ASYMMETRIC SYNTHESIS OF 3-QUINOLYLALKYLAMINE BY ENANTIOSELECTIVE ALKYLATION OF *N*-DIPHENYL-PHOSPHINYL-3-QUINOLYLIMINE USING CHIRAL β-AMINO ALCOHOLS

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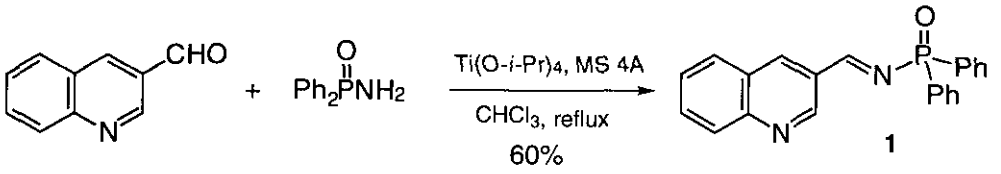
Abstract - Chiral N-diphenylphosphinyl-3-quinolylamines (DPP amines) with up to 74.9% e.e. were obtained by the enantioselective alkylation using dialkylzincs in the presence of various chiral amino alcohols. The acidic hydrolysis of the chiral DPP amine afforded optically active chiral 3-quinolylamine without racemization.

The quinoline skeleton[1] is one of the most basic structures in alkaloids, and many quinoline alkanoids and their derivatives[2] have physiological or pharmacological activities.[3] Therefore the development of asymmetric synthesis of chiral compounds possessing the quinoline ring would provide a useful method for assay-examination. One of the direct methods for the synthesis of chiral amines is an asymmetric alkylation of imines. However, compared with the alkylation of aldehydes, oxygen analogue of imines, only a few enantioselective alkylation of imines have been reported by us[4] and others.[5] To the best of our knowledge, however, no report about an asymmetric synthesis of quinolyl alkanamine has appeared.

Here we report the preparation of optically active quinolyl alkanamines by an enantioselective addition of dialkylzinc in the presence of chiral β-amino alcohols as chiral ligands. We have examined the enantioselective alkylation using dialkylzincs to imine activated by diphenylphosphinyl (DPP) group and

have achieved high enantioselectivities using chiral amino alcohols[4a,c] and polymer-supported amino alcohols[4b,d,e] as chiral ligands. We considered that DPP group effectively controls the stereochemical course also in the enantioselective alkylation of 3-quinolyl imine.

N-Diphenylphosphinyl-3-quinolyl imine (**1**) was found to be synthesized in 60% by titanium(IV) tetraisopropoxide:[6] $Ti(O\text{-}i\text{-}Pr)_4$ promoted a reaction between quinoline-3-carbaldehyde and diphenylphosphinyl amide in the presence of molecular sieves 4A .



Enantioselective ethylation of DPP imine (**1**) using diethylzinc was examined in the presence of various chiral amino alcohols (**3** - **6**) derived from norephedrine or ephedrine (Table 1). A chiral DPP amine (**2**) was obtained in moderate yield and optical yield using (1S,2R)-N,N-dibutylnorephedrine (**3**, DBNE)[7] (Entry 1). Both the yield and optical yield were increased in the presence of (1R,2S)-N-vinylbenzylephedrine (**4**) (VBE)[4c,8] (Entry 2), which is highly enantioselective ligand for the ethylation of DPP imine prepared from benzaldehyde. When (1S,2R)-2-morpholino-1-phenylpropan-1-ol (**5**) (MOPEP)[4a] was utilized, the enantioselectivity reached 70.3% e.e. (Entry 3). However, (1S,2R)-2-thiomorpholino-1-phenylpropan-1-ol (**6**) (TOPEP) gave a poorer result than that of the oxygen analogue (**5**) (Entry 4). Elevation of reaction temperature from 0 ℃ to room temperature caused higher chemical yield but lower enantioselectivity (Entry 5). Therefore chiral DPP amine (**2**) was obatained in the highest optical yield, when the ethylation was performed at 0 ℃ using MOPEP as a chiral ligand (Entry 3).

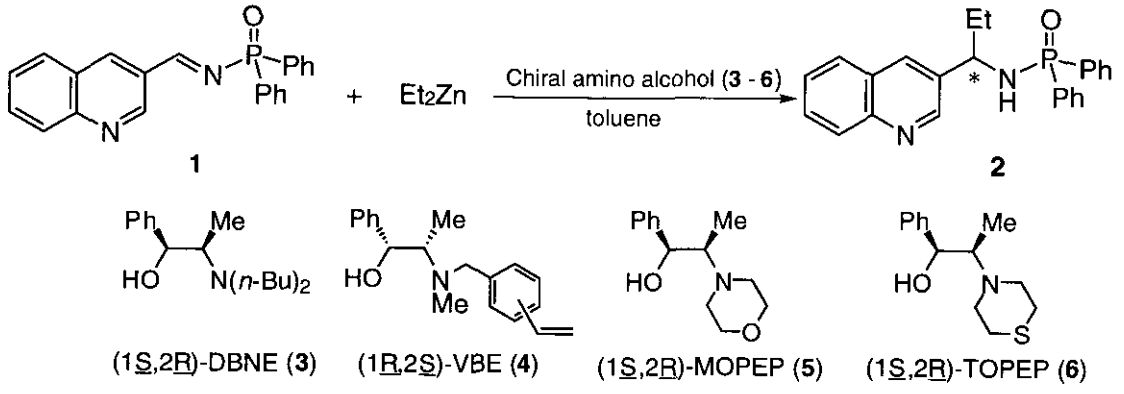
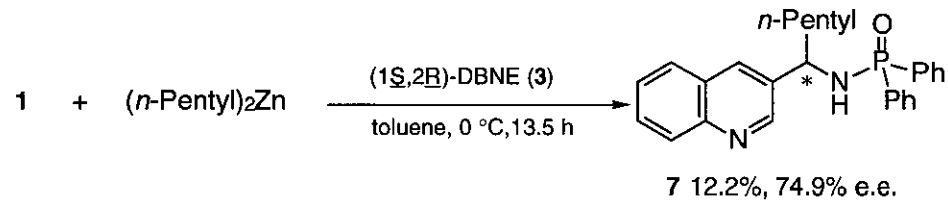


Table 1. Enantioselective ethylation of **1** using chiral amino alcohols (**3** - **6**)

Entry[a]	Chiral ligand	Temp (℃)	Time (h)	Yield (%)	E.e. (%)[b, c]
1	(1S,2R)-DBNE (**3**)	0	39	53.6	53.6 (*S*)
2	(1R,2S)-VBE (**4**)	0	41	59.6	64.0 (*R*)
3	(1S,2R)-MOPEP (**5**)	0	22	62.9	70.3 (*S*)
4	(1S,2R)-TOPEP (**6**)	0	21	44.3	53.9 (*S*)
5	(1S,2R)-MOPEP (**5**)	r t	14	68.2	65.9 (*S*)

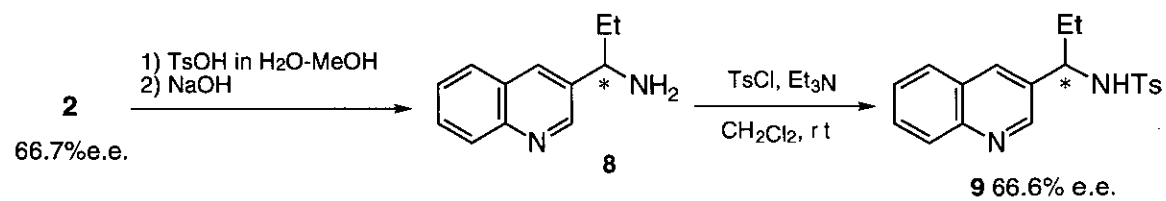
[a] Molar ratio was as follows. Chiral amino alcohol : **1** : Et_2Zn = 1.0 : 1.0 : 3.0. [b] E.e. was determined by HPLC analysis using a chiral column (See experimental section in details). [c] Absolute configuration was tentatively assigned by the comparison of the result which was obtained in the enantioselctive ethylation of DPP imine prepared from benzaldehyde using the same chiral ligand.[4a]

Under the best reaction conditions described above, enantioselective pentylation was also examined using di(n-pentyl)zinc. As a result, a chiral amine (**7**) was afforded in higher optical yield of 74.9% e.e.



7 12.2%, 74.9% e.e.

Then, hydrolysis of diphenylphosphinyl group[9] was examined using DPP amine (**2**) (66.7% e.e.).[10] 3-Quinolylamine (**8**) was obtained by the treatment with p-toluenesulfonic acid (TsOH) in H_2O-MeOH and its optical purity was determined to be 66.6% e.e. as its tosylate (**9**). This result implies that the deprotection of DPP group proceeded without racemization.[4a, c]



9 66.6% e.e.

Thus, enantioselective alkylation of DPP 3-quinolyl imine by dialkylzincs provides a tool for the preparation of chiral 3-quinolyl alkanamines.

EXPERIMENTAL

General. Optical rotation was measured by Jasco DIP-1000 polarimeter. IR spectra were recorded with Horiba FT210 spectrophotometer. ^1H NMR spectra (300 MHz) were measured with Bruker DPX300

spectrometer using tetramethylsilane as an internal standard and $CDCl_3$ was used as solvent. High resolution mass spectra (HRMS) were obtained with JEOL JMS-SX102A mass spectrometer.

Chloroform was distilled from calcium chloride and dried over molecular sieves 4A (MS 4A). Toluene was distilled from calcium hydride and dried over molecular sieves 4A (MS 4A). All reactions were carried out under an argon atmosphere.

Preparation of N-(3-quinolylmethylidene)-P,P-diphenylphosphinamide (1). In the presence of molecular sieves 4A (500 mg), a chloroform solution (10 mL) of diphenylphosphinyl amide (391 mg, 1.5 mmol) and quinoline-3-carbaldehyde (283 mg, 1.8 mmol) was injected to a flask. Titanium(IV) tetraisopropoxide (0.67 mL, 2.3 mmol) was added at 0 ℃. The mixture was refluxed for 6 h, then the reaction was quenched by the addition of sat. aq. $NaHCO_3$ (2 mL) at 0 ℃. The resultant mixture was filtered using celite and the precipitate was washed with chloroform. The combined filtrate was dried over anhydrous sodium sulfate and evaporated to dryness under reduced pressures. In order to exclude excess aldehyde, the obtained crude mixture was stirred in a mixed solvent (hexane/ethyl acetate = 5/1) at 70 ℃, then the remaining precipitate (pure DPP imine (**1**)) was collected by filtration. Yield 60%. White solid. mp 215 - 216 ℃. IR (KBr disk) 1670, 1207 cm^{-1}; ^1H NMR δ= 7.45-7.53 (m, 6H), 7.65 (dd, J= 7.3, 7.3 Hz, 1H) 7.85 (dd, J= 7.3, 8.5 Hz, 1H), 7.96-8.02 (m, 5H), 8.18 (d, J= 8.5 Hz, 1H), 8.65 (d, J= 2.0 Hz, 1H), 9.52 (d, J= 27.4 Hz, 1H), 9.58 (d, J= 2.0 Hz, 1H); HRMS Found m/z 356.1075. Calcd for $C_{22}H_{17}ON_2P$: M, 356.1079.

General procedure for the enantioselective alkylation of DPP 3-quinolyl imine (1) using amino alcohols (3-6) as chiral ligands. DPP imine (**1**) (71.3 mg, 0.2 mmol) and chiral amino alcohol (0.2 mmol) was placed in a flask and toluene (5 mL) was injected. To the white suspension, 1 M toluene solution of dialkylzinc (0.6 mL, 0.6 mmol) was added at 0 ℃. The reaction mixture was stirred for 21- 41 h at 0 ℃, then quenched by the addition of sat. aq. $NaHCO_3$ (2 mL) at 0 ℃. The resultant mixture was filtered using celite and the precipitate was washed with a mixted solvent (ethyl acetate/methanol = 9/1). The combined filtrate was dried over anhydrous sodium sulfate and evaporated to dryness under reduced pressures. Purification of the crude residue on silica gel TLC gave the pure DPP amines (**2** or **7**).

N-[1-(3-Quinolyl)propyl]-P,P-diphenylphosphinamide (2). White solid. mp 106-107 ℃. Optical purity of was determined to be 66.7% e.e. by HPLC analysis using a chiral column (Daicel Chiralpak AD: 4 x 250 mm, 254 nm UV detector, rt, eluent: 10% 2-propanol in hexane, flow rate: 1.0

mL/min, retention time: 32 min for minor isomer and 60 min for major isomer). $[\alpha]^{22}_{D}$ -46.01° (*c* 0.7, $CHCl_3$) [prepared in the presence of (1S,2R)-chiral ligands]; IR (neat) 3197, 1200 cm^{-1}; ^1H NMR δ= 0.86 (t, J= 7.4 Hz, 3H), 1.92-2.17 (m, 2H), 3.73 (dd, J= 5.5, 9.4 Hz, 1H), 4.33 (ddd, J= 7.8, 8.4, 9.4 Hz, 1H), 7.20-7.54 (m, 7H), 7.66-7.74 (m, 4H), 8.08 (d, J= 8.5 Hz, 1H), 8.78 (d, J= 2.0 Hz, 1H); HRMS Found m/z 386.1541. Calcd for $C_{24}H_{23}N_2OP$: M, 386.1548.

N-[1-(3-Quinolyl)hexyl]-P,P-diphenylphosphinamide (7). Brown oil. Optical purity was determined to be 74.9% e.e. by HPLC analysis using a chiral column (Daicel Chiralpak AD: 4 x 250 mm, 254 nm UV detector, rt, eluent: 10% 2-propanol in hexane, flow rate: 1.0 mL/min, retention time: 22.5 min for minor isomer and 35 min for major isomer). $[\alpha]^{25}_{D}$ -61.05° (*c* 0.70, $CHCl_3$); IR (neat) 3656, 1192 cm^{-1}; ^1H NMR δ= 0.81 (t, J= 6.8 Hz, 3H), 1.21-2.10 (m, 8H), 3.39 (dd, J= 5.5, 9.5 Hz, 1H), 4.39 (ddd, J= 7.8, 8.4, 9.5 Hz, 1H), 7.19-7.55 (m, 8H), 7.67-7.91 (m, 7H), 8.08 (d, J= 8.5 Hz, 1H), 8.76 (d, J= 2.0 Hz, 1H); HRMS Found m/z 429.2088. Calcd for $C_{27}H_{30}ON_2P$: M, 429.2098.

N-(4-Methylphenyl)sulfonyl-1-(3-quinolyl)propylamine (9). White solid. mp 161-162 ℃. Optical purity was determined to be 66.6% e.e. by HPLC analysis using a chiral column (Daicel Chiralpak AD: 4 x 250 mm, 254 nm UV detector, rt, eluent: 10% 2-propanol in hexane, flow rate: 1.0 mL/min, retention time: 52 min for major isomer and 70 min for minor isomer). $[\alpha]^{23}_{D}$ -50.50° (*c* 1.31, $CHCl_3$); IR (neat) 3059, 1327 cm^{-1}; ^1H NMR δ=0.87 (t, J= 7.4 Hz, 3H), 1.76-1.98 (m, 2H), 2.13 (s, 3H), 4.44 (ddd, J= 6.8, 6.8, 6.8 Hz, 1H), 5.40 (d, J= 6.8 Hz, 1H), 6.93 (d, J= 8.2 Hz, 2H), 7.48 (d, 8.2 Hz, 2H), 7.52 (d, J= 8.3 Hz, 1H), 7.61-7.67 (m, 2H), 7.74 (d, J= 2.0 Hz, 1H), 8.02 (d, J= 8.3 Hz, 1H), 8.60 (d, J= 2.0 Hz, 1H); HRMS Found m/z 340.1244. Calcd for $C_{19}H_{20}O_2N_2S$: M, 340.1247.

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10. DPP amine (**2**) with 66.7% e.e. was prepared by mixing product (**2**) which was obtained using (1S,2R)-chiral ligands (**3**, **5**, **6**).

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