

Chelation—Controlled Stannylacetylene Additions to β-Alkoxy Aldehydes Promoted by Alkylaluminum Halide Lewis Acids

David A. Evans*, David P. Halstead, and Brett D. Allison

Department of Chemistry and Chemical Biology, Harvard University, Cambridge, Massachusetts 02138

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Abstract: Lewis acid-mediated additions of stannylacetylenes to β -alkoxy aldehydes are reported. High levels of chelation control are observed with dimethylaluminum chloride (Me₂AlCl) and methylaluminum dichloride (MeAlCl₂). © 1999 Elsevier Science Ltd. All rights reserved.

In the preceding Letter, we documented the exceptional chelating potential of Me₂AlCl and MeAlCl₂ in addition reactions to aldehydes 1a,b.¹ The purpose of this communication is to describe the application of these Lewis acids to the diastereoselective addition of stannylacetylenes to β -alkoxy and β -silyloxy-aldehydes, a reaction relevant to the C_7 - C_8 bond construction in the discodermolide skeleton (eq 1).²

In conjunction with an ongoing approach to the synthesis of discodermolide, we considered the addition of metal acetylides to the illustrated aldehyde; however, a survey of the literature revealed that these additions tend to be either poorly diastereoselective or unsuitable for the union of complex fragments.³ We then turned to an investigation of the analogous Lewis acid promoted addition of stannylacetylenes as a potential alternative.⁴ This Letter presents our results in this area culminating in a mild, stereoselective addition process.

The study began with the catalyzed addition of trimethylstannyl phenylacetylene⁵ to α -methyl- β -alkoxy aldehydes 1 (eq 2, Table 1). We have studied this aldehyde extensively, and the stereochemical outcome of these reactions must be carefully interpreted.⁶ For example, it is erroneous to conclude that the observance of the anti-Felkin/chelation product 3 is supportive of a chelate-controlled addition process. When the nucleophilic component in additions to 1 is not sterically demanding, dominant β -heteroatom control may lead to the anti-Felkin adduct even when chelation is not possible.⁶ This generalization is in accord with the observation that the illustrated additions to 1 exhibit anti-Felkin selectivity (91:9) with BF3•OEt2 activation despite the inability of BF3•OEt2 to engage in chelation (entry A). The alkylaluminum Lewis acids Me2AlCl and MeAlCl2 (2.5 equiv) are also selective for the anti-Felkin/chelation product 3 (entry B, C); however, the evidence that these reactions are proceeding via chelate organization is strong based on the analogies presented in the preceding study.¹

Table 1. Acetylene Additions to Aldehyde 1 (P = Bn, TBS) (eq 2)^a 1a P = Bn1b P = TBS2:3 (%)^b Lewis acid 2:3(%)b Α BF3 OEt2 09:91 (48) 28:72 (26)c В Me₂AlCl 03:97 (34) 19:81 (50)^c Γ MeAICI: 04:96 (68) 06:94 (81)

^aReactions were run with 1.0 equiv of BF₃•OEt₂ and 2.5 equiv of Me₂AlCl and MeAlCl₂. ^b Yields are the combined isolated yields of the both diastereomers. ^cThese reactions were run at -40 °C.

The extension of these reactions to β -alkoxyaldehyde 4 is provided in Table 2 (eq 3). The alkylaluminum Lewis acids provided 1,3-anti selectivities in excess of 90% affording adduct 6 in good yields. Again, the preceding study supports the contention that the silyloxy substituent is capable of chelating with both Me₂AlCl and MeAlCl₂.¹ A modest improvement in selectivity was also observed upon switching solvent from dichloromethane to toluene (entries C, D), conditions that were chosen for more complex addition processes (Scheme 1).

Table 2.	Acetylene Additions to Aldehyde 3 (eq 3) ^a	
entry	Lewis acida	1,3-syn: 1,3-anti (%)b
A	BF ₃ •OEt ₂	17:83 (32)
В	TiCl3(O-iPr)	71:29 (33)
C	Me ₂ AlCl	09:91 (68)
D	Me ₂ AlCl	06:94 (74) ^c
eactions were run with 1.0 south of DE sOFt and		

TiCl3(O-iPr), or 2.5 equiv of Me2AlCl and MeAlCl₂. The combined isolated yields of the both diastereomers. Columne was used as solvent.

In both of the reactions summarized below, good diastereoselectivity was obtained for the stannylacetylene additions to aldehyde 7. While some deterioration in stereoselectivity was observed in the formation of adduct 10 (eq 5), it should be recognized that this is a double stereodifferentiating addition reaction. In this instance we have no information as to whether this reaction is matched or mismatched. Related bond constructions have appeared in other published discodermolide syntheses, and problems associated with reaction diastereoselection have been a recurring theme.⁷ In summary, Me₂AlCl and MeAlCl₂ are good chelating Lewis acids for both β -alkoxy and β -silyloxy aldehyde addition reactions. The scope of these addition reactions will be reported shortly.

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References and Footnotes

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