 6, two possible diasteromers **5** and **6** can be formed from the (Z)-enolate and the α-methyl aldehyde. There are also two possible diasteromers **7** and **8** that can be formed from the (E)-enolate and the α-methyl aldehyde. Notice that the stereochemistry of all four diastereomers **5**,**6**,**7** and **8** at the α-methyl stereocenter of the aldehyde has not changed after the aldol reaction.

Scheme 6



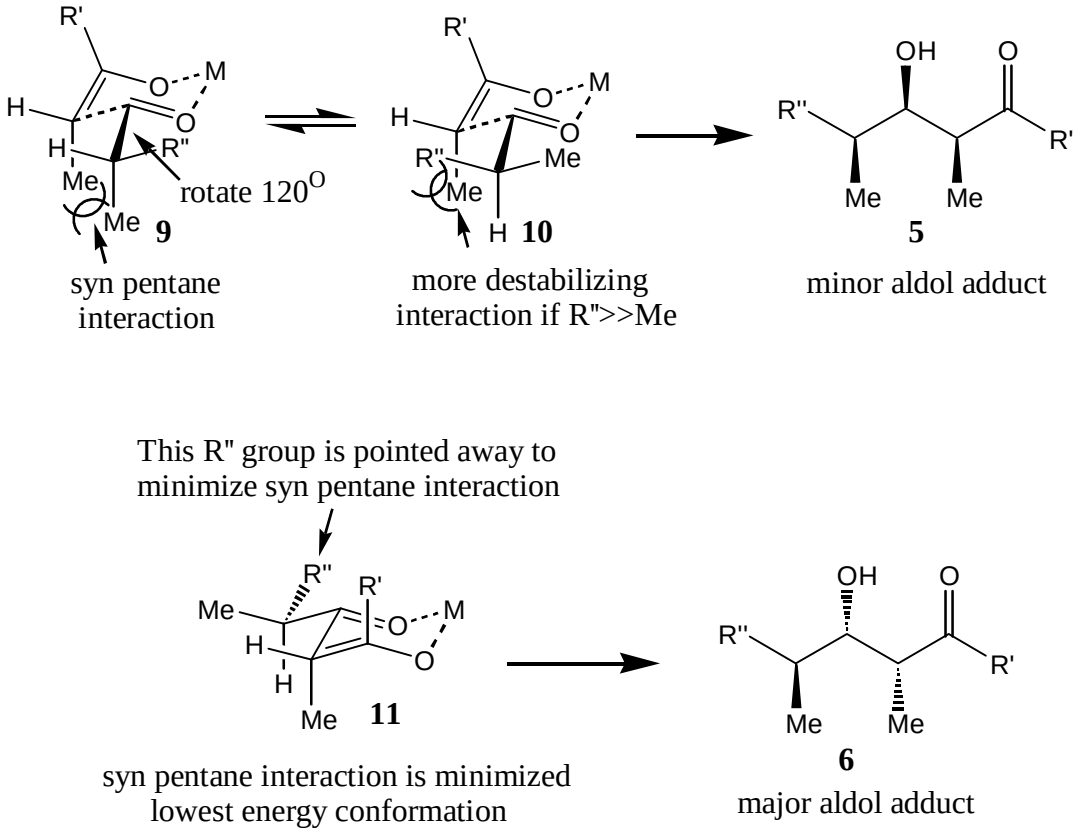
Roush determined that the 2,3-syn-3,4-anti diasteromer **6** was the major aldol adduct, whereas the 2,3-syn-3,4-syn diasteromer **5** was the minor aldol adduct from the (Z)-enolate aldol reaction.[22] On the other hand, he experimentally determined that the

[22] Roush, W. R.; *J. Org. Chem*. **1991**, 56, 4152-4156.

2,3-anti-3,4-syn diasteromer **7** was the major aldol adduct, and the 2,3-anti-3,4-anti diasteromer **8** was the minor aldol adduct from the (E)-enolate aldol reaction. In order to rationalize these results, one needs to take a closer look at how the closed transition state evolves during the course of the aldol reaction.

Roush believes that the minor diasteromer **5** is formed through the destabilized closed transition state **9** as depicted in Scheme 7. There is a destabilizing syn pentane interaction[22] between the methyl group of the (Z)-enolate and the α-methyl chiral center of the aldehyde. Furthermore, this syn pentane interaction becomes increasingly more destabilizing as the R" group becomes more bulky. Instability results from the 120^0 rotation of the C-C_α bond next to the carbonyl of the aldehyde, forming conformation **10**. As a result, the diastereomer **5** is the minor aldol adduct. However, the closed transition state **11** does not possess a strong syn pentane interaction for diasteromer **6** because both the methyl group of the (Z)-enolate and the chiral aldehyde are far apart from each other (Scheme 7). The closed transition state **11** is the most stable conformation, and the diastereomer **6** is formed as the major aldol adduct.

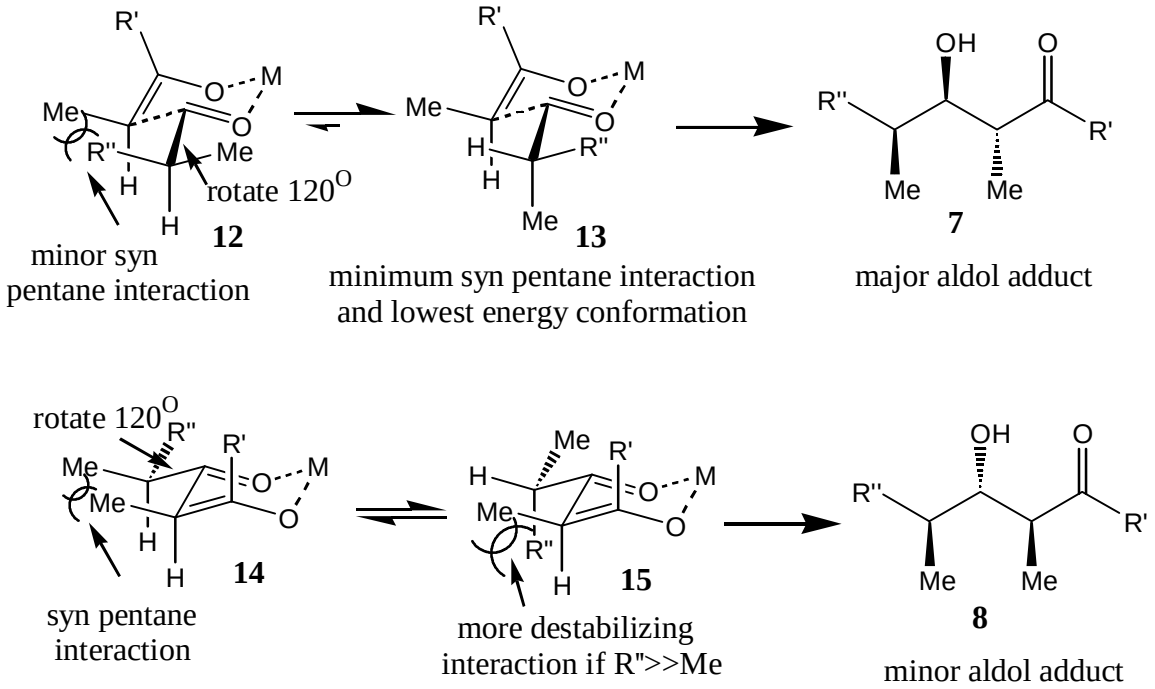
Scheme 7



As previously shown, the minimization of the syn pentane interaction in the closed transition state favors the desired aldol adduct. This is also true for the reaction of the (E)-enolate with the α-methyl chiral aldehyde. The closed transition state **14** as depicted in Scheme 8 disfavors the formation of the diasteromer **8**. It is disfavored because there is a syn pentane interaction between the methyl group of the (E)-enolate and the α-methyl chiral aldehyde. In addition, the syn pentane interaction becomes increasingly more destabilizing as the R" group becomes more bulky. Again, instability results from the 120^0 rotation of the C-C_α bond next to the carbonyl of the aldehyde, forming conformation **15**. The destabilizing syn pentane interaction between the methyl group of the (E)-enolate and

the bulky R" group of the aldehyde in conformation **15** further disfavors the formation of the diastereomer **8**. As a result, the diastereomer **8** is the minor aldol adduct. On the other hand, the diastereomer **7** is the major product formed because the syn pentane interaction is in the minimium in the closed transition state **13**. As depicted in Scheme 8, the closed transition state **13** is more favored than the closed transition state **12** because a 120^0 rotation in the C-C_α bond next to the carbonyl of the aldehyde can give the most stable transition state **13** that favors the formation of diasteromer **7**.

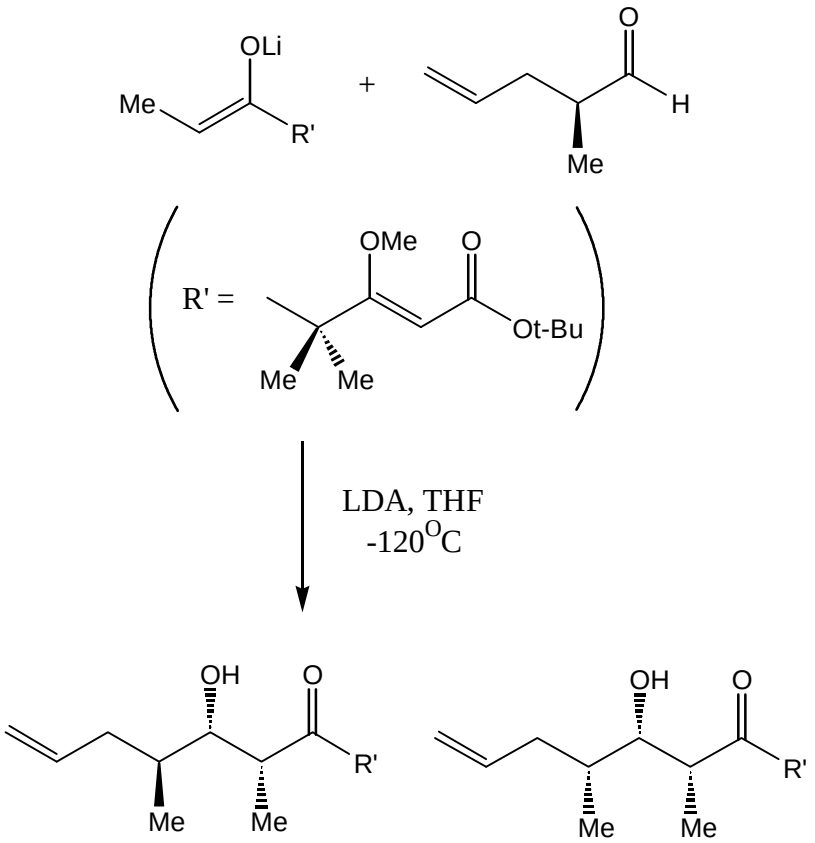
Scheme 8



The α-methyl group and the R" group of an aldehyde have a big impact in the stereoselectivity of the aldol reaction. Therefore, continued exploration into the effects of the R'' group of an aldehyde on stereoselectivity for the aldol reaction is important.

Recently, Danishefsky and coworkers found that unsaturated long chains or sterically undemanding ("flat") groups, such as the phenyl group, of the α-methyl chiral aldehyde favored the formation of the syn-aldol adduct **16** from the (Z)-enolate (Scheme 9).[23] The syn-aldol adduct **17** is the minor product, and the stereocenter of the syn-aldol adduct **17** from the α-methyl chiral aldehyde is reversed. The reason for this change is not yet known.

Scheme 9



16
major *syn*-aldol

17
minor *syn*-aldol

16 : **17** = 84 : 16 selectivity
60 % yield

[23] Danishefsky, S. J.; Harris, C. R.; Kuduk, S. D.; Balog, A.; Savin, K. A.; *Tetrahedron Letters*. **1999**, 40, 2267-2269.

Danishefsky's research group used various long-chain α-methyl unsaturated aldehydes in the aldol reaction. LDA was used to form the enolate. Danishefsky indicated there might be a "stabilizing space interaction" between the double bond and the aldehyde carbonyl that increased the distereoselectivity of the addition. In addition, the electronic effect of the aldehyde was an important factor for good distereoselection.

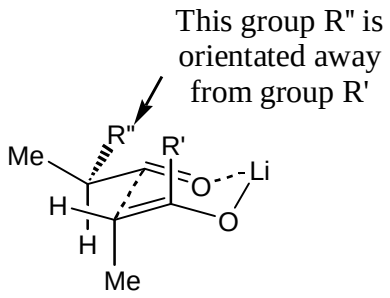


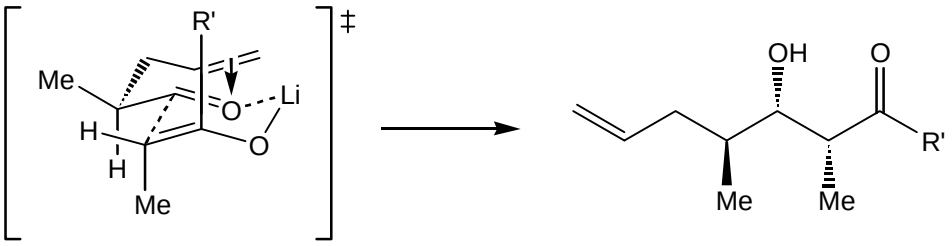
Figure 6.
Proposed transition state
by Danishefsky.

Danishefsky proposes the closed transition state model for the aldol reaction, as depicted in Figure 6 and similar to Scheme 7. The R" group of the α-methyl aldehyde is orientated away from the R' group of the enolate to avoid the unfavorable destabilizing syn pentane interaction.[24] This closed transition state model is very similar to the closed transition state **11** in Scheme 7, and transition states **14** and **15** in Scheme 8. The methyl group of the chiral aldehyde is pointed away from the methyl group of the enolate in the axial position to minimize the destabilizing 1,3-diaxial interaction. With this general closed transition state model in mind, we can analyze stabilization effects through space. For

[24] Roush, W. R.; *J. Org. Chem*. **1991**, 56, 4154-4156.

example, in Scheme 10, the double bond of the chiral aldehyde “interacts” with the aldehyde carbonyl, causing a stabilizing electronic effect due to π-electrons flowing to the oxygen atom in the closed transition state **18**. To further explore this hypothesis, a “flat” sterically undemanding benzene ring is used (Scheme 11). Again, the π-electrons of the benzene ring can interact with the aldehyde carbonyl in a through-space interaction as shown in transition state **20**. Electron withdrawing groups, such as ortho or para NO_2 substituted benzene rings gave poor distereoselectivity control. Electron donating groups, such as ortho or para methoxy and dimethylamino, gave good distereoselectivity control. The data clearly supports the electronic effect hypothesis. Besides, continued increase in the length of the alkyl chain results in poor stereoselectivity because of the fact that the unsaturated double bond can no longer “interact” with the aldehyde carbonyl. All these pieces of evidence support that there is likely an efficient electronic effect governing the through-space interactions between the unsaturated double bond and the carbonyl group of the chiral aldehyde.

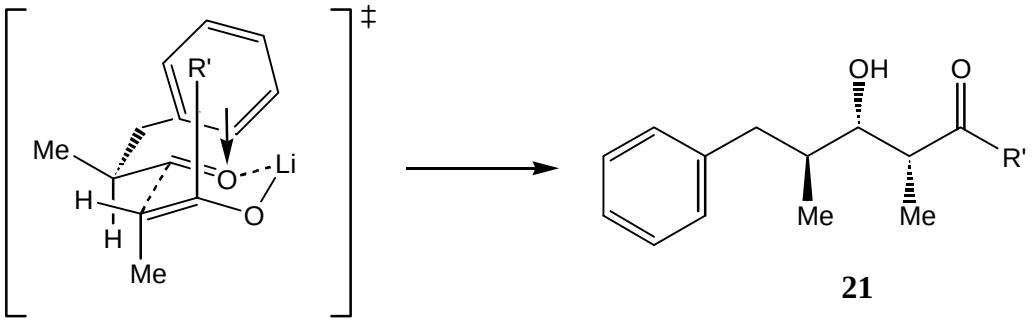
Scheme 10



18 **19**

84 : 16 selectivity

Scheme 11



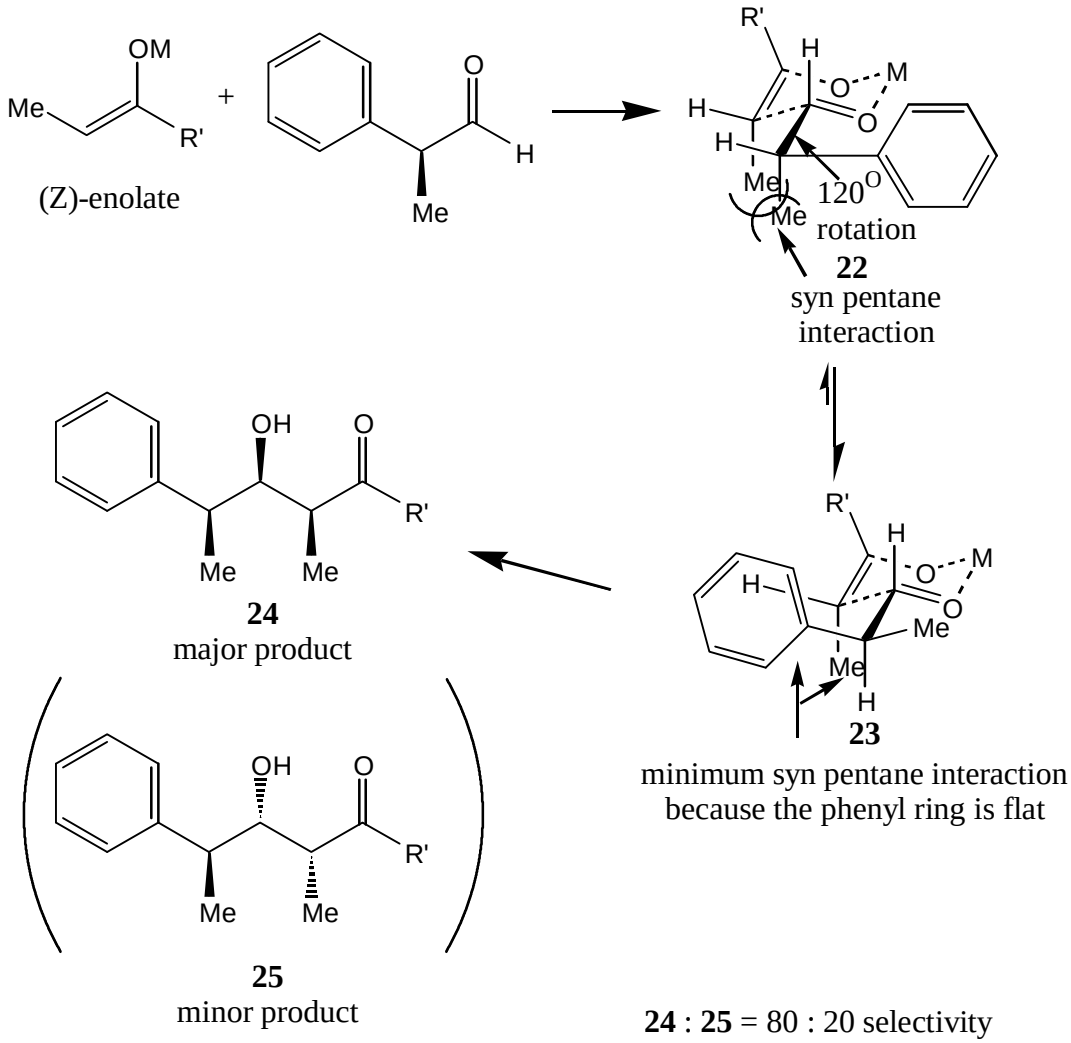
20 **21**

83 : 17 selectivity

Roush used a flat phenyl group in the α-methyl chiral aldehyde, although the major aldol adduct was the 2,3-syn-3,4-syn **24** instead of the 2,3-syn-3,4-anti **21** obtained by Danishefsky.[24] There was a slight difference between the phenyl group in Roush's α-methyl aldehyde and Danishefsky's α-methyl aldehyde. The phenyl group attached to Roush's aldehyde was one carbon bond closer than Danishefsky's aldehyde. However, this slight difference dramatically reversed the stereochemistry of the aldol adducts **21** and **24** at the C-2 and C-3 carbon. This suggested that the aldol adduct **24** must not come from closed transition state **20**. Presumably, the phenyl group attached to the aldehyde was not "long" enough for the through-space interaction between the unsaturated double bond and the carbonyl group of the chiral aldehyde. Therefore, the aldol reaction passed through a different transition state (Scheme 12). The closed transition state **22** was destabilized because of a significant syn pentane interaction between the methyl group of the (Z)-enolate and the chiral aldehyde. However, the C-C_α carbon bond next to the carbonyl rotated 120^0 causing the equilibrium shift to the closed transition state **23**. The phenyl group was flat, and the syn pentane interaction was minimized between the methyl group

of the (Z)-enolate and the phenyl group of the chiral aldehyde. Therefore, the 2,3-syn-3,4-syn-aldol adduct **24** was the major product from the closed transition state **23**.

Scheme 12



In summary, this chapter describes the effect of the enolate geometry in the stereoselectivity in aldol reactions. Moreover, the effect of the aldehyde (or ketone) geometry plays another important role in the stereoselectivity in aldol reactions. The Zimmerman-Traxler transition state model, also known as the closed transition state

model, is a powerful tool to understand the stereoselectivity in the reaction. The most challenging part is to understand the effect of sterics and electronics and the criteria for blocking one face of the enolate during the aldehyde's (or ketone's) approach. Later in the discussion, we see that the closed transition state model is limited in predicting the stereochemistry of the aldol adduct. As a result, an open transition state model is another alternative model to explain the stereochemistry of the aldol adduct. Because of the complexity of the transition state involved in the aldol reaction, researchers often use computer-modeling methods such as molecular mechanics or semi-empirical calculations to aid them in predicting the correct transition state.[25]

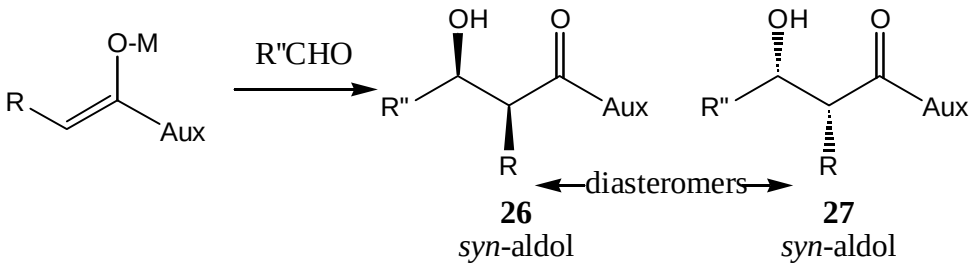
In the next chapter, we expand on another important methodology for stereochemical control – the chiral auxiliary methodology – that was briefly introduced in this chapter. In this method, the chiral center of the auxiliary group of the enolate "directs" the formation of the two new stereocenters in the aldol reaction. This methodology is the most widely used method because of its great success for controlling the stereochemistry in the aldol reaction. Furthermore, we discuss the effect of the bulky chiral ligands on the Lewis acid that is responsible for the stereochemistry in the aldol reaction.

[25] Gennari, C.; Hewkin, C. T.; Molinari, F.; Bernardi, A.; Comotti, A.; Goodman, J. M.; Paterson, I.; *J. Org. Chem.* **1992**, 57, 5175-5176.

Chapter Three. Chiral Auxiliary & Chiral Ligands

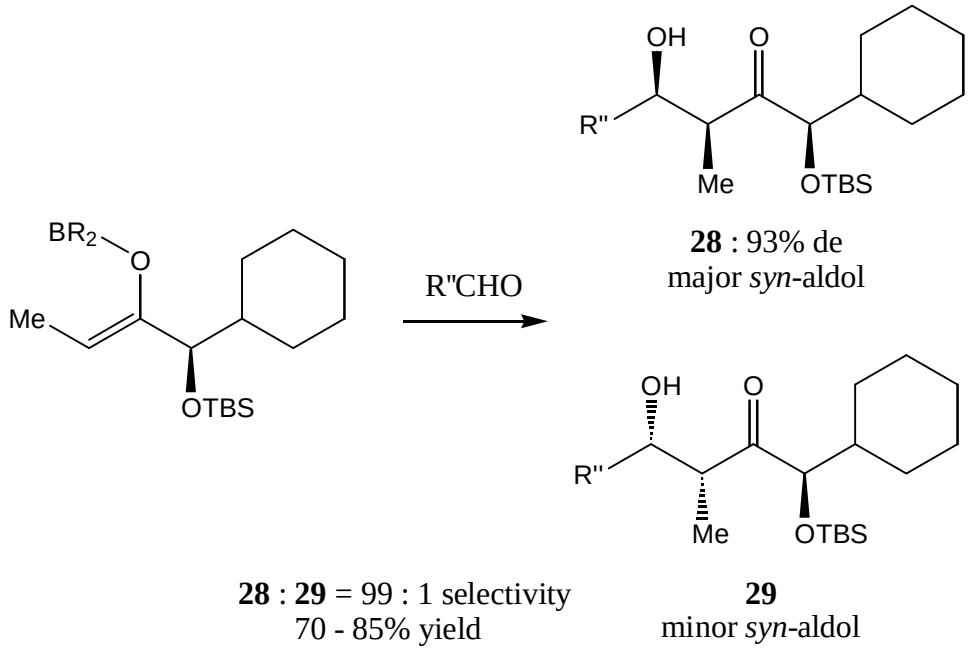
In asymmetric aldol reactions, the chiral auxiliary in the enolate can dramatically enhance the stereoselectivity because controlling the enolate geometry or aldehyde geometry alone is inadequate. One needs to optimize the stereoselectivity by integrating several methodologies. From the last chapter, the "face" of the enolate approached by the aldehyde determines which stereoisomer is formed. The use of the chiral auxiliary methodology enhances the "blocking" of one face of the enolate. From Scheme 13, it is possible to selectively obtain either one of the syn-aldol adducts **26** or **27** by choosing the appropriate chiral auxiliary. The symbol "Aux" in Scheme 13 represents the general chiral auxiliary that gives diastereomers **26** and **27**.

Scheme 13



Masamume and coworkers developed a chiral auxiliary that selectively gives the major syn-aldol adduct **28** and the minor syn-aldol adduct **29** (Scheme 14).[18] Dialkyl boron triflate (R_2BOTf) and a weak bulky base N,N-diisopropylethylamine ($(i\text{-}Pr_2)NEt$) were used to form the (Z)-boron enolate. Experimental data supported that the (Z)-boron enolate gave moderate stereoselectivity without using a hindered chiral auxiliary in the aldol reaction.

Scheme 14

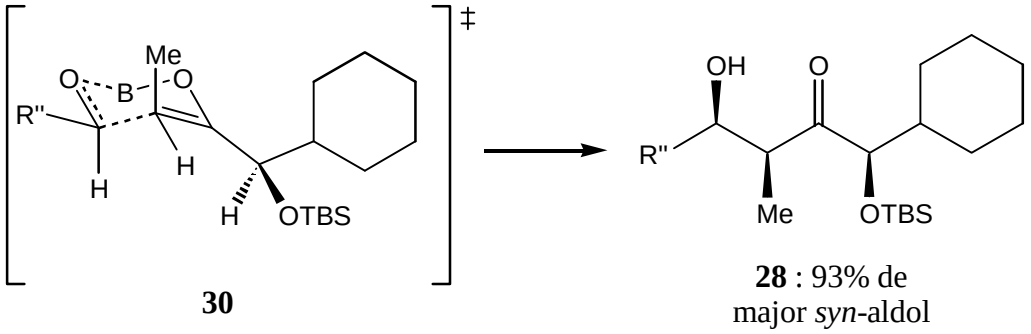


To control the stereochemistry of the two new chiral centers in aldol adducts **28** and **29**, one looks at the conformation of the chiral auxiliary in the closed transition state carefully (Scheme 15). In Scheme 15, the conformation of the chiral auxiliary in the closed transition state **30** is controlled by the chiral OTBS group in the auxiliary. The OTBS group is orientated away from the oxygen atom of the enolate to minimize strong dipole-dipole repulsions.[26] This conformation is believed to be the lowest energy form, and it is reasonable to assume the chiral auxiliary group "locks" itself into this stable conformational state. This stable conformation in transition state **30** prevents the aldehyde's approach from the "front" face (re-face attack) because of the blocking by the cyclohexane ring. Hence, the aldehyde approaches the enolate from the "back" face (si-face attack) because there is no blocking due to the cyclohexane ring. This closed

[26] Proctor, G.; *Asymmetric Synthesis*. **1996**, 75.

transition state model is consistent with the stereochemical outcome of the syn-aldol adduct **28** as the major product.

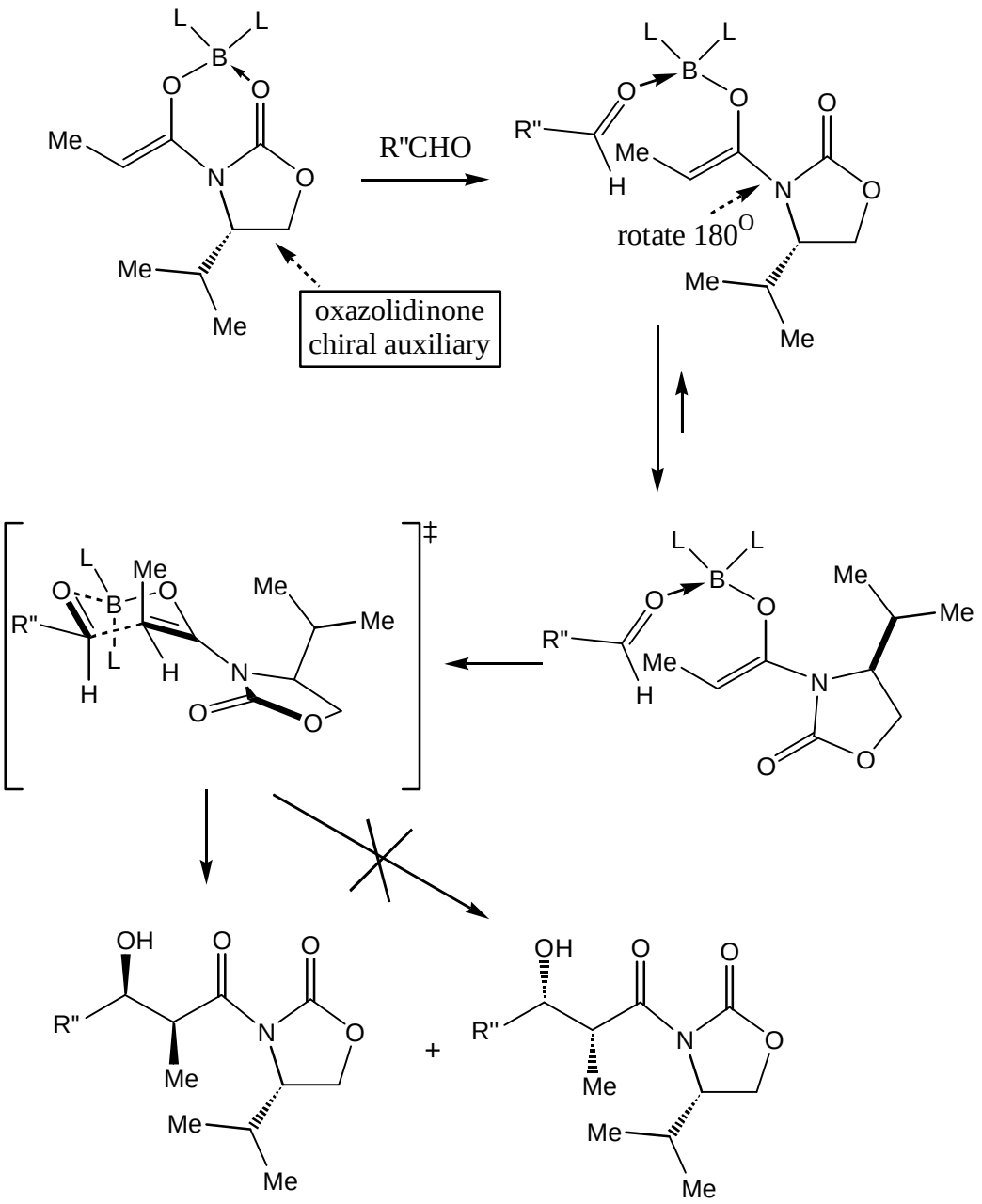
Scheme 15



The oxazolidinone chiral auxiliary is the most widely used chiral auxiliary in Evans's research group.[19, 27] Evans and coworkers found that the oxazolidinone chiral auxiliary favored the formation of the syn-aldol adduct **31** over the syn-aldol adduct **32** (Scheme 16).[27] Dialkyl boron triflate (R_2BOTf) and a hindered amine base N,N-diisopropylethylamine (iPr_2NEt) are used to optimize the formation of the (Z)-boron enolate. From Scheme 16, Evans proposed that the coordination between the boron and the oxazolidinone carbonyl must be broken in order for the aldehyde carbonyl to coordinate with boron. If boron is still coordinated to the oxazolidionone carbonyl, the aldehyde carbonyl can no longer coordinate with boron to give the Zimmerman-Traxler transition state model.

[27] Evans, D. A.; Bartrolli, J.; Shih, T. L.*; J. Am. Chem. Soc*. **1981**, 103, 2127-2129.

Scheme 16



31 : > 99% de
major *syn*-aldol

32
minor *syn*-aldol

31 : **32** = > 99 : 1 selectivity
75 - 91% yield

In Scheme 16, the carbon-nitrogen (C-N) bond rotates 180^0 orientating the carbonyl oxygen atom of the auxiliary away from the enolate oxygen atom to minimize destabilizing electron pair dipole-dipole repulsions.[28] The conformational change in this example is similar to the previous example, that the OTBS group is pointed away from the oxygen atom of the enolate as depicted in Scheme 15. From the closed transition state in Scheme 16, the aldehyde cannot approach the enolate from the "front" face (re-face attack) because the aldehyde is completely blocked by the bulky oxazolidinone auxiliary. Therefore, the aldehyde must approach the enolate from the "back" face (si-face attack). The closed transition state model in Scheme 16 is consistent with the syn-aldol adduct **31** as the major product in the aldol reaction.

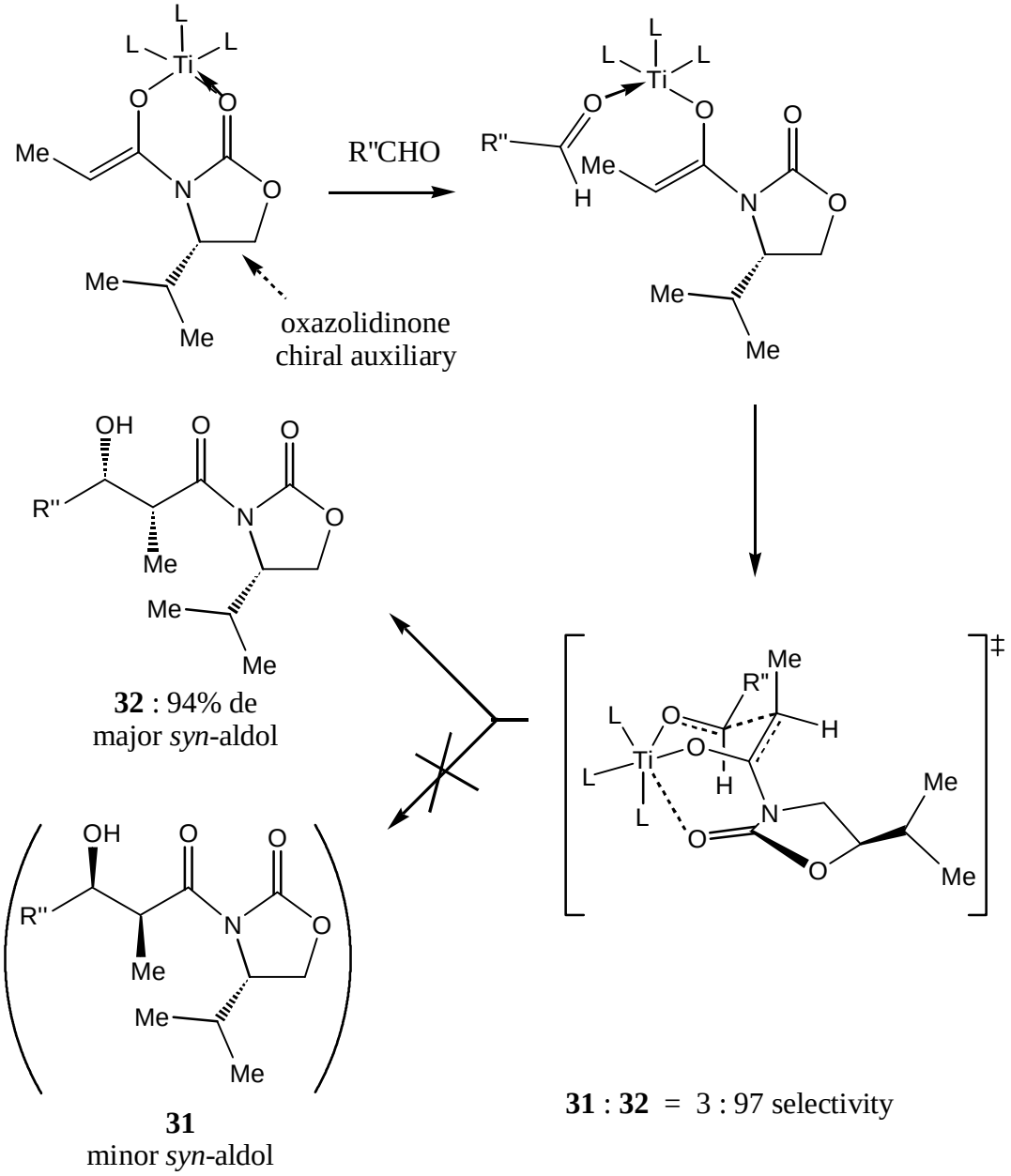
Surprisingly, Thornton and coworkers discovered that the syn-aldol adduct **32** was the major product when titanium(IV) ($Ti(OCH(CH_3)_2)_3Cl$) was used as a Lewis acid instead of boron (Scheme 17).[29] This example shows the choice of a Lewis acid had a great impact on the stereoselectivity in the aldol reaction, and the transition state evolved in this example might be different than the previous one. Several researchers attempted to use different Lewis acids to reverse the stereochemistry in aldol reactions with some success. Thus, continued in-depth exploration on the effect of the Lewis acid in the aldol reaction was necessary.

Thornton believes that the oxazolidinone carbonyl coordinates to the titanium(IV) in the closed transition state as depicted in Scheme 17. Unlike boron, titanium(IV) is capable of coordinating the oxazolidinone carbonyl because titanium(IV) has six

[28] Proctor, G.; *Asymmetric Synthesis*. **1996**, 79.
[29] Thornton, E. R.; Nerz-Stormes, M.; *J. Org. Chem*; **1991**, 56, 2489-2498.

coordination sites.[30] The aldehyde approaches from the "top" face (re-face attack) in the closed transition state that gives the correct prediction for the syn-aldol adduct **32** as the major product.

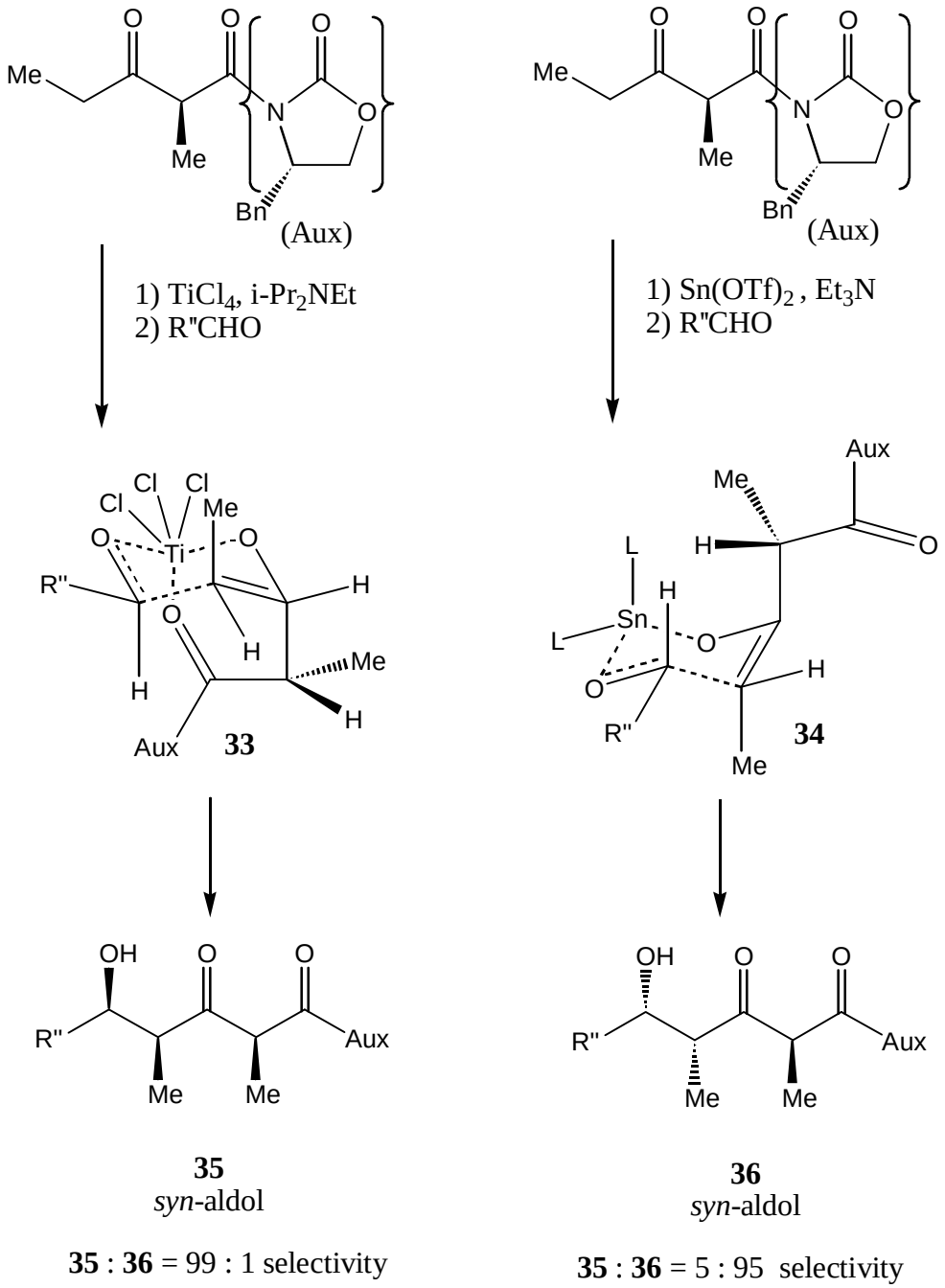
Scheme 17



[30] Santelli, M.; Pons, J. M.; *Lewis Acids and Selectivity in Organic Synthesis*. **1996**, 163-164.

Evans and coworkers modify the oxazolidinone chiral auxiliary by extending the chain with an α-methyl-β-carbonyl group (Scheme 18).[3] Tin(II) triflate ($Sn(OTf)_2$) or titanium(IV) tetrachloride ($TiCl_4$) are used to chelate the aldehyde and the enolate. Surprisingly, the Ti(IV) enolate gives the syn-aldol adduct **35**, whereas the Sn(II) enolate gives the syn-aldol adduct **36**. This is another example showing that good stereochemical control can be achieved by simply choosing the appropriate Lewis acid. In Scheme 18, the two closed transition states **33** and **34** predict the correct syn-aldol adducts **35** and **36**, respectively. In the closed transition state **33**, the carbonyl oxygen next to the oxazolidinone auxiliary is coordinated to the titanium(IV) metal to give the aldol adduct **35**. This coordination is possible because titanium(IV) is capable of having six coordination sites as mentioned earlier. On the other hand, the carbonyl oxygen next to the oxazolidinone auxiliary cannot coordinate to tin(II) metal because tin(II) metal is limited to four coordination sites analogous to boron. Therefore, the tin(II) metal coordination sites are saturated when the enolate and the aldehyde are chelated. As a result, tin(II) cannot coordinate to the carbonyl oxygen as shown in the closed transition state **34**. The transition state **34** gives the aldol adduct **36** correctly. In later chapters, we see that each different kind of Lewis acid has a great impact on the stereochemistry of the aldol adducts in great detail.

Scheme 18



35 : **36** = 99 : 1 selectivity

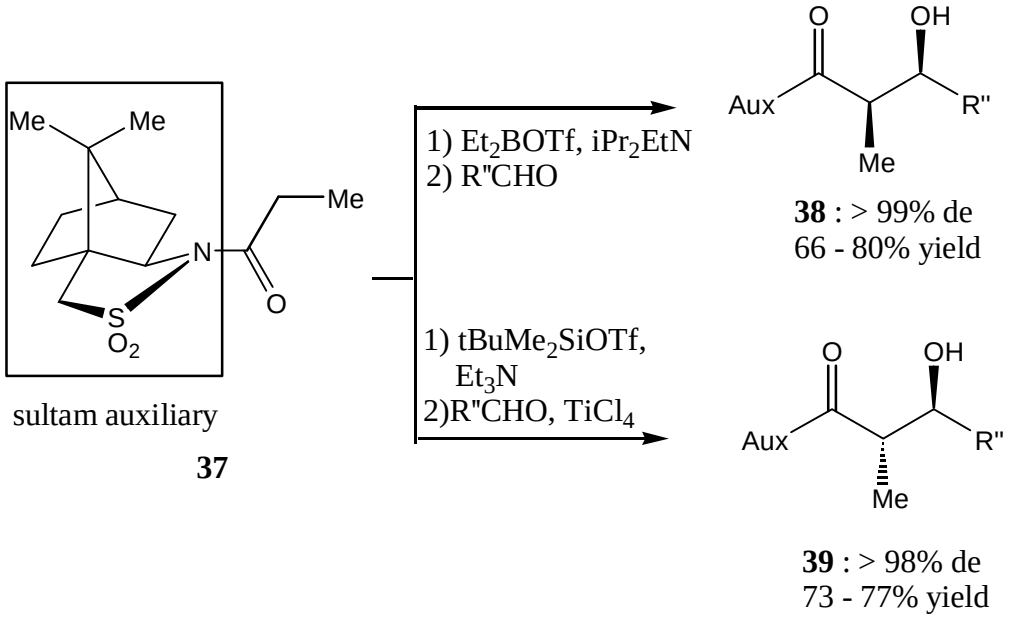
35 : **36** = 5 : 95 selectivity

71 - 86% yield

Chiral sultams are another well-known bulky chiral auxiliary used widely by several research groups to control the stereochemistry of the aldol reaction. Oppolzer and

coworkers determined that the sultam auxiliary **37** gave good stereochemical control yielding the syn-aldol adduct **38** and the anti-aldol adduct **39** by choosing the appropriate Lewis acid (Scheme 19).[31] Diethyl boron triflate was used to give the syn-aldol adduct **38**, and titanium(IV) tetrachloride was used to give the anti-aldol adduct **39** respectively.

Scheme 19

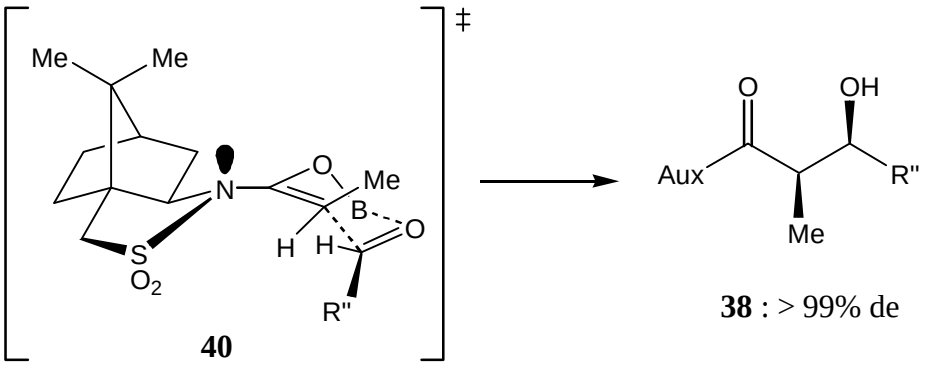


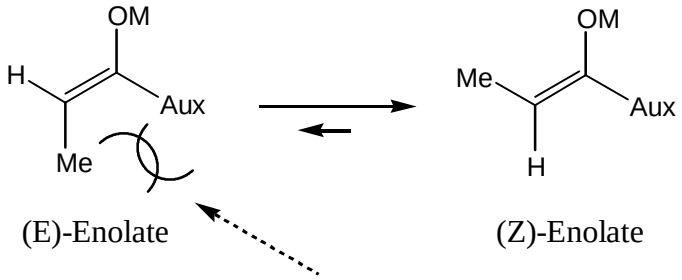
The closed transition state **40** in Scheme 20 gives the syn-aldol adduct **38**. Presumably, the sultam auxiliary blocks the front face of the enolate, and the aldehyde must approach the enolate from the back face (si-face attack). The closed transition state **40** is very similar to other transition states that we have discussed by using a bulky or

[31] (a) Oppolzer, W.; Blagg, J.; Rodriquez, I.; Walter, E.; *J. Am. Chem. Soc*. **1990**, 112, 2767-2770. (b) Oppolzer, W.; Lienard, P.; *Tetrahedron Letters*. **1993**, 34, 4321-4324.

sterically demanding auxiliary to block one face of the enolate to achieve excellent stereoselection.

Scheme 20





As the sultam auxiliary group (Aux) is getting bulkier, there is a destabilizing steric interaction between Aux and the methyl group of the enolate. Thus, the (Z)-enolate forms favorably over the (E)-enolate.

Figure 7. Formation of the (Z)-enolate.

Special attention is noted for anti-aldol adduct **39**. In Chapter two, we learned the (E)-enolate gives the anti-aldol adduct exclusively. However, the starting material **37** (Scheme 19) is more likely to generate the (Z)-enolate because of sterics (Figure 7). The

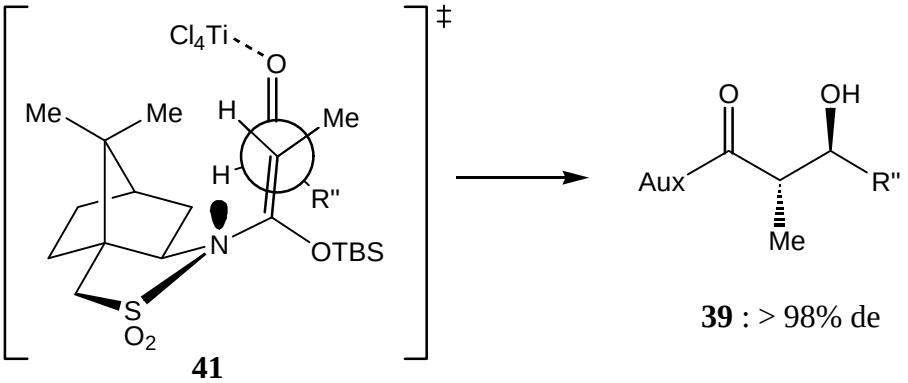
sultam auxiliary is enormously sterically demanding, and the methyl group of the enolate is unlikely to point in the same direction as the sultam auxiliary forming the (E)-enolate. The (Z)-enolate is formed preferentially because the methyl group and the sultam auxiliary are pointing away from each other. The destabilizing steric interaction is minimized in the (Z)-enolate over the (E)-enolate.

So, why does the (Z)-enolate give the anti-aldol adduct **39**? One possible way to explain this dramatic phenomenon is that the closed transition state model is no longer valid. Many researchers believe that the acyclic transition state, also known as the open transition state, is responsible for giving the anti-aldol adduct from the (Z)-enolate.[32] Therefore, the acyclic transition state **41** represents an alternative model which explains the anti-aldol adduct **39** that is produced (Scheme 21). The aldehyde approaches from the back face of the enolate because the sultam auxiliary blocks the front face of the enolate (Scheme 21). The R" group of the aldehyde points away from the sultam auxiliary to minimize a destabilizing steric interaction. Ti(IV) is capable of coordinating the aldehyde, and this can “freeze” the lowest energy conformation.[33] Freezing the lowest energy conformation is necessary because there are significantly more degrees of freedom in the open transition state than the closed transition state. The energy levels of each different conformation are nearly identical, so it is very difficult to obtain a particular low energy conformation to form a desired aldol adduct. Without the Lewis acid coordinating the aldehyde in the open transition state, it is impossible to get the lowest energy

[32] Yamamoto, Y.; Yatagaki, H.; Naruta, Y.; Maruyama, K.; *J. Am. Chem. Soc*. **1980**, 102, 7107-7110.
[33] Mahrwald, R.; *Chem Review*, **1999**, 99, 1095-1107.

conformation. Therefore, controlling the stereochemistry in the aldol reaction is not accurate or reliable when the reaction proceeds by an open transition state.[34]

Scheme 21



There were other chiral auxiliaries similar to Oppolzer's sultam, and it would be expected that these similar structures would give similar stereoselectivity in the aldol reaction. Yan and coworkers developed a camphor-derived boron enolate, and titanium(IV) tetrachloride ($TiCl_4$) or tin(IV) tetrachloride ($SnCl_4$) were used as catalysts to coordinate the aldehyde.[35] Both of the catalysts afforded the anti-aldol adduct **44** as the major product, and the syn-aldol adduct **45** was formed as the minor product (Scheme 22). The open transition state model **42** was proposed because the anti-aldol adduct **44** was selectively formed from the (Z)-boron enolate, but not from the (E)-boron enolate. The open transition state model **43** gave the syn-aldol adduct **45**, which was similar to the previous open transition state model in Scheme 21. For the open transition state **42**, the

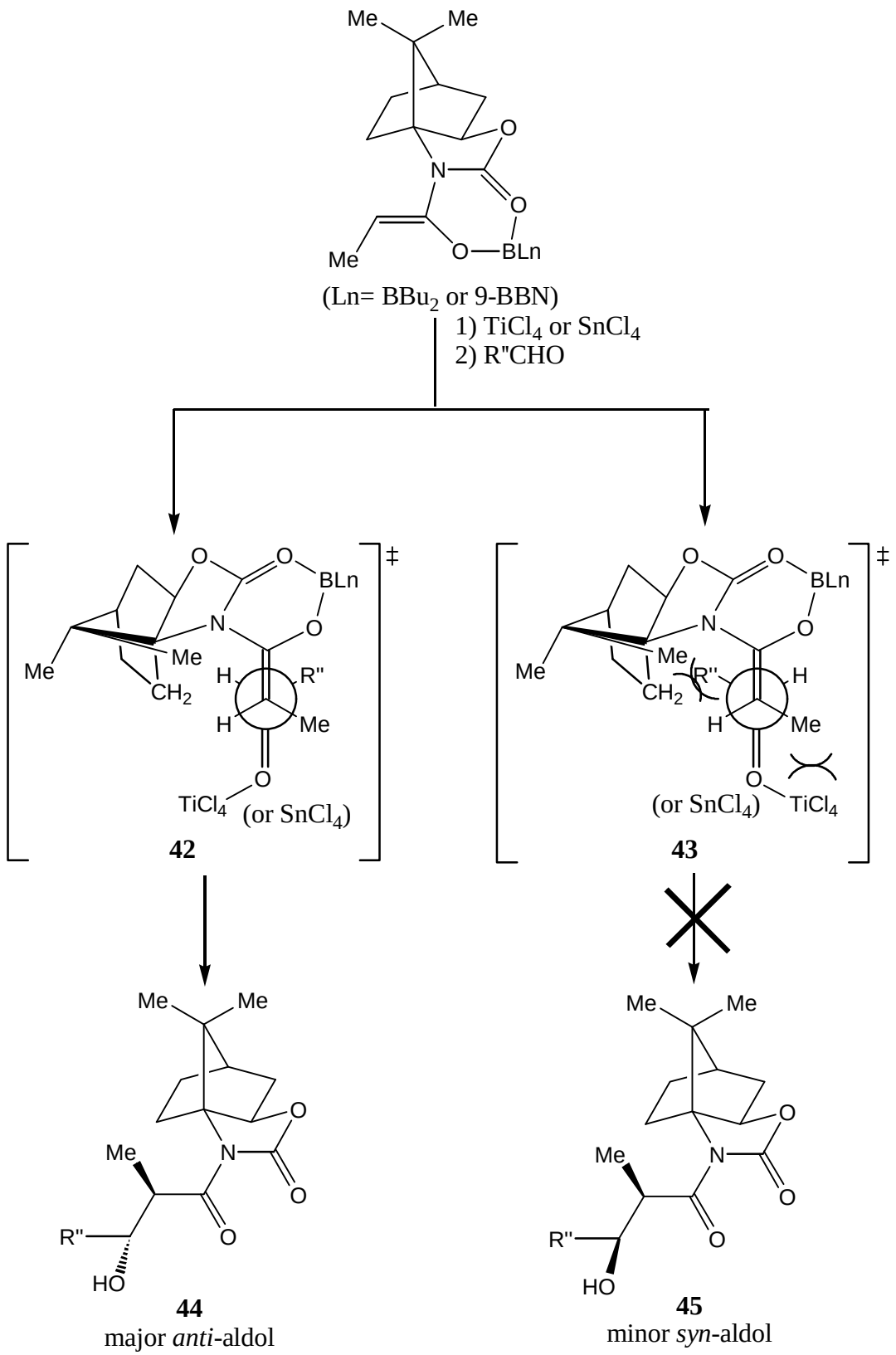
[34] Proctor, G.; *Asymmetric Synthesis*. **1996**, 87.

aldehyde approached from the back face of the enolate because the bulky camphor-derived auxiliary blocked the front face. More importantly, the R" group of the aldehyde was pointing away from the chiral auxiliary to minimize the destabilizing steric interaction. This open transition state model **42** gave the anti-aldol adduct **44** as the major product. On the other hand, when the R" group was pointing towards the chiral auxiliary as also depicted in Scheme 22, the open transition state **43** should give the syn-aldol adduct **45** as the minor product. The open transition state **43** was highly unfavored because there was a strong destabilizing steric interaction between the R" group of the aldehyde and the methylene group of the chiral auxiliary. Furthermore, there might be a strong steric destabilizing interaction between the Lewis acid $TiCl_4$ (or $SnCl_4$) and the methyl group of the enolate, which further disfavored the open transition state **43**.

Scheme 22

(Diagrams on next page)

[35] Yan, T. H.; Wang, Y. C.; Hung, A. W.; Chang, C. S.; *J. Org. Chem*. **1996**, 61, 2038-2041.



From $TiCl_4$, **44** : **45** = 99 : 1 selectivity
From $SnCl_4$, **44** : **45** = 96 : 4 selectivity
85 - 90% yield

We have seen several examples illustrating the importance of the chiral auxiliary to achieving stereochemical control in the aldol reaction. However, there is one major drawback in this method. After the creation of the two new stereocenters in the aldol adduct, the chiral auxiliary needs to be removed efficiently for further synthesis. Most procedures to remove the chiral auxiliary are quite effective, but there is a tendency for a low aldol adduct yield. Maximizing the aldol adduct yield in each step is very important. Otherwise, the yield of the final target molecule is almost zero.

Using enolate geometry, aldehyde (or ketone) geometry, or the chiral auxiliary to control the stereochemistry of the aldol reaction is called "substrate control" methodology because these are the substrates in stoichiometric amount in the aldol reaction.[36] Unfortunately, the substrate control methodology is not efficient enough for further synthesis. As a result, researchers have tried to develop an alternative method. Several researchers placed large and sterically demanding chiral ligands on the Lewis acid to control the stereochemistry, and this method is widely known as "reagent control" methodology. As previously shown, metals such as boron, titanium(IV) or tin(IV) have coordination sites that can be attached to any sterically hindered alkyl group. Using chiral ligands in the Lewis acid is analogous to using the chiral auxiliary in the enolate. Both methods basically take advantage of any large and sterically demanding bulky structure blocking one face of the enolate to achieve excellent stereoselection. Theoretically, using chiral ligands is more versatile than using the chiral auxiliary because the former does not require an extra synthetic step to remove them. Therefore, better yields of the final target molecule are theoretically possible.

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[36] Paterson, I.; Goodman, J. M.; Isaka, M.; *Tetrahedron Letters*. **1989**, 30, 7121-7122.

The reagent control methodology works well in theory, but practically it is less successful in the laboratory. Searching through the chemical literature, there are fewer examples using the reagent control methodology than the substrate control methodology. Besides, boron is widely used in the reagent control methodology. Two questions need to be addressed at this point. First, why is boron the first choice for chiral ligands? Second, why is the reagent control methodology far less effective when other metals are used?

In order to understand these two questions, one needs to understand the importance of bond length in the closed transition state model in the aldol reaction. The bond length in the closed transition state is an important criterion to understanding the stereoselectivity. For example, the B-O bond length is 1.36-1.47 angstrom, whereas the Ti-O bond length is 1.62-1.73 angstrom (Figure 8).[28] The shorter B-O bond length gives a "tighter" closed transition state than the titanium(IV) metal does.[24] Despite the fact that boron possesses four coordination sites compared to titanium(IV) which possesses six coordination sites; the extent of "tightness" in the closed transition state dominates in this case. The shorter B-O bond length means the closed transition state is more "tight" and less "deviated" from the traditional cyclohexane chair conformation. Therefore, boron is more widely used than titanium(IV) in the aldol reaction. However, the use of titanium (IV) and tin(IV) as Lewis acids in the aldol reaction is increasing exponentially in recent years, especially with the use of another catalyst to promote good diastereoselection.[37]

B—O	Ti—O	C—C	C═O
1.36 - 1.47 A	1.62 - 1.73 A	1.43 - 1.54 A	1.22 - 1.45 A

Figure 8. Some Typical Bond Length in Angstroms.

[37] Kobayashi, S.; Uchiro, H.; Fujishita, Y.; Shiina, I.; Mukaiyama, T.; *J. Am. Chem. Soc*. **1991**, 113, 4247-4248.

There is another reason to explain why using chiral ligands present more difficulties in achieving good stereochemical control over the use of chiral auxiliaries. For the chiral auxiliary, the closed transition state involved in the aldol reaction has fewer degrees of freedom. The orientation of the chiral auxiliary is basically locked or fixed to give the most stable conformation. On the other hand, chiral ligands have more degrees of freedom because the ligands can move or rotate to give a different conformation in the closed transition state. Because of this reason, the blocking of one face of the enolate is not very effective. However, the reagent control methodology is still being actively researched, and Professor Paterson is actively using it for stereochemical control in the aldol reaction.

Paterson and coworkers are the pioneers of using boron as a Lewis acid in research.[15a] Specifically, he developed bulky isopinocamphenyl (Ipc) ligands attached to boron (Figure 9). Compounds **47** and **48** are enantiomers, and each of them can be prepared from the enantiomeric α-pinene **46**.[38] The preparation of the enantiomeric isopinocamphenyl chiral ligands is straightforward. With careful design in chiral ligands, obtaining either one of the enantiomeric aldol adducts is possible. In this case, using chiral ligands is more advantageous than using a chiral auxiliary.

[38] Bernardi, A.; Capelli, A. M.; Comotti, A.; Gennari, C.; Gardner, M.; Goodman, J. M.; Paterson, I.; *Tetrahedron*. **1991**, 47, 3472-3473.

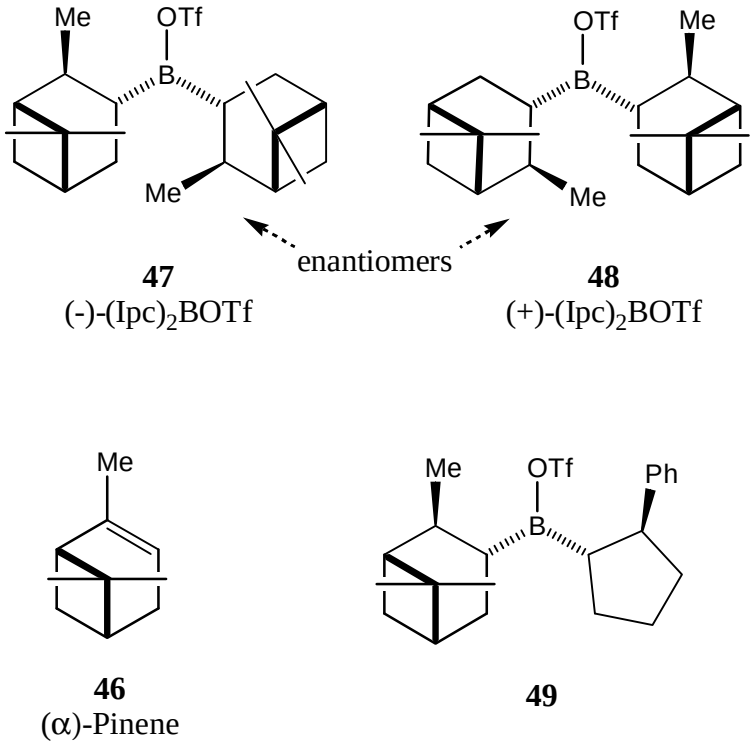
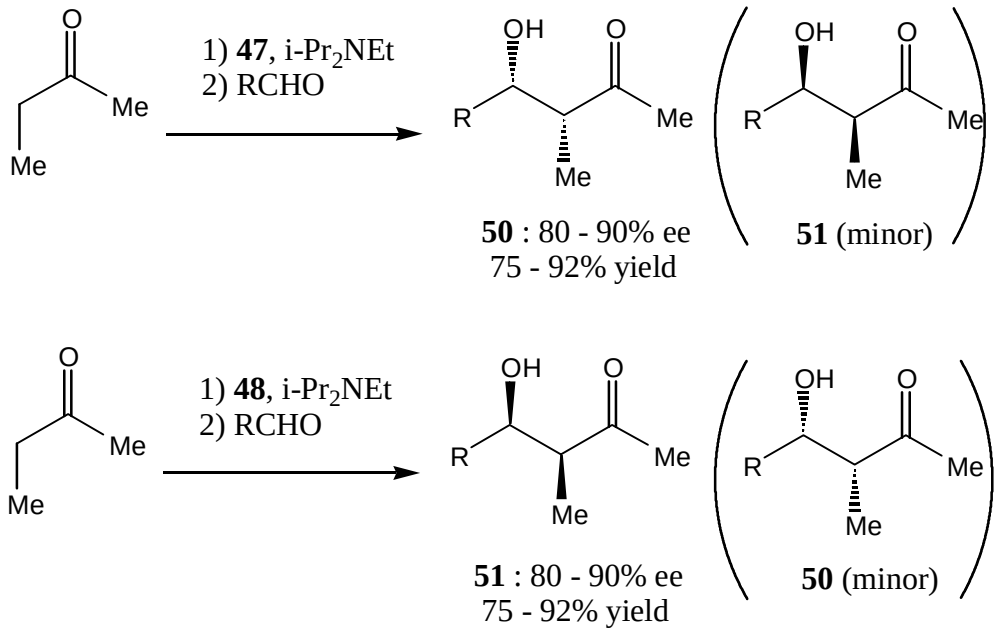


Figure 9

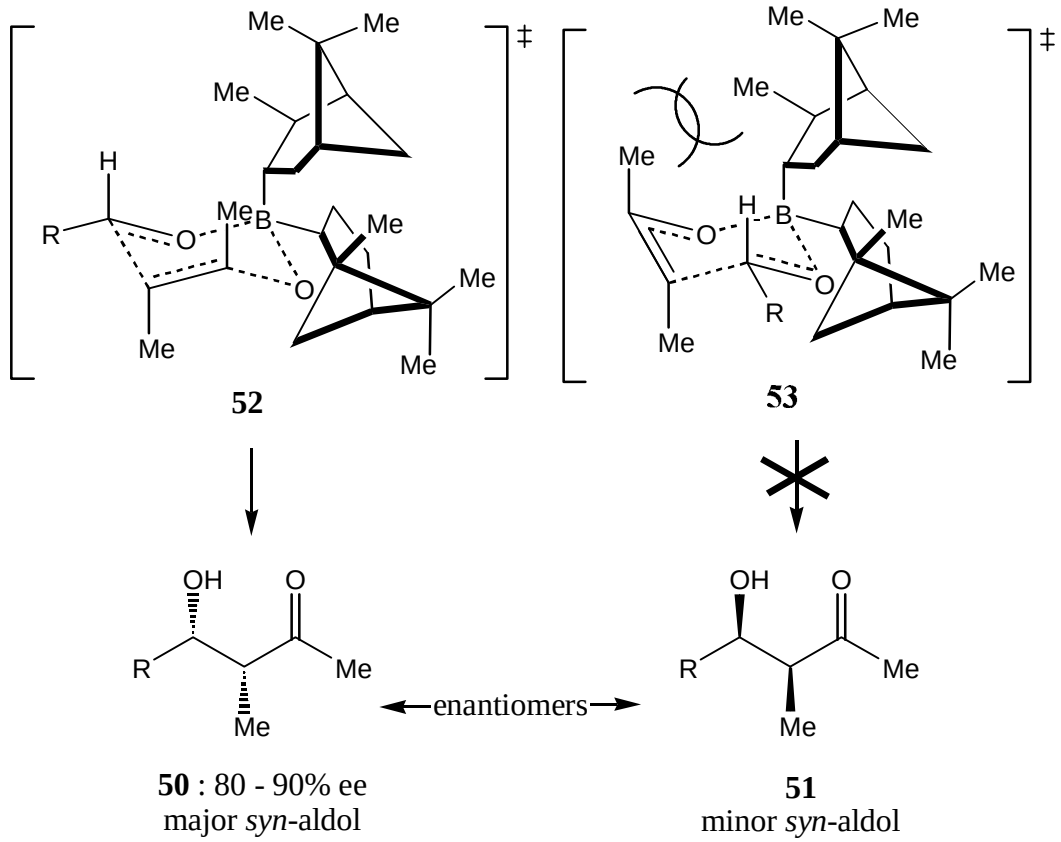
Paterson treated an ethyl ketone with reagent **47** to give an enolate that selectively gave the syn-aldol adduct **50** as the major product, whereas the enolate derived from reagent **48** gave the syn-aldol adduct **51** as the major product (Scheme 23).[39] That switching the enantiomer of the Ipc reagent used reversed the stereochemical orientations in the aldol adduct was very interesting, and one must investigate by looking at the transition state closely.

[39] Paterson, I.; Goodman, J. M.; *Tetrahedron Letters*. **1989**, 30, 997-998.

Scheme 23

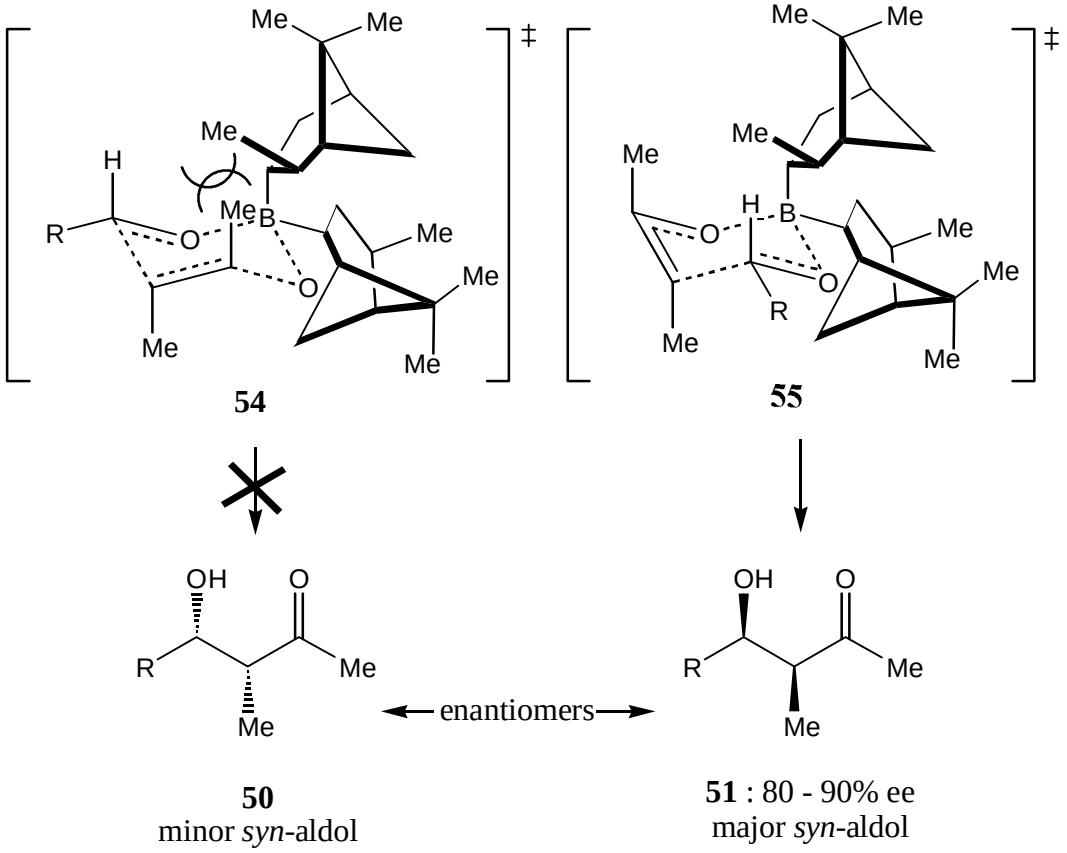


Scheme 24



One of the methyl groups in Ipc reagents **47** and **48** in Figure 9 is thought to play an important role in the stereoselectivity in the aldol reaction. In the proposed closed transition state **52** containing the Ipc reagent **47** (Scheme 24), the aldehyde approaches the enolate from the back side (re-face attack) to give the syn-aldol adduct **50**. However, if the aldehyde approaches the enolate from the front side (si-face attack), the syn-aldol adduct **51** is the correct product by way of transition state **53**. But this transition state **53** is

Scheme 25



disfavored because of the destabilizing steric interaction between the methyl group of the Ipc ligand and the methyl group of the enolate. The closed transition state **53** gives the syn-aldol adduct **51**, but the strong destabilizing steric effect disfavors the formation of the closed transition state **53**. Therefore, the syn-aldol adduct **50** is formed as the major product, and the syn-aldol adduct **51** is formed as the minor product in the aldol reaction.

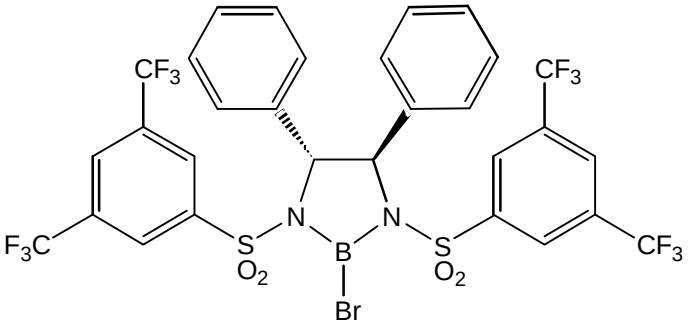
However, when reagent **48** is used, the stereochemical orientation is reversed from Scheme 24 (Scheme 25). The proposed closed transition state **55** is more favored than the closed transition state **54** as depicted in Scheme 25. In the closed transition state **54**, there is a strong destabilizing steric interaction between the methyl group of the Ipc ligand and the methyl group of the enolate. Therefore, one expects the syn-aldol adduct **51** to be the major product in this case. All the proposed transition structures **52, 53, 54,** and **55** are predicted to give aldol adducts **50** and **51** in Scheme 23.

So far, rationalizing the major (or minor) aldol adduct produced is possible by looking at the closed transition state in most examples. Sometimes, the closed transition state cannot be rationalized through computer modeling, especially when the chiral ligands are sterically demanding and complicated. Hence, the role of the sterically hindered chiral ligand is often difficult to rationalize in the closed transition state by computer modeling. For example, the chiral reagent **56** (Figure 10) is bulky and hindered, and it is difficult to rationalize its "orientation" in the closed transition state by computer modeling. Corey and Kim developed this effective chiral reagent **56** for the achiral propionate ester in the aldol reaction.[40] In Corey and Kim's paper, they used the notation $R^*_2B(Br)$ in their proposed

[40] Corey, E. J.; Kim, S. S.; *J. Am. Chem. Soc*. **1990**, 112, 4977-4979.

transition state because they do not know the exact “orientation” of bulky ligands in the transition state. In a limited sense, they propose that the possible transition state is the Zimmerman-Traxler closed transition state previously discussed (see Scheme 2, 3 and 4).

The chiral reagent **56** is treated with t-butyl propionyl ester **57** and triethylamine to form the (E)-enolate **58**, which gives the anti-aldol adduct **59** as the major product (Scheme 26). This result is consistent with the earlier discussion in which the (E)-enolate selectively gives the anti-aldol adduct (see Schemes 2 and 4). However, Corey and Kim still do not know the “orientated” conformation of the bulky chiral ligands (R^*_2B) in the closed transition state. Therefore, we are not certain how the use of chiral ligands enhances the stereoselectivity in the aldol reaction.

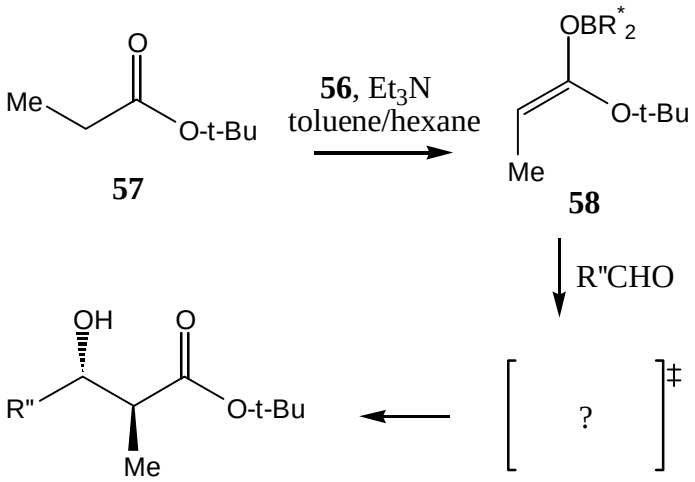


abbreviated as (R^*_2B-Br)

56

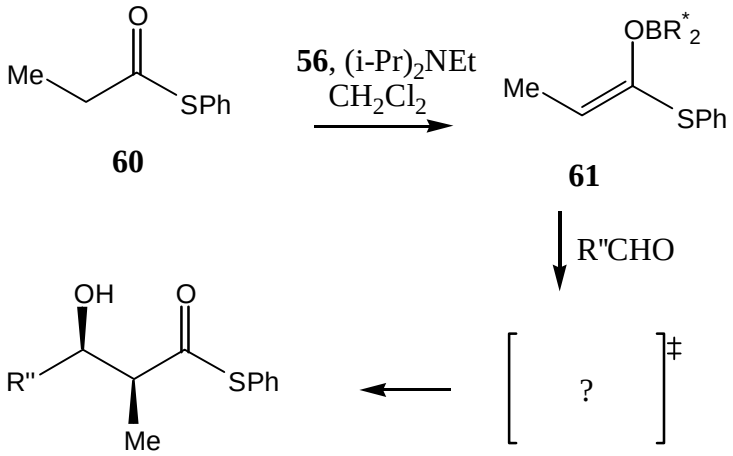
Figure 10. The Bulky Chiral Reagent from Corey & Kim.

Scheme 26



59 : 90 - 98% ee
82 - 93% yield

Scheme 27



62 : 90 - 97% ee
80 - 93% yield

In scheme 27, the thiophenyl ester **60** reacted with chiral reagent **56** and N, N-diisopropylethylamine to give (Z)-enolate **61**. The formation of the syn-aldol adduct **62** from the (Z)-enolate **61** in this example is consistent with our earlier discussion. The (Z)-

enolate gives the syn-aldol adduct from the closed transition state model (see Scheme 2 and 3). Again, we are not sure of the orientation of the bulky chiral ligands in the closed transition state. Besides, we are not certain why the chiral reagent **56** is specific to ester and thioester in the aldol reaction. The specificity of the substrate may be linked to some destabilizing steric interaction between the ester (or thioester) and the bulky ligands that both selectively favor one of the stereoisomers.[41]

Both the chiral auxiliary and chiral ligands methodologies are very efficient at selectively controlling the stereochemistry of the aldol adduct. Unfortunately, stoichiometric amount of chiral auxiliary or chiral ligands must be used. Besides, the use of chiral auxiliary requires tedious procedures for adding and removing it from the aldol adduct for further synthesis. Therefore, using both methods in the laboratory is expensive for large-scale synthesis. To solve this problem, researchers seek to develop different catalysts.

Asymmetric catalysis is the most attractive method, and it has been actively developed within this decade. This method saves time and money in large-scale synthesis. However, the overall reaction and the mechanism are not as well understood as the other methodologies in the asymmetric aldol reaction. To explain why a catalyst works in the aldol reaction is speculative because most of the transition state models are hypothetical. Further experimental data is needed to confirm the identity of the hypothetical transition state. Understanding and drawing conclusions for the reaction mechanism from the transition state is always the most challenging part in asymmetric catalysis.

[41] Masamune, S.; Sato, T.; Kim, B.M.; Wollmann, T. A.; *J. Am. Chem. Soc*. **1986**, 108, 8279-8281.

Although asymmetric catalysis of the aldol reaction is actively being pursued, there are few catalysts that perform well in the aldol reaction. In the next chapter, we explore the use of those chiral catalysts in the aldol reaction.

Chapter Four. Asymmetric Chiral Catalysis

Asymmetric chiral catalysis is one of the most fascinating methods in aldol reactions. The impact of using this methodology is enormous. First, one can generate a large number of chiral molecules with a trace amount of chiral catalytic molecules. In addition, the chiral catalyst is regenerated after the aldol reaction. Therefore, it can be reused and thereby reducing the cost of synthesis. Second, a chiral catalyst can create a chiral center (or centers) from the achiral enolate and/or the achiral aldehyde. A chiral catalyst serves as a "chiral promotor" and creates a chiral center from the achiral substrates. Third, chiral catalysis does not require the tedious procedures for adding and removing the chiral auxiliary after the reaction. Therefore, chiral catalysis gives ample versatility when designing a synthetic route for a target molecule. Theoretically, chiral catalysis is more efficient than the use of chiral auxiliaries or chiral ligands in the aldol reaction.

Most of the catalysts for the aldol reaction are Lewis acids. The term "chiral Lewis acid" is synonymous with the "chiral catalyst" in the aldol reaction. Furthermore, Mukaiyama and coworkers have developed a large number of chiral catalysts for more than two decades.[42] As a result, the term "Mukaiyama aldol reaction" is widely used to refer to the "catalytic aldol reaction." The term "Mukaiyama aldol reaction" is also used to refer to the "catalytic aldol reaction" in this chapter.

The classic example of asymmetric aldol catalysis came from the work of Ito, Sawamura, and Hayashi.[43] The research group reported the gold(I) complex **64** from the

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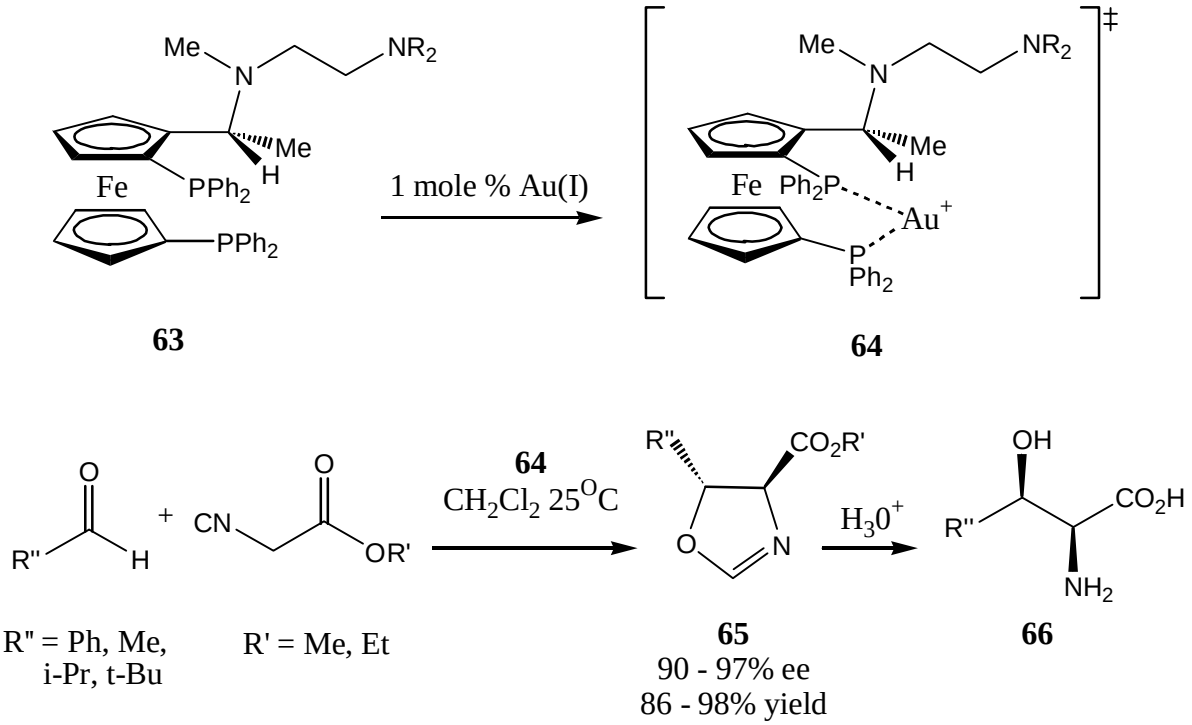
[42] (a) Mukaiyama, T.; Narasaka, K.; Banno, K.; *Chem. Lett.* **1973**, 1012-1013. (b) Saigo, K.; Osaki, M.; Mukaiyama, T.; *Chem. Lett*. **1975**, 989. (c) Mukaiyama, T.; *Org. React*. **1982**, 28, 203-205.
[43] (a) Ito, Y.; Sawamura, M.; Hayashi, T.; *J. Am. Chem. Soc*. **1986**, 108, 6405-6406. (b) Ito, Y.; Sawamura, M.; Hayashi, T.; *Tetrahedron*. **1992**, 48, 1999-2005.

chiral ferrocenylphosphine ligands **63** catalyzed the aldol reaction of α-isocyanoacetate and several aldehydes (Scheme 28). This reaction was catalytically efficient because 1 mole % of gold(I) was used to generate the gold(I) complex **64**. The optically active *trans*-5-alkyl-2-oxazoline-4-carboxylate **65** was formed as the important precursor for the β-hydroxy-α-amino acid **66** and its derivatives (Scheme 28).

Scheme 28



The terminal tertiary amine of complex **63** (or **64**) was found to be the most important factor for high stereoselectivity in the gold(I) catalyzed aldol reaction. Using a primary or secondary terminal amine gave poor stereoselectivity. Moreover, the terminal tertiary amine must be two carbons away from the first tertiary amine on the substituted ferrocenylmethyl position. Increased length of the carbon chain on the terminal tertiary

amine gave poor stereoselectivity. These pieces of evidence indicated that the presence of the terminal tertiary amine in the proper carbon chain position was essential for high stereoselectivity. Presumably, these pieces of evidence also indicated that the transition state might be complicated.

The exact transition state model for the gold-catalyzed aldol reaction is yet to be determined. However, Ito and coworkers propose the hypothetical open transition state model in Figure 11. The tertiary amine in the terminal position abstracts one of the α-methylene protons of the isocyanoacetate to form the positively charged ammonium salt. The positive charge on the nitrogen coordinates the enolate oxygen anion. As previously mentioned, the tertiary amine in the terminal position is responsible for high stereoselectivity. To explain this experimental result, the formation of the ammonium salt is very likely because the ion pair between the enolate oxygen anion and the positive charge on the nitrogen can create the ideal stereodifferentiating environment for the aldehyde. The aldehyde can coordinate to gold(I) and the enolate in a well-defined space as depicted in Figure 11. As a result, high stereoselection is achieved in the gold-catalyzed aldol reaction.

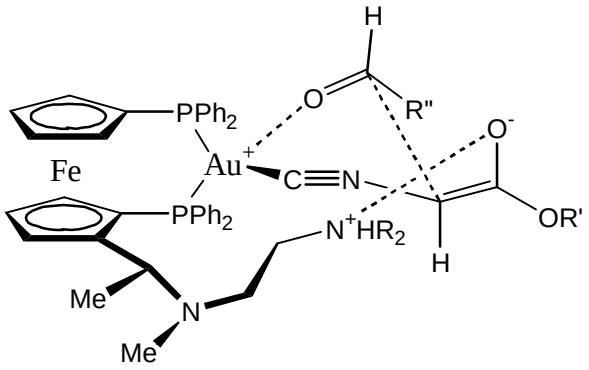
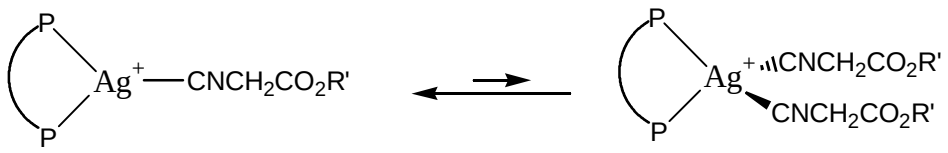


Figure 11. Proposed hypothetical open transition state by Ito and coworkers.

Silver(I) was also used as a catalyst in the aldol reaction of α-isocyanoacetate and aldehyde by the same research group.[44] However, the stereoselectivity in this reaction was lower than the gold-catalyzed reaction. Ito and coworkers proposed that silver(I) formed the tetra-coordinated complex as depicted in Scheme 29. The more favored tri-coordinated silver(I) complex equilibrated with the less favored tetra-coordinated silver(I) complex (Scheme 29). The aldehyde could no longer coordinate to the tetra-coordinated silver(I) complex because the silver(I) coordination sites were saturated (Figure 12). The formation of the tetra-coordinated silver(I) complex is a good model to explain a slightly lower stereoselection.

Scheme 29



more stereoselective with aldehyde

less stereoselective with aldehyde

[44] Hayashi, T.; Uozumi, Y.; Yamazaki, A.; Sawamura, M.; Hamashima, H.; Ito,Y., *Tetrahedron Letters.* **1991**, 32, 2799-2801.

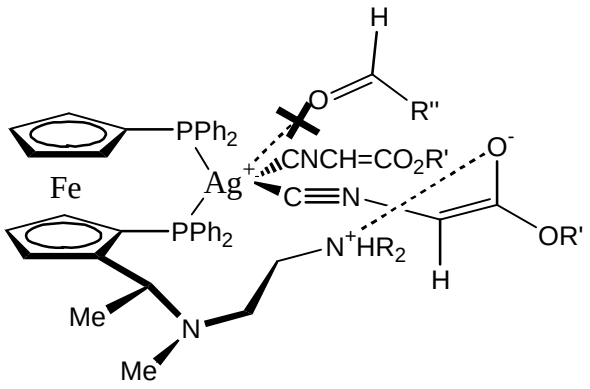


Figure 12. Aldehyde can no longer coordinate to the silver(I) tetracoordinated complex.

Unfortunately, the gold(I) or the silver(I) catalyzed Mukaiyama aldol reaction is specific to isocyanoacetate. The gold(I) or the silver(I) catalyzed aldol reaction does not proceed with other ketones or esters except isocyanoacetate. This is one of the major drawbacks to the catalytic aldol reaction. The catalytic aldol reaction is less general than the substrate or reagent controlled aldol reactions. Designing a chiral catalyst for a variety of substrates poses a challenging task for researchers. Researchers are continuously developing more efficient chiral catalysts that are applicable in the aldol reaction, but the progress is slow.

Evans and coworkers developed a bidentate (box) bis(oxazolinyl) copper(II) catalyst **67** and tridentate (pybox) bis(oxazolinyl) pyridyl copper(II) catalyst **68** (Figure 13) in the Mukaiyama aldol reaction of pyruvate ester and enolate (Scheme 31), and α-(benzyloxy) acetaldehyde and enolate, respectively (Scheme 30).[45, 46] A catalytic amount of 5 to 10 mole % of the copper(II) catalyst were used in both reactions to give excellent stereoselectivity.

[45] Evans, D. A.; Murry, J. A.; Kozlowski, M. C.; *J. Am. Chem. Soc.* **1996**, 118, 5814-5815.

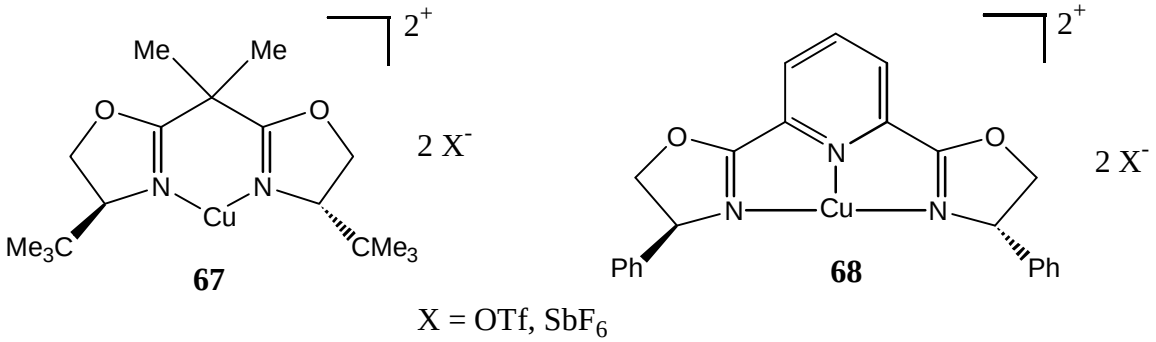
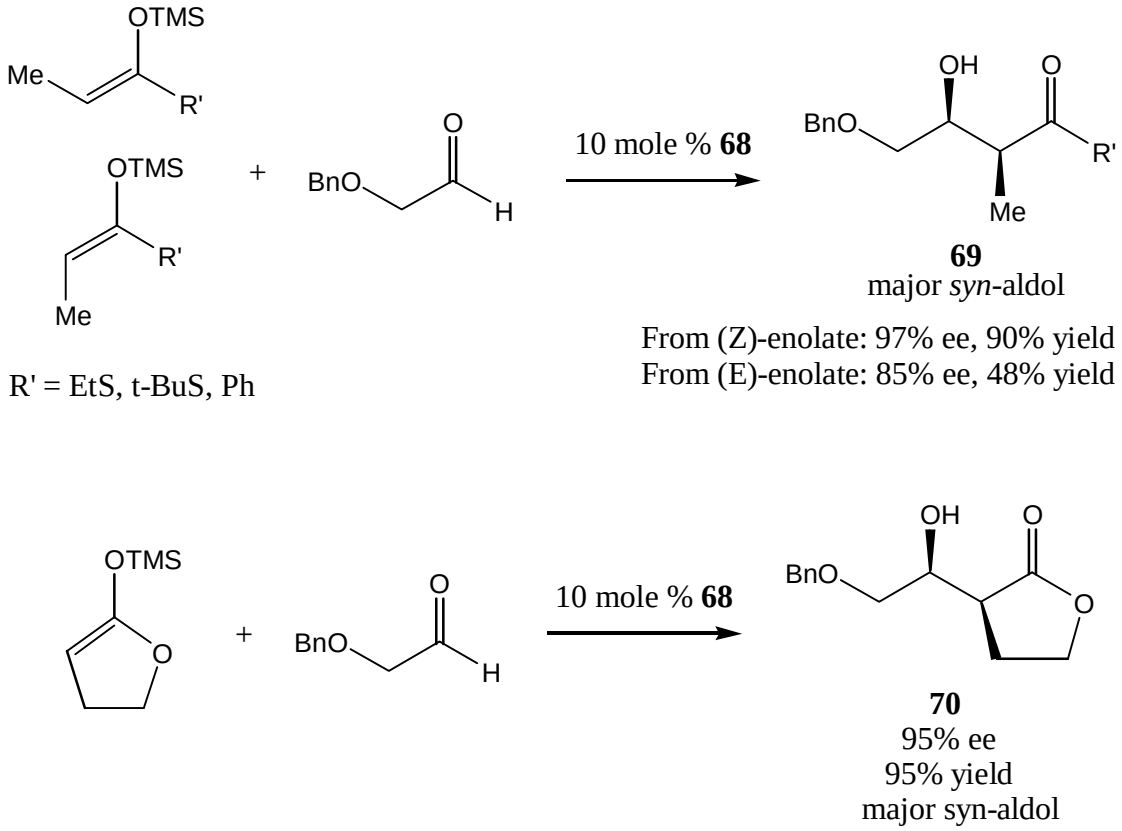


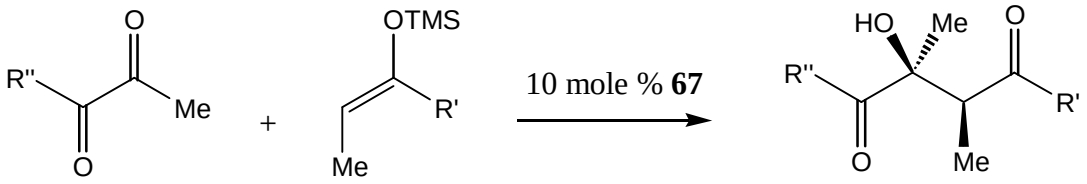
Figure 13. Box and pybox Cu(II) complex.

Scheme 30



[46] Evans, D. A.; Kozlowski, M. C.; Burgey, C. S.; MacMillan, D. W. C.; *J. Am. Chem. Soc*. **1997**, 119, 7893-7894.

Scheme 31



R'' = Me, Et, t-Bu, OMe, Bn

R' = EtS, t-BuS, Ph

71
96 - 98% ee
88 - 97% yield
major *syn*-aldol

In Scheme 30, both the syn-aldol adducts **69** and **70** are the major products. The syn-aldol adduct **69** is the major product regardless of the starting material (E) or (Z)-enolate. This catalytic aldol reaction is selective to α-(benzyloxy) acetaldehyde only. Reaction with other aldehydes such as benzaldehyde is nonselective. This piece of evidence discredits the closed transition state model for this reaction. The reaction must go through the acyclic open transition state to support the experimental result. Evans et al. propose the aldehyde carbonyl and the aldehyde α-(benzyloxy) oxygen atom coordinate to copper(II) forming a penta-coordinate square pyramid in the pybox open transition state (Figure 14). Spectroscopic analysis supports the bidentate square pyramidal complex alternative over the trigonal bipyramidal complex. In Figure 14, copper(II) chelates the aldehyde carbonyl and the α-(benzyloxy) oxygen atom, and the re-face of the aldehyde is shielded by the phenyl group in the oxazolindine ring. Therefore, the si-face of the aldehyde is available for nucleophilic attack from the enolate. This hypothetical open transition state model explains why the reactions of other aldehydes, such as benzaldehyde, are nonselective. The phenyl group in benzaldehyde does not have an electronegative

oxygen atom that can coordinate to copper(II) to provide a stereodifferentiating environment for good stereoselection.

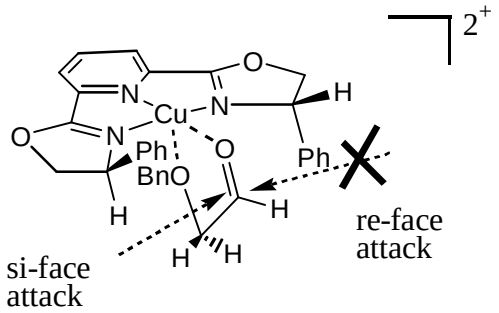


Figure 14. Proposed hypothetical square pyramidal open transition state model for pybox Cu(II) complex.

Evans proposes a similar bicheating open transition state model in the aldol reaction of pyruvate ester and aldehyde for Scheme 31. In Figure 15, the two carbonyl oxygens in the pyruvate ester are chelated by copper(II) forming a five-membered ring that is similar to Figure 14. The top portion (re-face) of the pyruvate ester is shielded by the bulky t-butyl group in the oxazolidine ring (Figure 15). The enolate is unlikely to attack the re-face of the pyruvate ester. Therefore, the enolate must attack the si-face of the pyruvate ester to give the syn-aldol adduct **71**. This hypothetical open transition state model provides a viable rationale for the results of this type of Mukaiyama aldol reaction.

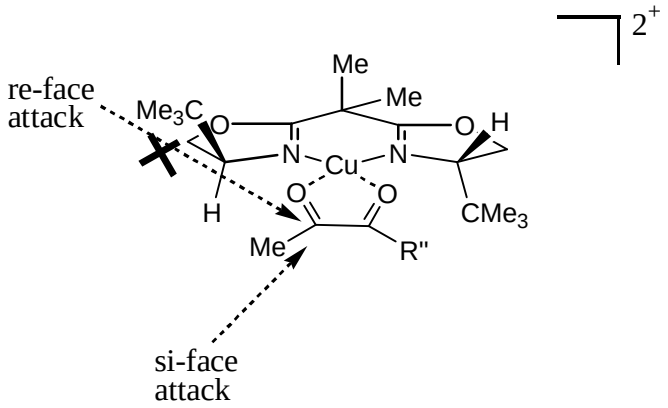


Figure 15. Proposed hypothetical square pyramidal open transition state model for box Cu(II) complex.

Surprisingly, replacing copper(II) with tin(II) for the box and the pybox catalysts **72** and **73** give the anti-aldol adduct in the aldol reaction of pyruvate ester and silyl enolate (Figure 16 and Scheme 32).[47] The enantiomeric anti-aldol adducts **74** and **75** are selectively formed from the tin(II) box **72** and tin(II) pybox **73**, respectively (Scheme 32). Unlike copper(II) box **67** and pybox **68**, the two triflate groups are thought to coordinate tin(II) in box **72** and pybox **73** (Figure 16). Tin(II) is a group four element that is capable forming at least four bonds. However, the role of the two triflate groups in the tin(II) transition state is not clear. Evans suggests that there may be a rapid ligand substitution between the two triflate groups of the complex and the two carbonyl oxygen groups of the pyruvate ester. This unknown mechanism may be responsible for the anti-selectivity. Furthermore, Evans also suggests that the transition state of tin(II) box and tin(II) pybox shall be similar to the copper(II) box and the copper(II) pybox hypothetical open transition state as shown in Figure 14 and Figure 15, respectively. The exact transition state is still not known.

[47] Evans, D. A.; MacMillan, D. W. C.; Campos, K. R.; *J. Am. Chem. Soc*. **1997**, 119, 10859-10860.

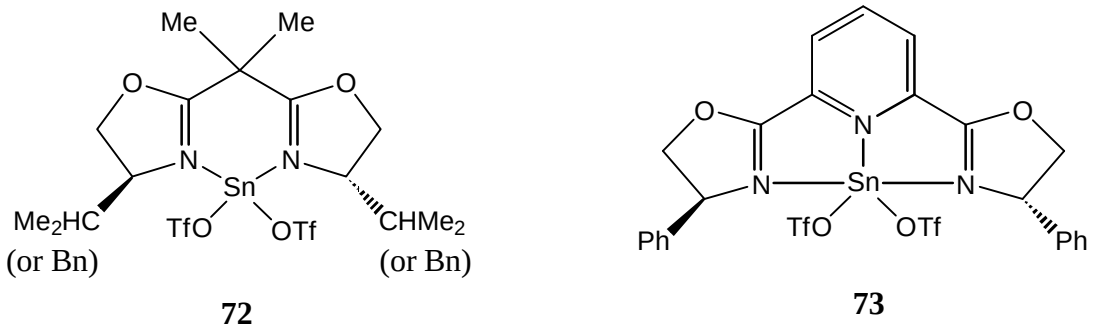
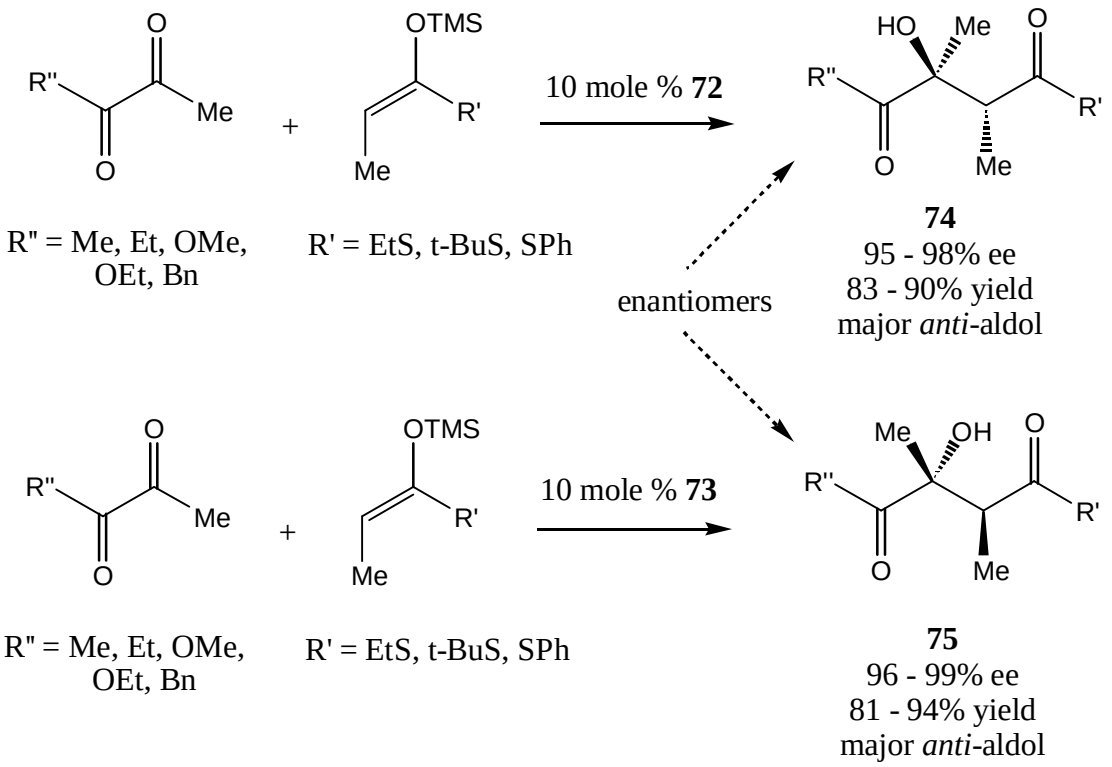


Figure 16. Box and pybox Sn(II) complex.

Scheme 32

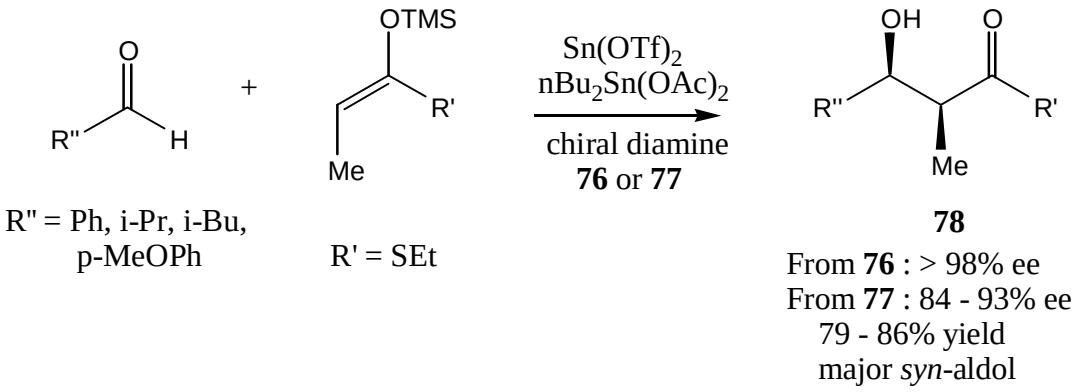


Kobayashi and coworkers develop an efficient catalytic method using tin(II) as a Lewis acid in the Mukaiyama aldol reaction.[48] In this reaction, the method for preparing

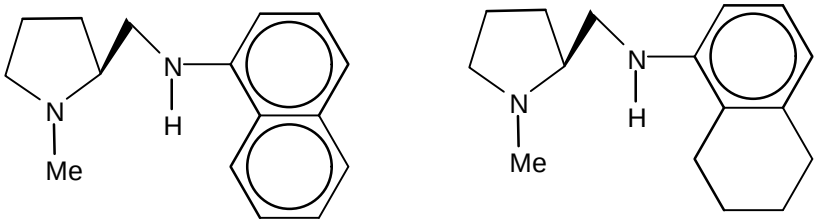
[48] Kobayashi, S.; Uchiro, H.; Fujishita, Y.; Shiina, I.; Mukaiyama, T.; *J. Am. Chem. Soc*. **1991**, 113, 4247-4250.

the catalyst is different than the other methods that we have previously discussed. Instead of synthesizing the catalyst before running the aldol reaction, he uses the tin(II) triflate and the chiral diamine ligands in-situ in the aldol reaction of silyl enolate and aldehyde. Tributyltin fluoride, dibutyltin difluoride, or dibutyltin diacetate (Scheme 33) facilitate the reaction. This well-designed method omits several tedious steps to synthesize the catalyst. He experimentally determined that the complexes derived from both chiral diamines **76** and **77** afford 100% diastereoselectivity in favor of the syn-aldol adduct **78**. Furthermore, greater than 98% ee is achieved when using the chiral diamine **76**.

Scheme 33



chiral diamine



76 **77**

Kobayashi determined that the bicyclic system in the chiral diamine (Figure 17) worked best in the Mukaiyama aldol reaction. A benzene or cyclohexane ring alone gave poor stereoselectivity. This piece of evidence strongly suggested that the bicyclic system might effectively "shield" one face of the aldehyde. The proposed transition state as depicted in Figure 18 showed the aldehyde coordinated to tin(II), and the re-face of the aldehyde was blocked by the bicyclic rings.[49] As a result, the si-face attack of the aldehyde was favored because there was no blocking from the bicyclic rings. Special attention should be given to the two triflate groups in the transition state. Presumably, the tin(II) was coordinated to the two triflate groups, but there was a strong debate about this. Tin(II) can form four bonds, but in the hypothetical transition state in Figure 18, tin(II) formed five bonds. Whether there was a full or partial bond between tin(II) and the triflate group was not clear.

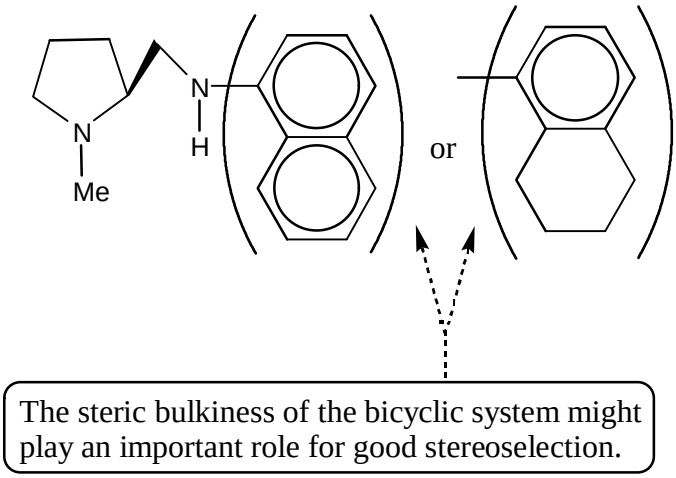


Figure 17.

[49] Sawamura, M.; Ito, Y.; *Catalytic Asymmetric Synthesis*. I. Ojima ed. **1993**, 382.

Until now, we have seen numerous examples showing the importance of blocking one face of the aldehyde to achieve good stereoselection. We will continue to discuss many of these examples. There are more examples included herein for discussion.

Recently, Kobayashi and coworkers developed two new chiral diamines **79** and **80** for the Mukaiyama aldol reaction of dihydroxythioesters and aldehydes (Scheme 34).[50] The chemical structures of both chiral diamines were similar to diamines **76** and **77**. Surprisingly, by modifying the position of the benzene ring around the bicyclic system of the chiral diamine **79**, the other enantiomeric syn-aldol adduct was formed (Scheme 34). As depicted in Scheme 34, the chiral diamine **79** was used to form the syn-aldol adduct **81**, and the chiral diamine **80** was used to form the syn-aldol adduct **82**, the enantiomer of syn-aldol adduct **81**. In this example, one could see it was not necessary to use a different enantiomer of the catalyst to get the enantiomer of the syn-aldol adduct.

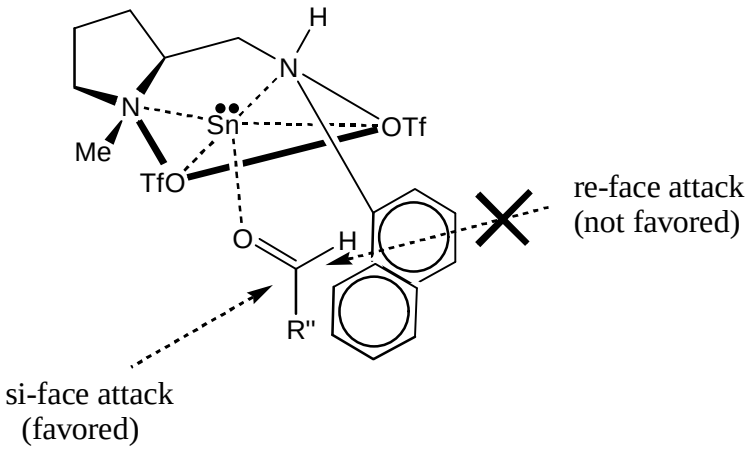
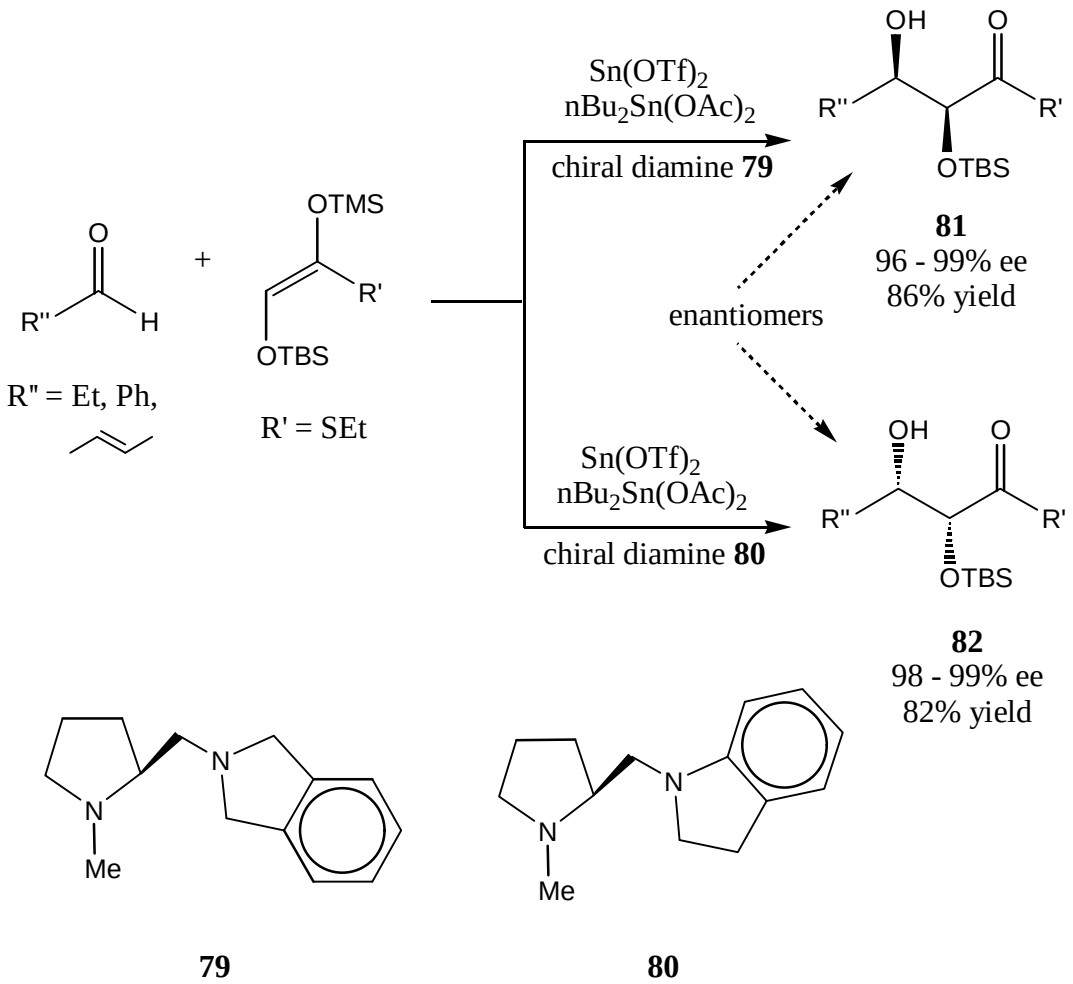


Figure 18. Proposed open transition state for Sn(II) complex by Kobayashi.

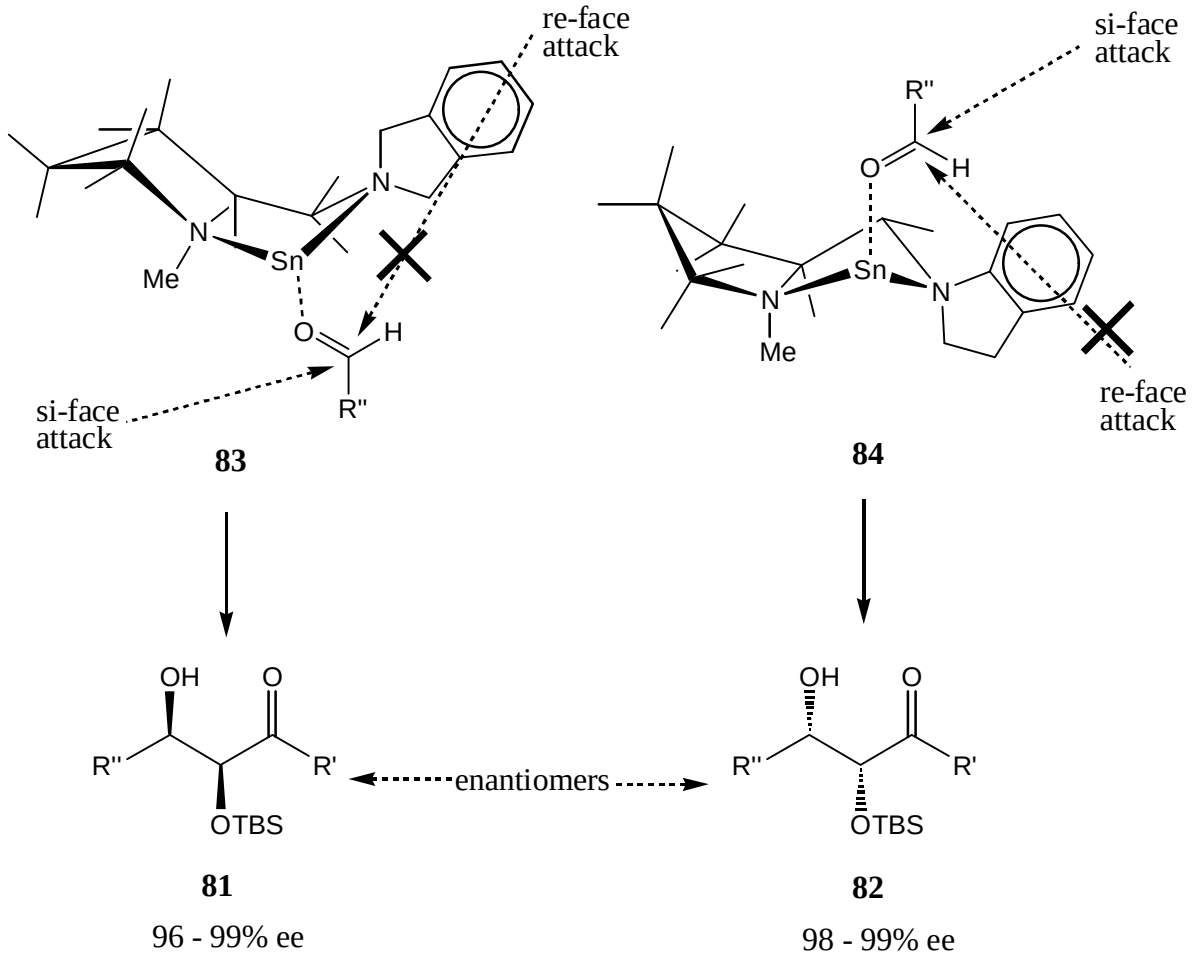
[50] Kobayashi, S.; Horibe, M.; *Chem. Eur. J.* **1997**, 3, 1472-1481.

Scheme 34



The proposed open transition states **83** and **84** are shown in Scheme 35. In the transition state **83**, the aldehyde coordinates the tin(II) on the bottom face because there is no steric involvement from the bicyclic ring. The bicyclic ring blocks the back face (re-face) of the aldehyde. Thus, the enolate approaches the front face (si-face) of the aldehyde to form the aldol-adduct **81**. On the other hand, the aldehyde in the transition state **84** is coordinated to tin(II) on the top face to avoid any sterics from the bicyclic ring. The bicyclic ring blocks the front face (re-face) of the aldehyde, and therefore the enolate must approach to the back face (si-face) of the aldehyde to give the aldol-adduct **82**.

Scheme 35



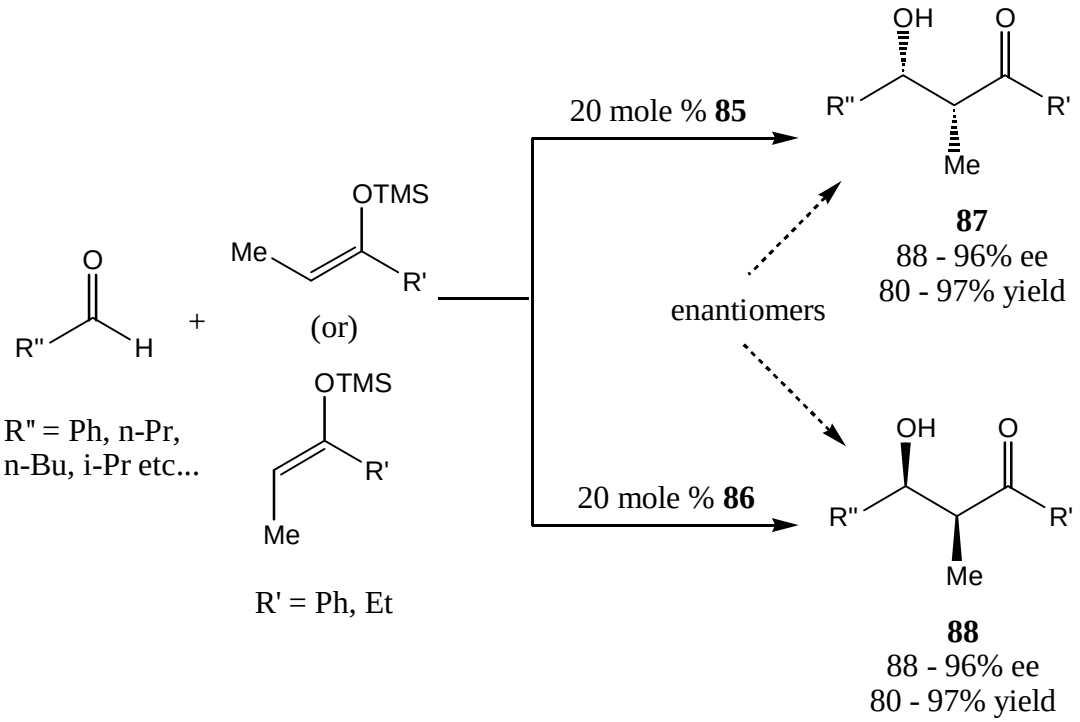
In Chapter three, the widely used chiral auxiliary containing boron was introduced. Unfortunately, chiral catalysts containing boron are less efficient. This is due to the fact that the sterically bulky groups (ligands) in a catalyst usually occupy all the coordination sites on boron. Because of this reason, boron has no sites open to coordinate the aldehyde. But with careful design, boron can still be used as an efficient catalyst in the Mukaiyama aldol reaction.

Yamamoto and coworkers have developed a successful boron catalyst for the Mukaiyama aldol reaction of enolates and aldehydes.[51] Enantiomeric chiral (acyloxy)borane (CAB) catalysts **85** and **86** were used to give the enantiomeric syn-aldol adducts **87** and **88**, respectively (Scheme 36). Both enantiomeric CAB catalysts were easily prepared from readily available pure enantiomers of the starting compound. Notice both syn-aldol adducts **87** or **88** could be selectively formed from either the E or Z enolate. This piece of evidence strongly suggested that the acyclic open transition state was more likely in this reaction. Details on how the "sterics" of the CAB catalyst in the transition state explain the stereoselectivity were uncertain.

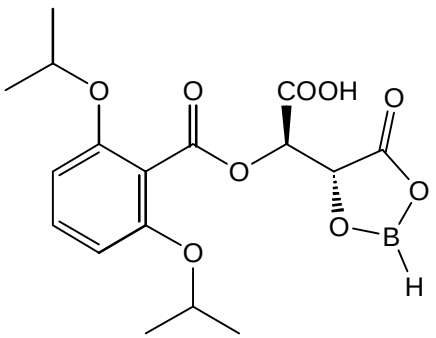
In addition, the researchers have limited understanding of the acyclic transition state. The classical acyclic open transition states **89** and **90** as depicted in Scheme 37 did not account for the bulky group on the boron. Therefore, both open transition states **89** and **90** cannot explain why the syn-aldol adduct **87** is favored over the syn-aldol adduct **88**, and the anti-aldol adduct **91** is favored over the anti-aldol adduct **92**, respectively. But nevertheless, both open transition states **89** and **90** can still be used to explain why the syn-aldol adduct **87** (or **88**) is selectively formed over the anti-aldol adduct **91** (or **92**). In the transition state **90**, there is a steric destabilizing interaction between the R" group of the aldehyde and the methyl group of the enolate. Therefore, the anti-aldol adduct **91** (or **92**) is not formed.

[51] (a)Yamamoto, H.; Furuta, K.; Maruyama, T.; *J. Am. Chem. Soc*. **1991**, 113, 1041-1042. (b)Deloux, L.; Srebnik, M.; *Chem. Review*. **1993**, 93, 780. (c)Yamamoto, H.; Ishihara, K.; *Eur. J. Org. Chem*. **1999**, 527-529, 533-534.

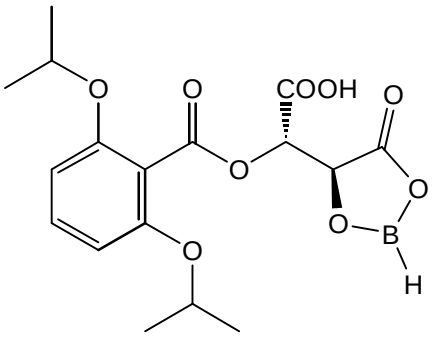
Scheme 36



CAB catalyst

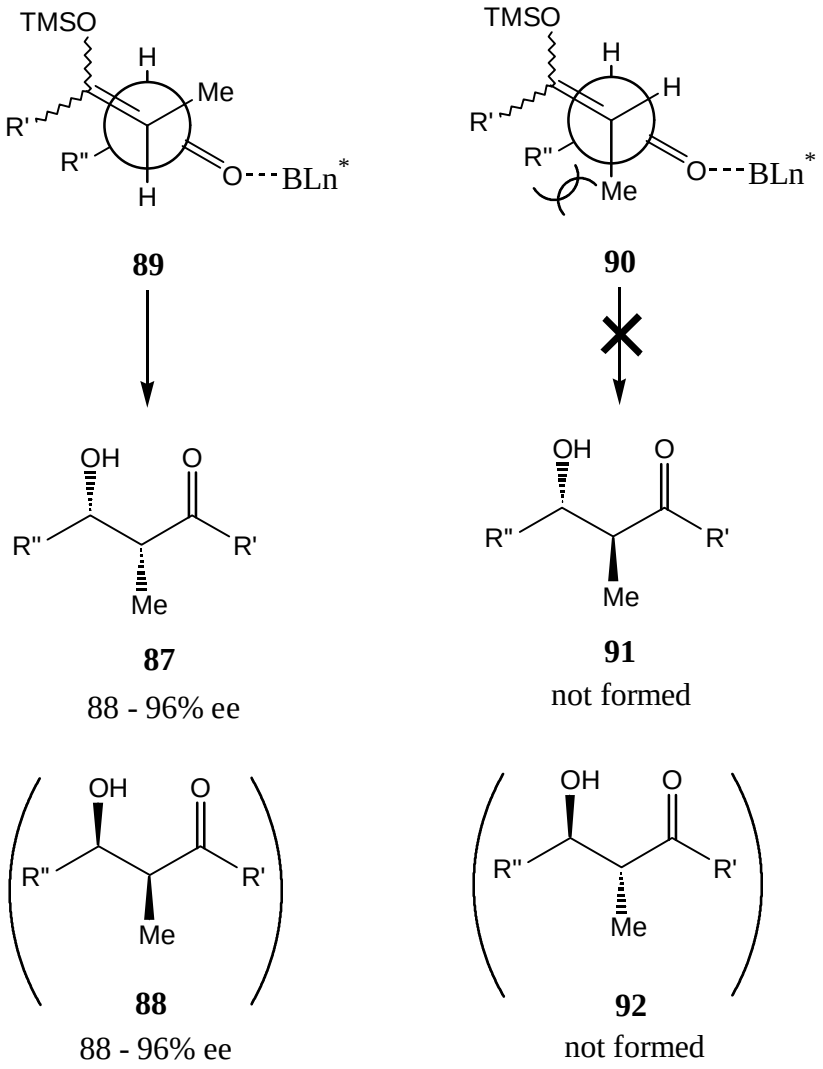


85

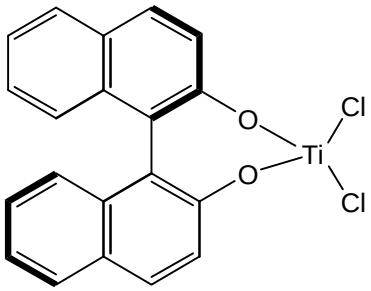


86

Scheme 37

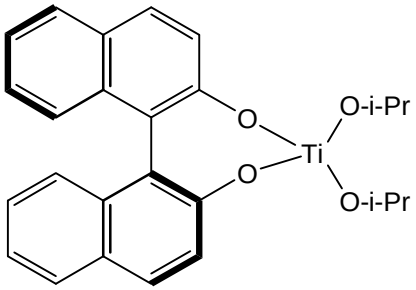


Three independent research groups develop three chiral titanium(IV) catalysts based on the structure of BINOL (BINOL = 2,2'-dihydroxy-1,1'-biphenyl) for the Mukaiyama aldol reaction (Figure 19). Both enantiomeric (R)-BINOL and the (S)-BINOL are readily available, and are used in preparing the chiral titanium(IV) catalyst in Figure 19. Furthermore, all three BINOL-based titanium(IV) catalysts are very efficient in controlling the stereoselectivity in the aldol reaction.



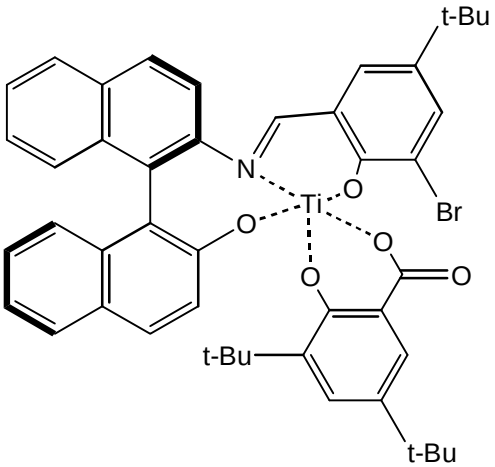
(R)-BINOL Ti(IV) catalyst

93



(S)-BINOL Ti(IV) catalyst

94



(R)-BINOL Ti(IV) catalyst

95

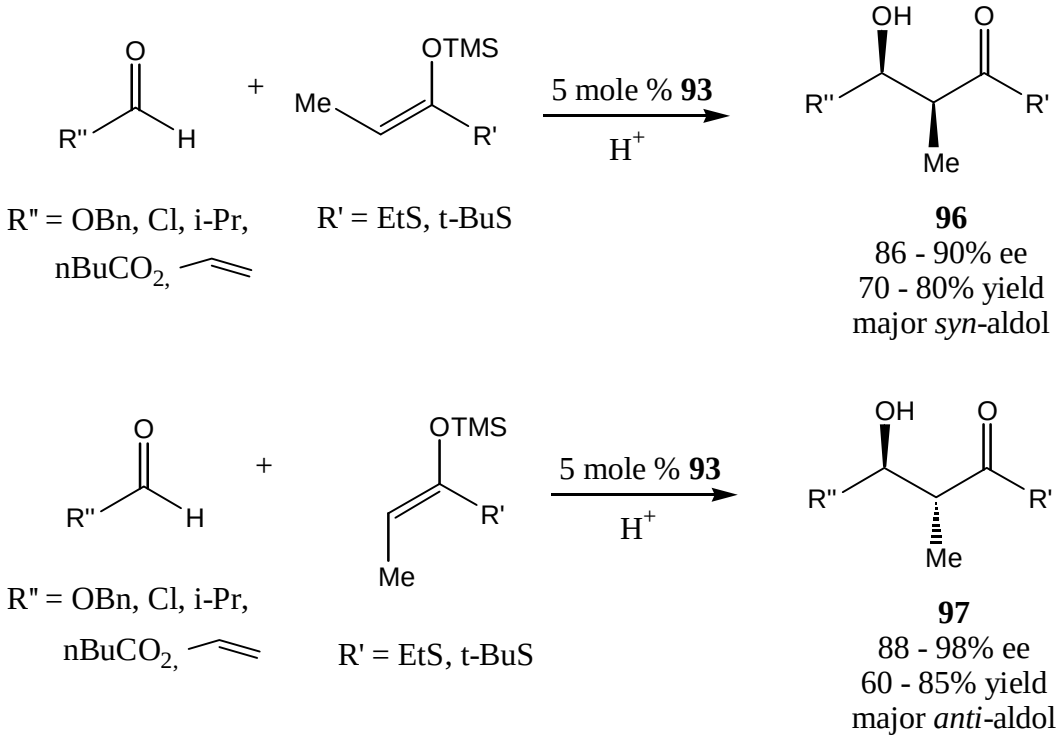
Figure 19. Titanium(IV) catalysts based on the structure of BINOL.

The (R)-BINOL titanium(IV) catalyst **93** was developed by Mikami et al.[52] The catalytic aldol reaction of (E)-thioenolate and aldehyde with 5 mole % of catalyst **93** selectively gave the syn-aldol adduct **96**, whereas the (Z)-thioenolate and aldehyde with

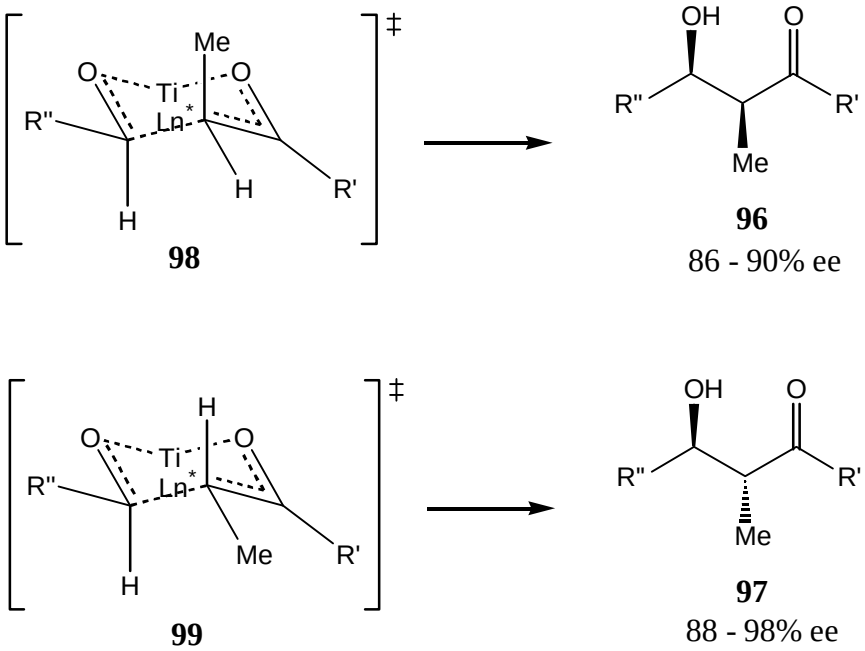
[52] (a) Mikami, K.; Matsukawa, S.; *J. Am. Chem. Soc*. **1993**, 115, 7039-7040. (b) Mikami, K.; Matsukawa, S.; *J. Am. Chem. Soc*. **1994**, 116, 4077-4078.

the same catalyst selectively gave the anti-aldol adduct **97** (Scheme 38). In this reaction, the geometry of the thioenolate gave the specific aldol-adduct suggested that the aldol reaction must proceed through the closed transition state (Scheme 39). However, one could also argue that the sterically demanding BINOL structure disfavored the closed transition state, and the acyclic open transition state was favored.[32] Many researchers thought that the bulky BINOL structure might block one face of the aldehyde to form the specific aldol-adduct from the acyclic open transition state. However, when the stereoselectivity of the aldol reaction is highly dependent on the geometry of the enolate, the closed transition state model supports the argument better than the open transition state model (Scheme 39).

Scheme 38



Scheme 39

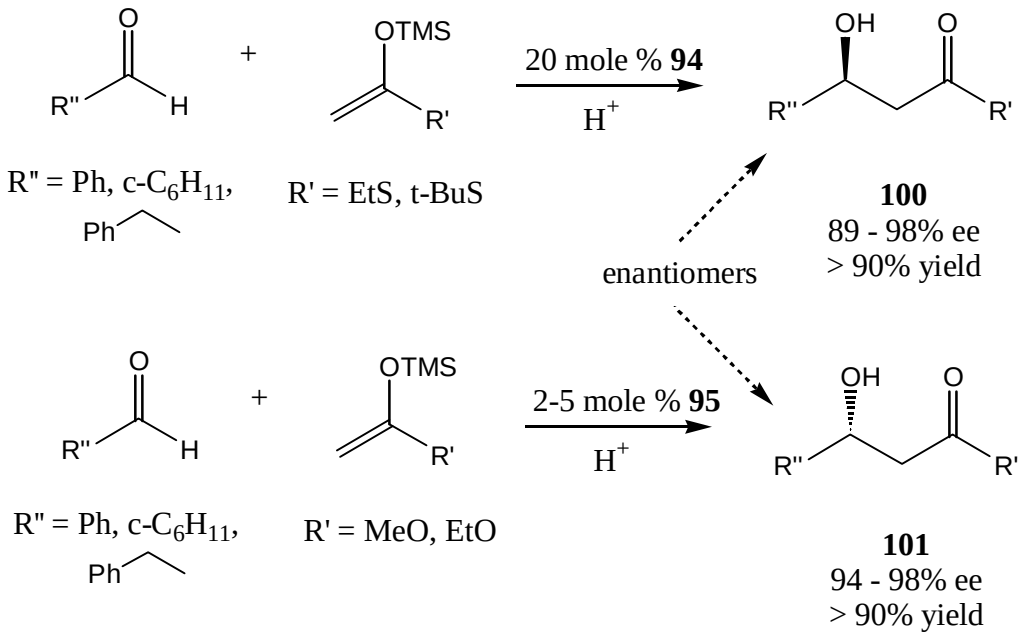


Keck[53] and Carreira[54] developed the (S)-BINOL titanium(IV) catalyst **94** and the (R)-BINOL titanium(IV) catalyst **95** respectively for the Mukaiyama aldol reaction as depicted in Scheme 40. Twenty mole % of catalyst **94** was used in the aldol reaction of thioenolate and aldehyde, but only 2 to 5 mole % catalyst **95** was necessary in the aldol reaction of enolate and aldehyde. The role between the thioalkyl group and the alkoxy group of the enolate reversed the stereochemistry of the hydroxy group in aldol-adducts **100** and **101** were not clear. This stereochemical outcome was more likely controlled from either the (R) or (S) configuration of the bulky BINOL group. The (R) or (S) configuration of the BINOL group had a big impact on the stereochemistry, but the closed transition state

[53] Keck, G. E.; Krishnamurthy, D.; *J. Am. Chem. Soc*. **1995**, 117, 2363-2364.
[54] (a) Carreira, E. M.; Singer, R. A.; Lee, W.; *J. Am. Chem. Soc*. **1994**, 116, 8837-8838. (b) Carreira, E. M.; Lee, W.; Singer, R. A.; *J. Am. Chem. Soc*. **1995**, 117, 3649-3650.

model failed to explain this phenomenon. Some researchers argued that the closed transition state might not be correct, and they thought the open transition state was a better model to explain the stereoselectivity. Whether or not this aldol reaction goes through the similar closed transition state as shown in Scheme 39 is still under strong debate.

Scheme 40



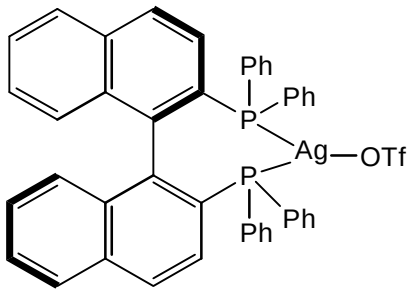
Yamamoto and coworkers have developed the chiral (R)-BINAP-silver(I) catalyst **102** (BINAP = 1,1'-dinaphthalene)-2,2'-diylbis(diphenylphosphine)) for the Mukaiyama aldol reaction (Figure 20).[55] The exact chemical structure of (R)-BINAP-silver(I) catalyst is still under investigation, but the proposed structure **102** is shown in Figure 20. The

[55] Yanagisawa, A.; Matsumoto, Y.; Nakashima, H.; Asakawa, K.; Yamamoto, H.; *J. Am. Chem. Soc*. **1997**, 119, 9319-9320.

silver(I) catalyst proceeds smoothly with the tributyltin enolate instead of the “traditional” silyl enolate (Scheme 41). Yamamoto proposes the hypothetical closed transition state model that may be helpful to explain this phenomenon (Scheme 42).

In Scheme 42, the silver(I) catalyst is not chelated to the aldehyde carbonyl and the enolate anion. This suggests that the tributyltin is chelated to the aldehyde and the enolate anion. If silver(I) chelate to the aldehyde carbonyl and the enolate anion, both tributyltin enolate and silyl enolate should give similar stereoselectivity from the closed transition state. Therefore, this piece of evidence supports that the silver(I) catalyst is not chelating the aldehyde carbonyl and the enolate anion in the closed transition state. Furthermore, the stereoselectivity depends on the geometry of the enolate. The (Z)-enolate gives the syn-aldol adduct **103**, whereas the (E)-enolate gives the anti-aldol adduct **104** (Scheme 41). This is another piece of evidence to support the closed transition state model over the open transition state model.

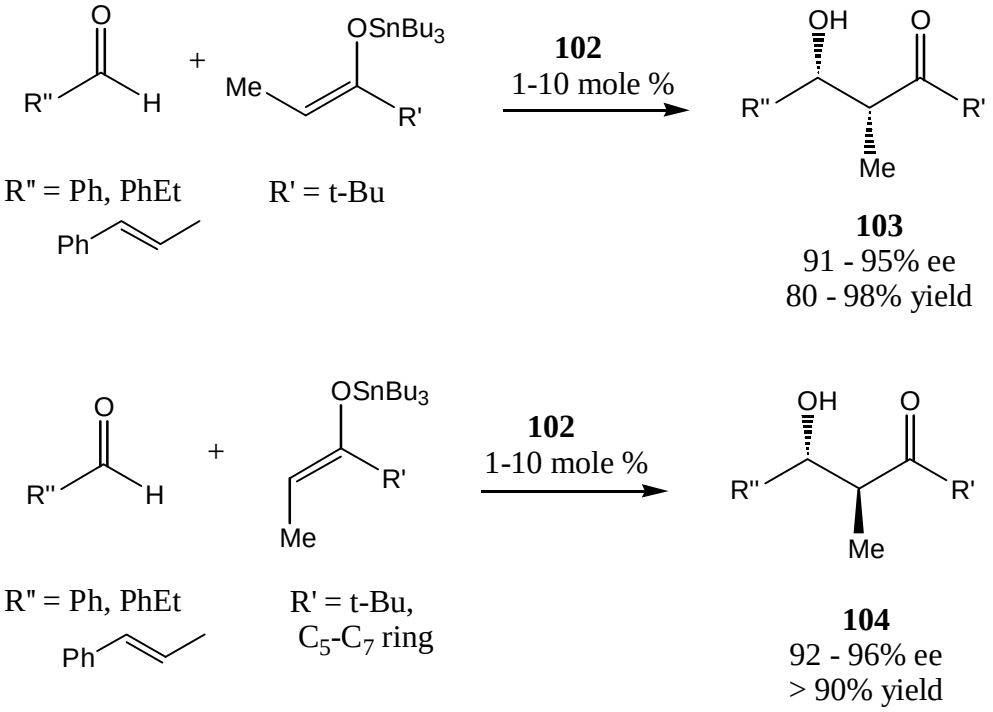
Yamamoto’s research group suggest the silver(I) catalyst may coordinate to the aldehyde carbonyl in the closed transition state to create an asymmetric environment for good stereoselection (Scheme 42). However, the exact role of the silver(I) catalyst in the closed transition state is still unknown.



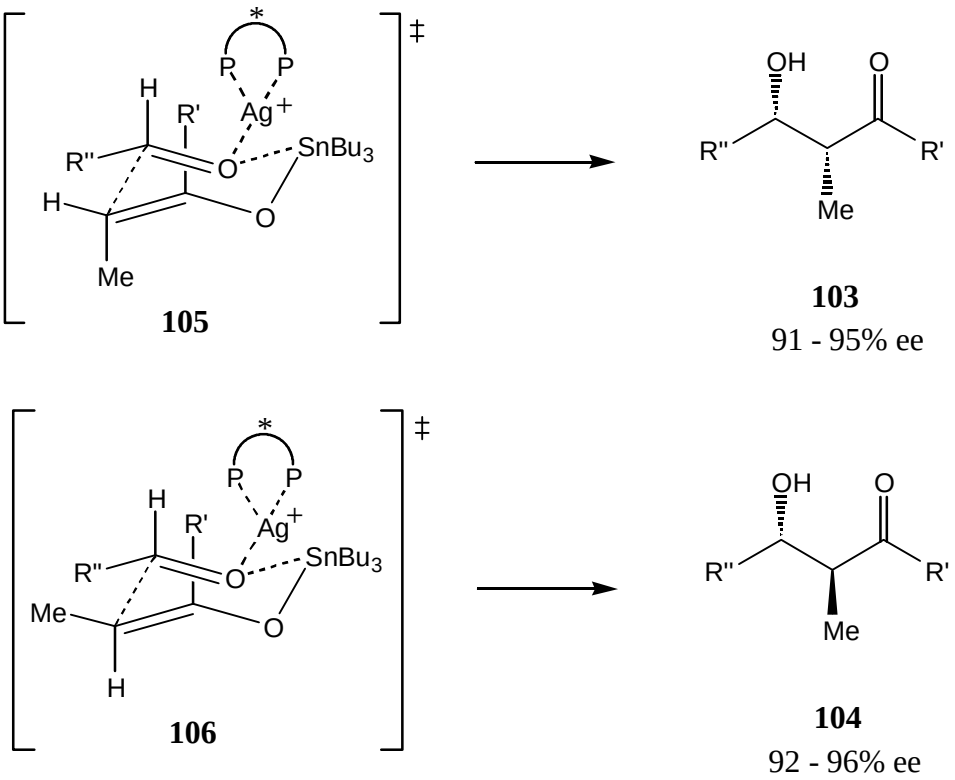
102

Figure 20. Proposed (R)-BINAP Ag(I) Catalyst

Scheme 41

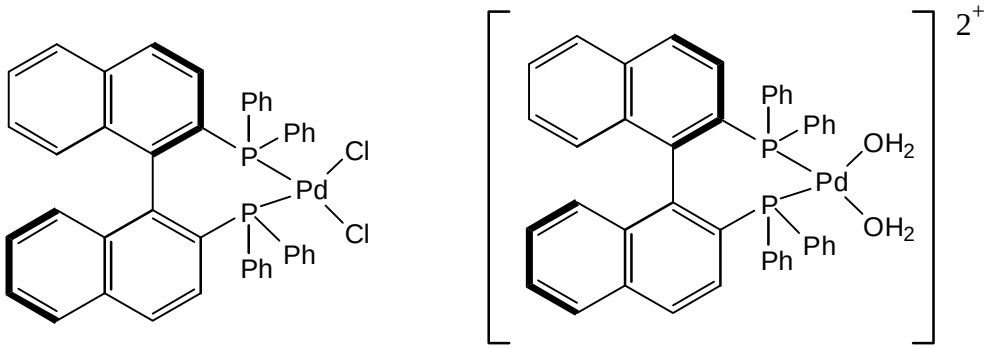


Scheme 42



Shibasaki et al. have developed the (R)-BINAP-palladium(II) catalyst **107** (Figure 21) for the Mukaiyama aldol reaction of silyl enolate and aldehyde (Scheme 43).[56] The palladium catalyst needs to be activated by AgOTf, and researchers are investigating this phenomenon (Scheme 44).[57] Surprisingly, this aldol reaction proceeds in the presence of water. Organic solvents are the most widely used because most of the aldol reactions are very sensitive to water. But in this special case, Shibasaki has decided to modify the (R)-BINAP-palladium(II) catalyst **107** to the (R)-BINAP-palladium(II) catalyst **108** that is more suitable in the aqueous media (Figure 21). Note the two water ligands in the chiral catalyst **108** substitute the two chlorine ligands in the chiral catalyst **107** in Figure 21.

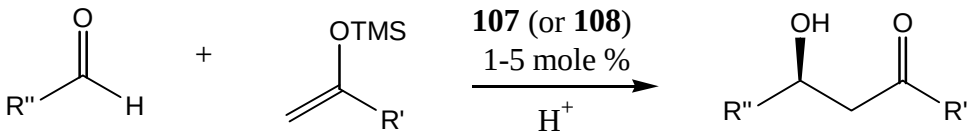
[56] Sodeoka, M.; Tokunoh, R.; Miyazaki, F.; Hagiwara, E.; Shibasaki, M.; *Synlett*, **1997**, 463-466.
[57] Sodeoka, M.; Ohrai, K.; Shibasaki, M.; *J. Org. Chem.* **1995**, 60, 2648-2649.



107 **108**

Figure 21. (R)-BINAP Pd(II) Catalyst

Scheme 43



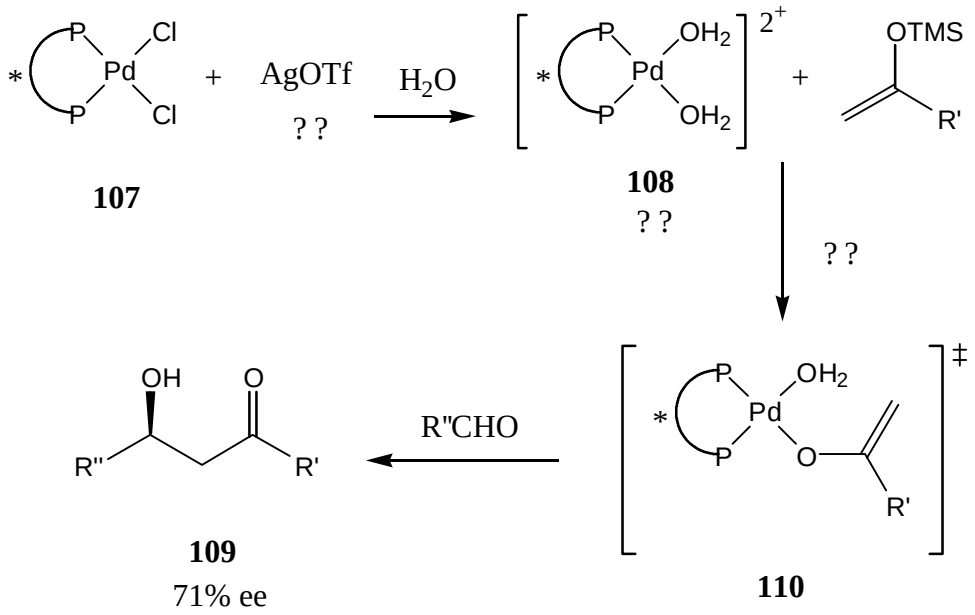
R'' = Ph R' = Ph

109
71% ee
21% yield

According to Shibasaki, the acyclic open transition state model dominates in this aldol reaction. However, the open transition state model in this aldol reaction is different than the other acyclic open transition state models that we have studied previously. With careful NMR studies, he points out that the chiral catalyst **107** (or **108**) is coordinated to the enolate instead of the aldehyde as depicted in **110** in Scheme 44. Which face of the enolate attacks the aldehyde is unknown. Furthermore, other researchers do not agree with Shibasaki's transition state model because his proposed mechanism in Scheme 44 raises a lot of questions that cannot be answered. For example, we are not sure whether the chiral

catalyst **108** is actually formed from the chiral catalyst **107** in the aqueous media. Also, the role of the AgOTf that is used to activate the catalyst is not clear either.

Scheme 44



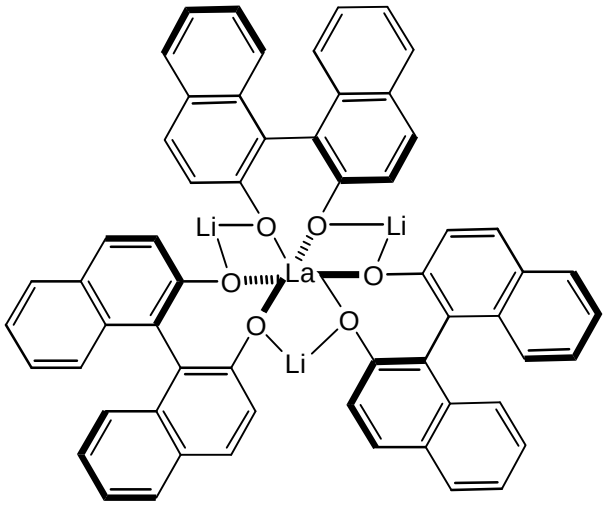
Shibasaki has developed a new sterically demanding lanthanum $LaLi_3$tris[(R)-binaphthoxide] catalyst **111**, also known as the (R)-LLB catalyst (Figure 22), for the aldol reaction of unmodified ketone and aldehyde (Scheme 45).[58] The advantage of using the unmodified ketone is that we do not have to generate the enolate first in the aldol reaction. Hence, we do not have to control the E or Z enolate geometry before we start the reaction.

There are some theories to explain the catalyzed aldol reaction. Unmodified ketones can be used because the Li-O unit of the catalyst **111** acts as a Brϕnsted base to

[58] Yamada, Y. M. A.; Yoshikawa, N.; Sasai, H.; Shibasaki, M.; *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 1871-1873.

abstract the α-proton of the unmodified ketone to form the enolate. At the same moment, the lanthanum Lewis acid is coordinated to the aldehyde just after the enolate is formed. Therefore, the stereodifferentiating environment is created to achieve high stereoselectivity. However, the detailed mechanism and the exact transition state are still not known, and both are under intense investigation.

Currently, Shibasaki is developing a barium catalyst **113** (abbreviated as (R)-BaB-M) that is similar to a lanthanum catalyst **111** for the same aldol reaction of unmodified ketone and aldehyde (Scheme 45).[59] The exact structure of the barium catalyst is uncertain, but it was determined that **113** is the most likely structure from mass spectrometry (Figure 23). The barium catalyst **113** is prepared in a straightforward manner from four equivalents of (R)-BINOL-Me **112** and one equivalent of $Ba(O\text{-}i\text{-}Pr)_2$ in DME as outlined in Scheme 46.

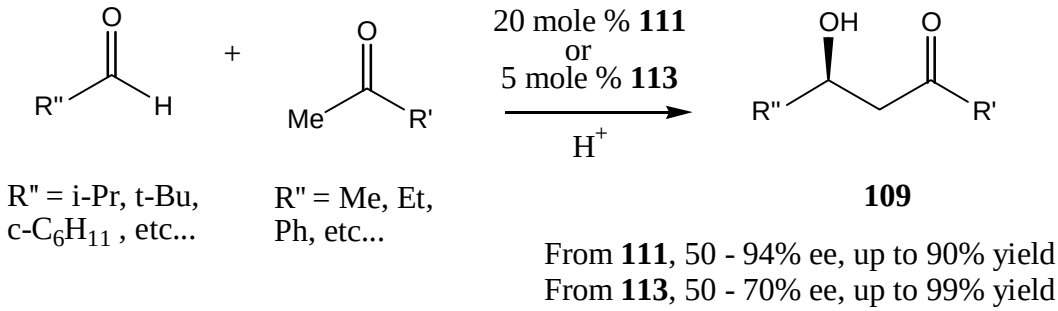


111

Figure 22. Lanthanum $LaLi_3$tris[(R)-binaphthoxide] catalyst.

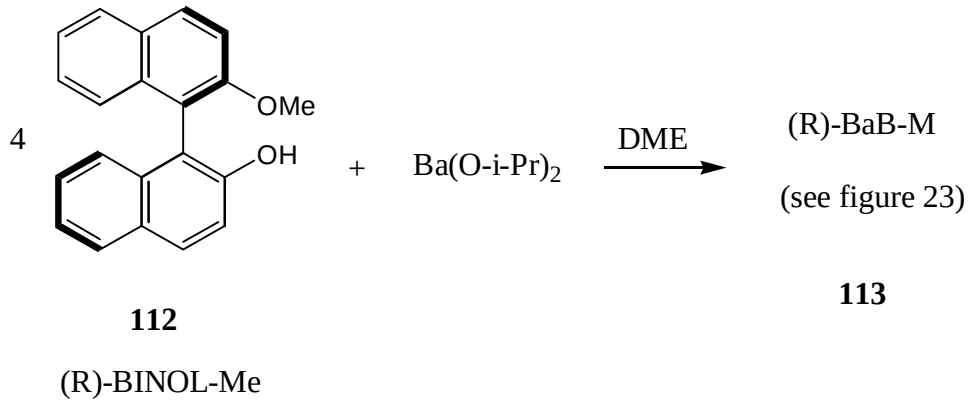
[59] Yamada, Y. M. A.; Shibasaki, M.; *Tetrahedron Letters*, **1998**, 39, 5561-5564.

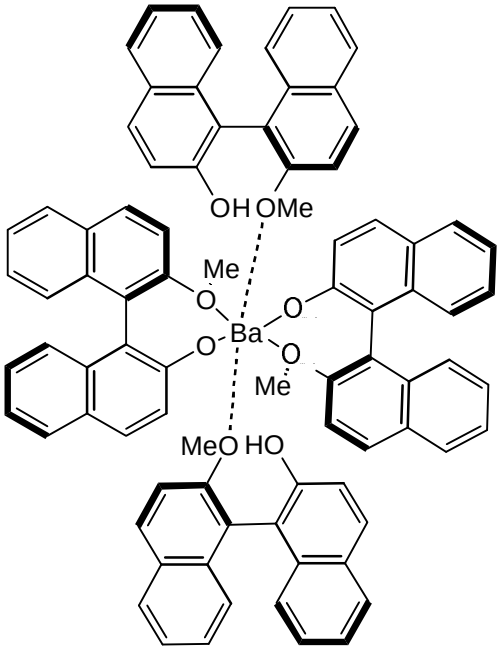
Scheme 45



Shibasaki proposes similar theories to explain the barium-catalyzed aldol reaction. The methoxy group (or maybe the hydroxy group) in the catalyst **113** acts as a Brϕnsted base to abstract the α-proton of the unmodified ketone to form the enolate. Once the enolate is formed, the aldehyde that is coordinated to the barium Lewis acid attacks the enolate in a stereodifferentiating environment. However, we still need to confirm these hypotheses by first determining the exact transition state model.

Scheme 46





113

Figure 23. Proposed barium (R)-BaB-M catalyst.

Up to this point, we have discussed metals that have been used to design catalysts in the aldol reaction. Most of the catalysts give moderate to good stereoselectivity, and there is room for improvement. To further increase the stereoselectivity, researchers are continuing to refine the existing catalysts or to develop the new catalysts. Currently, Kobayashi is developing a simple scandium tritriflate ($Sc(OTf)_3$) catalyst for the aldol reaction of enolate and aldehyde.[60] Other metals have also been used, such as aluminum

[60] Kobayahi, S.; *Eur. J. Org. Chem.* **1999**, 15-17.

(Al)[61], rhodium (Rh)[62], zirconium (Zr)[63] and many more. Unfortunately, all these catalysts currently give poor stereoselectivity. Nevertheless, there is a great possibility that these catalysts can be modified to achieve good stereoselectivity in the aldol reaction.

Chiral catalysis is the most challenging method, and the most useful and efficient method in the aldol reaction. Unfortunately, chiral catalysis is still in its infancy. As presented in this chapter, the exact catalyst structures, mechanisms, and transition state models are not well understood and explanations are tentative. Most of the mechanisms and transition state models are hypothetical, and further characterization is necessary. Therefore, it is projected that chiral catalysis will continue to develop further beyond the year 2000. Perhaps chiral catalysis is going to be another important methodology for synthetic organic chemistry, medicinal chemistry, and natural product chemistry in the twenty-first century.

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[61] Reetz, M. T.; Voungoukas, A. E.; *Tetrahedron Lett*. **1987**, 28, 793.
[62] Reetz, M. T.; Kyung, S.-H.; Bolm, C.; Zierke, T.; *Chem. Ind*. **1986**, 824.
[63] Lin, S.; Bondar, G. V.; Levy, C. J.; Collins, S.; *J. Org. Chem*. **1998**, 63, 1885-1890.

Chapter Five. Conclusion

Controlling the stereochemistry of the aldol adduct is the most challenging aspect in asymmetric aldol reaction. The aldol reaction of an E or Z enolate and an aldehyde can create two new stereocenters in the aldol adduct, and this reaction can be utilized for each synthetic step. However, controlling the stereochemistry of the aldol adduct becomes more difficult as one approaches the target polyketide.

We have presented numerous different methodologies that attempt to synthesize the polyketide synthon. In Chapter Two, we confirmed that the enolate geometry has a great impact on the stereoselectivity in the aldol reaction. The (Z)-enolate gives the syn-aldol adduct, whereas the (E)-enolate gives the anti-aldol adduct, both through the "Zimmerman-Traxler" closed transition state. Besides, we discussed how the chiral aldehyde (or ketone) geometry controls the stereoselectivity. The key is to minimize the syn pentane interaction between the enolate and the aldehyde in the closed transition state, and the lowest energy (more stable) transition state gives the desired product. With careful control on the enolate geometry and the aldehyde geometry, both simple methodologies can maximize the stereoselectivity in the aldol reaction.

Just controlling the enolate geometry and the aldehyde geometry are not enough. Therefore, other methodologies should be used in addition to controlling the enolate geometry and the aldehyde geometry. In Chapter Three, we showed the great impact of the chiral auxiliary and the chiral ligands on the stereoselectivity in the aldol reaction. The relative facial position of approach to the enolate by the aldehyde determines which stereoisomer is formed. In other words, the chiral auxiliary blocks one face of the enolate, so that the aldehyde must approach the enolate on the other face. As a result, only one

stereoisomeric aldol adduct is formed. The chiral ligands also work in a similar fashion to the chiral auxiliary. These two methodologies perform well in the aldol reaction, but they have some drawbacks. First, both methods require a stoichiometric amount of chiral auxiliary and chiral ligands in the reaction. Second, removing the chiral auxiliary of the enolate after the aldol reaction takes away the efficiency for further synthesis.

Chiral catalysis is the best solution to overcome the difficulties mentioned above. Chiral catalysis has been actively developed within this decade because a small amount of catalyst can generate a large number of chiral molecules. This methodology reduces the number of synthetic steps dramatically, and therefore it is cost efficient. Unfortunately, chiral catalysis is still in its infancy. There are only a few catalysts that perform well in the aldol reaction. Furthermore, these catalysts are very specific to a certain kind of substrate. Because of this, chiral catalysis is less practical in the laboratory. However, if a catalyst is discovered that can function with a variety of substrates successfully, then the final impact is enormous. Therefore, chiral catalysis is still under intense development and refinement all over the world.

All of the methodologies that presented in this report have their advantages and their disadvantages. One should try to apply these methodologies wisely when planning a synthetic route to a target molecule.

Vita

Samuel Lou was born in Macau on December 24, 1973. He received his Bachelor of Science in Chemistry from University of California-Irvine in June 1997. In December 1998, he joined Dr. Michael Calter research's group at Virginia Polytechnic Institute and State University. There he received his Master of Science in Chemistry in May 2000.