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Fluorous Mitsunobu reagents and reactions

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Abstract—A fully fluorous Mitsunobu reaction procedure is introduced. This employs both existing [$(C_6F_{13}CH_2CH_2C_6H_4)_2PPh$] and new [$C_8F_{17}CH_2CH_2C_6H_4PPh_2$] fluorous phosphines and a new fluorous azodicarboxylate ($C_6F_{13}CH_2CH_2OC(O)N{=}NCOOCH_2CH_2C_6F_{13}$). A procedure involving parallel reactions with representative nucleophiles and alcohols under typical Mitsunobu conditions in THF followed by rapid solid phase extraction (spe) over fluorous silica provides clean products in excellent yields. The fluorous fraction containing the oxidized phosphine oxide and the reduced hydrazide can be readily separated and the starting reagents can be regenerated by appropriate redox reactions in high yield for reuse.

1. Introduction

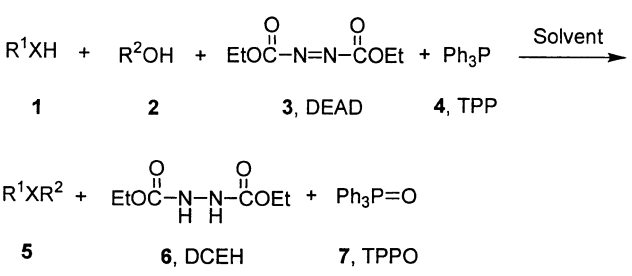
Fluorous methods for synthesis and separation are poised to move from a relatively small, specialized community into the mainstream of organic synthesis.[1] Early fluorous techniques were based on liquid–liquid separations, and these techniques are increasing in importance in catalysis and other areas.[2] Typically, a large number of fluorines (39 and up) is used to ensure high solubility of the fluorous component in a suitable highly fluorinated solvent. In 1997, we reported the first solid–liquid separations based on fluorous silica gel (silica gel with a fluorocarbon bonded phase).[3] Solid–liquid separations are operationally convenient, and relatively few fluorines are needed to effect a simple binary separation of a mixture into 'fluorous' and 'non-fluorous' (that is, organic) fractions.[4] The efficiency of the separations over fluorous reverse phase silica gel enables the use of fluorous reagents and catalysts with lower molecular weight and improved solubility in organic solvents.[5] A recent 'New Tools in Synthesis' article highlights fluorous silica gel and its uses in fluorous synthesis techniques.[6a]

The usefulness of fluorous methods in mainstream synthesis depends on the availability of a diverse assortment of proven reagents, catalysts, tags, protecting groups and scavengers. A partial list of useful fluorous compounds includes a wide assortment of fluorous phosphines[2] and tin reagents[7] as well as an increasing assortment of oxygen[8] and nitrogen[4,6b] protecting groups.

Herein we describe new fluorous dialkylazodicarboxyates and we use these in combination with known and new fluorous phosphines to perform a fluorous Mitsunobu reaction. After a standard solution phase Mitsunobu coupling, all the reagent-derived products can be separated from the desired organic products by rapid filtration through fluorous silica gel. The fluorous byproducts can be separated from each other and reconverted to the starting reagents for reuse. We have recently learned that Dobbs and McGregor-Johnson have also made the same fluorous azodicarboxylate and used it in some Mitsunobu reactions. They used this reagent with triphenylphosphine and separated the fluorous hydrazine by the complementary method of liquid–liquid extraction.[9] This leaves the substitution product contaminated with triphenylphospine oxide; however, highly fluorinated phosphines that could complement a liquid–liquid separation are already known.[2,6]

Eq. (1) shows a generic Mitsunobu reaction of an acidic pronucleophile **1** and an alcohol **2** promoted by diethylazodicarboxylate **3** (DEAD) and triphenylphosphine **4** (TPP).[10] This reaction produces the coupled product **5** along with dicarboethoxyhydrazine **6** (DCEH) and triphenylphosphine oxide **7** (TPPO). The lack of atom economy detracts somewhat from large scale applications, but the Mitsunobu reaction has been enduringly popular for small scale and

The Mitsunobu Reaction



(1)

Keywords: fluorous; Mitsunobu; solid phase extraction; triphenylphosphine; diethylazodicarboxylate.

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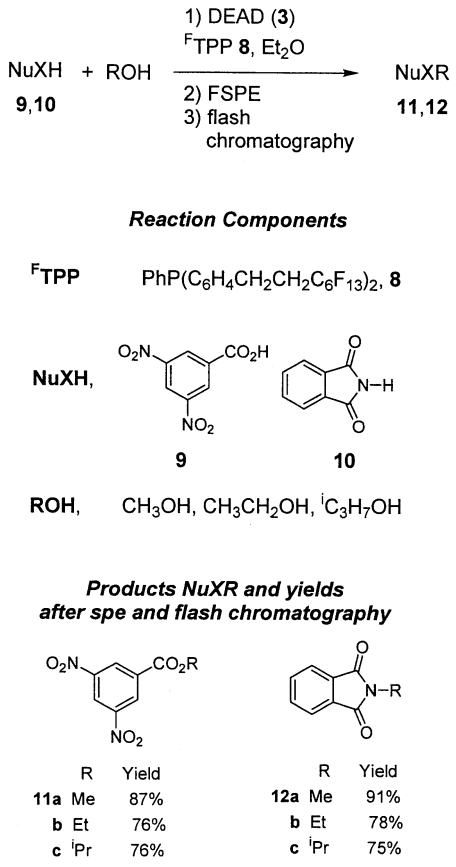


Figure 1. Mitsunobu reactions with fluorous phosphine **8** and DEAD.

discovery chemistry because of its scope, stereoselectivity and mild reaction conditions. The separation of the reagent-derived byproducts from the desired coupled products is almost invariably the most time- and resource-consuming part of the Mitsunobu reaction.

To avoid chromatography, an assortment of separation-friendly Mitsunobu reagents have been introduced. Both polymer-bound phosphines[11] and azodicarboxylates[12] have been used, though large excesses are needed for convenient rates and conversions. And the two polymeric reagents presumably cannot be used together since their interaction would be prevented by phase isolation. Suitably substituted reagents can be removed by acid–base extractions (either directly[13] or after chemical activation[14]) or by decomposition to volatile products. Residual reagents and byproducts can also be polymerized for removal by filtration in a technique called 'impurity annihilation'.[15] These methods allow solution phase reactions, but they require extra reaction chemistry to effect the separation. This potentially adds time, limits scope, and renders difficult or impossible the recycling of the reagents. The fluorous Mitsunobu reactions and reagents described herein offer an appealing solution to the nagging separation problems of the Mitsunobu reaction without compromising the reaction itself.

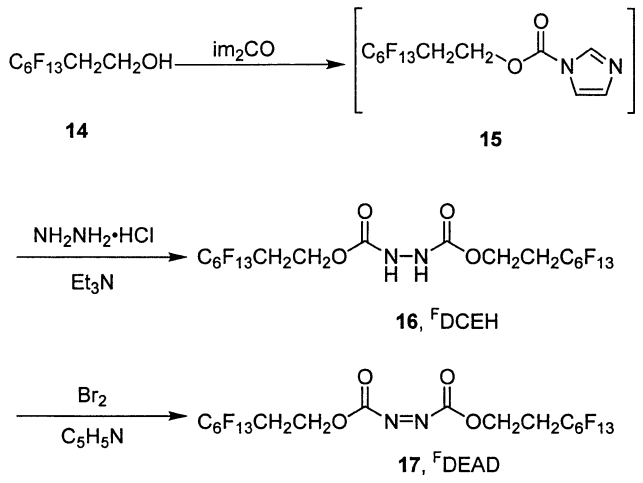
2. Results and discussion

A fully fluorous Mitsunobu reaction requires both a fluorous phosphine and a fluorous azodicarboxylate. A number of fluorous analogs of triphenylphosphine (abbreviated as ^{F}TPP) were already available in our group,[5] and these provided a ready departure point for Mitsunobu chemistry. Based on retention times on a fluorous hplc column, we initially selected phosphine **8** $PhP(C_6H_4CH_2CH_2C_6F_{13})_2$ (Fig. 1) with one unsubstituted phenyl ring and two substituted rings bearing perfluorohexyl groups insulated by ethylene spacers. Fluorous phosphines with longer chains or with three fluorous phenyl rings are also available, but hplc studies[5] suggested that the longer retentions and added molecular weight of these analogs was not needed for solid phase extraction (spe) separations. The molecular weight of **8** is 954.

The fluorous phosphine **8** was paired with the classical DEAD reagent **3** and this combination was then tested for its applicability in Mitsunobu reactions. Esterification of 3,5-dinitrobenzoic acid and N-alkylation of phthalimide with methanol, ethanol and isopropanol were conducted, and the results of this series of experiments are shown in Fig. 1.

Reactions with 3,5-dinitrobenzoic acid **9** were conducted by adding a solution of ^{F}TPP **8** (1 equiv.) and the alcohol (2 equiv.) in ether to a solution of DEAD **3** (1 equiv.) and 3,5-dinitrobenzoic acid (1 equiv.) in ether.[16] This order of addition is hereafter called Procedure A. Reactions with phthalimide **10** were conducted by adding a solution of DEAD **3** (1 equiv.) in THF to a solution of phthalimide (1 equiv.), ^{F}TPP **8** (1 equiv.), and the alcohol (2 equiv.). This order of addition is called Procedure B. After 12–16 h, the solvent was evaporated and the crude reaction mixture (~200 mg) was taken up in methanol and charged onto 2 g of homemade[17] fluorous silica gel. Elution with 10 mL of 80% MeOH/water gave a mixture of the Mitsunobu adducts **11** or **12** along with dicarboethoxyhydrazine (DCEH) **6**. While the fluorous solid phase extraction completely removed the fluorous phosphine oxide **13** $PhP(O)(C_6H_4CH_2CH_2C_6F_{13})_2$ from **11** or **12**, chromatography was needed to remove the hydrazine **6**. The isolated yields of **11** or **12** after normal silica gel chromatography are shown in the bottom of Fig. 1 and range from 75 to 91%. These results clearly show that fluorous phosphine **8** is effective in typical Mitsunobu reactions.

The new fluorous DEAD reagent **17** (hereafter called '^{F}DEAD', pronounced 'eff-dead') required to complement the fluorous phosphine was synthesized as shown in Scheme 1. 2-Perfluorohexyl ethanol **14** was treated with 1,1′-carbonyldiimidazole (1.2 equiv.) at room temperature in THF. Quenching with water and extraction with ether provided a crude product (presumably imidazolide **15**), which was directly reacted with hydrazine hydrochloride and triethylamine. The fluorous hydrazine **16** was isolated as a white powder in 85% yield after standard chromatography. Oxidation of **16** with iodosobenzene diacetate[18] was not clean, but **17** was produced smoothly on exposure of **16** to bromine and pyridine in dichloromethane.[19] Standard workup and concentration of the dichloromethane gave the ^{F}DEAD reagent **17** as a yellow solid (molecular weight 810) in quantitative yield. The purity of **17** was excellent as judged



Scheme 1.

by ^{1}H, ^{13}C and ^{19}F NMR spectroscopy, and hence it was used without further purification in the following Mitsunobu reactions. A solid sample of ^{F}DEAD **17** has been stored at ambient temperature for several months without apparent decomposition, and a solution of **17** in $CDCl_3$ (0.02 M) did not deteriorate over 2 weeks as assayed by ^{1}H NMR spectroscopy.

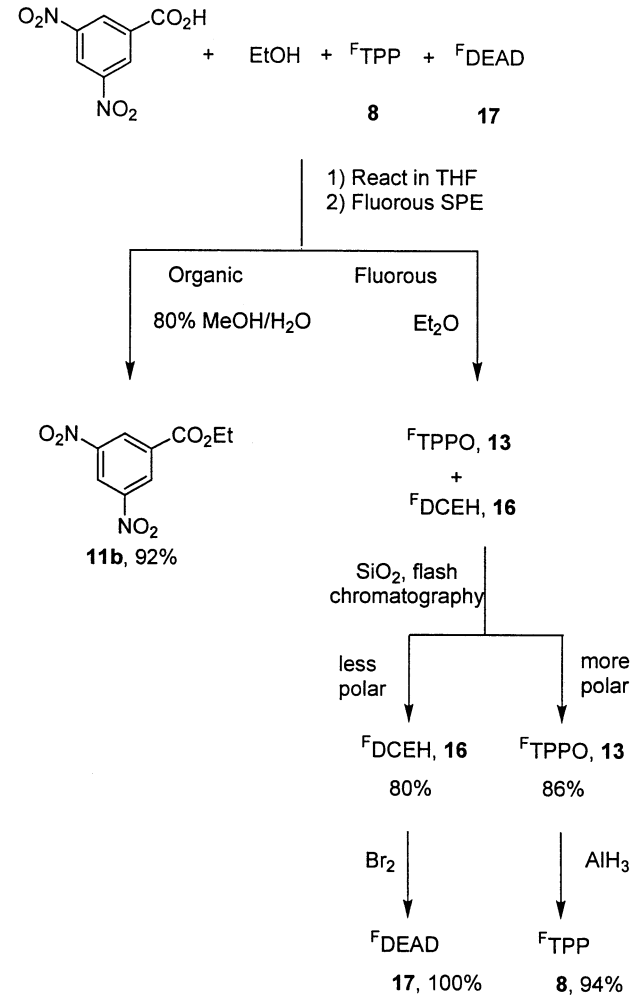


Figure 2. Fluorous Mitsunobu reaction with separation of fluorous byproducts and recycling.

To test the reactivity of the ^{F}DEAD reagent **17** in Mitsunobu reactions and to investigate the possibility of separating the fluorous phosphine oxide and hydrazine byproducts, we reacted it with 3,5-dinitrobenzoic acid **9**, ethanol and ^{F}TPP **8** (Fig. 2) by Procedure A. After about 16 h, the solvent was evaporated, the crude reaction mixture (~200 mg) was taken up in MeOH and loaded on to 2 g of fluorous silica. Elution with 80% MeOH gave the Mitsunobu adduct **11a** in 92% yield free of any impurities as judged by GC-MS analysis and ^{1}H NMR spectroscopy. Further elution with ether gave a mixture of the fluorous phosphine oxide **13** and the fluorous hydrazine **16** (^{F}DCEH). This fluorous byproduct mixture was readily separated on normal silica gel by eluting with 3:2 hexane/EtOAc. The less polar hydrazine **16** emerged first and was isolated in 80% yield; the more polar phosphine oxide **13** followed in 86% yield.

The ease of separation of the fluorous reagent-based byproducts **13** and **16** is handy because the reagents can then be recycled. Both the reduction of the fluorous phosphine oxide **13** (with alane[20]) to return **8** and the oxidation of the fluorous hydrazine **16** to regenerate **17** are clean, high yielding reactions.

We next conducted four experiments to test the compatibility of the fluorous Mitsunobu reagents **8** and **17** with each other and with the regular organic reagents triphenylphosphine and DEAD. 3,5-Dinitrobenzoic acid was coupled with MeOH by reacting all four possible combinations of fluorous (^{F}TTP **8** and ^{F}DEAD **17**) and organic reagents (TPP **4**, and DEAD **3**) by Procedure A. After 12 h, the solvent was evaporated and each reaction mixture was individually subjected to an identical fluorous solid phase extraction. The organic fraction from each experiment was concentrated and analyzed by ^{1}H NMR spectroscopy. These four NMR spectra are reproduced in Fig. 3.

In the reaction with both standard reagents (TPP and DEAD), the spe has no effect and the product **11a** is isolated mixed with TPPO **7** and DCEH **6**. With fluorous azodicarboxylate **17** and TPP **4**, the fluorous hydrazine **16** (^{F}DCEH) is retained, but the TPPO **7** passes through with the product **11a**. In the reverse combination (^{F}TPP **8** and DEAD **3**), the fluorous phosphine oxide (^{F}TPPO) **13** is retained but the DCEH **6** passes through. However, in the experiment where both fluorous reagents (^{F}TPP **8** and ^{F}DEAD **17**) were used, both derived fluorous products (^{F}TPPO **13** and ^{F}DCEH **16**) were retained and the pure product **11a** eluted. These results provide compelling evidence of the simplicity and effectiveness of the separation of fluorous compounds from organic ones on fluorous silica.

Several parallel experiments were conducted to explore the scope of these fluorous reagents with a representative selection of simple alcohols and nucleophiles. These parallel experiments are enabled by the fluorous spe since all the reaction mixtures can be purified in just a few minutes. Nine experiments combining three nucleophiles (3,5-dinitrobenzoic acid, phthalimide and *N*-(*t*-butoxycarbonyl)–*p*-toluene sulfonamide[21]) with three different alcohols (MeOH, allyl alcohol and *p*-fluorobenzylalcohol) were

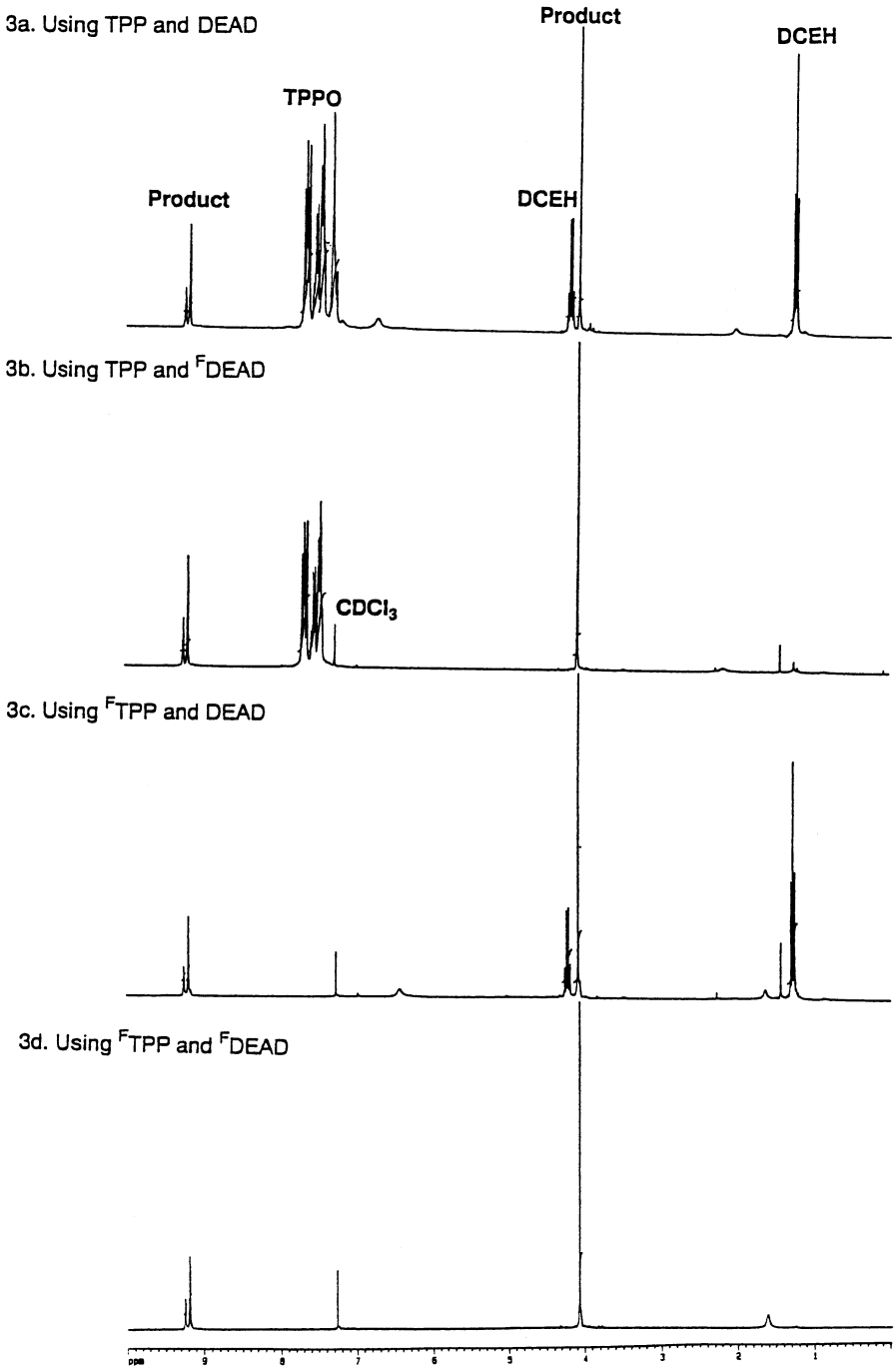
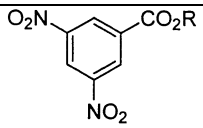
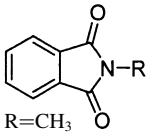
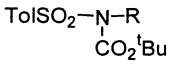
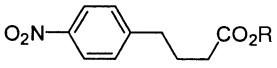


Figure 3. Mitsunobu reactions of 3,5,-dinitrobenzoic acid and methanol with all possible combinations of TPP, DEAD, ^{F}TPP and ^{F}DEAD. (a) Using TPP and DEAD, (b) Using TPP and ^{F}DEAD, (c) Using ^{F}TPP and DEAD, (d) Using ^{F}TPP and ^{F}DEAD.

conducted as usual (Procedure A was used for the acid and B was used for the imide and sulfonamide). After fluorous spe, the solvent was evaporated and the organic product was weighed and analyzed by GC-MS and ^{1}H NMR spectroscopy. The products from *p*-fluorobenzylalcohol reactions were also analyzed by ^{19}F NMR spectroscopy with the fluorine atom serving as an internal standard. Results are summarized in Table 1, entries 1–9.

The results of the six reactions with 3,5-dinitrobenzoic acid and phthalimide (entries 1–6) were highly satisfactory; yields of products ranged from 75–93% and in five of six cases the GC chromatogram exhibited only a single peak. In the sixth case (entry 3), the product was 91% pure. The two products from *p*-fluorobenzyl alcohol (entries 3, 6) exhibited single resonances in their ^{19}F NMR spectra; no CF_3 or CF_2 resonances from the fluorous products were evident. However, the results with *N*-(*t*-butoxycarbonyl)-*p*-toluenesulfonamide (entries 7–9) were not fully satisfactory. The reaction with MeOH (entry 7) occurred in 100% conversion, but the reaction with allyl alcohol was only about 41% complete (entry 8). No conversion at all was observed with *p*-fluorobenzyl alcohol (entry 9).

Table 1. Products, structures, conversions, yields and GC purities of fluorous Mitsunobu reactions

Entry	Structure	Procedure[a]	Conversion (%)[b]	Yield (%)[c]	Purity (%)[d]
					
(1)	R=CH_3	A	100	93	100
(2)	R=$CH_2CH{=}CH_2$	A	100	85	100
(3)	R=*p*-$FC_6H_4CH_2$	A	100	75	91[e]
					
(4)	R=CH_3	B	100	91	100
(5)	R=$CH_2CH{=}CH_2$	B	100	79	100
(6)	R=*p*-$FC_6H_4CH_2$	B	100	75	100[e]
					
(7)	R=CH_3	B	100	N.D.	N.D.
(8)	R=$CH_2CH{=}CH_2$	B	41	N.D.	N.D.
(9)	R=*p*-$FC_6H_4CH_2$	B	0	N.D.	N.D.
(10)	R=CH_3	C	100	90	100
(11)	R=$CH_2CH{=}CH_2$	C	91	95	100
(12)	R=*p*-$FC_6H_4CH_2$	C	96	88	100[e]
					
(13)	R=CH_3	C	100	93	100
(14)	R=$CH_2CH{=}CH_2$	C	100	78	100
(15)	R=*p*-$FC_6H_4CH_2$	C	100	88	100

N.D=Not determined.
[a] (A) ^{F}TPP and alcohol added to ^{F}DEAD and nucleophile; (B) ^{F}DEAD, ^{F}TPP and alcohol added in sequence to nucleophile; (C) nucleophile, alcohol and ^{F}DEAD added in sequence to ^{F}TPP.
[b] Determined by ^{1}H NMR.
[c] Determined by weight.
[d] Determined by GCMS (100% means only a single peak was observed).
[e] Exhibits a single resonance in its ^{19}F NMR spectrum.

The order of addition of reagents is known to affect some Mitsunobu reactions,[22] so a third mode of addition (Procedure C) was investigated with the sulfonamide and the three alcohols. A solution of ^{F}DEAD **17** (1.5 equiv.) in THF was added to a solution of ^{F}TPP **8** (1.5 equiv.) in THF at 0°C to generate the adduct, then the alcohol (1.5 equiv.) was added neat and followed by the *N*-(*t*-butoxycarbonyl)-*p*-toluenesulfonamide (1 equiv.). After 3 h, the solvent was evaporated and the reaction mixture was subjected to spe and the products were analyzed as above. The results from this mode of addition are summarized in Table 1, entries 10–12. Conversions were much improved (91–100%) and yields and purities were excellent. Once again, *N*-*p*-fluorobenzyl-*N*-(*t*-butoxycarbonyl)-*p*-toluene sulfonamide (entry 12) showed a single peak in its ^{19}F NMR spectrum, indicating absence of fluorous impurities in the product.

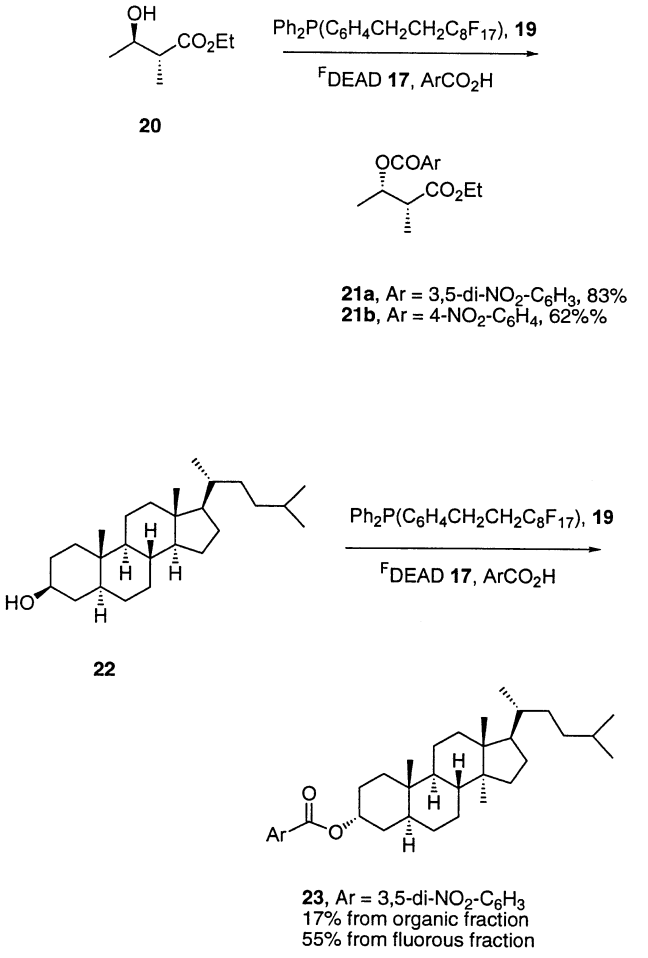
To extend the scope of the fluorous Mitsunobu reaction and verify the generality of Procedure C, we conducted three additional couplings of the same set of alcohols with a new nucleophile, 4-(4-nitrophenyl)butyric acid. The results of these experiments are summarized in entries 13–15. All three reactions were complete and gave pure products (single GC peak) in good (78–93%) yields after spe.

We concluded this work by briefly exploring the possibility for reducing the fluorous content of the DEAD and phosphine reagents, and by verifying that the reactions occurred with inversion. The lighter ^{F}DEAD reagent with a propylene spacer $C_4F_9(CH_2)_3OC(O)N{=}NCOO(CH_2)_3C_4F_9$ **18** was prepared starting from $C_4F_9(CH_2)_3OH$ by the route shown in Scheme 1.[23] The precursor hydrazine (not shown) was tested for spe under the standard conditions with new FluoroFlash™ cartridges that became commercially available towards the end of this work.[24] However, substantial amounts (>10%) of the hydrazine broke through the column during the fluorophobic pass. A homolog of **17** with the same number of fluorines and a propylene spacer behaved similarly to **17** in a few experiments.[23]

In contrast, hplc experiments suggested that a lighter phosphine (MW=754) with only one fluorous phenyl ring but with a longer fluorous tag ($Ph_2PC_6H_4$–*p*-$(CH_2)_2C_8F_{17}$ **19**) would behave well in separation.[25] This new compound was readily prepared by following the procedure for the lower (C_6F_{13}) homolog[5] (see Section 4), and both it and the derived phosphine oxide (not shown) were well retained during a test fluorophobic pass on FluoroFlash™ silica.

The lighter phosphine **19** was used under the standard

conditions (Procedure A) with ^{F}DEAD **17** for the three coupling reactions shown in Eq. (2). Reaction of *anti*-3-hydroxy-2-methylbutyric acid ethyl ester **20** with 3,5-dinitrobenzoic acid and 4-nitrobenzoic acid produced the expected *syn* (inverted) products **21a**, **b** in 83 and 62% yields after spe over FluroFlash™ silica.[26] However, while the reaction with cholestanol **22** was complete by tlc, only 17% of the inverted product **23** was isolated from the fluorophobic pass. The ^{1}H NMR spectrum of the fluorous fraction showed substantial amounts of the expected product **23** along with the fluorous products. Flash chromatography readily separated this mixture and additional pure **23** was isolated in 55% yield, bringing the total yield to 72%.



(2)

Ester **23** cannot be retained on fluorous silica under these conditions, so it must precipitate on the column during the fluorophobic pass, and then redissolve and elute during the fluorophilic pass. In turn, this suggests that the spe procedure may be limited by precipitation when highly hydrophobic substrates are produced.[27] However, even when this happens, the desired product is not lost and it should be readily separable from the fluorous products by traditional chromatography in the vast majority of cases.

3. Conclusions

Fluorous Mitsunobu reactions with ^{F}TPPs **8** and **19** and ^{F}DEAD **17** are exceptionally convenient to conduct and workup. While all three procedures that have been tested are useful, Procedure C entailing sequential addition of the nucleophile, the alcohol and the ^{F}DEAD to the ^{F}TPP seems to be the most general. Solvent evaporation followed by solid phase extraction over fluorous silica gel provides products that are sufficiently pure to use in subsequent steps without chromatography. The expended fluorous products (^{F}DCEH **16** and ^{F}TPPO **13**) can readily be recovered from the spe column, separated by standard flash chromatography, and reconverted to the ^{F}DEAD and ^{F}TPP reagents. Concurrent work of Dobbs and McGregor-Johnson[9] has shown that ^{F}DCEH **16** can be removed by liquid–liquid extraction, and fluorocarbon-soluble fluorous phosphines are already known,[2,6] so a fully fluorous Mitsunobu procedure with complementary liquid–liquid separation may be close at hand.

These fluorous Mitsunobu reagents and reactions are applicable to chemical discovery exercises such as analog synthesis or natural product synthesis and are especially convenient for solution phase parallel synthesis. The ability to recover and reuse the reagents encourages larger scale use by increasing efficiency. Since the completion of this work, all of the components of these fluorous Mitsunobu reactions (reagents and silica) have been made commercially available by Fluorous Technologies, Inc.,[28] so reagent or silica synthesis is no longer a barrier for those wishing to try these reactions.

4. Experimental

4.1. Procedure for reduction of fluorous phosphine oxide (13)[20]

A solution of alane–*N*,*N*-dimethylamine complex (0.5 M in toluene, 6.24 mL, 3.12 mmol) was slowly added to a solution of **13** (2.02 g, 2.08 mmol) in toluene (20 mL). After stirring at 90°C for 3 h, the reaction mixture was cooled to room temperature, quenched with methanol (3 mL) and passed through a short column of celite. The celite column was then washed with hot THF and the washings were added to the filtered reaction mixture, which was concentrated and subjected to silica gel chromatography (20:1 hexane/ethyl acetate) to obtain **8** (1.87 g, 94%).

4.2. Mitsunobu reactions of 3,5-dinitrobenzoic acid promoted by fluorous phosphine 8 and DEAD

These were carried out by Procedure A (see below) with fluorous phosphine **8** (200 mg, 0.21 mmol), alcohol (0.42 mmol), DEAD (33 μL, 0.21 mmol) and 3,5-dinitrobenzoic acid (44 mg, 0.21 mmol). All the products are known and CAS Registry numbers are provided: Methyl 3,5-dinitrobenzoate, [2702-58-1]; Ethyl 3,5-dinitrobenzoate, [618-71-3]; Isopropyl 3,5-dinitrobenzoate, [10477-99-3].

4.3. *N*-Alkylation of phthalimide using fluorous phosphine 8 and DEAD

These were done by Procedure B (see below) with DEAD (33 μL, 0.210 mmol), phthalimide (30 mg, 0.210 mmol),

alcohol (0.420 mmol) and fluorous phosphine **8** (200 mg, 0.420 mmol). All the products are known and CAS Registry numbers are provided: *N*-Methylphthalimide, [550-44-7]; *N*-Ethylphthalimide, [5022-29-7]; *N*-Isopropylphthalimide, [304-17-6].

4.3.1. Bis(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)hydrazine dicarboxylate (16). 3,3,4,4,5,5,6,6,7,7,8,8,8-Tridecafluoro-1-octanol **14** (10 g, 27.5 mmol) was slowly added to a solution of 1,1′-carbonyldiimidazole (5.35 g, 33 mmol) in THF (80 mL). After stirring for 30 min at room temperature, the crude reaction mixture was taken up in ether (200 mL) and quenched with water (40 mL). The aqueous layer was further extracted with ether (3×20 mL). The organic layers were combined and dried with magnesium sulfate. The solvent was removed under reduced pressure and the residue was dried under high vacuum. The crude imidazolide **15** was taken up in THF (14 mL) and hydrazine monohydrochloride (942 mg, 13.75 mmol) and triethylamine (9.6 mL, 68.75 mmol) were added at room temperature. After 3 d, the reaction mixture was quenched with water (50 mL) and extracted with ether (3×50 mL). The organic layers were combined, dried with magnesium sulfate and concentrated. Flash column chromatography on silica gel (3:2 hexane/ethyl acetate) gave bis(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)hydrazine dicarboxylate **16** (9.52 g, 85%) as a white solid, mp 105°C: ^{1}H NMR (acetone-d^6) δ 8.48 (b, 2H), 4.32 (t, J=6.1 Hz, 4H), 2.70 (m, 4H); ^{13}C NMR (acetone-d^6) δ 156.2, 121.4–108.3 (m), 57.2, 30.2 (t, J=21.2 Hz); ^{19}F NMR δ −80.6 (6F), −112.9 (4F), −121.4 (4F), −122.4 (4F), −123.0 (4F), −126.3 (4F); IR (thin film): 3271, 1743 cm^{-1}; HRMS calculated 812.0225, found 812.0239.

4.3.2. Bis(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)diazo dicarboxylate 17. The fluorous hydrazine **16** (2.0 g, 2.46 mmol) and pyridine (0.4 mL, 4.92 mmol) were taken up in methylene chloride (25 mL) and the mixture was cooled to 0°C. Bromine (590 mg, 3.69 mmol) was slowly added. The ice bath was removed after the addition and the reaction was vigorously stirred at room temperature for 2 h. The reaction mixture was then diluted with methylene chloride (150 mL) and was washed with sodium sulfite solution, sodium bicarbonate solution, brine and water. The organic layer was dried with magnesium sulfate and concentrated to give bis(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)diazo dicarboxylate **17** as a yellow solid (1.99 g, 100%), mp 61°C: ^{1}H NMR (acetone-d^6) δ 4.87 (t, J=5.9 Hz, 4H), 2.91 (tt, J=5.9, 19 Hz, 4H); ^{13}C NMR (acetone-d^6) δ 161.2, 125–104 (m), 62.7, 31.3 (t, J=21.1 Hz); ^{19}F NMR (acetone d^6) δ −80.6 (6F), −112.9 (4F), −121.3 (4F), −122.3 (4F), −123 (4F), −123.6 (4F), −125.7 (4F); IR (thin film): 1787 cm^{-1}; LRMS 812 (M$^+$+2, 55%), 449 (91%), 327 (85%), 131 (100%).

The following compounds were prepared by similar procedures.

4.3.3. Bis(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononyl)hydrazine dicarboxylate. White solid; mp 98–99°C; ^{1}H NMR (acetone-d^6) δ 8.31 (b, 2H), 4.19 (t, J=6.2 Hz, 4H), 2.41–2.23 (m, 4H), 1.98–1.89 (m, 4H); ^{13}C NMR (acetone-d^6) δ 157.9, 125–110 (m), 64.9, 28.5 (t, J=22.1 Hz), 21.5; ^{19}F NMR δ −80.6 (6F), −113.8 (4F), −121.4 (4F), −122.4 (4F), −122.9 (4F), −125.7 (4F); IR (thin film) 3271, 1741 cm^{-1}; HRMS calculated 840.0554, found 840.0538.

4.3.4. Bis(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononyl)diazo dicarboxylate. Yellow solid; mp 51–52°C; ^{1}H NMR (acetone-d^6) δ 4.66 (t, J=6.1 Hz, 4H), 2.56–2.38 (m, 4H), 2.25–2.16 (m, 4H); ^{13}C NMR (acetone-d^6) δ 161.3, 124.2–105.3 (m), 68.9, 28.2 (t, J=22.0 Hz), 20.7; ^{19}F NMR (acetone-d^6) δ −79.6 (6F), −113.3 (4F), −120.8 (4F), −121.7 (4F), −122.3 (4F), −125 (4F); LRMS 840 (M$^+$+2, 6%), 463 (6%), 436 (15%), 341 (32%), 295 (25%), 91 (100%); IR (thin film) 1783 cm^{-1}.

4.3.5. Bis(4,4,5,5,6,6,7,7,7-nonafluoroheptyl)hydrazine dicarboxylate. White solid; ^{1}H NMR (acetone-d^6) δ 8.34 (b, 2H), 4.21 (t, J=6.2 Hz, 4H), 2.43–2.25 (m, 4H), 2.01–1.91 (m, 4H); ^{13}C NMR (acetone-d^6) δ 157.7, 125–106 (m), 64.6, 28.2 (t, J=21.9 Hz), 21.2; ^{19}F NMR δ −80.8 (6F), −114.0 (4F), −123.8 (4F), −125.6 (4F); IR (thin film) 1730, 3310 cm^{-1}; HRMS calculated 640.0681, found 640.0666.

4.3.6. Bis(4,4,5,5,6,6,7,7,7-nonafluoroheptyl)diazo dicarboxylate (18). Yellow solid; ^{1}H NMR ($CDCl_3$) δ 4.55 (t, J=6.1 Hz, 4H), 2.32–2.13 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 159.9, 124.2–105.3 (m), 67.1, 27.4 (t, J=22.6 Hz), 19.9; ^{19}F NMR ($CDCl_3$) δ −81.6 (6F), −115.1 (4F), −124.9 (4F), −126.6 (4F).

4.3.7. Bis(2,2,3,3,4,4,4-hepatafluorobutyl)hydrazine dicarboxylate. White solid; ^{1}H NMR (acetone-d^6) δ 9.02 (b, 2H), 4.84 (t, J=14.0 Hz, 4H); ^{13}C NMR (acetone-d^6) δ 155.8, 124–109 (m), 60.8 (t, J=26.4 Hz); ^{19}F NMR δ −80.7 (6F), −120.3 (4F), −127.2 (4F); IR (thin film) 1746, 3314 cm^{-1}; HRMS calculated 484.0117, found 484.0104.

4.3.8. Bis(2,2,3,3,4,4,4-hepatafluorobutyl)diazo dicarboxylate. White solid; ^{1}H NMR ($CDCl_3$) δ 4.75 (t, J=12.5 Hz, 4H); ^{13}C NMR ($CDCl_3$) δ 148.1, 124–104 (m), 62.7 (t, J=28.5 Hz); ^{19}F NMR ($CDCl_3$) δ −81.6 (6F), −121.5 (4F), −128.3 (4F).

4.3.9. Bis(4,4,5,5,5-pentafluoropentyl)hydrazine dicarboxylate. White solid; ^{1}H NMR (acetone-d^6) δ 8.30 (b, 2H), 4.20 (t, J=6.2 Hz, 4H), 2.36–2.18 (m, 4H), 1.98–1.89 (m, 4H); ^{13}C NMR (acetone-d^6) δ 157.6, 124–113 (m), 64.6, 27.9 (t, J=21.8 Hz), 21.3; ^{19}F NMR δ −85.1 (6F), −117.7 (4F); IR (thin film) 1739, 3303 cm^{-1}; HRMS calculated 440.0801, found 440.0794.

4.4. Mitsunobu reactions of 3,5-dinitrobenzoic acid promoted by fluorous phosphine 8 and ^{F}DEAD 17 (Procedure A)

A solution of fluorous phosphine **8** (100 mg, 0.105 mmol) and an alcohol (0.105 mmol) in THF (0.5 mL) was slowly added to a solution of ^{F}DEAD **17** (85 mg, 0.105 mmol) and 3,5-dinitrobenzoic acid (15 mg, 0.07 mmol) in THF (0.5 mL). After stirring overnight, the solvent was evaporated from the reaction mixture and the residue was loaded on to 2 g of fluorous silica using methanol. Elution with 80% MeOH (10 mL) gave 3,5-dinitrobenzoyl ester. A second

elution with ether was done to collect the mixture of fluorous phosphine oxide **13** and fluorous hydrazine **16**.

4.4.1. Allyl 3,5-dinitrobenzoate. CAS Registry Number [6183-32-0]; ^{1}H NMR ($CDCl_3$) δ 9.25 (t, J=2 Hz, 1H), 9.19 (d, J=2 Hz, 2H), 6.08 (ddt, J=6.0, 10.4, 16.4 Hz, 1H), 5.49 (dd, J=17.2, 1.3 Hz, 1H), 5.41 (dd, J=10.4, 1.0 Hz, 1H), 4.97–4.95 (m, 2H); LRMS *m/z* (relative intensity) 195 (M^+, 100%), 149 (38%), 75 (56%).

4.4.2. *p*-Fluorobenzyl 3,5-dinitrobenzoate. Mp 124–125°C; ^{1}H NMR δ 9.24 (t, J=2.1 Hz, 1H), 9.15 (d, J=2.1 Hz, 2H), 7.51–7.45 (m, 2H), 7.16–7.09 (m, 2H), 5.45 (s, 2H); ^{19}F NMR ($CDCl_3$) δ −110.8; ^{13}C NMR ($CDCl_3$) δ 163.0 (d, ^1J=247 Hz), 162.3, 148.6, 133.7, 131.0 (d, ^3J=8.4 Hz), 130.4 (d, ^4J=3.1 Hz), 129.5, 122.5, 115.9 (d, ^2J=21.5 Hz), 67.8; ^{19}F NMR ($CDCl_3$) δ −110.8; IR (thin film) 1734, 1548, 1345, 1276, 910 cm^{-1}; LRMS *m/z* (relative intensity) 320 (M^+, 8%), 196 (33%), 109 (100%); HRMS calculated 320.0445, found 320.0445.

4.4.3. General procedure for Mitsunobu reactions of phthalimide promoted by fluorous phosphine 8 and fluorous DEAD 17 (Procedure B). A solution of ^{F}DEAD **17** (85 mg, 0.105 mmol) in THF (0.5 mL) was slowly added to a solution of phthalimide (10 mg, 0.07 mmol), an alcohol (0.105 mmol) and fluorous phosphine **8** (100 mg, 0.210 mmol) in THF (0.5 mL). After stirring overnight, the solvent was evaporated and the residue was loaded on to 2 g of FRPS using methanol. Elution with 80% MeOH (10 mL) provided the *N*-alkyl phthalimide. A second elution with ether (20 mL) gave a mixture of the fluorous phosphine oxide **13** and the fluorous hydrazine **16**.

4.4.4. *N*-Allylphthalimide. CAS Registry Number [5428-09-1]; ^{1}H NMR ($CDCl_3$) δ 7.90–7.84 (m, 2H), 7.80–7.72 (m, 2H), 5.96–5.83 (m, 1H), 5.29–5.19 (m, 2H), 4.32–4.3 (m, 2H); LRMS *m/z* (relative intensity) 187 (M^+, 100%), 169 (53%), 76 (68%).

4.4.5. *N*-(*p*-Fluorobenzyl)phthalimide. CAS Registry Number [318-49-0]; ^{1}H NMR δ 7.87–7.84 (m, 2H), 7.74–7.70 (m, 2H), 7.46–7.40 (m, 2H), 7.04–6.96 (m, 2H), 4.82 (s, 2H); ^{19}F NMR ($CDCl_3$) δ −113.1; LRMS *m/z* (relative intensity) 255 (M^+, 100%), 237 (29%), 122 (63%), 76 (34%).

4.5. General procedure for Mitsunobu reactions of *N*-(*t*-butoxycarbonyl)-*p*-toluene sulfonamide promoted by fluorous phosphine 8 and fluorous DEAD 17 (Procedure C)

A solution of fluorous DEAD **17** (85 mg, 0.105 mmol) in THF (0.5 mL) was added to a solution of fluorous phosphine **8** (100 mg, 0.105 mmol) in THF (0.5 mL) at 0°C. Alcohol (0.105 mmol) was added neat followed by a solution of *N*-(*t*-butoxycarbonyl)-*p*-toluene sulfonamide (19 mg, 0.07 mmol) in THF (0.5 mL). After stirring at room temperature for 3 h the solvent was evaporated from the reaction mixture and the residue was loaded onto 2 g of fluorous silica using methanol. Elution with 80% MeOH/H_2O (10 mL) to give *N*-alkyl-*N*-(*t*-butoxycarbonyl)-*p*-toluenesulfonamide. A second elution with ether was done to collect a mixture of the fluorous phosphine oxide **13** and the fluorous hydrazine **16**.

4.5.1. *N*-Methyl-*N*-(*t*-butoxycarbonyl)-*p*-toluenesulfonamide. Oil; ^{1}H NMR δ 7.78 (d, J=8.2 Hz, 2H), 7.32 (d, J=8.1 Hz, 2H), 3.36 (151.2, 3H), 2.45 (s, 3H), 1.36 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 144.2, 137.1, 129.3, 127.6, 84.1, 33.3, 27.8, 21.6; IR (thin film) 1729, 1359, 1297, 1158 cm^{-1}; LRMS *m/z*(relative intensity) 185 (22%), 155 (18%), 91 (100%), 65 (32%); HRMS calculated ($M-C_4H_7$) 230.0487, found 230.0491.

4.5.2. *N*-Allyl-*N*-(*t*-butoxycarbonyl)-*p*-toluenesulfonamide. Oil; ^{1}H NMR ($CDCl_3$) δ 7.81–7.79 (m, 2H), 7.32–7.29 (m, 2H), 5.94 (ddt, J=5.9, 10.1, 17 Hz, 1H), 5.33 (dd, J=1.0, 17.1 Hz, 1H), 5.25 (dd, J=1, 10.3 Hz, 1H), 4.45 (d, J=5.6 Hz, 2H), 2.45 (s, 3H), 1.35 (s, 9H); IR (thin film) 1729, 1359, 1154 cm^{-1}; LRMS *m/z* (relative intensity) 210 (2%), 155 (17%), 91 (100%); HRMS calculated ($M-C_4H_8$) 255.0565, found 255.0556.

4.5.3. *N*-(*p*-Fluorobenzyl)-*N*-(*t*-butoxycarbonyl)-*p*-toluenesulfonamide. Oil; ^{1}H NMR δ 7.58–7.56 (m, 2H), 7.45–7.41 (m, 2H), 7.26–7.23 (m, 2H) 7.07–7.00 (m, 2H), 5.00 (s, 2H), 2.42 (s, 3H), 1.32 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 162.3 (d, ^1J=244 Hz), 151.0, 144.2, 136.9, 133.3, 130.1 (d, ^3J=8.0 Hz), 129.1, 127.8, 115.3 (d, ^2J=21.3 Hz), 84.5, 48.9, 27.8, 21.5; ^{19}F NMR ($CDCl_3$) δ −115.2; IR (thin film) 174, 1511, 1153, 912 cm^{-1}; LRMS *m/z* (relative intensity) 281 (2%), 206 (48%), 124 (80%), 91 (100%); HRMS calculated ($M-C_5H_9O_2$) 278.0651, found 278.0648.

Mitsunobu reactions of 4-(4-nitrophenyl)butyric acid promoted by fluorous phosphine **8** and fluorous DEAD **17** were carried out using Procedure C (see above).

4.5.4. Methyl 4-(4-nitrophenyl)butyrate. Oil; ^{1}H NMR ($CDCl_3$) δ 8.16 (d, J=8.6 Hz, 2H), 7.35 (d, J=8.6 Hz, 2H), 3.69 (s, 3H), 2.77 (t, J=7.7 Hz, 2H), 2.36 (t, J=7.3 Hz, 2H), 1.99 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 173.4, 149.2, 146.4, 129.2, 123.6, 51.6, 34.8, 33.0, 25.9; IR (thin film) 1732, 1520, 1347, 911 cm^{-1}; LRMS *m/z*(relative intensity) 223 (M^+, 66%), 192 (33%), 150 (76%), 74 (100%), 59 (15%); HRMS calculated 223.0845, found 223.0844.

4.5.5. Allyl 4-(4-nitrophenyl)butyrate. Oil; ^{1}H NMR ($CDCl_3$) δ 8.16 (d, J=8.7 Hz, 2H), 7.35 (d, J=8.6 Hz, 2H), 5.92 (ddt, J=5.9, 10.4, 16.3 Hz, 1H), 5.33 (ddt, J=1.4, 1.4, 17.1 Hz, 1H), 5.26 (ddt, J=1.05, 1.05, 10.4 Hz, 1H), 4.60–4.58 (m, 2H), 2.78 (t, J=7.7 Hz, 2H), 2.39 (t, J=7.3 Hz, 2H), 2.05–1.96 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 172.5, 149.2, 146.3, 132.0, 129.2, 123.5, 118.2, 65.0, 34.8, 33.2, 25.9; IR (thin film) 1731, 1521, 1347, 911 cm^{-1}; LRMS *m/z* (relative intensity) 249 (M^+ 53%), 208 (100%), 116 (76%); HRMS calculated 249.1001, found 249.1008.

4.5.6. *p*-Flurobenzyl 4-(4-nitrophenyl)butyrate. Oil; ^{1}H NMR ($CDCl_3$) δ 8.18–8.13 (m, 2H), 7.37–7.27 (m, 4H), 7.08–6.99 (m, 2H), 5.09 (s, 2H), 2.76 (t, J=7.6 Hz, 2H), 2.39 (t, J=7.4 Hz, 2H), 2.05–1.95 (m, 2H); ^{19}F NMR

($CDCl_3$) δ −112; ^{13}C NMR ($CDCl_3$) δ 172.6, 162.5 (d, ^1J=245 Hz), 149.1, 146.3, 133.5 (d, ^2J=19.4 Hz), 131.6 (d, ^4J=3 Hz), 130.2 (d, ^3J=11.0 Hz), 129.1, 115.1, 65.4, 34.7, 33.1, 25.8; ^{19}F NMR ($CDCl_3$) δ −112.2; IR (thin film) 1731, 1605, 1517, 1346, 1227, 913 cm^{-1}; LRMS *m/z* (relative intensity) 317 (26%), 208 (9%), 109 (100%); HRMS calculated 317.1064, found 317.1066.

4.5.7. Bis-phenyl-[4-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorooctyl)phenyl]phosphane (19). A solution of *t*-BuLi (1.7 M in pentane, 1.95 mL, 3.32 mmol) was added slowly to 1-bromo-4-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-tridecafluoro-octyl)benzene (1 g, 1.66 mmol) in ether (130 mL) at −40°C. After 1 h at −40°C, chlorodiphenylphosphine (0.36 mL, 1.99 mmol) was added; the reaction mixture was warmed to room temperature and stirred overnight. Then the reaction mixture was quenched with water (10 mL). The ether layer was separated. The aqueous layer was further extracted with ether (3×10 mL). The ether layers were then combined, dried with magnesium sulfate and concentrated under reduced pressure. TLC and ^1H NMR analysis showed predominantly phosphine oxide. The crude phosphine oxide was subjected to reduction with alane as described above to get bis-phenyl-[4-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorooctyl)phenyl]-phosphane as a white solid, 0.88 g, 75% yield from the fluorous bromobenzene; mp 76–77°C; ^1H NMR ($CDCl_3$) δ 7.37–7.30 (m, 12H), 7.24–7.21 (m, 2H), 2.98–2.93 (m, 2H), 2.51–2.33 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 139.8, 137.2 (d, J_{PC}=10.5 Hz), 135.6 (d, J_{PC}=10.5 Hz), 134.3 (d, J_{PC}=19.7 Hz), 133.7 (d, J_{PC}=19.4 Hz), 128.8, 128.6, 128.5, 121.4–106.7 (m, C_8F_{17}), 32.7 (t, J_{FC}=22.0 Hz), 26.2; ^{19}F NMR ($CDCl_3$) δ −79.5 (3F), −113.4 (2F), −120.2–−120.7 (6F), −121.5 (2F), −122.2 (2F), −124.9 (2F); ^{31}P NMR ($CDCl_3$) δ −4.8; HRMS calculated 708.0847, found 708.0875.

4.6. Mitsunobu reactions with hydroxy ester 20 and phoshine 19

Alcohol **20** (10.4 mg, 0.07 mmol), 3,5-dinitrobenzoic acid (30 mg, 0.14 mmol), ^{F}phosphine **19** (100 mg, 0.14 mmol), ^{F}DEAD **17** (114 mg, 0.14 mmol) and THF (2.5 mL) were combined as in Procedure A. After stirring at room temperature for 1 d, the reaction mixture was quenched with saturated $NaHCO_3$ solution. The aqueous layer was extracted with ether (3×20 mL). The organic layers were combined, dried with magnesium sulfate and concentrated. The crude reaction mixture was loaded on to a FluoroFlash™ column (containing 2 g of fluorous silica) using 0.6 mL of THF. Fluorous solid phase extraction was done as described above.

4.6.1. 3,5-Dinitrobenzoic acid *syn*-2-ethoxycarbonyl-1-methyl propyl ester (21a). Oil; yield 83%; ^1H NMR (500 MHz, $CDCl_3$) δ 9.24 (b, 1H), 9.14 (d, *J*=0.8 Hz, 2H), 5.56–5.51 (m, 1H), 4.23–4.17 (m, 2H), 2.87–2.82 (m, 1H), 1.46 (d, *J*=6.3 Hz, 3H), 1.32 (d, *J*=7.0 Hz, 3H), 1.27 (t, *J*=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 173.1, 161.7, 148.6, 134.0, 129.4, 122.4, 74.0, 60.9, 44.2, 17.4, 14.2, 12.3; IR (thin film) 2254, 1732, 1549, 1345 cm^{-1}; LRMS *m/z* (relative intensity) 340 (M^+, 6%), 296 (45%), 195 (51%), 149 (29%), 83 (52%), 75 (100%); HRMS calculated 340.0910, found 340.0907.

4.6.2. 4-Nitrobenzoic acid *syn*-2-ethoxycarbonyl-1-methyl propyl ester (21b). Oil; yield 62%; ^1H NMR ($CDCl_3$) δ 8.23–8.24 (m, 2H), 8.19–8.14 (m, 1H), 5.49–5.41 (m, 1H), 4.20–4.06 (m, 2H), 2.83–2.74 (m, 1H), 1.40 (d, *J*=6.4 Hz, 3H), 1.28 (d, *J*=7.1 Hz, 3H), 1.20 (t, *J*=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 173.3, 163.9, 150.5, 135.7, 130.7, 123.5, 72.9, 60.8, 44.4, 17.5, 14.2, 12.2; IR (thin film) 2254, 1727, 1277 cm^{-1}; LRMS *m/z* (relative intensity) 295 (M^+, 12%), 279 (11%), 150 (100%), 104 (36%), 83 (52%), 75 (100%); HRMS calculated 295.1063, found 295.1056.

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23. The following DEAD reagents ($ROC(O)N{=}NCO_2R$) and hydrazines ($ROC(O)NHNHCO_2R$) were also prepared by the route in Scheme 1: $R{=}C_3F_7CH_2{-}$, $C_4F_9(CH_2)_3{-}$, and $C_6F_{13}(CH_2)_3{-}$. This last reagent is the propylene spacer analog of **17**, and gave similar results in the reactions of methanol (succeeds) and allyl alcohol (fails) with $TolSO_2NHBoc$ by Procedure A (Table 1, entries 7 and 8).
24. Control experiments showed that the FluoroFlash™ cartridges were superior to the homemade silica in terms of loading and separation, and we now routinely use these cartridges for fluorous spe work.
25. Compare the following retention times under the standard hplc conditions described in Ref. 5: $Ph_2PC_6H_4{-}p{-}(CH_2)_2C_6F_{13}$, 13.9 min, $Ph_2PC_6H_4{-}p{-}(CH_2)_2C_8F_{17}$ **19**, 25.0 min, $PhP{-}(C_6H_4{-}p{-}(CH_2)_2C_6F_{13})_2$ **8**, 29.8 min. The derived phospine oxides eluted at 10.6, 22.5, and 28.3 min, respectively.
26. An authentic sample of the anti isomer was prepared by acylation of **20**, resonances from this product could not be detected in the crude ^1H NMR spectrum of **21a**.
27. The results also suggest the precipitation may be at least partly responsible for separation of the hydrophobic fluorous products as well. However, again we know by hplc and other control experiments that the fluorous products are strongly retained under these conditions (see Ref. 25), so the fluorous silica is not just behaving as a filter.
28. Fluorous Technologies, Inc., Harmarville, PA, www.fluorous.com.