Research Article

Journal of Physical Organic Chemistry

Received: 25 June 2008, Revised: 28 August 2008, Accepted: 30 August 2008, Published online in Wiley InterScience: 6 October 2008

(www.interscience.wiley.com) DOI 10.1002/poc.1454

Synthesis and stereochemical analysis of some norephedrine-derived isoxazolidines

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The diastereoselectivity in the cycloaddition reactions of several mono- and disubstituted alkenes with a (-)norephedrine-derived methylenenitrone has been investigated. The stereochemical analysis of the addition products (i.e., isoxazolidines) has been carried out by X-ray, NMR, and chemical conversions. The NMR spectra of the isoxazolidines at low temperatures indicated the presence of either a single or a predominant invertomer. The stereochemistry of the invertomers and nitrogen inversion barriers are determined using complete line-shape analysis and their dependence on solvent is discussed. Copyright © 2008 John Wiley & Sons, Ltd.

Keywords: isoxazoldines; nitrogen inversion; invertomers; inversion barriers; nitrone; cycloaddition reactions; asymmetric induction; stereochemistry

INTRODUCTION

1,3-Dipolar cycloaddition reaction of nitrones is the best chemical template for the construction of isoxazolidine ring; efficient incorporation of multiple stereocenters makes it an efficient key step in the synthesis of a great many natural products of biological interest.[1,2] In recent years, focus has been shifted towards asymmetric nitrone cycloaddition reactions, the efficiency of which very much depends on the ability of the chiral auxiliary to effectively transfer chirality to the newly created stereocenters.[3–8] Even though the nitrone cycloaddition reactions of *C,N*-disubstituted nitrones have been studied in great detail,[1,2] the chemistry of chiral (or even achiral) *N*-substituted nitrones (i.e., methylenenitrones) has only been investigated to a limited extent.[9–12] Here we report, for the first time, the stereochemical features associated with the cycloaddition of a norephedrine-derived chiral methylenenitrone **2** (Scheme 1) with several mono- and 1,1-disubstituted alkenes. The study would reflect the scope and limitations associated with the addition reactions of this important and readily accessible optically pure methylenenitrone. The NMR spectroscopy is utilized to examine the nitrogen inversion process and determine the configuration of the cycloadducts (isoxazolidines).

RESULTS AND DISCUSSION

Each nitrone (**2**)-alkene cycloaddition with **3** (or **6**) proceeded regiospecifically to afford a separable mixture of diastereomeric isoxazolidines **4** and **5 (**or **7** and **8)**, the compositions of which are given in Schemes 1 and 2. Since the nitrone is optically pure, the isoxazolidines differ only in the configuration of the C(5) substituents. The nitrone **2** is expected to assume the conformation as depicted in Scheme 1. The planar nitrone functionality is in H^a-eclipsed conformation[13–15] having Me and PhCHOH on the α- and β-faces, respectively. The J_{ab} value of 5.5 Hz, corresponding to a torsional angle of 40.5° as determined by Karplus rule, supports the gauche orientation between H_a and H_b. Since both the faces of the dipole, in the vicinity of *N*, have substituents, addition reaction does not offer any clear cut face selectivity. Sterically favored α-exo (R) or β-exo (R) mode of attack may happen with equal ease thereby giving the isoxaolidines **4** and **5** in almost equal yields (Scheme 1).

Since the addition reaction of methyl acrylate (**3c**) was found to have a preference to give the isoxazolidine **5c** by an α-exo (CO_2Me) mode of approach (Scheme 1), the major adduct in the addition reaction of methyl methacrylate (**6**) was similarly assigned the configuration of **8** obtained by a similar α-exo (CO_2Me) mode of attack (Scheme 2). However, in the absence of X-ray analysis (owing to difficulty in getting crystalline material), the configuration of the adduct could not be confirmed.

During the course of the structural investigation of the isomeric isoxazolidines, it was observed that the isoxazolidines were present either as a single invertomer or an equilibrating mixture of two invertomers in a ~80:20 ratio at lower temperatures in $CDCl_3$. Slow nitrogen inversion in most of the isoxazolidines has been observed to give broadened peaks in ^{1}H and ^{13}C spectra recorded at ambient temperature. On lowering the temperature, the spectral lines became sharper and showed two distinct forms of the compound. Around −10 °C, the ^{1}H NMR spectra of these compounds showed well separated signals for the two invertomers. Integration of the relevant peaks gives the population trends in these systems. The ^{13}C chemical shifts were assigned on the basis of DEPT experiment results, general chemical shifts arguments and consideration of substituent effects, and are given in Table 1.

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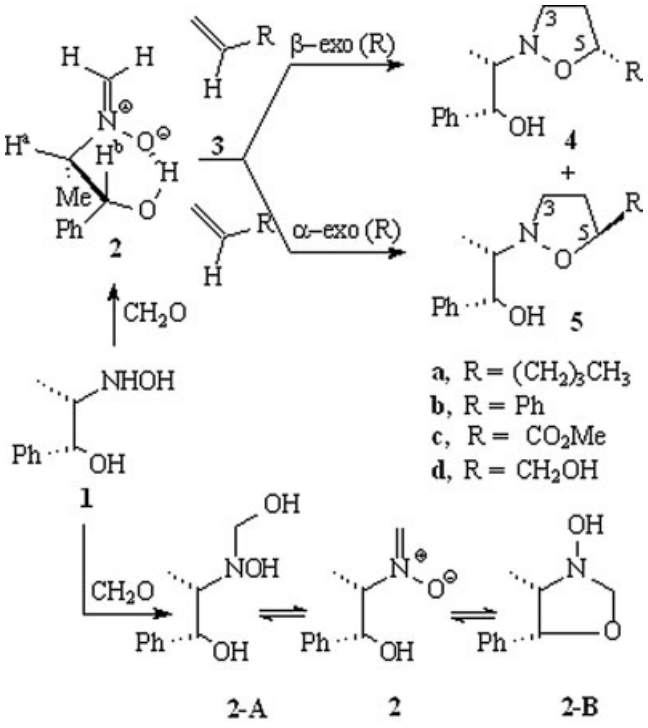
Journal of Physical Organic Chemistry



Reaction temp. (°C)	Time (h)	(Cycloadducts) ratio	Yields (%)
105	12	**(4a/5a)** 50:50	89
90	6	**(4b/5b)** 40:60	89
60	24	**(4c/5c)** 42:58	94
90	12	**(4d/5d)** 50:50	84

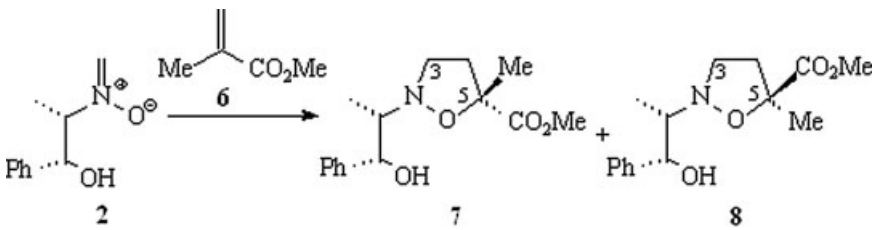
Scheme 1.

The nitrogen inversions barriers were determined using NMR band shape analysis. The proton spectra were used in the calculation of barriers in all compounds. The complete band shape analysis yielded the rate constants and the free energy of activation using Eyring equation. The complete band shape analysis yielded the rate constants and the free energy of activation using Eyring equation. Experimental and calculated spectra for one of the isoxazoli dines (4b) are shown in Figure 3.

The activation parameters $\Delta H^{\neq}$ and $\Delta S^{\neq}$ were calculated from plots of ln(k/T) *versus* 1/T. It is well known[16] that NMR band shape fitting frequently gives rather large but mutually compensating errors in $\Delta H^{\neq}$ and $\Delta S^{\neq}$ and as such their values are not reported here. However, band shape fitting is viewed as a method of getting rather accurate values of $\Delta G^{\neq}$ (probably within $\pm$0.3 kJ/mol) in the vicinity of the coalescence temperature. The $\Delta G^{\neq}$ values calculated at 0 °C are reported in Table 2, along with the invertomer ratios and ΔG° values.

Both the *cis*-1,3-dimethylcyclopentane and *cis*-1,3-dimethylcyclohexane are known[17] to be more stable than their *trans* counterparts by an enthalpy difference of 2.3 and 7.1 kJ/mol, respectively. The slight preference for the *cis* isomer in cyclopentane may be attributed to the disposition of the substituents in the pseudoequatorial orientations. The 2,5-disubstituted isoxaozolidines, however, have been found to have a slight preference for the *trans*-invertomers[18,19]; shortened bond lengths due to the presence of two heteroatoms are expected to augment the steric congestion between the *cis* substituents. The conformation of 5-membered ring system is indeed very complex to elucidate with some certainty. The complexity arises from the fact that changing the size of the substituent may lead to change in conformation (half chair/envelope/near planar) and the flap of the envelope. Earlier works[18,19] on 2,5-disubstituted isoxazolidines revealed the *trans*-invertomer as the major isomer. The 2-methyl-, 2-isopropyl-, and 2-^{t}butyl-5-^{t}butyldimethylsiloxymethylisoxazolidines were found to have the *trans*- and *cis*-invertomers in a ratio of 53:47, 55:45, and 63:37, respectively. The compounds studied in this work are sterically similar to the 2-isopropylisoxazolidines since they also contain a secondary alkyl substituent at the 2-position (Scheme 1).

To confirm the stereochemistry, adducts **5b** and **5c** were subjected to X-ray crystallographic analysis; the ORTEP representations are shown in Figs 1 and 2. The stereochemistry of the methyl acrylate adducts **4c** and **5c** were then correlated to allyl alcohol adducts **4d** and **5d** by conversions of the former isomers to the later by reduction with lithium aluminum hydride. It has been observed that the minor isomers (**4b, 4c**) in the addition reactions of styrene or methyl acrylate always eluted first during the silica gel chromatography. As a result, in the addition reaction of 1-hexene, adduct eluted first was given the configuration of **4a**. The X-ray analyses revealed the existence of both the adduts **5b** and **5c** in the *cis* invertomeric form. The chemical shift difference between the isomers for a particular ring carbon is generally less



Reaction temp. (°C)	Time (h)	(Cycloadducts) ratio	Yields (%)
60	24	**(7/8)** 35:65	95

Scheme 2.

Table 1. ^{13}C NMR chemical shifts of compounds studied in $CDCl_3$ at −40 °C

Compound	Invertomer[a]	C-3	C-4	C-5	C—OH	N—C	Me
4a {	Major (*RSR*)	52.32	33.90	76.75	72.59	65.68	10.88
	Minor (*RSS*)	52.06	33.81	77.50	74.81	67.26	7.12
5a {	Major (*RSR*)	53.13	33.61	77.48	72.31	68.02	10.75
	Minor (*RSS*)	51.87	34.24	74.38	73.96	65.93	7.42
4b {	Major (*RSR*)	53.02	37.48	77.57	72.44	66.31	10.73
	Minor (*RSS*)	52.38	36.97	78.95	75.68	66.71	6.44
5b {	Major (*RSR*)	53.90	36.93	78.77	71.98	68.15	10.65
	Minor (*RSS*)	52.54	37.51	78.85	74.70	65.99	7.45
4c	(*RSR*)	51.63	32.90	73.38	72.03	65.79	11.07
5c {	Major (*RSR*)	51.78	32.98	75.09	71.68	66.92	10.48
	Minor (*RSS*)	50.59	32.18	76.20	74.05	64.46	5.14
4d	(*RSR*)	53.03	29.44	77.47	71.71	67.30	10.36
5d {	Major (*RSR*)	53.64	30.03	77.67	71.61	67.98	10.62
	Minor (*RSS*)	52.26	29.26	78.07	74.72	66.09	7.37
7	(*RSR*)	52.50	39.13	81.11	71.90	65.81	10.80[b]
8 {	Major (*RSR*)	52.08	39.02	82.17	72.06	66.31	10.55[c]
	Minor (*RSS*)	51.06	38.10	81.63	76.91	64.06	4.00[d]

[a] Absolute configuration of the chiral centers as defined in Schemes 3 and 4.
[b] C(5) Me at 22.82 ppm.
[c] C(5) Me at 24.29 ppm.
[d] C(5) Me at 22.95 ppm.

than 1 ppm for most carbons and as such the C-13 shifts are not very sensitive to the difference in the isomeric configurations (Table 1). This is not surprising in view of the fact that the five-membered ring does not have the well-defined conformation of six-membered systems. However, one striking difference in the ^{13}C chemical shift values of **C**H_3C—N was observed; the signals for the major invertomers appeared at δ 10.7 ± 0.2 ppm, while the minor signal appeared at δ 6.8 ± 0.9. The C-3 and C—OH of the major invertomers invariably appeared downfield and upfield, respectively, in compare to the minor invertomers (Table 1). The benzylic proton NMR signals for all the major invertomers appeared downfield than the PhC**H**O of the

Table 2. Free energy of activation ($\Delta G^{\neq}$) for nitrogen inversion, ratio of the invertomers, and standard free energy change (ΔG°) for major ↔ minor isomerization in $CDCl_3$

Compound	$\Delta G^{\neq}$ (kJ/mol)[a]	$CDCl_3$ Invertomer ratio	ΔG° (kJ/mol)[b]
4a	59.5	83:17	+3.1
5a	59.4	89:11	+4.1
4b	59.4	88:12	+3.9
5b	59.8	90:10	+4.2
4c	—	100:0	—
4c[c]	56.9	83:17	+3.1
5c	58.5	79:21	+2.6
5c[c]	58.5	87:13	+3.7
4d	—	100:0	—
5d	60.3	84:16	+3.2
7	—	100:0	—
8	56.5	63:37	+1.0

[a] At 0 °C.
[b] At −40 °C.
[c] In CD_3OD.

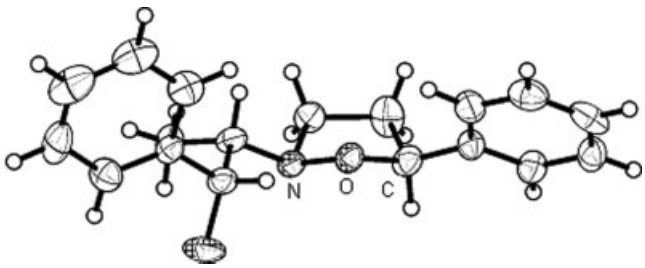


Figure 1. ORTEP drawing of **5b**. The Hydroxyl group could not be located in difference-Fourier maps most probably due to disorder

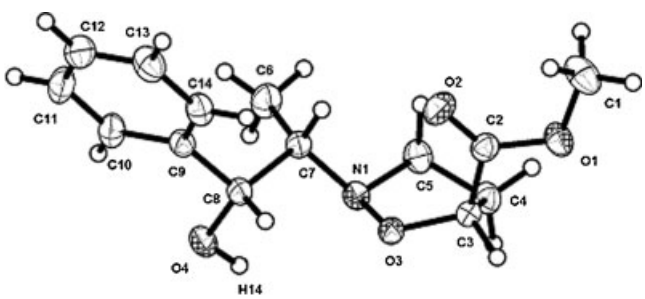


Figure 2. ORTEP drawing of **5c**

Table 3. ^{1}H NMR chemical shifts of C**H**$_3$C–N and PhC**H**O signals of the compounds studied in $CDCl_3$ at −40 °C

	CH_3C—N		PhCHO	
Isoxazolidine	Major[b] δ (ppm)	Minor[c] δ (ppm)	Major[b] δ (ppm)	Minor[c] δ (ppm)
4a	0.81	1.00	5.26	5.14
5a	0.81	Overlapped	5.35	5.00
4b	0.85	1.09	5.43	5.22
5b	0.94	1.02	5.43	—[a]
4c	0.78	—[b]	5.38	—[b]
4c[c]	0.77	1.02	5.37	5.17
5c	0.84	0.95	5.45	5.18
5c[c]	0.80	1.01	5.47	5.17
4d	0.85	—[b]	5.43	—[b]
5d	0.88	1.00	5.42	5.02
7	0.73	—[b]	5.39	—[b]
8	0.80	0.94	5.39	5.21

[a] overlapped.
[b] No minor invertomer.
[c] In CD_3OD.

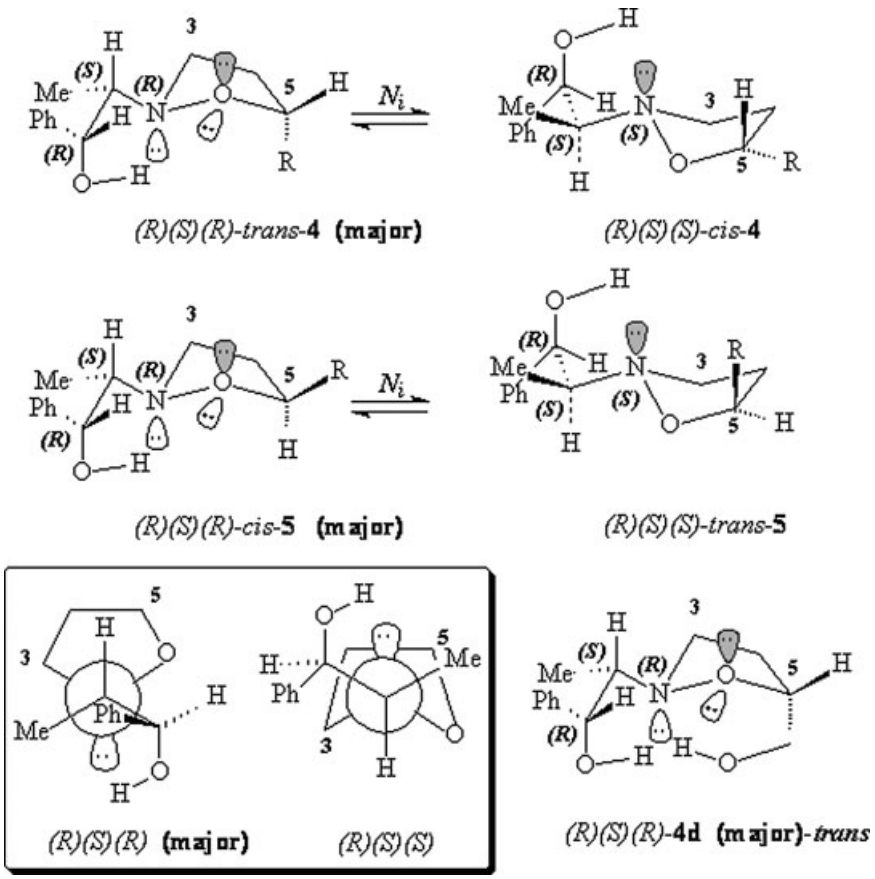
minor invertomers (Table 3). The methyl protons in C**H**$_3$C—N of the major and minor invertomers appeared upfield and downfield, respectively, in all the compounds studied. Similar trend in the chemical shift values of PhC**H**O and C**H**$_3$C—N protons (Table 3) and the **C**H$_3$C—N, C-3, and C—OH carbons (Table 1) between the major and minor invertomers strongly suggest the similarity in the configuration among all the major invertomers (or among all the minor invertomers). As supported by X-ray analyses, all the dominant or sole nitrogen invertomers are believed to have the identical configuration of (*R*), (*S*), and (*R*) at the three chiral centers at benzylic C, exocyclic C attached to nitrogen, and N, respectively.

X-ray analyses revealed that the proton in exocyclic C**H**—N is *anti* to the nitrogen lone pair as depicted in Scheme 3; the arrangement will have the lower number of *gauche* interactions (two in these cases) around the C—N bond. The protons in the exocyclic C**H**—N and PhC**H**O are not in expected *anti* dispositions; the torsional angle between them is found to be 63.3° in **5c** as a result of their gauche orientations (Scheme 3 and Fig. 2). Similar orientation is observed in the ORTEP diagram of **5b** (Fig. 1). Such an orientation will lead to a very low coupling constant ($J \approx 1.5$ Hz) between these protons as calculated using Karplus equation. The appearance of PhC**H**O proton of both the invertomers as a singlet (i.e., $J \approx 0$ Hz) in the ^{1}H NMR spectrum in $CDCl_3$ or CD_3OD confirmed the gauche orientation between these protons in solution as well as solid state. Such an orientation may be helpful in establishing intramolecular H-bond between the OH and nitrogen lone pair as depicted in Scheme 3. The sum of Van der Waal radii of H,N is known to be 2.75 Å, while the observed distance of 2.44 Å in **5c** (Fig. 2) suggest the presence of intramolecular H-bond. A look at the Newman projections (Scheme 3) revealed that the Me and C-3 are in the *gauche* conformations in the major invertomers, while they remain *anti* in the minor invertomers. We cannot offer a rationale, at this stage, for the considerable upfield shift by ~4 ppm for the methyl carbons in the methyl/C-3 *anti*-oriented minor invertomers.

The question remains: why are the (*R*),(*S*),(*R*)-diastereomers more stable than their corresponding (*R*),(*S*),(*R*)-invertomers? It may be the result of an energetically favorable orientation of the groups around C—N having the larger substituent (PhCHOH) in *gauche* orientation with the ring 'O' in the major invertomer. The Newman projections also reveals that the 'OH' in the major invertomers is also capable of forming H-bond with the ring 'O', while this is not possible with the minor form. The special stability imparted by the (*R*),(*S*),(*R*) arrangement does not mind the substituent at C-5 to be *trans* or *cis*-oriented. Note that while the 2,5 substituents in **4(a-d)** remain *trans* oriented in the major invertomers, the *cis* remains the stable form for the corresponding isoxazolidines **5(a-d)**. The isoxazolidines **4c** and **4d** remained exclusively in the (*R*),(*S*),(*R*) configurations; the presence of the minor invertomers could not be detected. Presumably, the pseudoaxial orintantion of the CO_2Me is better tolerated in (*R*),(*S*),(*R*) invertomer for its smaller size as a result of the sp^2-hybridized carbon. It is worth mentioning that the C(5)—CH_2OH in the exclusive invertomer of **4d** may gain additional stability as a result of intramolecular H-bonding with the nitrogen as depicted in Scheme 3.

The most interesting display of isomeric stability is found with the isoxazolidines **7** and **8**; while the former exists exclusively in the (*R*),(*S*),(*R*) form, the later remains in the (*R*),(*S*),(*R*) and (*R*),(*S*),(*S*) forms in a respective ratio of 63:37 (Scheme 4, Table 2). The C(5)Me carbon of (*R*),(*S*),(*R*)-**7**, (*R*),(*S*),(*S*)-**8**, and (*R*),(*S*),(*R*)-**8** appeared at δ22.82, 22.95, and 24.29 ppm, respectively; the similarity in the chemical shift values of the former two invertomers indicates the similar environments of the methyl group such as its *cis* orientation with the N(2)substituents. The extra stability enjoyed by the (*R*),(*S*),(R)-**7** invertomer could be attributed to the pseudoequatorial orientation of the bulkier substituents at C(5) and N(2), while the smaller CO_2Me is pseudoaxially-oriented.

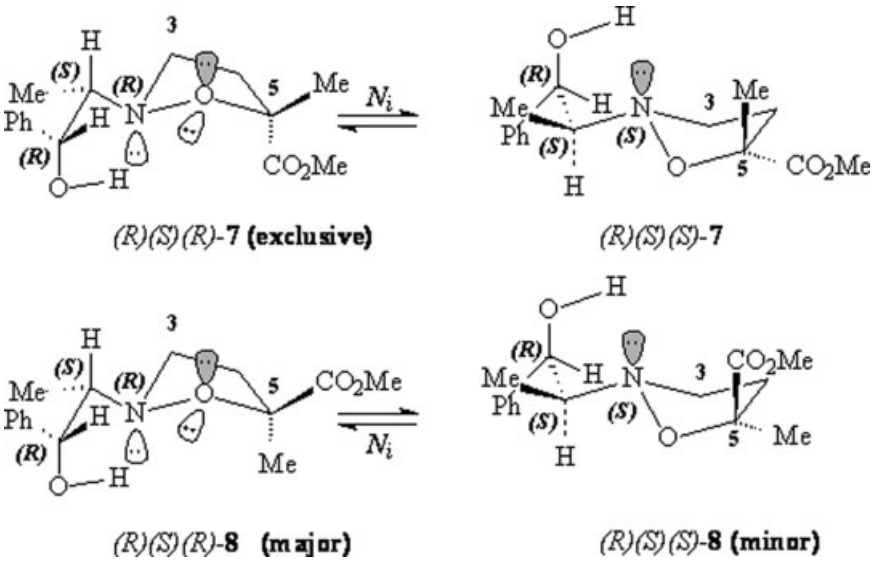
The nitrogen inversion barrier is expected to be high when an oxygen atom is directly attached to the nitrogen as in isoxazolidines.[20,21] The inversion barriers hover around 59 kJ/



Scheme 3.

mol for most of the isoxazoldines (Table 2). The similar barriers were expected since the steric requirements to attain the sp^2 hybridized transition state (through which the nitrogen inversion occurs) remains more or less similar as the substituents in the immediate vicinity of nitrogen remains the same in all the isoxazolidines. An increase in the inversion barrier in in isoxaolidines in CD_3OD is attributed to the extra energy required for breaking of H-bonding prior to inversion.[21] However, the inversion in the current compounds in $CDCl_3$ also involves the breaking of the intramolecular H-bonding. As a result the inversion barrier remains similar in hydrogen bonding solvent CD_3OD and non-protic $CDCl_3$ for the compound **5c** (Table 2).

The solvent effects provided the additional support for the assigned stereochemistry. In methanol, the intramolecular H-bonding is disrupted; the steric bulk of the solvation shell of



Scheme 4.

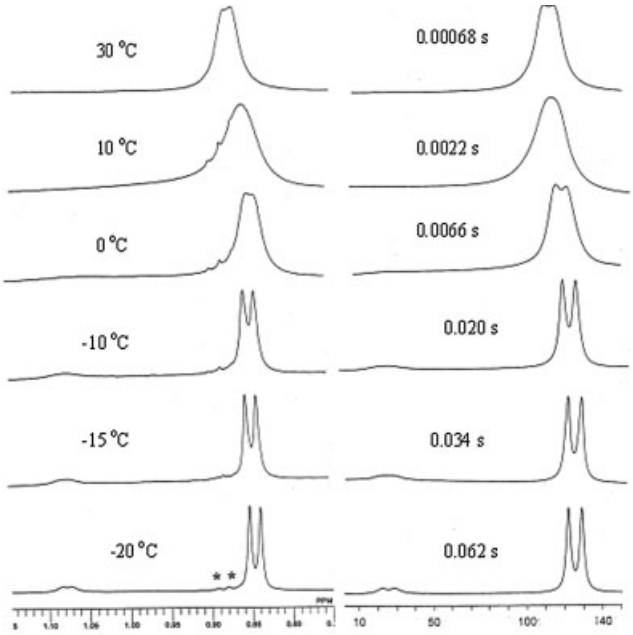


Figure 3. Experimental and calculated band shapes of the ^{1}H Me signals of **4b** in $CDCl_3$ at different temperatures. The temperatures and the corresponding life times of the minor specie are indicated respectively. *denotes peak from impurities

the nitrogen lone pair increases in hydrogen-bonding solvents. This should diminish the preference for the **4**-*trans*- and **5**-*trans* invertomers in CD_3OD since the steric bulk of the salvation lone pair salvation shell would interfere with the C(5) substituents (Scheme 3). This is exactly what is observed: the isoxazolidine *trans*-**4c** remained as the sole invertomer in $CDCl_3$ while in CD_3OD the **4**-*trans/cis* ratio becomes 83:17 (Table 2). For the isoxazolidine **5c** the *trans/cis* ratio of 21:79 in $CDCl_3$ is decreased to 13:87 in CD_3OD.

Conclusion

(-) Norephedrine is a readily available inexpensive starting material. The cycloaddition products from the norephedrine-derived isoxazolidines are readily separable to give optically pure products. The NMR study has successfully identified the configuration of the invertomers of the isoxazolidines. Currently we are working on improving the stereoselctivity of the cycloadition reactions.

EXPERIMENTAL

General. All m.p.s are uncorrected. I.r. spectra were recorded on a Perkin Elmer 16F PC FTir spectrometer. Elemental analysis was carried out on a *EuroVector* Elemental Analyzer Model EA3000. Silica gel chromatographic separations were performed with Silica gel 100 from Fluka Chemie AG (Buchs, Switzerland). Paraformaldehyde, 1-hexene, styrene, allyl alcohol, methyl acrylate, methyl methacrylate, (-) norephedrine from Fluka were used as received. All solvents were of reagent grade. Dichloromethane was passed through alumina before use. $MgBr_2$ was freshly prepared by reaction of Mg with 1,2-dibromoethane. All reactions were carried out under N_2.

The ^{13}C and variable temperature ^{1}H NMR spectra were recorded on a JEOL Lambda NMR spectrometer operating at 500.0 MHz. Most of the compounds were studied as 25 mg/cm^3 solutions in $CDCl_3$ and CD_3OD with TMS as internal standard. Multiplicities of the carbons were determined using DEPT experiments. X-ray crystallographic analysis was carried out on a Bruker-AXS Smart Apex system equipped with graphite-monochromatized Mo-Kα radiation ($\lambda = 0.71073$ Å). Optical rotations were measured in a JASCO (P-2000) polarimeter. Mass spectra were recorded on a GC/MS system (Agilent Technologies, 6890N).

Nitrone **2**. Chiral hydroxylamine **1** was prepared from (-) norephedrine in 38% yield using procedure as described.[22–24] The compound **1** was not fully characterized in the previous reports. M.p. 79–80 °C (ether-hexane); $[\alpha]^{23}_D$ −26.3 (c 2.00, methanol). (Found: C, 64.5; H, 7.7; N, 8.3. $C_9H_{13}NO_2$ requires C, 64.65; H, 7.84; N, 8.38%.);ν_{max} (KBr) 3480, 3270, 3239, 3081, 3055, 3025, 2974, 2933, 2897, 2877, 2795, 1488, 1442, 1380, 1350, 1314, 1243, 1200, 1140, 1092, 1070, 1049, 1034, 988, 942, 914, 890, 850, 736, and 691 cm^{-1}; δ_H($CDCl_3$, +25 °C): 0.85 (3H, d, *J* 6.7 Hz), 3.24 (1H, dq, *J* 2.8, 6.7 Hz), 5.17 (1H, d, *J* 2.8 Hz), 5.54 (2H, br, NHOH), 7.31 (5H, m); δ_C($CDCl_3$, +25 °C) 10.25, 62.70, 71.93, 125.92 (2C), 127.21, 128.26 (2C), 141.37.

Nitrone **2**, prepared *via* condensation of hydroxylamine **1** with paraformaldehyde, was not isolated (*vide infra*). But a crude ^{1}H NMR spectrum revealed the following signals attributed to the nitrone: δ_H($CDCl_3$, +20 °C): 1.36 (3H, d, *J* 6.8 Hz), 4.10 (1H, m), 5.42 (1H, d, *J* 5.5 Hz), 6.38 (1H, d, *J* 7.1 Hz; CH═N), 6.54 (1H, d, *J* 7.1 Hz; CH═N), 7.35 (5H, m). However, the nitrone functionality accounted for only 20% of the product mixture as indicated by the integration of the olefinic protons of the nitrone functionalty *versus* the aromatic protons. The complicated spectra indicated the involvement of several compounds (e.g., **2-A**, **2-B**, etc) under equilibration with nitrone **2** as outlined in Scheme 1.

Cycloaddition of nitrone ***2*** *with 1-hexene* ***(3a)***. To a solution of hydroxylamine **1** (670 mg, 4.0 mmol) in toluene (10 cm^3) was added paraformaldehyde (200 mg, 6.7 mmol) and 1-hexene (3 cm^3). The mixture was stirred using a magnetic stir bar in the closed vessel under N_2 at 105 °C for 12 h. After removal of the solvent the residual mixture was chromatographed over silica using ether/hexane mixture as eluant to give pure isomer **4a** followed by a mixture of the adducts **4a** and **5a** as a colorless liquid. The combined yield of the cycloadducts was found to be 89%. Spectral analysis adducts revealed the presence of **4a/5a** in a ratio of 50:50, respectively, as determined by integration and peak heights of C(5)H signals.

4a: $[\alpha]^{23}_D$ -8.5 (*c* 0.946, methanol); *m/z* 156 [M^+-107 (PhCHOH)]; (Found: C, 72.8; H, 9.5; N, 5.2. $C_{16}H_{25}NO_2$ requires C, 72.97; H, 9.57; N, 5.32%.); ν_{max} (neat) 3517, 3214, 3061, 3027, 2956, 2930, 2859, 1495, 1451, 1379, 1332, 1231, 1198, 1097, 1067, 999, 878, 750, and 702 cm^{-1}; δ_H($CDCl_3$, +20 °C): 0.81 (3H, m), 0.91 (3H, t, *J* 7.0 Hz) 1.15–2.00 (7H, m), 2.36 (1H, m), 2.50–3.50 (4H, m), 4.13 (1H, m), 5.20 (1H, apparent s), 7.30 (5H, m).

The ^{1}H NMR spectrum in $CDCl_3$ at −40 °C revealed the presence of two invertomers in a 83:17 ratio as determined by integration of several proton signals.

Major invertomer: δ_H($CDCl_3$, −40 °C): 0.81 (3H, d, *J* 6.4 Hz), 0.92 (3H, t, *J* 7.0 Hz) 1.15–1.55 (5H, m), 1.72 (1H, m), 1.93 (1H, m), 2.39 (1H, m), 2.83 (1H, m), 2.90 (1H, m), 3.26 (1H, m), 3.98 (1H, br, OH),

4.20 (1H, quint, *J* 6.3 Hz), 5.26 (1H, d, *J* 3.0 Hz), 7.35 (5H, m); δ_C($CDCl_3$, −40 °C) 10.88, 14.26, 22.72, 28.42, 33.90, 35.13, 52.32, 65.68, 72.59, 76.75, 125.96 (2C), 126.73, 127.89 (2C), 140.94.

Minor invertomer: The minor invertomer has the follwing non-overlapping signals:δ_H($CDCl_3$, −40 °C) 1.00 (3H, d, *J* 6.5 Hz), 3.05 (1H, m), 3.51 (1H, m), 4.05 (1H, quint, *J* 6.9 Hz), 5.14 (1H, d, *J* 5.2 Hz); δ_C($CDCl_3$, −40 °C) 7.12, 14.21, 22.77, 28.24, 33.81, 34.23, 52.06, 67.26, 74.81, 77.50, 125.71 (2C), 126.84, 127.99 (2C), 141.24.

5a: The second fraction was contaminated with a minor amount of **4a**. The following signals were attributed to **5a**. The ^{1}H NMR spectrum in $CDCl_3$ at −40 °C revealed the presence of two invertomers in a 89:11 ratio as determined by integration of benzylic proton signals. (Found: C, 72.7; H, 9.4; N, 5.2. $C_{16}H_{25}NO_2$ requires C, 72.97; H, 9.57; N, 5.32%.);); *m/z* 156 [M^+-107 (PhCHOH)]; ν_{max} (neat) 3424, 3062, 3027, 2958, 2929, 2858, 1494, 1452,1379, 1336, 1197, 1097, 1020, 999, 911, 751, 731, and 702 cm^{-1}.

Major invertomer: δ_H($CDCl_3$, −40 °C): 0.81 (3H, d, *J* 6.3 Hz), 0.87 (3H, t, *J* 6.7 Hz), 1.15–2.00 (7H, m), 2.40 (1H, m), 2.60 (1H, m), 2.91 (1H, m), 3.33 (1H, m), 4.05 (1H, m), 4.22 (1H, br, OH), 5.35 (1H, d, *J* 2.5 Hz), 7.35 (5H, m); δ_C($CDCl_3$, −40 °C) 10.75, 14.25, 22.82, 28.26, 33.61, 34.56, 53.13, 68.02, 72.31, 77.48, 126.15 (2C), 126.69, 127.87 (2C), 141.22.

Minor invertomer: The minor invertomer has the following non-overlapping signals: δ_H($CDCl_3$, −40 °C) 5.00 (1H, d, *J* 5.0 Hz). δ_C($CDCl_3$, −40 °C) 7.42, 12.54, 22.72, 28.40, 33.83, 34.24, 51.87, 65.93, 73.96, 74.38, 125.63 (2C), 126.95, 128.25 (2C), 141.00.

*Cycloaddition of nitrone **2** with styrene **(3b)***. To a solution of the hydroxylamine **1** (670 mg, 4.0 mmol) in toluene (10 cm^3) was added paraformaldehyde (200 mg, 6.7 mmol) and styrene (3 cm^3). The mixture was stirred using a magnetic stir bar in the closed vessel under N_2 at 90 °C for 6 h. After removal of the solvent and excess styrene the residual mixture was chromatographed over silica using 9:1 ether/hexane mixture as eluant to give pure isomer **4b** followed by a mixture of the adducts **4b** and **5b**. Continued elution afforded the pure adduct **4b**. The combined yield of the cycloadducts was found to be 89%. Spectral analysis adducts revealed the presence of **4/5** in a ratio of 40:60, respectively, as determined by integration of several non-overlapping signals of the C(5)H and Me doublets.

Minor isomer **4b**: Mp 65–66 °C (ether-pentane); *m/z* 176 [M^+-107 (PhCHOH)]; $[\alpha]^{23}_D$ +37.1 (*c* 0.488, methanol). (Found: C, 76.1; H, 7.5; N, 4.8. $C_{18}H_{21}NO_2$ requires C, 76.30; H, 7.47; N, 4.94%.);ν_{max} (KBr) 3423, 3081, 3055, 3025, 2984, 2948, 2897, 2831, 1595, 1488, 1447, 1437, 1380, 1334, 1299, 1278, 1197, 1105, 1094. 1023, 1013, 916, 885, 854, 798, 752, and 696 cm^{-1}.

The ^{1}H NMR spectrum in $CDCl_3$ at −40 °C revealed the presence of two invertomers in a 88:12 ratio as determined by integration of several proton signals.

Major invertomer: δ_H($CDCl_3$, −40 °C): 0.85 (3H, d, J 6.4 Hz), 2.38 (1H, m), 2.82 (1H, m), 2.96 (2H, m), 3.44 (1H, m), 3.62 (1H, OH), 5.27 (1H, apparent t, *J* 7.2 Hz), 5.43 (1H, s), 7.35 (10H, m); δ_C($CDCl_3$, −40 °C) 10.73, 37.48, 53.02, 66.31, 72.44, 77.57, 125.67 (2C), 125.88 (2C), 126.81, 127.48, 127.99 (2C), 128.54(2C), 140.71, 142.57.

Minor invertomer: The minor invertomer has the following non-overlapping signals:δ_H($CDCl_3$, −40 °C) 1.09 (3H, d, *J* 6.4 Hz), 3.18 (1H, m), 3.70 (1H, m), 5.07 (1H, apparent t, *J* 7.2 Hz), 5.22 (1H, s); δ_C($CDCl_3$, −40 °C) 6.44, 36.97, 52.38, 66.71, 75.68, 78.95, 125.75 (2C), 126.60 (2C), 126.75, 127.00, 128.05 (2C), 128.44 (2C), 140.34, 141.01.

Major isomer **5b**: Mp 74–75 °C (ether-pentane); *m/z* 176 [M^+-107 (PhCHOH)]; $[\alpha]^{23}_D$ −17.8 (*c* 0.386, methanol); (Found: C, 76.2; H, 7.3; N, 5.0. $C_{18}H_{21}NO_2$ requires C, 76.30; H, 7.47; N, 4.94%.);ν_{max} (KBr) 3375, 3029, 2980, 2937, 2851, 1603, 1493, 1450, 1381, 1367, 1341, 1327, 1284, 1241, 1204, 1156, 1096, 1043, 1001, 944, 919, 880, 823, 753, and 699 cm^{-1}.

The ^{1}H NMR spectrum in $CDCl_3$ at −40 °C revealed the presence of two invertomers in a 87:13 ratio as determined by integration of Me doublets.

Major invertomer: δ_H($CDCl_3$, −40 °C) 0.94 (3H, d, *J* 6.7 Hz), 2.15 (1H, m), 2.74 (2H, m), 3.02 (1H, m), 3.47 (1H, m), 4.49 (1H, s, OH), 5.06 (1H, m), 5.43 (1H, s), 7.35 (10H, m); δ_C($CDCl_3$, −40 °C) 10.65, 36.93, 53.90, 68.15, 71.98, 78.77, 125.99 (2C), 126.69, 126.76 (2C), 127.88, 127.93 (2C), 128.39 (2C), 140.79, 141.44.

Minor invertomer: The minor invertomer has the following non-overlapping signals:δ_H($CDCl_3$, −40 °C) 1.02 (3H, d, *J* 6.5 Hz). δ_C($CDCl_3$, −40 °C) 7.45, 37.51, 52.54, 65.99, 74.70, 78.85, 125.68 (2C), 125.88, 126.08 (2C), 127.05, 128.09 (2C), 128.52 (2C), 140.79, 141.44.

*Cycloaddition of nitrone **2** with methyl acrylate **(3c)***. A mixture of the hydroxylamine **1** (670 mg, 4.0 mmol) and paraformaldehyde (200 mg, 6.7 mmol) in chloroform (15 cm^3) was stirred using a magnetic stir bar in a closed vessel under N_2 at 65 °C for 2 h. Methyl acrylate (2 cm^3) was then added to the resulting nitrone solution (at 25 °C) and stirring was continued at 60 °C for 24 h. After removal of the solvent and excess alkene, the residual mixture was chromatographed over silica using 9:1 hexane/ether mixture as eluant to give the minor isomer **4c** (417 mg). Continued elution afforded the pure sample of the major isomer **5c (**580 mg**)**. Adducts **4c** and **5c** were thus formed in a ratio of 42:58, respectively. The ^{1}H NMR analysis of the crude cycloadducts also supported the ratio obtained from the chromatographic separation. The combined yield of the cycloadducts was found to be 94%.

Minor isomer **4c:** Mp 68–69 °C (ether-pentane); *m/z* 158 [M^+-107 (PhCHOH)]; $[\alpha]^{23}_D$ −48.3 (*c* 0.425, methanol); (Found: C, 63.2; H, 7.1; N, 5.2. $C_{14}H_{19}NO_4$ requires C, 63.38; H, 7.22; N, 5.28%.); ν_{max} (KBr) 3485 (sharp), 3061, 2986, 2958, 2847, 1746, 1496, 1451, 1430, 1380, 1337, 1286, 1205, 1177, 1086, 1026, 1003, 812, 752, and 705 cm^{-1}.

Sharp ^{1}H NMR signals at room temperature indicated the presence of a single invertomer: δ_H($CDCl_3$, +25 °C): 0.78 (3H, d, *J* 6.7 Hz), 2.48–2.70 (3H, m), 2.92 (1H, m), 3.32 (1H, m), 3.57 (1H, s, OH), 3.80 (3H,s), 4.63 (1H, dd, *J* 3.9, 9.7 Hz), 5.38 (1H, s), 7.33 (5H, m). The spectrum at −40 °C remained similar to that at +25 °C. δ_C($CDCl_3$, −40 °C) 11.07, 32.90, 51.63, 52.73 (OMe), 65.79, 72.03, 73.38, 125.69 (2C), 126.80, 128.01 (2C), 140.25, 173.87.

In CD_3OD (−40 °C) the ^{1}H NMR spectrum revealed several non-overlapping minor signals indicating the major/minor invertomers of **4c** in a ratio of 83:17. The CH_3 doublets appeared at δ0.77 (major, d, $J = 6.7$ Hz) and δ1.02 (minor, d, $J = 6.1$ Hz). The benzylic proton appeared at δ5.38 (major, s) and δ5.17 (minor, s).

Major isomer **5c:** Mp 60–61 °C (ether-pentane);); *m/z* 158 [M^+-107 (PhCHOH)]; $[\alpha]^{23}_D$ −26.4 (*c* 0.872, methanol); (Found: C, 63.3; H, 7.1; N, 5.2. $C_{14}H_{19}NO_4$ requires C, 63.38; H, 7.22; N, 5.28%.); ν_{max} (KBr) 3543 (sharp), 3081, 2990, 2942, 2908, 2869, 1754, 1492, 1453, 1434, 1409, 1378, 1349, 1328, 1284, 1262, 1198, 1088, 1061, 996, 964, 949, 877, 854, 795, 763, and 706 cm^{-1}.

The ^{1}H NMR spectrum in $CDCl_3$ at −40 °C revealed the presence of two invertomers in a 79:21 ratio as determined by integration of several proton signals.

Major invertomer: δ_H($CDCl_3$, −40 °C): 0.84 (3H, d, J 6.7 Hz), 2.39 (1H, m), 2.66 (1H, m), 2.89 (1H, m), 3.11 (1H, m), 3.31 (1H, m), 3.75 (1H, s, OH), 3.83 (3H, s), 4.64 (1H, dd, J 5.8, 9.2 Hz), 5.45 (1H, s), 7.37 (5H, m); δ_C($CDCl_3$, −40 °C) 10.48, 32.98, 51.78, 52.67 (OMe), 66.92, 71.68, 75.09, 125.84 (2C), 126.70, 127.95 (2C), 141.09, 172.47.

Minor invertomer: The non-overlapping ^{1}H signals at δ_H($CDCl_3$, −40 °C) 0.95 (3H, d, *J* 6.7 Hz), 5.18 (1H, s); δ_C($CDCl_3$, −40 °C) 5.14, 32.18, 50.59, 52.79 (OMe), 64.46, 74.05, 76.20, 125.66 (2C), 127.00, 128.06 (2C), 140.57, 173.33.

In CD_3OD (−40 °C) the ^{1}H NMR spectrum revealed several non-overlapping minor signals indicating the major/minor invertomers of **5c** in a ratio of 87:13. The CH_3 doublets appeared at δ0.80 (major, d, $J = 6.7$ Hz) and δ1.01 (minor, d, $J = 6.1$ Hz). The benzyl protons appeared at δ5.47 (major, s) and δ5.17 (minor, s).

*Lithium aluminium hydride reduction of cycloadducts methyl acrylate adducts (**4c, 5c**) to allyl alcohol adducts (**4d, 5d**)*. **4d**: To a stirred solution of **4c** (120 mg, 0.45 mmol) in ether (15 cm^3) was added lithium aluminium hydride (100 mg, 2.7 mmol) at room temperature. The reaction was complete in 10 min as indicated by TLC experiment (silica, ether). To the reaction mixture was added water (0.1 g), 10% NaOH solution (0.1 g) and water (0.4 g). The mixture was stirred for 1 h and was then decanted and the residue washed with CH_2Cl_2. The organic layer was dried (Na_2SO_4), concentrated, and purified by silica gel chromatography using a 95:5 CH_2Cl_2/methanol as the eluant to give **4d** as a colorless liquid (100 mg, 94%), $[\alpha]^{23}_D$ −38.7 (*c* 1.53, methanol); *m/z* 130 [M^+-107 (PhCHOH)]; (Found: C, 65.6; H, 7.8; N, 5.7. $C_{13}H_{19}NO_3$ requires C, 65.80; H, 8.07; N, 5.90%.); $\nu_{max.}$ (neat) 3402, 3060, 3027, 2981, 2940, 1494, 1450, 1380, 1334, 1236, 1199, 1097, 1041, 993, 859, 807, 736, and 703 cm^{-1}.

Sharp ^{1}H NMR signals at room temperature indicated the presence of a single invertomer. The spectrum at −40 °C remained similar to that at +25 °C.

Single invertomer: δ_H($CDCl_3$, −40 °C) 0.85 (3H, d, *J* 6.4 Hz), 2.13 (1H, m), 2.30 (1H, m), 2.72 (1H, m), 2.81 (1H, m), 3.22 (1H, m), 3.72 (2H, m), 4.37 (1H, m), 4.75 (1H, broad, OH), 4.89 (1H, broad, OH), 5.43 (1H, s), 7.35 (5H, m). δ_C ($CDCl_3$, −40 °C) 10.36, 29.44, 53.03, 63.60, 67.30, 71.71, 77.47, 125.86 (2C), 126.73, 127.94 (2C), 141.40.

5d: Adduct **5c** was reduced with $LiAlH_4$ using procedure as described above to give **5d** (95%) as a colorless liquid; $[\alpha]^{23}_D$ −18.4 (*c* 1.58, methanol); *m/z* 130 [M^+-107 (PhCHOH)]; (Found: C, 65.5; H, 7.9; N, 5.8. $C_{13}H_{19}NO_3$ requires C, 65.80; H, 8.07; N, 5.90%); $\nu_{max.}$ (neat) 3286, 2982, 2880, 1494, 1451, 1381, 1336, 1198, 1041, 999, 887, 829, 751, and 703 cm^{-1}.

The ^{1}H NMR spectrum in $CDCl_3$ at −40 °C revealed the presence of two invertomers in a 84:16 ratio as determined by integration of several proton signals.

Major invertomer: δ_H($CDCl_3$, −40 °C) 0.88 (3H, d, *J* 6.7 Hz), 1.85 (1H, m), 2.33 (1H, m), 2.44 (1H, m), 2.87 (1H, m), 3.37 (1H, m), 3.64 (1H, m), 3.81 (1H, m), 4.41 (2H, m, including an OH), 4.87 (1H, broad s, OH), 5.42 (1H, s), 7.35 (5H, m); δ_C($CDCl_3$, −40 °C) 10.62, 30.03, 53.64, 64.29, 67.98, 71.61, 77.67, 125.99 (2C), 126.71, 127.91 (2C), 141.08.

Minor invertomer: The minor invertomer has the non-overlapping ^{1}H signals at: δ_H($CDCl_3$, −40 °C) 1.00 (3H, d, J 6.4 Hz), 5.02 (1H, s); δ_C($CDCl_3$, −40 °C) 7.37, 29.26, 52.26, 63.84, 66.09, 74.72, 78.07, 125.67 (2C), 127.13, 128.09 (2C), 140.85.

*Cycloaddition of nitrone **2** with allyl alcohol **(3d)***. To a solution of the hydroxylamine **1** (670 mg, 4.0 mmol) in toluene (10 cm^3) was added paraformaldehyde (200 mg, 6.7 mmol) and allyl alcohol (3 cm^3). The mixture was stirred using a magnetic stir bar in the closed vessel under N_2 at 90 °C for 12 h. After removal of the solvent the residual mixture was chromatographed over silica using 98:2 dicholromethane/methanol mixture as eluant to give a non-separable mixture of adducts **4d** and **5d** as a colorless liquid (0.80 g, 84%). Spectral analysis revealed the presence of **4d/5d** in a ratio of 50:50.

*Cycloaddition of nitrone **2** with allyl alcohol **(3d)** in the presence of $MgBr_2$*. To a solution of hydroxylamine **1** (167 mg, 1.0 mmol) in dichloromethane (20 cm^3), was added paraformaldehyde (34 mg, 1.13 mmol) and the mixture was stirred in a closed vessel under N_2 at 65 °C for 2 h. Thereafter, the solution was cooled to room temperature and the volume of the solution was reduced to 5 cm^3 by gently blowing N_2 at 40 °C. This process is expected to remove moisture (H_2O) by evaporation along with CH_2Cl_2. Then $MgBr_2$ (184 mg, 1.0 mmol) was added to the solution. The resulting suspension was stirred at 20 °C for 15 min after which allyl alcohol **(3d)** (4.0 mmol) was added. The reaction mixture was then stirred at 65 °C in the closed vessel under N_2 for 48 h. After the elapsed time, the reaction mixture was cooled to room temperature and was taken up in 10% K_2CO_3 (20 cm^3) and extracted with CH_2Cl_2 (3 × 20 cm^3). The combined organic layers were dried (Na_2SO_4), concentrated and purified by silica gel chromatography using 98:2 dichloromethane/methanol mixture as eluent to give a non-separable mixture of isomers **4d** and **5d** as a colorless liquid (190 mg, 80%). The ratio of **4d** and **5d** was found to be 50:50, respectively, as determined by ^{1}H NMR spectroscopic analysis (*vide supra*). The Lewis acid catalyzed [9–11] cycloaddition thus failed to improve the diastereselectivity of the addition reaction.

*Cycloaddition of nitrone **2** with methyl methacrylate **(6)***. A mixture of the hydroxylamine **1** (670 mg, 4.0 mmol) and paraformaldehyde (200 mg, 6.7 mmol) in chloroform (15 cm^3) was stirred using a magnetic stir bar in the closed vessel under N_2 at 65 °C in a closed vessel for 2 h. Methyl methacrylate (**6**) (2 cm^3) was then added to the resulting nitrone solution (at 25 °C) and stirring was continued at 60 °C for 24 h. After removal of the solvent and excess alkene, the residual mixture was chromatographed over silica using 9:1 hexane/ether mixture as eluant to give the minor isomer **7** (371 mg). Continued elution afforded the pure sample of the major isomer **8** (690 mg). Adducts **7** and **8** were thus formed in a ratio of 35:65, respectively. The ^{1}H NMR integration of the benzylic proton signals ($CDCl_3$, +25 °C) of the crude cycloadducts at δ 5.39 (minor) and 5.26 (major) also supported the ratio obtained from the chromatographic separation. The combined yield of the cycloadducts was found to be 95%.

7: Single invertomer: Mp 78–79 °C (ether-pentane); *m/z* 172 [M^+-107 (PhCHOH)]; $[\alpha]^{23}_D$ −70.8 (*c* 0.267, methanol). (Found: C, 64.3; H, 7.4; N, 4.9. $C_{15}H_{21}NO_4$ requires C, 64.50; H, 7.58; N, 5.01%.); ν_{max} (KBr) 3502 (very sharp), 3059, 2994, 2955, 2882, 2840, 1738, 1499, 1449, 1409, 1383, 1341, 1279, 1232, 1201, 1126, 1070, 1023, 1002, 971, 933, 906, 848, 818, 752, and 706 cm^{-1}; δ_H($CDCl_3$, +25 °C): 0.73 (3H, d, *J* 6.7 Hz), 1.56 (3H, s), 2.13 (1H, ddd, *J* 2.1, 9.1 12.7 Hz), 2.60 (1H, m), 2.84 (1H, td, *J* 8.7, 12.6 Hz), 2.91 (1H, dq, *J* 2.9, 6.6 Hz), 3.29 (1H, dt, *J* 2.1, 8.7 Hz), 3.58 (1H, s, OH), 3.80 (3H,s), 5.39 (1H, br s), 7.33 (5H, m). Identical ^{1}H NMR spectrum was obtained at −40 °C. δ_C($CDCl_3$, −40 °C) 10.80, 22.82, 39.13, 52.50, 52.89 (OMe), 65.81, 71.90, 81.11, 125.70 (2C), 126.73, 127.96 (2C), 140.31, 176.31.

8: Mp 49–50 °C (ether-pentane); *m/z* 172 [M^+-107 (PhCHOH)]; $[\alpha]^{23}_D$ +13.5 (*c* 0.942, methanol); (Found: C, 64.4; H, 7.6; N, 4.9. $C_{15}H_{21}NO_4$ requires C, 64.50; H, 7.58; N, 5.01%.); ν_{max} (KBr) 3408, 2999, 2948, 2854, 1741, 1495, 1450, 1383, 1316, 1278, 1203, 1147, 1099, 1064, 1032, 988, 926, 871, 756, and 705 cm^{-1}.

The ^{1}H NMR spectrum in $CDCl_3$ at −40 °C revealed the presence of two invertomers in a 63:37 ratio as determined by integration of several proton signals.

Major invertomer: δ_H($CDCl_3$, −40 °C): 0.80 (3H, d, *J* 6.7 Hz), 1.57 (3H, s), 2.26 (1H, m), 2.71 (1H, m), 2.83–3.25 (2H, m), 3.34 (1H, m), 3.67 (1H, s, OH), 3.84 (3H, s), 5.39 (1H, s), 7.37 (5H, m); δ_C($CDCl_3$, −40 °C) 10.55, 24.29, 39.02, 52.08, 52.94 (OMe), 66.31, 72.06, 82.17, 125.82 (2C), 126.69, 127.92 (2C), 141.04, 174.73.

Minor invertomer: The invertomer has the following non-overlapping ^{1}H signals at δ_H($CDCl_3$, −40 °C) 0.94 (3H, d, *J* 6.7 Hz), 2.11 (1H, m), 1.55 (3H, s), 3.98 (1H, s, OH), 5.21 (1H, s); δ_C($CDCl_3$, −40 °C) 4.00, 22.95, 38.10, 51.06, 52.90 (OMe), 64.06, 76.91, 81.63, 125.60 (2C), 126.90, 128.04 (2C), 140.64, 176.01.

Inversion barrier calculations. Simulations of exchange-affected proton spectra for all compounds were carried out using a computer program AXEX,[25] corresponding to a two non-coupled sites exchange with unequal populations. The following signals were utilized: **4a (or 5a)**, benzyl protons at δ5.26 (major, s) and δ5.14 (minor, s); **5a (or 4a)**, benzyl protons at δ5.35 (major, s) and δ5.00 (minor, s); **4b**: ($CDCl_3$), CH_3 doublets appeared at δ0.85 (major) and δ1.09 (minor); **5b**: ($CDCl_3$), CH_3 doublets appeared at δ0.94 (major) and δ1.02 (minor); **4c**: (CD_3OD), CH_3 doublets appeared at δ0.77 (major) and δ1.02 (minor); **5c**: ($CDCl_3$), benzyl protons at δ5.45 (major, s) and δ5.18 (minor, s); **5c**: (CD_3OD), methyl doublets at δ0.80 (major) and δ1.01 (minor); **5d**: ($CDCl_3$), benzyl protons at δ5.42 (major, s) and δ5.02 (minor, s); **8**: ($CDCl_3$), benzyl protons at δ5.39 (major, s) and δ5.21 (minor, s). Experimental and calculated spectra for one of the ioxazolidines (**4b)** are shown in Figure 3.

Simulations of exchange affected triplets were carried out by modifying the two-site exchange program.[26] The first order coupling to these protons is simply assumed as giving overlapping two site exchanges with the same population ratio and equal rates of exchange. Simulations of exchange affected doublet of doublets were carried out by modifying the two-site exchange program.[26] The first order coupling to these protons is simply assumed as giving overlapping two site exchanges with the same population ratio and equal rates of exchange.

Acknowledgements

The facilities provided by the King Fahd University of Petroleum and Minerals, Dhahran, are gratefully acknowledged.

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