



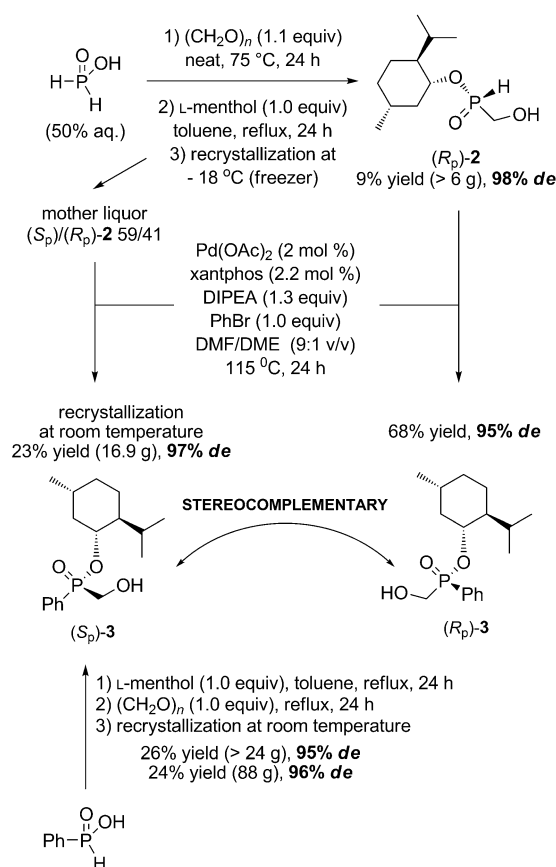
A General Strategy for the Synthesis of P-Stereogenic Compounds**

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Preparing P-stereogenic compounds is one of the biggest challenges of organophosphorus chemistry.^[1] Although various methods have been reported for the preparation of specific P-stereogenic building blocks, based on kinetic resolution, or on chiral auxiliaries, typically these have severe limitations in the scope of their application.^[1] More than 40 years ago, Mislow and others pioneered the field of P-stereogenic compounds and the study of their reactivities.^[2] A case in point is menthyl phenyl-*H*-phosphinate PhP(O)(OMen)H (**1**), which has since been employed in various reactions such as cross-coupling, substitution, or hydrophosphinylation.^[3] However, enriched diastereomers of **1** remain difficult to prepare as their isolation requires low-temperature recrystallization (multiple crystallizations below -30°C or at -70°C), and yields of isolated products were not reported. Similar chemistry using MenOPCl₂ and aryl Grignard reagents was reported recently.^[4] In the final analysis, these methods still require cumbersome crystallization procedures and are limited in terms of the phosphorus compounds that are accessible and therefore the final products (usually P-stereogenic phosphines) that can be derived from them.

Herein, we report an extremely simple and inexpensive approach to versatile P-stereogenic building blocks, on multigram scales, and without the need for R₃PCl₂ precursors. The new intermediates also allow much more flexibility for their functionalization into a broad variety of useful P-stereogenic compounds. Compound **2** is prepared from hypophosphorous acid, paraformaldehyde, and (–)-menthol in 9% yield (>6 g), and compound **3** is prepared from phenyl-*H*-phosphinic acid, (–)-menthol, and paraformaldehyde in 26% yield (>24 g) (Scheme 1). The two building blocks (*R_P*)-**2** and (*S_P*)-**3** are crystallized in high (>95%) diastereomeric purities at -18°C (in a freezer) or at room temperature, respectively. While the yields are relatively low, these still compare to the yields of literature methods, and multigram quantities are available in a single preparation. The latter reaction was also scaled up uneventfully to produce 88 g of (*S_P*)-**3** (24% yield, 96% *de*). The structures of (*R_P*)-**2** and (*S_P*)-**3** were confirmed by single X-ray crystallography.^[15]

To improve the value of the reaction leading to **2**, the mother liquor was directly cross-coupled with bromobenzene



Scheme 1. Preparation of **2** and **3**.

using our own conditions.^[5] Crystallization of the resulting reaction mixture at room temperature led to **3** in good yield (23% yield, 97% *de*; Scheme 1). This diastereomer is identical to the one obtained directly from PhP(O)(OH)H (Scheme 1). On the other hand, cross-coupling of crystalline (*R_P*)-**2** with bromobenzene gave (*R_P*)-**3** in 68% yield. Thus the same reaction sequence can be used to make either P configuration simply depending on the starting material: the mother liquor or the crystalline diastereomer! An overall yield of 33% of useful P-stereogenic compounds is easily achieved through the reaction of H₃PO₂. This yield is much higher than that of any literature method which employs PCl₂ intermediates or/and Grignard reagents.

Besides improved crystallization properties (all compounds were obtained after a single crystallization!), these P-stereogenic building blocks have the advantage of containing a hydroxymethyl handle, which offers two major ways to functionalization (Scheme 2)—either with preservation of the hydroxymethyl carbon atom or through oxidation to the corresponding *H*-phosphinate. We recently reported that the Corey–Kim oxidation of (hydroxymethyl)phosphinates gives

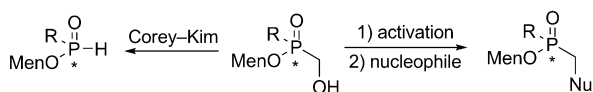
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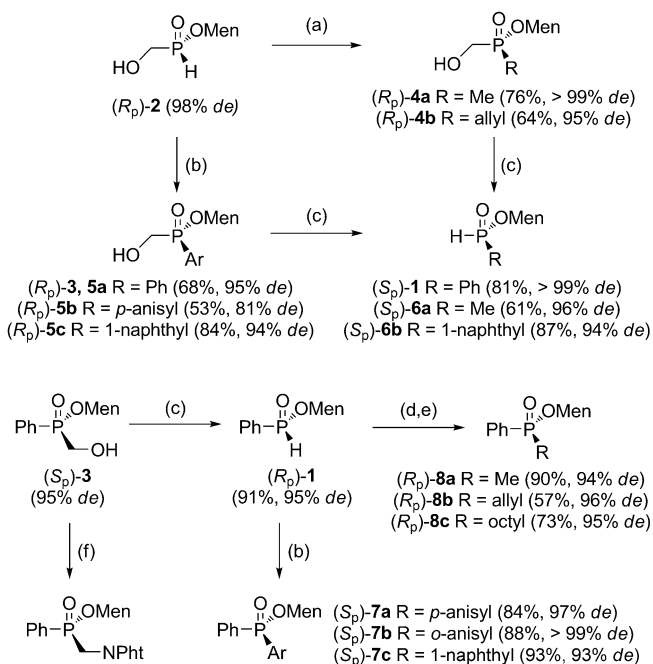
the corresponding *H*-phosphinates in a highly stereoselective way.^[6]

Diastereomer (*R_p*)-**2** is clearly the most versatile P-stereogenic building block to date (Scheme 3). Cross-coupling of (*R_p*)-**2** with bromobenzene gives (*R_p*)-**5a** (= (*R_p*)-**3**) in



Scheme 2. Functionalization of P-stereogenic (hydroxymethyl)phosphinates.

68 % yield, and subsequent oxidative cleavage delivers (*S_p*)-**1** in 81 % yield. Compound (*S_p*)-**3** can also be oxidized to form stereospecifically (*R_p*)-**1** in 91 % yield (Scheme 3). Therefore, cross-coupling of **2** followed by oxidation of **3** also leads to either P configuration of **1** using inexpensive (–)-menthol in all cases. Previous methods by Mislow and Han to prepare either P stereoisomer of **1** relied on (–)-menthol and (+)-menthol, respectively.^[3c] (+)-Menthol is fifty times more expensive than (–)-menthol. Because of the ease of obtaining **2** and **3**, and then **1**, this approach is clearly

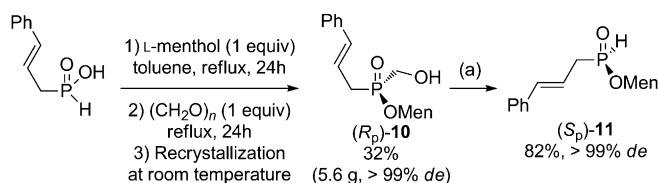


Scheme 3. Functionalization of **2** and **3**, and stereodivergent synthesis of PhP(O)(OMe)H (**1**). a) 1) Me₃SiN=C(OSiMe₃)Me (2 equiv), CH₂Cl₂; 2) MeI (1 equiv), 0 °C to RT, 20 h; or allylBr (2 equiv), 0 °C to RT, 36 h. b) ArBr (1 equiv), Pd(OAc)₂ (2 mol %), xantphos (2.2 mol %), *i*Pr₂NEt (1.3 equiv), DMF/DME or toluene/ethylene glycol (9:1, v/v), 115 °C, 24 h. c) 1) *N*-chlorosuccinimide (3 equiv), Me₂S (3 equiv), CH₂Cl₂, –78 °C, 10 min. 2) **3** or **5a** or **5c** (1 equiv), –78 °C, 3 h. 3) Et₃N (5 equiv), –78 °C to RT, 1 h. d) 1) Me₃SiN=C(OSiMe₃)Me (2 equiv), CH₂Cl₂; 2) MeI (2 equiv), 0 °C, 2 h; or allylBr (2 equiv), RT, 4 days. e) 1-octene (1 equiv), Et₃B (1 equiv), hexane, RT, air, 20 h. f) phthalimide (1.3 equiv), PyPPh₂ (1.3 equiv), DIAD (1.3 equiv), CH₂Cl₂, RT, 24 h. DIAD: diisopropyl azodicarboxylate.

competitive with the synthesis of **1** from PhPCl₂ or Men-OPCl₂.^[2–4]

The usefulness of compound **1** in asymmetric organophosphorus synthesis is well-established. However, it can only be used for the synthesis of phenyl-containing products. To obtain other substitution patterns, crystallization must be optimized for each case.^[4] Therefore the novel building block (*R_p*)-**2** offers much flexibility previously unavailable. Compound (*R_p*)-**2** can be viewed as a protected chiral equivalent of alkyl phosphinates ROP(O)H₂, since it can be stereospecifically alkylated to form **4**, or cross-coupled to form **5**, and the hydroxymethyl moiety can subsequently be cleaved to form *H*-phosphinates like **1** and **6**. Also, the presence of the hydroxymethyl group in both **2** and **3** provides further opportunities for functionalization since the carbon atom can be preserved if desired. For example, Mitsunobu reaction of **3** with phthalimide gives **9** in 70 % yield (Scheme 3).

Our method is not limited to compounds **2** and **3**. For example, cinnamyl-*H*-phosphinic acid^[7] can be esterified and hydroxymethylated in one pot to form (*R_p*)-**10** in 32 % yield and > 99 % *de* (Scheme 4) after a single crystallization at room temperature.^[8] Oxidation of (*R_p*)-**10** provides menthyl cinnamyl-*H*-phosphinate (*S_p*)-**11** in 82 % yield and > 99 % *de*.



Scheme 4. Synthesis of P-stereogenic cinnamyl derivatives. Step (a) Corey–Kim: 1) *N*-chlorosuccinimide (3 equiv), Me₂S (3 equiv), CH₂Cl₂, –78 °C, 1 h. 2) **10** (1 equiv), –78 °C, 30 min. 3) Et₃N (5 equiv), –78 °C to RT, 1 h.

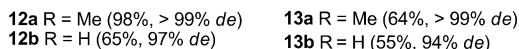
Table 1 summarizes the oxidation of various (hydroxymethyl)phosphinates. As can be seen the reaction is general and proceeds in good yields and excellent stereoselectivities. Thus, the present work also provides a general route to P-stereogenic *H*-phosphinates that is much simpler and cheaper than the desymmetrization of alkyl phosphinates.^[9]

An example of the exploitation of the CH₂OH moiety is the Wittig rearrangement^[10] (Scheme 5). Allylation of **3** gives

Table 1: Summary of the oxidative cleavage reactions.^[a]

R	A		yield [%]	B	
	<i>de</i> [%]	config.		<i>de</i> [%]	config.
Ph	95	<i>S_p</i>	91	95	<i>R_p</i>
Ph	95	<i>R_p</i>	81	> 99	<i>S_p</i>
Me	> 99	<i>R_p</i>	61	96	<i>S_p</i>
1-naphthyl	94	<i>R_p</i>	87	94	<i>S_p</i>
cinnamyl	> 99	<i>R_p</i>	82	> 99	<i>S_p</i>

[a] For details, see the Supporting Information.



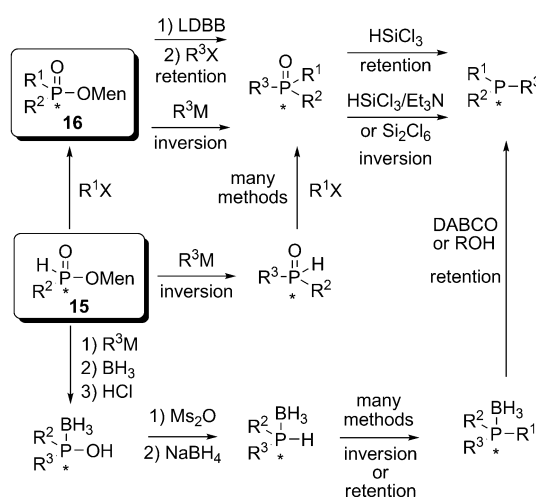
Scheme 5. Stereospecific Wittig rearrangement. a) 1) NaH (1.5 equiv), THF, 0°C to RT; 2) R¹R²C=CHCH₂Br (1.2 equiv), THF, RT, 3 h. b) sBuLi (2 equiv), THF, -78°C, 4 h.

intermediate **12**. Subsequent treatment of **12** with *s*BuLi delivers the rearranged product **13**. In both instances, a single diastereomer is obtained. Stereochemical assignment was established on **13b** through X-ray crystallography.^[15]

H-Phosphinate (R_p)-**2** was converted into menthyl thiophosphonic monoester **14** in quantitative yield [Eq. (1)]. In the past, P-stereogenic compounds have been prepared by resolving thiophosphonic acid monoesters with chiral bases (quinine, brucine),^[11] which requires optimization for each case.



The preparation of a variety of P-stereogenic organophosphorus compounds from **1** and from other menthyl phosphinic esters is well-known (Scheme 6).^[1] For example, treatment of menthyl *H*-phosphinates **15** with organometallic reagents gives the corresponding secondary phosphine oxides with high stereoselectivity (inversion). Similarly, disubstituted menthyl phosphinates **16** are alkylated after LDBB (lithium



Scheme 6. Transformations of P-stereogenic menthyl phosphinates, described in the literature.

para,para'-di-*tert*-butylbiphenylide) reduction^[12] or substituted with organometallic entities. The latter method was used in the historic synthesis of the P-stereogenic bidentate phosphine ligand DiPAMP.^[2a] The groups of Pietrusiewicz^[13a] and Buono^[13b,4] have developed a very nice method to convert *H*-phosphinates into secondary phosphine–borane complexes. Finally, many methods are established to convert tertiary phosphine oxides into the corresponding P-stereogenic phosphines through either retention or inversion of configuration.^[1] To date, the major limitation in using the reactions shown in Scheme 6 has been the preparation of the required starting materials **15** and **16**. This fact has also prompted many different methods to access P-stereogenic compounds.^[1] For example, the enzymatic resolution of (hydroxymethyl)phosphinates requires significant optimization and the use of expensive lipases/esterases.^[14] In contrast, our approach employs one of the cheapest chiral alcohols available: (–)-menthol. With the present strategy, accessing a wide variety of compounds **15** and **16** is straightforward and inexpensive; so our method should be applicable to the synthesis of virtually any P-stereogenic phosphine.

In summary, we have prepared numerous versatile and inexpensive P-stereogenic phosphinate building blocks. The reaction of H_3PO_2 or $\text{RP}(\text{O})(\text{OH})\text{H}$ with (–)-menthol and paraformaldehyde is apparently a general method. Menthyl (hydroxymethyl)phosphinates display favorable crystallization properties and synthetic versatility. These are obtained in multigram quantities through simple and practical crystallization conditions (most often at room temperature!). The method does not rely on any chlorophosphine intermediate. One illustration of the synthetic flexibility is the stereo-divergent preparation of both (R_p)-**1** and (S_p)-**1** from the same (–)-menthol auxiliary. The presence of the hydroxymethyl group not only eases the crystallization process, but also offers the possibility to maintain the methylene carbon atom in other P-stereogenic derivatives, or to be cleaved to P-stereogenic *H*-phosphinates. Compound (R_p)-**2** represents a novel chiral version of hypophosphorous esters, from which virtually any organophosphorus compound can be synthesized. We believe that our method represents a great leap forward toward the general synthesis of P-stereogenic compounds. This should provide a revival of older menthol-based methods and promote the development of novel phosphine ligands for asymmetric synthesis. Further work to improve the yields of (R_p)-**2** and related compounds through additional reactions of the mother liquor, and to develop, expand, and apply this method, is currently underway.

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- [1] Reviews on P-stereogenic compounds: a) O. I. Kolodiazhnyi, *Tetrahedron: Asymmetry* **2012**, 23, 1–46; b) J. S. Harvey, V. Gouverneur, *Chem. Commun.* **2010**, 46, 7477–7485; c) A. Grabulosa, J. Granell, G. Muller, *Coord. Chem. Rev.* **2007**, 251, 25–90; d) D. S. Glueck, *Synlett* **2007**, 2627–2634; e) R. Engel,

- J. I. Rizzo, *Curr. Org. Chem.* **2006**, *10*, 2393–2405; f) M. J. Johansson, N. C. Kann, *Mini-Rev. Org. Chem.* **2004**, *1*, 233–247; g) K. V. L. Crépy, T. Imamoto, *Top. Curr. Chem.* **2003**, *229*, 1–40; h) L. A. Wozniak, A. Okruszek, *Chem. Soc. Rev.* **2003**, *32*, 158–169; i) O. I. Kolodiaznyy, *Tetrahedron: Asymmetry* **1998**, *9*, 1279–1332; j) M. Ohff, J. Holz, M. Quirnbach, A. Börner, *Synthesis* **1998**, 1391–1415; k) K. M. Pietrusiewicz, M. Zablocka, *Chem. Rev.* **1994**, *94*, 1375–1411; l) “Optically active phosphines: preparation, uses and chiroptical properties”: H. B. Kagan, M. Sasaki in *Organophosphorus Compounds* (Ed.: F. R. Hartley), Wiley, New York, **1990**, pp. 51–102 (part of the series *PATAI'S Chemistry of Functional Groups*); m) H. B. Kagan in *Asymmetric Synthesis*, Vol. 5 (Ed.: J. D. Morrison), Academic Press, New York, **1985**, pp. 1–39; n) D. Valentine Jr. in *Asymmetric Synthesis*, Vol. 4 (Eds.: J. D. Morrison, J. W. Scott), Academic Press, New York, **1984**, pp. 263–312.
- [2] a) B. D. Vineyard, W. S. Knowles, M. J. Sabacky, G. L. Bachman, D. J. Weinkauff, *J. Am. Chem. Soc.* **1977**, *99*, 5946–5952; b) J. Donohue, N. Mandel, W. B. Farnham, R. K. Murray, Jr., K. Mislow, H. P. Benshop, *J. Am. Chem. Soc.* **1971**, *93*, 3792–3793; c) W. B. Farnham, R. K. Murray, Jr., K. Mislow, *J. Am. Chem. Soc.* **1970**, *92*, 5809–5810; d) L. P. Reiff, H. S. Aaron, *J. Am. Chem. Soc.* **1970**, *92*, 5275–5276; e) R. A. Lewis, K. Mislow, *J. Am. Chem. Soc.* **1969**, *91*, 7009–7012; f) O. Korpiun, R. A. Lewis, J. Chickos, K. Mislow, *J. Am. Chem. Soc.* **1968**, *90*, 4842–4846; g) T. L. Emmick, R. L. Letsinger, *J. Am. Chem. Soc.* **1968**, *90*, 3459–3465; h) O. Korpiun, K. Mislow, *J. Am. Chem. Soc.* **1967**, *89*, 4784–4786.
- [3] a) Y. Zhou, G. Wang, Y. Saga, R. Shen, M. Goto, Y. Zhao, L.-B. Han, *J. Org. Chem.* **2010**, *75*, 7924–7927; b) G. Wang, R. Shen, Q. Xu, M. Goto, Y. Zhao, L.-B. Han, *J. Org. Chem.* **2010**, *75*, 3890–3892; c) Q. Xu, C.-Q. Zhao, L.-B. Han, *J. Am. Chem. Soc.* **2008**, *130*, 12648–12655; d) L.-B. Han, C.-Q. Zhao, *J. Org. Chem.* **2005**, *70*, 10121–10123; e) L.-B. Han, C.-Q. Zhao, S.-y. Onozawa, M. Goto, M. Tanaka, *J. Am. Chem. Soc.* **2002**, *124*, 3842–3843.
- [4] G. Gatineau, L. Giordano, G. Buono, *J. Am. Chem. Soc.* **2011**, *133*, 10728–10731, and references therein.
- [5] O. Berger, C. Petit, E. L. Deal, J.-L. Montchamp, *Adv. Synth. Catal.* **2013**, *355*, 1361–1373.
- [6] a) O. Berger, L. Gavara, J.-L. Montchamp, *Org. Lett.* **2012**, *14*, 3404–3407. For the cleavage of (hydroxymethyl)phosphine–boranes, see: b) K. Nagata, S. Matsukawa, T. Imamoto, *J. Org. Chem.* **2000**, *65*, 4185–4188.
- [7] a) K. Bravo-Altamirano, J.-L. Montchamp, *Org. Synth.* **2008**, *85*, 96–105; b) K. Bravo-Altamirano, J.-L. Montchamp, *Org. Lett.* **2006**, *8*, 4169–4171.
- [8] The absolute configuration of (*R_p*)-**10** was determined by comparison with the product obtained from the cross-coupling of (*R_p*)-**2** with cinnamyl acetate.
- [9] K. Bravo-Altamirano, L. Coudray, E. L. Deal, J.-L. Montchamp, *Org. Biomol. Chem.* **2010**, *8*, 5541–5551.
- [10] T. Nakai, K. Mikami, *Org. React.* **1994**, *46*, 105–209.
- [11] a) L. K. Kuo, S. K. Glazier, *Inorg. Chem.* **2012**, *51*, 328–335; b) Y. Kobayashi, F. Morisawa, K. Saigo, *J. Org. Chem.* **2006**, *71*, 606–615; c) R. Allahyari, P. W. Lee, G. H. Y. Lin, R. M. Wing, T. R. Fukuto, *J. Agric. Food Chem.* **1977**, *25*, 471–478; d) M. Mikołajczyk, M. Leitloff, *Russ. Chem. Rev.* **1975**, *44*, 670–686; e) H. S. Aaron, J. Braun, T. M. Shryne, H. F. Frack, G. E. Smith, R. T. Uyeda, J. I. Miller, *J. Am. Chem. Soc.* **1960**, *82*, 596–598; f) H. S. Aaron, T. M. Shryne, J. I. Miller, *J. Am. Chem. Soc.* **1958**, *80*, 107–110.
- [12] Y. Koide, A. Sakamoto, T. Imamoto, *Tetrahedron Lett.* **1991**, *32*, 3375–3376.
- [13] a) M. Stankevič, K. M. Pietrusiewicz, *J. Org. Chem.* **2007**, *72*, 816–822; b) D. Moraleda, D. Gatineau, D. Martin, L. Giordano, G. Buono, *Chem. Commun.* **2008**, 3031–3033.
- [14] a) T. Yamagishi, J.-i. Mori, T. Haruki, T. Yokomatsu, *Tetrahedron: Asymmetry* **2011**, *22*, 1358–1363; b) C. Nowlan, Y. Li, J. C. Hermann, T. Evans, J. Carpenter, E. Ghanem, B. K. Shoichet, F. M. Raushel, *J. Am. Chem. Soc.* **2006**, *128*, 15892–15902; c) K. Shioji, Y. Kurauchi, K. Okuma, *Bull. Chem. Soc. Jpn.* **2003**, *76*, 833–834; d) P. Kielbasinski, M. Albrycht, J. Łuczak, M. Mikołajczyk, *Tetrahedron: Asymmetry* **2002**, *13*, 735–738.
- [15] CCDC 952809 (C₁₁H₂₃O₃P), 952808 (C₁₇H₂₇O₃P), and 952807 (C₂₀H₃₁O₃P) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.