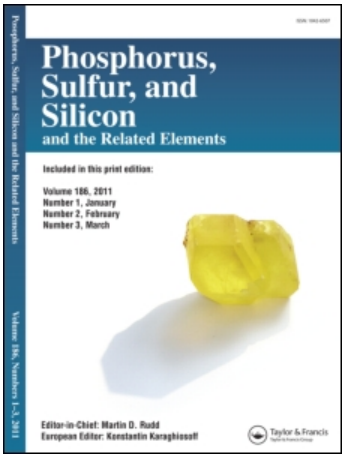

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Studies on the Base-Promoted Enantioselective Aldol Reaction between an (S,S)-2-OXO-2-Propionyl-1,3,2- Oxazaphosphorinane and Benzaldehyde

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STUDIES ON THE BASE-PROMOTED ENANTIOSELECTIVE ALDOL REACTION BETWEEN AN (S,S)-2-OXO-2-PROPIONYL-1,3,2-OXAZAPHOSPHORINANE AND BENZALDEHYDE.

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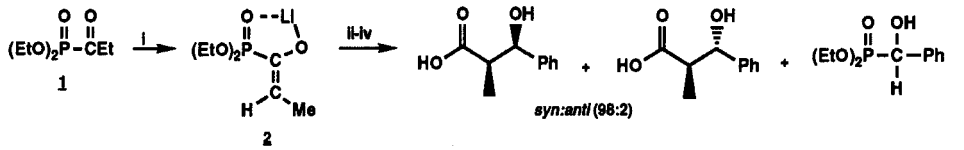
Abstract: The synthesis of an (S,S)-2-oxo-2-propionyl-1,3,2-oxazaphosphorinane, via the condensation of (*S*)-1-*N*-isopropylbutan-2-ol (**3**) with methyl dichloro phosphite (CH_3OPCl_2) followed by the Michaelis-Arbusov condensation reaction with propionyl chloride, will be described. We will also present the results of our investigations which describe the nature of the aldol reaction involving the enolate of oxazaphosphorinane **5** with benzaldehyde.

The aldol reaction has emerged as one of the most intensely studied reactions in modern organic chemistry[1] and this interest is driven by the need for, and the application of, unique β-hydroxyl carbonyl fragments in natural product synthesis.[2] Previous work[3] performed in this laboratory has demonstrated that the lithium enolate of diethyl propionyl phosphonate (**1**) undergoes highly syn diastereoselective (>98% d.e.) aldol reactions with a range of aromatic[3a] and aliphatic[3b] aldehydes (See **Scheme 1**).

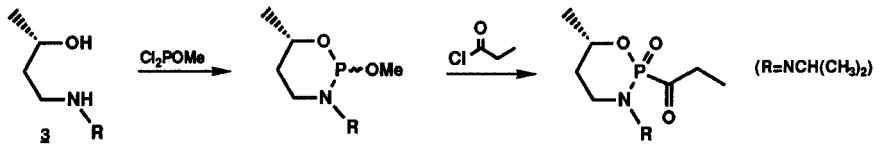
Scheme 1



Reagents and conditions: i, LiHMDS, -78°C; ii, 2.2 equiv. PhCHO, -78°C; iii, OH^-/H_2O; iv, H^+, ether extraction.

We envisioned that the chair conformation of a cyclic oxazaphosphorinane substructure (i.e. **5**) should provide good opportunities for enantiofacial bias,[4] particularly when the *N*-R substituent exhibits considerable steric bulk. Thus the (S)-1-*N*-isopropylbutan-2-ol (**3**) was envisioned as the requisite precursor for the synthesis of the required oxazaphosphorinane (**Scheme 2**).

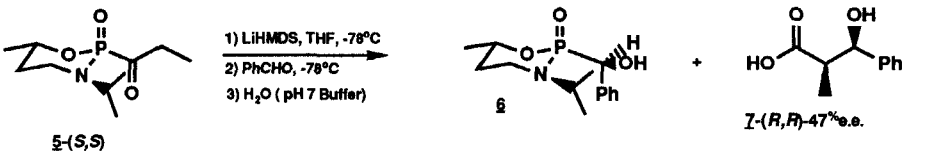
Scheme 2



Condensation of (*S*)-1-*N*-isopropylbutan-2-ol (**3**) with methyl dichlorophosphite in diethyl ether in the presence of triethylamine (2 equiv.) gave, after purification by vacuum distillation (bath temp. 90°C, 2 mm Hg), phosphite (*trans*- and *cis*-**4**) as a 92:8 ratio of diastereomers (81% yield). The major isomer was assigned as *trans*-**4** based on its higher field ^{31}P NMR resonance and known

greater thermodynamic stability.[5] The Michaelis-Arbusov reaction was performed by adding propionyl chloride (3 equiv.) dropwise to a solution of a diastereomeric mixture of phosphites **4** in dichloromethane at -78°C, which was then stirred at -13°C (ice-acetone bath) until the reaction was complete (as determined by ^{31}P NMR). This resulted in the formation of a 92:8 ratio of isomers of (*S,S*)-2-oxo-2-propionyl-1,3,2- oxazaphosphorinane (**5**) (>95% yield), the major isomer was confirmed as having the α-acyl group in the pseudoequatorial conformation from the interpretation of the X-ray structural data of the hydroxy benzyl oxazaphosphorinane(**6**) formed. The latter was formed in a 3:1 ratio of diastereomers (major isomer shown), as a trapping product during aldol reaction (**Scheme 3**).

Scheme 3



5-(*S,S*) 6 7-(*R,R*)-47%e.e.

The results of the aldol reaction between (*S,S*)-**5** and benzaldehyde are shown in **Table 1**. Entry 1(**Table 1**) shows the results obtained under standard conditions. A number of excellent reports have demonstrated that the nature of lithium enolates in solution is complicated, with indications that they exist and may even react in aggregated states;[6] consequently, the magnitude of enantioselectivity could vary depending on the degree of aggregation of the enolate. Addition of lithium salts and tetramethyl- ethylenediamine (TMEDA) have been shown to disrupt aggregates and discourage their formation. For example lithium salts can form mixed aggregates and TMEDA may complex lithium ion in a bidentate fashion leading to lower order aggregates.[7] These modifications (entries 3 and 4) led to decreases in both diastereomeric and enantiomeric selectivities. Interestingly, the addition of lithium bromide caused a substantial reduction in both diastereo- and enantio-selectivity. A decrease in solvent polarity and an increase in temperature often lead to higher order aggregates.[8] The results shown in entry 4 (**Table 1**) indicate a lower selectivity.

Table 1. The influence of various additives on the aldol reaction between *oxazaphosphorinane* 5 *and benzaldehyde.*

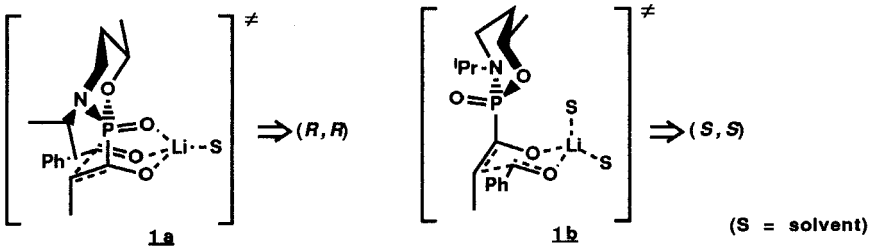
Entry	Enolate Counter-ion	Solvent	Additive	Temp.(°C)	Diastereomer [a] ratio (syn:anti)	Syn %e.e.[b]	Corrected[c] Syn %e.e.
1	Li	THF	—	-78	94:6	47	56
2	Li	THF	LiBr(1eq.)	-78	82:18	20	24
3	Li	THF	TMEDA (2eq.)	-78	90:10	30	36
4	Li	Hexane :THF	—	-22	80:20	24	29
5	Li	THF	—	-108	89:11	32	38
6	Na	THF	—	-78	78:22	18	21
7	Bu_2B	CH_2Cl_2	—	-78-0	—[d]	—[d]	—[d]

a) Determined by ^1H NMR spectroscopy.
b) Determined by ^1H NMR spectroscopic chiral shift reagent studies.
c) Corrected for isomer ratio of starting material,((*S,S*):(*S,R*)=92:8).
d) Failed to undergo aldol reaction.

These experimental findings and the fact that ^{31}P NMR spectroscopy of the lithium enolate of **5**, under a variety of conditions, is indicative of only one species at δ 24.3 ppm, strongly suggest that the aldol reactions reported here occur via a monomeric lithium enolate species. We

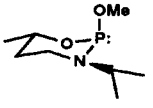
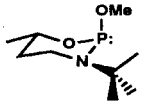
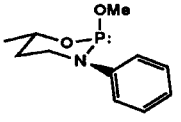
speculate that the reaction probably proceeds via a transition state similar to that described in **Figure 1a**. The disruption of this, fairly organized, cyclic chelated transition state, with added lithium salts or a chelating reagent (*e.g.* LiBr or TMEDA) or temperature increase, should encourage the release of the phosphoryl oxygen from the chelate. This would create competitive opposing enantiofacial bias, **Figure 1b**, as dipolar repulsions would be expected to control the conformation of the phosphorinane auxiliary orientation and hence result in poorer enantioselectivity. The predominance of the (R,R)-syn aldol (**7**)[9] in all cases supports the notion that the aldol reaction proceeds via a closed transition state (*e.g.* **Figure 1a**).

Figure 1



As previously mentioned, we have also obtained insight into the mechanism of benzaldehyde trapping of the lithio-phosphite species generated during the course of the aldol reaction. The addition of the achiral phosphites (*trans*- and *cis*-**4**, 92:8) to a solution of $BF_3.Et_2O$/LiI/aldehyde (1:1:2 ratio) in THF at -78°C results in diastereomeric hydroxy oxazaphosphorinanes with diastereomer excesses ranging from 4-40% for a series of aliphatic and aromatic aldehydes (see **Table 2**).

Table 2. The diastereomeric excesses from the condensations of phosphite with aryl and aliphatic aldehydes.

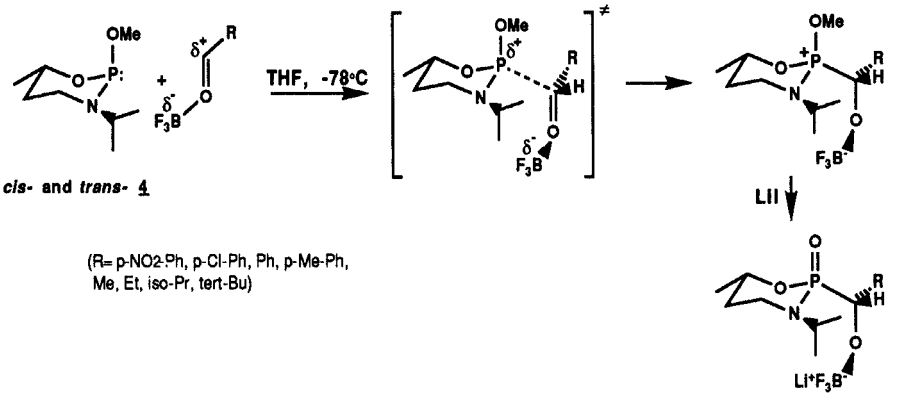
Phosphite[a]	Aldehyde	Diastereomer Excess[b]
	p-Me-PhCHO	40
	PhCHO	32
	p-Cl-PhCHO	22
	p-NO_2-PhCHO	4
	MeCHO	8
	EtCHO	12
	iso-PrCHO	16
	tert-BuCHO	18
	p-Me-PhCHO	70
	PhCHO	65
	p-Cl-PhCHO	64
	p-NO_2-PhCHO	36
	p-Me-PhCHO	43
	PhCHO	42
	p-Cl-PhCHO	42
	p-NO_2-PhCHO	42

a) Major phosphite isomer only.
b) Prefered isomer has relative configuration of **6**, determined by ^{31}P and ^{1}H NMR spectroscopy.

The major diastereomer in all cases has the same relative configuration as that obtained during the aldol reaction between (*S,S*)-2-oxo-2- propionyl-1,3,2-oxazaphosphorinane and benzaldehyde, the structure of which was unambiguously assigned from X-ray crystallographic data. An excellent

correlation with Hammett σ values[10] indicates an early transition state, the reaction proceeding as shown in **Scheme 4**. The selectivity determining step is formation of the phosphonium ion, which occurs rapidly (reaction is essentially complete after 20 s at -80°C as determined by ^{31}P NMR spectroscopy) with iodide cleavage of the methyl ether, to afford the phosphoryl-oxygen moiety. The rate constant for this latter reaction is 6.54 x10^{-3} L mol^{-1} s^{-1} at 226K.

Scheme 4



cis- **and** *trans-* **4**

(R= p-NO2-Ph, p-Cl-Ph, Ph, p-Me-Ph, Me, Et, iso-Pr, tert-Bu)

Using this model, phosphites with *N*-tert-butyl (**9**) and *N*-phenyl (**10**) substitution have been synthesized, according to known synthetic methodology, and their facial selectivities determined for the same series of aromatic aldehydes (see **Table 2**). The results for the *N*-phenyl phosphite (**10**) were unexpected and are undoubtably due to an electronic effect, the nature of which we are currently investigating. The increase in selectivity for the sterically more encumbered *N*-tert-butyl phosphite (**9**) is as expected, and we are currently synthesizing the analogous chiral propionyl oxazaphosphorinane for evaluation in the aldol reaction.

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8) Footnotes 22, 25, 27, 30, 42(c), 94, 125 and 126 in reference 10).
9) Chirality determined by its optical rotation, this and all analyses consistent with the literature, see reference 2 and; W. Oppolzer, J.Blagg, I. Rodriguez and E. Walther, *J. Am. Chem. Soc.*, **112**, 2767 (1990), and references therein.
10) From O. Exner published in; "Similarity Models in Organic Chemistry, Biochemistry, and Related Fields", R.I. Zalewski, T.M. Krygowski, J. Shorter, Eds.; Elsevier: pp 79, Amsterdam (1991).