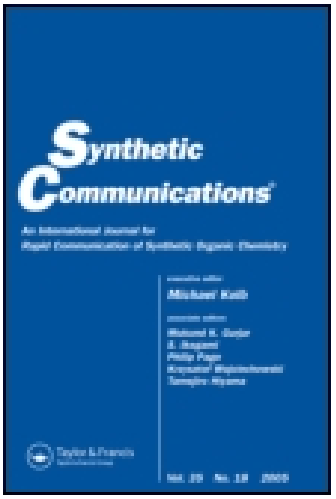

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Remarkable Stereocontrol in 1,3-Dipolar Cycloaddition of Acyclic Nitrones: Investigation of the Cycloaddition of C,N-Diaryl Nitrones to Methyl Cinnamate Under Different Reaction Conditions

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REMARKABLE STEREOCONTROL IN 1,3-DIPOLAR CYCLOADDITION OF ACYCLIC NITRONES: INVESTIGATION OF THE CYCLOADDITION OF *C,N*-DIARYL NITRONES TO METHYL CINNAMATE UNDER DIFFERENT REACTION CONDITIONS

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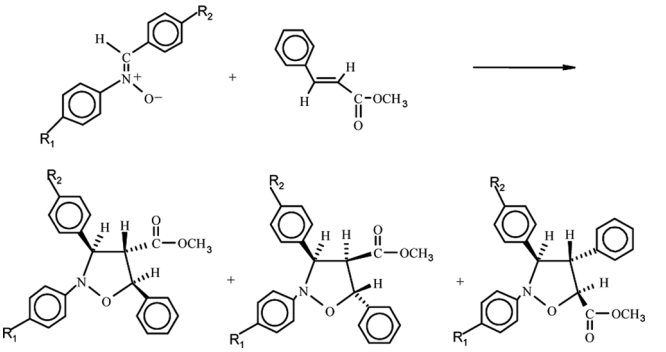
GRAPHICAL ABSTRACT



Abstract *Investigation of the cycloaddition of* C,N-*diarylnitrones to methyl cinnamate under different reaction conditions were carried out. Two diastereoisomeric and one regioisomeric cycloadducts were isolated and characterized by spectroscopic and x-ray data. Remarkable change in selectivity was noticed in solvent-free condition and in the presence of ytterbium triflate as catalyst.*

Keywords Cycloaddition; isoxazolidine; methyl cinnamate; nitrone; ytterbium triflate

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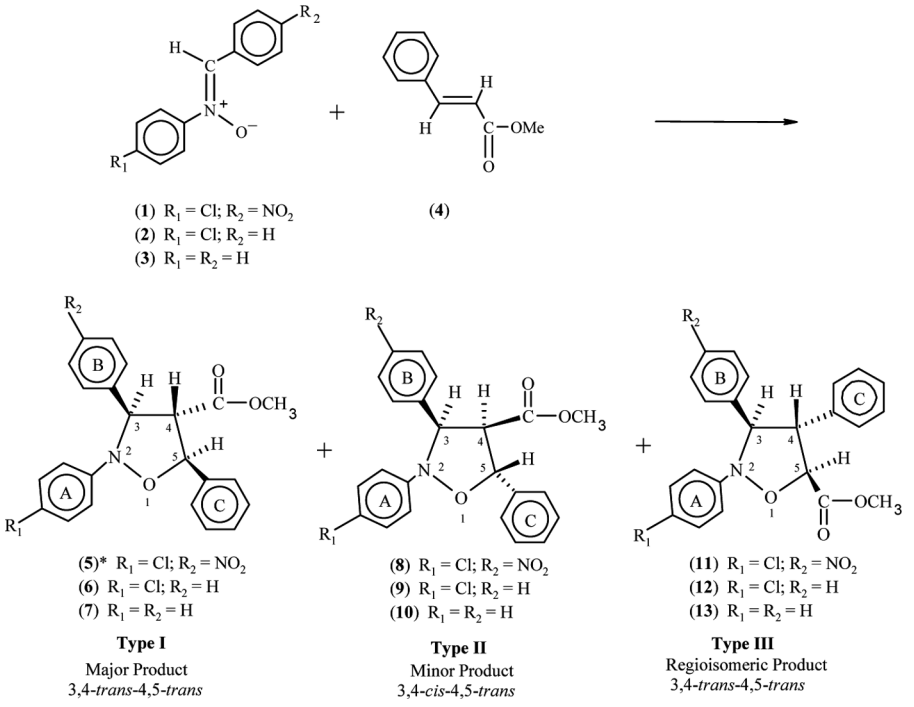
INTRODUCTION

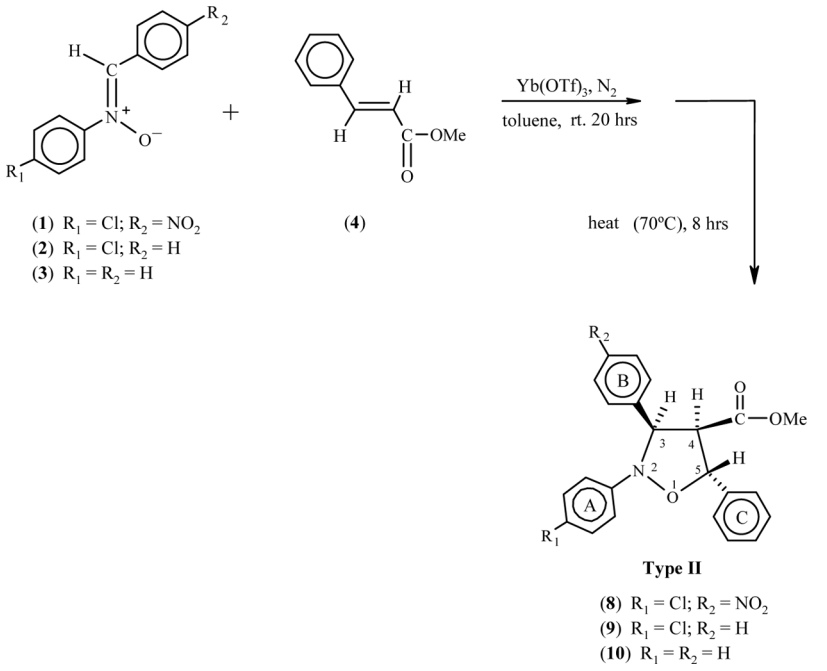
The 1,3-dipolar cycloaddition (1,3-DC) of nitrones to electron-deficient olefins is the best procedure for the synthesis of isoxazolidines.[1–4] By exploiting this strategy as the key step, several classes of biologically active compounds as well as natural products have been synthesized.[2–5] As a part of our investigation in this particular field,[6–11] we have recently carried out the $\pi^4s + \pi^2s$ cycloaddition of *C,N*-diaryl nitrones to methyl cinnamate under different conditions. The main objective of this investigation was to study the regio- and stereochemical courses of nitrone cycloaddition reaction to 1,2-disubstituted olefin as well as the substitution effect on the aryl ring of the substrate. The effect of rare-earth triflate (yitterbium triflate) as catalyst on 1,3-DC of nitrones has also been studied. This article gives a concise report of this investigation.

RESULTS AND DISCUSSION

Three nitrones [viz., *C*-(4-nitrophenyl)-*N*-(4′-chlorophenyl), *C*-phenyl-*N*-(4-chlorophenyl) and *C,N*-diphenyl nitrone] were chosen for the present cycloaddition studies. A total of 12 reactions were carried out under different reaction conditions (Schemes 1 and 2). The nitrones were initially synthesized by the conventional



Scheme 1. Reaction conditions: (i) in refluxing toluene (~110 °C); molar ratio nitrone/methyl cinnamate 1:3; time 15 h, nitrogen atmosphere; and (ii) solvent-free condition; molar ratio nitrone/methyl cinnamate 1:5; temperature ~110 °C, time 4 h, nitrogen atmosphere. *Corresponding carbocyclic acid (**5a**) was obtained.



(**1**) $R_1 = Cl$; $R_2 = NO_2$
(**2**) $R_1 = Cl$; $R_2 = H$
(**3**) $R_1 = R_2 = H$

(**4**)

Type II

(**8**) $R_1 = Cl$; $R_2 = NO_2$
(**9**) $R_1 = Cl$; $R_2 = H$
(**10**) $R_1 = R_2 = H$

Scheme 2. 1,3-Dipolar cycloaddition of C,N-diaryl nitrones to methyl cinnamate in the presence of $Yb(OTf)_3$.

procedure of heating the corresponding hydroxylamines with the appropriate aldehydes in ethanol. Subsequently, an improved microwave-assisted procedure similar to that developed by the authors for the *C*-aryl-*N*-methyl nitrones[11] was used.

1,3-DC of *C*-(4-nitrophenyl)-*N*-(4′-chlorophenyl) nitrone to methyl cinnamate was performed in the usual way in refluxing toluene (~110 °C) and also in solvent-free conditions at 110 °C, with excess of the dipolarophile. When the reaction was carried out in refluxing toluene, three-fold molar excess of the dipolarophile was used to enhance the reaction rates and hence yields in 15 h. This afforded a mixture of diastereoisomeric products (types **I**, **II**) and small amounts of regioisomaric product (type **III**). The same reaction was performed under solvent-free conditions for about 4 h, resulting only one compound (type **I**). The all-*trans* isomer (type **I**) was the major product isolated from all the reactions [condition (i), Scheme 1]. The diastereoisomeric 3,4-*cis* 4,5-*trans* (type **II**) 5-aryl-4-carbomethoxyisoxazolidine and the regioisomeric (type **III**) 4-aryl-5-carbomethoxyisoxazolidine were isolated as minor products from the reaction where toluene used as solvent. The product ratio was found to be as 85:8:7 (**5a**/**8**/**11**), but in solvent-free conditions only the all-*trans* product was obtained. An identical protocol was followed for the reactions between the other two nitrones (**2** and **3**) with methyl cinnamate (**4**) either in solvent (toluene) or in solvent-free conditions, and the same result was obtained.

All the isolated products showed ester bands at 1736–1706 cm^{-1} in their respective infrared (IR) spectra. The three types of cycloadducts (viz., type **I**,

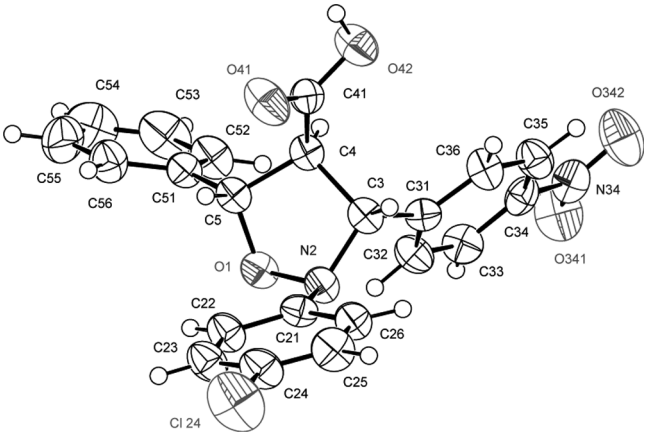


Figure 1. X-ray crystallographic structure (ORTEP projection) of **5a**.

type **II**, and type **III**) could be differentiated from their ^{1}H and ^{13}C NMR characteristics. The C(3)H appeared at δ 5.54 ppm in **5a** and δ 5.72 ppm in **8**. C(4)H were shielded by ~2.0 and 1.85 ppm respectively, compared to **5a** in which the benzylic H-4 (triplet) was deshielded by ~1.0 ppm. These relationships were typical of all the compounds belonging to different series.

The x-ray crystallographic analysis of the representative compound of type **I** (viz., **5a**) showed (ORTEP projection, Fig. 1) that it had a carboxyl group at C-4, and 3,4-*trans* configuration between H-3 and H-4 protons and also *trans* configuration between H-4 and H-5 protons. Thus the inferences regarding the relative stereochemistry of **5a** made from the magnitude of the NMR coupling constant in the isoxazolidine ring are fully supported by x-ray crystallographic data. Interestingly, compound **5a** exists in intermolecular association as a classic head-to-head dimer (PLUTO projection, Fig. 2) via hydrogen bonding of the carboxylate group. The relative configuration of the minor cycloadducts [viz., 3,4-*cis* (type **II**) and the

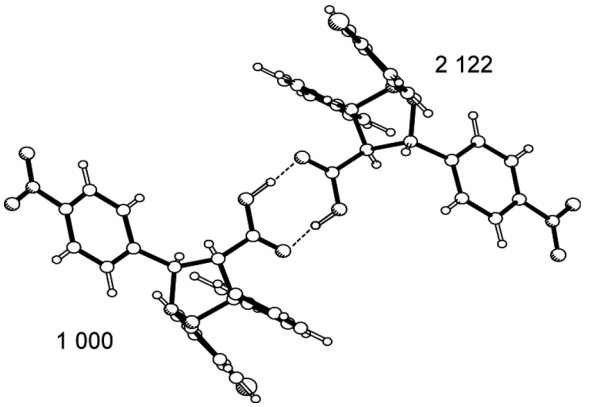


Figure 2. X-ray crystallographic structure (PLUTO projection) of **5a** (dimer).

regioisomer of type **I** (i.e., type **III**)] were obtained on the basis of NMR comparisons with the similar cycloadducts derived from *C*-aryl-*N*-phenyl nitrones,[10,11] for which the x-ray crystallographic analysis was performed.

The all-*trans* isomer is obtained by the favorable *endo*-mode of approach of the dipolarophile with respect to the carbonyl group. Several publications have analyzed the regioselectivity and diastereoselectivity of the 1,3-dipolar cycloadditions of nitrones on the basis of frontier molecular orbital (FMO) interactions.[12–15] Most authors have explained the favored *endo*-mode of approach, with respect to the carbonyl group, to be due to favorable secondary orbital interactions. Accordingly, type **I** should be the major product, which gets support from our experimental findings when the cycloadditions were carried out in solvent (toluene). On the other hand, our experimental results seem to indicate that steric and dipolar factors, which favor exclusively the all-*trans*-cycloadduct, might play a significant role in the transition state, resulting in type **I** cycloadducts as the sole products in each of the three cases.

In addition to these reactions, the effect of rare-earth triflate (ytterbium triflate) as catalyst on 1,3-DC of nitrones has been studied. As of now, very little information[16,17] exists on this aspect of 1,3-DCs; hence, to study the effect of ytterbium triflate (20 mol% of nitrone) as a catalyst, the following cycloadditions were performed.

Cycloadition of *C*-(4-nitrophenyl)-*N*-(4′-chlorophenyl) nitrone (**1**) with methyl cinnamate in the presence of $Yb(OTf)_3$ (20 mol% of nitrone) was carried out both in solvent (toluene) and solvent-free conditions. In both cases, only one compound (**8**) corresponding to type **II** was identified, which could be confirmed from the chemical shift, and the coupling values of H-3 (5.72 ppm, $J_{3,4} = 9.6$ Hz) and H-5 (5.05 ppm, $J_{4,5} = 10.2$ Hz) indicated the 3,4-*cis*, 4,5-*trans* configuration for this regioisomeric compound (**8**).

Following a similar sequence, the reactions of *C*-phenyl-*N*-(*4*-chlorophenyl) nitrone (**2**) and *C*-phenyl-*N*-phenyl nitrone (**3**) with methyl cinnamate in the presence of $Yb(OTf)_3$ in dry toluene afforded only type **II** compounds (**9** and **10**, respectively). The nonaromatic protons H-3 and H-5 of compound **9** appeared at δ 5.37 ppm and δ 5.17 ppm respectively as doublets [$J_{3,4} = 8.7$ Hz and $J_{4,5} = 6.6$ Hz], and for compound **10** H-3 appeared at δ 5.39 ppm and H-5 appeared δ 5.24 ppm, both as doublets [$J_{3,4} = 8.7$ Hz and $J_{4,5} = 9.5$ Hz respectively]. The coupling constant values $J_{3,4}$ of H-3 and H-4 protons confirm compounds **9** and **10** to be the *cis* isomer.

In conclusion, a critical study regarding the regio- and stereoselectivity in the 1,3-DC of three acyclic nitrones with methyl cinnamate has been carried out, which revealed the following: (i) Uncatalyzed thermal reaction (a) in solvent (toluene) yields type **I** cycloadducts as the major isomer, in addition to the stereoisomeric type **II** and regioisomeric type **III** cycloadducts as minor products, (b) in solvent-free conditions, type **I** cycloadducts are obtained as sole products; that is, the reaction becomes regio- as well as stereoselective. This may be because the all-*trans* isomer (i.e., type **I**) is obtained by the favorable *endo*-mode of approach of the dipolarphile with respect to the carbonyl group, stabilized further by favorable secondary orbital interactions. (ii) In the presence of ytterbium triflate [$Yb(OTf)_3$] as a catalyst (20 mol% of nitrone) and in the presence of solvent

and solvent-free conditions, type **II** cycloadducts were obtained as the sole products in all the cases. The probable reason may be like that the reaction is primarily controlled by the interaction between highest occupied molecular orbital $(HOMO)_{nitrone}$ and lowest unoccupied molecular orbital $(LUMO)_{dipolarophile}$. By the application of ytterbium triflate, a Lewis acid catalyst that acts as an electron acceptor, the LUMO energy of the dipolarophile was lowered by coordination of the α,β-unsaturated carbonyl to the ytterbium triflate. As a result of the decreased energy gap between the interacting FMOs, a rate acceleration of the reaction is achieved. The selectivity may also be due to this concomitant coordination. So, with 1,3-dipolar cycloaddition in the presence of ytterbium triflate, the selectivity of the reaction changed significantly, and the *endo*- type **II** was obtained as a single diastereoisomer. Most recently, Ess and Houk reported[18] that the energy to distort the 1,3-dipole and dipolarophile to the transition-state geometry is the major factor that actually controls reactivity differences of 1,3-dipoles. Interaction energies between the 1,3-dipole and the dipolarophile differentiate reactivity for a series of substituted alkenes when the distortion energies are nearly constant.

EXPERIMENTAL

Melting points were recorded on a Köfler block apparatus and are uncorrected. Neutral alumina was used for column chromatography, and silica gel (60–120 mesh) was used for thin-layer chromatography (TLC). Petrol refers to the petroleum ether AR (bp 60–80 °C). Analytical samples were routinely dried over $CaCl_2$ in vacuo at room temperature. IR spectra were recorded in KBr pellets with a Perkin-Elmer RX-1 Fourier transform (FT)-IR, and ultraviolet spectra were measured in spectroscopic-grade ethanol (Merck) with a Hitachi U-3501 instrument. Elemental analysis (C, H, N) were conducted using the Perkin-Elmer 2400 series II elemental analyzer, and their results were found to be in good agreement (±0.2%) with the calculated values for C, H, and N. ^{1}H NMR (300 MHz) and ^{13}C NMR (75.5 MHz) were recorded in $CDCl_3$ and dimethylsulfoxide (DMSO)-d_6 solution with a Bruker AM-300L spectrometer (chemical shift in δ ppm and *J* in hertz).

The compound *N*-(4-chlorophenyl)hydroxylamine, mp 89–90 °C, was prepared from 4-chloronitrobenzene by adopting the method used for obtaining *N*-phenylhydroxylamine from nitrobenzene.[19] Initially the nitrones were prepared as described in our early communications.[9–11] The *C*-aryl-*N*-(4′-chlorophenyl) nitrones were also synthesized by a more convenient method using microwave irradiation techniques from the appropriate aromatic aldehyde and *N*-(4′-chlorophenyl)hydroxylamine. This improved procedure was similar to that developed by the authors for *C*-aryl-*N*-methyl nitrones.[11] In this procedure, the aromatic aldehyde was taken with a small excess of *N*-(4-chlorophenyl)hydroxylamine (1:1.2 molar ratio) in dry dichloromethane in an Erlenmeyer flask. The reaction mixture was subjected to microwave irradiation for periods varying from 1–4 min (yield 91.5%). At the end of the reaction period, the postreaction mixture was worked up, and the residue was analyzed by ^{1}H NMR. The nitrones were crystallized from ethanol, methanol, or petrol–benzene mixture and characterized from their FT-IR, ^{1}H NMR, and ^{13}C NMR spectra.

General Method for the Reaction of Nitrones (1–3) with Methyl Cinnamate

A hot solution of nitrones **1**–**3** (0.0066 mol) in anhydrous toluene (20 ml) was added to a solution of methyl cinnamate (3×0.0066 mol) in anhydrous toluene (20 ml). In solvent-free conditions, the nitrone **1** (0.0022 mol) was directly added to methyl cinnamate (5×0.0022 mol). The reaction mixture was refluxed under a nitrogen atmosphere for 4–15 h. The reaction was monitored by TLC and by ^{1}H NMR analyses. The solvent was removed from the crude reaction mixture, and the mixture was chromatographed over neutral alumina to separate the products. In the catalytic reactions, both in solvent and solvent-free conditions, ytterbium triflate (20 mol% of nitrone) was used.

Reaction of *C*-(4-Nitrophenyl)-*N*-(4′-chlorophenyl) Nitrone (1) with Methyl Cinnamate (4) in Refluxing Toluene

3*RS*-(3*R,4*S**,5*R**)-2-(4′-Chlorophenyl)-3-(4′′-nitrophenyl)-5-phenyl-4-carboxyisoxazolidine (5a).** $C_{22}H_{17}N_2O_5Cl$, white crystals, mp 192 °C, yield: 1.63 g (85%). IR: $\nu = 2931$, 2830 (m, aliphatic –CH– stretching), 1706 (s, carboxylic acid >C=O), 1522, 1340 (s, aromatic $-NO_2$), 1097 (m, aryl-Cl), 834 (m, 1,4-disubstituted benzene ring), 757, 694 (m, monosubstituted benzene ring) cm^{-1}; UV: λ_{max} (log ε) = 253 (4.37) nm; ^{1}H NMR (DMSO-d_6, δ, 300 MHz): 5.54 (1H, d, $J = 8.4$, H-3), 3.54 (1H, dd, $J = 8.4$, 8.7, H-4), 5.33 (1H, d, $J = 8.7$, H-5), 7.10 (2H, d, $J = 9.0$, A,H-2,6), 7.35 (2H, d, $J = 9.0$, A,H-3,5), 7.82 (2H, d, $J = 8.7$, B,H-2,6), 8.26 (2H, d, $J = 8.7$, B,H-3,5), 7.36–7.39 (5H, m, C,H-2,3,4,5,6) ppm; ^{13}C NMR (DMSO-d_6, δ, 75.5 MHz): 72.3 (C-3), 65.0 (C-4), 83.1 (C-5), 171.1 (>C=O), 149.3 (A,C-1), 115.9 (A,C-2,6), 127.9 (A,C-3,5), 136.0 (A,C-4), 147.1 (B,C-1), 127.3 (B,C-2,6), 124.1 (B,C-3,5), 149.2 (B,C-4), 125.9 (C,C-1), 128.7 (C,C-2,6), 129.9 (C,C-3,5), 129.1 (C,C-4) ppm. The structure has been finally confirmed[18] by x-ray crystallographic analysis. Anal. calcd. for $C_{22}H_{17}N_2O_5Cl$: C, 63.11; H, 4.40; N, 6.38. Found: C, 62.98; H, 4.31; N, 6.33.

1*RS*-(1*R,2*R**,3*S**)-1′-[*N*-Hydroxy-*N*-(*4*-chlorophenyl) amino]-1′-(4′-nitrophenyl)-3-hydroxy-2-phenyl propanoyl cinnamate (8).** $C_{23}H_{21}N_2O_6Cl$, colorless solid, mp 175 °C, yield: 0.22 g (8.0%). IR: $\nu = 3420$–3340 (m, -OH), 2934, 2825 (m, aliphatic –CH– stretching), 1726 (s, ester >C=O), 1520, 1345 (s, aromatic $-NO_2$), 1090 (m, aryl-Cl), 830 (m, 1,4-disubstituted benzene ring), 760, 690 (m, monosubstituted benzene ring) cm^{-1}; UV: λ_{max} (log ε) = 250 (4.35) nm; ^{1}H NMR ($CDCl_3$, δ, 300 MHz): 5.72 (1H, d, $J = 9.7$, H-3), 3.47 (1H, t, $J = 9.5$, H-4), 4.45 (1H, d, $J = 9.5$, H-5), 3.19 (3H, s, -OCH_3), 7.06 (1H, d, $J = 2.3$, >N-OH), 3.70 (1H, s, 5-OH), 6.77 (2H, d, J = 8.3, A,H-2,6), 7.65 (2H, d, $J = 8.3$, A,H-3,5), 7.74 (2H, d, $J = 8.7$, B,H-2,6), 8.30 (2H, d, $J = 8.7$, B,H-3,5), 7.34 (2H, dd, $J = 6.8$, 3.2, C,H-2,6), 6.98–6.95 (3H, m, C,H-3,4,5) ppm. ^{13}C NMR ($CDCl_3$, δ, 75.5 MHz): 72.0 (C-3), 65.5 (C-4), 83.5 (C-5), 51.25 (-OCH_3), 172.1 (>C=O), 150.0 (A,C-1), 115.0 (A,C-2,6), 127.0 (A,C-3,5), 136.5 (A,C-4), 147.4 (B,C-1), 127.4 (B,C-2,6), 124.3 (B,C-3,5), 149.0 (B,C-4), 125.3 (C,C-1), 128.6 (C,C-2,6), 129.4 (C,C-3,5), 129.2 (C,C-4) ppm. Anal. calcd. for $C_{23}H_{21}N_2O_6Cl$: C, 60.52; H, 4.60; N, 6.14. Found: C, 60.30; H, 4.46; N, 6.21.

3*RS*-(3*R,4*S**5*R**)-2-(4-Chlorophenyl)-3-(4′-nitrophenyl)-4-phenyl-5-carbomethoxyisoxazolidine (11).** $C_{23}H_{19}N_2O_5Cl$, microcrystalline solid, mp 180 °C, yield: 0.1 g (7%). IR: $\nu = 2921$, 2853 (m, aliphatic –CH– stretching), 1734 (s, ester, >C=O), 1517, 1347 (s, aromatic $-NO_2$), 1095 (m, aryl-Cl), 816 (m, 1,4-disubstituted benzene ring), 701 (m, monosubstituted benzene ring) cm^{-1}; UV: λ_{max} log $\varepsilon) = 252$ (3.82) nm; ^1H NMR ($CDCl_3$, δ, 300 MHz): 5.03 (1H, d, $J = 7.4$, H-3), 3.25 (1H, t, $J = 7.8$, H-4), 4.97 (1H, d, $J = 8.3$, H-5), 3.16 (3H, s, -OCH_3), 6.33 (2H, d, $J = 8.8$, A,H-2,6), 6.97 (2H, d, $J = 8.8$, A,H-3,5), 7.47 (2H, d, $J = 8.7$, B,H-2,6), 8.08 (2H, d, $J = 8.7$, B,H-3,5), 7.27–7.19 (5H, m, C, H,2,3,4,5,6) ppm. ^{13}C NMR ($CDCl_3$, δ, 75.5 MHz): 74.16 (C-3), 59.26 (C-4), 85.0 (C-5), 51.64 (-OCH_3), 172.0 (>C=O), 147.0 (A,C-1), 115.3 (A,C-2,6), 128.2 (A,C-3,5), 135 (A,C-4), 143.0 (B,C-1), 126.6 (B,C-2,6), 123.7 (B,C-3,5), 146.5 (B,C-4), 128.3 (C,C-1), 127.8 (C,C-2,6), 129.1 (C,C-3,5), 129.0 (C,C-4) ppm. Anal. calcd. for $C_{23}H_{19}N_2O_5Cl$: C, 63.01; H, 4.37; N, 6.40. Found: C, 63.08; H, 4.42; N, 6.48.

Reaction of *C*-Phenyl-*N*-(4-chlorophenyl) Nitrone (2) with Methyl Cinnamate (4) in Refluxing Toluene

3*RS*-(3*R,4*S**,5*R**)-2-(4-Chlorophenyl)-3-phenyl-5-phenyl-4-carbomethoxyisoxazolidine (6).** $C_{23}H_{20}NO_3Cl$, white crystals, mp 180 °C, yield: 1.52 g (81%). IR: $\nu = 2929$, 2835 (m, aliphatic –CH– stretching), 1730 (s, ester >C=O), 1090 (m, aryl-Cl), 830 (m, 1,4-disubstituted benzene ring), 753, 692 (m, monosubstituted benzene ring) cm^{-1}; UV: λ_{max} (log $\varepsilon) = 251$ (4.32) nm; ^1H NMR ($CDCl_3$, δ, 300 MHz): 5.51 (1H, d, $J = 8.1$, H-3), 3.52 (1H, dd, $J = 8.1$, 8.5, H-4), 5.31 (1H, d, $J = 8.5$, H-5), 3.15 (3H, s, -OCH_3), 7.11 (2H, d, $J = 8.9$, A,H-2,6), 7.32 (2H, d, $J = 8.9$, A,H-3,5), 7.52 (2H, d, $J = 8.1$, B,H-2,6), 7.30–7.40 (3H, m, B,H-3,4,5), 7.32–7.42 (5H, m, C,H-2,3,4,5,6) ppm; ^{13}C NMR ($CDCl_3$, δ, 75.5 MHz): 72.1 (C-3), 65.2 (C-4), 83.3 (C-5), 50.62 (-OCH_3), 172.1 (>C=O), 149.1 (A,C-1), 115.2 (A,C-2,6), 127.3 (A,C-3,5), 136.2 (A,C-4), 147.3 (B,C-1), 127.5 (B,C-2,6), 124.5 (B,C-3,5), 128.2 (B,C-4), 125.4 (C,C-1), 128.2 (C,C-2,6), 129.2 (C,C-3,5), 129.5 (C,C-4) ppm. Anal. calcd. for $C_{23}H_{20}NO_3Cl$: C, 70.14; H, 5.12; N, 3.56. Found: C, 69.91; H, 5.10; N, 3.48.

3*RS*-(3*R,4*R**,5*S**)-2-(4-Chlorophenyl)-3-phenyl-5-phenyl-4-carbomethoxyisoxazolidine (9).** $C_{23}H_{20}NO_3Cl$, colorless solid; mp 172 °C; yield: 0.20 g (6.8%). IR: $\nu = 2932$, 2822 (m, aliphatic –CH– stretching), 1723 (s, ester >C=O), 1091 (m, aryl-Cl), 832 (m, 1,4-disubstituted benzene ring), 761, 692 (m, monosubstituted benzene ring) cm^{-1}; UV: λ_{max} (log $\varepsilon) = 251$ (4.36) nm; ^1H NMR ($CDCl_3$, δ, 300 MHz): 4.72 (1H, d, $J = 9.6$, H-3), 3.46 (1H, t, $J = 9.2$, H-4), 4.43 (1H, d, $J = 9.2$, H-5), 3.17 (3H, s, -OCH_3), 6.75 (2H, d, $J = 8.1$, A,H-2,6), 7.62 (2H, d, $J = 8.1$, A,H-3,5), 7.72 (2H, d, $J = 8.3$, B,H-2,6), 7.28–7.39 (3H, m, B,H-3,4,5), 7.32 (2H, dd, $J = 6.6$, 3.1, C,H-2,6), 6.96–6.93 (3H, m, C,H-3,4,5) ppm. ^{13}C NMR ($CDCl_3$, δ, 75.5 MHz): 72.1 (C-3), 65.4 (C-4), 83.3 (C-5), 51.23 (-OCH_3), 172.0 (>C=O), 150.1 (A,C-1), 115.2 (A,C-2,6), 127.2 (A,C-3,5), 136.4 (A,C-4), 147.2 (B,C-1), 127.2 (B,C-2,6), 124.1 (B,C-3,5), 149.2 (B,C-4), 125.2 (C,C-1), 128.3 (C,C-2,6), 129.2 (C,C-3,5), 129.3 (C,C-4) ppm. Anal. calcd. for $C_{23}H_{20}NO_3Cl$: C, 70.14; H, 5.12; N, 3.56. Found: C, 69.88; H, 5.06; N, 3.51.

3*RS*-(3*R,4*S**5*R**)-2-(4-Chlorophenyl)-3,4-diphenyl-5-carbomethoxyisoxazolidine (12).** $C_{23}H_{20}NO_3Cl$, microcrystalline solid, mp 175 °C, yield: 0.12 g (5.4%). IR: $\nu = 2918$, 2845 (m, aliphatic –CH– stretching), 1730 (s, ester, >C=O), 1090 (m, aryl-Cl), 814 (m, 1,4-disubstituted benzene ring), 705 (m, monosubstituted benzene ring) cm^{-1}; UV: λ_{max} (log ε) = 250 (3.80) nm; ^1H NMR ($CDCl_3$, δ, 300 MHz): 5.01 (1H, d, $J = 7.2$, H-3), 3.22 (1H, t, $J = 7.6$, H-4), 4.95 (1H, d, $J = 8.1$, H-5), 3.14 (3H, s, -OC*H*$_3$), 6.31 (2H, d, $J = 8.6$, A,H-2,6), 6.93 (2H, d, $J = 8.6$, A,H-3,5), 7.43 (2H, d, $J = 8.4$, B,H-2,6), 7.27–7.39 (3H, m, B,H-3,4,5), 7.25–7.22 (5H, m, C, H,2,3,4,5,6) ppm. ^{13}C NMR ($CDCl_3$, δ, 75.5 MHz): 74.14 (C-3), 59.23 (C-4), 85.3 (C-5), 51.62 (-OC*H*$_3$), 172.5 (>C=O), 147.2 (A,C-1), 115.5 (A,C-2,6), 128.4 (A,C-3,5), 136 (A,C-4), 143.3 (B,C-1), 126.4 (B,C-2,6), 123.5 (B,C-3,5), 146.2 (B,C-4), 128.2 (C,C-1), 127.5 (C,C-2,6), 129.0 (C,C-3,5), 129.2 (C,C-4) ppm. Anal. calcd. for $C_{23}H_{20}NO_3Cl$: C, 70.14; H, 5.12; N, 3.56. Found: C, 69.85; H, 5.02; N, 3.48.

Reaction of *C,N*-Diphenyl Nitrone (3) with Methyl Cinnamate (4) in Refluxing Tolune

3*RS*-(3*R,4*S**,5*R**)-2,3,5-Triphenyl-4-carbomethoxyisoxazolidine (7).** $C_{23}H_{21}NO_3$, white crystals, mp 175 °C, yield: 1.50 g (80%). IR: $\nu = 2931$, 2830 (m, aliphatic –CH– stretching), 1715 (s, ester >C=O), 750, 690 (m, mono-substituted benzene ring) cm^{-1}; UV: λ_{max} (log ε) = 252 (4.33) nm; ^1H NMR ($CDCl_3$, δ, 300 MHz): 5.52 (1H, d, $J = 8.2$, H-3), 3.53 (1H, dd, $J = 8.2$, 8.5, H-4), 5.32 (1H, d, $J = 8.5$, H-5), 3.19 (3H, s, -OC*H*$_3$), 7.15 (2H, d, $J = 9.2$, A,H-2,6), 7.12–7.22 (3H, m, A,H-3,4,5), 7.35 (2H, d, $J = 8.2$, B,H-2,6), 7.25–7.32 (3H, m, B,H-3,4,5), 7.31–7.35 (5H, m, C,H-2,3,4,5,6) ppm; ^{13}C NMR ($CDCl_3$, δ, 75.5 MHz): 72.1 (C-3), 65.2 (C-4), 83.2 (C-5), 50.25 (-OCH_3), 172.3 (>C=O), 149.1 (A,C-1), 115.7 (A,C-2,6), 127.5 (A,C-3,5), 136.2 (A,C-4), 147.3 (B,C-1), 127.1 (B,C-2,6), 124.3 (B,C-3,5), 149.3 (B,C-4), 125.7 (C,C-1), 128.5 (C,C-2,6), 129.7 (C,C-3,5), 129.2 (C,C-4) ppm. Anal. calcd. for $C_{23}H_{21}NO_3$: C, 76.86; H, 5.89; N, 3.89. Found: C, 76.76; H, 5.81; N, 3.79.

3*RS*-(3*R,4*R**,5*S**)-2,3,5-Triphenyl-4-carbomethoxyisoxazolidine (10).** $C_{23}H_{21}NO_3$, Colorless solid, mp 160 °C, yield: 0.21 g (6.5%). IR: $\nu = 2930$, 2820 (m, aliphatic –CH– stretching), 1720 (s, ester >C=O), 761, 691 (m, monosubstituted benzene ring) cm^{-1}; UV: λ_{max} (log ε) = 252 (4.35) nm; ^1H NMR ($CDCl_3$, δ, 300 MHz); 4.77 (1H, d, $J = 9.5$, H-3), 3.45 (1H, t, $J = 9.3$, H-4), 4.43 (1H, d, $J = 9.3$, H-5), 3.17 (3H, s, -OC*H*$_3$), 6.77 (2H, d, $J = 8.1$, A,H-2,6), 7.15–7.21 (3H, m, A,H-3,4,5), 7.72 (2H, d, $J = 8.3$, B,H-2,6), 7.30–7.36 (3H, m, B,H-3,4,5), 7.32 (2H, dd, $J = 6.6$, 3.1, C,H-2,6), 6.96–6.93 (3H, m, C,H-3,4,5) ppm. ^{13}C NMR ($CDCl_3$, δ, 75.5 MHz): 72.1 (C-3), 65.3 (C-4), 83.3 (C-5), 51.22 (-OCH_3), 172.2 (>C=O), 150.1 (A,C-1), 115.2 (A,C-2,6), 127.3 (A,C-3,5), 136.2 (A,C-4), 147.3 (B,C-1), 127.2 (B,C-2,6), 124.1 (B,C-3,5), 149.2 (B,C-4), 125.1 (C,C-1), 128.3 (C,C-2,6), 129.3 (C,C-3,5), 129.2 (C,C-4) ppm. Anal. calcd. for $C_{23}H_{21}NO_3$: C, 76.86; H, 5.89; N, 3.89. Found: C, 76.79; H, 5.83; N, 3.82.

3*RS*-(3*R,4*S**,5*R**)-2,3,4-Triphenyl-5-carbomethoxyisoxazolidine (13).** $C_{23}H_{21}NO_3$, microcrystalline solid, mp 182 °C, yield: 0.13 g (5.5%). IR: $\nu = 2921$,

2855 (m, aliphatic –CH– stretching), 1731 (s, ester, >C=O), 703 (m, mono-substituted benzene ring) cm^{-1}; UV: λ_{max} (log ε) = 253 (3.83) nm; ^1H NMR ($CDCl_3$, δ, 300 MHz): 5.13 (1H, d, $J = 7.5$, H-3), 3.22 (1H, t, $J = 7.6$, H-4), 4.95 (1H, d, $J = 8.2$, H-5), 3.16 (3H, s, -OCH_3), 6.30 (2H, d, $J = 8.6$, A,H-2,6), 7.31–7.41 (3H, m, A,H-3,4,5), 7.45 (2H, d, $J = 8.4$, B,H-2,6), 7.25–7.33 (3H, m, B,H-3,4,5), 7.23–7.19 (5H, m, C, H,2,3,4,5,6) ppm. ^{13}C NMR ($CDCl_3$, δ, 75.5 MHz): 74.15 (C-3), 59.24 (C-4), 85.3 (C-5), 51.63 (-OCH_3), 172.5 (>C=O), 147.6 (A,C-1), 115.6 (A,C-2,6), 128.4 (A,C-3,5), 137.0 (A,C-4), 143.2 (B,C-1), 126.3 (B,C-2,6), 123.5 (B,C-3,5), 146.2 (B,C-4), 128.1 (C,C-1), 127.5 (C,C-2,6), 129.3 (C,C-3,5), 129.2 (C,C-4) ppm. Anal. calcd. for $C_{23}H_{21}NO_3$: C, 76.86; H, 5.89; N, 3.89. Found: C, 76.82; H, 5.84; N, 3.81.

Reaction of *C*-(4-Nitrophenyl)-*N*-(4′-chlorophenyl) Nitrone (1) with Methyl Cinnamate (4) in Solvent-Free Conditions

3*RS*-(3*R,4*S**,5*R**)-2-(4-Chlorophenyl)-3-(4′-nitrophenyl)-5-phenyl-4-carbomethoxyisoxazolidine (5).** $C_{23}H_{19}N_2O_5Cl$, white crystals, mp 130 °C, yield: 0.86 g (90%). IR: $\nu = 2954$, 2830 (m, aliphatic –CH– stretching), 1736 (s, ester, >C=O), 1495, 1343 (s, aromatic –NO_2), 1100 (m, aryl –Cl), 825 (m, 1,4-disubstituted benzene ring), 749, 695 (m, monosubstituted benzene ring) cm^{-1}; UV: λ_{max} (log ε) = 250 (4.22) nm; ^1H NMR ($CDCl_3$, δ, 300 MHz): 5.41 (1H, d, $J = 8.5$, H-3), 3.53 (1H, dd, $J = 8.5$, 6.1, H-4), 5.35 (1H, d, $J = 6.1$, H-5), 3.70 (3H, m, -OCH_3), 7.70 (2H, d, $J = 8.9$, A,H-2,6), 7.75 (2H, d, $J = 8.9$, A,H-3,5), 7.76 (2H, d, $J = 8.7$, B,H-2,6), 8.26 (2H, d, $J = 8.7$, B,H-3,5), 7.36–7.41 (5H, m, C,H-2,3,4,5,6) ppm; ^{13}C NMR ($CDCl_3$, δ, 75.5 MHz): 72.91 (C-3), 65.88 (C-4), 83.15 (C-5), 52.82 (-OCH_3), 170.2 (>C=O), 148.9 (A,C-1), 115.8 (A,C-2,6), 128.7 (A,C-3,5), 136.2 (A,C-4), 147.8 (B,C-1), 127.4 (B,C-2,6), 124.2 (B,C-3,5), 148.2 (B,C-4), 127.7 (C,C-1), 128.9 (C,C-2,6), 129.1 (C,C-3,5), 126.7 (C,C-4) ppm. Anal. calcd. for $C_{23}H_{19}N_2O_5Cl$: C, 63.01; H, 4.37, N, 6.40. Found: C, 62.95; H, 4.32; N, 6.34.

Reaction of *C*-Phenyl-*N*-(4-chlorophenyl) Nitrone (2) with Methyl Cinnamate (4) in Solvent-Free Conditions

3*RS*-(3*R,4*S**,5*R**)-2-(4-Chlorophenyl)-3-phenyl-5-phenyl-4-carbomethoxy-isoxazolidine (6).** $C_{23}H_{20}NO_3Cl$, white crystals, mp 180 °C; yield: 1.52 g (81%). IR: $\nu = 2929$, 2835 (m, aliphatic –CH– stretching), 1730 (s, ester >C=O), 1090 (m, aryl-Cl), 830 (m, 1,4-disubstituted benzene ring), 753, 692 (m, monosubstituted benzene ring) cm^{-1}; UV: λ_{max} (log ε) = 251 (4.32) nm; ^1H NMR ($CDCl_3$, δ, 300 MHz): 5.52 (1H, d, $J = 8.1$, H-3), 3.51 (1H, dd, $J = 8.1$, 8.5, H-4), 5.32 (1H, d, $J = 8.5$, H-5), 3.15 (3H, s, -OCH_3), 7.11 (2H, d, $J = 8.9$, A,H-2,6), 7.32 (2H, d, $J = 8.9$, A,H-3,5), 7.52 (2H, d, $J = 8.1$, B,H-2,6), 7.30–7.40 (3H, m, B,H-3,4,5), 7.32–7.42 (5H, m, C,H-2,3,4,5,6) ppm; ^{13}C NMR ($CDCl_3$, δ, 75.5 MHz): 72.2 (C-3), 65.1 (C-4), 83.2 (C-5), 50.62 (-OCH_3), 172.1 (>C=O), 149.1 (A,C-1), 115.2 (A,C-2,6), 127.3 (A,C-3,5), 136.2 (A,C-4), 147.3 (B,C-1), 127.5 (B,C-2,6), 124.5 (B,C-3,5), 128.2 (B,C-4), 125.4 (C,C-1), 128.2 (C,C-2,6), 129.2 (C,C-3,5), 129.5 (C,C-4) ppm. Anal. calcd. for $C_{23}H_{20}NO_3Cl$: C, 70.14; H, 5.12; N, 3.56. Found: C, 69.91; H, 5.10; N, 3.48.

Reaction of *C,N*-Diphenyl Nitrone (3) with Methyl Cinnamate (4) in Solvent-Free Conditions

***3RS*-(3*R**,4*S**,5*R**)-2,3,5-Triphenyl-4-carbomethoxyisoxazolidine (7).** $C_{23}H_{21}NO_3$, white crystals, mp: 175 °C; yield: 1.50 g (80%). IR: $\nu = 2931$, 2830 (m, aliphatic –CH– stretching), 1715 (s, ester >C=O), 750, 690 (m, monosubstituted benzene ring) cm^{-1}; UV: λ_{max} (log ε) = 252 (4.33) nm; ^{1}H NMR ($CDCl_3$, δ, 300 MHz): 5.52 (1H, d, $J = 8.2$, H-3), 3.51 (1H, dd, $J = 8.2$, 8.5, H-4), 5.32 (1H, d, $J = 8.5$, H-5), 3.19 (3H, s, -OC*H*$_3$), 7.15 (2H, d, $J = 9.2$, A,H-2,6), 7.12–7.22 (3H, m, A,H-3,4,5), 7.35 (2H, d, $J = 8.2$, B,H-2,6), 7.25–7.32 (3H, m, B,H-3,4,5), 7.31–7.35 (5H, m, C,H-2,3,4,5,6) ppm; ^{13}C NMR ($CDCl_3$, δ, 75.5 MHz): 72.1 (C-3), 65.2 (C-4), 83.2 (C-5), 50.25 (-OCH_3), 172.3 (>C=O), 149.1 (A,C-1), 115.7 (A,C-2,6), 127.5 (A,C-3,5), 136.2 (A,C-4), 147.3 (B,C-1), 127.1 (B,C-2,6), 124.3 (B,C-3,5), 149.3 (B,C-4), 125.7 (C,C-1), 128.5 (C,C-2,6), 129.7 (C,C-3,5), 129.2 (C,C-4) ppm. Anal. calcd. for $C_{23}H_{21}NO_3$: C, 76.86; H, 5.89; N, 3.89. Found: C, 76.76; H, 5.81; N, 3.79.

Reaction of *C*-(4-Nitrophenyl)-*N*-(4′-chlorophenyl) Nitrone (1) with Methyl Cinnamate (4) in the Presence of $Yb(OTf)_3$, Using Toluene as Solvent

1*RS*-(1*R,2*R**,3*S**)-1′-[*N*-Hydroxy-*N*-(4-chlorophenyl)amino]-1′-(4′-nitrophenyl)-3-hydroxy-2-phenyl propanoyl cinnamate (8).** $C_{23}H_{21}N_2O_6Cl$, colorless solid, mp 175 °C, yield: 0.22 g (7.0%). IR: $\nu = 3420$–3340 (m, -OH), 2934, 2825 (m, aliphatic –CH– stretching), 1726 (s, carboxylic acid >C=O), 1520, 1345 (s, aromatic –NO_2), 1090 (m, aryl-Cl), 830 (m, 1,4-disubstituted benzene ring), 760, 690 (m, monosubstituted benzene ring) cm^{-1}; UV: λ_{max} (log ε) = 250 (4.35) nm; ^{1}H NMR ($CDCl_3$, δ, 300 MHz): 4.78 (1H, d, $J = 9.7$, H-3), 3.48 (1H, t, $J = 9.5$, H-4), 4.46 (1H, d, $J = 9.5$, H-5), 3.19 (3H, s, -OC*H*$_3$), 7.06 (1H, d, $J = 2.3$, >N-OH), 3.70 (1H, s, 5-OH), 6.77 (2H, d, $J = 8.3$, A,H-2,6), 7.65 (2H, d, $J = 8.3$, A,H-3,5), 7.74 (2H, d, $J = 8.7$, B,H-2,6), 8.30 (2H, d, $J = 8.7$, B,H-3,5), 7.34 (2H, dd, $J = 6.8$, 3.2, C,H-2,6), 6.98–6.95 (3H, m, C,H-3,4,5) ppm. ^{13}C NMR ($CDCl_3$, δ, 75.5 MHz): 72.1 (C-3), 65.6 (C-4), 83.6 (C-5), 51.25 (-OCH_3), 172.1 (>C=O), 150.0 (A,C-1), 115.0 (A,C-2,6), 127.0 (A,C-3,5), 136.5 (A,C-4), 147.4 (B,C-1), 127.4 (B,C-2,6), 124.3 (B,C-3,5), 149.0 (B,C-4), 125.3 (C,C-1), 128.6 (C,C-2,6), 129.4 (C,C-3,5), 129.2 (C,C-4) ppm. Anal. calcd. for $C_{23}H_{21}N_2O_6Cl$: C, 60.52; H, 4.60; N, 6.14. Found: C, 60.30; H, 4.46; N, 6.21.

Reaction of *C*-Phenyl-*N*-(4-chlorophenyl) Nitrone (2) with Methyl Cinnamate (4) in the Presence of $Yb(OTf)_3$, Using Toluene as Solvent

3*RS*-(3*R,4*R**,5*S**)-2-(4-Chlorophenyl)-3-phenyl-5-phenyl-4-carbomethoxyisoxazolidine (9).** $C_{23}H_{20}NO_3Cl$, Colorless solid, mp 172 °C, yield: 0.20 g (6.8%). IR: $\nu = 2932$, 2822 (m, aliphatic –CH– stretching), 1723 (s, ester >C=O), 1091 (m, aryl-Cl), 832 (m, 1,4-disubstituted benzene ring), 761, 692 (m, monosubstituted benzene ring) cm^{-1}; UV: λ_{max} (log ε) = 251 (4.36) nm; ^{1}H NMR ($CDCl_3$, δ, 300 MHz); 4.71 (1H, d, $J = 9.6$, H-3), 3.45 (1H, t, $J = 9.2$, H-4), 4.44 (1H, d, $J = 9.2$, H-5), 3.17 (3H, s, -OC*H*$_3$), 6.75 (2H, d, $J = 8.1$, A,H-2,6), 7.62 (2H, d, $J = 8.1$, A,H-3,5), 7.72

(2H, d, $J = 8.3$, B,H-2,6), 7.28–7.39 (3H, m, B,H-3,4,5), 7.32 (2H, dd, $J = 6.6$, 3.1, C,H-2,6), 6.96–6.93 (3H, m, C,H-3,4,5) ppm. ^{13}C NMR ($CDCl_3$, δ, 75.5 MHz): 72.2 (C-3), 65.5 (C-4), 83.4 (C-5), 51.23 (-OCH_3), 172.0 (>C=O), 150.1 (A,C-1), 115.2 (A,C-2,6), 127.2 (A,C-3,5), 136.4 (A,C-4), 147.2 (B,C-1), 127.2 (B,C-2,6), 124.1 (B,C-3,5), 149.2 (B,C-4), 125.2 (C,C-1), 128.3 (C,C-2,6), 129.2 (C,C-3,5), 129.3 (C,C-4) ppm. Anal. calcd. for $C_{23}H_{20}NO_3Cl$: C, 70.14; H, 5.12; N, 3.56. Found: C, 69.88; H, 5.06; N, 3.51.

Reaction of *C,N*-Diphenyl Nitrone (3) with Methyl Cinnamate (4) in the Presence of Yb(OTf)$_3$, Using Toluene as Solvent

3*RS*-(3*R,4*R**,5*S**)-2,3,5-Triphenyl-4-carbomethoxyisoxazolidine (10).** $C_{23}H_{21}NO_3$, colorless solid, mp 160 °C, yield: 0.21 g (6.5%). IR: $\nu = 2930$, 2820 (m, aliphatic –CH– stretching), 1720 (s, ester >C=O), 761, 691 (m, monosubstituted benzene ring) cm^{-1}; UV: λ_{max} (log ε) = 252 (4.35) nm; ^{1}H NMR ($CDCl_3$, δ, 300 MHz); 4.76 (1H, d, $J = 9.5$, H-3), 3.46 (1H, t, $J = 9.3$, H-4), 4.42 (1H, d, $J = 9.3$, H-5), 3.17 (3H, s, -OC*H*$_3$), 6.77 (2H, d, $J = 8.1$, A,H-2,6), 7.15–7.21 (3H, m, A,H-3,4,5), 7.72 (2H, d, $J = 8.3$, B,H-2,6), 7.30–7.36 (3H, m, B,H-3,4,5), 7.32 (2H, dd, $J = 6.6$, 3.1, C,H-2,6), 6.96–6.93 (3H, m, C,H-3,4,5) ppm. ^{13}C NMR ($CDCl_3$, δ, 75.5 MHz): 72.2 (C-3), 65.4 (C-4), 83.4 (C-5), 51.22 (-OCH_3), 172.2 (>C=O), 150.1 (A,C-1), 115.2 (A,C-2,6), 127.3 (A,C-3,5), 136.2 (A,C-4), 147.3 (B,C-1), 127.2 (B,C-2,6), 124.1 (B,C-3,5), 149.2 (B,C-4), 125.1 (C,C-1), 128.3 (C,C-2,6), 129.3 (C,C-3,5), 129.2 (C,C-4) ppm. Anal. calcd. for $C_{23}H_{21}NO_3$: C, 76.86; H, 5.89; N, 3.89. Found: C, 76.79; H, 5.83; N, 3.82.

Reaction of *C*-(4-Nitrophenyl)-*N*-(4′-Chlorophenyl) Nitrone (1) with Methyl Cinnamate (4) in the Presence of Yb(OTf)$_3$ and in the Absence of Any Solvent

1*RS*-(1*R,2*R**,3*S**)-1′-[*N*-Hydroxy-*N*-(4-chlorophenyl)amino]-1′-(4′-nitrophenyl)-3-hydroxy-2-phenyl propanoyl cinnamate (8).** $C_{23}H_{21}N_2O_6Cl$, colorless solid, mp 175 °C, yield: 0.22 g (7.0%). The IR and NMR data are identical to those of compound **8**.

Reaction of *C*-Phenyl-*N*-(*4*-chlorophenyl) Nitrone (2) with Methyl Cinnamate (4) in the Presence of Yb(OTf)$_3$ and in the Absence of Any Solvent

3*RS*-(3*R,4*R**,5*S**)-2-(4-Chlorophenyl)-3-phenyl-5-phenyl-4-carbomethoxyisoxazolidine (9).** $C_{23}H_{20}NO_3Cl$, colorless solid, mp 172 °C, yield: 0.20 g (6.8%). The IR and NMR data are identical to those of compound **9**.

Reaction of *C,N*-Diphenyl Nitrone (3) with Methyl Cinnamate (4) in the Presence of Yb(OTf)$_3$ and in the Absence of Any Solvent

3*RS*-(3*R,4*R**,5*S**)-2,3,5-Triphenyl-4-carbomethoxyisoxazolidine (10).** $C_{23}H_{21}NO_3$, colorless solid, mp 160 °C, yield: 0.21 g (6.5%). The IR and NMR data are identical to those of compound **10**.

X-Ray Crystallographic Data

X-ray crystallographic data were recorded with an automatic charge coupled device (CCD) Nonius diffractometer. The wavelength of MoKα radiation is 0.7107 Å. The structure was solved by the direct method and refined with the SHELXS program. Recording was done under cryotemperature conditions, at $-50\,^{\circ}C$. The crystals were triclinic, space group P-1, with molecule asymmetric unit. An ORTEP projection is shown in Fig. 1. Crystallographic data for compound **5a** have been deposited with the Cambridge Crystallographic Data Centre as CCDC 251186. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 IEZ, UK (fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

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