Catalytic Asymmetric Synthesis of α-Amino Phosphonates Using Lanthanoid–Potassium–BINOL Complexes

Hiroaki Sasai,† Shigeru Arai,† Yoshihiro Tahara,‡ and Masakatsu Shibasaki*,†

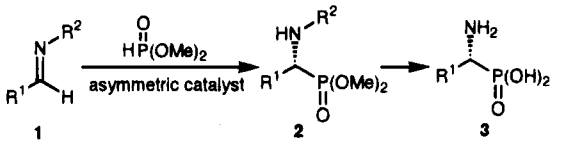
Faculty of Pharmaceutical Sciences, University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113, Japan, and Fine Chemicals Research Laboratories, Hokko Chemical Industry Co., Ltd., Toda, Atsugi-shi, Kanagawa 243, Japan

Received July 17, 1995

α-Amino phosphonic acids **3** are interesting compounds in the design of enzyme inhibitors. The concept of mimicking tetrahedral transition states of enzyme-mediated peptide bond hydrolysis previously led to the successful design and synthesis of phosphonamide-containing peptides as a promising new class of proteinase inhibitors.[1] It is not surprising that the absolute configuration of the α-carbon strongly influences the biological properties of **3**. Several methods for the synthesis of optically active α-aminophosphonic acids have been published.[2] We report here the first example of a catalytic asymmetric hydrophosphonylation to imines using lanthanoid–potassium–BINOL heterobimetallic complexes (LnPB, Ln = lanthanoid metal), which gives optically active α-amino phosphonates in modest to high enantiomeric excess.

We recently developed several heterobimetallic asymmetric catalysts. For example, lanthanoid–lithium–BINOL complexes (LnLB) are quite useful for catalytic asymmetric nitroaldol reactions,[3] and lanthanoid–sodium–BINOL complexes (LnSB) are very effective for catalytic asymmetric Michael reactions.[4] These results suggested that a catalytic asymmetric hydrophosphonylation to imines using these heterobimetallic complexes could be used to produce optically active α-amino phosphonates.[5] At the outset, we prepared imine **1a**[6] and examined the possibility of a catalytic asymmetric hydrophosphonylation under various conditions. However, these reactions proceeded at 60 °C only in the presence of a stoichiometric amount of the heterobimetallic asymmetric complexes, showing that the lanthanum–sodium–BINOL complex (LSB) and the lanthanum–potassium–BINOL complex (LPB)[7] were more effective than lanthanum–lithium–BINOL complex (LLB) in this type of reaction. For example, treatment of imine **1a** with 5 equiv of dimethyl phosphite and 1 equiv of LSB in THF at 60 °C for 18 h gave α-aminophosphonate **2a** with 69% ee[8] in 47% yield.[9] To increase the reactivity of imines, we next examined the reaction of imine **1b**,[6] prepared from 2-methylpropanal and 4-methoxy-α-(4-methoxyphenyl)benzenemethanamine, with dimethyl phosphite under various conditions. As shown in Table 1, the reaction proceeded at room temperature even in the

Table 1. Catalytic Asymmetric Hydrophosphonylation[a]



1 2 3

1a : R^1 = Et, R^2 = Tr
1b : R^1 = *i*-Pr, R^2 = DAM
1c : R^1 = *i*-Pr, R^2 = $CHPh_2$
1d : R^1 = Me, R^2 = $CHPh_2$
1e : R^1 = Et, R^2 = $CHPh_2$
1f : R^1 = C_5H_{11}, R^2 = $CHPh_2$
1g : R^1 = (*E*)-PhCHCH, R^2 = $CHPh_2$
1h : R^1 = cyclohexyl, R^2 = $CHPh_2$
1i : R^1 = cyclohexyl, R^2 = *p*-$MeOC_6H_4$

2a : R^1 = Et, R^2 = Tr
2b : R^1 = *i*-Pr, R^2 = DAM
2c : R^1 = *i*-Pr, R^2 = $CHPh_2$
2d : R^1 = Me, R^2 = $CHPh_2$
2e : R^1 = Et, R^2 = $CHPh_2$
2f : R^1 = C_5H_{11}, R^2 = $CHPh_2$
2g : R^1 = (*E*)-PhCHCH, R^2 = $CHPh_2$
2h : R^1 = cyclohexyl, R^2 = $CHPh_2$
2i : R^1 = cyclohexyl, R^2 = *p*-$MeOC_6H_4$

run	imine	cat. (mol %)	conditions	time (h)	yield (%)	ee of **2** (%)
1	**1a**	LSB(100)	A	18	**2a** : 47	69
2	**1b**	LSB(20)	B	18	**2b** : 25	55
3	**1b**	LPB(20)	B	18	**2b** : 27	71
4	**1b**	LPB(20)	C	21	**2b** : 62	**91**
5	**1b**	LSB(20)	C	21	**2b** : 38	49
6	**1b**	LLB(20)	C	21	**2b** : 46	38
7	**1b**	LPB(10)	C	96	**2b** : 70	**96**
8	**1c**	LPB(5)	C	143	**2c** : 82	**92**
9	**1d**	LPB(20)	C	70	**2d** : 73	75
10	**1e**	LPB(20)	C	70	**2e** : 80	**91**
11	**1f**	LPB(20)	C	87	**2f** : 87	**85**
12	**1g**	GdPB(20)	D	40	**2g** : 86	66
13	**1i**	PrPB(20)	C	68	**2i** : 75	66
14	**1i**	LPB(20)	C	89	**2i** : 71	49

[a] All reactions were performed in the presence of 5 equiv of dimethyl phosphite except runs 7 and 8 (1.5 equiv). Condition A:60 °C in THF. Condition B: room temperature in THF. Condition C: room temperature in toluene–THF (7:1). Condition D:50 °C in toluene–THF (7:1).

† University of Tokyo.
‡ Hokko Chemical Industry Co., Ltd.

(1) For comprehensive reviews, see: Kafarski, P.; Lejczak, B. *Phosphorus, Sulfur Silicon Relat. Elem.* **1991**, *63*, 193. Bartlett, P. A.; Marlowe, C. K.; Giannousis, P. P.; Hanson, J. E. *Cold Spring Harbor Symp. Quant. Biol.* **1987**, *LII*, 83.

(2) (a) Sawamura, M.; Itoh, Y.; Hayashi, T. *Tetrahedron Lett.* **1989**, *30*, 2247. (b) Hanessian, S.; Bennani, Y. L. *Tetrahedron Lett.* **1990**, *31*, 6465. (c) Ferrari, M.; Jommi, G.; Miglierini, G.; Pagliarin, R.; Sisti, M. *Synth. Commun.* **1992**, *22*, 107. (d) Yager, K. M.; Taylor, C. M.; Smith, A. B., III. *J. Am. Chem. Soc.* **1994**, *116*, 9377, and references cited therein.

(3) (a) Sasai, H.; Suzuki, T.; Arai, S.; Arai, T.; Shibasaki, M. *J. Am. Chem. Soc.* **1992**, *114*, 4418. (b) Sasai, H.; Suzuki, T.; Itoh, N.; Shibasaki, M. *Tetrahedron Lett.* **1993**, *34*, 851. (c) Sasai, H.; Itoh, N.; Suzuki, T.; Shibasaki, M. *Tetrahedron Lett.* **1993**, *34*, 855. (d) Sasai, H.; Suzuki, T.; Itoh, N.; Arai, S.; Shibasaki, M. *Tetrahedron Lett.* **1993**, *34*, 2657. (e) Sasai, H.; Kim, W.-S.; Suzuki, T.; Shibasaki, M.; Mitsuda, M.; Hasegawa, J.; Ohashi, T. *Terahedron Lett.* **1994**, *35*, 6123. (f) Sasai, H.; Suzuki, T.; Itoh, N.; Tanaka, K.; Date, T.; Okamura, K.; Shibasaki, M. *J. Am. Chem. Soc.* **1993**, *115*, 10372. (g) Sasai, H.; Yamada, Y. M. A.; Suzuki, T.; Shibasaki, M. *Tetrahedron* **1994**, *50*, 12313.

(4) Sasai, H.; Arai, T.; Satow, Y.; Houk, K. N.; Shibasaki, M. *J. Am. Chem. Soc.* **1995**, *117*, 6194.

(5) Shibuya and Spilling independently reported a catalytic asymmetric hydrophosphonylation to aldehydes using our heterobimetallic catalyst (LLB). See: (a) Yokomatsu, T.; Yamagishi, T.; Shibuya, S. *Tetrahedron: Asymmetry* **1993**, *4*, 1783. (b) Rath, N. P.; Spilling, C. D. *Tetrahedron Lett.* **1994**, *35*, 227.

(6) Only the *anti*-isomer was formed.

(7) General procedure for preparation of the LPB complex. To a stirred solution of (*R*)-BINOL (402.9 mg, 1.4 mmol) in THF (13.6 mL) was added a solution of La(O-*i*-Pr)$_3$ (148.6 mg, 0.47 mmol), purchased from Kojundo Chemical Laboratory Co. Ltd., Saitama, Japan and Soekawa Rikagaku Co. Ltd., Tokyo, Japan, in THF (2.4 mL), KHMDS (279.3 mg, 1.4 mmol) in toluene (2.8 mL), and H_2O (8.5 mg, 0.47 mmol) in THF (47 μL) at rt under argon atmosphere. After the solution was stirred for 1 h, the solvent was removed under vacuum, and toluene–THF (7:1) (18.8 mL) was added.

(8) Enantiomeric excess was determined by HPLC analysis using DAICEL CHIRALPAK, AD or AS, with hexane–*i*-PrOH. **2b** was converted to corresponding **3b** (100%) by treatment with concentrated HCl at reflux temperature for 14 h, and the absolute configuration was determined by the optical rotation, $[\alpha]^{24}_D$ −2.4° (*c* 2.4, H_2O). **1e** was converted to corresponding **3e** (90%) in a two-step sequence of reactions (H_2–5 mol % $Pd(OH)_2$ in MeOH and concentrated HCl at reflux temperature), and the absolute configuration was determined by the optical rotation, $[\alpha]^{25}_D$ −12.2° (*c* 1.9, H_2O), $[\alpha]^{25}_D$ −11.0° (*c* 1.9, 1 N NaOH), $[\alpha]_{577}$ −9.4° (*c* 1.9, 1 N NaOH). See: (a) Hurber, R.; Kniezinger, A.; Obrecht, J.-P.; Vasella, A. *Helv. Chim. Acta* **1985**, *68*, 1730. (b) Hanessian, S.; Behnaani, Y. L. *Tetrahedron Lett.* **1990**, *31*, 6465. The absolute configurations of other α-amino phosphonates were assigned by similarity in optical rotations and patterns of separation on the chiral stationary phase column.

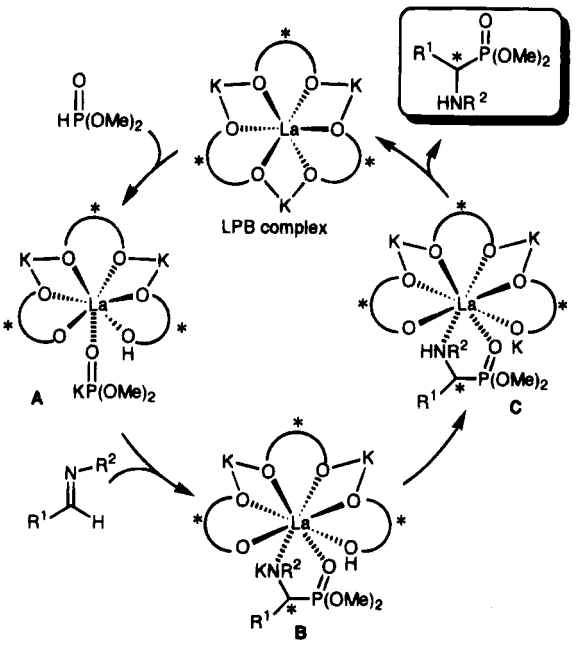
(9) LLB (23% ee, 33%), LPB (69% ee, 16%), LSB (diethyl phosphite, 67% ee, 8%).

0022-3263/95/1960-6656$09.00/0

presence of a catalytic amount of LPB (20 mol %), giving α-amino phosphonate **2b** with 71% ee,[8] albeit in 27% yield. Encouraged by this interesting result, solvent effects were then investigated. We were pleased to find that treatment of imine **1b** with 1.5 equiv of dimethyl phosphite and 10 mol % of LPB in toluene–THF (7:1) at room temperature for 96 h gave α-amino phosphonate **2b** with 96% ee[8] in 70% yield (run 7, Table 1).[10] Further studies were performed to improve the catalyst turnover in asymmetric hydrophosphonylation. We expected that a lower electron density for the product nitrogen would improve the catalyst turnover.[11] Thus, the reaction of imine **1c**,[6] prepared from 2-methylpropanal and α-phenylbenzenemethanamine, with dimethyl phosphite was examined. As expected, treatment of **1c** with 1.5 equiv of dimethyl phosphite and 5 mol % of LPB in toluene–THF (7:1) at room temperature for 143 h (run 8, Table 1) gave α-amino phosphonate **2c** with 92% ee[8] in 82% yield.[10] Likewise, imine **1d**[12] and **1e**[13] were converted to corresponding α-amino phosphonate **2d** with 75% ee[8] in 73% yield and **2e** with 91% ee[8] in 80% yield, respectively (runs 9, and 10, Table 1),[10] and imine **1f**[6] was transformed into α-amino phosphonate **2f** with 85% ee[8] in 87% yield (run 11, Table 1).[10] In these cases, however, 20 mol % of LPB was required to achieve efficient conversion. In marked contrast to these results, imine **1g**,[6] prepared from cinnamaldehyde and α-phenylbenzenemethanamine, was transformed into α-amino phosphonate **2g** with only 20% ee[8] in 54% yield. After several attempts, as shown in Table 1 (run 12), we were pleased to find that treatment of **1g** with 5 equiv of dimethyl phosphite and 20 mol % of gadolinium–potassium–BINOL complex (GdPB)[14] in toluene–THF (7:1) at 50 °C for 40 h gave α-amino phosphonate **2g** with 66% ee[8] in 86% yield. The reaction of imine **1h**,[6] prepared from cyclohexanecarboxaldehyde and α-phenylbenzenemethanamine, with dimethyl phosphite was investigated using 20 mol % of LPB. However, this reaction gave α-amino phosphonate **2h** with 54% ee[8] in only 63% yield, indicating that the turnover was less efficient. Among the several imines prepared from cyclohexanecarboxaldehyde, we found that treatment of imine **1i**[6] with 5 equiv of dimethyl phosphite and 20 mol % of praseodymium–potassium–BINOL complex (PrPB)[14] at room temperature for 68 h gave α-amino phosphonate **2i** with 66% ee[8] in 75% yield.[15]

The proposed mechanism of this catalytic asymmetric hydrophosphonylation is shown in Scheme 1. The first step of this reaction is the deprotonation of dimethyl phosphite by LPB to generate the potassium dimethyl phosphite **A**. This potassium phosphite **A** immediately coordinates to a rare earth due to the strong oxophilicity of rare earth metals.[16] **A** then reacts with an imine to give an optically active potassium salt of α-amino phosphonate. A proton-exchange reaction produces an α-amino phosphonate and LPB, thereby making possible the catalytic asymmetric hydrophosphonylation.[17] Since an α-amino phosphonate is likely to coordinate rather strongly to a rare earth metal, the dissociation of an α-amino phosphonate from a rare earth is important to achieve a high catalyst turnover. We believe that the α-amino phosphonate produced from **1c** dissociated relatively smoothly from the rare earth metal, thereby enabling a slightly higher catalyst turnover.

Scheme 1. Proposed Catalytic Cycle



In conclusion, we have realized a catalytic asymmetric hydrophosphonylation to imines using LnPB as a catalyst. As shown in Scheme 1, LPB appears to act as a multifunctional asymmetric catalyst to produce α-amino phosphonates of modest to high enantiomeric excess.[17] Although the catalyst turnover is not satisfactory at present, the results described here may lead to further progress.

Acknowledgment. This work was supported by a Grant in Aid for Scientific Research on Priority Areas from the Ministry of Education, Science and Culture, Japan.

Supporting Information Available: Spectral and analytical data of **2b–g,i** (4 pages).

JO951280H

(10) La gave the best result.

(11) It seems likely that **2c** would coordinate to a lanthanum slightly more weakly than **2b**.

(12) The *anti*-isomer and the *syn*-isomer were formed in a ratio of 10:1.

(13) The *anti*-isomer and the *syn*-isomer were formed in a ratio of 2:1.

(14) General procedure for preparation of the LnPB complex (Ln = Gd and Pr). To a stirred solution of (*R*)-BINOL (198.1 mg, 0.69 mmol) in THF (6.7 mL) was added a solution of Ln(O-*i*-Pr)$_3$ (0.23 mmol), purchased from Kojundo Chemical Laboratory Co. Ltd., Saitama, Japan and Soekawa Rikagaku Co. Ltd., Tokyo, Japan, in THF (1.2 mL), KHMDS (137.6 mg, 0.69 mmol) in toluene (1.2 mL), and H_2O (4.1 mg, 0.23 mmol) in THF (23 μL) at rt under argon atmosphere. After being stirred for 1 h at rt, the solvent was removed under vacuum, and toluene–THF (7:1) (9.2 mL) was added.

(15) General procedure for catalytic asymmetric hydrophosphonylation. Synthesis of **2f**. To imine **1f** (62.9 mg, 0.19 mmol) and dimethyl phosphite (87.1 μL, 0.95 mmol) was slowly added a solution of LPB complex (0.038 mmol) in toluene–THF (7:1) (1.5 mL) at rt under argon atmosphere. After being stirred for 90 h, the mixture was quenched with H_2O and extracted with ethyl acetate (15 mL × 3). The combined organic layer was dried over anhydrous Na_2SO_4. Removal of the solvent and flash column chromatography (silica gel, 1:2, hexane–EtOAc) gave the desired coupling product **2f** (73.3 mg, 87%, 85% ee) as a colorless oil: ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.17–7.45 (m, 10H), 5.23 (s, 1H), 3.79 (d, J = 0.6 Hz, 3H), 2.80–2.92 (m, 1H), 1.13–1.87 (m, 9H), 0.87 (t, J = 6.9 Hz, 3H); IR (neat) 1493, 1453, 1246 cm^{-1}; MS m/z 376 (M + H$^+$), 344, 265, 167 (base peak); $[\alpha]^{25}_D$ −168.6 ° (c 0.7, $CHCl_3$). Anal. Calcd for $C_{21}H_{30}NO_3P$: C, 67.19; H, 8.05: N, 3.73. Found: C, 66.90; H, 8.05; N, 3.48.

(16) (a) Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693. (b) Imamoto, T.; Kusumoto, T.; Tawarayama, Y.; Sugiura, Y.; Hatanaka, Y.; Yokoyama, M. *J. Org. Chem.* **1984**, *49*, 3904. (c) Molander, G. A. *Chem. Rev.* **1992**, *92*, 29 and references cited therein. (d) Giardello, M. A.; Yamamoto, Y.; Brard, L.; Marks, T. J. *J. Am. Chem. Soc.* **1995**, *117*, 3276.

(17) We believe that aldehydes and/or α,β-unsaturated ketones coordinate to rare earth metals in catalytic asymmetric nitroaldol and Michael reactions (see refs 3 and 4). In catalytic asymmetric hydrophosphonylations, however, coordination of an imine to a rare earth may be difficult. Thus, LnPB might be a better asymmetric catalyst than LnLB or LnSB.