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Methanesulfonamide: a Cosolvent and a General Acid Catalyst in Sharpless Asymmetric Dihydroxylations

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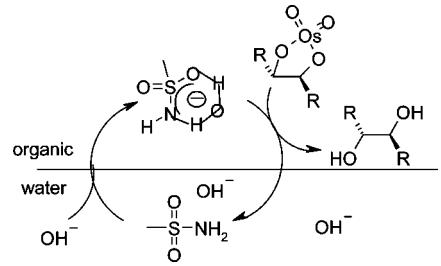

To obtain information about the effect that methanesulfonamide has in the hydrolysis step in Sharpless asymmetric dihydroxylation, a series of aliphatic and conjugated aromatic olefins were dihydroxylated with and without methanesulfonamide. The hypothesis in this study was that methanesulfonamide is a cosolvent that aids in the transfer of the hydroxide ions from the water phase to the organic phase. A plot of *t*90% versus the computational partition coefficient clog *P* of the intermediate osmate ester of nonterminal aliphatic olefins revealed that the polarity of the intermediate osmate ester has a significant effect on the reaction time and methanesulfonamide effect. The more polar the intermediate osmate ester, the faster is the reaction without methanesulfonamide and the smaller the accelerating methanesulfonamide effect. Methanesulfonamide had no accelerating effect in the asymmetric dihydroxylation of short chain terminal aliphatic olefins as a result of easier accessibility of terminal osmate ester groups to the water phase. A cosolvent hypothesis was found not to be valid in asymmetric dihydroxylations of conjugated aromatic olefins. In the reaction conditions used in Sharpless asymmetric dihydroxylation, weakly acidic methanesulfonamide was found to be a general acid catalyst that protonates the intermediate osmate esters of conjugated aromatic olefins in the hydrolysis step.

Introduction

During the early 1990s developments in Sharpless asymmetric dihydroxylation (AD) led to a protocol that uses potassium ferricyanide as the stoichiometric oxidant.[1] Potassium ferricyanide was used in biphasic reaction conditions with which the enantioselectivity-deteriorating secondary cycle was nearly completely avoided. The turnover rate of the new catalytic cycle depended on the rate of the hydrolysis of the intermediate osmate(VI) ester. Methanesulfonamide ($CH_3SO_2NH_2$) was found to be an additive that accelerates the rate-limiting hydrolysis step under the heterogeneous reaction conditions.[2] For reasons that were not understood then, addition of $CH_3SO_2NH_2$ accelerated the hydrolysis of osmate esters derived from 1,2-disubstituted and trisubstituted olefins but slowed the catalytic AD of monosubstituted and 1,1-disubstituted olefins. So, today the recommended procedure in Sharpless AD is to add 1 equiv of $CH_3SO_2NH_2$ per 1 equiv of olefin for the AD of nonterminal olefins.

Reaction time can be significantly shorter in the presence of $CH_3SO_2NH_2$. It has been reported that in the absence of $CH_3SO_2NH_2$ *trans*-5-decene is only partially (70%) converted to the corresponding diol after 3 days at 0 °C, whereas the diol is isolated in 97% yield after only 10 h at 0 °C in the presence

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(2) Sharpless, K. B.; Amberg, W.; Youssef, L. B.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768–2771.

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of $CH_3SO_2NH_2$.[2] Under certain reaction conditions $CH_3SO_2NH_2$ can be omitted also with nonterminal olefins. Mehltretter et al. have reported that by providing the constant high pH value of 12.0, *trans*-5-decene can be dihydroxylated even faster than in the presence of $CH_3SO_2NH_2$.[3] We have reported that nonterminal olefins react quickly without $CH_3SO_2NH_2$ if sodium chlorite ($NaClO_2$) is used as the stoichiometric oxidant.[4] $NaClO_2$ oxidizes the osmate(VI) ester to the more reactive osmate(VIII) ester prior hydrolysis.[5] In addition, the pH of the reaction medium stays at a high level since dihydroxylations with $NaClO_2$ do not consume any hydroxide ions. Sodium hypochlorite (NaOCl) as the stoichiometric oxidant has provided similar results.[6] So far, there has not been a report to explain why nonterminal olefins benefit from the addition of $CH_3SO_2NH_2$ and why terminal olefins do not benefit, nor have there been any other studies of the details of the $CH_3SO_2NH_2$ effect in Sharpless AD except for those mentioned above. Here we present the first systematic study of the $CH_3SO_2NH_2$ effect in Sharpless asymmetric dihydroxylation.

Our hypothesis for this study was that in an alkaline biphasic *tert*-butanol/water solvent system $CH_3SO_2NH_2$ aids in the transfer of hydroxide ions from the water phase to the organic phase. Therefore the accessibility of the osmate ester group in the intermediate (the species that reacts during the hydrolysis step) to the water phase is decisive in terms of the reaction time and $CH_3SO_2NH_2$ effect. The more polar the intermediate osmate esters, the more water-soluble they are and the faster the rate-limiting hydrolysis of the intermediate osmate esters will be. Also, as the intermediate osmate ester becomes more polar and thus dissolves better in water, the accelerating effect of $CH_3SO_2NH_2$ will be smaller. As a measure of the polarity of the intermediate osmate ester we used computational octanol/water partition coefficient clog *P*.[7]

Results and Discussion

A qualitative indication of the hydroxide ion transfer to the organic phase by $CH_3SO_2NH_2$ in the AD was obtained by taking aliquots from the organic *tert*-butanol phase of the alkaline biphasic reaction mixture and adding the sample to a phenolphthalein indicator solution. The color of the indicator solution changed from colorless to red only if $CH_3SO_2NH_2$ was added to the reaction mixture, indicating the presence of hydroxide ions in the organic phase. The importance of the hydrogen bonding ability of the organic solvent to the hydroxide ion transfer by $CH_3SO_2NH_2$ was revealed in an experiment where protic *tert*-butanol was changed to aprotic *tert*-butyl methyl ether. Aliquots from the *tert*-butyl methyl ether phase of the alkaline biphasic reaction mixture did not change the color of the phenolphthalein indicator solution even if $CH_3SO_2NH_2$ was added to the reaction mixture, indicating that there were not hydroxide ions in the organic phase.

The common protocol of Sharpless AD was used in ADs of several olefins, and *t*90% was measured for all of those olefins

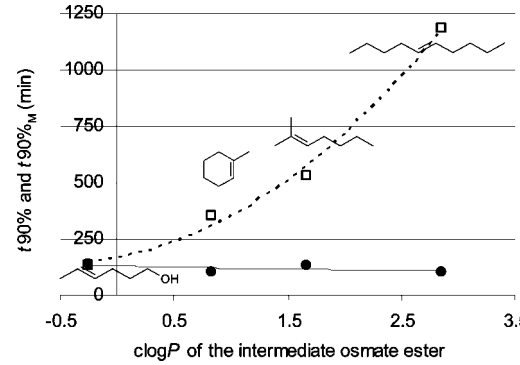


FIGURE 1. *t*90% values of Sharpless ADs of nonterminal aliphatic olefins with (●) and *t*90%$_M$ without (□) $CH_3SO_2NH_2$ versus computational partition coefficient clog *P*'s of the intermediate osmate esters.

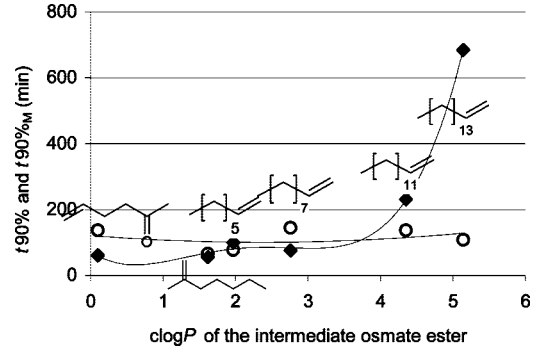


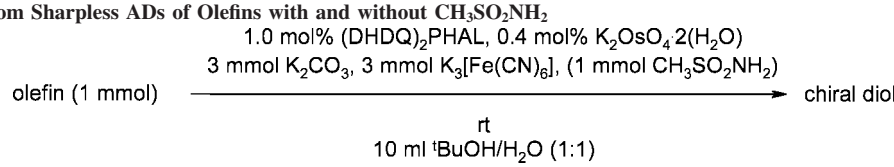
FIGURE 2. *t*90% values of Sharpless ADs of terminal aliphatic olefins with (○) and *t*90%$_M$ without (■) $CH_3SO_2NH_2$ versus computational partition coefficient clog *P*'s of the intermediate osmate esters.

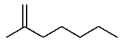
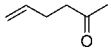
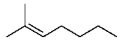
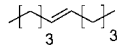
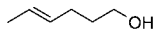
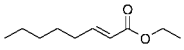
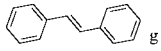
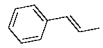
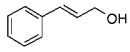
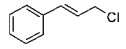
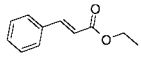
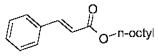
in reactions without $CH_3SO_2NH_2$ and *t*90%$_M$ in the presence of $CH_3SO_2NH_2$.[8] In Figure 1 are presented the *t*90% and *t*90%$_M$ of nonterminal aliphatic olefins, and in Figure 2 are the *t*90% and *t*90%$_M$ in ADs of terminal aliphatic olefins versus clog *P*'s of the intermediate osmate esters. From Figure 1 it is quite evident that even though the correlation between the *t*90% time and clog *P* is not linear, the polarity and thus the solubility of the intermediate osmate ester to water is a very significant factor in the *t*90% of the AD of nonterminal aliphatic olefins. The *t*90% is 1180 min in the AD of *trans*-5-decene, the compound that has the least water-soluble osmate ester intermediate (clog $P = 2.85$), almost nine times higher than the *t*90% of 135 min in the AD of *trans*-4-hexen-1-ol, which has the most water-soluble osmate ester intermediate (clog $P = -0.25$). Figure 1 shows that in the presence of $CH_3SO_2NH_2$ the *t*90%$_M$ in the AD of nonterminal aliphatic olefins is evened out. The difference between the shortest and the longest *t*90% times decreases from about 1050 to 40 min if $CH_3SO_2NH_2$ is used. The rate acceleration by $CH_3SO_2NH_2$ is most effective with the olefins that have the least water-soluble intermediate osmate esters. The *t*90%$_M$ of 105 min in the AD of *trans*-5-decene is more than 11 times shorter, whereas the *t*90%$_M$ of 140 min in the AD of *trans*-4-hexen-1-ol is slightly longer than the corresponding *t*90%.

From Figure 1 we draw a conclusion that if $CH_3SO_2NH_2$ is not used, the hydrolysis of the intermediate osmate esters takes place in the water phase, rather than in the interphase of the

(3) Mehltretter, G. M.; Döbler, C.; Sundmermeier, U.; Beller, M. *Tetrahedron Lett.* **2000**, *41*, 8083–8087.
(4) Junttila, M. H.; Hormi, O. E. O. *J. Org. Chem.* **2004**, *69*, 4816–4820.
(5) Junttila, M. H.; Hormi, O. E. O. *J. Org. Chem.* **2007**, *72*, 2956–2961.
(6) (a) Mehltretter, G. M.; Bhor, S.; Klawonn, M.; Döbler, C.; Sundermeier, U.; Eckert, M.; Militzer, H.-C.; Beller, M. *Synthesis* **2003**, *2*, 295–301. (b) Sundermeier, U.; Döbler, C.; Beller, M. In *Modern Oxidation Methods*; Bäckvall, J.-E., Ed.; VCH Publishers: Weinheim, 2004; pp 1−20.
(7) http://www.chemaxon.com/demosite/marvin/index.html (method, weighted; method weights, VG 1, KLOP 1, PHYS 1, User defined 0; Cl^- concentration (mol/dm^3) 0.1; Na^+K^+ concentration (mol/dm^3) 0.1; type log *P*).
(8) Becker, H.; Sharpless, K. B. In *Asymmetric Oxidation Reactions*; Katsuki, T., Ed.; Oxford University Press: New York, 2001; pp 81−104.

TABLE 1. Results from Sharpless ADs of Olefins with and without $CH_3SO_2NH_2$



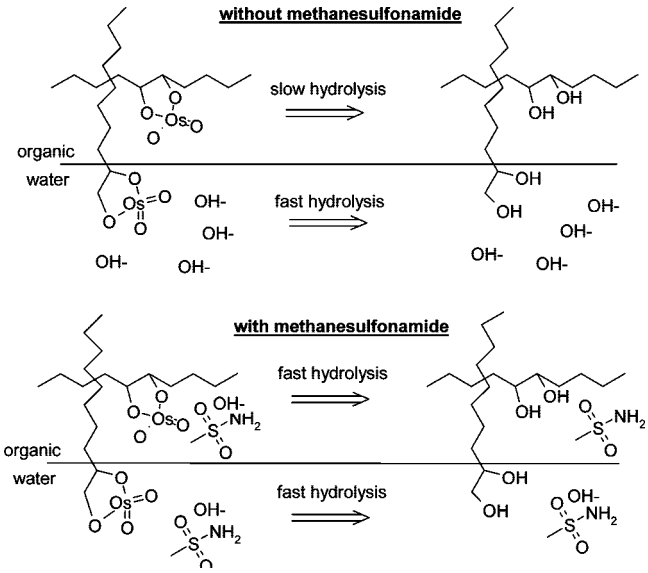
Olefin	*t*90% (min)	*t*90%$_M$ (min)	*t*90% / *t*90%$_M$	clog*P*[a]	Yield%	Yield%$_M$	Ee%[b]	Ee%$_M$[b]	Config.[c]
	685	110	6.23	5.14	56	55	72	76	R
	230	135	1.70	4.35	79	74	75	75	R
	75	145	0.52	2.76	63	79	81	80	R
	100	75	1.33	1.97	95	75	80	79	R
	55	65	0.85	1.62	66	71	72[d]	71[d]	R
	60	135	0.44	0.10	93[e]	86[e]			
	530	135	3.93	1.67	57	52	96	97	
	1180	105	11.24	2.85	77	86	97	97	5R,6R
	135	140	0.96	-0.25	64	58	80	77	4S,5S
	355	100	3.55	0.84	63	78	50	50	1S,2R
	110	110	1.00	1.68	59	75	98	97	2S,3R
	310	370	0.84	1.35	77	70	97	97	R
	45	60	0.75	3.20	82	83	>99.5	>99.5	R,R
	150	200	0.75	1.76	92	88	99	99	1R,2R
	295	220	1.34	0.68	64	83	95[d]	95[d]	1R,2S
	95	90	1.05	2.12	47	48	98	98	1R,2R
	200	120	1.67	1.46	90	86	99	99	2S,3R
	1165	495	2.35	3.91	70	72	99	99	
	550	630	0.87	1.40	98	87	41	37	1R,2S

[a] Computational partition coefficient clog *P*'s of the intermediate osmate esters. [b] Enantiomeric excesses were determined by analyzing chiral GC data (Lipodex E) of the TFA-derivatives of the diols or by analyzing the ^{1}H NMR spectra of the bisMosher ester of the diol. [c] Configuration of the major enantiomer was determined by comparing the optical rotation to literature values. [d] Enantiomeric excess was determined by comparing the optical rotation to literature values. [e] Crude yield; we were not able to purify the product. [f] Reactions were performed at 0 °C. [g] 0.5 mmol of olefin.

water and organic phases. The most evident result in Figure 1 in favor of the hydrolysis taking place in the water phase is that the smaller the clog *P* value is, i.e., the greater the amount of intermediate osmate ester in the water phase, the faster the AD. If the hydrolysis of the intermediate osmate ester took place in the interphase, one could expect that the sterically more hindered and, due to alkyl groups, more electron-rich trisubstituted olefins such as 1-methylcyclohexene and 2-methylhept-2-ene would react more slowly than the sterically less hindered and more electron-poor disubstituted *trans*-5-decene. Yet there is a significant difference in *t*90% in favor of the trisubstituted olefins. Also, if the hydrolysis of the intermediate osmate ester took place in the interphase, it would be difficult to see why disubstituted nonterminal olefins presented in Figure 1 would react so differently in the presence of methanesulfonamide. $CH_3SO_2NH_2$ accelerates significantly the AD of disubstituted *trans*-5-decene and decelerates slightly the AD of disubstituted *trans*-4-hexen-1-ol. In fact, all of these observations support our hypothesis that the accessibility of the osmate ester intermediate to the water phase is decisive in terms of the reaction time and also that the $CH_3SO_2NH_2$ is aiding in the transfer of hydroxide ions to the organic phase.

From Figure 2 one can see that in the case of terminal aliphatic olefins there is no similar correlation between the *t*90%

SCHEME 1. Schematic Presentation of the Hydrolysis of Intermediate Osmate Esters of *trans*-5-Decene and 1-Decene with and without $CH_3SO_2NH_2$



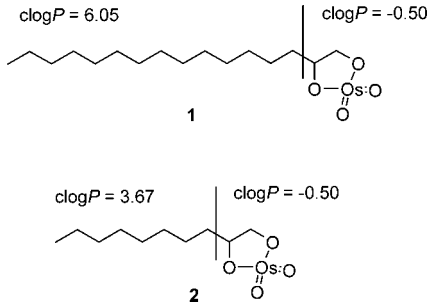
in ADs without $CH_3SO_2NH_2$ and clog *P*'s of the intermediate osmate esters, as there is with the nonterminal aliphatic olefins. Quite surprisingly the major difference in reaction times in the AD of terminal olefins is due to the elongation of the carbon chain. There is a significant change in reaction time after the carbon chain is longer than 13 carbons. The *t*90% in the AD of 1-hexadecene is more than six times longer than the *t*90% in the AD of other terminal aliphatic olefins except for 1-tetradecene (Table 1). As it was with the nonterminal aliphatic olefins, $CH_3SO_2NH_2$ evens out the reaction times in the AD of terminal aliphatic olefins. The difference between the *t*90% in the AD of 1-hexadecene and 2-methylheptene decreases from 630 to 45 min if $CH_3SO_2NH_2$ is used (Table 1). Again, the most significant $CH_3SO_2NH_2$ rate-accelerating effect is with the olefins that are slowest to react in the AD without $CH_3SO_2NH_2$, and also the addition of $CH_3SO_2NH_2$ has no significant accelerating effect or retards slightly the reaction times in the AD of those terminal aliphatic olefins that react quickly without $CH_3SO_2NH_2$.

Osmate esters of *trans*-5-decene and 1-decene have almost the same clog *P*'s (2.85 and 2.76, respectively), but their *t*90% values in Sharpless AD without $CH_3SO_2NH_2$ differ significantly (1200 and 75 min). In Scheme 1 is presented the major difference in the hydrolysis step in Sharpless ADs of terminal and nonterminal aliphatic olefins. The osmate ester group is highly hydrophilic: clog *P* of the osmate ester of ethylene is −0.50. In aliphatic terminal olefins, the osmate ester end of the chain is extremely hydrophilic and in the biphasic reaction conditions can easily enter the water phase. So, the hydrolysis of the terminal osmate ester group in 1-decene takes place quickly in alkaline water phase as presented in Scheme 1. In nonterminal olefins the hydrophilic osmate ester group is between hydrophobic groups, which diminishes the accessibility of the osmate ester group to the water phase. Therefore the *t*90% is much longer in the AD of nonterminal *trans*-5-decene. Nonterminal olefins can also react quickly without $CH_3SO_2NH_2$ if the whole molecule is hydrophilic and has easy access to the water phase, as is the case in the AD of *trans*-4-hexen-1-ol (clog $P = -0.25$ for the intermediate osmate ester).

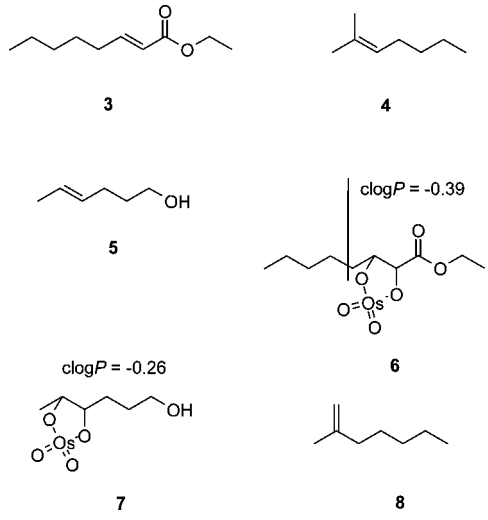
In addition to the different *t*90% values in the AD without $CH_3SO_2NH_2$, the $CH_3SO_2NH_2$ effect on the $t90\%_M$ in Sharpless AD of *trans*-5-decene and 1-decene is different: in the presence of $CH_3SO_2NH_2$ the $t90\%_M$ of 105 min in the AD of *trans*-5-decene is about 1/11 of the *t*90% of 1180 min in the AD of *trans*-5-decene without $CH_3SO_2NH_2$, and the $t90\%_M$ of 145 min in the AD of 1-decene is almost two times longer than the *t*90% of 75 min in the AD of 1-decene without $CH_3SO_2NH_2$ (Table 1). $CH_3SO_2NH_2$ accelerates considerably the AD of *trans*-5-decene and decelerates the corresponding reaction of 1-decene. In Scheme 1 is presented a rationalization for their different behavior in Sharpless AD without $CH_3SO_2NH_2$ and in the presence of $CH_3SO_2NH_2$. If $CH_3SO_2NH_2$ is not used, the hydroxide ions required in the hydrolysis step are in the water phase, into which the nonterminal osmate ester can not enter as easily as the terminal osmate ester in 1-decene. If $CH_3SO_2NH_2$ is used, then hydroxide ions resides in both the water and the organic phase and therefore the rate-limiting hydrolysis step can occur quickly regardless of the position of the osmate ester group. Hydroxide ions, attached to the $CH_3SO_2NH_2$, are less nucleophilic than the free hydroxide ions. A consequence of the decrease in nucleophilicity of the hydroxide ion in the presence of $CH_3SO_2NH_2$ is the slight increase in *t*90% in the AD of 1-decene and other aliphatic olefins that react quickly without $CH_3SO_2NH_2$.

1-Hexadecene is a terminal olefin, yet the $CH_3SO_2NH_2$ effect in the AD of 1-hexadecene resembles more the $CH_3SO_2NH_2$ effect in the AD of nonterminal olefins than the $CH_3SO_2NH_2$ effect in the AD of other terminal olefins (Figure 2). The *t*90% of 685 min in the AD of 1-hexadecene without $CH_3SO_2NH_2$ and the $CH_3SO_2NH_2$ effect ($t90\%/t90\%_M = 6.23$) are similar to those of ADs of nonterminal olefins such as *trans*-5-decene. We believe that there are two factors that prevent the terminal osmate ester group in 1-hexadecene and other long chain terminal olefins to react in a similar manner as other terminal olefins: (1) as the size of the molecule increases, the probability that the molecule, originally in the organic phase, approaches the water phase in a way that the hydrophilic osmate ester group can enter the water phase becomes smaller, and (2) as the size of the hydrophobic part of the molecule increases, the time that the osmate ester group spends in the water phase, if it gets there, becomes shorter than the time required for the hydrolysis to take place. The hydrophilicity of the terminal osmate ester group is the same in the osmate esters of 1-hexadecene **1** and 1-decene **2**, but there is a significant difference in the hydrophobicity of the water-insoluble part of the molecule: clog *P*'s are 6.05 and 3.67, respectively. The more hydrophobic the water-insoluble part of the terminal olefin, the stronger it pulls the osmate ester group from the water phase into the organic phase. We think that there is a certain limit, after which the hydrophobic part of the molecule starts to increase the reaction time by decreasing the time that the osmate ester group spends in the water phase, so that there is not enough time for hydrolysis to take place. In the case of terminal straight chain olefins, that limit seems to be clog$P > 5.2$ (n-$C_{12}H_{28}$) for the hydrophobic part of the molecule.

Ethyl-*trans*-2-octenoate **3** is a nonterminal olefin, yet its *t*90% in Sharpless AD without $CH_3SO_2NH_2$ does not fit the curve presented in Figure 1. The clog *P* of 1.68 of the osmate ester of ethyl-*trans*-2-octenoate is almost the same as the clog *P* of 1.67 for the osmate ester of 2-methylhept-2-ene **4**, yet the *t*90% of 110 min in the AD of ethyl-*trans*-2-octenoate is almost five



times shorter than the *t*90% of 530 min in the AD of 2-methylhept-2-ene. The *t*90% in the AD of ethyl-*trans*-2-octenoate is even shorter than the *t*90% of 135 min in the AD of *trans*-4-hexen-1-ol **5** (clog $P = -0.25$). Also the $CH_3SO_2NH_2$ effect is different in the AD of ethyl-*trans*-2-octenoate than it is in the AD of 2-methylhept-2-ene: $CH_3SO_2NH_2$ has no effect on the *t*90% in the AD of ethyl-*trans*-2-octenoate, whereas in the AD of 2-methylhept-2-ene the $t90\%_M$ is one-fourth of the *t*90%. It seems that ethyl-*trans*-2-octenoate reacts almost as if it is a terminal olefin. In the osmate ester of ethyl-*trans*-2-octenoate **6**, despite the ethyl group, the osmate ester and ester groups form an almost as highly hydrophilic end (clog $P = -0.39$) to the molecule as there is in terminal osmate esters **1** and **2** (clog $P = -0.50$). Hydrophilicity of the osmate ester of *trans*-4-hexen-1-ol **7** is smaller (clog $P = -0.26$), and therefore a slightly slower AD occurs with *trans*-4-hexen-1-ol.



The pair of 2-methylhept-2-ene **4** and 2-methylheptene **8** gives an excellent example of the importance the position of the double bond in olefin to the reaction time in Sharpless AD. In the absence of $CH_3SO_2NH_2$, the *t*90% of 55 min in the AD of terminal 2-methylheptene is almost 1/10 the *t*90% of 530 min in the AD of nonterminal 2-methylhept-2-ene. One could say that the difference in *t*90% can be attributed to the larger steric crowding in the osmate ester of nonterminal 2-methylhept-2-ene than in the osmate ester of terminal 2-methylheptene or that the osmate ester of 2-methylhept-2-ene is less electrophilic because there are more electron-donating alkyl groups than there are in 2-methylheptene. We think that steric crowding and electronic effects due to alkyl groups have only minor effect in the *t*90% in the AD of 2-methylhept-2-ene and 2-methylheptene. The steric crowding or the electronic effects are not changed if hydrolysis aid $CH_3SO_2NH_2$ is used, yet the $CH_3SO_2NH_2$ has a

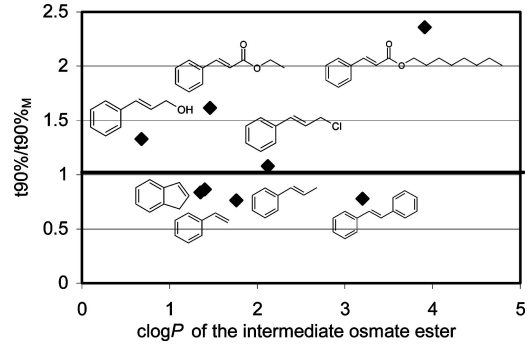


FIGURE 3. Computational partition coefficient clog *P*'s of the intermediate osmate esters of conjugated aromatic olefins versus t90%/$t90\%_M$ of the Sharpless ADs of corresponding olefins.

completely different effect in the AD of 2-methylhept-2-ene than it has in the AD of 2-methylheptene. The $t90\%_M$ of 135 min in the AD of 2-methylhept-2-ene in the presence $CH_3SO_2NH_2$ is one-fourth the *t*90% of 530 min in the AD without $CH_3SO_2NH_2$, and the $t90\%_M$ of 65 min in the AD of 2-methylheptene with $CH_3SO_2NH_2$ is slightly higher than the corresponding *t*90% of 55 min without $CH_3SO_2NH_2$. In other words, $CH_3SO_2NH_2$ accelerates significantly the AD of nonterminal 2-methylhept-2-ene and decelerates slightly the AD of terminal 2-methylheptene. It is difficult, if not even impossible, to see why steric crowding or electronic effects would have such a different effect in the *t*90% and $t90\%_M$ values of 2-methylhept-2-ene and 2-methylheptene. What has already been said about the accessibility of the osmate ester group in the intermediate to the water phase applies also here. As a result of easier accessibility of the osmate ester group to water phase, the rate-determining hydrolysis of the intermediate osmate ester occurs more quickly if the osmate ester group is in the terminal position, as it is in 2-methylheptene. Hydroxide ion attached to $CH_3SO_2NH_2$, being a weaker nucleophile than free hydroxide ion, accelerates the Sharpless AD of aliphatic olefins if the osmate ester group in the intermediate is predominantly in the organic phase, as it is in the case of AD of the nonterminal 2-methylhept-2-ene.

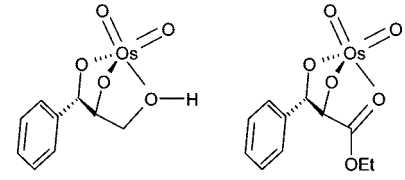
Our hypothesis of the $CH_3SO_2NH_2$ effect in Sharpless AD applied well with ADs of aliphatic olefins. ADs of conjugated aromatic olefins seem not to be as straightforward as ADs of aliphatic olefins. In Figure 3 are presented the results from the ADs of conjugated aromatic olefins. The *x*-axis is the computational partition coefficient clog *P* of the intermediate osmate esters, and the *y*-axis is the *t*90% in ADs without $CH_3SO_2NH_2$ divided by the $t90\%_M$ in ADs with $CH_3SO_2NH_2$. If $t90\%/t90\%_M > 1$, then $CH_3SO_2NH_2$ accelerates the AD of that particular olefin, and if $t90\%/t90\%_M < 1$, then $CH_3SO_2NH_2$ decelerates the AD. From Figure 3, one can see clearly that the polarity of the intermediate osmate ester is not a factor that determines the effect that $CH_3SO_2NH_2$ has on the reaction times in ADs of conjugated aromatic olefins, as in ADs of nonterminal aliphatic olefins. In our series of conjugated aromatic olefins, the ADs of olefins that have the most and the least polar intermediate osmate esters benefit from the addition of $CH_3SO_2NH_2$. In between those two olefins, there is a series of both terminal and nonterminal conjugated aromatic olefins for which $CH_3SO_2NH_2$ has a decelerating effect on their *t*90% in ADs. It seems that polarity of the intermediate osmate ester can be used to predict the reaction time and $CH_3SO_2NH_2$ effect in Sharpless AD of conjugated aromatic olefins only if the molecules are alike, such as the ethyl ester and octyl ester of cinnamic acid.

The intermediate osmate ester of the octyl ester of cinnamic acid (clog $P = 3.91$) is less polar than the corresponding intermediate of the ethyl ester of cinnamic acid (clog $P = 1.46$), which correlates with a longer reaction time and stronger $CH_3SO_2NH_2$ effect as it does also with nonterminal aliphatic olefins.

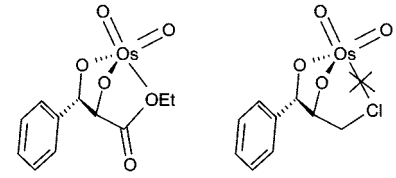
Another striking difference in ADs of conjugated aromatic olefins compared to aliphatic olefins is that $CH_3SO_2NH_2$ does not necessarily accelerate the ADs of those olefins that are the slowest to react in the absence of $CH_3SO_2NH_2$. For instance, the osmate ester intermediate of indene is one of the highest polarity in our series of conjugated aromatic olefins, yet its $t90\%$ = 550 min in the AD without $CH_3SO_2NH_2$ is the second longest, and in the presence of $CH_3SO_2NH_2$, its $t90\%_M = 630$ min is the longest. Another difference in the AD of conjugated aromatic olefins compared to AD of aliphatic olefins is that $CH_3SO_2NH_2$ does not even out the $t90\%$ values in the AD of conjugated aromatic olefins as much as it does in the AD of aliphatic olefins. The difference in $t90\%$ and $t90\%_M$ values between the fastest and the slowest ADs of conjugated aliphatic olefins without $CH_3SO_2NH_2$ is 1090 min and with $CH_3SO_2NH_2$ 540 min. The corresponding differences in $t90\%$ and $t90\%_M$ values in ADs of aliphatic olefins are 1125 and 80 min.

Interestingly, our results seem to show that $CH_3SO_2NH_2$ has an accelerating effect in ADs of aromatic conjugated olefins only if there is an electron-withdrawing group, such as a hydroxy or an ester group, attached to the carbon next to the double bond and to a lesser extent if there is a halogen attached to the carbon next to the double bond (Figure 3). A plausible rationalization for the observed phenomenon is that the osmate esters of unfunctionalized conjugated aromatic olefins are less electrophilic than the corresponding esters of functionalized olefins. Aromatic group(s) and alkyl group(s) donate electron density toward the osmate ester group and thus make it less reactive toward nucleophiles, and if the hydroxide ion nucleophile is weakened by the interaction with $CH_3SO_2NH_2$, the reaction is even slower. Regardless of the polarity of the intermediate osmate ester or the substitution pattern of the olefin, in our study $CH_3SO_2NH_2$ decelerated the ADs of all unfunctionalized conjugated aromatic olefins starting from indene, which has the most polar intermediate, to *trans*-stilbene, which has the least polar intermediate. However, if there is an allylic electron-withdrawing group in the olefin, such as chlorine, the electrophilicity of the osmate ester group is increased and $CH_3SO_2NH_2$ does not decelerate the AD of that olefin, as is the case for instance in the AD of cinnamyl chloride. Unfortunately, as convincing as this explanation may appear, it does not stand a more detailed analysis of the results.

The electron-withdrawing nature of the alcohol, ester, and halogen groups cannot account for all of results that we see in Figure 3 and Table 1, for instance, why, whether the $CH_3SO_2NH_2$ is used or not, cinnamyl alcohol and the ethyl ester of cinnamic acid react more slowly in ADs than cinnamyl chloride does and why the $CH_3SO_2NH_2$ effect is more significant in ADs of cinnamyl alcohol and ethyl ester of cinnamic acid than it is in the AD of cinnamyl chloride, even though their intermediate osmate esters are more polar than the intermediate osmate ester of the cinnamyl chloride. Allylic alcohol in cinnamyl alcohol **9** and allylic ester groups in esters of cinnamic acid **10** and **11** are capable of donating electron density intramolecularly toward the electron-poor osmium center in the osmate ester intermediate, whereas the halogen in cinnamyl chloride **12** is not. The same interaction plays a vital role in Sharpless asymmetric epoxidation of allylic alcohols.[9] The intramolecular electron donation effect can be seen in the $t90\%$ values in the AD of cinnamyl alcohol and ethyl ester of cinnamic acid without $CH_3SO_2NH_2$. The $t90\%$ of 295 min in the AD of cinnamyl alcohol and the $t90\%$ of 200 min in the AD of ethyl ester of cinnamic acid are more than twice the $t90\%$ of 95 min in the AD of cinnamyl chloride, even though their osmate ester intermediates are more polar.



9 **10**



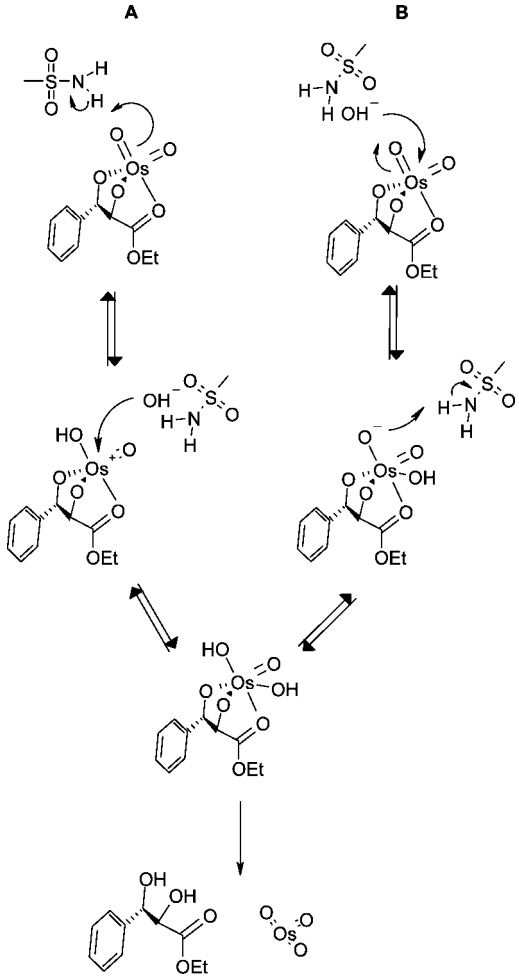
11 **12**

Why is it then that hydroxide ion attached to $CH_3SO_2NH_2$, being less nucleophilic than free hydroxide ion, seems to accelerate more the hydrolysis of more electron-rich and thus less nucleophilic osmate esters? A plausible explanation is that the hydrolysis pathway is different in the AD of conjugated aromatic olefins that have electron-rich osmate ester intermediates. In Scheme 2 is presented two possible reaction pathways: (A) general acid-catalyzed and (B) nucleophilic attack of hydroxide ion pathway. $CH_3SO_2NH_2$ is a weak acid (pK_a = 10.8) and thus capable of protonating the electron-rich intermediate osmate ester in the rate-limiting hydrolysis step as presented in Scheme 2.[10] AD of the ethyl ester of cinnamic acid and, to our surprise, also AD of *trans*-methyl styrene in the presence of $CH_3SO_2NH_2$ were found to follow pseudo-zero-order kinetics with respect to the olefin as presented in Figure 4. Aliphatic 1-decene, *trans*-5-decene, and 2-methylhept-2-ene followed pseudo-first-order kinetics with respect to the olefin in the presence of $CH_3SO_2NH_2$ (Figure 5). Clearly, in the presence of $CH_3SO_2NH_2$, the mechanism of the hydrolysis step in the AD of conjugated aromatic olefins is different from the mechanism of hydrolysis step in the AD of aliphatic olefins. Usually zero-order kinetics is associated with catalytic reactions where catalyst is saturated with the substrate. In AD of conjugate aromatic olefins the pseudo-zero-order kinetics is due to the osmate ester intermediate being saturated with the proton-donating catalyst $CH_3SO_2NH_2$. At pH 10.8 the concentration of the intermediate osmate ester is less than 1/100 the concentration of $CH_3SO_2NH_2$. Experiments performed at elevated alkaline conditions support the proposed general acid-catalyzed reaction mechanism. When the pH of the reaction mixture was elevated from 10.7 to 11.9 and maintained there during the reaction with 12 M NaOH, the ADs of the ethyl

(9) Johnson, R. A.; Sharpless, K. B. *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; VCH Publishers: New York, 2000; pp 231−280.

(10) Trepka, R. D.; Harrington, J. K.; Belisle, J. W. *J. Org. Chem.* **1974**, *39*, 1094–1098.

SCHEME 2. Two Proposed Reaction Pathways of the Hydrolysis Step in Sharpless AD in the Presence of $CH_3SO_2NH_2$



ester of cinnamic acid and *trans*-methyl styrene were almost two times slower than the ADs performed at lower pH. At elevated alkaline conditions $CH_3SO_2NH_2$ is in ionized form and therefore not capable of donating a proton to the intermediate osmate ester. It is known from the literature that at elevated alkaline conditions the AD of aliphatic *trans*-5-decene is faster than at lower pH and $CH_3SO_2NH_2$ can even be omitted if highly alkaline conditions are maintained during the reaction.[3]

Enantioselectivity of the Sharpless AD depends partly on the reaction rate, which is usually the same as the hydrolysis rate

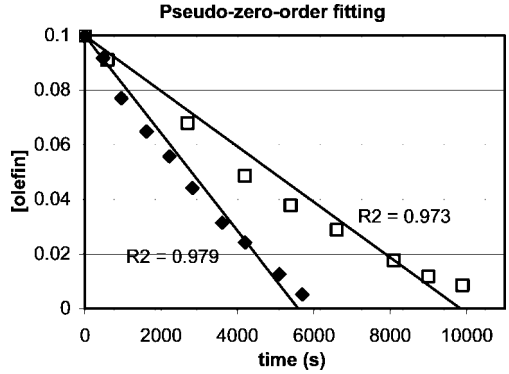


FIGURE 4. Pseudo-zero-order fittings of asymmetric dihydroxylations of (♦) *trans*-methyl styrene and (□) ethyl ester of cinnamic acid.

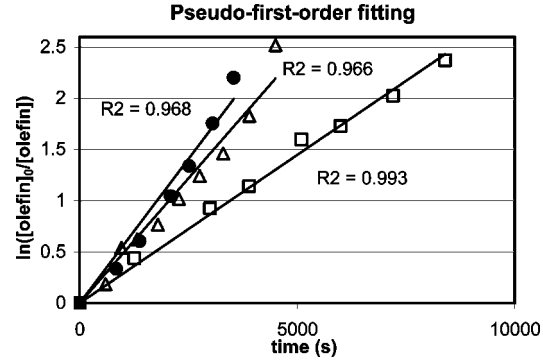
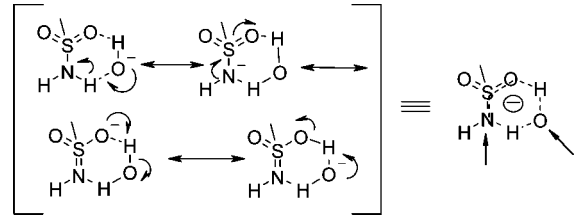


FIGURE 5. Pseudo-first-order fittings of asymmetric dihydroxylations of (□) 1-decene, (Δ) 2-methylhept-2-ene, and (●) *trans*-5-decene.

SCHEME 3. Resonance Structures of the Methanesulfonamide-Hydroxide Ion Pair



of the intermediate osmate ester. In the so-called secondary cycle, a second olefin reacts with the intermediate osmate ester without enantioselection.[1e] The slower the hydrolysis of the intermediate osmate ester, the more olefins react through the secondary cycle. In Table 1 are presented the enantioselectivities of our ADs with and without $CH_3SO_2NH_2$. In our series of olefins it is always so that $CH_3SO_2NH_2$ improves enantioselectivity if it accelerates the AD and decreases enantioselectivity if it decelerates the AD. The differences in enantioselectivities between ADs with and without $CH_3SO_2NH_2$, even though the rate acceleration can be quite significant, are only small, varying from 0 to 4 percentage units. The small differences are due to the fact that the secondary cycle is slow in ADs if potassium ferricyanide is used as the stoichiometric oxidant.[1e]

The indirect evidence from the different ADs and the actual finding of hydroxide ions in the organic *tert*-butanol phase if $CH_3SO_2NH_2$ is present have conclusively shown that $CH_3SO_2NH_2$ is a cosolvent that aids in the solvation of hydroxide ions to the organic *tert*-butanol phase. Consequently, there has to be such an interaction between the hydroxide ion and $CH_3SO_2NH_2$ that delocalizes sufficiently the negative charge on the hydroxide ion. The most obvious such intermolecular interaction would be hydrogen bonding, but since the *tert*-butanol is also capable of forming hydrogen bonds with hydroxide ions, hydrogen bonding cannot account for the interaction that explains the $CH_3SO_2NH_2$ effect in Sharpless ADs of aliphatic olefins. In Scheme 3 is presented our proposal of the more efficient delocalization of the negative charge on hydroxide ion. In our proposal $CH_3SO_2NH_2$ and the hydroxide ion form a resonance-stabilized six-membered ring intermediate. The structure presented in Scheme 3 is held together by both hydrogen bonding and resonance. In this structure the negative charge is delocalized so that a protic solvent such as *tert*-butanol can solvate it.

There are actually two nucleophilic sites in the structure presented in Scheme 3 (shown by arrows). If nucleophilicities of the hydroxide ion and deprotonated methanesulfonamide are

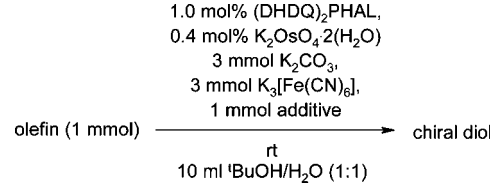
estimated by their pK_{aH} values (15.7 and 10.8, respectively) it is obvious that hydroxide ion is more nucleophilic, but in a structure presented in Scheme 3 one can not deduce the reactive site on the basis of pK_{aH} values. Decisive in terms of the reactive nucleophilic site is the location of the negative charge and availability of the free electron pair that forms the bond to the electrophilic osmium in osmate ester. The free electron pair on the amide nitrogen is shielded by the neighboring methyl group, double-bonded oxygen and its free electron pairs, and the hydrogen attached to the nitrogen. All of these shielding effects are missing in the two free electron pairs on hydroxide ion oxygen.

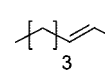
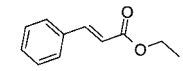
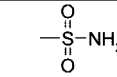
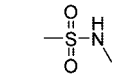
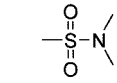
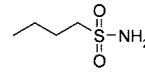
The structure presented in Scheme 3 explains not only the solvation of hydroxide ions in *tert*-butanol but also the different effects $CH_3SO_2NH_2$ has on the reaction times in Sharpless AD of structurally diverse olefins. There is a water-like substructure in the structure presented in Scheme 3. The water-like substructure, which is less nucleophilic than hydroxide ion but more nucleophilic than a water molecule, reacts as a nucleophile in the rate-limiting hydrolysis of the aliphatic intermediate osmate esters. If the osmate ester group in the intermediate has easy access to the water phase, then in the presence of $CH_3SO_2NH_2$ the overall reaction is usually slower because the reactive nucleophile is weaker than the free hydroxide ion. If the osmate ester in the intermediate has no easy access to the water phase, $CH_3SO_2NH_2$ accelerates the reaction by providing the organic phase with a nucleophile, albeit a weaker one than a naked hydroxide ion.

If the structure presented in Scheme 3 exists, one would expect to see differences in the chemical shifts of nitrogen in $CH_3SO_2NH_2$ acidic and in alkaline conditions. Bagno et al. have reported a small +8 ppm shift in the ^{14}N signal of $CH_3SO_2NH_2$ when conditions were changed from 0.1 M HCl to 1 M NaOH.[11] Kricheldorf has reported a similar +11 ppm shift in the ^{15}N signal of $CH_3SO_2NH_2$ when the pH of the media was changed from 1.0 to 12.3.[12] One could argue that the deshielding of the nitrogen nucleus in alkaline conditions is due to the double bond formation between nitrogen and sulfur. Results from the NMR experiments do not explicitly confirm the structure presented in Scheme 3 but do not rule it out either. Results from the NMR studies are in favor of some resonance taking place in $CH_3SO_2NH_2$ in alkaline conditions.

We were interested in to know if Sharpless ADs in the presence of other sulfonamides would support our results, and conclusions presented. In Table 2 are presented the $t90\%_M$ of ADs of *trans*-5-decene and the ethyl ester of cinnamic acid in the presence of methanesulfonamide, *N*-methyl methanesulfonamide, *N*,*N*-dimethyl methanesulfonamide, and butanesulfonamide. Even though *N*-methyl methanesulfonamide is capable of forming a similar structure as presented for methanesulfonamide in Scheme 3, *N*-methyl methanesulfonamide does not accelerate the AD of *trans*-5-decene nearly as efficiently as methanesulfonamide. Compared with methanesulfonamide the electron-donating methyl group in *N*-methyl methanesulfonamide destabilizes the resonance stabilization shown in Scheme 3. The charge distribution of hydroxide ion is not as efficient in the presence of *N*-methyl methanesulfonamide as it is in the presence of methanesulfonamide, which leads to poorer solubility of hydroxide ions in the organic phase. *N*-Methyl methanesulfonamide is a weaker acid than methanesulfonamide, and

TABLE 2. Results from Sharpless ADs of *trans*-5-Decene and the Ethyl Ester of Cinnamic Acid in the Presence of Different Additives



additive	 $t90\%_M$ (min)	$\frac{t90\%^a}{t90\%_M}$	 $t90\%_M$ (min)	$\frac{t90\%^b}{t90\%_M}$
	105	11.24	120	1.67
	590	2.00	220	0.91
	1440	0.82	325	0.62
	400	2.95	635	0.31
$[C_{16}TMA][Br]^c$	285	4.14	190	1.05

[a] With no additive $t90\% = 1180$ min. [b] With no additive $t90\% = 200$ min. [c] $CH_3(CH_2)_{15}N(CH_3)_3Br$.

therefore the AD of the ethyl ester of cinnamic acid is slower in the presence of *N*-methyl methanesulfonamide than in the presence of methanesulfonamide. In fact, in the presence of *N*-methyl methanesulfonamide, the AD of ethyl ester of cinnamic acid is even slower than with no additives. Interaction between the hydroxide ion and *N*-methyl methanesulfonamide decreases the nucleophilicity of hydroxide ion compared to naked hydroxide ion so that even if the hydrolysis of osmate ester intermediate is not acid-catalyzed, the hydrolysis by nucleophilic attack of hydroxide ion to the osmate ester intermediate is slower in the presence of *N*-methyl methanesulfonamide than without.

N,*N*-Dimethyl methanesulfonamide does not have amide protons, so it is not capable of forming the structure presented in Scheme 3. As expected, *N*,*N*-dimethyl methanesulfonamide does not accelerate the AD of *trans*-5-decene (Table 2). Also, as a result of the lack of an acidic proton, *N*,*N*-dimethyl methanesulfonamide does not accelerate the AD of the ethyl ester of cinnamic acid. However, there is interaction between hydroxide ion and *N*,*N*-dimethyl methanesulfonamide because reaction times are longer in the presence of *N*,*N*-dimethyl methanesulfonamide than with no additive.

Butanesulfonamide (clog $P = -0.06$) is less hydrophilic than methanesulfonamide (clog $P = -1.54$), but contrary to what one might expect, butanesulfonamide is not as efficient in transferring hydroxide ions to the organic phase as is methanesulfonamide (Table 2). Reaction time in the AD of *trans*-5-decene is almost four times longer in the presence of butanesulfonamide than in the presence of methanesulfonamide; probably a smaller amount of cosolvent in the water layer increases reaction time. The most surprising result was the huge increase in reaction time in the AD of the ethyl ester of cinnamic

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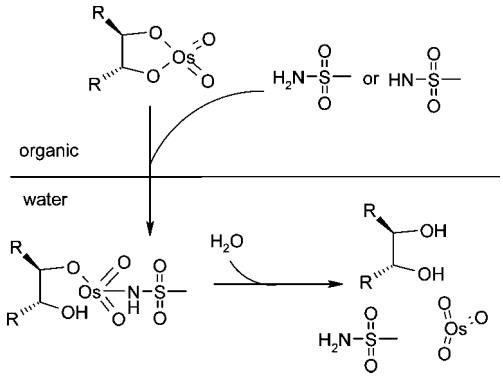
(12) Kricheldorf, H. R. *Angew. Chem.* **1978**, *6*, 489–490.

SCHEME 4. Hydrolysis of the Osmate Ester via Os-Amide Intermediate



acid in the presence of butanesulfonamide. With butanesulfonamide reaction time was more than three times longer than the reaction time with no additives and more than five times longer than the reaction time with methanesulfonamide. The AD of ethyl ester of cinnamic acid in the presence of butanesulfonamide followed pseudo-zero-order kinetics with respect to olefin. Therefore we believe that reaction is general acid-catalyzed as is the AD of ethyl ester of cinnamic acid in the presence of methanesulfonamide. Acid strengths of butanesulfonamide and methanesulfonamide are the same, so the difference in reaction times rises probably from the different hydrophilicities of the additives. It seems that in biphasic reaction conditions butanesulfonamide and the intermediate osmate ester do not meet efficiently enough so that a fast reaction is obtained.

Branco et al. have reported recently Sharpless AD in the presence of different surfactants.[13] In Table 2 are presented results from our experiments with *N*-cetyl-*N*,*N*,*N*-trimethylammoniumbromid surfactant. Reaction time in the AD of aliphatic *trans*-5-decene is significantly decreased by adding surfactant into the reaction mixture. Still surfactant is not nearly as efficient as a rate-accelerating additive in the AD as is methanesulfonamide. Reaction time is more than 2.5 times longer in the presence of surfactant than it is in the presence of methanesulfonamide. Either the nucleophilicity of the hydroxide ion is reduced more if surfactant is used or surfactant does not assist the transfer of hydroxide ions to organic phase as effectively as methanesulfonamide does. Surfactant had no effect in reaction time in the AD of ethyl ester of cinnamic acid. In the AD of more hydrophobic octyl ester of cinnamic acid surfactant did not show any better results since the $t90\%/t90\%_M$ was 1.13.

Under the alkaline reaction conditions used in Sharpless AD, there is in addition to hydroxide ions other nucleophiles present. One could argue that the rate acceleration is due to that methanesulfonamide or deprotonated methanesulfonamide reacts as a nucleophile toward the osmium center in the intermediate osmate ester prior hydrolysis as presented in Scheme 4. Similar reaction takes place in Sharpless asymmetric aminohydroxylation between *N*-halogenated sulfonamides and the azaglycolates prior hydrolysis.[14] Due to the increased polarity the supposed Os-amide intermediate migrates into the water phase and a faster hydrolysis would occur. Which one of the nucleophiles reacts with the osmate ester depends on the nucleophilicity of the species and which one of the species can be found in the organic phase. We have already shown that hydroxide ions can be found in the organic phase if methanesulfonamide is added to the reaction mixture. As a charge neutral compound methanesulfonamide dissolves in organic phase but it is significantly poorer nucleophile than deprotonated methanesulfonamide and also poorer nucleophile than hydroxide ion even if hydroxide ion is attached to methanesulfonamide. In fact, if nucleophilicity is estimated by their pK_{aH} values methanesulfonamide is poorer nucleophile than water.[15] If we estimate nucleophilicity of the hydroxide ion and nucleophilicity of the deprotonated methanesulfonamide from their pK_{aH} values (15.7 and 10.8 correspondingly), we can assume that the nucleophilicity of the hydroxide ion attached to methanesulfonamide and nucleophilicity of the deprotonated methanesulfonamide are probably quite similar. Even though deprotonated methanesulfonamide can delocalize its charge via resonance, it is highly hydrophilic (clog $P = -2.48$) and does not dissolve in organic phase easily. Delocalization of the negative charge on deprotonated methanesulfonamide can take place in a similar way as presented in Scheme 3. Instead of hydroxide ion, deprotonated methanesulfonamide forms a resonance stabilized pair with water molecule, which is an identical structure as presented for methanesulfonamide-hydroxide ion pair in Scheme 3. Even though the acceleration of hydrolysis step in Sharpless AD can in principle take place via Os-amide intermediate if deprotonated methanesulfonamide acts as a nucleophile, we think that the most plausible explanation for the rate acceleration is the cosolvent effect of the methanesulfonamide.

Conclusions

The $CH_3SO_2NH_2$ effect in Sharpless AD was found in our study to be two different effects: a general acid-catalyzed hydrolysis and a cosolvent of hydroxide ion. Electron-rich osmate ester intermediates of conjugate aromatic olefins are protonated by acidic $CH_3SO_2NH_2$ in the hydrolysis step. $CH_3SO_2NH_2$ accelerates the AD of aliphatic olefins by aiding in the transfer of nucleophilic hydroxide ions to the organic phase. A simple rule to divide olefins to terminal and nonterminal, when one considers whether to add $CH_3SO_2NH_2$ to accelerate the Sharpless AD, was in our study founded not to be valid. There were ADs of both terminal and nonterminal olefins that benefited from the addition of $CH_3SO_2NH_2$. There were also ADs of both terminal and nonterminal olefins that, if $CH_3SO_2NH_2$ had any effect on their reaction times, were decelerated if $CH_3SO_2NH_2$ was added to the reaction mixture. The accessibility of the osmate ester group in the intermediate osmate ester to the water phase was the most significant factor in the reaction time in the AD of aliphatic olefins and also in the $CH_3SO_2NH_2$ effect. Sharpless ADs of conjugated aromatic olefins was not as straightforward as for aliphatic olefins. If one wants to play safe, one can use $CH_3SO_2NH_2$ in every Sharpless AD since the decelerating effect of $CH_3SO_2NH_2$ in most cases is not very significant.

Experimental Section

General Procedure for the Determination of the *t*90% and *t*90%$_M$ Times. A 50 mL three-necked flask was equipped with a magnetic stirring bar, pH electrode, and thermometer. The flask

(13) Branco, L. C.; Ferreira, F C.; Santos, J. L.; Crespo, J. G.; Afonso, C. A. M. *Adv. Synth. Catal.* **2008**, *350*, 2086–2098.

(14) Bodkin, J. A.; McLeod, M. D. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2733–2746.

(15) The pK_{aH} of *N*-methylmethanesulfonamide is −6.0, and the pK_{aH} of *N*,*N*-dimethylmethanesulfonamide is −5.5. Laughlin, R. G. *J. Am. Chem. Soc.* **1967**, *89*, 4268–4271. The pK_{aH} of water is −1.7.

was charged with 1 mmol of olefin, 7.7 mg (0.1 mmol, 1 mol%) of ligand $(DHQD)_2PHAL$, 0.414 g (3 mmol) of K_2CO_3 and 0.990 g (3 mmol) of $K_3[Fe(CN)_6]$. If $CH_3SO_2NH_2$ was used, the amount was 95 mg (1 mmol). Reagents were dissolved in 10 mL of *t*-BuOH/H_2O (1:1) mixture. The reactions were initiated by adding 1.5 mg (0.04 mmol, 0.4 mol%) of $K_2OsO_4 \cdot 2H_2O$. The reactions were performed at room temperature. The reactions were followed by monitoring the consumption of olefin. Aliquots of 20 μL were withdrawn from the reaction mixture after periods of time. The reaction was quenched by diluting the sample with a mixture containing 20 μL of a 60 mM solution of Na_2SO_3 and 100 μL of 0.02 M 1-phenylethanol (standard) in EtOAc. The sample was dried with Na_2SO_4 prior to analysis with GC. After all olefin had been consumed, 0.8 g (6.3 mmol) of Na_2SO_3 was added, and the reaction mixture was stirred for 30 min. The reaction mixture was extracted in 50 mL separating funnel with 3 × 5 mL of EtOAc. If $CH_3SO_2NH_2$ was used, the combined organic layers were extracted with 5 mL of 2 M NaOH. The combined organic layers were dried with Na_2SO_4 and filtered, and the solvent was removed on a rotary evaporator. The crude products were purified by flash chromatography using EtOAc/*n*-hexane or EtOAc/MeOH as the eluent.

Reaction Order. The general AD procedure was used with minor change in the reactions where reaction order was determined: pH of the reaction medium was kept constant by adding 12 M NaOH via syringe during the reaction and in high pH reaction elevated with 12 M NaOH and kept constant by adding 12 M NaOH via syringe during the reaction.

Hexadecane-1,2-diol. ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.67 (m, 2H), 3.45 (m, 1H), 1.97 (d, J = 4.3 Hz, 1H), 1.84 (dd, J = 5.2, 6.3 Hz, 1H), 1.44 (m, 2H), 1.26 (m, 24H), 0.89 (t, J = 6.2 Hz, 3H); HRMS *m*/*z* found 281.2464, calcd 281.2457 ($C_{16}H_{34}O_2Na$).

Tetradecane-1,2-diol. ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.67 (m, 2H), 3.45 (m, 1H), 1.97 (d, J = 4.3 Hz, 1H), 1.84 (dd, J = 5.2, 6.3 Hz, 1H), 1.44 (m, 2H), 1.26 (m, 20H), 0.89 (t, J = 6.2 Hz, 3H); HRMS *m*/*z* found 253.2154, calcd 253.2144 ($C_{14}H_{30}O_2Na$).

Decane-1,2-diol. ^{1}H NMR (200 MHz, $CDCl_3$) 3.67 (d, J = 11.0 Hz, 2H), 3.44 (dd, J = 8.0, 10.8 Hz, 1H), 2.14 (br, 1H), 2.05 (br, 1H), 1.43 (br, 4H), 1.28 (br, 10H), 0.88 (t, J = 6.0 Hz, 3H); HRMS *m*/*z* found 197.1519, calcd 197.1517 ($C_{10}H_{22}O_2Na$).

Octane-1,2-diol. ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.67 (m, 2H), 3.45 (m, 1H), 1.97 (d, J = 4.1 Hz, 1H), 1.84 (dd, J = 5.2, 6.3 Hz, 1H), 1.44 (m, 2H), 1.26 (m, 20H), 0.89 (t, J = 6.2 Hz, 3H); HRMS *m*/*z* found 169.1198, calcd 169.1204 ($C_8H_{18}O_2Na$).

2-Methylheptane-1,2-diol. ^{1}H NMR (200 MHz, $CDCl_3$) 3.50 (d, J = 10.9 Hz, 1H), 3.41 (d, J = 10.8 Hz, 1H), 1.81 (br, 1H), 1.61 (br, 1H), 1.47 (m, 2H), 1.32 (m, 6H), 1.18 (s, 3H), 0.90 (t, J = 6.9 Hz, 3H); HRMS *m*/*z* found 169.1201, calcd 169.1204 ($C_8H_{18}O_2Na$).

2-Methylheptane-2,3-diol. ^{1}H NMR (200 MHz, $CDCl_3$) 3.37 (d, J = 8.8 Hz, 1H), 2.10 (br, 1H), 1.04 (br, 1H), 1.54 (m, 2H), 1.35 (m, 4H), 1.22 (s, 3H), 1.17 (s, 3H), 0.93 (t, J = 6.8 Hz, 3H); HRMS *m*/*z* found 169.1212, calcd 169.1204 ($C_8H_{18}O_2Na$).

1-Methylcyclohexane-1,2-diol. ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.42 (m, 1H), 1.89−1.19 (br, 10H), 1.26 (s, 3H); HRMS *m*/*z* found 153.0902, calcd 153.0891 ($C_7H_{14}O_2Na$).

Hexane-1,4,5-triol. ^{1}H NMR (200 MHz, *d*-DMSO) 4.35 (t, J = 5.0 Hz, 1H), 4.27 (d, J = 4.8 Hz, 2H), 3.38 (m, 3H), 3.15 (br, 1H), 1.45 (m, 3H), 1.19 (m, 1H), 0.96 (d, J = 6.2 Hz, 3H); HRMS *m*/*z* found 157.0848, calcd 157.0841 ($C_6H_{14}O_3Na$).

Decane-5,6-diol. ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.42 (m, 2H), 2.00 (d, J = 4.5 Hz, 2H), 1.42 (m, 12H), 0.92 (t, J = 6.5 Hz, 6H); HRMS *m*/*z* found 197.1523, calcd 197.1517 ($C_{10}H_{22}O_2Na$).

Ethyl 2,3-dihydroxyoctanoate. ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.30 (q, J = 7.3 Hz, 2H), 4.09 (m, 1H), 3.89 (q, J = 6.9 Hz, 1H), 3.05 (d, J = 5.0 Hz, 1H), 1.87 (d, J = 9.1 Hz, 1H), 1.58 (br, 3H), 1.41 (br, 5H) 1.33 (t, J = 7.1 Hz, 3H), 0.90 (t, J = 6.3 Hz, 3H); HRMS *m*/*z* found 227.1268, calcd 227.1259 ($C_{10}H_{20}O_4Na$).

Indane-1,2-diol. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.44 (m, 1H), 7.29 (m, 3H), 5.03 (dd, J = 5.1, 7.4 Hz), 4.54 (m, 1H), 3.15 (dd, J = 5.7, 16.4 Hz, 1H), 2.97 (dd, J = 3.7, 16.3 Hz, 1H), 2.43 (d, J = 7.4, 1H), 2.36 (d, J = 6.1 Hz, 1H); HRMS *m*/*z* found 173.0576, calcd 173.0578 ($C_9H_{10}O_2Na$).

1-Phenylethane-1,2-diol. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.37 (m, 5H), 4.85 (dt, J = 3.6, 7.9 Hz, 1H), 3.73 (m, 2H), 2.49 (d, J = 3.3 Hz, 1H), 2.04 (dd, J = 4.8, 7.3 Hz, 1H); HRMS *m*/*z* found 161.0574, calcd 161.0578 ($C_8H_{10}O_2Na$).

1,2-Diphenylethane-1,2-diol. ^{1}H NMR (200 MHz, *d*-acetone) δ 7.15 (m, 10H), 4.65 (br, 2H), 4.59 (br, 1H); HRMS *m*/*z* found 237.0889, calcd 237.0891 ($C_{14}H_{14}O_2Na$).

1-Phenylpropane-1,2-diol. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.36 (m, 5H), 4.40 (dd, J = 3.2, 7.4 Hz, 1H), 3.89 (m, 1H), 2.59 (d, J = 3.4 Hz, 1H), 2.46 (d, J = 3.4 Hz, 1H), 1.08 (d, J = 6.3 Hz, 3H); HRMS *m*/*z* found 175.0739, calcd 175.0735 ($C_9H_{12}O_2Na$).

Ethyl 2,3-Dihydroxy-3-phenylpropanoate. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.38 (m, 5H), 5.02 (dd, J = 3.1, 7.1 Hz, 1H), 4.38 (dd, J = 3.1, 5.9 Hz, 1H), 4.28 (q, J = 7.2 Hz, 2H), 3.11 (d, J = 5.8 Hz, 1H), 2.74 (d, J = 7.2 Hz, 1H), 1.29 (t, J = 7.2 Hz, 3H); HRMS *m*/*z* found 233.0806, calcd 233.0790 ($C_{11}H_{14}O_4Na$).

Octyl 2,3-Dihydroxy-3-phenylpropanoate. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.38 (m, 5H), 5.00 (dd, J = 3.1, 6.9 Hz, 1H), 4.37 (dd, J = 3.3, 5.7 Hz), 4.20 (t, J = 6.7 Hz, 2H), 3.16 (d, J = 5.9 Hz, 1H), 2.81 (d, J = 7.1 Hz, 1H), 1.63 (br, 2H), 1.29 (br, 12H), 0.90 (t, J = 6.0 Hz, 3H); HRMS *m*/*z* found 317.1731, calcd 317.1729 ($C_{17}H_{26}O_4Na$).

3-Chloro-1-phenylpropane-1,2-diol. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.40 (br, 5H), 4.77 (d, J = 6.6 Hz, 1H), 3.92 (dd, J = 5.8, 9.7 Hz, 1H), 3.60 (dd, J = 3.9, 11.5 Hz, 1H), 3.42 (dd, J = 5.8, 11.5 Hz, 1H), 2.77 (br, 2H); HRMS *m*/*z* found 209.0354, calcd 209.0345 ($C_9H_{11}O_2NaCl$).

1-Phenylpropane-1,2,3-triol. ^{1}H NMR (200 MHz, *d*-acetone) δ 7.33 (m, 5H), 4.69 (dd, J = 4.3, 5.2 Hz, 1H), 4.30 (d, J = 4.3 Hz, 1H), 3.89 (d, J = 4.8 Hz, 1H), 3.63 (m, 2H), 3.45 (m, 2H); HRMS *m*/*z* found 191.0685, calcd 191.0684 ($C_9H_{12}O_3Na$).

Supporting Information Available: Example of the *t*90% and $t90\%_M$ measurements, experimental procedures for the synthesis of derivatives for determinations of enantiomeric excesses, ^{1}H NMR spectra of the isolated products, ^{1}H NMR spectra of the bisMosher esters of the isolated products, and chiral GC chromatograms of the TFA derivatives of the isolated products. This material is available free of charge via the Internet at http://pubs.acs.org.

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