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Research Article

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Synthesis of 2,2-difluoro-2-arylethylamines as fluorinated analogs of octopamine and noradrenaline

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Abstrtact: A series of 2,2-difluoro-2-arylethylamines was synthesized as fluorinated analogs of octopamine and noradrenaline with the expectation of bioisosteric OH/F exchanges. The syntheses of these compounds were performed by a Suzuki–Miyaura cross-coupling reaction of 4-(bromodifluoroacetyl)morpholine with aryl boronic acids to produce the intermediate 2,2-difluoro-2-arylacetamides, followed by transformation of difluoroacetamide to difluoroethylamine.

Keywords: difluoroacetamide, fluorine analogue, Suzuki–Miyaura coupling, octopamine, noradrenaline

1 Introduction

Noradrenaline and octopamine, very important neurotransmitters and hormones for controlling the physiological response of human and insect activities [1–7], are composed of two types of alcohols, catechols and benzylic hydroxy groups, both of which are important functionalities to form stable complexes with an adrenergic receptor for stimulating the adrenergic activity [8,9]. To avoid overstimulation, excess and unnecessary noradrenaline released for signaling are disabled upon enzymatic methylation of the alcohols by catechol-*O*-methyltransferase, enabling appropriate interaction with adrenergic receptors [10–12]. This mechanism suggests that the catechol hydroxy groups of noradrenaline play a key role in the biological response to maintain physiological homeostasis.

Conversely, recent studies of fluorine chemistry suggest that a fluorine substituent can mimic a hydroxy group in some biological responses because of the isoelectronic nature of fluorine and oxygen [13,14]. To date, some fluorinated pharmaceuticals or bioactive compounds have been developed with the aim of bioisosteric OH/F exchanges. For example, Tafluprost, a potential drug for glaucoma and ocular hypertension, is a structural and functional analog of prostaglandin $F_{2\alpha}$, the structure of which contains fluorine atoms to mimic a hydroxy group (Figure 1(a)). Tafluprost possesses a strong agonistic effect toward prostaglandin F receptor that is 12 times larger than the agonistic effect of Latanoprost, a drug commonly used for glaucoma [15]. In view of this success, we envisioned that the OH/F exchange approach is applicable to noradrenaline and octopamine to gain insight into the adrenergic activity of fluorine-substituted analogs. To address this challenge, we first designed target compounds **1a**–**d**, a series of fluorinated analogs of octopamine and noradrenalin, in which fluorine atoms were substituted for hydroxy groups to allow for OH/F bioisomeric exchange (Figure 1(b)). Among **1a**–**d**, **1a** and **d** have already been synthesized by Silverman and Bingham [16,17] even though the synthesis involves long and tedious operation in the difluorination process in which ketone must be converted to difluoromethylene by using *N*,*N*-diethylaminosulfar trifluoride (DAST) over 7 days. To circumvent this drawback, we explored a new strategy for the cross-coupling reaction to construct a core structure and finally discovered a straightforward access to the target compounds by the reaction of 4-(2-bromo-2,2-difluoroacetyl)morpholine **2** with arylboronic acids. Herein, we report an efficient synthetic method for preparing fluorinated analogs of octopamine and noradrenalin based on OH/F bioisomeric replacement, including a cross-coupling reaction of arylboronic acid and **2** followed by a functional modification for nitrogen insertion. In addition, we performed in silico docking study to evaluate the compatibility

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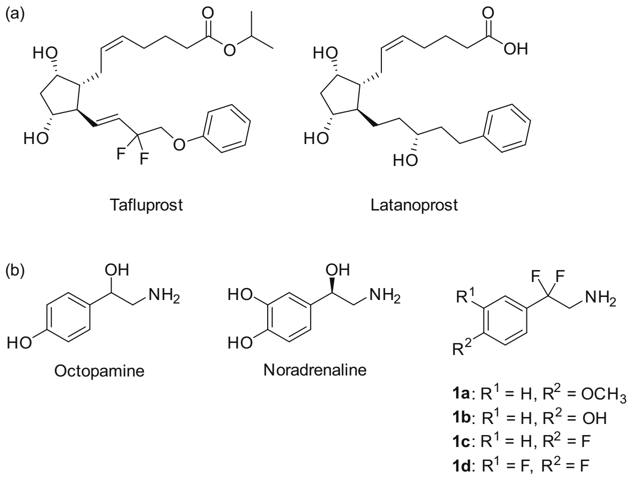


Figure 1: (a) Structure of tafluprost designed with bioisosteric OH/F exchanges approach and (b) structure of octopamine, noradrenaline, and four target analogs designed with bioisosteric OH/F exchanges.

of **1a**–**d** against the ligand-binding pocket of the β2-adrenergic receptor.

2 Results and discussion

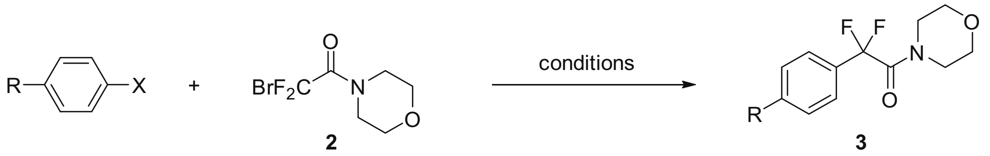
We commenced our study with the cross-coupling reaction of **2** with 4-methoxyphenylzinc chloride in a variant of our previously reported procedure for the Negishi coupling reaction (Table 1, entry 1) [18]. Although the reaction proceeded effectively to afford **3a** in excellent yield, the reaction was not scalable, leading to a significant decrease in the chemical yield when the reaction was conducted on a gram scale. This result forced us to explore new methods that would be scalable to the gram level. Among various cross-coupling reactions examined for introducing a difluoroethylene unit [19–23], using a method reported by Zhang's group [22], the reaction of **2** with arylboronic acid did not occur with a $NiCl_2$/DME complex. However, using a palladium catalyst to react arylboronic acid with two equivalents of **2** enabled the production of **3b** in 45% yield (Table 1, entries 2 and 3) [23]. While the use of $Ni(NO_3)_2/6H_2O$ as a catalyst retarded the reaction to give **3b** in 27% yield, the addition of PPh_3 improved the yield of the reaction significantly up to 69% yield (entries 4 and 5). Moreover, the addition of molecular sieves was effective, providing **3b** in 76% yield, which was found to be the optimal condition and also scalable to a gram-scale reaction (entry 6). For easy modification, ethyl bromodifluoroacetate instead of amide **2** was used for the cross-coupling reaction under the optimal conditions; however, the reaction yield was decreased to 44% (entry 7).

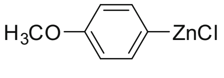
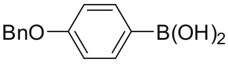
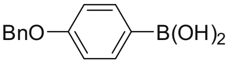
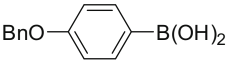
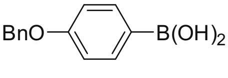
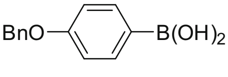
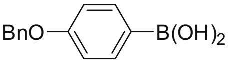
We next attempted to obtain analogs **3a** and **3c–d** using arylboronic acids with different substitution patterns under the optimal conditions thus established. All coupling reactions for **3** were carried out successfully in good yields. We then examined the functional modification of **3a–d** to **1a**–**d** (Scheme 1). Reduction of the amide moiety of **3** was conducted effectively according to Hartwig's method to provide the corresponding alcohols **5a–d**, suggesting that $NaBH_4$ was the reducing agent for the conversion of the difluoroamide moiety to difluoroethanol [24]. Transformation of difluoroethanol to difluoroethylamine was carried out by a two-step procedure of azide insertion followed by reduction, in which the hydroxy group was initially converted to triflate and the azide group was nucleophilically added [25], and then, the azide group was reduced to an amino group by catalytic hydrogenation.

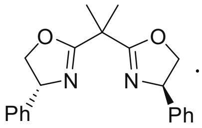
As mentioned earlier, noradrenaline is an endogenous ligand that acts on adrenergic receptors. Figure 2a shows the binding of noradrenaline to the β2-adrenergic receptor prepared from an adrenaline complex. The aromatic ring of noradrenaline forms π-interactions with Phe290, and the OH group on the phenyl ring forms a hydrogen bond with Asn293. In addition, the part that forms ammonium salts in the biological condition forms hydrogen bonds and ionic interactions with Asp113 and cation-π interactions with Phe193. The binding models for our compounds **1b** and **1d** were also prepared, and their interactions were evaluated (Figure 2b and c). The results show that the compounds are expected to form π-interactions with Phe290, hydrogen bonds and ionic interactions with Asp113, and cation-π interactions with Phe193.

The docking study was then performed to evaluate the compatibility of our synthesized compounds (**1a**–**d**) against the ligand-binding pocket of the β2-adrenergic receptor. The co-crystal structure of the adrenergic receptor with catecholamine (4LDO) was obtained from the Protein Data Bank. Fred [26] was used for the docking to obtain 20 scores (i.e., Chemgauss4 scores) for each of **1a**–**1d** and noradrenaline. As a result, the scores of noradrenaline exhibited the best among the five compounds (Figure 3). The results showed that the scores were better in the order of noradrenaline > **1b** > **1d** > **1c** > **1a**. As noradrenaline is an endogenous ligand, the docking result that noradrenaline has the best compatibility with adrenergic receptors seems to be reasonable. Among the derivatives we synthesized, **1b** appears to have the best compatibility with adrenergic receptors.

Table 1: Cross-coupling reaction of **2** for the formation of **3**



Entry	Cat. (mol%)/ligand (mol%)/additive (equiv.)	Substrate	Solvent	Temp. (°C)	Time	Product	Yield (%)
1	$NiCl_2$·DME (5)/oxazoline ligand[a] (6)	 (3 equiv)	THF	0	0.5	**3a**	91 (42)[b]
2	$NiCl_2$·DME (5)/bpy (5)/K_2CO_3 (2 equiv.)	 (1.5 equiv)	1,4-Dioxane	80	21	**3b**	0
3	$Pd(PPh_3)_4$ (5)/CuI (5)/Xanthophos (10)/K_2CO_3 (2 equiv.)	 (1.5 equiv)	1,4-Dioxane	80	24	**3b**	45
4	$Ni(NO_3)_2·6H_2O$ (5)/bpy (5)/K_2CO_3 (2 equiv.)	 (1.5 equiv)	1,4-Dioxane	80	24	**3b**	27
5	$Ni(NO_3)_2·6H_2O$ (5)/bpy (5)/PPh_3 (5)/K_2CO_3 (2 equiv.)	 (2 equiv)	1,4-Dioxane	80	24	**3b**	69
6	$Ni(NO_3)_2·6H_2O$ (5)/bpy (5)/PPh_3 (5)/K_2CO_3 (2 equiv.)/MS 4Å	 (2 equiv)	1,4-Dioxane	80	24	**3b**	76 (80)[c]
7[d]	$Ni(NO_3)_2·6H_2O$ (5)/bpy (5)/PPh_3 (5)/K_2CO_3 (2 equiv.)/MS 4Å	 (2 equiv)	1,4-Dioxane	80	24	**4**[e]	44

[a] 

. [b]Reaction carried out on a gram scale, 10 mmol of **2**. [c]Reaction carried out on a gram scale, 5 mmol of **2**. [d]Ethyl bromodifluoroacetate was used instead of **2**. [e]The product was the corresponding ethyl ester.

3 Conclusion

In conclusion, we have successfully synthesized a series of fluorinated analogs of octopamine and noradrenaline in which hydroxy groups have been replaced by fluorine atoms. For the synthesis, the cross-coupling reaction of arylboronic acid with **2** was carried out on a gram scale to construct core structures. Subsequent structural modification led to the formation of a difluoroaminoethyl moiety. In the view of bioisosteric rationale and in silico study, these compounds might be expected to mimic the behavior of octopamine and noradrenaline to some extent in biological systems. Examination of the ability of these compounds to mimic the biological responses of naturally occurring bioactive compounds is currently underway in our laboratory.

4 Experimental

NMR spectra were obtained from a solution in dimethyl sulfoxide (DMSO)-d_6 or $CDCl_3$ using 600 and 400 MHz for ^{1}H NMR, 100 MHz for ^{13}C, 376 MHz for ^{19}F NMR. DMSO-d_6 solution of NMR samples was recorded at 40°C, unless noted otherwise. Chemical shifts of ^{1}H and ^{13}C NMR are

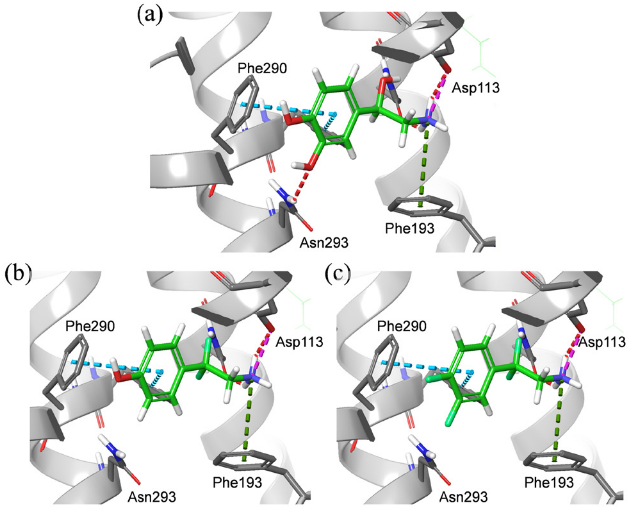


Figure 2: Binding models of (a) noradrenaline, (b) **1b**, and (c) **1d** with β2-adrenoceptor prepared from an adrenaline complex (PDBID 4LDO). A red dashed line indicates a hydrogen bond, a blue dashed line indicates π-interactions, a green dashed line indicates cation-π interactions, and a purple dashed line indicates ionic interactions.

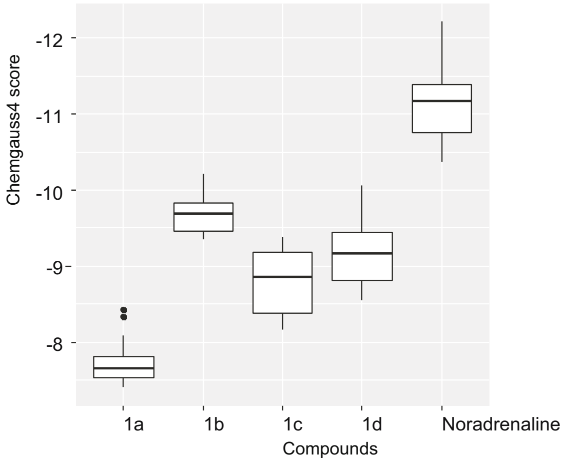
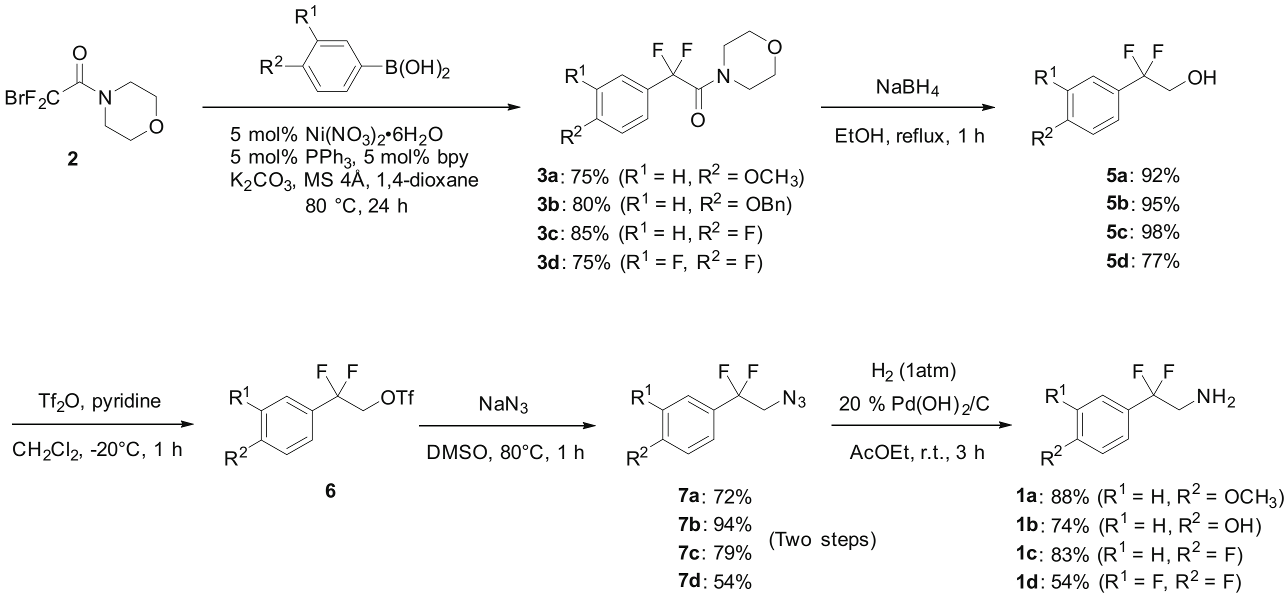


Figure 3: Distribution of docking scores for compounds **1a**–**1d** and noradrenaline.

reported in ppm downfield of TMS (^{1}H = 0.00) and DMSO-d_6 (^{1}H δ = 2.49, ^{13}C δ = 39.5). Chemical shifts of ^{19}F NMR are reported in ppm from $CFCl_3$ as an internal standard. ^{13}C NMR spectra were obtained with ^{1}H decoupling. All data are reported as follows: chemical shifts, multiplicity (standard abbreviations), coupling constants (Hz), and relative integration value. HRMS experiments were measured on a double-focusing mass spectrometer with an ionization mode of EI. All experiments were carried out under an argon atmosphere in flame-dried glassware using the standard inert techniques for introducing reagents and solvents unless otherwise noted. All commercially available materials were used as received without further purification. Solvents were heated to reflux over Na metal with benzophenone ketyl (THF, 1,4-dioxane), P_2O_5 (CH_2Cl_2), CaH_2 (DMSO, AcOEt), and Mg metal (EtOH) under argon atmosphere and collected by distillation just before use. All compounds were purified by silica gel column chromatography, unless noted otherwise.



Scheme 1: Synthesis of fluorinated CF_2 analogs of octopamine and noradrenaline.

4.1 A typical procedure for the synthesis of 2-aryl-2,2-difluoroacetamide (3a)

To a vial containing $Ni(NO_3)_2\cdot 6H_2O$ (29.0 mg, 10 mol%), bpy (15.6 mg, 10 mol%), Ph_3P (26.2 mg, 10 mol%), molecular sieve (MS) 4 Å (400 mg), 4-metnoxyphenylboronic acid (607.8 mg, 4.0 mmol), K_2CO_3 (552.0 mg, 4.0 mmol), and 2-bromo-2,2-difluoro-1-morpholinoethan-1-one (**2**, 448.1 mg, 2.0 mmol), 1,4-dioxane (14 mL) was added. The reaction mixture was heated at 80°C, and then, the whole mixture was stirred at the same temperature for 24 h. The mixture was diluted in EtOAc, and the dilution was filtered through Celite pad. The solvent was concentrated in vacuo. Then, the crude mixture was purified with flash column chromatography using hexane/AcOEt (7:3) as the eluent to give the pure product **3a**.

4.2 A typical procedure for the transformation of 3a to 3-aryl-2,2,-difluoroethylamine (1a)

To a vial containing $NaBH_4$ (2.247 g, 59 mmol) in EtOH (18 mL), a solution of **3a** (3.9 mmol) in EtOH (17 mL) was added at room temperature, and then, the reaction mixture was heated to reflux for 1 h. The mixture was cooled to room temperature and was poured into H_2O. The whole mixture was extracted with AcOEt, and the combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The crude mixture was purified with flash column chromatography using hexane/AcOEt (7:3) as the eluent to give the reduced alcohol **5a**. To the obtaining alcohol **5a** (564.2 mg, 3.0 mmol) in CH_2Cl_2 (18 mL), pyridine (1.45 mL, 18 mmol) was added, and the mixture was cooled to −20°C. Then, trifluoromethanesulfonic acid anhydride (1.48 mL, 9.0 mmol) was added, and the reaction mixture was stirred at the same temperature for 1 h. The reaction was quenched by saturated NH_4Cl and then extracted with AcOEt. The extract was washed with brine, and the solvent was removed in vacuo. The crude triflate **6a** was used in the next step without purification. The crude **6a** was dissolved in DMSO (9 mL), and then NaN_3 (234.0 mg, 3.6 mmol) was added. The resulting mixture was heated at 80°C, and then, the whole mixture was stirred at the same temperature for 1 h. The mixture was cooled to room temperature and was poured into H_2O. The whole mixture was extracted with AcOEt, and the combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The crude mixture was purified with flash column chromatography using hexane/AcOEt (95:5) as the eluent to give the azide **7a**. To a reaction vessel containing the azide **7a** (445.9 mg, 2.1 mmol) and 20% $Pd(OH)_2/C$ (44.6 mg), AcOEt (10 mL) was added, and then, the reaction mixture was stirred at room temperature under H_2 atmosphere (1 atm) for 3 h. The Pd catalyst was removed from the reaction mixture by filtration, and the solvent was concentrated in vacuo. The crude mixture was purified with flash column chromatography using hexane/AcOEt (2:8) as the eluent to give the 2,2-difluoroethylamine **1a**.

5 Characterization of compounds

5.1 2,2-Difluoro-2-(4-methoxyphenyl)-1-morpholinoethan-1-one (3a)

Yield 75% (0.407 g, 2 mmol scale), colorless liquid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, J = 8.7 Hz, 2H), 6.97 (d, J = 8.7 Hz, 2H), 3.85 (s, 3H), 3.71 (s, 4H), 3.48 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3 (t, J = 30.8 Hz), 161.4, 126.8 (t, J = 5.8 Hz), 125.5 (t, J = 25.0 Hz), 115.6 (t, J = 249.5 Hz), 114.1, 66.7, 66.4, 55.4, 46.7, 43.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ −92.8 (s, 2 F). MS m/z = 271 [M^+]; HRMS (EI): m/z [M^+] calculated for $C_{13}H_{15}F_2NO_3$: 271.1020; found: 271.1014.

5.2 2,2-Difluoro-2-(4-methoxyphenyl) ethan-1-ol (5a)

Yield 92% (0.675 g, 3.9 mmol scale), colorless solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, J = 9.2 Hz, 2H), 6.95 (d, J = 9.2 Hz, 2H), 3.95 (t, J = 13.4 Hz, 2H), 3.84 (s, 3H), 1.96 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.0, 127.0 (t, J = 6.1 Hz), 126.5 (t, J = 26.0 Hz), 120.8 (t, J = 243.7 Hz), 113.9, 66.1 (t, J = 32.7 Hz), 55.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ −105.5 (t, J = 13.5 Hz, 2 F). MS m/z = 188 [M^+]; HRMS (EI): m/z [M^+] calculated for $C_9H_{10}F_2O_2$: 188.0649; found: 188.0645.

5.3 1-(2-Azido-1,1-difluoroethyl)-4-methoxybenzene (7a)

Yield 72% (0.460 g, 3.0 mmol scale), colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, J = 9.2 Hz, 2H), 6.96 (d, J = 9.2 Hz, 2H), 3.84 (s, 3H), 3.67 (t, J = 13.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.2, 126.8 (t, J = 6.1 Hz), 126.3

(t, J = 25.9 Hz), 120.4 (t, J = 245.1 Hz), 114.0, 56.1 (t, J = 33.1 Hz), 55.4; ^{19}F NMR (376 MHz, CDCl$_3$) δ −99.5 (t, J = 13.1 Hz, 2 F). MS m/z = 213 [M$^+$]; HRMS (EI): m/z [M$^+$] calculated for $C_9H_9F_2N_3O$: 213.0714; found: 213.0714.

5.4 2,2-Difluoro-2-(4-methoxyphenyl) ethan-1-amine (1a)

Yield 88% (345.1 mg, 2.1 mmol scale), colorless oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.40 (d, J = 8.7 Hz, 2H), 6.94 (d, J = 8.7 Hz, 2H), 3.83 (s, 3H), 3.15 (t, J = 14.3 Hz, 2H), 1.44 (brs, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 160.1, 127.7 (t, J = 26.7 Hz), 126.7 (t, J = 6.1 Hz), 121.8 (t, J = 242.1 Hz), 113.9, 55.4, 49.5 (t, J = 31.3 Hz); ^{19}F NMR (376 MHz, CDCl$_3$) δ −104.1 (t, J = 14.5 Hz, 2 F). MS m/z = 187 [M$^+$]; HRMS (EI): m/z [M$^+$] calculated for $C_9H_{11}F_2NO$: 187.0809; found: 187.0814.

5.5 2-(4-(Benzyloxy)phenyl)-2,2-difluoro-1-morpholinoethan-1-one (3b)

Yield 80% (1.395 g, 5 mmol scale), colorless solid, mp 95.0–95.2°C (recrystallized from C6). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.48–7.32 (m, 7H), 7.36 (d, J = 8.8 Hz, 2H), 5.10 (s, 2H), 3.70 (s, 4H), 3.48 (s, 4H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 162.3 (t, J = 30.3 Hz), 160.7, 136.2, 128.7, 128.2, 127.5, 126.8 (t, J = 5.0 Hz), 125.8 (t, J = 25.1 Hz), 115.7 (t, J = 250.1 Hz), 115.0, 70.1, 66.7, 66.4, 46.7, 43.5; ^{19}F NMR (376 MHz, CDCl$_3$) δ −92.9 (s, 2 F). MS m/z = 347 [M$^+$]; HRMS (EI): m/z [M$^+$] calculated for $C_{19}H_{19}F_2NO_3$: 347.1333; found: 347.1331.

5.6 2-(4-(Benzyloxy)phenyl)-2,2-difluoroethan-1-ol (5b)

Yield 95% (1.260 g, 5 mmol scale), colorless solid, mp 82.4–82.5°C (recrystallized from C6). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.43–7.31 (m, 7H), 7.02 (d, J = 8.5 Hz, 2H), 5.09 (s, 2H), 3.94 (t, J = 13.2 Hz, 2H), 1.85 (brs, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 160.2, 136.5, 128.7, 128.2, 127.5, 127.0 (t, J = 5.8 Hz), 126.7 (t, J = 26.0 Hz), 120.7 (t, J = 243.7 Hz), 114.8, 70.0, 66.0 (t, J = 33.7 Hz); ^{19}F NMR (376 MHz, CDCl$_3$) δ −105.5 (t, J = 13.2 Hz, 2 F). MS m/z = 264 [M$^+$]; HRMS (EI): m/z [M$^+$] calculated for $C_{15}H_{14}F_2O_2$: 264.0962; found: 264.0956.

5.7 1-(2-Azido-1,1-difluoroethyl)-4-(benzyloxy)benzene (7b)

Yield 94% (1.271 g, 4.7 mmol scale), colorless solid, mp 73.8–74.1°C (recrystallized from C6). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.44–7.32 (m, 7H), 7.03 (d, J = 8.6 Hz, 2H), 5.09 (s, 2H), 3.67 (t, J = 13.1 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 160.4, 136.4, 128.7, 128.2, 127.5, 126.8 (t, J = 6.0 Hz), 126.6 (t, J = 26.0 Hz), 120.4 (t, J = 245.6 Hz), 114.9, 70.1, 56.1 (t, J = 32.7 Hz); ^{19}F NMR (376 MHz, CDCl$_3$) δ −99.5 (t, J = 13.2 Hz, 2 F). MS m/z = 289 [M$^+$]; HRMS (EI): m/z [M$^+$] calculated for $C_{15}H_{13}F_2N_3O$: 289.1023; found: 289.1029.

5.8 4-(2-Amino-1,1-difluoroethyl)phenol (β, β-CF$_2$-Tyramine) (1b)

Note: The product was purified by only filtration from the reaction mixture and washing cold Et$_2$O (without chromatography). This product was unstable in a solution.

Yield 74% (38.6 mg, 0.3 mmol scale), colorless solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.82 (brs, 1H), 7.31 (d, J = 8.7 Hz, 2H), 7.02 (d, J = 8.7 Hz, 2H), 3.07 (t, J = 14.7 Hz, 2H), 1.61 (brs, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.6, 126.7 (t, J = 6.0 Hz), 125.9 (t, J = 26.6 Hz), 122.5 (t, J = 240.8 Hz), 114.9, 48.1 (t, J = 30.8 Hz); ^{19}F NMR (376 MHz, DMSO-d_6) δ −99.5 (t, J = 15.1 Hz, 2 F).

5.9 2,2-Difluoro-2-(4-fluorophenyl)-1-morpholinoethan-1-one (3c)

Yield 85% (1.103 g, 5 mmol scale), colorless solid. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.56–7.53 (m, 2H), 7.18–7.14 (m, 2H), 3.71 (s, 4H), 3.54 (s, 4H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 164.1 (dt, J = 251.2, 1.9 Hz), 161.9 (t, J = 30.6 Hz), 129.6 (td, J = 25.3, 3.3 Hz), 127.6 (dt, J = 8.7, 5.8 Hz), 115.9 (d, J = 22.3 Hz), 115.7 (t, J = 251.8 Hz), 66.7, 66.4, 46.7 (m), 43.6; ^{19}F NMR (376 MHz, CDCl$_3$) δ −93.8 (d, J = 2.8 Hz, 2 F), −108.8 to −108.9 (m, 1 F). MS m/z = 259 [M$^+$]; HRMS (EI): m/z [M$^+$] calculated for $C_{12}H_{12}F_3NO_2$: 259.0820; found: 259.0823.

5.10 2,2-Difluoro-2-(4-fluorophenyl)ethan-1-ol (5c)

Yield 98% (0.692 g, 4 mmol scale), colorless solid, mp 37.5–39.0°C (recrystallized from C6). ^{1}H NMR (400 MHz,

$CDCl_3$) δ 7.53–7.50 (m, 2H), 7.15–7.11 (m, 2H), 3.95 (td, J = 13.3, 6.9 Hz, 2H), 2.11 (t, J = 6.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8 (d, J = 250.0 Hz), 130.5 (td, J = 26.3, 3.4 Hz), 127.7 (dt, J = 8.7, 5.8 Hz), 120.3 (t, J = 243.7 Hz), 115.7 (d, J = 21.9 Hz), 66.0 (t, J = 33.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −105.9 (td, J = 13.3, 2.9 Hz, 2 F), −110.3 to −110.2 (m, 1 F). MS m/z = 176 [M^+]; HRMS (EI): m/z [M^+] calculated for $C_8H_7F_3O$: 176.0449; found: 176.0450.

5.11 1-(2-Azido-1,1-difluoroethyl)-4-fluorobenzene (7c)

Yield 79% (0.597 g, 3.75 mmol scale), colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52–7.49 (m, 2H), 7.17–7.13 (m, 2H), 3.69 (t, J = 12.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9 (d, J = 250.5 Hz), 130.2 (td, J = 26.1, 3.2 Hz), 127.5 (dt, J = 8.7, 6.1 Hz), 120.0 (t, J = 245.8 Hz), 115.9 (d, J = 22.2 Hz), 56.0 (t, J = 32.8 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −100.0 (td, J = 12.9, 2.2 Hz, 2 F), −109.5 to −109.6 (m, 1 F). MS m/z = 201 [M^+]; HRMS (EI): m/z [M^+] calculated for $C_8H_8F_3N_3$: 201.0514; found: 201.0522.

5.12 2,2-Difluoro-2-(4-fluorophenyl)ethan-1-amine (1c)

Yield 83% (0.389 g, 2.70 mmol scale), colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49–7.46 (m, 2H), 7.15–7.11 (m, 2H), 3.16 (t, J = 14.6 Hz, 2H), 1.35 (brs, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6 (d, J = 249.4 Hz), 131.6 (td, J = 26.7, 3.1 Hz), 127.4 (dt, J = 8.6, 6.2 Hz), 121.4 (t, J = 242.6 Hz), 115.6 (d, J = 22.0 Hz), 49.5 (t, J = 30.8 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −104.7 (td, J = 14.6, 1.9 Hz, 2 F), −110.8 to −110.7 (m, 1 F). MS m/z = 175 [M^+]; HRMS (EI): m/z [M^+] calculated for $C_8H_8F_3N$: 175.0609; found: 175.0601.

5.13 2-(3,4-Difluorophenyl)-2,2-difluoro-1-morpholinoethan-1-one (3d)

Yield 75% (1.037 g, 5 mmol scale), colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.37 (m, 1H), 7.32–7.23 (m, 2H), 3.74–3.69 (m, 4H), 3.61 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.4 (t, J = 30.8 Hz), 151.9 (dd, J = 253.4, 12.5 Hz), 150.3 (dd, J = 251.0, 13.5 Hz), 130.5 (m), 122.3–122.0 (m), 117.8 (d, J = 18.3 Hz), 115.4 (dt, J = 20.2, 6.7 Hz), 115.1 (t, J = 254.3 Hz), 66.7, 66.5, 46.6 (m), 43.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ −94.3 (d, J = 2.9 Hz, 2 F), −133.2 to −133.3 (m, 1 F), −135.2 (ddd, J = 21.3, 10.5, 6.5 Hz, 1 F). MS m/z = 277 [M^+]; HRMS (EI): m/z [M^+] calculated for $C_{12}H_{11}F_4NO_2$: 277.0726; found: 277.0726.

5.14 2-(3,4-Difluorophenyl)-2,2-difluoroethan-1-ol (5d)

Yield 77% (0.563 g, 3.75 mmol scale), colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.34 (m, 1H), 7.30–7.21 (m, 2H) 3.94 (t, J = 13.0 Hz, 1H), 2.48 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.6 (dd, J = 251.9, 12.5 Hz), 150.3 (dd, J = 250.0, 13.5 Hz), 131.05 (m), 122.3–122.0 (m), 119.5 (t, J = 244.7 Hz), 117.7 (d, J = 17.3 Hz), 115.4 (dt, J = 12.8, 6.4 Hz), 65.7.0 (t, J = 33.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −105.9 (t, J = 13.0 Hz, 2 F), −134.7 to −134.6 (m, 1 F), −136.0 (ddd, J = 21.0, 10.5, 6.9 Hz, 1 F). MS m/z = 194 [M^+]; HRMS (EI): m/z [M^+] calculated for $C_8H_6F_4O$: 194.0355; found: 194.0360.

5.15 4-(2-Azido-1,1-difluoroethyl)-1,2-difluorobenzene (7d)

Yield 54% (0.457 g, 2.90 mmol scale), colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.33 (m, 1H), 7.28–7.25 (m, 2H), 3.69 (t, J = 12.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.7 (dd, J = 253.0, 12.4 Hz), 150.3 (dd, J = 250.7, 13.0 Hz), 131.2 (m), 122.2–121.9 (m), 119.2 (t, J = 246.4 Hz), 117.9 (d, J = 17.8 Hz), 115.3 (dt J = 19.9, 6.1 Hz), 55.9 (t, J = 32.8 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −100.0 (td, J = 12.8, 2.2 Hz, 2 F), −133.7 to −133.9 (m, 1 F), −135.3 to −135.4 (m, 1 F). MS m/z = 219 [M^+]; HRMS (EI): m/z [M^+] calculated for $C_8H_5F_4N_3$: 219.0420; found: 219.0425.

5.16 2-(3,4-Difluorophenyl)-2,2-difluoroethan-1-amine (1d)

Yield 54% (0.163 g, 1.57 mmol scale), colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.30 (m, 1H), 7.28–7.20 (m, 2H), 3.16 (t, J = 14.4 Hz, 2H), 1.40 (brs, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.4 (dd, J = 251.4, 12.5 Hz), 150.2 (dd, J = 249.5, 12.5 Hz), 132.6 (m), 121.9–121.7 (m), 120.6

(t, $J = 243.7$ Hz), 117.7 (d, $J = 17.3$ Hz), 115.2 (td, $J = 12.8$, 6.4 Hz), 49.3 (t, $J = 30.3$ Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −104.7 (t, $J = 14.4$ Hz, 2 F), −135.0 to −135.1 (m, 1 F), −135.9 to −136.0 (m, 1 F). MS $m/z = 193$ [M$^+$]; HRMS (EI): m/z [M$^+$] calculated for $C_8H_7F_4N$: 193.0515; found: 193.0516.

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