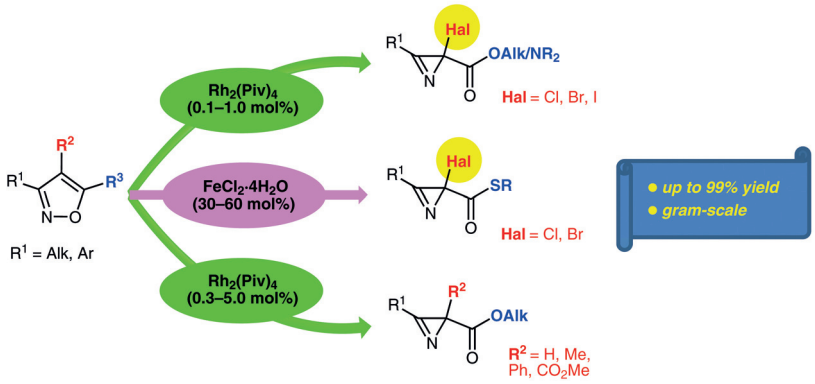
Synthesis N. V. Rostovskii et al. Paper

Metal-Catalyzed Isomerization of 5-Heteroatom-Substituted Isoxazoles as a New Route to 2-Halo-2*H*-azirines

Nikolai V. Rostovskii
Anastasiya V. Agafonova
Ilia A. Smetanin
Mikhail S. Novikov*
Alexander F. Khlebnikov
Julia O. Ruvinskaya
Galina L. Starova

Saint Petersburg State University, Institute of Chemistry, 7/9 Universitetskaya nab., St. Petersburg, 199034, Russian Federation
m.novikov@spbu.ru

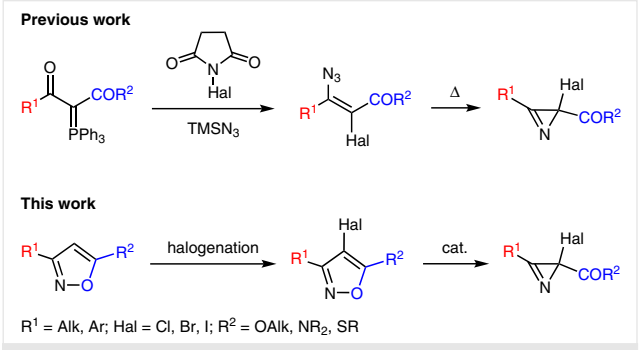


Received: 17.05.2017
Accepted after revision: 03.06.2017
Published online: 03.08.2017
DOI: 10.1055/s-0036-1590822; Art ID: ss-2017-t0340-op

Abstract A convenient gram-scale method for the preparation of 2-halo-2*H*-azirine-2-carboxylic acid esters, thioesters and amides via metal-catalyzed isomerization of 5-heteroatom-substituted 4-haloisoxazoles is developed. The formation of the esters and amides is efficiently catalyzed by $Rh_2(Piv)_4$, while $FeCl_2{\cdot}4H_2O$ is the catalyst of choice for the synthesis of the thioesters. In addition, rhodium catalysis is successfully applied in the synthesis of azirine-2-carboxylates from non-halogenated 5-alkoxyisoxazoles.

Key words azirines, isoxazoles, haloheterocycles, rhodium(II) carboxylates, iron(II) chloride, catalysis, isomerization

2*H*-Azirine-2-carboxylic acid derivatives have attracted increased attention in recent years due to their unique biological and chemical properties.[1] In particular, molecules containing this structural element, *viz.* azirinomycin, dysidazirine and antazirine, are found in nature and exhibit a broad range of biological activity.[2] A number of novel methods to access useful nitrogen-containing heterocycles, such as pyrroles,[3] imidazoles,[3c,4] pyridines,[5] and pyrazines,[6] have been recently developed employing azirine-2-carboxylates and their isosteres as building blocks. Azirines containing a good leaving group, such as Cl, Br or I, at the C2 position are of special interest due to their ability to undergo various transformations both with retention of the azirine system and ring expansion.[7] For example, 2-bromoazirine-2-carboxylates have been recently used as starting materials for the synthesis of functionalized azirines.[8] The presence of a halogen atom at the C2 position of the azirine ring can also substantially expand the range of the heterocycles that can be synthesized via azirine ring expansion. Thus, 2,3-dihydroazetes,[9] oxazolines,[8a,9b] oxazoles,[10] isoxazoles,[11] quinoxalines,[8a] 2*H*-1,4-oxazines,[8a] and 5*H*-1,4-benzodiazepines,[12] were synthesized via a one-, two-, or three-atom ring expansion of 2-haloazirines. Further development of these methodologies requires a wide range of 2-haloazirines, the synthesis of which is often a serious problem. Currently, the Neber approach via dehydration of ketoximes[13] and the 'non-classical Wittig reaction–vinyl azide thermal decomposition' sequence[14] are used for the preparation of 2-heteroatom-substituted 2*H*-azirines including 2-haloazirine-2-carboxylates (Scheme 1).[14a] The vinyl azides are prepared by acylation of α-oxophosphonium ylides with acyl chlorides followed by azidohalogenation using the azidotrimethylsilane/*N*-halosuccinimide system.

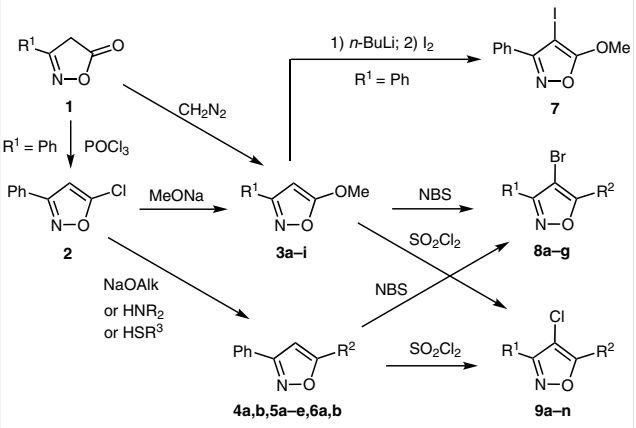


Scheme 1 Synthesis of 2-halo-2*H*-azirine-2-carboxylates

The reaction is applicable for a variety of substituents and usually gives high product yields. However, this method, as we have found out, does not apply in the case of the synthesis of 2-halo-2*H*-azirine-2-carboxylates with electron-poor aryl substituents.[9b] Here, chromatographic purification of the products is required, due to non-quantitative yields in the last step, that leads to further diminishing of the yields in the case of acid-sensitive azirines.

In a search for a concise and reliable method for the preparation of a wide range of 2-haloazirine-2-carboxylic acid derivatives in sizeable quantities, devoid of the above disadvantages, we turned our attention to the isoxazole–azirine rearrangement.[15] There are several reports describing catalytic variants of this reaction.[16] In 1997, Auricchio et al. reported that 5-alkoxy- and 5-aminoisoxazoles isomerize smoothly into the corresponding 2*H*-azirine-2-carboxylates/carboxamides under iron(II) chloride ($FeCl_2$) catalysis.[16c] We assumed that the use of readily available 4-haloisoxazoles in such a reaction might provide a concise approach to 2-halo-2*H*-azirine-2-carboxylic acid derivatives (Scheme 1). Herein, we report a general method for the synthesis of 2-halo-2*H*-azirines with 2-alkoxycarbonyl, 2-carbamoyl or 2-sulfanylcarbonyl substituents via catalytic N–O bond cleavage of 4-haloisoxazoles under Rh(II) or Fe(II) catalysis.

A variety of methods for the synthesis of isoxazoles have been developed to date.[17] In the current study, 4-bromo-, 4-chloro-, and 4-iodoisoxazoles were synthesized starting from the same precursors, isoxazolones **1**, according to the reaction sequence depicted in Scheme 2. 5-Methoxyisoxazoles **3** were readily prepared from the corresponding isoxazolones **1** in two steps via 5-chloro-3-phenylisoxazole (**2**),[18] or in one step using diazomethane.[9c] Other 5-alkoxyisoxazoles **4**,[18] 5-aminoisoxazoles **5**[19] and 5-sulfanylisoxazoles **6**[18,19] were synthesized via replacement of chlorine in 5-chloro-3-phenylisoxazole (**2**). 4-Bromo- and 4-chloro-substituted isoxazoles **8** and **9** were obtained from the corresponding 4-unsubstituted isoxazoles **3**–**6** by treatment with *N*-bromosuccinimide[9c] or sulfuryl chloride,[19] respectively. 4-Iodoisoxazole **7** was prepared via the known reaction of the corresponding 4-lithioisoxazole derivative with iodine.[18]



1, 3: R^1 = Ph (**a**), 4-MeC_6H_4 (**b**), 4-$MeOC_6H_4$ (**c**), 3,4-$[O(CH_2)_2O]C_6H_3$ (**d**), 4-ClC_6H_4 (**e**), 4-$O_2NC_6H_4$ (**f**), 2,5-$(Me)_2C_6H_3$ (**g**), Me (**h**), cyclopropyl (**i**)
4: R^2 = OHex (**a**), OBn (**b**)
5: R^2 = pyrrolidin-1-yl (**a**), morpholin-4-yl (**b**), N(Me)Bn (**c**), NEt_2 (**d**), $NHCH_2Ad$ (**e**)
6: R^2 = SCH_2CF_3 (**a**), SPh (**b**)

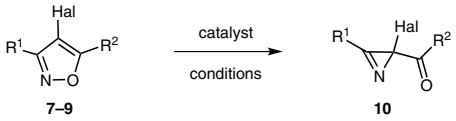
Scheme 2 Synthesis of 4-haloisoxazoles

Our first experiments showed that the isomerization of 4-bromo-5-methoxy-3-phenylisoxazole (**8a**) proceeded smoothly under $FeCl_2{\cdot}4H_2O$ (30 mol%) catalysis in acetonitrile at ambient temperature within 24 hours, affording the corresponding 2-bromo-2*H*-azirine **10a** in good yield (Table 1, entry 1). A decrease in the catalyst loading led to incomplete conversion of the 5-methoxyisoxazole. Despite the high efficiency of the reaction, chromatographic purification for removal of iron-containing compounds cannot be avoided. This fact prompted us to perform an additional screening of catalysts for the isomerization. It is known that $Rh_2(OAc)_4$ isomerizes 2*H*-azirine-2-carbaldehydes into the more thermodynamically stable 3-aryl/3,4-diaryl isoxazoles, probably via formation of a rhodium(II)–nitrene complex.[20] In contrast, according to quantum chemical calculations, azirine-2-carboxylic acid derivatives are more thermodynamically stable than their isoxazole isomers.[15] We speculated, based on these facts, that $Rh_2(OAc)_4$ can induce the isomerization of 4-haloisoxazoles into azirines. When isoxazole **8a** was treated with $Rh_2(OAc)_4$ (0.5 mol%) in toluene under reflux, azirine **10a** was formed quantitatively within 1 hour (entry 2). Dirhodium tetrapivalate [$Rh_2(Piv)_4$] proved to be a much more effective catalyst, enabling the completion of the reaction in 0.5 hours at 0.1 mol% catalyst loading (entry 3). Since most 2-haloazirines are solids, simple washing of the crude residue, obtained by concentration of the reaction mixture in vacuo, with hexane–diethyl ether mixture, was sufficient to remove $Rh_2(Piv)_4$ traces from the product. To our delight, the use of $Rh_2(Piv)_4$ led to a smooth isomerization of 4-iodoisoxazole **7** to afford 2-iodoazirine **10b** in 92% yield (entry 4). Further isomerization reactions were carried out in refluxing toluene using $Rh_2(Piv)_4$ as the catalyst.

By using this procedure, 2-bromoazirines **10c**–**g** with electron-donating and electron-withdrawing substituents on the phenyl ring were obtained in excellent yields (Table 1, entries 5–9). In addition, various 2-chloro-substituted azirines **10h**–**q** were efficiently synthesized by using the above procedure (entries 10–19). It should be noted that azirines **10f**,**g**,**j** are unstable on silica, so their synthesis can only be performed by a chromatography-free procedure (entries 8, 9 and 12). 5-Aminoisoxazoles **9f**–**i** proved to be less reactive than 5-alkoxyisoxazoles and underwent isomerization into the corresponding 2-haloazirines **10m**–**p** within 8–44 hours with higher catalyst loadings (entries 15–18). An exception to this was the isomerization of *N*-(1-adamantylmethyl)isoxazole (**9j**) which, surprisingly, displayed a reactivity comparable with that of 5-alkoxyisoxazoles (entry 19).

To test the ability to scale up the synthesis, a gram-scale reaction of 4-bromoisoxazole **8a** (3.56 g, 14 mmol) in the presence of $Rh_2(Piv)_4$ (8.5 mg, 0.1 mol%) was carried out giving 2-bromoazirine **10a** in 96% yield. This is the same yield as that observed in the small-scale reaction (entry 3).

Table 1 Isomerization of 4-Haloisoxazoles into 2-Halo-2*H*-azirines[a]



7–9 **10**

Entry	Isoxazole	R^1	Halide	R^2	Catalyst (mol%)	Time	Yield of **10** (%)[b]
1	**8a**	Ph	Br	MeO	$FeCl_2·4H_2O$ (30)	24 h	95 (**10a**)
2	**8a**	Ph	Br	MeO	$Rh_2(OAc)_4$ (0.5)	1 h	95 (**10a**)
3	**8a**	Ph	Br	MeO	$Rh_2(Piv)_4$ (0.1)	0.5 h	96[c] (**10a**)
4	**7**	Ph	I	MeO	$Rh_2(Piv)_4$ (0.2)	1 h	92 (**10b**)
5	**8b**	4-MeC_6H_4	Br	MeO	$Rh_2(Piv)_4$ (0.1)	0.5 h	95 (**10c**)
6	**8c**	4-$MeOC_6H_4$	Br	MeO	$Rh_2(Piv)_4$ (0.1)	0.5 h	97 (**10d**)
7	**8d**	3,4-$[O(CH_2)_2O]C_6H_3$	Br	MeO	$Rh_2(Piv)_4$ (0.1)	0.5 h	95 (**10e**)
8	**8e**	4-ClC_6H_4	Br	MeO	$Rh_2(Piv)_4$ (0.1)	0.5 h	94 (**10f**)
9	**8f**	4-$O_2NC_6H_4$	Br	MeO	$Rh_2(Piv)_4$ (0.1)	0.5 h	97 (**10g**)
10	**9a**	Ph	Cl	MeO	$Rh_2(Piv)_4$ (0.1)	0.5 h	96 (**10h**)
11	**9b**	2,5-$(Me)_2C_6H_3$	Cl	MeO	$Rh_2(Piv)_4$ (0.1)	0.75 h	97 (**10i**)
12	**9c**	4-ClC_6H_4	Cl	MeO	$Rh_2(Piv)_4$ (0.1)	0.5 h	95 (**10j**)
13	**9d**	Ph	Cl	HexO	$Rh_2(Piv)_4$ (0.2)	2.5 h	97 (**10k**)
14	**9e**	Ph	Cl	BnO	$Rh_2(Piv)_4$ (0.2)	1 h	85 (**10l**)
15	**9f**	Ph	Cl	pyrrolidin-1-yl	$Rh_2(Piv)_4$ (1.0)	8 h	92 (**10m**)
16	**9g**	Ph	Cl	morpholin-4-yl	$Rh_2(Piv)_4$ (0.5)	28 h	90 (**10n**)
17	**9h**	Ph	Cl	Bn(Me)N	$Rh_2(Piv)_4$ (0.6)	44 h	58 (**10o**)
18	**9i**	Ph	Cl	Et_2N	$Rh_2(Piv)_4$ (1.0)	44 h	60 (**10p**)
19	**9j**	Ph	Cl	1-$AdCH_2NH$	$Rh_2(Piv)_4$ (0.1)	0.5 h	77 (**10q**)
20	**9k**	Ph	Cl	CF_3CH_2S	$Rh_2(Piv)_4$ (1.5)	18 h	20[d] (**10r**)
21	**9k**	Ph	Cl	CF_3CH_2S	$FeCl_2·4H_2O$ (60)	7 d	66 (**10r**)
22	**9l**	Ph	Cl	PhS	$FeCl_2·4H_2O$ (60)	36 h	67 (**10s**)
23	**8g**	Ph	Br	PhS	$FeCl_2·4H_2O$ (60)	36 h	90 (**10t**)
24	**9m**	Me	Cl	MeO	$FeCl_2·4H_2O$ (30)	6 d	85 (**10u**)

[a] Reaction conditions: isoxazole (1 mmol), $Rh_2(Piv)_4$, toluene (3 mL), 110 °C, or $FeCl_2·4H_2O$, MeCN (3 mL), r.t.; Piv = pivalate, Ad = 1-adamantyl.
[b] Yield of isolated product.
[c] Azirine **10a** (3.4 g, 96%) was obtained in a gram-scale reaction.
[d] Isoxazole **9k** (70%) was recovered.

Attempts to convert chlorinated 5-sulfanylisoxazole **9k** into thioester **10r** under Rh(II) catalysis failed (Table 1, entry 20). Only a low conversion of the starting material was observed, due to a strong complexation of the catalyst with the sulfur atom. However, the replacement of $Rh_2(Piv)_4$ by $FeCl_2·4H_2O$ permits the preparation of thioesters **10r–t** in good yields from isoxazoles **9k,l** and **8g** (entries 21–23). It should be noted that the synthesis of thioesters **10r–t** is the first example of catalytic isomerization of 5-sulfanylisoxazoles.[21] Rh(II)-catalyzed isomerization at 110 °C was also found to be unsuitable for the synthesis of 3-methyl-2-chloroazirine **10u**, probably due to its thermal instability. In contrast, a mild isomerization in the presence of $FeCl_2·4H_2O$ provided the desired azirine **10u** in good yield (entry 24). Unfortunately, all attempts to transform 4-chloro-3-cyclopropyl-5-methoxyisoxazole (**9n**) into its corresponding azirine failed, regardless of the catalyst and conditions used.

All compounds **10** were characterized by ^1H, ^{13}C NMR and HRMS data. The structures of azirines **10a** (Figure 1) and **10b** (Figure 2) were additionally confirmed by X-ray crystallography.[22] All the synthesized 2-haloazirines **10** are quite stable compounds and can be stored at 4 °C for months without decomposition.

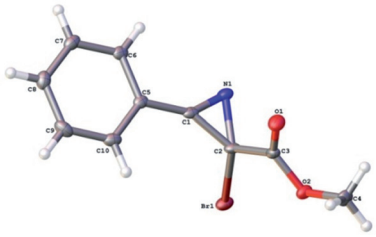


Figure 1 X-ray crystal structure of azirine **10a**

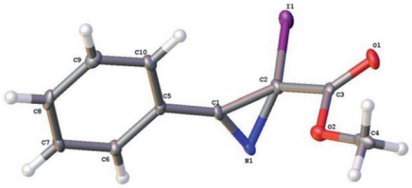
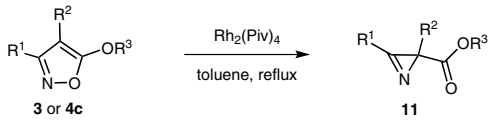


Figure 2 X-ray crystal structure of azirine **10b**

The Rh(II)-catalyzed isomerization can also be applied to a range of non-halogenated 5-alkoxyisoxazoles (Table 2). Alkyl, aryl, and methoxycarbonyl substituents at the C-4 position of the isoxazole are well tolerated in the reaction (entries 3–5). The isomerization of 5-*tert*-butoxyisoxazole **4c** requires a higher catalyst loading and a prolonged reaction time, resulting in a lower product yield (entry 6). Fortunately, $Rh_2(Piv)_4$ can be fully recovered from the reactions of non-halogenated isoxazoles if pure chloroform is used as the eluent for chromatography.

Table 2 Isomerization of Non-Halogenated 5-Alkoxyisoxazoles into Azirine-2-carboxylates[a]



3 or **4c** **11**

Entry	Isoxazole	R^1	R^2	R^3	$Rh_2(Piv)_4$ (mol%)	Time (h)	Yield of **11** (%)[b]
1	**3a**	Ph	H	Me	5.0	3	96 (**11a**)
2	**3j**	4-NCC_6H_4	H	Me	1.0	3	90 (**11b**)
3	**3k**	Ph	Me	Me	2.0	9	92 (**11c**)
4	**3l**	Ph	Ph	Me	1.0	3	90 (**11d**)
5	**3m**	Ph	CO_2Me	Me	0.3	5	92 (**11e**)
6	**4c**	Ph	H	*t*-Bu	3.0	20	81 (**11f**)

[a] Reaction conditions: isoxazole (1 mmol), $Rh_2(Piv)_4$, toluene (3 mL), 110 °C.
[b] Yield of isolated product.

Unlike other eluents, such as hexane–ethyl acetate or hexane–diethyl ether mixtures, chloroform destroys the azirine–$Rh_2(Piv)_4$ complex and, therefore, allows successful separation of the catalyst.

In summary, we have developed a simple, atom-economic synthesis of 2*H*-azirine-2-carboxylic acid derivatives via metal-catalyzed N–O bond cleavage of readily available 5-heteroatom-substituted isoxazoles including 4-halogenated isoxazoles. The latter, in turn, can be easily obtained in two or three steps from the corresponding isoxazolones. The isomerization of 4-haloisoxazoles into 2-haloazirines was found to be efficiently catalyzed by Rh(II) carboxylates at very low catalyst loading. 2-Halo-2*H*-azirines can be prepared on gram scale by this method, and in some cases, in a chromatography-free manner. 3-Methyl- and 5-sulfanyl-substituted 4-haloisoxazoles can be transformed into the corresponding 2-haloazirines only under $FeCl_2$ catalysis. The ability of $Rh_2(Piv)_4$ to catalyze the transformation of non-halogenated 5-alkoxyisoxazoles into azirine-2-carboxylates is also demonstrated for the first time. These syntheses can be performed with practically complete regeneration of the rhodium catalyst.

All solvents were distilled and dried prior to use. Toluene was distilled and stored over sodium metal. Chloroform was washed with concentrated H_2SO_4 and water, then distilled from P_2O_5 and stored refrigerated in the dark over anhydrous K_2CO_3. Acetonitrile was distilled from P_2O_5 and redistilled from K_2CO_3. The catalyst $Rh_2(Piv)_4$ was prepared by the reported procedure.[23] Thin-layer chromatography (TLC) was conducted on aluminum sheets precoated with SiO_2 ALUGRAM SIL G/UV254. Column chromatography was performed on Macherey-Nagel silica gel 60 M (0.04–0.063 mm). Melting points were determined on an SMP30 melting point apparatus. ^1H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on a Bruker AVANCE 400 spectrometer in $CDCl_3$. Chemical shifts (δ) are reported in ppm downfield from tetramethylsilane. Electrospray ionization (ESI), positive mode, mass spectra were measured on a Bruker MaXis mass spectrometer using acetonitrile for dilution of samples. Elemental analysis was performed using a Euro EA3028-HT analyzer. Single-crystal X-ray data were collected using an Agilent Technologies 'Xcalibur' diffractometer.

5-Alkoxyisoxazoles 3a,4a–c; General Procedure A

To a stirred suspension of NaH (60% in mineral oil, 440 mg, 11 mmol, prewashed with hexane) in anhydrous THF (20 mL) was added the appropriate alcohol (15 mmol) at r.t. and the reaction mixture was stirred for 0.5 h. Next, 5-chloro-3-phenylisoxazole (**2**)[21] (1.0 g, 5.6 mmol) was introduced as a solid and the mixture was refluxed for 1 h. After cooling to r.t., the mixture was quenched with H_2O (20 mL). For **4a** and **4b**, the resulting precipitate was collected, washed with H_2O and recrystallized from hexane–Et_2O mixture. For **3a**, the reaction mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to give isoxazole **3a**. 5-*tert*-Butoxy-3-phenylisoxazole (**4c**)[3k,18] was synthesized analogously using commercially available potassium *tert*-butoxide.

5-Alkoxyisoxazoles 3a–m; General Procedure B

To a stirred suspension/solution of isoxazolone[24] (5.6 mmol) in anhydrous Et_2O (50 mL) was added dropwise at 0 °C a solution of diazomethane (11.2 mmol) in Et_2O, prepared from *N*-nitroso-*N*-methylurea

and KOH. The resulting mixture was stirred at r.t. for 2 h and then concentrated in vacuo. The residue was purified by column chromatography on silica gel (PE–EtOAc, 3:1).

Alkoxyisoxazoles **3a–e**,**j**[9c] and **3f**,**h**[3k] are known compounds and have full characterization data.

5-Methoxy-3-phenylisoxazole (3a)[9c]

Yield according to general procedure A: 877 mg (89%); yield according to general procedure B: 745 mg (76%); colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82–7.72 (m, 2 H), 7.51–7.41 (m, 3 H), 5.55 (s, 1 H), 4.06 (s, 3 H).

3-(2,5-Dimethylphenyl)-5-methoxyisoxazole (3g)

Yield: 706 mg (62%); pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32 (s, 1 H), 7.22–7.13 (m, 2 H), 5.41 (s, 1 H), 4.06 (s, 3 H), 2.45 (s, 3 H), 2.37 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.8, 165.2, 135.4, 133.5, 130.9, 130.2, 129.8, 129.1, 78.1, 58.7, 20.8, 20.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{14}NO_2$: 204.1019; found: 204.1025.

3-Cyclopropyl-5-methoxyisoxazole (3i)

Yield: 226 mg (29%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.68 (s, 1 H), 3.42 (s, 3 H), 1.56 (tt, *J* = 8.3, 5.0 Hz, 1 H), 1.17–1.10 (m, 2 H), 0.85–0.78 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.9, 171.1, 84.2, 37.8, 8.6, 7.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_7H_{10}NO_2$: 140.0706; found: 140.0710.

5-Methoxy-4-methyl-3-phenylisoxazole (3k)[25]

Yield: 636 mg (60%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72–7.62 (m, 2 H), 7.53–7.42 (m, 3 H), 4.15 (s, 3 H), 1.98 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.6, 164.7, 130.3, 129.4, 128.7, 127.7, 86.5, 57.8, 6.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{12}NO_2$: 190.0863; found: 190.0868.

5-Methoxy-3,4-diphenylisoxazole (3l)

Yield: 886 mg (63%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53–7.22 (m, 10 H), 4.21 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.9, 163.6, 129.62, 129.57, 129.1, 129.0, 128.5, 128.44, 128.37, 126.9, 93.5, 58.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{14}NO_2$: 252.1019; found: 252.1026.

Methyl 5-Methoxy-3-phenylisoxazole-4-carboxylate (3m)

Yield: 450 mg (85%); colorless solid; mp 105–106 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71–7.60 (m, 2 H), 7.54–7.41 (m, 3 H), 4.31 (s, 3 H), 3.76 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.5, 165.2, 161.5, 130.0, 129.2, 128.5, 128.0, 87.2, 58.5, 51.3.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{11}NO_4Na$: 256.0580; found: 256.0587.

5-Hexyloxy-3-phenylisoxazole (4a)

Yield: 1.26 g (92%); colorless solid; mp 54–55 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82–7.73 (m, 2 H), 7.51–7.41 (m, 3 H), 5.52 (s, 1 H), 4.25 (t, *J* = 6.5 Hz, 2 H), 1.92–1.80 (m, 2 H), 1.55–1.44 (m, 2 H), 1.43–1.31 (m, 4 H), 1.00–0.88 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.9, 164.1, 129.9, 129.7, 128.7, 126.4, 75.6, 72.5, 31.3, 28.8, 25.3, 22.5, 13.9.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{19}NO_2Na$: 268.1308; found: 268.1309.

5-Benzyloxy-3-phenylisoxazole (4b)[26]

Yield: 1.28 g (91%); colorless solid; mp 136–137 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82–7.73 (m, 2 H), 7.53–7.37 (m, 8 H), 5.58 (s, 1 H), 5.32 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.4, 164.2, 134.3, 130.0, 129.5, 129.0, 128.78, 128.76, 128.0, 126.4, 76.6, 73.8.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{13}NO_2Na$: 274.0838; found: 274.0841.

5-Aminoisoxazoles 5a–e; General Procedure

A mixture of 5-chloro-3-phenylisoxazole (**2**)[21] (5 mmol), amine (10 mmol) and K_2CO_3 (15 mmol) in DMF (25 mL) was refluxed under stirring for 1.5 h. The reaction mixture was cooled and diluted with cold H_2O (40 mL). For **5a** and **5b**, the resulting precipitate was collected, washed with H_2O and recrystallized from hexane–Et_2O. For **5c–e**, the reaction mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane–EtOAc, 5:1).

5-Aminoisoxazoles **5a**[27] and **5b**[19,28] are known compounds and have full characterization data.

***N*-Benzyl-*N*-methyl-3-phenylisoxazol-5-amine (5c)**

Yield: 1.02 g (77%); colorless solid; mp 65–66 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83–7.74 (m, 2 H), 7.49–7.29 (m, 8 H), 5.29 (s, 1 H), 4.57 (s, 2 H), 3.01 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.1, 163.8, 136.5, 130.1, 129.5, 128.7, 128.6, 127.7, 127.6, 126.6, 75.2, 55.0, 36.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{17}N_2O$: 265.1335; found: 265.1338.

***N*,*N*-Diethyl-3-phenylisoxazol-5-amine (5d)**

Yield: 896 mg (83%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.81–7.75 (m, 2 H), 7.47–7.39 (m, 3 H), 5.19 (s, 1 H), 3.41 (q, *J* = 7.1 Hz, 4 H), 1.26 (t, *J* = 7.1 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.2, 163.6, 130.3, 129.4, 128.5, 126.5, 74.0, 43.8, 13.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{17}N_2O$: 217.1335; found: 217.1335.

***N*-(1-Adamantylmethyl)-3-phenylisoxazol-5-amine (5e)**

Yield: 893 mg (58%); colorless solid; mp 121–123 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82–7.72 (m, 2 H), 7.48–7.38 (m, 3 H), 5.27 (s, 1 H), 4.64 (br t, *J* = 6.2 Hz, 1 H), 2.92 (d, *J* = 6.6 Hz, 2 H), 2.04 (br s, 3 H), 1.81–1.63 (m, 6 H), 1.58 (br d, *J* = 2.4 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.1, 163.5, 130.1, 129.5, 128.6, 126.6, 74.7, 57.1, 40.2, 36.9, 34.2, 28.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{25}N_2O$: 309.1961; found: 309.1958.

5-Sulfanylisoxazoles 6a,b; General Procedure

A mixture of 5-chloro-3-phenylisoxazole (**2**)[21] (5 mmol), thiol (10 mmol) and K_2CO_3 (15 mmol) in DMF (25 mL) was stirred for 36 h at r.t. The reaction mixture was diluted with H_2O (40 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on silica gel using hexane–EtOAc as the eluent to give the desired compound.

3-Phenyl-5-[(2,2,2-trifluoroethyl)sulfanyl]isoxazole (6a)

Yield: 1.28 g (99%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85–7.75 (m, 2 H), 7.54–7.44 (m, 3 H), 6.69 (s, 1 H), 3.66 (q, *J* = 9.3 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.5, 162.3, 130.4, 129.0, 128.3, 126.8, 124.5 (q, *J* = 277 Hz), 105.0, 35.3 (q, *J* = 34.4 Hz).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_9F_3NOS$: 260.0351; found: 260.0355.

3-Phenyl-5-(phenylsulfanyl)isoxazole (6b)

Yield: 1.18 g (93%); colorless solid; mp 55–56 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83–7.74 (m, 2 H), 7.61–7.53 (m, 2 H), 7.51–7.44 (m, 3 H), 7.43–7.37 (m, 3 H), 6.51 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.0, 163.0, 132.1, 130.6, 130.2, 129.6, 128.9, 128.8, 128.6, 126.7, 104.5.

HRMS (ESI): *m*/*z* [M + Ag]$^+$ calcd for $C_{15}H_{11}NOS^{107}Ag$: 359.9607; found: 359.9591.

4-Iodo-5-methoxy-3-phenylisoxazole (7)[18]

To a stirred solution of isoxazole **3a** (525 mg, 3 mmol) in anhydrous THF (8 mL) at –78 °C under argon was added dropwise *n*-BuLi (1.33 mL, 2.5 M in hexane, 3.3 mmol). The reaction mixture was stirred at the same temperature for 30 min, and then a solution of iodine (838 mg, 3.3 mmol) in anhydrous THF (10 mL) was introduced in one portion. The mixture was allowed to warm to r.t. and stirred for an additional 20 min at r.t. The solvent was removed in vacuo, and the residue was treated with H_2O (50 mL) and extracted with EtOAc (3 × 15 mL). The organic layer was washed with sat. $Na_2S_2O_3$ (2 × 20 mL), dried (Na_2SO_4), and concentrated in vacuo. The product was purified by flash chromatography on silica gel using hexane–EtOAc (10:1) as the eluent.

Yield: 541 mg (81%); colorless solid; mp 89–90 °C (Et_2O–hexane) (Lit.[18] 89–91 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88–7.75 (m, 2 H), 7.58–7.44 (m, 3 H), 4.23 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.2, 164.6, 130.2, 129.0, 128.5, 128.2, 58.5, 30.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_9INO_2$: 301.9672; found: 301.9665.

4-Bromoisoxazoles 8a–g; General Procedure

A solution of isoxazole **3a–f**,**6b** (2 mmol) and *N*-bromosuccinimide (2.2 mmol) in AcOH (20 mL) was heated at 75 °C under stirring for 40 min. The reaction mixture was cooled and diluted with cold H_2O (60 mL). The resulting precipitate was collected, washed with H_2O and recrystallized from hexane–Et_2O to give the desired compound.

4-Bromoisoxazoles **8a–e** are known compounds.[9c] 4-Bromoisoxazole **8g**, without purification (not characterized spectroscopically), was converted into 2-bromoazirine **10t**.

4-Bromo-5-methoxy-3-(4-nitrophenyl)isoxazole (8f)

Yield: 532 mg (89%); colorless solid; mp 63–66 °C (Et_2O–hexane).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.40–8.29 (m, 2 H), 8.13–8.00 (m, 2 H), 4.27 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.9, 160.6, 148.9, 134.4, 128.9, 123.8, 66.7, 58.7.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{10}H_7{}^{79}BrN_2O_4Na$: 320.9481; found: 320.9483.

4-Chloroisoxazoles 9a–n; General Procedure

To a stirred solution of isoxazole **3a**,**e**,**g–i**,**4a**,**b**,**5a–e**,**6a**,**b** (4 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added dropwise SO_2Cl_2 (4 mmol). The mixture was allowed to warm to r.t. and then refluxed for 20 min. The reaction mixture was cooled and washed with $NaHCO_3$ solution (20 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by column chromatography on silica gel using hexane–EtOAc as the eluent to give the desired compound.

4-Chloro-5-methoxy-3-phenylisoxazole (9a)

Yield: 821 mg (98%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95–7.80 (m, 2 H), 7.56–7.45 (m, 3 H), 4.24 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.9, 161.5, 130.3, 128.7, 127.9, 127.7, 83.0, 58.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_9{}^{35}ClNO_2$: 210.0316; found: 210.0311.

4-Chloro-3-(2,5-dimethylphenyl)-5-methoxyisoxazole (9b)

Yield: 931 mg (98%); colorless solid; mp 52–53 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26–7.16 (m, 3 H), 4.25 (s, 3 H), 2.38 (s, 3 H), 2.34 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.3, 163.9, 135.3, 134.2, 130.8, 130.4, 130.3, 126.8, 84.2, 58.4, 20.8, 19.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{13}{}^{35}ClNO_2$: 238.0629; found: 238.0633.

4-Chloro-3-(4-chlorophenyl)-5-methoxyisoxazole (9c)

Yield: 781 mg (80%); colorless solid; mp 69–71 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88–7.77 (m, 2 H), 7.53–7.42 (m, 2 H), 4.24 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.0, 160.5, 136.6, 129.0, 128.9, 126.4, 83.0, 58.5.

HRMS (ESI): *m*/*z* [M + K]$^+$ calcd for $C_{10}H_7{}^{35}Cl_2KNO_2$: 281.9485; found: 281.9489.

4-Chloro-5-hexyloxy-3-phenylisoxazole (9d)

Yield: 1.08 g (97%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92–7.82 (m, 2 H), 7.56–7.45 (m, 3 H), 4.51 (t, *J* = 6.6 Hz, 2 H), 1.95–1.81 (m, 2 H), 1.58–1.45 (m, 2 H), 1.43–1.32 (m, 4 H), 1.00–0.85 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.9, 161.3, 130.2, 128.7, 128.1, 127.7, 83.5, 72.5, 31.3, 29.2, 25.1, 22.5, 13.9.

HRMS (ESI): *m*/*z* [M + K]$^+$ calcd for $C_{15}H_{18}{}^{35}ClKNO_2$: 318.0658; found: 318.0673.

5-Benzyloxy-4-chloro-3-phenylisoxazole (9e)

Yield: 434 mg (38%); colorless solid; mp 58–59 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94–7.81 (m, 2 H), 7.56–7.40 (m, 8 H), 5.52 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.5, 161.3, 134.3, 130.3, 129.2, 128.8, 128.7, 128.5, 128.0, 127.7, 84.3, 73.7.

HRMS (ESI): *m*/*z* [M + Ag]$^+$ calcd for $C_{16}H_{12}{}^{107}Ag^{35}ClNO_2$: 391.9602; found: 391.9588.

4-Chloro-3-phenyl-5-(pyrrolidin-1-yl)isoxazole (9f)

Yield: 776 mg (78%); colorless solid; mp 68–70 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86–7.77 (m, 2 H), 7.52–7.43 (m, 3 H), 3.81–3.69 (m, 4 H), 2.06–1.94 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.7, 161.1, 129.7, 128.6, 128.4, 128.1, 79.4, 47.7, 25.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{14}{}^{35}ClN_2O$: 249.0789; found: 249.0790.

4-(4-Chloro-3-phenylisoxazol-5-yl)morpholine (9g)

Yield: 995 mg (94%); colorless solid; mp 96–97 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.84–7.76 (m, 2 H), 7.54–7.45 (m, 3 H), 3.91–3.80 (m, 4 H), 3.71–3.60 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.7, 161.6, 130.0, 128.5, 128.1 (2 C), 83.9, 66.3, 46.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{14}{}^{35}ClN_2O_2$: 265.0738; found: 265.0748.

***N*-Benzyl-4-chloro-*N*-methyl-3-phenylisoxazol-5-amine (9h)**

Yield: 812 mg (68%); colorless solid; mp 45–47 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89–7.78 (m, 2 H), 7.54–7.46 (m, 3 H), 7.45–7.31 (m, 5 H), 4.75 (s, 2 H), 3.14 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.0, 161.7, 136.6, 129.8, 128.7, 128.5, 128.4, 128.1, 127.8 (2 C), 81.3, 54.5, 36.0.

HRMS (ESI): *m*/*z* [M + Ag]$^+$ calcd for $C_{17}H_{15}{}^{107}Ag^{35}ClN_2O^+$: 404.9918; found: 404.9903.

4-Chloro-*N*,*N*-diethyl-3-phenylisoxazol-5-amine (9i)

Yield: 782 mg (78%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85–7.77 (m, 2 H), 7.52–7.45 (m, 3 H), 3.58 (q, *J* = 7.1 Hz, 4 H), 1.30 (t, *J* = 7.1 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.2, 161.5, 129.7, 128.6, 128.4, 128.2, 79.9, 43.5, 14.2.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{15}{}^{35}ClN_2NaO$: 273.0765; found: 273.0770.

***N*-(1-Adamantylmethyl)-4-chloro-3-phenylisoxazol-5-amine (9j)**

Yield: 879 mg (64%); colorless solid; mp 139–141 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92–7.82 (m, 2 H), 7.52–7.44 (m, 3 H), 4.62 (br t, *J* = 6.4 Hz, 1 H), 3.15 (d, *J* = 6.8 Hz, 2 H), 2.04 (br s, 3 H), 1.81–1.65 (m, 6 H), 1.58 (br d, *J* = 2.4 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.6, 159.5, 129.9, 128.5, 128.3, 127.7, 79.4, 54.8, 39.9, 36.9, 34.0, 28.2.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{23}{}^{35}ClN_2NaO$: 365.1391; found: 365.1387.

4-Chloro-3-phenyl-5-[(2,2,2-trifluoroethyl)sulfanyl]isoxazole (9k)

Yield: 1.07 g (91%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93–7.85 (m, 2 H), 7.58–7.48 (m, 3 H), 3.68 (q, *J* = 9.2 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.4, 159.1, 130.7, 128.9, 127.9, 126.8, 124.2 (q, *J* = 277 Hz), 111.4, 34.6 (q, *J* = 34.7 Hz).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_7{}^{35}ClF_3NNaOS$: 315.9781; found: 315.9787.

4-Chloro-3-phenyl-5-(phenylsulfanyl)isoxazole (9l)

Yield: 1.14 g (99%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96–7.85 (m, 2 H), 7.59–7.47 (m, 5 H), 7.44–7.33 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.5, 160.2, 132.0, 130.5, 129.6, 129.5, 128.83, 128.78, 127.9, 127.2, 112.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{11}{}^{35}ClNOS$: 288.0244; found: 288.0256.

4-Chloro-5-methoxy-3-methylisoxazole (9m)

Yield: 383 mg (65%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.15 (s, 3 H), 2.22 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.9, 161.0, 83.9, 58.3, 10.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_5H_7{}^{35}ClNO_2$: 148.0167; found: 148.0160.

4-Chloro-3-cyclopropyl-5-methoxyisoxazole (9n)

Yield: 438 mg (63%); colorless solid; mp 51–52 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.42 (s, 3 H), 1.62 (tt, *J* = 8.5, 5.4 Hz, 1 H), 1.30–1.10 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.6, 164.0, 94.6, 39.2, 7.2, 5.9.

HRMS (ESI): *m*/*z* [M + K]$^+$ calcd for $C_7H_8{}^{35}ClKNO_2$: 211.9875; found: 211.9869.

Rh(II)-Catalyzed Synthesis of 2-Halo-2*H*-azirines 10a–r; General Procedure

A solution of 4-haloisoxazole **7**,**8a–f**,**9a–k** (1 mmol) and $Rh_2(Piv)_4$ (0.1–1.5 mol%) in toluene (3 mL) was refluxed for 0.5–44 h (see Table 1). The solvent was removed in vacuo and the residue was purified by flash chromatography on silica gel (hexane–EtOAc) to give the desired product. If the azirine is a solid, it can be washed with hexane–Et_2O instead of chromatography.

Fe(II)-Catalyzed Synthesis of 2-Halo-2*H*-azirines 10a,r–u; General Procedure

A solution of 4-haloisoxazole **8a**,**g**,**9k–m** (1 mmol) and $FeCl_2·4H_2O$ (30–60 mol%) in MeCN (3 mL) was stirred at ambient temperature for a period of 24 h to 7 d (see Table 1). The insoluble inorganic material was filtered off and the filtrate concentrated in vacuo. The residue was purified by flash chromatography on silica gel (hexane–EtOAc) to give the desired product.

Methyl 2-Bromo-3-phenyl-2*H*-azirine-2-carboxylate (10a)[14a]

Yield: 241 mg (95%) [catalyst: $Rh_2(OAc)_4$ (0.5 mol%)]; 3.4 g (96%) in a gram-scale reaction [catalyst: $Rh_2(Piv)_4$ (0.1 mol%)]; 242 mg (95%) [catalyst: $FeCl_2·4H_2O$ (30 mol%)]; colorless solid; mp 74–76 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00–7.96 (m, 2 H), 7.79–7.73 (m, 1 H), 7.68–7.63 (m, 2 H), 3.84 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.1, 164.3, 135.1, 130.8, 129.6, 119.6, 54.1, 43.7.

Methyl 2-Iodo-3-phenyl-2*H*-azirine-2-carboxylate (10b)[14a]

Yield: 277 mg (92%); colorless solid; mp 87–88 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00–7.92 (m, 2 H), 7.79–7.73 (m, 1 H), 7.69–7.62 (m, 2 H), 3.81 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.3, 165.3, 135.0, 130.8, 129.7, 120.0, 54.3, 13.6.

HRMS (ESI): *m*/*z* [M + K]$^+$ calcd for $C_{10}H_8IKNO_2$: 339.9231; found: 339.9229.

Methyl 2-Bromo-3-(4-methylphenyl)-2*H*-azirine-2-carboxylate (10c)

Yield: 255 mg (95%); colorless solid; mp 61–63 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95–7.78 (m, 2 H), 7.54–7.39 (m, 2 H), 3.82 (s, 3 H), 2.51 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.4, 163.9, 146.6, 131.0, 130.4, 116.8, 54.1, 43.9, 22.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{10}{}^{79}BrNNaO_2$: 289.9787; found: 289.9794.

Methyl 2-Bromo-3-(4-methoxyphenyl)-2*H*-azirine-2-carboxylate (10d)[9b]

Yield: 275 mg (97%); colorless solid; mp 67–69 °C (Lit.[9b] 59–63 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94–7.88 (m, 2 H), 7.15–7.09 (m, 2 H), 3.94 (s, 3 H), 3.82 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.5, 165.1, 162.9, 133.2, 115.3, 111.6, 55.7, 54.0, 44.3.

Methyl 2-Bromo-3-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-2*H*-azirine-2-carboxylate (10e)

Yield: 296 mg (95%); colorless solid; mp 122–124 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56–7.40 (m, 2 H), 7.14–7.04 (m, 1 H), 4.46–4.28 (m, 4 H), 3.82 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.4, 163.2, 149.8, 144.4, 125.2, 120.0, 118.8, 112.3, 64.8, 64.0, 54.1, 44.4.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{10}{}^{79}BrNNaO_4$: 333.9685; found: 333.9691.

Methyl 2-Bromo-3-(4-chlorophenyl)-2*H*-azirine-2-carboxylate (10f)

Yield: 271 mg (94%); colorless solid; mp 69–70 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96–7.88 (m, 2 H), 7.68–7.60 (m, 2 H), 3.84 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.0, 163.9, 141.9, 132.0, 130.2, 118.2, 54.2, 43.5.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{10}H_7{}^{79}Br{}^{35}ClNNaO_2$: 309.9241; found: 309.9251.

Methyl 2-Bromo-3-(4-nitrophenyl)-2*H*-azirine-2-carboxylate (10g)

Yield: 290 mg (97%); colorless solid; mp 116–119 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.54–8.47 (m, 2 H), 8.23–8.15 (m, 2 H), 3.86 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.5, 164.5, 151.4, 131.7, 125.4, 124.8, 54.4, 43.0.

Anal. Calcd for $C_{10}H_7BrN_2O_4$: C, 40.16; H, 2.36; N, 9.37. Found: C, 40.77; H, 2.60; N, 9.10.

Methyl 2-Chloro-3-phenyl-2*H*-azirine-2-carboxylate (10h)

Yield: 201 mg (96%); colorless solid; mp 62–63 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01–7.90 (m, 2 H), 7.79–7.70 (m, 1 H), 7.68–7.58 (m, 2 H), 3.82 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.8, 163.5, 135.1, 130.8, 129.6, 119.6, 53.9, 53.8.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{10}H_8{}^{35}ClNO_2Na$: 232.0136; found: 232.0147.

Methyl 2-Chloro-3-(2,5-dimethylphenyl)-2*H*-azirine-2-carboxylate (10i)

Yield: 231 mg (97%); colorless solid; mp 68–70 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.61 (br s, 1 H), 7.45–7.39 (m, 1 H), 7.36–7.30 (m, 1 H), 3.84 (s, 3 H), 2.65 (s, 3 H), 2.43 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.2, 162.5, 139.4, 136.6, 135.7, 132.6, 131.3, 118.3, 53.9, 53.1, 20.6, 19.3.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{12}{}^{35}ClNNaO_2$: 260.0449; found: 260.0453.

Methyl 2-Chloro-3-(4-chlorophenyl)-2*H*-azirine-2-carboxylate (10j)

Yield: 232 mg (95%); colorless solid; mp 76–78 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00–7.82 (m, 2 H), 7.72–7.56 (m, 2 H), 3.84 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.6, 163.1, 141.8, 132.0, 130.2, 118.2, 54.0, 53.8.

HRMS (ESI): *m*/*z* [M + K]$^+$ calcd for $C_{10}H_7{}^{35}Cl_2KNO_2$: 281.9485; found: 281.9488.

Hexyl 2-Chloro-3-phenyl-2*H*-azirine-2-carboxylate (10k)

Yield: 271 mg (97%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01–7.93 (m, 2 H), 7.79–7.71 (m, 1 H), 7.69–7.60 (m, 2 H), 4.29–4.16 (m, 2 H), 1.72–1.58 (m, 2 H), 1.38–1.19 (m, 6 H), 0.94–0.78 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.4, 163.8, 135.0, 130.8, 129.6, 119.9, 67.4, 54.1, 31.2, 28.3, 25.3, 22.4, 13.8.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{18}{}^{35}ClNNaO_2$: 302.0918; found: 302.0933.

Benzyl 2-Chloro-3-phenyl-2*H*-azirine-2-carboxylate (10l)

Yield: 243 mg (85%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98–7.91 (m, 2 H), 7.78–7.71 (m, 1 H), 7.69–7.59 (m, 2 H), 7.40–7.30 (m, 5 H), 5.37–5.19 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.3, 163.6, 135.0, 134.9, 130.9, 129.6, 128.6, 128.4, 128.0, 119.7, 68.6, 54.0.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{12}{}^{35}ClNNaO_2$: 308.0449; found: 308.0451.

(2-Chloro-3-phenyl-2*H*-azirin-2-yl)(pyrrolidin-1-yl)methanone (10m)

Yield: 229 mg (92%); colorless solid; mp 72–73 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15–8.06 (m, 2 H), 7.74–7.67 (m, 1 H), 7.66–7.58 (m, 2 H), 4.19–3.99 (m, 2 H), 3.60–3.41 (m, 2 H), 2.15–1.87 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.9, 163.3, 134.8, 131.0, 129.4, 120.9, 57.3, 46.9, 46.2, 26.2, 23.9.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{13}{}^{35}ClN_2NaO$: 271.0609; found: 271.0616.

(2-Chloro-3-phenyl-2*H*-azirin-2-yl)(morpholin-4-yl)methanone (10n)

Yield: 238 mg (90%); colorless solid; mp 78–79 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.23–8.04 (m, 2 H), 7.80–7.69 (m, 1 H), 7.68–7.57 (m, 2 H), 4.31–4.09 (m, 2 H), 3.98–3.54 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.0, 163.6, 135.0, 131.1, 129.5, 120.7, 66.8, 66.5, 56.3, 46.7, 42.3.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{13}{}^{35}ClN_2NaO_2$: 287.0558; found: 287.0567.

***N*-Benzyl-2-chloro-*N*-methyl-3-phenyl-2*H*-azirine-2-carboxamide (10o)**

Yield: 173 mg (58%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ (rotameric mixture) = 8.24–8.10 (m, 2 H), 7.75–7.67 (m, 1 H), 7.66–7.57 (m, 2 H), 7.44–7.24 (m, 5 H), 5.34 and 5.13 (AB-q, *J* = 15.5 Hz, 0.8 H), 4.68 and 4.56 (AB-q, *J* = 14.7 Hz, 1.3 H), 3.50 (s, 1.9 H), 2.85 (s, 1.2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (rotameric mixture) = 171.3, 171.1, 165.2, 165.0, 136.0, 135.6, 134.8, 131.0, 129.3, 128.60, 128.58, 127.8, 127.7, 127.5, 120.65, 120.62, 57.0, 56.6, 53.6, 50.8, 35.0, 32.3.

HRMS (ESI): *m*/*z* [M + K]$^+$ calcd for $C_{17}H_{15}{}^{35}ClKN_2O$: 337.0504; found: 337.0509.

2-Chloro-*N*,*N*-diethyl-3-phenyl-2*H*-azirine-2-carboxamide (10p)

Yield: 150 mg (60%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.19–8.10 (m, 2 H), 7.74–7.67 (m, 1 H), 7.65–7.58 (m, 2 H), 4.02 (q, *J* = 7.1 Hz, 2 H), 3.50–3.30 (m, 2 H), 1.39 (t, *J* = 7.1 Hz, 3 H), 1.18 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.7, 164.4, 134.8, 131.1, 129.4, 120.9, 57.3, 42.3, 39.6, 14.0, 12.2.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{15}{}^{35}ClN_2NaO$: 273.0765; found: 273.0767.

***N*-(1-Adamantylmethyl)-2-chloro-3-phenyl-2*H*-azirine-2-carboxamide (10q)**

Yield: 264 mg (77%); colorless solid; mp 111–113 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05–7.91 (m, 2 H), 7.78–7.68 (m, 1 H), 7.67–7.57 (m, 2 H), 6.90 (br s, 1 H), 3.09 (qd, *J* = 13.5, 6.3 Hz, 2 H), 2.03 (br s, 3 H), 1.81–1.62 (m, 6 H), 1.56 (br d, *J* = 2.1 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.2, 165.0, 134.8, 130.9, 129.5, 120.2, 58.1, 52.2, 40.1, 36.8, 33.8, 28.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{23}{}^{35}ClN_2NaO$: 365.1391; found: 365.1395.

***S*-(2,2,2-Trifluoroethyl) 2-Chloro-3-phenyl-2*H*-azirine-2-carbothioate (10r)**

Yield: 59 mg (20%) [catalyst: $Rh_2(Piv)_4$ (1.5 mol%)]; 194 mg (66%) [catalyst: $FeCl_2{\cdot}4H_2O$ (60 mol%)]; colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99–7.93 (m, 2 H), 7.81–7.75 (m, 1 H), 7.70–7.63 (m, 2 H), 3.67 (qd, *J* = 9.7, 1.2 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.4, 163.2, 135.7, 131.2, 129.8, 124.4 (q, *J* = 276 Hz), 118.7, 60.1, 32.2 (q, *J* = 34.3 Hz).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_7{}^{35}ClF_3NNaOS$: 315.9781; found: 315.9792.

***S*-Phenyl 2-Chloro-3-phenyl-2*H*-azirine-2-carbothioate (10s)**

Yield: 192 mg (67%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06–7.99 (m, 2 H), 7.82–7.75 (m, 1 H), 7.72–7.65 (m, 2 H), 7.47–7.41 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.5, 163.6, 135.4, 134.6, 131.1, 129.84, 129.77, 129.3, 126.9, 119.2, 60.6.

HRMS (ESI): *m*/*z* [M + K]$^+$ calcd for $C_{15}H_{10}{}^{35}ClKNOS$: 325.9803; found: 325.9800.

***S*-Phenyl 2-Bromo-3-phenyl-2*H*-azirine-2-carbothioate (10t)**

Obtained from isoxazole **6b** (1 mmol) in two stages without purification of 4-bromoisoxazole **8g**. Yield: 299 mg (90% calculated based on **6b**); colorless solid; mp 50–52 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11–8.00 (m, 2 H), 7.84–7.77 (m, 1 H), 7.75–7.66 (m, 2 H), 7.51–7.38 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.5, 164.5, 135.5, 134.6, 131.2, 129.8 (2 C), 129.3, 127.0, 119.2, 51.2.

HRMS (ESI): *m*/*z* [M + K]$^+$ calcd for $C_{15}H_{10}{}^{79}BrKNOS$: 369.9298; found: 369.9298.

Methyl 2-Chloro-3-methyl-2*H*-azirine-2-carboxylate (10u)

Yield: 125 mg (85%); unstable colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.82 (s, 3 H), 2.62 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.0, 165.6, 53.8, 53.3, 10.8.

Rh(II)-Catalyzed Synthesis of Non-Halogenated 2*H*-Azirine-2-carboxylates 11a–f; General Procedure

A solution of 5-alkoxyisoxazole **3a,j–m**,**4c** (1 mmol) and $Rh_2(Piv)_4$ (0.3–5 mol%) in toluene (3 mL) was refluxed for 3–20 h (see Table 2). The solvent was removed in vacuo and the residue was purified by flash chromatography on silica gel ($CHCl_3$) to give the desired compound and recovered $Rh_2(Piv)_4$.

Methyl 3-Phenyl-2*H*-azirine-2-carboxylate (11a)[29]

Yield: 168 mg (96%); pale yellow solid; mp 44–46 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95–7.87 (m, 2 H), 7.71–7.56 (m, 3 H), 3.77 (s, 3 H), 2.89 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.1, 158.5, 133.9, 130.5, 129.3, 122.2, 52.3, 29.5.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{10}H_9O_2NNa$: 198.0525; found: 198.0528.

Methyl 3-(4-Cyanophenyl)-2*H*-azirine-2-carboxylate (11b)

Yield: 180 mg (90%); colorless solid; mp 86–87 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03 (d, *J* = 8.4 Hz, 2 H), 7.90 (d, *J* = 8.4 Hz, 2 H), 3.78 (s, 3 H), 2.97 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.2, 158.6, 133.0, 130.7, 126.2, 117.4, 117.3, 52.5, 30.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_8N_2O_2Na$: 223.0478; found: 223.0482.

Methyl 2-Methyl-3-phenyl-2*H*-azirine-2-carboxylate (11c)[29]

Yield: 174 mg (92%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91–7.80 (m, 2 H), 7.69–7.54 (m, 3 H), 3.70 (s, 3 H), 1.65 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.5, 163.5, 133.6, 130.1, 129.3, 122.5, 52.4, 35.4, 17.7.

Methyl 2,3-Diphenyl-2*H*-azirine-2-carboxylate (11d)[29]

Yield: 226 mg (90%); colorless solid; mp 75–77 °C (Et_2O–hexane) (Lit.[29] 70–71 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01–7.91 (m, 2 H), 7.70–7.64 (m, 1 H), 7.63–7.57 (m, 2 H), 7.56–7.50 (m, 2 H), 7.39–7.29 (m, 3 H), 3.78 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.6, 160.7, 136.2, 133.9, 130.4, 129.4, 128.22, 128.15, 127.8, 122.0, 52.7, 41.1.

Dimethyl 3-Phenyl-2*H*-azirine-2,2-dicarboxylate (11e)

Yield: 214 mg (92%); colorless solid; mp 87–90 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97–7.90 (m, 2 H), 7.74–7.67 (m, 1 H), 7.65–7.58 (m, 2 H), 3.79 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.5, 155.2, 134.6, 131.0, 129.5, 120.2, 52.9, 38.6.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{11}NNaO_4$: 256.0580; found: 256.0574.

***tert*-Butyl 3-Phenyl-2*H*-azirine-2-carboxylate (11f)**[30]

Yield: 176 mg (81%); colorless solid; mp 56–58 °C (Lit.[30] 71–72 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94–7.86 (m, 2 H), 7.69–7.55 (m, 3 H), 2.78 (s, 1 H), 1.49 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.8, 158.9, 133.6, 130.3, 129.3, 122.7, 81.6, 30.5, 28.0.

Funding Information

We gratefully acknowledge the financial support of the Russian Science Foundation (Grant No. 17-13-01078). This research used resources of the 'Magnetic Resonance Research Centre', the 'Chemical Analysis and Materials Research Centre', the 'Centre for X-ray Diffraction Studies' and the 'Chemistry Educational Centre' of the Research Park of St. Petersburg State University.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1590822.

References

(1) For recent reviews on 2*H*-azirine chemistry, see: (a) Khlebnikov, A. F.; Novikov, M. S. *Tetrahedron* **2013**, *69*, 3363. (b) Huang, C.-Y.; Doyle, A. G. *Chem. Rev.* **2014**, *114*, 8153. (c) Khlebnikov, A. F.; Novikov, M. S. *Top. Heterocycl. Chem.* **2016**, *41*, 143.

(2) (a) Miller, T. W.; Tristram, E. W.; Wolf, F. J. *J. Antibiot.* **1971**, *24*, 48. (b) Stapley, E. O.; Hendlin, D.; Jackson, M.; Miller, A. J. *J. Antibiot.* **1971**, *24*, 42. (c) Molinski, T. F.; Ireland, C. M. *J. Org. Chem.* **1988**, *53*, 2103. (d) Salomon, C. E.; Williams, D. H.; Faulkner, D. J. *J. Nat. Prod.* **1995**, *58*, 1463. (e) Skepper, C. K.; Molinski, T. F. *J. Org. Chem.* **2008**, *73*, 2592.

(3) (a) Qi, X.; Xu, X.; Park, C.-M. *Chem. Commun.* **2012**, *48*, 3996. (b) Jiang, Y.; Chan, W. C.; Park, C.-M. *J. Am. Chem. Soc.* **2012**, *134*, 4104. (c) Auricchio, S.; Truscello, A. M.; Lauria, M.; Meille, S. V. *Tetrahedron* **2012**, *68*, 7441. (d) Khlebnikov, A. F.; Tomashenko, O. A.; Funt, L. D.; Novikov, M. S. *Org. Biomol. Chem.* **2014**, *12*, 6598. (e) Galenko, A. V.; Khlebnikov, A. F.; Novikov, M. S.; Avdontceva, M. S. *Tetrahedron* **2015**, *71*, 1940. (f) Wang, Y.; Lei, X.; Tang, Y. *Chem. Commun.* **2015**, *51*, 4507. (g) Zhao, Y.-Z.; Yang, H.-B.; Tang, X.-Y.; Shi, M. *Chem. Eur. J.* **2015**, *21*, 3562. (h) Pawar, S. K.; Sahani, R. L.; Liu, R.-S. *Chem. Eur. J.* **2015**, *21*, 10843. (i) Galenko, E. E.; Galenko, A. V.; Khlebnikov, A. F.; Novikov, M. S.; Shakirova, J. R. *J. Org. Chem.* **2016**, *81*, 8495. (j) Funt, L. D.; Tomashenko, O. A.; Khlebnikov, A. F.; Novikov, M. S.; Ivanov, A. Y. *J. Org. Chem.* **2016**, *81*, 11210. (k) Rostovskii, N. V.; Ruvinskaya, J. O.; Novikov, M. S.; Khlebnikov, A. F.; Smetanin, I. A.; Agafonova, A. V. *J. Org. Chem.* **2017**, *82*, 256.

(4) Cardoso, A. L.; Lemos, A.; Pinho e Melo, T. M. V. D. *Eur. J. Org. Chem.* **2014**, 5159.

(5) (a) Shimada, N.; Ashburn, B. O.; Basak, A. K.; Bow, W. F.; Vicic, D. A.; Tius, M. A. *Chem. Commun.* **2010**, *46*, 3774. (b) Loy, N. S. Y.; Singh, A.; Xu, X.; Park, C.-M. *Angew. Chem. Int. Ed.* **2013**, *52*, 2212. (c) Prechter, A.; Henrion, G.; Faudot dit Bel, P.; Gagosz, F. *Angew. Chem. Int. Ed.* **2014**, *53*, 4959. (d) Jiang, Y.; Park, C.-M.; Loh, T.-P. *Org. Lett.* **2014**, *16*, 3432. (e) Jiang, Y.; Park, C-M. *Chem. Sci.* **2014**, *5*, 2347.

(6) Ryu, T.; Baek, Y.; Lee, P. H. *J. Org. Chem.* **2015**, *80*, 2376.

(7) For a review on 2-halo-2*H*-azirine chemistry, see: Pinho e Melo, T. M. V. D.; d'A Rocha Gonsalves, A. M. *Curr. Org. Synth.* **2004**, *1*, 275.

(8) (a) Pinho e Melo, T. M. V. D.; Lopes, C. S. J.; d'A Rocha Gonsalves, A. M.; Beja, A. M.; Paixão, J. A.; Silva, M. R.; da Veiga, L. A. *J. Org. Chem.* **2002**, *67*, 66. (b) Pinho e Melo, T. M. V. D.; Cardoso, A. L.; d'A Rocha Gonsalves, A. M. *Tetrahedron* **2003**, *59*, 2345.
(9) (a) Novikov, M. S.; Smetanin, I. A.; Khlebnikov, A. F.; Rostovskii, N. V.; Yufit, D. S. *Tetrahedron Lett.* **2012**, *53*, 5777. (b) Smetanin, I. A.; Novikov, M. S.; Rostovskii, N. V.; Khlebnikov, A. F.; Starova, G. L.; Yufit, D. S. *Tetrahedron* **2015**, *71*, 4616. (c) 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.
(10) (a) Shah, S. R.; Navathe, S. S.; Dikundwar, A. G.; Guru Row, T. N.; Vasella, A. T. *Eur. J. Org. Chem.* **2013**, 264. (b) Lopes, S.; Nunes, C. M.; Fausto, R.; Pinho e Melo, T. M. V. D. *J. Mol. Struct.* **2009**, *919*, 47.
(11) Pinho e Melo, T. M. V. D.; Lopes, C. S. J.; d'A Rocha Gonsalves, A. M.; Storr, R. C. *Synthesis* **2002**, 605.
(12) Randles, K. R.; Storr, R. C. *J. Chem. Soc., Chem. Commun.* **1984**, *26*, 1485.
(13) Cardoso, A. L.; Gimeno, L.; Lemos, A.; Palacios, F.; Pinho e Melo, T. M. V. D. *J. Org. Chem.* **2013**, *78*, 6983.
(14) (a) Pinho e Melo, T. M. V. D.; Lopes, C. S. J.; Cardoso, A. L.; d'A Rocha Gonsalves, A. M. *Tetrahedron* **2001**, *57*, 6203. (b) Cardoso, A. L.; Sousa, C.; Henriques, M. S. C.; Paixão, J. A.; Pinho e Melo, T. M. V. D. *Molecules* **2015**, *20*, 22351.
(15) Galenko, E. E.; Khlebnikov, A. F.; Novikov, M. S. *Chem. Heterocycl. Compd.* **2016**, *52*, 637.
(16) (a) Komendantov, M. I.; Bekmukhametov, R. R. *Chem. Heterocycl. Compd.* **1975**, 1127. (b) Auricchio, S.; Vajna de Pava, O. *J. Chem. Res., Synop.* **1983**, 132. (c) Auricchio, S.; Bini, A.; Pastormerlo, E.; Truscello, A. M. *Tetrahedron* **1997**, *53*, 10911.
(17) (a) Pinho e Melo, T. M. V. D. *Curr. Org. Chem.* **2005**, *9*, 925. (b) Galenko, A. V.; Khlebnikov, A. F.; Novikov, M. S.; Pakalnis, V. V.; Rostovskii, N. V. *Russ. Chem. Rev.* **2015**, *84*, 335. (c) Hu, F.; Szostak, M. *Adv. Synth. Catal.* **2015**, *357*, 2583.
(18) Micetich, R. G.; Chin, C. G. *Can. J. Chem.* **1970**, *48*, 1371.
(19) Carr, J. B.; Durham, H. G.; Hass, D. K. *J. Med. Chem.* **1977**, *20*, 934.
(20) Brahma, S.; Ray, J. K. *J. Heterocycl. Chem.* **2008**, *45*, 311.
(21) For an example of thermal isomerization, see: Nishiwaki, T.; Kitamura, T.; Nakano, A. *Tetrahedron* **1970**, *26*, 453.
(22) CCDC 1515810 (**10a**) and CCDC 1528056 (**10b**) contain the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.
(23) Cotton, F. A.; Felthouse, T. R. *Inorg. Chem.* **1980**, *19*, 323.
(24) Clark, A. D.; Janowski, W. K.; Prager, R. H. *Tetrahedron* **1999**, *55*, 3637.
(25) Boulton, A. J.; Katritzky, A. R. *Tetrahedron* **1961**, *12*, 41.
(26) Stevens, R. V.; Albizati, K. F. *Tetrahedron Lett.* **1984**, *25*, 4587.
(27) Galenko, E. E.; Galenko, A. V.; Khlebnikov, A. F.; Novikov, M. S. *RSC Adv.* **2015**, *5*, 18172.
(28) Lasri, J.; Mukhopadhyay, S.; Charmier, M. A. J. *J. Heterocycl. Chem.* **2008**, *45*, 1385.
(29) Davis, F. A.; Liu, H.; Liang, C.-H.; Reddy, G. V.; Zhang, Y.; Fang, T.; Titus, D. D. *J. Org. Chem.* **1999**, *64*, 8929.
(30) Sakai, T.; Liu, Y.; Ohta, H.; Korenaga, T.; Ema, T. *J. Org. Chem.* **2005**, *70*, 1369.