Synthesis and Enantioselective Aldol Reaction of a Chiral 2-Oxo-2-propionyl-1,3,2-oxazaphosphorinane

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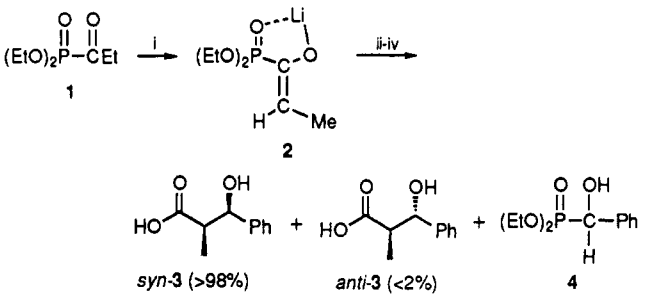
Summary: The synthesis of *cis*- and *trans*-2-oxo-2-propionyl-1,3,2-oxazaphosphorinane (*cis*- and *trans*-**7**), via the condensation of (*S*)-*N*-isopropyl-4-aminobutan-2-ol (**5**) with methyl dichlorophosphite (CH_3OPCl_2), followed by the Michaelis–Arbusov coupling with propionyl chloride is described, and our preliminary research involving metal-directed diastereo- and enantioselective aldol reactions between the lithio enolate of *trans*-oxazaphosphorinane **7** and benzaldehyde are also discussed.

The aldol reaction has emerged as one of the most intensely studied reactions in modern organic chemistry within the last decade, and the enhancement of metal-directed diastereo- and enantiofacial selectivities within β-hydroxyl carbonyl fragments has commanded the bulk of the research emphasis.[1,2] Previous work[3] performed in this laboratory has demonstrated that lithium enolate **2** from diethyl propionyl phosphonate (**1**) exhibits high *syn* diastereoselectivity in aldol reactions with a range of aromatic[3a] and aliphatic[3b] aldehydes (see Scheme I for an example).

Steric repulsions caused by the close proximity between the vinyl methyl and the phosphoryl moiety in the *E*-isomer would encourage a *Z*-enolate diastereomer preference in lithio enolate **2**. Furthermore, the *s-cis* rotamer benefits from the strong chelation of the enolate lithium atom with the proximal phosphoryl oxygen atom. The aldol reaction between lithium enolate **2** [from the lithiation of α-acyl phosphonate **1** with lithium hexamethyldisilazane (LiHMDS)] and benzaldehyde led to excellent *syn* diastereoselection (>98 % de) and this result was adequately rationalized by a "closed transition state" model (Figure 1).[1a,3]

The design and placement of elements of chirality proximal to the phosphoryl group to induce an enantiofacial bias in the transition state attending the carbon–carbon bond formation process was the primary objective. We envisioned that the six-membered ring possessing a chair conformation characterized by the oxazaphosphorinane substructure (*i.e.*, **7**) would provide excellent opportunities for enantiofacial bias, particularly when the *N*-R substituent possessed considerable steric bulk. Thus, (*S*)-*N*-isopropyl-4-aminobutan-2-ol (**5**) was envisioned as the appropriate precursor for the synthesis of the required

Scheme I[a]



[a] Reagents and conditions: (i) LiHMDS, −78 °C; (ii) 2.2 equiv of PhCHO, −78 °C; (iii) OH^-/H_2O; (iv) H^+, ether extraction.

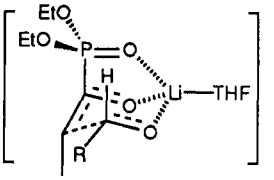
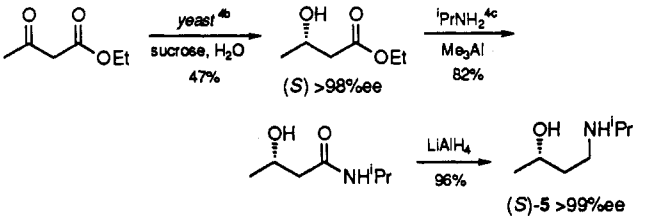


Figure 1.

Scheme II



oxazaphosphorinane (Scheme III), and its enantiomeric homogeneity was secured from a sequence of reactions beginning with an enzymatic reduction of ethyl acetoacetate employing bakers' yeast/sucrose formulation (Scheme II).[4]

Condensation of (*S*)-aminol **5** with methyl dichlorophosphite in diethyl ether solvent (2 equiv of triethylamine) gave, after purification by vacuum distillation (bath temperature, 90 °C, 2 mmHg), *trans*- and *cis*-2-methoxy-3-isopropyl-6-methyl-1,3,2-oxazaphosphorinanes (**6**) as a 92:8 ratio of diastereomers (81% yield). The major isomer was assigned *trans*-**6** on the basis of its higher-field ^{31}P NMR resonance (*trans*-**6**; $CDCl_3$, δ 135.3; *cis*-**6**, $CDCl_3$, δ 137.2).[5] From our experience, thermal equilibrations of analogous dioxaphosphorinanes occur during distillation and the preference for the *trans* isomer is consistent with the thermodynamic driving force favoring an axial P–OMe

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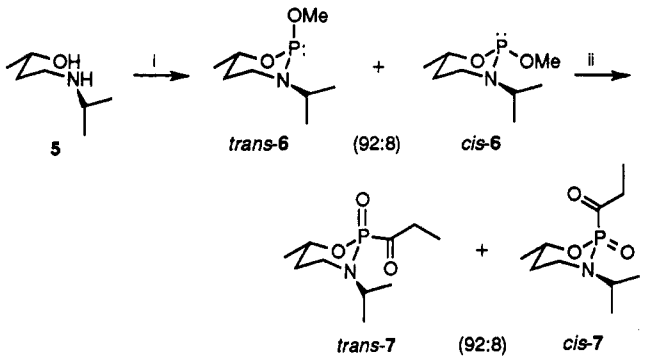
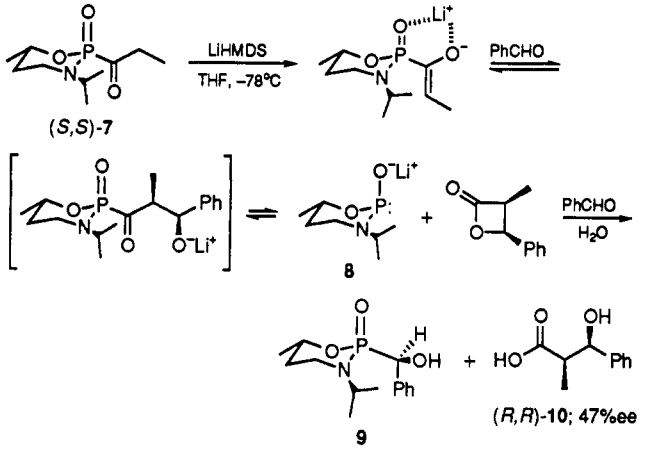
Scheme III[a]



[a] Reagents and conditions: (i) Cl_2POMe, Et_3N (2 equiv), Et_2O, −10 °C; (ii) $CH_3CH_2C(O)Cl$, CH_2Cl_2, −78 °C.

Scheme IV



group.[6] The Michaelis–Arbusov reaction was performed by adding propionyl chloride (3 equiv) dropwise to a solution of the diastereomeric mixture of oxazaphosphorinanes **6** in dichloromethane solvent at −78 °C. The reaction mixture was warmed to −13°C (ice–acetone bath) and then stirred until the condensation reaction was complete (^{31}P NMR). A 92:8 mixture of *trans*- and *cis*-2-oxo-2-propionyl-1,3,2-oxazaphosphorinanes **7** was obtained in >95% yield. The major diastereomer was assigned *trans* assuming that the Michaelis–Arbusov reaction was stereospecific.[7] Our stereochemical assignments were confirmed by the X-ray structural parameters obtained for the hydroxy benzyl oxazaphosphorinane **9**. During the aldol reaction, the diastereomers of **9** were formed in a 3:1 ratio (major isomer shown) *via* benzaldehyde trapping of the lithio oxazaphosphite **8** (Scheme IV).[8] Since benzyl oxazaphosphorinanes **9** differ in configuration *only* at the new carbinol stereogenic center, we conclude that the configurational integrity at the phosphorus atom was maintained throughout the entire sequence of reactions (Scheme IV).

The results of the aldol reaction between (*S,S*)-**7** and benzaldehyde are summarized in Table 1. Entry 1 shows the results obtained under standard conditions (*i.e.*, THF solvent, −78 °C). A number of excellent reports have

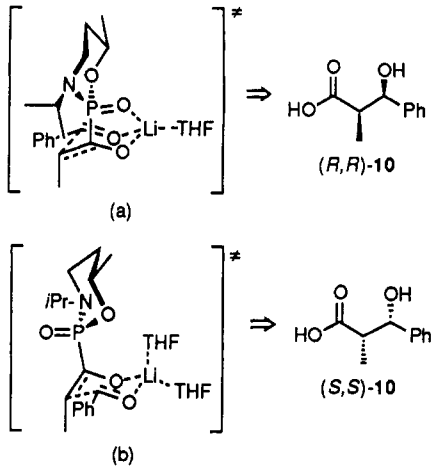


Figure 2.

demonstrated that the compositional nature of lithium enolates in solution is complex and that some lithium enolates may react from within aggregate arrays which are themselves participants in dynamic equilibration;[9] consequently, the magnitude of the enantioselection may be dependent on the degree(s) of aggregation of the lithium enolate. Lithium salts (*i.e.*, LiX) and tetramethylethylenediamine (TMEDA) have been shown to undermine the stability of the higher-ordered aggregates[9] through LiX "interaggregate exchange" to form "mixed aggregates" and through TMEDA competition for the "aggregated lithium cations" using bidentate chelation.[10] Thus, the presence of LiX or TMEDA was intended to disrupt the aggregate structure(s), and promote more of the "monomeric enolate" (*i.e.*, lithio enolate **2**). In practice, the presence of LiBr or TMEDA (entries 2 and 3, Table I) actually led to *decreases* in both diastereomeric and enantiomeric selectivities.

A decrease in solvent polarity coupled with higher reaction temperatures often leads to the formation of higher-order aggregates.[11] Assuming that these expectations are valid, the results in entry 4 (Table I) show that both diastereo- and enantiofacial selectivities are significantlly diminished. The most surprising result, for which we have no plausible explanation, is that the selectivity decreases with a decrease in temperature (entry 5,Table I). The lower selectivity observed in the experiment involving the sodium cation (entry 6, Table I) seemed reasonable on the basis of the greater sodium to enolate oxygen bond length, affording a structurally-less rigid transition state, and reducing the impact of the steric interactions which are responsible for enantiofacial selection.[1a] The dibutylboryl enolate (entry 7, Table I) simply failed to react with benzaldehyde because of the stablility of the enolate–phosphoryl boron complex, and the absence of a potential coordination site on tetracoordinated boron.[1b]

These early experimental findings and the fact that according to ^{31}P NMR spectroscopy, the lithium enolate of **7**, under a variety of conditions, is observed as a single

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Table I. Influence of Various Additives on the Aldol Reaction between Oxazaphosphorinane 7 and Benzaldehyde

entry	enolate counterion	solvent	additive	temp (°C)	diastereomer[a] ratio (syn:anti)	syn % ee[b]	corrected[c] Syn % ee
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.

resonance (δ 24.3), suggest that the aldol reactions reported here probably occur via a *monomeric* lithium enolate species. We speculate that the reaction probably proceeds via a transition state similar to that described in Figure 2a. The disruption of chelated enolate **2** and/or the proposed, cyclic chelated transition state, with added lithium salts or a chelating reagent (*e.g.* LiBr or TMEDA) or by a temperature increase, would encourage the release of the phosphoryl oxygen from both chelated structures. Competitive and opposing enantiofacial bias (Figure 2b) could then occur as dipolar repulsions initiate rotamer control of the 2-oxophosphorinane auxiliary. The overall result is a diminished diastereo- and enantioselective aldol reaction. However, the predominance of the (*R*,*R*)-syn aldol **10**[12] in all cases supports the notion that this particular aldol reaction prefers a closed transition state (*e.g.* Figure 2a).

Further work designed to synthetically modify the "phosphorus-based" chiral auxillary to increase the selectivities is currently in progress.

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Supplementary Material Available: Characterization of all new compounds (**6**, **7** and **9**) as well as their NMR spectra and an ORTEP diagram (11 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.

(12) The chirality was determined by examining the sign of the optical rotation of the sample. All analytical data were consistent with those reported in the literature, see ref 2, Oppolzer, W.; Blagg, J.; Ridriguez, I.; Walther, E. *J. Am. Chem. Soc.* **1990**, *112*, 2767 and references cited therein.