anti-Selective Asymmetric Synthesis of β-Hydroxy-α-amino Acid Esters by the *in situ* Generated Chiral Quaternary Ammonium Fluoride-Catalyzed Mukaiyama-Type Aldol Reaction

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Received: April 16, 2004; Accepted: July 26, 2004

Abstract: The aldol coupling of ketene silyl acetal **2** derived from the glycinate Schiff base with aldehydes can be efficiently catalyzed by an *in situ* generated, chiral quaternary ammonium fluoride of type **1** under mild, neutral conditions, affording the corresponding *anti*-β-hydroxy-α-amino esters predominantly with excellent enantioselectivities.

Keywords: aldol reaction; asymmetric synthesis; chiral quaternary ammonium salt; diastereoselectivity; β-hydroxy-α-amino acid; potassium fluoride

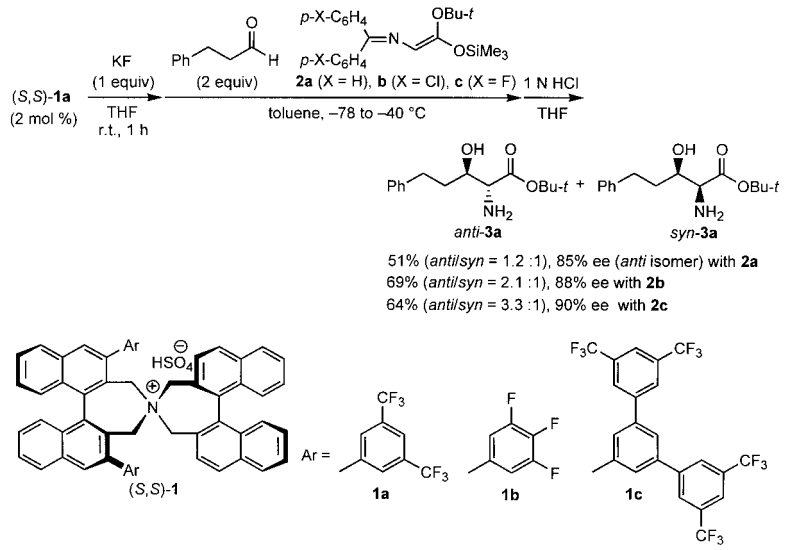
The occurrence of optically active β-hydroxy-α-amino acids as natural products as well as components of more complex biologically active cyclic peptides has made their synthesis of great importance, especially from the pharmaceutical viewpoint.[1] They have also been used as useful chiral building blocks in organic synthesis.[2–5] Accordingly, numerous studies on the asymmetric synthesis of this class of compounds have been made using different strategies.[6,7] However, the asymmetric aldol strategy employing catalytic amounts of chiral sources is still limited,[8,9] despite its obvious advantage for the simultaneous construction of the primary structure and the stereochemical integrity of β-hydroxy-α-amino acids. In connection with our recent study on the *in situ* generation of the chiral quaternary ammonium fluoride of type **1** from the corresponding hydrogen sulfate and its utilization for the fluoride ion-catalyzed asymmetric carbon–carbon bond formation reactions,[10] we have been interested in its application to the aldol reaction of the glycine-derived ketene silyl acetal **2** with aldehydes under mild, neutral conditions.[11,12] Here we report the *anti*-selective, highly enantioselective synthesis of various β-hydroxy-α-amino acid esters based on this approach.

As shown in Scheme 1, a mixture of chiral ammonium hydrogen sulfate **1a**[10] (2 mol %) and commercially available potassium fluoride (KF, 1 equiv.) in THF was well stirred at room temperature for 1 h. Then, 3-phenylpropanal (2 equivs.) and a toluene solution of ketene silyl acetal **2a**[11] were added sequentially at −78 °C and continued stirring at −78 °C for 13 h and at −40 °C for 5 h followed by acidic hydrolysis with 1 N HCl afforded the corresponding β-hydroxy-α-amino ester **3a** in 51% yield with an *anti*/*syn* ratio of 1.2:1. The enantiomeric excess of the *anti* isomer was determined to be 85% ee after conversion to its *N*-benzoate. It is of interest that the introduction of electron-withdrawing substituents at the *para*-position of the benzophenone moiety of **2** affected the diastereo- and enantioselectivities,[12c] and that *anti*-**3a** was obtained with 90% ee in the reaction with the fluoro-substituted ketene silyl acetal **2c** (64% yield, *anti*/*syn* = 3.3:1).

Based on these results, we examined the effect of the 3,3′-aryl substituents of the catalyst precursor **1** on the stereoselectivity in the reaction of **2c** with 3-phenylpropanal. Although the use of **1b**[10,13] having a 3,4,5-trifluorophenyl group led to a slight decrease of both diastereo- and enantioselectivities (entry 1 in Table 1), an improvement of *anti* selectivity was achieved by employing **1c**[12b] (77% yield, *anti*/*syn* = 8.3:1) with preservation of the excellent enantioselectivity (92% ee for *anti* isomer) (entry 2). The results of this Mukaiyama-type aldol reaction of ketene silyl acetal **2c** with other representative aldehydes under the optimized conditions are summarized in Table 1. The high preference for the formation of *anti*-**3** was consistently observed with unbranched as well as branched aldehydes, and the enantioselectivities generally exceeded 90% ee; this is in sharp contrast to the cinchonidine-derived ammonium bifluoride-catalyzed system.[11] In particular, the reaction with isobutyraldehyde proceeded with rigorous relative and absolute stereochemical control, providing a facile entry to (2*R*,3*R*)-β-hydroxyleucine (entry 6).[14]

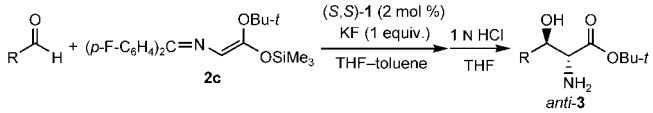
In summary, we have successfully demonstrated that the *in situ* generated chiral C_2-symmetrical quaternary ammonium fluoride of type **1** efficiently catalyzes the Mukaiyama-type aldol reaction of glycine-derived ketene silyl acetal **2** with various aldehydes, giving the corresponding *anti*-β-hydroxy-α-amino esters predominantly with excellent enantioselectivity. The present catalytic asymmetric aldol strategy is complementary to the

 DOI: 10.1002/adsc.200404111



Scheme 1.

Table 1. Asymmetric aldol reactions of **2c** with aldehydes catalyzed by chiral ammonium fluoride generated from **1** and KF.[a]



Entry	Aldehyde (R)	Catalyst precursor	Conditions [°C, h]	Yield [%][b] (*anti*/*syn*) [c]	% ee[d]
1	$Ph(CH_2)_2$	**1b**	–78, 12; –40, 3	76 (3.1 : 1)	82
2		**1c**	–78, 12; –40, 3	77 (8.3 : 1)	92
3	$CH_3(CH_2)_4$	**1c**	–78, 12; –40, 3	58 (8.4 : 1)	91
4	$CH_3(CH_2)_5$	**1c**	–78, 12; –40, 2	72 (11 : 1)	90
5	*i*-Bu	**1c**	–78, 16; –40, 3	70 (7.2 : 1)	90
6	*i*-Pr	**1c**	–78, 11; –40, 1	65 (6.7 : 1)	97

[a] The reaction was carried out with 2 equivs. of aldehyde in the presence of 2 mol % of (*S*,*S*)-**1** and 1 equiv. of KF in THF-toluene under the given reaction conditions.
[b] Yield of isolated product.
[c] Determined by ^{1}H NMR analysis.
[d] Enantiomeric excess of the major *anti*-**3**, which was determined by HPLC analysis of its *N*-benzoate using a chiral column (DAICEL Chiralcel OD-H) with hexane-2-propanol or hexane-ethanol as solvent.

Corey's procedure,[11] certainly revealing the unique feature of our approach based on the use of designer chiral quaternary ammonium salts.

Experimental Section

Representative Procedure for the Aldol Reaction (Entry 2 in Table 1)

A mixture of (*S*,*S*)-**1c** (16.7 mg, 0.01 mmol) and potassium fluoride (KF, 19.3 mg, 0.5 mmol) in THF (1.0 mL) was stirred for 1 h at room temperature under an argon atmosphere and then cooled to –78 °C. To this mixture was added 3-phenylpropanal (132 μL, 1.0 mmol) followed by dropwise introduction of freshly prepared ketene silyl acetal **2c**[11] (0.5 mmol) in toluene (1.0 mL). The reaction mixture was stirred at –78 °C for 12 h and at –40 °C for additional 3 h. As the yellow color disappeared, the whole mixture was diluted with water and ether. The ether phase was separated and washed with brine. The organic phase was dried over Na_2SO_4 and concentrated. The resulting crude products were dissolved into THF (8.0 mL) and treated with 1.0 N HCl (1.0 mL) at 0 °C for 1 h. After removal of THF under vacuum, the aqueous solution was washed with ether three times and neutralized with $NaHCO_3$. The mixture was then extracted with CH_2Cl_2 three times. The combined extracts were dried over Na_2SO_4 and concentrated. Purification

of the residue by column chromatography on silica gel (MeOH/CH_2Cl_2 = 1:15 as eluent) afforded the corresponding β-hydroxy-α-amino ester **3a** as a mixture of diastereomers; yield: 102 mg (0.385 mmol; 77%, *anti*/*syn* = 8.3:1); *anti*-**3a**:[11] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26–7.29 (2H, m, Ph), 7.16–7.20 (3H, m, Ph), 3.77 (1H, ddd, *J* = 7.6, 4.4, 3.2 Hz, C<u>H</u>OH), 3.47 (1H, d, *J* = 4.4 Hz, C<u>H</u>NH_2), 2.84–2.91 (1H, ddd, *J* = 14.0, 9.2, 4.8 Hz, PhCH), 2.65–2.73 (1H, dt, *J* = 14.0, 8.0 Hz, PhCH), 1.85 (3H, br, OH and NH_2), 1.65–1.75 (1H, m, $PhCH_2C$<u>H</u>), 1.53–1.62 (1H, m, $PhCH_2C$<u>H</u>), 1.41 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.8, 141.8, 128.4, 128.3, 125.7, 81.7, 71.0, 59.0, 33.8, 32.0, 28.1; IR (neat): ν = 3373, 2977, 2934, 1730, 1602, 1456, 1367, 1252, 1153, 1051, 849, 748, 700 cm^{-1}; *syn*-**3a**:[11] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26–7.29 (2H, m, Ph), 7.16–7.22 (3H, m, Ph), 3.70 (1H, ddd, *J* = 7.6, 5.2, 4.8 Hz, C<u>H</u>OH), 3.24 (1H, d, *J* = 5.2 Hz, C<u>H</u>NH_2), 2.82–2.90 (1H, ddd, *J* = 13.6, 9.0, 6.2 Hz, PhCH), 2.67–2.74 (1H, ddd, *J* = 13.6, 8.8, 7.2 Hz, PhCH), 2.17 (3H, br, OH and NH_2), 1.78–1.85 (2H, m, $PhCCH_2$), 1.46 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.2, 141.9, 128.3, 128.2, 125.7, 81.8, 71.4, 58.8, 36.0, 32.0, 28.1; IR (neat): ν = 3377, 2977, 2934, 1730, 1603, 1456, 1393, 1369, 1250, 1155, 847, 750, 700 cm^{-1}. The enantiomeric excess of the major *anti* isomer was determined to be 92% ee after conversion to its *N*-benzoate with benzoyl chloride and pyridine in CH_2Cl_2. HPLC conditions: DAICEL Chiralcel OD-H, hexane/2-propanol = 12:1, flow rate = 1.0 mL/min, retention time; 8.8 min (minor isomer) and 15.5 min (major isomer).

Acknowledgements

We are grateful to Dr. Manabu Horikawa (Suntory Institute for Bioorganic Research) for valuable information regarding the preparation of ***2****. This work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan. K. D. thanks the Japan Society for the Promotion of Science for Young Scientists for a Research Fellowship.*

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