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Catalytic Asymmetric Mukaiyama Aldol Reactions in Aqueous Media

Shū Kobayashi,* Satoshi Nagayama, Tsuyoshi Busujima

Graduate School of Pharmaceutical Sciences, The University of Tokyo,

Hongo, Bunkyo-ku, Tokyo 113-0033

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Abstract: Chiral copper(II)-catalyzed asymmetric aldol reactions of silyl enol ethers with aldehydes (the Mukaiyama aldol reaction) have been performed in an ethanol-water solution. The use of the protic solvent including water is a key to achieve these reactions. Moreover, a catalytic asymmetric aldol reaction in pure water without using organic solvents has also been successfully carried out. This report has proposed and demonstrated a new concept for solvents in catalytic asymmetric aldol reactions.

Chiral Lewis acid-catalyzed aldol reactions of silyl enol ethers with aldehydes (the Mukaiyama reaction)[1] provide one of the most powerful carbon-carbon bond-forming processes affording synthetically useful chiral β-hydroxy ketones and esters.[2] After the first report using a chiral tin(II) Lewis acid appeared in 1990,[3] several successful examples have been reported.[2] 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. On the other hand, organic reactions in aqueous media without using harmful organic solvents are of great current interest especially in relation to today's environmental concerns.[6] However, the use of water in organic reaction processes is rather limited because many organic materials do not dissolve in water and many reactive intermediates and catalysts are decomposed in water. This is the case in the above catalytic asymmetric aldol reactions which are carried out under strict anhydrous conditions, and there have been no reports so far to perform the reactions even in protic solvents. In this paper, we report an example which breaks with such traditions; copper(II)-catalyzed asymmetric aldol reactions of silyl enol ethers with aldehydes in an ethanol-water solution.[7] It has been demonstrated that high yields and selectivities were attained at -15 - 0 °C *not in aprotic solvents but in protic solvents including water*. An example of catalytic asymmetric aldol reactions in pure water is also described.

We have recently investigated Lewis acid catalysis in water and performed aldol reactions of silyl enol ethers with aldehydes in aqueous media.[8] 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.[9] 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, we have found that 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).[10] In addition to these findings, it was expected in the above asymmetric aldol reactions that undesired achiral side reactions would be suppressed in aqueous media and that desired enantioselective

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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) that was revealed to be one of the most promising metals.[11] An aldol reaction of benzaldehyde with (*Z*)-2-methyl-1-trimethylsiloxy-1-phenylethene was performed in the presence of copper-bis(oxazoline) **1a**[12-14] (20 mol%). The reaction proceeded smoothly in ethanol-water (9:1) at 0 °C to afford the desired aldol adduct in 97% yield with *syn*/*anti* = 3.0/1, and the enantiomeric excess (ee) of the *syn* adduct was proved to be 48% as determined by HPLC analysis. Several other ligands were examined and the results are summarized in Table 1. The best ee (61%) was obtained when bis(oxazoline) **1b** was used. While high *syn* selectivity was observed using bis(oxazolinyl)pyridine (pibox) **2**,[12c] the yield and ee were lower. On the other hand, higher ee (67%) was obtained when the reaction was performed using **1a** at -10 °C, while the reaction proceeded very slowly at -10 °C using **1b** as a catalyst.

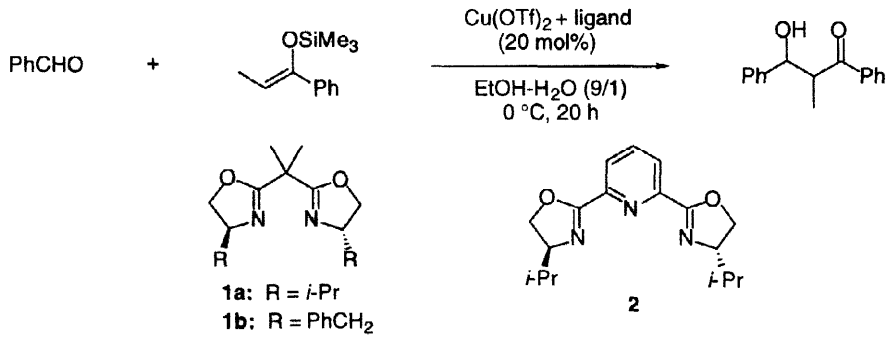


Table 1. Effect of Ligands

Entry	Ligand	Yield/%	*syn*/*anti*	ee/%[a]
1	**1a** (R = *i*-Pr)	97	3.0/1	48
2	**1** (R = *t*-Bu)	92	9.0/1	-15
3	**1** (R = $CH_2CH(CH_3)_2$)	98	2.6/1	37
4	**1b** (R = $PhCH_2$)	quant	2.0/1	61
5	**1** (R = 1-Nap-CH_2)	63	1.4/1	31
6	**1** (R = 2-Nap-CH_2)	86	1.8/1	47
7	**2**	31	11.5/1	23

[a]Ee of the *syn* adduct.

Several solvents which were combined with water were then studied (Table 2). While lower yields and selectivities were obtained in most cases, better results were observed when alcohol-water solvents were used. Among them, *n*-butanol-water system gave the highest ee (55%) at this stage.

Several examples of the catalytic asymmetric aldol reactions of silyl enol ethers with aldehydes are shown in Table 3. From a practical point of view, reactions were carried out in ethanol-water (9:1) using copper(II)-**1a** or **1b** as a catalyst. It was found that (*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 aliphatic aldehydes reacted smoothly under these reaction conditions to afford the corresponding aldol adducts in moderate to high yields and selectivities.

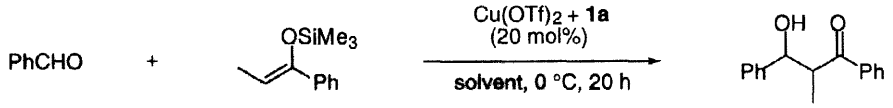
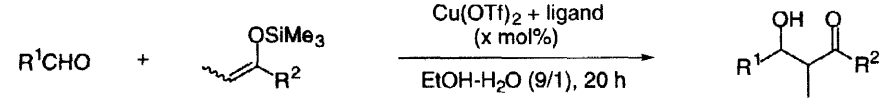


Table 2. Effect of Solvents

Entry	Solvent	Yield/%	*syn/anti*	ee/%[a]
1	EtOH-H_2O (9/1)	97	3.0/1	48
2	THF-H_2O (9/1)	47	3.0/1	25
3	CH_2Cl_2-H_2O (9/1)	trace	—	—
4	toluene-H_2O (9/1)	trace	—	—
5	CH_3CN-H_2O (9/1)	11	2.2/1	43
6	DMF-H_2O (9/1)	19	4.0/1	30
7	DMSO-H_2O (9/1)	12	3.8/1	32
8	*n*-BuOH-H_2O (9/1)	83	3.0/1	55
9	*t*-BuOH-H_2O (9/1)	12	1.9/1	48
10	*i*-PrOH-H_2O (9/1)	42	2.8/1	53

[a]Ee of the *syn* adduct.

Table 3. Catalytic Asymmetric Aldol Reactions in Aqueous Media

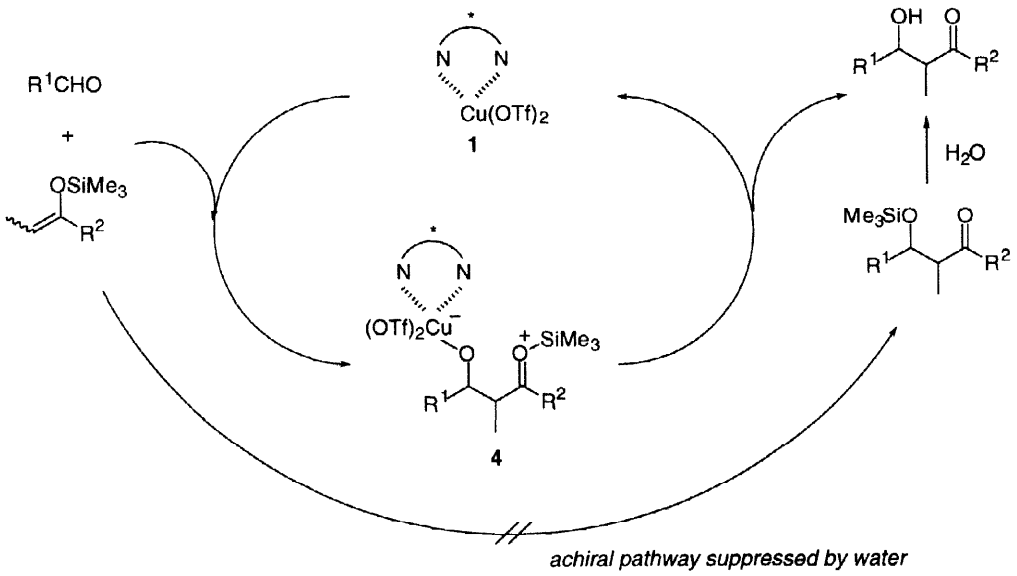


R^1	R^2	*E/Z*	Ligand (x/mol%)	Temp /°C	Yield/%	*syn/anti*	ee/%[a]
Ph	Ph	*Z*[b]	**1a** (20)	-10	74	3.2/1	67[e]
Ph	Ph	*Z*	**1b** (20)	0	98	2.6/1	61[e]
Ph	Et	*Z*[b]	**1a** (20)	-15	81	3.5/1	81
Ph	Et	*Z*	**1a** (10)	-15	64	3.7/1	80
Ph	Et	*Z*	**1a** (5)	-15	34	3.7/1	76
Ph	Et	*E*[c]	**1a** (20)	-10	32	1.6/1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

[a]Ee of the *syn* adduct. [b]*E/Z* = <1/>99. [c]*E/Z* = 77/23. [d]*E/Z* = 2/98. [e](2*S*, 3*S*). See Ref. 22.

The important role of water in these reactions were confirmed by the following control experiments. While the aldol reaction of **3**[15] with benzaldehyde proceeded smoothly in ethanol-water (9:1) at -15 °C to afford the corresponding adduct in 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 11% yield with *syn/anti* = 2.1/1 (*syn* = 20% ee).[14,16,17] It was assumed that dissociated copper(II) coordinated by bis(oxazoline) **1** is an active catalyst in these catalytic asymmetric aldol reactions, and that silicon-catalyzed undesired achiral side reactions which proceed rapidly in aprotic solvents[18] are inhibited in aqueous media.

The following catalytic cycle in this asymmetric reaction (Scheme 1) was strongly suggested by these results. Namely, chiral copper(II) catalyst **1** activates an aldehyde and a silyl enol ether attacks this aldehyde to form intermediate **4**. The silicon of **4** is supposed to catalyze the aldol reaction of an aldehyde with a silyl enol ether to afford the achiral aldol adduct in anhydrous aprotic solvents. While this achiral reaction is expected to be suppressed in the presence of water, intermediate **4** immediately reacts with water to form the aldol adduct as a free alcohol with the regeneration of catalyst **1** in aqueous media. It is noted that our kinetic study has shown that the aldol reaction obeys a second-order rate law (aldehyde and silyl enol ether).



Scheme 1. Assumed Catalytic Cycle

An important key to perform catalytic asymmetric reactions in aqueous media is that coordination of a chiral ligand to a metal is superior to that of water to the metal. For copper(II), it was well-known that Cu(II)-ethylenediamine complex is stable in water[19] and therefore, copper(II)-bis(oxazoline) complex is expected to be stable in the presence of a large amount of water. Actually, the same selectivities were observed during the reaction course (Table 4), which demonstrated the stability of the chiral catalyst in the ethanol-water (9/1) solution.

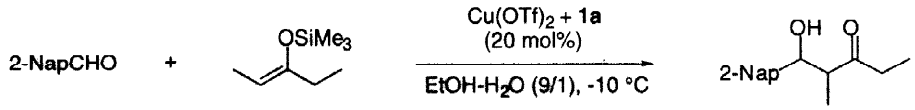
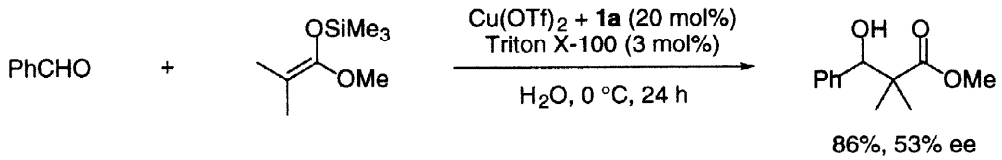


Table 4. Reaction Time vs. Yield and Selectivity

Time/h	Yield/%	*syn/anti*	ee/%[a]
1	17	3.5/1	78
2	33	3.5/1	79
3	47	3.5/1	78
4	62	3.5/1	79
7	73	3.5/1	79
10	80	3.5/1	79
15	90	3.5/1	79
20	91	3.5/1	79

[a]Ee of the *syn* adduct.

Finally, catalytic asymmetric aldol reactions in pure water were investigated. It was found that in the presence of 20 mol% of $Cu(OTf)_2$-bis(oxazoline) **1a** and 3 mol% of Triton X-100[20] benzaldehyde reacted with the ketene silyl acetal of methyl isobutyrate at 0 °C for 24 h in water to afford the corresponding aldol adduct in 86% yield with 53% ee.



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. It is noteworthy that chiral Lewis acid catalysis has been successfully carried out in water solutions.[21] The synthetic utility of these novel aqueous asymmetric reactions is obvious; the experimental procedure is very simple, and strict anhydrous conditions are not required. An ethanol-water 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 water as solvents is essential in these reactions, and that this report has proposed and demonstrated a new concept for solvents in catalytic asymmetric aldol reactions.

Experimental Section

General. Melting points are uncorrected. IR spectra were recorded on a Jasco FT/IR-610.. ^1H and ^{13}C NMR spectra were recorded on a JEOL JNM-LA300, JNM-LA400, or JNM-LA500 spectrometer in $CDCl_3$. Tetramethylsilane (TMS) served as internal standard ($\delta = 0$) for ^1H NMR, and $CDCl_3$ was used as internal standard ($\delta = 77.0$) for ^{13}C NMR. Mass spectra were measured on a JEOL DX-303HF spectrometer. Column chromatography was performed on Silica gel 60 (Merck) or Wakogel B5F.

Typical Procedure of Reactions of Silyl Enol Ethers with Aldehydes in EtOH-H_2O: An aldehyde (0.5 mmol), a silyl enol ether (0.75 mmol), and catalyst **1** (5-20 mol%) were combined in an ethanol-

water solution (9/1, 1.5 ml) at the temperature shown in Table 3. 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.

1,3-Diphenyl-3-hydroxy-2-methyl-1-propanone:[22] (*syn/anti* = 3.2/1) IR (neat); 3467, 1678 cm^{-1}; ^1H NMR δ 1.05 (d, 0.72 H, *J* = 7.2 Hz), 1.19 (d, 2.28H, *J* = 7.2 Hz), 3.10 (brs, 1H), 3.66-3.89 (m, 1H), 4.98 (d, 0.24H, *J* = 8.1 Hz), 5.22 (d, 0.76H, *J* = 3.1 Hz), 7.22-7.58 (m, 8H), 7.90-7.97 (m, 2H); ^{13}C NMR δ 11.2, 15.6, 47.0, 47.9, 73.1, 76.7, 126.0, 126.7, 127.2, 127.8, 128.2, 128.3, 128.40, 128.44, 128.6, 128.7, 133.2, 133.5, 135.6, 136.7, 141.8, 142.2, 204.8, 205.6

1-Hydroxy-2-methyl-1-phenyl-3-pentanone:[23] (*syn/anti* = 3.5/1) IR (neat); 3462, 1707 cm^{-1}; ^1H NMR δ 0.89 (d, 0.66H, *J* = 7.3 Hz), 0.96 (t, 2.34H, *J* = 7.2 Hz), 1.02 (t, 0.66H, *J* = 7.2 Hz), 1.07 (d, 2.34H, *J* = 7.3 Hz), 2.25-2.60 (m, 2H), 2.75-2.79 (m,1H), 3.12 (brs, 0.22H), 3.31 (brs, 0.78H), 4.70 (d, 0.22H, *J* = 8.3 Hz), 4.99 (d, 0.78H, *J* = 4.2 Hz), 7.22-7.35 (m, 5H); ^{13}C NMR δ 7.25, 7.30, 10.7, 14.3, 35.3, 36.3, 52.3, 52.5, 73.3, 76.5,125.8, 126.4, 127.2, 127.8, 128.1, 128.3, 141.8, 142.2, 216.0 , 216.1

2,4-Dimethyl-1-hydroxy-1-phenyl-3-pentanone: (*syn/anti* = 4.0/1) IR (neat); 3462, 1706 cm^{-1}; ^1H NMR δ 0.81-1.01 (m, 9 H), 2.38-2.59 (m, 1H), 2.94-3.10 (m, 1H), 3.23 (brs, 0.2H), 3.44 (brs, 0.8H), 4.77 (d, 0.2H, *J* = 7.5 Hz), 5.01 (d, 0.8H, *J* = 4.6 Hz), 7.27-7.37 (m, 3H), 7.61-7.70 (m, 4H); ^{13}C NMR δ 11.1, 14.9, 17.6, 17.7, 17.9, 40.4, 41.3, 50.6, 50.8, 73.5, 76.9, 123.9, 124.1, 124.9, 125.5, 125.7, 125.8, 126.0, 126.1, 127.5, 127.6, 127.8, 127.87, 127.89, 128.2, 132.7, 132.95, 133.03, 133.1, 139.3, 139.8, 219.27, 219.31; HRMS calcd for $C_{13}H_{18}O_2$ (M^+) 206.1307, found 206.1303.

3-(4'-Chlorophenyl)-3-hydroxy-2-methyl-1-phenyl-1-propanone: (*syn/anti* = 1.6/1) IR (neat); 3395, 1671 cm^{-1}; ^1H NMR δ 1.05 (d, 1.17H, *J* = 7.2 Hz), 1.17 (d, 1.83H, *J* = 7.2 Hz), 3.10 (brs, 0.39H), 3.61-3.69 (m, 0.61H), 3.80 (brs, 0.61H), 3.72-3.82 (m, 0.39H), 4.95 (d, 0.39H, *J* = 8.1 Hz), 5.18 (d, 0.61H, *J* = 3.3 Hz), 7.28-7.59 (m, 7H), 7.89-7.96 (m, 2H); ^{13}C NMR δ 11.2, 15.5, 46.9, 47.8, 72.5, 75.9, 127.4, 128.0, 128.3, 128.5, 128.6, 128.73, 128.77, 132.9, 132.9, 133.4, 133.6, 133.9, 135.4, 136.5, 140.3, 140.7, 204.7, 205.6; HRMS calcd for $C_{16}H_{15}ClO_2$ (M^+) 274.0761, found 274.0746.

1-(4'-Chlorophenyl)-1-hydroxy-2-methyl-3-pentanone: (*syn/anti* = 2.6/1) IR (neat); 3428, 1707 cm^{-1}; ^1H NMR δ 0.91 (d, 0.84H, *J* = 7.2 Hz), 1.00 (t, 2.16H, *J* = 7.2 Hz), 1.02 (t, 0.84H, *J* = 7.2 Hz), 1.05 (d, 2.16H, *J* = 7.2 Hz), 2.29-2.59 (m, 2H), 2.75-2.90 (m,1H), 3.28 (brs, 0.28H), 3.45 (brs, 0.72H), 4.70 (d, 0.28H, *J* = 7.8 Hz), 5.01 (d, 0.72H, *J* = 3.7 Hz), 7.22-7.31 (m, 4H); ^{13}C NMR δ 7.31, 7.37, 10.4, 14.3, 35.3, 36.3, 52.0, 52.4, 72.5, 75.8, 127.2, 127.8, 128.3, 128.4, 132.9, 133.4, 140.3, 140.7, 215.8, 216.0; HRMS calcd for $C_{12}H_{15}ClO_2$ (M^+) 226.0761, found 226.0756.

1-Hydroxy-1-(2'-methoxyphenyl)-2-methyl-3-pentanone: (*syn/anti* = 2.9/1) IR (neat); 3464, 1706 cm^{-1}; ^1H NMR δ 0.98 (d, 0.78H, *J* = 7.2 Hz), 1.00 (t, 0.78H, *J* = 7.3 Hz) 1.01 (t, 2.22H, *J* = 7.3 Hz), 1.03 (d, 2.22H, *J* = 7.2 Hz), 2.31-2.59 (m, 2H), 2.99-3.17 (m,1H), 3.34 (brs, 0.26H), 3.37 (brs, 0.74H), 3.83 (s, 2.22H), 3.85 (s, 0.78H), 5.02 (brs, 0.26H), 5.24 (brs, 0.74H), 6.84-6.98 (m, 2H), 7.21-7.40 (m, 2H); ^{13}C NMR δ 7.3, 7.5, 10.3, 14.5, 35.2, 36.3, 49.3, 51.1, 55.1, 55.3, 69.4, 72.8, 110.0, 110.5, 120.5, 120.7, 127.6, 127.8, 128.1, 128.6, 129.5, 130.0, 155.6, 156.5, 216.2, 216.5; HRMS calcd for $C_{13}H_{18}O_3$ (M^+) 222.1256, found 222.1236.

1-Hydroxy-2-methyl-1-(2'-naphthyl)-3-propanone: (*syn/anti* = 4.0/1) IR (neat); 3450, 1705 cm^{-1}; ^1H NMR δ 0.85-1.04 (m, 6 H), 2.20-2.56 (m, 2H), 2.81-3.00 (m, 1H), 3.23 (brs, 1H), 4.82 (d, 0.2H, *J* = 8.3 Hz), 5.13 (d, 0.8H, *J* = 4.1 Hz), 7.28-7.42 (m, 3H), 7.65-7.75 (m, 4H); ^{13}C NMR δ 7.4, 7.5, 10.5, 14.5, 35.3, 36.5, 52.0, 52.4, 73.2, 76.8, 123.9, 124.2, 124.8, 125.7, 125.8, 126.0, 126.1, 126.2, 127.58, 127.62, 127.93, 127.96, 128.3, 132.7, 133.0, 139.2, 216.0, 216.3; HRMS calcd for $C_{16}H_{18}O_2$ (M^+) 242.1307, found 242.1304.

2,4-Dimethyl-1-hydroxy-1-(2'-naphtyl)-3-pentanone: (*syn/anti* = 4.0/1) IR (neat); 3442, 1703 cm^{-1}; ^1H NMR δ 0.86-1.03 (m, 9 H), 2.46-2.61 (m, 1H), 2.90-3.02 (m, 1H), 3.17 (brs, 0.2H), 3.44 (brs, 0.8H), 4.66 (d, 0.2H, *J* = 8.3 Hz), 4.92 (d, 0.8H, *J* = 4.2 Hz), 7.15-7.29 (m, 5H); ^{13}C NMR δ 11.2, 14.9,

17.6, 17.65, 17.70, 127.9, 40.5, 41.3, 50.8, 51.0, 73.6, 76.8, 126.0, 126.4, 127.4, 127.7, 128.2, 128.4, 141.9, 142.4, 219.4; HRMS calcd for $C_{17}H_{20}O_2$ (M^+) 256.1463, found 256.1437.

1-(2'-Furyl)-1-hydroxy-2-methyl-3-pentanone: (*syn/anti* = 4.0/1) IR (neat); 3406, 1708 cm^{-1}; ^1H NMR δ 0.98 (d, 0.60H, *J* = 7.1 Hz), 1.00 (t, 2.40H, *J* = 7.2 Hz), 1.04 (t, 0.60H, *J* = 7.2 Hz), 1.17 (d, 2.40H, *J* = 7.1 Hz), 2.34-2.64 (m, 2H), 3.01-3.07 (m, 0.8H), 3.13-3.20 (m, 0.2H), 3.29 (brs, 0.80H), 3.32 (brs, 0.20H), 4.78 (dd, 0.20H, *J* = 5.2, 7.9 Hz), 4.98 (m, 0.80H), 6.24-6.32 (m, 2H), 7.34-7.37 (m, 1H); ^{13}C NMR δ 7.31, 7.35, 11.6, 13.9, 34.9, 36.0, 49.6, 49.8, 68.4, 69.8, 106.6, 107.3, 110.1, 110.2, 141.6, 142.1, 154.5, 154.6, 215.0, 215.6; HRMS calcd for $C_{10}H_{14}O_3$ (M^+) 182.0943, found 182.0925.

1-Hydroxy-2-methyl-1-(2'-thiophenyl)-3-pentanone: (*syn/anti* = 5.7/1) IR (neat); 3405, 1707 cm^{-1}; ^1H NMR δ 0.991 (t, 2.55H, *J* = 7.3 Hz) 0.993 (d, 0.45H, *J* = 7.1 Hz), 1.05 (t, 0.45H, *J* = 7.3 Hz), 1.19 (d, 2.55H, *J* = 7.1 Hz), 2.28-2.62 (m, 2H), 2.88-3.02 (m,1H), 3.38 (brs, 1H), 5.01 (d, 0.15H, *J* = 8.3 Hz), 5.24 (d, 0.85H, *J* = 5.0 Hz), 6.88-6.96 (m, 2H), 7.21-7.23 (m, 1H); ^{13}C NMR δ 7.3, 11.5, 14.4, 35.3, 36.3, 52.8, 52.9, 70.4, 72.5, 123.6, 124.2, 124.7, 125.0, 126.5, 126.6, 145.8, 146.2, 215.5, 215.7; HRMS calcd for $C_{10}H_{14}O_2S$ (M^+) 198.0715, found 198.0723.

1-Heptene-3-hydroxy-4-methyl-1-phenyl-5-one: (*syn/anti* = 2.3/1) IR (neat); 3443, 1706 cm^{-1}; ^1H NMR δ 0.99 (t, 3.0H, *J* = 7.3 Hz), 1.05 (d, 0.3H, *J* = 7.1 Hz), 1.11 (d, 0.7H, *J* = 7.3 Hz), 2.39-2.56 (m, 2H), 2.62 (brs, 0.3H), 2.67-2.75 (m, 1H), 2.85 (brs, 0.7H),4.30 (d, 0.3H, *J* = 7.1 Hz), 4.54 (d, 0.7H, *J* = 4.7 Hz), 6.02-6.13 (m, 1H), 6.54 (d, 0.3H, *J* = 15.9 Hz), 6.56 (d, 0.7H, *J* = 15.8 Hz), 7.11-7.31 (m, 5H); ^{13}C NMR δ 7.45, 7.51, 11.0, 14.2, 35.4, 36.2, 50.4, 51.1, 72.4, 75.1, 126.4, 126.5, 127.7, 127.8, 128.5, 128.6, 129.0, 129.6, 131.1, 132.1, 215.7, 215.9; HRMS calcd for $C_{14}H_{18}O_2$ (M^+) 218.1307, found 218.1309.

3-Hydroxy-4-methyl-1-phenyl-5-heptanone:[23] (*syn/anti* = 4.0/1) IR (neat); 3458, 1705 cm^{-1}; ^1H NMR δ 1.04 (t, 3 H, *J* = 7.2 Hz), 1.10-1.18 (m, 3H), 1.50-1.95 (m, 3H), 2.30-3.00 (m, 4H), 3.62-3.78 (m, 0.2H), 3.87-4.00 (m, 0.8H), 7.10-7.40 (m, 5H); ^{13}C NMR δ 7.45, 7.52, 10.1, 14.3, 17.3, 18.5, 35.0, 35.8, 36.0, 36.7, 50.0, 51.0, 71.4, 73.0, 125.8, 128.37, 128.42, 141.83, 216.7

3-Cyclohexyl-3-hydroxy-2-metyl-1-phenyl-1-propanone: (*syn/anti* = 4.6/1) IR (neat); 3442, 1704 cm^{-1}; ^1H NMR δ 1.17-1.88 (m, 13H), 2.03 (d, 0.82H, *J* = 11.8 Hz), 2.19 (d, 0.18H, *J* = 12.3 Hz), 3.07-3.16 (m, 1H), 3.62-3.85 (m, 2H), 7.54-7.70 (m, 3H), 8.00-8.06 (m, 2H); ^{13}C NMR δ 10.5, 16.2, 25.8, 26.3, 26.1, 26.3, 26.4, 27.7, 29.15, 29.23, 29.4, 30.2, 40.2, 41.3, 41.8, 75.4, 78.9, 128.3, 128.39, 128.41, 128.74, 133,3, 133.4, 135.9, 136.6, 205.9, 206.4; HRMS calcd for $C_{16}H_{22}O_2$ (M^+) 246.1620, found 246.1654.

Methyl 3-hydroxy-2,2-dimethyl-3-phenylpropionate:[24] Benzaldehyde (0.5 mmol), the ketene silyl acetal of methyl isobutyrate (0.75 mmol), catalyst **1a** (20 mol%), and Triton X-100 (3 mol%, 5M solution) were combined in water (1.5 ml) at 0 °C. The mixture was stirred for 24 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 methyl 3-hydroxy-2,2-dimethyl-3-phenylpropionate. The enantiomeric excess was determined by HPLC analysis using a chiral column. Mp. 69.5-70.5 ℃; IR (KBr); 3495, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.97 (s, 3H), 1.05 (s, 3H), 3.25 (brs, 1H), 3.52 (s, 3H), 4.72 (s, 1H), 7.06-7.26 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 19.0, 23.0, 47.7, 52.1, 78.6, 127.6, 127.7, 139.9, 178.2

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