Solid-Phase Organic Synthesis of Difluoroalkyl Entities using a Novel Fluorinating Cleavage Strategy: Part 2. Synthesis of Three Small *gem*-Difluorinated Compound Libraries using a Dithiane Linker

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Three small compound biaryl libraries featuring a novel fluorinating cleavage strategy for preparation of a difluoromethyl group were assembled on solid supports. The average reaction yield per step was up to 96% in a synthetic sequence over five to six steps. Key features were Suzuki coupling reactions, transesterification with potassium cyanide and amidation reaction with trimethyl aluminum on solid supports.

Introduction

In the first part of this series,[1] we developed a linker system enabling the detachment of *gem*-difluorinated molecules from solid supports and presented its scope and limitations.[2]

Herein, we describe the synthesis of small compound libraries using this technique. As core structure, we have chosen 3,5-disubstituted biaryls because they elicit various biological activities. For example the naturally occurring antifungal biaryl systems[3] aucuparin and isoaucuparin[4] (Figure 1) contain this moiety. Another example is the early (but nevertheless efficient) prostaglandin synthetase modulator, 4′-chloro-5-methoxy-3-biphenylylacetic acid (DKA-9),[5] which is of current biological interest.[6]

To explore the effect of replacing the functional groups, such as the methoxy groups in aucuparin, with other bioisosteres, we designed the target libraries depicted in Figure 2 consisting of amide (library I), reverse amide (library II), and ester functionalities (library III).

Results and Discussion

Library I: Amide Structures. The retrosynthetic analysis for library **I** is displayed in Scheme 1. While the biaryl moiety will be constructed via Suzuki coupling reactions,[7] the amide can be introduced in a classical amide forming reaction. The trifunctional building block **5** serves as the key intermediate for this library.

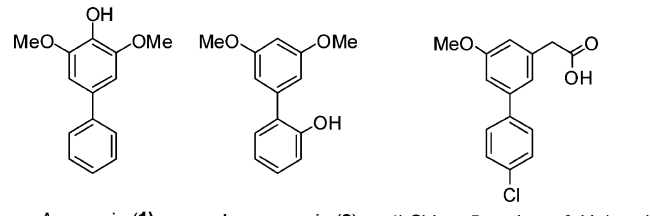
The synthesis of **5** proceeded smoothly in 73% yield over two steps by bromination of 3-nitroacetophenone (**6**)[8] with dibromoisocyanuric acid (DIB) as a strong bromination agent for deactivated aromatic systems. The α-bromoketone formed during this reaction can be easily transformed into the desired compound by reaction with a catalytic amount of sodium iodide in acetic acid (Scheme 2).[9]

The ketone **5** was then immobilized on the dithiol linker **7** under conditions which were described previously.[1]

The reduction of the nitro group of **8** using tin(II) chloride furnished quantitatively the amine **9**. The two-dimensional array was accomplished using four acid chlorides and four boronic acids to give the biaryl amides **13**{*1*−*4*;*1*−*4*} (Table 1). The amides were formed by reacting amine resin **9** with acid chlorides **10**{*1*−*4*} and triethylamine in dichloromethane and the biaryl units were built by reacting the resulting amides **11**{*1*−*4*} with boronic acids **12**{*1*−*4*} using palladium(tetrakistriphenylphosphine) as catalyst (THF, 80 °C, two days). The key steps (at least one of the amide forming reactions and one of the Suzuki couplings) were monitored by gel-phase ^{13}C NMR to check qualitatively the course of the reaction.

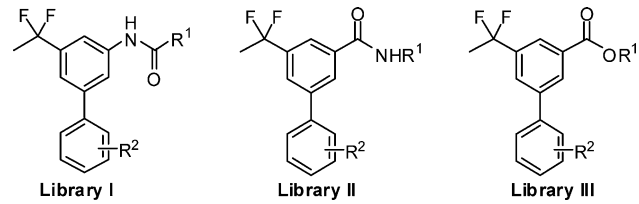
Detachment from the solid support gave the difluorobiaryls in moderate to good yields (up to 37% over 6 steps, i.e. 85% in average). The yields are computed based on the initial loading of the thioester linker precursor which is easily converted into dithiol linker **7** in one high yielding step (see part 1 of this series).

The products were obtained in high purity after simple filtration through silica gel to remove small amounts of the



Aucuparin (**1**) Isoaucuparin (**2**) 4′-Chloro-5-methoxy-3-biphenylylacetic acid (DKA-9) (**3**)

Figure 1. Aucuparin, isoaucuparin, and DKA-9.



Library I Library II Library III

Figure 2. Target structures of the three libraries.

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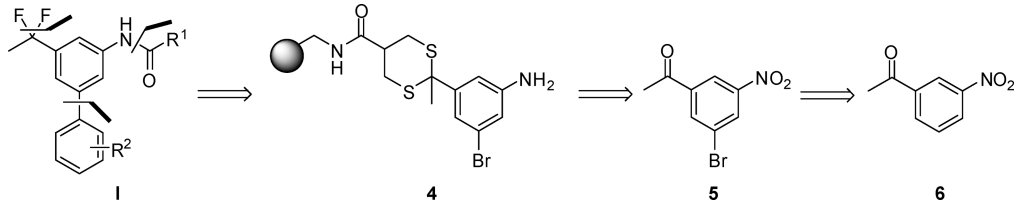
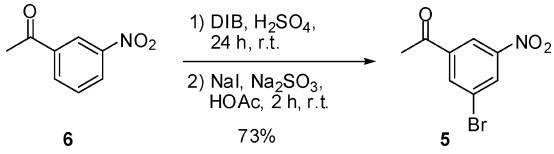
Scheme 1. Retrosynthetic Approach of Target Structure **I**



Scheme 2. Synthesis of Key Building Block 3-Bromo-5-nitroacetophenone (**5**)



carbonyl compounds formed by premature solvolysis and the remains of the palladium catalyst from the precedent cross coupling reaction. Two points should be commented at this stage. First, dithioacetals are apparently fully compatible with palladium catalysis. Second, thiophene rings are stable toward the acidic cleavage conditions.

Library II and III: Reverse Amide and Ester Structures. The next two libraries, the reverse amide **II** and the corresponding biaryl ester **III**, originate from the common building block **16** featuring an ester functionality. The latter should be accessible from dimethyl ester **17** (Scheme 3).

The diester **17** was converted into the monoketone using a protocol originally developed by King et al.[10] Thus, the diester was treated with methyl Grignard reagent in the presence of lithium hexamethyldisilazide to yield the ketone **16** in 75% yield (Scheme 4). Our optimized protocol seems to be a higher yielding than the original (55%).[11]

Attachment to the resin **7** gave rise to the dithioacetal **18** (Table 2). We initially intended to build the amide moiety using a standard liquid-phase chemistry approach: hydrolysis of the methyl ester and subsequent transformation of the acid with different amines in the presence of activating agents. However, whereas the saponification could be easily achieved using potassium trimethylsilanolate in THF,[12] neither DIC/HOBt nor PyBrOP/DIPEA protocols afforded satisfying results for the reaction of the immobilized benzoic acid derivative with the amines. The transformation into amides was finally achieved using a direct amidation protocol developed by Weinreb.[13] Thus, trimethyl aluminum and the required primary amines **19**{*1*−*4*} was reacted at elevated temperatures with resin **18** to yield the amides **20**{*1*−*4*} in almost quantitative conversion as shown by gel-phase ^{13}C NMR. Suzuki coupling with the boronic acids **21**{*1*−*3*} then furnished the biaryls **22**{*1*−*4*,*1*−*3*}. Fluorinating cleavage followed by flash filtration yielded the target matrix **23**{*1*−*4*,*1*−*3*} in good to very good overall yields (up to 81% over 5 steps, i.e., up to 96% average yields) and excellent purities. The results show that anilines seem to be more suitable in the amidation reaction than aliphatic amines, since the corresponding fluorinated target structures were generally obtained in higher yields after cleavage.

A similar strategy led to the target structures of ester library III (Table 3). With the ester **18** in hand, transesterification with primary, secondary, or benzylic alcohols and potassium cyanide (55 mol %)[14] yielded esters **25**{*2*−*4*}. The biaryl system was assembled using a Suzuki reaction as before. Fluorinating cleavage gave the biaryls **28**{*2*−*4*;*1*−*4*} in up to 47% yield over five steps (i.e., 86% in average per step) and in the case of unmodified methyl ester **28**{*1*;*1*−*4*} in up to 74% over four steps (i.e., 93% per step).

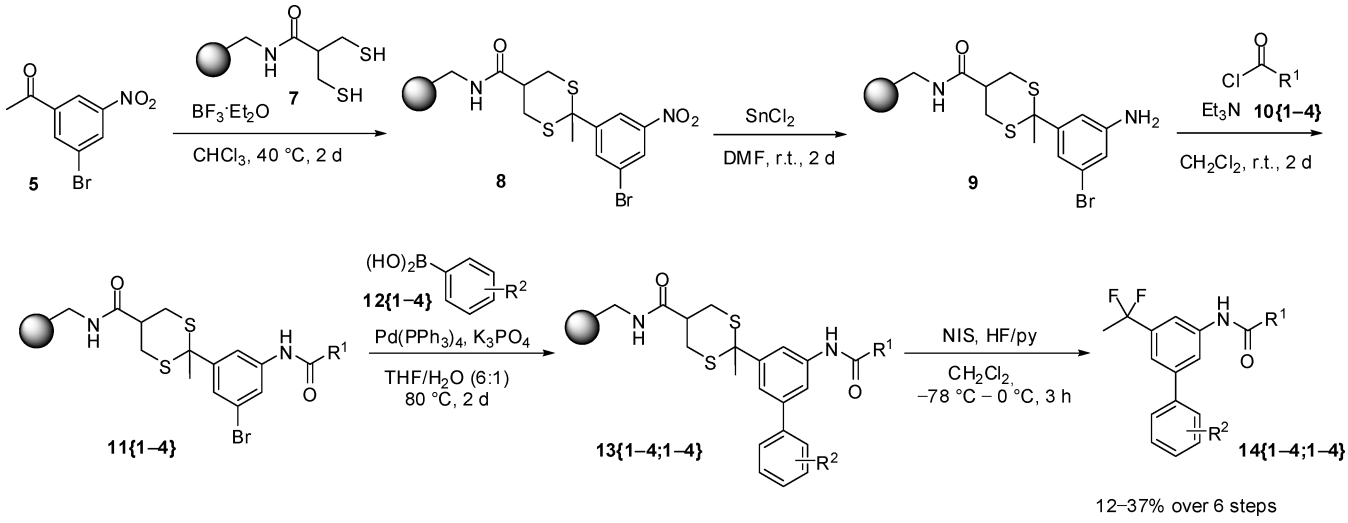
Conclusion

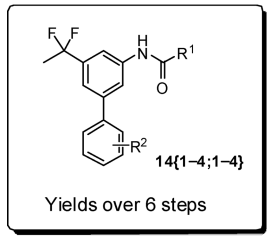
In summary, the novel multifunctional dithian linker proved to be an appropriate system with a high potential for the design and synthesis of *gem*-difluorinated compound libraries in solid-phase synthesis. Three small biaryl libraries featuring a difluoromethyl unit could be synthesized in good to excellent yields of up to 81% over five or six steps, respectively, and in high purities. These libraries have been submitted to biological testing which will be reported in due course. The manuscript demonstrates the application of our new fluorinating cleavage strategy to generate the first libraries of small *gem*-difluoroalkyl-substituted entities.

Experimental Section

Instrumentation and Reagents. ^1H NMR spectra were recorded on Bruker AM 250 (250 MHz), *Bruker* AM 400 (400 MHz), and Bruker AM 500 (500 MHz) spectrometers. Chemical shifts are expressed in parts per million (δ/ppm) downfield from tetramethylsilane (TMS) and are referenced to $CDCl_3$ (7.26 ppm) or acetone[d_6] (2.09 ppm) as internal standard. All couplings constants are absolute values, and *J* values are expressed in hertz (Hz). The description of signals include s = singlet, d = doublet, bd = broad doublet, t = triplet, dd = doublet of doublet, dt = doublet of triplet, and m = multiplet. The spectra were analyzed according to first order. ^{13}C NMR spectra were recorded on Bruker AM 250 (62.5 MHz), Bruker AM 400 (100 MHz), and Bruker AM 500 (125 MHz) spectrometers. Chemical shifts are expressed in parts per million (ppm, δ) downfield from tetramethylsilane (TMS) and are referenced to $CDCl_3$ (77.4 ppm) or acetone[d_6] (30.6 ppm) as internal standard. For measurement of ^{13}C NMR-Gel-Spectra, 60−100 mg of the resin were swollen in a NMR-tube with the appropriate amount of solvent). All ^{13}C NMR signals are given except of those that derive from the polystyrene resin or from the linker molecule. Some of the expected signals of the attached molecules are superimposed by the polystyrene core and can therefore not be detected. The NMR-spectrometer was run with pulse program zgpg30 (Relaxation delay D1 = 0.2 s, linebroadening LB = 9.0 Hz, 5120 scans). MS (EI) (electron impact mass spectrometry): Finnigan MAT 90 (70 eV). The molecular fragments are quoted as the relation between mass

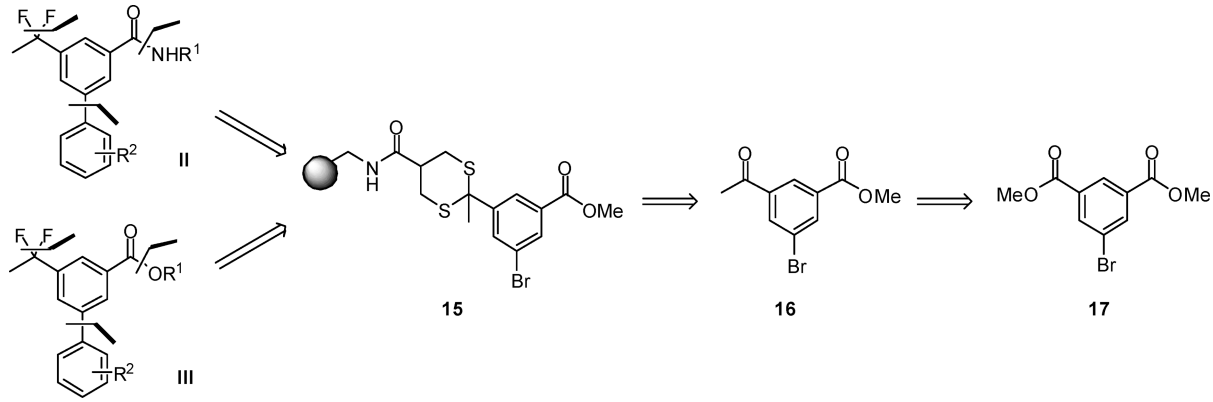
Table 1. Synthesis of the Difluoro Biaryl Amide Library **I**





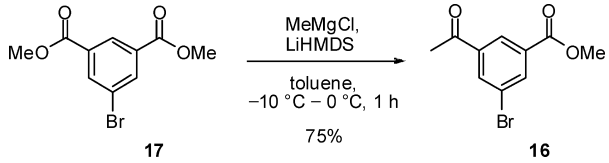
R^2 = / R^1 =				
H	**14{1;1}** 19%	**14{2;1}** 34%	**14{3;1}** 13%	**14{4;1}** 21%
4-Me	**14{1;2}** 37%	**14{2;2}** 19%	**14{3;2}** 30%	**14{4;2}** 29%
4-Cl	**14{1;3}** 19%	**14{2;3}** 23%	**14{3;3}** 24%	**14{4;3}** 13%
4-F	**14{1;4}** 12%	**14{2;4}** 16%	**14{3;4}** 20%	**14{4;4}** 13%

Scheme 3. Retrosynthetic Approach of Target Structures **II** and **III**



and charge (*m*/*z*), the intensities as a percentage value relative to the intensity of the base signal (100%). The abbreviation [M^+] refers to the molecule ion. IR (infrared spectroscopy): FTIR Bruker IFS 88. IR spectra of solids were recorded in KBr, and as thin films on KBr for oils and liquids. The deposit of the absorption band was given in wave numbers in cm^{-1}. The forms and intensities of the bands were characterized as follows: vs = very strong 0−10% T, s = strong 10−40% T, m = medium 40−70% T, w = weak 70−90% T, vw = very weak 90−100% T. Routine monitoring of reactions were performed using Silica gel coated aluminum plates (Merck, silica gel 60, F_{254}), which were

Scheme 4. Synthesis of Keto Ester **16**



analyzed under UV-light at 254 nm or dipped into a solution of molybdato phosphate (5% phosphor molybdic acid in ethanol, dipping solution) and heated with a heat gun. Solvent mixtures are understood as volume/volume. Solid materials were powdered. Solvents, reagents, and chemicals were purchased from Aldrich, Fluka and Acros. Tetrahydrofuran and diethyl ether were distilled from sodium/benzophenone under argon prior to use. Dichloromethane, cyclohexane, and ethyl acetate were distilled from calcium hydride. All reactions involving moisture sensitive reactants were executed under an argon atmosphere using oven- or flame-dried glassware; all other solvents, reagents, and chemicals were used as purchased unless stated otherwise. Aminomethyl resin was purchased from Polymer Laboratories (PL-AMS Resin, 2.06 mmol/g, 75−150 μm, AMS 118). Unless not stated otherwise, vials from Macherey-Nagel were used for all reactions beyond room temperature (size 20−20 and 20−10, in combination with N20 oA and N20 TB/oA-M septa).

General Washing Procedure for Resins (GP1). Method 1 (GP1a). The resins were washed with the following solvents (1 mL per 100 mg resin): (1) dichloromethane/methanol/dichloromethane/methanol/dichloromethane, (2) methanol/water/methanol/water/methanol, and (3) dichloromethane/methanol/dichloromethane/methanol/dichloromethane. Finally, the resins were washed three times with dichloromethane and dried for 24 h under high vacuum.

Method 2 (GP1b). The resins were washed with the following solvents (1 mL per 100 mg resin): (1) THF/water/methanol/THF/water/methanol and (2) dichloromethane/methanol/dichloromethane/methanol/dichloromethane/methanol. Finally, the resins were washed three times with dichloromethane and dried for 24 h under high vacuum.

General Procedure for the Attachment of Aldehydes and Ketones to the Dithiol Linker 7 (GP2). In a vial, 1.00 equiv of resin **7** (loading: 1.40 mmol/g) was covered with dry chloroform (10 mL per 1.00 g resin) under argon atmosphere and shaken for 30 min. After it was cooled to 0 °C, 5.00 equiv of the carbonyl compound dissolved in 5 mL of chloroform and 5.00 equiv $BF_3 \cdot Et_2O$ were added; the vial was sealed, and the mixture was shaken for 24 h at 40 °C. Finally, the reaction mixture was filtered off and washed according to GP1a, and the resin was dried under high vacuum. ^{13}C NMR-gel phase spectra were measured for qualitative reaction control.

General Procedure for the Synthesis of the Amides 11 on the Resin (GP3). In a vial, 1.00 equiv of the resin was covered with 10 mL of dry dichloromethane and shaken for 30 min. After the addition of 3.00 equiv of acid chloride and 3.00 equiv of triethylamine, the mixture was shaken at room temperature for 24 h. The reaction mixture was filtered off, washed according to GP1a, and dried under high vacuum. ^{13}C NMR-gel phase spectra were measured for qualitative reaction control.

General Procedure for the Suzuki Coupling Reactions (GP4). In a vial, 1.00 equiv of the resin was covered with 6 mL of dry THF under argon and shaken for 30 min. After the addition of 5.00 equiv of boronic acid and 5.00 equiv of K_3PO_4 (dissolved in 1 mL of water), the mixture was degassed for 5 min, and 0.1 equiv of $Pd(PPh_3)_4$ was added; the vial was sealed and shaken at 80 °C for 48 h. The resin was filtered off, washed according to GP1b, and dried under high vacuum. In most cases, ^{13}C NMR gel-phase spectra were measured for qualitative reaction control.

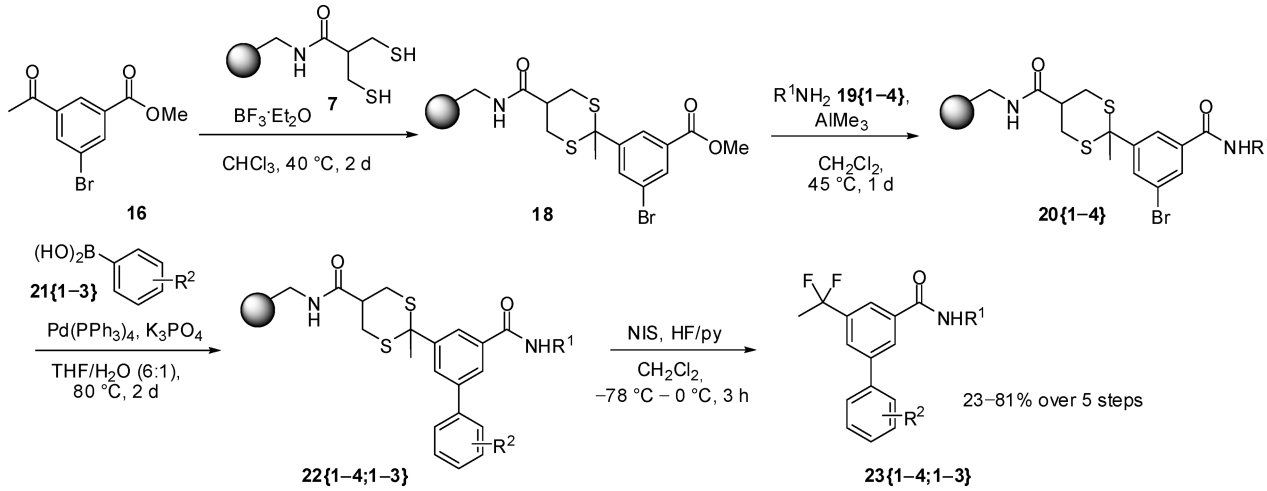
General Procedure for the Synthesis of Amides 20 on the Resin Using $AlMe_3$ (GP5). In a vial, 3.00 equiv of the amine was suspended under argon in 5 mL of dry CH_2Cl_2 and cooled to 0 °C before 3.00 equiv of trimethylaluminium (1.0 M in heptane) was added dropwise. The mixture was stirred for 30 min and allowed to warm to room temperature. After the stirring bar had been removed, 1.00 equiv of the resin was added, and the mixture was shaken for 2 days at 45 °C. The resin was filtered off, washed according to GP1a, and dried under high vacuum. ^{13}C NMR gel-phase spectra were measured for qualitative reaction control.

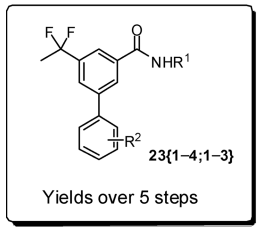
General Procedure for the Transesterifications to Give Compounds 25 on the Resin Using KCN (GP6). In a vial, 1.00 equiv of the resin was suspended in 5 mL of the alcohol (in the case of 4-*tert*-butylbenzylalcohol, 20.0 equiv of the alcohol was used dissolved in dry DMF), 0.1 equiv of KCN was added, and the sealed vial was shaken for 2 days at 100 °C. Then the resin was filtered off, washed with water/acetone/water/acetone/water/acetone and finally three times with dichloromethane, and dried for 24 h under high vacuum.^{13}C NMR gel-phase spectra were measured for qualitative reaction control.

General Procedure for the Fluorinating Cleavage of the Compounds from the Resin (GP7). The cleavage reactions were performed under argon atmosphere in 100 mL Teflon-coated flasks. Four equivalents of *N*-iodosuccinimide was suspended in 10 mL of dry dichloromethane. After the mixture was cooled to −78 °C, 40.0 equiv of HF (70% in pyridine) was added, and the mixture was stirred for 10 min. Then 1.00 equiv of resin was swollen in the 2-fold volume dry dichloromethane and transferred into the flask. The reaction was stirred for 3 h while warming up to 0 °C. Twenty milliliters of dichloromethane was added, followed by 10 mL of 5% $NaHSO_3$ solution. After the red color disappeared, the pH of 10 was adjusted using ∼20 mL of 20:1 mixture of a saturated $NaHCO_3$ solution and 1 M NaOH solution. The resin was filtered off; the layers were separated, and the water phase was extracted two times with dichloromethane. The combined organic phases were dried over $MgSO_4$, and the solvent was removed under reduced pressure to yield the crude products, which were purified by flash column chromatography on silica gel.

The yields of the products are in all cases computed in relation to the stable linker precursor **7a** because the determination of the loading by sulfur elemental analysis of **7a** is more precise than the calculation by gravimetric measurements after subsequent steps. (Precursor **7a** is

Table 2. Synthesis of the Difluoro Biaryl Amide Library II

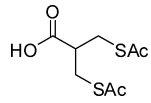




R^2 = \ R^1 =				
4-Me	**23{1;1}** 37%	**23{2;1}** 70%	**23{3;1}** 81%	**23{4;1}** 57%
4-Cl	**23{1;2}** 29%	**23{2;2}** 27%	**23{3;2}** 37%	**23{4;2}** 52%
4-*tert*-Bu	**23{1;3}** 31%	**23{2;3}** 23%	**23{3;3}** 53%	**23{4;3}** 54%

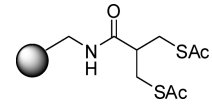
easily converted into dithiol linker **7** in one step.) Therefore the given yields are total yields over 4, 5, or 6 steps, respectively.

Synthesis of the Dithiol Linker 7. 3-(Acetylthio)-2-(acetylthiomethyl)propanoic Acid.



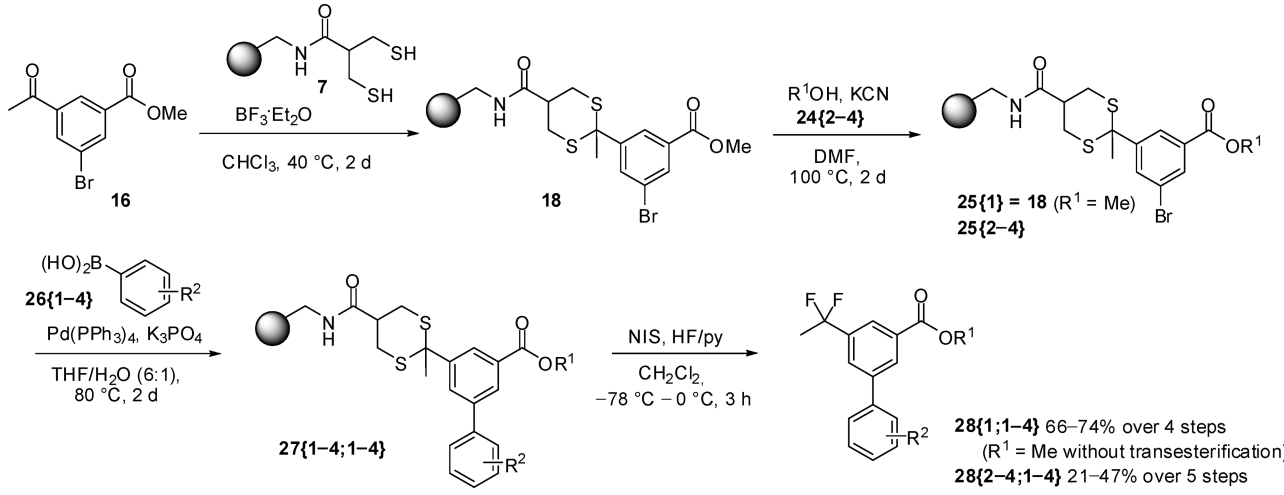
A solution of 5.50 g (52.0 mmol, 1.73 equiv) of Na_2CO_3 in 20 mL of water was added in small portions to a suspension of 4.95 g (30.0 mmol, 1.00 equiv) of 2-(bromomethyl)acrylic acid in 100 mL of water at 0 °C. Then 2.33 g (30.5 mmol, 1.02 equiv) of thioacetic acid was added slowly, and the mixture was stirred for 30 min; the pH of 1 was adjusted using diluted HCl solution. The mixture was extracted three times with ethyl acetate; the combined organic phases were dried over $MgSO_4$, and the solvent was removed under reduced pressure to yield 4.79 g (29.8 mmol) of 2-(acetylthiomethyl)acrylic acid as a colorless solid. The acid was dissolved in 50 mL of ethyl acetate, and 3.43 g (45.0 mmol, 1.50 equiv) of thioacetic acid was added; the reaction mixture was stirred for 24 h. The mixture was concentrated at reduced pressure removing the solvent and the excess of thioacetic acid to give 7.01 g (29.7 mmol, 99%) of the product as an orange oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.31 (s, 6 H, $COCH_3$), 2.88 (quin, 1 H, $^3J_{HH}$ = 6.5 Hz, $CH(CH_2)_2$), 3.17 (m, 4 H, CH_2S), 10.81 (s, 1 H, O*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.1 (CH_2S), 30.5 ($COCH_3$), 45.0 (*C*H), 177.8 (*C*OOH), 195.6 ($COCH_3$) ppm. IR (KBr): ν = 2991 (m, ν(OH)), 2927 (m), 2651 (w), 1695 (s, ν(CO)), 1423 (m), 1355 (m), 1305 (w), 1244 (m), 1133 (s), 958 (m), 852 (w), 806 (w), 688 (vw), 625 (m) cm^{-1}. MS (EI): *m*/*z* (%): 236 (1) [M$^+$], 219 (20) [M$^+$ − OH], 193 (30) [M$^+$ − $COCH_3$], 176 (52) [M$^+$ − $C_2H_4O_2$], 133 (60) [M$^+$ − $C_4H_7O_3$], 43 (100) [$C_2H_3O^+$]. HRMS ($C_8H_{12}O_4S_2$): calcd 236.0177, found 236.0180. EA ($C_8H_{12}O_4S_2$): calcd C 40.66, H 5.12, S 27.14; found C 40.43, H 5.35, S 27.89.

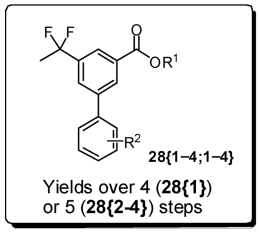
3-(Acetylthio)-2-(acetylthiomethyl)-*N*-methylpolystyryl-propanamide (7a).



5.00 g (10.3 mmol, 1.00 equiv) of aminomethyl polystyrene resin (loading 2.06 mmol/g) was covered with 50 mL of dry dichloromethane and shaken for 30 min. Then, 7.29 g (30.9 mmol, 3.00 equiv) of thioester was dissolved in 25 mL of dry dichloromethane and added to the resin. Afterward, 9.60 g (20.6 mmol, 2.00 equiv) of PyBrOP

Table 3. Synthesis of the Difluoro Biaryl Ester Library III

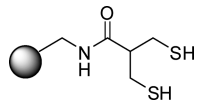




R^2 = \ R^1 =	Me			
H	**28{1;1}** 66%	**28{2;1}** 47%	**28{3;1}** 29%	**28{4;1}** 31%
4-Me	**28{1;2}** 74%	**28{2;2}** 37%	**28{3;2}** 21%	**28{4;2}** 30%
4-Cl	**28{1;3}** 67%	**28{2;3}** 39%	**28{3;3}** 28%	**28{4;3}** 25%
4-*tert*-Bu	**28{1;4}** 67%	**28{2;4}** 32%	**28{3;4}** 26%	**28{4;4}** 31%

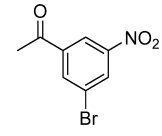
and 4.80 mL (30.9 mmol, 3.00 equiv) of DIPEA were added, and the mixture was shaken at room temperature. After 48 h, the reaction mixture was filtered off, washed according to GP1b, and dried under high vacuum to give 6.96 g of white resin **7a**. The yield and the loading of **7a** were determined using sulfur elemental analysis (87% yield, loading 1.23 mmol/g). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.4 (CH_2S), 30.6 ($COCH_3$), 53.5 ($COCH$), 171.5 ($NHCO$), 195.7 ($SCOCH_3$) ppm. IR (KBr): ν = 3564 (w), 3415 (m), 3336 (m), 3115 (w), 2979 (w), 2935 (w), 2784 (vw), 2688 (vw), 2305 (w), 1973 (w), 1894 (w), 1698 (s, ν(CO)), 1504 (m), 1469 (m), 1427 (m), 1406 (m), 1352 (m), 1232 (m), 1164 (m), 1132 (m), 1103 (m), 1039 (m), 995 (m), 954 (m), 856 (w). EA ($C_{44}H_{48}NS_2O_3$): calcd C 75.21, H 6.88, N 1.99, S 9.11; found C 74.92, H 6.22, N 2.09, S 7.90.

3-Mercapto-2-(mercaptomethyl)-*N*-methylpolystyrylpropanamide (7).



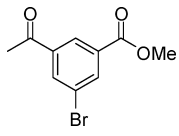
To 1.00 g (1.23 mmol, 1.00 equiv) of resin **7a** in 20 mL of chloroform was added 10 mL of HCl (1.25 M in methanol, 12.5 mmol, 10.0 equiv) under argon. After the mixture was shaken for 24 h at 50 °C, the volatile compounds were removed under reduced pressure, and the resin was dried 3 h under high vacuum and stored under argon atmosphere; 890 mg of white resin **7** was obtained (quantitative yield, loading 1.40 mmol/g). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.1 (CH_2SH), 54.7 ($COCH$), 171.7 ($NHCO$) ppm. IR (KBr): ν = 3408 (w), 3338 (w), 3024 (vw), 2925 (vw), 2562 (w, ν(SH)), 1731 (w), 1695 (m, ν(CO)), 1525 (w), 1407 (w), 1236 (w), 1172 (w), 1132 (w), 1089 (w), 1040 (w), 995 (w), 929 (w), 730 (w), 647 (w), 538 (vw). EA ($C_{40}H_{42}NS_2O$): calcd C 77.66, H 6.84, N 2.26, S 10.33; found C 76.87, H 6.78, N 2.36, S 8.95.

Syntheses in Liquid Phase. 3-Bromo-5-nitroacetophenone (5).



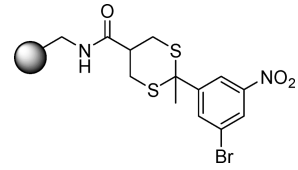
In a 250 mL round-bottom flask, 3.31 g (20.0 mmol, 1.00 equiv) of *m*-nitroacetophenone was dissolved in 80 mL of concentrated H_2SO_4. A solution of 6.32 g (22.0 mmol, 1.10 equiv) of dibromoisocyanuric acid (DIB) in 40 mL of concentrated H_2SO_4 was slowly added. After the reaction mixture had been stirred for 16 h at room temperature, it was carefully poured into the 2-fold volume of an ice/water mixture and extracted with ethyl acetate. The insoluble cyanuric acid was filtered off, and the organic layer was washed with saturated $NaHCO_3$ solution. After the mixture was dried over $MgSO_4$, the solvent was removed under reduced pressure to give 6.30 g of a yellow oil. The intermediate compound was dissolved in 70 mL of glacial acetic acid, and 600 mg (4.00 mmol, 0.20 equiv) of NaI, followed by 10.1 g (80.0 mmol, 4.00 equiv) of Na_2SO_3, was added. After 1 h, the mixture was diluted with 100 mL of water and extracted with ethyl acetate. The organic layer was washed several times with saturated Na_2CO_3 solution and dried over $MgSO_4$, and the solvent was removed under reduced pressure. Flash column chromatography on silica gel (cyclohexane/ethyl acetate 4:1, $R_f = 0.4$) gave 3.54 g (14.5 mmol, 73%) of the product as a bright yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.68$ (s, 3 H, CH_3CO), 8.39 (t,$^3J = 1.8$ Hz, 1 H, H_{Ar}), 8.55 (t,$^3J = 1.8$ Hz, 1 H, H_{Ar}), 8.68 (t,$^3J = 1.8$ Hz, 1 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 26.6$ (CH_3CO), 121.8 (C_{Ar}), 123.6 (C_{Ar}Br), 130.4 (C_{Ar}), 136.8 (C_{Ar}), 139.4 (C_{Ar}), 149.0 (C_{Ar}-NO_2), 194.3 (*C*O) ppm. IR (KBr): $\nu = 3977$ (w), 3373 (w), 3088 (m), 3013 (w), 2870 (m), 2329 (w), 2225 (w), 1796 (w), 1695 (s, ν(CO)), 1602 (m), 1568 (m), 1530 (s), 1421 (m), 1354 (s), 1258 (s), 1127 (m), 1077 (m), 1018 (m), 998 (m), 972 (m), 930 (m), 890 (m), 796 (m), 734 (m), 666 (m), 601 (m), 552 (w), 492 (m) cm^{-1}. MS (EI): *m*/*z* (%): 245/243 (32/32) [M^+], 230/228 (99/100) [$M^+ - CH_3$], 184/182 (14/14) [$C_7H_3BrO^+$], 75 (27) [$C_6H_3^+$]. HRMS ($C_8H_6BrNO_3$): calcd 242.9531; found 242.9528. EA ($C_8H_6BrNO_3$): calcd C 39.37, H 2.48, N 5.74; found C 38.96, H 2.49, N 5.58.

Methyl 3-Acetyl-5-bromobenzoate (16).



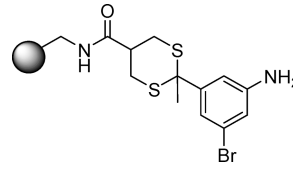
A solution of 36.6 mL (36.6 mmol, 2.20 equiv) of LiHMDS (1 M in THF) was cooled to −10 °C under argon atmosphere, and 6.10 mL (18.3 mmol, 1.10 equiv) of MeMgCl solution (3 M in THF) was added. After the mixture was stirred for 10 min at the same temperature, the mixture was added dropwise to a −10 °C cooled solution of 4.51 g (16.6 mmol, 1.00 equiv) of dimethyl 5-bromoisophthalate (**17**) in 120 mL of dry toluene. The mixture was kept at 0 °C for 1 h and then quenched by the addition of saturated NH_4Cl solution, followed by 1 M HCl solution. The reaction mixture was extracted with ethyl acetate; the organic layer washed with saturated $NaHCO_3$ solution and dried over $MgSO_4$, and the solvent was removed under reduced pressure. Flash column chromatography on silica gel (pentane/ethyl acetate 10:1, $R_f = 0.4$) gave 3.19 g (12.4 mmol, 75%) of the product as a colorless solid. ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 2.66$ (s, 3 H, COCH_3), 3.97 (s, 3 H, OCH_3), 8.28 (bs, 1 H, H_{Ar}), 8.36 (bs, 1 H, H_{Ar}), 8.51 (bs, 1 H, H_{Ar}) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 26.8$ (COCH_3), 52.8 (OCH_3), 123.2 (C_{Ar}Br), 128.1 (C_{Ar}), 132.4 (C_{Ar}), 135.3 (C_{Ar}), 136.7 (C_{Ar}COOCH$_3$), 138.7 (C_{Ar}COCH$_3$), 165.1 (*C*OOCH$_3$), 195.9 (*C*OCH$_3$) ppm. IR (KBr): $\nu = 3355$ (vw), 3070 (w), 3006 (w), 2952 (w), 1860 (vw), 1825 (vw), 1722 (w, ν(CO)), 1686 (w, ν(CO)), 1592 (w), 1571 (w), 1440 (w), 1420 (w), 1357 (w), 1297 (w), 1235 (w), 1186 (w), 1121 (w), 1090 (vw, ν(C_{aryl}Br)), 986 (w), 963 (w), 925 (vw), 902 (w), 860 (vw), 792 (w), 766 (w), 723 (w), 678 (w), 599 (w), 526 (w), 503 (vw), 487 (w), 468 (w), 454 (w), 432 (w), 418 (w), 410 (vw) cm^{-1}. MS (EI): *m*/*z* (%): 256/258 (17/16) [M^+], 241/243 (54/52) [$M^+ - CH_3$], 75 (14), 58 (23), 43 (100) [$C_2H_3O^+$]. HRMS ($C_{10}H_9BrO_3$): calcd 255.9735; found 255.9738. EA ($C_{10}H_9BrO_3$): calcd C 46.72, H 3.53; found C 46.46, H 3.55.

Attachment to the Solid Phase. 2-Methyl-*N*-methylpolystyryl-2-(5-bromo-3-nitrophenyl)-1,3-dithiane-5-carboxamide (8).



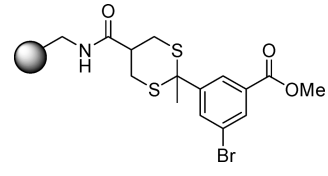
Following GP2, 3.26 g (13.4 mmol) of 3-bromo-5-nitroacetophenone (**5**) was reacted with 1.92 g (2.67 mmol) of resin **7** and 1.99 g (13.4 mmol) of BF_3*Et_2O. After the product was washed following GP1a and dried under high vacuum, 2.60 g of beige resin **8** was obtained. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 29.9$ (*C*H$_3$), 127.7 (C_{Ar}), 136.4 (C_{Ar}), 144.0 (C_{Ar}) ppm.

2-Methyl-*N*-methylpolystyryl-2-(3-amino-5-bromophenyl)-1,3-dithiane-5-carboxamide (9).



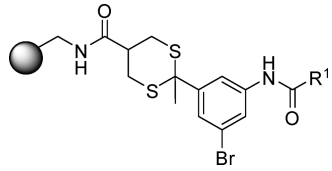
To 2.60 g (2.67 mmol, 1.00 equiv.) of resin **8** in 40 mL of dry DMF was added 5.01 g (26.7 mmol, 10.0 equiv) $SnCl_2$, and the mixture was shaken for 2 days at room temperature. The resin was filtered off, washed with DMF, H_2O/THF (1:1), CH_2Cl_2/MeOH/CH_2Cl_2/MeOH/CH_2Cl_2, and finally three times with CH_2Cl_2, and dried under high vacuum overnight to give 2.71 g of yellow resin **9**. The resin was used for the next step without ^{13}C NMR measurement. Loading: 0.98 mmol/g.

2-Methyl-*N*-methylpolystyryl-2-(5-bromo-3-(1-methoxyacetyl)phenyl)-1,3-dithiane-5-carboxamide (18).



Following GP2, 3.44 g (13.4 mmol) of methyl 3-acetyl-5-bromobenzoate (16) was reacted with 1.92 g (2.67 mmol) of resin 7 and 1.99 g (13.4 mmol) $BF_3 \cdot Et_2O$. After washing following GP1a and drying under high vacuum, 2.74 g of beige resin 18 was obtained. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 29.9$ (CH_3), 53.6 (OCH_3), 140.7 (C_{Ar}), 145.0 (C_{Ar}), 165.3 (COOMe) ppm. Loading: 0.97 mmol/g.

Synthesis of Library I. Amide Forming Reactions to Give Resins 11.



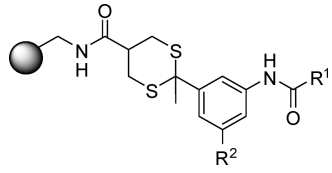
11{*1*} (R^1 = 4-Nitrophenyl). Following GP3, 840 mg (4.50 mmol) of 4-nitrobenzoyl chloride **10**{*1*} was reacted with 1.53 g (1.50 mmol) of resin **9** to give 1.76 g of orange resin **11**{*1*}. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 32.0$ (CH_3), 123.4 ($C_{Ar}C_{Ar}NO_2$), 164.0 (NH*C*O) ppm.

11{*2*} (R^1 = 2-Thienyl). Following GP3, 670 mg (4.50 mmol) of thiophene-2-carbonyl chloride **10**{*2*} was reacted with 1.53 g (1.50 mmol) of resin **9** to give 1.70 g of orange resin **11**{*2*}. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 29.9$ (CH_3), 162.1 (NH*C*O) ppm.

11{*3*} (R^1 = 1-Ethylpropyl). Following GP3, 610 mg (4.50 mmol) of 2-ethylbutanoyl chloride **10**{*3*} was reacted with 1.53 g (1.50 mmol) of resin **9** to give 1.68 g of orange resin **11**{*3*}. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 11.9$ (CH_3CH_2), 25.2 (CH_3CH_2), 31.0 (CH_3), 46.6 (CO*C*H(CH_2)$_2$), 166.0 (NH*C*O) ppm.

11{*4*} (R^1 = *tert*-Butyl). Following GP3, 540 mg (4.50 mmol) of pivaloyl chloride **10**{*4*} was reacted with 1.53 g (1.50 mmol) of resin **9** to give 1.65 g of orange resin **11**{*4*}. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 27.2$ (C(CH_3)$_3$), 31.0 (CH_3), 43.3 (*C*(CH_3)$_3$), 162.0 (NH*C*O) ppm.

Suzuki Coupling Reactions to Give Resins 13.



13{*1*;*1*} (R^1 = 4-Nitrophenyl, R^2 = Phenyl). Following GP4, 140 mg (1.15 mmol) of phenylboronic acid **12**{*1*} was reacted with 270 mg (0.230 mmol) of resin **11**{*1*} to give 302 mg of brown resin **13**{*1*;*1*}. The resin was used for the next step without ^{13}C NMR measurement.

13{*1*;*2*} (R^1 = 4-Nitrophenyl, R^2 = 4-Methylphenyl). Following GP4, 150 mg (1.10 mmol) of 4-methylphenylboronic acid **12**{*2*} was reacted with 260 mg (0.220 mmol) of resin **11**{*1*} to give 300 mg of brown resin **13**{*1*;*2*}. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 29.7$ (CH_3), 31.3 (CH_3), 162.0 (NH*C*O) ppm.

13{*1*;*3*} (R^1 = 4-Nitrophenyl, R^2 = 4-Chlorophenyl). Following GP4, 235 mg (1.50 mmol) of 4-chlorophenylboronic acid **12**{*3*} was reacted with 355 mg (0.300 mmol) of resin **11**{*1*} to give 414 mg of brown resin **13**{*1*;*3*}. The resin was used for the next step without ^{13}C NMR measurement.

13{*1*;*4*} (R^1 = 4-Nitrophenyl, R^2 = 4-Fluorophenyl). Following GP4, 210 mg (1.50 mmol) of 4-fluorophenylboronic acid **12**{*4*} was reacted with 355 mg (0.300 mmol) of resin **11**{*1*} to give 406 mg of brown resin **13**{1;4}. The resin was used for the next step without ^{13}C NMR measurement.

13{*2*;*1*} (R^1 = 2-Thienyl, R^2 = Phenyl). Following GP4, 135 mg (1.10 mmol) of phenylboronic acid **12**{*1*} was reacted with 250 mg (0.220 mmol) of resin **11**{*2*} to give 278 mg of brown resin **13**{*2*;*1*}. The resin was used for the next step without ^{13}C NMR measurement.

13{*2*;*2*} (R^1 = 2-Thienyl, R^2 = 4-Methylphenyl). Following GP4, 157 mg (1.15 mmol) of 4-methylphenylboronic acid **12**{*2*} was reacted with 263 mg (0.230 mmol) of resin **11**{*2*} to give 299 mg of brown resin **13**{*2*;*2*}. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.3$($C_{Ar}CH_3$), 31.0 (CH_3), 162.2 (NH*C*O) ppm.

13{*2*;*3*} (R^1 = 2-Thienyl, R^2 = 4-Chlorophenyl). Following GP4, 235 mg (1.50 mmol) of 4-chlorophenylboronic acid **12**{*3*} was reacted with 340 mg (0.300 mmol) of resin **11**{*2*} to give 392 mg of brown resin **13**{*2*;*3*}. The resin was used for the next step without ^{13}C NMR measurement.

13{2;4} (R^1 = 2-Thienyl, R^2 = 4-Fluorophenyl). Following GP4, 170 mg (1.20 mmol) of 4-fluorophenylboronic acid **12**{*4*} was reacted with 275 mg (0.240 mmol) of resin **11**{*2*} to give 312 mg of brown resin **13**{*2*;*4*}. The resin was used for the next step without ^{13}C NMR measurement.

13{*3*;*1*} (R^1 = 1-Ethylpropyl, R^2 = Phenyl). Following GP4, 140 mg (1.15 mmol) of phenylboronic acid **12**{*1*} was reacted with 260 mg (0.230 mmol) of resin **11**{*3*} to give 287 mg of brown resin **13**{*3*;*1*}. The resin was used for the next step without ^{13}C NMR measurement.

13{*3*;*2*} (R^1 = 1-Ethylpropyl, R^2 = 4-Methylphenyl). Following GP4, 157 mg (1.15 mmol) of 4-methylphenylboronic acid **12**{*2*} was reacted with 260 mg (0.230 mmol) of resin **11**{*3*} to give 304 mg of brown resin **13**{*3*;*2*}. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 11.9$ (CH_3CH_2), 21.6 ($C_{Ar}CH_3$), 25.2 (CH_3CH_2), 31.0 (CH_3), 46.6 (CO*C*H(CH_2)$_2$), 166.0 (NH*C*O) ppm.

13{*3*;*3*} (R^1 = 1-Ethylpropyl, R^2 = 4-Chlorophenyl). Following GP4, 235 mg (1.50 mmol) of 4-chlorophenylboronic acid **12**{*3*} was reacted with 340 mg (0.300 mmol) of resin **11**{*3*} to give 388 mg of brown resin **13**{*3*;*3*}. The resin was used for the next step without ^{13}C NMR measurement.

13{*3*;*4*} (R^1 = 1-Ethylpropyl, 4-Fluorophenyl). Following GP4, 210 mg (1.50 mmol) of 4-fluoro-phenylboronic acid **12**{*4*} was reacted with 340 mg (0.300 mmol) of resin **11**{*3*} to give 385 mg of brown resin **13**{*3*;*4*}. The resin was used for the next step without ^{13}C NMR measurement.

13{*4*;*1*} (R^1 = *tert*-Butyl, R^2 = Phenyl). Following GP4, 140 mg (1.15 mmol) of phenylboronic acid **12**{*1*} was reacted with 255 mg (0.230 mmol) of resin **11**{*4*} to give 276 mg of brown resin **13**{*4*;*1*}. The resin was used for the next step without ^{13}C NMR measurement.

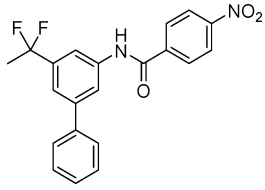
13{*4*;*2*} (R^1 = *tert*-Butyl, R^2 = 4-Methylphenyl). Following GP4, 157 mg (1.15 mmol) of 4-methylphenylboronic acid **12**{*2*} was reacted with 255 mg (0.230 mmol) of resin

11{*4*} to give 277 mg of brown resin **13**{*4*;*2*}. The resin was used for the next step without ^{13}C NMR measurement.

13{*4*;*3*} (R^1 = *tert*-Butyl, R^2 = 4-Chlorophenyl). Following GP4, 235 mg (1.50 mmol) of 4-chlorophenylboronic acid **12**{*3*} was reacted with 332 mg (0.300 mmol) of resin **11**{*4*} to give 358 mg of brown resin **13**{*4*;*3*}. The resin was used for the next step without ^{13}C NMR measurement.

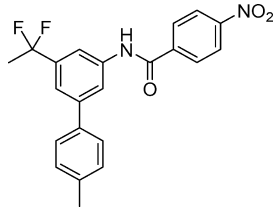
13{*4*,*4*} (R^1 = *tert*-Butyl, R^2 = 4-Fluorophenyl). Following GP4, 268 mg (1.90 mmol) of 4-fluorophenylboronic acid **12**{*4*} was reacted with 420 mg (0.380 mmol) of resin **11**{*4*} to give 459 mg of brown resin **13**{*4*;*4*}. The resin was used for the next step without ^{13}C NMR measurement.

Fluorinating Cleavage to Give Compounds 14. *N*-(5-(1,1-Difluoroethyl)biphenyl-3-yl)-4-nitrobenzamide (14{*1*;*1*}).



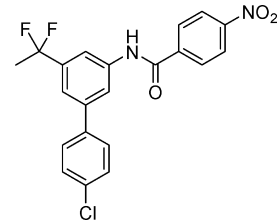
Following GP7, 302 mg (0.230 mmol) of resin **13**{*1*;*1*} was reacted with 203 mg (0.900 mmol) of NIS and 0.25 mL (10 mmol) of HF/py. After purification, 15.0 mg (0.039 mmol, 19% over 6 steps) of a white solid was obtained (cyclohexane/ethyl acetate 10:1, R_f = 0.2). ^1H NMR (250 MHz, $CDCl_3$): δ = 2.05 (t, $^3J_{HF}$ = 18.2 Hz, 3 H, C$H_3$$CF_2$), 7.42−7.57 (m, 5 H, H_{Ar}), 7.61 (m, 1 H, H_{Ar}), 7.82 (m, 1 H, H_{Ar}), 8.06 (m, 1 H, H_{Ar}), 8.13 (d, ^3J = 8.9 Hz, 2 H, H_{Ar}), 8.42 (d, ^3J = 8.9 Hz, 2 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.0 (t, $^2J_{CF}$ = 29.3 Hz, CH_3CF_2), 115.5 (t, $^3J_{CF}$ = 6.6 Hz, $C_{Ar}C_{Ar}CF_2$), 120.3 (t, $^3J_{CF}$ = 6.6 Hz, $C_{Ar}C_{Ar}CF_2$), 121.5 (t, $^1J_{CF}$ = 239.5 Hz, CF_2), 124.1 (C_{Ar}), 127.1 (C_{Ar}), 127.2 (C_{Ar}), 128.1 (C_{Ar}), 128.3 (C_{Ar}), 129.0 (C_{Ar}), 137.9 ($C_{Ar}CO$), 139.7 (t, $^2J_{CF}$ = 12.0 Hz, $C_{Ar}CF_2$), 139.9 (C_{Ar}), 140.0 ($C_{Ar}NH$), 143.0 (C_{Ar}), 149.9 ($C_{Ar}NO_2$), 163.8 (CO) ppm. ^{19}F NMR (376 MHz, H-decoupled, $CDCl_3$): δ = −88.0 ppm. IR (KBr): ν = 3302 (m, $\nu(NH_{trans})$), 3080 (w, ν(CH)), 2918 (w, $\nu(CH_3)$), 2852 (w, $\nu(CH_3)$), 2366 (vw), 1946 (w), 1730 (w), 1653 (m, ν(CO)), 1601 (m), 1549 (m), 1523 (m, ν_{AS}(Aryl-NO_2)), 1488 (m), 1463 (m), 1427 (m), 1385 (m), 1346 (m, ν_S(Aryl-NO_2)), 1326 (m), 1293 (m), 1251 (m, $\nu(C_{alkyl}F)$), 1182 (m), 1127 (m), 1106 (m), 1076 (w), 1046 (w), 1013 (w), 997 (w), 964 (w), 923 (m), 873 (m), 849 (m), 812 (w), 762 (m), 717 (m), 700 (m), 643 (w), 597 (m), 540 (w), 501 (w) cm^{-1}. MS (EI): *m*/*z* (%): 382 (69) [M^+], 150 (65) [$C_7H_4NO_3^+$], 104 (15), 58 (33), 43 (100). HRMS ($C_{21}H_{16}F_2N_2O_3$): calcd 382.1129; found 382.1127.

***N*-(5-(1,1-Difluoroethyl)-4′-methylbiphenyl-3-yl)-4-nitrobenzamide (14{*1*;*2*}).**



Following GP7, 300 mg (0.220 mmol) of resin **13**{*1*;*2*} was reacted with 200 mg (0.880 mmol) of NIS and 0.25 mL (10 mmol) of HF/py. After purification, 33.0 mg (0.083 mmol, 37% over 6 steps) of a bright yellow solid was obtained (cyclohexane/ethyl acetate 8:1, R_f = 0.3). ^1H NMR (400 MHz, acetone-d_6): δ = 2.04 (t, $^3J_{HF}$ = 18.4 Hz, 3 H, C$H_3$$CF_2$), 2.39 (s, 3 H, $C_{Ar}CH_3$), 7.33 (d, ^3J = 8.3 Hz, 2 H, H_{Ar}), 7.59 (m, 1 H, H_{Ar}), 7.61 (d, ^3J = 8.3 Hz, 2 H, H_{Ar}), 8.09 (m, 1 H, H_{Ar}), 8.26 (m, 1 H, H_{Ar}), 8.30 (d, ^3J = 9.0 Hz, 2 H, H_{Ar}), 8.40 (d, ^3J = 9.0 Hz, 2 H, H_{Ar}), 10.07 (bs, 1 H, NH) ppm. ^{13}C NMR (100 MHz, acetone-d_6): δ = 22.0 ($C_{Ar}CH_3$), 26.0 (t, $^2J_{CF}$ = 29.3 Hz, CH_3CF_2), 117.0 (t, $^3J_{CF}$ = 5.9 Hz, $C_{Ar}C_{Ar}CF_2$), 120.6 (t, $^3J_{CF}$ = 5.9 Hz, $C_{Ar}C_{Ar}CF_2$), 121.6 (C_{Ar}), 123.9 (t, $^1J_{CF}$ = 238.2 Hz, CF_2), 125.5 (C_{Ar}), 128.7 (C_{Ar}), 130.9 (C_{Ar}), 131.5 (C_{Ar}), 139.0 (C_{Ar}), 139.7 ($C_{Ar}CH_3$), 141.3 (t, $^2J_{CF}$ = 26.3 Hz, $C_{Ar}CF_2$), 141.7 (C_{Ar}), 142.6 ($C_{Ar}CO$), 144.0 ($C_{Ar}NH$), 151.7 ($C_{Ar}NO_2$), 165.9 (CO) ppm. ^{19}F NMR (376 MHz, H-decoupled, acetone-d_6): δ = −87.5 ppm. IR (KBr): ν = 3289 (m, $\nu(NH_{trans})$), 3075 (w), 3051 (w, ν(CH)), 2923 (w, $\nu(CH_3)$) 2858 (w, $\nu(CH_3)$), 1902 (vw), 1804 (w), 1653 (m, ν(CO)), 1601 (m), 1556 (m), 1522 (m, ν_{AS}(Aryl-NO_2)), 1479 (m), 1435 (m), 1401 (m), 1383 (m), 1346 (m, ν_S(Aryl-NO_2)), 1295 (m), 1252 (m, $\nu(C_{alkyl}F)$), 1183 (m), 1129 (m), 1105 (m), 1014 (w), 998 (w), 917 (m), 872 (m), 849 (m), 814 (m), 775 (w), 740 (w), 717 (m), 701 (m), 591 (w), 558 (w), 528 (m), 510 (m), 493 (m), 457 (w), 425 (w), 409 (vw) cm^{-1}. MS (EI): *m*/*z* (%): 396 (100) [M^+], 247 (17) [$M^+ - C_7H_3NO_3$], 150 (83) [$C_7H_4NO_3^+$], 104 (21), 91 (12) [$C_7H_7^+$]. HRMS ($C_{22}H_{18}F_2N_2O_3$): calcd 396.1285; found 396.1288.

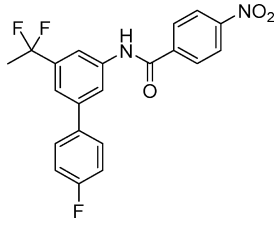
***N*-(4′-Chloro-5-(1,1-difluoroethyl)biphenyl-3-yl)-4-nitrobenzamide (14{*1*;*3*}).**



Following GP7, 414 mg (0.300 mmol) of resin of **13**{*1*;*3*} was reacted with 270 mg (1.20 mmol) of NIS and 0.30 mL (12 mmol) of HF/py. After purification, 24.0 mg (0.058 mmol, 19% over 6 steps) of a colorless solid was obtained (cyclohexane/ethyl acetate 7:1, R_f = 0.35). ^1H NMR (250 MHz, $CDCl_3$): δ = 1.98 (t, $^3J_{HF}$ = 18.3 Hz, 3 H, C$H_3$$CF_2$), 7.44 (d, ^3J = 8.5 Hz, 2 H, H_{Ar}), 7.51 (m, 1 H, H_{Ar}), 7.56 (d, ^3J = 8.5 Hz, 2 H, H_{Ar}), 7.72 (m, 1 H, H_{Ar}), 8.03 (m, 2 H, H_{Ar} and NH), 8.07 (d, ^3J = 8.5 Hz, 2 H, H_{Ar}), 8.37 (d, ^3J = 8.5 Hz, 2 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.0 (t, $^2J_{CF}$ = 29.2 Hz, CH_3CF_2), 113.2 (t, $^1J_{CF}$ = 242.7 Hz, CF_2), 115.7 (t, $^3J_{CF}$ = 6.5 Hz, $C_{Ar}C_{Ar}CF_2$), 120.0 (t, $^3J_{CF}$ = 6.5 Hz, $C_{Ar}C_{Ar}CF_2$), 121.4 (C_{Ar}), 124.2 (C_{Ar}), 128.3 (C_{Ar}), 128.5 (C_{Ar}), 129.1 (C_{Ar}), 131.3 ($C_{Ar}Cl$), 134.3 ($C_{Ar}CO$), 138.0 (t, $^2J_{CF}$ = 26.5 Hz, $C_{Ar}CF_2$), 138.2 (C_{Ar}), 140.0 (C_{Ar}), 141.8 ($C_{Ar}NH$), 149.9 ($C_{Ar}NO_2$), 163.8 (CO) ppm. ^{19}F NMR (376 MHz, H-decoupled, $CDCl_3$): δ = −88.0 ppm. IR (KBr): ν = 3291 (w, $\nu(NH_{trans})$), 3106 (w), 3005 (w, ν(CH)), 2923 (w, $\nu(CH_3)$), 2855 (w, $\nu(CH_3)$), 1897 (vw), 1653 (m, ν(CO)),

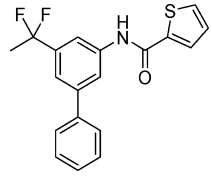
1602 (m), 1556 (m), 1523 (m, ν_{AS}(Aryl-NO_2)), 1490 (w), 1453 (m), 1434 (m), 1393 (w), 1346 (m, ν_S(Aryl-NO_2)), 1326 (w), 1294 (m), 1249 (m, ν(C_{alkyl}F)), 1180 (w), 1129 (w), 1105 (w), 1093 (w, ν(C_{aryl}Cl)), 1013 (w), 917 (w), 872 (w), 849 (w), 826 (m), 716 (w), 646 (w), 591 (w), 527 (w), 508 (w), 478 (w) cm^{-1}. MS (EI): *m/z* (%): 418/416 (27/84) [M^+], 150 (100) [$C_4H_7NO_3^+$], 104 (46), 76 (13). HRMS ($C_{21}H_{15}ClF_2N_2O_3$): calcd 416.0739; found 416.0742.

***N*-(5-(1,1-Difluoroethyl)-4′-fluorobiphenyl-3-yl)-4-nitrobenzamide (14{*1*;*4*}).**



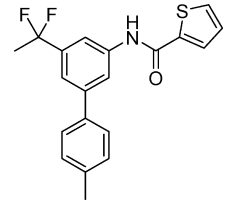
Following GP7, 406 mg (0.300 mmol) of resin **13**{*1*;*4*} was reacted with 270 mg (1.20 mmol) of NIS and 0.30 mL (12 mmol) of HF/py. After purification, 15.0 mg (0.037 mmol, 12% over 6 steps) of a colorless solid was obtained (cyclohexane/ethyl acetate 7:1, R_f = 0.3). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.98 (t, $^3J_{HF}$ = 18.0 Hz, 3 H, C$H_3$$CF_2$), 7.15 (t, ^3J = 8.5 Hz, 2 H, H_{Ar}), 7.50 (m, 1 H, H_{Ar}), 7.54−7.62 (m, 2 H, H_{Ar}), 7.70 (m, 1 H, H_{Ar}), 7.98 (bs, 1 H, N*H*), 8.01 (m, 1 H, H_{Ar}), 8.07 (d, ^3J = 8.5 Hz, 2 H, H_{Ar}), 8.37 (d, ^3J = 8.5 Hz, 2 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, acetone-d_6): δ = 26.9 (t, $^2J_{CF}$ = 29.3 Hz, CH_3CF_2), 117.2 (t, $^3J_{CF}$ = 6.6 Hz, $C_{Ar}C_{Ar}CF_2$), 117.6 (d, $^2J_{CF}$ = 22.0 Hz, $C_{Ar}C_{Ar}F$), 120.8 (t, $^3J_{CF}$ = 6.6 Hz, $C_{Ar}C_{Ar}CF_2$), 121.8 (C_{Ar}), 123.9 (t, $^1J_{CF}$ = 238.6 Hz, CF_2), 125.5 (C_{Ar}), 130.8 (d, $^3J_{CF}$ = 8.1 Hz, $C_{Ar}C_{Ar}C_{Ar}F$), 130.9 (C_{Ar}), 138.3 (d, $^4J_{CF}$ = 3.7 Hz, $C_{Ar}C_{Ar}C_{Ar}C_{Ar}F$), 141.4 (t, $^2J_{CF}$ = 26.7 Hz, $C_{Ar}CF_2$), 141.7 (C_{Ar}CO), 142.5 (C_{Ar}), 143.0 (C_{Ar}NH), 151.7 ($C_{Ar}NO_2$), 164.6 (d, $^1J_{CF}$ = 245.2 Hz, $C_{Ar}F$), 166.0 (*C*O) ppm. ^{19}F NMR (376 MHz, H-decoupled, acetone-d_6): δ = −87.4 (CF_2), −116.2 ($C_{Ar}F$) ppm. IR (KBr): ν = 3303 (w, ν(NH_{trans})), 3080 (w, ν(CH)), 2928 (vw, ν(CH_3)), 2857 (vw, ν(CH_3)), 2447 (vw), 1893 (vw), 1652 (m, ν(CO)), 1602 (m), 1551 (m), 1522 (m, ν_{AS}(Aryl-NO_2)), 1489 (w), 1455 (m), 1435 (m), 1400 (w) 1386 (w), 1347 (m, ν_S(Aryl-NO_2)), 1326 (m), 1295 (m), 1274 (m), 1251 (m, ν(C_{alkyl}F)), 1183 (m), 1160 (m), 1128 (w), 1105 (w, ν(C_{aryl}F)), 1014 (w), 922 (w), 872 (m), 850 (m), 836 (m), 785 (w), 755 (w), 717 (m), 701 (m), 649 (w), 596 (w), 557 (w), 513 (w), 420 (w) cm^{-1}. MS (EI): *m/z* (%): 400 (100) [M^+], 150 (89) [$C_7H_4NO_3^+$], 104 (24). HRMS ($C_{21}H_{15}F_3N_2O_3$): calcd 400.1035; found 400.1038.

***N*-(5-(1,1-Difluoroethyl)biphenyl-3-yl)thiophene-2-carboxamide (14{*2*;*1*}).**



Following GP7, 278 mg (0.220 mmol) of resin **13**{*2*;*1*} was reacted with 200 mg (0.900 mmol) of NIS and 0.25 mL (10 mmol) of HF/py. After purification, 26.0 mg (0.076 mmol, 34% over 6 steps) of a colorless solid was obtained (cyclohexane/ethyl acetate 10:1, R_f = 0.25). ^{1}H NMR (500 MHz, acetone-d_6): δ = 2.03 (t, $^3J_{HF}$ = 18.5 Hz, 3 H, C$H_3$$CF_2$), 7.19−7.23 (m, 1 H, H_{Ar}), 7.41 (t, ^3J = 7.2 Hz, 1 H, H_{Ar}), 7.50 (t, ^3J = 7.8 Hz, 2 H, H_{Ar}), 7.56 (m, 1 H, H_{Ar}), 7.69−7.72 (m, 2 H, H_{Ar}), 7.79−7.81 (m, 1 H, H_{Ar}), 7.97−7.99 (m, 1 H, H_{Ar}), 8.04 (m, 1 H, H_{Ar}), 8.25 (m, 1 H, H_{Ar}), 9.76 (bs, 1 H, N*H*) ppm. ^{13}C NMR (125 MHz, acetone-d_6): δ = 26.9 (t, $^2J_{CF}$ = 29.4 Hz, CH_3CF_2), 117.0 (t, $^3J_{CF}$ = 6.4 Hz, $C_{Ar}C_{Ar}CF_2$), 120.3 (t, $^3J_{CF}$ = 6.4 Hz, $C_{Ar}C_{Ar}CF_2$), 121.6 (C_{Ar}), 123.9 (t, $^1J_{CF}$ = 238.2 Hz, CF_2), 128.9 (C_{Ar}), 129.7 (C_{Ar}), 129.8 (C_{Ar}), 130.5 (C_{Ar}), 130.8 (C_{Ar}), 133.5 (C_{Ar}), 141.3 (t, $^2J_{CF}$ = 26.7 Hz, $C_{Ar}CF_2$), 141.8 (C_{Ar}CO), 141.9 (C_{Ar}), 142.0 (C_{Ar}), 144.0 (C_{Ar}NH), 162.1 (*C*O) ppm. ^{19}F NMR (376 MHz, H-decoupled, acetone-d_6): δ = −87.8 ppm. IR (KBr): ν = 3855 (vw), 3309 (w, ν(NH_{trans})), 3088 (w), 3001 (vw, ν(CH)), 2926 (w, ν(CH_3)), 2853 (vw, ν(CH_3)), 2347 (vw), 1702 (w), 1638 (w, ν(CO)), 1615 (w), 1551 (w), 1498 (w), 1448 (w), 1383 (w), 1352 (w), 1294 (w), 1250 (w, ν(C_{alkyl}F)), 1208 (vw), 1178 (w), 1098 (w), 1076 (vw), 1028 (vw), 911 (w), 878 (w), 846 (w), 809 (w), 763 (w), 722 (w), 701 (w), 639 (w), 602 (w), 578 (w), 477 (vw) cm^{-1}. MS (EI): *m/z* (%): 343 (51) [M^+], 233 (10) [M^+ − C_5H_2OS], 111 (100) [$C_5H_3OS^+$], 83 (14) [$C_4H_3S^+$], 43 (81). HRMS ($C_{19}H_{15}F_2NOS$): calcd 343.0842; found 343.0840.

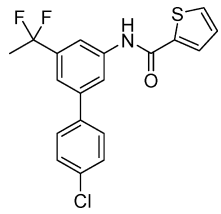
***N*-(5-(1,1-Difluoroethyl)-4′-methylbiphenyl-3-yl)thiophene-2-carboxamide (14{*2*;*2*}).**



Following GP7, 299 mg (0.230 mmol) of resin **13**{*2*;*2*} was reacted with 200 mg (0.900 mmol) of NIS and 0.25 mL (10 mmol) of HF/py. After purification, 15.0 mg (0.042 mmol, 19% over 6 steps) of a colorless solid was obtained (cyclohexane/ethyl acetate 8:1, R_f = 0.3). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.95 (t, $^3J_{HF}$ = 18.3 Hz, 3 H, C$H_3$$CF_2$), 2.40 (s, 3 H, $C_{Ar}CH_3$), 7.11−7.16 (m, 1 H, H_{Ar}), 7.24 (d, ^3J = 8.2 Hz, 2 H, H_{Ar}), 7.50 (d, ^3J = 8.2 Hz, 2 H, H_{Ar}), 7.55−7.59 (m, 1 H, H_{Ar}), 7.66−7.69 (m, 1 H, H_{Ar}), 7.71 (m, 1 H, H_{Ar}), 7.95 (m, 2 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.2 ($C_{Ar}CH_3$), 26.0 (t, $^2J_{CF}$ = 29.2 Hz, CH_3CF_2), 115.1 (t, $^3J_{CF}$ = 6.5 Hz, $C_{Ar}C_{Ar}CF_2$), 119.3 (t, $^3J_{CF}$ = 6.5 Hz, $C_{Ar}C_{Ar}CF_2$), 119.9 (C_{Ar}), 121.6 (t, $^1J_{CF}$ = 239.6 Hz, CF_2), 127.0 (C_{Ar}), 127.9 (C_{Ar}), 128.6 (C_{Ar}), 129.6 (C_{Ar}), 131.2 (C_{Ar}), 136.9 ($C_{Ar}CH_3$), 137.8 (C_{Ar}), 138.2 (C_{Ar}), 138.9 (C_{Ar}), 139.5 (t, $^2J_{CF}$ = 26.3 Hz, $C_{Ar}CF_2$), 142.6 (C_{Ar}NH), 160.1 (*C*O) ppm. ^{19}F NMR (376 MHz, H-decoupled, $CDCl_3$): δ = −87.8 ppm. IR (KBr): ν = 3334 (m, ν(NH_{trans})), 3109 (m), 3085

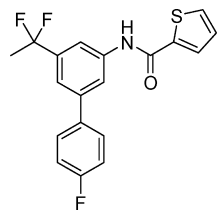
(m), 3004 (m, ν(CH)), 2917 (m, $\nu(CH_3)$), 2861 (m, $\nu(CH_3)$), 1906 (w), 1772 (w), 1631 (s, ν(CO)), 1614 (m), 1551 (s), 1454 (s), 1382 (m), 1350 (m), 1295 (s), 1252 (s, $\nu(C_{alkyl}F)$), 1202 (m), 1176 (m), 1144 (m), 1102 (m), 1071 (m), 1019 (m), 964 (m), 927 (m), 904 (m), 880 (m), 853 (m), 812 (m), 774 (m), 727 (s), 704 (m), 650 (m), 619 (m), 605 (m), 582 (m), 550 (m), 507 (m), 486 (m), 432 (w), 408 (w) cm^{-1}. MS (EI): *m*/*z* (%): 357 (50) $[M^+]$, 247 (28) $[M^+ - C_5H_2OS]$, 111 (58) $[C_5H_3OS^+]$, 43 (100). HRMS ($C_{20}H_{17}F_2NOS$): calcd 357.0999; found 357.1002.

***N*-(4′-Chloro-5-(1,1-difluoroethyl)biphenyl-3-yl)thiophene-2-carboxamide (14{*2*;*3*}).**



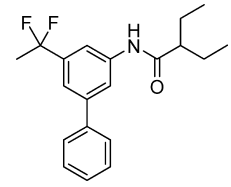
Following GP7, 392 mg (0.300 mmol) of resin **13**{*2*;*3*} was reacted with 270 mg (1.20 mmol) of NIS and 0.30 mL (12 mmol) of HF/py. After purification, 26.0 mg (0.069 mmol, 23% over 6 steps) of a colorless solid was obtained (cyclohexane/ethyl acetate 10:1, $R_f = 0.15$). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.95 (t, $^3J_{HF}$ = 18.3 Hz, 3 H, CH_3CF$_2$), 7.11−7.16 (m, 1 H, H_{Ar}), 7.40 (d, ^3J = 8.5 Hz, 2 H, H_{Ar}), 7.45 (m, 1 H, H_{Ar}), 7.52 (d, ^3J = 8.5 Hz, 2 H, H_{Ar}), 7.56−7.60 (m, 1 H, H_{Ar}), 7.66−7.69 (m, 2 H, H_{Ar}), 7.94 (bs, 1 H, N*H*), 8.00 (m, 1 H, H_{Ar}) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.0 (t, $^2J_{CF}$ = 30.3 Hz, *C*H$_3$CF$_2$), 115.5 (t, $^3J_{CF}$ = 6.4 Hz, $C_{Ar}C_{Ar}CF_2$), 119.3 (t, $^3J_{CF}$ = 6.4 Hz, $C_{Ar}C_{Ar}CF_2$), 120.0 (C_{Ar}), 121.5 (t, $^1J_{CF}$ = 239.9 Hz, *C*F$_2$), 128.0 (C_{Ar}), 128.5 (C_{Ar}), 128.7 (C_{Ar}), 129.0 (C_{Ar}), 131.3 (C_{Ar}), 134.1 (C_{Ar}Cl), 138.3 (C_{Ar}), 138.4 (C_{Ar}CO), 138.7 (C_{Ar}), 139.8 (t, $^2J_{CF}$ = 26.7 Hz, $C_{Ar}CF_2$), 141.5 (C_{Ar}NH), 160.1 (*C*O) ppm. ^{19}F NMR (376 MHz, H-decoupled, $CDCl_3$): δ = −88.0 ppm. IR (KBr): ν = 3303 (w, $\nu(NH_{trans})$), 3090 (w), 3000 (w, ν(CH)), 2926 (w, $\nu(CH_3)$), 1900 (vw), 1639 (m, ν(CO)), 1613 (m), 1550 (m), 1493 (m), 1453 (m), 1432 (m), 1393 (m), 1351 (m), 1292 (m), 1249 (m, $\nu(C_{alkyl}F)$), 1209 (w), 1177 (m), 1145 (m), 1094 (m, $\nu(C_{aryl}Cl)$), 1045 (w), 1013 (m), 912 (m), 880 (m), 846 (m), 826 (m), 720 (m), 646 (w), 601 (w), 578 (w), 477 (w) cm^{-1}. MS (EI): *m*/*z* (%): 379/377 (12/35) $[M^+]$, 111 (100) $[C_5H_3OS^+]$, 83 (6) $[C_4H_3S^+]$, 57 (6) $[C_4H_9^+]$. HRMS ($C_{19}H_{14}ClF_2NOS$): calcd 377.0453; found 377.0456.

***N*-(5-(1,1-Difluoroethyl)-4′-fluorobiphenyl-3-yl)thiophene-2-carboxamide (14{*2*;*4*}).**



Following GP7, 312 mg (0.240 mmol) of resin **13**{*2*;*4*} was reacted with 225 mg (1.00 mmol) of NIS and 0.25 mL (10 mmol) of HF/py. After purification, 14.0 mg (0.039 mmol, 16% over 6 steps) of a colorless solid was obtained (cyclohexane/ethyl acetate 10:1, $R_f = 0.15$). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.95 (t, $^3J_{HF}$ = 18.0 Hz, 3 H, CH_3CF$_2$), 7.08−7.17 (m, 3 H, H_{Ar}), 7.44 (m, 1 H, H_{Ar}), 7.52−7.60 (m, 3 H, H_{Ar}), 7.65−7.70 (m, 2 H, H_{Ar}), 7.94 (bs, 1 H, N*H*), 7.99 (m, 1 H, H_{Ar}) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.0 (t, $^2J_{CF}$ = 30.3 Hz, *C*H$_3$CF$_2$), 115.2 (t, $^3J_{CF}$ = 6.6 Hz, $C_{Ar}C_{Ar}CF_2$), 115.8 (d, $^2J_{CF}$ = 21.2 Hz, $C_{Ar}C_{Ar}$F), 119.3 (t, $^3J_{CF}$ = 6.6 Hz, $C_{Ar}C_{Ar}CF_2$), 120.0 (C_{Ar}), 121.5 (t, $^1J_{CF}$ = 239.7 Hz, *C*F$_2$), 128.0 (C_{Ar}), 128.7 (C_{Ar}), 128.9 (d, $^3J_{CF}$ = 8.8 Hz, $C_{Ar}C_{Ar}C_{Ar}$F), 131.3 (C_{Ar}), 136.0 (d, $^4J_{CF}$ = 3.7 Hz, $C_{Ar}C_{Ar}C_{Ar}C_{Ar}$F), 138.3 (C_{Ar}CO), 138.8 (C_{Ar}), 139.7 (t, $^2J_{CF}$ = 27.1 Hz, $C_{Ar}CF_2$), 141.7 (C_{Ar}NH), 160.1 (*C*O), 163.8 (d, $^1J_{CF}$ = 247.4 Hz, C_{Ar}F) ppm. ^{19}F NMR (376 MHz, H-decoupled, $CDCl_3$): δ = −88.2 (CF_2), −114.7 ($C_{Ar}F$) ppm. IR (KBr): ν = 3286 (m, $\nu(NH_{trans})$), 3112 (w), 3089 (w, ν(CH)), 2996 (w, $\nu(CH_3)$) 2854 (vw, $\nu(CH_3)$), 1639 (m, ν(CO)), 1613 (m), 1548 (m), 1510 (m), 1456 (m), 1437 (m), 1416 (m), 1400 (m), 1382 (m), 1353 (m), 1306 (m), 1280 (m), 1250 (m, $\nu(C_{alkyl}F)$), 1220 (m), 1179 (m), 1159 (m), 1140 (m), 1116 (w, $\nu(C_{aryl}F)$), 1101 (m), 1013 (w), 922 (m), 883 (w), 831 (m), 782 (w), 744 (w), 724 (m), 703 (m), 650 (w), 599 (w), 578 (w), 553 (w), 510 (w) cm^{-1}. MS (EI): *m*/*z* (%): 361 (95) $[M^+]$, 111 (100) $[C_5H_3OS^+]$, 83 (6) $[C_4H_3S^+]$. HRMS ($C_{19}H_{14}F_3NOS$): calcd 361.0748; found 361.0750.

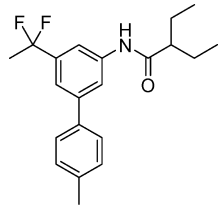
***N*-(5-(1,1-Difluoroethyl)biphenyl-3-yl)-2-ethylbutanamide (14{*3*;*1*}).**



Following GP7, 287 mg (0.230 mmol) of resin **13**{3;1} was reacted with 203 mg (0.900 mmol) of NIS and 0.25 mL (10 mmol) of HF/py. After purification, 10.0 mg (0.030 mmol, 13% over 6 steps) of a colorless solid was obtained (cyclohexane/ethyl acetate 7:1, $R_f = 0.4$). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.98 (t, ^3J = 7.3 Hz, 6 H, CH_2CH_3), 1.50−1.80 (m, 4 H, CH_2CH$_3$), 1.96 (t, $^3J_{HF}$ = 18.3 Hz, 3 H, CH_3CF$_2$), 2.05−2.15 (m, 1 H, CH(CH$_2$)$_2$), 7.33−7.49 (m, 5 H, H_{Ar}), 7.57−7.65 (m, 2 H, H_{Ar} and N*H*), 7.66 (m, 1 H, H_{Ar}), 7.94 (m, 1 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.1 (CH_2CH_3), 25.9 (*C*H$_2$CH$_3$), 26.0 (t, $^2J_{CF}$ = 30.0 Hz, *C*H$_3$CF$_2$), 52.5 (*C*H(CH$_2$H$_3$)$_2$), 114.9 (t, $^3J_{CF}$ = 6.6 Hz, $C_{Ar}C_{Ar}CF_2$), 119.2 (t, $^3J_{CF}$ = 6.6 Hz, $C_{Ar}C_{Ar}CF_2$), 119.8 (C_{Ar}), 121.6 (t, $^1J_{CF}$ = 239.4 Hz, *C*F$_2$), 127.2 (C_{Ar}), 127.9 (C_{Ar}), 128.8 (C_{Ar}), 138.5 (C_{Ar}), 139.5 (t, $^2J_{CF}$ = 26.7 Hz, $C_{Ar}CF_2$), 140.0 (C_{Ar}NH), 142.6 (C_{Ar}), 174.5 (*C*O) ppm. ^{19}F NMR (376 MHz, H-decoupled, $CDCl_3$): δ = −87.9 ppm. IR (KBr): ν = 3260 (m, $\nu(NH_{trans})$), 3108 (m, ν(CH)), 2960 (m, $\nu(CH_3)$), 2930 (m, $\nu(CH_2)$), 2872 (m, $\nu(CH_3)$) 1949 (w), 1782 (w), 1660 (m, ν(CO)), 1614 (m), 1562 (m), 1498 (m), 1465 (m, $\delta(CH_2)$), 1427 (m), 1380 (m), 1250 (m, $\nu(C_{alkyl}F)$), 1178 (m), 1117 (m), 1075 (m), 1031 (w), 971 (w), 910 (m), 876 (m), 832 (w), 808 (m), 762 (m), 728 (m, $\delta(CH_2)$), 701 (m), 641 (w), 603 (m), 590 (w), 528 (w), 509 (w), 434 (w), 408 (w) cm^{-1}. MS (EI): *m*/*z* (%): 331 (32) $[M^+]$, 233

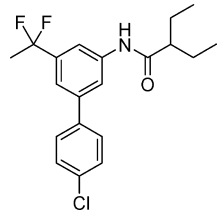
(100) [$M^+ - C_6H_{10}O$], 71 (11) [$C_5H_{11}^+$], 43 (16). HRMS ($C_{20}H_{23}F_2NO$): calcd 331.1748; found 331.1750.

***N*-(5-(1,1-Difluoroethyl)-4′-methylbiphenyl-3-yl)-2-ethylbutanamide (14{*3*;*2*}).**



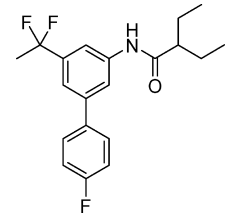
Following GP7, 304 mg (0.230 mmol) of resin **13**{*3*;*2*} was reacted with 200 mg (0.900 mmol) of NIS and 0.25 mL (10 mmol) of HF/py. After purification, 23.0 mg (0.067 mmol, 30% over 6 steps) of a colorless solid was obtained (cyclohexane/ethyl acetate 7:1, $R_f = 0.35$). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.97 (t, ^3J = 7.6 Hz, 6 H, CH_2CH_3), 1.50−1.80 (m, 4 H, CH_2CH_3), 1.95 (t, $^3J_{HF}$ = 18.3 Hz, 3 H, CH_3CF_2), 2.05−2.15 (m, 1 H, $CH(CH_2)_2$), 2.39 (s, 3 H, $C_{Ar}CH_3$), 7.24 (d, ^3J = 7.9 Hz, 2 H, H_{Ar}), 7.35 (bs, 1 H, N*H*), 7.45 (m, 1 H, H_{Ar}), 7.50 (d, ^3J = 7.9 Hz, 2 H, H_{Ar}), 7.64 (m, 1 H, H_{Ar}), 7.91 (m, 1 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.1 (CH_2CH_3), 21.1 ($C_{Ar}CH_3$), 25.9 (CH_2CH_3), 26.0 (t, $^2J_{CF}$ = 30.0 Hz, CH_3CF_2), 52.5 ($CH(CH_2H_3)_2$), 114.6 (t, $^3J_{CF}$ = 6.6 Hz, $C_{Ar}C_{Ar}CF_2$), 118.9 (t, $^3J_{CF}$ = 6.6 Hz, $C_{Ar}C_{Ar}CF_2$), 119.5 (C_{Ar}), 121.6 (t, $^1J_{CF}$ = 239.4 Hz, CF_2), 127.0 (C_{Ar}), 129.5 (C_{Ar}), 137.0 (C_{Ar}), 137.8 ($C_{Ar}CH_3$), 138.5 (C_{Ar}), 139.4 (t, $^2J_{CF}$ = 27.0 Hz, $C_{Ar}CF_2$), 142.5 (C_{Ar}NH), 174.5 (*C*O) ppm. ^{19}F NMR (376 MHz, H-decoupled, $CDCl_3$): δ = −88.0 ppm. IR (KBr): ν = 3262 (m, $\nu(NH_{trans})$), 3106 (m, ν(CH)), 2964 (m, $\nu(CH_3)$), 2931 (m, $\nu(CH_2)$), 2873 (m, $\nu(CH_3)$), 1907 (w), 1660 (m, ν(CO)), 1613 (m), 1554 (m), 1457 (m, $\delta(CH_2)$), 1379 (m), 1349 (m), 1280 (m), 1253 (m, $\nu(C_{alkyl}F)$), 1228 (m), 1177 (m), 1043 (w), 1019 (w), 998 (w), 958 (m), 909 (m), 881 (m), 818 (m), 773 (m), 703 (m, $\delta(CH_2)$), 638 (w), 593 (w), 528 (w), 509 (w), 410 (w) cm^{-1}. MS (EI): *m*/*z* (%): 345 (37) [M^+], 247 (100) [$M^+ - C_6H_{10}O$], 71 (17) [$C_5H_{11}^+$], 43 (14). HRMS ($C_{21}H_{25}F_2NO$): calcd 345.1904; found 345.1906.

***N*-(4′-Chloro-5-(1,1-difluoroethyl)biphenyl-3-yl)-2-ethylbutanamide (14{*3*;*3*}).**



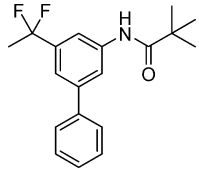
Following GP7, 388 mg (0.300 mmol) of resin **13**{*3*;*3*} was reacted with 270 mg (1.20 mmol) of NIS and 0.30 mL (12 mmol) of HF/py. After purification, 26.0 mg (0.071 mmol, 24% over 6 steps) of a colorless solid was obtained (cyclohexane/ethyl acetate 7:1, R_f = 0.4). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.97 (t, ^3J = 7.6 Hz, 6 H, CH_2CH_3), 1.60−1.80 (m, 4 H, CH_2CH_3), 1.95 (t, $^3J_{HF}$ = 18.0 Hz, 3 H, CH_3CF_2), 2.03−2.11 (m, 1 H, $CH(CH_2)_2$), 7.32 (m, 1 H, H_{Ar}), 7.40 (d, ^3J = 8.5 Hz, 2 H, H_{Ar}), 7.54 (d, ^3J = 8.5 Hz, 2 H, H_{Ar}), 7.60 (m, 1 H, H_{Ar}), 7.98 (m, 1 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.1 (CH_2CH_3), 25.9 (CH_2CH_3), 26.0 (t, $^2J_{CF}$ = 29.2 Hz, CH_3CF_2), 52.5 ($CH(CH_2CH_3)_2$), 115.0 (t, $^3J_{CF}$ = 6.2 Hz, $C_{Ar}C_{Ar}CF_2$), 118.9 (t, $^3J_{CF}$ = 6.2 Hz, $C_{Ar}C_{Ar}CF_2$), 119.6 (C_{Ar}), 121.5 (t, $^1J_{CF}$ = 239.8 Hz, CF_2), 128.5 (C_{Ar}), 129.0 (C_{Ar}), 134.1 (C_{Ar}), 138.4 (C_{Ar}), 138.6 (C_{Ar}), 139.7 (t, $^2J_{CF}$ = 26.8 Hz, $C_{Ar}CF_2$), 141.4 (C_{Ar}NH), 174.5 (*C*O) ppm. ^{19}F NMR (376 MHz, H-decoupled, $CDCl_3$): δ = −88.2 ppm. IR (KBr): ν = 3256 (m, $\nu(NH_{trans})$ 3105 (m, ν(CH)), 2961 (m, $\nu(CH_3)$), 2936 (m, $\nu(CH_2)$), 2875 (m, $\nu(CH_3)$), 1899 (vw), 1659 (m, ν(CO)), 1611 (m), 1555 (m), 1494 (m), 1456 (s, $\delta(CH_2)$), 1430 (m), 1381 (m), 1349 (m), 1279 (m), 1250 (m, $\nu(C_{alkyl}F)$), 1230 (m), 1180 (m), 1115 (m), 1092 (m, $\nu(C_{aryl}Cl)$), 1012 (m), 956 (w), 929 (m), 909 (m), 896 (m), 882 (m), 829 (m), 774 (w), 728 (m, $\delta(CH_2)$), 703 (m), 667 (w), 644 (w), 605 (w), 592 (w), 526 (w), 498 (w), 477 (w), 437 (w), 409 (w) cm^{-1}. MS (EI): *m*/*z* (%): 367/365 (25/70) [M^+], 294 (5) [$M^+ - C_5H_{11}^+$], 267 (100) [$M^+ - C_6H_{10}O$], 99 (2) [$C_6H_{11}O^+$], 71 (4) [$C_5H_{11}^+$]. HRMS ($C_{20}H_{22}ClF_2NO$): calcd 365.1358; found 365.1355.

***N*-(5-(1,1-Difluoroethyl)-4′-fluorobiphenyl-3-yl)-2-ethylbutanamide (14{*3*;*4*}).**



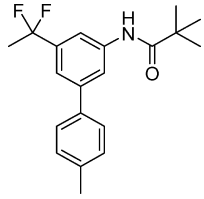
Following GP7, 385 mg (0.300 mmol) of resin **13**{*3*;*4*} was reacted with 270 mg (1.20 mmol) of NIS and 0.30 mL (12 mmol) of HF/py. After purification, 21.0 mg (0.060 mmol, 20% over 6 steps) of a colorless solid was obtained (cyclohexane/ethyl acetate 10:1, R_f = 0.3). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.97 (t, ^3J = 7.7 Hz, 6 H, CH_2CH_3), 1.53−1.80 (m, 4 H, CH_2CH_3), 1.95 (t, $^3J_{HF}$ = 18.4 Hz, 3 H, CH_3CF_2), 2.01−2.11 (m, 1 H, $CH(CH_2CH_3)_2$), 7.12 (t, $^3J_{HF}$ = 8.6 Hz, 2 H, H_{Ar}), 7.34 (bs, 1 H, N*H*), 7.41 (m, 1 H, H_{Ar}), 7.54−7.58 (m, 2 H, H_{Ar}), 7.59 (m, 1 H, H_{Ar}), 7.96 (m, 1 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.1 (CH_2CH_3), 25.9 (CH_2CH_3), 26.0 (t, $^2J_{CF}$ = 30.0 Hz, CH_3CF_2), 52.5 ($CH(CH_2CH_3)_2$), 114.8 (t, $^3J_{CF}$ = 6.6 Hz, $C_{Ar}C_{Ar}CF_2$), 115.7 (d, $^2J_{CF}$ = 21.2 Hz, $C_{Ar}C_{Ar}F$), 118.9 (t, $^3J_{CF}$ = 6.6 Hz, $C_{Ar}C_{Ar}CF_2$), 119.6 (C_{Ar}), 121.5 (t, $^1J_{CF}$ = 239.6 Hz, CF_2), 128.9 (d, $^3J_{CF}$ = 8.0 Hz, $C_{Ar}C_{Ar}C_{Ar}F$), 136.1 (d, $^4J_{CF}$ = 2.2 Hz, $C_{Ar}C_{Ar}C_{Ar}C_{Ar}F$), 138.6 ($C_{Ar}$), 139.6 (t, $^2J_{CF}$ = 26.3 Hz, $C_{Ar}CF_2$), 141.7 (C_{Ar}NH), 162.7 (d, $^1J_{CF}$ = 247.4 Hz, $C_{Ar}F$), 174.6 (*C*O) ppm. ^{19}F NMR (376 MHz, H-decoupled, $CDCl_3$): δ = −88.0 (CF_2), −114.5 ($C_{Ar}F$) ppm. IR (KBr): ν = 3261 (m, $\nu(NH_{trans})$), 3166 (m), 3108 (m, ν(CH)), 2961 (m, $\nu(CH_3)$), 2930 (m, $\nu(CH_2)$), 2873 (m, $\nu(CH_3)$), 1895 (w), 1660 (m, ν(CO)), 1615 (m), 1556 (m), 1511 (m), 1458 (m, $\delta(CH_2)$), 1431 (m), 1402 (m), 1381 (m), 1350 (m), 1250 (m, $\nu(C_{alkyl}F)$), 1225 (m), 1179 (m), 1160 (m), 1116 (m, $\nu(C_{aryl}F)$), 1099 (m), 1075 (m), 1014 (m), 929 (m), 913 (m), 880 (m), 837 (m), 785 (m), 728 (m, $\delta(CH_2)$), 703 (m), 651 (w), 605 (w), 590 (w), 557 (w), 527 (m), 511 (w), 451 (w), 411 (w) cm^{-1}. MS (EI): *m*/*z* (%): 349 (33) [M^+], 251 (100) [$M^+ - C_6H_{10}O$], 99 (6) [$C_6H_{11}O^+$], 71 (38) [$C_5H_{11}^+$]. HRMS ($C_{20}H_{22}F_3NO$): calcd 349.1653; found 349.1650.

***N*-(5-(1,1-Difluoroethyl)biphenyl-3-yl)pivalamide (14{*4*;*1*}).**



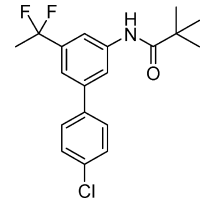
Following GP7, 276 mg (0.230 mmol) of resin **13**{*4*;*1*} was reacted with 203 mg (0.900 mmol) of NIS and 0.25 mL (10 mmol) of HF/py. After purification, 15.0 mg (0.048 mmol, 21% over 6 steps) of a colorless solid was obtained (cyclohexane/ethyl acetate 7:1, $R_f = 0.25$). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.35 (s, 9 H, C(C*H*$_3$)$_3$), 1.96 (t, $^3J_{HF}$ = 18.3 Hz, 3 H, C*H*$_3$CF$_2$), 7.35−7.50 (m, 5 H, H_{Ar}), 7.58−7.63 (m, 2 H, H_{Ar} and N*H*), 7.64 (m, 1 H, H_{Ar}), 7.91 (m, 1 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.0 (t, $^2J_{CF}$ = 30.0 Hz, *C*H$_3$CF$_2$), 27.6 (C(*C*H$_3$)$_3$), 39.7 (*C*(CH$_3$)$_3$), 115.0 (t, $^3J_{CF}$ = 5.9 Hz, $C_{Ar}C_{Ar}CF_2$), 119.1 (t, $^3J_{CF}$ = 5.9 Hz, $C_{Ar}C_{Ar}CF_2$), 119.9 (C_{Ar}), 121.6 (t, $^1J_{CF}$ = 239.7 Hz, *C*F$_2$), 127.2 (C_{Ar}), 127.9 (C_{Ar}), 128.9 (C_{Ar}), 138.6 (C_{Ar}), 139.5 (t, $^2J_{CF}$ = 27.0 Hz, $C_{Ar}CF_2$), 140.0 (C_{Ar}NH), 142.6 (C_{Ar}), 176.9 (*C*O) ppm. ^{19}F NMR (376 MHz, H-decoupled, $CDCl_3$): δ = −88.0 ppm. IR (KBr): ν = 3342 (m, ν(NH$_{trans}$)), 3060 (w, ν(CH)), 2968 (m, ν(CH$_3$)), 2871 (w, ν(CH$_3$)), 1953 (vw), 1657 (m, ν(CO)), 1612 (m), 1548 (m), 1479 (m), 1461 (m), 1447 (m), 1382 (m), 1348 (m), 1289 (m), 1251 (m, ν(C$_{alkyl}$F)), 1214 (m), 1164 (m) 1076 (w), 1027 (w), 965 (m), 928 (m), 902 (m), 879 (m), 806 (w), 763 (m), 700 (m), 643 (w), 599 (w), 574 (w) 528 (w), 509 (w), 451 (w) cm^{-1}. MS (EI): *m*/*z* (%): 317 (72) [M$^+$], 233 (53) [M$^+$ − C$_5$H$_8$O], 57 (51) [C$_4$H$_9^+$], 43 (100). HRMS (C$_{19}$H$_{21}$F$_2$NO): calcd 317.1591; found 317.1588.

***N*-(5-(1,1-Difluoroethyl)-4′-methylbiphenyl-3-yl)pivalamide (14{*4*;*2*}).**



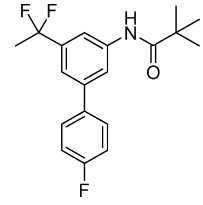
Following GP7, 277 mg (0.230 mmol) of resin **13**{*4*;*2*} was reacted with 203 mg (0.900 mmol) of NIS and 0.25 mL (10 mmol) of HF/py. After purification, 21.0 mg (0.063 mmol, 29% over 6 steps) of a colorless solid was obtained (cyclohexane/ethyl acetate 7:1, $R_f = 0.4$). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.35 (s, 9 H, C(C*H*$_3$)$_3$), 1.95 (t, $^3J_{HF}$ = 18.3 Hz, 3 H, C*H*$_3$CF$_2$), 2.40 (s, 3 H, $C_{Ar}CH_3$), 7.25 (d, ^3J = 8.2 Hz, 2 H, H_{Ar}), 7.45 (m, 2 H, H_{Ar} and N*H*), 7.51 (d, ^3J = 8.2 Hz, 2 H, H_{Ar}), 7.63 (m, 1 H, H_{Ar}), 7.88 (m, 1 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.1 ($C_{Ar}CH_3$), 26.0 (t, $^2J_{CF}$ = 30.0 Hz, *C*H$_3$CF$_2$), 27.6 (C(*C*H$_3$)$_3$), 39.7 (*C*(CH$_3$)$_3$), 114.8 (t, $^3J_{CF}$ = 5.9 Hz, $C_{Ar}C_{Ar}CF_2$), 118.9 (t, $^3J_{CF}$ = 5.9 Hz, $C_{Ar}C_{Ar}CF_2$), 119.6 (C_{Ar}), 121.6 (t, $^1J_{CF}$ = 239.5 Hz, *C*F$_2$), 127.2 (C_{Ar}), 129.5 (C_{Ar}), 137.0 ($C_{Ar}CH_3$), 137.8 (C_{Ar}), 138.6 (C_{Ar}), 139.4 (t, $^2J_{CF}$ = 26.3 Hz, $C_{Ar}CF_2$), 142.5 (C_{Ar}NH), 176.8 (*C*O) ppm. ^{19}F NMR (376 MHz, H-decoupled, $CDCl_3$): δ = −87.7 ppm. IR (KBr): ν = 3340 (w, ν(NH$_{trans}$)), 2968 (w, ν(CH$_3$)), 2870 (vw, ν(CH$_3$)), 1904 (vw), 1764 (vw), 1658 (m, ν(CO)), 1613 (w), 1551 (w), 1478 (w), 1454 (w) 1424 (w), 1350 (w), 1319 (w), 1288 (w), 1249 (w, ν(C$_{alkyl}$F)), 1211 (w), 1167 (w), 1020 (vw), 927 (w), 901 (w), 877 (w), 817 (w), 773 (vw), 706 (w), 654 (vw), 608 (vw), 558 (vw), 528 (vw), 509 (vw), 451 (vw), 433 (vw), 424 (vw), 408 (w) cm^{-1}. MS (EI): *m*/*z* (%): 331 (100) [M$^+$], 247 (36) [M$^+$ − C$_5$H$_8$O], 57 (72) [C$_4$H$_9^+$], 43 (13). HRMS (C$_{20}$H$_{23}$F$_2$NO): calcd 331.1748; found 331.1750.

***N*-(4′-Chloro-5-(1,1-difluoroethyl)biphenyl-3-yl)pivalamide (14{*4*;*3*}).**



Following GP7, 358 mg (0.300 mmol) of resin **13**{*4*;*3*} was reacted with 270 mg (1.20 mmol) of NIS and 0.30 mL (12 mmol) of HF/py. After purification, 14.0 mg (0.040 mmol, 13% over 6 steps) of a colorless solid was obtained (cyclohexane/ethyl acetate 7:1, $R_f = 0.5$). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.35 (s, 9 H, C(C*H*$_3$)$_3$), 1.95 (t, $^3J_{HF}$ = 18.3 Hz, 3 H, C*H*$_3$CF$_2$), 7.40 (d, ^3J = 8.5 Hz, 2 H, H_{Ar}), 7.46 (m, 1 H, H_{Ar}), 7.54 (d, ^3J = 8.5 Hz, 2 H, H_{Ar}), 7.59 (m, 1 H, H_{Ar}), 7.94 (m, 1 H, H_{Ar}), 8.94 (bs, 1 H, N*H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.0 (t, $^2J_{CF}$ = 29.4 Hz, *C*H$_3$CF$_2$), 27.6 (C(*C*H$_3$)$_3$), 39.8 (*C*(CH$_3$)$_3$), 115.3 (t, $^3J_{CF}$ = 5.5 Hz, $C_{Ar}C_{Ar}CF_2$), 118.9 (t, $^3J_{CF}$ = 5.5 Hz, $C_{Ar}C_{Ar}CF_2$), 119.7 (C_{Ar}), 121.5 (t, $^1J_{CF}$ = 239.9 Hz, *C*F$_2$), 128.5 (C_{Ar}), 129.0 (C_{Ar}), 134.0 (C_{Ar}Cl), 138.5 (C_{Ar}), 138.8 (C_{Ar}), 139.7 (t, $^3J_{CF}$ = 26.7 Hz, $C_{Ar}CF_2$), 141.4 (C_{Ar}NH), 176.9 (*C*O) ppm. ^{19}F NMR (376 MHz, H-decoupled, $CDCl_3$): δ = −88.2 ppm. IR (KBr): ν = 3348 (w, ν(NH$_{trans}$)), 3082 (vw, ν(CH)), 2968 (w, ν(CH$_3$)), 2928 (w), 2871 (w, ν(CH$_3$)), 1903 (vw), 1659 (m, ν(CO)), 1612 (w), 1550 (w), 1493 (w), 1478 (w), 1454 (m), 1424 (w), 1382 (w), 1350 (w), 1320 (vw), 1289 (w), 1249 (w, ν(C$_{alkyl}$F)), 1216 (w), 1170 (w), 1146 (w), 1092 (w, ν(C$_{aryl}$Cl)), 1013 (w), 929 (w), 902 (w), 879 (w), 830 (w), 806 (w), 767 (vw), 703 (w), 640 (vw), 605 (vw), 575 (vw), 506 (w), 477 (w) cm^{-1}. MS (EI): *m*/*z* (%): 353/351 (20/59) [M$^+$], 294 (4) [M$^+$ − C$_4$H$_9$], 267 (32) [M$^+$ − C$_5$H$_8$O], 57 (100) [C$_4$H$_9^+$], 41 (12) [C$_3$H$_5^+$]. HRMS (C$_{19}$H$_{20}$ClF$_2$NO): calcd 351.1201; found 351.1204.

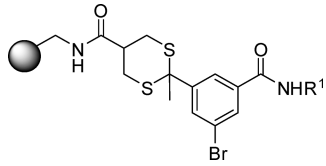
***N*-(5-(1,1-Difluoroethyl)-4′-fluorobiphenyl-3-yl)pivalamide (14{*4*;*4*}).**



Following GP7, 459 mg (0.380 mmol) of resin **13**{*4*;*4*} was reacted with 342 mg (1.52 mmol) of NIS and 0.38 mL (16 mmol) of HF/py. After purification, 17.0 mg (0.051 mmol, 13% over 6 steps) of a colorless solid was obtained (cyclohexane/ethyl acetate 7:1, R_f = 0.5). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.35 (s, 9 H, C(C*H*$_3$)$_3$), 1.95 (t, $^3J_{HF}$ = 18.0 Hz, 3 H, C*H*$_3$CF$_2$), 7.12 (t, ^3J = 8.9 Hz, 2 H, H_{Ar}),

7.41 (m, 1 H, H_{Ar}), 7.47 (bs, 1 H, N*H*), 7.53−7.59 (m, 3 H, H_{Ar}), 7.92 (m, 1 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.0 (t, $^2J_{CF}$ = 30.0 Hz, *C*H_3CF$_2$), 27.6 (C(*C*H$_3$)$_3$), 39.7 (*C*(CH$_3$)$_3$), 115.0 (t, $^3J_{CF}$ = 5.8 Hz, $C_{Ar}C_{Ar}CF_2$), 115.7 (d, $^2J_{CF}$ = 21.2 Hz, $C_{Ar}C_{Ar}F$), 118.9 (t, $^3J_{CF}$ = 5.8 Hz, $C_{Ar}C_{Ar}CF_2$), 121.5 (t, $^1J_{CF}$ = 239.5 Hz, *C*F$_2$), 123.9 (C_{Ar}), 128.7 (d, $^3J_{CF}$ = 8.0 Hz, $C_{Ar}C_{Ar}C_{Ar}F$), 136.1 (d, $^4J_{CF}$ = 4.4 Hz, $C_{Ar}C_{Ar}C_{Ar}C_{Ar}F$), 138.7 ($C_{Ar}$), 139.5 (t, $^3J_{CF}$ = 27.0 Hz, $C_{Ar}CF_2$), 141.6 (C_{Ar}NH), 162.7 (d, $^1J_{CF}$ = 251.8 Hz, $C_{Ar}F$), 176.9 (*C*O) ppm. ^{19}F NMR (376 MHz, H-decoupled, $CDCl_3$): δ = −87.8 (C*F*$_2$), −114.7 (C_{Ar}*F*) ppm. IR (KBr): ν = 3322 (m, ν(NH$_{trans}$)), 3114 (w), 3074 (w, ν(CH)), 2975 (w, ν(CH$_3$)), 2873 (w, ν(CH$_3$)), 1894 (w), 1649 (m, ν(CO)), 1613 (m), 1560 (m), 1531 (m), 1510 (m), 1478 (m), 1457 (m), 1430 (m), 1399 (m), 1383 (m),1348 (m), 1293 (w), 1251 (m, ν(C_{alkyl}F)), 1218 (m), 1162 (m), 1102 (w, ν(C_{aryl}F)), 1015 (w), 967 (w), 926 (m), 905 (m), 875 (w), 835 (m), 815 (w), 785 (w), 700 (m), 646 (w), 605 (w), 576 (w), 557 (w), 511 (w), 438 (w) cm^{-1}. MS (EI): *m*/*z* (%): 335 (71) [M$^+$], 251 (46) [M$^+$-C$_5$H$_8$O], 85 (20) [C$_5$H$_9$O$^+$], 57 (100) [C$_4$H$_9^+$], 43 (88). HRMS ($C_{19}H_{20}F_3NO$): calcd 335.1497; found 335.1494.

Synthesis of Library II. Amide Forming Reactions to Give Resins 20.



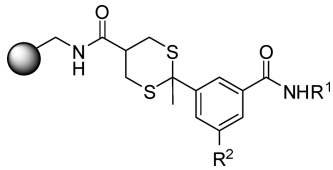
20{*1*} (R^1 = Butyl). Following GP5, 172 mg (2.35 mmol) of 1-butyl amine **19**{*1*} was reacted with 805 mg (0.780 mmol) of resin **18** to give 902 mg of yellow resin **20**{*1*}. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0 (*C*H$_3$CH$_2$), 20.3 (CH$_3$*C*H$_2$), 30.4 (*C*H$_3$), 31.7 (NHCH$_2$*C*H$_2$), 40.2 (NH*C*H$_2$), 164.1 (NH*C*O) ppm.

20{*2*} (R^1 = 4-Chlorobenzyl). Following GP5, 335 mg (2.35 mmol) of 4-chlorobenzyl amine **19**{*2*} was reacted with 805 mg (0.780 mmol) of resin **18** to give 965 mg of yellow resin **20**{*2*}. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.2 (*C*H$_3$), 42.1 (NH*C*H$_2$), 162.4 (NH*C*O) ppm.

20{*3*} (R^1 = 4-Ethylphenyl). Following GP5, 303 mg (2.35 mmol) of 4-ethylaniline **19**{*3*} was reacted with 805 mg (0.780 mmol) of resin **18** to give 965 mg of orange resin **20**{*3*}. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.9 (*C*H$_3$CH$_2$), 28.5 (CH$_3$*C*H$_2$), 31.0 (*C*H$_3$), 161.0 (NH*C*O) ppm.

20{*4*} (R^1 = 4-*tert*-Butylphenyl). Following GP5, 350 mg (2.35 mmol) of 4-*tert*-butylaniline **19**{*4*} was reacted with 805 mg (0.780 mmol) of resin **18** to give 995 mg of orange resin **20**{*4*}. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.0 (*C*H$_3$), 31.4 (C(*C*H$_3$)$_3$), 34.4 (*C*(CH$_3$)$_3$), 163.5 (NH*C*O) ppm.

Suzuki Coupling Reactions to Give Resins 22.



22{*1*;*1*} (R^1 = Butyl, R^2 = 4-Methylphenyl). Following GP4, 136 mg (1.00 mmol) of 4-methylphenylboronic acid **21**{*1*} was reacted with 232 mg (0.200 mmol) of resin **20**{*1*} to give 249 mg of brown resin **22**{*1*;*1*}. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1 (*C*H$_3$CH$_2$), 20.4 (CH$_3$*C*H$_2$), 21.3 (C_{Ar}*C*H$_3$), 30.1 (*C*H$_3$), 31.9 (NHCH$_2$*C*H$_2$), 40.5 (NH*C*H$_2$), 164.9 (NH*C*O) ppm.

22{*1*;*2*} (R^1 = Butyl, R^2 = 4-Chlorophenyl). Following GP4, 156 mg (1.00 mmol) of 4-chlorophenylboronic acid **21**{*2*} was reacted with 232 mg (0.200 mmol) of resin **20**{*1*} to give 257 mg of brown resin **22**{*1*;*2*}. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2 (*C*H$_3$CH$_2$), 20.4 (CH$_3$*C*H$_2$), 30.4 (*C*H$_3$), 31.9 (NHCH$_2$*C*H$_2$), 40.5 (NH*C*H$_2$), 164.8 (NH*C*O) ppm.

22{*1*;*3*} (R^1 = Butyl, R^2 = 4-*tert*-Butylphenyl). Following GP4, 180 mg (1.00 mmol) of 4-*tert*-butylphenylboronic acid **21**{*3*} was reacted with 232 mg (0.200 mmol) of resin **20**{*1*} to give 264 mg of brown resin **22**{*1*;*3*}. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0 (*C*H$_3$CH$_2$), 20.3 (CH$_3$*C*H$_2$), 30.7 (*C*H$_3$), 31.5 (C(*C*H$_3$)$_3$), 31.7 (NHCH$_2$*C*H$_2$), 34.7 (*C*(CH$_3$)$_3$), 40.5 (NH*C*H$_2$), 164.9 (NH*C*O) ppm.

22{*2*;*1*} (R^1 = 4-Chlorobenzyl, R^2 = 4-Methylphenyl). Following GP4, 136 mg (1.00 mmol) of 4-methylphenylboronic acid **21**{*1*} was reacted with 250 mg (0.200 mmol) of resin **20**{*2*} to give 267 mg of brown resin **22**{*2*;*1*}. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.5 (C_{Ar}*C*H$_3$), 30.7 (*C*H$_3$), 42.5 (NH*C*H$_2$), 163.5 (NH*C*O) ppm.

22{*2*;*2*} (R^1 = 4-Chlorobenzyl, R^2 = 4-Chlorophenyl). Following GP4, 87.0 mg (0.550 mmol) of 4-chlorophenylboronic acid **21**{*2*} was reacted with 135 mg (0.110 mmol) of resin **20**{*2*} to give 146 mg of brown resin **22**{*2*;*2*}. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.9 (*C*H$_3$), 42.1 (NH*C*H$_2$), 164.4 (NH*C*O) ppm.

22{*2*;*3*} (R^1 = 4-Chlorobenzyl, R^2 = 4-*tert*-Butylphenyl). Following GP4, 98.0 mg (0.550 mmol) of 4-*tert*-butylphenylboronic acid **21**{*3*} was reacted with 135 mg (0.110 mmol) of resin **20**{*2*} to give 154 mg of brown resin **22**{*2*;*3*}. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.2 (*C*H$_3$), 31.5 (C(*C*H$_3$)$_3$), 34.7 (*C*(CH$_3$)$_3$), 42.6 (NH*C*H$_2$), 127.7 (C_{Ar}-C_{Ar}C(CH$_3$)$_3$), 162.4 (NH*C*O) ppm.

22{*3*;*1*} (R^1 = 4-Ethylphenyl, R^2 = 4-Methylphenyl). Following GP4, 136 mg (1.00 mmol) of 4-methylphenylboronic acid **21**{*1*} was reacted with 250 mg (0.200 mmol) of resin **20**{*3*} to give 276 mg of brown resin **22**{*3*;*1*}. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.9 (*C*H$_3$CH$_2$), 21.4 (C_{Ar}*C*H$_3$), 28.5 (CH$_3$*C*H$_2$), 30.8 (*C*H$_3$), 120.9 ($C_{Ar}C_{Ar}$NH), 163.0 (NH*C*O) ppm.

22{*3*;*2*} (R^1 = 4-Ethylphenyl, R^2 = 4-Chlorophenyl). Following GP4, 87.0 mg (0.550 mmol) of 4-chlorophenylboronic acid **21**{*2*} was reacted with 135 mg (0.110 mmol) of resin **20**{*3*} to give 149 mg of brown resin **22**{*3*;*2*}. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.9 (*C*H$_3$CH$_2$), 28.5 (CH$_3$*C*H$_2$), 31.1 (*C*H$_3$), 120.1 ($C_{Ar}C_{Ar}$NH), 162.0 (NH*C*O) ppm.

22{*3*;*3*} (R^1 = 4-Ethylphenyl, R^2 = 4-*tert*-Butylphenyl). Following GP4, 80.0 mg (0.450 mmol) of 4-*tert*-butylphenylboronic acid **21**{*3*} was reacted with 111 mg (0.090 mmol) of resin **20**{*3*} to give 129 mg of brown resin **22**{*3*;*3*}. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.9 (*C*H$_3$CH$_2$), 28.5 (CH$_3$*C*H$_2$), 31.0 (*C*H$_3$), 31.5 (C(*C*H$_3$)$_3$), 34.7 (*C*(CH$_3$)$_3$), 121.1 ($C_{Ar}C_{Ar}$NH), 162.1 (NH*C*O) ppm.

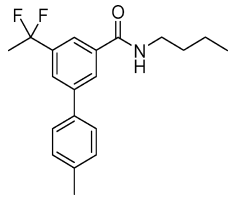
22{*4*;*1*} (R^1 = 4-tert-Butylphenyl, R^2 = 4-Methylphenyl). Following GP4, 136 mg (1.00 mmol) of 4-methylphe-

nylboronic acid **21**{*1*} was reacted with 255 mg (0.200 mmol) of resin **20**{*4*} to give 277 mg of brown resin **22**{*4*;*1*}. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.6 ($C_{Ar}CH_3$), 31.0 (CH_3), 31.4 ($C(CH_3)_3$), 34.4 ($C(CH_3)_3$), 120.6 ($C_{Ar}C_{Ar}NH$), 163.4 (NH*C*O) ppm.

22{*4*;*2*} (R^1 = 4-tert-Butylphenyl, R^2 = 4-Chlorophenyl). Following GP4, 156 mg (1.00 mmol) of 4-chlorophenylboronic acid **21**{*2*} was reacted with 255 mg (0.200 mmol) of resin **20**{*4*} to give 275 mg of brown resin **22**{*4*;*2*}. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.9 (CH_3), 31.5 ($C(CH_3)_3$), 34.6 ($C(CH_3)_3$), 120.6 ($C_{Ar}C_{Ar}NH$), 163.5 (NH*C*O) ppm.

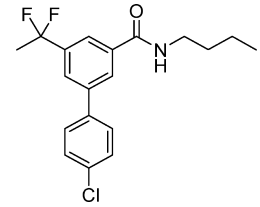
22{*4*;*3*} (R^1 = 4-tert-Butylphenyl, R^2 = 4-*tert*-Butylphenyl). Following GP4, 180 mg (1.00 mmol) of 4-*tert*-butylphenylboronic acid **21**{*3*} was reacted with 255 mg (0.200 mmol) of resin **20**{*4*} to give 282 mg of brown resin **22**{*4*;*3*}. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.0 (CH_3), 31.5 ($C(CH_3)_3$), 34.6 ($C(CH_3)_3$), 120.5 ($C_{Ar}C_{Ar}NH$), 163.7 (NH*C*O) ppm.

Fluorinating Cleavage to Give Compounds 23. *N*-Butyl-5-(1,1-difluoroethyl)-4′-methylbiphenyl-3-carboxamide (23{*1*;*1*}).



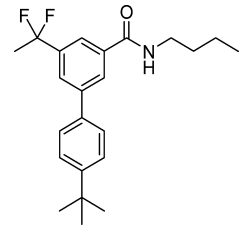
Following GP7, 249 mg (0.200 mmol) of resin **22**{*1*;*1*} was reacted with 180 mg (0.800 mmol) of NIS and 0.20 mL (8.0 mmol) of HF/py. After purification, 24.0 mg (0.073 mmol, 37% over 5 steps) of a colorless solid was obtained (cyclohexane/ethyl acetate 10:1, R_f = 0.2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.96 (t, ^3J = 7.3 Hz, 3 H, CH_2CH_3), 1.42 (sex, ^3J = 7.3 Hz, 2 H, $CH_2CH_2CH_3$), 1.62 (quin, ^3J = 7.3 Hz, 2H, $CH_2CH_2CH_2$), 1.97 (t, $^3J_{HF}$ = 18.4 Hz, 3 H, CH_3CF_2), 2.41 (s, 3 H, $C_{Ar}CH_3$), 3.42−3.51 (m, 2 H, NHCH_2), 6.30 (bs, 1 H, N*H*), 7.27 (d, ^3J = 8.1 Hz, 2 H, H_{Ar}), 7.51 (d, ^3J = 8.1 Hz, 2 H, H_{Ar}), 7.81 (m, 2 H, H_{Ar}), 8.01 (m, 1 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8 (CH_2CH_3), 20.1 (CH_2CH_3), 21.1 ($C_{Ar}CH_3$), 26.0 (t, $^2J_{CF}$ = 29.3 Hz, CH_3CF_2), 31.7 ($CH_2CH_2CH_3$), 40.0 (CH_2NH), 121.4 (t, $^3J_{CF}$ = 5.9 Hz, $C_{Ar}C_{Ar}CF_2$), 121.5 (t, $^1J_{CF}$ = 239.7 Hz, CF_2), 126.0 (t, $^3J_{CF}$ = 5.9 Hz, $C_{Ar}C_{Ar}CF_2$), 126.8 (C_{Ar}), 127.1 (C_{Ar}), 129.7 (C_{Ar}), 135.9 (C_{Ar}), 136.6 (C_{Ar}), 138.1 ($C_{Ar}CH_3$), 139.1 (t, $^2J_{CF}$ = 27.1 Hz, $C_{Ar}CF_2$), 142.1 ($C_{Ar}CO$), 166.9 (*C*O) ppm. ^{19}F NMR (376 MHz, H-decoupled, $CDCl_3$): δ = −88.0 ppm. IR (KBr): ν = 3252 (m, $\nu(NH_{trans})$), 3085 (m), 3000 (m, ν(CH)), 2963 (m, $\nu(CH_3)$), 2929 (m, $\nu(CH_2)$), 2861 (m, $\nu(CH_3)$), 1904 (vw), 1845 (vw), 1632 (m, ν(CO)), 1599 (m), 1555 (m), 1516 (m), 1442 (m, $\delta(CH_2)$), 1379 (m), 1347 (m), 1311 (m), 1289 (m), 1255 (m, $\nu(C_{alkyl}F)$), 1226 (m), 1181 (m), 1128 (m), 1080 (w), 1018 (w), 977 (w), 905 (m), 815 (m), 733 (m, $\delta(CH_2)$), 647 (w), 631 (w), 610 (w), 566 (w), 497 (w), 432 (w) cm^{-1}. MS (EI): *m*/*z* (%): 331 (52) [M^+], 289 (68), 259 (100) [$C_{16}H_{13}F_2O^+$]. HRMS ($C_{20}H_{23}F_2NO$): calcd 331.1748; found 331.1745.

***N*-Butyl-4′-chloro-5-(1,1-difluoroethyl)biphenyl-3-carboxamide (23{*1*;*2*}).**



Following GP7, 257 mg (0.200 mmol) of resin **22**{*1*;*2*} was reacted with 180 mg (0.800 mmol) of NIS and 0.20 mL (8.0 mmol) of HF/py. After purification, 20.0 mg (0.057 mmol, 29% over 5 steps) of a colorless solid was obtained (cyclohexane/ethyl acetate 10:1, R_f = 0.15). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.97 (t, ^3J = 7.5 Hz, 3 H, CH_2CH_3), 1.42 (sex, ^3J = 7.5 Hz, 2 H, $CH_2CH_2CH_3$), 1.59−1.66 (m, 2H, $CH_2CH_2CH_3$), 1.97 (t, $^3J_{HF}$ = 18.2 Hz, 3 H, CH_3CF_2), 3.46−3.51 (m, 2 H, NHCH_2), 6.27 (bs, 1 H, N*H*), 7.43 (d, ^3J = 8.5 Hz, 2 H, H_{Ar}), 7.54 (d, ^3J = 8.5 Hz, 2 H, H_{Ar}), 7.78 (m, 1 H, H_{Ar}), 7.83 (m, 1 H, H_{Ar}), 8.00 (m, 1 H, H_{Ar}) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.8 (CH_2CH_3), 20.2 (CH_2CH_3), 26.0 (t, $^2J_{CF}$ = 29.4 Hz, CH_3CF_2), 31.7 ($CH_2CH_2CH_3$), 40.0 (CH_2NH), 121.4 (t, $^1J_{CF}$ = 239.9 Hz, CF_2), 122.0 (t, $^3J_{CF}$ = 6.4 Hz, $C_{Ar}C_{Ar}CF_2$), 125.9 (t, $^3J_{CF}$ = 6.4 Hz, $C_{Ar}C_{Ar}CF_2$), 127.0 (C_{Ar}), 128.5 (C_{Ar}), 129.2 (C_{Ar}), 134.4 (C_{Ar}Cl), 136.1 (C_{Ar}), 137.9 (C_{Ar}), 139.4 (t, $^2J_{CF}$ = 26.7 Hz, $C_{Ar}CF_2$), 141.0 (C_{Ar}CO), 166.6 (*C*O) ppm. ^{19}F NMR (376 MHz, H-decoupled, $CDCl_3$): δ = −88.0 ppm. IR (KBr): ν = 3261 (m, $\nu(NH_{trans})$), 3085 (m), 2930 (m, $\nu(CH_2)$), 2872 (m, $\nu(CH_3)$), 1899 (w), 1634 (m, ν(CO)), 1602 (m), 1554 (m), 1495 (m), 1445 (m, $\delta(CH_2)$), 1344 (m), 1288 (m), 1251 (m, $\nu(C_{alkyl}F)$), 1186 (m), 1144 (m), 1091 (m, $\nu(C_{aryl}Cl)$), 1012 (m), 977 (m), 934 (m), 902 (m), 827 (m), 738 (m, $\delta(CH_2)$), 644 (w), 626 (w), 607 (w), 551 (w), 502 (w), 429 (w) cm^{-1}. MS (EI): *m*/*z* (%): 353/351 (17/53) [M^+], 309 (45), 281/279 (30/100) [$C_{15}H_{10}ClF_2O^+$], 251 (11) [$C_{14}H_{10}ClF_2^+$]. HRMS ($C_{19}H_{20}ClF_2NO$): calcd 351.1201; found 351.1198.

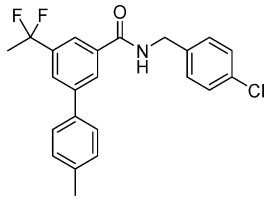
4′-*tert*-Butyl-*N*-butyl-5-(1,1-difluoroethyl)biphenyl-3-carboxamide (23{*1*;*3*}).



Following GP7, 264 mg (0.200 mmol) of resin **22**{*1*;*3*} was reacted with 180 mg (0.800 mmol) of NIS and 0.20 mL (8.0 mmol) of HF/py. After purification, 23.0 mg (0.062 mmol, 31% over 5 steps) of a colorless solid was obtained (cyclohexane/ethyl acetate 10:1, R_f = 0.4). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.97 (t, ^3J = 7.3 Hz, 3 H, CH_2CH_3), 1.37 (s, 9 H, $C(CH_3)_3$), 1.43 (sex, ^3J = 7.3 Hz, 2 H, $CH_2CH_2CH_3$), 1.58−1.67 (m, 2H, $CH_2CH_2CH_3$), 1.97 (t, $^3J_{HF}$ = 18.2 Hz, 3 H, CH_3CF_2), 3.45−3.52 (m, 2 H,

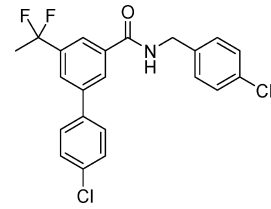
NHCH_2), 6.20 (m, 1 H, NH), 7.49 (d, ^3J = 8.6 Hz, 2 H, H_{Ar}), 7.56 (d, ^3J = 8.6 Hz, 2 H, H_{Ar}), 7.82 (m, 2 H, H_{Ar}), 8.01 (m, 1 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8 (CH_2CH_3), 20.2 (CH_2CH_3), 26.0 (t, $^2J_{CF}$ = 29.3 Hz, CH_3CF_2), 31.3 ($C(CH_3)_3$), 31.7 ($CH_2CH_2CH_3$), 34.6 ($C(CH_3)_3$), 40.0 (CH_2NH), 121.5 (t, $^3J_{CF}$ = 6.0 Hz, $C_{Ar}C_{Ar}CF_2$), 121.5 (t, $^1J_{CF}$ = 239.7 Hz, CF_2), 125.9 (C_{Ar}), 126.0 (t, $^3J_{CF}$ = 6.0 Hz, $C_{Ar}C_{Ar}CF_2$), 126.8 (C_{Ar}), 126.9 (C_{Ar}), 135.9 (C_{Ar}), 136.6 (C_{Ar}), 139.1 (t, $^2J_{CF}$ = 7.1 Hz, $C_{Ar}CF_2$), 142.1 ($C_{Ar}CO$), 151.4 ($C_{Ar}C(CH_3)_3$), 166.9 (CO) ppm. ^{19}F NMR (376 MHz, H-decoupled, $CDCl_3$): δ = −87.7 ppm. IR (KBr): ν = 3242 (m, $\nu(NH_{trans})$), 3083 (m), 2960 (m, $\nu(CH_3)$), 2869 (m, $\nu(CH_3)$), 1727 (w), 1635 (m, ν(CO)), 1601 (m), 1556 (m), 1447 (m, $\delta(CH_2)$), 1382 (m), 1349 (m), 1292 (m), 1252 (m, $\nu(C_{alkyl}F)$), 1182 (m), 1145 (m), 1079 (w), 1016 (w), 926 (m), 898 (m), 834 (m), 815 (m), 739 (m, $\delta(CH_2)$), 697 (m), 633 (w), 607 (w), 542 (w), 507 (w), 446 (vw) cm^{-1}. MS (EI): m/z (%): 373 (2) [M^+], 332 (34), 317 (100) [$C_{19}H_{21}F_2NO^+$], 295 (61), 169 (24), 43 (11). HRMS ($C_{23}H_{29}F_2NO$): calcd 373.2217; found 373.2219.

***N*-(4-Chlorobenzyl)-5-(1,1-difluoroethyl)-4′-methylbiphenyl-3-carboxamide (23{*2*;*1*}).**



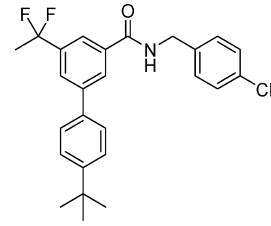
Following GP7, 267 mg (0.200 mmol) of resin **22**{*2*;*1*} was reacted with 180 mg (0.800 mmol) of NIS and 0.20 mL (8.0 mmol) of HF/py. After purification, 56.0 mg (0.140 mmol, 70% over 5 steps) of a colorless solid was obtained (cyclohexane/ethyl acetate 6:1, R_f = 0.3). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.92 (t, $^3J_{HF}$ = 18.4 Hz, 3 H, CH_3CF$_2$), 2.37 (s, 3 H, $C_{Ar}CH_3$), 4.55 (d, ^3J = 5.6 Hz, 2 H, NHCH_2), 6.84 (t, ^3J = 5.6 Hz, 1 H, NH), 7.22 (d, ^3J = 8.3 Hz, 2 H, H_{Ar}), 7.23−7.25 (m, 4 H, H_{Ar}), 7.45 (d, ^3J = 8.3 Hz, 2 H, H_{Ar}), 7.79 (m, 1 H, H_{Ar}), 7.82 (m, 1 H, H_{Ar}), 8.01 (m, 1 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.1 ($C_{Ar}CH_3$), 25.9 (t, $^2J_{CF}$ = 29.3 Hz, CH_3CF_2), 43.5 (CH_2NH), 121.5 (t, $^1J_{CF}$ = 239.7 Hz, CF_2), 121.6 (t, $^3J_{CF}$ = 5.9 Hz, $C_{Ar}C_{Ar}CF_2$), 126.2 (t, $^3J_{CF}$ = 5.9 Hz, $C_{Ar}C_{Ar}CF_2$), 126.9 (C_{Ar}), 127.0 (C_{Ar}), 128.8 (C_{Ar}), 129.2 (C_{Ar}), 129.7 (C_{Ar}), 133.4 ($C_{Ar}Cl$), 135.1 ($C_{Ar}CH_3$), 136.4 ($C_{Ar}CH_2$), 136.5 (C_{Ar}), 138.2 (C_{Ar}), 139.2 (t, $^2J_{CF}$ = 27.1 Hz, $C_{Ar}CF_2$), 142.2 ($C_{Ar}CO$), 166.8 (CO) ppm. ^{19}F NMR (376 MHz, H-decoupled, $CDCl_3$): δ = −88.0 ppm. IR (KBr): ν = 3279 (m, $\nu(NH_{trans})$), 3078 (w), 3002 (w, ν(CH)), 2924 (w, $\nu(CH_2)$), 1814 (w), 1632 (m, ν(CO)), 1599 (m), 1549 (m), 1492 (m), 1423 (m), 1381 (m), 1344 (m), 1287 (m), 1253 (m, $\nu(C_{alkyl}F)$), 1178 (m), 1107 (w), 1090 (m, $\nu(C_{aryl}Cl)$), 1039 (w), 1014 (m), 935 (m), 900 (m), 864 (w), 820 (m), 797 (m), 768 (w), 731 (m, $\delta(CH_2)$), 703 (m), 633 (w), 606 (w), 565 (w), 531 (w), 484 (w), 450 (w), 418 (w) cm^{-1}. MS (EI): m/z (%): 401/399 (36/100) [M^+], 259 (49) [$C_{16}H_{13}F_2O^+$], 231 (7) [$C_{15}H_{13}F_2^+$]. HRMS ($C_{23}H_{20}ClF_2NO$): calcd 399.1201; found 399.1205.

4′-Chloro-*N*-(4-chlorobenzyl)-5-(1,1-difluoroethyl)biphenyl-3-carboxamide (23{*2*;*2*}).



Following GP7, 146 mg (0.110 mmol) of resin **22**{*2*;*2*} was reacted with 90.0 mg (0.400 mmol) of NIS and 0.10 mL (4.0 mmol) of HF/py. After purification, 12.0 mg (0.029 mmol, 27% over 5 steps) of a colorless solid was obtained (cyclohexane/ethyl acetate 10:1, R_f = 0.2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.97 (t, $^3J_{HF}$ = 17.6 Hz, 3 H, CH_3CF$_2$), 4.64 (d, ^3J = 5.7 Hz, 2 H, NHCH_2), 6.55 (m, 1 H, NH), 7.30 (d, ^3J = 8.5 Hz, 2 H, H_{Ar}), 7.33 (d, ^3J = 8.5 Hz, 2 H, H_{Ar}), 7.44 (d, ^3J = 8.5 Hz, 2 H, H_{Ar}), 7.54 (d, ^3J = 8.5 Hz, 2 H, H_{Ar}), 7.80 (m, 1 H, H_{Ar}), 7.85 (m, 1 H, H_{Ar}), 8.03 (m, 1 H, H_{Ar}) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.0 (t, $^2J_{CF}$ = 28.5 Hz, CH_3CF_2), 43.6 (CH_2NH), 121.3 (t, $^1J_{CF}$ = 240.1 Hz, CF_2), 122.0 (t, $^3J_{CF}$ = 5.5 Hz, $C_{Ar}C_{Ar}CF_2$), 126.3 (t, $^3J_{CF}$ = 5.5 Hz, $C_{Ar}C_{Ar}CF_2$), 127.1 (C_{Ar}), 128.5 (C_{Ar}), 129.0 (C_{Ar}), 129.2 (C_{Ar}), 129.3 (C_{Ar}), 133.6 ($C_{Ar}Cl$), 134.5 ($C_{Ar}Cl$), 135.4 ($C_{Ar}CH_2$), 136.4 (C_{Ar}), 137.8 (C_{Ar}), 139.5 (t, $^2J_{CF}$ = 27.6 Hz, $C_{Ar}CF_2$), 141.2 ($C_{Ar}CO$), 166.4 (CO) ppm. ^{19}F NMR (376 MHz, H-decoupled, $CDCl_3$): δ = −87.7 ppm. IR (KBr): ν = 3278 (m, $\nu(NH_{trans})$), 3085 (m), 3003 (w, ν(CH)), 2922 (m, $\nu(CH_2)$), 2286 (vw), 1905 (w), 1633 (m, ν(CO)), 1602 (m), 1552 (m), 1493 (m), 1448 (m, $\delta(CH_2)$), 1424 (m), 1383 (m), 1343 (m), 1286 (m), 1251 (m, $\nu(C_{alkyl}F)$), 1180 (m), 1134 (m), 1092 (m, $\nu(C_{aryl}Cl)$), 1075 (m), 1040 (m), 1014 (m), 935 (m), 919 (m), 902 (m), 865 (m), 831 (m), 797 (m), 768 (m), 741 (m), 703 (m, $\delta(CH_2)$), 657 (m), 643 (m), 625 (m), 605 (m), 529 (m), 477 (w), 460 (w), 444 (w), 419 (w) cm^{-1}. MS (EI): m/z (%): 421/419 (56/87) [M^+], 281/279 (24/80) [$C_{15}H_{10}ClF_2O^+$], 84 (100), 43 (55). HRMS ($C_{22}H_{17}Cl_2F_2NO$): calcd 419.0653; found 419.0655.

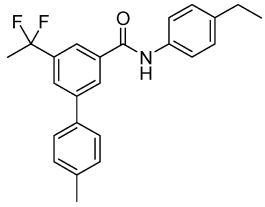
4′-*tert*-Butyl-*N*-(4-chlorbenzyl)-5-(1,1-difluoroethyl)biphenyl-3-carboxamide (23{*2*;*3*}).



Following GP7, 154 mg (0.110 mmol) of resin **22**{*2*;*3*} was reacted with 90.0 mg (0.400 mmol) of NIS and 0.10 mL (4.0 mmol) of HF/py. After purification, 11.0 mg (0.025 mmol, 23% over 5 steps) of a colorless solid was obtained (cyclohexane/ethyl acetate 10:1, R_f = 0.2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.36 (s, 9 H, $C(CH_3)_3$), 1.97 (t, $^3J_{HF}$ = 18.2 Hz, 3 H, CH_3CF$_2$), 4.64 (d, ^3J = 5.8 Hz, 2 H, NHCH_2), 6.58 (m, 1 H, NH), 7.30 (d, ^3J = 8.8 Hz, 2 H, H_{Ar}), 7.33 (d,

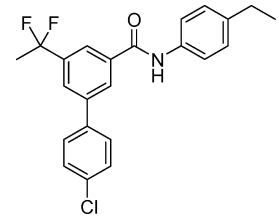
^3J = 8.8 Hz, 2 H, H_{Ar}), 7.49 (d, ^3J = 8.3 Hz, 2 H, H_{Ar}), 7.55 (d, ^3J = 8.3 Hz, 2 H, H_{Ar}), 7.84 (m, 2 H, H_{Ar}), 8.05 (m, 1 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.0 (t, $^2J_{CF}$ = 29.3 Hz, CH_3CF_2), 31.3 ($C(CH_3)_3$), 34.6 ($C(CH_3)_3$), 43.5 (CH_2NH), 121.5 (t, $^1J_{CF}$ = 239.8 Hz, CF_2), 121.6 (t, $^3J_{CF}$ = 6.6 Hz, $C_{Ar}C_{Ar}CF_2$), 126.0 (C_{Ar}), 126.4 (t, $^3J_{CF}$ = 6.6 Hz, $C_{Ar}C_{Ar}CF_2$), 126.8 (C_{Ar}), 126.9 (C_{Ar}), 128.9 (C_{Ar}), 129.3 (C_{Ar}), 133.5 ($C_{Ar}Cl$), 135.1 ($C_{Ar}CH_2$), 136.4 (C_{Ar}), 136.5 (C_{Ar}), 139.3 (t, $^2J_{CF}$ = 27.1 Hz, $C_{Ar}CF_2$), 142.3 ($C_{Ar}CO$), 151.5 ($C_{Ar}C(CH_3)_3$), 166.7 (CO) ppm. ^{19}F NMR (376 MHz, H-decoupled, $CDCl_3$): δ = −87.7 ppm. IR (KBr): ν = 3241 (m, $\nu(NH_{trans})$), 3074 (m), 2957 (m, $\nu(CH_3)$), 2868 (m, $\nu(CH_3)$), 1898 (vw), 1730 (w), 1635 (m, ν(CO)), 1600 (m), 1552 (m), 1492 (m), 1431 (m), 1385 (m), 1363 (m), 1346 (m), 1291 (m), 1252 (m, $\nu(C_{alkyl}F)$), 1182 (m), 1137 (m), 1088 (m, $\nu(C_{aryl}Cl)$), 1015 (m), 998 (w), 924 (m), 897 (m), 835 (m), 815 (m), 798 (m), 702 (m, $\delta(CH_2)$), 656 (w), 633 (w), 606 (w), 545 (w), 528 (w), 511 (w), 435 (w) cm^{-1}. MS (EI): *m/z* (%): 443/441 (34/100) [M^+], 426 (79) [$C_{25}H_{23}ClF_2NO^+$], 301 (18) [$C_{19}H_{19}F_2O^+$], 295 (56), 125 (44) [$C_7H_6Cl^+$], 43 (90). HRMS ($C_{26}H_{26}ClF_2NO$): calcd 441.1671; found 441.1673.

5-(1,1-Difluoroethyl)-*N*-(4-ethylphenyl)-4′-methylbiphenyl-3-carboxamide (23{*3*;*1*}).



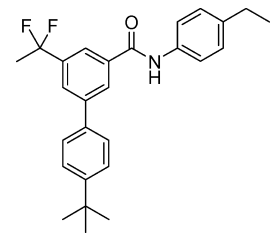
Following GP7, 247 mg (0.200 mmol) of resin **22**{*3*;*1*} was reacted with 180 mg (0.800 mmol) of NIS and 0.20 mL (8.0 mmol) of HF/py. After purification, 62.0 mg (0.164 mmol, 81% over 5 steps) of a colorless solid was obtained (cyclohexane/ethyl acetate 10:1, R_f = 0.4). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.24 (t, ^3J = 7.6 Hz, 3 H, CH_2CH_3), 1.95 (t, $^3J_{HF}$ = 18.2 Hz, 3 H, CH_3CF_2), 2.40 (s, 3 H, $C_{Ar}CH_3$), 2.64 (q, ^3J = 7.6 Hz, 2 H, CH_2CH_3), 7.17 (d, ^3J = 8.1 Hz, 2 H, H_{Ar}), 7.24 (d, ^3J = 8.1 Hz, 2 H, H_{Ar}), 7.48 (d, ^3J = 8.1 Hz, 2 H, H_{Ar}), 7.56 (d, ^3J = 8.1 Hz, 2 H, H_{Ar}), 7.82 (m, 1 H, H_{Ar}), 7.90 (m, 1 H, H_{Ar}), 8.08 (m, 1 H, H_{Ar}), 8.30 (bs, 1 H, N*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.6 (CH_2CH_3), 21.1 ($C_{Ar}CH_3$), 25.9 (t, $^2J_{CF}$ = 29.3 Hz, CH_3CF_2), 28.3 (CH_2CH_3), 120.6 (C_{Ar}), 121.5 (t, $^1J_{CF}$ = 239.9 Hz, CF_2), 121.7 (t, $^3J_{CF}$ = 6.6 Hz, $C_{Ar}C_{Ar}CF_2$), 126.1 (t, $^3J_{CF}$ = 6.6 Hz, $C_{Ar}C_{Ar}CF_2$), 126.8 (C_{Ar}), 126.9 (C_{Ar}), 128.3 (C_{Ar}), 129.7 (C_{Ar}), 135.3 ($C_{Ar}CH_3$), 136.0 ($C_{Ar}NH$), 136.3 (C_{Ar}), 138.1 (C_{Ar}), 139.2 (t, $^2J_{CF}$ = 27.1 Hz, $C_{Ar}CF_2$), 140.8 ($C_{Ar}CH_2CH_3$), 142.1 ($C_{Ar}CO$), 165.2 (CO) ppm. ^{19}F NMR (376 MHz, H-decoupled, $CDCl_3$): δ = −88.0 ppm. IR (KBr): ν = 3287 (w, $\nu(NH_{trans})$), 3121 (w), 3031 (w), 3001 (w, ν(CH)), 2964 (w, $\nu(CH_3)$), 2929 (w, $\nu(CH_2)$), 2871 (w, $\nu(CH_3)$), 1902 (vw), 1802 (vw), 1646 (m, ν(CO)), 1599 (m), 1515 (m), 1449 (w, $\delta(CH_2)$), 1411 (w), 1383 (w), 1347 (w), 1313 (w), 1253 (w, $\nu(C_{alkyl}F)$), 1178 (w), 1148 (w), 1125 (w), 1066 (vw), 1019 (vw), 956 (w), 930 (w), 913 (w), 895 (w), 817 (w), 782 (w), 758 (w), 700 (w, $\delta(CH_2)$), 648 (vw), 632 (vw), 609 (vw), 565 (vw), 547 (vw), 507 (vw) cm^{-1}. MS (EI): *m/z* (%): 379 (10) [M^+], 290 (56), 259 (52) [$C_{16}H_{13}F_2O^+$], 165 (38), 114 (37), 73 (40), 43 (100). HRMS ($C_{24}H_{23}F_2NO$): calcd 379.1748; found 379.1743.

4′-Chloro-5-(1,1-difluoroethyl)-*N*-(4-ethylphenyl)biphenyl-3-carboxamide (23{*3*;*2*}).



Following GP7, 149 mg (0.110 mmol) of resin **22**{*3*;*2*} was reacted with 90.0 mg (0.400 mmol) of NIS and 0.10 mL (4.0 mmol) of HF/py. After purification, 16.0 mg (0.041 mmol, 37% over 5 steps) of a colorless solid was obtained (cyclohexane/ethyl acetate 10:1, R_f = 0.4). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.24 (t, ^3J = 7.6 Hz, 3 H, CH_2CH_3), 1.99 (t, $^3J_{HF}$ = 18.2 Hz, 3 H, CH_3CF_2), 2.65 (q, ^3J = 7.6 Hz, 2 H, CH_2CH_3), 7.21 (d, ^3J = 8.3 Hz, 2 H, H_{Ar}), 7.44 (d, ^3J = 8.6 Hz, 2 H, H_{Ar}), 7.55 (d, ^3J = 8.6 Hz, 2 H, H_{Ar}), 7.56 (d, ^3J = 8.3 Hz, 2 H, H_{Ar}), 7.82 (m, 1 H, H_{Ar}), 7.92 (m, 1 H, H_{Ar}), 7.96 (bs, 1 H, N*H*), 8.09 (m, 1 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.6 (CH_2CH_3), 26.0 (t, $^2J_{CF}$ = 29.3 Hz, CH_3CF_2), 28.3 (CH_2CH_3), 120.5 (C_{Ar}), 121.4 (t, $^1J_{CF}$ = 240.0 Hz, CF_2), 122.1 (t, $^3J_{CF}$ = 5.9 Hz, $C_{Ar}C_{Ar}CF_2$), 126.3 (t, $^3J_{CF}$ = 5.9 Hz, $C_{Ar}C_{Ar}CF_2$), 127.1 (C_{Ar}), 128.4 (C_{Ar}), 128.5 (C_{Ar}), 129.2 (C_{Ar}), 134.5 ($C_{Ar}Cl$), 135.2 ($C_{Ar}NH$), 136.3 (C_{Ar}), 137.8 ($C_{Ar}CO$), 139.6 (t, $^2J_{CF}$ = 27.1 Hz, $C_{Ar}CF_2$), 141.1 ($C_{Ar}CH_2CH_3$), 141.2 (C_{Ar}), 164.8 (CO) ppm. ^{19}F NMR (376 MHz, H-decoupled, $CDCl_3$): δ = −87.7 ppm. IR (KBr): ν = 3287 (w, $\nu(NH_{trans})$), 3120 (w), 3034 (w), 3002 (w, ν(CH)), 2965 (m, $\nu(CH_3)$), 2931 (w, $\nu(CH_2)$), 2872 (w, $\nu(CH_3)$), 1900 (vw), 1709 (w), 1647 (m, ν(CO)), 1600 (m), 1516 (m), 1496 (m), 1448 (m, $\delta(CH_2)$), 1411 (m), 1384 (m), 1348 (m), 1312 (m), 1251 (m, $\nu(C_{alkyl}F)$), 1178 (m), 1148 (m), 1126 (m), 1093 (m, $\nu(C_{aryl}Cl)$), 1067 (w), 1013 (w), 956 (w), 910 (m), 828 (m), 776 (w), 759 (w), 732 (m, $\delta(CH_2)$), 700 (w), 644 (w), 627 (w), 606 (w), 547 (w), 510 (vw) cm^{-1}. MS (EI): *m/z* (%):401/399 (0.1/0.2) [M^+], 310 (62), 281/279 (10/31) [$C_{15}H_{10}ClF_2O^+$], 166 (17), 84 (100), 43 (49). HRMS ($C_{23}H_{20}ClF_2NO$): calcd 399.1201; found 399.1208.

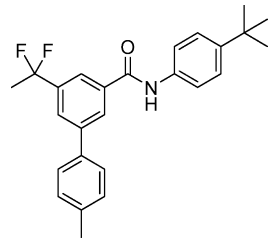
4′-*tert*-Butyl-5-(1,1-difluoroethyl)-*N*-(4-ethylphenyl)biphenyl-3-carboxamide (23{*3*;*3*}).



Following GP7, 129 mg (0.090 mmol) of resin **22**{*3*;*3*} was reacted with 81.0 mg (0.360 mmol) of NIS and 0.10 mL (4.0 mmol) of HF/py. After purification, 20.0 mg (0.048 mmol, 53% over 5 steps) of a colorless solid was obtained (cyclohexane/

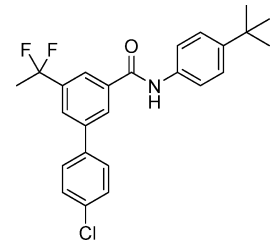
ethyl acetate 6:1, $R_f = 0.5$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.24 (t, ^3J = 7.7 Hz, 3 H, CH_2CH_3), 1.37 (s, 9 H, $C(CH_3)_3$), 1.99 (t, $^3J_{HF}$ = 18.2 Hz, 3 H, CH_3CF_2), 2.65 (q, ^3J = 7.7 Hz, 2 H, CH_2CH_3), 7.21 (d, ^3J = 8.3 Hz, 2 H, H_{Ar}), 7.50 (d, ^3J = 8.3 Hz, 2 H, H_{Ar}), 7.56 (d, ^3J = 8.3 Hz, 2 H, H_{Ar}), 7.57 (d, ^3J = 8.3 Hz, 2 H, H_{Ar}), 7.87 (m, 1 H, H_{Ar}), 7.92 (m, 1 H, H_{Ar}), 7.94 (bs, 1 H, N*H*), 8.11 (m, 1 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.6 (CH_2CH_3), 26.0 (t, $^2J_{CF}$ = 29.3 Hz, CH_3CF_2), 28.3 (CH_2CH_3), 31.3 ($C(CH_3)_3$), 34.6 ($C(CH_3)_3$), 120.5 (C_{Ar}), 121.5 (t, $^1J_{CF}$ = 239.5 Hz, CF_2), 121.7 (t, $^3J_{CF}$ = 5.9 Hz, $C_{Ar}C_{Ar}CF_2$), 126.0 (C_{Ar}), 126.4 (t, $^3J_{CF}$ = 5.9 Hz, $C_{Ar}C_{Ar}CF_2$), 126.8 (C_{Ar}), 126.9 (C_{Ar}), 128.4 (C_{Ar}), 135.3 (C_{Ar}NH), 136.1 (C_{Ar}), 136.4 (C_{Ar}CO), 139.3 (t, $^2J_{CF}$ = 27.1 Hz, $C_{Ar}CF_2$), 140.9 ($C_{Ar}CH_2CH_3$), 142.3 (C_{Ar}), 151.5 ($C_{Ar}C(CH_3)_3$), 165.0 (*C*O) ppm. ^{19}F NMR (376 MHz, H-decoupled, $CDCl_3$): δ = −87.8 ppm. IR (KBr): ν = 3295 (w, $\nu(NH_{trans})$), 3127 (vw), 2964 (w, $\nu(CH_3)$), 2869 (w, $\nu(CH_3)$), 1649 (w, ν(CO)), 1601 (w), 1541 (w), 1514 (w), 1436 (w), 1412 (w), 1381 (w), 1353 (w), 1316 (w), 1258 (w, $\nu(C_{alkyl}F)$), 1177 (w), 1147 (w), 1065 (vw), 1015 (vw), 930 (w), 897 (w), 834 (w), 736 (w), 702 (w), 648 (vw), 606 (w), 555 (w) cm^{-1}. MS (EI): *m*/*z* (%): 421 (95) [M^+], 317 (62), 301 (100) [$C_{19}H_{19}F_2O^+$], 295 (60). HRMS ($C_{27}H_{29}F_2NO$): calcd 421.2217; found 421.2213.

***N*-(4-*tert*-Butylphenyl)-5-(1,1-difluoroethyl)-4′-methylbiphenyl-3-carboxamide (23{*4*;*1*}).**



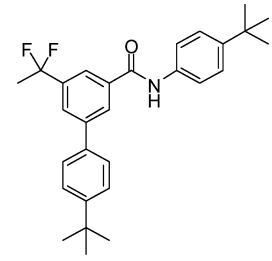
Following GP7, 277 mg (0.200 mmol) of resin **22**{*4*;*1*} was reacted with 180 mg (0.800 mmol) of NIS and 0.20 mL (8.0 mmol) of HF/py. After purification, 46.0 mg (0.113 mmol, 57% over 5 steps) of a colorless solid was obtained (cyclohexane/ethyl acetate 10:1, R_f = 0.5). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.33 (s, 9 H, $C(CH_3)_3$), 1.97 (t, $^3J_{HF}$ = 18.2 Hz, 3 H, CH_3CF_2), 2.32 (s, 3 H, $C_{Ar}CH_3$), 7.26 (d, ^3J = 8.5 Hz, 2 H, H_{Ar}), 7.38 (d, ^3J = 8.1 Hz, 2 H, H_{Ar}), 7.50 (d, ^3J = 8.1 Hz, 2 H, H_{Ar}), 7.57 (d, ^3J = 8.5 Hz, 2 H, H_{Ar}), 7.84 (m, 1 H, H_{Ar}), 7.90 (m, 1 H, H_{Ar}), 8.01 (m, 1 H, H_{Ar}), 8.11 (bs, 1 H, N*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.2 ($C_{Ar}CH_3$), 26.0 (t, $^2J_{CF}$ = 29.6 Hz, CH_3CF_2), 31.4 ($C(CH_3)_3$), 34.5 ($C(CH_3)_3$), 120.1 (C_{Ar}), 120.3 (C_{Ar}), 121.6 (t, $^1J_{CF}$ = 240.1 Hz, CF_2), 125.7 (C_{Ar}), 125.9 (t, $^3J_{CF}$ = 5.9 Hz, $C_{Ar}C_{Ar}CF_2$), 126.9 (C_{Ar}), 127.0 (t, $^3J_{CF}$ = 5.9 Hz, $C_{Ar}C_{Ar}CF_2$), 129.8 (C_{Ar}), 135.1 (C_{Ar}), 136.1 (C_{Ar}), 136.4 (C_{Ar}), 138.2 (C_{Ar}), 139.3 (t, $^2J_{CF}$ = 27.1 Hz, $C_{Ar}CF_2$), 142.3 (C_{Ar}), 147.8 (C_{Ar}), 165.2 (*C*O) ppm. ^{19}F NMR (376 MHz, H-decoupled, $CDCl_3$): δ = −87.6 ppm. IR (KBr): ν = 3286 (w, ν(NH)), 3035 (w), 2962 (m), 2867 (w), 1903 (vw), 1647 (m, ν(CO)), 1599 (m), 1518 (m), 1447 (w), 1405 (m), 1383 (w), 1347 (w), 1317 (m), 1298 (w), 1253 (m, ν(CF)), 1178 (w), 1127 (w), 1069 (vw), 1018 (w), 956 (vw), 910 (m), 817 (m), 778 (vw), 751 (w), 733 (m), 701 (w), 673 (vw), 648 (vw), 632 (vw), 609 (vw), 556 (w) cm^{-1}. MS (EI): *m*/*z* (%): 407 (8) [M^+], 392 (10) [$M^+ - CH_3$], 84 (100). HRMS ($C_{26}H_{27}F_2NO$): calcd 407.2061; found 407.2065.

***N*-(4-*tert*-Butylphenyl)-4′-chloro-5-(1,1-difluoroethyl)biphenyl-3-carboxamide (23{*4*;*2*}).**



Following GP7, 275 mg (0.200 mmol) of resin **22**{*4*;*2*} was reacted with 180 mg (0.800 mmol) of NIS and 0.20 mL (8.0 mmol) of HF/py. After purification, 44.0 mg (0.103 mmol, 52% over 5 steps) of a colorless solid was obtained (cyclohexane/ethyl acetate 10:1, R_f = 0.5). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.33 (s, 9 H, $C(CH_3)_3$), 1.96 (t, $^3J_{HF}$ = 18.2 Hz, 3 H, CH_3CF_2), 7.25−7.30 (m, 4 H, H_{Ar}), 7.39 (d, ^3J = 8.5 Hz, 2 H, H_{Ar}), 7.47 (d, ^3J = 8.5 Hz, 2 H, H_{Ar}), 7.69 (m, 1 H, H_{Ar}), 7.82 (m, 1 H, H_{Ar}), 7.96 (m, 1 H, H_{Ar}), 8.25 (bs, 1 H, N*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.9 (t, $^2J_{CF}$ = 29.3 Hz, CH_3CF_2), 31.0 ($C(CH_3)_3$), 34.6 ($C(CH_3)_3$), 120.3 (C_{Ar}), 121.4 (t, $^1J_{CF}$ = 240.5 Hz, CF_2), 122.3 (t, $^3J_{CF}$ = 5.9 Hz, $C_{Ar}C_{Ar}CF_2$), 125.9 (C_{Ar}), 126.2 (t, $^3J_{CF}$ = 5.9 Hz, $C_{Ar}C_{Ar}CF_2$), 127.1 (C_{Ar}), 128.4 (C_{Ar}), 129.2 (C_{Ar}), 134.5 (C_{Ar}Cl), 135.0 (C_{Ar}NH), 136.3 (C_{Ar}), 137.7 (C_{Ar}CO), 139.5 (t, $^2J_{CF}$ = 27.1 Hz, $C_{Ar}CF_2$), 141.0 (C_{Ar}), 148.0 ($C_{Ar}C(CH_3)_3$), 166.0 (*C*O) ppm. ^{19}F NMR (376 MHz, H-decoupled, $CDCl_3$): δ = −87.7 ppm. IR (KBr): ν = 3288 (w, ν(NH)), 3056 (w), 2962 (w), 2868 (w), 1902 (vw), 1708 (w), 1647 (m, ν(CO)), 1599 (m), 1521 (m), 1497 (w), 1447 (w), 1406 (w), 1383 (w), 1348 (w), 1316 (w), 1300 (w), 1251 (m, ν(CF)), 1178 (w), 1127 (w), 1093 (w), 1068 (w), 1013 (w), 911 (w), 827 (m), 761 (w), 731 (w), 700 (w), 670 (vw), 643 (vw), 627 (vw), 606 (vw), 555 (w), 477 (vw) cm^{-1}. MS (EI): *m*/*z* (%): 429/427 (8/20) [M^+], 312/310 (44/100). HRMS ($C_{25}H_{24}ClF_2NO$): calcd 427.1514; found 427.1510.

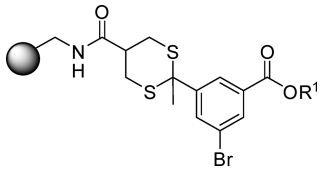
4′-*tert*-Butyl-*N*-(4-*tert*-butylphenyl)-5-(1,1-difluoroethyl)biphenyl-3-carboxamide (23{*4*;*3*}).



Following GP7, 282 mg (0.200 mmol) of resin **22**{*4*;*3*} was reacted with 180 mg (0.800 mmol) of NIS and 0.20 mL (8.0 mmol) of HF/py. After purification, 48.0 mg (0.107 mmol, 54% over 5 steps) of a colorless solid was obtained (cyclohexane/ethyl acetate 10:1, R_f = 0.6). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.36 (s, 9 H, $C(CH_3)_3$), 1.39 (s, 9 H, $C(CH_3)_3$), 1.99 (t, $^3J_{HF}$ = 18.2 Hz, 3 H, CH_3CF_2), 7.42 (d, ^3J = 8.6 Hz, 2 H, H_{Ar}), 7.52 (d, ^3J = 8.5 Hz, 2 H, H_{Ar}), 7.59 (d, ^3J = 8.5 Hz, 2 H, H_{Ar}), 7.62 (d, ^3J = 8.6 Hz, 2 H, H_{Ar}), 7.88 (m, 1 H, H_{Ar}), 7.96 (m, 1 H, H_{Ar}), 8.10 (bs, 1 H, N*H*),

8.13 (m, 1 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.0 (t, $^2J_{CF}$ = 29.3 Hz, CH_3CF_2), 31.3 ($C(CH_3)_3$), 31.4 ($C(CH_3)_3$), 34.5 ($C(CH_3)_3$), 34.7 ($C(CH_3)_3$), 120.1 (C_{Ar}), 121.5 (t, $^1J_{CF}$ = 240.5 Hz, CF_2), 121.8 (C_{Ar}), 125.9 (t, $^3J_{CF}$ = 5.9 Hz, $C_{Ar}C_{Ar}CF_2$), 126.0 (C_{Ar}), 126.1 (t, $^3J_{CF}$ = 5.9 Hz, $C_{Ar}C_{Ar}CF_2$), 126.9 (C_{Ar}), 127.0 (C_{Ar}), 135.1 (C_{Ar}), 136.1 (C_{Ar}), 136.4 (C_{Ar}), 139.3 (t, $^2J_{CF}$ = 27.1 Hz, $C_{Ar}CF_2$), 142.3 (C_{Ar}), 147.8 ($C_{Ar}C(CH_3)_3$), 151.5 ($C_{Ar}C(CH_3)_3$), 165.2 (CO) ppm. ^{19}F NMR (376 MHz, H-decoupled, $CDCl_3$): δ = −88.1 ppm. IR (KBr): ν = 3285 (w, ν(NH)), 3033 (w), 2962 (m), 2904 (m), 2867 (m), 1905 (vw), 1649 (m, ν(CO)), 1599 (m), 1519 (m), 1447 (m), 1405 (m), 1383 (m), 1363 (m), 1317 (m), 1298 (m), 1252 (m, ν(CF)), 1178 (m), 1128 (m), 1068 (w), 1013 (w), 932 (w), 895 (w), 834 (m), 762 (w), 741 (w), 701 (m), 672 (w), 632 (w), 608 (w), 554 (w), 517(w) cm^{-1}. MS (EI): *m*/*z* (%): 449 (100) [M^+], 434 (100) [$M^+ - CH_3$], 317 (80) [$M^+ - C_6H_4C(CH_3)_3$], 301 (74) [$M^+ - NHC_6H_4C(CH_3)_3$]. HRMS ($C_{29}H_{33}F_2NO$): calcd 449.2530; found 449.2533.

Synthesis of Library III. Transesterification Reactions to Give Resins 25{*2*−*4*}.

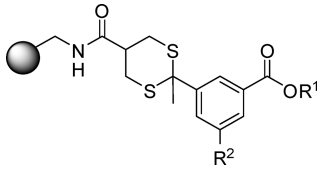


25{*2*} (R^1 = Butyl). Following GP6, 5 mL of 1-butanol **24**{*2*} was reacted with 805 mg (0.780 mmol) of resin **18** to give 875 mg of beige resin **25**{*2*}. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0 (CH_3CH_2), 19.4 (CH_3CH_2), 30.5 (CH_3), 30.8 (OCH_2CH_2), 65.6 (OCH_2), 165.5 (OCO) ppm.

25{*3*} (R^1 = Isopropyl). Following GP6, 5 mL of 2-propanol **24**{*3*} was reacted with 805 mg (0.780 mmol) of resin **18** to give 865 mg of beige resin **25**{*3*}. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.0 ((CH_3)$_2$CH), 30.9 (CH_3), 69.2 (OCH), 165.2 (OCO) ppm.

25{*4*} (R^1 = 4-*tert*-Butylbenzyl). Following GP6, 2.58 g (15.6 mmol) of 4-*tert*-butylbenzyl alcohol **24**{*4*} was reacted with 805 mg (0.780 mmol) of resin **18** to give 915 mg of beige resin **25**{*4*}. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.0 (CH_3), 31.5 ($C(CH_3)_3$), 34.8 ($C(CH_3)_3$), 67.1 (OCH_2), 151.6 ($C_{Ar}C(CH_3)_3$), 166.0 (OCO) ppm.

Suzuki Coupling Reactions to Give Resins 27.



27{*1*;*1*} (R^1 = Methyl, R^2 = Phenyl). Following GP4, 153 mg (1.25 mmol) of phenylboronic acid **26**{*1*} was reacted with 260 mg (0.250 mmol) of resin **18** to give 277 mg of brown resin **27**{*1*;*1*}. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.0 (CH_3), 53.6 (OCH_3), 165.9 ($COOMe$) ppm.

27{*1*;*2*} (R^1 = Methyl, R^2 = 4-Methylphenyl). Following GP4, 170 mg (1.25 mmol) of 4-methylphenylboronic acid **26**{*2*} was reacted with 260 mg (0.250 mmol) of resin **18** to give 282 mg of brown resin **27**{*1*;*2*}. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.4 ($C_{Ar}CH_3$), 30.9 (CH_3), 53.4 (OCH_3), 165.6 ($COOMe$) ppm.

27{*1*;*3*} (R^1 = Methyl, R^2 = 4-Chlorophenyl). Following GP4, 195 mg (1.25 mmol) of 4-chlorophenylboronic acid **26**{*3*} was reacted with 260 mg (0.250 mmol) of resin **18** to give 287 mg of brown resin **27**{*1*;*3*}. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.9 (CH_3), 53.6 (OCH_3), 165.3 ($COOMe$) ppm.

27{*1*;*4*} (R^1 = Methyl, R^2 = 4-*tert*-Butylphenyl). Following GP4, 224 mg (1.25 mmol) of 4-*tert*-butylphenylboronic acid **26**{*4*} was reacted with 260 mg (0.250 mmol) of resin **18** to give 299 mg of brown resin **27**{*1*;*4*}. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.9 (CH_3), 31.5 ($C(CH_3)_3$), 34.6 ($C(CH_3)_3$), 53.5 (OCH_3), 165.5 ($COOMe$) ppm.

27{*2*;*1*} (R^1 = Butyl, R^2 = Phenyl). Following GP4, 185 mg (1.50 mmol) of phenylboronic acid **26**{*1*} was reacted with 340 mg (0.300 mmol) of resin **25**{*2*} to give 361 mg of brown resin **27**{*2*;*1*}. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9 (CH_3CH_2), 19.4 (CH_3CH_2), 30.5 (CH_3), 30.8 (OCH_2CH_2), 65.2 (OCH_2), 132.1 (C_{Ar}), 165.4 (OCO) ppm.

27{*2*;*2*} (R^1 = Butyl, R^2 = 4-Methylphenyl). Following GP4, 150 mg (1.10 mmol) of 4-methylphenylboronic acid **26**{*2*} was reacted with 250 mg (0.220 mmol) of resin **25**{*2*} to give 271 mg of brown resin **27**{*2*;*2*}. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0 (CH_3CH_2), 19.4 (CH_3CH_2), 21.3 ($C_{Ar}CH_3$), 30.7 (CH_3), 30.9 (OCH_2CH_2), 65.2 (OCH_2), 129.7 (C_{Ar}), 165.5 (OCO) ppm.

27{*2*;*3*} (R^1 = Butyl, R^2 = 4-Chlorophenyl). Following GP4, 172 mg (1.10 mmol) of 4-chlorophenylboronic acid **26**{*3*} was reacted with 250 mg (0.220 mmol) of resin **25**{*2*} to give 275 mg of brown resin **27**{*2*;*3*}. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0 (CH_3CH_2), 19.4 (CH_3CH_2), 30.7 (CH_3), 30.9 (OCH_2CH_2), 65.4 (OCH_2), 166.5 (OCO) ppm.

27{*2*;*4*} (R^1 = Butyl, R^2 = 4-*tert*-Butylphenyl). Following GP4, 268 mg (1.50 mmol) of 4-*tert*-butylphenylboronic acid **26**{*4*} was reacted with 340 mg (0.300 mmol) of resin **25**{*2*} to give 381 mg of brown resin **27**{*2*;*4*}. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0 (CH_3CH_2), 19.4 (CH_3CH_2), 30.5 (CH_3), 30.8 (OCH_2CH_2), 31.4 ($C(CH_3)_3$), 34.7 ($C(CH_3)_3$), 65.3 (OCH_2), 132.0 (C_{Ar}), 165.8 (OCO) ppm.

27{*3*;*1*} (R^1 = Isopropyl, R^2 = Phenyl). Following GP4, 91 mg (0.750 mmol) of phenylboronic acid **26**{*1*} was reacted with 170 mg (0.150 mmol) of resin **25**{*3*} to give 186 mg of brown resin **27**{*3*;*1*}. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.9 ((CH_3)$_2$CH), 68.9 (OCH), 166.1 (OCO) ppm.

27{*3*;*2*} (R^1 = Isopropyl, R^2 = 4-Methylphenyl). Following GP4, 102 mg (0.750 mmol) of 4-methylphenylboronic acid **26**{*2*} was reacted with 167 mg (0.150 mmol) of resin **25**{*3*} to give 188 mg of brown resin **27**{*3*;*2*}. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.6 ($C_{Ar}CH_3$), 22.0 ((CH_3)$_2$CH), 30.9 (CH_3), 68.1 (OCH), 165.2 (OCO) ppm.

27{*3*;*3*} (R^1 = Isopropyl, R^2 = 4-Chlorophenyl). Following GP4, 118 mg (0.750 mmol) of 4-chlorophenylboronic acid **26**{*3*} was reacted with 167 mg (0.150 mmol) of resin **25**{*3*} to give 190 mg of brown resin **27**{*3*;*3*}. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.1 ((CH_3)$_2$CH), 30.9 (CH_3), 67.2 (OCH), 165.0 (OCO) ppm.

27{*3*;*4*} (R^1 = Isopropyl, R^2 = 4-*tert*-Butylphenyl). Following GP4, 135 mg (0.750 mmol) of 4-*tert*-butylphenylboronic acid **26**{*4*} was reacted with with 170 mg (0.150 mmol) of resin **25**{*3*} to give 202 mg of brown resin **27**{*3*;*1*}. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.0 ((*C*H$_3$)$_2$CH), 30.9 (*C*H$_3$), 31.8 (C(*C*H$_3$)$_3$), 34.4 (*C*(CH$_3$)$_3$), 69.2 (O*C*H), 165.2 (O*C*O) ppm.

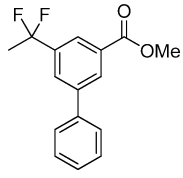
27{*4*;*1*} (R^1 = 4-*tert*-Butylbenzyl, R^2 = Phenyl). Following GP4, 120 mg (1.00 mmol) of phenylboronic acid **26**{*1*} was reacted with 240 mg (0.200 mmol) of resin **25**{*4*} to give 266 mg of brown resin **27**{*4*;*1*}. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.0 (*C*H$_3$), 31.9 (C(*C*H$_3$)$_3$), 34.6 (*C*(CH$_3$)$_3$), 67.1 (O*C*H$_2$), 150.1 (*C*$_{Ar}$C(CH$_3$)$_3$), 164.0 (O*C*O) ppm.

27{*4*;*2*} (R^1 = 4-*tert*-Butylbenzyl, R^2 = 4-Methylphenyl). Following GP4, 150 mg (1.10 mmol) of 4-methylphenylboronic acid **26**{*2*} was reacted with 260 mg (0.220 mmol) of resin **25**{*4*} to give 287 mg of brown resin **27**{*4*;*2*}. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.3 (C$_{Ar}$*C*H$_3$), 31.0 (*C*H$_3$), 31.4 (C(*C*H$_3$)$_3$), 34.7 (*C*(CH$_3$)$_3$), 66.8 (O*C*H$_2$), 125.6 (*C*$_{Ar}$), 150.6 (*C*$_{Ar}$C(CH$_3$)$_3$), 169.0 (O*C*O) ppm.

27{*4*;*3*} (R^1 = 4-*tert*-Butylbenzyl, R^2 = 4-Chlorophenyl). Following GP4, 118 mg (1.10 mmol) of 4-chlorophenylboronic acid **26**{*3*} was reacted with 260 mg (0.220 mmol) of resin **25**{*4*} to give 283 mg of brown resin **27**{*4*;*3*}. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.0 (*C*H$_3$), 31.5 (C(*C*H$_3$)$_3$), 34.7 (*C*(CH$_3$)$_3$), 66.8 (O*C*H$_2$), 125.6 (*C*$_{Ar}$), 150.6 (*C*$_{Ar}$C(CH$_3$)$_3$), 170.6 (O*C*O) ppm.

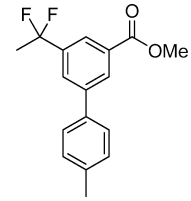
27{*4*;*4*} (R^1 = 4-*tert*-Butylbenzyl, R^2 = 4-*tert*-Butylphenyl). Following GP4, 180 mg (1.00 mmol) of 4-*tert*-butylphenylboronic acid **26**{*4*} was reacted with 240 mg (0.200 mmol) of resin **25**{*4*} to give 288 mg of brown resin **27**{*4*;*4*}. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.0 (*C*H$_3$), 31.5 (C(*C*H$_3$)$_3$), 31.9 (C(*C*H$_3$)$_3$), 34.3 (*C*(CH$_3$)$_3$, 34.8 (*C*(CH$_3$)$_3$), 68.1 (O*C*H$_2$), 150.6 (*C*$_{Ar}$C(CH$_3$)$_3$), 166.0 (O*C*O) ppm.

Fluorinating Cleavage to Give Compounds 28. Methyl 5-(1,1-Difluoroethyl)biphenyl-3-carboxylate (28{*1*;*1*}).



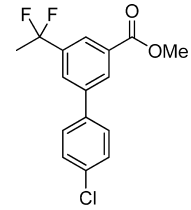
Following GP7, 277 mg (0.250 mmol) of resin **27**{*1*;*1*} was reacted with 225 mg (1.00 mmol) of NIS and 0.25 mL (10 mmol) of HF/py. After purification, 45.0 mg (0.163 mmol, 66% over 4 steps) of a colorless oil was obtained (cyclohexane/ethyl acetate 8:1, R_f = 0.7). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.01 (t, $^3J_{HF}$ = 18.2 Hz, 3 H, C*H*$_3$CF$_2$), 4.00 (s, 3 H, OC*H*$_3$), 7.44 (m, 1 H, *H*$_{Ar}$), 7.51 (m, 2 H, *H*$_{Ar}$), 7.66 (m, 2 H, *H*$_{Ar}$), 7.95 (m, 1 H, *H*$_{Ar}$), 8.18 (m, 1 H, *H*$_{Ar}$), 8.37 (m, 1 H, *H*$_{Ar}$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.0 (t, $^2J_{CF}$ = 29.2 Hz, *C*H$_3$CF$_2$), 52.4 (O*C*H$_3$), 121.4 (t, $^1J_{CF}$ = 240.5 Hz, *C*F$_2$), 124.7 (t, $^3J_{CF}$ = 5.9 Hz, *C*$_{Ar}$C$_{Ar}$CF$_2$), 127.2 (*C*$_{Ar}$), 127.6 (t, $^3J_{CF}$ = 5.9 Hz, *C*$_{Ar}$C$_{Ar}$CF$_2$), 128.2 (*C*$_{Ar}$), 129.0 (*C*$_{Ar}$), 129.5 (*C*$_{Ar}$), 131.2 (*C*$_{Ar}$), 139.2 (t, $^2J_{CF}$ = 27.1 Hz, *C*$_{Ar}$CF$_2$), 139.4 (*C*$_{Ar}$), 142.1 (*C*$_{Ar}$), 166.1 (*C*O) ppm. ^{19}F NMR (376 MHz, H-decoupled, $CDCl_3$): δ = −87.9 ppm. IR (KBr): ν = 3002 (w), 2952 (w), 1727 (s, ν(CO)), 1601 (w), 1499 (vw), 1437 (m), 1384 (m), 1349 (m), 1250 (s, ν(CF)), 1178 (m), 1124 (m), 1071 (m), 986 (w), 933 (m), 897 (m), 861 (w), 813 (w), 759 (m), 744 (m), 699 (m), 643 (w), 602 (vw), 473 (w) cm^{-1}. MS (EI): *m*/*z* (%): 276 (100) [M$^+$], 261 (8) [M$^+$ − CH$_3$], 245 (63) [M$^+$ − OCH$_3$]. HRMS (C$_{16}$H$_{14}$F$_2$O$_2$): calcd 276.0962; found 276.0965.

Methyl 5-(1,1-Difluoroethyl)-4′-methylbiphenyl-3-carboxylate (28{*1*;*2*}).



Following GP7, 282 mg (0.250 mmol) of resin **27**{*1*;*2*} was reacted with 225 mg (1.00 mmol) of NIS and 0.25 mL (10 mmol) of HF/py. After purification, 53.0 mg (0.184 mmol, 74% over 4 steps) of a bright yellow oil was obtained (cyclohexane/ethyl acetate 8:1, R_f = 0.6). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.00 (t, $^3J_{HF}$ = 18.2 Hz, 3 H, C*H*$_3$CF$_2$), 2.42 (s, 3 H, C*H*$_3$), 3.99 (s, 3 H, OC*H*$_3$), 7.32 (d, ^3J = 8.5 Hz, 2 H, *H*$_{Ar}$), 7.57 (d, ^3J = 8.5 Hz, 2 H, *H*$_{Ar}$), 7.92 (m, 1 H, *H*$_{Ar}$), 8.15 (m, 1 H, *H*$_{Ar}$), 8.35 (m, 1 H, *H*$_{Ar}$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.1 (C$_{Ar}$*C*H$_3$), 25.9 (t, $^2J_{CF}$ = 29.3 Hz, *C*H$_3$CF$_2$), 52.4 (O*C*H$_3$), 121.4 (t, $^1J_{CF}$ = 240.5 Hz, *C*F$_2$), 124.4 (t, $^3J_{CF}$ = 5.9 Hz, *C*$_{Ar}$C$_{Ar}$CF$_2$), 127.0 (*C*$_{Ar}$), 127.4 (t, $^3J_{CF}$ = 5.9 Hz, *C*$_{Ar}$C$_{Ar}$CF$_2$), 129.2 (*C*$_{Ar}$), 129.7 (*C*$_{Ar}$), 131.1 (*C*$_{Ar}$), 135.4 (*C*$_{Ar}$CH$_3$), 138.1 (*C*$_{Ar}$), 139.1 (t, $^2J_{CF}$ = 27.0 Hz, *C*$_{Ar}$CF$_2$), 142.0 (*C*$_{Ar}$), 166.4 (*C*O) ppm. ^{19}F NMR (376 MHz, H-decoupled, $CDCl_3$): δ = −87.5 ppm. IR (KBr): ν = 3001 (w), 2952 (w), 1728 (s, ν(CO)), 1609 (w), 1518 (w), 1434 (m), 1384 (m), 1349 (m), 1250 (s, ν(CF)), 1178 (m), 1145 (m), 1069 (m), 988 (w), 932 (m), 899 (m), 862 (vw), 817 (m), 769 (m), 737 (w), 699 (w), 632 (w), 609 (vw), 565 (vw), 492 (vw) cm^{-1}. MS (EI): *m*/*z* (%): 290 (100) [M$^+$], 275 (8) [M$^+$ − CH$_3$], 259 (38) [M$^+$ − OCH$_3$]. HRMS (C$_{17}$H$_{16}$F$_2$O$_2$): calcd 290.1118; found 290.1116.

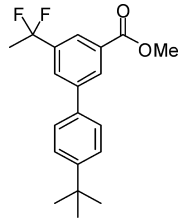
Methyl 4′-Chloro-5-(1,1-difluoroethyl)biphenyl-3-carboxylate (28{*1*;*3*}).



Following GP7, 287 mg (0.250 mmol) of resin **27**{*1*;*3*} was reacted with 225 mg (1.00 mmol) of NIS and 0.25 mL (10 mmol) of HF/py. After purification, 52.0 mg (0.168 mmol, 67% over 4 steps) of a colorless oil was obtained (cyclohexane/ethyl acetate 8:1, R_f = 0.7). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.00 (t, $^3J_{HF}$ = 18.2 Hz, 3 H, C*H*$_3$CF$_2$), 4.00 (s, 3 H, OC*H*$_3$), 7.47 (d, ^3J = 8.6 Hz, 2 H, *H*$_{Ar}$), 7.58 (d, ^3J = 8.6 Hz, 2 H, *H*$_{Ar}$), 7.90 (m, 1 H, *H*$_{Ar}$), 8.18 (m, 1 H, *H*$_{Ar}$), 8.31 (m, 1 H, *H*$_{Ar}$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.0 (t, $^2J_{CF}$ = 29.2 Hz, *C*H$_3$CF$_2$), 52.5 (O*C*H$_3$), 121.3 (t, $^1J_{CF}$ = 240.5 Hz, *C*F$_2$), 125.0 (t, $^3J_{CF}$ = 5.9 Hz, *C*$_{Ar}$C$_{Ar}$CF$_2$), 127.3 (t, $^3J_{CF}$ = 5.9 Hz, *C*$_{Ar}$C$_{Ar}$CF$_2$), 128.5 (*C*$_{Ar}$),

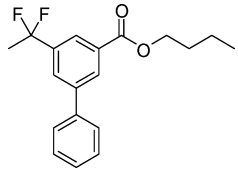
129.2 (C_{Ar}), 129.3 (C_{Ar}), 131.1 (C_{Ar}), 134.5 ($C_{Ar}Cl$), 137.8 (C_{Ar}), 139.4 (t, $^2J_{CF}$ = 27.0 Hz, $C_{Ar}CF_2$), 140.9 (C_{Ar}), 166.2 (*C*O) ppm. ^{19}F NMR (376 MHz, H-decoupled, $CDCl_3$): δ = −88.0 ppm. IR (KBr): ν = 3436 (w), 3002 (w), 2952 (w), 2109 (vw), 1727 (s, ν(CO)), 1608 (w), 1497 (m), 1434 (m), 1384 (m), 1349 (s), 1250 (s, ν(CF)), 1179 (m), 1146 (m), 1094 (m), 1068 (m), 1013 (m), 987 (m), 932 (m), 900 (m), 861 (vw), 829 (m), 770 (m), 748 (m), 699 (m), 643 (w), 627 (w), 605 (vw), 495 (vw) cm^{-1}. MS (EI): *m*/*z* (%): 312/310 (32/100) [M^+], 281/279 (16/51) [$M^+ - OCH_3$]. HRMS ($C_{16}H_{13}F_2ClO_2$): calcd 310.0572; found 310.0575.

Methyl 4′-*tert*-Butyl-5-(1,1-difluoroethyl)biphenyl-3-carboxylate (28{*1*;*4*}).



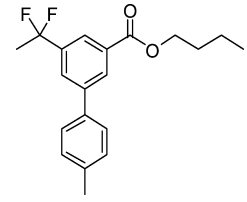
Following GP7, 299 mg (0.250 mmol) of resin **27**{*1*;*4*} was reacted with 225 mg (1.00 mmol) of NIS and 0.25 mL (10 mmol) of HF/py. After purification, 55.0 mg (0.166 mmol, 67% over 4 steps) of a bright yellow oil was obtained (cyclohexane/ethyl acetate 8:1, R_f = 0.7). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.38 (s, 9 H, C(C*H*$_3$)$_3$), 2.01 (t, $^3J_{HF}$ = 18.2 Hz, 3 H, C*H*$_3$CF$_2$), 4.00 (s, 3 H, OC*H*$_3$), 7.53 (d, ^3J = 8.5 Hz, 2 H, H_{Ar}), 7.61 (d, ^3J = 8.5 Hz, 2 H, H_{Ar}), 7.95 (m, 1 H, H_{Ar}), 8.17 (m, 1 H, H_{Ar}), 8.37 (m, 1 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.7 (t, $^2J_{CF}$ = 29.2 Hz, *C*H$_3$CF$_2$), 31.4 (C(*C*H$_3$)$_3$), 34.7 (*C*(CH$_3$)$_3$), 52.5 (OCH$_3$), 121.4 (t, $^1J_{CF}$ = 240.5 Hz, *C*F$_2$), 124.5 (t, $^3J_{CF}$ = 5.9 Hz, $C_{Ar}C_{Ar}CF_2$), 126.0 (C_{Ar}), 126.9 (C_{Ar}), 127.5 (t, $^3J_{CF}$ = 5.9 Hz, $C_{Ar}C_{Ar}CF_2$), 129.3 (C_{Ar}), 131.1 (C_{Ar}), 135.4 (C_{Ar}), 139.1 (t, $^2J_{CF}$ = 27.0 Hz, $C_{Ar}CF_2$), 142.0 (C_{Ar}), 151.4 ($C_{Ar}C(CH_3)_3$), 166.4 (*C*O) ppm. ^{19}F NMR (376 MHz, H-decoupled, $CDCl_3$): δ = −87.8 ppm. IR (KBr): ν = 3032 (w), 3000 (w), 2965 (m), 2870 (w), 1826 (w), 1718 (m, ν(CO)), 1604 (w), 1515 (w), 1434 (m), 1386 (w), 1350 (m), 1263 (s, ν(CF)), 1175 (m), 1140 (m), 1071 (w), 1017 (w), 993 (m), 937 (m), 926 (m), 904 (m), 844 (m), 834 (m), 811 (w), 772 (m), 753 (w), 742 (w), 699 (m), 648 (w), 634 (w), 605 (w), 579 (w), 519 (w), 466 (vw) cm^{-1}. MS (EI): *m*/*z* (%): 332 (40) [M^+], 317 (100) [$M^+ - CH_3$]. HRMS ($C_{20}H_{22}F_2O_2$): calcd 332.1588; found 332.1590.

Butyl 5-(1,1-Difluoroethyl)Biphenyl-3-carboxylate (28{*2*;*1*}).



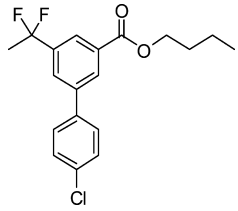
Following GP7, 361 mg (0.300 mmol) of resin **27**{*2*;*1*} was reacted with 270 mg (1.20 mmol) of NIS and 0.30 mL (12 mmol) of HF/py. After purification, 45.0 mg (0.142 mmol, 47% over 5 steps) of a colorless solid was obtained (cyclohexane/ethyl acetate 10:1, R_f = 0.7). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.00 (t, ^3J = 7.4 Hz, 3 H, CH$_2$C*H*$_3$), 1.49 (sex, ^3J = 7.4 Hz, 2 H, C*H*$_2$CH$_3$), 1.79 (quin, ^3J = 7.8 Hz, 2 H, C*H*$_2$CH$_2$CH$_3$), 1.99 (t, $^3J_{HF}$ = 18.2 Hz, 3 H, C*H*$_3$CF$_3$), 4.38 (t,^3J = 6.7 Hz, 2 H, OC*H*$_2$CH$_2$), 7.42 (m, 1 H, H_{Ar}), 7.49 (m, 2 H, H_{Ar}), 7.63 (m, 2H, H_{Ar}), 7.92 (s, 1 H, H_{Ar}), 8.15 (s, 1 H, H_{Ar}), 8.33 (s, 1 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8 (CH$_2$*C*H$_3$), 19.3 (*C*H$_2$CH$_3$), 26.0 (t, ^2J = 29.7 Hz, *C*H$_3$CF$_2$), 30.8 (*C*H$_2$CH$_2$CH$_3$), 65.3 (O*C*H$_2$CH$_2$), 121.5 (t, $^1J_{CF}$ = 239.5 Hz, *C*F$_2$), 124.5 (t, $^3J_{CF}$ = 5.8 Hz, C_{Ar}-$C_{Ar}CF_2$), 127.3 (C_{Ar}), 127.6 (t, $^3J_{CF}$ = 5.8 Hz, $C_{Ar}C_{Ar}CF_2$), 128.2 (C_{Ar}), 129.0 (C_{Ar}), 129.5 (C_{Ar}), 131.6 (C_{Ar}), 139.2 (t, $^2J_{CF}$ = 27.0 Hz, $C_{Ar}CF_2$), 139.5 (C_{Ar}), 142.0 ($C_{Ar}CO$), 166.0 (*C*O) ppm ^{19}F-NMR (376 MHz, H-decoupled, $CDCl_3$): δ = −88.7 ppm. IR (KBr): ν = 2961 (m, ν(CH$_2$)), 2874 (w), 1722 (m, ν(CO)), 1602 (w), 1460 (w), 1385 (m), 1346 (m), 1247 (s, ν(C_{alkyl}F)), 1179 (m), 1126 (m), 1071 (m), 1019 (w), 933 (m), 898 (m), 814 (w), 760 (m), 700 (m), 643 (w), 602 (w) cm^{-1}. MS (EI): *m*/*z* (%): 318 (30) [M^+], 262 (61) [$M^+ - C_4H_9$], 245 (22), 58 (23), 43 (100) [$C_3H_7^+$]. HRMS ($C_{19}H_{20}F_2O_2$): cald. 318.1431; found 318.1429.

Butyl 5-(1,1-Difluoroethyl)-4′-methylbiphenyl-3-carboxylate (28{*2*;*2*}).



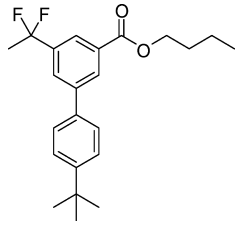
Following GP7, 271 mg (0.220 mmol) of resin **27**{*2*;*2*} was reacted with 200 mg (0.880 mmol) of NIS and 0.25 mL (10 mmol) of HF/py. After purification, 27.0 mg (0.081 mmol, 37% over 5 steps) of a colorless solid was obtained (cyclohexane/ethyl acetate 20:1, R_f = 0.5). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.00 (t, ^3J = 7.4 Hz, 3 H, CH$_2$C*H*$_3$), 1.49 (sex, ^3J = 7.4 Hz, 2 H, C*H*$_2$CH$_3$), 1.79 (quin, ^3J = 7.4 Hz, 2 H, CH$_2$C*H*$_2$CH$_2$), 1.99 (t, $^3J_{HF}$ = 18.2 Hz, 3 H, C*H*$_3$CF$_2$), 2.42 (s, 3 H, $C_{Ar}CH_3$), 4.38 (t,^3J = 6.7 Hz, 2 H, OC*H*$_2$CH$_2$), 7.29 (d, ^3J = 8.0 Hz, 2 H, H_{Ar}), 7.53 (d, ^3J = 8.0 Hz, 2 H, H_{Ar}), 7.90 (s, 1 H, H_{Ar}), 8.12 (s, 1 H, H_{Ar}), 8.31 (s, 1 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8 (CH$_2$*C*H$_3$), 19.3 (*C*H$_2$CH$_3$), 21.2 ($C_{Ar}CH_3$), 26.0 (t, $^2J_{CF}$ = 29.6 Hz, *C*H$_3$CF$_2$), 30.8 (*C*H$_2$CH$_2$CH$_3$), 65.3 (OCH$_2$), 121.5 (t, $^1J_{CF}$ = 239.9 Hz, *C*F$_2$), 124.3 (t, $^3J_{CF}$ = 5.9 Hz, $C_{Ar}C_{Ar}CF_2$), 127.1 (C_{Ar}), 127.3 (t, $^3J_{CF}$ = 5.9 Hz, $C_{Ar}C_{Ar}CF_2$), 129.3 (C_{Ar}), 129.8 (C_{Ar}), 131.5 (C_{Ar}), 136.6 (C_{Ar}), 138.1 ($C_{Ar}CH_3$), 139.1 (t, $^2J_{CF}$ = 26.9 Hz, $C_{Ar}CF_2$), 142.0 ($C_{Ar}CO$), 166.0 (*C*O) ppm. ^{19}F NMR (376 MHz, H-decoupled, $CDCl_3$): δ = −88.6 ppm. IR (KBr): ν = 2961 (m), 2874 (w), 1723 (s, ν(CO)), 1609 (w), 1518 (w), 1456 (m), 1385 (m), 1346 (m), 1246 (s,)1179 (m), 1148 (m), 1069 (m), 1019 (w), 933 (m), 901 (m), 818 (m), 770 (m), 737 (w), 700 (m), 650 (vw), 633 (w), 609 (w), 565 (vw), 498 (vw) cm^{-1}. MS (EI): *m*/*z* (%): 332 (100) [M^+], 312 (35), 295 (31), 276 (66) [$M^+ - C_4H_9$], 259 (35) [$C_{16}H_{13}F_2O^+$]. HRMS ($C_{20}H_{22}F_2O_2$): calcd 332.1588; found 332.1585.

Butyl 4′-Chloro-5-(1,1-difluoroethyl)biphenyl-3-carboxylate (28{*2*;*3*}).



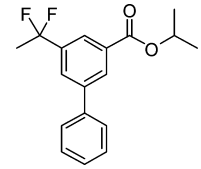
Following GP7, 275 mg (0.220 mmol) of resin **27**{*2*;*3*} was reacted with 200 mg (0.880 mmol) of NIS and 0.25 mL (10 mmol) of HF/py. After purification, 30.0 mg (0.085 mmol, 39% over 5 steps) of a colorless solid was obtained (cyclohexane/ethyl acetate 20:1, $R_f = 0.5$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.00 (t, ^3J = 7.5 Hz, 3 H, CH_2CH_3), 1.48 (sex, ^3J = 7.5 Hz, 2 H, CH_2CH_3), 1.78 (quin, ^3J = 7.5 Hz, 2 H, $CH_2CH_2CH_2$), 1.99 (t, $^3J_{HF}$ = 18.2 Hz, 3 H, CH_3CF_2), 4.38 (t,^3J = 6.8 Hz, 2 H, OCH_2CH_2), 7.45 (d, ^3J = 8.6 Hz, 2 H, H_{Ar}), 7.56 (d, ^3J = 8.6 Hz, 2 H, H_{Ar}), 7.87 (s, 1 H, H_{Ar}), 8.15 (s, 1 H, H_{Ar}), 8.28 (s, 1 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8 (CH_2CH_3), 19.3 (CH_2CH_3), 26.0 (t, $^2J_{CF}$ = 29.7 Hz, CH_3CF_2), 30.8 ($CH_2CH_2CH_3$), 65.4 (OCH_2), 121.4 (t, $^1J_{CF}$ = 239.8 Hz, CF_2), 124.9 (t, $^3J_{CF}$ = 5.9 Hz, $C_{Ar}C_{Ar}CF_2$), 127.3 (t, $^3J_{CF}$ = 5.9 Hz, $C_{Ar}C_{Ar}CF_2$), 128.5 (C_{Ar}), 129.2 (C_{Ar}), 129.3 (C_{Ar}), 131.7 (C_{Ar}), 134.4 (C_{Ar}), 137.9 ($C_{Ar}Cl$), 139.3 (t, $^2J_{CF}$ = 26.9 Hz, $C_{Ar}CF_2$), 140.8 ($C_{Ar}CO$), 165.8 (CO) ppm. ^{19}F NMR (376 MHz, H-decoupled, $CDCl_3$): δ = −88.6 ppm IR (KBr): ν = 2961 (m, $\nu(CH_2)$), 2874 (w), 1722 (s, ν(CO)), 1608 (w), 1497 (m), 1453 (m, $\delta(CH_2)$), 1385 (m, $\delta(CH_3)$), 1346 (m), 1247 (s, $\nu(C_{alkyl}F)$), 1179 (m), 1148 (m), 1094 (m), 1067 (m), 1014 (m, $\nu(C_{aryl}Cl)$), 933 (m), 901 (m), 829 (m), 770 (m), 752 (w, $\delta(CH_2)$), 699 (w), 644 (w), 627 (w), 606 (w), 497 (vw) cm^{-1}. MS (EI): *m*/*z* (%): 354/352 (25/78) [M^+], 312 (46), 298/296 (35/100) [$M^+ - C_4H_9$], 281/279 (23/42) [$C_{15}H_{10}F_2ClO^+$]. HRMS ($C_{19}H_{19}F_2ClO_2$): calcd 352.1041; found 352.1038.

Butyl 4′-*tert*-Butyl-5-(1,1-difluoroethyl)biphenyl-3-carboxylate (28{*2*;*4*}).



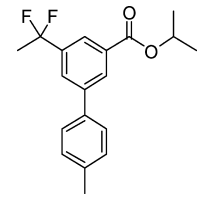
Following GP7, 381 mg (0.300 mmol) of resin **27**{*2*;*4*} was reacted with 270 mg (1.20 mmol) of NIS and 0.30 mL (12 mmol) of HF/py. After purification, 36.0 mg (0.096 mmol, 32% over 5 steps) of a colorless solid was obtained (cyclohexane/ethyl acetate 10:1, $R_f = 0.7$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.00 (t, ^3J = 7.4 Hz, 3 H, CH_2CH_3), 1.38 (s, 9 H, $C(CH_3)_3$), 1.49 (sex, ^3J = 7.6 Hz, 2 H, CH_2CH_3), 1.79 (quin, ^3J = 7.3 Hz, 2 H, $CH_2CH_2CH_3$), 1.99 (t, $^3J_{HF}$ = 18.2 Hz, 3 H, CH_3CF_3), 4.38 (t,^3J = 6.7 Hz, 2 H, OCH_2CH_2), 7.51 (d, ^3J = 8.6 Hz, 2 H, H_{Ar}), 7.58 (d, ^3J = 8.6 Hz, 2 H, H_{Ar}), 7.91 (s, 1 H, H_{Ar}), 8.13 (s, 1 H, H_{Ar}), 8.33 (s, 1 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8 (CH_2CH_3), 19.3 (CH_2CH_3), 26.0 (t, ^2J = 29.7 Hz, CH_3CF_2), 30.8 ($CH_2CH_2CH_3$), 31.3 ($C(CH_3)_3$), 34.6 ($C(CH_3)_3$), 65.3 (OCH_2CH_2), 121.5 (t, $^1J_{CF}$ = 239.9 Hz, CF_2), 124.3 (t, $^3J_{CF}$ = 5.8 Hz, $C_{Ar}C_{Ar}CF_2$), 126.0 (C_{Ar}), 126.9 (C_{Ar}), 127.4 (t, $^3J_{CF}$ = 5.8 Hz, $C_{Ar}C_{Ar}CF_2$), 129.3 (C_{Ar}), 131.5 (C_{Ar}), 136.6 (C_{Ar}), 139.1 (t, $^2J_{CF}$ = 27.1 Hz, $C_{Ar}CF_2$), 142.0 (C_{Ar}-CO),151.3 ($C_{Ar}C(CH_3)_3$), 166.0 (CO) ppm ^{19}F-NMR (376 MHz, H-decoupled, $CDCl_3$): δ = −88.7 ppm. IR (KBr): ν = 3421 (w), 3033 (w), 2962 (m, $\nu(CH_2)$), 2872 (m), 1722 (m, ν(CO)), 1610 (w), 1517 (w), 1454 (m, $\delta(CH_2)$), 1385 (m), 1347 (m), 1245 (m, $\nu(C_{alkyl}F)$), 1180 (m), 1125 (m), 1069 (m), 1018 (w), 933 (m), 901 (w), 836 (m), 814 (w), 772 (m), 742 (w), 700 (w), 650 (w), 633 (w), 609 (w), 530 (w) cm^{-1}. MS (EI): *m*/*z* (%): 374 (36) [M^+], 360 (11), 359 (100) [$M^+ - CH_3$]. HRMS ($C_{23}H_{28}F_2O_2$): calcd. 374.2057; found 374.2056.

Isopropyl 5-(1,1-Difluoroethyl)-4′-methylbiphenyl-3-carboxylate (28{*3*;*1*}).



Following GP7, 186 mg (0.150 mmol) of resin **27**{*3*;*1*} was reacted with 200 mg (0.600 mmol) of NIS and 0.15 mL (6.0 mmol) of HF/py. After purification, 13.0 mg (0.043 mmol, 29% over 5 steps) of a colorless solid was obtained (cyclohexane/ethyl acetate 10:1, $R_f = 0.4$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.40 (d, ^3J = 6.2 Hz, 6 H, $OCH(CH_3)_2$), 1.99 (t, $^3J_{HF}$ = 18.2 Hz, 3 H, CH_3CF_2), 5.30 (sep, ^3J = 6.2 Hz, 1 H, $OCH(CH_3)_2$), 7.41 (m, 1 H, H_{Ar}), 7.47 (m, 2 H, H_{Ar}), 7.64 (d, ^3J = 7.2 Hz, 2 H, H_{Ar}), 7.90 (s, 1 H, H_{Ar}), 8.13 (s, 1 H, H_{Ar}), 8.31 (s, 1 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.9 ($C(CH_3)_2$), 26.0 (t, $^2J_{CF}$ = 29.6 Hz, CH_3CF_2), 69.0 ($C(CH_3)_2$), 121.5 (t, $^1J_{CF}$ = 239.5 Hz, CF_2), 124.6 (t, $^3J_{CF}$ = 5.8 Hz, $C_{Ar}C_{Ar}CF_2$), 127.3 (C_{Ar}), 127.5 (t, $^3J_{CF}$ = 5.8 Hz, $C_{Ar}C_{Ar}CF_2$), 128.1 (C_{Ar}), 129.0 (C_{Ar}), 129.5 (C_{Ar}), 131.9 (C_{Ar}), 139.1 (t, $^2J_{CF}$ = 26.9 Hz, $C_{Ar}CF_2$), 139.6 (C_{Ar}), 142.0 ($C_{Ar}CO$), 165.4 (CO) ppm. ^{19}F-NMR (376 MHz, H-decoupled, $CDCl_3$): δ = −87.9 ppm. IR (KBr): ν = 2981 (w), 2931 (w), 1720 (w, (CO)), 1602 (vw), 1548 (w), 1500 (vw), 1453 (w, $\delta(CH_2)$), 1364 (w), 1342 (w), 1249 (m, $\nu(C_{alkyl}F)$), 1180 (w), 1106 (w), 1069 (w), 920 (w), 898 (vw), 833 (w), 814 (vw), 760 (w), 741 (vw), 700 (w), 643 (vw), 602 (vw) cm^{-1}. MS (EI): *m*/*z* (%): 304 (100) [M^+], 262 (87) [$M^+ - C_3H_6$], 245 (78) [$M^+ - OC_3H_7$], 43 (57) [$C_3H_7^+$]. HRMS ($C_{18}H_{18}F_2O_2$): calcd 304.1275; found 304.1273.

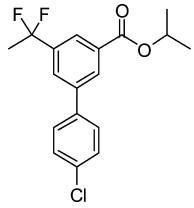
Isopropyl 5-(1,1-Difluoroethyl)-4′-methylbiphenyl-3-carboxylate (28{*3*;*2*}).



Following GP7, 188 mg (0.150 mmol) of resin **27**{*3*;*2*} was reacted with 200 mg (0.600 mmol) of NIS and 0.15 mL (6.0 mmol) of HF/py. After purification 10.0 mg (0.032 mmol, 21% over 5 steps) of a colorless solid was obtained (cyclohexane/

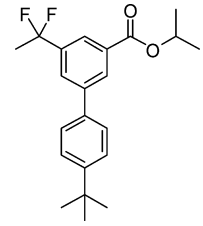
ethyl acetate 10:1, $R_f = 0.6$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.40 (d, ^3J = 6.2 Hz, 6 H, CH(CH_3)$_2$), 1.99 (t, $^3J_{HF}$ = 18.2 Hz, 3 H, CH_3CF$_2$), 2.42 (s, 3 H, C$_{Ar}$CH_3), 5.30 (sept, ^3J = 6.2 Hz, 1 H, CH(CH$_3$)$_2$), 7.29 (d, ^3J = 8.0 Hz, 2 H, H_{Ar}), 7.53 (d, ^3J = 8.0 Hz, 2 H, H_{Ar}), 7.88 (s, 1 H, H_{Ar}), 8.11 (s, 1 H, H_{Ar}), 8.30 (s, 1 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.2 (C$_{Ar}$CH$_3$), 22.0 (C(CH$_3$)$_2$), 26.0 (t, $^2J_{CF}$ = 29.6 Hz, CH$_3$CF$_2$), 68.9 (OC(CH$_3$)$_2$), 121.5 (t, $^1J_{CF}$ = 239.8 Hz, CF$_2$), 124.3 (t, $^3J_{CF}$ = 5.9 Hz, C$_{Ar}$C$_{Ar}$CF$_2$), 127.1 (C$_{Ar}$), 127.2 (t, $^3J_{CF}$ = 5.9 Hz, C$_{Ar}$C$_{Ar}$CF$_2$), 129.3 (C$_{Ar}$), 129.7 (C$_{Ar}$), 131.9 (C$_{Ar}$), 136.6 (C$_{Ar}$), 138.1 (C$_{Ar}$CH$_3$), 139.0 (t, $^2J_{CF}$ = 26.9 Hz, C$_{Ar}$CF$_2$), 142.0 (C$_{Ar}$CO), 165.5 (CO) ppm. ^{19}F NMR (376 MHz, H-decoupled, $CDCl_3$): δ = −87.7 ppm. IR (KBr): ν = 3441 (vw), 2981 (w, ν(CH$_3$)), 2926 (w, ν(CH$_2$)), 1719 (m, ν(CO)), 1608 (w), 1517 (w), 1453 (w, δ(CH$_2$)), 1384 (w), 1362 (m), 1341 (w), 1249 (m, ν(C$_{alkyl}$F)), 1180 (m), 1145 (m), 1106 (m), 1067 (w), 920 (w), 900 (w), 817 (m), 771 (w), 735 (vw, δ(CH$_2$)), 699 (w), 632 (vw), 608 (vw), 656 (vw), 500 (vw) cm^{-1}. MS (EI): *m*/*z* (%): 318 (100) [M$^+$], 290 (21), 276 (48) [M$^+$ − C$_3$H$_7$], 276 (24), 259 (46) [C$_{16}$H$_{13}$F$_2$O$^+$], 43 (12) [C$_3$H$_7^+$]. HRMS (C$_{19}$H$_{20}$F$_2$O$_2$): calcd 318.1431; found 318.1436.

Isopropyl 4′-Chloro-5-(1,1-difluoroethyl)biphenyl-3-carboxylate (28{*3*;*3*}).



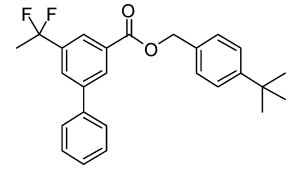
Following GP7, 190 mg (0.150 mmol) of resin **27**{*3*;*3*} was reacted with 200 mg (0.600 mmol) of NIS and 0.15 mL (6.0 mmol) of HF/py. After purification, 14.0 mg (0.042 mmol, 28% over 5 steps) of a colorless solid was obtained (cyclohexane/ethyl acetate 10:1, R_f = 0.5). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.40 (d, ^3J = 6.2 Hz, 6 H, CH(CH_3)$_2$), 1.99 (t, $^3J_{HF}$ = 18.2 Hz, 3 H, CH_3CF$_2$), 5.31 (sept, ^3J = 6.2 Hz, 1 H, CH(CH$_3$)$_2$), 7.45 (d, ^3J = 8.5 Hz, 2 H, H_{Ar}), 7.56 (d, ^3J = 8.5 Hz, 2 H, H_{Ar}), 7.86 (s, 1 H, H_{Ar}), 8.14 (s, 1 H, H_{Ar}), 8.27 (s, 1 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.0 (C(CH$_3$)$_2$), 26.0 (t, $^2J_{CF}$ = 29.6 Hz, CH$_3$CF$_2$), 69.1 (OC(CH$_3$)$_2$), 121.4 (t, $^1J_{CF}$ = 239.7 Hz, CF$_2$), 124.9 (t, $^3J_{CF}$ = 5.7 Hz, C$_{Ar}$C$_{Ar}$CF$_2$), 127.2 (t, $^3J_{CF}$ = 5.7 Hz, C$_{Ar}$C$_{Ar}$CF$_2$), 128.5 (C$_{Ar}$), 129.2 (C$_{Ar}$), 129.9 (C$_{Ar}$), 132.1 (C$_{Ar}$), 134.4 (C$_{Ar}$), 138.0 (C$_{Ar}$Cl), 139.3 (t, $^2J_{CF}$ = 27.2 Hz, C$_{Ar}$CF$_2$), 140.8 (C$_{Ar}$CO), 165.2 (CO) ppm. ^{19}F NMR (376 MHz, H-decoupled, $CDCl_3$): δ = −88.1 ppm. IR (KBr): ν = 3434 (vw), 2982 (m, ν(CH$_3$)), 2936 (w, ν(CH$_2$)), 1719 (s, ν(CO)), 1608 (w), 1497 (m), 1453 (m, δ(CH$_2$)), 1384 (m), 1363 (m), 1341 (m), 1246 (s, ν(C$_{alkyl}$F)), 1180 (m), 1145 (m), 1126 (m), 1106 (m, ν(C$_{aryl}$Cl)), 1013 (w), 955 (w), 920 (m), 901 (m), 829 (m), 771 (m), 747 (w), 700 (w), 644 (vw), 627 (vw), 606 (w), 499 (vw) cm^{-1}. MS (EI): *m*/*z* (%): 340/338 (33/100) [M$^+$], 298/296 (26/81) [M$^+$ − C$_3$H$_7$], 281/279 (40/59) [C$_{15}$H$_{10}$F$_2$ClO$^+$], 43 (60) [C$_3$H$_7^+$]. HRMS (C$_{18}$H$_{17}$F$_2$ClO$_2$): calcd 338.0885; found 338.0887.

Isopropyl 4′-*tert*-Butyl-5-(1,1-difluoroethyl)biphenyl-3-carboxylate (28{*3*;*4*}).



Following GP7, 202 mg (0.150 mmol) of resin **27**{*3*;*4*} was reacted with 200 mg (0.600 mmol) of NIS and 0.15 mL (6.0 mmol) of HF/py. After purification, 14.0 mg (0.039 mmol, 26% over 5 steps) of a colorless solid was obtained (cyclohexane/ethyl acetate 10:1, R_f = 0.6). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.37 (s, 9 H, C(CH_3)$_3$), 1.39 (d, ^3J = 6.3 Hz, 6 H, OCH(CH_3)$_2$), 1.99 (t, $^3J_{HF}$ = 18.2 Hz, 3 H, CH_3CF$_2$), 5.30 (sep, ^3J = 6.3 Hz, 1 H, OCH(CH$_3$)$_2$), 7.51 (d, ^3J = 8.5 Hz, 2 H, H_{Ar}), 7.58 (d, ^3J = 8.4 Hz, 2 H, H_{Ar}), 7.89 (s, 1 H, H_{Ar}), 8.11 (s, 1 H, H_{Ar}), 8.31 (s, 1 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.0 (C(CH$_3$)$_2$), 26.0 (t, $^2J_{CF}$ = 29.7 Hz, CH$_3$CF$_2$), 31.3 (C(CH$_3$)$_3$), 34.6 (C(CH$_3$)$_3$), 68.9 (C(CH$_3$)$_2$), 120.6 (t, $^1J_{CF}$ = 239.1 Hz, CF$_2$), 124.3 (t, $^3J_{CF}$ = 5.9 Hz, C$_{Ar}$C$_{Ar}$CF$_2$), 126.0 (C$_{Ar}$), 127.0 (C$_{Ar}$), 127.3 (t, $^3J_{CF}$ = 5.6 Hz, C$_{Ar}$C$_{Ar}$CF$_2$), 129.3 (C$_{Ar}$), 131.9 (C$_{Ar}$), 136.7 (C$_{Ar}$), 139.0 (t, $^2J_{CF}$ = 26.9 Hz, C$_{Ar}$CF$_2$), 141.9 (C$_{Ar}$CO), 151.3 (C$_{Ar}$C(CH$_3$)$_3$), 165.5 (CO) ppm. ^{19}F-NMR (376 MHz, H-decoupled, $CDCl_3$): δ = −87.7 ppm. IR (KBr): ν = 2964 (w), 1720 (m, (CO)), 1609 (vw), 1516 (vw), 1453 (vw, δ(CH$_2$)), 1385 (w), 1364 (w), 1249 (m, ν(C$_{alkyl}$F)), 1180 (w), 1145 (w), 1107 (w), 1067 (w), 920 (w), 900 (vw), 833 (w), 813 (vw), 772 (w), 699 (w), 632 (vw), 608 (vw) cm^{-1}. MS (EI): *m*/*z* (%): 360 (44) [M$^+$], 345 (100) [M$^+$ - CH$_3$], 332 (18), 317 (61) [M$^+$ - C$_3$H$_7$], 303 (13), 58 (13), 43 (53) [C$_3$H$_7^+$]. HRMS (C$_{22}$H$_{26}$F$_2$O$_2$): calcd 360.1901; found 360.1898.

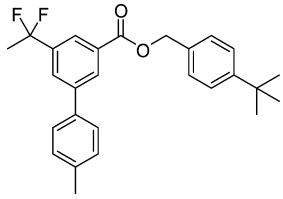
4-*tert*-Butylbenzyl 5-(1,1-Difluoroethyl)biphenyl-3-carboxylate (28{*4*;*1*}).



Following GP7, 266 mg (0.200 mmol) of resin **27**{*4*;*1*} was reacted with 180 mg (0.800 mmol) of NIS and 0.20 mL (8.0 mmol) of HF/py. After purification, 25.0 mg (0.062 mmol, 31% over 5 steps) of a colorless solid was obtained (cyclohexane/ethyl acetate 10:1, R_f = 0.5). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.34 (s, 9 H, C(CH_3)$_3$), 1.98 (t, ^3J = 18.2 Hz, 3 H, CH_3CF$_2$), 5.39 (s, 2 H, OCH_2), 7.40−7.50 (m, 7 H, H_{Ar}), 7.62 (d, ^{3}J = 7.1 Hz, 2 H, H_{Ar}), 7.91 (s, 1 H, H_{Ar}), 8.18 (s, 1 H, H_{Ar}), 8.35 (s, 1 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.0 (t, $^2J_{CF}$ = 29.7 Hz, CH$_3$CF$_2$), 31.3 (C(CH$_3$)$_3$), 34.7 (C(CH$_3$)$_3$), 67.0 (OCH$_2$), 121.4 (t, $^1J_{CF}$ = 239.9 Hz, CF$_2$), 124.8 (t, $^3J_{CF}$ = 5.8 Hz, C$_{Ar}$C$_{Ar}$CF$_2$), 125.6 (C$_{Ar}$), 127.3 (C$_{Ar}$), 127.7 (t, $^3J_{CF}$ = 5.8 Hz, C$_{Ar}$C$_{Ar}$CF$_2$), 128.2 (C$_{Ar}$), 128.3 (C$_{Ar}$), 129.0 (C$_{Ar}$), 129.6 (C$_{Ar}$), 131.3 (C$_{Ar}$), 132.8 (C$_{Ar}$), 136.8 (C$_{Ar}$), 139.2 (t, $^2J_{CF}$ = 27.2 Hz, C$_{Ar}$CF$_2$), 142.1 (C$_{Ar}$CO), 151.5 (C$_{Ar}$C(CH$_3$)$_3$), 165.8

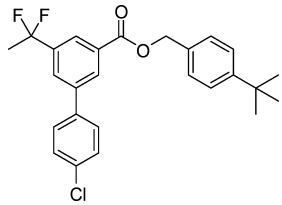
(*C*O) ppm. ^{19}F-NMR (376 MHz, H-decoupled, $CDCl_3$): $\delta = -87.8$ ppm. IR (KBr): $\nu = 3059$ (w), 2959 (m), 2868 (w), 1716 (m, ν(CO)), 1603 (w), 1515 (w), 1463 (m, $\delta(CH_2)$), 1415 (w), 1384 (m), 1363 (w), 1343 (w), 1258 (m, $\nu(C_{alkyl}F)$), 1173 (m), 1074 (w), 1022 (w), 970 (w), 939 (m), 896 (m), 833 (m), 819 (m), 758 (m), 703 (m), 642 (w), 630 (w), 600 (w), 562 (w), 523 (w), 484 (w) cm^{-1}. MS (EI): *m*/*z* (%): 408 (61) [M^+], 393 (100) [$M^+ - CH_3$], 245 (79), 147 (17), 43 (29) [$C_3H_7^+$]. HRMS ($C_{26}H_{26}F_2O_2$): calcd 408.1901; found 408.1903.

4-*tert*-Butylbenzyl 5-(1,1-Difluoroethyl)-4′-methylbiphenyl-3-carboxylate (28{*4*;*2*}).



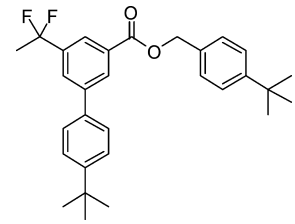
Following GP7, 287 mg (0.220 mmol) of resin **27**{*4*;*2*} was reacted with 200 mg (0.880 mmol) of NIS and 0.25 mL (10 mmol) of HF/py. After purification, 27.0 mg (0.064 mmol, 30% over 5 steps) of a colorless solid was obtained (cyclohexane/ethyl acetate 20:1, $R_f = 0.5$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.34 (s, 9 H, C(CH_3)$_3$), 1.98 (t, $^3J_{HF}$ = 18.2 Hz, 3 H, CH_3CF$_2$), 2.42 (s, 3 H, C$_{Ar}$CH_3), 5.39 (s, 2 H, OCH_2), 7.29 (d, ^3J = 7.9 Hz, 2 H, H_{Ar}), 7.41 (d, ^3J = 8.2 Hz, 2 H, H_{Ar}), 7.43 (d, ^3J = 7.9 Hz, 2 H, H_{Ar}), 7.53 (d, ^3J = 8.2 Hz, 2 H, H_{Ar}), 7.90 (s, 1H, H_{Ar}), 8.16 (s, 1H, H_{Ar}), 8.35 (s, 1H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.2 (C$_{Ar}$CH$_3$), 26.0 (t, $^2J_{CF}$ = 29.6 Hz, *C*H$_3$CF$_2$), 31.3 (C(*C*H$_3$)$_3$), 34.6 (*C*(CH$_3$)$_3$), 67.0 (O*C*H$_2$), 121.5 (t, $^1J_{CF}$ = 239.6 Hz, *C*F$_2$), 124.5 (t, $^3J_{CF}$ = 5.9 Hz, *C*$_{Ar}$C$_{Ar}$CF$_2$), 125.6 (*C*$_{Ar}$), 127.1 (*C*$_{Ar}$), 127.5 (t, $^3J_{CF}$ = 5.9 Hz, C$_{Ar}$*C*$_{Ar}$CF$_2$), 128.3 (*C*$_{Ar}$), 129.4 (*C*$_{Ar}$), 129.7 (*C*$_{Ar}$), 131.2 (*C*$_{Ar}$), 132.8 (*C*$_{Ar}$), 136.5 (*C*$_{Ar}$), 138.1 (*C*$_{Ar}$CH$_3$), 139.1 (t, $^2J_{CF}$ = 27.1 Hz, *C*$_{Ar}$CF$_2$), 142.1 (*C*$_{Ar}$CO), 151.5 (*C*$_{Ar}$C(CH$_3$)$_3$), 165.9 (*C*O) ppm. ^{19}F NMR (376 MHz, H-decoupled, $CDCl_3$): $\delta = -87.5$ ppm. IR (KBr): ν = 2962 (m, $\nu(CH_3)$), 2868 (w), 1723 (m, ν(CO)), 1609 (w), 1517 (w), 1453 (w, $\delta(CH_2)$), 1382 (m), 1343 (m), 1236 (s, $\nu(C_{alkyl}F)$), 1179 (m), 1110 (m), 1067 (m), 1020 (w), 963 (w), 931 (m), 900 (m), 816 (m), 769 (m), 736 (w, $\delta(CH_2)$), 699 (w), 670 (vw), 632 (w), 608 (w), 565 (w) cm^{-1}. MS (EI): *m*/*z* (%): 422 (100) [M^+], 407 (71) [$M^+ - CH_3^+$], 317 (67), 259 (89) [$C_{16}H_{13}F_2O^+$], 84 (50), 43 (64). HRMS ($C_{27}H_{28}F_2O_2$): calcd 422.2057; found 422.2054.

4-*tert*-Butylbenzyl 4′-Chloro-5-(1,1-difluoroethyl)biphenyl-3-carboxylate (28{*4*;*3*}).



Following GP7, 283 mg (0.220 mmol) of resin **27**{*4*;*3*} was reacted with 200 mg (0.880 mmol) of NIS and 0.25 mL (10 mmol) of HF/py. After purification, 24.0 mg (0.054 mmol, 25% over 5 steps) of a colorless solid was obtained (cyclohexane/ethyl acetate 20:1, $R_f = 0.5$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.33 (s, 9 H, C(CH_3)$_3$), 1.98 (t, $^3J_{HF}$ = 18.2 Hz, 3 H, CH_3CF$_2$), 5.40 (s, 2 H, OCH_2), 7.45 (m, 4 H, H_{Ar}), 7.49 (d, ^3J = 8.6 Hz, 2 H, H_{Ar}), 7.55 (d, ^3J = 8.6 Hz, 2 H, H_{Ar}), 7.87 (s, 1 H, H_{Ar}), 8.18 (s, 1 H, H_{Ar}), 8.31 (s, 1 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.0 (t, $^2J_{CF}$ = 29.6 Hz, *C*H$_3$CF$_2$), 31.3 (C(*C*H$_3$)$_3$), 34.7 (*C*(CH$_3$)$_3$), 67.1 (O*C*H$_2$), 121.3 (t, $^1J_{CF}$ = 239.7 Hz, *C*F$_2$), 125.1 (t, $^3J_{CF}$ = 5.8 Hz, *C*$_{Ar}$C$_{Ar}$CF$_2$), 125.6 (*C*$_{Ar}$), 127.5 (t, $^3J_{CF}$ = 5.8 Hz, *C*$_{Ar}$C$_{Ar}$CF$_2$), 127.7 (*C*$_{Ar}$), 128.3 (*C*$_{Ar}$), 129.2 (*C*$_{Ar}$), 129.4 (*C*$_{Ar}$), 131.5 (*C*$_{Ar}$Cl), 132.7 (*C*$_{Ar}$CH$_2$), 134.4 (*C*$_{Ar}$), 137.8 (*C*$_{Ar}$), 139.4 (t, $^2J_{CF}$ = 27.2 Hz, *C*$_{Ar}$CF$_2$), 140.9 (*C*$_{Ar}$CO), 151.6 (*C*$_{Ar}$C(CH$_3$)$_3$), 165.7 (*C*O) ppm. ^{19}F NMR (376 MHz, H-decoupled, $CDCl_3$): $\delta = -87.8$ ppm. IR (KBr): ν = 2963 (m, $\nu(CH_3)$), 1724 (s, ν(CO)), 1608 (w), 1516 (w), 1497 (m), 1452 (m), 1383 (m), 1343 (m), 1238 (s, $\nu(C_{alkyl}F)$), 1179 (m), 1122 (m), 1094 (m, $\nu(C_{aryl}Cl)$), 1066 (m), 1013 (m), 932 (m), 829 (m), 769 (m), 734 (m, $\delta(CH_2)$), 699 (m), 645 (w), 605 (w) cm^{-1}. MS (EI): *m*/*z* (%): 444/442 (12/32) [M^+], 429/427 (19/56) [$M^+ - CH_3$], 324 (50), 317 (100) [$C_{19}H_{19}F_2O_2^+$], 281/279 (28/75) [$C_{15}H_{10}F_2ClO^+$], 169 (53). HRMS ($C_{26}H_{25}F_2ClO_2$): calcd 442.1511; found 442.1516.

4-*tert*-Butylbenzyl 4′-*tert*-Butyl-5-(1,1-difluorethyl)biphenyl-3-carboxylate (28{*4*;*4*}).



Following GP7, 288 mg (0.200 mmol) of resin **27**{*4*;*4*} was reacted with 180 mg (0.800 mmol) of NIS and 0.20 mL (8.0 mmol) of HF/py. After purification, 29.0 mg (0.062 mmol, 31% over 5 steps) of a colorless solid was obtained (cyclohexane/ethyl acetate 10:1, $R_f = 0.6$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.34 (s, 9 H, C(CH_3)$_3$), 1.37 (s, 9 H, C(CH_3)$_3$), 1.98 (t, ^3J = 18.2 Hz, 3 H, CH_3CF$_2$), 5.39 (s, 2 H, OCH_2), 7.39−7.45 (m, 4 H, H_{Ar}), 7.50 (d, ^3J = 8.6 Hz, 2 H, H_{Ar}), 7.56 (d, ^3J = 8.6 Hz, 2 H, H_{Ar}), 7.90 (s, 1 H, H_{Ar}), 8.15 (s, 1 H, H_{Ar}), 8.35 (s, 1 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.0 (t, $^2J_{CF}$ = 29.5 Hz, *C*H$_3$CF$_2$), 31.3 (C(*C*H$_3$)$_3$), 31.4 (C(*C*H$_3$)$_3$), 34.5 (*C*(CH$_3$)$_3$), 34.6 (*C*(CH$_3$)$_3$), 67.0 (O*C*H$_2$), 121.5 (t, $^1J_{CF}$ = 239.7 Hz, *C*F$_2$), 124.5 (t, $^3J_{CF}$ = 5.5 Hz, *C*$_{Ar}$C$_{Ar}$CF$_2$), 125.6 (*C*$_{Ar}$), 126.0 (*C*$_{Ar}$), 126.9 (*C*$_{Ar}$), 127.6 (t, $^3J_{CF}$ = 5.5 Hz, *C*$_{Ar}$C$_{Ar}$CF$_2$), 128.3 (*C*$_{Ar}$), 129.4 (*C*$_{Ar}$), 131.2 (*C*$_{Ar}$), 132.8 (*C*$_{Ar}$), 136.5 (*C*$_{Ar}$), 139.1 (t, $^2J_{CF}$ = 27.1 Hz, *C*$_{Ar}$CF$_2$), 142.0 (*C*$_{Ar}$CO), 151.3 (*C*$_{Ar}$C(CH$_3$)$_3$), 151.4 (*C*$_{Ar}$C(CH$_3$)$_3$), 165.9 (*C*O) ppm. ^{19}F-NMR (376 MHz, H-decoupled, $CDCl_3$): $\delta = -87.7$ ppm. IR (KBr): ν = 2962 (m, $\nu(CH_3)$), 2868 (w), 1723 (m, ν(CO)), 1610 (vw), 1516 (w), 1452 (w, $\delta(CH_2)$), 1382 (w), 1364 (w), 1344 (w), 1235 (m, $\nu(C_{alkyl}F)$), 1179 (w), 1122 (w), 1067 (w), 1019 (vw), 964 (w), 931 (w), 834 (w), 815 (w), 770 (w), 741 (vw), 699 (w), 632 (vw), 607 (vw), 571 (vw) cm^{-1}. MS (EI): *m*/*z* (%): 464 (88) [M^+], 449 (100) [$M^+ - CH_3$], 301 (40), 217 (33), 147 (23). HRMS ($C_{30}H_{34}F_2O_2$): calcd 464.2526; found 464.2525.

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Supporting Information Available. Spectroscopic data (^{1}H NMR) of the *gem*-difluorinated compounds. This information is available free of charge via the Internet at http://pubs.acs.org.

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