# Chiral Lewis Acid Catalysis in Aqueous Media. Catalytic Asymmetric Aldol Reactions of Silyl Enol Ethers with Aldehydes in a Protic Solvent Including Water

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Chiral copper(II)-catalyzed asymmetric aldol reactions of silyl enol ethers with aldehydes have been successfully carried out in a water-ethanol solution. The use of the protic solvent including water is essential in these reactions, and this report has proposed and demonstrated a new concept for solvents in catalytic asymmetric aldol reactions.

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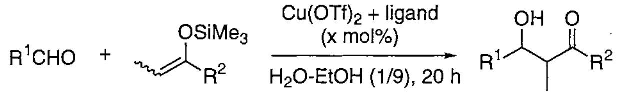
Catalytic asymmetric aldol reactions provide one of the most powerful carbon-carbon bond-forming processes affording synthetically useful chiral β-hydroxy ketones and esters.[1] Chiral Lewis acid-catalyzed reactions of silyl enol ethers with aldehydes (the Mukaiyama reaction)[2] are among the most convenient and promising, and several successful examples have been reported since the first chiral tin(II)-catalyzed reactions appeared in 1990.[3] Some common characteristics of these catalytic asymmetric reactions are the use of aprotic anhydrous solvents such as dichloromethane, toluene, and propionitrile,[4] and low reaction temperatures (-78 °C),[5] which are also observed in many other catalytic asymmetric reactions. In this paper, we report an example which breaks with such traditions in asymmetric reactions; copper(II)-catalyzed asymmetric aldol reactions of silyl enol ethers with aldehydes in an ethanol-water solution. It has been demonstrated that high yields and selectivities were attained at -15 - 0 °C not in aprotic solvents but in a protic solvent including water.

We have recently developed Lewis acid-catalyzed aldol reactions of silyl enol ethers with aldehydes in aqueous media.[6] Although Lewis acids and silyl enol ethers were believed to be decomposed in the presence of water, the aldol reactions proceeded smoothly in aqueous solutions using new types of Lewis acids.[7] In the course of our investigations to develop new chiral catalysts and catalytic asymmetric reactions in water, we focused on several elements whose salts are stable and work as Lewis acids in water. Quite recently, the stability and activity of Lewis acids in water were related to hydration constants and exchange rate constants for substitution of inner-sphere water ligands of elements (cations).[8] In addition to these findings, it was expected that undesired achiral side reactions would be suppressed in aqueous media and that desired enantioselective reactions would be accelerated in the presence of water (*vide infra*). Moreover, besides metal chelations, other factors such as hydrogen bonds, specific solvation, and hydrophobic interactions are anticipated to increase enantioselectivities in such media.

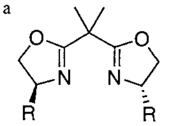
We first chose copper(II)[9] and an aldol reaction of benzaldehyde with (*Z*)-2-methyl-1-trimethylsiloxy-1-phenylethene was tested in the presence of copper-bis(oxazoline) **1**[10-12] (20 mol%). The reaction proceeded smoothly in ethanol-water (9:1) at -10 °C to afford the desired aldol adduct in an 80% yield with *syn*/*anti* = 3.3/1, and the enantiomeric excess of the *syn* adduct was proved to be 64% as determined by HPLC analysis. The same levels of diastereo- and enantioselectivities were obtained using chiral ligand **2** instead of **1**. Several examples of the catalytic asymmetric aldol reactions of silyl enol ethers with aldehydes are summarized in Table 1. (*Z*)-3-Trimethylsiloxy-2-pentene (**3**) also worked well to give the desired aldol adducts in good selectivities. For the geometry of the enolates, a (*Z*)-isomer gave higher yields and diastereo- and enantioselectivities than an (*E*)-isomer. For aldehydes, not only aromatic but also α,β-unsaturated, heterocyclic, and even aliphatic aldehydes reacted smoothly under these reaction

**Table 1.** Catalytic asymmetric aldol reactions in aqueous media



| $R^1$ | $R^2$ | *E*/*Z* | ligand[a] (x/mol%) | temp /°C | yield /% | *syn*/*anti* | ee/% (*syn*) |
|---|---|---|---|---|---|---|---|
| Ph | Ph | *Z*[b] | **1** (20) | -10 | 74 | 3.2/1 | 67[e] |
| Ph | Ph | *Z* | **2** (20) | 0 | 98 | 2.6/1 | 61[e] |
| Ph | Et | *Z*[b] | **1** (20) | -15 | 81 | 3.5/1 | 81 |
| Ph | Et | *Z* | **1** (10) | -15 | 64 | 3.7/1 | 80 |
| Ph | Et | *Z* | **1** (5) | -15 | 34 | 3.7/1 | 76 |
| Ph | Et | *E*[c] | **1** (20) | -10 | 32 | 1.6/1 | 32 |
| Ph | *i*-Pr | *Z*[d] | **1** (20) | 0 | 17 | 4.0/1 | 85 |
| Ph | *i*-Pr | *Z* | **1** (20) | 5 | 95 | 4.0/1 | 77 |
| *p*-ClPh | Ph | *Z* | **2** (20) | 0 | 56 | 1.6/1 | 67 |
| *p*-ClPh | Et | *Z* | **1** (10) | -10 | 88 | 2.6/1 | 76 |
| *p*-ClPh | Et | *Z* | **1** (5) | -10 | 78 | 2.4/1 | 75 |
| *o*-MeOPh | Et | *Z* | **1** (10) | -10 | 87 | 2.9/1 | 75 |
| 2-naphthyl | Et | *Z* | **1** (20) | -10 | 91 | 4.0/1 | 79 |
| 2-naphthyl | Et | *Z* | **1** (10) | -10 | 87 | 4.0/1 | 76 |
| 2-naphthyl | *i*-Pr | *Z* | **1** (20) | -10 | 97 | 4.0/1 | 81 |
| 2-furyl | Et | *Z* | **1** (20) | -10 | 86 | 4.0/1 | 76 |
| 2-thiophene | Et | *Z* | **1** (10) | -10 | 78 | 5.7/1 | 75 |
| PhCH=CH | Et | *Z* | **1** (20) | -10 | 94 | 2.3/1 | 57 |
| $Ph(CH_2)_2$ | Et | *Z* | **1** (20) | -5 | 37 | 4.6/1 | 59 |
| *c*-$C_6H_{11}$ | Ph | *Z* | **2** (20) | 0 | 77 | 4.6/1 | 42 |

[a]



**1**: R = *i*-Pr
**2**: R = $CH_2Ph$

[b] *E*/*Z* = <1/>99.
[c] *E*/*Z* = 77/23.
[d] *E*/*Z* = 2/98.
[e] (2*S*, 3*S*). See Ref. 19.

conditions to afford the corresponding aldol adducts in moderate to high yields and selectivities.[13]

A typical experimental procedure is described as follows: an aldehyde (0.5 mmol), a silyl enol ether (0.75 mmol), and catalyst **1** (5-20 mol%) were combined in a water-ethanol solution (1/9, 1.5 ml) at the temperature shown in Table 1. The mixture was stirred for 20 h at the same temperature, and sat. $NaHCO_3$ aq. was added to quench the reaction. After a usual work-up, the crude product was purified by column chromatography on silica gel to afford the corresponding aldol adduct. The diastereomers were separated, and the enantiomeric excess was determined by HPLC analysis using a chiral column.

Our working hypothesis that desired chiral reactions would be accelerated and undesired achiral side reactions would be suppressed in aqueous media, was demonstrated by the following control experiments. While the aldol reaction of **3** with benzaldehyde proceeded smoothly in water-ethanol (1:9) at -15 °C to afford the corresponding adduct in a high yield with good selectivities (quant., *syn*/*anti* = 3.3/1, *syn* = 75% ee), much lower yield and selectivities were observed in ethanol (without water) under the same reaction conditions (10% yield, *syn*/*anti* = 2.3/1, *syn* = 41% ee). Furthermore, when the reaction was performed in dichloromethane at -15 °C, the aldol adduct was obtained in an 11% yield with *syn*/*anti* = 2.1/1 (*syn* = 20% ee).[12,14,15] It was assumed that dissociated copper(II) coordinated by bis(oxazoline) **1** or **2** is an active catalyst in these catalytic asymmetric aldol reactions, and that undesired achiral side reactions which proceed rapidly in aprotic solvents[16] are inhibited in aqueous media.

In summary, copper(II)-catalyzed enantioselective aldol reactions of silyl enol ethers with aldehydes in aqueous media have been developed. To the best of our knowledge, this is the first example of catalytic asymmetric aldol reactions in aqueous media.[17] It is noteworthy that chiral Lewis acid catalysis has been successfully carried out in aqueous media.[18] The synthetic utility of these novel aqueous asymmetric reactions is obvious; the experimental procedure is very simple, and strict anhydrous conditions are not required. A water-ethanol solution is a clean and environmentally desirable solvent system. No harmful organic solvents are used, and low temperature (-78 °C) is not needed. It should be noted that the use of a protic solvent including water is essential in these reactions, and that this report has proposed and demonstrated a new concept for solvents in catalytic asymmetric aldol reactions.

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