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The Enantioselective Addition of Dialkylphosphites to Aldehydes: Catalysis by a Lanthanum Binaphthoxide Complex

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Abstract: The enantioselective addition of dialkylphosphites to aldehydes was catalyzed by a lanthanum (*R*)-binaphthoxide complex to give (*S*)-hydroxy phosphonates in good yield and modest enantioselectivity.

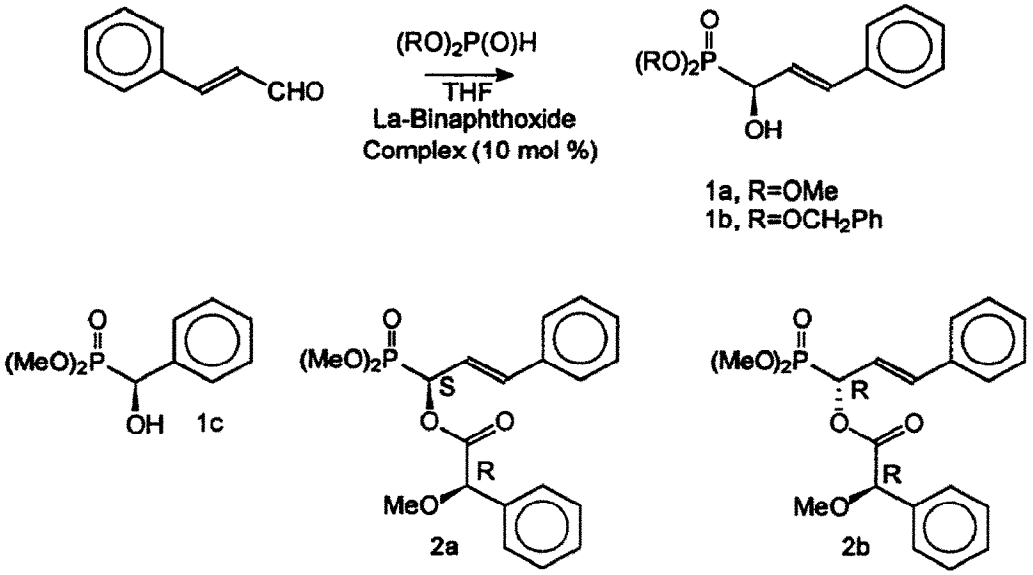
α-Hydroxy phosphoryl compounds (phosphonates and phosphonic acids) are biologically active and have been shown to inhibit enzymes such as renin,[1] EPSP synthase,[2] and HIV protease.[3] In addition, α-hydroxy-phosphonates are useful intermediates in the synthesis of other α-substituted phosphonates and phosphonic acids.[4] The absolute configuration at the α-position in substituted phosphonic acids was shown to be important for biological activity.[5] Allylic α-hydroxy phosphonates serve as precursors, via 1,3 interchange of functionality,[6] for γ-substituted vinyl phosphonates and phosphonic acids. γ-Amino phosphonic acids are also biologically active,[7] and are accessible from allylic α-hydroxy phosphonates by reactions known to preserve stereochemistry.[6] In contrast to the more extensively studied α-amino phosphoryl compounds,[8] chiral, non-racemic hydroxy phosphoryl compounds have only recently begun to receive attention.[9]

As part of our ongoing program[10] aimed at developing phosphorus reagents for enantioselective synthesis, we recently[11] began to explore chiral catalysis in the Pudovik reaction (the addition of dialkylphosphites to aldehydes). The report by Shibasaki and coworkers on the application of chiral lanthanide catalysts[12] to enantioselective nitroaldol reactions caught our attention since this catalyst system appeared to have properties compatible with the Pudovik reaction. This conclusion was also arrived at independently by Shibuya *et. al.*.[13]

Our interest in allylic hydroxy phosphonates led us to study the reaction of dimethylphosphite with cinnamaldehyde. A solution of catalyst was prepared from lithium (*R*) binaphthoxide and $LaCl_3$ according to the published procedure.[12] Addition of the catalyst solution (10 mol%) in THF to a solution of dimethylphosphite (5 eq.) and cinnamaldehyde in THF at -70°C gave, after 7 hours, the scalemic hydroxy phosphonate **1a** in 73% isolated yield.[14] The phosphonate **1a** had $[\alpha]_D$ -4.5° and showed a negative cotton effect at 320 nm. Formation of the mandelate ester[15] gave two diastereoisomeric mandelates (ratio 2.4:1 by ^1H nmr, 41% ee) which were separated by chromatography on silica gel. The major diastereoisomer **2a**

(less polar) was an oil, and the minor diastereoisomer **2b** (more polar) was a colorless crystalline solid. The X-ray structure[16] (Figure 1) showed that the minor isomer **2b** was the *R,R* diastereoisomer and therefore demonstrating that the (*R*) binaphthoxide complex is selective for the (*S*) hydroxy phosphonate. The hydroxy phosphonate **1a** enantiomers were separated by HPLC on a chiral stationary phase.[17] HPLC analysis of the scalemic phosphonate **1a** gave two peaks eluting at 7.0 mins (R isomer) and 10.8 mins (S isomer) in a ratio of 1:2.4 respectively, confirming the enantiomeric excess as 41%.

Scheme 1



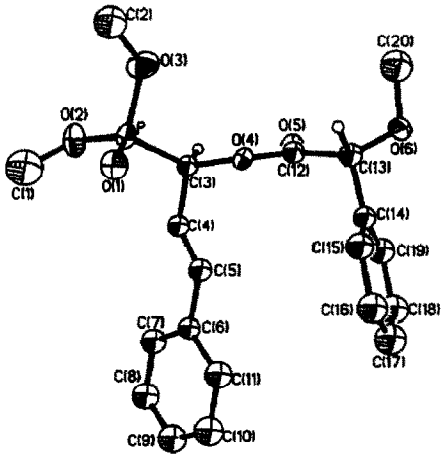


Figure 1: The molecular structure (projection plot) of mandelate 2b shown with 50% probability ellipsoids. Due to the lack of observed reflections, positional and isotropic thermal parameters were refined for the hydrogens atoms on the symmetric carbon atoms, C3 and C13, only.

We have observed some variation in ee between catalyst batches. Addition of dimethylphosphite to cinnamaldehyde (-65°C, 7 hrs.,) using catalyst (10 mol%) prepared on a larger scale resulted in a reduced ee (33%).[18] All subsequent experiments were performed using this batch of catalyst (Table 1). Reactions run at temperatures between -75 and -25°C showed little variation in enantioselectivity, although temperatures above -15°C gave reduced selectivity. Experiments performed with less than 10 mol% catalyst (1 and 0.1 mol%) failed to produce any significant quantity of hydroxy phosphonate. However, the amount of phosphite used could be successfully reduced (entries 5 and 6). Optimum conditions are -45°C with 2.5 eq. of phosphite and 10 mol% catalyst for 3 to 7 hours.

Table I. Addition of Dimethylphosphite to Cinnamaldehyde

Entry	Time (Hrs.)	Temp. (°C)	Equivs. of phosphite	Yield %	Ee %
1	7	-65	5	76	33
2	7	-45	5	87	27
3	4	-25	5	100	31
4	2.25	+5	5	98	9
5	3	-15	2.5	90	8
6	4	-15	1.2	51	6

Reactions were performed using 10 mol% catalyst and 2mmol of aldehyde in a total reaction volume of 5ml of THF.

A control experiment employing 10 mol% of lithium binaphthoxide, without $LaCl_3$, resulted in the rapid formation (2 hrs.) of racemic phosphonate **1a** (76%). The sterically larger dibenzylphosphite (2.5 eq.) was reacted with cinnamaldehyde (-45°C, 3 hrs.) to give the hydroxy phosphonate **1b** (88% isolated yield, 32% ee). Dibenzylphosphite is apparently more reactive under these reaction conditions. Reaction of dimethylphosphite (5 eq.) with benzaldehyde (at -45°C, 5 hrs.) gave phosphonate **1c** in 58% yield and 28% ee. In comparison, Shibuya *et. al.* reported that the reaction (20 mol% catalyst, -40°C, 15 hrs.) of diethylphosphite and benzaldehyde gives a 98% yield with an ee of 20%. Recrystallization of the phosphonates **1a-c** gave crystals with reduced ee, and phosphonate recovered from the mother liquor with enhanced ee (33% to 38% for **1b**), indicating preferential crystallization as the racemate.

In summary, we have demonstrated the potential of chiral lanthanum complexes for asymmetric catalysis in the addition of dialkylphosphites to aldehydes.

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14. The hydroxy phosphonates **1a-c** gave nmr spectra identical to racemic standards. Racemic **1a** and **1c** Texier-Boullet, F.; Foucaud, A. *Synthesis*, **1982**, 165; (*S*)-**1a** $[a]_D$ -23.6° (c=2.74 $CHCl_3$), Blazis, V.B.; Koeller, K.J.; Rath, N.P.; Spilling, C.D. manuscript in preparation; (*S*)-**1c** see reference 9e. Satisfactory spectroscopic data and elemental analysis was obtained for all new compounds.
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16. Slow diffusion of hexane into an ethyl acetate solution gave crystals, m.p. 87-88 °C, suitable for X-ray diffraction analysis. The absolute configuration was established using Roger's η test. Final cell parameters are as follows: a=5.763(2), b=10.006(4), c=17.981(7) Å. The structure was solved and successfully refined in monoclinic space group $P2_1$. Full details will be reported elsewhere.
17. Chiralpak AS column; EtOH-hexanes, 2:8; 1 ml/min, detection at 254nm.
18. The initial batch of catalyst was prepared on 1 mmol scale, an additional batch on 5 mmol scale, both according to reference 12. NaOH was used as the hydroxide source.

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