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# A Straightforward Synthesis of Allyl Amines from α-Amino Acids without Racemization

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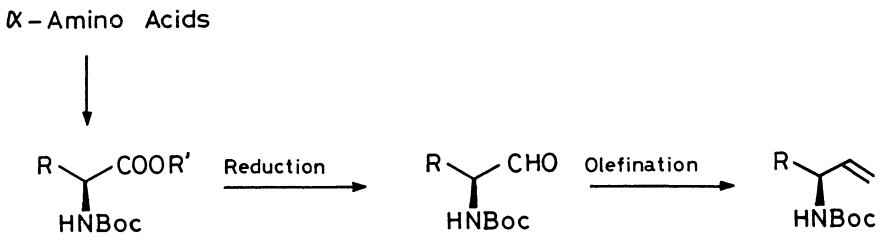
An extremely simple and practical synthesis of allyl amine derivatives from α-amino acids has been developed involving aldehyde olefination pathway with $AlMe_3$-Zn-$CH_2I_2$ reagent which has proven to be crucial for preservation of stereochemical integrity.

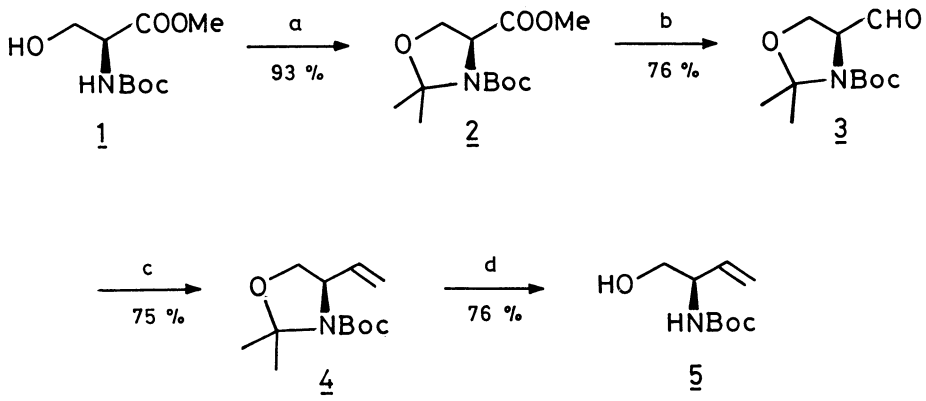
Naturally-occurring amino acids and their equivalents have successfully been employed to embed them into an essential backbone of natural products.[1] In this context a number of strategies for manipulating optically pure amino acids directed to versatile chiral building blocks has been explored so far. Among them a series of transformations indicated in Scheme 1 which leads to allyl amine derivatives should be one of the most straightforward and practical entry. However, the final step in this pathway, an olefination of intermediary formyl functionality, has universally been recognized as highly challenging because of an unavoidable racemization[2] in spite of numerous executions of possible candidates such as Wittig, Peterson, or Wadsworth-Emmons protocols. In this communication we will disclose a general promising protocol, thus for the first time in this sense, for such transformation as described in Scheme 1, overcoming racemization. The detail will be presented in the case of D-vinylglycine equivalent,[3] *i.e.*, (2*R*)-2-amino-3-buten-1-ol starting from L-serine, which has been demonstrated to be reliable chiral building block in the total synthesis of Aspergillomarasamine A[4] and Galantinic acid.[5]




*Scheme 1.*

Although a starting *N,O*-acetonide derivative (**2**) of *N*-*t*-butoxycarbonyl-L-serine methyl ester can be obtained through acid (TsOH) catalyzed condensation

with dimethoxypropane (DMP) in 60% yield,[6,2a] we have found that $BF_3.OEt_2$ is much more preferable catalyst and the reaction employing such Lewis acid gave **2** in 93% yield: $[\alpha]_D^{23}$ -55° (c 4.5, $CHCl_3$).[7] Ensuing reduction with DIBAL-H at -78 °C led to the aldehyde (**3**) in 78% yield.[8] Though α-(*N*-protected-amino)aldehydes are well known to be chromatographically labile to result in a significant recemization,[9] this aldehyde **3** has proven to be configurationally stable even under such conditions.




a) $BF_3OEt_2$/$(MeO)_2CMe_2$/Acetone/r.t., 12 h; b)DIBAL-H/$PhCH_3$/-78 °C, 1.5 h; c)$AlMe_3$/Zn/$CH_2I_2$/THF/r.t., 12 h; d)p-TsOH/MeOH/r.t., 24 h.

*Scheme 2.*

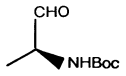
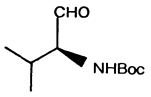
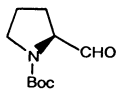
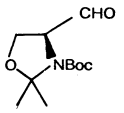
In order to test the possibility for available traditional protocols to effect the olefination of thus-obtained aldehyde functionality without racemization, **3** was subjected first to Wittig condition ($Ph_3PMeBr$/KH/benzene). This actually led to the olefin (**4**) in a 66% yield but it turned out that **4** was completely recemized. Such drawback (racemization problem) has been able to be avoided by the second candidate, *i.e.*, the reaction of **4** with trimethylsilylmethylmagnesium chloride,[10] giving rise to desired adduct, β-hydroxysilane derivative (**6**), in 64% yield. To our disappointment, however, an attempted elimination reaction of **6** under various conditions,[11] gave deteriorated product mixture in which desired vinyl derivative has never been detected at all.

Oshima and Nozaki have disclosed that metallo-organic reagents generated *in situ* from such systems as $AlMe_3$-Zn-$CH_2I_2$ or $TiCl_4$-Zn-$CH_2I_2$ provide a highly electrophilic, mild, and, more importantly, non-basic system for carbonyl olefination and play almost no role to enhance enolization of carbonyl compounds such as ketone.[12] This extraordinary fascinating feature has prompted us to test the feasibility of this reagent to fulfill our requirement. Thus **3** was exposed to $AlMe_3$-Zn-$CH_2I_2$ system in THF for 12 hour, the reaction being quenched and the product being isolated to afford **4** in 75% yield: $[\alpha]_D^{28}$ +15° (c 2.5, $CHCl_3$).[13] A usual deacetonization of **4** (TsOH/MeOH) proceeded smoothly and led to (2*R*)-2-(*N*-*t*-

Boc-amino)-3-buten-1-ol (5) in 76% yield after silica gel chromatography which exhibited $[\alpha]_D^{26}$ +29° (c 2.1, $CHCl_3$)[14] completely consistent with that reported for the optically pure 5.[4]

A general applicability of the present transformations has become quickly apparent. Thus, both *N*-Boc-alanine, *N*-Boc-valine, and *N*-Boc-proline methyl esters gave the corresponding allyl amines in moderate yields without any racemization: the optical purities for these allyl amines are determined to be >99%.[15] The present method for the synthesis of optically pure allyl amine derivatives from α-amino acids is obviously straightforward and hold an exceptional simplicity in operation as well. Thus, it will be given a irreplaceable place in organic synthesis.

Table 1. Olefination of α-(*N*-Boc-amino)aldehyde With $CH_2I_2$-Zn-$AlMe_3$ System[a)]

| Entry | Aldehyde | Temp/°C | Time/h | Yield/%[b)] | $[\alpha]_D$/°[c)] | $([\alpha]_D)$/°[d)] |
|---|---|---|---|---|---|---|
| 1 |  | 0 | 8 | 35 | -6.33 | (-2.15) |
| 2 |  | -50 | 4 | 48 | 25.0 | (9.69) |
| 3 |  | rt | 10 | 62 | -13.4 | (-7.81) |
| 4 |  | rt | 12 | 76 | 29 | (0) |

a) Aldehyde/(Reagent) ratio: 1/(3:9:0.6); titanium version, unsatisfactory for every entry.

b) For chromatographically pure product which shows satisfactory spectral properties such as NMR($^1H$ and $^{13}C$) and IR: reaction conditions not optimized.

c) Determined at 26—28 °C in $CHCl_3$.

d) For the same products stemmed from Wittig olefination pathway: KH-$Ph_3PCH_3Br$-THF.

We are gratefully indebted to FT-NMR Facilities of School of Engineering, Okayama University for measurements of $^1H$-NMR (100 MHz) and $^{13}C$-NMR (25 MHz) spectra.

References

1) For leading reference, see I. Wagner and H. Musso, *Angew. Chem., Int. Ed. Engl.*, 22, 816 (1983).

2) a) A. Ito, R. Takahashi, and Y. Baba, *Chem. Pharm. Bull.*, 23, 3081 (1975);
b) B. Shimizu, A. Saito, A. Ito, K. Tokawa, K. Maeda, and H. Umezawa, *J.*

*Antibiot. (Tokyo)*, 25, 515 (1972); c) H. Khatri and C. H. Stammer, *J. Chem. Soc., Chem. Commun.*, 1979, 79; d) K. E. Rittle, C. F. Homnick, G. S. Ponticello, and B. E. Evans, *J. Org. Chem.*, 47, 3016 (1982); e) S. Kobayashi, T. Isobe, and M. Ohno, *Tetrahedron Lett.*, 25, 5079 (1984); f) M. M. Hann, P. G. Sammes, P. D. Kennewell, and J. B. Taylor, *J. Chem. Soc., Perkin Trans. 1*, 1982, 307; g) R. L. Johnson, *J. Med. Chem.*, 27, 1351 (1984).

3) a) A. Afzali-Aradakani and H. Rapoport, *J. Org. Chem.*, 45, 4817 (1980); b) S. Hanessian and S. P. Sahoo, *Tetrahedron Lett.*, 25, 1425 (1984); c) J. R. Luly, J. F. Dellaria, J. J. Plattner, J. L. Soderquist, and N. Yi, *J. Org. Chem.*, 52, 1487 (1987).

4) Y. Ohfune and N. Kurokawa, *Tetrahedron Lett.*, 25, 1071 (1984).

5) Y. Ohfune and N. Kurokawa, *Tetrahedron Lett.*, 25, 1587 (1984).

6) P. Garner and J. M. Park, *J. Org. Chem.*, 52, 2361 (1987).

7) **2**: NMR ($CDCl_3$) δ 1.42(bs, 9H), 1.52(bs, 3H), 1.68 (s, 3H), 3.76 (s, 3H), 4.0-4.62 (m, 3H); IR (film) 1760, 1710, 1390, 1360, 1200, 1170, 1090 $cm^{-1}$; lit.$[\alpha]_D$ -46.7° (c 1.30, $CHCl_3$) (Ref. 6).

8) **3**: NMR (CDCl3) δ 1.34 (s, 15H), 1.50 (s, 9H), 3.82 (ddd, J=17, 8.5, and 3.8 Hz, 1H), 4.32 (m, 1H), 9.67 (s, 1H); IR (film) 1735, 1700, 1390, 1360 $cm^{-1}$; $[\alpha]_D^{29}$ -90.8° (c 1.24, $CHCl_3$) (lit.$[\alpha]_D^{27}$ -91.7° (c 1.34, CHCl3) (Ref. 6).

9) W. D. Lube and H. Rapoport, *J. Am. Chem. Soc.*, 109, 236 (1987) and references cited therein.

10) D. J. Peterson, *J. Org. Chem.*, 33, 780 (1968).

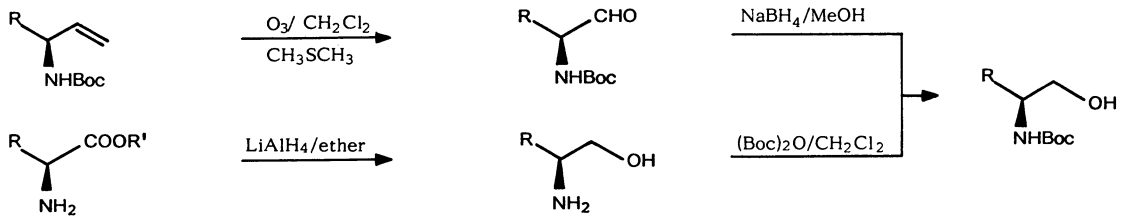
11) W. P. Weber,"*Silicone Reagents for Organic Synthesis*," Springer-Verlag, New York (1983), Chap. 6, pp. 58-78.

12) a) K. Takai, Y. Hotta, K. Oshima, and H. Nozaki, *Tetrahedron Lett.*, 1978, 2417; b) K. Takai, Y. Hotta, K. Oshima, and H. Nozaki, *Bull. Chem. Soc. Jpn.*, 53, 1698 (1980); c) L. Lambardo, *Org. Synth.*, 65, 81 (1987): see the discussion described in this article.

13) **4**: NMR ($CDCl_3$) δ 1.48 (s, 9H), 1.52 (s, 3H), 1.62 (s, 3H) 3.62-4.50 (m, 3H), 4.98-5.34 (m, 2H), 5.55-6.12 (m, 1H); IR (film) 1700, 1390, 1360 $cm^{-1}$.

14) **5**: NMR ($CDCl_3$) δ 1.48 (s, 9H), 2.91 (bt, H), 3.68 (bm, 2H), 4.25 (m, 1H), 4.98-5.45 (m, 2H), 5.60- 6.26 (m, 1H); IR (film) 3350, 1695, 1510, 1365, 1085 $cm^{-1}$.

15) All allyl amines in hand have been converted into amino alcohol derivatives, $[\alpha]_D$ values of which have been compared with authentic samples derived from α-amino acids, observing the same values between them for every entry:

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