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Fluorous, Chromatography-Free Mitsunobu Reaction

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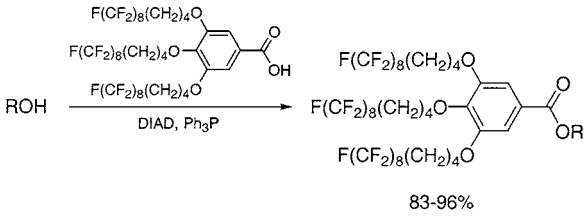
ABSTRACT



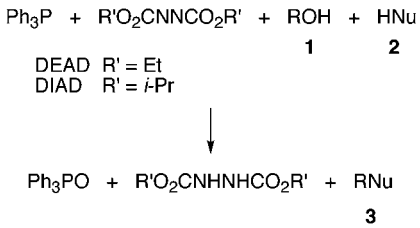
The reaction of secondary and primary alcohols with highly fluorinated 3,4,5-tris(5,5,6,6,7,7,8,8,9,9,10,10,11,11,12,12,12-heptadecafluorododecan-1-yloxy)benzoic acid in the presence of Ph_3P and DIAD in THF at room temperature (fluorous Mitsunobu) resulted in a simple, chromatography-free isolation protocol with excellent yields (83–96%).

The term "fluorous" has been introduced as an analogue to "aqueous" for a highly fluorinated alkane, ether, or tertiary amine.[1] Such compounds are very nonpolar. They commonly form bilayers with organic solvents at room temperature; however, many of these combinations become miscible at elevated temperatures. Many are commercially available.[2]

Fluorous chemistry develops a "parallel universe" of organic molecules[3] and is designed to facilitate separation of catalysts or isolation of products. Many applications of fluorous methodology have been developed over the past few years focusing mainly on the development of fluorous catalysts,[4] fluorous silica gel,[5] or a "tagging" protocol.[4a,6] Fluorous compounds are separable or recoverable with fluorous solvents or fluorous stationary phases.[4] Recent advances include triphase[7] and organic liquid/fluorous solid systems.[8]

Reactions that furnish easily isolable products are of great interest in the development of environmentally friendly technologies. Although the number is increasing, fluorous analogues of traditional organic reactions remain surprisingly scarce.[6,9−14] The Mitsunobu protocol (Scheme 1), which, as initially formulated, involves the reaction of diethyl azodicarboxylate (DEAD, R′ = Et) with triphenylphosphine,[15] has

Scheme 1. Mitsunobu Reaction



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been widely used in organic synthesis, in particular for the inversion of configuration in secondary alcohols (**1**). Synthetic advances have been summarized in reviews,[15,16] and the general mechanistic features have recently received additional insight.[17] Recent improvements in the isolation protocol include the use of solid support, such as (diphenylphosphino)polystyrene.[18] Furthermore, impurity annihilation during aqueous acidic (CF_3COOH) treatment has simplified workup procedures.

The "tagging" methodology, conceptually introduced by Curran and Wipf,[6] is based on the introduction of a fluorous "ponytail" into the product and subsequent exploitation for separation, followed by "detagging". We have found this concept to be well suited for the Mitsunobu reaction,[19,20] where separation usually requires column chromatography.

Achieving high fluorous partition significantly improves separation. For best results, the total fluorine content of fluorous-compatible molecules should be above 60%.[1,5a] The number of perfluoroalkyl groups is also an important factor controlling the partition coefficient, because appropriate shielding of the hydrocarbon domain leads to higher fluorous solubility and higher partition.[21] Considering the above, we have developed a tagging unit from inexpensive gallic acid. Etherification of gallic acid methyl ester with perfluoroalkyl iodide $F(CF_2)_8(CH_2)_4I$[22] and subsequent base hydrolysis gave 3,4,5-tris(5,5,6,6,7,7,8,8,9,9,10,10,11,11,12,12,12-heptadecafluorododecan-1-yloxy)benzoic acid (**2**, Figure 1) with yields

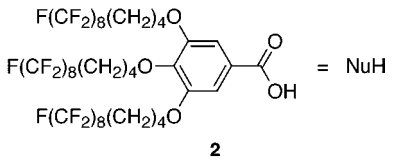

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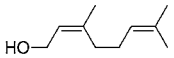
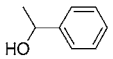
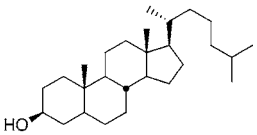
Figure 1.

comparable to those reported earlier.[23] The three perfluoroalkyl ponytails provide appropriate shielding, and a fluorine content of 60.9% for the ArCOO (Nu, MW = 1592) unit exceeds the requirements for good fluorous partition.[1,5a]

The use of fluorous **2** as the nucleophile in the Mitsunobu reaction offers two other advantages: (i) fluorous esters **3** are solids and can be easily isolated by simple crystallization, and (ii) the fluorous part (Nu) can be readily disassociated from the organic products by saponification with excellent yield,[23] thereby providing facile recycling opportunities.

The reactions of several representative alcohols with various functional groups and different carbon skeletons were investigated. All reactions were carried out in the absence of a fluorous solvent, since THF provided good solubility for **2**. The literature does not provide support for any advantage of DEAD over DIAD;[16a] therefore, we choose the less expensive *i*-Pr derivative. The results are summarized in Table 1. Initially, ethanol (entry a) afforded almost

Table 1. Mitsunobu Reaction of Primary and Secondary Alcohols **1** with Tris(heptadecafluorododecanyloxy)benzoic Acid **2**

entry[a]	alcohol **1**	conditions[b]	yield (%) of **3**[c]
a		24 h, r. t. 1.1/0.77/1.0	95
b		40 h, r. t. 2.1/0.77/1.9	83
c		40 h, r. t. 2.0/0.73/1.9	92
d		40 h, r. t. 2.1/0.79/2.0	93
e		40 h, r. t. 2.0/0.75/1.9	96
f		40 h, r. t. 2.0/0.75/1.9	94

[a] All reactions were conducted with DIAD (R′ = *i*-Pr) in THF. [b] Reaction time and stoichiometry were not optimized. Number of equivalents refers to the Ph_3P, **2**, and DIAD with respect to **1**. [c] Calculated with regard to **2**.

complete reaction and quantitative isolation with respect to the fluorous tagging group. The THF solution of tris(heptadecafluorododecanyloxy)benzoic acid **2** (1.0 equiv) and Ph_3P (1.4 equiv), when treated with an excess of ethanol (1.3

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equiv) and DIAD (R′ = *i*-Pr, 1.3 equiv), afforded ester **3a** in 95% yield after 24 h (room temperature) and workup (Scheme 1). Next, alternative isolation procedures were investigated for geraniol (**1b**). This aliphatic alcohol increased the organic (nonfluorous) domain in ester **3b** (fluorous content 56.0%). The reaction was carried out in a similar manner for 40 h. The solvent (THF) was evaporated to dryness, and the remaining solid residue was treated in three different ways. Supercritical CO_2 extraction, which has been applied in a fluorous protocol,[24] gave the **3b**/Ph_3PO mixture in a nearly equimolar ratio. Single extraction of the second portion with a fluorous solvent (perfluorocyclohexane) at room temperature gave ester **3b** (79%), contaminated with Ph_3PO (<7% as established by ^1H NMR). The best results (83%, entry b) were achieved when the crude reaction mixture was crystallized from 1:1 $CHCl_3$/MeOH, which may be classified in the organic liquid/fluorous solid category.[8] Finally, representative racemic (entries c−e) and optically active (entry f) secondary alcohols were examined. Isolation by simple crystallization in an analogous way gave analytically pure esters **3c**−**f** with excellent yields (92−96%).[25] The somewhat lower yield of geranyl ester **3b** (83%) was attributed to poor separation due to the relatively low melting point, rather than to contribution of the increased organic component. The more organic-rich cholestanyl ester **3f** (49.4% fluorous content) was isolated in 94% yield. We have noted that an excess of nucleophile **2** relative to alcohol **1** resulted in isolation of a **2**/**3** mixture, which was difficult to separate. Esters **3a**−**f**, all white solids, were soluble in THF and $CHCl_3$ and characterized by ^1H and ^{13}C NMR spectroscopy and MS. All gave the correct elemental analyses.

A representative alcohol was also disassociated from the fluorous part (Nu) in high yield. A 5α-cholestan-3α-ol was isolated in 94% yield after saponification of the fluorous ester **3f**[26] (obtained from 5α-cholestan-3*β*-ol). Then, the tagging acid **2** was isolated in 78% yield; it was also recycled efficiently in a separate experiment from the combined **3a**−**e** in a one-vessel procedure.

In conclusion, we have applied a highly fluorous nucleophilic partner in the Mitsunobu reaction, which results in a simple, chromatography-free separation protocol and excellent yields.

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Supporting Information Available: Synthetic procedures and ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(25) **Representative Experimental Procedure.** A round-bottom flask was charged with **2** (0.478 g, 0.300 mmol), THF (10 mL), and triphenylphosphine (0.211 g, 0.804 mmol). The mixture was stirred under a nitrogen atmosphere at room temperature. 3-Butyn-2-ol (10% solution in THF (v/v), 0.30 mL, 0.38 mmol) was added to the reaction mixture, followed by DIAD (0.15 mL, 0.76 mmol). The reaction mixture was stirred for 40 h. The solvent was evaporated by rotary evaporation and the residue recrystallized from 1:1 v/v $CHCl_3$/MeOH. A white solid of **3d** was isolated by filtration and dried over P_2O_5 under an oil pump vacuum (0.458 g, 0.278 mmol, 93%).

(26) A round-bottom flask was charged with **3f** (0.500 g, 0.255 mmol), 1:1 v/v THF/methanol (30 mL), and KOH (10 M, 0.6 mL). The mixture was refluxed for 1.5 h, cooled, and acidified with diluted HCl. The solvent was removed by rotary evaporation (water pump). The solid residue was extracted with CH_2Cl_2 and filtered on a silica gel pad. The solvent was removed by rotary evaporation to give 5α-cholestan-3α-ol as a white solid (0.093 g, 0.24 mmol, 94%). The silica gel pad with remaining solid was washed with THF. The solvent was removed by rotary evaporation and crystallized from 1:1 v/v $CHCl_3$/MeOH. Filtration gave **2** (0.317 g, 0.199 mmol, 78%).