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Second-Generation Tags for Fluorous Chemistry Exemplified with a New Fluorous Mitsunobu Reagent†

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ABSTRACT

A new fluorous DEAD reagent bearing two perfluoro-*tert*-butyloxy groups with propylene spacers shows excellent promise for use in fluorous Mitsunobu reactions. Pure target products were obtained in good yields after removing fluorous byproducts by FSPE. The new reagent serves as a prototype for a greener second generation of fluorous reagents bearing tags that are not expected to degrade in the environment to compounds that are highly persistent or that bioaccumulate in higher organisms.

Fluorous techniques for synthesis and separation are finding increasing use in small molecule synthesis, large molecule synthesis, proteomics, and microarraying, among other applications.[1,2] Most techniques are loosely classed as "light" or "heavy" depending on the number and size of fluorous tags.[3] Heavy fluorous molecules typically have 39 or more fluorine atoms, and separations usually involve either fluorous liquids or precipitation. Light fluorous molecules usually have 17 fluorines or fewer and are separated with the aid of a fluorous stationary phase (often fluorous silica gel). Despite the diversity of fluorous reaction and separation methods, almost all fluorous molecules are fashioned from the same two linear perfluoroalkyl groups, perfluorohexyl (C_6F_{13}) and perfluorooctyl (C_8F_{17}), along with a spacer. The combination of the perfluoroalkyl group and the spacer is called a fluorous tag or ponytail.[4]

The initial vision for fluorous chemistry of Horváth and Rábai was as a green method for large-scale chemical production,[5] but much of the subsequent development of the field has been in the direction of small-scale chemical discovery. The original vision still holds promise, but a significant problem has arisen—it is now widely recognized that perfluorocarbons and associated compounds that have no carbon−hydrogen bonds are environmentally persistent because of their exceptional chemical stability.[6] Solvents such as FC-72 (perfluorohexanes) can potentially end up in the atmosphere, where they have exceptionally long half-lives (tens of thousands of years) and significant global warming potential.[7] Alternative hydrofluoroether (HFE) solvents[8a] are much more readily degraded in the environment than perfluorocarbons and can even outperform

† Dedicated to Professor Dr. Daniel Belluš on the occasion of his 70th birthday.

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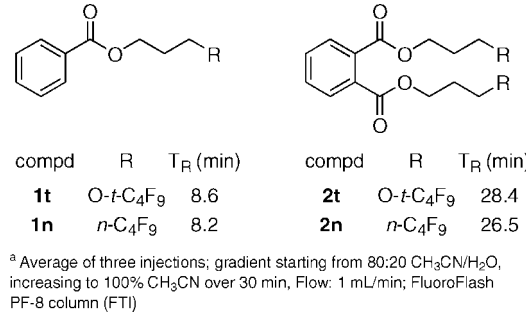
them in some applications.[8b,c]

At first blush, the persistence problem seems limited to fluorous solvents because fluorous reaction components inevitably have a large organic domain that is subject to degradation upon disposal. The concern is that if this degradation occurs in an oxidative environment, then the residual fluorous domain will potentially end up as a perfluorocarboxylic acid.[9] The degraded acids resulting from the current generation fluorous tags, perfluoroheptanoic acid ($C_6F_{17}CO_2H$) and perfluorononanoic acid ($C_8F_{17}CO_2H$), bracket the very well-known perfluorooctanoic acid (PFOA).[10] This and related compounds (for example, perfluorooctane sulfonic acid, PFOS) are persistent in the environment and bioaccumulate in higher organisms.

These environmental concerns can potentially be addressed by using smaller perfluoroalkyl groups, and many materials applications now focus on perfluorobutyl groups.[11] The perfluoro-*tert*-butyl group ranks very high on Rábai's scale of fluorophilicity,[12] and perfluoro-*tert*-butanol (1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)-2-propanol, $(CF_3)_3COH$), has recently become commercially available at a reasonable price.[13] Rábai has fashioned a family of amines bearing one or several fluorous *tert*-butyloxy groups and suggested that they may be useful fluorous tagging reagents (ponytails).[14]

Here we realize the goal of using perfluoro-*tert*-butyloxy groups as fluorous tags for synthesis and separation in a Mitsunobu setting.[15] Taken together, Rábai's results[14] and ours suggest that the pairing of a perfluoro-*tert*-butyloxy group with a suitable spacer could form the basis of a second generation of fluorous tags that will be superior for green chemistry applications to today's first-generation tags.

To quickly probe the ability of the perfluoro-*tert*-butyloxy group to retain compounds on fluorous silica gel, we prepared benzoate ester **1t** and a control bearing a perfluoro-*n*-butyl group **1n** along with the analogous phthalates **2t** and **2n** bearing two *t*-C_4F_9O or *n*-C_4F_9 groups, respectively (see Supporting Information). Each sample was injected onto a Fluoro*Flash* PF-C8 HPLC column (4.6 mm × 150 mm) with a fluorocarbon bonded phase.[16] The samples were analyzed with a standard gradient starting from 80% aqueous acetonitrile, increasing to 100% acetonitrile over 30 min. The retention times of the esters are shown in Figure 1.



compd	R	T_R (min)	compd	R	T_R (min)
1t	O-*t*-C_4F_9	8.6	**2t**	O-*t*-C_4F_9	28.4
1n	*n*-C_4F_9	8.2	**2n**	*n*-C_4F_9	26.5

[a] Average of three injections; gradient starting from 80:20 CH_3CN/H_2O, increasing to 100% CH_3CN over 30 min, Flow: 1 mL/min; FluoroFlash PF-8 column (FTI)

Figure 1. Structures of model compounds **1t**,**n** and **2t**,**n** and retention times on fluorous HPLC.[a]

Pleasingly, the pair of compounds **1t**,**2t** bearing the perfluoro-*t*-butyloxy groups had marginally longer retention times than the controls **1n**,**2n** with perfluoro-*n*-butyl groups. Because the pairs of compounds are not isomers (the "**t**" series compounds have an extra oxygen atom compared to the "**n**" series), it is not safe to conclude that compounds bearing perfluoro-*t*-butyl groups will be better retained than those bearing perfluoro-*n*-butyl groups. Nonetheless, it is clear that the two groups are, at a minimum, roughly comparable in retention behavior. The pair of compounds **2t**/**2n** with the two C_4F_9 groups were also very well retained (T_R > 25 min), and they are accordingly projected to be easily separated from organic compounds by standard fluorous solid phase extraction.

To evaluate prospects for FSPE separations,[2a] we selected the Mitsunobu setting[15] because of its importance in synthesis because Mitsunobu reagents conveniently accommodate two fluorous groups and, finally, because we have made and tested several dozen fluorous Mitsunobu reagents over the past several years.[17] This collection of reagents serves as a convenient calibration for reaction and separation properties of new reagents.

Since spacer effects can be very important in fluorous Mitsunobu reactions, we initially targeted a pair of hydrazides **5e**,**p** with ethylene (**e**) and propylene (**p**) spacers, respectively. Fluorous hydrazide **5p** was synthesized from perfluoro-*t*-butanol in three steps in 66% overall yield as shown in Scheme 1. Specifically, treatment of the alcohol with KOH in THF followed by addition of $BrCH_2CH_2CH_2OH$ gave fluorous alcohol **3p** in 79% yield after distillation. Alcohol **3p** was reacted with carbonyl diimidazole (CDI) to provide an intermediate (presumably imidazolide **4p**),[17b] which was directly reacted with hydrazine monohydrogen chloride and triethylamine. The fluorous hydrazide **5p** was isolated as a

(9) Prevedouros, K.; Cousins, I. T.; Buck, R. C.; Korzeniowski, S. H. *Environ. Sci. Technol.* **2006**, *40*, 32–44.

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(11) For example, 3M reformulated Scotchgard to substitute perfluorobutane sulfonic acid (PFBS) for PFOS: http://en.wikipedia.org/wiki/Scotchgard.

(12) Kiss, L. E.; Kovesdi, I.; Rabai, J. *J. Fluorine Chem.* **2001**, *108*, 95–109.

(13) Ryan Scientific (www.ryansci.com) offers perfluoro-*tert*-butanol 1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)-2-propanol (or nonafluoro-*tert*-butanol, $(CF_3)_3COH$, CAS 2378-02-1) at a price of $3420/kg for 1 kg and $2700/kg for 10 kg.

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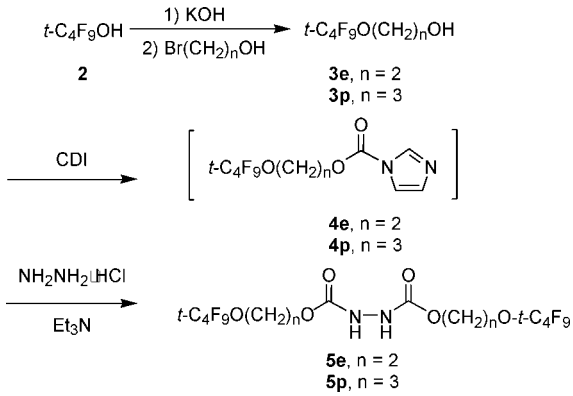
(16) (a) The FHPLC column, FSPE cartridge, and Mitsunobu reagents are commercially available from Fluorous Technologies, Inc. (b) DPC owns an equity interest in this company.

(17) (a) Dandapani, S.; Curran, D. P. *Tetrahedron* **2002**, *58*, 3855–3864. (b) Dandapani, S.; Curran, D. P. *J. Org. Chem.* **2004**, *69*, 8751–8757. (c) Curran, D. P.; Bajpai, R.; Sanger, E. *Adv. Synth. Catal.* **2006**, *348*, 1621–1624.

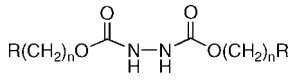
Scheme 1. Synthesis of Spacer Reagents **3e**,**p** and Hydrazides **5e**,**p**



white solid in 83% yield after standard chromatography. Fluorous hydrazide **5e** was synthesized by a similar route starting with $BrCH_2CH_2OH$ and was isolated in 63% overall yield. The simple, high-yielding preparation of alcohols **3e** and **3p** recommends them as general reagents to introduce *t*-C_4F_9O groups with spacers in place.

Hydrazides are the byproducts of Mitsunobu reactions that need to be separated from target products. To evaluate the performance of the new fluorous hydrazides, samples of **5e**, **5p**, and control fluorous hydrazides **5n** (bearing (perfluoro-*n*-butyl)propyl groups) and **6n** (bearing larger (perfluoro-*n*-hexyl)propyl groups) were injected onto FluoroFlash HPLC under the above conditions.

The retention times for these injections are listed in Figure 2. The retention times of **5e** (13.4 min) and **5p** (16.9 min)



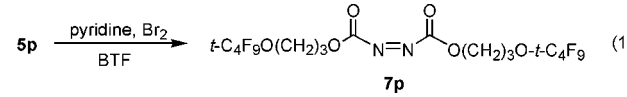
compd	n	R	T_R (min)
5p	3	O-*t*-C_4F_9	16.9
5e	2	O-*t*-C_4F_9	13.4
5n	3	*n*-C_4F_9	15.4
6n	3	*n*-C_6F_{13}	34.7

[a] Same conditions as Figure 1

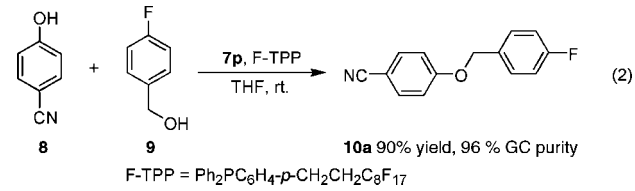
Figure 2. Structures of new (**5p**,**e**) and control hydrazides and retention times on fluorous HPLC.[a]

are much shorter than that of the phthalates **2t** (28.4 min, Figure 1). This is because of the polar hydrazide functionality. The fluorous hydrazide **5p** with propylene spacer showed a retention time of about 1.5 min longer than the control **5n** (15.4 min). As before, the compounds are not isomers, but this result reinforces the conclusion that compounds with O-*t*-C_4F_9 groups will be better retained on fluorous silica gel compared to those with *n*-C_4F_9 groups. We expected the hydrazide with the ethylene spacer **5e** to have a shorter retention time,[17b] and indeed, it eluted about 3.5 min before **5p**. Not surprisingly, hydrazide **6n** with eight more fluorines than the other three compounds shows a significantly longer retention time (34.7 min).

Under these HPLC conditions, compounds with retention times more than about 12 min should be suitable for FSPE separation. We expected the Mitsunobu reagent derived from **5p** to exhibit superior reaction performance to that derived from **5e**,[17b] and conveniently, **5p** was also better retained than **5e**. Thus, the preferred Mitsunobu reagent is clearly **7p** (eq 1), which was produced in quantitative yield by exposure of **5p** to bromine and pyridine in benzotrifluoride ($C_6H_5CF_3$, BTF). The crude bright yellow liquid **7p** obtained upon workup exhibited excellent purity by ^1H NMR analysis and was used as is in subsequent reactions.



The Mitsunobu reaction between 4-cyanophenol **8** and *p*-fluorobenzyl alcohol **9** was chosen as a first test for fluorous DEAD **7p** (eq 2) because its success has been shown to be predicted on the presence of suitable spacers in the fluorous Mitsunobu reagent.[17b] A solution of **7p** (0.42 mmol) in THF (5 mL) was slowly added to a solution of **8** (0.42 mmol), **9** (0.23 mmol), and a fluorous triphenylphosphine ($Ph_2PC_6H_4$-*p*-$CH_2CH_2C_8F_{17}$, F-TPP, 0.42 mmol) in THF (5 mL). After 8 h, the crude mixture was concentrated and the residue taken up in ether and washed with aqueous sodium hydroxide (to remove excess phenol).



The concentrated crude reaction mixture was then loaded onto a 20 g Fluoro*Flash* cartridge[18] with MeOH.[16] With the aid of a new SPE apparatus (see Supporting Information), the cartridge was washed with MeOH/H_2O (80/20) to elute the organic product. The MeOH/H_2O fraction was concentrated and dried to give 4-cyanophenyl 4-fluorobenzyl ether **10a** in 90% yield and 96% GC purity. A second wash with 100% MeOH eluted **5p** and the fluorous triphenylphosphine oxide (F-TPPO) in 95% recovery. Hydrazide **5p** and F-TPPO were separated by flash chromatography. The reagents were reactivated for later use for other experiments.

To explore the scope of the new fluorous DEAD reagent, five different nucleophiles with various pK_a's were coupled with assorted primary and secondary alcohols using **7p** and

(18) This corresponds to about a 3% weight loading of the cartridge. We attempted a similar experiment with a 5 g cartridge (the size used for the standard Mitsunobo reagent with 26 fluorines), but significant breakthrough (~20%) of the fluorous products into the organic fraction was observed. Thus, the presence of fewer fluorines in **7p** (18 fluorines) must be offset by lower loading in the FSPE.

F-TPP. The products were isolated by FSPE as above, and their structures along with yields and purities are summarized in Figure 3.

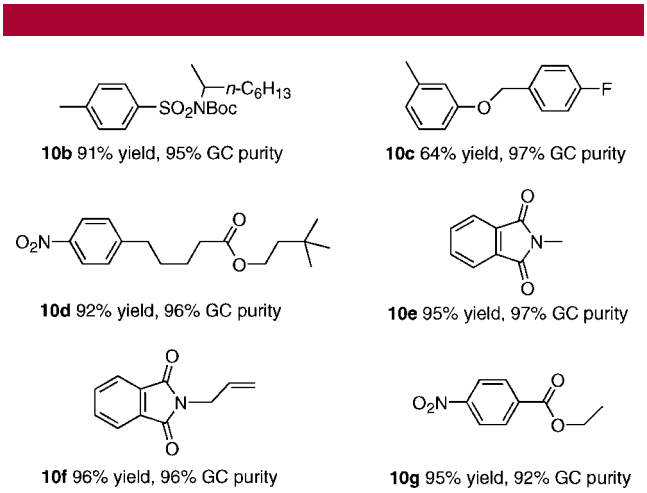


Figure 3. Yield and purities of products from Mitsunobu reactions with **7p**.

In five of the six reactions, including the one with 2-octanol, the yields were higher than 90% and crude product purities were very good (92−97%). The reaction of 3-methylphenol and *p*-fluorobenzyl alcohol provided **10c** in 64% yield, which is comparable to the result with the commercial reagent **6n** (60%).[17b] The moderate yield is presumably due to the relatively high pK_a of 3-methylphenol.

In summary, a new fluorous DEAD reagent **7p** bearing two perfluoro-*t*-butyloxy groups with propylene spacers shows excellent promise for use in fluorous Mitsunobu reactions. Following reactions of assorted nucleophiles and alcohols with **7p** and a fluorous phosphine, we obtained pure target products in good yield after removing fluorous byproducts by FSPE. The FSPEs succeed even though **7p** has eight fewer fluorines than the current commercial reagent **6n**, but this lower fluorine content must be offset by lower loading on FSPE. Reagent **7p** serves as a prototype for a greener second generation of fluorous reagents bearing tags that are not expected to degrade in the environment to compounds that are highly persistent or that bioaccumulate in higher organisms.

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Supporting Information Available: Complete experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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