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Formation of scalemic α,β-epoxysulfones

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Abstract—This report describes the preparation of optically active α,β-epoxysulfones using an asymmetric phase-transfer catalyzed epoxidation of α,β-unsaturated sulfones.

α,β-Epoxysulfones are useful intermediates for additional synthetic transformations.[1] These substrates have been synthesized in two ways using chiral phase-transfer catalysis. The *trans* (*S*,*S*) α,β-epoxysulfones have been prepared from chloromethyl phenylsulfone and aromatic aldehydes using a quinine salt in a Darzens reaction in 69% ee.[2] Alternatively, polyamino acids have been employed as phase-transfer catalysts in the epoxidation of α,β-unsaturated sulfones with enantioselectivities of 53%.[3] In order to improve the enantioselectivity of the epoxidation reaction, the use of *N*-9-anthracenylmethyl cinchonidinium salts with α,β-unsaturated sulfones and hypochlorite akin to that reported by Lygo[4] and Corey[5] with α,β-unsaturated ketones appeared a viable option. These studies are reported herein.

Based on the nucleophilic epoxidation mechanism proposed by Corey,[5] α,β-unsaturated sulfones seemed to be ideal substrates for this asymmetric transformation. The reactions were studied using (*E*)-phenyl styrylsulfone, which was prepared from methyl phenylsulfone and benzaldehyde.[6] By analogy to Corey's mechanistic proposal, this substrate was expected to yield the (*R*,*R*) epoxide with high enantiochemical purity. One of the sulfone oxygens should be situated in the vicinity of the quaternary amine with the benzene ring of the sulfone being in the proximity of the quinoline ring. The vinylic phenyl group is expected to interact with the anthracene moiety by π-stacking. The hypochlorite oxygen should then be correctly positioned for enantioselective nucleophilic attack with the chloride ion being close to the quaternary amine (Fig. 1).

While the reactions were generally performed at −35 °C for three days, numerous parameters were varied in order to optimize the epoxidation reaction (Table 1). These included the reaction solvent, the type of hypochlorite (either Na or K), and the catalyst structure. Given the literature precedent, it was expected that the 9-anthracenylmethyl alkaloid salts would provide the highest selectivities.[4,5] As shown in entries 1 and 7, this was indeed realized with (*E*)-phenyl styrylsulfone since the dihydrocinchonidine 9-anthracenylmethyl salt formed a 91:9 mixture of (*R*,*R*):(*S*,*S*) epoxides while the corresponding 1-napthalenylmethyl salt yielded a

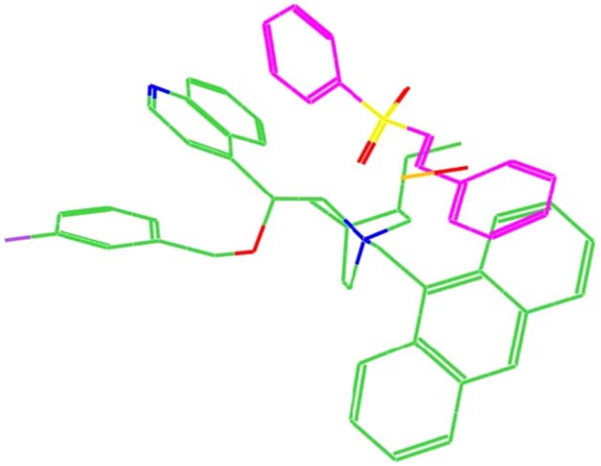

Figure 1. Possible arrangement of components for the enantioselective epoxidation of vinyl sulfones.

Keywords: Asymmetric epoxidation; Phase-transfer catalysis; α,β-Unsaturated sulfones.

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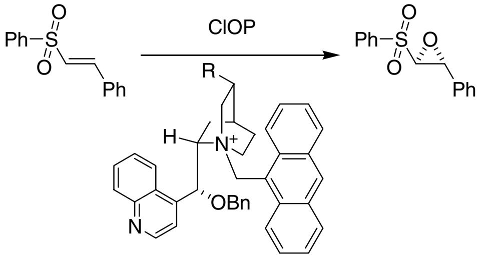
Table 1. Optimization of epoxidation reaction



Entry	R	P	Solvent	Conv (%)	Days	Temp (°C)	(*R*,*R*):(*S*,*S*)
1	Ethyl	K	Toluene	85	3	−40	91:9
2	Ethyl	K	Cumene	60	3	−30	82.5:17.5
3	Ethyl	Na	Toluene	76	2.5	20	81:19
4	Ethyl	K	CH_2Cl_2	14	3	−30	76.5:23.5
5	Ethyl	K	Xylene	57	3	−30	70.5:29.5
6	Vinyl	Na	Toluene	33	6	20	70.5:29.5
7[a]	Ethyl	K	Toluene	56	3	−30	69.5:30.5

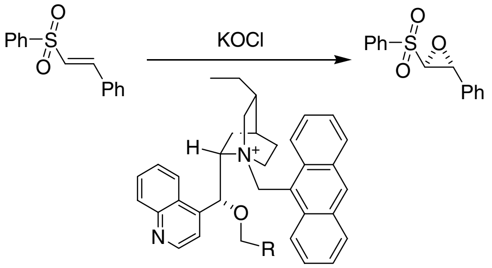
[a] The 1-napthalenylmethyl salt was used instead of the 9-anthracenylmethyl.

69:31 mixture. Thus, all further studies employed the 9-anthracenylmethyl group.

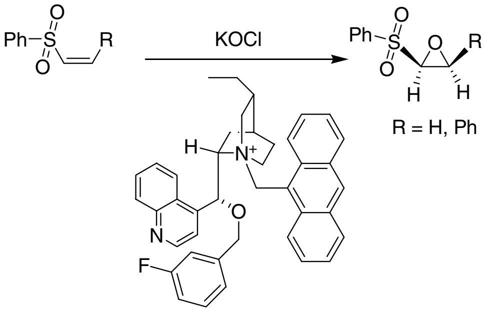
The dihydrocinchonidine salts provided higher selectivities than the cinchonidine salts (entries 3 and 6). Similar to the enone epoxidations, KOCl was more effective than NaOCl due to its greater reactivity since the KOCl reactions were performed at −30 °C to −40 °C while the NaOCl reactions were run at room temperature (entries 1 and 3).[5] The effect of solvent on the epoxidation using KOCl and the 9-anthracenylmethyl dihydrocinchonidine salts was also studied. Toluene was more effective than any other solvent employed, so it was adopted as the solvent of choice.

With this preliminary optimization, the following standard conditions were adopted to further explore this epoxidation reaction. A solution of the catalyst (0.1 equiv) and the sulfone was prepared in toluene (20 mL/g of sulfone) and then cooled to −35 °C. An aqueous KOCl solution[5] (4 equiv; 6.4 M) was then added, and the biphasic mixture was stirred vigorously for three days.[7] The low reaction temperature resulted in long reaction times, but higher temperatures gave lower enantioselectivities (e.g., 72% ee at −20 °C vs 82% ee at −35 °C). It was found that within experimental error the enantioselectivity remained constant throughout the course of the reaction (i.e., 76% ee at

Table 2. Effect of ether substituent on the epoxidation reaction



Entry	R	Conv (%)	Days	Temp (°C)	(*R*,*R*):(*S*,*S*)
1	*3-Fluorophenyl*	*96*	*3*	*−35*	*91.5:8.5*
2	3-Pyridyl	26	2	−40	91.5:8.5
3	Phenyl	85	3	−30	91:9
4	4-Nitrophenyl	8	3	−30	91:9
5	3-Me-Phenyl	100	2	−35	90:10
6	2-Pyridyl	19	3	−30	89:11
7	$3\text{-}CF_3$-Phenyl	25	3	−35	88.5:11.5
8	3-OMe-Phenyl	58	3	−30	88.5:11.5
9	Cinnamyl	4	3	−30	88.5:11.5
10	4-Br-Phenyl	22	3	−30	88:12
11	4-Pyridyl	12	2	−40	87.5:12.5
12	2-Furfuryl	85	2	−35	85:15
13	Vinyl	55	2	−20	83.5:16.5
14	2-OMe-Phenyl	19	3	−30	83.5:16.5
15	3,5-Me-Phenyl	36	3	−35	78:22
16	–CH=CMe_2	4	3	−30	76:24



Scheme 1.

31% conversion, 74% ee at 54% conversion, and 77% ee at 58% conversion).

Using the information that had been gained, further catalyst optimization was done. Neither Lygo[4] nor Corey[5] had reported a detailed study in which the ether moiety of the dihydrocinchonidine salts had been varied. Thus, a variety of catalysts were prepared following the literature precedent in order to test the effect of the ether substituent on the epoxidations run as described above (Table 2 with entry 3 as the base case).[8]

Clearly, the ether substituent has a significant effect on both the enantioselectivity of the epoxidation as well as on the reaction conversion. Overall, benzylic ethers are superior to allylic ethers (entry 3 vs 9, 13, and 16) while pyridyl methyl ethers are less effective than benzylic ethers (entries 2, 6, and 11 vs 3). In comparing entries 8 and 14, it seems that a *meta* substituent on the aromatic ring is advantageous relative to an *ortho* substituent. However, the use of a 3,5-disubstituted aromatic ring is deleterious compared to a monosubstituted ring (entries 5 and 15). The most effective catalyst in terms of both selectivity and conversion is that which contains the 3-fluorophenyl methyl ether providing the (*R*,*R*) epoxide with 96% conversion in 83% ee (entry 1). The 3-fluorobenzyl ether may promote additional catalyst rigidity through π-stacking with the quinoline ring as suggested by Corey for the superiority of α,β unsaturated 4-fluorophenyl ketones compared to the corresponding phenyl ketones in the enone epoxidation reactions.[5] This provides an explanation for both the higher enantioselectivity as well as the improved conversion since the reagents are arranged in a manner which facilitates the epoxidation reaction.

Although the sense of asymmetric induction was not determined, the epoxidation reaction was also tested with both phenyl vinyl sulfone as well as (*Z*)-phenyl styrylsulfone (Scheme 1).[9] The use of these substrates permitted a study of the effect of the vinylic phenyl group on the enantioselectivity of the epoxidation. It was expected that the epoxidation of phenyl vinyl sulfone would occur with lower enantioselectivity than with (*E*)-phenyl styrylsulfone since the rigidity of the transition state would be abridged due to the decrease in the π-stacking interactions with the anthracene moiety. This prediction was realized as the epoxidation of a toluene solution of phenyl vinyl sulfone and 10% catalyst with 4 equiv of 6.4 M KOCl occurred with 74:26 selectivity and 78% conversion after 2 days at −35 °C. Unlike *cis* α,β-unsaturated ketones which yield only *trans* epoxides, it was expected that the use of (*Z*)-phenyl styrylsulfone would give rise to *cis* epoxides.[10] In addition, a lower enantioselectivity was also expected due to a less rigid transition state. Both of these expectations were realized as only the *cis* epoxide formed in a 58:42 enantiomeric ratio when a toluene solution of (*Z*)-phenyl styrylsulfone and 10% catalyst was treated with 4 equiv of a 6.4 M KOCl solution at −35 °C for 3 days.[7] Further exploration of the phase-transfer catalyzed epoxidation of α,β-unsaturated sulfones is planned.[11]

Acknowledgements

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References and notes

1. (a) Diez, D.; Beneitez, M. T.; Gil, M. J.; Moro, R. F.; Marcos, I. S.; Garrido, N. M.; Basabe, P.; Urones, J. G. *Synthesis* **2005**, 565; (b) Mori, Y.; Yaegashi, K.; Furukawa, H. *J. Am. Chem. Soc.* **1997**, *119*, 4557; (c) Mori, Y.; Yaegashi, K.; Furukawa, H. *J. Am. Chem. Soc.* **1996**, *118*, 8158; (d) Mori, Y.; Yaegashi, K.; Iwase, K.; Yamamori, Y.; Furukawa, H. *Tetrahedron Lett.* **1996**, *37*, 2605.
2. (a) Arai, S.; Ishida, T.; Shioiri, T. *Tetrahedron Lett.* **1998**, *39*, 8299; (b) Arai, S.; Shioiri, T. *Tetrahedron* **2002**, *58*, 1407.
3. Geller, T.; Krueger, C. M.; Militzer, H.-C. EP 1279671, 2003.
4. (a) Lygo, B.; Wainwright, P. G. *Tetrahedron Lett.* **1998**, *39*, 1599; (b) Lygo, B.; Wainwright, P. G. *Tetrahedron* **1999**, *55*, 6289; (c) Lygo, B.; To, D. C. M. *Tetrahedron Lett.* **2001**, *42*, 1343.
5. Corey, E. J.; Zhang, F.-Y. *Org. Lett.* **1999**, *1*, 1287.
6. Julia, M.; Paris, J.-M. *Tetrahedron Lett.* **1973**, *14*, 4833.
7. The enantioselectivities were determined by chiral HPLC on a ChiracelOJ column with a mobile phase of 50:50 EtOH/Hept, flow rate = 0.5 mL/min, and UV detection at 210 nm.
8. Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414.
9. Truce, W. E.; Simms, J. A. *J. Am. Chem. Soc.* **1956**, *78*, 2756.
10. Curci, R.; DiFuria, F. *Tetrahedron Lett.* **1974**, *15*, 4085.
11. Ooi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **1999**, *121*, 6519.