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Increased Felkin–Anh selectivity in nucleophilic additions to α-chiral aldehydes using vinylalanes

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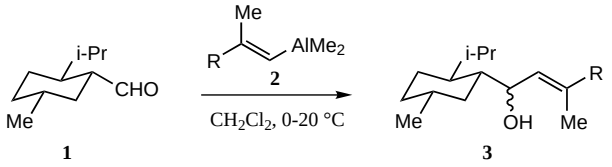
Abstract—Vinylalanes, prepared from the zirconium-catalyzed carboalumination of alkynes, were added directly to aldehydes bearing an alpha chiral carbon to give good yields of the corresponding alcohols. The addition was more stereoselective than the addition of the corresponding vinyllithium or vinylmagnesium bromide. © 2002 Published by Elsevier Science Ltd.

The stereoselectivity of nucleophilic addition to chiral aldehydes and ketones was rationalized thanks to contributions by Felkin, Anh, and Eisenstein many years ago.[1,2] Although the Felkin–Anh rule has proven a highly reliable tool for predicting the stereochemical outcome of the irreversible addition of nucleophiles to aldehydes and ketones, the selectivities are generally modest for Grignard-type nucleophiles.[3] This is especially true for aldehydes bearing two alpha *n*-alkyl groups.

Recently, we disclosed our findings that vinylalanes added to menthylcarboxaldehyde **1** with high stereoselectivity, while the corresponding or similar vinyllithiums or vinylmagnesium bromides added with selectivities of 2–3:1 (Table 1).[4] The good chemical yields obtained in theses additions were also a pleasant surprise. A prior report by Newman[5] indicated that the direct addition of vinylalanes afforded alcohols in poor yield. Perhaps this explains why vinylalanes are generally transformed to the corresponding vinylhalide first and metalated again before addition to aldehydes or ketones. As far as we know, the stereoselectivity of the addition of vinylalanes and trialkylalanes onto chiral aldehydes has not been probed in detail. We are aware of only two reports of the stereoselective addition of trivinylalane to Garner's aldehyde giving a modest ratio of 2:1.[6,7]

Curious to see if vinylalanes added selectively to other chiral aldehydes,[8] we initiated a comparative study of their addition to various aldehydes with respect to vinyllithium and magnesium (Table 2).[9] Vinylalane **8a** added to aldehyde **4** (Fig. 1) with superior diastereoselectivity to **8b** and **8c** (entry 1). Wipf and co-workers reported that the vinylzinc corresponding to **2a** (Table 1, $AlMe_2 = ZnMe$) added to aldehyde **4** to give a 5.6:1 ratio of alcohols.[10] In the case of **8a**, when dichloromethane was replaced by tetrahydrofuran prior to the addition of aldehyde **4**, a 16:1 ratio of alcohols was obtained. This suggests that the solvent is not a major factor in the selectivity of addition of vinylalanes to **4**. Aldehyde **5** was converted to the corresponding alcohol by vinylalane **8a** with good stereoselectivity (entry 3). The 2:1 ratio of diastereomers of the starting aldehyde **5** was unchanged in the product. While the

Table 1. Ratio and yield of **3** generated in the addition of vinylalanes **2** to chiral aldehyde **1**



Entry	2	R	3 (β:α)[a]	Yield (%)[b]
1	**a**	*n*-Bu	12:1	70
2	**b**	$TBSO(CH_2)_3$	8:1	68
3	**c**	$HOCH_2$	10:1	85
4	**d**	*c*-C_6H_{11}	14:1	80
5	**e**	Ph	18:1	63
6	**f**	$PhCH_2$	11:1	76

[a] Ratios determined by GC.

[b] Isolated yield of pure mixtures of isomers. All isomers were separable by normal silica gel column chromatography.

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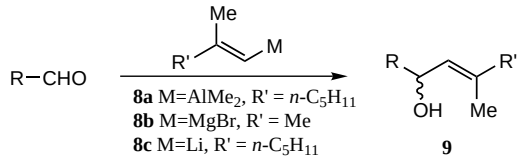
Table 2. Ratio and yield of allylic alcohols **9** generated in the addition of vinylmetals **8** to chiral aldehydes[11]



Entry	R-CHO	**9** from **8a**	**9** from **8b**	**9** from **8c**
1	**1**	15:1 (83)[a]	2:1 (62)	2:1 (62)
2	**4**[b]	20:1 (85)	4:1 (60)	9:1 (55)
3	**5**[c]	12:1 (65)	3:1 (45)	2.5:1 (34)
4	**6a**	3:1 (87)	1.5:1 (46)	1.5:1 (56)
5	**6b**	1:1 (84)	1:1 (58)	1:1 (57)
6	**7a**	2:1 (46)	2:1 (12)	1:2 (11)
7	**7b**	2.5:1 (82)	4:1 (47)	3:1 (49)

[a] All ratios determined by GC and % isolated yield of pure **9** as mixtures of isomers in parentheses. Isomers from aldehydes **1**, **5** and **7a** were separable by chromatography, all others were not.

[b] A ratio of 5.6:1 was obtained when a vinylzinc was added to **4**; see Ref. 10.

[c] The 2:1 ratio of diastereomers in the starting aldehyde **5** was unchanged in product.

selectivity of addition of vinylalane **8a** to aldehyde **6a**, bearing a *n*-alkyl chain, proceeded with modest selectivity (3:1), the same addition using vinyllithium or vinylmagnesium bromide gave a nearly equal mixture of both diastereomers (entry 4). A β-chiral center had no influence on the selectivity as shown by the non-stereoselective addition of all vinylmetals to aldehyde **6b** (entry 5).

When a chelating group was present on the alpha carbon, as in aldehydes **7a** or **7b**, the stereoselectivity dropped, a result consistent with the findings of Garner and Coleman (entries 6 and 7).[4,5] Interestingly, the sense of induction for aluminum and lithium was opposite that of magnesium, though the differences were small. The major isomer in the case of the vinylmagnesium halide addition corresponded to a Cram-chelate addition while the other two vinylmetals furnished Felkin–Anh products.

We also investigated the selectivity of addition of alkylmetals to aldehyde **4**. Surprisingly, trimethylaluminum added to aldehyde **4** with low stereoselectivity (Table 3, entry 1) compared to vinylalane **8a** (Table 2, entry 2). This was not the case with methyllithium and methylmagnesium bromide (Table 3, entries 3 and 4), which added to aldehyde **4** with selectivities similar to the

Table 3. Ratio and yield of allylic alcohols generated in the addition of alkylmetals to chiral aldehyde **2**

Entry	Reagent	Solvent	Ratio	Yield[a]
1	$AlMe_3$	CH_2Cl_2	2.6:1	87
2	$AlMe_3$	THF	–	0
3	MeMgBr	THF	3.8:1	52
4	MeLi	THF	10.6:1	47

[a] % isolated yield.

addition of vinyl Grignard reagents **8b** and **8c**, respectively (Table 2, entry 2). This observation is puzzling and suggests that the rational for the stereoselective addition of vinylalanes may be more complex than first anticipated. We initially believed that the size of the metal in vinylalanes as compared to the corresponding lithium or magnesium derivatives was the main factor for the stereoselectivity of addition. Indeed, this argument has been used many times to explain the differences in Felkin–Anh selectivity between various alkylmetals.[1] However, our result with trimethylaluminum seems to contradict that hypothesis. Performing the addition of trimethylaluminum in tetrahydrofuran killed the reaction entirely (entry 2, Table 3).

In conclusion, we have shown that vinylalanes derived from the zirconium-catalyzed carboalumination of alkynes add stereoselectively to α-chiral aldehydes. Other vinylmetals give lower selectivities and often lower yields as well. Accessibility to a wide variety of vinylalanes remains an issue to be solved. Trialkylalanes are less selective, a result that poses a very interesting mechanistic question. Investigations are continuing in our laboratories.

Acknowledgements

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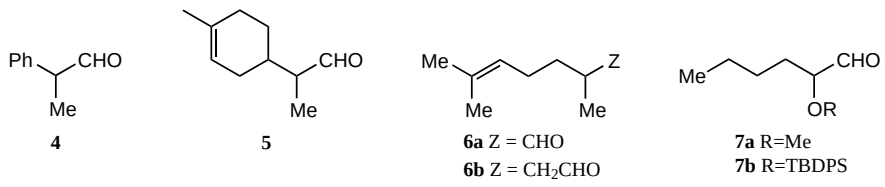

Figure 1. Aldehydes used in the additions listed in Table 2.

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8. Typical experimental procedure: Dichlorobiscyclopentadienyl zirconium (0.558 g, 1.91 mmol) was dissolved in dichloromethane (25 mL). Neat trimethylaluminum (0.22 mL, 2.29 mmol) was added dropwise and the yellowish solution was stirred 10 min before cooling to 0°C. *n*-Heptyne (0.10 mL, 0.76 mmol) was then added and the mixture stirred for 24 h. The resulting solution containing the vinylalane was cooled to −78°C and 2-phenylpropionaldehyde **4** (78 μL, 0.59 mmol) in THF was added. The reaction was monitored by TLC and warmed to 0°C before a saturated aqueous potassium carbonate solution was added slowly until gas evolution ceased. The white suspension was taken up in 1N HCl and the mixture vigorously stirred for 30 min. A typical work-up was then performed, extracting with dichloromethane. Final purification was done by silica gel flash column chromatography. The ratios of products were determined by GC on the crude product after identification of each GC peak was ascertain by GC mass spec. on the purified mixture. Ratios were corroborated by proton NMR. Isomers of **9** obtained from aldehydes **1**, **5**, and **7a** were separable by chromatography on silica gel.
9. All new compounds gave satisfactory ^{1}H NMR, IR, and mass spec. data.
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11. Major isomer of **9** from **4**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36–7.17 (m, 5H), 5.08 (dd, 1H, $J=8.8$, 0.6 Hz), 4.44 (dd, 1H, $J=8.9$, 6.2 Hz), 2.88 (qi, 1H, $J=6.9$ Hz), 1.91 (t, 2H, $J=7.5$ Hz), 1.53 (d, 3H, $J=0.8$ Hz), 1.41 (s, 1H), 1.34 (d, 3H, $J=7.1$ Hz), 1.33–1.07 (m, 6H), 0.87 (t, 3H, $J=7.2$ Hz); IR (neat, cm^{-1}): 3376; LRMS (m/z): 228 ($M-H_2O$, 10), 86 (90), 84 (100); exact mass calcd for $C_{17}H_{24}$ (M^+-H_2O): 228.1878, found: 228.1874. Major isomer **9** from **5**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.38 (s, 1H), 5.18 (d, 1H, $J=8.6$ Hz), 4.30 (t, 1H, $J=8.5$ Hz), 2.03–1.88 (m, 5H), 1.80–1.69 (m, 3H), 1.67 (d, 3H, $J=0.8$ Hz), 1.64 (s, 3H), 1.60–1.55 (m, 3H), 1.46–1.21 (m, 6H), 0.91–0.86 (m, 3H), 0.75 (d, 3H, $J=7.0$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): 139.6 (d), 133.9 (s), 126.2 (d), 120.8 (s), 70.0 (d), 43.6 (d), 39.7 (d), 33.9 (t), 31.5 (t), 30.9 (t), 28.1 (t), 27.4 (t), 26.4 (t), 23.4 (t), 22.5 (q), 16.6(q), 14.0 (q), 10.4 (q); IR (pur, cm^{-1}): 3389; LRMS (m/z): 264 (M^+, 5), 246 [(M^+-H_2O), 20], 152 (100), 141 (95), 95 (80), 94 (90); exact mass calcd for $C_{18}H_{32}O$: 264.2453, found: 264.2457. **9** from **6a** ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.19 (d,1H, $J=8.9$ Hz), 5.13–5.06 (m, 1H), 4.20–4.14 (m, 1H), 2.08–1.90 (m, 4H), 1.67 (d, 3H, $J=2.7$ Hz), 1.66 (d, 3H, $J=0.8$ Hz), 1.67–1.01 (m, 10H), 0.94 (d, 3H, $J=6.6$ Hz), 0.95–0.85 (m, 6H); IR (pur, cm^{-1}): 3353; LRMS (m/z): 252 (M^+), 141 (100); exact mass calcd for $C_{17}H_{32}O$: 252.2453, found: 252.2458. Major isomer of **9** from **7a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.13 (d, 1H, $J=9.3$ Hz), 4.25 (t, 1H, $J=8.4$ Hz), 3.44 (s, 3H), 3.08–3.02 (m, 1H), 2.02 (t, 2H, $J=7.5$ Hz), 1.70 (s, 3H), 1.68–1.10 (m, 13H), 0.93–0.86 (m, 6H); IR (neat, cm^{-1}): 3439; LRMS (m/z): 225 (M–OH, 20), 141 (100), 101 (95); exact mass. calcd for $C_{15}H_{29}O$: 225.2218, found: 225.2213.