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Highly Enantioselective Synthesis of Propargyl Alcohols

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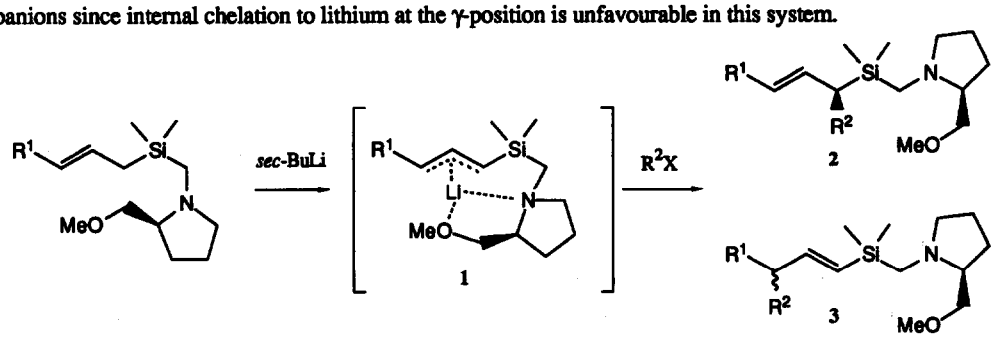
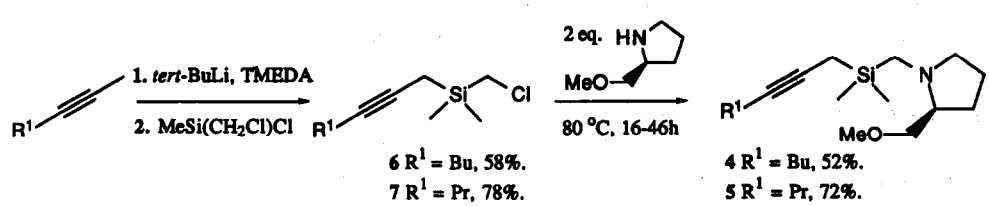
Silylpropargyl carbanions bearing a chiral auxiliary on silicon have been alkylated with excellent regio and diastereoselectivity. The effect of the solvent has been investigated and propargyl alcohols have been synthesised in high enantiomeric excess.

The use of chiral organosilicon compounds in asymmetric synthesis is an exciting new area of research.[1] Recently it was reported that α-silylbenzyl carbanions with a proline-derived chiral auxiliary can be alkylated with high diastereoselectivity,[2] and that α-silylallyl carbanions **1** can be alkylated at the α-position to give allyl silanes **2** with a high degree of diastereoselectivity[3] but that the regioselectivity is strongly dependent on the size of the alkyl iodide used (*scheme 1*).[4] Some diastereoselectivity was observed in the γ-alkylation products **3** so that the α-silylallyl carbanions **1** were believed to have the chelated structure shown, where the lithium may be associated with either end of the allyl moiety and still be chelated to the auxiliary. We now report that excellent α-selectivity and even more impressive diastereoselectivity can be obtained in alkylations of α-silylpropargyl carbanions since internal chelation to lithium at the γ-position is unfavourable in this system.



Scheme 1

Propargyl silanes **4** and **5** were made by the route shown (*scheme 2*). Coupling of the lithium salt of 2-heptyne or 2-hexyne with chloro(chloromethyl)dimethylsilane gave silanes **6** and **7** in sufficient purity for the next stage in 58% and 78% yield respectively. Heating these with two equivalents of the proline-derived amine gave the propargyl silanes **4** and **5** in 52% and 72% yield respectively.



6 R^1 = Bu, 58%.
7 R^1 = Pr, 78%.

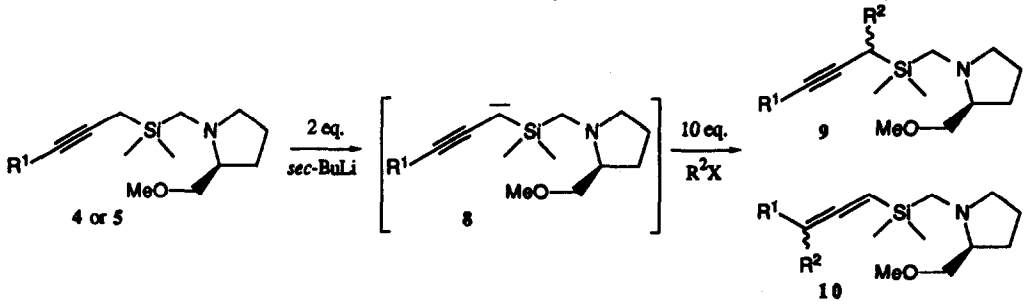
4 R^1 = Bu, 52%.
5 R^1 = Pr, 72%.

Scheme 2

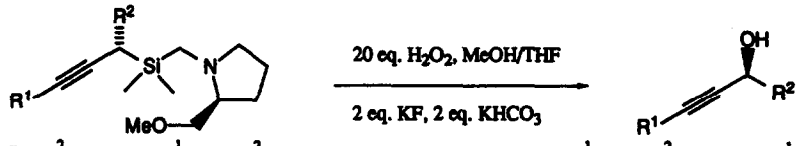
Each propargyl silane (**4** and **5**) was deprotonated with *sec*-butyl lithium to give carbanion **8** at –78 °C and an alkyl halide was added. After 1.5 h the reaction was quenched at the same temperature (Procedure A) and

the ratio of α **9** and γ **10** products was determined by ^{1}H NMR (*scheme 3*, *table 1*). The effect of varying the alkylating agent and the solvent was investigated.

In THF methylation proceeded with complete α-selectivity, but ethylation, allylation and hexylation gave increasing amounts of γ-adducts **10** (entries 1-4, *table 1*). In ether methylation again proceeded smoothly but with ethyl and allyl iodide there was less than 50% conversion to the alkylation products **9** and **10** (entries 5-8, *table 1*). If after the alkylating agent was added the mixture was allowed to warm up to -10 °C at 20 °C per hour and quenched at this temperature after 0.5 h (Procedure B), then alkylation in ether almost always gave total α-selectivity (entries 9-12, *table 1*). When ethyl iodide is the alkylating agent another product competes under these conditions, but this does not affect the selectivity of the reaction. Finally when the reaction was carried out in THF with 2 equivalents of HMPA, the ratio of **9**:**10** changed to 59:41 (entries 13-14, *table 1*).



Scheme 3



11 R^1 = Bu, R^2 = Me, **12** R^1 = Bu, R^2 = Et,
13 R^1 = Bu, R^2 = Hex, **14** R^1 = Bu, R^2 = Allyl,
15 R^1 = Pr, R^2 = Me, **16** R^1 = Pr, R^2 = Et.

17 R^1 = Bu, R^2 = Me, **18** R^1 = Bu, R^2 = Et,
19 R^1 = Bu, R^2 = Hex, **20** R^1 = Bu, R^2 = Allyl,
21 R^1 = Pr, R^2 = Me, **22** R^1 = Pr, R^2 = Et.

Scheme 4

Oxidative removal of the silicon moiety from the unpurified propargylsilanes **11-16** with retention of configuration[5] gave enantiomerically-enriched S-propargyl alcohols **17-22** in 40-61% yield (see last column of *table 1*).[6] The high enantiomeric excesses are believed to result from diastereoselectivity in α-alkylation of the carbanion **8**. The degree of diastereoselectivity parallels that of regioselectivity. To explain this we propose that the carbanion **8** exists in two forms in equilibrium: the internally chelated structure **23** and the free anion structure **24** (*figure 1*). Structure **23** gives only the S α adducts **11-16** on reaction with the alkyl or allyl halides and structure **24** gives a mixture of α and γ adducts with no diastereoselectivity. The more coordinating the solvent the less unfavourable is structure **24** relative to structure **23** and hence the regioselectivity and diastereoselectivity are lower. In the rates of alkylation of **23** and **24**, k_1 will be more reduced by bulky alkylating agents than will k_2, hence there regioselectivity, stereoselectivity and reactivity are reduced by bulky alkylating agents (entries 1-4, 5-8, *table 1*).

The *Exo* structure **23** which gives S-adducts is formed exclusively, as the *Endo* structure **25** which gives R-adducts is destabilised either by electrostatic repulsion between the triple bond and the lone pair on

oxygen or by steric interaction between the triple bond and the methyl group (*figure 1*). Here it is reasonably assumed that the solvent -lithium bond is longer than the bond between the oxygen of the methoxy group and the lithium ion.

Table 1 Selectivity in Alkylations of α-Silyl Anions

Entry	Substrate	Reagent	Solvent	Procedure	%Yield[a]	Selectivity[b] α : γ	% ee[c]
1	4	MeI	THF	A	91	>98:2	95.0 (S)
2	4	EtI	THF	A	89	93:7	91.5 (S)
3	4		THF	A	85	92:8	77.5
4	4	HexI	THF	A	90	89:11	80.0
5	4	MeI	Et_2O	A	82	>98:2	>99.0 (S)
6	5	MeI	Et_2O	A	90	>98:2	98.5 (S)
7	4	EtI	Et_2O	A	less than 46% conversion by GC		
8	4		Et_2O	A	less than 47% conversion by GC		
9	4	EtI	Et_2O	B	76	>98:2	99.0 (S)
10	4	EtBr	Et_2O	B	75	>98:2	97.5 (S)
11	5	EtBr	Et_2O	B	94[d]	>94±2:6	95.5 (S)
12	4	HexI	Et_2O	B	83	>98:2	95.5
13	4	EtI	THF, HMPA	A	81	59:41	18.0 (S)
14	4	HexI	THF, HMPA	A	63	59:41	12.5

a. Combined yield of crude material. b. By ^1H NMR. c. Enantiomeric excess of alcohol from chiral GC of the acetate ester or 500 MHz ^1H NMR of the Mosher ester presented to the nearest 0.5%. The configuration[6] is in parenthesis. d. 62:38 product : unalkylated.

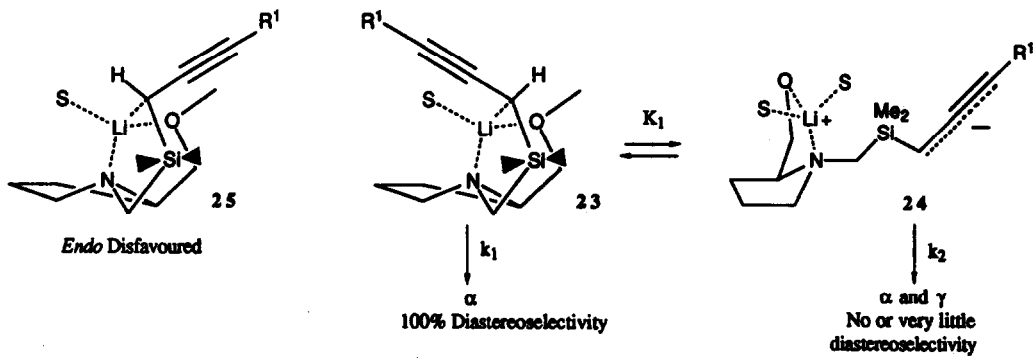


Figure 1 S = Solvent

The model allows the α-γ regioselectivity in the alkylation of the free anion **24** by each alkylating agent to be correlated with the α-diastereoselectivity according to the following equation:

$$\frac{\text{α-alkylation of 24}}{\text{γ-alkylation of 24}} = \frac{\text{total α-alkylation (1 – \%ee/100)}}{\text{total γ-alkylation}}$$

Using ethyl iodide as the standard alkylating agent, the ratio of α to γ alkylation was found to be 53:47 for THF (from entry 2, *table 1*) and 54:46 for THF/HMPA (from entry 13, *table 1*). Similar consistency can be obtained for other electrophiles.

In summary we have shown that α-silylpropargyl carbanions bearing a proline-derived chiral auxiliary can be alkylated or allylated with excellent regioselectivity and diastereoselectivity and believe this to be a general method for the synthesis of S-propargyl alcohols in very high enantiomeric purity.[7-10] We have also presented a working hypothesis that explains this selectivity and this should help in the design of other chiral auxiliaries. Attempts to optimise the synthesis of the propargyl silanes and to recycle the chiral auxiliary are underway.

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6. For **17** >99% ee $[\alpha]_D^{19} = -25.9$ (*c* 1.79, $CHCl_3$), lit.[7] >95% ee (S) $[\alpha]_D^{25} = -26.3$ (*c* 2.03, $CHCl_3$). For **18** 99.0% ee $[\alpha]_D^{21} = -3.8$ (*c* 1.75, $CHCl_3$), lit.[7] >95% ee (S) $[\alpha]_D^{25} = -4.67$ (*c* 1.07, $CHCl_3$). For **21** 98.5% ee $[\alpha]_D^{21} = -27.6$ (*c* 0.57, $CHCl_3$), lit.[8] 78% ee (R) $[\alpha]_D^{25} = 14.8$.(*c* 0.662, $CHCl_3$). For **22** 95.5% ee $[\alpha]_D^{21} = -5.8$ (*c* 0.98, $CHCl_3$), $[\alpha]_D^{21} = -33.5$ (*c* 0.40, Et_2O), lit.[9] 5% ee (R) $[\alpha]_D^{25} = 2.01$.(*c* = 7.97, Et_2O).
   The major enantiomer of the acetate derivatives of alcohols **17**, **18**, **20-22** was always the second to be eluted from the 2,6-Di-O-pentyl-3-O-trifluoroacetyl-γ-cyclodextrin GC column.[11]
   Alcohol **17** was contaminated with 4.5% 2-heptyn-1-ol and alcohol **21** with 2% 2-hexyn-1-ol.
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