



A NOVEL DIASTEREOSELECTIVE SYNTHESIS OF CHIRAL, NON-RACEMIC UNSYMMETRICAL THIOACETALS USING SILICON-INDUCED PUMMERER-TYPE REACTION

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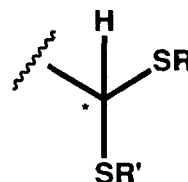
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Abstract: Chiral, non-racemic sulfoxides were reacted with thiols and BSA in the presence of a catalytic amount of TMSOTf in MeCN at rt overnight to give the corresponding chiral, non-racemic *anti*-thioacetals with high diastereoselectivity.

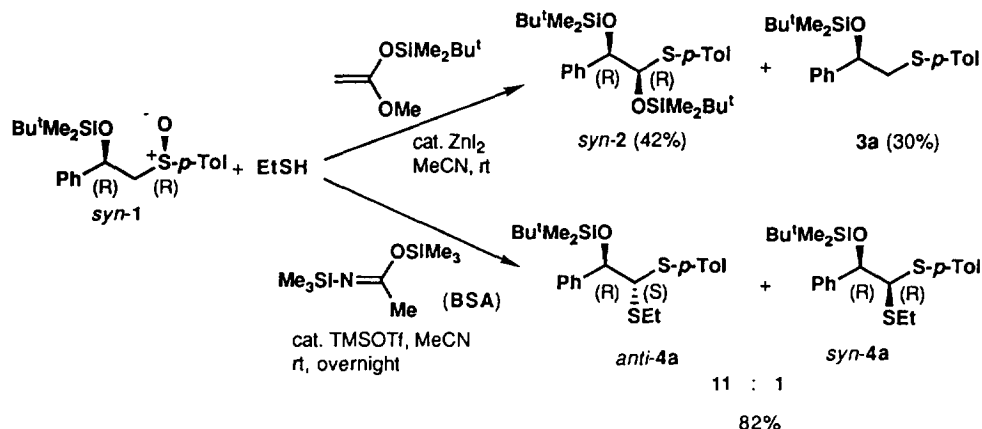
Although several methods for the synthesis of racemic unsymmetrical thioacetals have been reported, there is no useful method for the synthesis of chiral, non-racemic unsymmetrical thioacetals,¹ which are expected to be useful precursors^{2,3} for an asymmetric synthesis. Among the methods for racemic thioacetals; the reaction of α -chlorosulfides⁴ or *O*, *S*-acetals with thiolate anions,⁵ the sulfonylation of α -lithiosulfides,⁶ the Grignard reaction of thiocarbonyl compounds,⁷ the thiophilic allylation of dithioesters or trithiocarbonyl compounds,⁸ and the Pummerer reaction of sulfoxides in the presence of thiols,^{9, 10} the Pummerer reaction seems to be an efficient method for the synthesis of the chiral, non-racemic unsymmetrical thioacetals because of the ready availability of the starting optically active sulfoxides¹¹ and mild reaction conditions. Thus, Tanikaga reported¹⁰ the synthesis of unsymmetrical thioacetals by the reaction of sulfoxides with thiols in the presence of trifluoroacetic anhydride (TFAA). This procedure, however, is limited to the synthesis of simple thioacetals.¹² We also observed that some chiral, non-racemic sulfoxides reacted with TFAA to give the deoxygenated product exclusively¹³ without producing the desired thioacetals. As an extension of our silicon-induced asymmetric Pummerer-type reaction,¹⁴⁻¹⁶ we now undertook the asymmetric synthesis of chiral, non-racemic unsymmetrical thioacetals using silylating agents and found that the use of *N*, *O*-bistrimethylsilylacetoamide (BSA) in the presence of thiols gave the chiral, non-racemic thioacetals with high diastereoselectivity.

At first, we examined the reaction of the chiral, non-racemic sulfoxide with thiol using our silicon-induced Pummerer-type rearrangement conditions.¹⁵ The treatment of the optically active sulfoxide (*syn*-1) with EtSH and *O*-methyl-*O*-*tert*-butyldimethylsilyl ketene acetal in the presence of a catalytic amount of ZnI₂ in MeCN gave a mixture of the chiral, non-racemic *O*, *S*-acetal (*syn*-2, a normal Pummerer-type rearrangement product) and the sulfide (3a, a reduction product). We then investigated the reaction of *syn*-1 with EtSH in the presence of various other silylating agents. The desired chiral, non-racemic unsymmetrical thioacetals (*anti*- and *syn*-4a) were obtained from *syn*-1 by the reaction with BSA in the presence of a catalytic amount of



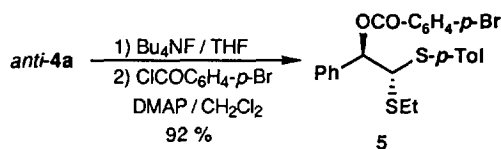
chiral, non-racemic
unsymmetrical thioacetals

TMSOTf. Treatment of *syn*-1 (1 eq.) with EtSH (1.5 eq.) and BSA (5 eq.) in the presence of TMSOTf (0.1 eq.) in MeCN at rt overnight gave an 11:1 diastereomixture of *anti*-4a and *syn*-4a in 82% yield (Scheme 1).



Scheme 1

The stereochemistry of the products (*anti*- and *syn*-4a) was determined using X-ray crystallographic analysis¹⁷ of the *p*-bromobenzoyl ester (5) of the major isomer (Scheme 2, Fig. 1).



Scheme 2

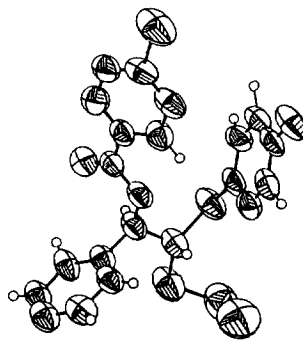


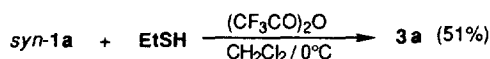
Fig. 1 X-Ray crystallographic structure of 5.

Similarly, chiral, non-racemic sulfoxides (1 and 6) were reacted with various types of thiols and BSA under the same conditions. All reactions proceeded with good chemical yields (Table 1). A high *anti*-selectivity of the product was observed for both the *syn* and *anti*-sulfoxides. Although the mechanism of the predominant formation of the *anti*-isomer is not well understood, it may proceed by the cyclic Cram model of the silicon coordinated intermediate^{18,19} or the Cram model of the thionium intermediate²⁰ (Scheme 3).

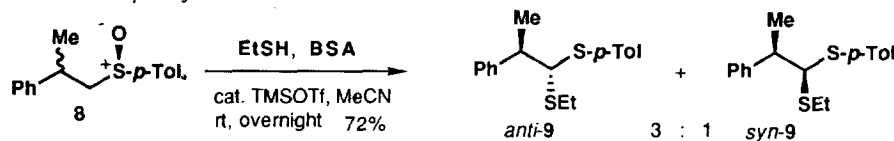
In conclusion, we report the novel stereoselective synthesis of chiral, non-racemic thioacetals using the silicon-induced Pummerer-type reaction. Application of these optically active thioacetals to an asymmetric synthesis is now under investigation.²¹

References and Notes

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17. The crystal data for **5** are as follow: orthorhombic; $P2_12_12_1$ with $a=13.932(3)$, $b=27.308(5)$, $c=6.079(2)$ Å, $V=2312.7(8)$ Å³, $Z=4$, and $\mu(\text{Cu K}\alpha)=40.18\text{cm}^{-1}$ by Mac Science MXC 18 instrument. Final R value was 0.068 for 1381 reflections. The supplementary materials have been deposited at the Cambridge Crystallographic Data Centre.
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21. From a preliminary experiment, a site-selective sulfoxidation ($-\text{S}(\text{O})\text{R}$) of *anti*-**4a** was observed by the treatment with *m*-chloroperbenzoic acid.