Easy Access to 2-Fluoro- and 2-Iodo-2*H*-azirines via the Halex Reaction

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Abstract A simple gram-scale method for the preparation of esters and dialkylamides of 2-(fluoro/iodo)-2*H*-azirine-2-carboxylic acids via the halogen exchange (Halex) reaction of 2-bromo-substituted analogues is reported. The method operates with inexpensive and safe reagents, Bu₄NF and potassium iodide, providing high product yields. Alternatively, 2-fluoro-2*H*-azirine-2-carboxylates can be prepared from 2-iodo- and 2-chloro-analogues. The latter compounds can be obtained in practically quantitative yield by treating the 2-iodo- and 2-bromo-2*H*-azirine-2-carboxylic esters with Bu₄NCl.

Key words azirines, halogen exchange reaction, fluorine, iodine, nucleophilic substitution

Fluorination and iodination are fundamental transformations in organic chemistry, and fluorinated¹ and iodinated² compounds are of extreme importance as building blocks in organic synthesis. In particular, organic iodides are considered among the best substrates for cross-coupling reactions,² and the rapid development of modern coupling methods have greatly increased the demand for iodinated compounds as starting materials. Fluorinated compounds have found a variety of applications³ especially as pharmaceuticals.⁴ It is well known that the introduction of a fluorine atom into a certain position of a bioactive compound may remarkably reduce its toxicity, or improve its efficiency. Furthermore, both organic fluorides and iodides are used as imaging agents for positron emission tomography (PET) scanning.⁵ This method requires the use of a fluorine-containing agent enriched with the ¹⁸F nucleus⁶ or an iodine-containing agent enriched with the ¹²³I, ¹²⁴I, or ¹³¹I nucleus.⁷ These isotopes have half-life times from hundreds of minutes to several days, thus imposing strict requirements for the speed and operational simplicity of reactions used for the introduction of fluorine or iodine atoms into imag-

ing probes. Such reactions, in particular, include nucleophilic substitution reactions, which can use commercially available isotopically labeled alkali metal fluorides and iodides as reagents.

One of the challenges of this chemistry is the introduction of halogen atoms into labile structures, which are easily destroyed by standard halogenating agents. It is particularly true for 2*H*-azirines, the strain energy of the three-membered ring of which makes them attractive building blocks for the synthesis of four-, five-, and six-membered heterocycles.⁸ Examples of the use of 2-bromoazirines for the preparation of the azete and oxazoline derivatives, proceeding with the preservation of the halogen atom in the product have also been reported.⁹ 2-Fluoro- and 2-iodoazirines are much less accessible compounds, and their chemistry is practically unexplored. Besides, 2-iodo-2*H*-azirines are much more reactive in substitution reactions than 2-bromoazirines, and there are cases when less accessible iodides cannot be replaced by more accessible bromides.¹⁰

The known methods for the synthesis of these compounds are based on two strategies. In the framework of the first strategy, the 2-haloazirine ring is formed through the cyclization of halogenated open-chain precursor, for example, through thermal cyclization of a 2-halovinylazide. Some 2-iodo- and 2-fluorovinylazides can be obtained by dehydrohalogenation of 1-azido-2,2-dihalo derivatives¹¹ or from α -oxophosphonium ylides and *N*-iodosuccinimide in the presence of azidotrimethylsilane (Scheme 1, reaction 1).¹² The reaction of β -carbonyl-substituted enamines with PhIF₂ generated in situ from PhIO and Et₃N·3HF was used for the preparation of 2-fluoroazirines, containing a carbonyl substituent at the C2 atom (reaction 4).¹³ Another strategy for the synthesis of 2-fluoro- and 2-iodoazirine-2-carboxyls is based on the metal-catalyzed ring contraction of 4-fluoro- and 4-iodoisoxazoles (reactions 2 and 3).^{14,15} Unfortunately, the methods noted above require either po-

tentially explosive compounds or expensive reagents. For the preparation of starting materials such as 4-fluoro- and 4-iodoisoxazoles, butyllithium is required. All of this calls into question the scalability of such protocols and stimulates the search for new methods for the preparation of 2-fluoro- and 2-iodoazirines.

One powerful method for the introduction of halogen atoms into a cyclic molecule is the halogen exchange (Hal-ex) reaction. A transition-metal-free version of this method is widely used for the preparation of haloarenes¹⁶ and, to a lesser extent, for the synthesis of haloheteroarenes, such as fluorotriazoles¹⁷ and fluoropyridines.¹⁸ In this work, a new method for the synthesis of 2-fluoro- and 2-iodoazirine-2-carbonyls based on the halogen exchange reaction is developed (Scheme 1, reaction 5). This method uses easily available 2-bromo-2H-azirine-2-carboxylic acid derivatives as starting materials and inexpensive and safe reagents for the introduction of fluorine and iodine into the azirine ring.

Recently, we have shown that a bromine atom in 2-bromo-2H-azirine-2-carboxylates can be easily substituted with acyloxy-, alkoxy-, alkenyloxy-¹⁰ and azoly¹⁹ substituents under mild conditions. These transformations take place under the action of the corresponding O- and N-nucleophiles via a cascade $S_N2'-S_N2''$ mechanism, which imposes high requirements on both the nucleophilicity and the nucleofugality of the reagent. Thus, aliphatic and aromatic carboxylic acids react with methyl 2-bromo-3-phenyl-2H-azirine-2-carboxylate (**1a**) in the presence of Et_3N to afford 2-acyloxy derivatives in high yields, while with substantially more acidic trichloroacetic acid the reaction does not occur.¹⁰ As far as we know, there is no information in

the literature on the use of halide ions as nucleophiles in such reactions.

We began our study with the search for optimal conditions for the preparation of fluoroazirine **2a** via the halogen exchange reaction of 2-bromoazirine **1a**. The latter was chosen because of its synthetic accessibility and high reactivity in the substitution reactions.^{10,19}

It was found that **1a** reacted with tetrabutylammonium fluoride hydrate (TBAF·H₂O) in toluene at ambient temperature to afford the target fluoride **2a** in good yield (Table 1, entry 1). Screening of other sources of fluoride ion and solvents (entries 2–6) showed that the highest yield of fluoride **2a** from bromide **1a** was achieved using TBAF·H₂O (1.3 equiv) in dichloromethane (DCM) at room temperature (entry 2). These conditions were used in further experiments carried out to evaluate the substrate scope of the reaction.

Table 1 Optimization of Azirine **2a** Synthesis

Entry	Reagent (equiv)	Solvent	Time (h)	Yield of 2a (%) ^a
1	TBAF·H ₂ O (1.3)	toluene	4	76
2	TBAF·H ₂ O (1.3)	DCM	4	80
3	KF (1.5)	DMSO	12	33
4	CsF (1.5)	DMSO	12	45
5	CoF ₂ (1.5)	DMSO	48	trace
6	FeF ₂ (1.5)	toluene	12	0

^a Yield of isolated product.

Bromoazirines **1a–n** required for the experiments were prepared from 5-(alkoxy/amino)isoxazoles **5a–n** by bromination using *N*-bromosuccinimide (NBS) followed by $FeSO_4$ -catalyzed isomerization of bromoisoxazoles **6a–n** (Scheme 2).^{14a} Isoxazoles **5** were synthesized from either 5-chloroisoxazoles **3** or isoxazol-5-ones **4**.^{14b}

The substitution reaction worked well with 2-bromo-3-aryl-2H-azirine-2-carboxylic esters containing both electron-withdrawing (Scheme 3, compound **2e**) and electron-donating (Scheme 3, compound **2g**) aryl group and afforded the fluoroazirines in good to excellent yields. The reaction was also insensitive to steric hindrance introduced by bulky *ortho*-substituted aryl groups that could restrict the approach of the nucleophile (Scheme 3, compounds **2d,f,h**). This simple protocol could also be applied to 2-bromo-3-aryl-2H-azirine-2-carboxamides, but the yields of the fluoroazirine-2-carboxamides were significantly lower (Scheme 3, compounds **2k,l**). To test the ability to scale-up the synthesis of fluoroazirines **2**, a gram-scale reaction of bromoazirine **1a** (2.2 g, 8.66 mmol) with TBAF·H₂O (3.14 g, 11.26 mmol) was carried out to give fluoroazirine **2a** in 80% (1.34 g) yield.

It was also shown that the treatment of bromoazirine **1a** with potassium iodide in acetone allowed the replacement of the bromine with iodine in high yield (Scheme 4, compound **7a**). For the complete conversion of bromoazirines **1a,b,e,j**, having no alkoxy groups in the aryl substituent, three equivalents of potassium iodide were required. When using tetrabutylammonium iodide (3 equiv) instead of potassium iodide, no reaction was observed. Unexpectedly, the conversion of alkoxy-substituted bromoazirines **1m,n** into iodoazirines **7d,e** under the standard conditions was

only 27%; after this the reaction stopped. Iodoazirines **7d,e** were obtained in 90% yield only when a 15-fold excess of KI was used. This may be due to a significantly higher solubility of KBr, compared with KI in solutions containing ether compounds,²⁰ to which can be attributed compounds **1m,n** and **7d,e**.

It was found that fluoroazirine **2a** can be alternatively synthesized from iodoazirine **7a** or chloroazirine **8a** under the standard conditions (Scheme 5). The latter compound, in turn, can be obtained in practically quantitative yield by treating azirine **1a** or **7a** with tetrabutylammonium chloride in DCM. Unfortunately, the reverse transformation of chloroazirine **8a** into bromoazirine **1a** using tetrabutylammonium bromide (3 equiv) could not be carried out. This reaction does not occur at all. However, bromoazirine **1a** was obtained by treating iodoazirine **7a** with Bu₄NBr (2 equiv) in DCM at room temperature in practically quantitative yield (Scheme 5).

Taking into account the results of the calculations and experimental data obtained for the halogen substitutions in 2-halo-2H-azirine-2-carboxylates with O- and N-nucleophiles,^{10,19} we believe that the halogen exchange reactions described above also proceed via a cascade S_N2'–S_N2' mechanism.

All the newly synthesized haloazirines **1**, **2**, and **7** were characterized based of ¹H, ¹³C NMR spectroscopic and HRMS data.

In summary, we have developed a simple synthesis of esters and dialkylamides of 2-(fluoro/iodo)-2H-azirine-2-carboxylic acids from much more synthetically accessible 2-bromo-analogues by the halogen exchange (Halex) reaction. The method operates with inexpensive and safe reagents, TBAF and potassium iodide, and provides high product yields. For the synthesis of the 2-fluoro-substituted azirine from the corresponding bromides, a small excess of TBAF is sufficient. A threefold excess of KI in acetone is required to replace bromine with iodine in most 3-aryl-2-

Scheme 5 Halalex reactions of methyl 2-halo-3-phenylazirine-2-carboxylates

bromo-2*H*-azirine-2-carboxylates, with the exception of those that contain alkoxy groups in the aryl substituent. In the latter case, a 15-fold excess of the reagent enables high yields of the iodoazirines to be achieved. Alternatively, 2-fluoro-2*H*-azirine-2-carboxylates can be prepared from 2-iodo- and 2-chloro-analogues. The latter compounds, in turn, can be obtained in practically quantitative yield by treating the 2-iodo- and 2-bromoazirines with Bu₄NCl.

Melting points were determined with a SMP30 melting point apparatus. ¹H (400 MHz) and ¹³C (100 MHz) NMR spectra were recorded with a Bruker AVANCE 400 spectrometer in CDCl₃. Chemical shifts (δ) are reported in ppm downfield from tetramethylsilane. Electrospray ionization (ESI), positive mode, mass spectra were measured with a Bruker MaXis mass spectrometer using acetonitrile for dilution of samples. Thin-layer chromatography (TLC) was conducted on aluminum sheets precoated with SiO₂ ALUGRAM SIL G/UV254. Column chromatography was performed on Macherey-Nagel silica gel 60 M (0.04–0.063 mm). All solvents were distilled and dried prior to use. Toluene was distilled and stored over sodium metal. Dichloromethane was washed with concentrated H₂SO₄ and water, then distilled from P₂O₅ and stored over anhydrous K₂CO₃. Acetone was distilled from anhydrous CaCO₃.

Bromoazirines **1a,b,e,g,k,l,n**¹⁴ are known compounds and have full characterization data. They were synthesized according to the reported procedures that are illustrated in Scheme 2.

Synthesis of Bromoazirines **1c,f,h–j,m**

Isoxazoles **5f** and **5i**; General Procedure

To a stirred suspension of NaH (60% in oil, 440 mg, 11 mmol, pre-washed with hexane) in anhydrous THF (20 mL), alcohol (15 mmol) was added at ambient temperature and the reaction mixture was stirred for 0.5 h. 5-Chloro-3-arylisoazole **3a** (R = 2-BrC₆H₄) or **3b** (R = Ph)^{21a} (5.6 mmol) was added and the mixture was heated at reflux for 1 h. The mixture was cooled to ambient temperature, the reaction was quenched with water (20 mL) and the mixture was extracted with CH₂Cl₂ (3 × 20 mL). The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure to give pure compound **5f** or **5i**.

3-(2-Bromophenyl)-5-methoxyisoxazole (**5f**)

Yield: 1.31 g (92%) (from isoxazole **3a**); colorless oil.

¹H NMR (400 MHz, CDCl₃): δ = 7.72–7.66 (m, 1 H), 7.66–7.60 (m, 1 H), 7.44–7.36 (m, 1 H), 7.36–7.29 (m, 1 H), 5.67 (s, 1 H), 4.07 (s, 3 H).

¹³C NMR (100 MHz, CDCl₃): δ = 173.6, 164.3, 133.6, 131.1, 130.0, 130.9, 127.5, 122.1, 76.7, 58.8.

HRMS (ESI): *m/z* [M + Na]⁺ calcd for C₁₀H₈⁸¹BrNNaO₂⁺: 277.9610; found: 277.9606.

5-Isobutoxy-3-phenylisoxazole (**5i**)

Yield: 1.20 g (99%) (from isoxazole **3b**); colorless solid; mp 76–77 °C.

¹H NMR (400 MHz, CDCl₃): δ = 7.82–7.74 (m, 2 H), 7.48–7.42 (m, 3 H), 5.52 (s, 1 H), 4.03 (d, *J* = 6.6 Hz, 2 H), 2.26–2.10 (m, 1 H), 1.07 (d, *J* = 6.7 Hz, 6 H).

¹³C NMR (100 MHz, CDCl₃): δ = 174.0, 164.1, 129.9, 129.7, 128.8, 126.4, 78.4, 75.6, 28.1, 18.8.

HRMS (ESI): *m/z* [M + Na]⁺ calcd for C₁₃H₁₅NNaO₂⁺: 240.0995; found: 240.0998.

Preparation of 3-(3,4-Dimethoxyphenyl)-5-methoxyisoxazole (**5m**)

A solution of diazomethane (31.5 mmol) in Et₂O, prepared from *N*-nitroso-*N*-methylurea and KOH, was added dropwise at 0 °C to a stirred suspension of 3-(3,4-dimethoxyphenyl)-5-methoxyisoxazolone (**4a**)^{21b} (10.5 mmol) in anhydrous Et₂O (50 mL). The resulting mixture was stirred at ambient temperature for 2 h and then concentrated under reduced pressure. The residue was purified by column chromatography (silica gel; hexane/EtOAc, 3:1), followed by crystallization from Et₂O–hexane.

Yield: 1.88 g (76%); colorless solid; mp 69–71 °C.

¹H NMR (400 MHz, CDCl₃): δ = 7.42–7.34 (m, 1 H), 7.27–7.22 (m, 1 H), 6.96–6.88 (m, 1 H), 5.50 (s, 1 H), 4.05 (s, 3 H), 3.95 (s, 3 H), 3.93 (s, 3 H).

¹³C NMR (100 MHz, CDCl₃): δ = 174.3, 163.9, 150.6, 149.2, 122.3, 119.7, 111.0, 108.9, 75.1, 58.8, 56.0, 55.9.

HRMS (ESI): *m/z* [M + Na]⁺ calcd for C₁₂H₁₃NNaO₄⁺: 258.0737; found: 258.0739.

Bromoisoxazoles **6f** and **6h**; General Procedure

A solution of the isoxazole **5f** or **5h** (2 mmol) and *N*-bromosuccinimide (392 mg, 2.2 mmol) in CHCl₃ (25 mL) was stirred at ambient temperature for 3 h. The reaction mixture was diluted with 10% Na₂S₂O₃ (60 mL), and extracted with CH₂Cl₂ (3 × 20 mL). The combined organic extracts were dried over anhydrous Na₂SO₄, the solvent was removed under reduced pressure, and the product was purified by silica gel flash chromatography (hexane/EtOAc, 5:1), followed by crystallization from Et₂O–hexane.

4-Bromo-3-(2-bromophenyl)-5-methoxyisoxazole (**6f**)

Yield: 466 mg (70%) (from isoxazole **5f**); colorless solid; mp 108–109 °C.

¹H NMR (400 MHz, CDCl₃): δ = 7.75–7.69 (m, 1 H), 7.48–7.34 (m, 3 H), 4.26 (s, 3 H).

¹³C NMR (100 MHz, CDCl₃): δ = 169.0, 164.5, 133.1, 131.5 (2C), 129.7, 127.3, 123.1, 68.9, 58.6.

HRMS (ESI): *m/z* [M + Na]⁺ calcd for C₁₀H₇⁷⁹Br⁸¹BrNNaO₂⁺: 355.8716; found: 355.8718.

4-Bromo-3-(2,4-dimethoxyphenyl)-5-methoxyisoxazole (6h)

Yield: 440 mg (70%) (from isoxazole **5h**); colorless solid; mp 71–73 °C.

¹H NMR (400 MHz, CDCl₃): δ = 7.37–7.31 (m, 1 H), 6.62–6.55 (m, 2 H), 4.21 (s, 3 H), 3.87 (s, 3 H), 3.85 (s, 3 H).

¹³C NMR (100 MHz, CDCl₃): δ = 168.6, 162.9, 162.7, 158.7, 131.7, 110.0, 104.7, 98.9, 69.4, 58.3, 55.6, 55.4.

HRMS (ESI): *m/z* [M + H]⁺ calcd for C₁₂H₁₃⁷⁹BrNO₄⁺: 314.0022; found: 314.0027.

Bromoazirines 1c,d,f,h; General Procedure

A suspension of isoxazole **6c,d,f,h** (2 mmol) and FeSO₄·7H₂O (239 mg, 1.2 mmol, 60 mol%) in MeCN (15 mL) was stirred at ambient temperature for 5 h, then the solvent was removed under reduced pressure. In order to remove iron compounds, the product was purified by silica gel flash chromatography (hexane/EtOAc, 10:1), followed by crystallization from Et₂O–hexane.

Methyl 2-Bromo-3-[4-(tert-butyl)phenyl]-2H-azirine-2-carboxylate (1c)

Yield: 608 mg (98%) (from isoxazole **6c**²²); colorless solid; mp 85–86 °C.

¹H NMR (400 MHz, CDCl₃): δ = 7.94–7.88 (m, 2 H), 7.70–7.64 (m, 2 H), 3.82 (s, 3 H), 1.40 (s, 9 H).

¹³C NMR (100 MHz, CDCl₃): δ = 167.4, 163.8, 159.5, 130.9, 126.8, 116.7, 54.1, 43.9, 35.6, 31.0.

HRMS (ESI): *m/z* [M + Na]⁺ calcd for C₁₄H₁₆⁷⁹BrNNaO₂⁺: 332.0257; found: 332.0259.

Methyl 2-Bromo-3-(2,4-dimethylphenyl)-2H-azirine-2-carboxylate (1d)

Yield: 485 mg (86%) (from isoxazole **6d**²³); colorless solid; mp 60–61 °C.

¹H NMR (400 MHz, CDCl₃): δ = 7.75–7.68 (m, 1 H), 7.28–7.22 (m, 2 H), 3.83 (s, 3 H), 2.67 (s, 3 H), 2.46 (s, 3 H).

¹³C NMR (100 MHz, CDCl₃): δ = 167.6, 162.9, 146.3, 142.6, 132.5, 132.3, 127.6, 115.8, 54.1, 43.5, 21.9, 19.7.

HRMS (ESI): *m/z* [M + Na]⁺ calcd for C₁₂H₁₂⁷⁹BrNNaO₂⁺: 303.9944; found: 303.9948.

Methyl 2-Bromo-3-(2-bromophenyl)-2H-azirine-2-carboxylate (1f)

Yield: 619 mg (93%) (from isoxazole **6f**); colorless solid; mp 83–84 °C.

¹H NMR (400 MHz, CDCl₃): δ = 8.07–8.00 (m, 1 H), 7.86–7.79 (m, 1 H), 7.65–7.55 (m, 2 H), 3.84 (s, 3 H).

¹³C NMR (100 MHz, CDCl₃): δ = 167.0, 164.9, 136.0, 134.4, 133.6, 128.2, 126.3, 120.8, 54.2, 45.0.

HRMS (ESI): *m/z* [M + Na]⁺ calcd for C₁₀H₇⁷⁹Br⁸¹BrNNaO₂⁺: 355.8716; found: 355.8734.

Methyl 2-Bromo-3-(2,4-dimethoxyphenyl)-2H-azirine-2-carboxylate (1h)

Yield: 616 mg (98%) (from isoxazole **6h**); colorless solid; mp 85–86 °C.

¹H NMR (400 MHz, CDCl₃): δ = 7.72–7.66 (m, 1 H), 6.71–6.65 (m, 1 H), 6.59–6.56 (m, 1 H), 3.99 (s, 3 H), 3.93 (s, 3 H), 3.80 (s, 3 H).

¹³C NMR (100 MHz, CDCl₃): δ = 167.9, 167.2, 162.8, 159.6, 134.7, 106.4, 101.4, 98.7, 56.1, 55.9, 53.9, 43.7.

HRMS (ESI): *m/z* [M + Na]⁺ calcd for C₁₂H₁₂⁷⁹BrNNaO₄⁺: 335.9842; found: 335.9845.

Bromoazirines 1i,j,m; General Procedure

A solution of isoxazole **5i,j,m** (2 mmol) and *N*-bromosuccinimide (392 mg, 2.2 mmol) in CHCl₃ (25 mL) was stirred at ambient temperature for 3 h. The reaction mixture was diluted with 10% Na₂S₂O₃ (60 mL), and extracted with CH₂Cl₂ (3 × 20 mL). The combined organic extracts were dried over anhydrous Na₂SO₄. The solvent was removed under reduced pressure, and the obtained bromoisoxazole **6i,j,m** was used in the next step without further purification. A suspension of isoxazole **6i,j,m** and FeSO₄·7H₂O (239 mg, 1.2 mmol, 60 mol%) in MeCN (15 mL) was stirred at ambient temperature for 5 h, then the solvent was removed under reduced pressure. In order to remove iron compounds, the product was purified by silica gel flash chromatography (hexane/EtOAc, 10:1), followed by crystallization from Et₂O–hexane.

Isobutyl 2-Bromo-3-phenyl-2H-azirine-2-carboxylate (1i)

Yield: 539 mg (91%) (from isoxazole **5i**); colorless oil.

¹H NMR (400 MHz, CDCl₃): δ = 8.02–7.93 (m, 2 H), 7.79–7.71 (m, 1 H), 7.69–7.60 (m, 2 H), 4.08–3.94 (m, 2 H), 2.06–1.88 (m, 1 H), 0.95–0.86 (m, 6 H).

¹³C NMR (100 MHz, CDCl₃): δ = 166.7, 164.6, 135.0, 130.8, 129.6, 119.8, 73.2, 44.2, 27.6, 18.8.

HRMS (ESI): *m/z* [M + Na]⁺ calcd for C₁₃H₁₄⁷⁹BrNNaO₂⁺: 318.0100; found: 318.0093.

Benzyl 2-Bromo-3-phenyl-2H-azirine-2-carboxylate (1j)

Yield: 594 mg (90%) (from isoxazole **5j**^{14a}); colorless solid; mp 60–61 °C.

¹H NMR (400 MHz, CDCl₃): δ = 7.98–7.92 (m, 2 H), 7.78–7.72 (m, 1 H), 7.67–7.61 (m, 2 H), 7.39–7.30 (m, 5 H), 5.28 (s, 2 H).

¹³C NMR (100 MHz, CDCl₃): δ = 166.6, 164.4, 135.1, 134.9, 130.9, 129.6, 128.5, 128.4, 127.9, 119.6, 68.7, 43.9.

HRMS (ESI): *m/z* [M + Na]⁺ calcd for C₁₆H₁₂⁷⁹BrNNaO₂⁺: 351.9944; found: 351.9949.

Methyl 2-Bromo-3-(3,4-dimethoxyphenyl)-2H-azirine-2-carboxylate (1m)

Yield: 597 mg (95%) (from isoxazole **5m**); colorless solid; mp 102–103 °C.

¹H NMR (400 MHz, CDCl₃): δ = 7.61–7.49 (m, 1 H), 7.49–7.39 (m, 1 H), 7.13–7.03 (m, 1 H), 4.01 (s, 3 H), 3.98 (s, 3 H), 3.82 (s, 3 H).

¹³C NMR (100 MHz, CDCl₃): δ = 167.4, 163.3, 154.9, 150.0, 126.3, 111.9, 111.7, 111.4, 56.3, 56.2, 54.1, 44.6.

HRMS (ESI): *m/z* [M + Na]⁺ calcd for C₁₂H₁₂⁷⁹BrNNaO₄⁺: 335.9842; found: 335.9835.

2-Fluoro-2H-azirines 2a–l; General Procedure

A solution of 2-bromo-2H-azirines **1a–l** (1 mmol) and TBAF·H₂O (363 mg, 1.3 mmol) in DCM (5 mL) was stirred at ambient temperature for 4 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (hexane–EtOAc mixture) to give fluoroazirines **2a–l**.

Methyl 2-Fluoro-3-phenyl-2H-azirine-2-carboxylate (2a)¹³

Yield: 155 mg (80%) (from azirine **1a**); colorless solid; mp 58–59 °C.

^1H NMR (400 MHz, CDCl_3): δ = 8.02–7.94 (m, 2 H), 7.77–7.71 (m, 1 H), 7.68–7.61 (m, 2 H), 3.88 (s, 3 H).

^{13}C NMR (100 MHz, CDCl_3): δ = 167.0 (d, J = 43.4 Hz), 166.0 (d, J = 11.5 Hz), 135.0, 130.7, 129.6, 120.2, 78.1 (d, J = 264.6 Hz), 53.3.

HRMS (ESI): m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{10}\text{H}_8\text{FNNaO}_2^+$: 216.0431; found: 216.0428.

Methyl 2-Fluoro-3-(*p*-tolyl)-2H-azirine-2-carboxylate (2b)¹³

Yield: 170 mg (82%) (from azirine **1b**); colorless solid; mp 44–45 °C.

^1H NMR (400 MHz, CDCl_3): δ = 7.89–7.83 (m, 2 H), 7.47–7.40 (m, 2 H), 3.86 (s, 3 H), 2.50 (s, 3 H).

^{13}C NMR (100 MHz, CDCl_3): δ = 167.2 (d, J = 43.9 Hz), 165.4 (d, J = 11.5 Hz), 146.4, 130.8, 130.3, 117.3, 78.1 (d, J = 263.0 Hz), 53.3, 22.0.

HRMS (ESI): m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{11}\text{H}_{10}\text{FNNaO}_2^+$: 230.0588; found: 230.0579.

Methyl 3-[4-(*tert*-Butyl)phenyl]-2-fluoro-2H-azirine-2-carboxylate (2c)

Yield: 202 mg (81%) (from azirine **1c**); colorless oil.

^1H NMR (400 MHz, CDCl_3): δ = 7.95–7.87 (m, 2 H), 7.69–7.64 (m, 2 H), 3.87 (s, 3 H), 1.40 (s, 9 H).

^{13}C NMR (100 MHz, CDCl_3): δ = 167.3 (d, J = 43.9 Hz), 165.4 (d, J = 10.9 Hz), 159.4, 130.7, 126.7, 117.4, 78.1 (d, J = 262.9 Hz), 53.9, 35.6, 31.0.

HRMS (ESI): m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{14}\text{H}_{16}\text{FNNaO}_2^+$: 272.1057; found: 272.1057.

Methyl 3-(2,4-Dimethylphenyl)-2-fluoro-2H-azirine-2-carboxylate (2d)

Yield: 190 mg (86%) (from azirine **1d**); colorless solid; mp 64–65 °C.

^1H NMR (400 MHz, CDCl_3): δ = 7.76–7.69 (m, 1 H), 7.27–7.20 (m, 2 H), 3.87 (s, 3 H), 2.65 (s, 3 H), 2.45 (s, 3 H).

^{13}C NMR (100 MHz, CDCl_3): δ = 167.5 (d, J = 44.4 Hz), 164.3 (d, J = 11.0 Hz), 146.1, 142.1, 132.21, 132.15, 127.5, 116.2, 77.2 (d, J = 261.9 Hz), 53.2, 21.9, 19.6.

HRMS (ESI): m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{12}\text{H}_{12}\text{FNNaO}_2^+$: 244.2168; found: 244.2169.

Methyl 2-Fluoro-3-(4-nitrophenyl)-2H-azirine-2-carboxylate (2e)

Yield: 155 mg (65%) (from azirine **1e**); colorless solid; mp 115–116 °C.

^1H NMR (400 MHz, CDCl_3): δ = 8.53–8.48 (m, 2 H), 8.22–8.16 (m, 2 H), 3.91 (s, 3 H).

^{13}C NMR (100 MHz, CDCl_3): δ = 166.3 (d, J = 10.8 Hz), 166.1 (d, J = 43.3 Hz), 151.4, 131.6, 125.8, 124.7, 77.8 (d, J = 268.8 Hz), 53.6.

HRMS (ESI): m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{10}\text{H}_7\text{FN}_2\text{NaO}_4^+$: 261.0282; found: 261.0289.

Methyl 3-(2-Bromophenyl)-2-fluoro-2H-azirine-2-carboxylate (2f)

Yield: 204 mg (75%) (from azirine **1f**); colorless solid; mp 45–46 °C.

^1H NMR (400 MHz, CDCl_3): δ = 8.13–8.06 (m, 1 H), 7.84–7.77 (m, 1 H), 7.63–7.55 (m, 2 H), 3.89 (s, 3 H).

^{13}C NMR (100 MHz, CDCl_3): δ = 166.74 (d, J = 12.2 Hz), 166.73 (d, J = 43.2 Hz), 136.0, 134.1, 132.8, 128.2, 126.5, 121.3, 78.2 (d, J = 266.5 Hz), 53.4.

HRMS (ESI): m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{10}\text{H}_7^{79}\text{BrFNNaO}_2^+$: 293.9536; found: 293.9529.

Methyl 2-Fluoro-3-(4-methoxyphenyl)-2H-azirine-2-carboxylate (2g)

Yield: 181 mg (81%) (from azirine **1g**); colorless solid; mp 53–54 °C.

^1H NMR (400 MHz, CDCl_3): δ = 7.95–7.87 (m, 2 H), 7.15–7.08 (m, 2 H), 3.94 (s, 3 H), 3.86 (s, 3 H).

^{13}C NMR (100 MHz, CDCl_3): δ = 167.4 (d, J = 44.7 Hz), 165.0, 164.3 (d, J = 10.9 Hz), 133.0, 115.2, 112.3, 78.2 (d, J = 262.7 Hz), 55.7, 53.2.

HRMS (ESI): m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{11}\text{H}_{10}\text{FNNaO}_3^+$: 246.0537; found: 246.0539.

Methyl 3-(2,4-Dimethoxyphenyl)-2-fluoro-2H-azirine-2-carboxylate (2h)

Yield: 192 mg (76%) (from azirine **1h**); colorless solid; mp 120–121 °C.

^1H NMR (400 MHz, CDCl_3): δ = 7.57–7.51 (m, 1 H), 7.49–7.43 (m, 1 H), 7.09–7.03 (m, 1 H), 4.00 (s, 3 H), 3.98 (s, 3 H), 3.87 (s, 3 H).

^{13}C NMR (100 MHz, CDCl_3): δ = 167.3 (d, J = 44.5 Hz), 164.4 (d, J = 11.3 Hz), 154.8, 149.9, 126.1, 112.3, 111.8, 111.3, 78.4 (d, J = 263.0 Hz), 56.3, 56.2, 53.3.

HRMS (ESI): m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{12}\text{H}_{12}\text{FNNaO}_4^+$: 276.0643; found: 276.0651.

Isobutyl 2-Fluoro-3-phenyl-2H-azirine-2-carboxylate (2i)

Yield: 195 mg (83%) (from azirine **1i**); colorless oil.

^1H NMR (400 MHz, CDCl_3): δ = 8.01–7.94 (m, 2 H), 7.77–7.70 (m, 1 H), 7.68–7.62 (m, 2 H), 4.11–4.01 (m, 2 H), 2.06–1.93 (m, 1 H), 0.95–0.90 (m, 6 H).

^{13}C NMR (100 MHz, CDCl_3): δ = 166.6 (d, J = 43.2 Hz), 166.2 (d, J = 11.5 Hz), 134.9, 130.7, 129.6, 120.4, 78.1 (d, J = 264.5 Hz), 72.4, 27.6, 18.8.

HRMS (ESI): m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{13}\text{H}_{14}\text{FNNaO}_2^+$: 258.0901; found: 258.0907.

Benzyl 2-Fluoro-3-phenyl-2H-azirine-2-carboxylate (2j)

Yield: 256 mg (95%) (from azirine **1j**); colorless solid; mp 52–53 °C.

^1H NMR (400 MHz, CDCl_3): δ = 7.99–7.93 (m, 2 H), 7.77–7.71 (m, 1 H), 7.67–7.61 (m, 2 H), 7.41–7.35 (m, 5 H), 5.32 (s, 2 H).

^{13}C NMR (100 MHz, CDCl_3): δ = 166.6 (d, J = 43.2 Hz), 166.1 (d, J = 11.2 Hz), 135.0, 134.8, 130.8, 129.6, 128.7, 128.6, 128.3, 120.9, 78.2 (d, J = 265.1 Hz), 68.1.

HRMS (ESI): m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{16}\text{H}_{12}\text{FNNaO}_2^+$: 292.0744; found: 292.0733.

(2-Fluoro-3-phenyl-2H-azirin-2-yl)(pyrrolidin-1-yl)methanone (2k)

Yield: 149 mg (64%) (from azirine **1k**); colorless solid; mp 67–68 °C.

^1H NMR (400 MHz, CDCl_3): δ = 8.05–7.98 (m, 2 H), 7.72–7.66 (m, 1 H), 7.63–7.58 (m, 2 H), 4.11–4.01 (m, 1 H), 3.94–3.84 (m, 1 H), 3.63–3.56 (m, 2 H), 2.12–1.87 (m, 4 H).

^{13}C NMR (100 MHz, CDCl_3): δ = 169.7 (d, J = 12.9 Hz), 163.3 (d, J = 39.3 Hz), 134.5, 130.7, 129.3, 121.3, 82.3 (d, J = 274.9 Hz), 47.1 (d, J = 9.2 Hz), 47.0, 26.3 (d, J = 3.2 Hz), 23.7.

HRMS (ESI): m/z [M + H]⁺ calcd for C₁₃H₁₄FN₂O⁺: 233.1085; found: 233.1086.

(2-Fluoro-3-phenyl-2H-azirine-2-yl)(morpholino)methanone (2l)

Yield: 99 mg (40%) (from azirine **1l**); colorless solid; mp 53–54 °C.

¹H NMR (400 MHz, CDCl₃): δ = 8.11–8.02 (m, 2 H), 7.77–7.69 (m, 1 H), 7.68–7.60 (m, 2 H), 4.14–4.01 (m, 2 H), 3.90–3.65 (m, 6 H).

¹³C NMR (100 MHz, CDCl₃): δ = 171.0 (d, J = 13.0 Hz), 163.1 (d, J = 39.3 Hz), 134.9, 130.8, 129.5, 121.1, 82.2 (d, J = 274.2 Hz), 67.1, 66.4, 46.5, 42.9.

HRMS (ESI): m/z [M + Na]⁺ calcd for C₁₃H₁₃FN₂NaO₂⁺: 271.0853; found: 271.0855.

Gram-Scale Synthesis of Fluoroazirine **2a** from Bromoazirine **1a**

A solution of azirine **1a** (2.2 g, 8.66 mmol) and Bu₄NF·H₂O (3.14 g, 11.26 mmol) in DCM (40 mL) was stirred at ambient temperature for 4 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (hexane/EtOAc mixture) to give methyl 2-fluoro-3-phenyl-2H-azirine-2-carboxylate **2a** (1.34 g, 80%).

2-Iodo-2H-azirines **7a–f**; General Procedure

A solution of 2-bromo-2H-azirines **1a,b,e,j,m,n** (1 mmol) and KI (332 mg, 2 mmol) in acetone (5 mL) was stirred at ambient temperature for the time indicated below. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (hexane/EtOAc mixture) and crystallization from Et₂O–hexane to give iodoazirines **7a–f**.

Methyl 2-Iodo-3-phenyl-2H-azirine-2-carboxylate (**7a**)^{14a}

Yield: 271 mg (90%) (from azirine **1a**, 30 h); colorless solid; mp 87–88 °C (lit.^{14a} 87–88 °C).

Methyl 2-Iodo-3-(*p*-tolyl)-2H-azirine-2-carboxylate (**7b**)

Yield: 290 mg (92%) (from azirine **1b**, 48 h); colorless solid; mp 81–82 °C.

¹H NMR (400 MHz, CDCl₃): δ = 7.89–7.81 (m, 2 H), 7.50–7.43 (m, 2 H), 3.80 (s, 3 H), 2.51 (s, 3 H).

¹³C NMR (100 MHz, CDCl₃): δ = 166.5, 164.8, 146.5, 130.9, 130.5, 117.2, 54.3, 22.1, 14.0.

HRMS (ESI): m/z [M + Na]⁺ calcd for C₁₁H₁₀INNaO₂⁺: 337.9648; found: 337.9643.

Methyl 2-Iodo-3-(4-nitrophenyl)-2H-azirine-2-carboxylate (**7c**)

Yield: 277 mg (80%) (from azirine **1e**, 40 h); colorless solid; mp 131–133 °C.

¹H NMR (400 MHz, CDCl₃): δ = 8.58–8.42 (m, 2 H), 8.26–8.10 (m, 2 H), 3.84 (s, 3 H).

¹³C NMR (100 MHz, CDCl₃): δ = 165.7, 165.3, 151.3, 131.6, 125.8, 124.8, 54.6, 12.2.

HRMS (ESI): m/z [M + Na]⁺ calcd for C₁₀H₇IN₂NaO₄⁺: 368.9343; found: 368.9348.

Methyl 3-(3,4-Dimethoxyphenyl)-2-iodo-2H-azirine-2-carboxylate (**7d**)

Yield: 325 mg (90%) [from azirine **1m**, KI (2.5 g, 15 mmol), 120 h]; colorless solid; mp 93–94 °C.

¹H NMR (400 MHz, CDCl₃): δ = 7.58–7.49 (m, 1 H), 7.46–7.40 (m, 1 H), 7.12–7.03 (m, 1 H), 4.01 (s, 3 H), 3.99 (s, 3 H), 3.81 (s, 3 H).

¹³C NMR (100 MHz, CDCl₃): δ = 166.6, 164.2, 154.9, 150.1, 126.2, 112.1, 111.8, 111.4, 56.3, 56.2, 54.3, 14.9.

HRMS (ESI): m/z [M + Na]⁺ calcd for C₁₂H₁₂INNaO₄⁺: 383.9703; found: 383.9686.

Methyl 3-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)-2-iodo-2H-azirine-2-carboxylate (**7e**)

Yield: 323 mg (90%) [from azirine **1n**, KI (2.5 g, 15 mmol), 120 h]; colorless solid; mp 109–110 °C (dec.).

¹H NMR (400 MHz, CDCl₃): δ = 7.54–7.42 (m, 2 H), 7.15–7.05 (m, 1 H), 4.42–4.33 (m, 4 H), 3.80 (s, 3 H).

¹³C NMR (100 MHz, CDCl₃): δ = 166.5, 164.1, 149.7, 144.4, 125.1, 119.9, 118.8, 112.7, 64.8, 64.0, 54.3, 14.6.

HRMS (ESI): m/z [M + Na]⁺ calcd for C₁₂H₁₀INNaO₄⁺: 381.9547; found: 381.9547.

Benzyl 2-Iodo-3-phenyl-2H-azirine-2-carboxylate (**7f**)

Yield: 373 mg (99%) (from azirine **1j**, 48 h); colorless oil.

¹H NMR (400 MHz, CDCl₃): δ = 8.00–7.90 (m, 2 H), 7.80–7.72 (m, 1 H), 7.70–7.61 (m, 2 H), 7.41–7.29 (m, 5 H), 5.25 (s, 2 H).

¹³C NMR (100 MHz, CDCl₃): δ = 165.8, 165.3, 135.0 (2C), 130.9, 129.7, 128.5, 128.4, 127.9, 120.1, 69.0, 13.8.

HRMS (ESI): m/z [M + Na]⁺ calcd for C₁₆H₁₂INNaO₂⁺: 399.9805; found: 399.9800.

Synthesis of Bromoazirine **1a** from 2-Iodoazirine **7a**

A solution of iodoazirine **7a** (301 mg, 1 mmol) and Bu₄NBr (645 mg, 2.0 mmol) in DCM (5 mL) was stirred at ambient temperature for 15 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (hexane/EtOAc, 4:1) to give bromoazirine **1a** (252 mg, 99%).

Synthesis of Chloroazirine **8a** from Bromoazirine **1a**

A solution of bromoazirine **1a** (254 mg, 1 mmol) and Bu₄NCl (417 mg, 1.5 mmol) in DCM (5 mL) was stirred at ambient temperature for 12 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (hexane/EtOAc, 4:1) to give chloroazirine **8a** (205 mg, 98%).

Synthesis of Chloroazirine **8a** from 2-Iodoazirine **7a**

A solution of iodoazirine **7a** (301 mg, 1 mmol) and Bu₄NCl (249 mg, 1.5 mmol) in DCM (5 mL) was stirred at ambient temperature for 6 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (hexane/EtOAc, 4:1) to give chloroazirine **8a** (205 mg, 98%).

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Supporting Information

Supporting information for this article is available online at <https://doi.org/10.1055/s-0039-1690200>.

References

- (1) Groult, H.; Leroux, F.; Tressaud, A. *Modern Synthesis Processes and Reactivity of Fluorinated Compounds*, 1st ed; Elsevier: Amsterdam, **2016**.
- (2) Dohi, T.; Kita, Y. In *Iodine Chemistry and Applications*; Kaiho, T., Ed.; Wiley: Hoboken, **2014**, 303.
- (3) Berger, R.; Resnati, G.; Metrangolo, P.; Weber, E.; Hulliger, J. *Chem. Soc. Rev.* **2011**, *40*, 3496.
- (4) (a) Zhou, Y.; Wang, J.; Gu, Z.; Wang, S.; Zhu, W.; Aceña, J. L.; Soloshonok, V. A.; Izawa, K.; Liu, H. *Chem. Rev.* **2016**, *116*, 422. (b) Barnes-Seeman, D.; Beck, J.; Springer, C. *Curr. Top. Med. Chem.* **2014**, *14*, 855.
- (5) *Fluorine and Health: Molecular Imaging, Biomedical Materials and Pharmaceuticals*; Tressaud, A.; Haufe, G., Ed.; Elsevier: Amsterdam, **2008**.
- (6) Ametamey, S. M.; Honer, M.; Schubiger, P. A. *Chem. Rev.* **2008**, *108*, 1501.
- (7) (a) Chacko, A. M.; Divgi, C. R. *Med. Chem.* **2011**, *7*, 395. (b) Koehler, L.; Gagnon, K.; McQuarrie, S.; Wuest, F. *Molecules* **2010**, *15*, 2686.
- (8) For recent reviews on 2H-azirine chemistry, see: (a) Khlebnikov, A. F.; Novikov, M. S.; Rostovskii, N. V. *Tetrahedron* **2019**, *75*, 2555. (b) Zhou, H.; Shen, M.-H.; Xu, H.-D. *Synlett* **2016**, 27, 2171. (c) Khlebnikov, A. F.; Novikov, M. S. *Top. Heterocycl. Chem.* **2015**, *41*, 143. (d) Huang, C.-Y.; Doyle, A. G. *Chem. Rev.* **2014**, *114*, 8153. (e) Khlebnikov, A. F.; Novikov, M. S. *Tetrahedron* **2013**, *69*, 3363.
- (9) Smetanin, I. A.; Novikov, M. S.; Rostovskii, N. V.; Khlebnikov, A. F.; Starova, G. L.; Yufit, D. S. *Tetrahedron* **2015**, *71*, 4616.
- (10) Rostovskii, N. V.; Smetanin, I. A.; Agafonova, A. V.; Sakharov, P. A.; Ruvinskaya, J. O.; Khlebnikov, A. F.; Novikov, M. S. *Org. Biomol. Chem.* **2018**, *16*, 3248.
- (11) (a) Alonso-Cruz, C. R.; Kennedy, A. R.; Rodríguez, M. S.; Suárez, E. *J. Org. Chem.* **2008**, *73*, 4116. (b) Alonso-Cruz, C. R.; Kennedy, A. R.; Rodríguez, M. S.; Suárez, E. *Tetrahedron Lett.* **2007**, *48*, 7207.
- (12) Pinho e Melo, T. M. V. D.; Lopes, C. S. J.; Cardoso, A. L.; Rocha Gonsalves, A. M. d'A. *Tetrahedron* **2001**, *57*, 6203.
- (13) Zhang, Y.; Zhao, X.; Zhuang, C.; Wang, S.; Zhang-Negrerie, D.; Du, Y. *Adv. Synth. Catal.* **2018**, *360*, 2107.
- (14) (a) Rostovskii, N. V.; Agafonova, A. V.; Smetanin, I. A.; Novikov, M. S.; Ruvinskaya, J. O.; Starova, G. L.; Khlebnikov, A. F. *Synthesis* **2017**, 49, 4478. (b) Agafonova, A. V.; Smetanin, I. A.; Rostovskii, N. V.; Khlebnikov, A. F.; Novikov, M. S. *Chem. Heterocycl. Compd.* **2017**, *53*, 1068.
- (15) Okamoto, K.; Nanya, A.; Eguchi, A.; Ohe, K. *Angew. Chem. Int. Ed.* **2018**, *57*, 1039.
- (16) (a) Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214. (b) Langlois, B.; Gilbert, L.; Forat, G. *Ind. Chem. Libr.* **1996**, *8*, 244.
- (17) Worrell, B. T.; Hein, J. E.; Fokin, V. V. *Angew. Chem. Int. Ed.* **2012**, *51*, 11791.
- (18) Allen, L. J.; Muhuhi, J. M.; Bland, D. C.; Merzel, R.; Sanford, M. S. *J. Org. Chem.* **2014**, *79*, 5827.
- (19) Agafonova, A. V.; Rostovskii, N. V.; Smetanin, I. A.; Starova, G. L.; Khlebnikov, A. F.; Novikov, M. S. *J. Org. Chem.* **2018**, *83*, 13473.
- (20) Bounioux, C.; Bar-Hen, A.; Yerushalmi-Rozen, R. *Chem. Commun.* **2015**, 51, 6343.
- (21) (a) Nishiwaki, T.; Kitamura, T.; Nakano, A. *Tetrahedron* **1970**, *55*, 453. (b) Clark, A. D.; Janowski, W. K.; Prager, R. H. *Tetrahedron* **1999**, *55*, 3637.
- (22) Golubev, A. A.; Smetanin, I. A.; Agafonova, A. V.; Rostovskii, N. V.; Khlebnikov, A. F.; Starova, G. L.; Novikov, M. S. *Org. Biomol. Chem.* **2019**, *17*, 6821.
- (23) Smetanin, I. A.; Novikov, M. S.; Agafonova, A. V.; Rostovskii, N. V.; Khlebnikov, A. F.; Kudryavtsev, I. V.; Terpilowski, M. A.; Serebriakova, M. K.; Trulioff, A. S.; Goncharov, N. V. *Org. Biomol. Chem.* **2016**, *14*, 4479.