Tetrahedron Letters, Vol. 34, No. 4, pp. 677-680, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

anti-Selective Aldol Reactions of Titanium Enolates of *N*-Alkylideneglycinates. Stereoselective Synthesis of *anti*-Isomers of β-Hydroxy-α-amino Esters

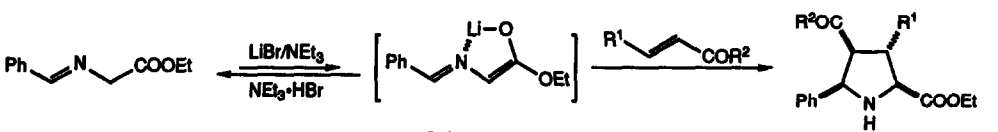
Shuji Kanemasa,* Takashi Mori,† Eiji Wada, and Akira Tatsukawa††

Institute of Advanced Material Study, Kyushu University, Kasugakoen, Kasuga 816, Japan
†Department of Molecular Science and Technology, Interdisciplinary Graduate School of Engineering Sciences, Kyushu University, Kasugakoen, Kasuga 816, Japan
††Department of Chemistry, Faculty of Science, Kochi University, Akebono-cho, Kochi 780, Japan

Keywords: anti-Selective aldol reaction, Titanium enolate, N-Alkylideneglycinate, β-Hydroxy-α-amino Ester

Abstract: *Titanium enolates of N-alkylideneglycinates and derivatives react with aldehydes to give anti-isomers of β-hydroxy-α-amino esters and derivatives. Combination of the titanium enolates, generated by transmetalation of the corresponding lithium enolates with dichloroditsopropoxytitanium, and bulky aliphatic aldehydes is most effective for the favored formation of anti-isomers.*

High synthetic potential of nucleophilic glycine equivalents has been well explored by reactions with a variety of electrophiles.[1] Among them, alkylation of metalated glycinates with carbonyl compounds is especially important as a useful entry to β-hydroxy α-amino acids.[2,3] We[4] and others[5] have found that metalated *N*-benzylideneglycinates as a nucleophilic glycine equivalent undergo *endo*-selective cycloadditions to α,β-unsaturated carbonyl compounds to give imidazolidine-4-carboxylates (Scheme 1). *Anti*-selective Michael additions to α,β-unsaturated carbonyl compounds are on the same basis.[6] Our recent finding of stereoselective cycloadditions of *N*-benzylideneglycinates to imine functions promoted us to examine the reactions with carbonyl acceptors.[7] We expect a highly stereoselective outcome in the cycloadditions of metalated *N*-alkylideneglycinates to carbonyl compounds. Subsequent hydrolysis would open a new entry to stereoselective synthesis of β-hydroxy α-amino esters.

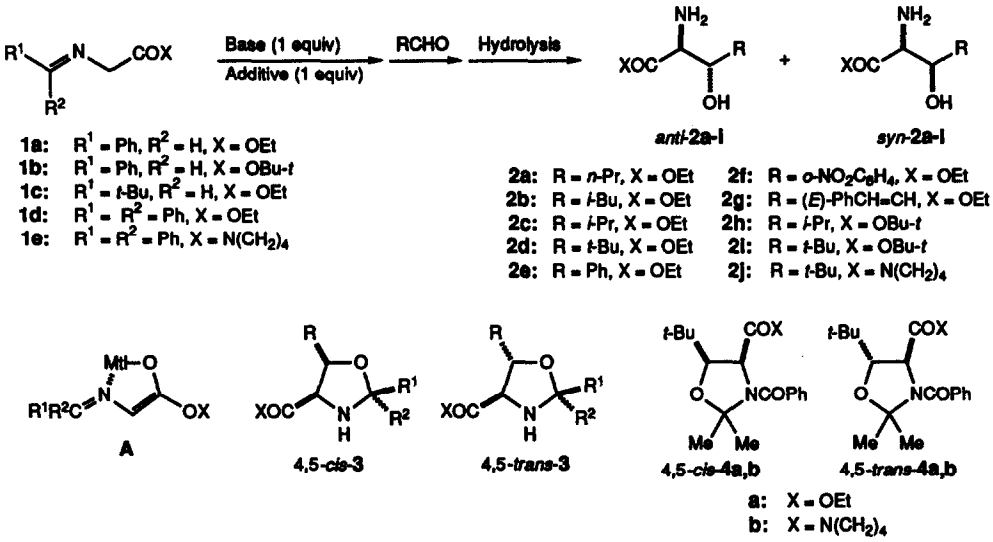


Scheme 1.

This communication presents an unusual aldol reaction of titanium enolates of *N*-alkylideneglycinates and derivatives which proceeds in a highly *anti*-selective manner. Bulk of the *N*-alkylidene group as well as the use of aliphatic aldehydes rather than aromatic ones is a point to attain the high *anti*-selectivity.

Ethyl *N*-benzylideneglycinate (**1a**) was metalated with LDA, LiBr/Et_3N, LiBr/DBU, Me_2AlCl/Et_3N, $TiCl_2(OPr\text{-}i)_2/Et_3N$, or *t*-BuMgCl in THF. Reactions of the resulting enolates A with *o*-nitrobenzaldehyde gave mixtures of stereoisomeric cycloadducts, ethyl 5-(*o*-nitrophenyl)-2-phenyloxazolidine-4-carboxylates, 4,5-*cis*-**3** and 4,5-*trans*-**3** (R = *o*-nitrophenyl, X = OEt, R^1 = Ph, R^2 = H). Since these cycloadducts are quite labile to hydrolysis, the mixture was subjected, without separation, to hydrolysis with hydrochloric acid at room temperature to give mixtures of β-amino alcohols *anti*-**2f** and *syn*-**2f** (Scheme 2).

Aldol reaction of magnesium enolate A (Mtl = MgCl) was *syn*-selective (*anti:syn* = 11:89; *t*-BuMgCl, –59 °C, 12 h), while other reactions showed no selectivities.[8] Reaction of aluminum enolate A (Mtl = MeAlCl) at 0 °C was found to be thermodynamically controlled at 0 °C, where *anti*-adduct *anti*-**2f** was more stable isomer.[8,9]



Scheme 2.

Table 1. Aldol Reactions of Metal Enolates of *N*-Alkylideneglycinate **1a** to Aldehydes[a]

Entry	Base[b]	Additive[b]	RCHO	Solvent[c]	Time/h	Product	Yield/%[d]	*anti:syn*[e]
1	*t*-BuMgCl	-	*i*-PrCHO	THF	2	**2c**	77	64:36
2	*t*-BuMgCl	-	*t*-BuCHO	DCM	1	**2d**	74	87:13
3	LDA	Me_2AlCl	*i*-PrCHO	THF	2	**2c**	70	82:18
4	LDA	Me_2AlCl	*t*-BuCHO	THF	1	**2d**	74	87:13
5	LDA	$TiCl_2(OPr\text{-}i)_2$	*i*-PrCHO	THF	2	**2c**	62	93:7
6	LDA	$TiCl_2(OPr\text{-}i)_2$	*t*-BuCHO	THF	1	**2d**	78	>99:1
7	LDA	$TiCl(OPr\text{-}i)_3$	*t*-BuCHO	THF	4	**2d**	57	83:17
8	LDA	$ZrCl_2Cp_2$	*t*-BuCHO	THF	2	**2d**	44	47:53

[a]Each one equivalent of **1a**, base, additive, and aldehyde was used. All reactions were performed at –78 °C. [b]Imine **1a** was treated with a base and then an additive. [c]THF: tetrahydrofuran; DCM: dichloromethane. [d]Yield of isolated mixture of isomers. [e]Based on ^1H NMR or ^{13}C NMR spectrum of the crude reaction mixture.

Thus, aldol reactions of A with *o*-nitrobenzaldehyde were either thermodynamically controlled or poor in selectivities. This may be partly due to the employment of aromatic aldehydes.[10] We decided to use aliphatic aldehydes to avoid such thermodynamic control of reaction and also with a hope of high kinetic selectivity. Imine **1a** was metalated with a variety of metalation reagents such as *t*-BuMgCl, LDA/Me_2AlCl, LDA/$TiCl_2(OPr\text{-}i)_2$, LDA/$TiCl(OPr\text{-}i)_3$, LDA/$ZrCl_2Cp_2$, and the resulting metalated species were allowed to react with aliphatic aldehydes at –78 °C (Table 1). General procedure is as follows: To a THF solution of LDA (1.15 mmol in hexane) is added the imine **1** (1 mmol) at –78 °C. After being stirred for 15 min, a metal halide (1.2 mmol) is added and the stirring is continued (15 to 30 min at –78 °C). An aldehyde (1.2 mmol) is added and the reaction is performed under the conditions of Table 1. After quenched with saturated aqueous

solution of potassium sodium tartarate, the mixture is hydrolyzed by stirring with 4*N* hydrochloric acid in methanol at room temperature for 2 h. The mixture is washed with ether several times and the aqueous solution is neutralized with sodium hydroxide. Extraction with dichloromethane gives a stereoisomeric mixture of the adduct **2**.

Except for the case of zirconium enolate (entry 8), *anti*-adducts **2c,d** were obtained as major products. The reaction of A (Mtl = $TiCl(OPr\text{-}i)_2$) with *t*-BuCHO at –78°C in THF was exclusively *anti*-selective (entry 6). Although the same enolate A (Mtl = $TiCl(OPr\text{-}i)_2$) could be generated reversibly with $TiCl_2(OPr\text{-}i)_2/Et_3N$ (or DBU) at –78 °C, the transmetalation method provided better yields of the adducts **2c,d**. Structures of **2c,d** were assigned on the basis of spectral data, especially by comparison of ^{13}C chemical shifts between two stereoisomers.[11] NOE Spectra of the cyclized derivatives **4a,b** also offered useful informations for the stereochemical elucidation.[12]

In the aldol reactions of titanium enolate A (Mtl = $TiCl(OPr\text{-}i)_2$, X = OEt, R^1 = Ph, R^2 = H), stereoselectivity was not exclusively high unless bulky aldehyde acceptors were employed (Table 2, entries 1-3). Use of *N*-alkylideneglycinate **1b** bearing a bulky ester group was quite effective (entries 4, 5), while imine **1c** bearing a bulky alkylidene substituent was comparable to **1a** in selectivity (entries 6, 7). When benzophenone imine **1d** was employed, excellent selectivities were recorded for aliphatic aldehydes (entries 8-10), but the reactions with aromatic aldehyde and α,β-unsaturated aldehyde were much less selective again (entries 12, 13).

Table 2. Aldol Reactions of Titanium Enolates of *N*-Alkylideneglycinates **1a-d** or -glycinamide **1e** to Aldehydes Followed by Acid Hydrolysis[a]

Entry	Imine	R^1	R^2	X	R^3CHO	Time/h	Product	Yield/%[b]	*anti*:*syn*[c]
1	**1a**	Ph	H	OEt	*i*-BuCHO	2.5	**2b**	68	91:9
2	**1a**				*i*-PrCHO	2	**2c**	62	93:7
3	**1a**				*t*-BuCHO	1	**2d**	78	>99:1
4	**1b**	Ph	H	OBu-*t*	*i*-PrCHO	2	**2h**	70	>99:1
5	**1b**				*t*-BuCHO	1	**2i**	45	>99:1
6	**1c**	*t*-Bu	H	OEt	*i*-PrCHO	2	**2c**	43	92:8
7	**1c**				*t*-BuCHO	1	**2d**	70	98:2
8	**1d**	Ph	Ph	OEt	*n*-PrCHO	2	**2a**	65	90:10
9	**1d**				*i*-BuCHO	2	**2b**	64	94:6
10	**1d**				*i*-PrCHO	2	**2c**	59	98:2
11	**1d**				PhCHO	2.5	**2e**	34	65:35
12	**1d**				(*E*)-PhCH=CHCHO	4	**2g**	64	65:35
13	**1e**	Ph	Ph	$N(CH_2)_4$	*t*-BuCHO	2	**2j**	75	>99:1

[a]Titanium enolates A were generated by treating imines **1** with LDA and then $TiCl_2(OPr\text{-}i)_2$ in THF. The aldol reactions were followed by acid hydrolysis (See Ref. 11). [b]Yield of isolated mixture of isomers. [c]Based on ^1H NMR or ^{13}C NMR spectrum of the crude reaction mixture.

It is known that aldol reactions with titanium enolates mostly proceed in a *syn*-selective fashion regardless of the geometry of enolates.[13,14] In addition, aldol reactions of nucleophilic glycine equivalents are also *syn*-selective;[2] *anti*-selective reaction is quite rare.[3] The high *anti*-selectivity observed in the aldol reactions of metalated *N*-alkylideneglycinates A is noteworthy. These reactions provide a usuful method for the preparation of unnatural *anti*-stereoisomers of β-hydroxy α-amino acids and derivatives.[15] However, we can not so far propose any clear mechanism to explain such unusual selectivity.

Applications to asymmetric reactions of the *anti*-selective aldol reaction of **1** by using optically pure *N*-bornylideneglycinates were unsuccessful. Transmetalation of the lithium enolates to the titanium enolates was awfully slow presumably because of a steric reason.

This work has been partly supported by Grant-in-Aid for Scientific Research (No. 03453095) from the Ministry of Education, Science and Culture.

References and Note

1. Barrett, G. C. "Synthesis of Amino Acids," in "Chemistry and Biochemistry of Amino Acids," ed by Barrett, G. C. Chapman and Hall, London (1985), Chap. 8, pp. 246-296.
2. (a) Guanti, G.; Banfi, L.; Narisano, E.; Scolastico, C. *Tetrahedron Lett.* **1984**, *25*, 4693-4696. (b) Schöllkopf, U.; Nozulak, J.; Grauert, M. *Synthesis* **1985**, 55-56. (c) Evans, D. A.; Weber, A. E. *J. Am. Chem. Soc.* **1986**, *108*, 6757-6771. (d) Georg, G. I.; Akgün E. *Tetrahedron Lett.* **1991**, *40*, 5521-5524.
3. van der Werf, A. W.; Kellog, R. M.; van Bolhuis, F. *J. Chem. Soc., Chem. Commun.* **1991**, 682-683.
4. (a) Tsuge, O.; Kanemasa, S.; Yoshioka, M. *J. Org. Chem.* **1988**, *53*, 1384-1391. (b) Kanemasa, S.; Yoshioka, M.; Tsuge, O. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 869-874. (c) Kanemasa, S.; Yoshioka, M.; Tsuge, O. *ibid.* **1989**, *62*, 2196-2200. (d) Kanemasa, S.; Uchida, O.; Wada, E.; Yamamoto, H. *Chem. Lett.* **1990**, 105-108.
5. (a) Barr, D. A.; Grigg, R.; Gunaratune, H. Q. N.; Kemp, J.; McMeekin, P.; Sridharan, V. *Tetrahedron* **1988**, *44*, 557-570. (b) Amornraksa, K.; Donegan, G.; Grigg, R.; Ratananukul, P.; Sridharan, V. *ibid.* **1989**, *45*, 4649-4668. (c) Grigg, R.; Heaney, F.; Idle, J.; Somasunderam, A. *Tetrahedron Lett.* **1990**, *31*, 2767-2770. (d) Rao, K. R.; Bhanumathi, N.; Sattur, P. B; *ibid.* **1990**, *31*, 3201-3204. (e) Barr, D. A.; Dorrity, M. J.; Grigg, R.; Malone, J. F.; Montgomery, J.; Rajviroongit, S.; Stevenson, P. *ibid.* **1990**, *31*, 6569-6572. (f) Allway, P.; Grigg, R. *ibid.* **1991**, *32*, 5817-5820.
6. (a) Kanemasa, S.; Tatsukawa, A.; Wada, E. *J. Org. Chem.* **1991**, *56*, 2875-2883. (b) Yamamoto, H.; Kanemasa, S.; Wada, E. *Bull. Chem. Soc. Jpn.*. **1991**, *64*, 2739-2743.
7. Imine 1a stereoselectively reacts with *N*-alkylidenecarbamates or 1a (Kanemasa, S.; Mori, T.; Wada, E.; Tatsukawa, A. Unpublished results).
8. *anti*:*syn* = 53:47 (LDA, –78 °C, 1 h), 68:32 (LiBr/Et_3N, –78 °C, 20 h), 52:48 (LiBr/DBU, –78 °C, 5 h), 50:50 (Me_2AlCl/Et_3N, –78 °C, 1 h), 71:29 (Me_2AlCl/Et_3N, 0 °C, 64 h), 53:47 ($TiCl_2(OPr\text{-}i)_2$, rt, 24 h).
9. Reversible aldol reactions of lithium enolates: (a) Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066-1081. (b) Mulzer, J.; Zippel, M.; Bmtrup, G.; Segner, J.; Finke, J. *Liebigs Ann. Chem.* **1980**, 1108-1134. (c) Wei, Y.; Bakthavatchalam, R. *Tetrahedron Lett.* **1991**, *32*, 1535-1538. Silyl enolates: (d) Kleschick, W. A.; Buse, C. T.; Heathcock, C. H. *J. Am. Chem. Soc.* **1977**, *99*, 247-248. (e) Noyori, R.; Yokoyama, K.; Sakata, J.; Kuwajima, I.; Nakamura, E.; Shimizu, M. *ibid.* **1977**, *99*, 1265-1267. Zinc enolate: (f) Heng, K. K.; Smith, R. A. J. *Tetrahedron* **1979**, *35*, 425-435.
10. The reaction with benzaldehyde provided similar results.
11. Characterization of new compounds discussed in the text was based on spectral data as well as analyses. Some typical spectral data are as follows: *anti*-**2d**: ^1H NMR ($CDCl_3$) δ 0.94 (9H, s, *t*-Bu), 1.30 (3H, t, J = 7.2 Hz, OEt), 2.33 (3H, br, OH and NH_2), 3.39 (1H, d, J = 3.7 Hz, H-3), 3.57 (1H, d, J = 3.7 Hz, H-2), and 4.18 (2H, q, J = 7.2 Hz, OEt); ^{13}C NMR ($CDCl_3$) δ 13.99 (OEt), 26.29, 35.19 (each *t*-Bu), 54.88 (C-2), 61.07 (OEt), and 175.53 (COOEt). *syn*-**2d**: ^1H NMR ($CDCl_3$) δ 0.97 (9H, s, *t*-Bu), 1.29 (3H, t, J = 7.1 Hz, OEt), 2.33 (3H, br, OH and NH_2), 3.46 (1H, d, J = 2.9 Hz, H-3), 3.61 (1H, d, J = 2.9 Hz, H-2), and 4.17 (2H, q, J = 7.1 Hz, OEt); ^{13}C NMR ($CDCl_3$) δ 14.07 (OEt), 26.11, 35.32 (each *t*-Bu), 53.53 (C-2), 61.33 (OEt), and 173.13 (COOEt). 4,5-*cis*-**4**: ^1H NMR ($CDCl_3$) δ 0.94 (9H, s, *t*-Bu), 1.15 (3H, t, J = 7.1 Hz, OEt), 1.73, 1.93 (each 3H, s, 2-Me), 3.91 (1H, d, J = 5.9 Hz, H-5), 3.98 (2H, q, J = 7.1 Hz, OEt), 4.12 (1H, d, J = 5.9 Hz, H-4), and 7.2 - 7.4 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ 13.75 (OEt), 23.94, 24.95 (each 2-Me), 25.86, 32.19 (each *t*-Bu), 61.25 (OEt), 63.22 (C-4), 85.19 (C-5), 95.50 (C-2), 125.42, 128.55, 129.28, 137.78 (each Ph), 168.25, and 170.33 (each CON). 4,5-*trans*-**4**: ^1H NMR ($CDCl_3$) δ 0.95 (9H, s, *t*-Bu), 1.82, 1.84 (each 3H, s, 2-Me). Other signals are overlapping with those of 4,5-*cis*-**4**; ^{13}C NMR ($CDCl_3$) δ 13.81 (OEt), 25.25, 25.48 (each 2-Me), 25.30, 33.45 (each *t*-Bu), 61.32 (OEt), 67.81 (C-4), 85.60 (C-5), 95.18 (C-2), 168.75, and 171.30 (each CON). Other signals are overlapping with those of 4,5-*cis*-**4**.
12. Clear signal enhancements were observed between H-4 (δ 4.15, d, $J_{4\text{-}5}$ = 5.9 Hz) and H-5 (δ 3.91, d, $J_{5\text{-}4}$ = 5.9 Hz) in the NOE spectrum of 4,5-*cis*-**4b**.
13. (a) Evans, D. A.; McGee, L. R. *Tetrahedron Lett.* **1980**, *21*, 3975-3978. (b) Yamamoto, Y.; Maruyama, K. *ibid.* **1980**, *21*, 4607-4610. (c) Reetz, M. T.; Peter, R. *ibid.* **1981**, *22*, 4691-4694. (d) Nerz-Stormes, M.; Thornton, E. D. *J. Org. Chem.* **1991**, *56*, 2489-2498.
14. Bold, G.; Duthaler, R. O.; Riediker, M. *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 497-498.
15. Synthesis of *anti*-isomers of β-hydroxy α-amino acids: (a) Saito, S.; Bunya, N.; Inaba, M.; Moriwake, T.; Torii, S. *Tetrahedron Lett.* **1985**, *26*, 5309-5312. (b) Reetz, M. T.; Drewers, M. W.; Schmitz, A. *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 1141-1143.

(Received in Japan 31 August 1992)