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A 100 Gram-Scale Production of a Key Building Block of Antibacterial Vancomycin: The Use of an Air-Stable Chiral Zirconium Catalyst and Complete Recovery of a Silicon Source in Catalytic Asymmetric Mukaiyama Aldol Reaction

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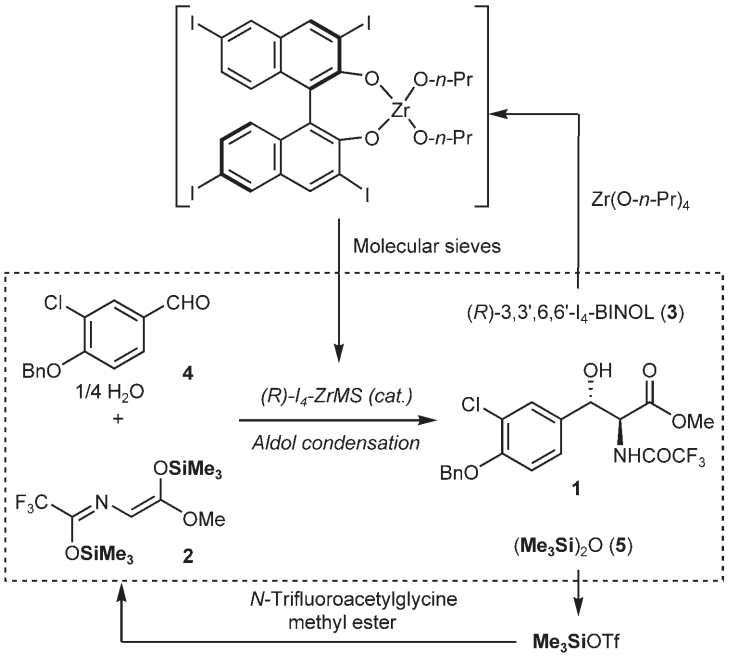
Abstract: We have achieved a 100 gram-scale production of *anti*-(2*S*,3*S*)-β-(*p*-benzyloxy-*m*-chloro)-phenyl-*N*-trifluoroacetyl-L-serine methyl ester (**1**) in high yield with high diastereo- and enantioselectivities based on a catalytic asymmetric Mukaiyama aldol reaction. The use of an air-stable zirconium-molecular sieves combined catalyst [(*R*)-I_4-ZrMS] facilitates easy manufacturing operation and reproducibility. Moreover, this is the first example of the complete recovery of the silicon source in a Mukaiyama aldol reaction.

Keywords: aldol reaction; amino acids; asymmetric catalysis; chiral zirconium catalyst; silicon enolate

The Lewis acid-mediated aldol reaction is one of the most powerful tools for carbon-carbon bond formation.[1] In particular, the Mukaiyama aldol reaction has attracted much attention because the reaction proceeds in high yield and with excellent selectivity under mild conditions. Due to the ever-increasing demand for optically active compounds, a great deal of attention has focused on catalytic asymmetric synthesis, and in this context asymmetric variants of the Mukaiyama aldol reaction, along with the development of novel chiral Lewis acids, have played a leading role.[2] However, to the best of our knowledge, there have been few reports on an industrial scale synthesis of optically active compounds using the catalytic asymmetric Mukaiyama aldol reaction. We reasoned that this might be due to two major obstacles to the successful scale-up of the procedure.[3] First, many of the catalysts employed in the Mukaiyama aldol reaction are chiral Lewis acids that are often moisture-sensitive and/or have to be prepared *in situ* immediately prior to use, which sometimes leads to problems of reproducibility. Second is the issue arising from the necessity of the use of silicon enolates which, while offering an advantage in that silicon enolates can be prepared from many carbonyl compounds such as ketones, aldehydes, esters, amides, and lactones, etc., also suffers from the disadvantage that the silicon source must be removed after acidic work-up and in most cases is not recoverable. To address these issues, we have developed an air-stable chiral zirconium catalyst and have now achieved complete recovery of the silicon source in a catalytic asymmetric Mukaiyama aldol reaction. Herein, we describe a 100 gram-scale production of *anti*-(2*S*,3*S*)-β-(*p*-benzyloxy-*m*-chloro)phenyl-*N*-trifluoroacetyl-L-serine methyl ester **1**,[4,5] a key building block of the antibacterial vancomycin,[6] using a catalytic asymmetric Mukaiyama aldol reaction of aldehydes with the trifluoroacetylglycine-derived silicon enolate **2**[7] in the presence of a chiral zirconium-BINOL complex developed in our laboratory as a catalyst for the synthesis of *anti*-β-hydroxy-α-amino acid derivatives in high yields with high stereoselectivities.[8] While the original report of this catalyst employed an *in situ* prepared zirconium complex, we examined the use of a zirconium-molecular sieves combined catalyst (ZrMS)[9] in the large-scale production (Scheme 1).

In the first small-scale trial, 10 mol% of powdered (*R*)-I_4-ZrMS, prepared by mixing $Zr(O\text{-}n\text{-}Pr)_4$, (*R*)-3,3′,6,6′-$I_4$-BINOL **3**,[10] and well-dried molecular sieves (MS-5 Å) in toluene followed by concentrating the mixture to dryness, was used.[6] (*R*)-I_4-ZrMS was aged with a small amount of water and *n*-PrOH in a mixture of toluene and *t*-BuOMe at 5 °C, and the re-



Scheme 1. Process for *anti*-β-aryl-L-serine **1** including recycling of starting materials.

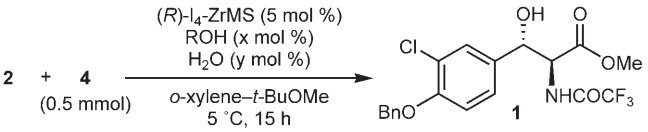
action of *p*-benzyloxy-*m*-chlorobenzaldehyde **4**[5a,b] with silicon enolate **2** was conducted using a slow addition procedure. As a result, **1** was obtained in good yield with excellent stereoselectivity[11] (77%, *anti*/*syn* = 89/11, *anti* = 96% *ee*).

With the aim of developing a large-scale procedure including recovery of the silicon source, we next focused on the nature of the solvents and on reducing the amount of catalyst. Since we planned to recover the silicon source in the form of Me_3SiOR (R = *n*-Pr: bp 100 °C) or $(Me_3Si)_2O$ (**5**: bp 101 °C) by distillation, we sought to use a solvent with a higher boiling point than that of toluene (bp 110 °C).

The solvent system of *t*-BuOMe (bp 55 °C) and *o*-xylene (bp 143 °C) was tested and found to afford virtually the same result as that obtained with toluene (Table 1, entry 1). In addition, it was found that under these conditions the reaction was tolerant of the presence of up to 30 mol% of water (entry 2). The robustness of the catalyst system towards moisture is of considerable importance in view of the difficulty of maintaining an anhydrous environment during large-scale synthesis.

Optimization studies of the reaction conditions using 5 mol% of (*R*)-I_4-ZrMS were carried out, and the results are summarized in Table 1. Surprisingly, reduction of the amount of catalyst by half affected both yield and stereoselectivity significantly (entry 3). Two additives, alcohol and water, were found to be essential in this catalytic reaction, and they seemed to play a specific role as already discussed in our previous report.[10] The addition of several alcohols was examined (entries 4–8), and among them *i*-PrOH was

Table 1. Optimization of reaction conditions.[a]



Entry	R	x	y	Yield [%]	*Anti*/*syn*	*ee* [%]
1[b]	*n*-Pr	300	10	77	96/4	96
2[b]	*n*-Pr	300	30	79	92/8	97
3	*n*-Pr	300	30	23	61/39	54
4	*n*-Pr	200	30	29	66/34	74
5	Bn	200	30	73	53/47	68
6	*t*-Bu	200	30	50	54/46	72
7	*s*-Bu	200	30	63	75/25	88
8	*i*-Pr	200	30	81	81/19	94
9	*i*-Pr	200	0	83	83/17	91
10	*i*-Pr	300	0	89	90/10	96
11	*i*-Pr	400	0	89	92/8	98

[a] A 0.12 M solution of **2** (2.0 equivs.) was added over 8 h with stirring, and the mixture was stirred for additional 7 h.

[b] 10 mol% of (*R*)-I_4-ZrMS was used.

found to improve both yield and stereoselectivity dramatically (entry 8). After investigations on the volume of the additives (entries 9–11), **1** was obtained in high yield with high diastereo- and enantioselectivities (89%, *anti*/*syn* = 92/8, *anti* = 98% *ee*, entry 11). Moreover, the allowable range of the volume of water was found to be wide (entries 8 and 9), and this feature worked well for a scale-up production (*vide infra*).

We then proceeded to conduct a large-scale production of **1** as shown in Table 2. In the first run, the synthesis was performed on an 8 mmol scale under the above optimized conditions (Table 2, entry 1) in which no water, except for the 1/4 hydrate of **4**, was added. Under these conditions the stereoselectivity was observed to decrease. We ascribed this result to the lack of free water, which was needed to activate the catalyst. In the second run, 30 mol% of water was added to address this issue (entry 2). As expected, the stereoselectivity increased to the same level as that obtained in the small-scale experiment, while the yield was lower. In the third run, *i*-PrOH was added independently to prevent the decomposition of the catalyst. As a result of the 32 mmol scale experiment, **1** was obtained in excellent yield with high stereoselectivity (entry 3). In the final run, this procedure was carried out on a 220 mmol scale production to yield *ca.* 100 g of **1** with good reproducibility (entry 4).

Table 2. Scale-up production of **1** and the recovery of silicon source as **5**.[a]

Entry	**4** [mmol]	H_2O [mol %]	Yield [%]	*Anti*/*syn*	*ee* [%]	Yield of **5** [%]
1	8	0	98	72/28	66	–
2	8	30	55	80/20	94	–
3[b]	32	30	92	90/10	94	86
4[b]	200	30	94	89/11	94	100

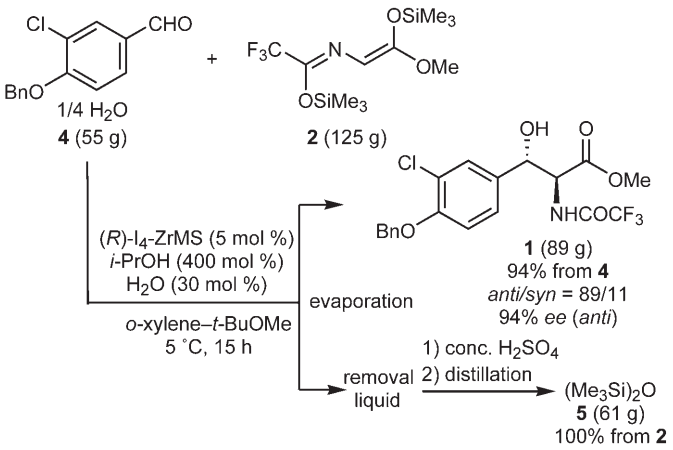
[a] A 0.12 M solution of **2** (2.0 equivs.) was added over 8 h with stirring, and the mixture was stirred for additional 7 h.

[b] 10 mol% of (*R*)-I_4-ZrMS was used.[a] Unless noted otherwise, the reaction was carried out at 5 °C in the presence of (*R*)-I_4-ZrMS (5 mol%) and *i*-PrOH (400 mol%). **2** (1.5–1.7 equivs.) was added over 8 h with stirring, and the mixture was stirred for additional 7 h.

[b] *i*-PrOH (200 mol%) was added initially, and an additional *i*-PrOH (200 mol%) was added over 8 h at the same period of the addition of **2**.

Through these scale-up experiments, we also examined the possibility of recovering the silicon source. We initially attempted to isolate Me_3SiO-*i*-Pr (bp 84 °C), which was generated when the (*R*)-I_4-ZrMS catalyst was employed in the reaction of **2** with **4**,[10] by distillation from the reaction mixture. However, Me_3SiO-*i*-Pr proved difficult to separate entirely from *t*-BuOMe (bp 55 °C), which is an essential solvent in this reaction. At this point, we turned our attention from Me_3SiO-*i*-Pr to **5**, formed from Me_3SiO-*i*-Pr by exposure to sulfuric acid through hydrolysis and dehydration.[12] A simple procedure to obtain **5** was established as follows: (1) an initial removal of solvents including Me_3SiO-*i*-Pr from the reaction mixture; (2) the removed liquid was mixed with an excess of sulfuric acid, and the mixture was washed with water; (3) the organic layer was separated and fractionally distilled to give **5** in quantitative yield from **2**. Indeed, we could get Me_3SiOTf for the next run as shown in Scheme 1 from the above obtained **5** according to the literature method.[13]

In conclusion, we have achieved a 100 gram-scale production of the target molecule **1** in high yield with high diastereo- and enantioselectivities (Scheme 2)[14] based on a catalytic asymmetric Mukaiyama aldol reaction. The use of an air-stable (*R*)-I_4-ZrMS catalyst facilitates easy manufacturing operation and reproducibility. Moreover, this is the first example of the complete recovery of the silicon source in a Mukaiyama aldol reaction. Further application to the synthesis of other *anti*-β-aryl-D- or -L-serine derivatives is now under investigation.



Scheme 2. Established procedure for large-scale production including the recovery of the silicon source.

Experimental Section

Preparation of (*R*)-I_4-ZrMS

To a solution of $Zr(O\text{-}n\text{-}Pr)_4$ in *n*-PrOH (70 wt%, 7.50 g, 16 mmol) in toluene (320 mL) was added (*R*)-3,3′,6,6′-tetraiodo-1,1′-binaphthalene-2,2′-diol [(*R*)-3,3′,6,6′-I_4-BINOL

(**3**), 12.6 g, 16 mmol], and the mixture was stirred for 30 min at room temperature. Powdered MS-5 Å (17.9 g) was added and the mixture was stirred for additional 15 min at the same temperature. The solvent was removed under reduced pressure and the residue was dried under vacuum for 2 h to give (*R*)-I_4-ZrMS catalyst as a powder.

Aldol Condensation on a Small Scale: Enantio- and Diastereoselective Synthesis of *anti*-(2*S*,3*S*)-*N*-Trifluoroacetyl-β-(*m*-chloro-*p*-benzyloxy)phenyl-L-serine Methyl Ester (1) (Table 1, Entry 11)

To a suspension of (*R*)-I_4-ZrMS catalyst (59 mg, 5 mol%) in *o*-xylene (0.75 mL) was added *i*-PrOH (0.15 mL, 2.0 mmol, 400 mol%) at room temperature, and the mixture was stirred for 30 min. After the addition of aldehyde **4** (125 mg, 0.5 mmol) and *t*-BuOMe (0.05 mL) at the same temperature, the mixture was allowed to cool to 5 °C. To a resultant suspension was slowly added silicon enolate **2** (329 mg, 1 mmol, 200 mol%) in a mixed solvent of *o*-xylene (0.5 mL) and *t*-BuOMe (1.25 mL) over 8 h, and the mixture was stirred for additional 7 h at 5 °C. The reaction was quenched with 0.5 mol/L aqueous $KHSO_4$ (2 mL) and AcOEt (4 mL) was added to the mixture. The organic layer was separated and the aqueous layer was extracted with AcOEt (4 mL). The combined organic layer was washed with saturated aqueous $NaHCO_3$ and brine, and then dried over Na_2SO_4. After filtration and concentration under reduced pressure, the crude product was purified by preparative TLC on silica gel to afford the desired aldol adduct **1** as crystals (89% yield, *anti/syn* = 92/8, *anti* = 98% *ee*). The diastereomer ratio was determined by ^{1}H NMR analysis and the optical purity was determined by HPLC analysis using a chiral column as below. ^{1}H NMR ($CDCl_3$): *anti*-isomer: $\delta = 3.70$ (s, 3H), 4.90 (dd, 1H, $J = 4.4$, 8.4 Hz), 5.13–5.15 (m, 3H), 6.95–7.43 (m, 8H); *syn*-isomer (detectable peaks): $\delta = 3.82$ (s, 3H), 4.80 (dd, 1H, $J = 2.4$, 9.2 Hz); HPLC (Daicel Chiralcel OD-H, hexane/*i*-PrOH = 96/4, 1.3 mL min^{-1}, 254 nm) *anti*-isomers at 30.5 min (minor) and 39.1 min (major), *syn*-isomers at 43.2 min (major) and 89.8 min (minor).

Other physical and analytical data were collected using optically pure **1** and are described in the Supporting Information.

Aldol Condensation in a Large Scale Involving the Hexamethyldisiloxane (5) Recovery Process (Table 2, Entry 4)

To a suspension of (*R*)-I_4-ZrMS catalyst (26.35 g, 5 mol%) in *o*-xylene (362 mL) was added water (1.20 g, 66.45 mmol, 30 mol%) in *i*-PrOH (33.7 mL, 443 mmol, 200 mol%) at room temperature, and the mixture was stirred for 10 min. After the addition of aldehyde **4** (55.14 g, 220 mmol) and *t*-BuOMe (22.1 mL) at the same temperature, the mixture was allowed to cool to 5 °C. To a resulted suspension was slowly added silicon enolate **2** (124.79 g, 374 mmol, 170 mol%) in *t*-BuOMe (510 mL) over 9 h and independently, 2-propanol (33.7 mL, 443 mmol, 200 mol%) in *o*-xylene (151 mL) was added over the same period, and the mixture was stirred for additional 13 h at 5 °C.

The reaction mixture was concentrated under vacuum and the solvents were removed into a cold trap. The recovered solvent included three silico-materials, $(Me_3Si)_2O$, Me_3SiOH and Me_3SiO-*i*-Pr, that were estimated from three peaks at 0.05, 0.09 and 0.12 ppm detected by ^{1}H NMR analysis. To the recovered solvent was added sulfuric acid (156.7 mL, 2.94 mol) at 5 °C and the mixture was vigorously stirred for 30 min and then quenched with cold water (313 mL). The organic layer was separated and washed successively with water, saturated aqueous $NaHCO_3$ and brine, and then dried over Na_2SO_4. After filtration and fractional distillation under air, $(Me_3Si)_2O$ (**5**, 61 g, 374 mmol) was isolated in quantitative yield.

To a concentrated residue was added AcOEt (250 mL), and the mixture was quenched with 0.5 mol/L aqueous $KHSO_4$ (250 mL) and then filtered through a pad of celite. The organic layer of the filtrate was separated and the aqueous layer was extracted with AcOEt (100 mL). The combined organic layer was washed with saturated aqueous $NaHCO_3$ and brine, and then dried over Na_2SO_4. After filtration and concentration under reduced pressure, the crude product was purified by column chromatography (SiO_2 480 g, hexane/AcOEt = 10/1–1/1) to afford both (*R*)-3,3′,6,6′-I_4-BINOL (**3**, 8.9 g, 11 mmol) and aldol adduct **1** (net 89.0 g, 94% yield, *anti/syn* = 89/11, *anti* = 94% *ee*).

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