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Iron- and Ruthenium-Lewis Acid Catalyzed Asymmetric 1,3-Dipolar Cycloaddition Reactions between Enals and Diaryl Nitrones

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Dedicated to Professor Ryoji Noyori on the occasion of his 70th birthday

Abstract: The highly tuned, one-point binding cationic cyclopentadienyl-iron and -ruthenium complexes **1** and **2** that incorporate chiral bidentate pentafluoroaryl-phosphinite ligands selectively coordinate and activate α,β-unsaturated carbonyl compounds towards asymmetric catalytic cycloaddition reactions with diaryl nitrones. The reaction gives isoxazolidine products in good yields, with complete *endo* selectivity and high enantioselectivity. The products are obtained as a mixture of regioisomers in ratios varying from 96:4 to 15:85. The regioselectivity correlates directly with the electronic properties of the nitrone. This is shown by the experimental and computational data.

Keywords: cycloaddition · iron · Lewis acids · regioselectivity · ruthenium

Introduction

Isoxazolidines are heterocycles with a high synthetic potential. These compounds can incorporate up to three contiguous stereogenic centers and contain a readily cleavable N–O bond, thus giving access to a variety of applications either as heterocycles or as acyclic chiral building blocks. A straightforward route to isoxazolidines is by a 1,3-dipolar cycloaddition reaction between an alkene and a nitrone. Following the pioneering work of Huisgen,[1] this approach has continued to flourish, with the diastereoselective reactions taking an important part. These reactions involve either chiral nitrones or chiral dipolarophiles. Catalytic reactions have made their entry and have stimulated much new interest and activity in recent years.[2]

Asymmetric catalytic reactions, in which the dipolarophile is activated by a chiral Lewis acid, initially were successful only for bidentate substrates, notably, 3-(2-alkenoyl)-2-oxazolidinols (oxazolidinones).[2a,e,3] The reason lies in the preferential (or competitive) coordination of nitrones to the Lewis acid over that of enals or α,β-unsaturated ketones. This prevents a catalytic reaction and the racemic cycloadduct formed is the result of the uncatalyzed process.[4]

The first breakthrough for the asymmetric cycloaddition reaction of enals with nitrones came in 2000 from the McMillan laboratory with the use of a chiral organocatalyst that converted the enals into the corresponding chiral iminium ions.[5] This approach has since seen further developments.[6] Lewis acid activation of enals towards nitrone cycloaddition made its entry a few years later. For the racemic reaction, Kanemasa et al. showed that the bulky aluminum-tris(2,6-diphenylphenoxide) [ATPH][7] preferred enal coordination over that of the sterically more congested nitrones.[8] Kanemasa coined the term "pinhole catalyst" and showed that by judicious design of the catalytic site, the requisite control of coordination could be achieved and that this [3+2] cycloaddition could be catalyzed by Lewis acids.[8] We had worked along the same line of thought but had added ligand chirality whilst using transition-metal Lewis acids, and reported the first highly enantioselective Lewis acid catalyzed enal/nitrone cycloadditions.[9] The catalysts that we developed were the cationic cyclopentadienyl-iron and -ruthenium complexes **1** and **2** that incorporate the chiral bidentate pentafluoroaryl-phosphinite ligands. These catalysts had been successfully used previously in Diels–Alder reactions between enals and dienes.[10] More recently, **2** has

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found application in cycloadditions between dienes and α,β-unsaturated ketones.[11] Also in 2002, Yamada and co-workers published their first results on nitrone/enal [3+2] cycloaddition reactions catalyzed by β-ketoiminato Co^{II} complexes.[12] A subsequent full study showed the efficiency and versatility of these catalysts for the reaction of various diarylnitrones and α,β-unsaturated aldehydes.[13]

The field has seen considerable development in the past years. The group of Carmona and Oro showed dicationic, half-sandwich-rhodium and -iridium complexes containing diphosphine or PN ligands to provide good catalysts for this transformation.[14] The same group recently reported the first examples of asymmetric catalytic cycloaddition reactions of nitrones with methacrylonitrile.[15] In situ prepared complexes of Ni, Zn, and Mg with DBFOX (dibenzofuran-oxazoline) ligands were also found to be good catalysts.[16] Less active *N*-benzyl aryl nitrones posed problems with many catalysts, but these and *N*-diphenylmethyl aryl nitrones are efficient substrates when binol (1,1′-bi-2-naphthol) Ti-complexes are used as catalysts. Maruoka and co-workers thus showed an efficient, highly regioselective access to enantiopure isoxazoldines bearing readily cleavable groups at the nitrogen.[17]

In previous research, we have shown the well-defined, mild chiral Lewis acid complexes of Fe and Ru, such as those presented in Figure 1, to selectively bind and activate α,β-unsaturated carbonyl compounds.[9–11] Competitive ni-

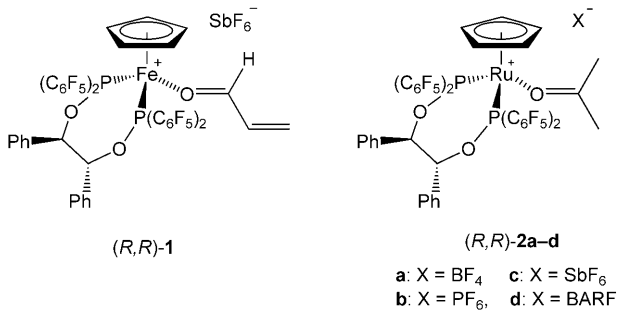


Figure 1. Chiral Fe and Ru Lewis acid precatalysts.

trone-enal coordination at the Lewis acid was studied by ^{31}P NMR spectroscopy, and showed a clear preference of enal coordination and reversible binding of both substrates at the metal center. In a preliminary communication, we showed that the Fe and Ru complexes efficiently catalyze the cycloadditions between nitrones and α,β-unsaturated aldehydes, giving the desired cycloadducts in good yields and enantioselectivities, and with complete diastereoselectivity.[9]

Recently, the catalyzed asymmetric [3+2] cycloaddition was extended to reactions with nitrile oxides. Despite the strongly coordinating and very active dipoles, in the presence of the Ru complex (*R*,*R*)-**2a** and methacrolein, the desired isoxazoles were obtained in moderate to good yields and enantiomeric excess of up to 93%.[18]

Looking back at our preliminary results with acyclic diaryl nitrones, we were intrigued by the change in the ratio of regioisomers upon variation of the substitution in the C-aryl ring of the nitrone.[9] Although Maruoka and co-workers were able to achieve excellent control of the regioselectivity by introducing a bulky substituent at the nitrone's N atom,[17b] variation of the regioisomeric-product ratio by means of the electronic effects, appears to have not been previously investigated, with the single exception of a communication published shortly before submission of this manuscript.[19] Herein, we report our results and interpretation of this phenomenon.

Computational Methods

The geometry parameters and selected electronic properties of *para*-substituted diphenylnitrones involved in the 1,3-dipolar cycloadditions were investigated with the density functional (DFT) method. More specifically, the PBE1PBE functional[20] within the Gaussion 03 package[21] was used as the main computational method throughout this study. This particular functional was shown to yield very good results for many organic substrates.[22] The structure optimization and energy calculations were typically performed with the 6-311++G** basis set. For selected structures, the geometry optimizations were also performed with Moller–Plesset methods, such as MP2, with a smaller 6-311G** basis set.[23] The nature of optimized minima was further checked by the computations of the analytical harmonic frequencies, in which the Hessian matrix was at the same time examined to verify the absence of negative eigenvalues for minima.

The electronic transition from the initial ground state of the neutral system to the lowest-energy state of the cation corresponds to the vertical ionization potential (VIP). The adiabatic energy difference between the minima of the two states additionally takes into account the geometry relaxation, which takes place in the excited state. The adiabatic ionization potential (AIP) can further be improved by incorporating the zero point vibrational energy (ZPE) corrections to obtain AIP(0). In the present project, the AIP(0) values were computed as they usually correlate quite well with the experimental results.

Both ab initio and DFT methods have been widely employed to compute the ionization potential.[24] In this context, the PBE1PBE method was reported[25] to outperform other functionals when combined with the 6-311++G** or 6-311G** basis sets. To compute the ionization potentials, the geometry optimizations and energy calculations for neutral nitrones were done with the DFT method at levels of theory described previously. The lowest states of all diphenylnitrones were also optimized for the calculation of adiabatic ionization potentials. Finally, the ZPE obtained from the vibrational-frequency analysis at the same level as the energy calculations have been included to obtain AIP(0).

Results and Discussion

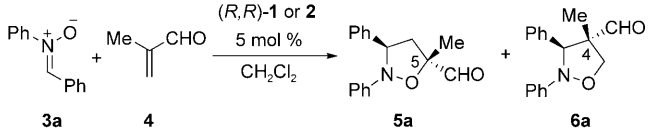
Diphenyl Nitrone

Before setting out to investigate more closely the nitrone C-aryl substituent effects mentioned in the introduction, we optimized reaction conditions for the two catalytic systems using diphenyl nitrone **3a** as a substrate. The optimal catalyst loading for this process was found to be 5 mol%, with a ratio dipole/dipolarophile of 2:3 and with reactions carried out in dry CH_2Cl_2. Reactions catalyzed by the Fe complex **1** were performed in the presence of 5 mol% of lutidine (2,6-dimethyl pyridine) as acid-impurities scavenger, as reported for the Diels–Alder reactions.[10a]

The initial set of reactions were carried out at −20°C, at which temperature the noncatalyzed reaction is being completely suppressed. Whereas reactions with catalyst (*R*,*R*)-**1** shows a higher selectivity than those with the Ru analogue, (*R*,*R*)-**2c**, the Ru catalyst is less sensitive to water and oxygen, and is easier to recover. In these initial reactions, a concentrated solution of the nitrone in CH_2Cl_2 was added dropwise to a mixture of the catalyst and the enal in CH_2Cl_2 (1 mL) at −20°C, as the solid nitrone was not very soluble at the required temperature (Table 1, entries 2 and 3). Our previous work on Diels–Alder cycloadditions had shown that reactions were best carried out in concentrated media.[10a] For the reaction depicted above, NMR analysis showed, that although present, the noncatalyzed reaction is very slow at −10°C compared to the catalyzed reaction. This simplified the procedure, and the reactions reported in Table 1, entries 4–8 were carried out by adding the nitrone as a solid and in one portion to a mixture of the ruthenium catalyst (*R*,*R*)-**2c** and the enal in CH_2Cl_2 (1 mL) at −10°C. This procedure was found perfectly reproducible from 0.5 to 2 mmol scale.

Varying the catalyst's counterion showed the same effect on the rate of the cycloaddition, as has already been observed and discussed previously.[10b,e,14a,b] Thus, rates are in the order of **2a** (BF_4^-) < **2b** (PF_6^-). No significant improvement over **2c** (SbF_6^-) was found for **2d** ($BARF^-$). This series reflects decreasing coordinating behavior of the anion and the passage from tight to loose ion pairs in the solution. Lower catalyst activity (e.g. **2a**) also leads to an erosion of the asymmetric induction, presumably, by the now competitive achiral-background reaction. The product *ee* values were determined by both NMR (integration of signals corresponding to the two diastereomeric imines formed with *R*(+)-α-methylbenzylamine) and HPLC analyses of the cycloadducts after $NaBH_4$ reduction of the aldehyde function.

Table 1. Asymmetric 1,3-dipolar cycloaddition of the diphenylnitrone and methacrolein catalyzed by **1** and **2**.



3a **4** **5a** **6a**

Entry	Catalyst (*R*,*R*)	*T* [°C]	*t* [h]	Isolated yield [%]	**5a**/**6a**[a]	*ee* [%] **5a**/**6a**[b]
1	–	25	24	95	100:0	0:–
2[c]	**1**	−20	32	85	80:20	87:91
3	**2c**	−20	32	92	60:40	76:94
4[d]	**2c**	−10	14	99	67:33	75:94
5[e]	**2c**	−10	16	94	62:38	75:93
6[d]	**2b**	−10	20	52	67:33	56:44
7[d]	**2a**	−10	22	77	64:36	73:94
8[d]	**2d**	−10	12	80	63:37	77:94

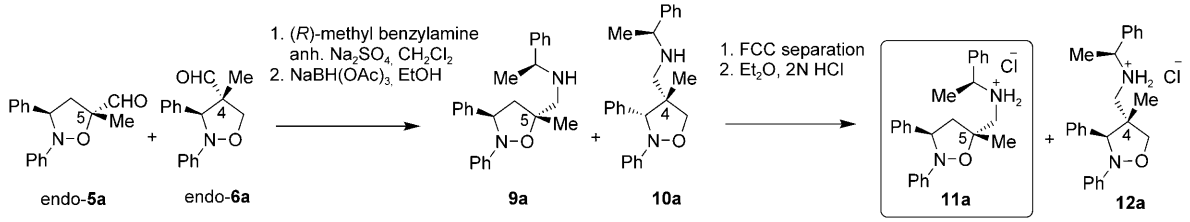
[a] determined by NMR integration; [b] determined by HPLC analysis of the corresponding primary alcohols; [c] reaction carried out in the presence of 2,6-lutidine (5 mol%); [d] reaction carried on 0.5 mmol scale in CH_2Cl_2 (1 mL). [e] reaction carried on 2 mmol scale.

Absolute Configuration

The stereochemical outcome of the enal/nitrone cycloaddition catalyzed by (*R*,*R*)-**1** is in line with an approach of the dipole on the available C_α-*Si* face of the O-coordinated methacrolein-alkene moiety (see Scheme 1). Diastereoselectivity arises from a preferred *endo* approach of the nitrone to the dipolarophile (see Figure 2).

The model in Figure 2 is based on the X-ray structure of [Ru((*R*,*R*)-BIPHOP-F)Cp(methacrolein)][SbF_6],[10b] and shows that the pathway leading to the *exo* product would result in unfavorable steric interactions between one of the ligand's perfluorophenyl groups and the approaching nitrone. The *endo* approach of pyrrolidine *N*-oxide to methacrolein coordinated to complex (*R*,*R*)-**1** is favored and yields the *S*,*S* product.

The absolute configuration of the cycloadducts was assigned based on the model presented in Figure 2, our earlier X-ray data and independent diastereoselective synthesis of reaction products with cyclic nitrones,[9] and on comparison of the literature data.[14b] Confirmation came from the X-ray structure determination of the reductive hydroamination product **11a** (see Figure 3) after chromatographic separation of the two regioisomeric amines.



Scheme 1. Derivatization of the cycloaddition product.

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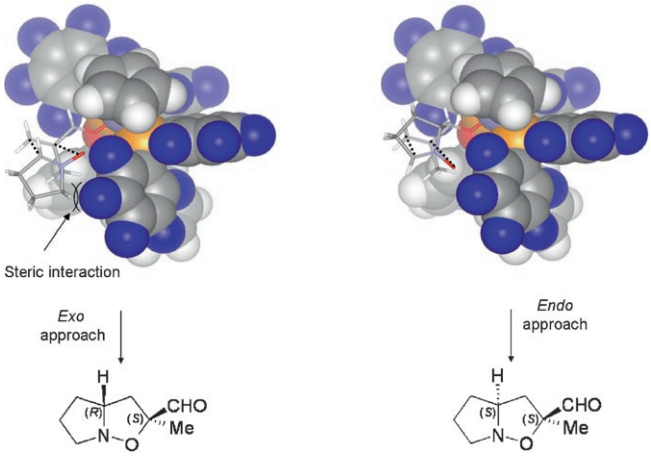


Figure 2. Proposed model for the nitrone approach on the more accessible face of the methacrolein coordinated in the chiral-catalyst site.

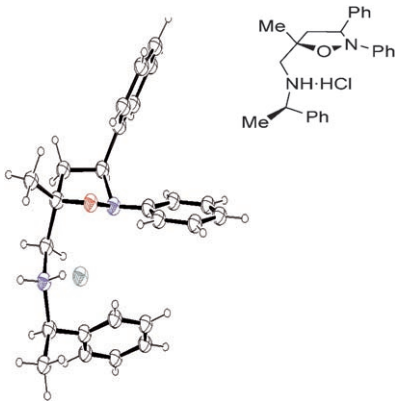


Figure 3. X-ray structure of the reductive amination product (**11a**) derived from isoxazolidine ***endo*-5a**.

Crystallization of **11a** by vapor diffusion from ethanol/diisopropyl ether afforded fine, needle-shaped crystals. For **11a**, a suitable crystal was collected and determined by X-ray analysis.[26]

The absolute configuration corresponds to C1(*S*), C3(*S*), C18(*R*), as is expected from an *endo* approach of the *Z*-configured nitrone to the accessible C_α-*Si* face of the double bond of the methacrolein coordinated in the chiral pocket of the [Ru(acetone)(*R*,*R*-BIPHOP-F)Cp][SbF_6] complex (*R*,*R*)-**2c**.

N-phenyl, *α*-Aryl Nitrones

The influence of the electronic properties of the nitrones on the regioselectivity of the cycloaddition reaction was studied by introducing the substituents in the α-phenyl moiety of the nitrone. The nitrones were readily prepared in good yields by condensation of phenylhydroxylamine with the corresponding *para*-substituted benzaldehydes.

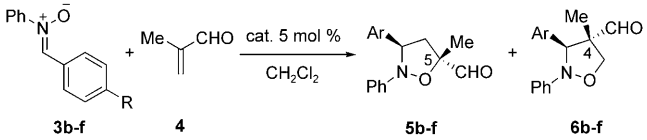
For comparison of the Fe and Ru catalysts, the reactions were initially carried out at −20 °C, which is the temperature required to avoid Fe-catalyst degradation. Subsequently, the ruthenium-catalyzed reactions were performed at −10 °C for the reasons outlined for diphenyl nitrone.

Racemic product samples for HPLC analysis were obtained by stirring the diarylnitrone and methacrolein in CH_2Cl_2 at room temperature for about 12–48 h. In all cases, the only product observed in the non catalyzed reaction is the *endo*-5-regioisomer.

The data in Table 2 show a clear dependence of the ratio of regioisomers on the electronic properties of the aryl substituent. The same trend was observed by Doyle and coworkers using a chiral dirhodium(II)-carboxamidate catalyst.[19] Enantioselectivities for the 4-regioisomer (90–95 % *ee*) exceed those of the 5-regioisomer (75–80 % *ee*). This is as expected given that the background reaction leads to the 5-regioisomer exclusively. Sensitivity of the catalytic system (in the case of Fe) and potential decomposition of the nitrone by the Lewis acid complexes account for the poor yields obtained for some of the examples.[14b,27] The low solubility of the diaryl nitrones at −20 °C required the use of more solvent and this, in turn, led to long reaction times.

The use of *N*-phenyl, α-4-cyano-phenyl nitrone **3g** as a substrate for the catalyzed reaction, afforded a 96:4 mixture of **5g**/**6g** regioisomers in 23 % isolated yield after 77 h.

Table 2. Asymmetric catalytic 1,3-dipolar cycloaddition reactions of diarylnitrones with methacrolein.



3b-f **4** **5b-f** **6b-f**

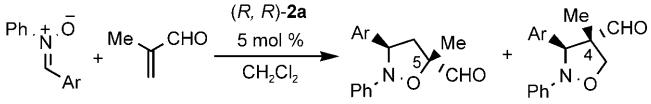
R	Catalyst[a] (*R*,*R*)	*T* [°C]	*t* [h]	Isolated yield [%]	**5**/**6**[b]	*ee* [%] **5**/**6**[c]
NO_2 (**3b**)	**1**	−20	>120	Traces	–:–	–:–
	2a	−20	>120	16	96:4	78:60
	2a	−10	74	16	95:5	71:–
CF_3 (**3c**)	**1**	−20	>120	34	97:3	59:–
	2a	−20	96	79	90:10	74:–
	2a	−10	64	99	91:9	74:88
Cl (**3d**)	**1**	−20	>120	36	86:14	64:–
	2a	−20	>120	80	71:29	70:83
	2a	−10	64	89	73:27	77:89
Me (**3e**)	**1**	−20	120	50	64:36	46:92
	2a	−20	96	88	43:57	76:94
	2a	−10	22	99	41:59	74:95
OMe (**3f**)	**1**	−20	120	53	28:72	81:95
	2a	−20	96	82	15:85	76:93
	2a	−10	22	99	21:79	75:92

[a] reactions catalyzed by (*R*,*R*)-**1** were carried out in the presence of 2,6-lutidine (5 mol %); [b] determined by NMR integration; [c] determined by HPLC analysis of the corresponding primary alcohols.

HPLC analysis of the alcohol revealed that the mixture is racemic. We presume that aryl nitrile irreversibly binds to the ruthenium, thus blocking the catalytic cycle. Nitriles are good ligands for the Ru^{II} system, and ligand exchange takes place only slowly even at room temperature.[15]

Other aromatic moieties can be introduced at the nitrone α-position as shown by the two examples in Table 3.

Table 3. *N*-phenyl, α-2-naphthyl, and *N*-phenyl, α-2-furyl nitrones as 1,3-dipoles.



3h, i 4 5h, i 6h, i

Ar	*t* [h]	Isolated yield [%]	**5:6**[a]	*ee* [%] **5/6**[b]
2-naphthyl (**3h**)	23	80	63:37	70:91
2-furyl (**3i**)	64	72	60:40	70:91

[a] determined by NMR integration; [b] determined by HPLC analysis of the corresponding primary alcohols.

Hammett plots

The data was correlated by plotting log[(% **5**-R/% **6**-R)/(% **5**-H/% **6**-H)] versus the Hammett-σ_P^+ electronic parameter,[28,29] in which, R and H represent the corresponding substituents in the nitrone (see Figure 4). The ratios are based on ^{1}H NMR integration.[28c]

The standardized trendline assigned to this semilogarithmic equation gives ρ (the reaction constant) equal to +1.34 (99% fit). Thus, an appreciable dependence of the reaction outcome on the electronic effects of the substituent becomes important, and the positive ρ value confirms that the cycloaddition is assisted by electron-poor substituents placed on the nitrone.[30]

Preference for the selective formation of the *endo* cycloadducts is in good agreement with the previous studies on the Lewis acid catalyzed cycloaddition reactions.[31] The experimental results represent the first instance of a "gradual regiochemical switch" based on the variation of the electronic properties of the nitrone. All previous examples of regiocontrol were based on the variation of the electronic properties of the alkene.[30b,32] These two systems can be considered equivalent, knowing that in the transition state for the 1,3-dipolar cycloaddition of nitrones with electron-deficient alkenes, both types of HOMO–LUMO interactions become important.[28a,33] An NMR investigation of the substitution effects in this series of diarylnitrones confirms the good correlation between key ^{13}C and ^{1}H shifts, and the corresponding Hammett parameters.[34] Considering that the initial differences in the electronic properties of the diarylnitrones are reflected in the regioisomeric ratio of the cycloadducts, we postulate that the Ru-catalyzed 1,3-dipolar cycloaddition reaction involves an early transition state with a highly asynchronous character.

To determine if the variations observed can be rationalized computationally, the study was extended using DFT methods.[30a,32b]

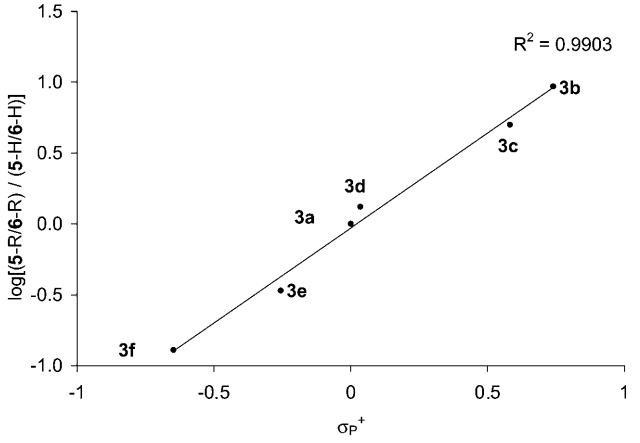


Figure 4. Hammett plot of the observed regioisomeric product ratio as a function of the electronic parameter (σ_P^+) of the nitrone substituents.

Modelling

The parent diarylnitrone **3a** was investigated previously by using B3LYP/6-31G* methods in the context of 1,3-dipolar cycloadditions.[35] However, this was not the case for the diphenylnitrones substituted in the *para* position of the α-phenyl. Therefore, in an effort to provide further evidence for the interesting reversal of the regioselectivity observed in the context of the present work, we undertook a computational investigation of the series of diphenylnitrones substituted in at the *para* position of the α-phenyl.

The distortion from planarity of the two aryls is a notable structural feature of the unsubstituted diphenylnitrone **3a**. Indeed, using the B3LYP method for the optimization of diphenylnitrone **3a**, Salvatella and co-workers reported the dihedral angle of CPh–CPh–N–O as 31.6°.[36] This angle is an appropriate descriptor revealing the distortion between the planes of the two aryl rings. In the present work, the PBE1PBE functional with larger basis sets indicated for **3a**, shows a similar distortion with a dihedral angle of 33.7°. To verify whether this distortion is independent of the computational method, we also optimized the geometry of **3a** with the post Hartre–Fock ab initio method. To our satisfaction, the geometry optimization using the MP2/6-311G** method provided very similar results. Its structural parameters and the CPh–CPh–N–O dihedral angle in particular, were in good agreement with the PBE1PBE results, as well as results reported in the literature (Table 4, entry 1).[35,36] These results indicate, on one hand, no matter which computational method is used, the conjugation between the nitrone and the *N*-phenyl group will be perturbed as a consequence of this distortion. On the other hand, the *C*-phenyl remains fully conjugated with the nitrone as confirmed by the methods cited previously. This observation is important when deciding on which phenyl the *para* substituent would most effectively modulate the electronic properties of the nitrone

Table 4. Total energies and selected properties for diphenylnitrones computed at PBE1PBE/6-311++G** level of theory.

Entry	R	E_{tot}[a] neutral [hartree]	E_{tot}[a] cation [hartree]	ZPE[b] neutral [hartree]	ZPE[b] cation [hartree]	AIP(0)[c] [eV]	Oxygen[d] charge	Dih.[e] angle [deg]
1	H	−631.331660	−631.059523	0.208755	0.208816	7.41	−0.54	33.7
2	NO_2	−835.690505	−835.397243	0.211456	0.210915	7.97	−0.51	34.5
3	CF_3	−968.165340	−967.879996	0.213525	0.213426	7.76	−0.52	34.2
4	Cl	−1090.795617	−1090.522469	0.199209	0.199382	7.44	−0.54	33.7
5	CH_3	−670.610378	−670.346024	0.235988	0.235984	7.19	−0.54	33.3
6	OMe	−745.763189	−745.508918	0.241338	0.241941	6.94	−0.55	32.5

[a] Total electronic energies. [b] Zero-point vibrational-energy corrections using the harmonic approach. [c] Adiabatic ionization potentials including the ZPE correction. [d] NBO charge on the N−oxygen of diphenylnitrone. [e] C_{Ph}–C_{Ph}–N–O dihedral angle.

moiety. Consequently, while the *para*-substitution effects on the *N*-phenyl would be perturbed by the distortion from the planarity, the site of choice for effective substituent effects is the *para* position on the *C*-phenyl.

For the series of the *para*-substituted diphenylnitrones, our geometry optimizations with the DFT methods revealed the same type of out-of-planarity distortion between the two aryls as was observed for the non substituted species **3a**. Indeed, the dihedral angle CPh−CPh−N−O remains in quite a narrow range between 32.5° and 33.7° (Table 4). Also, no meaningful correlation could be established between the substituents at the *para* position and the out-of-planarity distortion of the two aryls in diphenylnitrones.

This contribution aims to provide the rationale for the changes in the regioselectivity of 1,3-dipolar cycloadditions as a function of nitrone properties. As the series of substituted diphenylnitrones react with the same dipolarophile, it is suggested that the variation in electronic properties of the nitrone governs the regiochemical outcome of this cycloaddition. For the series of substituted diphenylnitrones, we therefore plotted the adiabatic ionization potentials AIP(0) with the log of ratio between 5-substituted and 4-substituted adducts (Figure 5). A very good correlation factor of 0.993 is obtained for the decrease of the ionization potential, whereas the regioselectivity changes progressively from 5-cycloadducts to 4-cycloadducts. In view of the correlation depicted in Figure 4, the increased proportion of 4-regioisomer reflects stronger nitrone HOMO–dipolarophile LUMO interactions. This is in agreement with the reports in the literature that the regioselectivity switches from the usually observed 5-adducts to 4-adducts when the ionization potential of the nitrone decreases.[37]

With the full conjugation of the α-phenyl with the dipole, the *para* position is also well-suited to modify the charges in the nitrone moiety. Specifically, the accumulation of charge on the oxygen atom can contribute to the enhanced formation of 4-substituted isoxazolidine, as the stabilizing, possibly, electrostatic interaction between the nitrone oxygen and the β-carbon of the dipolarophile takes place. Even though the computed NBO charges for the series of substituted substrates, **3b** to **3f,** are within quite a narrow range, they nevertheless also correlate quite well (correlation factor 0.96) with the ratio between the 5-cycloadducts and the 4-cycloadducts (Figure 6). It appears that, in addition to increasing the nitrone HOMO–dipolarophile LUMO interactions, the *para* substitution pattern at the α-phenyl position also increases the nucleophilicity of the nitrone moiety and the propensity to form the 4-cycloadduct. In this evolution, the gradual modification of the electronic properties at the oxygen terminus of the nitrone also plays an active role.

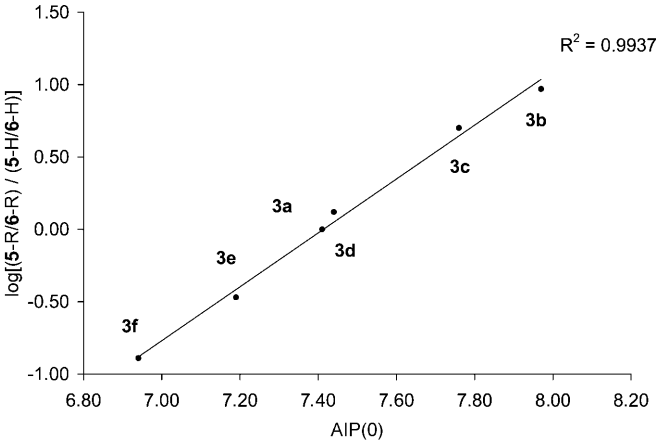


Figure 5. Linear correlation of the adiabatic ionization potentials (AIP(0)) with the observed regioisomeric ratio.

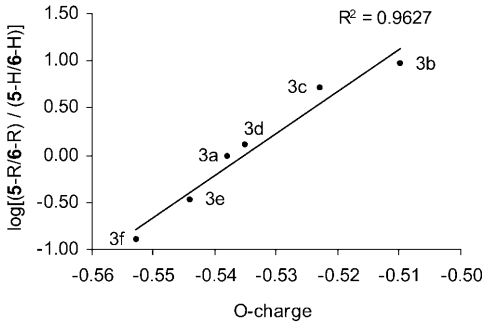


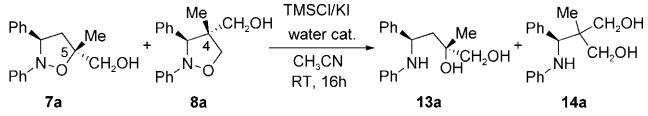
Figure 6. Correlation of the NBO charges on nitrone oxygen (O-charge) with the observed regioisomeric product ratio.

Opening of the Isoxazolidine Core

Reductive cleavage of the N−O bond in the isoxazolidines gives access to acyclic building blocks that carry multiple stereogenic centers and diverse functionalities. A variety of reducing methods were developed for this purpose, including the catalytic hydrogenation over Raney nickel,[38] Pd,[39] Pt,[40] Rh,[41] Al amalgam,[42] $LiAlH_4$,[43] or Zn–Al bimetallic systems.[44] Lewis acids have also been shown to ring-open

the isoxazolidines.[45] However, we found most of these methods to be substrate-specific, low yielding, and, in our case, led to secondary products.

Konwar and co-worker reported a mild, clean, and general procedure for the reductive cleavage of isoxazolidines and 1,2-benzisoxazoles based on the use of iodo trimethylsilane (generated in situ from chloro trimethylsilane and potassium iodide in acetonitrile, with traces of water).[46] This procedure also worked for the isoxazolidines reported in this study. Thus, starting from a mixture of the alcohols **7a** and **8a** in acetonitrile, the addition of 3 equivalents of iodo trimethylsilane afforded the desired aminodiols in 90% isolated yield (see Scheme 2).



Scheme 2. Ring-opening of the isoxazolidine ring.

Conclusions

The asymmetric iron- and ruthenium-Lewis acid catalyzed dipolar cycloaddition reaction between diaryl nitrones and methacrolein has afforded isoxazolidine products in good yields, high enantioselectivity, and with complete *endo* selectivity. The products are obtained as regioisomeric mixtures in ratios varying from 96:4 to 15:85. The regioselectivity correlates directly with the electronic properties of the nitrone. The experimental and computational data provide a full rationale for this observation.

Experimental Section

General

Complexes (*R*,*R*)-**1** and (*R*,*R*)-**2a–d** were prepared by using our previously published procedures.[10] Reactions were carried out under a positive pressure of nitrogen unless otherwise stated. Glassware was oven-dried, and further dried by placing under vacuum, and heated with a heat gun for approximately 5 min as necessary. Purification of THF, diethyl ether, *n*-hexane, toluene, and dichloromethane were carried out by using a SolvtekH® purification system. The nitrones **3a–j** were synthesized by the condensation of the appropriate substituted benzaldehyde with phenylhydroxylamine[47] Other commercially available chemicals were used as supplied unless stated otherwise. Flash column chromatography was carried out using silica gel (60 L, 32–63 mesh, Brunschwig SA, Basel). Thin-layer chromatography was performed on precoated aluminum plates (Merck silica 60F254), and visualized using UV light, aqueous $KMnO_4$, or ceric ammonium molybdate acidic solution. ^1H, ^{31}P, and ^{13}C NMR spectra were recorded on Bruker AMX 300, 400, and 500 spectrometers. Chemical shifts are quoted relative to tetramethylsilane and referenced to the residual solvent peaks as appropriate. Infrared spectra were recorded on a Perkin–Elmer Spectrum One spectrophotometer as neat liquids using a Golden Gate accessory. Polarimetry was performed using a Perkin–Elmer 241 Polarimeter with a Na lamp (589 nm, continuous), and circular dichroism spectra were recorded with a JASCO J-715 spectropolarimeter. LRMS were acquired using a Varian CH4 or SM1 spectrometer with the ionizing voltage at 70 eV, whereas HRMS were measured using a positive TOF mode in the ESI-MS mode using an Applied Biosystems/Scix (Q-STA) spectrometer. HPLC analyses were recorded on an Agilent HP 1100 Series instrument (hexanes/2-propanol mixtures).

Crystallographic Data

11a: $(C_{25}H_{29}N_2O)^+ Cl^-$; $M_r = 409.0$, Orthorhombic, $P2_12_12_1$, $a = 6.8037(3)$, $b = 15.5597(9)$, $c = 21.8068(13)$ Å, $V = 2308.5(2)$ Å^3; $Z = 4$, $\mu = 0.183$ mm^{-1}, $d_x = 1.177$ g cm^{-3}, $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å); 19653 reflections measured at 150 K on a STOE IPDS diffractometer, 4441 unique reflections of which 2165 with $|F_o| > 4\sigma(F_o)$. Data were corrected for Lorentz and polarization effects, and for absorption (T_{min}, $T_{max} = 0.9828$, 0.9930). The structure was solved by the direct methods (SIR97).[48] All calculations were performed with the XTAL system.[49] Full-matrix least-squares refinement based on F using weights of $1/(\sigma^2(F_o) + 0.0003(F_o^2))$ gave final values $R = 0.032$, $\omega R = 0.027$, and $S = 0.93(2)$ for 263 variables and 2283 contributing reflections. The Flack parameter $x = -0.07(10)$ and the CD spectrum of the crystal used for X-ray diffraction study was fully superimposable to the spectrum of the bulk of **11a.** CCDC 652569 contains the supplementary crystallographic data for **11a**. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

Non Catalyzed 1,3-Dipolar Cycloaddition Reactions

In a Schlenk tube (50 mL) equipped with a magnetic stirring bar, the nitrone (1 equiv) in CH_2Cl_2 (2–5 mL) was stirred at RT to give a clear pale-yellow solution. Methacrolein (1.2 equiv) was added dropwise using a syringe at RT. The reaction mixture was stirred at RT until TLC analysis (SiO_2, CH_2Cl_2, or AcOEt/cyclohexane 2:3) showed no unreacted nitrone. Addition of dry hexane (10 mL), filtration (P3-frit, Celite 545, $H_{dry} = 1.5$ cm, $\Phi_e = 2$ cm), and in vacuo removal of solvents afforded a colorless oil. Purification by column chromatography (SiO_2, $H_{dry} = 15$ cm, $\Phi_e = 2$ cm) in CH_2Cl_2 ($R_f = 0.64$) or gradient cyclohexane/ethylacetate (10:1, 55 mL; 8:1, 45 mL; 6:1, 47 mL) gave viscous, clear oils that solidify at −30 °C. The regioisomeric ratio was determined by ^1H NMR of the crude mixture. In all instances only the *endo*-5-substituted isoxazolidine was isolated. Baseline separation of signals for the racemic mixtures was obtained by HPLC analysis of the corresponding primary alcohols (CHIRACEL OD-H, Grad. 99+1–90+10, solvent 1 mL min^{-1}, 60 min, 254 nm).

***rac*-5a:** (*rac*-5-methyl-2-*N*-3-diphenyl-isoxazoline-5-carbaldehyde) Obtained in 93% yield according to the general procedure, after 19 h. IR, ^1H NMR, ^{13}C NMR, MS and HRMS analyses matched to the previously described data.[9,14c]

***rac*-5b**: (*rac*-5-methyl-3-(4-nitro-phenyl)-2-phenyl-isoxazoline-5-carbaldehyde) Obtained in 81% yield according to the general procedure, after 25 h. IR, ^1H NMR, ^{13}C NMR, MS and HRMS analyses matched to the previously described data.[9]

***rac*-5c**: (*rac*-5-methyl-3-(4-trifluoromethyl-phenyl)-2-phenyl-isoxazoline-5-carbaldehyde) Obtained in 96% yield according to the general procedure, after 26 h. IR, ^1H NMR, ^{13}C NMR, MS and HRMS analyses matched to the previously described data.[9]

***rac*-5d**: (*rac*-5-methyl-3-(4-chloro-phenyl)-2-phenyl-isoxazoline-5-carbaldehyde) Obtained in 91% yield according to the general procedure, after 66 h. IR (CH_2Cl_2): $\tilde{\nu} = 726$, 829, 909, 1014, 1091, 1490, 1598, 1731, 2250, 2988, 3029 cm^{-1}; ^1H NMR (400 MHz, C_6D_6): $\delta = 1.01$ (s, 3H, CH_3), 1.67–1.69 (dd, 1H, $J = 4.2$, 6.8 Hz, C(4)-H_A), 2.83–2.88 (dd, 1H, $J = 4.2$, 6.8 Hz, C(4)-H_B), 4.34–4.38 (t, 1H, $J = 6.8$ Hz, C(3)-H), 6.75–6.78 (m, 1H, H_{arom}), 6.88–6.91 (m, 4H, H_{arom}), 7.00–7.06 (m, 4H, H_{arom}), 9.42 ppm (s, 1H, CHO); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 18.7$, 45.9, 67.8, 87.1, 114.9, 123.2, 128.0, 128.7, 128.9, 133.3, 139.5, 149.5, 201.2 ppm; MS (EI): *m*/*z* (%): 301 [M^+, 38], 230 (23), 216 (28), 139 (42), 121 (100), 111 (26), 104 (15), 93 (86), 91 (66), 77 (53), 66 (45); HRMS (ESI+) *m*/*z* (%) calcd for $C_{17}H_{16}ClNO_2$: 301.0871 [$M+H$]$^+$; found: 301.0865.

***rac*-5e**: (*rac*-5-methyl-3-(4-methyl-phenyl)-2-phenyl-isoxazoline-5-carbaldehyde) Obtained in 77% yield according to the general procedure, after 49 h. IR (CH_2Cl_2): $\tilde{\nu} = 970$, 1386, 1488, 1598, 1731, 2091, 2197, 2301, 2875, 2988, 3029, 3340 cm^{-1}; ^1H NMR (400 MHz, C_6D_6): $\delta = 1.27$ (s, 3H, CH_3), 1.88–1.91 (dd, 1H, $J = 4.8$, 6.0 Hz, C(4)-H_A), 2.03 (s, 3H, CH_3), 2.92–2.97

(dd, 1H, $J=4.8$, 6.0 Hz, C(4)-H_B), 4.49–4.53 (t, 1H, $J=6.8$ Hz, C(3)-H), 6.74–6.77 (m, 1H, H_{arom}), 6.90–6.92 (d AB, 2H, $J=7.8$ Hz, H_{arom}), 6.99–7.07 (m, 4H, H_{arom}), 7.14 (m, 3H, H_{arom}), 9.49 ppm (s, 1H, CHO); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta=19.1$, 21.3, 46.8, 68.8, 87.5, 115.5, 122.0, 127.2, 129.1, 129.9, 137.9, 138.8, 150.6, 201.8 ppm; MS (EI) *m/z* (%): 281 (M^+, 38), 238 (27), 210 (54), 196 (48), 173 (26), 160 (38), 145 (84), 121 (46), 117 (38), 104 (22), 91 (69), 77 (34); HRMS (ESI+) *m/z* (%) calcd for $C_{18}H_{19}NO_2$: 281.1408 $[M+H]^+$; found: 281.1411.

***rac*-5f**: (*rac*-5-methyl-3-(4-methoxy-phenyl)-2-phenyl-isoxazoline-5-carbaldehyde) Obtained in 67% yield according to the general procedure, after 60 h. IR (CH_2Cl_2): $\tilde{\nu}=667$, 833, 970, 1177, 1386, 1489, 1512, 1598, 1731, 2003, 2091, 2197, 2301, 2599, 2875, 2990, 3029, 3340 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta=1.53$ (s, 3H, CH_3), 2.30–2.38 (dd, 1H, $J=8$, 12.6 Hz, C(4)-H_A), 3.17–3.27 (dd, 1H, $J=8$, 12.6 Hz, C(4)-H_B), 3.80 (s, 3H, OCH_3), 4.66–4.74 (t, 1H, $J=8$ Hz, C(3)-H), 6.84–7.01 (m, 5H, H_{arom}), 7.17–7.37 (m, 4H, H_{arom}), 9.68 ppm (s, 1H, CHO); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta=19.2$, 46.8, 55.7, 68.6, 87.4, 114.6, 115.6, 122.1, 128.5, 129.1, 133.6, 150.6, 159.6, 201.9 ppm; MS (EI) *m/z* (%) = 297 [M^+, 95], 226 (28), 210 (33), 189 (86), 178 (61), 162 (67), 134 (42), 121 (33), 104 (24), 91 (100), 77 (65); HRMS (ESI+) *m/z* (%) calcd for $C_{18}H_{19}NO_3$: 297.1355 $[M+H]^+$; found: 297.1363.

***rac*-5g**: (*rac*-5-methyl-3-(4-cyano-phenyl)-2-phenyl-isoxazoline-5-carbaldehyde) Obtained in 80% yield according to the general procedure, after 18 h. IR ($CHCl_3$): $\tilde{\nu}=693$, 756, 836, 886, 946, 1020, 1031, 1086, 1105, 1179, 1201, 1248, 1292, 1375, 1414, 1453, 1489, 1597, 1729, 1929, 2229, 2810, 2979, 3441 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.50$ (s, 3H, CH_3), 2.17–2.22 (dd, 1H, $J=4.8$, 6.8 Hz, C(4)-H_A), 3.32–3.37 (dd, 1H, $J=4.8$, 6.8 Hz, C(4)-H_B), 3.98–4.00 (d, 1H, $J=8.8$ Hz, C(3)-H), 4.41–4.43 (d, 1H, $J=8.8$ Hz, 4-H_B-C_5), 4.84–4.88 (t, 1H, $J=6.8$ Hz, 5-H-C_3), 4.99 (s, 1H, 4-H-C_3), 6.88–6.94 (m, 3H, H_{arom}), 7.12–7.27 (m, 2H, H_{arom}), 7.54–7.56 (d AB, 2H, $J=8$ Hz, H_{arom}), 7.63–7.65 (d AB, 2H, $J=8$ Hz, H_{arom}), 9.66 ppm (s, 1H, 4-CHO); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta=18.6$, 45.4, 67.7, 114.7, 127.4, 128.9, 132.7, 122.1, 200.8 ppm; MS (TS) *m/z* (%): 293.5 [$M+1$], 264.3, 208.3, 207.3; HRMS (ESI+) *m/z* (%) calcd for $C_{18}H_{17}N_2O_2$: 293.1284 $[M+H]^+$; found: 293.1289.

***rac*-5h**: (*rac*-5-methyl-3-(2-naphthyl)-2-phenyl-isoxazoline-5-carbaldehyde) Obtained in 97% yield according to the general procedure, after 24 h. IR ($CHCl_3$): $\tilde{\nu}=693$, 754, 820, 859, 890, 1031, 1085, 1125, 1373, 1452, 1489, 1597, 1730, 2808, 2932, 3059 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=$ 1.54 (s, 3H, CH_3), 2.34–2.39 (dd, 1H, $J=7.6$, 12.8 Hz, C(4)-H_A), 3.33–3.38 (dd, 1H, $J=8.0$, 12.8 Hz, C(4)-H_B), 4.93–4.97 (t, 1H, $J=7.6$ Hz, C(3)-H), 6.89–6.93 (m, 1H, H_{arom}), 7.02–7.04 (m, 2H, H_{arom}), 7.19–7.23 (m, 2H, H_{arom}), 7.48–7.53 (m, 2H, H_{arom}), 7.59–7.61 (m, 1H, H_{arom}), 7.84–7.92 (m, 4H, H_{arom}), 9.74 ppm (s, 1H, CHO); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta=$ 18.9, 46.3, 69.0, 87.4, 114.9, 121.9, 124.5, 125.6, 126.2, 126.5, 127.9, 128.1, 128.9, 129.0, 133.0, 137.6, 138.7, 150.3, 201.4 ppm; MS (TS) *m/z* (%): 350.5 [$M+CH_3OH$], 318.5 [$M+1$], 289.3, 232.3, 193.3, 178.3; HRMS (ESI+) *m/z* (%) calcd for $C_{22}H_{24}NO_3$: 350.1750 $[M+CH_3OH]^+$; found: 350.1740.

***rac*-5i**: (*rac*-5-methyl-3-(2-furyl)-2-phenyl-isoxazoline-5-carbaldehyde) Obtained in 77% yield according to the general procedure, after 24 h. IR ($CHCl_3$): $\tilde{\nu}=696$, 753, 820, 859, 890, 1031, 1085, 1125, 1372, 1452, 1489, 1597, 1735, 2808, 2932, 3059 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.57$ (s, 3H, CH_3), 2.46–2.50 (dd, 1H, $J=4.6$, 12.8 Hz, C(4)-H_A), 3.17–3.22 (dd, 1H, $J=8.4$, 12.8 Hz, C(4)-H_B), 4.94–4.98 (q, 1H, $J=4.6$, 8.4 Hz, C(3)-H), 6.23–6.29 (m, 2H, H_{arom}), 6.96–6.99 (m, 1H, H_{arom}), 7.04–7.06 (m, 2H, H_{arom}), 7.24–7.29 (m, 2H, H_{arom}), 7.35–7.36 (m, 1H, H_{arom}), 9.69 ppm (s, 1H, CHO); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta=18.8$, 41.7, 61.9, 86.5, 108.3, 110.5, 116.1, 122.6, 128.7, 142.5, 148.5, 152.7, 202.4 ppm.

***rac*-5j**: (*rac*-5-methyl-3-phenyl-2-(4-methoxy-phenyl)-isoxazoline-5-carbaldehyde) Obtained in 95% yield according to the general procedure, after 25 h. IR ($CHCl_3$): $\tilde{\nu}=691$, 756, 823, 889, 1029, 1107, 1180, 1192, 1241, 1299, 1393, 1454, 1505, 1606, 1879, 2835, 2930, 3030, 3337 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.50$ (s, 3H, CH_3), 2.33–2.39 (dd, 1H, $J=8$, 12.8 Hz, C(4)-H_A), 3.23–3.28 (dd, 1H, $J=8.0$, 12.8 Hz, C(4)-H_B), 3.76 (s, 3H, OMe), 4.65–4.69 (t, 1H, $J=8$ Hz, C(3)-H), 6.79 (d, 2H, $J=$ 8.8 Hz, H_{arom}), 7.76 (d, 2H, $J=8.8$ Hz, H_{arom}), 7.29–7.33 (m, 3H, H_{arom}), 7.36–7.40 (m, 1H, H_{arom}), 7.45–7.48 (m, 1H, H_{arom}), 9.73 ppm (s, 1H, CHO); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta=19.5$, 55.5, 69.6, 86.6, 114.0, 118.0, 127.1, 118.0, 127.1, 127.8, 128.8, 140.4, 143.4, 155.5, 201.3 ppm.

General Procedure for the Reduction of the Cycloadducts

In a flask (10–25 mL) equipped with a magnetic stirring bar, the cycloadduct (1 equiv) and excess $NaBH_4$ (4–8 equiv) were loaded and absolute ethanol was added by syringe (5 mL). The reaction was followed by TLC analysis (cyclohexane/AcOEt 3:2), and upon complete reduction of the aldehyde, water (5 mL) was added to quench the excess borohydride. The mixture was extracted with Et_2O (3×10 mL), dried on anhydrous Na_2SO_4, filtered, and solvents were removed in vacuo to give a crude mixture that was further purified by flash column chromatography (SiO_2, cyclohexane/AcOEt 3:2). The procedure applies for the non racemic cycloadducts as well.

***rac*-7a:** (*rac*-5-methyl-2-*N*-3-diphenyl-isoxazoline-5-methanol) Obtained in 90% yield according to the general procedure. IR, ^{1}H NMR, ^{13}C NMR, MS and HRMS analyses matched to the previously described data.[16b]

***rac*-7b**: (*rac*-5-methyl-3-(4-nitro-phenyl)-2-phenyl-isoxazoline-5-methanol) Obtained in 86% yield according to the general procedure. IR ($CHCl_3$): $\tilde{\nu}=760$, 838, 855, 1048, 1109, 1180, 1346, 1453, 1490, 1519, 1598, 2935, 3423 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6): $\delta=1.47$ (s, 3H, CH_3), 1.90 (br s, 1H, OH), 2.17–2.22 (dd, 1H, $J=7.6$, 12.4 Hz, C(4)-H_A), 3.01–3.06 (dd, 1H, $J=7.6$, 12.4 Hz, C(4)-H_B), 3.48–3.61 (m, 2H, C**H**$_2$OH), 4.76–4.81 (t, 1H, $J=7.6$ Hz, C(3)-H), 6.86–6.89 (m, H_{arom}), 6.92–6.96 (m, H_{arom}), 7.19–7.24 (m, H_{arom}), 7.63–7.66 (d AB, 2H, $J=8.8$ Hz, H_{arom}), 8.22–8.24 ppm (d AB, 2H, $J=8.8$ Hz, H_{arom}); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta=18.75$, 45.58, 67.61, 87.45, 114.88, 122.34, 124.26, 127.74, 129.07, 147.53, 148.83, 149.21 ppm; MS (TS) *m/z* (%): 315.5 [$M+1$], 284.3, 241.5, 227.3, 181.5, 168.3; HRMS (ESI+) *m/z* (%) calcd for $C_{17}H_{18}N_2O_4$: 315.1339 $[M+H]^+$; found: 315.1335; HPLC (CHIRACEL OD-H, Grad. 99+–90+10, 1 mL min^{-1}, 60 min, 254+340 nm): t_R (min.) = 55.01 (50.5%), 57.98 (49.5%).

***rac*-7c**: (*rac*-5-methyl-3-(4-trifluoromethyl-phenyl)-2-phenyl-isoxazoline-5-methanol) Obtained in 98% yield according to the general procedure. IR ($CHCl_3$): $\tilde{\nu}=694$, 757, 838, 1018, 1066, 1120, 1163, 1322, 1419, 1454, 1489, 1598, 1619, 2876, 2936, 3422 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6): $\delta=$ 1.47 (s, 3H, CH_3), 1.93 (br s, 1H, OH), 2.17–2.22 (dd, 1H, $J=8.0$, 12.4 Hz, C(4)-H_A), 2.97–3.02 (dd, 1H, $J=8.0$, 12.4 Hz, C(4)-H_B), 3.47–3.60 (m, 2H, CH_2OH), 4.70–4.74 (t, 1H, $J=8.0$ Hz, C(3)-H), 6.88–6.95 (m, H_{arom}), 7.19–7.27 (m, H_{arom}), 7.58–7.60 (d AB, 2H, $J=8$ Hz, H_{arom}), 7.62–7.64 ppm (d AB, 2H, $J=8$ Hz, H_{arom}); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta=19.02$, 46.05, 68.42, 87.88, 115.21, 122.33, 128.01, 126.25, 129.33, 146.29, 150.25 ppm; MS (TS) *m/z* (%): 338.3 [$M+1$], 307.5, 264.3, 250.1; HRMS (ESI+) *m/z* (%) calcd for $C_{18}H_{18}F_3NO_2$: 338.1362 [$M+$ H]$^+$; found: 338.1368; HPLC (CHIRACEL OD-H, Grad. 99+1–90+10, 1 mL min^{-1}, 60 min, 254+340 nm): t_R (min.) = 31.69 (48.4%), 34.78 (50.2%).

***rac*-7d**: (*rac*-5-methyl-3-(4-chloro-phenyl)-2-phenyl-isoxazoline-5-methanol) Obtained in quantitative yield according to the general procedure. IR ($CHCl_3$): $\tilde{\nu}=760$, 826, 854, 888, 945, 1014, 1048, 1089, 1290, 1375, 1409, 1453, 1489, 1597, 2935, 3425 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6): $\delta=$ 1.47 (s, 3H, CH_3), 1.86 (bs, 1H, OH), 1.87–1.94 (dd, 1H, $J=5.6$, 12.4 Hz, C(4)-H_A), 2.93–2.99 (dd, 1H, $J=8.0$, 12.4 Hz, C(4)-H_B), 3.40–3.61 (m, 2H, CH_2OH), 4.61–4.66 (t, 1H, $J=8.0$ Hz, C(3)-H), 6.91–7.05 (m, H_{arom}), 7.21–7.25 (m, H_{arom}), 7.29–7.44 ppm (m, H_{arom}); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta=19.2$, 46.3, 68.3, 89.2, 115.7, 124.1, 129.2, 130.1, 132.2, 134.7, 141.5, 152.1 ppm; MS (TS) *m/z* (%): 304.5 [$M+1$], 273.3, 230.3, 218.3, 216.3, 194.3, 180.5, 163.3; HRMS (ESI+) *m/z* (%) calcd for $C_{17}H_{18}ClNO_2$: 304.1098 $[M+H]^+$; found: 304.1095; HPLC (CHIRACEL OD-H, Grad. 99+1–90+10, 1 mL min^{-1}, 60 min, 254+340 nm): t_R (min.) = 41.63 (51.0%), 46.90 (49.0%).

***rac*-7e**: (*rac*-5-methyl-3-(4-methyl-phenyl)-2-phenyl-isoxazoline-5-methanol) Obtained in 80% yield according to the general procedure. IR ($CHCl_3$): $\tilde{\nu}=693$, 752, 819, 889, 1041, 1179, 1378, 1452, 1488, 1514, 1598, 2871, 2924, 3402 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6): $\delta=1.56$ (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 1.93 (br s, 1H, OH), 2.27–2.34 (dd, 1H, $J=8.4$, 12.6 Hz, C(4)-H_A), 2.97–3.04 (dd, 1H, $J=8.4$, 12.6 Hz, C(4)-H_B), 4.64–

4.70 (t, 1H, J=8.4 Hz, C(3)-H), 6.88–6.97 (m, H_{arom}), 6.96–7.01 (m, H_{arom}), 7.24–7.29 (m, H_{arom}), 7.40–7.44 ppm (m, H_{arom}); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=19.2, 46.3, 68.3, 89.2, 115.7, 124.1, 129.2, 130.1, 132.2, 134.7, 141.5, 152.1 ppm; MS (TS) m/z (%): 284.5 [M+1], 254.5, 236.3, 224.5, 210.3, 196.5, 162.3; HRMS (ESI+) m/z (%) calcd for $C_{18}H_{21}NO_2$: 284.1624 $[M+H]^+$; found: 284.1632; HPLC (CHIRACEL OD-H, Grad. 99+1–90+10, 1 mL min^{-1}, 60 min, 254+340 nm): t_R (min.)=39.10 (52.1%), 43.08 (47.9%).

***rac*-7f**: (*rac*-5-methyl-3-(4-methoxy-phenyl)-2-phenyl-isoxazoline-5-methanol) Obtained in 92% yield according to the general procedure. IR ($CHCl_3$): $\tilde{\nu}$=838, 1034, 1174, 1247, 1302, 1463, 1489, 1511, 1598, 1612, 2872, 2934, 3436 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6): δ=1.48 (s, 3H, CH_3), 1.79 (br s, 1H, OH), 2.17–2.24 (dd, 1H, J=8.4, 12.3 Hz, C(4)-H_A), 2.87–2.94 (dd, 1H, J=8.4, 12.3 Hz, C(4)-H_B), 3.44–3.61 (m, 2H, CH_2OH), 3.82 (s, H, OCH_3), 4.52–4.58 (t, 1H, J=8.4 Hz, C(3)-H), 6.87–6.92 (m, H_{arom}), 7.15–7.18 (d AB, 2H, J=8.4 Hz, H_{arom}), 7.18–7.21 (m, H_{arom}), 7.34–7.37 ppm (d AB, 2H, J=8.4 Hz, H_{arom}); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=18.2, 22.5, 22.7, 43.1, 48.7, 53.6, 55.4, 67.3, 69.6, 74.2, 74.8, 83.3, 114.1, 114.4, 114.9, 115.4, 121.5, 128.0, 128.9, 129.2, 131.7, 151.5, 159.1 ppm; MS (TS) m/z (%): 300.5 [M+1], 270.5, 252.5, 236.3, 224.3, 212.3, 177.3, 161.3; HRMS (ESI+) m/z (%) calcd for $C_{18}H_{22}NO_3$: 300.1594 $[M+H]^+$; found: 300.1599; HPLC (CHIRACEL OD-H, Grad. 99+1–90+10, 1 mL min^{-1}, 60 min, 254+340 nm): t_R (min.)=44.37 (50.0%), 48.38 (50.0%).

***rac*-7g**: (*rac*-5-methyl-3-(4-cyano-phenyl)-2-phenyl-isoxazoline-5-methanol) Obtained in 92% yield according to the general procedure. IR ($CHCl_3$): $\tilde{\nu}$=759, 836, 1050, 1105, 1178, 1291, 1412, 1453, 1489, 1598, 2229, 2934, 3460 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.46 (s, 3H, CH_3), 1.95–1.98 (m, 1H, OH), 2.14–2.19 (dd, 1H, J=4.8, 7.8 Hz, C(4)-H_A), 2.98–3.03 (dd, 1H, J=4.8, 7.8 Hz, C(4)-H_B, 3.46–3.60 (m, 2H, CH_2OH), 4.70–4.74 (t, 1H, J=7.8 Hz, C(3)-H), 6.86–6.88 (m, 2H, H_{arom}), 6.88–6.95 (m, 1H, H_{arom}), 7.19–7.24 (m, 2H, H_{arom}), 7.57–7.59 (d AB, 2H, J=8.4 Hz, H_{arom}), 7.65–7.67 ppm (d AB, 2H, J=8.4 Hz, H_{arom}); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=22.3, 26.9, 47.9, 66.9, 68.8, 114.8, 127.3, 129.0, 132.8, 122.0 ppm; MS (TS) m/z (%): 295.5 [M+1], 264.5, 221.3, 207.3; HRMS (ESI+) m/z (%) calcd for $C_{18}H_{19}N_2O_2$: 295.1441 $[M+H]^+$; found: 295.1438; HPLC (CHIRACEL OD-H, Grad. 99+1–85+15, 1 mL min^{-1}, 120 min, 254+320 nm): t_R (min.)=53.72 (52.6%), 55.79 (47.4%).

***rac*-7h**: (*rac*-5-methyl-3-(2-naphthyl)-2-phenyl-isoxazoline-5-carbaldehyde) Obtained in quantitative yield according to the general procedure. IR ($CHCl_3$): $\tilde{\nu}$=693, 752, 822, 859, 889, 950, 1042, 1124, 1373, 1452, 1488, 1508, 1597, 1930, 2871, 2933, 3058, 3414 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.54 (s, 3H, CH_3), 2.17 (br s, 1H, OH), 2.30–2.35 (dd, 1H, J=7.6, 12.8 Hz, C(4)-H_A), 3.00–3.05 (dd, 1H, J=8.0, 12.8 Hz, C(4)-H_B), 3.52–3.63 (d, 2H, CH_2OH), 4.79–4.84 (t, 1H, J=7.6 Hz, C(3)-H), 6.90–6.94 (m, 1H, H_{arom}), 6.98–7.00 (m, 2H, H_{arom}), 7.18–7.22 (m, 2H, H_{arom}), 7.48–7.53 (m, 2H, H_{arom}), 7.62–7.65 (m, 1H, H_{arom}), 7.83–7.93 ppm (m, 4H, H_{arom}); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=22.6, 48.5, 67.1, 70.1, 83.6, 100.1, 115.0, 121.8, 124.7, 125.4, 126.1, 126.4, 127.9, 128.0, 128.9, 129.0, 133.0, 133.6, 139.4, 1851.2 ppm; MS (TS) m/z (%): 320.5 [M+1], 289.3, 246.3, 232.3, 162.3, 153.3; HRMS (ESI+) m/z (%) calcd for $C_{21}H_{22}NO_2$: 320.1645 $[M+H]^+$; found: 320.1636; HPLC (CHIRACEL OD-H, Grad. 99+1–90+10, 0.75 mL min^{-1}, 100 min, 254+340 nm): t_R (min.)=47.58 (48.7%), 53.07 (49.1%).

***rac*-7i**: (*rac*-5-methyl-3-(2-furyl)-2-phenyl-isoxazoline-5-carbaldehyde) Obtained in quantitative yield according to the general procedure. IR ($CHCl_3$): $\tilde{\nu}$=692, 757, 781, 884, 925, 1011, 1044, 1150, 1181, 1232, 1340, 1379, 1453, 1489, 1598, 2875, 2935, 3409 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.50 (s, 3H, CH_3), 2.26 (br s, 1H, OH), 2.42–2.47 (dd, 1H, J=4.6, 12.8 Hz, C(4)-H_A), 2.79–2.84 (dd, 1H, J=8.4, 12.8 Hz, C(4)-H_B), 3.50–3.61 (d, J=11.6, 2H, CH_2OH), 4.73–4.77 (q, 1H, J=4.6, 8.4 Hz, C(3)-H), 6.25–6.32 (m, 2H, H_{arom}), 6.93–7.02 (m, 1H, H_{arom}), 7.04–7.06 (m, 3H, H_{arom}), 7.21–7.27 (m, 2H, H_{arom}), 7.39 ppm (m, 1H, H_{arom}); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=22.2, 43.4, 63.5, 67.7, 83.3, 107.8, 110.5, 115.7, 122.4, 128.8, 142.4, 150.1, 153.2 ppm; MS (TS) m/z (%): 260.3 [M+1], 229.3, 212.5, 194.3, 186.5, 172.5, 170.3, 162.3, 158.3; HRMS (ESI+) m/z (%) calcd for $C_{15}H_{18}NO_3$: 260.1281 $[M+H]^+$; found: 240.1270; HPLC (CHIRACEL OD-H, Grad. 99+1–90+10, 0.75 mL min^{-1}, 100 min, 254+340 nm): t_R (min.)=39.73 (49.0%), 43.40 (48.6%).

***rac*-7j:** (*rac*-5-methyl-3-phenyl-2-(4-methoxy-phenyl)-isoxazoline-5-methanol) Obtained in 66% yield according to the general procedure. IR ($CHCl_3$): $\tilde{\nu}$=762, 830, 939, 1045, 1180, 1241, 1297, 1375, 1455, 1505, 2835, 2871, 3450 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.50 (s, 3H, CH_3), 2.17 (br s, 1H, OH), 2.19–2.25 (dd, 1H, J=7.6, 12.8 Hz, C(4)-H_A), 2.91–2.96 (dd, 1H, J=8.0, 12.8 Hz, C(4)-H_B), 3.48–3.63 (d, 2H, CH_2OH), 3.72 (s, 3H, OMe), 4.40–4.44 (t, 1H, J=7.6 Hz, C(3)-H), 6.72–6.76 (d, 2H, J=8.8 Hz, H_{arom}), 6.91–6.95 (d, 2H, J=8.8 Hz, H_{arom}), 7.25–7.29 (m, 3H, H_{arom}), 7.32–7.36 (m, 1H, H_{arom}), 7.42–7.44 ppm (m, 1H, H_{arom}); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=23.5, 27.1, 48.8, 55.6, 67.5, 70.9, 82.6, 114.1, 118.9, 127.2, 127.7, 128.9, 141.1, 143.8, 155.7 ppm; MS (TS) m/z (%):300.5 [M+1], 269.5, 226.5, 213.5, 212.5, 197.3, 168.3; HRMS (ESI+) m/z (%) calcd for $C_{18}H_{22}NO_3$: 300.1594 $[M+H]^+$; found: 300.1575; HPLC (CHIRACEL OD-H, Grad. 99+1–90+10, 0.75 mL min^{-1}, 100 min, 254+340 nm): t_R (min.)=44.77 (50.09%), 59.18 (49.91%); HPLC (CHIRALPACK AD, Grad. 99+1–85+15, 0.5 mL min^{-1}, 80 min, 254+340 nm): t_R (min.)=36.44 (50.2%), 37.35 (49.8%).

General Procedure for the Reactions Performed at −20°C

In a Schlenk tube (50–100 mL) equipped with a magnetic stirring bar, the catalyst (0.025 mmol, 0.05 equiv) and methacrolein (0.75 mmol, 1.5 equiv) in dry CH_2Cl_2 (1 mL) were stirred at −20°C. Using a syringe, a solution of the nitrone (0.5 mmol, 1 equiv) in the smallest amount of CH_2Cl_2 required for the complete dissolution of the nitrone was added dropwise over a period of 10 min. The reaction was followed by TLC analysis (cyclohexane/AcOEt 3:2), and upon complete conversion of the nitrone, hexanes (10 mL) were added to the reaction mixture to precipitate the catalyst. The mixture was filtered on a Celite 545 plug and the precipitate was washed with hexanes (10 mL). At this point, the Ru complex could be recovered by elution of the solid with acetone followed by precipitation and washing with ether. Volatiles were removed in vacuo from the hexanes solution and the crude reaction mixture was further purified by flash column chromatography (SiO_2, CH_2Cl_2). For all the examples, only the *endo* cycloadducts were observed.

General Procedure for the Reactions Performed at −10°C

In a Schlenk tube (50–100 mL) equipped with a magnetic stirring bar, the catalyst (0.025 mmol, 0.05 equiv) and methacrolein (0.75 mmol, 1.5 equiv) in dry CH_2Cl_2 (1 mL) were stirred at −10°C. Under N_2, the nitrone was added to the reaction as a solid and in one portion. The reaction was followed by TLC analysis (cyclohexane/AcOEt 3:2), and upon complete conversion of the nitrone, hexanes (10 mL) were added to the reaction mixture to precipitate the catalyst. The mixture was filtered on a Celite 545 plug and the precipitate was washed with hexanes (10 mL). At this point, the Ru complex could be recovered by elution of the solid with acetone followed by precipitation and washing with ether. Volatiles were removed in vacuo from the hexanes solution and the crude reaction mixture was further purified by flash column chromatography (SiO_2, CH_2Cl_2). For all the examples, only the *endo* cycloadducts were observed.

5a and 6a: ((3*S*,5*S*)-5-methyl-2-*N*-3-diphenyl-isoxazoline-5-carbaldehyde and (3*S*,4*S*)-4-methyl-2-*N*-3-diphenyl-isoxazoline-4-carbaldehyde) Obtained according to the general procedure in quantitative yield after 14 h. The regioisomeric ratio **5a**/**6a** of 67:33 was determined by ^{1}H NMR integration. IR, ^{1}H NMR, ^{13}C NMR, MS and HRMS analyses matched to the previously described data.[9,14c]

7a and 8a: ((3*S*,5*S*)-5-methyl-2-*N*-3-diphenyl-isoxazoline-5-methanol and (3*S*,4*S*)-4-methyl-2-*N*-3-diphenyl-isoxazoline-4-methanol) Obtained according to the general procedure in 95% yield. Partial data for 8a (in the mixture): IR ($CHCl_3$): $\tilde{\nu}$=695, 755, 888, 1045, 1364, 1452, 1489, 1598, 2873, 2934, 3029, 3414 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6): δ=1.25 (s, 3H, CH_3), 1.6 (br s, OH), 3.69 (s, 1H, C(5)-H_A), 3.92–4.15 (dd, J=12 Hz, 2H, CH_2OH), 4.45 (s, 1H, C(3)-H), 4.67–4.71 (t, J=8 Hz, 1H, C(5)-H_B), 6.94–6.98 (m, H_{arom}), 7.22–752 ppm (m, H_{arom}); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=19.0, 46.5, 68.8, 87.4, 115.1, 121.9, 126.8, 127.8, 128.9, 129.0, 141.3,150.2 ppm; MS (TS) m/z (%): 270.5 [M+1], 239.5, 222.3, 196.5,

182.5, 162.3; HRMS (ESI+) *m/z* (%) calcd for $C_{17}H_{19}NO_2$: 240.1488 $[M+H]^+$; found: 240.1480; HPLC (CHIRACEL OD-H, Grad. 99+1–90+10, 0.75 mL min^{-1}, 100 min, 254+340 nm): t_R = 40.30 (52.2%, **7a**, maj.), 45.28 (1.0%, **8a**, min.), 50.36 (7.5%, **7a**, min.), 72.75 (32.9%, **8a**, maj.).

5b and 6b: (3*S*,5*S*)-5-methyl-3-(4-nitro-phenyl)-isoxazoline-5-carbaldehyde and (3*S*,4*S*)-4-methyl-3-(4-nitro-phenyl)-isoxazoline-4-carbaldehyde Obtained according to the general procedure in 16% yield after 74 h. The regioisomeric ratio **5b**/**6b** of 95:5 was determined by ^{1}H NMR integration. IR, ^{1}H NMR, ^{13}C NMR, MS and HRMS analyses matched to the previously described data.[9]

7b and 8b: ((3*S*,5*S*)-5-methyl-3-(4-nitro-phenyl)-2-phenyl-isoxazoline-5-methanol and (3*S*,4*S*)-4-methyl-3-(4-nitro-phenyl)-2-phenyl-isoxazoline-4-methanol) Obtained according to the general procedure in 95% yield. Partial data for **8b** (in the mixture): IR ($CHCl_3$): $\tilde{\nu}$ = 760, 838, 855, 1048, 1109, 1180, 1346, 1453, 1490, 1519, 1598, 2935, 3423 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6): δ = 1.47 (s, 3H, CH_3), 1.60 (br s, 1H, OH), 3.48–3.61 (m, 2H, CH_2OH), 3.86–3.88 (d AB, 1H, J = 8.4 Hz, C(5)-H_A), 4.07–4.09 (d AB, 1H, J = 8.4 Hz, C(5)-H_B), 4.62 (s, 1H, C(3)-H), 6.86–6.89 (m, H_{arom}), 6.92–6.96 (m, H_{arom}), 7.19–7.24 (m, H_{arom}), 7.63–7.66 (d AB, 2H, J = 8.8 Hz, H_{arom}), 8.22–8.24 ppm (d AB, 2H, J = 8.8 Hz, H_{arom}); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 18.75, 45.58, 67.61, 87.45, 114.88, 122.34, 124.26, 127.74, 129.07, 147.53, 148.83, 149.21 ppm; MS (TS) *m/z* (%): 315.5 [*M*+1], 284.3, 241.5, 227.3, 181.5, 168.3; HRMS (ESI+) *m/z* (%) calcd for $C_{17}H_{18}N_2O_4$: 315.1339 $[M+H]^+$; found: 315.1329; HPLC (CHIRALPAK AD, Grad. 99+1–85+15, 1 mL min^{-1}, 80 min, 254+320 nm): t_R = 49.28 (77.2%, **7b**, maj.), 52.89 (19.1%, **7b**, min.), 55.03 (0.4%, **8b**, min.), 72.62 (3.3%, **8b**, maj.).

5c and 6c: ((3*S*,5*S*)-5-methyl-3-(4-trifluoromethyl-phenyl)-isoxazoline-5-carbaldehyde and (3*S*,4*S*)-4-methyl-3-(4-trifluoromethyl-phenyl)-isoxazoline-4-carbaldehyde) Obtained according to the general procedure in 99% yield after 64 h. The regioisomeric ratio **5c**/**6c** of 91:9 was determined by ^{1}H NMR integration. IR, ^{1}H NMR, ^{13}C NMR, MS and HRMS analyses matched to the previously described data.[9]

7c and 8c: ((3*S*,5*S*)-5-methyl-3-(4-trifluoromethyl-phenyl)-2-phenyl-isoxazoline-5-methanol and (3*S*,4*S*)-4-methyl-3-(4-trifluoromethyl-phenyl)-2-phenyl-isoxazoline-4-methanol) Obtained according to the general procedure in 95% yield. Partial data for **8c** (in the mixture): IR ($CHCl_3$): $\tilde{\nu}$ = 694, 757, 838, 1018, 1066, 1120, 1163, 1322, 1419, 1454, 1489, 1598, 1619, 2876, 2936, 3422 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6): δ = 1.29 (s, 3H, CH_3), 1.63 (bs, 1H, OH), 3.47–3.60 (m, 2H, CH_2OH), 3.86–3.88 (d, 1H, J = 8.4 Hz, C(5)-H_A), 4.07–4.09 (d, 1H, J = 8.4 Hz, C(5)-H_A), 4.53 (s, 1H, C(3)-H), 6.88–6.95 (m, H_{arom}), 7.19–7.27 (m, H_{arom}), 7.58–7.60 (d AB, 2H, J = 8 Hz, H_{arom}), 7.62–7.64 ppm (d AB, 2H, J = 8 Hz, H_{arom}); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 19.02, 46.05, 68.42, 87.88, 115.21, 122.33, 128.01, 126.25, 129.33, 146.29, 150.25; MS (TS) *m/z* (%): 338.3 [*M*+1], 307.5, 264.3, 250.1 ppm; HRMS (ESI+) *m/z* (%) calcd for $C_{18}H_{18}F_3NO_2$: 338.1362 $[M+H]^+$; found: 338.1362; HPLC (CHIRACEL OD-H, Grad. 99+1–90+10, 1 mL min^{-1}, 60 min, 254+340 nm): t_R = 8.03 (79.9%, **7c**, maj.), 9.33 (11.8%, **7c**, min.), 20.96 (8.2%, **8c**, maj.).

5d and 6d: ((3*S*,5*S*)-5-methyl-3-(4-chloro-phenyl)-isoxazoline-5-carbaldehyde and (3*S*,4*S*)-4-methyl-3-(4-chloro-phenyl)-isoxazoline-4-carbaldehyde) Obtained according to the general procedure in 89% yield after 64 h. The regioisomeric ratio **5d**/**6d** of 73:27 was determined by ^{1}H NMR integration. Partial data for 6d (in the mixture): IR (CH_2Cl_2): $\tilde{\nu}$ = 726, 829, 909, 1014, 1091, 1490, 1598, 1731, 2250, 2988, 3029 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6): δ = 0.77 (s, 3H, CH_3), 3.99–4.01 (d, 1H, J = 9.2 Hz, C(5)-H_A), 4.42–4.44 (d, 1H, J = 9.2 Hz, C(5)-H_B), 4.99 (s, 1H, C(3)-H), 6.91–6.93 (m, H_{arom}), 7.19–7.24 (m, H_{arom}), 7.55–7.57 (d AB, 2H, J = 8 Hz, H_{arom}), 7.60–7.62 (d AB, 2H, J = 8 Hz, H_{arom}), 9.66 ppm (s, 1H, CHO); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 18.7, 45.9, 67.8, 87.1, 114.9, 123.2, 128.0, 128.7, 128.9, 133.3, 139.5, 149.5, 201.2 ppm; MS (EI) *m/z* (%): 301 [M^+, 38], 230 (23), 216 (28), 139 (42), 121 (100), 111 (26), 104 (15), 93 (86), 91 (66), 77 (53), 66 (45); HRMS (ESI+) *m/z* (%) calcd for $C_{17}H_{16}ClNO_2$: 301.0871 $[M+H]^+$; found: 301.0870.

7d and 8d: ((3*S*,5*S*)-5-methyl-3-(4-chloro-phenyl)-2-phenyl-isoxazoline-5-methanol and (3*S*,4*S*)-4-methyl-3-(4-chloro-phenyl)-2-phenyl-isoxazoline-4-methanol) Obtained according to the general procedure in 95% yield. Partial data for 8d (in the mixture): IR ($CHCl_3$): $\tilde{\nu}$ = 760, 826, 854, 888, 945, 1014, 1048, 1089, 1290, 1375, 1409, 1453, 1489, 1597, 2935, 3425 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6): δ = 0.77 (s, 3H, CH_3), 1.86 (br s, 1H, OH), 3.40–3.61 (m, 2H, CH_2OH), 3.85–3.87 (d, 1H, J = 8.4 Hz, C(5)-H_A), 4.07–4.09 (d AB, 1H, J = 8.4 Hz, C(5)-H_B), 4.21 (s, 1H, C(3)-H), 6.91–7.05 (m, H_{arom}), 7.21–7.25 (m, H_{arom}), 7.29–7.44 ppm (m, H_{arom}); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 19.2, 46.3, 68.3, 89.2, 115.7, 124.1, 129.2, 130.1, 132.2, 134.7, 141.5, 152.1 ppm; MS (TS) *m/z* (%): 304.5 [*M*+1], 273.3, 230.3, 218.3, 216.3, 194.3, 180.5, 163.3; HRMS (ESI+) *m/z* (%) calcd for $C_{17}H_{18}ClNO_2$: 304.1098 $[M+H]^+$; found: 304.1086; HPLC (CHIRALPAK AD, Grad. 99+1–85+15, 1 mL min^{-1}, 80 min, 254+320 nm): t_R = 30.94 (65.1%, **7d**, maj.), 35.08 (1.4%, **8d**, min.), 37.67 (8.4%, **7d**, min.), 55.17 (24.3%, **8d**, maj.).

5e and 6e: ((3*S*,5*S*)-5-methyl-3-(4-methyl-phenyl)-isoxazoline-5-carbaldehyde and (3*S*,4*S*)-4-methyl-3-(4-methyl-phenyl)-isoxazoline-4-carbaldehyde) Obtained according to the general procedure in quantitative yield after 22 h. The regioisomeric ratio **5e**/**6e** of 41:59 was determined by ^{1}H NMR integration. Partial data for **6e** (in the mixture): IR (CH_2Cl_2): $\tilde{\nu}$ = 970, 1386, 1488,1598, 1731, 2091, 2197, 2301, 2875, 2988, 3029, 3340 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6): δ = 0.89 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 3.97–3.99 (d, 1H, J = 8.8 Hz, C(5)-H_A), 4.41–4.43 (d, 1H, J = 8.8 Hz, C(5)-H_B), 4.85 (s, 1H, C(3)-H), 6.88–6.97 (m, H_{arom}), 7.12–7.24 (m, H_{arom}), 7.27–7.36 (m, H_{arom}), 9.68 ppm (s, 1H, CHO); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 19.1, 21.3, 46.8, 68.8, 87.5, 115.5, 122.0, 127.2, 129.1, 129.9, 137.9, 138.8, 150.6, 201.8 ppm; MS (EI) *m/z* (%): 281 [M^+, 38], 238 (27), 210 (54), 196 (48), 173 (26), 160 (38), 145 (84), 121 (46), 117 (38), 104 (22), 91 (69), 77 (34); HRMS (ESI+) *m/z* (%) calcd for $C_{18}H_{19}NO_2$: 281.1408 $[M+H]^+$; found: 281.1416.

7e and 8e: ((3*S*,5*S*)-5-methyl-3-(4-methyl-phenyl)-2-phenyl-isoxazoline-5-methanol and (3*S*,4*S*)-4-methyl-3-(4-methyl-phenyl)-2-phenyl-isoxazoline-4-methanol) Obtained according to the general procedure in 95% yield. Partial data for **8e** (in the mixture): IR ($CHCl_3$): $\tilde{\nu}$ = 693, 752, 819, 889, 1041, 1179, 1378, 1452, 1488, 1514, 1598, 2871, 2924, 3402 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6): δ = 1.52 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 1.73 (br s, 1H, OH), 3.53–3.72 (m, 2H, CH_2OH), 3.94–3.97 (d, 1H, J = 8.4 Hz, C(5)-H_A), 4.15–4.18 (d, 1H, J = 8.4 Hz, C(5)-H_B), 4.43 (s, 1H, C(3)-H), 6.88–6.97 (m, H_{arom}), 6.96–7.01 (m, H_{arom}), 7.24–7.29 (m, H_{arom}), 7.40–7.44 ppm (m, H_{arom}); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 19.2, 46.3, 68.3, 89.2, 115.7, 124.1, 129.2, 130.1, 132.2, 134.7, 141.5, 152.1 ppm; MS (TS) *m/z* (%): 284.5 [*M*+1], 254.5, 236.3, 224.5, 210.3, 196.5, 162.3; HRMS (ESI+) *m/z* (%) calcd for $C_{18}H_{21}NO_2$: 284.1624 $[M+H]^+$; found: 284.1645; HPLC (CHIRACEL OD-H, Grad. 99+1–90+10, 1 mL min^{-1}, 60 min, 254+340 nm): t_R = 28.29 (37.5%, **7e**, maj.), 30.97 (1.6%, **8e**, min.), 31.87 (5.1%, **7e**, min.), 46.97 (55.7%, **8e**, maj.).

5f and 6f: ((3*S*,5*S*)-5-methyl-3-(4-methoxy-phenyl)-isoxazoline-5-carbaldehyde and (3*S*,4*S*)-4-methyl-3-(4-methoxy-phenyl)-isoxazoline-4-carbaldehyde) Obtained according to the general procedure in quantitative yield after 22 h. The regioisomeric ratio **5f**/**6f** of 21:79 was determined by ^{1}H NMR integration. Partial data for **6f** (in the mixture): IR (CH_2Cl_2): $\tilde{\nu}$ = 667, 833, 970, 1177, 1386, 1489, 1512, 1598, 1731, 2003, 2091, 2197, 2301, 2599, 2875, 2990, 3029, 3340 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6): δ = 0.90 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 3.97–3.99 (d, 1H, J = 8.8 Hz, C(5)-H_A), 4.41–4.43 (d, 1H, J = 8.8 Hz, C(5)-H_B), 4.83 (s, 1H, C(3)-H), 6.91–6.97 (m, H_{arom}), 7.19–7.24 (m, H_{arom}), 7.33–7.35 (m, H_{arom}), 9.67 ppm (s, 1H, CHO); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 19.2, 46.8, 55.7, 68.6, 87.4, 114.6, 115.6, 122.1, 128.5, 129.1, 133.6, 150.6, 159.6, 201.9 ppm; MS (EI) *m/z* (%): 297 [M^+, 95], 226 (28), 210 (33), 189 (86), 178 (61), 162 (67), 134 (42), 121 (33), 104 (24), 91 (100), 77 (65); HRMS (ESI+) *m/z* (%) calcd for $C_{18}H_{19}NO_3$: 297.1355 $[M+H]^+$; found: 297.1365.

7f and 8f: ((3*S*,5*S*)-5-methyl-3-(4-methoxy-phenyl)-2-phenyl-isoxazoline-5-methanol and (3*S*,4*S*)-4-methyl-3-(4-methoxy-phenyl)-2-phenyl-isoxazoline-4-methanol) Obtained according to the general procedure in 95% yield. Partial data for **8f** (in the mixture): IR ($CHCl_3$): $\tilde{\nu}$ = 838, 1034, 1174, 1247, 1302, 1463, 1489, 1511, 1598, 1612, 2872, 2934, 3436 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6): δ = 0.76 (s, 3H, CH_3), 1.63 (br s, 1H, OH), 3.44–3.61 (m, 2H, CH_2OH), 3.81 (s, H, OCH_3), 3.85–3.88 (d, 1H, J = 8.4 Hz, C(5)-H_A), 4.06–4.09 (d, 1H, J = 8.4 Hz, C(5)-H_B), 4.33 (s, 1H,

C(3)-H), 6.87–6.92 (m, H_{arom}), 7.15–7.18 (d AB, 2H, $J=8.4$ Hz, H_{arom}), 7.18–7.21 (m, H_{arom}), 7.34–7.37 ppm (d AB, 2H, $J=8.4$ Hz, H_{arom}); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta=18.2$, 22.5, 22.7, 43.1, 48.7, 53.6, 55.4, 67.3, 68.0, 69.6, 74.2, 74.8, 76.8, 83.3, 114.1, 114.4, 114.9, 115.4, 121.5, 121.9, 128.0, 128.8, 128.9, 129.2, 131.4, 131.7, 151.5, 159.1 ppm; MS (TS) m/z (%): 300.5 $[M+1]$, 270.5, 252.5, 236.3, 224.3, 212.3, 177.3, 161.3; HRMS (ESI+) m/z (%) calcd for $C_{18}H_{22}NO_3$: 300.1594 $[M+H]^+$; found: 300.1602; HPLC (CHIRALPAK AD, Grad. 99+1–85+15, 1 mL min^{-1}, 80 min, 254+320 nm): $t_R=36.57$ (14.6%, **7f**, maj.), 39.99 (4.1%, **7f**, min.), 50.90 (0.5%, **8f**, min.), 57.87 (80.8%, **8f**, maj.).

5g and 6g: ((3*S*,5*S*)-5-methyl-3-(4-cyano-phenyl)-isoxazoline-5-carbaldehyde and (3*S*,4*S*)-4-methyl-3-(4-cyano-phenyl)-isoxazoline-4-carbaldehyde) Obtained according to the general procedure in 23% yield after 77 h. The regioisomeric ratio **5g**/**6g** of 96:4 was determined by ^1H NMR integration. Partial data for **6g** (in the mixture): IR ($CHCl_3$): $\tilde{\nu}=693$, 756, 836, 886, 946, 1020, 1031, 1086, 1105, 1179, 1201, 1248, 1292, 1375, 1414, 1453, 1489, 1597, 1729, 1929, 2229, 2810, 2979, 3441 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta=1.50$ (s, 3H, CH_3), 3.98–4.00 (d, 1H, $J=8.8$ Hz, C(5)-H_A), 4.41–4.43 (d, 1H, $J=8.8$ Hz, C(5)-H_B), 4.99 (s, 1H, C(3)-H), 6.88–6.94 (m, 3H, H_{arom}), 7.12–7.27 (m, 2H, H_{arom}), 7.54–7.56 (d AB, 2H, $J=8$ Hz, H_{arom}), 7.63–7.65 (d AB, 2H, $J=8$ Hz, H_{arom}), 9.64 ppm (s, 1H, 5-CHO); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta=18.6$, 45.4, 67.7, 114.7, 127.4, 128.9, 132.7, 122.1, 200.8 ppm; MS (TS) m/z (%): 293.5 $[M+1]$, 264.3, 208.3, 207.3; HRMS (ESI+) m/z (%) calcd for $C_{18}H_{17}N_2O_2$: 293.1284 $[M+H]^+$; found: 293.1279.

7g and 8g: ((3*S*,5*S*)-5-methyl-3-(4-cyano-phenyl)-2-phenyl-isoxazoline-5-methanol and (3*S*,4*S*)-4-methyl-3-(4-cyano-phenyl)-2-phenyl-isoxazoline-4-methanol) Obtained according to the general procedure in 70% yield. Partial data for **8g** (in the mixture): IR ($CHCl_3$): $\tilde{\nu}=759$, 836, 1050, 1105, 1178, 1291, 1412, 1453, 1489, 1598, 2229, 2934, 3460 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta=1.46$ (s, 3H, CH_3), 1.95 (br s, 1H, OH), 3.46–3.60 (m, 2H, CH_2OH), 6.86–6.88 (m, 2H, H_{arom}), 6.88–6.95 (m, 1H, H_{arom}), 7.19–7.24 (m, 2H, H_{arom}), 7.57–7.59 (d AB, 2H, $J=8.4$ Hz, H_{arom}), 7.65–7.67 ppm (d AB, 2H, $J=8.4$ Hz, H_{arom}); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta=22.3$, 26.9, 47.9, 66.9, 68.8, 114.8, 127.3, 129.0, 132.8, 122.0 ppm; MS (TS) m/z (%): 295.5 $[M+1]$, 264.5, 221.3, 207.3; HRMS (ESI+) m/z (%) calcd for $C_{18}H_{19}N_2O_2$: 295.1441 $[M+H]^+$; found: 295.1427; HPLC (CHIRACEL OD-H, Grad. 99+1–90+10, 1 mL min^{-1}, 60 min, 254+340 nm): t_R (min.) = 68.89 (53.5%), 76.39 (46.5).

5h and 6h: ((3*S*,5*S*)-5-methyl-3-(2-naphthyl)-isoxazoline-5-carbaldehyde and (3*S*,4*S*)-4-methyl-3-(2-naphthyl)-isoxazoline-4-carbaldehyde) Obtained according to the general procedure in 80% yield after 23 h. The regioisomeric ratio **5h**/**6h** of 63:37 was determined by ^1H NMR integration. Partial data for **6h** (in the mixture): IR ($CHCl_3$): $\tilde{\nu}=693$, 754, 820, 859, 890, 1031, 1085, 1125, 1373, 1452, 1489, 1597, 1730, 2808, 2932, 3059 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta=0.95$ (s, 3H, CH_3), 4.08–4.10 (d, 1H, $J=8.8$ Hz, C(5)-H_A), 4.49–4.51 (d, 1H, $J=8.8$ Hz, C(5)-H_B), 5.12 (s, 1H, C(3)-H), 6.91–8.04 (m, H_{arom}), 10.2 ppm (s, 1H, 4-CHO); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta=18.9$, 46.3, 69.0, 87.4, 114.9, 121.9, 124.5, 125.6, 126.2, 126.5, 127.9, 128.1, 128.9, 129.0, 133.0, 137.6, 138.7, 150.3, 201.4 ppm; MS (TS) m/z (%): 350.5 $[M+CH_3OH]$, 318.5 $[M+1]$, 289.3, 232.3, 193.3, 178.3; HRMS (ESI+) m/z (%) calcd for $C_{22}H_{24}NO_3$: 350.1750 $[M+CH_3OH]^+$; found: 350.1721.

7h and 8h: ((3*S*,5*S*)-5-methyl-3-(2-naphthyl)-2-phenyl-isoxazoline-5-methanol and (3*S*,4*S*)-4-methyl-3-(2-naphthyl)-2-phenyl-isoxazoline-4-methanol) Obtained according to the general procedure in quantitative yield. Partial data for 8 h (in the mixture): IR ($CHCl_3$): $\tilde{\nu}=693$, 752, 822, 859, 889, 950, 1042, 1124, 1373, 1452, 1488, 1508, 1597, 1930, 2871, 2933, 3058, 3414 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta=0.81$ (s, 3H, CH_3), 2.16 (bs, 1H, OH), 3.68–3.75 (d, 2H, CH_2OH), 3.96–3.98 (d, 1H, $J=8.8$ Hz, C(5)-H_A), 4.16–4.18 (d, 1H, $J=8.8$ Hz, C(5)-H_B), 4.61 (s, 1H, C(3)-H), 6.91–7.97 ppm (m, H_{arom}); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta=22.6$, 48.5, 67.1, 70.1, 83.6, 100.1, 115.0, 121.8, 124.7, 125.4, 126.1, 126.4, 127.9, 128.0, 128.9, 129.0, 133.0, 133.6, 139.4, 1851.2 ppm; MS (TS) m/z (%): 320.5 $[M+1]$, 289.3, 246.3, 232.3, 162.3, 153.3; HRMS (ESI+) m/z (%) calcd for $C_{21}H_{22}NO_2$: 320.1645 $[M+H]^+$; found: 320.1632; HPLC (CHIRACEL OD-H, Grad. 99+1–90+10, 0.75 mL min^{-1}, 100 min, 254+340 nm): $t_R=46.22$ (49.5%, **7h**, maj.), 51.87 (10.5%, **7h**, min.), 56.16 (1.1%, **8h**, min.), 75.08 (32.0%, **8h**, maj).

5i and 6i: ((3*S*,5*S*)-5-methyl-3-(2-furyl)-isoxazoline-5-carbaldehyde and (3*S*,4*S*)-4-methyl-3-(2-furyl)-isoxazoline-4-carbaldehyde) Obtained according to the general procedure in 72% yield after 64 h. The regioisomeric ratio **5i**/**6i** of 60:40 was determined by ^1H NMR integration. Partial data for **6i** (in the mixture): IR ($CHCl_3$): $\tilde{\nu}=696$, 753, 820, 859, 890, 1031, 1085, 1125, 1372, 1452, 1489, 1597, 1735, 2808, 2932, 3059 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta=1.09$ (s, 3H, CH_3), 4.03–4.06 (d, 1H, $J=9.2$ Hz, C(5)-H_A), 4.46–4.48 (d, 1H, $J=9.2$ Hz, C(5)-H_B), 5.01 (s, 1H, C(3)-H), 6.23–7.45 (m, H_{arom}), 9.69 ppm (s, 1H, 4-CHO); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta=18.8$, 41.7, 61.9, 86.5, 108.3, 110.5, 116.1, 122.6, 128.7, 142.5, 148.5, 152.7, 202.4 ppm.

7i and 8i: ((3*S*,5*S*)-5-methyl-3-(2-furyl)-2-phenyl-isoxazoline-5-methanol and (3*S*,4*S*)-4-methyl-3-(2-furyl)-2-phenyl-isoxazoline-4-methanol) Obtained according to the general procedure in quantitative yield. Partial data for **8i** (in the mixture): IR ($CHCl_3$): $\tilde{\nu}=692$, 757, 781, 884, 925, 1011, 1044, 1150, 1181, 1232, 1340, 1379, 1453, 1489, 1598, 2875, 2935, 3409 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta=0.96$ (s, 3H, CH_3), 2.35 (br s, 1H, OH), 3.61–3.65 (d, 2H, CH_2OH), 3.89–3.92 (d, 1H, $J=9.2$ Hz, C(5)-H_A), 4.07–4.09 (d, 1H, $J=9.2$ Hz, C(5)-H_B), 4.48 (s, 1H, C(3)-H), 6.28–7.47 ppm (m, H_{arom}); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta=22.2$, 43.4, 63.5, 67.7, 83.3, 107.8, 110.5, 115.7, 122.4, 128.8, 142.4, 150.1, 153.2 ppm; MS (TS) m/z (%): 260.3 $[M+1]$, 229.3, 212.5, 194.3, 186.5, 172.5, 170.3, 162.3, 158.3; HRMS (ESI+) m/z (%) calcd for $C_{15}H_{18}NO_3$: 260.1281 $[M+H]^+$; found: 240.1275; HPLC (CHIRACEL OD-H, Grad. 99+1–90+10, 0.75 mL min^{-1}, 100 min, 254+340 nm): $t_R=39.22$ (46.2%, **7i**, maj.), 42.93 (8.4%, **7i**, min.), 57.49 (1.2%, **8i**, min.), 66.54 (42.1%, **8i**, maj.).

5j and 6j: ((3*S*,5*S*)-5-methyl-3-phenyl-2-(4-methoxy-phenyl)-isoxazoline-5-carbaldehyde and (3*S*,4*S*)-4-methyl-3-phenyl-2-(4-methoxy-phenyl)-isoxazoline-4-carbaldehyde) Obtained according to the general procedure in 95% yield after 25 h. The regioisomeric ratio **5j**/**6j** of 80:20 was determined by ^1H NMR integration. Partial data for **6j** (in the mixture): IR ($CHCl_3$): $\tilde{\nu}=691$, 756, 823, 889, 1029, 1107, 1180, 1192, 1241, 1299, 1393, 1454, 1505, 1606, 1879, 2835, 2930, 3030, 3337 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta=1.54$ (s, 3H, CH_3), 3.77 (s, 3H, 4-OMe), 3.99–4.01 (d, 1H, $J=8.8$ Hz, C(5)-H_A), 4.47–4.49 (d, 1H, $J=8.8$ Hz, C(5)-H_B), 4.81 (s, 1H, C(3)-H), 6.78–6.82 (m, 2H, H_{arom}), 6.97–7.04 (m, 2H, H_{arom}), 7.29–7.33 (m, H_{arom}), 7.28–7.51 (m, H_{arom}), 9.73 ppm (s, 1H, CHO); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta=19.5$, 55.5, 69.6, 86.6, 114.0, 118.0, 127.1, 118.0, 127.1, 127.8, 128.8, 140.4, 143.4, 155.5, 201.3 ppm.

7j and 8j: ((3*S*,5*S*)-5-methyl-3-phenyl-2-(4-methoxy-phenyl)-isoxazoline-5-methanol and (3*S*,4*S*)-4-methyl-3-phenyl-2-(4-methoxy-phenyl)-isoxazoline-4-methanol) Obtained according to the general procedure in quantitative yield. Partial data for **8j** (in the mixture): IR ($CHCl_3$): $\tilde{\nu}=762$, 830, 939, 1035, 1112, 1180, 1241, 1297, 1367, 1455, 1505, 1605, 2835, 2871, 2933, 3420 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta=0.79$ (s, 3H, CH_3), 2.10 (br s, 1H, OH), 3.54–3.69 (d, 2H, CH_2OH), 3.77 (s, 3H, OMe), 3.91–3.93 (d, 1H, $J=8.8$ Hz, C(5)-H_A), 4.15–4.17 (d, 1H, $J=8.8$ Hz, C(5)-H_B), 4.32 (s, 1H, C(3)-H), 6.78–6.81 (m, 2H, H_{arom}), 6.95–6.99 (m, 2H, H_{arom}), 7.29–7.49 (m, 3H, H_{arom}), 7.28–7.51 ppm (m, 4H, H_{arom}); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta=23.5$, 27.1, 48.8, 55.6, 67.5, 70.9, 82.6, 114.1, 118.9, 127.2, 127.7, 128.9, 141.1, 143.8, 155.7 ppm; MS (TS) m/z (%): 300.5 $[M+1]$, 269.5, 226.5, 213.5, 212.5, 197.3, 168.3; HRMS (ESI+) m/z (%) calcd for $C_{18}H_{22}NO_3$: 300.1594 $[M+H]^+$; found: 300.1584; HPLC (CHIRACEL OD-H, Grad. 99+1–90+10, 0.75 mL min^{-1}, 100 min, 254+340 nm): $t_R=44.21$ (71.2%, **7j**, maj.), 58.63 (9.5%, **7j**, min.), 60.57 (18.3%, **8j**, maj.), 65.37 (0.5%, **8j**, min.).

Reductive Amination[50]

A mixture of **5a/6a** (100 mg, 0.37 mmol, 1 equiv), *R*-(+)-methylbenzylamine (0.047 mL, 0.37 mmol, 1 equiv), and anhydrous Na_2SO_4 (~20 mg) were placed in a Schlenk tube (50 mL) equipped with a magnetic stirring bar. The walls of the tube were washed with dry CH_2Cl_2 (2 mL). After 24 h of stirring at RT, $NaBH(OAc)_3$ (220 mg, 1.11 mmol, 4 equiv) and dry CH_2Cl_2 (2 mL) were added, and the mixture was stirred vigorously. After 6 h, water (5 mL) was added to quench the excess borohydride, and the aqueous solution was extracted with CH_2Cl_2 (10 mL + 3×5 mL), then

AcOEt (20 mL), and dried over anhydrous Na_2SO_4. Volatiles were removed in vacuo to give the crude amine, which was further purified by flash column chromatography (SiO_2, $H_{dry}=15$ cm, $\Phi_e=1$ cm, gradient cyclohexane/ethylacetate 95:5, 90:10, 50:50). Two fractions corresponding to the two diastereomeric amines were isolated to give a good quantitative overall yield (56 mg of **10a**, 97.5% *de* by NMR and 95 mg of **9a**, 88.1% *de* by NMR). The spectral data below is given for the major diastereoisomer only.

9a: ((3*S*,5*S*,8*R*)-5-methyl-2-*N*-3-diphenyl-isoxazoline-5-methyl-*N*-methylbenzylamine) IR (CH_2Cl_2): $\tilde{\nu}=696$, 849, 888, 912, 1029, 1075, 1128, 1179, 1249, 1278, 1370, 1451, 1490, 1598, 2928, 2970, 3027 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta=1.36$ (s, 3H, CH_3), 1.56 (s, 3H, CH_3), 1.64 (br s, NH), 2.22–2.27 (dd, $J=8.6$, 12.1 Hz, 1H, C(4)-H_A), 2.48–2.69 (dd, $J=12.1$ Hz, CH_2), 3.03–3.08 (dd, $J=8.3$, 12.1 Hz, 1H, C(4)-H_B), 3.73–3.78 (dd, $J=6.6$ Hz, CH_2), 4.67–4.71 (t, $J=8.4$ Hz, 1H, C(3)-H), 6.99–7.03 (m, H_{arom}), 7.25–7.32 (m, H_{arom}), 7.34–7.38 (m, H_{arom}), 7.43–7.47 (m, H_{arom}), 7.55–7.57 ppm (m, H_{arom}); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta=14.6$, 19.1, 31.2, 51.2, 59.5, 68.1, 76.7, 79.7, 115.9, 121.9, 126.9, 127.6, 128.8, 129.0, 151.8 ppm; MS (TS) *m*/*z* (%): 373.7 [*M*+1], 355.5, 250.5, 234.5, 196.5, 194.5, 186.5, 169.5; HRMS (ESI+) *m*/*z* (%) calcd for $C_{17}H_{19}NO_2$: 373.2274 $[M+H]^+$; found: 373.2286.

(10a):[14b] ((3*S*,4*S*,8*R*)-4-methyl-2-*N*-3-diphenyl-isoxazoline-4-methyl-*N*-methylbenzylamine) IR (CH_2Cl_2): $\tilde{\nu}=694$, 758, 784, 886, 1009, 1029, 1048, 1076, 1123, 1174, 1207, 1290, 1369, 1453, 1490, 1599, 2858, 1966, 3027 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta=0.74$ (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 2.53–2.65 (dd, $J=11.9$ Hz, CH_2), 3.69–3.75 (dd, $J=6.6$ Hz, CH_2), 3.84–3.86 (d, $J=8.1$ Hz, 1H, C(5)-H_A), 4.01–4.03 (d, $J=8.1$ Hz, 1H, C(5)-H_B), 4.43 (s, 1H, C(3)-H), 6.87–6.92 (m, H_{arom}), 7.16–7.24 (m, H_{arom}), 7.25–7.31 (m, H_{arom}), 7.35–7.39 (m, H_{arom}), 7.46–7.47 ppm (m, H_{arom}); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta=14.6$, 19.7, 24.4, 31.2, 51.2, 58.9, 68.2, 77.4, 114.7, 122.2, 127.6, 128.6, 128.8, 129.7, 135.5, 149.3 ppm; MS (TS) *m*/*z* (%): 373.7 [*M*+1], 268.5, 240.5, 222.5, 195.5, 182.5; HRMS (ESI+) *m*/*z* (%) calcd for $C_{17}H_{19}NO_2$: 373.2274 $[M+H]^+$; found: 373.2276.

Formation of 11a and 12a

In a conical-bottom flask (10 mL) equipped with a magnetic stirring bar, to the amine in dry Et_2O (2 mL), a solution of hydrochloric acid (2N) was added by a syringe as a solution in dry Et_2O (1 mL). Immediately, a fine, white solid precipitated from the mixture. The solid was filtered on a frit and washed with Et_2O, then dried to give the desired product as an amorphous white solid in quantitative yield. Crystals suitable for the X-ray analysis were obtained for the diastereomer corresponding to the 4-substituted isoxazolidine **11a** by vapor-diffusion crystallization from the EtOH/iPr_2O solvent system.

11a: (3*S*,5*S*,8*R*)-5-methyl-2-*N*-3-diphenyl-isoxazoline-5-methyl-*N*-methylbenzylammonium chloride) $[\alpha]_D^{20}=-90.48$ ($c=10$ mg mL^{-1}, ethanol, 88% *ee*); mol CD (0.033 mM, acetonitrile, 20°C): $\lambda=249$ ($-14.12e^{-14}$), 221 ($-4.33e^{-4}$), 213 ($-2.21e^{-3}$); IR (CH_2Cl_2): $\tilde{\nu}=670$, 755, 849, 889, 953, 1029, 1085, 1128, 1155, 1211, 1266, 1383, 1453, 1490, 1598, 2732, 2939 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta=1.59$ (s, 3H, CH_3), 1.84 (s, 3H, CH_3), 1.64 (br s, NH_2^+), 2.21–2.28 (m, 1H, C(4)-H_A), 2.95 (br s, 2H, CH_2), 3.51–3.56 (m, 1H, C(4)-H_B), 3.70–3.75 (dd, $J=6.6$ Hz, CH_2), 4.45 (bs, 1H, C(3)-H), 4.82 (br t, 1H, CH-NH_2^+), 6.81–6.83 (m, H_{arom}), 6.89–6.92 (m, H_{arom}), 7.15–7.25 (m, H_{arom}), 7.33–7.38 (m, H_{arom}), 7.50–7.53 ppm (m, H_{arom}); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta=14.7$, 18.9, 24.3, 31.2, 51.2, 59.5, 68.1, 77.4, 79.7, 115.9, 121.9, 127.9, 128.4, 128.9, 129.7, 137.7, 151.8 ppm; MS (TS) *m*/*z* (%): 373.7 [*M*+1], 355.5, 250.5, 234.5, 196.5, 194.5, 186.5, 182.3, 169.5; HRMS (ESI+) *m*/*z* (%) calcd for $C_{17}H_{19}NO_2$: 373.2274 $[M+H]^+$; found: 373.2278.

12a:[14b] (3*S*,4*S*,8*R*)-4-methyl-2-*N*-3-diphenyl-isoxazoline-4-methyl-*N*-methylbenzylammonium chloride) $[\alpha]_D^{20}=+78.78$ ($c=10$ mg mL^{-1}, methanol, 97.5% *ee*); mol CD (0.033 mM, acetonitrile, 20°C): $\lambda=284$ ($2.79e^3$), 238 ($10.33e^{10}$), 204 ($0.85e^1$); IR (CH_2Cl_2): $\tilde{\nu}=698$, 740, 762, 780, 849, 895, 1004, 1030, 1073, 1261, 1377, 1455, 1490, 1578, 2698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta=0.93$ (s, 3H, CH_3), 1.61 (s, 3H, CH_3), 2.81–2.97 (m, CH_2), 3.70–3.76 (dd, $J=6.6$ Hz, CH_2), 4.05–4.07 (d, $J=8.1$ Hz, 1H, C(5)-H_A), 4.18 (s, 1H, C(3)-H), 4.20–4.22 (d, $J=8.1$ Hz, 1H, C(5)-H_B), 4.45–4.47 (br t, 1H, CH-NH_2^+), 6.78–6.80 (m, H_{arom}), 6.85–6.90 (m, H_{arom}), 7.12–7.17 (m, H_{arom}), 7.28–7.31 (m, H_{arom}), 7.41–7.44 (m, H_{arom}), 7.59–7.62 ppm (m, H_{arom}); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta=14.6$, 19.1, 24.4, 31.2, 51.0, 59.7, 68.2, 77.4, 79.9, 115.9, 122.2, 127.1, 127.7, 128.3, 128.9, 129.7, 135.5, 149.2 ppm; MS (TS) *m*/*z* (%): 373.7 (M+1), 341.5, 268.5, 222.5, 195.5, 182.3, 180.5; HRMS (ESI+) *m*/*z* (%) calcd for $C_{17}H_{19}NO_2$: 373.2274 $[M+H]^+$; found: 373.2275.

Ring-Opening with TMSI[46]

TMSCl (160 μL, 1.23 mmol, 3 equiv) and KI (204 mg, 1.23 mmol, 3 equiv) were stirred in CH_3CN (5 mL), at room temperature for 30 min, to give a white, cloudy, suspension. To this suspension, a solution of the isoxazoldine alcohols **7a/8a** (110 mg, 0.41 mmol, 1 equiv) in CH_3CN (5 mL) was added, followed by traces of water (5 μL). Upon stirring at room temperature for 16 h, volatiles were removed in vacuo, and to the brown oily residue, water (20 mL) was added, and the resulting mixture was stirred for 20 min before extracting with AcOEt (3×30 mL). The combined organic extracts were washed with an aqueous solution of $Na_2S_2O_3$ (20 mL, 5%). The color of the solution immediately turned from brown to pale yellow. The organic extracts were dried on anhydrous Na_2SO_4, filtered, and the solvent was removed on the rotary evaporator, and further dried on the high-vacuum pump to give a pale-yellow oily residue that was further purified by FCC (SiO_2, AcOEt/CyH 2:3 1:1 3:2, $\Phi_e=2$ cm, $H_{dry}=25$ cm). The product is a pale-yellow dense oil (100 mg, 90%).

13a and 14a: ((2*R*,4*R*)-2-methyl-4-phenyl-4-(phenylamino)butane-1,2-diol and (*S*)-2-methyl-2-(phenyl(phenylamino)methyl)propane-1,3-diol) IR ($CHCl_3$): $\tilde{\nu}=630.8$, 702.7, 750.8, 892.5, 992.8, 1031.5, 1266.9, 1320.0, 1357.2, 1426.2, 1453.2, 1500.3, 1601.3, 2051.0, 3378.0 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta=0.75$–0.77 (br d, 3H, CH_3), 1.25–1.30 (m, 3H. CH_3), 1.95–2.12 (bm, 2H, CH_2), 3.52–3.80 (br m, 6H, CH_2 + CH), 4.55–4.67 (br m, 6H, CH_2 + CH), 6.35–6.37 (m, 1H, H_{arom}), 6.61–6.76 (m, 3H, H_{arom}), 7.09–7.16 (m, 2H, H_{arom}), 7.26–7.43 ppm (m, 6H, H_{arom}); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta=15.4$, 17.5, 25.9, 42.7, 47.3, 55.9, 62.5, 62.9, 66.0, 67.2, 67.8, 69.0, 70.0, 73.3, 78.2, 114.3, 114.7, 116.2, 117.9, 118.5, 126.1, 127.2, 128.2, 128.6, 128.9, 129.0, 129.3, 137.7, 139.4, 139.7, 144.3, 147.2 ppm; MS (TS) *m*/*z*=272.5 [*M*+1], 220.1, 182.3, 161.3, 155.3; HRMS (ESI+) *m*/*z*: calcd. for $C_{17}H_{21}NO_2$ $[M+H]^+$: 272.1645, found: 272.1655.

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