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Highly Stereoselective Vinylogous Pummerer Reaction Mediated by Me_3SiX

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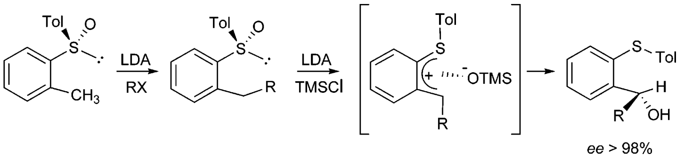
ABSTRACT



A highly stereoselective vinylogous Pummerer rearrangement involving 1,4-migration of the sulfinyl oxygen atom occurs when *ortho*-sulfinyl benzyl carbanions are treated with trimethylsilyl halides. The reaction proceeds in good yield and affords optically pure benzyl alcohols with extremely high enantioselectivity (ee > 98%).

Since the initial report in 1909,[1] the Pummerer reaction has established itself as a very useful method for the preparation of α-substituted sulfides. The reaction has been widely studied and has received considerable attention as a valuable synthetic process.[2] Pummerer thionium ions are generally formed by treating a sulfoxide bearing an α-hydrogen with acetic anhydride.[3] The finding that thionium ions may serve as electrophiles in electrophilic substitution chemistry has greatly extended the synthetic range of the Pummerer reaction.[4] Thus, both inter- and intramolecular versions of the process have been used to prepare a wide assortment of compounds.[5] Currently, Pummerer-based transformations are finding widespread application in carbo- and heterocyclic synthesis by reaction of the initially generated thionium ion with internally disposed nucleophiles.[6]

The related vinylogous Pummerer reaction of vinylic sulfoxides also proceeds by an electrophilic thionium ion intermediate formed by γ-proton loss followed by sulfoxide S−O bond scission.[7,8] The unsaturated thionium ion is then intercepted by a nucleophile at the γ-position. Recently, our two research groups discovered a new type of vinylogous tin-Pummerer rearrangement that occurs with benzyl-tin derivatives such as **1** that possess a sulfinyl group at the ortho position of the aromatic ring.[9] When treated with an acyl chloride, the reaction proceeds by a halide-induced cleavage of the Sn−C bond followed by nucleophilic attack of the leaving carboxylate at the γ-position of the conjugated

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(1) Pummerer, R. *Chem. Ber.* **1909**, *42*, 2282.

(2) (a) De Lucchi, O.; Miotti, U.; Modena, G. In *Organic Reactions*; Paquette, L. A., Ed.; Wiley: 1991; Chapter 3, p 157. (b) Grierson, D. S.; Husson, H. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol. 6, p 909. (c) Kennedy, M.; McKervey, M. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol. 7, p 193.

(3) (a) Padwa, A.; Gunn, D. E.; Osterhout, H. M. *Synthesis* **1997**, 1353. (b) Padwa, A. *Pure Appl. Chem.* **2003**, *75*, *47*.

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(7) Leading references to vinylogous Pummerer reactions can be found in: (a) Padwa, A.; Kuethe, J. T. *J. Org. Chem.* **1998**, *63*, 4256. (b) Marino, J. P.; Bogdan, S.; Kimura, K. *J. Am. Chem. Soc.* **1992**, *114*, 5566.

(8) For a new variant of the vinylogous Pummerer reaction, see: (a) Feldman, K. S.; Vidulova, D. B. *Org. Lett.* **2004**, *6*, 1869. (b) Feldman, K. S.; Karatjas, A. G. *Org. Lett.* **2004**, *6*, 2849.

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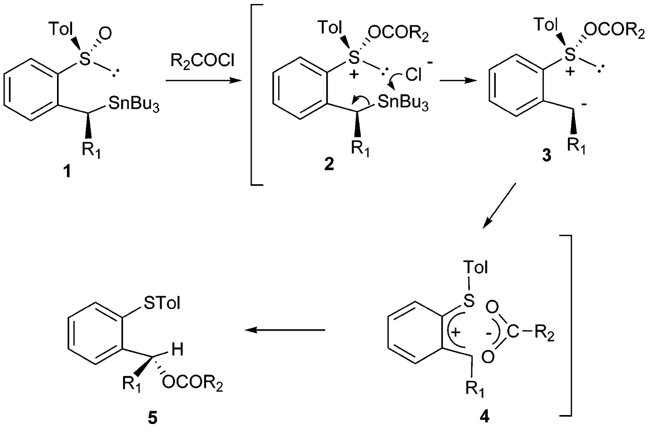
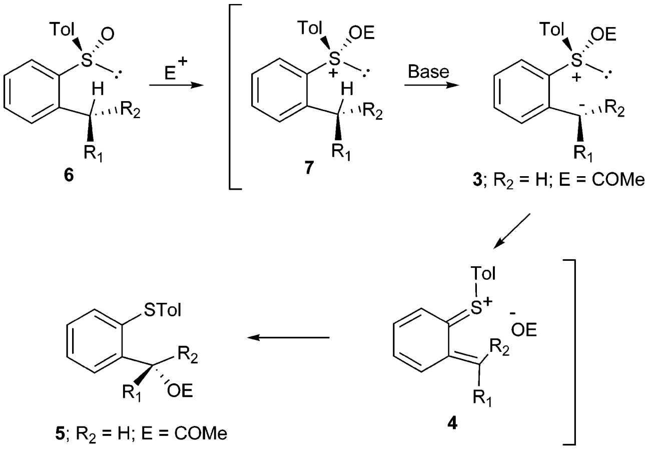
Scheme 1



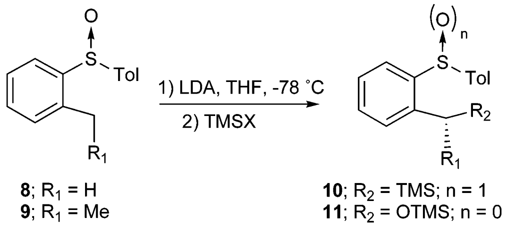
thionium ion (Scheme 1).[10] Our continuing interest in this reaction derives from the complete stereoselectivity observed in the migration of the RCO_2^- group, thereby permitting the synthesis of enantiomerically pure benzyl alcohols. Efficient asymmetric syntheses of benzylic alcohols are of considerable interest because of their importance in biological systems and their usefulness as chiral building blocks in organic synthesis.[11] The main drawback of the vinylogous tin-Pummerer sequence shown in Scheme 1 is the need to prepare the toxic benzyl tin derivative **1** in a diastereomerically pure form. We reasoned that generation of the key intermediate **3** could also be accomplished by a simple deprotonation at the benzylic position of an oxysulfonium salt (i.e., **7**) (Scheme 2). This modified reaction sequence would allow for the synthesis of optically pure benzylic alcohols provided one could find the necessary experimental conditions to permit the 1,4-migration of the OE group to occur with high stereoselectivity. In this communication, we report results showing that optically pure benzylic alcohols can be obtained with >98% enantioselectivity when *ortho*-sulfinyl-substituted benzyl carbanions are treated with trimethylsilyl halides.

Scheme 2



The first model system we examined focused on the simple sulfoxides **8** ($R_1 = H$) and **9** ($R_1 = Me$) (Table 1). The initial trial experiments involved treating **8** with several different anhydrides. However, only $(Tf)_2O$ was capable of forming the acyloxysulfonium salt (i.e., **7**), but the TfO anion was not basic enough to generate the benzylic carbanion **3**. When stronger bases were added to the salt, a complex reaction mixture was obtained. Considering our lack of success using these conditions, we decided to invert the order of addition of the reagents. The use of LDA as a base is known to efficiently lead to *ortho*-sulfinyl-substituted benzyl carbanions that can act as nucleophiles in many different reaction pathways.[12] The resulting benzyl carbanions are easily recognized by the intense purple coloration of the solution. The critical problem was to identify a proper electrophile that would regioselectively react at the sulfinyl oxygen rather than at the anionic carbon atom. We noted that the addition of acyl halides[13] resulted in a complex mixture of products. After trying various electrophiles, we found that trimethyl-

Table 1. Reactions of **8** and **9** with Different Electrophiles



entry	R_1	X	n value in $(O)_n$	product (R_2)	yield	ee
1	H	Cl	1	**10** (TMS)	43	
2	H	Cl	1	**10** (TMS)	57[a]	
3	H	Br	1	**10** (TMS)	63	
4	H	I	1	**10** (TMS)	48	
5	Me	Cl	0	**11** (OTMS)	65	>98
6	Me	Br	0	**11** (OTMS)	40	>98
7	Me	I	0	**11** (OTMS)	<10	
8	Me	OTf	0	**11** (OTMS)	<10	
9	Me	Cl	0	**11** (OTMS)	70[a]	>98
10[b]	Me	Cl	0	**11** (OTMS)	30	>98
11[c]	Me	Cl	0	**11** (OTMS)		

[a] TMSCl redistilled. [b] Solvent: Et_2O. [c] Solvent: CH_2Cl_2.

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(10) For some examples of the tin-Pummerer reaction, see: (a) Beddoes, R. L.; MacLeod, D.; Moorcroft, D.; Quayle, P.; Zhao, Y.; Davies, G. M. *Tetrahedron Lett.* **1992**, *33*, 417. (b) Pohmakotr, M.; Sithikanchanakul, S. *Tetrahedron Lett.* **1989**, *30*, 6773.

(11) For some leading references, see: (a) Ponzo, V. L.; Kaufman, T. S. *Synlett* **2002**, 1128. (b) Hillier, M. C.; Desrosiers, J. N.; Marcoux, J. F.; Grabowski, E. J. J. *Org. Lett.* **2004**, *6*, 573. (c) Nakamura, S.; Oda, M.; Yasuda, H.; Toru, T. *Tetrahedron* **2001**, *57*, 8459.

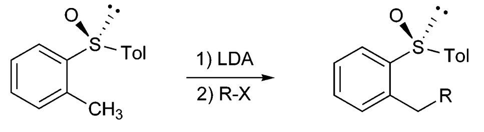
(12) For reaction with carbonyl groups, see: (a) García Ruano, J. L.; Aranda, M.; Carreño, M. C.; Toledo, M. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 2736. For reaction with imines, see: (b) García Ruano, J. L.; Alemán, J.; Soriano, J. F. *Org. Lett.* **2003**, *5*, 677. (c) García Ruano, J. L.; Alemán, J. *Org. Lett.* **2003**, *5*, 4513.

silylbromide produced the silylated product **10** in good yield (63%). Other unidentifiable products were produced when TMSCl or TMSI was used.[14] The above result suggests that the reactivity of the benzyl carbanion derived from **8** is higher at the carbon atom than at the sulfinyl oxygen position.

Most interestingly, when the closely related benzyl sulfoxide **9** (R_1 = Me) was treated under an identical set of conditions, trimethylsilyloxy-thioether **11** was the major product isolated (entry 5, Table 1) and is the result of a vinylogous Pummerer rearrangement.[15] The exclusive formation of **11** suggests that the relative reactivity of the two nucleophilic centers (carbon and oxygen) in the benzyl carbanion derived from **9** is inverted with respect to the situation encountered with the carbanion derived from **8**. In the case of sulfoxide **9**, the sulfinyl oxygen atom corresponds to the most reactive site of the sulfinyl benzyl carbanion. Notably, the enantiomeric purity of the resulting product **11** has the remarkably high value of 98% ee. This value was determined by cleavage of the Si−O bond using Bu_4NF followed by an examination of the NMR spectrum of the Mosher ester derived from the corresponding alcohol.[16] In an attempt to improve the overall yield of the reaction, we evaluated the role of different parameters such as concentration, solvent, and the nature of the silylated electrophile (Table 1). TMSCl was found to be the most efficient electrophile (entry 5), whereas TMSI and TMSOTF gave much lower yields of product (entries 7 and 8). The optimal conditions consisted of using redistilled TMSCl at a concentration of 0.1 M and at −78 °C (entry 9). Lower or higher concentrations resulted in a diminished yield.

To further evaluate the scope and generality of the asymmetric vinylogous Pummerer reaction, it became necessary to prepare several more highly substituted sulfinyl derivatives (i.e., **12**−**19**). The method previously used to synthesize **8**[12a] and **9**[12b] was based on the sulfinylation of the Grignard derivatives derived from 2-bromotoluene and 2-bromoethylbenzene. This procedure is severely limited using the more highly substituted bromides due to the unavailability of the starting materials. Instead, we opted to carry out a base-induced alkylation of *ortho*-sulfinyl toluene **8** that proceeded in high yield (Table 2). Thus, the reaction of **8** with LDA in THF at −78 °C furnished the expected anion, which readily reacted with various halides. The reaction proceeded best when alkyl iodides were employed, although the yield was respectable with the corresponding bromides. It was not possible to carry out an alkylation using secondary halides due to a competitive elimination.[17] Interestingly, when 2-phenethyl iodide or bromide was used, the substitution product **14** (entry 5/6) was obtained and only trace quantities of styrene were detected in the crude reaction mixture.[18] The last five entries in Table 2 demonstrate the flexibility of the alkylation when more complicated halides are used as the electrophiles.

Table 2. Alkylation Reactions of Compound **8**



8 **12-19**

entry	alkyl halide	product (R)	yield (%)
1	methyl iodide	CH_3 (**9**)	98
2	ethyl bromide	CH_3CH_2 (**12**)	85
3	ethyl iodide	CH_3CH_2 (**12**)	92
4	benzyl bromide	$PhCH_2$ (**13**)	93
5	2-phenylethyl bromide	$PhCH_2CH_2$ (**14**)	59
6	2-phenylethyl iodide	$PhCH_2CH_2$ (**14**)	81
7	2-(3,4-dimethoxyphenyl)ethyliodide	(3,4-dimethoxyphenyl)CH_2CH_2 (**15**)	85
8	2-bromopropane	starting material	
9	1-bromoethylbenzene	starting material	
10	allyl bromide	$CH_2CH{=}CH_2$ (**16**)	82
11	ICH_2OMe	CH_2OMe (**17**)	94
12	$BrCH_2CH_2OTIPS$	CH_2CH_2OTIPS (**18**)	15
13	ICH_2CH_2OTIPS	CH_2CH_2OTIPS (**18**)	55
14	ICH_2CH_2NPht[a]	CH_2CH_2NPht (**19**)	51

[a] Pht = phthalimide.

With these sulfinyl compounds in hand, we proceeded to investigate their vinylogous Pummerer behavior. Using the conditions described in Table 1, the reactions were found to occur rapidly and furnished a wide variety of benzylic alcohols (Table 3) in yields ranging between 50 and 70% for the three-step sequence. Complete stereoselectivity (ee > 98%) was observed in all of the cases examined. The presence of a heteroatom on the side chain was found to influence the reaction course. Thus, 2-*p*-tolylsulfinyl styrene (**27**) was the only product obtained starting from **17** (entry 8), thereby indicating that elimination of the methoxy group is preferred over the rearrangement. In contrast, the homologous compound **18** afforded diol **26** in 56% yield under the reaction conditions. Finally, the more heavily substituted amide **19** failed to undergo the reaction.[19]

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(13) García Ruano, J. L.; Alemán, J.; Aranda, M. T.; Fernández-Ibáñez, M. A.; Rodríguez-Fernández, M. M.; Maestro, M. C. *Tetrahedron* **2004**, *60*, 10067.

(14) R_3N and R_3SiX have also been used in some cases to produce the normal Pummerer reaction; see: Tokitoh, N.; Igarashi, Y.; Ando, W. *Tetrahedron Lett.* **1987**, *28*, 5903.

(15) Under similar conditions, ethylphenylsulfoxide underwent C-silylation; see: Miller, R. D.; Hassig, R. *Tetrahedron Lett.* **1984**, *25*, 5351. An alternative vinylogous silicon-Pummerer rearrangement could have also been invoked (see: Brook, A. G.; Anderson, D. G. *Can. J. Chem.* **1968**, *46*, 2115. Shainyan, B. A.; Kipichenko, S. V.; Freeman, F. *J. Am. Chem. Soc.* **2004**, *124*, 11456) to explain the stereochemical results encountered. However, we could not obtain any evidence indicating the formation of a *C*-silyl derivative, even when working in the presence of HMPA, which would enhance the nucleophilicity at the carbon atom.

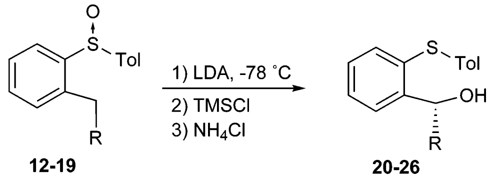
(16) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.

(17) This behavior is also found with the alkylation of other sulfinyl carbanions; see: Drabowicz, J.; Kielbasinski, P.; Mikolajczky, M. In *The Chemistry of Sulphones and Sulphoxides*; Patai, S., Rappoport, Z., Stirling, C., Eds.; Wiley: Chichester, 1988; pp 305−317.

(18) There are some examples in the literature where substitution rather than elimination was observed with phenylethyl-substituted systems; see: Solladié-Cavallo, A.; Martin-Cabrejas, L. M.; Caravatti, G.; Lang, M. *Tetrahedron: Asymmetry* **2001**, *12*, 967.

(19) Stabilization of the carbanionic intermediate by the nitrogen atom may be responsible for the lack of reactivity of **19**.

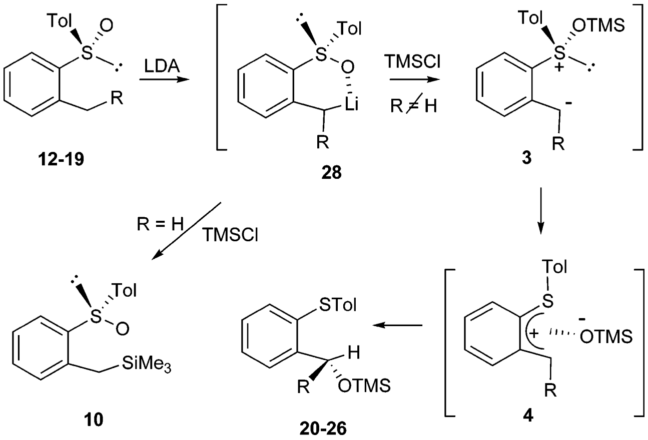
Table 3. Scope of the Sila-Pummerer Reaction



entry	R (product)	yield (%)	ee (%)
1	CH_3 (**20**)	69	>98
2	CH_2CH_3 (**21**)	67	>98
3	CH_2Ph (**22**)	51	>98
4	CH_2CH_2Ph (**23**)	54	>98
5	3,4-$(OMe)_2(C_6H_3)CH_2CH_2$ (**24**)	58	>98
6	$CH_2CH{=}CH_2$ (**25**)	65	>98
7	CH_2CH_2OH (**26**)	56	>98
8	CH_2OMe	see text	
9	CH_2CH_2NPht	no reaction	

The observed stereochemical results can best be explained by assuming that the benzyl lithiate intermediate **28** (generated from LDA) reacts with TMSCl at the benzylic carbon position when the R substituent is a hydrogen atom ($R = H$) to give **10**[20] (Scheme 3). However, when an alkyl substituent is present ($R \neq H$) (i.e., **12**−**19**), the oxygen atom of the sulfoxide group preferentially reacts with TMSCl as a consequence of the diminished nucleophilicity on the carbon atom (more hindered position). The overall reaction produces the trimethylsilyloxy sulfonium ion **3**. This transient species readily eliminates Me_3SiO^- and furnishes the conjugated thionium salt **4**, which reacts further at the benzylic position to give compounds **20**−**26**. The complete stereoselectivity encountered in this reaction suggests that an intimate ion pair is involved (Scheme 3). This species maintains the Me_3SiO^- ion on the same face it originally occupied in its most stable conformation and ultimately leads to the (*R*)-alcohols by internal collapse. Alternatively, a concerted migration of the Me_3SiO^- ion to the benzylic position is also possible. An attempt to trap the conjugated thionium ion intermediate **4** by using the activated 3,4-dimethoxy-phenylethyl substituent (i.e., **15**) failed to capture the cation. Only the vinylogous Pummerer product **24** was obtained. Although the failure to intramolecularly trap the cationic center in **4** is consistent with a concerted migration, it can also be attributed to the fact that the collapse of **4** to **24** is simply much faster than intramolecular cyclization.

Scheme 3



In conclusion, we have described herein a highly stereoselective vinylogous Pummerer rearrangement that proceeds by a 1,4-migration of the sulfinyl oxygen atom. The reaction occurs in good yield and with high enantioselectivity when *ortho*-sulfinyl-substituted benzyl carbanions are treated with trimethylsilyl halides. The influence of the reaction conditions and the nature of the electrophile suggests that the rearrangement proceeds by an intimate ion pair as a reaction intermediate. The extremely high stereoselectivity achieved (ee > 98%) allows for some interesting synthetic possibilities for the synthesis of optically pure benzyl alcohols.

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Supporting Information Available: Experimental procedures and spectroscopic data for compounds **8**−**27**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[20] Compound **10** was recovered unchanged when heated at 60 °C (CH_2Cl_2) or at 120 °C (toluene) in a sealed reaction vessel, thereby indicating that it does not undergo a thermal silicon-Pummerer rearrangement.