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Highly Stereoselective Asymmetric Pummerer Reactions That Incorporate Intermolecular and Intramolecular Nonbonded S···O Interactions

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Abstract: New chiral sulfoxides (R_S,*S*)-**3**, (S_S,*S*)-**3**, (R_S,*S*)-**4**, and (S_S,*S*)-**4** and known chiral sulfoxides (R_S)-**5**, (R_S)-**6**, and (R_S)-**7** were synthesized, and the stereochemistry of the new sulfoxides (R_S,*S*)-**3** and (R_S,*S*)-**4** was determined by X-ray crystallographic analysis. In their crystallographic structures, the intramolecular nonbonded S···O close contacts were recognized. Analyses of several sulfoxide complexes including *rac*-**11** with *N*,*N*-dimethylacetamide (DMAC) or *N*-methyl-2-pyrrolidone (NMP) in a MeOH solution utilizing cold-spray ionization mass spectrometry provided, for the first time, direct information for intermolecular nonbonded S···O interactions between sulfoxides and amide (or lactam) in a solution. Highly diastereoselective and enantioselective Pummerer reactions based on the concept of intermolecular and intramolecular nonbonded S···O interactions were performed by treatment of several chiral sulfoxides (R_S, *S*)-**3**, (S_S, *S*)-**3**, (R_S, *S*)-**4**, (S_S, *S*)-**4**, (R_S)-**5**, (R_S)-**6**, and (R_S)-**7** with acetic anhydride and trimethylsilyl triflate (TMSOTf) in DMAC, NMP, *N*,*N*-dimethylformamide, and *N*-formylpiperidine. Mechanistic studies on these facile stereoselective Pummerer reactions revealed the necessity for the amide/TMSOTf complex, such as **26** or **27**, to be an efficient activation reagent for Ac_2O and a trapping reagent for the released acetate ion, and that DMAC and NMP had a positive effect on this highly stereoselective chiral transfer reaction.

Introduction

Asymmetric Pummerer reactions,[1] which provide various chiral α-substituted sulfides from the corresponding chiral sulfoxides, have attracted considerable attraction in regard to their value in the synthesis of natural products and biologically active compounds[2] and in regard to their reaction mechanisms.[3] In general, asymmetric Pummerer reactions of chiral sulfoxides with acetic anhydride (Ac_2O) under heating have turned out to be unsatisfactory from the viewpoint of optical yield due to the formation of an achiral sulfurane intermediate, **1**, or a sulfonium ion, **2**, involving the resultant acetate ion.[4] To resolve this issue, some fascinating and elaborate methods have been explored, such as using Ac_2O and 1,3-dicyclohexylcarbodiimide for trapping the acetate ion[5] or using ethoxy vinyl acetate without the release of an acetate ion.[6] *O*-Methyl-*O*-*tert*-butyldimethylsilyl ketene acetal was also developed for highly stereoselective silicon-induced Pummerer-type reactions by Kita et al.[7] Furthermore, enantioselective Pummerer-type reactions of the chiral

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(1) (a) Stridsberg, B.; Allenmark, S. *Acta Chem. Scand*. **1974**, *B28*, 591. (b) Stridsberg, B.; Allenmark, S. *Acta Chem. Scand*. **1976**, *B30*, 219. (c) Numata, T.; Itoh, O.; Oae, S. *Chem. Lett*. **1977**, 909. (d) Masuda, T.; Numata, T.; Furukawa, N.; Oae, S. *Chem. Lett*. **1977**, 903. (e) Numata, T.; Oae, S. *Tetrahedron Lett*. **1977**, 1337. (f) Mikolajczyk, M.; Zatorski, A.; Grzejszczak, S.; Costisella, B.; Midura, W. *J. Org. Chem.* **1978**, *43*, 2518. (g) Wolfe, S.; Kazmaier, P. M.; Auksi, H. *Can. J. Chem.* **1979**, *57*, 7, 2404. (h) Kosugi, H.; Tagami, K.; Takahashi, A.; Kanna, H.; Uda, H. *J. Chem. Soc., Perkin Trans. 1* **1989**, 935. (i) Ferreira, J. T. B.; Marques, J. A.; Marino, J. P. *Tetrahedron: Asymmetry* **1994**, *5*, 641. (j) Abe, H.; Itani, J.; Masunari, C.; Kashino, S.; Harayama, T. *J. Chem. Soc., Chem. Commun.* **1995**, 1197. (k) Volonterio, A.; Zanda, M.; Bravo, P.; Fronza, G.; Cavicchio, G.; Crucianelli, M. *J. Org. Chem.* **1997**, *62*, 8031. (l) Crucianelli, M.; Bravo, P.; Arnone, A.; Corradi, E.; Meille, S. V.; Zanda, M. *J. Org. Chem.* **2000**, *65*, 2965.
(2) (a) De Lucchi, O.; Miotti, U.; Modena, G. *Org. React*. **1991**, *40*, 157. (b) Carreño, M. C. *Chem. Rev.* **1995**, *95*, 1717. (c) Padwa, A.; Gunn, D. E., Jr.; Osterhout, M. H. *Synthesis* **1997**, 1353.
(3) (a) Oae, S.; Numata, T. In *Isotopes in Organic Chemistry*, Buncel, E., Lee, C. C., Ed., Elsevier: New York, 1980; pp 45−102. (b) Oae, S.; Numata, T.; Yoshimura, T. In *The Chemistry of the Sulphonium Group, Part 2*; Stirling, C. J. M., Patai, S., Ed.; John Wiley and Sons: New York, 1981; pp 571−672. (c) Numata, T.; Itoh, O.; Yoshimura, T.; Oae, S. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 257. (d) Kita, Y.; Shibata, N. *Synlett* **1996**, 289.
(4) (a) Jonsson, E. *Tetrahedron Lett*. **1967**, 3675. (b) Oae, S.; Kise, M. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 1416. (c) Wolfe, S.; Kazmaier, P. M. *Can. J. Chem.* **1979**, *57*, 2397. (d) Shimada, K.; Kikuta, Y.; Koganebuchi, H.; Yonezawa, F.; Aoyagi, S.; Takikawa, Y. *Tetrahedron Lett*. **2000**, *41*, 4637.
(5) Numata, T.; Itoh, O.; Oae, S. *Tetrahedron Lett*. **1979**, 1869.
(6) (a) Kita, Y.; Shibata, N.; Kawano, N.; Fukui, S.; Fujimori, C. *Tetrahedron Lett.* **1994**, *35*, 3575. (b) Shibata, N.; Matsugi, M.; Kawano, N.; Fukui, S.; Fujimori, C.; Gotanda, K.; Murata, K.; Kita, Y. *Tetrahedron: Asymmetry* **1997**, *8*, 303.
(7) (a) Kita, Y.; Shibata, N.; Yoshida, N. *Tetrahedron Lett*. **1993**, *34*, 4063. (b) Kita, Y.; Shibata, N.; Yoshida, N.; Fujita, S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3335. (c) Kita, Y.; Shibata, N.; Kawano, N.; Tohjo, T.; Fujimori, C.; Ohishi, H. *J. Am. Chem. Soc.* **1994**, *116*, 5116.

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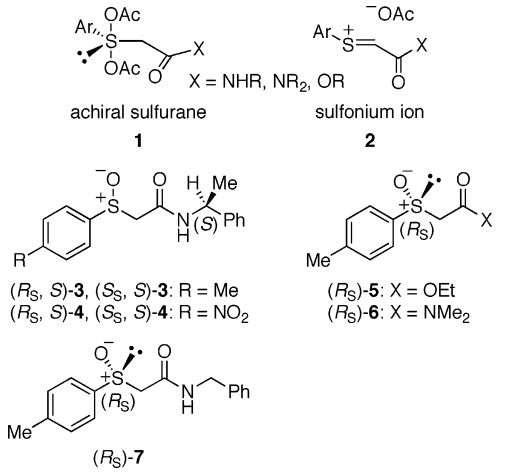


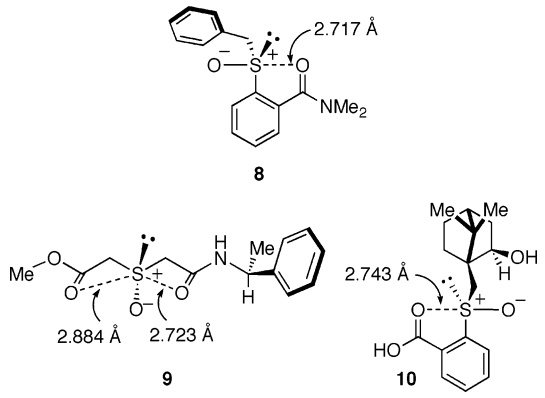


Figure 1. Intramolecular nonbonded S···O interactions in the crystal structures **8**−**10**.

aryl(substituted-methyl) sulfoxides bearing electron-withdrawing groups such as CO_2Et and $CONMe_2$, when developed using these well-established methods, have never exceeded 90% ee. We have developed highly diastereoselective and enantioselective Pummerer reactions of the chiral sulfoxides (R_S,*S*)-**3**, (S_S,*S*)-**3**, (R_S,*S*)-**4**, (S_S,*S*)-**4**, (R_S)-**5**, (R_S)-**6**, and (R_S)-**7** based on the concept of intermolecular and intramolecular nonbonded S···O interactions; this novel simple procedure and the related nonbonded S···O interactions are herein described.

Results and Discussion

Various intramolecular nonbonded 1,4 and 1,5 types of S···O interactions (the S···O distances being shorter than the sum (S + O = 3.32 Å) of the van der Waals radii) in the sulfoxides (e.g., compounds **8**−**10**,[8] Figure 1), and numerous other organosulfur compounds[9] have been observed in their crystal structures. Specifically, in molecular structure **8**[8b] bearing the 1,5-type S···O interaction, the amide carbonyl oxygen atom is seen to be close to the S atom on the opposite site of the oxide ion. In the amide moiety of crystalline structure **9**, an intramolecular nonbonded 1,4-type S···O interaction (2.723 Å) that is stronger than that (2.884 Å) in the ester moiety can be recognized, as represented in Figure 1.[8d,e] Such an intramolecular nonbonded S···O interaction in the crystalline state of the sulfoxides bearing the CO_2R or $CONR_2$ group may be possible even in a solution, based on the information of similar organosulfur and organoselenium compounds.[9g,10]

Thus, we anticipated the possibility of an intermolecular nonbonded S···O interaction between a sulfonium ion of sulfoxides and an amide oxygen atom, especially after acetylation of the sulfinyl moiety. However, to our knowledge, there has been no attempt to detect an intermolecular nonbonded S···O interaction between a sulfoxide compound and an amide compound in a solution, possibly because there has been no method for detecting such a weak charge−charge attraction. We have attempted detection of weak complexes (nonbonded interactions) of several sulfoxides with *N*,*N*-dimethylacetamide (DMAC) or *N*-methyl-2-pyrrolidone (NMP) in a MeOH solution by utilizing cold-spray ionization mass spectrometry (CSI-MS), a variant of electrospray ionization (ESI) MS operating at low temperature. This particular CSI-MS method allows facile and precise characterization of labile organic species bearing noncovalent bonding interactions such as hydrogen bonding,[9g] chelation involving a metal ion, and electrostatic interactions.[11]

CSI-MS spectra of mixtures (1:1) of selected chiral sulfoxides (R_S,*S*)-**3**, (R_S)-**5**, and (R_S)-**7** with an equimolecular amount of either DMAC or NMP in MeOH at −10 °C were determined as follows. The corresponding molecular ion peaks, *m*/*z* 389 due to [(R_S,*S*)-**3**···DMAC complex + H]$^+$ (for $C_{21}H_{28}N_2O_3S$ + H) and *m*/*z* 411 due to [(R_S,*S*)-**3**···DMAC complex + Na]$^+$ (for $C_{21}H_{28}N_2O_3S$ + Na), *m*/*z* 401 due to [(R_S,*S*)-**3**···NMP complex + H]$^+$ (for $C_{22}H_{28}N_2O_3S$ + H) and *m*/*z* 423 due to [(R_S,*S*)-**3**···NMP complex + Na]$^+$ (for $C_{22}H_{28}N_2O_3S$ + Na), *m*/*z* 314 due to [(R_S)-**5**···DMAC complex + H]$^+$ (for $C_{15}H_{23}NO_4S$ + H), *m*/*z* 326 due to [(R_S)-**5**···NMP complex + H]$^+$ (for $C_{16}H_{23}NO_4S$ + H) and *m*/*z* 348 due to [(R_S)-**5**···NMP complex + Na]$^+$ (for $C_{16}H_{23}NO_4S$ + Na), *m*/*z* 375 due to [(R_S)-**7**···DMAC complex + H]$^+$ (for $C_{20}H_{26}N_2O_3S$ + H) and *m*/*z* 397 due to [(R_S)-**7**···DMAC complex + Na]$^+$ (for $C_{20}H_{26}N_2O_3S$ + Na), and *m*/*z* 387 due to [(R_S)-**7**···NMP complex + H]$^+$ (for $C_{21}H_{26}N_2O_3S$ + H) and *m*/*z* 409 due to [(R_S)-**7**···NMP complex + Na]$^+$ (for $C_{21}H_{26}N_2O_3S$ + Na) on each respective CSI-MS spectrum were clearly observed (Supporting Information). To confirm the exclusive participation of the sulfinyl moiety in this particular intermolecular nonbonded S···O interaction, we examined the CSI-MS determination of a known racemic ethyl methyl sulfoxide, *rac*-**11**,[12] as a molecule without aromatic, amide, and ester groups, in the presence of DMAC or NMP under the same conditions as those used for the determination of several chiral sulfoxides. Thus, the corresponding molecular ion peak *m*/*z* 202 due to (*rac*-**11**···DMAC complex + Na)$^+$

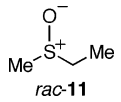
(8) (a) Kucksman, A.; Kapovits, I. *Organic Sulfur Chemistry: Theoretical and Experimental Advances*; Bernardi, F., Csizmadia, I. G., Mangini, A., Eds.; Elsevier: Amsterdam, 1985; pp 191−245 and references therein. (b) Iwasaki, F.; Toyoda, N.; Yamazaki, N. *Acta Crystallogr.* **1989**, *C45*, 1914. (c) Zhang, J.; Saito, S.; Koizumi, T. *J. Am. Chem. Soc.* **1998**, *120*, 1631. (d) Nagao, Y.; Miyamoto, S.; Hayashi, K.; Mihira, A.; S. Sano, *Tetrahedron Lett.* **2002**, *43*, 1519. (e) Nagao, Y.; Miyamoto, S.; Hayashi, K.; Mihira, A.; Sano, S. *Chem. Pharm. Bull.* **2002**, *50*, 558.

(9) (a) Kapecki, J. A.; Baldwin, J. E.; Paul, I. C. *J. Am. Chem. Soc.* **1968**, *90*, 5800. (b) Nagao, Y.; Hirata, T.; Goto, S.; Sano, S.; Kakehi, A.; Iizuka, K.; Shiro, M. *J. Am. Chem. Soc.* **1998**, *120*, 3104 and references therein. (c) Kumagai, T.; Tamai, S.; Abe, T.; Matsunaga, H.; Hayashi, K.; Kishi, I.; Shiro, M.; Nagao, Y. *J. Org. Chem.* **1998**, *63*, 8145. (d) Nagao, Y.; Nishijima, H.; Iimori, H.; Ushirogochi, H.; Sano, S.; Shiro, M. *J. Organomet. Chem.* **2000**, *611*, 172. (e) Nagao, Y.; Iimori, H.; Nam, K. H.; Sano, S.; Shiro, M. *Chem. Pharm. Bull.* **2001**, *49*, 1660. (f) Nagao, Y.; Iimori, H.; Goto, S.; Hirata, T.; Sano, S.; Chuman, H.; Shiro, M. *Tetrahedron Lett.* **2002**, *43*, 1709. (g) Nagao, Y.; Honjo, T.; Iimori, H.; Goto, S.; Sano, S.; Shiro, M.; Yamaguchi, K.; Sei, Y. *Tetrahedron Lett.* **2004**, *45*, 8757.

(10) (a) Komatsu, H.; Iwaoka, M.; Tomoda, S. *Chem. Commun*. **1999**, 205. (b) Iwaoka, M.; Komatsu, H.; Katsuda, T.; Tomoda, S. *J. Am. Chem. Soc.* **2004**, *126*, 5309.

(11) Yamaguchi, K. *J. Mass. Spectrom.* **2003**, *38*, 473 and references therein.

(12) Bulman Page, P. C.; Graham, A. E.; Bethell, R.; Kevin Park, B. *Synth. Commun.* **1993**, *23*, 1507.



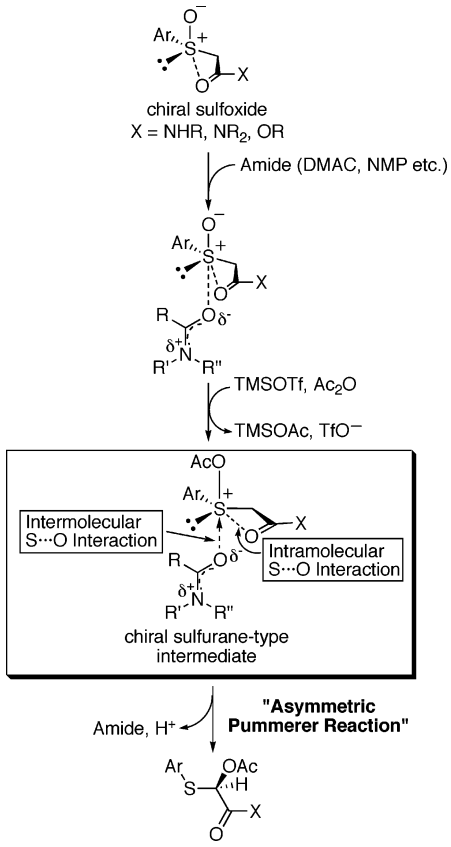
rac-**11**

(for $C_7H_{17}NO_2S$ + Na) or *m*/*z* 214 due to (*rac*-**11**···NMP complex + Na)$^+$ (for $C_8H_{17}NO_2S$ + Na) was clearly recognized. Consequently, we propose that the CSI-MS detection method can provide significant direct evidence for evaluation of the intermolecular nonbonded S···O interaction in a solution. The peaks assigned to [dimeric DMAC + H (or Na)]$^+$, [dimeric NMP + H (or Na)]$^+$, [dimeric (R_S,*S*)-**3** + H]$^+$, [dimeric (R_S)-**5** + H]$^+$, [dimeric (R_S)-**7** + H]$^+$, and [dimeric *rac*-**11** + Na]$^+$ were also recognized on the CSI-MS charts of the corresponding sulfoxide and DMAC (or NMP). Although the sulfoxide itself (compounds **3**, **4**, **6**, and **7**) has an internal amide, the participation of this amide in association with another identical molecule of sulfoxide ["dimerization" in MeOH (CSI-MS analysis)] should be negligible in an excess amount of amide solvent such as DMAC or NMP that has a stronger electron-donating character than the amides having an electron-withdrawing α-sulfinyl group.

The molecular structure characteristics of sulfoxides **8**−**10** involving an intramolecular nonbonded S···O interaction in their crystalline structures and the possible intermolecular nonbonded S···O interaction of chiral and achiral sulfoxides, (R_S,*S*)-**3**, (R_S)-**5**, (R_S)-**7**, and *rac*-**11** with DMAC or NMP in a MeOH solution prompted us to investigate a novel approach to the asymmetric Pummerer reactions. Thus, we envisioned a unique and simple design involving a chiral sulfurane-type intermediate that can be generated by treatment of chiral sulfoxides with Ac_2O−TMSOTf (trimethylsilyl triflate) in amide and lactam solvents such as DMAC, *N*,*N*-dimethylformamide (DMF), NMP, *N*-formylpiperidine (NFP), etc. (vide infra), as illustrated in Scheme 1.

Scheme 2 represents a synthetic route for the new chiral sulfoxides, (R_S,*S*)-**3**, (S_S,*S*)-**3**, (R_S,*S*)-**4**, and (S_S,*S*)-**4**, employed for the asymmetric Pummerer reactions. Namely, treatment of thiols **12** and **13** with sodium hydride and then ethyl bromoacetate gave thioethers **14** in 91% yield and **15** in 96% yield, respectively. Alkaline hydrolysis of **14** with NaOH in H_2O−EtOH followed by oxidation with 30% H_2O_2 in 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) afforded racemic sulfinyl carboxylic acid **16** in 97% yield. Dehydrative condensation of **16** with (*S*)-α-methylbenzylamine in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC·HCl) and 4-(dimethylamino)pyridine (DMAP) and then chromatographic separation of the resulting diastereomeric mixture on a silica gel column with *n*-hexane−AcOEt furnished optically pure (R_S,*S*)-**3** and (S_S,*S*)-**3** each in 44% yield. Carboxylic acid **17** (89% yield) obtained by alkaline hydrolysis of **15** was subjected to dehydrative amidation with (*S*)-α-methylbenzylamine to give amide **18** in 85% yield. Oxidation of **18** with 30% H_2O_2 in HFIP followed by chromatographic separation on a silica gel column with *n*-hexane−AcOEt afforded pure chiral sulfoxides (R_S,*S*)-**4** and (S_S,*S*)-**4** in 48% and 50% yields, respectively. Known chiral sulfoxides (R_S)-**5** and (R_S)-**6** were prepared by the previously reported methods.[3c,7b] Chiral sulfoxide (R_S)-**7** was prepared by dehydrative condensation of the carboxylic acid, which was obtained by alkaline hydrolysis of (R_S)-**5**, with benzylamine. The stereochemistry of new chiral sulfoxides, (R_S,*S*)-**3**, (S_S,*S*)-**3**, (R_S,*S*)-**4**, and (S_S,*S*)-**4**, was determined on the basis of X-ray crystallographic analysis of (R_S,*S*)-**3** and (R_S,*S*)-**4**; the crystal structures are shown in Figure 2. In the represented crystalline structures, significant 1,4-type S···O close contact [3.142(4) Å for (R_S,*S*)-**3** or 2.925(2) Å for (R_S,*S*)-**4**] was recognized, as we expected. Such a difference of the S···O distances in these two sulfoxides may be due to the fact that the electron density of the sulfur atom with the electron-withdrawing *p*-nitrophenyl group in (R_S,*S*)-**4** was lower than that of the sulfur atom with the electron-donating *p*-tolyl group in (R_S,*S*)-**3**.

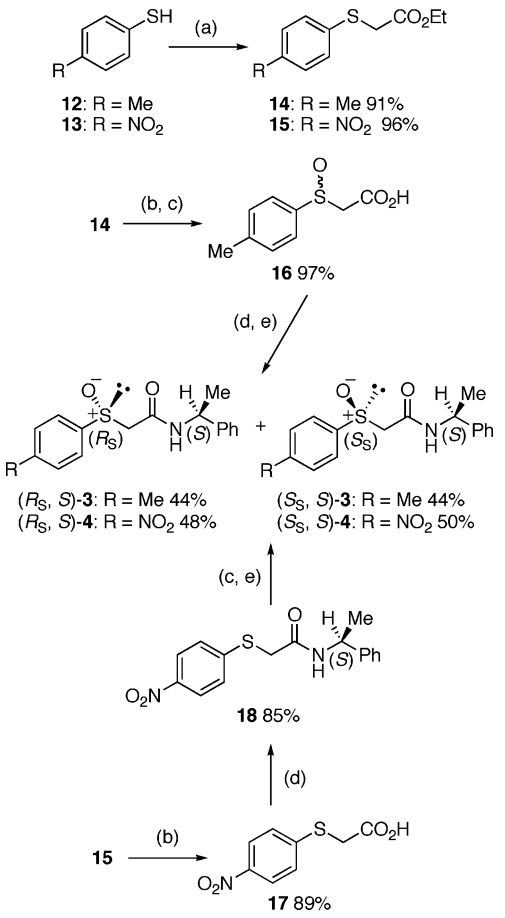
Scheme 1. Asymmetric Pummerer Reaction Based on the Inter- and Intramolecular Nonbonded S···O Interactions



First, to compare the new procedures (vide infra), the Pummerer reactions of (R_S,*S*)-**3**, (S_S,*S*)-**3**, (R_S,*S*)-**4**, and (S_S,*S*)-**4** were attempted utilizing our reagent system,[8d,e] as summarized in Table 1. Namely, the chiral sulfoxides were treated with Ac_2O (2.0 mol equiv) in the presence of TMSOTf (2.0 mol equiv)[8d,e] in CH_2Cl_2 at −40 or 0 °C to give the corresponding α-acetoxy sulfides, (*R*,*S*)-**19**, (*S*,*S*)-**19**, (*R**,*S*)-**20**, and (*S**,*S*)-**20**, as diastereomeric mixtures in 83−89% yields but with low de (0.3−20%) of each major diastereomer (Table 1). The stereochemistry of (*R*,*S*)-**19** and (*S*,*S*)-**19** will be described later. These poor diastereoselectivities can be attributed to racemization of the chiral sulfoxides involving an achiral sulfurane intermediate and the Pummerer products via enolization in the use of the Ac_2O−TMSOTf reagent system in CH_2Cl_2 (vide infra). The magnitude of the racemization is dependent upon the reaction time (entries 1 and 2 vs 3 and 4).

Subsequently, the asymmetric Pummerer reactions of (R_S,*S*)-**4** with Ac_2O (2.0 mol equiv) and TMSOTf (2.0 mol equiv) were investigated in detail in CH_2Cl_2 and several aprotic dipolar solvents at room temperature, and the results are summarized in Table 2. Interestingly, when the electron-donation number

Scheme 2. Synthesis of New Chiral Sulfoxides[a]



[a] Reagents and conditions: (a) NaH, $BrCH_2CO_2Et$, THF; (b) NaOH, H_2O−EtOH; (c) 30% H_2O_2, HFIP; (d) (*S*)-α-methylbenzylamine, EDC·HCl, DMAP, CH_2Cl_2; (e) silica gel column (*n*-hexane−AcOEt).

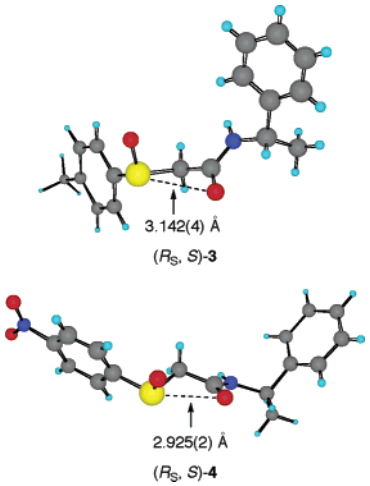


Figure 2. Computer-generated drawings derived from the X-ray coordinates of (R_S,*S*)-**3** and (R_S,*S*)-**4**.

(EDN) of the solvent was considered [e.g., AcOEt (EDN 17.1), Et_2O (EDN 19.2), DMF (EDN 26.6), and DMAC (EDN 27.8)],[13] the de% value of the major product (*R**,*S*)-**20** appeared to increase in near-dependence upon the EDN, as shown in Table 2 (entries 3−6).

As shown in Table 3, treatment of chiral sulfoxides (R_S,*S*)-**3** or (S_S,*S*)-**3** with Ac_2O (2.0 mol equiv) and TMSOTf (3.0 mol equiv) in DMAC at room temperature for 6 h proceeded highly diastereoselectively to afford α-acetoxy sulfides (*R*,*S*)-**19** in 73% yield with 94% de (entry 1 in Table 3) or (*S*,*S*)-**19** in 79% yield with 96% de (entry 2 in Table 3), as we expected. A similar treatment of (R_S,*S*)-**4** and (S_S,*S*)-**4** in DMAC for 24 h gave (*R**,*S*)-**20** in 82% yield with 84% de (entry 3 in Table 3) or (*S**,*S*)-**20** in 78% yield with 92% de (entry 4 in Table 3), respectively. These excellent diastereoselectivities obtained in DMAC (Table 3) contrast significantly with the disappointing results in CH_2Cl_2 (Table 1).

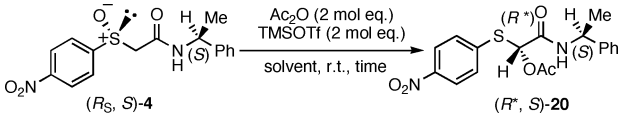
Consequently, a range of amide and lactam solvents were utilized in enantioselective reactions as follows. Chiral sulfoxides

Table 1. Asymmetric Pummerer Reactions of Chiral Sulfoxides Using Ac_2O and TMSOTf in CH_2Cl_2

entry	sulfoxide	temp (°C)	time (h)	product	yield[a]/de[b] (%)
1	(R_S,*S*)-**3**	−40	18	(*R*,*S*)-**19**	87/0.5
2	(S_S,*S*)-**3**	−40	18	(*S*,*S*)-**19**	86/0.3
3	(R_S,*S*)-**4**	0	5	(*R**,*S*)-**20**	83/20
4	(S_S,*S*)-**4**	0	5	(*S**,*S*)-**20**	89/2.8

[a] Total isolated yield of a mixture of diastereomers. [b] Determined by ^1H NMR (400 MHz, $CDCl_3$ or C_6D_6) analysis.

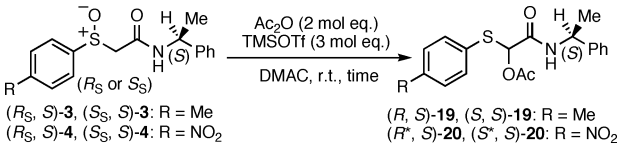
Table 2. Solvent Effect on Asymmetric Pummerer Reaction of (R_S, *S*)-**4**



entry	solvent (EDN[a])	time (h)	yield[b]/de[c] (%) of (*R**,*S*)-**20**
1	CH_2Cl_2 (−)	1	85/28
2	MeCN (14.1)	3	69/30
3	AcOEt (17.1)	0.5	84/16
4	Et_2O (19.2)	5	79/28
5	DMF (26.6)	48	84/66
6	DMAC (27.8)	48	80/82

[a] EDN = $-\Delta H$ (kcal/mol): Complexation enthalpies of basic solvents with $SbCl_5$ in 1,2-dichloroethane.[13] [b] Total isolated yield of a mixture of diastereomers. [c] Determined by ^1H NMR (400 MHz, $CDCl_3$ or C_6D_6) analysis.

Table 3. Diastereoselective Asymmetric Pummerer Reactions of Chiral Sulfoxides in DMAC



entry	sulfoxide	time (h)	product	yield[a]/de[b] (%)
1	(R_S,*S*)-**3**	6	(*R*,*S*)-**19**	73/94 (97:3)[c]
2	(S_S,*S*)-**3**	6	(*S*,*S*)-**19**	79/96 (2:98)[c]
3	(R_S,*S*)-**4**	24	(*R**,*S*)-**20**	82/84 (92:8)[c]
4	(S_S,*S*)-**4**	24	(*S**,*S*)-**20**	78/92 (4:96)[c]

[a] Total isolated yield of a mixture of diastereomers. [b] Determined by ^1H NMR (400 MHz, $CDCl_3$ or C_6D_6) analysis. [c] Diastereomer ratio.

(13) Gutmann, V. *Electrochim. Acta* **1976**, *21*, 661.

Table 4. Enantioselective Pummerer Reactions of Chiral Sulfoxides in DMAC, DMF, NMP, and NFP

(R_S)-**5**: X = OEt
(R_S)-**6**: X = NMe_2
(R_S)-**7**: X = NHBn

(R^*)-**21**: X = OEt
(*R*)-**22**: X = NMe_2
(*R*)-**23**: X = NHBn

entry	sulfoxide	solvent	time (h)	product	yield[a]/ee (%)
1	(R_S)-**5**	DMAC	1.5	(R^*)-**21**	47/90[b]
2	(R_S)-**5**	DMF	4	(R^*)-**21**	76/90[b]
3	(R_S)-**5**	NMP	4	(R^*)-**21**	80/92[b]
4	(R_S)-**6**	DMAC	4	(*R*)-**22**	58/82[c]
5	(R_S)-**7**	DMAC	6	(*R*)-**23**	46/93[d]
6	(R_S)-**7**	NMP	4	(*R*)-**23**	61/95[d]
7	(R_S)-**7**	NFP	4	(*R*)-**23**	75/86[d]

[a] Isolated yield. [b] Determined by HPLC [CHIRALCEL OD, *n*-hexane−propan-2-ol (50:1)] analysis. [c] Determined by HPLC [CHIRALCEL AD, *n*-hexane−ethanol (6:1)] analysis. [d] Determined by HPLC [CHIRALCEL OD, *n*-hexane−propan-2-ol (4:1)] analysis.

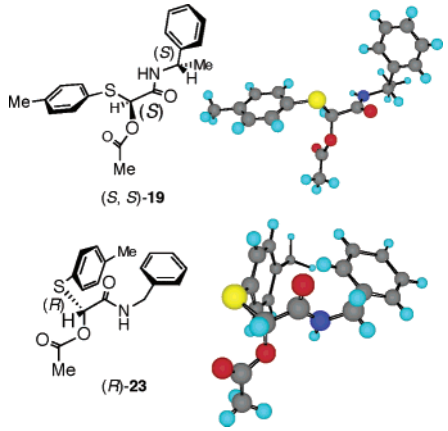


Figure 3. Computer-generated drawings derived from the X-ray coordinates of (*S*,*S*)-**19** and (*R*)-**23**.

(R_S)-**5**, (R_S)-**6**, and (R_S)-**7** were allowed to react with Ac_2O (2.0 mol equiv) and TMSOTf (3.0 mol equiv) in an amide or a lactam solvent (DMAC, DMF, NMP, or NFP) at room temperature for 1.5−6 h. The experimental results are summarized in Table 4. In all cases, the highly enantioselective Pummerer reaction proceeded to give known chiral α-acetoxy sulfides (R^*)-**21**,[1c−e,3c] (*R*)-**22**,[1c−e,3c] and (*R*)-**23** in 82−95% ee. The results obtained using NMP were superior in both chemical yield and ee to those obtained using DMAC and DMF (entries 3 and 6 vs entries 1, 2, and 5 in Table 4).

Fortunately, the stereochemistries of unstable (*S*,*S*)-**19** and (*R*)-**23** were clarified by their X-ray crystallographic analyses; the crystal structures are shown in Figure 3. On the basis of the structure of (*S*,*S*)-**19**, the stereochemistry of its diastereomer (*R*,*S*)-**19** was also precisely determined.

Although the absolute configuration of the newly formed chiral carbon atom (*R** or *S**) of (*R**,*S*)-**20**, (*S**,*S*)-**20**, and (R^*)-**21** has not yet been determined, it is expected to be identical to the corresponding sulfinyl chirality because the sulfinyl chirality of (R_S,*S*)-**3**, (S_S,*S*)-**3**, (R_S,*S*)-**4**, and (S_S,*S*)-**4** explicitly reflects the corresponding diastereomer ratio mode of the Pummerer products (all entries in Tables 1−3), and the same chirality (R_S→*R* or S_S→*S*) has been transferred from (R_S,*S*)-**3**, (S_S,*S*)-**3**, (R_S)-**6**, and (R_S)-**7** to the corresponding (*R*,*S*)-**19**, (*S*,*S*)-**19**, (*R*)-**22**, and (*R*)-**23**, respectively (entries 1 and 2 in Table 3 and entries 4−7 in Table 4). This stereoselective outcome was thought to have resulted from intramolecular nonbonded 1,4 types of S···O interaction in the chiral sulfoxides and the intermolecular nonbonded S···O interaction between the chiral sulfoxides and DMAC (or NMP) (vide infra).

Scheme 3. Attempt at Asymmetric Pummerer Reaction of (R_S)-**24**

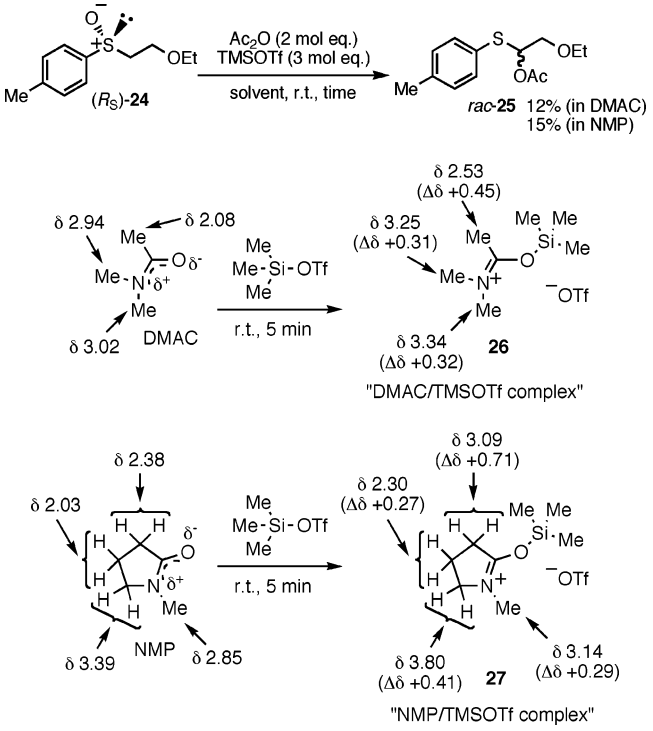


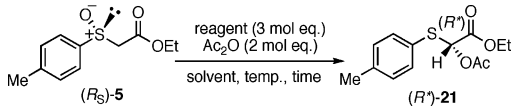
Figure 4. Possible structures for DMAC/TMSOTf complex **26** and NMP/TMSOTf complex **27** based on their ^1H NMR analysis (400 MHz, $CDCl_3$).

A chiral sulfoxide (R_S)-**24** without the β-carbonyl group was synthesized by a method described in the literature.[14] Then, this chiral compound [>99% ee (HPLC analysis)] was similarly treated with Ac_2O (2.0 mol equiv) and TMSOTf (3.0 mol equiv) in DMAC or NMP at room temperature for 40 or 45 h to give a Pummerer reaction product, **25**, as each racemate in 12% or 15% yield (Scheme 3). The same reaction of (R_S)-**24** with Ac_2O (2.0 mol equiv) and TMSOTf (3.0 mol equiv) in CH_2Cl_2 for 44 h resulted in recovery (50%) of the starting sulfoxide. Thus, in highly diastereo- and enantioselective amide-promoted Pummerer reactions employing the chiral sulfoxides such as (R_S,*S*)-**3**, (S_S,*S*)-**3**, (R_S,*S*)-**4**, (S_S,*S*)-**4**, (R_S)-**5**, (R_S)-**6**, and (R_S)-**7**, the existence of the β-carbonyl group in their molecules is thought to be essential. On the basis of the unsuccessful asymmetric Pummerer reaction of (R_S)-**24**, which probably included an intermolecular nonbonded S···O (amide solvents) interaction [cf. CSI-MS of a mixture of *rac*-**11** and DMAC (or NMP)], a fairly strong intramolecular nonbonded S···O (ester or amide group) interaction should play an important role [e.g., restriction of the free rotation of the CH_2COX group (Scheme 1 and Figure 6)] in the highly stereoselective Pummerer reactions in an amide solvent.

TMSOTf (Lewis acid) instantly reacted exothermically with an equimolecular amount of DMAC (Lewis base) or NMP (Lewis base) at room temperature to give the corresponding complex, **26** or **27**, as a colorless oil or a colorless hygroscopic

(14) (a) Mikolajczyk, M.; Perlikowska, W. *J. Org. Chem.* **1998**, *63*, 9716. (b) Alexandre, C.; Belkadi, O.; Maignan, C. *Synthesis* **1992**, 547.

Table 5. Asymmetric Pummerer Reactions of (R_S)-**5** with/without **26** or **27**



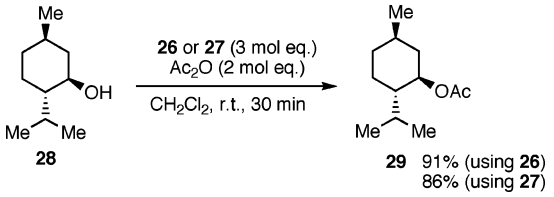
entry	reagent	solvent	temp (°C)	time	yield[a]/ee[b] (%) of (*R**)-**21**
1	**26**	DMAC	r.t.	4 h	47/89
2	**27**	NMP	r.t.	4 h	83/91
3	**27**	CH_2Cl_2	r.t.	5 min	85/72
4	TMSOTf	CH_2Cl_2	r.t.	3.5 h	61/0
5	none	DMAC	110	48 h	46/72

[a] Isolated yield. [b] Determined by HPLC [CHIRALCEL OD, *n*-hexane−propan-2-ol (50:1)] analysis.

powder in a quantitative yield, respectively.[15] These complex structures could be rationalized by comparing their ^{1}H NMR chemical shifts with those of DMAC or NMP itself in $CDCl_3$, as shown in Figure 4. The amide carbonyl moiety of α-sulfinyl amides [e.g., (R_S)-**7**] should less coordinated to TMSOTf than that of DMAC in excess DMAC. We experienced previously the interesting chemoselective Pummerer reactions in DMF to prove that the amide carbonyl group of DMF can more predominantly coordinated to TMSOTf than that of a sulfoxide substrate like compound **9**.[8d] This may be because the nucleophilicity of DMF, DMAC, and NMP is stronger than that of the α-sulfinyl amides bearing an electron-withdrawing sulfinyl group (vide supra).

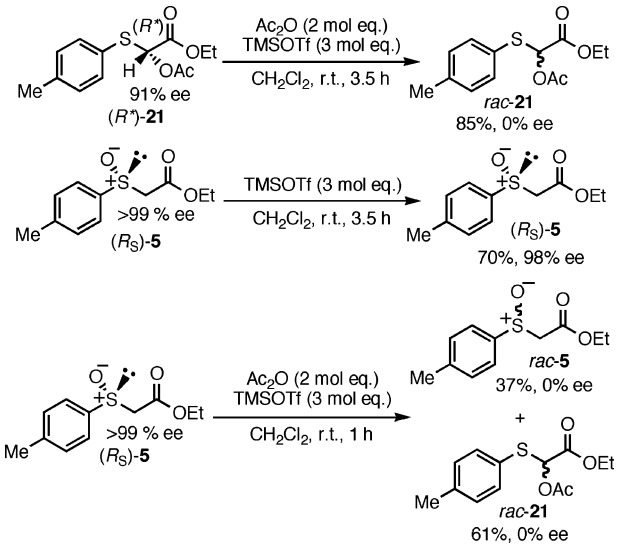
To confirm the activity of the complexes **26** and **27** to Ac_2O, the following acetylation reactions were examined. Treatment of *l*-menthol **28** with Ac_2O in the presence of **26** or **27** in CH_2Cl_2 smoothly gave acetoxy compound **29**[16] in excellent yield, as we expected (Scheme 4).

Scheme 4. Acetylation of *l*-Menthol **28** with Ac_2O in the Presence of **26** or **27**



Thus, treatment of (R_S)-**5** with Ac_2O (2.0 mol equiv) and a 3 mol equiv of **26** or **27** in DMAC, NMP, or CH_2Cl_2 gave the product (*R**)-**21** in 47−85% yields with 72−91% ee, as shown in Table 5 (entries 1−3). The results of entries 1 and 2 in Table 5 were almost the same as those for entries 1 and 3 in Table 4. Hence, in the facile Pummerer reactions employing Ac_2O and TMSOTf in an amide solvent, the amide/TMSOTf complex such as **26** or **27** generated in situ must become a real active species for Ac_2O and a trapping reagent for the released acetate ion. The stereochemical outcome (72% ee) of entry 3 employing **27** even in CH_2Cl_2 can be understood in terms of the intermolecular nonbonded S···O interaction (just like an intermolecular O→S coordination) between the resulting acetoxysulfonium intermediate and the NMP released by acetylation of (R_S)-**5** with **27**. The reaction results of entry 3 involving the rapid reaction time (5 min) and the high chemical yield (85%) of (*R**)-**21** (72% ee) are very similar to those of the experiment [reaction time (5 min) and 74% ee and 99% yield of (*R**)-**21**] in Figure 5 (vide infra).

Scheme 5. Investigation of Racemization of Chiral Pummerer Product (*R**)-**21** and Chiral Sulfoxide (R_S)-**5**



Interestingly, the Pummerer reaction of (R_S)-**5** with Ac_2O (2.0 mol equiv) in DMAC, even without the use of TMSOTf, under heating at 110 °C for 48 h gave (*R**)-**21** [46% yield with recovery (13%) of (R_S)-**5**] in 72% ee (entry 5 in Table 5). Hence, DMAC and NMP should greatly benefit this highly stereoselective chiral transfer reaction based on the intermolecular nonbonded S···O interaction, as described above. On the other hand, treatment of (R_S)-**5** with TMSOTf (3 mol equiv) and Ac_2O (2 mol equiv) in CH_2Cl_2 at room temperature gave a racemic product, **21** (0% ee), in 61% yield (entry 4 in Table 5). This outcome seemed to be due to racemization of the chiral product (*R**)-**21** and/or the starting chiral sulfoxide (R_S)-**5**.

Then, we investigated some important reactions in order to inspect the racemization reaction of (*R**)-**21** and (R_S)-**5** as follows (Scheme 5). The chiral product (*R**)-**21** (91% ee) was readily racemized by its treatment with a mixture of Ac_2O and TMSOTf to afford *rac*-**21** in 85% recovery and 0% ee. This racemization is likely attributable to the fact that (*R**)-**21** is enolized with TMSOTf (strong Lewis acid) in the presence of Ac_2O. Treatment of (R_S)-**5** (>99% ee) with TMSOTf alone in CH_2Cl_2 gave the starting chiral sulfoxide (R_S)-**5** (98% ee) in 70% recovery. Hence, TMSOTf is not responsible for the racemization of (R_S)-**5**. However, when (R_S)-**5** (>99% ee) was treated with a mixture of Ac_2O and TMSOTf in CH_2Cl_2 for 1 h, *rac*-**5** (0% ee) and *rac*-**21** (0% ee) were obtained in 37% and 61% yields, respectively. In particular, facile racemization of the chiral Pummerer reaction product should be a serious problem.

In the reactions (Table 1, entry 4 in Table 5, and Scheme 5) without the use of any amide solvent or compound, the existence of the intermolecular nonbonded S···O interaction between the chiral acetoxysulfonium intermediate and the amide should be

(15) Djuric, S. W. *J. Org. Chem.* **1984**, *49*, 1311.
(16) Ishihara, K.; Kubota, M.; Kurihara, H.; Yamamoto, H. *J. Org. Chem.* **1996**, *61*, 4560.
(17) *Rigaku 1998 PROCESS-AUTO: Automatic data acquisition and processing package for imaging plate diffractometer*; Rigaku Corporation: Tokyo.
(18) Sheldrick, G. M. *SHELXS97, Program for the solution of crystal structures*. University of Göttingen: Göttingen, Germany, 1997.
(19) Sheldrick, G. M. *SHELXL97*; University of Göttingen: Göttingen, Germany, 1997.

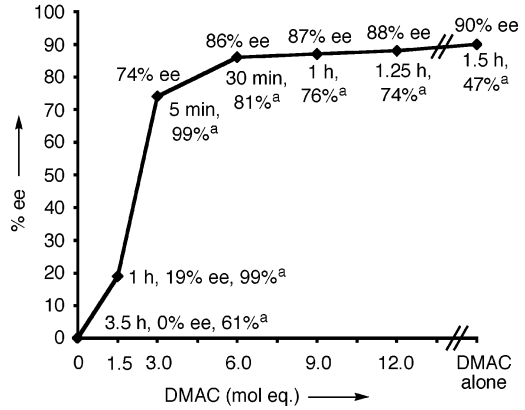


Figure 5. Effect of DMAC on the asymmetric Pummerer reaction [(R_S)-**5**→(*R**)-**21**] in CH_2Cl_2. [a]Isolated yield.

impossible. Therefore, racemization of (R_S)-**5** may be caused by formation of the achiral diacetoxy sulfurane **1** on the basis of participation of the acetate ion obtained from a possible equilibrium condition, as shown in eq 1.[2a,4a]

$$\text{TMSOAc} + {}^{-}\text{OTf} \rightleftharpoons \text{TMSOTf} + \text{AcO}^{-} \qquad (1)$$

Furthermore, the effect of DMAC on the asymmetric Pummerer reactions of (R_S)-**5** was examined by using Ac_2O (2 mol equiv) and TMSOTf (3 mol equiv) in the presence of different mol equivs of DMAC in CH_2Cl_2 at room temperature. The results are graphically illustrated in Figure 5. They reveal a clear trend toward higher %ee value for production of (*R**)-**21** as the amount of DMAC increases. Interestingly, when an equimolecular amount (each 3 mol equiv) of TMSOTf and DMAC in the presence of Ac_2O (2 mol equiv) was employed, the reaction proceeded to completion within 5 min to furnish (*R**)-**21** in 99% yield with 74% ee. This result strongly supports the likelihood that there is rapid and quantitative generation of the active species **26** (vide supra, entry 1 in Table 5), which makes an important contribution to acetylation of the sulfinyl group and trapping of the released acetate ion, as shown in Figure 6. The Pummerer reactions of (R_S)-**5** with Ac_2O using greater or smaller molecular amounts of DMAC with respect to TMSOTf proceeded more slowly than when equimolecular amounts were used. These results suggested that an excess amount of TMSOTf may disturb acetylation of the sulfinyl group by its coordination to the Si atom. An excess amount of DMAC may also disturb acetylation of the sulfinyl group by coordination of DMAC to the Si atom of the DMAC/TMSOTf complex **26** generated in situ. However, excess DMAC and the DMAC released from **26** by its acetylation of (R_S)-**5** participate in an intermolecular nonbonded S···O interaction and an intermolecular coordination O→S interaction between the S^+ atom of the starting sulfinyl compound and the acetoxysulfonium intermediate and the $O^{\delta+}$ atom of DMAC, as shown in Figure 6.

Through the asymmetric Pummerer reactions (e.g., entries 1 and 2 in Table 5), we realized that the amide/TMSOTf complex in the corresponding amide solvent does not readily promote racemization of the chiral product probably due to deactivation of the Lewis acidity of the original TMS group by exchange of TfO^- for the amide. Thus, solvent amide silylation in situ should be very important in order to prevent this particular asymmetric Pummerer reaction from racemizing the chiral product and the starting chiral sulfoxide.

Finally, we propose a plausible mechanism of the highly stereoselective Pummerer reaction in an amide or lactam solvent involving intermolecular and intramolecular nonbonded S···O interactions and solvent amide silylation, as shown in Figure 6. The solvent amide or lactam instantly coordinates to TMSOTf to generate an amide (or lactam)/TMSOTf complex **A** and also approaches to the S^+ atom of a chiral sulfoxide substrate to form the structures **B** and **C** bearing the intermolecular and intramolecular nonbonded S···O interactions. However, structure **B** (see the X-ray structures in Figure 2) should be more stable than structure **C** since the steric repulsion between the aryl group and the carbonyl group in **C** is absent in **B**. Then, acetylation of the sulfinyl oxygen atom of **B** with Ac_2O in the presence of the real active species **A** affords a chiral sulfurane-type intermediate, **D**, in which fairly strong and tight coordination of the amide or lactam to the S^+ atom of acetoxysulfonium must

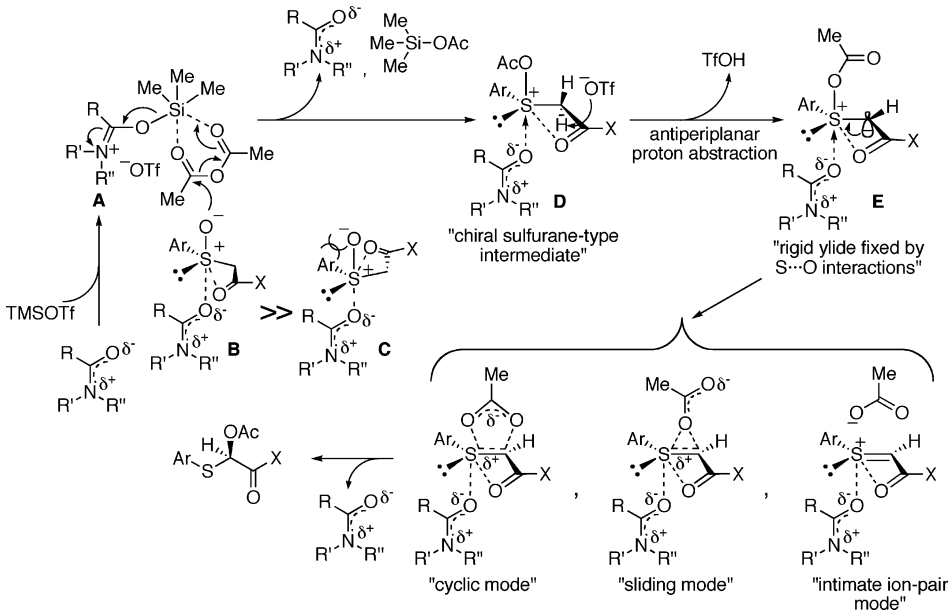


Figure 6. Possible mechanism of the highly stereoselective Pummerer reaction with TMSOTf and Ac_2O in an amide or lactam solvent.

be possible. Antiperiplanar-mode abstraction[3d] of the methylene α-hydrogen atom with a base (e.g., TfO^-) in intermediate **D** would generate a rigid ylide intermediate **E** fixed by both nonbonded S···O interactions. Stereoselective 1,2-acetoxy transfer in **E** may proceed via three kinds of plausible modes based on the Oae-proposed cyclic and/or sliding modes[3c] and/or the Kita-proposed intimate ion-pair mode[6b,3d] to furnish the desired chiral Pummerer product.

In conclusion, we have presented the first evidence for the intermolecular nonbonded S···O interactions between several sulfoxides and DMAC (or NMP) in a solution by utilizing the CSI-MS analytical method and have demonstrated a novel simple procedure for highly stereoselective Pummerer reactions based on the concept of inter- and intramolecular nonbonded S···O interactions and the solvent amide silylation with TMSOTf.

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Supporting Information Available: Experimental procedures; characterization of the products; X-ray data (CIF); and CSI-MS experiments including CSI mass spectral charts. This material is available free of charge via the Internet at http://pubs.acs.org.

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