

Aqueous Asymmetric Mukaiyama Aldol Reaction Catalyzed by Chiral Gallium Lewis Acid with Trost-Type Semi-Crown Ligands

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Abstract: The combination of Ga(OTf)₃ with chiral semi-crown ligands (**1a–e**) generates highly effective chiral gallium Lewis acid catalysts for aqueous asymmetric aldol reactions of aromatic silyl enol ethers with aldehydes. A ligand-acceleration effect was observed. Water is essential for obtaining high diastereoselectivity and enantioselectivity. The *p*-phenyl substituent in aromatic silyl enol ether (**2h**) plays an important role and increases the enantioselectivity up to 95% ee. Although aliphatic silyl enol ethers provided low enantioselectivities and silylketene acetal is easily

hydrolyzed in aqueous alcohol, the aldol reactions of silylketene thioacetal (**12**) with aldehydes in the presence of gallium-Lewis acid catalysts give the β -hydroxy thioester with reasonable yields and high diastereo- (up to 99:1) and enantioselectivities (up to 96% ee).

Keywords: aqueous asymmetric C–C bond-forming reaction; chiral semi-crown ligand; gallium-Lewis acid catalyst, Mukaiyama aldol reaction

Introduction

Among the Lewis acid-catalyzed carbon-carbon bond forming reactions, the aldol-type reaction of silyl enol ethers with carbonyl compounds (the Mukaiyama reaction)^[1] has been recognized as one of the most important. In 1990 Mukaiyama^[2] reported the first asymmetric aldol reaction of silyl enol ethers catalyzed by chiral diamine/Sn(OTf)₂. Since then, several successful examples of the catalytic asymmetric Mukaiyama aldol reaction have been developed, including the use of *p*-Tol-BINAP with AgF^[3] or CuF,^[4] BINOL with Zr(O-*t*-Bu)₄^[5] or Ti(O-*i*-Pr)₄,^[6] and chiral bis(oxazoline) with Cu(II)^[7] or Sc(III)^[8] as chiral catalysts. However, most of these reactions must be conducted at low reaction temperatures in aprotic anhydrous solvents. Recently, the performance of organic reactions in water^[9] has attracted considerable attention, which was followed by a growing interest in the development of asymmetric Mukaiyama-type reaction in aqueous media.^[10] Kobayashi and co-workers^[11] have reported excellent results using the combination of Cu(OTf)₂ with a chiral bis(oxazoline) ligand,^[12] Pb(OTf)₂ with a chiral crown ether^[13] and Ln(OTf)₃ [e.g., Nb(OTf)₃, Ce(OTf)₃ and Pr(OTf)₃] with chiral

bis-pyridino-18-crown-6^[14] for asymmetric Mukaiyama aldol reactions in aqueous ethanol (ethanol-water = 9:1). However, when the amount of water in the mixture was increased, yields and selectivities of the reaction decreased remarkably and, in water alone, both low yield (4%) and selectivity (ee 15%) were observed.^[14] Furthermore, compared to “heavier” metals, the use of ‘light’, main-group metal catalysts has environmental benefits and is more attractive. More recently, Kobayashi reported the catalytic asymmetric hydroxymethylation of silicon enolates with formaldehyde in aqueous solution with up to 90% ee by using a chiral scandium complex as catalyst^[15] and Jankowska reported an asymmetric Mukaiyama aldol reaction in aqueous media with up to 75% ee by using Zn-based chiral Lewis acid.^[16]

On the other hand, there are still various challenging problems to face in developing catalytic asymmetric reaction in aqueous media. Will water promote or prevent the reaction? How do we address the hydrolysis and solubility of the substrate in water? How do we balance the binding affinity of the metal with the ligand for asymmetric induction and reactivity of the chiral catalyst in water (i.e., how to complete the catalytic cycle in water)? Recently, Trost developed a chiral semi-crown ligand/di-

nuclear zinc catalyst system, which has been successfully applied in catalytic enantioselective direct aldol reactions,^[17] nitroaldol (Henry) reactions,^[18] Mannich-type reactions^[19] and diol-desymmetrizations.^[20] As shown by Trost, the semi-crown ligand (bearing more hydroxy groups) has more binding sites towards metals, which can meet both requirements of good affinity to metals and higher catalytic activity. It appears that these compounds are highly promising chiral ligands in asymmetric reactions in aqueous media. Herein, we report on the use of chiral gallium catalysts with chiral semi-crown ligands for a catalytic asymmetric Mukaiyama reaction in aqueous media.^[21]

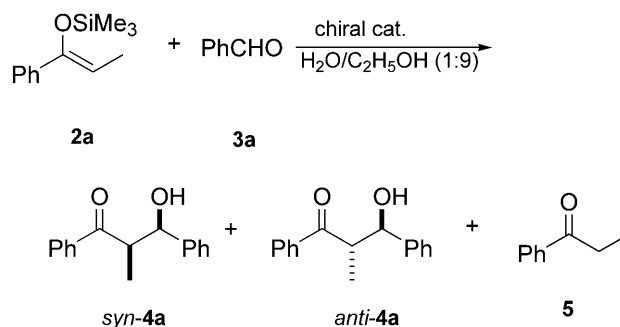
Results and Discussion

According to the literature methods^[16], the chiral semi-crown type ligands **1a–g** used in our study were synthesized (Figure 1) by two synthetic routes. The mono-arm ligand **1h** was prepared similarly starting from 2-methanol-4-*t*-butylphenol. Treatment of various ketones with NaH in toluene followed by reaction with chlorotrimethylsilane gave the corresponding (*Z*)-silyl enol ethers (*Z*/*E* = > 99:1). After establishing an optimized experimental procedure and ratio of the reactants used, the chiral Lewis acid catalysts were prepared by stirring a mixture of the metal salt with the chiral ligand (1:1.2) in dichloromethane at room temperature for 2 h. After evaporation of the solvent and other volatile compounds, the solid complex thus obtained was employed as catalyst in the aldol reaction without further purification.

At first, (*Z*)-1-phenyl-1-trimethylsiloxypropene (**2a**) was reacted with benzaldehyde (**3a**) in aqueous ethanol (C₂H₅OH/H₂O = 9:1) in the presence of various Lewis acid catalysts (20 mol %), which were prepared from

Sc(OTf)₃, Nd(OTf)₃, Pb(ClO₄)₂, Cu(OTf)₂, Zn(OTf)₂, and In(OTf)₃ with the chiral semi-crown ligand (*S,S*)-**1a** (Scheme 1). Although, in all cases, the reaction proceeded smoothly to give the aldol product **4a** in good yields (75–90%) and diastereoselectivities (*syn*:*anti* > 80:20), the enantioselectivities of the formed *syn*-**4a** were very poor (0–5%). Fortunately, when a catalytic amount of Ga(OTf)₃ (20 mol %) was used under the same reaction conditions, the ee of *syn*-**4a** was increased remarkably to 80%. It is noteworthy to mention that although there are extensive reports on the use of chiral aluminium Lewis acids in asymmetric reactions, there are only few examples of chiral gallium-Lewis acid-catalyzed asymmetric reactions.^[21]

Subsequently, various gallium-Lewis acids prepared by chiral semi-crown ligands (**1a–g**) or mono-arm-type ligands (**1h, i**) with Ga(OTf)₃ were examined in the asymmetric aldol reaction of **2a** with **3a** in aqueous alcohol (C₂H₅OH/H₂O = 9:1) (Table 1). It is seen in Table 1 that the use of chiral ligand (*S,S*)-**1b** (R = *t*-butyl) provided a slightly higher enantioselectivity (87% ee) than chiral ligand (*S,S*)-**1a** (R = methyl) (80% ee) (entries 2 vs. 1). The use of chiral ligand (*S,S*)-**1c** (R = F) re-



Scheme 1.

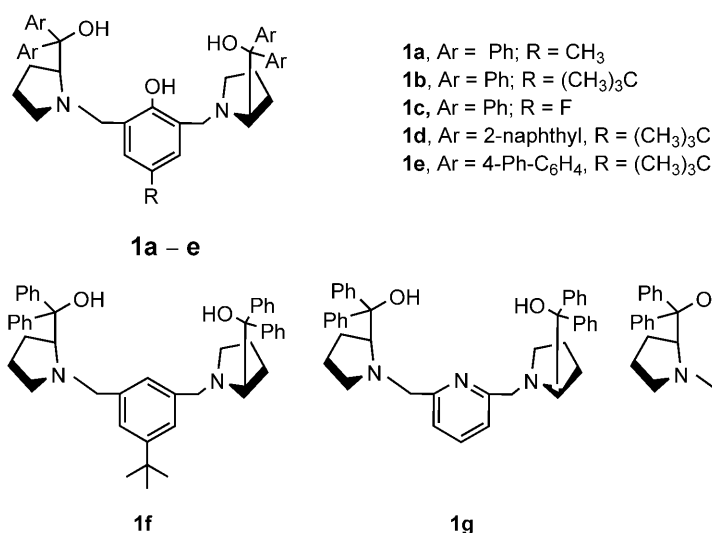


Figure 1. Chiral semi-crown type ligands **1a–g** and mono-arm-type ligands **1h, i**.

Table 1. The reaction of **2a** with **3a** in aqueous media.^[a]

Entry	Chiral catalyst ^[b] [L* + Ga(OTf) ₃]	Reaction time ^[c] [h]	Yield of 4a ^[d] [%] (<i>syn/anti</i>) ^[e]	ee of <i>syn</i> - 4a ^[f] [%]	Yield of 5 ^[d] [%]
1	1a	36	80 (87/13)	80	5
2	1b	36	89 (89/11)	87	trace
3	1b + GaCl ₃	36	61 (84/16)	78	–
4	1c	24	76 (88/12)	78	5
5	1d	8	81 (90/10)	87	–
6	1e	8	84 (95/5)	86	–
7	1f	36	–	–	98
8	1g	36	65 (85/15)	44	31
9	1h	36	72 (89/11)	5	20
10	1i	36	49 (90/10)	2	48
11	Ga(OTf) ₃	15 min	–	–	98
12	GaCl ₃	36	trace	–	–

^[a] In H₂O/C₂H₅OH (1:9).^[b] Catalyst loading: 20 mol %.^[c] Reaction temperature: 0–5 °C.^[d] Yield of isolated product.^[e] Determined by ¹H NMR.^[f] Determined by chiral HPLC.

sulted in a decrease in the enantioselectivity (78% ee, entry 4). The use of non-C₂-symmetrical mono-prolinol ligands (*S*)-**1h** and (*S*)-**1j** did not provide any significant enantioselectivity (entries 9 and 10).

There are two competing reactions in the aqueous reaction of silyl enol ether with aldehyde: the aldol reaction and hydrolysis of the silyl enol ether. If Ga(OTf)₃ (without the chiral ligand) was used alone in the aqueous aldol reaction, silyl enol ether **2a** hydrolyzed completely in only 15 min to give 1-phenylpropanone (**5**) (entry 11); whereas the use of GaCl₃ alone as catalyst, although no hydrolyzed product **5** was obtained, resulted in only trace amounts of aldol product after stirring for 36 h (entry 12). However, when the Ga-Lewis acid catalysts [prepared from semi-crown ligand **1b** and Ga(OTf)₃ or GaCl₃] were employed, the aqueous aldol reaction of **2a** with **3a** provided both good yield and enantioselectivity of the aldol product **4a** together with a trace amount of **5** (entries 2 and 3). These results suggested that the ligand played an important role in accelerating the aldol reaction and suppressing the hydrolysis of silyl enol ethers in aqueous media. The reaction was further accelerated with the use of ligands **1d** and **1e**, in which the phenyl group on the chiral ligand was replaced by 2-naphthyl and 4-biphenyl groups: the reaction time was shortened from 24 h to 8 h with a slightly higher diastereoselectivity (*syn/anti* = 95:5) and the same enantioselectivities of *syn*-**4a** (86% ee) (entries 5 and 6).

In order to elucidate the binding ability of the semi-crown ligands with Ga³⁺ in aqueous media, UV-vis titration of the chiral ligands with Ga(OTf)₃ was performed. The plotting of the change of optical density (C₀/ΔOD) against OD^{−1} afforded a line with linear correlation coefficients (R) when mixing the chiral ligands with

Ga(OTf)₃ in H₂O/C₂H₅OH (1:9), indicating the formation of a 1 + 1 complex. The values of the corresponding R (0.9973–0.9999) (Table 2) indicated a very good linear relationship and also show the reliability of the plots in extracting the association constants. The introduction of a solution of the prepared complex **1b**/Ga(OTf)₃ in H₂O/C₂H₅OH (1:9) to an electrospray mass spectrometer provided two peaks at *m/e* = 748.8 (calcd. for C₄₆H₅₀GaN₂O₃: 748.6) and 899.8 (calcd. for C₄₇H₅₂F₃GaN₂O₆S: 899.6) that correspond to M + 1 and M + 1 + HOTf, respectively. The results also demonstrated the formation of a 1 + 1 complex in aqueous alcohol. However, no peak was observed in the electrospray mass spectrum of the complex **1f**/Ga(OTf)₃ under the same conditions. Based on the Benesi–Hildebrand relationship,^[22] the association constant could be determined by the UV-vis titration of chiral ligand with the solution of Ga(OTf)₃ in H₂O/C₂H₅OH (1:9) (Table 2). As shown in Table 2, the complex of the semi-crown li-

Table 2. Association constants of the complex in H₂O/C₂H₅OH (1:9).

Complex [ligand/Ga(OTf) ₃]	Association constant ^[a] [M ^{−1}]	R ^[b]
1a + Ga(OTf) ₃	5.89 × 10 ³	0.9973
1b + Ga(OTf) ₃	1.20 × 10 ⁴	0.9979
1c + Ga(OTf) ₃	4.44 × 10 ²	0.9997
1f + Ga(OTf) ₃	6.69 × 10 ²	0.9999
1g + Ga(OTf) ₃	3.73 × 10 ³	0.9998
1h + Ga(OTf) ₃	5.08 × 10 ²	0.9996

^[a] Measured by UV-vis titration.^[b] Linear correlation coefficient.

gand bearing a phenol hydroxy group and a *tert*-butyl group in the phenyl ring (**1b**) with Ga(OTf)₃ has the largest association constant ($1.20 \times 10^4 \text{ M}^{-1}$), and exhibits the highest binding ability of the semi-crown ligand to Ga³⁺ in aqueous media. The ligand **1f** (with two alkyl hydroxy and without a phenol hydroxy group) and mono-arm ligand **1h** (with one alkyl hydroxy and one phenol hydroxy group) also have relatively low association constants (6.69×10^2 and 5.08×10^2 , respectively), which correspond to weak bonding. Thus, the Trost ligand has more binding sites and can generate a stronger [O–Ga] bond through the removal of HOTf from the reaction of OH with Ga(OTf)₃. On the other hand, the complex of ligand **1g** (with a pyridine group) with Ga³⁺, which generates a N···Ga coordination bond, has a slightly lower association constant (3.73×10^3). On the basis of these results, it can be postulated that there is a dynamic equilibrium between the complex and the gallium species as well as the ligand in aqueous media. For the complex (S,S)-**1b**/Ga(OTf)₃, the equilibrium shifted more to the side of forming the chiral and reactive catalyst complex, leading to a higher yield of aldol product and asymmetric induction (Table 1, entry 2). Whereas, since the complex **1f**/Ga(OTf)₃ has a low binding ability (lower value of R) in aqueous media, the equilibrium shifted towards the side of dissociation, generating a gallium species that is inactive in catalyzing the aldol reaction and leading to hydrolysis of the silyl enol ether (Table 1, entry 7).

In view of the above results, the chiral catalyst [(S,S)-**1b**/Ga(OTf)₃] was selected for further studies. The effect of the reaction solvent on the reaction was also examined (Table 3). Since the complex **1b**/Ga(OTf)₃ has the strongest binding ability in aqueous media, both diastereo- and enantioselectivities remained high with an increase of the water content in the mixture-solvent and with water alone as the solvent (Table 3, entries 2–5). However, in water alone the reaction was slow and gave a lower yield of the aldol reaction product. In this

case, the addition of a surfactant (SDS) did not improve the yield of the reaction. On the other hand, the use of ethanol as solvent decreased the enantioselectivity of *syn*-**4a** significantly (entry 1). In anhydrous THF, the reaction offered the aldol product in a low yield (47%) together with lower diastereo- (*syn/anti* = 77:23) and enantioselectivities (44% ee of *syn*-**4a**); the addition of a small amount of water dramatically improved the yield (80%), diastereoselectivity (88:12) and enantioselectivity (80% ee) (entries 6 and 7). Only a trace amount of the aldol product was detected when dichloromethane was used as solvent under the same reaction conditions (entry 8).

Subsequently, various aromatic aldehydes were employed in the asymmetric aldol reaction in water/ethanol (9:1) under the same reaction conditions catalyzed by the chiral gallium-Lewis acid [Ga(OTf)₃]/(S,S)-**1b**. In all cases, the reactions provided good yields (77–90%), diastereoselectivities (*syn/anti* = 80/20–90/10) and enantioselectivities of *syn*-products (78–88% ee) (Table 4). The presence of an electron-withdrawing group on the phenyl ring of the aldehyde (e.g., Cl) decreased the enantioselectivity (entry 4). The effect is more prominent in the case of *p*-nitrobenzaldehyde (**3g**), generating *syn*-**4g** in 62% ee (entry 7). The absolute configuration of *syn*-**4a** and its analogues were determined as 2*R*,3*R* by comparing the optical rotation of *syn*-**4a** ([α]_D: –11.5) and *syn*-**4f** ([α]_D: –101.5) with those of the authentic compounds (2*S*,3*S* enantiomers: [α]_D: +11.7 and +103.6, respectively).^[24] The reaction of an aliphatic aldehyde (**3h**) gave a lower ee (30%) (entry 8). No reaction was observed with simple ketones under the current conditions.

In order to investigate the relationship of the structure of silyl enol ether with the enantioselectivity, various silyl enol ethers **6a–e** and **2a–h** were synthesized and employed in aldol reactions with aldehydes (Scheme 2). Since **6a** is less stable in water, the yield of the aldol product is low (30%, Table 5, entry 1). The increase of the

Table 3. The reaction of **2a** with **3a** in various solvents.^[a]

Entry	Solvent	Reaction time ^[b]	Yield of 4a ^[c] [%] (<i>syn/anti</i>) ^[d]	ee of <i>syn</i> - 4a ^[e] [%]
1	C ₂ H ₅ OH	36 h	75 (88/12)	58
2	H ₂ O/C ₂ H ₅ OH (1:9)	36 h	89 (89/11)	87
3	H ₂ O/C ₂ H ₅ OH (1:1)	36 h	84 (82/18)	82
4	H ₂ O/C ₂ H ₅ OH (9:1)	36 h	85 (85/15)	85
5	H ₂ O	3 d	41 (90/10)	84
6	THF	36 h	47 (77/23)	44
7	H ₂ O/THF (1:4)	36 h	80 (88/12)	80
8	CH ₂ Cl ₂	3 d	trace	

^[a] Catalyst: **1b**/Ga(OTf)₃ (20 mol %).

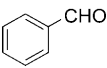
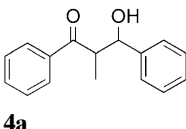
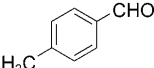
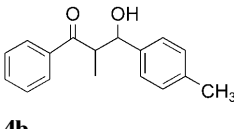
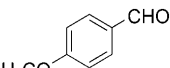
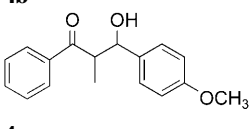
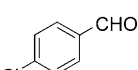
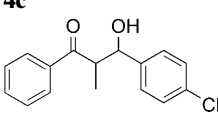
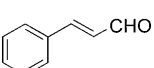
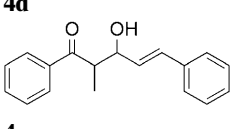
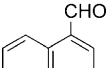
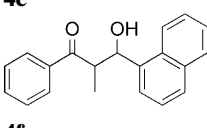
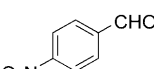
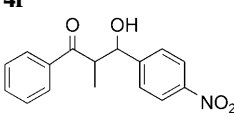
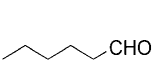
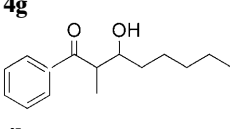
^[b] Reaction temperature: 0–5 °C.

^[c] Yield of isolated product.

^[d] Determined by ¹H NMR.

^[e] Determined by chiral HPLC.

Table 4. The reactions of **2a** with various aldehydes (**3a–h**) in aqueous media.^[a]

Entry	Aldehyde (R)	Product (R)	Yield of 4 ^[b] [%] (<i>syn/anti</i>) ^[c]	ee of <i>syn-4</i> ^[d] [%]
1	 3a	 4a	85 (85/15)	85
2	 3b	 4b	89 (90/10)	88
3	 3c	 4c	80 (88/12)	84
4	 3d	 4d	77 (82/18)	78
5	 3e	 4e	90 (90/10)	86
6	 3f	 4f	87 (80/20)	82
7	 3g	 4g	82 (77/23)	62
8	 3h	 4h	78 (87/18)	30

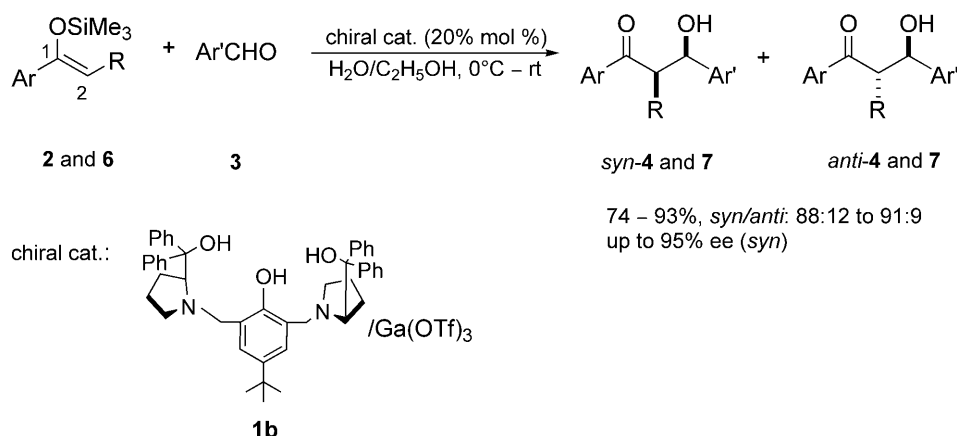
^[a] In H₂O/C₂H₅OH (9:1), reaction temperature: 0–5 °C.^[b] Yield of isolated product.^[c] Determined by ¹H NMR.^[d] Determined by chiral HPLC.

bulkiness of substituents at the 2-position of the silyl enol ether affected the stereochemistry of the reaction strongly, and resulted in low enantioselectivities (46–59% ee) (Table 5, entries 3–6).

However, variation of the aryl group at the 1-position of the silyl enol ethers gave very interesting results: when 1-(4'-biphenyl)-1-trimethylsiloxy-1-propene (**2h**) was used, the diastereoselectivity of the aldol reaction is *syn/anti*=90:10 and the enantioselectivity of the *syn*-aldol product (*syn-4p*) reached up to 95% ee (Table 6, entry 9); although the aldol reaction of aromatic aldehydes bearing an electron-withdrawing group [such as chloro (**3d**) and bromo (**3i**)] gave relatively

low enantioselectivities of the *syn*-aldol product in general, the reaction of **2h** with **3d** or **3i** gave >90% ee (entries 10 and 11). The high enantioselectivity can be attributed to the hydrophobic π – π stacking between the aromatic silyl enol ether and aromatic aldehyde in aqueous media.

The silyl enol ethers (**9a** and **9b**) prepared from aliphatic ketones are generally unstable in aqueous media and undergo hydrolysis readily to form ketones. In the current reaction, an excess amount of silyl enol ethers is required (**9a** or **9b**:**3a**=3:1) and the yields of aldol products are also relatively lower (Table 7, entries 1 and 2). The use of these compounds also led to lower



Scheme 2.

Table 5. The reaction of silyl enol ether **2a**, **6a–e** with benzaldehyde (**3a**) in aqueous media.^[a]

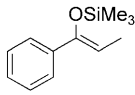
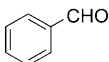
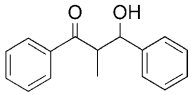
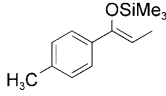
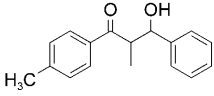
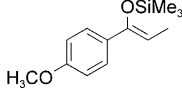
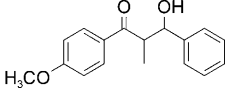
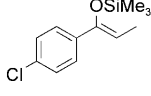
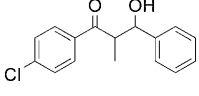
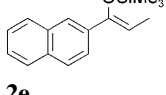
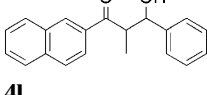
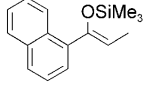
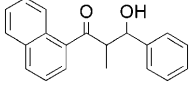
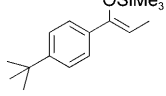
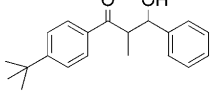
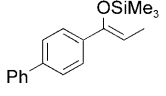
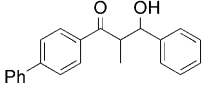
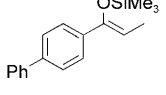
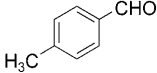
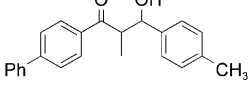
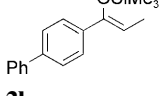
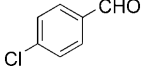
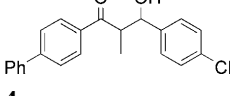
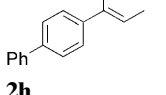
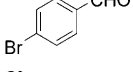
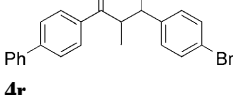
Entry	Silyl enol ether (R)	Product (R)	Yield of 7 ^[b] [%] (<i>syn/anti</i>) ^[c]	ee of <i>syn</i> - 7 [%] ^[d]
1			30	66
2			89 (89/11)	87
3			91 (83/17)	46
4			93 (71/29)	53
5			88 (82/18)	59
6			83 (58/42)	51

^[a] In $\text{H}_2\text{O}/\text{C}_2\text{H}_5\text{OH}$ (1:9), reaction temperature: room temperature.^[b] Yield of isolated product.^[c] Determined by ^1H NMR.^[d] Determined by chiral HPLC.

enantioselectivity (71–73% ee) compared with the reaction of aromatic silyl enol ethers with benzaldehyde. Silylketene acetal **11** is even more unstable and only hydrolysis product was isolated after stirring for 24 h. Previously, Kobayashi^[14b] reported that the aqueous asym-

metric reactions of silyl ketene thioacetal with aldehyde gave optically active β -hydroxy thioesters in 78–83% ee of the *syn*-products, which are useful compounds for synthesizing optically pure alcohols. Because silylketene thioacetals are more sensitive to water, 2,6-di-*tert*-

Table 6. The reaction of aromatic silyl enol ethers with aldehydes in aqueous media.^[a]

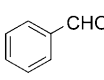
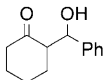
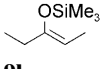
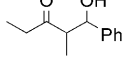
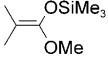
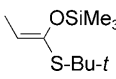
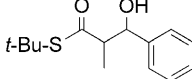
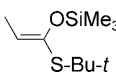
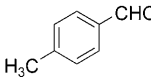
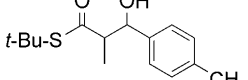
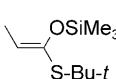
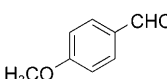
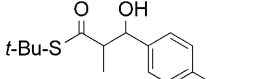
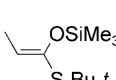
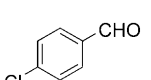
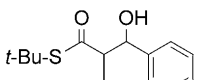
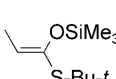
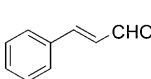
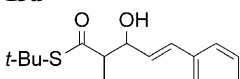
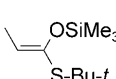
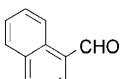
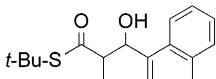
Entry	Silyl enol ether	Aldehyde	Product	Yield [%] ^[b] (<i>syn/anti</i>) ^[c]	ee of <i>syn</i> - 4 ^[d] [%]
1	 2a	 3a	 4a	89 (89/11)	87
2	 2b		 4i	85 (88/12)	85
3	 2c		 4j	84 (90/10)	82
4	 2d		 4k	87 (90/10)	77
5	 2e		 4l	93 (92/8)	88
6	 2f		 4m	87 (90/10)	86
7	 2g		 4n	86 (95/5)	88
8	 2h		 4o	92 (91/9)	94
9	 2h	 3b	 4p	88 (90/10)	95
10	 2h	 3d	 4q	81 (89/11)	92
11	 2h	 3i	 4r	74 (90/10)	91

^[a] In H₂O/C₂H₅OH (1:9), reaction temperature: room temperature.^[b] Yield of isolated product.^[c] Determined by ¹H NMR.^[d] Determined by chiral HPLC.

butylpyridine (30 mol %) must be added in order to suppress the competing hydrolysis reaction effectively. The addition of 2,6-di-*tert*-butylpyridine is not necessary in

the current reaction. By using the Trost ligand/Ga(OTf)₃ as chiral catalyst, the reaction of silylketene thioacetal **12** with aldehydes in aqueous alcohol (H₂O/C₂H₅

Table 7. The reaction of silyl substrates with aldehydes in aqueous media.^[a]

Entry	Silyl substrate	Aldehyde	Reaction time ^[b] [h]	Product	Yield ^[c] [%] (<i>syn/anti</i>) ^[d]	ee of <i>syn</i> -[%] ^[e]
1	 9a	 3a	16	 10a	66 (90/10)	73
2	 9b		16	 10b	64 (84/16)	71
3	 11		24	—	—	—
4	 12		48	 13a	67 (91/9)	84
5	 12	 3b	72	 13b	64 (99/1)	87
6	 12	 3c	72	 13c	69 (91/9)	88
7	 12	 3d	72	 13d	70 (83/17)	80
8	 12	 3e	72	 13e	76 (88/12)	90
9	 12	 3f	72	 13f	72 (99/1)	96

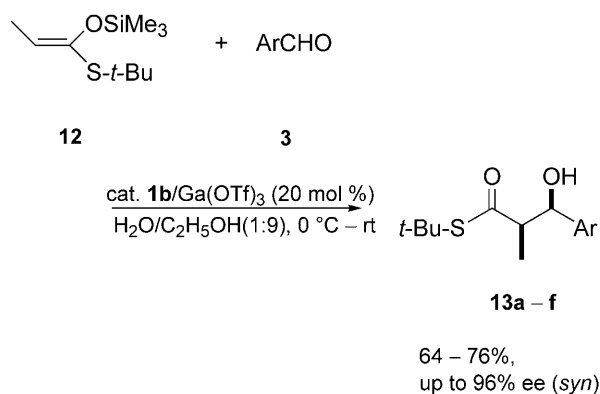
^[a] In H₂O/C₂H₅OH (1 : 9).^[b] Reaction temperature: room temperature.^[c] Yield of isolated product.^[d] Determined by ¹H NMR.^[e] Determined by chiral HPLC.

OH = 1 : 9) gave the corresponding aldol products **13a–f** in the reasonable yields 64–76% and high diastereoselectivities (*syn/anti* = 83 : 17 to 99 : 1) (Scheme 3). When 1-naphthylaldehyde (**3f**) was used, the enantioselectivity of the product *syn*-**13f** reached 96% ee (entry 9). The configuration of the *syn*-β-hydroxy thioesters was deduced as *2R,3R* by comparing the retention time of authentic compound^[14b] with that of *syn*-**13c** on chiral HPLC (using the same column: Daicel Chiralcel OD):

t_R = 16.2 (major) and 26.2 min (minor) vs. *t_R* = 16.2 (major) and 25.0 min (minor).

Conclusion

Chiral gallium-Lewis acids with chiral semi-crown ligands (Trost's ligand) have been developed for catalytic asymmetric Mukaiyama aldol reactions in aqueous me-



Scheme 3.

dia. The strong binding of Ga³⁺ with the semi-crown ligands and the ligand acceleration effect of the chiral gallium catalysts exerted in the aldol reaction are responsible for the high enantioselectivities of the aqueous asymmetric reactions. The scope and applications of such chiral gallium catalysts in asymmetric C–C bond-forming reactions in aqueous media are under further investigation.

Experimental Section

General Remarks

IR spectra were recorded on a Perkin-Elmer 782 infra-red spectrometer. ¹H and ¹³C NMR spectra were measured with Varian XL-300 and Bruker DMX-300 (300 MHz) spectrometers in CDCl₃ with tetramethylsilane as an internal standard. Mass spectra were recorded on a Bruker APEX-2 spectrometer using the FBA technique. Electrospray ionization mass spectrometry (ESI-MS) analyses were performed using an LCMS-2010 mass spectrometer (Shimadzu, JAP). The sample solution (5 μL) was directly delivered into the ESI source with a syringe. The mobile phase was C₂H₅OH:H₂O (9:1, v/v). HPLC spectra were performed on a Shimadzu CTO-10ASVP equipped with the stated chiral columns. Optical rotation was measured on a Perkin-Elmer 241 (589 nm). The UV-vis titration was performed on a Techcomp UV-2410 spectrometer. Melting points were measured using a Beijing-Taike X-4 apparatus and are uncorrected. Sample **1i** is a gift kindly provided by Dr. H. Chen of Peking University.

Synthesis of the Chiral Ligands

Chiral ligands **1b–h** were synthesized according to the literature procedure for the synthesis of (S,S)-**1a**.^[17]

Ligand (S,S)-1b: A light yellow solid, mp 96–98 °C; [α]_D: +46.0 (c 1.0, CH₂Cl₂); IR: ν = 3424, 3058, 3028, 2960, 2870, 1600, 1485, 1448, 1116 cm⁻¹; ¹H NMR: δ = 1.24 (9H, s), 1.54–2.04 (8H, m), 2.42 (2H, m), 2.81 (4H, m), 3.26, 3.42 (4H, ABq, J = 12.7 Hz), 6.80 (2H, s), 7.12–7.35 (12H, m), 7.58 (4H, d, J = 7.8 Hz), 7.73 (4H, d, J = 7.8 Hz); ¹³C NMR: δ = 29.7, 23.5,

31.7, 34.0, 55.0, 57.7, 71.4, 78.9, 124.0, 125.9, 126.0, 126.4, 126.6, 127.1, 128.0, 128.2, 128.8, 146.4, 147.0, 152.6; HR-MS (FAB): *m/z* = 681.4066, calcd. for C₄₆H₅₂N₂O₃: 681.4066.

Synthesis of (Z)-Silyl Enol Ethers

To a suspension of sodium hydroxide (114 mg, 6 mmol) in toluene (25 mL), aryl ketone (4 mmol) and trimethylchlorosilane (0.76 mL, 6 mmol) were added dropwise, followed by refluxing for 12 h. Upon cooling to room temperature, triethylamine (0.83 mL, 6 mmol) was added, and the mixture was poured into a mixture of hexane/ice water. The organic layer was separated and dried over Na₂SO₄. After evaporation of solvent, the crude material was purified by flash chromatography on silica column (eluent: hexane) to give the product. All the prepared silyl enol ethers have predominantly the (Z)-configurations

(Z/E = > 99:1) as determined by ¹H NMR.

Aldol Reaction of Silyl Enolate with Aldehydes in the Presence of a Chiral Catalyst

Preparation of the chiral catalyst: A solution of the chiral ligand (0.12 mmol) and Ga(OTf)₃ (51.7 mg, 0.1 mmol) in methylene chloride (1 mL) was stirred for 6 h at room temperature. The solvent was evaporated to give a slightly yellow solid that was used as the chiral catalyst directly.

Typical experimental procedure for the aldol reaction: Benzaldehyde (**3a**; 5 mL, 0.5 mmol) and silyl enol ether **2a** (154.5 mg, 0.75 mmol) were added into a solution of the above-prepared catalyst in a mixed solvent (H₂O/C₂H₅OH = 1:9) at 0–5 °C, followed by stirring for 36 h at 0 °C to room temperature. The reaction was quenched with aqueous NaHCO₃. The mixture was extracted with ether (3 ×), and the combined organic phase was dried over Na₂SO₄ and concentrated. The crude product was purified by flash chromatography on silica gel (eluent: ethyl acetate-petroleum ether = 1:10) to give a mixture of *syn*- and *anti*-**4a**. The *syn/anti* ratio was determined by ¹H NMR and the ee of *syn*-**4a** by chiral HPLC.

Characterization data of compounds **1**, **2**, **4**, and **13** can be found in the Supporting Information.

Acknowledgements

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