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Fluoroaziridines as novel substrates in the modified Petasis reaction: synthesis of monofluorinated propargyl amines

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Abstract

Reaction of 2-fluoroaziridines with potassium alkynyltrifluoroborates in the presence of $BF_3 \cdot OEt_2$ leads to fluorinated propargyl amines in moderate to good yields. The reaction proceeds as an in situ isomerization of 2-fluoroaziridines to α-fluorinated imines, followed by the reaction of the imine with alkynyldifluoroborane, which is generated in situ from the potassium alkynyltrifluoroborates and $BF_3 \cdot OEt_2$.

Keywords: Fluoroaziridines; Fluorinated amines; Fluorinated aldimines; Boron; Petasis

1. Introduction

Propargyl amines find application in treatment of various diseases, such as depression, panic disorder, social phobia,[1–5] and Parkinson's disease.[6–9] For example, *N*-alkyl-*N*-(1,1-dialkyl-3-arylprop-2-ynyl)amines have been found to be useful in the treatment of anxiety, psychotic states, and aggressive behavior in affected animals.[10]

In addition to their pharmacological use, propargyl amines are useful building blocks for the synthesis of multifunctionalized nitrogen compounds.[11–18] Application of fluorinated propargyl amines would thus allow synthesizing fluorine-containing multifunctionalized amino compounds, which are of potential interest due to the unique effect of the fluorine atom on properties of bioactive compounds.[19–21] Preparation of propargyl trifluoro- and difluoromethyl amines has been described.[13,16–18,22–26] However, to the best of our knowledge, only rare examples of monofluorinated propargyl amines are known.[27,28]

Recently, Stas and Abbaspour Tehrani have reported a modified Petasis reaction involving the use of α,α-dichlorinated imines, potassium alkynyltrifluoroborates, and a Lewis acid.[29] Also, Billard and Langlois reported about the reaction of potassium trifluoroborates with iminium species, generated in situ from hemiaminals upon activation by Lewis acid.[30] On the other hand, we have recently reported the Lewis acid catalyzed isomerization of 2-fluoro-3,3-diphenylaziridines to α-fluoroimines.[31] These aziridines are readily available from benzophenone imines and fluorocarbene, generated by reduction of $CHFBr_2$ with active lead.[31,32] With the above mentioned results in mind it was supposed that a sequence involving aziridine isomerization followed by the reaction of the resulting imine **2** with potassium alkynyltrifluoroborates would present a simple and elegant route to multifunctionalized fluorinated compounds **4**, containing β-fluoroamine and propargyl amine moieties (Scheme 1). In the present article, we report our results in this direction.

2. Results and discussion

Since boronic acids are commonly used in the Petasis reaction,[33–46] we decided first to examine the reaction of imine **2a**

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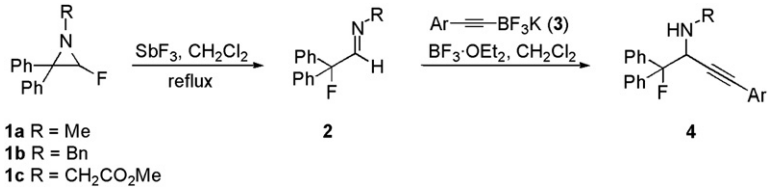


Scheme 1. Synthesis of fluoroamines.

with styrylboronic acid. A mixture of aziridine **1a**, SbF_3, and styrylboronic acid was refluxed in dichloromethane. As described above, aziridines **1** are known to produce imines **2** while being refluxed in dichloromethane with SbF_3. However, no addition product of the styryl group to the azomethine bond of **2** was formed under these conditions. Carrying out the reaction in refluxing toluene did not give positive results either.

Then, we turned our attention to potassium styryltrifluoroborate, which upon activation by Lewis acid is more active toward the azomethine group than styrylboronic acid. Imine **2a** was synthesized by isomerization of aziridine **1a** with SbF_3[31] and reacted, without isolation of the imine, with potassium styryltrifluoroborate under conditions optimized by Stas and Abbaspour Tehrani.[29] The mixture of imine **2a** with potassium styryltrifluoroborate in CH_2Cl_2/HFIP (9:1) in the presence of 1 equiv of $BF_3\cdot OEt_2$ was stirred for 20 h at room temperature. However, no olefinic signals were distinguished in the ^1H NMR spectrum of the basically treated reaction mixture. Next to traces of the starting α-fluoro imine and/or -aldehyde, many signals of unidentified products were observed.

Since it has been reported that phenylethynyldifluoroborane, generated from potassium phenylethynyltrifluoroborate, is more reactive toward azomethine bonds than vinylic derivatives,[29] we turned our attention to this compound.

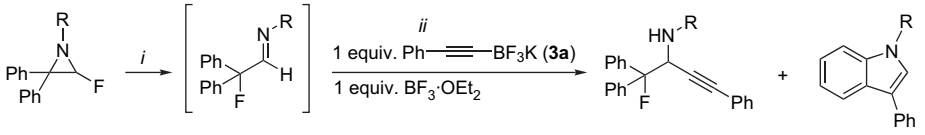
First, the reactivity of fluorinated imines **2** toward potassium alkynyltrifluoroborates was investigated. Thus, the mixture of imine **2a** with borate **3a** in CH_2Cl_2/HFIP (9:1) in the presence of $BF_3\cdot OEt_2$ was stirred for 6 h at room temperature (Table 1, entry 1). No signals of the expected amine could be observed in the ^1H NMR spectrum of the crude reaction mixture. Only the signals of the starting imine and acetophenone were observed. Therefore, the same reaction of imine **2a** with borate **3a**, but without HFIP, was repeated and stirred for 24 h (entry 2). In this case, the target amine **4aa** was isolated in 22% yield by column chromatography (calculated from aziridine **1a**).

Small scale reactions of imines **2b**,**c** (20 mg) with borate **3a**, carried out in the same way, also led to the formation of the corresponding amines **4b**,**c**. However, along with the desired amines **4** also indoles **5b**,**c** were formed as a byproduct, with the indole/amine ratio varying between 1:2.8 for **5b/4ba** and 1:3.7 for **5c/4ca**. Indeed, it has been shown previously that isomerization of 2-fluoroaziridines **1** into α-fluoro imines **2** may compete with their transformation into 3-phenylindoles **5**, with the imine/indole ratio depending on the Lewis acid used.[31] Seemingly, the same process takes place in the reaction of imines **2b**,**c** with borate **3a** in the presence of $BF_3\cdot OEt_2$.

By analogy with the conversion of aziridines **1** into imines **2** in the presence of catalytic SbF_3, the same isomerization was expected with $BF_3\cdot OEt_2$ or an in situ formed organodifluoroborane. This approach would save one reaction step and would probably increase the yield, due to the reduced contact time of the imine with $BF_3\cdot OEt_2$. Indeed, stirring aziridine **1a** with borate **2a** in the presence of $BF_3\cdot OEt_2$ in dichloromethane at room temperature for 24 h (entry 5) gave rise to amine **4aa** in 30% isolated yield.

Thus, taking into account that the first approach, in which imine **2** was synthesized prior to its reaction with borate **3**, gave a lower yield of 22% compared to the last approach, where aziridine **1** was reacted directly with borate **3** (entry 2 versus entry 5), we decided to generate imines **2a–c** in situ from aziridines **1a–c** and $BF_3\cdot OEt_2$.

Table 1
Optimization of the reaction conditions for the synthesis of amines **4**



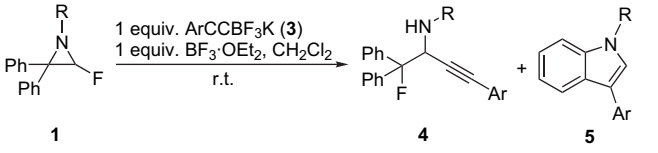
Entry (product)	R	Reaction conditions	Yield[a] **4** (%)	Ratio[b] **5/4**
1 (**4aa**)	Me	(i) 0.1 equiv SbF_3, CH_2Cl_2, reflux, 14 h; (ii) CH_2Cl_2/HFIP (9:1), 6 h, rt.	0	—
2 (**4aa**)	Me	(i) 0.1 equiv SbF_3, CH_2Cl_2, reflux, 14 h; (ii) CH_2Cl_2, 24 h, rt.	22	—
3 (**4ba**)	Bn	(i) 0.14 equiv SbF_3, CH_2Cl_2, reflux, 14 h; (ii) CH_2Cl_2, 24 h, rt.	—	1:2.8
4 (**4ca**)	CH_2CO_2Me	(i) 0.14 equiv, SbF_3, CH_2Cl_2, reflux, 14 h; (ii) CH_2Cl_2, 24 h, rt.	—	1:3.7
5 (**4aa**)	Me	(i and ii) CH_2Cl_2, 24 h, rt.	30	—

[a] Isolated yields calculated from aziridine **1**.
[b] Calculated from ^1H NMR of the reaction mixture.

This one-pot procedure was further extended to a series of reactions of aziridines **1a–c** with differently substituted arylethynyltrifluoroborates **3a–c** in CH_2Cl_2 at room temperature in the presence of equimolar amounts of $BF_3\cdot Et_2O$. These reactions gave amines **4**, which could be isolated in 30–66% yield by flash chromatography (Table 2). Also, during these reactions, indoles **5b**,**c** were formed as by-products but, in most cases, did not interfere in the separation process.

The obtained results and the literature data cited above lead us to the following hypothesis for the reaction mechanism (Scheme 2). Potassium organotrifluoroborates are known to form organodifluoroboranes in the presence of Lewis acids, e.g., $BF_3\cdot OEt_2$.[29,30,47,48] Aziridines **1** isomerize to imines **8** complexed with a Lewis acid or transform into indoles **5** in the presence of a Lewis acid (either $BF_3\cdot OEt_2$ or organodifluoroborane). The above mentioned Lewis acid activation of the azomethine function eases the nucleophilic addition of the alkynyl moiety of **9** to C=N, thus leading to the propargyl amines **4**.

Table 2
One-pot synthesis of amines **4**



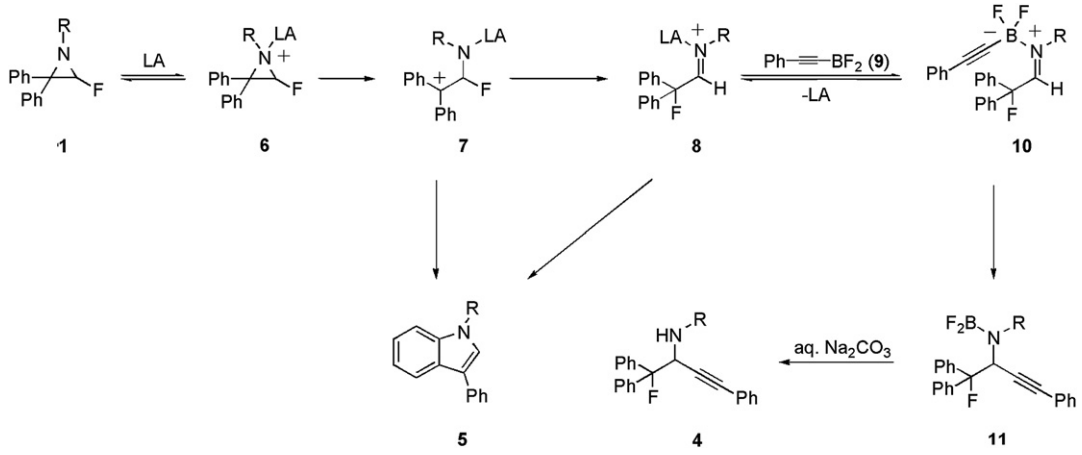
1 **4** **5**

Entry (product)	R (**1**)	Ar (**3**)	Reaction time (h)	Yield[a] **4** (%)	Yield[a] **5** (%)
1 (**4aa**)	Me (**1a**)	Ph (**3a**)	24	30	—
2 (**4ba**)	Bn (**1b**)	Ph (**3a**)	5	42	28
3 (**4ca**)	MeO_2CCH_2 (**1c**)	Ph (**3a**)	2	44	ca. 5[b]
4 (**4bb**)	Bn (**1b**)	3-$MeOC_6H_4$ (**3b**)	2	31	29
5 (**4cb**)	MeO_2CCH_2 (**1c**)	3-$MeOC_6H_4$ (**3b**)	2	66	13[c]
6 (**4bc**)	Bn (**1b**)	4-EtC_6H_4 (**3c**)	3	36	24
7 (**4cc**)	MeO_2CCH_2 (**1c**)	4-EtC_6H_4 (**3c**)	2	40	14[d]

[a] Isolated yields, unless otherwise specified.
[b] Estimated on the basis of ^{1}H NMR spectra of the reaction mixture.
[c] Isolated as a mixture with 30% of amine **4cb**.
[d] Isolated as a mixture with 50% of amine **4cc**.

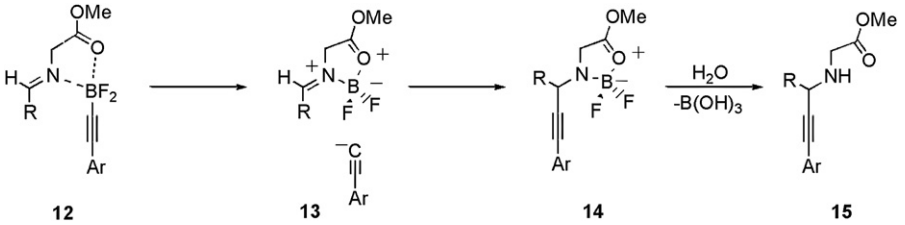
To determine whether it is $PhC{\equiv}CBF_2$ (**9**) or $BF_3\cdot OEt_2$, which participates as a Lewis acid in the aziridine isomerization, the following experiments were carried out. In the first experiment, a mixture (1:1) of borate **3a** and $BF_3\cdot OEt_2$ in dichloromethane was stirred at room temperature for 5 min. To the solution of RBF_2 thus obtained, aziridine **1b** was added and the reaction mixture was stirred at room temperature for 24 h. According to the ^{1}H NMR spectrum, the mixture contains indole **5b** and amine **4b** in 8.8:1 ratio along with some unidentified compounds. At the same time, in a second experiment, the mixture obtained by stirring aziridine **1b**, borate **3a**, and $BF_3\cdot OEt_2$ at room temperature for 24 h was shown to contain indole **5b** and amine **4b** in 1:5.8 ratio. If only $PhC{\equiv}CBF_2$ (**9**) participated as a Lewis acid in the isomerization of aziridines, the ratio would be similar to the first experiment, while as a matter of fact it is almost inversed. This indicates that the isomerization of aziridines **1** proceeds mainly by the action of $BF_3\cdot OEt_2$, though the participation of $PhC{\equiv}CBF_2$ (**9**) cannot be excluded. It should also be mentioned that a 3:4 indole **5b**/amine **4b** ratio was obtained in case the reaction time was 5 h (Table 2, entry 2). The difference can be explained by gradual decomposition of the indole in the presence of Lewis acid.

As can be seen from Table 2, yields of amines **4ca**,**cb**,**cc** derived from aziridine **1c** are somewhat higher and much less of the competing indole is formed, than in the case of aziridines **1a**,**b**. The electron withdrawing properties of the carboxymethyl nitrogen substituent diminish the nucleophilicity of nitrogen in the corresponding intermediate, and hence the cyclization into the indole proceeds relatively more slowly in this case. Another possible explanation for this observation may lie in the hypothetical intermediate **12** in which the carbonyl oxygen atom promotes the dissociation of the B–C bond by an intramolecular S_N reaction at the boron atom (Scheme 3).[49] The resulting carbanion is then situated near the activated C=N bond and is able to add to it, forming intermediate **14**, which upon hydrolysis gives the desired amine **15**. Imines **2a**,**b** lack a substituent that would be able to form an intramolecular complex with boron and therefore the transfer of the alkynyl group is slower and other reactions



1 **6** **7** **8** **10** **5** **4** **11**

Scheme 2. Reaction mechanism.



Scheme 3. Explanation for the higher yields of *N*-propargyl glycinates **15**.

of the imine, such as isomerization to indole, can compete with it.

In conclusion, we have shown that the reaction of 2-fluoro-1,1-diphenylaziridines **1** with arylethynylborates **2** in the presence of $BF_3 \cdot OEt_2$ leads to monofluorinated propargyl amines **3** in 30–66% yield, allowing the synthesis of multifunctional fluorinated compounds in a simple one-pot procedure.

3. Experimental section

3.1. General

GC–MS analyses were performed using an Interscience GC 8000 series gas chromatograph with an EC™-5 column (length: 30 m, internal diameter: 0.32 mm, film thickness: 0.25 μm). Products are injected in a split injector (250 °C); the inert carrier gas is helium. The mass spectrometer is a Fisons Instruments MD 800 using electron impact (70 eV) as ionization method. High-resolution ^{1}H NMR (250 MHz), ^{13}C NMR (62.90 MHz), and ^{19}F NMR (235.3 MHz) spectra were recorded in $CDCl_3$ on a Bruker Avance DRX 250 spectrometer. ^{11}B NMR (160.5 MHz) spectra were recorded on a Bruker Avance II 500 spectrometer. Chemical shifts are reported in parts per million downfield from TMS. ^{13}C NMR assignments were made using DEPT spectra. Infrared spectra were recorded with an Avatar 370 FTIR apparatus (Thermo Nicolet). Unless otherwise stated, the IR spectra were recorded using the attenuated total reflection technology. Flash chromatography was performed using Merck silica (diameter: 40–63 μm). TLC analysis was performed on glass backed plates (Merck) coated with 0.2 mm silica with UV-indicator $60F_{254}$. Melting points were determined on a Buchi Melting Point B540 apparatus and are uncorrected. Microanalyses were performed on a EuroEA3000 (Eurovector). Methylene chloride was dried by distillation over CaH_2 and $BF_3 \cdot OEt_2$ was distilled under reduced pressure prior to use. Aziridines **1** were prepared according to the published procedures.[31,32] Borate **3a** was prepared according to Molander et al.[50] Borates **3b**,**c** were prepared previously.[29]

3.2. Reaction of aziridine *1a* with SbF_3 and potassium phenylethynyltrifluoroborate (*3a*)

A mixture of aziridine **1a** (200 mg, 0.88 mmol), SbF_3 (16 mg, 0.089 mmol), and CH_2Cl_2 (50 mL) was refluxed for 14 h. Borate **3a** (184 mg, 0.88 mmol) was added to a resulting solution of imine **2a**. $BF_3 \cdot OEt_2$ (126 mg, 0.89 mmol) was added dropwise to the stirred mixture and the resulting mixture was stirred at room temperature for 24 h. The reaction mixture was treated with 0.2 M aq Na_2CO_3 (20 mL) and the aqueous layer was washed with CH_2Cl_2 (3×10 mL). The combined organic phases were dried (Na_2SO_4), filtered, concentrated, and the residue was purified by column chromatography (silica gel) to give *N-(4-fluoro-1,4,4-triphenylbut-1-yne-3-yl)methylamine* (**4aa**). Yield: 64 mg (22%), orange oil. R_f=0.27 (2:1 petroleum ether–Et_2O). IR (neat): 3341 (NH), 2230 (C≡C) cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ=1.73 (1H, br s, NH), 2.61 (3H, s, CH_3), 4.46 (1H, d, J_{H-F}= 17.8 Hz, CH), 7.1–7.8 (15H, m, Ph). ^{13}C NMR (63.0 MHz, $CDCl_3$): δ=34.8 (CH_3), 60.3 (d, J=25.9 Hz, CH), 86.6 (d, J=5.7 Hz, *C*≡CPh), 86.9 (C≡*C*Ph), 99.7 (d, J= 183.0 Hz, CF), 122.9 (C^{ipso}C≡C), 126.2 (d, J=8.8 Hz, $C^{ortho}_{Ph_2CF}$), 126.4 (d, J=7.7 Hz, $C^{ortho}_{Ph_2CF}$), 127.96 (d, J=1.4 Hz, $C^{para}_{Ph_2CF}$), 128.02 (d, J=0.9 Hz, $C^{meta}_{Ph_2CF}$), 128.1 (3C, $C^{para}_{Ph_2CF}$, $C^{meta}_{Ph_2CF}$), 128.17 ($C^{para}_{PhC\equiv C}$), 128.2, 131.6 ($C^{meta}_{PhC\equiv C}$, $C^{ortho}_{PhC\equiv C}$), 140.97 (d, J=23.0 Hz, $C^{ipso}_{Ph_2CF}$), 141.01 (d, J=22.8 Hz, $C^{ipso}_{Ph_2CF}$). ^{19}F NMR (235 MHz, $CDCl_3$): δ=–151.2 (d, J= 17.8 Hz). MS (ESI): *m/z* (%)=330 (28) [M+H$^+$], 310 (100) [M+H$^+$–HF].

3.3. Typical procedure for the synthesis of amines *4*: one-pot reaction of aziridine *1a* with $BF_3 \cdot OEt_2$ and potassium phenylethynyltrifluoroborate (*3a*)

$BF_3 \cdot OEt_2$ (65 mg, 0.46 mmol) was added dropwise to a stirring mixture of aziridine **1a** (100 mg, 0.44 mmol), borate **3a** (100 mg, 0.48 mmol), and CH_2Cl_2 (10 mL). The reaction mixture was stirred at room temperature for 24 h and then treated with 0.2 M aq Na_2CO_3 (10 mL). The aqueous layer was washed with CH_2Cl_2 (3×4 mL), the combined organic phases were dried (Na_2SO_4), filtered, concentrated, and the residue was purified by column chromatography to give *N-(4-fluoro-1,4,4-triphenylbut-1-yne-3-yl)methylamine* (**4aa**). Yield: 43 mg (30%).

3.3.1. N-Benzyl-(4-fluoro-1,4,4-triphenylbut-1-yne-3-yl) amine (*4ba*)

From aziridine **1b** (100 mg, 0.33 mmol), borate **3a** (69 mg, 0.33 mmol), and $BF_3 \cdot OEt_2$ (45 mg, 0.32 mmol) after stirring for 5 h at room temperature and treatment as described above **4ba** was obtained. Yield: 56 mg (42%), colorless crystals, mp 87–89 °C. R_f=0.25 (10:1 petroleum ether–Et_2O). IR (neat): 3343 (NH), 2222 (C≡C) cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ=1.75 (1H, br s, NH), 3.98 and 4.13 (2×1H, 2×d, J=13.4 Hz, CH_2), 4.44 (1H, d, J_{H-F}=20.2 Hz, CH), 7.2–7.6

(20H, m, Ph). ^{13}C NMR (63.0 MHz, $CDCl_3$): δ=51.3 (CH_2), 56.7 (d, J=24.5 Hz, CH), 86.7 (d, J=4.5 Hz, $C{\equiv}$CPh), 86.8 (d, J=0.6 Hz, C$\equiv C$Ph), 99.9 (d, J=183.8 Hz, CF), 122.9 ($C^{ipso}{\equiv}$C), 126.1 (d, J=8.8 Hz, $C^{ortho}_{Ph_2CF}$), 126.3 (d, J=8.2 Hz, $C^{ortho}_{Ph_2CF}$), 127.1 (HC_{Ph}), 127.8 (2C, d, J=1.6 Hz, $C^{para}_{Ph_2CF}$), 127.9 (4C), 128.09, 128.15, 128.3, 128.6, 131.6 (HC_{Ph}), 139.3 ($C^{ipso}_{PhCH_2}$), 140.9 (d, J=23.2 Hz, $C^{ipso}_{Ph_2CF}$), 141.4 (d, J=22.9 Hz, $C^{ipso}_{Ph_2CF}$). ^{19}F NMR (235 MHz, $CDCl_3$): δ=−154.9 (d, J=20.2 Hz). MS (ESI): m/z (%)=406 (33) [M+H$^+$], 386 (100) [M+H$^+$−HF]. Anal. Calcd for $C_{29}H_{24}FN$: C, 85.90; H, 5.97; N, 3.45. Found: C, 86.03; H, 5.99; N, 3.33. *1-Benzyl-3-phenylindole (**5b**).* Yield: 26 mg (28%), colorless crystals, mp 64–66 °C (petroleum ether–Et_2O), lit. mp 62–64 °C.[31] ^{1}H and ^{13}C NMR spectra were in accordance with previous syntheses of this compound.[31] However, other literature data were not in accordance with our spectra and our mp.[51] Since in this reference a synthesis of both 1-benzyl-3-phenylindole and 1-benzyl-2-phenylindole was reported, we suppose the authors confused both isomers.[51]

3.3.2. Methyl 2-[(4-fluoro-1,4,4-triphenylbut-1-yne-3-yl)amino]acetate (*4ca*)

From aziridine **1c** (100 mg, 0.35 mmol), borate **3a** (75 mg, 0.36 mmol), and $BF_3{\cdot}OEt_2$ (50 mg, 0.35 mmol) after stirring for 2 h at room temperature and treatment as described above **4ca** was obtained. Yield: 59 mg (43%), colorless crystals, mp 83–84 °C (petroleum ether–Et_2O). R_f=0.25 (2:1 petroleum ether–Et_2O). IR (ATR): 3345 (NH), 1744 (CO) cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ=1.91 (1H, br s, NH), 3.64 and 3.76 (2×1H, 2×d, J=17.6 Hz, CH_2), 3.70 (3H, s, CH_3), 4.81 (1H, d, J_{H-F}=19.1 Hz, CH), 7.1–7.5 (11H, m, Ph), 7.5–7.8 (4H, m, Ph). ^{13}C NMR (63.0 MHz, $CDCl_3$): δ=48.2 (CH_2), 51.7 (CH_3), 57.6 (d, J=25.1 Hz, CH), 85.5 (d, J=5.6 Hz, $C{\equiv}$CPh), 87.5 (d, J=0.7 Hz, C$\equiv C$Ph), 99.8 (d, J=184.4 Hz, CF), 122.6 ($C^{ipso}{\equiv}$C), 126.1 (d, J=8.8 Hz, $C^{ortho}_{Ph_2CF}$), 126.4 (d, J=8.1 Hz, $C^{ortho}_{Ph_2CF}$), 127.92 ($C^{para}_{Ph_2CF}$), 127.95 (d, J=1.0 Hz, $C^{meta}_{Ph_2CF}$), 128.07 ($C^{para}_{Ph_2CF}$), 128.11 (d, J=0.5 Hz, $C^{meta}_{Ph_2CF}$), 128.13 (PhC≡C), 128.3 ($C^{para}_{PhC{\equiv}C}$), 131.5 (PhC≡C), 140.5 (d, J=23.0 Hz, $C^{ipso}_{Ph_2CF}$), 140.9 (d, J=23.0 Hz, $C^{ipso}_{Ph_2CF}$), 172.5 (C=O). ^{19}F NMR (235 MHz, $CDCl_3$): δ=−153.8 (d, J=19.1 Hz). MS (ESI): m/z (%)=388 (50) [M+H$^+$], 368 (100) [M+H$^+$−HF]. Anal. Calcd for $C_{25}H_{22}FNO_2$: C, 77.50; H, 5.72; N, 3.62. Found: C, 77.43; H, 5.76; N, 3.66.

3.3.3. N-Benzyl-[4,4-diphenyl-4-fluoro-1-(3-methoxyphenyl)but-1-yn-3-yl]amine (*4bb*)

From aziridine **1b** (100 mg, 0.33 mmol), borate **3b** (79 mg, 0.33 mmol), and $BF_3{\cdot}OEt_2$ (45–47 mg, 0.32–0.33 mmol) after stirring for 2 h at room temperature and treatment as described above amine **4bb** and indole **5b** (27 mg, 29%) were obtained. *Compound **4bb***. Yield: 44 mg (31%), colorless crystals, mp 69–71 °C (petroleum ether–Et_2O). R_f=0.15 (10:1 petroleum ether–Et_2O). IR (ATR): 3329 (NH) cm^{-1}. IR (neat): 3341 (NH), 2246 (C≡C) cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ=1.74 (1H, br s, NH), 3.75 (3H, s, CH_3), 3.98 and 4.12 (2×1H, 2×d, J=13.4 Hz, CH_2), 4.43 (1H, d, J_{H-F}=20.2 Hz, CH), 6.6–7.0 (3H, m, Ar), 7.0–7.8 (16H, m, Ar). ^{13}C NMR (63.0 MHz, $CDCl_3$): δ=51.3 (CH_2), 55.2 (CH_3), 56.7 (d, J=24.5 Hz, CH), 86.6 (d, J=4.5 Hz, $C{\equiv}$CAr), 86.7 (d, J=0.7 Hz, C$\equiv C$Ar), 99.9 (d, J=183.8 Hz, CF), 114.6 ($HC_{ArC{\equiv}C}$), 116.5 ($HC_{ArC{\equiv}C}$), 123.9 ($C^{ipso}{\equiv}$C), 124.1 ($HC_{ArC{\equiv}C}$), 126.1 (d, J=8.8 Hz, $C^{ortho}_{Ph_2CF}$), 126.3 (d, J=8.2 Hz, $C^{ortho}_{Ph_2CF}$), 127.1 ($PhCH_2$), 127.78 (d, J=1.0 Hz, $C^{para}_{Ph_2CF}$), 127.80 (d, J=1.0 Hz, $C^{para}_{Ph_2CF}$), 127.9 (4C, $C^{meta}_{Ph_2CF}$), 128.3 ($PhCH_2$), 128.6 ($PhCH_2$), 129.2 (ArC≡C), 139.2 ($C^{ipso}_{PhCH_2}$), 140.8 (d, J=23.1 Hz, $C^{ipso}_{Ph_2CF}$), 141.4 (d, J=22.9 Hz, $C^{ipso}_{Ph_2CF}$), 159.1 (CH_3OC). ^{19}F NMR (235 MHz, $CDCl_3$): δ=−154.9 (d, J=20.2 Hz). MS (ESI): m/z (%)=436 (80) [M +H$^+$], 416 (100) [M+H$^+$−HF]. Anal. Calcd for $C_{30}H_{26}FNO$: C, 82.73; H, 6.02; N, 3.22. Found: C, 82.79; H, 6.01; N, 3.12.

3.3.4. Methyl 2-[(4-fluoro-4,4-diphenyl-1-(3-methoxyphenyl)but-1-yne-3-yl)amino]acetate (*4cb*)

From aziridine **1c** (100 mg, 0.35 mmol), borate **3b** (84 mg, 0.35 mmol), and $BF_3{\cdot}OEt_2$ (49–52 mg, 0.35–0.37 mmol) after stirring for 2 h at room temperature and treatment as described above amine **4cb** was obtained. Yield: 97 mg (66%), colorless crystals, mp 94–97 °C (petroleum ether–Et_2O). R_f=0.18 (2:1 petroleum ether–Et_2O). IR (ATR): 3332 (NH), 1737 (CO) cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ=2.15 (1H, br s, NH), 3.64 (1H, d, J=17.5 Hz, CH_2), 3.70 (3H, s, CH_3O_2C), 3.74 (3H, s, CH_3O), 3.75 (1H, d, J=17.5 Hz, CH_2), 4.81 (1H, d, J_{H-F}=19.3 Hz, CH), 6.7–6.9 (3H, m, Ar), 7.05–7.2 (1H, m, Ar), 7.2–7.5 (6H, m, Ar), 7.5–7.7 (4H, m, Ar). ^{13}C NMR (63.0 MHz, $CDCl_3$): δ=48.2 (CH_2), 51.7 (CH_3O_2C), 55.2 (CH_3OAr), 57.5 (d, J=25.0 Hz, CH), 85.3 (d, J=5.5 Hz, $C{\equiv}$CPh), 87.4 (d, J=0.8 Hz, C$\equiv C$Ph), 99.8 (d, J=184.5 Hz, CF), 114.8 ($C_{PhC{\equiv}C}$), 116.4 ($C_{PhC{\equiv}C}$), 123.5 ($C^{ipso}_{PhC{\equiv}C}$C), 124.0 ($HC_{PhC{\equiv}C}$), 126.1 (d, J=8.8 Hz, $C^{ortho}_{Ph_2CF}$), 126.4 (d, J=8.1 Hz, $C^{ortho}_{Ph_2CF}$), 127.90 ($C^{para}_{Ph_2CF}$), 127.94 (d, J=1.1 Hz, $C^{meta}_{Ph_2CF}$), 128.07 ($C^{para}_{Ph_2CF}$), 128.10 ($C^{meta}_{Ph_2CF}$), 129.2 (PhC≡C), 140.5 (d, J=23.0 Hz, $C^{ipso}_{Ph_2CF}$), 140.9 (d, J=23.0 Hz, $C^{ipso}_{Ph_2CF}$), 159.1 (C^{ipso}OMe), 172.4 (C=O). ^{19}F NMR (235 MHz, $CDCl_3$): δ=−154.0 (d, J=19.3 Hz). MS (ESI): m/z (%) 418 (70) [M+H$^+$], 398 (100) [M+H$^+$−HF], 329 (40), 205 (39), 159 (34), 133 (69). Anal. Calcd for $C_{26}H_{24}FNO_3$: C, 74.80; H, 5.79; N, 3.36. Found: C, 74.70; H, 5.84; N, 3.16.

A 3:7 mixture (^{1}H NMR) of amine **4cb** and indole **5c** was also isolated from the reaction mixture as 20 mg of an orange oil. This allows estimating the yield of indole **5c** in 12 mg (13%).

3.3.5. N-Benzyl-[4,4-diphenyl-4-fluoro-1-(4-ethylphenyl)but-1-yn-3-yl]amine (*4bc*)

From aziridine **1b** (100 mg, 0.33 mmol), borate **3c** (78 mg, 0.33 mmol), and $BF_3{\cdot}OEt_2$ (45–47 mg, 0.32–0.33 mmol) after stirring for 3 h at room temperature and treatment as described above amine **4bc** and indole **5b** (22 mg, 24%) were obtained. *Compound **4bc***. Yield: 51 mg (36%), colorless crystals, mp 63–65 °C (petroleum ether–Et_2O). R_f=0.27 (10:1

petroleum ether–Et_2O). IR (neat): 3342 (NH), 2222 (C≡C) cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ=1.20 (3H, t, J=7.6 Hz, CH_3), 1.74 (1H, br s, NH), 2.61 (2H, q, J=7.6 Hz, CH_2), 3.98 and 4.12 (2×1H, 2×d, J=13.4 Hz, CH_2), 4.43 (1H, d, J_{H-F}=20.0 Hz, CH), 7.08 (2H, pseudo d, J=8.1 Hz, Ar), 7.19 (2H, pseudo d, J=8.1 Hz, Ar), 7.25–7.45 (13H, m, Ph), 7.45–7.7 (2H, m, Ph). ^{13}C NMR (63.0 MHz, $CDCl_3$): δ=15.4 (CH_3), 28.8 (CH_2CH_3), 51.3 (CH_2Ph), 56.8 (d, J=24.6 Hz, CH), 86.0 (d, J=4.8 Hz, C≡CAr), 86.9 (d, J=0.6 Hz, C≡CAr), 99.9 (d, J=183.5 Hz, CF), 120.1 ($HC_{ArC\equiv C}$), 126.1 (d, J=8.7 Hz, $C^{ortho}_{Ph_2CF}$), 126.4 (d, J=8.2 Hz, $C^{ortho}_{Ph_2CF}$), 127.1 ($PhCH_2$), 127.7 (Ar), 127.8 (2C, $C^{para}_{Ph_2CF}$), 127.9 (4C, $C^{meta}_{Ph_2CF}$), 128.3 ($PhCH_2$), 128.6 ($PhCH_2$), 131.5 ($ArC\equiv C$), 139.3 ($C^{ipso}_{PhCH_2}$), 141.0 (d, J=23.2 Hz, $C^{ipso}_{Ph_2CF}$), 141.4 (d, J=22.9 Hz, $C^{ipso}_{Ph_2CF}$), 144.5 (Et*C*). ^{19}F NMR (235 MHz, $CDCl_3$): δ=−154.6 (d, J=20.0 Hz). MS (ESI): *m/z* (%) 434 (26) [M+H^+], 414 (100) [M+H^+−HF]. Anal. Calcd for $C_{31}H_{28}FN$: C, 85.88; H, 6.51; N, 3.23. Found: C, 85.81; H, 6.57; N, 3.10.

*3.3.6. Methyl 2-[(1-(4-ethylphenyl)-4-fluoro-4,4-diphenylbut-1-yne-3-yl)amino]acetate (**4cc**)*

From aziridine **1c** (100 mg, 0.35 mmol), borate **3c** (83 mg, 0.35 mmol) and $BF_3\cdot OEt_2$ (49–52 mg, 0.35–0.37 mmol) after stirring for 2 h at room temperature and treatment as described above amine **4cc** was obtained. Yield: 58 mg (40%), colorless crystals, mp 71–72 °C (petroleum ether–Et_2O). R_f= 0.29 (2:1 petroleum ether–Et_2O). IR (ATR): 3356 (NH), 1724 (CO) cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ=1.19 (3H, t, J=7.6 Hz, CH_3CH_2), 1.90 (1H, br s, NH), 2.60 (2H, q, J=7.6 Hz, CH_3CH_2), 3.64 and 3.75 (2×1H, 2×d, J=17.7 Hz, CH_2), 3.70 (3H, s, CH_3O), 4.80 (1H, d, J_{H-F}= 18.9 Hz, CH), 7.0–7.2 (4H, m, Ar), 7.2–7.5 (6H, m, Ar), 7.5–7.8 (4H, m, Ar). ^{13}C NMR (63.0 MHz, $CDCl_3$): δ=15.3 (CH_3CH_2), 28.7 (CH_2CH_3), 48.2 (CH_2), 51.7 (CH_3O), 57.6 (d, J=25.3 Hz, CH), 84.7 (d, J=5.7 Hz, C≡CPh), 87.7 (C≡CPh), 99.8 (d, J=184.3 Hz, CF), 119.7 (C^{ipso}C≡C), 126.2 (d, J=8.8 Hz, $C^{ortho}_{Ph_2CF}$), 126.4 (d, J=8.1 Hz, $C^{ortho}_{Ph_2CF}$), 127.7 ($ArC\equiv C$), 127.89 ($C^{para}_{Ph_2CF}$), 127.92 (d, J=1.1 Hz, $C^{meta}_{Ph_2CF}$), 128.05 ($C^{para}_{Ph_2CF}$), 128.09 ($C^{meta}_{Ph_2CF}$), 131.5 ($ArC\equiv C$), 140.6 (d, J=22.9 Hz, $C^{ipso}_{Ph_2CF}$), 140.9 (d, J=23.0 Hz, $C^{ipso}_{Ph_2CF}$), 144.7 (Et*C*), 172.5 (C=O). ^{19}F NMR (235 MHz, $CDCl_3$): δ=−153.6 (br s). MS (ESI): *m/z* (%) 416 (100) [M+H^+], 396 (84) [M+H^+−HF], 327 (42). Anal. Calcd for $C_{27}H_{26}FNO_2$: C, 78.05; H, 6.31; N, 3.37. Found: C, 78.07; H, 6.51; N, 3.50.

A 1:1 mixture (^1H NMR) of amine **4cc** and indole **5c** was also isolated from the reaction mixture as 33 mg of an orange oil. This allows estimating the yield of indole **5c** in 13 mg (14%). Attempts to isolate from this mixture amine **4cc** by crystallization were unsuccessful.

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References and notes

1. Dowson, J. H. *J. Neural Transm.* **1987**, *23*, 121.
2. Krishnan, K. R. R. *The American Psychiatric Association Textbook of Psychopharmacology*; Schatzberg, A. F., Nemeroff, C. B., Eds.; APA: Washington, DC, 1998; p 239.
3. Nies, A.; Robinson, D. S. *Monoamine Oxidase Inhibitors*; Youdim, M. B. H., Paykel, E. S., Eds.; John Wiley and Sons: New York, NY, 1981; p 141.
4. Tyrer, P.; Gardner, M.; Lambourn, J.; Whitford, M. *Monoamine Oxidase Inhibitors*; Youdim, M. B. H., Paykel, E. S., Eds.; John Wiley and Sons: New York, NY, 1981; p 149.
5. Baker, G. B.; Urichuk, L. J.; McKenna, K. F.; Kennedy, S. H. *Cell. Mol. Neurobiol.* **1999**, *19*, 411.
6. Knoll, J.; Ecsery, Z.; Nievel, J. B.; Kelemen, K.; Knoll, B. *Arch. Int. Pharmacodyn. Ther.* **1965**, *155*, 154.
7. Knoll, J. *Monoamine Oxidase: Structure, Function, and Altered Functions*; Singer, T. P., Korff, R. W. V., Murphy, D. L., Eds.; Academic: New York, NY, 1979; pp 431–446.
8. Ling, L.; Urichuk, L. J.; Duff Sloley, B.; Coutts, R. T.; Baker, G. B.; Shan, J. J.; Pang, P. K. T. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2715 and references cited therein.
9. D'hooghe, M.; Van Brabandt, W.; De Kimpe, N. *J. Org. Chem.* **2004**, *69*, 2703 and references cited therein.
10. Salvador, R.; Simon, D. Z.; Leonard, L. WO9320804, 1993; *Chem. Abstr.* **1994**, *120*, 216929.
11. Porco, J. A., Jr.; Schoenen, F. J.; Stout, T. J.; Clardy, J.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 7410.
12. Murai, T.; Mutoh, Y.; Ohta, Y.; Murakami, M. *J. Am. Chem. Soc.* **2004**, *126*, 5968.
13. Magueur, G.; Crousse, B.; Bonnet-Delpon, D. *Tetrahedron Lett.* **2005**, *46*, 2219.
14. Trost, B. M.; Chen, S.-F. *J. Am. Chem. Soc.* **1986**, *108*, 6053.
15. Clive, D. L. J.; Cole, D. C.; Tao, Y. *J. Org. Chem.* **1994**, *59*, 1396.
16. Osipov, S. N.; Tsouker, P.; Hennig, L.; Burger, K. *Tetrahedron* **2004**, *60*, 271.
17. Semeril, D.; Le Notre, J.; Bruneau, C.; Dixneuf, P.; Kolomiets, A. F.; Osipov, S. N. *New J. Chem.* **2001**, *25*, 16.
18. Moroni, M.; Koksch, B.; Osipov, S. N.; Crucianelli, M.; Frigerio, M.; Bravo, P.; Burger, K. *J. Org. Chem.* **2001**, *66*, 130.
19. Smart, B. E. *J. Fluorine Chem.* **2001**, *109*, 3.
20. Prakesch, M.; Gree, D.; Chandrasekhar, S.; Gree, R. *Eur. J. Org. Chem.* **2005**, 1221.
21. Ismail, F. M. D. *J. Fluorine Chem.* **2002**, *118*, 27.
22. Crucianelli, M.; De Angelis, F.; Lazzaro, F.; Malpezzi, L.; Volonterio, A.; Zanda, M. *J. Fluorine Chem.* **2004**, *125*, 573.
23. Lebouvier, N.; Laroche, C.; Huguenot, F.; Brigaud, T. *Tetrahedron Lett.* **2002**, *43*, 2827.
24. Xu, Y.; Dolbier, W. R., Jr. *J. Org. Chem.* **2000**, *65*, 2134.
25. Park, H. M.; Uegaki, T.; Konno, T.; Ishihara, T.; Yamanaka, H. *Tetrahedron Lett.* **1999**, *40*, 2985.
26. Osipov, S. N.; Golubev, A. S.; Sewald, N.; Burger, K. *Tetrahedron Lett.* **1997**, *38*, 5965.
27. Hansen, D., Jr.; Webber, R. K.; Pitzele, B. S.; Awasthi, A. K. PCT Int. Appl., WO 2002022561 A1 20020321, 2002; *Chem. Abstr.* **2002**, *136*, 263464.
28. Hansen, D., Jr.; Webber, R. K.; Pitzele, B. S.; Awasthi, A. K.; Sikorski, J.; Trivedi, M.; Moorman, A. E. PCT Int. Appl., WO 2002022558 A2 20020321, 2002; *Chem. Abstr.* **2002**, *136*, 220536.
29. Stas, S.; Abbaspour Tehrani, K. *Tetrahedron* **2007**, *63*, 8921.
30. Billard, T.; Langlois, B. R. *J. Org. Chem.* **2002**, *67*, 997.
31. Konev, A. S.; Novikov, M. S.; Khlebnikov, A. F. *Russ. J. Org. Chem.* **2007**, *43*, 286.

32. Konev, A. S.; Novikov, M. S.; Khlebnikov, A. F. *Tetrahedron Lett.* **2005**, *46*, 8337.
33. Petasis, N. A.; Akritopoulou, I. *Tetrahedron Lett.* **1993**, *34*, 583.
34. Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1997**, *119*, 445.
35. Grigg, R.; Sridharan, V.; Thayaparan, A. *Tetrahedron Lett.* **2003**, *44*, 9017.
36. Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1998**, *120*, 11798.
37. Prakash, G. K. S.; Mandal, M.; Schweizer, S.; Petasis, N. A.; Olah, G. A. *J. Org. Chem.* **2002**, *67*, 3718.
38. Petasis, N. A.; Goodman, A.; Zavialov, I. A. *Tetrahedron* **1997**, *53*, 16463.
39. Petasis, N. A.; Boral, S. *Tetrahedron Lett.* **2001**, *42*, 539.
40. Jiang, B.; Yang, C. G.; Gu, X. H. *Tetrahedron Lett.* **2001**, *42*, 2545.
41. Berrée, F.; Debache, A.; Marsac, Y.; Carboni, B. *Tetrahedron Lett.* **2001**, *42*, 3591.
42. Portlock, D. E.; Naskar, D.; West, L.; Li, M. *Tetrahedron Lett.* **2002**, *43*, 6845.
43. Naskar, D.; Roy, A.; Seibel, W. L. *Tetrahedron Lett.* **2003**, *44*, 8861.
44. Naskar, D.; Roy, A.; Seibel, W. L.; Portlock, D. E. *Tetrahedron Lett.* **2003**, *44*, 5819.
45. Schlienger, N.; Bryce, M. R.; Hansen, T. K. *Tetrahedron Lett.* **2000**, *41*, 1303.
46. Jourdan, H.; Gouhier, G.; Van Hijfte, L.; Angibaud, P.; Piettre, S. R. *Tetrahedron Lett.* **2005**, *46*, 8027.
47. Frohn, H.-J.; Franke, H.; Fritzen, P.; Bardin, V. V. *J. Organomet. Chem.* **2000**, *598*, 127.
48. Tremblay-Morin, J.-P.; Raeppel, S.; Gaudette, F. *Tetrahedron Lett.* **2004**, *45*, 3471.
49. Wu, T. R.; Chong, J. M. *Org. Lett.* **2006**, *8*, 15.
50. Molander, G. A.; Katona, B. W.; Machrouchi, F. *J. Org. Chem.* **2002**, *67*, 8416.
51. Bedford, R. B.; Betham, M. *J. Org. Chem.* **2006**, *71*, 9403.