Communications

Regioselective Cyclodehydration of Chiral Diols with Diethoxytriphenylphosphorane, Triphenylphosphine-Tetrachloromethane-Potassium Carbonate, and Triphenylphosphine-Diethyl Azodicarboxylate Reagents. A Comparative Study

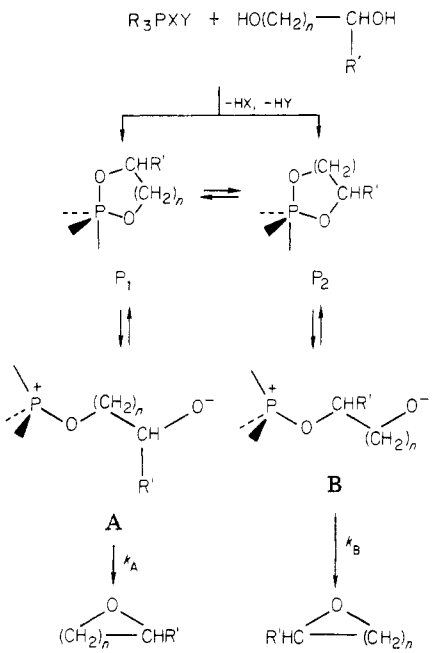
Summary: The regioselectivity of cyclodehydration of chiral diols has been examined with the reagents diethoxytriphenylphosphorane, triphenylphosphine-tetrachloromethane-potassium carbonate, and triphenylphosphine-diethyl azodicarboxylate. (*S*)-(+)-Propane-1,2-diol and (*R*)-(−)-pentane-1,4-diol afford 80–87% retention of stereochemistry at the chiral carbon in the ether while (*S*)-(+)-phenylethane-1,2-diol affords essentially racemic styrene oxide with all three reagents.

Sir: Information on the one-step neutral, regioselective cyclodehydration of chiral, unsymmetrical diols to cyclic ethers could have important synthetic consequences toward providing useful preparative routes to optically active ethers. The ready availability of a variety of chiral diols[1] from relatively inexpensive chiral precursors[1,2] serves to extend the application of chiral ethers as building blocks[3] and synthons[3] in natural products synthesis as well as asymmetric synthesis.[4]

Phosphoranes[5] and oxyphosphonium salts[6] (and some sulfuranes[7]) effectively promote cyclodehydration of diols to cyclic ethers, but little is currently known of the extent of regioselection occurring during the phosphorane-mediated cyclodehydration of unsymmetrical, chiral diols. Here, we present some of our preliminary findings on this subject.

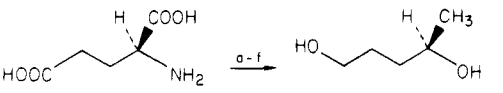
Phosphorane-promoted cyclodehydration of an unsymmetrical chiral diol (Scheme I) can, in principle, give enantiomeric ethers by either of two diastereoisomeric routes. Presumably, separate *stepwise*[8a] decomposition of oxyphosphonium betaines, A and B, although preceded by a number of rapid exchange processes, could ultimately afford a regioselective distribution of cyclic ethers. Of the two possible betaines, ether formation from collapse of A should be favored on the basis of favorable steric considerations during the intramolecular alkoxide displacement of triphenylphosphine oxide.[8b,9]

Scheme I[a]



[a] R = Ph; R' = Me, Ph; n = 1, 3; X = Y = OEt; X = Cl, Y = CCl_3; X = Y = EtCOON=NCOOEt.

Scheme II[a]



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[a] a, $NaNO_2$, H_2SO_4; b, $SOCl_2$; c, $NaBH_4$, CH_3OH; d, *p*-TsCl, pyridine; e, $LiAlH_4$, THF; f, NaOH, H_2O.

The predictions are that (a) cyclodehydration of unsymmetrical chiral diols should afford predominantly the chiral ether with *retained* stereochemistry at the chiral carbon and (b) as the steric bulk of the attached R' group increases, the percent of regioselection should also increase.

To test these predictions, we prepared (*S*)-(+)-propane-1,2-diol [1; 71%; $[\alpha]^{23}_D$ +14.20° (neat)][10] by lithium aluminum hydride reduction of (*S*)-(−)-ethyl lactate,[11]

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(6) See, for example: (a) Selve, C.; Castro, B. *Tetrahedron Lett.* **1973**, 4459. (b) Boigegrain, R.; Castro, B. *Ibid.* **1976**, *32*, 1283.

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(8) A concerted decomposition pathway for phosphoranes is, in fact, symmetry allowed for some equatorial–equatorial or apical–apical substituents, but numerous, if not all, phosphoranes with alkoxy substituents prefer the stepwise route. See: Emsley, J.; Hall, D. "The Chemistry of Phosphorus"; Wiley: New York, 1976.

(9) Ruzicka, L. *Helv. Chim. Acta* **1926**, *9*, 230.

(10) This sample of (*S*)-(+)-propane-1,2-diol represents 85.5% ee based on the largest observed optical rotation, $[\alpha]^{20}_D$ +16.6° (neat). See: Gombos, J.; Haslinger, E.; Schmidt. U. *Chem. Ber.* **1976**, *109*, 2645.

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Table I. Cyclodehydration of Optically Active Diols with "Activated" Phosphorus Reagents

entry	diol	dehydrating reagent (solvent)	temp, °C	ether (%)	% ret[a]
1	(S)-(+)-propane-1,2-diol (1)	TPP-CCl_4-K_2CO_3 (CCl_4)	76	2-methyloxirane (85)	81.7
2	(S)-(+)-propane-1,2-diol (1)[b]	TPP-DEAD (C_6H_6)[c,d]	25	2-methyloxirane	83.5-84.8
3	(S)-(+)-propane-1,2-diol (1)	$Ph_3P(OEt)_2$ (CH_2Cl_2)	55	2-methyloxirane (82)	83.3
4	(S)-(+)-phenylethane-1,2-diol (2)	TPP-CCl_4-K_2CO_3 (CCl_4)	76	2-phenyloxirane (68)	50
5	(S)-(+)-phenylethane-1,2-diol (2)	$Ph_3P(OEt)_2$ (CH_2Cl_2)	55	2-phenyloxirane (92)	50
6	(S)-(+)-phenylethane-1,2-diol (2)	Ph_3P-$C_2H_5COON)_2$	25	2-phenyloxirane	55.0
7	(R)-(−)-pentane-1,4-diol (3)	TPP-CCl_4-K_2CO_3 (CCl_4)	76	2-methyloxolane	87.8
8	(R)-(−)-pentane-1,4-diol (3)	$Ph_3P(OEt)_2$ (CH_2Cl_2)	55	2-methyloxolane (82)	80.5
9	(R)-(−)-pentane-1,4-diol (3)	Ph_3P-$(C_2H_5COON)_2$	25	2-methyloxolane	85.7

[a] Percent retention (% ret) equals percent regioselectivity. [b] The % ee is estimated at >96%. See footnote *d* and: Schurig, V.; Koppenhoefer, B.; Buerkle, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 937. [c] Diethyl azodicarboxylate. [d] Schurig, V.; Koppenhoefer, B.; Buerkle, W. *J. Org. Chem.* **1980**, *45*, 538-541.

(S)-(+)-phenylethane-1,2-diol [**2**; 70%; $[\alpha]^{18}_D$ +51.57° (*c* 0.785 benzene)][12] from borane reduction of (S)-(+)-mandelic acid[13] and (4R)-(−)-pentane-1,4-diol [**3**; 11%; $[\alpha]^{21}_D$ −13.06° (neat)][14] from the series of reactions shown in Scheme II.[15]

The regiochemical modes of cyclodehydration of these optically active diols were examined by using the reagents, diethoxytriphenylphosphorane (DTPP),[5b,16] triphenylphosphine (TPP)–tetrachloromethane (CCl_4)–potassium carbonate (K_2CO_3),[17] and triphenylphosphine (TPP)–diethyl azodicarboxylate [$(C_2H_5COON)_2$].[5c,18] The results are summarized in Table I.

The percent regioselection (82%) in the cyclodehydration of diol **1** to (S)-(+)-propylene oxide with DTPP clearly shows predominant retention of stereochemistry at C_2. If k_A and k_B are rate limiting and equilibration of betaines A and B (through phosphoranes, P_1 and P_2) is rapidly accomplished, then the regioselection results indicate that collapse of betaine A is kinetically favored over collapse of betaine B (i.e., $k_A > k_B$). The similarity in percent regioselection (82–85%) for formation of (S)-(+)-propylene oxide from diol **1** employing the three different cyclodehydrating reagents (entries 1–3 in Table I) strongly implies that cyclic phosphoranes P_1 and P_2 as well as betaines A and B are prerequisite intermediates in *all three reactions*.[5b-d]

If R′ is a large group (i.e., R′ = C_6H_5), one might anticipate (a) the equilibrium distribution between betaines A and B to increasingly favor A (compared to R = CH_3) and (b) $k_A/k_B > 1$. With these expectations in mind, we examined the cyclodehydration of (S)-(+)-phenylethane-1,2-diol (**2**) with the reagents DTPP, TPP–CCl_4–K_2CO_3, and TPP–$(C_2H_5CO_2N)_2$ in an effort to increase the percent regioselection. While all three reactions gave good yields of styrene oxide (68–92%), ^{1}H NMR analysis of the product using the chiral shift reagent Eu(hfc)$_3$[19] revealed that the styrene oxide was completely racemic when DTPP and TPP–CCl_4–K_2CO_3 were used and the percent enantiomeric excess was only 9% when TPP–$(C_2H_5CO_2N)_2$ was used (i.e., the styrene oxide was significantly racemized with this reagent as well).

We have prepared and independently demonstrated that (S)-(+)-styrene oxide is configurationally stable under the "DTPP" reaction conditions.[20] Also, possible ring-opening reactions involving styrene oxide and TPP do not, in fact, jeopardize the configurational stability of the initially formed styrene oxide.[21] Several possibilities exist for rationalization, including (a) $k_A = k_B$ and (b) formation of $PhC^+HCH_2O^-$(H) through ionization of PhPO. We also speculate that rationalization may occur *within* the cyclic dioxyphosphorane by initial ionization of the *equatorial* phosphoryl oxygen to the carbon bond. Of the two dioxyphosphoranes P_1 and P_2 the carbon–oxygen bond in the equatorial –PO–C–Ph fragment in dioxyphosphorane P_2 should be more susceptible to rupture than its apical counterpart in P_1. This seems reasonable because the propensity for carbon–oxygen ionization should be facilitated by (a) favorable 2p–3d$_\pi$ bonding interactions between the equatorial phosphoryl oxygen and the phosphorus atom in the trigonal-bipyramidal conformer P_2,[22] and (b) the potential for stabilization of the incipient carbocation by the phenyl group. In fact, some oxyphosphoranes possessing equatorial P–O$^-$ groups may be "conformationally demanding" due to the strong p–d$_\pi$ interactions between oxygen and phosphorus.[23] Extensive

(11) (S)-(−)-Ethyl lactate was purchased from Eastman Chemical Co. and distilled twice before use. The largest reported optical rotation for optically pure (S)-ethyl lactate is $[\alpha]^{20}_D$ −14.6° (neat); therefore, we calculate that the optical purity of our sample is 85.5% based on the observed rotation, $[\alpha]^{20}_D$ −12.48° (neat). See: Golding, B. T.; Hall, D. R.; Sakriker, S. *J. Chem. Soc., Perkin Trans. 1*, **1973**, 1214.

(12) Comparison of the optical rotation of this sample with the highest known optical rotation of the *R* enantiomer, $[\alpha]^{18}_D$ −51.9° (C 0.77, benzene), indicates that our sample of the *S* enantiomer is 99.4% optically pure. See: Fischer, E. *Chem. Ber.* **1912**, *63*, 2447.

(13) (S)-(+)-Mandelic acid was purchased from Aldrich Chemical Co. with an optical rotation of $[\alpha]^{20}_D$ +154° (water).

(14) (R)-(−)-Pentane-1,4-diol was purified by preparative GLC and is 97.3% ee based on $[\alpha]_{22}$ −13.4° (neat). See: Karrer, P.; Reschofsky, H.; Kaase, W. *Helv. Chim. Acta* **1947**, *30*, 271.

(15) Eguchi, C.; Kawata, A. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 1704.

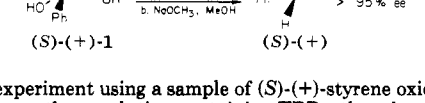
(16) Cyclodehydration with DTPP involved treatment of diethyl peroxide (11 mmol) with TPP (11 mmol) in dichloromethane (5 mL) at ambient temperature. After refluxing for 0.5 h, the diol (10 mmol) was added, and the reflux period was continued (27–90 h). Removal of the solvent and distillation or rapid preparative chromatography gave the product, which was analyzed by ^{1}H NMR.

(17) When the TPP–CCl_4–K_2CO_3 reagent was used, the following experimental procedure was employed. A mixture of TPP (7.5 mol), the diol (5 mmol), and potassium carbonate (10 mmol) in anhydrous tetrachloromethane (10 mL) was refluxed for 24 h. The ethers were isolated by distillation or rapid preparative chromatography and analyzed by ^{1}H NMR.

(18) When the TPP–$(C_2H_5CO_2N)_2$ reagent was used, the following experimental procedure was employed. TPP (10 mmol), diethyl diazodicarboxylate (10 mmol), and the diol (10 mmol) in dichloromethane (10 mL) were stirred for 25 h at ambient temperature. Removal of the solvent gave the ether.

(19) Tris[3-(heptafluoropropyl)hydroxymethylene]-*d*-camphorato]europium(III) was obtained from the Aldrich Chemical Co.

(20) A sample of (S)-(+)-styrene oxide [>95% ee by ^{1}H NMR; using Eu(hfc)$_3$] was prepared by the scheme shown below [Dupin, C.; Dupin, J.-F. *Bull. Soc. Chim. Fr.* **1970**, 249–251].



(S)-(+)-1 (S)-(+)

A control experiment using a sample of (S)-(+)-styrene oxide (>95% ee) in a dichloromethane solution containing TPP, ethanol, and TPPO was refluxed for 48 h. Isolation of styrene oxide followed by ^{1}H NMR examination using Eu(hfc)$_3$ indicated no racemization.

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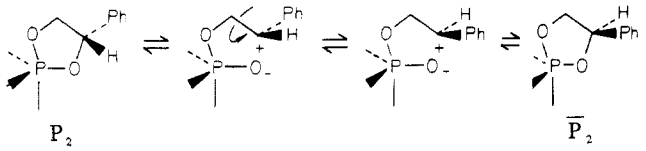
rotational freedom of the carbocation would obviously racemize P_2 (i.e., $P_2 \rightleftarrows \bar{P}_2$), and through pseudorotation, P_1 is also racemized; therefore, oxyphosphonium betaines A and B would be without stereochemical integrity as would the final product, styrene oxide.



P_2 $\bar{P}_2$

The thermodynamic facility for closure of chains to three- and five-membered rings is often quite similar, and there exists extensive documentation for a host of different reactions.[24] Because of the similarity in energetic considerations, we anticipated that the cyclodehydration of chiral 1,4-diols would show regioselectivity for tetrahydrofuran formation paralleling that observed for the conversion of chiral 1,2-diols to epoxides (assuming the R′ group is the same). We examined the reaction of (*R*)-(−)-pentane-1,4-diol (**3**) with DTPP, TPP–CCl_4–K_2CO_3, and TPP–$(C_2H_5CO_2N)_2$ and found that (*R*)-(−)-2-methyltetrahydrofuran was the predominant enantiomer reflecting largely retention of stereochemistry at C2. The percent regioselection ranged from 81–88% and is in accord with the results for formation of (*S*)-propylene oxide (vide supra).

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Registry No. **1**, 4254-15-3; **2**, 25779-13-9; **3**, 56718-04-8; DTPP, 18509-25-6; TPP, 603-35-0; CCl_4, 56-23-5; K_2CO_3, 584-08-7; $(C_2H_5COON)_2$, 1972-28-7; styrene oxide, 67253-49-0; diethyl peroxide, 628-37-5; (*S*)-(−)-ethyl lactate, 687-47-8; (*S*)-(+)-mandelic acid, 17199-29-0; glutamic acid, 56-86-0; (*S*)-(+)-propylene oxide, 16088-62-3; (*R*)-(−)-2-methyltetrahydrofuran, 63798-13-0; (*S*)-(+)-styrene oxide, 20780-54-5.

Supplementary Material Available: Full experimental details for compounds **1–3** (5 pages). Ordering information is given on any current masthead page.

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Allylboronate Synthesis. Synthesis of a β-Alkoxy Carbanion Equivalent

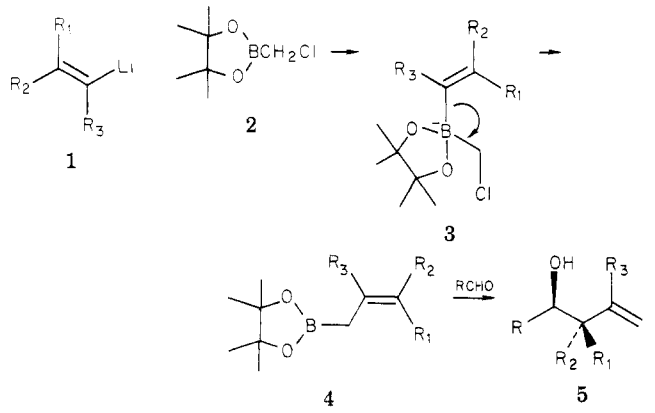
Summary: A stereospecific synthesis of allylboronates has been developed by the reaction of vinyllithium reagents with α-chloroboronic esters. This approach enables the inclusion of diverse substitution patterns as well as the inclusion of a variety of functional groups.

Sir: The isolation and structural elucidation of a diversity of biologically important propionate and acetate derived natural products from fungal and bacterial phyla has led to an intense effort in the development of methodology for the assembly of acyclic molecular substructures by a number of groups.[1]

Our interest in the macrolides and ionophores has led us to explore the application of allylboronates in their synthesis, primarily because of their known ability to condense with aldehydes in a stereospecific manner,[2] their neutrality, their low reduction potential,[3] their chemoselectivity,[4] and the potential for securing them in a geometrically homogeneous form.[5]

In general, allylboronates are most conveniently prepared by the addition of a suitable Grignard or lithium reagent to borate esters, boron trihalides, and haloborate esters[6] or by transmetalation of allyltin reagents with chloroborate esters.[7] Although these approaches are experimentally simple, they suffer from a general lack of regio- and stereospecificity as well as the inability to include leaving groups in the δ-position of the allyl Grignard or lithium reagents due to elimination. In light of the

Scheme I



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