JOC Article

Neighboring Group Participation of Phosphine Oxide Functionality in the Highly Regio- and Stereoselective Iodohydroxylation of 1,2-Allenylic Diphenyl Phosphine Oxides

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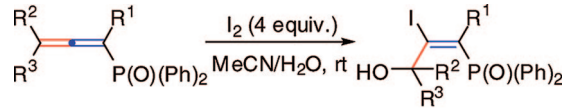

When R^1 = Ar, R^2 = R^3 = H, $AgNO_3$ (6 equiv.) was required.

Two sets of reaction conditions were established to enable the highly regio- and stereoselective iodohydroxylation of 1,2-allenylic diphenyl phosphine oxides, yielding (*E*)-2-iodo-3-hydroxy-1-alkenyl diphenyl phosphine oxides with very high stereoselectivity. The scope of this reaction was examined extensively. Notably, studies on the reactivity of optically active substrates indicated that the axial chirality in the starting allenes may be efficiently transferred to the center chirality of the products with no discernible loss of enantiopurity. Due to the importance of phosphine-containing compounds, both as reagents and ligands, this reaction shows potentials in organic synthesis. Investigations using ESI-MS technology on the ^{18}O-labeled product, which was prepared using ^{18}O-water as the solvent, indicated that the ^{18}O atom was bound to phosphorus in the final product and the oxygen atom of the hydroxyl comes from the phosphinyl functionality of the allene reactant. These results provided solid evidence for the formation of a five-membered cyclic intermediate from the neighboring group participation of the diphenylphosphinyl group. To the best of our knowledge, this is the first time that the neighboring group participation of this type of group was observed.

Introduction

2-Iodo-substituted alkenols are a class of important chemicals and applied in many transformations since they have iodide, carbon−carbon double bond, and hydroxyl functionalities.[1] Thus, highly selective methods to prepare this type of compounds are highly desirable. During the continuous research work of the hydrohalogenation reaction of electron-deficient allenes in our group,[2] we observed the halohydroxylation of allenylic sulfoxides[3] and sulfones,[4] which provided an approach for the highly stereoselective synthesis of (*E*)-2-halo-3-hydroxy-1-alkenyl sulfoxides and sulfones. Further research in the halohydroxylation of allenylic sulfides[5] or selenides[5b] led to a stereoselective route to (*Z*)-2-halo-3-hydroxy-1-alkenyl sulfides or selenides, in which the opposite stereoselectivity was observed. Recently, we also reported the iodohydroxylation of non-heteroatom-substituted allenes affording 4-(3′-hydroxy-2′-iodoalk-1′(*Z*)-enyl)-2(5*H*)-furanone derivatives.[6] Allenylic phosphonates, phosphine oxides, or phosphonic acids are a class of important allene chemicals.[7] Recently, we have reported the hydroarylation of allenylic phosphonates,[8] the semihydrogenation of allenylic phosphonates and phosphine oxides,[9] and the

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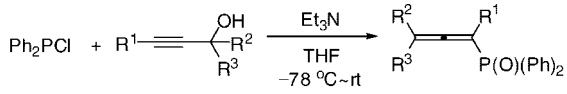
SCHEME 1. Preparation of 1,2-Allenylic Diphenyl Phosphine Oxides 1a−r

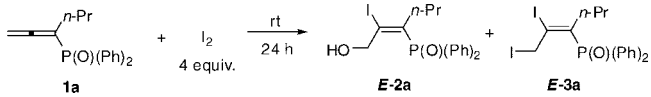


1

yield: 47-80 %

1a: R^1 = *n*-Pr, R^2 = R^3 = H; **1b**: R^1 = Me, R^2 = R^3 = H; **1c**: R^2 = Me, R^1 = R^3 = H;
1d: R^2 = *n*-Pr, R^1 = R^3 = H; **1e**: R^2 = *n*-C_5H_{11}, R^1 = R^3 = H; **1f**: R^1 = H, R^2 = R^3 = Me;
1g: R^1 = H, R^2 = R^3 = Et; **1h**: R^1 = H, R^2, R^3 = -$(CH_2)_4$-; **1i**: R^1 = Et, R^2 = Me, R^3 = H;
1j: R^1 = *n*-Bu, R^2 = *n*-Pr, R^3 = H; **1k**: R^1 = Ph, R^2 = Me, R^3 = H; **1l**: R^1 = Ph, R^2 = *n*-Pr, R^3 = H;
1m: R^1 = R^2 = R^3 = H; **1n**: R^1 = *n*-Bu, R^2 = Me, R^3 = Et; **1o**: R^1 = Ph, R^2 = Me, R^3 = Et;
1p: R^1 = Ph, R^2 = R^3 = H; **1q**: R^1 = *p*-$CHOC_6H_4$, R^2 = R^3 = H; **1r**: R^1 = *p*-MeC_6H_4, R^2 = R^3 = H

TABLE 1. Iodohydroxylation of 1a under Different Conditions[a]



1a ***E*-2a** ***E*-3a**

		NMR yield (%)[b]		
entry	CH_3CN:H_2O	(*E*)-**2a**	(*E*)-**3a**	(*E*)-**2a**:(*E*)-**3a**[b]
1	5:1	18	56	24:76
2	3:1	23	55	29:71
3	1:1	47	33	59:41
4	1:3	87	4	96:4
5	1:5	90 (78)[c]	0	>99:1
6	0:100	86	7	92.8
7[d]	1:5	60	0	>99:1
8[e]	1:5	95	5	95:5

[a] The reaction was carried out at rt for 24 h using **1a** (0.1 mmol) and I_2 (4.0 equiv). [b] Determined by 300 MHz ^{1}H NMR analysis of the crude reaction mixture using CH_2Br_2 as the internal standard. [c] Isolated yield. [d] The reaction was carried out at 60 °C for 20 h. [e] The reaction was carried out for 37 h using I_2 (3.0 equiv).

cyclization−Heck reaction of allenylic phosphonic acids with alkenes or allyl bromide.[10] Subsequently, we wish to see the effect of phosphine oxide on determining the regio- and stereoselectivity in the iodohydroxylation of 1,2-allenylic diphenyl phosphine oxides.

Results and Discussion

It is known that 1,2-allenylic diphenyl phosphine oxides **1** can be easily prepared from the reaction of corresponding propargylic alcohols with Ph_2PCl.[11] Eighteen such compounds were synthesized accordingly (Scheme 1).

We first tried the iodohydroxylation of hexa-1,2-dien-3-yl diphenyl phosphine oxide **1a** with 4 equiv of I_2 at rt in CH_3CN:H_2O = 5:1 (entry 1, Table 1); the iodohydroxylation product (*E*)-**2a** was generated in a yield of 18% by ^{1}H NMR analysis as the only stereoisomer. In addition, the corresponding diiodide (*E*)-**3a** was also formed with a ratio of (*E*)-**2a**/(*E*)-**3a** being 24:76, which was different from the results of the halohydroxylation of allenylic sulfoxides[3] or sulfones.[4] The configurations of the C=C bonds in (*E*)-**2** and (*E*)-**3** were determined by the X-ray diffraction study of (*E*)-**2a**[12] (see Figure S1 in the Supporting Information) and (*E*)-**3p**[13] (vide infra) (see Figure S2 in the Supporting Information).

On the basis of this result, we set to study the solvent effect (entries 1−6, Table 1). The results indicated that the ratio of CH_3CN and H_2O has a profound effect on this reaction: as expected, with the increased amount of H_2O, both the selectivity of the iodohydroxylation product (*E*)-**2a** versus diiodination product (*E*)-**3a** and the yield of (*E*)-**2a** went up, but when we used pure H_2O as the solvent, the ratio of (*E*)-**2a**/(*E*)-**3a** went down to 92:8 (entry 6, Table 1). The best result was given when CH_3CN:H_2O = 1:5 was used as the solvent, affording (*E*)-**2a** as the only product in 78% isolated yield (entry 5, Table 1). When the reaction was carried out at 60 °C, the yield was lower (entry 7, Table 1). Finally, we also checked the influence of the amount of I_2 (entry 8, Table 1). Surprisingly, with 3 equiv of I_2, the selectivity of (*E*)-**2a**/(*E*)-**3a** dropped (entry 6, Table 1). Thus, we applied Conditions A (4 equiv of I_2, CH_3CN:H_2O = 1:5, and rt) for the reaction of 1,2-allenylic diphenyl phosphine oxides.

Then we investigated this reaction of different 1,2-allenylic diphenyl phosphine oxides **1a−l** under Conditions A. It was observed that alkyl groups may be introduced into the different position of allene moiety, affording (*E*)-2-iodo-3-hydroxy-1-alkenyl diphenyl phosphine oxides (*E*)-**2** as the only product in the isolated yields of 56−93% (entries 1−10, Table 2). In addition, 1-phenyl-3-alkyl-1,2-allenylic diphenyl phosphine oxides **1k** and **1l** could also be applied under Conditions A, affording (*E*)-**2k** and (*E*)-**2l** in 79 and 85% isolated yield (entries 11 and 12, Table 2). However, when we tried this reaction of propa-1,2-dienyl diphenyl phosphine oxide **1m** under Conditions A, a complicated reaction mixture was generated. We also tried 1,3,3-trisubstituted 1,2-allenylic diphenyl phosphine oxides **1n** and **1o** under Conditions A, and no expected product was formed, and 66 and 76% of the starting materials were recovered, respectively. Their low reactivities may be explained by the steric effect of the fully substituted nature of these 1,2-allenylic diphenyl phosphine oxides.

In order to study the possibility of chirality transfer and the steric chemical outcome of this reaction, we also studied the reaction of optically active 1,2-allenylic diphenyl phosphine oxides (*R*)-**1c**, (*S*)-**1c**, (*R*)-**1e**, and (*S*)-**1e**, which were easily prepared from the corresponding optically active propargylic

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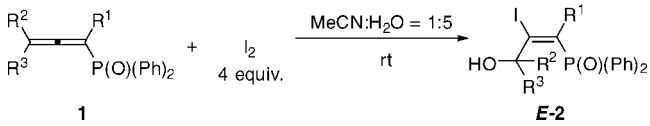
(12) For crystal data of (*E*)-**2a**, see Supporting Information.

(13) For crystal data of (*E*)-**3p**, see Supporting Information.

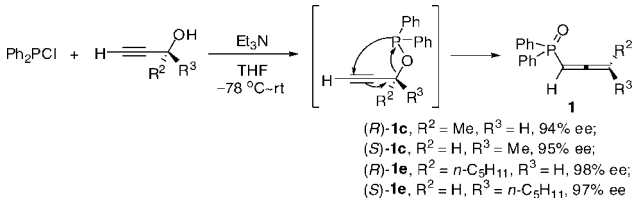
TABLE 2. Iodohydroxylation of 1a−l under Conditions A[a,b]



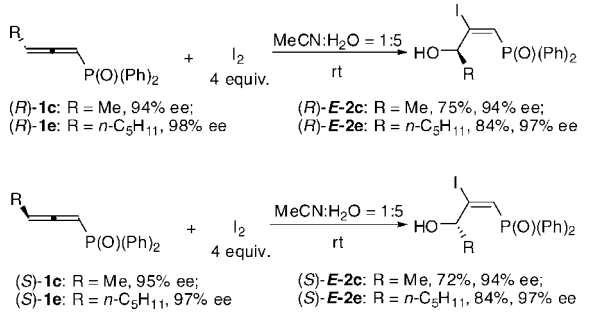
entry	**1** (R^1, R^2, R^3)	time (h)	isolated yield of (*E*)-**2** (%)
1	**1a** (*n*-Pr, H, H)	24	(*E*)-**2a** (76)
2	**1b** (Me, H, H)	21	(*E*)-**2b** (70)
3	**1c** (H, Me, H)	8	(*E*)-**2c** (67)
4	**1d** (H, *n*-Pr, H)	9	(*E*)-**2d** (82)
5	**1e** (H, *n*-C_5H_{11}, H)	9	(*E*)-**2e** (80)
6	**1f** (H, Me, Me)	5	(*E*)-**2f** (93)
7	**1g** (H, Et, Et)	8	(*E*)-**2g** (84)
8	**1h** (H, -$(CH_2)_4$-)	9	(*E*)-**2h** (56)
9	**1i** (Et, Me, H)	21	(*E*)-**2i** (80)
10	**1j** (*n*-Bu, *n*-Pr, H)	8	(*E*)-**2j** (77)
11	**1k** (Ph, Me, H)	24	(*E*)-**2k** (79)
12	**1l** (Ph, *n*-Pr, H)	23	(*E*)-**2l** (85)

[a] The reaction was carried out at rt using **1** (0.2 mmol) and I_2 (4.0 equiv) in 6 mL of solvent (CH_3CN:H_2O = 1:5). [b] The regio- and stereoselectivities were determined by 300 MHz ^{1}H NMR analysis of the crude reaction mixture.

SCHEME 2. Preparation of Optically Active 1,2-Allenylic Diphenyl Phosphine Oxides (*R*)-1c, (*S*)-1c, (*R*)-1e, and (*S*)-1e



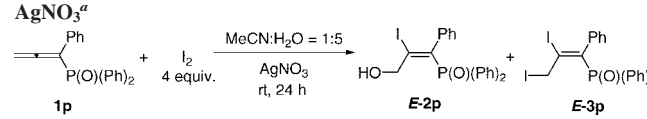
SCHEME 3. Iodohydroxylation of (*R*)-1c, (*S*)-1c, (*R*)-1e, and (*S*)-1e under Conditions A



alcohols with Ph_2PCl according to the literature procedure (Scheme 2).[11,14] When these optically active 1,2-allenylic diphenyl phosphine oxides (*R*)-**1c**, (*S*)-**1c**, (*R*)-**1e**, and (*S*)-**1e** were treated with I_2 and H_2O, the axial chirality of the allene moiety was smoothly transferred into the center chirality of the allylic alcohols (*R*)-(*E*)-**2c**, (*S*)-(*E*)-**2c**, (*R*)-(*E*)-**2e**, and (*S*)-(*E*)-**2e** efficiently (Scheme 3). The absolute configurations of the chiral center connecting the hydroxy group were determined by the X-ray diffraction study of (*R*)-(*E*)-**2c**[15] (see Figure S3 in the Supporting Information).

When we tried to extend this chemistry to 1-phenyl(propa-1,2-dienyl) diphenyl phosphine oxide **1p** (Conditions A), a mixture of iodohydroxylation product (*E*)-**2p** and diiodide (*E*)-**3p** (72:28) was formed (entry 1, Table 3). In order to optimize

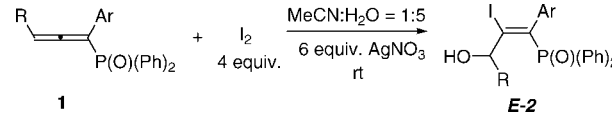
TABLE 3. Iodohydroxylation of 1p Using Different Amount of $AgNO_3$[a]



entry	$AgNO_3$ (equiv)	NMR yield (%)[b] (*E*)-**2p**	NMR yield (%)[b] (*E*)-**3p**	(*E*)-**2p**:(*E*)-**3p**[b]
1		(64)[c]	(16)[c]	72:28
2	3	71	11	87:13
3	4	82	3	96:4
4	5	97	2	98:2
5	6	>99 (87)[c]	0	>99:1
6[d]	3	complicated		

[a] The reaction was carried out at rt using **1p** (0.1 mmol) and I_2 (4.0 equiv) in 6 mL of solvent (CH_3CN:H_2O = 1:5) for 24 h. [b] Determined by 300 MHz ^{1}H NMR analysis of the crude reaction mixture using CH_2Br_2 as the internal standard. [c] Isolated yield. [d] I_2 (2.0 equiv) was applied.

TABLE 4. Iodohydroxylation of 1-Aryl-Substituted 1,2-Allenylic Diphenyl Phosphine Oxides under Conditions B[a,b]



entry	**1** (Ar, R)	time (h)	isolated yield of (*E*)-**2** (%)
1	**1p** (Ph, H)	24	(*E*)-**2p** (84)
2	**1q** (*p*-$CHOC_6H_4$, H)	48	(*E*)-**2q** (57)
3	**1r** (*p*-MeC_6H_4, H)	61	(*E*)-**2r** (77)
4	**1k** (Ph, Me)	24	complicated
5	**1l** (Ph, *n*-Pr)	22	complicated

[a] The reaction was carried out at rt using **1** (0.2 mmol), I_2 (4.0 equiv), and $AgNO_3$ (6.0 equiv) in 6 mL of solvent (CH_3CN:H_2O = 1:5). [b] The regio- and stereoselectivities were determined by 300 MHz ^{1}H NMR analysis of the crude reaction mixture.

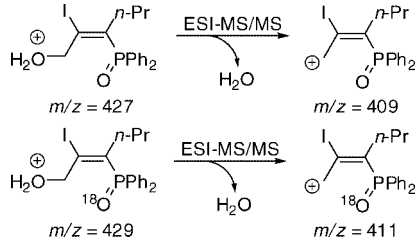
the reaction conditions for this substrate, $AgNO_3$ was applied to remove the I^- in the reaction mixture. The results indicated that the ratio of (*E*)-**2p**/(*E*)-**3p** increased when more $AgNO_3$ was used (entries 2−5, Table 3). The best result was observed when 6 equiv of $AgNO_3$ were applied, affording (*E*)-**2p** in 87% isolated yield as the only product. With fewer amounts of I_2 and $AgNO_3$, the reaction was complicated (entry 6, Table 3). Thus, we applied Conditions B (4.0 equiv of I_2, 6.0 equiv of $AgNO_3$, CH_3CN:H_2O = 1:5, and rt) for the iodohydroxylation of 3-unsubstituted 1-aryl-substituted 1,2-allenylic diphenyl phosphine oxides.

Some typical results under Conditions B are listed in Table 4. For the 1-aryl-substituted propa-1,2-dienyl phosphine oxides **1p**−**r**, the 1-aryl group may be either electron-withdrawing or -donating group substituted, affording only the *E*-products (*E*)-**2p**−**r** (entries 1−3, Table 4). The reaction of 1-phenyl-3-alkyl-1,2-allenylic diphenyl phosphine oxides **1k** and **1l** under Conditions B turned out to be complicated (compare entries 11 and 12, Table 2 with entries 4 and 5, Table 4).

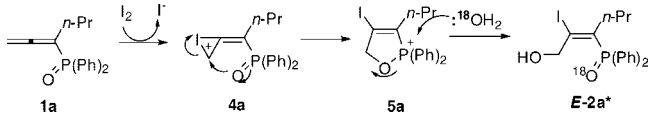
We also tried the iodohydroxylation of 1,3,3-trisubstituted 1,2-allenylic diphenyl phosphine oxides **1n** and **1o** under Conditions B. Disappointingly, the resulting reaction mixtures were both complicated. To study whether $AgNO_3$ was needed to avoid the formation of the diiodide product when an electron-donating group was introduced to the 1-phenyl group, the iodohydroxylation of **1r** under Conditions A was tried, which yielded a 66:34 mixture of iodohydroxylation

(14) Boisselle, A. P.; Meinhardt, N. A. *J. Org. Chem.* **1962**, *27*, 1828.
(15) The absolute configuration of (*R*)-(*E*)-**2c** was determined by the Flack parameter. For crystal data of (*R*)-(*E*)-**2c**, see Supporting Information.

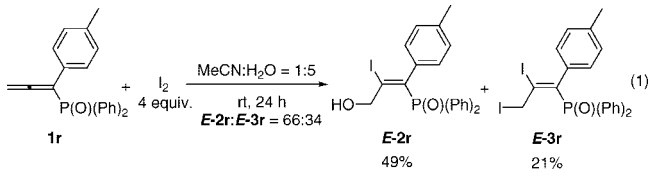
SCHEME 4. ESI-MS/MS Study for the $[M + H]^+$ Ions of (*E*)-2a at *m/z* = 427 and (*E*)-2a* at *m/z* = 429



SCHEME 5. Proposed Mechanism



product (*E*)-**2r** and diiodide (*E*)-**3r** together with an unidentified byproduct, indicating that $AgNO_3$ is still required (eq 1).



In terms of reaction mechanism, we carried out this iodohydroxylation of **1a** using water and ^{18}O-labeled water. The normal product (*E*)-**2a** and the ^{18}O-labeled product (*E*)-**2a*** were isolated and studied by ESI-MS technique (see Figures S4 and S5 in the Supporting Information). The ESI-MS/MS spectra showed that the $[M + H]^+$ ion of (*E*)-**2a** at *m/z* = 427 fragmented to yield the daughter ion at *m/z* = 409 while that of (*E*)-**2a*** at *m/z* = 429 displayed the same type of fragmentation to yield the corresponding daughter ion at *m/z* = 411 (Scheme 4). It should be noted that the treatment of (*E*)-**2a** at rt in the mixed solvent of CH_3CN:$H_2{}^{18}O$ = 1:5 for 24 h yielded (*E*)-**2a*** in only ≤1.5%. These results led to the conclusion that the ^{18}O atom was bound to phosphorus in the final products, indicating that the oxygen atom of the hydroxyl comes from the phosphinyl of the allene reactant and water attacks the phosphorus atom.

On the basis of these results, a possible mechanism was proposed (Scheme 5). In the first step, the iodonium intermediate **4a** is produced by the reaction of the relatively electron-rich carbon−carbon double bond with I^+. Subsequently, a five-membered intermediate **5a** is formed via neighboring group participation of the oxygen atom of the diphenylphosphinyl group, which is similar to what was observed in the iodohydroxylation of allenylic sulfoxides[3b] or the bromohydroxylation of allenylic sulfones.[4] Finally, the water molecule attacks at the positively charged phosphorus atom to cleave the P−O bond, which results in the formation of final product (*E*)-**2a***.

Conclusions

In conclusion, we have developed a highly regio- and stereoselective iodohydroxylation reaction of 1,2-allenylic diphenyl phosphine oxides, which yields (*E*)-2-iodo-3-hydroxy-1-alkenyl diphenyl phosphine oxides. The mechanism as well as the stereochemistry is the same as we observed in the halohydroxylation of 1,2-allenylic sulfoxides[3] and sulfones.[4] The neighboring group participation effect of the diphenylphosphinyl group was observed for the first time. Due to the importance of phosphine-containing 2-iodo-substituted 2-alkenols[1] for further coupling reaction, reduction of the phosphine oxide functionality, and transformation of the hydroxyl group, this reaction may show a broad range of utility in organic synthesis. Further studies on the scope and the synthetic applications of this reaction are being carried out in our laboratory.

Experimental Section

Typical Procedure I for the Synthesis of the Starting Materials. Synthesis of Hexa-1,2-dien-3-yl diphenyl phosphine oxide (1a):[11] To a solution of hex-2-yn-1-ol (979 mg, 10.0 mmol) and Et_3N (2.1 mL, *d* = 0.726 g/mL, 1.5 g, 15.1 mmol) in THF (30 mL) was added Ph_2PCl (2.7 mL, *d* = 1.229 g/mL, 3.3 g, 15.0 mmol) dropwise at −78 °C. After the addition, the cooling bath was removed, and the reaction mixture was allowed to warm up to room temperature naturally. After complete conversion of the corresponding propargylic alcohol as monitored by TLC (ether), the mixture was filtered off. Evaporation of the solvent and flash chromatography on silica gel (eluent: petroleum ether/ether = 1:1) afforded 1.826 g (65%) of **1a**: solid, mp 70−72 °C (ethyl acetate/petroleum ether); ^1H NMR (300 MHz, $CDCl_3$) δ 7.78−7.67 (m, 4 H), 7.58−7.40 (m, 6 H), 4.70 (dt, *J* = 17.4, 3.6 Hz, 2 H), 2.25−2.12 (m, 2 H), 1.61−1.46 (m, 2 H), 0.90 (t, *J* = 7.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 210.8 (d, J_{PC} = 6.9 Hz), 131.61 (d, J_{PC} = 2.7 Hz), 131.58 (d, J_{PC} = 104.7 Hz), 131.49 (d, J_{PC} = 10.5 Hz), 128.1 (d, J_{PC} = 11.7 Hz), 97.3 (d, J_{PC} = 100.8 Hz), 77.2 (d, J_{PC} = 13.3 Hz), 29.0 (d, J_{PC} = 5.7 Hz), 21.3 (d, J_{PC} = 6.0 Hz), 13.5 (d, J_{PC} = 2.3 Hz); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ 30.6; MS (*m/z*) 282 (M^+, 20.18), 201 (100); IR (neat) 1936, 1438, 1190, 1118 cm^{-1}. Anal. Calcd for $C_{18}H_{19}OP$: C, 76.58; H, 6.78. Found: C, 76.40; H, 6.91.

Typical Procedure II (Conditions A). Synthesis of 1-Hydroxy-2-iodohex-2(*E*)-en-3-yl diphenyl phosphine oxide ((*E*)-2a): A solution of I_2 (203 mg, 0.80 mmol) and **1a** (56 mg, 0.20 mmol) in CH_3CN (1 mL) and H_2O (5 mL) was stirred at rt, and the reaction was monitored by TLC (eluent: ether). When the reaction was complete, saturated sodium thiosulfate was added to remove the excess I_2. Then the mixture was extracted with ethyl acetate (10 mL × 3), and the organic layer was dried over $MgSO_4$. Filtration and evaporation afforded the crude reaction mixture, which was analyzed with 300 MHz ^1H NMR spectra. Flash chromatography on silica gel (eluent: ether) afforded 65 mg (76%) of (*E*)-**2a**: solid, mp 130−132 °C (ether); ^1H NMR (300 MHz, $CDCl_3$) δ 7.71−7.55 (m, 6 H), 7.53−7.43 (m, 4 H), 5.24 (t, *J* = 7.2 Hz, 1 H), 4.76 (d, *J* = 7.2 Hz, 2 H), 2.19−2.04 (m, 2 H), 1.05−0.91 (m, 2 H), 0.55 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 139.9 (d, J_{PC} = 77.1 Hz), 132.2 (d, J_{PC} = 2.9 Hz), 131.4 (d, J_{PC} = 10.3 Hz), 131.2 (d, J_{PC} = 103.6 Hz), 128.4 (d, J_{PC} = 12.1 Hz), 128.3 (d, J_{PC} = 10.9 Hz), 72.0 (d, J_{PC} = 7.5 Hz), 44.2 (d, J_{PC} = 12.1 Hz), 20.1, 13.6; ^{31}P NMR (121.5 MHz, $CDCl_3$) δ 31.0; MS (ESI) (*m/z*) 427 ($M^+ + 1$); IR (neat) 3313, 1574, 1462, 1437, 1171, 1116, 1097, 1045 cm^{-1}. Anal. Calcd for $C_{18}H_{20}O_2PI$: C, 50.72; H, 4.73. Found: C, 50.59; H, 4.70.

Typical Procedure III (Conditions B). Synthesis of 3-Hydroxy-2-iodo-1-phenylprop-1(*E*)-enyl diphenyl phosphine oxide ((*E*)-2p): A solution of $AgNO_3$ (206 mg, 1.22 mmol), **1p** (64 mg, 0.20 mmol), and I_2 (204 mg, 0.80 mmol) in CH_3CN (1 mL) and H_2O (5 mL) was stirred at rt, and the reaction was monitored by TLC (eluent: ether). When the reaction was complete, saturated sodium thiosulfate was added to remove the excess I_2. Then the mixture was extracted with ethyl acetate (10 mL × 3), and the organic layer was dried over $MgSO_4$. Filtration and evaporation afforded the crude reaction mixture, which was analyzed with 300 MHz ^1H NMR spectra. Flash chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 1:1) afforded 77 mg (84%) of (*E*)-**2p**: solid, mp

149−151 °C (ethyl acetate/petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59−7.42 (m, 6 H), 7.41−7.28 (m, 4 H), 7.16−7.01 (m, 3 H), 6.64 (d, J = 7.8 Hz, 2 H), 5.81 (t, J = 7.8 Hz, 1 H), 5.00 (dd, J = 1.8, 7.8 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 143.5 (d, J_{PC} = 9.8 Hz), 143.1 (d, J_{PC} = 78.3 Hz), 132.2 (d, J_{PC} = 2.9 Hz), 132.1 (d, J_{PC} = 10.3 Hz), 130.7 (d, J_{PC} = 106.5 Hz), 130.5 (d, J_{PC} = 10.9 Hz), 128.9 (d, J_{PC} = 3.5 Hz), 128.3 (d, J_{PC} = 12.4 Hz), 128.2 (d, J_{PC} = 1.7 Hz), 127.6 (d, J_{PC} = 2.3 Hz), 72.7 (d, J_{PC} = 6.3 Hz); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ 30.1; MS (ESI) (m/z) 499 ($M + K^+$), 483 ($M + Na^+$), 461 ($M^+ + 1$); IR (neat) 3301, 1578, 1486, 1437, 1168, 1116, 1098, 1071 cm^{-1}. Anal. Calcd for $C_{21}H_{18}O_2PI$: C, 54.80; H, 3.94. Found: C, 54.61; H, 4.05.

Synthesis of 1,2-Diiodohex-2(*E*)-en-3-yl diphenyl phosphine oxide ((*E*)-3a): A solution of I_2 (205 mg, 0.81 mmol) and **1a** (55 mg, 0.20 mmol) in CH_3CN (5 mL) and H_2O (1 mL) was stirred at rt, and the reaction was monitored by TLC (eluent: ether). When the reaction was complete, saturated sodium thiosulfate was added to remove the excess I_2. Then the mixture was extracted with ethyl acetate (10 mL × 3), and the organic layer was dried over $MgSO_4$. Filtration and evaporation afforded the crude reaction mixture, which was analyzed with 300 MHz ^{1}H NMR spectra. Flash chromatography on silica gel (eluent: petroleum ether/ether = 2:1) afforded 36 mg (42%) of (*E*)-**2a** and 40 mg (37%) of (*E*)-**3a**. (*E*)-**3a**: solid, mp 89−90 °C (ethyl acetate/petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72−7.43 (m, 10 H), 5.40 (s, 2 H), 2.14−1.98 (m, 2 H), 1.01−0.86 (m, 2 H), 0.53 (t, J = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 139.4 (d, J_{PC} = 86.0 Hz), 132.3 (d, J_{PC} = 3.0 Hz), 131.7 (d, J_{PC} = 10.2 Hz), 131.3 (d, J_{PC} = 104.0 Hz), 128.6 (d, J_{PC} = 12.3 Hz), 125.2 (d, J_{PC} = 9.3 Hz), 44.8 (d, J_{PC} = 12.6 Hz), 20.4 (d, J_{PC} = 1.1 Hz), 17.6 (d, J_{PC} = 7.2 Hz), 13.7; ^{31}P NMR (121.5 MHz, $CDCl_3$) δ 28.9; MS (ESI) (m/z) 559 ($M + Na^+$), 537 ($M^+ + 1$); IR (neat) 1567, 1461, 1436, 1193, 1156, 1116 cm^{-1}. Anal. Calcd for $C_{18}H_{19}OPI_2$: C, 40.32; H, 3.57. Found: C, 40.63; H, 3.75.

Synthesis of ^{18}O-Labeled 1-Hydroxy-2-iodohex-2(*E*)-en-3-yl diphenyl phosphine oxide ((*E*)-2a*): The starting material **1a** was dried in vacuo over P_2O_5 at rt for 3 days. MeCN was first treated with CaH_2 under reflux in an argon atmosphere for 24 h. Then the distilled MeCN was treated with P_2O_5 under reflux in an argon atmosphere for another 24 h. After distillation, the generated anhydrous MeCN was kept with molecular sieve in the glovebox under nitrogen atmosphere. $H_2{}^{18}O$ (92%) was bought from J&K Chemical Ltd. All the operation was carried out in the glovebox under nitrogen atmosphere.

A solution of I_2 (207 mg, 0.81 mmol) in CH_3CN (0.2 mL) and $H_2{}^{18}O$ (0.4 mL) was stirred at rt for 6 h. Then it was added into a solution of **1a** (57 mg, 0.20 mmol) in $H_2{}^{18}O$ (1 mL), which had also been stirred at rt for 6 h. CH_3CN (0.2 mL × 3) and $H_2{}^{18}O$ (2.6 mL) were sequentially used to wash the container for **1a**, with the resulting solution being transferred into the reaction mixture. After being stirred at rt for 24 h, the reaction mixture was directly purified with flash chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 1:1) to afford 60 mg (69%) of (*E*)-**2a*** (86% of ^{18}O incorporation): solid, mp 130−131 °C (ethyl acetate/petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71−7.54 (m, 6 H), 7.53−7.42 (m, 4 H), 5.26 (t, J = 6.9 Hz, 1 H), 4.77 (d, J = 6.9 Hz, 2 H), 2.19−2.04 (m, 2 H), 1.07−0.90 (m, 2 H), 0.55 (t, J = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 140.5 (d, J_{PC} = 77.2 Hz), 132.5 (d, J_{PC} = 2.1 Hz), 131.7 (d, J_{PC} = 10.6 Hz), 131.4 (d, J_{PC} = 103.9 Hz), 128.6 (d, J_{PC} = 11.7 Hz), 127.8 (d, J_{PC} = 10.3 Hz), 73.0 (d, J_{PC} = 7.3 Hz), 44.6 (d, J_{PC} = 12.3 Hz), 20.3, 13.8; ^{31}P NMR (121.5 MHz, $CDCl_3$) δ 30.9; MS (ESI) (m/z) 451 ($M + Na^+$), 429 ($M^+ + 1$); IR (neat) 3319, 1581, 1461, 1438 cm^{-1}; HRMS (ESI) (m/z) calcd for $C_{18}H_{21}IO^{18}OP^+$ [$M^+ + 1$] 429.0366, found 429.0351. The incorporation of ^{18}O was obtained by calculating the ratio of the intensities of the $[M + H]^+$ ion peak of $C_{18}H_{21}IO_2P^+$ and $C_{18}H_{21}IO^{18}OP^+$ in the same ESI-MS spectra of the (*E*)-**2a*** sample prepared in this reaction:[16]

$$\frac{I'}{I+I'}\times 100\% = \frac{10635477.4}{1752612.2 + 10635477.4}\times 100\% = 86\%$$

I = the intensity of the $[M + H]^+$ ion peak of 426.96 (referred to $C_{18}H_{21}IO_2P^+$)

I' = the intensity of the $[M + H]^+$ ion peak of 428.94 (referred to $C_{18}H_{21}IO_{18}OP^+$)

Treatment of (*E*)-2a at Room Temperature in the Mixed Solvent of CH_3CN:$H_2{}^{18}O$ = 1:5. A solution of (*E*)-**2a** (86 mg, 0.20 mmol) in CH_3CN (0.2 mL) and $H_2{}^{18}O$ (1.0 mL) was stirred at rt for 24 h in a glovebox under a nitrogen atmosphere. Then the mixture was extracted with ethyl acetate (5 mL × 3), and the organic layer was dried over $MgSO_4$. Filtration and evaporation afforded 80 mg (93%) of (*E*)-**2a**. The incorporation of ^{18}O should be ≤1.5% as analyzed by ESI-MS study.

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Supporting Information Available: Detailed experimental procedure, the spectroscopic data not listed in the main text, ^{1}H/^{13}C/^{31}P NMR spectra for all compounds, and the.CIF files of (*E*)-**2a**, (*E*)-**3p**, and (*R*)-(*E*)-**2c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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