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Stereoselective Synthesis of Styrene Oxides via a Mitsunobu Cyclodehydration

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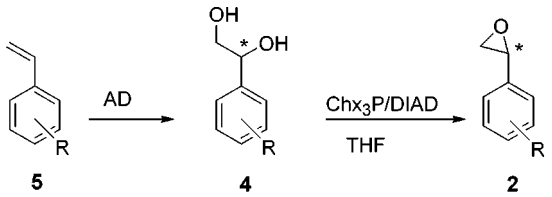
ABSTRACT



The Mitsunobu cyclodehydration of chiral phenethane-1,2-diols (4), readily accessed from the styrene derivative (5), has been demonstrated to provide the corresponding styrene oxides (2) with high levels of stereoretention (up to 99%). Optimized reaction conditions are described, from which the combination of tricyclohexylphosphine (Chx_3P) and diisopropylazodicarboxylate (DIAD) in THF and R = EWG provides the best results.

The utility of enantiomerically enriched styrene oxide derivatives as chiral buildings blocks for the synthesis of natural products and biologically active compounds is well-documented.[1] Accordingly, tremendous efforts have been aimed at developing catalytic, stereoselective epoxidation methodologies.[2] However, terminal olefins, such as styrene, still remain a challenge for this powerful methodology. The hydrolytic kinetic resolution of styrene oxides with (salen)-cocatalyst[3] and epoxide hydrolases[4] have also been developed for this purpose. Indirect routes to these epoxides are based mainly on asymmetric dihydroxylation (AD) chemistry,[5] which provides ready access to a range of chiral arenethane-1,2-diols, which upon stereospecific cyclodehydration give the chiral epoxides. Examples include dehydration via the Sharpless acetoxonium ion,[6] base-induced dehydration of the corresponding cyclic sulfate,[7] and selective hydroxyl activation followed by base-mediated ring closure.[8]

The Mitsunobu reaction,[9] traditionally a proven regioselective cyclodehydration methodology, had yet to be successfully applied to the synthesis of optically active styrene oxides. Evans demonstrated that the triphenylphosphine/diethylazodicarboxylate (DEAD) combination upon reaction with (S)-phenethane-1,2-diol gave essentially racemic styrene oxide.[10] It was postulated that the two regioisomeric oxyphosphonium betaine intermediates (**A** and **B**)

(1) For recent examples, see: (a) Hattori, K.; Nagano, M.; Kato, T.; Nakanishi, I.; Imai, K.; Kinoshita, T.; Sakane, K. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2821. (b) Di Fabio, R.; Pietra, C.; Thomas, R. J.; Ziviani, L. *Bioorg. Med. Chem.* **1995**, 551. (c) Sher, P. M.; Mathur, A.; Fisher, L. G.; Wu, G.; Skwish, S.; Michel, I. M.; Seiler, S. M.; Dickinson, K. E. J. *Bioorg. Med. Chem.* **1997**, *7*, 1583.

(2) (a) Collman, J. P.; Wang, Z.; Straumanis, A.; Quelquejeu, M.; Rose, E. *J. Am. Chem. Soc.* **1999**, *121*, 460. (b) Palucki, M.; Popisil, P. J.; Zhang, W.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1994**, *116*, 9333. (c) For a review, see: Jacobsen, E. N.; Wu, M. H. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999; Vol. II, Chapter 18.2. (d) Tian, H.; She, X.; Xu, J.; Shi, Y. *Org. Lett.* **2001**, *3*, 1929.

(3) (a) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936. (b) Brandes, B. D.; Jacobsen, E. N. *Tetrahedron: Asymmetry* **1997**, *8*, 3927.

(4) For example, see: Pedragosa-Moreau, S.; Morriseau, C.; Zylber, J.; Archelas, A.; Baratti, J.; Furstoss, R. *J. Org. Chem.* **1996**, *61*, 7402.

(5) For a review, see: Kolb, H. C.; Sharpless, K. B. *Transition Met. Org. Synth.* **1998**, *2*, 219.

(6) Kolb, H.; Sharpless, K. B. *Tetrahedron* **1992**, *48*, 10515.

(7) Jang, D. O.; Joo, Y. H.; Cho, D. H. *Synth. Commun.* **2000**, 4489.

(8) For review, see: Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483. (b) Adiyaman, M.; Khanapure, S. P.; Hwang, S. W.; Rokack, J. *Tetrahedron Lett.* **1995**, 7367. (c) O'Donnell, C. J.; Burke, S. D. *J. Org. Chem.* **1998**, *63*, 8614.

(9) For a review, see: Hughes, D. L. *Org. React.* **1992**, *42*, 335.

(10) Robinson, P. L.; Barry, C. N.; Bass, S. W.; Jarvis, S. E.; Evans, S. A., Jr. *J. Org. Chem.* **1983**, *48*, 5396.

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collapse at the same rate to give retention and inversion of configuration, respectively, thus yielding racemic oxide (Figure 1).

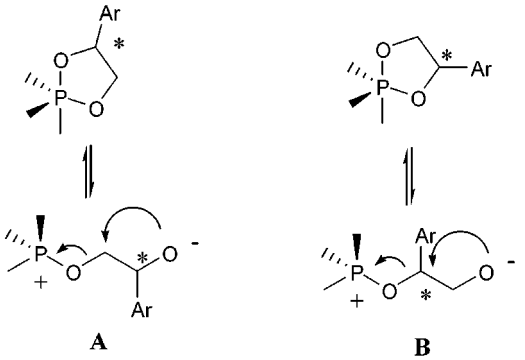
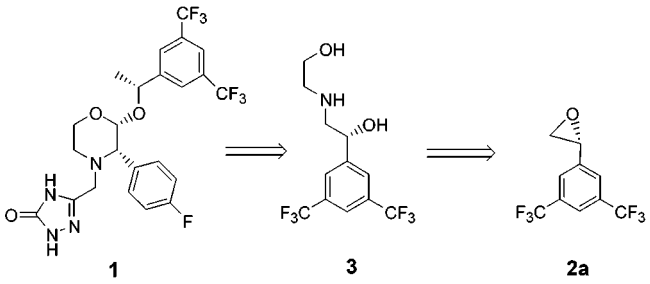


Figure 1.

During the course of our work on the synthesis of Substance P Inhibitor/NK_1 antagonist **1**,[11] we required (*R*)-3,5-bis(trifluoromethyl)styrene oxide **2a** en route to amino-diol derivative **3** (Scheme 1) and sought to employ the

Scheme 1

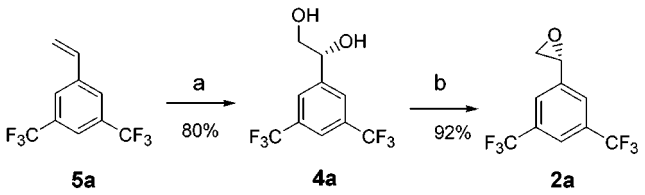


cyclodehydration of the corresponding diol **4a** via the Mitsunobu reaction. The stereocenter in **2a** subsequently controls the remaining stereocenters in **1**, and thus it was crucial to induce a high level of asymmetry.

Although the utility of tributylphosphine (TBP) in the Mitsunobu reaction is well documented,[12] this more basic reagent (relative to the more commonly employed triphenylphosphine) had not been studied in connection with the dehydration of phenethane-1,2-diols. Herein, we describe the successful use of the Mitsunobu reaction for the stereoselective synthesis of styrene oxide derivatives.

Thus, a modified Sharpless asymmetric dihydroxylation[13] of 3,5-bis(trifluoromethyl)styrene **5a** with $(DHQ)_2$−PHAL ligand provided (*S*)-diol **4a**[14] in 80% yield (92% ee). The material was upgraded to 97−99% ee via a single recrystallization from EtOAc/hexanes. Gratifyingly, the Mitsunobu cyclodehydration of **4a** with TBP/DIAD in THF provided epoxide **2a** of 96% ee (92% yield) with retention of configuration (Scheme 2).[15] This result prompted a systematic

Scheme 2[a]



[a] Reagents and conditions: (a) $K_2OsO_2(OH)_4$ (1 mol %), $(DHQ)_2$−PHAL (1 mol %), NMO, aq *t*-BuOH, 6 h/20 °C (ref 14); (b) Chx_3P, DIAD, THF, 3 h/0−25 °C.

study of the dehydration reaction parameters using commercially available (*S*)-(+)-1-phenyl-1,2-ethane-diol as the substrate under standardized conditions.[16]

Initially, a series of solvents were screened in the standard reaction, from which THF emerged as the solvent of choice (Table 1).[17]

Table 1. Effect of Solvent on Formation of (*S*)-Styrene Oxide[a]

solvent	% ee[b]	solvent	% ee[b]
THF	82[c], 75[d]	toluene	68[d]
ethyl ether	81[c]	MeCN	65[d]
MTBE	78[c]	$CHCl_3$	58[c]
DMF	70[d]		

[a] Reactions were run according to ref 16. [b] Determined by GC (Chiraldex γ-cyclodextrin trifluoroacetyl column); absolute configuration based on comparison with authentic sample (Aldrich). [c] Chx_3P employed; [d] TBP employed.

Next, a series of commercially available phosphines were screened using THF as the solvent. A dramatic effect was observed, with tricyclopentyl (Cp) and tricyclohexyl (Chx) phosphine emerging as the preferred phosphines (Table 2).

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(13) Ahrgren, L.; Sutin, L. *Org. Process Res. Dev.* **1997**, *1*, 425.

(14) Owen, S. N.; Seward, E. M.; Swain, C. J.; Williams, B. J. WO 0056727, 2000.

(15) This stereospecific outcome is consistent with the Mitsunobu cyclodehydration of propane-1,2-diol, which also gave 82−85% retention of configuration. See ref 10. Retention should also be favored here on the basis of steric considerations as the least hindered alcohol of vicinal diols is typically activated.

(16) **Standard Conditions.** The phosphine (1.5 equiv) was combined with the solvent (1.3 M) at 5 °C, followed by dropwise addition of the DIAD (1.45 equiv) and warming to 15 °C. After aging for 15 min, the solution was cooled to 5−10 °C and the diol was added (1 M in the solvent), followed by warming to room temperature. Reactions were typically complete within 2 h at 25−40 °C.

(17) Ethyl acetate showed low conversion in the standard reaction.

Table 2. Effect of Phosphine on Steroretention of Styrene Oxide[a]

phosphine	% ee[b]	phosphine	% ee[b]
Cp_3P	84	$(Chx)Ph_2P$	25
Chx_3P	82	Ph_3P	−10[c]
i-Bu_3P	80	*t*-Bu_3P	nr[d]
n-Bu_3P	75	$(Bn)_3P$	nr
i-Pr_3P	60	*o*-$tolyl_3P$	nr
n-Pr_3P	47		

[a] Reactions run according to ref 16. [b] Determined by GC (Chiraldex γ-cyclodextrin TFA column). [c] Gave inversion of configuration. [d] nr = no reaction.

In general, the branched trialkylphosphines performed better than the straight chain analogues, and the aryl-based phosphines gave only marginal results. The result giving 84% ee styrene oxide compares favorably to those obtained using the catalytic asymmetric epoxidation routes (83−86% ee).[2]

A brief screening of azodicarboxylates showed that the diisopropyl derivative (DIAD) gave better results than the *tert*-butyl analogue. The piperidinyl derivative gave no reaction under the standard conditions.

Thus, the optimized combination of Chx_3P/DIAD in THF was selected for the subsequent studies to expand the scope of this methodology to a series of substituted terminal styrene derivatives (Table 3). The reactions were performed under the standard conditions[16] and were complete within 3 h at 25−40 °C.[18] The yields ranged from 65% to 92%. The level of stereospecificity for the reaction is highest for the arenediols containing electron-withdrawing groups (EWG), only satisfactory for mildly electron-donating groups (entry f), and poor for electron-donating groups (entry h).

Table 3. Synthesis of Styrene Oxides (**2**) from Styrenes (**5**) via Phenethane Diols (**4**)

entry	R	% ee diol **4**[a,b]	% yield **2**[c]	% ee epoxide **2**[b]	optical yield[d]
a	3,5-CF_3	97 (S)	92	96.4 (S)	99.7
b	H	99 (S)	80	81 (S)	91
c	3-Cl	97.5 (S)	65	94 (S)	98
d	4-Cl	93 (S)	75	87.4 (S)	97
e	4-F	95 (S)	90	84 (S)	94.4
f	4-Me	92 (S)	92	55 (S)	81
g	4-CF_3	98.4 (S)	87	96 (S)	98.8
h	4-MeO	97.5 (R)	74	6 (R)	54

[a] Diols **4a** and **c**−**g** were prepared using either AD-mix-α or the $(DHQ)_2$-PHAL/$K_2OsO_2(OH)_4$/NMO combination; diol **4h** was prepared using AD-mix-β. Diol **4b** was purchased from Aldrich. [b] Percent ee measured by either GC (Chiraldex γ-cyclodextrin trifluoroacetyl column, entries **2a**−**d, 4a**; **4e, 4g** assayed as the acetonides), HP chiral (20% permethylated β-cyclodextrin, entries **2e**−**g**), or SFC (Chiralpak AD column, entry **2h**; OD column, entries **4d, 4f, 4h**; AD column, entry **4c**). Absolute configurations were determined by comparison to an authentic sample (entries **2a**−**b**) or by measurement of optical rotation in chloroform and comparison to literature values (entries **2c**−**f**, **h**) or were inferred on the basis of analogous behavior with other entries (entry **2g**). [c] HPLC assay yield measured versus authentic material. [d] Defined as % major enantiomer in **2**/% same enantiomer in **4**.

A Hammett plot of log((100 + ee)/(100 − ee))[19] versus Σσ of the substituents reveals a clear trend (Figure 2). The positive slope could be attributed to the expected stabilizing effect of electron-withdrawing groups on the incipient oxygen anion at the benzylic position in the betaine intermediate (**A** from Figure 1), which gives rise to the epoxide with retention of configuration.

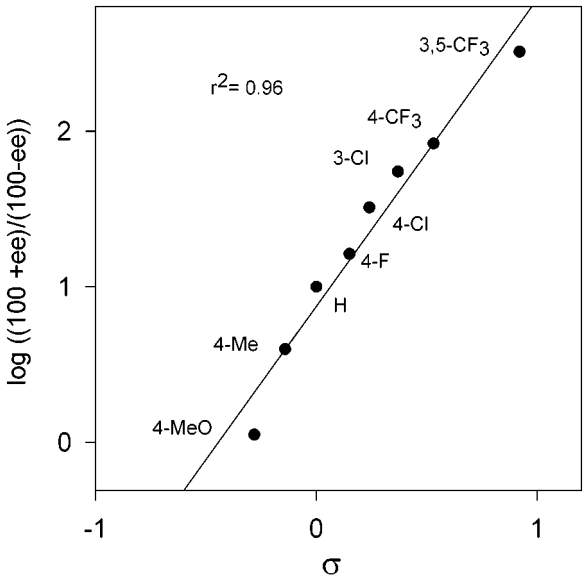

Figure 2. Hammett plot of optical yield vs Σσ of phenyl substituents.

In conclusion, the Mitsunobu cyclodehydration of chiral phenethane-1,2-diols has been demonstrated to provide the corresponding epoxide with high levels of stereoretention in substrates lacking electron-donating groups on the arene ring. The facile access to both enantiomers of a wide range of arenethane-1,2-diols via the Sharpless AD reaction makes this an attractive route to this important class of molecules.

Acknowledgment. The authors wish to thank Drs. Chris Welch and Dave Mathre for assistance in developing chiral assays and Dr. Phil Pye for providing selected characterization data for diol **4a** and epoxide **2a**.

Supporting Information Available: Representative experimental descriptions for diol **4a** and epoxide **2a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) Pure epoxides were obtained by column chromatography of the reaction mixture after removal of the volatiles in vacuo. See Supporting Information.

(19) The term log((100 + ee)/(100 − ee)) equals $-\Delta\Delta G^{\ddagger}/RT$ where $-\Delta\Delta G^{\ddagger}$ is the free energy difference between two diastereomeric transition states leading to enantiomeric products.