CHEMISTRY LETTERS, pp. 815-818, 1986. 

# A SELECTIVE 1,2-REDUCTION OF γ-AMINO-α,β-UNSATURATED ESTERS BY MEANS OF $BF_3 \cdot OEt_2$—DIBAL-H SYSTEM. HIGHLY VERSATILE CHIRAL BUILDING BLOCKS FROM α-AMINO ACIDS

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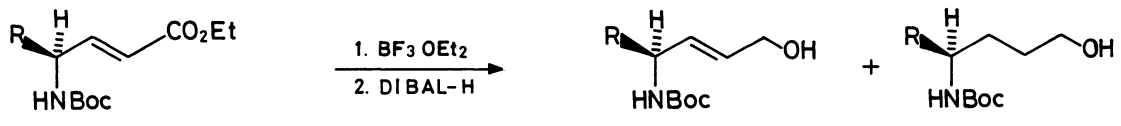
A combination of DIBAL-H with $BF_3 \cdot OEt_2$ has been demonstrated to be a promising agent for a selective 1,2-reduction of γ-amino-α,β-unsaturated esters, which, otherwise, is difficult to realize and provides the route to potent chiral building blocks from α-amino acids.

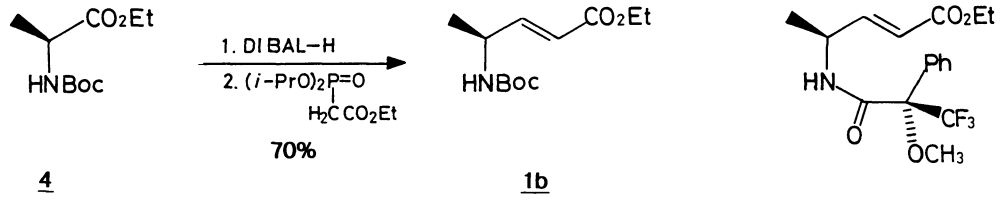
Natural protein amino acids and their derivatives are enjoying increasing popularity as synthetically useful chiral building blocks in organic chemistry.[1] We have become interested in an efficient utilization of α-amino acids as chiral building blocks directed to nitrogen-containing natural product synthesis and, especially, in 4-amino-allylic alcohol frameworks (**2**), which could be led from optically active α-amino acids by reasonable pathways, because a novel route to amino polyols or pyrrolidine backbones would become feasible through further elaboration of the allylic alcohol functionality, relying on, for instance, Sharpless epoxidation[2] or Claisen rearrangement. In a synthetic endeavour toward **2**, we have met with the difficulty that 1,2-reduction of γ-amino-α,β-unsaturated esters (**1**) was not effected by usual metal-hydride reagents which are well known to be successful for the similar transformation if the amino group is lacking. It turned out, however, that $BF_3 \cdot OEt_2$—DIBAL-H system gave a quick solution to the problem as shown in Scheme 1 and proved to have general applicability as the selective 1,2-reducing agent for **1**, which will be communicated here.




**1** **2** 84% (R=$CH_3$) **3** 1–3%

**Scheme 1.**

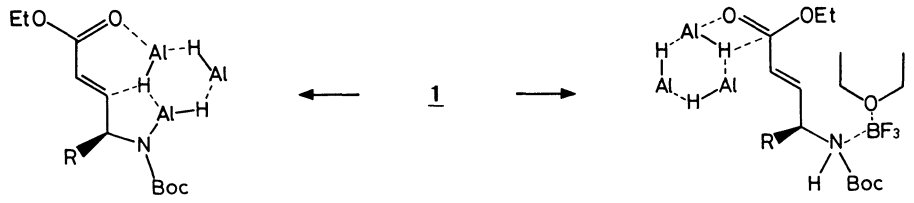
At the outset of this project, we have contemplated to transform corresponding α-amino aldehyde rather directly to **2** *via* Wittig condensation with 2-hydroxyethylidenetriphenylphosphorane equivalent such as 2-(*p*-chlorophenoxy)ethylidene- or 2-oxidoethylidenetriphenylphosphorane.[3] The reactions, however, resulted in the formation of complex mixture or elimination of triphenylphosphine oxide in a fashion to form not internal but undesired terminal olefinic linkage, respectively. Consequently, we turned our attention to the route as **1** → **2**. Thus, *N*-Boc-L-alanine ethyl ester (**4**) was reduced with DIBAL-H (2 equiv./PhMe/-78 °C), giving rise to *N*-Boc-L-alanal (**5**)[4] in 74% yield, which was condensed with diisopropyl ethoxycarbonylmethylphosphonate (NaH/THF/0 °C) to afford **1b** in 94% yield (>95% *E*). During these reactions, no racemization was observed as verified by $^1$H-NMR diagnosis for the corresponding MTPA-amide (**6**).[6]




**4** **1b** **6**

**Scheme 2.**

Reduction of **1b** iwth typical metal-hydride reagents such as DIBAL-H, $LiAlH_4$, or $LiEt_3BH$ proceeded in a non-selective manner to leave a mixture of **2b** and **3b** in 35% and 22% yield, respectively, for every case. The idea to remedy this drawback, for which a hypothetical transition state ($\mathbf{T_A}$) might be responsible, is to make it impossible for trimeric DIBAL-H to come in contact with the amino moiety of **1b**. The simplest way to realize such situation was considered to add an appropriate Lewis acid to the reaction [7] before reduction starts.



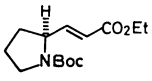

**3** $T_A$ $T_B$ **2**

In the event, to a solution of **1b** (889 mg, 3.38 mmol) in $CH_2Cl_2$ (7 ml) was added $BF_3 \cdot OEt_2$ (0.46 ml, 3.77 mmol) at -78 °C, the mixture being stirred at that temperature for 30 min. Then, DIBAL-H (10.5 ml of 1 M hexane solution)[8] was introduced into the cooled solution and the resultant mixture was stirred at -78 °C for 45 min before quenching the reaction with acetic acid (6.3 ml, 5 M $CH_2Cl_2$ solution).[8] The reaction was allowed to warm up to room temperature and poured into 10% aqueous tartaric acid, the product being extracted with $CH_2Cl_2$ (10 ml×3). The $CH_2Cl_2$

solutions were washed with $NaHCO_3$ and brine, dried ($Na_2SO_4$), and concentrated to afford an oil, which, on $SiO_2$ chromatography (hexane/EtOAc = 3/1), gave **2** (R=$CH_3$, 585 mg, 84%) as a colorless oil:[9] the saturated alcohol **3** (R=$CH_3$) stemmed from 1,4-reduction was obtained only in 1—3% yield. To make the reaction undergo *via* a hypothetical transition state ($T_B$) led to 1,2-reduction, it is strictly required that the Lewis acid must be added to the reaction before introducing the metal-hydride reagent. For example, if a mixture of DIBAL-H and $BF_3 \cdot OEt_2$ was added to a solution of **1** (R=$CH_3$) at -78 °C, the reaction has left behind deteriorated mixture similarly to the case without the Lewis acid. Obviously, under such conditions, $BF_3 \cdot OEt_2$ plays no role as it does when being added prior to the introduction of DIBAL-H.

To our delight the protocol as mentioned above has proven highly effective for 1,2-reduction of γ-amino-α,β-unsaturated esters derived from α-amino acids other than L-alanine. The results were shown in the Table 1 together with those obtained in the absence of the Lewis acid for comparison. As recognized immediately from the entries, 1,2-reduction selectivity has been upgraded greatly in every case. For the entry 6 in which no hydrogen is remaining on the nitrogen atom, a satisfactory 1,2-selectivity was observed even in the absence of the Lewis acid, indicating that illustrative transition state ($T_A$) seems probable.

**Table 1. Selective 1,2-Reduction of γ-Amino-α,β-unsaturated Esters by means of $BF_3 \cdot OEt_2$–DIBAL-H System[a]**

| Entry | Substrate, **1** | | Yield of **2** / %[b] | |
|---|---|---|---|---|
| | | | DIBAL-H[c] | $BF_3 \cdot OEt_2$–DIBAL-H[d] |
| 1 | R= H | (**1a**) | 42 | 84 |
| 2 | $CH_3$ | (**1b**) | 35 | 84 |
| 3 | $(CH_3)_2CH$ | (**1c**) | 26 | 83 |
| 4 | $C_6H_5$ | (**1d**)[e] | 33 | 65 |
| 5 |  | (**1e**)[f] | 15 | 75 |
| 6 |  | (**1f**) | 71 | 80 |

a) Under the same reaction conditions as described in the text unless otherwise noted. b) Isolated yield ($SiO_2$). c) Conducted in toluene as solvent. d) $[\alpha]_D$ for **2b**, **2c**, **2e**, and **2f**, -23.3° (c 2.36, $CHCl_3$), +8.7° (c 1.09, $CHCl_3$), +15.4° (c 1.48, $CHCl_3$), and -30.3° (c 2.88, $CHCl_3$), respectively. e) Racemic mixture. f) S. Saito, N. Bunya, M. Inaba, T. Moriwake, and S. Torii, Tetrahedron Lett., **26**, 5309 (1985).

In summary, a convenient synthesis of optically pure 4-amino-allylic alcohol derivatives have been demonstrated. We believe that the pathway from natural or unnatural α-amino acids to **2** is expected to play an important role in nitrogen-containing natural product synthesis, which is currently in progress.

We wish to thank Mr. Matsumoto for his active contribution to a part of this work. We are gratefully indebted to FT-NMR Facilities of School of Engineering, Okayama University for measurements of $^{1}$H-NMR and $^{13}$C-NMR spectra.

**References**

1) S. Hanessian,"Total Synthesis of Natural Products: the 'Chiron' Approach," ed by J. E. Baldwin, Pergamon Press, Oxford (1983); for recent review on the utilization of amino acids in asymmetric synthesis, see K. Drauz, A. Kleeman, and J. Martens, Angew, Chem., Int. Ed. Engl., **21**, 584 (1985).

2) T. Katsuki and K. B. Sharpless, J. Am. Chem. Soc., **102**, 5974 (1984) and C. E. Adams, F. J. Walker, and K. B. Sharpless, J. Org. Chem., **50**, 420 (1985).

3) A. Maercker, "Organic Reactions," ed by A. C. Cope, Wiley, New York (1965), Vol. 14, Chap. 3.

4) A. Ito, R. Takahashi, and Y. Baba, Chem. Pharm. Bull., **23**, 3081 (1975).

5) NMR ($CDCl_3$, 60 MHz) δ 1.26 (q, 3H, *J*=7.0 Hz), 1.27 (t, 3H, *J*=6.4 Hz), 1.41 (s, 9H), 4.12 (q, 2H, *J*=6.4 Hz), 4.19–4.64 (bs, 1H), 4.92–5.33 (bs, 1H), 5.77 (bd, 1H, *J*=16 Hz), 6.78 (dd, 1H, *J*=16, 5.0 Hz); IR ($CHCl_3$) 3354, 2980, 1720–1670, 1654, 1514, 1362, and 1271 $cm^{-1}$; $[\alpha]_D^{27}$ -27.3° (c 1.5, $CHCl_3$).

6) J. A. Dale, D. L. Dull, and H. S. Mosher, J. Org. Chem., **34**, 2543 (1969); NMR ($CDCl_3$, 100 MHz) for MTPA-amide of DL-**1b**: δ 1.29 (t, *J*=6.6 Hz), 1.32 (d, *J*=7.1 Hz), 1.36 (d, *J*=6.8 Hz), 3.14 (m), 4.19 (q, *J*=7.1 Hz), 4.21 (q, *J*=7.1 Hz), 4.64–4.69 (m), 5.81 (dd, *J*=16, 1.7 Hz), 5.92 (dd, *J*=16, 1.7 Hz), 6.74–7.00 (m), 7.28 7.60 (m); NMR ($CDCl_3$, 100 MHz) for **6**: δ 1.29 (t, 3H, *J*=6.6 Hz), 1.33 (d, 3H, *J*=7.1 Hz), 3.41 (q, 3H, *J*=1.5 Hz), 4.21 (q, 2H, *J*=6.6 Hz), 4.78 (qd, 1H, *J*=7.1, 1.7 Hz), 5.92 (dd, 1H, *J*=16, 1.7 Hz), 6.88 (dd, 1H, *J*=16, 4.9 Hz), 6.79–7.00 (bs, 1H), 7.26–7.54 (m, 5H).

7) Prof. H. Yamamoto and his collaborators have shown that Lewis acid such as $(CH_3)_3Al$ can readily coordinate to the nitrogen atom of α-substituted 6-membered cyclic imine, which dramatically changes the steric course of the reduction of imine with $LiAlH_4$: Y. Matsumura, K. Maruoka, and H. Yamamoto, Tetrahedron Lett., **23**, 1929 (1982).

8) 1 M= 1 mol $dm^{-1}$.

9) When two-molar equivalent of DIBAL-H was employed, **1** was recovered unchanged in a significant amount: NMR ($CDCl_3$, 60 MHz) δ 1.17 (d, 3H, *J*=6.8 Hz), 1.41 (s, 9H), 3.22–3.48 (bs, 1H), 3.89–4.36 (bs, 3H), 4.67–4.96 (bd, 1H, *J*=7 Hz); IR ($CHCl_3$) 3468, 2990, 2947, 1708, 1399, 1454, 1391, 1366, 1242, and 1129 $cm^{-1}$; $[\alpha]_D^{26}$ -23.3° (c 2.36, $CHCl_3$).

(Received March 4, 1986)