Tetrahedron Letters,Vol.30,No.17,pp 2247-2250,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

Asymmetric Synthesis of (1-Aminoalkyl)phosphonic Acids via Asymmetric Aldol Reaction of (Isocyanomethyl)phosphonates Catalyzed by a Chiral Ferrocenylphosphine-Gold(I) Complex

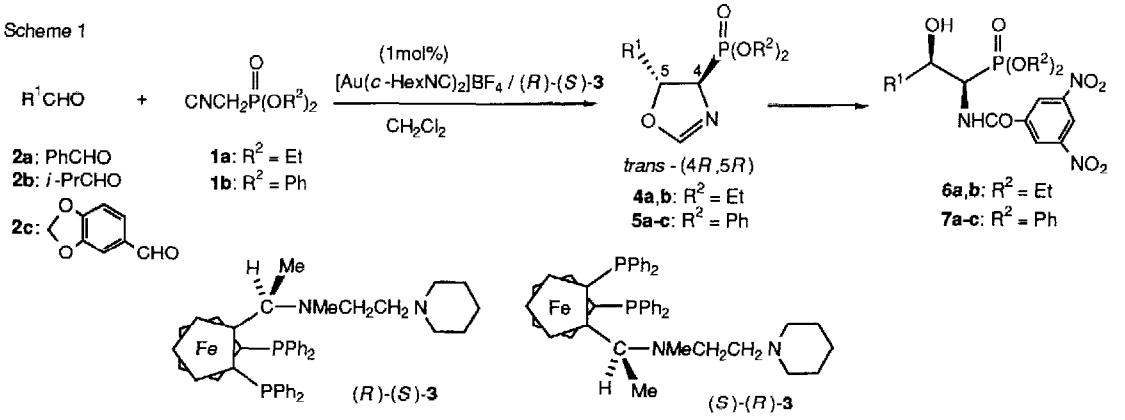
Masaya Sawamura, Yoshihiko Ito,* and Tamio Hayashi*
Department of Synthetic Chemistry, Kyoto University, Kyoto 606, Japan

Summary: Reaction of aldehydes (R^1CHO: R^1 = Ph, i-Pr, 3,4-OCH_2O-C_6H_3) with (isocyanomethyl)phosphonates ($CNCH_2P(O)(OR^2)_2$: R^2 = Et, Ph) in the presence of 1 mol% of a chiral ferrocenylphosphine-gold(I) catalyst gave high yields of optically active trans-5-alkyl-2-oxazoline-4-phosphonates with % ee ranging between 88%-96%, which were readily converted to phosphonic acid analogs of optically active phenylalanine and β-alkylserines.

(1-Aminoalkyl)phosphonic acids, which are phosphonic acid analogs of α-amino acids, have received much attention in the past decade owing to their potential biological activity.[1] It is highly desirable to develop an efficient method for the preparation of optically active phosphonic acids since their activity usually depends on their absolute configuration.[1] There have appeared nevertheless few papers dealing with the preparation by stereoselective asymmetric reactions.[1-3] Here we wish to report an efficient asymmetric synthesis of phosphonic acid analogs of phenylalanine and β-alkylserines[4] through gold(I)-catalyzed asymmetric aldol reaction[5] of (isocyanomethyl)phosphonates with aldehydes producing optically active trans-5-alkyl-2-oxazoline-4-phosphonates.

Diethyl (isocyanomethyl)phosphonate (**1a**)[6] was subjected to aldol reaction with aldehydes in the presence of 1 mol% of the gold(I) catalyst bearing chiral ferrocenylphosphine ligand (R)-N-methyl-N-[2-(piperidino)ethyl]-1-[(S)-1',2-bis(diphenylphosphino)ferrocenyl]-ethylamine [(R)-(S)-**3**].[5b,7] The aldol reaction of **1a**, which was slightly less reactive than methyl isocyanoacetate, proceeded smoothly at 60 °C to give high yield of 5-alkyl-2-oxazoline-4-phosphonates **4**[8] with high enantioselectivity and diastereoselectivity (>98% trans)

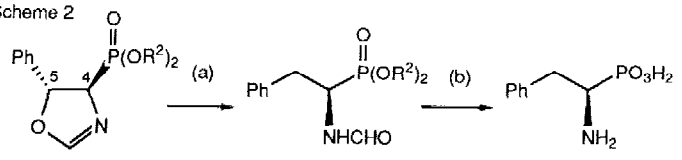
Scheme 1



(Scheme 1). A typical procedure is given for the reaction of **1a** with benzaldehyde (**2a**): In a sealed degassed glass tube, a mixture of 5.0 mg (0.010 mmol) of bis(cyclohexyl isocyanide)gold(I) tetrafluoroborate, 7.9 mg (0.011 mmol) of (R)-(S)-**3**, 0.175 g (0.988 mmol) of **1a**, and 0.122 g (1.15 mmol) of **2a** in 1 mL of dry dichloromethane was warmed at 60 °C for 60 h. The mixture was passed through short florisil column (ethyl acetate) and bulb-to-bulb distillation (ca. 100 °C/0.5 mmHg) gave 0.249 g (89%) of oxazoline **4a** ($[\alpha]_D^{20}$ +146° (c 1.1, THF)) which was isomerically pure trans isomer.[9] The enantiomeric purity was determined to be 90% ee by HPLC analysis of 3,5-dinitrobenzamide **6a** (1. conc HCl/EtOH. 2. $ArCOCl/Et_3N$) with a chiral stationary phase column (Sumitomo Chemical Co., Sumipax OA-4100, hexane/dichloroethane/ethanol = 25/10/1).

Palladium-catalyzed hydrogenolysis of oxazoline **4a** (90% ee) followed by acidic hydrolysis of the resulting formamide **8** ($[\alpha]_D^{20}$ -39.7° (c 2.3, $CHCl_3$)) with 40% hydrobromic acid in acetic acid gave (R)-(-)-(1-amino-2-phenylethyl)phosphonic acid (**10**)[10] ($[\alpha]_D^{20}$ -47.9° (c 0.48, 2 N NaOH), phosphonic acid analog of (S)-phenylalanine (Scheme 2).[11] The absolute configuration of oxazoline trans-(+)-**4a** is deduced to be (4R,5R). Amino ester hydrochloride **11a** obtained by treatment of **4a** (90% ee) with conc HCl in ethanol was readily made enantiomerically pure by recrystallization from ethanol/ether with high recovery.[12] Optically pure **11a** ($[\alpha]_D^{20}$ -32.0° (c 1.1, MeOH)) was converted by the reaction with iodotrimethylsilane to (1R,2R)-(1-amino-2-hydroxy-2-phenylethyl)phosphonic acid (**12a**) ($[\alpha]_D^{20}$ -24.7° (c 1.0, 2 N NaOH)) (Scheme 3).

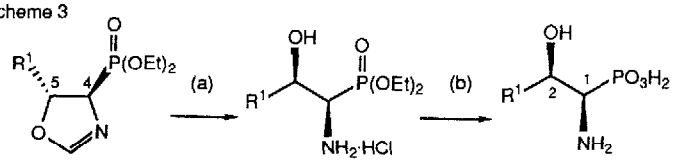
Scheme 2



(4*R*,5*R*)-**4a**
(4*R*,5*R*)-**5a**
8: R^2 = Et
9: R^2 = Ph
(*R*)-**10**

(a) H_2 (145 atm for **4a**, 50 atm for **5a**), 10% Pd / C, EtOH, r.t., 20 h (**8**: 94%, **9**: 90%).
(b) (i) 40% HBr / AcOH (1/1), reflux, 13-23 h.
(ii) propylene oxide / EtOH (1/5-10)
(**10**: 93% from **8**, 94% from **9**).

Scheme 3

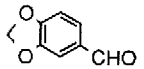


(4*R*,5*R*)-**4a** (R^1 = Ph)
(4*R*,5*R*)-**4b** (R^1 = *i*-Pr)
11a,b
(1*R*,2*R*)-**12a,b**

(a) conc HCl, EtOH, 70 °C, 2 h
{**11a**: 64% (recrystallization), **11b**: 100%}.
(b) (i) $NaHCO_3$, H_2O.
(ii) Me_3SiI (4 eq), CH_2Cl_2, r.t., 1h.
(iii) propylene oxide/EtOH (1/10)
(**12a**: 91%, **12b**: 71%).

Representative results summarized in Table 1 were obtained under similar reaction conditions.[13] Both antipodes of oxazoline **4a** were obtained since both antipodes of chiral ligand **3** are equally available (entries 1 and 2).[14] High stereoselectivity was also observed in the reaction of **1a** with aliphatic aldehyde **2b** yielding trans-oxazoline **4b** of 88% ee (entry 4). This oxazoline was converted to (1R,2R)-(1-amino-2-hydroxy-3-methylbutyl)phosphonic acid (**12b**).[15] Diphenyl (isocyanomethyl)phosphonate (**1b**)[16] was more reactive and enantioselective than diethyl ester **1a** in the reaction with both aromatic and aliphatic

Table 1. Reaction of (Isocyanomethyl)phosphonates 1 with Aldehydes 2 Catalyzed by the Chiral Ferrocenylphosphine-Gold Complex.[a]

entry	1	2	temp. (°C)	time (h)	product	yield (%)	% ee[b] (config)	$[\alpha]_D^{20}$[c]
1	$CNCH_2PO(OEt)_2$ (**1a**)	PhCHO (**2a**)[e]	60	60	**4a**	89[g]	90 (4R,5R)[i]	+146°
2[d]	**1a**	**2a**[e]	60	60	**4a**	85[g]	90 (4S,5S)[i]	-145°
3	**1a**	**2a**[e]	40	90	**4a**	78[g]	92 (4R,5R)[i]	
4	**1a**	i-PrCHO (**2b**)[f]	60	99	**4b**	85[g]	88 (4R,5R)[j]	+151°
5	$CNCH_2PO(OPh)_2$ (**1b**)	PhCHO (**2a**)[e]	60	39	**5a**	94[h]	93 (4R,5R)[i]	+193°
6	**1b**	**2a**[f]	40	40	**5a**	94[h]	95 (4R,5R)[i]	+194°
7	**1b**	**2a**[f]	25	156	**5a**	83[h]	96 (4R,5R)[i]	+195°
8	**1b**	i-PrCHO (**2b**)[f]	40	75	**5b**	88[h]	95 (4R,5R)[j]	+186°
9	**1b**	 (**2c**)[f]	40	98	**5c**	92[h]	95 (4R,5R)[j]	+223°

[a] The reaction was carried out in dichloromethane in a degassed sealed tube. [b] Determined by HPLC analysis of N-(3,5-dinitrobenzoyl) derivatives of (1-amino-2-hydroxyalkyl)phosphonates **6** and **7** with a chiral stationary phase column (Sumitomo Chemical Co., Sumipax OA series, hexane/dichloroethane/ethanol): OA-4100 for **6a,b**, OA-4500 for **7a,b**, and OA-1100 for **7c**. [c] c 1.0-1.5, THF. [d] (S)-(R)-**3** was used as a chiral ligand. [e] **1**/**2**/catalyst = 1/1.1/0.01. [f] **1**/**2**/catalyst = 1/2/0.01. [g] Isolated yield by distillation based on **1**. [h] Isolated yield by MPLC (silica gel, ethyl acetate/hexane) based on **1**. [i] The determination of the configuration is described in the text. [j] Configuration assigned by similarity in optical rotations and in patterns of separation on the chiral stationary phase column.

aldehydes to give trans-oxazolines **5** of over 93% ee (entries 5-9). Highest value (96% ee) was obtained in the reaction with benzaldehyde (**2a**) at 25 °C. Oxazoline **5a** (93% ee) was converted to known aminophosphonic acid (R)-(-)-**10**[10,17] by the hydrogenolysis followed by acidic hydrolysis, indicating that oxazoline **5a** has absolute configuration (4R,5R).

All the oxazolines shown in Table 1 have absolute configuration (4R,5R) which is the same, though differently expressed by the sequence rule, as the configuration of (4S,5R)-5-alkyl-2-oxazoline-4-carboxylates previously obtained in the reaction of α-isocyanocarboxylates with the chiral catalyst (R)-(S)-**3**/Au.[5] It seems probable that the transition state of the reaction of (isocyanomethyl)phosphonates is similar to that of α-isocyanocarboxylates and the exclusive trans-selectivity is due to the steric repulsion between large dialkoxyphosphinyl moiety and alkyl substituent of aldehydes.

We are grateful to Professor U. Schöllkopf (University of Göttingen) for sending us experimental procedure for the conversion of diethyl phosphonates to phosphonic acids with iodotrimethylsilane.

REFERENCES AND NOTES

1 For a pertinent review: Dhawan, B.; Redmore, D. Phosphorous and Sulfur **1987**, 32, 119, and references cited therein.

2 High stereoselectivity has been reported in asymmetric alkylation of a Shiff base obtained from (+)-camphor and (aminomethyl)phosphonate: Schöllkopf, U.; Schütze, R. Liebigs Ann. Chem. **1987**, 45.

3 Preparation by rhodium-catalyzed asymmetric hydrogenation has been reported: Schöllkopf, U.; Hoppe, I.; Thiele, A. Liebigs Ann. Chem. **1985**, 555.

4 For the asymmetric synthesis of phosphonic acid analogs of Serine and Threonine: (a) Huber,R.; Knierzinger, A.; Obrechet, J.P.; Vasella, A. Helv. Chim. Acta **1985**, 68, 1730. (b) Renaud, P.; Seebach, D. Angew. Chem. Int. Ed. Engl. **1986**, 25, 843.

5 (a) Ito, Y.; Sawamura, M.; Hayashi, T. J. Am. Chem. Soc. **1986**, 108, 6405. (b) Ito, Y.; Sawamura, M.; Hayashi, T. Tetrahedron Lett. **1987**, 28, 6215. (c) Ito, Y.; Sawamura, M.; Shirakawa, E.; Hayashizaki, K.; Hayashi, T. Tetrahedron **1988**, 44, 5253. (d) Ito, Y.; Sawamura, M.; Kobayashi, M.; Hayashi, T. Tetrahedron Lett. **1988**, 29, 6321.

6 Schöllkopf, U.; Schröder,R.; Stafforst, D. Liebigs Ann. Chem. **1974**, 44.

7 Hayashi, T.; Kawamura, N.; Ito, Y. J. Am. Chem. Soc. **1987**, 109, 7876.

8 (a) Base-catalyzed reaction of the diethyl (isocyanomethyl)phosphonate with aldehydes forming oxazolines has been reported in ref 6. (b) For the Cu_2O-catalyzed reaction and transformation of oxazolines to phosphonic acid analogs of racemic serines: Schöllkopf, U.; Wintel, T. Synthesis **1984**, 1033.

9 The cis-isomer was not detected by ^1H NMR analysis of the crude reaction mixture, and trans-stereochemistry of the oxazoline was assigned by $^1H\{^1H\}$ NOE experiments.

10 The reported rotation (ref 2) for (S)-**10** (94% ee) is $[\alpha]_D^{20}$ +41.5° (c 0.53, 2 N NaOH).

11 Hydrolysis of the formamide **8** with conc hydrochloric acid in ethanol gave (R)-(-)-diethyl (1-amino-2-phenylethyl)phosphonate ($[\alpha]_D^{20}$ -15.6° (c 1.9, $CHCl_3$)), phosphonate analog of (S)-phenylalanine. The reported rotation (ref 2) for the phosphonate is $[\alpha]_D^{20}$ +14.04° (c 1.07, $CHCl_3$) for the (S) isomer of 95% ee.

12 Recrystallization by addition of ether to an ethanol solution of crude **11a** obtained from **4a** (90% ee) gave 64% yield (based on **4a**) of enantiomerically pure **11a**. The enantiomeric purity was confirmed by the HPLC analysis of amide **6a**.

13 Satisfactory spectral and analytical data were obtained on all new compounds. ^1H NMR spectra ($CDCl_3$/TMS, 400 or 200 MHz) for oxazolines are as follows: **4a**: 1.355 and 1.356 (a pair of dt, J_{P-H} = 3.3 Hz, J_{H-H} = 7.1 Hz, 6 H), 4.15-4.3 (m, 5 H), 5.699 (dd, J_{P-H} = 20.4 Hz, J_{H-H} = 8.0 Hz, 1 H), 7.983 (dd, J_{P-H} = 4.2 Hz, J_{H-H} = 2.2 Hz, 1 H), 7.3-7.45 (m, 5 H). **4b**: 0.946 (d, J = 6.7 Hz, 3 H), 0.955 (d, J = 6.8 Hz, 3 H), 1.347 (dt, J_{P-H} = 1.7 Hz, J_{H-H} = 7.1 Hz, 3 H), 1.348 (dt, J_{P-H} = 1.6 Hz, J_{H-H} = 7.1 Hz, 3 H), 1.833 (octet, J = 6.6 Hz, 1 H), 4.007 (ddd, J_{P-H} = 14.2 Hz, J_{H-H} = 7.1 and 2.1 Hz, 1 H), 4.1-4.3 (m, 4 H), 4.560 (ddd, J_{P-H} = 20.6 Hz, J_{H-H} = 7.1 and 5.9 Hz, 1 H), 6.919 (dd, J_{P-H} = 4.3 Hz, J_{H-H} = 2.1 Hz, 1 H). **5a**: 4.586 (ddd, J_{P-H} = 13.4 Hz, J_{H-H} = 7.8 and 2.2 Hz, 1 H), 5.935 (dd, J_{P-H} = 21.7 Hz, J_{H-H} = 7.8 Hz, 1 H), 7.1-7.45 (m, 16 H). **5b**: 0.991 (d, J = 6.7 Hz, 3 H), 1.002 (d, J = 6.8 Hz, 3 H), 1.909 (octet, J = 6.6 Hz, 1 H), 4.361 (ddd, J_{P-H} = 13.3 Hz, J_{H-H} = 7.0 and 2.1 Hz, 1 H), 4.800 (ddd, J_{P-H} = 21.9 Hz, J_{H-H} = 7.0 and 5.9 Hz, 1 H), 7.027 (dd, J_{P-H} = 4.6 Hz, J_{H-H} = 2.0 Hz, 1 H), 7.05-7.4 (m, 10 H). **5c**: 4.55 (ddd, J_{P-H} = 13.6 Hz, J_{H-H} = 7.8 and 2.0 Hz, 1 H), 5.83 (dd, J_{P-H} = 21.6 Hz, J_{H-H} = 7.8 Hz, 1 H), 5.97 (s, 2 H), 6.75-6.9 (m, 3 H), 7.16 (dd, J_{P-H} = 4.4 Hz, J_{H-H} = 2.0 Hz, 1 H), 7.2-7.4 (m, 10 H).

14 Hayashi, T.; Kumada, M. Acc. Chem. Res. **1982**, 15, 395, and references cited therein.

15 Phosphonic acid **12b** purified by recrystallization from methanol/ethanol has the rotation $[\alpha]_D^{20}$ +5.2° (c 1.0, 2 N NaOH)) and mp 202 °C.

16 Prepared from diphenyl chlorophosphate and 2.4 equiv. of isocyanomethyllithium according to the procedure described for diethyl ester **1a** in ref 6 (62% yield).

17 $[\alpha]_D^{20}$ -49.8° (c 0.50, 2 N NaOH). Recrystallization from aqueous methanol gave **10** of higher optical rotation ($[\alpha]_D^{20}$ -51.3° (c 0.48, 2 N NaOH)) with 90% recovery.

(Received in Japan 30 January 1989)