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OBSERVATIONS ON THE CHOICE OF LEWIS ACID AND MODE OF ADDITION FOR THE LEWIS ACID MEDIATED REACTION OF CROTYLTRI-n-BUTYLSTANNANE WITH ALDEHYDES: CONVENIENT AND HIGHLY SELECTIVE ACCESS TO BOTH ERYTHRO AND THREO PRODUCTS

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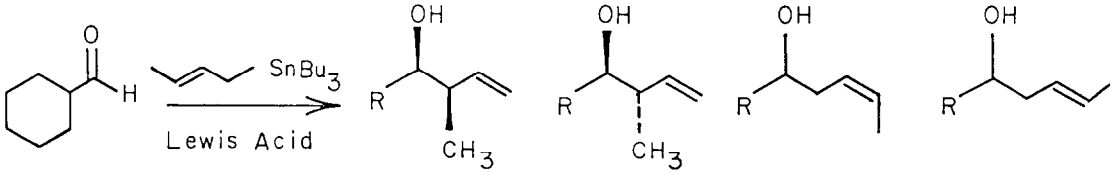
Summary: For additions of crotyltri-n-butylstannane to simple aldehydes mediated by $BF_3 \cdot Et_2O$, erythro selectivity may be increased considerably (25:1 vs. 9:1, for example) by simply using 2 eq. of stannane, $TiCl_4$ mediated additions give high erythro or threo selectivity depending simply on the order in which reactants are mixed; and other Lewis acids are also evaluated in such reactions.

The Lewis acid mediated addition of allylstannanes and allylsilanes to carbonyl compounds is now well known. Yamamoto and coworkers reported in 1980 the somewhat surprising result that both cis and trans crotyltri-n-butylstannane react with aldehydes in the presence of $BF_3 \cdot Et_2O$ at -78° to yield predominantly erythro products with good to excellent selectivity, and proposed an extended transition state to account for this result.[2] Since this time, surprisingly little work has been reported addressing the extent to which choice of Lewis acid may control product stereochemistry in such reactions.

Thus we have investigated the reaction of simple aldehydes with crotyltri-n-butylstannane and various Lewis acids, including three ($MgBr_2$, ZnI_2, and $TiCl_4$) which we have demonstrated to be particularly effective in controlling diastereofacial selectivity in additions to chiral α-alkoxyaldehydes.[3] The results for the case of cyclohexanecarboxaldehyde are summarized in equation (1) and Table I below.



2. 3. 4. 5.

Table I

Entry	Lewis Acid (Eq)	Eq. Stannane	2	3	4	5	2/3 Ratio	
1[4]	$BF_3 \cdot Et_2O$ (1.05)	1.0	90.0	10.0	---	---	9:1	
2[4,6]	$BF_3 \cdot Et_2O$ (1.05)	2.10	96.1	3.9	---	---	25:1	
3[4,7]	$BF_3 \cdot Et_2O$ (1.05)	2.10	96.1	3.9	---	---	25:1	(94%)
4[5,6]	$BF_3 \cdot Et_2O$ (1.05)	2.10	92.2	7.8	---	---	12:1	
5	$MgBr_2$ (1.0)	1.0	52.2	36.3	11.6	---	1.4:1	
6	ZnI_2 (1.0)	1.05	33.7	29.8	29.3	7.2	1.1:1	
7[6]	$SnCl_4$ (1.3)	0.8	22.8	26.0	36.4	14.8	1:1.1	
8[7]	$SnCl_4$ (1.3)	0.8	21.8	74.9	1.2	2.2	1:3.4	
9[6]	$TiCl_4$ (1.05)	1.05	90.5	7.0	2.1	0.5	13:1	
10[7]	$TiCl_4$ (2.1)	2.0	4.4	90.8	---	4.9	1:21	(86%)

The $BF_3 \cdot Et_2O$ mediated reactions consistently show high erythro-threo ratios which are unaffected by the mode of addition of reagents (runs 2 and 3). However, an increase in erythro selectivity is observed if excess stannane is used (runs 1 and 2). By using 2 eq. of mixtures of crotyltri-n-butylstannane of varying composition and by analyzing both product ratios and recovered crotyltri-n-butylstannane, it can be shown that the trans isomer reacts somewhat faster than the cis, and also gives higher erythro selectivity, although a slower, but still competing, cis-trans isomerization under the reaction conditions complicates precise analysis of relative rates and selectivities.[8] Thus, in the run corresponding to entry 2 in Table I, a cis-trans mixture containing 43.4% cis isomer and 56.6% trans isomer gave a 56.7:43.3 cis-trans mixture of recovered crotyltri-n-butylstannane, while a comparable blank, containing cis rich organostannane (64.3:35.7) and $BF_3 \cdot Et_2O$, but no substrate, gave a 46.7:53.3 mixture of recovered material. If cis rich (64:36) material is employed for reaction (entry 3) lower erythro selectivity is noted, and recovered organostannane is an 89:11 cis-trans mixture. The higher erythro selectivity in run 2 versus run 1 can thus be accounted for by the availability of more trans-crotyltri-n-butylstannane.

All other Lewis acids examined provide varying amounts of products 4 and 5, which must arise by pathways involving either: (a) reaction of the Lewis acid with crotyltri-n-butylstannane to produce a reagent which reacts (at least in a formal sense) by both S_E and S_E' pathways, or (b) S_E' reaction of Lewis acid with the stannane followed by S_E' reaction of the new organometallic reagent with substrate, in competition with "normal" crotylstannane addition to the aldehyde. This complication is minimal with $MgBr_2$, more serious with ZnI_2,

and perhaps best indicated by the case of $SnCl_4$. "Normal" addition using $SnCl_4$ (i.e. addition of crotyltri-n-butylstannane to a solution of aldehyde and $SnCl_4$ at -78° (entry 7) gives roughly equal amounts of 2-5, which can be accounted for by competition between the expected addition process and formation of 3-methyl-3-trichlorostannyl-1-propene (6) by reaction of $SnCl_4$ and crotyltri-n-butylstannane, which can then add to the aldehyde to yield 4 and 5. If crotyltri-n-butylstannane is added dropwise to $SnCl_4$ in CH_2Cl_2 at 23°, the clean formation of crotyltrichlorostannane (as a cis-trans mixture of isomers) is observed (NMR analysis), presumably via the formation of 6 followed by isomerization.[9] Cooling this solution to -78° followed by addition of aldehyde then results in the predominant formation of products 2 and 3, but in only a 1:3.4 ratio.

The titanium tetrachloride results are certainly the most striking and useful observations regarding choice of Lewis acid we have made to date. Using normal addition (entry 9, crotyltri-n-butylstannane added last at -78°) very good (93:7) erythro selectivity is obtained, and only minor amounts (<3%) of products 4 and 5 are observed. On the other hand, dropwise addition of stannane to a solution of $TiCl_4$ in CH_2Cl_2 at -78°, stirring at that temperature for 8-10 min., and dropwise addition of aldehyde affords threo product 3 with excellent (21:1) selectivity[10] (entry 10); again only minor amounts (<5% combined) of 4 and 5 are observed.[11]

It seems clear that rather different mechanisms are involved in these two cases: bimolecular reaction of crotyltri-n-butylstannane with a $TiCl_4$-aldehyde complex in the former case, and reaction of aldehyde with some sort of crotyltitanium species (perhaps trans $CH_3CH{=}CH{-}CH_2TiCl_3$) in the latter.[12]

Regardless of the mechanistic details, the experimental simplicity of the $TiCl_4$ mediated reaction, the low cost and ease of access to the requisite reagents, and the high degree of stereoselectivity now available for both erythro selective and threo selective additions should secure a niche for such an organostannane approach to acyclic stereoselection amongst both aldol and other organometallic approaches.[13]

Stereoselectivities (as threo:erythro ratios) and isolated yields obtained using the inverse $TiCl_4$ procedure with some other simple aldehydes were as follows: 2-methylpropanal --26:1, 91%; benzaldehyde--15:1, 94%; poor results --6:1, 89%; were obtained with decanal. Further studies are in progress.[14]

References & Notes

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

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

(b) More recently, synclinal transition state geometries have been suggested for similar reactions: S. E. Denmark and E. J. Weber, Helv. Chim. Acta, **66**, 1655 (1983). Note also reference 8.

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

b) G. E. Keck and E. P. Boden, Tetrahedron Lett. **25**, 1879 (1984).

4. This experiment was performed using a 43.4:56.6 mixture of cis and trans crotyltri-n-butylstannane.

5. This experiment was performed using a 65.3:35.7 mixture of cis and trans crotyltri-n-butylstannane.

6. This experiment was performed using "normal" addition--i.e. addition of crotyltri-n-butylstannane to a solution containing Lewis acid and aldehyde.

7. This experiment was performed using "inverse" addition--i.e. addition of aldehyde to a solution prepared from Lewis acid and crotyltri-n-butylstannane.

8. Parallel results have been observed for the analogous silanes. Note T. Hayashi, K. Kabeta, I. Hamachi, and M. Komada, Tetrahedron Lett., 24, 2865 (1983).

9. Note G. E. Keck and D. A. Abbott, Tetrahedron Lett. **25**, 1883 (1984) and references therein.

10. Product ratios expressed in this way should not be regarded as "hard" numbers for ratios greater than ~20:1 since such ratios increase rapidly with very small changes in measured amounts of products. For example, a 95.24/4.76 distribution corresponds to 20:1 selectivity, while a 97.56/2.44 distribution corresponds to 40:1 selectivity.

11. Best results are obtained at very low substrate concentrations (ca. 0.025 M); at higher concentrations (up to 0.5 M) good threo selectivity is preserved, but products 4 and 5 increase to 10-25% of the product. These materials are easily removed by chromatography over silica gel, however (Rf 0.29 for 4 and 5 vs. 0.36 for 2 and 3 , 20% Et_2O-hexane).

12. Threo stereochemistry would be expected for trans $CH_3CH{=}CH{-}CH_2TiCl_3$ via an internal delivery of the crotyl unit with a chairlike transition state. For a recent review of organotitanium compounds in organic synthesis, note B. Weidmann and D. Seebach, Angew. Chem. Int. Ed. Engl. **22**, 31 (1983).

13. For reviews, note:

a) R. W. Hoffman, Angew. Chem. Int. Ed. Engl. **21**, 555 (1982);

b) Y. Yamamoto and K. Maruyama, Heterocycles, **18**, 357 (1982). Note also reference 12.

14. Support of this research by the Alfred P. Sloan Foundation and the National Institutes of Health (through grant GM-28961) is gratefully acknowledged.

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