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CHIRAL SILICON IN ASYMMETRIC SYNTHESIS. ADDITION OF ORGANOMETALLIC REAGENTS TO A SILYL THIONE CHIRAL AT SILICON

BIANCA F. BONINI, GAETANO MACCAGNANI, STEFANO MASIERO,
GERMANA MAZZANTI and PAOLO ZANI

Dipartimento di Chimica Organica, Università di Bologna,
Viale Risorgimento 4, 40136 Bologna, Italy

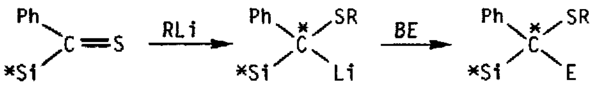
Summary - The reaction of R-(-)-methyl- α-naphtyl-phenylsilyl phenyl thioketone 1 with organolithium derivatives and Grignard reagents *gives the* α*-silylsulphides 3 with medium to good levels of asymmetric* induction. The asymmetry induced at the α-carbon is retained in the subsequent desilylation.

Organosilicon compounds chiral at silicon are potentially useful reagents for asymmetric synthesis, due to the possibility of transferring chirality from asymmetric silicon to carbon and for the easy removal of the silyl group. To our knowledge only few examples are known[1-7] on the use of chiral silicon in asymmetric synthesis and in most cases, low levels of asymmetric induction were obtained.

We previously reported[7] the synthesis of a silyl thione chiral at silicon, viz. *R-(-)-methyl-* α*-naphtyl-phenylsilyl phenyl thioketone* 1, *and its reactions with* buta-1,3-diene and methyllithium, from which medium levels of diastereoselection were obtained.

With the aim of increasing the level of chiral induction, we performed the reaction of 1 with several organometallics (organolithium and Grignard reagents) under various conditions. In these reactions invariably products of a thiophilic addition were found (Scheme 1).

Scheme 1



1 2 3

a:R=Me, E=H
b:R=Me, E=D
c:R=n-Bu, E=H
d:R=t-Bu, E=H
e:R=Ph, E=H
f:R=p-Tol, E=H

*Si= α-Napht.,Ph,MeSi

The reaction of 1 with methyllithium was investigated varying the molar ratio of substrate **1** and MeLi, the solvent, the reaction time and the quenching agent BE, at the constant temperature of -80°C for both the addition and the quenching steps. (Scheme 1, Table 1).

Table 1. Reactions of **1** with MeLi[8]

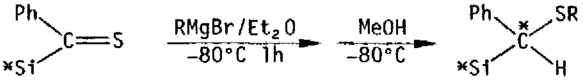
entry	solvent	time (min.)	BE	1:MeLi	yield%	d.e.%[9]
1	Et_2O	60	MeOH	1:1	55	53
2	Et_2O	60	MeOH	1:2	40	45
3	Et_2O	15	MeOH	1:1	18	14
4	Et_2O	60	EtOH	1:1	54	43
5	Et_2O	60	HCl/Et_2O	1:1	40	37
6	Et_2O	60	D_3COD	1:1	54[10]	48
7	THF	60	MeOH	1:1	60	40
8	THF/HMPA	60	MeOH	1:1	10	44

A variation of the molar ratio of **1** and MeLi from 1:1 to 1:2 caused a decrease of the yield of the silyl sulphide, due to a concurrent desilylation reaction; in fact a small amount of desilylated product was found. Moreover, also the optical yield was lowered (entry 2). Shortening of the reaction time also lowered the chemical as well as the optical yields (entry 3). The effect of the quenching agent BE was tested in diethyl ether with a reaction time of 1h; the best results were obtained with methanol (entry 1) and deuteriomethanol (entry 6). The use of THF as the solvent, alone (entry 7) or in the presence of HMPA (entry 8), did not give results significantly different from those obtained in diethyl ether. The best d.e. value was obtained under the conditions reported in entry 1. Under these optimum conditions silylthione **1** was then reacted with various other organolithium derivatives, viz. n-BuLi, t-BuLi and PhLi, leading to the α-silylsulphides **3c-e**.[9] The results are reported in Table 2. The highest chiral induction was obtained with MeLi, even though no substantial variation was observed in changing the organolithium derivative. These results point to the fact that chiral information may be transmitted from silicon to carbon in the addition step with the probable formation of two diastereomeric lithiated sulphides **2**.[7] This hypothesis is supported by the reaction between racemic α-silylsulphide **3a** with MeLi at -20°C, followed by quenching with D_3COD at -80°C, from which racemic **3b** (D content 98%) was obtained. Therefore in the quenching step no chiral discrimination occurs, but only replacement of lithium by hydrogen or deuterium.

Silylthione 1 was then reacted with Grignard reagents, viz. Me, n-Bu, Ph and p-TolMgBr, from which the α-silylsulphides 3a[7] and 3c,e,f[9] were obtained.

The reactions were carried out in diethyl ether at -80°C for 1 h, and the reaction mixture was quenched with methanol at the same temperature (Scheme 2).

Scheme 2



The results obtained are reported in Table 3.

Table 2. Reactions of 1 with RLi[8]

R	Yield%	d.e.%[9]
Me	55	53
n-Bu	44	35
t-Bu	16	35
Ph	63	40

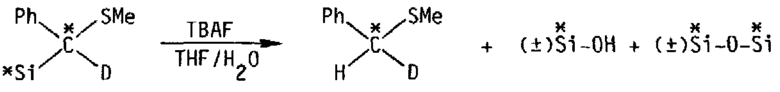
Table 3. Reactions of 1 with RMgBr[8]

R	Yield%	d.e.%[9]
Me	80	40
n-Bu	44	63
Ph	60	76
p-Tol	48	35

In the reactions with PhMgBr and n-BuMgBr, the d.e. values are higher than those obtained with the corresponding organolithium compounds; they represent two of the highest values of asymmetric induction ever reported up to now[1,7] using chiral auxiliaries at silicon. In contrast, the d.e. value obtained with p-TolMgBr is only moderate and the d.e. value observed in the reaction with MeMgBr is lower than that for MeLi. These contradictory results could derive from a competition among different mechanisms, which is not unusual for Grignard reagents.[11] At this stage of our work more information is necessary to rationalize the results obtained.

The mixture of the two diastereomeric α-deuterio-α-silylsulphides 3b (d.e. 48%, Table 1, entry 6), was protiodesilylated with tetrabutylammonium fluoride (TBAF) in THF/H_2O giving α-deuteriobenzylmethylsulphide **4**[12] in 75% yield $[\alpha]_D^{25}$ -0.70° (c 1.15, ethanol) (value corrected for the deuterium percentage)[10] together with silanol and disiloxane both racemic.[7] (Scheme 3)

Scheme 3



3b
d.e. 48%

4
e.e.45%

The enantiomeric excess (e.e.) of **4** was determined to be 45% on the basis of the $[\alpha]_D^{25}$ max values reported in the literature.[12,13] It follows from this data that desilylation of α-silyl methyl sulphides is a stereoselective process in accordance with results obtained[7] in the desilylation of similar cyclic compounds. Hence the conclusion is allowed that protiodesilylation at saturated carbon is a stereoselective process, as is required for the possible utilization of silicon as a chiral auxiliary in asymmetric synthesis.

References and Notes

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8. All reactions were performed on racemic **1**, except the one reported in entry 6, Table 1, and were repeated at least twice.
9. Compounds **3a-f** were characterized as a mixture of the two diastereoisomers, whose ratio was determined by H-NMR analysis at 200 MHz. **3a**: see ref 7. **3b**: δ(CDCl$_3$) 0.57 and 0.70 (3H, 2s, SiMe), 1.87 and 1.93 (3H, 2s, SMe), and 7.1-8.2 (17H, m, ArH) ppm; m/e = 385 (M$^+$). **3c**: δ(CDCl$_3$) 0.58 and 0.72 (3H, 2s, SiMe), 0.8-1.73 (7H, m), 2.08-2.53 (2H, m, SCH), 3.98 and 4.03 (1H, 2s, CH), 6.8-8.1 (17H, m, ArH) ppm; m/e 426 (M$^+$). **3d**: δ(CDCl$_3$) 0.50 and 0.67 (3H, 2s, SiMe), 1.0 and 1.17 (9H, 2s, t-Bu), 4.03 and 4.13 (1H, 2s, CH) and 6.8-8.0 (17H, m, ArH) ppm; m/e = 426 (M$^+$). **3e**: δ(CDCl$_3$) 0.73 and 0.91 (3H, 2s, SiMe), 4.51 and 4.56 (1H, 2s, CH) and 7.0-8.1 (22H, m, ArH) ppm; m/e=446 (M$^+$). **3f**: δ(CDCl$_3$) 0.70 and 0.85 (3H, 2s, SiMe), 2.25 (3H, s, Me), 4.44 and 4.49 (1H, 2s, CH) and 6.9-8.0 (21H, m, ArH) ppm; m/e=460 (M$^+$).
10. Deuterium content 65% (determined by MS).
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