"*Syn*-Effect" in Nucleophilic Addition of Amines to 1,3-Dienylsulfone

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The stereochemistry of the nucleophilic addition of amines to 1,3-dienylsulfone was investigated. The Z/E ratios of the resulting allylic sulfones varied with amines, solvents, temperature, and concentrations. The predominant formation of (*Z*)-isomer was rationalized by a "*syn*-effect," which could be mainly elucidated by $n/\sigma \rightarrow \pi^*$ interaction.

Previously, we investigated the stereochemistry of the isomerization of α-unsubstituted (*E*)-vinylic sulfones to the corresponding allylic sulfones in the presence of a base and found that the sterically unfavorable (*Z*)-allylic sulfones were predominantly formed.[1] This result was rationalized by a "*syn*-effect,"[2,3] which is primarily caused by $\sigma \rightarrow \pi^*$ interaction and/or 6π-electron homoaromaticity (Figure 1).[3]

Recently, we revealed that the "*syn*-effect" works also in the desulfonylation reaction of α,α-dialkylated (*E*)-allylic sulfones,[3a] the isomerization of (*E*)-α-fluorovinylic sulfones to the corresponding allylic sulfones under basic conditions,[3b] the conversion of (*E*)-α,β-unsaturated esters and aldehydes into the corresponding β,γ-unsaturated esters and silyl enol ethers,[3c,3e] respectively, the desilylation reaction of γ-silylated allylic and vinylic sulfones,[3d] the elimination reaction of (*E*)-allylic acetates catalyzed by palladium under the specific conditions utilizing a base,[3f] and the 1,4-eliminative ring opening of (*E*)-1-propenyloxirane derivatives by treatment with metal amides.[3g]

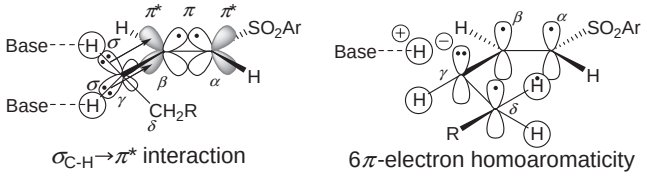
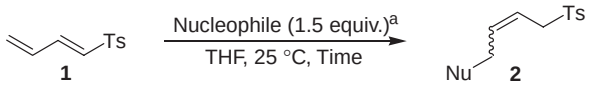


Figure 1.

Table 1. The stereochemistry of the nucleophilic addition of various amines to 1,3-dienylsulfone **1**



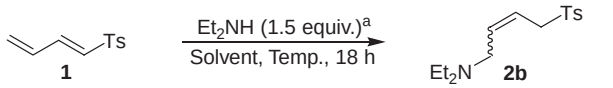
Entry	Nucleophile		Time/h	**1**/**2**[b]	Yield/%[c]	Z/E[d]
1	Me_2NH[e]	**a**	24	0/100	91	60/40
2	Et_2NH	**b**	72	19/81	75	74/26
3	$^nPr_2NH$	**c**	72	52/48	43	85/15
4	$^iPr_2NH$	**d**	72	100/0	—	—
5	$^nBu_2NH$	**e**	72	48/52	46	87/13
6	^{n}BuN(H)Me	**f**	72	0/100	85	72/28
7	^{i}PrN(H)Me	**g**	72	38/62	58	80/20
8	Pyrrolidine	**h**	6	0/100	83	44/56
9	Piperidine	**i**	12	0/100	85	55/45
10[f]	$^nPrNH_2$	**j**	72	11/89	70	21/79
11[f]	$^nBuNH_2$	**k**	72	11/89	71	23/77

[a]Concentration was 150 mM in all cases. [b]The ratios were determined based on the isolated yields. [c]Isolated total yield of **2**. [d]The ratios were determined by 400 MHz ^{1}H NMR spectra. [e]A commercially available 2.0 M solution of Me_2NH in THF was used. [f]Formation of $(TsCH_2CH{=}CHCH_2)_2NR$ (R = ^{n}Pr, 5%; ^{n}Bu, 7%) was observed.

For the preparation of allylic sulfones, nucleophilic addition to (*E*)-1-tosyl-1,3-butadiene (**1**) is a useful way. Interestingly, it was reported that addition of lithium dibutylcuprate to **1** gave only (*Z*)-1-tosyl-2-octene.[4] However, both isomers were obtained in 96% yield with *Z*-preference (Z/E = 65/35) as the result of our reexamination. This inconsistent result prompted us to investigate the stereochemistry of the nucleophilic addition of various amines to 1,3-dienylsulfone **1** in THF at 25 °C and the results are summarized in Table 1. The Z/E ratios of the produced allylic sulfones **2a**–**2k** varied depending on the kinds of amines. Acyclic secondary amines, especially $^nBu_2NH$ and $^nPr_2NH$, showed relatively high *Z*-preference.

Next, the stereochemistry of the nucleophilic addition of Et_2NH to 1,3-dienylsulfone **1** was examined in detail, paying attention to the effect of solvents, temperature, and concentrations, and the results are summarized in Tables 2 and 3. It was found that polar and less bulky ethers, such as DME and THF, showed high *Z*-selectivity (Table 2, Entries 2 and 5). It is noteworthy that the *Z*-selectivities were enhanced when the reaction was carried out at higher temperature (Entries 1–6).

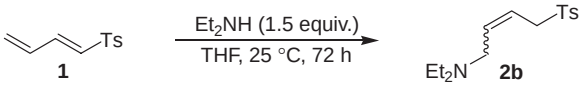
Table 2. The stereochemistry of the nucleophilic addition of Et_2NH to 1,3-dienylsulfone **1** in various solvents



Entry	Solvent	Temp./°C	**1**/**2b**[b]	Yield/%[c]	Z/E[d]
1	DME	0	84/16	16	67/33
2		25	58/42	40	82/18
3		60	33/67	61	88/12
4	THF	0	65/35	28	52/48
5		25	59/41	38	78/22
6		60	27/73	64	86/14
7	1,4-Dioxane	25	32/68	61	64/36
8	THP	25	41/59	48	61/39
9	Et_2O	25	61/39	35	31/69
10	^{t}BuOMe	25	52/48	47	28/72
11	Pyridine	25	3/97	73	71/29
12	*N*-Methylmorpholine	25	71/29	26	63/37
13	*N*-Methylpyrrolidine	25	81/19	15	53/47
14	$CHCl_3$	25	44/56	56	44/56
15	Tetrahydrothiophene (THT)	25	0/100	90	41/59
16	Benzene	25	27/73	70	30/70
17	MeCN	25	0/100	98	37/63
18	DMSO	25	0/100	77	27/73

[a]Concentration was 150 mM in all cases. [b]The ratios were determined based on the isolated yields. [c]Isolated total yield of **2b**. [d]The ratios were determined by 400 MHz ^{1}H NMR spectra.

Table 3. The effect of concentration on the nucleophilic addition of Et_2NH to 1,3-dienylsulfone **1**



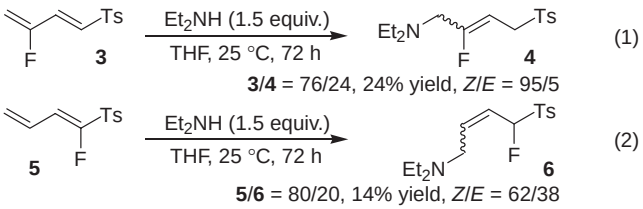
Entry	Conc. of Et_2NH/mM	**1**/**2b**[a]	Yield/%[b]	*Z*/*E*[c]
1	150	19/81	75	74/26
2	75	51/49	48	93/7
3	50	59/41	39	95/5
4	37.5	64/36	33	96/4
5[d]	37.5	38/62	50	96/4
6	15	86/14	12	94/6

[a]The ratios were determined based on the isolated yields. [b]Isolated total yield of **2b**. [c]The ratios were determined by 400 MHz ^{1}H NMR spectra. [d]The reaction was carried out at 60 °C.

The effect of concentration is shown in Table 3. The lower concentration of Et_2NH remarkably increased the *Z*-selectivity of **2b** (Entries 2–4 and 6), though the reaction became sluggish.

The mechanism for predominant formation of (*Z*)-allylic sulfones **2b** is not yet clear.[5] To confirm the possibility of a concerted 1,4-addition mechanism (Figure 2, **A**), nucleophilic addition of Et_2NH (150 mM) to 3-fluoro-1-tosyl-1,3-butadiene (**3**) was investigated (Scheme 1, eq 1). Selective formation of (*Z*)-3-fluoroallyl sulfone derivative **4** excluded the 1,4-addition mechanism. Furthermore, addition of Et_2NH (150 mM) to 1-fluoro-1,3-dienylsulfone **5** mainly gave (*Z*)-allylic sulfone **6** (Scheme 1, eq 2), even though its *syn*-transition state forms 8π-electron system **C** which is not stabilized by the homoaromaticity. Thus, the contribution of 6π-electron homoaromaticity (Figure 2, **B**) was also ruled out.

Finally, the selective formation of (*Z*)-allylic sulfone **2b** was rationalized by a "*syn*-effect," which could be mainly elucidated by $n/\sigma \rightarrow \pi^*$ interaction, but not 6π-electron homoaromaticity (Scheme 2). That is, when a pair of electrons on nitrogen atom of Et_2NH interacts with π^* orbital of $C_\gamma{=}C_\delta$ at $\delta-$position of **1** or **3**, an anion would develop on γ-carbon changing from sp^2 to sp^3. The *n*-electron pair of γ-carbanion can more effectively interact with π^* orbital of $C_\alpha{=}C_\beta$ in the eclipsed conformations **D** and **E**, in both of which the *n*-orbital is aligned with the π^* orbital ($n \rightarrow \pi^*$ interaction), and the conformation **F** can be neglected.[6] Further, the contribution of $\sigma \rightarrow \pi^*$ interaction might determine



Scheme 1.

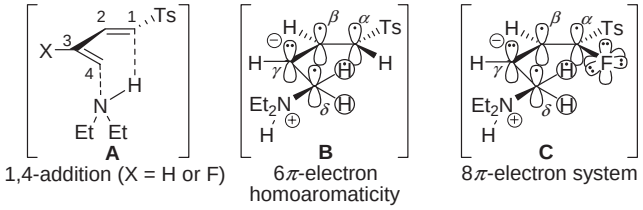
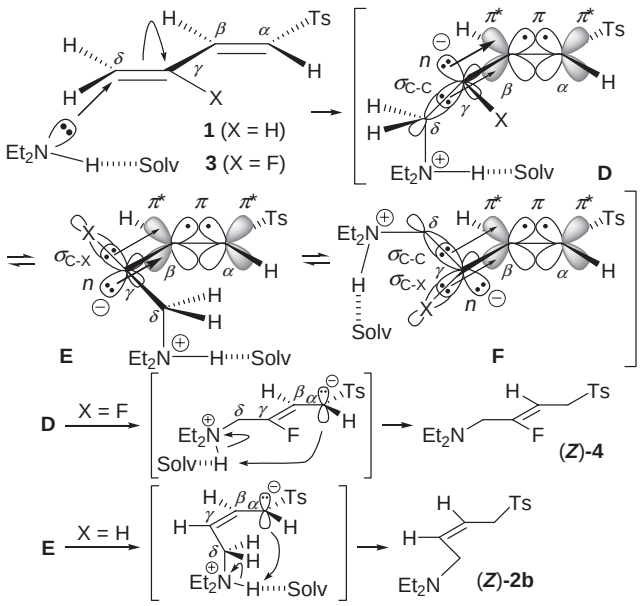


Figure 2.



Scheme 2.

the preference of **D** or **E**, because $\sigma \rightarrow \pi^*$ interactions increase in the order of $\sigma_{C-H} \rightarrow \pi^* > \sigma_{C-C} \rightarrow \pi^* > \sigma_{C-F} \rightarrow \pi^*$, (*Z*)-**2b** was predominantly obtained in the case of **1** (X = H) via conformation **E**, while (*Z*)-**4** was formed from **3** (X = F) via **D**.

Higher temperature and lower concentration might dissociate the aggregation of dialkylamine via hydrogen bonding to afford the more nucleophilic monomeric amine.

In conclusion, the *Z*-selective nucleophilic addition of amines to 1,3-dienylsulfone was well rationalized by a "*syn*-effect" which could be mainly elucidated by $n/\sigma \rightarrow \pi^*$ interaction.

References and Notes

1 T. Hirata, Y. Sasada, T. Ohtani, T. Asada, H. Kinoshita, H. Senda, K. Inomata, *Bull. Chem. Soc. Jpn.* **1992**, *65*, 75.

2 The "*syn*-effect" is herein defined as an effect which stabilizes the *syn*-conformation against the steric hindrance at the transition state.

3 Related studies on the "*syn*-effect": a) A. Shibayama, T. Nakamura, T. Asada, T. Shintani, Y. Ukaji, H. Kinoshita, K. Inomata, *Bull. Chem. Soc. Jpn.* **1997**, *70*, 381. b) T. Nakamura, S. K. Guha, Y. Ohta, D. Abe, Y. Ukaji, K. Inomata, *Bull. Chem. Soc. Jpn.* **2002**, *75*, 2031. c) S. K. Guha, A. Shibayama, D. Abe, Y. Ukaji, K. Inomata, *Chem. Lett.* **2003**, *32*, 778. d) S. K. Guha, Y. Ukaji, K. Inomata, *Chem. Lett.* **2003**, *32*, 1158. e) S. K. Guha, A. Shibayama, D. Abe, M. Sakaguchi, Y. Ukaji, K. Inomata, *Bull. Chem. Soc. Jpn.* **2004**, *77*, 2147. f) H. Takenaka, Y. Ukaji, K. Inomata, *Chem. Lett.* **2005**, *34*, 256. g) N. Takeda, T. Chayama, H. Takenaka, Y. Ukaji, K. Inomata, *Chem. Lett.* **2005**, *34*, 1140.

4 F. Näf, R. Decorzant, S. D. Escher, *Tetrahedron Lett.* **1982**, *23*, 5043.

5 Radical mechanism could be ruled out because the presence of TEMPO, *N*-hydroxyphthalimide, galvinoxyl free radical did not affect the *Z*/*E* ratios.

6 The effective $n \rightarrow \pi^*$ interaction cannot be involved in the conformation **F**.

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