Solid-Phase Organic Synthesis of Difluoroalkyl Entities using a Novel Fluorinating Cleavage Strategy: Part 1. Linker Development: Scope and Limitations

Matthias S. Wiehn,[†] Stephen D. Lindell,[‡] and Stefan Bräse*,[†]

Institut für Organische Chemie, Karlsruhe Institute of Technology, Fritz-Haber-Weg 6, 76131 Karlsruhe, Germany, and Bayer CropScience AG, Industriepark Hoechst, G836, 65926 Frankfurt am Main, Germany

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An efficient method to synthesize *gem*-difluorinated compounds on solid supports is described. The strategy is based on the design of a novel sulfur linker system that enables, to the best of our knowledge for the first time, the release of target structures from the resin under simultaneous fluorination. Starting from an immobilized dithiol, coupling with an excess of aldehyde or ketone furnished dithianes. These can be further functionalized prior to release from the resin using our newly developed fluorinating cleavage conditions. Amide forming reactions, palladium-catalyzed reactions (Heck, Suzuki, and Sonogashira couplings), reductions, alkylations, and olefinations were successfully explored on the linker. The difluorinated target substances were obtained in modest to excellent yields and in high purities.

Introduction

Organofluorine compounds play an essential role in the modern drug discovery process. Since the first fluorine containing agent developed in the late 1950s,[1] more than 150 fluorinated drugs have come onto the market and now make up about 20% of all pharmaceuticals and about 30−40% of all agrochemicals.[2] The fact that the cholesterol reducer atorvastatin (Lipitor) and the asthma agent fluticasone propionate (Advair) were at on the top of the sales ranking of prescription drugs in 2006 outlines the steadily increasing relevance of fluorine containing compounds.[3] Other important fluorinated drugs, among many others, are the blockbuster antidepressant fluoxetine (Prozac), the entry inhibitor maraviroc (Celsentri) used for the treatment of HIV, mefloquine (Lariam) for the prophylaxis and the treatment of malaria, and eflornithine (α-difluoromethylornithine or DFMO, Ornidyl), a rationally designed ornithine decarboxylase inhibitor used to treat *Trypanosoma gambiense* infections.[4]

In addition, positron electron tomography (PET) largely uses ^{18}F-labeled molecules.[5,6] ^{18}F is a very well suited radioisotope for the preparation of PET radiopharmaceuticals because of its relatively long half-life ($t_{1/2}$ = 109.8 min) and low positron energy. Recently, nucleophilic fluorination was explored as the detagging process in the synthesis of ^{18}F radiotracers.[7]

Fluorinated compounds represent a class of particular interest as dramatic changes in the physical properties and the chemical reactivity, as well as the biological activity, can be achieved by introduction of fluorine containing substituents.[8] The most common reason to add fluorine into drugs is the belief that it will stop metabolism, although this is not necessarily always true.[9]

In addition to this, fluorine and fluoromethyl groups are often used as bioisosteric units:[2] the C−F group is reported to be bioisosteric with C−OH, carbonyl groups or nitrile groups,[10] the trifluoromethyl group can be seen as a bioisostere of the isopropyl group due to the similar size and as an electronic bioisostere of bromine or a nitrile group.[11] Moreover, amide and ester units can be replaced by fluorolefins.[12] However, the occurrence of fluorinated compounds in nature is very rare: Compared to a few hundred chlorinated natural products isolated so far, there are only about a dozen fluorine containing analogues.[13] Therefore, efforts to prepare organofluorine compounds synthetically are steadily increasing and several interesting new methods have been developed, particularly in the recent past, for the introduction of fluorine into organic molecules.[14]

However, the incorporation of fluorine substituents often causes difficulties during subsequent synthetic steps because of the changed electron density in the molecule. Fluorine containing substituents lower the reactivity of aromatic systems in electrophilic substitution reactions drastically and nucleophilic substitution on aliphatic carbon atoms bearing fluorine groups is hardly possible.[15] Hence, it is to the best advantage to introduce fluorine into the target structures in a late stage, if possible in the last synthetic step. Moreover the introduction at the end of synthesis is the strategy of choice in the design of the above-mentioned ^{18}F PET ligands.[16]

Results and Discussion

We recently reported on a novel strategy for the design of geminal difluoro compounds *via* solid-phase organic synthesis (SPOS), which combines the advantages of SPOS

* To whom correspondence should be addressed. E-mail: braese@kit.edu. Fax: +49 721 608 8581.
[†] Karlsruhe Institute of Technology.
[‡] Bayer CropScience AG.

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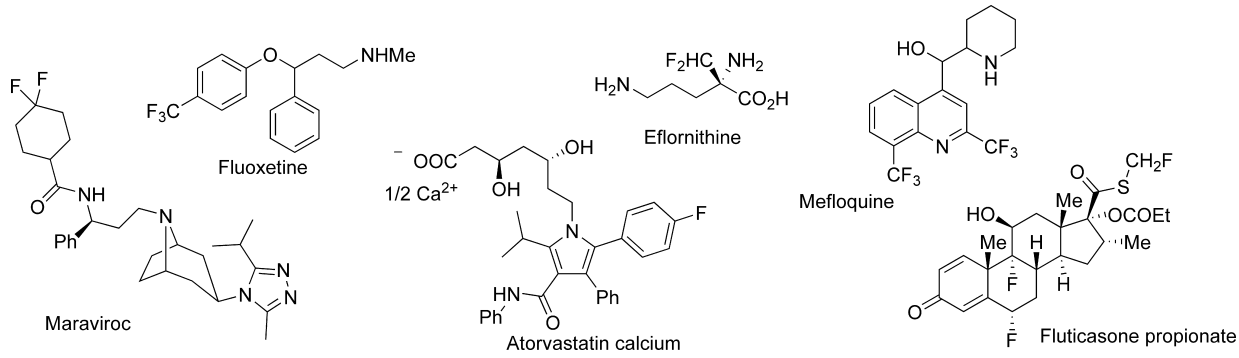
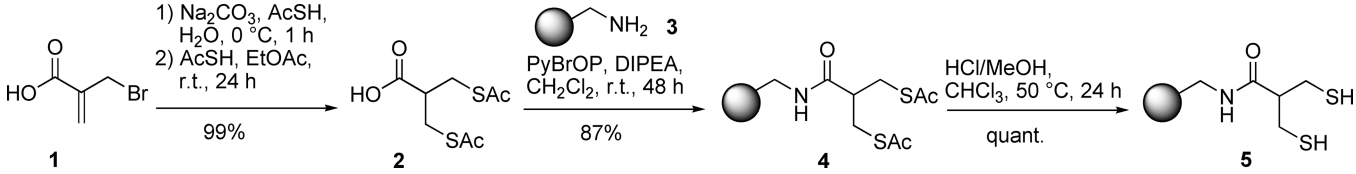


Figure 1. Important fluorine containing drugs.

Scheme 1. Synthesis of the Dithiol Linker **5** Starting from 2-(Bromomethyl)Acrylic Acid (**1**)



as a well established method in the combinatorial chemistry with the incorporation of fluorine substituents at the end of the synthesis.[17,18] For these purposes the first linker system was developed which enables the release of the target structures from the resin with simultaneous fluorination.[19,20] We herein present in detail the scope and limitations of this novel linker system.

The strategy is based on the easy transformation of C−S into C−F bonds, as first explored by Kollonitsch et al. and Katzenellenbogen,[21] in which sulfur is oxidized by a halonium species thus forming a good leaving group in the presence of a nucleophilic fluoride source. Based upon this precedent, we synthesized a dithiane linker to which different aldehydes and ketones were attached, modified and finally cleaved from the solid support to give *gem*-difluoro compounds. In contrast to the dithiane linker prepared by Huwe et al.,[22] the new linker system is achiral and therefore avoids possible formation of diastereomers and hence facilitates the analysis of chiral compounds attached to the resin using ^{13}C NMR spectra (vide infra).

The precursor **2** of the linker was synthesized starting from 2-(bromomethyl)acrylic acid (**1**) in an excellent yield of 99% over two steps[23] and subsequently attached to aminomethyl polystyrene resin (**3**, loading 2.06 mmol/g, 1% DVB) using bromotrispyrrolidinophosphonium hexafluorophosphate (PyBrOP) and diisopropylethylamine (DIPEA). The conversion and the resultant loading of resin **4** with the linker molecule were determined via sulfur elemental analysis. The resin **4** is very stable and can be stored at room temperature for an extended time (months). As basic hydrolysis inevitably leads to the formation of the disulfide, the two thioester groups have to be cleaved under acidic conditions. This proceeds easily in a HCl/methanol mixture at 50 °C and yields the free dithiol linker **5** quantitatively (Scheme 1) which can be monitored by gel-phase ^{13}C NMR spectroscopy.[24]

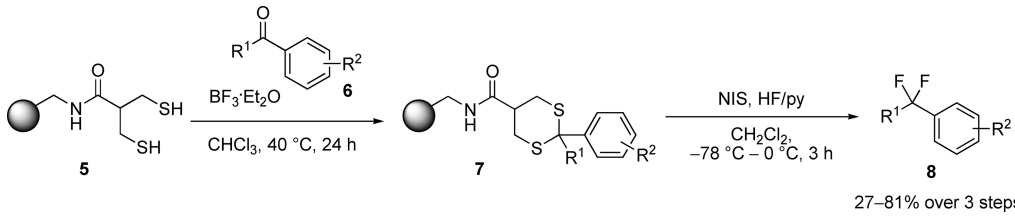
We tested the attachment-detachment procedure with a number of aldehydes and ketones in order to optimize the cleavage conditions. Thus, different aromatic aldehydes and ketones **6** were attached to the free dithiol unit furnishing the corresponding dithianes **7** under Lewis acidic conditions.[25,26]

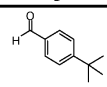
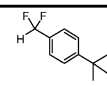
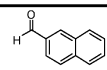
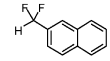
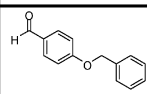
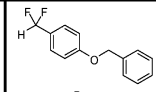
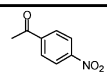
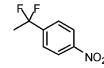
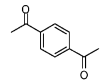
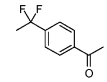
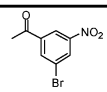
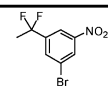
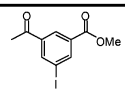
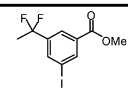
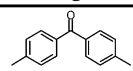
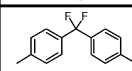
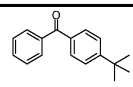
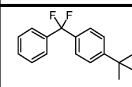
For the cleavage under fluorinating conditions the resins were treated with a combination of *N*-iodosuccinimide (NIS) as oxidizing agent and HF/pyridine complex (70%) as fluoride source giving the *gem*-difluoro compounds **8** in yields of up to 89% over 3 steps, based upon the loading of resin **4** (Table 1). We also tested different cleavage procedures using DeoxoFluor (BAST) or a SelectFluor/HF combination as fluorinating agents, both well-known for the transformation of C−S into C−F bonds,[29] but the desired fluorinated compounds were not obtained (Table 1, entries 1 and 8, conditions B). In general, NIS was more suitable than *N*-bromosuccinimide (NBS) or 1,3-dibromo-5,5-dimethylhydantoin (DBH). When NIS was exchanged for these bromonium reagents, additional bromination, especially of electron-rich aromatic substrates, was observed as a side reaction (entries 2 and 9, conditions B). Notable was the purity of the crude products (>90%), which was quantified using ^{1}H NMR spectroscopy. Exposure to water should be avoided during the cleavage reaction to suppress the formation of the carbonyl compounds (entry 6). Besides traces of the corresponding carbonyl compound derived from hydrolysis, only small amounts of succinimide could be detected as impurities. The crude products were, if necessary, easily purified by column chromatography or by flash filtration.

The average overall yield for these transformations is between 40% and 50% over three steps. It should be noted that the conversion of dithianes into difluoro compounds is seldom quantitative: An analysis of roughly 200 reactions in the literature revealed an average yield of around 65% over one step (according to SciFinder). It should also be noted that there are not many examples for the conversion of methyl ketones into difluoroethyl groups[27] or aromatic aldehydes into difluoromethylarenes.[28]

To investigate the scope of the novel linker system several compounds were modified in different reactions on the solid support and subsequently cleaved from the resin under fluorinating conditions.

Table 1. Attachment of Various Aldehydes and Ketones and Cleavage to give *gem*-Difluoro Compounds



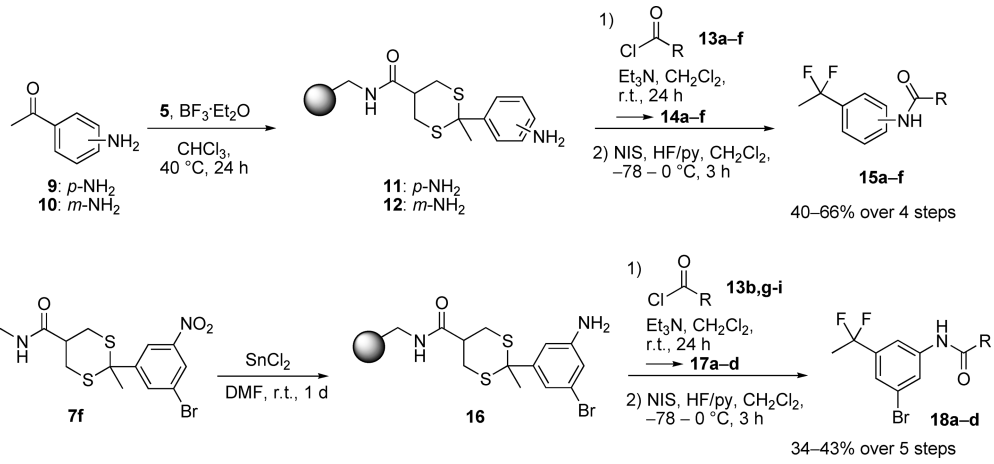
Entry	Carbonyl compound	Resin	Cleavage conditions	Product	Yield (%)[a]
1	 **6a**	**7a**	A: NIS, HF/py B: BAST, EtOH	 **8a**	29 (A) traces (B)
2	 **6b**	**7b**	A: NIS, HF/py B: NBS, HF/py	 **8b**	60 (A) 58 (B)[b]
3	 **6c**	**7c**	NIS, HF/py	 **8c**	32
4	 **6d**	**7d**	NIS, HF/py	 **8d**	89
5	 **6e**	**7e**	NIS, HF/py	 **8e**	27
6	 **6f**	**7f**	NIS, HF/py	 **8f**	39[c]
7	 **6g**	**7g**	NIS, HF/py	 **8g**	81
8	 **6h**	**7h**	A: NIS, HF/py B: SelectFluor/HF	 **8h**	30 (A) 0 (B)
9	 **6i**	**7i**	A: NIS, HF/py B: DBH, HF/py	 **8i**	60 (A) 63 (B)[b]

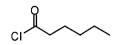
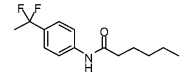
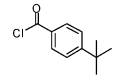
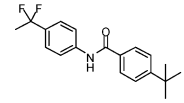
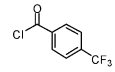
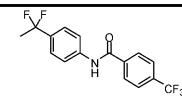
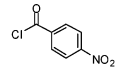
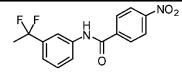
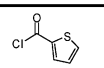
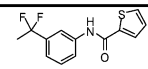
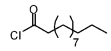
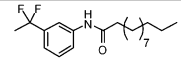
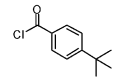
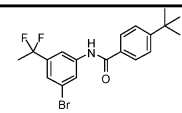
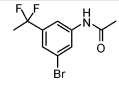
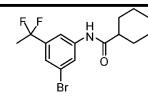
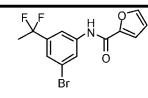
[a] Yield of isolated product over 3 steps. [b] Mixture of desired product and brominated byproduct which could not be separated. [c] About 25% of the corresponding carbonyl compound was isolated as byproduct when an older batch of dichloromethane was used.

First various amides were synthesized using two slightly different methods on bead, as the amide bond is one of the most common units in a large number of potential drug structures. Thus, *p*-aminoacetophenone (**9**) and *m*-aminoacetophenone (**10**) were attached to the resin **5** and reacted with different acid chlorides **13a**−**f** yielding the corresponding amides **14a**−**f**. The successful course of the on-bead reactions was monitored qualitatively via gel-phase ^{13}C NMR spectroscopy. The *gem*-difluorinated amides **15a**−**f** were obtained in good yields of 40−66% over 4 steps after cleavage from the resin (Table 2). A slightly different procedure was chosen to obtain amides **18a**−**d**. The nitro group of resin **7f** was reduced using $SnCl_2$ in DMF and subsequently transformed into amides **17a**−**d**. The resin **16** bears a second functionality, namely, the bromo substituent, making it a potentially very interesting structure for the synthesis of more diverse compound libraries (see part 2 of this series). After cleavage, the corresponding *gem*-difluoro amides **18a**−**d** were obtained in 34−43% over 5 steps. It is notable that electron-rich, as well as electron-deficient, amides and even heterocycles, such as furan and thiophene, were not affected by the cleavage conditions. The crude products showed in both cases a high purity of >80% (^1H NMR).

Furthermore, different palladium-catalyzed cross-coupling reactions for the formation of C−C-bonds could be performed on the dithiane linker system[30] (Table 3). Suzuki couplings were demonstrated on resin-bound iodoarenes

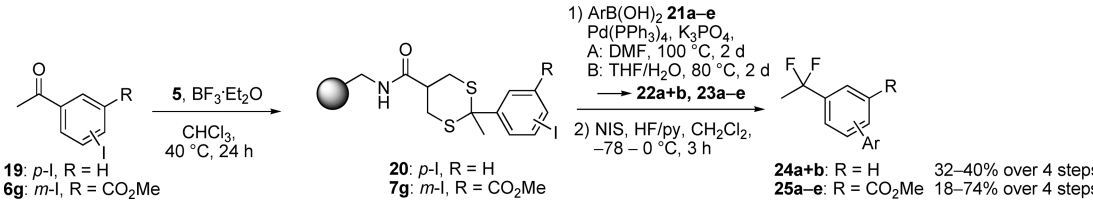
Table 2. Amide Coupling with Immobilized Amines and Subsequent Fluorinating Cleavage

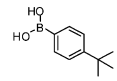
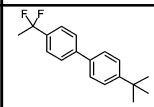
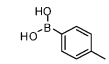
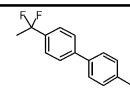
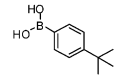
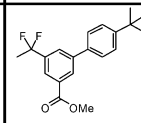
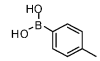
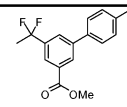
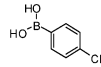
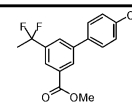
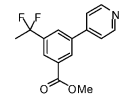
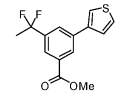


Entry	Resin	Acid chloride	Intermediate resin	Amide	Yield [%][a]
1	**11**	 **13a**	**14a**	 **15a**	40[b]
2	**11**	 **13b**	**14b**	 **15b**	60[b]
3	**11**	 **13c**	**14c**	 **15c**	58[b]
4	**12**	 **13d**	**14d**	 **15d**	60[b]
5	**12**	 **13e**	**14e**	 **15e**	63[b]
6	**12**	 **13f**	**14f**	 **15f**	66[b]
7	**16**	 **13b**	**17a**	 **18a**	34[c]
8	**16**	 **13g**	**17b**	 **18b**	43[c]
9	**16**	 **13h**	**17c**	 **18c**	41[c]
10	**16**	 **13i**	**17d**	 **18d**	34[c]

[a] Yield of isolated product after purification via flash chromatography. [b] Yield over 4 steps. [c] Yield over 5 steps.

Table 3. Palladium-Catalyzed Suzuki Reactions (Two Procedures, A and B) and Subsequent Cleavage



Entry	Resin	Boronic acid	Procedure	Intermediate resin	Biaryl	Yield (%)[a]
1	**20**	 **21a**	A	**22a**	 **24a**	40
2	**20**	 **21b**	A	**22b**	 **24b**	32
3	**7g**	 **21a**	B	**23a**	 **25a**	74
4	**7g**	 **21b**	B	**23b**	 **25b**	67
5	**7g**	 **21c**	B	**23c**	 **25c**	67
6	**7g**	 **21d**	B	**23d**	 **25d**	18
7	**7g**	 **21e**	B	**23e**	 **25e**	30

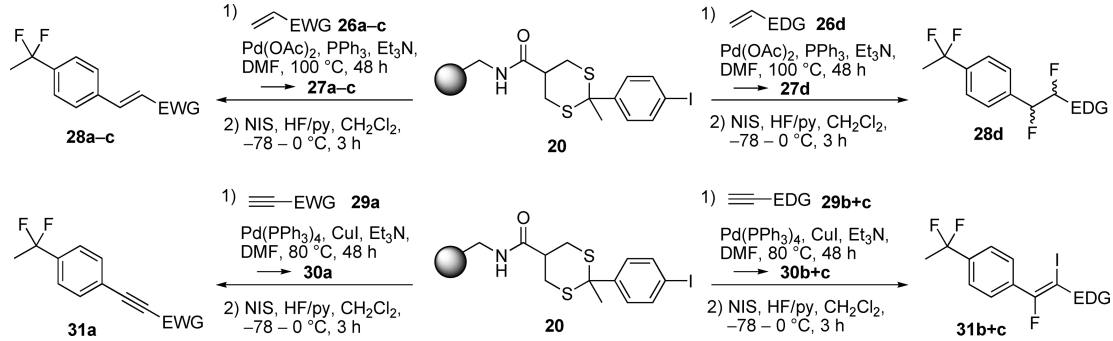
[a] Yield of isolated product after purification via flash chromatography over 4 steps.

starting from 4-iodoacetophenone (**19**) or methyl 3-acetyl-5-iodobenzoate (**6g**) with different aryl boronic acids **21a**−**e**. The investigation of two different reaction conditions showed that the Suzuki couplings proceeded better in a THF/H_2O (6:1) mixture at 80 °C (procedure B) than in DMF at 100 °C (procedure A). Palladium(tetrakistriphenylphosphine) was used in both procedures as the catalyst. While the *gem*-difluorinated biphenyls **24a** and **b** could be obtained in 32−40% yield after cross coupling under conditions A followed by fluorinating cleavage (entries 1 and 2), the superior procedure B yielded the desired biphenyl derivatives **25a**−**c** in good yields of 67−74% over four steps with the same or similar boronic acids (entries 3−5). The heteroaryl boronic acids 4-pyridine (**21d**) and 3-thiophene boronic acid (**21e**) gave lower yields, possibly because of their lower stability[31] or because of their lower solubility, especially in the case of pyridine boronic acid (entry 6).

The aryl iodide resin **20** was also used to explore two additional, important palladium-catalyzed cross-coupling reactions on the dithiane linker to form C−C double and triple bonds: the Heck and the Sonogashira reaction (Table 4).

Cross-coupling reactions on resin **20** were carried out successfully with the terminal olefins **26** or the alkynes **29**, as monitored by NMR analysis of the resulting resins **27** or **30**. However, differences between the substrates were observed during the cleavage procedure. Olefins bearing an electron-withdrawing substituent such as a carbonyl or a carboxylic group (**26a**−**c**) proved to be appropriate substrates. The corresponding *gem*-difluorinated compounds **28a**−**c** were obtained in modest yields of up to 21% over 4 steps. With the more electron-rich olefin **26d**, an additional vicinal difluorination of the double bond was observed during cleavage from the resin. Most likely, the electron-rich double

Table 4. Palladium-Catalyzed Heck and Sonogashira Reactions and Subsequent Cleavage



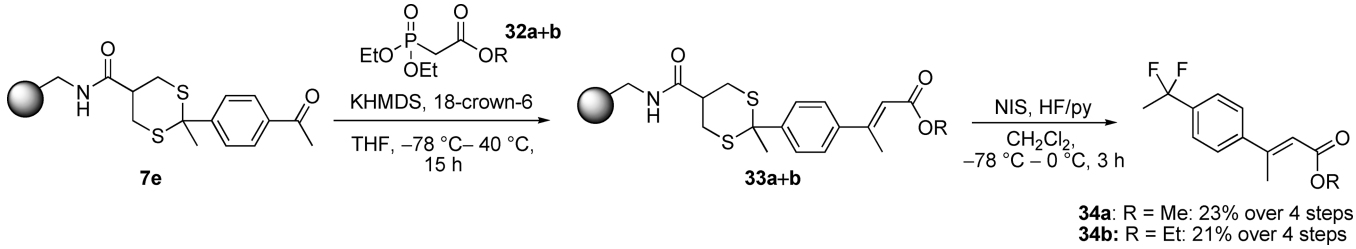
Entry	Resin	Olefin/Alkyne	Intermediate resin	Product	Yield (%)[a]
1	**20**	**26a**	**27a**	**28a**	21
2	**20**	**26b**	**27b**	**28b**	15
3	**20**	**26c**	**27c**	**28c**	18
4	**20**	**26d**	**27d**	**28d**	20 (1.1:1)[b]
5	**20**	**29a**	**30a**	**31a**	7
6	**20**	**29b**	**30b**	**31b**	13
7	**20**	**29c**	**30c**	**31c**	12

[a] Yield of isolated product after purification via flash chromatography over 4 steps. [b] Mixture of diastereomers, calculated from ^{1}H and ^{19}F NMR. Ratio in parentheses.

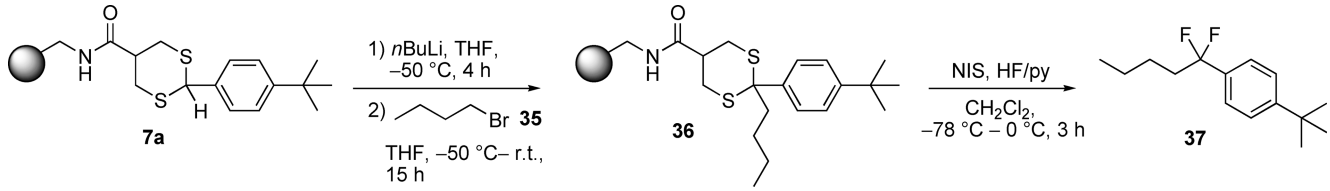
bond is initially iodofluorinated under the cleavage conditions. Then in a second step the iodide exchanges quantitatively with fluoride since no iodofluorinated byproduct could be detected in the crude product analyzed by ^{1}H NMR spectroscopy and GC mass spectrometry. A similar tendency was observed in the Sonogashira couplings, followed by fluorinating cleavage: While the triple bond of the electron-deficient alkyne resin **30a** gave compound **31a** (albeit in low yield), the electron-rich solid supported alkynes **30b** and **c** underwent an additional iodofluorination reaction to give selectively, but also in low yields, the (*E*)-1-fluoro-2-iodoolefins **31b** and **c** after the cleavage step.

These results are consistent with previous reports about the reactivity of double and triple bonds in the presence of halogen cations and fluoride sources.[32] Generally, the crude products of the cross-coupling reactions showed a lower purity than those of the amides **15** and **18** after cleavage because of contamination by palladium catalyst, but purification was easily accomplished by flash filtration.

Scheme 2. HWE Reaction, followed by Fluorinating Cleavage



Scheme 3. Umpolung Reaction, followed by Fluorinating Cleavage



Apart from the cross coupling reactions, we also tested the linker system in Wittig and Horner−Wadsworth−Emmons (HWE) reactions, which are both valuable transformations for the generation of C−C double bonds. Whereas the reaction of resin-bound diacetyl benzene **7e** with Wittig salts did not provide satisfying results, the desired *gem*-difluorinated compounds could be obtained in moderate yields after HWE reaction and subsequent cleavage from the solid support. For this purpose, resin **7e** was reacted with diethyl phosphonates **32a** and **b** using KHMDS and 18-crown-6 in THF (Scheme 2). The resulting double bond was stable under the cleavage conditions (because of the electron-withdrawing carboxyl substituent) to give compounds **34a** and **b** in reasonable yields of 23% and 21% over four steps, respectively.

Finally, because dithianes are well established for the Umpolung[33] reaction of the carbonylic C-atom, this reaction was also successfully investigated on the linker system.[14] Such transformations on the solid support are quite difficult to achieve and are only reported in a few examples.[34] In our case, the desired product **37** was isolated in a modest yield of 16% over four steps (Scheme 3). We are currently investigating whether the Umpolung and olefination reactions can be improved by masking the amide N−H present in the linker.

Conclusion

In summary, a novel linker system for solid-phase synthesis has been developed that enables for the first time the introduction of fluorine substituents into target structures during the cleavage step. This dithiane linker proved to be compatible with various important synthetic transformations in organic chemistry including amide bond formation, reductions, Suzuki, Heck, and Sonogashira C−C coupling reactions, HWE reactions, and Umpolung chemistry. Hence the methodology possesses a high potential for a combinatorial application in industrial drug research and development programs (see part 2 of this series).[35] We are currently working on the extension of our strategy to other linker systems.

Experimental Section

Instrumentation and Reagents. ^{1}H 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 chloroform (7.26 ppm) or acetone (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 doublets, dt = doublet of triplets, 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 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 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 pow-

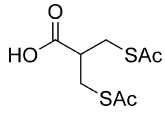
dered. Solvents, reagents, and chemicals were purchased from Aldrich, Fluka, and Acros. Tetrahydrofuran and diethyl ether were distilled from sodium/benzophenone under argon prior to use. Dichloromethane, cyclohexane, and ethyl acetate were distilled from calcium hydride. Dry dichloromethane under argon over molecular sieve for the cleavage reactions was purchased from Acros. 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). As 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) DMF/methanol/water/DMF/methanol/DMF, (2) methanol/dichloromethane/methanol/dichloromethane/methanol, and (3) dichloromethane/pentane/dichloromethane/pentane/dichloromethane. Finally, the resins were washed three times with dichloromethane and dried for 24 h under high vacuum.

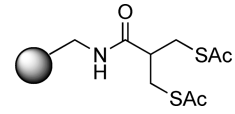
Method 3 (GP1c). The resins were washed with the following solvents (1 mL per 100 mg resin): (1) THF/water/methanol/THF/water/methanol and (2) dichloromethane/methanol/dichloromethane/methanol/dichloromethane/methanol. Finally, the resins were washed three times with dichloromethane and dried for 24 h under high vacuum.

Synthesis of the Dithiol Linker 5. 3-(Acetylthio)-2-(acetylthiomethyl)propanoic Acid (2).



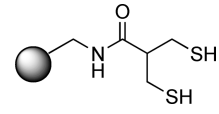
A solution of 5.50 g (52.0 mmol, 1.73 equiv) of Na_2CO_3 in 20 mL of water was added in small portions to a suspension of 4.95 g (30.0 mmol, 1.00 equiv) of 2-(bromomethyl)acrylic acid (**1**) in 100 mL water at 0 °C. Then 2.33 g (30.5 mmol, 1.02 equiv) of thioacetic acid was added slowly, and the mixture 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 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 to remove 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 (4).



Five grams (10.3 mmol, 1.00 equiv) of aminomethyl polystyrene resin (**3**, 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 **2** 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 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 following GP1a, and dried under high vacuum to give 6.96 g of white resin **4**. The yield and the loading of **4** 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 (*C*OCH), 171.5 (NH*C*O), 195.7 (S*C*OCH_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.

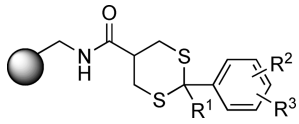
3-Mercapto-2-(mercaptomethyl)-*N*-methylpolystyrylpropanamide (5).



To 1.00 g (1.23 mmol, 1.00 equiv) of resin **4** in 20 mL of chloroform was added 10.0 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 **5** was obtained (quantitative yield, loading 1.40 mmol/g). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.1 (CH_2SH), 54.7 (*C*OCH), 171.7 (NH*C*O) 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.

General Procedure for the Attachment of Aldehydes and Ketones to the Dithiol Linker 5 (GP2).



In a vial, 1.00 equiv of resin **5** (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 the mixture was cooled to 0 °C, 5.00 equiv of the carbonyl compound dissolved in 5 mL of chloroform and 5.00 equiv of $BF_3 \cdot Et_2O$ were added; the vial was sealed, and the mixture was shaken for 24 h at 40 °C. Finally, the resin was washed following GP1a and dried under high vacuum. ^{13}C NMR gel-phase spectra were measured for qualitative reaction control.

7a (R^1 = H, R^2 = 4-*t*Bu, R^3 = H). The reaction of 300 mg (0.420 mmol) of resin **5** with 340 mg (2.10 mmol) of 4-*tert*-butylbenzaldehyde (**6a**) and 0.30 mL (298 mg, 2.10 mmol) of $BF_3 \cdot Et_2O$ gave 335 mg of bright brown resin **7a**. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.7 ($C(CH_3)_3$), 34.5 ($C(CH_3)_3$), 145.4 ($C_{Ar}C(CH_3)_3$) ppm.

7b (R^1 = H, R^2 = 2-naphthyl). The reaction of 210 mg (0.300 mmol) of resin **5** with 235 mg (1.50 mmol) of 2-naphthalenaldehyde (**6b**) and 0.20 mL (212 mg, 1.50 mmol) of $BF_3 \cdot Et_2O$ gave 250 mg of beige resin **7b**. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 50.4 (S*C*HS), 122.8 (C_{Ar}), 126.2 (C_{Ar}), 133.0 (C_{Ar}) ppm.

7c (R^1 = H, R^2 = 4-OBn). The reaction of 210 mg (0.300 mmol) of resin **5** with 318 mg (1.50 mmol) of 4-benzyloxybenzaldehyde (**6c**) and 0.20 mL (212 mg, 1.50 mmol) of $BF_3 \cdot Et_2O$ gave 259 mg of beige resin **7c**. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 50.4 (S*C*HS), 66.2 (CH_2), 120.3 (C_{Ar}) ppm.

7d (R^1 = Me, R^2 = 4-NO_2, R^3 = H). The reaction of 300 mg (0.420 mmol) of resin **5** with 345 mg (2.10 mmol) of 4-nitroacetophenone (**6d**) and 0.30 mL (298 mg, 2.10 mmol) of $BF_3 \cdot Et_2O$ gave 360 mg of yellow resin **7d**. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.9 (CH_3) ppm.

7e (R^1 = Me, R^2 = 4-Ac, R^3 = H). The reaction of 1.00 g (1.40 mmol) of resin **5** with 1.13 g (7.00 mmol) of 1,4-diacetylbenzene (**6e**) and 0.90 mL (990 mg, 7.00 mmol) of $BF_3 \cdot Et_2O$ gave 1.19 g of orange resin **7e**. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.2 (CH_3), 195.5 ($COCH_3$) ppm.

7f (R^1 = Me, R^2 = 3-Br, R^3 = 5-NO_2). The reaction of 400 mg (0.560 mmol) of resin **5** with 683 mg (2.80 mmol) of 3-bromo-5-nitroacetophenone (**6f**) and 0.40 mL (397 mg, 2.80 mmol) of $BF_3 \cdot Et_2O$ gave 528 mg of beige resin **7f**. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.9 (CH_3), 127.7 (C_{Ar}), 136.4 (C_{Ar}), 144.0 (C_{Ar}) ppm.

7g (R^1 = Me, R^2 = 3-I, R^3 = 5-CO_2Me). The reaction of 300 mg (0.420 mmol) of resin **5** with 638 mg (2.10 mmol) of 3-iodo-5-carboxymethylacetophenone (**6g**) and 0.30 mL (298 mg, 2.10 mmol) of $BF_3 \cdot Et_2O$ gave 440 mg of bright brown resin **7g**. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.9 (CH_3), 53.6 (OCH_3), 94.4 ($C_{Ar}I$), 140.7 ($C_{Ar}C_{Ar}I$), 165.3 (*C*OOMe) ppm.

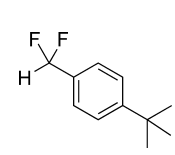
7h (R^1 = *p*-Tol, R^2 = 4-Me, R^3 = H). The reaction of 300 mg (0.420 mmol) of resin **5** with 440 mg (2.10 mmol) of 4,4′-dimethylbenzophenone (**6h**) and 0.30 mL (298 mg, 2.10 mmol) of $BF_3 \cdot Et_2O$ gave 355 mg of bright brown resin **7h**. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.2 ($C_{Ar}CH_3$) ppm.

7i (R^1 = Ph, R^2 = 4-*t*Bu, R^3 = H). The reaction of 300 mg (0.420 mmol) of resin **5** with 500 mg (2.10 mmol) of 4-*tert*-butylbenzophenone (**6i**) and 0.30 mL (298 mg, 2.10 mmol) of $BF_3 \cdot Et_2O$ gave 372 mg of bright brown resin **7i**. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.4 ($C(CH_3)_3$), 34.5 ($C(CH_3)_3$) ppm.

General Procedure for the Fluorinating Cleavage of the Compounds from the Resin (GP3). The cleavage reactions were performed under argon atmosphere in 100 mL Teflon-coated flasks. Four equivalents of *N*-iodosuccinimide were suspended in 10 mL of dry dichloromethane. After cooling to −78 °C, 40.0 equiv. of HF (70% in pyridine) were 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 mixture was stirred for 3 h, while it was warmed up to 0 °C. Twenty milliliters of dichloromethane was added, followed by 10 mL 5% $NaHSO_3$ solution. After the red color had disappeared, pH 10 was adjusted using $NaHCO_3$/NaOH (20:1) 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 washed with diluted HCl solution (pH 2) and 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 given in relation to the stable linker precursor **4** because the determination of the loading by sulfur elemental analysis of **4** is more precise than the calculation by gravimetric measurements after subsequent steps. Therefore the given yields are yields over 3, 4, or 5 steps, respectively.

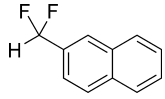
1-*tert*-Butyl-4-(difluoromethyl)benzene (8a).



Following GP3, 335 mg (0.420 mmol) of resin **7a** was reacted with 380 mg (1.68 mmol) of NIS and 0.40 mL (16 mmol) of HF/py. After purification 22.0 mg (0.120 mmol, 29% over 3 steps) of a bright yellow oil was obtained (pentane/diethylether 40:1, R_f = 0.7). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.26 (s, 9 H, $C(CH_3)_3$), 6.55 (t, $^2J_{HF}$ = 56.6 Hz, 1 H, CHF_2), 7.51 (d, ^3J = 8.3 Hz, 2 H, H_{Ar}), 7.74 (d, ^3JB = 8.3 Hz, 2 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.7 ($C(CH_3)_3$), 33.9 ($C(CH_3)_3$), 113.9 (t, $^1J_{CF}$ = 237.9 Hz, CHF_2), 125.4 (C_{Ar}), 125.9 (C_{Ar}), 127.4 (t, $^2J_{CF}$ = 23.1 Hz, $C_{Ar}CF_2$), 153.0 ($C_{Ar}C(CH_3)_3$) ppm. ^{19}F NMR (376 MHz, H-decoupled, $CDCl_3$): δ = −109.8 ppm. MS (EI): *m*/*z* (%):

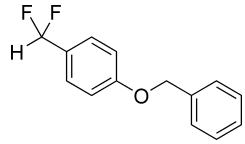
184 (30) [M^+], 169 (100) [$M^+ - CH_3$]. HRMS (+Na) ($C_{11}H_{14}F_2Na$): calcd 207.0961; found 207.0958.

2-(Difluoromethyl)naphthalene (8b).



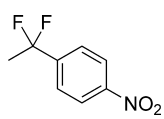
Following GP3, 250 mg (0.300 mmol) of resin **7b** was reacted with 270 mg (1.20 mmol) of NIS and 0.30 mL (12 mmol) of HF/py. After purification, 32.0 mg (0.180 mmol, 60% over 3 steps) of a colorless solid was obtained (cyclohexane/ethyl acetate 10:1, $R_f = 0.7$). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.81$ (t, $^3J = 56.4$ Hz, 1 H, C*H*F$_2$), 7.55−7.61 (m, 3 H, H_{Ar}), 7.88−7.98 (m, 4 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 115.0$ (t, $^1J_{CF} = 238.6$ Hz, *C*HF$_2$), 122.0 (t, $^3J_{CF} = 4.9$ Hz, $C_{Ar}C_{Ar}CHF_2$), 125.9 (t, $^3J_{CF} = 7.4$ Hz, $C_{Ar}C_{Ar}CHF_2$), 126.8 (C_{Ar}), 127.4 (C_{Ar}), 127.9 (C_{Ar}), 128.5 (C_{Ar}), 128.9 (C_{Ar}), 131.6 (t, $^2J_{CF} = 22.6$ Hz, $C_{Ar}CHF_2$), 132.6 (C_{Ar}), 134.3 (C_{Ar}) ppm. ^{19}F NMR (376 MHz, H-decoupled, $CDCl_3$): $\delta = -109.7$ ppm. IR (KBr): $\nu = 3069$ (w), 2924 (m), 2853 (m), 2089 (vw), 1938 (w), 1804 (w), 1718 (w), 1634 (w), 1603 (w), 1510 (m), 1475 (m), 1403 (m), 1377 (m), 1361 (m), 1340 (m), 1275 (w), 1263 (m, $\nu(C_{alkyl}F)$), 1218 (w), 1180 (m), 1128 (m), 1082 (m), 1017 (m), 976 (m), 958 (m), 904 (m), 871 (m), 832 (m), 788 (m), 767 (m), 752 (m), 663 (w), 633 (w), 612 (w), 524 (w), 486 (m) cm^{-1}. MS (EI): *m*/*z* (%): 178 (100) [M^+], 159 (12) [$M^+ - F$], 128 (23) [$C_{10}H_{7P}^+$]. HRMS ($C_{11}H_8F_2$): calcd 178.0594; found 178.0597.

1-(Benzyloxy)-4-(difluoromethyl)benzene (8c).



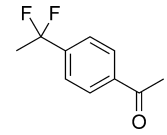
Following GP3, 259 mg (0.300 mmol) of resin **7c** was reacted with 270 mg (1.20 mmol) of NIS and 0.30 mL (12 mmol) of HF/py. After purification, 22.0 mg (0.095 mmol, 32% over 3 steps) of a colorless solid was obtained (cyclohexane/ethyl acetate 30:1, $R_f = 0.6$). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 5.11$ (s, 2 H, CH_2), 6.60 (t, $^3J = 56.7$ Hz, 1 H, C*H*F$_2$), 7.02 (d, ^3JB = 8.6 Hz, 2 H, H_{Ar}), 7.35−7.48 (m, 5 H, H_{Ar}), 7.48 (d, ^3JB = 8.6 Hz, 2 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 70.1$ (*C*H$_2$), 114.9 (C_{Ar}), 115.0 (t, $^1J_{CF} = 238.6$ Hz, *C*HF$_2$), 127.0 (t, $^3J_{CF} = 5.9$ Hz, $C_{Ar}C_{Ar}CHF_2$), 128.1 (C_{Ar}), 128.4 (t, $^2J_{CF} = 24.3$ Hz, $C_{Ar}CHF_2$), 129.0 (C_{Ar}), 129.7 (C_{Ar}), 136.5 (C_{Ar}), 160.5 (C_{Ar}) ppm. ^{19}F NMR (376 MHz, H-decoupled, $CDCl_3$): $\delta = -108.8$ ppm. IR (KBr): $\nu = 3032$ (w), 2926 (w), 1736 (vw), 1690 (w), 1614 (w), 1516 (w), 1453 (w), 1382 (w), 1304 (w), 1249 (m, $\nu(C_{alkyl}F)$), 1175 (w), 1072 (w), 1006 (m), 939 (w), 912 (w), 868 (w), 819 (w), 746 (w), 696 (w), 653 (w) cm^{-1}. MS (EI): *m*/*z* (%): 234 (18) [M^+], 91 (100) [$C_7H_{7P}^+$]. HRMS ($C_{14}H_{12}F_2O$): calcd 234.0856; found 234.0853.

1-(1,1-Difluoroethyl)-4-nitrobenzene (8d).



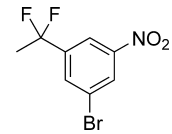
Following GP3, 360 mg (0.420 mmol) of resin **7d** was reacted with 380 mg (1.68 mmol) of NIS and 0.40 mL (16 mmol) of HF/py. After purification, 70.0 mg (0.374 mmol, 89% over 3 steps) of a yellow oil was obtained (pentane/diethylether 10:1, $R_f = 0.5$). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.89$ (t, $^3J_{HF} = 18.2$ Hz, 3 H, CH_3CF$_2$), 7.65 (d, ^3JB = 8.3 Hz, 2 H, H_{Ar}), 8.18 (d, ^3JB = 8.3 Hz, 2 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 24.9$ (t, $^2J_{CF} = 29.2$ Hz, *C*H$_3$CF$_2$), 119.8 (t, $^1J_{CF} = 240.5$ Hz, *C*F$_2$), 125.0 (C_{Ar}), 128.3 (C_{Ar}), 143.2 (t, $^2J_{CF} = 23.5$ Hz, $C_{Ar}CF_2$), 148.0 ($C_{Ar}NO_2$) ppm. ^{19}F NMR (376 MHz, H-coupled, $CDCl_3$): $\delta = -89.9$ (q,$^3J_{HF} = 18.2$ Hz) ppm. MS (EI): *m*/*z* (%): 187 (100) [M^+], 172 (46) [$M^+ - CH_3$], 141 (84) [$M^+ - NO_2$]. HRMS ($C_8H_7F_2NO_2$): calcd 187.0445; found 187.0443.

1-(4-(1,1-Difluoroethyl)phenyl)ethanone (8e).



Following GP3, 175 mg (0.200 mmol) of resin **7e** was reacted with 180 mg (0.800 mmol) of NIS and 0.40 mL (8.0 mmol) of HF/py. After purification, 10.0 mg (0.054 mmol, 27% over 3 steps) of a yellow solid was obtained (cyclohexane/ethyl acetate 10:1, $R_f = 0.3$). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.86$ (t, $^3J_{HF} = 18.2$ Hz, 3 H, CH_3CF$_2$), 2.56 (s, 3 H, CH_3CO), 7.52−7.59 (m, 2 H, H_{Ar}), 7.91−7.97 (m, 2 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 25.9$ (t, $^2J_{CF} = 29.5$ Hz, *C*H$_3$CF$_2$), 26.8 (*C*H$_3$CO), 121.4 (t, $^1J_{CF} = 239.7$ Hz, CH$_3$*C*F$_2$), 125.0 (t, $^3J_{CF} = 6.0$ Hz, $CF_2C_{Ar}C_{Ar}$), 128.5 (C_{Ar}), 138.1 (C_{Ar}CO), 142.5 (t, $^2J_{CF} = 26.8$ Hz, CF_2C_{Ar}), 197.4 (CH$_3$*C*O). IR (KBr): $\nu = 3363$ (w), 2924 (w), 2852 (w), 1741 (w), 1688 (m, ν(CO)), 1612 (w), 1407 (w), 1359 (w), 1305 (w), 1266 (m, $\nu(C_{alkyl}F)$), 1209 (w), 1176 (w), 1114 (w), 1075 (w), 1017 (w), 989 (w), 959 (w), 920 (w), 839 (w), 719 (w), 685 (w), 623 (w), 608 (w), 481 (w) cm^{-1}. MS (EI): *m*/*z* (%): 184 (1) [M^+], 169 (5) [$M^+ - CH_3$], 58 (30), 43 (100) [CH_3CO^+]. HRMS ($C_{10}H_{10}F_2O$): calcd 184.0700; found 184.0697.

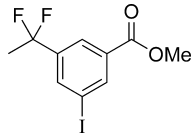
1-Bromo-3-(1,1-difluoroethyl)-5-nitrobenzene (8f).



Following GP3, 528 mg (0.560 mmol) of resin **7f** was reacted with 630 mg (2.80 mmol) of NIS and 0.70 mL (28 mmol) of HF/py. After purification, 58.0 mg (0.218 mmol, 39% over 3 steps) of a colorless solid was obtained (cyclohexane/ethyl acetate 4:1, $R_f = 0.75$). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.98$ (t, $^3J_{HF} = 18.2$ Hz, 3 H, CH_3CF$_2$), 7.98 (m, 1 H, H_{Ar}), 8.31 (m, 1 H, H_{Ar}), 8.44 (m, 1 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 25.8$ (t, $^2J_{CF} = 29.4$ Hz, *C*H$_3$CF$_2$), 118.9 ($^3J_{CF} = 6.0$ Hz, $C_{Ar}C_{Ar}CF_2$), 119.9 (t, $^1J_{CF} = 240.5$ Hz, *C*F$_2$), 123.4 (C_{Ar}), 127.9 (C_{Ar}), 133.9 ($^3J_{CF} = 6.0$ Hz, $C_{Ar}C_{Ar}CF_2$), 141.5 (t, $^2J_{CF} = 28.5$ Hz, $C_{Ar}CF_2$), 148.8 ($C_{Ar}NO_2$) ppm. ^{19}F NMR (376 MHz, H-decoupled, $CDCl_3$): $\delta = -88.3$ ppm. IR (KBr): $\nu = 3089$ (m), 2922

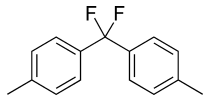
(m), 2851 (m), 1699 (m), 1654 (w), 1605 (w), 1539 (m), 1456 (m), 1420 (m), 1385 (m), 1348 (m), 1285 (m), 1253 (m, ν(CF)), 1182 (m), 1129 (m), 938 (m), 890 (m), 786 (w), 736 (m), 683 (m), 614 (w), 478 (w) cm^{-1}. MS (EI): *m/z* (%): 267/265 (95/98) [M^+], 221/219 (38/40) [M^+-NO_2], 43 (100). HRMS ($C_8H_6BrF_2NO_2$): calcd 264.9550; found 264.9552.

Methyl 3-(1,1-Difluoroethyl)-5-iodobenzoate (8g).



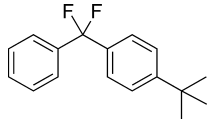
Following GP3, 440 mg (0.420 mmol) of resin **7g** was reacted with 380 mg (1.68 mmol) of NIS and 0.40 mL (16 mmol) of HF/py. After purification, 111 mg (0.340 mmol, 81% over 3 steps) of a bright yellow solid was obtained (cyclohexane/ethyl acetate 10:1, $R_f = 0.6$). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.84$ (t, $^3J_{HF} = 18.2$ Hz, 3 H, CH_3CF_2), 3.85 (s, 3 H, OCH_3), 7.92 (s, 1 H, H_{Ar}), 8.06 (s, 1 H, H_{Ar}), 8.36 (s, 1 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 25.8 (t, $^2J_{CF} = 29.1$ Hz, CH_3CF_2), 52.7 (OCH_3), 93.7 ($C_{Ar}I$), 120.4 (t, $^1J_{CF} = 240.5$ Hz, CF_2), 125.3 (C_{Ar}), 132.2 (C_{Ar}), 137.9 (C_{Ar}), 139.8 (C_{Ar}), 140.4 (t, $^2J_{CF} = 23.5$ Hz, $C_{Ar}CF_2$), 164.9 (*C*O) ppm. ^{19}F NMR (376 MHz, H-decoupled, $CDCl_3$): $\delta = -88.6$ ppm. MS (EI): *m/z* (%): 326 (100) [M^+], 295 (92) [$M^+ - OCH_3$], 267 (18) [$M^+ - CO_2CH_3$]. HRMS ($C_{10}H_9F_2IO_2$): calcd 325.9615; found 325.9613.

Difluorodi-*p*-tolylmethane (8h).



Following GP3, 355 mg (0.420 mmol) of resin **7h** was reacted with 380 mg (1.68 mmol) of NIS and 0.40 mL (16 mmol) of HF/py. After purification, 28.0 mg (0.121 mmol, 30% over 3 steps) of a bright yellow oil was obtained (pentane, $R_f = 0.9$). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.31$ (s, 6 H, CH_3), 7.23 (d, ^3JB = 8.3 Hz, 4 H, H_{Ar}), 7.44 (d, ^3JB = 8.3 Hz, 4 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 21.9 (CH_3), 113.8 (t, $^1J_{CF} = 246.5$ Hz, CF_2), 119.0 (t, $^2J_{CF} = 23.5$ Hz, $C_{Ar}CF_2$), 124.0 (C_{Ar}), 128.8 (C_{Ar}), 138.6 ($C_{Ar}CH_3$) ppm. ^{19}F NMR (376 MHz, H-decoupled, $CDCl_3$): $\delta = -87.5$ ppm. MS (EI): *m/z* (%): 232 (20) [M^+], 217 (100) [$M^+ - CH_3$], 141 (9) [$M^+ - C_6H_4CH_3$], 91 (40) [$C_6H_4CH_{3P}^+$]. HRMS ($C_{15}H_{14}F_2$): calcd 232.1064; found 232.1067.

1-*tert*-Butyl-4-(difluoro(phenyl)methyl)benzene (8i).



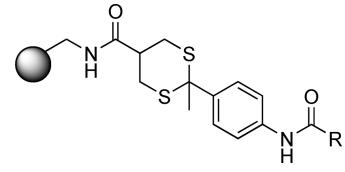
Following GP3, 372 mg (0.420 mmol) of resin **7i** was reacted with 380 mg (1.68 mmol) of NIS and 0.40 mL (16 mmol) of HF/py. After purification, 65.0 mg (0.250 mmol, 60% over 3 steps) of a bright yellow oil was obtained (pentane/diethylether 40:1, $R_f = 0.7$). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.25$ (s, 9 H, $C(CH_3)_3$), 7.28−7.50 (m, 7 H, H_{Ar}), 7.72 (m, 2 H, H_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 29.9 ($C(CH_3)_3$), 33.7 ($C(CH_3)_3$), 119.8 (t, $^1J_{CF} = 241.0$ Hz, CF_2), 124.3 (C_{Ar}), 124.5 (C_{Ar}), 124.8 (C_{Ar}), 127.5 (C_{Ar}), 128.3 (C_{Ar}), 133.8 (t, $^2J_{CF} = 28.5$ Hz, $C_{Ar}CF_2$), 136.8 (t, $^2J_{CF} =$ 28.5 Hz, $C_{Ar}CF_2$), 152.0 ($C_{Ar}C(CH_3)_3$) ppm. ^{19}F NMR (376 MHz, H-decoupled, $CDCl_3$): $\delta = -88.1$ ppm. MS (EI): *m/z* (%): 260 (26) [M^+], 245 (100) [$M^+ - CH_3$], 133 (3) [$C_6H_4C_4H_{9P}^+$], 127 (20) [$M^+ - C_6H_4C_4H_{9P}^+$]. HRMS ($C_{17}H_{18}F_2$): calcd 260.1377; found 260.1378.

General Procedure for the Synthesis of the *gem*-Difluorinated Amides (GP4). The resins were covered with 10 mL dry dichloromethane in a vial and shaken for 30 min. After addition of 5 equiv of acid chloride and 5 equiv of triethylamine, the mixture was shaken at room temperature for 24 h. The resin was filtered off, washed following GP1a, and dried under high vacuum. ^{13}C NMR gel-phase spectra were measured for qualitative reaction control. Finally, the amides were cleaved from the resin following GP3 to give the fluorinated compounds.

Synthesis of Resins 11 and 12 (following GP2). 11 (R^1 = Me, R^2 = 4-NH_2, R^3 = H). The reaction of 1.00 g (1.40 mmol) of resin **5** with 945 mg (7.00 mmol) of 4-aminoacetophenone (**9**) and 0.90 mL (990 mg, 7.00 mmol) of $BF_3 \cdot Et_2O$ gave 1.18 g of bright brown resin. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 30.1$ (CH_3) 118.2 ($C_{Ar}C_{Ar}NH_2$) ppm.

12 (R^1 = Me, R^2 = 3-NH_2, R^3 = H). The reaction of 1.00 g (1.40 mmol) of resin **5** with 945 mg (7.00 mmol) of 3-aminoacetophenone (**10**) and 0.90 mL (990 mg, 7.00 mmol) of $BF_3 \cdot Et_2O$ gave 1.19 g of bright brown resin. The resin was used for the next step without gel-phase spectra measurement.

Resins 14a−c (following GP4).

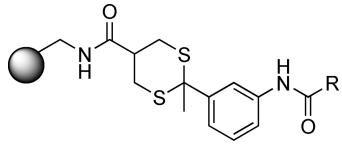


Resin 14a (R= *n*-Pentyl). The reaction of 390 mg (0.460 mmol) of resin **11** with 310 mg (2.30 mmol) hexanoyl chloride (**13a**) gave 429 mg bright orange resin. - ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.1$ (CH_3CH_2), 22.5 (CH_2), 24.6 (CH_2), 25.4 (CH_2), 31.3 (CH_3), 37.6 (CH_2CO), 52.5 (S*C*S), 119.0 ($C_{Ar}C_{Ar}NH$), 172.4 (NH*C*O) ppm.

Resin 14b (R= 4-*t*Bu-C_6H_4). The reaction of 390 mg (0.460 mmol) of resin **11** with 450 mg (2.30 mmol) of 4-*tert*-butylbenzoyl chloride (**13b**) gave 454 mg of bright orange resin. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 31.2$ ($C(CH_3)_3$), 31.7 (CH_3), 35.1 ($C(CH_3)_3$), 52.5 (S*C*S), 120.3 (C_{Ar}), 166.4 (NH*C*O) ppm.

Resin 14c (R = 4-CF_3-C_6H_4). The reaction of 390 mg (0.460 mmol) of resin **11** with 475 mg (2.30 mmol) of 4-trifluoromethylbenzoyl chloride (**13c**) gave 456 mg orange resin. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 31.7$ (CH_3), 52.2 (S*C*S), 122.1 (C_{Ar}), 133.9 (C_{Ar}), 137.6 (C_{Ar}), 171.9 (NH*C*O) ppm.

Resins 14d−f (following GP4).

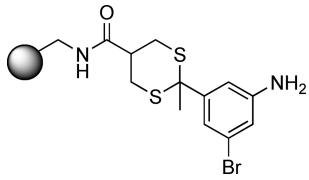


Resin 14d (R = 4-NO_2-C_6H_4). The reaction of 340 mg (0.400 mmol) of resin **12** with 370 mg (2.00 mmol) of 4-nitrobenzoyl chloride (**13d**) gave 406 mg of orange resin. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 32.0 (CH_3), 123.3 (C_{Ar}), 171.4 (NH*C*O) ppm.

Resin 14e (R = 2-Thienyl). The reaction of 340 mg (0.400 mmol) of resin **12** with 290 mg (2.00 mmol) of thiophene-2-carbonyl chloride (**13e**) gave 386 mg of orange resin. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.8 (CH_3), 160.1 (NH*C*O) ppm.

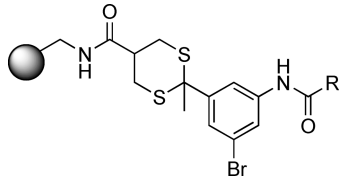
Resin 14f (R = Undecanoyl). The reaction of 340 mg (0.400 mmol) of resin **12** with 436 mg (2.00 mmol) of dodecanoyl chloride (**13f**) gave 421 mg yellow resin. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.3 (CH_3CH_2), 22.8 (CH_2), 24.9 (CH_2), 25.7 (CH_2), 29.2 (CH_2), 29.3 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 29.7 (CH_2), 31.9 (CH_3), 32.0 (CH_2), 37.8 (CO*C*H_2), 52.6 (S*C*S), 119.2 (C_{Ar}), 172.8 (NH*C*O) ppm.

2-Methyl-*N*-methylpolystyryl-2-(3-amino-5-bromophenyl)-1,3-dithiane-5-carboxamide (16).



To 1.50 g (1.59 mmol) of resin **7f** in 20 mL of dry DMF was added 2.99 g (15.9 mmol) $SnCl_2$, 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 1.60 g of yellow resin. The resin was used for the next steps without ^{13}C NMR measurement.

Resins 18a−d (following GP4).



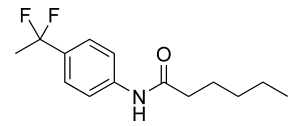
Resin 17a (R = 4/*t*/butyl-C_6H_4). The reaction of 203 mg (0.200 mmol) of resin **16** with 197 mg (1.00 mmol) of 4-*tert*-butylbenzoyl chloride (**13b**) gave 239 mg of orange resin. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.6 (C(*C*H_3)$_3$), 34.7 (*C*(CH$_3$)$_3$), 125.9 (C_{Ar}), 171.2 (NH*C*O) ppm.

Resin 17b (R = CH_3). The reaction of 203 mg (0.200 mmol) of resin **16** with 79.0 mg (1.00 mmol) of acetyl chloride (**13g**) gave 212 mg of orange resin. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.1 (CH_3), 30.6 (CH_3), 170.6 (NH*C*O) ppm.

Resin 17c (R = Cyclohexyl). The reaction of 203 mg (0.200 mmol) of resin **16** with 147 mg (1.00 mmol) of cyclohexylcarboxyl chloride (**13h**) gave 234 mg of orange resin. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.2 (CH_2), 25.6 (CH_2), 25.7 (CH_2), 28.9 (CH_2), 29.7 (CH_2), 32.0 (CH_3), 45.1 (CO*C*H), 174.3 (NH*C*O) ppm.

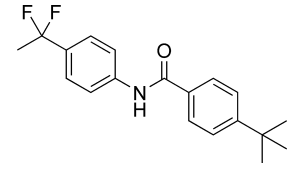
Resin 17d (R = Furan-2-carbonyl). The reaction of 151 mg (0.15 mmol) of resin **16** with 99.0 mg (0.750 mmol) of furan-2-carbonyl chloride (**13i**) gave 167 mg of orange resin. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.0 (CH_3), 112.7 (C_{Ar}), 141.0 (C_{Ar}), 146.2 (C_{Ar}), 157.4 (NH*C*O) ppm.

***N*-(4-(1,1-Difluoroethyl)phenyl)hexylamide (15a).**



Following GP3, 429 mg (0.460 mmol) of resin **14a** was reacted with 410 mg (1.84 mmol) of NIS and 0.45 mL (18 mmol) of HF/py. After purification, 46.0 mg (0.180 mmol, 40% over 4 steps) of a white solid was obtained (cyclohexane/ethyl acetate 5:1, R_f = 0.5). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.89 (t, ^3JB = 6.9 Hz, 3 H, CH_2CH_3), 1.35 (m, 4 H, $CH_2CH_2CH_3$), 1.74 (m, 2 H, $COCH_2CH_2$), 1.91 (t, $^3J_{HF}$ = 18.2 Hz, 3 H, CH_3CF_2), 2.38 (t, ^3JB = 6.9 Hz, 2 H, $COCH_2$), 7.35 (s, 1 H, N*H*), 7.46 (d, ^3JB = 8.3 Hz, 2 H, H_{Ar}), 7.58 (d, ^3JB = 8.3 Hz, 2 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9 (CH_2CH_3), 22.4 (CH_2CH_3), 25.2 ($COCH_2CH_2$), 25.5 (t, $^2J_{CF}$ = 29.2 Hz, CH_3CF_2), 31.4 ($CH_2CH_2CH_3$), 37.8 ($COCH_2$), 119.4 (C_{Ar}), 121.7 (t, $^1J_{CF}$ = 240.5 Hz, CF_2), 125.5 (C_{Ar}), 135.4 (t, $^2J_{CF}$ = 26.9 Hz, $C_{Ar}CF_2$), 139.2 (C_{Ar}NH), 171.6 (*C*O) ppm. ^{19}F NMR (376 MHz, H-decoupled, $CDCl_3$): δ = −86.6 ppm. MS (EI): *m*/*z* (%): 255 (28) [M^+], 157 (100) [$CH_3CF_2C_6H_4NH_2$]. HRMS ($C_{14}H_{19}F_2NO$): calcd 255.1435; found 255.1432.

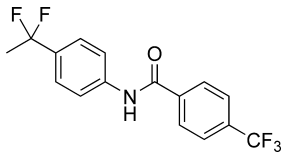
4-*tert*-Butyl-*N*-(4-(1,1-difluoroethyl)phenyl)benzamide (15b).



Following GP3, 454 mg (0.460 mmol) of resin **14b** was reacted with 410 mg (1.84 mmol) of NIS and 0.45 mL (18 mmol) of HF/py. After purification, 89.0 mg (0.280 mmol, 60% over 4 steps) of a bright yellow solid was obtained (cyclohexane/ethyl acetate 5:1, R_f = 0.4). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.25 (s, 9 H, C(CH_3)$_3$), 1.88 (t, $^3J_{HF}$ = 18.2 Hz, 3 H, CH_3CF_2), 7.43 (d, ^3JB = 8.3 Hz, 2 H, H_{Ar}), 7.46 (d, ^3JB = 8.3 Hz, 2 H, H_{Ar}), 7.65 (d, ^3JB = 8.3 Hz, 2 H, H_{Ar}), 7.78 (d, ^3JB = 8.3 Hz, 2 H, H_{Ar}), 8.01 (s, 1 H, N*H*),ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.9 (t, $^2J_{CF}$ = 29.2 Hz, CH_3CF_2), 31.0 (C(CH_3)$_3$), 35.0 (*C*(CH$_3$)$_3$), 119.8 (t, $^1J_{CF}$ = 240.5 Hz, CF_2), 119.8 (C_{Ar}), 125.5 (C_{Ar}), 125.7 (t, $^2J_{CF}$ = 26.9 Hz, $C_{Ar}CF_2$), 126.7 (C_{Ar}), 126.9 (C_{Ar}), 130.5 (C_{Ar}), 131.8 (C_{Ar}NH), 155.4 (C_{Ar}C(CH$_3$)$_3$), 166.5 (*C*O) ppm. ^{19}F NMR (376 MHz, H-decoupled, $CDCl_3$): δ = −86.9 ppm. MS (EI): *m*/*z* (%): 317 (60) [M^+], 161 (100)

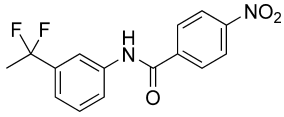
[$COC_6H_4C(CH_3)_{3P}^+$]. HRMS ($C_{19}H_{21}F_2NO$): calcd 317.1591; found 317.1593.

***N*-(4-(1,1-Difluoroethyl)phenyl)-4-(trifluoromethyl)benzamide (15c).**



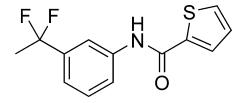
Following GP3, 456 mg (0.460 mmol) of resin **14c** was reacted with 410 mg (1.84 mmol) of NIS and 0.45 mL (18 mmol) of HF/py. After purification 90.0 mg (0.274 mmol, 58% over 4 steps) of a white solid was obtained (cyclohexane/ethyl acetate 5:1, $R_f = 0.5$). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.97$ (t, $^3J_{HF} = 18.2$ Hz, 3 H, CH_3CF$_2$), 7.58 (d, ^3JB = 8.3 Hz, 2 H, H_{Ar}), 7.89 (d, ^3JB = 8.3 Hz, 2 H, H_{Ar}), 7.92 (d, ^3JB = 8.3 Hz, 2 H, H_{Ar}), 8.18 (d, ^3JB = 8.3 Hz, 2 H, H_{Ar}), 10.65 (s, 1 H, N*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.0 (t, $^2J_{CF} = 29.2$ Hz, *C*H$_3$CF$_2$), 120.0 (C_{Ar}), 122.2 (t, $^1J_{CF}$ = 241.2 Hz, *C*F$_2$), 124.6 (q, $^1J_{CF} = 243.2$ Hz, *C*F$_3$), 125.2 (C_{Ar}), 125.9 (C_{Ar}), 128.6 (C_{Ar}), 131.6 (q, $^2J_{CF} = 29.2$ Hz, C_{Ar}CF$_3$), 132.7 (t, $^2J_{CF} = 29.1$ Hz, C_{Ar}CF$_2$), 138.4 (C_{Ar}NH), 140.3 (C_{Ar}CO), 164.6 (*C*O) ppm. ^{19}F NMR (376 MHz, H-decoupled, $CDCl_3$): $\delta = -61.7$ (CF$_3$), -84.2 (CF$_2$) ppm. MS (EI): *m*/*z* (%): 329 (36) [M$^+$], 173 (100) [$COC_6H_4C(CF_3)_3$]. HRMS ($C_{16}H_{12}F_5NO$): calcd 329.0839; found 329.0842.

***N*-(3-(1,1-Difluoroethyl)phenyl)-4-nitrobenzamide (15d).**



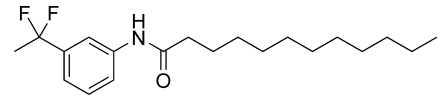
Following GP3, 406 mg (0.400 mmol) of resin **14d** was reacted with 360 mg (1.60 mmol) of NIS and 0.40 mL (16 mmol) of HF/py. After purification, 72.0 mg (0.239 mmol, 60% over 4 steps) of a colorless solid was obtained (cyclohexane/ethyl acetate 4:1, $R_f = 0.4$). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.92$ (t, $^3J_{HF} = 18.2$ Hz, 3 H, CH_3CF$_2$), 7.32 (d, $^3J = 8.0$ Hz, 1 H, H_{Ar}), 7.43 (t, ^3JB = 8.0 Hz, 1 H, H_{Ar}), 7.74 (m, 2 H, H_{Ar}), 8.02 (d, $^3J = 8.8$ Hz, 2 H, H_{Ar}), 8.14 (s, 1 H, N*H*), 8.30 (d, $^3J = 8.8$ Hz, 2 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 25.9$ (t, $^2J_{CF} = 29.2$ Hz, *C*H$_3$CF$_2$), 116.7 (t, $^3J_{CF} = 6.1$ Hz, $C_{Ar}C_{Ar}CF_2$), 121.4 (t, $^1J_{CF}$ = 240.5 Hz, *C*F$_2$), 121.5 (t, $^3J_{CF} = 6.1$ Hz, $C_{Ar}C_{Ar}CF_2$), 121.7 (C_{Ar}), 123.8 (C_{Ar}), 128.3 (C_{Ar}), 129.7 (C_{Ar}), 137.5 (C_{Ar}NH), 139.6 (t, $^2J_{CF} = 26.9$ Hz, C_{Ar}CF$_2$), 140.1 (C_{Ar}), 149.8 (C_{Ar}NO$_2$), 163.9 (*C*O) ppm. ^{19}F NMR (376 MHz, H-decoupled, $CDCl_3$): $\delta = -88.1$ ppm. IR (KBr): ν = 3299 (m), 3077 (w), 2926 (vw), 2859 (vw), 1942 (vw), 1654 (m, ν(CO)), 1602 (m), 1552 (m), 1523 (m), 1491 (m), 1425 (w), 1380 (w), 1346 (m), 1315 (w), 1265 (m, ν(CF)), 1220 (w), 1183 (w), 1105 (w), 1082 (w), 1014 (w), 930 (w), 873 (m), 850 (m), 793 (w), 734 (w), 717 (m), 696 (m), 588 (w), 509 (w), 455 (vw) cm^{-1}. MS (EI): *m*/*z* (%): 306 (59) [M$^+$], 150 (100) [$C_7H_4NO_{3P}^+$]. HRMS ($C_{15}H_{12}N_2F_2O_3$): calcd 306.0816; found 306.0814.

***N*-(3-(1,1-Difluoroethyl)phenyl)thiophene-2-carboxamide (15e).**



Following GP3, 386 mg (0.400 mmol) of resin **14e** was reacted with 360 mg (1.60 mmol) of NIS and 0.40 mL (16 mmol) of HF/py. After purification, 67.0 mg (0.251 mmol, 63% over 4 steps) of a colorless solid was obtained (cyclohexane/ethyl acetate 4:1, $R_f = 0.4$). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.91$ (t, $^3J_{HF} = 18.2$ Hz, 3 H, CH_3CF$_2$), 7.10 (dd, $^3J = 4.9$ Hz, $^3J = 3.7$ Hz, 1 H, H_{Ar}), 7.28 (d, ^3JB = 8.1 Hz, 1 H, H_{Ar}), 7.40 (t, $^3J = 8.0$ Hz, 1 H, H_{Ar}), 7.54 (d, ^3JB = 4.9 Hz, 1 H, H_{Ar}), 7.66 (d, $^3J = 3.7$ Hz, 1 H, H_{Ar}), 7.72 (d, $^3J = 8.1$ Hz, 1 H, H_{Ar}), 7.76 (s, 1 H, H_{Ar}), 8.14 (s, 1 H, N*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 25.9$ (t, $^2J_{CF} = 29.2$ Hz, *C*H$_3$CF$_2$), 116.6 (t, $^3J_{CF}$ = 5.9 Hz, $C_{Ar}C_{Ar}CF_2$), 120.8 (t, $^3J_{CF} = 5.9$ Hz, $C_{Ar}C_{Ar}CF_2$), 121.4 (t, $^1J_{CF} = 240.0$ Hz, *C*F$_2$), 121.6 (C_{Ar}), 127.8 (C_{Ar}), 128.7 (C_{Ar}), 129.4 (C_{Ar}), 131.1 (C_{Ar}), 137.9 (C_{Ar}NH), 138.9 (C_{Ar}CO), 139.2 (t, $^2J_{CF} = 26.9$ Hz, C_{Ar}CF$_2$), 160.1 (*C*O) ppm. ^{19}F NMR (376 MHz, H-decoupled, $CDCl_3$): δ = -87.9 ppm. IR (KBr): ν = 3282 (m), 3091 (w), 3004 (w), 2817 (vw), 1824 (vw), 1639 (m, ν(CO)), 1610 (m), 1541 (m), 1516 (m), 1490 (m), 1432 (m), 1382 (w), 1356 (m), 1312 (m), 1274 (m, ν(CF)), 1251 (w), 1224 (w), 1168 (m), 1101 (w), 1082 (w), 1006 (vw), 946 (w), 925 (m), 904 (w), 877 (m), 841 (m), 792 (m), 727 (m), 700 (m), 666 (w), 625 (w), 605 (w), 573 (w), 509 (w) cm^{-1}. MS (EI): *m*/*z* (%): 267 (38) [M$^+$], 111 (100) [$C_5H_3OS^+$]. HRMS ($C_{13}H_{11}NSF_2O$): calcd 267.0529; found 267.0526.

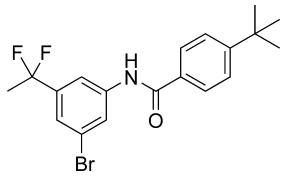
***N*-(3-(1,1-Difluoroethyl)phenyl)dodecanamide (15f).**



Following GP3, 421 mg (0.400 mmol) of resin **14f** was reacted with 360 mg (1.60 mmol) of NIS and 0.40 mL (16 mmol) of HF/py. After purification, 90.0 mg (0.265 mmol, 66% over 4 steps) of a colorless solid was obtained (cyclohexane/ethyl acetate 4:1, $R_f = 0.6$). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.90$ (t, $^3J = 7.5$ Hz, 3 H, CH_3CH$_2$), 1.27 (m, 16 H, CH_2), 1.74 (quin, $^3J = 7.5$ Hz, 2 H, COCH$_2$CH_2), 1.91 (t, $^3J_{HF} = 18.2$ Hz, 3 H, CH_3CF$_2$), 2.38 (t, $^3J = 7.5$ Hz, 2 H, COCH_2), 7.25 (d, $^3J = 7.9$ Hz, 1 H, H_{Ar}), 7.31 (t, ^3JB = 7.9 Hz, 1 H, H_{Ar}), 7.49 (bs, 1 H, N*H*), 7.64 (d, $^3J = 7.9$ Hz, 1 H, H_{Ar}), 7.68 (s, 1 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1 (*C*H$_3$CH$_2$), 22.7 (*C*H$_2$), 25.5 (*C*H$_2$),B 25.9 (t, $^2J_{CF} = 29.2$ Hz, *C*H$_3$CF$_2$), 29.2 (*C*H$_2$), 29.3 (*C*H$_2$), 29.4 (*C*H$_2$), 29.5 (*C*H$_2$), 29.6 (*C*H$_2$), 29.7 (*C*H$_2$), 31.9 (*C*H$_2$), 37.8 (COCH$_2$), 116.0 (t, $^3J_{CF} = 5.9$ Hz, $C_{Ar}C_{Ar}CF_2$), 120.3 (t, $^3J_{CF}$ = 5.9 Hz, $C_{Ar}C_{Ar}CF_2$), 121.0 (C_{Ar}), 121.6 (t, $^1J_{CF} = 240.0$ Hz, *C*F$_2$), 129.2 (C_{Ar}), 138.2 (C_{Ar}NH), 139.0 (t, $^2J_{CF} = 26.9$ Hz, C_{Ar}CF$_2$), 171.7 (*C*O) ppm. ^{19}F NMR (376 MHz, H-decoupled, $CDCl_3$): $\delta = -87.7$ ppm. IR (KBr): ν = 3299 (m), 3162 (w), 3086 (w), 2916 (m), 2850 (m), 1956 (vw), 1774 (vw), 1658 (m, ν(CO)), 1600 (m), 1548 (m), 1450 (m),

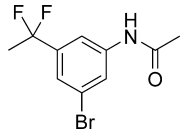
1382 (w), 1308 (m), 1277 (m, ν(CF)), 1248 (w), 1229 (w), 1205 (w), 1174 (m), 1082 (w), 1002 (w), 965 (w), 927 (m), 894 (m), 879 (w), 841 (m), 797 (m), 753 (w), 703 (m), 634 (w), 595 (w), 558 (w), 512 (w), 410 (vw) cm^{-1}. MS (EI): *m/z* (%): 339 (12) [M^+], 199 (20) [$C_{10}H_{11}F_2NO^+$], 157 (100) [$C_8H_9F_2N^+$]. HRMS ($C_{20}H_{31}NF_2O$): calcd 339.2374; found 339.2372.

***N*-(3-Bromo-5-(1,1-difluoroethyl)phenyl)-4-*tert*-butylbenzamide (18a).**



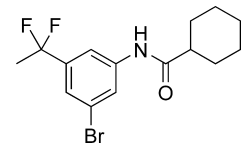
Following GP3, 239 mg (0.200 mmol) of resin **17a** was reacted with 180 mg (0.800 mmol) of NIS and 0.20 mL (8.0 mmol) of HF/py. After purification, 26.0 mg (0.067 mmol, 34% over 5 steps) of a colorless solid was obtained (cyclohexane/ethyl acetate 10:1, $R_f = 0.6$). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.35$ (s, 9 H, C(CH_3)$_3$), 1.90 (t, $^3J_{HF} =$ 18.2 Hz, 3 H, CH_3CF_2), 7.40 (s, 1 H, H_{Ar}), 7.49 (d, ^3JB = 8.4 Hz, 2 H, H_{Ar}), 7.68 (s, 1 H, H_{Ar}), 7.79 (d, $^3J = 8.4$ Hz, 2 H, H_{Ar}), 8.02 (m, 2 H, H_{Ar}+N*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 25.8$ (t, $^2J_{CF} = 29.2$ Hz, CH_3CF_2), 31.0 (C(CH_3)$_3$), 35.0 (C(CH_3)$_3$), 115.0 (t, $^3J_{CF} = 6.1$ Hz, C_{Ar}-$C_{Ar}CF_2$), 120.8 (t, $^1J_{CF} = 240.5$ Hz, CF_2), 122.9 (C_{Ar}), 123.6 (t, $^3J_{CF} = 6.1$ Hz, $C_{Ar}C_{Ar}CF_2$), 124.1 (C_{Ar}), 125.9 (C_{Ar}), 126.9 (C_{Ar}), 131.2 (C_{Ar}), 139.5 (C_{Ar}NH), 140.6 (t, $^2J_{CF} = 26.9$ Hz, $C_{Ar}CF_2$), 156.1 (C_{Ar}), 165.7 (*C*O) ppm. ^{19}F NMR (376 MHz, H-decoupled, $CDCl_3$): $\delta = -88.4$ ppm. - IR (KBr): $\nu =$ 3325 (m), 3090 (m), 2965 (m), 2870 (m), 1923 (w), 1773 (m), 1653 (s, ν(CO)), 1609 (m), 1589 (m), 1540 (m), 1511 (m), 1451 (m), 1420 (m), 1381 (m), 1364 (m), 1321 (m), 1281 (m), 1247 (m, ν(CF)), 1219 (m), 1177 (m), 1145 (m), 1127 (m), 1018 (m), 997 (m), 928 (m), 903 (m), 857 (m), 831 (m), 778 (m), 767 (m), 734 (m), 691 (m), 634 (m), 596 (m), 578 (m), 540 (m), 485 (w), 407 (w) cm^{-1}. MS (EI): *m/z* (%): 397/395 (30/28) [M^+], 161 (100) [$C_{11}H_{13}O^+$]. HRMS ($C_{19}H_{20}BrF_2NO$): calcd 395.0696; found 395.0698.

***N*-(3-Bromo-5-(1,1-difluoroethyl)phenyl)acetamide (18b).**



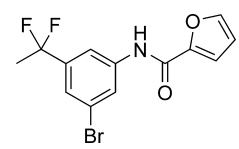
Following GP03, 212 mg (0.200 mmol) of resin **17b** was reacted with 180 mg (0.800 mmol) of NIS and 0.20 mL (8.0 mmol) of HF/py. After purification, 24.0 mg (0.086 mmol, 43% over 5 steps) of a colorless solid was obtained (cyclohexane/ethyl acetate 10:1, $R_f = 0.4$). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.96$ (t, $^3J_{HF} = 18.2$ Hz, 3 H, CH_3CF_2), 2.26 (s, 3 H, CH_3CO), 7.40 (s, 1 H, H_{Ar}), 7.52 (s, 1 H, H_{Ar}), 7.56 (s, 1 H, H_{Ar}), 7.95 (br s, 1 H, N*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 24.6$ (CH_3CO), 25.8 (t, $^2J_{CF} = 29.2$ Hz, CH_3CF_2), 114.6 (t, $^3J_{CF} = 6.0$ Hz, $C_{Ar}C_{Ar}CF_2$), 120.7 (t, $^1J_{CF}$ = 240.6 Hz, CF_2), 122.8 (C_{Ar}), 123.6 (t, $^3J_{CF} = 6.1$ Hz, $C_{Ar}C_{Ar}CF_2$), 123.8 (C_{Ar}), 139.3 (C_{Ar}NH), 140.6 (t, $^2J_{CF} =$ 26.9 Hz, $C_{Ar}CF_2$), 168.5 (*C*O) ppm. ^{19}F NMR (376 MHz, H-decoupled, $CDCl_3$): $\delta = -88.3$ ppm. IR (KBr): $\nu = 3310$ (m), 3195 (m), 3120 (m), 3005 (m), 2932 (w), 2216 (w), 1804 (w), 1669 (m, ν(CO)), 1609 (m), 1590 (m), 1552 (m), 1451 (m), 1416 (m), 1369 (m), 1322 (m), 1293 (m), 1246 (m, ν(CF)), 1212 (m), 1173 (m), 1149 (m), 1078 (m), 1021 (m), 997 (m), 984 (w), 933 (m), 893 (m), 861 (m), 814 (w), 777 (m), 693 (m), 637 (w), 608 (w), 595 (w), 540 (w), 487 (w), 408 (vw) cm^{-1}. MS (EI): *m/z* (%): 279/277 (30/32) [M^+], 237/235 (100) [$C_8H_8BrF_2N^+$]. HRMS ($C_{10}H_{10}$-BrF_2NO): calcd 276.9914; found 276.9912.

***N*-(3-Bromo-5-(1,1-difluoroethyl)phenyl)cyclohexanecarboxamide (18c).**



Following GP3, 234 mg (0.200 mmol) of resin **17c** was reacted with 180 mg (0.800 mmol) of NIS and 0.20 mL (8.0 mmol) of HF/py. After purification, 28.0 mg (0.081 mmol, 41% over 5 steps) of a colorless solid was obtained (cyclohexane/ethyl acetate 10:1, $R_f = 0.3$). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.18-1.99$ (m, 10 H, CH_2) 1.92 (t, $^3J_{HF} = 18.2$ Hz, 3 H, CH_3CF_2), 2.10−2.20 (m, 1 H, C*H*CO), 7.28 (s, 1 H, H_{Ar}), 7.51 (s, 1 H, H_{Ar}), 7.82 (s, 1 H, H_{Ar}), 8.50 (br s, 1 H, N*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 25.1$ (CH_2), 25.6 (CH_2), 25.9 (t, $^2J_{CF} = 29.4$ Hz, CH_3CF_2), 25.6 (CH_2CHCO), 40.8 (*C*HCO), 114.6 (t, $^3J_{CF} = 6.0$ Hz, $C_{Ar}C_{Ar}CF_2$), 120.8 (t, $^1J_{CF} = 240.4$ Hz, CF_2), 122.8 (C_{Ar}), 123.3 (t, $^3J_{CF} = 6.1$ Hz, $C_{Ar}C_{Ar}CF_2$), 123.7 (C_{Ar}), 139.5 (C_{Ar}NH), 140.5 (t, $^2J_{CF} = 26.9$ Hz, $C_{Ar}CF_2$), 174.6 (*C*O) ppm. ^{19}F NMR (376 MHz, H-decoupled, $CDCl_3$): $\delta = -88.2$ ppm. IR (KBr): $\nu = 3452$ (m), 3324 (m), 3114 (w), 3005 (w), 2931 (m), 2855 (w), 2672 (vw), 1794 (m), 1664 (m, ν(CO)), 1610 (m), 1582 (m), 1545 (m), 1449 (m), 1384 (w), 1318 (m), 1220 (w, ν(CF)), 1178 (w), 1114 (w), 1090 (w), 1072 (w), 1029 (w), 1002 (w), 967 (w), 933 (w), 907 (w), 783 (w), 860 (w), 838 (w), 781 (w), 759 (w), 737 (w), 692 (w), 631 (w), 584 (vw), 565 (vw), 511 (vw), 482 (vw), 438 (vw), 428 (vw), 408 (vw) cm^{-1}. MS (EI): *m/z* (%): 347/345 (12/12) [M^+], 237/235 (100) [$C_8H_8BrF_2N^+$], 111 (56) [$C_7H_{11}O^+$], 83 (100) [$C_6H_{11P}{}^+$]. HRMS ($C_{15}H_{18}BrF_2NO$): calcd 345.0540; found 345.0538.

***N*-(3-Bromo-5-(1,1-difluoroethyl)phenyl)furan-2-carboxamide (18d).**



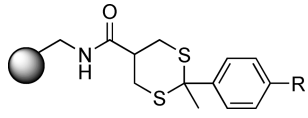
Following GP3, 167 mg (0.150 mmol) of resin **17d** was reacted with 135 mg (0.600 mmol) of NIS and 0.15 mL (6.0 mmol) of HF/py. After purification, 17.0 mg (0.051 mmol, 34% over 5 steps) of a colorless solid was obtained (cyclohexane/ethyl acetate 3:1, $R_f = 0.5$). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.94$ (t, $^3J_{HF} = 18.2$ Hz, 3 H, CH_3CF_2), 6.60 (dd, $^3J = 3.6$ Hz, $^3J = 1.7$ Hz, 1 H, H_{Ar}), 7.27 (dd, $^3J = 3.6$

Hz, ^3J = 0.8 Hz, 1 H, H_{Ar}), 7.40 (s, 1 H, H_{Ar}), 7.42 (dd, ^3J = 1.7 Hz, ^3J = 0.8 Hz, 1 H, H_{Ar}), 7.52 (m, 2 H, H_{Ar} + N*H*), 7.67 (s, 1 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.9 (t, $^2J_{CF}$ = 29.2 Hz, *C*H_3CF_2), 112.6 (C_{Ar}), 119.4 (C_{Ar}), 120.4 (t, $^1J_{CF}$ = 240.6 Hz, *C*F_2), 120.7 (t, $^3J_{CF}$ = 6.0 Hz, $C_{Ar}C_{Ar}CF_2$), 121.4 (C_{Ar}), 122.7 (C_{Ar}), 127.8 (t, $^3J_{CF}$ = 6.0 Hz, $C_{Ar}C_{Ar}CF_2$), 129.5 (C_{Ar}), 140.8 (t, $^2J_{CF}$ = 27.2 Hz, $C_{Ar}CF_2$), 144.9 (C_{Ar}NH), 146.1 (C_{Ar}CO), 156.8 (*C*O) ppm. ^{19}F NMR (376 MHz, H-decoupled, $CDCl_3$): δ = −88.3 ppm. IR (KBr): ν = 3330 (vw), 2963 (w), 2123 (m), 2090 (m), 1780 (w), 1705 (m ν(CO)), 1583 (m), 1538 (w), 1508 (m), 1450 (m), 1391 (w), 1364 (w), 1284 (m, ν(CF)), 1166 (w), 1038 (w), 1011 (w), 918 (w), 884 (w), 865 (w), 831 (w), 764 (w), 692 (w), 593 (vw), 547 (vw) 1804 (w), 1669 (m, ν(CO)), 1609 (m), 1590 (m), 1552 (m), 1451 (m), 1416 (m), 1369 (m), 1322 (m), 1293 (m), 1246 (m, ν(CF)), 1212 (m), 1173 (m), 1149 (m), 1078 (m), 1021 (m), 997 (m), 984 (w), 933 (m), 893 (m), 861 (m), 814 (w), 777 (m), 693 (m), 637 (w), 608 (w), 595 (w), 540 (w), 487 (w), 408 (vw) cm^{-1}. MS (EI): *m*/*z* (%): 331/329 (1/1) [M^+], 175 (36), 132 (100). HRMS ($C_{13}H_{10}BrF_2NO_2$): calcd 328.9863; found 328.9865.

Cross Coupling Reactions. Synthesis of Resins 20 and 7g. 20 (R^1 = Me, R^2 = 4-I, R^3 = H). The reaction of 1.00 g (1.40 mmol) of resin **5** with 1.72 g (7.00 mmol) of 4-iodoacetophenone (**19**) and 0.90 mL (990 mg, 7.00 mmol) of $BF_3 \cdot Et_2O$, following GP2 gave 1.24 g bright brown resin **20**. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.1 (*C*H_3), 92.4 (C_{Ar}I), 137.9 ($C_{Ar}C_{Ar}$I) ppm.

7g. The synthesis of compound **7g** was described above.

General Procedure for the Synthesis of the *gem*-Difluorinated Biphenyls (GP5). Suzuki Coupling: Procedure A (GP5a).

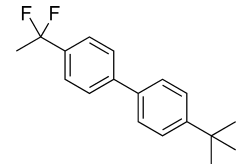


In a vial, 1.00 equiv of resin **20** was covered with 6 mL of dry DMF under argon and shaken for 30 min. After addition of 5.00 equiv of boronic acid **21**, 5.00 equiv of K_3O_4 (dissolved in 1 mL of water), and 0.100 equiv of $Pd(PPh_3)_4$, the vial was sealed and shaken at 100 °C for 48 h. The resin was filtered off, washed following GP1b, and dried under high vacuum. ^{13}C NMR gel-phase spectra were measured for qualitative reaction control. Finally, the biphenyls were cleaved from the resin following GP3 to give the fluorinated compounds.

Resin 22a (R = 4-*t*Bu-C_6H_4). The reaction of 360 mg (0.400 mmol) of resin **20** with 356 mg (2.00 mmol) of 4-*tert*-butyl-phenylboronic acid (**21a**) gave 422 mg brown resin. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.9 (*C*H_3), 31.6 (C(*C*H_3)$_3$), 34.7 (*C*(CH$_3$)$_3$) ppm.

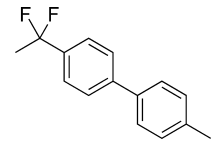
Resin 22b (R = 4-toluoyl). The reaction of 360 mg (0.400 mmol) of resin **20** with 272 mg (2.00 mmol) of 4-methylphenylboronic acid (**21b**) gave 404 mg brown resin. - ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.3 (C_{Ar}*C*H_3), 31.6 (*C*H_3) ppm.

4-*tert*-Butyl-4′-(1,1-difluoroethyl)biphenyl (24a).



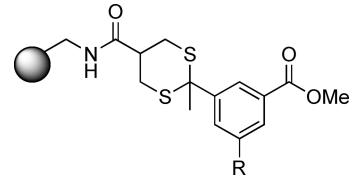
Following GP3, 422 mg (0.400 mmol) of resin **22a** was reacted with 360 mg (1.60 mmol) NIS and 0.40 mL (16 mmol) HF/py. After purification 43.0 mg (0.158 mmol, 40% over 4 steps) of a white solid was obtained (pentane, R_f = 0.8). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.29 (s, 9 H, C(C*H*$_3$)$_3$), 1.90 (t, $^3J_{HF}$ = 18.2 Hz, 3 H, C*H*$_3$CF$_2$), 7.38−7.62 (m, 8 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.9 (t, $^2J_{CF}$ = 29.2 Hz, *C*H$_3$CF$_2$), 30.3 (C(*C*H$_3$)$_3$), 33.6 (*C*(CH$_3$)$_3$), 118.0 (t, $^1J_{CF}$ = 240.0 Hz, *C*F$_2$), 123.8 (C_{Ar}), 124.8 (C_{Ar}), 125.9 (C_{Ar}), 127.4 (C_{Ar}), 130.5 (C_{Ar}), 136.3 (t, $^2J_{CF}$ = 26.9 Hz, $C_{Ar}CF_2$), 141.4 (C_{Ar}), 150.4 (C_{Ar}C(CH$_3$)$_3$) ppm. ^{19}F NMR (376 MHz, H-coupled, $CDCl_3$): δ = −87.2 (q,$^3J_{HF}$ = 18.2 Hz) ppm. MS (EI): *m*/*z* (%): 274 (38) [M^+], 259 (100) [M^+ − CH_3]. HRMS ($C_{18}H_{20}F_2$): calcd 274.1533; found 274.1536.

4-(1,1-Difluoroethyl)-4′-methylbiphenyl (24b).



Following GP3, 404 mg (0.400 mmol) of resin **22b** was reacted with 360 mg (1.60 mmol) of NIS and 0.40 mL (16 mmol) of HF/py. After purification, 30.0 mg (0.129 mmol, 32% over 4 steps) of a colorless solid was obtained (pentane, R_f = 0.8). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.88 (t, $^3J_{HF}$ = 18.2 Hz, 3 H, C*H*$_3$CF$_2$), 2.32 (s, 3 H, C_{Ar}C*H*$_3$), 7.18 (d, ^3JB = 8.1 Hz, 2 H, H_{Ar}), 7.42 (d, ^3JB = 8.1 Hz, 2 H, H_{Ar}), 7.48 (d, ^3JB = 8.3 Hz, 2 H, H_{Ar}), 7.54 (d, ^3JB = 8.3 Hz, 2 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.0 (C_{Ar}*C*H$_3$), 24.8 (t, $^2J_{CF}$ = 29.4 Hz, *C*H$_3$CF$_2$), 120.8 (t, $^1J_{CF}$ = 239.8 Hz, *C*F$_2$), 124.7 (C_{Ar}), 126.0 (C_{Ar}), 126.1 (C_{Ar}), 128.4 (C_{Ar}), 135.7 (t, $^2J_{CF}$ = 26.9 Hz, $C_{Ar}CF_2$), 136.4 (C_{Ar}), 136.5 (C_{Ar}), 141.6 (C_{Ar}CH$_3$) ppm. ^{19}F NMR (376 MHz, H-coupled, $CDCl_3$): δ = −87.2 (q,$^3J_{HF}$ = 18.2 Hz) ppm. MS (EI): *m*/*z* (%): 232 (100) [M^+], 217 (84) [M^+ − CH_3]. HRMS ($C_{15}H_{14}F_2$): calcd 232.1063; found 232.1060.

Suzuki Coupling: Procedure B (GP5b).



In a vial, 1.00 equiv of resin **7g** was covered with 6 mL of dry THF under argon and shaken for 30 min. After addition of 5.00 equiv of boronic acid **21** and 5.00 equiv of K_3O_4 (dissolved in 1 mL water), the mixture was degassed for 5 min, and 0.100 equiv $Pd(PPh_3)_4$ was added; the vial was sealed and shaken at 80 °C for 48 h. The resin was filtered off, washed following GP 1c and dried under high

vacuum. ^{13}C NMR gel-phase spectra were measured for qualitative reaction control. Finally, the biphenyls were cleaved from the resin following GP3 to give the fluorinated compounds.

Resin 23a (R = 4-*t*Bu-C$_6$H$_4$). The reaction of 270 mg (0.250 mmol) of resin **7g** with 223 mg (1.25 mmol) of 4-*tert*-butylphenylboronic acid (**21a**) gave 323 mg of dark red resin. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.2 (CH_3), 31.5 ($C(CH_3)_3$), 34.7 ($C(CH_3)_3$), 52.4 (OCH_3), 126.0 (C_{Ar}), 166.9 (COO) ppm.

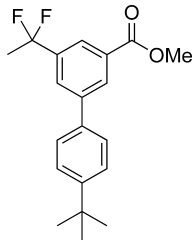
Resin 23b (R = 4-toluoyl). The reaction of 265 mg (0.250 mmol) of resin **7g** with 170 mg (1.25 mmol) of 4-methylphenylboronic acid (**21b**) gave 312 mg of dark red resin. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.2 ($C_{Ar}CH_3$), 31.2 (CH_3), 52.5 (OCH_3), 166.0 (COO) ppm.

Resin 23c (R = 4-Cl-C$_6$H$_4$). The reaction of 210 mg (0.250 mmol) of resin **7g** with 195 mg (1.25 mmol) of 4-chlorophenylboronic acid (**21c**) gave 317 mg of dark red resin. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.1 (CH_3), 52.5 (OCH_3), 166.3 (COO) ppm.

Resin 23d (R = 4-Pyridinyl). The reaction of 265 mg (0.200 mmol) of resin **7g** with 123 mg (1.00 mmol) of 4-pyridinyl boronic acid (**21d**) gave 299 mg of brown resin (1 mL of EtOH and 1 mL of dry DMF were added for better solubility of the boronic acid). The resin was used for the next steps without ^{13}C NMR measurement.

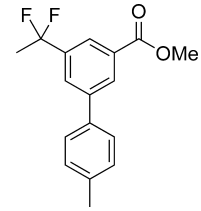
Resin 23e (R = 3-Thienyl). The reaction of 320 mg (0.300 mmol) of resin **7g** with 192 mg (1.50 mmol) of 3-thienyl boronic acid (**21c**) gave 373 mg of brown resin. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.3 (CH_3), 52.4 (OCH_3), 121.5 (C_{Ar}), 142.1 (C_{Ar}), 166.7 (COO) ppm.

Methyl 4′-*tert*-Butyl-5-(1,1-difluoroethyl)biphenyl-3-carboxylate (25a).



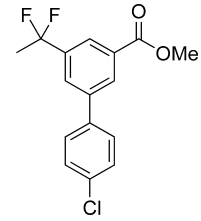
Following GP3, 323 mg (0.250 mmol) of resin **23a** was reacted with 225 mg (1.00 mmol) of NIS and 0.25 mL (10 mmol) of HF/py. After purification, 55.0 mg (0.166 mmol, 67% over 4 steps) of a bright yellow oil was obtained (cyclohexane/ethyl acetate 8:1, R_f = 0.7). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.38 (s, 9 H, $C(CH_3)_3$), 2.01 (t, $^3J_{HF}$ = 18.2 Hz, 3 H, CH_3CF_2), 4.00 (s, 3 H, OCH_3), 7.53 (d, ^3J = 8.5 Hz, 2 H, H_{Ar}), 7.61 (d, ^3JB = 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, CH_3CF_2), 31.4 ($C(CH_3)_3$), 34.7 ($C(CH_3)_3$), 52.5 (OCH_3), 121.4 (t, $^1J_{CF}$ = 240.5 Hz, CF_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 (CO) 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.

Methyl 5-(1,1-Difluoroethyl)-4′-methylbiphenyl-3-carboxylate (25b).



Following GP3, 312 mg (0.250 mmol) of resin **23b** 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). ^1H NMR (400 MHz, $CDCl_3$): δ = 2.00 (t, $^3J_{HF}$ = 18.2 Hz, 3 H, CH_3CF_2), 2.42 (s, 3 H, CH_3), 3.99 (s, 3 H, OCH_3), 7.32 (d, ^3J = 8.5 Hz, 2 H, H_{Ar}), 7.57 (d, ^3JB = 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 ($C_{Ar}CH_3$), 25.9 (t, $^2J_{CF}$ = 29.3 Hz, CH_3CF_2), 52.4 (OCH_3), 121.4 (t, $^1J_{CF}$ = 240.5 Hz, CF_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 (CO) 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 ($C_{17}H_{16}F_2O_2$): calcd 290.1118; found 290.1116.

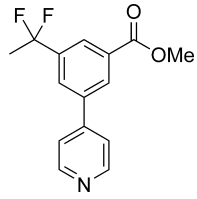
Methyl 4′-Chloro-5-(1,1-difluoroethyl)biphenyl-3-carboxylate (25c).



Following GP3, 317 mg (0.250 mmol) of resin **23c** 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). ^1H NMR (400 MHz, $CDCl_3$): δ = 2.00 (t, $^3J_{HF}$ = 18.2 Hz, 3 H, CH_3CF_2), 4.00 (s, 3 H, OCH_3), 7.47 (d, ^3J = 8.6 Hz, 2 H, H_{Ar}), 7.58 (d, ^3JB = 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

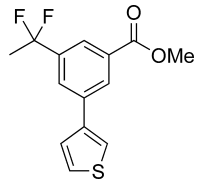
Hz, CH_3CF_2), 52.5 (OCH_3), 121.3 (t, $^1J_{CF} = 240.5$ Hz, CF_2), 125.0 (t, $^3J_{CF} = 5.9$ Hz, $C_{Ar}C_{Ar}CF_2$), 127.3 (t, $^3J_{CF} = 5.9$ Hz, $C_{Ar}C_{Ar}CF_2$), 128.5 (C_{Ar}), 129.2 (C_{Ar}), 129.3 (C_{Ar}), 131.1 (C_{Ar}), 134.5 ($C_{Ar}Cl$), 137.8 (C_{Ar}), 139.4 (t, $^2J_{CF} = 27.0$ Hz, $C_{Ar}CF_2$), 140.9 (C_{Ar}), 166.2 (CO) ppm. ^{19}F NMR (376 MHz, H-decoupled, $CDCl_3$): $\delta = -88.0$ ppm. IR (KBr): $\nu = 3436$ (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 3-(1,1-Difluoroethyl)-5-(pyridin-4-yl)benzoate (25d).



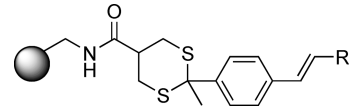
Following GP3, 299 mg (0.200 mmol) of resin **23d** was reacted with 180 mg (0.800 mmol) of NIS and 0.20 mL (8.0 mmol) of HF/py. After purification, 10.0 mg (0.036 mmol, 18% over 4 steps) of a bright yellow oil was obtained (cyclohexane/ethyl acetate/triethylamine 25:5:1, $R_f = 0.15$). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.99$ (t, $^3J_{HF} = 18.2$ Hz, 3 H, CH_3CF_2), 3.99 (s, 3 H, OCH_3), 7.56 (d, $^3J = 6.0$ Hz, 2 H, H_{Ar}), 7.96 (m, 1 H, H_{Ar}), 8.24 (m, 1 H, H_{Ar}), 8.37 (m, 1 H, H_{Ar}), 8.73 (d, $^3J = 6.0$ Hz, 2 H, H_{Ar}) ppm. - ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 26.0 (t, $^2J_{CF} = 29.2$ Hz, CH_3CF_2), 52.6 (OCH_3), 121.2 (t, $^1J_{CF} = 240.3$ Hz, CF_2), 121.7 (C_{Ar}), 126.4 (t, $^3J_{CF} = 5.8$ Hz, $C_{Ar}C_{Ar}CF_2$), 127.5 (t, $^3J_{CF} = 5.8$ Hz, $C_{Ar}C_{Ar}CF_2$), 129.4 (C_{Ar}), 131.7 (C_{Ar}), 139.2 (C_{Ar}), 139.8 (t, $^2J_{CF} = 27.1$ Hz, $C_{Ar}CF_2$), 146.6 (C_{Ar}), 150.6 (C_{Ar}), 165.9 (CO) ppm. ^{19}F NMR (376 MHz, H-decoupled, $CDCl_3$): $\delta = -88.2$ ppm. IR (KBr): $\nu = 3433$ (w), 3030 (w), 3001 (w), 2953 (w), 2919 (w), 2850 (w), 1726 (m, ν(CO)), 1595 (m), 1552 (w), 1443 (m), 1407 (m), 1386 (m), 1350 (m), 1252 (s, ν(CF)), 1179 (m), 1126 (m), 1075 (m), 988 (w), 932 (m), 903 (w), 865 (vw), 818 (m), 769 (m), 746 (w), 698 (w), 668 (vw), 641 (w), 631 (w), 603 (w), 474 (vw) cm^{-1}. MS (EI): *m/z* (%): 277 (76) [M^+], 262 (8) [$M^+ - CH_3$], 246 (100) [$M^+ - OCH_3$]. HRMS ($C_{15}H_{13}NF_2O_2$): calcd 277.0914; found 277.0916.

Methyl 3-(1,1-Difluoroethyl)-5-(thiophen-3-yl)benzoate (25e).



Following GP3, 373 mg (0.30 mmol) of resin **23e** was reacted with 270 mg (1.20 mmol) of NIS and 0.30 mL (12 mmol) of HF/py. After purification, 25.0 mg (0.089 mmol, 30% over 4 steps) of a colorless solid was obtained (cyclohexane/ethyl acetate 10:1, $R_f = 0.4$). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.97$ (t, $^3J_{HF} = 18.1$ Hz, 3 H, CH_3CF_2), 3.97 (s, 3 H, OCH_3), 7.01 (d, $^3J = 5.5$ Hz, 1 H, H_{Ar}), 7.54 (d, $^3J = 5.5$ Hz, 1 H, H_{Ar}), 7.87 (s, 1 H, H_{Ar}), 8.18 (m, 1 H, H_{Ar}), 8.24 (m, 2 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 25.9$ (t, $^2J_{CF} = 29.2$ Hz, CH_3CF_2), 52.5 (OCH_3), 121.2 (t, $^1J_{CF} = 240.3$ Hz, CF_2), 125.1 (t, $^3J_{CF} = 5.9$ Hz, $C_{Ar}C_{Ar}CF_2$), 128.7 (C_{Ar}), 129.5 (t, $^3J_{CF} = 5.9$ Hz, $C_{Ar}C_{Ar}CF_2$), 131.8 (C_{Ar}), 136.1 (C_{Ar}), 137.4 (C_{Ar}), 138.2 (C_{Ar}), 139.4 (t, $^2J_{CF} = 27.1$ Hz, $C_{Ar}CF_2$), 145.0(C_{Ar}), 147.0 (C_{Ar}), 166.1 (CO) ppm. ^{19}F NMR (376 MHz, H-decoupled, $CDCl_3$): $\delta = -88.3$ ppm. IR (KBr): $\nu = 3436$ (vw), 3080 (vw), 2999 (w), 2950 (w), 1724 (s, ν(CO)), 1605 (w), 1439 (m), 1384 (m), 1299 (m), 1250 (s, ν(CF)), 1179 (m), 1126 (m), 993 (w), 932 (m), 901 (m), 829 (w), 771 (m), 759 (w), 726 (w), 712 (m), 699 (m), 655 (w), 605 (w), 473 (vw) cm^{-1}. MS (EI): *m/z* (%): 282 (1) [M^+], 251 (4) [$M^+ - OCH_3$], 222 (10) [$C_{12}H_8F_2S^+$], 43 (100). HRMS ($C_{15}H_{13}NF_2O_2$): calcd 282.0526; found 282.0529.

General Procedure for Heck Coupling Reactions (GP6).



In a vial, 1.00 equiv of resin **20** was covered with 6 mL of dry DMF under argon and shaken for 30 min. After addition of 5.00 equiv of the olefin **26**, 1.00 equiv of triethylamine, 0.100 equiv of $Pd(OAc)_2$, and 0.500 equiv of PPh_3, the vial was sealed and shaken at 100 °C for 48 h. The resin was filtered off and washed following GP1b and dried under high vacuum. ^{13}C NMR gel-phase spectra were measured for qualitative reaction control. Finally, the molecules were cleaved from the resin following GP3 to give the fluorinated compounds.

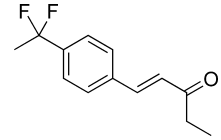
Resin 27a (R = $COCH_2CH_3$). The reaction of 410 mg (0.460 mmol) of resin **20** with 195 mg (2.30 mmol) of pent-1-en-3-on (**26a**) gave 398 mg of black resin. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 8.4$ (CH_3CH_2), 30.3 (CH_3), 34.2 (CH_3CH_2), 198.1 (CO) ppm.

Resin 27b (R = CO_2tBu). The reaction of 410 mg (0.460 mmol) of resin **20** with 300 mg (2.30 mmol) of *tert*-butyl acrylate (**26b**) gave 430 mg of brown resin. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 28.3$ ($OC(CH_3)_3$), 30.1 (CH_3), 81.1 ($OC(CH_3)_3$), 167.2 (COO) ppm.

Resin 27c (R = CHO). The reaction of 225 mg (0.250 mmol) of resin **20** with 56.0 mg (1.00 mmol) of acrylaldehyde (**26c**) gave 230 mg of brown resin. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 30.1$ (CH_3) ppm. The attachment could be monitored by the disappearance of the signals at 92.4 ($C_{Ar}I$) and 137.9 ($C_{Ar}C_{Ar}I$) ppm.

Resin 27d (R = Ph). The reaction of 410 mg (0.460 mmol) of resin **20** with 240 mg (2.30 mmol) of styrene (**26d**) gave 392 mg of black resin. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 30.2$ (CH_3) ppm. The attachment could be monitored by the disappearance of the signals at 92.4 ($C_{Ar}I$) and 137.9 ($C_{Ar}C_{Ar}I$) ppm.

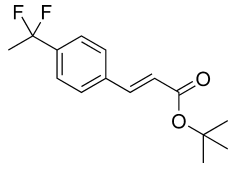
(*E*)-1-(4-(1,1-Difluoroethyl)phenyl)pent-1-en-3-one (28a).



Following GP3, 398 mg (0.460 mmol) of resin **27a** was reacted with 405 mg (1.80 mmol) of NIS and 0.45 mL (18 mmol) of HF/py. After purification, 21.0 mg (0.095 mmol, 21%

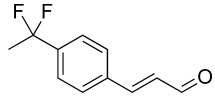
over 4 steps) of a colorless oil was obtained (pentane/diethylether 50:1, $R_f = 0.8$). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 1.10 (t, $^3J = 8.3$ Hz, 3 H, CH_2CH_3), 1.88 (t, $^3J_{HF} = 18.2$ Hz, 3 H, CH_3CF_2), 2.65 (q, $^3J = 8.3$ Hz, 2 H, CH_2CH_3), 6.72 (d, $^3J = 16.2$ Hz, 1 H, C*H*CO), 7.46 (d, ^3JB = 8.4 Hz, 2 H, H_{Ar}), 7.50 (d, ^3J= 8.4 Hz, 2 H, H_{Ar}), 7.54 (d, $^3J = 16.2$ Hz, 1 H, C*H*C_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 9.1$ (CH_3CH_2), 24.2 (t, $^2J_{CF} = 29.2$ Hz, CH_3CF_2), 33.4 (CH_3CH_2), 119.6 (t, $^1J_{CF} = 240.0$ Hz, CF_2), 121.5 (*C*HCO), 125.5 (C_{Ar}), 129.1 (C_{Ar}), 135.0 (C_{Ar}*C*H), 137.1 (t, $^2J_{CF} = 26.9$ Hz, $C_{Ar}CF_2$), 141.3 (C_{Ar}CH), 199.3 (*C*O) ppm. ^{19}F NMR (376 MHz, H-decoupled, $CDCl_3$): $\delta = -88.7$ ppm. MS (EI): *m*/*z* (%): 224 (22) [M^+], 195 (100) [$M^+ - CH_2CH_3$]. HRMS ($C_{13}H_{14}F_2O$): calcd 224.1013; found 224.1016.

(*E*)-*tert*-Butyl 3-(4-(1,1-difluoroethyl)phenyl)acrylate (28b).



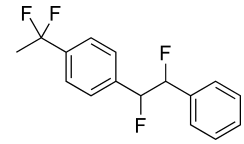
Following GP3, 430 mg (0.460 mmol) of resin **27b** was reacted with 405 mg (1.80 mmol) of NIS and 0.45 mL (18 mmol) of HF/py. After purification, 19.0 mg (0.071 mmol, 15% over 4 steps) of a bright yellow oil was obtained (pentane/diethylether 5:1, $R_f = 0.6$). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.46$ (s, 9 H, C(CH_3)$_3$), 1.87 (t, $^3J_{HF} = 18.2$ Hz, 3 H, CH_3CF_2), 6.34 (d, $^3J = 16.0$ Hz, 1 H, C*H*CO), 7.44 (d, ^3JB = 8.4 Hz, 2 H, H_{Ar}), 7.50 (d, ^3JB = 8.4 Hz, 2 H, H_{Ar}), 7.52 (d, $^3J = 16.0$ Hz, 1 H, C*H*C_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 24.8$ (t, $^2J_{CF} = 29.2$ Hz, CH_3CF_2), 27.7 (OC(CH_3)$_3$), 79.8 (O*C*-(CH_3)$_3$), 120.4 (t, $^1J_{CF} = 240.0$ Hz, CF_2), 120.5 (*C*HCO), 124.9 (C_{Ar}), 127.0 (C_{Ar}), 135.0 (C_{Ar}*C*H), 138.4 (t, $^2J_{CF} =$ 26.9 Hz, $C_{Ar}CF_2$), 141.3 (*C*HC_{Ar}), 165.0 (*C*O) ppm. ^{19}F NMR (376 MHz, H-decoupled, $CDCl_3$): $\delta = -87.7$ ppm. MS (EI): *m*/*z* (%): 268 (24) [M^+], 212 (100) [$M^+ + H -$ C(CH_3)$_3$], 195 (60) [$M^+ -$ OC(CH_3)$_3$]. HRMS ($C_{15}H_{18}F_2O_2$): calcd 268.1275; found 268.1272.

(*E*)-3-(4-(1,1-Difluoroethyl)phenyl)acrylaldehyde (28c).



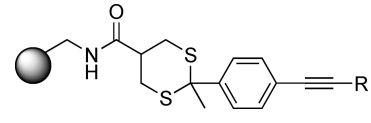
Following GP3, 230 mg (0.250 mmol) of resin **27c** was reacted with 225 mg (1.00 mmol) of NIS and 0.25 mL (10 mmol) of HF/py. After purification, 9.0 mg (0.046 mmol, 18% over 4 steps) of a colorless solid was obtained (cyclohexane/ethyl acetate 4:1, $R_f = 0.4$). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.92$ (t, $^3J_{HF} = 18.2$ Hz, 3 H, CH_3CF_2), 6.75 (dd, $^3J_{trans} = 16.0$ Hz,$^3J = 7.6$ Hz, 1 H, C*H*CHO), 7.32 (m, 1 H, C_{Ar}C*H*), 7.57 (d, $^3J = 8.4$ Hz, 2 H, H_{Ar}), 7.62 (d, ^3JB = 8.4 Hz, 2 H, H_{Ar}), 9.73 (d, $^3J = 7.6$ Hz, 1 H, C*H*O) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 25.9$ (t, $^2J_{CF} = 29.4$ Hz, CH_3CF_2), 121.4 (t, $^1J_{CF} = 240.0$ Hz, CF_2), 125.4 (t, $^3J_{CF} = 5.9$ Hz, $C_{Ar}C_{Ar}CF_2$), 128.6 (C_{Ar}), 129.5 (C_{Ar}), 131.6 (*C*CHO), 140.7 (t, $^2J_{CF} = 26.6$ Hz, $C_{Ar}CF_2$), 151.3 ($C_{Ar}C_{olefin}$), 193.5 (*C*HO) ppm. ^{19}F NMR (376 MHz, H-decoupled, $CDCl_3$): $\delta = -88.1$ ppm. IR (KBr): $\nu =$ 3432 (w), 3051 (w), 2924 (w), 1897 (vw), 1810 (vw), 1679 (m, ν(CO)), 1625 (w), 1585 (w), 1571 (w), 1479 (w), 1434 (m), 1394 (w), 1296 (m, ν(CF)), 1181 (m), 1097 (m), 1016 (w), 998 (w), 918 (w), 827 (w), 744 (w), 691 (m), 639 (w), 584 (w), 527 (m), 493 (w), 456 (w) cm^{-1}. MS (EI): *m*/*z* (%): 196 (8) [M^+], 131 (20) [$C_9H_7O^+$], 43 (100) [$C_2H_3O^+$]. HRMS ($C_{11}H_{10}F_2O$): calcd 196.0700; found 196.0701.

1-(1,2-Difluoroethyl-2-phenylethyl)-4-(1,1-difluoroethyl)-benzene (28d).



Following GP3, 392 mg (0.460 mmol) of resin **27d** was reacted with 405 mg (1.80 mmol) of NIS and 0.45 mL (18 mmol) of HF/py. After purification, 26.0 mg (0.092 mmol, 20% over 4 steps) of a colorless oil was obtained as a 1.1:1 mixture of two diastereomers (pentane/diethylether 40:1, $R_f = 0.8$). The diastereomers could not be separated completely, and the NMR data of the major diastereomer is given. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.85$ (t, $^3J_{HF} = 18.2$ Hz, 3 H, CH_3CF_2), 5.62 (ddd, $^2J_{HF} = 60.4$ Hz, $^3J_{HF} = 31.4$ Hz, $^3J_{HH} = 4.2$ Hz, 2 H, C*H*F), 7.10 (m, 2 H, H_{Ar}), 7.20 (d, ^3JB = 8.4 Hz, 2 H, H_{Ar}), 7.29 (m, 3 H, H_{Ar}), 7.43 (d, ^3JB = 8.4 Hz, 2 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 25.9$ (t, $^2J_{CF} = 29.6$ Hz, CH_3CF_2), 92.8 (dd, $^1J_{CF} = 180.0$ Hz, $^2J_{CF} = 26.6$ Hz, *C*HF), 93.0 (dd, $^1J_{CF} = 180.0$ Hz, $^2J_{CF} =$ 26.7 Hz, *C*HF), 120.1 (t, $^1J_{CF} = 240.0$ Hz, CF_2), 124.5 (t, $^3J_{CF} = 6.0$ Hz, $C_{Ar}C_{Ar}CF_2$), 126.7 (C_{Ar}), 126.9 (C_{Ar}), 128.3(C_{Ar}), 129.4 (C_{Ar}), 134.4 (d, $^2J_{CF} = 27.3$ Hz, C_{Ar}CHF), 136.1 (d, $^2J_{CF} = 27.3$ Hz, C_{Ar}CHF), 138.7 (t, $^2J_{CF} = 27.3$ Hz, $C_{Ar}CF_2$) ppm. ^{19}F NMR (376 MHz, H-decoupled, $CDCl_3$): $\delta = -87.7$ (CF_2), -186.8 (d, $^3J_{FF} = 17.9$ Hz, C*F*H), -187.7 (d, $^3J_{FF} = 17.9$ Hz, C*F*H) ppm. MS (EI): *m*/*z* (%): 282 (20) [M^+], 263 (12) [M^+ - F], 173 (24) [M^+ - C_6H_5CHF], 109 (100) [C_6H_5CHF]. HRMS ($C_{16}H_{14}F_4$): calcd 282.1032; found 282.1033.

General Procedure for Sonogashira Coupling Reactions (GP6).



In a vial, 1.00 equiv of resin **20** was covered with 10 mL of dry DMF under argon and shaken for 30 min. After addition of 5.00 equiv of the acetylene **29**, 1.00 equiv of triethylamine, 0.500 equiv of CuI, and 0.010 equiv of $Pd(PPh_3)_4$, the vial was sealed and shaken at 80 °C for 48 h. The resin was filtered off, washed following GP1b, and dried under high vacuum. ^{13}C NMR gel-phase spectra were measured for qualitative reaction control. Finally, the molecules were cleaved from the resin following GP3 to give the fluorinated compounds.

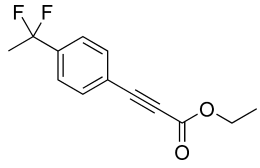
Resin 30a (R = $CO_2CH_2CH_3$). The reaction of 225 mg (0.250 mmol) of resin **20** with 195 mg (1.00 mmol) of ethyl

propiolate (**29a**) gave 280 mg black resin. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.3 (CH_3CH_2), 30.1 (CH_3), 60.8 (OCH_2), 165.1 (CO) ppm.

Resin 30b (R = Ph). The reaction of 410 mg (0.460 mmol) of resin **20** with 235 mg (2.30 mmol) of ethynylbenzene (**29b**) gave 435 mg of black resin. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.2 (CH_3), 95.2 ($C_{Ar}CCC_{Ar}$), 131.9 ($C_{Ar}C_{Ar}C$) ppm.

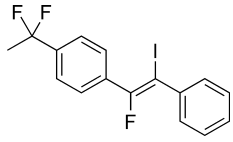
Resin 30c (R = *n*-Bu). The reaction of 410 mg (0.460 mmol) of resin **20** with 190 mg (2.30 mmol) of hex-1-yne (**29c**) gave 427 mg of black resin. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9 (CH_2CH_3), 19.3 (CCH_2), 22.1 (CH_2CH_3), 30.2 (CH_3), 30.9 ($CH_2CH_2CH_3$) ppm.

Ethyl 3-(4-(1,1-Difluoroethyl)phenyl)propiolate (31a).



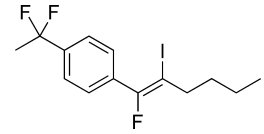
Following GP3, 280 mg (0.250 mmol) of resin **30a** was reacted with 225 mg (1.00 mmol) of NIS and 0.25 mL (10 mmol) of HF/py. After purification, 4.0 mg (0.017 mmol, 7% over 4 steps) of a colorless solid was obtained (cyclohexane/ethyl acetate 10:1, R_f = 0.5). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.36 (t, ^3J = 7.2 Hz, 3 H, CH_3CH_2), 1.91 (t, $^3J_{HF}$ = 18.1 Hz, 3 H, CH_3CF_2), 4.31 (t, ^3J = 7.2 Hz, 2 H, $COCH_2$), 7.51 (d, ^3J = 8.3 Hz, 2 H, H_{Ar}), 7.63 (d, ^3JB = 7.9 Hz, 2 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0 (CH_3CH_2), 25.9 (t, $^2J_{CF}$ = 29.4 Hz, CH_3CF_2), 62.0 (OCH_2), 81.5 ($CCOO$), 84.8 ($C_{Ar}C$), 121.2 ($C_{Ar}C$), 121.3 (t, $^1J_{CF}$ = 240.0 Hz, CF_2), 125.0 ($^3J_{CF}$ = 5.9 Hz, $C_{Ar}C_{Ar}CF_2$), 133.1 (C_{Ar}), 140.1 (t, $^2J_{CF}$ = 26.9 Hz, $C_{Ar}CF_2$), 153.9 (COO) ppm. ^{19}F NMR (376 MHz, H-decoupled, $CDCl_3$): δ = −87.9 ppm. IR (KBr): ν = 3443 (vw), 2927 (vw), 2238 (vw), 1710 (m, ν(CO)), 1612 (w), 1511 (w), 1446 (w), 1403 (w), 1384 (w), 1293 (m, ν(CF)), 1197 (m), 1107 (w), 1087 (w), 1018 (w), 917 (w), 839 (w), 748 (w), 691 (w), 603 (vw), 580 (vw) cm^{-1}. MS (EI): *m*/*z* (%): 238 (34) [M^+], 193 (100) [$M^+ - OC_2H_5$], 166 (100) [$C_{10}H_8F_{2P}^+$]. HRMS ($C_{13}H_{12}F_2O_2$): calcd 238.0805; found 238.0808.

(*E*)-1-(1,1-Difluoroethyl)-4-(1-fluoro-2-iodo-2-phenylvinyl)-benzene (31b).



Following GP3, 435 mg (0.460 mmol) of resin **30b** was reacted with 405 mg (1.80 mmol) of NIS and 0.45 mL (18 mmol) of HF/py. After purification, 22.0 mg (0.057 mmol, 13% over 4 steps) of a colorless solid was obtained (pentane/diethylether 40:1, R_f = 0.8). Slight impurities by the fluorinated iodide derived from the incomplete coupling reaction could not be removed. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.83 (t, $^3J_{HF}$ = 18.2 Hz, 3 H, CH_3CF_2), 7.38 (d, ^3JB = 8.4 Hz, 2 H, H_{Ar}), 7.30−7.55 (m, 5 H, H_{Ar}), 7.72 (d, ^3JB = 8.4 Hz, 2 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.9 (t, $^2J_{CF}$ = 29.6 Hz, CH_3CF_2), 68.0 (d, $^2J_{CF}$ = 27.5 Hz, CI), 116.1 (t, $^1J_{CF}$ = 240.0 Hz, CF_2), 124.5 (C_{Ar}), 127.9 (C_{Ar}), 128.1 (C_{Ar}), 128.4 (C_{Ar}), 129.6 (C_{Ar}), 130.2 (C_{Ar}), 131.7 ($C_{Ar}CF$), 140.1 (t, $^2J_{CF}$ = 26.9 Hz, $C_{Ar}CF_2$), 164.1 (d, $^1J_{CF}$ = 254.0 Hz, CF) ppm. ^{19}F NMR (376 MHz, H-decoupled, $CDCl_3$): δ = −75.7 (CF), −87.6 (CF_2) ppm. MS (EI): *m*/*z* (%): 388 (18) [M^+], 140 (100) [$M^+ - C_6H_5ClCFH$]. HRMS ($C_{16}H_{12}F_3I$): calcd 387.9936; found 387.9937.

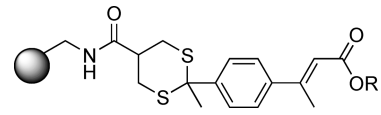
(*E*)-1-(1,1-Difluoroethyl)-4-(1-fluoro-2-iodohex-1-enyl)benzene (31c).



Following GP3, 427 mg (0.460 mmol) of resin **30c** was reacted with 405 mg (1.80 mmol) of NIS and 0.45 mL (18 mmol) of HF/py. After purification, 20.0 mg (0.055 mmol, 12% over 4 steps) of a colorless solid was obtained (pentane/diethylether 20:1, R_f = 0.8). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.92 (t, ^3JB = 7.4 Hz, 3 H, CH_2CH_3), 1.35 (sext, ^3JB = 7.4 Hz, 2 H, CH_2CH_3), 1.51 (quin, ^3JB = 7.4 Hz, 2 H, $CH_2CH_2CH_3$), 1.88 (t, $^3J_{HF}$ = 18.2 Hz, 3 H, CH_3CF_2), 2.67 (m, 2 H, $ClCH_2$), 7.42 (d, ^3JB = 8.4 Hz, 2 H, H_{Ar}), 7.62 (d, ^3JB = 8.4 Hz, 2 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9 (CH_2CH_3), 21.6 (CH_2), 25.8 (t, $^2J_{CF}$ = 29.6 Hz, CH_3CF_2), 31.9 (CH_2), 36.2 (CH_2), 85.2 (d, $^2J_{CF}$ = 27.5 Hz, CI), 121.5 (t, $^1J_{CF}$ = 240.0 Hz, CF_2), 124.3 (C_{Ar}), 126.5 (C_{Ar}), 129.6 (C_{Ar}), 134.6 (d, $^2J_{CF}$ = 27.5 Hz, $C_{Ar}CF$), 153.6 (d, $^1J_{CF}$ = 254.0 Hz, CF) ppm. ^{19}F NMR (376 MHz, H-decoupled, $CDCl_3$): δ = −82.6 (CF), −87.8 (CF_2) ppm. MS (EI): *m*/*z* (%): 368 (100) [M^+], 349 (10) [$M^+ - F$]. HRMS ($C_{14}H_{16}F_3I$): calcd 368.0249; found 368.0251.

Horner−Wadsworth−Emmons Reactions. The synthesis of resin **7e** was described above.

General Procedure for Horner−Wadsworth−Emmons Reaction (GP7).

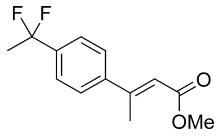


In a vial, 5.00 equiv of the HWE reagent and 5.00 equiv of 18-crown-6 were dissolved in 5 mL of dry THF and cooled to −78 °C. Then 5.00 equiv of a KHMDS solution (0.5 M in toluene) was added, and the mixture was allowed to warm to room temperature within 1 h. Resin **7e** (1.00 equiv) was swollen in dry THF and transferred to the reaction mixture. After it was shaken for 15 h at 40 °C, the resin was filtered off, washed three times with THF and then following GP1a and dried under high vacuum. Finally, the molecules were cleaved from the resin following GP3 to give the fluorinated compounds.

Resin 33a (R = CH_3). The reaction of 215 mg (0.250 mmol) of resin **7e** with 263 mg (1.25 mmol) of methyl-2-(diethoxyphosphoryl) acetate (**32a**) gave 260 mg of brown resin. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.5(CH_3), 30.1 (CH_3), 53.5 (OCH_3), 166.1 (COO) ppm.

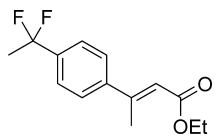
Resin 33b (R = CH_2CH_3). The reaction of 600 mg (0.700 mmol) of resin **7e** with 785 mg (3.50 mmol) of ethyl-2-(diethoxyphosphoryl) acetate (**32b**) gave 645 mg of brown resin. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.5 (CH_3CH_2), 18.0 (CH_3), 30.4 (CH_3), 62.0 (OCH_2), 166.2 (COO) ppm.

(*E*)-Methyl 3-(4-(1,1-Difluoroethyl)phenyl)but-2-enoate (34a).



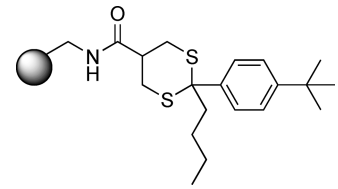
Following GP3, 260 mg (0.250 mmol) of resin **33a** was reacted with 225 mg (1.00 mmol) of NIS and 0.25 mL (10 mmol) of HF/py. After purification, 14.0 mg (0.057 mmol, 23% over 4 steps) of a colorless solid (cyclohexane/ethyl acetate 10:1, R_f = 0.5) was obtained. Slight impurities by the *Z*-isomer could not be removed completely. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.89 (t, $^3J_{HF}$ = 18.2 Hz, 3 H, CH_3CF_2), 2.51 (d, ^4JB = 1.3 Hz, 3 H, CH_3), 3.53 (s, 3 H, OCH_3), 6.11 (q, ^4JB = 1.3 Hz, 1 H, $CHCO$), 7.40−7.45 (m, 4 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.4 (CH_3), 26.2 (t, $^2J_{CF}$ = 29.2 Hz, CH_3CF_2), 51.6 (OCH_3), 118.0 ($CHCO$), 121.9 (t, $^1J_{CF}$ = 239.1 Hz, CF_2), 125.1 (t, $^3J_{CF}$ = 5.9 Hz, $C_{Ar}C_{Ar}CF_2$), 125.6 (C_{Ar}), 138.7 (t, $^2J_{CF}$ = 26.9 Hz, $C_{Ar}CF_2$), 141.2 ($C_{Ar}CCHCO$), 155.2 ($C_{Ar}CCHCO$), 168.9 (CO) ppm. ^{19}F NMR (376 MHz, H-decoupled, $CDCl_3$): δ = −88.5 ppm. IR (KBr): ν = 3449 (vw), 2999 (w), 2952 (w), 1811 (vw), 1744 (m, ν(CO)), 1629 (w), 1435 (w), 1408 (w), 1382 (w), 1338 (w), 1296 (m, ν(CF)), 1270 (w), 1172 (m), 1121 (m), 1094 (m), 1017 (w), 917 (w), 838 (w), 801 (vw), 597 (w) cm^{-1}. MS (EI): *m*/*z* (%): 240 (43) [M^+], 209 (33) [$M^+ - OCH_3$], 187 (100) [$C_{12}H_{11}O_{2P}^+$]. HRMS ($C_{13}H_{14}F_2O_2$): calc. 240.0962; found 240.0960.

(*E*)-Ethyl 3-(4-(1,1-Difluoroethyl)phenyl)but-2-enoate (34b).



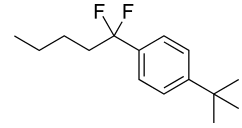
Following GP3, 645 mg (0.700 mmol) of resin **33b** was reacted with 630 mg (2.80 mmol) of NIS and 0.70 mL (28 mmol) of HF/py. After purification, 37.0 mg (0.146 mmol, 21% over 4 steps) of a colorless solid (pentane/diethylether 10:1, R_f = 0.8) was obtained. Slight impurities by the *Z*-isomer could not be removed completely. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.23 (t, ^3JB = 7.2 Hz, 3 H, CH_2CH_3), 1.85 (t, $^3J_{HF}$ = 18.2 Hz, 3 H, CH_3CF_2), 2.50 (d, ^4JB = 1.3 Hz, 3 H, CH_3), 4.14 (q, ^3JB = 7.2 Hz, 2 H, CH_2CH_3), 6.09 (q, ^4JB = 1.3 Hz, 1 H, $CHCO$), 7.45 (m, 2 H, H_{Ar}), 7.68 (m, 2 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.1 (CH_3CH_2), 18.3 (CH_3), 24.6 (t, $^2J_{CF}$ = 29.2 Hz, CH_3CF_2), 61.0 (OCH_2), 118.8 ($CHCO$), 121.2 (t, $^1J_{CF}$ = 240.0 Hz, CF_2), 125.9 (C_{Ar}), 128.0 (C_{Ar}), 138.1 (t, $^2J_{CF}$ = 26.9 Hz, $C_{Ar}CF_2$), 143.0 ($C_{Ar}CCHCO$), 154.1 ($C_{Ar}CCHCO$), 166.7 (CO) ppm. ^{19}F NMR (376 MHz, H-decoupled, $CDCl_3$): δ = −87.8 ppm. MS (EI): *m*/*z* (%): 254 (80) [M^+], 225 (40) [$M^+ - CH_2CH_3$], 209 (100) [$M^+ - OCH_2CH_3$]. HRMS ($C_{14}H_{16}F_2O_2$): calcd 254.1118; found 254.1115.

Umpolung Reaction.



In a vial, 335 mg (0.42 mmol, 1.00 equiv) of resin **7a** was covered with dry THF in a vial under argon, and the mixture was shaken for 30 min. After the mixture was cooled at −50 °C, 0.50 mL (2.5 M in hexane, 1.20 mmol, 3.00 equiv) of *n*-butyllithium was added, and the mixture was shaken for 4 h under warming to −20 °C. The mixture was cooled again at −50 °C, and 570 mg (4.20 mmol, 10.0 equiv) of *n*-butyl bromide (**35**) was added; then, the reaction mixture was allowed to warm slowly to 0 °C over 15 h. The resin was filtered off, washed three times with THF, following GP1c, and dried under high vacuum to yield 350 mg of brown resin **36**. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2 (CH_2CH_3), 22.0 (CH_2CH_3), 22.6 ($CH_2CH_2CH_3$), 31.5 ($C(CH_3)_3$), 34.5 ($C(CH_3)_3$) ppm.

1-*tert*-Butyl-4-(1,1-difluoropentyl)benzene (37).



Following GP3, 350 mg (0.420 mmol) of resin **36** was reacted with 380 mg (1.70 mmol) of NIS and 0.45 mL (17 mmol) of HF/py. After purification, 16.0 mg (0.067 mmol, 16% over 4 steps) of a bright yellow oil (pentane/diethylether 40:1, R_f = 0.8) was obtained. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.97 (t, ^3J = 7.4 Hz, 3 H, CH_3), 1.26 (s, 9 H, $C(CH_3)_3$), 1.33 (sext, ^3J = 7.4 Hz, 2 H, CH_2CH_3), 1.66 (m, 2 H, $CH_2CH_2CH_3$), 2.78 (m, 2 H, CH_2CF_2), 7.21 (d, ^3J = 8.3 Hz, 2 H, Ar-*H*), 7.48 (d, ^3J = 8.3 Hz, 2 H, Ar-*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9 (CH_2CH_3), 23.5 (CH_2), 24.7 (CH_2), 31.3 ($C(CH_3)_3$), 34.4 (t, $^2J_{CF}$ = 27.7 Hz, CH_2CF_2), 35.2 ($C(CH_3)_3$), 123.4 (t, $^1J_{CF}$ = 241.5 Hz, CF_2), 125.0 (C_{Ar}), 128.7 (C_{Ar}), 134.9 (t, $^2J_{CF}$ = 26.9 Hz, $C_{Ar}CF_2$), 149.9 ($C_{Ar}C(CH_3)_3$) ppm. ^{19}F-NMR (376 MHz, H-decoupled, $CDCl_3$): δ = −94.1 ppm. MS (EI): *m*/*z* (%): 240 (14) [M^+], 225 (100) [$M^+ - CH_3$]. HRMS ($C_{15}H_{22}F_2$): calcd 240.1690; found 240.1693.

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Supporting Information Available. Spectroscopic data (^{1}H NMR) of the *gem*-difluorinated compounds. This infor-

mation is available free of charge via the Internet at http://pubs.acs.org.

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