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Synthesis of 2-Fluoro-1,4-benzoxazines and 2-Fluoro-1,4-benzoxazepin-5-ones by Exploring the Nucleophilic Vinylic Substitution (S_NV) Reaction of *gem*-Difluoroenamides

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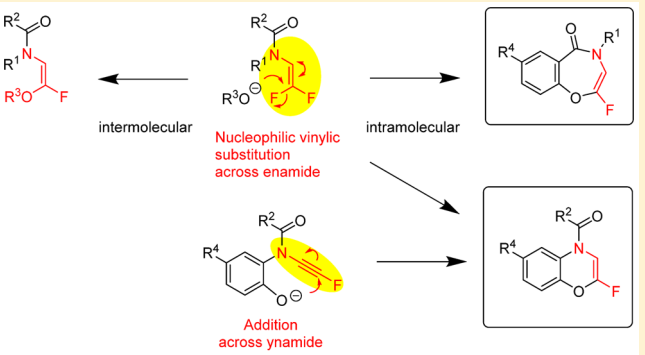
Supporting Information

ABSTRACT: *N*-Benzoyl *β*,*β*-difluoroenamides and *N*-benzoyl fluoroynamides are novel structural units which have been explored as precursors in heterocyclic synthesis. The presence of two fluorine atoms at the *β*-position of the enamide moiety endows unique electrophilic reactivity. Treatment of these enamides with oxygen nucleophiles gives rise to a nucleophilic vinylic substitution (S_NV) reaction, which was directed toward 2-fluoro-1,4-benzoxazines and 2-fluoro-1,4-benzoxazepin-5-ones. Furthermore, fluorinated ynamides, a new type of building block, were prepared in excellent yields for the first time. In this case, *β*-addition of nucleophiles across the triple bond is observed also.



INTRODUCTION

Enamides represent an interesting group of compounds because they demonstrate an enhanced stability as compared to enamines but still exhibit a rather nucleophilic reactivity.[1] A significant amount of research has already been devoted to the class of *β*,*β*-dihaloenamines and *β*,*β*-dihalogenated enamides.[2] In contrast, while some difluorinated enamines have been used as building blocks, for example, in the synthesis of difluorocysteine and -serine derivatives,[3] dipeptides,[4] difluoroimines,[5] and various *α*,*α*-difluoro-*β*-hydroxycarbonyl compounds,[6] the chemistry of difluoroenamides has received only very limited attention. To our knowledge, this reactivity was exploited only twice toward the synthesis of fluorinated heterocycles, more specifically toward isoxazolidines and dihydropyrans[7] or oxazoles.[8] Furthermore, one example was found in which the intermediacy of a difluoroenamide was postulated in the synthesis of morpholino-fused diketopiperazines.[9] Also, while *gem*-difluoroalkenes have been used in a nucleophilic vinylic substitution (S_NV) reaction for the synthesis of a variety of fluorinated heterocycles,[10] their nitrogen-substituted analogues have received less attention. This is remarkable because the presence of two fluorine atoms at the *β*-carbon atom of enamide **3** in combination with an electron-withdrawing acyl or sulfonyl group (R^2) at nitrogen will lead to a highly polarized double bond and an electron-deficient difluorinated carbon atom (Figure 1). If this effect could predominate in the electron-donating effect of the enamide nitrogen atom, enamide **3** would be an example of an electrophilic enamide readily reacting with nucleophiles. In this way, the introduction of two fluorine atoms at the *β*-position

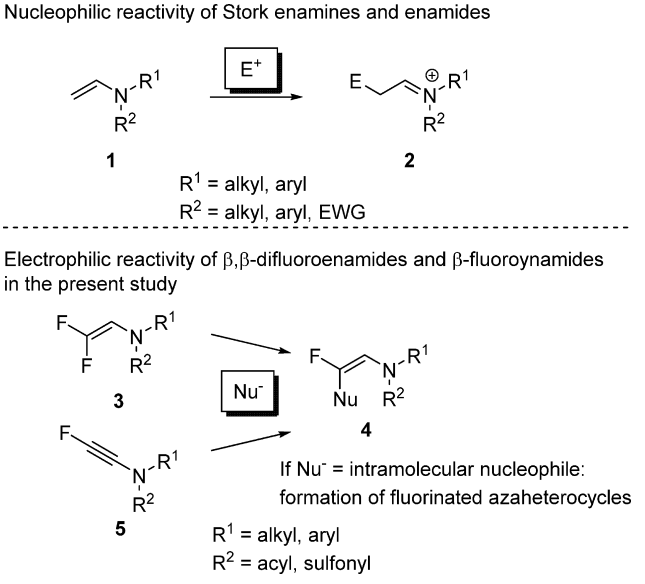


Figure 1. Comparison between the reactivity of Stork enamines and enamides **1**, difluoroenamides **3**, and fluoroynamides **5**.

could be seen as an efficient way to induce umpolung of the enamide functionality.[11] The potential to use this reactivity in a way that fundamentally deviates from the reactivity of Stork enamines and enamides **1**[12] is the basis of the present study

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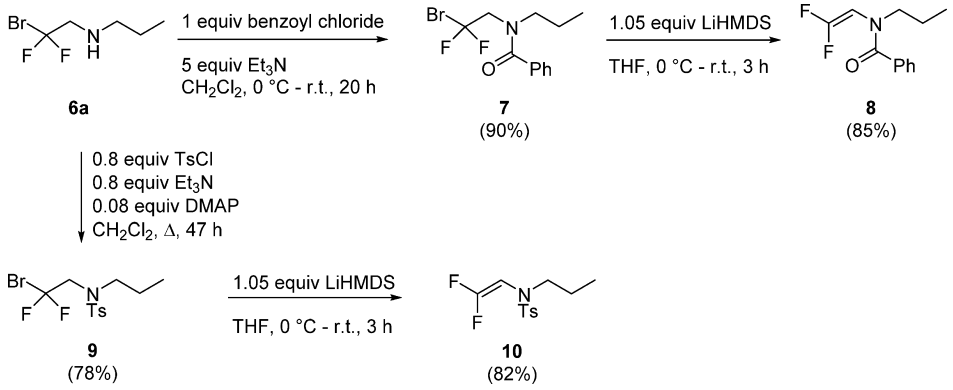
Scheme 1. Synthesis of Enamides 8 and 10



(Figure 1). Treatment of these difluoroenamides **3** and the corresponding hitherto unexplored fluorinated ynamides **5** with nucleophiles may lead to the formation of *β*-fluoroenamides **4**. By incorporating the nucleophile in the enamide, this method could give rise to the formation of fluorinated heterocycles such as 1,4-benzoxazines and 1,4-benzoxazepin-5-ones.

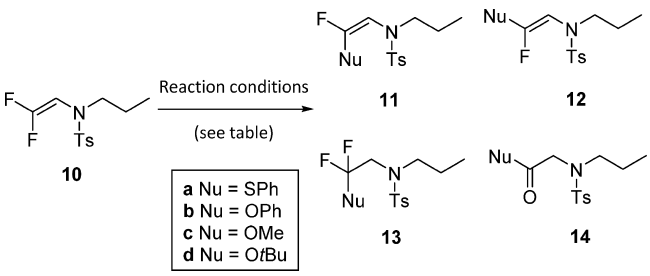
1,4-Benzoxazines have been shown to possess interesting biological activities.[13] An example of a natural product containing the 1,4-benzoxazine core is cappamensin A, which was isolated from the roots of the native Taiwanese shrub *Capparis sikkimensis*, and shows promising antitumor activity.[14] Another interesting class of benzo-fused heterocycles comprises 1,4-benzoxazepin-5-ones. An important example of this type of compound is piclozotan, a selective 5-HT_{1A} receptor partial agonist, showing in vivo neuroprotective effects.[15] Due to fluorine's unique properties (high electronegativity, small van der Waals radius),[16] its introduction in organic compounds can induce significant changes in their chemical and pharmacological properties.[17] Therefore, in the pharmaceutical industry, there is a great interest in the synthesis of fluorinated compounds, with a profound focus on heterocyclic compounds.[18] Although benzoxazines and benzoxazepines containing a CF_3 group have already been synthesized,[19] examples of compounds carrying the fluorine substituent directly attached to the heterocyclic ring are barely known.[20] Only one example of a 2-fluoro-1,4-benzoxazine derivative was found in the literature.[21] Additionally, no reports were found on the synthesis of 2- or 3-fluoro-1,4-benzoxazepin-5-ones. In view of these gaps in the chemistry of fluorinated benzo-fused heterocycles, a synthetic route toward 2-fluoro-1,4-benzoxazines and 2-fluoro-1,4-benzoxazepin-5-ones was developed, exploiting the unique electrophilic reactivity of difluorinated enamides and elusive fluorinated ynamides.

RESULTS AND DISCUSSION

In the first part of this work, the synthesis of novel difluoroenamides **8** and **10** was developed (Scheme 1). To this end, amine **6a**[22] was protected as benzamide **7** or tosylamide **9** in good yield by treatment with benzoyl chloride or *p*-toluenesulfonyl chloride, respectively, in dichloromethane in the presence of a base. In the next step, treatment of benzamide **7** and tosylamide **9** with LiHMDS in THF, to achieve dehydrobromination, smoothly led to the formation of new difluorinated enamides **8** and **10** (82−85% yield).

Subsequently, the reactivity of enamide **10** toward sulfur and oxygen nucleophiles was investigated (Table 1). Reaction with thiophenol afforded a mixture of the isomeric fluorinated

Table 1. Reactivity of Difluorinated Enamide 10 toward Nucleophiles



entry	nucleophile (equiv)	reaction conditions	ratio **11**:**12**:**13**:**14**	compound (%)[a]
1	thiophenol (1.2)	1.2 equiv of KOH, CH_3CN, 82 °C, 20 h	8:2:0:0	**11a** (69)
2	phenol (1.2)	1.2 equiv of KOH, CH_3CN, 82 °C, 20 h	4:2:1:3	**13b** (10) + **14b** (85)[b]
3	phenol (1.2)	1.2 equiv of KOH, CH_3CN, 82 °C, 20 h	4:2:1:3	**11b**/**12b** (32)[c]
4	NaOMe (1.1)[d]	THF, rt, 3 h	8:2:0:0	**11c** (57) + **12c** (15)
5	KO*t*Bu (1.1)	THF, 0 °C to rt, 2 h	8:2:0:0	**11d** (46)

[a]Isolated yield. [b]Formed due to hydrolysis of **11b**/**12b** upon prolonged exposure to silica. [c]Ratio **11b**:**12b** = 8:2; the isomers could not be separated. [d]1 M in MeOH.

enamides **11a** and **12a** (ratio **11a**:**12a** = 8:2) from which enamide **11a** could be isolated in 69% yield (Table 1, entry 1). *β*-Fluoroenamides **11a** and **12a** are the products of a nucleophilic substitution at the vinylic CF_2 carbon atom of enamide **10**, most probably via a nonconcerted two-step process (S_NV reaction),[10a,23] i.e., addition of the nucleophile across the double bond is followed by elimination of fluoride. When enamide **10** was treated with 1.2 equiv of phenol in the presence of KOH, four different products were detected in the reaction mixture after workup, i.e., the isomeric enamides **11b** and **12b**, addition product **13b**, and amino ester **14b**, in a ratio of **11b**:**12b**:**13b**:**14b** = 4:2:1:3. After purification of this mixture (column chromatography, SiO_2), only two compounds were isolated, more specifically adduct **13b** (10%) and amino ester **14b** (85%) (Table 1, entry 2). Apparently, enamides **11b** and **12b** were not stable upon prolonged exposure to SiO_2 and hydrolyzed toward amino ester **14b**. When the reaction of enamide **10** with phenol was repeated and the reaction mixture was purified via flash column chromatography (SiO_2), a mixture of isomers **11b** and **12b** was isolated in 32% total yield (ratio **11b**:**12b** = 8:2) (Table 1, entry 3). Furthermore, the reaction of

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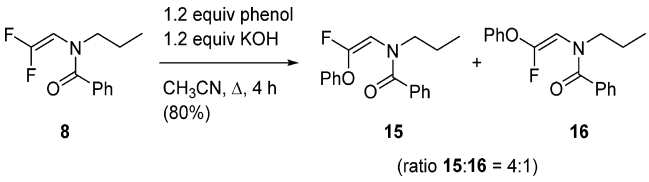
enamide **10** with both NaOMe (in MeOH/THF) and KO*t*Bu (in THF) resulted in smooth conversion toward a mixture of isomers **11** and **12**.

These *β*-fluoroenamides are new compounds and the differentiation between the two isomeric *β*-fluoroenamides **11** and **12** could be made based on comparison of the value of the vicinal coupling constant $^{3}J_{H,F}$ of the signal of the hydrogen atom at the *α* position of the vinylic double bond. More specifically, in the case of oxygen-substituted monofluorinated enamides **11b−d** and **12b−d**, *Z*-$^{3}J_{H,F}$ (H and F in a *Z* configuration) has a value of 0.7−1.7 Hz, while *E*-$^{3}J_{H,F}$ (H and F in an *E* configuration) results in a much larger value of 19−22 Hz. For the sulfur analogues **11a** and **12a**, larger coupling constants were observed, with a value of 5.5 Hz for *Z*-$^{3}J_{H,F}$ and a larger value of 25.0 Hz for *E*-$^{3}J_{H,F}$.

Furthermore, the reaction of enamide **8** with phenol also led to the formation of a mixture of enamides **15** and **16**, which could not be separated via column chromatography, in 80% yield (Scheme 2).

Scheme 2. Reaction of Difluoroenamide 8 with Phenol



A possible explanation of the moderate stereoselectivity of this addition−elimination reaction toward enamides **11** and **15** (H and F in a *Z* configuration) can be found by evaluating the preferred conformation of the intermediate carbanions after addition of the nucleophile (Figure 2). To allow fluoride

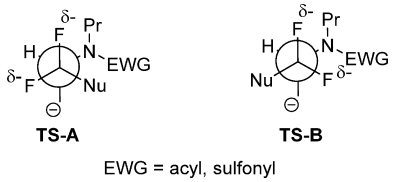


Figure 2. Possible transition state models in the addition−elimination reaction.

elimination, the lone pair of the intermediate carbanion and the fluorine atom must adopt antiperiplanar positions, which is the case in two possible transition state models **TS-A** and **TS-B**. In **TS-B**, the substituted nitrogen atom is situated in a gauche conformation between the two fluorine atoms, generating an important electronic repulsion. In **TS-A**, only one repulsive interaction between the nitrogen atom and fluorine is present, rendering this conformer energetically more favored. On the other hand, in **TS-A** a mild sterical hindrance is present between the nitrogen atom and the nucleophile. The combination of these two factors, more specifically electronic repulsion (which is the main factor) and sterical hindrance, leads to the moderate stereoselectivity.[24]

An alternative pathway for the formation of the substituted enamides **11**, **12**, **15**, and **16** comprises initial formation of the corresponding ynamide due to a base-promoted elimination of HF from enamides **8** and **10**, followed by the addition of the nucleophile. In this case, however, formation of the ynamide moiety by dehydrofluorination would result in protonation of the nucleophile and formation of the conjugated acid. For example, if treatment of enamide **10** with NaOMe (Table 1, entry 4) would lead to the corresponding ynamide, MeOH should be a good nucleophile to add across the triple bond. However, upon stirring ynamide **25a** (vide infra) in MeOH for a prolonged time, no addition of MeOH was observed. Therefore, it is believed that these transformations operate through an initial addition of the nucleophile, followed by elimination of fluoride.

In a next part, this promising methodology was expanded to the synthesis of novel heterocyclic monofluorinated compounds by incorporating the oxygen nucleophile and the electrophilic difluoroenamide unit in the same precursor, thus enabling an intramolecular vinylic nucleophilic substitution. In view of the synthesis of fluorinated six- and seven-membered heterocycles, the precursor had to contain a two- or three-carbon linker between the enamide nitrogen atom and the nucleophilic oxygen atom. For the synthesis of the six-membered analogues, i.e., 2-fluoro-1,4-benzoxazines, 2-aminophenols **17a** and **17b** were chosen as the building blocks (Scheme 3).

In the first step, the reaction of phenols **17** with ethyl bromodifluoroacetate **18** proceeded selectively toward amides **19**. Protection of the phenolic oxygen atom was achieved by treatment of benzamides **19** with TBDMSCl in the presence of imidazole. Amides **20** were in turn reduced toward the secondary amines **21** using an excess of borane dimethylsulfide complex in CH_2Cl_2. The next step involved the protection of the nitrogen atom of amines **21**. Because the introduction of a tosyl group proceeded very slowly, the use of a benzoyl protecting group was evaluated instead. Treatment of *β*-bromo-*β*,*β*-difluoroamines **21** with different benzoyl chlorides **22** in the presence of Et_3N led to the formation of *N*-(2-bromo-2,2-difluoroethyl)benzamides **23** as suitable precursors for the synthesis of fluorinated 1,4-benzoxazines.

The key step in the reaction sequence concerned the conversion of precursors **23** toward the envisioned 1,4-benzoxazines (Table 2). Therefore, benzamide **23a** was treated with LiHMDS, which led to the formation of a mixture of difluoroenamide **24a** and fluorinated ynamide **25a**, resulting from the LiHMDS-induced elimination of HF from enamide **24a** (Table 2, entry 1). Increasing the number of equivalents of LiHMDS led to a full conversion of amide **23a** toward ynamide **25a**, which was isolated in an excellent yield of 97% (Table 2, entry 2). The formation of ynamide **25a** can be explained by C−F bond activation by coordination of fluorine to the silicon atom in the *tert*-butyldimethylsilyl protecting group, enhancing the leaving group capacity of fluoride.[10a,25] This could also explain why amides **7** and **9** were not converted into the corresponding ynamides upon treatment with LiHMDS. Next, benzamide **23a** was treated with 1 equiv of KO*t*Bu, leading to a selective conversion toward the envisioned benzoxazine **26a**, which could be isolated in 80% yield (Table 2, entry 3). Because the use of LiHMDS or KO*t*Bu led to a different reaction outcome, other bases were evaluated in order to investigate the possible reaction pathway. It was remarkable that the cleavage of the silyl ether did not occur upon treatment of benzamide **23a** with 2.2 equiv of LiHMDS, even though under these conditions fluoride is expelled from the substrate (Table 2, entry 2). To test the influence of the cation, the reaction was repeated with NaHMDS and KHMDS (Table 2, entries 4 and 5). Thus, benzamide **23a** was treated with 1 equiv

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Scheme 3. Synthesis of Benzamides 23

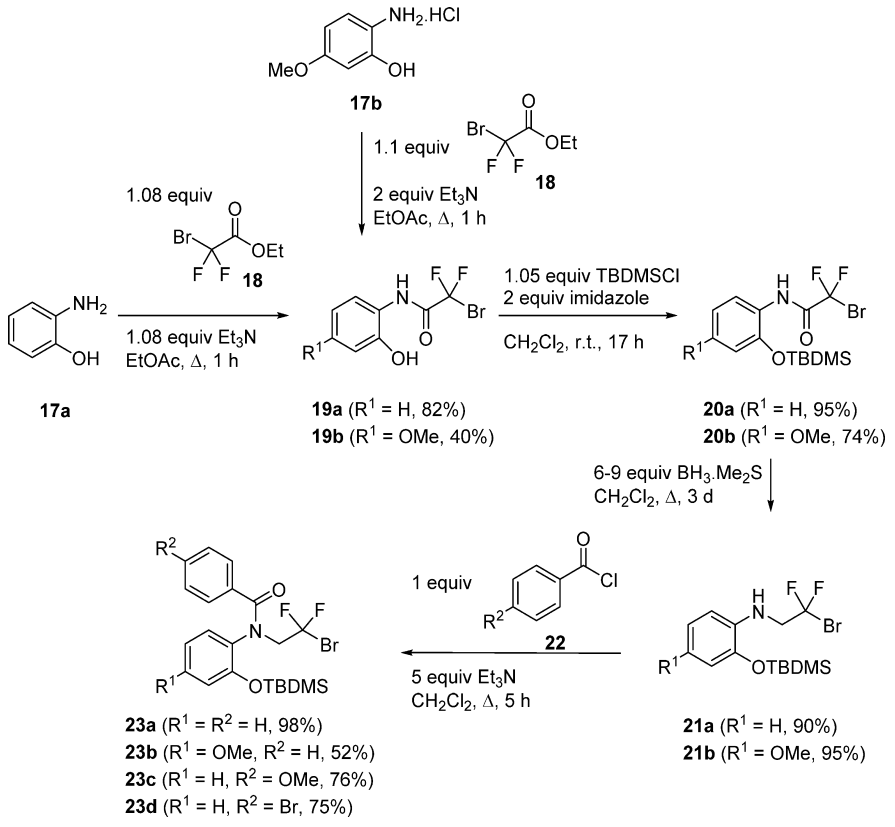
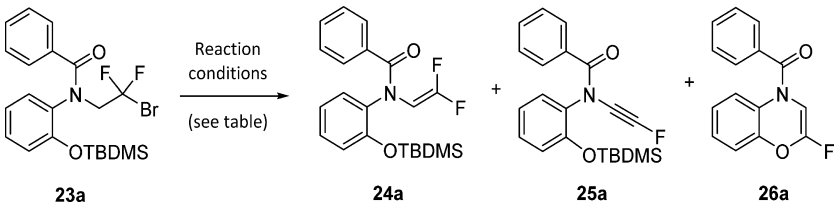


Table 2. Reactivity of Benzamide 23a toward Different Bases



entry	reaction conditions	ratio **23a**:**24a**:**25a**:**26a**	compound (%)[a]
1	1.1 equiv of LiHMDS, THF, 0 °C, 3 h	3:3:4:0	–
2	2.2 equiv of LiHMDS, THF, rt, 2.5 h	0:0:1:0	**25a** (97)
3	1 equiv of KO*t*Bu, THF, rt, 2 h	0:0:0:1	**26a** (80)
4	2 equiv of NaHMDS[b], THF, rt, 6 h	0:4:0:6	–
5	2 equiv of KHMDS[b], THF, rt, 6 h	0:0:0:1	**26a** (54)
6	1 equiv of LiO*t*Bu, THF, 66 °C, 1.5 h	0:1:0:0	**24a** (73)

[a]Isolated yield. [b]Second equivalent was added after 3 h.

of NaHMDS. LC-MS analysis of the reaction mixture after 15 min indicated the presence of four compounds, i.e., benzamide **23a**, enamide **24a**, ynamide **25a**, and benzoxazine **26a**. Follow-up via LC-MS indicated no further progress of the reaction, so an extra 1 equiv of NaHMDS was added after 3 h. After being stirred for an additional 3 h, the reaction was stopped and a mixture of enamide **24a** and benzoxazine **26a** was obtained in a ratio of 4:6, which could not be separated via column chromatography (Table 2, entry 4). Subsequently, benzamide **23a** was treated with 1 equiv of KHMDS, which also led to the formation of a mixture of compounds **23a**, **24a**, **25a**, and **26a** after 15 min of reaction at room temperature. Also in this case, an extra 1 equiv of base was added after 3 h, and the reaction was stopped after an additional 3 h. After workup, only benzoxazine **26a** was detected, so it was assumed that both enamide **24a** and ynamide **25a** were intermediates in the formation of benzoxazine **26a**. It was concluded that the cation of the base plays an important role in the reaction outcome due to the different properties of the corresponding fluoride salts. Upon use of LiHMDS as the base, the reaction terminates at the stage of ynamide **25a** in which the silyl ether is not deprotected, so apparently the fluoride anion in LiF is not available for this reaction. When KHMDS is used, KF is formed, in which the fluoride anion is available for the deprotection reaction, because this reaction leads to the formation of benzoxazine **26a** after ring closure. This reactivity of alkali-metal fluorides may be explained by the higher lattice energy of LiF in comparison with NaF and KF.[26] Following

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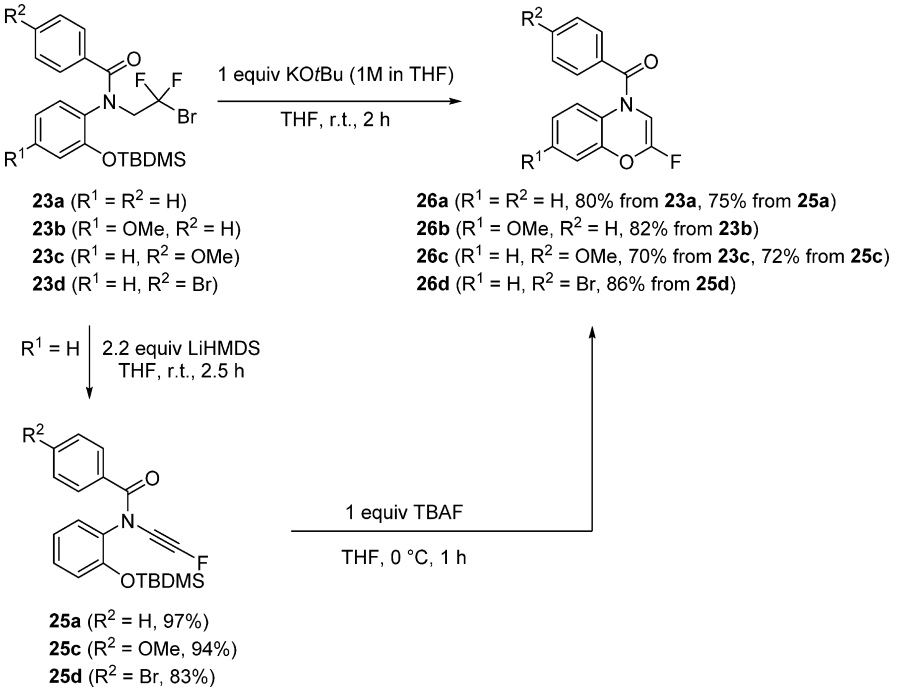
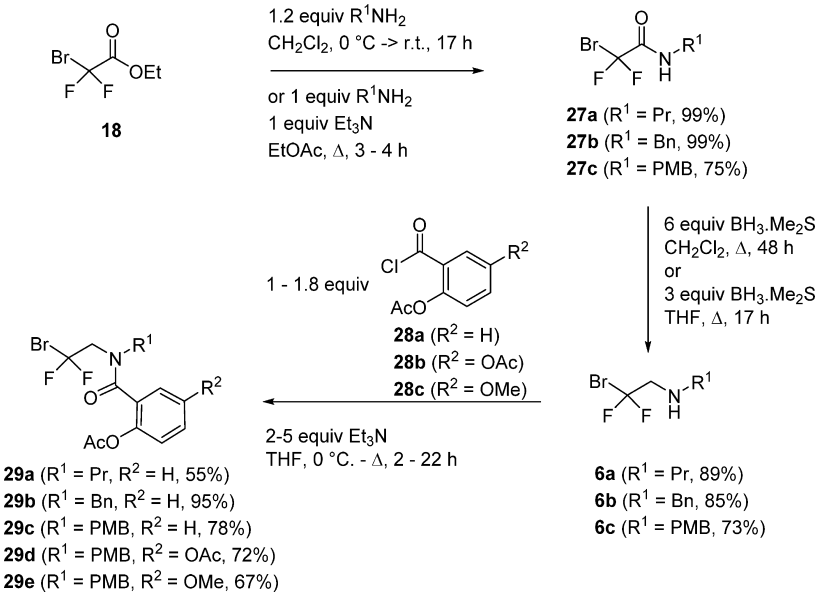
Scheme 4. Transformation of Benzamides 23 into Ynamides 25 and Benzoxazines 26



Scheme 5. Synthesis of Benzamides 29



these results, the use of LiO*t*Bu should also lead to the formation of a TBDMS-protected end product. Indeed, the reaction of benzamide **23a** with 1 equiv of LiO*t*Bu afforded enamide **24a** as the sole end product, which was isolated in 73% yield (Table 2, entry 6).

Subsequently, the optimized reaction conditions were used to convert benzamides **23a–d** toward benzoxazines **26** and ynamides **25** in good to excellent yields (Scheme 4). In an attempt to prove the intermediacy of ynamides **25** in the formation of benzoxazines **26**, compounds **25** were treated with TBAF in THF, which led directly to the formation of benzoxazines **26**. The triple bond in ynamides **25** has an electrophilic reactivity which is prone to nucleophilic attack by the phenolic oxygen atom, leading to a smooth conversion toward benzoxazines **26** (Scheme 4).

The chemistry of halogenated ynamides has only been explored to a limited extent. While 2-iodoynamides have been used in for example cycloaddition[27] and benzannulation[28] reactions, the synthesis and reactivity of fluorinated ynamides is a totally unexplored field in organic chemistry. Only one report has been published in which the formation of a fluorinated ynamine was described, albeit in a very low yield of 5%.[29] Over the last years, the chemistry of ynamides has received much attention.[30] Due to the polarization of the triple bond, α-addition of nucleophiles across the triple bond is more common than β-addition, although a few examples of β-addition have been described.[31] Umpolung of the ynamide

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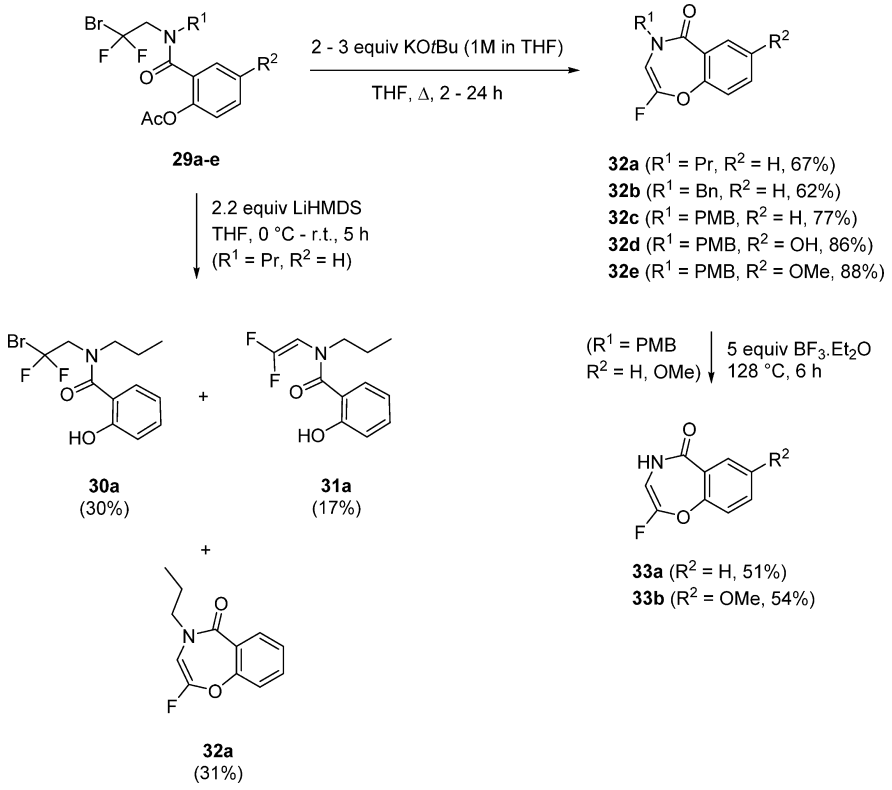
Scheme 6. Conversion of Benzamides 29 into Benzoxazepinones 32



functionality, leading to addition of nucleophiles at the β-position, is usually achieved via a metal-catalyzed reaction. In this work, umpulong is achieved by the presence of a fluorine substituent at the β-position of the ynamide in combination with the electron-withdrawing group at nitrogen, leading to selective addition of the oxygen nucleophile at the β-position without the need of a metal catalyst.

In the last part of this work, the synthesis of novel fluorinated benzo-fused seven-membered rings was developed. In the precursor, a three-carbon atom-containing linker had to be positioned between the enamide nitrogen atom and the oxygen nucleophile, in order to be able to form a seven-membered ring via the vinylic nucleophilic substitution reaction. In the synthetic route toward benzoxazines **26**, the oxygen nucleophile was already incorporated in the fluorinated secondary amines **21**, after which a benzoyl protecting group was introduced at nitrogen (Scheme 3). In the synthetic route toward the seven-membered ring analogues, it was chosen to incorporate the oxygen nucleophile in the aroyl group attached to nitrogen (Scheme 5). Therefore, a variety of secondary fluorinated amines was synthesized by reacting ethyl bromodifluoroacetate **18** with different amines, leading to amides **27**, which in turn were reduced using borane dimethylsulfide complex in dichloromethane under reflux. Subsequently, a functionalized benzoyl group was introduced at the nitrogen atom by treatment with *O*-acetylsalicyloyl chloride **28a**, leading to the formation of benzamides **29a−c**. Benzamides **29** are suitable precursors for the synthesis of fluorinated seven-membered rings, because there is a three-carbon linker in between the nitrogen and oxygen atom. An advantage of this synthetic route is the possibility of a late stage functionalization, because various derivatives of 2-acetylsalicylic acid can be used for the introduction of the group at nitrogen. For example, acetylsalicyloyl chlorides **28b,c**, which were prepared from the corresponding carboxylic acids by reaction with thionyl chloride, were reacted with amine **6c**, leading to the formation of benzamides **29d,e** (Scheme 5).

To achieve the ring closure, benzamide **29a** (R^1 = Pr, R^2 = H) was treated with 2.2 equiv of LiHMDS, which led to the formation of a mixture of three reaction products, i.e., benzamide **30a**, enamide **31a**, and benzoxazepinone **32a** (Scheme 6). The composition of this reaction mixture supports the intermediacy of enamide **31a** in the formation of benzoxazepinone **32a**. Subsequently, the use of KO*t*Bu was evaluated for the conversion of benzamides **29** into benzoxazepinones **32**. In that regard, benzamides **29a−e** were stirred in THF under reflux in the presence of KO*t*Bu, which gave a clean conversion toward the envisioned benzoxazepinones **32a−e** (Scheme 6). In a last step, the deprotection of benzoxazepinones **32c,e** was achieved by heating in the presence of 5 equiv of boron(III) fluoride etherate resulting in 4*H*-benzoxazepinones **33a,b**, enabling further functionalization of this scaffold.

CONCLUSIONS

In conclusion, a straightforward synthesis toward novel 2-fluoro-1,4-benzoxazines and 2-fluoro-1,4-benzoxazepin-5-ones was developed. The key step in this reaction sequence is a base-induced ring closure of the corresponding difluorinated benzamides, via an S_NV reaction, which either proceeds via an addition−elimination reaction at the vinylic CF_2 carbon atom or via formation of fluorinated ynamides which undergo nucleophilic attack by the phenolic oxygen in a second step. The synthesis of these fluorinated ynamides comprises the first example of an efficient route toward this unexplored class of fluorinated compounds.

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EXPERIMENTAL SECTION

Synthesis of *N*-Propyl-2-bromo-2,2-difluoroacetamide 27a. To an ice-cooled solution of ethyl bromodifluoroacetate **18** (5.07 g, 25 mmol) in CH_2Cl_2 (40 mL) was added a solution of propylamine (1.77 g, 30 mmol, 1.2 equiv) in CH_2Cl_2 (20 mL). This mixture was warmed to room temperature, and after being stirred for 17 h at this temperature, the solvent and excess propylamine were removed in vacuo, affording *N*-propyl-2-bromo-2,2-difluoroacetamide **27a** (5.35 g) in 99% yield.

***N*-Propyl-2-bromo-2,2-difluoroacetamide 27a.** Colorless oil. Yield: 99% (5.35 g). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.97 (3H, t, J = 7.2 Hz), 1.63 (2H, sextet, J = 7.2 Hz), 3.34 (2H, q, J = 6.8 Hz), 6.31 (1H, br s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.1, 22.3, 41.9, 111.9 (t, J = 316.1 Hz), 160.3 (t, J = 27.1 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ −60.40 (2F, s). IR (ATR, cm^{-1}): ν_{NH} = 3304, $\nu_{C=O}$ = 1698, ν_{max} = 1542, 1130. MS (ES$^-$): m/z (%): 214/16 (M − H$^+$, 100).

Synthesis of Acetamides 27b and 27c and Bromodifluoroacetanilides 19a and 19b. The synthesis of *N*-(4-methoxybenzyl)-2-bromo-2,2-difluoroacetamide **27c** is given as a representative example. To a solution of ethyl bromodifluoroacetate **18** (2.23 g, 11 mmol) in EtOAc (50 mL) were added 4-methoxybenzylamine (1.51 g, 11 mmol, 1 equiv) and Et_3N (1.11 g, 11 mmol, 1 equiv), after which the mixture was stirred at reflux for 4 h. Subsequently, H_2O (30 mL) was added and an extraction with EtOAc (3 × 30 mL) was performed. After drying of the organic layer ($MgSO_4$), filtration, and evaporation of the solvent, yellow crystals were obtained, which were recrystallized from Et_2O, affording pure amide **27c** as white crystals (2.43 g) in 75% yield.

***N*-(4-Methoxybenzyl)-2-bromo-2,2-difluoroacetamide 27c.** White crystals. Melting point: 89−90 °C. R_f 0.05 (petroleum ether/EtOAc 9/1). Yield: 75% (2.43 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.78 (3H, s), 4.42 (2H, d, J = 5.8 Hz), 6.79 (1H, br s), 6.87 (2H, d, J = 8.7 Hz), 7.21 (2H, d, J = 8.7 Hz). ^{13}C NMR (100.6 MHz, ref = $CDCl_3$): δ 43.7, 55.4, 111.9 (t, J = 316.1 Hz), 114.4 (2×), 128.3, 129.4 (2×), 159.6, 160.0 (t, J = 27.5 Hz). ^{19}F NMR (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ −60.99 (2F, s). IR (ATR, cm^{-1}): ν_{NH} = 3233, $\nu_{C=O}$ = 1695, ν_{max} = 1514, 1169, 1125, 820. MS (ES$^+$): m/z (%): 311/13 (M + NH_4^+, 20), 221 (100). HRMS (ES$^-$): calcd for $C_{10}H_9BrF_2NO_2^-$: 291.9790, found 291.9790.

***N*-(2-Hydroxy-4-methoxyphenyl)-2-bromo-2,2-difluoroacetamide 19b.** Brown crystals. Melting point: 159−160 °C. Yield: 40% (0.067 g). ^{1}H NMR (400 MHz, CD_3CN): δ 3.79 (3H, s), 6.53 (1H, dd, J = 8.6 Hz, 2.6 Hz), 6.56 (1H, d, J = 2.6 Hz), 7.52 (1H, d, J = 8.6 Hz), 7.60 (1H, br s), 8.62 (1H, br s). ^{13}C NMR (100.6 MHz, CD_3COCD_3): δ 55.6, 102.8, 105.6, 112.9 (t, J = 315.5 Hz), 117.6, 124.9, 150.9, 158.5 (t, J = 27.1 Hz), 159.7. ^{19}F NMR (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ −60.53 (2F, s). IR (ATR, cm^{-1}): ν_{NH} = 3386, ν_{OH} = 3244, $\nu_{C=O}$ = 1685, ν_{max} = 1547, 1151, 1110. MS (ES$^+$): m/z (%): 296/98 (M + H$^+$, 30), 313/15 (M + NH_4^+, 20). HRMS (ES$^-$): calcd for $C_9H_7BrF_2NO_3^-$: 293.9583, found 293.9572. Anal. Calcd for $C_9H_8BrF_2NO_3$: C 36.51, H 2.72, N 4.73. Found: C 36.86, H 2.68, N 4.57.

The spectral data of *N*-benzyl-2-bromo-2,2-difluoroacetamide **27b** and *N*-(2-hydroxyphenyl)-2-bromo-2,2-difluoroacetamide **19a** were in accordance with those reported in the literature.[32]

Synthesis of *N*-Propyl-2-bromo-2,2-difluoroethylamine 6a. *N*-Propyl-2-bromo-2,2-difluoroethylamine **6a** was synthesized following a literature procedure.[22]

***N*-Propyl-2-bromo-2,2-difluoroethylamine 6a.** Colorless oil. Yield: 89% (5.33 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.93 (3H, t, J = 7.3 Hz), 1.47 (1H, br s), 1.50 (2H, sextet, J = 7.3 Hz), 2.72 (2H, t, J = 7.3 Hz), 3.36 (2H, t, $J_{H,F}$ = 12.6 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 11.5, 23.4, 51.2, 59.4 (t, J = 23.3 Hz), 123.9 (t, J = 309.1 Hz). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ −51.15 (2F, t, $J_{H,F}$ = 12.6 Hz). IR (ATR, cm^{-1}): ν_{NH} = 3216, ν_{max} = 1462, 1195, 1094, 904. MS (ES$^+$): m/z (%): 202/04 (M + H$^+$, 100). HRMS (ES$^+$): calcd for $C_5H_{11}BrF_2N^+$: 202.0037, found 202.0033.

Synthesis of Amines 6b, 6c, 21a, and 21b. Amines **6b**, **6c**, **21a**, and **21b** were synthesized via a slightly modified literature procedure.[22] The synthesis of amine **6c** is given as a representative example.

To a solution of *N*-(4-methoxybenzyl)-2-bromo-2,2-difluoroacetamide **27c** (1.94 g, 6.9 mmol) in anhydrous THF (40 mL) was added borane dimethylsulfide complex (1.58 g, 21 mmol, 3 equiv) with a syringe. Subsequently, this mixture was stirred at reflux for 17 h after which it was slowly quenched with a mixture of water and methanol (H_2O/MeOH: 1/1, 50 mL). After extraction with EtOAc (3 × 50 mL), drying ($MgSO_4$), filtration, and evaporation of the solvent, the residue was redissolved in MeOH and stirred in the presence of Pd/C at room temperature for 2 h. After filtration, the crude amide **6c** was purified by column chromatography (SiO_2, PE/EtOAc 92/8) and obtained in 73% yield (1.41 g).

***N*-Benzyl-2-bromo-2,2-difluoroethylamine 6b.** Yellow oil. R_f 0.42 (petroleum ether/EtOAc 9/1). Yield: 85% (5.40 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.86 (1H, br s), 3.36 (2H, t, $J_{H,F}$ = 12.5 Hz), 3.95 (2H, s), 7.27−7.37 (5H, m). ^{13}C NMR (100.6 MHz, ref = $CDCl_3$): δ 52.8, 58.3 (t, J = 23.5 Hz), 123.7 (t, J = 308.9 Hz), 127.4, 128.1 (2×), 128.6 (2×), 139.3. ^{19}F NMR (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ −51.34 (2F, t, J = 12.5 Hz). IR (ATR, cm^{-1}): ν_{NH} = 3360, ν_{max} = 1117, 909, 889, 697. MS (ES$^+$): m/z (%): 250/52 (M + H$^+$, 20), 150 (100). HRMS (ES$^+$): calcd for $C_9H_{11}BrF_2N^+$: 250.0037, found 250.0036.

***N*-(4-Methoxybenzyl)-2-bromo-2,2-difluoroethylamine 6c.** Colorless oil. R_f 0.12 (petroleum ether/EtOAc 92/8). Yield: 73% (1.41 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.78 (1H, br s), 3.34 (2H, t, $J_{H,F}$ = 12.6 Hz), 3.81 (3H, s), 3.88 (2H, s), 6.88 (2H, d, J = 8.8 Hz), 7.25 (2H, d, J = 8.8 Hz). ^{13}C NMR (100.6 MHz, ref = $CDCl_3$): δ 52.2, 55.2, 58.1 (t, J = 23.5 Hz), 113.9 (2×), 123.8 (t, J = 308.8 Hz), 129.3 (2×), 131.3, 158.9. ^{19}F NMR (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ −51.23 (2F, t, $J_{H,F}$ = 12.7 Hz). IR (ATR, cm^{-1}): ν_{NH} = 3362, ν_{max} = 1512, 1246, 1033. MS (ES$^+$): m/z (%): 121 (100).

***N*-{2-[(*tert*-Butyldimethylsilyl)oxy]phenyl}-2-bromo-2,2-difluoroethylamine 21a.** Yellow oil. R_f 0.14 (petroleum ether/EtOAc 99/1). Yield: 90% (3.10 g). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.25 (6H, s), 1.02 (9H, s), 3.95 (2H, td, $J_{H,F}$ = 11.8 Hz, J = 3.4 Hz), 4.65 (1H, br s), 6.65 (1H, ddd, J = 7.8 Hz, 7.4 Hz, 1.5 Hz), 6.70 (1H, d, J = 7.9 Hz), 6.77 (1H, dd, J = 7.8 Hz, 1.4 Hz), 6.87 (1H, ddd, J = 7.9 Hz, 7.4 Hz, 1.4 Hz). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ −4.2 (2×), 18.3, 25.9, 54.3 (t, J = 25.4 Hz), 110.9, 118.0, 118.3, 122.0, 122.6 (t, J = 309.2 Hz), 138.0, 142.7. ^{19}F NMR (282 MHz, $CDCl_3$, ref = $CFCl_3$): δ −53.30 (t, $J_{H,F}$ = 11.8 Hz). IR (ATR, cm^{-1}): ν_{NH} = 3446, ν_{max} = 1514, 1254, 916, 781. MS (ES$^+$): m/z (%): 366/68 (M + H$^+$, 100). HRMS (ES$^+$): calcd for $C_{14}H_{23}BrF_2NOSi^+$: 366.0695, found 366.0702.

***N*-{4-Methoxy-2-[(*tert*-butyldimethylsilyl)oxy]phenyl}-2-bromo-2,2-difluoroethylamine 21b.** Yellow oil. R_f 0.57 (petroleum ether/EtOAc 9/1). Yield: 95% (0.25 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.26 (6H, s), 1.02 (9H, s), 3.73 (3H, s), 3.89 (2H, td, $J_{H,F}$ = 12.1 Hz, J = 7.2 Hz), 4.33 (1H, t, J = 7.2 Hz), 6.42 (1H, d, J = 2.8 Hz), 6.44 (1H, dd, J = 8.4 Hz, 2.8 Hz), 6.62 (1H, d, J = 8.4 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ −4.3 (2×), 18.2, 25.8, 55.1 (t, J = 24.9 Hz), 55.6, 105.5, 106.2, 111.5, 122.6 (t, J = 309.2 Hz), 132.1, 143.6, 152.5. ^{19}F NMR (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ −53.13 (2F, t, $J_{H,F}$ = 12.1 Hz). IR (ATR, cm^{-1}): ν_{NH} = 3442, ν_{max} = 1518, 1163, 837, 780. MS (ES$^+$): m/z (%): 396/98 (M + H$^+$, 100). HRMS (ES$^+$): calcd for $C_{15}H_{25}BrF_2NO_2Si^+$: 396.0801, found 396.0813.

Synthesis of *N*-2-Bromo-2,2-difluoroethyl-*N*-propylbenzamide 7. To a mixture of *N*-propyl-2-bromo-2,2-difluoroethylamine **6a** (0.33 g, 1.7 mmol) and Et_3N (0.84 g, 8.3 mmol, 5 equiv) in anhydrous CH_2Cl_2 (20 mL) was added a solution of benzoyl chloride (0.23 g, 1.7 mmol, 1 equiv) in anhydrous CH_2Cl_2 (5 mL) slowly at 0 °C. After being stirred at room temperature for 20 h, the reaction mixture was washed with an aqueous solution of HCl (5%, 10 mL) and $NaHCO_3$ (aq satd). After drying ($MgSO_4$) and filtration, the solvent was evaporated in vacuo. Column chromatography (SiO_2, PE/EtOAc 8/2) afforded pure benzamide **7** in 90% yield (0.41 g).

***N*-2-Bromo-2,2-difluoroethyl-*N*-propylbenzamide 7.** Yellow oil. R_f 0.34 (petroleum ether/EtOAc 8/2). Yield: 90% (0.41 g). ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C): δ 0.79 (3H, t, J = 7.2 Hz), 1.52−1.58 (2H, m), 3.45 (2H, t, J = 6.8 Hz), 4.33 (2H, t, $J_{H,F}$ = 11.2 Hz),

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7.39−7.46 (5H, m). ^{13}C NMR (100.6 MHz, ref = $CDCl_3$): δ 10.8, 21.1, 51.3, 52.1, 121.2 (t, J = 308.8 Hz), 126.8 (2×), 128.6 (2×), 129.9, 135.6, 172.8. ^{19}F NMR (376.5 MHz, $CDCl_3$): δ −50.02 (2F, br s). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1647, ν_{max} = 1407, 1089, 1021, 935, 699. MS (ES$^+$): m/z (%): 306/08 (M + H$^+$, 100). HRMS (ES$^+$): calcd for $C_{12}H_{15}BrF_2NO^+$: 306.0300, found 306.0295.

Synthesis of *N*-Propyl-*N*-tosyl-2-bromo-2,2-difluoroethylamine 9. To a mixture of *N*-propyl-2-bromo-2,2-difluoroethylamine **6a** (5.00 g, 25 mmol), Et_3N (4.00 g, 21 mmol, 0.8 equiv), and DMAP (0.26 g, 2.1 mmol, 0.08 equiv) in anhydrous CH_2Cl_2 (100 mL) was added a solution of *p*-toluenesulfonyl chloride (2.12 g, 21 mmol, 0.8 equiv) in anhydrous CH_2Cl_2 (25 mL) at 0 °C. The reaction mixture was stirred at reflux temperature for 47 h, poured in 1 N HCl (50 mL), and extracted with CH_2Cl_2 (3 × 50 mL). After drying of the organic phase ($MgSO_4$), filtration of the drying agent, and evaporation of the solvent in vacuo, *N*-propyl-*N*-tosyl-2-bromo-2,2-difluoroethylamine **16** was obtained in 78% yield (5.81 g).

***N*-Propyl-*N*-tosyl-2-bromo-2,2-difluoroethylamine 9.** White crystals. Melting point: 56−57 °C. Yield: 78% (5.81 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.82 (3H, t, J = 7.4 Hz), 1.58 (2H, sextet, J = 7.6 Hz), 2.43 (3H, s), 3.18−3.22 (2H, m), 4.10 (2H, t, $J_{H,F}$ = 13.3 Hz), 7.31 (2H, d, J = 8.1 Hz), 7.71 (2H, d, J = 8.1 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 10.9, 20.8, 21.5, 50.9, 56.0 (t, J = 24.2 Hz), 120.6 (t, J = 309.5 Hz), 127.3 (2×), 129.8 (2×), 136.6, 143.9. ^{19}F NMR (376.5 MHz, $CDCl_3$): δ −51.47 (2F, t, $J_{H,F}$ = 13.3 Hz). IR (ATR, cm^{-1}): ν_{max} = 1345, 1154, 942, 732. MS (ES$^+$): m/z (%): 373/75 (M + NH_4^+, 100), 356/58 (M + H$^+$, 80). HRMS (ES$^+$): calcd for $C_{12}H_{17}BrF_2NO_2S^+$: 356.0126, found 356.0125.

Synthesis of β,β-Difluoroenamides 8 and 10. The synthesis of benzamide **8** is given as a representative example. To a solution of *N*-2-bromo-2,2-difluoroethyl-N-propylbenzamide **7** (1.29 g, 4.2 mmol) in anhydrous THF (40 mL) was added a solution of LiHMDS in THF (1 M, 4.4 mL, 1.05 equiv) at 0 °C. The reaction mixture was stirred at room temperature for 3 h, after which it was quenched with $NaHCO_3$ (aq satd) and extracted with EtOAc (3 × 50 mL). After drying of the combined organic phases ($MgSO_4$), filtration, and evaporation of the solvent, crude benzamide **8** was obtained, which was purified via column chromatography (SiO_2, PE/EtOAc 9/1), affording pure amide **8** in 85% yield (0.80 g).

***N*-(2,2-Difluorovinyl)-*N*-propylbenzamide 8.** Yellow oil. R_f 0.23 (petroleum ether/EtOAc 9/1). Yield: 85% (0.80 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.94 (3H, br s), 1.62−1.68 (2H, m), 3.57 (2H, br s), 5.42 (1H, br s), 7.36−7.46 (5H, m). ^{13}C NMR (100.6 MHz, ref = $CDCl_3$): δ 11.2, 20.9, 49.4, 89.0−89.5 (m), 127.5 (2×), 128.3 (2×), 130.3, 135.7, 155.5 (t, J = 289.9 Hz), 171.1. ^{19}F NMR (376.5 MHz, $CDCl_3$): δ −87.75 (1F, dd, J = 40.2 Hz, $J_{H,F}$ = 18.2 Hz), −100.56 (1F, d, J = 37.6 Hz). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1647, ν_{max} = 1407, 1089, 1021, 935, 699. MS (ES$^+$): m/z (%): 226 (M + H$^+$, 100). HRMS (ES$^+$): calcd for $C_{12}H_{14}F_2NO^+$: 226.1038, found 226.1038.

***N*-(2,2-Difluorovinyl)-*N*-tosylpropylamine 10.** Yellow crystals. Melting point: 51−52 °C. R_f 0.30 (petroleum ether/EtOAc 10/1). Yield: 82% (4.27 g). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.92 (3H, t, J = 7.2 Hz), 1.54 (2H, sextet, J = 7.2 Hz), 2.44 (3H, s), 3.10 (2H, t, J = 7.2 Hz), 4.87 (1H, dd, $J_{H,F}$ = 18.3 Hz, 2.8 Hz), 7.33 (2H, d, J = 8.3 Hz), 7.68 (2H, d, J = 8.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.9, 21.4, 21.6, 51.6, 84.9 (dd, J = 49.6 Hz, 13.9 Hz), 127.4 (2×), 129.8 (2×), 134.8, 143.9, 159.5 (dd, J = 300.0 Hz, 289.6 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ −83.20 (1F, dd, J = 28.3 Hz, $J_{H,F}$ = 18.3 Hz), −93.38 (1F, d, J = 28.3 Hz). IR (ATR, cm^{-1}): ν_{max} = 1749, 1341, 1240, 1164. MS (ES$^+$): m/z (%): 276 (M + H$^+$, 100), 293 (M + NH_4^+, 33). HRMS (ES$^+$): calcd for $C_{12}H_{16}F_2NO_2S^+$: 276.0864, found 276.0863.

Synthesis of Enamides 11a, 11b, and 12b, amine 13b, and glycinate 14b. The synthesis of enamide **11a** is described as a representative example. To a solution of *N*-(2,2-difluorovinyl)-*N*-tosylpropylamine **10** (0.21 g, 0.78 mmol) in acetonitrile (5 mL) were added thiophenol (0.103 g, 0.93 mmol, 1.2 equiv) and KOH (0.052 g, 0.93 mmol, 1.2 equiv). After the reaction mixture was stirred for 20 h at reflux, an aqueous solution of HCl (1 N, 10 mL) was added and an extraction with EtOAc (3 × 10 mL) was performed. The combined organic layers were dried ($MgSO_4$) and filtered, and the solvent was removed in vacuo. After column chromatography (SiO_2, PE/EtOAc 24/1), enamide **11a** was isolated in 69% yield (0.20 g).

(*Z*)-*N*-[2-Fluoro-2-(phenylthio)vinyl]-*N*-propyl-4-methylbenzenesulfonamide 11a. White crystals. Melting point: 85−86 °C. R_f 0.13 (petroleum ether/EtOAc 24/1). Yield: 69% (0.20 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.96 (3H, t, J = 7.4 Hz), 1.58 (2H, sextet, J = 7.3 Hz), 2.43 (3H, s), 3.19 (2H, t, J = 7.2 Hz), 5.89 (1H, d, $J_{H,F}$ = 5.5 Hz), 7.30−7.33 (5H, m), 7.38−7.40 (2H, m), 7.69 (2H, d, J = 8.3 Hz). ^{13}C NMR (100.6 MHz): δ 11.2, 21.6 (2×), 52.0, 115.1 (d, J = 52.2 Hz), 127.5 (2×), 128.2, 129.2 (2×), 129.77 (2×), 129.85, 131.5 (2×), 134.8, 143.9, 158.9 (d, J = 297.3 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ −98.83 (1F, d, $J_{H,F}$ = 5.5 Hz). IR (ATR, cm^{-1}): ν_{max} = 1344, 1161, 1145, 672. MS (ES$^+$): m/z (%): 366 (M + H$^+$, 100). Anal. Calcd for $C_{18}H_{20}FNO_2S_2$: C 59.15, H 5.52, N 3.83. Found: C 59.35, H 5.72, N 3.73. HRMS (ES$^+$): calcd for $C_{18}H_{21}FNO_2S_2^+$: 366.0992, found 366.0989.

Enamides 11b (major) and 12b (minor) Were Obtained as an Inseparable Mixture (ratio 11b:12b = 4:1). (*E*)-*N*-(2-Fluoro-2-phenoxyvinyl)-*N*-propyl-4-methylbenzenesulfonamide 11b and (*Z*)-*N*-(2-Fluoro-2-phenoxyvinyl)-*N*-propyl-4-methylbenzenesulfonamide 12b. Yellow oil. R_f 0.13 (petroleum ether/EtOAc 95/5). Yield: 32% (0.13 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 (2.4H, t, J = 7.4 Hz (major)), 0.94 (0.6H, t, J = 7.4 Hz (minor)), 1.56 (2H, sextet, J = 7.3 Hz), 2.36 (2.4H, s (major)), 2.39 (0.6H, s (minor)), 3.15 (0.4H, t, J = 7.1 Hz (minor)), 3.21 (1.6H, t, J = 7.0 Hz (major)), 4.88 (0.2H, d, $J_{H,F}$ = 19.3 Hz (minor)), 5.33 (0.8H, d, $J_{H,F}$ = 1.0 Hz (major)), 6.91−6.93 (1.6H, m (major)), 7.07−7.37 (4H, m (major)), 7.07−7.37 (1.4H, m (minor)), 7.64−7.67 (1.6H, m (major)), 7.69 (0.4H, d, J = 8.4 Hz (minor)). ^{13}C NMR (100.6 MHz, ref = $CDCl_3$): δ 11.0, 21.48 (major), 21.50 (minor), 21.53 (major), 21.6 (minor), 51.5, 91.9 (d, J = 20.7 Hz (minor)), 92.8 (d, J = 60.3 Hz (major)), 116.8 (2× (minor)), 116.9 (2× (major)), 124.5 (major), 124.8 (minor), 127.4 (2× (major) and 2× (minor)), 129.60 (2× (major)), 129.62 (2× (major)), 129.7 (2× (minor)), 130.0 (2× (minor)), 135.1 (minor), 135.4 (major), 143.6 (major), 143.7 (minor), 153.5 (d, J = 1.2 Hz (major)), 154.6 (d, J = 1.5 Hz (minor)), 156.5 (d, J = 283.9 Hz (major)), 157.5 (d, J = 290.0 Hz (minor)). ^{19}F NMR (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ −84.57 (0.2F, d, $J_{H,F}$ = 19.3 Hz (minor)), −95.80 (0.8F, s (major)). IR (ATR, cm^{-1}): ν_{max} = 1341, 1190, 1163, 748, 658. MS (ES$^+$): m/z (%): 350 (M + H$^+$, 100). HRMS (ES$^+$): calcd for $C_{18}H_{21}FNO_3S^+$: 350.1221, found 350.1224.

***N*-(2,2-Difluoro-2-phenoxyethyl)-*N*-propyl-4-methylbenzenesulfonamide 13b.** White crystals. Melting point: 77−78 °C. R_f 0.08 (petroleum ether/EtOAc 95/5). Yield: 10% (0.051 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.86 (3H, t, J = 7.4 Hz), 1.67 (2H, sextet, J = 7.5 Hz), 2.41 (3H, s), 3.27−3.31 (2H, m), 3.96 (2H, t, $J_{H,F}$ = 9.3 Hz), 7.03−7.06 (2H, m), 7.18−7.22 (1H, m), 7.27−7.33 (4H, m), 7.76 (2H, d, J = 8.3 Hz). ^{13}C NMR (100.6 MHz): δ 11.0, 20.9, 21.5, 49.5 (t, J = 34.5 Hz), 50.4, 121.7 (2×), 122.2 (t, J = 270.2 Hz), 125.8, 127.4 (2×), 129.4 (2×), 129.6 (2×), 137.3, 143.4, 149.7. ^{19}F NMR (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ −73.49 (2F, t, $J_{H,F}$ = 9.3 Hz). IR (ATR, cm^{-1}): ν_{max} = 1336, 1264, 1146, 994. MS (ES$^+$): m/z (%): 370 (M + H$^+$, 100), 387 (M + NH_4^+, 12). HRMS (ES$^+$): calcd for $C_{18}H_{22}F_2NO_3S^+$: 370.1283, found 370.1279. Anal. Calcd for $C_{18}H_{21}F_2NO_3S$: C 58.52, H 5.73, N 3.79. Found: C 58.53, H 5.32, N 3.66.

Phenyl *N*-Propyl-*N*-tosylglycinate 14b. White crystals. Melting point: 88−89 °C. R_f 0.03 (petroleum ether/EtOAc 95/5). Yield: 85% (0.29 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89 (3H, t, J = 7.4 Hz), 1.61 (2H, sextet, J = 7.4 Hz), 2.38 (3H, s), 3.24−3.28 (2H, m), 4.27 (2H, s), 6.98−7.01 (2H, m), 7.18−7.22 (1H, m), 7.27 (2H, d, J = 8.1 Hz), 7.31−7.36 (2H, m), 7.77 (2H, d, J = 8.3 Hz). ^{13}C NMR (100.6 MHz): δ 11.1, 21.3, 21.5, 48.1, 50.2, 121.2 (2×), 126.1, 127.4 (2×), 129.4 (2×), 129.6 (2×), 136.6, 143.5, 150.2, 167.7. IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1769, ν_{max} = 1334, 1148, 656. MS (ES$^+$): m/z (%): 348 (M + H$^+$, 100), 365 (M + NH_4^+, 58). HRMS (ES$^+$): calcd for $C_{18}H_{22}NO_4S^+$: 348.1264, found 348.1273.

Synthesis of Enamides 11c and 12c. To a solution of enamide **10** (0.15 g, 0.55 mmol) in anhydrous THF (10 mL) was added a

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solution of NaOMe in MeOH (1 M, 0.55 mL, 1 equiv). This mixture was stirred for 3 h at room temperature. Subsequently, an aqueous solution of NH_4Cl (10 mL) was added, followed by an extraction with EtOAc (3 × 10 mL). After drying of the combined organic phases ($MgSO_4$), filtration, and evaporation of the solvent under reduced pressure, a mixture of two isomers **11c** and **12c** was obtained. After column chromatography (SiO_2, PE/EtOAc 9/1), enamides **11c** and **12c** were isolated in 57% (0.090 g) and 15% (0.024 g) yield, respectively.

(*E*)-*N*-(2-Fluoro-2-methoxyvinyl)-*N*-propyl-4-methylbenzenesulfonamide 11c. Yellow oil. R_f 0.31 (petroleum ether/EtOAc 9/1). Yield: 57% (0.090 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.91 (3H, t, J = 7.4 Hz), 1.53 (2H, sextet, J = 7.3 Hz), 2.42 (3H, s), 3.10 (2H, td, J = 7.2 Hz, 0.8 Hz), 3.71 (3H, d, J = 1.0 Hz), 4.63 (1H, d, $J_{H,F}$ = 0.7 Hz), 7.30 (2H, d, J = 8.1 Hz), 7.68 (2H, d, J = 8.1 Hz). ^{13}C NMR (100.6 MHz, ref = $CDCl_3$) δ 10.9, 21.3, 21.4, 51.9 (d, J = 1.2 Hz), 57.4 (d, J = 6.0 Hz), 86.5 (d, J = 64.1 Hz), 127.4 (2×), 129.4 (2×), 135.1, 143.4, 161.7 (d, J = 280.1 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ −97.22 (1F, s). IR (ATR, cm^{-1}): ν_{max} = 1721, 1339, 1161, 732. MS (ES$^+$): m/z (%): 288 (M + H$^+$, 25). HRMS (ES$^+$): calcd for $C_{13}H_{19}FNO_3S^+$: 288.1064, found 288.1068.

(*Z*)-*N*-(2-Fluoro-2-methoxyvinyl)-*N*-propyl-4-methylbenzenesulfonamide 12c. Yellow oil. R_f 0.12 (petroleum ether/EtOAc 9/1). Yield: 15% (0.024 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.92 (3H, t, J = 7.4 Hz), 1.54 (2H, sextet, J = 7.4 Hz), 2.42 (3H, s), 3.14 (2H, t, J = 7.2 Hz), 3.69 (3H, s), 4.39 (1H, d, $J_{H,F}$ = 21.6 Hz), 7.29 (2H, d, J = 8.3 Hz), 7.69 (2H, d, J = 8.3 Hz). ^{13}C NMR (100.6 MHz, ref = $CDCl_3$): δ 11.0, 21.4, 21.5, 52.1 (d, J = 1.8 Hz), 57.0 (d, J = 3.6 Hz), 81.6 (d, J = 20.4 Hz), 127.4 (2×), 129.5 (2×), 135.4, 143.4, 162.5 (d, J = 268.9 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ −85.13 (1F, d, $J_{H,F}$ = 21.6 Hz). IR (ATR, cm^{-1}): ν_{max} = 1348, 1166, 998, 665. MS (ES$^+$): m/z (%): 288 (M + H$^+$, 25). HRMS (ES$^+$): calcd for $C_{13}H_{19}FNO_3S^+$: 288.1064, found 288.1059.

Synthesis of Enamide 11d. To a solution of enamide **10** (0.36 g, 1.3 mmol) in anhydrous THF (20 mL) was added a solution of KO*t*Bu in THF (1 M, 1.44 mL, 1.1 equiv) at 0 °C. After this reaction mixture was stirred for 2 h at room temperature, a saturated solution of NH_4Cl in H_2O (20 mL) was added. Upon subsequent extraction with EtOAc (3 × 20 mL), drying of the organic layers ($MgSO_4$), filtration, and evaporation of the solvent in vacuo, a mixture of enamides **11d** and **12d** was obtained (**11d**:**12d** = 8:2), from which enamide **11d** could be isolated in 46% yield (0.20 g) via column chromatography (SiO_2, PE/EtOAc 97/3).

(*E*)-*N*-(2-Fluoro-2-(*tert*-butoxy)vinyl)-*N*-propyl-4-methylbenzenesulfonamide 11d. White crystals. Melting point: 91−92 °C. R_f 0.24 (petroleum ether/EtOAc 97/3). Yield: 46% (0.20 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89 (3H, t, J = 7.4 Hz), 1.34 (9H, d, J = 0.8 Hz), 1.52 (2H, sextet, J = 7.3 Hz), 2.42 (3H, s), 3.14 (2H, td, J = 7.2 Hz, 0.8 Hz), 4.88 (1H, d, $J_{H,F}$ = 1.2 Hz), 7.29 (2H, d, J = 8.1 Hz), 7.69 (2H, d, J = 8.1 Hz). ^{13}C NMR (100.6 MHz): δ 11.2, 21.3, 21.5, 28.6, 51.8, 84.7, 90.2 (d, J = 69.9 Hz), 127.5 (2×), 129.5 (2×), 135.8, 143.3, 159.3 (d, J = 284.9 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ −85.62 (1F, s). IR (ATR, cm^{-1}): ν_{max} = 1343, 1165, 1151, 1137, 660. MS (ES$^+$): m/z (%): 352 (M + Na$^+$, 10). HRMS (ES$^+$): calcd for $C_{16}H_{25}FNO_3S^+$: 330.1534, found 330.1542.

Synthesis of Enamides 15 and 16. To a solution of enamide **8** (0.045 g, 0.20 mmol) in acetonitrile (5 mL) were added phenol (0.023 g, 0.24 mmol, 1.2 equiv) and KOH (0.013 g, 0.24 mmol, 1.2 equiv). After this reaction mixture was stirred for 4 h at reflux, a saturated solution of NH_4Cl in H_2O (5 mL) was added. Upon subsequent extraction with EtOAc (3 × 10 mL), drying of the organic layers ($MgSO_4$), filtration, and evaporation of the solvent in vacuo, enamides **15** and **16** were isolated as a mixture (ratio **15**:**16** = 4:1) in 80% yield (0.048 g) after preparative TLC (SiO_2, PE/EtOAc 9/1).

Enamides 15 (major) and 16 (minor) Were Obtained as an Inseparable Mixture (ratio 15:16 = 4:1). (*E*)-*N*-(2-Fluoro-2-phenoxyvinyl)-*N*-propylbenzamide 15 and (*Z*)-*N*-(2-Fluoro-2-phenoxyvinyl)-*N*-propylbenzamide 16. Yellow oil. R_f 0.18 (petroleum ether/EtOAc 9/1). Yield: 80% (0.048 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.94 (3H, br s), 1.70 (2H, br s), 3.63 (2H, br s), 5.43 (0.2H, d, $J_{H,F}$ = 19.7 Hz (minor)), 5.76 (0.8H, br s (major)), 6.81−6.91 (3H, m), 7.13−7.56 (7H, m). ^{13}C NMR (100.6 MHz, ref = $CDCl_3$): δ 11.2, 20.8, 49.4, 96.8 (minor), 97.4 (d, J = 57.0 Hz (major)), 115.4, 116.4, 120.0, 124.4, 127.6, 127.9, 128.1, 128.3, 129.4, 129.8, 129.9, 130.2, 130.3, 135.8, 152.8 (d, J = 281.0 Hz (minor)), 154.7 (d, J = 323.4 Hz (major)), 171.3. ^{19}F NMR (282 MHz, $CDCl_3$): δ −87.11 (1F, d, $J_{H,F}$ = 20.0 Hz (minor)), −100.96 (1F, s (major)). IR (ATR, cm^{-1}): ν_{max} = 1627, 1191, 1164, 751, 691. MS (ES$^+$): m/z (%): 300 (M + H$^+$, 100). HRMS (ES$^+$): calcd for $C_{18}H_{19}FNO_2^+$: 300.1394, found 300.1408.

Synthesis of Silyl Ethers 20a and 20b. The synthesis of silyl ether **20a** is given as representative example. To a mixture of amide **19a** (2.00 g, 7.5 mmol) and imidazole (1.02 g, 15.0 mmol, 2 equiv) in anhydrous CH_2Cl_2 (40 mL) under N_2 atmosphere was added TBDMSCl (1.19 g, 7.9 mmol, 1.05 equiv) at room temperature. This mixture was stirred for 17 h at room temperature. Subsequently, H_2O (40 mL) was added and an extraction was performed with CH_2Cl_2 (3 × 30 mL). After drying of the combined organic phases ($MgSO_4$), filtration, and evaporation of the solvent under reduced pressure, acetamide **20a** was obtained as orange crystals in 95% yield (2.71 g).

***N*-{2-[(*tert*-Butyldimethylsilyl)oxy]phenyl}-2-bromo-2,2-difluoroacetamide 20a.** Orange crystals. Melting point: 56−57 °C. Yield: 95% (2.71 g). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.30 (6H, s), 1.03 (9H, s), 6.88 (1H, dd, J = 7.7 Hz, 1.7 Hz), 7.01 (1H, ddd, J = 7.7 Hz, 7.7 Hz, 1.7 Hz), 7.71 (1H, ddd, J = 7.7 Hz, 7.7 Hz, 2.2 Hz), 8.30 (1H, dd, J = 7.7 Hz, 2.2 Hz), 8.55 (1H, br s). ^{13}C NMR (75 MHz, $CDCl_3$): δ −4.4 (2×), 18.1, 25.6, 111.6 (t, J = 316.1 Hz), 117.5, 120.2, 121.9, 125.7, 127.3, 144.7, 156.8 (t, J = 27.7 Hz). ^{19}F NMR (282 MHz, $CDCl_3$, ref = $CFCl_3$): δ −60.87 (2F, s). IR (ATR, cm^{-1}): ν_{NH} = 3398, $\nu_{C=O}$ = 1717, ν_{max} = 1458, 1100, 783, 752. MS (ES$^+$): m/z (%): 380/82 (M + H$^+$, 100). HRMS (ES$^+$): calcd for $C_{14}H_{21}BrF_2NO_2Si^+$: 380.0488, found 380.0478.

***N*-{4-Methoxy-2-[(*tert*-butyldimethylsilyl)oxy]phenyl}-2-bromo-2,2-difluoroacetamide 20b.** Brown crystals. Melting point: 69−70 °C. R_f 0.36 (petroleum ether/EtOAc 9/1). Yield: 74% (0.033 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.30 (6H, s), 1.03 (9H, s), 3.79 (3H, s), 6.45 (1H, d, J = 2.7 Hz), 6.55 (1H, dd, J = 9.0 Hz, 2.7 Hz), 8.30 (1H, d, J = 9.0 Hz), 8.36 (1H, br s). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ −4.4 (2×), 18.1, 25.6, 55.5, 105.1, 105.5, 111.7 (t, J = 316.8 Hz), 120.8, 120.9, 145.9, 156.5 (t, J = 27.2 Hz), 157.4. ^{19}F NMR (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ −60.61 (2F, s). IR (ATR, cm^{-1}): ν_{NH} = 3404, $\nu_{C=O}$ = 1717, ν_{max} = 1530, 1109, 834. MS (ES$^+$): m/z (%): 410/12 (M + H$^+$, 100). Anal. Calcd for $C_{15}H_{22}BrF_2NO_3Si$: C 43.91, H 5.40, N 3.41. Found: C 44.02, H 5.74, N 3.35.

Synthesis of Benzamides 23a−d. The synthesis of *N*-(2-bromo-2,2-difluoroethyl)-*N*-{2-[(*tert*-butyldimethylsilyl)oxy]phenyl}-benzamide **23a** is given as a representative example. To a mixture of amine **21a** (0.27 g, 0.74 mmol) and benzoyl chloride (0.10 g, 0.74 mmol, 1 equiv) in anhydrous CH_2Cl_2 (20 mL) was added triethylamine (0.37 g, 3.7 mmol, 5 equiv) slowly. Subsequently, this reaction mixture was stirred at reflux temperature for 5 h. After the addition of an aqueous solution of HCl (1 M, 20 mL) and extraction with CH_2Cl_2 (3 × 15 mL), the combined organic phases were dried ($MgSO_4$) and filtered and the solvent was removed under reduced pressure. Purification of the crude mixture via column chromatography (SiO_2, PE/EtOAc 9/1) afforded pure benzamide **23a** in 98% yield (0.34 g).

***N*-(2-Bromo-2,2-difluoroethyl)-*N*-{2-[(*tert*-butyldimethylsilyl)oxy]phenyl}benzamide 23a.** White crystals. Melting point: 89−90 °C. R_f 0.23 (petroleum ether/EtOAc 9/1). Yield: 98% (0.34 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.26 (3H, s), 0.32 (3H, s), 1.02 (9H, s), 4.00 (1H, ddd, $J_{H,F}$ = 18.5 Hz, J = 14.9 Hz, $J_{H,F}$ = 4.2 Hz), 5.44 (1H, ddd, $J_{H,F}$ = 18.9 Hz, J = 14.9 Hz, $J_{H,F}$ = 10.3 Hz), 6.74−6.77 (2H, m), 7.06−7.15 (4H, m), 7.21−7.22 (1H, m), 7.28−7.30 (2H, m). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ −4.4, −3.9, 18.2, 25.7, 56.4 (dd, J = 25.0 Hz, 22.4 Hz), 118.6, 120.7 (dd, J = 311.4 Hz, 308.4 Hz), 121.0, 127.5 (2×), 128.0 (2×), 129.3, 129.9, 131.7, 132.9, 134.9, 150.7, 171.3. ^{19}F NMR (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ −49.08 (1F, ddd, J = 154.5 Hz, $J_{H,F}$ = 18.9 Hz, 4.2 Hz),

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−50.75 (1F, ddd, J = 154.5 Hz, $J_{H,F}$ = 18.5 Hz, 10.3 Hz). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1658, ν_{max} = 1285, 909, 783. MS (ES^+): m/z (%): 470/72 (M + H^+, 100). HRMS (ES^+): calcd for $C_{21}H_{27}BrF_2NO_2Si^+$: 470.0957, found 470.0957. Anal. Calcd for $C_{21}H_{26}BrF_2NO_2Si$: C 53.62, H 5.57, N 2.98. Found: C 53.53, H 5.90, N 2.91.

***N*-(2-Bromo-2,2-difluoroethyl)-*N*-{[4-methoxy-2-(*tert*-butyldimethylsilyl)oxy]phenyl}benzamide 23b.** White crystals. Melting point: 119−120 °C. R_f 0.13 (petroleum ether/EtOAc 9/1). Yield: 52% (0.16 g). ^1H NMR (400 MHz, $CDCl_3$): δ 0.26 (3H, s), 0.31 (3H, s), 1.02 (9H, s), 3.70 (3H, s), 4.91 (1H, ddd, $J_{H,F}$ = 18.4 Hz, J = 14.9 Hz, $J_{H,F}$ = 4.3 Hz), 5.43 (1H, ddd, $J_{H,F}$ = 18.7 Hz, J = 14.9 Hz, $J_{H,F}$ = 10.5 Hz), 6.28−6.31 (2H, m), 6.99−7.01 (1H, m), 7.13−7.17 (2H, m), 7.21−7.24 (1H, m), 7.29−7.31 (2H, m). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ −4.4, −3.9, 18.2, 25.7, 55.3, 56.6 (dd, J = 24.9 Hz, 22.4 Hz), 105.1, 105.3, 120.9 (dd, J = 311.3 Hz, 308.3 Hz), 126.2, 127.5 (2×), 127.9 (2×), 129.8, 132.0, 135.1, 151.6, 160.0, 171.6. ^{19}F NMR (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ −49.12 (1F, ddd, J = 154.5 Hz, $J_{H,F}$ = 18.7 Hz, 4.3 Hz), −50.71 (1F, ddd, J = 154.5 Hz, $J_{H,F}$ = 18.4 Hz, 10.5 Hz). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1652, ν_{max} = 1509, 1171, 833. MS (ES^+): m/z (%): 500/02 (M + H^+, 100). HRMS (ES^+): calcd for $C_{22}H_{29}BrF_2NO_3Si^+$: 500.1063, found 500.1067.

***N*-(2-Bromo-2,2-difluoroethyl)-*N*-(2-((*tert*-butyldimethylsilyl)oxy)phenyl)-4-methoxybenzamide 23c.** Colorless oil. R_f 0.29 (petroleum ether/EtOAc 95/5). Yield: 76% (0.74 g). ^1H NMR (400 MHz, $CDCl_3$): δ 0.19 (3H, s), 0.27 (3H, s), 0.97 (9H, s), 3.60 (3H, s), 4.00 (1H, ddd, $J_{H,F}$ = 19.0 Hz, J = 15.0 Hz, $J_{H,F}$ = 3.8 Hz), 5.40 (1H, ddd, $J_{H,F}$ = 19.3 Hz, J = 15.0 Hz, $J_{H,F}$ = 9.6 Hz), 6.58 (2H, d, J = 8.7 Hz), 6.72−6.76 (1H, m), 6.76 (1H, d, J = 8.2 Hz), 7.05 (1H, ddd, J = 8.2 Hz, 7.6 Hz, 1.6 Hz), 7.11 (1H, d, J = 7.6 Hz), 7.26 (2H, d, J = 8.7 Hz). ^{13}C NMR (100.6 MHz, ref = $CDCl_3$): δ −4.6, −4.1, 18.0, 25.5, 54.9, 56.6 (dd, J = 23.7 Hz, 23.1 Hz), 112.6 (2×), 118.7, 120.8 (dd, J = 311.1 Hz, 308.9 Hz), 121.1, 126.6, 129.1, 130.3 (2×), 131.2, 133.3, 150.5, 160.8, 170.4. ^{19}F NMR (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ −48.91 (1F, ddd, J = 153.2 Hz, $J_{H,F}$ = 19.3 Hz, 3.8 Hz), −50.74 (1F, ddd, J = 153.2 Hz, $J_{H,F}$ = 19.0 Hz, 9.6 Hz). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1657, ν_{max} = 1497, 1253, 909, 782. MS (ES^+): m/z (%): 500/02 (M + H^+, 100). HRMS (ES^+): calcd for $C_{22}H_{29}BrF_2NO_3Si^+$: 500.1063, found 500.1070.

***N*-(2-Bromo-2,2-difluoroethyl)-*N*-{2-[(*tert*-butyldimethylsilyl)oxy]phenyl}-4-bromobenzamide 23d.** White crystals. Melting point: 83−84 °C. R_f 0.57 (petroleum ether/EtOAc 9/1). Yield: 75% (0.69 g). ^1H NMR (400 MHz, $CDCl_3$): δ 0.24 (3H, s), 0.31 (3H, s), 1.01 (9H, s), 4.00 (1H, ddd, $J_{H,F}$ = 18.7 Hz, J = 15.0 Hz, $J_{H,F}$ = 4.2 Hz), 5.43 (1H, ddd, $J_{H,F}$ = 19.0 Hz, J = 15.0 Hz, $J_{H,F}$ = 10.1 Hz), 6.75−6.79 (2H, m), 7.07−7.14 (2H, m), 7.20 (2H, d, J = 8.5 Hz), 7.26 (2H, d, J = 8.5 Hz). ^{13}C NMR (100.6 MHz, ref = $CDCl_3$): δ −4.4, −4.0, 18.0, 25.6, 56.5 (dd, J = 24.8 Hz, 22.6 Hz), 118.7, 120.5 (dd, J = 311.2 Hz, 308.4 Hz), 121.2, 124.4, 129.5, 129.7 (2×), 130.6 (2×), 131.3, 132.6, 133.6, 150.6, 171.1. ^{19}F NMR (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ −49.27 (1F, ddd, J = 154.4 Hz, $J_{H,F}$ = 19.0 Hz, 4.2 Hz), −50.85 (1F, ddd, J = 154.4 Hz, $J_{H,F}$ = 18.7 Hz, 10.1 Hz). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1664, ν_{max} = 1479, 1282, 1100, 908, 732. MS (ES^+): m/z (%): 548/50/52 (M + H^+, 100). HRMS (ES^+): calcd for $C_{21}H_{26}Br_2F_2NO_2Si^+$: 548.0062, found 548.0063.

Synthesis of Enamide 24a. To a solution of benzamide **23a** (0.11 g, 0.24 mmol) in anhydrous THF (10 mL) was added a solution of LiO*t*Bu in THF (1 M, 0.24 mL, 1 equiv). After this reaction mixture was stirred at room temperature for 1.5 h, a saturated solution of NH_4Cl in H_2O (10 mL) was added. After extraction with EtOAc (3 × 10 mL), drying ($MgSO_4$), filtration, and evaporation of the solvent in vacuo, crude enamide **24a** was obtained. Purification via preparative TLC (SiO_2, PE/EtOAc 95/5) afforded pure enamide **24a** in 73% yield (0.067 g).

***N*-{2-[(*tert*-Butyldimethylsilyl)oxy]phenyl}-*N*-(2,2-difluorovinyl)benzamide 24a.** Colorless oil. R_f 0.43 (petroleum ether/EtOAc 9/1). Yield: 73% (0.067 g). ^1H NMR (400 MHz, $CDCl_3$, 50 °C): δ 0.23 (6H, s), 0.99 (9H, s), 6.22 (1H, br s), 6.75 (1H, d, J = 7.4 Hz), 6.83 (1H, t, J = 7.5 Hz), 7.08−7.18 (4H, m), 7.24−7.28 (1H, m), 7.34−7.42 (2H, m). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ −4.3 (2×), 18.2, 25.7, 89.3 (d, J = 53.8 Hz), 119.1, 121.2, 127.5 (2×), 128.3 (2×), 129.2, 130.0, 130.2, 132.0, 134.7, 151.2, 154.6 (dd, J = 297.3 Hz, 280.2 Hz), 169.9. ^{19}F NMR (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ −89.07 (1F, dd, J = 52.2 Hz, $J_{H,F}$ = 18.2 Hz), −103.03 (1F, d, J = 52.2 Hz). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1663, ν_{max} = 1327, 1284, 913, 781, 714, 695. MS (ES^+): m/z (%): 390 (M + H^+, 100). HRMS (ES^+): calcd for $C_{21}H_{26}F_2NO_2Si^+$: 390.1695, found 390.1693.

Synthesis of Ynamides 25. The synthesis of *N*-{2-[(*tert*-butyldimethylsilyl)oxy]phenyl}-*N*-(2-fluoroethynyl)benzamide **25a** is given as representative example. To a solution of benzamide **23a** (0.30 g, 0.64 mmol) in anhydrous THF (30 mL) was added a solution of LiHMDS in THF (1 M, 1.40 mL, 2.2 equiv) at 0 °C. The reaction mixture was allowed to warm to room temperature and was stirred at that temperature for 2.5 h. Subsequently, an aqueous solution of NH_4Cl (30 mL) was added and this mixture was extracted with EtOAc (3 × 20 mL). Drying of the combined organic layers ($MgSO_4$), filtration, and evaporation of the solvent under reduced pressure afforded ynamide **19a**, which was purified via column chromatography (SiO_2, PE/EtOAc 95/5) (97% yield, 0.23 g).

***N*-{2-[(*tert*-Butyldimethylsilyl)oxy]phenyl}-*N*-(2-fluoroethynyl)benzamide 25a.** Pale yellow crystals. Melting point: 72−73 °C. R_f 0.21 (petroleum ether/EtOAc 95/5). Yield: 97% (0.23 g). ^1H NMR (300 MHz, $CDCl_3$): δ 0.18 (6H, s), 0.94 (9H, s), 6.68−6.80 (1H, m), 6.83−6.92 (1H, m), 7.11−7.13 (2H, m), 7.24−7.41 (5H, m). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ −4.6 (2×), 18.4, 27.5, 98.5 (d, J = 55.4 Hz), 116.4, 124.5, 125.0, 126.6, 128.1 (2×), 128.4 (2×), 129.8, 130.3, 135.3, 150.8, 162.5 (d, J = 274.6 Hz), 169.5. ^{19}F NMR (282 MHz, $CDCl_3$, ref = $CFCl_3$): δ −89.78 (1F, s). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1657, ν_{max} = 1491, 1347, 1244. MS (ES^+): m/z (%): 370 (M + H^+, 100). HRMS (ES^+): calcd for $C_{21}H_{25}FNO_2Si^+$: 370.1633, found 370.1643.

***N*-{2-[(*tert*-Butyldimethylsilyl)oxy]phenyl}-*N*-(2-fluoroethynyl)-4-methoxybenzamide 25c.** Yellow oil. R_f 0.63 (petroleum ether/EtOAc 9/1). Yield: 94% (0.160 g). ^1H NMR (400 MHz, $CDCl_3$): δ 0.14 (6H, s), 0.92 (9H, s), 3.77 (3H, s), 6.77 (2H, d, J = 8.5 Hz), 6.90−6.94 (2H, m), 7.09−7.12 (2H, m), 7.32 (2H, d, J = 8.5 Hz). ^{13}C NMR (100.6 MHz, ref = $CDCl_3$): δ −4.70, −4.67, 18.3, 27.3, 55.2, 98.7 (d, J = 54.3 Hz), 113.2 (2×), 116.2, 124.5, 125.0, 126.3, 127.4, 130.2, 130.6 (2×), 150.8, 161.1, 162.4 (d, J = 274.3 Hz), 168.7. ^{19}F NMR (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ −89.92 (1F, s). IR (ATR, cm^{-1}): $\nu_{C\equiv C}$ = 2244, $\nu_{C=O}$ = 1649, ν_{max} = 1245, 732. MS (ES^+): m/z (%): 400 (M + H^+, 100). HRMS (ES^+): calcd for $C_{22}H_{27}FNO_3Si^+$: 400.1739, found 400.1748.

***N*-{2-[(*tert*-Butyldimethylsilyl)oxy]phenyl}-*N*-(2-fluoroethynyl)-4-bromobenzamide 25d.** Yellow crystals. Melting point: 87−88 °C. R_f 0.63 (petroleum ether/EtOAc 9/1). Yield: 83% (0.14 g). ^1H NMR (400 MHz, $CDCl_3$): δ 0.18 (6H, s), 0.93 (9H, s), 6.73 (1H, br s), 6.91 (1H, ddd, J = 8.0 Hz, 6.5 Hz, 2.1 Hz), 7.11−7.17 (4H, m), 7.41 (2H, d, J = 8.5 Hz). ^{13}C NMR (100.6 MHz, ref = $CDCl_3$): δ −4.6, −4.5, 18.4, 27.4, 89.5 (d, J = 54.9 Hz), 116.6, 124.7, 124.8, 124.9, 126.8, 129.5, 130.1 (2×), 131.3 (2×), 134.1, 150.7, 162.5 (d, J = 274.1 Hz), 168.2. ^{19}F NMR (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ −89.49 (1F, s). IR (ATR, cm^{-1}): $\nu_{C\equiv C}$ = 2247, $\nu_{C=O}$ = 1651, ν_{max} = 1247, 730. MS (ES^+): m/z (%): 448/50 (M + H^+, 100). Anal. Calcd for $C_{21}H_{23}BrFNO_2Si$: C 56.25, H 5.17, N 3.12. Found: C 56.30, H 4.73, N 3.02. HRMS (ES^+): calcd for $C_{21}H_{24}BrFNO_2Si^+$: 448.0738, found 448.0734.

Synthesis of Benzoxazines 26a−c. The synthesis of benzoxazine **26a** is described as a representative example. To a solution of benzamide **23a** (0.10 g, 0.21 mmol) in anhydrous THF (10 mL) was added a solution of KO*t*Bu in THF (1 M, 0.21 mL, 1 equiv). After this reaction mixture was stirred at room temperature for 2 h, a saturated solution of NH_4Cl in H_2O (10 mL) was added. After extraction with EtOAc (3 × 10 mL), drying ($MgSO_4$), filtration, and evaporation of the solvent in vacuo, crude benzoxazine **26a** was obtained. Purification via preparative TLC (SiO_2, PE/EtOAc 95/5) afforded pure benzoxazine **26a** in 80% yield (0.043 g).

4-Benzoyl-2-fluorobenzo[*b*][1,4]oxazine 26a. Yellow oil. R_f 0.33 (petroleum ether/EtOAc 9/1). Yield: 80% (0.043 g). ^1H NMR (300 MHz, $CDCl_3$): δ 6.16 (1H, br s), 6.98−7.14 (3H, m), 7.40−7.56 (6H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 89.4 (d, J = 48.5 Hz), 117.1,

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123.2, 125.0, 126.7, 127.7, 128.1 (2×), 128.8 (2×), 131.1, 134.7, 147.2, 153.1 (d, J = 259.6 Hz), 167.5. ^{19}F NMR (282 MHz, $CDCl_3$, ref = $CFCl_3$): δ −112.33 (1F, br s). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1657, ν_{max} = 1490, 1340, 1243, 748, 697. MS (ES$^+$): m/z (%): 256 (M + H$^+$, 30). HRMS (ES$^+$): calcd for $C_{15}H_{11}FNO_2^+$: 256.0768, found 256.0780.

4-Benzoyl-2-fluoro-7-methoxybenzo[*b*][1,4]oxazine 26b. Yellow oil. R_f 0.22 (petroleum ether/EtOAc 9/1). Yield: 82% (0.048 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.78 (3H, s), 6.12 (1H, br s), 6.57−6.58 (2H, m), 7.40−7.54 (6H, m). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 55.8, 89.5 (d, J = 47.2 Hz), 103.0, 110.1, 120.7, 123.7, 128.0 (2×), 128.7 (2×), 130.8, 135.1, 147.9, 152.8 (d, J = 258.7 Hz), 158.2, 167.2. ^{19}F NMR (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ −113.34 (1F, br s). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1651, ν_{max} = 1503, 1307, 1246, 699. MS (ES$^+$): m/z (%): 286 (M + H$^+$, 100). HRMS (ES$^+$): calcd for $C_{16}H_{13}FNO_3^+$: 286.0874, found 286.0879.

4-(4-Methoxybenzoyl)-2-fluorobenzo[*b*][1,4]oxazine 26c. Yellow crystals. Melting point: 68−69 °C. R_f 0.06 (petroleum ether/EtOAc 9/1). Yield: 70% (0.077 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.84 (3H, s), 6.22 (1H, d, J = 2.8 Hz), 6.90 (2H, d, J = 8.9 Hz), 6.98 (1H, ddd, J = 9.6 Hz, 7.1 Hz, 1.6 Hz), 6.98−7.00 (1H, m), 7.08 (1H, ddd, J = 8.4 Hz, 7.1 Hz, 1.4 Hz), 7.51−7.55 (3H, m). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 55.4, 89.5 (d, J = 47.6 Hz), 113.8 (2×), 117.0, 123.0, 124.8, 126.3, 126.5, 128.1, 130.3 (2×), 147.1, 153.0 (d, J = 261.6 Hz), 161.8, 169.9. ^{19}F NMR (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ −113.01 (1F, d, $J_{H,F}$ = 2.5 Hz). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1652, ν_{max} = 1605, 1238, 1180, 756. MS (ES$^+$): m/z (%): 286 (M + H$^+$, 100). HRMS (ES$^+$): calcd for $C_{16}H_{13}FNO_3^+$: 286.0874, found 286.0880.

Synthesis of Benzoxazine 26d. To a solution of *N*-{2-[(*tert*-butyldimethylsilyl)oxy]phenyl}-*N*-(2-fluoroethynyl)-4-bromobenzamide **25d** (0.11 g, 0.23 mmol) in anhydrous THF (10 mL) at 0 °C was added a solution of TBAF in THF (1 M, 0.23 mL, 1 equiv). Stirring was continued for 1 h at the same temperature. Subsequently, the reaction mixture was quenched with H_2O (10 mL) and extracted with EtOAc (3 × 10 mL). After drying of the organic layers ($MgSO_4$), filtration, and evaporation of the solvent, crude benzoxazine **26d** was obtained. Purification by means of preparative TLC (SiO_2, PE/EtOAc 9/1) afforded benzoxazine **26d** in 86% yield (0.067 g)

4-(4-Bromobenzoyl)-2-fluorobenzo[*b*][1,4]oxazine 26d. Yellow oil. R_f 0.40 (petroleum ether/EtOAc 9/1). Yield: 86% (0.067 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.14 (1H, br s), 7.00−7.03 (2H, m), 7.13 (1H, ddd, J = 8.1 Hz, 7.4 Hz, 1.4 Hz), 7.41−7.58 (5H, m). ^{13}C NMR (100.6 MHz): δ 89.1 (d, J = 47.7 Hz), 117.1, 123.0, 124.9, 125.6, 126.8, 127.4, 129.7 (2×), 131.9 (2×), 133.4, 147.1, 153.2 (d, J = 263.2 Hz), 166.1. ^{19}F NMR (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ −111.80 (1F, d, $J_{H,F}$ = 2.6 Hz). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1654, ν_{max} = 1489, 1345, 1242, 750. MS (ES$^+$): m/z (%): 334/36 (M + H$^+$, 100). HRMS (ES$^+$): calcd for $C_{15}H_{10}BrFNO_2^+$: 333.9873, found 333.9875.

Synthesis of Benzamides 29a−c. The synthesis of benzamide **29a** is described as representative example. To a mixture of *N*-propyl-2-bromo-2,2-difluoroethylamine **6a** (0.54 g, 2.7 mmol) and *O*-acetylsalicyloyl chloride **28a** (0.53 g, 2.7 mmol, 1 equiv) in THF (30 mL) was slowly added triethylamine (1.35 g, 13 mmol, 5 equiv) at room temperature. After this reaction mixture was stirred at the same temperature for 2 h, an aqueous solution of HCl (1 N, 30 mL) was added and an extraction with Et_2O (3 × 20 mL) was performed. After drying ($MgSO_4$), filtration, and evaporation of the solvent, benzamide **29a** was purified via column chromatography (SiO_2, PE/EtOAc 85/15) and obtained in 55% yield (0.53 g).

2-Acetoxy-*N*-(2-bromo-2,2-difluoroethyl)-*N*-(propyl)-benzamide 29a. Colorless oil. R_f 0.29 (petroleum ether/EtOAc 85/15). Yield: 55% (0.53 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.74 (2.3H, t, J = 7.4 Hz (major)), 0.98 (0.7H, t, J = 7.3 Hz (minor)), 1.50 (1.5H, sextet, J = 7.4 Hz (major)), 1.68 (0.5H, sextet, J = 7.3 Hz (minor)), 2.26 (3H, s), 3.28 (2H, t, J = 7.6 Hz), 3.83−4.62 (2H, m), 7.20 (1H, d, J = 8.1 Hz), 7.30 (1H, d, J = 6.7 Hz), 7.33 (1H, ddd, J = 7.3 Hz, 7.3 Hz, 1.7 Hz), 7.45 (1H, ddd, J = 8.2 Hz, 7.3 Hz, 1.9 Hz). ^{13}C NMR (100.6 MHz, ref = $CDCl_3$, 50 °C): δ 10.6 (major), 11.2 (minor), 19.8 (minor), 20.7, 20.9 (major), 47.7 (minor), 50.6 (major), 51.8 (t, J = 23.7 Hz (major)), 57.7 (t, J = 23.3 Hz (minor)), 120.5 (t, J = 309.6 Hz), 123.1, 125.9, 127.4, 130.4 (4× (major)), 122.9, 126.0, 128.0, 130.6 (4× (minor)), 128.7 (minor), 128.8 (major), 146.6, 168.6, 168.7, 168.9. ^{19}F NMR (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ −50.86 (2F, br s). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1767, $\nu_{C=O}$ = 1651, ν_{max} = 1192, 1177, 1078. MS (ES$^+$): m/z (%): 364/66 (M + H$^+$, 100). HRMS (ES$^+$): calcd for $C_{14}H_{17}BrF_2NO_3^+$: 364.0354, found 364.0355.

2-Acetoxy-*N*-(2-bromo-2,2-difluoroethyl)-*N*-(benzyl)-benzamide 29b. Yellow oil. R_f 0.15 (petroleum ether/EtOAc 85/15). Yield: 95% (5.66 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.03 (0.7H, s (minor)), 2.32 (2.3H, s (major)), 3.57−4.43 (2H, br s), 4.57 (2H, s), 7.12 (2H, d, J = 6.8 Hz), 7.21−7.46 (7H, m). ^{13}C NMR (100.6 MHz, ref = $CDCl_3$): δ 20.6 (minor), 20.8 (major), 47.9 (minor), 51.5 (t, J = 23.6 Hz (major)), 53.0 (major), 56.0 (t, J = 23.9 Hz (minor)), 120.4 (t, J = 309.5 Hz), 123.0 (minor), 123.3 (major), 126.2, 127.3 (2×), 127.5, 128.2, 128.4 (minor), 128.5 (major), 128.9 (2× (minor)), 129.1 (2× (major)), 130.8, 135.2 (major), 147.0 (major), 135.8 (minor), 146.5 (minor), 168.81, 168.85, 168.9, and 169.1 (2× major and 2× minor). ^{19}F NMR (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ −49.11−52.76 (2F, m). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1767, $\nu_{C=O}$ = 1656, ν_{max} = 1190, 1076, 910, 730. MS (ES$^+$): m/z (%): 412/14 (M + H$^+$, 100). HRMS (ES$^+$): calcd for $C_{18}H_{17}BrF_2NO_3^+$: 412.0354, found 412.0361.

2-Acetoxy-*N*-(2-bromo-2,2-difluoroethyl)-*N*-(4-methoxybenzyl)benzamide 29c. White crystals. Melting point: 109−110 °C. R_f 0.11 (petroleum ether/EtOAc 9/2). Yield: 78% (1.21 g). ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C): δ 2.04 (0.6H, s (minor)), 2.30 (2.4H, s (major)), 3.80 (3H, s), 3.89 (0.4H, br s (minor)), 4.30 (1.6H, br s (major)), 4.49 (2H, s), 6.86−6.88 (2H, m), 7.02−7.04 (2H, m), 7.20−7.27 (2H, m), 7.38−7.45 (2H, m). ^{13}C NMR (100.6 MHz, ref = $CDCl_3$): δ 20.6 (minor), 20.8 (major), 47.2 (minor), 51.0 (t, J = 23.7 Hz (major)), 52.4 (major), 55.2, 55.8 (t, J = 23.5 Hz (minor)), 114.2 (2× (minor)), 114.4 (2× (major)), 120.5 (t, J = 309.5 Hz), 123.0 (minor), 123.2 (major), 126.2, 126.8, 127.6 (major), 127.8 (minor), 128.26 (minor), 128.33 (2× (minor)), 128.5 (major), 128.8 (2× (major)), 130.4 (minor)), 130.8 (major), 146.4 (minor), 146.9 (major), 159.5, 168.7, 168.8, 168.9. ^{19}F NMR (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ −48.54 to −52.33 (2F, m). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1765, $\nu_{C=O}$ = 1654, ν_{max} = 1188, 1080, 925, 790. MS (ES$^+$): m/z (%): 442/44 (M + H$^+$, 100). HRMS (ES$^+$): calcd for $C_{19}H_{19}BrF_2NO_4^+$: 442.0460, found 442.0458.

Synthesis of Benzamides 29d,e. The synthesis of benzamide **29d** is described as representative example. A solution of 2,5-diacetoxybenzoic acid (0.22 g, 0.94 mmol) in $SOCl_2$ (distilled, 1 mL) was stirred at reflux temperature for 15 min. Subsequently, the residual $SOCl_2$ was evaporated under reduced pressure. The resulting acid chloride was used without purification and redissolved in anhydrous THF (20 mL), and *N*-(4-methoxybenzyl)-2-bromo-2,2-difluoroethylamine **6c** (0.26 g, 1 equiv) and Et_3N (0.19 g, 2 equiv) were added at 0 °C. Subsequently, the reaction mixture was stirred at room temperature for 22 h, after which H_2O (20 mL) was added and an extraction was performed with EtOAc (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and filtered, and the solvent was removed in vacuo. Purification via flash chromatography (SiO_2, PE/EtOAc 7/3) afforded benzamide **29d** in 72% yield (0.34 g).

2,5-Diacetoxy-*N*-(2-bromo-2,2-difluoroethyl)-*N*-(4-methoxybenzyl)benzamide 29d. Yellow oil. R_f 0.17 (petroleum ether/EtOAc 7/3). Yield: 72% (0.34 g). ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C): δ 2.03 (0.9H, br s (minor)), 2.27 (3H, s), 2.29 (2.1H, br s (major)), 3.80 (3H, s), 3.89 (0.6H, br s (minor)), 4.27 (1.4H, br s (major)), 4.50 (2H, br s), 6.86−6.88 (2H, m), 7.03−7.05 (2H, m), 7.15−7.25 (3H, m). ^{13}C NMR (100.6 MHz): δ 20.6 (minor), 20.8 (major), 21.0, 47.4 (minor), 51.0 (t, J = 23.6 Hz (major)), 52.6 (major), 55.3, 55.8 (t, J = 24.0 Hz (minor)), 114.3 (2× (minor)), 114.5 (2× (major)), 120.5 (t, J = 309.3 Hz), 120.9 (major), 121.6 (minor), 123.9, 124.0 (minor), 124.2 (major), 126.6, 129.17 (2× (major)), 129.24 (2× (minor)), 130.5, 143.8 (minor), 144.2 (major), 148.0, 159.5 (minor), 159.6 (major), 167.6 (minor), 167.8 (major), 168.8 (2×). ^{19}F NMR (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ −48.49 to −51.32 (2F, m). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1763, $\nu_{C=O}$ = 1655, ν_{max} = 1201, 1163. MS (ES$^+$): m/z (%): 517/19 (M + NH_4^+, 100), 500/02 (M + H$^+$, 98). HRMS (ES$^+$): calcd for $C_{21}H_{21}BrF_2NO_6^+$: 500.0515, found 500.0496.

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2-Acetoxy-5-methoxy-*N*-(2-bromo-2,2-difluoroethyl)-*N*-(4-methoxybenzyl)benzamide 29e. White crystals. Melting point: 94−95 °C. R_f 0.12 (petroleum ether/EtOAc 9/2). Yield: 67% (0.19 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.02 (0.7H, s (minor)), 2.29 (2.3H, s), 3.75 (3H, s), 3.80 (3H, s), 3.81 (2H, br s), 4.51 (2H, br s), 6.86−6.88 (3H, m), 6.95 (1H, dd, J = 9.0 Hz, 2.9 Hz), 7.04 (2H, d, J = 8.6 Hz), 7.12 (1H, d, J = 9.0 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 18.8 (minor), 19.0 (major), 49.4 (t, J = 23.1 Hz), 50.7, 53.5, 53.9, 110.5 (major), 110.9 (minor), 112.4 (2× (minor)), 112.6 (2× (major)), 114.4 (major), 114.8 (minor), 118.6 (t, J = 309.6 Hz), 122.2 (minor), 122.4 (major), 125.1 (major), 125.9 (minor), 127.0 (2× (major)), 127.4 (2× (minor)), 128.7, 137.9 (minor), 138.4 (major), 155.4, 157.7, 166.7 (minor), 166.9 (major), 167.4 (minor), 167.5 (major). ^{19}F NMR (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ −48.56 to −52.09 (2F, m). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1762, $\nu_{C=O}$ = 1650, ν_{max} = 1188, 1110, 1029. MS (ES$^+$): m/z (%): 472/74 (M + H$^+$, 100). HRMS (ES$^+$): calcd for $C_{20}H_{21}BrF_2NO_5^+$: 472.0566, found 472.0557. Anal. Calcd for $C_{20}H_{20}BrF_2NO_5$: C 50.86, H 4.27, N 2.97. Found: C 50.73, H 4.21, N 2.92.

Synthesis of Benzamide 30a, Enamide 31a, and 2-Fluoro-1,4-benzoxazepin-5-one 32a. To an ice-cooled solution of benzamide **29a** (0.086 g, 0.24 mmol) in anhydrous THF (5 mL) was added a solution of LiHMDS in THF (1 M, 0.52 mL, 2.2 equiv), and the resulting mixture was stirred at room temperature for 5 h. Subsequently, the reaction mixture was poured into a saturated solution of NH_4Cl in H_2O (5 mL) and extracted with EtOAc (3 × 10 mL). Drying ($MgSO_4$), filtration of the drying agent, and removal of the solvent afforded benzamide **30a**, enamide **31a**, and 2-fluoro-1,4-benzoxazepin-5-one **32a**, which were further purified in 30% (0.024 g), 17% (0.010 g), and 31% (0.0.16 g) yield, respectively, by preparative TLC (PE/EtOAc 9/1).

***N*-2-Bromo-2,2-difluoroethyl-*N*-propyl-(2-hydroxy)-benzamide 30a.** Yellow oil. R_f 0.04 (petroleum ether/EtOAc 9/1). Yield: 30% (0.024 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.82 (3H, t, J = 7.4 Hz), 1.60 (2H, sextet, J = 7.4 Hz), 3.64 (2H, t, J = 7.4 Hz), 4.40 (2H, t, $J_{H,F}$ = 12.3 Hz), 6.91 (1H, ddd, J = 7.8 Hz, 7.3 Hz, 0.9 Hz), 7.03 (1H, dd, J = 8.3 Hz, 0.9 Hz), 7.33 (1H, dd, J = 7.8 Hz, 1.6 Hz), 7.37 (1H, ddd, J = 8.3 Hz, 7.3 Hz, 1.6 Hz), 8.76 (1H, br s). ^{13}C NMR (100.6 MHz, ref = $CDCl_3$): δ 10.9, 21.1, 51.6, 53.9, 117.8, 118.7, 119.4, 120.9 (t, J = 309.5 Hz), 128.1, 132.6, 157.0, 173.4. ^{19}F NMR (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ −50.47 (2H, t, $J_{H,F}$ = 12.3 Hz). IR (ATR, cm^{-1}): ν_{OH} = 3174, $\nu_{C=O}$ = 1620, ν_{max} = 1595, 1083, 751. MS (ES$^+$): m/z (%): 322/24 (M + H$^+$, 100). HRMS (ES$^+$): calcd for $C_{12}H_{15}BrF_2NO_2^+$: 322.0249, found 322.0247.

***N*-2,2-Difluorovinyl-*N*-propyl-(2-hydroxy)benzamide 31a.** White powder. Melting point: 59−60 °C. R_f 0.11 (petroleum ether/EtOAc 9/1). Yield: 17% (0.010 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.96 (3H, t, J = 7.5 Hz), 1.69 (2H, sextet, J = 7.5 Hz), 3.60 (2H, t, J = 7.5 Hz), 5.61 (1H, dd, $J_{H,F}$ = 19.3 Hz, 2.1 Hz), 6.83 (1H, ddd, J = 7.9 Hz, 7.3 Hz, 1.0 Hz), 7.00 (1H, dd, J = 8.3 Hz, 1.0 Hz), 7.35 (1H, ddd, J = 8.3 Hz, 7.3 Hz, 1.5 Hz), 7.43 (1H, dd, J = 7.9 Hz, 1.5 Hz), 9.95 (1H, br s). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 11.2, 20.6, 50.3, 89.6 (dd, J = 49.4 Hz, 13.3 Hz), 116.3, 118.1, 118.3, 128.7, 133.5, 155.4 (dd, J = 295.9 Hz, 287.7 Hz), 159.8, 171.6. ^{19}F NMR (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ −87.33 (1F, dd, J = 40.8 Hz, $J_{H,F}$ = 19.3 Hz), −99.90 (1F, d, J = 40.8 Hz). IR (ATR, cm^{-1}): ν_{OH} = 3159, $\nu_{C=O}$ = 1616, ν_{max} = 1233, 760. MS (ES$^+$): m/z (%): 242 (M + H$^+$, 100). HRMS (ES$^+$): calcd for $C_{12}H_{14}F_2NO_2^+$: 242.0987, found 242.0987.

2-Fluoro-4-propylbenzo[*f*][1,4]oxazepin-5-one 32a. Pale yellow oil. R_f 0.17 (petroleum ether/EtOAc 9/1). Yield: 31% (0.016 g) (67% (0.076 g) yield was obtained following the procedure described below). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.97 (3H, t, J = 7.4 Hz), 1.70 (2H, sextet, J = 7.4 Hz), 3.57−3.61 (2H, m), 5.50 (1H, d, $J_{H,F}$ = 3.7 Hz), 7.11 (1H, dd, J = 8.2 Hz, 1.1 Hz), 7.29 (1H, ddd, J = 7.8 Hz, 7.4 Hz, 1.1 Hz), 7.48 (1H, ddd, J = 8.2 Hz, 7.4 Hz, 1.8 Hz), 7.92 (1H, dd, J = 7.8 Hz, 1.8 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 11.1, 21.1, 49.9, 95.8 (d, J = 57.7 Hz), 119.4, 125.98, 126.02, 132.6, 133.3, 156.8 (d, J = 279.7 Hz), 159.7 (d, J = 4.3 Hz), 165.1. ^{19}F NMR (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ −99.24 (1F, d, $J_{H,F}$ = 3.7 Hz). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1639, ν_{max} = 1453, 1411, 1192, 759. MS (ES$^+$): m/z (%): 222 (M + H$^+$, 100). HRMS (ES$^+$): calcd for $C_{12}H_{13}FNO_2^+$: 222.0925, found 222.0930.

Synthesis of Benzo[*f*][1,4]oxazepin-5-ones 32a−e. As a representative example, the synthesis of 2-fluoro-4-(4-methoxybenzyl)-benzo[*f*][1,4]oxazepin-5-one **32c** is described here. To a solution of benzamide **29c** (1.15 g, 2.6 mmol) in anhydrous THF (30 mL) was added a solution of KO*t*Bu in THF (1 M, 5.2 mL, 2 equiv) at room temperature. After the reaction mixture was stirred at reflux temperature for 3 h, a saturated aqueous solution of NH_4Cl (30 mL) was added. After extraction (3 × 30 mL EtOAc), drying with $MgSO_4$, filtration of the drying agent, and evaporation of the solvent, crude oxazepin-5-one **32c** was obtained. Purification by means of column chromatography (SiO_2, PE/EtOAc 9/1) afforded pure oxazepin-5-one **32c** in 77% yield (0.60 g).

4-Benzyl-2-fluorobenzo[*f*][1,4]oxazepin-5-one 32b. White crystals. Melting point: 65−66 °C. R_f 0.19 (petroleum ether/EtOAc 9/1). Yield: 62% (0.40 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.85 (2H, s), 5.49 (1H, d, $J_{H,F}$ = 3.7 Hz), 7.11 (1H, dd, J = 8.2 Hz, 1.1 Hz), 7.28−7.38 (5H, m), 7.49 (1H, ddd, J = 8.2 Hz, 7.4 Hz, 1.8 Hz), 7.99 (1H, dd, J = 7.8 Hz, 1.8 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 51.5, 95.3 (d, J = 58.1 Hz), 119.5, 125.6 (d, J = 2.1 Hz), 126.1, 127.8, 128.0 (2×), 128.8 (2×), 132.8, 133.6, 136.0, 156.9 (d, J = 280.1 Hz), 159.7 (d, J = 4.4 Hz), 165.3. ^{19}F NMR (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ −98.64 (1F, d, $J_{H,F}$ = 3.7 Hz). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1627, ν_{max} = 1451, 1420, 1196, 692. MS (ES$^+$): m/z (%): 270 (M + H$^+$, 100). HRMS (ES$^+$): calcd for $C_{16}H_{13}FNO_2^+$: 270.0925, found 270.0921.

2-Fluoro-4-(4-methoxybenzyl)benzo[*f*][1,4]oxazepin-5-one 32c. Yellow oil. R_f 0.12 (petroleum ether/EtOAc 9/1). Yield: 77% (0.60 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.80 (3H, s), 4.78 (2H, s), 5.48 (1H, d, $J_{H,F}$ = 3.7 Hz), 6.88 (2H, d, J = 8.6 Hz), 7.11 (1H, dd, J = 8.2 Hz, 1.0 Hz), 7.27 (2H, d, J = 8.6 Hz), 7.31 (1H, ddd, J = 7.8 Hz, 7.4 Hz, 1.0 Hz), 7.49 (1H, ddd, J = 8.2 Hz, 7.4 Hz, 1.8 Hz), 7.98 (1H, dd, J = 7.8 Hz, 1.8 Hz). ^{13}C NMR (100.6 MHz, ref = $CDCl_3$): δ 50.8, 55.0, 95.2 (d, J = 58.1 Hz), 114.0 (2×), 119.3, 125.5 (d, J = 2.1 Hz), 125.9, 128.0, 129.3 (2×), 132.6, 133.4, 156.6 (d, J = 279.9 Hz), 159.2, 159.5 (d, J = 4.3 Hz), 165.0. ^{19}F NMR (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ −98.67 (1F, d, $J_{H,F}$ = 3.7 Hz). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1640, ν_{max} = 1246, 1218, 1200, 1137, 760. MS (ES$^+$): m/z (%): 300 (M + H$^+$, 100). HRMS (ES$^+$): calcd for $C_{17}H_{15}FNO_3^+$: 300.1030, found 300.1023.

2-Fluoro-7-hydroxy-4-(4-methoxybenzyl)benzo[*f*][1,4]-oxazepin-5-one 32d. Brown crystals. Melting point: 108−109 °C. Yield: 86% (0.10 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.80 (3H, s), 4.77 (2H, s), 5.39 (1H, br s), 5.44 (1H, d, $J_{H,F}$ = 3.8 Hz), 6.88 (2H, d, J = 8.7 Hz), 6.94−7.00 (2H, m), 7.24−7.26 (2H, m), 7.44 (1H, d, J = 2.9 Hz). ^{13}C NMR (100.6 MHz, ref = $CDCl_3$): δ 51.5, 55.4, 94.9 (d, J = 60.2 Hz), 114.3 (2×), 118.2, 120.7, 121.4, 125.5, 127.6, 129.5 (2×), 153.1 (d, J = 4.4 Hz), 154.8, 157.4 (d, J = 282.4 Hz), 159.4, 166.1. ^{19}F NMR (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ −97.96 (1F, s). IR (ATR, cm^{-1}): ν_{OH} = 3336, $\nu_{C=O}$ = 1634, ν_{max} = 1454, 1219, 1174, 813. MS (ES$^+$): m/z (%): 316 (M + H$^+$, 100). HRMS (ES$^+$): calcd for $C_{17}H_{15}FNO_4^+$: 316.0980, found 316.0975.

2-Fluoro-7-methoxy-4-(4-methoxybenzyl)benzo[*f*][1,4]-oxazepin-5-one 32e. Yellow oil. R_f 0.17 (petroleum ether/EtOAc 8/2). Yield: 88% (0.059 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.80 (3H, s), 3.83 (3H, s), 4.78 (2H, s), 5.44 (1H, d, $J_{H,F}$ = 3.8 Hz), 6.88 (2H, d, J = 8.8 Hz), 7.00−7.01 (2H, m), 7.27 (2H, d, J = 8.8 Hz), 7.44 (1H, dd, J = 2.4 Hz, 1.0 Hz). ^{13}C NMR (100.6 MHz, ref = $CDCl_3$): δ 51.2, 55.3, 55.9, 95.0 (d, J = 58.5 Hz), 114.3 (2×), 115.4, 120.3, 120.5, 126.2 (d, J = 2.2 Hz), 128.1, 129.5 (2×), 153.6 (d, J = 4.4 Hz), 157.26, 157.28 (d, J = 281.1 Hz), 159.4, 165.2. ^{19}F NMR (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ −98.49 (1F, d, $J_{H,F}$ = 3.8 Hz). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1640, ν_{max} = 1429, 1244, 1214, 1174, 1032. MS (ES$^+$): m/z (%): 330 (M + H$^+$, 100). HRMS (ES$^+$): calcd for $C_{18}H_{17}FNO_4^+$: 330.1136, found 330.1137.

Synthesis of Benzo[*f*][1,4]oxazepin-5-ones 33a,b. The synthesis of 2-fluorobenzo[*f*][1,4]oxazepin-5-one **33a** is described as representative example. A solution of 2-fluoro-4-(4-methoxybenzyl)-benzo[*f*][1,4]oxazepin-5-one **32c** (0.12 g, 0.38 mmol) in BF_3·OEt_2 (0.27 g, 5 equiv, 0.24 mL) was stirred at 128 °C for 6 h. Subsequently,

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Et_2O (10 mL) and $NaHCO_3$ (10 mL) were added and an extraction was performed with EtOAc (3 × 10 mL). After drying ($MgSO_4$), filtration, and evaporation of the organic phase in vacuo, Et_2O (10 mL) was added and the precipitate was filtered off. After evaporation, crude benzoxazepinone **33a** was obtained and recrystallized from Et_2O, affording pure benzoxazepinone **33a** in 51% yield (0.035 g).

2-Fluorobenzo[*f*][1,4]oxazepin-5-one 33a. White crystals. Melting point: 173−174 °C. Yield: 51% (0.035 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.60 (1H, t, $J_{H,F}$ = 4.0 Hz), 6.46 (1H, br s), 7.15 (1H, d, J = 8.1 Hz), 7.32 (1H, ddd, J = 7.8 Hz, 7.4 Hz, 0.7 Hz), 7.55 (1H, ddd, J = 8.1 Hz, 7.4 Hz, 1.7 Hz), 7.95 (1H, dd, J = 7.8 Hz, 1.7 Hz). ^{13}C NMR (100.6 MHz): δ 90.6 (d, J = 58.9 Hz), 120.2, 124.6 (d, J = 2.2 Hz), 126.1, 132.4, 134.4, 156.0 (d, J = 275.8 Hz), 158.7, 166.3. ^{19}F NMR (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ −100.91 (1F, br s). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1675, ν_{max} = 1223, 1180, 786, 752. MS (ES^+): m/z (%): 180 (M + H$^+$, 100). HRMS (ES^+): calcd for $C_9H_7FNO_2^+$: 180.0455, found 180.0454.

2-Fluoro-7-methoxybenzo[*f*][1,4]oxazepin-5-one 33b. White crystals. Melting point: 105−106 °C. Yield: 54% (0.044 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.83 (3H, s), 5.56 (1H, t, $J_{H,F}$ = 4.1 Hz), 6.50 (1H, br s), 7.05−7.06 (2H, m), 7.39−7.40 (1H, m). ^{13}C NMR (100.6 MHz, ref = $CDCl_3$): δ 56.0, 90.6 (d, J = 58.9 Hz), 115.0, 121.2, 121.3, 125.3 (d, J = 2.3 Hz), 152.7 (d, J = 3.7 Hz), 156.4 (d, J = 277.7 Hz), 157.3, 167.1. ^{19}F NMR (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ −100.65 (1F, d, $J_{H,F}$ = 4.1 Hz). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1673, ν_{max} = 1487, 1432, 1216, 1186, 768. MS (ES^+): m/z (%): 210 (M + H$^+$, 100). HRMS (ES^+): calcd for $C_{10}H_9FNO_3^+$: 210.0561, found 210.0558.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H NMR and ^{13}C NMR spectra of all new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b00507.

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Notes

The authors declare no competing financial interest.

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