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CHELATION CONTROLLED DIASTEREOFACIAL SELECTIVITY IN CROTYLTRI-n-BUTYLSTANNANE ADDITIONS TO α-ALKOXYALDEHYDES

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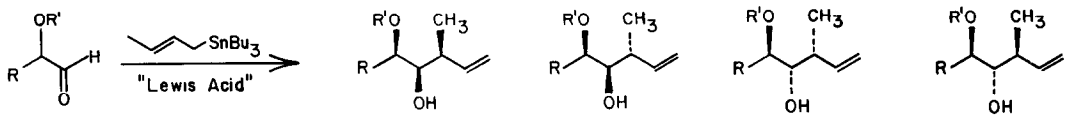
Summary: Lewis acid mediated additions of crotyltri-n-butylstannane to chiral α-alkoxyaldehydes generally show excellent (>99:1) diastereofacial selectivity; proper choice of Lewis acid is crucial for controlling erythro/threo selectivity in the bond formation.

Recently[2] we reported that the Lewis acid mediated addition of allyltri-n-butylstannane to derivatives of α-hydroxyaldehydes, chiral by virtue of asymmetric α substitution, could be controlled so as to yield either erythro or threo diols by proper choice of Lewis acid and protecting group for the α-hydroxy function. This initial study focussed on establishing Lewis acid-protecting group combinations which led to high diastereofacial selectivity for the bond construction process, to yield one of two possible diastereomers. We now report our results on the more demanding process summarized in equation (1) below, the Lewis acid mediated addition of crotyltri-n-butylstannane to such chiral α-alkoxyaldehydes, for which both diastereofacial selectivity and stereochemistry associated with the bond construction must be controlled.



1 2 3 4 5

Prerequisite to addressing the chemical problems posed by such additions to any material of structure 1 is a demonstrated solution to the analytical problem presented by the mixture of diastereomeric products 2-5. Aldehyde 1a (R=cyclohexyl, R'=CH_2Ph) utilized in our previous study was therefore reacted with crotyltri-n-butylstannane[3,4] using $BF_3 \cdot Et_2O$ as catalyst to afford the expected mixture of products 2a-5a, which proved to be separable by capillary vpc using a J & W 30m DX-4 column.[5] Product structures were verified and stereochemistry assigned by independent synthesis of 2a-5a via known methods.[6]

With a solution to the analytical problem in hand, we turned our attention to crotyl additions using 1a and three Lewis acids (ZnI_2, $MgBr_2$, and $TiCl_4$) which our previous study had shown to be highly efficient (97:3 to >250:1) in yielding diastereofacial selectivity

consistent with a "chelation controlled" addition of allyltri-n-butylstannane to 1a. The results are summarized in Table I below.[7]

Table I

Lewis Acid (eq.)	Eq. Stannane	2a (C,E)	3a (C,T)	4a (F,E)	5a (F,T)	Chelation/Felkin
$BF_3 \cdot Et_2O$ (1.1)	2.0	66.0	1.1	26.2	6.7	67:33
ZnI_2 (1.05)	1.1	48.6	49.4	0.9	1.1	98:2
$TiCl_4$ (1.1)	1.1	63.3	36.7	---	---	>200:1
$TiCl_4$ (1.1)	2.2	63.0	37.0	---	---	>200:1
$MgBr_2$ (1.0)	1.2	92.5	7.5	---	---	>200:1
$MgBr_2$ (1.0)	2.2	92.4	7.6	---	---	>200:1

These results show that the exceptionally high levels of diastereofacial selectivity observed for the allyl additions are preserved for the case of crotyl addition. Thus, the ratio of (2a+3a)/(4a+5a) reflects the preference for "chelation control" over "Felkin-Anh[7,8] control," and is minimally 98:2, as in the ZnI_2 case.[9] However, in this case, the erythro selectivity for bond construction which is normally observed for reaction of achiral aldehydes with crotyltri-n-butylstannane[10] is totally absent in both the chelation (2a/3a) and Felkin-Anh (4a/5a) manifolds. The same is true for $TiCl_4$; diastereofacial selectivity appears complete, as 4a and 5a are not detected, but erythro-threo selectivity for the bond construction is very low. However, erythro selectivity in the normal range for such reactions is restored when $MgBr_2$ is employed as catalyst.

We have also examined other substrates of general structure 1 to determine the effect of structural variations in R on both diastereofacial selectivity and bond construction stereoselectivity in such reactions. For comparison, allylstannane additions were also investigated. The results obtained are summarized in Table II below.

Table II

R	R'	Stannane (eq.)	Lewis Acid (eq.)	2(C,E)	3(C,T)	4(F,E)	5(F,T)	Chelation/Felkin
n-Bu	CH_2Ph	Allyl (1.2)	$MgBr_2$(1.1)	----------				99:0:1.0
n-Bu	CH_2Ph	Crotyl (1.1)	$MgBr_2$(1.1)	90.8	9.2	---	---	>200:1
n-Bu	CH_2Ph	Crotyl (2.2)	$MgBr_2$(1.1)	93.4	6.6	---	---	>200:1
n-Bu	CH_2Ph	Crotyl (1.1)	$BF_3 \cdot Et_2O$	39.1	4.2	45.0	11.7	43:57

R	R'	Stannane (eq.)	Lewis Acid (eq.)	2(C,E)	3(C,T)	4(F,E)	5(F,T)	Chelation/Felkin
n-Bu	OCH_2OBn	Allyl (1.1)	$MgBr_2$ (1.1)	----------				98.7:1.3
n-Bu	OCH_2OBn	Crotyl (1.1)	$MgBr_2$ (1.1)	90.5	9.5	---	---	>200:1
n-Bu	OCH_2OBn	Crotyl (2.2)	$MgBr_2$ (1.1)	91.0	9.0	---	---	>200:1
n-Bu	OCH_2OBn	Crotyl (1.1)	$BF_3{\cdot}Et_2O$ (1.1)	22.7	3.1	66.2	8.0	26:74
CH_3	OCH_2OBn	Allyl (1.1)	$MgBr_2$ (1.1)	----------				93.0:7.0
CH_3	OCH_2OBn	Crotyl (1.1)	$MgBr_2$ (1.1)	89.2	9.9	0.6	0.3	99:1
CH_3	OCH_2OBn	Crotyl (2.2)	$MgBr_2$ (1.1)	89.3	9.8	0.6	0.2	99:1
CH_3	OCH_2OBn	Crotyl (1.1)	$BF_3{\cdot}Et_2O$	33.2	3.3	53.5	10.0	36:64

Several conclusions derive from the foregoing data. First of all, the benzyloxymethyl protecting group, which is functionally equivalent to benzyl with respect to removal, but much more easily installed, can be used without any significant change in stereoselectivity for the addition process. With respect to reaction stereochemistry, the following trends are noted:

1) Diastereofacial selectivity increases, as expected, in the series R=CH_3, n-Bu, cyclohexyl;
2) Crotyl additions, in all cases, show significantly higher diastereofacial selectivities than do allyl additions;
3) For crotyl additions, erythro selectivity for the bond construction increases in the series R=CH_3, n-Bu, cyclohexyl;
4) Within the chelation manifold for crotyl addition (i.e. formation of products 2 and 3) erythro selectivity for the bond construction is consistently >90:10. However, in the Felkin-Anh manifold[7,8] (i.e. formation of products 4 and 5) erythro selectivity drops dramatically, ranging downward from a maximum of ca. 90:10, with selectivities on the order of 70:30 being typical.[11]
5) There is little difference in stereochemistry for $MgBr_2$ mediated reactions using 1.1 or 2.2 equivalents of crotyltri-n-butylstannane except for the case of R=n-Bu and R'=CH_2Ph, which shows somewhat higher erythro-threo selectivity using 2.2 equivalents of stannane.[12]

The simple process described herein is of obvious import for "acyclic stereocontrol" in natural product total synthesis. Moreover, these studies mark the first attempt to utilize structural control elements in crotylstannane addition reactions and to define variables which control stereochemistry in such reactions. Further studies are in progress.[13]

References and Notes

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

2. G. E. Keck and E. P. Boden, Tetrahedron Lett. **25**, 265 (1984).

3. (a) The crotyltri-n-butylstannane employed in this work was a 44:56 mixture of cis-trans isomers.
   (b) Crotyltri-n-butylstannane was prepared according to the general procedure of D. Seyferth and M. A. Weiner, J. Org. Chem., **26**, 4797 (1961).

4. All reactions were performed in CH_2Cl_2 as solvent, at temperatures of -78° ($BF_3 \cdot Et_2O$, $TiCl_4$), -22° ($MgBr_2$) or 0° → 23° (ZnI_2).

5. Retention times (min) for products 2a-5a using a temperature program of 200-240°C at 5°/min: 6.42, 6.50, 7.11, 7.19.

6. Full details will be provided in our full paper.

7. (a) "Chelation" and "Felkin-Anh"[8] (equivalent to "anti-Cram" and "Cram" respectively) are not meant to convey any mechanistic proposals, but merely the structures of 2+3 relative to those of 4+5. For convenience, abbreviations for diastereofacial selectivity (C or F) and bond construction stereochemistry (E or T) follow the structure numbers.
   (b) Chemical yields for all $MgBr_2$ mediated reactions described herein were >85%.

8. N. T. Anh and O. Eisenstein, Nouv. J. Chim., **1**, 61 (1977), and references therein.

9. The ZnI_2 mediated reaction is actually more complex than indicated, as ZnI_2 reacts with crotyltri-n-butylstananne to produce a reagent(s) which results in the addition of either end of the crotyl unit to the aldehyde carbonyl, leading to the production of six products.[6]

10. Y. Yamamoto, H. Yatagai, Y. Naruta, and K. Maruyama, J. Am. Chem. Soc., **102**, 7107 (1980).

11. This result is unexpected. However, it is consistent with our observations[6] on $BF_3 \cdot Et_2O$ mediated additions of crotyltri-n-butylstannane to α-silyloxyaldehydes, which also show unexpectedly low erythro selectivity. Moreover, diastereofacial selectivity for allyl-additions to such substrates is low unless the β carbon is branched.[6]

12. (a) These experiments were predicated upon our observation that trans-crotyltri-n-butylstannane reacts more rapidly than cis in such reactions, and also gives higher erythro selectivity.[6] For parallel observations on the analogous silanes, note: T. Hayashi, K. Kabeta, I. Hamachi, and M. Kumada, Tetrahedron Lett., **24**, 2865 (1983).

    (b) It is of interest to note that $MgBr_2$ mediated crotyltri-n-butylstannane additions to simple achiral, non-oxygenated aldehydes (e.g. cyclohexanecarboxaldehyde) exhibit essentially no erythro selectivity in the bond construction, consistent with different stereochemistry for Lewis acid complexation in the α-alkoxy case.[6]

13. Support of this research by the Alfred P. Sloan Foundation, Eli Lilly and Co., and the National Institutes of Health (through grant #GM-28961) is gratefully acknowledged.

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