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A STEREOSELECTIVE SYNTHESIS OF VINYL ETHERS FROM α-ALKOXYALDEHYDES

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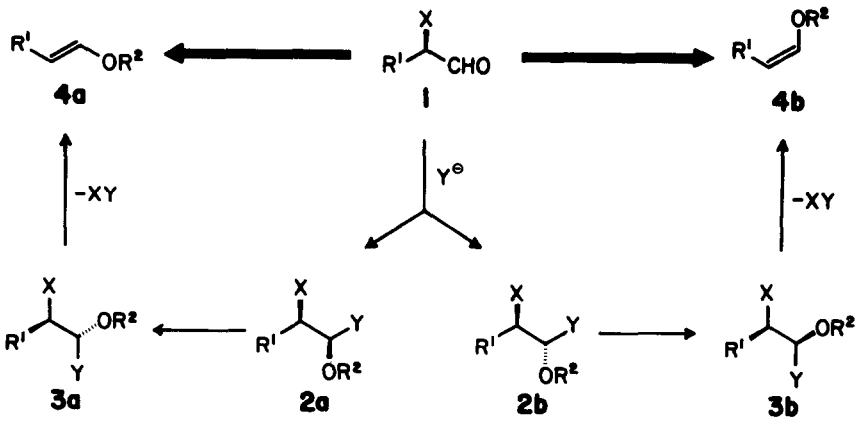
Abstract: A general, stereoselective approach to vinyl ethers from α-alkoxyaldehydes is described which features a stereocontrolled tri-n-butylstannyl addition/elimination sequence.

In spite of the natural occurrence[1] and demonstrated synthetic utility of vinyl ethers,[2] there are relatively few reports addressing a general preparation of these species.[3,4] In our studies directed toward the synthesis of highly oxygenated natural products, we required access to a variety of substituted E- and Z-vinyl ethers containing oxygen substituents which are not easily accommodated by present methods. Herein we report our initial studies directed toward developing a general, stereoselective synthesis of vinyl ethers.

As outlined in Scheme I, our strategy involves the elaboration of α-heteroatom substi-

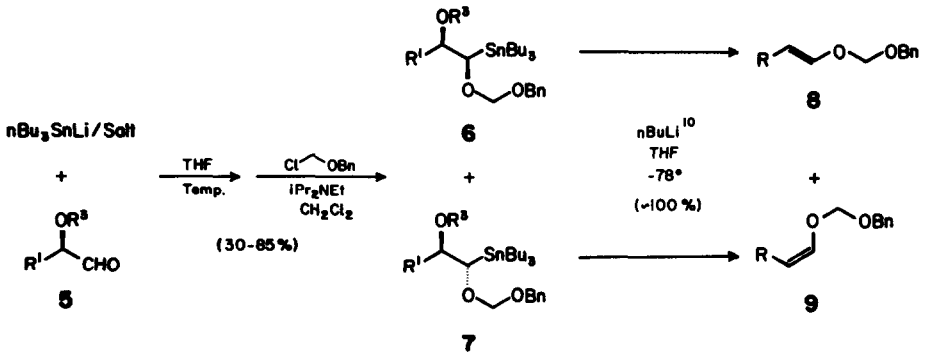


Scheme I.

tuded aldeyhydes (1) into the desired vinyl ethers through an addition/anti-elimination sequence. Assuming strict stereoelectronic control in the elimination step (3a/b → 4a/b), the overall stereoselectivity of the route is governed by the selection observed in the addition step (1 → 2a/b). This approach promises to satisfy our requirement for structural flexibility through the availability of a variety of compounds 1, while the intermediacy of adduct 2a/b should allow substantial variation in oxygen substitution (R^2). Finally, this route is compatible with the sensitivity of the product vinyl ethers since the elimination may be induced under non-acidic conditions.

We chose to implement this strategy using α-alkoxyaldehydes (1, X=OR^3), which may be readily obtained from α-amino acids,[5a,b] carbohydrates,[5c] and homologation of existing alde-

hydes,[5d,e] among other methods. Given the propensity of β-substituted stannanes toward elimination to form olefins[6] and the encouraging stereoselectivity observed in the addition of stannyl anions to β-alkoxyaldehydes,[7] the use of Y=nBu$_3$Sn in the scheme was especially attractive. Scheme II outlines the approach we decided to investigate.



Scheme II.

In view of previous observations,[7] a particularly interesting facet of our study was the examination of the stereoselection realized in the addition of nBu$_3$SnM species to α-alkoxyaldehydes. As indicated in the Table, a range of stannyl-metal species were exam-

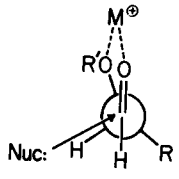
TABLE.

Entry	Aldehyde 5	Salt	Temp.	8a-d/9a-d[a]
1	5a	none	-78°	75:25
2		$ZnBr_2$	0°	83:17
3	5b	none	-78°	55:45
4		none[a]	-78°	63:37
5		ZnI_2	0°	72:28
6		$ZnBr_2$	0°	74:26
7		CuBr·DMS	-78°	78:22
8	5c	none	-78°	75:25
9		CuBr·DMS	-78°	80:20
10		$ZnBr_2$	0°	84:16
11	5d	none	-78°	56:44
12		$MgBr_2$	0°	50:50
13		PhSCu	-78°	46:54
14		$ZnBr_2$	0°	33:67
15		ZnI_2	0°	23:77

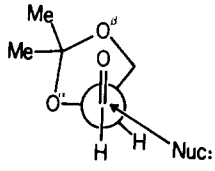
[a] This condensation was carried out in DME solvent.

ined on various substrates in an effort to optimize the 1,2-asymmetric induction of the condensations. The aldehydes were treated with 2 equivalents of nBu_3SnM at the indicated temperatures to afford a mixture of adducts which were protected, then purified by flash chromatography. For analytical purposes, the adducts were subjected to quantitative conversion to the indicated vinyl ethers through stoichiometric treatment with nBuLi at low temperature (THF,-78°C)[9] and the isomer ratios determined by NMR.[10]

In the cases of aldehydes 5a-c, reasonable selectivity for the syn-adduct 6 was observed when the stannyl anion was modified by the softer metal salts $ZnBr_2$ and CuBr.[11] This stereoselection is consistent with the intervention of an α-chelate of the type A.[12] Aldehyde 5d, in contrast, favored the anti-adduct 7 when treated with similar reagents.[11] In this instance, the bicyclic arrays resulting from α or β-chelation are probably energetically unfavorable, arguing for stereoselection resulting from the Felkin-Ahn transition state B.[13]



A



B

These studies demonstrate the feasibility of this strategy and provide a concise route to valuable vinyl ethers from readily available α-alkoxyaldehydes. Of particular preparative utility is the structural latitude accommodated by this approach, allowing access to compounds that are difficult to prepare by existing methods. Finally, it is anticipated that improved efficiency and stereoselection will follow from investigation of other aldehyde precursors 1 and alternative reaction conditions during the stannyl addition and elimination steps.

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8. NMR coupling constants for -HC=CH-: 8a (J=12.5 Hz), 9a (J=6.0 Hz), 8b (J=12.3 Hz), 9b (J=6.3 Hz), 8c (J=12.4 Hz), 9c (J=6.3 Hz), 8d (J=12.0 Hz), 9d (J=6.0 Hz).
9. Elimination of the adducts of aldehyde 5c was accompanied by substantial decomposition affording 8c/9c in an isolated yield of only 36%.
10. Within the limits of NMR detection, the ratios of products 8 and 9 accurately reflected the isomer ratios of adducts 6 and 7.
11. No condensation was observed when MgX_2 salts were used.
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