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An isomerization—1,3-dipolar cycloaddition tandem reaction towards the synthesis of 3-aryl-4-methyl-5-*O*-substituted isoxazolines from *O*-allyl compounds

Stanisław Krompiec [a,*], Piotr Bujak [a], Joanna Malarz [a], Michał Krompiec [a], Łukasz Skórka [a], Tadeusz Pluta [a], Witold Danikiewicz [b], Magdalena Kania [b], Joachim Kusz [c]

[a] Institute of Chemistry, Faculty of Mathematics, Physics and Chemistry, University of Silesia, ul. Szkolna 9, 40-007 Katowice, Poland
[b] Institute of Organic Chemistry, Polish Academy of Sciences, ul. Kasprzaka 44/52, 01-224 Warszawa 42, PO Box 58, Poland
[c] Institute of Physics, Faculty of Mathematics, Physics and Chemistry, University of Silesia, ul. Uniwersytecka 4, 40-007 Katowice, Poland

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ABSTRACT

A new strategy for the synthesis of 3-aryl-4-methyl-5-*O*-substituted isoxazolines via tandem catalytic isomerization of *O*-allyl systems to *O*-(1-propenyl) systems—1,3-dipolar cycloaddition (1,3-DC) to nitrile oxides is presented. The influence of the heteroatom in Ph-X-CH=CHCH$_3$ (X=O, S, or Se) on the regio- and stereoselectivity of ArCNO 1,3-cycloaddition to these dipolarophiles is analyzed as well. The dipolarophiles were obtained via [RuClH(CO)(PPh$_3$)$_3$]–, [RuH$_2$(CO)(PPh$_3$)]– or base (KOH/18-crown-6)-catalyzed double bond migration in corresponding allyl ethers, *O*-allyl acetals, Ph*S*– and Ph*Se*–allyl systems. Cycloadditions of nitrile oxides to *O*-(1-propenyl) systems were fully regioselective whereas in the reactions of ArCNO with the Ph*S*–(1-propenyl) and Ph*Se*–(1-propenyl) systems both possible regioisomers were formed. It was established that within the majority of dipolarophiles of ROCH=CHCH$_3$ type 1,3-DC is concerted, while for some dipolarophiles of RXCH=CHCH$_3$ (X=O and R=Ph$_3$C, 2,3-dihydroxypropyl, tetrahydropyran-2-yl; X=S or Se and R=Ph) type 1,3-DC turns into a two-step reaction with simultaneous rotation about C–C bond. The results of the experiments have been analyzed theoretically using DFT calculations. The results of these calculations agreed well with the experimental data.

1. Introduction

Functionalized isoxazolines are important heterocycles in both organic and medicinal chemistry and have been reviewed excellently.[1–6] From the synthetic point of view, the isoxazoline ring is a reactive heterocyclic system, which the synthesis of β-hydroxy ketones,[7–9] β-hydroxy nitriles,[10] β-amino acids,[11,12] and γ-amino alcohols.[13–15] Moreover, the 5-hydroxy-2-isoxazoline ring is presented in the literature as a versatile synthon for the syntheses of isoxazoles, β-hydroxy oximes, and *N*-aryl-β-lactams.[16] Isoxazolines have also been reported as biologically active compounds with antifungal,[17] antibacterial,[18] antidiabetic,[19,20] and anti-stress[21] properties. A number of 3-bromo-4,5-dihydroisoxazoles were obtained and examined for their capability to irreversibly inhibit human transglutaminase 2, an enzyme that plays an important role in the pathogenesis of diverse disorders, including celiac sprue and certain types of tumour.[22] In addition, 3,4,5-trisubstituted isoxazolines were examined for their in vitro and in vivo antithrombotic efficacy.[23,24] Moreover, the product obtained by the functionalization of benzimidazole with spiro–isoxazoline substituent was investigated as a transient receptor potential melastatin 8 (TRPM8) receptor antagonist.[1] TRPM8 is expressed in a range of organs, predominately in the prostate and liver and, to a lesser degree, in brain, lung, bladder, gastrointestinal tract, blood vessels, and immune cells.[1] Most often and most conveniently, isoxazolines (including 5-*O*-substituted ones) are obtained by the 1,3-dipolar cycloaddition of nitrile oxides to functionalized alkenes.[6,25–30]

In this paper, we show that 1,3-dipolar cycloaddition of nitrile oxides to 1-propenyl systems obtained via isomerization of corresponding allyl systems (allyl ethers and *O*-allyl acetals), provides a versatile route towards the synthesis of 3-aryl-4-methyl-5-*O*-substituted 4,5-dihydroisoxazoles. It is noteworthy that a potentially alternative synthetic method for obtaining such isoxazolines via functionalization (alkylation or acylation) of 5-OH substituted isoxazolines has not been reported so far. In our previous work we described the preparation of a number of 5-*N*-substituted isoxazolines according to the analogous method, that is, the

* Corresponding author. Tel.: +48 32 3591646; fax: +48 32 2599978; e-mail address: stanislaw.krompiec@us.edu.pl (S. Krompiec).

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cycloaddition of *N*-(1-propenyl) compounds, obtained from the corresponding *N*-allyl systems to ArCNO.[31] Furthermore, in our short communications we reported on the syntheses of some 5-*O*–, 5-*S*–, and 5-*Si*–substituted isoxazolines using allyl compounds, nitrile oxides and tandem isomerization (allyl compounds to 1-propenyl derivatives)—1,3-DC (to 1-propenyl compounds) reactions.[32,33] Herein, we also present studies on the regioselectivity and stereoselectivity in 1,3-dipolar cycloaddition of nitrile oxide to RXCH=CHCH$_3$ (R=alkyl, aryl; X=O, S or Se) type of dipolarophiles, with the aid of DFT calculations for the regioselectivity in model systems (model dipolarophiles of MeXCH=CHCH$_3$ type, where X=O, S, or Se).

2. Results and discussion

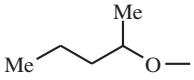
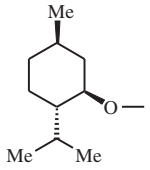
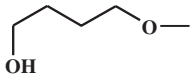
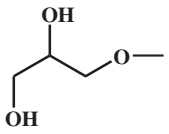
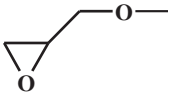
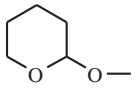
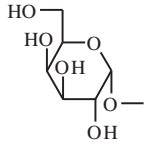
The general idea of the synthesis of trisubstituted isoxazolines, including 3-aryl-4-methyl-5-*O*, 5-*S* and 5-*Se*-substituted ones, from appropriate allyl compounds and nitrile oxides is presented in Scheme 1. The greatest advantages of such a method are: (a) simple and versatile synthesis of dipolarophiles from either commercially or synthetically accessible allyl sources, (b) fast incorporation of a variety of substituents (*O*-alkyl, *O*-aryl, *S*-alkyl, *N*-alkyl$_2$, etc.) to the 5-position, unavailable in other synthetic procedures, (c) robust and convenient protocol. Of particular importance is that the vast majority of reactions incorporating dipolarophiles of ROCH=CHCH$_3$ type, were completely regioselective resulting in the exclusive formation of B-regioisomer—Scheme 1.

Q=Ph, Me$_2$N, alkylO, arylO, alkylS, arylS, PhSe and others; cat.=[RuHCl(CO(PPh$_3$)$_3$)], [RuH$_2$(CO(PPh$_3$)$_3$)], KOH/18-crown-6 and others; Ar=2,6-dichlorophenyl, 2,4,6-trimethylphenyl, *o*-methoxyphenyl, 2-pyridyl and others; base=Et$_3$N, Na$_2$CO$_3$ and others.

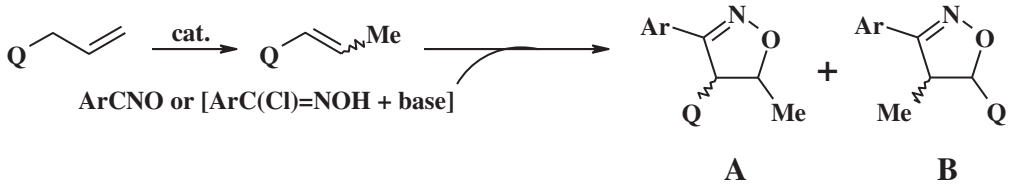
Firstly, we synthesized 5-*O*-substituted isoxazolines (presented in Table 2) via the 1,3-DC of very stable 2,6-dichlorobenzonitrile oxide with various dipolarophiles of ROCH=CHCH$_3$ type. Then, we turned to the synthesis of 5-*O*-substituted isoxazolines (presented in Table 3) in variation of 1,3-DC where the nitrile oxide—ArCNO—was moderately stable (Ar=Ph, *o*-MeOC$_6$H$_4$, *p*-O$_2$NC$_6$H$_4$, 2-pyridyl) and the propenyl system consisted of PhOCH=CHCH$_3$. The adopted synthetic procedure (presented in Tables 2 and 3) allowed the synthesis of various 3-aryl-4-methyl-5-*O*-substituted isoxazolines. A great amount of 5-*O*-substituted isoxazolines has been reported so far in the literature, however, 3-aryl-4-methyl-5-*O*-substituted isoxazolines have been unknown until now. Moderately stable nitrile oxides were generated in situ from corresponding oximoyl chlorides and Et$_3$N, as described in our previous papers.[31–33] On the other hand, more stable 2,6-dichlorobenzonitrile oxide was used after purification procedure.

Allyl compounds, widely utilized in the syntheses of dipolarophiles were either commercially accessible or had been

Table 1
The isomerization of *O*-allyl systems ROCH$_2$CH=CH$_2$ type to *O*-(1-propenyl) systems ROCH=CHCH$_3$ type[a]

1a-l	RO	Catalyst (% mol)	*t*[°C] (τ[*h*])	**2a-l** *E*/*Z*
1a	***n*-BuO–**	RuClH(CO)(PPh$_3$)$_3$ (0.5)[b]	100 (3)	0.70
1b	***t*-BuO–**	RuClH(CO)(PPh$_3$)$_3$ (0.5)[b]	100 (3)	0.70
1c		RuClH(CO)(PPh$_3$)$_3$ (2.0)[c]	60 (4)	0.40
		RuClH(CO)(PPh$_3$)$_3$ (0.2)[b]	120 (2)	0.44
1d		RuClH(CO)(PPh$_3$)$_3$ (2.0)[b]	100 (4)	0.44
1e	**Ph$_3$CO–**	RuClH(CO)(PPh$_3$)$_3$ (2.0)[c]	80 (3)	0.25
1f	**PhO–**	RuClH(CO)(PPh$_3$)$_3$ (0.1)[b]	120 (3)	0.44
		RuH$_2$(CO)(PPh$_3$)$_3$ (0.1)[b]	120 (3)	0.45
1g		RuH$_2$(CO)(PPh$_3$)$_3$ (0.1)[b]	120 (3)	0.72
		RuClH(CO)(PPh$_3$)$_3$ (0.1)[b]	80 (3)	0.66
1h		RuH$_2$(CO)(PPh$_3$)$_3$ (0.1)[b]	120 (3)	0.70
		RuClH(CO)(PPh$_3$)$_3$ (0.1)[b]	80 (2)	0.72
1i		RuClH(CO)(PPh$_3$)$_3$ (2.0)[d]	60 (3)	0.77
1j		RuClH(CO)(PPh$_3$)$_3$ (1.0)[b]	80 (3)	0.66
1k		RuClH(CO)(PPh$_3$)$_3$ (2.0)[b]	100 (3)	0.36
1l		RuClH(CO)(PPh$_3$)$_3$ (2.0)[e]	60 (4)	0.20

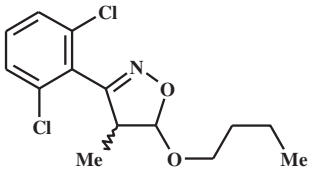
[a] Conversion and selectivity was >99 in all cases.
[b] Without solvent.
[c] In C$_6$H$_6$ (1.0 mL/1 mmol substrate).
[d] In 1,4-dioxane (1.0 mL/1 mmol substrate).
[e] In acetone (2.0 mL/1 mmol substrate).



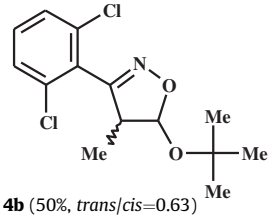
Q = Ph, Me$_2$N, alkylO, arylO, alkylS, arylS, PhSe and others; cat. = [RuHCl(CO(PPh$_3$)$_3$], [RuH$_2$(CO(PPh$_3$)$_3$], KOH/18-crown-6 and others; Ar = 2,6-dichlorophenyl, 2,4,6-trimethylphenyl, *o*-methoxyphenyl, 2-pyridyl and others; base = Et$_3$N, Na$_2$CO$_3$ and others

Scheme 1. Synthesis of dihydroisoxazoles from allyl compounds—a general idea.[31–33]

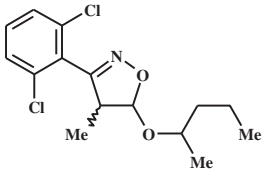
Table 2
Synthesis of derivatives of 5-*O*-substituted 4,5-dihydroisoxazoles via 1,3-dipolar cycloaddition of 2,6-$Cl_2C_6H_3CNO$ to *O*-(1-propenyl) systems[a,b]



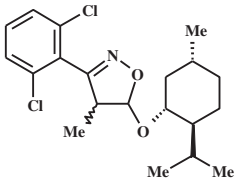
4a (91%, *trans*/*cis*=0.79)



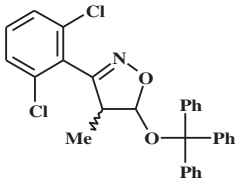
4b (50%, *trans*/*cis*=0.63)



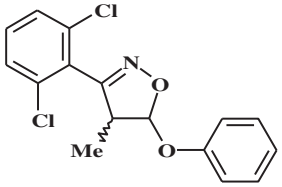
4c (60%, *trans*/*cis*=0.27)



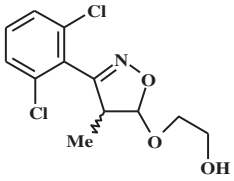
4d (79%, *trans*/*cis*=0.46)



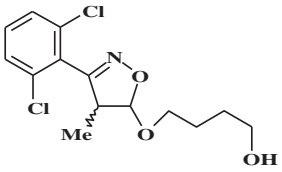
4e (40%, *trans*/*cis*=0.51)[c]



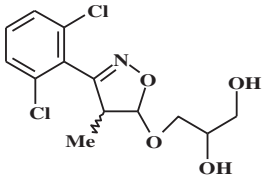
4f(86%, *trans*/*cis*=0.47)



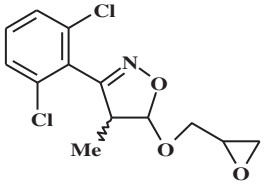
4g (85%, *trans*/*cis*=0.82)



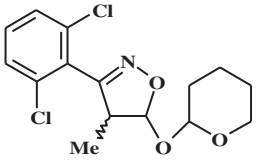
4h (80%, *trans*/*cis*=0.56)



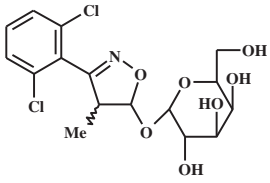
4i (60%, *trans*/*cis*=0.43)



4j (66%, *trans*/*cis*=0.70)



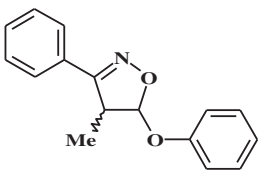
4k (62%, *trans*/*cis*=0.67)



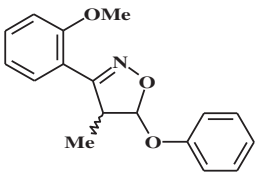
4l (58%, *trans*/*cis*=0.21)

[a] Reaction conditions: *O*-(1-propenyl) substrate (1.3 mmol) and 2,6-$Cl_2C_6H_3CNO$ (1.3 mmol) refluxed in dichloromethane (10 mL) for 4 h.
[b] Isolated yield.
[c] *E*/*Z*=0.11 for unreacted $Ph_3COCH{=}CHCH_3$.

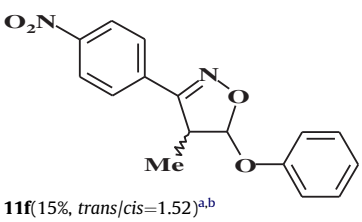
Table 3
Synthesis of 3-substituted 4-methyl-5-phenoxy-4,5-dihydroisoxazoles via 1,3-dipolar cycloaddition of various nitrile oxide to (*E*+*Z*) phenyl (1-propenyl) ether **2f**



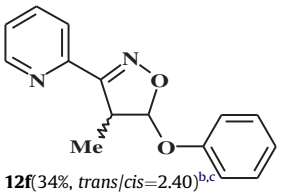
9f(34%, *trans*/*cis*=1.00)[a,b]



10f(74%, *trans*/*cis*=0.63)[a,b]



11f(15%, *trans*/*cis*=1.52)[a,b]



12f(34%, *trans*/*cis*=2.40)[b,c]

[a] Reaction conditions: oximoyl chloride:phenyl (1-propenyl) ether:triethylamine=1:1:1.1 (or 2:1:2.2), in dichloromethane, rfx, 24 h.
[b] Isolated yield.
[c] Reaction conditions: oximoyl chloride:phenyl (1-propenyl) ether:triethylamine=2:1:2.2, in DMF, rfx, 24 h.

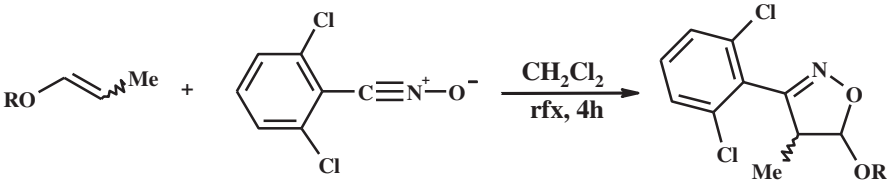
synthesized earlier (see experimental). Dipolarophiles themselves were obtained in isomerization reactions of corresponding allyl derivatives in either [$RuClH(CO)(PPh_3)_3$]- or [$RuH_2(CO)(PPh_3)_3$]-mediated reactions—Scheme 2 and Table 1. Several catalytic systems for the isomerization of *O*-allyl compounds, in particular allyl ethers and allyl alcohols have been reported to date, however, the most robust and effective ones are those derived from transition metal complexes, as they provide mild reaction conditions, low catalyst loading, and chemo-, regio- and, stereoselectivity.[34] So far reported allyl ethers were isomerized to their corresponding vinyl ethers in the presence of Ru,[35] Rh,[36] Ir,[37] Pd,[38] Fe,[39] Cr[40] or other transition metal complexes. The isomerization of *O*-allyl acetals has always been conducted inruthenium-catalyzed reactions.[41] Both our study and other reports revealed that the most effective systems for isomerization of ethers and *O*-allyl acetals are those derived from [$RuClH(CO)(PPh_3)_3$] and [$RuH_2(CO)(PPh_3)$].[42–44] Each allyl ether and acetal was transformed easily to a mixture of the corresponding (*E*)- and (*Z*)-1-propenyl ethers or (*E*)- and (*Z*)-*O*-(1-propenyl) acetals when subjected to [$RuClH(CO)(PPh_3)_3$] or [$RuH_2(CO)(PPh_3)$] with 100% chemoselectivity and quantitative yield (100%), resulting from the high equilibrium constant $K_{1\text{-propenyl/allyl}}>1000$.[35] After solvent (if used) evaporation 1-propenyl ethers (**2a**–**2j**) and *O*-(1-propenyl) acetals (**2k** and **2l**) were used in the cycloaddition reaction without removal of the ruthenium complexes. The residual compounds of the catalytic system did not influence the cycloaddition reaction and were easily removed during column chromatography (they deposited on the top of the silica gel and were not eluted). Moreover, a competitive method for the removal of ruthenium residual compounds (<1 ppm Ru) from 1-propenyl compounds (ethers, amides) based on the adsorption on either active carbon or on functionalized MCF (Mesoporous Cellular Foam) was established by our group.[34,44]

Scheme 2. Isomerization of *O*-allyl compounds mediated by ruthenium complexes (see Table 1).

Dipolarophiles listed in Table 1 were then subjected to 1,3-DC reaction with pure, stable 2,6-dichlorobenzonitrile oxide **3** (in CH_2Cl_2, 4h, rfx)—Scheme 3 and Table 2. Oxide **3** was obtained in the reaction of Et_3N with appropriate oximoyl chloride, derived from 2,6-dichlorobenzaldoxime and NCS. Both oximoyl chloride and the pure oxide were prepared according to previously reported procedure,[31–33] further described by other authors.[26,45] Nitrile oxides are generated as a result of elimination of HCl from hydroximoyl chloride in the presence of a base.[46] Recently, a method for the synthesis of nitrile oxides in magtrieve™ (CrO_2) and MnO_2 mediated oxidation of aldoximes has been described.[47] Hydroximoyl chlorides can be prepared from corresponding oximes and electrophilic chlorine-containing sources, such as NCS, NaOCl, Cl_2, chloramine-T, etc.[21,46,48–51]

All of the investigated 1,3-DC reactions showed outstanding regioselectivity; only 5-*O*-substituted isoxazolines were formed (**4a**–**l**) with the isolated yields ranging from 50 to 91%. Moderate yields were observed only when a dipolarophile with bulky Q group was used (for trityl group the yield of **4e** was 40%). In this case it was a result of incomplete conversion of *O*-(1-propenyl) system (50%). Among other dipolarophiles the conversion was either quantitative or higher than 96% (see Table 1). Moderate yield (50–66%) in isoxazolines **4b**, **4c**, **4j**, **4k** was the result of losses during column chromatography procedure. In general, 1,3-dipolar cycloaddition of nitrile oxides to ROCH=$CHCH_3$ systems gives rise to two asymmetric centres in the product. Analysis of the ^1H NMR spectra of the obtained products, allowed us to define the quantity of diastereomers in the final mixture, described as *trans*/*cis* ratio (see Table 2). *cis* and *trans* Isomers were distinguished using spin-spin coupling constant values, which were in this case greater for *cis* than for *trans* isomers. Moreover, the chemical shifts of the isoxazoline ring protons (bonded to C4 and C5) have greater values for the *cis* isomers than for *trans* isomers. On the other hand, the ^{13}C chemical shifts of C4 and C5 are greater for *trans* isomers than for *cis* isomers. This conclusion is accurately supported by our previous results for over 40 isoxazolines and it is also consistent with the observations of other authors.[52] What is more, the crystal structure of the *cis*-**4a** isoxazoline obtained from the X-ray analysis is fully consistent with the NMR (^1H and ^{13}C NMR) measurements. In the case of dipolarophiles **2a**, **2b**, **2e**, **2f**, **2g**, and **2f** the ^1H and ^{13}C NMR analyses revealed the presence of two isomers (*cis* and *trans*). When the dipolarophiles possessed stereogenic carbon atoms (**2c**, **2i**, **2j**, and **2k** as racemic mixtures or **2d** and **2l** as pure enantiomers) the corresponding products consisted of four isomers denoted as *cis*-1, *cis*-2 and *trans*-1, *trans*-2 (see experimental). Therefore, in the case of isoxazolines **4c**, **4d**, **4e**, **4i**, **4j**, **4l**, and **4k** the *trans*/*cis* ratio was calculated as follows: (*trans*-1+*trans*-2)/(*cis*-1+*cis*-2). In general, a formation of all possible stereoisomeric isoxazolines was seen in each reaction.

Several isoxazolines (**9f**–**12f**) were also synthesized in 1,3-DC reactions from less stable nitrile oxides (benzonitrile oxide **5**, *o*-methoxybenzonitrile oxide **6**, *p*-nitrobenzonitrile oxide **7** and pyridine-2-carbonitrile oxide **8**) to (*E*+*Z*) phenyl 1-propenyl ether, in CH_2Cl_2 (or in DMF) solution (rfx, 24 h)—Table 3. The oxides proved to be stable enough to obtain isoxazolines via 1,3-DC reaction. Under the applied conditions (CH_2Cl_2, 40 °C, 24 h) only *p*-$O_2NC_6H_4CNO$ is capable of forming dimers in 20–30%. As for the other three oxides, their stability is comparable to that of *p*-ClC_6H_4CNO, which undergoes slow dimerization in 1,2-dichloroethane and chloroform at 40 °C.[53] In order to avoid unfavourable dimerization reaction the aforementioned oxides were generated in situ, in the presence of a dipolarophile, in the reaction of corresponding oximoyl chloride (obtained in situ from a suitable oxime and NCS) with triethylamine. Again, as for the reaction with oxide **3** (Table 2), the regioselectivity of the cycloaddition was as high as 100%. The isolated yields were rather moderate (with the exception of **10f**) because of low stability of the starting oxides, which could undergo side reactions like dimerization, what is a well-known phenomenon.[26,54] Isoxazoline



Scheme 3. Synthesis of derivatives of 5-*O*-substituted 4,5-dihydroisoxazoles via 1,3-dipolar cycloaddition of 2,6-$Cl_2C_6H_3CNO$ to *O*-(1-propenyl) systems (ArCNO/dipolarophile=1/1).

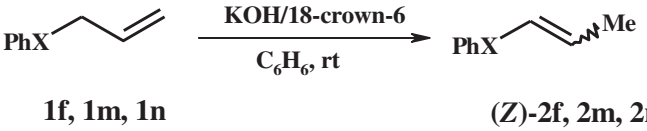
10f was obtained with superior yield mainly as a consequence of the fact that *o*-methoxybenzonitrile oxide **6** possesses enhanced stability due to a steric effect (MeO substituent in *ortho* position). Increasing of the oxide: dipolarophile ratio resulted in a substantial growth of the yield from 47% to 74%. Further addition of the oxide did not turn out to be beneficial, because of the difficulties in the isolation of the products with satisfactory purity. Besides, for **9f**, **11f**, and **12f** the increase in the oxide/dipolarophile ratio was not as effective as for **10f**; giving yields improved by less than 5% with growing separation problems. It was a result of decreasing concentration of the expected isoxazoline in the reaction mixture, and other dimerization side reactions.[26,54]

The influence of substitution of a heteroatom in dipolarophiles Ph-X-CH=CHCH$_3$ (X=O, S, or Se) on the regioselectivity of 1,3-DC reactions was also investigated in a parallel study. Attention was also paid to the influence of the configuration of a selected dipolarophile [(*Z*)-PhOCH=CHCH$_3$] on the stereoselectivity of the resulting product (using 2,6-dichlorobenzonitrile oxide as a dipole source). First, corresponding dipolarophiles were synthesized by the isomerization of their allyl precursors mediated by a basic catalytic system composed of KOH/18-crown-6 in benzene solution—Table 4 and Scheme 4. It is worth of noting that the synthesis of 1-propenyl selenide via isomerization of its allyl precursor has not been reported so far. Another innovative idea was introduced in the isomerization of allyl phenyl ether and sulfide, as a catalytic system like KOH/18-crown-6 has only been applied to isomerization of several selected *N*-allylamines.[31] The conversion and chemoselectivity observed in these reactions was nearly quantitative and, what is even more important, the isomerization of PhOallyl was exclusively *Z*-selective. Isomerization of allyl ether to (*Z*)-(1-propenyl) derivatives was so far achieved using either *t*-BuOK in DMSO[55] or [NiCl$_2$(dppb)]/Li[BHEt$_3$] in THF[56] or in particular LDA in THF.[57] Moreover, our efforts to apply transition metal complexes ([RuClH(CO)(PPh$_3$)$_3$], [RuH$_2$(CO)(PPh$_3$)$_3$], [RuCl$_2$(PPh$_3$)$_3$], and [RhH(CO)(PPh$_3$)$_3$]) as catalysts for the isomerization of allyl phenyl sulfides and selenides were ineffective. The aforementioned situation is a direct consequence of the fact that for the *R*-X-allyl systems (X=S or Se), the reaction with ruthenium and rhodium metal complexes proceeds with a cleavage of the C–S or C–Se bond, unless *R* is bulky enough.[35,58,59]

Table 4
Synthesis of Ph-X-CH=CHCH$_3$ via isomerization of Ph–X–CH$_2$CH=CH$_2$[a,b]

PhX		No	[%] (*E*/*Z*)
1f	**PhO**–	**(*Z*)-2f**	>99.9 *Z* only
1m	**PhS**–	**2m**	99.5 (0.75)
1n	**PhSe**–	**2n**	99.5 (0.78)

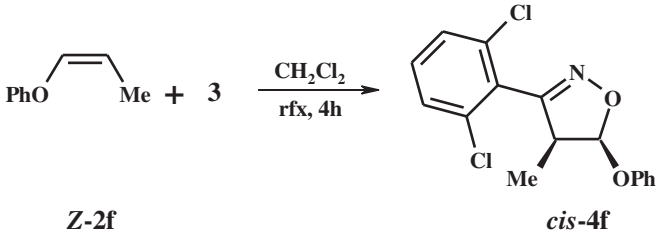
[a] Reaction conditions: allyl substrate (1.3 mmol), KOH (3.9 mmol), and 18-crown-6 (0.189 mmol) in benzene (4 mL), rt, 24 h.
[b] 1-Propenyl systems yield (determined by ^{1}H NMR).



Scheme 4. Isomerization of Ph-X-allyl (X=O, S, or Se) catalyzed by KOH/18-crown-6.

As described above, 1,3-dipolar cycloaddition of nitrile oxides to *O*-(1-propenyl) systems leads solely to 5-*O*-substituted isoxazolines. The same regioselectivity was observed earlier for 2,3-dihydrofuran and (1-propenyl) methyl ether.[52] In the case of cycloaddition of moderately electrophilic nitrile oxides to electron-rich dipolarophiles, which is the case of 1-propenyl ethers, the interaction between dipole LUMO and dipolarophile HOMO is dominating.[60] In the case of an electron-rich dipolarophiles, the coefficient on the α carbon atom of its HOMO is smaller than the coefficient on the β carbon atom of its HOMO (in the case of 2,3-dihydrofuran those coefficients are 0.43 and 0.53, respectively[60]), which leads to the formation of 5-*O*-substituted isoxazolines.

We observed that the 1,3 DC of 2,6-dichlorobenzonitrile oxide **3** to (*Z*)-phenyl (1-propenyl) ether (***Z***)-**2f** results in the exclusive formation of *cis*-5-*O*-substituted isoxazoline (*Z*)-**4f** (Scheme 5), which has been confirmed by X-ray crystallography (Fig. 1). The analysis of the ^{1}H and ^{13}C NMR spectra did not confirm the presence of *trans* diastereomer, when dipolarophile (***Z***)-**2f** was used, which suggested a concerted character of the cycloaddition. What is more, a good agreement (within ^{1}H NMR experimental error, that is, ±0.05) between *E*/*Z* ratio (for dipolarophile) and *trans*/*cis* ratio (for the resulting isoxazoline) for the tested ROCH=CHCH$_3$ systems (with the exceptions of **2e**, **2i** and **2k** as starting materials) suggested concerted 1,3-DC character in the aforementioned cases. Only for dipolarophiles **2e**, **2i** and **2k** the *E*/*Z* and *trans*/*cis* ratios were significantly different, which suggested a two-step 1,3-DC reaction with rotation about the C–C bond. Similar observation can be made in the case of the cycloaddition of oxide **3** to PhSCH=CHCH$_3$ and PhSeCH=CHCH$_3$—see Scheme 6. There is no doubt that when *trans*/*cis*≠*E*/*Z* the reaction must occur in two-steps with the possibility of rotation about the C–C bond. A different *trans*/*cis* and *E*/*Z* ratios were observed before in our study, when cycloaddition of ArCNO to *N*-(1-propenyl) systems was investigated.[31] The most spectacular example of abovementioned study was the reaction of (*E*)-Me$_2$NCH=CHCH$_3$, where only *cis* isoxazoline was obtained in quantitative conversion, instead of the anticipated *trans*-isoxazoline.[31] The analysis of the results of cycloaddition reactions of various ArCNOs (in our cases mostly 2,6-dichlorobenzonitrile oxide) to many QCH=CHCH$_3$ systems, introduced in this and our previous papers, revealed that the 1,3-DC reactions may proceed via to either a fully concerted or a two-step mechanism. For Q substituents like PhO, *t*-BuO and other, the reactions follow the concerted pattern, which is consistent with the observations made by other authors,[26,61] and the recently published theoretical calculations.[61] However, for several Q substituents like Me$_2$N, PhS, PhSe, etc., the reactions are a two-step process. The most convincing proof of this assumption is the substantial difference in the *E*/*Z* ratio for the dipolarophile before the reaction and the *trans*/*cis* ratio of the corresponding isoxazoline after the reaction. The *trans*/*cis* ratio is determined by the speed of the rotation about the C–C bond in the intermediate formed soon after the complete formation of the first bond.



Scheme 5. Synthesis of *cis*-3-(2,6-dichlorophenyl)-4-methyl-5-phenoxy-4,5-dihydroisoxazole ***cis*-4f** from (*Z*)-phenyl (1-propenyl) ether and 2,6-dichlorobenzonitrile oxide **3**.

Several examples of nitrile oxide 1,3-dipolar cycloadditions to *S*-vinyl systems (obtained via isomerization of corresponding

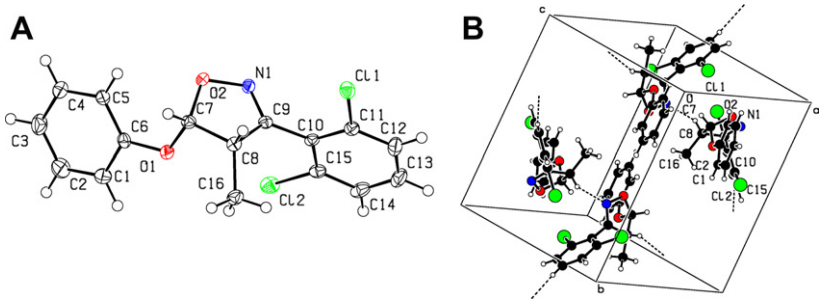
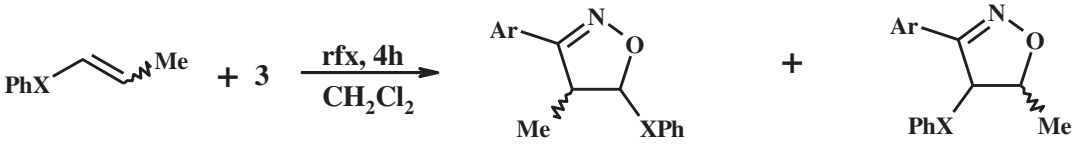


Fig. 1. X-ray structure of *cis*-3-(2,6-dichlorophenyl)-4-methyl-5-phenoxy-4,5-dihydroisoxazole ***cis*-4f** (A). Crystal structure packing of ***cis*-4f** in the unit cell (B).



X = S	**yield 50%; *trans/cis* = 0.94**	**yield 7%; *trans/cis* = 2.00**
	13m	**14m**
X = Se	**yield 41%; *trans/cis* = 1.00**	**yield 21%; *trans/cis* = 1.82**
	15n	**16n**

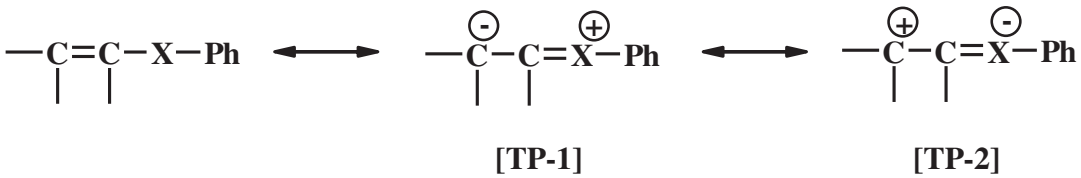
Scheme 6. Cycloaddition of 2,6-dichlorobenzonitrile oxide to (*E*+*Z*)-Ph-X-CH=CHCH$_3$ (X=S or Se) in CH_2Cl_2.

allyl precursors) were described in the literature, for instance 2,3-dihydrothiophene,[52] methyl (1-propenyl) sulphide,[52] and phenyl (1-propenyl) sulphide.[62] There is also one paper concerning 1,3-DC to PhSeCH=CHR (*R*=H, Me or Ph) obtained in Wittig reaction.[63] The isomerization reaction we adopted allowed obtaining *PhS*- and *PhSe*-(1-propenyl) systems in a simple procedure, which were further used in 1,3-dipolar cycloaddition with 2,6-dichlorobenzonitrile oxide **3** (Scheme 6).

In these reactions mixtures of regioisomers have been obtained. In the case of sulfuric dipolarophile 5-*S*- and 4-*S*-substituted isoxazoline **13m** and **14m** were obtained in 50% and 7% yield, respectively, while in the case of phenyl (1-propenyl) selenide 5-*Se*- and 4-*Se*-substituted isoxazoline **15n** and **16m** were obtained in 41% and 21% yield, respectively, which is consistent with previous reports.[52,63] By comparing the regioselectivity of those three analogues, we can state that in the case of oxygen system, the presence of only one possible resonance structure, described as [TP-1] on Scheme 7, may have a beneficial influence on regioselectivity. However, when X=S or Se, also [TP-2] form is present, in which substituent XPh becomes the acceptor of the π-bond electrons through its d orbitals. Such a structure allows obtaining second regioisomer.[52] Throughout the analysis of *trans*/*cis* ratios of the obtained mixtures of each of the regioisomer, it can be concluded that in the case of 5-*S*-substituted and 5-*Se*-substituted isoxazolines regioisomers, differences from the starting *E*/*Z* mixtures are minor, which further proves the concerted mechanism in these cases. However, in the case of 4-*S*-substituted **14m** and 4-*Se*-substituted **16n** isoxazoline, the *trans* isomer is dominant in the mixture.

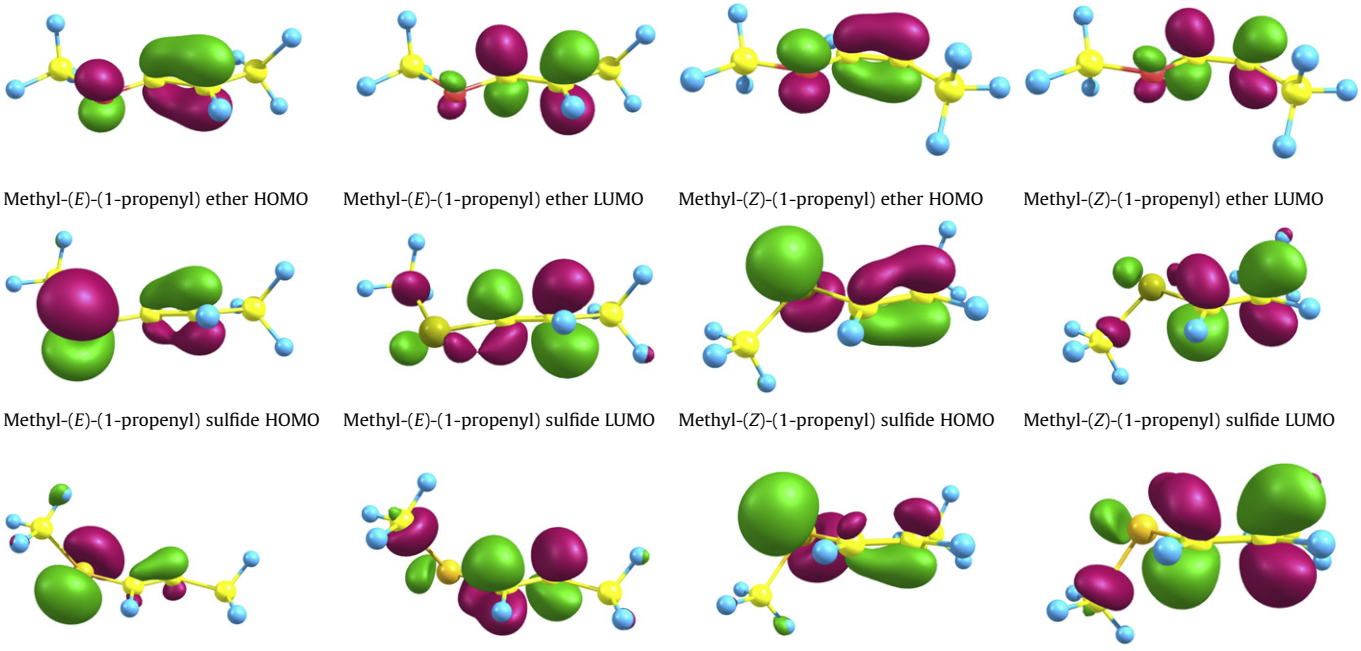
The regioselectivity observed in our study was explained theoretically by means of DFT calculations. Six dipolarophiles ((*E*)- and (*Z*)-methyl–propenyl ether, (*E*)- and (*Z*)-methyl–propenyl sulfide and (*E*)- and (*Z*)-methyl–propenyl selenide) were used as model compounds for the abovementioned investigation. The calculations were carried out on B3LYP/6-31G(d,p) level of theory with Gaussian09[64] package (for further details see Experimental Section).

In order to explain the differences in regioselectivity ranging from *O*-propenyl to *Se*-propenyl systems Mulliken charges and frontier molecular orbitals (FMO) at optimized geometries were

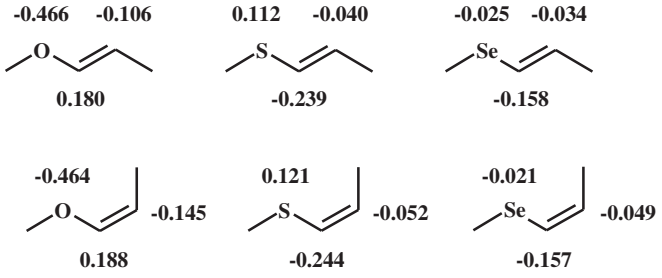


Scheme 7. Resonance structures of X-(1-propenyl) systems (X=O, S, Se [TP-1], X=S, Se [TP-2]).

Table 5
Projections of frontier molecular orbitals for the model compounds



examined. Projections of FMO and Mulliken atomic charges for the previously mentioned compounds are presented in Table 5 and in Scheme 8, respectively. It is worth noting that the results obtained for each isomeric pair reveal a very similar pattern. Starting from the 1-propenyl ether one can easily distinguish a lower contribution from C^1 and an increased contribution of heteroatom in the HOMO when moving to selenide. In the LUMO, on the other hand, the contribution from both C^1 and C^2 remains on the same level, however, a rise of the coefficient on heteroatom is seen in the case of the selenide. As for the atomic charges the results correspond very accurately to the structures presented in Scheme 7. In oxygen-containing systems, C^1 and C^2 possess positive and negative charges, respectively, owing to strong resonance effect and therefore a substantial contribution of TP-1 structure. In the case of the sulfide and the selenide the situation is opposite (due to lack of resonance effect and the remaining inductive effect) and the negative charge is localized more on C^1 leaving C^2 charge almost equal to zero.



Scheme 8. Mulliken atomic charges.

Results of the model calculations led to the conclusion that the regioselectivity of the reactions is mostly charge-controlled. The high regioselectivity in the case of propenyl ethers may be attributed to strong localization of the negative charge on C^2. In sulfide and selenide the situation is inverted and that leads to deviations from formation of 5-X substituted derivative exclusively.

3. Conclusions

A new strategy for the synthesis of 3-aryl-4-methyl-5-*O*-substituted isoxazolines via tandem catalytic isomerization of *O*-allyl systems to *O*-(1-propenyl) systems—nitrile oxides 1,3-dipolar cycloaddition to *O*-(1-propenyl) was presented. A series of novel 3-aryl-4-methyl isoxazolines, additionally 5-OR substituted (R=*O*-alkyl, *O*-hydroxyalkyl, *O*-oxiranyl, *O*-tetrahydropyran-2-yl, and carbohydrate moiety) were synthesized and characterized. A competitive synthetic route, different from the tandem isomerization/1,3-dipolar cycloaddition, would be difficult or simply impossible. Allyl compounds were either commercially accessible or synthesized, if necessary. The influence of the heteroatom in Ph–X–CH=CHCH$_3$ (X=O, S or Se) on the regio- and stereoselectivity of 1,3-DC reaction was also investigated. Dipolarophiles (Q-CH=CHCH$_3$) were synthesized via [RuClH(CO)(PPh$_3$)$_3$], [RuH$_2$(CO)(PPh$_3$)] and base (KOH/18-crown-6) catalyzed double bond migration in the corresponding allyl ethers and *O*-allyl acetals, Ph*S*- and Ph*Se*-allylic systems. Cycloadditions of nitrile oxides to *O*-(1-propenyl) systems were fully regioselective—only 3-aryl-4-methyl-5-*O*-substituted isoxazolines were formed. When Ph*S*-(1-propenyl) system and Ph*Se*-(1-propenyl) were subjected to cycloaddition with ArCNO both regioisomers were formed. It was assumed, that in the majority of the dipolarophiles used (ROCH=CHCH$_3$) the 1,3-DC reaction was either concerted or highly ansynchronously concerted, while for some other dipolarophiles RXCH=CHCH$_3$ (X=O, R=Ph$_3$C, 2,3-dihydroxypropyl, tetrahydropyran-2-yl; R=Ph but X=S or Se), the reaction had an undoubtedly two-step character. The results of the experiments were investigated theoretically using density functional theory. The information obtained from these calculations agreed well with the experimental data. The aforementioned regioselectivity was attributed to different charge distribution, as confirmed by DFT calculations.

4. Experimental

4.1. General

The solvents were purified and dried using standard methods. The ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, on a Bruker 400. Low resolution mass spectra were recorded in methanol on a Varian LC-920. HRMS spectra were recorded in methanol on Mariner ESI-TOF (Applied Biosystems) mass spectrometer using polyethylene glycol 400 (PEG 400) sodiated ions as internal standard. IR-spectra were recorded on a Magna 500 Nicolet spectrophotometer. Crystallographic data were collected on a Kuma KM-4-CCD automatic diffractometer equipped with a CCD detector and graphite monochromated Mo Kα radiation (λ=0.71073 Å). Calculations were done using Gaussian09 package. Becke 3-parameter Lee-Yang-Parr functional (B3LYP), as implemented in Gaussian09 and 6-31G(d,p) basis set were used for geometry optimizations and charge calculations. Molecular orbitals plots were visualized in Chemcraft.

4.2. Allyl compounds, oximes, and isomerization catalysts

Allyl compounds **1a**, **1f**, **1g**, **1i**–**n** and catalysts [$RuClH(CO)(PPh_3)_3$], [$RuH_2(CO)(PPh_3)_3$] and 18-crown-6 were purchased from Aldrich. Syntheses of allyl compounds **1b**–**e**, **1h** (using literature methods or methods developed by us) were described in our earlier papers.[34,35,44] Oximes (from 2,6-dichlorobenzaldehyde, benzaldehyde, *o*-methoxybenzaldehyde, *p*-nitrobenzaldehyde, pyridine-2-carboxaldehyde, Aldrich) were prepared by methods adapted from literature.[46,65]

4.3. *O*–, *S*–, *Se*–(1-propenyl) compounds

*4.3.1. Isomerization of O-allyl systems **1a**–**l** to **2a**–**l**, respectively, in the presence of [Ru].* *O*-Allyl substrate was heated with catalyst ([$RuClH(CO)(PPh_3)_3$] or [$RuH_2(CO)(PPh_3)_3$]) and solvent (if used) under argon atmosphere in screw-capped ampoules, under predetermined temperature (±0.1 °C), within appropriate time, with intense stirring on a magnetic plate. Reaction time, temperature and the proportions of the substrate, the catalyst and the solvent are presented in Table 1. After removal of the solvent (if used) on a rotary evaporator, the obtained dipolarophile $ROCH{=}CHCH_3$ was used in the cycloaddition without removal of [Ru].

*4.3.2. Isomerization of PhO–, PhS–, PhSe–allyl systems **1f**, **1m**, and **1n** to (Z)-**2f**, **2m** and **2n**, respectively, in the presence of KOH/18-crown-6.* To **1f**, **1m** or **1n** (1.3 mmol) in benzene (4 mL) were added powdered KOH (0.22 g, 3.9 mmol) and 18-crown-6 (50 mg, 0.189 mmol). After stirring at room temperature for 24 h the organic layer was washed two times with saturated aqueous NaCl solution (3 mL). Then, benzene layer was dried over anhydrous $MgSO_4$, the solvent was removed on a rotary evaporator, and the dipolarophile was used in the cycloaddition without further purification.

4.4. Cycloadditions: synthesis and separation of isoxazolines

4.4.1. General procedure for hydroximoyl chloride preparations. To a stirred solution of oxime (1.3 mmol) in CH_2Cl_2 (10 mL) (or in DMF for pyridine-2-carboxaldoxime) at room temperature was added solid NCS (0.187 g, 1.4 mmol). The reaction was initiated by the addition of one drop of concd hydrochloric acid. After stirring for 4 h, the solution of hydroximoyl chloride in CH_2Cl_2 (or in DMF) was used in the cycloaddition. Yield >98%.

*4.4.2. Cycloaddition of stable 2,6-dichlorobenzonitrile oxide to O–, PhS–, PhSe-(1-propenyl) systems (**2a**–**n**).* To a stirred solution of 2,6-dichlorobenzohydroximoyl chloride (0.292 g, 1.3 mmol) in CH_2Cl_2 (10 mL), at 0–5 °C, triethylamine (0.20 mL, 1.4 mmol) was added. After stirring for 1 h, the mixture was washed with brine (2×5 mL), dried over $MgSO_4$, and the solvent was evaporated (yield of almost pure ArCNO>98%). Separated pure nitrile oxide was added to the *O*–, Ph*S*– and Ph*Se*-(1-propenyl) systems (1.3 mmol) and refluxed in CH_2Cl_2 (10 mL) for 4 h. After the reaction the solvent was evaporated on a rotary evaporator. Pure isoxazolines were isolated by the methods A and B described in the section 4.4.4.

*4.4.3. Cycloaddition of less stable nitrile oxides (**5**–**8**) to phenyl (1-propenyl) ether **2f**.* The obtained solution of hydroximoyl chloride (1.3 mmol) (from benzaldoxime, *o*-methoxybenzaldoxime and *p*-nitrobenzaldoxime) in CH_2Cl_2 (10 mL) (or from pyridine-2-carboxaldoxime in DMF) was added to (*E*+*Z*)-phenyl (1-propenyl) ether **2f**, with subsequent injection of triethylamine (0.20 mL, 1.4 mmol). The mixture was stirred for 24 h under reflux. The post-reaction mixture was washed with water (3×10 mL), dried over $MgSO_4$ and then the solvent was removed on a rotary evaporator. Pure isoxazolines were isolated by the method A described in the section 4.4.4.

4.4.4. Separation of pure isoxazolines.

(A) The crude products (except **4i** and **4l**) were purified via column chromatography on silica gel (Merck, 230–400 mesh, 10 g/0.2 g crude product). The pure products **4b**, **4e**, **9f**, **13m**, **14m**, were eluted with toluene, while in the case of **4a**, **4c**, **4d**, **4f**–**4h**, **4j**, **4k**, **10f**–**12f**, **15n**, **16n** dichloromethane was applied.

(B) Isoxazolines **4i** and **4l** were purified through adsorption of impurities and ruthenium compounds on active carbon (20 mg Norit CN-1/100 mg product). The solutions of crude products (100 mg) in benzene (10 mL) were mixed with active carbon (20 mg) for 24 h, at room temperature. After filtration the volatile fractions were evaporated on a rotary evaporator and pure products were obtained.

*4.4.5. 5-Butoxy-3-(2,6-dichlorophenyl)-4-methyl-4,5-dihydroisoxazole (**4a**).* Obtained as light yellow oil (350 mg, 91%); *trans*/*cis*=0.79; R_f (CH_2Cl_2)=0.68. Compound *cis*-**4a** ^{1}H NMR (400 MHz, $CDCl_3$) δ=0.87–0.94 ppm (m, 3H, CH_3CH_2 (*n*-C_4H_9)), 1.07 (d, 3H, *J*=7.5 Hz, CH_3CH), 1.33–1.44 (m, 2H, CH_3CH_2 (*n*-C_4H_9)), 1.48–1.69 (m, 2H, CH_2CH_2O (*n*-C_4H_9)), 3.39–3.44 (m, 2H, CH_2CH_2O (*n*-C_4H_9)), 3.81 (dq, 1H, *J*=6.7 Hz, *J*=7.5 Hz, CH_3CH), 5.55 (d, 1H, *J*=6.7 Hz, OCHO), 7.22–7.54 (m, 3H, C_{Ar-H}). ^{13}C NMR (100 MHz, $CDCl_3$) δ=7.4 ppm (CH_3CH), 13.8 (CH_3CH_2, (*n*-C_4H_9)), 19.2 (CH_3CH_2, (*n*-C_4H_9)), 31.6 (CH_2CH_2O, (*n*-C_4H_9)), 47.8 (CH_3CH), 68.0 (CH_2CH_2O, (*n*-C_4H_9)), 103.9 (OCHO), 127.9, 128.1, 130.9, 131.5 (C_{Ar}), 159.1 (C=N). Compound *trans*-**4a** ^{1}H NMR (400 MHz, $CDCl_3$) δ=0.87–0.94 ppm (m, 3H, CH_3CH_2 (*n*-C_4H_9)), 1.19 (d, 3H, *J*=7.6 Hz, CH_3CH), 1.33–1.44 (m, 2H, CH_3CH_2 (*n*-C_4H_9)), 1.48–1.69 (m, 2H, CH_2CH_2O (*n*-C_4H_9)), 3.51–3.61 (m, 2H, CH_2CH_2O (*n*-C_4H_9)), 3.90 (qd, 1H, *J*=7.6 Hz, *J*=1.7 Hz, CH_3CH), 5.34 (d, 1H, *J*=1.7 Hz, OCHO), 7.22–7.54 (m, 3H, C_{Ar-H}). ^{13}C NMR (100 MHz, $CDCl_3$) δ=9.1 ppm (CH_3CH), 13.9 (CH_3CH_2, (*n*-C_4H_9)), 19.4 (CH_3CH_2, (*n*-C_4H_9)), 32.0 (CH_2CH_2O, (*n*-C_4H_9)), 51.7 (CH_3CH), 65.2 (CH_2CH_2O, (*n*-C_4H_9)), 104.3 (OCHO), 128.0, 128.2, 131.0, 131.6 (C_{Ar}), 158.8 (C=N). IR (film): 3079, 2959, 2953, 2873, 1734, 1581, 1559, 1451, 1430, 1380, 1318, 1194, 1153, 1088, 1036, 901, 851, 789, 730, 708 cm^{-1}. MS (ESI^+) *m*/*z* 302.1 $[M+H]^+$, 324.1 $[M+Na]^+$, 627.1 $[2M+Na]^+$, HRMS (ESI^+): calcd for $C_{14}H_{17}{}^{35}Cl_2NO_2Na$ $[M+Na]^+$ 324.0529 found 324.0542.

*4.4.6. 5-tert-Butoxy-3-(2,6-dichlorophenyl)-4-methyl-4,5-dihydroisoxazole (**4b**).* Obtained as light yellow oil (188 mg, 50%); *trans*/*cis*=0.63; R_f (toluene)=0.24. Compound *cis*-**4b** ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.03 ppm (d, *J*=7.6 Hz, 3H, CH_3CH), 1.31 (s, 9H, $(CH_3)_3$C), 3.76 (dq, *J*=7.1 Hz, *J*=7.6 Hz, 1H, CH_3C*H*), 5.85 (d, *J*=7.1 Hz, 1H, OCHO), 7.25–7.68 (m, 3H, C_{Ar-H}). ^{13}C NMR (100 MHz, $CDCl_3$) δ=8.0 ppm (*C*H_3CH), 28.7 ((*C*H_3)$_3$C), 47.3 (CH_3*C*H), 75.2 ((*C*H_3)$_3$*C*), 99.3 (OCHO), 128.2, 128.5, 130.9, 132.1 (C_{Ar}), 158.6 (C=N). Compound *trans*-**4b** ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.17 ppm (d, *J*=7.6 Hz, 3H, CH_3CH), 1.33 (s, 9H, $(CH_3)_3$C), 3.50 (qd, *J*=7.6 Hz, *J*=2.9 Hz, 1H, CH_3C*H*), 5.60 (d, *J*=2.9 Hz, 1H, OCHO), 7.25–7.68 (m, 3H, C_{Ar-H}). ^{13}C NMR (100 MHz, $CDCl_3$) δ=13.7 ppm (*C*H_3CH), 28.9 ((*C*H_3)$_3$C), 51.9 (CH_3*C*H), 75.5 ((*C*H_3)$_3$*C*), 105.9 (OCHO), 128.3, 128.6, 130.9, 132.2 (C_{Ar}), 158.5 (C=N). IR (film): 3079, 2976, 2934, 2877, 2849, 2236, 1713, 1580, 1559, 1430, 1368, 1194, 1144, 1085, 853, 787, 729, 698 cm^{-1}. MS (ESI$^+$) *m*/*z* 324.0 $[M+Na]^+$, HRMS (ESI$^+$): calcd for $C_{14}H_{17}{}^{35}Cl_2NO_2Na$ $[M+Na]^+$ 324.0534 found 324.0531.

*4.4.7. 3-(2,6-Dichlorophenyl)-4-methyl-5-(1-methylbutoxy)-4,5-dihydroisoxazole (**4c**).* Obtained as light yellow oil (200 mg, 50%); *trans*/*cis*=0.27; R_f (CH_2Cl_2)=0.77. Compound *cis*-1-**4c** ^{1}H NMR (400 MHz, acetone-d_6) δ=0.87–0.94 ppm (m, 3H, CH_3CHCH_2-CH_2CH_3), 1.04 (d, *J*=7.5 Hz, 3H, CH_3CHCH), 1.16–1.25 (m, 3H, CH_3CHCH$_2$CH$_2$CH$_3$), 1.33–1.57 (m, 4H, $CH_3CHCH_2CH_2CH_3$), 3.60–3.74 (m, 1H, $CH_3CHCH_2CH_2CH_3$), 3.84 (dq, *J*=6.7 Hz, *J*=7.5 Hz, 1H, CH_3CHCH), 5.75 (d, *J*=6.7 Hz, 1H, CH_3CHCH), 6.94–7.77 (m, 3H, C_{Ar-H}). ^{13}C NMR (100 MHz, $CDCl_3$) δ=8.6 ppm (*C*H_3CHCH), 14.1 ($CH_3CHCH_2CH_2CH_3$), 18.4 ($CH_3CHCH_2CH_2CH_3$), 19.6 (CH_3CHCH_2-CH_2CH_3), 39.4 ($CH_3CHCH_2CH_2CH_3$), 47.8 (CH_3CHCH), 75.4 ($CH_3CHCH_2CH_2CH_3$), 103.8 (CH_3CHCH), 128.1, 128.5, 131.1, 135.4 (C_{Ar}), 158.9 (C=N). Compound *cis*-2-**4c** ^{1}H NMR (400 MHz, acetone-d_6) δ=0.87–0.94 ppm (m, 3H, $CH_3CHCH_2CH_2CH_3$), 1.06 (d, *J*=7.6 Hz, 3H, CH_3CHCH), 1.16–1.25 (m, 3H, CH_3CHCH$_2$CH$_2$CH$_3$), 1.34–1.57 (m, 4H, $CH_3CHCH_2CH_2CH_3$), 3.60–3.74 (m, 1H, $CH_3CHCH_2CH_2CH_3$), 3.94 (dq, *J*=6.6 Hz, *J*=7.6 Hz, 1H, CH_3CHCH), 5.76 (d, *J*=6.6 Hz, 1H, CH_3CHCH), 6.94–7.77 (m, 3H, C_{Ar-H}). ^{13}C NMR (100 MHz, $CDCl_3$) δ=7.5 ppm (*C*H_3CHCH), 14.2 ($CH_3CHCH_2CH_2CH_3$), 18.7 (CH_3-$CHCH_2CH_2CH_3$), 19.2 ($CH_3CHCH_2CH_2CH_3$), 38.8 (CH_3CHCH_2-CH_2CH_3), 47.6 (CH_3CHCH), 72.4 ($CH_3CHCH_2CH_2CH_3$), 101.3 (CH_3CHCH), 128.1, 128.4, 130.9, 135.0 (C_{Ar}), 159.0 (C=N). Compound *trans*-1-**4c** ^{1}H NMR (400 MHz, acetone-d_6) δ=0.87–0.95 ppm (m, 3H, $CH_3CHCH_2CH_2CH_3$), 1.10 (d, *J*=7,1 Hz, 3H, CH_3CHCH), 1.16–1.25 (m, 3H, CH_3CHCH$_2$CH$_2$CH$_3$), 1.34–1.57 (m, 4H, $CH_3CHCH_2CH_2CH_3$), 3.20 (qd, *J*=7.1 Hz, *J*=2.0 Hz, 1H, CH_3CHCH), 3.60–3.74 (m, 1H, $CH_3CHCH_2CH_2CH_3$), 5.52 (d, *J*=2.0 Hz, 1H, CH_3CHCH), 6.94–7.77 (m, 3H, C_{Ar-H}). ^{13}C NMR (100 MHz, $CDCl_3$) δ=13.6 ppm (*C*H_3CHCH), 14.0 ($CH_3CHCH_2CH_2CH_3$), 18.5 ($CH_3CHCH_2CH_2CH_3$), 19.2 (CH_3CHCH_2-CH_2CH_3), 39.4 ($CH_3CHCH_2CH_2CH_3$), 51.9 (CH_3CHCH), 75.2 ($CH_3CHCH_2CH_2CH_3$), 109.7 (CH_3CHCH), 128.2, 128.3, 132.1, 135.6 (C_{Ar}), 158.7 (C=N). Compound *trans*-2-**4c** ^{1}H NMR (400 MHz, acetone-d_6) δ=0.87–0.95 ppm (m, 3H, $CH_3CHCH_2CH_2CH_3$), 1.14 (d, *J*=7.6 Hz, 3H, CH_3CHCH), 1.17–1.25 (m, 3H, CH_3CHCH$_2$CH$_2$CH$_3$), 1.34–1.57 (m, 4H, $CH_3CHCH_2CH_2CH_3$), 3.47 (qd, *J*=7.6 Hz, *J*=1.6 Hz, 1H, CH_3CHCH), 3.60–3.74 (m, 1H, $CH_3CHCH_2CH_2CH_3$), 5.53 (d, *J*=1.6 Hz, 1H, CH_3CHCH), 6.94–7.77 (m, 3H, C_{Ar-H}). ^{13}C NMR (100 MHz, $CDCl_3$) δ=13.9 ppm (*C*H_3CHCH), 14.0 (CH_3CHCH_2-CH_2CH_3), 18.6 ($CH_3CHCH_2CH_2CH_3$), 19.6 ($CH_3CHCH_2CH_2CH_3$), 38.8 ($CH_3CHCH_2CH_2CH_3$), 51.8 (CH_3CHCH), 72.0 ($CH_3CHCH_2CH_2CH_3$), 106.8 (CH_3CHCH), 128.2, 128.8, 132.0, 135.6 (C_{Ar}), 158.9 (C=N). IR (film): 3081, 2963, 2934, 2873, 1795, 1695, 1581, 1559, 1451, 1430, 1378, 1317, 1194, 1155, 1084, 900, 851, 788, 729, 705 cm^{-1}. MS (ESI$^+$) *m*/*z* 338.1 $[M+Na]^+$, HRMS (ESI$^+$): calcd for $C_{15}H_{20}{}^{35}Cl_2NO_2$ $[M+H]^+$ 316.0871 found 316.0895; calcd for $C_{15}H_{19}{}^{35}Cl_2NO_2Na$ $[M+Na]^+$ 338.0685 found 338.0686.

*4.4.8. 3-(2,6-Dichlorophenyl)-5-[(2-isopropyl-5-methylcyclohexyl)oxy]-4-methyl-4,5-dihydroisoxazole (**4d**).* Obtained as light yellow oil (385 mg, 79%); *trans*/*cis*=0.46; R_f (CH_2Cl_2)=0.81. Compound *cis*-1-**4d** ^{1}H NMR (400 MHz, acetone-d_6) δ=0.78–0.96 ppm (m, 12H, menthyl), 1.08 (d, *J*=7.4 Hz, 3H, CH_3CH), 1.22–1.51 (m, 2H, menthyl), 1.56–1.72 (m, 2H, menthyl), 2.18–2.39 (m, 2H, menthyl), 3.63 (td, *J*=10.5 Hz, *J*=4.2 Hz, 1H, OCH–menthyl), 3.86 (dq, *J*=6.8 Hz, *J*=7.4 Hz, 1H, CH_3C*H*), 5.75 (d, *J*=6.8 Hz, 1H, OCHO), 7.46–7.62 (m, 3H, C_{Ar-H}). ^{13}C NMR (100 MHz, $CDCl_3$) δ=7.8 ppm (*C*H_3CH), 15.8 (CH_3-menthyl), 15.8 (CH_3–menthyl), 21.0 (CH_3–menthyl), 23.0 (CH_2–menthyl), 23.3 (CH–menthyl), 25.3 (CH–menthyl), 31.4 (CH_2–menthyl), 42.9 (CH_2–menthyl), 48.0 (CH–menthyl), 51.8 (CH_3CH), 74.8 (OCH–menthyl), 105.2 (OCHO), 128.4, 131.0, 132.1, 135.6 (C_{Ar}), 158.8 (C=N). Compound *cis*-2-**4d** ^{1}H NMR (400 MHz, acetone-d_6) δ=0.78–0.96 ppm (m, 12H, menthyl), 1.04 (d, *J*=7.5 Hz, 3H, CH_3CH), 1.22–1.51 (m, 2H, menthyl), 1.56–1.72 (m, 2H, menthyl), 2.18–2.39 (m, 2H, menthyl), 3.64 (td, *J*=10.6 Hz, *J*=4.2 Hz, 1H, OCH–menthyl), 3.85 (dq, *J*=6.5 Hz, *J*=7.5 Hz, 1H, CH_3C*H*), 5.81 (d, *J*=6.5 Hz, 1H, OCHO), 7.46–7.62 (m, 3H, C_{Ar-H}). ^{13}C NMR (100 MHz, $CDCl_3$) δ=7.6 ppm (*C*H_3CH), 15.8 (CH_3–menthyl), 16.2 (CH_3–menthyl), 21.1 (CH_3–menthyl), 22.4 (CH_2–menthyl), 23.2 (CH–menthyl), 25.2 (CH–menthyl), 34.6 (CH_2–menthyl), 39.8 (CH_2–menthyl), 48.1 (CH–menthyl), 50.1 (CH_3CH), 75.1 (OCH–menthyl), 99.9 (OCHO), 128.2, 130.9, 131.9, 135.7 (C_{Ar}), 159.1 (C=N). Compound *trans*-1-**4d** ^{1}H NMR (400 MHz, acetone-d_6) δ=0.78–0.96 ppm (m, 12H, menthyl), 1.18 (d, *J*=7.6 Hz, 3H, CH_3CH), 1.22–1.51 (m, 2H, menthyl), 1.56–1.72 (m, 2H, menthyl), 2.18–2.39 (m, 2H, menthyl), 3.49 (td, *J*=10.6 Hz, *J*=4.3 Hz, 1H, OCH–menthyl), 3.56 (qd, *J*=7.6 Hz, *J*=2.2 Hz, 1H, CH_3C*H*), 5.51 (d, *J*=2.2 Hz, 1H, OCHO), 7.46–7.62 (m, 3H, C_{Ar-H}). ^{13}C NMR (100 MHz, $CDCl_3$) δ=13.9 ppm (*C*H_3CH), 16.5 (CH_3–menthyl), 16.5 (CH_3–menthyl), 21.2 (CH_3–menthyl), 22.0 (CH_2–menthyl), 23.5 (CH–menthyl), 25.9 (CH–menthyl), 31.7 (CH_2–menthyl), 42.8 (CH_2–menthyl), 48.4 (CH–menthyl), 50.9 (CH_3CH), 71.5 (OCH–menthyl), 111.5 (OCHO), 128.0, 131.1, 132.3, 135.6 (C_{Ar}), 158.6 (C=N). Compound *trans*-2-**4d** ^{1}H NMR (400 MHz, acetone-d_6) δ=0.78–0.96 ppm (m, 12H, menthyl), 1.19 (d, *J*=7.6 Hz, 3H, CH_3CH), 1.22–1.51 (m, 2H, menthyl), 1.56–1.72 (m, 2H, menthyl), 2.18–2.39 (m, 2H, menthyl), 3.31 (td, *J*=10.5 Hz, *J*=4.3 Hz, 1H, OCH–menthyl), 3.47 (qd, *J*=7.6 Hz, *J*=1.3 Hz, 1H, CH_3C*H*), 5.58 (d, *J*=1.3 Hz, 1H, OCHO), 7.46–7.62 (m, 3H, C_{Ar-H}). ^{13}C NMR (100 MHz, $CDCl_3$) δ=13.6 ppm (*C*H_3CH), 15.9 (CH_3–menthyl), 16.0 (CH_3–menthyl), 21.1 (CH_3–menthyl), 22.3 (CH_2–menthyl), 23.2 (CH–menthyl), 25.8 (CH–menthyl), 34.4 (CH_2–menthyl), 39.7 (CH_2–menthyl), 47.7 (CH–menthyl), 52.1 (CH_3CH), 80.4 (OCH–menthyl), 105.4 (OCHO), 128.3, 130.9, 132.2, 135.5 (C_{Ar}), 159.0 (C=N). IR (film): 3080, 2953, 2869, 2723, 2237, 1715, 1580, 1560, 1431, 1369, 1319, 1194, 1143, 1084, 1045, 848, 788, 729 cm^{-1}. MS (ESI$^+$) *m*/*z* 406.2 $[M+Na]^+$, 791.3 $[2M+Na]^+$, HRMS (ESI$^+$): calcd for $C_{20}H_{27}{}^{35}Cl_2NO_2Na$ $[M+Na]^+$ 406.1311 found 406.1326.

*4.4.9. 3-(2,6-Dichlorophenyl)-4-methyl-5-(triphenylmethoxy)-4,5-dihydroisoxazole (**4e**).* Obtained as light yellow solid (252 mg, 40%); mp=54 °C; *trans*/*cis*=0.51; R_f (toluene)=0.37. Compound *cis*-**4e** ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.07 ppm (d, *J*=7.6 Hz, 3H, CH_3CH), 3.58 (dq, *J*=6.8 Hz, *J*=7.6 Hz, 1H, CH_3C*H*), 5.42 (d, *J*=6.8 Hz, 1H, OCHO), 7.12–7.44 (m, 15H+3H, C_{Ar-H}). ^{13}C NMR (100 MHz, $CDCl_3$) δ=8.6 ppm (*C*H_3CH), 48.3 (CH_3*C*H), 61.8 (OCPh$_3$), 99.7 (OCHO), 127.2, 127.6, 127.9, 128.7, 128.8, 128.8, 129.1, 131.2 (C_{Ar}), 159.6 (C=N). Compound *trans*-**4e** ^{1}H NMR (400 MHz, $CDCl_3$) δ=0.75 ppm (d, *J*=7.6 Hz, 3H, CH_3CH), 3.42 (qd, *J*=7.6 Hz, *J*=0.9 Hz, 1H, CH_3C*H*), 5.22 (d, *J*=0.9 Hz, 1H, OCHO), 7.12–7.44 (m, 15H+3H, C_{Ar-H}). ^{13}C NMR (100 MHz, $CDCl_3$) δ=13.4 ppm (*C*H_3CH), 52.7 (CH_3*C*H), 65.8 (OCPh$_3$), 105.6 (OCHO), 127.3, 127.7, 127.9, 128.7, 128.7, 128.8, 129.1, 131.1 (C_{Ar}), 158.9 (C=N). IR (film): 3086, 3058, 3032, 2973, 2933, 2875, 2236, 1709, 1602, 1560, 1489, 1387, 1196, 1141, 1081, 960, 849, 796,

703, 634 cm^{-1}. MS (ESI^+) *m/z* 510.1 $[M+Na]^+$, HRMS (ESI^+): calcd for $C_{29}H_{23}{}^{35}Cl_2NO_2Na$ $[M+Na]^+$ 510.1003 found 510.1004.

*4.4.10. 3-(2,6-Dichlorophenyl)-4-methyl-5-phenoxy-4,5-dihydroisoxazole (**4f**).* Obtained as light yellow solid (342 mg, 86%); mp=44 °C; *trans*/*cis*=0.47; R_f (CH_2Cl_2)=0.51. Compound *cis*-**4f** ^1H NMR (400 MHz, $CDCl_3$) δ=1.27 ppm (d, 3H, *J*=7.5 Hz, C*H*$_3$CH), 4.06 (dq, *J*=6.7 Hz, *J*=7.5 Hz, 1H, CH$_3$C*H*), 6.18 (d, 1H, *J*=6.7 Hz, OCHO), 7.04–7.40 (m, 5H+3H, C_{Ar-H}). ^{13}C NMR (100 MHz, $CDCl_3$) δ=7.7 ppm (*C*H$_3$CH), 48.4 (CH$_3$*C*H), 102.1 (OCHO), 116.9, 122.7, 127.5, 128.4, 129.6, 131.4, 135.6, 156.5 (C_{Ar}), 159.1 (C=N). X-ray analysis of *cis*-**4f**: (Table 6 and Table 7).

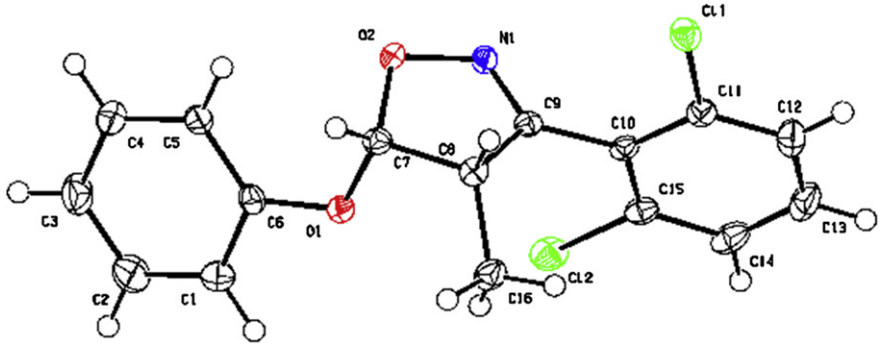
Crystallographic data for the structure reported in this paper was deposited in the Cambridge Crystallographic Data Centre as deposition no. CCDC 837926. Copies of the data can be obtained free of charge upon application to the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk.

Compound *trans*-**4f** ^1H NMR (400 MHz, $CDCl_3$) δ=1.30 ppm (d, 3H, *J*=7.7 Hz, C*H*$_3$CH), 3.88 (qd, 1H, *J*=7.7 Hz, *J*=1.5 Hz, CH$_3$C*H*), 5.96 (d, 1H, *J*=1.5 Hz, OCHO), 7.04–7.40 (m, 5H+3H, C_{Ar-H}). ^{13}C NMR (100 MHz, $CDCl_3$) δ=13.9 ppm (*C*H$_3$CH), 52.4 (CH$_3$*C*H), 107.5 (OCHO), 117.2, 122.8, 127.4, 128.4, 129.6, 131.3, 135.6, 156.7 (C_{Ar}), 159.4 (C=N). IR (film): 3077, 2978, 2941, 2879, 2234, 1708, 1587, 1496, 1429, 1310, 1217, 1136, 1004, 916, 836, 781, 755, 690 cm^{-1}. MS (ESI^+) *m/z* 322.0 $[M+H]^+$, 344.0 $[M+Na]^+$, HRMS (ESI^+): calcd for $C_{16}H_{13}{}^{35}Cl_2NO_2Na$ $[M+Na]^+$ 344.0216 found 344.0229.

*4.4.11. 2-{[3-(2,6-Dichlorophenyl)-4-methyl-4,5-dihydroisoxazol-5-yl]oxy}ethanol (**4g**).* Obtained as light yellow oil (305 mg, 85%); *trans*/*cis*=0.82; R_f (CH_2Cl_2)=0.77. Compound *cis*-**4g** ^1H NMR (400 MHz, $CDCl_3$) δ=1.11 ppm (d, *J*=7.6 Hz, 3H, C*H*$_3$CH), 3.78 (dq, *J*=6.6 Hz, *J*=7.6 Hz, 1H, CH$_3$C*H*), 3.84–3.86 (m, 2H, C*H*$_2$OH), 3.94–3.97 (m, 2H, OC*H*$_2$CH$_2$OH), 4.81 (t, *J*=4.7 Hz, 1H, CH$_2$O*H*), 5.65 (d, *J*=6.6 Hz, 1H, OCHO), 7.31–7.41 (m, 3H, C_{Ar-H}). ^{13}C NMR (100 MHz, $CDCl_3$) δ=8.0 ppm (*C*H$_3$CH), 46.0 (CH$_3$*C*H), 61.8 (OCH$_2$-*C*H$_2$OH), 70.5 (OCH$_2$CH$_2$OH), 105.4 (OCHO), 127.8, 128.3, 131.3, 135.4 (C_{Ar}), 159.2 (C=N). Compound *trans*-**4g** ^1H NMR (400 MHz, $CDCl_3$) δ=1.21 ppm (d, *J*=7.6 Hz, 3H, C*H*$_3$CH), 3.61 (qd, *J*=7.6 Hz, *J*=1.6 Hz, 1H, CH$_3$C*H*), 3.84–3.86 (m, 2H, C*H*$_2$OH), 3.94–3.97 (m, 2H, OC*H*$_2$-CH$_2$OH), 4.81 (t, *J*=4.7 Hz, 1H, CH$_2$O*H*), 5.43 (d, *J*=1.6 Hz, 1H, OCHO), 7.31–7.41 (m, 3H, C_{Ar-H}). ^{13}C NMR ($CDCl_3$) δ=8.7 ppm (*C*H$_3$CH), 48.0 (CH$_3$*C*H), 61.6 (OCH$_2$*C*H$_2$OH), 70.1 (O*C*H$_2$CH$_2$OH), 104.3 (OCHO), 127.5, 128.4, 131.2, 135.3 (C_{Ar}), 159.4 (C=N). IR (film): 3388, 3081, 2976, 2939, 2880, 2661, 2250, 1712, 1578, 1560, 1431, 1195, 1148, 1089, 852, 788, 733, 647 cm^{-1}. MS (ESI^-) *m/z* 282.8 $[M-Li]^-$, HRMS (ESI^+): calcd for $C_{12}H_{13}{}^{35}Cl_2NO_3Na$ $[M+Na]^+$ 312.0170 found 312.0167.

*4.4.12. 4-{[3-(2,6-Dichlorophenyl)-4-methyl-4,5-dihydroisoxazol-5-yl]oxy}butan-1-ol (**4h**).* Obtained as light yellow oil (320 mg, 80%); *trans*/*cis*=0.56; R_f (CH_2Cl_2)=0.75. Compound *cis*-**4h** ^1H NMR (400 MHz, $CDCl_3$) δ=1.07 ppm (d, *J*=7.6 Hz, 3H, C*H*$_3$CH), 1.62–1.75 (m, 4H, OCH$_2$C*H*$_2$C*H*$_2$CH$_2$O), 3.58–3.65 (m, 2H, C*H*$_2$OH), 3.81 (dq, *J*=6.7 Hz, *J*=7.6 Hz, 1H, CH$_3$C*H*), 3.84–3.96 (m, 2H, OC*H*$_2$CH$_2$), 4.57 (t,

Table 6
Crystal data and structure refinement for *cis*-**4f**



Empirical formula	$C_{16}H_{13}Cl_2NO_2$
Formula weight	322.17
Temperature	100 (1) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2(1)/c
Unit cell dimensions	*a*=12.6896 (2) Å, alpha=90° *b*=12.9053 (2) Å, beta=107.628 (2)° *c*=9.6837 (1) Å, gamma=90°
Volume	1511.37 (4) $Å^3$
Z, Calculated density	4, 1.416 Mg/m^3
Absorption coefficient	0.432 mm^{-1}
F (100)	664
Crystal size	0.54×0.42×0.27 mm
Theta range for data collection	2.71–25.06°
Limiting indices	−15≤h≤15 −13≤k≤15 −9≤l≤11
Reflections collected/unique	9854/2670 (R_{int}=0.0160)
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	2670/0/205
Goodness-of-fit on F^2	1.063
Final *R* indices [$I>2\sigma(I)$]	*R*1=0.0236, *wR*2=0.0626
R indices (all data)	*R*1=0.0262, *wR*2=0.0636

Table 7
Bond lengths [Å] and angles [o] for *cis*-**4f**

Cl(1)–C(11)	1.7398 (13)
Cl(2)–C(15)	1.7381 (14)
O(1)–C(6)	1.3828 (15)
O(1)–C(7)	1.4063 (15)
O(2)–C(7)	1.4375 (15)
O(2)–N(1)	1.4388 (13)
N(1)–C(9)	1.2725 (16)
C(1)–C(2)	1.380 (2)
C(1)–C(6)	1.3837 (19)
C(1)–H(1)	0.9500
C(2)–C(3)	1.389 (2)
C(2)–H(2)	0.9500
C(3)–C(4)	1.379 (2)
C(3)–H(3)	0.9500
C(4)–C(5)	1.3921 (19)
C(4)–H(4)	0.9500
C(5)–C(6)	1.3872 (18)
C(5)–H(5)	0.940 (16)
C(7)–C(8)	1.5186 (17)
C(7)–H(8W)	0.976 (14)
C(8)–C(9)	1.5142 (17)
C(8)–C(16)	1.5225 (18)
C(8)–H(9W)	0.965 (15)
C(9)–C(10)	1.4847 (17)
C(10)–C(11)	1.3931 (18)
C(10)–C(15)	1.4017 (18)
C(11)–C(12)	1.3849 (19)
C(12)–C(13)	1.382 (2)
C(12)–H(12)	0.9500
C(13)–C(14)	1.384 (2)
C(13)–H(13)	0.937 (18)
C(14)–C(15)	1.3838 (19)
C(14)–H(14)	0.9500
C(16)–H(16A)	0.9800
C(16)–H(16B)	0.9800
C(16)–H(16C)	0.9800
C(6)–O(1)–C(7)	119.55 (10)
C(7)–O(2)–N(1)	107.74 (9)
C(9)–N(1)–O(2)	107.74 (10)
C(2)–C(1)–C(6)	119.72 (13)
C(2)–C(1)–H(1)	120.1
C(6)–C(1)–H(1)	120.1
C(1)–C(2)–C(3)	120.72 (14)
C(1)–C(2)–H(2)	119.6
C(3)–C(2)–H(2)	119.6
C(4)–C(3)–C(2)	119.06 (14)
C(4)–C(3)–H(3)	120.5
C(2)–C(3)–H(3)	120.5
C(3)–C(4)–C(5)	121.01 (13)
C(3)–C(4)–H(4)	119.5
C(5)–C(4)–H(4)	119.5
C(6)–C(5)–C(4)	119.00 (13)
C(6)–C(5)–H(5)	120.2 (9)
C(4)–C(5)–H(5)	120.8 (9)
O(1)–C(6)–C(1)	114.44 (11)
O(1)–C(6)–C(5)	125.07 (12)
C(1)–C(6)–C(5)	120.47 (13)
O(1)–C(7)–O(2)	110.74 (10)
O(1)–C(7)–C(8)	107.78 (10)
O(2)–C(7)–C(8)	103.99 (10)
O(1)–C(7)–H(8W)	111.8 (8)
O(2)–C(7)–H(8W)	107.8 (8)
C(8)–C(7)–H(8W)	114.4 (8)
C(9)–C(8)–C(7)	98.51 (10)
C(9)–C(8)–C(16)	116.29 (10)
C(7)–C(8)–C(16)	117.13 (11)
C(9)–C(8)–H(9W)	106.7 (9)
C(7)–C(8)–H(9W)	107.7 (9)
C(16)–C(8)–H(9W)	109.6 (9)
N(1)–C(9)–C(10)	120.91 (11)
N(1)–C(9)–C(8)	114.08 (11)
C(10)–C(9)–C(8)	125.01 (10)
C(11)–C(10)–C(15)	116.71 (11)
C(11)–C(10)–C(9)	122.06 (11)
C(15)–C(10)–C(9)	121.19 (11)
C(12)–C(11)–C(10)	122.28 (12)
C(12)–C(11)–Cl(1)	118.66(10)
C(10)–C(11)–Cl(1)	119.06 (10)
C(13)–C(12)–C(11)	119.23 (13)
C(13)–C(12)–H(12)	120.4
C(11)–C(12)–H(12)	120.4
C(12)–C(13)–C(14)	120.47 (13)
C(12)–C(13)–H(13)	119.0 (10)
C(14)–C(13)–H(13)	120.5 (10)
C(15)–C(14)–C(13)	119.37 (13)
C(15)–C(14)–H(14)	120.3
C(13)–C(14)–H(14)	120.3
C(14)–C(15)–C(10)	121.93 (13)

J=5.6 Hz, 1H, CH_2OH), 5.57 (d, *J*=6.7 Hz, 1H, OCHO), 7.25–7.46 (m, 3H, C_{Ar-H}). ^{13}C NMR (100 MHz, $CDCl_3$) δ=8.3 ppm (CH_3CH), 29.3 ($OCH_2CH_2CH_2CH_2OH$), 29.9 ($OCH_2CH_2CH_2CH_2OH$), 47.9 (CH_3CH), 62.3 (CH_2OH), 65.7 (OCH_2CH_2), 103.9 (OCHO), 128.4, 129.8, 131.2, 135.5 (C_{Ar}), 159.1 (C=N). Compound *trans*-**4h** ^1H NMR (400 MHz, $CDCl_3$) δ=1.19 ppm (d, *J*=7.6 Hz, 3H, CH_3CH), 1.62–1.75 (m, 4H, $OCH_2CH_2CH_2CH_2O$), 3.54 (qd, *J*=7.6 Hz, *J*=1.6 Hz, 1H, CH_3CH), 3.58–3.65 (m, 2H, CH_2OH), 3.84–3.96 (m, 2H, OCH_2CH_2), 4.57 (t, *J*=5.6 Hz, 1H, CH_2OH), 5.35 (d, *J*=1.6 Hz, 1H, OCHO), 7.25–7.46 (m, 3H, C_{Ar-H}). ^{13}C NMR (100 MHz, $CDCl_3$) δ=8.7 ppm (CH_3CH), 29.4 ($OCH_2CH_2CH_2CH_2OH$), 29.8 ($OCH_2CH_2CH_2CH_2OH$), 46.1 (CH_3CH), 62.0 (CH_2OH), 65.7 (OCH_2CH_2), 104.0 (OCHO), 128.0, 130.4, 133.8, 136.67 (C_{Ar}), 158.9 (C=N). IR (film): 3408, 3081, 2941, 2878, 2739, 2655, 2599, 1713, 1459, 1380, 1355, 1315, 1225, 1195, 1139, 1088, 1061, 973, 732, 648 cm^{-1}. MS (ESI) *m*/*z* 340.1 $[M+Na]^+$, HRMS (ESI^+): calcd for $C_{14}H_{17}{}^{35}Cl_2NO_3Na$ $[M+Na]^+$ 340.0478 found 340.0475.

*4.4.13. 3-{[3-(2,6-Dichlorophenyl)-4-methyl-4,5-dihydroisoxazol-5-yl]oxy}propane-1,2-diol (**4i**).* Obtained as light yellow oil (246 mg, 60%); *trans*/*cis*=0.43. Compound *cis*-1-**4i** ^1H NMR (400 MHz, $CDCl_3$) δ=1.09 ppm (d, *J*=7.5 Hz, 3H, CH_3CH), 3.56–3.59 (m, 2H, CH_2O), 3.62–3.68 (m, 3H, $CH_2(OH)CH(OH)$), 3.82 (dq, *J*=6.6 Hz, *J*=7.5 Hz, 1H, CH_3CH), 5.72 (d, *J*=6.6 Hz, 1H, OCHO), 7.49–7.74 (m, 3H, C_{Ar-H}). ^{13}C NMR (100 MHz, $CDCl_3$) δ=7.2 ppm (CH_3CH), 47.9 (CH_3CH), 63.5 ($CH_2(OH)CH(OH)$), 69.7 ($CH_2(OH)CH(OH)$), 70.7 (CH_2O), 104.1 (OCHO), 127.4, 128.6, 131.1, 133.7 (C_{Ar}), 152.7 (C=N). Compound *cis*-2-**4i** ^1H NMR (400 MHz, $CDCl_3$) δ=1.10 ppm (d, *J*=7.5 Hz, 3H, CH_3CH), 3.56–3.59 (m, 2H, CH_2O), 3.62–3.68 (m, 3H, $CH_2(OH)CH(OH)$), 3.86 (d, *J*=6.5 Hz, *J*=7.5 Hz, 1H, CH_3CH), 5.73 (d, *J*=6.5 Hz, 1H, OCHO), 7.49–7.74 (m, 3H, C_{Ar-H}). ^{13}C NMR (100 MHz, $CDCl_3$) δ=7.1 ppm (CH_3CH), 47.9 (CH_3CH), 63.5 ($CH_2(OH)CH(OH)$), 69.7 ($CH_2(OH)CH(OH)$), 70.7 (CH_2O), 104.1 (OCHO), 127.4, 128.6, 131.1133.7, 134.0 (C_{Ar}), 152.7 (C=N). Compound *trans*-1-**4i** ^1H NMR (400 MHz, $CDCl_3$) δ=1.19 ppm (d, *J*=7.6 Hz, 3H, CH_3CH), 3.56–3.59 (m, 2H, CH_2O), 3.62–3.68 (m, 3H, $CH_2(OH)CH(OH)$), 3.71 (qd, *J*=7.6 Hz, *J*=1.5 Hz, 1H, CH_3CH), 5.51 (d, *J*=1.5 Hz, 1H, OCHO), 7.49–7.74 (m, 3H, C_{Ar-H}). ^{13}C NMR (100 MHz, $CDCl_3$) δ=13.5 ppm (CH_3CH), 51.8 (CH_3CH), 63.5 ($CH_2(OH)CH(OH)$), 69.5 ($CH_2(OH)CH(OH)$), 70.6 (CH_2O), 109.7 (OCHO), 127.5, 128.7, 131.2, 134.0 (C_{Ar}), 154.0 (C=N). Compound *trans*-2-**4i** ^1H NMR (400 MHz, $CDCl_3$) δ=1.20 ppm (d, *J*=7.7 Hz, 3H, CH_3CH), 3.56–3.59 (m, 2H, CH_2O), 3.62–3.68 (m, 3H, $CH_2(OH)CH(OH)$), 3.74 (qd, *J*=7.7 Hz, *J*=1.5 Hz, 1H, CH_3CH), 5.49 (d, *J*=1.5 Hz, 1H, OCHO), 7.49–7.74 (m, 3H, C_{Ar-H}). ^{13}C NMR (100 MHz, $CDCl_3$) δ=13.4 ppm (CH_3CH), 51.8 (CH_3CH), 63.6 ($CH_2(OH)CH(OH)$), 69.5 ($CH_2(OH)CH(OH)$), 70.5 (CH_2O), 109.6 (OCHO), 127.5, 128.7, 131.2, 134.0 (C_{Ar}), 154.1 (C=N). IR (film): 3388, 3080, 2937, 2878, 2501, 2236, 1869, 1677, 1580, 1560, 1432, 1316, 1109, 903, 852, 784, 728, 697 cm^{-1}. MS (ESI^+) *m*/*z* 342.0 $[M+Na]^+$, HRMS (ESI^+): calcd for $C_{13}H_{15}{}^{35}Cl_2NO_4Na$ $[M+Na]^+$ 342.0270 found 342.0260.

*4.4.14. 3-(2,6-Dichlorophenyl)-4-methyl-5-(oxiran-2-ylmethoxy)-4,5-dihydroisoxazole (**4j**).* Obtained as light yellow oil (250 mg, 66%); *trans*/*cis*=0.70; R_f (CH_2Cl_2)=0.63. Compound *cis*-1-**4j** ^1H NMR

(400 MHz, $CDCl_3$) δ=1.09 ppm (d, J=7.6 Hz, 3H, CH_3CH), 2.61 (dd, J=5.1 Hz, J=2.6 Hz, 1H, OCH$_2$CHCH_2), 2.79 (dd, J=5.1 Hz, J=4.4 Hz, 1H, OCH$_2$CHCH_2), 3.19–3.25 (m, 1H, OCH$_2$CHCH$_2$), 3.47 (dd, J=11.5 Hz, J=7.0 Hz, 1H, OCH_2CHCH$_2$), 3.85 (dq, J=6.6 Hz, J=7.6 Hz, 1H, CH$_3$CH), 4.14 (dd, J=11.5 Hz, J=2.8 Hz, 1H, OCH_2CHCH$_2$), 5.60 (d, J=6.6 Hz, 1H, OCHO), 7.29–7.39 (m, 3H, C_{Ar-H}). ^{13}C NMR (100 MHz, $CDCl_3$) δ=7.4 ppm (CH_3CH), 44.4 (OCH$_2$CHCH$_2$), 48.2 (OCH$_2$CHCH$_2$), 50.5 (CH$_3$CH), 69.7 (OCH$_2$CHCH$_2$), 103.9 (OCHO), 128.2, 131.2, 132.1, 135.5 (C_{Ar}), 159.3 (C=N). Compound *cis*-2-**4j** ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.13 ppm (d, J=7.6 Hz, 3H, CH_3CH), 2.61 (dd, J=5.1 Hz, J=2.6 Hz, 1H, OCH$_2$CHCH_2), 2.79 (dd, J=5.1 Hz, J=4.4 Hz, 1H, OCH$_2$CHCH_2), 3.19–3.25 (m, 1H, OCH$_2$CHCH$_2$), 3.50 (dd, J=11.5 Hz, J=6.8 Hz, 1H, OCH_2CHCH$_2$), 3.86 (dq, J=6.6 Hz, J=7.6 Hz, 1H, CH$_3$CH), 4.14 (dd, J=11.5 Hz, J=2.8 Hz, 1H, OCH_2CHCH$_2$), 5.65 (d, J=6.6 Hz, 1H, OCHO), 7.29–7.39 (m, 3H, C_{Ar-H}). ^{13}C NMR (100 MHz, $CDCl_3$) δ=7.4 ppm (CH_3CH), 44.2 (OCH$_2$CHCH$_2$), 48.2 (OCH$_2$CHCH$_2$), 50.9 (CH$_3$CH), 69.7 (OCH$_2$CHCH$_2$), 103.8 (OCHO), 128.3, 131.2, 132.0, 135.6 (C_{Ar}), 159.4 (C=N). Compound *trans*-1-**4j** ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.21 ppm (d, J=7.7 Hz, 3H, CH_3CH), 2.75 (dd, J=5.2 Hz, J=4.2 Hz, 1H, OCH$_2$CHCH_2), 2.84 (dd, J=5.2 Hz, J=2.5 Hz, 1H, OCH$_2$CHCH_2); 3.19–3.25 (m, 1H, OCH$_2$CHCH$_2$), 3.64 (qd, J=7.7 Hz, J=1.4 Hz, 1H, CH$_3$CH), 3.89 (dd, J=12.0 Hz, J=3.0 Hz, 1H, OCH_2CHCH$_2$), 3.99 (dd, J=12.0 Hz, J=3.5 Hz, 1H, OCH_2CHCH$_2$), 5.43 (d, J=1.4 Hz, 1H, OCHO), 7.29–7.39 (m, 3H, C_{Ar-H}). ^{13}C NMR (100 MHz, $CDCl_3$) δ=13.7 ppm (CH_3CH), 44.4 (OCH$_2$CHCH$_2$), 50.8 (CH$_3$CH), 52.1 (OCH$_2$CHCH$_2$), 67.0 (OCH$_2$CHCH$_2$), 109.4 (OCHO), 128.3, 131.1, 132.0, 135.5 (C_{Ar}), 159.2 (C=N). Compound *trans*-2-**4j** ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.20 ppm (d, J=7.6 Hz, 3H, CH_3CH), 2.75 (dd, J=5.2 Hz, J=4.2 Hz, 1H, OCH$_2$CHCH_2), 2.84 (dd, J=5.2 Hz, J=2.5 Hz, 1H, OCH$_2$CHCH_2), 3.19–3.25 (m, 1H, OCH$_2$CHCH$_2$), 3.59 (qd, J=7.6 Hz, J=1.4 Hz, 1H, CH$_3$CH), 3.90 (dd, J=12.0 Hz, J=3.0 Hz, 1H, OCH_2CHCH$_2$), 4.00 (dd, J=12.0 Hz, J=3.6 Hz, 1H, OCH_2CHCH$_2$), 5.39 (d, J=1.4 Hz, 1H, OCHO), 7.29–7.39 (m, 3H, C_{Ar-H}). ^{13}C NMR (100 MHz, $CDCl_3$) δ=13.6 ppm (CH_3CH), 44.5 (OCH$_2$CHCH$_2$), 50.4 (CH$_3$CH), 52.0 (OCH$_2$CHCH$_2$), 66.9 (OCH$_2$CHCH$_2$), 109.5 (OCHO), 128.4, 131.3, 131.9, 135.5 (C_{Ar}), 159.2 (C=N). IR (film): 3419, 3080, 2976, 2936, 2879, 2237, 1738, 1678, 1581, 1560, 1432, 1278, 1195, 1083, 852, 788, 729, 698 cm^{-1}. MS (ESI$^+$) m/z 324.0 $[M+Na]^+$, HRMS (ESI$^+$): calcd for $C_{13}H_{13}{}^{35}Cl_2NO_3Na$ $[M+Na]^+$ 324.0165 found 324.0152.

*4.4.15. 3-(2,6-Dichlorophenyl)-4-methyl-5-(tetrahydro-2H-pyran-2-yloxy)-4,5-dihydroisoxazole (**4k**).* Obtained as light yellow oil (252 mg, 62%); *trans*/*cis*=0.67; R_f (CH_2Cl_2)=0.65. Compound *cis*-1-**4k** ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.08 ppm (d, J=7.6 Hz, 3H, CH_3CH), 1.55–1.92 (m, 6H, CH$_2$CH$_2$CH$_2$), 3.58 (dq, J=6.9 Hz, J=7.6 Hz, 1H, CH$_3$CH), 3.81–3.93 (m, 2H, OCH$_2$), 4.98–4.99 (m, 1H, OCHOCHOCH$_2$), 5.81 (d, J=6.9 Hz, 1H, OCHOCHOCH$_2$), 7.28–7.68 (m, 3H, C_{Ar-H}). ^{13}C NMR (100 MHz, $CDCl_3$) δ=8.5 ppm (CH_3CH), 22.8 (CH$_2$CH$_2$CH$_2$), 25.5 (CH$_2$CH$_2$CH$_2$), 32.1 (CH$_2$CH$_2$CH$_2$), 46.9 (CH$_3$CH), 63.4 (OCH$_2$), 94.9 (OCHOCHOCH$_2$), 98.8 (OCHOCHOCH$_2$), 128.2, 128.5, 131.2, 135.9 (C_{Ar}), 159.4 (C=N). Compound *cis*-2-**4k** ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.16 ppm (d, J=7.5 Hz, 3H, CH_3CH), 1.55–1.92 (m, 6H, CH$_2$CH$_2$CH$_2$), 3.53–3.64 (m, 2H, OCH$_2$), 3.89 (dq, J=6.6 Hz, J=7.5 Hz, 1H, CH$_3$CH), 5.18–5.20 (m, 1H, OCHOCHOCH$_2$), 5.93 (d, J=6.6 Hz, 1H, OCHOCHOCH$_2$), 7.28–7.68 (m, 3H, C_{Ar-H}). ^{13}C NMR (100 MHz, $CDCl_3$) δ=7.6 ppm (CH_3CH), 22.8 (CH$_2$CH$_2$CH$_2$), 25.4 (CH$_2$CH$_2$CH$_2$), 31.7 (CH$_2$CH$_2$CH$_2$), 48.0 (CH$_3$CH), 62.6 (OCH$_2$), 94.8 (OCHOCHOCH$_2$), 99.0 (OCHOCHOCH$_2$), 128.3, 128.4, 131.2, 135.8 (C_{Ar}), 159.5 (C=N). Compound *trans*-1-**4k** ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.27 ppm (d, J=7.3 Hz, 3H, CH_3CH), 1.55–1.92 (m, 6H, CH$_2$CH$_2$CH$_2$), 3.53–3.64 (m, 2H, OCH$_2$), 3.84 (qd, J=7.3 Hz, J=2.0 Hz, 1H, CH$_3$CH), 5.02–5.04 (m, 1H, OCHOCHOCH$_2$), 5.58 (d, J=2.0 Hz, 1H, OCHOCHOCH$_2$), 7.28–7.68 (m, 3H, C_{Ar-H}). ^{13}C NMR (100 MHz, $CDCl_3$) δ=12.1 ppm (CH_3CH), 23.1 (CH$_2$CH$_2$CH$_2$), 25.6 (CH$_2$CH$_2$CH$_2$); 30.4 (CH$_2$CH$_2$CH$_2$), 48.1 (CH$_3$CH), 53.3 (OCH$_2$), 95.7 (OCHOCHOCH$_2$), 104.6 (OCHOCHOCH$_2$), 128.0, 128.5, 131.2, 135.9 (C_{Ar}), 159.1 (C=N). Compound *trans*-2-**4k** ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.22 ppm (d, J=7.7 Hz, 3H, CH_3CH), 1.55–1.92 (m, 6H, CH$_2$CH$_2$CH$_2$), 3.61 (qd, J=7.7 Hz, J=1.5 Hz, 1H, CH$_3$CH), 3.81–3.93 (m, 2H, OCH$_2$), 5.10–5.12 (m, 1H, OCHOCHOCH$_2$), 5.72 (d, J=1.5 Hz, 1H, OCHOCHOCH$_2$), 7.28–7.68 (m, 3H, C_{Ar-H}). ^{13}C NMR (100 MHz, $CDCl_3$) δ=11.6 ppm (CH$_3$CH), 22.9 (CH$_2$CH$_2$CH$_2$), 25.6 (CH$_2$CH$_2$CH$_2$), 29.8 (CH$_2$CH$_2$CH$_2$), 48.8 (CH$_3$CH), 52.1 (OCH$_2$), 95.8 (OCHOCHOCH$_2$), 104.9 (OCHOCHOCH$_2$), 128.3, 128.4, 131.2, 135.8 (C_{Ar}), 159.3 (C=N). IR (film): 3078, 2943, 2871, 2746, 2234, 2056, 1728, 1560, 1352, 1201, 1122, 1036, 967, 905, 856, 788, 723, 697 cm^{-1}. MS (ESI$^+$) m/z 352.0 $[M+Na]^+$, HRMS (ESI$^+$): calcd for $C_{15}H_{17}{}^{35}Cl_2NO_3Na$ $[M+Na]^+$ 352.0478 found 352.0479.

*4.4.16. 3-(2,6-Dichlorophenyl)-5-(O-α-D-galactopyranosyl)-4-methyl-4,5-dihydroisoxazole (**4l**).* Obtained as light yellow oil (320 mg, 58%); *trans*/*cis*=0.21. Compound *cis*-1-**4l** ^{1}H NMR (400 MHz, D_2O) δ=1.09 ppm (d, J=7.1 Hz, 3H, CH_3CH), 3.46–3.96 (m, 6H, CH(OH) CH(OH)CH(OH)CHCH$_2$(OH)), 3.92 (dq, J=6.6 Hz, J=7.1 Hz, 1H, CH$_3$CH), 5.32 (d, J=3.7 Hz, 1H, CH(OH)CHOCH), 5.96 (d, J=6.6 Hz, 1H, OCHO), 7.31–7.47 (m, 3H, C_{Ar-H}). ^{13}C NMR (100 MHz, DMSO-d_6) δ=7.0 ppm (CH$_3$CH), 42.1 (CH$_3$CH), 59.6 (CH$_2$OH–galactopyranose), 67.6 (CHOH–galactopyranose), 68.3 (CHOH–galactopyranose), 69.4 (CHOH–galactopyranose), 71.5 (CHCH$_2$OH–galactopyranose), 79.2 (OCHO–galactopyranose), 99.1 (OCHO), 128.4, 129.4, 131.3, 134.4 (C_{Ar}), 158.5 (C=N). Compound *cis*-2-**4l** ^{1}H NMR (400 MHz, D_2O) δ=1.06 ppm (d, J=7.2 Hz, 3H, CH_3CH), 3.46–3.96 (m, 6H, CH(OH) CH(OH)CH(OH)CHCH$_2$(OH)), 3.96 (dq, J=6.4 Hz, J=7.2 Hz, 1H, CH$_3$CH), 5.26 (d, J=3.7 Hz, 1H, CH(OH)CHOCH), 5.88 (d, J=6.4 Hz, 1H, OCHO), 7.31–7.47 (m, 3H, C_{Ar-H}). ^{13}C NMR (100 MHz, DMSO-d_6) δ=8.4 ppm (CH$_3$CH), 45.6 (CH$_3$CH), 60.6 (CH$_2$OH–galactopyranose), 67.7 (CHOH–galactopyranose), 68.3 (CHOH–galactopyranose), 69.4 (CHOH–galactopyranose), 72.3 (CHCH$_2$OH–galactopyranose), 79.6 (OCHO–galactopyranose), 99.7 (OCHO), 128.6, 129.1, 131.4, 134.1 (C_{Ar}), 158.7 (C=N). Compound *trans*-1-**4l** ^{1}H NMR (400 MHz, D_2O) δ=1.04 ppm (d, J=6.8 Hz, 3H, CH_3CH), 3.46–3.96 (m, 6H, CH(OH) CH(OH)CH(OH)CHCH$_2$(OH)), 4.10 (qd, J=6.8 Hz, J=1.5 Hz, 1H, CH$_3$CH), 5.24 (d, J=3.70 Hz, 1H, CH(OH)CHOCH), 5.75 (d, J=1.5 Hz, 1H, OCHO), 7.31–7.47 (m, 3H, C_{Ar-H}). ^{13}C NMR (100 MHz, DMSO-d_6) δ=12.1 ppm (CH$_3$CH), 47.4 (CH$_3$CH), 60.6 (CH$_2$OH–galactopyranose), 66.2 (CHOH–galactopyranose), 68.1 (CHOH–galactopyranose), 68.7 (CHOH–galactopyranose), 71.3 (CHCH$_2$OH–galactopyranose), 95.1 (OCHO–galactopyranose), 103.8 (OCHO), 128.0, 129.2, 131.9, 134.5 (C_{Ar}), 165.0 (C=N). Compound *trans*-2-**4l** ^{1}H NMR (400 MHz, D_2O) δ=1.02 ppm (d, J=7.0 Hz, 3H, CH_3CH), 3.46–3.96 (m, 6H, CH(OH) CH(OH)CH(OH)CHCH$_2$(OH)), 4.05 (qd, J=7.0 Hz, J=0.9 Hz, 1H, CH$_3$CH), 5.31 (d, J=3.7 Hz, 1H, CH(OH)CHOCH), 5.69 (d, J=0.9 Hz, 1H, OCHO), 7.31–7.47 (m, 3H, C_{Ar-H}). ^{13}C NMR (100 MHz, DMSO-d_6) δ=13.4 ppm (CH$_3$CH) 47.6 (CH$_3$CH), 60.6 (CH$_2$OH–galactopyranose), 67.5 (CHOH–galactopyranose), 68.2 (CHOH–galactopyranose), 68.8 (CHOH–galactopyranose), 71.4 (CHCH$_2$OH–galactopyranose), 97.9 (OCHO–galactopyranose), 105.9 (OCHO), 128.3, 129.1, 131.9, 134.5 (C_{Ar}), 165.3 (C=N). IR (film): 3399, 3074, 2922, 1605, 1581, 1560, 1431, 1384, 1328, 1243, 1149, 1074, 1037, 911, 870, 786, 723, 693 cm^{-1}. MS (ESI$^+$) m/z=430.0 $[M+Na]^+$, HRMS (ESI$^+$): calcd for $C_{16}H_{19}{}^{35}Cl_2NO_7Na$ $[M+Na]^+$ 430.0431 found 430.0421.

*4.4.17. 4-Methyl-5-phenoxy-3-phenyl-4,5-dihydroisoxazol (**9f**).* Obtained as white solid (110 mg, 34%); mp=68 °C; *trans*/*cis*=1.00; R_f (toluene)=0.58. Compound *cis*-**9f** ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.44 ppm (d, J=7.5 Hz, 3H, CH_3CH), 3.94 (dq, J=7.1 Hz, J=7.5 Hz, 1H, CH$_3$CH), 6.18 (d, J=7.1 Hz, 1H, OCHO), 7.04–7.64 (m, 5H+5H, C_{Ar-H}). ^{13}C NMR (100 MHz, $CDCl_3$) δ=9.8 ppm (CH$_3$CH), 46.2 (CH$_3$CH), 102.7 (OCHO), 117.0, 122.7, 127.5, 128.6, 128.7, 129.5, 130.1, 156.7 (C_{Ar}), 161.5 (C=N). Compound *trans*-**9f** ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.38 ppm (d, J=7.6 Hz, 3H, CH_3CH), 3.81 (qd, J=7.6 Hz, J=0.9 Hz, 1H, CH$_3$CH), 5.88 (d, J=0.9 Hz, 1H, OCHO),

7.07–7.77 (m, 5H+5H, C_{Ar-H}). ^{13}C NMR (100 MHz, $CDCl_3$) δ=14.9 ppm (CH_3CH), 49.1 (CH_3CH), 107.3 (OCHO), 116.8, 122.5, 127.2, 127.8, 128.9, 129.5, 130.4, 156.3 (C_{Ar}), 161.9 (C=N). IR (film): 3060, 3040, 2948, 2923, 2851, 1640, 1598, 1587, 1456, 1359, 1224, 1120, 1085, 1036, 916, 870, 840, 752, 693, 673 cm^{-1}. MS (ESI^+) *m*/*z* 254.1 $[M+H]^+$, 276.1 $[M+Na]^+$, HRMS (ESI^+): calcd for $C_{16}H_{15}NO_2Na$ $[M+Na]^+$ 276.0995 found 276.0996.

*4.4.18. 3-(2-Methoxyphenyl)-4-methyl-5-phenoxy-4,5-dihydroisoxazol (**10f**).* Obtained as light yellow oil (270 mg, 74%); *trans*/*cis*=0.63; R_f (CH_2Cl_2)=0.53. Compound *cis*-**10f** ^1H NMR (400 MHz, $CDCl_3$) δ=1.24 ppm (d, *J*=7.4 Hz, 3H, CH_3CH), 3.83 (s, 3H, CH_3O), 4.12 (dq, *J*=7.1 Hz, *J*=7.4 Hz, 1H, CH_3CH), 6.10 (d, *J*=7.1 Hz, 1H, OCHO), 6.93–7.56 (m, 5H+4H, C_{Ar-H}). ^{13}C NMR (100 MHz, $CDCl_3$) δ=8.7 ppm (CH_3CH), 47.9 (CH_3CH), 55.3 (CH_3O), 102.4 (OCHO), 110.9, 116.9, 120.9, 122.4, 129.4, 130.5, 131.5, 131.9, 156.8, 157.1 (C_{Ar}), 162.2 (C=N). Compound *trans*-**10f** ^1H NMR (400 MHz, $CDCl_3$) δ=1.23 ppm (d, *J*=7.6 Hz, 3H, CH_3CH), 3.87 (s, 3H, CH_3O), 4.14 (qd, *J*=7.6 Hz, *J*=1.3 Hz, 1H, CH_3CH), 5.88 (d, *J*=1.3 Hz, 1H, OCHO), 6.93–7.56 (m, 5H+4H, C_{Ar-H}). ^{13}C NMR (100 MHz, $CDCl_3$) δ=14.5 ppm (CH_3CH), 51.1 (CH_3CH), 55.5 (CH_3O), 107.4 (OCHO), 111.5, 116.8, 120.8, 122.3, 129.4, 130.2, 131.5, 131.7, 156.8, 157.0 (C_{Ar}), 161.4 (C=N). IR (film): 3068, 3039, 2941, 2878, 2838, 2036, 1688, 1599, 1492, 1465, 1340, 1223, 1116, 1024, 839, 755, 692, 646 cm^{-1}. MS (ESI^+) *m*/*z* 284.1 $[M+H]^+$, 306.1 $[M+Na]^+$, HRMS (ESI^+): calcd for $C_{17}H_{18}NO_3$ $[M+H]^+$ 284.1281 found 284.1270, calcd for $C_{17}H_{17}NO_3Na$ $[M+Na]^+$ 306.1101 found 306.1096.

*4.4.19. 4-Methyl-3-(4-nitrophenyl)-5-phenoxy-4,5-dihydroisoxazol (**11f**).* Obtained as light yellow solid (58 mg, 15%); mp=98 °C; *trans*/*cis*=1.52; R_f (CH_2Cl_2)=0.65. Compound *cis*-**11f** ^1H NMR (400 MHz, $CDCl_3$) δ=1.48 ppm (d, *J*=7.5 Hz, 3H, CH_3CH), 3.98 (dq, *J*=7.2 Hz, *J*=7.5 Hz, 1H, CH_3CH), 6.26 (d, *J*=7.2 Hz, 1H, OCHO), 7.06–8.33 (m, 5H+4H, C_{Ar-H}). ^{13}C NMR (100 MHz, $CDCl_3$) δ=9.7 ppm (CH_3CH), 45.6 (CH_3CH), 107.9 (OCHO), 116.9, 123.0, 124.1, 128.3, 128.5, 129.6, 134.8, 156.4 (C_{Ar}), 159.8 (C=N). Compound *trans*-**11f** ^1H NMR (400 MHz, $CDCl_3$) δ=1.41 ppm (d, *J*=7.6 Hz, 3H, CH_3CH), 3.85 (qd, *J*=7.6 Hz, *J*=0.9 Hz, 1H, CH_3CH), 5.96 (d, *J*=0.9 Hz, 1H, OCHO), 7.06–8.33 (m, 5H+4H, C_{Ar-H}). ^{13}C NMR (100 MHz, $CDCl_3$) δ=14.7 ppm (CH_3CH), 48.5 (CH_3CH), 103.2 (OCHO), 116.8, 122.9, 124.0, 128.3, 128.5, 129.6, 134.8, 156.1 (C_{Ar}), 160.0 (C=N). IR (film): 3102, 3068, 3054, 2959, 2923, 2850, 2230, 1707, 1606, 1570, 1524, 1347, 1290, 1262, 1197, 1106, 1013, 852, 729, 682 cm^{-1}. MS (ESI^+) *m*/*z* 299.1 $[M+H]^+$, 321.1 $[M+Na]^+$, 619.2 $[2M+Na]^+$, HRMS (ESI^+): calcd for $C_{16}H_{14}N_2O_4Na$ $[M+Na]^+$ 321.0846 found 321.0847.

*4.4.20. 2-(4-Methyl-5-phenoxy-4,5-dihydroisoxazol)pyridine (**12f**).* Obtained as light yellow oil (100 mg, 34%); *trans*/*cis*=2.40; R_f (CH_2Cl_2)=0.68. Compound *cis*-**12f** ^1H NMR (400 MHz, $CDCl_3$) δ=1.58 ppm (d, *J*=7.4 Hz, 3H, CH_3CH), 4.09 (dq, *J*=7.3 Hz, *J*=7.4 Hz, 1H, CH_3CH), 6.22 (d, *J*=7.3 Hz, 1H, OCHO), 6.78–8.59 (m, 5H+4H, C_{Ar-H}). ^{13}C NMR (100 MHz, $CDCl_3$) δ=9.4 ppm (CH_3CH), 46.3 (CH_3CH), 103.3 (OCHO), 117.0, 122.7, 123.0, 124.3, 129.6, 136.5, 149.2, 156.8 (C_{Ar}), 161.8 (C=N). Compound *trans*-**12f** ^1H NMR (400 MHz, $CDCl_3$) δ=1.47 ppm (d, *J*=7.5 Hz, 3H, CH_3CH), 4.05 (qd, *J*=7.5 Hz, *J*=1.0 Hz, 1H, CH_3CH), 5.92 (d, *J*=1.0 Hz, 1H, OCHO), 7.02–8.67 (m, 5H+4H, C_{Ar-H}). ^{13}C NMR (100 MHz, $CDCl_3$) δ=14.8 ppm (CH_3CH), 49.2 (CH_3CH), 107.7 (OCHO), 116.8, 122.4, 122.6, 124.5, 129.5, 136.7, 148.3, 149.4, 156.4 (C_{Ar}), 163.3 (C=N). IR (film): 3063, 2963, 2937, 2877, 2233, 1717, 1587, 1495, 1471, 1361, 1222, 1115, 1041, 957, 843, 789, 755, 696 cm^{-1}. MS (ESI^+) *m*/*z* 255.1 $[M+H]^+$, 277.1 $[M+Na]^+$, 531.2 $[2M+Na]^+$, HRMS (ESI^+): calcd for $C_{15}H_{15}NO_2$ $[M+H]^+$ 255.1128 found 255.1126.

*4.4.21. 3-(2,6-Dichlorophenyl)-4-methyl-5-(phenylthio)-4,5-dihydroisoxazole (**13m**).* Obtained as light yellow oil (218 mg, 50%); *trans*/*cis*=0.94; R_f (toluene)=0.46. Compound *cis*-**13m** ^1H NMR (400 MHz, $CDCl_3$) δ=1.25 ppm (d, *J*=7.4 Hz, 3H, CH_3CH), 4.20 (dq, *J*=9.2 Hz, *J*=7.4 Hz, 1H, CH_3CH), 6.22 (d, *J*=9.2 Hz, 1H, OCHS), 7.09–7.59 (m, 5H+3H, C_{Ar-H}). ^{13}C NMR (100 MHz, $CDCl_3$) δ=9.1 ppm (CH_3CH), 43.8 (CH_3CH), 80.1 (OCHS), 128.2, 128.3, 128.5, 128.7, 129.1, 129.2, 131.8, 132.1 (C_{Ar}), 153.8 (C=N). Compound *trans*-**13m** ^1H NMR (400 MHz, $CDCl_3$) δ=1.25 ppm (d, *J*=7.4 Hz, 3H, CH_3CH), 3.71 (dq, *J*=6.5 Hz, *J*=7.4 Hz, 1H, CH_3CH), 5.72 (d, *J*=6.5 Hz, 1H, OCHS), 7.09–7.59 (m, 5H+3H, C_{Ar-H}). ^{13}C NMR (100 MHz, $CDCl_3$) δ=9.10 ppm (CH_3CH), 43.6 (CH_3CH), 81.2 (OCHS), 127.6, 128.8, 128.3, 128.5, 129.1, 129.2, 131.7, 132.0 (C_{Ar}), 153.6 (C=N). IR (film): 3076, 3059, 2975, 2933, 2874, 2240, 1711, 1559, 1480, 1430, 1317, 1194, 1095, 1026, 864, 781, 743, 692 cm^{-1}. MS (ESI^+) *m*/*z* 359.9 $[M+Na]^+$, HRMS (ESI^+): calcd for $C_{16}H_{13}{}^{35}Cl_2NSONa$ $[M+Na]^+$ 359.9987 found 359.9994.

*4.4.22. 3-(2,6-Dichlorophenyl)-5-methyl-4-(phenylthio)-4,5-dihydroisoxazole (**14m**).* Obtained as light yellow oil (26 mg, 7%); *trans*/*cis*=2.00; R_f (toluene)=0.65. Compound *cis*-**14m** ^1H NMR (400 MHz, $CDCl_3$) δ=1.60 (d, *J*=6.3 Hz, 3H, CH_3CH), 5.02 (dq, *J*=8.8 Hz, *J*=6.3 Hz, 1H, CH_3CH), 5.14 (d, *J*=8.8 Hz, 1H, OCHS), 7.09–7.60 (m, 5H+3H, C_{Ar-H}). ^{13}C NMR (100 MHz, $CDCl_3$) δ=19.5 ppm (CH_3CH), 47.2 (CH_3CH), 79.9 (OCHS), 127.1, 128.0, 128.7, 129.5, 129.6, 129.9, 131.4, 131.6 (C_{Ar}), 153.1 (C=N). Compound *trans*-**14m** ^1H NMR (400 MHz, $CDCl_3$) δ=1.80 (d, *J*=6.8 Hz, 3H, CH_3CH), 4.86 (dq, *J*=5.8 Hz, *J*=6.8 Hz, 1H, CH_3CH), 4.75 (d, *J*=5.8 Hz, 1H, OCHS), 7.09–7.60 (m, 5H+3H, C_{Ar-H}). ^{13}C NMR (100 MHz, $CDCl_3$) δ=19.2 ppm (CH_3CH), 47.6 (CH_3CH), 81.0 (OCHS), 127.2, 128.1, 128.5, 129.3, 129.4, 129.5, 131.3, 131.5 (C_{Ar}), 153.0 (C=N). IR (film): 3076, 3059, 2975, 2933, 2874, 2240, 1711, 1559, 1480, 1430, 1317, 1194, 1095, 1026, 864, 781, 743, 692 cm^{-1}. MS (ESI^+) *m*/*z* 359.9 $[M+Na]^+$, HRMS (ESI^+): calcd for $C_{16}H_{13}{}^{35}Cl_2NSONa$ $[M+Na]^+$ 359.9987 found 359.9997.

*4.4.23. 3-(2,6-Dichlorophenyl)-4-methyl-5-(phenylseleno)-4,5-dihydroisoxazole (**15n**).* Obtained as red oil (201 mg, 41%); *trans*/*cis*=1.00; R_f (CH_2Cl_2)=0.80. Compound *cis*-**15n** ^1H NMR (400 MHz, $CDCl_3$) δ=1.15 ppm (d, *J*=7.4 Hz, 3H, CH_3CH), 4.04 (dq, *J*=8.9 Hz, *J*=7.4 Hz, 1H, CH_3CH), 6.42 (d, *J*=8.9 Hz, 1 Hz, OCHSe), 6.99–7.44 (m, 5H+3H, C_{Ar-H}). ^{13}C NMR (100 MHz, $CDCl_3$) δ=8.5 ppm (CH_3CH), 52.8 (CH_3CH), 80.7 (OCHSe), 126.5, 128.2, 129.1, 129.7, 131.2, 131.4, 133.0, 133.7 (C_{Ar}), 155.5 (C=N). Compound *trans*-**15n** ^1H NMR (400 MHz, $CDCl_3$) δ=1.12 ppm (d, *J*=7.3 Hz, 3H, CH_3CH), 3.69 (dq, *J*=6.3 Hz, *J*=7.3 Hz, 1H, CH_3CH), 5.85 (d, *J*=6.3 Hz, 1H, OCHSe), 6.99–7.44 (m, 5H+3H, C_{Ar-H}). ^{13}C NMR (100 MHz, $CDCl_3$) δ=12.5 ppm (CH_3CH), 49.3 (CH_3CH), 85.5 (OCHSe), 126.6, 128.1, 129.6, 130.2, 131.1, 131.3, 131.4, 134.7 (C_{Ar}), 153.5 (C=N). IR (film): 3070, 3056, 2969, 2910, 2823, 2236, 1713, 1606, 1560, 1475, 1431, 1352, 1250, 1195, 1021, 962, 841, 787, 734, 689 cm^{-1}. MS (ESI^+) *m*/*z* 384.9 $[M]^+$, HRMS (ESI^+): calcd for $C_{16}H_{13}{}^{35}Cl_2SeNO$ 384.9539 $[M]^+$ found 384.9552.

*4.4.24. 3-(2,6-Dichlorophenyl)-5-methyl-4-(phenylseleno)-4,5-dihydroisoxazole (**16n**).* Obtained as red oil (101 mg, 21%); *trans*/*cis*=1.82; R_f (CH_2Cl_2)=0.70. Compound *cis*-**16n** ^1H NMR (400 MHz, $CDCl_3$) δ=1.54 ppm (d, *J*=6.3 Hz, 3H, CH_3CH), 4.84 (dq, *J*=8.6 Hz, *J*=6.3 Hz, 1H, CH_3CH), 5.03 (d, *J*=8.6 Hz, 1H, OCHSe), 6.99–7.44 (m, 5H+3H, C_{Ar-H}). ^{13}C NMR (100 MHz, $CDCl_3$) δ=17.1 ppm (CH_3CHO), 56.3 (CH_3CHO), 91.0 (CHSe), 127.3, 128.1, 129.2, 129.7, 131.1, 131.3, 134.1, 134.3 (C_{Ar}), 159.4 (C=N). Compound *trans*-**16n** ^1H NMR (400 MHz, $CDCl_3$) δ=1.33 ppm (d, *J*=6.4 Hz, 3H, CH_3CH), 4.65 (d, *J*=4.9 Hz, 1H, OCHSe), 4.90 (dq, *J*=4.9 Hz, *J*=6.4 Hz, 1H, CH_3CH), 6.99–7.44 (m, 5H+3H, C_{Ar-H}). ^{13}C NMR (100 MHz, $CDCl_3$) δ=16.5 ppm (CH_3CHO), 54.8 (CH_3CHO), 89.3 (CHSe), 127.1, 128.1, 128.9, 129.6, 131.0, 131.3, 135.0, 135.1 (C_{Ar}), 159.8 (C=N). IR (film): 3070, 3056, 2969, 2910, 2823, 2236, 1713, 1606, 1560, 1475, 1431,

1352, 1250, 1195, 1021, 962, 841, 787, 734, 689 cm^{-1}. MS (ESI^+) *m/z* 384.9 $[M]^+$, HRMS (ESI^+): calcd for $C_{16}H_{13}{}^{35}Cl_2SeNO$ 384.9539 $[M]^+$ found 384.9550.

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