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The face selectivity of 1,3-dipolar cycloaddition reactions of 4-butyloxycarbonyl-3,4,5,6-tetrahydropyridine 1-oxide

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ABSTRACT

A study of the stereo- and face selectivity of the cycloaddition reactions of a series of mono- and disubstituted alkenes with 4-butyloxycarbonyl-3,4,5,6-tetrahydropyridine 1-oxide has been carried out. Rate constants for the cycloaddition of the nitrone to methyl acrylate, styrene, and methyl methacrylate have been determined at various temperatures by ^{1}H NMR spectroscopy. The activation parameters indicate the concerted nature of the reaction. The 4-substituted nitrone is found to be more reactive than its unsubstituted counterpart 3,4,5,6-tetrahydropyridine 1-oxide. The addition reactions have displayed a very high degree of face selectivity (9:1), and those reactions in micellar media are found to be very efficient. Conformational analysis and peracid-induced ring opening of a cycloadduct has been carried out to give second-generation cyclic nitrones.

1. Introduction

The nitrone functionality has etched a place of distinction in organic synthesis; its cycloaddition reaction with alkenes is indeed the best chemical template for constructing isoxazolidines in high yields.[1] Remarkable regio-, stereo-, face-, and chemo-selectivity along with efficient incorporation of multiple stereocenters have made the nitrone cycloaddition reaction an attractive and efficient key step[2] in the synthesis of a great many natural products of biological interest.[1] For instance, the cycloaddition reactions involving 6-substituted 3,4,5,6-tetrahydropyridine 1-oxides **1** and alkenes are reported to give single cycloadducts **2** in a regio-, face-, and stereo-selective manner (Scheme 1).[3] The addition of 3-substituted nitrone **3** to allyl alcohol gave a mixture of adducts **4** and **5** in 3:1 ratio as a result of a favorable approach of the alkene from the α-face of the nitrone.[2b,4] Nitrones generated by peracid-induced ring opening of the cycloaddition products derived from cyclic nitrones marked the beginning of the utilization of the second-generation of cyclic nitrones.[5] For instance, the oxidative ring opening of the trans- and cis invertomers of 6/5-fused isoxazolidines (e.g., **6**) is known to give a mixture of keto-(**7**) and aldonitrone (**8**), respectively,[3b,6] while the corresponding 5/5-fused isoxazolidines, which exist only as the cis invertomer give aldonitrones exclusively (Scheme 1).[7] Orientation of the nitrogen lone pair, and the trans/cis invertomer ratio dictate the regiochemical outcome of the oxidation process; the trans and cis invertomers afford the keto- and aldonitrones, respectively. However, the proper utilization of these second-generation nitrones has been hampered by the lack of selectivity[3a,8] in the oxidation process, which leads to the synthetically less important ketonitrone **7** either as the major or sole product.

To the best of our knowledge, the face selectivity associated with the cycloaddition reactions of a six-membered nitrone containing a substituent farthest from the nitrone moiety, i.e., at the C(4) or C(5) position (e.g., **12**, Scheme 2) has not been reported to date. Here we report the kinetic study and stereoselectivity of the addition reaction of a C(4)-substituted cyclic nitrone **12** with various alkenes. The piperidine-based nitrone **12** was chosen because of its importance in the synthesis of piperidine alkaloids, which are widespread in nature. The presence of a moderately long butyl group in the ester functionality of **12** was intended to suppress the solubility of the nitrone in water; this would indeed allow us to pursue one of our objectives to study the cycloadditions of a cyclic nitrone for the first time in micellar media. One of the objectives was also to investigate whether the substituent at the C-4 position can increase the cis/trans ratio of the invertomers of the cycloadducts in order to increase the formation of the synthetically important second-generation aldonitrones using peracid-induced ring opening (Scheme 1).

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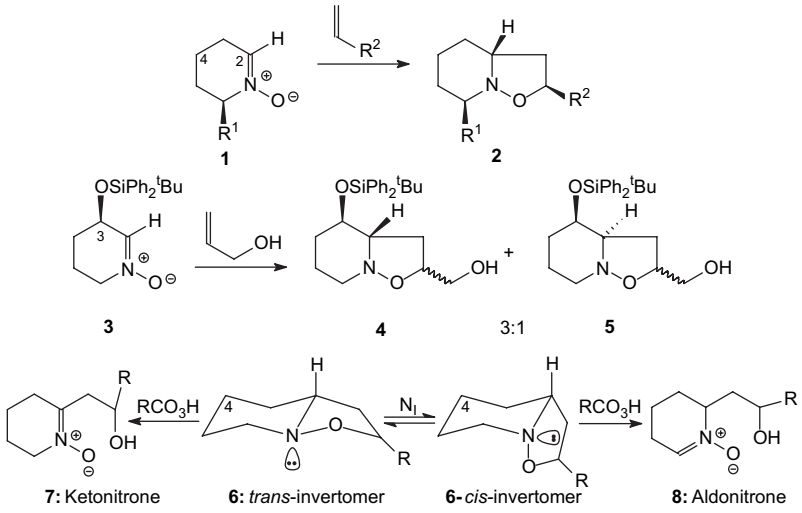
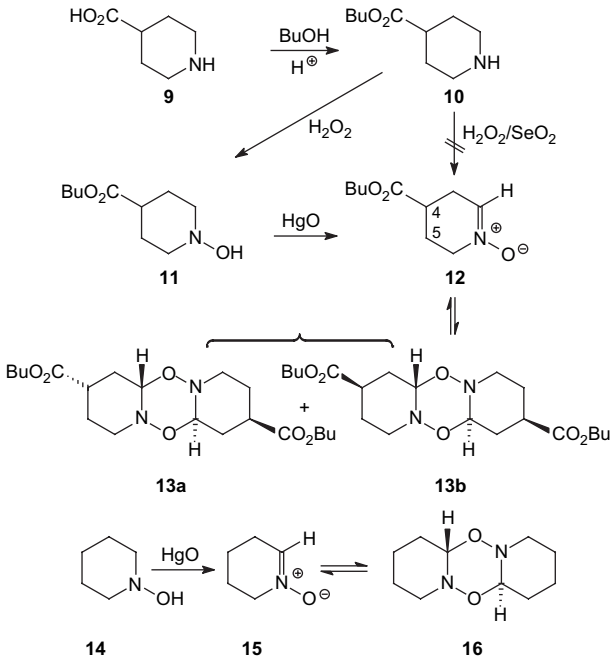


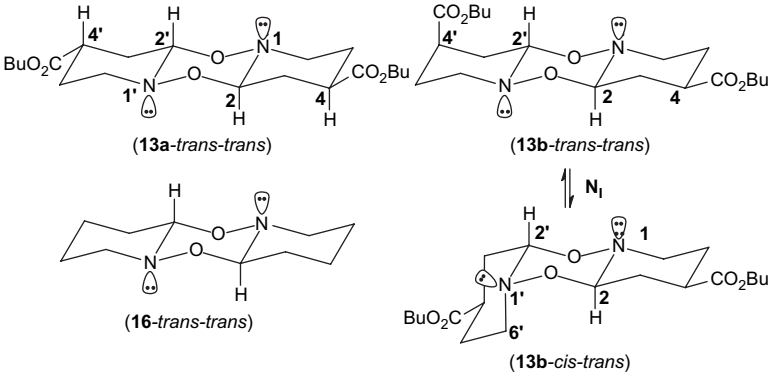
Scheme 1.



Scheme 2.

2. Results and discussion

The synthesis of nitrone **12** is outlined in Scheme 2. It was presumed at the outset that the preparation of the nitrone by direct oxidation of the secondary amine **9** will be a trivial matter. However, we were unable to obtain the nitrone by the procedure of Murahashi et al.[9] using hydrogen peroxide oxidation mediated by selenium dioxide either in acetone or methanol. The required nitrone was prepared by mercury(II) oxide oxidation of the hydroxylamine **11**, which, in turn, was prepared by usual oxidation with hydrogen peroxide. The behavior of the concentrated solutions of cyclic nitrones is known to be quite puzzling.[10] A concentrated solution of the nitrone **12** gave a mixture of the dimer **13a** and **13b** in a 1:2 ratio. While the parent nitrone **15** dimerizes to **16**, its five-membered counterpart is known to be stable. The seven- and eight-membered nitrones as well as the heterocyclic six-membered nitrones containing heteroatom (O or N), on the other hand, give polymeric materials.[10] However, dilute solution of all these nitrones in the presence of excess alkene ensures the suppression of the polymerization process and affords the cycloadducts in excellent yields. Even though the dimerization to **16** is well known,[11,12] the mechanistic pathway the nitrone traverses is not well understood, it still remains a matter of speculation. Note that the $(4\pi_s+4\pi_s)$ process leading to the dimer is not a thermally allowed process. The dimer **16** has been shown to be the trans isomer (i.e., trans relationship of the bridgehead Hs), which exists both in crystal and in solution in the tetraequatorial (eeee) conformation with a trans–trans ring fusion (Scheme 3).[13] Based on



Scheme 3.

NMR findings, both the minor **13a** as well as major dimer **13b** ($C_{20}H_{34}N_2O_6$) were assigned the trans configurations with a trans–trans ring fusion and 'eeee' conformation as depicted in Scheme 3. The ^{13}C spectrum of the centrosymmetric dimer **13a** showed 10 sharp signals at ambient as well as low temperatures, while the ^1H NMR spectrum, as anticipated, displayed 12 distinct sharp signals. The large coupling constant for the C(4), C(4′) protons at δ 2.49 (2H, tt, *J* 4.0, 12.8 Hz), and C(2), C(2′) protons at δ 4.32 (2H, dd, *J* 3.3, 10.8 Hz) ascertained their axial orientations. The major dimer **13b** was also assigned the trans form having the trans–trans ring fusion and 'eeee' conformation as depicted in Scheme 3. The NMR spectra, both ^1H and ^{13}C, showed appreciable broadening at various positions indicating the involvement of the nitrogen inversion ($\mathbf{N_I}$). The signals for the O–CH–N carbons were not even observed. At ambient temperatures the axially-oriented C(4)H, however, appeared as a sharp triplet of triplets at δ 2.49 (*J* 4.0, 12.5 Hz), whereas, the corresponding C(4′)H was displayed at δ 2.80 ppm as a very broad signal. Almost half the ring-protons as well as ring-carbon signals were sharp while the other half broad. It is logical in that case to assume that the ring on the left side is able to undergo nitrogen inversion since the process would place the ester functionality at C(4′) in the energetically favorable equatorial position. It would also impart stabilization derived from the anomeric effect of the *anti periplanar* arrangement between the N′ lone pair and C(2′)–O bond. Note that the conformation would also be destabilized due to the axial disposition of the N(1′)–C(6′) bond with respect to the middle ring. The NMR spectra at −40 °C revealed the two invertomers of **13b** in a ratio of 82:18. In the absence of symmetry, all 20 carbon signals of the major invertomer **13b**-*trans–trans* appeared in the ^{13}C spectrum. The large coupling constant for the C(2), C(2′) protons at δ 4.33 (1H, dd, *J* 3.05, 10.7 Hz) and 4.42 (1H, dd, *J* 3.05, 11.0 Hz) ascertained their axial orientations. The presence of the minor invertomer **13b**-*cis–trans* was revealed by the signals at δ 4.57 (1H, dd, *J* 2.5, 11.0 Hz) and 5.43 (1H, br s), attributed to the C(2)-axial and C(2′)-equatorial H, respectively. While the minor dimer **13a** remained stable for weeks in solution at ambient temperatures, the major dimer **13b** was seen equilibrating to the nitrone within a week.

Kinetic results obtained for the cycloaddition of nitrone **12** with different alkenes in $CDCl_3$ at various temperatures are shown in Table 1. All reactions were carried out under conditions that would reflect kinetic rather than thermodynamic factors. Cycloadditions were monitored by proton NMR technique as described before.[14] The ^1H NMR signals of C(2)-H of the nitrone and olefinic-protons of alkenes were free of any overlapping signals. Thus the ratio of concentration of nitrone and alkene were determined from time to time and second-order rate constants were obtained by linear-regression analysis. The cycloaddition products, nitrone and alkenes are all stable under the mild reaction conditions. Nitrone cycloaddition is a type II process,[15] where both HOMO–LUMO interactions contribute to the stabilization of the transition state.[16,17] As expected methyl acrylate being the most electron-deficient undergoes addition reaction faster among the three alkenes; it is found to be more reactive than styrene by a factor of 52 at 36 °C. Activation parameters, shown in Table 1, are derived from rate constants determined at three temperatures. Our results are consistent with those reported for cycloaddition reactions involving acyclic nitrones.[18] These low activation energies and large negative entropies of activation are a necessary condition for multicentered concerted cycloaddition reactions.[16] Note that the C(4)-substituted nitrone **12** is surprisingly found to be more reactive than the parent nitrone **15**[14] by a factor of ∼1.5 at 36 °C as shown in the last column of the table. In order to confirm our findings, a competing kinetic study was carried out to ensure the exactly identical conditions for the addition reactions. Thus a mixture of nitrones **12** and **15** and a limited quantity of methyl methacrylate in $CDCl_3$ at 36 °C was allowed to undergo cycloaddition reaction. A careful analysis of the ^1H NMR spectrum, after complete consumption of the alkene, revealed the rate ratio k_2(**12**)/k_2(**15**), as determined using the rate equation of Ingold and Shaw,[19] to be 1.42. In a similar competing reaction with methyl acrylate, the rate ratio was found to be 1.36. The rate ratio was thus found to be similar to that obtained from the reported values of the addition reaction of nitrone **15** (last column, Table 1).[14]

It is interesting to find out the relative rate of formation (k_{12}/k_{15}) of the nitrones **12** and **15** from their respective hydroxylamines **11** and **14**; the rate of formation of the substituted nitrone **12** is anticipated to be slower since its addition reactions are faster. In a competing reaction, when a mixture of the hydroxylamines in $CDCl_3$ was treated with a limited quantity of mercury(II) oxide at 20 °C, the ^1H NMR spectrum revealed the presence of the unreacted hydroxylamines as well as the nitrones **12** and **15**. The reactants and products were quantified by integration of several non-overlapping proton signals; then using the rate equation of Ingold and Shaw the k_{15}/k_{12} was found to be 3.59:1.[19] The rate of formation of the C(4)-substituted nitrone **12** was thus found to be slower while it undergoes faster cycloadditions. We are, at this stage, unable to offer a rationale for this behavior.

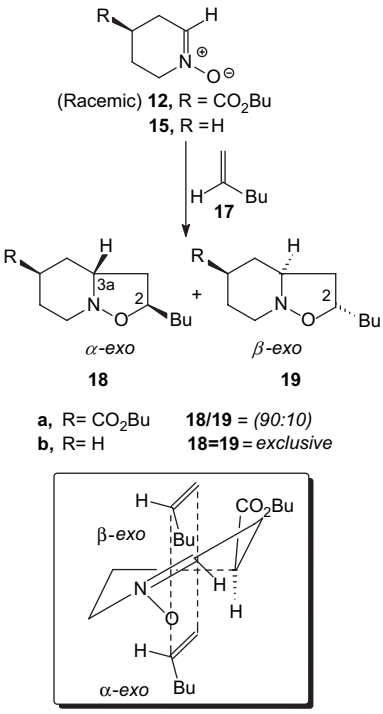
Next, we pursued the addition reaction of nitrone **12** with various alkenes. The addition of 1-hexene (**17**) was found to be regio-, stereo-, as well as highly face-selective; a mixture of diastereomers **18a** and **19a** (80% yield) was obtained in a ratio of 90:10, respectively, as determined by ^1H NMR spectroscopic analysis. The configuration of the major adduct **18a** was based on the *exo* approach of the Bu group from the less hindered face (i.e., α-face) of the nitrone (Scheme 4). Likewise, β-*exo* approach of the alkene afforded the adduct **18b**. It is indeed gratifying to find such a high face selectivity (9:1) exerted by the ester group positioned at the furthest point from the nitrone functionality. For the sake of comparison, the stereochemistry of the addition of the corresponding parent nitrone **15** is also given in Scheme 4; its addition to 1-hexene is known[3a,14a,20] to be regio- as well as stereo-selective to give **18b** via an *exo*-transition state.

Reaction of nitrone **12** with styrene (**20**) gave a mixture of diastereomers **21a**–**24a** in 84% yield in a respective ratio of

Table 1
Rate constants and activation parameters for the cycloaddition reactions of nitrone **12** in $CDCl_3$

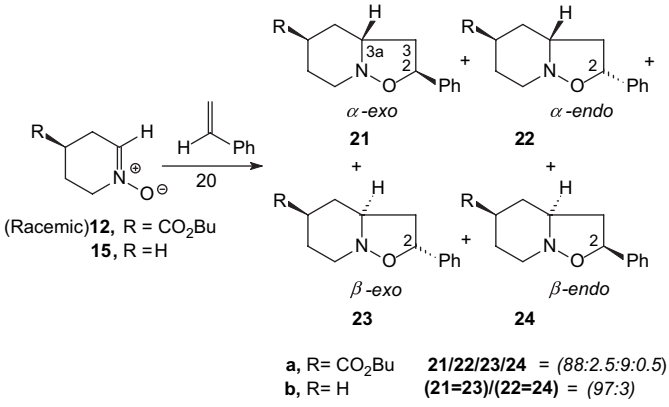
Alkene	Temp/°C	10^5k_2/l mol^{-1} s^{-1}	E_a/kJ mol^{-1}	$\Delta H^{\#}$/kJ mol^{-1}	$\Delta S^{\#}$/J mol^{-1} K^{-1}	k_2(**12**)/k_2(**15**)[a]
CO_2Me	26.0 36.0 46.0	253 509 866	48.9	46.3	−140	1.50[b]
Me, CO_2Me	26.0 36.0 46.0	76.6 161 304	54.7	52.2	−130	1.53[b]
H_2C=CHPh	36.0	9.82	_	_	_	1.3[b]

[a] From Ref. 14.
[b] Ratio of the rate constants for the cycloadditions of the nitrone (**12**)-alkene and nitrone (**15**)-alkene at 36 °C.



Scheme 4.

88:2.5:9:0.5 (Scheme 5). The face selectivity, as determined by the ratio of (**21a**+**22a**)/(**23a**+**24a**), is thus found to be 90.5:9.5. The *exo*/*endo* selectivities of the α- and β-face of the nitrone as determined by the composition of **21a**/**22a** and **23a**/**24a**, were found to be 97:3 and 95:5, respectively. A similar stereoselectivity of 97:3 was observed for the addition of the parent nitrone **15** with styrene.[21] It is worth mentioning at this stage that the *exo*/*endo* selectivity, especially of the α-face of the nitrone **12**, is assumed to be similar to that observed for the corresponding addition reactions of the parent nitrone **15**.[20] This logical assumption has indeed assisted in the deduction of the stereochemistry of the addition reactions under study. To confirm the stereochemistry, the major adduct **21a** was subjected to X-ray crystallographic analysis; the ORTEP representation is shown in Figure 1. The configuration of the overwhelmingly predominant adduct **21a** is consistent with an *exo* approach of the Ph group from the less hindered α-face of the nitrone.



Scheme 5.

Stereochemical analysis of the nitrone **12**–methyl acrylate addition products is indeed a cumbersome problem; the presence of eight cycloadducts and the slow nitrogen inversion give rise to

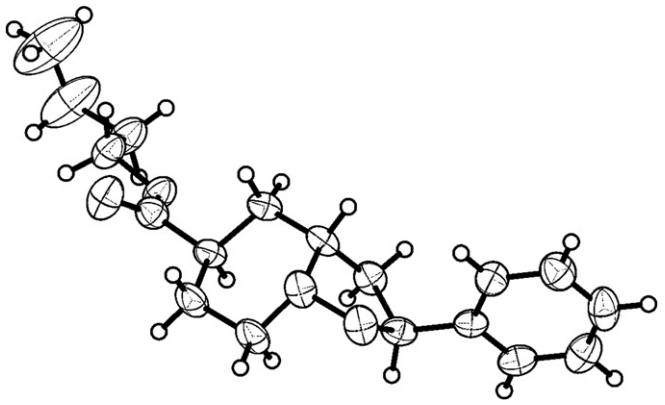


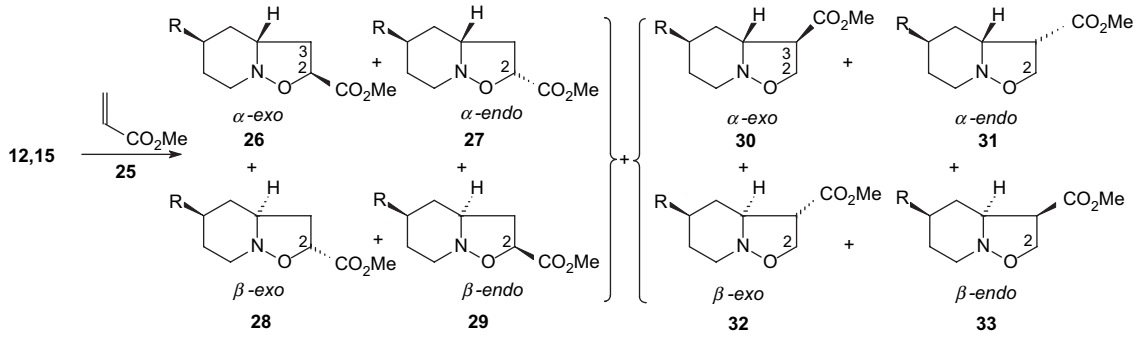
Figure 1. ORTEP drawing of **21a**.

a complex ^{1}H NMR spectrum (Scheme 6). Careful analysis of the C(2)H of the cycloadducts revealed the regioselectivity [i.e., the ratio of (**26a**–**29a**)/(**30a**–**33a**)] as 85:15, while for the addition of the parent nitrone **15**, the corresponding regioselectivity [i.e., (**26b**,**27b**)/(**30b**,**31b**)] was reported to be 84:16.[20] The ratio of the isomers **26a**, **27a**, (**28a**+**29a**), and (Σ**30a**−**33a**) has been found to be 62:16:7:15, respectively. An approximate ratio of 91:9, i.e., the ratio of (**26**+**27**)/(**28**+**29**) reflects the face selectivity associated with the addition of this alkene as far as the formation of the C(2)-substituted isomers is concerned. We were unable to determine the stereochemistry of the minor isomers **30a**–**33a**.

Methyl methacrylate (**34**) appears to undergo regioselective addition to **12** to give a mixture of isomers **35a**–**37a** in a ratio of 88:3:9, respectively (Scheme 7). The major adduct **35a** was assigned the configuration having the methoxycarbonyl group *endo*-oriented as a result of favorable secondary orbital interaction in the transition state.[20] An *exo*/*endo* selectivity of 95:5 was observed for the addition of the corresponding parent nitrone **15** (Scheme 7). The face selectivity [i.e., (88+3):9] was based on the assumption that nitrone **15** and the α-face of nitrone **12** should demonstrate similar *exo*/*endo* selectivity, and as such the α-*endo* adduct **36a** and β-*exo* adduct **37a** were assumed to be formed in a ratio of 3:9 rather than 9:3.

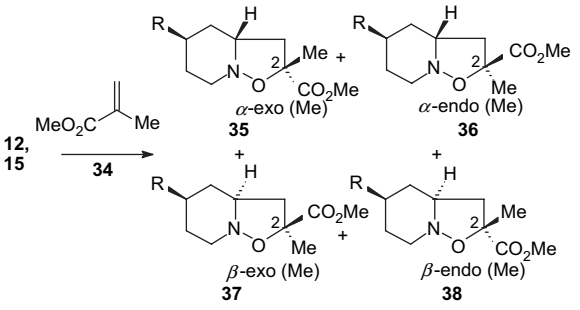
The addition of methyl crotonate (**39**) to **12** also demonstrated a very high face selectivity (97:3); a mixture of cycloadducts **40a**–**42a** was obtained in a ratio of 88:9:3, respectively, as determined by integration of C(2)H signals (Scheme 8). A similar *exo*/*endo* selectivity (i.e., 90:10) is observed for the corresponding addition reaction of the parent nitrone **15**, which gave the adducts **40b** and **41b** in a 90:10 ratio.[20] The face selectivity of 97:3 is found to be even better than that observed for the addition of the other alkenes (vide supra). This is presumably a result of severe steric interference in the β-*exo* (Me) approach of the alkene, which places the alkene–CO_2Me in close proximity to nitrone-C(4)-substituent.

We investigated the stereochemistry of the ring junction of some of the cycloaddition products. The 6/5 system can exist in three different forms, the trans conformer (**A**: '**ee**') and the cis pair (**B**: '**ea**' and **C**: '**ae**') (**a** and **e** represent the axial and equatorial substituents on the six-membered ring) (Scheme 9). While the cis pair is in rapid equilibrium between them by chair inversion ($\mathbf{C_I}$), the cis invertomer **B** is converted to the trans isomer **A** by a relatively slow nitrogen inversion process ($\mathbf{N_I}$). X-ray crystallographic analysis revealed that the compound **21a** exists in the solid state as the cis conformer **C** having one axial and two equatorial substituents in the six-membered ring (Fig. 1). Needless to say, the favorable conformation in the solid state, as dictated by the crystal packing forces, may not be the conformation of choice in the solution. However, it was found that the isoxazolidine prefers to be in



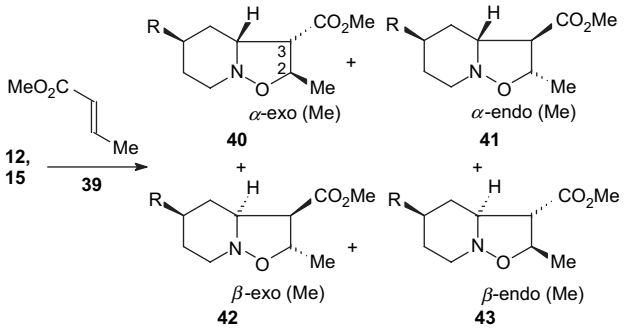
a, R= CO_2Bu **26/27/(28+29)/(Σ 30-33)** = *(62:16:7:15)*
b, R= H **26/27/30/31** = *(69:15:10:6)*

Scheme 6.



a, R= CO_2Bu **35/36/37/38** *=(88:3:9:~0)*
b, R= H **(35=37)/(36=38)** *=(95:5)*

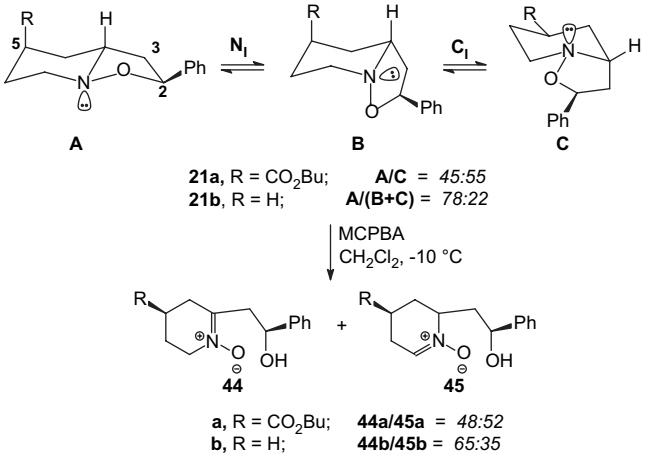
Scheme 7.



a, R= CO_2Bu **40/41/42/43** = *(88:9:3:~0)*
b, R= H **(40=42)/(41=43)** = *(90:10)*

Scheme 8.

the cis conformation as the sole invertomer in the solid as well as the major invertomer in the solution. The major (cis) and minor (trans) invertomers at +25 °C in $CDCl_3$ were found to be in a ratio of 55:45 as determined by integration of the C(2)H. The C(2)H of the cis invertomers is known to appear downfield compared to the trans invertomers.[21] In an experiment, a few crystals of **21a** (~6 mg) was added onto the solidified solvent CD_2Cl_2 in an NMR tube cooled to −120 °C. The NMR spectrum, taken immediately at a probe temperature of −90 °C, revealed the absence of the signals attributed to the minor trans invertomer. It indicated the presence of the major cis invertomer **C** thereby implying the similar conformation for the major invertomer in the solution as well as in the solid state. After a few minutes at −90 °C, the signals for the minor invertomer started to appear in the NMR spectrum. Peracid-induced ring opening of 6/5-fused isoxazolidines are known to give second-generation nitrones that can be used for further cycloadditions hence elaboration of the piperidine ring in organic synthesis.[3a,8] Unlike the 5/5-fused isoxazolidines, which can exist only as a cis invertomer,[7,22] the peracid-induced ring opening reaction of the 6/5-fused isoxazolidines is known to be nonregioselective;[3a,8] a mixture of minor aldo- and major keto-nitrones is obtained, the composition of which reflects approximately the ratio of the cis and trans invertomers. For instance the isoxazolidine **21b**, having the trans and cis invertomers in a 78:22 ratio, on treatment with peracid gives a mixture of the keto- (**44b**) and aldonitrone (**45b**) in a 65:35 ratio.[8] For the corresponding ring opening reaction of the isoxazolidine **21a**, having the trans and cis invertomers in a 45:55 ratio, a mixture of the keto- (**44b**) and aldonitrone (**45b**) in a respective ratio of 48:52 was obtained. It is gratifying to see an increase in the ratio in favor of the synthetically more useful aldonitrone **45b**. Note that by changing the sp^2 hybridized ester functionality at C(5) to a bulkier sp^3 hybridized alkyl group will increase the *syn* axial destabilization in the invertomer **A** of **21a**, and as such the nitrogen inversion equilibrium will be shifted more toward the cis invertomer **C**, which would preferably lead to the desired aldonitrone (Scheme 9). Changing the sp^2 hybridized ester functionality at C(4) in amine **10** to a sp^3 hybridized alkyl group may also alleviate the problem associated with the direct oxidation of **10** to nitrone **12** (Scheme 2). However, these propositions have to be tested in a future work.



21a, R = CO_2Bu; **A/C** = *45:55*
21b, R = H; **A/(B+C)** = *78:22*

a, R = CO_2Bu; **44a/45a** = *48:52*
b, R = H; **44b/45b** = *65:35*

Scheme 9.

Finally, we investigated the micellar cycloaddition reaction of nitrone **12**. To the best of our knowledge, the only nitrone cycloaddition reaction reported[23] so far involves the addition of some hydrophobic acyclic *C*,*N*-diarylnitrones to ethyl acrylate in the presence of the surfactant SDS or CTAB. The micellar cycloaddition reaction of the most important five- and six-membered cyclic nitrones (e.g., **15**) may not be carried out in micellar media since they are very much soluble in water. This is the reason we attached a relatively long alkyl chain as part of the ester functionality in **12** in order to suppress its solubility in water. Replacement of toxic organic solvents by water is one of the main features of environmentally benign green chemistry.[24] The cycloaddition of nitrone **12** with styrene (**20**) and methyl acrylate (**25**) using procedure as described[23] afforded cycloadducts **21a**–**24a** and **26a**–**33a**, respectively, in excellent yields. However, the regio- and stereoselectivity remained the same as observed in the addition reactions in the organic media (vide supra).

A systematic study of the kinetics and stereochemistry associated with the cycloaddition of a C(4)-substituted six-membered cyclic nitrone in organic and micellar media has been carried out for the first time. The stereochemistry and isolated yield of the addition reactions are given in Table 2. The remarkable *exo*/*endo*- and face selectivity observed in our study reflects the scope inherent in these important cycloaddition reactions. The study suggests that a bulkier substituent at C(4) may generate the synthetically important second-generation aldonitrones via peracid-induced ring opening of the cycloadducts.

Table 2
exo/*endo*- and face selectivity of the cycloaddition reactions of nitrone **12**

Alkene	α-*exo*/α-*endo*	β-*exo*/β-*endo*	(α-face)/(β-face)[a]	Yield (%)
17	100:0	100:0	90:10	80
20	97:3	95:5	90:10	84
25	80:20	—	92:8	87
34	97:3	100:~0	91:9	92
39	91:9	100:~0	97:3	77

[a] Ratio of (α-*exo*+α-*endo*) and (β-*exo*+β-*endo*) adducts.

3. Experimental

3.1. General

Elemental analysis was carried out on a *EuroVector* Elemental Analyzer Model EA3000. All melting points are uncorrected. IR spectra were recorded on a Perkin Elmer 16F PC FTIR spectrometer. ^{1}H and ^{13}C NMR spectra were measured in $CDCl_3$ using TMS as internal standard on a JEOL LA 500 MHz spectrometer. Silica gel chromatographic separations were performed with Silica gel 100 from Fluka Chemie AG (Buchs, Switzerland). Piperidine 4-carboxylic acid, 1-hexene, styrene, methyl acrylate, methyl methacrylate, methyl crotonate, *m*-chloroperbenzoic acid, CTAB, sodium dodecyl sulfate (SDS) from Fluka Chemie AG (Buchs, Switzerland) were used as-received. All solvents were of reagent grade. Dichloromethane was passed through alumina before use. All reactions were carried out under N_2.

3.2. Butyl 4-piperidinecarboxylate (10)

Dry HCl (9 g, 0.246 mol) was bubbled through a mixture of 4-piperidinecarboxylic acid (**9**) (50 g, 0.388 mol) in methanol (250 cm^3) at 10–20 °C. Thereafter a solution of HCl (7 g, 0.192 mol) in methanol (100 cm^3) was added to the above heterogeneous mixture. The mixture was then heated at reflux for 3 h; the mixture became homogeneous within minutes after heating to give the methyl ester. [The acid was insoluble in BuOH and this is why it was first converted to the methyl ester, which was subsequently transesterified with butanol.] Then the methanol was exchanged with ^{n}butanol (100 cm^3) by distilling off the methanol in the presence of butanol. Another portion of butanol (100 cm^3) and concentrated HCl (4 cm^3) was added to the reaction mixture and heated at 110 °C for 12 h with simultaneous distilling off the methanol. The ^{1}H NMR spectrum revealed almost complete exchange of the methyl with butyl ester. The homogeneous reaction mixture was concentrated by removal of butanol. The residual salt was triturated with hexane and filtered. The white salt was taken in water (200 cm^3) and neutralized with 1 equiv of NaOH (0.388 mol). The separated oil layer was extracted with ether (300 cm^3). The organic layer was dried (Na_2SO_4), filtered, concentrated, and distilled to give the ester **10** as a colorless liquid (65 g, 90%); $bp_{Hg\ 0.6\ mbar}$ 80 °C. (Found: C, 64.7; H, 10.2; N, 7.5. $C_{10}H_{19}NO_2$ requires C, 64.83; H, 10.34; N, 7.56%.) ν_{max} (neat) 3327, 2955, 2867, 1729, 1547, 1454, 1415, 1309, 1280, 1181, 1140, 1039, 971, 841, and 807 cm^{-1}; δ_H ($CDCl_3$, +25 °C) 0.94 (3H, t, *J* 7.5 Hz), 1.39 (2H, hex, *J* 7.5 Hz), 1.61 (4H, m), 1.88 (2H, apparent d, *J* 13.1 Hz), 2.20 (1H, br, NH), 2.42 (1H, m), 2.63 (2H, apparent t, *J* 11.9 Hz), 3.09 (2H, apparent d, *J* 12.5 Hz), 4.08 (2H, t, *J* 6.5 Hz); δ_C ($CDCl_3$, +25 °C) 13.72, 19.16, 29.37, 30.70, 41.74, 45.92, 64.20, 175.26.

3.3. Butyl *N*-hydroxy-4-piperidinecarboxylate (11)

To a stirring solution of the amine **10** (30 g, 162 mmol) at 0 °C under N_2 was added dropwise a 30% H_2O_2 solution (23 g, 200 mmol) in 15 min. After stirring at 10 °C for 1 h, methanol (20 cm^3) was added to homogenize the mixture and the stirring continued for an additional 2 h. The mixture was then stirred at room temperature for 8 h. The aqueous layer was extracted with CH_2Cl_2 (4×30 cm^3) and the combined organic layers were dried (Na_2SO_4), concentrated and the residual liquid was purified by chromatography over silica using 1:1 ether/hexane mixture as eluant to give the hydroxylamine **11** as a colorless liquid (10.5 g, 32%). (Found: C, 59.5; H, 9.4; N, 6.8. $C_{10}H_{19}NO_3$ requires C, 59.68; H, 9.52; N, 6.96%.) ν_{max} (neat) 3257, 2958, 2867, 2833, 1731, 1452, 1386, 1304, 1257, 1187, 1116, 1046, and 952 cm^{-1}; δ_H ($CDCl_3$, +25 °C) 0.94 (3H, t, *J* 7.3 Hz), 1.39 (2H, hex, *J* 7.5 Hz), 1.60 (2H, quint, *J* 7.0 Hz), 1.77 (2H, m), 2.03 (2H, apparent d, *J* 13.7 Hz), 2.28 (1H, m), 2.50 (2H, apparent t, *J* 11.8 Hz), 3.33 (2H, apparent d, *J* 10.7 Hz), 4.08 (2H, t, *J* 6.7 Hz); δ_C ($CDCl_3$, +25 °C) 13.70, 19.13, 28.09, 30.64, 40.36, 57.82, 64.34, 174.52.

3.4. 4-Butyloxycarbonyl-3,4,5,6-tetrahydropyridine 1-oxide (12)

To a solution of the hydroxylamine **11** (6.04 g, 30 mmol) in CH_2Cl_2 (150 cm^3) was added yellow HgO (16 g, 74 mmol) and the mixture was stirred using a magnetic stir bar at 20 °C for 1 h or until the oxidation was complete (as indicated by TLC analysis in ether). Anhydrous $MgSO_4$ (ca. 5 g) was added to the mixture, which was then filtered through a bed of Celite and anhydrous $MgSO_4$. The gray mercury salts were washed with dichloromethane. The nitrone solution was immediately kept in the refrigerator in order to avoid dimerization. The formation of the nitrone was assumed quantitative for the percent yield calculation of the cycloaddition reactions. ν_{max} ($CDCl_3$) 2964, 2935, 2873, 1729, 1617, 1446, 1312, 1194, 1060, and 987 cm^{-1}; δ_H ($CDCl_3$, +25 °C) 0.95 (3H, t, *J* 7.3 Hz), 1.38 (2H, hext, *J* 7.3 Hz), 1.63 (2H, quint, *J* 7.0 Hz), 2.16 (1H, m), 2.30 (1H, m), 2.75 (3H, m), 3.87 (2H, m), 4.16 (2H, t, *J* 6.8 Hz), 7.15 (1H, m); δ_C ($CDCl_3$, +25 °C) 13.68, 19.12, 25.38, 27.66, 30.58, 34.54, 56.77, 65.31, 134.71, 172.57.

*3.4.1. Relative rate of formation of the nitrones **12** and **15***

In a competing reaction, a mixture of hydroxylamines **11** (0.0802 mmol) and **14** (0.107 mmol) in $CDCl_3$ (1.3 cm^3) was treated with HgO (0.062 mmol) at 20 °C for 1 h. The ^{1}H NMR spectrum

revealed the presence of unreacted hydroxylamines **11** (0.0690 mmol) and **14** (0.0625 mmol) along with the presence of nitrones **12** (0.0112 mmol) and **15** (0.0449 mmol). The C(2)H of the nitrones **12** and **15** appeared at δ 7.17 and 7.20 ppm, respectively, while the corresponding 6(C)-Hs appeared at δ 3.88 and 3.80 ppm. The non-overlapping peaks at δ 3.33 (app d, 2H) and δ 3.28 (app d, 2H) belong to the hydroxylamines **11** and **14**, respectively. Careful integration of these signals helped us to quantify the reactants and products. Using the rate equation of Ingold and Shaw the k_{12}/k_{15} was found to be 1:3.59.[19]

3.5. Dimerization of the nitrone 12

A solution of nitrone **12** (1.0 mmol) in CH_2Cl_2 (1 cm^3) was kept at room temperature for 3 days. After removal of the solvent, the residual mixture was chromatographed over silica using 1:4 ether/hexane as eluant to afford the minor dimer **13a** (40 mg) as a white solid. Continued elution afforded the major dimer **13b** (83 mg) also as a white solid. The ratio of the minor and major dimers was thus found to be 2:1.

3.5.1. Minor dimer *13a*

The ^1H and ^{13}C NMR spectra of the dimer **13a** at 25 °C were sharp and indicated the presence of a single invertomer. The minor dimer has 10 carbon signals. Both the spectra revealed symmetric nature of the compound. Mp 123–124 °C (ether–hexane). (Found: C, 60.2; H, 8.5; N, 6.9. $C_{20}H_{34}N_2O_6$ requires C, 60.28; H, 8.60; N, 7.03%.) ν_{max} (KBr) 2960, 2870, 1726, 1460, 1363, 1268, 1193, 1141, 1099, 1026, 880, 839, and 783 cm^{-1}; δ_H ($CDCl_3$, +25 °C) 0.92 (6H, t, *J* 7.3 Hz), 1.36 (4H, hex, *J* 7.3 Hz), 1.59 (4H, quint, *J* 7.3 Hz), 1.71 (2H, dt, *J* 10.7, 12.8 Hz), 1.83 (2H, dq, *J* 3.7, 13.1 Hz), 2.03 (2H, m), 2.11 (2H, qd, *J* 3.1, 12.8 Hz), 2.49 (2H, tt, *J* 4.0, 12.8 Hz), 2.64 (2H, ddd, *J* 2.8, 10.4, 13.1 Hz), 3.32 (2H, td, *J* 3.4, 10.4 Hz), 4.08 (4H, dt, *J* 1.5, 6.4 Hz), 4.32 (2H, dd, *J* 3.3, 10.8 Hz); δ_C ($CDCl_3$, +25 °C) 13.68, 19.11, 27.09, 30.59, 30.90, 39.76, 51.34, 64.69, 94.76, 173.21. ^1H NMR and ^{13}C NMR spectra at −40 °C remained the same as that of 25 °C; no minor invertomer could be seen.

3.5.2. Major dimer *13b*

Some of the signals in the ^1H and ^{13}C NMR spectra of **13b** at 25 °C were broad and indicated the presence of two invertomers. Both the spectra revealed the unsymmetrical nature of the compound. The ^1H NMR spectrum at 25 °C revealed the presence of two triplets at δ 0.92 (3H, t, *J* 7.3 Hz) and 0.94 (3H, t, *J* 7.3 Hz) in equal ratio thereby implying the different environment for the Me groups attached to the alkyl chain-end. Unlike the minor dimer **13a**, the major dimer **13b** was equilibrated slowly in $CDCl_3$ to a mixture of the nitrone **12** and the dimmer, in a 27:73 ratio after 1 week at 20 °C. **13b**: Mp 85–86 °C (ether–hexane). (Found: C, 60.1; H, 8.4; N 6.9. $C_{20}H_{34}N_2O_6$ requires C, 60.28; H, 8.60; N, 7.03%.) ν_{max} (KBr) 2961, 2861, 1719, 1459, 1370, 1268, 1199, 1151, 1096, 1021, 951, and 849 cm^{-1}; δ_H ($CDCl_3$, +20 °C) 0.92 (3H, t, *J* 7.3 Hz), 0.94 (3H, t, *J* 7.3 Hz), 1.37 (4H, sharp m), 1.60 (4H, sharp m), 1.70 (1H, dt, *J* 10.7, 12.8 Hz), 1.83 (1H, dq, *J* 3.7, 13.0 Hz), 1.93 (2H, br), 2.03 (1H, sharp m), 2.07 (1H, sharp m), 2.15 (1H, br), 2.20 (1H, br), 2.49 (1H, tt, *J* 4.0, 12.8 Hz), 2.63 (1H, ddd, *J* 2.8, 10.4, 13.1 Hz), 2.70 (1H, br), 2.80 (1H, br), 3.25 (1H, br), 3.31 (1H, td, *J* 3.4, 10.4 Hz), 4.08 (4H, sharp m), 4.25–4.80 (2H, br m); δ_C ($CDCl_3$, +20 °C) 13.68, 13.71, 19.10, 19.15, 26.20 (br), 27.04, 30.15 (br), 30.58, 30.62, 30.91, 36.99 (br), 39.86, 49.50 (br), 51.45, 64.67, 64.81, 93.50 (very br), 94.90 (very br), 173.19, 173.50 (br).

At lower temperatures the ^1H and ^{13}C NMR spectra of **13b** revealed the presence of two invertomers in a ratio of 85:18.

3.5.3. Major invertomer of *13b*

δ_H ($CDCl_3$, −40 °C) 0.92 (3H, t, *J* 7.3 Hz), 0.94 (3H, t, *J* 7.3 Hz), 1.36 (4H, m), 1.55–2.85 (16H, m), 3.22 (1H, td, *J* 3.0, 10.4 Hz), 3.36 (1H, td, *J* 3.0, 10.7 Hz), 4.10 (4H, m), 4.33 (1H, dd, *J* 3.05, 10.7 Hz), 4.42 (1H, dd, *J* 3.05, 11.0 Hz); δ_C ($CDCl_3$, −40 °C) 13.83, 13.89, 19.04, 19.09, 25.43, 26.81, 29.46, 30.24, 30.28, 30.50, 36.99, 39.33, 49.49, 51.15, 64.79, 65.06, 93.39, 94.65, 173.23, 173.31.

3.5.4. Minor invertomer of *13b*

δ_H ($CDCl_3$, −40 °C) non-overlapping signals at δ 3.04 (1H, m), 3.33 (1H, m), 3.69 (1H, m), 4.57 (1H, dd, *J* 2.5, 11.0 Hz), 5.43 (1H, br s); δ_C ($CDCl_3$, −40 °C) 13.83, 13.89, 19.04, 19.09, 26.63, 27.43, 29.46, 30.24, 30.50, 31.29, 35.34, 39.64, 44.00, 51.65, 64.64, 64.79, 84.68, 87.95, 173.37 (2C).

3.6. NMR characterization of dimer 16

The dimer **16** was prepared as described in the literature,[11] mp 127–127.5 °C (lit.,[11] mp 126–127 °C). δ_H ($CDCl_3$, −50 °C) 1.42 (2H, tq, *J* 3.5, 13.4 Hz), 1.53 (2H, dq, *J* 3.5, 13.5 Hz), 1.67 (2H, tq, *J* 3.4, 13.1 Hz), 1.79 (4H, app d, *J* 12.2 Hz), 1.88 (2H, app d, *J* 12.5 Hz), 2.64 (2H, dt, *J* 2.5, 10.4 Hz), 3.31 (2H, d, *J* 9.8 Hz), 4.33 (2H, dd, *J* 3.2, 10.4 Hz); δ_C ($CDCl_3$, −30 °C) 22.23, 24.32, 28.63, 52.69, 96.22.

3.7. Kinetics of cycloaddition reaction

The kinetics of the cycloaddition reaction was studied by NMR technique as described before.[14] A stock solution of the nitrone **12** in $CDCl_3$ was prepared using procedure as described in Section 3.4. Thus a solution of the hydroxylamine **11** (604 mg, 3.0 mmol) in $CDCl_3$ (5 cm^3) was oxidized with yellow mercury(II) oxide (1.43 g, 6.6 mmol) for 1 h at 20 °C. After the completion of oxidation (as indicated by TLC analysis in ether), anhydrous $MgSO_4$ (ca. 1 g) was added to the mixture, which was then filtered through a small bed of Celite and anhydrous $MgSO_4$. The gray mercury salts were washed with $CDCl_3$ (~5 cm^3). The nitrone solution was immediately kept in the refrigerator in order to avoid dimerization. The molar concentration of the nitrone in the solution was determined by the ^1H NMR technique. A known volume (or weight) of the nitrone at 0 °C was added to a known amount of styrene in an NMR tube kept at 0 °C. The mixture was quickly mixed and inserted into the NMR probe, which was kept at a constant temperature throughout the kinetic measurements. In the kinetic study of more reactive methyl acrylate, however, a certain amount of addition reaction took place by the time the probe attained the temperature of the kinetic study. So the initial concentrations of the alkene and nitrone were readjusted by subtracting the concentration of the reacted reactants, which were determined by the integration of the 2-H of the nitrone at δ 7.15 ppm, olefininc protons, and C(2)H of the cycloadducts. The ratio of the concentrations of the reactants was determined from time to time by integration of signals due to the 2-H of the nitrone and the alkenic protons of the alkene. The second-order constant was determined by linear-regression analysis of the data and it was reproducible within 5%. The initial concentrations of nitrone–methyl acrylate, nitrone–methyl methacrylate, and nitrone–styrene were kept at ca. 0.100–0.220 M, 0.150–0.300 M, and 0.150–0.700 M, respectively. The additions were followed up to 40–80% chemical conversion.

3.7.1. Relative rate of addition reactions of nitrones *12* and *15* with alkenes

In order to correlate the reactivity of the nitrone **12** with that of the parent nitrone **15** the following competing reactions were carried out. A mixture of nitrones **15** (0.140 M) and **12** (0.146 M) and methyl methacrylate (0.147 M) in $CDCl_3$ at 36 °C was allowed to undergo cycloaddition reaction. A careful analysis of the ^1H NMR spectrum, after complete consumption of the alkene, revealed the presence of unreacted **15** (0.0577 M), **12** (0.0413 M), and the cycloaddition products. The rate ratio k_2(**12**)/k_2(**15**), as determined

using the rate equation of Ingold and Shaw[19] was found to be 1.42. In a similar competing reaction with methyl acrylate, the rate ratio was found to be 1.36. The rate ratio was thus found to be similar to that obtained from the reported values of the addition reaction of nitrone **15** (Table 1).[14]

3.8. Reaction of nitrone 12 with 1-hexene (17)

To a solution of nitrone **12** (5.0 mmol) in CH_2Cl_2 (50 cm^3), exchanged with toluene (25 cm^3), was added 1-hexene (4 cm^3). The mixture was heated at 90 °C for 12 h under N_2 in a closed vessel. After removal of the solvent and excess alkene the residual crude mixture of cycloadducts was separated by chromatography over silica using 80:20 hexane/ether as eluant to give **19a** as a colorless liquid. Continued elution gave a mixture **18a** and **19a** followed by a pure sample of **18a** as colorless liquid. The combined yield of the cycloadducts was found to be 80%. Careful ^1H NMR analysis of the non-overlapping signals at δ 3.48 (minor adduct) and 4.39 (major invertomer of the major adduct) and 4.02 (minor invertomer of the major adduct) of the crude and the separated fraction revealed the ratio of the isomers **18a** and **19a** as 90:10, respectively.

3.8.1. Major diastereomer *18a*

The ^1H spectrum at +25 °C revealed the presence of two invertomers by displaying C(2)H proton signals at δ 4.39 (major) and 4.02 (minor) ppm in a ratio of 58:42. The other non-overlapping signals were at δ 3.61 (major) and 3.35 (minor) ppm. (Found: C, 67.7; H, 10.2; N, 4.9. $C_{16}H_{29}NO_3$ requires C, 67.81; H, 10.31; N, 4.94%.) ν_{max} (neat) 2957, 2929, 2867, 1730, 1454, 1299, 1256, 1179, 1082, 1005, 938, and 841 cm^{-1}.

*3.8.1.1. Major invertomer of **18a**.* δ_H ($CDCl_3$, +25 °C) 0.92 (6H, m), 1.10–2.25 (18H, m), 3.11 (1H, dt, *J* 3.5, 10.7 Hz), 3.61 (1H, m), 4.08 (2H, m), 4.39 (1H, m); δ_C ($CDCl_3$, +25 °C) 13.71 (2C), 19.13, 22.71, 26.96, 27.75, 28.15, 30.65, 35.26, 35.43, 36.05, 48.65, 58.95, 64.51, 77.25, 174.68.

*3.8.1.2. Minor invertomer of **18a**.* δ_C ($CDCl_3$, +25 °C) 14.04 (2C), 19.22, 22.71, 26.17, 28.00, 30.65, 30.81, 34.91, 37.66, 39.86, 52.37, 62.96, 64.55, 76.15, 174.23.

3.8.2. Minor diastereomer *19a*

The sharp proton and carbon signals at +25 °C or −30 °C indicated the presence of a single invertomer. (Found: C, 67.6; H, 10.1; N, 4.8. $C_{16}H_{29}NO_3$ requires C, 67.81; H, 10.31; N, 4.94%.) ν_{max} (neat) 2958, 2931, 2872, 2822, 1732, 1468, 1455, 1380, 1362, 1249, 1183, 1147, 1134, 1062, 1010, 962, 905, and 780 cm^{-1}; δ_H ($CDCl_3$, +25 °C) 0.92 (6H, two overlapping triplets), 1.20–2.55 (19H, m), 3.48 (1H, m), 4.08 (2H, t, *J* 6.8 Hz), 4.08 (1H, overlapping m); δ_C ($CDCl_3$, +25 °C) 13.66, 13.96, 19.08, 22.65, 27.44, 27.94, 30.60, 31.80, 34.86, 39.57, 41.44, 53.61, 64.37, 65.37, 76.54, 174.29.

3.9. Reaction of nitrone 12 with styrene (20)

To a solution of nitrone **12** (5.0 mmol) in CH_2Cl_2 (50 cm^3), exchanged with toluene (25 cm^3), was added styrene (4 cm^3). The mixture was heated at 90 °C for 12 h under N_2 in a closed vessel. After removal of the solvent and excess alkene the residual crude mixture of cycloadducts was separated by chromatography over silica using 70:30 hexane/ether as eluant to give **23a** as a colorless liquid. Continued elution gave a mixture **21a**–**24a** followed by a pure sample of **21a** as white crystals. The combined yield of the cycloadducts was found to be 84%. A careful ^1H NMR ($CDCl_3$, −30 °C) analysis of the middle fraction revealed the presence of minor isomers **22a** and **24a**; the C(2)H of the invertomers of **22a** appeared at δ 5.29 (t, *J* 8.5 Hz) and 5.12 (t, *J* 8.5 Hz) in a ~60:40 ratio, while the signal at δ 5.22 ppm was attributed to the C(2)H of **24a**. The complete ^1H NMR analysis of the C(2)H of crude and the separated fraction revealed the ratio of the isomers **21a**–**24a** as 88:2.5:9:0.5, respectively.

3.9.1. Major diastereomer *21a*

Mp 61–62 °C (Hexane/ether). (Found: C, 71.1; H, 8.2; N, 4.5. $C_{18}H_{25}NO_3$ requires C, 71.26; H, 8.31; N, 4.62%.) ν_{max} (KBr) 3050, 2960, 2856, 1727, 1453, 1370, 1305, 1259, 1129, 1061, 1012, 942, 765, and 705 cm^{-1}. The major and minor invertomer at +25 °C was found to be in a ratio of 55:45 as determined by integration of the C(2)H. (The ratio becomes 60:40 at −40 °C).

*3.9.1.1. Major invertomer of **21a**.* δ_H ($CDCl_3$, +25 °C) 0.94 (3H, t, *J* 7.3 Hz), 1.39 (2H, m), 1.50–2.80 (9H, m), 2. 87 (1H, m), 3.25 (1H, m), 3.87 (1H, m), 4.10 (2H, m), 5.40 (1H, dd, *J* 4.0, 9.8 Hz), 7.34 (5H, m); δ_C ($CDCl_3$, +25 °C) 13.70, 19.13, 26.86, 27.64, 30.65, 36.07, 38.88, 48.87, 59.38, 64.59, 78.69, 126.30 (2C), 126.64, 128.47 (2C), 142.28, 175.51.

*3.9.1.2. Minor invertomer of **21a**.* δ_H ($CDCl_3$, +25 °C). Minor invertomer has the following non-overlapping signals: δ 5.02 (1H, dd, *J* 3.5 and 9.3 Hz), 3.44 (1H, m); δ_C ($CDCl_3$, +25 °C) 13.70, 19.23, 26.23, 30.70, 30.82, 37.61, 42.95, 52.50, 63.47, 64.59, 77.75, 126.80 (2C), 127.79, 128.47 (2C), 141.46, 174.20.

3.9.2. Minor diastereomer *23a*

The sharp proton and carbon signals at +25 °C or −40 °C indicated the presence of a single invertomer. Colorless liquid. (Found: C, 71.1; H, 8.1; N, 4.4. $C_{18}H_{25}NO_3$ requires C, 71.26; H, 8.31; N, 4.62%.) ν_{max} (neat) 3026, 2958, 2929, 2871, 1730, 1451, 1357, 1290, 1248, 1183, 1063, 1007, 947, 941, 758, and 700 cm^{-1}; δ_H ($CDCl_3$, +25 °C) 0.94 (3H, t, *J* 7.4 Hz), 1.38 (2H, m), 1.50–2.70 (11H, m), 3.57 (1H, m), 4.09 (2H, t, *J* 6.6 Hz), 5.08 (1H, dd, *J* 4.3, 9.5 Hz), 7.34 (5H, m); δ_C ($CDCl_3$, +25 °C) 13.71, 19.14, 27.54, 30.66, 31.82, 41.46, 42.65, 53.81, 64.51, 65.91, 78.17, 126.72 (2C), 127.85, 128.48 (2C), 142.28, 175.51.

3.10. Reaction of nitrone 12 with methyl acrylate (25)

To a solution of nitrone (5.0 mmol) in CH_2Cl_2 (50 cm^3) was added methyl acrylate (1.5 cm^3). The mixture was stirred at 20 °C for 2 h under N_2. After removal of the solvent and excess alkene the residual crude mixture of cycloadducts was purified by chromatography over silica using 1:1 hexane/ether as eluant to give a non-separable C(3)-substituted isomers **30a**–**33a** as a colorless liquid. Continued elution gave a non-separable mixture of C(2)-substituted isomers **26a**–**29a**. The combined yield of the cycloadducts was found to be 87%. The crude product is expected to contain eight possible isomers, each of which may have two invertomers, and as such it was extremely difficult to unambiguously assign regio- and stereochemistry of the isomers by NMR spectroscopy. However, an attempt was made to determine the composition of the cycloadducts by correlating their ^1H NMR with those of the methyl acrylate adducts **26b**, **27b**, **30b**, and **31b** of the corresponding parent nitrone **15**.[20] The C(2)Hs of the C(2)-substituted adducts **26b** and **27b** in $CDCl_3$ appeared at the chemical shifts δ >4.4 ppm, while the C(2)Hs of the C(3)-substituetd adducts **30b** and **31b** appeared in the range δ 4.0–4.25 ppm. Fortunately, the chromatography permitted the separation of the C(2)-substituted adducts **26a**–**29a** from the C(3)-substituted adducts **30a**–**33a**. A careful analysis of the crude and separated isomers revealed the ratio of C(2)-(**26a**–**29a**) and C(3)-substituted adducts (**30a**–**33a**) as 85:15, respectively. The ^1H NMR spectrum of the mixture of C(2)-substituted isomers (**26a**–**29a**) under fast nitrogen inversion in toluene-d_8 at 80 °C revealed the presence of isomer **26a**, **27a**, and

(**28a**+**29a**) in the percentages of 62, 16, and 7 (out of a total of 85%), respectively, as indicated by integration of the signals of the C(2)H at δ 4.44(1H, dd, *J* 3.7, 9.7 Hz), 4.24 (1H, t, *J* 8.0 Hz), and 4.36 (two overlapping signals, m). The ratio of the isomers **26a**, **27a**, (**28a**+**29a**), and (Σ**30a**−**33a**) thus becomes 62:16:7:15, respectively. An approximate ratio of (**26a**+**27a**) and (**28a**+**29a**), i.e., (62+16):7 or 91:9 reflects the face selectivity associated with the addition of this alkene leading to C(2)-substituted adducts. Note that the ^{1}H NMR spectrum of the methyl acrylate adducts **26b**, **27b**, **30b**, and **31b** of the parent nitrone **15** was also examined in this work. C(2)Hs appeared in the similar chemical shifts as that of the nitrone **12** adducts in toluene-d_8 at 80 °C. A non-separable mixture of the C(2) substituted isomers (**26a**–**29a**). Colorless liquid. (Found: C, 58.7; H, 8.0; N, 4.8. $C_{14}H_{23}NO_5$ requires C, 58.93; H, 8.12; N, 4.91%.) ν_{max} (neat) 2957, 2929, 2867, 1736, 1731, 1449, 1438, 1372, 1294, 1203, 1180, 1097, 1063, and 1022 cm^{-1}.

3.11. Cycloaddition of nitrone 12 with methyl methacrylate (34)

A solution of nitrone **12** (5.0 mmol) and methyl methacrylate (2 cm^3) in CH_2Cl_2 (50 cm^3) was heated in a closed vessel at 45 °C for 12 h. After removal of the solvent and excess alkene the residual crude mixture of cycloadducts was separated by chromatography over silica using 70:30 hexane/ether as eluant to give **37a**. Continued elution gave a mixture of **35a**–**37a** followed by a pure sample of **35a** as a colorless liquid. The combined yield of the cycloadducts was found to be 92%. A careful ^{1}H NMR ($CDCl_3$, −30 °C) analysis of the C(3a)H of the crude and the separated fraction revealed the ratio of the isomers **35a**–**37a** as 88:9:3, respectively. An analysis of the ^{1}H NMR spectrum of the fraction containing **35a**–**37a** revealed the C(3a)H of **37a** and **36a** as dt at δ 3.56 and 3.42 ppm, and CO_2Me singlets at δ 3.81 and 3.79 ppm, respectively. The C(3a)H of the major and minor invertomers of **35a** appeared at δ 3.47 and 3.21 ppm, and CO_2Me singlets at δ 3.80 and 3.82 ppm, respectively. We could not detect the isomer **38a**.

*3.11.1. Major diastereomer **35a***

(Found: C, 60.0; H, 8.3; N, 4.6. $C_{15}H_{25}NO_5$ requires C, 60.18; H, 8.42; N, 4.68%.) ν_{max} (neat) 2959, 2929, 2867, 1730, 1452, 1372, 1299, 1261, 1181, 1129, 1097, 1058, 1005, 986, 923, 841, and 754 cm^{-1}; δ_H ($CDCl_3$, +25 °C) 0.94 (3H, t, *J* 7.0 Hz), 1.39 (2H, m), 1.48 (3H, s), 1.63 (2H, m), 1.80–2.85 (9H, m), 3.17 (0.27×1H, m), 3.41 (0.73×1H, m), 3.76 (3H, s), 4.11 (2H, m). Room temperature proton spectrum revealed the presence of two invertomers in a ratio of 73:27 as indicated by the presence of signals at δ 3.17 (minor), and 3.41 (major) ppm attributed to the C(3a)H.

*3.11.1.1. Major invertomer of **35a**.* δ_H ($CDCl_3$, −30 °C) 0.95 (3H, t, *J* 7.0 Hz), 1.39 (2H, hex, *J* 7.4 Hz), 1.51 (3H, s), 1.63 (2H, m), 1.80–2.80 (9H, m), 3.47 (1H, td, *J* 3.9, 9.5 Hz), 3.80 (3H, s), 4.10 (2H, m); δ_C ($CDCl_3$, −30 °C) 13.84, 19.06, 24.69, 25.58, 29.89, 30.37, 37.05, 44.30, 52.48, 53.08, 63.33, 64.65, 79.92, 174.21, 175.74.

*3.11.1.2. Minor invertomer of **35a**.* ^{1}H NMR spectrum ($CDCl_3$, −30 °C) of **35a** revealed the non-overlapping signals for the minor invertomers at δ 0.93 (overlapping 3H, t), 1.54 (3H, s), 3.21 (1H, td, *J* 3.3, 10.7 Hz), 3.82 (3H, s); δ_C ($CDCl_3$, −30 °C) 13.84, 19.13, 25.76, 27.01, 29.89, 30.37, 35.55, 44.30, 49.57, 52.96, 59.38, 64.74, 84.14, 174.54, 175.54.

*3.11.2. Minor diastereomer **37a***

(Found: C, 59.9; H, 8.2; N, 4.5. $C_{15}H_{25}NO_5$ requires C, 60.18; H, 8.42; N, 4.68%.) ν_{max} (neat) 2958, 2929, 2867, 1732, 1455, 1371, 1298, 1258, 1174, 1148, 1097, 1062, 1020, and 927 cm^{-1}; δ_H ($CDCl_3$, +25 °C) 0.94 (3H, t, *J* 7.3 Hz), 1.38 (2H, hext, *J* 7.5 Hz), 1.48 (3H, s), 1.53 (2H, m), 1.80–2.55 (9H, m), 3.54 (1H, td, *J* 3.5, 9.5 Hz), 3.78 (3H, s), 4.07 (2H, t, *J* 6.8); δ_C ($CDCl_3$, +25 °C) 13.72, 19.12, 24.50, 27.14, 30.66, 31.33, 41.23, 44.33, 52.46, 53.74, 64.35, 65.85, 80.51, 173.76, 175.19. The spectra at room temperature as well as −30 °C have sharp and more or less similar signals, and indicated the absence of the minor invertomer.

3.12. Cycloaddition of nitrone 12 with methyl crotonate (39)

To a solution of nitrone **12** (5.0 mmol) in CH_2Cl_2 (50 cm^3), exchanged with toluene (25 cm^3), was added methyl crotonate (**39**) (4 cm^3). The mixture was heated at 90 °C for 12 h under N_2 in a closed vessel. After removal of the solvent and excess alkene the residual crude mixture of cycloadducts was purified by chromatography over silica using 70:30 hexane/ether as eluant to give a non-separable mixture of adducts **40a**–**42a** as a colorless liquid. The cycloadducts was isolated 77% yield. Careful ^{1}H NMR analysis of the C(2)H crude and the separated fraction revealed the ratio of the isomers **40a**–**42a** as 87:8:5, respectively, as determined by integration of C(2)H signals. The major and minor invertomers of **40a** at +25 °C were found to be in a ratio of 80:20 as determined by integration of the C(2)H, which appeared at δ 4.48 (quint, major) and 4.85 (br, minor). These signals broaden and coalesce at higher temperatures. The C(2)H of **41a** appeared at δ 4.35 ppm. We could not detect the minor invertomer of the compound **41a**. Another isomer **42a** was revealed by a sharp quintet at δ 4.54 (*J* 6.2 Hz). Mixture of non-separable isomers **40a**–**42a**. (Found: C, 59.9; H, 8.2; N, 4.6. $C_{15}H_{25}NO_5$ requires C, 60.18; H, 8.42; N, 4.68%.) ν_{max} (neat) 2860, 2929, 2867, 1730, 1439, 1381, 1328, 1299, 1181, 1102, 1063, 1024, 967, 904, 880, 841, and 769 cm^{-1}. The following NMR signals were attributed to the major invertomer of the major adduct **40a**: δ_H ($CDCl_3$, +25 °C) 0.95 (3H, t, *J* 7.4 Hz), 1.32 (3H, d, *J* 6.1 Hz), 1.30–2.00 (6H, m, excluding the doublet at 1.32), 2.10–2.65 (4H, m), 2.73 (1H, m), 2.86 (1H, m), 3.40 (1H, m), 3.73 (3H, s), 4.12 (2H, m), 4.48 (1H, *J* 5.8 Hz); δ_C ($CDCl_3$, −40 °C) 13.87, 19.13, 19.34, 25.44, 27.59, 30.33, 36.94, 52.30, 52.55, 56.45, 64.85, 65.88, 75.21, 172.31, 173.96. The spectrum at −40 °C was very much similar to that at +25 °C.

3.13. MCPBA oxidation of styrene adduct 21a

To a stirred solution of the cycloadduct **21a** (1.0 mmol) in dichloromethane (15 cm^3) at −10 °C was added MCPBA (1.1 mmol) in one portion. After 1 h at −5 to 0 °C the organic layer was washed with 5% $NaHCO_3$ solution (3×10 cm^3). The combined aqueous layers were re-extracted with CH_2Cl_2 (2×10 cm^3). The combined organic layers were dried (Na_2SO_4), concentrated to give a mixture of the aldo- and keto-nitrones in a ratio of 52:48, respectively, as a pale yellow liquid in almost quantitative yield. The mixture of nitrone was purified by chromatography over 95:5 ether/methanol mixture as the eluant to give a mixture of non-separable nitrones **44a** and **45a**. However, ketonitrone **44a** was separated by crystallizing a solution of the mixture in ether/dichloromethane.

*3.13.1. Compound **44a***

Mp 97–98 °C (ether/CH_2Cl_2). (Found: C, 67.6; H, 7.8; N, 4.3. $C_{18}H_{25}NO_4$ requires C, 67.69; H, 7.89; N, 4.39%.) ν_{max} (KBr) 3435, 3180, 2953, 2867, 1729, 1647, 1507, 1456, 1333, 1251, 1183, 1140, 1053, 745, and 692 cm^{-1}; δ_H ($CDCl_3$, +25 °C) 0.94 (3H, t, *J* 7.3 Hz), 1.36 (2H, hex, *J* 7.3 Hz), 1.60 (2H, quint, *J* 7.3 Hz), 1.98 (1H, m), 2.26 (1H, m), 2.35 (1H, m), 2.65 (1H, m), 2.72 (1H, m), 2.87 (1H, dd, *J* 2.5, 13.4 Hz), 3.11 (1H, dd, *J* 8.7, 13.4 Hz), 3.92 (2H, m), 4.10 (2H, m), 5.15 (1H, dd, *J* 2.5, 8.7 Hz), 6.96 (1H, br OH), 7.35 (5H, m); δ_C ($CDCl_3$, +25 °C) 13.68, 19.08, 25.34, 30.53, 32.85, 35.60, 42.77, 56.76, 65.29, 73.89, 125.26 (2C), 127.49, 128.45 (2C), 144.33, 147.57, 172.33. The aldonitrone **45a** has the following non-overlapping proton signals in the ^{1}H NMR spectrum of the mixture containing the nitrones **44a**

and **45a**: δ_H ($CDCl_3$, +25 °C) 0.93 (3H, t, *J* 7.3 Hz), 1.35 (2H, m), 5.06 (1H, m), 7.21 (1H, t, *J* 4.0 Hz).

3.14. Cycloaddition reaction of nitrone 12 in the micellar media

A solution of the nitrone **12** (0.5 mmol) in CH_2Cl_2 was exchanged with water (3 cm^3) containing the surfactant CTAB (0.05 mmol). The mixture was sonicated for 5 min, and stirred using a magnetic stir bar. Thereafter methyl acrylate (1 mmol) was added and the reaction mixture was stirred at 20 °C for 12 h. The cycloadducts were extracted with ether (3×15 cm^3). The combined organic layers were dried (Na_2SO_4), concentrated and purified by silica gel chromatography using hexane/ether mixtures as the eluant to give the cycloadducts **26a**–**33a** in 88% yield. ^{1}H NMR spectroscopy revealed the composition of the cycloadducts as similar to the cycloadducts obtained in the reaction carried out in the organic solvent (Section 3.9). When the above experiment was repeated by changing the amount of CTAB to 0.14, 0.25, 0.5 mmol, while keeping the other concentrations constant, each time a mixture of cycloadducts was obtained in similar yield and composition as above. Repeating the reaction in the presence of the surfactant SDS (0.05 mmol) (instead of the CTAB) and sucrose (0.05 mmol) gave cycloadducts **26a**–**33a**; however, no change in the composition of the adducts was observed.

The above micellar reactions involving SDS or CTAB were repeated using styrene in place of methyl acrylate at 40 °C for 36 h. Again a mixture of cycloadducts **21a**–**24a** (yields in the range 75–85%), having composition similar to that obtained in the reaction carried out in the organic solvent (Section 3.8), was formed.

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