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Reversal of the Importance of Steric and Electronic Effects in the Base-Promoted α-Silylation of Sulfides

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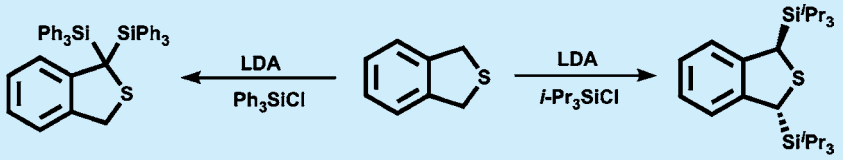
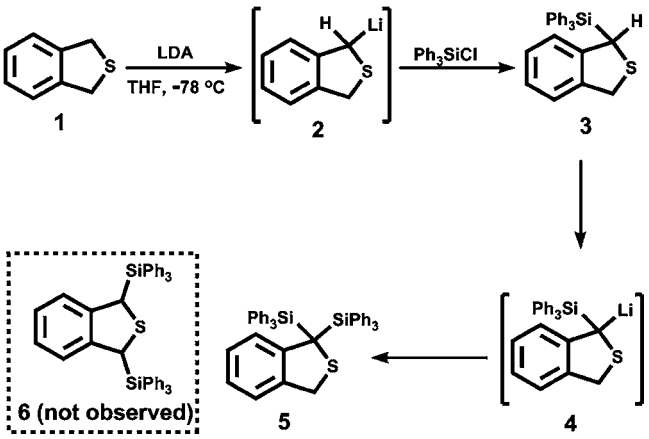
Supporting Information



ABSTRACT: Lithiation of α−C-H groups in organic substrates by RLi or R_2NLi followed by silylation with R'_3SiCl generally provides analogous products regardless of the R′ group of R'_3SiCl. A striking exception using 3,4-benzothiophane as substrate depending on whether R′ is methyl, phenyl, or isopropyl is demonstrated. With R′ = Me or Ph, the geminal α,α-bis-silylated products result whereas with *i*-Pr_3SiCl the *trans*-α,α′-bis-silylated sulfide is formed. The latter pathway provides ready access to the C_2-symmetric enantiomers of *trans*-2,5-bis(triisopropylsilyl)-3,4-benzothiophane.

A recent report from these laboratories described the surprising finding that the bis-α-silylation of 3,4-benzothiophane (**1**) even using LDA or other bulky organo lithium bases and Ph_3SiCl in THF at −78 °C produced only the geminal α,α-bis-silylated sulfide **5** via intermediates **2**−**4** (Scheme 1).[1] None of the isomeric α,α′-bis-silylated product **6** was formed in appreciable amounts (Scheme 1). The same behavior was observed with Me_3SiCl.

Scheme 1. Silylation of 1 with Ph_3SiCl



It was also found that the monolithiated product **2** could be formed cleanly at −78 °C using *n*-BuLi in THF ($t_{1/2}$ > 1 h), and it was shown by ^1H NMR studies to be stable at −78 °C for at least 2 days.[1] Reaction of **2** with Ph_3SiCl gave the monosilylated product **3** in high yield. Deprotonation of **3** was *much faster* than that of **1** and gave only the α-lithiated product **4**. Surprisingly, the rate of deprotonation of **3** to form **4** was fast compared with the rate of reaction of **4** with Ph_3SiCl at −78 °C to form **5** ($t_{1/2}$> 1 h) despite the steric hindrance of the benzylic proton by the α Ph_3Si group.[1] This fact together with other results from our studies shows that the electron-withdrawing, α-anion-stabilizing effect of Ph_3Si[2] far outweighs steric screening by that group, even with bulky bases such as LDA. In addition, it may also be that the benzylic methylene protons of **3** are less readily removed because of an electronic effect of Ph_3Si to destabilize negative charge on the other benzylic carbon δ to silicon. This effect, which would be the opposite of positive charge stabilization by β-silicon, seems reasonable.

The above consideration led us to examine the possibility that it might be possible to reverse the importance of electronic and steric effects of R_3Si in the 3,4-benzothiophane series by further increasing the size of the substituents on silicon. Some years ago, one of us pointed out that the triisopropylsilyl group was large enough to obstruct attack not only on the central Si but also on an α-C−H substituent and even on a carbon β to the *i*-Pr_3Si group;[3] this line of reasoning led to the very interesting findings that are reported herein.

Reaction of 3,4-benzothiophane (**1**) with 2 equiv of LDA and 2 equiv of triisopropylsilyl chloride (TIPSCl) in THF at −78 °C for 5 h gave the (±)-mono-TIPS derivative **7**, mp 62 °C, in 92% yield along with some unreacted **1**, from which it is evident that the *further* deprotonation of **7**, either at the benzylic methine or methylene subunits, is quite slow compared to that of **1**. Despite this result, we found that the reaction of **7** with 5 equiv of LDA at −55 °C for 24 h and further reaction with 2 equiv of TIPSCl at −55 °C in THF for 24 h produced diastereoselectively the racemic *trans*-α,α′-bis-silylated product (±)-**8**, mp 96 °C, in 89% yield (Scheme 2)

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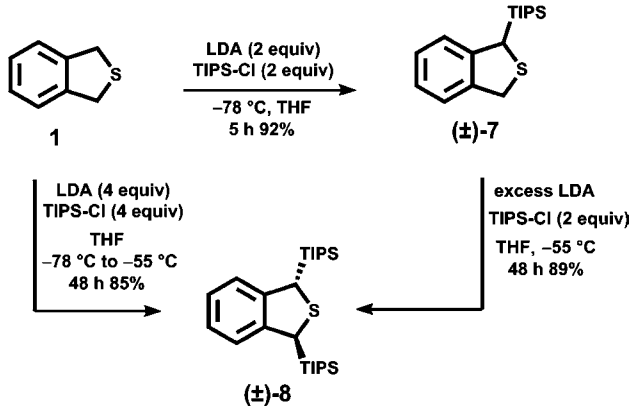
Scheme 2. Silylation of 1 with *i*-Pr_3SiCl



and that none of the *cis* isomer could be detected by ^{1}H NMR and chromatographic analysis. It is apparent that the high diastereoselectivity of the silylation of **7** to **8** is due to the large bulk of the TIPS group.

The structure of (±)-**8** was demonstrated clearly by the ^{1}H and ^{13}C NMR spectra, by the facile separation of enantiomers using HPLC with a Chiral Technologies Chiralcel OD-H column using *n*-hexane as solvent for elution, and by single-crystal X-ray diffraction analysis (Figure 1).[4] The HPLC

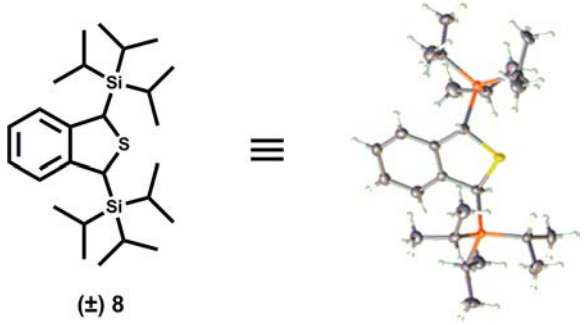


Figure 1. X-ray structure determined for (±)-**8** (Co crystal of (+) and (−) enantiomers).

separation of the (±)-mono-TIPS derivative **7** into the pure enantiomers is remarkably easy and clean. The observed retention times are very different: 6.7 and 12.3 min for the enantiomers with a flat baseline from 7 to 12 min using a Chiralcel OD-H column with hexane as moving phase. As a result, using a 5 cm Chiralcel OD-H column, 5 g of (±)-**7** was resolved cleanly in one pass. The resolution of (±)-**8** by HPLC is not as easy as for (±)-**7** since the retention times for the enantiomers are much closer (3.4 and 4.0 min using hexane, Chiralcel OD-H column and 1.0 mL/min flow rate).

The absolute configurations of the enantiomers of **8** were determined by X-ray crystallographic analysis. The enantiomer of **7** which eluted as the second peak from the Chiralcel OD-H separation (retention time 12.3 min, mp 58 °C, $[\alpha]_D^{23}$ = +157.4, *c* 2.1, $CHCl_3$) was treated with 5 equiv of LDA in THF at −55 °C for 24 h followed by 2 equiv of TIPSCl at −55 °C for 24 h to form (*S*,*S*)-*trans*-2,5-bis(triisopropylsilyl)-3,4-benzothiophane, mp 93 °C, $[\alpha]_D^{23}$ = +115.9 (*c* 1.45, $CHCl_3$), the structure and absolute configuration of which were revealed as **9** (Figures 2 and 3).

Figure 2. Assignment of absolute configuration.

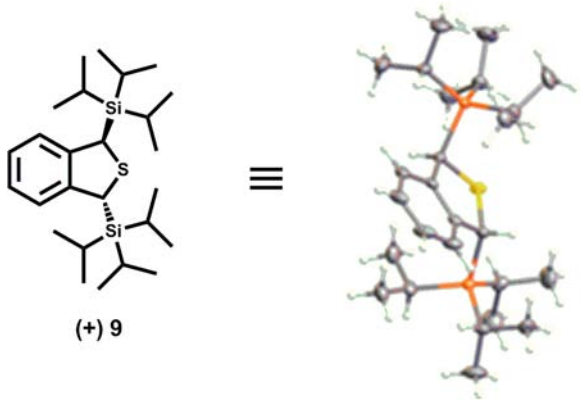


Figure 3. X-ray structure determined for (+)-*trans*-2,5-bis-(triisopropylsilyl)-3,4-benzothiophane (**9**).

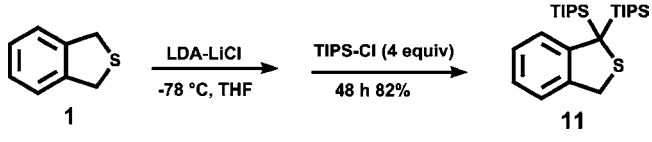
This result also shows that the dextrorotatory enantiomer of the mono-TIPS precursor of **9** possesses the structure **10** (Figure 2).

We have also evaluated (−)-sparteine-promoted enantioselective deprotonation[5] of **1** followed by reaction with TIPS chloride as a route to chiral **7**. For example, gradual addition of *n*-BuLi (1 equiv) to a mixture of **1** and (−)-sparteine (1.5 equiv) in dry diethyl ether at −78 °C followed by reaction with TIPSCl (1.1 equiv) gave (−)-**7** with 3:1 enantioselectivity over (+)-**7**. The enantioselectivity was not improved by the use of other solvents or *s*-BuLi. In view of the ease with which the enantiomers of **7** can be separated chromatographically, this approach was not pursued further.

A surprising result was attained when **1** was treated with 4 equiv of Collum's reagent, LDA−LiCl, and 4 equiv of TIPSCl at −78 °C in THF for 48 h. The major product was found to be the *gem*-bis-TIPS derivative **11** in 82% yield. The LDA−LiCl mixed aggregate not only leads to accelerated deprotonation as shown by Collum et al.[6] but also seems to be much less subjective to steric screening effects during deprotonation than the LDA dimer in THF (Scheme 3). It seems likely that Collum's reagent may be useful in other situations because of its faster deprotonation and smaller effective size relative to LDA dimer in THF.

The mono-TIPS sulfide **7** and the bis-TIPS sulfide **8** when exposed to O_2 or air at ambient temperatures over some days in hexane solution undergo gradual oxidative conversion to the corresponding 10-π-aromatic benzothiophenes, for example,

Scheme 3. Geminal Bis-silylation of 1 to 11



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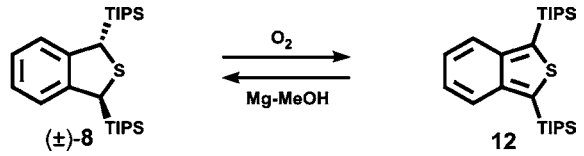
(±)-**8** to **12** (Scheme 4). This oxidative conversion appears to be a free-radical chain process, since it is completely inhibited by 1 mol % of 2,6-di-*tert*-butyl-4-methoxyphenol.

Scheme 4. Interconversion of Benzothiophane/ene 8 to 12



The benzothiophene **12** is readily reduced to (±)-**8** upon reduction with Mg turnings in methanol at ambient temperature for 8 h. The reaction is not completely diastereoselective since a small amount (~5%) of the *cis*-isomer of (±)-**8** is also formed.

In conclusion, the chiral silyl sulfide **9** and its enantiomer are now available by a four-step process starting with 3,4-benzothiophane **1**; these enantiomers are potentially useful ligands for metal-catalyzed asymmetric synthesis. This work also demonstrates a remarkable divergence in the pathways for the silylation of **1** between Me_3SiCl and Ph_3SiCl on one hand and *i*-Pr_3SiCl on the other, the difference being a consequence of the large size of the TIPS group which allows steric shielding to dominate over the electron-withdrawing properties of R_3Si attached to carbon.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for all reactions and products, including copies of ^1H NMR and ^{13}C NMR spectra and single-crystal X-ray diffraction analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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