# Fluorous Boc ($^F$Boc) Carbamates: New Amine Protecting Groups for Use in Fluorous Synthesis

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The first fluorous variants of the Boc (*tert*-butyloxycarbonyl) group have been prepared and tested for their suitability as nitrogen protecting groups. A group with two fluorous chains and an ethylene spacer, $(RfCH_2CH_2)_2(CH_3)COC(O)-$, was readily attached to a representative amine but was difficult to cleave. In contrast, groups with two fluorous chains and a propylene spacer, $(RfCH_2CH_2CH_2)_2(CH_3)COC(O)-$, or one fluorous chain and an ethylene spacer, $(RfCH_2CH_2)(CH_3)_2COC(O)-$, were readily formed and cleaved. The fluorous alcohol component of the $^F$Boc group can be removed by evaporation and can be recovered and reused. The utility of the new $^F$Boc group $(C_8F_{17}CH_2CH_2)(CH_3)_2COC(O)-$ was demonstrated in 16 and 96 compound library synthesis exercises. Separations can be achieved either by manual, parallel fluorous solid-phase extraction, or automated, serial fluorous chromatography. The results provide additional confirmation of the value of "light" fluorous synthesis techniques, and the new fluorous Boc groups expand the applicability of fluorous synthesis techniques to many classes of nitrogen-containing organic compounds.

## Introduction

In the recently introduced technique of "fluorous synthesis", small organic molecules are attached to fluorous (highly fluorinated) tags.[2] After reactions, these fluorous-tagged molecules can be separated from nontagged molecules by liquid−liquid extraction between an organic solvent and a fluorocarbon solvent. Unfortunately, unduly large numbers of fluorine atoms (60−120) can be needed to provide substantial solubilities of the fluorous-tagged molecules in fluorinated solvents,[3] and this leads to a number of practical problems including high molecular weights and low solubilities of the tagged molecules.

To unlock the potential of fluorous synthesis, we have more recently introduced "light fluorous" techniques.[4] Many fewer fluorines are used in the tag, and the liquid−liquid extraction is replaced by a solid−liquid extraction over fluorous reverse phase silica gel (silica gel with a fluorocarbon bonded phase).[5] Elution conditions are selected such that organic (nontagged) reagents, reactants, byproducts, etc. are not retained during an initial pass through the column, but the fluorous-tagged compounds are retained. A second pass with a more powerfully eluting solvent then extracts the fluorous-tagged compounds off the column. Fluorous solid phase extractions are especially straightforward to conduct, either individually or in parallel.

Light fluorous synthesis techniques were first demonstrated with simple perfluoroacyl amides, as illustrated by the example in eq 1. Isonipecotic acid **1a** was coupled with acid chloride **2** to give fluorous-tagged amino acid **3**. Reaction of **3** with isoquinoline **4a** (and other amines) under standard amide coupling conditions, followed by fluorous solid-phase extraction to remove all the reagent and reactant remnants, provided clean amide **5**. This was deprotected with base to provide amino amide **6**. While these experiments clearly demonstrated the potential use of small fluorous tags coupled with solid phase extraction, the practical utility is limited because perfluoroacyl groups are a relatively minor class of amide protecting groups. Some problems were also encountered in the cleavage of the perfluoroacyl groups, although several different hydrolytic and reductive conditions were developed.

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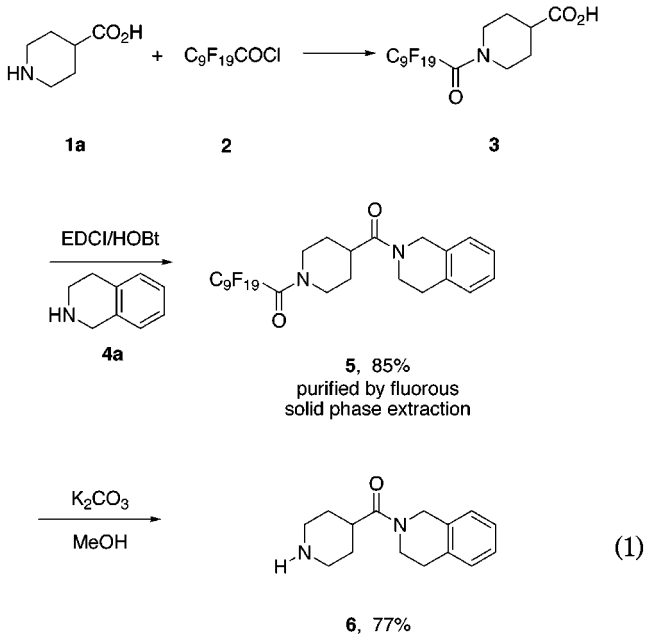
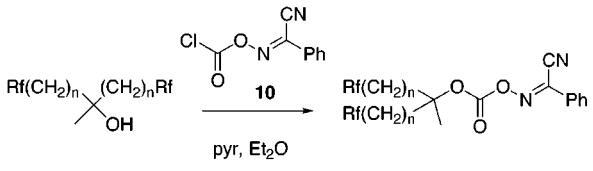



(1)

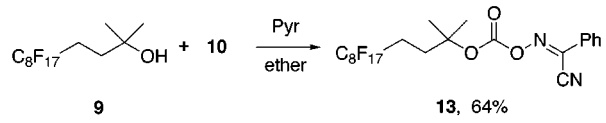
Carbamates are probably the most widely used class of amine protecting groups, both in and beyond peptide chemistry.[6] Among the many variants, *tert*-butyloxycarbonyl (Boc) carbamates are popular because they are readily formed and cleaved, and are stable under many types of reaction conditions. Accordingly, with the aim of producing a more generally useful fluorous nitrogen protecting group, we decided to investigate the synthesis and reactions of fluorous analogues of the Boc group. We introduce herein the first fluorous carbamate protecting groups and demonstrate their utility in typical amide coupling reactions.

## Results and Discussion

Initial experiments focused on identifying minimally fluorous carbamate groups that could be readily introduced and cleaved. Four groups were prepared and tested, and the results of these experiments are shown in eq 2. These groups are analogues of the standard Boc group in which one of the hydrogens on one or two methyl groups is replaced by a fluorous chain. We use "$^{F}$Boc" as the generic abbreviation for a fluorous Boc group. Fluorous alcohols **7** and **9** bearing an ethylene spacer, and **8a,b** bearing a propylene spacer, were prepared by appropriate nucleophilic addition reactions of Grignard or lithium reagents to ethyl acetate (**7**, **8a,b**) or acetone (**9**). Following the procedure of Itoh,[7] each of these alcohols was then treated with in situ generated oxyimino-2-phenyl acetonitrile reagent **10** and pyridine in ether to give the $^{F}$Boc transfer reagents **11**, **12a,b**, and **13** in the indicated yields after chromatographic purification. For reasons that are unclear, the two propylene spacer reagents (**12a**,**b**) were isolated in poor yields (27% and 9%), while the yields for the ethylene spacer reagents **11** and **13** were satisfactory (49% and 64%). Neither of the propylene reagents was selected for development in this work; however, we have learned recently that yields for the formation of these reagents can be improved by using isolated **10**.[8]

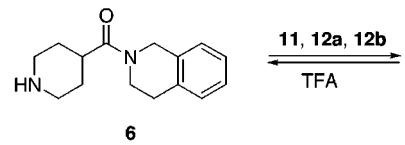


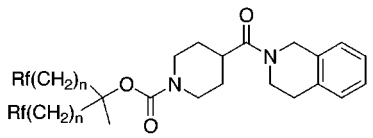

| | n | Rf | |
|---|---|---|---|
| **7** | 2 | $C_6F_{13}$ | **11**, 49% |
| **8a** | 3 | $C_6F_{13}$ | **12a**, 27% |
| **8b** | 3 | $C_4F_9$ | **12b**, 9% |




**9** **13**, 64% (2)

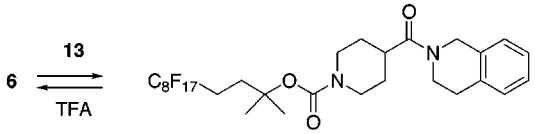
Amino amide **6** was then treated individually with all four $^{F}$Boc reagents under standard conditions ($CH_2Cl_2$, 2−5 h) to provide $^{F}$Boc protected amides **14**, **15a,b**, and **16** in excellent yields (79−100%) after purification by standard flash chromatography (eq 3). The purified $^{F}$Boc protected amides were then cleaved with TFA to return the starting amino amide **6**. The propylene spacer groups **15a**,**b** with two fluorous chains and the ethylene spacer group bearing only one fluorous chain **16** were all deprotected over 40 min. In contrast, the deprotection of **14** having two fluorous chains with ethylene spacers was very slow according to TLC analysis. Nonetheless, after 63 h, the reaction was complete and the amine **6** was recovered in 69% yield after purification by flash chromatography.




**14**, **15a**, **15b**

| | n | Rf | formation | cleavage (time) |
|---|---|---|---|---|
| **11** | 2 | $C_6F_{13}$ | **14**, 96% | 69% (63 h) |
| **12a** | 3 | $C_6F_{13}$ | **15a**, 81% | 100% (40 min) |
| **12b** | 3 | $C_4F_9$ | **15b**, 79% | 100% (40 min) |




**16** formation, 100%
cleavage, 100% (40 min) (3)

To evaluate the "fluorousness" of carbamates **14**, **15a,b**, and **16**, individual samples of each carbamate were

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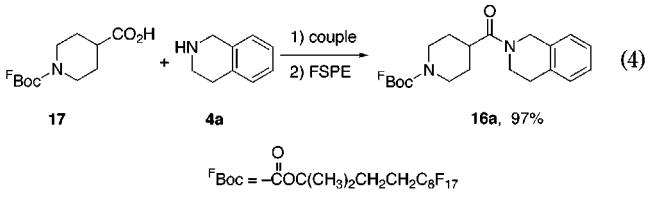
(8) Unpublished results of D. P. Curran and Y. Oderaotoshi.

**Table 1. HPLC Retention Times of Carbamates 14, 15a,b, and 16 and Amide 5**

| compound | # of fluorines | weight of fluorine (%) | retention time (min) |
|---|---|---|---|
| **14** | 26 | 49 | 33.4 |
| **15b** | 18 | 41 | 24.1 |
| **15a** | 26 | 48 | 33.8 |
| **16** | 17 | 42 | 22.5 |
| **5** | 19 | 49 | 22.0 |

injected onto a Fluofix analytical column (bonded phase, $-Si(Me)_2(CH_2)_3C(CF_3)_2C_3F_7$) eluting with a gradient starting from 80:20 MeOH−$H_2O$ to 100% MeOH over 30 min and then to 90:10 MeOH−THF over 30 min. The retention times of these compounds together with that of the amide **5** are listed in Table 1. We noticed that for structurally similar compounds, the retention times of fluorinated molecules are governed by their fluorine content. For instance, the retention time of amide **14** bearing 26 fluorines is about the same as that of **15a** which also possesses 26 fluorines (33−34 min). The same is true for amides **15b**, **16**, and **5**, which bear 17−19 fluorines (22−24 min).

As can be seen from Table 1, the retention time of fluorous Boc protected amide **16** is marginally longer than that of amide **5**. Since amide **5** and related amides have already been purified by fluorous solid-phase extraction (FSPE), we hypothesized that amide **16** could also be purified by FSPE. To test this, acid **17** (0.025 mmol) (see below for its preparation) was coupled with amine **4a** (4 equiv) in the presence of EDCI, HOBt, and $Et_3N$ (eq 4). The crude mixture was charged onto a short column packed with fluorous reverse phase silica gel (1 g). The column was eluted with MeOH−$H_2O$ (7:3) and THF sequentially. Evaporation of the THF fraction provided amide **16** in 97% yield. The proton NMR spectrum of amide **16** purified by solid-phase extraction was indistinguishable from that of an authentic sample purified by flash chromatography.

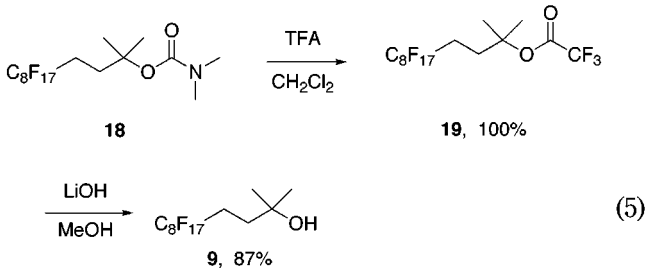



**17** **4a** **16a**, 97% (4)

$^F$Boc = $-\overset{O}{\overset{\|}{C}}OC(CH_3)_2CH_2CH_2C_8F_{17}$

We next conducted experiments to identify the nature of the fluorous products in the deprotection reaction. After evaporation of the TFA, there were no vinyl proton resonances evident in the crude proton NMR spectra in the deprotection of carbamates **14**−**16**. This excludes the possibility of the formation of alkenes as fluorous products. To identify the remnants of the fluorous Boc group, fluorous *N*,*N*-dimethyl carbamate **18** was treated with 30:70 $CH_2Cl_2$−TFA at room temperature for 1 h (eq 5). (2-Perfluorooctylethyl)isopropyl trifluoroacetate **19** was isolated in quantitative yield after evaporation to remove the liberated dimethylamine and TFA. The deprotection of carbamate **18** was much slower in neat TFA, presumably due to its poor solubility.

To recycle the fluorous Boc reagent, we attempted to convert (2-perfluorooctylethyl)isopropyl trifluoroacetate **19** to alcohol **9**. This reaction was not satisfactory with $K_2CO_3$/MeOH; however, ester **19** was hydrolyzed with LiOH/MeOH within 30 min to give alcohol **9** in 87%




**18** **19**, 100%

**9**, 87% (5)

isolated yield (eq 5). Alcohol **9** is the starting material for the preparation of fluorous Boc reagent **13** (eq 2), so the fluorous portion of the Boc group is recyclable.

When the crude reaction mixture from the deprotection of **16** (eq 3) was dried under high vacuum for 5 h, $^1$H NMR analysis of the residue revealed that only amide **6** remained and ester **19** was completely removed. This was further confirmed by $^{19}$F NMR analysis since no resonances could be detected in the spectrum of the residue after high vacuum evaporation. This shows that by using fluorous Boc **13** as a tag in the solution phase synthesis, the byproduct of the fluorous tag can be removed from desired products by simple high vacuum evaporation.

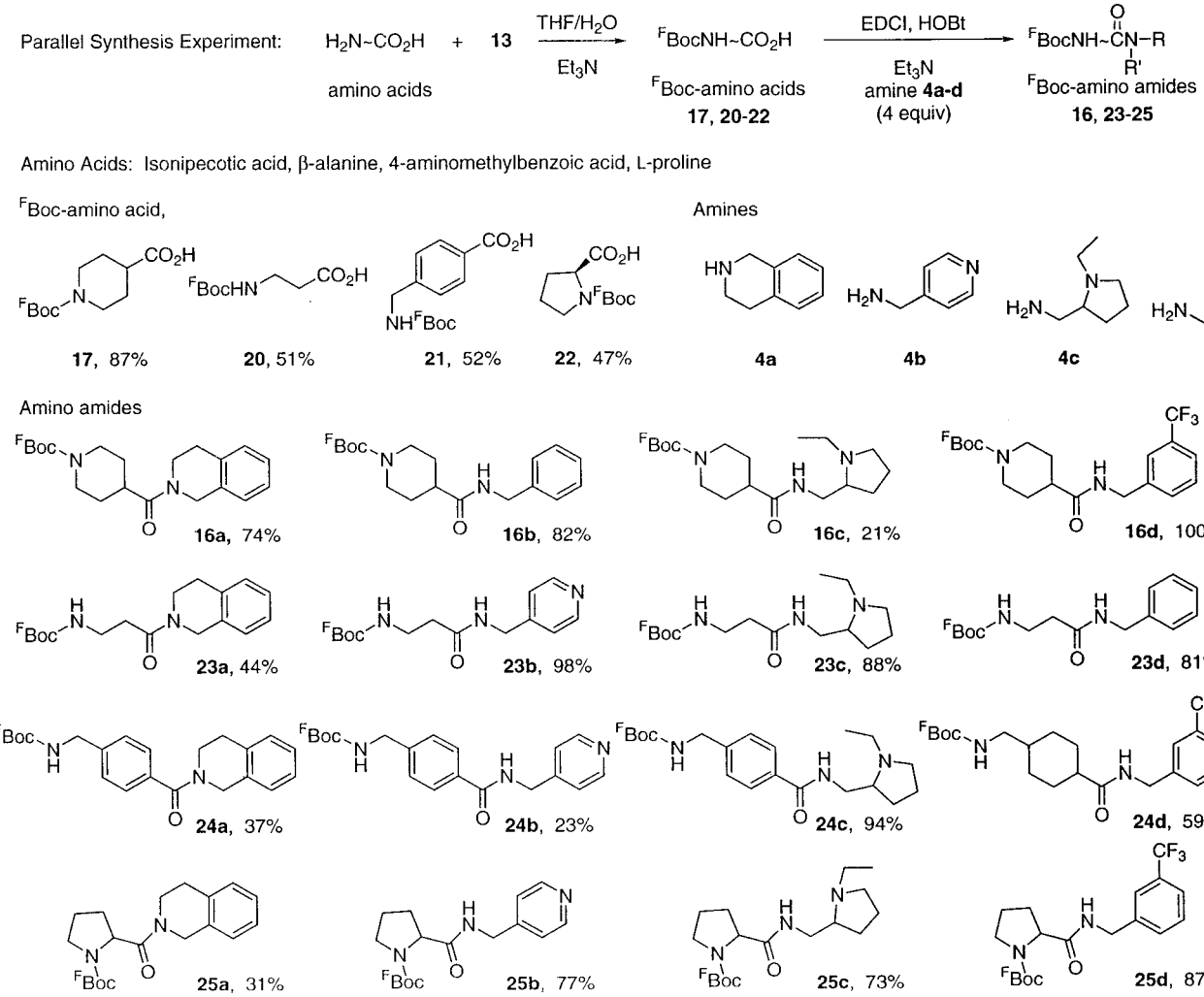
These preliminary experiments led to the selection of $^F$Boc reagent **13** for further study. This group contains relatively few fluorines (17), yet the trial tagged molecule **16** was still well retained on the fluorous column. The reagent can be prepared and attached in good yield, the cleavage occurs cleanly, and the remnants of the $^F$Boc group (presumably the trifluoroacetate **19**) can be removed by evaporation.

To test the usefulness of the new $^F$Boc group, we conducted a parallel synthesis of a library of 16 amides using fluorous Boc **13** as a fluorous tag. This experiment was conducted with the same components and on the same scale as a prior parallel experiment using the fluorous acyl (perfluorodecanoyl) tag.[4] In contrast to the unsuccessful protection of amino acids that was experienced with perfluorodecanoyl chloride,[4] isonipecotic acid, $\beta$-alanine, 4-aminomethylbenzoic acid and, L-proline were smoothly protected with fluorous Boc reagent **13** in a mixture of THF and $H_2O$ (Scheme 1). Because these reactions were carried out on small scale, fluorous Boc protected amino acids **17** and **20**−**22** were purified by flash chromatography. These four acids (0.06 mmol) were coupled with amines **4a**−**d** (0.24 mmol) in a parallel experiment under the standard conditions with EDCI, HOBt, triethylamine.

As an alternative to manual, parallel solid-phase extraction, we envisioned that serial HPLC separations with a new preparative Fluofix column would also be effective to purify the library of amides. A secondary goal of this experiment was to test the loading capacity of the preparative HPLC column for this type of solid-phase extraction and to compare it to more standard chromatographic loadings. The sixteen crude reaction mixtures were concentrated and injected onto a preparative Fluofix HPLC column[9] (1EW125) and eluted with 90:10 MeOH−$H_2O$ for 25 min followed by pure MeOH for 20 min. Excess amines and coupling reagents all eluted early between 5 and 10 min and the fluorous Boc protected amides emerged between 20 and 40 min. To illustrate the efficiency of purification, a representative HPLC

(9) Preparative Fluofix Column can be purchased from Keystone Scientific, Inc.

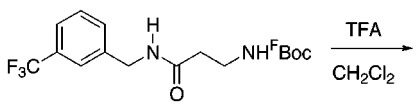
**Scheme 1**



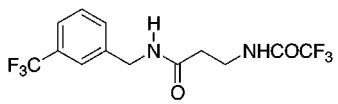

chromatogram for the purification of **25d** is shown in Figure 1 of the Supporting Information.

The isolated yields of the library are shown under the structures in Scheme 1, and ranged from 21% to 100%. We attempted to assess the purities of the library by LC-MS; however, these amides had very strong retention on the C-18 reverse phase HPLC column used in the LC-MS. Nevertheless, by direct injection without the HPLC column all of the molecular ions of the amino amides were detected by LC-MS. Unlike those amides with a perfluorodecanoyl tag prepared in our previous work (eq 1),[5] these fluorous Boc tagged amides were not volatile enough to be detected in GC analysis. $^1$H NMR spectra were recorded for all of the amino amides and these showed that the purities were excellent. These spectra are contained in the Supporting Information.

Deprotection of the library of $^F$Boc-amino amides was carried out in 30:70 $CH_2Cl_2$−TFA at room temperature for 17 h. After removal of TFA, the residues were partitioned between ethyl acetate and basic water (pH = 11). The ethyl acetate layers were evaporated with a vacuum centrifuge. Unfortunately, the deprotection results were far from satisfactory. The cleavage of the isonipecotic acid series (**16a**−**d**) appeared to proceed smoothly. However, there was nothing left in those vials that should have contained products from the precursors **4c** and **4d** with additional basic sites. We also noticed that some of the amine products were apparently acylated by TFA so that the corresponding trifluoroacetamides were obtained instead of free amino amides. For instance, treatment of amide **23d** with TFA in dichloromethane gave trifluoroacetamide **26d** as the major product together with trace amount of the corresponding amine (eq 6).

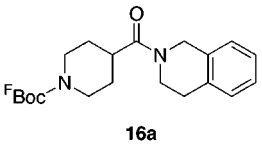



**23d**

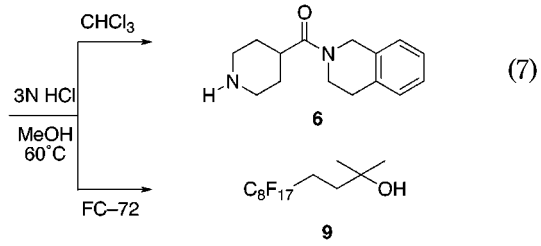


**26d** (6)

We solved the deprotection problem by using 3N HCl/MeOH instead of TFA. In a test experiment, carbamate **16** (eq 7) was treated with 3N HCl/MeOH at 60 °C for 5 h. After neutralization of the HCl and evaporation of solvent, the crude mixture was partitioned between FC-72 and chloroform. Amino amide **6** was isolated from the chloroform layer. Evaporation of the FC-72 phases gave (2-perfluorooctylethyl)isopropyl alcohol **9**. This could also be removed by sublimation when the alcohol was dried under high vacuum for 5 h. Yields of amino amide **6** and alcohol **9** were not recorded in this preliminary experi-



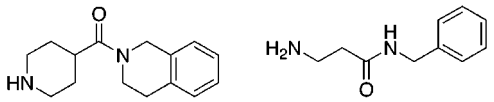
16a



(7)

ment but in the subsequent preparative experiment, amino amide **6** was isolated in 92% yield (see below).

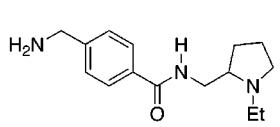
To test the cleavage procedure, we repeated the synthesis of amides **16**, **23b**, **24c**, and **25d**. This is the diagonal of the library in Scheme 1, so every component is represented once. The isolated yields were similar to those reported in Scheme 1, thereby demonstrating the reproducibility of the coupling reaction. The four amides were then heated with 3 N HCl/MeOH at 60 °C for 16 h. After removal of solvent, the residue was further dried under high vacuum to remove alcohol **9**. The calculated yields of the HCl salts of **6a**, **27b**, **28c**, and **29d**, using *p*-dimethoxybenzene as an internal standard in NMR analysis, are listed in eq 8. None of these final products



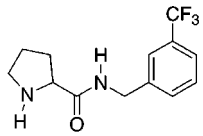
**6**, 92%



**27b**, 100%



**28c**, 53%



**29d**, 86%

showed any resonances in their $^{19}$F NMR spectra. Although only four members of library were tried, we presume the rest of the library could be deprotected under these conditions.

Since the fluorous Boc group of the amides made from **17** can be reliably cleaved, we decided to prepare a library of 96 piperidine derivatives as shown in Scheme 2. We planned to couple acid **17** with amines **30**{*1*−*8*}[10] to give eight-member library **31**{*1*−*8*}. After cleavage of the fluorous Boc group, *N*-alkylation of library **31** with halides **32**{*1*−*12*} will provide 96-member library **34**{*1*−*8*, *1*−*12*}. In the exercise, the $^F$Boc group is used to quickly make large quantities of precursors that are then cleaved, split, and further functionalized.

Thus, the fluorous Boc protected isonipecotic acid **17** (0.5 mmol) was stirred with amines **30** in the presence of EDCI, HOBt, and triethylamine at room temperature for 16 h. LC-MS analysis of the crude mixtures with C-18 reverse phase column showed that the starting acids were all consumed and amides **31**{*1*−*8*} were formed as a single peak. Considering the larger scale of these reactions, library **31** was purified by parallel fluorous solid-phase extraction instead of preparative HPLC. Excess amines and coupling reagents were removed by eluting the fluorous reverse phase silica gel with 80:20 MeOH−$H_2O$. Elution of the fluorous silica with MeOH followed by diethyl ether provided amides **31**{*1*−*8*}. The isolated yields of amides are listed in Scheme 2 underneath the structures of the amines used. The calculated yield for the amide **31**{*4*} is marginally higher than 100%, which is probably due to the presence of solvents. Though it was not assessed spectroscopically, we believe the purities of these amides were very high since they each exhibited single peaks in the LC-MS analysis (C-18) before FSPE.

Treatment of library **31** with neat TFA at room temperature for 2.5 h cleaved the fluorous Boc group. LC-MS analysis of the crude mixtures revealed the consumption of amides **31** and formation of single new products with the expected masses of the free amino amides **32**{*1*−*8*}. After evaporation of TFA by a vacuum centrifuge and addition of large excess of diisopropylethylamine, stock solutions of amine **32** and alkylating agents **33** were prepared and mixed combinatorially with a liquid handler. The plate with these 96 reaction vials was heated at 50 °C for 24 h. LC-MS analysis showed that in 89 cases the molecular ions of products **34** were present. A typical LC-MS for compound **34**{*1*,*7*} is shown in Figure 2 of the Supporting Information.

Without workup, these 96 crude mixtures were introduced directly onto a PrepLCMS system for purification. The preparative LCMS system consists of an autosampler, HPLC pumps, a preparative scale mixer, a 30 × 10 mm C-18 reverse phase preparative HPLC column, a UV detector, a fraction collector, and a mass spectrometer. The method uses real-time mass spectrometric signals to trigger the fraction collector only when the desired mass is detected. Using this intelligent fraction collection, 89 of the desired 96 compounds were isolated in yields (by weight) that range from 5% to 100% (Table 2). For both steric and electronic reasons, *N*-alkylation with halides **33**{*6*} and **33**{*9*} gave relatively lower yields of **34**{*1*,*1*−*8*,*6*} and **34**{*1*,*1*−*8*,*9*}. For those of **34** whose yields are listed with a parenthesis, proton NMR spectra are included in the Supporting Information.

## Conclusions

In this work, we prepared four fluorous Boc ($^F$Boc) reagents with different numbers of fluorines and different lengths of spacers for the use as amino protecting groups. Amines and amino acids were smoothly protected with these fluorous Boc reagents in common organic solvents with or without water as a cosolvent. Three of these four fluorous Boc groups were readily cleaved by TFA, though acylation of the resulting amine by TFA has been observed in some cases. This could be avoided by using HCl/MeOH for deprotection. In addition to the favorable features exhibited by all of the classes, the $^F$Boc reagents with a single $C_8F_{17}CH_2CH_2$− group are especially useful because the fluorous products after cleavage can be removed (and recovered) by high vacuum so a second fluorous solid phase extraction is not needed. Although only investigated briefly in this work, the reagents with two fluorous chains and a propylene spacer could well be useful in other settings.

The use of a preparative Fluofix HPLC column in the separation of reaction mixtures containing fluorous and

**Scheme 2**

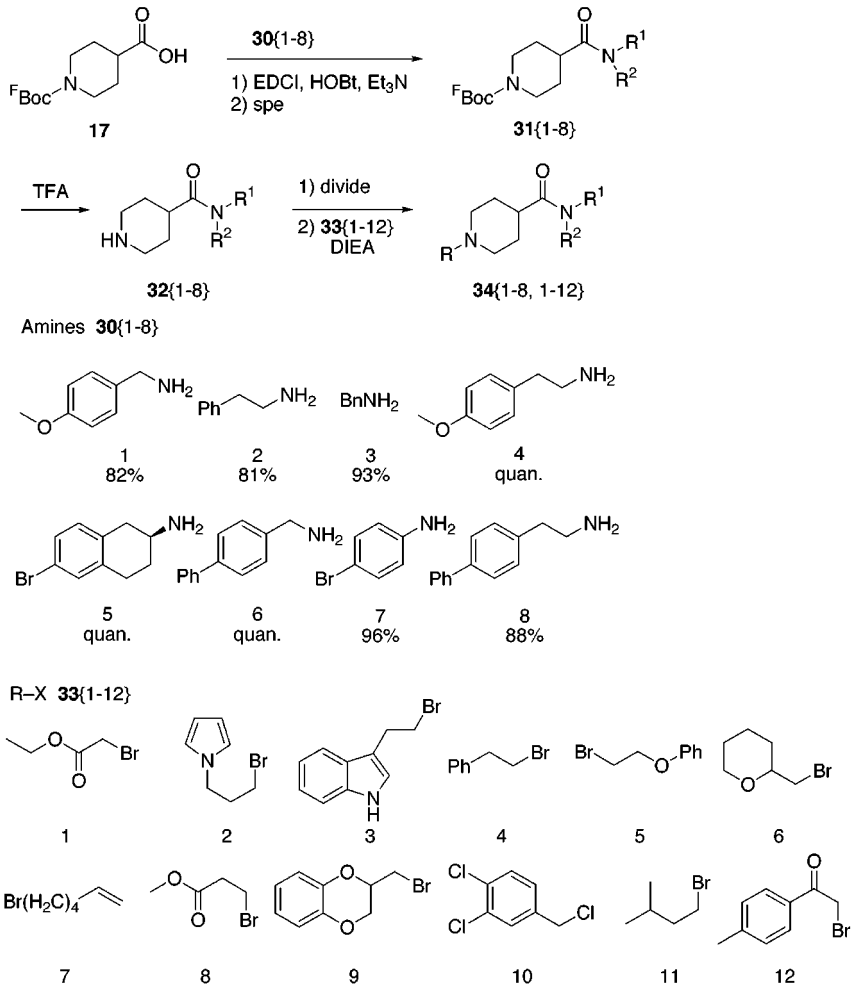



**Table 2. Isolated Yields (%) of Library 4a**

| | **30**{*1*} | **30**{*2*} | **30**{*3*} | **30**{*4*} | **30**{*5*} | **30**{*6*} | **30**{*7*} | **30**{*8*} |
|---|---|---|---|---|---|---|---|---|
| **33**{*1*} | (70) | quan | 94 | quan | 89 | 95 | 5 | 60 |
| **33**{*2*} | 71 | (80) | 84 | 80 | 61 | 70 | 48 | 48 |
| **33**{*3*} | 48 | 58 | 0 | 65 | 10 | 41 | (30) | 28 |
| **33**{*4*} | 46 | 62 | 85 | (50) | 50 | 43 | 36 | 32 |
| **33**{*5*} | 56 | 72 | 68 | 52 | (48) | 47 | 41 | 41 |
| **33**{*6*} | 12 | 9 | 10 | 10 | 0 | 9 | 0 | (9) |
| **33**{*7*} | 51 | 63 | (71) | 54 | 51 | 60 | 0 | 36 |
| **33**{*8*} | (72) | 82 | 83 | 94 | 81 | 82 | 5 | 56 |
| **33**{*9*} | 13 | (18) | 17 | 10 | 0 | 14 | 0 | 11 |
| **33**{*10*} | 61 | 77 | 68 | 81 | 52 | (71) | 11 | 40 |
| **33**{*11*} | 49 | 63 | 62 | 49 | (44) | 45 | 5 | 32 |
| **33**{*12*} | 27 | 38 | 31 | 32 | 0 | 25 | 14 | (14) |

[a] For yields in parentheses, $^1$H NMR spectra are contained in the Supporting Information.

organic compounds is reported in this paper for the first time. This has at least two advantages over the related fluorous solid-phase extraction. First, it is easier to automate because of the availability of serial HPLC instruments coupled with LC-MS detection. Second, if the reaction of a tagged substrate is incomplete or unclean, the desired product may be obtained with higher purity since unreacted tagged substrates or side products with fluorous tags may be separated by HPLC. In contrast, in fluorous solid-phase extraction all compounds with fluorous tag tend to elute as a mixture that may contain desired product and side products with fluorous tags. On the other hand, solid-phase extraction is faster than HPLC and uses less solvent. HPLC is useful in smaller libraries with serial separation while manual solid-phase extraction is useful in larger libraries with parallel separation.

These new $^F$Boc groups add to a small but growing list of groups that serve the dual purpose of protection of a target functionality and phase tagging for strategy-based separations. Other groups include silyl groups, benzyl groups, and acetals.[11] As the number of fluorous tagging groups expands, so too expands the applicability of fluorous strategies and methods in traditional and parallel organic synthesis.

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**Supporting Information Available:** Contains full experimental details, copies of the $^1$H NMR spectra of 28 representative products, and Figures 1 and 2. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) This is the *Journal of Combinatorial Chemistry* numbering scheme. Numbers in brackets represent the building blocks used to make the product whose number is bold.

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