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Asymmetric *anti*-Selective Aldol Reactions of Titanium *Z*-Enolates Derived from *N*-Alkylideneglycinamides Bearing a 2,2-Dimethyloxazolidine Chiral Controller

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Abstract: *Asymmetric aldol reactions of titanium Z-enolates of N-diphenylmethylene derivatives of glycinamides derived from (4S)-2,2-dimethyloxazolidine chiral auxiliaries are highly ul,ul-1,4-inductive. Hydrolytic removal of the chiral auxiliary from the aldol adducts provide optically active anti-isomers of α-amino-β-hydroxy acids with 2R-absolute configuration.*

In a preceding communication,[1] we have reported highly *anti*-selective aldol reactions of the titanium *Z*-enolates of *N*-alkylideneglycinates and -amides. Bulk of the *N*-alkylidene group and use of bulky aliphatic aldehydes rather than aromatic ones were essential to achieve high *anti*-selectivity. Since this new reaction offers an important entry to the highly stereoselective synthesis of *anti*-isomers of α-amino-β-hydroxy esters and amides,[2] we have examined its extension to an asymmetric reaction.

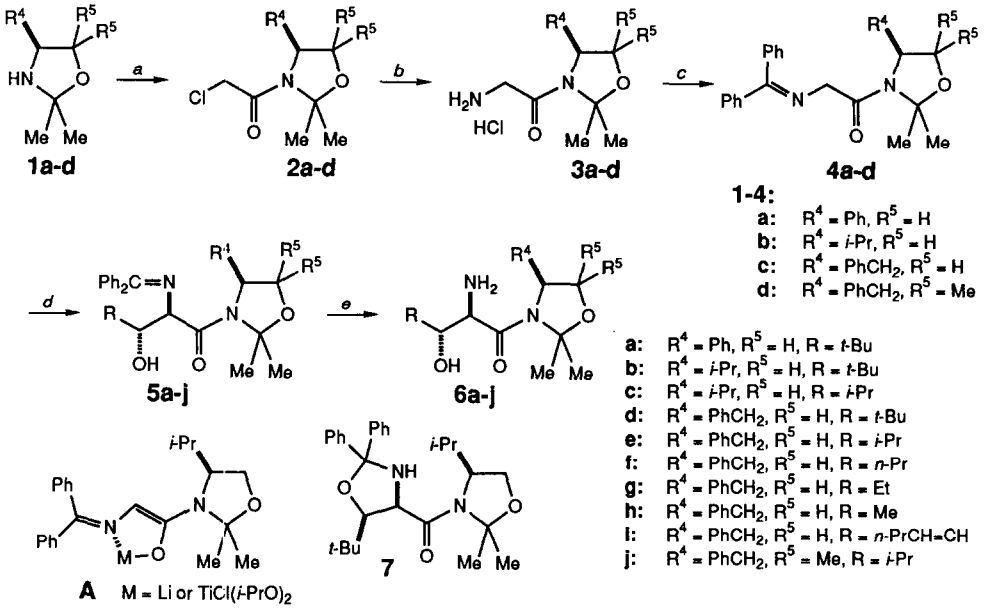
A new type of chiral auxiliary based on the conformational control of amide linkage has been recently developed in our group[3] and others.[4] α,β-Unsaturated amide derivatives of 4-chiral 2,2-dialkyloxazolidines predominantly occupy *syn/s-cis* conformation so that nucleophilic reactions onto the unsaturated moiety take place in a highly diastereoselective manner.[3c] To know the synthetic potential of our chiral auxiliaries in asymmetric enolate chemistry, the titanium *Z*-enolates of *N*-alkylideneglycinamides derived from 2,2-dimethyloxazolidines were employed in the above unusual aldol reactions.

In the present communication, highly *ul,ul*-1,4-inductive asymmetric aldol reactions of titanium *Z*-enolates of *N*-diphenylmethylene derivatives of glycinamides derived from 2,2-dimethyloxazolidine chiral auxiliaries are described. This asymmetric reaction offers a useful entry to optically active *anti*-isomers of α-amino-β-hydroxy acids with 2*R*-absolute configuration.

Chiral *N*-alkylideneglycinamides **4a-d** as donor molecules were prepared according to the following sequence of reactions (Scheme 1): (4*S*)-2,2-Dimethyloxazolidines **1a-d**[3b] were converted to 3-(chloroacetyl)oxazolidines **2a-d** (**2a**: 78%; **2b**: 74%; **2c**: 70%; **2d**: 69%) by treatment with chloroacetyl chloride and triethylamine in dichloromethane. Subsequent ammonolysis of **2a-d** in *N,N*-dimethylformamide led to the corresponding glycinamide hydrochlorides **3a-d** (**3a**: 92%; **3b**: 90%) which were then allowed to condense with benzophenone imine[5] to give *N*-(diphenylmethylene)glycinamides **4a-d** (**4a**: 90%; **4b**: 94%; **4c**: 70% based on **2c**; **4d**: 69% based on **2d**). These *N*-alkylideneglycinamides **4a-d** were labile to hydrolysis at the imine moiety so that their purification has to be done carefully in a short time by a chromatography through a short silica gel column.[6]

Lithiation of amide **4b** was completed in 30 min at –78 °C with lithium diisopropylamide (LDA) in tetrahydrofuran (THF). The resulting lithium *Z*-enolate **A** (M = Li) was totally inactive to 2,2-dimethylpropanal even at room temperature, the starting amide **4b** having been recovered quantitatively after

hydrolytic quench. The lithium enolate was therefore transmetalated, in an hour at –78 °C,[7] with a toluene solution of $TiCl_2(i\text{-}PrO)_2$ to generate the deeply purple-colored titanium *Z*-enolate **A** [M = $TiCl(i\text{-}PrO)_2$]. Although addition of 2,2-dimethylpropanal immediately faded the color of titanium enolate, the reaction was continued in an additional few hours at –78 °C to complete the reaction. Removal of the imine moiety by acid hydrolysis gave a 95:5 stereoisomeric mixture of *anti*- and *syn*-isomers of aldol adduct **6b** (Scheme 1 and Table 1, entry 2).



a: $ClCH_2COCl/Et_3N$ in CH_2Cl_2 at 0 °C to rt, 2 h. *b*: NH_4OH in DMF, rt, 2 h. *c*: $Ph_2C{=}NH$ in CH_2Cl_2, rt, 24 h. *d*: 1) LDA in THF, –78 °C, 30 min, 2) $TiCl_2(i\text{-}PrO)_2$, –78 °C, 1 h, 3) RCHO. *e*: 1N HCl, rt, 30 min

Scheme 1.

The initial aldol adduct **5b** could be isolated by hydrolytic quench of the reaction mixture with saturated ammonium chloride. Although adduct **5b**, separated immediately after the quenching, consisted of almost single diastereomer on the basis of ^1H NMR analysis, it gradually changed to the cyclized product **7** on standing at room temperature. Since such cyclization made it difficult to evaluate stereoselectivity of this reaction, the initial aldol adducts **5a-j** were subjected to acid hydrolysis with 1N HCl after the completion of aldol reaction to give α-amino-β-hydroxy amides **6a-j** as mixture of diastereomers (Table 1, entries 1-10).[8,9] The oxazolidine chiral controller was safe under the hydrolytic conditions.

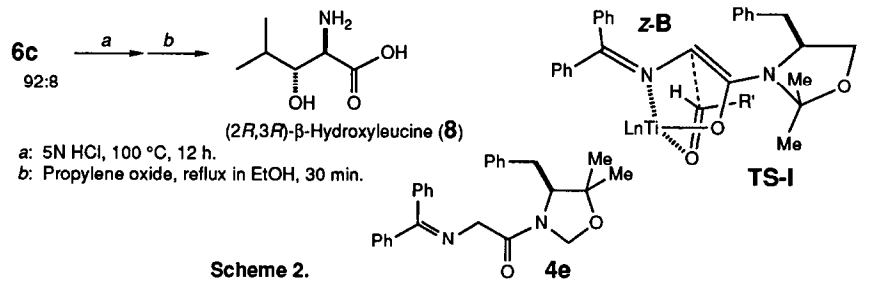
Although a low diastereoselectivity (67:33) was observed in the reaction of 2,2-dimethyl-4-phenyloxazolidine amide **4a** (Table 1, entry 1), those of 4-isopropyl- **4b** and 4-benzyloxazolidine amides **4c** were highly diastereoselective. Especially, the titanium *Z*-enolate *Z*-**B** derived from **4c** gave **6d** as a single diastereomer in the reaction with 2,2-dimethylpropanal (entry 4). Even with primary aliphatic aldehydes such as propanal and ethanal, satisfactory diastereoselectivities were obtained (entries 7 and 8). In some cases, selectivities were not confirmed because a trace amount of unidentified products was contained in the crude hydrolyzed products (entries 6 and 9). Amide **4d** derived from a highly effective chiral auxiliary, 4-benzyl-2,2,5,5-tetramethyloxazolidine **1d**,[10] showed rather a worse selectivity (entry 10).

Table 1. Asymmetric Aldol Reactions of the Titanium Enolates of Oxazolidine Amides **4a-d** Followed by Acid Hydrolysis Giving β-Amino-α-hydroxy Amides **6a-j**

Entry	Amide	R^4	R^5	RCHO	Product	R^4	R^5	R	Yield/%[a]	Isomer ratio[b]
1	**4a**	Ph	H	*t*-BuCHO	**6a**	Ph	H	*t*-Bu	35	67:33
2	**4b**	*i*-Pr	H	*t*-BuCHO	**6b**	*i*-Pr	H	*t*-Bu	59	95:5
3	**4b**			*i*-PrCHO	**6c**	*i*-Pr	H	*i*-Pr	61	90:10
4	**4c**	$PhCH_2$	H	*t*-BuCHO	**6d**	$PhCH_2$	H	*t*-Bu	46	≥99:1
5	**4c**			*i*-PrCHO	**6e**	$PhCH_2$	H	*i*-Pr	53	97:3
6	**4c**			*n*-PrCHO	**6f**	$PhCH_2$	H	*n*-Pr	50	-[c]
7	**4c**			EtCHO	**6g**	$PhCH_2$	H	Et	46	95:5
8	**4c**			MeCHO	**6h**	$PhCH_2$	H	Me	45	95:5
9	**4c**			*n*-PrCH=CHCHO	**6i**	$PhCH_2$	H	*i*-Pr	33	-[c]
10	**4d**	$PhCH_2$	Me	*i*-PrCHO	**6j**	$PhCH_2$	Me	*i*-Pr	33	81:19

[a]Yield of isolated mixture of stereoisomers based on **4a-d**. [b]Detremined by ^{13}C NMR of the crude reaction mixture of **6**. [c]Not determined due to the contamination by unidentified products.

Absolute configurations of the major diastereomers of *anti*-aldol products **6a-j** were determined to be 2*R*,3*R* stereochemistries on the basis of the hydrolytic removal of oxazolidine chiral auxiliary from **6c** (Scheme 2): Treatment of **6c** with 5N HCl at 100 °C and subsequent neutralization with propylene oxide gave (2*R*,3*R*)-β-hydroxyleucine (**8**) in 65% yield, whose absolute and relative configuration was confirmed by comparison of its optical rotation and melting point, $[\alpha]_D^{24} = -22.0°$ (*c* 0.96, H_2O) and mp 225 - 228 °C, with those of the reported values.[11,12]



Scheme 2.

It is most likely that the exclusive formation of *anti*-aldol adducts **6a-j** arises from a chelated and boat-shaped transition state such as **TS-I**[12] where the *re*-face of titanium *Z*-enolate *Z*-**B** interacts with the *si*-face of aldehyde acceptors (Scheme 2). Enolate *Z*-**B** occupies *syn*-conformation and its nucleophilic attack to aldehydes takes place exclusively at the diastereoface not facing the 4-substituent. When the oxazolidine chiral controller is sterically hindered as shown in the case of **4d**, diastereoselectivity is lowered. Probably some steric congestion around the oxazolidine ring would make the transition state unstable.

The titanium *Z*-enolate derived from 2-unsubstituted oxazolidine **4e** was much less effective than the enolates of 2,2-dimethyl derivatives **4a-d**: Its reaction with 2-methylpropanal gave an aldol product consisting of four isomers (53%, 72:17:6:5 by ^1H and ^{13}C NMR spectra). Such low selectivity may be because two rotational isomers (*syn* and *anti*) of titanium *Z*-enolate have participated in the reaction. Several rotational isomers are also contained in the aldol product, so determination of its purity was difficult.

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5. Pickert, P. L.; Tolbert, R. L. *Org. Synth.* **1973,** Coll. Vol. *V,* 520.
6. Silica gel FL100DX (Fuji-Davison Chemical Ltd.) was used (eluent: hexane - diethyl ether).
7. Transmetalation at an elevated temperature was deliberately avoided in fear of isomerization of the intramolecularly coordinated titanium *Z*-enolate A [M = $TiCl(i\text{-}PrO)_2$] (See Kanemasa, S.; Uchida, O.; Wada, E.; Yamamoto, H. *Chem. Lett.* **1990,** 105-108. Barr, D. A.; Grigg, R.; Sridharan, V. *Tetrahedron Lett.* **1989,** *30,* 4727-4730). This incomplete transmetalation might be a reason for the low yields observed in the present aldol reactions.
8. Minor diastereomers of **6b-i** were not isolated due to their low yield formation. Two diastereomers of **6a** were separated by silica gel column chromatography using EtOAc/EtOH as eluent.
9. New compounds discussed in this report were characterized by spectral and analytical data: (2*R*,3*R*)-**6a** (major isomer): Colorless solid (silica gel column chromatography with EtOAc/EtOH); $[\alpha]_D^{24} = -109.3°$ (*c* 0.16, $CHCl_3$); Rf = 0.1 (EtOAc); IR (KBr) 3410, 2950, 1620, 1420, 1360, 1045, and 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 0.45 (9H, s, *t*-Bu), 1.63, 1.86 (each 3H, s, 2-Me), 1.83, (3H, br s, NH_2 and OH), 3.02 (1H, d, $J_{3'\text{-}2'}$ = 2.0 Hz, H-3'), 3.17 (1H, d, $J_{2'\text{-}3'}$ = 2.0 Hz, H-2'), 3.89 (1H, dd, J_{gem} = 9.0 and $J_{5\text{-}4}$ = 1.5 Hz, one of H-5), 4.39 (1H, dd, J_{gem} = 9.0 and $J_{5\text{-}4}$ = 6.6 Hz, the other of H-5), 5.14 (1H, dd, $J_{4\text{-}5}$ = 6.6 and 1.5 Hz, H-4), and 7.26 - 7.36 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ = 22.05, 25.15 (each 2-Me), 26.05 (Me of *t*-Bu), 34.73 (C of *t*-Bu), 50.34 (C-5), 60.93 (C-2'), 71.13 (C-3'), 86.74 (C-4), 96.02 (C-2), 126.55, 128.29, 129.20, 142.08 (each Ph), and 173.86 (C-1'). Anal. Calcd for $C_{18}H_{28}N_2O_3$: C, 67.47; H, 8.81; N, 8.74%. Found: C, 67.13; H, 8.72, N, 8.55%. (2*S*,3*S*)-**6a** (minor isomer): Colorless solid (silica gel column chromatography with EtOAc); $[\alpha]_D^{24} = -84.9°$ (*c* 0.62, $CHCl_3$); Rf = 0.4 (EtOAc); ^1H NMR ($CDCl_3$) δ = 0.95 (9H, s, *t*-Bu), 1.25 (2H, br, NH_2), 1.62, 1.88 (each 3H, s, 2-Me), 1.83, (3H, br s, NH_2 and OH), 3.29 (2H, br s, H-2' and H-3'), 3.92 (1H, dd, J_{gem} = 9.0 and $J_{5\text{-}4}$ = 2.4 Hz, one of H-5), 4.40 (1H, dd, J_{gem} = 9.0 and $J_{5\text{-}4}$ = 6.6 Hz, the other of H-5), 4.45 (1H, br, OH), 4.99 (1H, dd, $J_{4\text{-}5}$ = 6.6 and 2.4 Hz, H-4), and 7.41 - 7.27 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ = 22.62, 25.27 (each 2-Me), 26.74 (Me of *t*-Bu), 35.1 (C of *t*-Bu), 52.21 (C-5), 61.52 (C-2'), 71.16 (C-3'), 83.68 (C-4), 96.31 (C-2), 126.89, 128.43, 129.44, 141.29 (each Ph), and 175.24 (C-1'). Anal. Calcd for $C_{18}H_{28}N_2O_3$: C, 67.47; H, 8.81; N, 8.74%. Found: C, 67.66; H, 9.00, N, 8.56%.
10. Effective shielding of the acryloyl moiety of 3-acryloyl derivative of **1d** by the 4-benzyl substituent was observed in ^1H NMR study (See Ref. 3b).
11. **8**: Colorless needles (aq EtOH); mp 225 - 228 °C; $[\alpha]_D^{24} = -22.0°$ (*c* 0.96, H_2O); IR (KBr) 3430, 3080, 1620, 1560, 1340, 1005, and 550 cm^{-1}; ^1H NMR (D_2O) δ = 0.83, 0.84 (each 3H, d, *J* = 6.8 Hz, *i*-Pr), 1.80 (1H, m, CH of *i*-Pr), 3.39 (1H, dd, $J_{3\text{-}CH}$ = 9.0 and $J_{3\text{-}2}$ = 2.9 Hz, H-3), 3.77 (1H, d, $J_{2\text{-}3}$ = 2.9 Hz, H-2), and 4.64 (4H, br s, OH, NH_2, and COOH); ^{13}C NMR (D_2O) δ = 21.24, 21.30 (each Me of *i*-Pr), 32.93 (C of *i*-Pr), 59.84 (C-2), 78.85 (C-3), and 174.52 (COOH). Anal. Calcd for $C_6H_{13}NO_3$: C, 48.96; H, 8.90; N, 9.52%. Found: C, 48.90; H, 8.76, N, 9.43%.
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13. A similar transition state has been proposed in the *anti*-selective aldol reactions of the titanium *Z*-enolates of α-alkoxy thioesters (See Ref. 2).

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