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Second Generation Fluorous DEAD Reagents Have Expanded Scope in the Mitsunobu Reaction and Retain Convenient Separation Features†

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First generation fluorous DEAD reagent bis(perfluorohexylethyl)azo dicarboxylate ($C_6F_{13}(CH_2)_2O_2CN{=}NCO_2(CH_2)_2C_6F_{13}$, F-DEAD-1) has been shown to underperform relative to diisopropylazodicarboxylate in difficult Mitsunobu reactions involving hindered alcohols or less acidic pronucleophiles (phenols). Two new second generation fluorous reagents bearing propylene spacers instead of the ethylene spacers show expanded reaction scope while retaining the easy fluorous separation features. Byproducts from "half fluorous" reagent perfluorooctylpropyl *tert*-butyl azo dicarboxylate ($C_8F_{17}(CH_2)_3O_2CN{=}NCO_2{}^tBu$, F-DEAD-2) can be removed by fluorous flash chromatography, and byproducts from bis(perfluorohexylpropyl)azo dicarboxylate ($C_6F_{13}(CH_2)_3O_2CN{=}NCO_2(CH_2)_3C_6F_{13}$, F-DEAD-3) can be removed by fluorous solid-phase extraction. The new reagents promise to provide general and complementary solutions for separation problems in Mitsunobu reactions without restricting reaction scope.

Introduction

The Mitsunobu reaction continues to enjoy a privileged role in organic synthesis and medicinal chemistry because of its scope, stereospecificity, and mild reaction conditions.[1] The Mitsunobu reaction involves the condensation of an acidic pronucleophile (R^1XH) and an alcohol (R^2OH) promoted by triphenylphosphine (TPP) and diethylazodicarboxylate (DEAD) or diisopropylazodicarboxylate (DIAD) (eq 1). This reaction produces the

$$R^1XH + R^2OH + \underset{\substack{\text{DEAD, R = Et}\\ \text{DIAD, R = }{}^i\text{Pr}}}{RO_2C{-}N{=}N{-}CO_2R} + \underset{\text{TPP}}{Ph_3P} \quad (1)$$

$$\xrightarrow{\text{solvent}} R^1XR^2 + \underset{\text{DCH}}{RO_2C{-}\overset{H}{N}{-}\overset{H}{N}{-}CO_2R} + \underset{\text{TPPO}}{Ph_3P{=}O}$$

coupled product (R^1XR^2) along with dicarboalkoxy hydrazine (DCH) and triphenylphosphine oxide (TPPO). The application of Mitsunobu reactions in both traditional and solution-phase parallel synthesis is limited by the difficulty involved in isolating the pure product from a crude reaction mixture containing excess and spent reagents.

An assortment of approaches have surfaced for tackling the separation problems in the Mitsunobu reaction at a strategy level, and these approaches have recently been reviewed.[2] Among these, the fluorous approach is attractive because it allows for simple reaction and separation.[3] In many other approaches, additional reactions are required after the Mitsunobu reaction itself in order to effect separation.

We have recently reported that the use of fluorous DEAD reagent **1** (F-DEAD-1) along with fluorous phosphine (F-TPP) enables rapid purification of Mitsunobu reactions by fluorous solid-phase extraction (FSPE) (Figure 1).[4] Concurrently Dobbs and McGregor-Johnson also reported the synthesis and application of **1** in Mitsunobu reactions.[5] In this paper, we identify serious limitations of the first generation reagent **1** relative to the standard (nonfluorous) DIAD (diisopropylazodicarboxylate) reagent. To overcome these limitations, we have synthesized a series of known and new fluorous hydrazides and studied their separation properties by fluorous HPLC. We have also identified the likely reason for the substandard performance of F-DEAD-1. Combining these results, we introduce two improved fluorous DEAD reagents, F-DEAD-2 (**2**) and F-DEAD-3 (**3**), for use in Mitsunobu reactions.

Results and Discussion

Limitations of F-DEAD-1. Despite the success of F-DEAD-1 and F-TPP in promoting several classes of

† Dedicated to Professor Robert K. Boeckman, Jr. in celebration of his 60th birthday.

(1) First report: (a) Mitsunobu, O.; Yamada, M.; Mukaiyama, T. *Bull. Chem. Soc. Jpn*. **1967**, *40*, 935. For reviews, see: (b) Mitsunobu, O. *Synthesis* **1981**, 1. (c) Hughes, D. L. *Org. React*. **1992**, *42*, 335. (d) Wisniewski, K.; Koldziejczyk, A. S.; Falkiewicz, B. *J. Pept. Sci.* **1998**, *4*, 1. (e) Hughes, D. L. *Org. Prep. Proced. Int.* **1996**, *28*, 127.

(2) (a) Dandapani, S.; Curran, D. P. *Chem. Eur. J*. **2004**, *10*, 3130. (b) Dembinski, R. *Eur. J. Org. Chem.* **2004**, 2763.

(3) Recently introduced methods based on cyclodextrin-binding groups also do not require additional reactions. See: (a) Blodgett, J.; Li, T. *Tetrahedron Lett.* **2004**, *45*, 6649. (b) Dandapani, S.; Newsome, J. J.; Curran, D. P. *Tetrahedron Lett*. **2004**, *45*, 6653.

(4) Dandapani, S.; Curran, D. P. *Tetrahedron* **2002**, *58*, 3855.

(5) Dobbs, A. P.; McGregor-Johnson, C. *Tetrahedron Lett.* **2002**, *43*, 2807.

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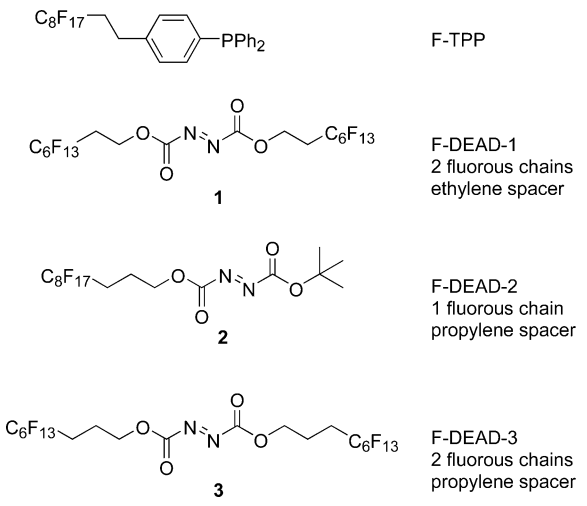
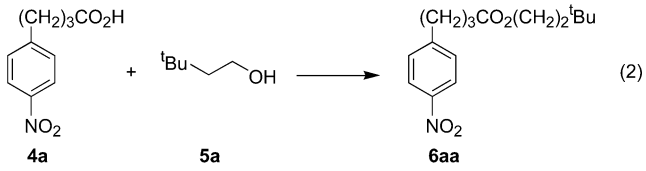


FIGURE 1. First and second generation fluorous Mitsunobu reagents

Mitsunobu reactions,[4,5] we subsequently found that this reagent combination underperforms compared to diisopropylazodicarboxylate (DIAD) and triphenylphosphine (TPP) in some instances. For example, the reaction of 4-(4-nitrophenyl)butyric acid **4a** with 3,3-dimethylbutanol **5a** was problematic with the fluorous reagent combination (eq 2). To isolate the problem, we conducted

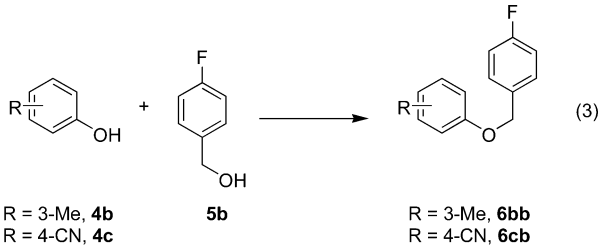


Entry	Phosphine	Azodicar -boxylate	Yield[a]
1	TPP	DIAD	100%
2	F-TPP	F-DEAD-1	0%
3	TPP	F-DEAD-1	0%
4	F-TPP	DIAD	92%

[a]Determined from the ratios of intensities of the GC signals of product **6aa** to the internal standard (undecane) and corrected for response factor differences

four reactions. In the control experiment, the standard reagents TPP and DIAD provided the coupled Mitsunobu product **6aa**[6] in 100% yield as assayed by GC (eq 2, entry 1). In contrast, when this reaction was attempted with the fluorous reagent pair F-DEAD-1 and F-TPP, **6aa** was not detected by GC (eq 2, entry 2). When the reaction was promoted by TPP and F-DEAD-1, **6aa** was again not detected by GC (eq 2, entry 3). However, **6aa** was formed in 92% yield with the reverse combination of F-TPP and DIAD (eq 2, entry 4).

These results suggest that F-DEAD-1 is inferior to DIAD for difficult Mitsunobu reactions. This suggestion was further confirmed by comparing the efficiency of F-DEAD-1 to that of DIAD in coupling phenols. The Mitsunobu coupling of *m*-cresol **4b** with *p*-fluorobenzyl alcohol **5b** gives 76% of the ether **6bb** after flash column chromatography (eq 3, entry 1). However, when this



Entry	Phosphine	Azodicar -boxylate	Product	Yield
1	TPP	DIAD	**6bb**	76%[a]
2	F-TPP	F-DEAD-1	**6bb**	18%[a]
3	F-TPP	F-DEAD-1	**6cb**	98%[b]
4	TPP	DIAD	**6cb**	96%[a]

[a]Purified by flash column on normal silica gel; [b]Purified by FSPE

reaction was attempted with F-TPP and F-DEAD-1, only 18% of the coupled product **6bb** was isolated (eq 3, entry 2). In contrast, the Mitsunobu coupling of the more acidic *p*-cyanophenol **4c** with *p*-fluorobenzyl alcohol **5b** to give the ether **6cb** proceeded in high yields with both F-DEAD-1 (98%) and DIAD (96%) (eq 3, entries 3 and 4). These results suggest that better fluorous Mitsunobu reagents are needed.

To identify improved fluorous DEAD reagents, we synthesized a series of fluorous hydrazides and measured their retention times in fluorous HPLC to evaluate their separation behavior. On the basis of the favorable retention times of their reduced hydrazides, we synthesized two new fluorous DEAD reagents **2** and **3** and found that the reactivities of these two reagents were much better than **1**.

Synthesis of Fluorous Hydrazides. Identification of improved fluorous Mitsunobu reagents started with synthesis of a series of 20 symmetrical and unsymmetrical fluorous hydrazides. The symmetrical fluorous hydrazides **7**−**11** (see Table 3 for structures) were synthesized by previously published procedures.[4] Two different approaches were followed for the design of unsymmetrical fluorous hydrazides. First, following the conventional wisdom that the retention time increases with increase in fluorine content, we synthesized a family of unsymmetrical fluorous hydrazides containing 17−26 fluorine atoms. Second, we probed the retaining effects of nonfluorous lipophilic groups in fluorous chromatography[7,8] by making a series of fluorous hydrazides containing a constant number of 17 fluorines.

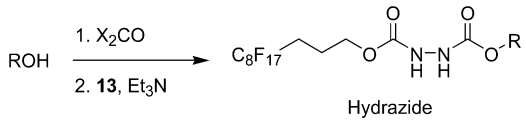
All of the unsymmetrical hydrazides ($R^1OCONHNHCO_2R^2$) were synthesized by condensing a carbazate ($R^1OCONHNH_2$) with a suitable acylating agent (R^2OCOX) derived from the alcohol (R^2OH). The key fluorous carbazate **13** was synthesized by condensing

(6) Throughout the paper, Mitsunobu products are numbered **6xy**, where **x** is the component derived from pronucleophile **4** and **y** is the component derived from alcohol **5**.

(7) Curran, D. P. In *Handbook of Fluorous Chemistry*; Gladysz, J. A., Horvath, I., Curran, D. P., Eds.; Wiley-VCH: Wienheim, 2004; Chapter 7, pp 101−128.

(8) Curran, D. P.; Oderaotoshi, Y. *Tetrahedron* **2001**, *57*, 5243.

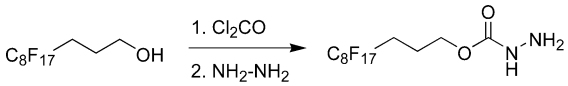
TABLE 1. Synthesis of Hydrazides from Carbazate 13[a]



entry	ROH[b]	hydrazide	yield (%)[c]	X_2CO
1	$CF_3CH_2CH_2CH_2OH$ **14**	**15**	70	im_2CO
2	$C_2F_5CH_2CH_2CH_2OH$ **16**	**17**	45	im_2CO
3	$C_3F_7CH_2CH_2CH_2OH$ **18**	**19**	49	im_2CO
4	^{t}BuCH$_2$CH$_2$OH **20**	**21**	73	im_2CO
5	TMSCH$_2$CH$_2$OH **22**	**23**	69	im_2CO
6	4-^{t}Bu-*c*-C$_6$H$_{10}$ **24**	**25**	75	Cl_2CO
7	(*c*-C$_6$H$_{11}$)$_2$CHOH **26**	**27**	92	Cl_2CO
8	AdCH$_2$CH$_2$OH **28**	**29**	84	Cl_2CO
9	$C_4F_9CH_2CH_2CH_2OH$ **30**	**31**	67	Cl_2CO
10	CF_3CH_2OH **32**	**33**	93[d]	$(CF_3CH_2O)_2CO$

[a] Yields are unoptimized. [b] TMS = trimethylsilyl; 4-^{t}Bu-*c*-C$_6$H$_{10}$ = 4-(*tert*-butyl)cyclohexyl; *c*-C$_6$H$_{11}$ = cyclohexyl; Ad = 1-adamantyl. [c] Overall yield for two steps. [d] Yield from carbonate.

the chloroformate derived from perfluorooctyl propanol **12** and excess hydrazine (eq 4).[9] Under optimized condi-



(4)

tions, this reaction gave the carbazate **13** in 85−91% yields on a 3 g scale.

The 10 unsymmetrical fluorous hydrazides shown in Table 1 were synthesized from the fluorous carbazate **13**. For example, 4,4,4-trifluorobutanol **14** was first reacted with carbonyl diimidazole (im_2CO), and the resulting crude product (presumably the corresponding imidazolide) was reacted with carbazate **13** and triethylamine to give the fluorous hydrazide **15** in 70% yield. Hydrazides shown in entries 2−5 were synthesized in a similar manner. Unlike the corresponding chloroformates, the imidazolides are not volatile. Hence the im_2CO route is attractive for the small-scale synthesis of hydrazides starting from low molecular weight alcohols. However, the chloroformates are more reactive compared to the corresponding imidazolides,[10] and hence the hydrazides shown in entries 6−9 were prepared from phosgene. Since the alcohols in entries 6−9 have relatively high molecular weights, the chloroformates can be conveniently synthesized even on smaller scales. Hydrazide **33** (entry 10) with the trifluoroethyl group was prepared from bis(2,2,2-trifluoroethyl)carbonate.

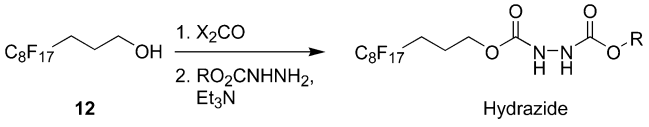
Table 2 shows the synthesis of a series of hydrazides with organic substituents. Since most of the simple carbazates described in Table 2 were commercially available, we synthesized the hydrazides **34**−**38** by reacting the chloroformate or the imidazolide from perfluorooctylpropanol **12** with nonfluorous carbazates.

HPLC Evaluation of Fluorous Hydrazides. All 20 fluorous hydrazides were evaluated by analytical fluorous HPLC. Pure samples were injected onto a commercially

(9) Merkley, N.; Warkentin, J. *Can. J. Chem.* **2000**, *78*, 942.

(10) Typically the reaction of imidazolides and carbazates needed elevated temperatures, whereas the choloroformates reacted with the carbazates at room temperature. See Supporting Information for the experimental details.

TABLE 2. Synthesis of Hydrazides from the Fluorous Alcohol 12



entry	R	carbazate	hydrazide	yield (%)	X_2CO
1	CH_3CH_2	**39**[a]	**34**	96	im_2CO
2	$(CH_3)_3C$	**40**[a]	**35**	97	Cl_2CO
3	$PhCH_2$	**41**[a]	**36**	98	im_2CO
4	$CF_3CH_2CH_2$	**42**[b]	**37**	90	Cl_2CO
5	*c*-C$_6$H$_{11}$	**43**[b]	**38**	93	Cl_2CO

[a] Commercially available. [b] Synthesized from the corresponding alcohol by the route shown in eq 4.

available Fluoro*Flash* PF-C8 HPLC column (4.6 mm × 150 mm) with a fluorocarbon bonded phase. All samples were analyzed under a gradient starting from 80% aqueous acetonitrile, increasing to 100% acetonitrile over 30 min, and then maintaining isocratic conditions with 100% acetonitrile up to 40 min (Conditions A). The results of these experiments are summarized in Table 3. For reference, nonfluorous compounds typically elute with the solvent front under these conditions.

Entries 1−5 of Table 3 show the retention times of the series of symmetrical fluorous hydrazides with differing perfluoroalkyl groups and spacers. Hydrazide **9** having 18 fluorine atoms and propylene spacers showed a retention time of 10.2 min (entry 3), whereas the other two hydrazides **7** (10 fluorines, entry 1) and **8** (14 fluorines, entry 2) with fewer fluorine atoms showed retention times under 5 min. Although the spacer lengths differ for **7**, **8**, and **9**, the retention times are predominantly controlled by the number of fluorine atoms. Fluorous hydrazides **10** and **11** have the same number of fluorine atoms (26) but differ in spacer lengths. Despite its lower percent-fluorine content, the propylene spacer analogue **11** (30.2 min, entry 5) has a retention time longer than that of the ethylene spacer hydrazide **10** (26.6 min, entry 4). The mechanism of retention of fluorous compounds in fluorous silica gel is not fully understood, but there is evidence that lipophilic groups of fluorous compounds increase retention time in fluorous HPLC.[7,8]

All of the remaining hydrazides (entries 6−20) have the same R^1 group ($C_8F_{17}CH_2CH_2CH_2$) with differing R^2 groups. The hydrazides in entries 6−11 have different fluoroalkyl groups R^2. Hydrazides **33**, **37**, and **15** (entries 6−8) having 20 fluorine atoms with different spacer lengths had retention times between 14.5 and 16.0 min. These are all higher than 10.2 min observed for **9** containing 18 fluorine atoms (entry 3). Following the general trend, hydrazides **17** and **19** with 22 and 24 fluorine atoms showed higher retention times of 20.9 and 26.7 min, respectively (entries 9 and 10). Fluorous hydrazide **31** with 26 fluorine atoms (C_8F_{17} and C_4F_9 groups) showed the highest retention time of 30.7 min (entry 11), which is close to the retention time of 30.2 min observed for its isomer **11** (entry 5, two C_6F_{13} groups).

Entries 12−20 of Table 3 show the retention time of unsymmetrical fluorous hydrazides with the same R^1 group ($C_8F_{17}CH_2CH_2CH_2$) but different organic (nonfluorous) domains as R^2. The retention times of this class of fluorous hydrazides were spread over a range of roughly

TABLE 3. Retention Times of Fluorous Hydrazides $R^1OCONHNHCO_2R^2$ [a]

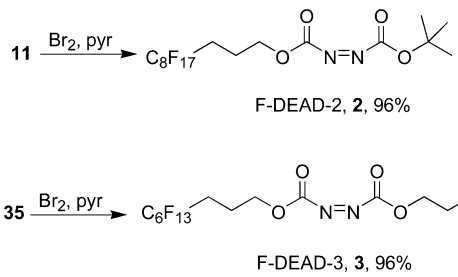
entry	hydrazide	R^1	R^2	total no. of F atoms	MW (daltons)	retention time (min)
1	**7**	$C_2F_5CH_2CH_2CH_2$	$C_2F_5CH_2CH_2CH_2$	10	440	3.2
2	**8**	$C_3F_7CH_2$	$C_3F_7CH_2$	14	484	4.3
3	**9**	$C_4F_9CH_2CH_2CH_2$	$C_4F_9CH_2CH_2CH_2$	18	640	10.2
4	**10**	$C_6F_{13}CH_2CH_2$	$C_6F_{13}CH_2CH_2$	26	812	26.6
5	**11**	$C_6F_{13}CH_2CH_2CH_2$	$C_6F_{13}CH_2CH_2CH_2$	26	840	30.2
6	**33**	$C_8F_{17}CH_2CH_2CH_2$	CF_3CH_2	20	662	15.1
7	**37**	$C_8F_{17}CH_2CH_2CH_2$	$CF_3CH_2CH_2$	20	676	14.5
8	**15**	$C_8F_{17}CH_2CH_2CH_2$	$CF_3CH_2CH_2CH_2$	20	690	16.0
9	**17**	$C_8F_{17}CH_2CH_2CH_2$	$C_2F_5CH_2CH_2CH_2$	22	740	20.9
10	**19**	$C_8F_{17}CH_2CH_2CH_2$	$C_3F_7CH_2CH_2CH_2$	24	790	26.7
11	**31**	$C_8F_{17}CH_2CH_2CH_2$	$C_4F_9CH_2CH_2CH_2$	26	840	30.7
12	**34**	$C_8F_{17}CH_2CH_2CH_2$	CH_3CH_2	17	608	12.2
13	**36**	$C_8F_{17}CH_2CH_2CH_2$	$PhCH_2$	17	670	11.8
14	**35**	$C_8F_{17}CH_2CH_2CH_2$	^{t}Bu	17	636	15.5
15	**38**	$C_8F_{17}CH_2CH_2CH_2$	*c*-C_6H_{11}	17	662	15.1
16	**25**	$C_8F_{17}CH_2CH_2CH_2$	4-^{t}Bu-*c*-C_6H_{10}	17	718	20.4 (*trans*)[b] 21.3 (*cis*)[b]
17	**29**	$C_8F_{17}CH_2CH_2CH_2$	$AdCH_2CH_2$	17	742	18.4
18	**27**	$C_8F_{17}CH_2CH_2CH_2$	(*c*-C_6H_{11})$_2$CH	17	758	22.1
19	**23**	$C_8F_{17}CH_2CH_2CH_2$	$TMSCH_2CH_2$	17	680	18.8
20	**21**	$C_8F_{17}CH_2CH_2CH_2$	^{t}BuCH_2CH_2	17	664	17.8

[a] Fluoro*Flash* Analytical HPLC column; 80:20 acetonitrile/water (t = 0 min) to 100% acetonitrile (t = 30 min) to 100% acetonitrile (t = 40 min); ELS detection. [b] Assigned on the basis of peak intensity; *trans*:*cis* ratio of 2.5:1 was determined by ^{1}H NMR spectroscopy.

10 min with the shortest time of 11.8 min observed for the benzyl hydrazide **36** (entry 13) and the longest time of 22.1 min for the (dicyclohexyl)methyl hydrazide **27** (entry 18). Replacing the ethyl group (**34**, 12.2 min, entry 12) with the *tert*-butyl group (**35**, 15.5 min, entry 14) resulted in approximately a 3 min increase in retention time. Both cyclohexyl hydrazide **38** (entry 15) and *tert*-butyl hydrazide **35** (entry 14) had roughly the same retention time of about 15 min. However, the retention time of the 4-(*tert*-butyl)cyclohexyl hydrazide **25** was around 20 min (entry 16). The *cis* and *trans* isomers of **25** had approximately a 1 min difference in retention time with *cis* (21.3 min) eluting after *trans* (20.4 min). The adamantyl hydrazide **29** had a retention time of 18.4 min (entry 17). Fluorous hydrazides with 3,3-dimethylbutyl (**21,** entry 20) and 2-(trimethylsilyl)ethyl (**23**, entry 19) domains had a retention time of roughly 18 min, indicating that replacing a carbon with a silicon atom has a negligible effect.

A good rule of thumb is that compounds with retention times of 12 min or higher under Conditions A can be separated from organics by FSPE.[7,11,12] Fluorous compounds with retention times of greater than 20 min can be very easily separated from organics with a minimum amount of fluorous silica gel. Fluorous compounds having retention times between 12 and 20 min can still be separated from organics, but the FSPE begins to resemble a fluorous chromatography. As the retention time decreases, loading of the mixture must be done with a minimum amount of solvent to avoid breakthrough and multiple fractions have to be collected and analyzed. On the basis of these guidelines and ease of synthesis, we chose hydrazide **11** with two perfluorohexylpropyl groups (30.2 min, entry 5) for applications in FSPE mode and the hydrazide **35** with one perfluorooctylpropyl group and a *tert*-butyl group (15.5 min, entry 14) for applications in fluorous chromatography mode.

New Fluorous Mitsunobu Reagents and Reactions. Fluorous hydrazides **11** and **35** were oxidized to the respective fluorous azodicarboxylates F-DEAD-2 (**2**) and F-DEAD-3 (**3**) in 96% yields by bromine and pyridine (eq 5). We next conducted a series of Mitsunobu reactions



(5)

with **2** and **3**. Figure 2 shows the nucleophiles **4a**−**f**, the alcohols **5a**−**f**, and the derived products **6** of all of these reactions, and Table 4 summarizes the results.

To compare the reactivity of the fluorous azodicarboxylates **2** and **3** with that of F-DEAD-1, we repeated the reactions described in eqs 2 and 3 with the new fluorous azodicarboxylate reagents **2** and **3**. To our delight, we found that the reagents **2** and **3** were much better than F-DEAD-1.[13] For example, the coupling of 4-(4-nitrophenyl)butyric acid **4a** and 3,3-dimethyl butanol **5a** proceeded in 99% or 92% yields using **2** (Table 4, entry 1) or **3** (entry 2), respectively, whereas none of the desired product **6aa** was isolated when this reaction was conducted with F-DEAD-1 (eq 2, entry 2). The isolated yields of the ester **6aa** from **2** or **3** compared favorably with the 95% yield obtained from the organic reagents TPP and DIAD (entry 3). Similarly, the coupling of *m*-cresol **4b** and *p*-fluorobenzyl alcohol **5b** to give the ether **6bb** proceeded in 61% or 60% yield using **2** (entry 4) or **3**

(11) Curran, D. P.; Luo, Z. *J. Am. Chem. Soc.* **1999**, *121*, 9069.

(12) Curran, D. P. *Synlett* **2001**, 1488.

(13) For previous examples where spacer affects the reactivity of fluorous compounds, see: (a) Luo, Z.; Williams, J.; Read, R. W.; Curran, D, P. *J. Org. Chem.* **2001**, *66*, 4261. (b) Curran, D. P.; Luo, Z.; Degenkolb, P. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2403. (c) Jiao, H.; Le Stang, 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.

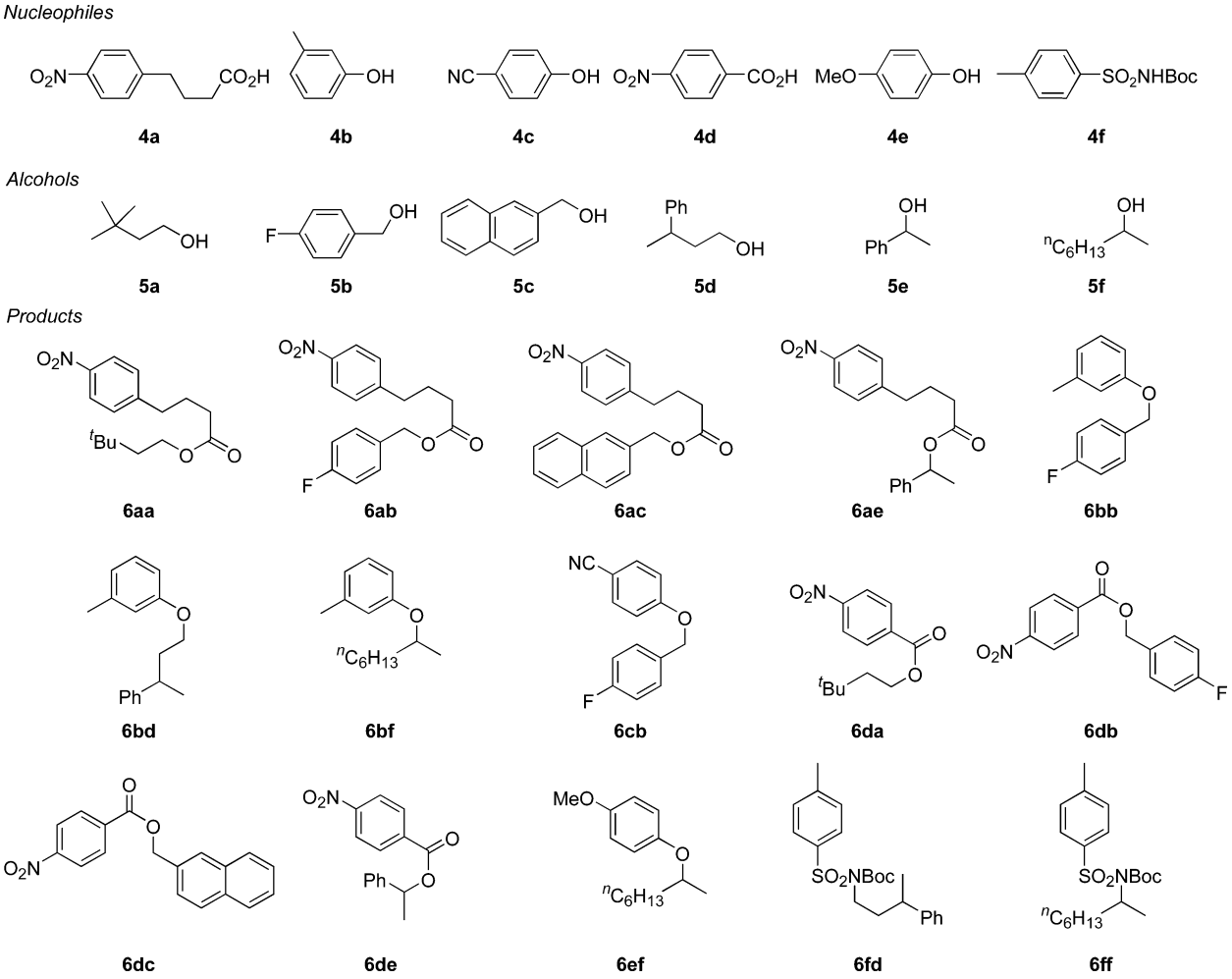


FIGURE 2. Structures of nucleophiles, alcohols, and the Mitsunobu products.

(entry 5), respectively, compared to 18% obtained from F-DEAD-1 (eq 3, entry 2). The isolated yields of the ether **6bb** from using **2** or **3** were about 15% lower than the yield obtained from TPP and DIAD (75%, entry 6).

To explore the scope of the new fluorous DEAD reagents, a representative collection of different classes of pronucleophiles (4-(4-nitrophenyl)butyric acid **4a**, *m*-cresol **4b**, 4-cyanophenol **4c**, 4-nitrobenzoic acid **4d**, 4-methoxyphenol **4e** and *N*-(*tert*-butoxycarbonyl)-*p*-toluenesulfonamide **4f**) were coupled with primary (3,3-dimethylbutanol **5a**, *p*-fluorobenzyl alcohol **5b**, 2-naphthalene methanol **5c**, and 3-phenyl-1-butanol **5d**) and secondary (*sec*-phenethyl alcohol **5e** and 2-octanol **5f**) alcohols using F-TPP and F-DEAD-2 **2** or F-DEAD-3 **3**, and the results are summarized in Table 4.

The aliphatic carboxylic acid 4-(4-nitrophenyl)butyric acid **4a** (entries 7−9) and the aromatic carboxylic acid 4-nitrobenzoic acid **4d** (entries 10−13) both underwent Mitsunobu reactions with F-TPP and **2** or **3**. After FSPE (for **3**) or fluorous flash column (for **2**), the desired ester products were isolated in 84−98% yields with purities ranging from 92% to 99%. The crude reaction mixtures from two of the reactions (entries 11 and 12) clogged the fluorous column and could not be separated. The clogging must have been the result of precipitation of the Mitsunobu products, **6db** and **6dc**, inside the fluorous column during the fluorophobic pass. These two reaction mixtures were not analyzed further.

The electron-poor (4-cyano-, **4c**, entry 14), the electron-rich (4-methoxy-, **4e**, entries 15 and 16), and electro-neutral (3-methyl, **4b**, entries 17 and 18) phenols also participated in fluorous Mitsunobu reactions promoted by **2** or **3**. The reaction in entry 15 represents a particularly challenging Mitsunobu reaction where a less acidic (and hence less reactive)[14] phenol **4e** was reacted with a less reactive secondary alcohol **5f**. This reaction yielded the desired ether **6ef** in 55% yield. Consistent with the previous observations with *m*-cresol **4b** (entries 4−6), the yield of the ether **6ef** was 19% higher when the organic reagents TPP and DIAD were used (entries 15 and 16).

N-(*tert*-Butoxycarbonyl)-*p*-toluenesulfonamide **4f** was efficiently alkylated with primary or secondary alcohols using **3** and F-TPP (entries 19 and 20). Unlike phenols, there was no reagent dependency of yield for the Mitsunobu reactions of *N*-(*tert*-butoxycarbonyl)-*p*-toluenesulfonamide, with both fluorous and control reagents giving 94% yield (entries 20 and 21).

Crude reaction products from reagents **2** and **3** were purified differently. The crude Mitsunobu reaction mixtures (approximately 650 mg) from **3** were purified by

(14) Dodge, J. A.; Trujillo, J. I.; Presnell, M. *J. Org. Chem.* **1994**, *59*, 234.

TABLE 4. Pronucleophiles, Alcohols, Products, Product Yields, and Purities of Mitsunobu Reactions Promoted by Fluorous and Organic Reagents

entry	pronucleophile	alcohol	product	reagents	yield (%)	GC purity (%)
1	**4a**	**5a**	**6aa**	F-TPP + **2**	99[a]	97
2	**4a**	**5a**	**6aa**	F-TPP + **3**	92[b]	99
3	**4a**	**5a**	**6aa**	TPP + DIAD	95[c]	nd
4	**4b**	**5b**	**6bb**	F-TPP + **2**	61[d]	98
5	**4b**	**5b**	**6bb**	F-TPP + **3**	60[b]	97
6	**4b**	**5b**	**6bb**	TPP + DIAD	75[c]	nd
7	**4a**	**5b**	**6ab**	F-TPP + **2**	84[a]	98
8	**4a**	**5c**	**6ac**	F-TPP + **2**	88[a]	92
9	**4a**	**5e**	**6ae**	F-TPP + **2**	96[a]	92
10	**4d**	**5a**	**6da**	F-TPP + **2**	95[a]	98
11	**4d**	**5b**	**6db**	F-TPP + **2**	na	na
12	**4d**	**5c**	**6dc**	F-TPP + **2**	na	na
13	**4d**	**5e**	**6de**	F-TPP + **2**	98[a]	94
14	**4c**	**5b**	**6cb**	F-TPP + **2**	98[d]	100
15	**4e**	**5f**	**6ef**	F-TPP + **3**	55[b]	97
16	**4e**	**5f**	**6ef**	TPP + DIAD	74[c]	nd
17	**4b**	**5d**	**6bd**	F-TPP + **3**	54[b]	99
18	**4b**	**5f**	**6bf**	F-TPP + **3**	55[b]	95
19	**4f**	**5d**	**6fd**	F-TPP + **3**	100[b]	95[e]
20	**4f**	**5f**	**6ff**	F-TPP + **3**	94[b]	96[e]
21	**4f**	**5f**	**6ff**	TPP + DIAD	94[c]	nd

[a] Purified by automated fluorous chromatography over 12+M Biotage cartridge. [b] Purified by FSPE over 5 g FluoroFlash cartridge. [c] Purified by flash column chromatography over normal silica gel. [d] Purified by manual fluorous chromatography over 20 g FluoroFlash cartridge. [e] Determined by LC-MS over C18 column.

FSPE over a 5 g fluorous cartridge.[15] This removed all fluorous products derived from both the Mitsunobu reagents and provided the crude target product **6**. That the retention of hydrazide **35** resulting from **2** was not long enough for removal by FSPE when using 80% MeOH was revealed by substantial (>5%) leaching during the fluorophobic pass of a control FSPE experiment using pure **35**. However, the crude Mitsunobu reaction mixtures (approximately 600 mg or 1.2 g) resulting from **2** were purified by fluorous flash chromatography using commercially available Fluoro*Flash* cartridges (containing 20 g of fluorous silica gel) or using fluorous columns (Biotage; 12+M size, containing approximately 12 g of fluorous silica gel) for automated medium-pressure liquid chromatography.

Mechanistic studies of the Mitsunobu reactions with the different fluorous DEAD reagents **1**−**3** were not undertaken. However, on the basis of the observations reported in this paper, we hypothesize that the rate of proton transfer from the pronucleophile to the betaine formed by the addition of phosphine to the azodicarboxylate is an important factor determining the extent of success of the Mitsunobu reactions.[16] The betaine formed from F-DEAD-1 is less basic because of the ethylene spacer, and hence difficult Mitsunobu reactions such as the ones involving less acidic phenols do not succeed. However, F-DEAD-2 and F-DEAD-3 have propylene spacers, and hence the betaines formed from these reagents are sufficiently basic to allow ready protonation by even less acidic pronucleophiles such as phenols.

Conclusions

We have demonstrated that the retention behavior of fluorous hydrazides on fluorous silica gel can be altered by varying the fluorine content as well as the organic content. Likewise, the reactivity can be tuned by varying the spacer. F-DEAD-1 with an ethylene spacer underperforms in several classes of Mitsunobu reactions with stiff resistance to promote alkylation of less acidic phenols. Both F-DEAD-2 and F-DEAD-3 with propylene spacers promote Mitsunobu reactions of not only phenols but also acids and sulfonamides. Although the yields for less acidic phenol coupling reactions with F-DEAD-2 and F-DEAD-3 are about 15% lower than with TPP and DIAD, pure products can be readily isolated by simple fluorous procedures, whereas the standard reagents must be separated by traditional silica chromatography. With acids and sulfonamides, pure products can be easily isolated in yields comparable to those of the organic reagents TPP and DIAD.

On the basis of these results, we recommend that the use of F-DEAD-1 for Mitsunobu reactions be discontinued. We recommend the light fluorous reagent F-DEAD-2 for applications in parallel or sequential separations with automated fluorous chromatography in a suitable medium-pressure LC instrument. For rapid FSPE isolation of products from all classes of Mitsunobu reactions, we recommend the fluorous reagent F-DEAD-3 in conjunction with F-TPP. These separation-friendly fluorous Mitsunobu reagents will widen the application of Mitsunobu reactions in medicinal chemistry since the major deterrence for conducting parallel Mitsunobu reactions is often the inefficient product isolation encountered with traditional reagents.

Experimental Section

The experimental details of synthesis and full characterization data for fluorous carbazate **13**, all new fluorous hydrazides, and fluorous DEAD reagents are given in Supporting Information. In this section, typical procedures for Mitsunobu reactions and separations with fluorous and organic reagents are exemplified with the coupling of acid **4a** with alcohol **5a** to give the ester **6aa**. The experimental details of synthesis, separation, and full characterization (of new compounds) of other Mitsunobu products are reported in Supporting Information.

4-(4-Nitrophenyl)butyric Acid 3,3-Dimethylbutyl Ester 6aa. (a) With F-TPP and F-DEAD-2. A solution of F-DEAD-2 **2** (450 mg, 0.71 mmol) in THF (5 mL) was slowly added to a solution of 4-(4-nitrophenyl)butyric acid **4a** (98 mg, 0.47 mmol), 3,3-dimethylbutanol **5a** (86 μL, 0.71 mmol), and F-TPP (500 mg, 0.71 mmol) in THF (5 mL) at room temperature. This mode of mixing the Mitsunobu substrates and reagents is also referred to as Procedure B in the earlier paper.[4] All Mitsunobu reactions in this paper were conducted by Procedure B. After stirring at room temperature for 3 h, the reaction mixture was concentrated.

Automated fluorous chromatography was carried out as follows. After loading the crude reaction mixture using THF (1 mL), the fluorous column (12+M size) was placed inside the steel casing of the Biotage Horizon system. The column was flushed with 80:20 MeOH/water (60 mL, 5 column volumes) to elute the organic product. The solvent system was

(15) (a) Fluoro*Flash* fluorous silica gel products were purchased from Fluorous Technologies, Inc. (www.fluorous.com). (b) DPC holds an equity interest in this company.

(16) Review on spacer effects: Gladysz, J. A. In *Handbook of Fluorous Chemistry*; Gladysz, J. A., Curran, D. P., Horvath, I., Eds.; Wiley-VCH: Weinheim, 2004; pp 41−55.

then changed to 100% MeOH in the shortest possible volume required for a gradient (3 mL). Isocratic 100% MeOH (120 mL, 10 column volumes) was maintained to elute the fluorous byproducts: yield of **6aa**, 136 mg (99%); yellow oil; ^{1}H NMR ($CDCl_3$) δ 8.12 (d, J = 8.7 Hz, 2H), 7.32 (d, J = 8.6 Hz, 2H), 4.11 (t, J = 7.5 Hz, 2H), 2.32 (t, J = 7.3 Hz, 2H), 1.96 (quintet, J = 7.4 Hz, 2H), 1.53 (t, J = 7.6 Hz, 2H), 0.91 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 173.0, 149.3, 146.4, 129.2, 123.6, 62.1, 41.6, 34.8, 33.4, 29.6, 29.4, 25.9; IR (thin film) 2956, 2867, 1731, 1519 cm^{-1}; LRMS 293 (M^+, 4%), 209 (45%), 69 (90%), 57 (100%); HRMS calcd 293.1627, found 293.1634.

(b) With F-TPP and F-DEAD-3. 4-(4-Nitrophenyl)butyric acid **4a** (74 mg, 0.35 mmol), 3,3-dimethylbutanol **5a** (30 μL, 0.24 mmol), F-TPP (250 mg, 0.35 mmol), and F-DEAD-3 (296 mg, 0.35 mmol) were combined by Procedure B in THF (2 mL). After 3 h at room temperature, the reaction mixture was diluted with ether (50 mL) and washed with aqueous saturated sodium bicarbonate solution (2 × 10 mL). The ether layer was dried with magnesium sulfate, concentrated, and dried. The crude reaction mixture was loaded on to a 5 g Fluoro*Flash* cartridge and washed with 80:20 MeOH/water (20 mL) to elute the organic product and then with MeOH (40 mL) to elute the fluorous byproducts. The 80:20 MeOH/water fraction was concentrated and dried to yield 65 mg (92%) of **6aa**.

(c) Controls with TPP and DIAD. 4-(4-Nitrophenyl)-butyric acid **4a** (74 mg, 0.35 mmol), 3,3-dimethylbutanol **5a** (30 μL, 0.24 mmol), triphenylphosphine (92 mg, 0.35 mmol), and diisopropylazodicarboxylate (69 μL, 0.35 mmol) were combined by Procedure B in THF (2 mL) at room temperature. After 3 h at room temperature, the reaction mixture was diluted with ether (50 mL) and washed with aqueous saturated sodium bicarbonate solution (2 × 10 mL). The ether layer was dried with magnesium sulfate, concentrated, and dried. Flash column chromatography on silica gel (4:1 hexane/ethyl acetate) gave 4-(4-nitrophenyl)butyric acid 3,3-dimethylbutyl ester **6aa** (67 mg, 95%).

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Supporting Information Available: Complete experimental and characterization details for all intermediates, reagents, and products. This material is available free of charge via the Internet at http://pubs.acs.org.

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