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[3+2] Route to Quaternary Oxaprolinol Derivatives as Masked Precursors of Disubstituted β^3,β^3-Amino Aldehyde

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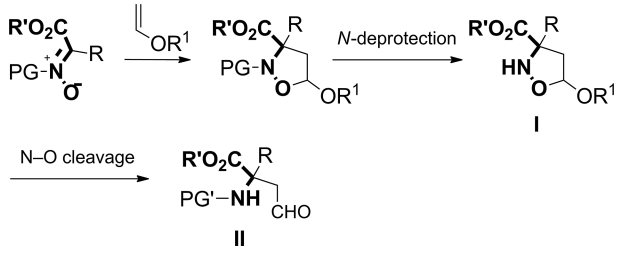
Bicyclic isoxazolidines displaying one or two quaternary stereocenter(s) were formed starting from functional cyclic ketonitrones equipped with a phenyl glycinol chiral auxiliary. The products were engaged in stereocontrolled 1,3-dipolar cycloaddition reactions with a range of electron-rich and electron-poor dipolarophiles. A new reductive removal of the phenyl glycinol chiral auxiliary was introduced and was shown to afford chemoselectively a quaternary isoxazolidine derivative (of oxaprolinol-type) without cleaving the N–O isoxazolidine bond. Keeping the aldehyde function masked as a cyclic pseudo-acetal, the liberated oxy-amine function was shown to be available for a pseudo-peptide coupling with various *N*-protected amino acids. The isoxazolidine ring was opened by a reductive N–O bond cleavage, giving a pseudo-dipeptide that was C-terminated with an aldehyde function.

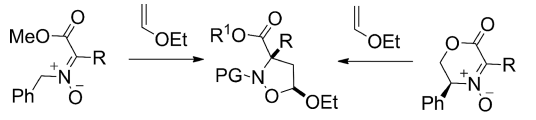
Introduction

1,3-Dipolar cycloaddition (1,3-DC) of nitrones is a very powerful reaction that is used to form five-membered rings with up to three contiguous stereocenters[1] as shown by the various examples of total syntheses for which 1,3-DC is a key-step.[2] Moreover, the 1,3-DC adducts could be transformed into β-amino acids[3] or, when the nitrone is directly equipped with an ester function, into oxaproline-type,[4,5] or other unnatural mono- or disubstituted amino acid derivatives.[5,6]

If vinyl ethers are used as dipolarophiles, we showed previously that quaternary β-amido aldehydes **II** could also be accessed via 5-alkoxy-isoxazolidines **I** (Scheme 1).[5a] It was underlined that the isoxazolidine ring remained intact during the N-deprotection step with the aldehyde function still masked under a cyclic pseudo-acetal form. For instance, aspartic aldehyde derivatives (R = CH_2CO_2Alk, Figure 1) were obtained by using either chiral aspartic nitrones[5b] or chiral vinyl ethers[5c] in efficient *exo* and asymmetrically controlled 1,3-DC reactions.[7]



Scheme 1. Access to substituted oxaprolines **I** and disubstituted amino aldehydes **II** with vinyl ethers as dipolarophiles.



	R	Acyclic	Cyclic	R	
Glycine	H	78:22	91:9	H	**3a** (Tamura)
Alanine	Me	75:25		**Alk**	**3** (our work)

Figure 1. Comparison of thermal cycloadditions of acyclic vs. cyclic nitrones with ethyl vinyl ether.[8,9]

With smaller substituents such as hydrogen (R = H[8]) or methyl (R = Me[9]), diastereoselectivity is limited even in the case of methyl ketonitrones of stable *E* geometry (Figure 1). Interestingly, Tamura et al.[10a–10e] and then Baldwin et al.[10f,10g] demonstrated that cyclic glycine-derived aldonitrones incorporating an (*R*)-phenylglycinol unit (**3a**; Figure 1) with a fixed *E* geometry, could be involved in efficient 1,3-DC reactions with different types of dipolarophiles.[11] Such cycloadditions proceed with good to total *trans* selectivity,[12] significantly higher than those observed from the corresponding acyclic aldonitrones (Figure 1). In addition, such chiral cyclic nitrones were found to induce high facial

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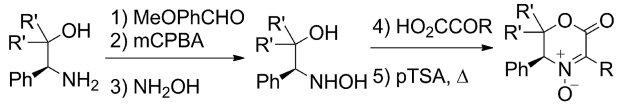
selectivity. However, removal of the chiral auxiliary under reductive conditions does not preserve the isoxazolidine ring,[10] which would be necessary to access a β-amino aldehyde in a convenient *N*-protected form. In the cyclic ketonitrones series, the only examples, developed by Heaney et al.,[13] concerned 1,3-DC reactions of racemic nitrones, which was never investigated in an asymmetric version.

In the present work, we report the results of our study on 1,3-DC reactions of new cyclic enantiopure ketonitrones such as **3** (Figure 1) towards representative electron-rich and electron-poor dipolarophiles. A main objective was to obtain evidence for a gain of diastereocontrol with cyclic ketonitrones as observed by Tamura in the aldonitrone series. Moreover, we describe the unprecedented removal of this type of chiral auxiliary that conserves the isoxazolidine ring by applying the chemoselective conditions that we previously disclosed in acyclic versions[5a] to obtain enantiopure *N*-deprotected, quaternary-containing isoxazolidines. Synthetic extensions to this synthon will be revealed to demonstrate its utility in peptide incorporation by 1) coupling this isoxazolidine with different *N*-protected amino acids and 2) showing the possible release of the aldehyde function after reductive N–O opening reaction.

Results and Discussion

Cyclic nitrones **3a**–**e** were synthesized in five steps (Table 1) by adaptation of Tamura's procedure that was previously described for cyclic aldonitrone **3a**.[10] Starting from aminoalcohol **1a** or **1b**,[14] the imine of *p*-anisaldehyde was formed, which was subsequently oxidized to the corresponding oxaziridine. This latter compound was treated with hydroxylamine hydrochloride to give substituted hydroxylamines **2a**–**b**. Cyclic nitrones **3a**–**e** were produced by reacting hydroxylamines **2a**–**b** either with hydrated glyoxylic acid (**3a**) or with the corresponding substituted pyruvic acid (**3b**–**e**), yields of nitrones so obtained ranged from 39 to 85%.

Table 1. Synthesis of cyclic nitrones **3a**–**e**.

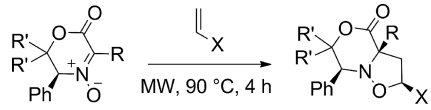


Entry	R	R′	Product	Yield (%)[a]
1	H	H	**3a**	80[b,c]
2	Me	H	**3b**	85
3	Et	H	**3c**	43
4	Ph	H	**3d**	58
5	Me	Me	**3e**	39[d,e]

[a] Isolated yield. [b] It was shown that, compared with Tamura's protocol, the yield of cyclic nitrone **3a** was maximized by using a glyoxylate solution dried by prior azeotropic distillation. [c] Ref.[10c] 85% yield. [d] The modest yield was due to partial decomposition of the nitrone in the acidic medium. [e] Synthesis of the dimethylated cyclic nitrone derived from glyoxylic acid was attempted but this compound was very unstable.

The reactivity of cyclic ketonitrones **3** was first tested in inverse 1,3-DC reactions with vinyl ethers, which were engaged in cycloaddition reactions with various electron-rich dipolarophiles (Table 2). Microwave conditions were employed to shorten reaction times of cycloaddition with ketonitrones, which are usually longer than with the corresponding aldonitrones. The reaction of **3a** with ethyl vinyl ether (entry 1) gave similar results to those obtained by Tamura under thermal nonmicrowave conditions.[10c] For nitrone **3b**, bearing a methyl substituent, yields were high (94–96%) and the major diastereoisomer was formed in the range of 67 to 84%.

Table 2. Cycloaddition of nitrones **3a**–**e** with electron-rich dipolarophiles.



Entry	Nitrone	R	R′	X	Product	Yield (%)	*dr*[f]
1	**3a**	H	H	OEt	**4a**	65[a,b]	84:8:8:0
2	**3b**	Me	H	OEt	**4b**	96	78:6:16:0
3	**3b**	Me	H	O*t*Bu	**4c**	94	81:9:10:0[g]
4	**3b**	Me	H	SEt	**4d**	44[c,d]	67:11:22:0
5	**3b**	Me	H	OAc	**4e**	75[e]	84:6:10:0
6	**3c**	Et	H	OEt	**4f**	79	75:5:20:0
7	**3c**	Et	H	O*t*Bu	**4g**	93	76:13:11:0
8	**3e**	Me	Me	OEt	**4h**	47	80:20:0:0

[a] Yield was 76% when the reaction was conducted in benzene at 30 °C. The same *dr* was obtained under both conditions. [b] Lit. 87% yield, *dr* 83:8:9.[10c] [c] Reaction conditions: 115 °C for 12 h. [d] Conversion was 63%. [e] Reaction conditions: 100 °C for 5 h. [f] *dr* expressed as *trans I*/*trans II*/*cis I*/*cis II* was measured by NMR spectroscopic analysis of the crude product. [g] *dr* could be improved by recrystallization to 93:7:0:0 (ca. 50% of enriched **4c** adduct).

Reaction of ethyl-substituted nitrone **3c** gave the expected cycloadducts in good yields (79–93%), albeit in slightly lower yield than for methyl-substituted compounds, which shows the deleterious steric effect of the substituent at the nascent quaternary center. This is more strongly marked with phenyl-substituted nitrone **3d**, which reacted sluggishly under these reaction conditions. The constrained, dimethyl-substituted nitrone **3e** reacted in 47% yield.

All these reactions gave a major *trans* adduct.[15] Overall *trans*/*cis* selectivities are usually high as a result of a strong *exo*-selective approach, which is typical for vinyl ethers.[7] In this case, they are better than the typical 75:25 diastereoselectivities observed for the corresponding open nitrones[5a] (84:16 for **4b**, entry 2; up to 90:10 for **4c** and **4e**), showing that the lactonic cycle, which imposes a strict (*E*)-nitrone configuration, is also beneficial.

The absolute configuration was assigned for compound **4c**, for which the structure of a derivative was obtained by X-ray crystallography (see compound **5c** in Scheme 2). Additionally, all major diastereoisomers **4a**–**h** exhibit similar

characteristic NOESY correlations (for example on **4c**, Figure 2) showing that H-7, H-2, and H-3α are all located on the lower side of the bicyclic structure, and that Me-3a and H-3β are both on the upper side, confirming the *trans* structure for all compounds. The facial selectivity results from an approach opposite to the phenyl moiety on the *Si*-face of the nitrone.

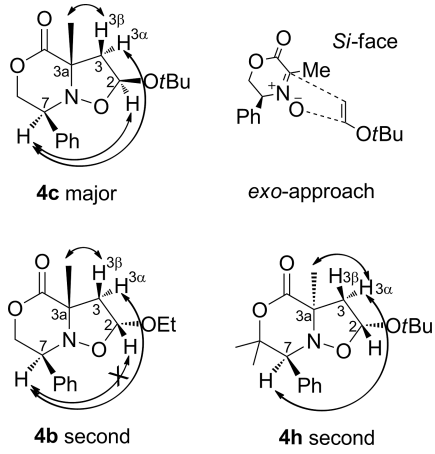


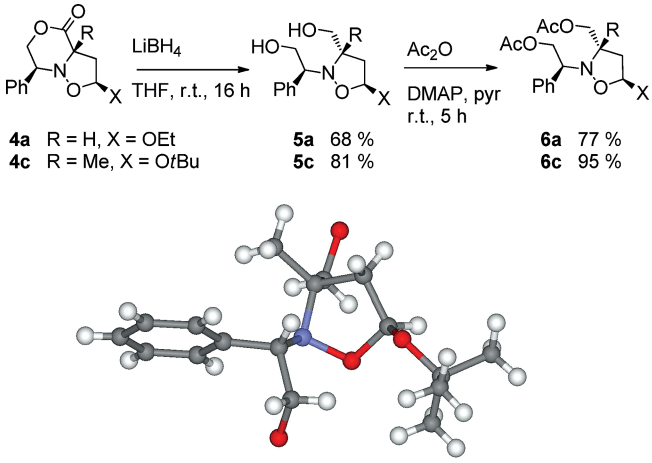
Figure 2. NOE correlations for the major diastereoisomer of cycloadduct **4c**, and *exo*-approach on the nitrone; NOE correlations for the second diastereoisomer of cycloadducts **4b** and **4h**.

The second diastereoisomer was attributed on the basis of characteristic NOESY correlations between H-7 and H-3α on one hand and between Me-3a and H-3β on the other hand, showing that it is an epimer in the C-2 position (no correlation between H-7 and H-2) with a cycloadduct of *cis* configuration. Additionally, we noticed a large chemical shift difference between both H-4 for the *trans* cycloadducts and a small shift difference for *cis* cycloadducts, which is typical for these types of isoxazolidines.[7]

In contrast, NOESY analysis of the second diastereoisomer of **4h** showed correlations between H-3α with both Me-3a and H-7, proving that the second diastereoisomer has a *trans* configuration with opposite stereochemistry. This shows that the steric effect exerted by the dimethyl groups favored the *exo*-approach but was also deleterious for the facial selectivity.

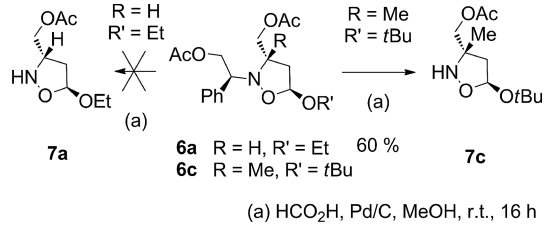
Unfortunately, the chiral auxiliary of cycloadducts **4a**–**h** could not be selectively removed by simple hydrogenolysis because debenzylation occurs with concomitant cleavage of the N–O bond, releasing together incompatible amino and aldehyde groups. We disclosed previously a debenzylation method (Pd/C, HCO_2H, MeOH, room temp.) that proved to be chemoselective over the N–O cleavage.[5a] When this method was tested on **4a** or **4c**, the starting materials were recovered even after prolonged reaction time. We assume that the blocked conformation of their bicyclic structure makes **4a** and **4c** highly constrained around the N–C bond, hindering hydrogenolysis.

To increase the accessibility of the benzylic bond, we decided to open the chiral auxiliary cycle (Scheme 2). After the failure of lithium hydroxide-mediated saponification,[16] lactone reduction was performed with lithium borohydride to obtain **5a** and **5c** with 68 and 81% yield, respectively. Importantly, it was possible to separate the diastereoisomers at this stage.[17] The major diastereoisomer of **5c** could be crystallized and its structure was determined by X-ray crystallography, which provided the absolute configuration (2*S*,3a*S*,7*S*) for **4c**. As the direct hydrogenolysis of compounds **5** did not work, the diol functions were protected as acetates.



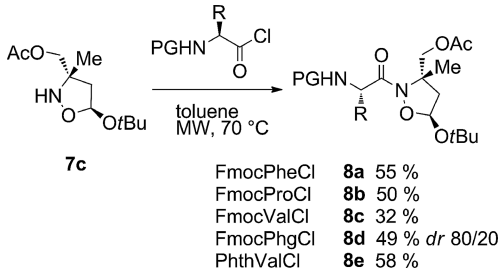
Scheme 2. Opening of the chiral auxiliary and structure of open cycloadduct **5c** determined by X-ray crystallography.

Formic acid mediated hydrogenolysis occurred for **6c** with 60% yield to form oxaprolinol derivative **7c**. The same reaction conditions applied to compound **6a** did not afford the N-deprotected product (Scheme 3).



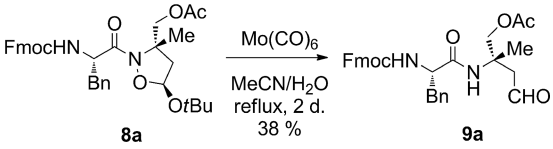
Scheme 3. Removal of the chiral auxiliary.

As a precursor of a disubstituted amino acid, it was interesting to couple isoxazolidine **7c** with an *N*-protected amino acid. Classical peptidic coupling failed on this highly bulky oxy-amine, giving only starting material.[18] On the other hand, compound **7c** was found to be reactive towards acylation with acetic or propionic anhydride. For this reason, we turned to more electrophilic acylating agents such as acyl chlorides.[19] When these were reacted with **7c** in toluene under microwave irradiation, the desired coupling product was formed as the only product (Scheme 4). Various pseudo-dipeptides could be formed with moderate yields. Importantly, this base-free reaction worked without any noticeable epimerization,[20] even for phthalyl-protected amino acyl chloride. The only exception was the highly epimerizable phenylglycine (Phg) residue.



Scheme 4. Coupling with protected amino acids.

At this point, it was possible to perform a classical peptide synthesis by N-elongation while keeping the oxaprolinol derivative on the C-terminus. However, this moiety also contains an aldehyde function in a masked cyclic pseudo-acetal form. We showed previously that cleavage of the N–O bond could be achieved with reducing agents such as $Mo(CO)_6$ or SmI_2 when the nitrogen is equipped with an electron-withdrawing group such as acetyl or trifluoroacetyl, giving access to the aldehyde or the ester.[5] This reaction, which has been shown to be sensitive to steric hindrance,[5c] has never been done previously on isoxazolidines with an aminoacyl group on the nitrogen. When **8a** was treated with SmI_2, no reaction occurred. In contrast, reaction with $Mo(CO)_6$ gave the opened product terminated by an aldehyde function, albeit in moderate yield (Scheme 5). This shows that the isoxazolidine route can be used effectively to obtain pseudo-peptides with a terminal quaternary β^3,β^3-amino aldehyde unit, which display the valuable property of unepimerizability.[21]

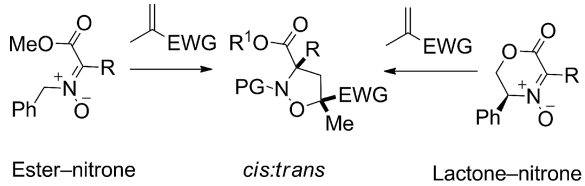


Scheme 5. Access to dipeptide aldehyde by reductive ring-opening.

The reactivity of electron-poor dipolarophiles towards cyclic ketonitrones **3** was then screened because a lack of diastereoselectivity is also observed with 1,3-DC reactions with acyclic nitrones (Figure 3). In the case of cyclic aldonitrones, Tamura et al. showed in this series a complete *cis* diastereocontrol.[6d]

Cyclic nitrones **3b–d** were engaged in 1,3-DC reaction with methacrolein or methyl methacrylate[23] under microwave conditions (Table 3). In both cases, one major diastereoisomer is formed with a very high selectivity in high yields, showing nearly no steric effect of the nitrone substituent.

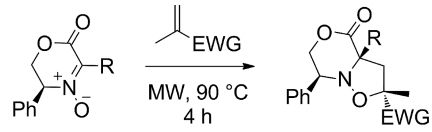
All these reactions were found to be completely *endo*-selective and gave a major *cis* adduct with excellent facial control, with *de* ranging from 82 to 100%. The absolute configuration was attributed for compound **10b**, for which a structure was obtained by X-ray crystallographic analysis (Figure 4). Additionally, all compounds **10a–f** exhibit characteristic NOESY correlations showing that H-7 and H-3α



	R	EWG	Acyclic	Cyclic	EWG	R	
Glycine	H	CHO	30:70	>98:<2	CO_2Me	H	**3a** (Tamura)
Alanine	Me	CHO	30:70			**Alk**	**3** (our work)

Figure 3. Comparison of cycloaddition reactions of acyclic vs. cyclic nitrones with electron-poor dipolarophiles.[6d,22]

Table 3. Cycloaddition of nitrones **3b–d** with electron-poor dipolarophiles.

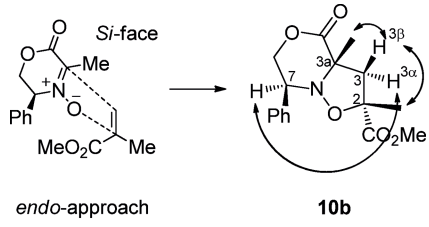


3b–d **10a–f**

Entry	Nitrone	R	EWG	Product	Yield (%)	*dr*[a]
1	**3b**	Me	CHO	**10a**	79	100:0:0:0
2	**3b**	Me	CO_2Me	**10b**	71	97:3:0:0
3	**3c**	Et	CHO	**10c**	84	96:4:0:0
4	**3c**	Et	CO_2Me	**10d**	>95	97:3:0:0
5	**3d**	Ph	CHO	**10e**	78	99:1:0:0
6	**3d**	Ph	CO_2Me	**10f**	>95	91:9:0:0

[a] *dr* expressed as *cis I*/*cis II*/*trans I*/*trans II* was measured by NMR spectroscopic analysis of the crude product.

are both located on the lower side of the bicyclic structure and that Me-3a, H-3β and Me-2 are all on the other side, confirming the *cis* structure for all compounds.



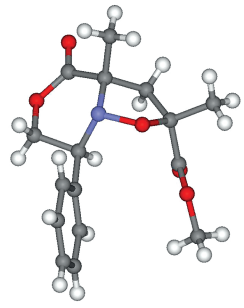
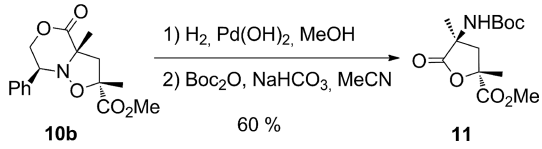


Figure 4. *endo*-Approach on the nitrone, NOESY correlations on major diastereoisomer of **10b** and structure determined by X-ray crystallographic analysis of **10b**.

The total *endo* selectivity is probably governed by the conjunction of the steric repulsive effect of the methyl substituent of the dipolarophile and the positive orbital overlapping between the carbonyl group and the nitrone. It corresponds to a reversal of selectivity compared with the 1,3-DC adducts obtained from the corresponding acyclic nitrones (Figure 3). As for electron-rich dipolarophiles, the facial selectivity results from an approach opposite to the phenyl moiety on *Si*-face of the nitrone.

As a first illustration of its synthetic potential and inspired from a sequence developed by Tamura in the aldonitrone series,[10a] the bis-quaternary center containing bicyclic adduct **10b** could be *N*-deprotected by hydrogenolysis, leading, after protection with Boc_2O, to lactone **11** in 60% yield (Scheme 6).



10b **11**

Scheme 6. Overall *N*-deprotection of **10b**.

Conclusions

A novel route to enantiopure disubstituted oxaprolinol derivatives through diastereoselective [3+2]-cycloaddition of chiral cyclic ketonitrones was successfully demonstrated and its efficiency for the diastereocontrol of the cycloaddition was established. The new quaternary isoxazolidine derivatives can be seen as masked β-amino aldehydes. A chemoselective reductive *N*-deprotection was developed that liberates the oxyamine without cleaving the N–O bond, keeping the aldehyde function protected. The oxy-amine was coupled with other *N*-protected amino acids. The masked aldehyde function can be released at a later stage and after coupling to allow the required transformations on the isoxazolidine framework. The diastereoselective [3+2]-cycloaddition was also studied with dipolarophiles of methacrylate-type and proved to be completely *cis*-selective, in contrast to the 1,3-DC reaction of acyclic nitrones, with high facial control.

Experimental Section

General Information: Reagents were purchased from commercial suppliers and used without additional purification. Methacrolein was distilled before use. Dichloromethane and THF were dried on a column of activated alumina in DRY STATION Glass Technology GTS 100 glassware. All reactions were conducted in oven-dried glassware under an inert atmosphere and were monitored by TLC with UV 254 silica gel-coated plates. Reactions under microwave conditions were performed with a CEM-Discover apparatus. Flash column chromatography was performed with silica gel (230–400 mesh) under medium pressure (1 bar). All melting points are uncorrected. Optical rotation measurements were performed in a 10 cm glass cell using a digital polarimeter equipped with a Peltier thermostated cell holder. ^1H and ^{13}C NMR spectra were recorded with 200 and 400 MHz spectrometers. Chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane (TMS) as reference for ^1H and ^{13}C. Infrared spectra were performed with an FT spectrophotometer. High-resolution mass spectra were performed with a GCT Premier Micromass. Compounds **1b**,[14] **2a**, and **3a**,[10c] and amino acyl chlorides[19] were fully described.

(*S*)-1-Hydroxyamino-2-methyl-1-phenylpropan-2-ol (2b): A solution of amino alcohol **1b** (100 mg, 0.6 mmol, 1 equiv.), and *para*-anisaldehyde (88 mg, 0.64 mmol, 1.1 equiv.) in toluene (2.5 mL) was heated at reflux with a Dean–Stark apparatus for 2 h. After cooling to room temperature, the mixture was concentrated under reduced pressure to give a red oil (194 mg, quantitative yield). ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 8.27 (s, 1 H), 7.71–7.76 (m, 2 H), 7.30–7.50 (m, 5 H), 6.93 (d, J = 10.0 Hz, 2 H), 4.22 (s, 1 H), 3.84 (s, 3 H), 1.23 (s, 3 H), 1.17 (s, 3 H) ppm. The crude imine was dissolved in dichloromethane (2 mL), and a solution of *meta*-chloroperbenzoic acid (75%, 181 mg, 0.82 mmol, 1.2 equiv.) in dichloromethane (6 mL) was added dropwise at 0 °C over 1.5 h. The mixture was stirred for 30 min and the white precipitate was then filtered off. The filtrate was washed with a 10% solution of K_2CO_3 (70 mL), dried with $MgSO_4$, and concentrated under reduced pressure to give a red oil (161 mg, 78% yield). ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.26–7.40 (m, 5 H), 6.77–7.08 (m, 4 H), 6.93 (d, J = 10.0 Hz, 2 H), 4.44 (s, 1 H), 3.75 (s, 3 H), 1.37 (s, 3 H), 1.29 (s, 3 H) ppm. The oxaziridine was dissolved in methanol (2 mL) and hydroxylamine hydrochloride (181 mg, 1.07 mmol, 2 equiv.) was added. The mixture was stirred overnight. Concentrated hydrochloric acid (1 mL) was added and the mixture was concentrated under reduced pressure. The residue was dissolved in water and ether and the aqueous phase was washed with diethyl ether until no nonpolar compounds were observed by TLC analysis. The aqueous phase was neutralized with sodium carbonate, saturated with sodium chloride, and then extracted with chloroform (8 × 5 mL). The organic phases were combined, dried with $MgSO_4$, and concentrated under reduced pressure to give a yellow oil (45 mg, 45% yield). This crude product was engaged in the next step without further purification. $[\alpha]_D^{20}$ = +3.4 (c = 0.15, CH_2Cl_2). ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.29–7.36 (m, 5 H), 4.01 (s, 1 H), 1.17 (s, 3 H), 1.15 (s, 3 H) ppm. IR (neat): $\tilde{\nu}$ = 3340, 2974, 2922, 1604, 1453, 1367, 1242 cm^{-1}.

General Procedure for the Synthesis of Cyclic Ketonitrones (3b–e): A solution of hydroxylamine (1 equiv.) and keto-acid (1.1 equiv.) in dichloromethane (2.5 mL/mmol of hydroxylamine) was stirred at room temperature overnight. Monohydrated *para*-toluenesulfonic acid (1.1 equiv.) was added to the solution, which was brought to reflux overnight. After cooling, the mixture was extracted with water, the aqueous layer was extracted with dichloromethane, and the organic phases were gathered, washed with a saturated solution of $NaHCO_3$, dried with $MgSO_4$, and concentrated under reduced pressure. Nitrones **3b–e** were purified by chromatography on silica gel column (cyclohexane/ethyl acetate, 1:1).

(*S*)-3-Methyl-4-oxy-5-phenyl-5,6-dihydro[1,4]oxazin-2-one (3b): Obtained by following the general procedure, starting from hydroxylamine **2a** (0.482 g, 3.15 mmol), yield 0.550 g (2.68 mmol, 85%); yellow solid; m.p. 98.6–100.0 °C; R_f 0.25 (cyclohexane/ethyl acetate, 1:1; UV visualization); $[\alpha]_D^{20}$ = –34.3 (c = 1.1, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.40–7.44 (m, 3 H), 7.32–7.37 (m, 2 H), 5.13 (t, J = 4.0 Hz, 1 H), 4.70, 4.83 (2dd, J = 4.0, 12.3 Hz, 2 H), 2.31 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 158.1, 136.2, 132.2, 129.6 (CH), 129.1 (2CH), 127.1 (2CH), 70.5 (CH), 66.8 (CH_2), 11.9 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 2985, 1716, 1552, 1301, 1127, 1071 cm^{-1}. HRMS (CI, NH_3): m/z calcd. for $C_{11}H_{11}NO_3$ [M + H^+] 206.0817; found 206.0818.

(*S*)-3-Ethyl-4-oxy-5-phenyl-5,6-dihydro[1,4]oxazin-2-one (3c): Obtained by following the general procedure, starting from hydroxylamine **2a** (0.630 g, 3.9 mmol), yield 0.363 g (1.66 mmol, 43%); yellow solid; m.p. 122.2–123.5 °C; R_f 0.46 (cyclohexane/ethyl acetate, 1:1, UV/vanilline visualization); $[\alpha]_D^{20}$ = –24.5 (*c* = 1.04, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.42 (m, 3 H), 7.33 (m, 2 H), 5.11 (t, *J* = 3.9 Hz, 1 H), 4.67, 4.82 (2dd, *J* = 3.9, 12.5 Hz, 2 H), 2.81 (m, 2 H), 1.18 (t, *J* = 7.3 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 158.8, 140.9, 132.3, 129.7 (CH), 129.4 (2CH), 127.0 (2CH), 70.7 (CH), 67.0 (CH_2), 19.3 (CH_2), 9.2 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 2986, 2935, 1715, 1553, 1301, 1126, 1072 cm^{-1}. HRMS (CI, NH_3): *m*/*z* calcd. for $C_{12}H_{14}NO_3$ [M + H$^+$] 220.0974; found 220.0976.

(*S*)-4-Oxy-3,5-diphenyl-5,6-dihydro[1,4]oxazin-2-one (3d): Obtained by following the general procedure, starting from hydroxylamine **2a** (0.23 g, 1.5 mmol), yield 0.30 g (0.9 mmol, 58%); pink solid; m.p. 147.0–148.1 °C; R_f 0.49 (cyclohexane/ethyl acetate, 1:1, UV/vanilline visualization); $[\alpha]_D^{20}$ = +24.7 (*c* = 1.1, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.77 (m, 2 H), 7.45 (m, 8 H), 5.28 (t, *J* = 3.7 Hz, 1 H), 4.83, 4.99 (2dd, *J* = 3.7, 12.5 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 158.7, 135.5, 132.1, 130.3 (CH), 130.1 (2CH), 129.7 (CH), 129.3 (2CH), 127.9 (2CH), 127.2, 127.1 (2CH), 72.0 (CH), 66.4 (CH_2) ppm. IR (neat): $\tilde{\nu}$ = 2924, 1712, 1551, 1361, 1199, 1013 cm^{-1}. HRMS (CI, NH_3): *m*/*z* calcd. for $C_{12}H_{14}NO_3$ [M + H$^+$] 220.0974; found 220.0976.

(*S*)-3,6,6-Trimethyl-4-oxy-5-phenyl-5,6-dihydro[1,4]oxazin-2-one (3e): Obtained by following general procedure, starting from hydroxylamine **2b** (0.20 g, 1.1 mmol) and pyruvic acid (106 mg, 1.2 mmol, 1.1 equiv.). Purified by chromatography, yield 0.10 g (0.43 mmol, 39%); glassy solid; $[\alpha]_D^{20}$ = +171 (*c* = 0.09, CH_2Cl_2); R_f 0.27 (cyclohexane/ethyl acetate, 1:1, UV/vanilline visualization). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.36–7.44 (m, 3 H), 7.22–7.28 (m, 2 H), 4.78 (s, 1 H), 2.33 (s, 3 H), 1.67 (s, 3 H), 1.23 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 159.3, 134.7, 132.3, 129.9 (CH), 129.2 (2CH), 128.1 (2CH), 80.4 (CH), 78.9, 27.4 (CH_3), 25.3 (CH_3), 11.9 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 2920, 2852, 1712, 1563, 1344, 1120 cm^{-1}. HRMS (CI, NH_3): *m*/*z* calcd. for $C_{13}H_{15}NO_3$ [M + H$^+$] 234.1130; found 234.1132.

General Procedure for the [3+2] Cycloaddition of Cyclic Ketonitrones (3a–e) with Electron-Rich Dipolarophiles: Nitrone **3** (1 equiv.) and dipolarophile were heated under the specified conditions with microwave irradiation. The reaction mixture was then concentrated under reduced pressure and the residue was purified by chromatography on silica gel.

(2*S*,3a*S*,7*S*)-2-Ethoxy-7-phenyl-tetrahydroisoxazolo[3,2-*c*][1,4]-oxazin-4-one and Its Diastereomers (4a):[10c] Obtained by following the general procedure (50 °C, 4 h, MW), starting from nitrone **3a** (100 mg, 0.52 mmol) and ethyl vinyl ether (0.5 mL, 5 mmol, 9 equiv.). Purified by chromatography on silica gel (hexane/ethyl acetate, 3:2), yield 89 mg (0.34 mmol, 65%); yellow oil; *dr* 84:8:8:0; R_f 0.54 (hexane/ethyl acetate, 3:2, vanilline and UV visualization). ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.32–7.51 (m, 5 H), 5.17 (d, *J* = 4.3 Hz, 1 H), 4.47 (t, *J* = 8.0 Hz, 1 H), 4.05–4.37 (m, 3 H), 3.63–3.78 (m, 1 H), 3.32–3.49 (m, 1 H), 3.08 (m, 1 H), 2.59–2.85 (m, 2 H) ppm.

(2*S*,3a*S*,7*S*)-2-Ethoxy-3a-methyl-7-phenyl-tetrahydroisoxazolo[3,2-*c*][1,4]oxazin-4-one and Its Diastereomers (4b): Obtained by following the general procedure (100 °C, 5 h, MW), starting from nitrone **3b** (300 mg, 1.46 mmol) and ethyl vinyl ether (1 mL, 10 mmol, 7 equiv.). Purified by chromatography on silica gel (cyclohexane/diethyl ether, 1:1) as a solid, yield 389 mg (1.40 mmol, 96%); *dr* 78:16:6:0; R_f 0.51 (cyclohexane/diethyl ether, 1:1, vanilline and UV visualization). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ (major *trans* diastereoisomer) = 7.44–7.50 (m, 2 H), 7.30–7.44 (m, 3 H), 5.16 (dd, *J* = 0.9, 5.7 Hz, 1 H), 4.28 (dd, *J* = 4.0, 9.9 Hz, 1 H), 4.23 (dd, *J* = 9.9, 11.9 Hz, 1 H), 4.09 (dd, *J* = 4.0, 9.9 Hz, 1 H), 3.69 (dq, *J* = 7.1, 9.6 Hz, 1 H), 3.38 (dq, *J* = 7.1, 9.6 Hz, 1 H), 2.92 (dd, *J* = 5.7, 13.6 Hz, 1 H), 2.45 (dd, *J* = 0.9, 13.6 Hz, 1 H), 1.78 (s, 3 H), 1.18 (t, *J* = 7.1 Hz, 3 H) ppm. δ (*cis* diastereoisomer) = 7.44–7.50 (m, 2 H), 7.30–7.42 (m, 3 H), 5.18 (dd, *J* = 2.4, 6.0 Hz, 1 H), 4.67 (dd, *J* = 3.9, 10.2 Hz, 1 H), 4.21 (dd, *J* = 3.9, 11.6 Hz, 1 H), 4.17 (dd, *J* = 10.2, 11.6 Hz, 1 H), 3.44 (dq, *J* = 7.1, 9.6 Hz, 1 H), 3.28 (dq, *J* = 7.1, 9.6 Hz, 1 H), 2.95 (dd, *J* = 2.4, 13.9 Hz, 1 H), 2.68 (dd, *J* = 6.0, 13.9 Hz, 1 H), 1.66 (s, 3 H), 1.11 (t, *J* = 7.1 Hz, 3 H) ppm. δ (characteristic signals of minor *trans* diastereoisomer) = 5.08 (t, *J* = 10.8 Hz, 1 H), 2.27 (dd, *J* = 3.2, 13.9 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ (major *trans* diastereoisomer) = 173.2, 136.2, 128.7 (2CH), 128.4 (CH), 127.4 (2CH), 100.7 (CH), 69.3 (CH_2), 67.1, 65.4 (CH), 63.4 (CH_2), 46.5 (CH_2), 27.4 (CH_3), 15.2 (CH_3) ppm. δ (*cis* diastereoisomer) = 172.1, 136.3, 128.4 (2CH), 127.9 (CH), 127.6 (2CH), 104.3 (CH), 70.2, 68.8 (CH_2), 64.8 (CH), 63.9 (CH_2), 48.5 (CH_2), 27.3 (CH_3), 14.8 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 2977, 2933, 1747, 1455, 1147, 1041 cm^{-1}. HRMS (CI, NH_3): *m*/*z* calcd. for $C_{15}H_{19}NO_4$ [M + H$^+$] 278.1392; found 278.1392.

(2*S*,3a*S*,7*S*)-2-*tert*-Butoxy-3a-methyl-7-phenyl-tetrahydroisoxazolo[3,2-*c*][1,4]oxazin-4-one and Its Diastereomers (4c): Obtained by following the general procedure (100 °C, 7 h, MW), starting from nitrone **3b** (7.27 g, 35.4 mmol) and *tert*-butyl vinyl ether (14 mL, 106 mmol, 3 equiv.). Purified by chromatography on silica gel (cyclohexane/diethyl ether, 1:1) and recrystallization [hexane/diethyl ether, 95:5 (100 mL)] as a solid, yield 10.16 g (33.3 mmol, 94%); crude *dr* 81:9:10:0. Major *trans* diastereoisomer could be enriched up to *dr* 93:7:0:0 by a second recrystallization. R_f 0.53 (cyclohexane/diethyl ether, 1:1, vanilline and UV visualization). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ (major *trans* diastereoisomer) = 7.44–7.50 (m, 2 H), 7.28–7.42 (m, 3 H), 5.45 (dd, *J* = 0.9, 6.1 Hz, 1 H), 4.27 (dd, *J* = 4.2, 11.9 Hz, 1 H), 4.22 (dd, *J* = 9.9, 11.9 Hz, 1 H), 4.06 (dd, *J* = 4.2, 9.9 Hz, 1 H), 2.90 (dd, *J* = 6.0, 13.3 Hz, 1 H), 2.35 (dd, *J* = 0.9, 13.3 Hz, 1 H), 1.79 (s, 3 H), 1.16 (s, 9 H) ppm. δ (minor *trans* diastereoisomer) = 7.44–7.50 (m, 2 H), 7.28–7.42 (m, 3 H), 5.45 (dd, *J* = 0.9, 6.1 Hz, 1 H), 4.72 (dd, *J* = 3.5, 10.6 Hz, 1 H), 4.15–4.30 (m, 2 H), 2.82 (dd, *J* = 3.2, 14.1 Hz, 1 H), 2.68 (dd, *J* = 6.5, 14.1 Hz, 1 H), 1.64 (s, 3 H), 1.00 (s, 9 H) ppm. δ (characteristic signals of *cis* diastereoisomer) = 5.10 (t, *J* = 11.2 Hz, 1 H), 3.22 (dd, *J* = 6.6, 13.7 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ (major *trans* diastereoisomer) = 173.4, 136.2, 128.6 (2CH), 128.3 (CH), 127.5 (2CH), 96.2 (CH), 74.9, 69.4 (CH_2), 67.5, 65.1 (CH), 47.2 (CH_2), 28.7 ($3CH_3$), 27.3 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 2969, 2934, 1748, 1127, 971 cm^{-1}. HRMS (CI, NH_3): *m*/*z* calcd. for $C_{17}H_{23}NO_4$ [M + H$^+$] 306.1705; found 306.1703.

(2*S*,3a*S*,7*S*)-2-Ethylsulfanyl-3a-methyl-7-phenyl-tetrahydroisoxazolo[3,2-*c*][1,4]oxazin-4-one and Its Diastereomers (4d): Obtained by following the general procedure (115 °C, 12 h, toluene, MW), starting from nitrone **3b** (52 mg, 0.25 mmol) and ethyl vinyl thioether (0.03 mL, 0.29 mmol, 1.1 equiv.). Purified by chromatography on silica gel (cyclohexane/ethyl acetate, 7:3) as a brown oil, yield 32 mg (0.11 mmol, 44%); crude *dr* 67:11:22:0; R_f 0.51 (cyclohexane/ethyl acetate, 7:3, vanilline and UV visualization). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ (major *trans* diastereoisomer) = 7.47 (m, 2 H), 7.36 (m, 3 H), 5.35 (dd, *J* = 5.8, 8.3 Hz, 1 H), 4.30 (dd, *J* = 3.4, 11.2 Hz, 1 H), 4.21 (m, 2 H), 3.30 (dd, *J* = 8.3, 13.9 Hz, 1 H), 2.57 (q, *J* = 7.5 Hz, 2 H), 2.34 (dd, *J* = 5.9, 13.9 Hz, 1 H), 1.76 (s, 3 H), 1.17 (t, *J* = 7.3 Hz, 3 H) ppm. δ (major *cis* diastereoisomer) = 7.47 (m, 2 H), 7.36 (m, 3 H), 5.39 (t, *J* = 7.1 Hz, 1 H), 4.91 (dd, *J* = 4.9, 9.5 Hz, 1 H), 4.22 (m, 2 H), 2.92 (dd, *J* =

7.6, 13.7 Hz, 1 H), 2.84 (dd, *J* = 6.6, 13.7 Hz, 1 H), 2.40–2.52 (m, 2 H), 1.68 (s, 3 H), 1.07 (t, *J* = 7.6 Hz, 3 H) ppm. δ (characteristic signals of minor *trans* diastereoisomer) = 5.43 (dd, *J* = 5.4, 8.3 Hz, 1 H), 4.84 (dd, *J* = 3.9, 12.5 Hz, 1 H), 5.09 (t, *J* = 4.6 Hz, 1 H), 4.75 (dd, *J* = 4.9, 12.5 Hz, 1 H), 3.43 (dd, *J* = 8.1, 13.4 Hz, 1 H), 2.65–2.75 (m, 2 H), 2.34 (dd, *J* = 5.4, 13.7 Hz, 1 H), 1.67 (s, 3 H), 1.28 (t, *J* = 7.3 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ (major *trans* diastereoisomer) = 172.3, 135.5, 128.8 (2CH), 128.4 (CH), 127.5 (2CH), 81.2 (CH), 69.4 (CH_2), 68.7, 62.9 (CH), 47.7 (CH_2), 27.1 (CH_2), 26.2 (CH_3), 15.1 (CH_3) ppm. δ (major *cis* diastereoisomer) = 171.5, 135.6, 128.8–127.5 (5CH), 82.9 (CH), 70.3 (CH_2), 67.5, 63.3 (CH), 47.3 (CH_2), 26.1 (CH_2), 25.9 (CH_3), 14.6 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 2928, 1738, 1115, 1030 cm^{-1}. HRMS (CI, NH_3): *m*/*z* calcd. for $C_{15}H_{20}NO_3S$ [M + H$^+$] 294.1163; found 294.1152.

(2*S*,3a*S*,7*S*)-3a-Methyl-4-oxo-7-phenyl-hexahydroisoxazolo[3,2-*c*]-[1,4]oxazin-2-yl Acetate and Its Diastereomers (4e): Obtained by following the general procedure (100 °C, 5 h, MW), starting from nitrone **3b** (40 mg, 0.19 mmol) and vinyl acetate (0.1 mL, 1.1 mmol, 6 equiv.). Purified by chromatography on silica gel (cyclohexane/diethyl ether, 1:1) as an oil, yield 34 mg (0.12 mmol, 60%); crude *dr* 84:6:10:0; R_f 0.51 (cyclohexane/diethyl ether, 1:1, vanilline and UV visualization). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ (major *trans* diastereoisomer) = 7.30–7.45 (m, 5 H), 6.40 (dd, *J* = 0.5, 5.7 Hz, 1 H), 4.32 (dd, *J* = 4.0, 12.2 Hz, 1 H), 4.27 (dd, *J* = 9.8, 12.2 Hz, 1 H), 4.12 (dd, *J* = 4.0, 9.8 Hz, 1 H), 3.11 (dd, *J* = 5.7, 14.2 Hz, 1 H), 2.56 (dd, *J* = 0.5, 14.2 Hz, 1 H), 2.07 (s, 3 H), 1.78 (s, 3 H) ppm. δ (characteristic signals of minor *trans* diastereoisomer) = 3.37 (dd, *J* = 6.9, 14.2 Hz, 1 H), 2.41 (dd, *J* = 3.0, 14.2 Hz, 1 H) ppm. δ (characteristic signals of *cis* diastereoisomer) = 2.78 (dd, *J* = 5.9, 14.2 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ (major *trans* diastereoisomer) = 172.3, 169.7, 135.4, 128.8 (2CH), 128.6 (CH), 127.4 (2CH), 94.5 (CH), 69.1 (CH_2), 66.7, 65.3 (CH), 46.2 (CH_2), 27.1 (CH_2), 21.2 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 1746, 1456, 1234, 1125 cm^{-1}. HRMS (CI, NH_3): *m*/*z* calcd. for $C_{15}H_{18}NO_5$ [M + H$^+$] 292.1185; found 292.1193.

(2*S*,3a*S*,7*S*)-2-Ethoxy-3a-ethyl-7-phenyl-tetrahydroisoxazolo[3,2-*c*][1,4]oxazin-4-one and Its Diastereomers (4f): Obtained by following the general procedure (90 °C, 4 h, MW), starting from nitrone **3c** (53 mg, 0.24 mmol) and ethyl vinyl ether (1.5 mL, 15 mmol, 64 equiv.). Purified by chromatography on silica gel (cyclohexane/ethyl acetate, 7:3) as a yellow solid, yield 57 mg (0.19 mmol, 79%); crude *dr* 75:5:20:0; R_f 0.59 (cyclohexane/ethyl acetate, 7:3, vanilline and UV visualization). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ (major *trans* diastereoisomer) = 7.48 (m, 2 H), 7.37 (m, 3 H), 5.20 (dd, *J* = 0.3, 6.4 Hz, 1 H), 4.18 (m, 2 H), 4.05 (dd, *J* = 6.4, 8.1 Hz, 1 H), 2.87 (dd, *J* = 6.1, 13.7 Hz, 1 H), 2.49 (dd, *J* = 0.3, 13.7 Hz, 1 H), 2.29 (dq, *J* = 7.3, 14.0 Hz, 1 H), 2.07 (dq, *J* = 7.3, 14.0 Hz, 1 H), 1.15 (t, *J* = 7.1 Hz, 3 H), 1.09 (t, *J* = 7.5 Hz, 3 H) ppm. δ (characteristic signals of major *cis* diastereoisomer) = 2.87 (m, 1 H), 2.70 (dd, *J* = 6.4, 14.2 Hz, 1 H) ppm. δ (characteristic signals of minor *trans* diastereoisomer) = 3.10 (dd, *J* = 6.4, 13.7 Hz, 1 H), 2.32 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ (major *trans* diastereoisomer) = 172.1, 136.3, 128.8 (2CH), 128.5 (CH), 127.4 (2CH), 101.1 (CH), 72.2, 69.6 (CH_2), 65.0 (CH), 63.9 (CH_2), 45.3 (CH_2), 32.1 (CH_2), 15.1 (CH_3), 9.7 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 2977, 1728, 1148, 1079, 1043 cm^{-1}. HRMS (CI, NH_3): *m*/*z* calcd. for $C_{16}H_{22}NO_4$ [M + H$^+$] 292.1549; found 292.1551.

(2*S*,3a*S*,7*S*)-2-*tert*-Butoxy-3a-ethyl-7-phenyl-tetrahydroisoxazolo-[3,2-*c*][1,4]oxazin-4-one and Its Diastereomers (4g): Obtained by following the general procedure (100 °C, 4 h, MW), starting from nitrone **3c** (69 mg, 0.32 mmol) and *tert*-butyl vinyl ether (1.4 mL, 10 mmol, 33 equiv.). Purified by chromatography on silica gel (cyclohexane/ethyl acetate, 8:2) as a colorless oil, yield 95 mg (0.3 mmol, 93%); crude *dr* 76:13:11:0; R_f 0.30 (cyclohexane/ethyl acetate, 8:2, vanilline and UV visualization). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ (major *trans* diastereoisomer) = 7.47 (m, 2 H), 7.35 (m, 3 H), 5.48 (dd, *J* = 1.7, 6.4 Hz, 1 H), 4.18 (m, 2 H), 4.05 (dd, *J* = 5.6, 8.3 Hz, 1 H), 2.88 (dd, *J* = 6.4, 13.4 Hz, 1 H), 2.37 (dd, *J* = 1.7, 13.4 Hz, 1 H), 2.28 (dq, *J* = 7.3, 14.0 Hz, 1 H), 2.08 (dq, *J* = 7.3, 14.0 Hz, 1 H), 1.14 (s, 9 H), 1.10 (t, *J* = 7.3 Hz, 3 H) ppm. δ (characteristic signals of major *cis* diastereoisomer) = 2.78 (dd, *J* = 3.4, 14.2 Hz, 1 H), 2.69 (dd, *J* = 6.6, 14.2 Hz, 1 H) ppm. δ (characteristic signals of minor *trans* diastereoisomer) = 3.08 (dd, *J* = 6.6, 13.4 Hz, 1 H), 2.24 (dd, *J* = 3.9, 13.4 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ (major *trans* diastereoisomer) = 172.3, 136.3, 128.6 (2CH), 128.4 (CH), 127.6 (2CH), 96.4 (CH), 75.0, 72.6, 69.7 (CH_2), 64.4 (CH), 46.1 (CH_2), 32.2 (CH_2), 28.7 ($3CH_3$), 9.7 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 2969, 1746, 1128, 975 cm^{-1}. HRMS (CI, NH_3): *m*/*z* calcd. for $C_{18}H_{26}NO_4$ [M + H$^+$] 320.1862; found 320.1857.

(2*R*,3a*R*,7*R*)-2-Ethoxy-3a,6,6-trimethyl-7-phenyl-tetrahydroisoxazolo[3,2-*c*][1,4]oxazin-4-one and Its Diastereomers (4h): Obtained by following the general procedure (110 °C, 5 h, MW), starting from nitrone **3e** (32 mg, 0.14 mmol) and ethyl vinyl ether (0.13 mL, 1.4 mmol, 10 equiv.). Purified by chromatography on silica gel (cyclohexane/diethyl ether, 1:1) as a solid, yield 20 mg (0.065 mmol, 47%); *dr* 81:19:0:0; R_f 0.71 (cyclohexane/diethyl ether, 1:1, vanilline and UV visualization). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ (major *trans* diastereoisomer) = 7.20–7.55 (m, 5 H), 5.18 (dd, *J* = 0.6, 6.2 Hz, 1 H), 3.79 (s, 1 H), 3.64 (dq, *J* = 7.0, 9.5 Hz, 1 H), 3.31 (dq, *J* = 7.0, 9.5 Hz, 1 H), 2.84 (dd, *J* = 6.2, 13.6 Hz, 1 H), 2.49 (dd, *J* = 0.6, 13.6 Hz, 1 H), 1.86 (s, 3 H), 1.40 (s, 3 H), 1.23 (s, 3 H), 1.14 (t, *J* = 7.0 Hz, 3 H) ppm. δ (minor *trans* diastereoisomer) = 7.20–7.55 (m, 5 H), 5.15 (dd, *J* = 3.7, 6.2 Hz, 1 H), 4.53 (s, 1 H), 3.10 (dq, *J* = 7.0, 9.5 Hz, 1 H), 3.04 (dq, *J* = 7.0, 9.5 Hz, 1 H), 2.81 (dd, *J* = 3.7, 14.2 Hz, 1 H), 2.76 (dd, *J* = 6.2, 14.2 Hz, 1 H), 1.65 (s, 3 H), 1.42 (s, 3 H), 1.27 (s, 3 H), 0.99 (t, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ (major *trans* diastereoisomer) = 172.3, 136.5, 129.0 (2CH), 128.2 (CH), 128.1 (2CH), 101.9 (CH), 83.6, 72.9 (CH), 67.5, 64.3 (CH_2), 45.8 (CH_2), 27.1 (CH_3), 25.7 (CH_3), 22.1 (CH_3), 15.2 (CH_3) ppm. δ (minor *trans* diastereoisomer) = 172.3, 136.7, 128.9 (2CH), 128.3 (CH), 127.9 (2CH), 104.7 (CH), 84.2, 71.9 (CH), 68.7, 64.2 (CH_2), 48.5 (CH_2), 26.9 (CH_3), 26.1 (CH_3), 21.8 (CH_3), 14.7 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 2982, 2937, 1736, 1373, 1273, 1171, 1110 cm^{-1}. HRMS (CI, NH_3): *m*/*z* calcd. for $C_{17}H_{24}NO_4$ [M + H$^+$] 306.1705; found 306.1694.

(2*S*)-2-[(3*S*,5*S*)-5-Ethoxy-3-(hydroxymethyl)isoxazolidin-2-yl]-2-phenylethanol (5a): The 84:8:8 mixture of cycloadducts **4a** (220 mg, 0.84 mmol) was dissolved in anhydrous THF (8 mL) under argon, and a solution of $LiBH_4$ (4 M in THF, 0.5 mL, 2.09 mmol, 2.5 equiv.) was added dropwise. The mixture was stirred at room temperature for 2 h, then water (5 mL) was added and the mixture was extracted with ethyl acetate (3 × 15 mL). Organic phases were dried on $MgSO_4$ and concentrated under reduced pressure. The white solid was purified by chromatography on silica gel (toluene/methanol, 9:1) to give a white solid, yield 150 mg (0.56 mmol, 68%); R_f 0.32 (toluene/methanol, 9:1, UV and vanilline visualization); m.p. 136.0–137.0 °C; $[\alpha]_D^{20}$ = +86.1 (*c* = 0.29, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.30–7.38 (m, 5 H), 5.28 (dd, *J* = 2.4, 5.6 Hz, 1 H), 5.13 (br. s, 2 H), 4.31 (t, *J* = 4.9 Hz, 1 H), 4.11 (dd, *J* = 4.9, 11.2 Hz, 1 H), 3.98 (dd, *J* = 5.1, 11.5 Hz, 1 H), 3.90 (dd, *J* = 7.1, 9.3 Hz, 1 H), 3.57 (dd, *J* = 7.1, 9.5 Hz, 1 H), 3.40 (m, 1 H), 3.24 (dd, *J* = 6.1, 11.2 Hz, 1 H), 3.08 (dd, *J* = 4.4,

11.0 Hz, 1 H), 2.37 (ddd, *J* = 2.4, 7.6, 13.4 Hz, 1 H), 2.28 (ddd, *J* = 4.9, 5.6, 13.4 Hz, 1 H), 1.28 (t, *J* = 7.1 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 138.6, 135.2, 128.9, 128.4, 128.3, 128.2 (4CH), 125.1 (CH), 105.8 (CH), 72.8 (CH), 66.6 (CH_2), 64.6 (CH_2), 63.7 (CH), 63.4 (CH_2), 37.7 (CH_2), 15.2 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 3407, 2974, 1604, 1454, 1375, 1056 cm^{-1}. MS (DCI, CH_4): *m*/*z* = 268.32 [M + H$^+$]. HRMS (ESI): *m*/*z* calcd. for $C_{14}H_{22}NO_4$ [M + H$^+$] 268.1543; found 268.1541; *m*/*z* calcd. for $C_{14}H_{21}NNaO_4$ [M + Na$^+$] 290.1363; found 290.1367.

(3*S*,5*S*)-2-[(1*S*)-2-Acetoxy-1-phenylethyl]-5-ethoxyisoxazolidin-3-ylmethyl Acetate (6a): Acetic anhydride (16 mL, 1.69 mmol, 3 equiv.) and DMAP (100 mg, 0.085 mmol, 0.15 equiv.) were added to cycloadduct **5a** (150 mg, 0.56 mmol). Pyridine (3.8 mL) was added after complete dissolution. The mixture was stirred at room temperature for 18 h, then the solution was concentrated under reduced pressure and transferred onto iced water (10 mL). The aqueous phase was extracted three times with dichloromethane and the organic phases were combined, dried with Na_2SO_4, and concentrated under reduced pressure. The product was purified by chromatography on silica gel (hexane/ethyl acetate, 2:1) to give a yellow oil, yield 151 mg (77%); R_f 0.43 (hexane/ethyl acetate, 2:1, UV and vanilline visualization). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.30–7.40 (m, 5 H), 5.31 (dd, *J* = 2.4, 6.1 Hz, 1 H), 4.72 (dd, *J* = 2.9, 10.0 Hz, 1 H), 4.42 (m, 2 H), 3.95 (dd, *J* = 7.1, 9.5 Hz, 1 H), 3.76 (dd, *J* = 2.9, 6.6 Hz, 2 H), 3.58 (dd, *J* = 7.1, 9.5 Hz, 1 H), 3.50 (m, 1 H), 2.43 (ddd, *J* = 2.7, 8.1, 13.7 Hz, 1 H), 2.20 (ddd, *J* = 3.7, 6.1, 13.7 Hz, 1 H), 1.95 (s, 3 H), 1.90 (s, 3 H), 1.27 (t, *J* = 7.1 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 170.4, 138.3, 128.6, 128.3, 128.1 (5CH), 105.5 (CH), 69.6 (CH), 66.2 (CH_2), 65.3 (CH_2), 64.4 (CH_2), 60.6 (CH), 37.9 (CH_2), 20.6 ($2CH_3$), 14.9 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 2978, 1737, 1370, 1231, 1042 cm^{-1}. MS (DCI, CH_4): *m*/*z* = 352.39 [M + H$^+$]. HRMS (ESI): *m*/*z* calcd. for $C_{18}H_{26}NO_6$ [M + H$^+$] 352.1755; found 352.1762.

(2*S*)-2-[(3*S*,5*S*)-5-*tert*-Butoxy-3-(hydroxymethyl)-3-methylisoxazolidin-2-yl]-2-phenylethanol (5c): The 93:7 mixture of cycloadducts **4c** (780 mg, 2.55 mmol) was dissolved in anhydrous THF (37 mL) under argon, and a solution of $LiBH_4$ (2 M in THF, 3.7 mL, 7.40 mmol, 3.0 equiv.) was added dropwise. The mixture was stirred at room temperature for 16 h, then water (20 mL) was added and the mixture was extracted with ethyl acetate (2 × 50 mL). The organic phases were dried on $MgSO_4$ and concentrated under reduced pressure. The product was purified by chromatography on silica gel (cyclohexane/ethyl acetate, 9:1 to 5:5) to give the major diastereoisomer (478 mg, 1.5 mmol) and the minor diastereoisomer (50 mg, 0.16 mmol) as white solids (65% combined yield). Hemiacetal (130 mg, 0.4 mmol, 17% yield) was also obtained and could be converted into diol (95% yield) by additional reduction with $LiBH_4$ (2 equiv.) with a global yield of 81%. Major diastereoisomer: R_f 0.27 (cyclohexane/ethyl acetate, 9:1, UV and vanilline visualization); m.p. 78.5 °C; $[\alpha]_D^{20}$ = +87 (*c* = 1.01, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.40–7.25 (m, 5 H), 5.47 (dd, *J* = 4.5, 6.5 Hz, 1 H), 4.28 (dd, *J* = 3.1, 6.5 Hz, 1 H), 4.03 (ddd, *J* = 4.1, 6.5, 11.5 Hz, 1 H), 3.71 (ddd, *J* = 3.1, 9.1, 11.5 Hz, 1 H), 3.41 (dd, *J* = 4.1, 9.1 Hz, 1 H), 3.31 (dd, *J* = 5.8, 10.7 Hz, 1 H), 2.98 (dd, *J* = 6.8, 10.7 Hz, 1 H), 2.45 (dd, *J* = 6.5, 13.5 Hz, 1 H), 2.25 (dd, *J* = 5.8, 6.8 Hz, 1 H), 2.10 (dd, *J* = 4.5, 13.5 Hz, 1 H), 1.29 (s, 9 H), 1.00 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 140.5, 128.7 (2CH), 127.8 (CH), 127.7 (2CH), 98.8 (CH), 75.6, 68.5 (CH), 68.4, 67.8 (CH_2), 67.4 (CH_2), 45.5 (CH_2), 28.5 ($3CH_3$), 19.4 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 3435, 2981, 2930, 2371, 1452, 1395, 1239, 1192, 1070, 1055, 970 cm^{-1}. HRMS (DCI, NH_3): *m*/*z* calcd. for $C_{17}H_{27}NO_4$ [M + H$^+$] 310.2005; found 310.2018. Minor diastereoisomer: R_f 0.25 (cyclohexane/ethyl acetate, 9:1, UV and vanilline visualization).

(2*S*)-2-[(3*S*,5*S*)-3-(Acetoxymethyl)-5-*tert*-butoxy-3-methylisoxazolidin-2-yl]-2-phenylethyl Acetate (6c): To a solution of diol **5c** (180 mg, 0.58 mmol) in pyridine (4.5 mL) were added dimethylaminopyridine (10 mg, 0.09 mmol, 0.15 equiv.) and acetic anhydride (0.16 mL, 1.74 mmol, 3 equiv.). The solution was stirred for 5 h at room temperature, then the solvent was removed in vacuo and the residue was poured into cold water (7 mL) and extracted with dichloromethane (2 × 10 mL). The combined organic layers were dried with $MgSO_4$ and concentrated under reduced pressure. Eventually, the purity of the crude product allowed its use without further purification. Otherwise, it could be purified by chromatography on silica gel (cyclohexane/ethyl acetate, 2:1), yield 217 mg (95% yield); R_f 0.57 (cyclohexane/ethyl acetate, 2:1, UV and vanilline visualization); $[\alpha]_D^{20}$ = +45.3 (*c* = 2.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.46–7.36 (m, 2 H), 7.35–7.25 (m, 3 H), 5.47 (dd, *J* = 4.3, 6.7 Hz, 1 H), 4.75 (dd, *J* = 2.1, 8.6 Hz, 1 H), 4.45 (dd, *J* = 2.1, 7.3 Hz, 1 H), 4.39 (dd, *J* = 7.3, 8.6 Hz, 1 H), 3.85 (d, *J* = 10.9 Hz, 1 H), 3.78 (d, *J* = 10.9 Hz, 1 H), 2.44 (dd, *J* = 6.7, 13.8 Hz, 1 H), 2.07 (dd, *J* = 4.3, 13.8 Hz, 1 H), 2.03 (s, 3 H), 1.87 (s, 3 H), 1.28 (s, 9 H), 0.93 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 170.8, 170.7, 140.4, 128.5 (2CH), 128.0 (2CH), 127.5 (CH), 98.9 (CH), 75.1, 68.7 (CH_2), 67.6, 67.1 (CH_2), 64.8 (CH), 45.5 (CH_2), 28.6 ($3CH_3$), 20.9 (CH_3), 20.8 (CH_3), 20.0 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 2977, 1743, 1374, 1234, 1045 cm^{-1}. HRMS (FD): *m*/*z* calcd. for $C_{21}H_{31}NO_6$ [M$^+$] 393.2151; found 393.2186.

[(3*S*,5*S*)-5-(*tert*-Butoxy)-3-methylisoxazolidin-3-yl]methyl Acetate (7c): Under argon, to a stirred solution of adduct **6c** (590 mg, 1.5 mmol) in methanol (1.7 M) and Pd/C (10%, 103 mg) was added dropwise formic acid (2.5 mL, 45 equiv.). After 16 h stirring at room temp., the reaction mixture was diluted with EtOAc (10 mL) and filtered through Celite. The filtrate was concentrated under reduced pressure, the viscous residue was partitioned between EtOAc (10 mL) and aqueous saturated $NaHCO_3$ (7 mL), and the aqueous phase was separated and extracted with EtOAc (2 × 7 mL). The combined EtOAc phases were washed with brine (15 mL), dried with $MgSO_4$, filtered, and concentrated under vacuum. The crude product was purified by silica gel chromatography (cyclohexane/ethyl acetate, 95:5), yield 208 mg (0.9 mmol, 60%); R_f 0.46 (petroleum ether/ethyl acetate, 1:1, UV and vanilline visualization); $[\alpha]_D^{20}$ = +149 (*c* = 1.02, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 5.58 (br. s, 1 H), 5.52 (dd, *J* = 1.4, 5.6 Hz, 1 H), 3.93 (d, *J* = 10.9 Hz, 1 H), 3.89 (d, *J* = 10.9 Hz, 1 H), 2.22 (dd, *J* = 5.6, 13.4 Hz, 1 H), 2.09 (s, 3 H), 1.79 (dd, *J* = 1.4, 13.4 Hz, 1 H), 1.31 (s, 3 H), 1.25 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 171.1, 100.7 (CH), 74.9, 68.6 (CH_2), 62.4, 46.8 (CH_2), 28.9 ($3CH_3$), 20.9 (CH_3), 20.3 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 3227, 2976, 1744, 1461, 1372, 1239, 1044 cm^{-1}. HRMS (FD): *m*/*z* calcd. for $C_{11}H_{21}NO_4$ [M$^+$] 231.1471; found 231.1478.

General Procedure for the Coupling of Compound 7c with Protected Amino Acyl Chlorides: The corresponding amino acyl chloride (1.25 equiv.) and **7c** (1.0 equiv.) were dissolved in anhydrous toluene (0.05 M), and the mixture was heated under the specified conditions under microwave irradiation and then evaporated under vacuum. Purification of the residue by preparative silica gel chromatography (cyclohexane/EtOAc, 1:1 or hexane/THF, 7:3) afforded the pure product.

(3*S*,5*S*)-5-*tert*-Butoxy-2-[(2*S*)-2-(9*H*-fluoren-9-ylmethoxycarbonylamino)-3-phenylpropionyl]-3-methylisoxazolidin-3-ylmethyl Acetate (8a): Obtained according to the general procedure (70 °C, 30 min,

MW), from **7c** (145 mg, 0.63 mmol) as an oil, yield 208 mg (0.35 mmol, 55%); R_f 0.18 (hexane/THF, 7:3, UV and vanilline visualization); $[\alpha]_D^{20}$ = +8.35 (c = 2.24, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.75 (d, J = 7.6 Hz, 2 H), 7.54 (dd, J = 5.9, 6.5 Hz, 2 H), 7.38 (t, J = 7.6 Hz, 2 H), 7.32–7.12 (m, 7 H), 5.52 (dd, J = 0.3, 5.5 Hz, 1 H), 5.52 (d, J = 8.6 Hz, 1 H), 4.98 (ddd, J = 4.7, 7.4, 8.6 Hz, 1 H), 4.46 (d, J = 11.2 Hz, 1 H), 4.38 (dd, J = 10.1, 13.4 Hz, 1 H), 4.24 (d, J = 11.2 Hz, 1 H), 4.15 (dd, J = 7.7, 13.4 Hz, 1 H), 4.15 (dd, J = 7.7, 10.1 Hz, 1 H), 3.16 (dd, J = 4.8, 13.8 Hz, 1 H), 2.87 (dd, J = 7.4, 13.8 Hz, 1 H), 2.58 (dd, J = 5.5, 12.7 Hz, 1 H), 2.08 (s, 3 H), 2.06 (dd, J = 0.3, 12.7 Hz, 1 H), 1.70 (s, 3 H), 1.31 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 170.5, 166.0, 155.5, 144.0, 143.9, 141.3 (2 C), 136.5, 129.6 (2CH), 128.3 (2CH), 127.6 (2CH), 127.0 (2CH), 126.8 (CH), 125.2 (2CH), 119.9 (2CH), 96.8 (CH), 76.0, 66.8 (CH_2), 65.8 (CH_2), 63.5, 53.3 (CH), 47.1 (CH), 45.7 (CH_2), 38.1 (CH_2), 28.6 ($3CH_3$), 21.5 (CH_3), 20.8 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 2976, 1724, 1640, 1451, 1242, 1054 cm^{-1}. HRMS (ESI): m/z calcd. for $C_{35}H_{41}N_2O_7$ $[M + H]^+$ 601.2908; found 601.2901; calcd. for $C_{35}H_{40}N_2NaO_7$ $[M + Na]^+$ 623.2728; found 623.2727.

9*H*-Fluoren-9-ylmethyl (2*S*)-2-[(3*S*,5*S*)-3-(Acetoxymethyl)-5-*tert*-butoxy-3-methylisoxazolidin-2-ylcarbonyl]pyrrolidine-1-carboxylate (8b): Obtained according to the general procedure (70 °C, 30 min, MW), from **7c** (80 mg, 0.34 mmol) as an oil, yield 95 mg (0.17 mmol, 50%); R_f 0.23 (hexane/THF, 7:3, UV and vanilline visualization); $[\alpha]_D^{20}$ = +2.91 (c = 0.94, CH_2Cl_2). This compound is a mixture of two rotamers in a 60:40 ratio. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ (major rotamer) = 7.75 (d, J = 7.2 Hz, 2 H), 7.61 (dd, J = 3.1, 7.2 Hz, 2 H), 7.39 (d, J = 7.2 Hz, 2 H), 7.30 (td, J = 1.6, 7.2 Hz, 2 H), 5.47 (dd, J = 1.0, 5.4 Hz, 1 H), 4.74 (dd, J = 2.1, 8.6 Hz, 1 H), 4.52 (d, J = 11.0 Hz, 1 H), 4.42 (dd, J = 7.5, 10.3 Hz, 1 H), 4.29 (dd, J = 7.1, 7.4 Hz, 1 H), 4.22 (d, J = 11.0 Hz, 1 H), 4.19 (dd, J = 7.1, 10.3 Hz, 1 H), 3.73 (m, 1 H), 3.56 (m, 1 H), 2.52 (dd, J = 5.4, 10.7 Hz, 1 H), 2.06 (s, 3 H), 2.2–1.9 (m, 4 H), 1.98 (dd, J = 1.0, 10.7 Hz, 1 H), 1.69 (s, 3 H), 1.31 (s, 9 H) ppm; δ (minor rotamer) = 7.74 (dd, J = 2.6, 7.2 Hz, 2 H), 7.66 (dd, J = 4.1, 7.2 Hz, 2 H), 7.36 (dd, J = 2.6, 7.2 Hz, 2 H), 7.29 (dt, J = 1.6, 7.2 Hz, 2 H), 5.49 (dd, J = 1.5, 5.5 Hz, 1 H), 4.81 (dd, J = 2.6, 8.8 Hz, 1 H), 4.55 (d, J = 11.0 Hz, 1 H), 4.42 (dd, J = 7.5, 10.3 Hz, 1 H), 4.29 (dd, J = 7.1, 7.4 Hz, 1 H), 4.28 (d, J = 11.0 Hz, 1 H), 4.19 (dd, J = 7.1, 10.3 Hz, 1 H), 3.73 (m, 1 H), 3.56 (m, 1 H), 2.55 (dd, J = 5.5, 10.7 Hz, 1 H), 2.07 (s, 3 H), 2.2–1.9 (m, 4 H), 2.03 (dd, J = 1.5, 10.7 Hz, 1 H), 1.71 (s, 3 H), 1.19 (s, 9 H) ppm. ^{1}H NMR (400 MHz, $CDCl_3$, 60 °C): δ (characteristic signals) = 7.75 (d, J = 7.2 Hz, 2 H), 7.66 (d, J = 7.2 Hz, 1 H), 7.61 (d, J = 7.2 Hz, 1 H), 7.39 (d, J = 7.2 Hz, 2 H), 7.30 (d, J = 7.2 Hz, 2 H), 5.47 (m, 1 H), 4.78 (m, 1 H), 4.55–4.15 (m, 5 H), 2.52 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ (major rotamer) = 170.4, 167.4, 154.9, 144.5, 144.0, 141.3, 141.1, 127.3 (2CH), 127.1 (2CH), 125.6 (2CH), 125.5 (2CH), 96.4 (CH), 75.7, 67.3 (CH_2), 65.7 (CH_2), 63.2, 58.8 (CH), 47.3 (CH), 46.8 (CH_2), 45.8 (CH_2), 34.2 (CH_2), 28.6 ($3CH_3$), 22.7 (CH_2), 21.7 (CH_3), 20.8 (CH_3) ppm; δ (minor rotamer) = 170.3, 167.1, 154.8, 144.4, 144.3, 141.2, 135.8, 127.0 (2CH), 126.9 (2CH), 125.4 (2CH), 125.3 (2CH), 96.6 (CH), 75.6, 68.0 (CH_2), 65.5 (CH_2), 63.3, 58.7 (CH), 47.5 (CH), 47.4 (CH_2), 45.9 (CH_2), 34.3 (CH_2), 28.7 ($3CH_3$), 22.6 (CH_2), 22.0 (CH_3), 20.8 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 2976, 1745, 1707, 1655, 1418, 1239 cm^{-1}. HRMS (ESI): m/z calcd. for $C_{31}H_{38}N_2O_7$ $[M + H]^+$ 551.2752; found 551.2723; calcd. for $C_{31}H_{37}N_2NaO_7$ $[M + Na]^+$ 573.2571; found 573.2555.

(3*S*,5*S*)-5-*tert*-Butoxy-2-[(2*S*)-2-(9*H*-fluoren-9-ylmethoxycarbonylamino)-3-methylbutyryl]-3-methylisoxazolidin-3-ylmethyl Acetate (8c): Obtained according to the general procedure (70 °C, 30 min, MW), from **7c** (135 mg, 0.58 mmol) as an oil, yield 103 mg (0.19 mmol, 32%); R_f 0.32 (hexane/THF, 7:3, UV and vanilline visualization); $[\alpha]_D^{20}$ = –3.28 (c = 3.9, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.76 (d, J = 7.5 Hz, 2 H), 7.61 (d, J = 7.6 Hz, 2 H), 7.39 (t, J = 7.6 Hz, 2 H), 7.31 (t, J = 7.6 Hz, 2 H), 5.51 (d, J = 9.4 Hz, 1 H), 5.48 (dd, J = 2.5, 5.6 Hz, 1 H), 4.62 (dd, J = 4.5, 9.4 Hz, 1 H), 4.52 (d, J = 11.3 Hz, 1 H), 4.41 (dd, J = 7.4, 10.1 Hz, 1 H), 4.30 (dd, J = 7.0, 10.1 Hz, 1 H), 4.26 (d, J = 11.3 Hz, 1 H), 4.24 (dd, J = 7.0, 7.4 Hz, 1 H), 2.58 (dd, J = 5.6, 12.7 Hz, 1 H), 2.05 (dd, J = 2.5, 12.7 Hz, 1 H), 2.30–2.22 (m, 1 H), 2.01 (s, 3 H), 1.63 (s, 3 H), 1.27 (s, 9 H), 1.01 (d, J = 6.9 Hz, 3 H), 0.90 (d, J = 6.9 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 170.5, 166.7, 156.5, 144.0 (2 C), 141.3 (2 C), 127.6 (2CH), 127.0 (2CH), 125.2 (2CH), 119.9 (2CH), 96.7 (CH), 76.0, 66.9 (CH_2), 65.9 (CH_2), 63.3, 56.7 (CH), 47.2 (CH), 45.9 (CH_2), 30.5 (CH), 28.6 ($3CH_3$), 21.3 (CH_3), 20.7 (CH_3), 19.8 (CH_3), 16.5 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 2972, 1743, 1639, 1450, 1238, 1057 cm^{-1}. HRMS (ESI): m/z calcd. for $C_{31}H_{41}N_2O_7$ $[M + H]^+$ 553.2908; found 553.2885; calcd. for $C_{31}H_{40}N_2NaO_7$ $[M + Na]^+$ 575.2728; found 575.2715.

(3*S*,5*S*)-5-*tert*-Butoxy-2-[(2*S*)-2-(9*H*-fluoren-9-ylmethoxycarbonylamino)-2-phenylacetyl]-3-methylisoxazolidin-3-ylmethyl Acetate (8d): Obtained according to the general procedure (70 °C, 30 min, MW), from **7c** (80 mg, 0.35 mmol) as an oil, yield 100 mg (0.17 mmol, 49%); 80:20 diastereomer ratio; R_f 0.47 (hexane/THF, 7:3, UV and vanilline visualization). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ (major diastereoisomer) = 7.74 (d, J = 7.6 Hz, 2 H), 7.54 (dd, J = 5.9, 6.5 Hz, 1 H), 7.38 (t, J = 7.6 Hz, 2 H), 7.32–7.12 (m, 7 H), 6.24 (d, J = 8.0 Hz, 1 H), 5.66 (d, J = 8.0 Hz, 1 H), 5.37 (dd, J = 1.0, 5.5 Hz, 1 H), 4.55 (d, J = 11.2 Hz, 1 H), 4.32 (m, 2 H), 4.18 (t, J = 7.2 Hz, 1 H), 4.08 (d, J = 11.2 Hz, 1 H), 2.47 (dd, J = 5.5, 12.7 Hz, 1 H), 2.00 (dd, J = 1.0, 12.7 Hz, 1 H), 1.76 (s, 3 H), 1.71 (s, 3 H), 1.31 (s, 9 H) ppm. δ (characteristic signals of minor diastereoisomer) = 5.99 (d, J = 8.8 Hz, 1 H), 5.76 (d, J = 8.6 Hz, 1 H), 5.40 (dd, J = 1.7, 5.6 Hz, 1 H), 4.63 (d, J = 11.0 Hz, 1 H), 2.55 (dd, J = 5.4, 12.5 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ (major diastereoisomer) = 170.3, 164.1, 155.2, 144.0, 143.9, 141.2 (2 C), 138.2, 128.5 (2CH), 127.9 (CH), 127.8 (2CH), 127.6 (2CH), 127.0 (2CH), 125.3 (CH), 125.2 (CH), 119.9 (2CH), 96.7 (CH), 75.9, 67.0 (CH_2), 64.9 (CH_2), 63.4, 56.2 (CH), 47.1 (CH), 45.4 (CH_2), 28.7 ($3CH_3$), 21.4 (CH_3), 20.4 (CH_3) ppm. δ (characteristic signals of minor diastereoisomer) = 170.6, 164.6, 155.6, 75.8, 67.9 (CH_2), 65.7 (CH_2), 63.6, 55.7 (CH) ppm. IR (neat): $\tilde{\nu}$ = 2976, 1744, 1639, 1450, 1238 cm^{-1}. HRMS (DCI, NH_3): m/z calcd. for $C_{34}H_{38}N_2O_7$ $[M + H^+]$ 587.2757; found 587.2745.

(3*S*,5*S*)-5-*tert*-Butoxy-2-[(2*S*)-2-(1,3-dioxo-1,3-dihydroisoindol-2-yl)-3-methylbutyryl]-3-methylisoxazolidin-3-ylmethyl Acetate (8e): Obtained according to the general procedure (110 °C, 60 min, MW), from **7c** (12 mg, 0.052 mmol) as an oil in an inseparable 60:40 mixture with remaining phthalyl valine (19 mg, 0.030 mmol **8e**, estimated yield 58%). R_f 0.45 (cyclohexane/EtOAc, 1:1, UV and vanilline visualization). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.85 (dd, J = 3.2, 5.4 Hz, 2 H), 7.70 (dd, J = 2.9, 5.4 Hz, 2 H), 5.44 (dd, J = 2.0, 5.4 Hz, 1 H), 4.86 (d, J = 10.0 Hz, 1 H), 4.59 (d, J = 11.2 Hz, 1 H), 4.27 (d, J = 11.2 Hz, 1 H), 3.03 (m, 1 H), 2.51 (dd, J = 5.4, 12.5 Hz, 1 H), 2.06 (s, 3 H), 1.97 (dd, J = 2.0, 12.7 Hz, 1 H), 1.59 (s, 3 H), 1.17 (s, 9 H), 1.11 (d, J = 6.8 Hz, 3 H), 0.93 (d, J = 6.6 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 170.5, 168.0, 163.2, 133.9 (CH), 131.9, 123.4 (CH), 96.6 (CH), 75.8, 65.5 (CH_2), 63.6, 58.1 (CH), 45.5 (CH_2), 28.3 ($3CH_3$), 27.5 (CH), 21.4 (CH_3), 20.8 (CH_3), 19.9, 19.8 ($2CH_3$) ppm. IR (neat): $\tilde{\nu}$ = 2973, 1743, 1638, 1450, 1238, 1056 cm^{-1}. HRMS (DCI, NH_3): m/z calcd. for $C_{24}H_{32}N_2O_7$ $[M + H^+]$ 461.2288; found 461.2294.

(2*S*)-2-[(2*S*)-2-(9*H*-Fluoren-9-ylmethoxycarbonylamino)-3-phenylpropionylamino]-2-methyl-4-oxobutyl Acetate (9a): A mixture of adduct **8a** (100 mg, 0.166 mmol) and $Mo(CO)_6$ (2 equiv.) was dissolved in a mixture of acetonitrile and water (10:3 v/v, 0.07 M). The mixture was heated for 3 d and then evaporated under vacuum. The residue was partitioned between ethyl acetate and brine, and the aqueous phase was extracted three times with ethyl acetate. The organic phase was dried with $MgSO_4$, filtered, and concentrated under reduced pressure to give a residue, which is purified by preparative silica gel chromatography (hexane/THF, 1:1) to give **9a** as an oil, yield 33 mg (0.062 mmol, 38%); R_f 0.43 (hexane/THF, 7:3, UV and vanilline visualization); $[\alpha]_D^{20}$ = –1.1 (*c* = 0.52, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 9.59 (d, *J* = 2.0 Hz, 1 H), 7.76 (d, *J* = 7.5 Hz, 2 H), 7.55 (dd, *J* = 4.3, 7.6 Hz, 2 H), 7.40 (dd, *J* = 7.3, 7.5 Hz, 2 H), 7.35–7.18 (m, 5 H), 7.31 (dd, *J* = 4.3, 7.5 Hz, 2 H), 6.13 (br. s, 1 H), 5.34 (br. s, 1 H), 4.43 (dd, *J* = 7.2, 10.4 Hz, 1 H), 4.40–4.25 (m, 2 H), 4.20 (dd, *J* = 6.9, 7.2 Hz, 1 H), 4.13 (d, *J* = 11.3 Hz, 1 H), 4.05 (d, *J* = 11.3 Hz, 1 H), 3.15–3.05 (m, 1 H), 3.05–2.95 (m, 1 H), 2.92 (dd, *J* = 2.0, 16.4 Hz, 1 H), 2.84 (dd, *J* = 2.0, 16.4 Hz, 1 H), 1.98 (s, 3 H), 1.30 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 199.6, 170.8, 170.6, 155.8, 143.7, 143.6, 141.3 (2 C), 136.3, 129.4–127.1 (9CH), 125.5 (2CH), 120.0 (2CH), 68.3 (CH_2), 67.1 (CH_2), 56.7 (CH), 54.7, 48.2 (CH_2), 47.1 (CH), 38.5 (CH_2), 22.2 (CH_3), 20.7 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 3065, 2927, 1721, 1661, 1539, 1236, 1043 cm^{-1}. HRMS (DCI, NH_3): *m*/*z* calcd. for $C_{31}H_{33}N_2O_6$ [M + H$^+$] 529.2339; found 529.2347.

General Procedure for the [3+2] Cycloaddition of Cyclic Ketonitrones (3b–e) with Electron-Poor Dipolarophiles: Nitrone (1 equiv.) and dipolarophile were heated under the specified conditions with microwave irradiation. The reaction mixture was then concentrated under reduced pressure and the residue was purified by chromatography on silica gel.

(2*R*,3a*S*,7*S*)-2,3a-Dimethyl-4-oxo-7-phenyl-hexahydroisoxazolo-[3,2-*c*][1,4]oxazine-2-carbaldehyde (10a): Obtained by following the general procedure (90 °C, 7 h, MW), starting from nitrone **3b** (63 mg, 0.31 mmol) and methacrolein (0.15 mL, 1.8 mmol, 6 equiv.). Purified by chromatography on silica gel (cyclohexane/ethyl acetate, 9:1) as a yellow oil, yield 43 mg (0.20 mmol, 79%); *dr* 100:0:0:0; R_f 0.43 (cyclohexane/ethyl acetate, 7:3, UV visualization); $[\alpha]_D^{20}$ = +5.5 (*c* = 1.14, CH_2Cl_2); GC (Restek β-Dex-sm 30 m × 0.25 mm 0.25 µm, Helium, 120 °C 1 min, 2 °C/min, 200 °C 30 min, 3 mL/min, T_{det} = 220 °C, T_{inj} = 220 °C): t_R = 42.93 min. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 9.47 (s, 1 H), 7.36–7.40 (m, 5 H), 4.17 (d, *J* = 6.8 Hz, 2 H), 3.89 (t, *J* = 6.8 Hz, 1 H), 3.36 (d, *J* = 13.6 Hz, 1 H), 2.29 (d, *J* = 13.6 Hz, 1 H), 1.79 (s, 3 H), 1.41 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 200.6, 171.1, 134.8, 129.1 (2CH), 128.9 (CH), 127.7 (2CH), 86.8, 71.0, 70.1 (CH_2), 62.9 (CH), 45.0 (CH_2), 26.4 (CH_3), 21.4 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 2931, 1728, 1455, 1395, 1144, 1071 cm^{-1}. HRMS (CI, NH_3): *m*/*z* calcd. for $C_{15}H_{18}NO_4$ [M + H$^+$] 276.1236; found 276.1223.

Methyl (2*R*,3a*S*,7*S*)-2,3a-Dimethyl-4-oxo-7-phenyl-hexahydroisoxazolo[3,2-*c*][1,4]oxazine-2-carboxylate (10b): Obtained by following the general procedure (100 °C, 5 h, MW), starting from nitrone **3b** (53 mg, 0.26 mmol) and methyl methacrylate (0.16 mL, 1.54 mmol, 10 equiv.). Purified by chromatography on silica gel (cyclohexane/ethyl acetate, 9:1) as a yellow solid, yield 51 mg (0.17 mmol, 65%); *dr* 97:3:0:0. A crystal of pure major diastereomer was obtained by long standing storage and was used for m.p. and X-ray analysis. R_f 0.67 (cyclohexane/ethyl acetate, 1:1, UV visualization); m.p. 130.0–131.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ (major diastereoisomer) = 7.30–7.45 (m, 5 H), 4.33 (dd, *J* = 3.9, 10.0 Hz, 1 H), 4.20 (dd, *J* = 3.9, 11.7 Hz, 1 H), 4.15 (dd, *J* = 10.3, 11.5 Hz, 1 H), 3.65 (s, 3 H), 3.57 (d, *J* = 13.7 Hz, 1 H), 2.42 (d, *J* = 13.7 Hz, 1 H), 1.75 (s, 3 H), 1.55 (s, 3 H) ppm. δ (characteristic signals of minor diastereoisomer) = 3.05 (d, *J* = 13.4 Hz, 1 H), 2.83 (d, *J* = 13.2 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 174.4, 171.5, 135.6, 128.7 (2CH), 128.6 (CH), 127.5 (2CH), 83.4, 70.2, 69.9 (CH_2), 62.8 (CH), 52.6 (CH_3), 49.4 (CH_2), 26.4 (CH_3), 24.9 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 2925, 1748, 1721, 1279, 1147 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{16}H_{19}NNaO_5$ [M + Na$^+$] 328.1155; found 328.1154.

(2*R*,3a*S*,7*S*)-3a-Ethyl-2-methyl-4-oxo-7-phenyl-hexahydroisoxazolo[3,2-*c*][1,4]oxazine-2-carbaldehyde (10c): Obtained by following the general procedure (90 °C, 4 h, MW), starting from nitrone **3c** (72 mg, 0.33 mmol) and methacrolein (1.5 mL, 18 mmol, 55 equiv.). Purified by chromatography on silica gel (cyclohexane/ethyl acetate, 7:3) as a white solid, yield 80 mg (0.28 mmol, 84%); *dr* 96:4:0:0; R_f 0.48 (cyclohexane/ethyl acetate, 7:3, UV visualization). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ (major diastereoisomer) = 9.48 (s, 1 H), 7.37–7.40 (m, 5 H), 4.13 (m, 2 H), 3.88 (dd, *J* = 5.4, 8.2 Hz, 1 H), 3.37 (d, *J* = 13.7 Hz, 1 H), 2.27 (d, *J* = 13.7 Hz, 1 H), 2.09 (m, 2 H), 1.37 (s, 3 H), 1.13 (t, *J* = 7.1 Hz, 3 H) ppm. δ (characteristic signals of minor diastereoisomer) = 9.60 (s, 1 H), 4.27–4.34 (m, 3 H), 2.85 (d, *J* = 13.4 Hz, 1 H), 2.73 (d, *J* = 13.9 Hz, 1 H), 1.34 (s, 3 H), 1.02 (t, *J* = 7.3 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 200.8, 170.8, 135.1, 129.1 (2CH), 128.9 (CH), 127.7 (2CH), 86.5, 76.0, 70.1 (CH_2), 62.7 (CH), 44.9 (CH_2), 32.2 (CH_2), 21.4 (CH_3), 10.0 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 2942, 1728, 1182, 1042 cm^{-1}. HRMS (CI, NH_3): *m*/*z* calcd. for $C_{16}H_{20}NO_4$ [M + H$^+$] 290.1392; found 290.1382.

Methyl (2*R*,3a*S*,7*S*)-2,3a-Dimethyl-4-oxo-7-phenyl-hexahydroisoxazolo[3,2-*c*][1,4]oxazine-2-carboxylate (10d): Obtained by following the general procedure (90 °C, 4 h, MW), starting from nitrone **3c** (76 mg, 0.35 mmol) and methyl methacrylate (1.5 mL, 14 mmol, 40 equiv.), as a white foam (0.84 g). Purified by chromatography on silica gel (cyclohexane/ethyl acetate, 7:3) as a white foam, yield 0.115 g (0.35 mmol, >95%); *dr* 97:3:0:0; R_f 0.42 (cyclohexane/ethyl acetate, 7:3, UV visualization). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ (major diastereoisomer) = 7.33–7.43 (m, 5 H), 4.28 (dd, *J* = 3.7, 10.0 Hz, 1 H), 4.14 (dd, *J* = 3.9, 11.7 Hz, 1 H), 4.10 (dd, *J* = 10.5, 11.5 Hz, 1 H), 3.65 (s, 3 H), 3.56 (d, *J* = 13.7 Hz, 1 H), 2.42 (d, *J* = 13.9 Hz, 1 H), 2.06 (m, 2 H), 1.52 (s, 3 H), 1.11 (t, *J* = 7.3 Hz, 3 H) ppm. δ (characteristic signals of minor diastereoisomer) = 3.15 (d, *J* = 13.7 Hz, 1 H), 2.78 (d, *J* = 13.4 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 174.7, 171.2, 135.8, 128.8 (2CH), 128.6 (CH), 127.5 (2CH), 83.2, 75.3, 70.1 (CH_2), 62.4 (CH), 52.7 (CH_3), 49.0 (CH_2), 32.1 (CH_2), 25.1 (CH_3), 10.0 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 2931, 1733, 1719, 1151 cm^{-1}. HRMS (CI, NH_3): *m*/*z* calcd. for $C_{17}H_{22}NO_5$ [M + H$^+$] 320.1498; found 320.1494.

(2*R*,3a*S*,7*S*)-2-Methyl-4-oxo-3a,7-diphenyl-hexahydroisoxazolo-[3,2-*c*][1,4]oxazine-2-carbaldehyde (10e): Obtained by following the general procedure (90 °C, 4 h, MW), starting from nitrone **3d** (42 mg, 0.16 mmol) and methacrolein (1.2 mL, 14.5 mmol, 90 equiv.). Purified by chromatography on silica gel (cyclohexane/ethyl acetate, 8:2) as a brown oil, yield 42 mg (0.12 mmol, 78%); *dr* 99:1:0:0; R_f 0.33 (cyclohexane/ethyl acetate, 8:2, UV visualization). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ (major diastereoisomer) = 9.50 (s, 1 H), 7.90 (d, *J* = 8.8 Hz, 2 H), 7.53 (d, *J* = 7.1 Hz, 2 H), 7.30–7.50 (m, 6 H), 4.42 (dd, *J* = 3.9, 11.0 Hz, 1 H), 4.22 (dd, *J* = 3.9, 12.0 Hz, 1 H), 4.14 (dd, *J* = 11.0, 12.0 Hz, 1 H), 3.71 (d, *J* = 13.6 Hz, 1 H), 2.71 (d, *J* = 13.6 Hz, 1 H), 1.16 (s, 3 H) ppm. δ (characteristic signals of minor diastereoisomer) = 4.54 (d, *J* = 5.4 Hz, 1 H), 3.85 (d, *J* = 6.1 Hz, 1 H), 3.54 (dd, *J* = 4.6, 5.0 Hz,

1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 199.3 (CH), 169.7, 138.7, 135.7, 130.0 (2CH), 128.9 (2CH), 128.8 (CH), 128.6 (CH), 127.6 (2CH), 126.7 (2CH), 86.5, 75.5, 69.4 (CH_2), 65.1 (CH), 48.6 (CH_2), 20.2 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 2925, 1735, 1455, 1043 cm^{-1}. HRMS (CI, NH_3): *m*/*z* calcd. for $C_{20}H_{20}NO_4$ [M + H$^+$] 337.1392; found 337.1388.

Methyl (2*R*,3a*S*,7*S*)-2-Methyl-4-oxo-3a,7-diphenyl-hexahydroisoxazolo[3,2-*c*][1,4]oxazine-2-carboxylate (10f): Obtained by following the general procedure (90 °C, 4 h, MW), starting from nitrone **3d** (40 mg, 0.15 mmol) and methyl methacrylate (1 mL, 9.3 mmol, 60 equiv.). Purified by chromatography on silica gel (cyclohexane/ethyl acetate, 7:3) as a yellow oil, yield 64 mg (0.15 mmol, > 95%); *dr* 91:9:0:0; R_f 0.43 (cyclohexane/ethyl acetate, 7:3, UV visualization). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ (major diastereoisomer) = 7.85 (m, 2 H), 7.53 (m, 2 H), 7.38 (m, 6 H), 4.96 (dd, *J* = 3.7, 11.5 Hz, 1 H), 4.16 (dd, *J* = 3.7, 11.7 Hz, 1 H), 4.06 (t, *J* = 11.7 Hz, 1 H), 3.75 (s, 3 H), 2.70, 3.88 (2d, *J* = 13.5 Hz, 2 H), 1.35 (s, 3 H) ppm. δ (characteristic signals of minor diastereoisomer) = 5.15 (d, *J* = 11.5 Hz, 1 H), 4.83 (d, *J* = 11.5 Hz, 1 H), 4.65 (d, *J* = 12.0 Hz, 1 H), 4.48 (d, *J* = 11.7 Hz, 1 H), 4.30 (d, *J* = 6.4 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 173.9, 169.9, 139.2, 136.7, 129.0 (2CH), 128.7 (2CH), 128.3 (2CH), 127.9 (2CH), 126.4 (2CH), 83.8, 74.8, 68.8 (CH_2), 65.5 (CH), 53.1 (CH_2), 52.9 (CH_3), 23.2 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 2952, 1741, 1198, 1115 cm^{-1}. HRMS (CI, NH_3): *m*/*z* calcd. for $C_{21}H_{22}NO_5$ [M + H$^+$] 368.1498; found 368.1488.

Methyl (2*R*,4*S*)-4-(*tert*-Butoxycarbonylamino)-2,4-dimethyl-5-oxotetrahydrofuran-2-carboxylate (11): To a solution of cycloadduct **10b** (125 mg, 0.41 mmol) in MeOH (3 mL), was added $Pd(OH)_2$ (10%mol, C, 125 mg) under Ar. The mixture was placed under 1 atm of H_2 and stirred for 5 h at room temp. The resulting mixture was filtered through Celite and the solvents were evaporated. The residue was diluted with MeCN (3 mL), then a saturated solution of $NaHCO_3$ (3 drops) and Boc_2O (446 mg, 2 mmol, 5 equiv.) was added and stirring was continued for 24 h at room temp. The mixture was diluted with H_2O (5 mL) and EtOAc (10 mL), and the aqueous layer was extracted with EtOAc (2 × 10 mL). The organic phases were dried with $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (cyclohexane/EtOAc, 1:1) to give a white solid, yield 71 mg (0.24 mmol, 60%); m.p. 159.1–160.3 °C; R_f 0.34 (cyclohexane/ethyl acetate, 1:1); $[a]_D^{20}$ = –13.4 (*c* = 0.37, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 4.93 (br. s, 1 H), 3.81 (s, 3 H), 2.72 (d, *J* = 13.6 Hz, 1 H), 2.66 (d, *J* = 13.6 Hz, 1 H), 1.75 (s, 3 H), 1.44 (s, 9 H), 1.40 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 176.2, 172.9, 154.2, 80.6, 71.2, 57.0, 53.0 (CH_3), 44.6 (CH_2), 28.3 ($3CH_3$), 25.1 (CH_3), 24.0 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 3363, 2983, 1793, 1747, 1708, 1160, 1083 cm^{-1}. HRMS (CI, NH_3): *m*/*z* calcd. for $C_{13}H_{22}NO_6$ [M + H$^+$] 288.1440; found 288.1447.

Ethyl (3*R,5*S**)-2-Benzyl-5-formyl-5-methylisoxazolidine-3-carboxylate (12):** *N*-(1-Ethoxy-1-oxoethylidene)-1-phenylmethanamine oxide (106 mg, 0.51 mmol) and methacroleine (0.42 mL, 5.1 mmol, 10 equiv.) were heated at 90 °C for 26 h in a sealed tube. The reaction mixture was then concentrated under reduced pressure and the residue was purified by chromatography on silica gel (cyclohexane/ethyl acetate 9:1) as a yellow oil, yield 89.5 mg (0.32 mmol, 63%); *dr* 70:30; R_f 0.36 (cyclohexane/ethyl acetate, 8:2, UV visualization). GC (DB-5MS, 30 m × 0.32 mm 0.25 µm, Helium, 80 °C 1 min, 5 °C/min, 200 °C 30 min, 3.5 mL/min, T_{det} = 220 °C, T_{inj} = 220 °C): t_R = 18.88 (major diastereomer), 19.24 (minor diastereomer) min. ^{1}H NMR (400 MHz, $CDCl_3$): δ (major diastereoisomer) = 9.56 (s, 1 H), 7.26–7.41 (m, 5 H), 4.28 (d, *J* = 13.9 Hz, 1 H), 4.11 (q, *J* = 7.1 Hz, 2 H), 3.98 (d, *J* = 13.9 Hz, 1 H), 3.51 (dd, *J* = 6.8, 9.5 Hz, 1 H), 2.83 (dd, *J* = 6.8, 12.7 Hz, 1 H), 2.28 (dd, *J* = 9.8, 13.0 Hz, 1 H), 1.29 (s, 3 H), 1.23 (t, *J* = 7.1 Hz, 3 H) ppm. δ (minor diastereoisomer) = 9.56 (s, 1 H), 7.26–7.41 (m, 5 H), 4.11 (m, 1 H), 4.20 (q, *J* = 7.1 Hz, 1 H), 4.01 (d, *J* = 13.4 Hz, 1 H), 3.79 (dd, *J* = 4.4, 8.3 Hz, 1 H), 2.92 (dd, *J* = 8.6, 13.0 Hz, 1 H), 2.39 (dd, *J* = 4.2, 13.0 Hz, 1 H), 1.39 (s, 3 H), 1.29 (t, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ (major diastereoisomer) = 204.2 (CH), 169.6, 136.3, 129.0–127.6 (CH), 84.5, 66.7 (CH), 61.4 (CH_2), 61.2 (CH_2), 41.0 (CH_2), 19.0 (CH_3), 14.1 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 2980, 2934, 1737, 1674, 1454, 1273 cm^{-1}. HRMS (CI, NH_3): *m*/*z* calcd. for $C_{15}H_{20}NO_4$ [M + H$^+$] 278.1392; found 278.1393.

X-ray Crystal Data: CCDC-1007248 (**5c**) and 1007249 (**10b**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[11] For other diastereoselective cycloadditions involving lactone- or lactam-containing aldonitrones equipped with a chiral auxiliary, see: a) ref.[4a,6b–c,6f–h]; b) S. W. Baldwin, A. Long, *Org. Lett.* **2004**, *6*, 1653–1656; c) P.-F. Wang, P. Gao, P.-F. Xu, *Synlett* **2006**, 1095–1099; d) K. Aouadi, S. Vidal, M. Msaddek, J.-P. Praly, *Synlett* **2006**, 3299–3303; e) K. Aouadi, E. Jeanneau, M. Msaddek, J.-P. Praly, *Synthesis* **2007**, 3399–3405; f) for intramolecular version of cycloaddition involving a cyclic ester-nitrone, see: R. E. Looper, M. T. C. Runnegar, R. M. Williams, *Tetrahedron* **2006**, *62*, 4549–4562, and references cited therein.

[12] Throughout this work, *trans*/*cis* selectivity refers to the position in the cycloadduct of the ester function (or lactone) of the nitrone relative to the functional group of the dipolarophile (ester, aldehyde, alkoxy substituents).

[13] For racemic cycloadditions involving cyclic ester–keto-nitrones, see: a) F. Heaney, C. O'Mahony, *J. Chem. Soc., Perkin Trans. 1* **1998**, 341–349; b) F. Heaney, J. Fenlon, C. O'Mahony, P. McArdle, D. Cunningham, *J. Chem. Soc., Perkin Trans. 1* **2001**, 3382–3392; c) F. Heaney, J. Fenlon, C. O'Mahony, P. McArdle, D. Cunningham, *Org. Biomol. Chem.* **2003**, *1*, 4302–4316.

[14] S. Tohma, K. Rikimaru, A. Endo, K. Shimamoto, T. Kan, T. Fukuyama, *Synthesis* **2004**, 909–917.

[15] The two major diastereoisomers were attributed to both *trans* adducts, as shown by the typical signals in the ^1H NMR spectra of the CH_2 group of the isoxazolidine ring (i.e., **6b** 2.92/2.45 for the major *trans* diastereomer; 2.95/2.68 for the minor *trans* diastereomer).

[16] Saponification attempts include aqueous lithium hydroxide (1N, 1.2 to 2 equiv.) in THF or MeOH at 0–36 °C. After 3 d at room temp., conversion was less than 30%.

[17] Diastereoisomeric purification was only rarely possible from bicyclic adducts.

[18] Classical peptidic conditions were tested such as EDCI/DMAP, EDCI/HOBt, IBCF/NMM, HATU/DIPEA. Starting materials were recovered under all these conditions.

[19] All amino acyl chlorides were prepared by following known procedures: a) L. A. Carpino, B. J. Cohen, K. E. Stephens, S. Y. Sadat-Aalaee, J.-H. Tien, D. C. Langridge, *J. Org. Chem.* **1986**, *51*, 3734–3736; b) L. A. Carpino, *J. Org. Chem.* **1988**, *53*, 875–878; c) T. Oshikawa, M. Yamashita, *Bull. Chem. Soc. Jpn.* **1990**, *63*, 2728–2730.

[20] Epimerization was found to occur when a base, such as pyridine, was added to trap hydrogen chloride or when the solvent was changed to chloroform or acetonitrile. It was also shown that, to avoid epimerization, shorter reaction times under microwave irradiation were preferable to longer thermic reactions.

[21] α-Peptide aldehydes are known to be sensitive to epimerization, see: a) C. Ganneau, A. Moulin, L. Demange, J. Martinez, J.-A. Fehrentz, *J. Pept. Sci.* **2006**, *12*, 497–501 and references cited therein. For other nonepimerizable β-amino-aldehydes obtained by a cycloaddition method, see for example: b) P. Shpak-Kraievskyi, B. Yin, A. Martel, R. Dhal, G. Dujardin, M. Y. Laurent, *Tetrahedron* **2012**, *68*, 2179–2188.

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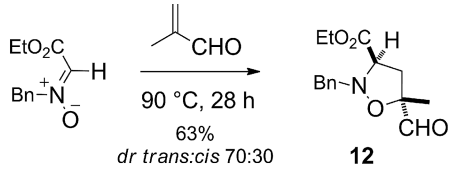

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In the case of ester ketonitrones of alanine-type, the diastereoisomeric ratio of cycloaddition in thermic conditions was typically around 70:30 (see ref.[22b]). Notably, efficient catalytic asymmetric cycloadditions were developed from the same nitrones with differently substituted enals as dipolarophiles, see: a) K. B. Selim, A. Beauchard, J. Lhoste, A. Martel, M. Y. Laurent, G. Dujardin, *Tetrahedron: Asymmetry* **2012**, *23*, 1670–1677; b) K. B. Selim, A. Martel, M. Y. Laurent, J. Lhoste, S. Py, G. Dujardin, *J. Org. Chem.* **2014**, *79*, 3414–3426.

[23] Other electron-poor dipolarophiles as acrolein or crotonaldehyde were tested and gave mixtures of regioisomers (3,5 vs. 3,4), see for example: S. Kanemasa, N. Ueno, M. Shirahase, *Tetrahedron Lett.* **2002**, *43*, 657–660.

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