The reaction mixture was further stirred overnight. Then the mixture was centrifuged, and the supernatant was diluted to 100 mL and applied to a column of Dowex 1-X8 (20–50 mesh, bicarbonate form, bed volume of 100 mL). The pH of the eluent and washings was readjusted to 5.5, and the resulting solution was again applied to the same column to ensure the adsorption of the desired product. After the column was washed with water, the desired product was eluted with a linear gradient of from 0 to 0.3 M ammonium bicarbonate. The product was further purified on a BioGel P-2 column (bed volume of 20 mL) to give 192 mg (33%) of **18**. The ^{1}H NMR spectrum was identical with that of the sample mentioned above.

Benzyl 2,4,5,7,8-Penta-*O*-acetyl-3-deoxy-α-D-*manno*-2-octulosonate (20b). A suspension of KDO ammonium salt monohydrate (160 mg, 0.59 mmol), acetic anhydride (3 mL), pyridine (3 mL), and 4-(*N*,*N*-dimethylamino)pyridine (DMAP, 2 mg) was stirred overnight at room temperature. Ice-cooled water was added, and the mixture was stirred for 30 min. After dilution with water, the pH of the mixture was adjusted to 3.5 by addition of Dowex 50W-X8 (H^+ form). The resin was filtered off, and the filtrate was concentrated in vacuo. The residue was diluted with a mixture of chloroform and toluene, and the solvent was evaporated. This procedure was repeated three times to remove traces of water. The residue was dissolved in anhydrous DMF. Benzyl bromide (161 mg, 0.94 mmol), Cs_2CO_3 (390 mg, 1.20 mmol), and tetrabutylammonium iodide (33 mg) were added, and the mixture was stirred for 4 h at room temperature under N_2. The mixture was diluted with 0.5 N ice-cooled hydrochloric acid and extracted twice with a mixture of diethyl ether and toluene (1:1). The organic layer was successively washed with water, saturated aqueous $NaHCO_3$, and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was chromatographed over silica gel (20 g). Elution with hexane/diethyl ether (2:1–1:1) afforded **15b**, which was recrystallized from diethyl ether to give 220 mg (70%) as colorless plates: mp 102–103 °C (lit.[26b] mp 98–99 °C); $[\alpha]^{26}_D$ +293° (*c* 1.0, $CHCl_3$) [lit.[26b] $[\alpha]^{25}_D$ +91.9° (*c* 0.9, $CHCl_3$)]. Its ^{1}H NMR spectrum ($CDCl_3$) was in good accordance with that reported previously. HRMS (M + Na^+) calcd 561.1584, found 561.1602.

2,4,5,7,8-Penta-*O*-acetyl-3-deoxy-α-D-*manno*-2-octulosonic Acid (20a). A mixture of **20b** (220 mg, 0.41 mmol) and Pd-C (10%, 55 mg) in ethanol (3 mL) was vigorously stirred under H_2 at room temperature for 1 h. After the catalyst was filtered off, the filtrate was concentrated in vacuo. The residue was recrystallized from diethyl ether to give **20a** (177 mg, 97%) as fine needles: mp 132–133 °C; $[\alpha]^{25}_D$ +374° (*c* 0.88, $CHCl_3$). Its ^{1}H NMR spectrum (C_6D_6) was identical with that reported previously.[26a]

1,3,4,6,7-Penta-*O*-acetyl-2-deoxy-β-D-*manno*-heptose (21). To a solution of acid chloride prepared from **20a** (30 mg, 0.067 mmol) in toluene was added dropwise a solution of *N*-hydroxythiopyridone (**22**) (11 mg, 0.09 mmol) and DMAP (2 mg) in toluene (0.5 mL) and pyridine (0.3 mL) at room temperature under N_2 in the dark. After the reaction mixture was stirred for 10 min, *tert*-butyl mercaptan (0.5 mL) was added and the mixture was irradiated with white light (tungsten lamp, 100 W) at room temperature. After the reaction mixture was stirred for 10 min, N_2 was introduced to the mixture under a slightly reduced pressure to remove residual *tert*-butyl mercaptan for 30 min. Usual workup and purification by silica gel preparative TLC [developed with hexane/Et_2O (1:1)] afforded **21** (18.5 mg, 68%) as an oil: $[\alpha]^{22}_D$ +36.8° (*c* 1.85, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.000–2.150 (2 H, m, H-2ax, H-2eq), 2.010 (6 H, s, acetyl), 2.082 (3 H, s, acetyl), 2.119 (3 H, s, acetyl), 2.137 (3 H, s, acetyl), 3.882 (1 H, dd, $J_{5,4}$ = 1.5 Hz, $J_{5,6}$ = 10.0 Hz, H-5), 4.115 (1 H, dd, $J_{7',6}$ = 4.5 Hz, $J_{7',7}$ = 12.5 Hz, H-7'), 4.437 (1 H, dd, $J_{7,6}$ = 2.5 Hz, $J_{7,7'}$ = 12.5 Hz, H-7), 5.073 (1 H, ddd, $J_{3,4}$ = 3.0 Hz, $J_{3,2eq}$ = 5.0 Hz, $J_{3,2ax}$ = 12.5 Hz, H-3), 5.165 (1 H, ddd, $J_{6,7}$ = 2.5 Hz, $J_{6,7'}$ = 4.5 Hz, $J_{6,5}$ = 10.0 Hz, H-6), 5.303 (1 H, dd, $J_{4,5}$ = 1.5 Hz, $J_{4,3}$ = 3.0 Hz, H-4), 5.748 (1 H, dd, $J_{1,2eq}$ = 3.0 Hz, $J_{1,2ax}$ = 10.0 Hz, H-1); ^{13}C NMR ($CDCl_3$) δ 20.59, 20.59, 20.65, 20.65, 20.84, 30.35, 62.26, 63.84, 67.32, 67.90, 71.62, 91.67, 168.60, 169.60, 169.83, 170.30, 170.54. HRMS (M + Cs^+) calcd $C_{17}H_{24}O_{11}Cs$ 537.0373, found 537.0359.

4-Acetamido-1,3,6,7,8-penta-*O*-acetyl-2,4-dideoxy-α-D-*glycero*-D-*galacto*-octose (24). A 25-mL two-necked flask equipped with a septum, a micro-scale Dean–Stark trap which was filled with 4-Å molecular sieves, and a reflux condenser was used as the reaction vessel. A mixture of **23a** (35.0 mg, 0.07 mmol), DMAP (12.3 mg, 1.5 equiv), **22** (41.0 mg, 5.0 equiv), and triethylamine (19 μL) in CH_2Cl_2 (1 mL) was placed in the flask described above. To this was successively added a solution of WSCI-Cl (20 mg) in CH_2Cl_2 (1 mL) and *tert*-butyl mercaptan (0.5 mL). The mixture was stirred and irradiated with white light (tungsten lamp, 100 W) at room temperature for 5 h. The reaction was worked up in a similar manner as described above. The crude product was purified by silica gel preparative TLC [developed with ethyl acetate/tetrahydrofuran (1:1)] to give **24** (8.7 mg, 27% from **23a**) as an oil: $[\alpha]^{22}_D$ +21.3° (*c* 2.87, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.908 (3 H, s, *N*-acetyl), 1.915 (1 H, ddd, $J_{2ax,1}$ = 10.3 Hz, $J_{2ax,3}$ = 11.5 Hz, $J_{2ax,2eq}$ = 12.4 Hz, H-2ax), 2.043 (3 H, s, *O*-acetyl), 2.051 (3 H, s, *O*-acetyl), 2.102 (3 H, s, *O*-acetyl), 2.107 (3 H, s, *O*-acetyl), 2.134 (3 H, s, *O*-acetyl), 2.219 (1 H, ddd, $J_{2eq,1}$ = 2.1 Hz, $J_{2eq,3}$ = 4.9 Hz, $J_{2eq,2ax}$ = 12.4 Hz, H-2eq), 3.764 (1 H, dd, $J_{5,6}$ = 2.4 Hz, $J_{5,4}$ = 10.4 Hz, H-5), 4.023 (1 H, dd, $J_{8,7}$ = 5.5 Hz, $J_{8,8'}$ = 12.6 Hz, H-8), 4.062 (1 H, ddd, $J_{4,NH}$ = 10.0 Hz, $J_{4,3}$ = 10.3 Hz, $J_{4,5}$ = 10.4 Hz, H-4), 4.389 (1 H, dd, $J_{8',7}$ = 2.6 Hz, $J_{8',8}$ = 12.6 Hz, H-8'), 5.127 (1 H, ddd, $J_{7,8'}$ = 2.6 Hz, $J_{7,8}$ = 5.5 Hz, $J_{7,6}$ = 7.3 Hz, H-7), 5.058 (1 H, ddd, $J_{3,2eq}$ = 4.9 Hz, $J_{3,4}$ = 10.3 Hz, $J_{3,2ax}$ = 11.5 Hz, H-3), 5.190 (1 H, d, $J_{NH,4}$ = 10.0 Hz, NH), 5.391 (1 H, dd, $J_{6,7}$ = 7.3 Hz, $J_{6,5}$ = 2.4 Hz, H-6), 5.646 (1 H, dd, $J_{1,2eq}$ = 2.1 Hz, $J_{1,2ax}$ = 10.3 Hz, H-1); ^{13}C NMR ($CDCl_3$) δ 20.70, 20.70, 20.75, 20.83, 20.83, 23.15, 35.09, 49.22, 61.98, 67.11, 70.23, 70.23, 73.67, 91.19, 168.75, 169.90, 170.12, 170.36, 170.59, 170.88. HRMS (M + Cs^+) calcd $C_{20}H_{29}O_{12}NCs$ 608.0744, found 608.0750.

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The Endocyclic Restriction Test: Determination of the Transition-Structure Geometry for the Transfer of Oxygen from *N*,*N*-Dialkylhydroxylamines to Triarylphosphines

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Abstract: The transfers of oxygen from nitrogen to phosphorus in the conversions of **1** to **2** and **3** to **4** are shown by kinetic, solvent-labeling, and double-labeling criteria to be intramolecular reactions. This information in conjunction with the stabilities of **13** and **14** is taken to rule out the mechanisms of classic linear S_N2 substitutions at oxygen or nitrogen, biphilic insertion, or a radical chain reaction and to favor reactions via a 10-P-5 species (**18**). These results appear to provide the first experimental demonstration that oxygen can be transferred at an oblique angle.

Steps in which an oxygen atom is transferred to phosphorus are involved in a number of reactions, including deoxygenations of a variety of substrates.[1] Our interest in evaluating the geometries of substitutions at heteroatoms by use of the endocyclic

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restriction test and in using that information to provide an understanding of the mechanisms of heteroatom transfer prompted us to investigate the reaction of *N,N*-dialkylhydroxylamines with triarylphosphines.[2-4]

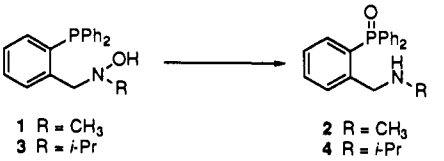
Deoxygenations of hydroxylamines by phosphorus reagents to give an amine and the corresponding oxidized phosphorus product have been reported by Horner and by Quin.[5,6] Initial mechanistic studies carried out by Luckenbach showed that the reaction proceeded with an overall 73% retention of configuration at phosphorus.[7] Stec and Okruszek studied the reactions between hydroxylamines and hydroxylamine hydrochlorides and dialkylarylphosphines in detail.[8] They found the reactions to be first order in each reactant and to proceed with predominant retention of configuration at phosphorus when optically active methylphenyl-*n*-propylphosphine was treated with hydroxylamine hydrochloride. On the other hand, when the phosphine was allowed to react with hydroxylamine in various polar solvents, the phosphine oxide was formed with moderate degrees of overall inversion of configuration at phosphorus. They also found that when the reaction with hydroxylamine was carried out in 20:1 EtOH–H_2O with water which contained 43.6% ^{18}O, the phosphine oxide which was formed contained 14.5% ^{18}O. However, a similar reaction with hydroxylamine hydrochloride gave no ^{18}O-enrichment in the phosphine oxide. Two different mechanisms for the transfer of oxygen from hydroxylamines to phosphines, shown as pathways 1 and 2, were proposed to explain these results.

$$R_3P + \overset{+}{N}HR_2OH\ Cl^- \longrightarrow R_3\overset{+}{P}{-}OH\ Cl^- + NR_2H \longrightarrow R_3P{=}O + \overset{+}{N}R_2H_2\ Cl^- \quad (1)$$

$$R_3P + NR_2OH \longrightarrow R_3\overset{+}{P}{-}NR_2\ OH^- \longrightarrow R{-}P(R)(R)(OH) \longrightarrow R_3P{=}O + NR_2H \quad (2)$$

In pathway 1, phosphorus acts as a nucleophile and is considered to attack oxygen in a classic S_N2 manner. This accounts for the lack of ^{18}O-incorporation and leads to high degrees of retention of configuration at phosphorus in the product. In pathway 2, phosphorus again acts as a nucleophile but attacks nitrogen in an S_N2 manner. This leads to the generation of hydroxide, which can exchange with ^{18}O-labeled water and add to phosphorus of the aminophosphonium salt. Decomposition of the pentacovalent intermediate then gives the corresponding phosphine oxide with ^{18}O-enrichment and overall inversion of configuration at phosphorus.

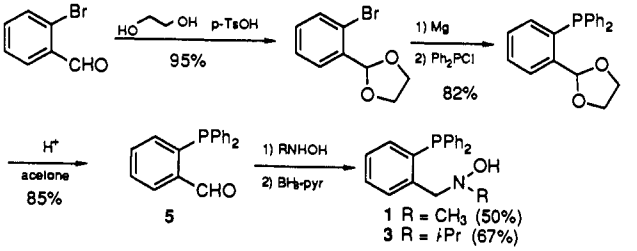
Application of the endocyclic restriction test to evaluate the geometry at oxygen for oxygen transfer from a *N,N*-dialkylhydroxylamine to a triarylphosphine is shown for the conversions of **1** to **2** and **3** to **4**.[4] In effect, if these conversions proceed in an intramolecular mode and the mechanism is a concerted or associative process, then the bond angles allowed for oxygen transfer can be accommodated within a six-membered ring. On the other hand, if the confines of the endocyclic ring do not allow intramolecular oxygen transfer, then the conversions will be intermolecular. Direct insertion and dissociative mechanisms with internal or external return must be ruled out in order for the results with **1** and **3** to be used to evaluate the geometry of the reaction. In this report, we establish that the transfer of oxygen from nitrogen to phosphorus can occur at an oblique angle. We provide data and discussion which rule out alternatives and favor an associative mechanism for the conversions of **1** to **2** and **3** to **4**.



1 R = CH_3 **2** R = CH_3
3 R = *i*-Pr **4** R = *i*-Pr

Results and Discussion

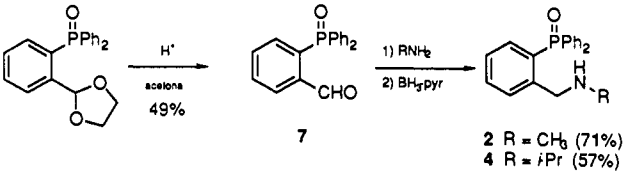
Synthesis. The syntheses of **1** and **3** from **5** were accomplished as shown, according to the procedures of Rauchfuss et al.[9] Protection of 2-bromobenzaldehyde with ethylene glycol gave the acetal, which when converted to the Grignard and treated with



1 R = CH_3 (50%)
3 R = *i*-Pr (67%)

Ph_2PCl gave the protected phosphine acetal. Deprotection with 6 N H_2SO_4 and treatment of the resulting aldehyde **5** with methylhydroxylamine in ethanol followed by borane–pyridine reduction gave **1**. Treatment of **5** with isopropylhydroxylamine, which had been synthesized by the $NaBH_3CN$ reduction of acetoxime, followed by in situ reduction with borane–pyridine gave **3**. Similar approaches were used with ^{13}C- and ^{18}O-labeled reactants to provide isotopically labeled **1**-^{13}C-^{18}O and **3**-^{13}C-^{18}O (vide infra). The ^{18}O-labeled isopropylhydroxylamine was synthesized from acetoxime-^{18}O by reduction with $NaBH_3CN$, while 5-*formyl*-^{15}C was prepared by treatment of (2-bromophenyl)diphenylphosphine with *n*-BuLi followed by addition of methyl formate-^{13}C.

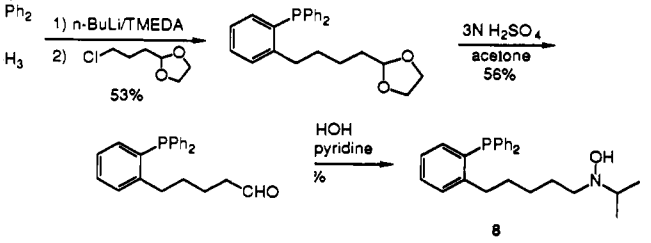
The syntheses of phosphine oxides **2** and **4**, the products of reaction of **1** and **3**, respectively, were carried out to provide authentic samples for comparison. The dioxolane was deprotected



2 R = CH_3 (71%)
4 R = *i*-Pr (57%)

with 6 N H_2SO_4 in acetone to give the benzaldehyde **7**. Treatment of **7** with aqueous methylamine in ethanol followed by in situ reduction with borane–pyridine gave **2**. Treatment of **7** with isopropylamine followed by borane–pyridine reduction gave **4**.

A chain-extended system (**8**) was prepared from *o*-tolyldiphenylphosphine by a sequence of lithiation and substitution,



8

(1) (a) Emsley, J.; Hall, D. *The Chemistry of Phosphorus*; John Wiley and Sons: New York, 1976. (b) Smith, D. J. H. *Compr. Org. Chem.* 1979, 2. In the present context, a classic linear S_N2 substitution refers to a substitution reaction which proceeds with a transition state which has a bond angle of ca. 180° between the entering and leaving groups and involves a formal inversion of configuration at the atom undergoing substitution.

(2) Beak, P. *Acc. Chem. Res.* **1992**, *25*, 215.

(3) For seminal cases using the endocyclic restriction test to evaluate transition-structure geometries, see: Tenud, L.; Farooq, S.; Seible, J.; Eschenmoser, A. *Helv. Chim. Acta* **1970**, *53*, 2059. Hogg, D. R.; Vipond, P. W. *J. Chem. Soc. C* **1970**, 2142.

(4) For an initial report of the reaction of **1**, see: Beak, P.; Loo, D. *J. Am. Chem. Soc.* **1986**, *108*, 3834.

(5) Horner, L.; Steppan, H. *Liebigs Ann. Chem.* **1957**, *606*, 33.

(6) Martz, M. D.; Quin, L. D. *J. Org. Chem.* **1969**, *34*, 3195.

(7) Luckenbach, R. *Tetrahedron Lett.* **1976**, *24*, 2017.

(8) Stec, W. J.; Okruszek, A. *J. Chem. Res., Synop.* **1977**, 142.

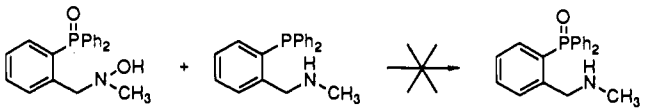
(9) The route used for synthesis of **6** is based on that developed by Hoots, J. E.; Rauchfuss, T. B.; Wrobleski, D. A. *Inorg. Synth.* **1982**, *21*, 175.

followed by hydrolysis to the aldehyde, subsequent formation of the nitrone, and finally in situ reduction.

Oxygen Transfers for 1 and 2. The oxygen transfers of **1** to give **2** and of **3** to give **4**, respectively, were accomplished by heating the reactants in toluene at 100 °C. The phosphine oxides were obtained in ≥95% yield as determined by ^{1}H NMR or in 90% yield by isolation. No other products or intermediates were observed. Five reasonable mechanisms can be considered for these conversions.

Classic Linear S_N2-like Substitution at Oxygen. Reactions in which trivalent phosphorus compounds act as nucleophiles are well-known, and the transfer of oxygen from nitrogen to phosphorus could occur by a classic S_N2 linear attack by phosphorus at oxygen.[1,8] This S_2N2 mechanism would require an approximately 180° bond angle between the entering and leaving groups. This could be achieved in the conversions of **1** to **2** and **3** to **4** only by an intermolecular and, therefore, bimolecular reaction.[3] In effect, a linear P–O–N bond angle cannot be achieved endocyclically and intramolecularly for these conversions. Kinetic analysis of the reaction of **1** at 100 °C showed it to be first order in **1** with a rate constant of $(5.0 \pm 1.0) \times 10^{-2}$ min^{-1} over a 5-fold concentration range between 0.02 and 0.10 M. Kinetic analysis of the rate of reaction of **3** gave a first-order rate constant of $(18.0 \pm 3.6) \times 10^{-2}$ min^{-1} at 100 °C.

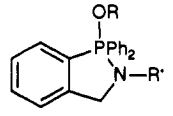
If the conversion of **1** to **2** were intermolecular, then the reaction would involve intermediates **9** and **10**. These compounds were



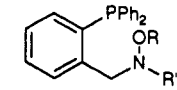
9 **10**

synthesized and heated together in toluene at the same concentration in each as for the reaction of **1**. After 3 h at 100 °C, no observable conversion to **2** was observed. These results rule out a linear classic S_N2 transition structure for these oxygen transfers.[10]

Biphilic Insertion. Reactions between trivalent phosphorus compounds and dialkyl peroxides or alkyl benzenesulfenates are considered to lead to pentacoordinate phosphoranes by mechanisms in which phosphorus inserts directly into the heteroatom–heteroatom bond.[11] Such a biphilic mechanism, as applied to the reactions of **1** or **3**, would proceed via the intermediates **11a** or **11b**. Ring opening of **11** with P–N bond cleavage and subsequent hydrogen transfer to nitrogen would give the phosphine oxides **2** and **4**. Since the initial biphilic insertion would involve only the N–O bond, replacement of the protons in **1** and **3** with a methyl group should give **12a** or **12b** if this reaction pathway is operative. The species **12** should either be stable or proceed to other products under the reaction conditions, but it is considered unlikely that it would return to reactant.



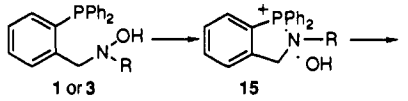
11a R = H, R' = CH_3
b R = H, R' = $CH(CH_3)_2$
12a R = CH_3, R' = CH_3
b R = CH_3, R' = $CH(CH_3)_2$



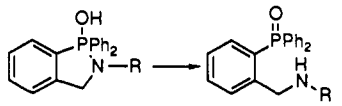
13 R = CH_3, R' = CH_3
14 R = CH_3, R' = $CH(CH_3)_2$

The methoxylamine **13** was prepared by reaction of **6** with *N,O*-dimethylhydroxylamine hydrochloride followed by in situ reduction with borane–pyridine, and **14** was prepared by alkylation of **3** with methyl iodide. The compounds **13** and **14** were heated in toluene at 100 °C in separate experiments. After 8 h, no change was observed in the ^{1}H NMR for either compound. A phosphorane related to **12** has a ^{31}P NMR signal at −49.3 ppm; however, we did not observe any ^{31}P NMR signals in the region of −30 to −70 ppm in our efforts to follow the reaction of **14**.[12] Based on the failure of **13** or **14** to provide **12** or products therefrom under these conditions, we rule out biphilic insertion as a mechanism for the conversion of **1** and **3** to **2** and **4**, respectively.[13]

Classic Linear S_N2 Substitution at Nitrogen. A mechanism in which there is an initial back-side nucleophilic displacement at nitrogen to produce the ion pair **15** (which could, by internal or external return of hydroxide ion, give **11** as the precursor to **2** or **4**) is precedented. Such a mechanism has been suggested by Stec and is supported by ^{18}O-incorporation from $H_2{}^{18}O$ into the phosphine oxide product.[8] In order to test this possibility, we carried out ^{18}O-labeling studies for three reactions.

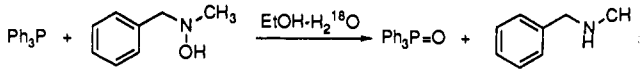


1 or 3 **15**



11 **2 or 4**

The conversion of **1** to **2** was carried out in 20:1 EtOH–$H_2{}^{18}O$, in which the water contained 50% ^{18}O-enrichment. Mass spectral analysis of **2** obtained after heating the solution at reflux for 48 h showed no ^{18}O-incorporation. We also carried out an ^{18}O-labeling experiment in which **3** contained ^{18}O-enrichment to be certain there was not an unexpected loss of label in the course of the reaction. Treatment of **3**-^{18}O containing 74% enrichment under conditions similar to those of the reaction of **1** gave **4**, which was found to contain 72% ^{18}O. Finally, we also carried out a bimolecular reaction in which triphenylphosphine was treated with hydroxylamine **16** at reflux for 40 h in 20:1 EtOH–$H_2{}^{18}O$, in which the water contained 50% ^{18}O-enrichment. The triphenylphosphine oxide produced contained no ^{18}O-enrichment.



16

The lack of ^{18}O-incorporation in the above reactions and the failures of **13** and **14** to undergo reaction can be taken as evidence against mechanisms of oxygen transfer for the reactions of **1** and of **3**, which involves displacements on nitrogen to give ion pairs which undergo either in-cage or external return at phosphorus. It also appears that the mechanism of oxygen transfer between these triarylphosphines and dialkylhydroxylamines and the dialkylphosphines and hydroxylamines studied by Stec and Okruszek are different since the observed ^{18}O-incorporations are different.[8]

Radical Chain Mechanism. Reactions between trivalent phosphorus compounds and radicals are well-known, and a radical chain mechanism can be proposed for the conversions of **1** to **2** and **3** to **4**.[14] The initiation step would be the formation of **17**, initiated by attack of an adventitious radical on **1** or **3**, and the

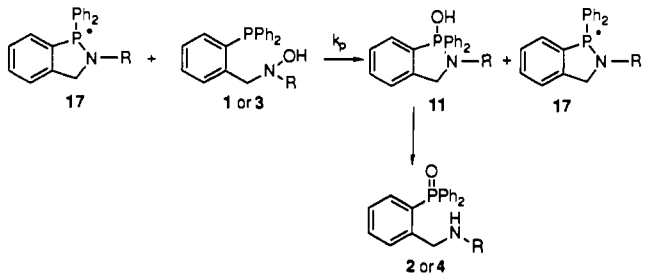
(10) First-order rate constants were measured for the conversion of **1** to **3** at 60, 80, and 100 °C and found to be $(2.0 \pm 0.4) \times 10^{-3}$, $(1.6 \pm 0.4) \times 10^{-2}$, and $(5.0 \pm 1.0) \times 10^{-2}$ min^{-1}, respectively. A plot of log k vs $1000/T$ and the Arrhenius equation of $k = Ae^{-E_a/RT}$ gives A and E_a values of 5.0×10^6 s^{-1} and 20.1 ± 1.5 kcal/mol, respectively. From these the values, $\Delta H^{\ddagger}$, $\Delta S^{\ddagger}$, and $\Delta G^{\ddagger}$ can be calculated to be 19.5 ± 1.5 kcal/mol, −20.8 ± 2.9 cal/mol·K, and 25.7 ± 1.5 kcal/mol at 298 K, respectively.

(11) For reactions with peroxides, see: Chang, L. L.; Denney, D. B.; Denney, D. Z.; Kazior, R. J. *J. Am. Chem. Soc.* **1977**, *99*, 2293 and references cited therein. Baumstark, A. L.; McCloskey, C. J.; Williams, T. E.; Chrisope, D. R. *J. Org. Chem.* **1980**, *45*, 3593. Clennan, E. J.; Heah, P. C. *J. Org. Chem.* **1981**, *46*, 4105. For reaction with sulfenates, see: Denney, D. B.; Denney, D. Z.; Gavrilovic, D. M. *Phosphorus Sulfur Relat. Elem.* **1981**, *11*, 1 and references cited therein.

(12) Ross, M. R.; Martin, J. C. *J. Am. Chem. Soc.* **1981**, *103*, 1234.

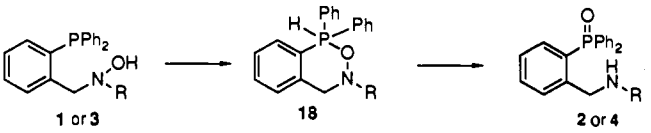
(13) The possibility that **12** is at low concentration in equilibrium with **14** would not be expected, considering that the P–O bond (ca. 90 kcal/mol) is strong relative to the much weaker N–O bond (ca. 60 kcal/mol): Goldwhite, H. *Introduction to Phosphorus Chemistry*, Cambridge University Press: New York 1981; p 30. Our efforts to prepare **12** by many different routes were not successful.

(14) For a review, see: Ingold, K. U.; Roberts, B. P. *Free Radical Substitution Reactions*; Wiley-Interscience: New York, 1971. For a case of reaction between trialkyl phosphorus and alkoxy radicals, see: Bentrude, W. G.; Moriyama, M.; Mueller, H. D.; Sopchik, A. E. *J. Am. Chem. Soc.* **1983**, *105*, 6053.



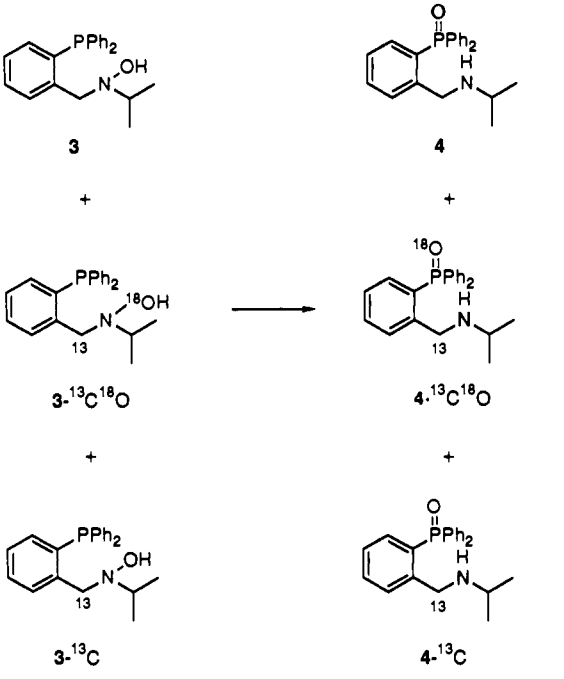
propagation step would be the formation of **11**.[15] Under this mechanism, the kinetics could be first order but the transfer of oxygen would be intermolecular. Experimental evidence on this point will be provided (vide infra).

Addition–Elimination. Addition–elimination mechanisms involving intermediate pentavalent species are generally invoked for substitutions at phosphorus.[1] For the intramolecular conversion of **1** to **2** and of **3** to **4**, an addition–elimination sequence would involve endocyclic oxygen transfer within a six-membered ring transition structure, as shown for reaction via intermediate **18**.



Analogies for the formation of **18** can be found both in the suggestion that the transesterification reactions between alcohols and phosphites involve the transfer of a proton from the alcohol to phosphorus followed by attack of the alkoxide at phosphorus to give a pentavalent intermediate and also in mechanisms proposed for the reaction between trivalent phosphorous compounds and *N*-oxides in which oxygen is suggested to add nucleophilically to phosphorus.[16,17] In addition, Martin has reported a stable 5-membered ring phosphorane analogous to **18**, in which a hydrogen resides on phosphorus.[12]

In order to distinguish between an addition–elimination mechanism involving **18**, which would be intramolecular, and a radical chain mechanism involving **15** (vide supra), which would involve intermolecular oxygen transfer, a double-labeling experiment was carried out. In this experiment, a mixture containing 56% unlabeled **3**, 33% **3**-^{13}O-^{18}O, and 10% **3**-^{13}C was subjected to the conditions for oxygen transfer. Formation of a product containing **4** that has the same isotopic distribution as the starting mixture would show oxygen transfer to be intramolecular. Formation of a product containing **4**,**4**-^{13}C, **4**-^{18}O, and **4**-^{13}C-^{18}O with a statistical distribution of the isotope would show oxygen transfer to be intermolecular. The experiment was carried out at 77 °C in toluene for 30 min to allow for the recovery of unreacted starting material along with product. The results are shown in Table I along with the values expected for intramolecular and intermolecular oxygen transfer. The isotopic distribution in the product, **4**,**4**-^{13}C, **4**-^{13}C-^{18}O, is within experimental error of that for the reactant, **3**,**3**-^{13}C, **3**-^{13}C-^{18}O, and shows that oxygen transfer is intramolecular. A similar result has been reported for



the reaction of a mixture of **1** and **3**-^{18}O.[4] On the basis of these findings, the intermolecular radical chain mechanism involving an adventitious radical can be ruled out. These labeling results also further rule out displacement by a classic S_N2 mechanism at oxygen or at nitrogen with external return. If the stabilities of **13** and **14** to the reaction conditions are taken to rule out the biphilic mechanism and substitution at nitrogen with internal return, then, of the mechanisms considered, only the addition–elimination mechanism involving **18** is consistent with all of the experimental results.[18]

Comparison of our results with those of Stec and Okruszek suggests that the mechanism of oxygen transfer from a hydroxylamine to phosphorus is substrate and condition dependent. With hydroxylamine itself and a dialkylarylphosphine, Stec reports that the reaction proceeds with predominant inversion at phosphorus and in ethanol–water with some incorporation of oxygen from the water.[8] The mechanism of nucleophilic displacement at nitrogen with external return by hydroxide suggested by Stec and Okruszek nicely accommodates their results. In the reactions of **1** and **3**, there is no incorporation of ^{18}O from water. That this difference is not due to the constraints of **1** and **3** is shown by the fact that there is no incorporation of ^{18}O for the reaction of triphenylphosphine and benzylisopropylhydroxylamine. The associative mechanism we propose is consistent with this result. It is reasonable that alkyl substitution at nitrogen could lead to different mechanisms for the oxygen transfers from hydroxylamine and *N*,*N*-dialkylhydroxylamines.

Inhibition of the Intramolecular Transfer. In order to investigate the course of oxygen transfer when the intramolecular reaction is hindered, we studied the conversion of **8** to **19**.[19] When a solution of **8**, at the same concentration as that used for the conversion of **2** to **4**, was heated in toluene-d_8 at 100 °C for 2 h, no reaction was observed by ^1H NMR. Only when the reaction was carried out for extended periods of time in toluene or in DMF at elevated temperatures was the expected product obtained. These results show that by extending the chain length in a system such as that of **1** or **3**, an intermolecular pathway for oxygen transfer

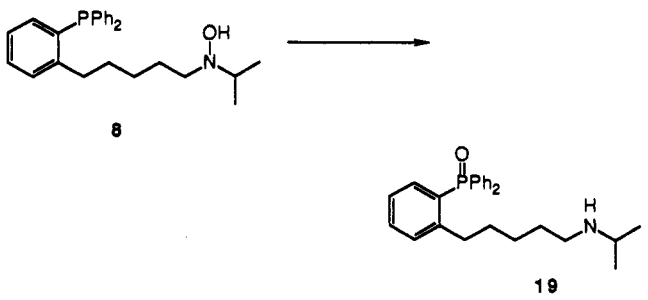
(15) Initiation by an unspecified adventitious radical could give a first-order reaction in reactant **1** or **3**. If homolytic dissociation of **1** or **3** is the initiating step, then the reaction would be expected to be second order in the reactants.

(16) Brazier, J. F.; Houalla, D.; Loenig, M.; Wolf, R. *Top. Phosphorus Chem.* **1976**, *8*, 99.

(17) For a summary of reactions of phosphites and alcohols, see: Ivanov, B. E.; Zheltukhin, V. F. *Russ. Chem. Rev.* **1970**, *39*, 358. For reactions between N-oxides and trivalent phosphorus compounds, see: Stec, W. J.; Okruszek, A.; Michalski, J. *Bull. Acad. Polon. Sci., Ser. Sci. Chim.* **1973**, *21*, 445. Ramirez, F.; Aguair, A. M. *Abstracts of Papers*, 134th National Meeting of the American Chemical Society, Chicago, IL, Sept. 7–12, 1958; American Chemical Society: Washington, DC, 1958; 42N. Emerson, T. R.; Rees, C. W. *J. Chem. Soc.* **1964**, 2319.

(18) We did not observe a significant kinetic H/D isotope effect for the reaction of **1**-OD nor catalysis of the reaction of **1** by acetic acid or pyridine. Apparently, the role of hydrogen in the formation or decomposition of **18** must not be rate determining.

(19) The formation of a ten-membered ring intermediate from **19**, required for an associative intramolecular reaction, should be substantially slower than the formation of **18** from **3**. Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95. Sicher, J. *Progr. Stereochem.* **1962**, *3*, 202.



becomes available, but the findings do not provide information on whether this pathway is dominant or incidental to an intramolecular reaction.[20]

Summary. This investigation of the conversions of **1** and **3** to **2** and **4**, respectively, establishes that the transfer of oxygen from nitrogen to phosphorus can occur formally within the endocyclic confines of a six-membered ring. The intermediacy of **18** is consistent with the kinetics, the labeling, and the reluctance of **8**, **12a**, and **12b** to undergo oxygen transfers. The ability of phosphorus to expand its octet to give **18** is considered essential for this mechanism and, therefore, for this transfer of oxygen at an oblique angle. This pathway is in contrast to the linear transfer of oxygen from a peroxide to a double bond.[21] Finally, this approach further illustrates the use of the endocyclic restriction test to define the bond angles in transition structures which involve nonstereogenic atoms and to provide information which allows for distinction between alternative mechanisms.[2]

Experimental Section

General Methods. Flash and medium-pressure liquid chromatography were performed using Merck 50–200-mm and 32–63-μm silica gel, respectively. Preparative thin-layer chromatography (prep TLC) was performed on kieselgel 60 F_{254} plates from Merck containing indicator with visualization by UV light. Analytical thin-layer chromatography was performed on Merck silica plates with F-254 indicator. Visualization was accomplished by UV light or iodine. Analytical gas chromatography was performed on a HP 5790S or a HP 5890A using a Hewlett-Packard fused silica capillary column cross-linked with 5% phenyl methyl silicone (column i.d. 0.20 mm; column length 25 m) equipped with a flame ionization detector. The injector temperature was 250 °C, and the detector temperature was 300 °C. When microanalysis data were not available, the purity of the title compounds was judged to be >90% by ^{1}H NMR spectral determinations unless otherwise noted. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected.

All solvents and reagents were obtained from commercial sources and used without further purification, except where noted. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium/benzophenone under an atmosphere of nitrogen. The ethyl acetate and hexane solvents used for MPLC and flash chromatography were distilled from bulk solvent over sodium carbonate and molecular sieves, respectively. ^{18}O-Labeled water (10, 50, and 98+% ^{18}O) was purchased from Cambridge Isotope Labs or Isotec, Inc. Methyl formate-^{13}C (99% ^{13}C) was purchased from Isotec, Inc.

Table I. Isotopic Composition of **4** from the Double-Labeling Experiment with **3**[a]

label	exptl	theoretical intramolecular	theoretical intermolecular
^{12}C-^{16}O	56	56	37
^{13}C-^{16}O	9	10	29
^{12}C-^{18}O	1	1	19
^{13}C-^{18}O	35	33	15

[a] Errors are estimated to be ±5%.

All organometallic reagents used were obtained commercially and titrated according to the procedures of Tischler,[22] Shapiro,[23] or Suffert[24] prior to use. All reactions involving air- or water-sensitive reagents were carried out under nitrogen or argon in oven-dried or flame-dried glassware which was cooled under a nitrogen atmosphere.

***N*-(2-(Diphenylphosphino)benzyl)-*N*-methylhydroxylamine (1).** To a solution of **5** (0.62 g, 1.8 mmol) in EtOH (50 mL) was added *N*-methylhydroxylamine (250 mg, 5.3 mmol), and the solution was stirred for 6 h. The mixture was cooled to 0 °C under a nitrogen atmosphere, borane–pyridine (1.5 mL) was added, and the solution was stirred for 3 h at room temperature. The mixture was cooled to 0 °C, 10% HCl (20 mL) was added dropwise, and stirring was continued for another 3 h until H_2 evolution ceased. The mixture was neutralized with saturated Na_2CO_3 to pH ≈ 12, extracted with CH_2Cl_2, dried over K_2CO_3, and evaporated in vacuo to provide a yellow solid, which was purified by MPLC (15% EtOAc/hexanes) to give 0.37 g (64%) of **1a** as white crystals: mp 134–136 °C; ^{1}H NMR δ 6.9–7.5 (m, 14 H), 5.7 (s, 1 H), 4.0 (s, 2 H), 2.5 (s, 3 H); ^{13}C NMR δ 137.5, 137.3, 133.86, 133.8, 133.76, 133.7, 133.5, 130.0, 129.9, 128.7, 128.6, 128.47, 128.4, 127.5, 64.4 (d, J = 16.5 Hz), 47.4; ^{31}P NMR δ-14.2; MS m/z (area) 321 (M^+, 787), 304 (31431), 226, (6100), 197 (5086), 183 (6321), 165 (6636); IR (CH_2Cl_2, cm^{-1}) 3059 (s), 2984 (s), 2303 (m), 1427 (s), 1293, 1237, 1156, 900. Anal. Calcd for $C_{20}H_{20}NOP$: C, 74.74; H, 4.36; N, 6.27; P, 9.65. Found: C, 74.93; H, 4.33; N, 6.18; P, 9.53.

***N*-(2-(Diphenylphosphino)benzyl)-*N*-isopropylhydroxylamine (3).** The same procedure was used as that for **1** except that 1.0 g (3.4 mmol) of **5** in EtOH (25 mL) was treated with 0.5 g (6.9 mmol) of *N*-isopropylhydroxylamine. A similar workup followed by chromatography (20% EtOAc/hexanes) and recrystallization from Et_2O/pentane gave 0.81 g (67%) of **1b**: mp 107–108.5 °C; ^{1}H NMR δ 6.9–7.5 (m, 14 H), 4.06 (s, 2 H), 4.0 (br, 1 H), 2.9 (m, J = 6.9 Hz, 1 H), 0.90 (d, J = 6.9 Hz, 6 H); ^{13}C NMR δ 143.5, 143.1, 138.2, 138.0, 136.6, 136.3, 134.3, 133.8, 133.5, 132.0, 131.9, 131.1, 130.0, 128.7, 128.5, 128.4, 127.3, 59.4 (d, J = 14.7 Hz), 56.9, 18.1; MS m/z (area) 349 (M^+, 2288), 332 (32760), 306 (15341), 288 (19908), 275 (32689). Anal. Calcd for $C_{22}H_{24}NOP$: C, 75.62; H, 6.92; N, 4.01; P, 8.87. Found: C, 75.28; H, 7.17; N, 3.92; P, 9.03.

***N*-(2-(Diphenylphosphinyl)benzyl)-*N*-methylamine (2).** To a solution of 0.22 g (0.7 mmol) of **8** in 20 mL of EtOH was added 2 mL of 40% aqueous methylamine. The solution was stirred for 8 h at room temperature, 1 mL of borane–pyridine was added under a nitrogen atmosphere, and stirring was continued for another 3 h. The mixture was cooled to 0 °C, 10 mL of 10% HCl was added dropwise, and stirring was continued for 2 h. The mixture was neutralized with saturated Na_2CO_3 to pH ≈ 12, extracted with CH_2Cl_2, dried over anhydrous K_2CO_3, filtered, and evaporated in vacuo to provide a yellow oil, which was purified on the chromatotron (10% CH_3OH/EtOAC) to give 0.17 g (71%) of **2** as a pale yellow oil: ^{1}H NMR δ 7.0–7.7 (m, 14 H), 3.85 (s, 2 H), 2.21 (s, 3 H); ^{13}C NMR δ 144.85, 144.80, 137.97, 133.82, 133.78, 133.52, 132.37, 132.31, 132.06, 132.00, 131.92, 131.86, 131.77, 131.72, 128.79, 128.55, 126.75, 126.49, 54.49 (d, J = 4.9 Hz), 35.79; MS m/z (area) 321 (M^+, 2533), 306 (11727), 291 (27577); IR (CCl_4, cm^{-1}) 3686 (w), 3030 (s), 3008 (m), 2401 (w), 1521 (m), 1422 (w), 1278 (s), 1241 (s), 1234 (s), 1195 (s), 1145 (s), 1108 (s), 928 (m), 803 (s). Anal. Calcd for $C_{20}H_{20}NOP$: C, 74.74; H, 6.27; N, 4.36; P, 9.65. Found: C, 74.42; H, 6.42; N, 4.23; P, 9.61.

***N*-(2-(Diphenylphosphinyl)benzyl)-*N*-isopropylamine (4)** was prepared in the same manner as **2** and gave 57% yield of **4** as a light yellow solid: mp 93–93 °C; ^{1}H NMR δ 6.8–7.8 (m, 14 H), 4.8 (s, 1 H), 3.85 (s, 2 H), 2.62 (m, J = 6.3 Hz, 1 H), 0.9 (d, J = 6.3 Hz, 6 H); ^{13}C NMR δ 145.6 (d, J_{PC} = 8.2 Hz), 133.9, 133.5, 133.3, 132.3, 132.1, 131.9, 131.8, 131.7, 131.5, 130.0, 128.6, 128.5, 128.4, 126.3, 126.1, 50.1 (d, J_{PC} = 5.3 Hz), 48.0, 22.6. Anal. Calcd for $C_{22}H_{24}NOP$: C, 75.62; H, 6.92; N, 4.01; P, 8.87. Found: C, 75.28; H, 7.09; N, 3.92; P, 8.70.

(20) Double-labeling experiments were carried out in both toluene and DMF at 100 and 129 °C, respectively, to determine whether the reaction was intramolecular or intermolecular; however, we were not able to obtain meaningful results. We observed apparent loss of ^{18}O-label in both cases. A reasonable explanation for this is that **19** arises as a result of adventitious oxidation of the deoxygenated intermediate. The two intermediates which would arise from a bimolecular reaction were also observed by TLC but were only identified by comparison with TLCs of authentic standards. To provide additional evidence that an intermolecular reaction occurred, a reaction was carried out between doubly labeled **8**, containing 74% ^{18}O-enrichment and Ph_3P. After the reaction mixture was heated at 100 °C for 33 h, analysis of the Ph_3P=O showed 35% ^{18}O-enrichment with the low extent of incorporation attributable to adventitious oxidation. A similar reaction between **2** and Ph_3P showed no oxidation of Ph_3P. These results show that at least a partial intermolecular reaction involving **8** could occur, although it offers no definitive information about the mechanism.

(21) Woods, K. W.; Beak, P. *J. Am. Chem. Soc.* **1991**, *113*, 6281. Bach, R. D.; Owensby, A. L.; Gonzalez, C.; Schlegel, H. B.; McDevall. J. J. *J. Am. Chem. Soc.* **1991**, *113*, 2338.

(22) Tischler, A. N.; Tischler, M. H. *Aldrichimica Acta* **1987**, *11*, 20.

(23) Lipton, M. F.; Sorensen, C. M.; Sadlet, A. C.; Shapiro, R. H. *J. Organomet. Chem.* **1980**, *186*, 155.

(24) Suffert, J. *J. Org. Chem.* **1989**, *54*, 509.

Conversion of 1 to 2 in Toluene. In a typical experiment, a solution of 0.35 g (1.0 mmol) of **1** in 10 mL of toluene was heated at reflux for 1 h under a nitrogen atmosphere. The solution was cooled to room temperature and evaporated in vacuo to provide a yellow oil, which was purified on a chromatotron with 5% MeOH/EtOAc as an eluent to give 0.32 g (90%) of **2** as a pale yellow solid with mp 93–95 °C and having spectroscopic characteristics identical with those of **2** prepared by an alternate route.

General Kinetic Procedure. In an NMR tube were placed a weighed amount of **1** and toluene-d_8 (0.59 mL). The tube was heated in a variable temperature NMR probe, and the reaction was followed by ^{1}H NMR. Data were collected for at least 2 half-lives. Integrations of the peaks for **1** and **2** were used to determine the concentration of **1** at specific times. The integration error was taken to be ±10%. A plot of ln [**1**] vs time was made to determine first-order rate constants. Data were acquired at 60, 80, and 100 °C at a concentration of 0.1 M and at 100 °C at 0.02 M and are shown in Table II in the supplementary material.

***N*-(2-(Diphenylphosphino)benzyl)-*N*-methylamine (10).** To a solution of **6** (0.40 g, 1.4 mmol) in MeOH (30 mL) was added a 2% methylamine in methanol solution (20 mL). The solution was stirred for 8 h at room temperature. Borane–pyridine (1 mL) was then added under nitrogen, and the solution was stirred for another 3 h. The mixture was cooled to 0 °C, 10% HCl (10 mL) was added dropwise, and stirring was continued for 2 h. The mixture was neutralized with saturated Na_2CO_3 to pH ≈ 12 and extracted with CH_2Cl_2. The combined organic layers were dried over K_2CO_3 and evaporated in vacuo to provide a pale yellow liquid, which was purified on the chromatotron (50% EtOAc/hexanes) to give 0.32 g (76%) of **10** as a pale yellow oil: ^{1}H NMR δ 6.8–7.6 (m, 14 H), 3.92 (s, 2 H), 2.3 (s, 3 H); ^{13}C NMR δ 144.4, 144.0, 136.7, 136.5, 135.7, 135.5, 134.0, 133.6, 133.4, 129.1, 129.0, 128.9, 128.8, 128.7, 128.6, 128.5, 128.4, 127.2, 54.2 (d, J = 4.6 Hz), 35.9; MS m/z (area) 305 (M^+, 5617), 290 (3151), 274 (24059), 228 (5370), 196 (9698). Anal. Calcd for $C_{20}H_{20}NP$: C, 78.66; H, 6.60; N, 4.58; P, 10.15. Found: C, 78.39; H, 6.68; N, 4.39; P, 10.32.

***N*-(2-(Diphenylphosphinyl)benzyl)-*N*-methylhydroxylamine (9).** To a solution of **8** (0.58 g, 1.9 mmol) and *N*-methylhydroxylamine (0.19 g, 4 mmol) in ethanol (10 mL) at 0 °C was added borane–pyridine (1 mL). The mixture was warmed to room temperature, stirred for 5 h, and cooled to 0 °C, and 10% HCl (15 mL) was added dropwise. The solution was then warmed to room temperature and stirred for 5 h. It was neutralized with saturated $NaHCO_3$ and solid NaOH to pH ≈ 14 and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried over K_2CO_3 and evaporated to provide a yellow oil, which was purified on the chromatotron (50% EtOAc/hexanes) to give 0.25 g (38%) of **9** as a yellow solid: mp 168–170 °C. ^{1}H NMR δ 7.0–7.8 (m, 14 H), 4.03 (s, 2 H), 2.28 (s, 3 H); ^{13}C NMR δ 143.4, 143.3, 135.0, 134.5, 134.2, 132.9, 132.1, 131.2, 130.7, 130.6, 130.4, 129.0, 128.5, 128.2, 126.8, 126.5, 64.1, 46.8; ^{31}P NMR δ 33.3; MS m/z (area) 337 (M^+, 431), 320 (31480), 304 (10795), 291 (25469). Anal. Calcd for $C_{20}H_{20}O_2NP$: C, 71.20; H, 5.98; N, 4.15; P, 9.19. Found: C, 71.04; H, 6.07; N, 3.57; P, 9.32.

Reaction between 9 and 10 To Give 2 in Dioxane. A solution of **10** (0.185 g, 6.0 mmol) and **9** (0.202 g, 6.0 mmol) in dioxane (30 mL) was heated at reflux under nitrogen for 10 h. The mixture was cooled to room temperature and evaporated in vacuo to provide a pale yellow oil. Only a trace amount of **2** could be detected in the ^{1}H NMR of the crude product mixture.

***N*-(2-(Diphenylphosphino)benzyl)-*N*-methylmethoxylamine (13).** To a solution of **5** (0.40 g, 1.38 mmol) in EtOH (30 mL) at room temperature was added *N*-methylmethoxylamine (0.17 g, 2.8 mmol). The mixture was stirred for 20 h before it was cooled to 0 °C and borane–pyridine (1 mL) was added. The solution was warmed to room temperature and stirred for 2 h before it was cooled to 0 °C and 10% HCl (15 mL) was added. The solution was warmed to room temperature, stirred for 2 h, and then neutralized with saturated Na_2CO_3. The aqueous layer was extracted with CH_2Cl_2, and the resulting organic layer was dried over K_2CO_3. Concentration in vacuo gave a pale yellow liquid, which was purified on the chromatotron (10% EtOAc/hexanes) to give 0.245 g (53%) of **13** as a colorless oil: ^{1}H NMR δ 6.9–7.5 (m, 14 H), 4.07 (d, J = 1.2 Hz, 2 H), 3.23 (s, 3 H), 2.48 (s, 3 H); ^{13}C NMR δ 142.7, 137.5, 137.3, 137.0, 136.8, 134.1, 133.7, 130.1, 128.8, 128.7, 128.66, 128.5, 128.4, 127.5, 62.8 (d, J_{PC} = 18.6 Hz), 59.6, 44.4; MS m/z (area) 320 (140), 304 (21186), 288 (873), 226 (5140).

***N*-(2-(Diphenylphosphino)benzyl)-*N*-isopropylmethoxylamine (14).** To a solution of **3** (100.0 mg, 0.29 mmol) in THF (10 mL) at −78 °C was added *n*-BuLi (0.19 mL, 0.30 mmol). After 10 min, the reaction was treated with CH_3I (18.5 μL, 0.30 mmol). The reaction was stirred at −78 °C for 3.5 h. It was then treated with saturated NH_4Cl and diluted with Et_2O. The organic layer was dried over Na_2SO_4 and concentrated to give a yellow oil. Column chromatography (10% EtOAc/hexanes) gave 34.5 mg (33%) of **14** as a light yellow oil: R_f = 0.68; ^{1}H NMR (toluene-d_8, 200 MHz) δ 6.94–7.37 (m 14 H), 4.26 (d, J = 1.9 Hz, 2 H), 3.10 (s, 3 H), 2.85 (m, J = 6.9 Hz, 1 H), 0.99 (d, J = 6.9 Hz, 6 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 127.20–134.28, 61.92, 57.45 (d, J = 19.2, CH_2), 55.63, 18.16; ^{31}P NMR ($CDCl_3$, 121 MHz) δ −16.5, −16.5 (AcOH-d_4), −15.9 (toluene-d_8); EIMS m/z 332 (M − OCH_3). Anal. Calcd for $C_{23}H_{26}NOP$: C, 76.01; H, 7.21; N, 3.86. Found: C, 76.04; H, 7.19; N, 3.71.

Acetone Oxime-^{18}O. The synthesis of acetone oxime-^{18}O was carried out in a manner similar to that reported by Van Etten.[25] To a solution of $NaNO_2$ (2.5 g, 18.6 mmol) in 5 mL of 98.7% ^{18}O-enriched water at −5 °C was added 0.128 mL of 12 M HCl. After 1 h at −5 °C, the solution was warmed to room temperature and allowed to stand for 24 h. It was then cooled to −5 °C while 64 mg of powdered sodium hydroxide was added. After the powder dissolved, the contents of the flask were placed under vacuum with an in-line dry ice–2-propanol trap to recover any ^{18}O-labeled water. After 15 h of being dried under vacuum at room temperature and 1 h at 60 °C, the ^{18}O-enriched $NaNO_2$ was stored in a glovebag under nitrogen.

To 1.25 g of the $NaN^{18}O_2$ in THF (25 mL) was added borane–dimethyl sulfide (3.70 mL, 39.0 mmol) dropwise. The reaction was stirred at room temperature for 14.5 h before being cooled to −5 °C. To the cooled reaction mixture was added water (7.4 mL) over 15 min followed by 6 M HCl (7.4 mL) over 20 min. After the mixture was stirred an additional 20 min, acetone (1.85 mL) was added. The aqueous layer was treated with 6 M NaOH (8 mL) after 15 min and saturated with solid sodium chloride. The layers were separated, and the aqueous layer was extracted twice with 25-mL portions of ether. The organic layer was then dried over sodium sulfate and concentrated to give 0.625 g of white solid. Sublimation (1–2 mm, room temperature) afforded 0.41 g (32%) of acetone oxime-^{18}O as clear, colorless crystals: mp 59.5–62.5 °C (lit.[26] mp 60–61 °C); FIMS m/z (relative intensity) for labeled acetone oxime 71 (0.9), 72 (1.7), 73 (28.6), 74 (12.1), 75 (100), 76 (19.8), 77 (0.8), and for unlabeled acetone oxime, 71 (2.3), 72 (3.7), 73 (100), 74 (13.6), 75 (3.3), 76 (0.4).

***N*-Isopropylhydroxylamine-^{18}O** was prepared in a manner similar to that reported by Borch et al.[27] To a solution of acetone oxime-^{18}O (250.6 mg, 3.3 mmol) in MeOH (5 mL) was added $NaBH_3CN$ (227 mg, 3.6 mmol) and a trace (<1 mg) of bromocresol green. The reaction mixture was then treated dropwise with 2 N HCl until the reaction mixture maintained a yellow–green to yellow color over 4 h. The solvent was then removed in vacuo, and 1 mL of water was added followed by 6 M NaOH (0.5 mL). The aqueous layer was then extracted with CH_2Cl_2 (3×). The combined organic layers were dried over $MgSO_4$ and concentrated to give 202 mg (78%) of *N*-isopropylhydroxylamine-^{18}O as a white solid: mp 83–85 °C (lit.[28] 86–87 °C).

***N*-(2-(Diphenylphosphino)benzyl)-*N*-isopropylhydroxylamine-^{18}O (3-^{18}O).** To a mixture of **5** (325.8 mg, 1.12 mmol) in EtOH (15 mL) was added isopropylhydroxylamine-^{18}O (150 mg, 1.95 mmol). The reaction was stirred for 13 h at room temperature. A TLC (30% EtOAc/hexanes) showed unreacted **5** present, so an additional 21 mg (0.28 mmol) of the hydroxylamine was added. After 3.5 h, the reaction was cooled to 0 °C while borane–pyridine (0.80 mL, 7.9 mmol) was added. After 22.5 h at room temperature, the reaction was cooled to 0 °C and 3 N HCl (25 mL) was added dropwise. After the mixture was allowed to stand for 4 h at 0 °C, the cooling bath was removed and stirring was continued for 30 min at room temperature. The reaction was treated with saturated Na_2CO_3 (25 mL) until CO_2 evolution ceased. The aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL), and the resulting organic layer was dried over $MgSO_4$. Concentration in vacuo gave a tan oil. Flash chromatography (20% EtOAc/hexanes) gave 284.5 mg of impure **3**-^{18}O. Purification on the chromatotron (20% EtOAc/hexanes) gave 178.1 mg (45%) of **3**-^{18}O as a white solid, which was identical by ^{1}H NMR with an authentic sample of **3**: FIMS m/z (relative intensity) for labeled **3**-^{18}O, 347 (4.5), 348 (5.4), 349 (41.8), 350 (28.2), 351 (100.0), 352 (38.2), 353 (6.2), and for unlabeled **3** run in duplicate, 347 (8.4, 11.6), 348 (14.3, 16.0), 349 (100.0, 100.0), 350 (38.3, 39.8), 351 (6.3, 7.7), 352 (0.7, 1.0).

Treatment of 3-^{18}O in 20:1 EtOH-H_2O. A solution of **3**-^{18}O (20.4 mg, 0.06 mmol) in a 20:1 EtOH–H_2O (0.77 mL) mixture was heated at 78 °C in an NMR tube for 4.5 h. The reaction mixture was diluted with CH_2Cl_2 and washed with brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo to give 21.9 mg of colorless oil. A ^{1}H NMR of the product mixture showed an apparent 82% conversion of **4**-^{18}O on the basis of integration of the peaks corresponding to the

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methylene protons of **3**-^{18}O and **4**-^{18}O. Preparative TLC (10% MeOH/EtOAc) gave two bands corresponding to **3**-^{18}O and **4**-^{18}O: FIMS m/z (relative intensity) for labeled **4**-^{18}O, 347 (3.6), 348 (2.5), 349 (44.2), 350 (18.9), 351 (100), 352 (33.7), 353 (5.1), and for unlabeled **4**, 347 (9.1), 348 (4.7), 349 (100), 350 (32.0), 351 (5.0); FIMS m/z (relative intensity) for labeled **3**-^{18}O, 347 (6.3), 348 (7.5), 349 (40.5), 350 (28.2), 351 (100), 352 (34.6), 353 (4.9), and for unlabeled **3**, 347 (2.8), 348 (6.6), 349 (100), 350 (31.9), 351 (4.8).

2-(Diphenylphosphino)benzaldehyde-*formyl*-^{13}C (5-^{13}C). To a solution of (2-bromophenyl)diphenylphosphine (0.667 g, 1.96 mmol) in Et_2O (50 mL) at −78 °C was added a solution of *t*-BuLi in hexanes (2.9 mL, 4.18 mmol, 1.44 M). The reaction was stirred for 0.5 h, during which time the solution became a cream-colored heterogeneous mixture. Methyl ^{13}C-formate (0.33 g, 5.4 mmol) was then added, and the reaction was allowed to warm slowly to room temperature over 7 h. It was then cooled to 0 °C while 3 M HCl (25 mL) was added dropwise. The organic layer was washed with water and brine and then dried over $MgSO_4$. Evaporation of the solvent afforded 0.536 g of a yellow solid, which was purified on the chromatotron (10% EtOAc/hexanes) to give 0.434 g (76%) of **5**-^{13}C as a yellow solid: mp 115–117 °C (lit.[9] mp 118–119 °C); ^1H NMR (200 MHz, $CDCl_3$) δ 10.50 (dd, J = 176.3 Hz, 5.4, 1 H), 6.96–7.97 (m, 14 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.6 (d, J = 19.1 Hz) and others; ^{31}P NMR (121 MHz, $CDCl_3$) δ −11.1 (d, J = 19.2 Hz); FIMS m/z (relative intensity) for **5**-^{13}C, 290 (1.8), 291 (100), 292 (19.9), 293 (2.3), and for unlabeled **5**, 290 (100), 291 (19.4), 292 (2.4).

***N*-(2-(Diphenylphosphino)benzyl-^{13}C)-*N*-isopropylhydroxylamine-^{18}O (3-^{13}C-^{18}O).** To a mixture of **5**-^{13}C (351.9 mg, 1.21 mmol) and *N*-isopropylhydroxylamine-^{18}O (138.3 mg, 1.79 mmol) was added ethanol (15 mL). The reaction was stirred for 33.5 h before an additional amount of isopropylhydroxylamine-^{18}O (25.0 mg, 0.32 mmol) dissolved in EtOH (1 mL) was added. After an additional 11 h, the reaction was cooled to 0 °C and borane–pyridine (0.86 mL, 8.51 mmol) was added. Stirring was continued for 23 h with slow warming to room temperature. The reaction was cooled to 0 °C, and 3 M HCl (25 mL) was added dropwise, followed by saturated Na_2CO_3 (25 mL) after 7 h. The aqueous layer was then extracted with CH_2Cl_2 (3×). The organic layer was dried over $MgSO_4$ and concentrated to give 710 mg of tacky solid, which was purified by column chromatography (10 % EtOAc/hexanes) to give 300.2 mg (70%) of **3**-^{13}C-^{18}O as a white solid: mp 107–111.5 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 6.91–7.42 (m, 14 H), 4.45 (br, 1 H), 4.03 (d, J = 13.4 Hz, 2 H), 2.86 (sep d, J = 6.3, 2.6 Hz, 1 H); ^{31}P NMR (121 MHz, $CDCl_3$) δ −14.5 (d, J_{PC} = 14.0 Hz); FIMS m/z (relative intensity) for **3**-^{13}C-^{18}O, 347 (14.3), 348 (4.6), 349 (8.8), 350 (41.9), 351 (29.0), 352 (100), 353 (36.8), 354 (6.2), and for unlabeled **3** (run in duplicate), 347 (12.0, 14.9), 348 (15.4, 17.3), 349 (100, 100), 350 (45.2, 34.9), 351 (8.5, 8.0), 352 (0.9, 0.9).

Double-Labeling Experiment of 3 and 3-^{13}C-^{18}O in Toluene. A solution of **3** (13.4 mg, 0.038 mmol) and **3**-^{13}C-^{18}O (13.1 mg, 0.037 mmol) in toluene-d_8 (1 mL) was prepared. An aliquot was removed for use as a reactant standard (3.7 mg). The reaction was then heated in an NMR tube under nitrogen at 77 °C for 30 min. The reaction was judged to be ≥50% complete after this time, as determined by ^1H NMR. The solvent was evaporated to give 34.2 mg of oil. Purification by preparative TLC (10% MeOH–EtOAc) gave 8.0 mg (35%) of **4** and 9.6 mg (42.1%) of **3**: FIMS m/z (relative intensity) for labeled **4**,**4**-^{13}C-^{18}O, 347 (4.5), 348 (4.0), 349 (100.0), 350 (56.0), 351 (15.0), 352 (64.4), 353 (22.5), 354 (3.8), and for unlabeled **4**, 347 (4.8), 348 (3.7), 349 (100.0), 350 (37.0), 351 (5.8), 352 (0.6); FIMS m/z (relative intensity). For labeled **3**,**3**-^{13}C-^{18}O, 347 (3.4), 348 (11.5), 349 (100.0), 350 (54.8), 351 (20.3), 352 (60.8), 353 (17.8), 354 (2.7), for labeled recovered **3**, 347 (3.7), 348 (13.3), 349 (100.0), 350 (58.1), 351 (22.8), 352 (70.9), 353 (22.4), 354 (3.2), and for unlabeled **3**, 347 (4.0), 348 (11.6), 349 (100.0), 350 (34.8), 351 (5.6), 352 (0.6).

2-(4-(2-(Diphenylphosphino)phenyl)butyl)-1,3-dioxolane (22). To a solution of (2-methylphenyl)diphenylphosphine (181 mg, 0.66 mmol) in hexanes (5 mL) was added TMEDA (0.12 mL, 0.80 mmol) followed by *n*-BuLi (0.56 mL, 0.81 mmol). After 1 h, the orange reaction mixture was cooled to −78 °C and a solution of the chloro dioxolane[29] (150 mg, 1.0 mmol) in Et_2O (5 mL) was quickly added. After 10 min, the cooling bath was replaced with an ice bath and the reaction was allowed to warm to room temperature over 2.5 h. After 20 h at room temperature, the reaction was quenched with H_2O and extracted with Et_2O. The organic layer was dried over Na_2SO_4 and concentrated to give 259 mg of a light brown oil. Chromatography (10% EtOAc/hexanes) gave 136 mg (53%) of **22** as a colorless oil: ^1H NMR δ 6.82–7.29 (m, 14 H), 4.77 (m, 1 H), 3.85 (m, 4 H), 2.86 (m, 2 H), 1.30–1.70 (m, 6 H); ^{13}C NMR δ 126.00–147.34, 104.43, 64.71, 34.40 (J = 20.9 Hz), 33.61, 31.20, 23.95; ^{31}P NMR δ −14.9. Anal. Calcd for $C_{25}H_{27}O_2P$: C, 76.90; H, 6.97; P, 7.93. Found: C, 76.89; H, 6.99; P, 7.86.

5-(2-(Diphenylphosphino)phenyl)pentanal (23). A solution **22** (570 mg, 1.46 mmol) in acetone (150 mL) containing 10 drops of 6 N H_2SO_4 was heated at reflux for a total of 2.5 h. After cooling, the reaction mixture was diluted with Et_2O and washed with saturated $NaHCO_3$ (1×) followed by H_2O (2×). The aqueous phases were back-extracted with Et_2O, and the combined organic layers were dried over $MgSO_4$. Concentration gave 490 mg of a cloudy light yellow oil, which contained mostly the desired product but also contained some **22**. The product mixture was resubjected to the same reaction conditions and workup conditions to give 340 mg of **23** free from **22**. Chromatography gave 237 mg (47%) of pure **23** along with 45 mg (56%) of a less pure fraction: ^1H NMR ($CDCl_3$) δ 9.65 (t, J = 1.7 Hz, 1 H), 7.34–6.86 (m, 14 H), 2.87 (m, 2 H), 2.32 (m, 2 H), 1.60–1.55 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 202.53, 126.90–136.77, 43.54, 34.04 (d, J = 20.7 Hz), 30.63, 21.78; ^{31}P NMR ($CDCl_3$) δ −14.9. Anal. Calcd for $C_{23}H_{23}OP$: C, 79.75; H, 6.69; P, 8.94. Found: C, 79.54; H, 6.68; P, 8.65.

***N*-(5-(2-(Diphenylphosphino)phenyl)pentyl)-*N*-isopropylhydroxylamine (8).** A solution of **23** (199 mg, 0.57 mmol) in EtOH (10 mL) was treated with isopropylhydroxylamine (63.3 mg, 0.84 mmol). The reaction was stirred for 4 h and then cooled to 0 °C while borane–pyridine (0.29 mL, 2.9 mmol) was added. After 1 h, the cooling bath was removed and stirring was continued at room temperature for 4 h. The reaction was cooled to 0 °C while 3 N HCl (10 mL) was added dropwise. After 1 h, the cooling bath was removed and stirring was continued at room temperature until H_2 evolution ceased. The reaction was basified with saturated Na_2CO_3 and extracted with Et_2O (3×). The organic layer was dried over Na_2SO_4 and concentrated in vacuo to give a colorless oil. Chromatography (30% EtOAc/hexanes) afforded 204 mg (88%) of **19** as a colorless oil: ^1H NMR ($CDCl_3$) δ 6.85–7.35 (m, 14 H), 2.86 (m, 2 H), 2.56 (m, 2 H), 1.52 (m, 4 H), 1.30 (m, 2 H), 1.07 (d, J = 6.9 Hz, 6 H); ^{13}C NMR ($CDCl_3$) δ 126.00–133.96, 57.10, 55.43, 34.48 (d, J = 21.0 Hz), 31.33, 27.34, 27.17, 18.30; ^{31}P NMR ($CDCl_3$) δ −14.92. Anal. Calcd for $C_{26}H_{32}NOP$: C, 77.01; H, 7.95; N, 3.46; P, 7.64. Found: C, 76.82; H, 7.99; N, 3.37; P, 7.49.

2-(4-(2-(Diphenylphosphinyl)phenyl)butyl)-1,3-dioxolane. A solution of **22** (130 mg, 0.33 mmol) in CH_3OH (5 mL) was treated with 30% H_2O_2 (5 drops). After the solution was allowed to stand overnight, CH_2Cl_2 was added along with $Na_2S_2O_3$ and H_2O. The organic layer was dried over Na_2SO_4 and concentrated to give a colorless oil. Purification by passage through a plug of silica (EtOAc) gave 129.7 mg (97%) of the phosphine oxide as a colorless oil: ^1H NMR δ 7.04–7.72 (m, 14 H), 4.74 (t, J = 4.8 Hz, 1 H), 2.84–3.93 (m, 6 H), 2.88 (m, 2 H), 1.26–1.50 (m, 6 H); ^{13}C NMR δ 124.97–133.86, 104.42, 84.91, 64.67, 34.21, 33.54, 31.12, 24.02; ^{31}P NMR δ +31.7. Anal. Calcd for $C_{25}H_{27}O_3P$: C, 73.87; H, 6.70; P, 7.62. Found: C, 73.55; H, 6.62; P 7.31.

5-(2-(Diphenylphosphinyl)phenyl)pentanal. A solution of the dioxolane–phosphine oxide (97.0 mg, 0.24 mmol) in acetone (10 mL) was treated with 10 drops of 3 N H_2SO_4 and heated at reflux for 3 h. The reaction was cooled and diluted with CH_2Cl_2. It was washed with dilute $NaHCO_3$, and the resulting organic layer was dried over $MgSO_4$. Concentration gave a yellow oil, which was purified by chromatography (50% EtOAc/hexanes) to give 70.7 mg of 5-(2-(diphenylphosphinyl)-phenyl)pentanal as a colorless oil. A ^1H NMR of the material showed that some of the dioxolane starting material was still present, but the product was judged pure enough to proceed to the next step: ^1H NMR δ 9.64 (t, J = 2.0 Hz, 1 H), 6.97–7.71 (m, 14 H), 2.90 (m, 2 H), 2.28 (m, 2 H), 1.49 (m, 4 H).

***N*-(5-(2-(Diphenylphosphinyl)phenyl)pentyl)-*N*-isopropylamine (19).** To a solution of the 5-(2-(diphenylphosphinyl)phenyl)pentanal (42.6 mg, 0.12 mmol) in EtOH (5 mL) was added isopropylamine (36 μL, 0.42 mmol). After 20 h, the reaction was cooled to 0 °C and $NaBH_4$ (16 mg, 0.42 mmol) was added. The reaction was stirred at room temperature for 70 h. It was treated with H_2O and 6 M HCl. After H_2 evolution ceased, the aqueous layer was basified with 6 M NaOH and extracted with CH_2Cl_2 (2×). The organic layer was dried over Na_2SO_4 and concentrated to give 29.5 mg (59%) of **19** as a light yellow oil: ^1H NMR δ 6.96–7.68 (m, 14 H), 3.77 (br s, 1 H), 2.94 (m, J = 6.8 Hz, 1 H), 2.82 (m, 2 H), 2.59 (m, 2 H), 1.45 (m, 4 H), 1.26 (m, 2 H), 1.17 (d, J = 6.4 Hz, 6 H); ^{13}C NMR δ 124.93–133.53, 48.64, 47.12, 34.17, 31.06, 29.71, 27.27, 22.66; ^{31}P NMR δ +32.2; FIMS m/z (M^+) 405.

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Supplementary Material Available: Additional experimental details; Tables II–IV of kinetic data for **1–4** (13 pages). Ordering information is given on any current masthead page.

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