The Kolbe Electrolytic Synthesis of Optically Active Bisphosphine Oxides

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Optically active ethano-bridged bisphosphine oxides were conveniently synthesized by Kolbe electrolytic coupling reaction of chiral [(1,1,3,3-tetramethylbutyl)methylphosphinoyl]acetic acid.

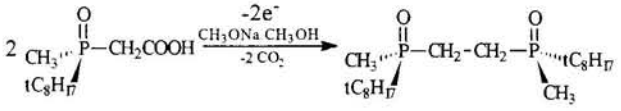
Recently, some chiral phosphine ligands have been used for the synthesis of optically active steroid hormones, α-amino acids, and perfumes, etc. In general, bisphosphine catalysts are not so much sensitive to reaction variables as monophosphine ones and excellent results are obtained at relatively high temperatures and pressures.

Bisphosphine oxides containing a chiral center at phosphorus atom have been prepared mainly by copper-promoted oxidative coupling of two chiral phosphine oxides,[1] which were then converted to chiral bisphosphines using hexachlorodisilane as a reducing agent with inversion at phosphorus chiral centers.[2] On the basis of the unique reactivities of phosphine-boranes, Imamoto *et al.* developed another route to optically pure bisphosphines.[3]

Now we wish to describe a new route for producing chiral bisphosphine oxide reagents by Kolbe electrolytic coupling reaction.

The mechanism of Kolbe reaction has been the subject of much discussion.[4] It seems most probable that a sequence of three processes occurs at the anode: (a) discharge of the carboxylate ions to give carboxylate radicals, (b) rapid decarboxylation of the latter with formation of alkyl radicals and carbon dioxide, and (c) dimerization of the alkyl radicals to yield the Kolbe product. Even when Kolbe coupling reaction was achieved with an α-substituted carboxylic acid, any optical activity associated with the α-carbon atom was apparently lost.[5] However, in the case that an asymmetric center is further from the carboxy group, the optical activity is preserved during Kolbe reaction.[6]

Accordingly, we expected that the Kolbe products of phosphinoyl-acetic acids containing asymmetric center on phosphorus atom, R = $R_1R_2P^*(O)$, should keep the optical activity in a similar manner of asymmetric carbon.



1 **2**

Scheme 1.

A typical experimental procedure is as follows (Scheme 1). To a 0.135 mol dm^{-3} methanol solution of (-)-(*S*)-**1**: [(1,1,3,3-tetramethylbutyl)methylphosphinoyl]acetic acid,[7] mp 99-100 °C, $[\alpha]^{25}_D$ -15.8° (*c* 1.04, $CHCl_3$), 98.6% optically pure,[8] was added sodium methoxide (12.3 mmol). The mixture was cooled with ice water, and the solution was electrolyzed in a cylindrical glass cell fitted with two parallel platinum electrodes (each 2 x 4 cm, 1mm apart) for 3 h. A constant current of 0.7 amp (current density 87.5 mA/cm^2) was applied until 7,560 coulombs were passed finally. The reaction was monitored by measuring the conversion ratio of the starting material by HPLC every hour. The conversion ratio changed from 87.9% to 98.2% and then 98.7% in 3 h. The colorless reaction mixture was then concentrated by a rotary evaporator. The resulting solid residue was dissolved in dichloromethane, and washed with 1 mol dm^{-3} sodium hydroxide aqueous solution, then with distilled water. The solution was dried with anhydrous sodium sulfate overnight, and after filtration, the solvent was removed under reduced pressure. Recrystallization of the residue from acetone gave colorless platelets (+)-(*S,S*)-**2**: 1,2-ethanediylbis[(1,1,3,3-tetramethylbutyl)methylphosphine oxide],[9] yield 35.2%; mp 117-119 °C; $[\alpha]^{23}_D$ +13.4° (*c* 1.04, $CHCl_3$).

The Kolbe electrolytic coupling reaction was also applied to racemic-**1**,[10] mp 127-129 °C, resulting in a 38.6% yield of racemic-**2**,[11] mp 199-200 °C.

Compounds **1** and **2** were identified by means of ^{1}H-NMR, ^{13}C-NMR, ^{31}P-NMR, and FAB-MS. In the ^{31}P-NMR spectra, single signals with chemical shifts δ_P 57.4 ppm ((+)-(*S,S*)-**2**) and 58.7 ppm (racemic-**2**) were observed, respectively. In the ^{1}H-NMR spectra of enantiomerically pure (+)-(*S,S*)-**2**, the chemical shifts of methylene protons next to the chiral phosphorus atom were not the same. One of the protons at δ 1.70-1.81 ppm falled within the domain of additional shielding and the other one at δ 2.17-2.29 ppm falled within the domain of deshielding,[9] whereas that of racemic-**2** gave multiplet signals at δ 1.83-2.02 ppm.[11] Consequently, it was shown that the chiral phosphorus atom has a profound effect on the chemical shifts of methylene protons. From these spectral data and previous studies,[1] it may be concluded that the Kolbe coupling products hold the specific configuration and have the opposite direction of optical rotation to the starting materials.

In summary, we demonstrated the synthesis of chiral bisphosphine oxides by employing Kolbe electrolytic coupling reaction of the chiral phosphinoyl-acetic acids containing asymmetric center on phosphorus atom.

References and Notes

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7 Spectroscopic data for (−)-(*S*)-**1**: ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.06 (s, -C(CH_3)$_3$, 9H), 1.34 (d, ^{3}J = 18.0 Hz, -C(CH_3)$_2$-, 6H), 1.53 (d, ^{3}J = 8.7 Hz, -C-CH_2-C-, 2H), 1.69 (d, ^{2}J = 12.0 Hz, P-CH_3, 3H), 2.71 (dd, ^{2}J = 9.6 Hz, J_{gem} = 13.4 Hz, P-CH_α-COO, 1H), 3.04 (dd, ^{2}J=15.3 Hz, J_{gem} = 13.4 Hz, P-CH_β-COO, 1H), 11.32 (s, COO*H*, 1H); ^{13}C-NMR ($CDCl_3$) δ: 9.19 (d, ^{1}J = 64.6 Hz, P-CH_3), 21.10 (d, ^{2}J = 5.5 Hz, - C(CH_3)$_2$-), 32.05 (s, -C(CH_3)$_3$), 33.04 (d, ^{1}J = 53.6 Hz, P- CH_2-COO), 33.28 (d, ^{2}J = 11.3 Hz, C-CH_2-C), 36.93 (d, ^{1}J = 66.4 Hz, P-C(CH_3)$_2$-), 45.48 (s, -C(CH_3)$_3$), 168.39 (d, ^{2}J = 6.1 Hz, *C*OOH); ^{31}P-NMR($CDCl_3$, internal standard 85% H_3PO_4) δ: 59.41 (s); FAB-MS(Pos.): 235 $[M+H]^+$

8 HPLC; column: CHIRALCEL OD-RH, eluent: 0.2 mol dm^{-3} phosphorus buffer (pH 2) / CH_3CN = 85 / 15 (v/v), flow rate: 0.2 ml/min, detection: 215 nm UV, temp.: 30 °C

9 Spectroscopic data for (+)-(*S,S*)-**2**: ^{1}H-NMR(300 MHz, $CDCl_3$) δ: 1.06 (s, -C(CH_3)$_3$, 18H), 1.31-1.41 (m, -C(CH_3)$_2$-, P-CH_3, 18H), 1.49-1.62 (m, C-CH_2-C, 4H), 1.70-1.81 (m, P-CH_α-, 2H), 2.17-2.29 (m, P-CH_β-, 2H); ^{13}C-NMR($CDCl_3$) δ: 9.76 (m, P-CH_3), 17.38 (m, P-CH_2CH_2-P), 21.53 (d, ^{2}J=4.9 Hz, P-C(CH_3)$_2$-), 32.12 (s, -C(CH_3)$_3$), 33.37 (t, ^{2}J= 7.0Hz, C- CH_2-C), 37.09 (m, P-C(CH_3)$_2$-), 45.97 (s, -C(CH_3)$_3$); ^{31}P-NMR($CDCl_3$, internal standard 85% H_3PO_4) δ: 57.39 (s); FAB-MS(Pos.): 379 $[M+H]^+$

10 Spectroscopic data for racemic-**1**: ^{1}H-NMR(300 MHz, $CDCl_3$) δ: 1.06 (s, -C(CH_3)$_3$, 9H), 1.34 (d, ^{3}J = 17.9 Hz, -C(CH_3)$_2$-, 6H), 1.52 (d, ^{3}J = 8.8 Hz, C-CH_2-C, 2H), 1.71 (d, ^{2}J = 12.3 Hz, P-CH_3, 3H), 2.71 (dd, ^{2}J = 9.2 Hz, J_{gem} = 13.4 Hz, P-CH_α-COO, 1H), 3.00 (dd, ^{2}J = 14.3 Hz, J_{gem} = 13.4 Hz, P-CH_β-COO, 1H), 10.78 (s, -COO*H*, 1H); ^{13}C-NMR($CDCl_3$) δ: 9.26 (d, ^{1}J=64.6 Hz, P-CH_3), 21.09 (s, -C(CH_3)$_2$-), 32.05 (s, -C(CH_3)$_3$), 32.99 (d, ^{1}J=34.1 Hz, P-CH_2- COO), 33.41 (s, C-CH_2-C), 36.90 (d, ^{1}J = 67.0 Hz, P-C(CH_3)$_2$-), 45.49 (s, -C(CH_3)$_3$), 168.17 (d, ^{2}J = 6.1 Hz, *C*OOH); ^{31}P-NMR($CDCl_3$, internal standard 85% H_3PO_4) δ: 59.56 (s); FAB-MS(Pos.): 235 $[M+H]^+$

11 Spectroscopic data for racemic-**2**: ^{1}H-NMR(300 MHz, $CDCl_3$) δ: 1.06 (s, -C(CH_3)$_3$, 18H), 1.32-1.41 (m, -C(CH_3)$_2$-, P-CH_3, 18H), 1.47-1.61 (m, C-CH_2-C, 4H), 1.83-2.02 (m, P-CH_2-CH_2-, 4H); ^{13}C-NMR($CDCl_3$) δ: 8.47 (m, P-CH_3), 16.50 (m, P-CH_2CH_2-P), 21.44 (d, ^{2}J = 4.2 Hz, P-C(CH_3)$_2$-), 32.12 (s, -C(CH_3)$_3$), 33.37 (t, ^{2}J = 7.3 Hz, C-CH_2-C), 36.74 (m, P-C(CH_3)$_2$-), 46.05 (s, -C(CH_3)$_3$); ^{31}P-NMR($CDCl_3$, internal standard 85% H_3PO_4) δ: 58.67 (s); FAB-MS(Pos.): 379 $[M+H]^+$