

## Chelation-Controlled Stannylacetylene Additions to $\beta$ -Alkoxy Aldehydes Promoted by Alkylaluminum Halide Lewis Acids

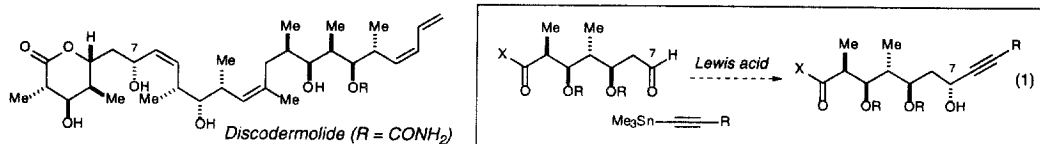
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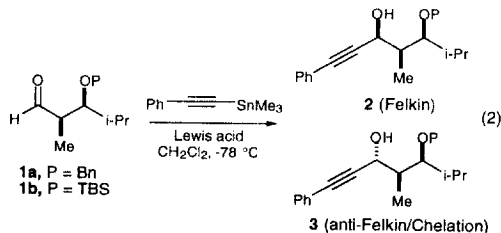
**Abstract:** Lewis acid-mediated additions of stannylacetylenes to  $\beta$ -alkoxy aldehydes are reported. High levels of chelation control are observed with dimethylaluminum chloride ( $\text{Me}_2\text{AlCl}$ ) and methylaluminum dichloride ( $\text{MeAlCl}_2$ ).  
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In the preceding Letter, we documented the exceptional chelating potential of  $\text{Me}_2\text{AlCl}$  and  $\text{MeAlCl}_2$  in addition reactions to aldehydes **1a,b**.<sup>1</sup> The purpose of this communication is to describe the application of these Lewis acids to the diastereoselective addition of stannylacetylenes to  $\beta$ -alkoxy and  $\beta$ -silyloxy-aldehydes, a reaction relevant to the  $\text{C}_7$ – $\text{C}_8$  bond construction in the discodermolide skeleton (eq 1).<sup>2</sup>



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.<sup>3</sup> We then turned to an investigation of the analogous Lewis acid promoted addition of stannylacetylenes as a potential alternative.<sup>4</sup> This Letter presents our results in this area culminating in a mild, stereoselective addition process.

The study began with the catalyzed addition of trimethylstannyl phenylacetylene<sup>5</sup> to  $\alpha$ -methyl- $\beta$ -alkoxy aldehydes **1** (eq 2, Table 1). We have studied this aldehyde extensively, and the stereochemical outcome of these reactions must be carefully interpreted.<sup>6</sup> 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  $\beta$ -heteroatom control may lead to the anti-Felkin adduct even when chelation is not possible.<sup>6</sup> This generalization is in accord with the observation that the illustrated additions to **1** exhibit anti-Felkin selectivity (91 : 9) with  $\text{BF}_3 \cdot \text{OEt}_2$  activation despite the inability of  $\text{BF}_3 \cdot \text{OEt}_2$  to engage in chelation (entry A). The alkylaluminum Lewis acids  $\text{Me}_2\text{AlCl}$  and  $\text{MeAlCl}_2$  (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.<sup>1</sup>

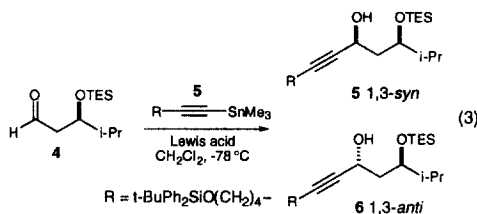


**Table 1.** Acetylene Additions to Aldehyde **1** (P = Bn, TBS) (eq 2)<sup>a</sup>

entry	Lewis acid <sup>a</sup>	<b>1a</b> P = Bn <b>2</b> : <b>3</b> (%) <sup>b</sup>	<b>1b</b> P = TBS <b>2</b> : <b>3</b> (%) <sup>b</sup>
A	$\text{BF}_3 \cdot \text{OEt}_2$	09 : 91 (48)	28 : 72 (26) <sup>c</sup>
B	$\text{Me}_2\text{AlCl}$	03 : 97 (34)	19 : 81 (50) <sup>c</sup>
C	$\text{MeAlCl}_2$	04 : 96 (68)	06 : 94 (81)

<sup>a</sup>Reactions were run with 1.0 equiv of  $\text{BF}_3 \cdot \text{OEt}_2$  and 2.5 equiv of  $\text{Me}_2\text{AlCl}$  and  $\text{MeAlCl}_2$ . <sup>b</sup>Yields are the combined isolated yields of the both diastereomers. <sup>c</sup>These reactions were run at  $-40^\circ\text{C}$ .

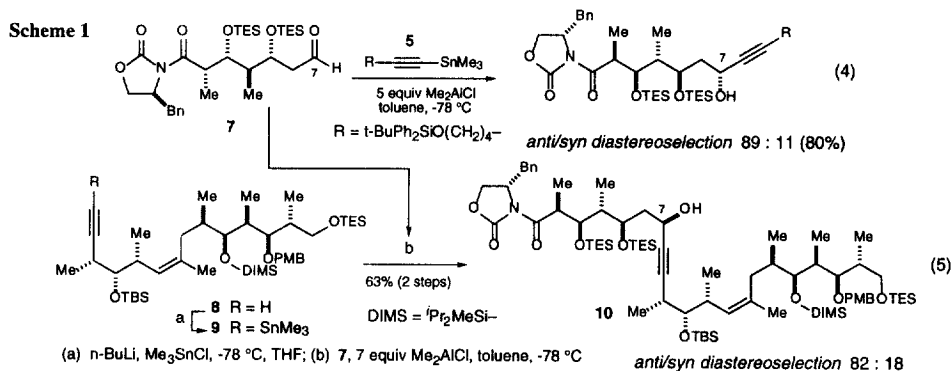
The extension of these reactions to  $\beta$ -alkoxyaldehyde **4** is provided in Table 2 (eq 3). The alkylaluminum Lewis acids provided 1,3-*anti* selectivities in excess of 90% affording adduct **6** in good yields. Again, the preceding study supports the contention that the silyloxy substituent is capable of chelating with both  $\text{Me}_2\text{AlCl}$  and  $\text{MeAlCl}_2$ .<sup>1</sup> 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).



entry	Lewis acid <sup>a</sup>	1,3- <i>syn</i> : 1,3- <i>anti</i> (%) <sup>b</sup>
A	$\text{BF}_3 \cdot \text{OEt}_2$	17 : 83 (32)
B	$\text{TiCl}_3(\text{O}-i\text{Pr})$	71 : 29 (33)
C	$\text{Me}_2\text{AlCl}$	09 : 91 (68)
D	$\text{Me}_2\text{AlCl}$	06 : 94 (74) <sup>c</sup>

<sup>a</sup>Reactions were run with 1.0 equiv of  $\text{BF}_3 \cdot \text{OEt}_2$  and  $\text{TiCl}_3(\text{O}-i\text{Pr})$ , or 2.5 equiv of  $\text{Me}_2\text{AlCl}$  and  $\text{MeAlCl}_2$ . <sup>b</sup>The combined isolated yields of the both diastereomers. <sup>c</sup>Toluene 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.<sup>7</sup> In summary,  $\text{Me}_2\text{AlCl}$  and  $\text{MeAlCl}_2$  are good chelating Lewis acids for both  $\beta$ -alkoxy and  $\beta$ -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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