JOC*Note*

Stereospecific Pd(0)-Catalyzed Arylation of an Allylic Hydroxy Phosphonate Derivative: Formal Synthesis of (*S*)-(+)-ar-Turmerone

Bradley J. Rowe and Christopher D. Spilling*

Department of Chemistry and Biochemistry, University of Missouri—St. Louis, 8001 Natural Bridge Road, St. Louis, Missouri 63121

cspill@umsl.edu

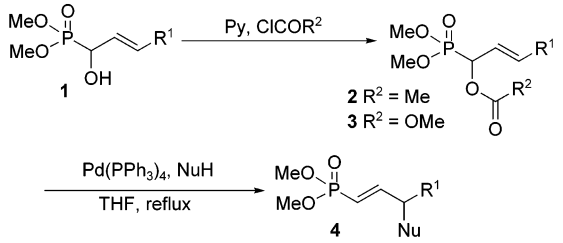
Received July 31, 2003

Abstract: Reaction of the (1*S*)-allylic hydroxy phosphonate **1(S)** with methyl chloroformate in pyridine yields the corresponding carbonate **3(S)**. The carbonate **3(S)** undergoes a palladium-catalyzed arylation with *p*-tolyl tributylstannane to give both the 1*E* and 1*Z* vinyl phosphonates **6** (85:15). The *E* and *Z* vinyl phosphonates **6** were shown to have the opposite configuration at C-3. The major vinyl phosphonate isomer (3*S*,1*E*), was converted to (3*S*)-3-(*p*-tolyl)-butanal **8(S)**, completing a formal total synthesis of (*S*)-ar-turmerone **5a**.

Allylic hydroxy phosphonates **1** display some of the rich chemistry associated with allylic alcohols; however, the steric and electronic influence of the phosphorus moiety can enhance the stereochemical and regiochemical outcome of the reactions.[1,2] This effect is well demonstrated in the palladium-catalyzed addition of nucleophiles to the corresponding acetate **2** and carbonate **3** derivatives (Scheme 1). The acetate and carbonate derivatives (**2** and **3**) undergo palladium-catalyzed regioselective addition of various nucleophiles to give γ-substituted vinyl phosphonates **4** in high yield.[1] The nucleophile adds exclusively to the 3 position, with migration of the double bond into "conjugation" with the phosphoryl group.[1] More generally, it has been shown that allylic hydroxy phosphonates can serve as useful intermediates in the synthesis of γ-substituted phosphonates by 1,3 transposition of functionality.[2]

The last 10 years have witnessed a rapid advance in methods for the enantioselective synthesis of hydroxy phosphonates giving access to compounds with high enantiomeric purity.[3−5] The allylic hydroxy phosphonates, in particular, are most efficiently accessed through the catalytic asymmetric phosphonylation of unsaturated aldehydes.[5] These nonracemic hydroxy phosphonates should be useful building blocks for asymmetric synthesis, provided that appropriate stereoselective or stereospecific transformations can be discovered. Having demonstrated that the palladium (0)-catalyzed addition of amines to nonracemic allylic hydroxy phosphonate derivatives proceeded with complete chirality transfer,[6] our attention turned to the exploration of reactions with carbon-based nucleophiles.[7]

SCHEME 1. Palladium(0)-Catalyzed Reactions of Allylic Hydroxy Phosphonate Derivatives



The aromatic bisabolenes **5a**−**m** are a series of monocyclic sesquiterpenes isolated from both terrestrial plants and marine organisms (Scheme 2).[8] The interesting biological properties displayed by some members of the aromatic bisabolene family has contributed to their attraction as targets for synthesis.[9] The aromatic bisabolenes contain a characteristic substituted phenyl ring with a methyl-bearing chiral benzylic carbon. Several methods have been reported for the enantioselective synthesis of the benzylic chiral center of the bisabolenes, including[10] enzyme-mediated reduction,[10a,b] enzyme-mediated kinetic resolution and desymmetrization,[10c−f] conjugate addition utilizing a chiral auxiliary,[10g−j] and the Sharpless epoxidation,[10k,l] among others.

An enantioselective synthesis of the aromatic bisabolene core structure was proposed (Scheme 3) wherein

(1) (a) Zhu, J.; Lu, X. *Tetrahedron Lett.* **1987**, *28*, 1897. (b) Zhu, J.; Lu, X. *J. Chem. Soc., Chem. Commun.* **1987**, 1318. (c) Öhler, E.; Kanzler, S. *Synthesis* **1995**, 539. (d) Ohler, E.; Kanzler, S. *Phosphorus, Sulfur Silicon* **1996**, *112*, 71. (e) Attolini, M.; Maffei, M.; Principato, B.; Peiffer, G. *Synlett* **1997**, 384. (f) Öhler, E.; Kanzler, S. *Liebigs Ann.* **1997**, 1437.

(2) (a) Shabany, H.; Spilling, C. D. *Tetrahedron Lett.* **1998**, *39*, 1465. (b) Cooper, D.; Trippett, S. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2127. (c) Öhler, E.; Kotzinger, S. *Synthesis* **1993**, 497. (d) Öhler, E.; Kanzler, S. *Liebigs Ann.* **1993**, 269. (e) Blackburn, G. M.; Kent, D. E. *J. Chem. Soc., Chem. Commun.* **1981**, 511. (f) Hammond, G. B.; de Mendonca *J. Fluorine Chem.* **1999**, 1.

(3) For reviews, see: (a) Wiemer, D. F. *Tetrahedron* **1997**, *53*, 16609. (b) Davies, S. R.; Mitchell, M. C.; Cain, C. P.; Devitt, P. G.; Taylor, R. J.; Kee, T. P. *J. Organomet. Chem.* **1998**, *550*, 29.

(4) For recent reports of the asymmetric synthesis of hydroxy phosphonates, see: (a) Burk, M. J.; Stammers, T. A.; Straub, J. A. *Org. Lett.* **1999**, *1*, 387. (b) Drescher, M.; Hammerschmidt, F. *Tetrahedron* **1997**, *53*, 4627 and references therein.

(5) (a) Rowe, B. J.; Spilling, C. D. *Tetrahedron: Asymmetry* **2001**, *12*, 1701. (b) Groaning, M. D.; Rowe, B. J.; Spilling, C. D. *Tetrahedron Lett.* **1998**, *39*, 5485. (c) Rath, N. P.; Spilling, C. D. *Tetrahedron Lett.* **1994**, *35*, 227. (d) Yokomatsu, T.; Yamagishi, T.; Shibuya, S. *Tetrahedron: Asymmetry* **1993**, *4*, 1783. (e) Yokomatsu, T.; Yamagishi, T.; Shibuya S. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1527. (f) Sasai, H.; Bougauchi, M.; Arai, T.; Shibasaki, M. *Tetrahedron Lett.* **1997**, *38*, 2717. (g) Yokomatsu, T.; Yamagishi, T.; Shibuya, S. *Tetrahedron: Asymmetry* **1993**, *4*, 1779. (h) Arai, T.; Bougauchi, M.; Sasai, H.; Shibasaki, M. *J. Org. Chem.* **1996**, *61*, 2926. (i) Duxbury, J. P.; Cawley, A.; Thorton-Pett, M.; Wantz, L.; Warne, J. N. D.; Greatrex, R.; Brown, D.; Kee, T. P. *Tetrahedron Lett.* **1999**, *40*, 4403. (j) Ward, C. V.; Jiang, M.; Kee, T. P. *Tetrahedron Lett.* **2000**, *41*, 6181.

(6) De la Cruz, M. A.; Shabany, H.; Spilling, C. D. *Phosphorus, Sulfur Silicon* **1999**, *144−146*, 181.

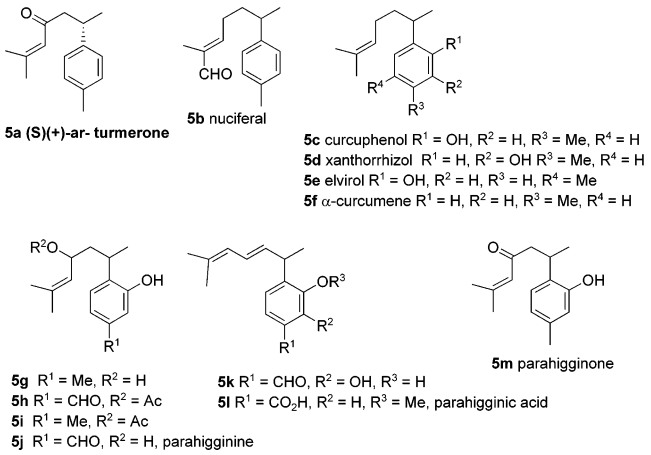
(7) The preliminary results of this work were presented at the 15th ICPC and published as part of the conference proceedings: Rowe, B. J.; Scholten, J.; Spilling, C. D. *Phosphorus, Sulfur Silicon* **2002**, *177*, 1881.

(8) (a) *The Merck Index*, 12th ed.; Budavari, S., Ed.: Merck & Co.: Rahway, NJ, 1996; pp 1674−1675. (b) Rupe, H.; Gassman, A. *Helv. Chim. Acta* **1936**, *19*, 569. (c) McEnroe, F. J.; Fenical, W. *Tetrahedron* **1978**, *34*, 1661. (d) Bohlmann, F.; Grenz, M. *Tetrahedron Lett.* **1969**, 1005. Chen, C.-Y.; Shen, Y.-C.; Chen, Y.-J.; Sheu, J.-H.; Duh, C.-Y. *J. Nat. Prod.* **1999**, *62*, 573.

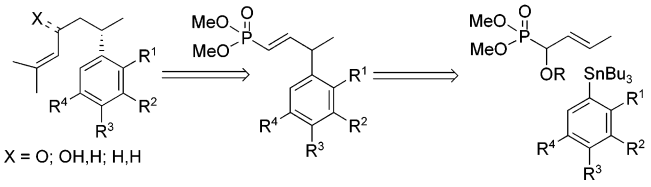
(9) Heathcock, C. H.; Graham, S. L.; Pirrung, M. C.; Plavac, F.; White, C. T. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; Wiley and Sons: New York, 1983; Vol. 5, pp 35−55. Pirrung, M. C.; Morehead, A. T., Jr. In *The Total Synthesis of Natural Products*; Goldsmith, D., Ed.; Wiley and Sons: New York, 1997; Vol. 10, pp 29−77.

10.1021/jo0351318 CCC: $25.00
Published on Web 10/31/2003

SCHEME 2. Some Examples of Aromatic Bisabolene Sesquiterpenes



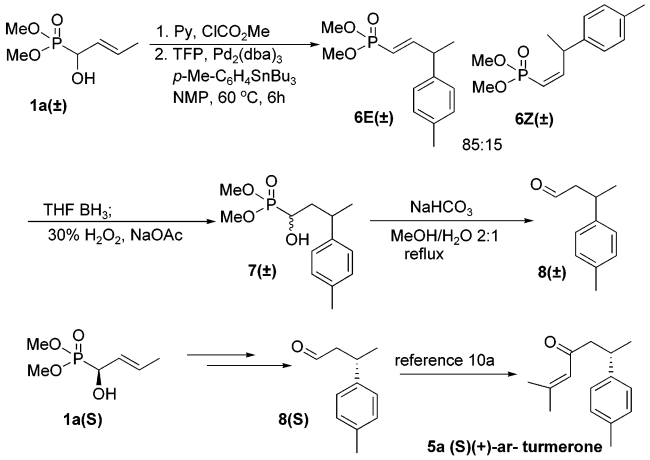
SCHEME 3. Proposed Synthesis of the Aromatic Bisabolene Sesquiterpenes



the benzylic chiral center is established by a palladium-catalyzed addition of an arylstannane to a chiral, non-racemic allylic hydroxy phosphonate derivative. (*S*)-(+)-ar-Turmerone was selected as a demonstration target for the method. (*S*)-(+)-ar-Turmerone was isolated from the rhizomes of *Curcuma longa*[8a,b] and has been the target of many successful syntheses.[9] Surprisingly, only a limited number of enantioselective routes have been reported.[10a,g,m]

In general, the reaction conditions required to promote oxidative addition of Pd(0) to an allylic acetate or carbonate (i.e., excess phosphine ligand) combined with the tight binding of the acetate or methoxide leaving group to the palladium in the π-allyl intermediate serve to retard the rate of transmetalation.[11] Therefore, to couple an allylic acetate or carbonate with an arylstannane, finely balanced reaction conditions are required. Stille and co-workers reported that allylic halides react with arylstannanes[12] under typical palladium-catalyzed coupling conditions with PPh_3 as ligand. Most allylic acetates, however, fail to react.[13,14] As a result, a "ligand-less" catalyst system was developed [$Pd_2(dba)_3$/LiCl in DMF], which allowed the successful coupling of arylstannanes with various allylic acetates.[14] Unfortunately, this system is incompatible with the dimethyl phosphonate group since the chloride ion in polar solvents leads to mono-demethylation. A more attractive solution for our purpose was reported by Farina,[15] who showed that the use of tri(2-furyl)phosphine as a ligand in palladium-catalyzed cross-coupling reactions led to significant rate enhancements. In related reactions, there have been some limited reports of the coupling of arylboronic acids and boronates with allylic acetates using palladium and nickel catalysts, respectively.[16]

SCHEME 4. Synthesis of Turmerone



The racemic hydroxy phosphonate **1a**(±) was converted to the carbonate **3** by reaction with methyl chloroformate in pyridine (79−89%). Reaction of the carbonate with *p*-tolyltributylstannane in *N*-methylpyrrolidinone (NMP) at 60 °C in the presence of palladium(0) trifurylphosphine (TFP) complex (formed in situ) gave a separable mixture the *E*-vinyl phosphonate **6E**(±) (57% isolated) and the *Z*-vinyl phosphonate **6Z**(±) (9% isolated) in an 85:15 ratio (Scheme 4).

The H−H and P−H couplings of the vinyl protons in the ^{1}H NMR spectra easily distinguish the *E* and *Z* isomers **6**. In particular, H-2 of the *Z*-vinyl phosphonate **6Z** exhibits a trans P−H coupling constant of 53 Hz, whereas H-2 of the *E*-vinyl phosphonate **6E** shows a cis P−H coupling constant of 22 Hz. The use of trifurylphosphine and NMP was critical in this reaction. Less polar solvents (THF) or the use triphenylphosphine and triphenylarsine as ligand resulted in slow reactions and led to complex mixtures predominated by materials derived

(10) (a) Fuganti, C.; Serra, S.; Dulio, A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 279. (b) Fuganti, C.; Serra, S. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3758. (c) Fuganti, C.; Serra, S. *Synlett* **1998**, 1252. (d) Ono, M.; Suzuki, K.; Tanikawa, S.; Akita, H. *Tetrahedron: Asymmetry* **2001**, *12*, 2597. (e) Takabatake, K.; Nishi, I.; Shindo, M.; Shishido, K. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1807. (f) Kosaka, T.; Bando, T.; Shishido, K. *J. Chem. Soc., Chem. Commun.* **1997**, 1167. (g) Meyers, A. I.; Smith, K. R. *Tetrahedron Lett.* **1979**, 2749. (h) Meyers, A. I.; Stoinova, D. *J. Org. Chem.* **1997**, *62*, 5219. (i) Asaoka, M.; Shima, K.; Takei, H. *Tetrahedron Lett.* **1987**, *28*, 5669. (j) Asaoka, M.; Shima, K.; Fujii, N.; Takei, H. *Tetrahedron* **1988**, *44*, 4757. (k) Takano, S.; Yanase, M.; Sugihara, T.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1988**, 1538. (l) Takano, S.; Goto, E.; Ogasawara, K. *Tetrahedron Lett.* **1982**, *23*, 5567. (m) Sato, T.; Kawara, T.; Nishizawa, A.; Fujisawa, K. *Tetrahedron Lett.* **1980**, *21*, 3377.

(11) Hegedus, L. S. *Transition Metals in the Synthesis of Complex Organic Molecules*, 2nd ed.; University Science Books: Sausalito, CA, 1999.

(12) Sheffy, F. K.; Stille, J. K. *J. Am. Chem. Soc.* **1983**, *105*, 7173. Sheffy, F. K.; Godschalx, J. P.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 4833. Moreno-Manas, M.; Pajuelo, F.; Pleixats, R. *J. Org. Chem.* **1995**, *60*, 2396.

(13) Trost, B. M.; Keinan, E. *Tetrahedron Lett.* **1980**, *21*, 2595.

(14) Del Valle, L.; Stille, J. K.; Hegedus, L. S. *J. Org. Chem.* **1990**, *55*, 3019.

(15) (a) Farina, V.; Baker, S. R.; Benigni, D.; Sapino, C., Jr. *Tetrahedron Lett.* **1988**, *29*, 5739. (b) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585. (c) Amatore, C.; Jutand, A.; Meyer, G.; Atmani, H.; Khalil, F.; Chahdi, F. O. *Organometallics* **1998**, *17*, 2958.

(16) (a) Uozumi, Y.; Danjo, H.; Hayashi, T. *J. Org. Chem.* **1999**, *64*, 3384. (b) Legros, J.-Y.; Fiaud, J.-C. *Tetrahedron Lett.* **1990**, *31*, 7453. (c) Kobayashi, Y.; Murugesh, M. G.; Nakano, M.; Takahisa, E.; Usmani, S. B.; Ainai, T. *J. Org. Chem.* **2002**, *67*, 7110. (d) Kobayashi, Y.; Ikeda, E. *J. Chem. Soc., Chem. Commun.* **1994**, 1789.

from reduction of the allylic carbonate (^{31}P NMR δ 29.7). The mixture of *E*- and *Z*-vinyl phosphonates **6**(±) (85:15) was subjected to hydroboration[17] to give exclusively the α-hydroxy phosphonate **7**(±) as a 1.5:1 mixture of diastereoisomers (70%). Treatment of the hydroxy phosphonate **7**(±) with sodium bicarbonate in refluxing methanol/water solution gave the racemic aldehyde **8**(±) (76%).

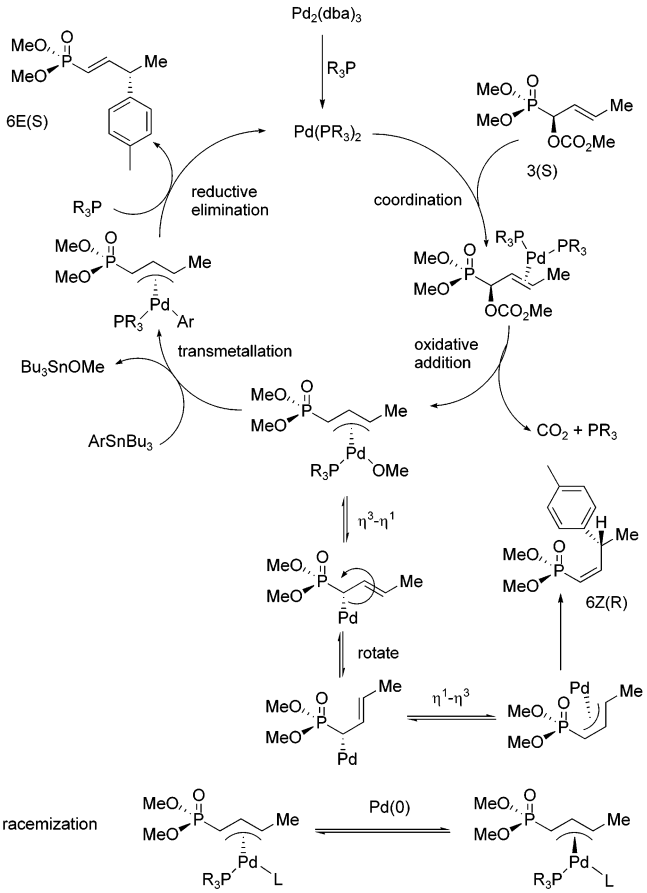
In an initial attempt to determine the stereochemical course of the arylation reaction, the (1*R*)-hydroxy phosphonate **1a(R)** was prepared[4b] in 65% ee and carried through the reaction sequence. Again, the mixture of *E*- and *Z*-vinyl phosphonates **6** (85:15) was subjected to hydroboration to give the α-hydroxy phosphonate **7(R)**. Treatment of the hydroxy phosphonate **7(R)** with sodium bicarbonate in refluxing methanol/water solution gave the (*R*) aldehyde **8(R)**, but with a significant erosion of the enantiomeric excess [[α]$_D$ −15.2 (*c* 1, $CHCl_3$), 37% ee]. The stereochemical assignment was made by comparison with (*S*)-(+)-3-(*p*-tolyl)butanal **8(S)** [[α]$_D$ +39.6 (*c* 1, $CHCl_3$), 95.5% ee].[10a] To synthesize (+)-ar-turmerone with the natural *S* configuration, the (1*S*)-hydroxy phosphonate is required. It was postulated that separation of the *E* and *Z* isomers prior to hydroboration would reduce the level of stereochemical erosion.

The (1*S*)-hydroxy phosphonate **1a(S)** was prepared by a previously published method in 86% ee.[4a] Again, carbonate formation and palladium-catalyzed arylation with *p*-tolyltributylstannane gave a separable mixture of the vinyl phosphonates **6E(S)** and **6Z(R)**. The isomers were separated and individually subjected to hydroboration to give the hydroxy phosphonates **7**. HPLC analysis of the hydroxy phosphonates **7** from both reactions confirmed that the vinyl phosphonates **6E(S)** and **6Z(R)** had the opposite configuration at C-3. However, HPLC also indicated that the enantiomeric excess for the hydroxy phosphonates **7(S)** and **7(R)**, derived from the **6E(S)** and **6Z(R)** respectively, had eroded to 73 ± 2%.

The hydroxy phosphonate **7(S)** derived from the major *E* vinyl phosphonate **6E(S)** was treated sodium bicarbonate in refluxing methanol/water solution to give the (*S*) aldehyde **8(S)**. The optical rotation of the aldehyde **8(S)** confirmed the absolute configuration [[α]$_D$ +32.2 (*c* 0.25, $CHCl_3$), 78% ee] and the magnitude of the rotation was consistent with enantiomeric excess determined by HPLC on the hydroxy phosphonate **7(S)**. Serra et al. reported the conversion of the (*S*)-aldehyde **8(S)** into (S)-*ar*-turmerone **5a** by reaction with 2-methyl-2-propenyl Grignard, followed by MnO_2 oxidation of the resulting alcohol.[10a] Thus, synthesis of aldehyde **8(S)** represents a formal synthesis of (*S*)-(+)-ar-turmerone.

The observed aldehyde stereochemistry is consistent with the expected reaction mechanism[11,12,18] that involves inversion of configuration during π-allyl formation and retention during transmetalation/reductive elimination (i.e., overall inversion). It is believed that the *Z*-vinyl phosphonate is formed (Scheme 5) from the initial π-allyl intermediate via a $\eta^3-\eta^1$ shift to give a σ-bound palladium species. Bond rotation and $\eta^1-\eta^3$ shift give rise to a new π-allyl complex, which upon transmetalation and reductive elimination would yield the *Z* vinyl phosphonate with the opposite (*R*) configuration at C-3. The 9% erosion in enantiomeric excess is probably due to a racemization mechanism involving back-face attack of a palladium nucleophile on the π-allyl intermediate. It is believed that a slow transmetalation step gives rise to a π-allyl intermediate which has a sufficiently long lifetime to suffer racemization via Pd(0) attack and rearrangement via $\eta^1-\eta^3$ shift. This is in contrast to the palladium-catalyzed intermolecular addition of amine nucleophiles where there was no stereochemical erosion and only formation of the *E* vinyl phosphonate was observed.[6]

SCHEME 5. Mechanism for the Arylation Reaction with the (*S*)-Phosphonate



In summary, the palladium-catalyzed addition of *p*-tolyltributylstannane to a (1*S*) phosphono allylic carbonate results in the formation of both *E* and *Z* vinyl phosphonates with the *S* and *R* configurations at C-3, respectively. The major 1*E*,3*S* isomer, formed with inversion of configuration, was converted to the known (*S*)-ar-turmerone precursor (3*S*)-3-(*p*-tolyl)butanal.

Experimental Section

(±)-(2*E*)-Dimethyl [1-(Methoxycarbonyloxy)-2-butenyl] Phosphonate 3(±). The hydroxy phosphonate **1a**(±)[19] (2.6 g, 14 mmol) was dissolved in acetonitrile (100 mL) and pyridine

(17) Agnel, G.; Negishi, E. *J. Am. Chem. Soc.* **1991**, *113*, 7424.

(18) (a) Faller, J. W.; Thomsen, M. E.; Mattina, M. J. *J. Am. Chem. Soc.* **1971**, *93*, 2642. (b) Trost, B. M.; Vanhoeven, T. R. *J. Am. Chem. Soc.* **1976**, *98*, 630. (c) Trost, B. M. *Acc. Chem. Res.* **1980**, *13*, 385. (d) Hayashi, T.; Hagihara, T.; Konishi, M.; Kumada, M. *J. Am. Chem. Soc.* **1983**, *105*, 7767. (e) Mackenzie, P. B.; Whelan, J.; Bosnich, B. *J. Am. Chem. Soc.* **1985**, *107*, 2046. (f) Granberg, K. L.; Bäckvell, J.-E. *J. Am. Chem. Soc.* **1992**, *114*, 6858.

(19) (a) Texier-Boullet, F.; Foucaud, A. *Synthesis* **1982**, 165. (b) Baraldi, P. G.; Guarneri, M.; Moroder, F.; Pollini, G. P.; Simoni, D. *Synthesis* **1982**, 653.

(10 mL, 123 mmol, 8.7 equiv), and then (dimethylamino)pyridine (DMAP) (15 mg) was added. The resulting solution was cooled to 0 °C, and methyl chloroformate (8.56 g, 90 mmol, 6 equiv) was added dropwise. The solution was allowed to warm to room temperature and then was stirred overnight. The solution was diluted with CH_2Cl_2 and washed with water (2×) and saturated copper sulfate solution (4×). The solvent was dried over $MgSO_4$, filtered, and evaporated in vacuo to give **(±)-(2*E*)-dimethyl [1-(methoxycarbonyloxy)-2-butenyl] phosphonate 3(±)** as a pale yellow oil (2.7 g, 79%): IR (neat, NaCl) 1754 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.99 (m, 1H), 5.59 (m, 1H), 5.45 (ddd, 1H, J_{HP} = 12 Hz, J_{HH} = 8, 0.8 Hz), 3.86 (d, 3H, J_{HP} = 11 Hz), 3.83 (s, 3H), 3.82 (d, 3H, J_{HP} = 11 Hz), 1.79 (m 3H); ^{13}C NMR ($CDCl_3$) δ 154.7, 134.1 (d, J_{CP} = 12.6 Hz), 121.6 (d, J_{CP} = 2.1 Hz), 73.1 (d, J_{CP} = 170 Hz), 55.51, 53.97 (d, J_{CP} = 6.4 Hz), 53.94 (d, J_{CP} = 6.2 Hz), 18.28 (d, J_{CP} = 1.2 Hz); ^{31}P NMR δ 20.1. Anal. Calcd for $C_8H_{15}O_6P$: C, 40.34; H, 6.35. Found: C, 40.22; H, 6.27.

Palladium-Catalyzed Arylation of (±)-(2*E*)-Dimethyl [1-(Methoxycarbonyloxy)-2-butenyl] phosphonate. $Pd_2(dba)_3$ (0.022 g, 0.01 equiv) and tri(2-furyl)phosphine (0.022 g, 0.04 equiv) were dissolved in distilled, degassed *N*-methylpyrrolidinone (6 mL). The mixture was stirred for 5 min while being heated to 60 °C in a preheated oil bath. The carbonate **3**(±) (0.59 g) and the aryltributylstannane (1.13 g, 1.2 equiv) were added, and heating was continued for 5 h. The reaction mixture was cooled, and Et_2O and aqueous KF were added. After the mixture was stirred for 15 min, the layers were separated and the aqueous layer was re-extracted with Et_2O. The combined Et_2O extracts were washed with H_2O and brine, dried ($MgSO_4$), and evaporated in vacuo to give a yellow oil. The crude product was purified by flash chromatography (SiO_2, gradient 100% hexanes to 100% ethyl acetate) to give **(±)-(1*Z*)-dimethyl [3-(*p*-tolyl)-1-butenyl] phosphonate 6Z(±)** (0.058 g, 9%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 7.19 (d, 2H, J_{HH} = 8 Hz), 7.12 (2H, d, J_{HH} = 8 Hz), 6.54 (ddd, 1H, J_{HP} = 52 Hz, J_{HH} = 13, 11 Hz), 5.48 (ddd, 1H, J_{HP} = 19 Hz, J_{HH} = 13, 0.5 Hz), 4.48 (m, 1H), 3.74 (d,3 H, J_{HP} = 11 Hz), 3.69 (d,3H, J_{HP} = 11.4 Hz), 2.32 (s, 3H), 1.39 (d, 3H, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 158.7 (d, J_{CP} = 4.6 Hz), 140.8, 136.1, 129.3, 126.9, 112.7 (d, J_{CP} = 183 Hz), 52.1 (d, J_{CP} = 5.5 Hz), 52.0 (d, J_{CP} = 5.6 Hz), 39.7 (d, J_{CP} = 7.7 Hz), 21.0, 20.9; ^{31}P NMR ($CDCl_3$) δ 20.4 and **(±)-(1*E*)-dimethyl [3-(*p*-tolyl)-1-butenyl] phosphonate 6E(±)** (0.36 g, 57%) as a colorless oil: ^1H NMR ($CDCl_3$ δ 7.13 (d, 2H, J = 9 Hz), 7.06 (d, 2H, J = 9.0 Hz), 6.95 (ddd, 1H, J_{HP} = 22 Hz, J_{HH} = 17, 6 Hz,), 5.60 (1H, ddd, J_{HP} = 21 Hz, J_{HH} = 17, 1.6 Hz, 1H), 3.70 (3H, d, J_{HP} = 11 Hz), 3.69 (3H, d, J_{HP} = 11 Hz), 3.58 (m, 2H), 2.33 (s, 3H), 1.41 (d, 3H, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 158.3 (d, J_{CP} = 4.5 Hz), 139.8, 136.4, 129.4, 127.3, 114.0 (d, J_{CP} = 187 Hz), 52.3 (d, J_{CP} = 5.5 Hz), 44.3 (d, J_{CP} = 21 Hz), 21.0, 20.1 ^{31}P NMR ($CDCl_3$) δ 23.1; HRMS (EI) (M^+) calcd for $C_{13}H_{19}O_3P$ 254.1072, found 254.1079.

Palladium-Catalyzed Arylation of (1*S*,2*E*)-Dimethyl [1-(Methoxycarbonyloxy)-2-butenyl] Phosphonate 3(S). The (1*S*) carbonate **3(S)** (2.0 g) was treated as described above to give a mixture of *E* and *Z* vinyl phosphonates **6** (1.3 g, 64%). Further careful chromatography resulted in the isolation of **(3*R*,1*Z*)-dimethyl [3-(*p*-tolyl)-1-butenyl] phosphonate 6Z-(R)** as a colorless oil (0.2 g, 10%) [^{31}P NMR ($CDCl_3$) δ 20.4] and **(3*S*,1*E*)-dimethyl [3-(*p*-tolyl)-1-butenyl] phosphonate 6E-(S)** as a colorless oil (0.7 g 35%): ^{31}P NMR ($CDCl_3$) δ 23.1.

Hydroboration of (±)-(1*Z*)- and (1*E*)-Dimethyl [3-(*p*-Tolyl)-1-butenyl] Phosphonate To Give Dimethyl [1-Hydroxy-3-(*p*-tolyl)butyl] Phosphonate 7(±). To a stirred solution of *E* and *Z* vinyl phosphonates **6**(±) (0.35 g, 1.4 mmol) in THF (1 mL) was added borane THF complex (1.5 M, 4.6 mL, 5 equiv) under argon at room temperature. After 45 min, 30% H_2O_2 (2.2 mL, xs) was added followed by slow addition of saturated sodium acetate solution (3.0 mL). The mixture was heated to 50 °C in a preheated oil bath and stirred for 15 min. The solution was then poured into cold brine and extracted with CH_2Cl_2 (2×). The combined extracts were dried over $MgSO_4$, filtered, and evaporated in vacuo to give a colorless liquid. The crude product was isolated by flash chromatography (SiO_2, 50: 50 ethyl acetate/hexanes, then 100% ethyl acetate) to give starting material (0.053 g) and **(±)-dimethyl [1-hydroxy-3-(*p*-tolyl)butyl] phosphonate 7(±)** (0.255 g, 70%) as a colorless oil: ^1H NMR (1.5:1 mixture of diastereoisomers) ^1H NMR ($CDCl_3$) δ 7.09 (m, 4H), 4.0 &3 3.9 (m, 1H), 3.78, 3.75 & 3.70 (d, 6H, J_{HP} = 10.4 Hz), 3.8 & 3.1 (m 1H), 2.31 (s, 3H), 1.99 (m, 2H), 1.27 & 1.25 (d, 3H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 144.1, 142.3, 135.7, 135.7, 129.3, 129.2 127.3, 126.9, 66.5 (d, J_{CP} = 160 Hz), 665.5 (d, J_{CP} = 160 Hz), 53.4 (m), 39.9, 39.5, 35.3 (m), 23.4, 21.4, 21.0; ^{31}P NMR ($CDCl_3$) δ 28.2 and 28.0; HRMS (EI) (M^+) calcd for $C_{13}H_{21}O_4P$ 272.1177, found 272.1173.

Hydroboration of the **(3*S*,1*E*)-vinyl phosphonate** as described above gave **(3*S*)-dimethyl [1-hydroxy-3-(*p*-tolyl)-butyl] phosphonate** (47%, 1.6:1 diastereoisomer ratio) (see the HPLC data).

Hydroboration of **(3*R*,1*Z*)-vinyl phosphonate** as described above gave **(3*R*)-dimethyl [1-hydroxy-3-(*p*-tolyl)butyl] phosphonate** (33%, 1.85:1 diastereoisomer ratio) (see the HPLC data).

(±)-3-(*p*-Tolyl)butanal 8(±). To a stirred solution of hydroxy phosphonate **7**(±) (0.93 mmol, 255 mg) in a methanol−water mixture (2:1, 10 mL) was added sodium bicarbonate (340 mg, 5 equiv). This solution was stirred at 50 °C until the starting material disappeared (^{31}P NMR, 3 h). The reaction mixture was then extracted with CH_2Cl_2 (3×). The combined extracts were dried over $MgSO_4$, filtered, and evaporated in vacuo to give a colorless oil. The crude product was purified by flash chromatography (SiO_2, 20% ethyl acetate/hexanes) to give **(±)-3-(*p*-tolyl)butanal 8(±)** (0.117 g, 76%) as a colorless liquid: IR (ATR) 1724 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.96 (t, J = 2 Hz, 1H), 7.09 (s, 4H), 3.30 (app sextet,1H, J = 7 Hz), 2.64 (m, 2H), 2.29 (s, 3H), 1.27 (d, J = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 202.2, 142.6, 136.3, 129.6, 126.8, 52.0, 34.2, 22.5, 21.2.

(*R*)-(−)-3-(*p*-Tolyl)butanal 8(R). Reaction of the (3*R*)-hydroxy phosphonate (0.32 g) [from (1*R*)-hydroxy phosphonate (**1**) 65% ee] as described above gave **(*R*)-(−)-3-(*p*-tolyl)butanal** [0.15 g crude, 0.095 g, 50% after column, $[\alpha]_D$ −15.2 (*c* 1, $CHCl_3$) (37% ee)].

(*S*)-(+)-3-(*p*-Tolyl)butanal 8(S). Reaction of the (3*S*)-hydroxy phosphonate (0.1 g) [from (1*S*)-hydroxy phosphonate (**1**) 86% ee] as described above gave **(*S*)-(+)-3-(*p*-tolyl)butanal** [(0.05 g, 85%): $[\alpha]_D$ +32.2 (*c* 0.25, $CHCl_3$) (78% ee)].

Acknowledgment. We are grateful to the donors of the Petroleum Research Fund, administered by the American Chemical Society (34428-AC1), for financial support of this project and the UMSL Graduate School for a fellowship for B.J.R. We are also grateful to the NSF, the US DoE, and the University of Missouri Research Board for grants to purchase the NMR spectrometers (CHE-9318696, CHE-9974801, DE-FG02-92-CH10499) and mass spectrometer (CHE-9708640) used in this work. We thank Anyu He for preparation of the arylstannane.

Supporting Information Available: General experimental and spectra for compounds **3**, **6E**, **6Z**, **7**, and **8** and a comparison of HPLC data for compound **7** prepared from (±)-**6**, **(3S,1E)-6**, and **(3R,1Z)-6**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0351318