

Oxidative Nucleophilic Substitution of Hydrogen in Nitroarenes with Carbanions of Protected Serine and Threonine Esters

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Dedicated to Professor Wojciech Stec on the occasion of his 70th birthday

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The reactions of carbanions of protected serine and threonine esters with nitroarenes were studied. The main process involves the addition of the carbanions to the *para* position of the nitroarenes, which is occupied by a hydrogen atom, to form σ^H adducts that are subsequently oxidized by 2,3-dichloro-5,6-dicyanobenzoquinone to give *p*-nitroaryl deriv-

atives of the protected serine and threonine. Oxidation of the σ^H adducts with dimethyldioxirane resulted in the formation of the corresponding *p*-hydroxyaryl derivatives of these amino acids. Addition of the carbanions of the protected threonine ester is a highly stereoselective process controlled by the second chiral center of threonine.

Introduction

Unnatural α -amino acids are important starting materials for the synthesis of pharmaceutically interesting molecules such as peptidomimetics, enzyme inhibitors, conformationally constrained peptides, and so on.^[1,2] Of particular interest are α,α -disubstituted α -amino acids because of their special properties as fragments of peptide chains and their use as building blocks for biologically active compounds.^[3–5] Due to the great importance of α,α -disubstituted α -amino acids, their synthesis was subject of intensive studies and a number of methods have been developed.^[3,6] Amongst α,α -disubstituted amino acids, α -substituted serine and threonine derivatives are of special interest because their hydroxy groups can stabilize the α -helical secondary structures of enzymes.^[7] They have been *inter alia* employed as components of biologically active peptidomimetics.^[8]

There are numerous methods elaborated for the introduction of substituents into the α -positions of serine and threonine, including reactions of electrophilic partners with carbanions of properly protected amino acids.^[9] However, to our best knowledge, there are no examples reported of the direct introduction of aryl groups by this way. α -Aryl serine derivatives are usually obtained through a multistep process based on the Strecker reaction,^[10a] or by addition of organolithium reagents to an imine bond.^[10b]

Recently, we published preliminary reports that *p*-nitroaryl substituents can be readily introduced into ala-

nine,^[11] serine,^[11] and proline^[12] molecules by oxidative nucleophilic substitution of hydrogen (ONSH) in nitroarenes with carbanions of properly protected amino acids. The carbanion of L-proline, protected in the form of the N,O-acetal of pivalaldehyde, added to the nitroarenes in the *para* position to the nitro group in a stereoselective manner to produce, after oxidation, one diastereoisomer of the nitro-arylated product.^[12] Thus, the ONSH reaction proceeded in this case with self-reproduction of chirality.^[13] Interestingly, the zinc enolate of *N*-TFA-protected *tert*-butyl glycinate does not react with nitroarenes by addition to the ring but by direct reaction with the nitro group.^[14]

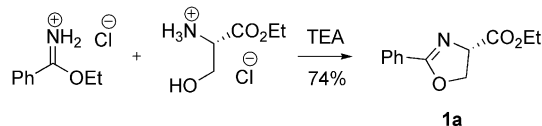
In this paper we present a full account of our studies of the ONSH reaction in nitroarenes with carbanions of protected serine and threonine that leads to α -(*p*-nitroarylated) and *p*-hydroxyarylated serine and threonine. The ONSH reaction consists of addition of nucleophilic agents to electron-deficient arenes in positions occupied by a hydrogen atom to form σ^H adducts that are subsequently oxidized by external oxidants to form products of nucleophilic substitution of hydrogen.^[15] The addition is, as a rule, a reversible process, and nucleophiles are sensitive to oxidation; thus, the reaction can proceed successfully when the addition equilibrium is shifted towards the σ^H adducts. Because nucleophiles add to electron-deficient aromatic rings in positions occupied by hydrogen faster than in equally activated positions occupied by halogen atoms or other substituents, the ONSH reaction is a process of general character and with a wide scope of applications.^[15] The reaction is of general character also with respect to the nucleophiles. This way, it is possible to introduce a variety of substituents, such as OH,^[16] NH₂,^[17] and P(O)Ph₂,^[18] and

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a wide range of carbon substituents^[11,12,19,20] into electron-deficient arenes. Of particular value is the oxidative nucleophilic alkylation of nitroarenes with Grignard reagents^[21a–21c] and alkyllithium compounds^[21f] and the synthesis of nitroarylated acetic acid derivatives.^[22] Oxidation of σ^H adducts of nucleophiles to nitroarenes can be effected by a variety of oxidants such as dichlorodicyanobenzoquinone (DDQ),^[11,12,19c,20c,23] bromine,^[23] KMnO_4 ,^[19a,19b,20c] oxygen,^[20] and cerium ammonium nitrate.^[24] There are many examples of anodic oxidation of σ^H adducts.^[25] The oxidation of σ^H adducts with these oxidants provides products in which the hydrogen atom in the nitro aromatic ring has been replaced by a nucleophilic moiety. The oxidation of σ^H adducts with dimethyldioxirane (DMD) proceeds differently. This oxidizing agent attacks the negatively charged nitro group of the σ^H adducts, giving substituted phenols as the products.^[26]

Results and Discussion

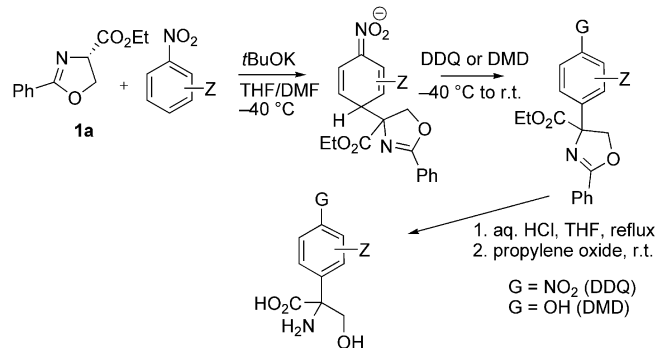
In our preliminary communication, it was reported that the carbanion of ethyl 2-phenyl-1,3-oxazoline-4-carboxylate (**1a**) adds to nitroarenes in the *para* position to the nitro group. Subsequent oxidation of the produced σ^H adducts with DDQ gave α -(*p*-nitroarylated) derivatives of serine. Although oxazoline **1a** was used in an enantiomerically pure form prepared from readily available L-serine, generation of the planar carbanion and further addition results in complete racemization. Protected serine derivative **1a** can be obtained in very good yield by direct condensation of L-serine ethyl ester hydrochloride with ethyl benzimidate hydrochloride in the presence of triethylamine (Scheme 1).^[27]



Scheme 1. Synthesis of protected serine in the form of oxazoline **1a**.

Oxazoline **1a**, being a reasonably strong CH acid, can be readily deprotonated by *t*BuOK in THF/DMF at low temperature. The produced carbanion is a sufficiently strong nucleophile, so its addition to nitrobenzene at -40°C proceeds to completion. Due to its bulkiness, the carbanion of **1a** (Scheme 2, Table 1) adds to nitrobenzenes selectively in the *para* position to the nitro group. Treatment of the produced solution of the σ^H adduct with DDQ dissolved in THF and warming of the mixture results in the formation of the expected *p*-nitrophenyl derivative of protected serine **2aa** in a good yield of 73%. Attempts to carry out the reaction in liquid ammonia with potassium permanganate as the oxidant and 2-cyanonitrobenzene (**10**) as the substrate at -78°C gave a mixture of product **10aa** (9%) and its amide (39%). An analogous reaction carried out in THF/DMF followed by treatment with solid potassium permanganate and liquid ammonia gave **10aa** in 42% yield and

its amide in 7% yield. Perhaps due to the bulkiness of the carbanion of **1a**, its σ^H adduct is not fully oxidized by permanganate; furthermore, partial ammonolysis of **1a** takes place during the reaction, which may also cause a partial reduction in the yield. We observed earlier that permanganate oxidation of σ^H adducts is very sensitive to steric hindrance.^[19]



Scheme 2. ONSH in nitroarenes with the carbanion of **1a**: synthesis of nitroarylated serine derivatives.

Table 1. Results of the ONSH reaction of nitroarenes with the carbanion of **1a** as in Scheme 2.

Nitroarene, Z		DDQ		DMD	
		G = NO ₂ Product	% Yield	G = OH Product	% Yield
H	2	2aa	73	2ab	53
2-F	3 ^[a]	3aa	54 ^[b]		
3-F	4	4aa	50	4aa	46
2-Cl	5 ^a	5aa	73	5ab	55
3-Cl	6	6aa	70	6ab	51
2-MeO	7			7ab	33
3-MeO	8	8aa	60	8ab	35
				8aa	30
3-Me	9	9aa	37		
2-CN	10	10aa	55	10aa	41
3-CN	11			11ab	59
3-CF ₃	12	12aa	25		
2-Cl-3-CN	13			13ab	50
4-EtO-2-NO ₂ Py	14	14aa	71		

[a] Reaction carried out at -78°C . [b] Additionally product of substitution of fluorine was obtained.

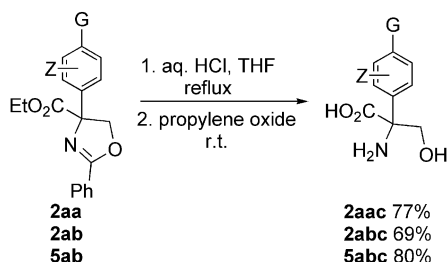
According to the same protocol, **1a** was treated with a series of *ortho*- and *meta*-substituted nitrobenzenes to give the expected *p*-nitroarylated protected serines **2aa–10aa**, usually in good yields. It should be stressed that the carbanion of **1a** is sufficiently nucleophilic to ensure its complete addition to nitroarenes even in the case of nitroarenes of lower activity such as nitrobenzene or 3-nitroanisole.

Interestingly, the reaction of the carbanion of **1a** with 2-chloronitrobenzene, when carried out at -40°C , gave a mixture of two products: the expected product of ONSH, **5aa**, and the product of substitution of chlorine. At -78°C , the reaction proceeded selectively as ONSH to give pure **5aa** in high yield. On the other hand, the reaction of the carbanion of **1a** with 2-fluoronitrobenzene, even if carried out at -78°C , proceeded partially as $\text{S}_\text{N}\text{Ar}$ of fluorine,

whereas at $-40\text{ }^{\circ}\text{C}$ $\text{S}_{\text{N}}\text{Ar}$ was the main process. Nitroarylated products **2aa–14aa** are stable compounds and can be isolated and purified by standard chromatographic techniques.

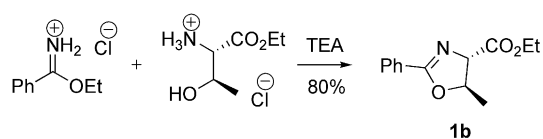
When a solution of the σ^{H} adduct of the carbanion of **1a** to nitrobenzene produced according to the standard procedure was treated with an acetone solution of DMD prepared in accordance with the procedure of Adam,^[28] the α -(*p*-hydroxyphenyl) derivative of **1a**, phenol **2ab**, was obtained. Similarly, the σ^{H} adducts produced by addition of the carbanion of **1a** to other nitroarenes upon oxidation by DMD in acetone gave expected *p*-hydroxyarylated oxazolines **3ab–10ab**. The oxidation step was not fully chemoselective, as mostly one product obtained from oxidation of the negatively charged nitro group in the σ^{H} adducts was produced. However, in the case of the σ^{H} adducts of **1a** to 2-cyanonitrobenzene (**10**) and 3-fluoronitrobenzene (**4**), oxidation with DMD gave exclusively nitroaryl derivative **10aa** and **4aa**, respectively. Related dichotomy in the DMD oxidation was observed in the case of the oxidation of nitrobenzylic carbanions. Depending on the nature of the carbanions and the conditions, the oxidation resulted in hydroxylation of the carbanionic moiety and/or conversion of the nitronate group into a carbonyl group, so methylene quinone derivatives are produced.^[29]

Nitroarylated oxazolines, for example, **2aa**, **2ab**, and **5ab**, can be readily hydrolyzed to nitroarylated serine derivatives by simple heating with aqueous HCl/THF followed by precipitation with propylene oxide. Representative yields are presented in Scheme 3.



Scheme 3. Hydrolysis of nitroarylated oxazolines.

Next, we studied the possibility of oxidative nitroarylation of the carbanion of L-threonine protected in the form of oxazoline **1b**. This precursor was obtained by an analogous reaction of the ethyl ester of L-threonine hydrochloride with ethyl benzimidate hydrochloride, as presented in Scheme 4.



Scheme 4. Synthesis of L-threonine protected in the form of oxazoline **1b**.

Oxazoline **1a** obtained from L-serine as one enantiomer, in the deprotonation–nitroarylation process gave racemic products **2aa–14aa**. In oxazoline **1b**, obtained from op-

tically pure L-threonine as one *anti* (*trans*) diastereoisomer, two chiral centers are presented. We expected that the stereochemistry of the addition of the carbanion of **1b** to nitroarenes should be controlled by the vicinal stereogenic center to produce single diastereomeric σ^{H} adducts, which upon oxidation with DDQ or DMD should give single diastereoisomers of the nitroarylated and hydroxyarylated products.

Thus, in this way, self-reproduction of chirality shall be observed.^[9a,30] Indeed, when a mixture of **1b** and nitrobenzene dissolved in THF/DMF was treated with *t*BuOK at low temperature ($-78\text{ }^{\circ}\text{C}$) and the produced σ^{H} adduct oxidized with DDQ, expected nitroarylated oxazoline **2ba** was obtained as one diastereoisomer in an excellent yield of 79%. The configuration of representative diastereomer **2ba** was established on the basis of ^1H NMR spectroscopic experiments through NOE analysis (Figure 1).

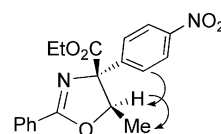


Figure 1. NOE experiment for **2ba**.

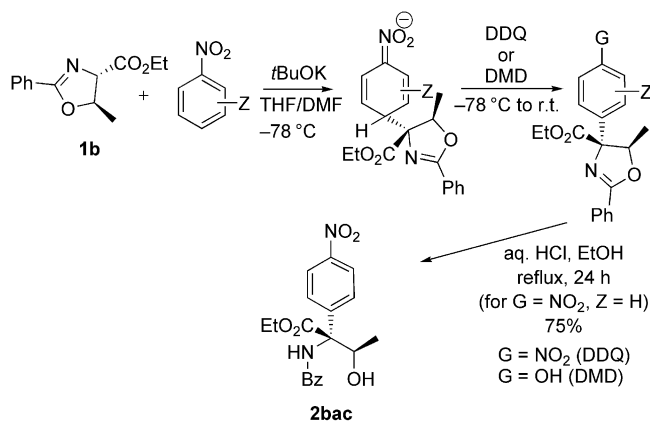
The product structure suggests that addition of the carbanions to the nitroarene proceeds from the opposite side in relation to the methyl group. The resulting configuration can be designated as D-*allo*-threonine.

In the ONSH reaction of the carbanion of **1b** with a series of nitroarenes, nitroarylated products **2ba–14ba** were obtained, usually in good and very good yields. Noteworthy is that the yields are significantly higher than those obtained for **1a**, although one might expect that the oxidation of the σ^{H} adduct derived from **1b** (Table 2, Scheme 5) should be more difficult than that obtained from **1a** due to the bulkiness of the former.

Table 2. Results of the ONSH reaction of nitroarenes with the carbanion of **1b** as in Scheme 5.

Nitroarene, Z		DDQ G = NO ₂		DMD G = OH	
		Product	% Yield	Product	% Yield
H	2	2ba	79	2bb	60
3-F	4	4ba	91	4bb	58
				4ba	20
2-Cl	5	5ba	79		
3-Cl	6	6ba	80	6bb	70
3-MeO	8	8ba	29		
2-CN	10	10ba	70	10ba	54
3-CN	11	11ba	79	11bb	59
4-EtO-2-NO ₂ Py	14	14ba	78		

The results of nitroarylation of **1b** are presented in Table 3. Oxidation of the σ^{H} adducts by DMD also resulted in the formation of the appropriate phenols in good yields. The oxidation chemoselectivity of these σ^{H} adducts by this oxidant is superior to the σ^{H} adduct of **1a** and the nitroarenes. Although oxidation of the σ^{H} adduct to 2-

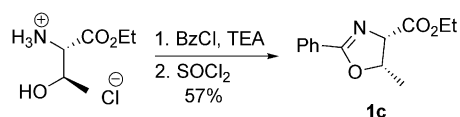
Scheme 5. ONSH in nitroarenes with carbanion of **1b**.

cyanonitrobenzene solely gave product **10ba**, in the reaction of 3-fluoronitrobenzene, desired phenol **4bb** was obtained as the main product.

Table 3. Results of the ONSH reaction of nitroarenes with the carbanion of **1c** as in Scheme 7.

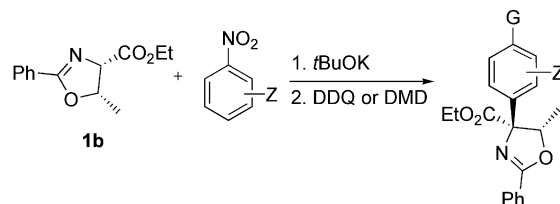
Nitroarene, Z		DDQ G = NO ₂		DMD G = OH	
		Product	% Yield	Product	% Yield
H	2	2ca	76	2cb	58
3-Cl	6	6ca	77	6cb	70
3-MeO	8	10ca	70		
3-CN	11			11cb	59

The chiral center in the β -position of the carbanion of **1b** controlled the stereochemistry of the addition of the carbanion to the nitroaromatic rings, so the obtained ONSH products have the D-*allo*-threonine configuration. One could therefore expect that the synthesis of the diastereoisomer of oxazoline **1b** being an epimer at the β carbon shall give access to its enantiomer with the L-*allo*-threonine configuration. The synthesis of such a carbanion precursor can be done by at least two ways. The simplest method, which is analogous to the synthesis of **1b**, starts with the ethyl ester of L-*allo*-threonine hydrochloride and ethyl benzimidate hydrochloride. Due to the high cost of pure L-*allo*-threonine, we decided to use another approach. Using the same threonine ester as in the synthesis of **1b** and conducting Nbenzoylation followed by cyclization by treatment of the benzoyl derivative with thionyl chloride, we obtained desired epimeric carbanion precursor **1c** (Scheme 6).

Scheme 6. Synthesis of protected diastereomeric oxazoline in the form of oxazoline **1c**.

As we expected, **1c** being the epimer of **1b** behaved in ONSH reaction analogously to **1b**. Treatment of a mixture of **1c** and nitroarene *t*BuOK at low temperature followed

by oxidation of the intermediate σ^H adducts with DDQ or DMD gave the appropriate nitroarylated and hydroxyarylated products as in Scheme 7. The results are presented in Table 3.

Scheme 7. ONSH reaction of nitroarenes with the carbanion of **1c**. Synthesis of nitroarylated L-*allo*-threonine derivatives.

The products of nitroarylation and hydroxyarylation of **1c** have the same analytical data as those obtained from **1b**, except for the optical rotation, thus proving that they are in fact enantiomers of the ONSH products obtained from **1b**.

Conclusions

We have elaborated a convenient method for the introduction of nitroaryl rings into serine and threonine derivatives by oxidative nucleophilic substitution of hydrogen (ONSH) of nitroarenes. Carbanions of appropriate esters of L-serine and L-threonine protected in the form of oxazolines (**1a** and **1b**, respectively) add to nitroarenes in the *para* position to the nitro group. Subsequent oxidation of the formed σ^H products with DDQ provides access to nitroarylated, quaternary, protected racemic serine and optically pure D-*allo*-threonine derivatives. Simple changing of the oxidant to an acetonic solution of DMD gave the respective *p*-hydroxyarylated derivatives. Furthermore, oxazoline **1c**, being a diastereoisomer of **1b**, obtained from threonine ethyl hydrochloride in a two-step procedure, enters the ONSH under the conditions optimized for **1b**, giving products with the L-*allo*-threonine configuration. Thus, starting from L-threonine we were able to obtain both enantiomers of α -(*p*-nitroaryl)-*allo*-threonine derivatives in addition to those of α -(*p*-hydroxyaryl)-*allo*-threonine derivatives. All oxazoline derivatives of serine and threonine can be simply hydrolyzed according to known procedures to give *p*-nitroaryl and *p*-hydroxyaryl derivatives as the pure free amino acids or their esters.

Experimental Section

General Methods: All reactions were carried out under an atmosphere of dry argon. THF was distilled from potassium benzophenone ketyl, and DMF was distilled from calcium hydride. All other solvents used in the purification step were distilled. Silica gel Merck 60 (230–400 mesh) was used for column chromatography. The ethyl ester of serine and threonine protected in the form of oxazolines were obtained by known procedures.^[31]

Procedure for the Nitroarylation of the Oxazoline Derivative of Serine (1a**) and Threonine (**1b** and **1c**):** To a solution of **1a**, **1b**, or **1c** (1.0 mmol) and nitroarene (2.0 mmol) in a mixture of THF (10 mL)

and DMF (2 mL) cooled to -40°C (**1a**) or -78°C (**1b** and **1c**, or for reaction **1a** with **3** or **5**) was added *t*BuOK (1.0 M in THF, 1.1 mL, 1.1 mmol) over 15 min. After 30 min at this temperature, a solution of DDQ (272 mg, 1.2 mmol) in THF (1 mL) was added. After 5 min, the cooling bath was removed, and the reaction mixture was allowed to reach room temperature. Then, the reaction mixture was poured into dichloromethane (75 mL) and washed with water (3×100 mL) and brine (100 mL). The organic phase was dried with anhydrous sodium sulfate, the solvents were evaporated, and the crude products were purified by column chromatography (hexane/ethyl acetate).

Procedure for the Hydroxyarylation of the Oxazoline Derivative of Serine (1a) and Threonine (1b and 1c): To a solution of **1a**, **1b**, or **1c** (1.0 mmol) and nitroarene (2.0 mmol) in a mixture of THF (10 mL) and DMF (2 mL) cooled to -40°C (**1a**) or -78°C (**1b** and **1c**, or for reaction **1a** with **3** or **5**) was added *t*BuOK (1.0 M in THF, 1.1 mL, 1.1 mmol) over 15 min. After 30 min at this temperature, a solution of DMD (1.2 mmol) in acetone was added. After 5 min, the cooling bath was removed, and the reaction mixture was allowed to reach room temperature. The solvents were evaporated under reduced pressure, and the residue was partitioned between water (50 mL) and dichloromethane (100 mL). The organic phase was dried with anhydrous sodium sulfate, the solvents were evaporated, and the crude products were purified by column chromatography (hexane/ethyl acetate).

Ethyl 4-(4-Nitrophenyl)-2-phenyl-1,3-oxazoline-4-carboxylate (2aa): Yield: 248 mg, 73%; oil. IR (film): $\tilde{\nu}$ = 2982, 1732, 1641, 1523, 1350, 1259, 1098, 856 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ = 8.26–8.22 (m, 2 H), 8.12–8.08 (m, 2 H), 7.70–7.65 (m, 2 H), 7.59–7.53 (m, 1 H), 7.50–7.45 (m, 2 H), 5.41 (d, J = 8.8 Hz, 1 H, $-\text{CH}_2-$), 4.41 (d, J = 8.8 Hz, 1 H, $-\text{CH}_2-$), 4.27–4.14 (m, 2 H, OCH_2CH_3), 1.22 (t, J = 7.2 Hz, 3 H, $-\text{OCH}_2\text{CH}_3$) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ = 171.1, 166.1, 148.7, 147.6, 132.3, 128.8, 128.5, 126.8, 126.6, 123.9, 80.6, 76.3, 62.7, 13.9 ppm. LRMS (ESI+): m/z = 341 $[\text{M} + \text{H}]^+$. $\text{C}_{18}\text{H}_{16}\text{N}_2\text{O}_5$ (340.34): calcd. C 63.53, H 4.74, N 8.23; found C 63.35, H 4.69, N 8.10.

Ethyl 4-(2-Fluoro-4-nitrophenyl)-2-phenyl-1,3-oxazoline-4-carboxylate (3aa): Yield: 193 mg, 54%; oil. IR (film): $\tilde{\nu}$ = 2989, 1741, 1641, 1528, 1348, 1236 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ = 8.10–8.08 (m, 3 H), 7.58–7.54 (m, 1 H), 7.52 (d, J = 1.8, 11.8 Hz, 1 H), 7.49–7.45 (m, 2 H), 7.41–7.37 (m, 2 H), 5.38 (d, J = 9.0 Hz, 1 H, $-\text{CH}_2-$), 4.40 (d, J = 9.0 Hz, 1 H, $-\text{CH}_2-$), 4.30–4.21 (m, 2 H, OCH_2CH_3), 1.17 (t, J = 7.2 Hz, 3 H, $-\text{OCH}_2\text{CH}_3$) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ = 170.6, 166.4, 155.6 (d, J = 212 Hz), 150.4 (d, J = 6.2 Hz), 136.7 (d, J = 6.3 Hz), 132.4, 128.9, 128.7, 128.6, 128.5, 126.5, 126.5 (d, J = 7.8 Hz), 121.8 (d, J = 3.5 Hz), 121.8 (d, J = 116.5 Hz), 80.2 (d, J = 0.8 Hz), 76.2 (d, J = 76.1 Hz), 62.8, 13.9 ppm. LRMS (ESI+): m/z = 359 $[\text{M} + \text{H}]^+$. $\text{C}_{18}\text{H}_{15}\text{FN}_2\text{O}_5$ (358.33): calcd. C 60.33, H 4.22, N 7.82; found C 60.52, H 4.21, N 7.92.

Ethyl 4-(2-Fluoro-4-nitrophenyl)-2-phenyl-1,3-oxazoline-4-carboxylate (4aa): Yield: 179 mg, 50%; white crystals; m.p. 113–115 $^{\circ}\text{C}$. IR (KBr): $\tilde{\nu}$ = 3088, 2979, 1740, 1636, 1524, 1358, 1247, 1098, 977 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ = 8.11–8.06 (m, 3 H), 7.98–7.91 (m, 2 H), 7.60–7.53 (m, 1 H), 7.50–7.43 (m, 2 H), 5.54 (dd, J = 1.6, 9.1 Hz, 1 H, 1 H, $-\text{CH}_2-$), 4.34 (dd, J = 1.6, 9.1 Hz, 1 H, $-\text{CH}_2-$), 4.32–4.14 (m, 2 H, OCH_2CH_3), 1.21 (t, J = 7.2 Hz, 3 H, OCH_2CH_3) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ = 169.6, 167.0, 158.7 (d, J = 250 Hz), 148.4 (d, J = 8.5 Hz), 137.1 (d, J = 16 Hz), 132.4, 129.3 (d, J = 5.1 Hz), 128.9, 128.5, 126.5, 119.6 (d, J = 3.4 Hz), 111.1 (d, J = 26 Hz), 77.6, 76.1 (d, J = 4.3 Hz), 62.8, 13.9 ppm. LRMS (ESI+): m/z = 359 $[\text{M} + \text{H}]^+$. $\text{C}_{18}\text{H}_{15}\text{FN}_2\text{O}_5$

(358.33): calcd. C 60.34, H 4.22, N 7.82; found C 60.19, H 4.21, N 7.65.

Ethyl 4-(3-Chloro-4-nitrophenyl)-2-phenyl-1,3-oxazoline-4-carboxylate (5aa): Yield: 273 mg, 73%; white crystals; m.p. 82–84 $^{\circ}\text{C}$. IR (KBr): $\tilde{\nu}$ = 3104, 2978, 1738, 1634, 1528, 1355, 1248, 1101 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ = 8.28 (d, J = 2.3 Hz, 1 H), 8.16 (dd, J = 2.3, 8.8 Hz, 1 H), 8.12–8.05 (m, 2 H), 8.03 (d, J = 8.8 Hz, 1 H), 7.60–6.50 (m, 1 H), 7.51–7.43 (m, 2 H), 5.66 (d, J = 9.2 Hz, 1 H, $-\text{CH}_2-$), 4.35 (d, J = 9.2 Hz, 1 H, $-\text{CH}_2-$), 4.35–4.26 (m, 1 H, OCH_2CH_3), 4.22–4.13 (m, 1 H, OCH_2CH_3), 1.21 (t, J = 7.2 Hz, 3 H, $-\text{OCH}_2\text{CH}_3$) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ = 169.7, 167.0, 147.9, 147.7, 132.4, 132.4, 129.8, 128.9, 128.5, 126.5, 124.7, 122.0, 80.1, 76.1, 62.9, 13.9 ppm. LRMS (ESI+): m/z = 375 $[\text{M} + \text{H}]^+$. $\text{C}_{18}\text{H}_{15}\text{ClN}_2\text{O}_5$ (374.78): calcd. C 57.69, H 4.03, N 7.47; found C 58.06, H 4.01, N 7.25.

Ethyl 4-(2-Chloro-4-nitrophenyl)-2-phenyl-1,3-oxazoline-4-carboxylate (6aa): Yield: 262 mg, 70%; oil. IR (film, CH_2Cl_2): $\tilde{\nu}$ = 2982, 1734, 1641, 1529, 1357, 1257, 1098 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ = 8.12–8.07 (m, 2 H), 7.90 (d, J = 8.5 Hz, 1 H), 7.74 (d, J = 1.9 Hz, 1 H), 7.59–7.44 (m, 4 H), 5.38 (d, J = 8.9 Hz, 1 H, $-\text{CH}_2-$), 4.40 (d, J = 8.9 Hz, 1 H, $-\text{CH}_2-$), 4.26 (dq, J = 5.2, 7.2 Hz, 2 H, OCH_2CH_3), 1.25 (t, J = 7.2 Hz, 3 H, $-\text{OCH}_2\text{CH}_3$) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ = 170.7, 166.3, 147.4, 147.2, 132.4, 129.5, 128.9, 128.5, 127.7, 126.4, 126.0, 125.0, 80.1, 76.20, 62.8, 13.9 ppm. LRMS (ESI+): m/z = 375 $[\text{M} + \text{H}]^+$. $\text{C}_{18}\text{H}_{15}\text{ClN}_2\text{O}_5$ (374.78): calcd. C 57.69, H 4.03, N 7.47; found C 57.48, H 4.04, N 7.33.

Ethyl 4-(2-Methoxy-4-nitrophenyl)-2-phenyl-1,3-oxazoline-4-carboxylate (8aa): Yield: 222 mg, 60%; white crystals; m.p. 80–83 $^{\circ}\text{C}$. IR (KBr): $\tilde{\nu}$ = 3109, 2981, 1736, 1643, 1521, 1345, 1246, 1022 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ = 8.10–8.06 (m, 2 H), 7.89 (dd, J = 2.2, 8.3 Hz, 1 H, 1 H), 7.81 (d, J = 8.3 Hz, 1 H), 7.72 (d, J = 2.2 Hz, 1 H), 7.57–7.52 (m, 1 H), 7.48–7.41 (m, 2 H), 5.56 (d, J = 9.1 Hz, 1 H, $-\text{CH}_2-$), 4.34–4.25 (m, 1 H), 4.19 (d, J = 9.1 Hz, 1 H, $-\text{CH}_2-$), 4.15–4.06 (m, 1 H, OCH_2CH_3), 3.93 (s, 3 H, OCH_3), 1.17 (t, J = 7.2 Hz, 3 H, $-\text{OCH}_2\text{CH}_3$) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ = 170.5, 166.6, 155.7, 148.6, 138.7, 132.2, 128.8, 128.4, 127.8, 126.9, 116.2, 105.2, 78.2, 76.5, 62.1, 56.0, 14.0 ppm. LRMS (ESI+): m/z = 371 $[\text{M} + \text{H}]^+$. $\text{C}_{19}\text{H}_{18}\text{N}_2\text{O}_6$ (370.36): C 61.61, H 4.90, N 7.56; found C 61.90, H 5.12, N 7.33.

Ethyl 4-(2-Methyl-4-nitrophenyl)-2-phenyl-1,3-oxazoline-4-carboxylate (9aa): Yield: 131 mg, 37%; white crystals; m.p. 147–148 $^{\circ}\text{C}$. IR (film, CH_2Cl_2): $\tilde{\nu}$ = 2982, 1734, 1641, 1523, 1347, 1235 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ = 8.16–8.07 (m, 2 H), 8.06–8.02 (m, 1 H), 7.99–7.91 (m, 1 H), 7.57–7.52 (m, 2 H), 7.49–7.43 (m, 2 H), 5.61 (d, J = 8.6 Hz, 1 H, $-\text{CH}_2-$), 4.25 (d, J = 8.6 Hz, 1 H, $-\text{CH}_2-$), 4.30–4.16 (m, 2 H, OCH_2CH_3), 2.28 (s, 3 H, CH_3), 1.21 (t, J = 7.2 Hz, 3 H, $-\text{OCH}_2\text{CH}_3$) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ = 170.6, 165.9, 147.9, 147.3, 135.5, 132.3, 128.8, 128.4, 128.3, 126.6, 125.6, 121.2, 80.2, 75.5, 62.3, 19.9, 13.9 ppm. LRMS (ESI+): m/z = 355 $[\text{M} + \text{H}]^+$. $\text{C}_{19}\text{H}_{18}\text{N}_2\text{O}_5$ (354.36): C 64.40, H 5.12, N 7.91; found C 64.33, H 5.13, N 7.70.

Ethyl 4-(3-Cyano-4-nitrophenyl)-2-phenyl-1,3-oxazoline-4-carboxylate (10aa): Yield: 201 mg, 55%; white crystals; m.p. 134–136 $^{\circ}\text{C}$. IR (KBr): $\tilde{\nu}$ = 3038, 2988, 2973, 2238, 1736, 1641, 1533, 1348 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ = 8.34 (d, J = 8.8 Hz, 1 H), 8.13–8.07 (m, 3 H), 7.29 (dd, J = 1.9, 8.8 Hz, 1 H), 7.61–7.65 (m, 1 H), 7.51–7.46 (m, 2 H), 5.40 (d, J = 8.9 Hz, 1 H, $-\text{CH}_2-$), 4.43 (d, J = 8.9 Hz, 1 H, $-\text{CH}_2-$), 4.26 (q, J = 7.2 Hz, 2 H, OCH_2CH_3), 1.25 (t, J = 7.2 Hz, 3 H, $-\text{OCH}_2\text{CH}_3$) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ = 170.3, 166.8, 149.1, 147.8, 133.5, 132.6, 131.2, 128.9, 128.6, 126.1, 125.8, 114.7, 108.4, 80.0, 76.1, 63.1, 29.7, 13.9 ppm. LRMS

(ESI+): m/z = 366 [M + H]⁺. C₁₉H₁₅N₃O₅ (356.35): C 62.46, H 4.14, N 11.50; found C 62.64, H 4.29, N 11.10.

Ethyl 4-[2-(Trifluoromethyl)-4-nitrophenyl]-2-phenyl-1,3-oxazoline-4-carboxylate (12aa): Yield: 102 mg, 25%; oil. IR (film, CH₂Cl₂): $\tilde{\nu}$ = 3091, 2984, 2258, 1745, 1642, 1532, 1312, 1176 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ = 8.59–8.54 (m, 1 H), 8.43–8.35 (m, 2 H), 8.11–8.06 (m, 2 H), 7.60–7.54 (m, 1 H), 7.50–7.44 (m, 2 H), 5.51 (d, J = 9.2 Hz, 1 H, -CH₂-), 4.39 (d, J = 9.2 Hz, 1 H, -CH₂-), 4.26–4.14 (m, 2 H, OCH₂CH₃), 1.19 (t, J = 7.2 Hz, 3 H, OCH₂CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 169.8, 166.5, 147.3, 146.5, 132.5, 131.2, 129.9, 128.1 (q, J = 33 Hz), 126.6, 126.4, 123.2 (q, J = 274 Hz), 123.1 (q, J = 5.2 Hz), 80.1, 76.3 (q, J = 6.9 Hz), 62.8, 13.7 ppm. LRMS (ESI+): m/z = 409 [M + H]⁺. C₁₉H₁₅F₃N₂O₅ (408.33): C 55.89, H 3.70, N 6.86; found C 55.78, H 3.62, N 6.78.

Ethyl 4-(3-Ethoxy-4-nitro-2-pyridyl)-2-phenyl-1,3-oxazoline-4-carboxylate (14aa): Yield: 273 mg, 71%; white crystals; m.p. 92–95 °C. IR (KBr): $\tilde{\nu}$ = 2985, 1739, 1638, 1602, 1519, 1356, 1255, 1027 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ = 8.93 (s, 1 H), 8.11–8.04 (m, 2 H), 7.58–7.53 (m, 1 H), 7.51–7.42 (m, 3 H), 5.42 (d, J = 9.4 Hz, 1 H, -CH₂-), 4.75 (d, J = 9.4 Hz, 1 H, -CH₂-), 4.40–4.17 (m, 4 H, OCH₂CH₃), 1.51 (t, J = 7.2 Hz, 3 H, OCH₂CH₃), 1.22 (t, J = 7.2 Hz, 3 H, OCH₂CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 169.9, 167.0, 166.6, 159.1, 146.6, 135.8, 132.3, 128.8, 128.5, 126.7, 107.2, 82.3, 75.0, 66.0, 62.6, 14.2, 14.0 ppm. LRMS (ESI+): m/z = 386 [M + H]⁺. C₁₉H₁₉N₃O₆ (385.38): C 59.22, H 4.97, N 10.90; found C 59.42, H 5.06, N 10.86.

Ethyl 4-(4-Hydroxyphenyl)-2-phenyl-1,3-oxazoline-4-carboxylate (2ab): Yield: 165 mg, 53%; yellow crystals; m.p. 145–147 °C. IR (film, CH₂Cl₂): $\tilde{\nu}$ = 3193 (br.), 2982, 1728, 1637, 1515, 1260 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ = 8.10–8.06 (m, 2 H), 6.81–6.76 (m, 2 H), 7.54–7.49 (m, 2 H), 7.45–7.40 (m, 1 H), 7.27–7.24 (m, 2 H), 5.30 (d, J = 8.8 Hz, 1 H, -CH₂-), 4.43 (d, J = 8.8 Hz, 1 H, -CH₂-), 4.30–4.14 (m, 2 H, OCH₂CH₃), 1.19 (t, J = 7.2 Hz, 3 H, OCH₂CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 172.3, 165.5, 155.9, 133.2, 132.1, 128.8, 128.4, 126.9, 126.7, 115.8, 80.1, 76.9, 62.2, 13.9 ppm. LRMS (ESI+): m/z = 312 [M + H]⁺. C₁₈H₁₇NO₄ (311.33): C 69.44, H 5.50, N 4.50; found C 68.93, H 5.48, N 4.66.

Ethyl 4-(3-Chloro-4-hydroxyphenyl)-2-phenyl-1,3-oxazoline-4-carboxylate (5ab): Yield: 190 mg, 55%; yellow crystals; m.p. 109–112 °C. IR (film, CH₂Cl₂): $\tilde{\nu}$ = 3200 (br.), 2983, 1729, 1637, 1497, 1294, 1259 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ = 8.11–8.07 (m, 2 H), 7.56–7.41 (m, 3 H), 7.26 (s, 1 H), 7.23 (dd, J = 2.3, 8.5 Hz, 1 H), 7.00 (d, J = 8.5 Hz, 1 H), 5.30 (d, J = 8.8 Hz, 1 H, -CH₂-), 4.39 (d, J = 8.8 Hz, 1 H, -CH₂-), 4.32–4.18 (m, 2 H, OCH₂CH₃), 1.23 (t, J = 7.2 Hz, 3 H, OCH₂CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 171.9, 165.6, 151.1, 135.0, 132.1, 128.8, 128.4, 127.0, 126.5, 125.6, 120.2, 116.4, 79.9, 76.7, 62.3, 14.0 ppm. LRMS (ESI+): m/z = 346 [M + H]⁺. C₁₈H₁₆ClNO₄ (345.78) C 62.52, H 4.66, N 4.05; found C 62.30, H 4.77, N 4.77.

Ethyl 4-(3-Chloro-4-hydroxyphenyl)-2-phenyl-1,3-oxazoline-4-carboxylate (6ab): Yield: 176 mg, 51%; yellow crystals; m.p. 137–140 °C. IR (film, CH₂Cl₂): $\tilde{\nu}$ = 3413 (br.), 2982, 1736, 1632, 1495, 1272, 1243 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ = 8.20–7.90 (m, 2 H), 7.56–7.52 (m, 2 H), 7.48–7.42 (m, 2 H), 6.88 (d, J = 2.6 Hz, 1 H), 6.71 (dd, J = 2.6, 8.6 Hz, 1 H), 5.64 (d, J = 8.8 Hz, 1 H, -CH₂-), 4.37 (d, J = 8.8 Hz, 1 H, -CH₂-), 4.32–4.25 (m, 1 H, OCH₂CH₃), 4.17–4.12 (m, 1 H, OCH₂CH₃), 1.20 (t, J = 7.2 Hz, 3 H, OCH₂CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 170.9, 166.8, 156.4, 132.5, 131.7, 130.1, 129.2, 129.0, 128.5, 126.5, 117.0, 114.1, 96.1, 79.3, 77.2, 62.6, 13.9 ppm. LRMS (ESI+): m/z = 346

[M + H]⁺. C₁₈H₁₆ClNO₄ (345.78): C 62.52, H 4.66, N 4.05; found C 62.88, H 4.54, N 4.22.

Ethyl 4-(3-Methoxy-4-hydroxyphenyl)-2-phenyl-1,3-oxazoline-4-carboxylate (7ab): Yield: 112 mg, 33%; yellow crystals; m.p. 75–79 °C. IR (film, CH₂Cl₂): $\tilde{\nu}$ = 3367 (br.), 2976, 2234, 1736, 1637, 1299 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ = 8.12–8.08 (m, 2 H), 7.55–7.50 (m, 1 H), 7.45–7.42 (m, 2 H), 7.05 (s, 1 H), 6.89 (d, J = 1.1 Hz, 2 H), 5.32 (d, J = 8.8 Hz, 1 H, -CH₂-), 4.40 (d, J = 8.8 Hz, 1 H, -CH₂-), 4.31–4.19 (m, 2 H, OCH₂CH₃), 3.90 (s, 3 H, OCH₃), 1.23 (t, J = 7.2 Hz, 3 H, OCH₂CH₃) ppm. ¹³C NMR (125 MHz, CDCl₃): δ = 172.2, 165.2, 146.6, 145.3, 133.8, 131.9, 128.8, 128.4, 127.2, 118.3, 114.5, 108.3, 80.4, 76.9, 62.1, 56.0, 14.0 ppm. LRMS (ESI+): m/z = 342 [M + H]⁺. C₁₉H₁₉NO₅ (341.36): C 66.85, H 5.61, N 4.10; found C 66.97, H 5.66, N 4.26.

Ethyl 4-(2-Methoxy-4-hydroxyphenyl)-2-phenyl-1,3-oxazoline-4-carboxylate (8ab): Yield: 119 mg, 35%; yellow crystals; m.p. 124–126 °C. IR (film, CH₂Cl₂): $\tilde{\nu}$ = 3198 (br.), 2979, 1735, 1634, 1497, 1252, 1200 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ = 8.12–8.08 (m, 2 H), 7.55–7.50 (m, 1 H), 7.48–7.42 (m, 2 H), 7.38 (d, J = 8.3 Hz, 1 H), 6.41 (d, J = 2.4 Hz, 1 H), 6.38 (dd, J = 2.4, 8.3 Hz, 1 H, -CH₂-), 5.52 (d, J = 8.8 Hz, 1 H, -CH₂-), 4.30–4.20 (m, 2 H, OCH₂CH₃), 3.72 (s, 3 H, OCH₃), 1.16 (t, J = 7.2 Hz, 3 H, -OCH₂CH₃) ppm. ¹³C NMR (125 MHz, CDCl₃): δ = 172.2, 165.2, 146.6, 145.3, 133.8, 131.9, 128.8, 128.4, 127.2, 118.3, 114.5, 107.0, 96.1, 77.5, 61.9, 55.3, 14.0 ppm. LRMS (ESI+): m/z = 342 [M + H]⁺. C₁₉H₁₉NO₅ (341.36): C 66.85, H 5.61, N 4.10; found C 66.56, H 5.43, N 4.41.

Ethyl 4-(2-Cyano-4-hydroxyphenyl)-2-phenyl-1,3-oxazoline-4-carboxylate (11ab): Yield: 198 mg, 59%; white crystals; m.p. 152–155 °C. IR (film, CH₂Cl₂): $\tilde{\nu}$ = 3367 (br.), 2976, 2234, 1736, 1637, 1299 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ = 8.08–8.05 (m, 2 H), 7.64 (d, J = 8.4 Hz, 1 H), 7.57–7.52 (m, 2 H), 7.47–7.43 (m, 2 H), 7.10 (d, J = 2.6 Hz, 1 H), 7.00 (dd, J = 2.9, 8.8 Hz, 1 H), 5.61 (d, J = 8.8 Hz, 1 H, -CH₂-), 4.46 (d, J = 8.8 Hz, 1 H, -CH₂-), 4.34–4.20 (m, 2 H, OCH₂CH₃), 1.25 (t, J = 7.2 Hz, 3 H, -OCH₂CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 170.7, 167.0, 155.8, 137.8, 132.4, 129.1, 128.9, 128.5, 126.4, 120.5 (2 C), 117.5, 110.6, 79.6, 77.0, 63.0, 13.9 ppm. LRMS (ESI+): m/z = 337 [M + H]⁺. C₁₉H₁₆N₂O₄ (336.35): C 67.85, H 4.79, N 8.33; found C 67.01, H 4.78, N 8.15.

Ethyl 4-(5-Chloro-2-cyano-4-hydroxyphenyl)-2-phenyl-1,3-oxazoline-4-carboxylate (13ab): Yield: 186 mg, 50%; white crystals. IR (film, CH₂Cl₂): $\tilde{\nu}$ = 3346 (br.), 2983, 2227, 1739, 1637, 1292, 1256, 1098, 695 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ = 8.09–8.06 (m, 2 H), 7.82 (s, 1 H), 7.57–7.52 (m, 1 H), 7.47–7.43 (m, 2 H), 7.27 (s, 1 H), 5.60 (d, J = 8.8 Hz, 1 H, -CH₂-), 4.45 (d, J = 8.8 Hz, 1 H, -CH₂-), 4.35–4.21 (m, 2 H, OCH₂CH₃), 1.25 (t, J = 7.2 Hz, 3 H, -OCH₂CH₃) ppm. ¹³C NMR (125 MHz, CDCl₃): δ = 170.1, 167.1, 151.8, 138.8, 132.5, 129.2, 128.9, 128.5, 126.2, 126.0, 121.1, 116.8, 109.0, 79.2, 76.7, 63.1, 13.9 ppm. LRMS (ESI+): m/z = 393 [M + Na]⁺. C₁₉H₁₅ClN₂O₅ (370.78): C 61.55, H 4.08, N 7.56, Cl 9.56; found C 61.28, H 4.15, N 7.79, Cl 9.40.

α -(4-Nitrophenyl)serine (2aac): Yield: 174 mg, 77%; white solid; m.p. >350 °C (decomp.). IR (KBr): $\tilde{\nu}$ = 3215, 3080, 2517, 1649, 1607, 1521, 1390, 1340 cm⁻¹. ¹H NMR (400 MHz, D₂O/DCl): δ = 8.26 (d, J = 9.1 Hz, 2 H), 7.69 (d, J = 9.1 Hz, 2 H), 4.42 (d, J = 12.1 Hz, 1 H, -CH₂-), 4.19 (d, J = 12.1 Hz, 1 H, -CH₂-) ppm. ¹³C NMR (100 MHz, D₂O/DCl): δ = 170.5, 148.5, 139.3, 127.6, 124.7, 66.8, 63.8 ppm. LRMS (ESI+): m/z = 227 [M + H]⁺.

α -(4-Hydroxyphenyl)serine (2abc): Yield: 115 mg, 69%; white solid; m.p. >350 °C (decomp.). IR (KBr): $\tilde{\nu}$ = 3440, 3261, 3098, 1653,

1568, 1518, 1376, 1186, 1057 cm^{-1} . ^1H NMR (400 MHz, $\text{D}_2\text{O}/\text{DCI}$): δ = 7.13 (d, J = 9.0 Hz, 2 H), 6.74 (d, J = 9.0 Hz, 2 H), 4.21 (d, J = 11.9 Hz, 1 H, $-\text{CH}_2-$), 4.00 (d, J = 11.4 Hz, 1 H, $-\text{CH}_2-$) ppm. ^{13}C NMR (100 MHz, $\text{D}_2\text{O}/\text{DCI}$): δ = 171.3, 156.8, 127.5, 123.4, 116.1, 66.2, 63.2 ppm. LRMS (ESI $^-$): m/z = 196 $[\text{M} - \text{H}]^-$.

α -(3-Chloro-4-hydroxyphenyl)serine (5abc): Yield: 184 mg, 80%; white solid; m.p. $>350^\circ\text{C}$ (decomp.). IR (KBr): $\tilde{\nu}$ = 3092, 2708, 1632, 1513, 1360, 1518, 1296, 1057 cm^{-1} . ^1H NMR (400 MHz, $\text{D}_2\text{O}/\text{DCI}$): δ = 7.31 (d, J = 2.4 Hz, 1 H), 7.07 (dd, J = 2.4, 8.6 Hz, 1 H), 6.88 (d, J = 8.8 Hz, 1 H), 4.21 (d, J = 12.1 Hz, 1 H, $-\text{CH}_2-$), 4.00 (d, J = 12.1 Hz, 1 H, $-\text{CH}_2-$) ppm. ^{13}C NMR (100 MHz, $\text{D}_2\text{O}/\text{DCI}$): δ = 170.8, 152.8, 127.8, 125.8, 124.6, 121.0, 117.3, 65.9, 63.2 ppm. LRMS (ESI $^-$): m/z = 230 $[\text{M} - \text{H}]^-$.

Ethyl (4*R*,5*R*)-5-Methyl-4-(4-nitrophenyl)-2-phenyl-1,3-oxazoline-2-carboxylate (2ba): Yield: 280 mg, 79%; oil. $[\alpha]_D^{20}$ = -36.0 (c = 1.100, CHCl_3). IR (film): $\tilde{\nu}$ = 3387, 2984, 1733, 1649, 1522, 1351, 1237 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ = 8.22 (d, J = 9.1 Hz, 2 H), 8.10–8.07 (m, 2 H), 7.85 (d, J = 9.1 Hz, 2 H), 7.58–7.52 (m, 1 H), 7.49–7.45 (m, 2 H), 4.98 (q, J = 6.6 Hz, 1 H, $\text{CH}-\text{CH}_3$), 4.28–4.20 (m, 2 H, OCH_2CH_3), 1.67 (d, J = 6.6 Hz, 3 H, $-\text{CH}-\text{CH}_3$), 1.26 (t, J = 7.2 Hz, 3 H, $-\text{CH}_2\text{CH}_3$) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ = 169.6, 165.3, 148.9, 147.4, 132.1, 128.7, 128.4, 127.7, 127.0, 123.3, 85.1, 82.3, 62.3, 17.6, 14.1 ppm. LRMS (ESI $^+$): m/z = 355 $[\text{M} + \text{H}]^+$. $\text{C}_{19}\text{H}_{18}\text{N}_2\text{O}_5$ (354.36): calcd. C 64.40, H 5.21, N 7.91; found C 64.23, H 5.21, N 7.81.

Ethyl (4*R*,5*R*)-5-Methyl-4-(3-fluoro-4-nitrophenyl)-2-phenyl-1,3-oxazoline-2-carboxylate (4ba): Yield: 339 mg, 91%; oil. $[\alpha]_D^{20}$ = -108.4 (c = 1.000, CHCl_3). IR (film): $\tilde{\nu}$ = 3111, 2985, 1739, 1652, 1530, 1353, 1235, 1081 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ = 8.12–8.04 (m, 4 H), 8.02–7.97 (m, 1 H), 7.58–7.31 (m, 1 H), 7.49–7.43 (m, 2 H), 5.00 (dq, J = 1.7, 6.4 Hz, 1 H, $\text{CH}-\text{CH}_3$), 4.29–4.18 (m, 2 H, OCH_2CH_3), 1.75 (dd, J = 1.7, 6.5 Hz, 3 H, $\text{CH}-\text{CH}_3$), 1.25 (t, J = 7.2 Hz, 3 H, OCH_2CH_3) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ = 168.4, 166.0, 160.0 (d, J = 250 Hz), 148.3 (d, J = 9.4 Hz), 137.2 (d, J = 13.7 Hz), 132.2, 129.7 (d, J = 5.2 Hz), 128.7, 128.4, 126.9, 119.1 (d, J = 3.5 Hz), 111.7 (d, J = 27.5 Hz), 84.9 (d, J = 4.3 Hz), 80.9 (d, J = 2.5 Hz), 62.3, 16.7, 14.0 ppm. ^{19}F NMR (376 MHz, CDCl_3): δ = -107.7 to -107.8 (m) ppm. LRMS (ESI $^+$): m/z = 373 $[\text{M} + \text{H}]^+$. $\text{C}_{19}\text{H}_{17}\text{FN}_2\text{O}_5$ (372.35): calcd. C 61.29, H 4.60, N 7.57; found C 61.06, H 4.77, N 7.44.

Ethyl (4*R*,5*R*)-5-Methyl-4-(2-chloro-4-nitrophenyl)-2-phenyl-1,3-oxazoline-2-carboxylate (5ba): Yield: 307 mg, 79%; oil. $[\alpha]_D^{20}$ = -31.7 (c = 0.525, CHCl_3). IR (film): $\tilde{\nu}$ = 2983, 1733, 1650, 1530, 1346, 1237, 1053 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ = 8.10–8.06 (m, 2 H), 7.90–7.87 (m, 1 H), 7.70 (dd, J = 2.0, 8.6 Hz, 1 H), 7.56–7.52 (m, 2 H), 7.50–7.44 (m, 2 H), 4.92 (q, J = 6.6 Hz, 1 H, $\text{CH}-\text{CH}_3$), 4.29–4.20 (m, 2 H, OCH_2CH_3), 1.65 (d, J = 6.6 Hz, 3 H, $\text{CH}-\text{CH}_3$), 1.27 (t, J = 7.2 Hz, 3 H, OCH_2CH_3) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ = 169.2, 165.6, 147.9, 147.1, 132.3, 130.4, 128.7, 128.5, 127.0, 128.8, 126.1, 125.4, 85.1, 81.8, 62.5, 17.5, 14.1 ppm. LRMS (ESI $^+$): m/z = 389 $[\text{M} + \text{H}]^+$. $\text{C}_{19}\text{H}_{17}\text{ClN}_2\text{O}_5$ (388.81): calcd. C 58.69, H 4.41, N 7.20; found C 58.93, H 4.60, N 7.08.

Ethyl (4*R*,5*R*)-5-Methyl-4-(3-chloro-4-nitrophenyl)-2-phenyl-1,3-oxazoline-2-carboxylate (6ba): Yield: 311 mg, 80%; oil. $[\alpha]_D^{20}$ = -219.7 (c = 1.150, CHCl_3). IR (film): $\tilde{\nu}$ = 2984, 2905, 1742, 1645, 1525, 1349, 1235 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ = 8.59–8.61 (m, 1 H), 8.36 (dd, J = 2.6, 8.8 Hz, 1 H), 8.19 (dd, J = 0.4, 8.8 Hz, 2 H), 7.60–7.55 (m, 2 H), 7.50–7.45 (m, 2 H), 5.82 (q, J = 6.4 Hz, 1 H, $\text{CH}-\text{CH}_3$), 4.44–4.25 (m, 2 H, OCH_2CH_3), 1.82 (d, J = 6.4 Hz, $\text{CH}-\text{CH}_3$), 1.31 (t, J = 7.2 Hz, 3 H, OCH_2CH_3) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ = 168.0, 166.0, 152.2, 147.0, 132.5, 129.9,

129.2, 128.9, 128.5, 127.0, 126.5, 116.8, 113.5, 84.9, 82.4, 63.0, 18.3, 14.0 ppm. LRMS (ESI $^+$): m/z = 389 $[\text{M} + \text{H}]^+$. $\text{C}_{19}\text{H}_{17}\text{ClN}_2\text{O}_5$ (388.81): calcd. C 58.69, H 4.41, N 7.20; found C 58.79, H 4.56, N 7.09.

Ethyl (4*R*,5*R*)-5-Methyl-4-(2-methoxy-4-nitrophenyl)-2-phenyl-1,3-oxazoline-2-carboxylate (8ba): Yield: 112 mg, 29%; oil. $[\alpha]_D^{20}$ = -174.8 (c = 0.500, CHCl_3). IR (film): $\tilde{\nu}$ = 2981, 2942, 1738, 1647, 1525, 1347, 1252, 1236, 1029 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ = 8.07–8.04 (m, 2 H), 7.89–7.85 (m, 2 H), 7.76 (d, J = 1.9 Hz, 1 H), 7.76–7.50 (m, 1 H), 7.47–7.42 (m, 2 H), 4.88 (q, J = 6.6 Hz, 1 H, $\text{CH}-\text{CH}_3$), 4.26–4.20 (m, 1 H, OCH_2CH_3), 4.16–4.10 (m, 1 H, OCH_2CH_3), 3.96 (s, 3 H), 1.80 (d, J = 6.6 Hz, 3 H, CHCH_3), 1.20 (t, J = 7.2 Hz, 3 H, OCH_2CH_3) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ = 169.0, 165.7, 157.1, 148.5, 132.0, 128.7, 128.4, 128.3, 127.4, 127.3, 116.0, 105.9, 85.4, 80.6, 61.5, 55.8, 17.3, 14.1 ppm. LRMS (ESI $^+$): m/z = 385 $[\text{M} + \text{H}]^+$. $\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}_6$ (384.34): calcd. C 62.49, H 5.24, N 7.29; found C 62.22, H 5.52, N 7.04.

Ethyl (4*R*,5*R*)-5-Methyl-4-(3-cyano-4-nitrophenyl)-2-phenyl-1,3-oxazoline-2-carboxylate (10ba): Yield: 266 mg, 70%; oil. $[\alpha]_D^{20}$ = -48.0 (c = 1.100, CHCl_3). IR (film): $\tilde{\nu}$ = 3070, 2984, 2235, 1734, 1648, 1534, 1346, 1232, 1052 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ = 8.32 (d, J = 8.8 Hz, 1 H), 8.24 (d, J = 1.7 Hz, 1 H), 8.14–8.06 (m, 3 H), 7.60–7.55 (m, 1 H), 7.51–7.44 (m, 3 H), 4.92 (q, J = 6.5 Hz, 1 H, $\text{CH}-\text{CH}_3$), 4.31–4.20 (m, 2 H, OCH_2CH_3), 1.69 (d, J = 6.5 Hz, 3 H, CHCH_3), 1.29 (t, J = 7.2 Hz, 3 H, OCH_2CH_3) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ = 168.8, 166.1, 149.3, 147.6, 134.2, 132.5, 132.2, 128.7, 128.5, 126.5, 125.3, 114.9, 107.8, 85.1, 81.8, 62.7, 17.5, 14.0 ppm. LRMS (ESI $^+$): m/z = 380 $[\text{M} + \text{H}]^+$. $\text{C}_{20}\text{H}_{17}\text{N}_3\text{O}_5$ (379.37): calcd. C 63.32, H 4.54, N 11.08; found C 63.35, H 4.76, N 10.69.

Ethyl (4*R*,5*R*)-5-Methyl-4-(2-cyano-4-nitrophenyl)-2-phenyl-1,3-oxazoline-2-carboxylate (11ba): Yield: 299 mg, 79%; white crystals; m.p. $94\text{--}95^\circ\text{C}$. $[\alpha]_D^{20}$ = -120.0 (c = 0.750, CHCl_3). IR (film): $\tilde{\nu}$ = 3083, 2985, 2233, 1735, 1649, 1532, 1354, 1239, 697 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ = 8.30 (d, J = 2.0 Hz, 1 H), 8.12 (d, J = 2.4 Hz, 1 H), 8.11–8.05 (m, 2 H), 7.96 (d, J = 8.6 Hz), 7.59–7.53 (m, 1 H), 7.50–7.44 (m, 2 H), 5.07 (q, J = 6.6 Hz, 1 H, $\text{CH}-\text{CH}_3$), 4.31–4.18 (m, 2 H, OCH_2CH_3), 1.98 (d, J = 6.6 Hz, 3 H, CHCH_3), 1.23 (t, J = 7.2 Hz, 3 H, OCH_2CH_3) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ = 168.1, 166.1, 147.7, 147.6, 134.0, 132.3, 129.7, 128.8, 128.5, 126.8, 125.5, 121.7, 85.2, 81.4, 62.2, 18.1, 13.9 ppm. LRMS (ESI $^+$): m/z = 380 $[\text{M} + \text{H}]^+$. $\text{C}_{20}\text{H}_{17}\text{N}_3\text{O}_5$ (379.37): calcd. C 63.32, H 4.54, N 11.08; found C 63.43, H 4.46, N 11.11.

Ethyl (4*R*,5*R*)-5-Methyl-4-(4-ethoxy-5-nitro-2-pyridyl)-2-phenyl-1,3-oxazoline-2-carboxylate (14ba): Yield: 311 mg, 78%; white crystals; m.p. $55\text{--}56^\circ\text{C}$. $[\alpha]_D^{20}$ = $+52.2$ (c = 0.750, CHCl_3). IR (KBr): $\tilde{\nu}$ = 2985, 1738, 1598, 1580, 1354, 1298, 1233 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ = 8.96 (s, 1 H), 8.10–8.02 (m, 2 H), 7.53 (s, 1 H), 7.56–7.48 (m, 2 H), 7.48–7.40 (m, 2 H), 5.59 (q, J = 6.6 Hz, 1 H, $\text{CH}-\text{CH}_3$), 4.30 (q, J = 7.0 Hz, 2 H, OCH_2CH_3), 4.22 (q, J = 7.2 Hz, 2 H, OCH_2CH_3), 1.69 (d, J = 6.5 Hz, 3 H, OCH_2CH_3), 1.50 (t, J = 7.0 Hz, 3 H, CHCH_3), 1.23 (t, J = 7.2 Hz, 3 H, $-\text{OCH}_2\text{CH}_3$) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ = 169.2, 166.1, 165.3, 158.6, 145.9, 135.8, 132.0, 128.5, 128.4, 128.3, 127.1, 127.0, 107.9, 83.9, 82.4, 65.8, 62.0, 17.0, 14.0 (2 C) ppm. LRMS (ESI $^+$): m/z = 400 $[\text{M} + \text{H}]^+$. $\text{C}_{20}\text{H}_{21}\text{N}_3\text{O}_6$ (399.40): calcd. C 60.14, H 5.30, N 10.52; found C 59.91, H 5.20, N 10.47.

Ethyl (4*R*,5*R*)-5-Methyl-4-(4-hydroxyphenyl)-2-phenyl-1,3-oxazoline-2-carboxylate (2bb): Yield: 195 mg, 60%; white crystals; m.p. $178\text{--}180^\circ\text{C}$. $[\alpha]_D^{20}$ = -13.3 (c = 1.000, CHCl_3). IR (KBr): $\tilde{\nu}$ = 3100 (br.), 2985, 2939, 1736, 1644, 1515, 1244, 1046, 697 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ = 8.06–8.02 (m, 2 H), 7.49–7.43 (m, 1 H),

7.40–7.33 (m, 4 H), 6.78–6.74 (m, 2 H), 5.04 (q, $J = 6.4$ Hz, 1 H, CH-CH_3), 4.20–4.11 (m, 2 H, OCH_2CH_3), 1.56 (d, $J = 6.5$ Hz, 3 H, CHCH_3), 1.17 (t, $J = 7.2$ Hz, 3 H, $-\text{OCH}_2\text{CH}_3$) ppm. ^{13}C NMR (100 MHz, CDCl_3): $\delta = 170.9, 164.7, 156.1, 132.8, 131.9, 128.6, 128.3, 127.4, 127.0, 115.5, 85.3, 81.9, 61.8, 17.5, 14.0$ ppm. LRMS (ESI⁺): $m/z = 326$ [$\text{M} + \text{H}$]⁺. $\text{C}_{19}\text{H}_{19}\text{NO}_4$ (325.36): calcd. C 70.14, H 5.89, N 4.30; found C 70.06, H 6.04, N 4.27.

Ethyl (4*R*,5*R*)-5-Methyl-4-(2-fluoro-4-hydroxyphenyl)-2-phenyl-1,3-oxazoline-2-carboxylate (4bb): Yield: 199 mg, 58%; oil. $[a]_D^{20} = -28.2$ ($c = 0.700$, CHCl_3). IR (film, CH_2Cl_2): $\tilde{\nu} = 3384$ (br.), 2982, 1737, 1627, 1451, 1240, 694 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): $\delta = 8.06$ – 8.02 (m, 2 H), 7.54–7.48 (m, 2 H), 7.46–7.38 (m, 2 H), 6.58–6.50 (m, 2 H), 5.06 (q, $J = 6.4$ Hz, 1 H, CH-CH_3), 4.25–4.15 (m, 2 H, OCH_2CH_3), 1.67 (d, $J = 6.4$ Hz, 3 H, CHCH_3), 1.22 (t, $J = 7.2$ Hz, 3 H, $-\text{OCH}_2\text{CH}_3$) ppm. ^{13}C NMR (100 MHz, CDCl_3): $\delta = 170.0, 165.3, 160.9$ (d, $J = 245$ Hz), 157.2 (d, $J = 12$ Hz), 132.0 (d, $J = 38$ Hz), 128.7 (d, $J = 6.1$ Hz), 128.6 (d, $J = 4.7$ Hz), 128.5 (d, $J = 12.5$ Hz), 121.2 (d, $J = 13$ Hz), 111.0, 103.9 (d, $J = 4.7$ Hz), 156.1, 132.8, 131.9, 128.6, 128.3, 127.4, 127.2, 127.0, 115.5, 85.3, 81.9, 61.8, 17.5, 14.0 ppm. LRMS (ESI⁺): $m/z = 344$ [$\text{M} + \text{H}$]⁺. $\text{C}_{19}\text{H}_{18}\text{FNO}_4$ (343.36): calcd. C 66.46, H 5.28, N 4.08; found C 67.00, H 5.31, N 4.21.

Ethyl (4*R*,5*R*)-5-Methyl-4-(2-chloro-4-hydroxyphenyl)-2-phenyl-1,3-oxazoline-2-carboxylate (6bb): Yield: 252 mg, 70%; white crystals; m.p. 146–147 °C. $[a]_D^{20} = -184.5$ ($c = 0.900$, CHCl_3). IR (KBr): $\tilde{\nu} = 3330$ (br.), 2983, 1738, 1639, 1495, 1450, 1235, 696 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): $\delta = 8.36$ – 8.08 (m, 2 H), 7.54–7.49 (m, 2 H), 7.46–7.38 (m, 2 H), 6.86 (d, $J = 2.5$ Hz, 1 H), 6.63 (dd, $J = 2.5, 8.6$ Hz, 1 H), 5.10 (q, $J = 6.5$ Hz, 1 H, CH-CH_3), 4.25–4.15 (m, 2 H, OCH_2CH_3), 1.79 (d, $J = 6.5$ Hz, 3 H, CHCH_3), 1.20 (t, $J = 7.2$ Hz, 3 H, $-\text{OCH}_2\text{CH}_3$) ppm. ^{13}C NMR (100 MHz, CDCl_3): $\delta = 169.9, 165.8, 156.4, 133.3, 132.1, 131.6, 128.9, 128.7, 128.4, 127.0, 118.0, 114.1, 85.5, 80.8, 61.9, 17.6, 13.9$ ppm. LRMS (ESI⁺): $m/z = 360$ [$\text{M} + \text{H}$]⁺. $\text{C}_{19}\text{H}_{18}\text{ClNO}_4$ (359.81): calcd. C 63.43, H 5.05, N 3.89; found C 63.17, H 5.15, N 4.07.

Ethyl (4*R*,5*R*)-5-Methyl-4-(2-cyano-4-hydroxyphenyl)-2-phenyl-1,3-oxazoline-2-carboxylate (11bb): Yield: 207 mg, 59%; white crystals; m.p. 118–119 °C. $[a]_D^{20} = -117.8$ ($c = 1.000$, CHCl_3). IR (KBr): $\tilde{\nu} = 3334$ (br.), 2985, 2228, 1738, 1645, 1495, 1451, 1239, 696 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): $\delta = 8.03$ – 8.01 (m, 2 H), 7.60 (d, $J = 8.8$ Hz, 1 H), 7.51–7.45 (m, 1 H), 7.43–7.35 (m, 2 H), 7.17 (d, $J = 2.7$ Hz, 1 H), 6.97 (dd, $J = 2.7, 8.5$ Hz, 1 H), 5.30 (q, $J = 6.4$ Hz, 1 H, CH-CH_3), 4.25–4.20 (m, 2 H, OCH_2CH_3), 1.72 (d, $J = 6.4$ Hz, 3 H, CHCH_3), 1.25 (t, $J = 7.2$ Hz, 3 H, $-\text{OCH}_2\text{CH}_3$) ppm. ^{13}C NMR (100 MHz, CDCl_3): $\delta = 169.7, 165.7, 156.3, 135.8, 132.3, 129.0, 128.7, 128.4, 126.5, 121.7, 120.2, 118.5, 111.8, 85.1, 81.6, 62.6, 17.8, 13.9$ ppm. LRMS (ESI⁺): $m/z = 351$ [$\text{M} + \text{H}$]⁺. $\text{C}_{20}\text{H}_{18}\text{N}_2\text{O}_4$ (350.37): calcd. C 68.56, H 5.18, N 8.00; found C 68.55, H 5.33, N 7.95.

Ethyl (4*S*,5*S*)-5-Methyl-4-(4-nitrophenyl)-2-phenyl-1,3-oxazoline-2-carboxylate (2ca): Yield: 269 mg, 76%; oil. $[a]_D^{20} = +36.2$ ($c = 1.100$, CHCl_3); analytical data identical to that of **2ba**.

Ethyl (4*S*,5*S*)-5-Methyl-4-(2-chloro-4-nitrophenyl)-2-phenyl-1,3-oxazoline-4-carboxylate (6ca): Yield: 300 mg, 77%; oil. $[a]_D^{20} = -229.1$ ($c = 1.150$, CHCl_3); analytical data identical to that of **6ba**.

Ethyl (4*S*,5*S*)-5-Methyl-4-(3-cyano-4-nitrophenyl)-2-phenyl-1,3-oxazoline-4-carboxylate (10ca): Yield: 265 mg, 70%; oil. $[a]_D^{20} = -51.0$ ($c = 1.100$, CHCl_3); analytical data identical to that of **10ba**.

Ethyl (4*S*,5*S*)-5-Methyl-4-(4-hydroxyphenyl)-2-phenyl-1,3-oxazoline-4-carboxylate (2cb): Yield: 188 mg, 58%; white crystals; m.p.

178–180 °C. $[a]_D^{20} = +13.9$ ($c = 1.000$, CHCl_3); analytical data identical to that of **2bb**.

Ethyl (4*S*,5*S*)-5-Methyl-4-(2-chloro-4-hydroxyphenyl)-2-phenyl-1,3-oxazoline-4-carboxylate (6cb): Yield: 252 mg, 70%; white crystals; m.p. 146–147 °C. $[a]_D^{20} = +189.0$ ($c = 0.900$, CHCl_3); analytical data identical to that of **6bb**.

Ethyl (4*S*,5*S*)-5-Methyl-4-(2-cyano-4-hydroxyphenyl)-2-phenyl-1,3-oxazoline-2-carboxylate (11cb): Yield: 207 mg, 58%; white crystals; m.p. 118–119 °C. $[a]_D^{20} = +119.1$ ($c = 1.000$, CHCl_3); analytical data identical to that of **11bb**.

Ethyl Ester of *N*-Benzoyl- α -(4-nitrophenyl)-D-allo-threonine (2bac): Yield: 279 mg, 75%; solidifying oil. $[a]_D^{20} = -31.5$ ($c = 0.275$, CHCl_3). IR (film, CH_2Cl_2): $\tilde{\nu} = 3386, 2983, 1825, 1653, 1522, 1349, 1271, 1109$ cm^{-1} . ^1H NMR (400 MHz, CDCl_3): $\delta = 8.16$ (d, $J = 8.9$ Hz, 2 H), 7.93 (d, $J = 8.9$ Hz), 7.81–7.92 (m, 2 H), 7.56–7.49 (m, 1 H), 7.42 (t, $J = 7.8$ Hz, 2 H), 6.03 (q, $J = 6.3$ Hz, 1 H, CH-CH_3), 4.31–4.16 (m, 2 H, $-\text{OCH}_2\text{CH}_3$), 1.42 (d, $J = 6.3$ Hz, 3 H, CHCH_3), 1.26 (t, $J = 7.1$ Hz, 3 H, $-\text{OCH}_2\text{CH}_3$) ppm. ^{13}C NMR (100 MHz, CDCl_3): $\delta = 171.5, 168.2, 147.7, 143.5, 133.3, 129.1, 128.4, 127.7, 127.3, 123.3, 74.1, 67.0, 62.4, 19.2, 15.3$ ppm. LRMS (ESI⁺): $m/z = 373$ [$\text{M} + \text{H}$]⁺. $\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}_6$ (372.38): calcd. C 61.28, H 5.41, N 7.52; found C 61.56, H 5.46, N 7.42.

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