

Stereoselective Reactions of α,β -Epoxy-Aldehydes; The Formation of "Chelation Controlled" Products

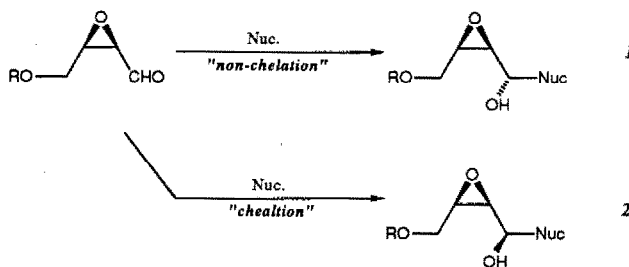
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Key Words: Stereoselective synthesis; Nucleophilic addition; α,β -Epoxy-aldehydes; Regioselective Lewis acid epoxide opening; Chelation control.

Abstract: Treatment of the α,β -epoxy-aldehydes (1) and (2) with Lewis acids followed by *in situ* reaction with carbon nucleophiles produces halohydrins of the products of "chelation controlled" addition to the aldehyde with high diastereoselectivity; The regiochemistry of epoxide opening is determined by choice of Lewis acid.

In a previous Letter we described our initial studies on the stereocontrolled addition of C-nucleophiles to the carbonyl group of α,β -epoxy-aldehydes, a reaction which we found to take place with good diastereoselectivity (up to 9:1).¹ In all cases where diastereoselectivity was observed, the major product corresponded to "non-chelation control" (Reaction 1). It would be useful to be able to carry out this reaction with "chelation control" (Reaction 2), but despite considerable experimentation we were unable to find conditions or reagents which would achieve this cleanly and reproducibly. During attempts to carry out "chelation controlled" additions to α,β -epoxy-aldehydes we often isolated material which appeared to correspond to the halohydrins of the addition products.

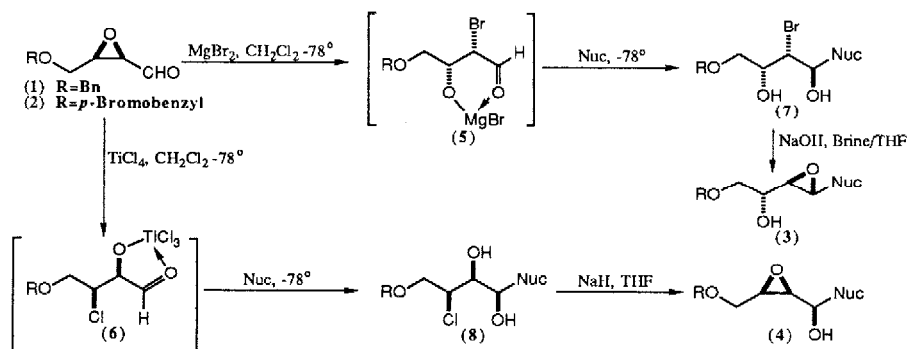


This observation prompted an investigation into the feasibility of opening the α,β -epoxy-aldehyde with the Lewis acid, followed by *in situ* reaction of the resulting intermediate with a carbon nucleophile. This intermediate would be expected to undergo "chelation controlled" addition by analogy with other α -oxygenated aldehydes,² and the addition product should be easily converted into the corresponding epoxide by treatment

with base.³ We report here the results of our initial studies on this two step process which can be regarded equivalent to "chelation controlled" addition to the α,β -epoxy-aldehyde (reaction 2).

The development of this approach, described in this Letter, was carried out with the α,β -epoxy-aldehyde (1) as a racemate and with (2) as the enantiomer shown.⁴ The *freshly purified* α,β -epoxy-aldehyde⁵ was treated with the Lewis acid in dichloromethane at -78° until completely consumed (t.l.c.), and a solution of the nucleophilic reagent was added to the reaction mixture at this temperature. The product of this reaction consisted of a mixture of halohydrins, usually with one isomer predominating. This mixture was treated with sodium hydroxide/ether or sodium hydride/THF to produce the corresponding epoxide mixture, which was analysed by high field ^1H n.m.r. (300 MHz). In the cases studied the ratio of isomers in the halohydrin mixture corresponded with the ratio of the diastereoisomeric epoxides. Stereochemical assignments were made by correlation with authentic materials,¹ and representative results are given in Scheme 1. We found that it was possible to achieve high levels of diastereoselectivity and to control regiochemistry of the initial epoxide opening simply by choice of the Lewis acid. In this way it is possible to obtain either the epoxide (3) or (4) with good to excellent stereochemical control (Scheme 1).

Scheme 1



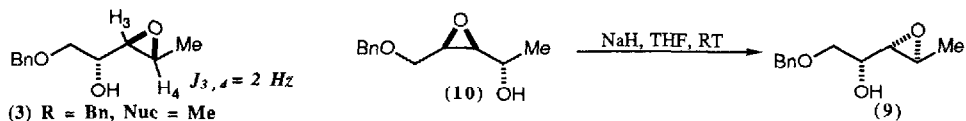
| Lewis Acid ^a | Nucleophile | (3) ^b | (4) ^b | Overall Yield ^c | |
|-------------------------|---|------------------|------------------|----------------------------|---------|
| | | | | R=Bn | R=pBrBn |
| MgBr ₂ | MeMgBr | >95:5 | | 67% | 60% |
| MgBr ₂ | C ₃ H ₅ SnBu ₃ | >95:5 | | 74% | |
| MgBr ₂ | C ₃ H ₅ MgBr | 89:11 | | 69% | |
| TiCl ₄ | MeMgBr | | >95:5 | 39% | 40% |
| TiCl ₄ | C ₃ H ₅ SnBu ₃ | | >95:5 | 37% | |
| TiCl ₄ | C ₃ H ₅ SiMe ₃ | | >95:5 | 43% | 72% |

^aMgBr₂.OEt₂ 5 equiv. used; TiCl₄ 1.1 equiv. used; ^bSelectivity of initial addition to the C=O group; ^cTotal yield of epoxides, not optimised.

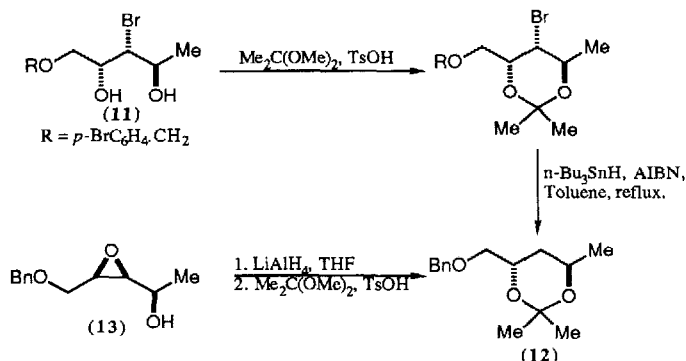
The presence of the chelated ring-opened aldehydes (5) and (6) as outlined in Scheme 1 is consistent with the isolation of (7) and (8). Attempts to isolate the aldehydes which correspond to (5) and (6) have led only to decomposition. The structure and stereochemistry of the chlorohydrin (8) follows from the formation of the known epoxide (4)¹ on ring closure (assuming that epoxide opening and closure follow their usual

stereochemical paths).

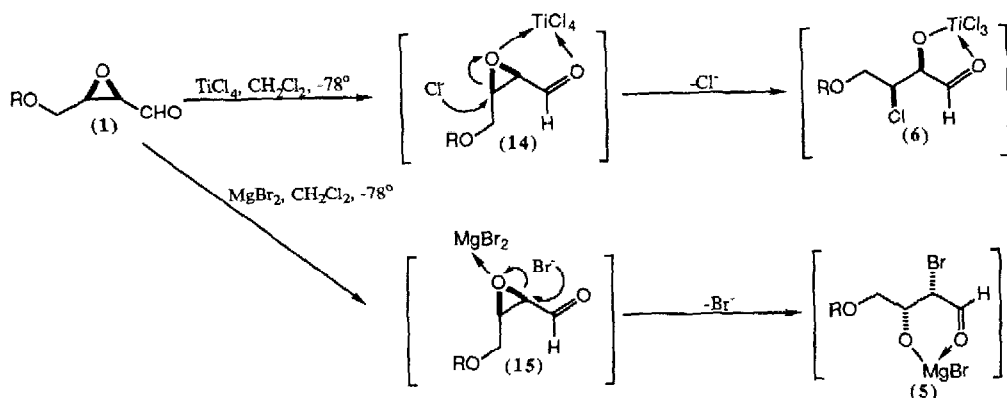
The unambiguous determination of the structure and stereochemistry of (3) and (7) required further work. This was carried out on the system in which R = Bn and Nuc = Me, and the other systems were assumed to be analogous. The regiochemistry of the epoxide (3) (R = Bn, Nuc = Me) was clear from the analysis of its 300 MHz ^1H nmr spectrum, which also showed it to be a *trans*-disubstituted epoxide. The only issue remaining was the stereochemistry of the hydroxyl group with respect to the epoxide. This was assigned as shown in (3) as the other diastereoisomer (9) prepared by Payne rearrangement of the epoxy-alcohol (10)^{1,6}, exhibited different physical properties (nmr, tlc).



With the stereochemistry of (3) reasonably certain, it is difficult to propose a sensible alternative regiochemistry and stereochemistry for the bromohydrin from which it is derived. Nevertheless since (7) is potentially interesting from both a synthetic and a mechanistic standpoint, the structure of (7) (R = Bn, Nuc = Me) was proved as follows. The bromohydrin (11), derived as in Scheme 1, was converted into the acetonide (12). The stereochemistry of this acetonide was confirmed by the preparation of (12) from (13) (the minor diastereoisomer from the addition of MeMgBr to the corresponding epoxy-aldehyde¹). Taken together these observations make it most unlikely that the structure of (7) is anything other than that shown.



The change in regiochemistry of the opening of the epoxy-aldehyde on switching from MgBr_2 to TiCl_4 was unexpected, but can be rationalised if it is assumed that the stronger Lewis acid TiCl_4 is chelated by the aldehyde $\text{C}=\text{O}$ and the epoxide oxygen, opening this species (14) then gives (6). This chelated species (14) is presumably rather strained, and it is not impossible that when using the weaker Lewis acid MgBr_2 , the energy of complexation does not offset the strain energy involved in the chelated system and opening occurs adjacent to the carbonyl group *via* (15).⁷ In addition to the strain which might be present in a chelated α,β -epoxy-aldehyde, chelation is presumably disfavoured by the relatively poor electron donating properties of the oxirane oxygen.⁸ Whatever the reasons, it is useful to be able to control the opening of the epoxy-aldehyde simply by the choice of Lewis acid, and we are currently investigating the scope and limitations of this approach and synthetic uses of the chemistry described in this Letter.⁹



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2. For a general review see Eliel, E.L. "Asymmetric Synthesis", Ed. Morrison, J.D., Vol 2, pp 125-155, Academic Press, New York, 1983. Chelation controlled additions to α - and β -oxygenated aldehydes have been described, e.g. Heathcock, C.H.; Kiyooka, S.; Blumenkopf, T.A. *J. Org. Chem.*, **1984**, *49*, 4212-4223. Keck, G.E.; Castellino, S. *J. Amer. Chem. Soc.*, **1986**, *108*, 3847-3849, and references cited in these papers. Recently α -haloaldehydes have been shown to undergo diastereoselective ene reactions with "non-chelation control", Mikami, K.; Loh, T.-P.; Nakai, T. *J. Chem. Soc., Chem. Commun.*, **1991**, 77-78.
3. Klunder, J.M.; Caron, M.; Uchiyama, M.; Sharpless, K.B. *J. Org. Chem.*, **1985**, *50*, 912-915.
4. The corresponding *p*-bromobenzyl protected epoxide-alcohol is readily available in essentially optically pure form, Chong, J.M.; Wong, S. *J. Org. Chem.*, **1987**, *52*, 2596-2598.
5. It is important to purify the aldehyde by chromatography to ensure clean ring opening and addition, the aldehyde substrates were prepared as in our previous work, reference 1.
6. This reaction was carried out on a 10:3 mixture of diastereoisomers of the methyl addition products, the major isomer being (10). After two days at room temperature, (10) was completely converted into (9), while the other diastereoisomer remained unchanged (total yield 96% after chromatography).
7. The situation is certainly more complicated than this, since magnesium iodide is reported to react with α,β -epoxy-esters via chelation resulting in the opposite regiochemistry to that observed in our work, Otsubo, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.*, **1987**, *28*, 4435-4436. See also Bonini, C.; Righi, G.; Sotgiu, G. *J. Org. Chem.*, **1991**, *56*, 6206-6209. The opening of α,β -epoxy-esters and amides with various nucleophiles has been discussed, Behrens, C.H.; Sharpless, K.B. *Aldrichimica Acta*, **1983**, *16*, 67-79.
8. The heats of mixing (cal/mol) with chloroform are as follows; Oxirane, 365; Oxetane, 760; Tetrahydrofuran, 750; Tetrahydropyran, 640; Diethyl ether 650. Searles, S.; Tamres, M.; Lippincott, E.R. *J. Amer. Chem. Soc.*, **1953**, *75*, 2775-2777.
9. During the preparation of this Letter the addition of chiral allylboronates to α,β -epoxy-aldehydes and conversion of the products to 2-deoxyhexoses was reported, Roush, W.R.; Straub, J.A.; VanNieuwenhze, M.S. *J. Org. Chem.*, **1991**, *56*, 1636-1648.

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