

Diastereoselective Condensation of Oxazaphosphites with Aliphatic and Aromatic Aldehydes

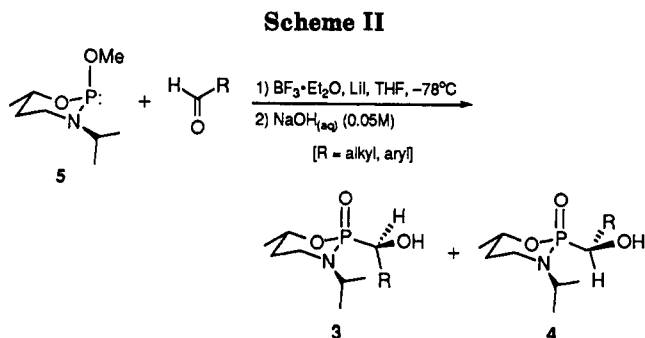
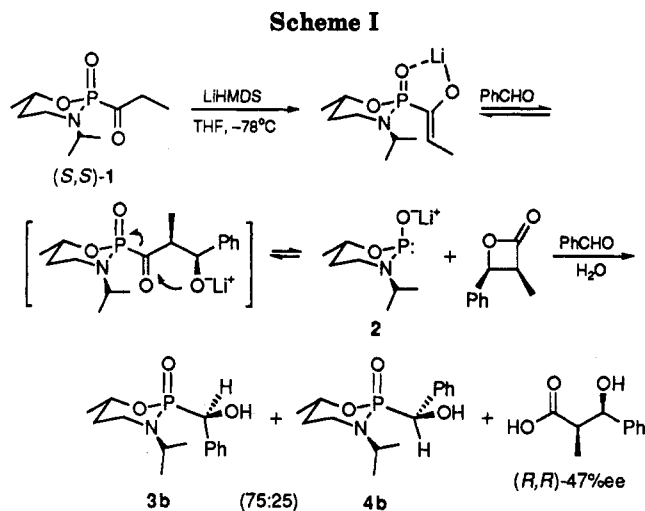
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Summary: The results of a preliminary investigation involving the condensations of diastereomeric 2-methoxy-1,3,2-oxazaphosphites (*cis*- and *trans*-5) with a variety of aldehyde-boron trifluoride etherate ($\text{BF}_3 \cdot \text{Et}_2\text{O}$) complexes to give diastereomerically-enriched mixtures of α -hydroxy-2-oxo-1,3,2-oxazaphosphorinanes (*cis*- and *trans*-3 and 4) are reported, and a mechanistic rationale consistent with the diastereofacial preference attending these reactions is proposed.

Numerous reports have shown that dialkyl trimethylsilyl phosphites¹ and dialkyl hydrogen phosphites are readily condensed with aldehydes to afford α -hydroxy phosphonates.²⁻⁴ During the course of our studies involving the aldol reaction between (*S,S*)-2-propionyl-2-oxo-1,3,2-oxazaphosphorinane (1) and benzaldehyde,^{5a} we determined that lithio oxazaphosphite 2, formed *in situ*, condensed with benzaldehyde to afford a 3:1 ratio of α -hydroxy-2-oxo-1,3,2-oxazaphosphorinane diastereomers 3b and 4b (Scheme I). The magnitude of the diastereoselection resulting from the condensation of phosphite 2 with benzaldehyde was sufficiently intriguing to merit a more intensive mechanistic study of this reaction. Specifically, we sought to (a) determine the stereochemistry of 3b or 4b by X-ray analysis and (b) define more clearly the reaction variables which would promote a highly selective, yet facile and irreversible, addition of 2-methoxy-1,3,2-oxazaphosphite 5 to an aldehyde. Phosphite 5 was selected because of its synthetic accessibility,^{5b,6} and boron



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(3) (a) Ruveda, M. A.; de Licastro, S. A. *Tetrahedron* 1972, 28, 6013.

(b) Texier-Boullet, F.; Foucaud, A. F. *Synthesis* 1982, 916.

(4) Texier-Boullet, F.; Foucaud, A. F. *Synthesis* 1982, 165.

(5) (a) Oxazaphosphite 5 is synthesized from the condensation of Cl_2POMe with the corresponding 1,3-amino alcohol in the presence of triethylamine (2 equiv) in diethyl ether solvent. After vacuum distillation, 5 was obtained as a 92:8 ratio of *trans*:*cis* isomers, where the configurational assignments were based on the ^{31}P NMR spectral shifts (*trans* is upfield) and the known axial thermodynamic preference for the $\text{P}-\text{OCH}_3$ group in the *trans* isomer. (b) Gordon, N. J.; Evans, S. A. Jr. *J. Org. Chem.*, previous communication in this issue.

(6) For convenience and clarity, only the *trans*-5 isomer is described in this manuscript; although, the *inseparable* diastereomeric mixture of 2-methoxy-1,3,2-oxazaphosphite 5 (*trans*:*cis* = 92:8) was actually used.

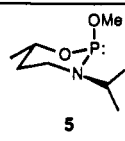
(7) Experimental Procedure. To a stirred solution of lithium iodide (147 mg, 1.10 mmol) in anhydrous THF (4.00 mL), under an argon atmosphere at -78°C , was added sequentially benzaldehyde (212 mg, 2.00 mmol), 2-methoxy-3-isopropyl-6-methyl-1,3,2-oxazaphosphite (191 mg, 1.00 mmol), and boron trifluoride etherate (156 mg, 1.10 mmol). The reaction was left for 10 min before being allowed to warm to 25°C . Aqueous NaOH (0.05 M, 4.00 mL) was then added, and after 1 h, the reaction mixture was extracted with dichloromethane (3×20 mL). The organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give α -hydroxy-2-benzyl-2-oxo-3-isopropyl-6-methyl-1,3,2-oxazaphosphorinanes 3b and 4b as a 7:3 ratio of diastereomers, respectively, in 96% yield. The major diastereoisomer 3b was isolated in homogeneous form *via* recrystallization from a tetrachloromethane/pentane solvent mixture (mp 177 – 179°C). The ^1H , ^{13}C , ^{31}P , and NMR and IR spectral data, X-ray parameters, and elemental analyses were consistent with the assigned structure.

trifluoride-complexed aldehydes provided access to a host of highly reactive carbonyl species (*vide infra*).

The reaction⁷ involving an equimolar mixture of phosphite 5 and the aldehyde in a solution of tetrahydrofuran (THF) at -78°C with LiI and $\text{BF}_3 \cdot \text{Et}_2\text{O}$ followed by treatment with aqueous NaOH gave diastereomeric α -hydroxy phosphorinanes 3b and 4b in a *ca.* 2:1 mixture (>95% overall yield; NMR spectroscopy; Scheme II). The diminished diastereoselectivity associated with the formation of 3b:4b (R = phenyl) in this latter case, as compared the *ca.* 3:1 ratio of 3b:4b obtained from the aldol reaction (*vide supra*), is probably the result of a more rapid and less discriminating reaction involving the BF_3 -complexed aldehyde and the lone pair of electrons on the phosphorus.

Overall, the results of the condensations of phosphite 5 with various BF_3 -complexed aldehydes are shown in Table I, where the major diastereomer in each case possessed the same relative configurations at the P-2 and C-6 stereogenic centers of the six-membered heterocycle. Diastereomer 3b, the major isomer arising from the reaction of phosphite 5 with benzaldehyde, was readily isolated and recrystallized to homogeneity affording crystals suitable for a determination of its X-ray crystallographic parameters.⁸ The data from the X-ray analysis showed that the phosphoryl group (*e.g.*, $\text{P}=\text{O}$) occupied the pseudoaxial array in a flattened-chair conformation

Table I. Diastereomeric Excesses of 3 Relative to 4 Obtained from the Reaction of Phosphite 5 with Aldehydes

phosphite	aldehyde	% de ^a of 3
 5	(a) <i>p</i> -Me-PhCHO	40
	(b) PhCHO	32
	(c) <i>p</i> -Cl-PhCHO	22
	(d) <i>p</i> -NO ₂ -PhCHO	4
	(e) MeCHO	8
	(f) EtCHO	12
	(g) <i>i</i> -PrCHO	16
	(h) <i>t</i> -BuCHO	18

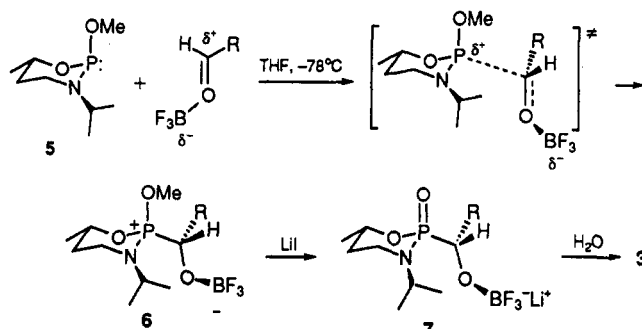
^a Determined from ³¹P and ¹H NMR spectral integration of the appropriate resonances.

and the carbinol carbon possessed the *R* configuration. From the X-ray structural analysis and the solution NMR spectral data of 3b, the stereochemical assignments of 3 and 4 were assessed on the basis of the differences in their NMR spectroscopic data using 3b as a reference.

Boron trifluoride (BF₃) forms relatively stable complexes with aromatic aldehydes⁹ and prefers an *anti* or *E* orientation about the carbonyl bond. These complexes are highly reactive and this characteristic is indicative of the strongly electropositive carbonyl carbon. In fact, the Lewis acid complexation at the carbonyl oxygen enhances the electrophilicity of the carbonyl group by simultaneously lowering the energy level of the LUMO and increasing the positive charge on the carbonyl carbon.¹⁰

Although the marginal increases in the diastereoselectivity (% de = 8–18%) appear to parallel the increase in the steric bulk of the alkyl groups in the aliphatic aldehyde series, it is surprising that the range of % de's is so low. Nevertheless, these findings imply that the preferred transition state leading to a preference for diastereomer 3 is best represented by the model in Scheme III. Here, the *R* group is vicinal to the smaller ring oxygen and the aldehydic hydrogen is proximal to the larger *N*-isopropyl group to minimize repulsive steric interactions. From an examination of molecular models, it seems likely that these vicinal relationships are not of sufficient conformational restriction to engender sizeable steric responses with progressively larger *R* groups. Finally, an antiperiplanar relationship between the —C=O—BF₃ and P—OCH₃ groups would also minimize any repulsive electrostatic interactions.

By contrast, the steric considerations are considerably less significant for the para-substituted benzaldehydes where a strong electronic influence is clearly evident. In fact, an excellent agreement ($\rho = -1.087$; $r^2 = 0.990$) is obtained if the logs of the % de's are correlated with the appropriate Hammett σ values for para-substituted ben-

Scheme III

zaldehydes. The strong influence of the para substituent on the timing of the diastereomeric transition states (or their positioning along the reaction coordinates) and hence their impact on the overall diastereoselectivity suggests that a field effect exerted by the para substituents influences the charge attending the carbonyl carbon atom. Consequently, the steric differences in the diastereomeric transition states are not easily realized with these highly reactive carbonyls. The less reactive carbonyls (*R* = CH₃) must attain a closer approach to the trivalent phosphorus for effective P—C bond formation. Under these circumstances, the steric interactions attending the two diastereomeric transition states are more pronounced, and the magnitude of the difference in these interactions is reflected in the increased levels of diastereoselectivity.

A ³¹P NMR study at -80 °C revealed that the reaction of oxazaphosphite 5 (δ 135.3) with the benzaldehyde—BF₃ complex was complete within 20 s (no reaction occurred between oxazaphosphite 5 and benzaldehyde at 25 °C in the absence of BF₃), producing two species (δ 36.7 and 37.9) which were attributed to the diastereomeric oxyphosphonium ions 6. Demethylation of phosphonium ions 6 with LiI (*in situ*) occurred with a specific rate constant of $6.54 \times 10^{-3} \text{ L mol}^{-1} \text{ s}^{-1}$ at -47 °C to afford diastereomeric borates 7 (δ 20.9 and 21.6).

A summary of the mechanistic proposal for the formation of diastereomers 3 (major isomers) is presented in Scheme III. The critical sequence that controls the diastereoselectivity is the addition step characterizing the combination of oxazaphosphite 5 with the aldehyde—BF₃ complex to give oxyphosphonium ion 6. Demethylation gives borate 7, and hydrolysis yields α -hydroxy phosphorane 3 with the same configurational history as oxyphosphonium ion 6.

In our future work, we envision using the results of these findings to evaluate and develop a more efficient oxazaphosphorus heterocycle to control chirality transfer at prochiral electrophilic centers.

Acknowledgment. We are grateful to the National Science Foundation for support of this research and to Dr. Peter White, our colleague at the University of North Carolina at Chapel Hill, for the determination of the X-ray crystallographic parameters of 3b.

Supplementary Material Available: NMR spectra and an ORTEP diagram (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(8) Interestingly, the X-ray data indicated that the heterocyclic ring was essentially planar about the O—P—N segment suggesting that delocalization of the oxygen and nitrogen lone pairs of electrons into the phosphoryl moiety might be responsible for this increase in ring planarity. X-ray crystallographic parameters for 3b have been submitted to the Cambridge Crystallographic Data Centre by the author. The coordinates can be obtained from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

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