Catalytic Asymmetric Synthesis of α-Hydroxy Phosphonates Using the Al−Li−BINOL Complex

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It is well known that α-hydroxy phosphonates and phosphonic acids inhibit enzymes such as renin, EPSP synthase, and HIV protease.[1] Moreover, other biologically significant α-substituted phosphonates and phosphonic acids are readily obtainable starting with α-hydroxy phosphonates.[2] Bioactive γ-amino phosphonic acids as well as γ-substituted vinyl phosphonates and phosphonic acids can also be obtained from allylic α-hydroxy phosphonates through a 1,3-interchange of functionality.[3] It is not surprising that the absolute configuration of these phosphoryl compounds influences their biological properties.[4] However, the synthesis of optically active phosphoryl compounds has only recently begun to receive attention.[5] In this paper, we report the catalytic asymmetric synthesis of α-hydroxy phosphonates using the Al−Li−BINOL complex (ALB),[6] a heterobimetallic multifunctional asymmetric catalyst we developed.

We recently reported the first example of an efficient catalytic asymmetric hydrophosphonylation of imines promoted by the La−K−BINOL complex (LPB).[7] As an extension of this research, we investigated the catalytic asymmetric hydrophosphonylation of aldehydes promoted by a heterobimetallic asymmetric catalyst. When we started this research, Shibuya and Spilling had independently reported[8] catalytic asymmetric hydrophosphonylations of aldehydes using the La−Li−BINOL complex (LLB). For example, using benzaldehyde (**1**) as a starting substrate, Shibuya reported the formation of **2** (98%, 20% ee, 20 mol % LLB), and Spilling announced the formation of **3** (58%, 28% ee, 10 mol % LLB). To improve on their results, we first attempted a catalytic asymmetric hydrophosphonylation of **1** using either LPB or the La−Na−BINOL complex (LSB). However, the enantiomeric excess of **3** was only 2% ee (LPB) and 32% ee (LSB). After several attempts, treatment of **1** with 1.1 equiv of dimethyl phosphite in THF containing 10 mol % ALB,[6] another heterobimetallic asymmetric catalyst, at −40 °C for 25 h gave **3** with 65% ee in 68% yield.[9] With this more satisfactory result, solvent effects were next examined in detail. We eventually found that exposure of **1** to dimethyl phosphite (1 equiv) in toluene containing 10 mol % ALB at −40 °C for 51 h afforded **3** with 85% ee in 90% yield.[10,11] The use of a slight excess of **1** (1.2 equiv) gave rise to **3** with 90% ee in 95% yield (9 mol % of ALB). To the best of our knowledge, this is the highest enantiomeric excess in a catalytic asymmetric hydrophosphonylation of **1**. Using the procedure described above, several *para*-substituted aromatic aldehydes were further subjected to catalytic asymmetric hydrophosphonylation. As shown in Table 1, *p*-chlorobenzaldehyde (**4**), *p*-tolualdehyde (**6**), *p*-anisaldehyde (**8**), and *p*-nitrobenzaldehyde (**10**) were transformed into the corresponding α-hydroxy phosphonates in an enantioselective manner (**5**; 83% ee, 80% yield, **7**; 86% ee, 82% yield, **9**; 78% ee, 88% yield, **11**; 71% ee, 85% yield). It is noteworthy that a single recrystallization of **3** (85% ee) from ethyl acetate provided optically pure **3** (60% yield).

Having developed an effective catalytic asymmetric hydrophosphonylation of aromatic aldehydes, we then turned our attention to hydrophosphonylation of α,β-unsaturated aldehydes. First, the reaction of cinnamaldehyde (**12**) was examined. Only one example of a catalytic asymmetric hydrophosphonylation of **12** has been previously reported, and LLB has given the corresponding α-hydroxy phosphonate **13** with 41% ee in 73% yield.[8] On the other hand, treatment of **12** with 1 equiv of dimethyl phosphite in toluene containing 10 mol %

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(9) The optical purities of all of the products were determined by chiral HPLC (DAICEL CHIRALPAK AS or AD), and the absolute configurations of all of the products were determined by the Mosher method.

(10) General procedure for catalytic asymmetric hydrophosphonylation. Synthesis of **3**. ALB was first prepared from $LiAlH_4$ and 2 molar equiv of (*R*)-BINOL in THF. See ref 6. After a THF solution of (*R*)-ALB (0.1 M, 0.4 mL, 0.04 mmol) was concentrated, the resulting (*R*)-ALB powder was redissolved in toluene (0.4 mL). To this toluene solution was added dimethyl phosphite (37 μL, 0.40 mmol) at room temperature, and the mixture was further stirred for 30 min at the same temperature. Benzaldehyde (41 μL, 0.4 mmol) was then added to the above mixture at −40 °C. After being stirred for 51 h at the same temperature, the reaction mixture was treated with 1 N HCl (1.0 mL) and extracted with EtOAc (10 mL × 3). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated to give a residue. Purification by flash chromatography (SiO_2, 20% acetone/hexane) gave the α-hydroxy phosphonate **3** (78 mg, 90%) with 85% ee as a colorless solid (mp = 86−87 °C).

(11) The use of diethyl phosphite and dibutyl phosphite gave the corresponding phosphonates with 73% ee, 39% yield and 67% ee, 42% yield, respectively.

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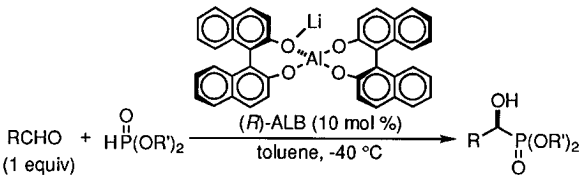
Table 1. Catalytic Asymmetric Hydrophosphonylation of Aldehydes Catalyzed by ALB



1: R = Ph
2: R = Ph, R' = Et
3: R = Ph, R' = Me
4: R = *p*-Cl-Ph
5: R = *p*-Cl-Ph, R' = Me
6: R = *p*-Me-Ph
7: R = *p*-Me-Ph, R' = Me
8: R = *p*-MeO-Ph
9: R = *p*-MeO-Ph, R' = Me
10: R = *p*-NO_2-Ph
11: R = *p*-NO_2-Ph, R' = Me
12: R = (*E*)-PhCH=CH
13: R = (*E*)-PhCH=CH, R' = Me
14: R = (*E*)-PhC(CH_3)=CH
15: R = (*E*)-PhC(CH_3)=CH, R' = Me
16: R = $(CH_3)_2$C=CH
17: R = $(CH_3)_2$C=CH, R' = Me
18: R = (*E*)-$CH_3(CH_2)_2$CH=CH
19: R = (*E*)-$CH_3(CH_2)_2$CH=CH, R' = Me

entry	aldehyde	product	time (h)	yield (%)	ee (%)
1	**1**	**2**	90	39	73
2	**1**	**3**	51	90	85
3[a]	**1**	**3**	90	95	90
4	**4**	**5**	38	80	83
5	**6**	**7**	92	82	86
6	**8**	**9**	115	88	78
7	**10**	**11**	66	85	71
8	**12**	**13**	83	85	82
9	**14**	**15**	83	93	89
10	**16**	**17**	94	72	68
11	**18**	**19**	39	53	55

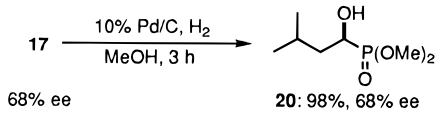
[a] Benzaldehyde (1.2 equiv) and ALB (9 mol %) were used.

ALB at −40 °C for 83 h furnished the α-hydroxy phosphonate **13** with 82% ee in 85% yield. The use of THF as a solvent gave less satisfactory results: i.e., **13** with 64% ee in 55% yield. The α,*β*-unsaturated aldehyde **14** was also converted to the α-hydroxy phosphonate **15** with 89% ee in 93% yield. Moreover, reactions of other α,*β*-unsaturated aldehydes such as **16** and **18** were also examined, affording **17** with 68% ee (72%) and **19** with 55% ee (53%), respectively.

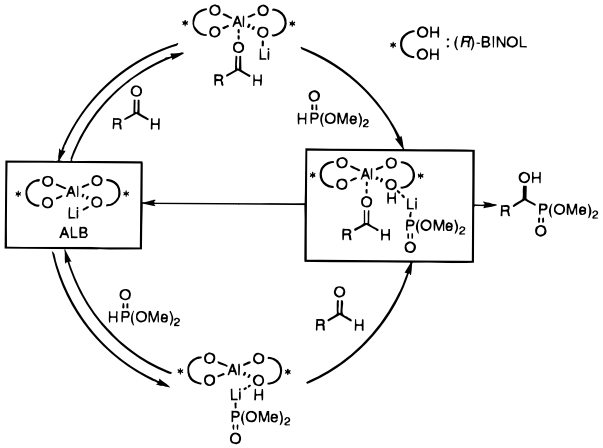
In striking contrast to these results, saturated aldehydes such as hexanal and cyclohexanecarboxaldehyde were converted to the corresponding α-hydroxy phosphonates in excellent chemical yields, albeit with low enantiomeric excesses ranging from 3 to 24%. This implies that the development of other types of heterobimetallic asymmetric catalysts is needed for a catalytic asymmetric hydrophosphonylation using saturated aldehydes. However, such α-hydroxy phosphonates were readily obtained from allylic α-hydroxy phosphonates with relatively high enantiomeric excesses by simple hydrogenation. For example, **17** with 68% ee underwent hydrogenation (10% Pd/C, MeOH, 1 atm H_2 pressure, room temperature, 3 h) to give **20** in 98% yield (Scheme 1). The enantiomeric excess of **20** was confirmed to be 68%, showing that no racemization occurred during hydrogenation.

A possible mechanism for catalytic asymmetric hydrophosphonylation of aldehydes is shown in Scheme 2. We

Scheme 1. Hydrogenation of Allylic α-Hydroxy Phosphonate



Scheme 2. Possible Mechanism for the Catalytic Asymmetric Hydrophosphonylation of Aldehydes



believe that ALB is a multifunctional asymmetric catalyst which effectively controls asymmetric hydrophosphonylations.[12] The lithium naphthoxide moiety functions as a Lowry−Brønsted base and the center aluminum functions as a Lewis acid. In fact, the reaction proceeded very slowly to give **3** with 30% ee in 37% yield (−40 °C, 132 h) when the asymmetric catalyst **21**[13] was used (10 mol %).

In conclusion, we have developed a general method for the catalytic asymmetric synthesis of α-hydroxy phosphonates using ALB as an asymmetric catalyst. Enantiomeric excesses as well as chemical yields of α-hydroxy phosphonates still need to be improved. However, we believe that the results described here may lead to further progress in this area.

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Supporting Information Available: Further details of the characterization of the compounds described (24 pages).

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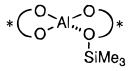
(12) For the discussion of the multifunctional activities of heterobimetallic asymmetric catalysts, see: Sasai, H.; Arai, T.; Satow, Y.; Houk, K. N.; Shibasaki, M. *J. Am. Chem. Soc.* **1995**, *117*, 6194−6198.

(13) The asymmetric catalyst **21** was prepared from ALB by treatment with trimethylsilyl chloride (1.2 equiv) in THF at −78 °C. This catalyst was then used in toluene as described in ref 10.



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