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Tin-mediated enantioselective aldol-type reaction for the asymmetric synthesis of α-substituted serines utilizing an external chiral ligand, (-)-sparteine

Shigeki Sano, Takahiro Ishii, Toshio Miwa, and Yoshimitsu Nagao*

Faculty of Pharmaceutical Sciences, The University of Tokushima, Sho-machi, Tokushima 770-8505, Japan

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Abstract

The enantioselective aldol-type reaction of ethyl 3,6-diethoxy-2,5-dihydro-2-pyrazinecarboxylate (**1**) with achiral aldehydes **2a-d** was investigated by employing $Sn(OSO_2CF_3)_2$-triethylamine in the presence of (-)-sparteine. Not only a stoichiometric amount, but also 0.3 mol equiv. of (-)-sparteine promoted the highly enantioselective aldol-type reaction.

Keywords: aldol reactions; amino acids and derivatives; asymmetric synthesis; enantioselection

The asymmetric synthesis of α-substituted α-amino acids is a topic of current interest,[1-3] the synthesis of α-substituted serines in particular being a major focus of study in recent years. We have previously reported diastereoselective reactions and chemoenzymatic enantiodivergent reactions useful for the asymmetric synthesis of α-substituted serines.[4-8] In these studies, the chiral recognition mode with $Sn(OSO_2CF_3)_2$-*N*-ethylpiperidine[9] was demonstrated to be quite different from that with $MgBr_2$-triethylamine in the diastereoselective aldol-type reaction of (5*R* or 5*S*)-3,6-diethoxy-2,5-dihydro-5-isopropyl-2-pyrazinecarboxylate with various aldehydes.[5,8] We now describe the Sn(II)-mediated enantioselective aldol-type reaction of ethyl 3,6-diethoxy-2,5-dihydro-2-pyrazinecarboxylate (**1**) employing (-)-sparteine[10] as an external chiral ligand (Scheme 1). The bislactim ether **1** was readily prepared from σ-symmetric diethyl aminomalonate and glycine.[5]

First of all, the diastereoselective mode of the Sn(II)- or Mg(II)-mediated aldol-type reaction of the newly designed achiral bislactim ether **1** with achiral aldehydes **2a-d**

* Corresponding author. Fax: +81-886-33-9503, E-mail: ynagao@ph2.tokushima-u.ac.jp

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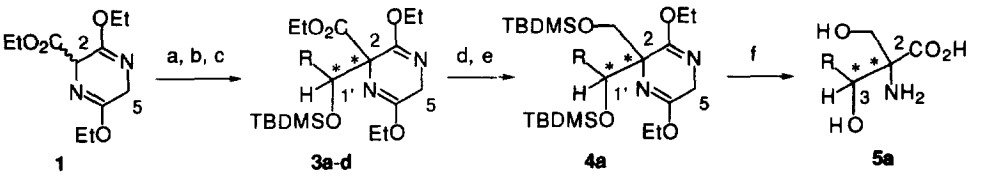

a: R = *i*-Pr, **b**: R = *n*-Bu, **c**: R = Ph, **d**: R = Me_2C=CH

Scheme 1 a) Sn(II) or Mg(II): see footnote for Table 1-4, b) RCHO (**2a-d**), c) Me_2(*t*-Bu)$SiOSO_2CF_3$ / 2,6-lutidine / CH_2Cl_2 / -45 °C, d) DIBAL / toluene / 0 °C, e) Me_2(*t*-Bu)$SiOSO_2CF_3$ / 2,6-lutidine / CH_2Cl_2 / rt, f) 12N HCl - CF_3CO_2H - *i*-PrOH (2 : 1 : 1) / 150 °C.

Table 1
Diastereoselective aldol-type reaction of bislactim ether **1** with aldehydes **2a-d**

Entry	Aldehyde	Conditions [a]	Time (h)	Yield (%) [b] of **3a-d**	Diastereomer Ratio [c] (2*S**,1'*R**) : (2*S**,1'*S**)
1	**2a**	A	2	74	84 : 16
2	**2a**	B	3.5	82	5 : 95
3	**2b**	A	2	87	84 [d] : 16 [d]
4	**2b**	B	2.5	91	5 [d] : 95 [d]
5	**2c**	A	3.5	73	4 [d] : 96 [d]
6	**2c**	B	2.5	80	21 [d] : 79 [d]
7	**2d**	A	4	85	47 [d] : 53 [d]
8	**2d**	B	2.5	77	7 [d] : 93 [d]

a) A: THF, -78 °C, **1** / $Sn(OSO_2CF_3)_2$ / *N*-ethylpiperidine / **2** (1 : 1.5 : 1.6 : 2); B: MeCN, -20 °C, **1** / $MgBr_2$ / triethylamine / **2** (1 : 2 : 4 : 2). b) Total isolation yield of diastereomers. c) ^{1}H NMR analysis (400 MHz NMR, $CDCl_3$). d) Relative configuration was assigned arbitrarily.

Table 2
Enantioselective aldol-type reaction of bislactim ether **1** with aldehydes **2a-d** in the presence of (-)-sparteine (1.5 mol equiv.) [a]

Entry	Aldehyde	Time (h)	Yield (%) [b] of **3a-d**	Diastereomer Ratio [c] (2*S**,1'*R**) : (2*S**,1'*S**)	Ee (%) [d] of (2*S*,1'*R*)-**3a-d**
1 [e]	**2a**	2	90	88 : 12	98
2	**2a**	2	89	82 : 18	95
3	**2b**	2	83	52 [f] : 48 [f,g]	98
4	**2c**	3.5	72	93 [f] : 7 [f]	95
5	**2d**	4	79	71 [f] : 29 [f]	84

a) CH_2Cl_2, -78 °C, **1** / $Sn(OSO_2CF_3)_2$ / triethylamine / (-)-sparteine / **2** (1 : 1.5 : 1.6 : 1.5 : 2). b) Total isolation yield of diastereomers. c) ^{1}H NMR analysis (400 MHz NMR, $CDCl_3$). d) HPLC analysis (Chiralcel OD, hexane / 2-propanol). e) *N*-ethylpiperidine was employed instead of triethylamine. f) Relative configuration was assigned arbitrarily. g) (2*S**,1'*S**)-**3b**: 84% ee.

proved to be similar to that with (5*R* or 5*S*)-3,6-diethoxy-2,5-dihydro-5-isopropyl-2-pyrazinecarboxylate (Table 1).[5,8] Namely, the aldol-type reaction with aliphatic aldehydes **2a,b** employing $Sn(OSO_2CF_3)_2$-*N*-ethylpiperidine or $MgBr_2$-triethylamine gave the different diastereomers **3a,b** as each major product after silylation of the aldol products (Table 1, entries 1-4). On the other hand, each major product was the same diastereomers **3c,d** in the similar Sn(II)- or Mg(II)-mediated reaction with unsaturated aldehydes **2c,d** (Table 1, entries 5-8). The diastereomer ratios of **3a-d** were determined by employing ^1H NMR analysis (400 MHz, $CDCl_3$).

Based on these results, the Sn(II)-mediated enantioselective aldol-type reactions of bislactim ether **1** with achiral aldehydes **2a-d** in the presence of a stoichiometric amount of (-)-sparteine were examined, as shown in Table 2. The aldol-type reactions of **1** with achiral aldehydes **2a-d** (2 mol equiv.) using $Sn(OSO_2CF_3)_2$ (1.5 mol equiv.) and triethylamine (1.6 mol equiv.) in the presence of (-)-sparteine (1.5 mol equiv.) in CH_2Cl_2 at -78 °C afforded compounds **3a-d** with enantioselectivities of up to 98% ee. The ee values of **3a-d** were determined by HPLC analysis (Daicel Chiralcel OD, hexane / 2-propanol). The absolute configuration of the major aldol product **3a** was confirmed to be (2*S*,1'*R*)-**3a** by its chemical conversion to the known α-substituted serine, as shown in Scheme 1.[8] Namely, reduction (36%) of **3a** (98% ee) with DIBAL at 0 °C followed by protection (59%) of the hydroxyl group with TBDMSOTf gave a diastereomerically pure **4a**, which was submitted to hydrolysis (46%) to obtain (2*S*,3*R*)-**5a** {$[\alpha]_D^{24}$ +29.7 (*c* 0.13, MeOH), lit.[8] (2*R*,3*S*)-**5a** $[\alpha]_D^{27}$ -26.1 (*c* 0.12, MeOH)}. The excellent Sn(II)-mediated asymmetric induction with **2a,b** (Table 2, entries 1 and 3) prompted us to examine the use of a catalytic amount of (-)-sparteine in these aldol-type reactions.

Table 3
Enantioselective aldol-type reaction of bislactim ether **1** with aldehyde **2a** in the presence of (-)-sparteine (0.3 mol equiv.) [a)]

Entry	Triethylamine (mol equiv.)	Yield (%) [b)] of **3a**	Diastereomer Ratio [c)] (2*S**,1'*R**) : (2*S**,1'*S**)	Ee (%) [d)] of (2*S*,1'*R*)-**3a**
1	1.6	65	80 : 20	68
2	4	64	80 : 20	76
3	6	65	84 : 16	80
4	8	69	85 : 15	94
5	16	62	84 : 16	93

a) CH_2Cl_2, -78 °C, 2 h, **1** / $Sn(OSO_2CF_3)_2$ / (-)-sparteine / **2** (1: 1.5 : 0.3 : 2). b) Total isolation yield of diastereomers. c) ^1H NMR analysis (400 MHz NMR, $CDCl_3$). d) HPLC analysis (Chiralcel OD, hexane / 2-propanol).

The results summarized in Table 3 revealed that 0.3 mol equiv. of (-)-sparteine induced high enantioselectivity in the presence of excess triethylamine (Table 3, entries 4 and 5). The scope of the reaction employing 0.3 mol equiv. of (-)-sparteine in the presence of 8 mol equiv. of triethylamine was also investigated, as shown in Table 4. The aldol-type

reactions with aldehydes **2a,b** afforded the corresponding chiral compounds **3a,b** in 94 and 92% ee (Table 4, entries 2 and 3), respectively. Although excellent stereocontrol can be achieved in the Sn(II)-mediated aldol-type reaction of enolsilanes,[11-13] to our knowledge, our method is the first example of an enantioselective aldol-type reaction involving the *in situ* formation of Sn(II)-enolate employing a catalytic amount of an external chiral ligand. Enolsilanes are not necessary to perform these catalytic enantioselective aldol-type reactions. We are currently pursuing studies on the reaction mechanism as well as on the design of new external chiral ligands.

Table 4
Enantioselective aldol-type reaction of bislactim ether **1** with aldehydes **2a-d** in the presence of (-)-sparteine (0.3 mol equiv.) [a]

Entry	Aldehyde	Time (h)	Yield (%) [b] of **3a-d**	Diastereomer Ratio [c] (2*S**,1'*R**) : (2*S**,1'*S**)	Ee (%) [d] of (2*S*,1'*R*)-**3a-d**
1 [e]	**2a**	2	59	85 : 15	88
2	**2a**	2	69	85 : 15	94
3	**2b**	2	65	43 [f] : 57 [f,g]	92
4	**2c**	3.5	57	91 [f] : 9 [f]	78
5	**2d**	4	67	74 [f] : 26 [f]	66

a) CH_2Cl_2, -78 °C, **1** / $Sn(OSO_2CF_3)_2$ / triethylamine / (-)-sparteine / **2** (1: 1.5 : 8 : 0.3 : 2). b) Total isolation yield of diastereomers. c) ^1H NMR analysis (400 MHz NMR, $CDCl_3$). d) HPLC analysis (Chiralcel OD, hexane / 2-propanol). e) *N*-ethylpiperidine was employed instead of triethylamine. f) Relative configuration was assigned arbitrarily. g) (2*S**,1'*S**)-**3b**: 68% ee.

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