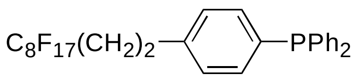
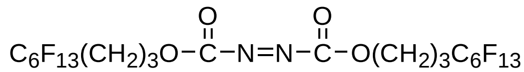
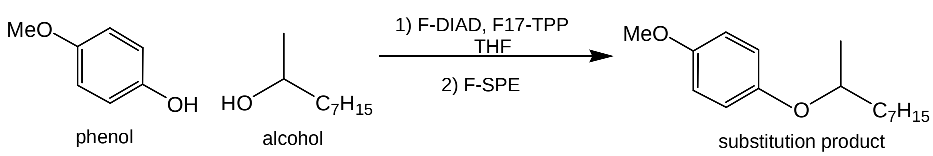




F017039		F026100	
Diphenyl-[4-(1*H*,1*H*,2*H*,2*H*-perfluorodecyl)phenyl]phosphine		*bis*(1*H*,1*H*,2*H*,2*H*,3*H*,3*H*-Perfluorononyl) azodicarboxylate	
Chemical Formula:	$C_{28}H_{18}F_{17}P$	Chemical Formula:	$C_{20}H_{12}F_{26}N_2O_4$
Formula Weight:	708.40	Formula Weight:	838.29
Abbreviation:	F17-TPP	Abbreviation:	F-DIAD
CAS Number:	462996-04-9	CAS Number:	462996-01-6
Appearance:	White, free-flowing solid; mp 76–77 °C	Appearance:	Yellow solid; mp 51–52 °C
Soluble in:	Dichloromethane, methanol, THF, ethyl acetate, and many other organic solvents	Soluble in:	Dichloromethane, methanol, THF, ethyl acetate, and many other organic solvents
Stability:	Similar to PPh_3, can be handled in air	Stability:	Store below –15 °C and away from light

Why Fluorous? The Mitsunobu reaction is the most popular method for direct substitution of alcohols.[1] Typically, the reaction between an acidic pronucleophile and an alcohol is promoted by an azodicarboxylate (DEAD or DIAD) and triphenylphosphine (TPP). Separation of the substitution product from one or more of the reagents or reagent-derived products is often problematic. Resin-bound reagents are available, but large excesses are prescribed, large volumes of wash solvents are needed, and the simultaneous use of two resin-bound reagents is not possible. F17-TPP and F-DIAD are used in traditional solution phase Mitsunobu chemistry.[2] All reagents and reagent-derived products are reliably separated from the substitution product by performing a quick fluorous solid phase extraction over Fluoro*Flash*® silica gel (F-SPE). The “one size fits all” feature of the F-SPE is attractive as development and purification times are minimized, especially in a parallel setting. Illustrated is an especially challenging substitution of a 2°-alcohol with a phenol.

TYPICAL PROCEDURE:[2]



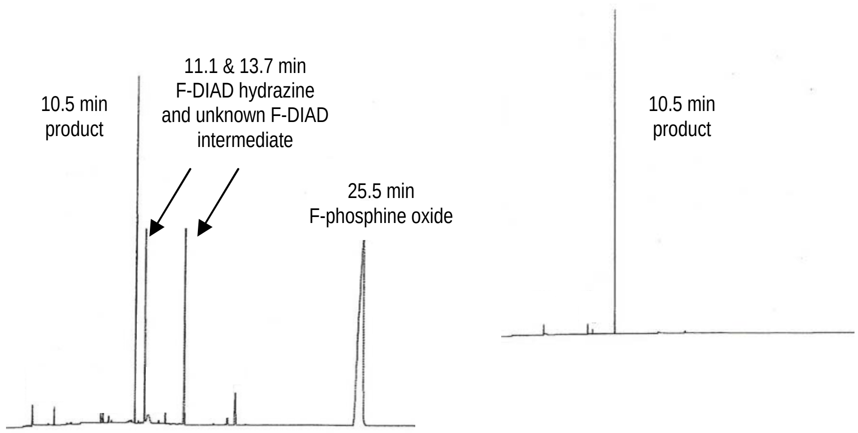
50% yield
97% GC purity

Materials Needed	**Quantity**
Alcohol	35 mg, 0.24 mmol
Phenol	37 mg, 0.30 mmol
F-DIAD	251 mg, 0.30 mmol
F17-TPP	213 mg, 0.30 mmol
THF (dry)	2 mL
DMF (not dry)	0.5 mL
Ether	10 mL
1M NaOH	2 x 10 mL
Fluoro*Flash*® SPE cartridge	1 x 5 g
MeOH:H_2O, 80/20	20 mL

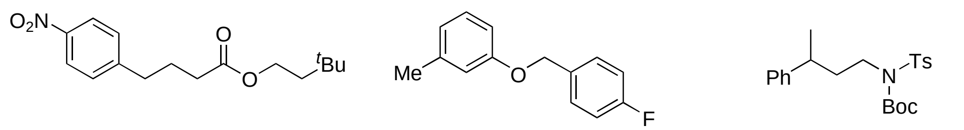
Stepwise Procedure:

1) Drop F-DIAD in THF (1 mL) into a solution of alcohol, phenol and F17-TPP in THF (1 mL);
2) Stir 3 h at room temperature;
3) Dilute reaction mixture with ether and wash with 1 M aq. NaOH solution to remove the excess phenol;
4) Dry (optional) and concentrate the ether solution;
5) Take up residue in DMF and charge to pre-conditioned F-SPE cartridge;
6) Elute cartridge with MeOH:H_2O and concentrate eluent to give 30.4 mg, 50% yield of product.

GC Chromatograms of the crude reaction mixture (left) and the product after F-SPE show how efficiently the reagent-derived products are removed:



Representative Examples[2]



Insider Tips:

- Loading solvents and volumes affect the reliability of the F-SPE in predictable ways. Be sure to read the application note on "Fluorous Solid Phase Extractions" if you are new to this technique.
- The spent F-SPE cartridge can be regenerated by washing with THF, then reconditioning according to the above application note.
- The base wash is optional and is used here to remove unreacted phenol. Or, you can use an acid scavenger or a basic ion exchange resin.
- The product of this Mitsunobu reaction is slightly volatile and evaporates under prolonged vacuum. For such molecules, better yields can be obtained by diluting the F-SPE eluent with water, extracting with ether, and back-washing with water prior to drying and evaporation.
- Different orders of addition and solvents are commonly used for Mitsunobu reactions. The same procedures for standard solution phase reactions can typically be used with the fluorous reagents. If you have favorite procedure, then just give it a try with the fluorous reagents and F-SPE.

ADDITIONAL OPTIONS:

Mixing and Matching with Resin-Bound Reagents: Either F-DIAD or F-TPP can be used with the complementary resin-bound reagent. Just follow the procedure for the resin bound reagent. After filtration to remove the resin and concentration, conduct the F-SPE as in steps 5 and 6 above.

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