Solvent Effect on Sulfur Ylide Mediated Epoxidation Reaction[†]

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Received June 21, 2007

The solvent effect on sulfur ylide mediated epoxidation reaction was studied systematically. While higher *trans/cis* ratio of the epoxide was obtained in the more polar solvent, protic solvent produced the lower *trans/cis* ratio than any aprotic solvent.

Key Words : Sulfur ylide, Epoxidation, Solvent effect, Stereoselectivity

Introduction

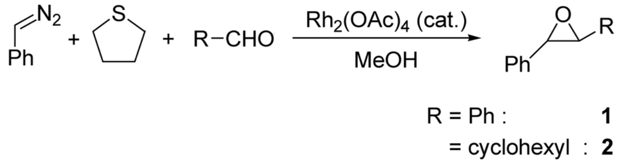
As alkene oxidation was the most widely used method for the preparation of epoxides,[1] reactions of aldehydes with α-bromoacetates (Darzen condensation)[2] or with sulfur ylides (Corey-Chaykovsky reaction)[3] have been attracting much less interest though these reactions offer convergent routes to epoxides. Preparation of epoxides from sulfur ylides draws much attention of organic synthetic community as the reaction has become enantioselective[4], catalytic[5] and practical.[6]

While much research effort was devoted to the enantioselectivity of the reaction, diastereoselectivity has not been systematically studied and even the origin of diastereoselectivity is still at issue as *trans* epoxides were much dominant products from aromatic aldehydes and *trans* epoxides were major product with low selectivity from aliphatic aldehydes. There have been a few attempts to understand the mechanism of the epoxide formation as well as the origin of stereoselectivity theoretically and experimentally.[7,8] Nevertheless, *trans* epoxides can now be obtained selectively in many cases.[9] It was also reported that additives such as Li salts or protic solvents reduced diastereoselectivity.[10] The *cis* selectivity was reported where vinyl epoxides were formed from the corresponding TMS-allyl sulfonium salts in the presence of Li salt.[11]

However, all these reports could not provide any directions to control the diastereoselectivity since the reaction conditions of the epoxide formation for stereoselectivity have not been studied systematically. Therefore, we embarked on the study to find a general trend of the diastereoselectivity and a way to control the diastereoselectivity according to the choice of the solvent.

Results and Discussion

The pure solvent effect on the reaction could be addressed as Aggarwal's new process to prepare ylides provided the ideal environment for the study of the solvent effect on the epoxidation reaction.[12] Under this mild and neutral condition, epoxidation reactions were carried out mainly from ylides and aldehydes in a solvent without being affected by other factors (Scheme 1).



Scheme 1

The result in a variety of different solvents was summarized in Table 1. The epoxidation reaction was proven to be flexible as the reaction proceeded in nonpolar, polar or even in protic solvents. With benzaldehyde, stilbene oxide was obtained in high yield with high selectivity for the *trans* isomer in most solvents. Diastereoselectivity was not influenced much by solvent variation. In contrast, the diastereoselectivity with cyclohexanecarboxaldehyde varied much with the solvents used. The selectivity trend in the table suggested that diastereomeric ratio is affected more by solvating power than polarity of the solvent.[13] Ethereal

Table 1. Solvent effect on diastereoselectivity[15]

Solvent	1		2	
	t : c[a]	Yield[b]	t : c[a]	Yield[b]
$PhCF_3$	95 : 5	98	64 : 36	70
DCM	96 : 4	99	67 : 33	78
CCl_4	95 : 5	88	68 : 32	66
Hexane	93 : 7	97	69 : 31	58
Et_2O	95 : 5	>99	73 : 27	63
MeCN	96 : 4	>99	75 : 25	83
Benzene	95 : 5	>99	77 : 23	73
DME	94 : 6	93	81 : 19	59
THF	95 : 5	>99	85 : 15	56
DMF	98 : 2	>99	88 : 12	85
DMSO	>99 : 1	68	>99 : 1	13
MeOH[c,d]	67 : 33	75	50 : 50	37

[a]NMR ratio. [b]Yield was estimated based on NMR integration using benzyl ether as an internal standard. [c]2 eq. of THT was used. [d]Addition was completed within 30 min and then the mixture stirred for 3 h.

[†] This paper is dedicated to Professor Sang Chul Shim on the occasion of his honorable retirement.

solvents such as THF and DME, which can solvate intermediates effectively, gave higher ratio of the *trans* epoxide to the *cis* epoxide. Chlorinated solvents that do not have strong solvating power gave the diastereomeric ratio as low as hexane. The *trans/cis* ratio was considerably high in benzene (as high as acetonitrile) though it is a nonpolar solvent. Since benzene is a π-electron donor, it is known to solvate charged species effectively in solution. Reduction of the electron density of the benzene ring by trifluoromethyl group in trifluorotoluene resulted in decreased diastereoselectivity. This selectivity trend is quite similar to the Wittig reaction though the mechanisms of the two reactions are not quite the same.[14] To our surprise, when the reaction was tested in methanol, a protic solvent, the reaction still proceeded and the diastereoselectivity became the highest for the *cis* isomer both with benzaldehyde and cyclohexanecarboxaldehyde though the yields were low. Low yields were presumed to be due to decomposition of the diazo compound into other compounds in alcoholic solvents. In order to minimize the loss of the diazo compound, 2 eq. of tetrahydrothiophene was used and the addition rate of phenyl diazomethane was doubled. In this way, we hoped to increase the chance for the carbene to react with the sulfide before the other undesired reaction occurred. Indeed, the yields were improved while diastereoselectivity remained unchanged. Interestingly, the reaction rate was slower in methanol than other solvents.

Contrasting result of methanol to other polar solvents in the Table 1 implies that there must be other effects of methanol on the selectivity. In addition to its high polarity and solvating power, methanol can be a hydrogen bonding donor. If this hydrogen bonding plays a critical role on the selectivity, it is also expected that even small amount of methanol as an additive could influence the selectivity. Thus, we tested reactions by using methanol as the additive in acetonitrile solvent. Table 2 shows the results on yields and diastereoselectivities of epoxides formed. Yields were not considerably affected by increasing the amount of methanol. In the case of benzaldehyde, *trans/cis* ratio was affected slightly as the amount of methanol increased. On the other hand, for cyclohexanecarboxaldehyde, the diastereoselectivity changed significantly. Furthermore, the *cis* epoxide became the major product when more than 5 eq. of methanol was added. It was noteworthy that 10 eq. of methanol resulted in higher *cis* selectivity than methanol as the solvent. Methanolic effect was not noticeable in polar solvents such as THF and DMSO.

Table 2. Effect of MeOH as the additive in CH_3CN

MeOH	**1**		**2**	
	t : c[a]	Yield[b]	t : c[a]	Yield[b]
None	96 : 4	>99	75 : 25	83
1 eq	95 : 5	>99	60 : 40	73
2 eq	94 : 6	99	55 : 45	70
5 eq	91 : 9	>99	49 : 51	65
10 eq	88 : 12	95	46 : 54	84

[a]NMR ratio. [b]Yield was estimated based on NMR integration using benzyl ether as an internal standard.

Table 3. Effect of additives on the *trans/cis* ratio for **2**

Additive	1 eq.		5 eq.	
	t : c[a]	Yield[b]	t : c[a]	Yield[b]
t-BuOH	68 : 32	90	61 : 39	79
i-PrOH	65 : 35	79	54 : 46	75
EtOH	63 : 47	78	52 : 48	71
MeOH	60 : 40	73	49 : 51	65
BnOH	56 : 44	76	47 : 53	59
CF_3CH_2OH	51 : 49	90	46 : 54	59
H_2O	64 : 36	80	54 : 46	76
PhOH[c]	59 : 41	57	–[c]	0

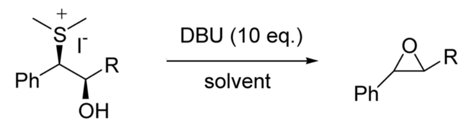
[a]NMR ratio. [b]Yield was estimated based on NMR integration using benzyl ether as an internal standard. [c]Phenyl benzyl ether was obtained as a major product.

Increased *cis* selectivities could be explained in part by solvation effect of methanol through hydrogen bonding, as it reduces the rotation barrier from cisoid betaine to transoid betaine resulting in retarded reversibility. Also, stabilized transoid betaine explains the observed slow reaction rate in methanol. As the result, the diastereoselectivity would be close to the kinetic ratio of betain formation.[7] Consequently, a stronger proton donor was expected to solvate betaines more efficiently and would provide the diastereoselectivity closer to the kinetic ratio of the betain formation. This assumption was tested by the effect of additives on diastereoselectivity using various alcohols. The results using different alcohols were summarized in Table 3.

As we have anticipated, more acidic alcohol, which is a better proton donor, yielded more *cis* product as expected. Increased amount of alcohol shifted the diastereoselectivity toward the *cis* isomer. Water also acted as a good proton donor in this system. Though there were reports of using water as a part of phase transfer catalysis reaction condition for sulfur ylide mediated epoxidation, erosion of the *trans* selectivity has not been observed. The current result indicates that other additives in the reaction also affect the diastereoselectivity. In the case of PhOH, the reaction of phenol with phenyl diazomethane competed with the sulfide and produced phenyl benzyl ether as a major by-product.

To confirm the inhibition of reversibility of betains by protic solvent, we prepared the corresponding sulfonium salts of the betaines following the Aggarwal's report[8a] and observed the effect of methanol on the epoxide formation. Scheme 2 summarized the results of the epoxide formation from the *syn*-hydroxy sulfonium salts since the *anti*-hydroxy sulfonium salts showed no reversibility with or without methanol as reported in the literature.[8a]

For the phenyl substitution, the betaine isomerized rapidly to form mostly the *trans* epoxide in acetonitrile. The isomerization reaction was slowed down with an addition of two equivalent of MeOH. When MeOH was used as the solvent the isomerization was suppressed substantially and produced the *cis* isomer as a major product. The methanol



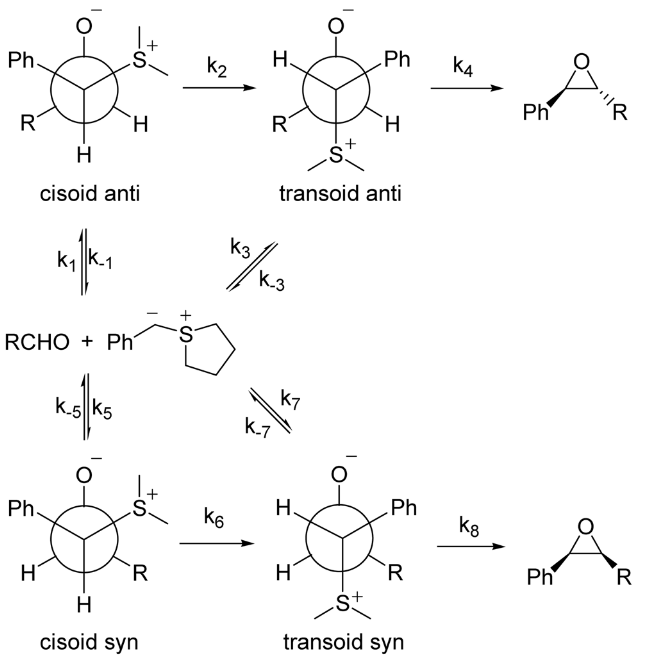
R	Solvent	Additive	*trans : cis*[c]
Ph	MeOH	None	26 : 74
	MeCN	None	91 : 9
		MeOH (2eq.)	84 : 16
Cyclohexyl[b]	MeOH	None	5 : 95
	MeCN	None	23 : 77
		MeOH (2eq.)	22 : 78

[a]10 eq. of DBU was used as the base. [b]*syn*:*anti* of the salt = 95:5. [c]NMR ratio

Scheme 2. *trans/cis* ratio from pre-formed *syn*-salts[a]

effect became much more significant for the cyclohexyl compound. With the cyclohexyl substitution, the isomerization of the betaine was relatively slow that the *cis* epoxide was the major product in acetonitrile. When methanol was used as a solvent, this isomerization was suppressed completely and the isomeric ratio of the salt remained the same in the ratio of two diastereomeric epoxides. The *syn* betain from **2** did not undergo reversion to the ylide and aldehyde in methanol solution. Though this result was not obtained under exactly the same reaction condition as it contained DBU and iodide anion, this result clearly shows that protic solvent or additive slows down the reversible reaction of the *syn* betain with the corresponding aldehyde and ylide.

According to Aggarwal's calculation,[8d] in nonploar solvents, cisoid betaines are preferentially obtained over transoid betaines. Bond rotation is the most important factor in determining the selectivity since there is no external interaction. Compared to aliphatic aldehyde, aromatic aldehyde has greater reversibility ($k_{-5} > k_6$) due to stabilization by developing conjugation of the π-orbital. In addition to reducing the rotation barrier, the alcohol prohibits the reversion of betaines to ylide and aldehyde because hydrogen bonding causes reduced nucleophilicity of oxygen. This effect can also account for slow reaction rate. Reduced selectivity by addition of protic solvent is well explained in this way ($k_{-5} < k_6$, $k_{-7} < k_8$).



Scheme 3. Reaction mechanism.

This bond rotation is not important any more in polar solvent as cisoid betaines readily overcome the rotation barrier to form their rotamer, transoid betaines with the aid of polar solvent. Therefore, ring formation steps (k_4 and k_8) are the rate determining steps. In this case, transoid *syn* betaine is readily reverted to ylide and aldehyde while transoid *anti* betaine forms epoxides ($k_{-7} > k_8$, $k_{-3} < k_4$). This is rationalized by different stabilities of two betaines. Along with stabilization of ylide, increased nucleophilicity of oxygen in polar solvent accelerates reversion of *syn* betaine. As a result, higher selectivity for the *trans* epoxide was observed in polar solvents. Addition of alcohol in polar solvent does not influence the selectivity since intermediates are mainly solvated by solvent and alcoholic effect is suppressed.

In alcohol as a solvent, cisoid addition is not dominant any more because interaction between lone pair electron on oxygen and positively charged sulfur does not have an advantage any more. Therefore, all of four possible betaines can be formed. Among these, transoid betaines directly produce epoxides and cisoid betaines give epoxides via rotation to transoid betaines. Reverse reaction of betaines to ylide and aldehyde slows down through hydrogen bonding. Thus, resulting ratio of *trans/cis* epoxide can be regarded as a ratio of betaines. As the amount of methanol in nonpolar solvent increased, the effect was enhanced. At a certain point, methanol began to act as a polar solvent more than a hydrogen bonding donor, which explains the slightly increased *trans/cis* ratio when methanol was used as a solvent.

In conclusion, we revealed that solvation is a crucial determinant of diastereoselectivity in Corey-Chaykovsky reaction. We also found an unusual protic solvent effect on this selectivity. It turned out that unique stabilization of intermediates through strong hydrogen bonding influenced the reaction rates of the very finely balanced reaction. From the current observation, it is hopeful that a general reaction condition for the *cis* selectivity could be achieved through additional additives and through controlling the reaction temperature.[15]

Experimental Scection

***N*-Benzyl-*p*-toluenesulfonamide.** To a solution of benzylamine (5.0 mL, 45.8 mmol) in pyridine (25 mL) was added tosyl chloride (10.5 g, 55.0 mmol) at 0 °C. The solution was stirred for 1 h at room temperature, and then water was added. The precipitate was filtered. The yellow solid was recrystalized ($CHCl_3$/hexane) to give a white solid (10.9 g, 91%); ^{1}H NMR (300 MHz, $CDCl_3$) 2.42 (3H, s), 4.10 (2H, d, $J = 5.9$ Hz), 4.61 (1H, m), 7.25-7.35 (7H, m), 7.73 (2H, d, $J = 8.3$ Hz).

***N*-Nitroso-*N*-benzyl-*p*-toluenesulfonamide.** A stirred solution of *N*-benzyl-*p*-toluenesulfonamide (3.74 g, 14.3 mmol) in glacial acetic acid (15 mL) and acetic anhydride (60 mL) was cooled to 5 °C. Powdered sodium nitrite (8.0 g) was added portions over period of 1 h. The temperature was kept below 10 °C at all times; the mixture was stirred at room temperature overnight. The reaction mixture was then poured over an excess of ice water with vigorous stirring and cooled for 1 h. The pale yellow precipitate was filtered, washed several times with cold water, and dried overnight in vacuum. The crude product was then recrystallized from ethanol to give a tiny yellow needle (2.8 g, 67%); ^{1}H NMR (300 MHz, $CDCl_3$) 2.39 (3H, s), 4.90 (2H, s), 7.00-7.25 (2H, m), 7.15-7.30 (5H, m), 7.70 (2H, d, $J = 8.3$ Hz).

Benzaldehyde tosylhydrazone. To a slurry of *p*-toluenesulfonhydrazide (5.0 g, 27 mmol) in methanol (10 mL) was added benzaldehyde (2.7 mL, 27 mmol) dropwise. Within 30 min the tosylhydrazone began to precipitate. The mixture was cooled to 0 °C and the product was removed by filtration. Recrystallization of the resultant solid from methanol gave the desired hydrazone as a white crystalline solid (5.4 g, 82%); ^{1}H NMR (300 MHz, $CDCl_3$) 2.37 (3H, s), 7.26-7.37 (5H, m), 7.52-7.61 (2H, m), 7.80 (1H, s), 7.89 (2H, d, $J = 9.0$ Hz), 8.44 (1H, br s).

Phenyldiazomethane

Method A: To a stirred mixture of sodium methoxide (160 mg, 2.80 mmol) in 1 mL of methanol and 6 mL of diethyl ether was added *N*-nitroso-*N*-benzyl-*p*-toluenesufonamide in portions over a period of 10 min. After the addition was completed, the mixture was stirred under reflux for 2 h. After cooling the reaction, water was added to dissolve the salts. The aqueous layer was discarded and the organic layer was washed with water, dried over Na_2SO_4, and filtered. The filtrate was concentrated under vacuum to give a red oil.

Method B: A 1.0 M sodium methoxide solution was prepared by adding sodium (230 mg, 10 mmol) to anhydrous methanol (10 mL) with external cooling. Once all of the metal had dissolved benzaldehyde tosylhydrazone (2.7 g, 10 mmol) was added and the mixture was stirred until the solid had dissolved. After stirring for 15 min., methanol was thoroughly removed under reduced pressure to give a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) 2.26 (3H, s), 7.29 (5H, m), 7.49 (2H, d, $J = 10.0$ Hz), 7.71 (2H, d, $J = 10.0$ Hz), 7.96 (1H, s). The solid hydrazone salt was placed in Kugelrohr. Red phenyldiazomethane was collected at 6 torr, 150 °C.

General procedure for epoxidation in various solvents. Phenyldiazomethane (80 mg, 0.66 mmol) in 1 mL of each anhydrous solvent was added to a solution of tetrahydrothiophene (29 μL, 0.33 mmol), rhodium acetate dimer (1.5 mg, 0.0030 mmol), protic solvent additive (0-3.3 mmol) and benzaldehyde (33 μL, 0.33 mmol) or cyclohexanecarboxaldehyde (40 μL, 0.33 mmol) in the same anhydrous solvent (1.0 mL) over 2 h by means of syringe pump. After the addition was complete the reaction mixture was stirred at room temperature for an additional hour. The solvent was removed in vacuo, and benzyl ether (11.5 μL, 0.0830 mmol) was added. In the presence of alcohol, addition was complete within 30 min. and the reaction was stirred for 3 h.

2,3-Diphenyloxirane: ^{1}H NMR (300 MHz, $CDCl_3$) *trans isomer*: 3.87 (2H, s), 7.16-7.37 (10H, m); *cis isomer*: 4.37 (2H, s), 7.01-7.15 (10H, m).

2-Cyclohexyl-3-phenyloxirane: ^{1}H NMR (300 MHz, $CDCl_3$) *trans isomer*: 0.94-1.95 (11H, m), 2.75 (1H, dd, $J = 2.1$, 6.9 Hz), 3.66 (1H, d, $J = 2.1$ Hz) 7.11-7.37 (5H, m); *cis isomer*: 0.94-1.95 (11H, m), 2.88-2.94 (1H, m), 4.06 (1H, d, $J = 4.2$ Hz), 7.11-7.37 (5H, m).

***Anti*-1,2-diphenyl-2-hydroxyethyl(dimethyl)-sulfonium iodide.** To a solution of *trans*-stilbene oxide (1.0 g, 5.1 mmol) in absolute ethanol (5 mL) was added sodium thiomethoxide (0.70 g, 10 mmol). The resulting solution was heated under reflux for 1 hr., stirred overnight at room temperature and then diluted with water (5-10 mL). Ethanol was removed in vacuo from the mixture and the residue was extracted with ethyl acetate (5 × 5 mL). The combined extracts were dried over $MgSO_4$, filtered and evaporated under reduced pressure to give the desired anti-hydroxysulfide as an off-white solid (0.90 g, 72%). The hydroxysulfide was stirred in methyl iodide (5.5 mL) for 2 h, and then methyl iodide was removed in vacuo and the resulting solid was washed with ether to give the desired sulfonium salt (0.84 g, 59%) as an off-white solid; ^{1}H NMR (300 MHz, $(CD_3)_2SO$) 2.58 (3H, s), 3.08 (3H, s), 5.14 (1H, d, $J = 4.0$ Hz), 5.52 (1H, m), 6.74 (1H, d, $J = 4.0$ Hz), 7.11-7.28 (10H, m).

***Syn*-1,2-diphenyl-2-hydroxyethyl(dimethyl)sulfonium iodide.** *Syn*-sulfonium salt was prepared in the same manner from *cis*-stilbene (0.70 g, 3.8 mmol). Off-white solid (0.75 g, 81%); NMR (300 MHz, $(CD_3)_2SO$) 2.87 (3H, s), 3.34 (3H, s), 5.23 (1H, d, $J = 10.0$ Hz), 5.47 (1H, dd, $J = 10.0$, 4.0 Hz), 6.90 (1H, d, $J = 4.0$ Hz), 7.14-7.32 (5H, m), 7.36-7.52 (5H, m).

***Syn*-2-cyclohexyl-1-phenyl-2-hydroxyethyl(dimethyl)-sulfonium iodide.** *Syn*-2-cyclohexyl-1-phenyl-2-hydroxyethyl(dimethyl)-sulfonium iodide salt was prepared in the same manner from *cis*-2-phenyl-3-cyclohexyloxirane (1.08 g, 5.40 mmol). Off-white solid (1.24 g, 60%); NMR (300 MHz, $(CD_3)_2SO$) 0.72-1.98 (11H, m), 2.41 (3H, s), 2.74 (3H, s), 4.17 (1H, dd, $J = 10.0$, 4.0 Hz), 5.09 (1H, d, $J = 10.0$ Hz), 6.19 (1H, d, $J = 4.0$ Hz), 7.43-7.65 (5H, m).

General procedure for the preparation of epoxides from sulfonium salts. To a solution of a sulfonium salt (0.25 mmol) in each solvent (5 mL) was added an appropriate base and the resulting mixture was stirred overnight. Water was added and the organic layer was extracted with ethyl acetate (3 × 5 mL). The combined organic layer was dried over $MgSO_4$, filtered and evaporated.

Acknowledgments. This work was supported by the Center for Molecular Design and Synthesis, and from MarineBio21, Ministry of Maritime Affairs and Fisheries, Korea.

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