

A Novel Asymmetric Vinylogous Tin-Pummerer Rearrangement

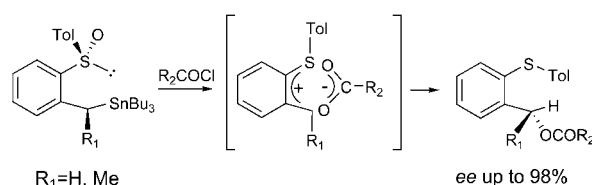
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ABSTRACT



A new type of vinylogous tin-Pummerer rearrangement reaction was observed when benzyl tin derivatives containing a sulfinyl group at the ortho position were allowed to react with acyl chlorides or TFAA. The reaction is thought to proceed by nucleophilic attack of the leaving carboxylate at the γ -position of the conjugated thionium ion. The enantioselectivity (*ee*) of the reaction can reach values as high as 98%. The observed stereoselectivity is related to the nature of the solvent, the temperature employed, and the stability of the migrating carboxylate anion.

The Pummerer rearrangement has been widely studied and has received considerable attention as a synthetically useful process.¹ The initial step of the reaction involves acylation of the sulfoxide oxygen to form an acyloxysulfonium salt, thereby converting this oxygen to a good leaving group. Removal of a proton from the α -carbon with elimination of the acyloxy group generates a thionium ion, which is trapped by one of the nucleophilic species present in the reaction medium. The intramolecular trapping of the α -acyl thionium ions has been used for the synthesis of a variety of heterocyclic ring systems.² 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.³ The resulting

unsaturated thionium ion is then intercepted by a nucleophile at the γ -position (Figure 1). The above reactions require the presence of an α - or γ -hydrogen in order to allow the formation of the thionium ion. Although the sila-Pummerer rearrangement has also proven to be a synthetically useful method,⁴ examples of the analogous tin-Pummerer reaction are rare.⁵

During the course of our studies dealing with remote stereoselective functionalization mediated by aryl sulfoxides,^{6,7} a novel example of this little studied reaction was observed. As part of our general program dealing with chiral sulfoxides, we had been investigating the coupling reaction of the tin derivative **7** with acetyl chloride in the presence of either a palladium(0)⁸ or rhodium(I) catalyst.⁹ Under

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(1) (a) Pummerer, R. *Chem Ber.* **1909**, *42*, 2282. (b) DeLucchi, O.; Miotti, U.; Modena, G. *Organic Reactions*; Paquette, L. A., Ed.; Wiley: 1991; Chapter 3, pp 157–184. (c) Grierson, D. S.; Husson, H. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol. 6, pp 909–947. (d) Kennedy, M.; McKervey, M. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol. 7, pp 193–217.

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

(3) Kueth, T.; Padwa, A. *J. Org. Chem.* **1998**, *63*, 4256.

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(5) (a) Beddoes, R. L.; Macleod, D.; Moorcroft, D.; Queayle, P.; Zhao, Y.; Davies, G. M. *Tetrahedron Lett.* **1992**, *33*, 417. (b) Pohmakotr, M.; Sithikanchanakul, S. *Tetrahedron Lett.* **1989**, *30*, 6773.

(6) For reaction with carbonyl groups, see: García Ruano, J. L.; Aranda, M.; Carreño, M. C.; Toledo, M. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 2736.

(7) For reaction with imines, see: (a) García Ruano, J. L.; Alemán, J.; Soriano, J. F. *Org. Lett.* **2003**, *5*, 677. (b) García Ruano, J. L.; Alemán, J. *Org. Lett.* **2003**, *5*, 4513.

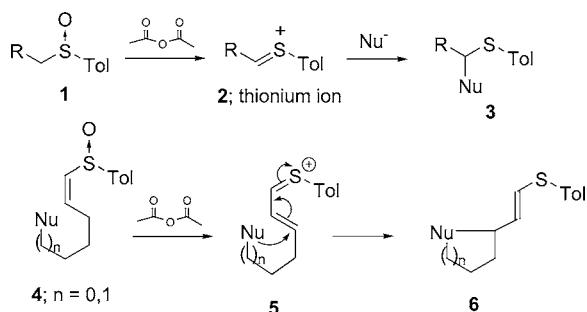
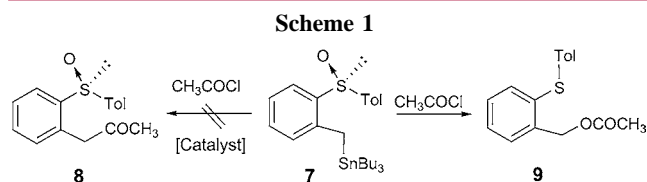


Figure 1. Mechanism of the Pummerer and Vinylogous Pummerer reaction.

the reported conditions for coupling we observed the exclusive formation of the acetoxy derivative **9** instead of the expected ketone **8** (Scheme 1). The formation of **9**, which



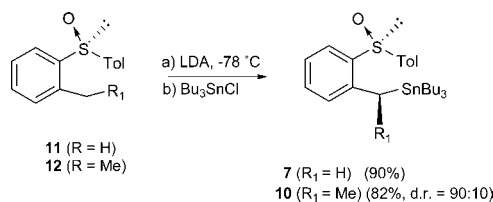
is also observed in the absence of any catalyst, is the result of the simultaneous oxidation at the benzylic position (γ with respect to sulfur) with concomitant reduction at the sulfur atom. In this communication, we report our results dealing with this unprecedented vinylogous tin-Pummerer rearrangement.

The synthesis of the tin derivatives **7** and **10** were carried out starting from sulfoxides **11**^{7a} and **12**⁶ following a method previously used to introduce various electrophilic groups at the benzylic position.⁶ Thus, sulfoxides **11** and **12** were treated with 1.2 equiv of LDA at $-78\text{ }^{\circ}\text{C}$ in THF. To the resulting solution (purple color indicates formation of the desired anion) was added 3 equiv of Bu_3SnCl . Compound **7** was obtained in 90% yield (after purification), while **10** was isolated in 82% yield as a mixture of epimers which could easily be separated by silica gel chromatography (Scheme 2). The highest diastereomeric ratio (90:10) was obtained at $-78\text{ }^{\circ}\text{C}$ (1 mmol scale). The stereoselectivity decreased somewhat (80:20) when the reaction was carried out at the 10 mmol scale, and these latter conditions were used to obtain the minor epimer. The relative configuration of both epimers **10** and **10'** has not been unequivocally established. Nevertheless, we assume the *S* configuration at the benzylic carbon for the major epimer **10** (Scheme 2) on the basis of stereochemical results that we have encountered with other electrophiles in our earlier studies.^{6,7}

(8) Labadie, J. W.; Stille, J. K. *J. Am. Chem. Soc.* **1983**, *105*, 6129.

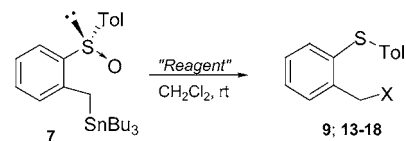
(9) Shie, J. Y.; Lin, Y. C.; Wang, Y. *J. Organomet. Chem.* **1989**, *3*, 383 and references therein.

Scheme 2



The results obtained for the reactions of the tin derivative **10** with a variety of different electrophiles are depicted in Table 1. Different acyl chlorides (methyl, vinyl, benzyl, and

Table 1. Reactions of **10** with Different Electrophiles



entry	reagent	product (X)	yield (%)
1	MeCOCl	9 (OCOMe)	61
2	$\text{CH}_2=\text{CHCOCl}$	13 (OCOCH=CH ₂)	72
3	PhCH ₂ COCl	14 (OCOCH ₂ Ph)	78
4	PhCOCl	15 (OCOPh)	67
5	TFAA	16 (OCOCF ₃)	72
6	TFAA	16 (OCOCF ₃)	76 ^a
7	Ac ₂ O	no reaction	
8	SOCl ₂	17 (Cl)	85
9	SOBr ₂	18 (Br)	81

^a Solvent-free conditions.

phenyl) show similar behavior, furnishing acyloxy thioethers **9** and **13–16** in 60–80% isolated yield (entries 1–4). The reactions are very clean, and only Bu_3SnCl was detected in addition to the acyloxy thioethers in the crude reaction mixture. Better yields were obtained in reactions with SOCl_2 and SOBr_2 (entries 8 and 9), which afforded the chloro (**17**) and bromo (**18**) derivatives.

By contrast, the reaction of **7** with Ac_2O only resulted in recovered starting material, even when the temperature was increased (CH_2Cl_2 reflux, entry 7). However, the reaction of **7** with TFAA did proceed smoothly, giving rise to trifluoroacetate **16** in good yield (entry 5). We also studied the reaction of **7** with TFAA in the absence of solvent, which proceeded to give **16** in 76% yield (entry 6).

To rationalize the experimental results, we propose a four-step reaction mechanism. Initially, the sulfinyl oxygen reacts with the added electrophile (Ac_2O is not reactive enough) to afford the acyloxy (**19**) (entries 1–6) or the corresponding halosulfinyloxy sulfonium salt (entries 8 and 9). The counterion of these salts (i.e., halide or trifluoroacetate) acts as a nucleophile in the second step and attacks the tin, producing a benzyl carbanion (**20**). This reactive intermediate then furnishes a thionium intermediate (**21** or **22**,¹⁰ Figure 2) by

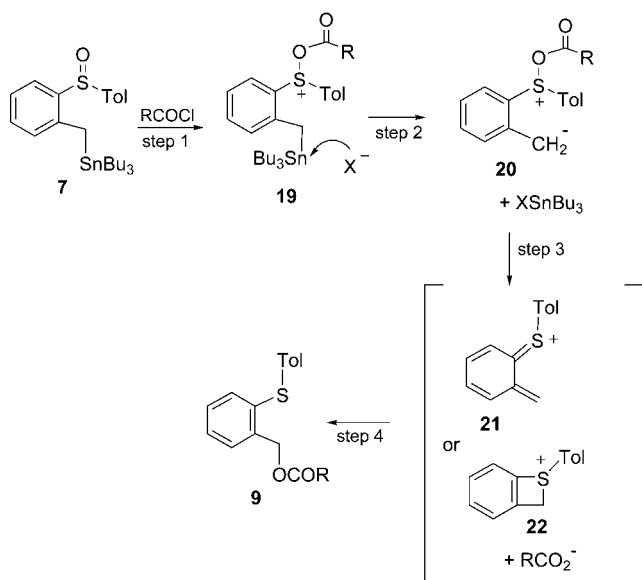


Figure 2. Mechanistic proposal for the reaction of **7** with various acid chlorides.

elimination of the RCO_2^- or X^- group (resulting in the extrusion of SO_2 from XSO_2^-). Steps 2 and 3 may or may not occur simultaneously. The final step involves nucleophilic addition of the acyloxy or halide ion onto the benzylic γ -carbon of the intermediate, thereby restoring the aromaticity of the system. The overall reaction can best be considered as a vinylogous tin-Pummerer rearrangement.

We have also studied the behavior of the tin-derivative **10** under similar conditions in order to ascertain the stereoselectivity of the reaction as well as to extend the scope of its synthetic applications. The results obtained are collected in Table 2. All the reactions proceed rapidly at room temperature (less than 15 min) and are instantaneous when TFAA is used. The enantiomeric excess of compounds **23**–**27** was established by reduction to the corresponding alcohol with LiAlH_4 and a subsequent transformation into its Mosher ester.¹¹ By means of this procedure, we were able to demonstrate that the major (or exclusive) enantiomer formed in these reactions possesses the *R* configuration. Enantioselectivity for the halo-derivatives **28** and **29** was determined by chiral HPLC (Chiralpak AD column).

The main feature of the results outlined in Table 2 centers around the stereoselectivity of the tin-Pummerer rearrangement. Interestingly, the enantioselectivity (ee) was found to decrease when the stability of the carboxylate anion increases (i.e., ee for $\text{AcO}^- > \text{PhCH}_2\text{CO}_2^- > \text{CH}_2=\text{CHCO}_2^- > \text{PhCO}_2^- > \text{CF}_3\text{CO}_2^-$). When the reactions of **10** with AcCl or TFAA were carried out in the absence of solvent, both

(10) Reactions involving the stereoselective formation of cyclobutanes from precursors of 1,4-zwitterionic species have been widely reported (see: Taylor, R. E.; Engelhardt, C. F.; Schmitt, M. J. *Tetrahedron* **2003**, *59*, 5623 and references therein). They are electronically similar to those involving the direct transformation of **19** into **22** in just one step.

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

Table 2. Reaction of **10** with Different Electrophiles

entry	reagent	product (X)	yield (%) ^b	ee (%) ^c
1	MeCOCl	23 (OCOMe)	73	>98
2	MeCOCl	23 (OCOMe)	79 ^a	>98
3	$\text{CH}_2=\text{CH}-\text{COCl}$	24 (OCOCH=CH ₂)	80	66
4	PhCH_2COCl	25 (OCOCH ₂ Ph)	70	81
5	PhCOCl	26 (OCOPh)	75	40
6	TFAA	27 (OCOCF ₃)	63	2
7	TFAA	27 (OCOCF ₃)	71 ^a	6
8	SOCl_2	28 (Cl)	70	2
9	SOBr_2	29 (Br)	71	1

^a Solvent free conditions. ^b All reactions were carried out at room temperature except entries 3 and 5, which were done at refluxing CH_2Cl_2 . ^c Entries 1–7 were determined from the Mosher ester and entries 8 and 9 by HPLC.

the yield and stereoselectivity slightly increased (compare entries 1 and 2 or 6 and 7). Reactions with SOX_2 proceeded with exceptionally low stereoselectivity (entries 8 and 9).

The stereochemical results outlined in Table 2 can be explained by assuming the formation of an intimate ion pair such as **32** (Figure 3) from compounds possessing the *S*

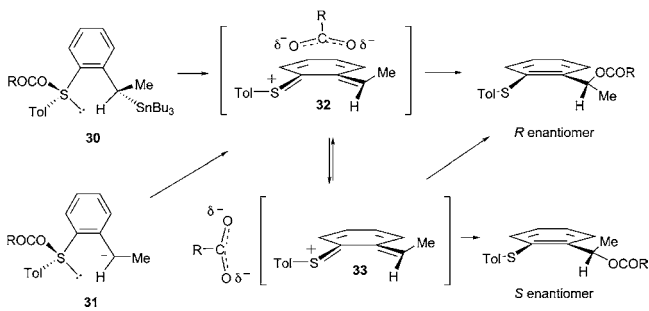
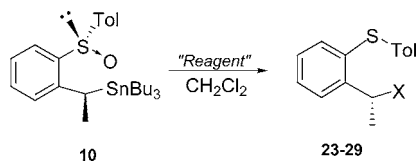


Figure 3. Stereochemical reaction of **10** with acid chlorides.

configuration at sulfur. This transient species has the anion occupying the pro-*R* face about the planar *o*-quinone methide cation because the acyloxy group of precursors **30** or **31** is oriented toward this face in its most stable conformation around the C–S bond. Internal collapse of the intimate ion pair affords the acyloxy derivative with the *R* configuration. Separation of the ions will lead to the formation of the achiral thionium intermediate **33**, whose subsequent conversion into both enantiomers would account for the incomplete stereoselectivity of many of these reactions. The low ee observed for **28** and **29** is not unexpected since the departing halide is not influenced by the proximal thionium ion, thus precluding the formation of an intimate ion pair.

Table 3. Influence of Solvent Polarity and Temperature on the Stereoselective Rearrangement of Tin Derivative **10**



entry	electrophile	temp	solvent	enantiomeric ratio	
				R:S	
1	MeCOCl	reflux	CH ₂ Cl ₂	97:3	
2	MeCOCl	rt	CH ₂ Cl ₂	>99:1	
3	MeCOCl	rt	CH ₃ CN	72:28	
4	TFAA	rt	CH ₂ Cl ₂	51:49	
5	TFAA	-78 °C	CH ₂ Cl ₂	59:41	
6	TFAA	rt	CCl ₄	67:33	
7	TFAA	-40 °C	CCl ₄	64:36	
8	BnCOCl	rt	CH ₂ Cl ₂	90:10	
9	BnCOCl	-15 °C	CH ₂ Cl ₂	97:3	
10	BnCOCl	rt	CCl ₄	no reaction	

According to the above proposal, those factors which control the shift of the equilibrium between species **32** and **33** will be responsible for the observed enantioselectivity. Species **32** should be favored with the less stable carboxylates (i.e., higher density of charge and therefore higher electrostatic attraction with the cation). Factors that disperse the charge at the anion will favor dissociation of the intimate ion pair (electrostatic attraction will be lower).

To provide some support for this proposal, we have studied the influence of different factors that affect the equilibrium between species **32** and **33**, such as the polarity of the solvent as well as the temperature. Polar solvents would be expected to favor the separate ion pair and therefore would decrease the overall stereoselectivity.

The results obtained from these studies are depicted in Table 3. The reaction of **10** with acetyl chloride, which normally proceeds with complete control of stereoselectivity at room temperature, was found to result in a slight decrease in ee by increasing the temperature (compare entries 1 and 2). In contrast, when CH₃CN was used instead of CH₂Cl₂ as the solvent, the ee of **23** was strongly diminished (entry 3),

in agreement with that expected from the stereochemical proposal of Figure 3. A similar influence of the solvent can be seen in the reactions of **10** with TFAA. In CH₂Cl₂ at room temperature, essentially racemic **27** was obtained (entry 4), whereas significant ee was observed at lower temperatures (18% at -78 °C, entry 5) and by using a less polar solvent (33% in CCl₄ at room temperature, entry 6). The simultaneous use of an apolar solvent and low temperatures did not improve the stereoselectivity (entry 7), probably a consequence of the low reactivity (much longer reaction times are required). The stereoselectivity of the reaction using 2-phenylacetyl chloride (80% ee at room temperature in CH₂Cl₂, entry 8) also increases by decreasing the temperature (94% at -15 °C, entry 9). Reactions conducted in CCl₄ did not work (entry 10), even under refluxing conditions.

In summary, we have described herein the stereoselective stannylation of benzylic positions mediated by sulfinyl groups at the adjacent ortho position. The reaction of these tin derivatives with acyl chlorides affording chiral benzyl alcohols constitutes the first example of a novel vinylogous tin-Pummerer reaction. The high stereoselectivity that can be achieved with acetyl chloride allows for some interesting synthetic perspectives in the synthesis of optically pure benzyl alcohols. The influence of the reaction conditions and the nature of the electrophile on the observed stereoselectivity suggests that the reaction proceeds by an intimate ion pair as a reaction intermediate. Further studies oriented toward the intramolecular capture of the conjugated thionium ion intermediate as well as a search for analogous reactions using 2-*p*-tolylsulfinyl alkylbenzenes are in progress and will be reported at a later date.

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Supporting Information Available: Experimental procedures and spectroscopic data for compounds **7**, **10**, **13–19**, and **23–29**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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