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1,3-Dibromo-1,1-difluoro-2-propanone as a Useful Synthon for a Chemoselective Preparation of 4-Bromodifluoromethyl Thiazoles

Marco Colella,[†] Pantaleo Musci,[†] Claudia Carlucci,[†] Samuele Lillini,[§] Mara Tomassetti,[§] Andrea Aramini,*[,‡,§] Leonardo Degennaro,*[,†] and Renzo Luisi*[,†]

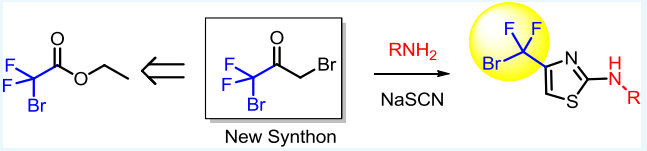
[†]Department of Pharmacy—Drug Sciences, University of Bari "A. Moro" Via E. Orabona 4, Bari 70125, Italy

[‡]Department of Discovery, Dompé Farmaceutici S.p.A., Via Campo di Pile, L'Aquila 67100, Italy

[§]Department of Discovery, Dompé Farmaceutici S.p.A., Via Pietro Castellino, Napoli 80131, Italy

Supporting Information

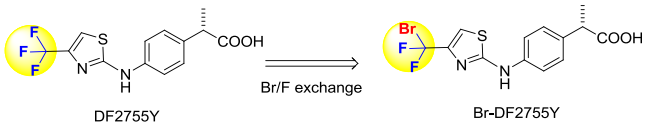
ABSTRACT: We report herein a synthetic protocol for the preparation of 1,3-dibromo-1,1-difluoro-2-propanone, a new synthon used for the first time in a reaction with aromatic amines and sodium thiocyanate, leading to thiazoles which are useful candidates in drug discovery programs. The new synthon allows to introduce a bromodifluoromethyl group at the C4 of the thiazole, and it is amenable of further transformation such as the Br/F exchange useful in radiopharmaceutics. Application of the strategy to the preparation of a precursor of the biologically relevant DF2755Y is also reported.



INTRODUCTION

The increased presence of fluorine in pharmaceuticals[1] and agrochemicals,[2] as well as in material sciences,[3] continues to stimulate research interests in the development of methodologies for the preparation of fluorine-containing compounds.[4] Among the several approaches for the introduction of a fluorinated moiety into organic molecules, methods for trifluoro- and difluoromethylation as well as difluoromethylenation have been widely provided in recent years.[5] In contrast, methods for the introduction of halodifluoromethyl units ($-CF_2X$) have received less attention. Thus, convenient strategies for introducing $-CF_2X$ groups are still in demand because halodifluoromethylated compounds are useful synthetic intermediates[6] for the preparation of biologically relevant compounds, as the difluoromethylene unit is considered isosteric and isopolar to an ethereal oxygen.[7] In addition, iodo, bromo, and chlorodifluoromethylated aromatics and heteroaromatics are recognized as potential candidates for undergoing the halogen/fluorine exchange processes,[8] and thus potential valuable precursors of [^{18}F]trifluoromethylated compounds for positron emission tomography imaging.[9] Moreover, because of the relatively short half-life (110 min) of the ^{18}F radioisotope, the (hetero)aryl $CF_2-[^{18}F]$ bond construction is often required as the late-stage synthetic step.[10] In this context, we became interested in the chemistry of fluorinated 2-aminothiazoles as structural elements screened in our drug discovery programs.[11] In particular, our recent efforts focused on (2*S*)-2-(4-{[4-(trifluoromethyl)-1,3-thiazol-2-yl]-amino}phenyl)propanoic acid (DF2755Y) (Scheme 1), a small molecule belonging to a novel allosteric dual CXCR1/CXCR2 inhibitor with a favorable oral pharmacokinetic profile. This molecule selectively inhibited neutrophil chemotaxis induced by CXCR1/2 ligands without affecting on CXCL8 binding to these receptors. The activation of CXCR1/2 has been implicated in the genesis of inflammatory and postoperative pain and progression of severe chronic diseases, including rheumatoid arthritis, chronic obstructive pulmonary disease, Alzheimer's disease, melanoma, and several urological diseases.[12] Furthermore, the results might suggest that this small molecule can be a candidate for a novel therapeutic option to control inflammatory and postoperative pain.[13]

Scheme 1



Given the importance in drug discovery of this promising molecule and other fluorinated aminothiazoles in the pipeline, we embarked in a project aimed at developing 4-bromodifluoromethyl aminothiazole scaffolds as potential precursors of [^{18}F]-radiotracers by a late-stage Br/F exchange reaction.

On the basis of these premises, we noticed that the main strategies available for introducing the CF_2Br group into (hetero)aromatic rings rely on: (a) a direct incorporation of the bromodifluoromethyl group as a $^{+}CF_2Br$ equivalent in the presence of arylmetal species (Scheme 2a),[14] (b) a direct radical bromodifluoromethylation of heteroaromatics (i.e. benzofurans or benzo[*b*]thiophene) using the $BrCF_2SO_2Na$ reagent (Scheme 2b),[15] and (c) a bromination with *N*-bromosuccinimide (NBS) or Br_2 of fluorine-containing compounds (Scheme 2c).[16] However, each strategy has

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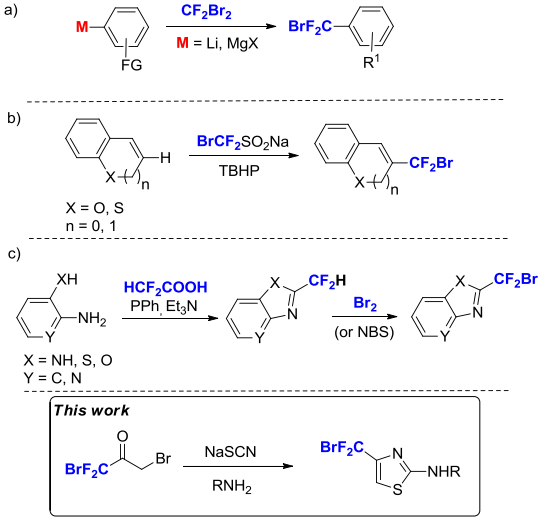
Scheme 2. Strategies (a−c) for the Construction of Bromodifluoromethylated Scaffolds



synthetic limitations, whereas complementary ways to CF_2Br-containing building blocks are quite rare and reported the use of $BrCF_2CO_2Et$ or the corresponding carboxylic acid as CF_2Br-containing building blocks for the synthesis of 2-CF_2Br-substituted 1,3-imidazolines, 1,3-oxazolines, 1,3-benzoxazole, and 5-(CF_2Br)-1,2,4-oxadiazoles for pharmaceutical scopes.[17] We reasoned that the use of a new CF_2Br-containing reagent could have been an alternative strategy to construct other CF_2Br-substituted heterocycles.

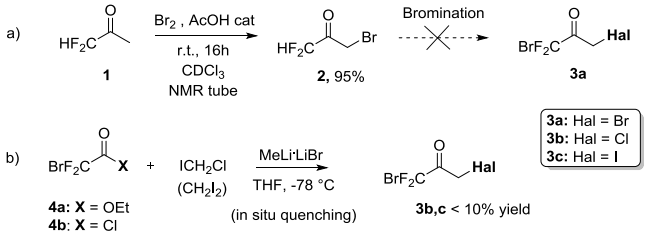
Various methodologies, such as Hantzsch and Cook−Heilbron, have been reported for the synthesis of aminothiazole and their derivatives. The Hantzsch thiazole synthesis, one of the widest used methodology, involves the reaction of α-halo carbonyl compounds with thiourea or thioamides.[18] To the best our knowledge, there are no reported examples on the use of the Hantzsch-type approach for the preparation of 4-CF_2Br-substituted 2-aminothiazoles, whereas it is reported an isolate example of direct C-5 bromodifluoromethylation of 2-trifluoroacetamido-4-(trifluoromethyl)thiazole by treatment with *n*-BuLi and CF_2Br_2 at low temperature.[19]

Thereby, we envisioned that a 1,3-dihalo-1,1-difluoro-2-propanone could be an attractive building block to provide straightforward access to 4-CF_2Br-substituted 2-aminothiazoles, by reaction with aromatic amines and sodium thiocyanate.[20] With our surprise, we were unable to find precedence about the synthesis of this type of synthon (Scheme 2).

RESULTS AND DISCUSSION

We started our investigation by exploring different synthetic pathways for obtaining the desired synthon **3** (Scheme 3). First, with the aim to introduce by a one-pot procedure two bromine atoms at 1,3-positions of commercially available 1,1-difluoropropanone, the commonly reported halogenation protocol with Br_2 or NBS was considered. In principle, the double bromination of this substrate, on both sp^3 carbons, could have directly provided us the desired product. However, monitoring this reaction in a NMR tube using Br_2, catalytic AcOH, and $CDCl_3$ as solvent, only mono bromination occurred with high selectivity at C-3, giving bromoketone **2** in good yield, whereas the CF_2H group resulted insensitive to

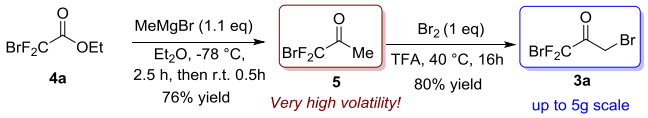
Scheme 3. Alternative Approaches (a,b) for the Synthesis of Synthon 3



bromine. All attempts, using Br_2 or NBS in the presence of acid or AIBN, to introduce a second bromine atom at C-1 failed. With these lines of evidence in hand, we explored a different strategy, evaluating the possibility of a direct introduction of the halomethyl moiety by nucleophilic addition of a metalated halomethyl group on a readily available difluoromethyl acetate **4a** or the corresponding acylchloride **4b** (Scheme 3b). Very recently, we developed an efficient flow method for the direct halomethylation of several electrophiles by trapping of halomethyllithium intermediates generated from haloiodomethanes.[21] Thus, we explored the reactivity of lithium carbenoids, derived from ICH_2Cl and I_2CH_2, with commercial ester **4a** and acyl chloride **4b** exhibiting the CF_2Br group. Under optimized reaction conditions, using MeLi·LiBr as a lithiating agent and 1:1 diethyl ether/tetrahydrofuran (THF) mixture as a solvent, at −78 °C under internal quenching conditions, ^{1}H NMR and GC−MS analysis (Scheme 3b) revealed the formation of a complex mixture, and all attempts to isolate the detected products **3b** and **3c** failed.

After these unsatisfactory results, a different approach was evaluated, and based on the preliminary introduction of a methyl group into ester **4a**, leading to ketone **5**, followed by a subsequent bromination step, as reported in Scheme 4. Thus,

Scheme 4. Two-Step Synthesis of Synthon 3



according to a reported protocol, we attempted the reaction of the commercially available ethyl 1-bromo-1,1-difluoroethanoate **4a** with methylmagnesium bromide, in diethyl ether at −78 °C. After ^{1}H, ^{19}F, and ^{13}C NMR analysis, we were pleased to confirm the presence of the expected ketone **5** (76% yield). Unfortunately, the high volatility of the product did not allow the complete removal of diethyl ether solvent. Therefore, the ethereal solution of **5**, titrated by ^{1}H NMR using mesitylene as the internal standard, was directly used for the following step.

The subsequent bromination step afforded **3a** in 80% yield (Scheme 4). The best reaction conditions for bromination used trifluoroacetic acid (TFA) as a solvent and heated at 40 °C for 16 h. To reduce the formation of polyhalogenated side products, Br_2 was added in portions, whereas reaction evolution was monitored by ^{1}H- and ^{19}F NMR. Under these conditions, the conversion of **5** was complete and the ketone **3a** was isolated in high purity by distillation (>90% by NMR). This halogenated ketone resulted sensitive to air and moisture, thus requiring inert atmosphere conditions, amber container, and because of its volatility, it is recommended for low-temperature (4 °C) storage.

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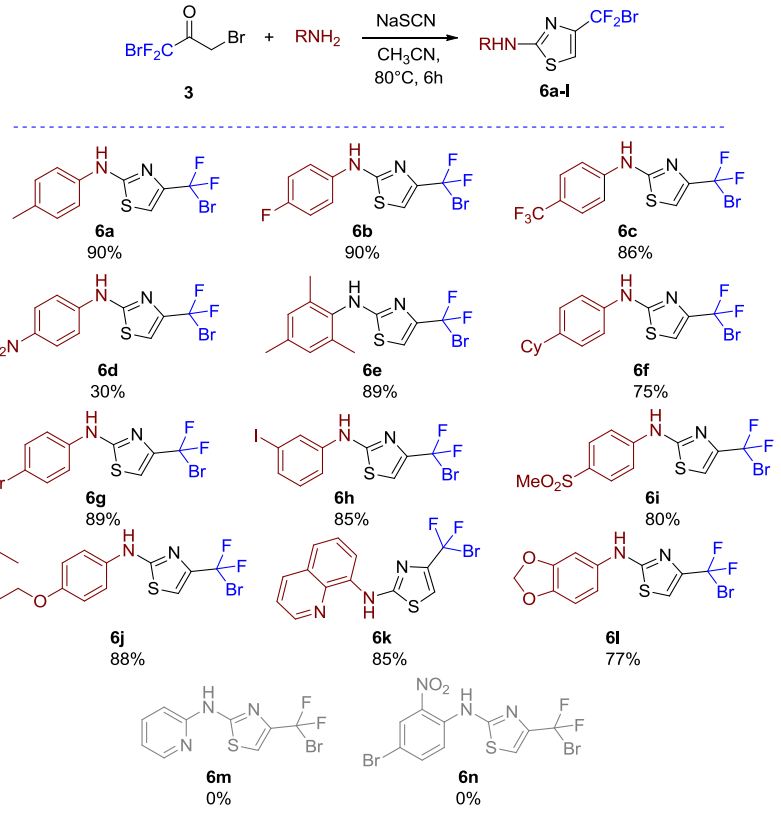
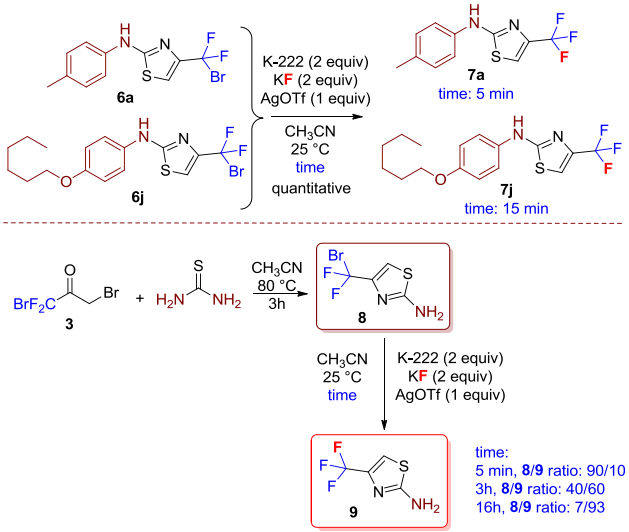
Scheme 5. Scope of the Reaction



With this new synthon in hand, the synthesis of 4-bromodifluoromethyl-thiazoles (**6a−l**) was directly carried out by condensation of ketone **3a** with several aromatic amines and in the presence of sodium thiocyanate (Scheme 5).[22] As reported in Scheme 4, the reaction worked well with several aromatic amines being tolerant to different substituents on the aromatic ring. The presence of a strong electron-withdrawing group as in the case of the *p*-nitroaniline provided low yield of the corresponding thiazole **6d**. In striking contrast, the reaction was not significantly affected by the presence of fluoro, trifluoromethyl, and methylsulfonyl groups, affording derivatives **6b**, **6c**, and **6i** in good yields. The presence on the aromatic ring of electron-donating substituents was also tolerated, leading to derivatives **6j** and **6l** in high yields. Unfortunately, the expected thiazoles **6m** and **6n** were not observed using 2-aminopyridine and 4-bromo-2-nitroaniline, likely because of an electronic effect that could decrease the nucleophilicity of the amine nitrogen.

With the aim to further validate the importance of this kind of functionalized bromodifluoromethylated thiazoles, we investigated the possibility to setup a fast and reproducible halogen/fluorine-exchange protocol. In particular, we were keen to demonstrate that the bromine atom could be replaced by the fluorine atom, using a fluoride anion as nucleophile, and in a reasonable time, compatible with ^{18}F-fluorination platforms. In fact, the use of anionic nucleophilic fluorination is preferred over electrophilic fluorination because of the higher specific activity after radiolabeling.[23] Derivatives **6a** and **6j** were used as test compounds and subjected to reaction under "cold" conditions using KF as the source of fluoride ions, kryptofix 222 as the cryptand for potassium cation, and AgOTf as the promoter in acetonitrile at room temperature (Scheme 6).

Scheme 6. Applications of Halogen/Fluorine Exchange



As reported in Scheme 6, the reaction performed very well providing the exchange products **7a** and **7j** quantitatively in only 5−15 min, as demonstrated by ^{19}F NMR monitoring (see Supporting Information). Nicely, the observed short reaction time for complete Br/F exchange could potentially be useful for a late-stage ^{18}F radiolabeling experiment. Next, the preparation of 2-aminothiazole **8** was also pursued using synthon **3a** in the presence of thiourea, obtaining thiazole **8** in almost quantitative yield. Exchange protocol on thiazole **8** provided the 2-amino-4-trifluoromethylthiazole **9**, a valuable building block in medicinal chemistry; however, at 25 °C, a variable degree of fluorine incorporation was observed,

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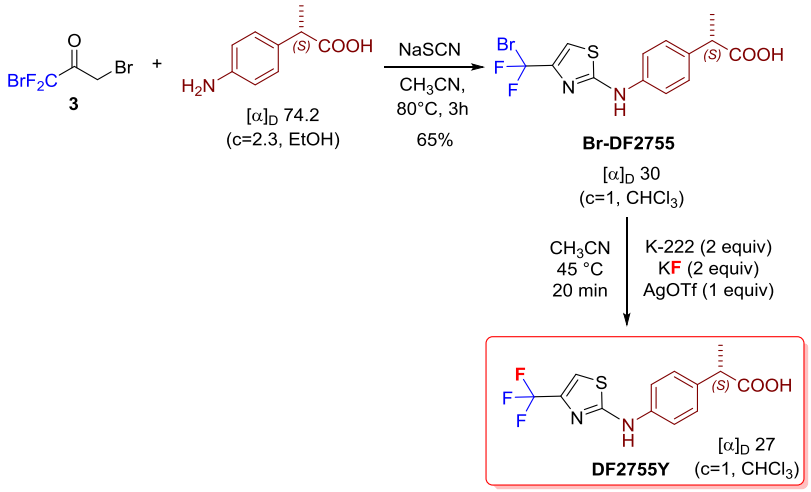
Scheme 7. Applications of the Strategy to DF2755Y



depending on the reaction time (Scheme 6). To further prove the usefulness of this approach, the synthon **3a** was tested for the preparation of Br-DF2755, a precursor of the drug candidate DF2755Y. As reported in Scheme 7, reacting **3a** with chiral (*S*)-*p*-aminophenylacetic acid in the presence of sodiumthiocyanate led to the target compound Br-DF2755 in good yield (Scheme 7). With the precursor Br-DF2755 in our hands, we investigated the possibility of Br/F exchange under optimized conditions. We were glad to observe a complete exchange in 20 min by using the optimized conditions adopted for **6a** and **6j** (Scheme 6) in terms of reagents stoichiometry but running the reaction at 80 °C. This represents a remarkable result for us because it opens the possibility either to develop a radiotracer for DF2755Y or to investigate the drug distribution in vivo.

CONCLUSIONS

In conclusion, we reported, for the first time, a new synthetic strategy for the synthesis of 4-CF_2Br-substituted 2-aminothiazoles based on the use of the 1,3-dibromo-1,1-difluoro-2-propanone as a useful synthon. The usefulness of this reagent has been demonstrated in preparation of several 4-bromodifluoromethyl thiazoles which are precursors for a Br/F exchange reaction. The strategy has been applied to the preparation of Br-DF2755, precursor of the biologically relevant DF2755Y. Further studies ongoing in our laboratories are aimed at preparing ^{18}F-labeled derivatives and at expanding the developed methodology. Results will be reported in due course.

EXPERIMENTAL SECTION

General (Standard Techniques). The chemicals (compounds **1**, **2**, **4a**, and **4b**) and solvents were purchased from TCI Europe, Fluorochem, VWR, Aldrich Chemical Company, and used without purification except Et_2O and THF which were distilled over Na/benzophenone prior to use. Melting points were measured with Büchi melting point B-545. ^{1}H NMR, ^{13}C NMR, and ^{18}F NMR spectra were recorded using Bruker 700, Agilent 300 and 500 MHz. $CDCl_3$, CD_3OD were used as solvents. Data are expressed as follows: chemical shift [multiplicity, coupling constant in Hz, integration]. Infrared spectra of the compounds were recorded by using a PerkinElmer 283 spectrometer or by using attenuated total reflection spectrophotometer in reciprocal centimeter. ESI-MS analyses performed on Agilent 110 LC/MSD mass spectrometer with ionic single quadrupole trap system and Exalibur data system. TLC was carried out on a 0.25 mm precoated silica gel thick plates (Merck) with a fluorescence indicator F-254; compounds were detected either under UV light (at 254 nm) or by spraying with sulfuric acid or permanganate solution. Silica gel 70−230 mesh and 230−400 mesh were used for flash chromatography on glass columns.

Procedure for the Preparation of 1,3-Dibromo-1,1-difluoropropan-2-one (3a). According to the reported procedure,[8] to a solution of ethyl 2-bromo-2,2-difluoroacetate (10 g, 49.3 mmol) in dry diethyl ether (54 mL) at −78 °C, methyl magnesiumbromide (3 M solution in diethyl ether, 18 mL) was added dropwise, and the mixture was stirred at −78 °C for 2.5 h and an additional 30 min at room temperature. The reaction was quenched with water (5 mL), and the organic phase was dried over sodium sulfate. The ethereal solution was filtrated and concentrated under moderate vacuum (600−700 Torr) until 30 mL of final volume because of the high volatility of the product. The concentration of 1-bromo-1,1-difluoropropan-2-one (**5**[1]) was evaluated by H NMR analysis using mesitylene as the internal standard (1.25 M), 76% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.46 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 189.4 (t, J = 27.3 Hz, C═O), 113.9 (t, $^1J_{(C-F)}$ = 319.2 Hz, CF_2Br), 22.3 (CH_3). ^{19}F NMR (282 MHz, $CDCl_3$): δ −65.6 (2F). To a titrated ethereal solution of 1-bromo-1,1-difluoropropan-2-one (**6**) (6.4 g, 37.4 mmol), TFA (980 μL, 12.8 mmol) was added dropwise. To this solution, Br_2 (1.9 mL, 37.4 mmol) was added in portions (200 μL each) while monitoring the progress of the reaction by ^{1}H- and ^{19}F NMR. The mixture was heated at 40 °C and stirred for 16 h. The reaction was quenched with aqueous solution of sodium metabisulfite (0.1 M, 100 μL). The crude was diluted with dichloromethane (15 mL) and washed with water (3 × 5 mL). The organic phase was dried over sodium sulfate and the solvent was removed under reduced pressure. The obtained brown oil was purified by bulb to bulb distillation (50 °C, 10^{-2} Torr), affording the 1,3-dibromo-1,1-difluoropropan-2-one (**3a**) as a colorless oil (4.7 g, 18.7 mmol), 80% yield. IR (film)/cm^{-1}: 2921, 2086, 1642. ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.35 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 183.7 (t, $^2J_{(C-F)}$ = 27.8 Hz, C═O), 112.0 (t,

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$^{1}J_{(C-F)}$ = 319.7 Hz, CF_2Br), 26.2 (s, CH_2Br). ^{19}F NMR (470 MHz, $CDCl_3$): δ −62.9 (2F). HRMS (ESI-TOF) m/z: calcd for $C_3H_1Br_2F_2O$ $[M - H]^-$, 250.8342; found, 250.8332.

General Procedure for the Preparation of Thiazole (6a−l). A solution of 1,3-dibromo-1,1-difluoropropan-2-one (**3a**) (98 mg, 0.39 mmol) and sodium thiocyanate (31 mg, 0.39 mmol) in dry acetonitrile (500 μL) in a sealed tube was stirred at ambient temperature for 15 min. Subsequently, *p*-toluidine (41 mg, 0.39 mmol) was added dropwise, and the mixture was heated to 80 °C for 3 h in an oil bath. After this time, the mixture was taken up with 5 mL of AcOEt and filtered on celite pad. The solvent was removed under reduced pressure, and the crude was purified by flash chromatography on silica gel to afford the desired product.

[4-(Bromodifluoromethyl)-1,3-thiazol-2-yl](p-tolyl)amine ***(6a)***. (111 mg, 90%). R_f 0.6 (30% EtOAc/*n*-hexane). mp 114−116 °C. ^{1}H NMR (700 MHz, $CDCl_3$): δ 7.33 (br s, 1H, NH), 7.21−7.19 (m, 4H, 4 × Ar-H), 6.90 (s, 1H, HetAr-H), 2.35 (s, 3H, CH_3). ^{13}C NMR (176 MHz, $CDCl_3$): δ 167.3 (C═N), 146.8 (t, $^{2}J_{(C-F)}$ = 28.6 Hz, Ar-Cq), 137.0 (Ar-Cq), 134.8 (Ar-Cq), 130.4 (2 × Ar-C), 120.3 (2 × Ar-C), 114.2 (t, $^{1}J_{(C-F)}$ = 302.0 Hz, CF_2Br), 106.5 (t, $^{3}J_{(C-F)}$ = 5.1 Hz, Ar-C), 21.0 (CH_3). ^{19}F NMR (470 MHz, $CDCl_3$): δ −46.5 (2F). IR (film)/cm^{-1}: 3188, 3085, 2957, 1591, 1575, 1514, 1353, 1191, 1119, 1069, 966, 794. HRMS (ESI-TOF) m/z: calcd for $C_{11}H_{10}BrF_2N_2S$ $[M + H]^+$, 318.9716; found, 318.9712.

[4-(Bromodifluoromethyl)-1,3-thiazol-2-yl](p-fluorophenyl)amine ***(6b)***. Orange oil (113 mg, 90%). R_f 0.6 (30% EtOAc/*n*-hexane). ^{1}H NMR (700 MHz, $CDCl_3$): 7.67 (br s, 1H, NH), 7.34 (dd, *J* = 8.6, 4.5 Hz, 2H, 2 × Ar-H), 7.10 (t, *J* = 8.6 Hz, 2H, 2 × Ar-H), 6.91 (s, 1H, HetAr-H). ^{13}C NMR (176 MHz, $CDCl_3$): δ 167.8 (C═N), 160.1 (d, $^{1}J_{(C-F)}$ = 244.9 Hz, Ar-Cq), 146.0 (t, $^{2}J_{(C-F)}$ = 28.5 Hz, Ar-Cq), 135.8 (d, $^{4}J_{(C-F)}$ = 3.0 Hz, Ar-Cq), 123.0 (d, $^{3}J_{(C-F)}$ = 8.2 Hz, 2 × Ar-C), 116.7 (d, $^{2}J_{(C-F)}$ = 22.8 Hz, 2 × Ar-C), 114.0 (t, $^{1}J_{(C-F)}$ = 300.0 Hz, CF_2Br), 106.7 (t, $^{3}J_{(C-F)}$ = 4.7 Hz, Ar-C). ^{19}F NMR (470 MHz, $CDCl_3$): δ −46.6 (2F), −117.1 (1F). IR (film)/cm^{-1}: 3148, 2919, 1581, 1509, 1440, 1212, 1197, 1133, 1078, 966, 802, 734. HRMS (ESI-TOF) m/z: calcd for $C_{10}H_7BrF_3N_2S$ $[M + H]^+$, 322.9465; found, 322.9451.

[4-(Bromodifluoromethyl)-1,3-thiazol-2-yl][p-(1,1,1-trifluoromethyl)phenyl]amine ***(6c)***. Orange oil (125 mg, 86%). Rf 0.6 (30% EtOAc/*n*-hexane). ^{1}H NMR (700 MHz, $CDCl_3$): δ 7.64 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.59 (br s, 1H, NH), 7.49 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.06 (s, 1H, HetAr-H). ^{13}C NMR (176 MHz, CDCl3): δ 164.2 (C═N), 146.9 (t, $^{2}J_{(C-F)}$ = 29.3 Hz, Ar-Cq), 142.4 (Ar-Cq), 127.1 (t, $^{3}J_{(C-F)}$ = 3.7 Hz, Ar-C), 125.5 (q, $^{2}J_{(C-F)}$ = 33.1 Hz, Ar-Cq), 124.2 (q, $^{1}J_{(C-F)}$ = 271.8 Hz, CF_3), 117.7 (2 × Ar-C), 113.9 (t, $^{1}J_{(C-F)}$ = 300.1 Hz, CF_2Br), 107.9 (q, $^{3}J_{(C-F)}$ = 4.6 Hz, 2 × Ar-C). ^{19}F NMR (282 MHz, $CDCl_3$): δ −46.7 (2F), −62.0 (3F). IR (film)/cm^{-1}: 3293, 2918, 2850, 1617, 1535, 1442, 1416, 1325, 1191, 1116, 1067, 968. HRMS (ESI-TOF) m/z: calcd for $C_{11}H_5BrF_5N_2S$ $[M - H]^-$, 370.9277; found, 370.9283.

[4-(Bromodifluoromethyl)-1,3-thiazol-2-yl][p-nitrophenyl]amine ***(6d)***. Orange oil (41 mg, 30%). Rf 0.6 (30% EtOAc/*n*-hexane). ^{1}H NMR (700 MHz, $CDCl_3$): δ 8.28 (d, *J* = 9.0 Hz, 2H, 2 × Ar-H), 7.64 (br s, 1H, NH), 7.58 (d, *J* = 9.0 Hz, 2H, 2 × Ar-H), 7.15 (s, 1H, HetAr-H). ^{13}C NMR (176 MHz, $CDCl_3$): δ 162.7 (C═N), 147.3 (t, $^{2}J_{(C-F)}$ = 29.1 Hz, Ar-Cq), 144.9 (Ar-Cq), 142.8 (Ar-Cq), 125.9 (2 × Ar-C), 116.8 (2 × Ar-C), 113.8 (t, $^{1}J_{(C-F)}$ = 300.1 Hz, CF_2Br), 109.1 (t, $^{3}J_{(C-F)}$ = 4.6 Hz, Ar-C). ^{19}F NMR (470 MHz CDCl3): δ -46.9 (2F). IR (film)/cm^{-1}: 3325, 2923, 2852, 1598, 1526, 1328, 1307, 1259, 1194, 1114, 1072, 968. HRMS (ESI-TOF) m/z: calcd for $C_{10}H_5BrF_2N_3O_2S$ $[M - H]^-$, 347.9254; found, 347.9258.

[4-(Bromodifluoromethyl)-1,3-thiazol-2-yl][1,3,5-trimethylphenyl]amine ***(6e)***. Orange solid (120 mg, 89%). R_f 0.6 (30% EtOAc/*n*-hexane). mp 153−155 °C. ^{1}H NMR (700 MHz, $CDCl_3$): δ 7.83 (br s, 1H, NH), 6.97 (s, 2H, 2 × Ar-H), 6.74 (s, 1H, HetAr-H), 2.32 (s, 3H, CH_3), 2.27 (s, 6H, 2 × CH_3). ^{13}C NMR (176 MHz, $CDCl_3$): δ 172.2 (C═N), 146.9 (t, $^{2}J_{(C-F)}$ = 28.2 Hz, Ar-Cq), 138.6 (Ar-Cq), 136.9 (2 × Ar-Cq), 134.4 (Ar-Cq), 129.9 (2 × Ar-C), 114.2 (t, $^{1}J_{(C-F)}$ = 300.3 Hz, CF_2Br), 106.2 (t, $^{3}J_{(C-F)}$ = 4.9 Hz, Ar-C), 21.2 (CH_3), 18.1 (2 × CH_3). ^{19}F NMR (282 MHz, $CDCl_3$): δ −46.2 (2F). IR (film)/cm^{-1}: 3175, 2921, 2858, 1610, 1574, 1428, 1353, 1192, 1123, 1072, 966, 800. HRMS (ESI-TOF) m/z: calcd for $C_{13}H_{14}BrF_2N_2S$ $[M + H]^+$, 347.0029; found, 347.0025.

[4-(Bromodifluoromethyl)-1,3-thiazol-2-yl]-cyclohexylamine ***(6f)***. Orange oil (113 mg, 75%). R_f 0.6 (30% EtOAc/*n*-hexane). ^{1}H NMR (700 MHz, $CDCl_3$): 7.34 (br s, 1H, *NH*), 7.23 (s, 4H, Ar-H), 6.90 (s, 1H, HetAr-H) 2.52−2.48 (m, 1H, cyclohexyl), 1.92−1.82 (m, 4H, cyclohexyl), 1.78−1.74 (m, 1H, cyclohexyl), 1.44−1.37 (m, 4H, cyclohexyl), 1.28−1.24 (m, 1H, cyclohexyl). ^{13}C NMR (176 MHz, $CDCl_3$): δ 167.1 (C═N), 146.9 (t, $^{2}J_{(C-F)}$ = 28.5 Hz, Ar-Cq), 144.9 (Ar-Cq), 137.3 (Ar-Cq) 128.2 (2 × Ar-C), 120.0 (2 × Ar-C), 114.3 (t, $^{1}J_{(C-F)}$ = 299.9 Hz, CF_2Br) 106.5 (t, $^{3}J_{(C-F)}$ = 4.7, Ar-C), 44.2 (Ph-$CH(CH_2)_2$), 34.7 (2 × CH_2), 27.0 (2 × CH_2), 26.3 (CH_2). ^{19}F NMR (282 MHz, $CDCl_3$): δ −46.5 (2F). IR (film)/cm^{-1}: 3245, 2924, 2851, 1600, 1548, 1515, 1447, 1194, 1121, 1071, 966, 797. HRMS (ESI-TOF) m/z: calcd for $C_{16}H_{18}BrF_2N_2S$ $[M + H]^+$, 387.0342; found, 387.0336.

[4-(Bromodifluoromethyl)-1,3-thiazol-2-yl][4-bromophenyl]amine ***(6g)***. Orange oil (133 mg, 89%). Rf 0.6 (30% EtOAc/*n*-hexane). ^{1}H NMR (700 MHz, $CDCl_3$): δ 7.49 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.27 (d, *J* = 8.8 Hz, 2H, Ar-H), 6.97 (s, 1H, HetAr-H). ^{13}C NMR (176 MHz, $CDCl_3$): δ 165.8 (C═N), 146.6 (t, $^{2}J_{(C-F)}$ = 28.8 Hz, Ar-Cq), 138.6 (Ar-Cq), 132.8 (2 × Ar-C), 120.8 (2 × Ar-C), 116.9 (Ar-Cq), 113.8 (t, $^{1}J_{(C-F)}$ = 300.1 Hz, CF_2Br), 107.1 (t, $^{3}J_{(C-F)}$ = 4.6 Hz, Ar-C). ^{19}F NMR (282 MHz, $CDCl_3$): δ −46.7 (2F). IR (film)/cm^{-1}: 3292, 3122, 2924, 1674, 1592, 1545, 1489, 1308, 1193, 1125, 1072, 967. HRMS (ESI-TOF) m/z: calcd for $C_{10}H_7Br_2F_2N_2S$ $[M + H]^+$, 384.8644; found, 384.8631.

[4-(Bromodifluoromethyl)-1,3-thiazol-2-yl][3-iodophenyl]amine ***(6h)***. Orange oil (142 mg, 85%). R_f 0.6 (30% EtOAc/*n*-hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69 (t, *J* = 2.2 Hz, 1H, Ar-H), 7.46 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.36 (dd, *J* = 8.0, 2.2 Hz, 1H, Ar-H), 7.11 (t, *J* = 8.0 Hz, 1H, Ar-H), 7.00 (s, 1H, HetAr-H). ^{13}C NMR (176 MHz, $CDCl_3$): δ 165.1 (C═N), 147.0 (t, $^{2}J_{(C-F)}$ = 30.9 Hz, Ar-Cq), 140.8 (Ar-Cq), 133.1 (Ar-C), 131.2 (Ar-C), 127.6 (Ar-C), 118.1 (Ar-C), 114.0 (t, $^{1}J_{(C-F)}$ = 299.6 Hz, CF_2Br), 107.5 (t, $^{3}J_{(C-F)}$ = 4.6 Hz, Ar-C), 94.8 (Ar-Cq). ^{19}F NMR (282 MHz, $CDCl_3$): δ −46.7 (s, 2F). IR (film)/cm^{-1}: 3121, 2922, 2851, 1587, 1538, 1474, 1444, 1306, 1194, 1121, 1072, 967. HRMS (ESI-TOF) m/z: calcd for $C_{10}H_7BrF_2IN_2S$ $[M + H]^+$, 430.8526; found, 430.8514.

[4-(Bromodifluoromethyl)-1,3-thiazol-2-yl][4-methansolfonylphenyl]amine ***(6i)***. Brown oil (119 mg, 80%).

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R_f 0.6 (30% *n*-hexane/EtOAc). ^{1}H NMR (700 MHz, acetone-D_6): δ 10.07 (br s, 1H, N−H), 7.97−7.92 (m, 4H, Ar-H), 7.50 (s, 1H, HetAr-H), 3.10 (s, 3H, CH_3).·^{13}C NMR (176 MHz, acetone-D_6): δ 164.8 (C═N), 147.1 (t, $^2J_{(C-F)}$ = 28.5 Hz, Ar-Cq), 145.8 (Ar-Cq), 135.1 (Ar-Cq), 129.8 (2 × Ar-C), 118.0 (2 × Ar-C), 115.3 (t, $^1J_{(C-F)}$ = 298.2 Hz, CF_2Br), 110.6 (t, $^3J_{(C-F)}$ = 4.8, Ar-C), 44.8 (CH_3). ^{19}F (470 MHz, acetone-D_6): δ -47.0 (2F). IR (film)/cm^{-1}: 3308, 3123, 2924, 1596, 1525, 1410, 1322, 1294, 1196, 1141, 1092, 965. HRMS (ESI-TOF) *m*/*z*: calcd for $C_{11}H_8BrF_2N_2O_2S_2$ [M − H]$^-$, 380.9179; found, 380.9185.

[4-(Bromodifluoromethyl)-1,3-thiazol-2-yl][4-hexyloxyphenyl]amine (**6j**). Orange oil (139 mg, 88%). R_f 0.6 (30% EtOAc/*n*-hexane). ^{1}H NMR (700 MHz, DMSO-D_6): δ 10.33 (br s, 1H, NH), 7.47 (d, *J* = 9.1 Hz, 2H, Ar-H), 7.39 (s, 1H, HetAr-H), 6.92 (d, *J* = 9.1 Hz, 2H, Ar-H), 3.92 (t, *J* = 6.7, 2H, O−CH_2−), 1.71−1.65 (m, 2H, CH_2), 1.43−1.37 (m, 2H, CH_2), 1.32−1.27 (m, 4H, 2 × CH_2), 0.89−0.86 (m, 3H, CH_3). ^{13}C NMR (176 MHz, DMSO-D_6): δ 165.5 (C═N), 154.3 (Ar-Cq), 145.1 (t, $^2J_{(C-F)}$ = 27.8 Hz, Ar-Cq), 133.8 (Ar-Cq), 119.5 (2 × Ar-C), 115.0 (2 × Ar-C), 114.5 (t, $^1J_{(C-F)}$ = 298.0 Hz, CF_2Br) 107.9 (t, $^3J_{(C-F)}$ = 4.7, Ar-C), 67.7 (O−CH_2), 31.1 (CH_2), 28.8 (CH_2), 25.3 (CH_2), 22.2 (CH_2), 14.0 (CH_3). ^{19}F NMR (470 MHz, DMSO-D_6): δ −49.9 (2F). IR (film)/cm^{-1}: 3177, 2927, 2857, 1579, 1510, 1435, 1241, 1193, 1122, 1076, 965, 793. HRMS (ESI-TOF) *m*/*z*: calcd for $C_{16}H_{18}BrF_2N_2OS$ [M − H]$^-$, 403.0291; found, 403.0288.

8-[4-(Bromodifluoromethyl)-1,3-thiazol-2-ylamino]-quinoline (**6k**). Orange oil (117 mg, 85%). R_f 0.5 (30% EtOAc/*n*-hexane). ^{1}H NMR (700 MHz, $CDCl_3$): δ 9.97 (br s, 1H, NH), 8.82 (d, *J* = 4.1 Hz, 1H, Ar-H), 8.45 (d, *J* = 8.0 Hz, 1H, Ar-H), 8.18 (d, *J* = 8.2 Hz, 1H, Ar-H), 7.60 (t, *J* = 8.2 Hz, 1H, Ar-H), 7.48 (dd, *J* = 8.0, 4.1 Hz, 1H, Ar-H), 7.46 (d, *J* = 8.2 Hz, 1H, Ar-H), 7.08 (s, 1H, HetAr-H). ^{13}C NMR (176 MHz, $CDCl_3$): δ 163.7 (NH−C═N), 148.1 (Ar-C), 147.1 (t, $^3J_{(C-F)}$ = 28.6 Hz, Ar-Cq), 137.9 (Ar-Cq), 136.5 (Ar-C), 135.9 (Ar-Cq), 128.3 (Ar-Cq), 127.6 (Ar-C), 122.0 (Ar-C), 120.2 (Ar-C), 114.3 (t, $^1J_{(C-F)}$ = 300.3 Hz, CF_2Br), 113.0 (Ar-C), 107.6 (t, $^3J_{(C-F)}$ = 4.6 Hz, Ar-C).^{19}F NMR (282 MHz, $CDCl_3$): δ −46.4 (s, 2F). IR (film)/cm^{-1}: 3126, 2923, 2851, 1574, 1538, 1426, 1329, 1195, 1119, 1072, 964, 789. HRMS (ESI-TOF) *m*/*z*: calcd for $C_{13}H_9BrF_2N_3S$ [M + H]$^+$, 355.9669; found, 355.9663.

N-(Benzo[d][1,3]dioxol-5-yl)-4-(bromodifluoromethyl)-thiazol-2-yl-amine (**6l**). Orange oil (104 mg, 77%). R_f 0.6 (30% EtOAc/*n*-hexane). ^{1}H NMR (700 MHz, $CDCl_3$): δ 7.38 (br s, 1H, NH), 6.90−6.87 (m, 2H, 1 × Ar-H overlapping 1 × HetAr-H), 6.81 (d, *J* = 8.2 Hz, 1H, Ar-H), 6.79−6.76 (m, 1H, Ar-H), 6.01 (s, 2H, O−CH_2−O). ^{13}C NMR (126 MHz, $CDCl_3$): δ 168.5 (C═N), 148.7 (Ar-Cq), 146.9 (t, $^2J_{(C-F)}$ = 28.4 Hz, Ar-Cq), 145.6 (Ar-Cq), 133.8 (Ar-Cq), 115.1 (Ar-C), 114.1 (t, $^1J_{(C-F)}$ = 300.1 Hz, CF_2Br), 108.9 (Ar-C), 106.6 (t, $^3J_{(C-F)}$ = 4.8 Hz, Ar-C), 103.9 (Ar-C), 101.8 (O−CH_2−O). ^{19}F NMR (282 MHz, $CDCl_3$): δ −46.6 (2F). IR (film)/cm^{-1}: 3418, 2091, 1634, 1505, 1488, 1451, 1238, 1188, 1123, 1071, 1038, 968. HRMS (ESI-TOF) *m*/*z*: calcd for $C_{11}H_6BrF_2N_2O_2S$ [M − H]$^-$, 346.9301; found, 346.9306.

2-[4-((4-(Bromodifluoromethyl)thiazol-2-yl)amino)-phenyl]propanoic Acid (**Br-DF2755Y**). Yellow solid (683 mg, 60%). R_f 0.6 (30% *n*-hexane/EtOAc). ^{1}H NMR (500 MHz, CD3CN): δ 8.55 (br s, 1H, NH), 7.51 (d, *J* = 8.5 Hz, 2H, Ar-H), 7.30 (d, *J* = 8.5 Hz, 2H, Ar-H), 7.15 (s, 1H, HetAr-H), 3.70 (q, *J* = 7.2 Hz, 1H, CH), 1.42 (d, *J* = 7.2 Hz, 3H, CH_3). ^{13}C NMR (126 MHz, CD_3CN): δ 176.0 (C═O), 166.3 (C═N), 146.8 (t, $^2J_{(C-F)}$ = 28.2 Hz, Ar-Cq), 140.2 (Ar-Cq), 136.6 (Ar-Cq), 129.2 (2 × Ar-C), 119.3 (2 × Ar-C), 115.4 (t, $^1J_{(C-F)}$ = 297.9 Hz, CF_2Br), 109.0 (t, $^3J_{(C-F)}$ = 4.9 Hz, Ar-C), 45.1 (CH), 18.7 (CH_3). ^{19}F NMR (470 MHz, $CDCl_3$): δ −51.3 (2F). HRMS (ESI-TOF) *m*/*z*: calcd for $C_{13}H_{10}BrF_2N_2O_2S$ [M − H]$^-$, 374.9614; found, 374.9631.

Procedure for the Synthesis of 4-(bromodifluoromethyl)thiazol-2-amine (8). To a solution of thiourea (30 mg, 0.39 mmol) in dry acetonitrile (500 μL) in a sealed tube, 1,3-dibromo-1,1-difluoropropan-2-one (**3a**) (100 mg, 0.39 mmol) was added dropwise, and the mixture was heated to 80 °C for 3 h. The reaction crude was diluted with ethyl acetate (3 mL) and washed with hexane. The organic phase was filtered and the solvent was removed under reduced pressure to afford thiazole **8** as a yellow solid (complete conversion). R_f 0.8 (30% EtOAc/*n*-hexane). ^{1}H NMR (700 MHz, $CDCl_3$): δ 6.88 (s, 1H, HetAr-H), 5.18 (br s, 2H, NH_2). ^{13}C NMR (176 MHz, $CDCl_3$): δ 168.3 (C═N), 146.7 (t, $^2J_{(C-F)}$ = 28.3 Hz, Ar-C_q), 114.0 (t, $^1J_{(C-F)}$ = 299.6 Hz, CF_2Br), 108.1 (t, $^3J_{(C-F)}$ = 4.9 Hz, Ar-C). ^{19}F NMR (282 MHz, $CDCl_3$): δ −46.5 (2F). IR (film)/cm^{-1}: 3290, 3121, 2925, 1722, 1633, 1548, 1471, 1286, 1196, 1122, 1072, 963. HRMS (ESI-TOF) *m*/*z*: calcd for $C_4H_4BrF_2N_2S$ [M + H]$^+$, 228.9241; found, 228.9251.

General Procedure for Br/F Exchange Reactions. Procedure A for conversion of **8** to **9** is reported. To a solution of **8** (25 mg, 0.11 mmol) in acetonitrile (500 μL) in a sealed tube, silver triflate (28 mg, 0.11 mmol), potassium fluoride (13 mg, 0.22 mmol), and Kriptofix (83 mg, 0.22 mmol) were consecutively added, and the mixture was stirred at room temperature until TLC or ^{19}F NMR sampling revealed the full conversion. The crude was diluted with ethyl acetate (3 mL) and washed with water (3 × 3 mL). The organic phase was dried over sodium sulfate and the solvent was removed under vacuum. Filtration on a pad of silica provided the analytically pure product. Procedure B was used for conversion of **Br-DF2755** to **DF2755Y**. To a solution of potassium fluoride (58 mg, 1.00 mmol) and Kriptofix (83 mg, 0.22 mmol) in dry DMF (0.5 mL) at 80 °C in a sealed tube, **Br-DF2755** (25 mg, 0.11 mmol) in 0.5 mL of dry DMF was added dropwise. The mixture was stirred at 80 °C for 5 min, cooled at room temperature, and 2 mL of a 1 M aqueous solution of HCl were added. The crude was extracted with ethyl acetate (3 × 3 mL), the organic phase was dried over sodium sulfate, and the solvent was removed under vacuum. Treatment with CH_2Cl_2 (2 mL) led to the precipitation of **DF2755Y** in an analytically pure form.

4-(Trifluoromethyl)-2-aminothiazole (**9**). Isolated as orange oil (17 mg, 90%) following the general procedure, full conversion was observed after stirring at room temperature for 16 h. ^{19}F NMR (470 MHz, $CDCl_3$): δ −64.8 (3F). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.90 (s, 1H), 6.00 (br s, 2H). Data are consistent with literature.[24]

[4-(Trifluoromethyl)-1,3-thiazol-2-yl](p-tolyl)amine (**7a**). Isolated as yellow oil (9 mg, 92%) following the general procedure, full conversion was observed after stirring at room temperature for 5 min. ^{1}H NMR (700 MHz, $CDCl_3$): δ 7.40 (br s, 1H, NH), 7.23−7.16 (m, 4H, Ar-H), 7.00 (s, 1H, HetAr-H), 2.35 (s, 3H, CH_3). ^{13}C NMR (176 MHz, $CDCl_3$): δ 167.9 (C═N), 140.9 (q, $^2J_{(C-F)}$ = 37.0 Hz, Ar-C_q), 137.1 (Ar-C_q),

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134.7 (Ar-C_q), 130.4 (2 × Ar-C), 120.5 (q, $^1J_{(C-F)}$ = 269.9 Hz, CF_3), 120.2 (2 × Ar-C), 109.0 (q, $^3J_{(C-F)}$ = 4.6 Hz, Ar-C), 21.0 (CH_3). ^{19}F NMR (282 MHz, $CDCl_3$): δ -65.1 (3F). IR (film)/cm^{-1}, 3196, 2924, 2854, 1600, 1552, 1514, 1375, 1231, 1166, 1132, 1079, 931. HRMS (ESI-TOF) m/z: calcd for $C_{11}H_8F_3N_2S$ $[M - H]^-$, 257.0360; found, 257.0366.

*N-(4-(Hexyloxy)phenyl)-4-(trifluoromethyl)thiazol-2-amine (**7j**).* Isolated as brown oil (19 mg, 87%) following the general procedure, full conversion was observed after stirring at room temperature for 15 min. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.43 (br s, 1H, *NH*), 7.23 (d, J = 8.9 Hz, 2H, Ar-*H*), 6.94 (s, 1H, HetAr-*H*), 6.92 (d, J = 8.9 Hz, 2H, Ar-*H*), 3.96 (t, J = 6.6 Hz, 2H, O−CH_2), 1.82−1.75 (m, 2H, CH_2), 1.50−1.43 (m, 2H, CH_2), 1.37−1.32 (m, 4H, 2 × CH_2), 0.91 (t, J = 6.9 Hz, 3H, CH_3). ^{13}C NMR (126 MHz, $CDCl_3$): δ 169.7 (C═N), 157.3 (Ar-C_q), 140.9 (q, $^2J_{(C-F)}$ = 37.0 Hz, Ar-C_q), 132.5 (Ar-C_q), 123.8 (2 × Ar-C), 120.5 (q, $^1J_{(C-F)}$ = 269.9 Hz, CF_3), 115.7 (2 × Ar-C), 108.8 (q, $^3J_{(C-F)}$ = 4.0 Hz, Ar-C), 68.5 (O−CH_2), 31.7 (CH_2), 29.4 (CH_2), 25.9 (CH_2), 22.8 (CH_2), 14.2 (CH_3). ^{19}F NMR (470 MHz, $CDCl_3$): δ −65.2 (3F). IR (film)/cm^{-1}: 3407, 3205, 2951, 1596, 1568, 1513, 1248, 1175, 1163, 1133, 1024, 737. HRMS (ESI-TOF) m/z: calcd for $C_{16}H_{18}F_3N_2OS$ $[M - H]^-$, 343.1092; found, 343.1096.

*(S)-2-(4-((4-(Trifluoromethyl)thiazol-2-yl)amino)phenyl)-propanoic Acid (**DF2755Y**).* Isolated as white solid (10 mg, 85%) following the general procedure, full conversion was observed after stirring at 80 °C for 20 min. $[\alpha]_D^{27}$ (c 1, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.25 (br s, 1H, NH), 7.40 (d, 2H, J = 7 Hz), 7.25 (d, 2H, J = 7 Hz), 7.00 (s, 1H), 3.80 (q, 1H, J = 7 Hz), 1.55 (d, 3H, J = 7 Hz). ^{19}F NMR (282 MHz, acetone-D_6): δ −65.6 (3F). HRMS (ESI-TOF) m/z: calcd for $C_{13}H_{10}F_3N_2O_2S$ $[M - H]^-$, 315.0415; found, 315.0449. Data are consistent with those reported into the literature.[25]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.8b02273.

Characterization of new compounds (^{1}H, ^{13}C, and ^{19}F NMR spectra) (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: andrea.aramini@dompe.com (A.A.).
*E-mail: leonardo.degennaro@uniba.it (L.D.).
*E-mail: renzo.luisi@uniba.it (R.L.).

ORCID

Leonardo Degennaro: 0000-0002-2187-9419
Renzo Luisi: 0000-0002-9882-7908

Notes

The authors declare no competing financial interest.

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