Diastereoselective Additions of Lithiated *N*-t-Butyldiphenylsilyl-*S*-benzyl-*S*-methylsulphoximine to Imines†

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Lithiated *N*-t-butyldiphenylsilyl-*S*-benzyl-*S*-methylsulphoximine undergoes highly diastereoselective, 1,2-addition to imines to give adducts with the 1*S**, 2*S**, S^*_S relative stereochemistry.

As part of a continuing programme to develop methods for preparing alkaloids in high enantiomeric purity[1,2] we have investigated the addition of benzyl carbanions that are stabilized by an α stereogenic sulphur group, to prochiral imines. We have found that addition of the lithium salts of benzyl alkyl sulphoxides to imines proceeded either with poor chemical yield or modest diastereoselectivity.[3,4] We report here, however, that the lithium salt of *N*-t-butyldiphenylsilyl-*S*-benzyl-*S*-methylsulphoximine **2** undergoes 1,2-addition to

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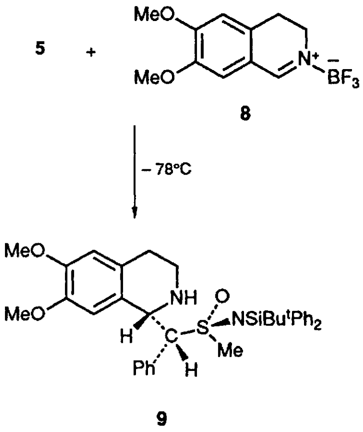
† For Part 12 of the series Chiral Sulphur Compounds, see S. G. Pyne and B. Dikic, *J. Chem. Res.*, *S*, 1990, 226.

Table 1 Reactions of lithiated **2** with imines **4**

Entry	R of imine (**4**)	Additive[a]	Yield (%)[b]	Diastereoselection[c]
1	Ph	—	60	79:21
2	Ph	BF_3	86	95:5
3	2-Furyl	BF_3	82	95:5
4	Et	—	66	82:18
5	Bu^i	BF_3	70	96:4
6	Pr^i	—	58	85:15
7	Pr^i	BF_3	80	>97:<3

[a] Imine **4** was pre-complexed with $BF_3{\cdot}Et_2O$ (1 equiv.) at −78 °C in THF prior to addition to lithiated **2**. [b] Yield of diastereomerically pure product after column chromatography. [c] Determined by ^1H NMR (400 MHz) spectroscopy on the crude reaction mixture.

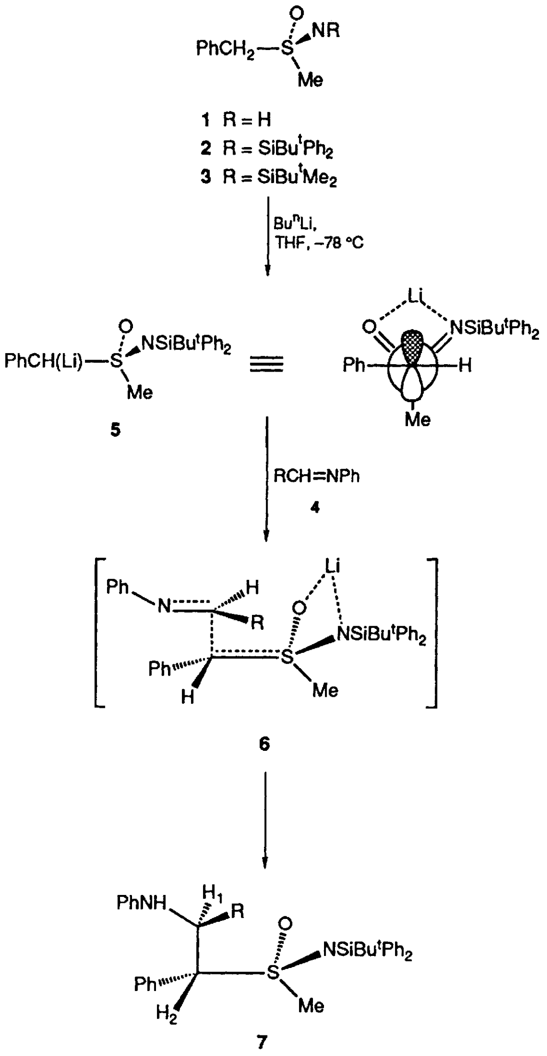


imines that have been activated by precomplexation with boron trifluoride–diethyl ether ($BF_3{\cdot}Et_2O$), with high diastereoselectivity.

Racemic sulphoximine **2** was prepared from the known sulphoximine **1**[5] by *N*-silylation with chloro-t-butyldiphenylsilane and imidazole in dimethylformamide.[6] Racemic **2** was lithiated at −78 °C in tetrahydrofuran (THF) by treatment with n-butyllithium (1.1 equiv.) for 10 min. The resulting organometallic species was then quenched by the addition of a THF solution of the imine **4** or a solution or suspension of the imine $\mathbf{4}{\cdot}BF_3$ complex that had been prepared at −78 °C. After a period of 1 h at −78 °C the pure β-amino sulphoximine products **7** could be obtained after a standard aqueous work-up followed by extraction into dichloromethane and then short-path column chromatography. The results of this investigation are presented in Table 1. It is important to note that in each case examined, only two of the four possible racemic diastereoisomeric products were formed. While the reaction of lithiated **2** with imine **4** (entries 1, 4 and 6) proceeded with moderate product diastereoselection the analogous reactions with $\mathbf{4}{\cdot}BF_3$ complex gave adducts **7** in consistently high diastereoselectivity (entries 2, 3, 5 and 7). In each case investigated the ^1H NMR spectrum of the major diastereoisomer **7** revealed a one-proton doublet at δ 4.3–4.4 with $J_{1,2}$ 2–4 H for the proton H-2 at the stereogenic benzylic carbon.

The analogous reactions of the *N*-t-butyldimethylsilylsulphoximine **3** were less diastereoselective. It appears that highly sterically demanding substituents are required at the sulphoximine nitrogen to ensure high diastereoselectivity in these and analogous reactions.[3,6,7]

The relative $1S^*,2S^*,S_S^*$ stereochemistry of **7** (R = Et) was unequivocally determined by a single-crystal X-ray structure analysis (Fig. 1).‡ It was of interest to note that the estimate of the dihedral angle between C-1–H-1 and C-2–H-2 in **7** (R = Et) from the structure analysis ($\phi_{1,2}$ *ca.* 77°) and the value of the H-1, H-2 coupling constant (J_{12} 3.2 Hz) from the ^1H NMR analysis of **7** (R = Et) in deuteriochloroform solution suggests that this compound adopts a similar conformation in the solid state and in solution.



Scheme 1

We suggest that the structure of lithiated **2** as shown by structure **5** (only the monomeric species is considered) in Scheme 1 may be similar to that of lithiated benzyl phenyl sulphone.[8] One would expect the benzylic carbon of **5** to be close to planar and the phenyl substituent to be *anti* to the bulky *N*-t-butyldiphenylsilyl moiety. The non-bonding orbital at the benzylic carbon would be approximately coplanar with the $S–CH_3$ σ bond due to a stabilizing $n_c \rightarrow \sigma^*$ s-c interaction.

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‡ *Crystal data*: $C_{33}H_{40}N_2OSSi$, M = 540.9, monoclinic, $P2_1/c$, a = 12.548(8), b = 13.662(6), c = 21.021(11) Å, β = 121.90(3)°, Z = 4. T ~295 K. 2959 Independent Mo-Kα diffractometer reflections [$I > 3\sigma(I)$] refined (full matrix; non-hydrogen atom thermal parameters anisotropic) to R = 0.041. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

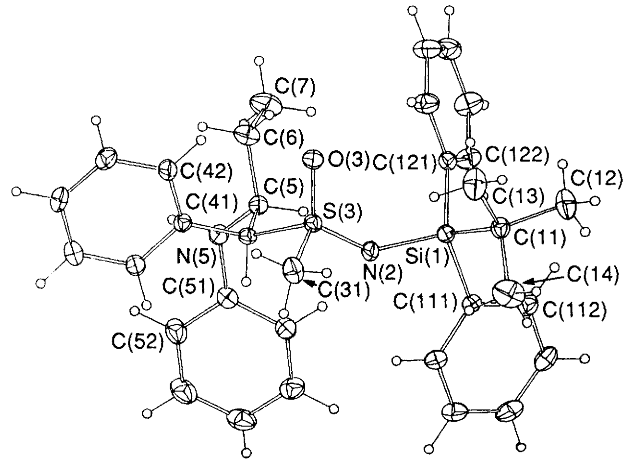

Fig. 1 Molecular projection of **7**. 20% Thermal ellipsoids and labelling are shown for non-hydrogen atoms; hydrogen atom positions are estimated and have arbitrary radii of 0.1 Å. Geometry of particular interest (distances, Å): Si(1)–N(2), 1.702(2); N(2)–S(3), 1.488(3); S(3)–O(3)–C(4), 1.449(3), 1.808(3); C(4)–C(5), 1.556(4); C(5)–N(5), 1.450(5); (angles, °); N(2)–Si(1)–C(11,111,121), 111.2(1), 104.3(2), 110.8(1); Si(1)–N(2)–S(3), 142.4(2); N(2)–S(3)–O(3), C(31,4), 120.6(2), 108.6(2), 106.5(2); O(3)–S(3)–C(21,4), 107.1(2), 109.9(1); C(4)–S(7)–C(71), 102.6(2); S(3)–C(4)–C(5,41), 112.1(2), 115.4(2); C(5)–C(4)–C(41), 113.3(2); N(5)–C(5)–C(4,6), 110.0(3), 109.0(2); C(4)–C(5)–C(6), 114.6(7); C(5)–N(5)–C(51), 123.0(2).

Electrophilic attack on **5** should occur from the less hindered diastereoface, that is, *anti* to the S–CH$_3$. An open transition state **6** in which R of the imine **4** and the phenyl substituent of **5** are *anti* is consistent with the stereochemical outcome. Indeed inspection of molecular models suggests a cyclic transition state may be too sterically congested.

The potential of this methodology for alkaloid synthesis was demonstrated by the reaction of lithiated **2** with the 3,4-dihydro-6,7-dimethoxyisoquinoline·BF$_3$ complex **8** to give 1-benzyltetrahydroisoquinoline **9** in a highly diastereoselective fashion (diastereoisomeric ratio 92:8). The relative stereochemistry ($J_{1,2}$ 2.9 Hz) was assigned by analogy with **7**.

In summary, a highly diastereoselective method for delivering a benzyl substituent to prochiral imines has been developed. In principle the sulphoximine **1** can be readily resolved into its pure enantiomers[9] from which enantiomerically pure **2** can be obtained. The synthesis of enantiomerically pure **2** and its application to preparing enantiomerically pure 1-benzyltetrahydroisoquinoline alkaloids and related compounds are currently under investigation.

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