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STEREOCONTROLLED ADDITIONS OF ALLYLTRI-n-BUTYL-STANNANE TO α-HYDROXYALDEHYDE DERIVATIVES. A USEFUL ROUTE TO MONOPROTECTED ERYTHRO OR THREO DIOLS.

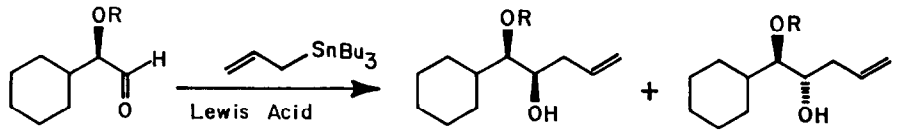
Gary E. Keck,* ‡ and Eugene P. Boden
Department of Chemistry, University of Utah
Salt Lake City, UT 84112

Summary: By proper choice of Lewis acid and protecting group, the Lewis acid mediated addition of allyltri-n-butylstannane to the α-hydroxyaldehyde derivatives 1b and 1c can be controlled to give excellent (95:5 to > 250:1) stereoselectivity for the formation of either erythro or threo products.

The general problem of the stereocontrolled construction of acyclic materials has been a topic of intensive investigation in recent years. Many approaches to this general problem have focussed on controlling diastereofacial selectivity in the addition of various nucleophiles to carbonyl compounds.[1] In this context, we report the results of a study of the Lewis acid mediated addition[2] of allyltri-n-butylstannane to chiral α-hydroxyaldehyde derivatives.

For this study, readily available[3] protected derivatives of α-hydroxyaldehyde 1a were chosen as substrates to evaluate the effects of protecting group, Lewis acid, and solvent on the diastereofacial selectivity of allylstannane addition. Mechanistic and theoretical reasoning suggested that derivatives 1b and 1c should suffice to determine trends in diastereofacial selectivity which should prove rather general, as well as synthetically useful, since the utility of benzyl and tert-butyldimethylsilyl functions as protecting groups in organic synthesis is well established. The overall reaction process and results obtained are summarized in equation 1 and Table I below.[4]

(1)



1a R = H
1b R = CH_2Ph
1c R = Si^tBuMe_2

2 3

TABLE I

Entry	Substrate	Lewis Acid[a]	Solvent, T(^{o}C)[b]	2/3 Ratio[c](Yield)
1	1b	$BF_3 \cdot Et_2O$	CH_2Cl_2(-78^{o})	39:61
2	1b	$MgBr_2$	Et_2O	94:6
3	1b	$MgBr_2$	THF	20:80
4	1b	$MgBr_2$	CH_2Cl_2(-23^{o})	> 250:1 (85%)
5	1b	$MgCl_2$	Et_2O	No reaction
6	1b	$MgCl_2$	THF	22:78
7	1b	$MgCl_2$	CH_2Cl_2	No reaction
8	1b	$Mg(ClO_4)_2$	Et_2O	69:31
9	1b	$ZnBr_2$	THF (67^{o})	27:73
10	1b	$ZnBr_2$	CH_2Cl_2	77:23
11	1b	$ZnBr_2$	Toluene	41:59
12	1b	ZnI_2	Et_2O	35:64
13	1b	ZnI_2	CH_2Cl_2	97:3 (92%)
14	1b	$TiCl_4$	CH_2Cl_2(-78°)	> 250:1 (75%)
15	1c	$TiCl_4$	CH_2Cl_2(-78°)	36:64
16	1c	$MgBr_2$	CH_2Cl_2	21:79
17	1c	ZnI_2	CH_2Cl_2	53:47
18	1c	$BF_3 \cdot Et_2O$	CH_2Cl_2(-78^{o})	9:91
19	1c	$BF_3 \cdot Et_2O$ (2 eq.)	CH_2Cl_2 (-78^{o})	5:95 (83%)

(a) Unless otherwise stated, 1.0-1.1 equivalents of Lewis acid were used.
(b) Unless otherwise indicated, reactions were initiated at 0^{o}C and allowed to warm to room temperature.
(c) Determined by capillary vpc analysis on a 32 m J & W-DB1701 column (after acetylation with acetic anhydride-pyridine) assuming equal response factors (flame ionization detector) for the diastereomeric acetates derived from alcohols 2 and 3.

Several of the results in Table I are quite striking. Perhaps most important, in a practical sense, is that the diastereofacial selectivity of the addition process can be controlled to give very highly stereoselective access to a monoprotected derivative of either the erythro or threo diol: the erythro material can be obtained with 95:5 selectivity (entry 19) using the tert-butyldimethylsiloxy substrate (1c) with 2.0 eq of $BF_3 \cdot Et_2O$ in CH_2Cl_2 at

-78° while the threo product is obtained with > 250:1 stereoselectivity using the benzyloxy substrate (1b) with $TiCl_4$ in CH_2Cl_2 at -78°.

This material, which corresponds to the product expected for a "chelation controlled" nucleophilic addition process, is also obtained as the major product (stereoselectivity of 94:6) using $MgBr_2$ as catalyst with ether as solvent. Even better selectivity is realized in dichloromethane at -23°C (entry 4). In sharp contrast, use of THF as solvent (entry 3) results in stereochemical reversal, and the "chelation controlled" product 2 becomes the minor component of an 80:20 mixture. It is also of interest that other sources of Mg^{+2} (entries 5-8) are considerably less effective catalysts (with regard to diastereofacial selectivity) and that the reaction of 1b with allylmagnesium bromide in ether does not show useful diastereofacial selectivity, affording a 58:42 mixture of 2 and 3.

The use of $ZnBr_2$ (entries 9-11) as catalyst gave relatively poor selectivity, and stereochemical reversal can again be observed (e.g., entries 8 and 9) upon changing solvents. However, ZnI_2 in CH_2Cl_2 gave excellent (97:3) selectivity for the formation of 2.

The pronounced tendency of $MgBr_2$, ZnI_2, and $TiCl_4$ to selectively catalyze the formation of 2 with benzyloxy substrate 1b is not observed with the tert-butyldimethylsiloxy substrate 1c (entries 15-17). However, excellent selectivity for the formation of the "Cram product"[7] 3 may be obtained with $BF_3 \cdot Et_2O$ in CH_2Cl_2 at -78°C (entries 18, 19). This result is in accord with the known[8] lower basicities of silyl ethers relative to alkyl ethers, which has been attributed to oxygen p π -silicon d π interactions. Hence bidentate chelation of Lewis acids such as $MgBr_2$ or ZnI_2 would be expected to be less effective in this case. Moreover, electron withdrawal from oxygen would be expected to result in a lowering of C-O σ^* and hence provide increased stabilization for a Felkin-Anh[9] antiperiplanar nucleophilic addition to the aldehyde carbonyl. The bulk of the tert-butyldimethylsilyl moiety may also play a helpful role in this regard, however; we prefer the electronic explanation advanced above as the dominant effect, since, in other systems, the tert-butyldimethylsiloxy moiety appears to exhibit steric requirements comparable to simple alkyl ethers[10], and the stereoselectivity obtained with 1b and BF_3 is very low. Similar effects have been observed previously, as in the reduction of α-alkoxy and α-siloxy ketones,[1c] but attributed to "bulkiness" of the silyl ethers.

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‡ Fellow of the Alfred P. Sloan Foundation, 1981-1985.

References and Notes:

1. For some recent leading references in this area, note:

   (a) W. C. Still and J. H. McDonald, III, Tetrahedron Lett., **21**, 1031 (1980); (b) W. C. Still and J. A. Schneider, Ibid., **21**, 1035 (1980. (c) L. E. Overman and R. J. McCready, Ibid., **23**, 2355 (1982). (d) M. D. Lewis and Y. Kishi, Ibid., **23** 2343 (1982); (e) J. Mulzer and A. Angermann, Ibid., **24**, 2843 (1983) (f) T. Nakata, M. Fukui, and T. Oishi, Ibid., **24**, 2657 (1983); (g) T. Nakata, M. Fukui H. Ohtsuka, and T. Oishi, Ibid., **24**, 2661 (1983; (h) T. Mukaiyama, T. Yamada, and K. Suzuki, Chem Lett., 5 (1983).

2. (a) Y. Naruta, S. Ushida, and K. Maruyama, Chem. Lett., 919 (1979);
   (b) A. Hosomi, H. Iguchi, M. Endo, and H. Sakurai, Ibid., 977 (1979).

3. Substrates 1b and 1c were prepared from cyclohexanecarboxaldehyde via reaction with vinylmagnesium bromide, followed by hydroxyl protection and ozonolysis.

4 (a) Workup for these reactions proceeded via addition of aq. $NaHCO_3$ solution, dilution with 1:1 ether-pentane, addition of aq. KF solution, and passage of the dried, concentrated organic phase through basic alumina using ca 2% THF-hexanes.

   (b) Product structures were confirmed by correlation with materials prepared by unambiguous independent synthesis. Thus, hydrogenation, protecting group removal, and acetonide formation yields the easily separable (capillary vpc) acetonides 4 (from 2) & 5 (from 3). These were independently synthesized by the sequence: 1) Wittig reaction of butylidenetriphenyl phosphorane with cyclohexanecarboxaldehyde (ether, -78°C) to yield an 85:15 cis-trans mixture of olefins; 2) cis-hydroxylation[5] (OsO_4, N-methylmorpholine-N-oxide, aqueous acetone; and 3) acetonide formation (dimethoxypropane, acetone, pTsOH) followed by chromatographic (column chromatography over silica gel) isolation.[6]

   (c) No attempt was made to determine isolated chemical yields for reactions which showed low diastereofacial selectivity.

5. V. Van Rheenen, R. C. Kelly, and D. Y. Cha, Tetrahedron lett., 1973 (1976).

6. Acetonides 4 and 5 are easily distinguished by their ^{13}C NMR Spectra (diagnostic resonances only) 4 ($CDCl_3$): δ 107.7, 85.8, 78.7; 5 ($CDCl_3$) 107.2, 82.5, 77.4.

7. (a) D. J. Cram and F. A. Abd. Elhafez, J. Am. Chem. Soc., **74** 5828 (1952);
   (b) D. J. Cram and K. R. Kopecky, Ibid., 81, 2748 (1959).

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9. N. T. Anh and O. Eisenstein, Nouv. J. Chim., 1 (1977).

10. For example, the tert-butyldimethylsilyl ether from cis-2-methylcyclohexanol appears to have an axially disposed siloxy group based upon the observed $w_{1/2}$ (9 Hz) for the C-1 methine proton, as compared to 22 Hz in the trans isomer.

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