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Lewis Acid-Mediated Reaction with Silyl Ketene Acetals and Allylstannane of the Aluminum Acetals Generated by DIBALH Reduction of α-Amino Acid Esters

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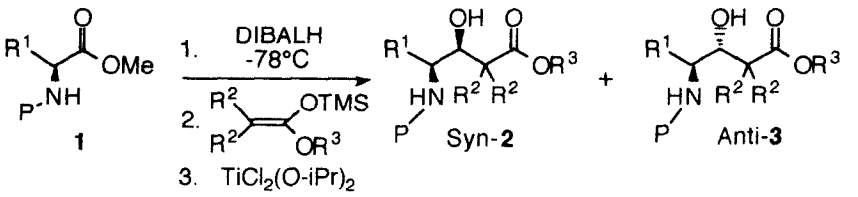
Abstract: The intermediates generated by DIBALH reduction of α-amino acid esters undergo condensation without racemization with silyl ketene acetals and allylstannane in the presence of Lewis acid to afford the corresponding β-hydroxy esters and homoallylic alcohols in good yields while achieving high syn selectivity via an aluminum-assisted chelation control.

Recently the intermediates involved in the low-temperature DIBALH reduction of carboxylic acid esters to aldehydes have been confirmed to be aluminum acetals by successfully trapping them with TMSOTf to isolate the corresponding stable monosilyl acetals.[2] One of the utilizations of such aluminum acetals for an effective carbon-carbon bond formation reaction was also achieved with silyl ketene acetals in the presence of Lewis acids to afford the aldol-type products[3] ; this methodology of directly converting carboxylic acid esters to aldols might be an alternative for a variety of reactions using considerably unstable aldehydes. Condensation reactions with optically pure α-amino aldehydes are somewhat troublesome because such aldehydes are prone to racemization.[4] We disclose herein an effective one-pot aldol reaction using the aluminum acetals from *N*-protected α-amino acid esters without racemization.

After the DIBALH reduction intermediates of *N*-protected α-amino acid esters in CH_2Cl_2 at -78°C were treated with $TiCl_2(O\text{-}iPr)_2$ and silyl ketene acetals and after the usual workup procedure, the corresponding β-hydroxy esters were obtained in good yields along with the primary alcohols (ca. 10%) as an overreduction product of the starting esters.[5] Syn selectivity was observed as shown in Table I. In each case of the esters from valine and *t*-leucine, only the syn product was obtained (entries 3, 9) ; the stereochemistry of the products was determined by ^{1}H-NMR analysis of their Mosher esters.[7] From all the Lewis acids examined, $TiCl_2(O\text{-}iPr)_2$ provided the most satisfactory results on selectivity. The reaction proceeded without racemization and the syn/anti isomers of the products (R^2=Me) could easily be separated by column chromatography.

The Lewis acid-mediated cleavage reactions of acetals have been interpreted individually to proceed according to direct displacement (S_N2) mechanism or oxocarbenium ion (S_N1) mechanism because of the obscure behaviors of the acetals varying in structure toward Lewis acids.[8] Polt suggested that the direct displacement of nucleophiles takes place in Grignard addition reactions to the DIBALH reduction intermediates,[9] while an S_N1 mechanism on the supposed aldehyde intermediate was reported by Yamamoto[6] and Kano.[10]

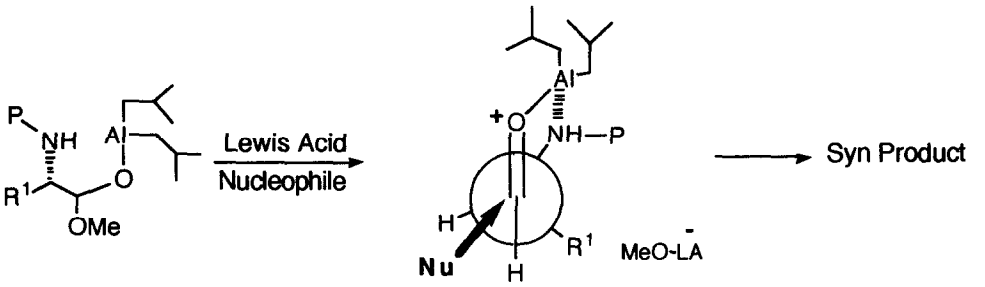
Table I. Reactions of the Intermediates in DIBALH Reduction of *N*-Protected α-Amino Acid Esters with Silyl Ketene Acetals in the Presence of $TiCl_2(O\text{-}iPr)_2$



Entry[a]	Ester		Silyl ketene acetal		Product[b]/Alcohol[c]	Ratio of diasetreomers[d]
	R^1	P	R^2	R^3	(%yield)	Syn(**2**):Anti(**3**)
1	Me	Cbz	Me	Me	**2a,3a** (66)/(10)	15 :1[e]
2	Me	Cbz	H	Ph	**2b,3b** (53)/(12)	4.6 :1
3	i-Pr	Cbz	Me	Me	**2c** (68)/(7)	syn only
4	i-Pr	Cbz	H	Ph	**2d,3d** (59)/(12)	>46 :1
5	s-Bu	Cbz	Me	Me	**2e,3e** (69)/(6)	7 :1
6	s-Bu	Cbz	H	Ph	**2f,3f** (53)/(7)	2.5 :1
7	$PhCH_2$	Cbz	Me	Me	**2g,3g** (60)/(6)	23 :1
8	$PhCH_2$	Cbz	H	Ph	**2h,3h** (59)/(7)	3.2 :1
9	t-Bu	Boc	Me	Me	**2i** (50)/(14)	syn only

[a]In entry 9, D-*t*-leucine was used. [b]Isolated yield. [c]The alcohols were obtained by overreduction of the starting esters. [d]Determined by HPLC analysis using a DAICEL CHIRALCEL OD. [e]Using $BF_3{\cdot}OEt_2$ instead of $TiCl_2(O\text{-}iPr)_2$, the syn/anti ratio of the product was 8 :1.

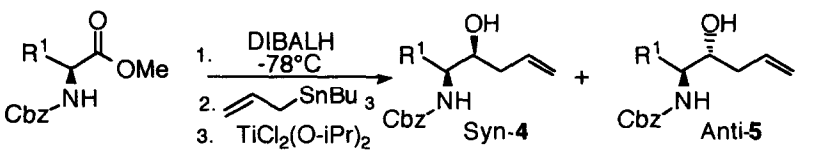
Although DIBALH reduction of (1*S*, 2*R*, 5*S*)-menthyl 3-phenylpropionate was trapped with TMSOTf to afford a 2.4 :1 mixture of the diastereoisomers of the corresponding monosilyl acetal,[2] the same aluminum acetal intermediate underwent condensation with a silyl ketene acetal in the presence of Lewis acid to produce a completely racemic β-hydroxy ester. This observation suggested that the Lewis acid used in the reaction plays the role of eliminating the alkoxy moiety from the aluminum acetal (an oxocarbenium ion mechanism) in order to lose its chirality. Furthermore we can interpret the high syn selectivity observed in the Lewis acid mediated reaction of the aluminum acetals as follows ; the residual aluminum in the oxocarbenium ion might coordinate to the α-nitrogen and concurrently assist the following chelation-controlled addition[11] of silyl nucleophiles, as illustrated in Scheme 1.



Scheme 1

In addition, the reactions of allylstannane[12] with the α-amino acid esters under similar conditions provided the corresponding homoallylic alcohols with fair to good syn selectivity without racemization, as shown in Table II.[13]

Table II. Reaction of the Intermediates in DIBALH Reduction of *N*-Cbz-Amino Acid Esters with Allylstannane in the Presence of $TiCl_2(O\text{-}Pr)_2$



Entry	R^1	Product [a]/Alcohol [b] (%yield)	Ratio of diastereomers [c] Syn(**4**):Anti(**5**)
1	Me	**4a,5a** (44)/(38)	10 :1
2	i-Pr	**4b,5b** (43)/(19)	14 :1
3	s-Bu	**4c,5c** (42)/(24)	4.8 :1
4	$PhCH_2$	**4d,5d** (43)/(32)	7 :1

[a]Isolated yield. [b]The alcohols were obtained by overreduction of the starting esters. [c]Determined by HPLC analysis using a DAICEL CHIRALCEL OD.

References and Notes

1. Present address : Department of Agriculture, University of Osaka Prefecture.
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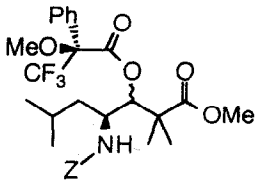
3. Kiyooka, S. -i.; Shirouchi, M. *J. Org. Chem.* **1992**, *57*, 1-2.
4. Rittle, K. E.; Homnick, C. F.; Ponticello, G. S.; Evans, B. E. *J. Org. Chem.* **1982**, *47*, 3016-3018.
5. **Typical Procedure** : To a solution of 273 mg(1 mmol) of methyl (*S*)-2-(*N*-benzyloxycarbonyl)-aminopropanoate in 5 ml of dry CH_2Cl_2 at -78°C under Ar was added dropwise 1.6 ml(1.6 mmol, 1 M solution in toluene) of DIBALH. The mixture was stirred at -78°C for 2 h, whereupon a solution of 377 mg(2 mmol) of 1-ethoxy-2-methyl-1-trimethylsiloxy-1-propene in 0.5 ml of CH_2Cl_2 and then 1.25 ml (1.25 mmol, 1 M solution in CH_2Cl_2) of $TiCl_2(O\text{-}iPr)_2$ were added. After the mixture was stirred at -78°C

for 3 h and then allowed to warm to room temperature, the reaction was quenched by the introduction of saturated aqueous Na_2CO_3 solution. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2(20 ml ×3). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel to give 204 mg(66%) of a mixture of **2a** and **3a**. All new compounds in the text gave satisfactory microanalysis and spectral data (^{1}H-, ^{13}C-NMR, IR). Racemization in the reaction was not observed as confirmed by HPLC analysis with chiral columns.

6. A similar syn selectivity (15 : 1) was observed in the reaction of vinylmagnesium chloride with the DIBALH reduction intermediate of Boc-(*S*)-alanine methyl ester ; Ibuka, T.; Habashita, H.; Otaka, A.; Fujii, N.; Oguchi, Y.; Uyehara, T.; Yamamoto, Y. *J. Org. Chem.* **1991**, *56*, 4370-4382. Angle, S. R.; Breitenbucher, J. G.; Arnaiz, D. O. *J. Org. Chem.* **1992**, *57*, 5947-5955.
7. The oxazolidinones were not derived from the products under the conditions of THF/MeOH/7.5 N-KOH whereas the acetonides were prepared with 2,2-dimethoxypropane but they could not be used for the determination of the stereochemistry because of the existence of rotamers. The stereochemistry of the products was determined by the ^{1}H-NMR analysis of the Mosher esters obtained from the β-hydroxy esters and (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid, according to Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543-2549 ; an example is as follows.



Chemical Shifts of Mosher Esters from the Products, 2e and 3e

Entry	δH C(4)	δH C(3)
syn(from **2e**)	4.054	5.322
anti(from **3e**)	3.950	5.279
Δδ=δ(syn)-δ(anti)	0.104	0.043

8. Bartlett, P. A.; Johnson, W. S.; Elliott, J. D. *J. Am. Chem. Soc.* **1983**, *105*, 2088-2089. Yamamoto, Y.; Nishi, S.; Yamada, J. *J. Am. Chem. Soc.* **1986**, *108*, 7116-7117. Denmark, S. E.; Willson, T. M.; Almsted, N. G. *J. Am. Chem. Soc.* **1989**, *111*, 9258-9260. Mori, I.; Ishihara, K.; Flippin, L. A.; Nozaki, K.; Yamamoto, H.; Bartlett, P. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 6107-6115. Denmark, S. E.; Almsted, N. G. *J. Org. Chem.* **1991**, *56*, 6458-6467. Sammakia, T.; Smith, R. S. *J. Am. Chem. Soc.* **1992**, *114*, 10998-10999.
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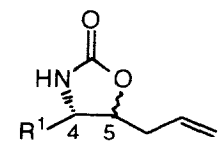
12. The reaction with allylsilane did not work well giving only 8% of the homoallylic alcohols along with a large amount of the alcohol from overreduction.
13. The treatment of the syn and anti homoallylic alcohols with THF/MeOH/7.5 N-KOH(4:2:1) provided the corresponding trans-**6** and cis-**7** oxazolidinones, respectively; Kano, S.; Yokomatsu, T.; Iwasawa, H.; Shibuya, S. *Tetrahedron Lett.* **1987**, *28*, 6331-6334.



6 and 7

Coupling Constants of the Oxazolidinone

Entry	Oxazolidinones (**6**, **7**)	$J_{H(4)-H(5)}$ Trans-**6**	Cis-**7**
1	(from **4a**,**5a**)	5.93	7.47
2	(from **4b**,**5b**)	4.40	6.82
3	(from **4c**,**5c**)	5.50	7.69
4	(from **4d**,**5d**)	5.27	7.03

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