# An Amino Acid Co-catalyzed Asymmetric Aldol Reaction

Ming Z. Gao, Jian Gao, Benjamin S. Lane, and Ralph A. Zingaro*
*Department of Chemistry, Texas A&M University, College Station, TX 77843-3255, U. S. A.*

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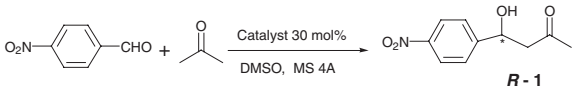
A series of chiral amino acids were found to be effective catalysts in an asymmetric aldol reaction between 4-nitrobenzaldehyde and acetone. Lewis acids and bases were found to effectively promote this reaction. Enantioselectivities greater than 74% (ee) and product yields over 85% were achieved under optimum conditions.

The aldol reaction is one of the most important carbon-carbon bond-forming reactions in synthetic organic chemistry. Investigation of this fundamental asymmetric reaction is important in understanding other carbon–carbon bond-forming reactions such as the Diels-Alder and Michael reactions. Earlier investigations indicate that useful catalytic systems include: 1) a reaction promoted by stoichiometric amounts of a chiral auxiliary,[1] 2) chiral Lewis acid-catalysis,[2] chiral Lewis base-catalyzed aldol reaction,[3] 3) the heteronuclear Lewis acid-catalyzed direct aldol reaction,[4] 4) aldol enzymes and antibody-catalyzed systems.[5]

Recently, a proline catalyzed aldol reaction has been reported.[6–8] However, other amino acids have not been investigated. This was the motivation for the current research. Herein is reported a successful aldol reaction catalyzed by several chiral amino acids together with Lewis acids or bases serving as co-catalysts.

The reported aldol addition takes place between acetone and 4-nitrobenzaldehyde (Scheme 1) in which acetone is a component of a solvent system with anhydrous DMSO (DMSO:acetone = 4:1). A large excess of acetone was used in the reaction in order to promote an equilibrium favoring the aldol addition product.




**Scheme 1.**

L-valine was first investigated as a catalyst for this reaction (Table 1). It was found that after stirring the homogeneous mixture for 48 h at room temperature, the reaction catalyzed by L-valine and Lewis acid (metal ions) resulted in a significant formation of the new product, 25–50% product yield, characterized to be β-hydroxyketone **1** resulting from the cross-aldol reaction.[9] Chiral-phase HPLC analyses indicated that **1** was formed in ca. 50% ee when a divalent metal ion served as the co-catalyst. Trivalent and monovalent metal ions gave either low product yields or low ee values, indicating that the Lewis acid plays an important role in this reaction.

Considering the influence of the chirality of amino acids upon the ee, a series of commercially available amino acids was investigated (Table 2). L-valine was found to be the most effective with respect to both yield and ee. These results are in agreement with the relationship known to exist between the enantioselectivity of the product and the chirality of the catalyst. It is interesting to note Entries 1 and 6 in Table 2 that an L-configuration of the amino acid always results in the formation of the *R* product, while the D-amino acid configuration leads to the *S* product. This result suggests that a complex transition state involving the amino acid is formed during the reaction. The observation of the change in ee which occurs under varied metal ion concentrations (Table 1, Entry 2 and Table 2, Entry 1), motivated the following investigation designed to study the influence of Lewis acid concentration upon the enantioselectivity of the reaction.

**Table 1.** L-valine catalyzed aldol reaction; amino acid and metal concentration are 30 mol% and 10 mol% respectively

| Entry | Lewis acid | Yield%[a] | ee %[b,c] |
|---|---|---|---|
| 1 | $Cd^{2+}$ | 40 | 49 |
| 2 | $Zn^{2+}$ | 38 | 51 |
| 3 | $La^{3+}$ | 50 | 21 |
| 4 | $Ni^{2+}$ | 33 | 56 |
| 5 | $Ag^{+}$ | 25 | 49 |
| 6 | $Fe^{3+}$ | 28 | 47 |

[a]Isolated after column chromatography.
[b]Determined by chiral HPLC analysis (Chiralpak AD column) and specific rotation.
[c]Product configuration is *R* (compared with ref. 6).

The effect of $Zn^{2+}$ was studied in this investigation (Table 3). The reaction temperature was maintained at 25°C and the concentration of amino acid was 30 mole percent. When the Lewis acid concentrations were increased from 0% to 30%, the product yield increased from 5% to 78%; however, the enantioselectivity decreased drastically. This may be attributed to the fact that the rapid reaction rate which is achieved at high concentrations of Zn(II) reduces the stereoselectivity. In the absence of Lewis acid, the product yield is greatly reduced. This

**Table 2.** Exploration of various amino acid as catalyst of the aldol reaction. $[Zn^{2+}] = 30$ mol%

| Entry | Catalyst | Yield % | ee % | Product configuration |
|---|---|---|---|---|
| 1 | L-/D-Valine | 78/77 | 21/20 | *R*/*S* |
| 2 | L-Cysteine | 43 | 15 | *R* |
| 3 | L-Cystine | 42 | 11 | *R* |
| 4 | L-Leucine | 72 | 19 | *R* |
| 5 | L-Glutamic acid | 67 | 11 | *R* |
| 6 | L-/D-Phenylglycine | 64/61 | 16/14 | *R*/*S* |

**Table 3.** Influence of $[Zn^{2+}]$ on the product ee value and yield

| Entry | $[Zn^{2+}]$ mol% | Yield % | ee % |
|---|---|---|---|
| 1 | 30 | 78 | 21 |
| 2 | 20 | 57 | 36 |
| 3 | 15 | 48 | 47 |
| 4 | 10 | 38 | 51 |
| 5 | 0 | 5 | — |

**Table 4.** Co-catalytic effects of Lewis bases on the aldol reaction. [L-valine] = 30 mol%

| Entry | Lewis base | Base mol% | Yield % % | ee % |
|---|---|---|---|---|
| 1 | DABCO[a] | 30 | 68 | 40 |
| 2 | DABCO | 10 | 72 | 47 |
| 3 | Imidazole | 30 | 85 | 57 |
| 4 | Imidazole | 10 | 78 | 59 |
| 5 | TDMPE[b] | 30 | 82 | 68 |
| 6 | TDMPE | 10 | 73 | 70 |

[a]DABOC denotes 1, 4-diazabicyclo[2.2.2]octane
[b]*trans*-2,5-Dimethylpiperazine

illustrates the importance of the Lewis acid in this reaction.

It was also found that some Lewis bases can promote this reaction under the conditions similar to those described in Table 1, but varying concentrations of Lewis base instead of metal ions. The results (Table 4) show that high concentrations of Lewis bases increase the yield, but have a somewhat unfavorable effect on ee. In the presence of *trans*-2,5-dimethylpiperazine (Entry 6) ee value reach a maximum value of 70%.

As an extension of the work, several substituted benzaldehydes were examined in this reaction with L-Valine serving as the catalyst and the Lewis base, *trans*-2,5-dimethylpiperazine as a co-catalyst. The experimental results are summarized in Table 5. A high enantioselectivity is found for 2-nitrobenzaldehyde with a 74% ee (Entry 3) with a product yield of 70%.

It is difficult to derive clear mechanistic conclusions in a complex system. In conclusion, certain commercially available chiral amino acids can effectively promote this asymmetric aldol reaction, Lewis acids and bases play an important role in the catalytic process. A more detailed mechanistic investigation with respect to the enantioselective steps is in progress.

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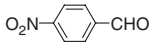
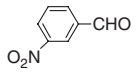
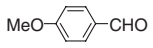
**Table 5.** Co-catalysed aldol reaction with substituted benzaldehydes. [L-valine] = 30 mol%, *trans*-2, 5-dimethylpiperazine = 30 mol%

| Entry | Benzal dehyde | Yield% | ee % |
|---|---|---|---|
| 1 |  | 82 | 68 |
| 2 |  | 79 | 67 |
| 3 |  | 70 | 74 |
| 4 |  | 80 | 63 |

**References and Notes**

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9 General procedure for the aldol reaction: to a mixture of anhydrous DMSO (8 mL), 4A Molecular Sieve (MS) and ketone (2 mL) was added the corresponding amino acid (0.3 mmol) and $ZnBr_2$ or TDMPE (0.1–0.3 mmol). The mixture was vigorously stirred for 4 h and was followed by the addition of 4-nitrobenzaldehyde (1 mmol). The resulting mixture was stirred at rt. for an additional 48 h and was then treated with aqueous solution of saturated ammonium chloride. The aqueous layer was separated and extracted with ethyl acetate, dried and evaporated. The pure aldol products were separated by column chromatography (silica gel, hexane/acetone). Compound *R*-1: $IR_\nu$, 3434(OH), 1713(C=O), 1600(Ar), 1516, 1376, 1343, 1240, 1164, 1079, 1012, 855, 839, 788, 748, 699, 542 $cm^{-1}$. $^1H$ NMR ($CDCl_3$), δ: 2.22(3H, s, $CH_3$), 2.85(2H, d, $J = 6.0$ Hz, $CH_2$), 4.72 (1H, bs, OH), 5.27(1H, dd, $J = 5.0$, 7.0 Hz, CH), 7.54(2H, d, $J = 9.0$, ArH), 8.21(2H, d, $J = 8.0$ Hz, ArH).

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