Stereoselective Additions of Chiral *(E)*-Crotylsilanes to Thionium Ions: Asymmetric Synthesis of Homoallylic Thioethers

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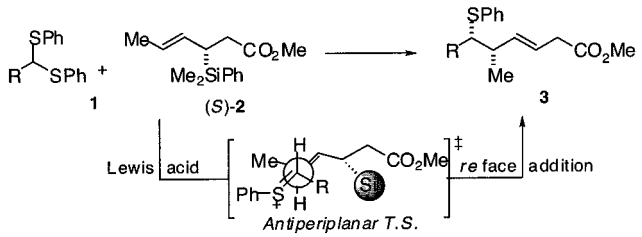
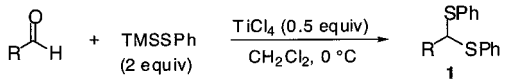
Abstract: Stereochemically well-defined homoallylic thioethers **3** are synthesized via Lewis acid promoted condensation reaction between chiral organosilane reagents **2** and *in situ* generated thionium ions. The stereochemical course of the reaction is consistent with earlier reports concerning crotylsilations of oxonium ions.

Thioethers are useful heteroatom functional groups in organic synthesis.[1] An extensive list of methods have been developed for the preparation of α-sulfenyl carbonyl compounds,[2] α-(α-sulfenyl)alkylated carbonyl compounds,[3] vicinal thioether alcohols,[4] and vicinal dithioethers.[5] A number of reports have recently appeared that describe the stereoselective synthesis of thioether derivatives and their use in asymmetric transformations.[6] To further support this notion Christoffers has recently reported that chiral bi- and tridentate ligands have been synthesized bearing a thioether moiety as an additional electron donor.[7] As a consequence of the growing importance of molecules bearing stereogenic C−S bonds, the development of a new stereoselective approach to this class of compounds would constitute a meaningful contribution to this area. Previous reports from our laboratory have described the use of chiral (*E*)-crotylsilanes as carbon nucleophiles in highly diastereo- and enantioselective addition reactions to acetals and aldehydes. Those studies resulted in the development of a useful strategy for the asymmetric construction of homoallylic ethers,[8] tetrahydrofurans,[9] γ-alkoxy-α-amino acid synthons,[10] subunits of many polyketide, and amino acid derived natural products. Applications have been illustrated with our syntheses of rutamycin/oligomycin[11] and motuporin.[12] In this paper, we report that the Lewis acid promoted crotylation reactions of chiral (*E*)-crotylsilanes[13] with *in situ* generated thionium ions provide stereochemically well-defined homoallylic thioethers.[14] The thioacetals **1**, readily available from the corresponding aldehydes, when condensed with chiral silane reagents afford under Lewis acid catalysis *syn*-homoallylic thioethers **3** with useful levels of selectivity (Scheme 1).

Scheme 1



Scheme 2



We began these experiments with the expectation that the chiral (*E*)-crotylsilane **2** would show similar characteristics for Lewis acid catalyzed reactions with thioacetals as we have previously documented with acetals.[7] Thioacetals **1** were prepared according to a procedure described by Evans and co-workers.[15] Treatment of aldehydes with (phenylthio)trimethylsilane in the presence of $TiCl_4$ cleanly produced diphenylthioacetal **1** (Scheme 2).

As one of the principle routes to thionium ions, Lewis acid mediated ionization of thioacetals was surveyed using five different Lewis acids. A summary of these experiments describing the addition reaction of organo silane (*R*)-**2** to diphenylthioacetal **1** is given in Table 1. In accordance with the observations of Heathcock et al.,[11] our experiments have also determined that 1.2−1.5 equiv of tin tetrachloride ($SnCl_4$) is the most effective Lewis

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‡ Division of Organic Chemistry ACS Graduate Fellow 2001−2002 sponsored by Wyeth-Ayerst.

§ Arthur C. Cope Scholar 2002.

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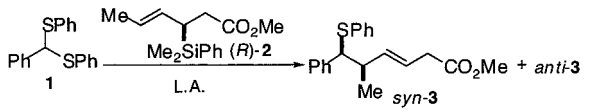
Table 1. Lewis Acid Promoted Addition Reaction of Silane (*R*)-2 to Thioacetal 1



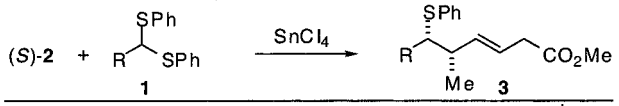
entry	Lewis acid[a]	diastereomer ratio (*syn*/*anti*[b])	% yield[c]
1	$BF_3{\cdot}OEt_2$	5:1	42
2	$TiCl_4$	–	<10
3	$SnCl_4$	7:1	94
4	$SbCl_5$	4:1	43
5	TMSOTf	–	0

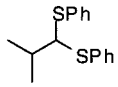
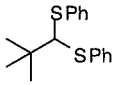
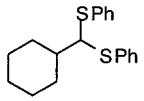
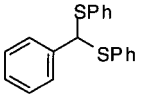
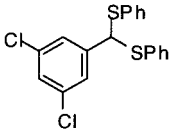
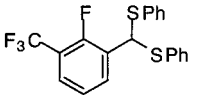
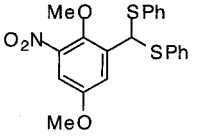
[a] All reactions were carried out in CH_2Cl_2 (0.25−0.3 M) at 0 °C to room temperature using 1.2−1.5 equiv of Lewis acids. [b] Ratios were determined by ^{1}H NMR on the crude reaction mixtures. [c] Yields were based on mixtures of diastereoisomers isolated by chromatography on SiO_2.

acid for promoting the asymmetric addition reaction between (*R*)-**2** and **1** for the formation of homoallylic thioether **3**.[16] As shown in Table 1 (entries 1, 2, and 5), the use of boron trifluoride etherate ($BF_3{\cdot}OEt_2$), titanium tetrachloride ($TiCl_4$), or antimony pentachloride ($SbCl_5$) resulted in a substantial decrease in reaction rate, and in one case only, trace amounts (<10%) of the desired product were detected. Although it is the Lewis acid of choice in the addition reactions of chiral silane reagents to oxygen based acetals, TMSOTf failed to deliver any amount of the desired product (entry 5).[7] The optimized conditions for the Lewis acid-catalyzed asymmetric addition of the chiral (*E*)-crotylsilane **2** to thioacetal **1** were determined to be 1.5 equiv of $SnCl_4$ with methylene chloride as the solvent for 16 h (0 °C → rt). Several other useful pieces of information emerged from the above experiments, which prompted us to further investigate the utility of the chiral silane reagents in enantioselective addition reactions. First, the $SnCl_4$-catalyzed reaction proceeded cleanly and efficiently at room temperature and was near completion in a matter of hours. Second, useful levels of diastereoface selectivity were reached under the described reaction conditions. Third, the formation of the isolated *syn*-homoallylic thioether product could be rationalized by the use of an *anti*-S_E' addition mode and is consistent with oxonium ions, and thus follows closely our previous work in the area.[17] This notion served as the basis for the assignment of absolute stereochemistry of the homoallylic thioether.[7]

Having established reaction conditions, the generality of this reaction was explored. A summary of experiments describing the enantioselective addition reactions to a variety of thioacetals is given in Table 2. As expected on the basis of the above Lewis acid study, $SnCl_4$ was found to be most effective and typically afforded high yields of the homoallylic thioether **3**. Acyclic and cyclic aliphatic thioacetals and aromatic thioacetals are all suitable substrates for this reaction, although branched aliphatic substrates generally gave higher levels of selectivity than aromatic substrates (entries 1−3 vs 4−7). The heteroaromatic thioacetals, such as oxazole-, furan-, and pyridine-derived thioacetals (not shown), did not yield the desired homoallylic thioethers under the reaction conditions investigated.

Table 2. $SnCl_4$-Promoted Addition Reactions of (*S*)-2 to Thioacetals 1



entry[a]	thioacetal		Product (% yield[b]; *syn*/*anti*[c])
1		**1a**	**3a** (94%; 10:1)
2		**1b**	**3b** (76%; 30:1)
3		**1c**	**3c** (86%; 15:1)
4		**1d**	**3d** (94%; 7:1)
5		**1e**	**3e** (89%; 8:1)
6		**1f**	**3f** (74%; 6:1)
7		**1g**	**3g** (80%; 8:1)

[a] All reactions were carried out in CH_2Cl_2 (0.25−0.3 M) at 0 °C to room temperature over a 16-h period using 1.5 equiv of $SnCl_4$. [b] Yields were based on mixtures of diastereomers isolated by chromatography on SiO_2. [c] Ratios were determined by ^{1}H NMR analysis on the crude reaction mixtures.

For the cases examined in this study, the additions proceeded with predictable diastereoface selectivity for the formation of the two stereogenic centers. A trend of diastereoselectivity has emerged that is consistent with a stereospecific *anti*-$S_{E'}$ pathway as originally documented by Fleming[14] and Kumada[18] and which has been confirmed by Nakai[19] and Marshall[20] as well as our laboratory.[21] This may be described by an open transition-state model as illustrated for the silane (*S*)-**2** in Scheme 1. In this arrangement the C−Si bond is positioned *anti* to the thionium ion and coplanar to the *p*-orbital of the adjacent π-bond allowing stabilization of the emerging secondary carbocation. The sense of induction is regulated by the absolute configuration at the stereogenic center bearing the silicon group.[18] For example, (*S*)-silane **2** adds preferentially to the *re* face of the thionium ion (Scheme 1) and (*R*)-**2** silane adds to the *si* face (Table 1).

The relative stereochemistry of the crotylation products **3a**−**f** has been assigned by correlation with the *anti*-

(16) All new compounds were isolated as chromatographically pure materials and exhibited acceptable ^{1}H NMR, ^{13}C NMR, IR, HRMS spectra data.

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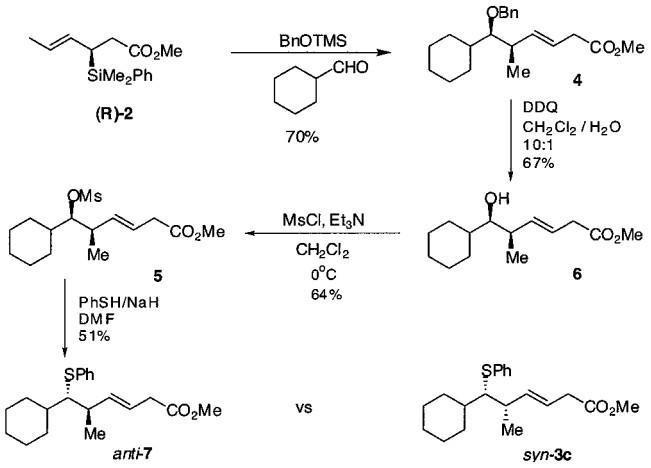
Scheme 3. Stereochemical Assignments of 5 via ^{1}H NMR Analysis



homoallylic phenyl sulfide, which was derived from the *syn*-homoallylic benzyl ether **4** through a classical S_N2 displacement reaction (Scheme 3). The formation of the major isomer (*syn*-**3c**) is consistent with previous studies from our laboratory concerning the reaction of (*E*)-crotylsilanes with unfunctionalized achiral acetals (aldehydes) which have demonstrated universal *syn*-selectivity in the formation of homoallylic ethers[7] and alcohols.[18] The homoallylic ether **4** was converted to the *anti*-phenyl sulfide **7** in a straightforward three-step sequence: (1) deprotection of the benzyl ether using DDQ, followed by (2) mesylation of the derived secondary alcohol (MsCl/Et_3N), and (3) S_N2 displacement of the mesylate using the sodium salt of thiophenol afforded the *anti*-diastereomer. This diastereomer displayed different NMR characteristics (i.e., chemical shifts and different three bond coupling constants when compared to the *syn*-diastereomer **3c**. The stereochemistry of the remaining crotylation products **3a**−**g** is assigned by analogy with **7**.

In closing, we have shown that the asymmetric additions of enantioenriched (*E*)-crotylsilane reagents to thionium ions generated through the ionization of the corresponding thioacetals expands the scope and utility of our evolving chiral silane-based bond construction methodology. Further studies concerning the application of these stereochemically well-defined homoallylic thioethers in organic transformations will be reported as permitted.

Experimental Section

General Method. ^{1}H NMR spectra were recorded on a 400 MHz spectrometer at ambient temperature unless otherwise states. ^{13}C NMR were recorded on a 75 MHz spectrometer at ambient temperature. Chemical shifts are reported in parts per million relative to chloroform (^{1}H, δ 7.24; ^{13}C, δ 77.0). All ^{13}C NMR were recorded with complete proton decoupling. Infrared spectra were recorded on an FT-spectrophotometer. High resolution mass spectra were obtained in the Boston University Mass Spectrometry Laboratory. Analytical thin-layer chromatography was performed on 0.25 mm silica gel 60-F plates. Flash chromatography was performed as previously described.[22] When specified as "anhydrous", solvents were distilled and/or stored over 4 Å molecular sieves prior to use. Yields refer to chromatographically pure materials unless otherwise stated. DriSolv DMF was used as supplied. Tin tetrachloride and titanium tetrachloride were distilled from copper prior to use. All other reagents were used as supplied by Aldrich and Alfa Aesar. All reactions were performed under a dry argon or nitrogen atmosphere in oven-dried glassware.

General Procedure for the Preparation of Dithioactals from Aldehydes Illustrated for 1a (also see ref 12). A solution of isopropyl aldehyde (1 g, 13.87 mmol) and trimethylsilyl thiophenol (5.05 g, 27.7 mmol) in CH_2Cl_2 (0.25 M) was cooled to 0 °C. Freshly distilled $TiCl_4$ (0.95 mL, 6.9 mmol) was added dropwise, and the solution was allowed to stir at 0 °C for approximately 45 min. The reaction was quenched with excess 1.0 M HCl, extracted with CH_2Cl_2, and dried over anhydrous $MgSO_4$. The crude product was purified via flash chromatography (SiO_2, 0% → 3% EtOAc/hexanes), affording 74% yield of pure **1a** ((3.161 g, 10.3 mmol) as a yellow oil.

General Procedure for the Preparation of Homoallylic Thioethers Illustrated for 3a. A solution of isopropyl aldehyde dithioacetal (126 mg, 0.46 mmol) and (*S*)-*E*-crotylsilane (100 mg, 0.38 mmol) in CH_2Cl_2 (0.25 **M**) was cooled to 0 °C. Freshly distilled $SnCl_4$ (0.10 mL, 0.57 mmol) was added dropwise, and the solution was stirred and allowed to warm to room temperature over a 16-h period. The reaction was quenched with excess aqueous $NaHCO_3$, extracted with CH_2Cl_2, and dried over anhydrous $MgSO_4$. The crude product was purified via flash chromatography (SiO_2 0%→3% EtOAc/hexanes), yielding 94% of pure **3a** (0.134 g, 0.43 mmol) as a yellow oil.

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Supporting Information Available: $[\alpha]^{26}_D$, IR, ^{1}H and ^{13}C NMR, MS spectral data for compounds **1**−**7**, and experimental procedures for the preparation of compounds **4**−**7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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