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Synthesis of 5-aminoisoxazolines from *N*-allyl compounds and nitrile oxides via tandem isomerization-1,3-dipolar cycloaddition

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ABSTRACT

A new strategy for the synthesis of derivatives of 5-aminoisoxazolines via tandem catalytic isomerization (of *N*-allyl systems to *N*-(1-propenyl) systems)—1,3-dipolar cycloaddition (of a stable nitrile oxide to *N*-(1-propenyl) systems) is presented. Rhodium and ruthenium complexes, Verkade's superbase, and 18-crown-6/KOH system were used for the syntheses of the *N*-(1-propenyl) systems. 4-*P*-substituted isoxazoline was also synthesized via cycloaddition of diphenyl(1-propenyl)phosphine (prepared via isomerization of allyldiphenylphosphine) to 2,6-dichlorobenzonitrile oxide. All cycloadditions were regioselective but not stereoselective and not concerted. Cycloaddition to all *N*-(1-propenyl) systems yielded 5-*N*-substituted isoxazolines, but cycloaddition to *P*-(1-propenyl) system lead to the formation of a 4-*P*-regioisomer. This difference in regioselectivity is predicted by opposite FMO reactivity indices calculated for model compounds: *N*-(1-propenyl)amine and *N*-(1-propenyl)phosphine.

1. Introduction

Substituted isoxazolines constitute an important class of compounds having a well-known but still investigated biological activity. Functionalized isoxazolines appear in papers on neurotransmitters,[1,2] and are used in the treatment of addictions, epilepsy, stroke, schizophrenia, and Parkinson's disease. Moreover, their activity as immunosuppressants[3] and blood coagulation factor Xa inhibitors,[4] as well as antibiotics of a broad antibacterial spectrum against both Gram-positive and Gram-negative bacteria[5] has been investigated. They are being tested for their antiviral properties, including HIV inhibition.[6] Isoxazoline rings are fundamental structural motifs of novel anti-tuberculosis agents[7] for the treatment of latent and drug-resistant *Mycobacterium tuberculosis* infections. A 5-*N*-substituted isoxazoline was studied as a protein tyrosine phosphatase 1B inhibitor, a potential drug for type-2 diabetes.[8] Isoxazolines are also used in the organic synthesis—as starting materials for syntheses of β-hydroxynitriles,[9] β-hydroxyketones,[10] β-hydroxyacids,[11] and β-aminoacids.[12]

Isoxazolines (including 5-*N*-substituted ones) are most often obtained by 1,3-dipolar cycloaddition of nitrile oxides to functionalized alkenes.[13,14] In the preparation of 5-*N*-substituted isoxazolines *N*-substituted unsaturated cyclic systems,[15–17] butadienylamines,[18] or *N*-vinylimidazole[8] served as dipolarophiles. Some 5-aminoisoxazolines were obtained in the reaction of *N*-cyclopropyl-*N*-alkylanilines with HNO_2.[19]

In the present work we demonstrated a new strategy for the synthesis of derivatives of 5-aminoisoxazolines: the 1,3-dipolar cycloaddition of nitrile oxides to *N*-(1-propenyl) systems, which are obtained by isomerization of respective *N*-allyl systems. This tandem reaction allows an easy preparation of many novel 5-*N*-substituted isoxazolines unavailable by other routes. We have proved its utility earlier, by showing new possibilities for the synthesis of 5-*O*- and 5-*S*-substituted isoxazolines.[20,21] In this paper we also analyze the mechanism of cycloaddition and, its regioselectivity in particular.

2. Results and discussion

The idea of a new strategy of the synthesis of 5-*N*-substituted isoxazolines from *N*-allyl compounds and stable nitrile oxide is shown in Scheme 1.

In the studied reactions, usually 2,6-dichloro-, 2,4,6-trimethyl-, and 2,4,6-trimethoxybenzonitrile oxide, which is one of the most stable nitrile oxides,[22] were used as the 1,3-dipoles. They were generated in situ from the corresponding oximoyl chlorides, in the reaction with triethylamine in methylene

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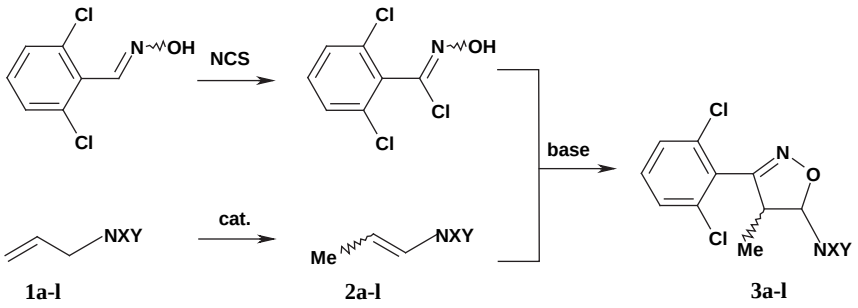


Scheme 1. Tandem: Isomerization (of *N*-allyl systems to *N*-(1-propenyl) systems)—Cycloaddition (of 2,6-dichlorobenzonitrile oxide to *N*-(1-propenyl) systems), for the synthesis of 5-aminoisoxazoline derivatives.

chloride[13,23] (or with Verkade's superbase, 2,8,9-triisopropyl-2,5,8,9-tetraza-1-phosphabicyclo[3.3.3]undecane). The oximoyl chlorides were, in turn, obtained in the reaction of appropriate oximes with NCS, in the presence of a catalytic amount of HCl.[14] The dipolarophiles, i.e., the *N*-(1-propenyl) systems (**2a**–**l**), were prepared via isomerization of the respective *N*-allyl systems (**1a**–**l**). All *N*-(1-propenyl) systems except **2i** and **2j** (see Table 1) were synthesized as described in our earlier papers,[24–32] via isomerization of respective allyl systems in the presence of $[RuHCl(CO)(PPh_3)_3]$ or $[RhH(CO)(PPh_3)_3]$. On the other hand, the dipolarophiles **2i** and **2j** were obtained by isomerization reactions of the corresponding *N*-allyl compounds, catalysed by 18-crown-6/KOH or/and Verkade's superbase, isomerization of **1i** being the first successful quantitative and stereoselective isomerization of *N*-allylazole (Table 1). Catalytic system consisting of 18-crown-6/KOH was particularly effective for the synthesis of **2i**, but not for **2j**, for which Verkade's superbase was needed. It is puzzling that the 18-crown-6/KOH system did not work in the synthesis of **2j** (it decomposed substrate **1j**), despite the fact that isomerization of **1k** to **2k** was quantitative in the presence of this system (see Table 1). 18-Crown-6/KOH was used previously for isomerization of a series of *N*-allylimines to 2-aza-1,3-dienes.[33] Furthermore, rhodium and ruthenium complexes, which are active isomerization catalysts for many *N*-allyl compounds, were completely ineffective or hardly effective for the synthesis of **2i** and **2j**. Moreover, *t*-BuOK (in DMSO) did not catalyze isomerizations leading to **2i** and **2j**. The successful preparations of **2i** (only the *Z* isomer) and **2j** are the first examples of isomerization of *N*-allyl compounds catalyzed by Verkade's superbase (2,8,9-triisopropyl-2,5,8,9-tetraza-1-phosphabicyclo [3.3.3]undecane), which was used before for a transesterification reaction.[34,35] Verkade's superbase was also applied in the synthesis of **2i** and the 2-aza-1,3-diene was obtained with the same yield as with $[RhH(CO)(PPh_3)_3]$, but with a different stereoselectivity (the *Z* isomer prevailed)—see Table 1. It is interesting to note that the superbase was used in a stoichiometric amount for the isomerization of **1i**, **1j**, and **1k** to, respectively, **2i**, **2j**, and **2k** and then it served also as the base in the cycloaddition step, generating the nitrile oxide. In these three cases the addition of triethylamine (as in the rest of the cycloadditions) was unnecessary.

We have started the studies on cycloaddition from checking if the nitrile oxides we used are stable in the conditions of cycloaddition reaction (in the presence of a base but in the absence of a dipolarophile) and, in particular, if they undergo dimerization. It was found that 2,4,6-trimethyl- and 2,4,6-trimethoxybenzonitrile oxides do not undergo dimerization or any other transformation during 24 h at room temperature in the CH_2Cl_2 solution. In turn, only 5% of 2,6-dichlorobenzonitrile oxide dimerized while other transformations were not observed, either.

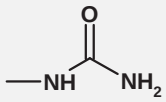
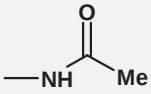
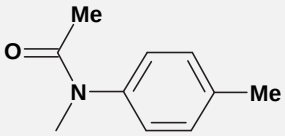
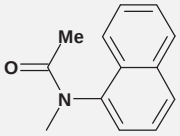
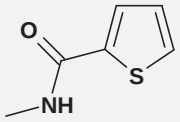
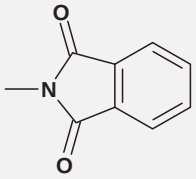
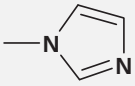
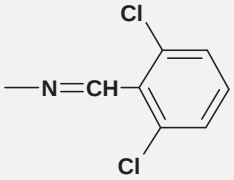
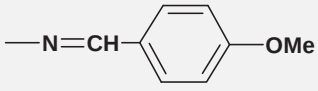
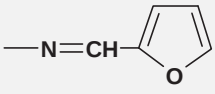
The results of the syntheses of 5-aminoisoxazolines **3a**–**l** (Scheme 1) are collected in Table 2. Apparently, all reactions are strictly regioselective. It is noteworthy that in the case of addition to 2-aza-1,3-dienes only 3,4-addition products (addition to C=C) are observed. 1,2-Adducts (to C=N) or 1,4-adducts are not formed at all. An analogous regioselectivity has been observed by Caramella and Bianchessi for the cycloaddition of benzonitrile oxide to 1-dimethylamino-1,3-butadiene.[18] Both for 2-aza-1,3-dienes and 1-dialkylamino-1,3-butadiene the addition is to the C=C bond conjugated with the nitrogen atom lone pair.

In almost all (except one, **3l**) the reactions studied, *E*/*Z* (in the dipolarophile) and trans/cis (in the adduct) ratios were completely different. This means that the investigated cycloadditions are not concerted reactions, but consist of at least two steps. Also the result received for **2a**, in the case of which a *cis*-adduct is obtained from a *E*-dipolarophile, confirms this conclusion: the rotation of the C–C bond is required. These results are in full accord with our previous research on the synthesis of 5-*O*-, 5-*Si*-, and 5-*S*-substituted isoxazolines.[20,21] Generally, 1,3-dipolar cycloadditions of nitrile oxides and related dipoles to the double bond can either be concerted (and stereospecific) or stepwise (and nonstereospecific), depending on the character and relative energies of FMOs of both reactants, which also, together with partial charge distribution, determine the regioselectivity.[36] Therefore, the regioselectivity and nonconcertedness of the reactions studied here stem from the charge distribution and FMOs of the nitrile oxide and *N*-(1-propenyl) dipolarophiles. Partial charges and frontier MOs of nitrile oxides [37] and some enamines and enamides [38] have been discussed before. In our opinion in the first step of the reaction the carbon–carbon bond is formed and only in the second step the carbon–oxygen is formed (see Scheme 2) Moreover, when the C–C bond is formed first, the transient product is formed, which is more stabilized. In the transient product [TP] (see Scheme 2) rotation of the C–C bond is possible and therefore formation of both stereoisomeric dihydroisoxazoles is observed (even when the dipolarophile is a single isomer). Another mechanism is also possible: the oxygen atom (being more nucleophilic than nitrogen) attacks the carbon atom of the double bond. An anion intermediate is formed, in which rotation around the C–C bond is possible, as in the intermediate discussed previously. Such mechanism was suggested by Huisgen for the regioselective but nonstereoselective cycloaddition of thiocarbonyl ylides to dimethyl 3,4-dicyanofumarate.[39]

We have also found that 2,4,6-trimethylbenzonitrile oxide and 2,4,6-trimethoxybenzonitrile oxide easily undergo cycloaddition to **2h**—see Scheme 3. This fact leads to the conclusion that our method of the synthesis of 5-*N*-substituted isoxazolines is of general applicability.

We have also found that the synthesis of 4-*P*-substituted isoxazolines from *P*-allyl compounds is also possible—see Scheme 4. Interestingly, the isomerization of diphenylallylphosphine to the

Table 1
The isomerization of *N*-allyl systems (CH_2=$CHCH_2NXY$) to *N*-(1-propenyl) systems (CH_3CH=$CHNXY$)

N-allyl systems		Catalyst	t[°C] (τ[h])	*N*-(1-propenyl) systems yield [%] (*E*/*Z*)
1a	$-NMe_2$	[Rh][a]	60 (2)	99 (only *E*)
1b	$-N(i\text{-Pr})_2$	[Rh][a]	80 (2)	99 (only *E*)
1c		[Ru][b]	80 (3)	99 (1.00)
1d		[Ru][c]	80 (2)	99 (1.40)
1e		[Ru][c]	80 (3)	99 (only *E*)
1f		[Ru][c]	80 (3)	99 (only *E*)
1g		[Ru][c]	70 (3)	99 (1.50)
1h		[Ru][c]	60 (3)	99 (only *E*)
1i		[Rh][a]	80 (4)	0 (—)
		Verkade's base[d]	140 (24)	68 (only *Z*)
		18-crown-6/KOH[e]	rt (24)	100 (only *E*)
1j		[Rh][a]	100 (4)	20 (0.20)
		Verkade's base[d]	60 (4)	99 (1.30)
		18-crown-6/KOH[e]	rt (24)	0 (—)[f]
1k		[Rh][a]	100 (3)	99 (0.5)
		Verkade's base[g]	120 (4)	99 (2.00)
		18-crown-6/KOH[e]	rt (24)	100 (1.20)
1l		[Rh][a]	100 (3)	99 (0.60)

[a] $[RhH(CO)(PPh_3)_3]$ (2 mol %) in C_6D_6 (1 mL/1 mmol substrate).
[b] $[RuClH(CO)(PPh_3)_3]$ (1 mol %) in THF (1 mL/1 mmol substrate).
[c] $[RuClH(CO)(PPh_3)_3]$ (1 mol %) in C_6D_6 (1 mL/1 mmol substrate).
[d] DMSO (50 mol %, 1 mL/1 mmol substrate).
[e] CH_2=$CHCH_2NXY$/KOH=1:3 (1 mL C_6D_6/1 mmol substrate).
[f] Decomposition of allyl substrate.
[g] Without solvent (50 mol %).

Table 2
Synthesis of derivatives of 5-aminoisoxazolines via 1,3-dipolar cycloaddition of 2,6-$Cl_2C_6H_3CNO$ to $CH_3CH{=}CHNXY$[a]

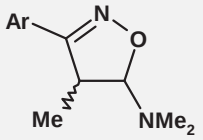
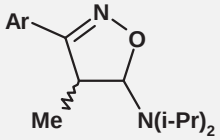
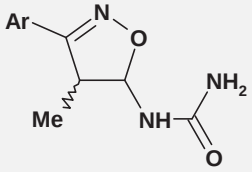
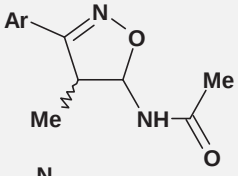
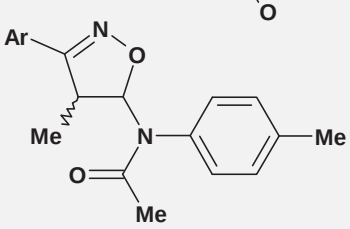
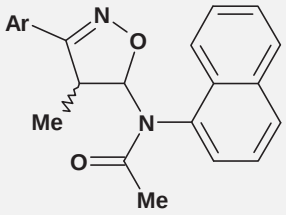
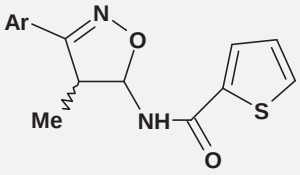
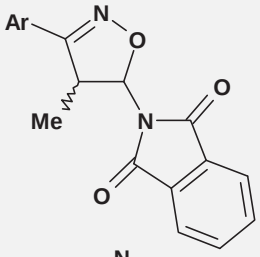
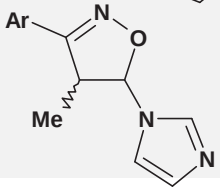
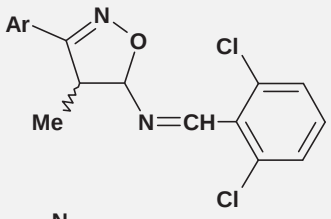
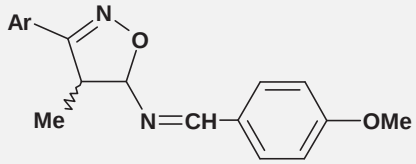
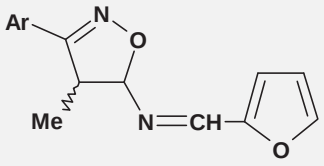
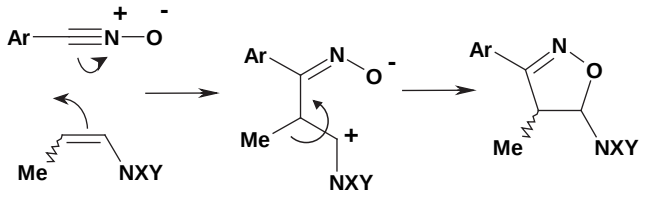
Isoxazolines		trans/cis (yield)[b]
3a		Only cis (75)
3b		0.31 (70)
3c		0.30 (70)
3d		0.71 (75)
3e		0.20 (80)
3f		0.19 (95)
3g		0.30 (80)
3h		0.18 (80)
3i		1.25 (75)

Table 2 (*continued*)

Isoxazolines		trans/cis (yield)[b]
3j		0.59 (80)
3k		0.90 (85) 0.12 (75)
3l		0.62 (70)

[a] Reaction conditions: rt, 24 h, 2,6-$Cl_2C_6H_3CNO$/$CH_3CH{=}CHNXY$/Et_3N=1:1:3; conversion: 100% in all cases.
[b] Isolated yield.

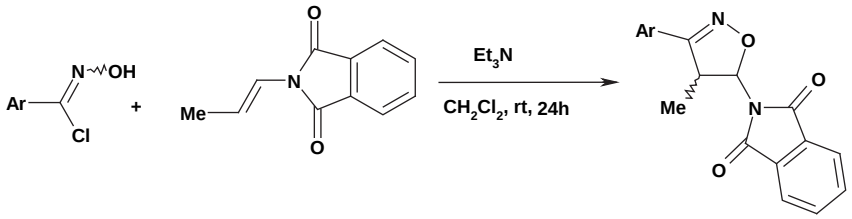


Scheme 2. Proposed mechanism of the two-step cycloaddition of nitrile oxide to *N*-(1-propenyl) compounds.

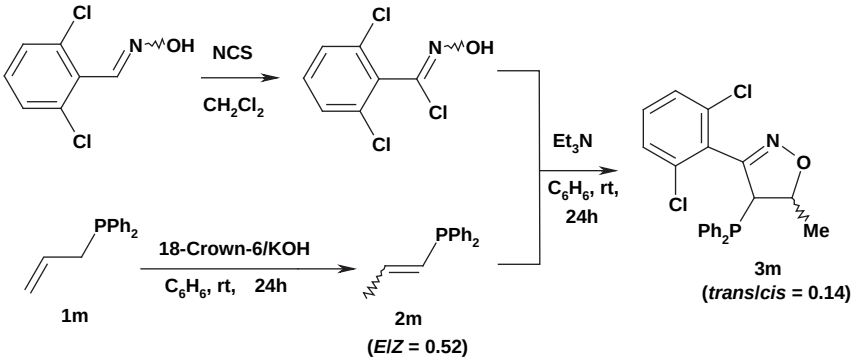
1-propenyl derivative in the presence of 18-crown-6/KOH system is the first successful reaction of this type. Other catalysts we have studied (superbase, $[RuClH(CO)(PPh_3)_3]$, $[RuCl_2(PPh_3)_3]$, $[RhH(CO)(PPh_3)_3]$, $[RuClH(CO)(PPh_3)_3]$, *t*-BuOK/DMSO), were completely ineffective in this reaction.

Isoxazoline obtained as shown in Scheme 4 (**3m**) is up till now the first 4-*P*-substituted derivative of dihydroisoxazole. The reaction was fully regioselective, as in the case of ArCNO cycloaddition to enamines. However, the regioisomer was formed (4-*P*-substituted) other than in the case of the addition to *N*-(1-propenyl) compound—5-*N*-substituted regioisomer was formed. Interestingly, the regioselectivity of the addition of ArCNO to *N*- and *P*-allyl compounds (**1a**, **1d**, **1k**, and **1m**) was identical (see Scheme 5) and similar to that reported earlier for *C*-, *O*-, and *S*-allyl systems.[20]

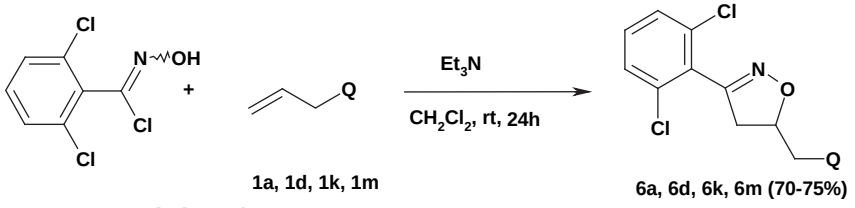
In order to explain the observed differences in the regioselectivity of addition to *N*-(1-propenyl) and *P*-(1-propenyl) compounds (in contrast to the same direction of addition to *N*-allyl and *P*-allyl compounds), theoretical calculations on model dipolarophiles, (*E*)-$H_2ACH{=}CHCH_3$ and $H_2ACH_2CH{=}CH_2$ (A=N or P), have been carried out using the DFT method with B3LYP functional (for details see Experimental section). First of all, it is worth noting that in (1-propenyl)amine the nitrogen lone pair is conjugated with the



Scheme 3. Cycloaddition of 2,4,6-trimethyl- and 2,4,6-trimethoxybenzonitrile oxide to (*E*)-*N*-(1-propenyl)phthalimide, for the synthesis of derivatives of 5-aminoisoxazolines. Ar=2,4,6-trimethylphenyl, **4h** (70%; trans/cis=0.10); 2,4,6-trimethoxyphenyl, **5h** (70%; trans/cis=0.12).

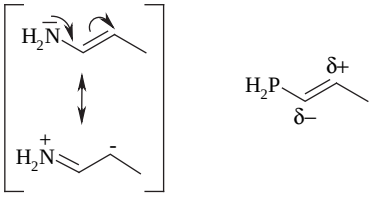


Scheme 4. Synthesis of 4-*P*-substituted isoxazoline **3m** (76%; trans/cis=0.14) from allyldiphenylphosphine **1m** and 2,6-dichlorobenzaldoxime.



Scheme 5. Cycloaddition of 2,6-dichlorobenzonitrile oxide to selected *N*-allyl systems and allyldiphenylphosphine (**1m**). Q=-NXY (**1a**, **1d**, **1k**); $-PPh_2$ (**1m**).

double bond, while in (1-propenyl)phosphine the phosphorous lone pair is orthogonal to the double bond. This has important consequences for the charge (or rather frontier density) distribution in these molecules. In (1-propenyl)amine, the influence of the nitrogen atom on the electronic structure of the double bond is resonant, resulting in no (frontier) charge change near C^1 and (frontier) charge accumulation on C^2, while in (1-propenyl)phosphine the heteroatom exerts only an inductive effect, which polarizes the π cloud toward C^1 (see Scheme 6).

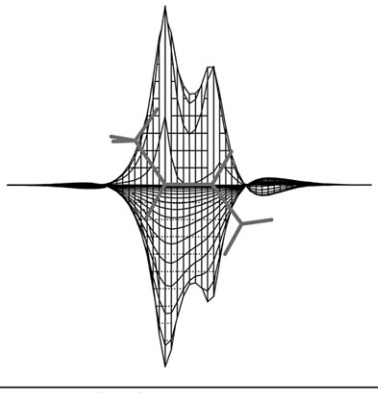
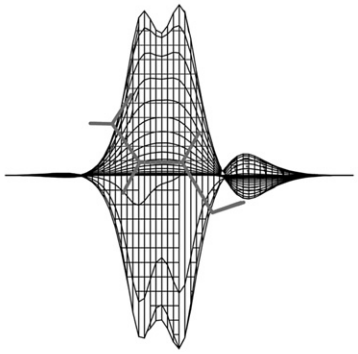
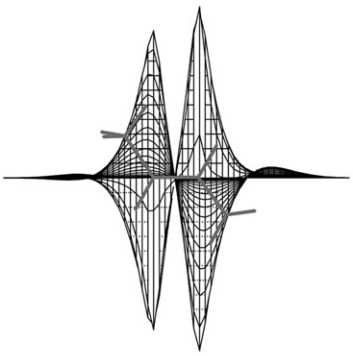
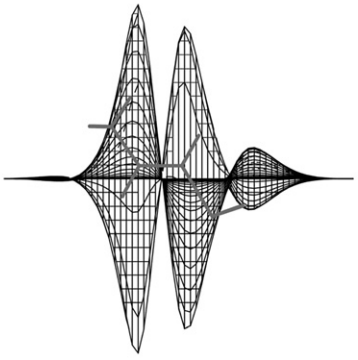


Scheme 6. Effect of the heteroatom on the double bond on $H_2ACH{=}CHCH_3$, A=N or P.

Standard reactivity indices (frontier molecular orbitals, Fukui functions r^+ and r^-, electrostatic potential) were analyzed in the vicinity of the double bond. For all the four studied compounds, maps of electrostatic potential above the double bond are rather symmetric, showing that the reaction is not charge-controlled, as expected. Frontier molecular orbitals are expected to govern the selectivity of this reaction and differences are found in the FMO densities, indeed (see Table 3 for graphs of FMOs). In (1-propenyl) amine, the HOMO (as well as ρ^+) is larger on C^2, while LUMO (and ρ^-) is larger on C^1. On the other hand, in (1-propenyl)phosphine, HOMO-1 (and ρ^+) is greater on C^1 (HOMO is essentially the lone pair on phosphorous) and LUMO is larger on C^2. Therefore, the FMO reactivity indices in (1-propenyl)phosphine are opposite to those in (1-propenyl)amine. This is the reason for opposite regioselectivity of dipolar cycloaddition of nitrile oxides to (1-propenyl)diphenylphosphine compared to enamines. It is noteworthy than in both 1-propenyl compounds the FMO indices match the polarity predicted by simple resonance/induction arguments (as in Scheme 6).

In the allyl systems, HOMO (or HOMO-1 in the case of allylamine, where N lone pair is HOMO) is larger on C^3, while LUMO is either similar on C^2 and C^3 (allylphosphine) or slightly greater on C^2 (allylamine). The FMO reactivity indices are therefore similar in both allyl compounds, leading to same regioselectivity of the dipolar addition.

Table 3
Graphs of frontier MOs (on the plane perpendicular to the plane of the double bond) of model 1-propenyl dipolarophiles

	
(1-propenyl)amine HOMO	(1-propenyl)phosphine HOMO-1
	
(1-propenyl)amine LUMO	(1-propenyl)phosphine LUMO

3. Conclusions

Results presented in this paper demonstrated that for all studied *N*-(1-propenyl) systems (enamines, enamides, and 2-aza-1,3-dienes) the 1,3-dipolar cycloaddition of 2,6-dichlorobenzonitrile oxide is a regioselective reaction. Also cycloadditions of two other stable nitrile oxides (2,4,6-trimethyl- and 2,4,6-trimethoxybenzonitrile oxide) to (*E*)-*N*-(1-propenyl)phthalimide were regioselective—for all *N*-(1-propenyl) systems exclusively 5-*N*-substituted isoxazolines were obtained. Therefore this reaction can be widely applied as a convenient method of the synthesis of 5-*N*-substituted 4,5-dihydroisoxazoles. For the first time the product of the cycloaddition of 2,6-dichlorobenzonitrile oxide to *P*-(1-propenyl) system (diphenyl-(1-propenyl)phosphine) was also obtained. However, the regioselectivity of this reaction was completely different from the regioselectivity of the cycloaddition of ArCNO to *N*-(1-propenyl) systems—we have obtained 4-*P*-substituted isoxazoline. Interestingly, the regioselectivity of the cycloaddition of *N*-allyl system and *P*-allyl systems was the same (5-substituted derivative was formed). This difference in regioselectivity is predicted by opposite FMO reactivity indices calculated for model compounds: *N*-(1-propenyl)amine and *N*-(1-propenyl) phosphine. Furthermore, the reactivity indices for allylamine and allylphosphine are similar, in accord with the experimental results. Rhodium and ruthenium complexes, Verkade's superbase and 18-Crown-6/KOH system were used for syntheses of the *N*-(1-propenyl) and *P*-(1-propenyl system) via isomerization of appropriate allyl systems. Metals Scavenging agent (STREM): phosphotungstic modified activated carbon (BASF MSA-FC) (1 g/10 mg Ru) were used for removal of ruthenium and rhodium from the products.

4. Experimental

4.1. General

The solvents were purified and dried using standard methods. The ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded at 400, 100, and 162 MHz, respectively, on a Bruker AM 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.

4.2. Allyl compounds, oximes, and isomerization catalysts

Allyl compounds **1a**, **1d**, and **1g** and catalysts [$RuCl(CO)(PPh_3)_3$], [$Rh(CO(PPh)_3]_3$, 2,8,9-triisopropyl-2,5,8,9-tetraza-1-phosphabicyclo[3.3.3]undecane, and 18-crown-6) were obtained from Aldrich. *N*-allylamides (**1e** and **1f**),[40] *N*-allylamines (**1b** and **1c**) [41,42] and *N*-allylimines (**1h**–**m**)[43–45] were synthesized according to the literature. Oximes (from 2,6-dichlorobenzaldehyde, 2,4,6-trimethylbenzaldehyde and 2,4,6-trimethoxybenzaldehyde, Aldrich) were prepared by methods from literature.[14,22]

4.3. *N*-(1-Propenyl) compounds

All 1-propenyl systems were prepared via isomerization of appropriate allyl systems.

*4.3.1. Isomerization of allyl systems **1i**, **1j**, and **1k** to **2i**, **2j**, and **2k**, respectively, in the presence of [Rh] or superbase.* Isomerization was

carried out in the screw-capped ampoules under an argon atmosphere: allyl substrate, catalyst ([RhH(CO)(PPh_3)$_3$] or Verkade's superbase) and solvent (if necessary), were stirred for a given period of time (reaction conditions see Table 1). After removal of the solvent, the dipolarophile was used in the cycloaddition directly (without removal of Rh or Verkade's base).

*4.3.2. Isomerization of allyl systems **1i**, **1j**, **1k** to **2i**, **2j**, **2k**, respectively, and diphenylallylphosphine **1m** to (1-propenyl)diphenylphosphine **2m** in the presence of 18-crown-6/KOH.* To a 1 mL 0.5 M solution of **1i**, **1j**, **1k**, or **1m** in benzene 0.3 g of powdered KOH and 25 mg of 18-crown-6 were added. After stirring at room temperature for 24 h the mixture was washed with saturated NaCl solution. Benzene layer was dried over anhydrous $MgSO_4$, the solvent was removed, and the dipolarophile was used in the cycloaddition.

*Isomerization of **1a**–**h** and **1l** was reported in our previous papers*[24–35].

4.4. Cycloadditions: synthesis and separation of isoxazolines

To a stirred solution of 1.3 mmol of 2,6-dichlorobenzaldoxime in 10 mL of CH_2Cl_2 at room temperature was added 1.4 mmol of solid NCS. The reaction was initiated by the addition of one drop of concd hydrochloric acid. After stirring for 4 h, the obtained solution of 2,6-dichlorobenzohydroximoyl chloride in CH_2Cl_2 was added to the isomerization product, at 0–5 °C and then the solution of triethylamine (3.9 mmol) in CH_2Cl_2 (at 0–5 °C) was added dropwise. Triethylamine was not added only if the dipolarophile was obtained in the presence of the superbase. The mixture was stirred for 24 h at room temperature. The post-reaction mixture was washed with water (3×10 ml), dried over Na_2SO_4, and dissolved in CH_2Cl_2 or hexane. The compounds in CH_2Cl_2 solutions were separated using column chromatography on silica gel (eluent: toluene or toluene/CH_2Cl_2). Pure and free from Ru and Rh isoxazolines were obtained with yields given in the table. The hexane solutions were mixed for 24 h with Metals Scavenging agent (STREM): phosphotungstic modified activated carbon (BASF MSA-FC) (1 g/10 mg Ru) and the ruthenium and rhodium complexes were quantitatively adsorbed. After filtration the volatile fractions were evaporated on a rotary evaporator and pure products were obtained.

*4.4.1. 3-(2,6-Dichlorophenyl)-N,N,4-methyl-4,5-dihydroisoxazol-5-amine (**3a**).* Obtained as yellow solid (266 mg, 75%). Compound *cis*-**3a** ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.22 ppm (d, J=7.3 Hz, 3H, CH_3CH), 2.52 (s, 6H, $(CH_3)_2$N), 3.57 (dq, J=5.8 Hz, J=7.3 Hz, 1H, CH_3CH), 5.176 (d, J=5.8 Hz, 1H, OCHN); 7.246–7.693 (m, 3H, C_{Ar-H}). ^{13}C NMR (100 MHz, $CDCl_3$) δ=16.2 ppm (CH_3CH), 39.7 (($CH_3)_2$N) 46.4 (CH_3CH), 106.0 (OCHN), 156.8 (C=N), 127.8, 128.2, 130.4, 135.6 (C_{Ar}). IR (film) 3584, 3155, 2981, 2254, 1794, 1604, 1561, 1470, 1433, 1382, 1096 cm^{-1}. MS (ESI$^+$) m/z 273.9 [M+H]$^+$, HRMS (ESI$^+$): calcd for $C_{14}H_{14}Cl_2N_2ONa$ [M+Na]$^+$ 295.0381 found 295.03459.

*4.4.2. 3-(2,6-Dichlorophenyl)-N,N-diisopropyl-4-methyl-4,5-dihydroisoxazol-5-amine (**3b**).* Obtained as yellow solid (290 mg, 70%). Compound *cis*-**3b** ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.07 ppm (d, J=6.7 Hz, 12H, 2×[($CH_3)_2$CH]), 1.40 (d, J=6.5 Hz, 3H, CH_3CH), 3.32 (dq, J=7.8, 6.5 Hz, 1H, CH_3CH), 3.43 (septet, J=6.7 Hz, 2H, 2×[($CH_3)_2$CH]), 5.42 (d, J=7.8 Hz, 1H, OCHN); 7.208–7.690 (m, 3H, C_{Ar-H}), ^{13}C NMR (100 MHz, $CDCl_3$) δ=15.5 ppm (CH_3CH), 22.62 (2×[($CH_3)_2$CH]), 45.05 (2×[($CH_3)_2$CH]), 47.02 (CH_3CH), 101.63 (OCHN), 157.551 (C=N), 127.9, 128.4, 130.6, 135.6 (C_{Ar}). Compound *trans*-**3b** ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.15 ppm (d, J=7.2 Hz, 12H, 2×[($CH_3)_2$CH]), 1.22 (d, J=6.6 Hz, 3H, CH_3CH); 3.44 (septet, J=7.2 Hz, 2H, 2×[($CH_3)_2$CH]), 3.60 (qd, J=6.6, 2.3 Hz, 1H, CH_3CH); 5.29 (d, J=2.3, 1H, OCHN), 7.21–7.69 (m, 3H, C_{Ar-H}), ^{13}C NMR (100 MHz, $CDCl_3$) δ=19.7 ppm (CH_3CH), 24.1 (2×[($CH_3)_2$CH]), 45.2 (2×[($CH_3)_2$CH]), 46.6 (CH_3CH), 100.1 (OCHN), 157.0 (C=N), 128.2, 129.5, 132.0, 135.4 (C_{Ar}). IR (film) 3153, 2971, 2935, 2874, 2755, 2252, 1579, 1561, 1431, 1380, 1198, 1121, 909, 782, 734, 649, 542 cm^{-1}. MS (ESI$^+$) m/z 329.1 [M+H]$^+$, HRMS (ESI$^+$): calcd for $C_{16}H_{22}Cl_2N_2ONa$ [M+Na]$^+$ 351.1001 found 351.1017.

*4.4.3. N-[3-(2,6-Dichlorophenyl)-4-methyl-4,5-dihydroisoxazol-5-yl] urea (**3c**).* Obtained as yellow solid (261 mg, 70%). Compound *cis*-**3c** ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.27 ppm (d, J=7.0 Hz, 3H, CH_3CH), 3.42 (q, J=7.0 Hz, 1H, CH_3CH), 5.91 (d, J=6.0 Hz, 1H, OCHN), 7.08–7.66 (m, 3H, C_{Ar-H}) ^{13}C NMR (100 MHz, $CDCl_3$) δ=13.8 ppm (CH_3CH), 65.7 (CH_3CH), 106.5 (OCHN), 152.7 (C=N), 154.2 (C=O), 126.9, 128.2, 132.8, 138.4 (C_{Ar}). Compound *trans*-**3c** ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.14 ppm (d, J=7.3 Hz, 3H, CH_3CH), 3.61 (q, J=7.30 Hz, 1H, CH_3CH), 6.104 (d, J=2.7 Hz, 1H, OCHN), 7.08–7.66 (m, 3H, C_{Ar-H}). ^{13}C NMR (100 MHz, $CDCl_3$) δ=12.4 ppm (CH_3CH), 64.5 (CH_3CH), 99.9 (OCHN), 153.1 (C=N), 155.4 (C=O), 124.8, 127.7, 132.4, 137.1 (C_{Ar}). IR (film) 3483, 3383, 3240, 2972, 2932, 2302, 1731, 1631, 1435, 1275, 1197, 1097, 783, 764, 699 cm^{-1}. MS (ESI$^+$) m/z 288.2 [M+H]$^+$, HRMS (ESI$^+$): calcd for $C_{11}H_{11}Cl_2N_3O_2Na$ [M+Na]$^+$ 310.0126 found 310.0130.

*4.4.4. N-[3-(2,6-Dichlorophenyl)-4-methyl-4,5-dihydroisoxazol-5-yl] acetamide (**3d**).* Obtained as yellow solid (279 mg, 75%). Compound *cis*-**3d** ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.08 ppm (d, J=7.6 Hz, 3H, CH_3CH), 2.05 (s, 3H, CH_3CO), 3.94 (dq, J=8.2 Hz, J=7.6 Hz, 1H, CH_3CH), 6.58 (d, J=8.20 Hz, 1H, OCHN), 7.19–7.67 (m, 3H, C_{Ar-H}). ^{13}C NMR (100 MHz, $CDCl_3$) δ=8.6 ppm (CH_3CH), 23.4 (CH_3CO), 45.7 (CH_3CH), 83.7 (OCHN), 127.8, 128.7, 132.8, 136.8, (C_{Ar}), 158.4 (C=N), 170.3 (C=O). Compound *trans*-**3d** ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.26 ppm (d, J=7.4 Hz, 3H, CH_3CH), 2.07 (s, 3H, CH_3CO), 3.54 (dq, J=4.2 Hz, J=7.4 Hz, 1H, CH_3CH), 6.14 (d, J=4.2 Hz, 1H, OCHN), 7.19–7.67 (m, 3H, C_{Ar-H}). ^{13}C NMR (100 MHz, $CDCl_3$) δ=8.9 ppm (CH_3CH), 23.3 (CH_3CO), 50.6 (CH_3CH), 88.2 (OCHN), 128.2, 128.9, 132.5, 136.1 (C_{Ar}), 158.7 (C=N), 170.4 (C=O). IR (film) 3400, 3055, 2979, 2913, 2232, 1683, 1633, 1607, 1562, 1435, 1196, 1108, 912, 783, 743, 696, 543, 526 cm^{-1}. MS (ESI$^+$) m/z 309.0 [M+Na]$^+$, HRMS (ESI$^+$): calcd for $C_{12}H_{12}Cl_2N_2O_2Na$ [M+Na]$^+$ 309.0168 found 309.0181.

*4.4.5. N-[3-(2,6-Dichlorophenyl)-4-methyl-4,5-dihydroisoxazol-5-yl]-N-(4-methylphenyl)acetamide (**3e**).* Obtained as yellow solid (390 mg, 80%). Compound *cis*-**3e** ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.25 ppm (d, J=7.4 Hz, 3H, CH_3CH), 1.88 (s, 3H, CH_3CO), 2.38 (s, 3H, CH_3–C_6H_4-), 3.53 (dq, J=7.6 Hz, J=7.4 Hz, 1H, CH_3CH), 7.02 (d, J=7.6 Hz, 1H, OCHN), 7.14–7.52 (m, 3H+4H, C_{Ar-H}). ^{13}C NMR (100 MHz, $CDCl_3$) δ=15.4 ppm (CH_3CH), 21.0 (CH_3–C_6H_4-), 23.4 (CH_3CO), 46.6 (CH_3CH), 92.0 (OCHN), 157.20 (C=N), 168.4 (CH_3CO), 127.5, 128.1, 128.7, 129.3, 130.9, 135.3, 138.4, 139.1 (C_{Ar}). Compound *trans*-**3e** ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.26 ppm (d, J=7.1 Hz, 3H, CH_3CH), 1.83 (s, 3H, CH_3CO), 2.39 (s, 3H, CH_3–C_6H_4-), 3.43 (q, J=7.1 Hz, 1H, CH_3CH), 7.17 (d, J=3.6 Hz, 1H, OCHN), 7.14–7.52 (m, 3H+4H, C_{Ar-H}). ^{13}C NMR (100 MHz, $CDCl_3$) δ=13.9 ppm (CH_3CH), 20.8 (CH_3–C_6H_4-), 24.4 (CH_3CO), 45.6 (CH_3CH), 91.0 (OCHN), 156.5 (C=N), 168.0 (CH_3CO), 127.5, 128.18, 128.7, 129.75, 131.00, 135.5, 138.2, 139.2 (C_{Ar}). IR (film) 3302, 2982, 2303, 2254, 1667, 1605, 1515, 1434, 1265, 909, 735, 650 cm^{-1}. MS (ESI$^+$) m/z 399.0 [M+Na]$^+$, HRMS (ESI$^+$): calcd for $C_{19}H_{18}Cl_2N_2O_2Na$ [M+Na]$^+$ 399.0638 found 399.0634.

*4.4.6. N-[3-(2,6-Dichlorophenyl)-4-methyl-4,5-dihydroisoxazol-5-yl]-N-1-naphthylacet-amide (**3f**).* Obtained as red solid (501 mg, 95%). Compound *cis*-**3f** ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.22 ppm (d, J=7.4 Hz, 3H, CH_3CH), 1.78 (s, 3H, CH_3CO), 3.26 (dq, J=7.1 Hz, J=7.4 Hz, 1H, CH_3CH), 7.12 (d, J=7.1 Hz, 1H, OCHN), 7.27–7.96 (m, 3H+9H, C_{Ar-H}). ^{13}C NMR (100 MHz, $CDCl_3$) δ=15.9 ppm (CH_3CH), 23.0 (CH_3CO), 45.7 (CH_3CH), 92.5 (OCHN), 157.112 (C=N), 172.8

(CH_3CO), 121.8, 126.6, 127.9, 128.0, 128.5, 128.6, 128.8, 129.2, 129.5, 130.9, 132.0, 134.2, 134.5 (C_{Ar}). Compound *trans*-**3f** ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.55 (d, J=6.7 Hz, 3H, CH_3CH), 1.74 (s, 3H, CH_3CO), 3.82 (dq, J=3.20, 6.7 Hz, 1H, CH_3CH); 7.215 (d, J=3.2 Hz, 1H, OCHN), 7.27–7.96 (m, 3H+9H, C_{Ar-H}). ^{13}C NMR (100 MHz, $CDCl_3$) δ=15.1 ppm (CH_3CH), 22.7 (CH_3CO), 41.8 (CH_3CH), 93.5 (OCHN), 159.1 (C=N), 168.9 (CH_3CO), 122.6, 126.8, 127.1, 127.3, 128.1, 128.2, 129.5, 129.7, 130.3, 130.4, 132.9, 133.1, 134.9 (C_{Ar}). IR (film) 3018, 2952, 1674, 1431, 1381, 1306, 1284, 1216, 770, 754, 669 cm^{-1}. MS (ESI$^+$) m/z 413.2 $[M+H]^+$, 435.1 $[M+Na]^+$, HRMS (ESI$^+$): calcd for $C_{22}H_{18}Cl_2N_2O_2Na$ $[M+Na]^+$ 435.0638 found 435.0648.

*4.4.7. N-[3-(2,6-Dichlorophenyl)-4-methyl-4,5-dihydroisoxazol-5-yl] thiophene-2-carbox-amide (**3g**).* Obtained as red solid (368 mg, 80%). Compound *cis*-**3g** ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.29 ppm (d, J=7.3 Hz, 3H, CH_3CH), 3.59 (q, J=7.3 Hz, 1H, CH_3CH), 6.57 (d, J=8.1 Hz, 1H, OCHN); 6.98–7.89 (m, 3H+3H, C_{Ar-H}). ^{13}C NMR (100 MHz, $CDCl_3$) δ=14.7 ppm (CH_3CH), 45.7 (CH_3CH), 88.7 (OCHN), 158.8 (C=N), 161.5 (C=O), 128.2, 128.5, 128.6, 132.0, 132.1, 134.0, 135.3, 138.4 (C_{Ar}). Compound *trans*-**3g** ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.14 ppm (d, J=7.4 Hz, 3H, CH_3CH), 3.66 (qd, J=7.40, 3.5 Hz, 1H, CH_3CH), 6.29 (dd, J=8.5, 3.5 Hz, 1H, OC*H*NH), 6.65 (d, J=8.5 Hz, 1H, OCHN*H*), 6.98–7.89 (m, 3H+3H, C_{Ar-H}) ^{13}C NMR (100 MHz, $CDCl_3$) δ=13.9 ppm (CH_3CH), 46.4 (CH_3CH), 84.2 (OCHN), 159.0 (C=N), 161.4 (C=O), 127.8, 128.0, 129.8, 131.6, 131.8, 135.2, 136.8, 137.64 (C_{Ar}). IR (film) 3407, 3292, 2973, 2250, 1643, 1532, 1499, 1433, 1291, 1196, 907, 731, 648 cm^{-1}. MS (ESI$^+$) m/z 357.2 $[M+H]^+$, HRMS (ESI$^+$): calcd for $C_{15}H_{13}Cl_2N_2O_2Na$ $[M+Na]^+$ 377.9972 found 377.9980.

*4.4.8. 2-[3-(2,6-Dichlorophenyl)-4-methyl-4,5-dihydroisoxazol-5-yl]-1H-isoindole-1,3(2H)-dione (**3h**).* Obtained as yellow solid (388 mg, 80%). Compound *cis*-**3h** ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.30 ppm (d, J=7.4 Hz, 3H, CH_3CH), 4.60 (dq, J=7.8, 7.4 Hz, 1H, CH_3CH), 6.35 (d, J=7.8 Hz, 1H, OCHN), 7.13–7.90 (m, 3H+4H, C_{Ar-H}). ^{13}C NMR (100 MHz, $CDCl_3$) δ=15.2 ppm (CH_3), 46.9 (CH_3CH), 88.0 (OCHN), 158.13 (C=N), 188.7 (C=O), 123.8, 127.3, 128.4, 131.6, 134.6, 135.6, 138.2 (C_{Ar}). Compound *trans*-**3h** ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.59 ppm (d, J=6.5 Hz, 3H, CH_3CH), 3.42 (q, J=6.5 Hz, 1H, CH_3CH), 5.84 (d, J=4.7 Hz, 1H, OCHN), 7.13–7.90 (m, 3H+4H, C_{Ar-H}). ^{13}C NMR (100 MHz, $CDCl_3$) δ=16.28 ppm (CH_3), 41.8 (CH_3CH), 79.1 (OCHN), 152.7 (C=N), 188.0 (C=O), 123.4, 128.0, 129.7, 131.2, 134.3, 136.0, 138.4 (C_{Ar}). IR (film) 3019, 1781, 1729, 1561, 1432, 1372, 1096, 1069, 1020, 881, 718 cm^{-1}. MS (ESI$^+$) m/z 376.9 $[M+H]^+$, HRMS (ESI$^+$): calcd for $C_{18}H_{12}Cl_2N_2O_3Na$ $[M+Na]^+$ 397.0123 found 397.0123.

*4.4.9. 2-(3-Mesityl-4-methyl-4,5-dihydroisoxazol-5-yl)-1H-isoindole-1,3(2H)-dione (**4h**).* Obtained as yellow solid (316 mg, 70%). Compound *cis*-**4h** ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.13 ppm (d, J=7.5 Hz, 3H, CH_3CH), 2.27 (s, 6H, 2×CH_3–C_{Ar}), 2.36 (s, 3H, CH_3–C_{Ar}), 4.16 (dq, J=6.8 Hz, J=7.5 Hz, 1H, CH_3CH); 6.18 (d, J=6.8 Hz, 1H, OCHN), 7.59–7.79 (m, 2H+4H, C_{Ar-H}). ^{13}C NMR (100 MHz, $CDCl_3$) δ=15.5 ppm (CH_3CH), 19.9 (CH_3–C_{Ar}), 20.3 (2×CH_3–C_{Ar}), 48.5 (CH_3CH), 87.3 (OCHN), 160.8 (C=N), 166.5 (C=O), 123.3, 123.7, 128.3, 128.8, 131.6, 134.2, 134.6 (C_{Ar}). Compound *trans*-**4h** ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.17 ppm (d, J=7.1 Hz, 3H, CH_3CH), 2.18 (s, 6H, 2×CH_3–C_{Ar}), 2.23 (s, 3H, CH_3–C_{Ar}), 4.04 (qd, J=7.1, 2.2 Hz, 1H, CH_3CH), 6.11 (d, J=2.2 Hz, 1H, OCHN), 7.59–7.79 (m, 2H+4H, C_{Ar-H}). ^{13}C NMR (100 MHz, $CDCl_3$) δ=8.6 ppm (CH_3CH), 20.6 (CH_3–C_{Ar}), 20.7 (2×CH_3–C_{Ar}), 48.4 (CH_3CH), 87.1 (OCHN), 161.1 (C=N), 166.8 (C=O), 123.9, 124.4, 127.4, 129.8, 132.8, 133.7, 135.6 (C_{Ar}). IR (film) 3257, 2964, 2923, 2857, 2288, 1778, 1720, 1469, 1392, 1377, 1148, 1065, 1020, 872, 714, 628 cm^{-1}. MS (ESI$^+$) m/z 371.2 $[M+Na]^+$, HRMS (ESI$^+$): calcd for $C_{21}H_{20}N_2O_3Na$ $[M+Na]^+$ 371.13716 found 371.13702.

*4.4.10. 2-[4-Methyl-3-(2,4,6-trimethoxyphenyl)-4,5-dihydroisoxazol-5-yl]-1H-isoindole-1,3 (2H)-dione (**5h**).* Obtained as yellow solid (360 mg, 70%). Compound *cis*-**5h** ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.09 ppm (d, J=7.3 Hz, 3H, CH_3CH), 2.13 (s, 6H, 2×CH_3O), 2.23 (s, 3H, CH_3O); 3.98 (q, J=7.3 Hz, 1H, CH_3CH), 6.65 (d, J=6.7 Hz, 1H, OCHN), 7.01–7.04 (m, 2H+4H, C_{Ar-H}). ^{13}C NMR (100 MHz, $CDCl_3$) δ=12.1 ppm (CH_3CH), 47.6 (CH_3CH), 52.1 (2×CH_3O), 52.9 (CH_3O), 89.2 (OCHN), 159.8 (C=N), 162.3 (C=O), 110.2, 115.2, 122.0, 124.0, 130.1, 131.8, 134.7 (C_{Ar}). Compound *trans*-**5h** ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.13 ppm (d, J=7.2 Hz, 3H, CH_3CH), 2.27 (s, 6H, 2×CH_3O), 2.31 (s, 6H, CH_3O), 3.82 (qd, J=7.2, 3.0 Hz, 1H, CH_3CH), 6.37 (d, J=3.0 Hz, 1H, OCHN), 7.01–7.04 (m, 2H+4H, C_{Ar-H}). ^{13}C NMR (100 MHz, $CDCl_3$) δ=10.2 ppm (CH_3CH), 48.2 (CH_3CH), 51.8 (2×CH_3O), 52.0 (CH_3O), 88.2 (OCHN), 157.6 (C=N), 163.4 (C=O), 112.1, 116.8, 123.0, 124.7, 129.8, 132.3, 135.3 (C_{Ar}). IR (film) 2987, 2856, 2281, 1772, 1698, 1489, 1387, 1367, 1137, 1054, 1025, 778, 716 cm^{-1}. MS (ESI$^+$) m/z 419.3 $[M+Na]^+$, HRMS (ESI$^+$): calcd for $C_{21}H_{20}N_2O_6Na$ $[M+Na]^+$ 419.121190 found 419.12121.

*4.4.11. 3-(2,6-Dichlorophenyl)-5-(1H-imidazol-1-yl)-4-methyl-4,5-dihydroisoxazole (**3i**).* Obtained as yellow solid (287 mg, 75%). Compound *cis*-**3i** ^{1}H NMR ($CDCl_3$) δ=1.25 ppm (d, J=7.2 Hz, 3H, CH_3CH), 5.51 (dq, J=8.7, 7.20 Hz, 1H, CH_3CH), 6.59 (dq, J=8.7, 1.70 Hz, 1H, OCHN), 7.13 (s, 1H, NCHC*H*), 7.29 (s, 1H, NC*H*CH), 7.39 (s, 1H, NCHN), 7.05–7.58 (m, 3H, C_{Ar-H}) ^{13}C NMR (100 MHz, $CDCl_3$) δ=12.5 ppm (CH_3CH), 41.7 (CH_3CH), 83.8 (OCHN), 154.2 (C=N), 123.5, 126.2, 127.9, 129.7, 131.0, 136.9, 137.1 (C_{Ar}). Compound *trans*-**3i** ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.37 ppm (d, J=7.5 Hz, 3H, CH_3CH), 3.92 (qd, J=7.5, 3.7 Hz, 1H, CH_3CH), 6.22 (d, J=3.7 Hz, 1H, OCHN), 7.11 (s, 1H, NCHC*H*), 7.27 (s, 1H, NC*H*CH), 7.36 (s, 1H, NCHN), 7.05–7.58 (m, 3H, C_{Ar-H}). ^{13}C NMR (100 MHz, $CDCl_3$) δ=14.8 ppm (CH_3CH), 52.9 (CH_3CH), 92.8 (OCHN), 157.9 (C=N), 124.1, 127.7, 128.1, 129.5, 133.9, 135.6, 138.4 (C_{Ar}). IR (film) 3409, 2974, 2924, 2360, 2342, 2252, 1683, 1561, 1497, 1436, 1292, 1228, 912, 742, 649 cm^{-1}. MS (ESI$^+$) m/z 318.0 $[M+Na]^+$, HRMS (ESI$^+$): calcd for $C_{13}H_{11}Cl_2N_3ONa$ $[M+Na]^+$ 318.0177 found 318.0178.

*4.4.12. 3-(2,6-Dichlorophenyl)-N-[1-(2,6-dichlorophenyl)methylene]-4-methyl-4,5-dihydro-isoxazol-5-amine (**3j**).* Obtained as red oil (417 mg, 80%). Compound *cis*-**3j** ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.17 ppm (d, J=7.6 Hz, 3H, CH_3CH), 4.26 (dq, J=8.6 Hz, J=7.6 Hz, 1H, CH_3CH), 6.42 (dd, J=8.6 Hz, J=1.8 Hz, 1H, OCHN), 7.15–8.00 (m, 3H+3H, C_{Ar-H}), 9.11 (d, J=1.8 Hz, 1H, CH=N). ^{13}C NMR (100 MHz, $CDCl_3$) δ=16.2 ppm (CH_3CH), 53.7 (CH_3CH), 99.5 (OCHN), 156.21 (CH=N), 165.21 (C=N),128.3, 128.56, 129.2, 131.2, 131.9, 132.5, 133.4. 135.57 (C_{Ar}). Compound *trans*-**3j** ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.45 ppm (d, J=7.5 Hz, 3H, CH_3CH), 3.74 (qd, J=7.5, 2.5 Hz, 1H, CH_3CH), 6.88 (dd, J=2.5, 1.8 Hz, 1H, OCHN), 7.15–8.00 (m, 3H+7H, C_{Ar-H}). 9.16 (d, J=1.8 Hz, 1H, CH=N). ^{13}C NMR (100 MHz, $CDCl_3$) δ=10.5 ppm (CH_3CH), 49.2 (CH_3CH), 94.5 (OCHN), 155.1 (CH=N), 164.2 (C=N), 128.1, 128.8, 129.2, 131.6, 131.8, 132.4; 133.5, 135.3 (C_{Ar}). IR (film) 3286, 3082, 3015, 2982, 2885, 2226, 1653, 1581, 1560, 1431, 1376, 1324, 1194, 1095, 924, 779, 742, 722, 645 cm^{-1}. MS (ESI$^+$) m/z 403.0 $[M+H]^+$, 425.0 $[M+Na]^+$, HRMS (ESI$^+$): calcd for $C_{17}H_{12}Cl_4N_2ONa$ $[M+Na]^+$ 422.9596 found 422.9600.

*4.4.13. 3-(2,6-Dichlorophenyl)-N-[1-(4-methoxyphenyl)methylene]-4-methyl-4,5-dihydro-isoxazol-5-amine (**3k**).* Obtained as yellow solid (400 mg, 85%). Compound *cis*-**3k** ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.08 ppm (d, J=7.6 Hz, 3H, CH_3CH), 3.83(CH_3O), 4.16 (dq, J=8.8, 7.6 Hz, 1H, CH_3CH), 6.28 (dd, J=8.8, 1.8 Hz, 1H, OCHN), 6.92–7.83 (m, 3H+4H, C_{Ar-H}), 8.43 (d, J=1.8 Hz, 1H, CH=N). ^{13}C NMR (100 MHz, $CDCl_3$) δ=15.5 ppm (CH_3CH), 52.7 (CH_3CH), 55.6 (CH_3O), 100.8 (OCHN), 158.3 (CH=N), 164.6 (C=N), 128.3, 128.6, 128.7, 130.3, 131.1, 131.9, 132.1, 135.5 (C_{Ar}). Compound *trans*-**3k** ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.38 ppm (d, J=7.5 Hz, 3H, CH_3CH), 3.62 (qd, J=7.5, 2.8 Hz, 1H, CH_3CH), 3.87 (CH_3O), 5.89 (dd, J=2.8, 1.8 Hz, 1H, OCHN), 6.92–7.83 (m, 3H+4H, C_{Ar-H}), 8.35 (d, J=1.8 Hz, 1H, CH=N).

^{13}C NMR (100 MHz, $CDCl_3$) δ=8.9 ppm (CH_3CH), 48.9 (CH_3CH), 55.4 (CH_3O), 95.9 (OCHN), 157.4 (CH=N), 162.1 (C=N), 128.2, 128.4, 128.5, 130.3, 131.1, 131.9, 132.1, 135.5 (C_{Ar}). IR (film) 3348, 2945, 2832, 1685, 1606, 1450, 1431, 1030, 734, 659 cm^{-1}. MS (ESI$^+$) *m/z* 363.8 $[M+H]^+$, HRMS (ESI$^+$): calcd for $C_{18}H_{16}Cl_2N_2O_2Na$ $[M+Na]^+$ 385.0486 found 385.0489.

*4.4.14. 3-(2,6-Dichlorophenyl)-N-(2-furylmethylene)-4-methyl-4,5-dihydroisoxazol-5-amine (**3l**).* Obtained as yellow solid (293 mg, 70%). Compound *cis*-**3l** ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.10 ppm (d, *J*=7.7 Hz, 3H, CH_3CH), 4.19 (dq, *J*=7.7, 8.7 Hz, 1H, CH_3CH), 6.35 (dd, *J*=8.7, 1.9 Hz, 1H, OCHN), 6.83–7.68 (m, 3H+3H, C_{Ar-H}), 8.33 (d, *J*=1.9 Hz, 1H, CH=N). ^{13}C NMR (100 MHz, $CDCl_3$) δ=12.5 ppm (CH_3CH), 64.1 (CH_3CH), 111.7 (OCHN), 154.1 (CH=N), 159.7 (C=N), 112.5, 115.0, 128.0, 128.4, 131.0, 135.0, 143.9, 144.7 (C_{Ar}). Compound *trans*-**3l** ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.38 ppm (d, *J*=7.5 Hz, 3H, CH_3CH), 3.67 (qd, *J*=7.5, 2.8 Hz, 1H, CH_3CH), 5.93 (dd, *J*=2.8, 1.8 Hz, OCHN), 6.83–7.68 (m, 3H+3H, C_{Ar-H}), 8.25 (d, *J*=1.8 Hz, 1H, CH=N). ^{13}C NMR (100 MHz, $CDCl_3$) δ=10.0 ppm (CH_3CH), 63.5 (CH_3CH), 111.62 (OCHN), 153.9 (CH=N), 157.7 (C=N), 113.9, 116.4, 128.0, 128.5, 131.9, 135.5, 144.9, 145.0 (C_{Ar}). IR (film) 3411, 3153, 3083, 2886, 2252, 1650, 1561, 1432, 1195, 1018, 907, 781, 730, 649 cm^{-1}, MS (ESI$^+$) *m/z* 323.1 $[M+H]^+$, HRMS (ESI$^+$): calcd for $C_{15}H_{12}Cl_2N_2O_2Na$ $[M+Na]^+$ 345.0173 found 345.0180.

*4.4.15. 3-(2,6-Dichlorophenyl)-4-(diphenylphosphino)-5-methyl-4,5-dihydroisoxazole (**3m**).* Obtained as yellow solid (375 mg, 76%). Compound *cis*-**3m** ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.98 ppm (ddd, *J*=6.6 Hz, J_{PH}=2.1 Hz, *J*=1.7 Hz, 3H, CH_3CHO), 6.27 (ddq, J_{PH}=24.2 Hz, *J*=16.8, 1.7 Hz, 1H, Ph_2PCH), 6.70 (ddq, J_{PH}=19.2 Hz, *J*=16.8, 6.6 Hz, 1H, CH_3CHO), 7.32–7.76 (m, 3H+10H, C_{Ar-H}). ^{13}C NMR (100 MHz, $CDCl_3$) δ=20.5 ppm (CH_3CH), 45.5 ($PCHCHCH_3$), 70.4 ($PCHCHCH_3$), 147.9 (C=N), 128.2, 128.4, 128.5, 131.2, 131.3, 131.6, 133.9, 138.4 (C_{Ar}). ^{31}P NMR (162 MHz, $CDCl_3$) δ=23.3 ppm. Compound *trans*-**3m** ^{1}H NMR (400 MHz, $CDCl_3$) δ=2.08 ppm (ddd, *J*=7.2 Hz, J_{PH}=3.1 Hz, *J*=1.6 Hz, 3H, CH_3CHO), 6.13 (ddq, J_{PH}=25.6 Hz, 12.8, 1.6 Hz, 1H, Ph_2PCH), 6.80 (ddq, J_{PH}=40.3 Hz, *J*=12.8, 7.2 Hz, 1H, CH_3CHO), 7.32–7.76 (m, 3H+10H, C_{Ar-H}). ^{13}C NMR (100 MHz, $CDCl_3$) δ=20.3 ppm (CH_3CH), 52.8 ($PCHCHCH_3$), 69.8 ($PCHCHCH_3$), 149.6 (C=N), 128.2; 128.3, 128.5, 130.8, 131.9, 132.1, 133.6, 138.4 (C_{Ar}). ^{31}P NMR (162 MHz, $CDCl_3$) δ=38.6 ppm. IR (film) 3359, 3079, 3061, 2915, 2226, 1711, 1634, 1561, 1437, 1179, 1113, 964, 924, 912, 804, 784, 742, 696, 549 cm^{-1}. MS (ESI$^+$) *m/z* 414.1 $[M+H]^+$, HRMS (ESI$^+$): calcd for $C_{22}H_{18}Cl_2NOPNa$ $[M+Na]^+$ 436.0401 found 436.0402.

*4.4.16. 3-(2,6-Dichlorophenyl)-5-[(diphenylphosphino)methyl]-4,5-dihydroisoxazole (**6m**).* Obtained as yellow solid (312 mg, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ=3.15 ppm (dd, *J*=14.5, 7.5 Hz, 2H, CH_2P), 5.12–5.18 (m, 2H, CH_2CH), 5.75–5.87 (m, 1H, CH_2CH), 7.40–7.77 (m, 3H+10H, C_{Ar-H}). ^{13}C NMR (100 MHz, $CDCl_3$) δ=25.2 ppm (CH_2P), 36.4 (CH_2CH), 76.3 (CH_2CH), 160.29 (C=N), 128.3, 128.4, 128.6, 128.7, 131.2, 131.3, 132.2, 132.9 (C_{Ar}). ^{31}P NMR (162 MHz, $CDCl_3$) δ=29.70 ppm. IR (film) 3082, 2925, 2854, 2359, 2341, 2230, 1720, 1709, 1578, 1396, 1200, 1175, 1121, 1064, 999, 828, 804, 694 cm^{-1}.

5. Theoretical calculations

Theoretical calculations on model compounds were carried out with the Firefly QC package [Alex; Granovsky, Firefly version 7.1.G, www http://classic.chem.msu.su/gran/gamess/index.html], which is partially based on GAMESS (US) [46] source code. Geometry optimizations were done at B3LYP/6-31G(d) level. The results were analyzed using MOLDEN.[47] Orbital plots were constructed on a plane containing the C=C bond, perpendicular to the plane defined by C=C–N or C=C–P atoms, respectively. Such plots were found to be much more sensitive to small differences in orbital shape than the usual isodensity surfaces.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2010.06.040. These data include MOL files and InChIKeys of the most important compounds described in this article.

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