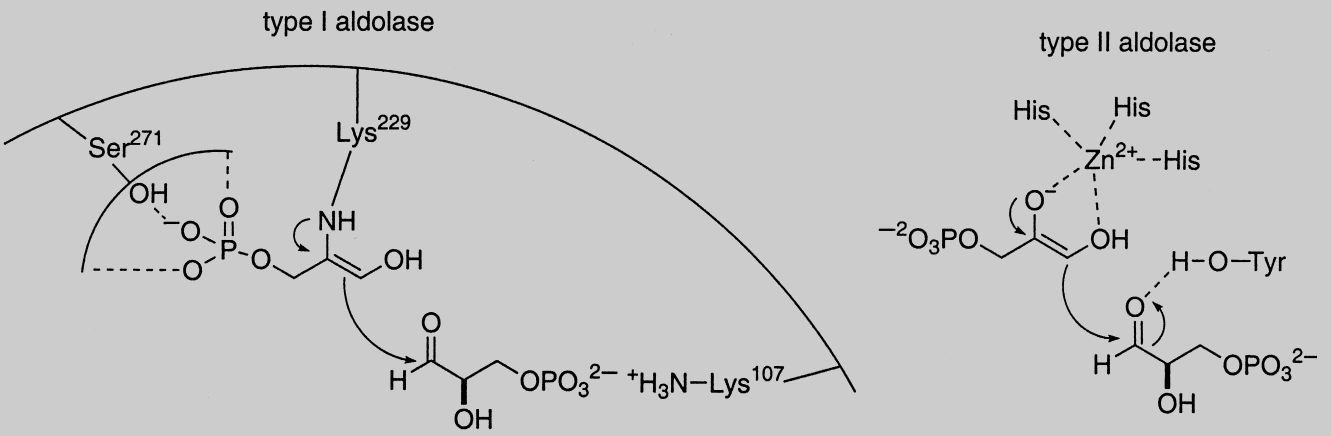
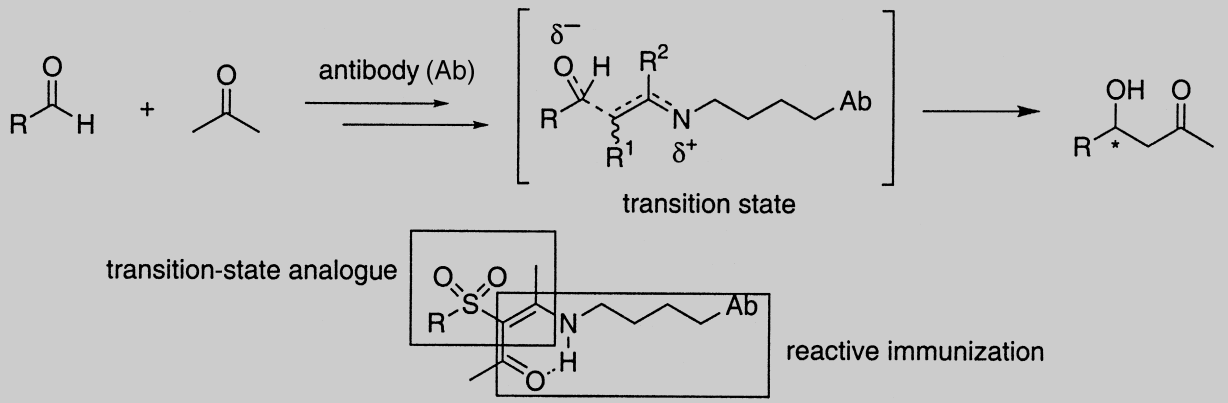
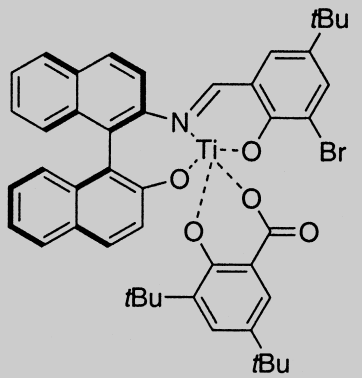
Aldolase-catalyzed reaction

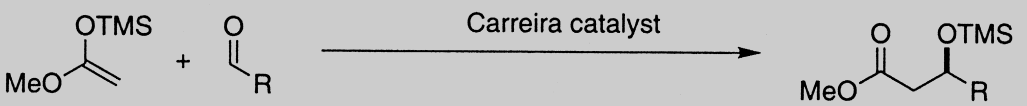


Antibody design and catalysis



Small-molecule catalyst





The Catalytic Asymmetric Aldol Reaction

Timothy D. Machajewski and Chi-Huey Wong*

Dedicated to Professor Richard A. Lerner

The construction of C–C bonds with complete control of the stereochemical course of a reaction is of utmost importance for organic synthesis. The aldol reaction—the simple addition of an enolate donor to a carbonyl acceptor—is one of the most powerful reactions available to the synthetic chemist. In general, control of the relative and absolute configuration of the newly formed stereogenic centers has been achieved through the use of chiral starting materials or chiral auxiliaries. In recent years the search for catalytic methods that efficiently and effectively transfer chirality information has become a major effort in synthetic organic chemistry. Two different approaches have been taken toward the catalytic asymmetric aldol reaction: biocatalysis and catalysis with small molecules. Both approaches have specific advantages and limitations, and as a result are complementary to each other. The important efforts toward both approaches are reviewed in this article.

Keywords: aldol reactions · asymmetric catalysis · catalytic antibodies · enzyme catalysis · organometallic catalysis

1. Introduction

The aldol reaction is one of the most powerful methods of forming carbon–carbon bonds. The ability to control the absolute configurations of the newly formed stereogenic centers is of paramount importance for the synthesis of natural products. In general, control of stereochemistry has been accomplished diastereomerically through either the use of chiral aldehyde starting materials or stoichiometric chiral auxiliaries attached to the donor enolate.[1] The control of stereochemistry using chiral aldehydes as substrates has some limitations. While chiral aldehydes undergo stereospecific addition in a very predictable fashion,[2] the formation of all possible stereoisomers from a single chiral aldehyde is not possible. Chiral auxiliaries have solved this problem and depending on the choice of auxiliary, all possible stereoisomers can be realized;[3] however, while this approach has been quite successful, it requires additional steps to introduce and remove the chiral auxiliary.

The search for methods that predictably transfer chirality efficiently and catalytically by reagent control has been a challenging goal in organic synthesis. A number of methods have been developed in recent years for the catalytic asymmetric aldol addition with both high efficiency and selectivity. This review will focus on those efforts in two areas: 1) the exploitation of biochemical catalysts such as aldolases and catalytic antibodies, and 2) the design of chiral chemical catalysts such as chiral Lewis acids and bases.

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2. Biochemical Catalysts

Enzymes are increasingly recognized as useful catalysts for organic synthesis.[4] Their attractiveness arises from a number of important advantages over traditional chemical methods. Enzymes are generally highly chemo-, regio-, diastereo-, and enantioselective. As a result of this high selectivity and the mild conditions employed, protecting group chemistry can be kept to a minimum. Since most enzymes operate at room temperature in aqueous solutions at or near neutral pH values, their reactions are often compatible with one another, making it possible to combine several enzymes in a one-pot, multistep operation. Their use in aqueous solution free of heavy metals and with biodegradability make enzymes an environmentally advantageous option, though in certain cases the reaction is limited to a narrow range of substrates and the isolation of the products from water could be a problem.

There are two types of enzymatic catalysts that effect the aldol addition: the aldolases, a group of naturally occurring enzymes that catalyze in vivo aldol condensations; and

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catalytic antibodies that have been developed in recent years to mimic the aldolases but with improved substrate specificity.

2.1. Aldolases

The aldolases are a specific group of lyases that typically catalyze the stereoselective addition of a ketone donor to an aldehyde acceptor. Over 30 aldolases have been identified to date. Two distinct types of aldolases have been identified and classified according to their mechanism (Scheme 1).[5] As a general rule type I aldolases are primarily found in animals and higher plants, while type II aldolases are found in bacteria and fungi.

Type I aldolases activate the donor by forming a Schiff base as an intermediate in the active site. This activated donor then adds stereoselectively to the acceptor aldehyde. In several cases the Schiff base has been isolated by reduction with borohydride,[6] but no three dimensional structure of the complex exists. Recently, however, a three-dimensional structure of the reduced Schiff base intermediate of transaldolase B from *Escherichia coli* was determined (Figure 1).[7] Crystallographic studies of free transaldolase reveal a similar three-dimensional structure and active site to other type I aldolases.[8–10]

Type II aldolases, on the other hand, contain a Zn^{2+} cofactor in the active site. There have been several mechanistic hypotheses for the mechanism of this class of aldolase. According to NMR and ESR studies on the relaxation rate of a Mn^{2+}-substituted holoenzyme, the Zn^{2+} ion polarizes the carbonyl donor through an intervening imidazole group of an amino acid side chain.[11] FT-IR spectroscopic and deuterium exchange studies led to the conclusion that activation occurs by an additional direct coordination of Zn^{2+} to the carbonyl donor.[12] A crystal structure of fuculose-1-phosphate aldolase containing an inhibitor that mimics the enediolate transition state of dihydroxyacetone phosphate (DHAP) was recently solved (Figure 2).[13]

A clearer picture of the mechanism of type II aldolases arises from this three-dimensional information. The active site is located at the interface of two subunits of a homotetramer, and contains the Zn^{2+} cofactor coordinated to three histidine residues (His-92, His-94, His-155). In the absence of DHAP a glutamate residue (Glu-73) further stabilizes the Zn^{2+} ion. The phosphate group is bound in a pocket containing several hydrogen-bond donors (Ser-72, Ser-71, Thr-43, Gly-44, Asn-29). The glutamate residue also functions as a base to remove the proton from the donor. A tyrosine residue (Tyr-113′) from the adjoining subunit assists in the activation of the incoming aldehyde by donating a proton to stabilize the developing charge. In both types of aldolases the formation of the enolate (that is, the deprotonation step) is rate determining. Armed with this structural and mechanistic information, site-directed mutagenesis and directed evolution may find use in developing new aldolases with improved substrate specificities and properties.

With only a few exceptions, the stereoselectivity in both types of aldolases is controlled by the enzyme and does not depend on the structure or stereochemistry of the substrate, which allows for highly predictable products. These enzymes generally tolerate a broad range of acceptor substrates but have stringent requirements for donor substrates.

The aldolases that have been investigated for their synthetic utility can be divided into four main groups on the basis of the donor substrate accepted by the enzyme. The first group uses dihydroxyacetone phosphate (DHAP) as the donor to

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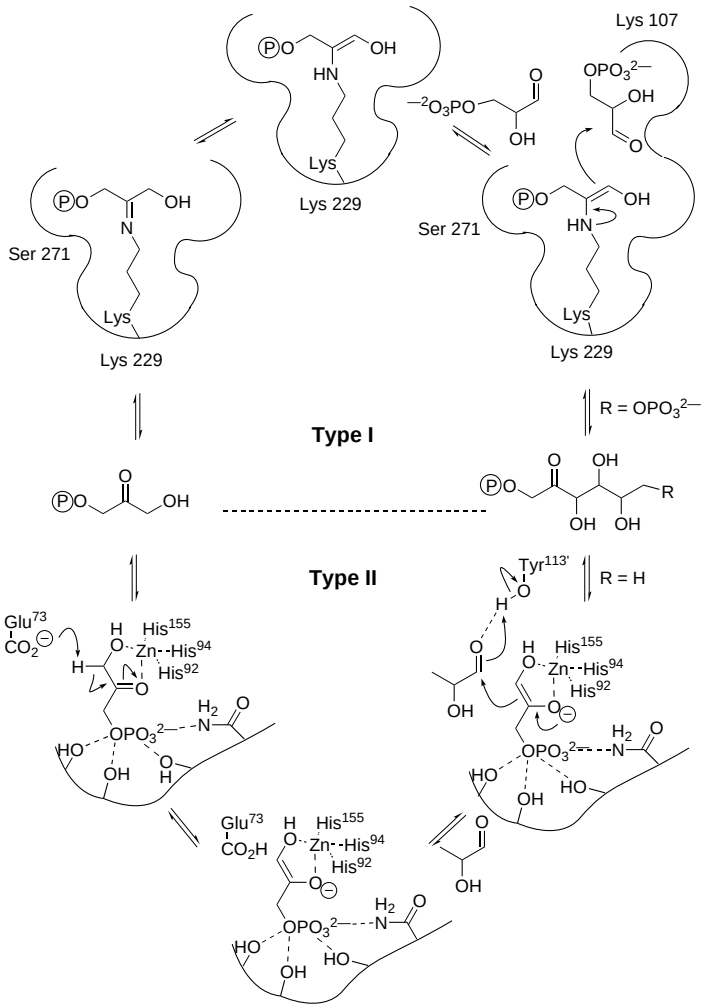
Chi-Huey Wong, born in 1948, received his BS and MS degrees from the National Taiwan University and his PhD in chemistry with George M. Whitesides from the Massachusetts Institute of Technology in 1982. He then moved with Professor Whitesides to Harvard University as a postdoctoral fellow for another year. He was appointed to the faculty of chemistry at Texas A&M University in 1983 and rose through the ranks in four years. Since 1989 he has been a Professor and Ernest W. Hahn Chair in Chemistry at The Scripps Research Institute. He has also been associated with the Skaggs Institute for Chemical Biology at Scripps since 1996 and was Head of the Frontier Research Program on Glycotechnology at RIKEN (Institute of Physical and Chemical Research) in Japan from 1991 to 1999. He has received numerous awards and is a member of the American Academy of Sciences. His current interests are in the areas of bioorganic and synthetic chemistry, especially in the development of new synthetic chemistry based on combined enzymatic and chemical reactions, the study of molecular glycobiology, and the rational development of mechanism-based inhibitors of enzymes and carbohydrate receptors.

Timothy D. Machajewski, born in 1966, received a BS degree from the University of Texas at Austin, and a PhD in chemistry from Stanford University under Barry M. Trost in 1997. He spent two years as a postdoctoral research associate at The Scripps Research Institute with C.-H. Wong. His research interests include the study of catalytic methods for asymmetric synthesis and the synthesis of bioactive natural products.



Scheme 1. The two types of aldolase mechanisms: The type I Schiff base forming aldolase is represented by rabbit muscle FDP aldolase (RAMA, top), and the type II zinc enolate aldolase is represented by fuculose-1-phosphate aldolase (bottom). Ⓟ = PO_3^{2-}.

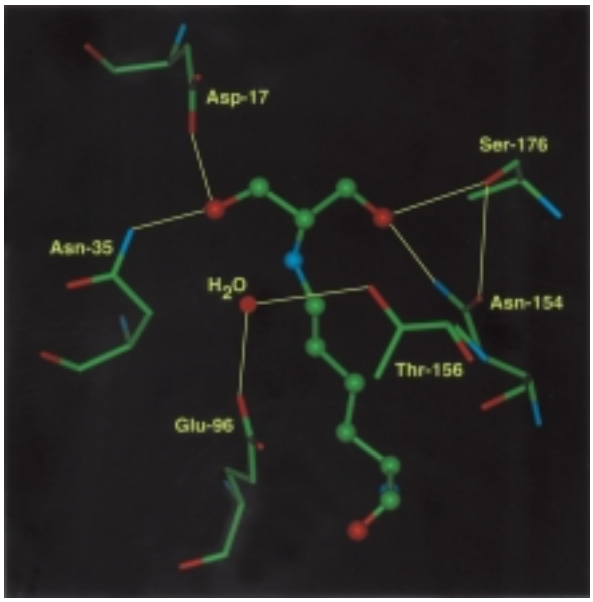


Figure 1. Structure of the active site of the reduced substrate–enzyme complex of transaldolase B (type I aldolase) as determined by X-ray crystallography.

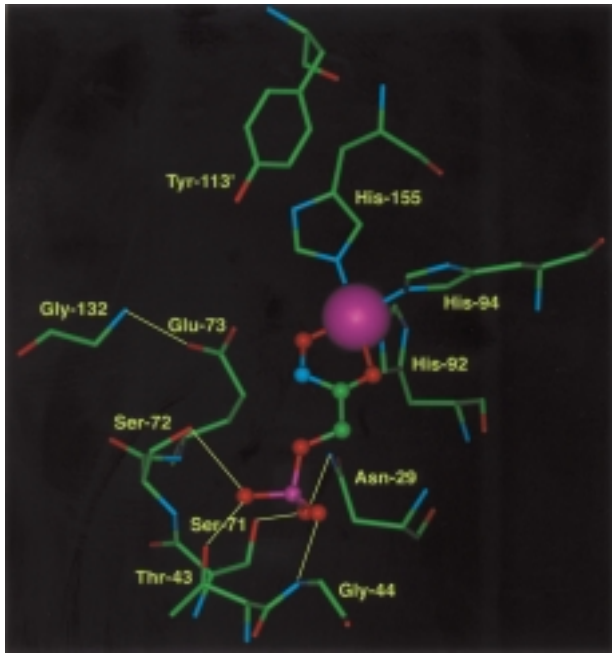


Figure 2. Structure of the active site of fuculose-1-phosphate aldolase (type II aldolase) as determined by X-ray crystallography.

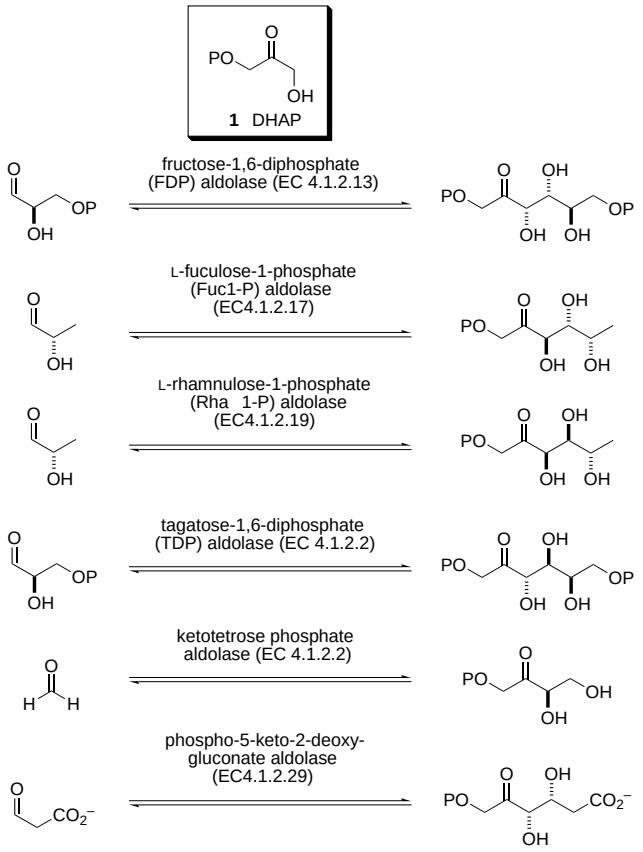
produce 2-keto-3,4-dihydroxy adducts. The second group uses pyruvate or phosphoenol pyruvate to form 3-deoxy-2-keto acids. The third group uses acetaldehyde as the donor, which results in the formation of 3-hydroxyaldehydes. The fourth group utilizes glycine as the donor to produce β-hydroxy-α-amino acids. As a consequence of the limited space available here, the other types of aldolases [4, 14] and transaldolases are not covered.

2.1.1. DHAP-Dependent Aldolases

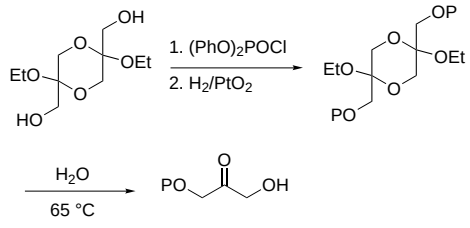
The known DHAP-dependent aldolases and their in vivo catalyzed reactions are shown in Scheme 2. These enzymes accept a broad range of acceptor substrates,[4] including unhindered aliphatic aldehydes, α-heteroatom substituted aldehydes,[15a] and monosaccharides and their derivatives.[15b] Aromatic aldehydes, sterically hindered aldehydes, and α,β-unsaturated aldehydes are generally not substrates;[15a] however, aromatic aldehydes and α-branched aldehydes have been reported to be substrates for cross-linked enzyme crystals.[16]

Since these aldolases show a very strict requirement for the donor substrate, an efficient method of DHAP preparation is essential. Several chemical and enzymatic methods for generating DHAP have been developed.[17–26] The use of relatively pure DHAP favors the formation of the aldol products and simplifies the purification process.

Phosphorylation of the dihydroxyacetone dimer with $(PhO)_2POCl$[25] followed by reductive cleavage of the phenyl esters gives the DHAP dimer, which can be easily hydrolyzed to provide clean DHAP in 61 % overall yield (Scheme 3). The phosphate group can be easily removed from the aldol product by enzymatic hydrolysis with acid phosphatase (EC 3.1.3.2).



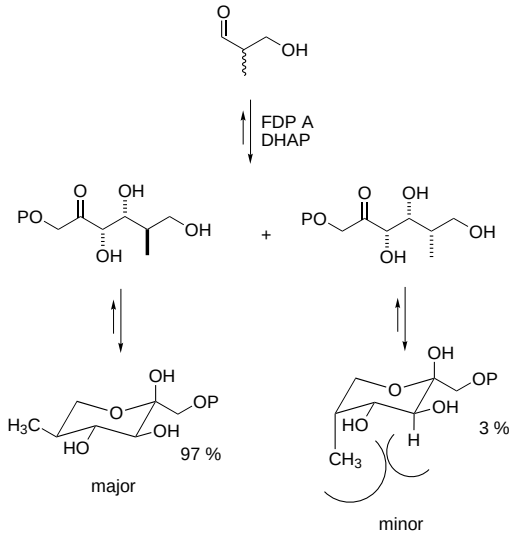
Scheme 2. Dihydroxyacetone phosphate (DHAP) dependent aldolases. $P = PO_3^{2-}$.



Scheme 3. Chemical synthesis of DHAP.

The configuration of the vicinal diols produced from the aldolase-catalyzed condensation of DHAP with unnatural acceptor aldehydes usually follows that of the natural substrates. Almost without exception, fructose-1,6-diphosphate (FDP) aldolase produces products with the D-*threo* configuration of FDP. L-Fuculose-1-phosphate (Fuc 1-P) aldolase and L-rhamnulose-1-phosphate (Rha 1-P) aldolase generate diols with the D-*erythro* and L-*threo* configurations, respectively. For a few substrates, however, the stereoselectivity at C4 is diminished.[27] In almost every case investigated, TDP aldolase yielded diastereomeric mixtures,[28–30] and for this reason it is not yet synthetically useful.

In many cases the aldehyde substrates may be used as racemic mixtures. For example, D-glyceraldehyde-3-phosphate (G3P) reacts with DHAP in the presence of FDP aldolase 20 times faster than L-G3P. Fuc 1-P aldolase and Rha 1-P aldolase show an even higher kinetic preference for the L-enantiomer of 2-hydroxyaldehydes (>95:5).[31] Therefore, as long as the reaction is stopped before reaching equilibrium, a kinetic resolution of the aldehyde substrate can be effected and a single diastereomeric and enantiomeric adduct can be obtained. In some cases, differentiation of racemic aldehydes can be accomplished under thermodynamic control. In cases where the aldol product can cyclize to form pyranoses, the product with an equatorial bulky substituent and the fewest 1,3-diaxial interactions will predominate at equilibrium, as illustrated in Scheme 4 for the reaction of 2-methyl-3-hydroxypropanol (**14**).



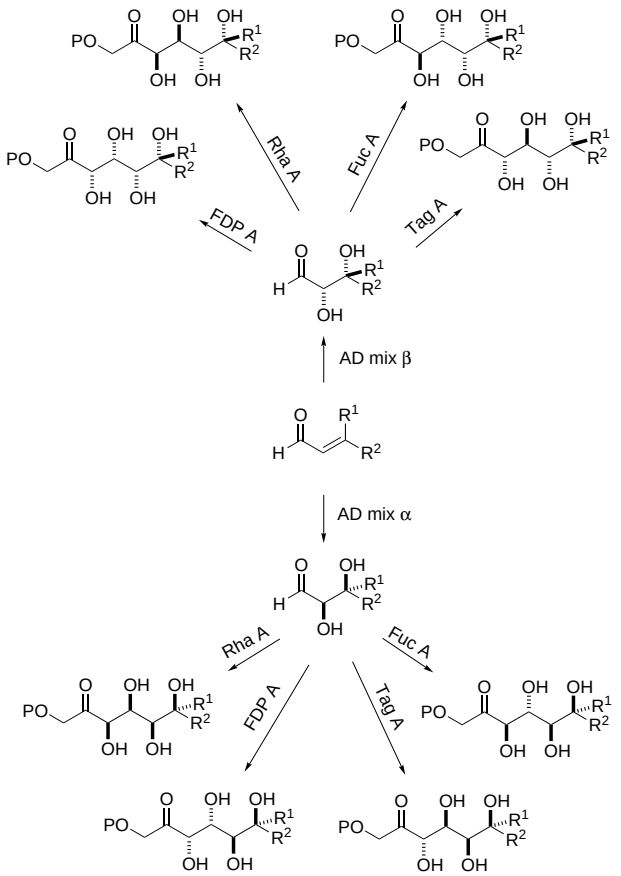
Scheme 4. Thermodynamic control of the product stereochemistry. A = aldolase.

The utility of the DHAP-dependent aldolases has been demonstrated in the synthesis of ^{13}C-labeled sugars, heteroatom-substituted sugars, deoxy sugars, fluoro sugars, long-chain sugars, and cyclitols. Well over 100 aldehydes have been used as acceptor substrates.[4, 32]

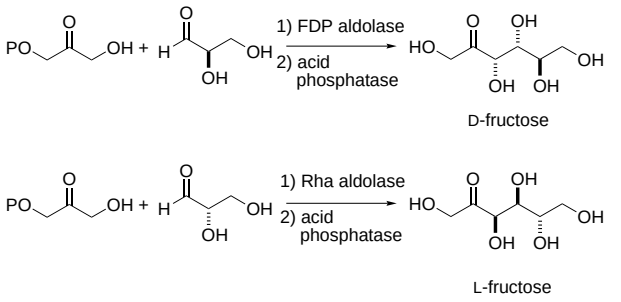
Tandem use of the Sharpless asymmetric dihydroxylation (AD) and aldolase-catalyzed addition provides a rapid method for the synthesis of both enantiomers with complete stereocontrol (Scheme 5).[33] A multitude of carbohydrates and derivatives are potentially accessible by the appropriate choice of alkenal, AD-mix, and aldolase. In addition to the natural D-sugars, L-sugars are easily prepared by the appropriate choice of aldolase. For example, while D-fructose is formed from the FDP-catalyzed reaction of D-glyceraldehyde and DHAP, L-fructose is prepared from the Rha 1-P-catalyzed reaction of DHAP with L-glyceraldehyde (Scheme 6).[34]

The aldolase-catalyzed reaction of DHAP and pentoses or hexoses provides access to novel long-chain sugars that are difficult to obtain from chemical synthesis or natural sources. Derivatives of sialic acid and 2-keto-3-deoxyoctanoate (KDO) have been prepared in this manner (Scheme 7).[15]

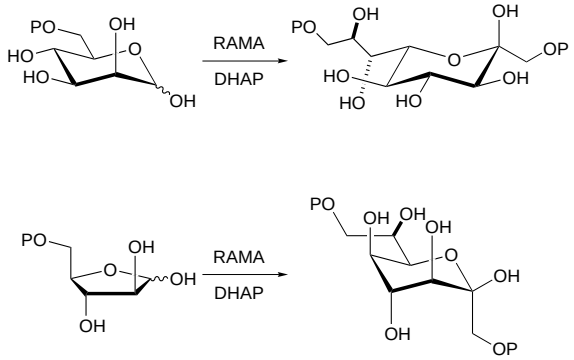
Heteroatom-substituted carbohydrates are readily assembled through the aldolase-catalyzed condensation of an appropriately substituted aldehyde with DHAP. Azides are well tolerated in the reaction and provide an efficient means



Scheme 5. Tandem asymmetric dihydroxylation (AD) and aldolase reaction.

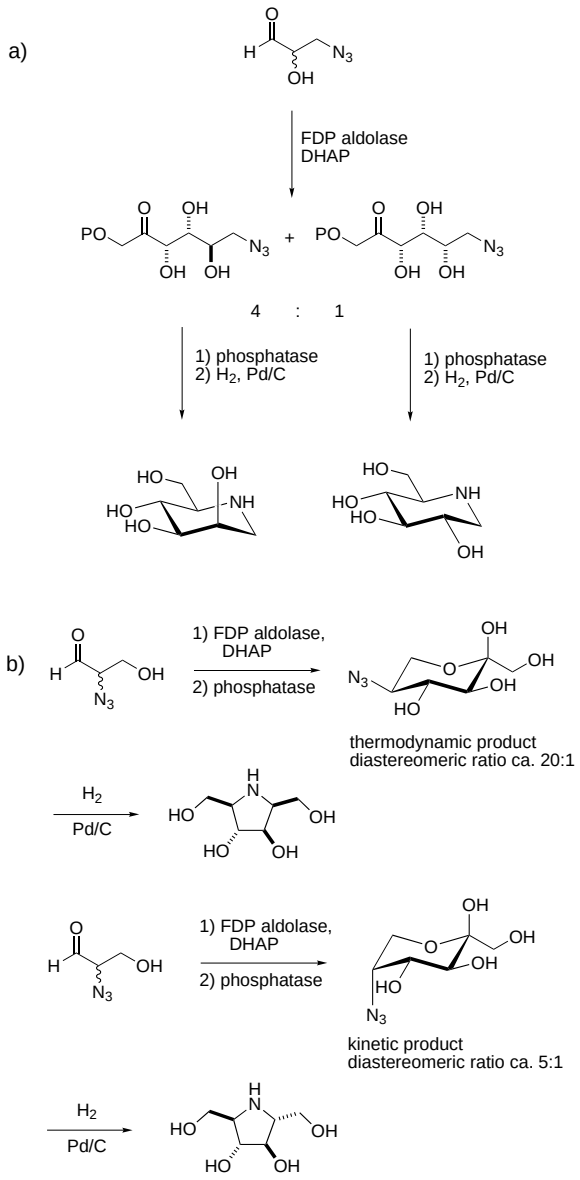


Scheme 6. Synthesis of D- and L-fructose by a reaction catalyzed by rhamnulose-1-phosphate aldolase and fructose-1-6-diphosphate aldolase, respectively.



Scheme 7. Synthesis of novel long-chain sugars.

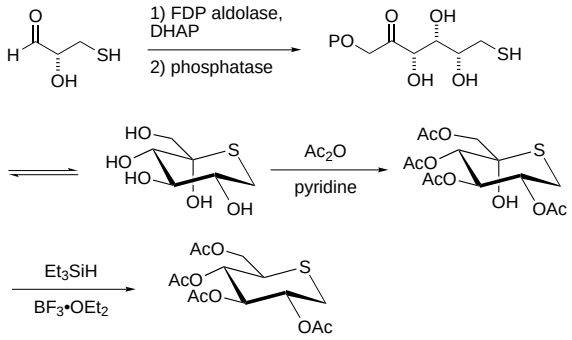
of preparing iminocyclitols, such as deoxynojirimycin and deoxymannojirimycin (Scheme 8a).[35, 36] Polyhydroxylated pyrrolidines can be synthesized with 2-azido aldehydes (Scheme 8b). The FDP aldolase catalyzed condensation of



Scheme 8. a) Synthesis of iminocyclitols from azidoaldehydes and DHAP. b) Synthesis of substituted pyrrolidines from azidoaldehydes and DHAP.

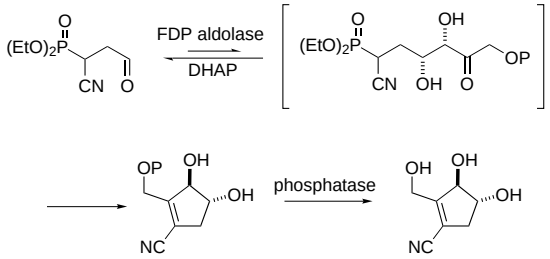
racemic 2-azido-3-hydroxypropanal with DHAP under thermodynamic control and subsequent removal of phosphate with acid phosphatase afforded the azido sugar. Reduction of the azide group with hydrogen and palladium on carbon afforded the substituted pyrrollidine.[37] The subsequent reaction under kinetic control afforded the diastereomeric azido sugar, which was converted into a substituted pyrrolidine.[38] The aldolase-catalyzed condensation of sulfur-substituted aldehydes with DHAP followed by reduction of the resulting thioketoses provides a rapid synthesis of thio sugars (Scheme 9).

Cyclitols, an interesting class of biologically active compounds, have been prepared chemoenzymatically from the



Scheme 9. Synthesis of thio sugars from thioaldehydes and DHAP.

reaction of nitroaldehydes[39a] and phosphonate-substituted aldehydes (Scheme 10).[39b] Other novel polyhydroxy structures prepared by aldolases are illustrated in Scheme 11.[4, 32, 40]



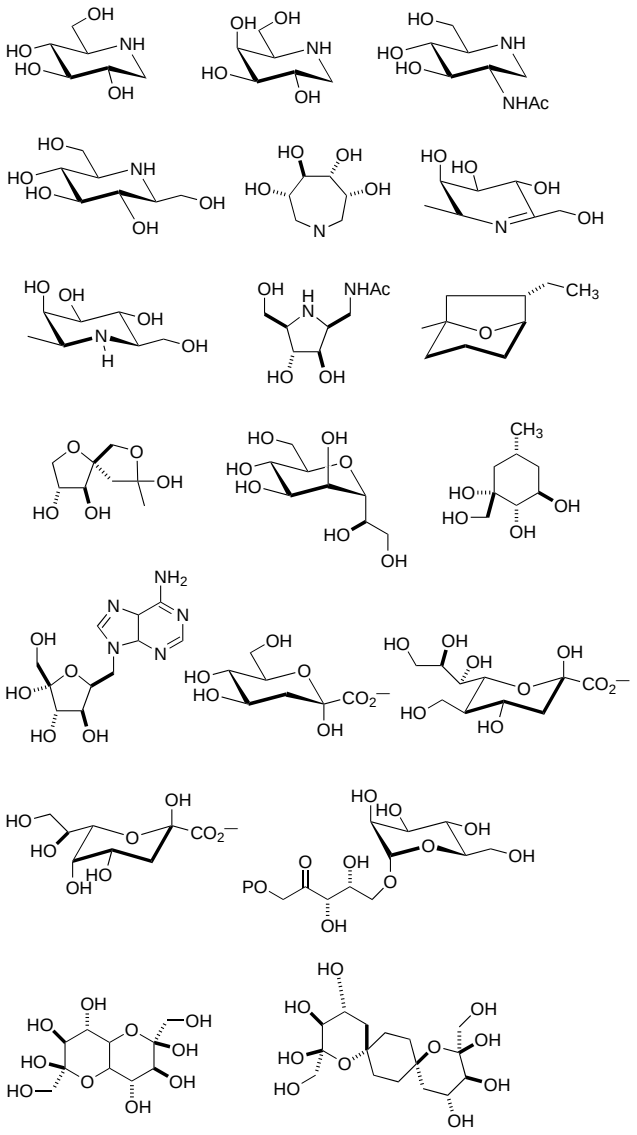
Scheme 10. Chemoenzymatic synthesis of cyclitols.

2.1.2. Pyruvate- and Phosphoenolpyruvate-Dependent Aldolases

The pyruvate-dependent aldolases (Scheme 12) and the phosphoenolpyruvate-dependent aldolases (Scheme 13) can be used to prepare similar α-keto acid products. The pyruvate-dependent aldolases have a catabolic function in vivo, whereas the phosphoenolpyruvate-dependent aldolases are involved in the biosynthesis of keto acids. For synthetic purposes the equilibrium of the pyruvate-dependent aldolases is shifted toward the condensation product through the use of excess pyruvate.[41] Purification of the products can be most easily achieved by decomposing the excess pyruvate with pyruvate decarboxylase.[42]

The commercial availability of *N*-acetylneuraminic acid (NeuAc) aldolase (also known as sialic acid aldolase) has led to extensive studies on this enzyme. It is highly specific for pyruvate as the donor substrate, but tolerates a variety of acceptor substrates, including hexoses, pentoses, and tetroses in both enantiomeric forms.[32] Substitutions at C4, C5, and C6 are allowed with slight preferences for the same absolute stereochemistry as the natural substrate, *N*-acetyl-D-mannosamine. The substitutions at C2 and C3 are more restrictive; the C2 position favors relatively small substituents with the natural stereochemistry and the C3 position requires a free hydroxyl group.[43]

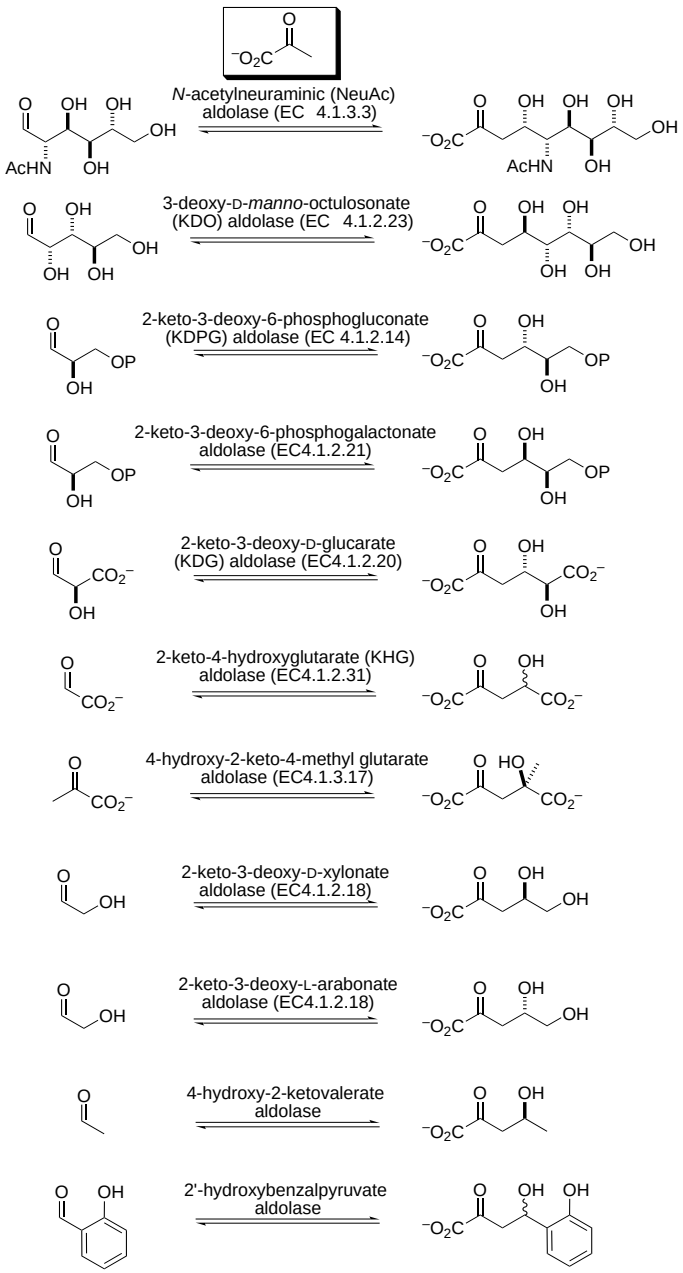
Unlike most aldolases the stereochemical outcome of reactions catalyzed by NeuAc aldolase depends on the structure of the substrate. In acceptor substrates with the



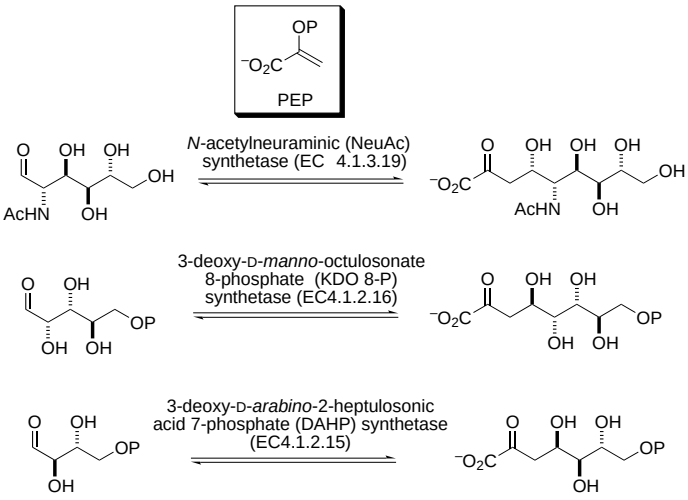
Scheme 11. Novel polyhydroxy structures prepared by aldolase-catalyzed reactions.

natural *S* configuration at C3, the carbonyl group is attacked from the *si*-face to form a new stereogenic center with *S* configuration. Substrates with the opposite configuration at C3, however, lead to attack of the carbonyl group from the *re* face, which gives rise to the *R* configuration (Scheme 14). In general, attack at the *si* face is kinetically favored over attack at the *re* face.[43] The stereochemical outcome seems to be under thermodynamic control. In all cases where *re*-face attack predominates, the resulting *R*-configured product is thermodynamically more favored with the newly formed stereocenter in the equatorial configuration. This substrate-controlled stereoselectivity has been used in the synthesis of D- and L-sialic acid analogues and several other novel sugars and their enantiomers.[42]

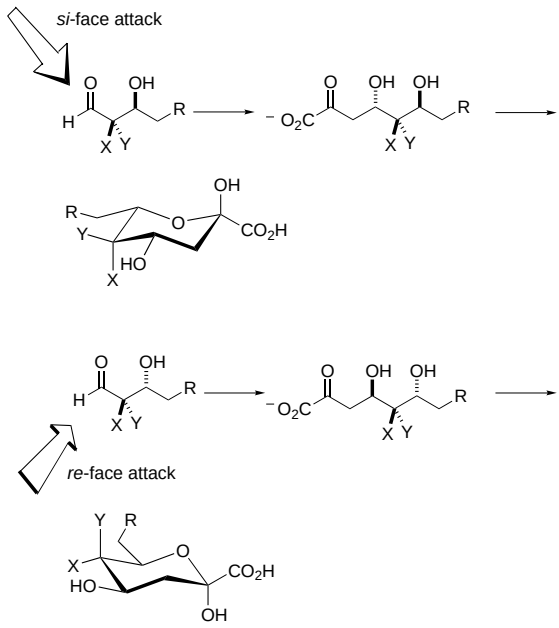
Aza sugars have been prepared with NeuAc aldolase.[44] The enzyme-catalyzed addition of pyruvate to *N*-Cbz-D-mannosamine followed by reductive amination gave the pyrrolidine, which was further converted into 3-(hydroxymethyl)-6-epicastanospermine (Scheme 15).



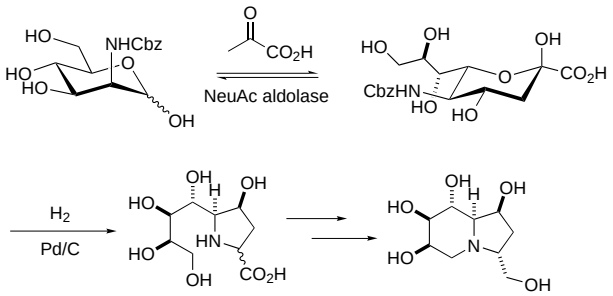
Scheme 12. Pyruvate-dependent aldolases and the reactions they catalyze.



Scheme 13. Phosphoenolpyruvate-dependent aldolases and the reactions they catalyze.

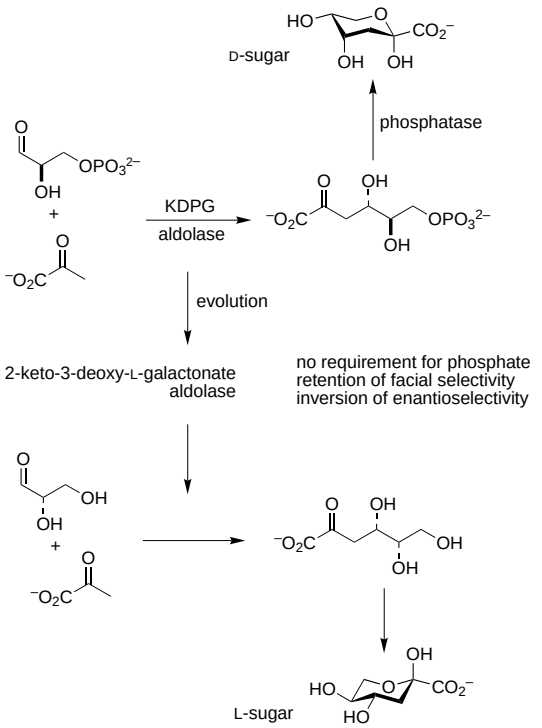


Scheme 14. Stereochemical outcome of the reaction catalyzed by sialic acid (NeuAc) aldolase: comparison of *re* (top) with *si* addition to the carbonyl group (bottom).



Scheme 15. NeuAc aldolase catalyzed preparation of aza sugars. Cbz = benzyloxycarbonyl.

Other pyruvate- and phosphoenolpyruvate-dependent aldolases have been isolated and purified, but have not been extensively investigated for their use in synthesis. KDO aldolase accepts D-ribose, D-xylose, D-lyxose, L-arabinose, D-arabinose-5-phosphate, and *N*-acetylmannosamine at less than 5% of the natural substrate, D-arbinose.[45] The enzyme is specific for substrates with the *R* configuration at C3. In all cases observed to date, the carbonyl group is attacked from the *re* face. 2-Keto-3-deoxy-6-phosphogluconate (KDPG) aldolase was shown to accept various unnatural substrates at very low rates (< 1%) relative to the natural substrate.[46a] The stereochemistry of the newly formed stereocenter invariably has the *S* configuration. By using the technique of directed evolution by DNA shuffling and error-prone polymerase chain reaction (PCR), KDPG has been altered with regard to its acceptor enantioselectivity and phosphate requirement to accept the non-phosphorylated enantiomeric aldehydes to form interesting L-sugars (Scheme 16).[46b]



Scheme 16. Directed evolution of KDPG aldolase to alter the acceptor enantioselectivity and to eliminate the requirement of a phosphate group in the substrate.

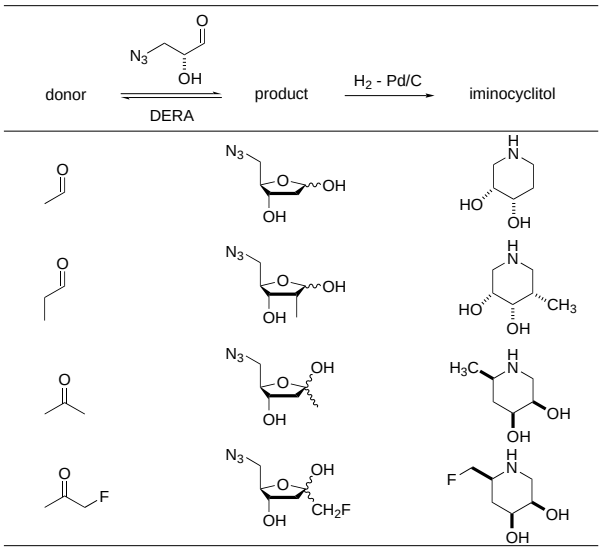
2.1.3. Acetaldehyde-Dependent Aldolases

Currently, there is only one known member of this class of aldolase: 2-deoxyribose-5-phosphate aldolase (DERA), which catalyzes the synthesis of 2-deoxyribose-5-phosphate from acetaldehyde and D-glyceraldehyde-3-phosphate. While not yet commercially available, it has been overexpressed in *E. coli* and large quantities of the enzyme can be simply and readily obtained.[47–49] DERA, a type I aldolase, is the only known aldolase that performs a cross-aldol reaction of two aldehydes.

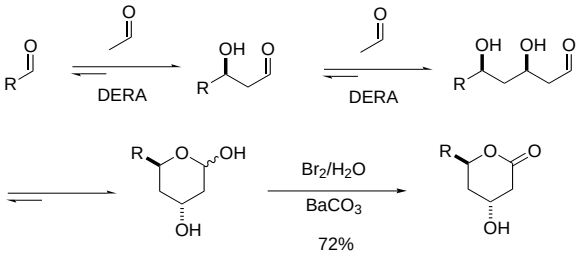
The enzyme shows a broad range of tolerance towards the acceptor substrate and a relatively large donor tolerence. In addition to acetaldehyde, the enzyme tolerates propanal, acetone, and fluoroacetone as donor substrates.[48] The acceptor substrates have very few structural requirements: 2-hydroxyaldehydes react fastest, with D-isomers preferred over L-isomers. Azidoaldehydes, thio-substituted aldehydes, and α-methylaldehydes are all accepted as substrates.[48] The configuration of the newly formed center is invariably determined by the enzyme and gives products that generally have the *S* configuration. Several iminocyclitols have been prepared from the DERA-catalyzed aldol condensation of various donors with 3-azido-2-hydroxypropanal (Table 1).

The products from the DERA-catalyzed reaction with acetaldehyde as the donor are themselves aldehydes, which can participate as an acceptor substrate for a second aldol condensation.[50] For aldehyde substrates that are substituted in the α-position and cannot cyclize to form a hemiacetal, a second reaction with acetaldehyde takes place. The products of the second addition cyclize to a stable hemiacetal, which

Table 1. DERA-catalyzed synthesis of iminocyclitols..



prevents further addition (Scheme 17). These products can be oxidized to provide the lactone moiety of the compactins in a remarkably short route starting from inexpensive, achiral starting materials.



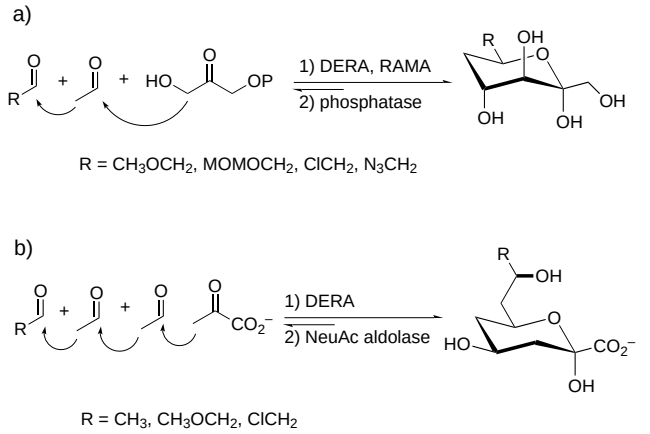
R = CH_3, CH_3OCH_2, $MOMOCH_2$, $ClCH_2$, N_3CH_2, $CH_2CH_2CO_2H$, CH_2OHCH_2OP

Scheme 17. Deoxyribose-5-phosphate aldolase (DERA) catalyzed, three component, double aldol condensation. MOM = methoxymethyl.

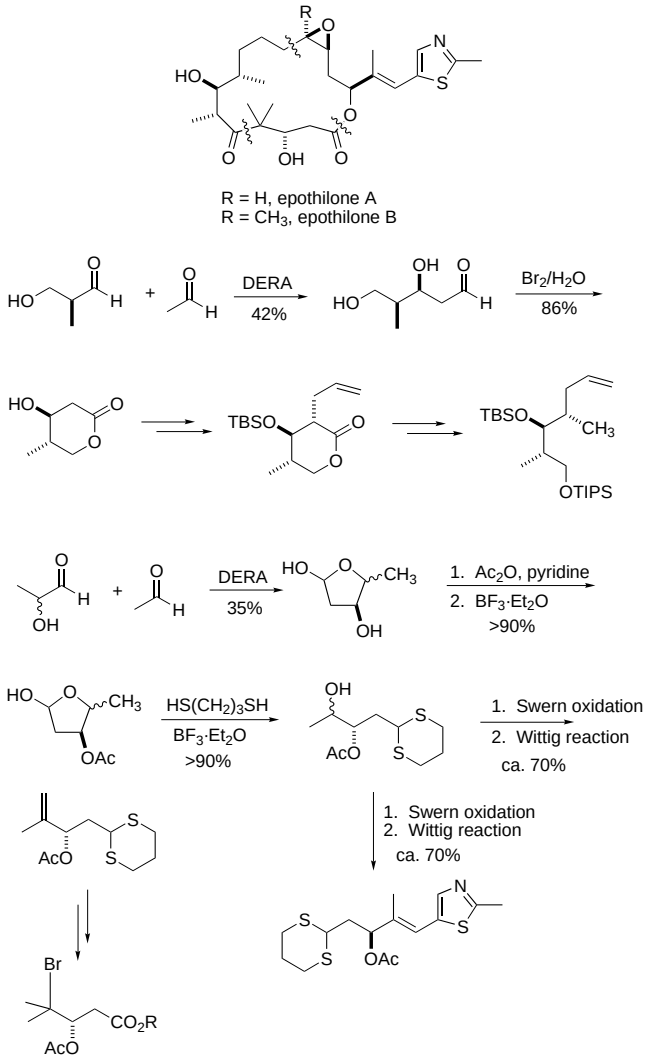
DERA can be combined with DHAP-dependent aldolases in a one-pot sequential reaction to produce 5-deoxy ketoses with three substituents in the axial position (Scheme 18a).[51a] The combination of DERA and NeuAc aldolase in a sequential manner gives deoxy sialic acid derivatives[51b] (Scheme 18b). This conversion was not possible in a one-pot system owing to the different reaction conditions needed for the two enzymes. The enzyme has also been used in the synthesis of key epothilone fragments (Scheme 19).[52]

2.1.4. Glycine-Dependent Aldolases

The glycine-dependent aldolases (Scheme 20) catalyze the reversible condensation of glycine with an aldehyde acceptor to form a β-hydroxy-α-amino acid. These enzymes have been used extensively for the resolution of racemic β-hydroxy-α-amino acids; however, only a few examples of their use in bond-forming reactions is known. L-Threonine aldolase was found to accept a broad range of substrates,[53] but often



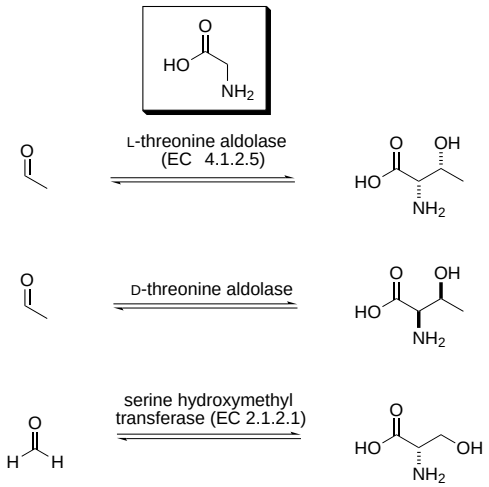
Scheme 18. a) DERA/RAMA-catalyzed tandem reaction. b) DERA/NeuAc aldolase catalyzed tandem reaction.



Scheme 19. DERA-catalyzed synthesis of key epothilone fragments. TBS = *tert*-butyldimethylsilyl, TIPS = triisopropylsilyl.

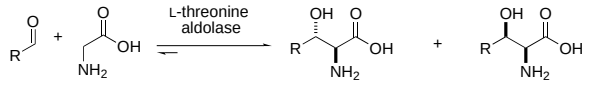
mixtures of *erythro* and *threo* products were formed, with the *erythro* product preferred (Table 2).

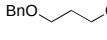
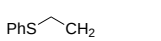
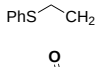
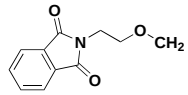
The use of hydroxyaldehydes gave complex mixtures of products as a result of interactions with free amino groups.



Scheme 20. Glycine-dependent aldolases and the reactions they catalyze.

Table 2. L-Threonine aldolase catalyzed synthesis of L-β-hydroxy α-amino acids.

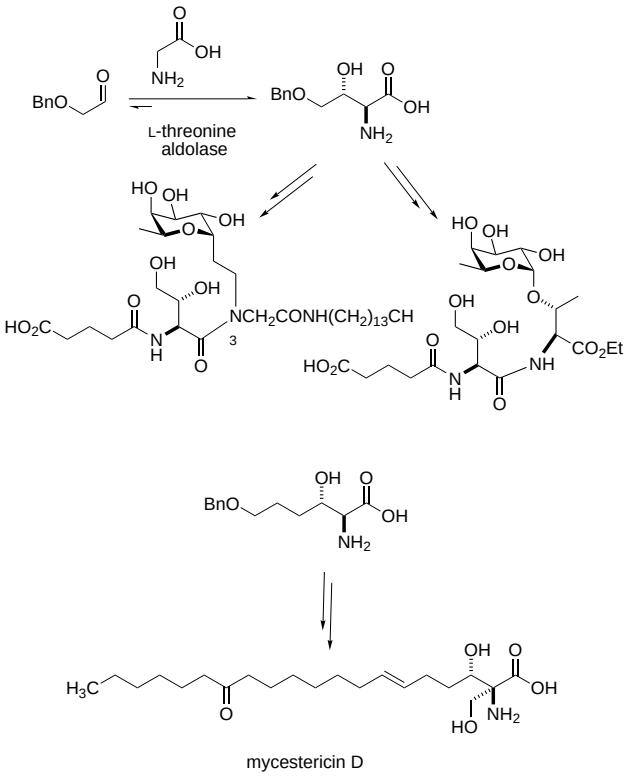


R	Yield [%]	*Erythro*:*threo*
CH_3	38	93:7
Ph	87	60:40
N_3CH_2	45–75	70:30 to 100:0
$BnOCH_2$	78	92:8
	53	53:47
	45	92:8
	80	50:50
	10	86:14

Protecting the hydroxyl group circumvented this problem. In general, heteroatom substitution in the α-position led to high *erythro*:*threo* ratios. As with the other types of aldolases, α,β-unsaturated aldehydes were not acceptor substrates; however, thiophenol-substituted aldehydes were accepted, which provided a potential route to unsaturated amino acids. The products resulting from the L-threonine aldolase catalyzed condensation of (benzyloxy)acetaldehyde and (benzyloxy)-butanal with glycine have been used in the synthesis of potent sialyl Le^x mimetics[54a,b] and the immunosuppressant mycestericin D (Scheme 21).[54c]

2.2. Catalytic Antibodies

In recent years catalytic-antibody technology has provided a method of developing new protein catalysts that catalyze a variety of reactions.[55] In the past several years monoclonal antibodies elicited against a number of haptens designed to

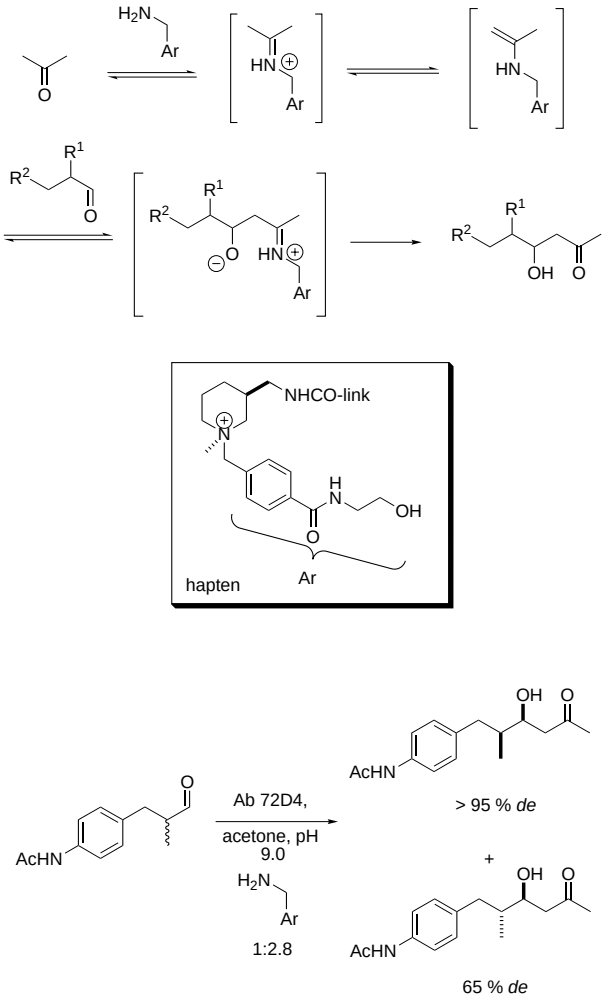


Scheme 21. L-Threonine aldolase route to sialyl Lewis^x mimetics. Bn = benzyl.

resemble the transition states of specific reactions have been shown to be capable of catalyzing those reactions with remarkable rate accelerations. By the appropriate design of the antigens, specific functional groups can be induced into the binding site of an antibody to perform general acid/base catalysis, nucleophilic/electrophilic catalysis, and catalysis by strain or proximity effects. To date, many new catalytic reactions, including those that are disfavorable or not attainable otherwise, or which have different reaction mechanisms or specificities compared to the corresponding enzymatic reactions, have been developed using the catalytic antibody approach. The antibodies are readily generated and prepared in large amounts. Aldolase catalytic antibodies developed recently have the ability to match the efficiency of the natural aldolases while accepting a more diverse range of substrates.

Initial progress in this area was made by developing antibodies that bind a primary amine cofactor as a mimic of the type I aldolases. The use of a designed hapten as a mimic of the transition state of the high-energy iminium ion resulted in the production of an antibody that catalyzed the aldol condensation of acetone and aldehyde acceptors (Scheme 22).[56] Even though no stereochemical information was built into the transition-state mimic, the antibody catalyzed the stereoselective addition to the *si* face of the aldehyde.

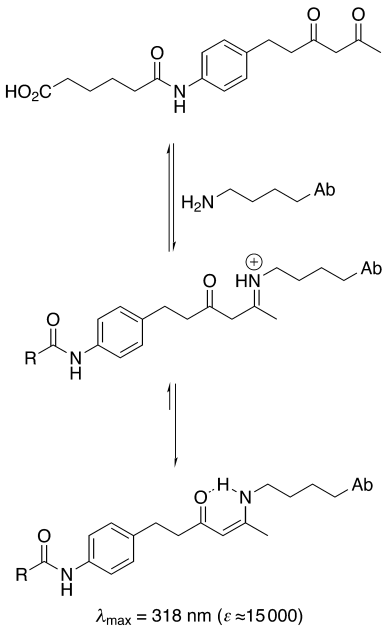
Further progress was made in this field with the development of the concept of reactive immunization.[57, 58] Rather than raise antibodies against a hapten that mimics the transition state, the antibodies were raised against a β-diketone that serves as a chemical trap to imprint the lysine-



Scheme 22. Preparation of the first generation of catalytic antibodies with aldolase activity. Ab = antibody.

dependent type I aldolase mechanism in the active site (Scheme 23).[59] The ε-amino group of a lysine side chain in the active site reacts with the β-diketone to give a β-ketoimine, which tautomerizes to the stable vinylogous amide. The formation of the vinylogous amide can be monitored by UV spectroscopy. By using this method two catalytic antibodies with aldolase selectivity, 38C2 and 33F12, were found and subsequently shown to have remarkable scope.[60] The structure of 33F12 has been determined and shown to have the Schiff base forming Lys residue buried in a hydrophobic pocket at the base of the binding site, which accounts for its lower pK_a value of 5.5 (Figure 3).[59]

Unlike natural aldolases, the catalytic antibodies were found to accept a wide range of ketone donor substrates (Figure 4a). Small aliphatic ketones were well tolerated; however, mixtures of products resulted with unsymmetrical ketones from the reaction at both α-positions. α-Heteroatom-substituted ketones showed much higher levels of regioselectivity, with reaction occurring almost exclusively at the carbon atom bearing the heteroatom. Interestingly, the regiochemistry of the reaction of fluoroacetone is opposite to that observed with the natural aldolase DERA, thus providing a complementary approach.



Scheme 23. Preparation of catalytic antibodies with aldolase activity by the reactive immunization approach.

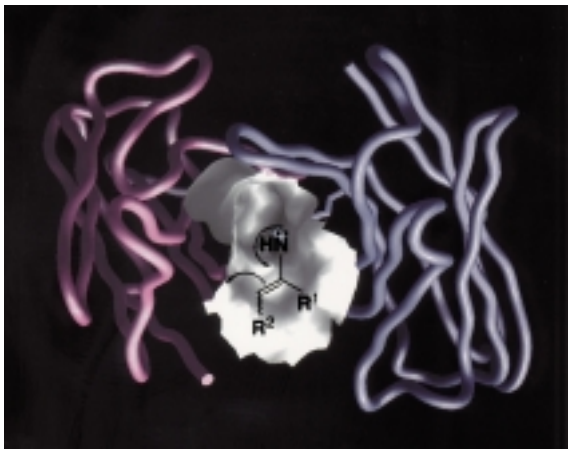


Figure 3. Spatial representation of the binding pocket of the Fab fragment of the catalytic antibody 33F12. The nucleophilic Lys^{H93} residue is found at the bottom of the hydrophobic environment.

A wide variety of aldehydes serve as acceptors (Figure 4b). In addition to aldehyde acceptors that resemble the hapten used to generate the antibody, simple aliphatic aldehydes are well tolerated. Polyhydroxylated aldehydes, such as glyceraldehyde, glucose, and ribose, were not substrates, most likely because of the hydrophobic nature of the active site. In contrast to the natural aldolases, aromatic and α,β-unsaturated aldehydes are excellent substrates.

The stereochemistry of the addition is donor dependent. When acetone is used as the donor substrate, addition occurs from the *si* face of the carbonyl group; with hydroxyacetone, addition occurs from the *re* face. The stereoselectivity is generally quite high, with *ee* values greater than 99% commonly observed. As a general rule, high enantioselectivity is observed with acceptors having an sp^2 center in the α-position. Somewhat lower enantioselectivities result from acceptors with an sp^3 center in the α-position.

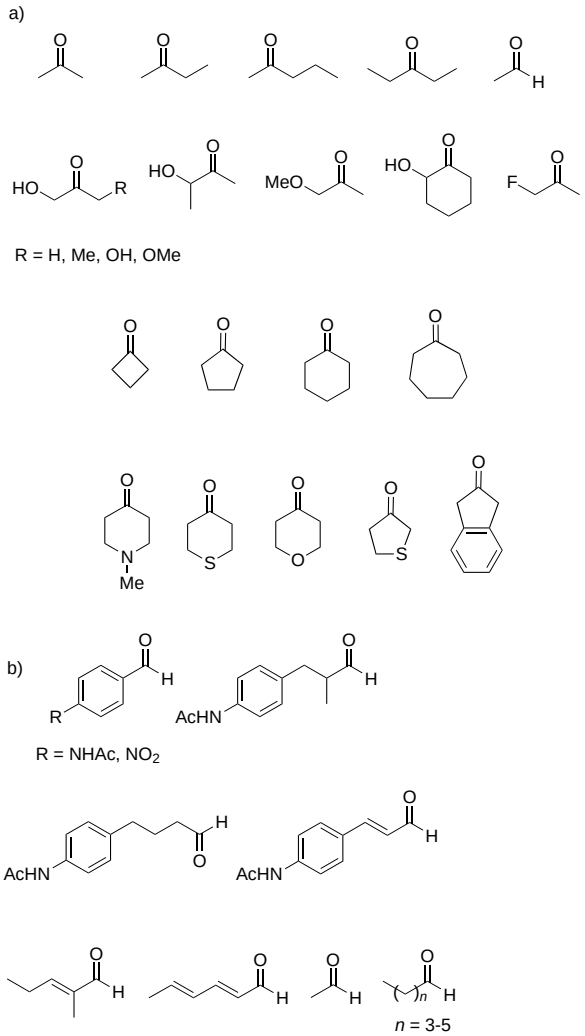
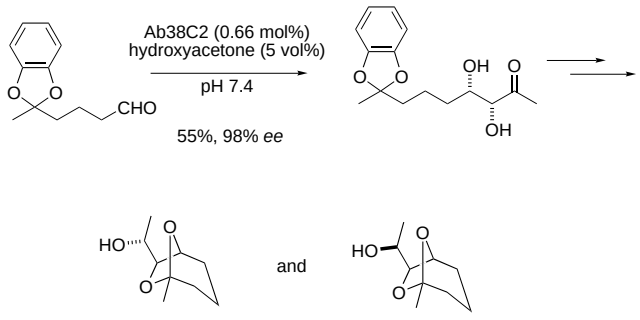
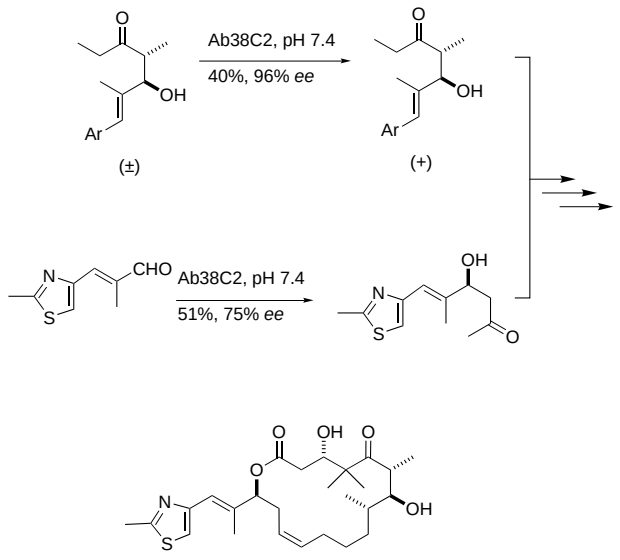


Figure 4. a) Donors and b) acceptors suitable as substrates for the catalytic antibodies with aldolase activity.

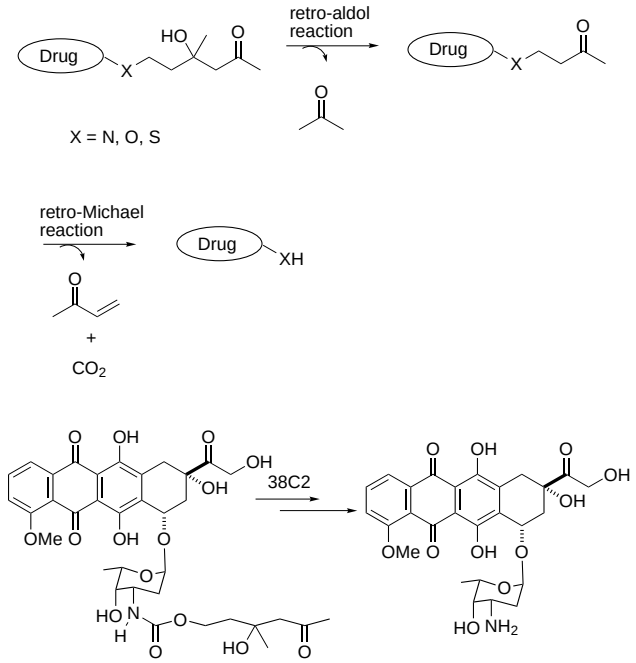
The utility of this method was demonstrated with the antibody-catalyzed aldolase approach to the brevicomins[61] (Scheme 24) and the epothilones[62] (Scheme 25). Antibody Ab38C2 is commercially available and has recently been used as a catalyst to activate prodrugs.[63] Generic, drug-masking groups can be selectively removed by sequential retro-aldol and retro-Michael reactions catalyzed by 38C2 (Scheme 26). The antibody was also used in the enantioselective retro-aldol reaction of tertiary aldols containing structurally varied



Scheme 24. Antibody-catalyzed approach to the brevocomins.

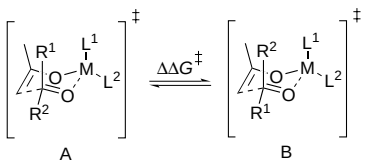


Scheme 25. Antibody-catalyzed approach to the epothilones.



Scheme 26. Top: prodrug activation by a sequential retro-aldol and retro-Michael reaction. Bottom: doxorubicin prodrug activation by antibody 38C2.

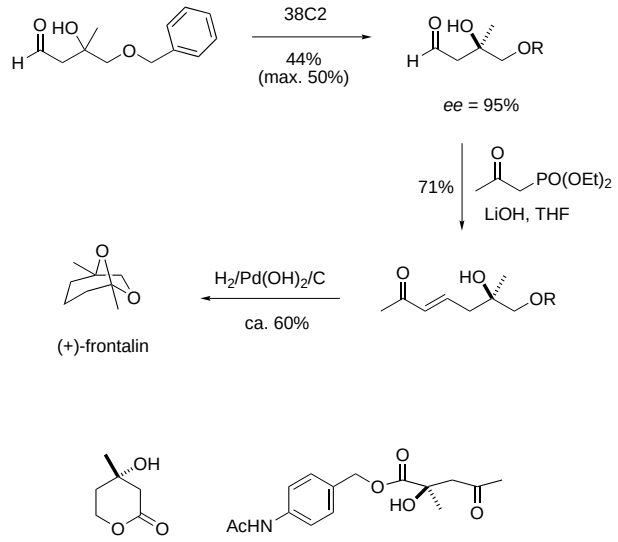
heteroatom-substituted quaternary carbon centers[64] to give enantiomerically enriched tertiary aldols, most with *ee* values greater than 95%. Synthesis of enantiomerically pure tertiary aldols using the catalytic asymmetric aldol reaction with ketone acceptors represents a significant challenge as the energy difference between the diastereomeric transition states complexed with a small ligand is relatively low (<0.5 kcal mol^{-1}) compared to the aldehyde acceptor case ($\Delta\Delta G^{\ddagger} \approx 1.7$ kcal mol^{-1}; Scheme 27). Several tertiary aldols prepared in this study have been used in the synthesis of (+)-frontalin, the side chain of saframycin H, and mevalonolactone (Scheme 28).



1) R^1 = H, R^2 = alkyl; $\Delta\Delta G^{\ddagger} = 1.7$ kcal mol^{-1}

2) R^1,R^2 = alkyl; $\Delta\Delta G^{\ddagger} = 0.1$–$0.5$ kcal mol^{-1}

Scheme 27. Proposed diastereomeric transition states in the synthesis of a tertiary aldol.



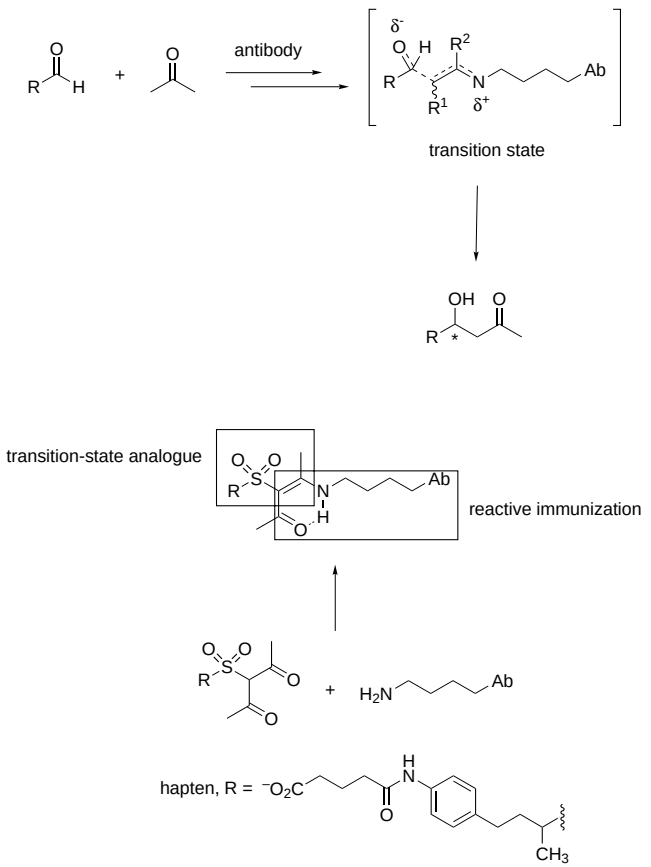
Scheme 28. Representative example of the synthesis of tertiary aldols using the catalytic antibody 38C2.

In order to further increase the repertoire and efficiency of the aldol reaction and to develop antibodies with complementary enantioselectivity, a β-diketone sulfone was used as the hapten[65] (Scheme 29). The tetrahedral geometry of the sulfone moiety in this hapten mimics the rate-determining, tetrahedral transition state of the C–C bond forming reaction and is thus expected to facilitate nucleophilic attack of the enaminone intermediate on the acceptor aldehyde. It was indeed demonstrated that more catalytic antibodies with a broad scope of reactions can be generated by using this approach. In addition, antibody 93F3 generated in this study was more efficient ($k_{cat} \approx 3$ min^{-1}) than and enantiocomplementary to 38C2, providing the unreacted (*S*)-aldol with $>96\%$ *ee*.

The mechanism-based approach to eliciting catalytic antibodies combined with the rapid, immune-selection process as illustrated in these studies provides a new exciting direction for catalyst design and development.

3. Chemical Methods

The search for simple catalysts that mimic the selectivity of biochemical methods yet offer more general substrate acceptance has been the subject of intense research in recent years.[66] Several excellent methods have been developed and



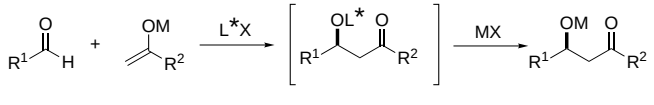
Scheme 29. Use of a β-diketone sulfone as a hapten to elicit catalytic antibodies.

for the purposes of this review, they will be grouped into the following categories: 1) activation of the acceptor; 2) activation of the donor; 3) simultaneous activation of the donor and acceptor.

3.1. Acceptor Activation

The catalytic activation of the acceptor aldehyde toward the addition of a silyl enol ether, commonly referred to as the Mukaiyama reaction,[67] has been a particularly successful means of performing aldol reactions. Since the initial discovery[68] that chiral Lewis acids promote enantioselective addition to the activated aldehyde partner, steady improvements have been realized.

Mechanistically, the catalyst coordinates to the aldehyde creating an asymmetric environment, which is then attacked by an enolate species from the less-hindered face to produce the aldol adduct. As shown in Scheme 30, an important exchange reaction between L* and M must then occur to regenerate the catalyst and for this reason the proper choice of L* is very important. A successful catalyst must coordinate strongly enough with the oxygen atom of the acceptor aldehyde to form a tight transition state for effective transfer of chirality and at the same time not form such a strong bond with the resulting alkoxide that turnover does not occur. A second common problem that must be overcome is the generation of M^+,[69] which may also catalyze the reaction through an achiral pathway and lead to decreased enantioselectivities. A number of systems have been developed using both metallic and nonmetallic Lewis acids to address these issues.



Scheme 30. The Mukaiyama reaction.

3.1.1. Tin Complexes

The first successful catalytic asymmetric Mukaiyama reactions were achieved with tin(II) complexes.[70] The catalysts are prepared in situ from the addition of tin(II) triflate (triflate = Tf = trifluoromethanesulfonate) to a chiral diamine derived from L-proline. Figure 5 shows the more successful diamines.

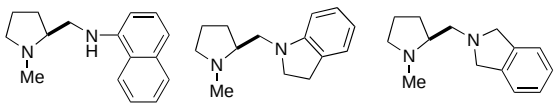
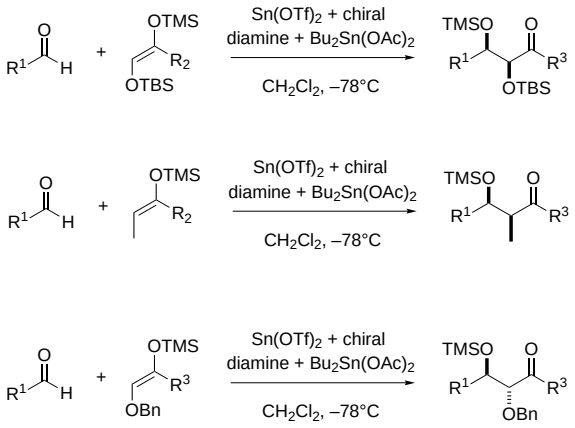


Figure 5. Chiral diamines used in the preparation of Sn(II) complexes that act as catalysts in the asymmetric Mukaiyama – aldol reaction.

The reaction between aldehydes and ketene silyl acetals prepared from either esters or thioesters is highly enantioselective with *ee* values usually greater than 98%. A cofactor, such as dibutyltin diacetate,[71] is required for high levels of enantioselectivity. The cofactor has an affinity for silicon and presumably serves to connect the silyl enolate with the promotor,[72] which leads to a tighter transition state and more effective transfer of chirality. NMR studies have shown that there is no metal exchange from silicon to tin in the silyl enol ether, which implies that the reaction does not proceed through a tin enolate.[73]

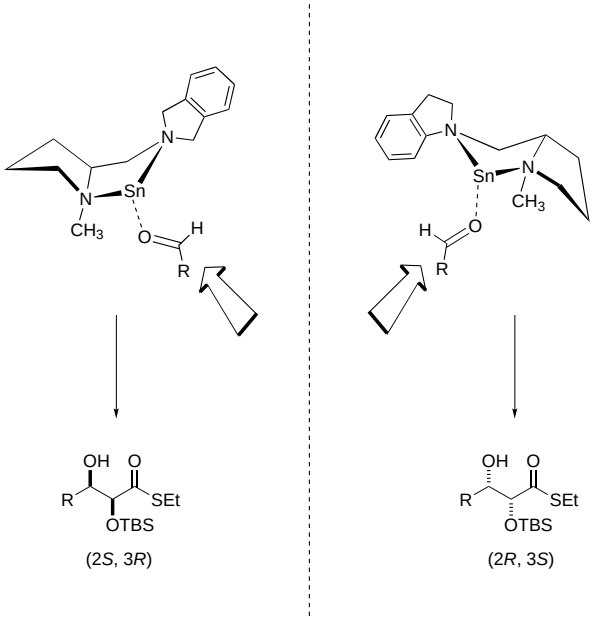
Both *syn* and *anti* diol products are possible with the proper choice of ketene silyl acetal (Scheme 31). Noncoordinating α-



Scheme 31. Tin(II)-catalyzed asymmetric Mukaiyama – aldol reaction. TMS = trimethylsilyl.

substitutents, such as alkyl and *tert*-butyldimethylsiloxy, are stereoselectively converted into the *syn* products. Coordinating subtituents, for example an α-benxyloxy group, coordinate to the tin and lead to the formation of *anti* products.[74] A wide range of aldehydes can be used: aliphatic, aromatic, and α,β-unsaturated aldehydes all afford products in high yield and with high levels of enantioselectivity.

The origin of the selectivity arises from the conformation of the tin(II)-diamine complex, which adopts a bicyclo[3.3.0]octane-like structure (Scheme 32).[75] The absolute configuration of the reaction can be controlled by the appropriate



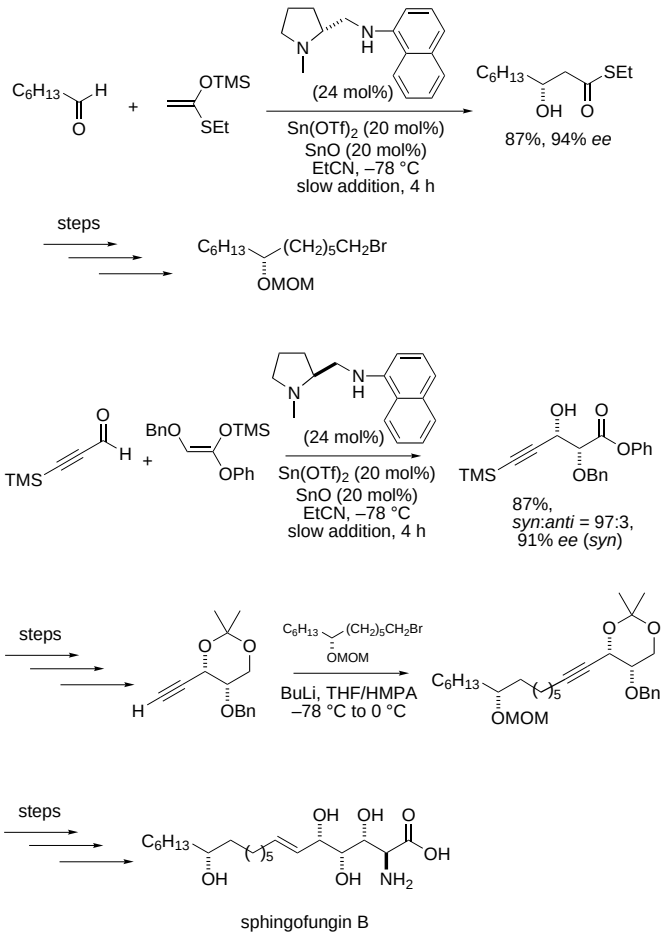
Scheme 32. Both enantiomers formed from catalysts derived from L-proline.

choice of chiral diamine. Remarkably, simply changing the point of attachment of a benzene ring leads to a complete reversal of configuration.[73] By changing the conformation of the catalyst the indoline and isoindoline groups provide pseudo-enantiotopic transition states (Scheme 32) and thus opposite stereoisomers. This catalyst system was successfully employed as a key step in the total synthesis of the antifungal sphingofungin natural products (Scheme 33)[76a] and febrifugine/isofebrifugine with antimalarial activity.[76b]

3.1.2. Titanium Complexes

Considerable attention has been paid to titanium(IV) catalysts for the asymmetric Mukaiyama aldol reaction.[69, 77–81] The most successful catalysts are derived from a titanium(IV) source and an (*R*)- or (*S*)-BINOL-type ligand (Figure 6), although some effort has been devoted to examining the effects of other ligands.[69, 74]

The simple BINOL catalysts are effective catalysts for the aldol reaction of aldehydes and ketene silyl acetals of thioesters (Scheme 34).[78, 81] Aromatic, aliphatic, α,β-unsaturated, α-heteroatom substituted, and α-branched aldehydes are all well tolerated, and afford the corresponding aldol



Scheme 33. Chiral tin(II)–diamine-catalyzed aldol addition approach to the sphingofungins. HMPA = hexamethyl phosphoramide.

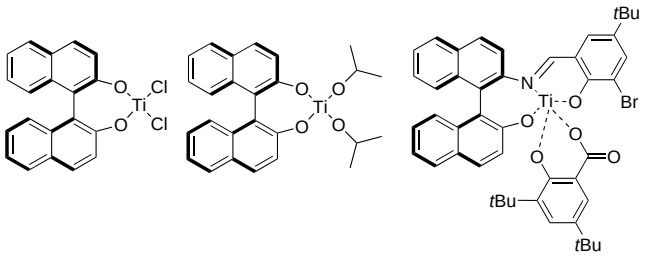
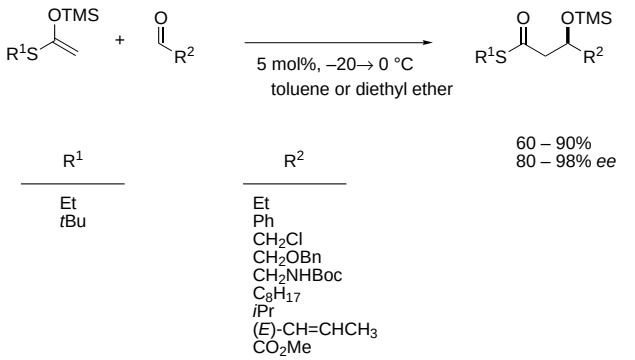
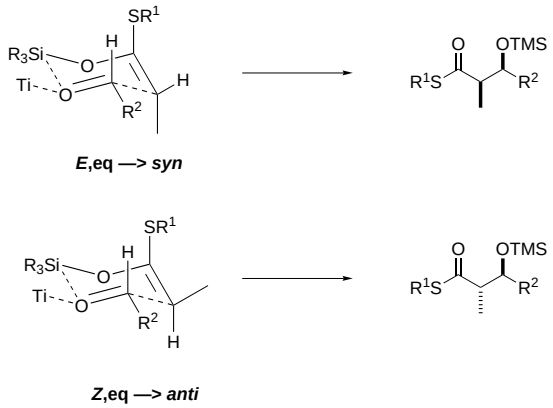


Figure 6. Titanium catalysts used successfully in the asymmetric Mukaiyama–aldol reaction.



Scheme 34. BINOL–titanium(IV)-catalyzed aldol reaction. Boc = *tert*-butoxycarbonyl.

adducts in good to excellent yields. Several factors contribute to the generally excellent enantioselectivity (up to 98% *ee*). The size of the group on the sulfur atom of the thioester-derived ketene silyl acetal is important: the larger *tert*-butyl group results in higher *ee* values than the smaller ethyl group.[81] Enantiofacial selectivity is influenced by the polarity of the solvent: the selectivity being enhanced in the toluene than the more polar solvents dichloromethane, propionitrile, and nitroethane.[81] However, diethyl ether also appears to be a good solvent in some cases.[78] Enantiofacial selectivity is quite predicatable, with the (*R*)-BINOL catalyst generally affording the *R*-configured product and the (*S*)-BINOL catalyst the *S*-configured product. With α-substituted ketene silyl acetals the relative configuration of the product is influenced by the olefin geometry: *E* isomers lead to *syn* products and *Z* isomers to *anti* products. A cyclic transition state model can be used to explain the stereospecificity (Scheme 35).[81]

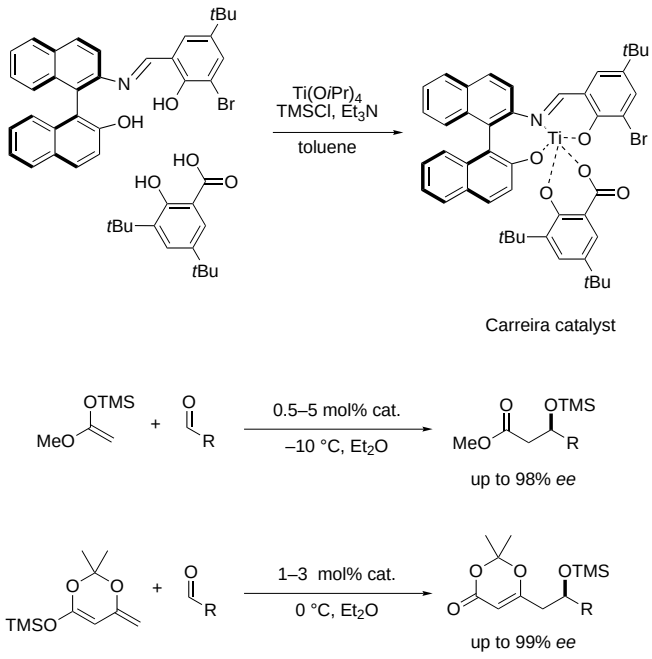


Scheme 35. Model of the silatropic ene transition state.

Further improvement was made with the Carreira catalyst,[80] which is prepared in situ by combining the tridentate ligand derived from BINOL, Ti(O*i*Pr)$_4$, and salicylic acid in the presence of trimethylsilyl chloride and triethyl amine (Scheme 36). This titanium species catalyzes the aldol reaction of a wide variety of aldehydes with ketene silyl acetals derived from esters and silyl dienolates.[82a] The reactions can be performed with as little as 0.5 mol% of catalyst at $-20\,^{\circ}C$. The salicylic acid probably serves to trap and transfer "Me_3Si^+", which is known to catalyze the reaction through an achiral pathway,[69] and thereby improves the enantioselectivity of the reaction.

The reaction of ketene silyl acetals derived from esters affords β-hydroxy ester products in high yields and up to 98% *ee* (Scheme 36). Aliphatic, aromatic, and unsaturated aldehydes are excellent substrates, with alkenyl and alkynal aldehydes being particularly good substrates. The silyl dienolate is an excellent donor substrate and results in the formation of acetoacetate adducts, also in high yield and enantioselectivity.[82a] This catalyst has been used in the synthesis of antibiotics such as macrolactin A[82b] and roflamycoin.[82c]

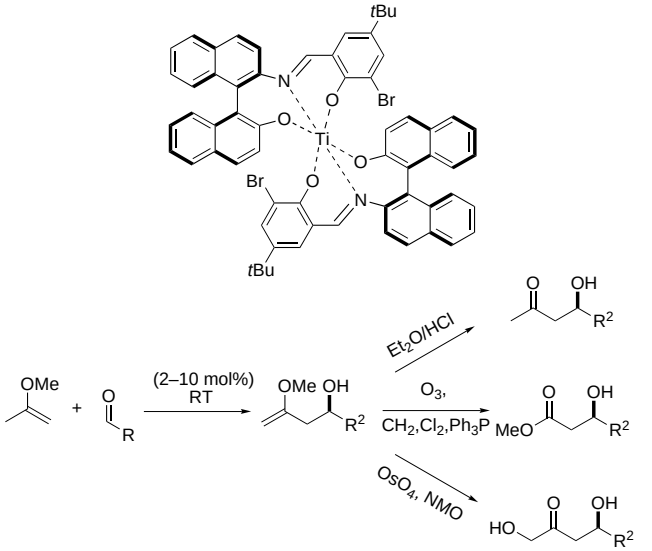
Solvent choice is an important consideration. The reaction is generally conducted in a nonpolar solvent such as toluene or



Scheme 36. Top: Preparation of the Carreira catalyst. Bottom: Reactions performed with the Carreira catalyst.

benzene to reduce the possibility of producing "Me_3Si^+", although high enatioselectivity is also observed in diethyl ether. Polar aprotic solvents such as dichloromethane and tetrahydrofuran, which favor the formation of "Me_3Si^+", result in a significant loss of enantioselectivity.

A similar catalyst derived from two equivalents of tridentate ligand in the presence of a hindered amine base catalyzes the aldol reaction of the commercially available 2-methoxypropene with a wide variety of aldehydes in 79–99% yields and up to 99% *ee* (Scheme 37).[83] Upon acid workup, β-hydroxyketone adducts are isolated. In the absence of an acid

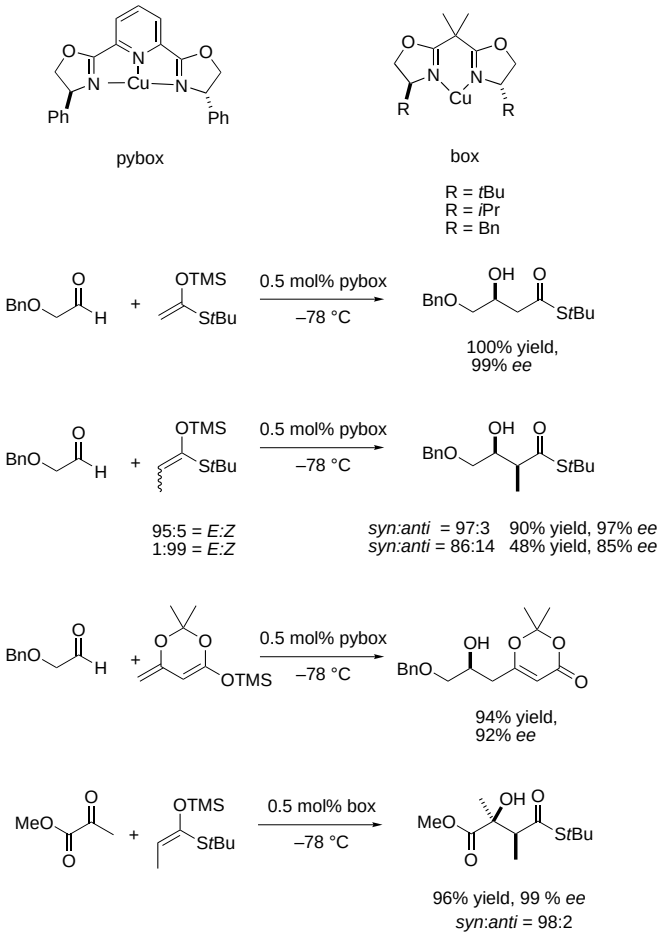


Scheme 37. Titanium-catalyzed asymmetric aldol reaction with 2-methoxypropene. The titanium catalyst is shown at the top. NMO = 4-methylmorpholine *N*-oxide.

workup, the vinyl ether intermediate can be isolated and further converted into a number of useful products.

3.1.3. Copper Complexes

Bis(oxazolinyl)copper(II) complexes have been shown to be effective chiral Lewis acid catalysts for the Mukaiyama aldol reaction of ketene silyl acetals (Scheme 38).[84, 85] Acceptor aldehydes with α-subtitution capable of chelation are required; α-benzyloxyaldehydes and pyruvate esters are very good substrates and afford the corresponding aldol adducts in very high yield (85–100%) with excellent enantiofacial selectivity (92–99% *ee*). The reaction with pyruvate esters provides an important method for the preparation of a tertiary alcohol.



Scheme 38. Copper-catalyzed asymmetric aldol reaction.

A five-membered chelate is essential; the reaction with β-(benzyloxy)propionaldehyde gives a racemic product. ESR studies reveal a square pyramidal catalyst–aldehyde complex.[84a] Two modes of binding are possible for the aldehyde: the stronger binding position lies in the plane of the ligands, and the weaker binding site in the axial configuration, which leads to a single mode of coordination of the substrate (Figure 7). Attack of the donor enolate occurs from the less sterically hindered *si* face.

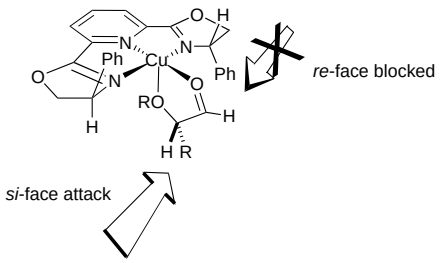


Figure 7. Complex formed between the copper catalyst and the aldehyde.

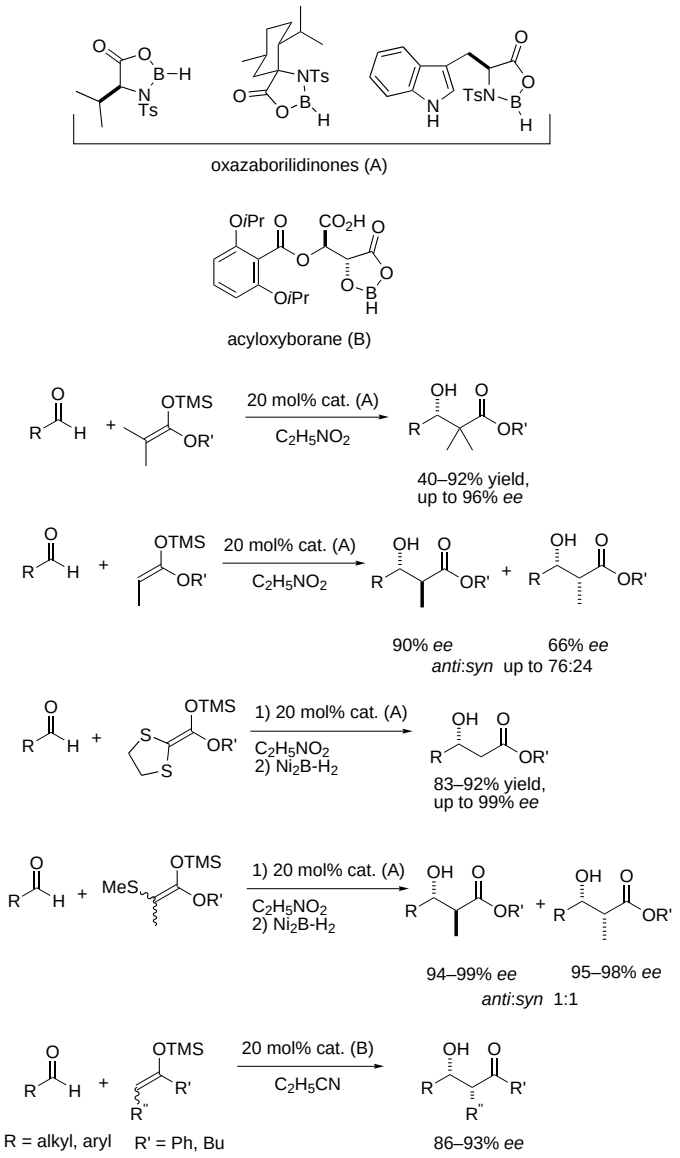
Both (*E*)- and (*Z*)-α-substituted ketene silyl acetals afford predominantly the *syn* adducts, but a significant reduction in both yield and facial selectivity is observed with the *E* isomer.[84a, 85] The BINAP–copper(II) complex developed by Carreira has been investigated mechanistically[86a] and applied to the synthesis of the polyol fragment of amphotericin.[86b] Remarkably, replacing Cu^{II} with Sn^{II} in the complex resulted in the highly selective formation of the *anti* adducts in the reaction with methyl pyruvate (*anti*:*syn* up to 99:1; up to 99% *ee*).[87] Recently, the copper(II) system complexed with bis(oxazoline) was shown to function in aqueous systems such as water and water/alcohol, although the enantiofacial selectivity and efficiency are lower than that in aprotic solvents.[85]

3.1.4. Boron Complexes

Achiral boron catalysts such as dibutylboron triflate (Bu_2BOTf)[88] were used in the synthesis of the anticancer agent altohyrtin C. Chiral boron catalysts, such as chiral oxazaborolidinones[89–91] and chiral (acyloxy)boranes,[92] have been used to catalyze the asymmetric aldol condensation of aldehydes with ketene silyl acetals and silyl enol ethers (Scheme 39). Both catalysts are prepared by simple addition of borane to either α-amino acids or tartaric acid derivatives. The reaction catalyzed by boranes derived from (*S*)-amino acids and natural tartrate lead to (*R*)-aldol adducts. Recently, a polymer-supported chiral oxazaborolidinone was described that demonstrated lower levels of enantioselectivity.[93]

In the reaction with ketene silyl acetals, α-substitution is important for high levels of enantioselectivity. The dimethyl- and monomethyl-substituted ketene silyl acetals are highly effective donors. With oxazaborilidinone catalysts, monosubstituted ketene silyl acetals give predominantly the *anti* products, but the enantioselectivity is somewhat lower. In contrast, the (acyloxy)boranes are highly *re*-face-selective on the aldehyde and *syn*-selective on the product in the reaction of silyl enol ethers, regardless of the starting enol geometry.

The parent unsubstituted ketene silyl acetal leads to products with greatly decreased enantioselectivity. To circumvent this problem, sulfur substituents can be introduced to provide the steric bulk required for high levels of enantioselectivity, then removed with a nickel borohydride reagent to provide the corresponding products in high yield and enantioselectivity. This approach has been used quite successfully in a short asymmetric synthesis of a portion of bryostatin.[94] A similar reaction can be accomplished with sulfur-substituted

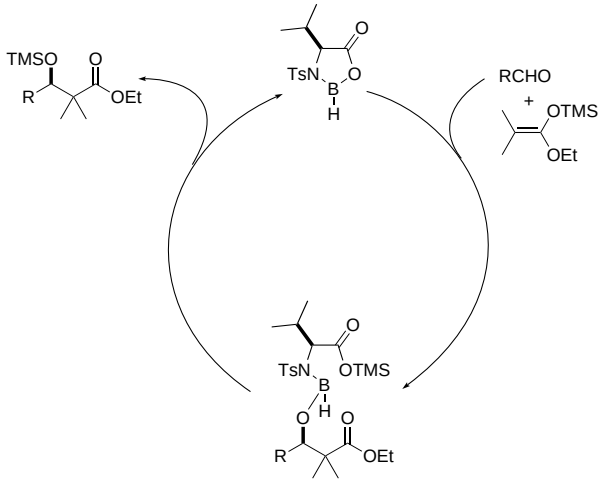


Scheme 39. Oxazaborolidinone-catalyzed asymmetric aldol reaction. Ni_2B-H_2 = nickel borahydride, Ts = toluene-4-sulfonyl.

propionate ketene silyl acetal. Both *syn*- and *anti*-aldol adducts are obtained with excellent enantioselectivity. However, a 1:1 *syn*:*anti* ratio results from a scrambling of the C2 stereochemistry during the radical desulfurization.

The tryptophan-derived oxazaborolidinone[90] performs best with terminal trimethylsilyl enol ethers derived from methyl ketones and a range of aldehydes to afford β-hydroxyketone products with high enantiomeric excess. Ketene silyl acetals react with poor enantioslectivities using this catalyst.

Mechanistically, an intramolecular B-Si exchange transfer involving the ligand may facilitate the important silicon transfer (Scheme 40). The metal affinity between aldehyde, enolate, and chiral ligand will thus affect catalyst turnover. The enantioselectivity can be explained by invoking a conformation of the aldehyde bound to the oxazaborolidinone that is fixed by a hydrogen-bonding interaction between the Lewis acid and the aldehyde (Figure 8).[95]



Scheme 40. Proposed mechanism for the oxazaborolidinone-catalyzed aldol reaction.

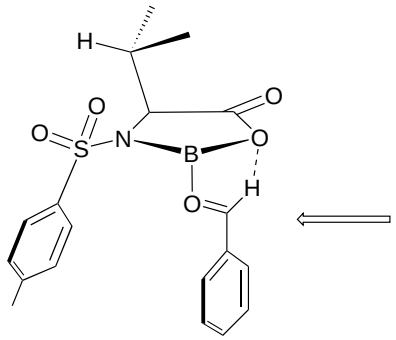
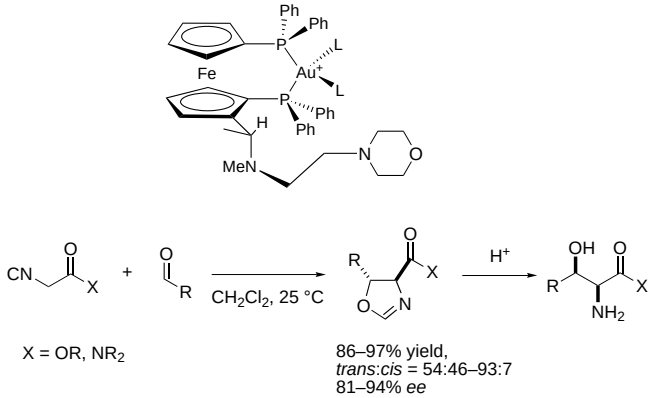


Figure 8. Three-dimensional structure of the aldehyde – oxazaborolidinone complex.

3.1.5. Gold and Silver Complexes

The first example of a catalytic asymmetric aldol reaction was the gold(I)-catalyzed reaction of an α-isocyanoacetate and an aldehyde reported in 1986.[96] The reaction is both diastereo- and enantioselective and gives *trans*-oxazolines with excellent enantioselectivities. These oxazolines can be converted into the corresponding *syn*-β-hydroxy-α-amino acids[97a] by hydrolysis (Scheme 41).



Scheme 41. Gold(I)-catalyzed reaction of α-isocyanocarboxylates or -amides with aldehydes.

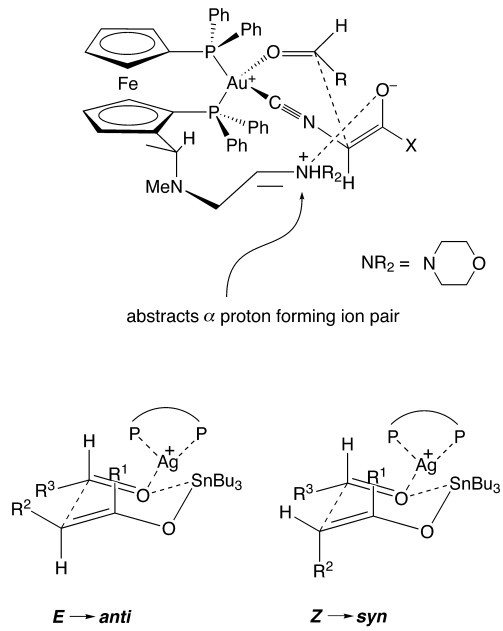


Figure 9. Proposed structure of the transition state of gold- and silver-catalyzed aldol reactions.

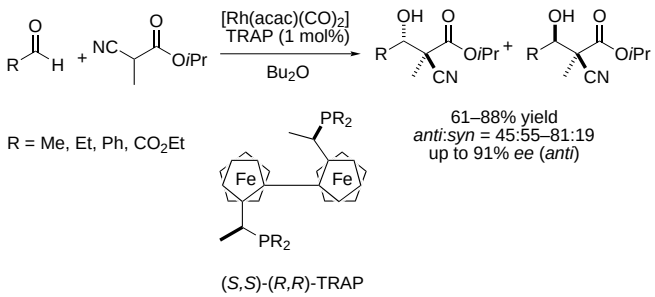
The high selectivity has been explained by a proposed transition state structure,[97b] where the terminal amino group abstracts one of the active methylene hydrogen atoms of the gold-coordinated isocyanoacetate derivative to form an ion pair between the enolate anion and the ammonium cation. The amine sidearm is important for high levels of enantioselectivity. The aldehyde binds to the gold center away from the sidearm (Figure 9). The aldol adduct immediately cyclizes to the oxazoline, which no longer coordinates to the gold center, thereby regenerating the catalyst. This catalytic system can also be considered as one in which both donors and acceptors are activated. A representative BINAP/AgOTf catalyst system reported by Yamamoto[98] for the reaction of tin enolates with aldehydes suggests that Ag is another effective metal Lewis acid catalyst. Transition-state models have been used to explain the *anti* selectivity from the (*E*)-enolate and the *syn* selectivity from the (*Z*)-enolate (Figure 9).

3.2. Donor Activation

Catalytic activation of the donor rather than the acceptor provides an alternative to the asymmetric Mukaiyama aldol reaction. Numerous approaches have been developed that incorporate a variety of catalysts from organometallic reagents to phosphoramide Lewis bases.

3.2.1. Rhodium Complexes

A rhodium-catalyzed asymmetric aldol reaction was described recently.[99] A rhodium(I) complex coordinated with the *trans*-chelating chiral diphosphane TRAP promotes the enantioselective condensation of α-cyanopropionates with aldehydes (Scheme 42). Bulky esters are required for high levels of enantioselectivity. The enantioselectivity is also



Scheme 42. Rhodium(I)–TRAP-catalyzed reaction of α-cyanocarboxylates or -amides with aldehydes.

dependent upon the choice of acceptor aldehyde. Simple aliphatic aldehydes afford products with modest to good enantioselectivities (up to 86% *ee*), while glyoxaldehyde results in the highest level of selectivity (91% *ee*). The *anti* isomers are generally formed preferentially, suggesting an open, anti-periplanar transition state (Figure 10).

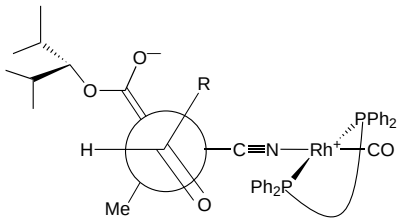
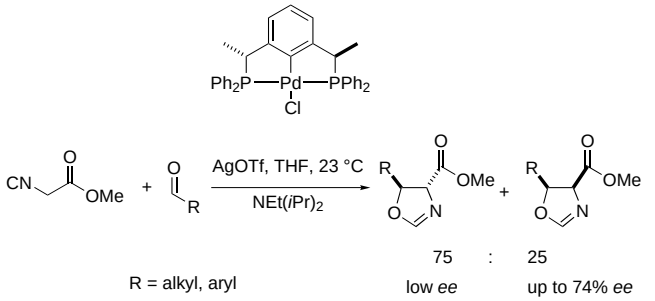


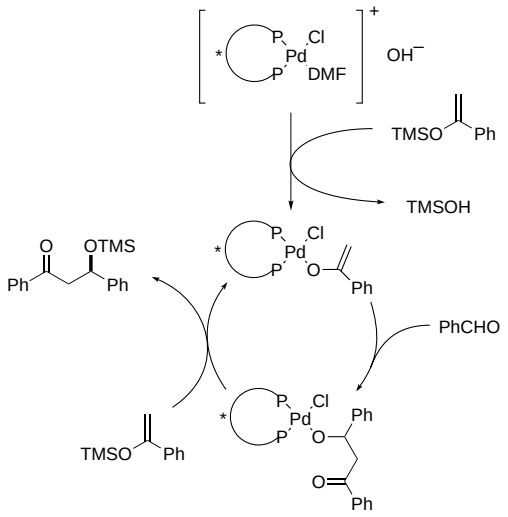
Figure 10. Proposed transition state of rhodium–TRAP-catalyzed aldol condensation of α-cyanoaldehydes.

3.2.2. Palladium Complexes

Palladium catalysts have shown an unsurpassed degree of flexibility in the reactions they catalyze. Two catalyst systems have been recently developed which catalyze the asymmetric aldol condensation. A palladium(II) complex with chiral PCP-type tridentate ligands has been shown to catalyze the asymmetric aldol condensation between methyl isocyanoacetate and aldehydes[100] (Scheme 43). Similar to the gold(I) catalyst, the reaction produces predominantly the *trans*-oxazoline; however, in contrast to the gold catalyst the *cis* isomer is formed in higher *ee* values (up to 74%). The deeper chiral pocket of the chiral PCP-type ligands effects the enantioselective bond formation without the need for the pendent amine that is required for the gold catalyst. Both aromatic and alkyl aldehydes were examined, with higher enantioselectivities observed with aliphatic aldehydes.

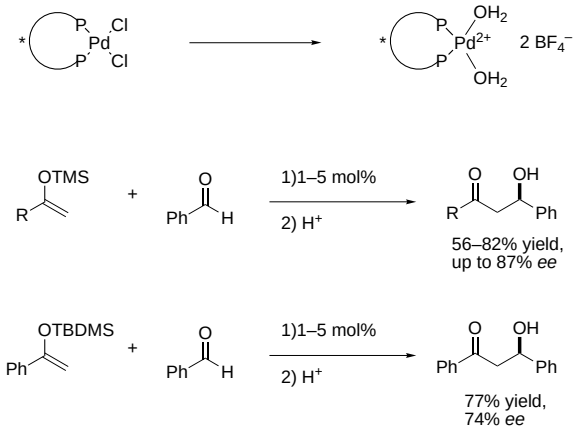


Scheme 43. PCP-Pd^{II}-catalyzed asymmetric aldol reaction.



Scheme 44. Pd^{II}-catalyzed asymmetric aldol reaction by formation of a Pd^{II}-enolate.

A second catalyst system based on palladium was described which proceeds through formation of a transition metal enolate (Scheme 44).[101a] The mechanism is similar to that of the achiral rhodium(I) complex studied extensively by Bergman, Heathcock, and Slough.[102] A dichloropalladium(II) complex with BINAP catalyzed the aldol condensation of silyl enol ethers derived from ketones with aldehydes. The reaction produces, after hydrolysis of the intermediate silyl ether, β-hydroxyketones in excellent yields and up to 78% *ee*. The air- and moisture-stable diaquapalladium(II)–BINAP complex, prepared from the dichloro complex, was shown to effect the same transformation with *ee* values up to 87% (Scheme 45). Of particular importance is the ability of this catalyst to activate *tert*-butyldimethylsilyl enol ethers, which are less susceptible to hydrolysis and therefore easier to purify and isolate. The X-ray crystal structure of the catalyst has been determined.[101b]



Scheme 45. Pd^{II}-catalyzed asymmetric aldol reaction.

3.2.3. Phosphoramides

In contrast to the organometallic reagents described above, phophoramides act as Lewis bases to catalyze the aldol reaction by coordinating temporarily to the electrophilic silicon atom of trichlorosilyl enolates, thus generating a strongly activated donor which reacts with a variety of aldehydes (Figure 11). In this process, the silicon center is able to expand its valence by two to coordinate both the aldehyde and the chiral ligand. In addition to silicon, tin, titanium, zirconium, and aluminum also possess such valence expansion properties. The ligand used in such a process should not be too nucleophilic to affect cleavage of the O–Si bond.[103] This effect was first noticed with hexamethyl phosphoramide (HMPA), which was found to catalytically accelerate the aldol reaction.[103] Chiral phosphoramides have been used successfully to afford aldol adducts in excellent yields with a high degree of enantioselectivity (up to 97% *ee*) (Scheme 46).[103, 104] The diphenyl-substituted catalyst was found to give the optimal results.

The phoshphoramide-catalyzed reaction of (*E*)-enolates affords mostly *anti*-aldol adducts (*anti*:*syn* ratio up to >99:1), which is in sharp contrast to the uncatalyzed reaction, where

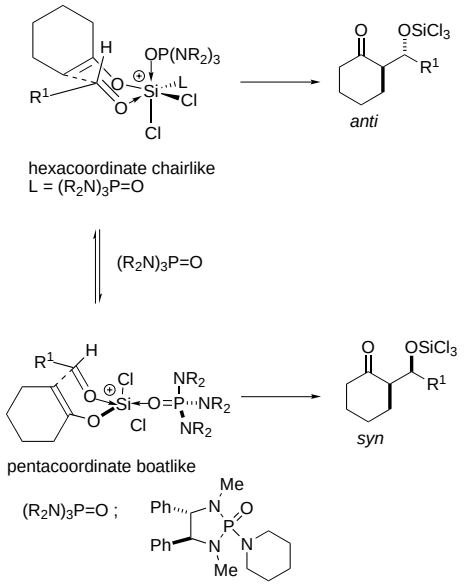
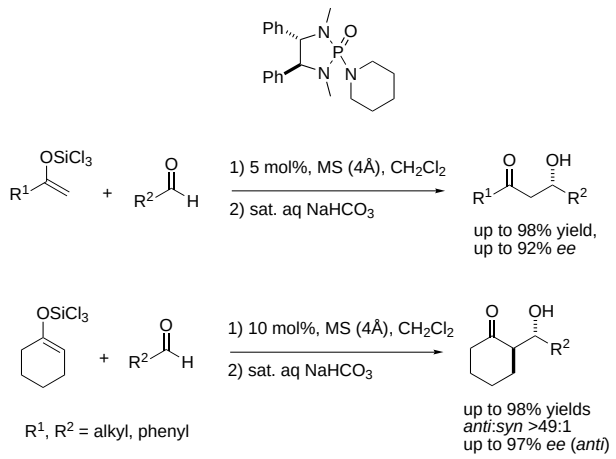


Figure 11. Proposed phosphoramide-mediated activation of trichlorosilylenolates. The chairlike hexacoordinate transition state gave the *anti* product, while the boatlike pentacoordinate transition state gave the *syn* product.



Scheme 46. Phosphoramide-catalyzed asymmetric aldol reaction. MS = molecular sieves.

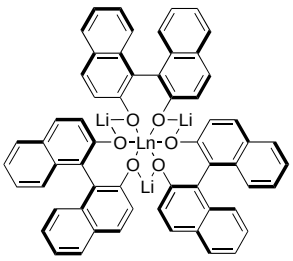
the *syn* isomer is the major product. It has been proposed that only the *anti* diastereomer proceeds through the hexacoordinate chairlike siliconate species coordinated to two chiral ligands.[105] The *syn* product arises from the pentacoordinate boat transition state with one chiral ligand (Figure 11).[105b] Further structural studies on the chiral ligand complexed with tin and benzaldehyde reveal a torsion around the P–N(piperidinyl) bond, which provides some insights into the origin of selectivity.[105c]

Simple alkyl- and aryl-substituted donor trichlorosilyl enol ethers and acceptor aldehydes function well in the reaction. More electron-rich aldehyde acceptors form a tighter transition structure, which leads to higher enantio- and diastereoselectivities.[105] The slow addition of aldehyde is crucial for high levels of diastereoselectivity.

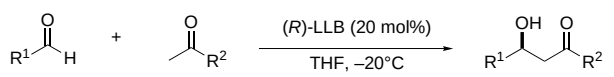
3.3. Activation of Both Donor and Acceptor (Bifunctional Catalysts)

While catalytic activation of aldehyde acceptors by chiral Lewis acids has achieved great success in the asymmetric aldol condensation, pre-conversion of the donor to a more reactive species such as enol silyl ether, enol methyl ether, or ketene silyl acetal is a necessity. Two catalysts have been developed that mimic the mechanism of the type II aldolases, where both Lewis acidic and Brønstead basic sites participate in the reaction, which catalyze the reaction of unmodified ketones with aldehydes.

The multifunctional catalyst LLB catalyzes the direct transformation of aldehydes and ketones to aldol adducts (Scheme 47).[106] The catalyst incorporates a central lanthanum atom, which serves as a Lewis acid, and a lithium binaphthoxide moiety, which serves as a Brønsted base. The reaction is speculated to proceed through the mechanism shown in Scheme 48. The synergistic effect of both functionalities allows the reaction to proceed without the need for any other activation of the starting materials. The reaction affords aldol adducts in good to excellent yields (45–90%) with moderate to high levels of enantiomeric excess (up to 94% *ee*). Higher yields and *ee* values are observed when excess ketone is used.

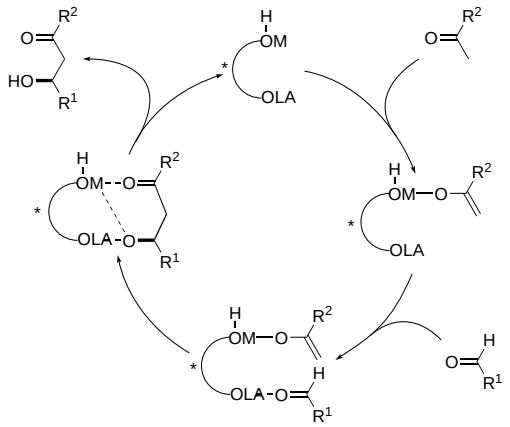


LLB



R^1	R^2
*t*Bu	Ph
$PhCH_2C(CH_3)_2$	1-naphthyl
cyclohexyl	CH_3
*i*Pr	Et
$Ph(CH_2)_2$	

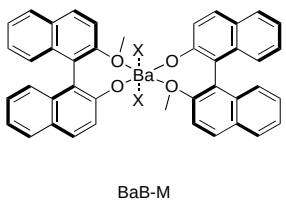
Scheme 47. LLB-catalyzed aldol condensation of ketones with aldehydes.



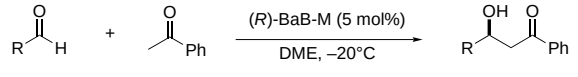
Scheme 48. Proposed mechanism of bifunctional catalysts. LA = Lewis acid, M = metal of the Brønsted base.

A major shortcoming of this catalyst is the need for excess ketone and long reaction times. The catalytic activity of LLB can be enhanced by the addition of lithium hydroxide, which forms an LLB · LiOH heteropolymetallic complex.[107] Recently, it was found that the addition of KOH (generated in situ from the reaction of potassium hexamethyldisilazane with water) results in a heteropolymetallic complex that rapidly promotes the aldol reaction when used in small amounts (3 mol%).[108] Cyclopentanone can be used directly for a diastereoselective aldol reaction without modification. This catalyst has been used in the synthesis of key fragments for the synthesis of epothilone A and bryostatin 7.[108] Mechanistic studies of the reaction suggest that deprotonation of the ketone is rate-determining and the water molecule may coordinate to La and K during the catalytic process.[108]

A similar catalyst derived from barium phenoxide was developed to eliminate the shortcomings of the LLB catalyst (long reaction times, excess ketone).[109] The catalyst, BaB-M, prepared from $Ba(OiPr)_2$ and BINOL-Me, effects the enantioselective aldol condensation of acetophenone and various aldehyde acceptors (Scheme 49). Reaction times are greatly



BaB-M



R
*t*Bu
$PhCH_2C(CH_3)_2$
cyclohexyl
*i*Pr
$BnOCH_2C(CH_3)_2$
$BnOC(CH_3)_2$

Scheme 49. BaB-M-catalyzed aldol condensation of ketones with aldehydes. DME = 1,2-dimethoxyethane.

reduced compared to those with the LLB catalyst. In addition to tertiary aldehydes, secondary aldehydes with acidic α-hydrogen atoms are suitable substrates and result in the cross-aldol condensation without the formation of self-aldol adducts. The enantioselectivities are currently modest (up to 70%), but there is great possibility for further improvement of this catalyst. Platinum–acyl complexes coordinated with BINAP or other phosphane ligands have been developed for the enantioselective aldol addition of ketene silyl acetals to aldehydes.[110] The presence of oxygen and water during activation of the catalyst is required to achieve enantioselectivity.

4. Summary and Outlook

The progress toward efficient, selective, and predictable catalysts in the asymmetric aldol reaction has been astounding. While aldolases and catalytic antibodies can tolerate substrates with unprotected functional groups and perform the reaction in aqueous solution, the chemical aldol reactions work well in various organic solvents with a wide range of less polar substrates. A high degree of complimentarity thus exists between biochemical catalysts and chemical catalysts. It is now possible to control the stereochemical outcome to produce any relative and absolute configuration desired. There is, however, room for improvement. There are still limitations with regard to the scope and catalyst preparation, which may present additional difficulties, especially on large scales.

The catalytic-antibody approach based on "reactive immunization" has been revolutionary, providing a new direction to the development of biochemical catalysts with a broader scope in substrate specificity and sterospecificity. In addition, recent structural studies of the aldolases and catalytic antibodies combined with techniques in molecular biology provide means to improve the preparation of catalysts and change the scope of the catalytic reactions, especially with regard to substrate acceptability, which renders them generally more useful. The future design of chemical catalysts that mimic the action of the aldolases offers great opportunity for the development of simple systems with high efficiency and selectivity and broad specificity. It is hoped that these two fields, namely the chemical and biological approaches to the development of the aldol reaction, will converge and a truly general solution to the catalytic asymmetric aldol reaction will emerge.

Our own work on the topic discussed in this review was supported by the National Institutes of Health and National science Foundation.

Received: July 23, 1999 [A356]

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