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PROTECTIVE GROUP TUNING IN THE STEREOSELECTIVE CONVERSION OF α-AMINO ALDEHYDES INTO AMINOALKYL EPOXIDES

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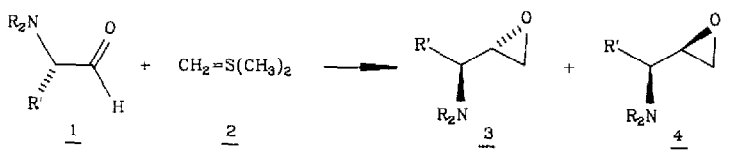
Abstract: Sulfonium and arsonium ylides of the type $CH_2=S(CH_3)_2$ and $CH_2=As(Ph)_3$ react with doubly protected α-amino aldehydes 1 derived from amino acids to form aminoalkyl epoxides 3/4, diastereofacial selectivity ranging between 86:14 and >95:<5.

Doubly protected α-amino aldehydes, prepared from the corresponding amino acids, are emerging as highly useful homochiral building blocks[1,2]. Addition reactions of RMgX, RLi, enolates and Me_3SiCN/ZnX_2 occur with high degrees of non-chelation-control[2], in contrast to the majority of stereorandom reactions of α-amino aldehydes bearing only one protective group (BOC, 9-fluorenyl, 9-phenyl-9-fluorenyl, etc.)[3]. It was of interest to see if this type of protective group tuning[4] is also effective in the reaction of α-amino aldehydes with sulfur ylides to form aminoalkyl epoxides. Previously, BOC(t-butoxycarbonyl)-protected aldehydes had been shown to react stereorandomly with $CH_2=S(CH_3)_2$ (1:1 diastereomeric mixtures of adducts in yields of less than 50%)[5]. This is unfortunate, since enantio- and diastereomerically pure aminoalkyl epoxides are highly useful intermediates in the synthesis of certain dipeptide isosteres and other pharmacologically important ethanolamino compounds[5,6].

Upon reacting the sulfonium ylide 2[7] with doubly protected aldehydes 1, the epoxides 3/4 were formed stereoselectively. The major diastereomers turned out to be the anti-adducts 3 (Table 1), which stereochemically correspond to the non-chelation-controlled Grignard and aldol adducts previously reported.



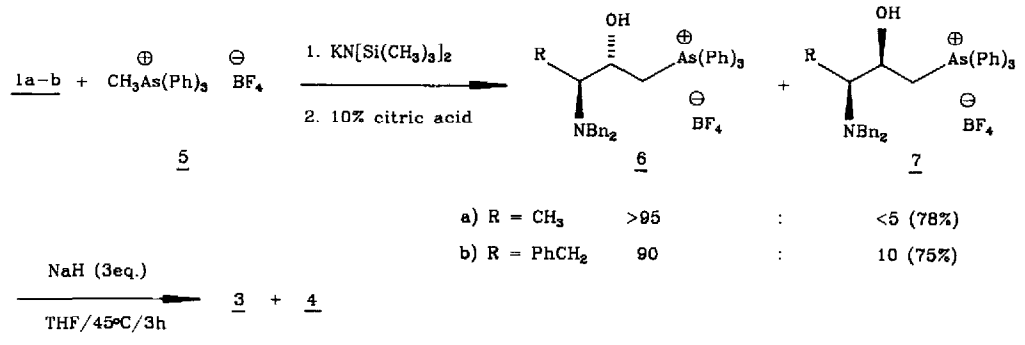
1 2 3 4

The results show that in going from BOC-protected amino aldehydes[5] to doubly protected analogs 1[1,2], diastereofacial selectivity increases dramatically[8]. Some differences are observed within the series N,N-dibenzyl, N,N-diallyl and N,N-di(o-methylbenzyl), the latter protective groups being the most bulky and leading to the highest levels of diastereoselectivity (entries 3 and 4 of Table 1). Diastereoselectivity is a little lower than previously observed for RMgX, RLi and enolate additions[1,9]. Although NaI is present in the ylide additions (from deprotonation of $(CH_3)_3SI$ by NaH), the degree of metal involvement is likely to be less than in Grignard and aldol additions. This could be the source of lower selectivity.

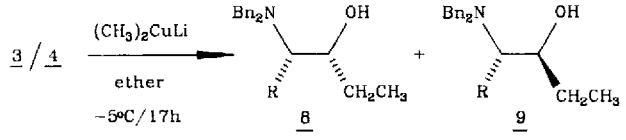
Table 1. Epoxide Formation by Addition of Ylide 2 to Aldehydes 1

Entry	Aldehyde		Yield of epoxide (%)	Ratio 3 : 4
1	1a	(R = $PhCH_2$; R'= CH_3)	73	87 : 13
2	1b	(R = R'= $PhCH_2$)	75	86 : 14
3	1c	(R = o-CH_3-$PhCH_2$; R'= CH_3)	50	91 : 9
4	1d	(R = o-CH_3-$PhCH_2$; R'= $PhCH_2$)	50	90 : 10
5	1e	(R = CH_2=$CHCH_2$; R'= $PhCH_2$)	45	87 : 13

Stereoselecitvity was similar when using the ylide CH_2=$S(Ph)_2$ or CH_2=$S(O)(CH_3)_2$, but pronounced effects were observed upon reacting the arsonium ylide obtained from the salt 5[10]. In the temperature range of -78°C to -40°C (2h), not the epoxides 3/4 were formed, but the ylide adducts 6/7 which were fully characterized[11]. They were transformed by NaH into the desired epoxides, the 3:4 ratios being >95:<5 (for 3a/4a; 65%) and 90:10 (for 3b/4b; 60%). The increased diastereoselectivity may be related to the greater bulk of the reagent (three phenyl groups on the As-moiety).



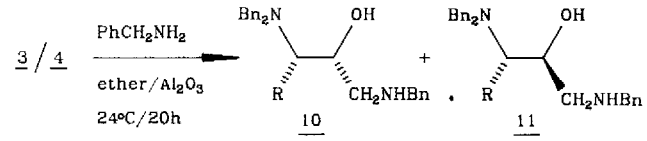
The configurational assignment was made by reacting the crude epoxides with $(CH_3)_2CuLi$, which afforded the amino alcohols 8/9. The 8:9 ratios correspond to the 3:4 ratios of epoxides used. The major diastereomers 8 turned out to be identical in every respect to the EtMgBr adducts of the aldehydes 1a-b[2,9], proving the relative configuration and the optical purity (>98%). The N-benzyl products were deprotected using Pd/H_2 (80-90%)[2].



a) R = CH_3 (75%)

b) R = $PhCH_2$ (67%)

Cuprate or hetero-nucleophile induced ring opening is expected to be synthetically useful in more complicated cases, e.g., reactions of amines in the presence of Al_2O_3[12] to form 2-hydroxy 1,3-diamines:



a) R = CH_3 (65%)

b) R = $PhCH_2$ (65%)

In summary, we have shown that stereoselective epoxide formation is possible when doubly protected α-amino aldehydes are treated with sulfonium or arsonium ylides. This methodology extends the use of amino acids as a pool of homochiral compounds.

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References and Notes:

1. The preceding publication describes new results from our laboratories as well as literature citations referring to novel applications recently reported by other groups.
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3. M.T. Reetz, Pure Appl. Chem. 60 (1988) 1607; J. Jurczak and A. Golebiowsky, Chem. Rev. 89 (1989) 1459; W.D. Lubell and H. Rapoport, J. Am. Chem. Soc. 109 (1987) 236.
4. In the case of α-hydroxy carbonyl compounds, the nature of the protective group can influence the direction and extent of diastereofacial selectivity of nucleophilic additon reactions; see for example: M.T. Reetz, Angew. Chem. 96 (1984) 542; Angew. Chem. Int. Ed. Engl. 23 (1984) 556; M.T. Reetz and M. Hüllmann, J. Chem. Soc. Chem. Commun. (1986) 1600; and literature cited therein.

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6. J.R. Luly, J.F. Dellaria, J.J. Plattner, J.L. Soderquist and N. Yi, J. Org. Chem. 52 (1987) 1487.
7. E.J. Corey and M. Chaykovsky, J. Am. Chem. Soc. 87 (1965) 1353.
8. Typical procedure: Under an atmosphere of nitrogen the suspension of NaH (219 mg; 7.3 mmol) in 10 ml of dry dimethylsulfoxide (DMSO) is heated at 75-80°C for about 45 min (until no more H_2 is evolved)[7]. At room temp. about 20 ml of THF is added and the mixture cooled -10°C. To the rapidly stirred mixture a solution of trimethylsulfonium iodide (1.45 g; 7.0 mmol) in 10 ml DMSO is added[7]. After 5-10 min the amino aldehyde 1 (6.9 mmol in 4 ml THF) is added and the mixture stirred at -10°C for about 0.5 h. After stirring at room temp. for another hour, the mixture is poured on 3 times the volume of H_2O and extracted 3 times with diethyl ether. The combined org. phases are washed with sat. NaCl solution, dried over Na_2SO_4 and concentrated. The crude product is flash-chromatographed over silica gel (pet-ether/ethyl acetate, about 30:1), providing pure epoxides 3/4. Separation of diastereomers is difficult, in contrast to ring-opened products of the type 8/9 and 10/11.
9. M.W. Drewes, Dissertation, Universität Marburg, 1988.
10. W.C. Still and V.J. Novack, J. Am. Chem. Soc. 103 (1981) 1283; review on arsonium ylides: H. Yaozeng and S. Yanchang, Adv. Organomet. Chem. 20 (1982) 115.
11. Still[10] employed higher temperatures and used HMPA as an additive, which led directly to epoxides. Under such conditions we obtained mixtures of 6/7 and 3/4. Best procedure: The suspension of methyltriphenylarsonium tetrafluoroborate[10] (9.3 mg; 2.3 mmol) in 15 ml of dry THF is treated under N_2 with 2.4 mmol of $KN(SiMe_3)_2$ at -40°C and stirred for 45 min. After cooling to -78°C, the stirred solution is treated with a cooled (-78°C) solution of amino aldehyde 1 (2.1 mmol in 10 ml THF), stirred for 1 h at -78°C and 1 h at -40°C. Then 10 % citric acid is added, the mixture brought to room temp. and extracted 3 times with CH_2Cl_2. The combined org. phases are washed with NaCl solution, dried over Na_2SO_4 and concentrated. The crude product is chromatographed over a short silica gel column ($HCCl_3/CH_3OH$, 20:1), affording the BF_4 salts 6/7. In the case of 6a, recrystallization from ether/ethanol provides an analytically pure crystalline product (m.p. 188-190°C); ^{13}C-NMR ($DCCl_3$): γ = 8.3, 34.3, 54.8, 60.1, 67.6, 122.4, 127.1, 128.4, 129.0, 130.6, 132.6, 133.8, 139.9 ppm. FD-MS: m/e = 574 ($M^+ - BF_4$; 100%).
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