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CHIRAL ORGANOSILICON COMPOUNDS IN SYNTHESIS: REGIO AND STEREOSELECTIVE ALKYLATION OF A CHIRAL α-SILYLCINNAMYL CARBANION

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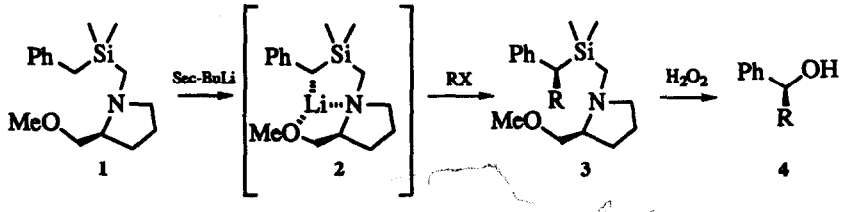
Abstract: Good regio- and stereoselectivity can be obtained in the alkylation of chiral α-silylcinnamyl carbanion **8** in toluene.

The use of chiral organosilicon compounds in asymmetric synthesis has gained considerable interest during the past decade [1]. We recently devised a short and highly enantioselective synthesis of arylcarbinols from chiral benzylic silane **1** (Scheme 1) [2]. It was found that the α-silyl carbanion **2** derived from **1** is alkylated with excellent diastereoselectivity to give compounds **3** which upon oxidative cleavage of the carbon-silicon bond [3] afforded optically active alcohols **4** (>95% ee). The extent of chiral induction was attributed to efficient internal chelation of lithium by the chiral auxiliary as depicted in structure **2**.



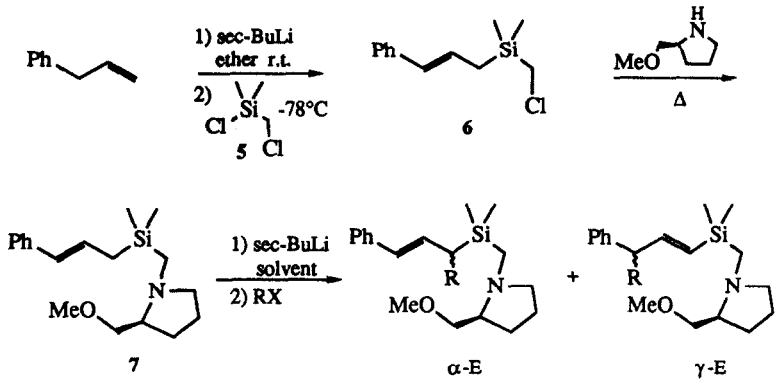
1 2 3 4

Scheme 1

In view of the high stereoselectivity obtained and the potential application of this approach for the synthesis of chiral drugs in the pharmaceutical industry, it appeared interesting to examine in more detail the alkylation behavior of other chiral silyl carbanions. We chose to study the reactivity of the cinnamyl type system **7** (Scheme 2). The control of stereoselectivity in allylic systems is particularly challenging because of the additional complication due to regioselectivity. Alkylation at the γ-position is generally preferred but it was recently demonstrated by this group that α-selectivity as well as diastereoselectivity can be obtained by using a chiral lithium chelating substituent remote from silicon [4].

The preparation of the requisite chiral allylic silane followed the path described in Scheme 2 [5]. Reaction of allylbenzene with sec-BuLi in ether at room temperature followed by quenching with chlorosilane **5** at -78°C afforded compound **6** in 90% yield and >92% isomeric purity. This compound was transformed into the desired aminosilane **7** [6] in 81% yield by reacting it neat with 2 equivalents of (S)(+)-methoxymethylpyrrolidine.

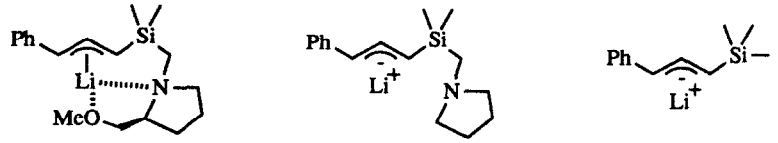
Generation of the silylallyl carbanion from **7** was carried out using sec-BuLi as the base in various solvents and alkylations gave mainly the adducts of E geometry (α-E and γ-E) in excellent combined yield (81-99%) regardless of the conditions used as shown in Table 1 [7].



Scheme 2

The control of regio- as well as diastereoselection depends critically on the choice of solvent as can be seen for alkylations with methyl iodide (entries 1-3). When the reaction was carried out in THF, regioselection was poor and both α and γ adducts were obtained with low diastereomeric excess. On the other hand, when diethyl ether was used as the solvent, the reaction afforded 81% of α-alkylated compound with 94% S-diastereoselection. It is believed that in these reactions, an internal chelation involving the methoxy group as in **8** is necessary for keeping the anionic center at the α-position and for creating a rigid environment from which diastereoselection is possible.

The solvent effect is explained by the stronger complexing ability of THF relative to diethyl ether [8]. The former competes with the methoxy group of the chiral auxiliary as ligand on the lithium cation thereby partially disrupting the internal complex **8**. Indeed, the α:γ ratio observed in THF (α:γ = 45:52, entry 1) is nearly the same as the α:γ ratio obtained in the methylation of cinnamyl anions **9** (α:γ = 45:55, THF or ether as solvent) [9] or **10** (α:γ = 50:50, THF as solvent) [9] where internal complexation is clearly not possible. In agreement with this explanation, reaction of **8** in toluene improved the α–selectivity even further (α:γ = 90:9, entry 3) with still excellent diastereocontrol. These results also suggest that the nitrogen atom, although important for deprotonation kinetics, is not responsible by itself for variations in regioselectivity.



8 **9** **10**

The same trend was observed with ethyl iodide (entries 4-6) with which α-alkylation ratio improved together with diastereoselection on going from THF to ether to toluene.

It is noteworthy that the regioselectivity of the alkylation is influenced [10] by the size of the alkylating agent. Under identical conditions, ethyl iodide is less α-selective than methyl iodide. Furthermore, the steric factor becomes quite strong when a secondary iodide is used (entries 7-9) where γ-alkylation is now favored.

Table 1. Alkylations of allylic silane7

Entry	Electrophile	Solvent	Yield[a] %	Product Distribution (%)[b]		
				α-E (de,conf)	γ-E (de,conf)	Z-isomers[f]
1	MeI	THF	99	45 (18%,R)[b]	52 (17%,S)[c]	3
2	MeI	Ether	92	81 (94%,S)[c]	15[d]	4
3	MeI	Toluene	89	90 (>92%,S)[b]	9[d]	1
4	EtI	THF	90	47 (13%,R)[b]	52 (10%[b],S[e])	1
5	EtI	Ether	99	68 (92%,S)[c]	19[d]	13
6	EtI	Toluene	81	79 (>92%,S)[b]	21[d]	0
7	i-PrI	THF	87	5[d]	90 (4%,S)[b]	5
8	i-PrI	Ether	89	15[d]	68 (64%,R)[c]	17
9	i-PrI	Toluene	89	8[d]	85 (78%,R)[c]	7

a) Crude yield of isomer mixture. b) Determined by VPC and/or ^{1}H NMR analysis. c) Determined as described in the text. d) de and configuration were not determined. e) Absolute configuration assumed on the basis of spectral correlation with other adducts. f) Their presence as a mixture of isomers was evident from ^{1}H NMR; their further characterization was not pursued.

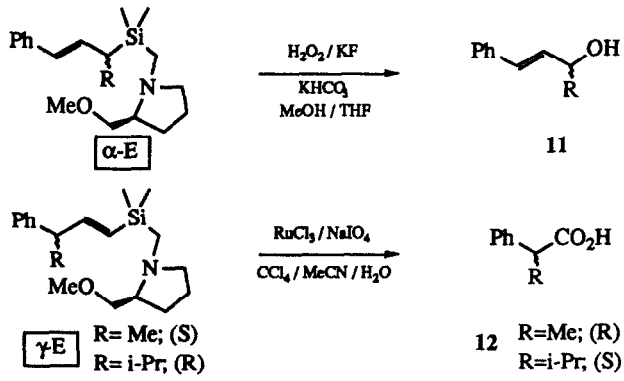
It is interesting to point out that the γ-adduct obtained with isopropyl iodide in toluene (entry 9) shows as much as 78% diastereomeric excess.

For the purpose of synthesis, it is useful to note that the α and γ isomers could be separated cleanly by column chromatography on silica gel.

Determination of absolute configuration of the alkylated compounds was made by transforming the adducts into known derivatives as depicted in Scheme 3. The α-adducts were treated according to the procedure described by Tamao [3] effecting oxidative cleavage of the carbon-silicon bond presumably with retention of configuration at the hydroxylated center. The signs of optical rotation of the resulting alcohols **11** were compared to literature [11] values and the accurate ee determination was made by ^{1}H NMR analysis of the corresponding MTPA esters [12].

In the case of the γ-adducts, the olefin was cleaved by oxidation with $RuCl_3/NaIO_4$ following the procedure described by Sharpless [13]. This reaction afforded the corresponding carboxylic acids **12** of which absolute configuration and enantiomeric excess were determined by comparison of their optical rotation values with those found in literature [14]. It should be pointed out that the absolute configurations of acids **12** and the corresponding precursor vinylsilanes γ-E have opposite "R,S" designations due to change in priority sequence.

Furthermore, for reactions in ether and toluene, eventhough the predominant α- or γ-regioisomers have opposite absolute configurations, they are in fact derived from electrophilic attack from the same face of transoid allylic carbanion 8.



Scheme 3

This work shows that it is possible to use chiral substitution remote from silicon to control alkylation pathways on silylallyl carbanions.

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REFERENCES AND NOTES

1. For lead references on the subject see ref. 2.
2. T.H. Chan and P. Pellon, J. Am. Chem. Soc., 1989, **111**, 8737.
3. K. Tamao, N. Ishida, T. Tanaka and M. Kumada, Organometallics, 1983, **2**, 1694.
4. R.F. Horvath and T.H. Chan, J. Org. Chem., 1989, **54**, 317.
5. All structures are in agreement with spectral data.
6. Compound **7**: IR ($CHCl_3$): 3023, 2955, 2875, 1113 cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm): 7.10-7.40 (m, 1H), 6.20-6.40 (m, 2H), 3.42 (dd, J=9.3 and 4.5 Hz, 1H), 3.34 (s, 3H), 3.24 (dd, J=9.3 and 6.5 Hz, 1H), 3.09 (m, 1H), 2.53 (d, J=14.3 Hz, 1H), 2.37 (m, 1H), 2.09 (q, J=8.5 Hz, 1H), 1.50-2.00 (m, 7H), 0.11 (s, 3H), 0.08 (s, 3H); HRMS: calcd for MH^+ 304.2098, found 304.2097; $[\alpha]_D^{25°}$ = -77.8° (c 2.54, $CHCl_3$).
7. General procedure for alkylation: To a solution of allylic silane **7** (1 mmol) in solvent (6 ml) at -78°C was added sec-BuLi (2 mmol). The mixture was stirred for 15-30 min at -78°C and alkylating agent was then added (2-10 mmol). The resulting mixture was stirred for 10 min at -78°C and quenched with saturated NH_4Cl solution when THF was the solvent or warmed up to room temperature prior to quenching when ether or toluene were used (this procedure did not affect product ratios significantly). Extraction with ether followed by washing with brine and drying over $MgSO_4$ afforded crude mixture of essentially pure alkylated products. In all cases, regioisomers could be separated by column chromatography on silica gel using ethyl acetate (10 to 100%) in hexanes elution.
8. Similar effects have been observed in other reactions: See S. Shirodkar, M. Nerz-Stormes and E.R. Thornton, Tetrahedron Lett., 1990, **31**, 4699 and references cited therein.
9. S. Lamothe, to be published.
10. Similar effects were noted for reactions of trialkylsilylallyl anions with substituted oxiranes : E. Schaumann and A. Kirshning, Tetrahedron Lett., 1988, **29**, 4281.
11. For **11** (R=methyl and ethyl), (S) enantiomer has negative $[\alpha]_D$: See respectively: M. Kawasaki, Y. Suzuki and S. Terashima, Chem. Lett., 1984, 239 and M. Kitamura, S. Suga, K. Kawai and R. Noyori, J. Am. Chem. Soc, 1986, **108**, 6071.
12. J.A. Dale, D.L. Dull and H.S. Mosher, J. Org. Chem., 1969, **34**, 2543.
13. P.H.J. Carlsen, T. Katsuki, V.S. Martin and K.B. Sharpless, J. Org. Chem., 1981, **46**, 3936.
14. R. Aaron, D. Dull, J.L. Schmiegel, D. Jaeger, Y. Ohashi and H.S. Mosher, J. Org. Chem., 1967, **32**, 2797: these authors report $[\alpha]_D^{25°}$ = +76.5° (c 2, $CHCl_3$) for pure (S)-**12** (R=methyl) and +62.5° (c 2, $CHCl_3$) for pure (S)-**12** (R=isopropyl). We obtained $[\alpha]_D^{25°}$ = -12° (c 0.25, $CHCl_3$) for **12** (R=methyl). As for **12** (R=isopropyl) we recorded $[\alpha]_D^{25°}$ =+40° (c 0.55, $CHCl_3$) for the oxidation product of the adduct obtained in ether and +52° (c 0.97, $CHCl_3$) for the one obtained from toluene.

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