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Diastereoselectivity Enhancement in Vinylcuprate Addition to β-Alkoxyaldehydes Via a Vinylsilane.

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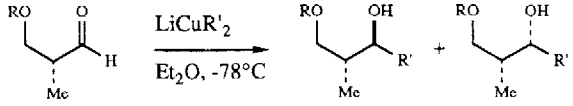
Summary: The presence of a removable 1-(trimethylsilyl) residue greatly increases the chelation-controlled diastereoselectivity in alkenylcuprate additions to chiral β-alkoxyaldehydes Several methods for protiodesilylation of the resultant allylic alcohols [5 → **2b** (R=$Me_3SiCH_2CH_2OCH_2$-, $PhCH_2OCH_2$-, and $PhCH_2$-)] are compared

Chelation-controlled addition of carbon nucleophiles to α- and β-alkoxy carbonyls has proven to be a powerful method for 1,2-asymmetric induction [2] The sequence in eq 1 is illustrative, where chelation-controlled addition to the α-chiral β-alkoxy aldehyde **1** leads mainly to diastereomer **2** The highly reactive aldehyde carbonyl and the need for a six-membered chelate dictate the use of cuprate nucleophiles for stereoselective addition. Unfortunately, cuprates wherein the carbon ligand is sp^2-hybridized exhibit poor-to-moderate stereoselectivity [2c] We report here a method for the highly stereoselective production of the desired isomer **2b**

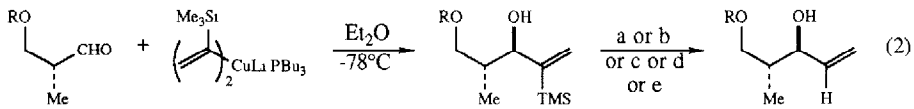


(a) R' = n-alkyl **2/3** ≥ 15:1
(b) R' = vinyl **2/3** ≤ 5 1 (1)

1 **2a, b major** **3a,b minor**

Addition of the α-(trimethylsilyl)vinyl cuprate **4**[3] to three β-alkoxy aldehydes of general structure **1** is detailed in eq. 2 and the accompanying table. The addition of the α-(trimethylsilyl)vinyl residue proceeded in high yield in each case (84 → 92%) and with high chelation-controlled selectivity (≥ 17 1), producing **5** as the major diastereomer

Several methods for the protiodesilylation of the vinylsilane residue to produce the general structure **2b** from **5** are also described in eq 2 and the table. Methods (a),[4] (b),[4] and (e)[5] involved fluoride-induced desilylation *C*-to-*O* silyl migration catalyzed by NaH in HMPA[6] or DMPU[6] provides the basis of methods (c) and (d) In the event of vinylsilane cleavage in the presence of the SEM-ether[7] (entry 1), method (a) was decidedly superior. Method (e) (entry 3) has proven to be especially convenient on large scale. At 0 5 M in DMF, the vinylsilane **5** (R=$PhCH_2$-) was treated with 3 equiv of $KF{\cdot}2H_2O$ in the presence of 0 5 equiv of 18[crown]6 at 85°C.[5]



(2)

1 **4** **5** **2b**

entry	R	% Yield **5**, Ratio①	Desilylation (method②, % Yield **2b**)
1	$Me_3SiCH_2CH_2OCH_2$–	88, 17:1	(a) 98, (b) 58; (c) 61, (d) 65
2	$PhCH_2OCH_2$–	84, 18·1	(a) 93; (b) 84, (c) 80; (d) 74
3	$PhCH_2$–	92, >20 1	(a) 85, (b) 73, (c) 78, (d) 77; (e) 98

① Ratios were determined by high-field ^1H NMR and HPLC.

② (a) $Bu_4NF{\cdot}3H_2O$, CH_3CN, 80°C (b) $Bu_4NF\ 3H_2O$, DMSO, 150°C. (c) 10 mol % NaH, HMPA, 25°C (d) 10 mol % NaH, DMPU, 25°C. (e) $KF{\cdot}2H_2O$, 18-C-6, DMF, 85°C

Representative Experimentals:

*Chelation-controlled cuprate addition, **1** → **5** (R=PhCH$_2$OCH$_2$-).* To a magnetically stirred solution of α-(trimethylsilyl)vinyl bromide[3b] (21 43 g, 119 6 mmol) in Et$_2$O (117 mL) at -78°C was added *t*-BuLi (1 7 **M** in pentane, 140 0 mL, 238 0 mmol) The solution was warmed to -50°C and stirred for 2 h. The vinyllithium reagent was then transferred via cannula to a solution of Bu$_3$P·CuI (22.68 g, 57 9 mmol) in ether (60 mL) at -78°C The solution was warmed to -40°C and stirred for 3 h Aldehyde **1**(R=PhCH$_2$OCH$_2$-, 7 92 g, 38 0 mmol) was added via syringe pump in ether (38 mL) over 30 minutes Stirring was continued for 2 h at -78°C The reaction mixture was then quenched with a 1 1 NH$_4$OH (3%)·NH$_4$Cl$_{(sat)}$ solution and the layers partitioned The aqueous layer was extracted with ether, the organics combined, dried (MgSO$_4$), filtered, concentrated *in vacuo* and the residue purified by flash column chromatography (elution with 3 1 hexane ether) to yield 9 88 g (84%) of **5** (R=PhCH$_2$OCH$_2$-) as an 18·1 ratio of diastereomers [8]

*Desilylation with Bu$_4$NF·3H$_2$O [Method (a)], **5** → **2b** (R=PhCH$_2$OCH$_2$-)* To a magnetically stirred solution of **5** (R=PhCH$_2$OCH$_2$-) (513 mg, 1.66 mmol) in CH$_3$CN (16 mL) was added Bu$_4$NF·3H$_2$O (1 03 g, 3 26 mmol) and stirring was continued at 80°C for 3 h The reaction mixture was concentrated to half of the original volume and partitioned between ether (20 mL) and water (20 mL) The layers were partitioned and the aqueous layer was saturated with NaCl and extracted with ether (2 x 20 mL) The organic layers were combined, dried (MgSO$_4$), filtered, concentrated, and the residue purified by flash column chromatography (elution with 1:1 ether hexane) to afford 364 mg (92%) of the desilylated product **2b** (R=PhCH$_2$OCH$_2$-) [9]

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1 (a) Recipient of a National Science Foundation Presidential Young Investigator Award (1984-89); Research Fellow of the Alfred P Sloan Foundation (1984-88) (b) Recipient of a Squibb Graduate Fellowship

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8 **Data for 5** (R=PhCH$_2$OCH$_2$-). Pale yellow oil, R$_f$ 0 29 (3.1 hexane.ether), IR (neat) 3495 (br), 3031, 2955, 2934, 2877, 1496, 1455, 1407, 1381, 1285, 1248, 1206, 1170, 1146, 1109, 1044, 1028, 997, 960, 935, 905, 839, 738, 697, 657 cm^{-1}, ^{1}H NMR (CDCl$_3$, 270 MHz) δ 7 33 (m, 5 H), 5 76 (dd, 1 H, J = 2.7, 1.3 Hz), 5.49 (dd, 1 H, J = 2.7, 0.9 Hz), 4.74 (s, 2 H), 4.59 (s, 2 H), 4 13 (m, 1 H), 3.71 and 3.60 (AB part of ABX, 2 H, J$_{AB}$ = 9 4 Hz, J$_{AX}$ = 9 4 Hz, J$_{BX}$ = 11 5 Hz), 3.06 (d, 1 H, J = 4 1 Hz), 1 94 (m, 1 H), 0 92 (d, 3H, J = 7 0 Hz), 0 13 (s, 9 H), ^{13}C NMR (CDCl$_3$, 67 5 MHz) δ 153 7, 137 6, 128 4, 127 9, 127.7, 125 9, 94 7, 82 1, 71 8, 69 5, 37.3, 15.0, -0 32, HRMS (70 eV) m/e (M-OH) 291 1779. {calcd for C$_{17}$H$_{28}$O$_3$Si, m/e (M-OH) 291 1780}

9 **Data for 2b**(R=PhCH$_2$OCH$_2$)· Yellow oil, R$_f$ 0 39 (1 1 ether hexane), IR (neat) 3462 (br), 3087, 3066, 3031, 3006, 2962, 2932, 2880, 1497, 1454, 1424, 1408, 1381, 1280, 1260, 1233, 1207, 1171, 1142, 1109, 1078, 1043, 1028, 995, 960 cm^{-1}, ^{1}H NMR (CDCl$_3$, 270 MHz) δ 7.36 (m, 5H), 5 87 (ddd, 1 H, J = 17.1, 10 4, 6 7 Hz), 5 28 (ddd, 1 H, J = 17 1, 3.0, 1 3 Hz), 5 18 (ddd, 1 H, J = 10 1, 2 7, 1 0 Hz), 4 76 (s, 2 H), 4 61 (s, 2 H), 4 05 (m, 1 H), 3 72 and 3.59 (AB part of ABX, 2 H, J$_{AB}$ = 9 61 Hz, J$_{AX}$ = 9 22 Hz, J$_{BX}$ = 12.86 Hz), 2.81 (d, 1 H, J = 3.6 Hz), 1.89 (m, 1 H), 0 95 (d, 3 H, J = 7 0 Hz), ^{13}C NMR (CDCl$_3$, 67 5 MHz) δ 139.3, 137.6, 128.4, 127.8, 127 7, 115.8, 94.6, 77 5, 71 3, 69.4, 38.5, 13 6: HRMS (70 eV) m/e (M-OCH$_2$C$_6$H$_5$) 129.0909. {calcd. for C$_{14}$H$_{20}$O$_3$, m/e (M-OCH$_2$C$_6$H$_5$) 129.0915}

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