

“Syn-Effect” in the Base-Induced Isomerization of Vinylic Sulfones to Allylic Sulfones and the Related Various Reactions

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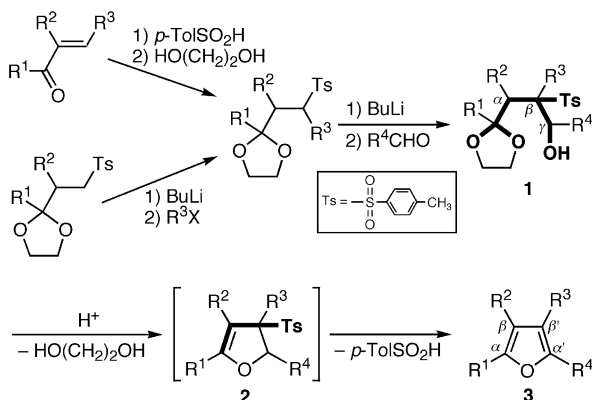
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Abstract: “Syn-effect” has been recognized as a major cause of stabilizing the *syn*-conformation at the transition state of a number of reactions against the steric hindrance. This account deals with the origin of the “*syn*-effect” on the basis of the stereochemical outcome in the isomerization of vinylic sulfones leading to the formation of allylic sulfones and in the related various reactions. We proposed that a $\sigma \rightarrow \pi^*$ interaction between the σ -orbital(s) of the allylic C–H σ -bond(s) (or of the C–H σ -bond(s) at the α -position for carbonyl compounds) and the antibonding orbital (π^*) of the C=C double bond (or of the C=O double bond for carbonyl compounds) is the most important and essential factor for the “*syn*-effect”, though the contribution of a 6π -electron homoaromaticity and/or of a hydrogen bonding cannot be entirely ruled out.

1. Introduction

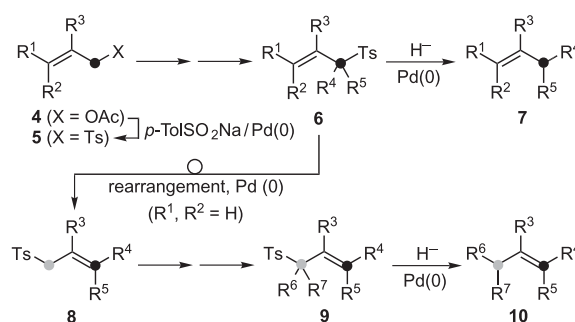
We have been engaged in a synthetic study of naturally occurring furans **3** with at least one substituent at the β -position (R^2 and/or $R^3 \neq H$) starting from readily available β -tosyl- γ -hydroxyacetal derivatives **1**, which possibly proceed via cyclic allylic sulfone intermediates **2** as shown in Scheme 1.^{1–6}

Scheme 1. A general method for the preparation of substituted furans **3** via allylic sulfone intermediates **2** from β -tosyl- γ -hydroxyacetal derivatives **1**.



Intrigued by a unique propensity of **2** to undergo facile elimination of a tosyl (Ts) group at the allylic position, we have also developed an alternative method for the preparation of allylic sulfones using Pd-catalyzed allylic substitution reaction as illustrated in Scheme 2. For example, allylic acetates **4** were readily converted to allylic sulfones **5** upon treatment with sodium *p*-toluenesulfonate in the presence of a catalytic amount of Pd(0) complex. Thus obtained allylic sulfones **5** served as versatile synthetic intermediates to provide a wide variety of allylic compounds including **7** and **10**,^{7–12} whose further synthetic elaboration furnished several naturally occurring substances such as squalene,⁹ methyl helepuberinate (unpublished work), coenzyme Q₁₀,¹¹ (\pm)-recifeioidide,⁸ (\pm)-lavandulol,¹² and isolavandulol¹² (Figure 1).

Scheme 2



The attractive features of the sulfonyl group in a series of transformations include the carbanion-stabilizing effect that allows regioselective reactions with various electrophiles as well as the ready detachment either by reduction or by elimination.

These results prompted us to revisit the classical base-promoted isomerization of vinylic sulfones into allylic sulfones, whose stereochemical course was not entirely clari-

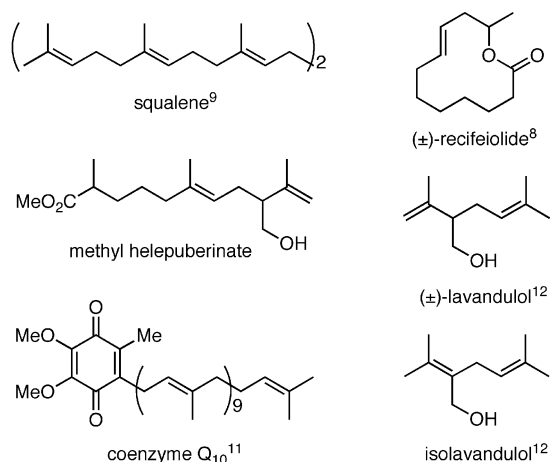
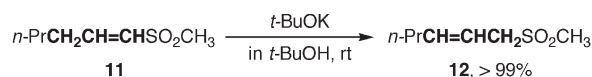


Figure 1. Natural compounds prepared by applying the procedure shown in Scheme 2.

Scheme 3. Isomerization of a vinylic sulfone to the corresponding allylic sulfone under basic conditions.



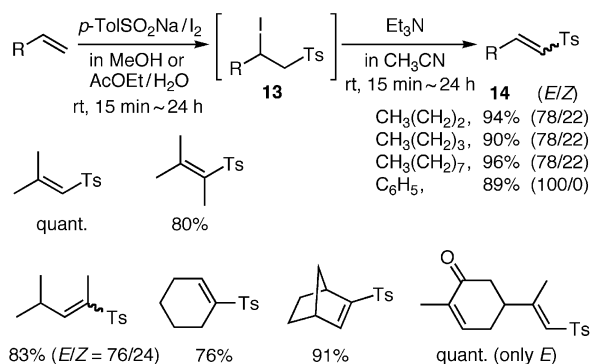
fied (Scheme 3).¹³

Therefore, we started to prepare stereochemically well-defined vinylic sulfones and study the detailed stereochemistry of the isomerization. Consequently, we have found that (*E*)-vinylic sulfones preferentially provided sterically unfavorable (*Z*)-allylic sulfones, whose stereochemical course was explainable by so-called “*syn*-effect”. Herein we will briefly introduce the stereochemical outcome in the isomerization of vinylic sulfones to allylic sulfones and in the related various reactions, and discuss the origin of this effect in detail.

2. Regio- and Stereoselective Preparation of Vinylic Sulfones

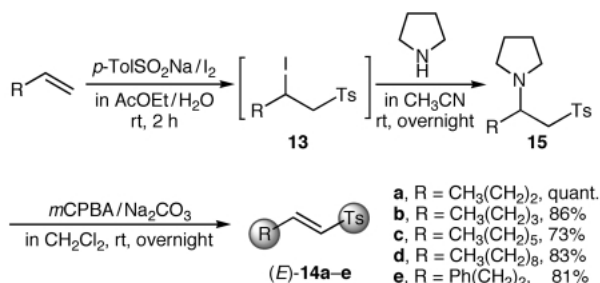
Our initial study focused on the stereoselective synthesis of (*E*)- and (*Z*)-vinylic sulfones **14**, since the iodotosylation of 1-alkenes followed by triethylamine-induced dehydroiodination of the resulting 2-iodo-1-tosylalkanes **13** mostly provided a mixture of (*E*)- and (*Z*)-isomers of vinylic sulfones **14** as summarized in Scheme 4 and their separation into pure isomers turned out to be difficult.^{14–16}

Scheme 4. Preparation of vinylic sulfones **14** from alkenes via iodotosylation.



Gratifyingly, 2-pyrrolidinyl-1-tosylalkanes **15** derived from **13** and an excess amount of pyrrolidine underwent a selective Cope elimination upon treatment of the crude products **15** with *m*CPBA in dichloromethane in the presence of Na₂CO₃ to provide stereochemically pure (*E*)-vinylic sulfones (*E*)-**14** in high yields (Scheme 5).¹⁷ This procedure was much easier than an alternative method via α -phenylselenation of 1-tosylalkanes¹⁶ and was applicable on a large scale.

Scheme 5. Regio- and stereoselective synthesis of (*E*)-vinylic sulfones.



A possible key factor for success in the exclusive formation of (*E*)-**14** may be the formation of **16** in favor of **17** in the transition state where the *N*-oxy-1-pyrrolidinyl group and the hydrogen should adopt eclipsed conformation, in order to avoid a severe steric congestion developed by an alkyl substituent R and the tosyl group (Ts) in **17** (Figure 2).

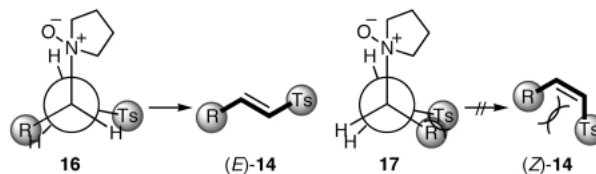
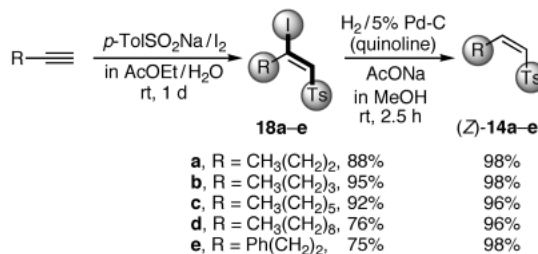


Figure 2. Stereoselectivity via *cis*-elimination.

The intermediary β -pyrrolidinylsulfones **15** were also used to prepare α -alkylated vinylic sulfones through α -alkylation followed by oxidative elimination of the pyrrolidinyl group.¹⁵

On the other hand, (*Z*)-**14** were selectively synthesized in high yields by the Pd-catalyzed hydrogenation of (*E*)-2-iodo-1-tosyl-1-alkenes **18**, which were prepared by the regio- and stereoselective iodotosylation of 1-alkynes as illustrated in Scheme 6.¹⁷

Scheme 6. Regio- and stereoselective synthesis of (*Z*)-vinylic sulfones.



3. Stereochemistry in the Base-Induced Isomerization of Vinylic Sulfones to Allylic Sulfones

As a variety of stereochemically well-defined (*E*)- and (*Z*)-vinylic sulfones [(*E*)-**14** and (*Z*)-**14**] were in hand, we began to study the influence of varying reaction conditions on the stereochemistry in a base-induced isomerization of (*E*)-**14d** into **19d** as a model reaction. Table 1 lists the representative results.¹⁶

On the contrary to our prediction based on the steric hindrance, (*Z*)-isomer [(*Z*)-**19d**] was preferentially formed in variable yields regardless of solvent and base under mild conditions (entries 1, 4–12). Notably, the *E/Z*-ratio reached up to 10/90 when the reaction was carried out for 12 h at room temperature in benzene containing DBU as a base (entry 9). In particular, lowering the reaction temperature to -20°C further increased the *E/Z*-ratio (3/97) albeit with modest conversion (23%) (entry 11). These results indicated that the initial *E/Z*-ratio might change along with the progress of the isomerization.

In fact, the extension of the reaction time in the isomerization of (*E*)-**14d** in *t*-BuOH containing *t*-BuOK under otherwise identical conditions significantly changed the modest *Z*-selectivity (*E/Z* = 41/59 after 0.5 h) into the high *E*-selectivity (*E/Z* = 86/14 after 15 h) (entries 1–3). Furthermore, when the isomerization of (*E*)-**14d** was carried out in ace-

Table 1. Isomerization of (*E*)-vinyl sulfone **14d** to allylic sulfones **19d** under basic conditions.

Entry	Base	Conditions	Products ratio 14d : 19d (<i>E/Z</i>)
1	<i>t</i> -BuOK	<i>t</i> -BuOH, 30 °C, 0.5 h	5 95 (41/59)
2	"	" 2 h	3 97 (63/37)
3	"	" 15 h	<1 >99 (86/14)
4	DBU	CH ₃ CN, rt, 12 h	3 97 (30/70)
5	"	DMF, rt, 12 h	5 95 (27/73)
6	"	THF, rt, 12 h	29 71 (18/82)
7	"	CH ₂ Cl ₂ , rt, 12 h	36 64 (22/78)
8	"	dioxane, rt, 12 h	54 46 (21/79)
9	"	benzene, rt, 12 h	68 32 (10/90)
10	"	CHCl ₃ , rt, 12 h	94 6 (20/80)
11	"	CH ₃ CN, -20 °C, 48 h	77 23 (3/97)
12	"	CH ₃ CN, 0 °C, 30 h	4 96 (22/78)
13	"	CH ₃ CN, reflux, 1.5 h	2 98 (78/22)

tonitrile containing DBU at higher temperature, the *Z*-selectivity (*E/Z* = 22/78 at 0 °C for 30 h) changed into the high *E*-selectivity (*E/Z* = 78/22 under reflux for 1.5 h) with excellent conversion yields (entries 11–13).

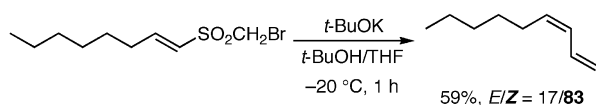
These results strongly suggested that (*Z*)-**19d** may be the kinetically-controlled product which is gradually isomerized into the thermodynamically more stable (*E*)-**19d**.

3.1 “*Syn*-Effect” in the Base-Induced Isomerization of (*E*)-Vinyl Sulfones to the Corresponding Allylic Sulfones

The question which arose from the above experimental results was why (*E*)-vinyl sulfone (*E*)-**14d** afforded predominantly (*Z*)-allylic sulfone (*Z*)-**19d** as a kinetically-controlled product.

At the almost same time, Block and his coworkers reported independently the similar results for the vinylogous Ramberg–Bäcklund reactions as shown in Scheme 7.¹⁸

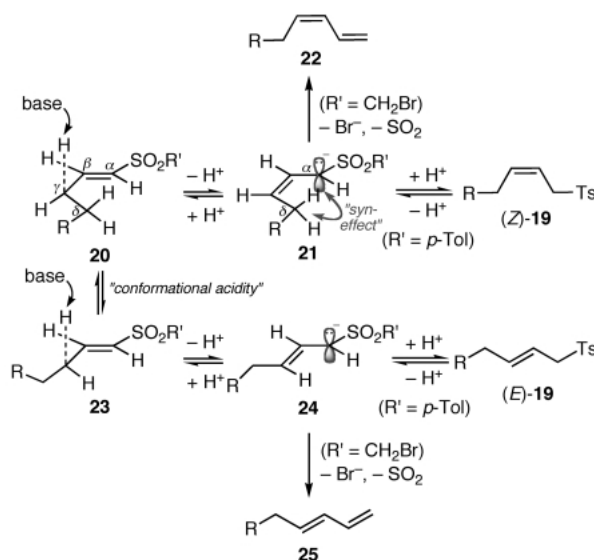
Scheme 7. Ramberg–Bäcklund reaction of a vinylsulfone.



They attributed the stereoselectivity of the reaction to a stabilizing, attractive interaction between the developing negative charge at the α -position and the CH₂ group at the δ -position (a “*syn*-effect”)^{18–23} favoring transition state **20** over **23** for deprotonation (Scheme 8).

The experimental results including ours suggested that the acidity of the γ -protons of vinyl sulfones varies remarkably depending on the conformation, i.e., the γ -proton is more acidic in the transition state **20** than in **23**. We proposed to call such an acidity of a proton characteristic to each conformation “*conformational acidity*” (a sort of kinetic acidity),¹⁷ which essentially depends on a “*syn*-effect”^{18–23} in the isomerization of vinyl sulfones. It should be noted that though the anionic intermediate **24** is thermodynamically more stable than its (*Z*)-isomer **21** as described above, such a result could not be observed in the Ramberg–Bäcklund reactions, since the desulfonylation from **21** to **22** (or from **24** to

Scheme 8. A probable course of the isomerization of (*E*)-vinyl sulfones to the corresponding allylic sulfones.



25) took place soon after the isomerization via **20** (or **23**) at low temperature.

Isomerization of other (*E*)-vinyl sulfones (*E*)-**14a–c,e** were also examined by using DBU as a base in a similar manner in acetonitrile at 10 and 25 °C as summarized in Table 2. It was found that the proportion of (*E*)- and (*Z*)-allylic sulfones (RCH=CHCH₂Ts, **19**) obtained from (*E*)-1-tosyl-1-alkenes (RCH₂CH=CHTs, **14**) with DBU was almost constant around 25/75 at 10 °C and 30/70 at room temperature (25 °C) after 12 h regardless of the length of alkyl substituents R (R = Et, *n*-Pr, *n*-Pen, *n*-Oct) at the γ -position except in the case of the benzyl group of (*E*)-**14e**, where (*E*)-**19e** predominantly formed at 25 °C, probably due to the bulkiness of the phenyl substituent. This result suggested that the steric difference among the linear alkyl substituents R in RCH₂CH=CHTs [(*E*)-**14**] is not so important when we determine the relative degree of “*syn*-effect” for γ -substituents. However, it should be noted that only (*E*)-allylic sulfones were obtained when R is a *t*-butyl group or a phenyl group (**30g,h** to **31g,h**) as shown in Table 3.

On the other hand, (*Z*)-vinyl sulfones (*Z*)-**14** gave the

Table 2. Isomerization of (*E*)- and (*Z*)-vinyl sulfones **14** to allylic sulfones **19** under basic conditions.

R	14a–e	T/°C	Yield 19 /% ^a	<i>E/Z</i> ratio of 19	T/°C	Yield 19 /% ^a	<i>E/Z</i> ratio of 19
CH ₃ CH ₂	a <i>E</i>	10	89 (7)	24/ 76	<i>Z</i> 10	93 (7)	94/ 6
		25	95 (5)	34/ 66	25	96 (1)	93/ 7
CH ₃ (CH ₂) ₂	b "	10	96 (4)	26/ 74	" 25	96 (1)	93/ 7
		25	96 (4)	35/ 65			
CH ₃ (CH ₂) ₄	c "	10	93 (4)	24/ 76	" 25	96 (1)	94/ 6
		25	97 (3)	30/ 70			
CH ₃ (CH ₂) ₇	d "	10	95 (5)	25/ 75	" 25	97 (1)	95/ 5
		25	97 (3)	30/ 70			
PhCH ₂	e "	10	98 (2)	44/ 56	" 25	94 (1)	90/ 10
		25	98 (1)	70/ 30			

^a Numbers in parentheses show recovery of **14**.

corresponding (*E*)-allylic sulfones (*E*)-**19** almost exclusively (Table 2).^{16,17} It seemed to be due to the steric congestion which precludes the possibility of a stabilizing *syn*-interaction between the α - and δ -positions as pointed out by Block *et al* (see Scheme 10).¹⁸

In conclusion, the stereochemical relationship between (*E*)- and (*Z*)-vinylic sulfones and the resulting allylic sulfones could be summarized as shown in Figure 3.

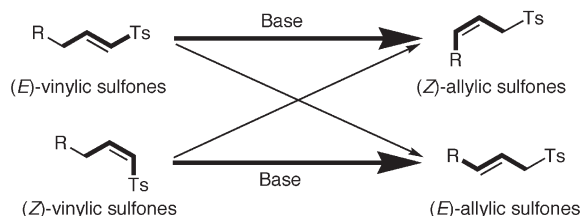


Figure 3. Stereochemical relationship in the isomerization of vinylic sulfones to the corresponding allylic sulfones.

There was a possibility that the (*E*)-vinylic sulfone itself has *syn*-conformation without treating it with a base. Therefore, a crystalline (*E*)-vinylic sulfone (*E*)-**26**, which has a 4-(triphenylmethyl)benzenesulfonyl group instead of a tosyl group in (*E*)-**14**, was prepared. Figure 4 shows the crystal structure of (*E*)-**26**, which has an *anticlinal*-conformation relative to the double-bond axis. However, when (*E*)-**26** was treated with DBU in acetonitrile in a similar manner described for (*E*)-**14**, the corresponding (*Z*)-isomer of allylic sulfone **27** was predominantly obtained (unpublished data. See also the result with **30a** in Table 3 for comparison). This result suggested clearly that the (*Z*)-selectivity of the isomerization of (*E*)-vinylic sulfones is not due to the original structure of the vinylic sulfone **26**, but the result of the kinetically-controlled reaction.

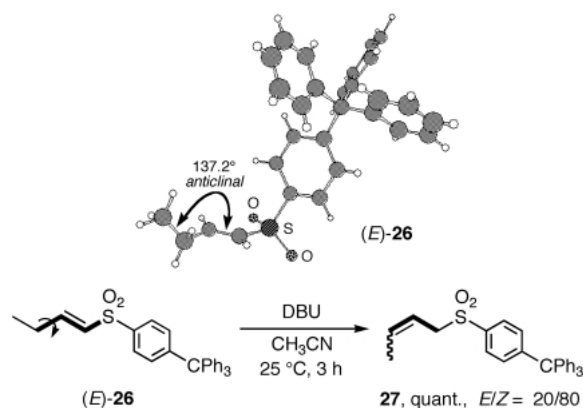
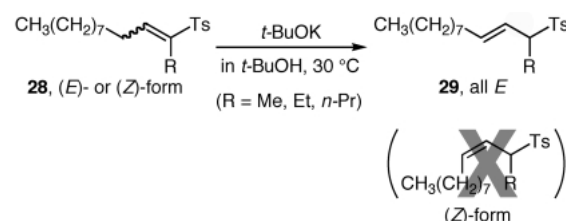


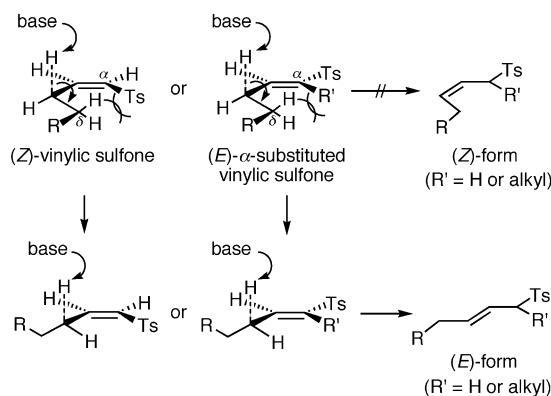
Figure 4. Crystal structure of (*E*)-1-[4-(triphenylmethyl)benzenesulfonyl]-but-1-ene [(*E*)-**26**] and stereochemistry of its isomerization to the corresponding allylic sulfone **27** under basic conditions.

On the other hand, α -substituted vinylic sulfones **28** gave the corresponding (*E*)-allylic sulfones **29** exclusively regardless of its stereochemistry as shown in Scheme 9.¹⁶ This result may be due to the steric congestion between the α -substituent and the CH_2 group at the δ -position, which precludes the possibility of a stabilizing *syn*-conformation of the transition state just like in the case of (*Z*)-vinylic sulfones (*Z*)-**14** (Scheme 10).

Scheme 9. Stereoselective formation of (*E*)-allylic sulfones **29** from α -substituted (*E*)- and (*Z*)-vinylic sulfones **28**.



Scheme 10. Stereoselective formation of (*E*)-allylic sulfones from (*Z*)-vinylic sulfones or (*E*)- α -substituted vinylic sulfones.



3.2 Relative Degree of “*Syn*-Effect” for the γ -Substituents of (*E*)-Vinylic Sulfones

Several explanations for the “*syn*-effect” or related phenomena have been proposed,^{19–23} namely: (1) 6π -electron homoaromaticity,²¹ (2) σ -orbital ($\sigma \rightarrow \sigma^*$ or $n \rightarrow \sigma^*$) interaction,^{20,22} (3) dipole-dipole (electrostatic) interaction including lone pair-lone pair repulsion,^{19,20,21d,23} (4) intramolecular hydrogen bonding,²⁰ and (5) chelation¹⁹ (see Figure 6).

In order to reveal which explanation is most reasonable in the case of the isomerization of vinylic sulfones to allylic sulfones, we tried to determine the relative degree of the “*syn*-effect” for the various γ -substituents by a series of experiments for γ -monosubstituted^{24b,25} and γ,γ -disubstituted²⁵ vinylic sulfones including the time-course of the reactions.^{24b}

γ -Monosubstituted (*E*)-1-tosyl-1-propenes (*E*)-**30** were treated with DBU in acetonitrile at room temperature (25 °C) to isomerize to the corresponding allylic sulfones **31** in a similar manner to that described above. The results are summarized in Table 3.^{24b}

It was found that (*E*)-vinylic sulfones (*E*)-**30** were preferentially isomerized to the corresponding (*Z*)-allylic sulfones (*Z*)-**31** except in the cases of **30f–i** bearing a bulky γ -substituent and γ -acetoxy substituted (*E*)-vinylic sulfone **30e**, the latter of which decomposed during the reaction. When a weak base, *N,N*-diisopropylethylamine, was used instead of DBU for the isomerization of (*E*)-3-methylthio-1-tosyl-1-propene [(*E*)-**30i**] to the corresponding allylic sulfone **31i**, (*Z*)-selectivity of **31i** remarkably increased compared with the case using DBU, though the reaction was sluggish.

Furthermore, the use of *N,N*-diisopropylethylamine as a base made it possible to compare the “*syn*-effect” among (*E*)-3-ethoxy-1-tosyl-1-propene [(*E*)-**30c**], (*E*)-**30i** and (*E*)-3-halo-1-tosyl-1-propenes [(*E*)-**30j,k**], avoiding the formation of the quaternary salts for the halogenated vinylic sul-

Table 3. Isomerization of γ -monosubstituted (*E*)- and (*Z*)-vinyl sulfones **30** to the corresponding allylic sulfones **31** under basic conditions.

Y	30a-k	Base	Time/h	Yield of 31a-k / % (<i>E/Z</i>)
CH ₃	a <i>E</i>	DBU	3	96 (15/85)
	<i>Z</i>	"	"	91 (90/10)
C ₂ H ₅	b^a <i>E</i>	DBU	12	89 (24/76)
	<i>Z</i>	"	"	93 (94/6)
C ₂ H ₅ O	c <i>E</i>	DBU	2	quant. (4/96)
	<i>Z</i>	"	"	quant. (42/58)
C ₆ H ₅ O	d <i>E</i>	DBU	2	quant. (3/97)
	<i>Z</i>	"	"	quant. (89/11)
AcO	e <i>E</i>	DBU	3	decomposed
	<i>Z</i>	"	"	decomposed
(CH ₃) ₂ CH	f <i>E</i>	DBU	17	92 (57/43)
(CH ₃) ₃ C	g <i>E</i>	"	48	98 (100/0)
C ₆ H ₅	h <i>E</i>	"	1	quant. (100/0)
CH ₃ S	i <i>E</i>	"	1	quant. (76/24)
CH ₃ S	i <i>E</i>	<i>i</i> -Pr ₂ NEt	24	98 (21/79)
Cl	j <i>E</i>	<i>i</i> -Pr ₂ NEt	24	90 (4/96)
Br	k <i>E</i>	<i>i</i> -Pr ₂ NEt	24	67 (21/79)
C ₂ H ₅ O	c <i>E</i>	<i>i</i> -Pr ₂ NEt	96	16 (0/100)

^a **30b** = **14a**

fonos (*E*)-**30j,k**, though the isomerization of (*E*)-**30c** was sluggish under the conditions (only 16% yield after 96 h at 25 °C).

By comparing the *E/Z* ratios of the resulting allylic sulfones in Table 3, the relative degree of the “*syn*-effect” for the γ -substituents Y was found to be as follows: C₆H₅O- \approx CH₃CH₂O- > Cl- > Br- > CH₃S-, and CH₃- > -CH₂- > (CH₃)₂CH- > CH₃S- > (CH₃)₃C- \approx C₆H₅-.

The order of CH₃- > -CH₂- > (CH₃)₂CH- was determined taking into account the fact that the *E/Z*-ratio of allylic sulfones (RCH=CHCH₂Ts, **19**) obtained from (*E*)-1-tosyl-1-alkenes (RCH₂CH=CHTs, **14**) with DBU was almost constant around 30/70 at 25 °C after 12 h regardless of the length of alkyl substituents R (R = Et, *n*-Pr, *n*-Pen, *n*-Oct) at the γ -position as described above (Table 2).

Table 4. Isomerization of γ,γ -disubstituted (*E*)-vinyl sulfones **32** to the corresponding allylic sulfones **33** under basic conditions.

32a-l	X	Y	Base	Time/h	Yield of 33a-l / % (<i>E/Z</i>)
a	C ₂ H ₅	CH ₃	DBU	6	68 (71/29) ^a
b	CH ₃	CH ₃ O	"	12	81 (22/78)
c	C ₂ H ₅	CH ₃ O	"	30	75 (10/90)
d	CH ₂ CH ₂ CH ₂ O	"	"	24	88 (16/84)
e	CH ₃	AcO	"	4	52 (29/71)
f	C ₂ H ₅	AcO	"	24	60 (20/80)
g	CH ₃	Cl	<i>i</i> -Pr ₂ NEt	100	93 (12/88)
h	C ₂ H ₅	Cl	"	100	86 (8/92)
i	CH ₃	Br	"	120	77 (13/87)
j	C ₂ H ₅	Br	"	96	59 (9/91)
k	CH ₃	CH ₃ S	DBU	1	quant. (66/34)
l	C ₂ H ₅	CH ₃ S	"	1	quant. (49/51)

^a “*syn*-effect”: CH₃ (= Y) > C₂H₅ (= X)

It is noteworthy that γ -phenoxy and γ -ethoxy substituted (*E*)-vinyl sulfones (*E*)-**30c,d** showed the highest “*syn*-effect” among the examined (*E*)-vinyl sulfones (*E*)-**30a-k**.

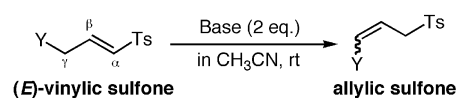
On the other hand, the (*Z*)-isomer of **30d** was predominantly converted to (*E*)-**31d** in accord with the tendency observed for (*Z*)-3-alkylated 1-tosyl-1-propenes (*Z*)-**14** [also (*Z*)-**30a,b** in Table 3], while (*Z*)-allylic sulfone **31c** was obtained as the major product from (*Z*)-3-ethoxy-1-tosyl-1-propene [(*Z*)-**30c**] in spite of the existence of unfavorable steric hindrance at the transition state, suggesting that (*Z*)-**31c** is favorable even thermodynamically.

Isomerization of γ,γ -disubstituted (*E*)-vinyl sulfones **32** to the corresponding allylic sulfones **33** was also investigated under basic conditions (Table 4).^{24b,25} The structures of (*E*)- and (*Z*)-isomers of the resulting allylic sulfones were determined by the measurement of NOE or based on the empirical rule²⁵ that the protons of alkyl group *syn* to the tosylmethyl group in an allylic sulfone appear at higher field in NMR spectrum than those *anti* to the tosylmethyl group.²⁶

The isomerization of vinyl sulfone **32a** was performed to determine the difference of “*syn*-effect” between methyl and ethyl groups. The experimental result clearly showed that methyl group prefers *syn*-geometry to ethyl group. Thus, we could confirm again that “*syn*-effect” of methyl group is higher than that of methylene group (CH₃- > -CH₂-).

The relative degree of the “*syn*-effect” for other γ -substituents was similarly examined. For the isomerization of (*E*)-3-halo-1-tosyl-1-alkenes [(*E*)-**32g,h** and (*E*)-**32i,j**] to the corresponding 3-halo-1-tosyl-2-alkenes (**33g,h** and **33i,j**), *N,N*-diisopropylethylamine was used as a base to avoid the formation of the quaternary ammonium salts. The difference of the degree of “*syn*-effect” between chloro and bromo groups was not clear from the results shown in the Table 4, while chloro group of (*E*)-**30j** was found to be a little more effective than bromo group of (*E*)-**30k** from the results shown in Table 3.

Based on the observation of *E/Z* ratios of the allylic sulfones obtained by the isomerization of the corresponding γ -mono- or γ,γ -disubstituted (*E*)-vinyl sulfones and other experimental data including time-course of the reactions,^{24b} the relative degree of “*syn*-effect” for the various γ -substituents of (*E*)-vinyl sulfones has been finally determined as follows: RO- (R = CH₃, C₂H₅) \approx ArO- (Ar = *p*-CH₃OC₆H₄, *p*-CH₃C₆H₄, C₆H₅, *p*-NO₂C₆H₄) \geq AcO- > Cl- \geq Br- > CH₃- > CH₃S- \geq -CH₂- (cyclic and acyclic) > (CH₃)₂CH- \gg (CH₃)₃C-, C₆H₅- (Figure 5).^{24b}



RO- (R = CH₃, C₂H₅) \approx **ArO-** (Ar = *p*-CH₃OC₆H₄, *p*-CH₃C₆H₄, C₆H₅, *p*-NO₂C₆H₄) \geq **AcO-** > **Cl-** \geq **Br-** > **CH₃-** > **CH₃S-** \geq **-CH₂-** (cyclic and acyclic) > **(CH₃)₂CH-** \gg **(CH₃)₃C-, C₆H₅-**

Figure 5. Relative degree of “*syn*-effect” for the γ -substituents of vinyl sulfones.

3.3 Origin of the “*Syn*-Effect” Found in the Isomerization of (*E*)-Vinyl Sulfones to the Corresponding Allylic Sulfones under Basic Conditions

From the results described above, 6 π -electron homoaro-

maticity seemed to be the most reasonable origin of the “*syn*-effect” among the several proposed explanations (Figures 6 and 7).^{19–23}

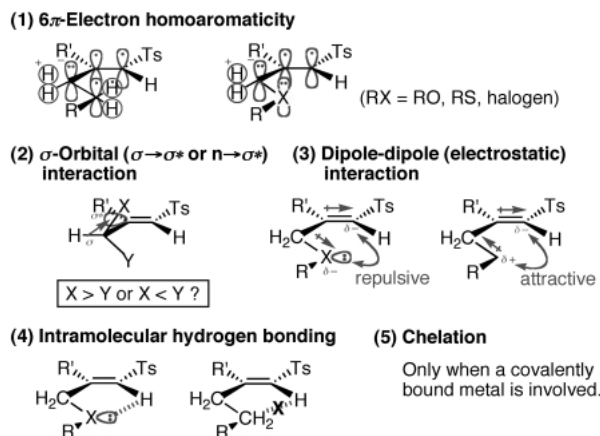


Figure 6. Proposed origins of “*syn*-effect”.

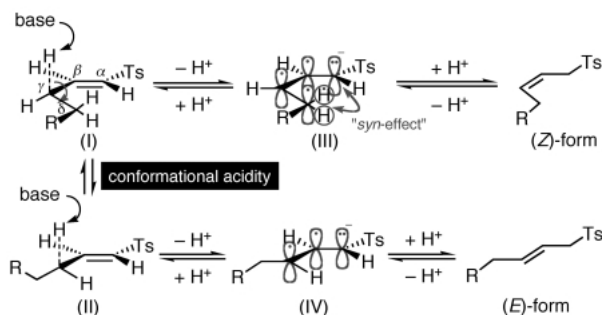


Figure 7. A probable course of the isomerization of (*E*)-vinyl sulfones to the corresponding (*Z*)-allylic sulfones via an intermediate (III) stabilized by 6 π -electron homoaromaticity.

Namely, (1) 6 π -electron homoaromaticity²¹ was applicable to all of the γ -substituents examined above except the cases such as *i*-propyl (**30f**), *t*-butyl (**30g**), and phenyl (**30h**) groups, which afforded (*E*)-allylic sulfones predominantly or exclusively (Table 3).

On the other hand, (2) σ -orbital ($\sigma \rightarrow \sigma^*$ or $n \rightarrow \sigma^*$) interaction^{20,22} cannot explain the difference of the “*syn*-effect” for the γ -substituents (X and Y in Figure 6 (2)) of γ,γ -disubstituted vinyl sulfones **32a–l**.

(3) Dipole–dipole (electrostatic) interaction^{19,20,21d,23} of γ -heteroatom substituted (*E*)-vinyl sulfones disfavors the *syn*-conformation due to their electrostatic repulsion.

(4) Intramolecular hydrogen bonding²⁰ must be involved at least in part in the cases of γ -aryloxy(or alkoxy)substituted (*E*)-vinyl sulfones as confirmed for (*E*)-3-phenoxy-1-tosyl-1-propene [(*E*)-**30d**] by X-ray crystallographic analysis (Figure 8).

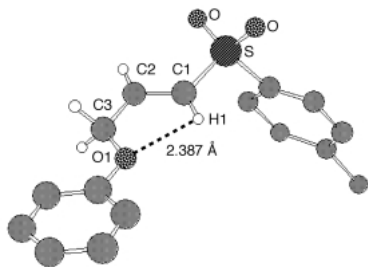


Figure 8. Crystal structure of (*E*)-3-phenoxy-1-tosyl-1-propene [(*E*)-**30d**].

sis (Figure 8).²⁴

From the crystal structure shown in Figure 8, it was found that H1, C1, C2, C3, and O1 exist on the same plane showing that “*syn*-effect” works even in the solid state of (*E*)-**30d**.²⁴ The *syn*-conformation seemed to arise from the intramolecular hydrogen bonding between the acidic α -hydrogen atom (H1), neighboring to the electron-withdrawing tosyl group, and the oxygen atom (O1) using the lone pair of the electrons in its sp^2 orbital (O1–H1, 2.39 Å). However, such a hydrogen bonding is impossible for (*E*)-1-tosyl-1-alkene (**14a–e**, **30a,b**),²⁷ even though they afforded (*Z*)-allylic sulfones predominantly. Furthermore, 6 π -electron homoaromaticity could not be excluded in spite of the long distance of O1–C1 (2.78 Å), because there is a p-orbital on the O1 conjugating with a phenyl group, which appears to correspond to the pseudo-p-orbital of the methylene group useful to stabilize *syn*-conformation of (*E*)-1-tosyl-1-alkene (**14a–e**, **30a,b**) by 6 π -electron homoaromaticity [see Figure 6 (1) and Figure 9].

(5) Chelation¹⁹ must be taken into account only when a covalently bound metal is involved in the reactions.

Next, to confirm that 6 π -electron homoaromaticity is really the origin of the “*syn*-effect”, we replaced a hydrogen atom at the α -position of (*E*)-vinyl sulfones by a fluorine atom,²⁸ because its size is not so very different from that of hydrogen and an extra unshared pair of electrons on it avoids 6 π -electron homoaromaticity by the formation of an 8 π -electron system in the *syn*-transition state (Figure 9).

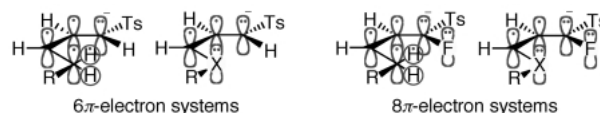


Figure 9. 6 π - and 8 π -Electron systems.

The experimental results of the isomerization of γ -substituted (*E*)- α -fluorovinyl sulfones **34** to the corresponding allylic sulfones **35** under mild basic conditions are summarized in Table 5. The ratios of (*Z*)-isomers of the resulting allylic sulfones **35** were lowered compared with those found in the case of isomerization of α -unfluorinated (*E*)-vinyl sulfones, probably due to lack of the 6 π -electron homoaromaticity and the steric factor of the fluorine atom of **34**. From the ratios of (*Z*)-isomers of **35**, the relative degree of the “*syn*-effect” for various γ -substituents R of (*E*)- α -fluoro-

Table 5. Isomerization of γ -substituted (*E*)- α -fluorovinyl sulfones **34** to the corresponding allylic sulfones **35** under basic conditions.

34a–h		35a–h			
R	34a–h	Time/h	34/35	<i>E/Z</i> of 35	Total yield/%
CH ₃	a	99	0/100	84/ 16	87
CH ₃ CH ₂	b	96	0/100	87/ 13	98
(CH ₃) ₂ CH	c	168	0/100	91/ 9	74
(CH ₃) ₃ C	d	197	7/93	100/ 0	91
Ph	e	2	0/100	100/ 0	quant.
F	f	2	18/82	27/ 73	90
EtO	g	96	0/100	63/ 37	99
PhCH ₂ S	h	96	0/100	87/ 13	95

F- >> EtO- > CH₃- > BnS- > -CH₂- > (CH₃)₂CH- > (CH₃)₃C-, C₆H₅-

vinyl sulfones **34** was determined as follows: F- \gg EtO- $>$ CH₃- $>$ BnS- \geq -CH₂- $>$ (CH₃)₂CH- $>$ (CH₃)₃C-, C₆H₅-.²⁸

The fluorine atom showed the highest “*syn*–effect” among the substituents we have investigated so far. The relative degree of the “*syn*–effect” for other substituents remains of the same order as found in the isomerization of α –unsubstituted (*E*)–vinyl sulfones to the corresponding allylic sulfones under similar conditions.

As mentioned above, the 6π –electron homoaromaticity is not applicable in the present reaction in which an α –hydrogen of (*E*)–vinyl sulfones was replaced by a fluorine atom to form an 8π –electron system (Figure 9). Nevertheless, we again observed the same tendency of the “*syn*–effect” for the γ –substituents R in the isomerization of (*E*)– α –fluorovinyl sulfones **34** to the corresponding allylic sulfones **35** as shown in Table 5.

The X–ray crystallography of (*E*)–1–fluoro–1–tosyl–1–butene (**34a**) was performed as shown in Figure 10, and it was found that the γ –methyl group (C4) has an *anticlinal*–conformation relative to the double–bond (C1=C2) axis suggesting that the “*syn*–effect” does not work in the solid state of **34a**, but at the transition state of the isomerization reaction with a base in the solution phase.²⁸ Hydrogen bonding seemed to be possible between H1 and fluorine atoms.

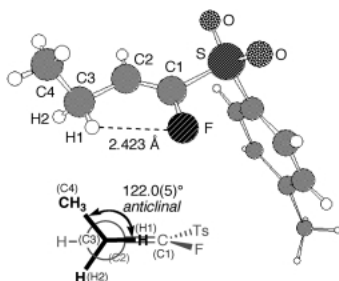


Figure 10. Crystal structure of (*E*)–1–fluoro–1–tosyl–1–butene (**34a**).

In the case of γ –ethoxy–substituted (*E*)– α –fluorovinyl sulfone (*E*)–**34g**, the ratio of the (*Z*)–allylic sulfone (*Z*)–**35g** was higher than that of the corresponding γ –alkyl–substituted allylic sulfones **35a–d**, even though it was not possible to use hydrogen bonding to stabilize the *syn*–conformation (Figure 11a) that was observed for (*E*)–3–phenoxy–1–tosyl–1–propene [(*E*)–**30d**] by X–ray crystallography (Figure 8). If anything, an electronic repulsion occurs between the lone pairs of the electrons on fluorine and oxygen atoms to destabilize the *syn*–conformation (Figure 11b).



Figure 11. Destabilizing factors for the *syn*–conformation of **34g**.

3.4 $\sigma \rightarrow \pi^*$ Interaction as an Origin of the “*Syn*–Effect”

Based on the experimental facts observed above, we proposed another possible origin of the “*syn*–effect” (Figure 12) as being a $\sigma \rightarrow \pi^*$ interaction between the σ –orbital(s) of the allylic C–H σ –bond(s) and the antibonding orbital (π^*) of the C=C double bond, which can be regarded as a sort of

hyperconjugation in the transition state, or a $\sigma \rightarrow \sigma^*_{\text{bent}}$ interaction between the σ –orbital(s) of the allylic C–H σ –bond(s) and the antibonding orbital(s) (σ^*) of the bent bonds of the C=C double bond (τ –bond model using only “single bonds”, as proposed by A. Eschenmoser in his suggestive report on the stereochemistry of E’– and E’’–reactions).²⁹ The σ/π and bent–bond descriptions of the carbon–carbon double bond might be essentially equivalent as mentioned by Wiberg.^{30,31}

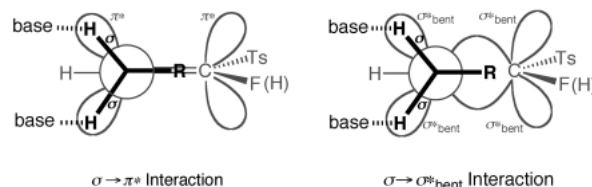


Figure 12. $\sigma \rightarrow \pi^*$ and $\sigma \rightarrow \sigma^*_{\text{bent}}$ Interactions as the origin of “*syn*–effect”.

Both π – and π^* –bonds are usually drawn with the two p–orbitals orthogonal to the C=C double bond axis, respectively, and only the phase of the combination of the p–orbitals is different. Nevertheless, the π –orbital should exist in the bonding region in contrast to the π^* –orbital which should be in the antibonding region of the C=C double bond as shown in Figure 13.

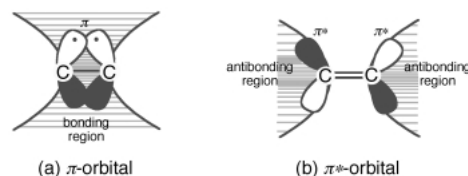


Figure 13. π – and π^* –Orbitals in the bonding and antibonding regions, respectively.

The stereochemistry of E2 reaction indicates an *anti* conformational arrangement of the hydrogen and the leaving group. That is, it can be considered to proceed through the interaction between the two orbitals in a molecule, an electron donating $\sigma_{\text{C–H}}$ orbital as a HOMO–like component and an electron accepting $\sigma^*_{\text{C–X}}$ orbital as a LUMO–like component, namely through a $\sigma \rightarrow \sigma^*$ interaction as shown in Figure 14.

When a proton of the C–H bond is removed by a base, the developing anion must efficiently interact with the vacant σ^* –orbital, which exists in the antibonding region of the C–X bond and is aligned with the $\sigma_{\text{C–H}}$ orbital on the same

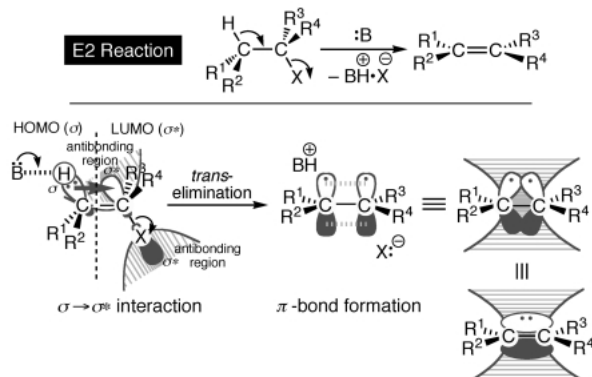


Figure 14. E2 Reaction facilitated by $\sigma \rightarrow \sigma^*$ interaction.

plane to facilitate the *trans*-elimination to form a double bond between two neighboring carbon atoms connected to the removed proton and the leaving group X, respectively.

This is well recognized as a stereoelectronic effect.³² In a similar manner, we can consider the isomerization of (*E*)-vinyl sulfones to the corresponding allylic sulfones under basic conditions as shown in Figure 15. When a base attacks the proton(s) at the γ -position of (*E*)-vinyl sulfones, the developing anion interacts with the neighboring vacant π^* -orbital, which exists in the antibonding region of the C=C double bond of (*E*)-vinyl sulfones, to facilitate the isomerization (Figure 15a). Thus, the γ -substituent R naturally has the *syn*-conformation at the transition state, if sterically possible, to afford the (*Z*)-allylic sulfones as major products.

Such a way of thinking may be applicable when the bent bond model is employed for the $\sigma \rightarrow \sigma^*_{\text{bent}}$ interaction to rationalize the same isomerization of (*E*)-vinyl sulfones (Figure 15b).

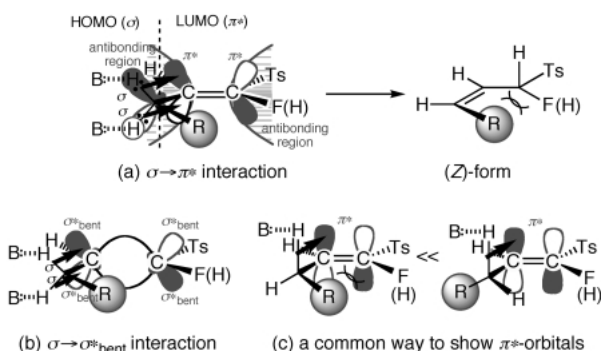


Figure 15. Possible orbital interactions for rationalizing the “*syn*-effect”.

If one draws the π -bond as usual by using p-orbitals perpendicular to the C=C bond axis, it is hard to understand why the *syn*-conformation is more favorable than the *anti*-conformation in the transition state (Figure 15c).

The observed relative degree of “*syn*-effect” for the γ -substituents R of (*E*)- α -fluorovinyl sulfone **34**, $\text{F}^- \gg \text{EtO}^- > \text{CH}_3^- > \text{BnS}^- \geq -\text{CH}_2^- > (\text{CH}_3)_2\text{CH}^- > (\text{CH}_3)_3\text{C}^-$, C_6H_5^- , seemed to reflect the electronegativity and/or electron donating ability of each substituent along with the steric hindrance supporting the $\sigma \rightarrow \pi^*$ interaction (Figure 16).

Because of the 8 π -electron system and the steric factor of the fluorine atom of (*E*)- α -fluorovinyl sulfone in the transi-

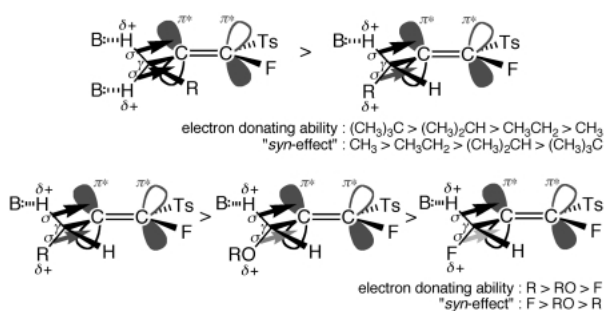


Figure 16. “*Syn*-effect” based on the $\sigma \rightarrow \pi^*$ interaction is affected by the difference of electron donating ability of each γ -substituent.

tion state, the ratio of the kinetically controlled (*Z*)-products is lowered compared with that of α -unfluorinated (*E*)-vinyl sulfones. However, the relative degree of the “*syn*-effect” for various substituents at the γ -position remained the same, as found in the isomerization of α -unfluorinated vinyl sulfones to the corresponding allylic sulfones. Thus, we have concluded that the $\sigma \rightarrow \pi^*$ interaction is the most important and essential factor to determine the relative degree of the “*syn*-effect” in the isomerization of (*E*)-vinyl sulfones to the corresponding allylic sulfones, though the contribution of a 6 π -electron homoaromaticity and/or of a hydrogen bonding cannot be entirely ruled out.²⁸

4. “*Syn*-Effect” Observed in Other Reactions

Regarding the $\sigma \rightarrow \pi^*$ interaction, we have performed X-ray crystallography for several compounds. Especially, the crystal structure of 2-ethyl-1-tosyl-1-butene (**36**), which afforded exclusively (*Z*)-2-ethyl-1-tosyl-2-butene (**37**) by treatment with DBU (Scheme 11),^{17,24a} revealed that “*syn*-effect” works in **36** itself as shown in Figure 17.^{17,24,25}

Scheme 11. Isomerization of 2-ethyl-1-tosyl-1-butene (**36**) to the corresponding 2-ethyl-1-tosyl-2-butene (**37**) with DBU as a base.

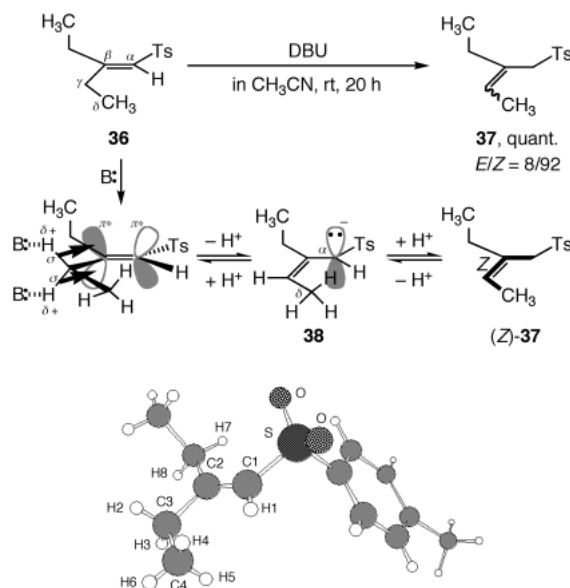


Figure 17. Crystal structure of 2-ethyl-1-tosyl-1-butene (**36**).

That is, H1, C1, C2, C3 and C4 exist on the same plane, and C3–H2 and C3–H3 bonds are aligned with π^* -orbital on C2 to allow the $\sigma \rightarrow \pi^*$ interaction.^{24,25} Such a structure makes the γ -protons H2 and H3 of the methylene *trans* to the sulfonyl group more reactive, i.e., more acidic, than H7 and H8 of the methylene *cis* to the sulfonyl group toward a base, and also allows the stabilization of the resulting anionic intermediate **38** by 6 π -electron homoaromaticity proposed as an explanation for the “*syn*-effect”.

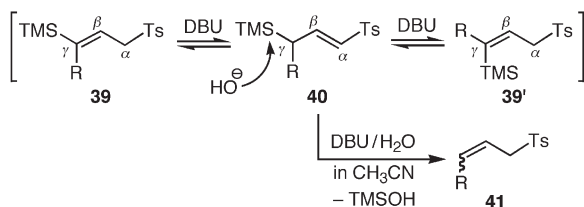
The “*syn*-effect” observed in other reactions will be described below.

4.1 “*Syn*-Effect” in the Desilylation Reaction of γ -Silylated Allylic and Vinyl Sulfones

The desilylation reaction of γ -silylated allylic sulfones **39** (or **39'**) was found to proceed through γ -silylated (*E*)-vinyl sulfones (**40**) to afford the corresponding desilylated allylic

sulfones **41** by treatment with DBU and H₂O (Scheme 12).³³ The relative degree of the “*syn*-effect” for the γ -substituents R of **39** (or **39'**, **40**) was determined by the *E/Z* ratios of the products **41** as follows: CH₃O- > CH₃- > -CH₂- > PhCH₂- > PhS- > (CH₃)₂CH- > Ph- > (CH₃)₃C-. This stereochemical outcome of the “*syn*-effect” was also rationalized by the $\sigma \rightarrow \pi^*$ interaction.

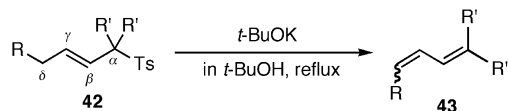
Scheme 12. Desilylation reaction of γ -silylated allylic and vinylic sulfones.



4.2 “*Syn*-Effect” in the Desulfonylation Reaction of α,α -Dialkylated (*E*)-Allylic Sulfones

It was found that the desulfonylation reaction of α,α -dialkylated (*E*)-allylic sulfones **42** with a base preferentially affords the sterically unfavorable (*Z*)-alkadienes **43** (Scheme 13).³⁴ The relative degree of the “*syn*-effect” was revealed for various substituents R at the δ -position of the (*E*)-allylic sulfones **42** to be as follows: RO- \gg CH₃- > RS- > -CH₂- > (CH₃)₂CH- \gg (CH₃)₃C- > Ph-. This finding was in accord with the tendency found above in the isomerization of α -unsubstituted (*E*)-vinylic sulfones to the corresponding allylic sulfones under basic conditions.

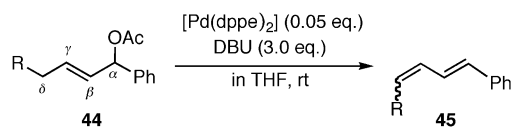
Scheme 13. Desulfonylation reaction of α,α -disubstituted (*E*)-allylic sulfones.



4.3 “*Syn*-Effect” in the Pd-Catalyzed Elimination Reaction of Acyclic (*E*)-Allylic Acetates

The stereochemistry of the Pd-catalyzed elimination reaction of acyclic (*E*)-allylic acetates **44** into the corresponding 1,3-dienes **45** was investigated in the presence of a base (Scheme 14).³⁵

Scheme 14. Pd-Catalyzed elimination reaction of acyclic (*E*)-allylic acetates.



The relative degree of the “*syn*-effect” depending on the δ -substituents R of (*E*)-allylic acetates **44** in E₂-elimination reaction via σ -allylpalladium complex was similar to that observed on the desulfonylation reaction of α,α -dialkylated (*E*)-allylic sulfones **42** as follows: BnO- > BnS- > CH₃- > -CH₂- > (CH₃)₂CH- > Ph- > (CH₃)₃C-. This result was elucidated based on the $\sigma \rightarrow \pi^*$ interaction.

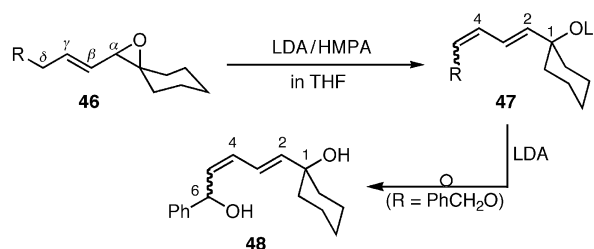
4.4 “*Syn*-Effect” in the 1,4-Eliminative Ring Opening Reaction of (*E*)-Vinyloxiranes to the Corresponding 2,4-Dienyl Alcohols

The stereochemistry of the 1,4-eliminative ring opening reaction of [δ -substituted (*E*)-1-propenyl]oxiranes **46** to the

corresponding 2,4-dienyl alcohols **47** by LDA was investigated (Scheme 15).³⁶ The relative degree of the “*syn*-effect” with respect to the δ -substituents R was found as follows: F- \approx PhCH₂O- > CH₃- > -CH₂- > (CH₃)₂CH- > PhCH₂S- > (CH₃)₃C- \approx Ph-.

These results were well rationalized by the “*syn*-effect” in the transition state of deprotonation, which mainly arose from the $\sigma \rightarrow \pi^*$ interaction. It is noteworthy that [1,2]-Wittig rearrangement following the 1,4-eliminative ring opening reaction proceeded to give a (*E,Z*)-2,4-dienyl-1,6-diol **48** in a completely stereoselective manner in the case of δ -benzyloxy-substituted vinyloxirane (**46**, R = BnO), which demonstrated a new entry of the “*syn*-effect” applied to the further stereoselective transformation.

Scheme 15. “*Syn*-effect” in the 1,4-eliminative ring opening reaction of (*E*)-vinyloxiranes and subsequent [1,2]-Wittig rearrangement.

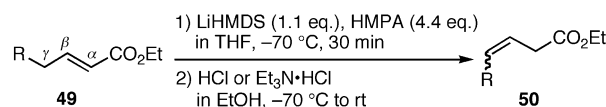


4.5 “*Syn*-Effect” in the Isomerization of (*E*)- α,β -Unsaturated Esters into the Corresponding β,γ -Unsaturated Esters

The stereochemistry in the isomerization of (*E*)- α,β -unsaturated esters **49** into the corresponding β,γ -unsaturated esters **50** was investigated under basic conditions (Scheme 16).^{37a,b} The *E/Z* ratios of the resulting β,γ -unsaturated esters **50** varied according to the γ -substituents of **49**, and the relative degree of the “*syn*-effect” depending on the γ -substituents R was found to be as follows: F- \approx BnO- > CH₃- > -CH₂- > (CH₃)₂CH- > BnS- > Ph- > (CH₃)₃C-.

The “*syn*-effect” was attributed primarily to the $\sigma \rightarrow \pi^*$ interaction^{37a,b,g} and/or 6π -electron homoaromaticity,^{37a,b} instead of the previously proposed stability of the produced anion or cyclic transition model during the deprotonation.^{37c-f}

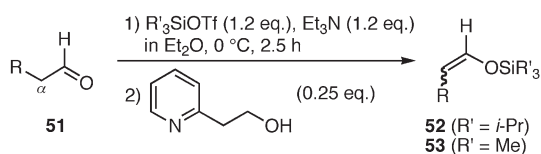
Scheme 16. “*Syn*-effect” in the isomerization of (*E*)- α,β -unsaturated esters into the corresponding β,γ -unsaturated esters.



4.6 “*Syn*-Effect” in the Conversion of Aldehydes into the Corresponding Silyl Enol Ethers

The stereochemistry in the conversion of aldehydes **51** into the corresponding silyl enol ethers **52** was also systematically investigated (Scheme 17).^{37b} The *E/Z* ratios of the resulting silyl enol ethers **52** varied according to the α -substituents R of the aldehydes **51**. In the reaction using silyl triflates, with which a strong $\sigma \rightarrow \pi^*$ interaction was anticipated, a higher *Z*-selectivity was observed, especially in the case

Scheme 17. “*Syn*-effect” in the conversion of aldehydes into the corresponding silyl enol ethers.



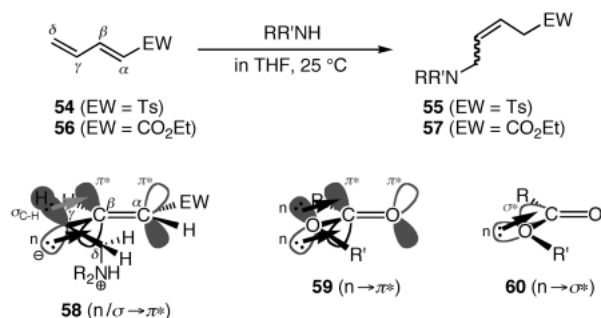
of aliphatic aldehydes. These results were well rationalized by the “*syn*-effect” based on the $\sigma \rightarrow \pi^*$ interaction and/or 6π -electron homoaromaticity.

4.7 “*Syn*-Effect” in Nucleophilic Addition of Amines to 1,3-Dienyl Sulfone and Ethyl (*E*)-2,4-Pentadienoate

The stereochemistry of nucleophilic addition of amines to (*E*)-1-tosyl-1,3-butadiene **54** was investigated (Scheme 18).³⁸ The *E/Z* ratios of the resulting allylic sulfones **55** varied with amines, solvents, temperature, and concentration. When diethylamine was reacted in low concentration at high temperature in polar and less bulky ethers, the corresponding sterically unfavorable (*Z*)-4-amino-2-butenyl sulfone **55** was preferentially obtained.

The stereochemistry of nucleophilic addition of amines to ethyl (*E*)-2,4-pentadienoate (**56**), which possesses an ester group as a conjugated electron-withdrawing group instead of a tosyl (Ts) group, was also found to realize similar high *Z*-selectivity of the addition products **57**. The predominant formation of *Z*-isomers in both cases was rationalized by the “*syn*-effect” based on the $n/\sigma \rightarrow \pi^*$ interaction (**58**) and/or 6π -electron homoaromaticity. A similar consideration seems to be applicable to elucidate other related phenomena,³² such as a favorable *syn*-conformation of esters (RCO₂R'), as shown in Scheme 18 as an $n \rightarrow \pi^*$ interaction (**59**) with a sp³ oxygen model for OR' instead of a usual $n \rightarrow \sigma^*$ interaction (**60**) with a sp² oxygen model.³²

Scheme 18. “*Syn*-effect” in nucleophilic addition of amines to 1,3-dienyl sulfone and ethyl (*E*)-2,4-pentadienoate.



5. Conclusions

There exist many examples in organic chemistry where one cannot invoke the intuitive concept of steric or nonbonded repulsion to predict the relative stabilities of geometrical or conformational isomers of organic molecules. The origin of these puzzling phenomena has remained unclear.

Toward elucidation of such a long-standing problem, we have been performing experimental investigations regarding the “*syn*-effect” observed first in the isomerization of α -unsubstituted (*E*)-vinyl sulfones to the corresponding allylic sulfones under mild basic conditions.

Finally, the “*syn*-effect” was rationalized by the concept

of $\sigma \rightarrow \pi^*$ interaction and/or 6π -electron homoaromaticity or hydrogen bonding, if possible, based on the experimental data from the various different types of reactions. We hope the newly proposed $\sigma \rightarrow \pi^*$ interaction (or $n/\sigma \rightarrow \pi^*$ interaction), taking account of the shape of π - and π^* -orbitals existing in the bonding and antibonding regions, respectively, or a $\sigma \rightarrow \sigma^*_{\text{bent}}$ interaction, which might be essentially equivalent to the $\sigma \rightarrow \pi^*$ interaction, will be applied both to analyze and to predict the stereochemistry of other organic compounds or reactions, the latter of which may proceed through the unfavorable *syn*-conformation at their transition states against the general concept of steric hindrance.

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