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# Stereospecific Coupling of *H*-Phosphinates and Secondary Phosphine Oxides with Amines and Alcohols: A General Method for the Preparation of Optically Active Organophosphorus Acid Derivatives†

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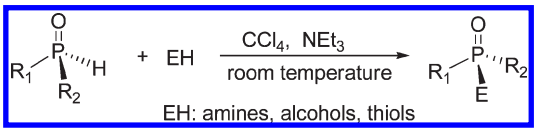
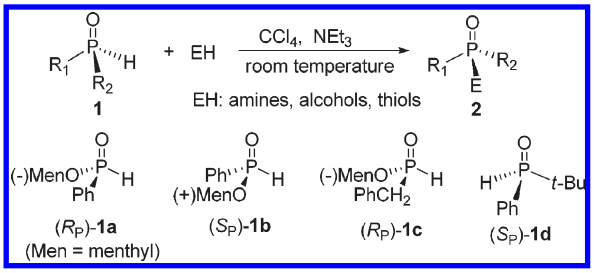



The reaction of *H*-phosphinates and secondary phosphine oxides with amines and alcohols proceeds highly stereospecifically to give the corresponding coupling products with inversion of configuration at the phosphorus center under the Atherton−Todd reaction conditions. This finding leads to the establishment of a general and efficient method for the synthesis of a variety of optically active organophosphorus acid derivatives from the easily available chiral *H*-phosphinates and secondary phosphine oxides.

Optically active organophosphorus acid derivatives **2**[1] such as amidophosphinates ($R_1$ = an alkyl or aryl, $R_2$ = an alkoxy group, E = an amino group) and phosphonates ($R_1$ = an alkyl or aryl, $R_2$ and $R_3$ = an alkoxy group) are important compounds which not only show diverse biological activities such as antibacterial, antipsoriatic, and anti-HIV effects[2] but also have potential applications in asymmetric synthesis.[3] However, methods for their preparation are rather limited.[1a,b,4] Thus, although a few synthetic routes have been reported by using chiral auxiliaries such as (−)-ephedrine, L-proline or (+)-d-glucose, the procedures were tedious, the yields were usually poor, and the generality was rather limited.[4b−e]

Herein, we report a general protocol for the preparation of optically active organophosphorus acid derivatives **2**. During an ongoing project on the preparation of optically active phosphorus compounds via the stereospecific transformation of the reactive H−P bonds of the relatively easily accessible *H*-phosphonates and *H*-phosphinates,[5] we found that **2** can be easily generated in high yields by a stereospecific coupling of the optically pure *H*-phosphinates and secondary phosphine oxides **1**[6] with amines and alcohols under mild Atherton−Todd reaction conditions (Scheme 1).[7,8] To the best of our knowledge, such a general method has not been revealed yet.

**SCHEME 1**




As demonstrated by the following experiment, this is an easily operating and highly efficient reaction. Thus, to a mixture of ($R_P$)-*l*-menthyl phenylphosphinate ($R_P$)-**1a** (5 mmol), $Et_3N$ (10 mmol), and $CCl_4$ (5 mL) in acetonitrile

† Dedicated to the memory of Professor Xian Huang.

(1) (a) Imamoto, T. In *Handbook of Organophosphorus Chemistry*; Engel, R., Eds.; Marcel Dekker: New York, 1992; Charpter 1, pp 5−8. (b) Quin, L. D. *A Guide to Organophosphorus Chemistry*; Wiley-Interscience: New York, 2000; Chapter 9, pp 272. (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. et al. *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.; Hawkins, P. C. D.; Hitchcock, P. B.; Gani, D. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 1047. (d) Camp, N. P.; Perry, D. A.; Kinchington, D.; Hawkins, P. C. D.; Hitchcock, P. B.; Gani, D. *Bioorg. Med. Chem.* **1995**, *3*, 297. (e) McLeod, D. A.; Brinkworth, R. I.; Ashley, J. A.; Janada, K. D.; Wirsching, P. *Bioorg. Med. Chem. Lett.* **1991**, *1*, 653.

(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) Gamble, M. P.; Smith, A. R. C.; Wills, M. *J. Org. Chem.* **1998**, *63*, 6068. (c) Brown, J. M.; Carey, J. V.; Russel, M. J. H. *Tetrahedron* **1990**, *46*, 4877. (d) Brunel, J. M.; Legrand, O.; Buono, G. *Eur. J. Org. Chem.* **2000**, 3313. (e) Legrand, O.; Brunel, J. M.; Buono, G. *Tetrahedron Lett.* **1998**, *39*, 9419. (f) Vinci, D.; Mateus, N.; Wu, X.; Hancock, F.; Steiner, A.; Xiao, J. *Org. Lett.* **2006**, *8*, 216.

(4) (a) Hall, C. R.; Inch, T. D. *Tetrahedron* **1980**, *36*, 2059. (b) Koizumi, T.; Yanada, R.; Takagi, H.; Hirai, H.; Yoshii, E. *Tetrahedron Lett.* **1981**, *22*, 477. (c) Koizumi, T.; Yanada, R.; Takagi, H.; Hirai, H.; Yoshii, E. *Tetrahedron Lett.* **1981**, *22*, 571. (d) Cooper, D. B.; Hall, C. R.; Harrison, J. M.; Inch, T. D. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1969. (e) Hall, C. R.; Inch, T. D.; Peacock, G.; Pottage, C.; Williams, N. E. *J. Chem. Soc., Perkin Trans. 1* **1984**, 669.

(5) (a) Han, L.-B.; Zhao, C.-Q.; Onozawa, S.; Goto, M.; Tanaka, M. *J. Am. Chem. Soc.* **2002**, *124*, 3842. (b) Han, L.-B.; Zhao, C.-Q. *J. Org. Chem.* **2005**, *70*, 10121.

(6) Optically pure *H*-P(O) compounds **1a**−**d** can be purchased from Katayama Chemical Industries Co. Ltd. (http://www.katayamakagaku.co.jp). For their preparation, see: (a) Farnham, W. B.; Murray, R. K.; Mislow, K. *J. Am. Chem. Soc.* **1970**, *92*, 5809. (b) Reiff, L. P.; Aaron, H. S. *J. Am. Chem. Soc.* **1970**, *92*, 5275. (c) Benschop, H. P.; Platenburg, D. H. J. M.; Meppelder, F. H.; Boter, H. J. *Chem. Commun.* **1970**, 33. (d) Bodalski, R.; Koszuk, J. *Phosphorus, Sulfur, Silicon Relat. Elem.* **1989**, *44*, 99. (e) Xu, Q.; Zhao, C.-Q.; Han, L.-B. *J. Am. Chem. Soc.* **2008**, *130*, 12648.

(7) (a) Atherton, F.; Openshaw, A.; Todd, A. *J. Chem. Soc.* **1945**, 660. (b) Atherton, F.; Todd, A. *J. Chem. Soc.* **1947**, 674.



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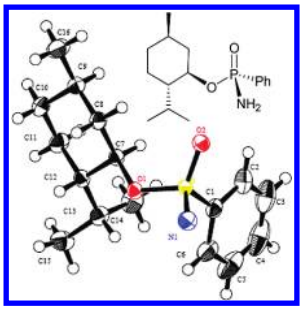
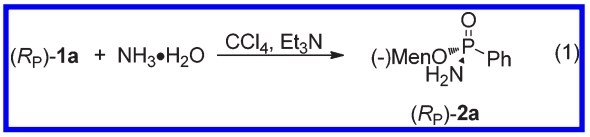


**FIGURE 1.** Single-crystal X-ray structure of compound (*Rp*)-**2a**.

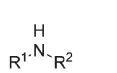
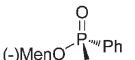
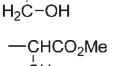
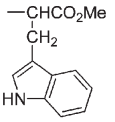
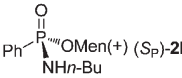
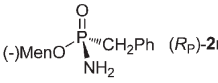
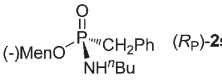
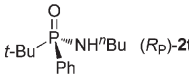
(25 mL) was added ammonia solution (28% in water, 5 mL) at 0 °C. The mixture was stirred at room temperature overnight to produce the expected amidophosphinate **2a** in 95% isolated yield as a single diastereomer (eq 1).




The facts that another diastereomer ($S_P$) could not be detected from the crude products by NMR spectroscopy and that when a diastereomeric mixture of **1a** ($R_P/S_P$ = 60/40) was employed as the substrate in the above reaction **2a** was obtained as a mixture of diastereomers in the same ratio ($R_P/S_P$ = 60/40) indicated that this reaction proceeded highly stereospecifically. In addition, the stereochemistry at phosphorus in **2a** was unambiguously determined by X-ray analysis, showing that this reaction proceeded with inversion of configuration at the phosphorus center in **1a** (Figure 1).

The results compiled in Table 1 clearly demonstrate that this stereospecific reaction is a highly general and efficient method for the preparation of a variety of optically pure organophosphorus acid derivatives. Thus, in addition to ammonia, primary amines such as *n*-butylamine, aniline, and benzylamine (runs 1−5) all reacted with ($R_P$)-**1a** to give the corresponding aminophospninates in high yields. Notably, the expected P−N coupling product ($R_P$)-**2c** was also obtained in high yield from 5-hydroxylpentan-1-amine and other amines bearing an OH group, indicating the higher reactivity of an amino group than that of a hydroxyl group (runs 2, 10, and 16). A wide range of amino acid esters can also be employed as substrates in the reaction with ($R_P$)-**1a**, readily yielding the corresponding optically active phosphoryl amino acid esters (entries 6−11). Compared to primary amines, the reaction with secondary amines proceeded a little slowly under the present reaction conditions. Nevertheless, the expected products were obtained stereospecifically and in good yields. For example, the reactions of diethylamine, dipropylamine, and pyrrolidine with ($R_P$)-**1a** afforded the corresponding optically active phosphinylamides in 77%, 74%, and 75% yields, respectively (runs 12, 13, and 15). Note that functionalized secondary amines such as diallylamine and bis(2-hydroxyethyl)amine could also be used as substrates to produce the corresponding products ($R_P$)-**2n** and ($R_P$)-**2p** in 79% and 64% yields (runs 14 and 16). Besides

**TABLE 1. Stereospecific Coupling Reaction of *H*-Phosphinates and Secondary Phosphine Oxides 1 with Amines** [a]

| run | P(O)H | amine | product | yield (%) |
|---|---|---|---|---|
| 1 | ($R_P$)-**1a** |  |  | 94% |
| | | $R^1$, $R^2$ = H, *n*-Bu | ($R_P$)-**2b** | |
| 2 | | $R^1$, $R^2$ = H, $(CH_2)_5OH$ | ($R_P$)-**2c** | 92% |
| 3 | | $R^1$, $R^2$ = H, Ph | ($R_P$)-**2d** | 90% |
| 4 | | $R^1$, $R^2$ = H, Bn | ($R_P$)-**2e** | 92% |
| 5 | | $R^1$, $R^2$ = H,  | ($R_P$)-**2f** | 91% |
| 6[c] | | $R^1$, $R^2$ = H, —CH(Me)$CO_2$Me | ($R_P$)-**2g** | 90% |
| 7[c] | | $R^1$, $R^2$ = H, —$CH_2CO_2$Me | ($R_P$)-**2h** | 86% |
| 8[c] | | $R^1$, $R^2$ = H, —CH($^i$Pr)$CO_2$Me | ($R_P$)-**2i** | 84% |
| 9[c] | | $R^1$, $R^2$ = H, —CH(Bn)$CO_2$Me | ($R_P$)-**2j** | 85% |
| 10[c] | | $R^1$, $R^2$ = H,  | ($R_P$)-**2k** | 80% |
| 11[c] | | $R^1$, $R^2$ = H,  | ($R_P$)-**2l** | 76% |
| 12[c] | | $R^1$ = $R^2$ = Et | ($R_P$)-**2m** | 77% |
| 13 | | $R^1$ = $R^2$ = *n*-Pr | ($R_P$)-**2n** | 74% |
| 14 | | $R^1$ = $R^2$ = allyl | ($R_P$)-**2o** | 79% |
| 15 | | $R^1$ = $R^2$ = —$CH_2CH_2$— | ($R_P$)-**2p** | 75% |
| 16 | | $R^1$ = $R^2$ = —$CH_2CH_2OH$ | ($R_P$)-**2q** | 64% |
| 17 | ($S_P$)-**1b** | $R^1$, $R^2$ = H, *n*-Bu |  ($S_P$)-**2b** | 94% |
| 18[d] | ($R_P$)-**1c** | $R^1$ = $R^2$ = H |  ($R_P$)-**2r** | 95% |
| 19 | | $R^1$, $R^2$ = H, *n*-Bu |  ($R_P$)-**2s** | 93% |
| 20 | ($S_P$)-**1d** | $R^1$, $R^2$ = H, *n*-Bu |  ($R_P$)-**2t** | 90% |

[a] 1 mmol of **1**, 2 mmol of $NEt_3$, and 2 mmol of amine dissolved in 5 mL of $CCl_4$, stirred at room temperature overnight. [b] Isolated yield. [c] 5 mL of $CH_2Cl_2$ was added. [d] 5 mL of $CH_3CN$ was added.

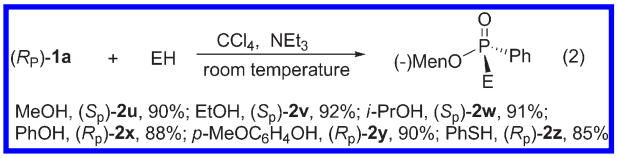
($R_P$)-*l*-menthyl phenylphosphinate (**1a**), ($S_P$)-*l*-menthyl phenylphosphinate ($S_P$)-**1b**, ($R_P$)-*l*-menthy benzylphosphinate (**1c**), and bulky ($S_P$)-*tert*-butylphenylphosphine oxide (**1d**), all served as good substrates to produce the corresponding optically active organophosphorus acid derivatives in high yields (entries 17−20).

In addition to amines, other nucleophiles such as alcohols and thiophenol could also be used as the substrates to produce the corresponding coupling compounds stereospecifically and in high yields (eq 2). However, when aliphatic

(8) For an early observation on the reaction of (*R*)-(−)-isopropyl methylphosphinate (4.6% optically pure) with aniline, see: Reiff, L. P.; Aaron, H. S. *J. Am. Chem. Soc.* **1970**, *92*, 5275.

(9) Aliphatic thiols themselves react with $CCl_4$ and $Et_3N$ under the present conditions.

thiols, e.g., *n*-BuSH and *n*-$C_8H_{17}SH$, were employed, the reaction did not give the corresponding products.[9]




In summary, we have demonstrated that a variety of optically pure phosphorus acids derivatives can be efficiently prepared via a simple stereospecific coupling of the corresponding P(O)H-type compounds with nucleophiles under the Atherton−Todd reaction conditions.

## Experimental Section

**Typical Procedure for the Synthesis of ($R_P$)-2a.** To a mixture of ($R_P$)-**1a** (5 mmol), $Et_3N$ (10 mmol), and $CCl_4$ (5 mL) in acetonitrile (25 mL) was added ammonia solution (28% in water, 5 mL) at 0 °C. The resulting mixture was allowed to stir at 0 °C for 30 min and then warmed to room temperature. After the mixture was stirred overnight, water was added. Extraction with ethyl acetate and removal of the solvent under a reduced pressure gave the crude product. Pure ($R_P$)-**2a** was obtained by passing the crude product through a short silica gel column using MeCN/EtOAc as eluent: 1.4 g, 95% yield; white solid; mp 143.1−143.4 °C; $[\alpha]^{24}_D = -67.9$ ($CHCl_3$, $c = 0.805$); $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.83−7.78 (m, 2H), 7.50−7.47 (m, 1H), 7.43−7.38 (m, 2H), 4.24−4.16 (m, 1H), 3.17 (s, 2H), 2.35 (d, $J$ = 12.1 Hz, 1H), 2.02−1.95 (m, 1H), 1.66−1.60 (m, 2H), 1.50−1.40 (m, 1H), 1.34−1.27 (m, 1H), 1.21 (q, $J$ = 12.0 Hz, 1H), 1.01−0.86 (m, 2H), 0.92 (d, $J$ = 6.4 Hz, 3H), 0.83 (d, $J$ = 7.2 Hz, 3H), 0.54 (d, $J$ = 6.8 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 132.5 (d, $J_{P-C}$ = 173.1 Hz), 131.6 (d, $J_{P-C}$ = 2.9 Hz), 131.3 (d, $J_{P-C}$ = 9.3 Hz), 128.2 (d, $J_{P-C}$ = 14.0 Hz), 76.5 (d, $J_{P-C}$ = 6.5 Hz), 48.7 (d, $J_{P-C}$ = 6.6 Hz), 43.6, 34.1, 31.6, 25.5, 22.7, 22.0, 21.0, 15.3; $^{31}$P NMR ($CDCl_3$, 160 MHz) $\delta$ 23.0; HRMS calcd for $C_{16}H_{26}NO_2P$ 295.1701, found 295.1696.

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