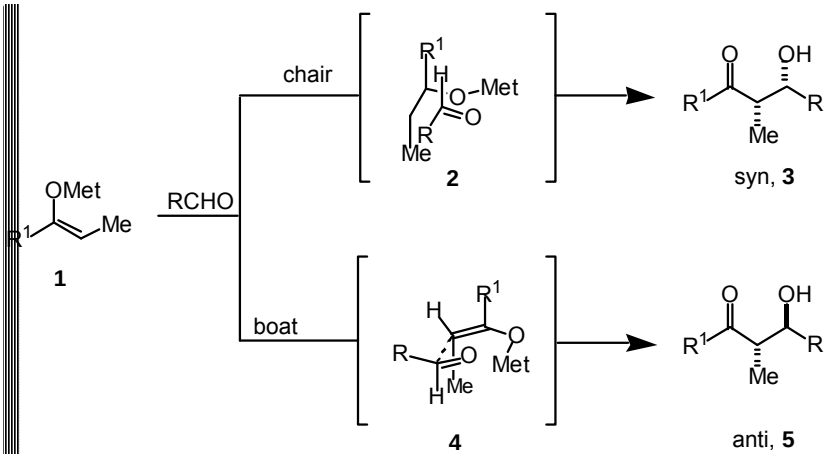
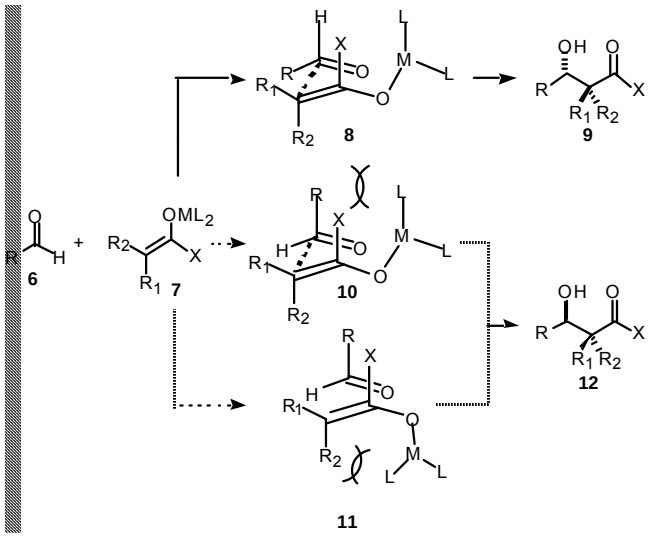
Chapter X: Mukaiyama Aldol

X.1 Introduction

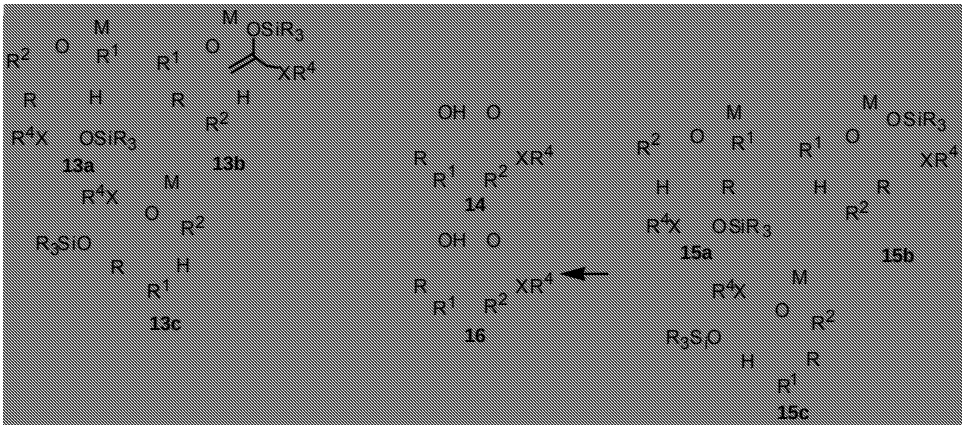
The asymmetric aldol reaction is perhaps one of the most formidable tools available for natural product synthesis. One of the reasons this reaction has documented wide applicability is that it achieves a fundamental transformation common to biological systems. Therefore, many natural products assembled by this reaction in vivo are readily prepared in the laboratory by asymmetric aldol methodology. In the transformation, one new carbon-carbon bond is created and up to two new stereocenters. Several excellent reviews exist on the aldol reaction.[1] Our discussion will be divided three reaction types: auxiliary, chiral reagent and catalytic methods. Due to the pioneering efforts of Carreira, Evans, Paterson, Heathcock, Masamune all three reaction types are highly advanced and provide product in excellent yields and with optical purities generally in excess of 90 % ee. Another classifying division for the aldol reaction is the relative stereochemistry of the condensation products. That is, either syn (**3**) or anti (**4**) diastereomers may be obtained, and the syn diastereomer often predominates.



The reason for the syn preference lies in the lower transition state energy of the chair versus the boat transition state conformation. Furthermore, the resulting stereochemistry can be explained by examination of the best chair or Zimmerman-Traxler transition state model. This model places the bulker groups in equatorial position as in structure **8** that avoids unfavorable eclipsing interactions.

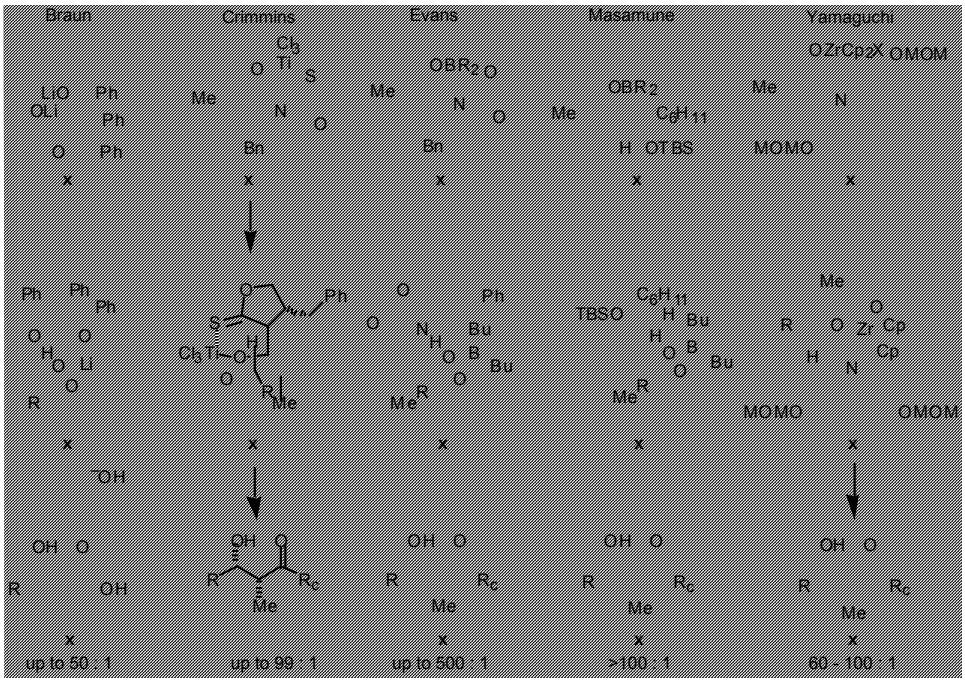


Methods that provide predominately anti-aldol addition products generally are obtained under conditions where a chair conformation is excluded for steric reasons or a counterion (ML_2) is employed that has a filled orbital valences and chelation is not posssible. In these cases an open transition state is presumed operative and the preference for the anti product is determined by minization of steric interactions, through an anti-periplanar approach X or X in the operative transition state.[2] These transition state models also show why Z-enolates favor syn products. However, the complexity involved in unraveling the stereoelctronic preferences of synclinal or anticlinal arrangements is not easily addressed simply by a steric analysis.[3] Furthermore, the number of successful promotors for this reaction hint at the difficulties in defining the reaction by a single mechanistic manifold. Keck aldol reference

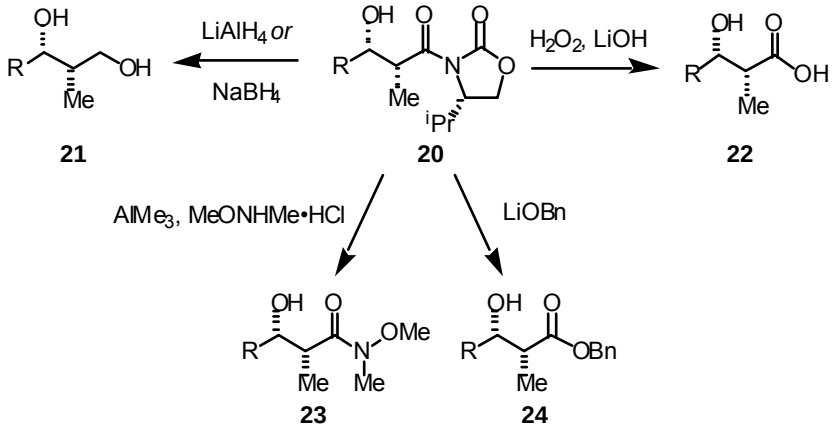


Syn Aldols.

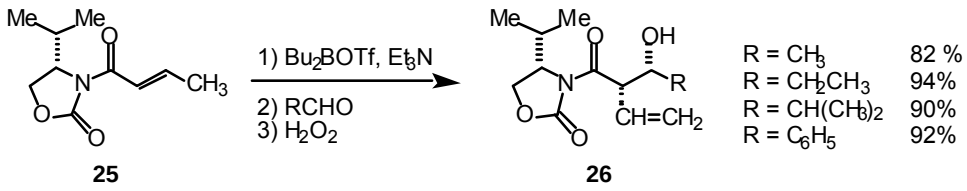
Several excellent chiral auxilaries have been developed that provide aldolates in high optical purity. The optical purity may be further enhanced by separation of diastereomers before removing the auxiliary. Five of these auxiliary based methods are shown below. The pioneering efforts in this area by Evans,[4] Masamune[5] and Yamaguchi[6] are exemplary methods based on their wide acceptance and utilization among synthetic chemists.



As discussed in Chaper X on enolate alkylations, the amino acid derived oxazolidinione auxiaries of Evans are readily available in either optical antipode. The imide can also be cleaved under a variety of conditions to afford alcohols, esters, thioesters or carboxyllic acids. These two properties, coupled with the typically high stereoselectivity observed with this auxiliary, engender desirable characteristics to the reaction that have contributed to its popularity.

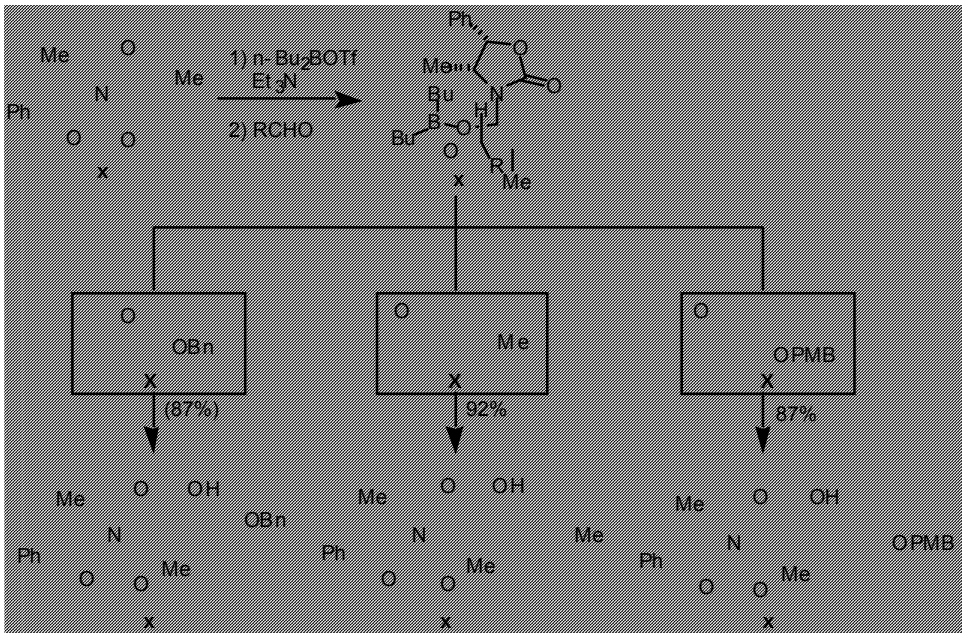


Another feature of the imide auxiliaries is that α,β-unsaturated imides work well, affording aldol adducts **26** as single diastereomers in usually better than 90% yield.[7] The products do not readily undergo tautomerization to the conjugated system.

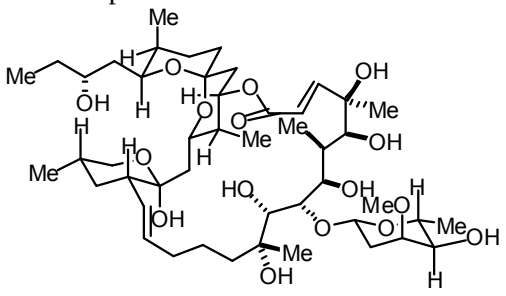


25 **26**

At its current state of development the Evans auxiliary is less successful with the direct aldolization of acetanoates (but methods have been devised that circumvent this limitation); however, the methodology excels for aldol reactions of propionate imides. Many important natural products display a propionate aldol retron, thus making them accessible by this methodology. Representative examples with the Evans auxiliary show its generality with aromatic, aliphatic, branched aliphatic, hetero-substituted and unsaturated aldehydes.



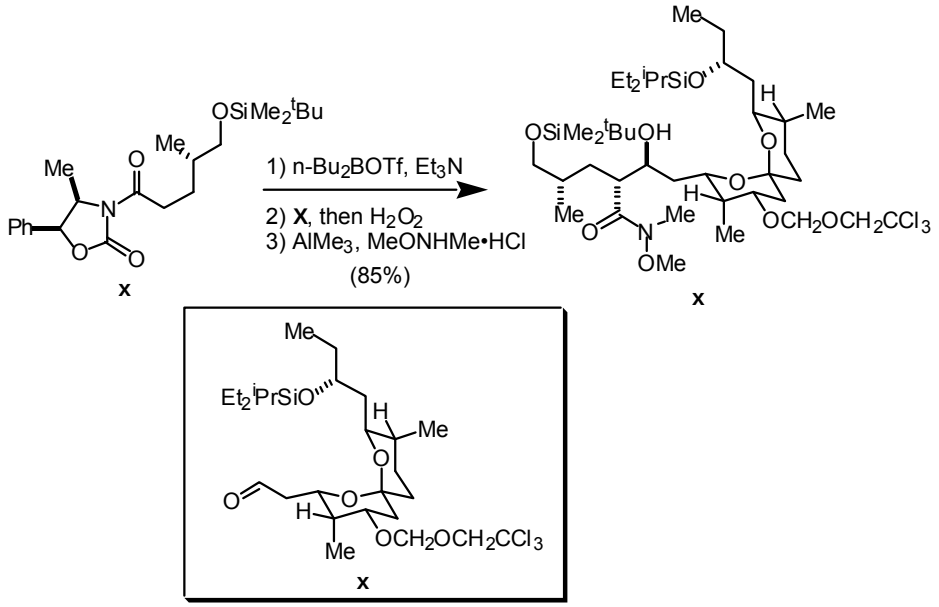
An inspiring synthetic accomplishment that highlights this methodolgy includes the synthesis of (–)-cytovaricin (**x**) by Evans.[8] In Evans' synthesis of this poly-propionate natural product five aldols set 9 of the chiral centers.



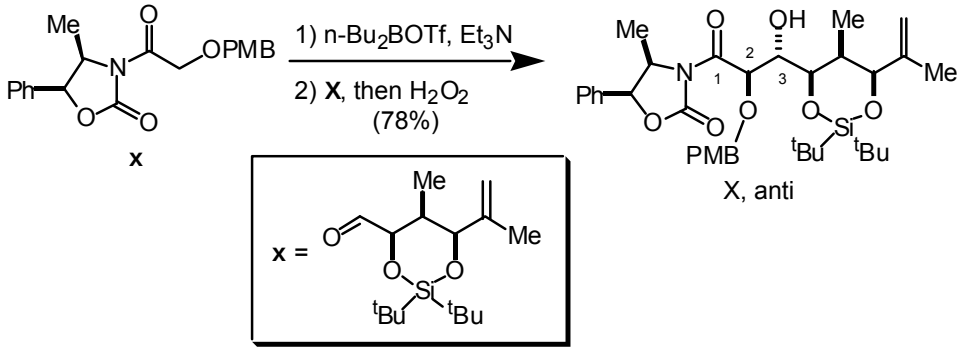
x, (–)-cytovaricin

The three aldol examples listed above were employed in this synthetic endeavor and the remaining aldols involved more complicated aldehydes as show

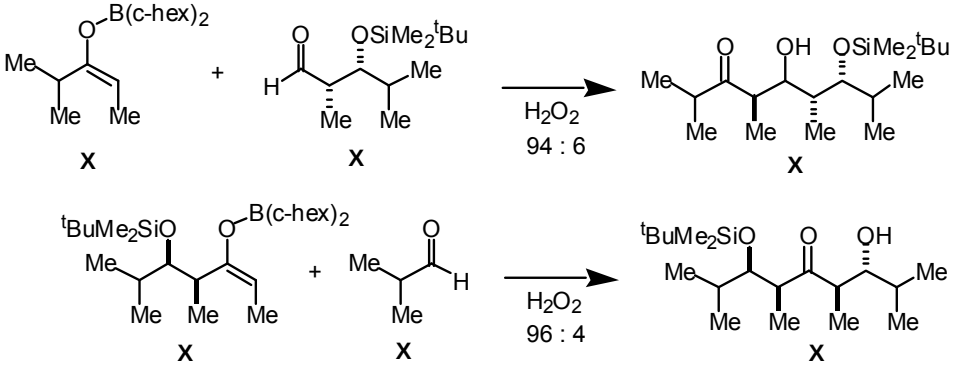
below. The condensation of **XX** with the spiroacetal **XX** afforded the desired aldolate in 85% overall yield.



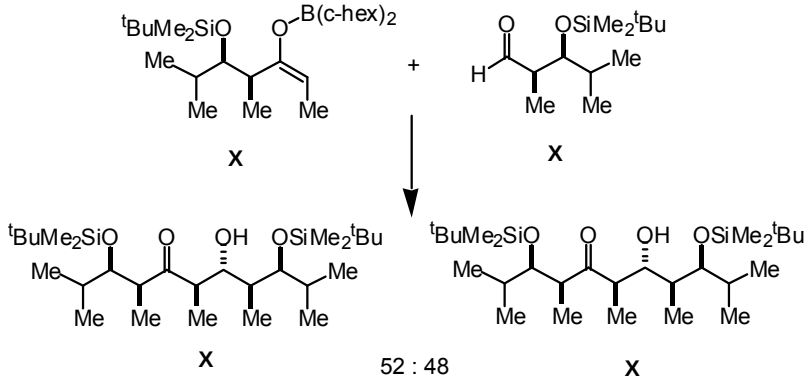
The final of the five asymmetric aldol coupling reactions displaying an unanticipated stereochemical result. Upon condensation with α-chiral aldehyde X the anti aldolate (anti between C2 and C3) was obtained in 78% yield. This example illustrates how the inherent facial selectivity of the aldehyde was able to overwhelm the normal sterochemical course of the reaction. Note that the stereochemistry at C2 is consistent with the normal stereochemistry obtained in these additions. However, the stereochemistry at C3 appears to have been dictated by the stereofacial bias of the aldehyde q



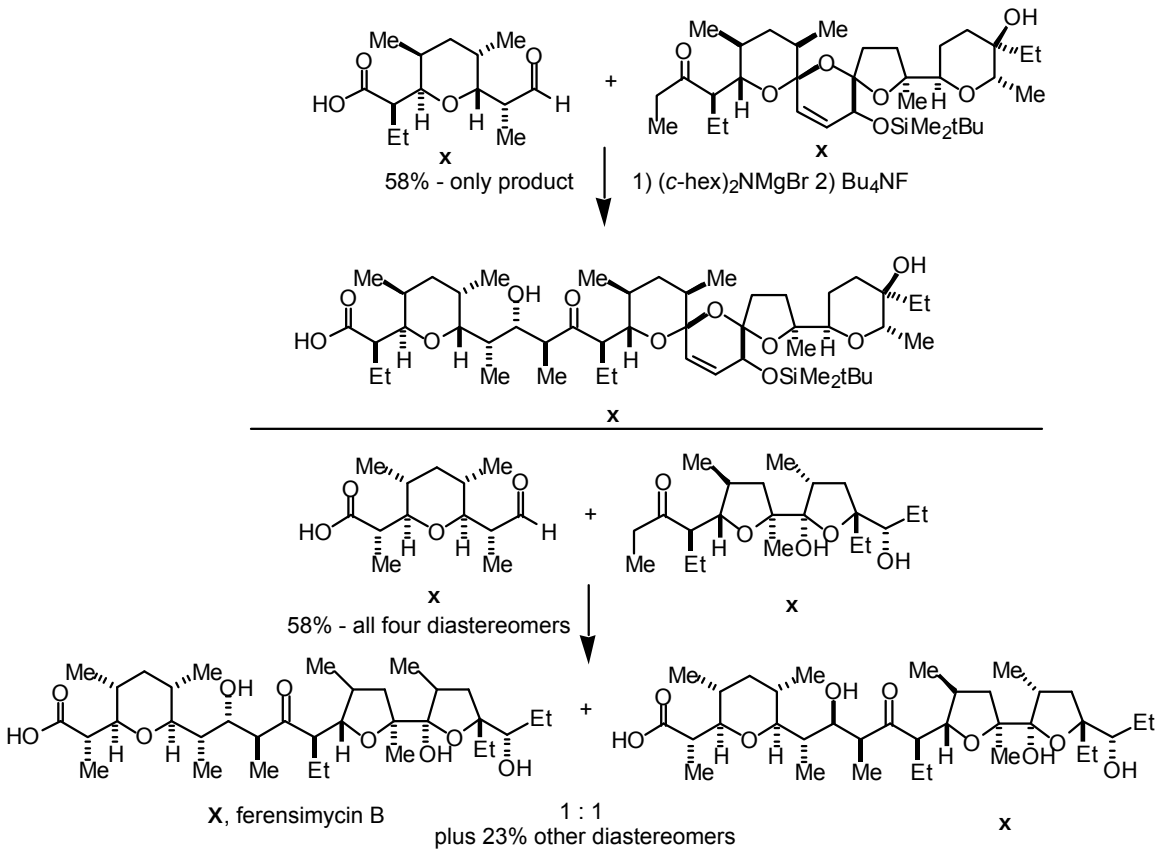
The divergent result obtained in the aldol reaction of **X** and **x** hints at the complexity of the reaction when both coupling fragments are chiral. In addition to auxiliary based asymmetric induction, the presence of a chiral center adjacent to either the enolate **x** or the aldehyde **x** can exert a powerful influence on the resultant stereochemistry. In both instances products are obtained with >94 : 6 selectivity.



It is also possible that the existing stereocenters each tend to prefer conformations leading to opposite product stereochemistry. When such a situation exists and there is a stereochemical mismatch very poor selectivity is observed.

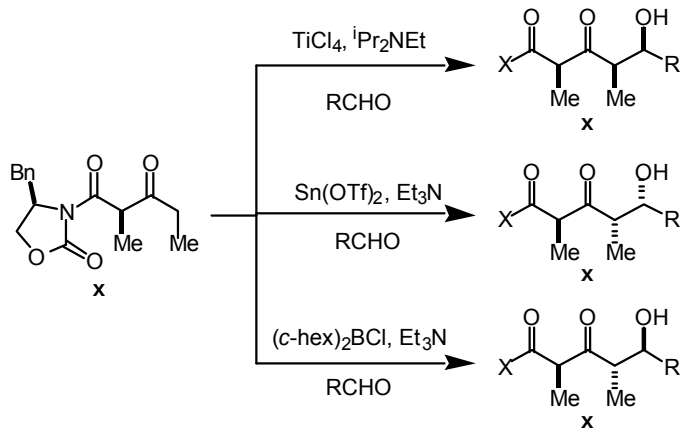


Wen both the enolate and aldehyde have α-substitution the situation is further complicated. Of the four possible products from the condensation of x and x, any one of these can predominate depending on subtle interactions from more remote sites in the molecule.

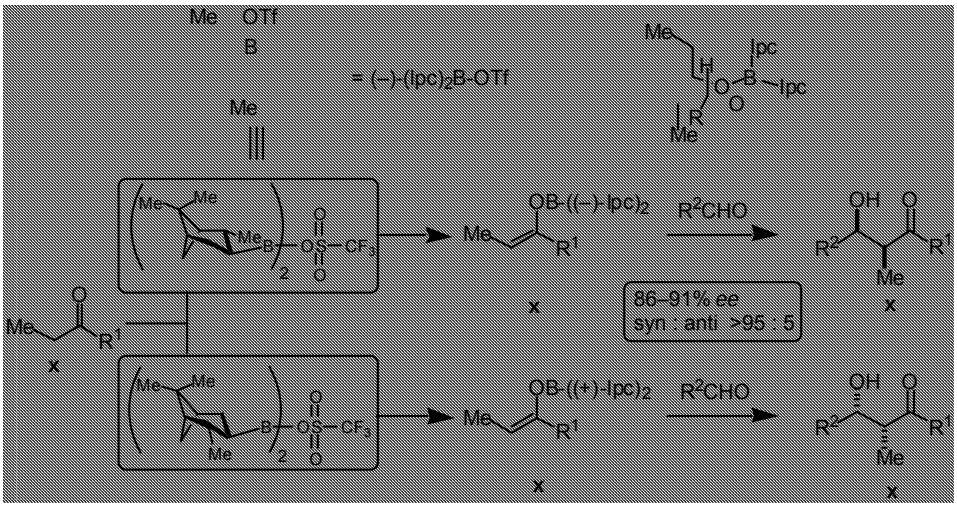


In the following two examples from Kishi's synthesis of XXX[9] and Evans' synthesis of ferensimycin B (X)[10] both coupling fragments have the identical substitution alpha to the aldehyde and enolate as shown for partial strucures **X** and **X**. The other general similarity of the reacting parners is also obvioius. In the condensation event, **X** and **X** provided 58% of **X** without any apparent formation of the other possible diastereomers. This is in contrast to the reaction of **X** and **X** where a nearly statistical mixture of the natural product **X** and its C8 ipimer. The subtle interplay of steric and electronic effects makes it difficult to synthesize a generalized model given the current available mechanistic data on the aldol reaction. However, for less complicated systems the general carbonyl addition guidelines of Cram, Felkin, Anh and others provide a vehicle for a rationalization of these effects, as discussed in Chapter xxx of this book.

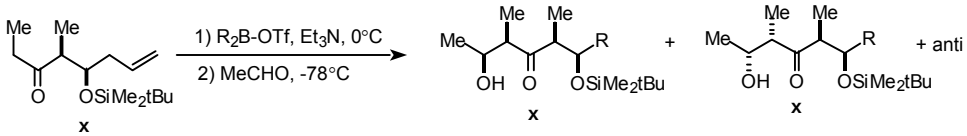
The product distribution in aldol reactions of chiral ethyl ketons can be funneled into a single diasteriomeric path by changing the metal and enolate geometries, as shown for ethyl ketone X. Another curious feature of these reactions is that enolization does not occur at between the b-dicarbonyl.



Chiral Borane Enoaltes.
Two chiral boranes have shown great efficiency in inducing asymmetry in aldol reactions of ketone and thioester enolates. The diisopinyl borotriflate (X) aldols developed by Paterson provide adducts with in up to 90% ee.[11,12]

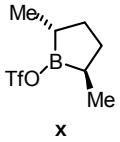


Perhaps one of the most powerful aspects of the diisopinyl borane enolate chemistry is in the area of double asymmetric synthesis.[13] That is, when the enolate is generated from a chiral ketone, the chiral ligands on boron can relate synergystically with the substrate to give enhanced selectivity. For example, with an achiral ligand the boron enolate of ketone X reacts with acetaldehyde to have two diastereotopic syn aldolates. With the (+)-antipode of diisopinyl borane a stereochemically "matched" situation exists and the selectivity increases to 98 : 2. With the enantiomeric borane, a "mismatched" scenario exists and the selectivity decreases to 75 : 25. Note that in the mismatched case the chiral borane causes a drop in selectivity, but does not override the inherent stereochemical bias of the substrate.

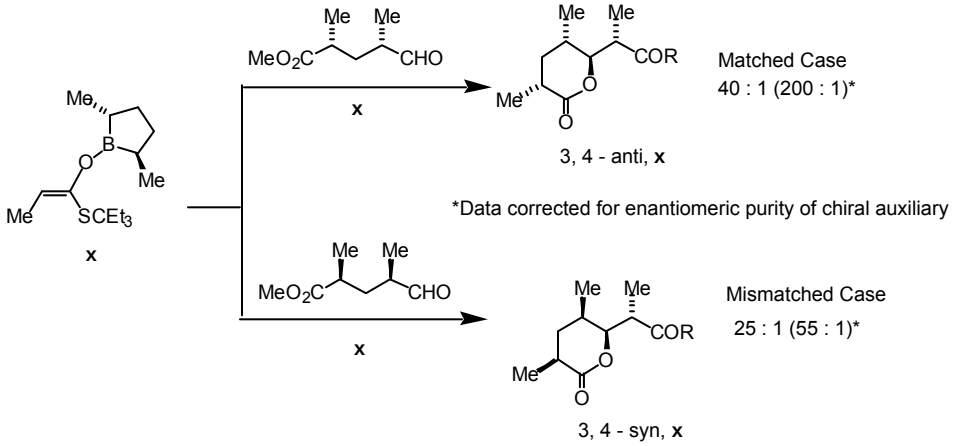


R_2B-OTf	enol geometry, Z : E	syn : anti	diastereoselectivity
9-BBN-OTf	91 : 1	90 : 10	92 : 8
(+)-$(IpC)_2$BOTf	97 : 3	96 : 4	98 : 2 "matched case"
(–)-$(IpC)_2$BOTf	97 : 1	96 : 4	75 : 25 "mismatched case"

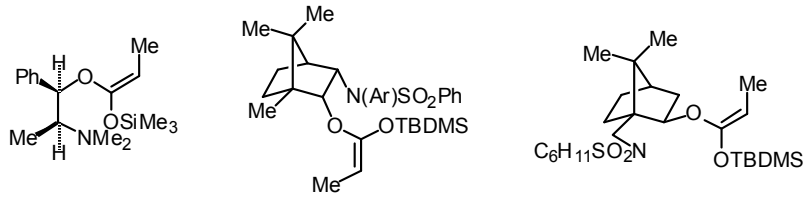
The chiral borolane **x** of Masamune excels in the arena of double asymmetric synthesis. This remarkable reagent is able to overwhelm the inherent facial selectivity of a substrate due to chiral centers alpha to the aldehyde carbonyl. For example, in the reaction of boron enolate X of a thioester, the sence of asymetric induction is conserved despite the stereochemistry in the aldehyde. In the "matched" case extremely high induction of over 200 : 1 is observed. In the "mismatched" case a quite respectable ratio of 55 : 1 is obtained.



x



Anti Aldols. Controlling the diastereoselectivity in aldol reactions to obtain enantiomerically pure anti-aldol products developed after the great strides in the development of syn-aldol chemistry. The most reliable methods to date are derived from the pioneering efforts of Gennari,[14] Heathcock,[15] Helmchen,[16] Oppolozer,[17] and Masamune.[18] All of these methods, except that of Heathcock, involve silyl enolates. These silyl enolates to not react through a chair or Zimmerman-Traxler transition state, but instead react via an open transition state. These reactions typically employ a hard Lewis acid such as $TiCl_4$ or Me_2AlCl premixed with the aldehyde to activate it towards nucleophilic attack.



Gennari Helmchen Oppolzer

The prize for the state of the art auxiliary for executing anti-aldols now goes to Masamune.[18] The remarkable features of his auxiliary based method is that exceedingly high diastereoselectivities (better than >94 % de in nearly every case) and it is tolerant of aliphatic, aromatic and a,b-unsaturated aldehydes. Table 2 shows the generality of the process.

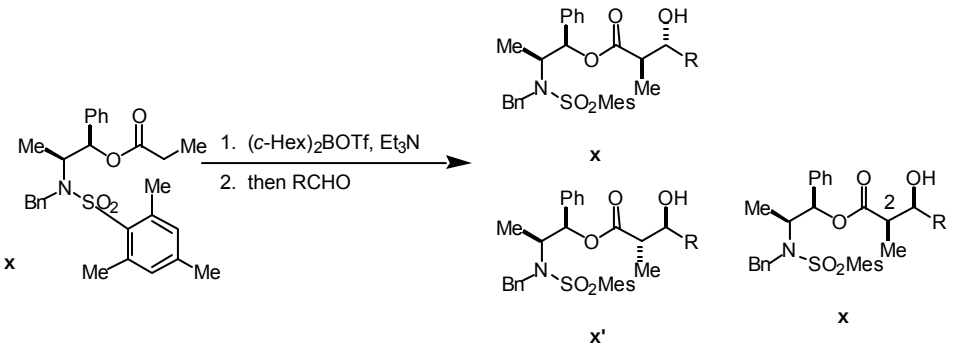
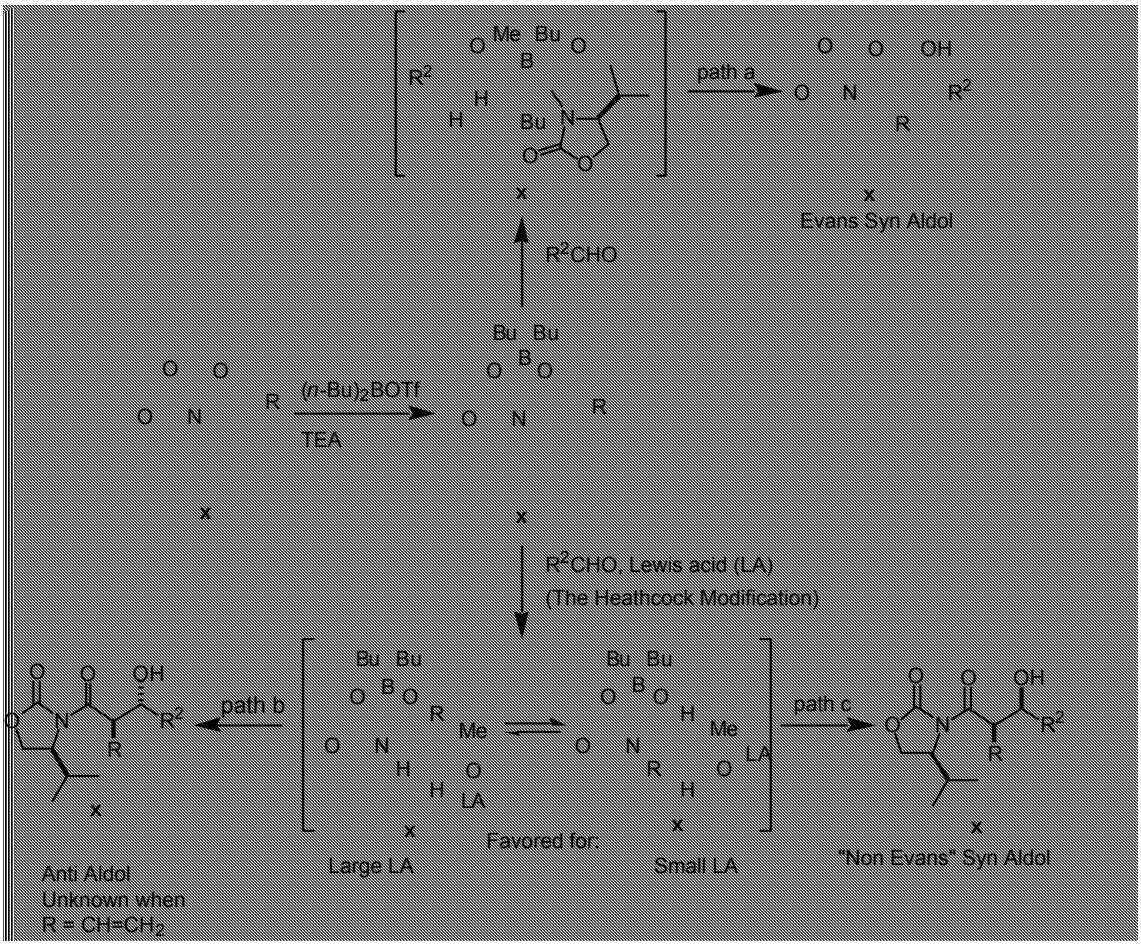


Table 2. Aldol Reaction of Ester X with Representative Aldehydes.

entry	RCHO	product	yield (%)	ds for anti (**x : x**[1])
1	EtCHO	**4a**	90	96.1:3.9
2	PrCHO	**4b**	95	95.2:4.8
3	i-PrCHO	**4c**	98	97.7:2.3
4	c-HexCHO	**4d**	91	95.2:4.8
5	t-BuCHO	**4e**	96	99.4:0.6
6	PhCHO	**4f**	93	94.7:5.3
7	(E)-MeCH=CHCHO	**4g**	96	98.0:2.0
8	CH_2=C(Me)CHO	**4h**	97	95.8:4.2
9	$BnOCH_2CH_2CHO$	**4i**	94	94.8:5.2
10	$BnOCH_2C(Me)_2CHO$	**4j**	98	95.7:4.3
11	i-PrCHO	ent-**4c**	91	97.7:2.3
12	PhCHO	ent-**4f**	95	94.6:5.4

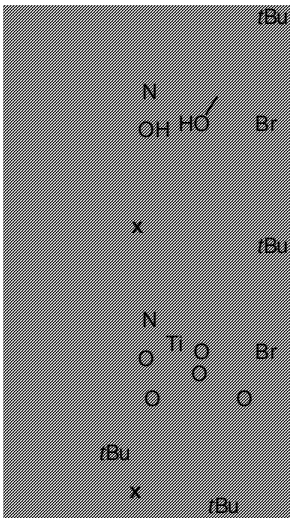
A widely effective alternative to the silyl enolate described above involves an insightful modification developed by Heathcock of the Evans' oxazolidinone auxilaries described above. The scope of the Evans' methodology was greatly extended by Heathcock to permit the fabrication of anti-aldols and "non-Evans" syn aldols *from the same starting oxazolidinones*.[19,20] Heathcock showed that when the Evans' boronate enol ethers were treated with aldehydes precomplexed with Lewis acids, the stereochemistry was altered to provide anti-aldols and "non-Evans" syn aldols with excellent diastereoselectivity and yield. The use of large Lewis acids, such as diethyl aluminum chloride, maximizes the formation of the anti-aldol product by favoring an open transition state. The formation of "non-Evans" syn aldols with thioimides has also been described by Crimmins with the use of titanium enolates of thioimides.[21]



Catalytic Aldol Reactions.

Lewis Acid Catalysis. One of the most successful areas of asymmetric catalysis is unquestionably in the area of aldol chemistry. Since Muayiami's disclosure that Lewis acids catalyze the condensation between silyl enol ethers or silyl-ketene acetals with aldehydes, a reaction with minimal rate under neutral conditions, numerous strategies have been employed to effect asymmetry throught the use of chiral Lewis acids. Additionally, fluoride[22] and phosphoramide[23] Lewis bases have been shown to effectively catalyze the process.

General mechanistic concepts for the catalyzed aldol reaction are similar to their stoichiometric relatives. However, a primary concern in the catalytic variation is control of silyl transfer. That is, the Lewis acid (MX_n, **X**) activates the aldehyde toward nucleophilic addition by the enol silane resulting in new carbon-carbon bond formation and generation of a new stereocenter in the aldolate X. The isolation of products X from the reaction mixture requires a silyl transfer step, presumably through an intermediates X-X. It is this latter parameter that has received the most attention in asymmetric Lewis acid catalyzed Mukayiama aldol reactions.[24,25] Importantly, effective control of the reaction suggests that an intramolecular silyl transfer is required, as the silyl cation is a efficient catalyst for the reaction. If the silyl cation escapes from the chiral environment of the Lewis acid complex, then the resulting silyl cation catalyzed will result in racemic products.



In consideration of these mechanistic discussions, a catalyst reported by Carreira was designed to address the issue of controlling silyl cation transfer. Specifically, the tridentate ligand X when complexed as the titanium complex X, functions exceedingly well in the asymmetric Mukaiyama aldol reaction providing aldolates from a variety of nucleophiles and aldehydes with as little as 0.2 mol % catalyst. On of the key components in this catalyst design is the bound salicylate ligand, that is thought to serve in the dual capacity of both a silyl cation trap and a silylating agent.

For the addition of simple methyl acetate-derived enol silane, the catalyst X performs admirably, giving products in up to 99 % *ee*.[26] A survey indicating the substrate scope with this catalyst is shown in table 3.

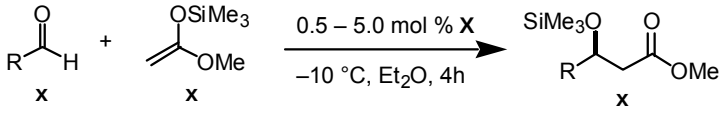


Table 3. Acetate Aldols with Carreira's Catalyst X.

entry	Aldehyde	yield	% ee
1	$Ph(CH_2)_3$—≡—CHO	84%	96%
2	Me, CHO	82%	98%
3	Ph, CHO	98%	94%
4	PhCHO	84%	96%
5	$^tBuPh_2SiO$, CHO	89%	91%
6	Ph, CHO, Me	92%	95%

Few other catalysts work as well as Carreira's catalyst for the addition of silyl ketene acetal **X**. However, a variety of catalysts systems perform well with thioacetate-derived silyl ketene acetals. In this regard, Mikami has developed a BINOL•$TiCl_2$ complex **X** that effectively catalyzes the addition of tert-butyl thioacetate-derived silyl ketene acetal X to aliphatic, a,b-unsaturated and a-hetero aldehydes in up to 96% *ee*.[27] A consideration of with this process is that either enatiomer of the BINOL ligand is commercially available.

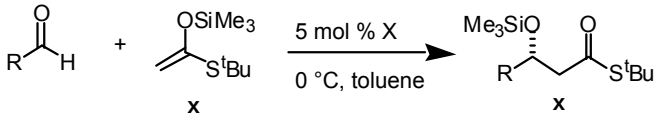


Table 4. Thioacetate Aldols with BINOL•$TiCl_2$ catalysis.

entry	aldehyde	yield	ee
1	BnO, CHO	81%	96%
2	C_6H_{17}, CHO	60%	91%
3	O, ^nBuO, CHO	64%	95%
4	Me, Me, CHO	61%	85%

A related Mukaiyama aldol catalyst system reported by Keck utilizes a BINOL•$Ti(OiPr)_2$ complex in the presence of 4Å molecular sieves.[28]

Interestingly, this same complex serves to acitvate aldehydes for the asymmetric addition of allyl stannanes.[29]

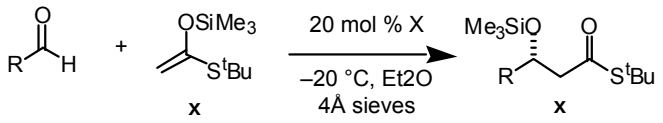
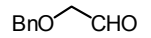
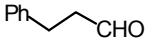
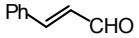


Table 5. Thioacetate Aldols with BINOL•$TiOiPr_2$ catalysis.

entry	aldehyde	yield	ee
1		90%	97%
2		80%	97%
3		76%	89%
4	PhCHO	82%	>98%

With asymmetric aldol addition of propionate derived enolates to aldehydes the possibility exists for the generation of two new stereocenters. Controlling the relative configuration at the two new stereocenters becomes a concern in these reactions. On of the more successful catalysts to effect this transformation is the chiral acyloxyborane (CAB, X) reagent extensively developed by Yamamoto. Although ketene acetals derived from ethyl and benzyl esters were ineffective, the phenyl acetate-derived trimethylsilyl ketene acetal X is an excellent nucleophilic partner with a variety of aldehydes with the CAB catalyst. In many instances good ratios of syn : isomers are obtained, with up to 90% selectivity.

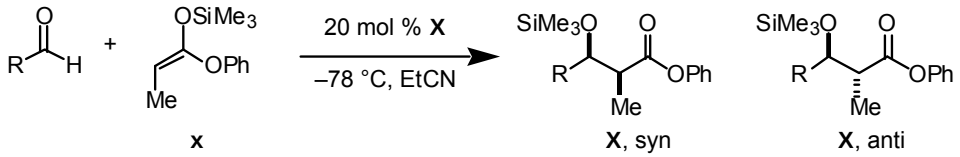
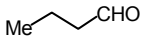
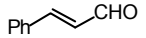
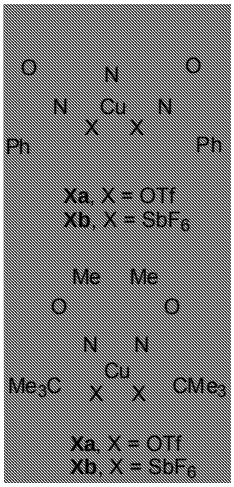


Table 6. Propionate Aldols with CAB catalysis.

entry	Aldehyde	yield	syn : anti	% *ee*
1	PhCHO	83%	79 : 21	92%
2		67%	63 : 35	88%
3		97%	96 : 4	97%

The use of chiral copper(II) Lewis acid complexes for the Mukaiyama aldol addition reaction has been extensively studied and developed by Evans.[30] The most striking characteristic of the bis(oxazolinyl) (box, X) and bis(oxazolinyl)pyridine (pybox, X) copper(II) complexes is their remarkable compatiblity with a variey of enolsilanes in the asymmetric addition to pyruvate esters and (bezyloxy)acetaldehyde with enantioselectivities up to 99% *ee*. Specifically, these catalysts achieve >98% enantioselectivity with both acetate and thio-acetate derived silylenolates (entries 1-3) and with dienolates (entry 4). Propionate derived enolates (entries 5 and 6) give predominately syn diastereomers with either geometry of starting enolate, with product diastereoselectivity up to 97 : 3 and in 97% *ee*.



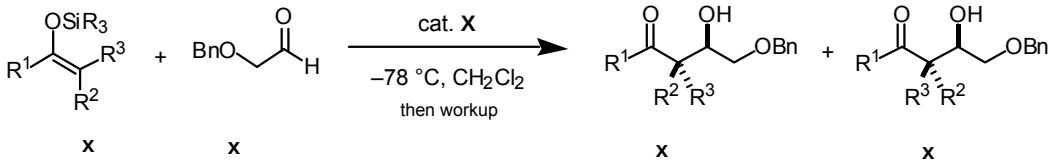
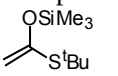
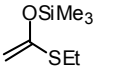
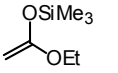
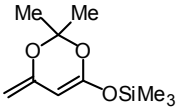
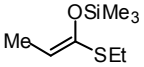
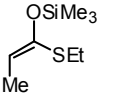
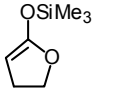


Table 7. Adol Additions to X catalyzed by pybox X.

entry	nucleophile	mol % **X**	yield	syn : anti	% ee
1		0.5	96%	-	99%
2		0.5	95%	-	98%
3		0.5	99%	-	98%
4		5	94%	-	92%
5		10	89%	97 : 3	91%
6		10	92%	86 : 14	95%
7		10	92%	96 : 4	95%

The box complex **X** effectively catalyzes the addition of enolsilanes to pyruvate esters in up to 99% *ee*. This reaction also displays a high degree of generality in terms of compatible nucleophiles as shown in table 8. Note that >94 : 6 syn products are obtained regarless of the geometry of the starting enolate (entries 4 and 5).

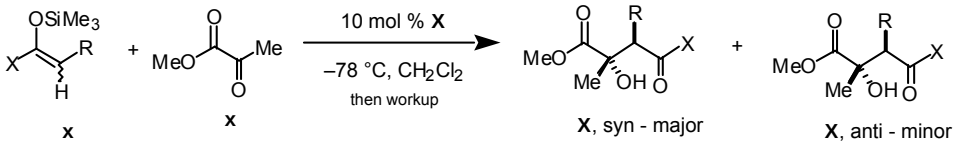
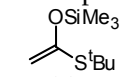
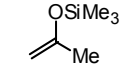
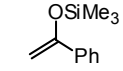
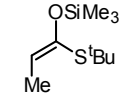
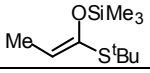
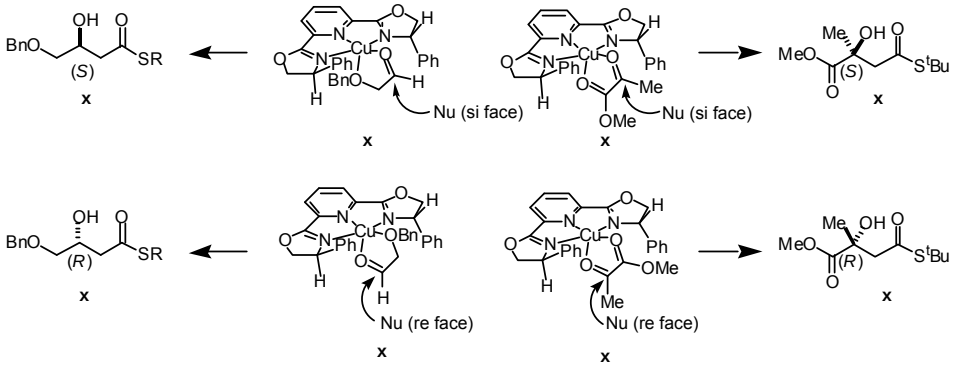


Table 7. Adol Additions to **X** catalyzed by box **X**.

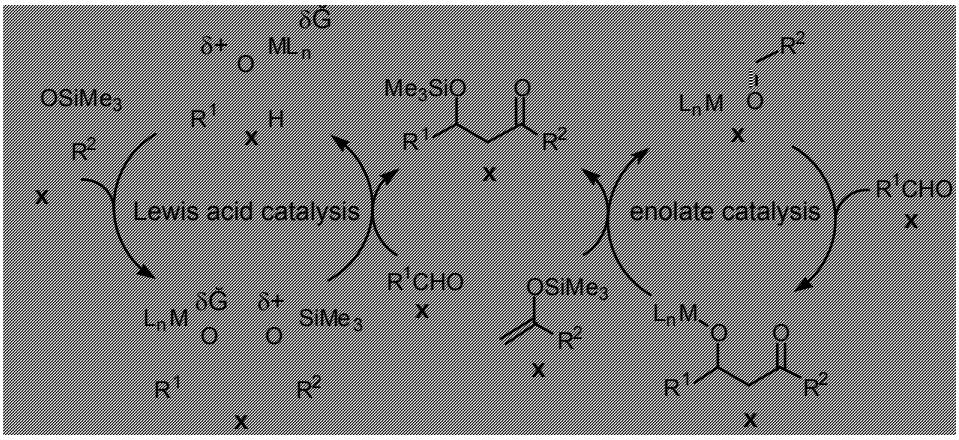
entry	nucleophile	yield	syn : anti	% ee
1		96%	-	99%
2		76%	-	93%
3		99%	-	77%
4		96%	94 : 6	96%
5		98%	95 : 5	88%

Some well defined transition state models have been designed to account for the observed stereochemistry in the aldol addition reactions catalyzed by **X** and **X**. Both the (benzyloxy)acetaldehyde and pyruvate esters are capable of forming a chelate with a Lewis acid **X**. In the metal and electrophile complex there are two distinct orientations for bidentate binding, where the aldehyde donor occupies an equatorial **X** or axial position **X**. Although the aldehyde is presumably activated towards nucleophilic attack in either conformation, the stereochemistry of the observed products is consistent with attack only when the aldehyde occupies the equatorial position. This result is not at all surprising given the well known Jahn-Teller distortions observed in square planar copper complexes. That is,

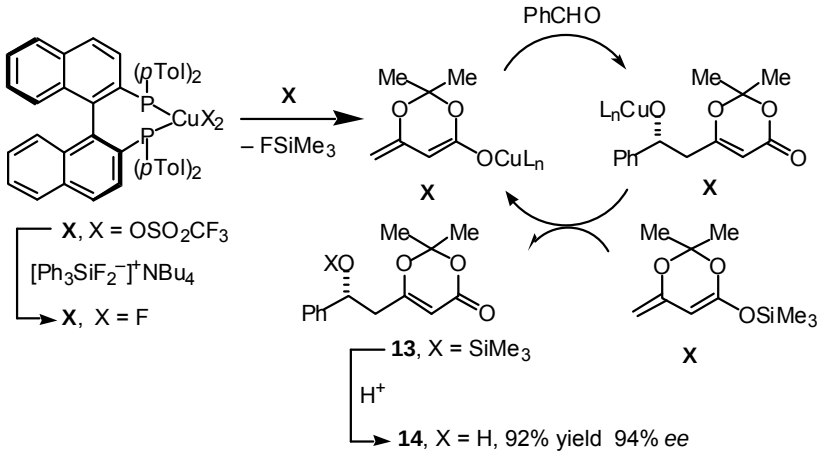


Mukaiyama Aldols via Metallo-enolates.

The search for improved catalysis design in the Mukaiyama aldol reaction has relied extensively on the improvement and optimization of ligands for complexation to a Lewis acid. However, there exists a mechanistic alternative in the Mukaiyama aldol reaction for effecting the same transformation. In this model chiral metal enolate participates in the catalytic cycle, thus the process may be termed enolate catalysis.



The concept of enolate catalysis has been explored in investigations by Bermann and Heatcock with the deployment of rhodium enolates for aldol reactions. Recently, Carreira and co-workers described a copper mediated process for the asymmetric addition of dioxinone derived silyl dienolate X to aromatic and a,b-unsaturated aldehydes. Mechanistic investigations suggest that the likely catalytically active species results from reaction of the bisphosphine•CuF_2 complex **9** with silyl dienolate **10** resulting in a copper(I) dienolate.[31]



The reaction is readily performed on multi-gram scale with as little as 0.5 mol % of bisphosphine•CuF_2 complex **x** go prepare provides synthetically useful aldolates in up to 96% *ee*.[32]

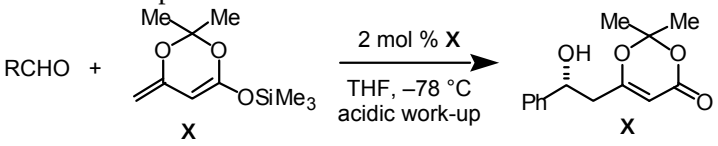
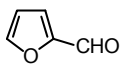
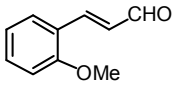


Table X. Carreira's Asymmetric Enolate Additions.

entry	aldehyde	yield	% ee
1	PhCHO	92%	94%
2		91%	94%
3		82%	90%

X.X Applications to Natural Product Synthesis.

You can pick these erick.

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