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Stereospecific Halogenation of P(O)-H Bonds with Copper(II) Chloride Affording Optically Active $Z_1Z_2P(O)Cl$

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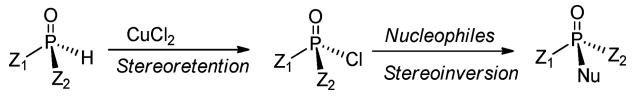


A general and efficient method for the preparation of optically active $Z_1Z_2P(O)Cl$ from the easily prepared optically active *H*-phosphinates and *H*-phosphine oxides was reported. *H*-Phosphinates and *H*-phosphine oxides react stereospecifically with $CuCl_2$ to produce the corresponding optically active $Z_1Z_2P(O)Cl$ with retention of configuration at the phosphorus center. Optically active $Z_1Z_2P(O)Cl$ reacts easily with a variety of nucleophiles to produce other chiral organophosphorus acid derivatives with inversion of configuration at phosphorus.

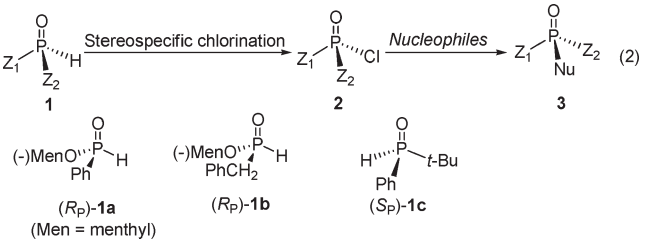
Optically active organophosphorus acid derivatives $Z_1Z_2P(O)Nu$[1] are important compounds that not only show a diverse biological activities such as antibacterial, antipsoriatic, and anti-HIV effect[2] but also are important chiral auxiliaries for asymmetric synthesis.[3] However, methods for their preparation are rather limited.[4]

The highly reactive organophosphorus chlorides $Z_1Z_2P(O)Cl$ easily couple with a variety of nucleophiles (Nu) (eq 1).[5] They are among the most frequently used starting chemicals for the preparation of organophosphorus derivatives.

$$Z_1Z_2P(O)Cl \xrightarrow{\text{Nucleophiles}} Z_1Z_2P(O)Nu \qquad (1)$$

We assumed that if an optically active $Z_1Z_2P(O)Cl$ could be easily prepared and if $Z_1Z_2P(O)Cl$ could react with a nucleophile stereospecifically, a variety of optically active organophosphorus acid derivatives $Z_1Z_2P(O)Nu$ would be readily prepared (eq 2). However, a literature search showed that although a racemic $Z_1Z_2P(O)Cl$ was readily available,[5a] the preparation of an optically active $Z_1Z_2P(O)Cl$ was rather difficult.[6] For example, optically active *t*-BuPhP(O)Br and *t*-BuPhP(S)Cl were obtained from the reactions of optically active *t*-BuPhP(O)H with *N*-bromosuccinimide (NBS) and *N*-chlorosuccinimide (NCS), respectively,[6a] whereas *t*-BuPhP(O)Cl was obtained from the reaction of an optically active *t*-BuPhP(O)H with $CH_3S(O)Cl$ (*ca.* 50% ee),[6b] NCS,[6c] or CCl_4 and Et_3N.[6d] *t*-Bu(MeO)P(O)Cl (ca. 66% ee) was obtained via a similar reaction.[6e] Recently, an optically active *t*-BuPhP(Se)Cl was prepared via the reaction of diastereomerically pure phosphinoselenoic acid salt with oxalyl chloride.[6f,g]

Herein we disclose our studies aiming at developing a general way for the preparation of these optically active $Z_1Z_2P(O)Cl$ **2** and its conversion to other optically active phosphorus compounds **3** via stereospecific nucleophilic substitution reactions (eq 2).



Our strategy for the preparation of **2** is to find an efficient way for the stereospecific halogenation of the relatively easily accessible secondary phosphine oxides and *H*-phosphinates[7] under mild reaction conditions. Along this line, a few known halogenation methods of P(O)-H racemates were tested.[5a] First, since phosphorochloridates $(RO)_2P(O)Cl$ were prepared

(1) (a) Imamoto, T. In *Handbook of Organophosphorus Chemistry*; Engel, R., Ed.; Marcel Dekker: New York, 1992; Chapter 1. (b) Quin, L. D. *A Guide to Organophosphorus Chemistry*; Wiley-Interscience: New York, 2000; Chapter 9. (c) Sasaki, M. In *Chirality in Agrochemicals*; Kurihara, N., Miyamoto, J., Eds.; Wiley & Sons: Chichester, U.K., 1998; p 85.

(2) (a) Kukhar, V. P.; Hudson, H. R. *Aminophosphonic and Aminophosphinic Acids: Chemistry and Biological Activity*; Wiley & Sons: Chichester, U.K., 2000. (b) Sawa, M.; Tsukamoto, T.; Kiyoi, T.; Kurokawa, K.; Nakajima, F.; Nakada, Y.; Yokota, K.; Inoue, Y.; Kondo, H.; Yoshino, K. *J. Med. Chem.* **2002**, *45*, 930. (c) Camp, N. P.; Perry, D. A.; Kinchington, D.; Hawkins, P. C. D.; Hitchcock, P. B.; Gani, D. *Bioorg. Med. Chem.* **1995**, *3*, 297.

(3) (a) Darcel, C.; Uziel, J.; Jugé, S. In *Phosphorous Ligands in Asymmetric Catalysis*; Börner, A., Ed.; Wiley-VCH: Weinheim, 2008; Vol. 3, pp 1211−1233. (b) Maj, A. M.; Pietrusiewicz, K. M.; Suisse, I.; Agbossou, F.; Mortreux, A. *Tetrahedron: Asymmetry* **1999**, *10*, 831. (c) Legrand, O.; Brunel, J. M.; Buono, G. *Tetrahedron lett.* **1998**, *39*, 9419. (d) Gamble, M. P.; Smith, A. R. C.; Wills, M. *J. Org. Chem.* **1998**, *63*, 6068. (e) Brown, J. M.; Carey, J. V.; Russel, M. J. H. *Tetrahedron* **1990**, *46*, 4877. (f) Brunel, J. M.; Legrand, O.; Buono, G. *Eur. J. Org. Chem.* **2000**, 3313. (g) Vinci, D.; Mateus, N.; Wu, X.; Hancock, F.; Steiner, A.; Xiao, J. *Org. Lett.* **2006**, *8*, 216. (h) Matsukawa, S.; Sugama, H.; Imamoto, T. *Tetrahedron Lett.* **2000**, *41*, 6461.

(4) (a) Koizumi, T.; Yanada, R.; Takagi, H.; Hirai, H.; Yoshii, E. *Tetrahedron lett.* **1981**, *22*, 477. (b) Hall, C. R.; Inch, T. D.; Peacock, G.; Pottage, C.; Williams, N. E. *J. Chem. Soc., Perkin Trans. 1* **1984**, 669. (c) Haynes, R. K.; Au-Yeung, T. L.; Chan, W. K.; Lam, W. L.; Li, Z. Y.; Yeung, L. L.; Chan, A. S. C.; Li, P.; Koen, M.; Mitchell, C. R.; Vonwiller, S. C. *Eur. J. Org. Chem.* **2000**, 3205. (d) Grabulosa, A.; Granell, J.; Muller, G. *Coord. Chem. Rev.* **2007**, *251*, 25. (e) Bergin, E.; O'Connor, C. T.; Robinson, S. B.; McGarrigle, E. M.; O'Mahony, C. P.; Gilheany, D. G. *J. Am. Chem. Soc.* **2007**, *129*, 9566.

(5) (a) Kosolapoff, G. M.; Maier, L. In *Organic Phosphorus Compounds*; Wiley-Interscience: New York, 1972; Vol. 4, Chapter 9. (b) Oliana, M.; King, F.; Horton, P. N.; Hursthouse, M. B.; Hii, K. K. *J. Org. Chem.* **2006**, *71*, 2472. (c) Li, Y. C.; Aubert, S. D.; Maes, E. G.; Raushel, F. M. *J. Am. Chem. Soc.* **2004**, *126*, 8888. (d) Clive, D. L. J.; Kang, S. Z. *J. Org. Chem.* **2001**, *66*, 6083. (e) Malachowski, W. P.; Coward, J. K. *J. Org. Chem.* **1994**, *59*, 7625.

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by reactions of $(RO)_2P(O)H$ with CCl_4 in the presence of a base (Atherton−Todd reaction),[8] we investigated the chlorination of phosphinate (R_P)-**1a** under the Atherton−Todd reaction conditions hoping that optically active phosphonic chloride **2a** could be obtained selectively. However, disappointedly, compound (R_P)-**1a** only sluggishly reacted with CCl_4 to yield the corresponding phosphonic chloride **2a** as a mixture of diastereomers (eq 3). Therefore, it was concluded that this reaction could not be applied to the preparation of the optically active $Z_1Z_2P(O)Cl$ **2**.

$$(R_P)\text{-}\mathbf{1a} \xrightarrow[\text{room temperature, 30 h}]{CCl_4,\ NEt_3} \underset{\mathbf{2a}}{((-)\text{MenO})\text{PhP(O)Cl}} \quad (3)$$
$$\text{ca. } 50\% \text{ conversion of } \mathbf{1a}$$
$$\text{diastereomeric ratio of } \mathbf{2a} = 70/30$$

We then turned our attention to another method for the chlorination of $(RO)_2P(O)H$: the chlorination of $(RO)_2P(O)H$ with $CuCl_2$ described by Smith in 1962.[9] Smith reported that $(RO)_2P(O)H$ could be converted to $(RO)_2P(O)Cl$ by $CuCl_2$ on heating at 100 °C in CCl_4 (eq 4). Because of the easy operation and handling of the chemicals, this method is highly attractive. However, it was realized that the harsh conditions used would not be suitable for the preparation of optically active **2** because the starting optically active compound H-P(O) **1** as well as the products **2** might be racemized under such harsh conditions.[7]

$$(RO)_2P(O)H + CuCl_2 \xrightarrow[CCl_4,\ 100\ ^\circ C]{} (RO)_2P(O)Cl \quad (4)$$

We reinvestigated this chlorination reaction and found that it was highly affected by the solvent used (Table 1). Thus, although the reaction slowly proceeded in CH_2Cl_2 or $CHCl_3$ at room temperature, in solvents such as THF, MeCN, acetone, and DMF, it completes rapidly to give a quantitative yield of $(i\text{-PrO})_2P(O)Cl$.

Encouraged by the above results, the chlorination of (R_P)-(L)-menthyl phenylphosphinate (R_P)-**1a** was studied. Thus, a solution of (R_P)-**1a** (1 mmol in 4 mL of THF) was added to a solution of $CuCl_2$ (2.1 mmol in 4 mL THF) at 0 °C. The mixture was stirred at room temperature for 10 min. GC analysis showed the complete consumption of **1a**. The volatiles were removed under a reduced pressure, and the residues were extracted with hexane (10 mL). Solvent was removed to leave **2a** in a quantitative yield (eq 5). In ^{31}P NMR, only one diastereomer of the product could be detected,

TABLE 1. Chlorination of $(i\text{-PrO})_2P(O)H$ with $CuCl_2$ at Room Temperature

$$\underset{1\text{ mmol}}{(i\text{-PrO})_2P(O)H} + \underset{2\text{ mmol}}{CuCl_2} \xrightarrow[25\ ^\circ C]{\text{solvent 5 mL}} (i\text{-PrO})_2P(O)Cl$$

entry	solvent	time (h)	GC yield (%)
1	acetone	0.5	quantitative
2	MeCN	0.5	quantitative
3	DMF	0.5	quantitative
4	THF	0.5	quantitative
5	Et_2O	1	73
6	CH_2Cl_2	4	32
7	$CHCl_3$	4	43

showing that this chlorination reaction took place highly stereospecifically (vide infra). Similar stereospecific chlorination also took place efficiently with another optically active phosphinate (R_P)-**1b** and an secondary phosphine oxide (S_P)-**1c** to quantitatively produce the corresponding optically active P(O)Cl compounds **2b** and **2c**, respectively.

$$\mathbf{1a-c} \xrightarrow[CuCl_2,\ THF,\ 0-25\ ^\circ C,\ <20\ min]{\text{stereospecific chlorination}} \underset{\text{quantitative}}{\mathbf{2a-c}} \quad (5)$$

As to the stereochemistry, crystals suitable for X-ray analysis were obtained by careful recrystallization of **2c** from hexane, which led to the successful determination of the absolute configuration at phosphorus to be R_P, indicating that the above chlorination reaction took place via retention of configuration at phosphorus (Figure 1).

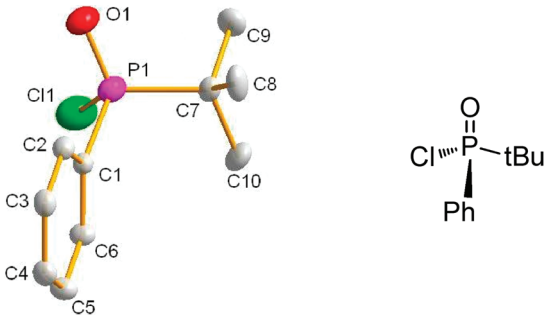


FIGURE 1. Single-crystal X-ray structure of compound (R_P)-**2c**.

To our surprise, although-moisture sensitive, these optically active compounds **2** are rather stable toward racemization. In hexane or $CHCl_3$ no racemization took place at room temperature for 1 week. Compound **2a** in benzene is stable even at 70 °C for 5 days.

As expected, these optically active P(O)Cl compounds are versatile starting materials for the preparation of a variety of optically active phosphorus compounds by a stereospecific replacement of the chlorine atom with a nucleophile. Thus, (S_P)-**2a** reacted stereospecifically (with inversion of the configuration at phosphorus) with MeMgCl, *i*-PrMgCl, $PhCH_2MgCl$, CH_2CHCH_2MgCl, and $TMSCH_2MgCl$ to give the corresponding optically active phosphinates in high yields (Table 2, entries 1−5). The stereochemistry at phosphorus of the product ((−)MenO)PhMeP(O) (Table 2, entry 1) was determined to be S_P by comparing its optical rotation with that of the literature,[10] showing the substitution

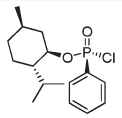
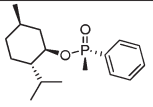
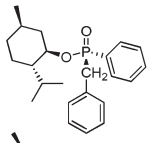
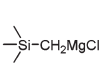
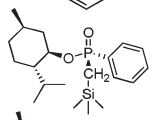
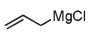
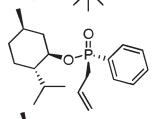
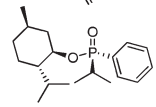
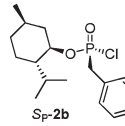
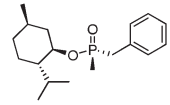
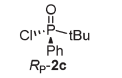
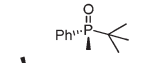
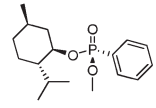
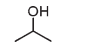
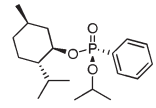
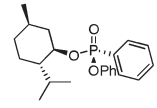
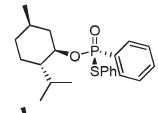
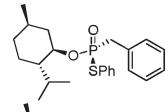
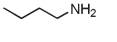
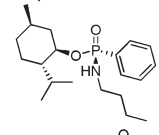
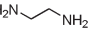
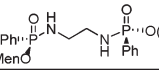
(6) (a) Au-Yeung, T. L.; Chan, K. Y.; Chan, W. K.; Haynes, R. K.; Williams, I. D.; Yeung, L. L. *Tetrahedron Lett.* **2001**, *42*, 453. (b) Drabowicz, J. *Heteroatom. Chem.* **2002**, *13*, 437. (c) Michalski, J.; Skrzypczyński, Z. *J. Chem. Soc., Chem. Commun.* **1977**, 66. (d) Skrzypczynski, Z.; Michalski, J. *J. Org. Chem.* **1988**, *53*, 4549. (e) Krawiecka, B.; Wojna-Tadeusiak, E. *J. Chem. Soc., Perkin Trans. 1* **1991**, 229. (f) Kimura, T.; Murai, T. *Chem. Commun.* **2005**, 4077. (g) Murai, T.; Kimura, T. *Curr. Org. Chem.* **2006**, *10*, 1963. (h) Perlikowska, W.; Gouygou, M.; Daran, J. C.; Balavoine, G.; Mikolajczyk, M. *Tetrahedron Lett.* **2001**, *42*, 7841. (i) Corriu, R. J. P.; Lanneau, G. F.; Leclercq, D. *Tetrahedron* **1980**, *36*, 1617.

(7) (a) Xu, Q.; Zhao, C. Q.; Han, L. B. *J. Am. Chem. Soc.* **2008**, *130*, 12648. (b) Wang, G.; Shen, R. W.; Xu, Q.; Goto, M.; Zhao, Y. F.; Han, L. B. *J. Org. Chem.* **2010**, *75*, 3890.

(8) (a) Atherton, F.; Openshaw, A.; Todd, A. *J. Chem. Soc.* **1945**, 660. (b) Atherton, F.; Todd, A. *J. Chem. Soc.* **1947**, 674. (c) For an early observation on the reaction of (*R*)-(−)-isopropyl methylphosphinate (4.6% optically pure) under Todd reaction conditions, see: Reiff, L. P.; Aaron, H. S. *J. Am. Chem. Soc.* **1970**, *92*, 5275.

(9) (a) Smith, T. D. *J. Chem. Soc.* **1962**, 1122. (b) Okamoto, Y.; Kusano, T.; Takamuku, S. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 3359.

TABLE 2. Stereospecific Substitution Reaction of Optically Active $Z_1Z_2P(O)Cl$ 2 with C-, O-, S-, and N-Nucleophiles

entry	$Z_1Z_2P(O)Cl$	nucleophile	product	yield (%)[a]
1	 (S_P-**2a**)	CH_3MgCl		98[b]
2	S_P-**2a**	$PhCH_2MgCl$		85[b]
3	S_P-**2a**			59[b]
4	S_P-**2a**			96[b]
5	S_P-**2a**			68[b]
6	 (S_P-**2b**)	CH_3MgCl		91[b]
7	 (R_P-**2c**)	CH_3Li		95[b]
8	S_P-**2a**	CH_3OH		98[c]
9	S_P-**2a**			90[c]
10	S_P-**2a**	PhOH		97[c]
11	S_P-**2a**	PhSH		98[c]
12	S_P-**2b**	PhSH		94[c]
13	S_P-**2a**			97[c]
14	S_P-**2a**			85[c]

[a]Isolated yield. [b]Reaction conditions: **2** (1 mmol), nucleophile (1.1 mmol) in dry THF (5 mL), −78 °C. [c]Reaction conditions: **2** (1 mmol), nucleophile (2 mmol), Et_3N (2 mmol) in dry THF (5 mL), 0 °C.

took place at phosphorus via inversion of configuration. (S_P)-**2a** also reacted efficiently with other nucleophiles such as MeOH, *i*-PrOH, PhOH, PhSH, *n*-$BuNH_2$, and $H_2NCH_2CH_2NH_2$ to give the corresponding optically active phosphorus acid derivatives highly selectively in high yields. These compounds are known compounds, and the absolute configurations around phosphorus were easily determined by comparing with authentic samples.[7b] The above substitution reactions also proceeded smoothly with (S_P)-**2b** and (R_P)-**2c**. To the best of our knowledge, there were no precedents of preparation of optically active organophosphorus acid derivatives by the stereospecific nucleophilic substitution of optically active P(O)Cl compounds.[6]

The stereospecific features of the halogenation of **1** by $CuCl_2$ forming **2** and the substitution reactions of **2** with nucleophiles forming **3** are confirmed by the following experiments using diastereomeric mixtures of **1a** and **2a** as substrates, respectively. Thus, reaction of **1a** (R_P/S_P = 64/36) with $CuCl_2$ produced a diastereometric mixture of **2a** with the same ratio of S_P/R_P = 64/36. Similarly, the substitution reaction of a diastereomeric mixture of **2a** (S_P/R_P = 64/36) with MeMgCl gave a diastereometric mixture of **3a** (S_P/R_P = 64/36)[10c] with inversion of configuration at the phosphorus atom.

In summary, we have demonstrated that optically pure phosphorus chlorides $Z_1Z_2P(O)Cl$ can be simply prepared via a stereospecific (retention of configuration) halogenation of the corresponding P(O)H compounds with $CuCl_2$ under mild conditions. These compounds are versatile starting materials for the preparation of other optically pure phosphorus acid derivatives, i.e., $Z_1Z_2P(O)Cl$ reacts with C-, O-, S-, and N-nucleophiles to produce the corresponding optically active phosphorus compounds via stereospecific replacement of the chlorine atom (inversion of configuration).

Experimental Section

Typical Procedure for the Synthesis of 2. To a solution of $CuCl_2$ (10.5 mmol in 10 mL THF) was added (R_P)-**1b** (5 mmol in 10 mL THF) at 0 °C. The cooling bath was removed, and the mixture was stirred at room temperature for 10 min. The volatiles were removed under vacuum. The residue was extracted with 30 mL of hexane and filtered. After evaporating the solvent, the desired product (S_P)-**2b** was obtained as a white solid in quantitative yield. Mp: 64−65 °C; $[\alpha]^{25}_D$ = −93.9 ($CHCl_3$, *c* 0.986). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36−7.28 (m, 5H), 4.42−4.33 (m, 1H), 3.60−3.45 (m, 2 H), 2.08 (d, J = 12.0 Hz, 1H), 1.93−1.88 (m,1H), 1.68−1.62 (m, 2H), 1.42−1.25 (m, 2H), 1.11−0.94 (m, 2H), 0.88−0.78 (m, 7H), 0.74 (d, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 130.2 (d, J_{P-C} = 7.6 Hz), 129.8 (d, J_{P-C} = 11.4 Hz), 128.6 (d, J_{P-C} = 3.9 Hz), 127.6 (d, J_{P-C} = 4.7 Hz), 80.9 (d, J_{P-C} = 9.5 Hz), 48.3 (d, J_{P-C} = 6.7 Hz), 42.8, 42.0 (d, J_{P-C} = 121.0 Hz), 33.9, 31.6, 25.5, 22.8, 21.8, 21.0, 15.7. ^{31}P NMR (162 MHz, $CDCl_3$): δ 37.8. Anal. Calcd for $C_{17}H_{26}ClO_2P$: C, 62.10; H, 7.97. Found: C, 62.29; H, 8.08.

Typical Procedure for the Stereospecific Substitution Reaction of 2. A solution of methylmagnesium chloride (1.1 mmol in 2 mL THF) was added to a solution of (S_P)-**2a** (1.0 mmol in 3 mL of THF) at −78 °C and stirred for 2 h, and then the reaction mixture was slowly warmed to −40 °C. The reaction mixture was quenched with saturated NH_4Cl solution, and the product was extracted with $CHCl_3$, dried over $MgSO_4$, and concentrated under vacuum to give NMR spectroscopically pure product (S_P)-((−)MenO)PhMeP(O) in 98% yield.[10] White solid. Mp: 80−81 °C; $[\alpha]^{30}_D$ = −92.6 (benzene, *c* 0.760). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.82−7.78 (m, 2H), 7.54−7.51 (m, 1H),

(10) (a) Nudelman, A.; Cram, D. J. *J. Org. Chem.* **1971**, *36*, 335. (b) Korpiun, O.; Lewis, R. A.; Chickos, J.; Mislow, K. *J. Am. Chem. Soc.* **1968**, *90*, 4842. (c) Dabkowski, W.; Ozarek, A.; Olejniczak, S.; Cypryk, M.; Chojnowski, J.; Michalski, J. *Chem.—Eur. J.* **2009**, *15*, 1747.

7.47−7.45 (m, 2H), 3.97−3.93 (m, 1H), 2.37 (d, J = 12.0 Hz, 1H), 1.93−1.87 (m, 1H), 1.70 (d, J = 15.0 Hz, 3H), 1.62−1.57 (m, 2H), 1.44−1.37 (m, 1H), 1.32−1.19 (m, 2H), 0.90 (d, J = 6.0 Hz, 3H), 0.88−0.83 (m, 2H), 0.81 (d, J = 6.5 Hz, 3H), 0.31 (d, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 133.4 (d, J_{P-C} = 128.8 Hz), 132.0 (d, J_{P-C} = 3.1 Hz), 131.1 (d, J_{P-C} = 10.3 Hz), 128.4 (d, J_{P-C} = 12.3 Hz), 76.8 (d, J_{P-C} = 7.3 Hz), 48.8 (d, J_{P-C} = 6.3 Hz), 43.8, 34.1, 31.5, 25.4, 22.7, 21.9, 21.0, 16.5 (d, J_{P-C} = 102.0 Hz), 15.2. ^{31}P NMR (202 MHz, $CDCl_3$): δ 40.6.

Supporting Information Available: General experimental procedures, spectroscopic data for compounds **2** and **3**, and X-ray data for compound (R_P)-**2c** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.