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Light, Medium, and Heavy Fluorous Triarylphosphines Exhibit Comparable Reactivities to Triphenylphosphine in Typical Reactions of Triarylphosphines

Dennis P. Curran,* Xiao Wang, and Qisheng Zhang

Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

curran@pitt.edu

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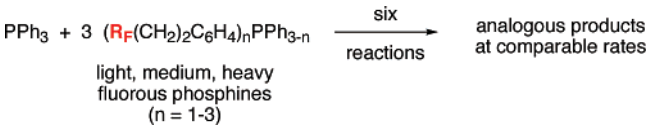

The relative reactivities of triphenylphosphine (PPh_3) and three fluorous triarylphosphines [$(p\text{-}R_F(CH_2)_2C_6H_4)_nPPh_{3-n}$, where $n = 1-3$] have been compared in internal competition experiments. Product ratios were determined by ^{31}P NMR spectroscopy. The four phosphines have about the same reactivities in oxidation, alkylation, and Staudinger reactions and give comparable yields in a preparative Mitsunobu reaction. Previously observed rate and yield differences in Staudinger reactions of the fluorous phosphines are attributed to solubility effects, not reactivity differences. A light fluorous phosphine [$(p\text{-}C_8F_{17}(CH_2)_2C_6H_4)PPh_2$] outperforms a commercially available resin-bound phosphine in a competitive benzylation experiment by a factor of about 4.

Organic compounds are rendered fluorous by the attachment of one or more perfluoroalkyl tags, which are often insulated by an alkylene or other spacer: $-(CH_2)_nR_F$. These tags render the tagged molecules susceptible to convenient fluorous separation techniques such as liquid–liquid and solid-phase extraction.[1] As the use of fluorous catalysts, reagents, and scavengers in organic synthesis grows,[2] it becomes increasingly important to better understand the reactivity of fluorous compounds relative to each other and to suitable nonfluorous models. We and others often advertise fluorous molecules as having reactivities comparable to those of their nonfluorous parents, but detailed spectroscopic and computational studies by Gladysz and others have shown that "it is very challenging to 'completely' insulate a reactive site from a perfluoroalkyl group in a fluorous molecule".[3]

For synthetic applications, the perfluoroalkyl group and the spacer are sometimes purposefully used to tune Lewis acid/base or other properties of a reactive functionality.[3,4] More typically, it is desirable that a functionality in a fluorous molecule has reactivity comparable to that of its nonfluorous parent. In such cases, it is not important to "completely" insulate a reactive group from a perfluoroalkyl tag, but it is important to "effectively" insulate it. By this we mean that the effects of the perfluoroalkyl group on relative reactivity are small enough (±10% or so) to be neglected for most preparative purposes.

Triphenylphosphine **1a** is a staple in organic synthesis, functioning as a ligand, a reagent, or a catalyst in a diverse assortment of important transformations.[5] Accordingly, light, medium, and heavy fluorous phosphines **1b**–**d** have been introduced as triphenylphosphine analogues with variable fluorine content suited to different types of fluorous separations.[6] But do phosphines **1b**–**d** exhibit comparable reactivities to each other and to **1a**? Lindsley and co-workers made the intriguing observation that phosphine **1b** outperformed **1c**, **1d**, and polymer-bound phosphines in Staudinger reactions.[7] But is the superiority of **1b** due to an inherent reactivity advantage? The fluorous phosphines **1b**–**d** are often made by the reactions of aryl anions with aryl phosphorus chlorides, and phosphine oxides are common byproducts of these reactions.[6c,d] Also, Schneider and Bannwarth reported that a phosphine closely related to **1d** was oxidized a little bit more readily than triphenylphosphine.[8] Does this mean that fluorous phosphines are easily susceptible to air oxidation?

To answer these questions, we selected representative transformations of triarylphosphines and conducted a series of competitive reaction experiments. All the phosphines are commercially available,[9] and their purities were checked by ^{31}P NMR prior to use. Competitive reactions were conducted in THF-d_8 to ensure that all four phosphines were soluble under the reaction conditions, and reaction progress was monitored periodically

(1) *Handbook of Fluorous Chemistry*; Gladysz, J. A., Curran, D. P., Horváth, I. T., Eds.; Wiley-VCH: Weinheim, 2004.

(2) (a) Curran, D. P. In ref 1, pp 101–127. (b) Curran, D. P. In ref 1, pp 128–156. (c) Zhang, W. *Tetrahedron* **2003**, *59*, 4475–4489. (d) Zhang, W. *Arkivoc* **2004**, 101–109. (e) Zhang, W. *Chem. Rev.* **2004**, *104*, 2531–2556.

(3) (a) Gladysz, J. A. In ref 1, pp 41–55. (b) Jiao, H.; LeStang, S.; Soos, T.; Meier, R.; Kowski, K.; Rademacher, P.; Jafarpour, L.; Hamard, J. B.; Nolan, S. P.; Gladysz, J. A. *J. Am. Chem. Soc.* **2002**, *124*, 1516–1523.

(4) Retarding spacer effects are evident in the rates of air oxidation of fluorous arylphosphines bearing perfluoroalkylmethoxy (R_FCH_2O) groups. Sinou, D.; Maillard, D.; Pozzi, G. *Eur. J. Org. Chem.* **2002**, 269–275.

(5) Cobb, J. E.; Cribbs, C. M.; Hanke, B. R.; Vehling, D. E. *Encyclopedia of Reagents for Organic Synthesis*, Paquette, L. A.; Ed; Wiley: Chichester; 1995; Vol. 8, pp 5357–5363.

(6) (a) Brief review: Dandapani, S. In ref 1, pp 175–181. (b) Phosphine **1d** was first described by Leitner: Kainz, S.; Koch, D.; Baumann, W.; Leitner, W. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1628–1630. (c) Zhang, Q.; Luo, Z.; Curran, D. P. *J. Org. Chem.* **2000**, *65*, 8866–8873. (d) Zhang, Q. Ph.D. Thesis, University of Pittsburgh, 2003.

(7) Lindsley, C. W.; Zhao, Z.; Newton, R. C.; Leister, W. H.; Strauss, K. A. *Tetrahedron Lett.* **2002**, *43*, 4467–4470.

(8) (a) Schneider, S.; Bannwarth, W. *Angew. Chem., Int. Ed.* **2000**, *39*, 4142–4145. (b) Schenider, S. Ph.D. Thesis, University of Freiburg, 2000. We thank Professor W. Bannwarth for providing a copy of the relevant pages of this thesis. In this work, phosphine oxidation experiments with air were conducted in separate NMR tubes without internal standards. A fluorous phosphine homologue of **1d** [$(p\text{-}C_8F_{17}C_6H_4)_3P$] was suggested to be more readily oxidized than triphenylphosphine. We conducted a single-point internal competition experiment with this phosphine and **1a**–**c** and found that all four oxidized to the same extent. Thus, $(p\text{-}C_8F_{17}C_6H_4)_3P$ has about the same reactivity towards O_2 in THF as **1d** and triphenylphosphine.

(9) Fluorous phosphines were purchased from Fluorous Technologies, Inc. (www.fluorous.com). D.P.C. holds an equity interest in this company.

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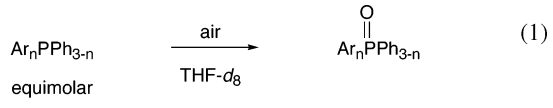
by ^{31}P NMR spectroscopy.[10] Conveniently, the phosphines and all of the derived products exhibited reliable differences in chemical shifts of the ^{31}P nucleus.[11] Authentic samples of all reaction products were either purchased (phosphine oxides) or made as standards. The results of the competitive experiments follow, grouped by reaction.

Oxidation (eq 1). Equimolar quantities of the four phosphines were dissolved in THF-d_8 in an NMR tube, and the tube was allowed to stand open and exposed to air. THF-d_8 was periodically added to replace the solvent lost by evaporation. After 4 days at ambient temperature, conversion to the phosphine oxides was negligible (<2%). After 17 days, about 4% of each of the four phosphines had been oxidized, and after 30 days the experiment was terminated at 7−8% oxidation of each phosphine. These experiments show that all four of the phosphines are oxidized at comparable rates. Further, the oxidation in solution is rather slow, so routine handling of these reagents in the atmosphere is not a problem. However, as usual with triarylphosphines, it is advisable to minimize exposure to oxygen during long-term storage (months, years). We conclude from these experiments that the phosphine oxide side products sometimes observed during the formation of the fluorous phosphines[6c,d] do not originate from air oxidation during reaction or workup, but instead from reagent-induced side reactions.

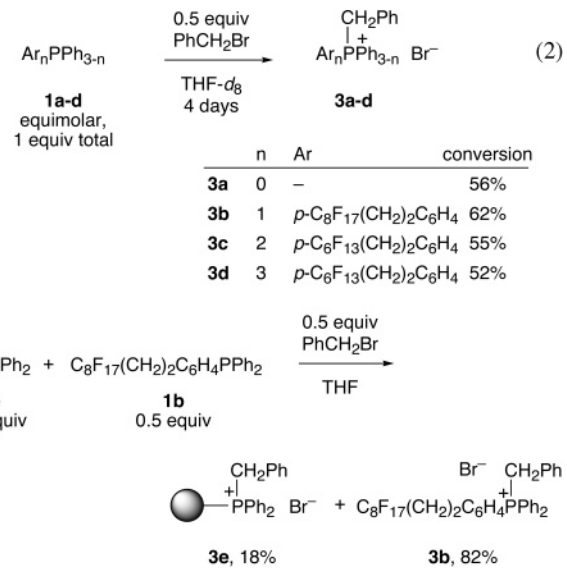


(1)

	n	Ar		conversion 17 days	conversion 30 days
1a	0	–	**2a**	4%	7%
1b	1	*p*-$C_8F_{17}(CH_2)_2C_6H_4$	**2b**	4%	7%
1c	2	*p*-$C_6F_{13}(CH_2)_2C_6H_4$	**2c**	4%	8%
1d	3	*p*-$C_6F_{13}(CH_2)_2C_6H_4$	**2d**	4%	7%

Alkylation (eq 2). Benzyl bromide (0.5 equiv) was added to an NMR tube containing the equimolar mixture of the four phosphines in THF-d_8 (1.0 equiv, total). By using a deficiency of benzyl bromide, the total conversion of all four phosphines is limited to about 50%, and significant differences in reactivity are then revealed simply by integrating the phosphine and phosphonium salt regions of the ^{31}P NMR spectrum. A white precipitate (phosphonium salts) gradually developed. After 4 days at ambient temperature, chloroform-d_1 was added to help dissolve the salts, the ^{31}P spectrum was recorded, and the product ratios are shown in eq 2. Conversions are roughly comparable with no apparent trend. We conclude from these results that the differences in relative reactivity of **1a**−**d** with benzyl bromide are negligible.

Previous work has shown that soluble fluorous reagents are typically more reactive than analogous solid-phase reagents.[12] To compare fluorous and solid-phase phosphines, we also conducted a competitive reaction between fluorous phosphine **1a** and commercial resin-bound phosphine **1e**. In a sense, the experiment is unfair, since the reaction is two phases (liquid phase and gel phase) and we do not know how the benzyl bromide partitions between these phases. But the experiment is nonetheless relevant since the performance of a resin-bound phosphine under biphasic conditions dictates its utility in synthetic applications.



We first verified that the manufacturer's loading level of 2.1 mequiv of phosphine per gram was correct by reacting the resin with a large excess of benzyl bromide, washing thoroughly, and measuring the weight gain (the weighed yield of the phosphonium bromide was 103%). Next, equimolar amounts of resin-bound phosphine **1e** and fluorous phosphine **1b** were added to THF along with 0.5 equiv of benzyl bromide. The mixture was stirred for 19 h, at which time the benzyl bromide was consumed. After filtration, the amounts of fluorous and resin-bound phosphonium salts were assessed in two complementary ways. First, the resin was weighed to assess the amount of resin-bound salt **3e**; simple subtraction then provides the amount of fluorous phosphonium salt **3b**. Second, the ^{31}P NMR spectrum of the filtrate provided the amount of fluorous phosphonium salt **3b**, from which the amount of resin-bound salt **3e** was calculated by subtraction. Results were comparable—about 82% of the benzyl bromide reacts with the fluorous phosphine and about 18% reacts with resin-bound phosphine. These numbers should not be construed as relative reaction rates for a number of reasons; nonetheless, they show the performance superiority of the fluorous phosphine. Or from another view, they show the inferiority of the resin-bound phosphine since fluorous phosphine **1b** has the same reactivity as triphenylphosphine **1a**.

Reaction with $CDCl_3$ (eq 3). By allowing the above reaction mixtures to stand, we began to observe the

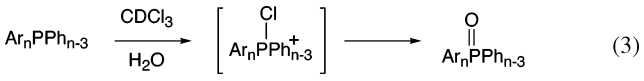
(10) Errors in these experiments could arise from differences in relaxation times or solubility. A long delay (80 s) was used to minimize errors in relaxation times, while additional solvent was added if visible precipitates appeared. Conversions to products were measured relative to the total integration of the four starting phosphines. See the Supporting Information for more details.

(11) Starting and ending ^{31}P NMR spectra for each experiment are provided in the Supporting Information. In all cases, the chemical shifts of products decreased in the following order: **1d** > **1c** > **1b** > **1a**.

(12) (a) Zhang, W. *The Worldwide PharmaChem Directory* **2003**, 18−20. (b) Zhang, W.; Curran, D. P.; Chen, C. H.-T. *Tetrahedron* **2002**, *58*, 3871−3875. (c) Zhang, W.; Chen, C. H.-T.; Nagashima, T. *Tetrahedron Lett.* **2003**, *44*, 2065−2068. (d) Zhang, W.; Chen, C. H.-T. *Mol. Diversity* **2005**, in press.

transformation of the unreacted phosphines to the phosphine oxides at rates much greater than that expected by air oxidation. By analogy with the known reaction of triphenylphosphine with carbon tetrachloride,[13] we consider that this reaction proceeds through chlorophosphonium salts **4a**−**d** as shown in eq 3.

To confirm that oxidation the was caused by the reactions of the phosphines with $CDCl_3$ and to probe the relative rates of this reaction, we dissolved an equimolar mixture of the four phosphines in $CDCl_3$ and then added 20 equiv of water. A few drops of DMSO-d_6 were added to the resulting cloudy solution to clarify it. Then the mixture was allowed to stand for 36 h. A solid was present at the end of the reaction. Additional $CDCl_3$ was added to dissolve the solid, and the conversion to phosphine oxides **2a**−**d** was measured as usual by ^{31}P NMR spectroscopy. Phosphines **1a**−**c** showed 32−33% conversion, while phosphine **1d** showed 26% conversion. We speculate that the slightly lower conversion for **1d** might be because it (or a derived intermediate) might not be completely soluble in the reaction medium (see below). In any event, the experiment confirms that the phosphines are oxidized by chloroform/water and does not reveal any preparatively significant differences in the rates of these phosphines with chloroform.



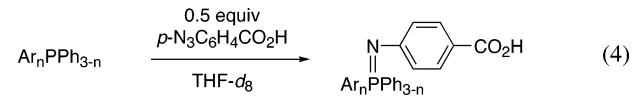
(3)

1a-d **4a-d** **2a-d**

	n	Ar	yld **2** at 36 h
2a	0	–	33%
2b	1	$C_8F_{17}(CH_2)_2C_6H_4$	33%
2c	2	$C_6F_{13}(CH_2)_2C_6H_4$	34%
2d	3	$C_6F_{13}(CH_2)_2C_6H_4$	26%

Staudinger Reactions (eq 4). The interesting observations of Lindsley and co-workers prompted us to look carefully at the Staudinger reaction.[14] Differences in performance of various phosphines could be due to inherent differences in rate in either the reaction with the azide or the subsequent reaction of the aza-ylide with water or to differing solubilities of various species.

We added 0.5 equiv of *p*-azidobenzoic acid (*p*-$N_3C_6H_4CO_2H$) to an equimolar solution of the four phosphines in THF-d_8 and then recorded a ^{31}P NMR spectrum after 30 min. The transformation of the azide to the aza-ylides **5a**−**d** was complete, and the four phosphines again reacted to approximately equal degrees (conversions of 54−55%). The NMR tube was allowed to stand for 15 h, but little change was observed. Deionized water (5 equiv) was then added, and the conversions of the aza-ylides to the phosphine oxides were followed by NMR spectroscopy as usual. These reactions were rather slow, requiring 3 days to complete, but each of the ylides reacted at approximately the same rate as shown by the time course data in eq 4.



(4)

1a-d equimolar, 1 equiv total **5a-d**

	n	Ar	yld of **5** 30 min	15 h
5a	0	–	52%	54%
5b	1	$C_8F_{17}(CH_2)_2C_6H_4$	52%	55%
5c	2	$C_6F_{13}(CH_2)_2C_6H_4$	52%	54%
5d	3	$C_6F_{13}(CH_2)_2C_6H_4$	46%	55%

H_2O, 5 equiv; Ar$_n$PPh$_{3-n}$(=O) **2a-d**

	yld of **2** 0.5 h	3 h	6 h	24 h	48 h	72 h	96 h
2a	6%	8%	14%	24%	38%	50%	57%
2b	8%	9%	13%	23%	41%	49%	57%
2c	6%	8%	14%	23%	42%	51%	58%
2d	8%	8%	15%	24%	40%	52%	59%

These results show that there is no significant difference in the reaction rates of the four phosphines in either the azide reduction or the hydrolysis step of the Staudinger reactions. Accordingly, it seems likely that the performance differences observed by Lindsley (**1b** better than **1c** better than **1d**) can be attributed to solubility effects. The reduction of the azide was conducted in THF, and we speculate that this step went smoothly in Lindsley's experiments for all three phosphines. But addition of excess water to affect the hydrolysis probably caused the (partial) precipitation of the aza-ylides bearing two and three fluorous chains, and this in turn retarded the hydrolysis to the phosphine oxide.

These results underscore the advantage of light fluorous reagents such as **1b**, which are often closely analogous to their nonfluorous parents. Medium and heavy fluorous reagents such as **1c** and **1d** still have similar reactivities to the parents. But they begin to have very different solubility profiles, especially toward fluorophobic solvents (polar solvents and water). Decreased reaction rates can be observed due to precipitation.

Mitsunobu Reaction (eq 5). Last, we evaluated the four phosphines in a typical Mitsunobu reaction.[15] The separation advantages of using fluorous reagents have been highlighted by several groups in the Mitsunobu setting.[16] Here, conducting a competitive reaction is complicated by the multistep mechanism of the reaction, so we simply did a typical performance evaluation by conducting separate reactions under identical conditions and measuring yields of isolated product **8**. Acid **6** and alcohol **7** were coupled with the standard diisopropylazodicarboxylate (DIAD) reagent and the four different phosphines in THF as usual. After 3 h, the solvent was evaporated and the residues were purified by flash chromatography to give product **8** in the indicated yields. While there is some range in these yields (89−98%), all of the reactions looked comparable by TLC analysis, and we suspect that the yield differences are due to handling

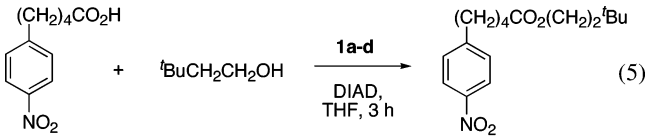
(13) The structure of intermediate **4** was tentatively assigned by analogy to the known reaction of triphenylphosphine with carbon tetrachloride: (a) Taschner, M. *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: Chichester; 1995; Vol. 8, pp 5367−5370. (b) Weiss, R. G.; Snyder, E. I. *J. Org. Chem.* **1970**, *35*, 1627−1632.

(14) Gololobov, Y. G.; Kasukhin, L. F. *Tetrahedron* **1992**, *48*, 1353−1406.

(15) (a) Hughes, D. L. *Org. Prep. Proced. Int.* **1996**, *28*, 127−164. (b) Dembinski, R. *Eur. J. Org. Chem.* **2004**, 2763−2772. (c) Dandapani, S.; Curran, D. P. *Chem. Eur. J.* **2004**, *10*, 3130−3138.

(16) (a) Markowicz, M. W.; Dembinski, R. *Org. Lett.* **2002**, *4*, 3785−3787. (b) Dobbs, A. P.; McGregor-Johnson, C. *Tetrahedron Lett.* **2002**, *43*, 2807−2810. (c) Dandapani, S.; Curran, D. P. *Tetrahedron* **2002**, *58*, 3855−3864. (d) Dandapani, S.; Curran, D. P. *J. Org. Chem.* **2004**, *69*, 8751−8757.

and chromatography variability and not to any inherent differences in reactivity. In effect, all four phosphines perform comparably in this Mitsunobu reaction.



(5)

phosphine	yield **8**
1a	89%
1b	92%
1c	98%
1d	95%

In summary, the reactivities of triphenylphosphine and all three of the fluorous phosphines are qualitatively comparable. In others words, provided that the phosphines are soluble in the reaction medium, they can be used more or less interchangeably with the basis for selection being the preferred method of separation or other criteria. The similarities in reactivity also suggest that the fluorous phosphines are not aggregating under the reaction conditions studied.[17]

The light fluorous phosphine **1b** has a broader solubility profile in common organic reactions solvents and can be separated by fluorous solid-phase extraction. The medium **1c** and heavy **1d** fluorous phosphines will be less soluble in fluorophobic organic solvents, but can be separated by solid−liquid and liquid−liquid techniques. All the phosphines can be expected to outperform typical resin-bound reagents such as **1e** when used in comparable quantities. Quantitatively, the relatively reactivities of phosphines **1a**−**d** cannot possibly be identical,[3] but the differences are small enough that more careful experiments would be needed to reveal them. Such small differences can be important for understanding electronic and other effects, but they have little preparative significance.

Experimental Section

See the Supporting Information for general methods.

Oxidation Reaction (eq 1). Triphenylphosphine **1a** (13.1 mg, 0.05 mmol), diphenyl(4-(1*H*,1H,2*H*,2*H*-perfluorodecyl)phenyl)phosphine **1b** (35.4 mg, 0.05 mmol), bis[4-(1*H*,1H,2*H*,2*H*-perfluorooctyl)phenyl]phenylphosphine **1c** (47.7 mg, 0.05 mmol), and tris[4-(1*H*,1H,2*H*,2*H*-perfluorooctylphenyl)phosphine **1d** (65.0 mg, 0.05 mmol) were dissolved in THF-d_8 (1 mL) in an NMR tube. A needle was pierced through the cap of tube to expose the mixture to air, and fresh solvent was added as needed to keep the volume approximately constant. The tube was allowed to stand for 30 days.

Alkylation Reaction (eq 2). Benzyl bromide (17.1 mg, 0.1 mmol) was added slowly to the same mixture of four phosphines described above. The NMR tube was sealed with Parafilm. After 4 days, the reaction mixture was poured into a small vial, $CDCl_3$ (2 mL) was added to dissolve the white precipitate, and a homogeneous solution formed.

The alkylation of polymer-supported phosphine versus the light fluorous phosphine was conducted by adding benzyl bromide (23.8 μL, 0.2 mmol) to a mixture of polymer-supported phosphine (95.2 mg, 0.2 mmol) from Argonaut and diphenyl(4-(1*H*,1*H*,2*H*,2*H*-perfluorodecyl)phenyl)phosphine **1b** (141.6 mg, 0.2 mmol) in THF (10 mL) in a flask equipped with a magnetic stirrer. After 18 h of gentle stirring, the mixture was filtered and the filtrate was evaporated. The dried beads and the residue from the filtrate were weighed, and a ^{31}P NMR spectrum was recorded on the filtrate residue to calculate the conversion of the light fluorous phosphine to the phosphonium salt.

Reaction of $CDCl_3$ and Water (eq 3). A mixture of **1a** (2.9 mg, 0.011 mmol), **1b** (7.7 mg, 0.01 mmol), **1c** (10.4 mg, 0.011 mmol), and **1d** (14.2 mg, 0.011 mmol) was dissolved in $CDCl_3$ (0.5 mL) in an NMR tube. Deionized water (3.9 mg, 0.22 mmol) was added, resulting in a cloudy solution. Several drops of DMSO-d_6 were added to clarify the mixture. After 36 h, a precipitate had formed, and more $CDCl_3$ was added to clarify the mixture prior to recording the NMR spectrum.

Staudinger Reaction (eq 4). In a small vial, a mixture of the four phosphines as described in the oxidation experiment (0.05 mmol each, 0.2 mmol total) was dissolved in THF-d_8 (1 mL). 4-Azidobenzoic acid (16.3 mg, 0.1 mmol) was dissolved in THF-d_8 (0.5 mL) in an NMR tube. The solution of phosphines was added dropwise to the NMR tube, and a ^{31}P NMR spectrum was recorded about 30 min later, right after the bubbling had stopped. After 15 h, deionized water (18.0 mg, 1 mmol) was added to the NMR tube.

Mitsunobu Reaction (eq 5). These four preparative reactions were conducted simultaneously in separate flasks. 4-(4-Nitrophenyl)butyric acid (74.0 mg, 0.35 mmol), 3,3-dimethylbutanol (30 μL, 0.24 mmol), and one of the four triaryl phosphines **1a**−**d** (0.35 mmol) were dissolved in THF (1 mL). Diisopropyl azodicarboxylate (69 μL, 0.35 mmol) was dissolved in THF (1 mL), and this solution was added slowly to the previous solution. After 3 h at room temperature, the reaction mixture was diluted with ether (50 mL) and washed with aqueous saturated sodium bicarbonate solution. The ether layer was dried with sodium sulfate, concentrated, and dried. Flash column chromatography of the residue on silica gel (4:1 hexane/ethyl acetate) gave a yellow oil, 4-(4-nitrophenyl)butyric acid 3,3-dimethylbutyl ester, which was vacuum-dried and weighed prior to ^{1}H NMR spectroscopic characterization for identity and purity.

Acknowledgment. We thank the National Institutes of Health for funding this work.

Supporting Information Available: Experimental descriptions and copies of the ^{31}P NMR spectra for the competitive experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Aggregation has been demonstrated with metal complexes of fluorous phosphines bearing many more fluorines than those studied here. See: deWolf, E.; Spek, A. L.; Kuipers, B. W. M.; Philipse, A. P.; Meeldijk, J. D.; Bomans, P. H. H.; Frederik, P. M.; Deelman, B. J.; van Koten, G. *Tetrahedron* **2002**, *58*, 3911−3922.