

Regio- and Stereo-selective Reaction of Chiral Alkoxy- and Aminomethyl-substituted α -Silylallyl Carbanions with Aldehydes†

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The reactions of chiral alkoxy- and aminomethyl-substituted α -silylallyl carbanions with aldehydes gave 1-silyl-homoallylic alcohols with high γ -regioselection and *E*-stereoselection, as well as a diastereomeric excess of 8–69%, depending on the chiral substituents on silicon, the aldehydes and the base used.

α -Silylallyl carbanions¹ have been used extensively as synthetic intermediates, since the silyl group can be subsequently transformed to other electrophile equivalents thus enhancing its usefulness in synthesis.² When the carbanions are allylic in nature, the reactions of silylallyl anion **1** with various electrophiles can occur at either the α - or the γ -position giving the α -product **2** or the γ -product **3** respectively. In the case of the γ -product **3**, there is an additional complexity in terms of the stereochemistry of the double bond produced which can have either the *E*- or the *Z*-configuration. It was found that changing the substituents on silicon showed some promise in the control of regio- and stereo-selectivity. If a chiral allylsilane was used to generate chiral α -silylallyl carbanion, asymmetric induction of the chiral substituent on silicon should be observed. Herein, we wish to report regio- and stereo-selectivity of the reactions of chiral alkoxy- and aminomethyl-substituted α -silylallyl carbanions with aldehydes.

The parent compounds, chiral alkoxyallyldimethylsilanes **4a–c**, were prepared through the condensation of allylchlorodimethylsilane **5** with chiral alcohols, (–)-menthol **6a** or *N*-methyl-(1*R*,2*S*)-(–)-ephedrine **6b**,³ while chiral allyl-(aminomethyl)dimethylsilanes **7a,b** were obtained via the condensation of allyl(chloromethyl)dimethylsilane **8** with chiral amines, *O*-methyl-(–)-ephedrine **9a** or (*S*)-(+)-2-(methoxymethyl)pyrrolidine **9b**.⁴

The reactions of chiral allylalkoxysilanes **4a–c** in the presence of Lewis base, Schlosser's base ($\text{Bu}^n\text{Li}-\text{Bu}^t\text{OK}$)⁵ or lithium diisopropylamide (LDA), generated the anions **10a–c**, which reacted with aldehydes giving γ -(*E*) products **11–13** exclusively in high yield (Table 1, Scheme 1). The *E*-configuration of the double bond formed was deduced by ¹H NMR: a double triplet at δ 6.2 and a doublet at δ 5.7 with *J* 18.2. It is interesting that the high γ -regioselection⁶ in the reactions of alkoxy-substituted α -silylallyl anion **10a–c**

with aldehydes contrasts the favorable α -regioselection for halides under the same Lewis base conditions.⁷ Diastereoselectivities (de) of the reactions of **10a,b** with aldehydes are low (8–16%), which was determined by the diastereomeric proton, and carbon resonances and the use of a chiral shift reagent [(+)-Eu(hfc)₃]. When 2-methylallylsilane **4c** was used, the de of the product **13** was improved slightly to 26%.

An aminomethyl substituent on silicon leads to another type of effective regio- and stereo-controlling group. Chan and coworkers⁴ reported that the asymmetric alkylation of chiral aminomethyl-substituted α -silylallyl anions with alkyl halides exhibited high α -selection and diastereoselectivity (de > 90%). These results encouraged us to investigate the regio- and stereo-chemistry of the reactions of chiral aminomethyl-substituted α -silylallyl carbanions with aldehydes. Chiral (aminomethyl)allylsilanes **7a,b** were deprotonated to the corresponding chiral aminomethyl-substituted silylallyl carbanions **14a,b** in the presence of Schlosser's base. **14a,b** reacted with aldehydes to give 1-silyl-homoallylic alcohols **15** and **16**. In contrast to the α -selection of the alkylation,⁴ all the reactions of aminomethyl-substituted α -silylallyl carbanions with aldehydes produced the γ -isomer exclusively, with the exception of the case of use of $\text{Bu}^n\text{Li}-\text{TMEDA}$ as Lewis base, in which the α -isomer (α -**15a**, 20% yield) was isolated from the product mixture (entry 7). On the other hand, the γ -products are a mixture of *E*- and *Z*-isomers (Table 1, Scheme 1). The *Z*-configuration of the double bond formed was proved by ¹H NMR: a double triplet at δ 5.6 and a doublet at δ 5.3 with *J* 15.4, while the *E*-configuration was shown by a double triplet at δ 6.05 and a doublet at δ 5.73. As Chan and Labrecque⁸ have demonstrated, the α -silylallyl anion can exist as three species: *exo*-**17**, *endo*-**18** and an open form **19**.⁹ The aminomethyl group on silicon may coordinate with a neighbouring metal ion, leading to *exo*-**17**, which effected

Table 1 Regio- and stereo-selection of silylallyl anions with aldehydes

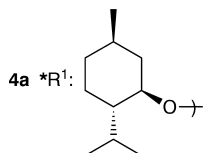
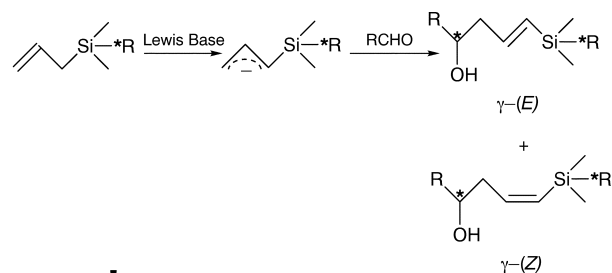
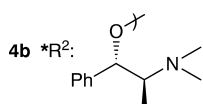
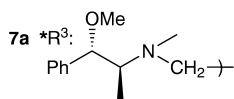
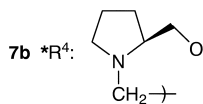
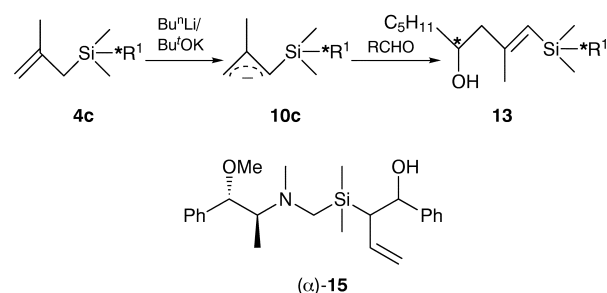
Entry	Silane ([α] _D)	Base ^a	Anion	Aldehyde (R)	Product	Yield (%) ^b ($\gamma_E + \gamma_Z$)	γ_E (de, %) : γ_Z (de, %)
1	4a (–59.7)	A	10a	C ₅ H ₁₁	11 γ -(<i>E</i>)	92	(8) — ^c
2	4a	B	10a	C ₅ H ₁₁	11 γ -(<i>E</i>)	60	(12) —
3	4b (–37.2)	A	10b	Ph	12a γ -(<i>E</i>)	82	(16) —
4	4b	A	10b	C ₅ H ₁₁	12b γ -(<i>E</i>)	75	(14) —
5	4c (–50.3)	A	10c	C ₅ H ₁₁	13 γ -(<i>E</i>)	70	(26) —
6	7a (–44.8)	A	14a	Ph	15a γ -(<i>E</i>)	90	(54) —
7	7a	C	14a	Ph	15a γ -(<i>E</i> + <i>Z</i>) + α - ^d	70	7 (48) : 1
8	7a	A	14a	C ₅ H ₁₁	15b γ -(<i>E</i> + <i>Z</i>)	75	1 (21) : 1.5 (8)
9	7b (–78.2)	A	14b	Ph	16a γ -(<i>E</i> + <i>Z</i>)	90	8 (69) : 1
10	7b	A	14b	C ₅ H ₁₁	16b γ -(<i>E</i> + <i>Z</i>)	87	1.2 (52) : 1 (14)
11	7b	A	14b	C ₂ H ₅	16c γ -(<i>E</i> + <i>Z</i>)	82	1 : 2 (11)

^aLewis base: A, $\text{Bu}^n\text{Li}-\text{Bu}^t\text{OK}$; B, LDA; C, $\text{Bu}^n\text{Li}-\text{TMEDA}$; ^bisolated yield; ^cexclusive γ -*E* isomer; ^d α -isomer in 20% isolated yield.

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the attack of the alkyl cation of alkyl halides occurring at the α -position. However, the aldehydic carbonyl would participate in coordination with the counterion (transition state **20**), so the attack of the carbonyl group took place at

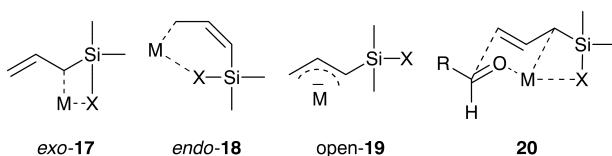
10a *R¹11 R: C₅H₁₁ *R¹10b *R²12a R: Ph *R²12b R: C₅H₁₁ *R²14a *R³15a R: Ph *R³15b R: C₅H₁₁ *R³14b *R⁴16a R: Ph *R⁴16b R: C₅H₁₁ *R⁴16c R: C₂H₅ *R⁴

(α)-15

Scheme 1

the γ -position via an S_E2' type process, leading to γ -selection. Meanwhile, the species *endo*-18 would be responsible for the formation of the *Z*-isomer and the open form 19 for both γ - and α -isomers, depending on the base used as in the case of entry 7. The *E/Z* ratios also depend on the structure of the aldehydes. For benzaldehyde, *E/Z* is larger than that for the aliphatic aldehydes (entries 6 and 9 *cf.* 8 and 10). For propionaldehyde (entry 11), the *E/Z* ratio of the product 16c is even reversed (1:2).

Change of the substituent on silicon from a chiral alkoxy group to a chiral aminomethyl group led to an increase in the *de* of the γ -(*E*) isomer produced of up to 69% (Table 1). Comparing the *de* of γ -(*E*)-12a (entry 3) with that of γ -(*E*)-15a (entry 6), it is worth noting that although the configuration of the chiral ephedrine moiety is the same (1*R*,2*S*) in 4b and 7a, and different only in the mode of connection of the chiral group with silicon, Si-O**R* and Si-C-N**R*, the *de* of the products is markedly different: 16% for 4b and 54% for 7a. This is ascribed to the fact that



Scheme 2

the aminomethyl group on silicon could coordinate with the metal ion forming a five-membered ring, which is more stable than the four-membered ring formed in the case of alkoxyallyl silanes. At the same time, the stereocontrol ability of the more rigid (*S*)-2-(methoxymethyl)pyrrolidine moiety is better (*de* of 16a up to 69%) than that of the *O*-methyl(-)-ephedrine moiety.

Experimental

General Procedure.—To an ice-cooled suspension of KOBu^t (22 mmol) in dried hexane (15 ml) BuⁿLi solution (1.6 M in hexane, 22 mmol) was added dropwise. The mixture was cooled to -70°C . Diethyl ether (10 ml) was added, followed by a solution of 7a (20 mmol) in diethyl ether (10 ml). The mixture was allowed to warm to room temperature for 4 h and cooled to -78°C before addition of benzaldehyde (20 mmol) in ether (10 ml). The mixture was stirred at this temperature for 6 h, and then at room temperature for 12 h. Then, the mixture was poured into an aqueous saturated solution of ammonium chloride (50 ml). The organic layer was dried (MgSO₄) and evaporated to produce crude product which was purified by flash chromatography (neutral Al₂O₃ column; eluent: light petroleum-ethyl acetate, 10:1) to give as a colorless liquid γ -(*E*)-15a (Found: C, 72.72; H, 8.87; N, 3.52. C₂₄H₃₅NO₂Si requires C, 72.49; H, 8.86; N, 3.52%). $\nu_{\text{max}}/\text{cm}^{-1}$ (film) 3350, 2940, 1610, 1250. δ_{H} 0.00 (6 H, s, SiCH₃), 1.02 (3 H, d, *J* 6.2, CH₃), 1.45 (1 H, br s, OH), 2.02 (2 H, d, *J* 8.2, NCH₂), 2.20 (3 H, s, NCH₃), 2.4–2.9 (2 H, m), 3.24 (3 H, s, OCH₃), 4.22 (1 H, d, *J* 6.0, PhCH), 4.6–4.8 (1 H, m, PhCH), 5.73 (1 H, d, *J* 18.6, 1-H), 6.05 (1 H, dt, *J* 18.6, 6, 2-H), 7.1–7.6 (10 H, m, Ar-H); δ_{C} -3.0 (-3.1), 7.4, 41.3, 44.8 (44.7), 47.0, 56.6, 66.3, 72.8 (72.9), 85.7, 128.5–125.7 (2 \times C₆H₅), 133.7, 144.0 (143.1). The NMR data in parentheses are for the second diastereoisomers (as below).

γ -(*E*)-15b, colorless liquid (Found: C, 70.51; H, 10.71; N, 3.46. C₂₃H₄₁NO₂Si requires C, 70.59; H, 10.48; N, 3.58%). $\nu_{\text{max}}/\text{cm}^{-1}$ (film) 3420, 2920, 1620, 1500. δ_{H} 0.01 (6 H, s, SiCH₃), 0.6–1.8 (16 H, m), 2.02 (2 H, d, *J* 8.0, NCH₂), 2.20 (3 H, s, NCH₃), 2.3–2.8 (2 H, m), 3.20 (3 H, s, OCH₃), 3.6 (1 H, m, OCH), 4.15 (1 H, d, *J* 5.8, PhCH), 5.68 (1 H, d, *J* 18.8, 1-H), 6.15 (1 H, dt, *J* 18.8, 6, 2-H), 7.1–7.5 (5 H, m, PhH). δ_{C} -3.0, 22.8, 25.8, 27.3, 41.3, 44.7, 46.0, 47.2, 56.6, 66.0, 72.1, 85.7, 125.0–128.5 (2 \times C₆H₅), 132.8, 142.0 (143.6).

γ -(*E*)-16a, colorless liquid (Found: C, 68.61; H, 9.52; N, 4.55. C₁₉H₃₁NO₂Si requires C, 68.42; H, 9.36; N, 4.20%). $\nu_{\text{max}}/\text{cm}^{-1}$ (film) 3400, 2950, 1610, 1240. δ_{H} 0.03 (6 H, s, SiCH₃), 1.4–2.0 (7 H, m), 2.0–2.2 (1 H, m), 2.3–2.7 (3 H, m), 3.0–3.3 (2 H, m), 3.33 (3 H, s, OCH₃), 3.4–3.5 (1 H, m), 4.6–4.8 (1 H, m, PhCH), 5.82 (1 H, d, *J* 19.0, 1-H), 6.12 (1 H, dt, *J* 19.0, 7, 2-H), 7.1–7.4 (5 H, m, Ar-H). δ_{C} -3.0, -2.2, 22.9, 28.0, 46.0, 47.2, 57.8, 59.1, 67.5, 72.5 (72.7), 75.7, 124.0–128.5 (2 \times C₆H₅), 132.4, 143.8 (144.1).

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