

Chiral anionic surfactants for asymmetric Mukaiyama aldol-type reaction in water[†]

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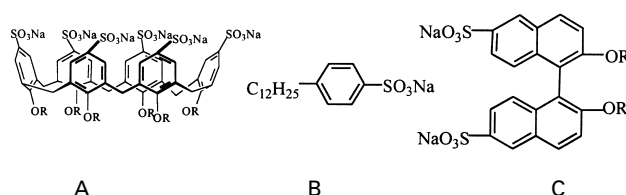
Sulfonate derivatives of chiral 1,1'-binaphthol were used as chiral anionic surfactants in asymmetric aldol-type reaction in water to give aldol adducts with moderate to good diastereo- and enantioselectivities; Ga(OTf)₃ and Cu(OTf)₂ were better than Sc(OTf)₃ as Lewis acid catalysts.

Keywords: chiral surfactant, asymmetric aldol-type reaction in water, Lewis acid catalyst

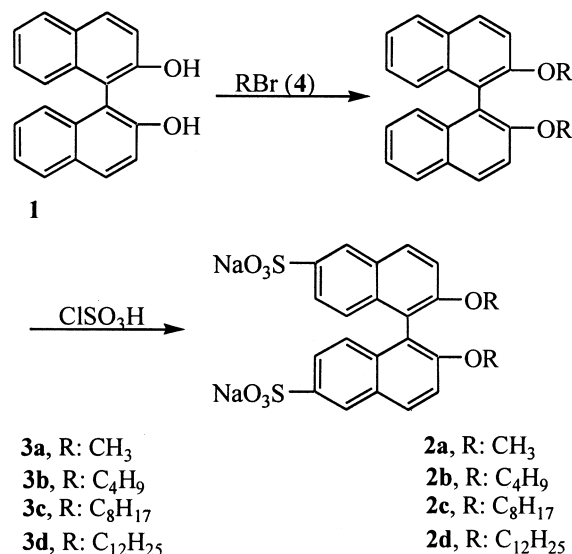
There is a great deal of interest in searching for alternative media and processes for chemical and organic synthesis on the basis of green chemistry.¹ Interest has grown in studying organic reactions in water.² The aldol-type reaction of silyl enol ethers with carbonyl compounds (the Mukaiyama reaction³) has been recognised as one of the most important carbon-carbon bond-forming reactions. Recently, while great progress has been made on aqueous Mukaiyama aldol reactions by using a series of water-tolerant Lewis acids, such as the lanthanide triflates, and metal salts,⁴ asymmetric Mukaiyama aldol reactions in water have been virtually unexplored.⁵ Very recently Kobayashi reported the first such study using lead or lanthanide reagents complex with chiral crown-ether in a co-solvent: ethanol/water.⁶ Related asymmetric reactions in aqueous media still remain challenging and also attractive. It was found that in order to promote the reactions in water alone, surfactants must be added to the lanthanide triflate-catalysed reaction medium, so that a micellar system is formed.⁷ So far as we know, chiral surfactants have been mainly applied in enantiomer separation by capillary electrochromatography,⁸ but there have been very few positive results concerning the use of chiral surfactant for asymmetric induction in aqueous reaction, for instance only in oxidation⁹ and reduction reaction.¹⁰ Herein, we report the investigation of chiral anionic surfactants for use in asymmetric Mukaiyama aldol reactions in water.

Results and discussion

Previously, we reported that calix[6]arene (A) and aromatic (B) sulfonate derivatives are particularly effective in effecting Mukaiyama aldol-type reactions with labile enol silyl ethers in water.¹¹ This was attributed to formation of micelles of the surfactants which had been used. 1,1'-Bi-2-naphthol is an important chiral auxiliary and a ligand for many asymmetric transformation.¹² It shows a stable chirality and structural rigidity which is essential for asymmetric induction. The sulfonate derivatives of chiral 1,1'-binaphthol (C) can be designed and synthesised as a chiral surfactants for aqueous asymmetric reactions. At the commencement of our study, starting from 1,1'-binaphthol, a variety of binaphthylene sulfonate derivatives **2a-d** were prepared by condensation of 1,1'-bi-2-naphthol (**1**) with alkyl bromides (**4**) and reaction with chlorosulfonic acid (Scheme 1). The ¹H NMR spectra of sulfonation products show one single peak of the protons at



5- and 5'-positions of 1,1'-binaphthylene moiety and four double peaks for the protons at the other eight positions. The results indicated that the sulfonation reaction occurred regioselectively at the 6- and 6'-positions of 1,1'-binaphthylene moiety to give bis-sulfonation products.



Scheme 1

The critical micelle concentrations (cmc) were measured by surface tension method. The surface tension for **2c** decreased gradually with the increase of the concentration and a break point appeared at [2c] = 0.42 × 10⁻⁴, which corresponds to the cmc of **2c**. Similarly, cmc of **2d** was measured as 0.27 × 10⁻⁴ mol/l. In contrast, for **2b** a significant change in surface tension was not observed. The results indicate that only **2c** and **2d** bearing longer alkyl chain have surface-active feature. The CD spectra of (R)- and (S)-**2d** in water (c: 5.8 × 10⁻⁴ mol/l) show the same CD bands at 229, 248, and induced bands at >300 nm with symmetrically opposite Cotton effect (Fig. 1).

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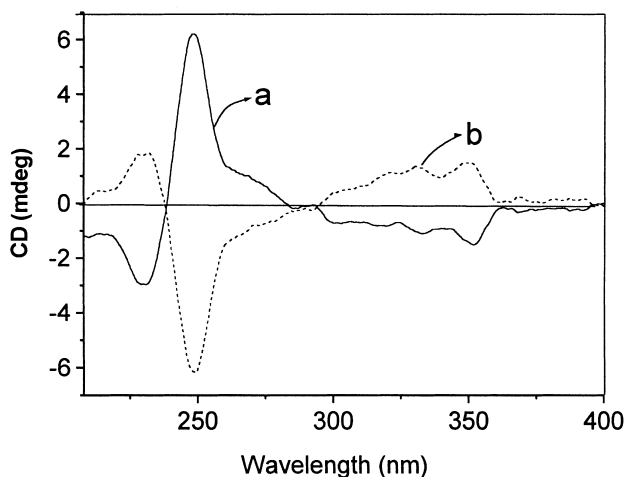
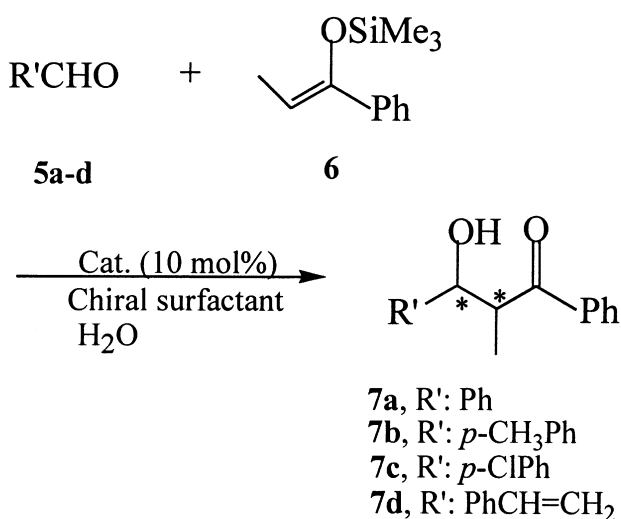


Fig. 1 CD spectra of (a) (-)-**2d**; (b) (+)-**2d**. [**2d**]= 5.8×10^{-4} mol/l.

At first, the reactions of 1-phenyl-1-trimethylsiloxypropene (**6**) with benzaldehyde **5a** were carried out in water at room temperature in the presence of the compounds **2a–d** (20 mol%) and catalyst $\text{Sc}(\text{OTf})_3$ (10 mol%) (Scheme 2). The effectiveness of compounds **2a–d** as surfactants in Mukaiyama aldol reaction was evaluated in reaction time and yield of the product **7a** (Table 1). The evaluation was performed by using racemic materials. It was found that, among the four compounds examined, **2a** and **2b** gave only very low yields of the product after stirring the reaction mixture for 2 days at room temperature (Table 1, entries 1 and 2). On the other hand, **2c** and **2d**, all gave the desired aldol reaction product in high yields 68–87% (Table 1, entries 3 and 4). As indicated above, the critical micelle concentrations (cmc) of **2c** and **2d** could be measured through surface tension method, while for **2a** and **2b** the cmc could not be observed. All these effective surfactants **2c–d** have relatively longer hydrophobic tails (C_8 to C_{12}) and **2d** exhibits a better ability in promoting the reaction in water. In contrast, for **2a–b** the yields were very low owing to the lack of surface-activity in water. The results support strongly the idea that the micelles formed in the case of **2c–d** should favorably promote the reaction in water due to the surface activities. At the same time, no reaction was observed with **2d** in the absence of scandium triflate [$\text{Sc}(\text{OTf})_3$] and a trace of the product was detected in the aqueous $\text{Sc}(\text{OTf})_3$ -catalysed reaction in the absence of **2d**.



Scheme 2

Table 1 The aldol reactions of **6** with benzaldehyde **5a** in the presence of compounds **2a–d**

Entry	Compound (R)	Reaction time	Yield of 7a /% ^a
1	2a , CH_3	2d	<5
2	2b , C_4H_9	2d	20
3	2c , C_8H_{17}	2d	68
4	2d , $\text{C}_{12}\text{H}_{25}$	10 h	87

^a Isolated yield

Subsequently, the Lewis acid-catalysed reactions of **6** with aldehydes **5a–d** were carried out in water in the presence of chiral surfactants (+)-**2c–d** in order to investigate their effectiveness in diastereoselectivity as well as in asymmetric induction (Table 2). In the case of catalyst $\text{Sc}(\text{OTf})_3$, the diastereoselectivities are low (*syn/anti*=51:49–55:45) and the asymmetric induction is also low (enantiomeric excess of *syn*-product (*syn*-**7**)= 6.6–17%). It should be pointed out that although the uses of $\text{Nd}(\text{OTf})_3$ and $\text{Zn}(\text{OTf})_2$ as the Lewis acid catalysts switched the diastereoselectivity efficiency enhanced as *syn/anti*=66:34 and 67:33, respectively, the asymmetric inductions for *syn*-diastereomer changed slightly with 12 ee% for $\text{Nd}(\text{OTf})_3$ (entry 3) and 17 ee% for $\text{Zn}(\text{OTf})_2$ (entry 4), respectively. On the other hand, no asymmetric induction was observed at all with lead perchlorate $\text{Pb}(\text{ClO}_4)_2$ in the presence of (+)-**2d**.

However, the use of $\text{Ga}(\text{OTf})_3$ and $\text{Cu}(\text{OTf})_2$ improves the diastereoselectivity and enantioselectivity noticeably. $\text{Ga}(\text{OTf})_3$ or $\text{Cu}(\text{OTf})_2$ were used as Lewis acid catalysts (10 mol%) in aqueous Mukaiyama aldol reactions of **6** with aldehydes **5a–d** in the presence of chiral surfactant (+)-**2d**. The diastereoselectivity (*syn/anti*-product) increased up to 78:22 with 32–48% ee of *syn*-**7a–d** (entries 6, 8, 10, 12 and 14). Although surfactant **2c** bearing C_8 chain provided the desired product in high yields, low enantioselectivities of the *syn*-product were observed (entries 5 and 7). The chiral surfactant **2d** with longer tail (C_{12}) is better for asymmetric induction. In comparison with (*R*)-(+)-**2d**, the corresponding enantiomer (*S*)-(-)-**2d** was used as a chiral surfactant in the aqueous aldol reaction under the same reaction conditions. For both (*R*)- and (*S*)-**2d** the similar diastereo- and enantioselectivities were observed, but with an opposite configuration deduced by optical rotation (entries 9, 11 and 15).

In order to examine the interaction between chiral surfactant and substrate, ^1H NMR and CD of the mixture of surfactant and substrates were recorded. ^1H NMR spectrum of a mixture of (-)-**2d** and **5a** in D_2O showed that the proton absorptions of naphthylene moiety of **2d** shifted to up-field compared with that in the ^1H NMR spectrum of (-)-**2d** in D_2O ($\Delta\delta = \delta_{(2\text{d}+5\text{a})} - \delta_{(2\text{d})} = 0.05\text{--}0.12$ ppm). Obviously, the differences in chemical shifts can be attributed to an interaction between chiral surfactant and substrate existing in water. It is interesting to investigate whether the conformation of the chiral surfactant changes upon addition of the substrates. As shown in Fig. 2, the CD bands of (-)-**2d** at 248 nm weakened as mixing with aldehyde **5a** occurred, but the band slightly changed with addition of silyl enol ether **6**. Based on these changes in the CD spectra it can be suggested that the interaction between chiral surfactant and substrate could make torsion between the two naphthyl ring changed and should result in asymmetric induction when the guest molecules are included in the micelles of chiral surfactants.

Experimental

IR spectra were recorded on a Perkin-Elmer 782 infrared spectrometer. ^1H NMR spectra were measured by Varian XL-300 spectrometer with tetramethylsilane as an internal standard. Mass spectra were recorded on a spectrometer. Optical rotations were recorded by a Perkin-Elmer 241 spectrometer at 589 nm. Circular Dichroism (CD)

Table 2 The aldol reactions of **6** with aldehydes **5a–d** in the presence of chiral surfactants

Entry	Surfactant	Aldehyde (R')	Catalyst	Product	Yield /% ^a (syn/anti) ^b	[α] _D	Ee /% ^c
1	(+)- 2d	5a , Ph	Sc(OTf) ₃	7a	89 (55/45)	1.5	12
2	(+)- 2d	5b , <i>p</i> -CH ₃ Ph	Sc(OTf) ₃	7b	86 (51/49)	3.3	17
3	(+)- 2d	5a	Nd(OTf) ₃	7a	80 (66/34)	1.5	12
4	(+)- 2d	5a	Zn(OTf) ₂	7a	79 (67/33)	2.3	17
5	(+)- 2c	5a	Ga(OTf) ₃	7a	69 (60/40)	1.2	9
6	(+)- 2d	5a	Ga(OTf) ₃	7a	63 (67/33)	6.3	47
7	(+)- 2c	5a	Cu(OTf) ₂	7a	78 (76/24)	1.1	8
8	(+)- 2d	5a	Cu(OTf) ₂	7a	67 (78/22)	4.3	32
9	(-)- 2d	5a	Cu(OTf) ₂	7a	79 (71/29)	-3.9	29
10	(+)- 2d	5b	Cu(OTf) ₂	7b	67 (73/27)	8.5	46
11	(-)- 2d	5b	Cu(OTf) ₂	7b	75 (77/23)	-8.7	45
12	(+)- 2d	5c , <i>p</i> -ClPh	Cu(OTf) ₂	7c	71 (76/24)	8.4	48
13	(-)- 2d	5c	Cu(OTf) ₂	7c	78 (67/33)	-7.4	42
14	(+)- 2d	5d , PhCH=CH	Cu(OTf) ₂	7d	73 (66/34)	17.1	34
15	(-)- 2d	5d	Cu(OTf) ₂	7d	80 (69/31)	-21.6	43

^a Isolated yield; ^b Determined by ¹H NMR; ^c Determined by ¹H NMR with (+)-Eu(hfc)₃ and chiral HPLC.

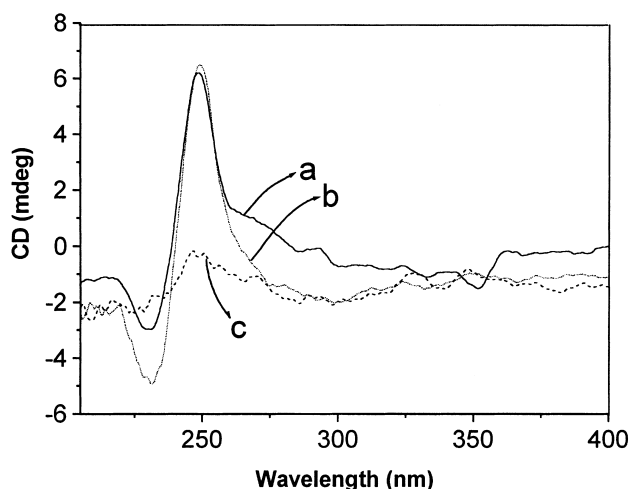


Fig. 2 CD spectra of (a) (-)-**2d**; (b) (-)-**2d**+**6**; (c) (-)-**2d**+**5a** [**2d**]= 5.8×10^{-4} mol/l.

spectra were recorded on a JASCO J-810 spectropolarimeter. Elemental analyses were performed on a Carlo Erba 1102 Element Analysis instrument. Surface tension/cmc was measured on a Kruss K12 MK5 tensiometer equipped with a Metrohm 665 Dosimat Platinum Plate. Diastereoselectivity was determined by ¹H NMR of a mixture of *syn* and *anti*-products. Enantioselectivity was determined from methyl proton resonance in the ¹H NMR of the *syn*-product with chiral shift reagent (+)-Eu(hfc)₃ and HPLC instrument: SHIMADZU, CTO-10ASVP equipped with a chiral column (Daicel Chiracel OD-H, hexane/2-PrOH=90:10).

Preparation of (*R*)-**2d**: A mixture of (*R*)-**1** (2.86 g, 10 mmol), potassium carbonate (10 g) and bromododecane (**4d**, 5 g, 20 mmol) in 100 mL DMF was stirred at 80 °C for 3 h. After cooling, DMF was removed under reduced pressure to give a yellow-green oil. The crude product was purified by flash chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 50:1) to afford product (*R*)-**3d** as a white solid, (7.8 g, 95%).

To a solution of (*R*)-(+)-**3d** (1.87 g, 3 mmol) in 30 ml dichloromethane a solution of chlorosulfonic acid (0.79 g, 6 mmol) in 15 ml CH₂Cl₂ was added dropwise at -10 °C. After the reaction was complete (monitored by TLC), the solvent was removed *in vacuo* at room temperature. The residue was dissolved in 15 ml water and neutralised to pH=7 with a saturated aqueous solution of Na₂CO₃. The solution was concentrated *in vacuo*, followed by adding acetone to precipitate the product. The solid obtained by filtration was dissolved in 10 ml water. The precipitate was recovered by diluting with acetone. The operation was repeated three times for purification to give product (*R*)-**2d** as a white solid (1.7 g, 70%). [α]_D = 5.6 (c 3.4, H₂O). IR ν_{\max} : 1025, 1105, 1200 cm⁻¹. δ_{H} (D₂O): 0.52 (6H, t), 0.58–1.13 (40H, m), 3.43 (4H, m), 6.62 (2H, d, *J* = 9.0 Hz), 6.92 (2H, d, *J* = 9.3 Hz), 7.09 (2H, d, *J* = 9.0 Hz), 7.66 (2H, d, *J* = 9.3 Hz), 8.21 (2H, s). FAB-MS *m/z*: 803 (M-Na). Elemental Anal: Calcd for

C₄₄H₆₀O₈S₂Na₂·H₂O: C 62.53%, H 7.40%; Found: C 62.05%, 7.67%. In the same procedure, (*S*)-(-)-**2d** was obtained with [α]_D = -5.1 (c 1.5, H₂O).

2a: δ_{H} (D₂O): 3.62 (6H, s), 6.80 (2H, d, *J* = 9.0 Hz), 7.19 (2H, d, *J* = 9.1 Hz), 7.55 (2H, d, *J* = 9.0 Hz), 8.13 (2H, d, *J* = 9.1 Hz), 8.29 (2H, s). FAB-MS *m/z*: 495 (M-Na). **2b**: IR ν_{\max} : 1025, 1100, 1175 cm⁻¹. FAB-MS *m/z*: 579 (M-Na). δ_{H} (D₂O): 0.29 (6H, m), 0.53 (4H, m), 1.03 (4H, m), 3.64 (4H, m), 6.92 (2H, d, *J* = 9.1 Hz), 7.15 (2H, d, *J* = 9.2 Hz), 7.29 (2H, d, *J* = 9.1 Hz), 8.03 (2H, d, *J* = 9.2 Hz), 8.20 (2H, s). Elemental Anal: Calcd for C₂₈H₂₈O₈S₂Na₂·H₂O: C 54.19%, H 4.87%; Found: C 53.60%, H 5.17%. (*R*)-(+)-**2c**: [α]_D = 6.0 (c 1.5, H₂O). IR ν_{\max} : 1025, 1105, 1175 cm⁻¹. δ_{H} (D₂O): 0.46 (6H, t), 0.58–0.95 (24H, m), 3.32 (4H, m), 6.75 (2H, d, *J* = 9.0 Hz), 6.93 (2H, d, *J* = 9.2 Hz), 7.19 (2H, d, *J* = 9.0 Hz), FAB-MS *m/z*: 691 (M-Na). Elemental Anal: Calcd for C₃₀H₄₄O₈S₂Na₂·H₂O: 59.00%, H 6.33%; Found: C 58.68%, H 6.89%.

A typical experimental procedure for Mukaiyama aldol reaction in water is as follow: A mixture of benzaldehyde (**5a**, 0.2 mmol), 1-phenyl-1-trimethylsilyloxypropene **6** (0.3 mmol), surfactant **2d** (0.2 equiv.), and Lewis acid catalyst (0.1 equiv.) in water (1 ml) was stirred at room temperature until the silyl enol ether disappeared on TLC. The mixture was then passed through a short silica gel pad and extracted with ethyl ether. The combined organic layer was dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 10:1) to afford the mixture of *syn*- and *anti*-aldol adducts (**7a**).¹³ The mixture of *syn*- and *anti*-**7a** was separated by flash chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 20:1) to give *syn*-**7a**.

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