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PALLADIUM-CATALYZED SYNTHESIS OF A PHOSPHINE OXIDE WITH A CHIRAL PHOSPHORUS CENTER VIA C-H PHOSPHINATION

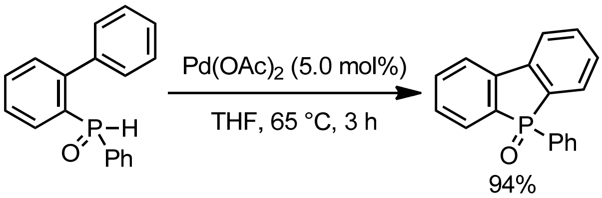
Yoichiro Kuninobu,*† Kazuki Origuchi, and Kazuhiko Takai*

Division of Chemistry and Biotechnology, Graduate School of Natural Science and Technology, Okayama University, 3-1-1 Tsushimanaka, Kita-ku, Okayama 700-8530, Japan

† Present address: Graduate School of Pharmaceutical Sciences, The University of Tokyo, 7-3-1, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

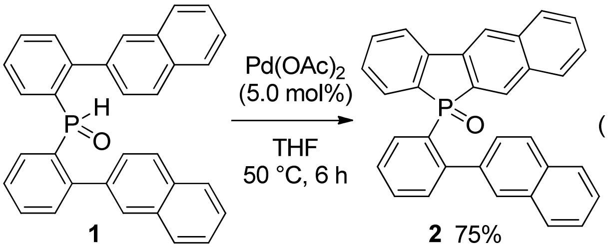
Abstract – A new phosphine oxide with a chiral phosphine center was synthesized from a bis(biphenyl)phosphine oxide by dehydrogenative intramolecular cyclization via P-H and C-H bond activation under palladium catalysis. The absolute configuration of one enantiomer of the phosphine oxide was determined by single crystal X-ray structure analysis. By reducing the phosphine oxide, the corresponding phosphine, which also has a chiral center, was produced. The phosphine compounds could be optically resolved by chiral HPLC column chromatography.

Chiral phosphine compounds are an important category of organic compounds and there have been many reports on their synthesis.[1] Many chiral phosphine compounds are employed as chiral ligands for transition metals. Monodentate chiral phosphine ligands are also well known in which the chiral center at the phosphorus atom controls the enantioselectivity.[2] We have previously reported the palladium-catalyzed synthesis of phosphafluorene oxides from secondary biarylphosphine oxides by intramolecular dehydrogenative cyclization via P-H and C-H bond cleavage (Scheme 1).[3] We anticipated that this reaction could be applied to the synthesis of phosphine oxides with a chiral phosphorus center, followed by reduction of the phosphine oxides to chiral phosphine derivatives. We report herein the palladium-catalyzed synthesis of a phosphine compound with a chiral center, which could be purified as a single enantiomer.



Scheme 1. Synthesis of phosphafluorene oxides by intramolecular dehydrogenative cyclization via P-H and C-H bond cleavage.

Treatment of bis(biphenyl)phosphine oxide **1** with a catalytic amount of palladium acetate Pd(OAc)$_2$ gave phosphafluorene oxide **2** in 75% yield (eq 1).[4] The product **2** has a chiral center and was obtained in racemic form [1:1 mixture of (*R*)-**2** and (*S*)-**2** isomers]. This indicated that chiral phosphine oxides must be formed using a palladium catalyst with a chiral ligand. Therefore, we investigated several combinations of Pd(OAc)$_2$ and chiral phosphine ligands. However, the cyclization reaction did not proceed, probably due to steric hindrance between the chiral phosphine ligands and **1**.



(1)

We next investigated the optical resolution of **2** using a chiral HPLC column [Chiralpak IB (2.0 cm I.D. x 25 cm L, Daicel Chemical Industries, LTD.); eluent: CH$_3$CN/ THF = 80/20; flow rate: 7.0 mL/min; temp = 25 °C; det. 300 nm (UV); injection: 9.45 mL (3.3 g/L in eluent)]. As a result, the two enantiomers could be separated completely (retention times: **2-a**, 16.7 min; **2-b**, 24.0 min). The structure of enantiomer **2-a** was determined by single crystal X-ray structure analysis (Figure 1), which showed that the absolute configuration of **2-a** is the (*S*)-form. The specific rotation value of **2-a** was -410° (**2-b**, +410°). Therefore, it is clear that phosphafluorene oxides **2-a** and **2-b** are enantiomers.

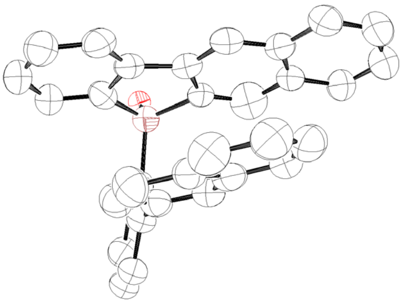
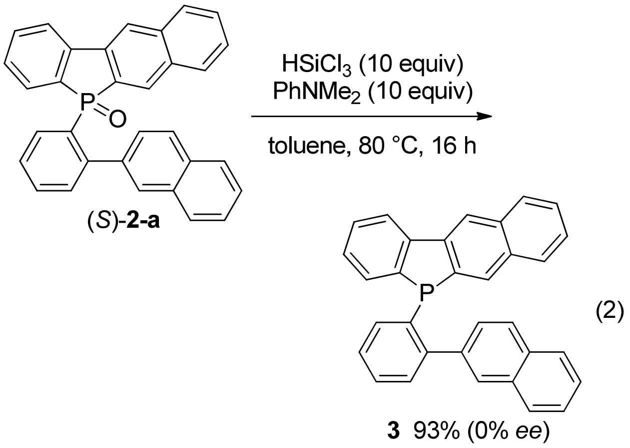


Figure 1. Single crystal X-ray structure of **2-a**.

It is well known that phosphine derivatives have trigonal pyramidal structures and stereoinversion of the phosphorus atoms typically does not occur because of the high energy of the reflecting barrier. Therefore, it is usually possible to use phosphines with three different substituents in an optically active manner. The reduction of (*S*)-**2-a** with trichlorosilane provided the corresponding phosphine **3** (eq 2). Unfortunately, stereoinversion at the phosphorus center occurred and **3** was obtained as a racemic mixture.[5] Therefore, optical resolution was again required after the reduction of **2**. As a result of the optical resolution of phosphine **3** using the chiral HPLC column [Chiralpak IB (2.0 cm I.D. x 25 cm L, Daicel Chemical Industries, LTD.); eluent: hexane/2-propanol = 20/1; flow rate: 7.0 mL/min; temp = 25 °C; det. 300 nm (UV); injection: 9.45 mL (3.3 g/L in eluent)], two enantiomers (*S*)-**3** and (*R*)-**3** could be obtained in enantiomerically pure forms (retention times: (*S*)-**3**, 12.6 min and (*R*)-**3**, 15.5 min).



(2)

In summary, we have succeeded in the synthesis of a phosphine oxide with a chiral phosphorus center from a bis(biphenyl)phosphine oxide by treatment with a catalytic amount of a palladium salt, $Pd(OAc)_2$. The obtained phosphine oxide was easily reduced to the corresponding phosphine in racemic form. The enantiomers of the phosphine oxide and phosphine could be separated completely by a chiral HPLC column. The structure of one enantiomer of the phosphine oxide was determined by single crystal X-ray structure analysis. Scope of substrates and the utility of the phosphine compound **3** are not clear at this stage. We hope that this synthesis of a phosphine oxide with a chiral phosphorus center provides useful insight into organophosphorus chemistry.

EXPERIMENTAL

General. All reactions were carried out in a dry solvent under an argon atmosphere. THF and 1,4-dioxane were purchased from Wako Pure Chemical Industries and were dried and degassed before use. $Pd(OAc)_2$ was purchased from Aldrich Co. 2-(2-Bromophenyl)naphthalene were prepared by Suzuki-Miyaura cross-coupling reaction between 2-bromonaphthalene and *o*-bromophenylboronic acid.[6,7]

^{1}H (400 MHz), ^{13}C (100 MHz), and ^{31}P (162 MHz) NMR spectra were recorded using a JEOL JNM-LA400 spectrometer. Proton chemical shifts are reported relative to Me_4Si ($CDCl_3$) at δ 0.00 ppm or residual solvent peak ($CDCl_3$ at δ 7.26 ppm). Carbon chemical shifts are reported relative to $CDCl_3$ at δ 77.00 ppm. Phosphorus chemical shifts are reported relative to an external 85% H_3PO_4 at δ 0.00 ppm. IR spectra were recorded on a SHIMADZU IRAFFINITY-1 100V J.

Typical Procedure for the Synthesis of Bis(biphenyl)phosphine Oxide 1: Magnesium turnings (0.535 g, 20.0 mmol) were suspended in THF (10 mL). A bead of iodine was added to the above mixture, and the mixture was stirred at room temperature until the color of iodine faded. To this mixture was added dropwise a solution of 2-(2-bromophenyl)naphthalene (5.10 g, 18.0 mmol) in THF (44 mL) over 5 min. The reaction mixture was stirred at 80 °C for 1 h and was then cool down to room temperature. To this Grignard reagent was added dropwise a solution of trichlorophosphine (1.24 g 9.00 mmol) in THF (4.50 mL) over 5 min. After the addition was completed, the mixture was stirred at 80 °C for 3 h and then cooled down to 0 °C. To this solution was added ca. 2 mL of water and the mixture was stirred at 0 °C for 10 min. The mixture was extracted with AcOEt (15 mL x 3), and the organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The product was isolated by column chromatography on silica gel (hexane / AcOEt = 1 / 1) to give a bis(biphenyl)phosphine oxide (**1**, 1.96 g, 48% yield).

Bis(biphenyl)phosphine Oxide 1: 48%, white solid, purification: silica gel column chromatography (hexane / AcOEt = 1 / 1), TLC (hexane / AcOEt = 1 / 2): $R_f = 0.32$, ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.77 (t, *J* = 7.6 Hz, 2H), 6.98 (s, 2H), 7.05 (t, *J* = 6.0 Hz, 2H), 7.17 (t, *J* = 7.6, 2H), 7.33-7.43 (m, 10H), 7.54 (d, *J* = 13.6 Hz, 1H), 7.59 (d, *J* = 13.2 Hz, 1H), 7.61 (d, *J* = 351.6 Hz, 1H), 7.70 (d, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 126.2, 126.3, 126.6, 126.7, 127.4, 127.5, 127.6, 128.0 (d, *J* = 9.1 Hz), 128.3, 130.2, 131.6, 132.4, 132.5, 132.8, 136.0 (d, *J* = 5.5 Hz), 145.6 (d, *J* = 9.1 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 14.3; IR (neat / cm^{-1}) 3051, 1543, 1265, 1180, 1130, 1080, 937, 899, 860, 822, 760, 671, 621, 478, 432, 409; HRMS (EI^{+}) Calcd for $C_{32}H_{23}OP$ (M^{+}) 454.1486, Found 454.1469.

Typical Procedure for the Synthesis of Phosphafluorene Oxide 2: A solution of bis(biphenyl)phosphine oxide (**1**, 1.11 g, 2.45 mmol) and $Pd(OAc)_2$ (27.5 mg, 0.120 mmol) in THF (2.45 mL) was stirred at 50 °C for 6 h. The mixture was cooled to room temperature, and concentrated under reduced pressure. The product was isolated by column chromatography on silica gel (hexane / AcOEt = 1 / 1) to give a phosphafluorene oxide (**2**, 0.83 g, 75% yield).

Phosphafluorene Oxide 2: 75%, white solid, purification: silica gel column chromatography (hexane / AcOEt = 1 / 1), TLC (hexane / AcOEt = 1 / 2): $R_f = 0.36$, ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.37 (d, *J* = 8.4 Hz, 1H), 6.56 (s, 1H), 6.64-6.98 (m, 1H), 7.05-7.06 (m, 1H), 7.11-7.25 (m, 3H), 7.28-7.35 (m, 2H), 7.38 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.45-7.65 (m, 7H), 7.70 (dd, *J* = 7.2, 7.2 Hz, 1H), 7.77 (d, *J* = 7.6 Hz, 1H), 8.04 (d, *J* =

10.4 Hz, 1H), 8.76-8.86 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 119.6 (d, *J* = 9.1 Hz), 121.2 (d, *J* = 10.9 Hz), 125.4, 125.5, 126.1, 126.4 (d, *J* = 105.5 Hz), 126.6, 126.7, 127.5, 127.9 (d, *J* = 96.4 Hz), 128.1, 128.6 (d, *J* = 103.6 Hz), 128.8 (d, *J* = 10.9 Hz), 128.9, 129.2 (d, *J* = 9.1 Hz), 130.8 (d, *J* = 10.9 Hz), 130.9, 131.0, 131.7, 131.88, 131.94, 132.8, 133.2 (d, *J* = 12.7 Hz), 134.6, 134.7, 135.5, 136.2 (d, *J* = 3.6 Hz), 137.0, 137.2, 142.0, 142.2, 145.8 (d, *J* = 10.9 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.3; IR (neat / cm^{-1}) 3050, 3001, 1188, 1134, 1080, 909, 891, 867, 818, 783, 758, 750, 729, 684, 605, 573, 556, 538, 529, 502, 484, 475, 436, 421; HRMS (EI$^+$) Calcd for $C_{32}H_{21}OP$ (M$^+$) 452.1330, Found 452.1319.

Typical Procedure for the Synthesis of Phosphafluorene 3: To a solution of phosphafluorene oxide (**2**, 0.264 g, 0.580 mmol) and *N*,*N*-dimethylaniline (0.703 g, 5.8 mmol) in toluene (5.8 mL) was added trichlorosilane (0.785 g, 5.8 mmol) dropwise at room temperature, and the mixture was stirred at 80 °C for 16 h. After the mixture was cooled to 0 °C, deoxygenated 1 M aq.NaOH (5.8 mL) was slowly added, and the mixture was warmed to room temperature, and then stirred at 50 °C for 0.5 h. The mixture was cooled to room temperature, and filtered through a pad of celite eluted with deoxygenate ethyl acetate. The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated on a rotary evaporator. The product was isolated by column chromatography on silica gel (hexane / AcOEt = 50 / 1) to give a phosphafluorene (**3**, 0.235 g, 93% yield).

Phosphafluorene 3: 93%, white solid, purification: silica gel column chromatography (hexane / AcOEt = 50 / 1), TLC (hexane / AcOEt = 10 / 1): R_f = 0.50, ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.80-6.86 (m, 1H), 7.05 (dd, *J* = 7.2, 7.2 Hz, 1H), 7.28-7.34 (m, 2H), 7.41-7.49 (m, 4H), 7.55-7.59 (m, 3H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.81 (d, *J* = 8.4 Hz, 1H), 7.85-8.05 (m, 7H), 8.26 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 119.6, 121.8, 125.8, 126.28 (d, *J* = 18.2 Hz), 126.34, 127.5, 127.7, 127.8, 127.9, 128.2, 128.7, 128.9, 129.1 (d, *J* = 21.8 Hz), 129.50, 129.54, 130.57, 130.63, 130.8 (d, *J* = 7.2 Hz), 131.0, 132.2, 132.9, 133.0, 133.2, 133.5, 135.6 (d, *J* = 23.6 Hz), 139.3 (d, *J* = 5.4 Hz), 141.1, 141.4, 143.3 (d, *J* = 18.2 Hz), 143.4 (d, *J* = 20.0 Hz), 148.2, 148.5; ^{31}P NMR (162 MHz, $CDCl_3$) δ -20.2; IR (neat / cm^{-1}) 3044, 2965, 1265, 1128, 1020, 939, 872, 864, 818, 770, 758, 743, 733, 683, 563, 525, 478, 469, 446; HRMS (EI$^+$) Calcd for $C_{32}H_{21}P$ (M$^+$) 436.1381, Found 436.1359; specific rotation values: (*S*)-**3**, $[\alpha]_D$ -19.0 and (*R*)-**3**, $[\alpha]_D$ +19.0.

ACKNOWLEDGEMENTS

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