Tetrahedron Letters, Vol. 34, No. 35, pp. 5545-5548, 1993
Printed in Great Britain

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

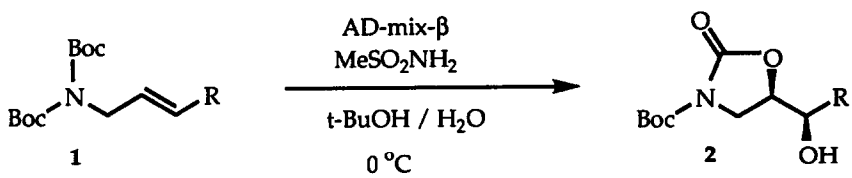
# Asymmetric Dihydroxylation (AD)/Cyclization of N-DiBoc Allylic and Homoallylic Amines: Selective Differentiation of the Hydroxyl Groups.

Patrick J. Walsh, Youssef L. Bennani and K. Barry Sharpless*

Department of Chemistry, The Scripps Research Institute, 10666 N. Torrey Pines Road, La Jolla, CA 92037, U.S.A.

***Abstract:*** *Asymmetric dihydroxylation of N-diBoc protected allylic and homoallylic amines with in situ cyclization affords the corresponding oxazolidinones in good yields. The enantioselectivity is dependent on the substitution pattern of the olefin and ranges from 34 - 98%. This methodology allows selective differentiation of the hydroxyl groups formed in the AD and increases the potential applications of the resulting products.*

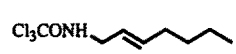
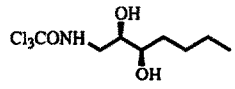
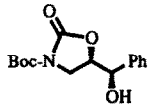
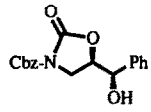
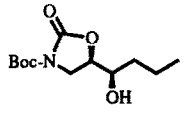
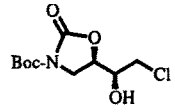
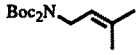
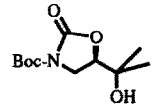
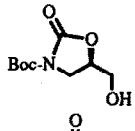
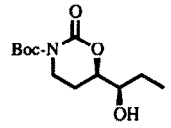
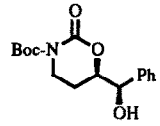
We have been interested in applying the asymmetric dihydroxylation (AD) to nitrogen bearing olefins such as amides and azides[1] and report here results on the catalytic AD of N-diBoc allylic and homoallylic amines. Our initial attempt to asymmetrically dihydroxylate monoacylated allylic amines (Table I, entry 1) resulted in a surprisingly low enantiomeric excess of 75 % (typically the ee of trans disubstituted olefins fall in the range of 95 ± 3 %).[2] It is possible that the presence of the N-H is responsible for the erosion in enantioselectivity through a hydrogen bonding interaction with the osmium tetroxide during the dihydroxylation.[3] To circumvent this problem the nitrogen was protected as the N-diBoc derivative **1**. This had the added advantage that the initial diol product cyclizes spontaneously to the Boc-protected carbamate **2**, thereby differentiating the newly introduced hydroxyl groups (equation 1).[4]




eq. 1

The allylic and homoallylic N-diBoc amines were easily prepared from $Boc_2NH$ (or $Cbz_2NH$)[5] and the alcohol by Mitsunobu coupling (entries 3, 4, 8 and 9),[6] from the allylic halide using a modified Gabriel synthesis (entry 5 and 6)[7] or from the allylic acetate and a catalytic amount of $Pd_2(dba)_3$ (entries 2 and 7).[8] We favored the Mitsunobu methodology due to its generality,

**Table 1**

| Entry | Substrate[a] | Product[a] | Yield[b] | % ee[c] | Config.[d] |
|---|---|---|---|---|---|
| 1. |  |  | 81% | 75 | *(2R3R)* |
| 2. |  |  | 78 % | 97 | *(2R,3R)* |
| 3. |  |  | 75 % | 96 | *(2R,3R)*[e] |
| 4. |  |  | 80 % | 90 | *(2R,3R)* |
| 5. |  |  | 80 % | 95 | *(2R,3S)* |
| 6. |  |  | 44 % | 47 | *(2R)* |
| 7. |  |  | 93 % | 34 | *(2R)* |
| 8. |  |  | 73 % | 89 | *(3R,4R)* |
| 9. |  |  | 73 % | 98 | *(3R,4R)* |

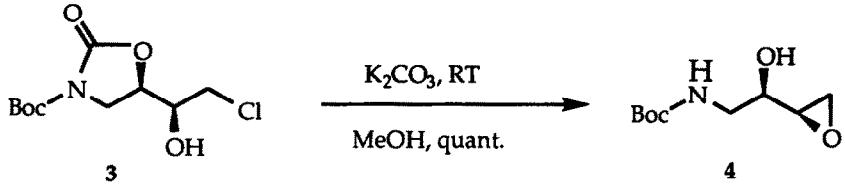
a. All substrates and products gave satisfactory $^{1}H$ and $^{13}C$ NMR, IR and HRMS spectroscopic data. b. Yields of isolated products. c. The ee was determined by $^{1}H$ NMR (entries 2, 5 and 7) analysis of the Mosher ester or by HPLC analysis of the underivitized product using a Chiralcel column (entries 1, 3, 4, 6, 8 and 9). d. All the configurations are tenatively assigned based on our mnemonic (for which there have been no exceptions to date for prochiral olefins).[2] e. Better conversion was observed at 25°C with 5 mol% ligand.

experimental simplicity, and the commercial availability of the allylic and homoallylic alcohol starting materials.

The procedure for the asymmetric dihydroxylation is similar to that previously published.[2,9] AD of *trans* disubstituted N-diBoc allylic amines (Table I, entries 2 - 5) resulted in the *in situ* cyclization of the diols to provide oxazolidinones in good yields. The regiochemistry of the ring closure was determined by $^1$H NMR after PCC oxidation of the hydroxyl group to the ketone. Strong coupling was observed between the protons α to the nitrogen and those on the oxygen bearing carbon, α to the ketone, indicating formation of the 5-membered ring.

The trisubstituted allylic amine derivative (entry 6) gave only 44% ee. This poor result can not be explained at present since the phthalazine ligands are generally excellent for trisubstituted olefins. Enantioselective dihydroxylation of terminal olefin substrates was also disappointing as illustrated in entry 7. We found that diBoc homoallylic amines are excellent substrates for this AD/cyclization procedure, however, the cyclization must be carried out in a separate step.[9] Thus, after isolation of the crude N-diBoc amino diol from the AD, it was subjected to treatment with NaH in THF at 0 °C. This resulted in rapid conversion to the cyclic 6-membered carbamate (entries 8 and 9).

AD of the *trans*-4-amino-1-chlorobutene N-diBoc derivative (entry 5) provided the chlorohydrin **3** in excellent yield and ee. Treatment of this product with $K_2CO_3$ in methanol at RT led to quantitative epoxide formation with concomitant deprotection of the cyclic carbamate group (equation 2). The chlorohydrin (**3**) and epoxide (**4**) are potentially valuable building blocks for asymmetric synthesis.




**3** **4** eq. 2

An important challenge in the application of vicinal diols in organic synthesis is the selective differentiation of the two hydroxyl groups. Several approaches to achieving this goal have already appeared.[4,10] This AD/cyclization procedure of N-diBoc protected allylic and homoallylic amines represents another solution.

## Acknowledgments

This work was supported by grants from The National Institutes of Health (GM-28384). PJW thanks the National Science Foundation for a Postdoctoral Fellowship (CHE-9002184).

## References

1. (a) Bennani, Y. L.; Sharpless, K. B. *Tetrahedron Lett.* **1993**, *34*, 2079; (b) Bennani, Y. L.; Sharpless, K. B. *Tetrahedron Lett.* **1993**, *34*, 2083; (c) Cinnamyl azide undergoes catalytic AD in 91% yield and >95% ee using AD-mix at 0 °C; Sharpless, K.B.; Bennani, Y.L. unpublished results.
2. (a) Sharpless, K.B.; Amberg, W.; Bennani, Y.L.; Crispino, G.A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K., Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768; (b) Amberg, W.; Bennani, Y.L.; Crispino, G.A.; Chadha, R. K.; Davis, W.; Hartung, J.; Jeong, K.-S.; Ogino; Y.; Shibata, T.; Sharpless, K.B. *J. Org. Chem.* **1993**, *58*, 844.
3. Xu, D.; Sharpless, K. B. unpublished results.
4. A similar strategy was used with β,γ and γ,δ-unsaturated esters see (a) Wang, Z.-M.; Zang, X.-L.; Sharpless, K.B.; Keinan E.; Sinha, S.A.; Sinha-Bagchi, A. *Tetrahedron Lett.*, **1992**, *33*, 6407; (b) Keinan E.; Sinha, S.C.; Sinha-Bagchi, A.; Wang, Z.-M.; Zang, X.-L.; Sharpless, K.B. *Tetrahedron Lett.* **1992**, *33*, 6411; (c) Keinan E.; Sinha, S.C. *J. Am. Chem. Soc.* in press.
5. (a) $Boc_2NH$ was purchased from Aldrich Chemical Company; (b) $Cbz_2NH$ was prepared following the method of Grehn, L.; Slmeida, M. L. S.; Ragnarsson, U. *Synthesis* **1988**, 992.
6. Mitsunobu, O. *Synthesis* **1981**, 1.
7. Ragnarsson, U.; Grehn, L. *Acc. Chem. Res.* **1991**, *24*, 285.
8. (a) Connell, R. D.; Rein, T.; Åkermark, B.; Helquist, P. *J. Org. Chem.* **1988**, *53*, 3845; (b) Connell, R. D.; Åkermark, B.; Helquist, P. *J. Org. Chem.* **1989**, *54*, 3359.
9. General procedure: A stirred solution of 1.4g of modified AD-mix-β [contains additional $K_2OsO_2(OH)_4$ to raise the total to 1 mol % ][2] and 95 mg $H_2NSO_2Me$ (1 mmol) in 10 mL of 1:1 tert-butyl alcohol-water (5 mL of each) was cooled to 0 °C. The protected amine derivative (1 mmol) was added and the mixture was stirred at 0 °C until the substrate was consumed as determined by TLC. $Na_2S_2O_5$ (1.5 g) was added and the solution allowed to warm to room temperature with stirring. The aqueous layer was extracted with ethyl acetate (4 X 5 mL) and the combined organic layers were washed with 1N NaOH and dried over $MgSO_4$. The cyclization procedure for the homoallylic amine derivatives (entries 8 and 9) was carried out as follows: The crude N-diBoc amino diol was dissolved in THF (10 mL) and cooled to 0 °C. Oil free NaH (2.6 mg, 0.1 mmol) was added and the solution was stirred for 20 min followed by quenching with 10 mL of $H_2O$. The reaction mixture was extracted with $CH_2Cl_2$ (3 X 10 mL) and chromatographed on silica gel.
10. Kolb, H. C.; Sharpless, K. B. *Tetrahedron* **1992**, *48*, 10515.

(Received in USA 2 June 1993; accepted 9 July 1993)