

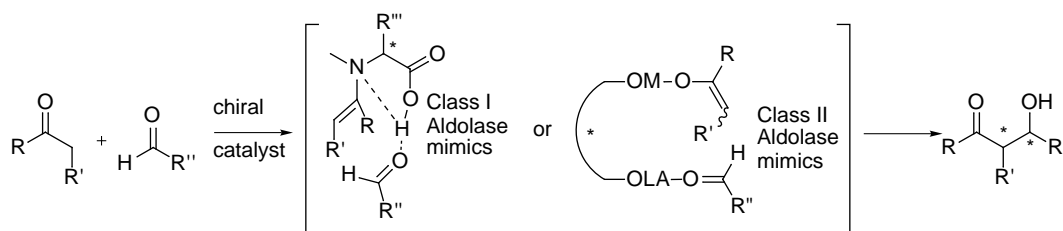
# Direct Small Molecule Catalyzed Asymmetric Aldol Reactions.

Ryan W. Van De Water

Department of Chemistry and Biochemistry, University of California, Santa Barbara, CA 93106

vandewater@chem.ucsb.edu

## ABSTRACT



**Enzymes have, until recently, been the most efficient means for asymmetrically catalyzing aldol reactions requiring no pre-activation of the donor or acceptor. Recent developments involving small molecule mimics of aldolase enzymes promise to extend the generality of this reaction to a greater number of substrates as well as increase its accessibility for use in the synthesis of complex molecules.**

The aldol reaction has emerged as one of the most utilized transformations in modern synthetic chemistry. The reaction, which forms a carbon-carbon bond along with the potential concomitant formation of two vicinal stereocenters, is an efficient method to rapidly construct complex molecules from small building blocks. With the current emphasis on enantioselective synthesis, it is not surprising that numerous, highly successful asymmetric versions of this reaction have been developed. Non-catalytic asymmetric versions involve the use of stoichiometric amounts of a chiral auxiliary in diastereoselective aldol reactions. Small molecule catalyzed aldol reactions<sup>1</sup> typically involve the use of a chiral Lewis acid for aldehyde activation or a chiral Lewis base for donor activation. While these methods have found widespread use in the synthesis of complex molecules, the search for more efficient methods continues.

The chiral auxiliary approach suffers from the need to use stoichiometric amounts of a chiral appendage necessitating additional steps for the attachment and removal of this group. Current indirect small molecule catalyzed aldol reactions all require pre-activation of the donor as a silyl enol ether, ketene acetal, or alkyl enol ether. The synthesis of these activated ethers often entails the use of expensive reagents and introduces additional synthetic operations.

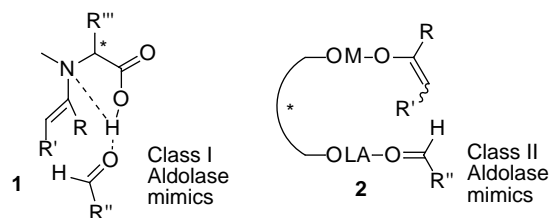
In order to solve the atom-economy problems posed by these previous methods, chemists have looked to nature for inspiration, finding it in the form of the aldolase enzymes. These enzymes directly catalyze the reaction of unactivated carbonyl donors with aldehyde acceptors in generally high enantioselectivity.<sup>1</sup> Two distinct classes of aldolases have been found. Class I aldolases catalyze the aldol reaction via the formation of an imine from the corresponding carbonyl donor with concomitant aldehyde activation occurring via a hydrogen bond with an acidic residue in the active site. The Class II aldolases contain a Zn<sup>2+</sup> co-factor in the active site for aldehyde activation as well as a Bronsted basic site for enolate generation. These enzymes are often highly specific for certain donor carbonyls while exhibiting a greater tolerance for the acceptor aldehyde. In addition to these enzymatic methods, the use of catalytic antibodies which mimic Class I enzymes have also been applied to the direct asymmetric aldol (DAA) reaction.<sup>1</sup> However, a small molecule catalyst for the aldol reaction, requiring no preactivation of the donor or aldehyde, remains an attractive goal with its promise of increased generality and easier applications to large scale reactions.

Several distinct small molecule catalysts have recently emerged for the DAA reaction. The guiding principle behind the design of these catalysts has been that the catalyst should simultaneously activate both the ketone donor and aldehyde acceptor. The catalysts developed to date can be classified as Class I or Class II aldolase mimics (Figure 1). The Class I aldolase mimics consist of amino

<sup>1</sup> For a recent review see: Machajewski, T. D.; Wong, C.-H. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 1352-1374.

acid catalysts which presumably activate the donor via enamine formation and the acceptor through a hydrogen bond with an acid functionality (**1**, figure 1). The Class II aldolase mimics consist of bimetallic catalysts containing a Lewis acidic metal for aldehyde activation and a Bronsted base for enolate generation to form the active complex **2**.

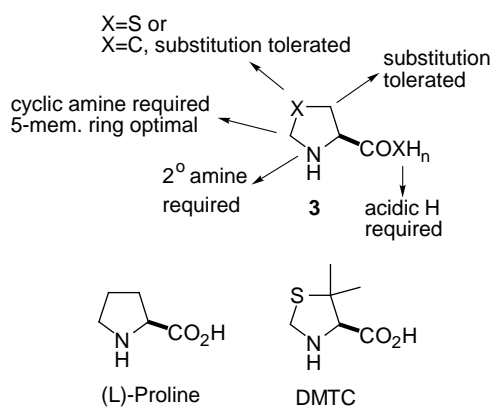
**Figure 1.** Class I and II Aldolase Mimics.



The simplest catalyst system reported for the DAA reaction involves the use of amino acid catalysts, which function as Class I aldolase mimics. Proline was first reported by Wiechert<sup>2</sup> as well as Hajos and Parrish<sup>3</sup> to catalyze an intramolecular asymmetric aldol reaction for the production of bicyclic systems. However, the intermolecular version of this reaction remained unexplored until a recent communication by List and coworkers in 2000.<sup>4</sup>

The structural requirements for a successful amino acid catalyst were first examined by List<sup>4</sup> and later supplemented with further structure-activity studies by Barbas, III<sup>7b</sup> (Figure 2). The authors concluded that a cyclic

**Figure 2.** Structure-Activity Study for Amino-Acids and Successful Catalysts.



secondary amine was required for effective catalysis as both primary and acyclic secondary amines gave little to none of the desired cross aldol product. When the carboxylic acid group of proline was replaced by a primary amine, the catalyst was found to be inactive. This led the authors to

<sup>2</sup> Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 496-497.

<sup>3</sup> Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615-1621.

<sup>4</sup> List, B.; Lerner, R. A.; Barbas, C. F., III *J. Am. Chem. Soc.* **2000**, *122*, 2395-2396.

conclude that an acidic proton in the correct spatial proximity is required for an active catalyst. Substitution at

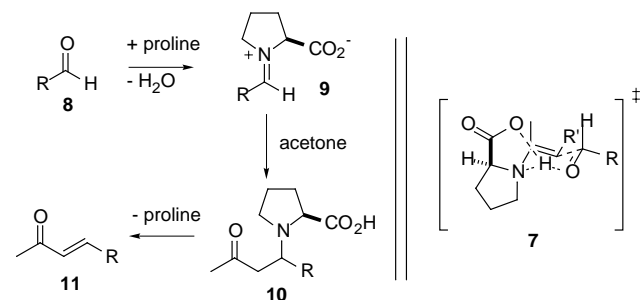
**Table 1.** Aldol Reactions of Acetone and Hydroxyacetone.

R'	R	preferred catalyst	solvent	yields	ee <sup>d</sup>
H	aromatic aldehydes	DMST	DMSO	54-94%	60-89%
OH	"	DMST	DMSO	52-95%	anti:syn 1:1-1.5:1
H	$\alpha$ -branched aliphatic aldehydes	proline	DMSO	60-97%	76-99%
OH	"	proline	DMSO	51-62%	anti:syn >20:1
H	$\alpha$ -unbranched aliphatic aldehydes	proline	CHCl <sub>3</sub>	22-35%	36-73%
OH	"	proline	DMSO	38%	anti:syn 1.7:1

<sup>a</sup> ee of the anti isomer. See ref. 6 and 7b for the ee of syn isomers. the two back carbons of the pyrrolidine ring lead to little change in catalytic activity. The two optimal catalysts were found to be proline<sup>5</sup> and 5,5-dimethyl thiazolidinium-4-carboxylate (DMTC). Of these two catalysts, proline has proven to be more general, with DMTC being preferable for use with aromatic aldehydes, leading to higher enantioselectivities with this class of acceptors.

In List's initial report,<sup>4</sup> acetone was shown to react with various aromatic aldehydes and one aliphatic aldehyde in the presence of proline (20-30 mol%) providing the aldol products **6**. The reaction was later extended to  $\alpha$ -mono and disubstituted aldehydes<sup>7b</sup> as well as  $\alpha$ -unsubstituted aldehydes<sup>6</sup> (Table 1). The reaction with  $\alpha$ -unsubstituted aldehydes has proven to be the least successful due to the formation of unsaturated condensation products as the

**Figure 3.** The Proposed Mannich Reaction Pathway and the Transition State for Proline-Catalyzed Aldol Reactions.



predominant products. List and co-workers suggest that these unsaturated aldol condensation products, **11**, are not formed from the corresponding aldol product of type **6** based on the fact that purified aldol products resubjected to

<sup>5</sup> For a recent review of proline catalyzed reactions see: Groger, H.; Wilken, J. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 529-532.

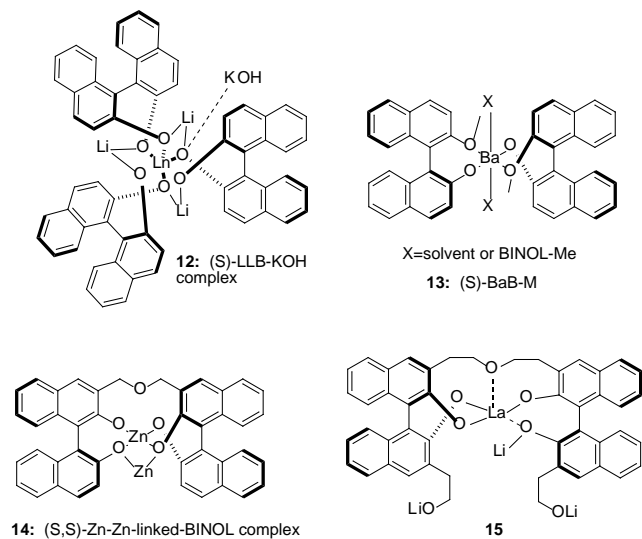
<sup>6</sup> List, B.; Pojarliev, P.; Castello, C. *Org. Lett.* **2001**, *3*, 573-575.

acetone and proline did not dehydrate even upon prolonged stirring. Instead, they propose the formation of enones occurs via a competitive Mannich condensation pathway (Figure 3).

Hydroxyacetone was also found to be a suitable donor for the direct amino acid catalyzed cross aldol reaction.<sup>7</sup> In reactions with  $\alpha$ -branched aldehydes a strong preference for the anti diastereomer was found and excellent enantioselectivities were obtained. However, aromatic and  $\alpha$ -unbranched aldehydes gave mixtures of both possible diastereomers with products of lower optical activity.

The proposed mechanism for proline catalyzed aldol reactions is thought to mimic that of the Class I aldolases.

**Figure 4.** Shibasaki's Bimetallic Catalysts for the Direct Aldol Reaction.



Carbonyl activation is first achieved via conversion of the ketone to its corresponding enamine. Subsequent aldehyde activation is then achieved through a hydrogen bond with the carboxylate OH giving rise to a proposed metal-free Zimmerman-Traxler like transition state leading to the observed aldol products (**7**, Figure 3). It is thought that the cases of poor anti to syn ratios are due to a competing boat transition state which becomes more important when the R group of the aldehyde is less sterically demanding.

Class II aldose mimics were the first small molecule catalysts to be developed for the DAA reaction. These catalysts are characterized as bimetallic complexes that contain both Lewis acidic and Bronsted basic sites. Shibasaki and co-workers first reported the use of such a catalyst in the aldol reaction in 1997,<sup>8</sup> demonstrating its potential with the reaction of various aldehydes and ketone

donors. Trost later introduced the dizinc catalyst, **21**, for use with acetophenone and hydroxyacetophenone donors.<sup>9</sup>

**Table 2.** Reactions of aldehydes and aromatic methyl ketones with aldehydes in the presence of Shibasaki's catalyst **12**.

R	catalyst	yields (%)	ee (%)
$\alpha$ -branched aliphatic aldehydes	<b>12</b> without KOH	43-81	44-91
$\alpha$ -unbranched aliphatic aldehydes	<b>12</b> without KOH	28-90	52-69
$\alpha$ -branched aliphatic aldehydes	<b>12</b>	60-90	33-88
$\alpha$ -unbranched aliphatic aldehydes	<b>12</b>	50-95	30-93

Shibasaki's early work involving catalyst **12**, not complexed with KOH, and catalyst **13** has been included in a recent review<sup>1</sup>.

In Shibasaki's original communication<sup>8</sup>, the tris-binaphthoxide complex **12**, without KOH, was used to catalyze the aldol reactions of various aromatic methyl ketones with aliphatic aldehydes (Table 2). The yields and optical activities of the products reported were varied with the  $\alpha$ -unbranched aldehydes typically giving the worst yields and enantioselectivities. Drawbacks include the necessity of using an excess of the ketone and long reaction times (3 days). However, this work provided the first example of a small molecule catalyzed DAA reaction and laid the foundation for later more successful catalysts.

Next, Shibasaki investigated the Barium BINOL-Me complex, **13**, in direct aldol reactions<sup>10</sup> in hopes that the increased Lewis basicity of the complex would result in lower catalyst loadings. The complex was successful with lower catalyst amounts (5 mol % vs. 20 mol %) leading to

**Table 3.** Reactions of Aldehydes and Hydroxyacetophenone in the Presence of Shibasaki's Catalysts **12** and **14**.

R	catalyst	yields (%)	dr (syn:anti)	ee (%)
$\alpha$ -unbranched aliphatic aldehydes	<b>12</b>	78-92	1:2 to 1:5	90-95
$\alpha$ -branched aliphatic aldehydes	<b>14</b>	79-92	2:1 to 7:1	67-79
$\alpha$ -unbranched aliphatic aldehydes	<b>14</b>	80-89	2:1 to 3:1	73-81

<sup>7</sup> (a) Notz, W.; List, B. *J. Am. Chem. Soc.* **2000**, *122*, 7386-7387. (b) Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F., III *J. Am. Chem. Soc.* **2001**, *123*, 5260-5267.

<sup>8</sup> Yamada, Y. M. A.; Yoshika N.; Sasai, H.; Shibasaki, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1871-1873.

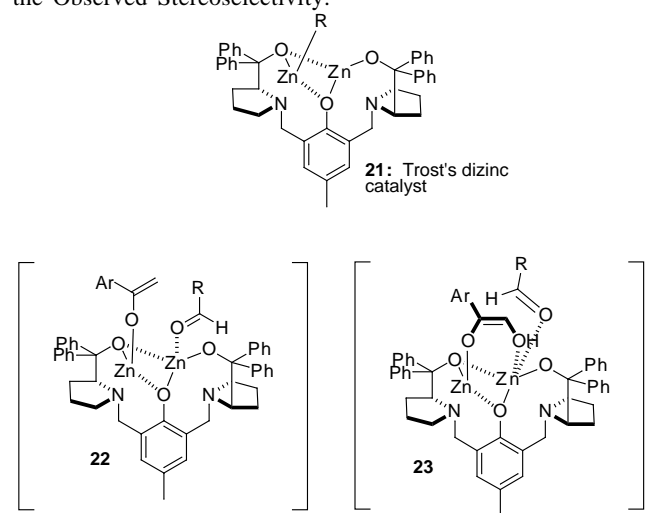
<sup>9</sup> (a) Trost, B. M.; Ito, H. *J. Am. Chem. Soc.* **2000**, *122*, 12003-12004. (b) Trost, B. M.; Ito, H.; Silcoff, E. R. *J. Am. Chem. Soc.* **2001**, *123*, 3367-3368.

<sup>10</sup> Yamada, Y. M. A.; Shibasaki, M. *Tetrahedron Lett.* **1998**, *39*, 5561-5564.

shorter reaction times, however, the highest enantioselectivities achieved were 70%. Further improvements to the catalyst were realized with the LLB-KOH complex **12**.<sup>11</sup> This complex first found use in nitroaldol reactions and was subsequently found to be a superior catalyst in the direct aldol reaction (Table 2). The high enantioselectivities achieved with this catalyst indicate that a tight complex occurs between the LLB and KOH with the competing, uncomplexed KOH catalyzed reaction pathway being of minimal importance. While there is room for improvement of the LLB-KOH complex, it has proven more successful than the corresponding amino acid catalysts in the direct aldol reaction with  $\alpha$ -unbranched aldehydes.

As a proof of synthetic utility, the aromatic ketone-aldol

**Figure 5.** Trost's Dizinc Catalyst and Proposed Models for the Observed Stereoselectivity.



products, **17**, were transformed into the more useful corresponding esters by Baeyer-Villiger oxidation. Complex **12** also proved its potential in large scale processes by its use in the resolution of a racemic aldehyde via the direct asymmetric aldol reaction in a total synthesis of Epithilones A and B.<sup>12</sup>

Further investigations by Shibasaki examined the use of hydroxyacetophenone as the donor for the synthesis of 1,2-diols (table 3).<sup>13</sup> The use of the LLB-KOH complex **12**, and the dizinc complex **14** were investigated. Catalyst **12** showed anti selectivity, giving excellent yields and enantioselectivities with  $\alpha$ -unsubstituted aldehydes (Table 3). However, the LLB-KOH complex was ineffective with  $\alpha$ -branched aldehydes leading to the development of the dizinc catalyst, **14**, which exhibited a syn preference providing the aldol products in high yields and enantioselectivities.

<sup>11</sup> Yoshikawa, N.; Yamada, Y. M. A.; Das, J.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1999**, *121*, 4168-4178.

<sup>12</sup> Sawada, D.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 10521-10532.

<sup>13</sup> Yoshikawa, N.; Kumagai, N.; Matsunaga, S.; Moll, G.; Ohshima, T.; Suzuki, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 2466-2467.

Shibasaki also investigated catalysts of type **15** (Figure 4).<sup>14</sup> It was hoped that tethering a Lewis basic site to the catalyst might further improve enantioselectivities and catalyst turnover. Catalyst **15**, was further expected to be readily modified with respect to the tether lengths leading to an easily optimized catalyst system. The results achieved with this catalyst have been moderate to date with enantiomeric excesses ranging from 40-74%.

**Table 4.** Reactions of Acetophenone and Derivatives with Aliphatic Aldehydes in the Presence of Catalyst **21**.

R'	R	yields (%)	dr (syn:anti)	ee (%)
H	$\alpha$ -branched aliphatic aldehydes	36-67	NA	93-99
H	$\alpha$ -unbranched aliphatic aldehydes	24-49	NA	56-74
OH	$\alpha$ -branched aliphatic aldehydes	74-90	6:1 to syn only	92-96
OH	$\alpha$ -unbranched aliphatic aldehydes	74-90	3.5:1 to 35:1	92-96

The initial report concerning catalyst **21** (figure 5) by Trost involved the reaction of various aromatic methyl ketones with aliphatic aldehydes (table 4). An excess of the ketone was necessary and results varied depending on the aldehyde used. A rationale for the stereochemical outcome, **22**, was proposed to account for the facial selectivity with respect to the aldehyde.

The catalyst was extended to the synthesis of 1,2-diols with the use of hydroxyacetophenone as the donor. The aldol products obtained were found to be of syn configuration in good yield and enantioselectivities. Interestingly, the facial selectivity of the aldehyde was reversed from the corresponding reaction with acetophenone. The authors hypothesized that coordination of the hydroxy group of the hydroxyacetophenone to the other zinc atom, as in structure **23**, led to the observed reversal in facial selectivity.

The direct small molecule catalyzed asymmetric aldol (DAA) reaction has made tremendous strides in the last five years. The reaction has proven especially successful with the use of hydroxyketones for the synthesis of 1,2-diols. Overall, the amino acid catalyzed DAA reaction shows significant limitations with  $\alpha$ -unbranched aldehydes. However, the bimetallic catalysts address this deficiency, providing typically higher yields and enantioselectivities with this difficult class of aldehyde acceptors. Future areas for improvement include the reduction of the excess amounts of ketone donor required for many of the reactions as well as an extension of this chemistry to the aldol reactions of esters and methylene ketones.

<sup>14</sup> Yoshikawa, N.; Shibasaki, M. *Tetrahedron* **2001**, *57*, 2569-2579.