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A simple route to side-chain fluorinated β-lactams from ring-fluorinated aziridines

Alexander S. Konev [a], Mikhail S. Novikov [a], Alexander F. Khlebnikov [a,*], Kourosch Abbaspour Tehrani [b]

[a] *Department of Chemistry, St. Petersburg State University, Universitetskii pr. 26, 198504 St. Petersburg, Petrodvorets, Russia*
[b] *Faculty of Science, Department of Applied Biological Sciences, Laboratory for Organic Chemistry, Vrije Universiteit Brussel, Pleinlaan 2, B-1050 Brussels, Belgium*

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Abstract

β-Lactams bearing a Ph_2CF substituent at the C(4)-atom were synthesized from *N*-alkyl-2-fluoro-3,3-diphenylaziridines. The transformation was realized using SbF_3-mediated isomerization of the monofluoroaziridines to fluorinated aldimines, followed by Staudinger reaction with ketenes. It was shown that this reaction sequence can be performed as a one-pot procedure.

Keywords: Fluoroaziridines; Fluorinated aldimines; Fluorine-containing β-lactams

1. Introduction

The synthesis of β-lactams and their biological application is an increasingly active area. The β-lactam structural fragment is the base of the family of bioactive compounds: antibiotics [1,2], fungicides [3,4], and antitumor agents [5].

It is well known that the introduction of fluorine atoms to bioactive molecules can often improve their pharmacological properties because of, for example, increased membrane permeability, enhanced hydrophobic binding, stability against metabolic transformations, and so on [6–10]. One can expect, therefore, that fluorine-containing β-lactams will serve as important and useful bioactive compounds for medicinal chemistry and chemical biology. For example, Ezetimibe, a β-lactam containing fluorine in the side chain, is the first of the selective cholesterol absorption inhibitors [11]. β-Lactams bearing a fluorine atom in the alpha position of the side chain have been intensively investigated as potential antibiotics [12–17]. In certain cases the CH_2F group in the fourth position of the azetidinone ring enhances the antibiotic activity of lactams [12] and their resistance [13] to β-lactamase. Fluorinated β-lactams are also of interest as synthetic building blocks for the preparation of fluorine- and nitrogen-containing compounds, such as for the synthesis of fluorinated amino acids, dipeptides, and fluoro-taxoids [18].

Approaches to β-lactams with fluorine in the 3-position of the ring [19,20] or F_2C- [18,21] and F_3C-groups in side chains [18] were elaborated. At the same time, the diversity of β-lactams with one α-fluorine atom in the side chain remains still limited to β-lactams bearing CFH_2 [12,13,15,17,22–26] or $CFXCO_2R$ (X = H, Alk [27], CO_2R [27,28]) groups. It was also found that the Ph_2F group enhances the effect of certain medicines [29].

[2 + 2]-Cycloaddition of imine to ketene is one of the simplest and well-developed direct routes to β-lactams (Scheme 1). β-Lactams with fluorine in the α-position of the side chain can be synthesized by this reaction from α-fluoroimines, preparation of which, however, is often not a trivial problem. That is the reason why the reported examples of application of such an approach are rare and limited to the use of *N*-(2-fluoroethylidene)amines for preparing 4-fluoromethylazetidine-2-ones [25,26].

Recently we have demonstrated that some fluorinated imines are accessible by isomerization of 2-fluoroaziridines, which in turn can be prepared by cycloaddition of monofluorocarbenes to imines [30,31]. In the present study reactions of diphenylketene

* Corresponding author. Tel.: +7 812 4284021; fax: +7 812 4286939.
E-mail address: Alexander.Khlebnikov@pobox.spbu.ru (A.F. Khlebnikov).

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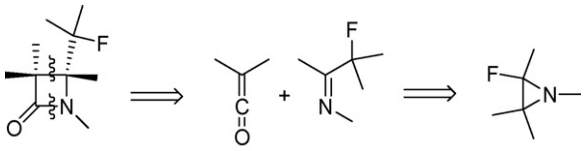


Scheme 1.

and ketenes, bearing oxy-groups, with α-fluoroimines generated from 2-fluoroaziridines were examined as a potential route to side-chain fluorinated β-lactams (Scheme 2).

2. Results and discussion

2-Fluoroaziridines **1a–c** were synthesized from *N*-benzyl-, *N*-methoxycarbonylmethyl- and *N*-methyl-imines of benzophenone and monofluorocarbene (generated by the reduction of $CHFBr_2$ with active lead according to the published procedure [31]). Diphenylketene **3a** was prepared according to the known procedure [32] and oxy-substituted ketenes **3b,c** were generated *in situ* from the appropriate acid chloride and triethylamine.

We recently found that 2-fluoroaziridines isomerize into α-fluoroimines or/and 1,3-disubstituted indoles under protic (TsOH) or Lewis acid ($ZnCl_2$, $TiCl_4$, SbF_3) catalysis. The most selective isomerization leading exclusively to α-fluoroimines was observed with SbF_3 [30]. It was supposed [30] that the coordination of the Lewis acid with the aziridine nitrogen or protonation of compounds **2** facilitates cleavage of the three-membered ring, like with dichloro- and chlorofluoro-substitted aziridines [33,34]. For preparation of target β-lactams isomerization of 2-fluoroaziridines into α-fluoroimines **2a–c** was carried out using SbF_3 as a catalyst. A solution of aziridine **1a–c** in CH_2Cl_2 was refluxed in the presence of SbF_3 until transformation of the aziridine to imine **2a–c** was completed.

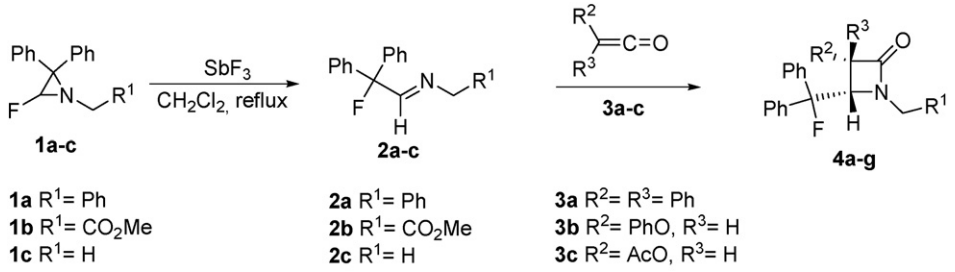
Table 1
Synthesis of lactams **4a–g**

Aziridine	Ketene	Lactam	R^1	R^2	R^3	Reaction conditions	Isolated yield of **4** (%)
1a	**3a**	**4a**	Ph	Ph	Ph	CH_2Cl_2, 40 °C	22
1a	**3b**	**4b**	Ph	PhO	H	CH_2Cl_2, rt	62
1a	**3c**	**4c**	Ph	AcO	H	CH_2Cl_2, rt	30
1b	**3a**	**4d**	CO_2Me	Ph	Ph	Toluene, 110 °C	22
1b	**3b**	**4e**	CO_2Me	PhO	H	CH_2Cl_2, rt	42
1c	**3b**	**4f**	H	PhO	H	CH_2Cl_2, rt	48
1c	**3c**	**4g**	H	AcO	H	CH_2Cl_2, rt	46

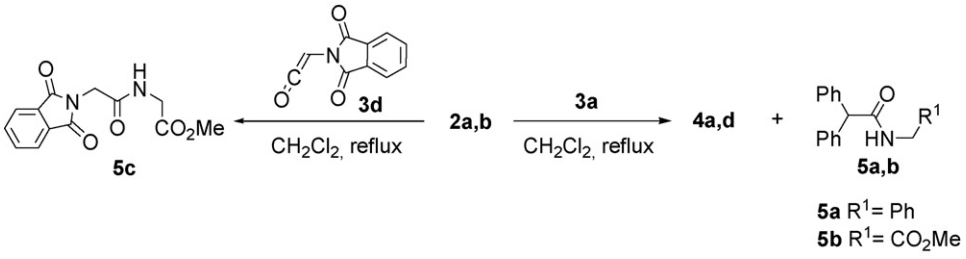
The catalyst was filtered off, ketene or the corresponding acid chloride and triethylamine was added and the mixture was stirred at room temperature. The products were isolated by crystallization or by using column chromatography on silica. The yields of synthesized lactams **4a–g** per starting aziridines **1a–c** are presented in Table 1.

The structure of compounds **4a–g** was proved from their IR, ^1H, ^{19}F and ^{13}C NMR spectra. The *cis*-configuration of lactams **4b,c,e–g** is evident from the values of J_{HH} (4.7–5.0 Hz) for H-3-4, since *trans*- and *cis*-vicinal $^2J_{HH}$ constants found for 3- and 4-monosubstituted β-lactams are 1–2 and 4–5 Hz, respectively [35].

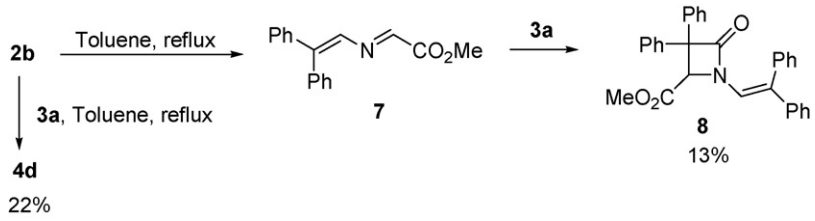
The resulting lactams from phenoxy- and acetoxy-ketenes are usually obtained in yields ranging from 42 to 62%. Yields of diphenylketene-derived lactams are lower in consequence of the formation of byproducts. Thus, in the reaction of imine **2a** with diphenylketene in CH_2Cl_2 at 40 °C, in addition to lactam **4a** (22%), amide **5a** (24%) was isolated (Scheme 3). In the reaction of imine **2b** with ketene **3d** amide **5c** was also isolated with 19% yield instead of the expected lactam.



Scheme 2.



Scheme 3.



Scheme 4.

Probably in the case of ketenes **3a,d** (having relatively low reactivity in [2 + 2]-cycloadditions) Staudinger reaction competes with hydrolysis of imine **2**, giving rise to amine which reacts with ketene with formation of corresponding amide.

The reaction of imine **2b** with diphenylketene in boiling toluene for 1.5 h gave rise to lactam **4d** (22%) and lactam **8** (13%) (Scheme 4). The latter is a product of the Staudinger reaction of the azadiene **7** which is formed as the result of dehydrofluorination of imine **2b**. The yield of **4d** in the reaction performed at room temperature was rather low. In this case amide **5b** was also isolated in 19% yield.

Synthesis of β-lactams from fluoroaziridines **1** can be also realized by a one-pot procedure. Thus, refluxing of aziridine **1c** in CH_2Cl_2 with a catalytic amount of SbF_3 for 14 h, followed by addition of phenoxyacetyl chloride and triethylamine gave lactam **4g** for 1 d at room temperature in 47% yield.

3. Experimental

3.1. General

Melting points were determined on a Boetius melting point apparatus; uncorrected values are given. The IR spectra were recorded on a Carl Zeiss UR-20 instrument. ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra were measured with a Bruker DPX 300 spectrometer and ^{19}F NMR (235 MHz) with Brucker Avance 250 spectrometer. The elemental compositions were determined on an HP-185B CHN analyzer. The progress of reactions was monitored by thin-layer chromatography using Silufol UV-254 plates. Silica gel Merck 60 was used for column chromatography. Methylene chloride was dried by distillation over P_2O_5.

3.2. 1-Benzyl-4-[fluoro(diphenyl)methyl]-3,3-diphenylazetidin-2-one (4a)

A mixture of 1-benzyl-3-fluoro-2,2-diphenylaziridine (**1a**) (100 mg, 0.33 mmol), SbF_3 (59 mg, 0.33 mmol) and CH_2Cl_2 (30 mL) was refluxed for 15 h. SbF_3 was filtered off, the solvent evaporated in vacuo and the residue treated with diphenylketene (**3a**) (61 mg, 0.31 mmol) solution in CH_2Cl_2 (4 mL). The resulting solution was refluxed for 9 h, then concentrated and chromatographed on silica, having compound **4a** [35 mg (22%), colorless crystals, mp 181–182 °C (Et_2O)] and *N*-benzyl-2,2-diphenylacetamide (**5a**) [24 mg (24%), colorless crystals, mp 126–128 °C (CH_2Cl_2–hexane), lit mp 126–128 °C [36]].

Compound **4a**: IR ($CHCl_3$): ν 1770 (C=O). ^1H NMR (300 MHz, $CDCl_3$): δ 3.32 (1H, d, J = 16.0 Hz, CH_2), 4.88 (1H, d, J = 16.0 Hz, CH_2), 5.45 (1H, d, J 25.8 Hz, CH), 6.4–7.6 (25H, m, Ph). ^{13}C NMR (75 MHz, $CDCl_3$): δ 44.8 (CH_2), 66.5 (d, J = 20.5 Hz, C-4), 71.2 (C-3), 95.7 (d, J = 189.5 Hz, CF), 123.6 (d, J = 10.0 Hz, C-Ph), 124.3 (d, J = 11.0 Hz, C-Ph), 126.5, 127.0, 127.26, 127.32, 127.6, 127.7 (d, J = 1.0 Hz, C-Ph), 127.9, 128.19 (4C, C-Ph), 128.23, 128.5 (C-Ph), 128.7 (d, J = 2.5 Hz, C-Ph), 130.0 (d, J = 3.0 Hz, C-Ph), 135.2, 137.0, 140.4 (C-Ph), 141.1 (d, J = 23.4 Hz, C-Ph), 142.3 (d, J = 24.4 Hz, C-Ph), 171.0 (C=O). ^{19}F NMR ($CDCl_3$): δ −172.4, broad singlet. Anal. calcd. for $C_{35}H_{28}FNO$: C, 84.5; H, 5.7; N, 2.8. Found: C, 84.6; H, 5.7; N, 2.6.

3.3. cis-1-Benzyl-4-[fluoro(diphenyl)methyl]-3-phenoxyazetidin-2-one (4b)

A mixture of 1-benzyl-3-fluoro-2,2-diphenylaziridine (**1a**) (100 mg, 0.33 mmol), SbF_3 (58 mg, 0.32 mmol) and CH_2Cl_2 (30 mL) was refluxed for 15 h. SbF_3 was filtered off and Et_3N (36 mg, 0.36 mmol) and phenoxyacetyl chloride (61 mg, 0.36 mmol) were added to the filtrate. The resulting solution was stirred at 14–17 °C for 18 h and then washed with 0.02 M aq. Na_2CO_3 (20 mL). The organic layer was dried over Na_2SO_4, filtered, concentrated and the residue was crystallized from ether to give compound **4b** [89 mg (62%), colorless crystals, mp 159–162 °C (Et_2O)]. IR ($CHCl_3$): ν 1760 (C=O). ^1H NMR (300 MHz, $CDCl_3$): δ 3.38 (1H, d, J = 15.2 Hz, CH_2), 4.80 (1H, d, J = 15.2 Hz, CH_2), 4.81 (1H, dd, J_{HF} = 24.3 Hz, J_{HH} = 5.0 Hz, H-4), 5.29 (1H, d, J = 5.0 Hz, H-3), 6.50–7.50 M (20H, m, Ph). ^{13}C NMR (75 MHz, $CDCl_3$): δ 44.9 (CH_2), 62.5 (d, J = 21.4 Hz, C-4), 81.6 (d, J = 1.0 Hz, C-3), 95.4 (d, J = 187.5 Hz, CF), 116.3, 122.2 (C-Ph), 124.75 (d, J = 8.0 Hz, C-Ph), 124.82 (d, J = 10.0 Hz, C-Ph), 127.68 (d, J = 1.5 Hz, C-Ph), 127.71 (C-Ph), 128.0 (d, J = 1.0 Hz, C-Ph), 128.2, 128.3, 128.6 (C-Ph), 128.7 (d, J = 2.0 Hz, C-Ph), 129.1, 134.9 (C-Ph), 141.1 (d, J = 22.4 Hz, C-Ph), 142.0 (d, J = 24.9 Hz, C-Ph), 158.0 (C-Ph), 167.5 (C=O). ^{19}F NMR ($CDCl_3$): δ −165.1 broad singlet. Anal. calcd. for $C_{29}H_{24}FNO_2$: C, 79.6; H, 5.5; N, 3.2. Found: C, 79.7; H, 5.5; N, 2.9.

3.4. cis-1-Benzyl-2-[fluoro(diphenyl)methyl]-4-oxoazetidin-3-yl acetate (4c)

A mixture of 1-benzyl-3-fluoro-2,2-diphenylaziridine (**1a**) (100 mg, 0.33 mmol), SbF_3 (59 mg, 0.33 mmol) and CH_2Cl_2 (30 mL) was refluxed for 15 h. SbF_3 was filtered off and Et_3N (37 mg, 0.37 mmol) and acetoxyacetyl chloride (50 mg, 0.37 mmol) were added to the filtrate. The resulting solution was stirred at room temperature for 2 d and then washed with 0.02 M aq. Na_2CO_3 (20 mL). The organic layer was dried over

Na_2SO_4, filtered, concentrated and the residue was crystallized from ether to give compound **4c** [40 mg (30%), colorless crystals, mp 177–178 °C (Et_2O–CH_2Cl_2)]. IR ($CHCl_3$): ν 1770 (C=O). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.50 (3H, s, CH_3), 3.29 (1H, d, J = 14.6 Hz, CH_2), 4.71 (1H, d, J_{HF} = 24.5 Hz, J_{HH} = 4.7 Hz, H-4), 4.78 (1H, d, J = 14.6 Hz, CH_2), 6.20 (1H, d, J = 4.7 Hz, H-3), 6.60–7.50 (15H, m, Ph). ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.6 (CH_3), 44.9 (CH_2), 62.0 (d, J = 20.0 Hz, C-4), 72.7 (C-3), 94.7 (d, J = 188.0 Hz, CF), 124.2 (d, J = 8.5 Hz, C-Ph), 124.4 (d, J = 10.0 Hz, C-Ph), 127.8 (C-Ph), 127.9 (d, J = 1.5 Hz, C-Ph), 128.00 (C-Ph), 128.04 (d, J = 1.0 Hz, C-Ph), 128.55 (C-Ph), 128.58 (d, J = 1.0 Hz, C-Ph), 128.9 (d, J = 2.0 Hz, C-Ph), 134.4 (C-Ph), 140.6 (d, J = 22.4 Hz, C-Ph), 141.6 (d, J = 25.4 Hz, C-Ph), 166.1 (C=O), 169.0 (C=O). ^{19}F NMR ($CDCl_3$): δ −169.3 (d, J = 24.5 Hz). Anal. calcd. for $C_{25}H_{22}FNO_3$: C, 74.4; H, 5.5; N, 3.5. Found: C, 74.5; H, 5.4; N, 3.4.

3.5. Methyl 2-[2-[fluoro(diphenyl)methyl]-4-oxo-3,3-diphenyl-1-azetidinyl]acetate (*4d*) and methyl 1-(2,2-diphenylvinyl)-4-oxo-3,3-diphenylazetidine-2-carboxylate (*8*)

a. A mixture of methyl 2-(3-fluoro-2,2-diphenylaziridin-1-yl)acetate (**1b**) (103 mg, 0.33 mmol), SbF_3 (59 mg, 0.33 mmol) and CH_2Cl_2 (20 mL) was refluxed for 2 h. SbF_3 was filtered off, the solvent was evaporated in vacuo and the residue treated with diphenylketene (**3a**) (70 mg, 0.36 mmol) solution in toluene (5 mL). The resulting solution was refluxed for 1.5 h, then concentrated and chromatographed on silica to give compound **4d** [38 mg, 22%, colorless crystals, mp 197–200 °C (Et_2O–CH_2Cl_2)] and compound **8** [21 mg (13%), colorless crystals, mp 209–212 °C (Et_2O–CH_2Cl_2)].

Compound **4d**: IR ($CHCl_3$): ν 1770 (C=O) and 1750 (C=O). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.89 (1H, d, J = 18.3 Hz, CH_2), 3.54 (3H, s, CH_3), 4.34 (1H, d, J = 18.3 Hz, CH_2), 6.04 (1H, d, J = 27.4 Hz, CH), 6.70–7.70 (20H, m, Ph). ^{13}C NMR (75 MHz, $CDCl_3$): δ 41.6 (CH_2), 52.0 (CH_3), 67.6 (d, J = 20.0 Hz, C-4), 71.4 (C-3), 95.7 (d, J = 189.5 Hz, CF), 123.7 (d, J = 10.0 Hz, C-Ph), 124.1 (d, J = 11.0 Hz, C-Ph), 126.7, 127.1, 127.2, 127.6 (d, J = 1.0 Hz, C-Ph), 127.8, 128.1, 128.4 (d, J = 1.5 Hz, C-Ph), 128.5 (C-Ph), 128.7 (d, J = 2.0 Hz, C-Ph), 129.9 (d, J = 2.5 Hz, C-Ph), 136.8 (d, J = 2.0 Hz, C-Ph), 140.1, 140.7 (d, J = 23.4 Hz, C-Ph), 142.4 (d, J = 25.5 Hz, C-Ph), 168.5 (C=O), 170.6 (C=O). ^{19}F NMR ($CDCl_3$): δ −173.3 (d, J = 27 Hz). Anal. calcd. for $C_{31}H_{26}FNO_3$: C, 77.6; H, 5.5; N, 2.9. Found: C, 77.6; H, 5.6; N, 2.7.

Compound **8**: IR ($CHCl_3$): ν 1760 (C=O). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.10 (3H, s, CH_3), 4.60 (1H, s, C-4), 6.70–8.00 M (21H, m, Ph, HC=). ^{13}C NMR (75 MHz, $CDCl_3$): δ 51.6 (CH_3), 65.7 (C-4), 71.9 (C-3), 117.1 (=CH), 127.0, 127.2, 127.3, 127.8, 128.1, 128.3, 128.8, 131.0, 136.4, 137.1, 138.6, 139.9, 166.6 (C=O), 167.1 (C=O). Anal. calcd. for $C_{31}H_{25}NO_3$: C, 81.0; H, 5.5; N, 3.1. Found: C, 81.1; H, 5.7; N, 3.0.

b. A mixture of methyl 2-(3-fluoro-2,2-diphenylaziridin-1-yl)acetate (**1b**) (105 mg, 0.37 mmol), SbF_3 (66 mg, 0.37 mmol) and CH_2Cl_2 (20 mL) was refluxed for 2 h. SbF_3 was filtered off and the filtrate was treated with diphenylketene (71 mg, 0.37 mmol). The resulting solution was kept at 5–15 °C for 3 d. The solvent was evaporated in vacuo, Et_2O was added to the residue and the mixture was seeded with a small crystal of compound **4d**. After crystallization compound **4d** (20 mg, 11%) was obtained. From the mother liquid was isolated methyl 2-[(2,2-diphenylacetyl)amino]acetate (**5b**) (20 mg, 19%), which was identified by comparison of ^{1}H and ^{13}C NMR with published data [37].

3.6. Methyl 2-[cis-2-[fluoro(diphenyl)methyl]-4-oxo-3-phenoxyazetidin-1-yl]acetate (*4e*)

A mixture of methyl 2-(3-fluoro-2,2-diphenylaziridin-1-yl)acetate (**1b**) (100 mg, 0.35 mmol), SbF_3 (63 mg, 0.35 mmol) and CH_2Cl_2 (20 mL) was refluxed for 2 h. SbF_3 was filtered off and Et_3N (40 mg, 0.40 mmol) and phenoxyacetyl chloride (66 mg, 0.39 mmol) were added to the filtrate. The resulting solution was stirred at 17 °C for 3 d and then washed with 0.02 M aq. Na_2CO_3 (20 mL). The organic layer was dried over Na_2SO_4, filtered, concentrated and the residue was crystallized from ether to give compound **4e** [(62 mg, 42%), colorless crystals, mp 136–138 °C (Et_2O)]. IR ($CHCl_3$): ν 1750 (C=O) and 1780 (C=O). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.95 (1H, d, J = 18.3 Hz, CH_2), 3.63 (3H, s, CH_3), 4.31 (1H, d, J = 18.3 Hz, CH_2), 5.38 (1H, dd, J_{HH} = 5.0 Hz, J_{HF} = 25.3 Hz, H-4), 5.49 (1H, d, J_{HH} = 5.0 Hz, H-3), 6.70–7.60 M (15H, Ph). ^{13}C NMR (75 MHz, $CDCl_3$): δ 41.6 (CH_2), 52.2 (CH_3), 63.6 (d, J = 20.9 Hz, C-4), 81.8 (C-3), 95.4 (d, J = 187.0 Hz, CF), 116.2, 122.2 (C-Ph), 124.5 (d, J = 10.0 Hz, C-Ph), 124.8 (d, J = 8.5 Hz, C-Ph), 127.8 (d, J = 1.0 Hz, C-Ph), 128.2 (d J = 1.0 Hz, C-Ph), 128.3 (C-Ph), 128.7 (d, J = 2.0 Hz, C-Ph), 129.2 (C-Ph), 140.5 (d, J = 22.4 Hz, C-Ph), 141.7 (d, J = 24.9 Hz, C-Ph), 157.9 (C-Ph), 167.5 (C=O), 168.4 (C=O). ^{19}F NMR ($CDCl_3$): δ -166.0, broad singlet. Anal. calcd. for $C_{25}H_{22}FNO_4$: C, 71.6; H, 5.3; N, 3.3. Found: C, 71.7; H, 5.3; N, 3.2.

3.7. cis-4-[Fluoro(diphenyl)methyl]-1-methyl-3-phenoxyazetidin-2-one (*4f*)

A mixture of 3-fluoro-1-methyl-2,2-diphenylaziridine (**1c**) (20 mg, 0.09 mmol), SbF_3 (16 mg, 0.09 mmol) and CH_2Cl_2 (5 mL) was refluxed for 14 h. SbF_3 was filtered off and the solvent was evaporated in vacuo to give ***N*-(2-fluoro-2,2-diphenylethylidene)methanamine** (**2c**) (20 mg) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.49 (3H, t, J_{HH} = J_{HF} = 1.7 Hz, CH_3,), 7.3–7.5 (10H, m, Ph), 8.15 (1H, dq, J_{HH} = 1.7 Hz, J_{HF} = 9.8 Hz, CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 48.0 (CH_3), 98.1 (d, J_{CF} = 173.0 Hz, CF), 127.0 (d, J_{CF} 3.0 Hz, C-*o*-Ph), 128.21 (C-*p*-Ph), 128.23 (d, J_{CF} = 2.5 Hz, C-*m*-Ph), 128.5 (d, J_{CF} = 2.0 Hz, C-*m*-Ph), 139.8 (d, J_{CF} = 22.7 Hz, C-*i*-Ph), 164.5 (d, J_{CF} = 32.2 Hz, HC = N).

A mixture of 3-fluoro-1-methyl-2,2-diphenylaziridine **1c** (110 mg, 0.48 mmol), SbF_3 (88 mg, 0.49 mmol) and CH_2Cl_2 (30 mL) was refluxed for 14 h. SbF_3 was filtered off and Et_3N (59 mg, 0.58 mmol) and phenoxyacetyl chloride (91 mg, 0.53 mmol) were added to the filtrate. The resulting solution was stirred at room temperature for 2 d and then washed with 0.02M aq. Na_2CO_3 (20 mL). The organic layer was dried over Na_2SO_4, filtered, concentrated and the residue was crystallized from ether to give compound **4f** [(84 mg, 48%), colorless crystals, mp 193–196 °C (Et_2O–CH_2Cl_2)]. IR ($CHCl_3$): ν 1770 (C = O). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.51 (3H, s, CH_3), 4.96 (1H, dd, J_{HF} = 24.1 Hz, J_{HH} = 4.9 Hz, H-4), 5.33 (1H, d, J = 4.9 Hz, H-3), 6.6–7.6 (15H, m, Ph). ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.1 (CH_3), 64.8 (d, J = 21.4 Hz, C-4), 81.6 (C-3), 95.5 (d, J = 186.5 Hz, CF), 116.2, 122.1 (C-Ph), 124.7 (d, J = 10.0 Hz, C-Ph), 124.9 (d, J = 8.5 Hz, C-Ph), 127.7 (d, J = 1.3 Hz, C-Ph), 128.0 (d, J = 1.2 Hz, C-Ph), 128.3, 128.7 (d, J = 1.5 Hz, C-Ph), 129.1, 140.8 (d, J = 22.9 Hz, C-Ph), 142.0 (d, J = 24.7 Hz, C-Ph), 158.0 (C-Ph), 167.3 (C=O). ^{19}F NMR ($CDCl_3$): δ -163.9 broad singlet. Anal. calcd. for $C_{23}H_{20}FNO_2$: C, 76.4; H, 5.6; N, 3.9. Found: C, 76.3; H, 5.6; N, 3.7.

*3.8. cis-2-[Fluoro(diphenyl)methyl]-1-methyl-4-oxoazetidin-3-yl]acetate (**4g**)*

A mixture of 3-fluoro-1-methyl-2,2-diphenylaziridine (**1c**) (100 mg, 0.44 mmol), SbF_3 (79 mg, 0.44 mmol) and CH_2Cl_2 (25 mL) was refluxed for 14 h. SbF_3 was filtered off and Et_3N (37 mg, 0.37 mmol) and acetoxyacetyl chloride (50 mg, 0.37 mmol) were added to the filtrate. The resulting solution was stirred at room temperature for 2 d and then washed with 0.02 M aq. Na_2CO_3 (20 mL). The organic layer was dried over Na_2SO_4. Concentration of the solution and purification by column chromatography on silica gave compound **4g** [66 mg (46%), colorless crystals, mp 179–181 °C (Et_2O–CH_2Cl_2)]. IR ($CHCl_3$): ν 1770 (C = O). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.53 (3H, s, CH_3CO), 2.43 (3H, s, CH_3N), 4.89 (1H, d, J_{HF} = 24.5 Hz, J_{HH} = 4.7 Hz, H-4), 6.21 (1H, d, J = 4.7 Hz, H-3), 7.2–7.6 (10H, m, Ph). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.1 (CH_3), 28.0 (CH_3N), 64.4 (d, J = 20.3 Hz, C-4), 72.9 (C-3), 94.6 (d, J = 187.7 Hz, CF), 124.17 (d, J = 10.4 Hz, C-*o*-Ph), 124.20 (d, J = 8.5 Hz C-*o*-Ph), 128.0 (d, J = 1.4 Hz, C-*p*-Ph), 128.1 (d, J = 1.2 Hz, C-*p*-Ph), 128.6 (d, J = 1.1 Hz, C-*m*-Ph), 128.8 (d, J = 2.0 Hz, C-*m*-Ph), 140.5 (d, J = 22.8 Hz, C-*i*-Ph), 141.7 (d, J = 25.3 Hz, C-*i*-Ph), 166.0 (C=O), 168.9 (C = O). ^{19}F NMR ($CDCl_3$): δ −169.0 (d, J = 24.5 Hz). Anal. calcd. for $C_{19}H_{18}FNO_3$: C, 69.7; H, 5.5; N, 4.3. Found: C, 69.5; H, 5.6; N, 4.2.

*3.9. "One-pot" synthesis of cis-4-[fluoro(diphenyl)methyl]-1-methyl-3-phenoxyazetidin-2-one (**4f**)*

A mixture of 3-fluoro-1-methyl-2,2-diphenylaziridine (**1c**) (93 mg, 0.41 mmol), SbF_3 (7 mg, 0.04 mmol) and CH_2Cl_2 (30 mL) was refluxed for 14 h. The resulting mixture was cooled and Et_3N (50 mg, 0.50 mmol) and phenoxyacetyl chloride (77 mg, 0.45 mmol) were added. The mixture was stirred at room temperature for 1 d and then washed with 0.02 M aq. Na_2CO_3 (20 mL). The organic layer was dried over Na_2SO_4, filtered, concentrated and the residue was crystallized from CH_2Cl_2–Et_2O to give compound **4** (70 mg, 47%).

*3.10. Reaction of methyl 2-[(2-fluoro-2,2-diphenylethylidene)amino]acetate (**2b**) with ketene **3d***

A mixture of methyl 2-(3-fluoro-2,2-diphenylaziridin-1-yl)acetate **(1b)** (112 mg, 0.39 mmol), SbF_3 (64 mg, 0.36 mmol) and CH_2Cl_2 (20 mL) was refluxed for 2 h. SbF_3 was filtered off and Et_3N (65 mg, 0.64 mmol) and phthalimidoacetyl chloride (131 mg, 0.59 mmol) were added to the filtrate. The resulting solution was stirred at 12–16 °C for 2 d and then washed with 0.02 M aq. Na_2CO_3 (20 mL). The organic layer was dried over Na_2SO_4, filtered, concentrated and the residue was crystallized from Et_2O–CH_2Cl_2 to give methyl 2-phtalimido-2-acetamidoacetate (**5c**) [21 mg (19%), colorless crystals, mp 201–204 °C (Et_2O–CH_2Cl_2)], lit. mp 203–204 °C (H_2O) [38].

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