# Zinc-Mediated Allylation of *N*-Protected α-Amino Aldehydes in Aqueous Solution. Stereoselective Synthesis of *Anti*- and *Syn*-β-Amino Alcohols with Functionalized Allyl Groups

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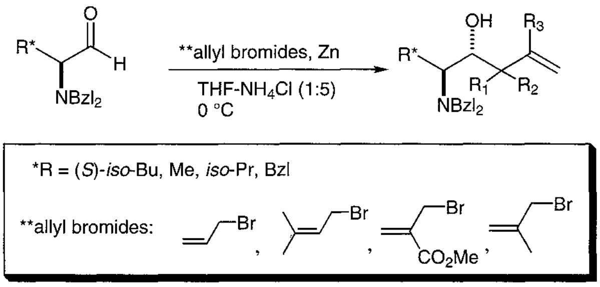
**Abstract:** *Anti*-β-amino alcohols with differently substituted allyl groups were obtained in high chemical yields and in good to excellent diastereoselectivities via Zn-mediated allylation of 2-(dibenzylamino)aldehydes in aqueous media. Swern oxidation, and reduction with $NaBH_4$ gave enantiopure *syn*-β-amino alcohols in good yields.

The formation of C-C bonds in aqueous media has been an area of substantial interest in recent years beause of environmental issues, and contrasting operational protocols compared to general organometallic reactions in organic solvents.[1] Among the examples of such reactions is the metal-mediated allylation of carbonyl compounds in aqueous solution.[1,2] The reactions of *N,N'*-dibenzyl α-amino aldehydes derived from α-amino acids with organometallic allylic reagents in organic solvents are well known,[3] and they proceed with good to excellent stereoselectivities with the allylic reagents. A recent report deals with the effects of *N*-protecting groups and substituents on the allylic reagent in chromium(II) chloride-mediated reactions.[4] In previous studies from our laboratory,[5] we have shown the versatility of the zinc-mediated allylation of glyoxylic acid *N*-benzyloxime and its esters in aqueous $NH_4Cl$. Highly diastereoselective reactions occurred with the corresponding camphorsultam derivatives, leading to a series of substituted allyl glycines. In the preceding letter, we reported on the extension of this method to the stereocontrolled synthesis of Phe-Phe hydroxyethylene isosteres.

We report herein the results of zinc-mediated C-C bond formation in aqueous solution of various substituted allyl bromides with a series of *N,N'*-dibenzyl α-amino aldehydes related to the natural amino acids (Scheme 1). The major diastereomer of the resulting α-amino alcohols was the *anti*-isomer as observed in organic solvents.[3,6]

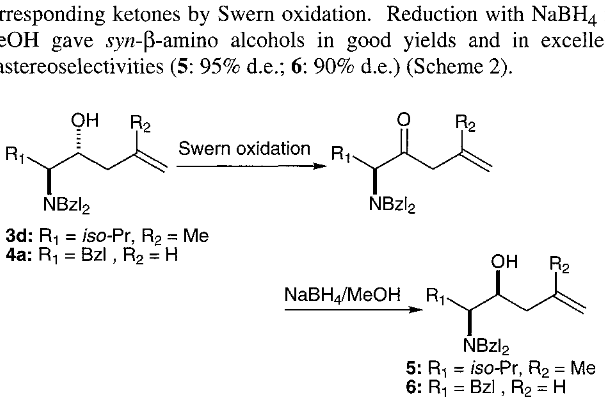
*Typical procedure*: Zinc power (6 mmole, Aldrich) was added to a solution of the (*S*)-2-*N,N'*-dibenzylamino aldehyde (1 mmole), readily available by a known procedure,[7] and allyl bromide (3 mmole) in saturated aqueous $NH_4Cl$-THF (5:1) at 0 °C. The reaction was completed in 30 min as judged by t.l.c. Filtration, extraction (EtOAc), and evaporation gave the desired products which were analyzed by $^1H$ NMR after short column chromatography (20% ethyl acetate in hexanes).

Table 1 lists the structures and relative ratios of the allylated products within each series. With few exceptions (entry 1b), the diastereoselectivities were good to excellent, and a number of the products could be purified to single isomers by column chromatography. The diastereoselectivities of the corresponding C-allylated *N*-Boc aldehydes was poor (20-44% de), although the yields were excellent.[8]



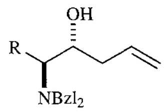
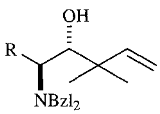
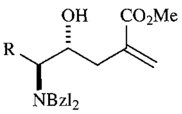
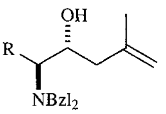
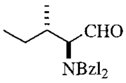
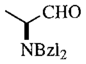
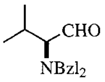
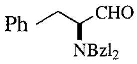
Scheme 1

Two of the *anti*-β-amino alcohol analogs[9] were converted to the corresponding ketones by Swern oxidation. Reduction with $NaBH_4$ in MeOH gave *syn*-β-amino alcohols in good yields and in excellent diastereoselectivities (**5**: 95% d.e.; **6**: 90% d.e.) (Scheme 2).



Scheme 2

**Table 1**. Summary of Yields and Diastereselectivities of Allylation Reactions[a]

| Entry | Aldehyde |  |  |  |  |
|---|---|---|---|---|---|
| 1 |  | **1a**, 86%,<br>(10:1) | **1b**, 95%,<br>(2.5:1) | **1c**, 87%,<br>(20:1) | **1d**, 95%,<br>(6.5:1) |
| 2 |  | **2a**, 95%,<br>(6:1) | **2b**, 90%,<br>(20:1) | **2c**, 95%,<br>(5.5:1) | **2d**, 95%,<br>(7:1) |
| 3 |  | **3a**, 84%,<br>(8:1) | **3b**, 81%,<br>(7.5:1) | **3c**, 92%,<br>(7.5:1) | **3d**, 79%,<br>(8:1) |
| 4 |  | **4a**, 90%,<br>(9:1) | **4b**, 87%,<br>(8:1) | **4c**, 95%,<br>(6:1) | **4d**, 85%,<br>(5.5:1) |

a. The ratios of diastereoselectivity were determined based on $^1H$ NMR and $^{13}C$ NMR at 300 MHz and 400 MHz.

The predominant *syn* selectivity in the reduction of the ketone has precedent in the literature,[10] and it can be explained on the basis of a non-chelated Felkin-Anh transition state (Figure 1). The relative stereochemistry of the two *syn*-amino alcohols **5** and **6** was ascertained by comparing their $^1$H NMR spectra with those of the reference samples isolated as the minor products in allylation reaction.[9]

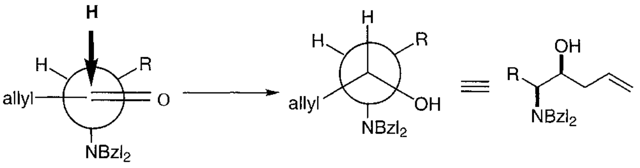
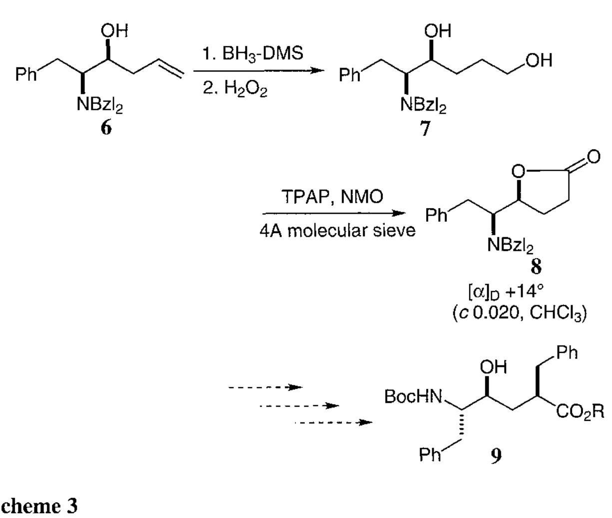


**Figure 1.** Felkin-Anh's Non-Chelation Transition State

**Figure 1**

Subsequent hydroboration-oxidation of the *syn*-amino alcohol (**6**) with $BH_3$-$Me_2S$ in THF gave the diol **7** in 52% yield after purification. Oxidation with TPAP[11] gave the known γ-lactone **8** in 66% isolated yield in addition to the keto aldehyde from **7** as a minor product (Scheme 3). The $^1$H NMR, $^{13}$C NMR and optical rotation of **8** were in agreement with the data in the literature.[10] The γ-lactone **8** has been a valuable and versatile intermediate for the synthesis of hydroxyethylene dipeptide isosteres such as **9**.[10]



**Scheme 3**

Thus, *anti*- and *syn*-amino alcohols with differently substituted allyl groups were prepared in high yields, and with good to excellent diastereoselectivities. The five-step synthesis of lactone **8**, an important chiron in the field of hydroxyethylene dipeptide isosteres, through the application of zinc-mediated C-allylation in aqueous solution, constitutes one of the shortest and most efficient routes available for this motif.

**Acknowledgment.** We thank NSERC for financial assistance through the Medicinal Chemistry chair program.

## References and Notes

(1) For recent reviews, see: (a) Li, C.-J. *Tetrahedron* **1996**, *52*, 5643. (b) Yamamoto, Y.: Asao, N. *Chem. Rev.* **1993**, *93*, 2207. (c) Li, C.-J. *Chem. Rev.* **1993**, *93*, 2023.

(2) See for example, Chattopadhyay, A. *J. Org. Chem.* **1996**, *61*, 6104; Durant, A.; Deplancke, J.-L.; Winard, R.; Reisse, J. *Tetrahedron Lett.*, **1995**, *36*, 4257; Oda, Y.; Matsuo, S.; Saito, K. *Tetrahedron Lett.*, **1992**, *33*, 97; Ahonen, M.; Sjöholm, R. *Chemistry Lett.* **1995**, 341; Sjöholm, R.; Rairama, R.; Ahonen, M. *J. Chem. Soc. Chem. Commun.* **1994**, 1217; F. Waldmann, H. *Synlett*, **1990**, 627; Chan, T. H.; Li, C. J. *Organometallics* **1990**, *9*, 2649; Kunz, T.; Reißig, H.-U. *Liebigs Ann. Chem.* **1989**, 891; (i) Petrier, C.; Einhorn, J.; Luche, J. L. *Tetrahedron Lett.* **1985**, 26, 910; Mattes, H.; Benezra, C. *Tetrahedron Lett.* **1985**, *26*, 5697.

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(7) O'Brien, P.; Warren, S. *Tetrahedron Lett.* **1996**, *37*, 4271; see also ref. 3a.

(8) The allylation of α-amino aldehydes bearing an N-Boc protecting group gave products with poor diastereoselectivities, a) allyl bromide, 90%; 26% de. b) 2-bromomethyl-1-propene, 90%; 44% de. c) (2-bromomethyl)acrylic acid, 92%; 20% de. d) methyl (2-bromomethyl)acrylic acid, 94%; 20% de. e) *tert*-butyl (2-bromomethyl)acrylic acid, 85%; 20% de. f) 4-bromo-2-methyl-2-butene, 95%; 41% de.

(9) Enantiomerically pure or highly enriched *anti*- and *syn*-β-amino alcohols were obtained by silica gel flash column chromatography (hexane:ethyl acetate=20:1) after aqueous workup.

(10) Reetz, M.T.; Drews, M.W.; Lennick, K.; Schmitz, A. *Tetrahedron: Asymmetry*, **1996**, *1*, 375; Alexander, C. W.; Liotta, D. C. *Tetrahedron Lett.* **1996**, *37*, 1961. Captain, L. F.; Xia, X.; Liotta, D. C. *Tetrahedron Lett.* **1996**, *37*, 4293.

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