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Phosphine-Dependent Stereoselectivity in the Mitsunobu Cyclodehydration of 1,2-Diols: Stereodivergent Approach to Triaryl-Substituted Epoxides

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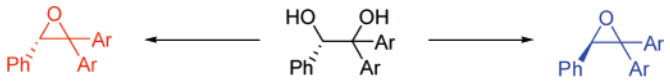
ABSTRACT



Triaryl-1,2-ethanediols, readily available from natural mandelic acid, can be stereospecifically converted into their corresponding chiral nonracemic epoxides by means of a Mitsunobu cyclodehydration reaction. Upon selection of the phosphine component in the reaction, the two enantiomers of the final epoxides are accessible in high enantiomeric excess. In view of this surprising phosphine-dependent stereoselectivity, here we examine the influence of the steric and electronic nature of both the phosphine and the substrate.

Chiral epoxides are highly valuable synthetic building blocks in asymmetric organic synthesis. In the last three decades, metal-catalyzed and organocatalytic enantioselective epoxidation technologies have advanced greatly, enabling the direct preparation of optically enriched oxiranes from the corresponding olefins.[1−5] Complementary methodologies for the preparation of chiral epoxides comprise the addition of sulfur ylides to aldehydes or ketones[6] and the cyclization of 1,2-diols. Chiral 1,2-diols, readily available through Sharpless asymmetric dihydroxylation,[7,8] represent a powerful alternative technology for the preparation of nonracemic epoxides. The transformation of 1,2-diol to epoxide can be achieved through several methodologies: selective hydroxyl activation followed by base-promoted cyclization,[8] dehydration via acetoxonium ion,[9] or cyclic sulfate dehydration.[10]

Mitsunobu reaction conditions (phosphine/ diazocarboxylate reagent) have also been applied to the dehydration of chiral 1,2-diols.[11] The mechanism for this transformation is proposed to occur via a five-membered ring phosphorane which evolves through an oxyphosphonium betaine (Scheme 1).[12,13] Intramolecular cyclization of this betaine provides the final epoxide product. For nonsymmetric 1,2-diols, two possible betaines may form. Depending on which of these two betaines is formed the reaction will take place with either retention or inversion of configuration. For terminal 1,2-alkanediols, the reaction occurs stereospecifically with retention via path A (Scheme 1).[14,15] This behavior has been explained

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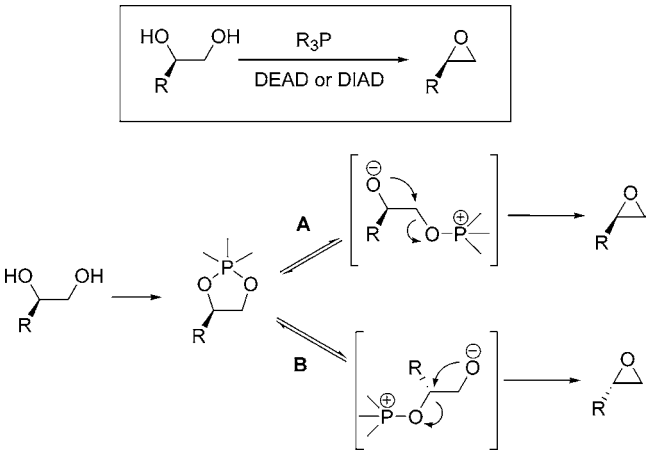
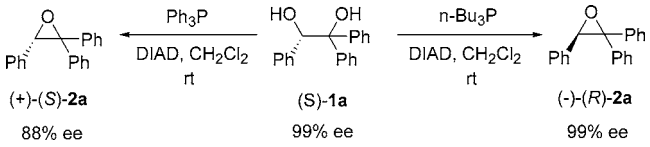
Scheme 1. Mitsunobu Cyclodehydration of 1,2-Diols: Commonly Accepted Mechanism



traditionally as the reaction pathway going through the less sterically demanding betaine, the one bearing the oxyphosphonium ion in terminal position (path A). This trend, however, does not apply to the cyclodehydration of styrene 1,2-diols. Evans and co-workers showed that the Mitsunobu dehydration of (*S*)-1-phenyl-1,2-ehtanediol (PPh_3/DEAD) provides essentially racemic epoxide.[12] It was postulated that the origin of racemization was that the corresponding betaines, paths A and B (Scheme 1), formed and collapsed at the same rate. Recently, Weissman and co-workers reported that the stereospecificity of the Mitsunobu dehydration of 1-aryl-1,2-ethanediols largely depends on the nature of the phosphine used and the aryl groups in the substrate.[16] Thus, electron-rich phosphines (e.g., PCy_3) and electron-withdrawing groups in the aryl 1,2-diol moiety provide the corresponding epoxide with retention of configuration (path A, Scheme 1).

As part of a project devoted to the preparation of sterically demanding chiral 1,2-amino alcohols and their use as a catalysts in the enantioselective dialkylzinc addition to carbonyl compounds,[17−19] we explored the preparation of optically active triphenylethylene oxide from the corresponding 1,1,2-triphenylethanediol by means of the Mitsunobu cyclodehydration reaction. With this purpose, we reacted optically pure (*S*)-1,1,2-triphenylethandiol (**1a**) with triphenylphosphine and diisopropylazodicarboxylate (DIAD) at room temperature in CH_2Cl_2 (Scheme 2). We isolated the corresponding oxirane **2a** with retention of configuration and a high optical purity (88% ee). Surprisingly, when the same reaction was performed with *n*-Bu_3P instead of PPh_3 we

Scheme 2. Phosphine-Dependent Stereodivergent Synthesis of Triphenyloxirane



isolated the product with opposite absolute configuration and exceptionally high ee (99%). In this case, an opposite stereochemical pathway yielded inversion of the initial 1,2-diol configuration. This example is an interesting case of phosphine-dependent stereoselectivity in the Mitsunobu cyclodehydration. To shed light on this subject, we undertook a study to establish how the electronic factors in the starting material affect the stereochemical outcome of the reaction.

Starting from optically pure (*S*)-mandelic acid and the corresponding bromo benzene derivatives several 1,1-diaryl-2-phenylethane-1,2-diols (Figure 1) were synthesized using

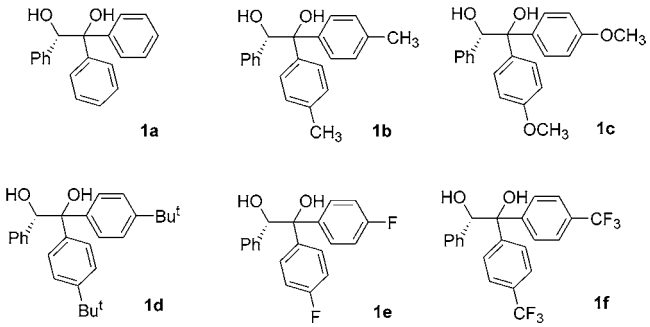


Figure 1. Chiral 1,1-diaryl-2-phenylethane-1,2-diols used in this study.

standard reaction procedures.[20] The aryl groups introduced were chosen to provide a diverse electronic environment at the 1,2-diol quaternary center. Product diols were purified by recrystallization until optically pure (99% ee) as determined by chiral HPLC.[21] With these compounds in hand, we examined the Mitsunobu cyclodehydration with DIAD and three different phosphines, Ph_3P, *n*-Bu_3P and Oct_3P, which are widely used in synthesis (Table 1).

As with the parent compound **1a**, cyclodehydration of diols **1b**, **1d**, **1e**, and **1f** also provided the corresponding epoxides from excellent to moderate yields. Only oxirane derived from **1c** could not be isolated or identified in the final reaction mixture. This was probably due to the intrinsic instability of the final product.[22] The electron-releasing nature of the *p*-methoxy-

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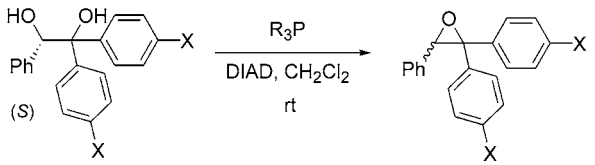
(21) Diol **1e** could not be purified by crystallization, and it was used as obtained in 93% enantiomeric excess.

(22) As suggested by a reviewer, the inability to find the expected epoxide could also be explained by the migration of the electron-rich aryl group and concomitant loss of triphenylphosphine oxide in the initial betaine to yield a rearranged ketone.

Table 1. Mitsunobu Cyclodehydration of Several (*S*)-1,1-Diaryl-2-phenylethane-1,2-diols



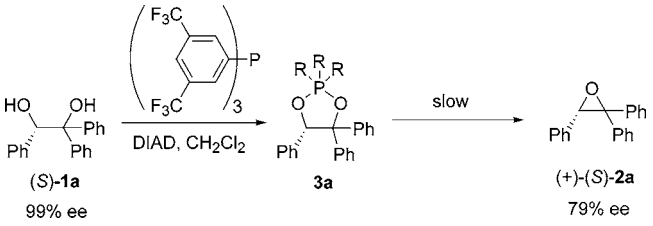
entry	R_3P	X	yield (%)	ee[a] (%)	er (*S*/*R*)	$[\alpha]_D$	oxirane
1	Ph_3P	*t*-Bu	57	79	8.3:1	(+)	**2d**
2	Ph_3P	Me	43	90	20.0:1	(+)	**2b**
3	Ph_3P	H	45	88	15.6:1	(+)	**2a**
4	Ph_3P	F	94	65 (72[b])	1:6.1[c]	(−)	**2e**
5	Ph_3P	CF_3	77	98	1:110	(−)	**2f**
6	*n*-Bu_3P	*t*-Bu	40	40	1:2.3	(−)	**2d**
7	*n*-Bu_3P	Me	57	60	1:4.0	(−)	**2b**
8	*n*-Bu_3P	H	70	99	1:198	(−)	**2a**
9	*n*-Bu_3P	F	81	93 (99[b])	1:199[c]	(−)	**2e**
10	*n*-Bu_3P	CF_3	63	>99	1:999	(−)	**2f**
11	Oct_3P	*t*-Bu	77	7	1.1:1	(+)	**2d**
12	Oct_3P	Me	99	45	1:2.6	(−)	**2b**
13	Oct_3P	H	99	84	1:11.4	(−)	**2a**
14	Oct_3P	F	61	93 (99[b])	1:199[c]	(−)	**2e**
15	Oct_3P	CF_3	83	99	1:255	(−)	**2f**

[a] Product enantiomeric excess determined by chiral HPLC. [b] Corrected ee based upon enantiomeric excess of starting material **1e** (93% ee). [c] Corrected er based on the enantiomeric ratio (*S*/*R*) of starting material **1e** (27:1, 93% ee).

benzene groups attached to the quaternary center facilitates the formation of carbocationic species, hence preventing the formation of the epoxide. When using triphenylphosphine, the 1,2-diols bearing electron-releasing groups (ERG) in the aryl moiety (Table 1, entries 1 and 2) provided the corresponding epoxide with retention of configuration, thus confirming the behavior observed for 1,1,2-triphenylethanediol (Table 1, entry 3). In contrast, when electron-withdrawing groups (EWG) were present the reaction occurred with inversion, which provided the (*R*) enantiomer as the major isomer (Table 1, entries 4 and 5). When using trialkylphosphines (Bu_3P and Oct_3P), the reaction took place mostly with inversion of configuration, to provide the (*R*) enantiomer (Table 1, entries 6−15). In this case, however, there was a clear trend by which EWG provided higher stereospecific reactions while electron-releasing substituents showed poor stereospecificity.

Furthermore, when using tricyclohexylphosphine (Cy_3P) in the cyclodehydration of (*S*)-1,1,2-triphenylethanediol (**1a**), a poor yield (2%) of the corresponding (*R*)-epoxide was obtained in high enantiomeric excess (96% ee). In contrast, when the electron-deficient tris[3,5-bis(trifluoromethyl)phenyl] phosphine was used, the corresponding intermediate phosphorane **3a** was isolated in (71%) yield (Scheme 3). Intermediate phosphorane species have traditionally been observed only in solution by NMR techniques.[13,23] In some instances, rigid 1,2-diols have provided stable phosphoranes that not undergo the corresponding cyclodehydration.[24] In our case, a characteristic ^{31}P resonance at −45.5 ppm could be observed for **3a**. Although phosphorane **3a** was fully characterized by spectroscopic techniques, it decomposed slowly to provide the corresponding epoxide. Decomposition of **3a** for over a month at room temperature in CH_2Cl_2 yielded the (*S*)-**2a** with 79% ee with retention of configuration. These two examples are not useful from a synthetic point of view; nevertheless, they confirm that electron-rich phosphines provide the inversion product in high stereospecificity, while electron-poor phosphines ensure retention of configuration.

Scheme 3. Formation of a Stable Phosphorane



From the results disclosed in Table 1, we may conclude that two reaction pathways lead to opposite configurations (*R* or *S*) in the final oxirane ring. Most intriguingly, depending on the phosphine used, either one of these two pathways will be favored. Linear fitting of the log *S*/*R* ratio, which is related to the $-\Delta\Delta G^{\ddagger}/2.3RT$ for the corresponding transition states vs the Hammett σ_p values when using triphenylphosphine, provided a negative slope (Figure 2).[25]

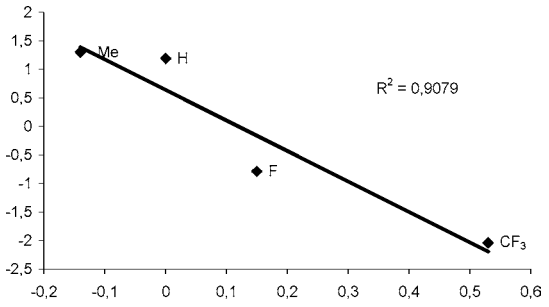


Figure 2. Hammett plot of log *S*/*R* ratio of enantiomers vs σ for the Mitsunobu cyclodehydration when using Ph_3P.

This graphical representation is indicative that ERG in the aromatic rings of the quaternary center favor the formation of the *S*-enantiomer (retention). From a mechanistic perspective, this behavior is indicative that a positive charge close to the aryl groups is involved in the reaction pathway leading to the *S*-enantiomer.[26] Alternatively, a Hammett plot of log *R*/*S* ratio of enantiomers vs σ_p when using Oct_3P provided a

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positive slope, indicating that, a negative charge close to aryl moieties is now involved in the mechanism that produces the inverted configuration (Figure 3).[16]

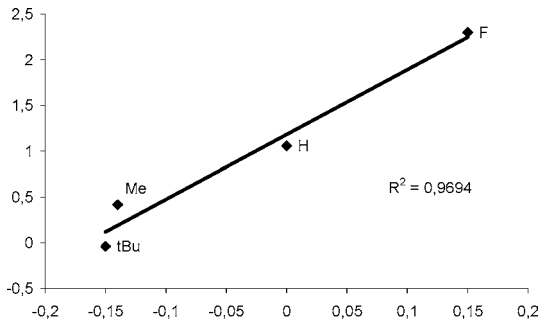
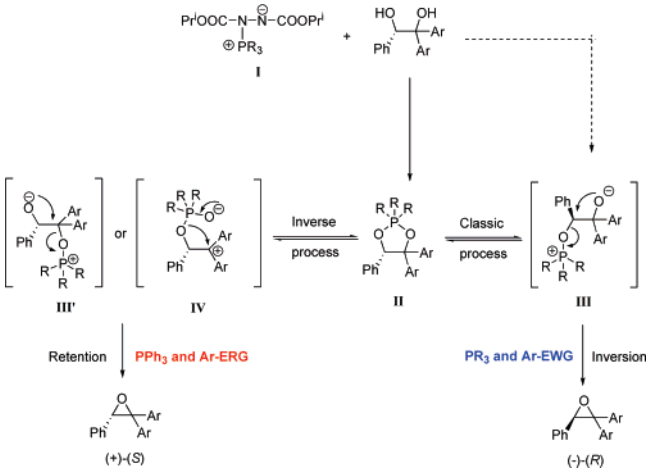


Figure 3. Hammett plot of log *R*/*S* ratio of enantiomers vs σ for the Mitsunobu dehydration of triarylethanediols when using Oct_3P.

When triphenylphosphine was used, cyclic phosphoranes (**II**) were detected as intermediates by ^{31}P NMR reaction progress analysis (Scheme 4). Thus, for example, when

Scheme 4. Proposed Reaction Pathways for the Phosphine-Dependent Mitsunobu Cyclodehydration



DIAD was added to a mixture of **1a** and Ph_3P, a major resonance at −39.5 ppm, attributed to phosphorane **II,** appeared along with a minor signal (45.7 ppm), attributed to **I**. These resonances over time (2 h) disappeared to yield triphenylphosphine oxide (29.3 ppm) and the corresponding epoxide. Alternatively, intermediate cyclic phosphoranes were not detected by ^{31}P NMR when *n*-Bu_3P was used instead of Ph_3P. Similar observations were made by Guthrie and Jenkins for the cyclodehydration of *trans*-1,2-cyclohexanediol. These authors proposed that oxophosphonium salts, like **III**, form rapidly when tributylphosphine is used.[23] These results indicate that when using electron-deficient phosphines (i.e., Ph_3P), cyclic phosphoranes are reaction intermediates with a prolonged half-life. This would also explain the extraordinary stability of phosphorane **3a**.

In this scenario, formation of betaine (**III**) in which the oxyphosphonium is placed at the less hindered oxygen atom and the subsequent ring closure with inversion of configuration explains the formation of the (*R*)-epoxide. Betaine **III** is formed rapidly either directly from **I** and the corresponding diol or through **II**. This reaction pathway should be favored by electron-rich phosphines (*n*-Bu_3P or Oct_3P), which stabilize the positive charge on phosphorus, and by EWG on the aryl groups, which stabilize the nearby negative charge on the alkoxide moiety of betaine **III**.

Alternatively, the use of triphenylphosphine ensures formation of cyclic phosphorane **II**, as determined by NMR experiments. From **II**, formation of regioisomeric betaine **III′** or a carbocationic intermediate **IV** may explain the retention product (Scheme 4). Observed electronic effects can be more satisfactorily explained if the oxygen-quaternary carbon bond is broken to yield a carbocationic intermediate like **IV** rather than **III′**.[12,27] In this case, the aryl substituents with ERG stabilize the tertiary carbocation, while the negative charge in the phosphorane moiety will be more effectively stabilized by electron-poor phosphines (e.g., Ph_3P). This mechanism is also consistent with the Hammett plot, which indicates the formation of a positive charge close to the aryl groups.[28] Steric effects should also favor reaction through **IV** rather than the sterically encumbered betaine **III′**. Evolution of intermediate **IV** through either a concerted or a stepwise elimination of triphenylphosphine oxide should eventually lead to the retention product.

In summary, an unexpected phosphine-dependent stereoselectivity has been disclosed for the Mitsunobu cyclodehydration of chiral triaryl-1,2-ethanediols. Electron-rich phosphines favor the inversion product while triphenylphosphine provides stereospecifically the retention epoxide. We also have studied here the electronic effects of the benzene groups attached to the quaternary center of the diol. Our results show that EWG favor the inversion process and vice versa. From the synthetic point of view, this stereochemical behavior allows the formation of the two enantiomers of the triphenylethylene oxide from a single diol precursor.

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Supporting Information Available: General methods, experimental procedures, and spectroscopic data for all new diols and epoxides. Copies of ^1H and ^{13}C NMR spectra for diols **1a**−**f**, epoxides **2a**−**f**, and phosphorane **3a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(27) Carbocationic intermediates have been invoked in the thermolysis of dioxaphosphoranes derived from (*S*)-1,1-diphenyl-1,2-propanediol and in the cyclodehydration of 1-phenyl-1,2-ethanediol to styrene oxide. See: Murray, W. T.; Evans, S. A., Jr. *J. Org. Chem.* **1989**, *54*, 2440−2446 and ref 12.

(28) For Ph_3P, a better fitting was obtained with σ rather than with σ^+. For a positive charge that enters in conjugation with the aryl moieties a better fitting with σ^+ should be expected (see ref 25). In the present case, the steric hindrance around the doubly benzylic carbocation hampers the coplanarity with the aryl moieties, thus interfering in the conjugation.