

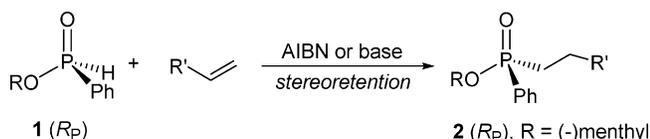
Stereospecific Addition of H–P Bond to Alkenes: A Simple Method for the Preparation of (*R_P*)-Phenylphosphinates

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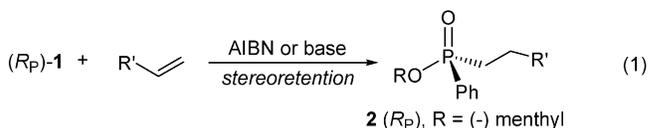
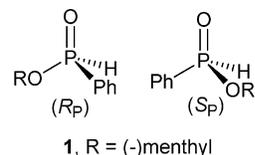
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A variety of functionalized optically pure (*R_P*)-alkylphenylphosphinates are readily prepared by stereospecific radical or base-catalyzed additions of the easily available (*R_P*)-menthyl phenylphosphinate to alkenes.

Optically active -stereogenic compounds have attracted growing attention because of their novel applications in organic synthesis and bioorganic chemistry.¹ However, their preparation usually requires tedious procedures.^{1e,2} By adopting a modified procedure of Mislow and co-workers,³ pure (-)-menthyl (*R_P*)-phenylphosphinate **1** (*R_P*/*S_P* > 99/1) can be easily prepared on a large scale.^{4,5} We have revealed that a palladium-catalyzed addition of (*R_P*)-**1** to alkynes took place stereospecifically to give high yields of (*R_P*)-alkenylphosphinates.⁴ However, attempts to extend this strategy to alkenes failed. As a complement of the palladium-catalyzed additions to alkynes,⁴ herein we report that highly stereospecific addition of (*R_P*)-**1** to alkenes can be alternatively achieved

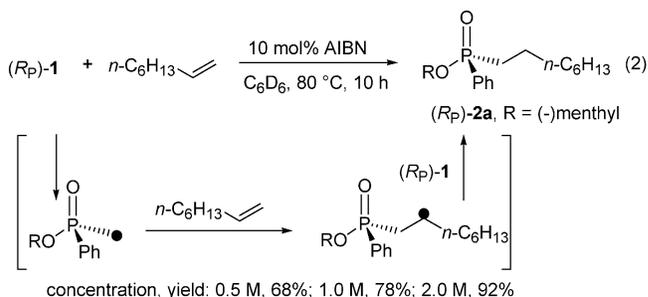
by using radical^{5f} or base-catalyzed reactions to give a variety of (-)-menthyl (*R_P*)-alkylphenylphosphinates **2** in good yields (eq 1). Although Mislow and co-workers briefly reported that a diastereomerically rich **1** added stereospecifically to cyclohexene in the presence of dibenzoyl peroxide,^{5f} applications of this kind of radical reaction for the synthesis of optically active alkylphenylphosphinates have not been investigated. In addition, the base-catalyzed stereospecific addition of (*R_P*)-**1** to alkenes appears to be new.



AIBN-Induced Stereospecific Radical Additions of (*R_P*)-**1** to Alkenes.

In the presence of AIBN, (*R_P*)-**1** can add stereospecifically to monosubstituted alkenes to give the corresponding adducts in high yields. Thus, as shown by ¹H NMR spectroscopy, though non-addition products could be detected from an equimolar mixture of (*R_P*)-**1** (1.0 mmol) with 1-octene (1.0 mmol) in benzene-*d*₆ (0.5 mL) after heating at 80 °C for 16 h, when a trace amount of AIBN (10 mol %) was added, the addition proceeded efficiently to give menthyl octylphenylphosphinate **2a** in 78% yield as a single diastereomer (which has an *R_P* configuration at phosphorus as deduced from the experiment described below) (eq 2). On the other hand, a similar addition using a diastereomeric mixture of **1** (*R_P*/*S_P* = 55/45) gave a diastereomeric mixture of **2a** with a ratio of *R_P*/*S_P* = 55/45, confirming that this AIBN-initiated radical addition proceeds stereospecifically.³

Note that the stereochemistry of (*R_P*)-**1** was maintained intact when it was heated in benzene at 80 °C for 16 h. In the presence of 10 mol % AIBN, however, ca. 2% of (*S_P*)-**1** was detected under similar conditions. The fact that only (*R_P*)-**2a** was formed and no racemization of (*R_P*)-**1** could be observed during the addition may indicate that, although there are two possible competing routes for the P-centered radical intermediate (i.e., racemization and stereospecific addition to alkene), the latter was preferentially favored.^{6,7}



(1) (a) Quin, L. D. *A Guide to Organophosphorus Chemistry*; Wiley-Interscience: New York, 2000. (b) Sasaki, M. In *Chirality in Agrochemicals*; Kurihara, N., Miyamoto, J., Eds.; Wiley & Sons: Chichester, 1998; pp 85–139. (c) Imamoto, T. In *Handbook of Organophosphorus Chemistry*; Engel, R., Ed.; Marcel Dekker: New York, 1992; Chapter 1. (d) Kagan H. B.; Sasaki, M. In *Chemistry of Organophosphorus Compounds*; Hartley, F. R., Ed.; Wiley & Sons: New York, 1990; Vol. 1, Chapter 3. (e) Dubrovina, N. V.; Börner, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 5883.

(2) (a) Pietrusiewicz, K. M.; Zablocka, M. *Chem. Rev.* **1994**, *94*, 1375. (b) 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. (c) Free Man, R. N.; Mitchell, C. R.; Vonwiller, S. C. *J. Org. Chem.* **1994**, *59*, 2919.

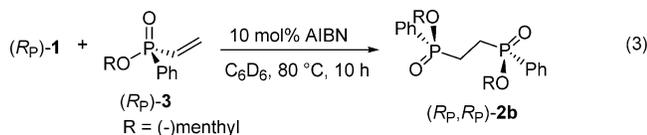
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(5) Known transformations of diastereomeric **1**. Stereospecific methylation with MeI: (a) Reference 3. Addition to aldehydes: (b) Imamoto, T.; Oshilki, T.; Onozawa, T.; Matsuo, M.; Hikosaka, T.; Yanagawa, M. *Heteroatom Chem.* **1992**, *3*, 563. (c) Cai, J.; Zhou, Z.; Zhao, G.; Tang, C. *Heteroatom Chem.* **2003**, *14*, 312. Addition to cyclohexene in the presence of dibenzoyl peroxide: (d) Benschop, H. P.; Platenburg, D. H. J. M. *J. Chem. Soc., Chem. Commun.* **1970**, 1098. (e) Berg, G. R. V. D.; Platenburg, D. H. J. M.; Benschop, H. P. *J. Chem. Soc., Chem. Commun.* **1971**, 606. (f) Farnham, W. B.; Murray, R. K.; Mislow, K. *J. Chem. Soc., Chem. Commun.* **1971**, 146.

This radical addition is highly affected by the concentrations of the substrates, and a high concentration of the substrates accelerates the reaction. Thus, as determined by ^1H NMR spectroscopy, while 68% yield of (R_P)-**2a** was obtained at 0.5 M concentration of the substrates, 78 and 92% yields of the adduct were obtained at concentrations of 1 and 2 M, respectively.

The configuration at phosphorus of the adduct **2a** is determined to be R_P on the basis of the following reaction. Thus, 45% yield of **2b** was obtained by a similar radical addition of (R_P)-**1** to an enantiomerically pure vinylphosphinate (R_P)-**3** (eq 3). The ^{31}P NMR spectroscopy of **2b** displays only one signal, indicating that the two phosphorus atoms have the same R_P configuration.



This stereospecific radical addition can be successfully applied to other alkenes to produce valuable optically pure phosphinates in good yields (Table 1). It is noteworthy that a variety of functionalities such as hydroxyl, alkoxy, acetoxy, thio, phosphino (PR_2), phosphinoyl ($\text{Ph}_2\text{P}(\text{O})$), silyl, and stannyl groups were tolerant under the reaction conditions, and the corresponding multifunctionalized adducts were obtained in good yields. Compared to terminal alkenes, the additions to simple internal alkenes proceeded slowly. Thus, the reaction with a large excess amount of cyclohexene, for example, required 40 h of heating to get an acceptable yield of the adduct (run 15). This difference in reactivity between terminal and internal alkenes, however, enables the selective introduction of the phosphinoyl group to the terminal carbon–carbon double bond when a terminal and an internal carbon–carbon double bond coexist in a substrate. For example, the reaction of 3-cyclohexenylethene with (R_P)-**1** (run 10) gave the addition product to the terminal C=C bond selectively.⁸ Expecting good diastereoselectivities when new chiral carbon centers are generated,⁹ we also conducted reactions with 2,3-dihydrofuran and others (runs 11–14). However, the diastereoselectivities were not satisfactory under the present conditions.⁹ As generally seen in radical additions of $\text{P}(\text{O})\text{--H}$ bonds to alkenes,¹⁰ **1** did not add to aromatic alkenes such as styrene and alkenes with an electron-withdrawing group (vide infra), where polymerization of the alkenes took place.

(6) A careful analysis of the reaction mixtures revealed that ca. 3% of a byproduct was also formed (estimated from ^{31}P NMR spectroscopy). This byproduct, however, is not (S_P)-**2a**, but appears to be that generated by the addition dimerization of 1-octene with (R_P)-**1**.

(7) As expected, when the alkene was consumed, racemization of (R_P)-**1** took place. For example, (S_P)-**1** was observed in the remaining **1** for a reaction using an excess of (R_P)-**1** (1.2 equiv to 1-octene) under the reaction conditions of eq 2.

(8) Although not distinguishable on ^1H or ^{31}P NMR spectroscopy, compound **2l** is assumed to be a diastereomeric mixture because of the chiral carbon at the cyclohexene ring.

(9) For stereoselective radical additions, see: Sibi, M. P.; Manyem, S.; Zimmerman, J. *Chem. Rev.* **2003**, *103*, 3263 and references therein. Improved diastereoselectivities are expected if the current reactions can be performed under milder conditions. Optimization of the reaction conditions is now in progress.

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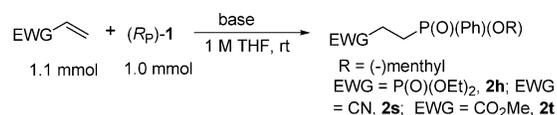
TABLE 1. Stereospecific Radical Addition of (R_P)-1** to Alkenes^a**

run	alkene	conditions	product	yield ^b
1		neat, 18 h		(2c) 93%
2		neat, 19 h		(2d) 89%
3		4M C_6H_6 , 20 h		(2e) 27%
4		neat, 16 h		(2f) 87% ^c
5		neat, 20 h		(2g) 63%
6		neat, 18 h		(2h) 49%
7		neat, 16 h		(2i) 84%
8		neat, 20 h		(2j) 52%
9		neat, 20 h		(2k) 58%
10		neat, 19 h		(2l) 53%
11		3M C_6H_6 , 20 h		(2m) 89% ^d
12		neat, 20 h		(2n) 78% ^e
13		neat, 24 h		(2o) 43% ^f
14		neat, 40 h		(2p) 97% ^g
15		neat, 40 h		(2q) 83% ^h
16		neat, 40 h		(2r) 89% ^h

^a R = (-)-menthyl; unless otherwise noted, an equimolar (R_P)-**1** and an alkene were heated at 80 °C in the presence of 10 mol % AIBN under the conditions shown in the table. ^b Yields refer to isolated yields. ^c H_2O_2 was added to the reaction mixture to convert **2f** to **2g**. The yield refers to that of **2g**. ^d A 46/54 diastereomer mixture. ^e A 47/53 diastereomer mixture. ^f A 35/65 diastereomer mixture. ^g A 48/52 diastereomer mixture. ^h Run in a sealed tube with 5 equiv of the alkene.

Stereospecific Michael Additions of (R_P)-1** to Electron-Deficient Alkenes.** As described above, the radical additions of (R_P)-**1** to electron-deficient alkenes such as methyl acrylate or acrylonitrile, which produce more valuable functionalized phosphorus compounds, hardly proceed. Since a base-catalyzed Michael addition of $\text{P}(\text{O})\text{--H}$ bonds to electron-deficient alkenes is well-

SCHEME 1

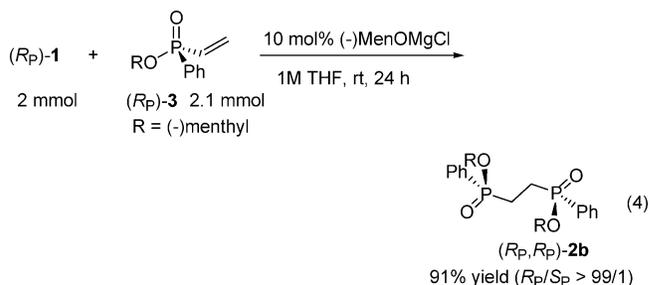


10 mol% *t*-BuONa, 48 h, 51% NMR yield **2h** (R_P/S_P = 48/52)
 5 mol% EtOMgCl, 24 h, 87% NMR yield **2h** (R_P/S_P = 94/6)
 5 mol% *i*-PrOMgCl, 24 h, 97% NMR yield **2h** (R_P/S_P = 96/4)
 5 mol% *t*-BuOMgCl, 24 h, 79% NMR yield **2h** (R_P/S_P > 99/1)
 10 mol% (-)-MenOMgCl, 12 h, 99% NMR yield **2h** (87% isolated yield) (R_P/S_P > 99/1)
 10 mol% (-)-MenOMgCl, 12 h, 74% isolated yield **2s** (R_P/S_P > 99/1)
 10 mol% (-)-MenOMgCl, 12 h, 64% isolated yield **2t** (R_P/S_P = 96/4)

known,¹⁰ we decided to investigate the addition of (R_P)-**1** in the presence of a base catalyst. However, since a rapid racemization of (R_P)-**1** takes place under basic conditions,¹¹ the initial attempts were disappointing. Thus, the *t*-BuONa-catalyzed addition of (R_P)-**1** to diethyl vinylphosphonate only gave a diastereomer mixture of **2h** in 51% yield (determined by ¹H NMR) (Scheme 1). Accidentally, however, we found that alkoxy magnesium halides are excellent catalysts for this Michael addition of (R_P)-**1** to produce the corresponding adducts efficiently and highly stereospecifically. Thus, the EtOMgCl-catalyzed addition of (R_P)-**1** to ethyl vinylphosphonate gave **2h** in 87% yield with an R_P/S_P ratio of 94/6. The diastereoselectivity was further improved as bulky alkoxy magnesium chlorides were used as the catalysts (i.e., ROMgCl/diastereoselectivity: *i*-PrOMgCl/92% and *t*-BuOMgCl/ca. 99%). A separate experiment confirmed that the exchange of the alkoxy group of EtOMgCl with menthoxy of **1**, but not that of **2h**, could take place to give a racemic EtO(Ph)-P(O)H under the reaction conditions in the absence of ethyl vinylphosphonate. As expected, similar transesterification was slow with bulky *i*-PrOMgCl, and no transesterification was observed with *t*-BuOMgCl. The formation of a trace amount of side products (EtO)₂-P(O)(CH₂)₂-P(O)Ph(OR) (R = Et, *i*-Pr) (ca. 3–5% yield) in the addition reactions is in agreement with the above observation. We assumed that this transesterification process (i.e., the attack of alkoxy group at P(O)) might cause, to some extent, the racemization of **1**,^{1a} and therefore the bulky *t*-BuOMgCl gave the best selectivity. Since *t*-BuOMgCl is not soluble in THF, handling of the catalyst is somehow difficult. This, however, could be overcome by employing (-)-MenOMgCl (Men represents menthyl group) as the catalyst that is soluble in THF and can give excellent yields and selectivity of the addition product.

As illustrated by eq 4, by using this strategy, a C_2 -symmetric bidentate P-stereogenic phosphorus compounds can be readily obtained. Thus, the (-)-MenOMgCl-catalyzed addition of (R_P)-**1** to **3** gave (R_P,R_P)-**2b** selectively in 87% isolated yield. Since **2b** can be converted stereospecifically into phosphine oxides¹² and these phosphine oxides can be further converted to C_2 -symmetric

phosphines by stereospecific reductions with LiAlH₄ or silanes,^{1a} **2b** is a versatile precursor for a variety of C_2 -symmetric bidentate phosphorus compounds. In conclu-



sion, a variety of (R_P)-menthyl alkylphenylphosphinates can be conveniently prepared by highly stereospecific radical and/or base-catalyzed Michael additions of (R_P)-**1** to alkenes. This stereospecific addition of (R_P)-**1** to alkenes is a complement to our previous reported metal-catalyzed stereospecific additions to alkynes and fulfills the strategy for the preparation of optically pure phosphinates by using the now readily available (R_P)-**1**.

Experimental Section

AIBN-Induced Free Radical Addition of (R_P)-(-)-Menthyl Phenylphosphinate **1a to 1-Octene: A Representative Procedure for the Radical Additions.** (R_P)-**1a** (280 mg, 1.0 mmol), 1-octene (112 mg, 1.0 mmol), and AIBN (16 mg, 0.1 mmol) were dissolved in 0.5 mL of dry benzene under nitrogen. The resulting solution was heated at 80 °C for 16 h. The solvent was evaporated under a reduced pressure to give an oil that was subjected to purification on a preparative GPC instrument (Japan Analytical Industry LC-908 equipped with 1H and 2H columns) using CHCl₃ as solvent to give pure **2a** in 87% yield (341 mg) as a colorless oil.

(-)-Menthoxy Magnesium Chloride Catalyzed Michael Addition of (R_P)-(-)-Menthyl Phenylphosphinate **1a to Diethyl Vinylphosphonate: A Representative Procedure for the Base-Catalyzed Michael Additions.** To a mixture of (R_P)-**1a** (280 mg, 1.0 mmol) and diethyl vinylphosphonate (1.1 mmol, 180 mg) in THF (1 mL) was added menthoxy magnesium chloride (0.1 mL, 1 M solution in THF). The resulting solution was stirred at room temperature for 12 h. The solvent was evaporated under a reduced pressure to give an oil that was subjected to purification on a preparative GPC instrument (Japan Analytical Industry LC-908 equipped with 1H and 2H columns) using CHCl₃ as solvent to give pure **2h** in 87% yield (387 mg) as a colorless oil.

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Supporting Information Available: Spectral and analytical data and copies of ¹H NMR spectra of the addition products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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