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# Increased Felkin–Anh Selectivity Using $AlMe_3$ in the Addition of Vinyllithiums to α-Chiral Aldehydes: Do “Ate” Complexes Play Any Role?

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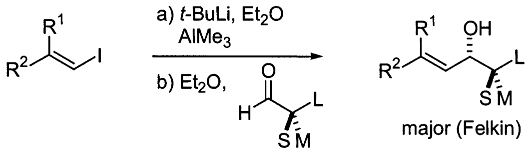
## ABSTRACT



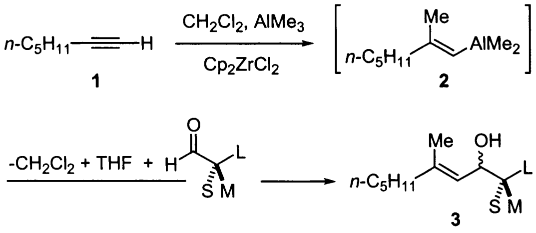
**$AlMe_3$ dramatically increases the diastereoselectivity of addition of vinyllithiums to α-chiral aldehydes but decreases that of methyllithium. Our results are explained in terms of an addition of the free vinyllithium on the $Me_3Al$–aldehyde complex.**

The addition of alkyl and alkenyl organometallics to α-chiral aldehydes bearing no chelating group generally proceeds with modest stereodifferentiation of the two faces of the carbonyl function (the Cram/anti-Cram problem).[1,2] The result is of course very dependent on the nature of the group α to the aldehyde, and in that respect, 2-phenylpropanal has served as a reference aldehyde against which selectivities are compared.[1a] The selectivity is also dependent on the nature and size of the alkyl portion of the nucleophile, the metallic counterion, and the solvent.[1a] Reports of the use of Lewis acids to enhance Cram diastereoselectivity with hard nucleophiles are scarce in the literature.[3−5] We wish to disclose a phenomenal increase in stereoselectivity in the addition of vinyllithiums to α-chiral aldehydes using $AlMe_3$ and discuss the reactivity of aluminum “ate” complexes in such additions.

We recently reported that vinylalanes could add to α-chiral aldehydes with stereoselectivities higher than that of the corresponding vinyllithium.[6] The vinylalanes in that study were all prepared by zirconium-catalyzed carboalumination of the corresponding alkyne, which involves 3 equiv of $AlMe_3$ in $CH_2Cl_2$. The aldehyde was then directly added to this mixture as a THF solution.

When we carried out experiments where the $CH_2Cl_2$ was evaporated from the vinylalane mixture and replaced by THF prior to adding the aldehyde (Scheme 1), we noticed a

**Scheme 1.** Additions of Vinylalanes to Aldehydes



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(1) (a) For a recent review, see: Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, *99*, 1191−1223. (b) See also: Yamaguchi, M. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I. Eds.; Pergamon: New York, 1991; Vol. 1, pp 325−353.

(2) (a) Barlett, P. A. *Tetrahedron* **1980**, *36*, 3−72. (b) Cram, D. J.; Abd Elhafez, F. A. *J. Am. Chem. Soc.* **1952**, *74*, 5828−5835.

(3) (a) Boucley, C.; Cahiez, G.; Carini, S.; Cerè, V.; Comes-Franchini, Knochel, P.; Pollicino, S.; Ricci, A. *J. Organomet. Chem* **2001**, *624*, 223−238. (b) Reetz, M. T.; Kyung, S. H.; Hüllmann, M. *Tetrahedron* **1986**, *42*, 2931−2935. (c) Lipshutz, B. H.; Ellsworth, E. L.; Siahaan, T. J. *J. Am. Chem. Soc.* **1988**, *110*, 4834−4835.

(4) For anti-Cram selectivity using bulky Al reagents, see: (a) Maruoka, K.; Itoh, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1985**, *107*, 4573−4576. (b) Maruoka, K.; Itoh, T.; Sakurai, M.; Nonoshita, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 3588−3597.

(5) Yamamoto, Y.; Yamada, J.-i. *J. Am. Chem. Soc.* **1987**, *109*, 4395−4396.

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dependence of the selectivity on the time of evaporation: longer evaporation times led to lower selectivities. Suspecting that varying quantities of $AlMe_3$ were being stripped from the solution in those experiments, we wondered if the excess $AlMe_3$ was in fact the cause of the higher selectivity observed in vinylalane additions. If so, could $AlMe_3$ be used to increase the stereoselectivity of addition of vinyllithiums to aldehydes?

Indeed, when varying quantities of $AlMe_3$ were added to an ethereal[7] solution of the vinyllithium derived from vinyliodides **7**−**9**[8] prior to the addition of the aldehyde (Figure 1), selectivities soared to levels even higher than that obtained from vinylalane additions (Table 1). The phenomenon seems to be general, and to the best of our knowledge, this is the first example where selectivities of addition of vinyllithiums to α-chiral aldehydes are dramatically increased by the use of a Lewis acid. Two aldehydes afforded >30:1 ratios of diastereomeric alcohols (entries 4 and 7). Aldehyde **6** gave ratios from 3:1 to 5:1, depending on the vinyllithium used (entry 10). This is substantially higher than the corresponding ratios obtained without $AlMe_3$ (entry 8). Three different di- or trisubstituted vinyllithiums gave similarly satisfying results (entry 4). The best results were obtained using 2.5 equiv of $AlMe_3$. However, catalytic amounts of $AlMe_3$ also increased the selectivity (entry 2).

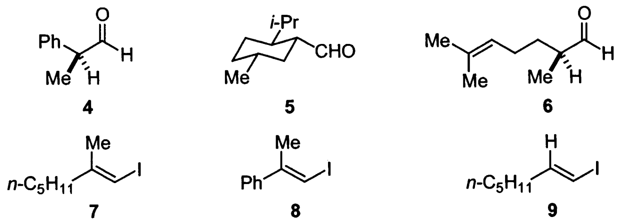
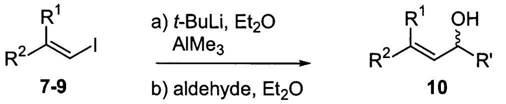


**Figure 1.** Aldehydes and vinyliodides of Table 1.

**Table 1.** Stereoselectivities of Addition of Vinyllithiums to Three Aldehydes in the Presence or Absence of $AlMe_3$



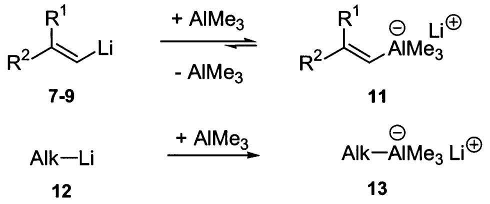
| | | $AlMe_3$ | Cram/anti Cram ratios[a] of **10** (% yield)[b] | | |
|---|---|---|---|---|---|
| entry | ald | (equiv) | from **7** | from **8** | from **9** |
| 1 | **4** | 0 | 12:1 (52) | 10:1 (62) | 10:1 (44) |
| 2 | **4** | 0.1 | 16:1 (57) | | |
| 3 | **4** | 1.0 | − (traces) | − (traces) | − (traces) |
| 4 | **4** | 2.5 | 40:1 (65) | 99:1 (56) | 41:1 (73) |
| 5 | **5** | 0 | 7:1 (75) | 5:1 (76) | |
| 6 | **5** | 1.0 | − (traces) | | |
| 7 | **5** | 2.5 | 80:1 (60) | 34:1 (50) | |
| 8 | **6** | 0 | 1.4:1 (59) | 1.4:1 (55) | |
| 9 | **6** | 1.0 | − (traces) | | |
| 10 | **6** | 2.5 | 3:1 (47) | 5:1 (60) | |

[a] Determined by GC. [b] Isolated yield.

Paradoxically, the addition of alkyllithiums to aldehyde **4** is less stereoselective in the presence of excess $AlMe_3$ than in the absence of $AlMe_3$. Indeed, the stereoselectivity of addition of methyllithium to aldehyde **4** fell from 7:1 with 0 equiv of $AlMe_3$ to 3:1 with 2 equiv of $AlMe_3$. Moreover, the addition of only 1 equiv of $AlMe_3$ affords no product. This observation was also noted in the addition of 1 equiv of vinyllithium **7** on all aldehydes with 1 equiv of $AlMe_3$ (Table 1, entries 3, 6, and 9).

In 1967, Zweifel and co-workers made ate complexes between vinylalanes (prepared by hydroalumination of terminal alkynes) and methyllithium and obtained 68% yield of alcohol upon reaction with acetaldehyde.[9] In contrast, tetralkylalanates were unreactive. They suggested that ate complexes were in fact unreactive and that the reactive species in the trialkylvinylalalanate reaction may not be the ate complex **11** but the free vinyllithium upon disproportionation (Scheme 2). They also suggested that the unfavorable dissociation of tetraalkyl ate complex **13** prevented its reaction.

**Scheme 2.** Disproportionation of Ate Complexes **11** and **13**



Many years ago, Heathcock proposed that a Lewis acid coordinated syn to the aldehydic hydrogen atom[10] forced a silyl enol ether to attack the carbonyl at an angle nearer to 90°, thus pushing it closer to the chiral center (Figure 2).[11]

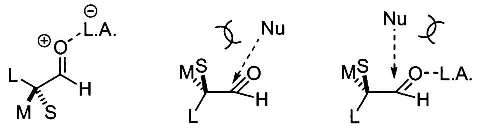


**Figure 2.** Effect of the Lewis acid on the angle of attack on the carbonyl.

In our case, it could be that the free vinyllithium (from the dissociation of **11**)[9] reacts with the reactive $Me_3Al$−aldehyde complex when there is excess $AlMe_3$, giving high diastereomeric ratios of **10** in accordance with Heathcock's hypothesis.[10]

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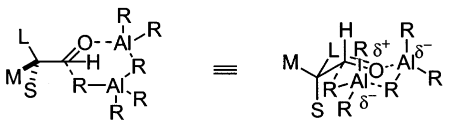
However, we cannot rule out the possibility that the ate complex adds to the activated aldehyde in this case. When we used a catalytic amount of $AlMe_3$ (Table 1, entry 2), most of the $AlMe_3$ is likely to be tied up as the ate complex **11**. It is possible in this case that the free vinyllithium adds mainly to unactivated aldehyde because of the low concentration of $AlMe_3$ available for coordination, resulting in a smaller increase in selectivity. However, if the disproportionation of **11** did not occur at all to release some $AlMe_3$ for coordination, we would expect no increase at all in the selectivity. Finally, if exactly 1 equiv of $AlMe_3$ is used, the concentrations of both the free vinyllithium and free $AlMe_3$ are low, resulting in a sluggish reaction.

How can we explain the fact that methyllithium does not add to α-chiral aldehydes with increased selectivity when in the presence of $AlMe_3$? If the disproportionation of the tetralkylalanate into alkyllithium and $AlMe_3$ is not favorable, as Zweifel suggested,[9] then the reactive species is likely to be the excess $AlMe_3$ itself. This is supported by the fact that a 1:1 mixture of RLi and $AlR_3$ is unreactive as well as by the fact that 1 equiv of MeLi in the presence of 3 equiv of $AlEt_3$ led exclusively to the ethylation of **4**.

We tested the stereoselectivity of addition of $Me_3Al$ alone to support this hypothesis and found that its addition to aldehyde **4** is only modestly stereoselective (3:1). This result may be explained by an intramolecular six-membered transition state (TS) (Scheme 3).[12,13] This particularity could force the nucleophile away from perpendicularity and partly cancel the effect shown in Figure 2.

**Scheme 3.** Six-Centered TS in the Addition of $AlR_3$



In conclusion, we have shown that the addition of vinyllithiums to α-chiral aldehydes is markedly more selective when $AlMe_3$ is added to the mixture. Our results open interesting questions about the mechanism of addition of organoaluminum to aldehydes and the role played, if any, by the ate complex. Further exploration of these issues is ongoing in our laboratory.

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**Supporting Information Available:** Experimental and NMR spectra for each compound. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) THF is decomposed rapidly by *t*-BuLi in the presence of trimethylaluminum even at −78 °C.

(8) Negishi, E.-i.; Van Horn, D. E.; Yoshida, T. *J. Am. Chem. Soc.* **1985**, *107*, 6639−6647.

(9) Zweifel, G.; Steele, R. B. *J. Am. Chem. Soc.* **1976**, *89*, 2754−2755.

(10) Reetz, M. T.; Hüllmann, M.; Massa, W.; Berger, S.; Rademacher, P.; Heymanns, P. *J. Am. Chem. Soc.* **1986**, *108*, 2405−2408.

(11) Heathcock, C. H.; Flippin, L. A. *J. Am. Chem. Soc.* **1983**, *105*, 1667−1668.

(12) Addition of $AlR_3$ onto carbonyls has been extensively studied, and the 6-centered transition state is thought to be favored when more than 1 equiv of $AlR_3$ is involved. See: Evans, D. A. *Science* **1988**, *240*, 420−426.

(13) (a) Ashby, E. C.; Smith, R. S. *J. Organomet. Chem.* **1982**, *225*, 71−85. (b) Ashby, E. C.; Smith, R. S. *J. Org. Chem.* **1977**, *42*, 425−427. (c) Neumann, H. M.; Laemmle, J.; Ashby, E. C. *J. Am. Chem. Soc.* **1973**, *95*, 2597−2603. (d) Ashby, E. C.; Laemmle, J.; Neumann, H. M. *J. Am. Chem. Soc.* **1968**, *90*, 5179−5188.