

## Chelate-Controlled Carbonyl Addition Reactions. The Exceptional Chelating Ability of Dimethylaluminum Chloride and Methylaluminum Dichloride

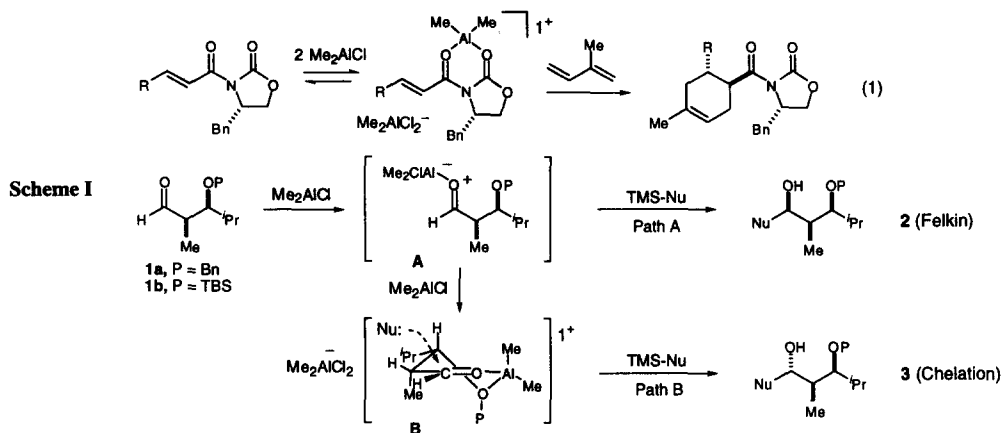
David A. Evans,\* Brett D. Allison, and Michael G. Yang

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

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**Abstract:** Highly selective chelation-controlled aldol and allyl nucleophile additions to  $\beta$ -alkoxy aldehydes promoted by dimethylaluminum chloride and methylaluminum dichloride are described. Cationic aluminum chelates are proposed as intermediates in these reactions. Evidence is provided to support the claim that chelate organization with  $\text{Me}_2\text{AlCl}$  and  $\text{MeAlCl}_2$  is possible even with  $\beta$ -*tert*-butyldimethyl-silyloxy groups. Stereoselectivity data comparing the chelating potential of  $\text{Me}_2\text{AlCl}$ ,  $\text{MeAlCl}_2$ ,  $\text{SnCl}_4$ , and  $\text{TiCl}_4$  is provided. © 1999 Elsevier Science Ltd. All rights reserved.

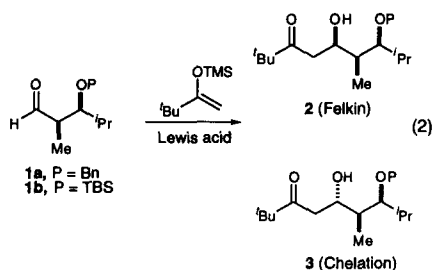
The incorporation of chelate organization into the design of stereoselective processes is widespread. Numerous examples may be found that incorporate this stereochemical control element into diastereoselective<sup>1</sup> and enantioselective<sup>2</sup> carbonyl addition, chiral enolate-electrophile reactions,<sup>3</sup> and cycloadditions.<sup>4</sup> During the development of the oxazolidinone-based Diels-Alder reactions (eq 1),<sup>4a</sup> we surveyed a number of Lewis acids, including both  $\text{SnCl}_4$  and  $\text{TiCl}_4$ , for their ability to both activate and chelate-organize the dienophilic component; however, none delivered either the reactivity or the diastereoselectivity obtained by dimethylaluminum chloride ( $\text{Me}_2\text{AlCl}$ ) which was proposed to chelate the substrate through the illustrated cationic complex.<sup>4a,5</sup> This Letter reports that the exceptional chelating potential of  $\text{Me}_2\text{AlCl}$  and  $\text{MeAlCl}_2$  may be extended to chelate-organized carbonyl addition reactions where the chelating  $\beta$ -heteroatom may even include hindered silyloxy substituents (Scheme 1).



We set out to establish an addition process whose stereochemical outcome would respond strongly to the intervention of chelate organization. To this end we selected the *syn*- $\alpha$ -methyl- $\beta$ -alkoxy aldehyde **1** for the carbonyl component.<sup>6</sup> By inspection, the vicinal *syn* stereocenters in chelate **B** mutually reinforce addition to the same carbonyl diastereoface to afford the chelate-derived diastereomer **3** (Path B).<sup>7</sup> In the absence of chelation (Path A), a nucleophile was required that would exhibit high levels of Felkin control<sup>8</sup> to afford the Felkin diastereomer **2**. Prior studies, have established that the pinacolone enolsilane exhibits the desired Felkin control in this addition process.<sup>9</sup> With the reaction partners chosen, we surveyed the potential for  $\text{Me}_2\text{AlCl}$  and  $\text{MeAlCl}_2$  to promote chelate controlled addition and compared these reagents to the more commonly employed chelating Lewis

acids  $\text{SnCl}_4$  and  $\text{TiCl}_4$  (Table 1, eq 2). In the ensuing studies,<sup>10</sup> all reactions were quenched after a 20-min reaction time irrespective of whether the aldehyde component was consumed. Under these circumstances, isolated unoptimized product yields provide a qualitative measure of conversion and hence relative activity of the various Lewis acids.

As indicated in Table 1, the control reaction with  $\text{BF}_3 \cdot \text{OEt}_2$  affords excellent Felkin selectivity (95:5) with benzyl-protected aldehyde **1a** to give adduct **2** (eq 2).<sup>11</sup> In contrast, the  $\text{Me}_2\text{AlCl}$ -promoted addition reveals a dramatic turnover in stereochemistry affording the chelation product **3** with 99:1 selectivity (entries A and E). Experimentally, it was determined that 2.5 equiv of  $\text{Me}_2\text{AlCl}$  was optimal (vide infra). The stereochemical outcome of the  $\text{SnCl}_4$  and  $\text{TiCl}_4$ -promoted processes was unexpected (entries B and C). The ability of a benzyloxy substituent to participate in chelation is documented,<sup>12</sup> and we expected to observe good levels of chelation selectivity with this aldehyde with Lewis acids recognized to have chelating ability. However, reactions of **1a** promoted with  $\text{SnCl}_4$  and  $\text{TiCl}_4$  exhibited Felkin selectivity (entries B, C). In addition, a side-reaction involving internal hydride transfer from the benzyl group to the aldehyde shunted a significant amount of aldehyde **1a** to undesired products.<sup>13</sup> When the TBS-protected aldehyde **1b** was employed, the  $\text{BF}_3 \cdot \text{OEt}_2$ ,  $\text{SnCl}_4$  and  $\text{TiCl}_4$  promoted addition reactions were all highly Felkin selective; however  $\text{Me}_2\text{AlCl}$  and  $\text{MeAlCl}_2$  both appear to effectively engage the OTBS substituent in an unprecedented chelate-controlled addition to afford **3** in 96:4 selectivity (entry E). While conventional wisdom states that hindered silyl protecting groups prevent chelation with most metal ions,<sup>14</sup> this case demonstrates that chelate control is possible with both  $\text{Me}_2\text{AlCl}$  and  $\text{MeAlCl}_2$ .



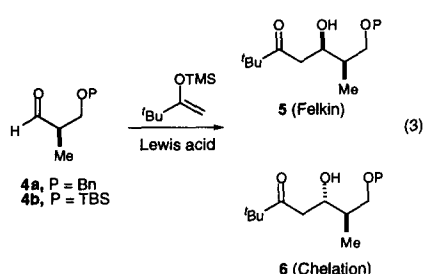
**Table 1.** Aldol Reactions of Aldehyde **1** (P = Bn, TBS) (eq 2)<sup>a</sup>

entry	Lewis acid	Lewis acid equiv	<b>1a</b> P = Bn <b>2</b> : <b>3</b> (% yield) <sup>b</sup>	<b>1b</b> P = TBS <b>2</b> : <b>3</b> (% yield) <sup>b</sup>
A	$\text{BF}_3 \cdot \text{OEt}_2$	1.0 <sup>c</sup>	95 : 05 (78)	96 : 04 (91)
B	$\text{SnCl}_4$	1.0 <sup>c</sup>	95 : 05 (32) <sup>d</sup>	99 : 01 (41)
C	$\text{TiCl}_4$	1.0 <sup>c</sup>	62 : 38 (22) <sup>d</sup>	98 : 02 (71)
D	$\text{Me}_2\text{AlCl}$	2.5	01 : 99 (73)	03 : 97 (51)
E	$\text{MeAlCl}_2$	2.5	01 : 99 (81)	04 : 96 (71)

<sup>a</sup>See Note 10 for reaction conditions. <sup>b</sup>Reactions were run for a fixed time period (20 min). Isolated yields reflect relative carbonyl activation of indicated Lewis acids.

<sup>c</sup>Reaction with 2.5 equiv Lewis acid had a minimal effect on stereoselectivity.

<sup>d</sup>By-products from internal hydride transfer to the aldehyde were observed (Note 13).



**Table 2.** Aldol Reactions of Aldehyde **4** (P = Bn, TBS) (eq 3)<sup>a</sup>

entry	Lewis acid	Lewis acid equiv	<b>4a</b> P = Bn <b>5</b> : <b>6</b> (% yield) <sup>b</sup>	<b>4b</b> P = TBS <b>5</b> : <b>6</b> (% yield) <sup>b</sup>
A	$\text{BF}_3 \cdot \text{OEt}_2$	1.0 <sup>c</sup>	75 : 26 (76)	91 : 09 (55)
B	$\text{SnCl}_4$	1.0 <sup>c</sup>	50 : 50 (87)	93 : 07 (41)
C	$\text{TiCl}_4$	1.0 <sup>c</sup>	03 : 97 (74)	93 : 07 (55)
D	$\text{Me}_2\text{AlCl}$	2.5	10 : 90 (45)	03 : 97 (62) <sup>d</sup>
E	$\text{MeAlCl}_2$	2.5	22 : 78 (70)	23 : 77 (55)

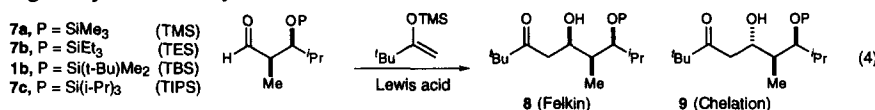
<sup>a</sup>See Note 10 for reaction conditions. <sup>b</sup>Reactions were run for a fixed time period (20 min). Isolated yields reflect relative carbonyl activation of indicated Lewis acids.

<sup>c</sup>Reaction with 2.5 equiv of Lewis acid had little or no effect on diastereoselectivity.

<sup>d</sup>This reaction was run at  $-90^\circ\text{C}$ ; at  $-78^\circ\text{C}$ , the ratio was 04:96 (35).

To ensure that the observed anti-Felkin selectivity was not a result of some dominant effect emanating from the  $\beta$ -stereocenter, we evaluated aldehydes **4a** and **4b**, lacking the  $\beta$ -stereocenter (eq 3). Table 2 summarizes the results of these aldol reactions. Reactions with  $\text{BF}_3 \cdot \text{OEt}_2$  are again Felkin selective (entry A) while  $\text{TiCl}_4$  appears to participate in chelation with **4a** (P = Bn) as expected (entry C). Finally, the aluminum reagents continue to exhibit chelation with **4a** although the selectivity is diminished somewhat with  $\text{MeAlCl}_2$ . Additions to aldehyde **4b** (P = TBS) demonstrate that  $\text{SnCl}_4$  and  $\text{TiCl}_4$  are incapable of chelating the OTBS group; however, turnover to the chelation-controlled product (97:3) is again observed for reactions with 2.5 equiv of  $\text{Me}_2\text{AlCl}$  and  $\text{MeAlCl}_2$ .

The generality of silyloxy group chelation with  $\text{Me}_2\text{AlCl}$  and  $\text{MeAlCl}_2$  was evaluated with aldehydes **7a–7c** (eq 4, Table 3). Excellent levels of chelation control are maintained with silyl groups sterically smaller than TBS; however, the chelating ability of the aluminum Lewis acids is partially curtailed by the sterically demanding triisopropylsilyl (TIPS) group in **7c**. Other nucleophiles such as allylsilanes and stannanes are also accommodated by the aluminum Lewis acids (eq 5, Table 4). Good to excellent chelation control is observed for all reactions of silyl-protected aldehyde **1b**. While these studies have emphasized the stereochemical elements of the addition process, these reactions perform successfully at preparative scale with no degradation of yield or stereoselectivity demonstrating the synthetic utility of these transformations.

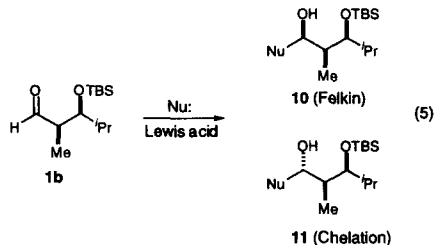


**Table 3.** Aldol Reactions of Silyl-protected Aldehydes **7a–7c**, **1b** (eq 4)<sup>a</sup>

entry	Lewis acid <sup>b</sup>	<b>7a</b> P = TMS ratio, <b>8:9</b>	<b>7b</b> P = TES ratio, <b>8:9</b>	<b>1b</b> P = TBS ratio, <b>8:9</b>	<b>7c</b> P = TIPS ratio, <b>8:9</b>
A	$\text{BF}_3 \cdot \text{OEt}_2$	95 : 05	98 : 02	96 : 04	97 : 03
B	$\text{Me}_2\text{AlCl}$	02 : 98	02 : 98	03 : 97	35 : 65
C	$\text{MeAlCl}_2$	02 : 98	10 : 90	04 : 96	38 : 62

<sup>a</sup>See Note 10 for reaction conditions. <sup>b</sup>Reactions were run with 1.0 equiv of neat  $\text{BF}_3 \cdot \text{OEt}_2$  and 2.5 equiv of  $\text{Me}_2\text{AlCl}$  and  $\text{MeAlCl}_2$  as 1.0 M solutions in hexane.

**Table 4.** Addition of Allylsilanes to Aldehyde **1b** (eq 5)<sup>a</sup>

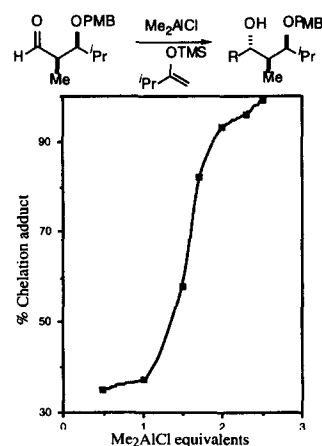


entry	nucleophile	Lewis acid <sup>b</sup>	<b>10 : 11</b> (% yield) <sup>c</sup>
A	$\text{Me}_3\text{Si}-\text{CH}_2\text{CH}=\text{CH}_2$	$\text{Me}_2\text{AlCl}$	01 : 99 (84)
B	$\text{Me}_3\text{Si}-\text{CH}_2\text{CH}=\text{CH}_2$	$\text{MeAlCl}_2$	05 : 95 (84)
C	$\text{Bu}_3\text{Sn}-\text{CH}_2\text{CH}=\text{CH}_2$	$\text{Me}_2\text{AlCl}$	07 : 93 (75)
D	$\text{Bu}_3\text{Sn}-\text{CH}_2\text{CH}=\text{CH}_2$	$\text{MeAlCl}_2$	14 : 86 (74)
E	$\text{Me}_3\text{Si}-\text{CH}(\text{Me})\text{CH}=\text{CH}_2$	$\text{Me}_2\text{AlCl}$	10 : 90 (63)
F	$\text{Me}_3\text{Si}-\text{CH}(\text{Me})\text{CH}=\text{CH}_2$	$\text{MeAlCl}_2$	12 : 88 (81)

<sup>a</sup>See Note 10 for reaction conditions. <sup>b</sup>Reactions were run with 2.5 equiv of  $\text{Me}_2\text{AlCl}$  and  $\text{MeAlCl}_2$  (1.0 M in hexanes). <sup>c</sup>Reactions were run for a fixed time period (20 min). Isolated yields reflect relative carbonyl activation of indicated Lewis acids.

**Rationale for Chelation Control.** Successful chelation control in reactions promoted by  $\text{Me}_2\text{AlCl}$  and  $\text{MeAlCl}_2$  is dependent upon the Lewis acid stoichiometry. Figure 1 shows the results of varying the stoichiometry of  $\text{Me}_2\text{AlCl}$  from 0.5 to 2.5 equiv in the indicated reaction. While the aldol addition is moderately Felkin selective with  $\leq 1$  equiv of  $\text{Me}_2\text{AlCl}$ , above one equiv of  $\text{Me}_2\text{AlCl}$  the reaction becomes highly chelation selective. An optimum level of chelation control (99:1 selectivity) is achieved at 2.5 equiv of  $\text{Me}_2\text{AlCl}$ . We attribute this dependence to the intermediacy of the cationic aluminum complex illustrated in Scheme 1 in direct analogy to our cited Diels–Alder precedent (eq 1).<sup>4a</sup> NMR Spectroscopic studies that support the illustrated complex will be reported in due course. This type of Lewis acid behavior has also been documented by others,<sup>15</sup> and extensions to other catalyzed processes have been recently reported.<sup>16</sup>

**Conclusion.** This study demonstrates that  $\text{Me}_2\text{AlCl}$  and  $\text{MeAlCl}_2$  can efficiently promote chelate-controlled aldol and related allylsilane additions. Strict stoichiometry requirements, *i.e.* greater than two equiv of Lewis acid, must be met to achieve chelation control, and we propose a chloride ion metathesis process to account for these results. The exceptionally Lewis acidic cationic aluminum reagents exhibit generality in chelating  $\beta$ -silyloxy



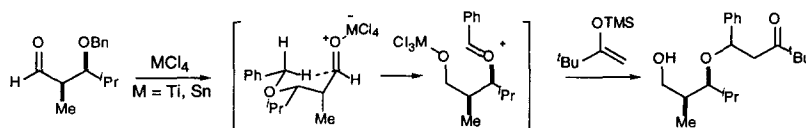
**Figure 1.** Selectivity vs. equiv of  $\text{Me}_2\text{AlCl}$ .

groups, and this observation eliminates the requirement of a specific alkoxy substituent to engage in chelate organization. We are pursuing the application of  $\text{Me}_2\text{AlCl}$  and  $\text{MeAlCl}_2$  in more complex aldol and other carbonyl addition processes.<sup>17</sup>

**Acknowledgment.** Support has been provided by the National Institutes of Health (GM-33327), Merck DuPont Pharmaceuticals, and Pfizer.

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- (9) See Ref. 6. In this study, we demonstrated that less sterically demanding enolsilanes, such as acetone enolsilane, will undergo anti-Felkin selective addition to aldehyde **1**.
- (10) General experimental procedure: Lewis acid was added to a solution of aldehyde (0.12-0.22 mmol) in  $\text{CH}_2\text{Cl}_2$  (0.1 M) at  $-78^\circ\text{C}$ . After 2 min, the enolsilane was added, the reaction was stirred 20 min. at  $-78^\circ\text{C}$ , and then quenched cold with saturated  $\text{NH}_4\text{Cl}$ . The mixture was warmed to room temp., poured into water, and extracted twice with  $\text{CH}_2\text{Cl}_2$ . The organic layers were dried ( $\text{MgSO}_4$ ), concentrated, and the unpurified product was purified by flash chromatography. Diastereoselectivity was determined by GLC analysis of the silyl (TMSCl) or acyl (Ac<sub>2</sub>O) derivative of the unpurified reaction mixture.
- (11) The stereochemistry of all products was established by  $^1\text{H}$  and  $^{13}\text{C}$  NMR analysis of acetone derivatives.
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