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Enantioselective Synthesis of α-Hydroxy Phosphonates Using the LaLi3tris(binaphthoxide) Catalyst (LLB), Prepared by an Improved Method

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Abstract: LaLi3tris(binaphthoxide) catalyst (LLB), which is prepared from $LaCl_3 \cdot 7H_2O$ (1 mol equiv), (*R*)- or (*S*)-BINOL dilithium salt (2.7 mol equiv), and NaO-*t*-Bu (0.3 mol equiv), is effective for the hydrophosphonylation of various aldehydes to give desired α-hydroxyphosphonates in up to 95% ee (88% yield). It is also noteworthy that with slow addition of the aldehydes the enantiomeric excesses of the products were increased. © 1997 Elsevier Science Ltd.

In recent years α-hydroxy phosphonates have attracted much attention due to their wide ranging biological activity[1] and their usefulness as synthetic intermediates for other biologically important α-substituted phosphoryl compounds.[2] Although the biological activities of α-substituted phosphoryl compounds depend on their absolute configuration,[3] syntheses of optically active phosphoryl compounds have only recently begun to be studied in detail.[4] Shibuya *et al.* and Spilling *et al.* have independently reported[5a,5b] enantioselective hydrophosphonylation of aldehydes using the $LaLi_3$tris(binaphthoxide) catalyst (LLB), prepared from lanthanum trichloride by the method we had previously reported for catalytic enantioselective nitroaldol reactions.[6] LLB can be prepared using either lanthanum trichloride[6a,6b] or a lanthanum alkoxide[6c] as the lanthanum source, and utilized as an efficient catalyst for nitroaldol reactions using nitromethane. However, in the course of our study of diastereoselective and enantioselective nitroaldol reactions using less reactive nitroalkanes,[6h] much lower efficiency was observed compared to that for La(O-*i*-Pr)$_3$ derived catalyst when anhydrous and/or hydrated lanthanum trichloride derived LLB was used. Moreover, quite recently we have succeeded in developing a new practical method for preparing more potent LLB, starting from $LaCl_3 \cdot 7H_2O$.[7] Thus, we reinvestigated the use of LLB as a catalyst in enantioselective hydrophosphonylation of aldehydes. We report here an efficient hydrophosphonylation of aldehydes using the LLB catalyst prepared under the best reaction conditions.

Improved conditions for the preparation of LLB have recently been determined, involving the mixing of inexpensive $LaCl_3 \cdot 7H_2O$ (1 mol equiv), (*R*)- or (*S*)-BINOL dilithium salt (2.7 mol equiv), and NaO-*t*-Bu (0.3 mol equiv) in THF at 50 °C.[7] In the presence of 10 mol % of LLB prepared by this method, the hydrophosphonylation of benzaldehyde (**1**) and cinnamaldehyde (**13**) with 1.3 equiv of dimethyl phosphite in THF at -40 °C gave the corresponding α-hydroxy phosphonates **2** and **14** in 76% ee (79% yield) and 72% ee (78% yield) respectively.[8] Shibuya *et al.* and Spilling *et al.* had reported that hydrophosphonylation of benzaldehyde using LLB prepared by the previous method gave the corresponding α-hydroxy phosphonates in less than 30% ee under similar conditions to our own.[5a,5b] As hoped, La(O-*i*-Pr)$_3$ derived LLB was found to give very similar selectivities to those described above.[9] The following results are also noteworthy. Firstly when using slow addition of the aldehydes the enantiomeric excesses of both **2** and **14** at -40 °C were increased to 83% ee (73% yield) and 79% ee (88% yield) respectively. Secondly, as a solvent, THF gave the best results in respect of the optical purity of **2** (cf.: toluene: 4% ee (*R*); dichloromethane: 16% ee (*S*); Et_2O: 4% ee (*S*), and DMF: 7% ee (*S*)).

With regard to hydrophosphonylation, we have reported analogous catalytic asymmetric hydrophosphonylations of aldehydes[10] and imines[11a,11b] using two other types of heterobimetallic catalysts, AlLibis(binaphthoxide) complex (ALB)[10,12] and LaK_3tris(binaphthoxide) complex (LPB),[11a,11b] respectively. The ALB-catalyzed hydrophosphonylation of aldehydes proceeds efficiently when α,β-unsaturated and especially aromatic aldehydes are utilized as the substrate, although the reactions proceed rather slowly. However, LLB catalyzed reactions proceeded very smoothly even at -78 °C. Representative results are summarized in Table 1 with a comparison of the results obtained by using ALB as an asymmetric catalyst. As shown in entries 5 to 12, for aromatic aldehydes of low reactivity and almost all aliphatic aldehydes LLB gave better results than those obtained with ALB.[13] For saturated aldehydes, hexanal (**19**) for example, the corresponding α-hydroxy phosphonate **20** was obtained in 61% ee and 88% yield by using LLB. In this case ALB catalyst gave **20** only in 16% ee. In the case of diastereoselective and enantioselective nitroaldol reactions, we have reported that introduction of trialkylsilylethynyl substituents to the 6- and 6'-positions of BINOL is an effective means of obtaining higher *syn*- and enantio-selectivity.[6h] However, using $LaLi_3$tris(6,6'-bis(trimethylsilylethynyl)binaphthoxide) (LLB*) as a catalyst, hydrophosphonylation of aldehydes proceeded very slowly and no improvement in optical purities and chemical yields was observed. Although the optical purity of α-hydroxy phosphonates from saturated aldehydes was not satisfactory, the crystalline nature of α-hydroxy phosphonic acids should give a reasonable chance of obtaining the products in an optically pure form by recrystallization. A typical result using LLB can also be seen for the reaction of *p*-dimethylaminobenzaldehyde (**11**). Although the hydrophosphonylation of **11** did not proceed at -40 °C when using ALB as a catalyst, a very high yield and an excellent enantiomeric excess were obtained when using LLB, even without slow addition of **11**. From the results mentioned above, the effects of slow addition of the aldehydes on the enantioselection can best be explained as follows. As we have previously reported, heterobimetallic catalysts such as LLB are believed to activate both nucleophiles and electrophiles.[14] For the hydrophosphonylation of comparatively unreactive aldehydes the activated phosphite can react only with aldehydes which are pre-coordinated to lanthanum (favorable route (A) in Figure 1). However, in the case of reactive aldehydes such as **1**, the Li-activated phosphite may be able to undergo a competing reaction with *unactivated* aldehyde (less favorable route (B) in Figure 1). If such aldehydes are added in one portion, the ee of the product will thus be reduced. Slow addition of aldehyde, in contrast, has the effect of maximizing the ratio of activated to unactivated aldehyde present in solution, by allowing time for the catalytic cycle to complete and regenerate the catalyst, thereby facilitating aldehyde activation. Reactive aldehydes should, therefore, be added slowly in order to avoid the side reaction which proceeds without activation of the aldehyde by LLB.

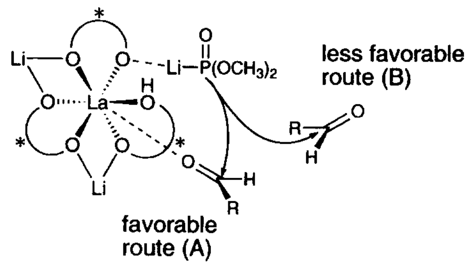
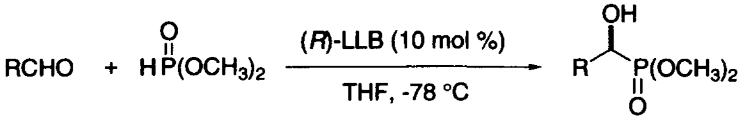
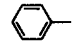
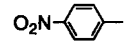
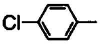
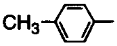
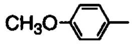
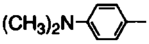
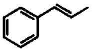
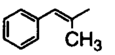


Figure 1. Proposed Mechanism for the Asymmetric Hydrophosphonylation Catalyzed by LLB.

Table 1. Catalytic Asymmetric Hydrophosphonylation of Aldehydes Catalyzed by LLB



entry	aldehyde	α-hydroxy phosphonate	R	LLB (-78 °C)		cf. ALB (-40 °C)$^{a, b}$	
				time (h)	yield (%) (ee (%))	time (h)	yield (%) (ee (%))
1	**1**	**2**		8	88 (79)	51	95 (90)
2	**3**	**4**		12	85 (36)	40	85 (71)
3	**5**	**6**		8	80(63)	38	80(83)
4	**7**	**8**		7	93 (78)	92	82 (86)
5	**9**	**10**		9	83 (88)^b	115	88 (78)
6	**9**	**10**		8	87 (93)	no reaction	
7	**11**	**12**		12	88 (95)^b		
8	**11**	**12**		12	80 (95)		
9	**13**	**14**		8	90 (84)	83	85 (82)
10	**15**	**16**		8	94 (92)	61	47 (56)
11	**17**	**18**		8	63 (75)	39	53 (55)
12	**19**	**20**		8	88 (61)	41	95 (16)

a) See, reference 10. b) Aldehyde was added at one portion. See, reference 13.

The general procedure is as follows: To a solution of LLB in THF[7] (1.0 mL, 0.03 M) was added dimethyl phosphite (36 µL, 0.39 mmol) at room temperature. After being stirred for 1 min, the solution was cooled to -78 °C and stirred for an additional 20 min. To this solution was added dropwise a THF solution of aldehyde (**15**) (42 µL in 1.0 mL of THF) using syringe pump over a period of 6 h then the reaction mixture was additionally stirred for 2 h at the same temperature. Reaction mixture was treated with 1 N HCl and extracted with EtOAc. Purification by flash chromatography (SiO_2, 20 % acetone/hexane) gave the α-hydroxy phosphonate.

In conclusion, LLB prepared by an improved method was shown to be an effective catalyst for the hydrophosphonylation of various aldehydes. LLB catalyzed hydrophosphonylation of aromatic aldehydes of low reactivity, and of almost all aliphatic aldehydes gave better results than those obtained using ALB. LLB and ALB can thus be used in a complementary manner for the hydrophosphonylation of aldehydes.

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7. Improved method for LLB from $LaCl_3 \cdot 7H_2O$ is as follows: To a solution of (*R*)-binaphthol (6.49 g, 22.7 mmol, dried at 50 °C for 2 h under reduced pressure) in THF (119 mL) was added 1.60 N BuLi (28.4 mL, 45.4 mmol) under Ar at 0 °C. A suspension of $LaCl_3 \cdot 7H_2O$ (3.12 g, 8.40 mmol) in THF (100 mL) was sonicated for 30 min at room temperature. To this suspension was then added the above-prepared solution of dilithium binaphthoxide and 0.52 N NaO-*t*-Bu in THF (4.85 mL, 2.52 mmol), dropwise at room temperature. After being stirred vigorously overnight at room temperature and then for 48 h at 50 °C, the reaction mixture was allowed to stand at room temperature. The resulting supernatant was used as an asymmetric catalyst (0.03 M). Sasai, H.; Watanabe, S.; Shibasaki, M. *Enantiomer*, in press.
8. The absolute configurations of the products except for **12** were determined by the Mosher method.
9. $La(O\text{-}i\text{-}Pr)_3$ derived LLB gave **2** in 45% ee (83% yield) even at -78 °C with a slow addition of **1**. The optical purity of **2** was increased (74% ee, 88% yield) when pumping dried LLB, all the solvent of LLB was removed by pumping up and then redissolved in THF, was utilized as a catalyst.
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14. For the discussion of the multifunctional activities of heterobimetallic asymmetric catalysts, see: Sasai, H.; Arai, T.; Satow, Y.; Houk, K. N.; Shibasaki, M. *J. Am. Chem. Soc.* **1995**, *117*, 6194-6198. See, also references 6h and 12a.

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