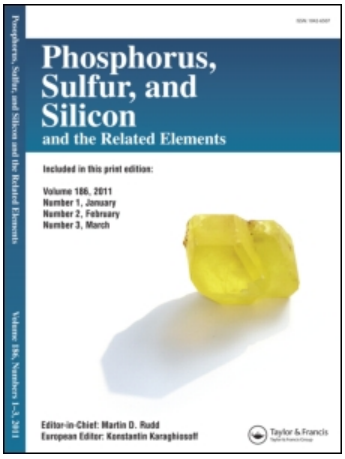

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REACTIVITY AND SYNTHETIC UTILITY OF 1,3,2λ^5-DIOXAPHOSPHOLANES

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Abstract The kinetics of Lewis acid-mediated decomposition and definitions of the synthetic applicability of 1,3,2λ^5-dioxaphospholanes for (i) the syntheses of highly-hindered epoxides, and (ii) the stereospecific functionalizati ons of stereocenters in 1,2-diol arrays are described.

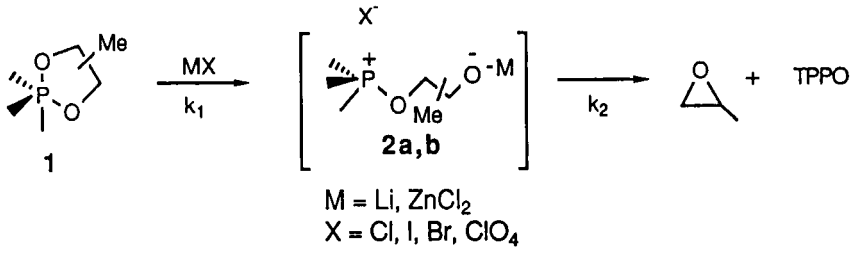
I. LEWIS ACID PROMOTED DECOMPOSITION OF 1,3,2λ^5-DIOXAPHOSPHOLANES

Transoxaphosphoranylation of mono- and di-substituted 1,2-diols with $Ph_3P(OEt)_2$ afford 1,3,2λ^5-dioxaphospholane intermediates which decompose to oxiranes in high yields. The sterically more congested, tri- and tetra-substituted 1,3,2λ^5-dioxaphospholanes require fairly strenuous conditions (80-100°C, 48 h) resulting in a diminution in the overall selectivity for epoxides and an increase in unwanted side-products.[1]

We speculated that the action of LiBr, presumably through cationic Li^+ coordination to the apical oxygen, would weaken the phosphorus-oxygen (P-O) bond and facilitate rapid formation of the requisite betaines from 1,3,2λ^5-dioxaphospholanes and ensure a smooth conversion to the epoxides.

In this light, we have studied[1,2] the kinetics attending the decomposition of 4-methyl-2,2,2-triphenyl-1,3,2λ^5-dioxaphospholane (1) in tetrahydrofuran(THF)/benzene-d_6 solution with several "cationic" species. Here, LiBr-promoted decomposition of 1 is significantly faster than via simple thermolysis. Minimal decomposition of 1 in the presence of n- $Bu_4N^+Br^-$ shows that the catalytic behavior of LiBr is associated with Li^+'s ability to enhance rupture of the P-O bond by cationic coordination. Similarly, $ZnCl_2$, a stronger Lewis acid than Li^+, is expected to promote a more dominant rate enhancement. In

fact, addition of $ZnCl_2$ to dioxaphospholane 1 at -78°C rapidly and quantitatively converts 1 to the Zn^{2+}-coordinated betaine

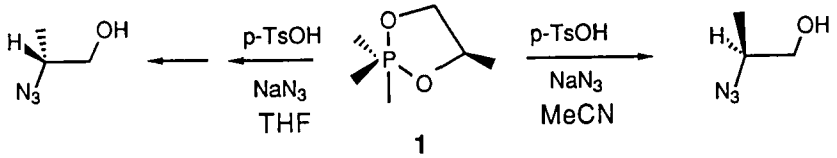


intermediates, 2a and 2b, whose identities were confirmed by ^{31}P NMR spectroscopy (δ 63.1 and 61.2 ppm). The pseudo-first order rate constant for ring opening of 1,3,2λ^5-dioxaphospholane 1 to 2a,b with $ZnCl_2$ is $k_1 = 3.1 \times 10^{-2}$ M^{-1} sec^{-1}. Decomposition of 2a,b by warming gives $k_2 = 1.2 \times 10^{-4}$ sec^{-1} at 273 K ($\Delta G^* = 20.8$ kcal/mol) for the "3-exo-tet" displacement of TPPO. The rate constant for conversion of 1 directly to epoxide in the presence of LiBr at 305 K is $k = 2.0 \times 10^{-4}$ M^{-1} sec^{-1}. With LiI as the catalyst, the rate constant increases slightly to $k = 2.7 \times 10^{-4}$ M^{-1} sec^{-1} at 305 K and finally, $LiClO_4$ causes a further rate enhancement: $k = 4.3 \times 10^{-4}$ M^{-1} sec^{-1}. Effective catalysis is a function of LiX aggregation as well as the availability of "effective cationic charge" on "Li^+" in the LiX salts. Formation of LiBr dimers in THF solvent reduces the "relative concentration" of free Li^+ cations available for catalysis as compared to monomeric LiI or $LiClO_4$.

II. STEREOSELECTIVE FUNCTIONALIZATION OF DIOXAPHOSPHOLANES

Ph_3P-benzoyl peroxide (TPP-BPO) reagent initates stereospecific benzoylation of secondary carbinol stereocenters of 1,2-diols with essentially complete inversion of stereochemistry.[3] Formation of a quintessential 1,3,2λ^5-dioxaphospholane intermediate, followed by activation of the dioxaphopholane ring through either complexation with benzoic acid or ring opening to the regioisomeric oxaphosphonium ions, followed by highly stereoselective Arbusov displacement of triphenylphosphine oxide by benzoate anion affords the C-2 benzoate.[4] Extension of this novel concept allows for insertion of different

nucleophiles at the secondary stereocenter without prior protection of the primary center. For example, oxaphospholane 1 reacts with p-TsOH/NaN_3 to afford two oxaphosphonium ions in a 1:1 ratio. In THF solvent, these ions collapse to a single tosylate diastereomer with accompanying inversion of stereochemistry. Subsequent heating of the reaction mixture containing the tosylate and NaN_3 gives the corresponding azide with the anticipated inversion of stereochemistry. Alternatively, in MeCN solvent, the regioisomeric oxaphosphonium ions are captured by the more soluble N_3^- with inversion of stereochemistry. It is apparent that highly



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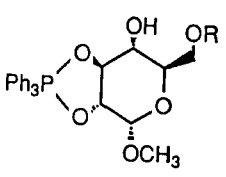
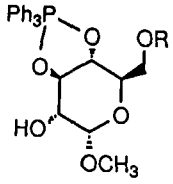
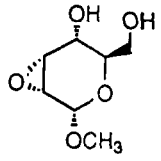
stereoselective approaches to both enantiomers is now available.[5] The synthetic utility of various epoxides having carbohydrate lineage is well established; consequently, we have explored the oxaphosphoranylation of methyl-α-D-glucopyranoside with $Ph_3P(OEt)_2$.[6] Two 1,3,2λ^5-dioxaphospholanes (R = H), 3a (^{31}P NMR δ -36.1) and 4a (δ -37.7 ppm) are formed in a kinetic ratio of 5:1. Thermal equilibration (25°C) in DMF solvent gives K_{eq} = 3.1 and ΔG° = -0.66 kcal/mol. When C-6 CH_2OR derivatives [i.e., R =-$SiPh_2{}^tBu$ and -CPh_3] are bisoxaphosphoranylated with DTPP, two 1,3,2λ^5-dioxaphospholanes for each C-6 substituted derivative [i.e., ^{31}P NMR 3b: δ -36.5; 4b: δ -38.2; 3c: δ -35.9; 4c: δ -37.8 ppm, respectively] are formed. At equilibrium (25°C), 3 predominates over 4 for R = -CPh_3 [K_{eq} = 1.5; ΔG° = -0.24 kcal/mol] and for R = -$SiPh_2{}^tBu$ [K_{eq} = 2.0; ΔG° = -0.41 kcal/mol] paralleling the diastereomer distribution for R = H. The larger ΔG° for 3b to 4b relative to 3c to 4c probably reflects the increased steric demands of the larger -$SiPh_2{}^tBu$ group over the -CPh_3. Two epoxides, methyl-2,3-anhydro-α-D-allopyranoside (5) and methyl-3,4-anhydro-α-D-galactopyranoside (6), are formed in a 1:1 ratio, respectively in DMF or toluene solvent by thermal decomposition of 1,3,2λ^5-dioxaphospholanes 3a and 4a.



3a R=H
3b R= -$SiPh_2{}^tBu$
3c R= $-CPh_3$



4a R=H
4b R= -$SiPh_2{}^tBu$
4c R= $-CPh_3$



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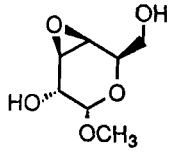

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