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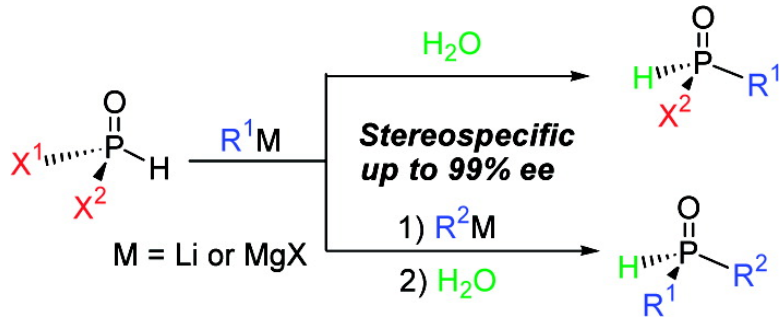


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# Stereospecific Nucleophilic Substitution of Optically Pure *H*-Phosphinates: A General Way for the Preparation of Chiral P-Stereogenic Phosphine Oxides

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***Abstract:*** Contrary to the generally held view, it is found that the rapid epimerization of (−)-menthyl ($R_P$)-phenylphosphinate under basic conditions is not due to the so far believed inherent stereolability of its corresponding anion but due to a reaction of the hydrogen phosphinate ester with a metal alkoxide. This finding successfully leads to a discovery that, by adding an *H*-phosphinate to organolithiums or Grignard reagents at a low temperature, the nucleophilic substitution of the alkoxy group of the *H*-phosphinate with organolithiums or Grignard reagents proceeds stereospecifically with inversion of configurations at phosphorus to give a wide range of P-stereogenic secondary phosphine oxides and tertiary phosphine oxides, by quenching the reaction mixture with water and alkyl halides, respectively. This finding establishes a general protocol for the preparation of optically active secondary phosphine oxides and tertiary phosphine oxides from the easily accessible optically pure *H*-phosphinates. Mechanistic studies show that the substitution reactions of *H*-phosphinates with organolithiums and Grignard reagents proceed via two competing reaction paths, that is, a two-step reaction path involving first a deprotonation of *H*-phosphinates followed by a substitution of the corresponding anion with inversion of configuration at phosphorus and a direct substitution of RM with *H*-phosphinates generating the SPO directly.

## Introduction

P-Stereogenic phosphorus compounds are of importance in organic synthesis, and asymmetric catalysis.[1] The recent realization that secondary phosphine oxides (SPOs) can serve as ligands in metal-catalyzed reactions[2] is boosting a new wave of studies on metal-catalyzed asymmetric reactions using unsymmetrical enantiomerically pure SPOs,[3] because of the easy operation of the metal-mediated reactions using the air-stable SPOs.[4] However, progress of such studies is bottlenecked by the limited availability of these optically pure SPOs since their preparations usually involve tedious procedures.[1,3,4] We are engaging in the preparation of optically active phosphorus compound via the stereospecific transformation of the reactive H−P bonds of the relatively easily accessible *H*-phosphonates and *H*-phosphinates.[5,6] We have revealed that a palladium-mediated addition to alkynes and a radical or base initiated addition to alkenes of the optically pure (−)-menthyl ($R_P$)-phenylphosphinate **1a** could take place stereospecifically to give high yields of ($R_P$)-phosphinates with retention of configuration at phosphorus (Scheme 1).[6] Since the preparation of SPOs via substitution of organolithiums or Grignard reagents with *H*-phosphonates and *H*-phosphinates is well-known,[7] we assume that if it can proceed stereospecifically, a variety of enantiomerically pure SPOs **2** and tertially phosphine oxides (TPOs) **3** will be readily prepared from an enantiomerically pure *H*-

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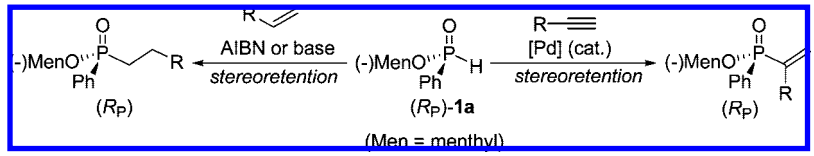
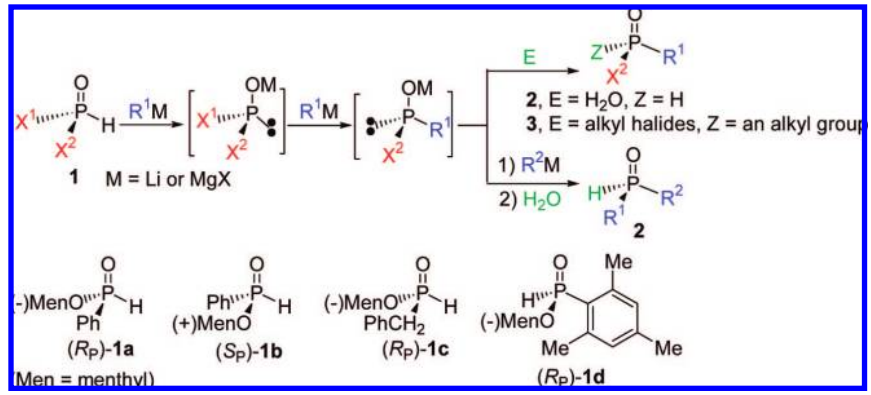
**10.1021/ja804412k CCC: $40.75** 

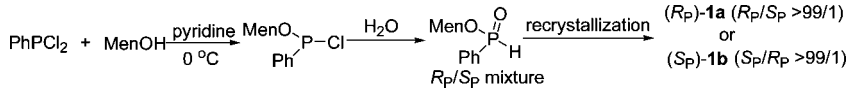
**Scheme 1**



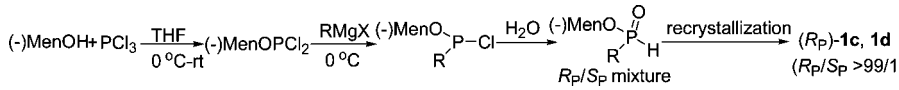

**Scheme 2**




**Scheme 3**




**Scheme 4**




phosphinates **1** (Scheme 2).[8,9] Moreover, if the two substituents $X^1$ and $X^2$ on **1** can be sequentially replaced, a vast number of the optically active SPOs can be generated by a simple combination of $R^1M$ and $R^2M$ (Scheme 2).

However, such a stereospecific transformation has not been discovered[9] until recently by us[10] and others.[11] In the past, optically active *H*-phosphinates were reported to rapidly epimerize in the presence of a base giving racemic products.[8,9,12] Thus, Mislow and co-workers found that the anion of ($R_P$)-**1a** is stereolabile and epimerization easily took place.[8a] Aaron and co-workers prepared optically active (*S*)-(+)-isopropyl methylphosphinate.[8b] They reported that treatment of (*S*)-(+)-isopropyl methylphosphinate with *n*-butyl lithium followed by quenching with benzyl bromide gave only racemic methylbutylbenzylphosphine oxide.[8b] Herein we disclose the details of our findings on the preparation of optically pure *H*-phosphinates **1a**−**d** and their conversions to optically active P-stereogenic secondary phosphine oxides (SPOs) **2** and tertiary phosphine oxides (TPOs) **3** via stereospecific nucleophilic substitutions of optically pure H-phosphinates **1** with organolithiums or Grignard reagents.

## Results and Discussion

**Preparation of Optically Pure H-Phosphinates 1.** As shown in the following Schemes, optically pure *H*-phosphinates **1a**−**d** (>99% de) were easily obtained (Schemes 3 and 4). A diastereomer mixture of (−)-menthyl phenylphosphinate **1a** was prepared from a $PhPCl_2$ and (L)-(−)-menthol as reported (Scheme 3).[8a,9a] It appeared that its preparation was first reported by Emmick and co-workers although they failed to separate the diastereomer mixture.[9a] Later Mislow et al. obtained an optically enriched ($R_P$)-**1a** (ca. $R_P/S_P$ = 95/5) by fractional recrystallization.[8a] We modified their procedure and found that pure ($R_P$)-**1a** ($R_P/S_P$ > 99/1) could be easily obtained by recrystallizing the $R_P/S_P$ diastereomer mixtures at −30 °C.[6] A similar

(7) (a) A general review: *Organic Phosphorus Compounds*; Kosolapoff, G. M., Maier, L., Eds.; Wiley-Interscience: New York, 1972; Vol. 3,Chapter 6. See also: (b) Hays, H. R. *J. Org. Chem.* **1968**, *33*, 3690. (c) Grim, S. O.; Satek, L. C. *J. Inorg. Nucl. Chem.* **1977**, *39*, 499. (d) Williams, R. H.; Hamilton, L. A. *J. Am. Chem. Soc.* **1952**, *74*, 5418.

(8) Optically pure *H*-phosphinates **1a**−**d** can be purchased from Katayama Chemical Industries Co.Ltd. (http://www.katayamakagaku.co.jp). Preparation of optically active *H*-phosphinates: (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) Reference 6.

(9) Early attempts to prepare chiral SPOs via similar substitution reactions only led to the nonselective formation of racemates, see: (a) Emmick, T. L.; Letsinger, R. L. *J. Am. Chem. Soc.* **1968**, *90*, 3459. (b) Farnham, W. B.; Murray, R. K.; Mislow, K. *J. Am. Chem. Soc.* **1970**, *92*, 5808. (c) Reference 8b.

(10) Han, L.-B.; Xu, Q. Japanese Patent JP2008-69103A (filed, 25 August 2006; opened, 3 March2008).

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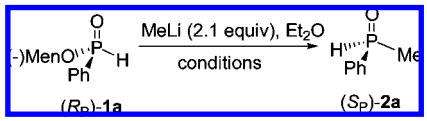
***Table 1.*** Stereospecific Nucleophilic Substitution of ($R_P$)-**1a** with MeLi




| entry | conditions[a] | yield %[b] | ee %[c] |
|---|---|---|---|
| 1 | room temperature (25 °C), 1 h | 99 | 60 |
| 2 | 0 °C, 1 h | 99 | 83 |
| 3 | −80 °C, 7 h | 84 | 97 |
| 4 | −80 °C, 30 min; 0 °C, 30 min | 99 | 97 |

[a] ($R_P$)-**1a** (1.0 M in THF) was added to 2.1 equiv MeLi (1.0 M in $Et_2O$) in a Schlenk tube under $N_2$. The reaction mixture was quenched with saturated aqueous $NH_4Cl$ solution and slowly warmed to room temperature. [b] Determined by $^1H$ NMR of the crude mixture. [c] Determined by HPLC analysis (UV) on a Chiralpak AS column using hexane/*i*-PrOH (1/1) as eluent (1 mL/min) at 30 °C.

method was used to prepare ($S_P$)-**1b** by using (D)-(+)-menthol instead of (L)-(−)-menthol (Scheme 3).

Other *H*-phosphinates **1c**,**d** were obtained by the reactions of the corresponding Grignard reagents with (−)-MenOPCl$_2$ which is easily prepared from $PCl_3$ and (L)-(−)-menthol[13] (Scheme 4). After recrystallization, optically pure *H*-phosphinates ($R_P$)-**1c** and ($R_P$)-**1d** were obtained ($R_P/S_P$ > 99/1). The absolute configuration of **1c** was determined to be $R_P$ at phosphorus (vide infra), which is in consistent with the literature data.[8d] The stereochemistry of ($R_P$)-**1d** was deduced on the basis of the stereochemistry of the substitution products of ($R_P$)-**1d** with organolithiums (vide infra).

**Stereospecific Nucleophilic Substitution of Optically Pure *H*-Phosphinates 1 Affording Optically Active Phosphine Oxides.** The reaction of ($R_P$)-**1a** with 2.1 equiv of MeLi was investigated first (Table 1). At room temperature, when ($R_P$)-**1a** was slowly added to MeLi, methylphenylphosphine oxide **2a** was obtained in 99% yield with 60% ee (entry 1). When the reaction was conducted at 0 °C, the ee of **2a** was improved to 83% (entry 2), and the ee of **2a** further increased to 97% at −80 °C (entry 3), though the yield of **2a** slightly decreased because part of ($R_P$)-**1a** remained unreacted. A high yield (99%) and high ee (97%) of **2a** was achieved by conducting the addition of ($R_P$)-**1a** to MeLi at −80 °C and then raising the temperature to 0 °C (entry 4). As shown below, this reaction could be easily carried out in a relatively large scale with good reproducibility. Thus, to MeLi (11 mmol, 1.0 M in $Et_2O$) at −80 °C was slowly added ($R_P$)-**1a** in THF (5 mmol in 5 mL of THF). The reaction mixture was kept at −80 °C for 30 min, and then slowly warmed to 0°. Saturated aqueous ammonium chloride (20 mL) was then added. The product **2a** is rather soluble in water. This leads to an easy isolation of the product by simply washing the aqueous phase with hexane to remove menthol and other organic substrates, followed by extraction of the product with chloroform. Thus, the resulted reaction mixture was first washed twice with hexane to remove menthol generated and other organic substrates, and then the aqueous phase was extracted with chloroform. Consequently, a colorless oil of NMR spectroscopically pure methylphenylphosphine oxide (**2a**)[14] was obtained (652 mg, 4.65 mmol, 93% yield, 97% ee) (entry 1, Table 2).

As demonstrated in Table 2, a variety of organolithiums and Grignard reagents are applicable to this reaction to produce the corresponding SPOs in high yields with high ee. Thus, under similar reaction conditions, primary (MeLi-LiBr, *n*-BuLi), secondary (*i*-PrLi), and tertiary (*t*-BuLi) alkyllithiums produced the corresponding optically active SPOs in 93% ee (**2a**), 99% ee (**2b**), 97% ee (**2c**), and 99% ee (**2d**), respectively (entries 2−5). A functionalized alkylithium reagent such as $Me_3SiCH_2Li$ could also be used in the reaction to give the unsymmetrical SPO **2e** in 92% yield with 96% ee (entry 6). As to the absolute configuration of the SPOs at phosphorus, the stereochemistry of **2d** (entry 5) was determined to be $S_P$ by comparing with the literature data,[4b] indicating that this substitution takes place through inversion of configuration at phosphorus. Under the same reaction condition, the reaction of ($S_P$)-**1b** with *n*-BuLi and *t*-BuLi produced the corresponding $R_P$ enantiomers of **2b** and **2d** in 95% ee and 93% ee, respectively (entries 7−8), showing the substitution reaction proceeded stereospecifically. Noteworthy, in addition to organolithiums, primary and secondary alkyl Grignard reagents could also be used as the substrates. Thus, methyl, butyl, *i*-propyl, allyl, and benzyl Grignard reagents all gave high yields of the products with high ee (entries 9−18). However, sterically bulky Grignard reagents could not be used in this reaction. For example, no substitution product was obtained with *t*-BuMgCl at −80 °C.[15] Although 76% yield of **2d** was obtained when the reaction was conducted at 0 °C, the ee of **2d** was only 48%.

Like ($R_P$)-**1a**,(−)-menthyl benzylphosphinate ($R_P$)-**1c** and(−)-menthyl mesitylphosphinate ($R_P$)-**1d** reacted similarly. Thus, ($R_P$)-**1c** and ($R_P$)-**1d** reacted with PhLi to give ($R_P$)-**2g** and ($S_P$)-**2h** in 97% and 94% ee, respectively (entries 19−22). By comparison of SPO ($R_P$)-**2g** (entries 19−20) with its enantiomer ($S_P$)-**2g** (entry 18), the absolute configuration of **1c** was deduced to be $R_P$ at phosphorus, which is also in consistent with the literature.[8d] The absolute configuration of ($R_P$)-**1d** was deduced similarly by the comparison of ($S_P$)-**2h** (entries 21−22) with ($R_P$)-**2h** (entry 42). Reactions of ($R_P$)-**1c** with other organolithiums under similar conditions also gave the corresponding SPOs **2i**−**k** in high ee (entries 23−25).

Aryllithiums also react efficiently with ($R_P$)-**1a** to give the corresponding unsymmetrical diarylphosphine oxides in high ee (entries 26, 28, 30, 32, 34, 36, 37, 39, 40). In addition, the lithioheterocyclic compounds such as 2-, or 3-lithiothiophene, and 2-lithiopyridine reacted efficiently to give the corresponding products in high ee (entries 37−41). As expected, organolithiums generated by the convenient lithium−tellurium exchange reactions of organotellurides with *n*-BuLi[16] can also be employed in these reactions (entries 27, 29, 31, 33, 35, 38, 41−43).

Moreover, we found that the benzyl group can also be replaced by organolithiums.[19] Thus, the reaction of ($R_P$)-**2j** (97% ee) with PhLi gave ($R_P$)-**2d** in a high selectivity (96% ee, entry

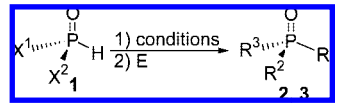
(12) Other early attempts to obtain chiral SPOs by reduction of the corresponding optically active P-stereogenic precursors using aluminium reagents also failed, see: (a) Reference 9a. (b) Henson, P. D.; Ockrymiek, S. B.; Markham, R. E., Jr. *J. Org. Chem.* **1974**, *39*, 2296. (c) Wetzel, R. B.; Kenyon, G. L. *J. Org. Chem.* **1974**, *39*, 1531. It was also reported that phosphine oxides undergo rapid stereomutation in the presence of aluminium reagents prior to reduction, see: (d) Henson, P. D.; Nauman, K.; Mislow, K. *J. Am. Chem. Soc.* **1969**, *91*, 5645. (e) Reference 9b.

(13) (a) Chen, W.-P.; Xiao, J.-L. *Tetrahedron Lett.* **2001**, *42*, 2897. (b) Yamanoi, Y.; Imamoto, T. *J. Org. Chem.* **1997**, *62*, 8560.

(14) We found that although stable under basic conditions, **2a** instantly epimerizes when treated with diluted hydrogen chloride acid. Even a trace amount of acid can cause this epimerization even at−80 °C. Thus, all glasswares used for keeping this compound were all carefully deacidified by washing them first with an alkaline solution and then with water.

(15) All ($R_P$)-**1a** used was recovered without epimerization.

***Table 2.*** Preparation of Optically Active P-Stereogenic Phosphine Oxides **2** and **3**[17]



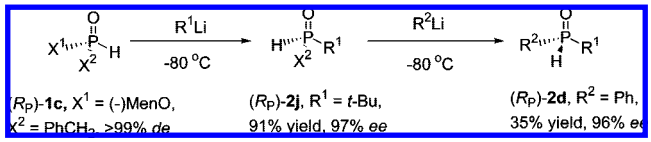

| entry | RLi or RMgX | substrate | conditions[a] | E | product: $R^1$, $R^2$, $R^3$ | yield % | ee % |
|---|---|---|---|---|---|---|---|
| 1[d] | MeLi | ($R_P$)-**1a** | $Et_2O$,−80 °C, 0.5 h;0 °C, 0.5 h | $H_2O$ | ($S_P$)-**2a**: Me, Ph, H | 93 | 97[b] |
| 2[d] | MeLi-LiBr | ($R_P$)-**1a** | $Et_2O$,−80 °C, 3 h | $H_2O$ | ($S_P$)-**2a** | 64 | 93[b] |
| 3[d] | *n*-BuLi | ($R_P$)-**1a** | hexane,−80 °C, 5 h | $H_2O$ | ($S_P$)-**2b**: *n*-Bu, Ph, H | 99 | 99[b] |
| 4[d] | *i*-PrLi | ($R_P$)-**1a** | pentane,−80 °C, 13 h | $H_2O$ | ($S_P$)-**2c**: *i*-Pru, Ph, H | 98 | 97[b] |
| 5[d] | *t*-BuLi | ($R_P$)-**1a** | pentane,−80 °C, 14 h | $H_2O$ | ($S_P$)-**2d**: *t*-Bu, Ph, H | 95 | 99[b] |
| 6[d] | $Me_3SiCH_2Li$ | ($R_P$)-**1a** | pentane,−80 °C, 23 h | $H_2O$ | ($S_P$)-**2e**: $Me_3SiCH_2$, Ph, H | 95 | 96[b] |
| 7[d] | *n*-BuLi | ($S_P$)-**1b** | hexane,−80 °C, 10 h | $H_2O$ | ($R_P$)-**2b**: Ph, *n*-Bu, H | 99 | 95[b] |
| 8[d] | *t*-BuLi | ($S_P$)-**1b** | pentane,−80 °C, 17 h | $H_2O$ | ($R_P$)-**2d**: Ph, *t*-Bu, H | 99 | 93[b] |
| 9[d] | MeMgI | ($R_P$)-**1a** | $Et_2O$,−80 °C, 6 h | $H_2O$ | ($S_P$)-**2a** | 82 | 97[b] |
| 10[d] | MeMgBr | ($R_P$)-**1a** | $Et_2O$,−80 °C, 4 h | $H_2O$ | ($S_P$)-**2a** | 93 | 92[b] |
| 11[d] | *n*-BuMgI | ($R_P$)-**1a** | $Et_2O$,−−80 °C, 14 h | $H_2O$ | ($S_P$)-**2b** | 78 | 99[b] |
| 12[d] | *n*-BuMgBr | ($R_P$)-**1a** | THF,−80 °C, 6 h | $H_2O$ | ($S_P$)-**2b** | 67 | 99[b] |
| 13[d] | *n*-BuMgCl | ($R_P$)-**1a** | THF,−80 °C, 11 h | $H_2O$ | ($S_P$)-**2b** | 99 | 91[b] |
| 14[d] | *i*-PrMgCl | ($R_P$)-**1a** | $Et_2O$,−80 °C, 20 h | $H_2O$ | ($S_P$)-**2c** | 94 | 91[b] |
| 15[d] | *i*-PrMgBr | ($R_P$)-**1a** | THF,−80 °C, 13 h | $H_2O$ | ($S_P$)-**2c** | 93 | 66[b] |
| 16[d] | $CH_2$═$CHCH_2MgCl$ | ($R_P$)-**1a** | THF,−80 °C, 14 h | $H_2O$ | ($S_P$)-**2f**: allyl, Ph, H | 99 | 97[c] |
| 17[d] | $CH_2$═$CHCH_2MgBr$ | ($R_P$)-**1a** | $Et_2O$,−80 °C, 14 h | $H_2O$ | ($S_P$)-**2f** | 99 | 97[c] |
| 18[d] | $PhCH_2MgBr$ | ($R_P$)-**1a** | THF,−80 °C, 14 h | $H_2O$ | ($S_P$)-**2g**: $PhCH_2$, Ph, H | 66 | 87[b] |
| 19[d] | PhLi | ($R_P$)-**1c** | $Et_2O$, −80 °C, 19 h | $H_2O$ | ($R_P$)-**2g**: Ph, $PhCH_2$, H | 50 | 97[b] |
| 20[d] | PhLi | ($R_P$)-**1c** | Pentane, −80 °C, 19 h | $H_2O$ | ($R_P$)-**2g** | 62 | 97[b] |
| 21[d] | PhLi | ($R_P$)-**1d** | $Et_2O$, −80 °C, 17 h | $H_2O$ | ($S_P$)-**2h**: Ph, mesityl, H | 93 | 94[b] |
| 22[d] | PhLi | ($R_P$)-**1d** | pentane, −80 °C, 17 h | $H_2O$ | ($S_P$)-**2h** | 89 | 94[b] |
| 23[d] | *n*-BuLi | ($R_P$)-**1c** | hexane,−80 °C, 14 h | $H_2O$ | ($S_P$)-**2i**: *n*-Bu, $PhCH_2$, H | 99 | 92[b] |
| 24[d] | *t*-BuLi | ($R_P$)-**1c** | pentane,−80 °C, 19 h | $H_2O$ | ($R_P$)-**2j**: *t*-Bu, $PhCH_2$, H | 91 | 97[b] |
| 25[d] | $Me_3SiCH_2Li$ | ($R_P$)-**1c** | pentane,−80 °C, 25 h | $H_2O$ | ($R_P$)-**2k**: $Me_3SiCH_2$, $PhCH_2$, H | 98 | 99[b] |
| 26[e] | 2-lithiotoluene | ($R_P$)-**1a** | THF,−80 °C, 22 h | $H_2O$ | ($R_P$)-**2l**: 2-tolyl, Ph, H | 91 | 98[c] |
| 27[f] | 2-lithiotoluene | ($R_P$)-**1a** | THF,−80 °C, 30 h | $H_2O$ | ($R_P$)-**2l** | 99 | 80[c] |
| 28[e] | 2-lithioanisole | ($R_P$)-**1a** | $Et_2O$,−80 °C, 24 h | $H_2O$ | ($R_P$)-**2m**: 2-anisyl, Ph, H | 99 | 79[b] |
| 29[f] | 2-lithioanisole | ($R_P$)-**1a** | $Et_2O$,−80 °C, 17 h | $H_2O$ | ($R_P$)-**2m** | 92 | 89[b] |
| 30[e] | 2,4-dimethoxy-phenyllithium | ($R_P$)-**1a** | $Et_2O$,−80 °C, 27 h | $H_2O$ | ($R_P$)-**2n**: 2,4-dimethoxy-phenyl, Ph, H | 98 | 92[b] |
| 31[f] | 2,4-dimethoxy-phenyllithium | ($R_P$)-**1a** | $Et_2O$,−80 °C, 50 h | $H_2O$ | ($R_P$)-**2n** | 96 | 92[b] |
| 32[e] | 1-lithionaphthalene | ($R_P$)-**1a** | THF,−80 °C, 22 h | $H_2O$ | ($R_P$)-**2o**: 1-naphthyl, Ph, H | 89 | 99[c] |
| 33[f] | 1-lithionaphthalene | ($R_P$)-**1a** | $Et_2O$,−80 °C, 39 h | $H_2O$ | ($R_P$)-**2o** | 81 | 82[c] |
| 34[e] | 2-lithionaphthalene | ($R_P$)-**1a** | THF,−80 °C, 18 h | $H_2O$ | ($R_P$)-**2p**: 2-naphthyl, Ph, H | 85 | 92[c] |
| 35[f] | 2-lithionaphthalene | ($R_P$)-**1a** | $Et_2O$,−80 °C, 39 h | $H_2O$ | ($R_P$)-**2p** | 93 | 89[c] |
| 36[g] | 9-lithiophenanthrene | ($R_P$)-**1a** | THF,−80 °C, 16 h | $H_2O$ | ($R_P$)-**2q**: 9-phenanthryl, Ph, H | 89 | 87[b] |
| 37[e] | 2-lithiothiophene | ($R_P$)-**1a** | $Et_2O$,−80 °C, 22 h | $H_2O$ | ($R_P$)-**2r**: 2-thiophenyl, Ph, H | 71 | 77[b] |
| 38[f] | 2-lithiothiophene | ($R_P$)-**1a** | THF,−80 °C, 21 h | $H_2O$ | ($R_P$)-**2r** | 40 | 77[b] |
| 39[e] | 3-lithiothiophene | ($R_P$)-**1a** | $Et_2O$,−80 °C, 24 h | $H_2O$ | ($R_P$)-**2s**: 3-thiophenyl, Ph, H | 91 | 99[c] |
| 40[e] | 2-lithiopyridine | ($R_P$)-**1a** | $Et_2O$,−80 °C, 24 h | $H_2O$ | ($R_P$)-**2t**: 2-pyridyl, Ph, H | 99 | 92[b] |
| 41[f] | 2-lithiopyridine | ($R_P$)-**1a** | $Et_2O$,−80 °C, 48 h | $H_2O$ | ($R_P$)-**2t** | 99 | 87[b] |
| 42[f] | lithiomesitylene | ($R_P$)-**1a** | THF,−80 °C, 72 h | $H_2O$ | ($R_P$)-**2h** | 74 | 64[b] |
| 43[f] | 4-lithioanisole | ($R_P$)-**1a** | THF,−80 °C, 13 h | $H_2O$ | ($R_P$)-**2u**: 4-anisyl, Ph, H | 89 | 74[b] |
| 44[d] | PhLi | ($R_P$)-**2j** | cyclohexane/$Et_2O$,−80 °C, 19 h | $H_2O$ | ($R_P$)-**2d** | 35 | 96[b] |
| 45[d] | *n*-BuLi | ($R_P$)-**1a** | hexane,−80 °C, 7 h | MeI 0 °C, 24 h | ($S_P$)-**3a**: *n*-Bu, Ph, Me | 84 | 93[b] |
| 46[d] | *n*-BuLi | ($R_P$)-**1a** | hexane,−80 °C, 7 h | $CH_2$═$CH$-$CH_2Br$ 0 °C, 24 h | ($R_P$)-**3b**: *n*-Bu, Ph, Allyl | 86 | 91[b] |
| 47[d] | *n*-BuLi | ($R_P$)-**1a** | hexane,−80 °C, 7 h | $PhCH_2Br$ 0 °C, 24 h | ($R_P$)-**3c**: *n*-Bu, Ph, $PhCH_2$ | 83 | 72[b] |

[a] All reactions were conducted at −80 °C by slowly adding optically pure **1** (>99% de) or ($R_P$)-**2j** (97% ee) (1.0 M in THF or pentane) to RM reagents (2.1 equiv). The reaction mixture was either quenched with saturated aqueous $NH_4Cl$ solution and slowly warmed to room temperature, or quenched with alkyl halides and stirred at 0 °C overnight. [b] Determined by HPLC analysis using a Chiralpak AS or AD column. [c] Determined by $^1H$ or $^{31}P$ NMR by adding an equimolar ratio of (*R*)-(+)-*tert*-butylphenylthiophosphinic acid.[18] [d] Organolithiums and Grignard reagents purchased. [e] Organolithiums generated from organobromides and *n*-butyllithium. [f] Organolithiums generated from butyltellurides and *n*-butyllithium[16]. [g] Organolithiums generated from 9-iodophenanthrene and *n*-butyllithium.

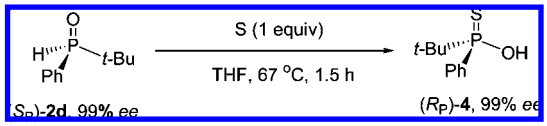
44). Given that ($R_P$)-**2j** was generated from ($R_P$)-**1c** via the replacement of the menthoxyl group with *t*-BuLi (entry 24), this reaction significantly expands the scope of the preparation of optically active SPOs via stereospecific substitutions, because, as shown in Scheme 5, the two groups (menthoxyl and benzyl) of ($R_P$)-**1c** can be sequentially replaced by organolithiums.

Finally, by switching the quenching reagent from water to alkyl halides, the corresponding optically active tertiary phosphine oxides (TPOs) could also be generated in moderate to high ee. For example, after the reaction mixture of ($R_P$)-**1a** (0.2 mmol in 0.8 mL pentane) and *n*-BuLi (0.42 mmol in 0.26 mL hexane) was kept at −80 °C for 7 h, MeI (0.6 mmol) was added (−80 °C, 30 min; 0 °C, overnight). The corresponding ($S_P$)-methylbutylphenylphosphine oxide **3a** was obtained in 84% yield with 93% ee (entry 45). Similarly, by employing allylbromide and benzylbromide as the substrate, ($R_P$)-allylbutylphe-

***Scheme 5***




***Scheme 6***




nylphosphine oxide **3b** and ($R_P$)-benzylbutylphenylphosphine oxide **3c** were obtained in 86% yield with 91% ee and 83% yield with 72% ee, respectively (entries 46, 47).

The diverse utility of optically active phosphorus compounds were well documented in the literature.[3,4,20] For example, SPO can readily react with sulfur stereospecifically to give the corresponding chiral thiophosphinic acid quantitatively. Thus, ($S_P$)-**2d** (99% ee) can be easily converted to the useful chemical shift reagent (*R*)-(+)-*tert*-butylphenylthiophosphinic acid **4** with retention of configuration at phosphorus[21] without the loss of ee, by simply heating **2d** with an equivalent sulfur in THF (Scheme 6). Chiral thiophosphinic acid **4** is an effective chemical shift reagent which has been prepared by a tedious separation process.[4b,c,18]

**Factors Affecting the ee of the Products.** During the course of this study, we noted that the following impurities from ($R_P$)-**1a** and organolithiums or Grignard reagents can significantly decrease the ee of the products: menthol, water, and metal alkoxide ROM (M = Li, MgX). Thus, to get high ee of the products, these reactions must be carried out under dry nitrogen atmosphere, using ($R_P$)-**1a** free of menthol and water and organolithiums or Grignards without the contamination of metal alkoxides ROM. Scheme 7 showed the possible routes for the formation of the minor enantiomer ($R_P$)-**2** in the stereospecific substitution of ($R_P$)-**1a** with RM. In addition to the instinct selectivity of the substitution of ($R_P$)-**5a** with RM, at least three epimerization paths could lead to the formation of the minor $R_P$ enantiomer. However, as experimentally confirmed below, the possibilities of paths 2 and 3 can be excluded under the present reaction conditions. Thus, the ee of ($S_P$)-**2a** PhMeP(O)H (95% ee), before and after being treated with an equivalent of MeLi to generate ($S_P$)-**6a** and then quenched with saturated aqueous $NH_4Cl$ solution, was essentially the same. Treatment of ($S_P$)-**2b** and ($S_P$)-**2d** with *n*-BuLi and *t*-BuLi gave the same results, ruling out the epimerization of ($S_P$)-**6a** to ($R_P$)-**6a** (path 3, Scheme 7) under the substitution reaction conditions.[20c] A similar deprotonation reaction of ($R_P$)-**1a** with organolithiums to generate ($R_P$)-**5a**, however, can not be used for the study of path 2, because (−)-MenOLi, generated from the substitution reaction of ($R_P$)-**1a** with the organolithium, can significantly lead to the epimerization of **1a** (vide infra). Thus the use of a bulky base, which deprotonates ($R_P$)-**1a** but does not replace (−)-MenO group is necessary. For this purpose, *t*-BuMgCl and LDA were used. We found that ($R_P$)-**1a** could be recovered in >99% yield with >99% de after treatment with *t*-BuMgCl at −80 °C.[15] Similarly, ($R_P$)-**1a** was allowed to react with LDA at −80 °C. Quenching the reaction mixture after 4 h at −80 °C with MeI afforded the methylation product (−)-menthyl ($R_P$)-methylphenylphosphinate **7** in 99% yield with $R_P/S_P$ = 98/2. Under similar conditions by quenching with saturated aqueous $NH_4Cl$, no epimerization of **1a** took place (**1a** was recovered in 99% yield with $R_P/S_P$ = 99/1). By conducting a similar reaction at −40 °C for 30 min, **1a** could also be recovered in 99/1 $R_P/S_P$ ratio. These results indicated that ($R_P$)-**5a** is stable under these conditions.

Indeed, ($R_P$)-**5a** is stable enough to be isolated and stored at room temperature. Treating ($R_P$)-**1a** with 1 equiv of LDA in $Et_2O$ at −80 °C followed by the removal of solvent and other volatiles under vacuum gave a white solid at room temperature. Hydrolysis of this solid with saturated aqueous ammonium chloride at −80 °C gave ($R_P$)-**1a** with 99/1 $R_P/S_P$ ratio, while the treatment of this solid with 1.2 equiv of *n*-BuLi at −80 °C gave ($S_P$)-**2b** in 80% yield and 92% ee, clearly indicating that (a) this solid ($R_P$)-**5a** is stable at room temperature and (b) ($R_P$)-**5a** readily reacts with *n*-BuLi with inversion of configuration at phosphorus to give the substitution product. Therefore, it can be concluded that, ($R_P$)-**5a** is a relatively stable intermediate and no epimerization took place under the present reaction conditions.[8a,9,11,12]

In contrast to paths 2 and 3, the epimerization of ($R_P$)-**1a** to ($S_P$)-**1a** (path 1, Scheme 7) does take place easily even at −80 °C in the presence of a metal alkoxide.[22] Thus, ($R_P$)-**1a**, when mixed with 1 equiv of (−)-MenOLi at −80 °C for 4 h and then quenched with saturated aqueous $NH_4Cl$ solution, gave a diastereomers mixture of **1a** ($R_P/S_P$ = 67/33 in $Et_2O$; $R_P/S_P$ = 51/49 in hexane). The epimerization of ($R_P$)-**1a** can also be confirmed by using MeI as the quenching reagent to give diastereomers mixture of **7** ($R_P/S_P$ = 68/32 in $Et_2O$; $R_P/S_P$ = 78/22 in hexane). In addition, this epimerization was also well reflected in the substitution reaction of ($R_P$)-**1a** with *n*-BuLi. Thus, after mixing ($R_P$)-**1a** with (−)-MenOLi at −80 °C for 4 h, the reaction with *n*-BuLi (2.1 equiv) only gave 16% ee selectivity of ($S_P$)-**2b**, while under similar conditions, the simultaneous addition of (−)-MenOLi (1 equiv) and *n*-BuLi (2.1 equiv) to ($R_P$)-**1a** gave a 93% ee of the product, which is slightly lower than that obtained from a reaction in the absence of (−)-

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(17) See Supporting Information for a table with chemical structures of the products.

(18) (a) Moriyama, M. *J. Synth. Org. Chem.* **1985**, *42*, 75. (b) Zhang, J.; Xu, Y.; Huang, G.; Guo, H. *Tetrahedron Lett.* **1988**, *29*, 1955. (c) Drabowicz, J.; Dudzinski, B.; Mikolajczyk, M. *Tetrahedron: Asymmetry* **1992**, *3*, 1231. (d) Omelanczuk, J.; Mikolajczyk, M. *Tetrahedron: Asymmetry* **1996**, *7*, 2687. (e) Drabowicz, J.; Dudzinski, B.; Mikolajczyk, M.; Colonna, S.; Gaggero, N. *Tetrahedron: Asymmetry* **1997**, *8*, 2267. (f) Drescher, M.; Felsinger, S.; Hammerschmidt, F.; Kählig, H.; Schmidt, S.; Wuggenig, F. *Phosphorus, Sulfur, Silicon Relat. Elem.* **1998**, *140*, 79.

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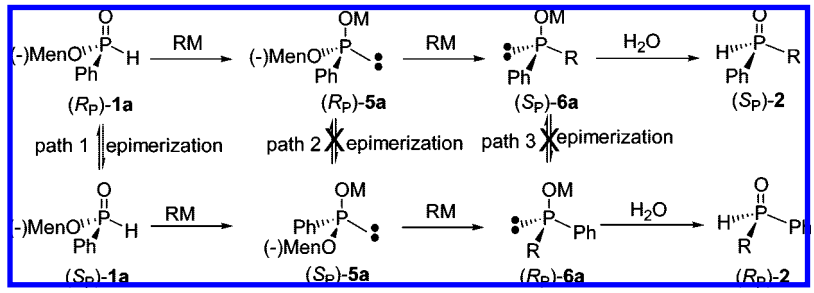
(20) (a) Haynes, R. K.; Lam, W. W.-L.; Yeung, L.-L. *Tetrahedron Lett.* **1996**, *37*, 4729. (b) Lam, W. W.-L.; Haynes, R. K.; Yeung, L.-L.; Chan, E. W.-K. *Tetrahedron Lett.* **1996**, *37*, 4733. (c) Haynes, R. K.; Lam, W. W.-L.; Williams, I. D.; Yeung, L.-L. *Chem.—Eur. J.* **1997**, *3*, 2052. (d) Au-Yrung, T.-L.; Chan, K.-Y.; Chan, W.-K.; Haynes, R. K.; Williams, I. D.; Yeung, L.-L. *Tetrahedron Lett.* **2001**, *42*, 453.

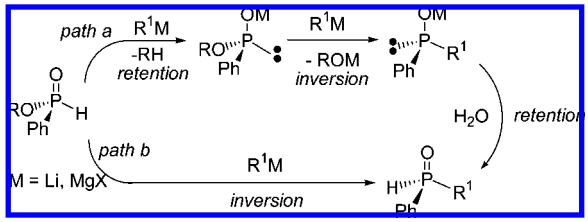
(21) (a) Michalski, J.; Skrzypczyński, Z. *J. Organomet. Chem.* **1975**, *97*, C31. (b) Krawiecka, B.; Michalski, J.; Wonjna-Tadeusiak, E. *J. Org. Chem.* **1986**, *51*, 4201.

(22) Sodium methoxide can cause the epimrization of (*R*)-(−)-isopropyl methylphosphinate (ref 8b). The epimerization of ($R_P$)-**1a** by *t*-BuONa and EtOMgCl were also noted (ref 6b).

**Scheme 7**




**Scheme 8**



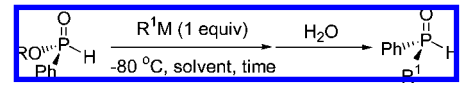

MenOLi (entry 3, Table 2). The epimerization of ($R_P$)-**1a** by (−)-MenOLi also well explained that a stepwise addition of *n*-BuLi to ($R_P$)-**1a** (the first 1 equiv of *n*-BuLi was added at −80 °C; another equivalent of *n*-BuLi was then added after 4 h) resulted in the decrease of the product's ee (90%), because of the formation of (−)-MenOLi by the first 1 equiv of *n*-BuLi added. As expected, other metal alkoxides also cause the epimerization of ($R_P$)-**1a**.[22] Thus, *i*-PrOLi caused a complete epimerization of ($R_P$)-**1a** under the similar condition. Note that isopropyl phenylphosphinate **8**, formed by transesterification, was obtained in 34% yield, clearly indicating that the epimerization of ($R_P$)-**1a** takes place by the attack of ROM at phosphorus.

Therefore, it was rationalized that in order to avoid the epimerization of ($R_P$)-**1a**, the best way for conducting this stereospecific nucleophilic substitution reaction is to add **1** to an excess of organolithiums or Grignard reagents (more than 2 equiv) at low temperatures.

**Mechanistic Study on the Stereospecific Nucleophilic Substitution Reaction.** As to the mechanism of the stereospecific substitution reaction, it is generally believed that the substitution reaction of *H*-phosphinates with $R^1M$ forming SPO takes place by the deprotonation of the *H*-phosphinate with 1 equiv of $R^1M$ giving the corresponding anion followed by its reaction with another equivalent of $R^1M$ to produce the corresponding SPO (path a, Scheme 8).[7] However, as described below, contrary to this commonly held view, we found that, to our surprise, there is a competing direct substitution path (path b, Scheme 8) leading to SPO, that can even be the main reaction path to SPO depending on the substrates used. Therefore, there are two routes leading to SPOs **2** (Scheme 8): (path a) a stereoretention deprotonation of (RO)PhP(O)H by the first equivalent of $R^1M$ working as a base forming (RO)PhP(OM), which is stable under the present reaction conditions as described above, followed by the substitution of (RO)PhP(OM) with another equivalent of $R^1M$ to give intermediate $R^1$PhP(OM) with inversion of configuration at phosphorus;[23] and (path b) a direct substitution of (RO)PhP(O)H by $R^1M$ with inversion of configuration to give the corresponding $R^1$PhP(O)H.

The reactions involved in path a have been discussed as above, confirming that **5a** (M = Li) could react with *n*-BuLi to give the corresponding SPO **2b** with inversion of configuration at phosphorus.[23] On the other hand, clear evidence supporting the direct substitution reaction path b was also obtained by carrying out reactions of (RO)PhP(O)H with 1 equiv of $R^1M$ (Table 3). As shown in Table 3, three *H*-phenylphosphonates bearing sterically different alkoxy groups increasing in bulkiness in the order of (EtO)PhP(O)H < (*i*-PrO)PhP(O)H < (*t*-BuO)-PhP(O)H and ($R_P$)-**1a** were allowed to react with an equivalent of a variety of $R^1M$ at −80 °C. The yields of the corresponding SPOs by the reaction of (EtO)PhP(O)H with four typical organolithiums (MeLi, *n*-BuLi, *t*-BuLi, and PhLi) and two Grignard reagents (MeMgCl and PhMgBr) are in a range of 74−89% (entries 1−6) all exceeding 50%, not only unambiguously showing that the direct substitution path b exists but also indicating that path b can even be the main reaction path in this case. When similar reactions were conducted using the bulkier (*i*-PrO)PhP(O)H, the yields of the corresponding SPOs decreased (entries 7−10). However, except in the case of PhLi (entry 10), the yields of SPOs still exceeded 50% (entries 7−9). The yields of SPOs constantly decreased when an even bulkier (*t*-BuO)PhP(O)H was used as the substrate (entries 11−14), though a considerable amount of the corresponding SPOs were

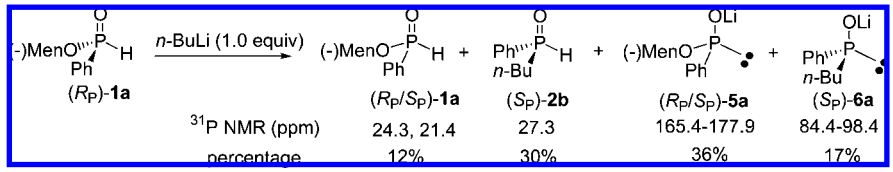
***Table 3.*** Reactions of *H*-Phenylphosphinates with 1 equiv of $R^1M$




| entry | *H*-phosphinate | $R^1M$ | conditions[a] | yield %[b] |
|---|---|---|---|---|
| 1 | (EtO)PhP(O)H | MeLi | $Et_2O$, 2 h | 89 |
| 2 | | *n*-BuLi | $Et_2O$, 2 h | 82 |
| 3 | | *t*-BuLi | $Et_2O$, 2 h | 81 |
| 4 | | PhLi | $Et_2O$, 2 h | 72 |
| 5 | | MeMgCl | THF, 2 h | 79 |
| 6 | | PhMgBr | THF, 2 h | 74 |
| 7 | (*i*-PrO)PhP(O)H | MeLi | $Et_2O$, 2 h | 60 |
| 8 | | *n*-BuLi | $Et_2O$, 2 h | 62 |
| 9 | | *t*-BuLi | $Et_2O$, 2 h | 60 |
| 10 | | PhLi | $Et_2O$, 2 h | 48 |
| 11 | (*t*-BuO)PhP(O)H | MeLi | $Et_2O$, 2 h | 37 |
| 12 | | *n*-BuLi | $Et_2O$, 2 h | 37 |
| 13 | | *t*-BuLi | $Et_2O$, 2 h | 40 |
| 14 | | PhLi | $Et_2O$, 2 h | 39 |
| 15 | ($R_P$)-**1a** | *n*-BuLi | $Et_2O$, 2 h | 42 |
| 16 | | MeLi | $Et_2O$, 0.5 h | 39 |
| 17 | | *n*-BuLi | pentane, 4 h | 46 |
| 18 | | *t*-BuLi | pentane, 23 h | 41 |
| 19 | | PhLi | pentane, 19 h | 43 |
| 20 | | MeMgCl | THF, 18 h | 36 |
| 21 | | *i*-PrMgBr | THF, 14 h | 22 |
| 22 | | *t*-BuMgCl | THF, 22 h | 0 |
| 23 | | PhMgBr | THF, 22 h | 6 |

[a] RM was added to *H*-phosphonate (1.0 M) at −80 °C under $N_2$. The reaction mixture was quenched with saturated aqueous $NH_4Cl$ solution. [b] Yields determined by $^{31}P$ NMR based on RM used.

*Scheme 9*




still generated. These results showed that path a and path b are two competing reaction paths involved in the reactions of hydrogen phosphinates with organolithiums or Grignard reagents to afford the same SPOs. Steric hindrance around phosphorus seems to determine the participation of these two paths in the reaction. Thus, for less bulky hydrogen phosphonates such as (EtO)PhP(O)H, the direct substitution path b is the main reaction path, however, the participation of the deprotonation path a increased as the hydrogen phosphinates become bulkier.

The yield of the corresponding SPO **2b** by the reaction of ($R_P$)-**1a** with BuLi was 42% yield (entry 15). This yield, lower than that of (*i*-PrO)PhP(O)H (entry 8) but higher than that of (*t*-BuO)PhP(O)H (entry 12), is well consistent with the order of the steric hindrance of the substrates. Although all organolithiums (MeLi, *n*-BuLi, *t*-BuLi, and PhLi) tested gave similar yield of the corresponding SPO (entries 16−19), in the case of alkyl Grignard reagents, the yields of SPOs did decrease as the Grignard reagent became bulkier, since the direct substitution path b became more difficult (entries 20−23). An extreme example is *t*-BuMgCl, which does not produce any substitution products under the present reaction conditions (entry 22).

The reaction mixture of ($R_P$)-**1a** with 1 equiv of *n*-BuLi before quenching with water can be determined easily by an NMR experiment (Scheme 9). Thus, in an NMR tube, 1 equiv of *n*-BuLi was added to ($R_P$)-**1a** in $d_8$-toluene at −80 °C to give a $^{31}$P NMR spectra in which ($R_P$)-**1a** completely epimerized to a $R_P/S_P$ mixtures appeared at 24.3 and 21.4 ppm, their corresponding anions ($R_P$)- and ($S_P$)-**5a** were observed around 165.4−177.9 ppm as a broad signal, the substitution product **2b** appears at 27.3 ppm, and its corresponding anion **6a** was observed at 84.4−98.4 ppm as a broad signal. The percentages of these phosphorus species could be obtained on the basis of the integrations, confirming the good yield (47%) of the substitution products (**2b** and **6a**).

## Conclusion

Contrary to the generally held view, we found that the so far reported rapid epimerization of a chiral hydrogen phosphinate ester under basic conditions is not due to the inherent stereolability of its corresponding anion but due to a transesterification reaction of the hydrogen phosphinate ester with a metal alkoxide. This finding successfully leads to the discovery of a general protocol for the preparation of the highly useful optically active secondary and tertiary phosphine oxides on the basis of the stereospecific nucleophilic substitution reactions of optically pure *H*-phosphinates with organolithiums and Grignard reagents which proceed by inversion of configuration at phosphorus via two competing reaction paths of (a) a two step reaction path involving first a deprotonation of *H*-phosphinates followed by a substitution of the corresponding anion by RM with inversion of configuration at phosphorus and (b) a direct substitution of RM with *H*-phosphinates generating the corresponding SPO with inversion of configuration at phosphorus.

(23) The deprotonation step has been shown to be stereoretention (ref 8a). The reaction of the isolated solid salt of ($R_P$)-**5a** with *n*-BuLi at low temperature indicated that this substitution took place with inversion of configuration at phosphorus via a similar mechanism for phosphites: Neuffer, J.; Richter, W. J. *J. Organomet. Chem.* **1986**, *301*, 289.

## Experimental Section

**General.** All reactions were carried out under dry nitrogen atmosphere. Solvents were dried and purified under nitrogen before use by standard procedure. Unless otherwise noted organolithiums and Grignard reagents were purchased and used as received. Other organolithiums were in situ prepared from the corresponding arylbromides, aryliodides, or butyltellurides with *n*-BuLi.[16] Optically pure *H*-phosphinates **1a** and **1b** were prepared according to literature's methods.[6] $^1$H, $^{13}$C, and $^{31}$P NMR spectra were recorded on a JEOL LA-500 instrument (500 MHz for $^1$H, 125.4 MHz for $^{13}$C, and 201.9 MHz for $^{31}$P NMR spectroscopy). Unless otherwise noted, $CDCl_3$ was used as the solvent. Chemical shift values for $^1$H and $^{13}$C were referred to internal $Me_4Si$ (0 ppm), and that for $^{31}$P was referred to $H_3PO_4$ (85% solution in $D_2O$, 0 ppm). Mass spectra were measured on a Shimadzu GC−MS-QP2010 spectrometer (EI). HRMS analysis was performed by the Analytical Center at the National Institute of Advanced Industrial Science and Technology. The optical purity of the products were determined by HPLC (Tosoh SC 8020 instrument) equipped with an UV detector (254 nm) using a Chiralpak AS or AD column (eluent: hexane/*i*-PrOH) or by $^1$H or $^{31}$P NMR using (*R*)-(+)-*tert*-butylphenyl-thiophosphinic acid [4b,c] as a chemical shift reagent. Optical rotations were recorded with a JAS CO DIP-370 Digital Polarimeter.

**A Typical Procedure for the Preparation of Optically Pure *H*-Phosphinates ($R_P$)-1a and ($S_P$)-1b.** The mixture of (L)-(−)-menthol (100 g, 641 mmol) and pyridine (51.3 mL, 641 mmol) in $Et_2O$ (200 mL) was added dropwise with stirring to a $PhPCl_2$ (87.2 mL, 641 mmol) solution in $Et_2O$ (400 mL) at 0 °C and then stirred at room temperature overnight. Water (12 mL, 667 mmol) was added, and the reaction mixture was washed with water and extracted with hexane. The hexane layer was dried over magnesium sulfate, filtered, and concentrated. Recrystallization of the mixture in hexane (twice) at −30 °C gave pure ($R_P$)-**1a** as a white crystal ($R_P$)-**1a** ($R_P/S_P$ >99/1). ($S_P$)-**1b** was prepared similarly from $PhPCl_2$ and (D)-(+)-menthol.

**(+)-Menthyl ($R_P$)-Phenylphosphinate (1a) and (+)-Menthyl ($S_P$)-Phenylphosphinate (1b).** $^1$H NMR: $\delta$ 7.83−7.79 (m, 2H), 7.64−7.61 (m, 1H), 7.56−7.52 (m, 2H), 7.68 (d, $J_{HP}$ = 553 Hz, 1H), 4.31 (m, 1H), 2.28−2.18 (m, 2H), 1.75−1.68 (m, 2H), 1.54−1.45 (m, 1H), 1.27 (q, $J$ = 11.8 Hz, 1H), 1.09 (qd, $J$ = 12.6 Hz, $J$ = 3.4 Hz, 1H), 0.99 (d, $J$ = 6.7 Hz, 3H), 0.92 (d, $J$ = 6.4 Hz, 3H), 0.89 (d, $J$ = 6.4 Hz, 3H). $^{31}$P NMR: $\delta$ 24.7. The preparation of a diastereomeric mixture of **1a**[9a] and an optically enriched ($R_P$)-**1a**[8a] have been reported.

**Preparation of *H*-Phosphinates ($R_P$)-1c and ($R_P$)-1d.** $PhCH_2$-MgCl (1.0 M in $Et_2O$, 800 mL, 800 mmol) was added dropwise to the $Et_2O$ (800 mL) solution of (−)-MenOPCl$_2$ (206.4 g, 800 mmol) at 0 °C and then stirred at room temperature overnight. Recrystallization of the mixture at −30 °C gave pure ($R_P$)-**1c** as white needles ($R_P/S_P$ >99/1). ($R_P$)-**1d** was prepared similarly starting from (−)-MenOPCl$_2$ and mesitylmagnesium bromide.

**Optically Pure (−)-Menthyl ($R_P$)-Benzylphosphinate 1c.** $^1$H NMR: $\delta$ 7.34−7.31 (m, 2H), 7.27−7.22 (m, 3H), 7.08 (d, $J_{HP}$ = 539 Hz, 1H), 4.02 (m, 1H), 3.21−3.17 (m, 2H), 2.18 (m, 2H), 1.64−1.56 (m, 4H), 1.46−1.37 (m, 1H), 1.33−1.27 (m, 1H), 1.20

(q, $J$ = 12.2 Hz, 1H), 0.98−0.78 (m, 2H), 0.89 (d, $J$ = 7.3 Hz, 3H), 0.78 (d, $J$ = 6.1 Hz, 3H), 0.59 (d, $J$ = 7.4 Hz, 3H). $^{31}$P NMR: $\delta$ 37.2. The preparation of a diastereomeric mixture of **1c** and optically pure ($R_P$)-**1c** has been reported.[8d]

**Optically Pure (−)-Menthyl ($R_P$)-Mesitylphosphinate 1d.** $^1$H NMR: $\delta$ 8.05 (d, $J_{HP}$ = 547 Hz, 1H), 6.86 (d, $J$ = 4.9 Hz, 2H), 4.22 (m, 1H), 2.57 (s, 6H), 2.34 (m, 2H), 2.29 (s, 3H), 2.08 (m, 1H), 1.68 (m, 2H), 1.49 (m, 1H), 1.39 (m, 1H), 1.26 (q, $J$ = 12.2 Hz, 1H), 1.04 (m, 1H), 0.93 (d, $J$ = 7.3 Hz, 3H), 0.90 (d, $J$ = 7.4 Hz, 3H), 0.87 (m, 1H), 0.82 (d, $J$ = 6.1 Hz, 3H). $^{31}$P NMR: $\delta$ 24.3.

**A General Procedure for the Preparation of Chiral Secondary Phosphine Oxide 2 (SPO).** To a Schlenk tube containing 2.1 equiv RM (M = Li, MgX) solution kept at −80 °C was added 0.1 mmol **1** (1.0 M solution in THF or pentane). The reaction mixture was stirred at −80 °C for the time as shown in Table 2, and was then quenched with 1 mL saturated aqueous $NH_4Cl$ solution, and slowly warmed to room temperature. Since the resulting SPOs are rather soluble in water, the reaction mixture was extracted with water and washed with hexane to remove menthol generated and other organic substrates. The water layer was then extracted with chloroform, dried over $MgSO_4$, filtered, and concentrated under vacuum to give NMR spectroscopically pure SPOs.

**Preparation of Optically Active Tertiary Phosphine Oxides 3.** To a Schlenk tube containing 2.1 equiv *n*-BuLi (in hexane) cooled at −80 °C was added 0.2 mmol ($R_P$)-**1a** (1.0 M in pentane) followed by the addition of 3 equiv of RX after 7 h at −80 °C. The mixture was then stirred at −80 °C for 30 min and 0 °C overnight. The product was isolated using a preparative GPC equipment using $CHCl_3$ as solvent.

**Preparation of ($R_P$)-(+)-*tert*-Butylphenylthiophosphinic Acid 4.** A mixture of ($S_P$)-*tert*-butylphenylphosphine oxide (**2d**) (99% ee, 45.5 mg, 0.25 mmol) and sulfur (8 mg, 0.25 mmol) was heated under $N_2$ in dry THF (0.5 mL) for 1.5 h. A complete conversion of ($S_P$)-**2d** was confirmed. Solvent was pumped off. The residue was recrystalized in hexane to give pure ($R_P$)-(+)-*tert*-butylphenylthiophosphinic acid **4** (44 mg, 0.206 mmol, 82% yield). $^1$H NMR: $\delta$ 7.81−7.67 (m, 2H), 7.48−7. 44 (m, 1H), 7.39−7.36 (m, 2H), 1.16 (d, $J_{HP}$ = 17.4 Hz, 9H). $^{31}$P NMR: $\delta$ 98.7. The absolute structure of the product was confirmed by comparing its NMR spectra in the presence of (*S*)-(−)-1-phenylethylamine (as a chemical shift reagent) with those of an authentic sample.[4b,c] Optical purity of ($R_P$)-**4** is >99% ee.

**Isolation of ($R_P$)-5a, ($R_P$/$S_P$)-5a, and ($S_P$)-6a.** The $Et_2O$ (2 mL) solution of ($R_P$)-**1a** (0.28 g, 1 mmol) was added dropwise with to LDA (1 mmol) in $Et_2O$ (3 mL) at −80 °C. $Et_2O$ was then removed under vacuum at −40 °C affording a white solid which was further dried at room temperature. Similarly, were prepared ($R_P$/$S_P$)-**5a** and ($S_P$)-**6a**.

**Typical Procedure for the Reaction of *H*-Phosphinates with 1 equiv of Organolithiums or Grignard Reagents.** To a Schlenk tube containing Ph(EtO)P(O)H (0.1123 g, 0.66 mmol) in $Et_2O$ (1 mL) was added 1 equiv of *n*-BuLi (1.65 M in hexane, 0.4 mL, 0.66 mmol) at −80 °C and stirred for 2 h at this temperature. The reaction mixture was then slowly warmed to room temperature (20 °C) with stirring and cooled to −80 °C again followed by quenching with 3 mL saturated aqueous $NH_4Cl$ solution. The reaction mixture was then extracted with chloroform, dried over $MgSO_4$, filtered, concentrated under vacuum, and measured by $^1$H and $^{31}$P NMR. Other reactions of entries 16−23 in Table 3 were conducted at −80 °C for a time shown and then quenched with saturated aqueous $NH_4Cl$ solution followed by the same workup procedure.

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**Supporting Information Available:** A list of spectroscopic data of **2** and **3**; copies of HPLC and NMR spectra of the products; copies of $^{31}$P NMR spectra related to mechanistic studies. This material is available free of charge via the Internet at http://pubs.acs.org.

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