Synthesis and Structure of Condensed Heterocycles Derived from Intramolecular 1,3-Dipolar Cycloaddition of Transient and Enantiomerically Pure α-Allylamino Nitrones and Nitrile Oxides in a High Level of Diastereoselectivity

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Abstract: A series of typical nitrone and nitrile oxide derivatives was generated in situ from the corresponding sulfonylated α-allylamino aldehydes and aldoximes, which afforded isoxazolidine and isoxazoline fused heterocycles by intramolecular 1,3-dipolar cycloaddition reactions with a high degree of diastereoselectivity. The structure as well as the absolute stereochemistry of the products were confirmed by extensive 2D-NMR spectroscopy and single crystal X-ray analyses and the reasons for the observed selectivity were explained by the energy calculations of the transition states using semiemprical (MOPAC AM1 and MOPAC PM3) and ab initio methods (3-21G* and 6-31G*).

Key words: 1,3-dipolar cycloaddition, nitrones, nitrile oxides, transition states, diastereoselectivity

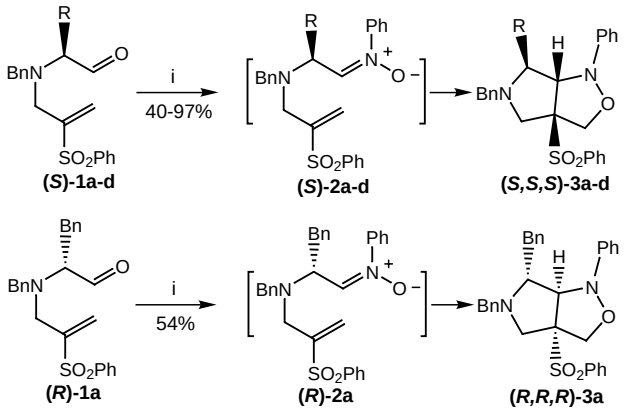
Reactions in which the formation of a new carbon-carbon or carbon-heteroatom bond provide new stereogenic centers with a high level of enantio- and diastereoselectivity are of special interest for asymmetric synthesis.[1] The 1,3-dipolar cycloaddition is such a reaction, which conserves the stereochemistry of the alkene, and in which, a stereocenter on the dipole is often able to influence the relative stereochemistry of the newly formed stereogenic centers in the product.[2] Even greater stereocontrol is possible when both reactants are a part of the same molecule, the intramolecular nature, which often enhances the stereoselectivity of the cyclization process.[3,4] As a result, this type of cyclization could be applied to the synthesis of targeted macromolecules, for example, sugar derivatives,[5] β-lactams,[6] amino acids,[7] alkaloids[8] and other interesting classes of compounds. Also, considerable attention has been paid to a basic survey of this process but the general rules for the regio- and stereoselectivities are still obscure.[9] Among the other 1,3-dipolar cycloadditions, the intramolecular nitrone olefin cycloaddition and intramolecular nitrile oxide olefin cycloaddition have been of considerable synthetic and mechanistic interest,[10,11] especially since the resulting heterocycles can serve as precursors of synthetic equivalents,[12] such as amino alcohols,[13] and hydroxy ketones,[14] or other functional groups.[15] More closely, while isoxazoli(di)nes are very readily available, their potential as latent synthetic equivalents has only recently begun to be realized.[16] On the other hand, the dipolarophilic activity of the C-C double, triple or heteromultiple bonds depends significantly on the belonging substituents and the introduction of electron-donating or electron-withdrawing substituents on the dipole or the alkene can alter the relative frontier orbital energies,[17–18] which could influence the reactivity as well as the selectivity of the process.[19]

Recently, we have described a series of chiral auxiliary controlled diastereoselective intramolecular Diels–Alder reactions of sulfonyl-substituted trienes.[20] In this paper, we report a series of intramolecular 1,3-dipolar cycloaddition reaction of nitrones and nitrile oxides with alkenes having an electron-withdrawing substituent and which contain a chiral auxiliary at the allylic position. In addition, the transition state energy of conformers responsible for producing the selective stereoisomers, the stereochemistry of the cycloadducts, and the subsequent ring opening reaction to synthetic equivalents are discussed.

As the nitrones **2a–d** are very unstable species (Scheme 1), they were generated in situ from the corresponding α-allylamino aldehydes[20] **1a–d** in anhydrous diethyl ether at room temperature and smoothly cyclized to afford the bicyclic heterocycles **3a–d** in good yields (Table 1).

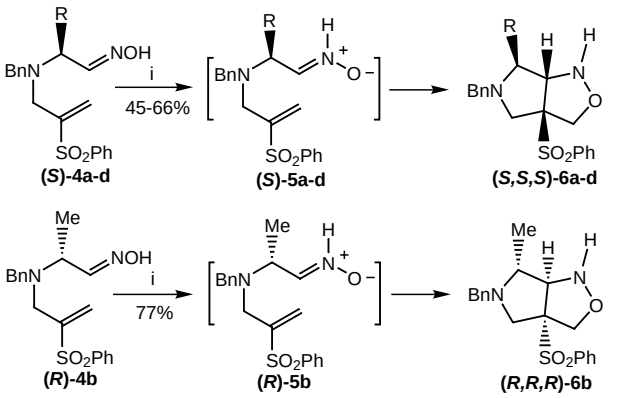
The oximation[2] of **1a–d** by hydroxylammonium chloride in aqueous ethanol in the presence of sodium hydroxide gave α-allylamino aldoximes **4a–d**, which were also catalytically tautomerized into their nitrones **5a–d** by zinc chloride in an in situ fashion (Scheme 2) in boiling benzene and were intramolecularly cyclized[17] to produce condensed heterocycles **6a–d** (Table 2).

The structural assignment of all the diastereomerically pure new molecules were ascertained by IR, ^{1}H and ^{13}C NMR, DEPT, 2D-COSY, HMQC, 2D-NOESY, and HRMS spectra and confirmed by a single crystal X-ray analysis of (*S*,*S*,*S*)-**3a** (Figure 1).



Reagents and conditions: i) $PhNHOH/CaCl_2/Et_2O$, 0°C to r. t.

Scheme 1



Reagents and conditions: i) $ZnCl_2$/benzene, reflux

Scheme 2

Table 1 Diastereoselective Synthesis of Compounds **3**

Product	R	Yield (%)	$[\alpha]_D^{25}$ (c=1.0, $CHCl_3$)	de[a] (%)
(*S*,*S*,*S*)-**3a**	Bn	77	+176.2[c]	>96[b]
(*S*,*S*,*S*)-**3b**	Me	63	+158.9[d]	>96[b]
(*S*,*S*,*S*)-**3c**	*i*-Pr	40	+230.7	>96[b]
(*S*,*S*,*S*)-**3d**	*i*-Bu	97	+148.0[e]	>96[b]
(*R*,*R*,*R*)-**3a**	Bn	54	–173.4[d]	>96[b]
(*S*,*R*,*S*)-**3e**	$(CH_2)_3$	65	+ 54.4	>96[b]

[a] The de values were determined by ^{1}H NMR spectroscopy (Bruker DRX 500 MHz spectrometer).
[b] In ^{1}H NMR spectrum there were no peaks corresponding to the other isomers.
[c] Recorded at 27°C.
[d] Recorded at 26°C.
[e] Recorded at 23°C.

Table 2 Diastereoselective Synthesis of Compounds **6**

Product	R	Yield (%)	$[\alpha]_D^{25}$ (c=1.0, $CHCl_3$)	de[a] (%)
(*S*,*S*,*S*)-**6a**	Bn	66	+156.9[c]	70
(*S*,*S*,*S*)-**6b**	Me	55	+137.6	>96[b]
(*S*,*S*,*S*)-**6c**	*i*-Pr	60	+238.7	77
(*S*,*S*,*S*)-**6d**	*i*-Bu	45	+101.9	82
(*R*,*R*,*R*)-**6b**	Bn	77	–131.3	>96[b]

[a] The de values were determined by ^{1}H NMR spectroscopy (Bruker DRX 500 MHz spectrometer).
[b] In ^{1}H NMR spectrum there were no peaks corresponding to the other isomers.
[c] Recorded at 26°C.

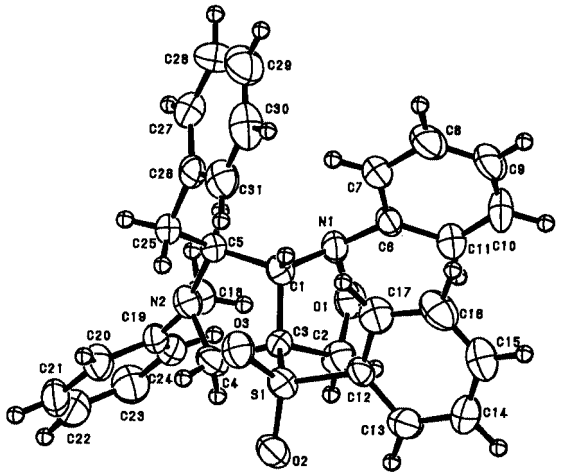


Figure 1 X-ray crystal structure of (*S*,*S*,*S*)-**3a**.
Selected bond lengths (Å) and bond angles (°): N1−C1 1.470 (8), O1−N1 1.440 (7), O1−C2 1.415 (8), C2−C3 1.550 (9), C3−C4 1.576 (9), C1−C3 1.533 (8), N2−C4 1.460 (8), N2−C5 1.469 (8), C1−C5 1.563 (8), O1−N1−C1 105.7 (5), N1−O1−C2 106.9 (5), O1−C2−C3 106.2 (5), C2−C3−C4 114.3 (6), C1−C3−C2 101.7 (5), C1−C3−C4 104.7 (5), C4−N2−C5 107.1 (5), N2−C4−C3 107.1 (5), N2−C5−C1 106.4 (5), C3−C1−C5 105.7 (5), N1−C1−C3 107.6 (5).[36]

The *cis*-selectivity can be explained by calculation of each transition state (**TS**) energy by CAChe MOPAC AM1 calculations (Figure 2), according to which, the heat of formation belonging to the *endo-re* (**TS 1**, 57.33 kcal/mol) conformer was 0.48 kcal/mol less than that of the *endo-si* facial congener (**TS 2**, 57.81 kcal/mol). On the other hand, the energy difference between the *exo-re* (**TS 3**) and *exo-si* (**TS 4**) facial conformers was 3.47 kcal/mol, but the mean difference between the energy of the two sets of transition states was considerable, i.e. the *endo*-set was 10.47 kcal/mol less than that of corresponding *exo*-set. Therefore, the *endo-re* facial transition state (**TS 1**) should be responsible for the observed selectivity. As the energy difference between *endo-re* (**TS 1**) and *endo-si* (**TS 2**) was very small, the absolute energy level of the *endo*-set was further calculated using ab initio methods (6-31G*) based

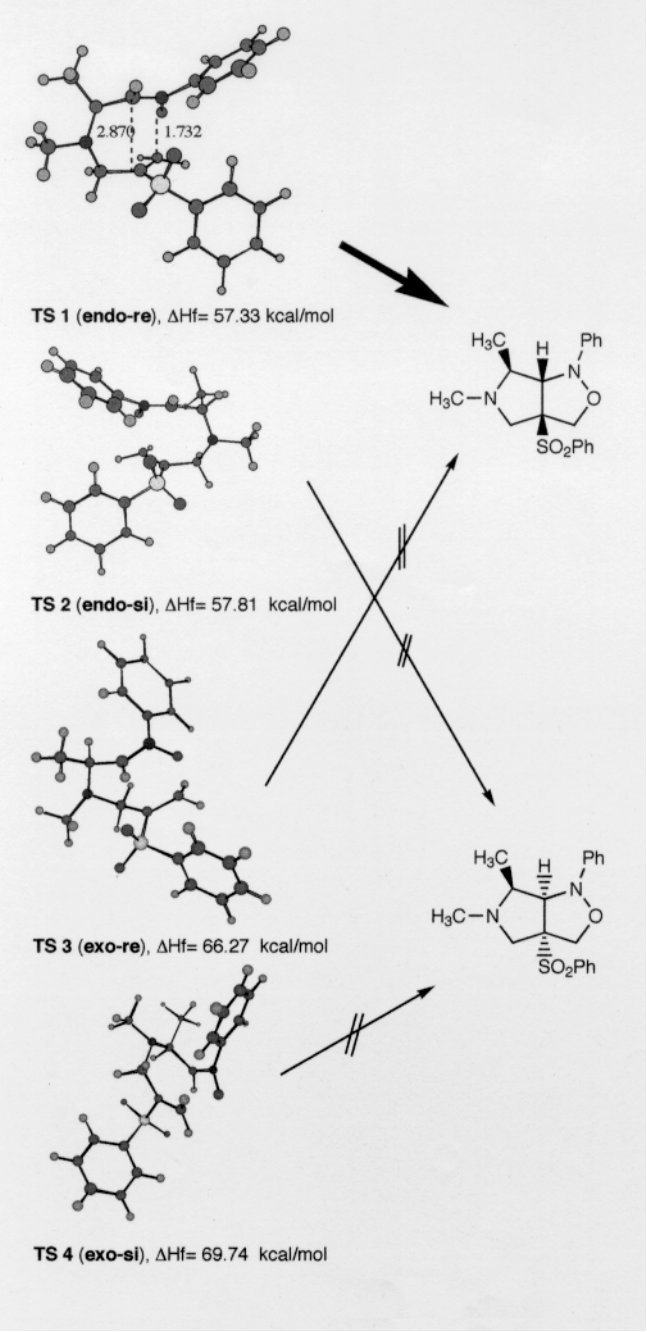


Figure 2 Transition state (TS) energies as calculated by MOPAC AM 1

on the structures located by AM1. The energies of **TS 1** and **TS 2** were estimated as −1463.0041051 and −1462.998336 Hartree respectively, from such values the difference in energies between **TS 1** and **TS 2** was calculated to be 0.0058 Hartree (3.58 kcal/mol), which is large enough to control the π-facial (*si*- face) selectivity. In a similar way, the facially identical conformers were assumed to be involved in the intramolecular cycloaddition of nitrone (*R*)-**2a** and (*R*)-**5b** to afford (*R,R,R*)-**3a** and (*R,R,R*)-**6b**, respectively. The optical characteristics of the cycloadducts having potentially opposite configurations were confirmed by the specific rotation and their circular dichroism spectra. The AM1 results would be due to the different appreciation of the steric repulsion between the oxygen of the nitrone and the substituent on the chiral center, which were more closer to **TS 2** compared to **TS 1**, as confirmed by the space filling model of individual transition states (Figure 3).

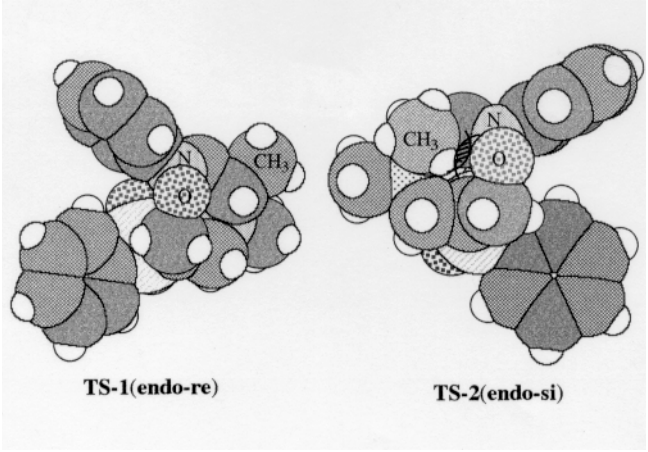
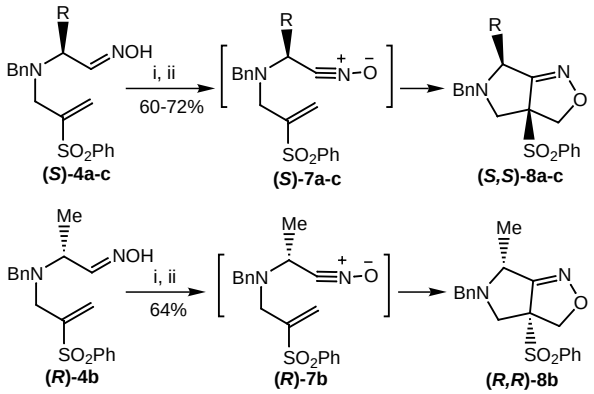


Figure 3 Space filling models of **TS-1** and **TS-2**

The chiral nitrile oxides **7a–c** were generated[21] from the oximes **4a–c** using NBS in THF in the presence of a catalytic amount of pyridine at room temperature in the same fashion. The cyclization[21] was performed in the presence of triethylamine in boiling toluene to give diastereomerically pure isoxazoline derivatives **8a–c** (Scheme 3, Table 3) in good yields.



Reagents and conditions: i) NBS/pyridine/THF, r.t.; ii) Et_3N/toluene, reflux

Scheme 3

A detailed analysis of the ^1H NMR spectra of the cycloadducts disclosed the coupling patterns which were confirmed by the 2D-COSY experiments. In fact, we have

Table 3 Diastereoselective Synthesis of Compounds **8**

Product	R	Yield (%)	de[a] (%)
(*S*,*S*)-**8a**	Bn	65	73[b]
(*S*,*S*)-**8b**	Me	60	>96[c]
(*S*,*S*)-**8c**	*i*-Pr	72	>96[c]
(*R*,*R*)-**8b**	Me	64	>96[c]

[a] The de values were determined by ^{1}H NMR spectroscopy (Bruker DRX 500 MHz spectrometer).
[b] Determined by Bruker DRX 400 MHz ^{1}H NMR spectrometer.
[c] In ^{1}H NMR spectrum there were no peaks corresponding to the other isomers.

often seen measurable coupling constants between the hydrogens located on the carbons α to an sp^2 center. The stereochemical information present in the dipolarophile was found to be retained in the cycloadducts confirmed by the 2D-NOESY spectra. In particular, irradiation of the H-10 signal (δ = 3.96) of (*S*,*S*)-**8c** resulted in a positive interaction of the signal for the Ph (ortho H) (δ = 7.53) group of SO_2Ph located at C-5 taken together with the absence of any such interaction between H-8 and SO_2Ph, suggesting a *cis*-relation among them (Figure 4)**.** Thus it was clear that in the current reaction, the stereocenter at the α-position to the nitrogen functionality can effectively control the formation of the new contiguous stereocenters and can regulate the process to produce one of the four possible stereoisomers in a selective fashion. We were pleased to observe the formation of the desired isoxazoline fused heterocyclic systems under a one-pot procedure by adapting the procedure of Kim et al.[21] with slight modifications. Subsequently, the analogs (*S*,*S*)-**8a**, (*S*,*S*)-**8b** and (*R*,*R*)-**8b** could be assigned as *cis*, based on their characteristic coupling patterns and NOESY behaviors. In general, the stereochemistry between the alkyl groups at C-8 and C-5 in the five membered rings fused to isoxazolines is predominantly *cis*; this observation has often been supported by energy calculations,[22,23] and examination of the molecular models reveals that the formation of pyrrolidine fused isoxazolines having *cis*-stereochemistry could take place via an *endo* transition state (Figure 5). This is in accord with the widely accepted view that approach of the dipole and dipolarophile takes place in two parallel planes[24,25] and that an *endo* transition state is preferred in the absence of obvious steric interactions.[26–29]

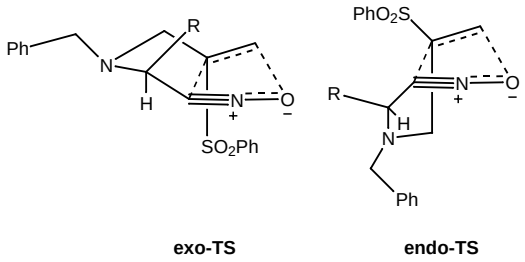
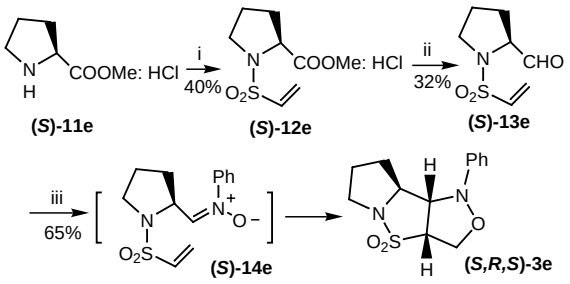


Figure 5 Transition states of nitrile oxide olefin cycloaddition

The reaction[30] of methyl L-prolinate hydrochloride [(*S*)-**11e**] with vinylsulfonyl chloride[31] in the presence of triethylamine at room temperature gave methyl *N*-(vinylsulfonyl) L-prolinate (*S*)-**12e** in 40% yield. A DIBAL reduction of (*S*)-**12e** in toluene at −78°C afforded *N*-vinylsulfonyl L-prolinal [(*S*)-**13e**] in 32% yield. The nitrone (*S*)-**14e** has been generated in situ from the reaction of (*S*)-**13e** with phenylhydroxylamine in THF in the presence of calcium chloride at room temperature and an intramolecular 1,3-dipolar cycloaddition which gave a tricyclic isoxazolidine derivative (*S*,*R*,*S*)-**3e** in 65% yield (Scheme 4 and Table 1).



Reagents and conditions: i) vinylsulfonyl chloride/Et_3N/CH_2Cl_2, r.t.; ii) DIBAL/toluene, −78°C; iii) $PhNHOH/CaCl_2$/THF, -10°C to r.t.

Scheme 4

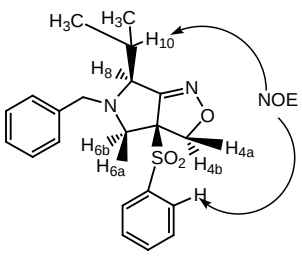
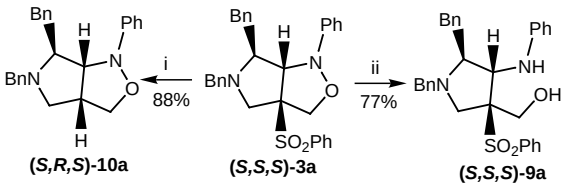


Figure 4 H-H NOE correlations of (*S*,*S*)-**8c.**

The structure of all the intermediate compounds were elucidated based on their IR, ^{1}H and ^{13}C NMR and DEPT spectra. The stereochemical courses of the cycloaddition of (*S*)-**14e** is comparable with the cycloaddition of analogous species (*S*)-**2a** because, in both cases the transition states afforded *N*-Ph substituted isoxazolidine systems, therefore, this can be assumed to have identical geometries, as it was confirmed by 2D-NOESY correlations for (*S*,*R*,*S*)-**3e**, which was further confirmed by a single crystal X-ray analysis (Figure 6). In addition, the transition state energy calculation is consistent with the observed

experimental results. Accordingly, the heat of formation of *re-re* and *si-si* facial transition states (Figure 7) differed by 3.68 kcal/mole, which was large enough to control the π-facial (*si*-face) selectivity. The reductive cleavage of the N-O bond of (*S*,*S*,*S*)-**3a** by Raney Ni (W-2) in anhydrous ethanol at room temperature afforded the γ-amino alcohol (*S*,*S*,*S*)-**9a** in good yield (Scheme 5). The presence of NH and OH groups was identified by the IR absorptions at ν = 3250 and at 3350 cm^{-1}, respectively. Furthermore, as expected, the stereochemical features acquired in the cycloaddition process have been retained in compound (*S*,*S*,*S*)-**9a**, as confirmed by the coupling constants and NOE experiments. In addition, the reductive desulfurization of (*S*,*S*,*S*)-**3a** by $LiAlH_4$ in THF at room temperature gave (*S*,*R*,*S*)-**10a** in 88% yield (Scheme 5), where the absorptions of NH and OH was not observed in the IR spectrum of **10a**.



Reagents and conditions: i) $LiAlH_4$/THF, reflux; ii) Raney Ni (W-2)/EtOH, r.t.

Scheme 5

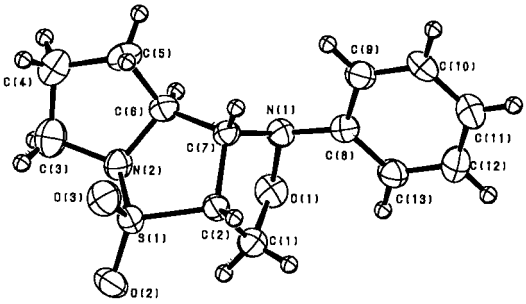


Figure 6 X-ray crystal structure of (*S*,*R*,*S*)-**3e**. Selected bond lengths (Å) and bond angles (°): S(1)−N(2) 1.660(6), N(2)−C(6) 1.491(8), C(6)−C(7) 1.549(8), C(2)−C(7) 1.565(8), N(1)−C(7) 1.460(8), O(1)−N(1) 1.430(7), O(1)−C(1) 1.465(8), C(1)−C(2) 1.52(1), S(1)−C(2) 1.773(6), S(1)−C(2)−(1) 114.6(5), N(2)−S(1)−C(2) 94.2(3), C(2)−C(7)−(6) 107.7(5), N(1)−C(7)−C(2) 104.3(5), S(1)−N(2)−C(6) 108.8(4), N(2)−C(6)−C(7) 109.1(5), N(1)−C(7)−C(6) 110.1(6), O(1)−N(1)−C(7) 104.1(4), N(1)−O(1)−C(1) 106.0(5).[36]

According to the basic investigation of Robb et al.[32] and Nguyen et al.[33] by ab initio studies, the intermolecular 1,3-dipolar cycloaddition of a simple nitrone and ethylene proceeded as a concerted process. Furthermore, Pascal and his co-workers[34] reported the semiempirical studies of the reactions. Their results were in good agreement with

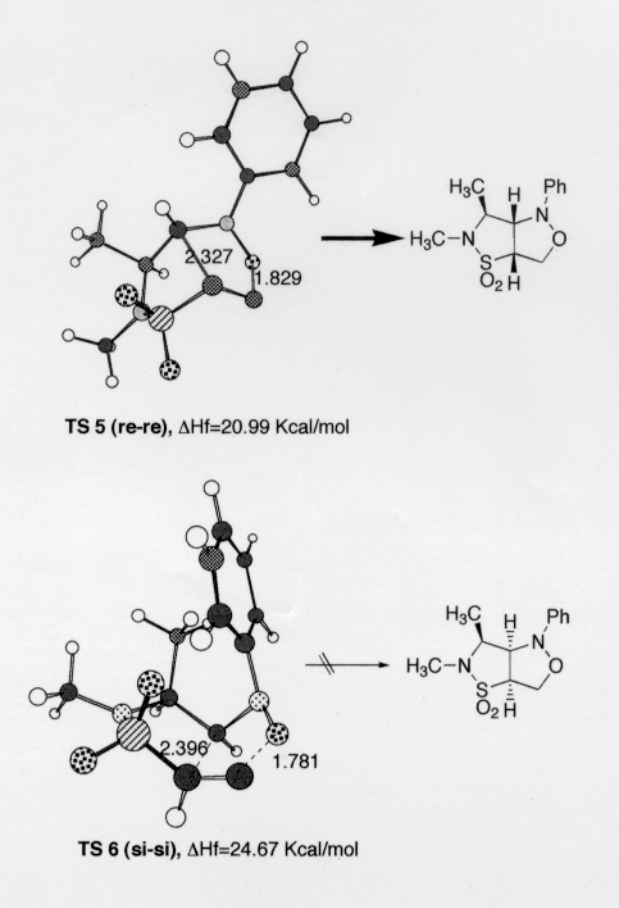


Figure 7 Transition state (**TS**) energies as calculated by MOPAC PM3

the concerted mechanism. In the present study, the interatomic distances of the involved atoms at transition state **TS 1** were 1.732Å for C−O and 2.870Å for C−C and their observed difference was 1.138Å. The difference between the C−O and C−C distance was too large for a concerted process. Furthermore, the electronic charges of the α-carbon of the sulfone in **TS 1** calculated by a Mulliken Population analysis (Table 4) were −0.692736 (3-21G*) and −0.479634 (6-31G*), and those of the β-carbon were estimated as −0.165666 (3-21G*) and −0.588774 (6-31G*), suggest that the reactions would proceed in a Michael addition manner, and not in a concerted pathway.

Table 4 Electronic Charges of **TS 1** Calculated by Mulliken Population Analysis

Elements	3-21G*	6-31G*
α-Carbon of sulfone	–0.692736	–0.479634
β-Carbon of sulfone	–0.165666	–0.087086
Carbon of nitrone	+0.360877	+0177413
Nitrogen of nitrone	–0.453827	–0.1090914
Oxygen of nitrone	–0.479241	–0.588774

Solvents and reagents were distilled from drying agents as follows: THF, Et_2O (Na-benzophenone); benzene, toluene (Na); CH_2Cl_2 (P_2O_5); MeOH (Mg), Et_3N (KOH). 1,3-Dichloro-2-phenylsulfonylpropane,[35] vinylsulfonyl chloride[31] and phenylhydroxylamine were prepared according to the reported procedures. Column chromatography was performed by using 230−400 mesh silica gel. Melting points were measured with a Yanagimoto micro melting apparatus. IR spectra were recorded as films on NaCl plates or as KBr pellets on a Jasco A-100 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on Jeol FX-90, Bruker DRX-400 and Bruker DRX-500 spectrometers. ^{1}H and ^{13}C chemical shifts are reported in (δ) ppm from TMS and coupling constants are in Hz. DEPT-^{13}C, HMQC, 2D-COSY, 2D-NOESY spectra were also measured on Bruker DRX-400 and Bruker DRX-500 spectrometers. Optical rotations were determined by a Jasco DIP 370 digital polarimeter. Mass spectra were taken with a Jeol JMS-DX303 spectrometer.

Preparation of Compounds 3; General Procedure

A solution of aldehyde **1** (5.77 mmol) in anhyd Et_2O (10 mL) was added to a mixture of phenylhydroxylamine (6.35 mmol) and $CaCl_2$ (2.31 mmol) in anhyd Et_2O (35 mL) at 0°C. The resultant mixture was stirred at r.t. for 2−3 d under N_2, after which $CaCl_2$ was filtered, the filtrate concentrated in vacuo and the residue chromatographed on silica gel (CH_2Cl_2) to give **3** as white to yellow crystals (Table 1), which were then analyzed (Table 5) for the determination of the structure and stereochemistry.

Preparation of Compounds 6; General Procedure

A solution of aldoxime **4** (1.38 mmol) in anhyd benzene (138 mL) containing a catalytic amount of $ZnCl_2$ (0.36 mmol) was refluxed for 6−16 h. The mixture was then cooled to r.t and quenched with 5% aq NH_3 (30 mL). The benzene layer was separated and washed several times with H_2O, then with saturated brine. After drying (Na_2SO_4), the benzene was evaporated in vacuo and the resultant

Table 5 Spectroscopic Data of the Cycloadducts **3a−e**

Product	IR (KBr/Neat) ν (cm^{-1})	^{1}H NMR (500 MHz, $CDCl_3$/TMS) δ, *J* (Hz)	^{13}C NMR (125.76 MHz, $CDCl_3$/TMS) δ	HRMS (FAB), m/z, (M)	
				calcd	found
(*S*,*S*,*S*)-**3a**[a]	3060, 3030, 2950, 2885, 1600, 1480, 1467, 1300, 1150, 1073, 760, 680	2.57 (d, 1H, *J* = 11.0), 3.01 (dd, 1 H, *J* = 14.3, 14.3), 3.09 (dd, 1 H, *J* = 14.3, 14.3), 3.18−3.16 (m, 1 H), 3.30 (d, 1 H, *J* = 13.4), 3.61 (d, 1 H, *J* = 11.0), 3.94 (d, 1 H, *J* = 9.3), 4.06 (d, 1 H, *J* = 13.4), 4.41 (s, 1 H), 4.42 (d, 1 H, *J* = 4.7), 7.53−6.45 (m, 20 H)	34.93 (CH_2), 56.35 (CH_2), 58.70 510.1977 (CH_2), 69.79 (CH), 72.49 (CH_2) 75.91 (CH), 82.58 (C−SO_2), 133.88−114.96 (Ph), 136.47 (PhN), 137.79 (*Ph*CH_2), 148.77 ($PhSO_2$)	510.1963	510.1963
(*S*,*S*,*S*)-**3b**[b]	2940, 1590 1450, 1290, 1130, 960, 910, 740, 720, 680	1.29 (d, 3 H, *J* = 6.1), 2.43 (d, 1 H, *J* = 11.3), 2.52−2.69 (m, 1 H), 3.03 (d, 1 H, *J* = 13.0), 3.53 (d, 1 H, *J* = 11.4), 3.86 (d, 1 H, *J* = 13.0), 3.92 (d, 1 H, *J* = 9.2), 4.35 (d, 1 H, *J* = 6.7), 4.52 (d, 1 H, *J* = 9.2), 6.91−7.72 (15 H, m)	16.64 (CH_3), 59.96 (CH_2), 56.51 (CH_2), 65.14 (CH), 72.16 (CH_2) 80.09 (CH), 82.52 (C−SO_2), 133.88−114.09 (Ph), 137.10 (PhN), 137.75 (*Ph*CH_2), 149.00 ($PhSO_2$)	434.1702	434.1663
(*S*,*S*,*S*)-**3c**[c]	3060, 2950, 2790, 1590, 1480, 1440, 1360, 1300 1210, 1140, 1080, 1020, 800, 670	0.90 (d, 3 H, *J* = 6.88), 1.07 (d, 3 H, *J* = 7.11), 2.38 (d, 1 H, *J* = 11.36), 2.18−2.15 (m, 1 H), 3.18−3.16 (m, 1 H), 2.54 (dd, 1H, *J* = 7.45, 7.44), 3.57 (d, 1 H, *J* = 11.33), 2.86 (d, 1 H, *J* = 13.06), 3.86 (d, 1 H, *J* = 9.08), 4.45 (d, 1 H,*J* = 9.10), 3.91 (d, 1 H, *J* = 13.09), 4.69 (d, 1 H, *J* = 7.48), 6.94−7.62 (m, 15 H)	15.75 (CH_3), 19.28 (CH_3), 26.71 (CH_2), 56.63 (CH_2), 60.63 (CH_2) 71.91 (CH), 72.27 (CH_2), 73.22 (CH) 82.10 (C−SO_2),133.89−114.03 (Ph), 148.24 ($PhSO_2$)	462.1975	462.2019
(*S*,*S*,*S*)-**3d**[d]	3060, 2990 2750, 1600, 1500, 1460, 1380, 1320, 1270, 1150, 1100, 1030, 960, 880, 760, 730	0.95 (d, 3 H, *J* = 6.10), 0.97 (d, 3 H, *J* = 6.20), 1.99−1.97 (m, 3 H), 2.39 (d, 1 H, *J* = 11.30), 2.76−2.56 (m, 1 H), 2.98 (d, 1H, *J* = 13.0), 3.52 (d, 1 H, *J* = 11.30), 2.86 (d, 1 H, *J* = 9.0), 3.97 (d, 1 H, *J* = 13.10), 4.40 (d, 1 H, *J* = 9. 10), 4.56 (d, 1 H, *J* = 6.80), 8.84−7.84 (m, 15 H)	22.82 (CH_3), 24.21 (CH_3), 25.07 (CH), 41.17 (CH_2), 56.93 (CH_2), 60.37 (CH_2), 68.11 (CH), 72.42 (CH_2), 78.62 (CH), 82.92 (C-SO_2), 133.83-114.44 (Ph), 137.45 (PhN), 138.08 (*Ph*CH_2), 148.85 ($PhSO_2$)	476.2131	476.2147
(*S*,*R*,*S*)-**3e**[e]	3050,2950 1600,1500, 1450,1300, 1230,1150, 1050,1000, 900,800, 750,680	2.06-1.98 (m, 2 H), 2.12−2.09 (m, 1 H), 2.32−2.30 (m, 1 H), 3.28−3.23 (m, 1 H), 3.73−3.96 (m, 1 H),3.91 (dd, 1 H, *J* = 2.82, 2.83), 4.08−4.07 (m, 1 H), 4.16 (dd, 1 H, *J* = 7.77, 7.79), 4.49 (dd, 1 H, *J* = 6.43, 6.45) 4.66 (dd, 1 H, *J* = 1.54, 1.55), 7.30−6.99 (m, 5 H)	24.37 (CH_2), 31.26 (CH_2), 47.58 (CH_2), 66.21 (CH), 66.66 (CH) 69.23 (CH_2), 74.38 (CH), 129.45−114.85 (Ph)	280.0880	280.0881

[a] White prisms, mp 108−109°C.
[b] Pale yellow solid, mp 98−99°C.
[c] White crystals, mp 100−101°C.
[d] Pale yellow solid, mp 120−121°C.
[e] Yellow needles, mp 130−131°C.

gummy mass was chromatographed on silica gel (hexane/EtOAc, 1:1) to give **6** as colored syrups or amorphous solids (Table 2), which were then analyzed (Table 6).

Preparation of Compounds 8; General Procedure

A solution of aldoxime **4** (0.65 mmol) in anhyd THF (2 mL) was added to a solution of NBS (0.67 mmol) in anhyd THF (2 mL) containing a catalytic amount of pyridine (0.03 mmol) and stirred at r.t. for 10 min under N_2. A solution of Et_3N (0.69 mmol) in anhyd THF (2 mL) was then added followed by distilled toluene (20 mL), and the mixture was subjected to reflux for 12−16 h. The cooled mixture was quenched with H_2O (15 mL). The organic layer was separated and washed several times with brine. After drying (Na_2SO_4), the solvent was evaporated and the residue was chromatographed on silica gel (hexane/EtOAc, 1:1) to afford **8** as colored syrups (Table 3), which were then analyzed (Table 7)

Reductive Ring Opening of (*S*,*S*,*S*)-3a; (2*S*, 3*S*, 4*S*)-3-Anilino-1,2-dibenzyl-4-hydroxymethyl-4-phenylsulfonylpyrrolidine (9a)

A solution of Raney Ni (W-2) (3.30 mL) in anhyd EtOH 10 mL) was added dropwise to a solution of (*S*,*S*,*S*)-**3a** (1.60 mmol) in anhyd EtOH (30 mL) at 25°C, which was stirred at r.t. for 17 h under N_2 (Scheme 5). The white crystals that appeared were dissolved in EtOAc and the solution was filtered. The filtrate was concentrated in vacuo to give a white solid, which was recrystallized from isopropyl alcohol to afford (*S*,*S*,*S*)-**9a** as white needles (77%); mp 180−181°C.

HRMS (FAB): *m*/*z* (M + 1) calcd for $C_{31}H_{33}N_2O_3S$: 513.2211, found: 513.2221.

IR(KBr): ν = 3480(OH) 3410(NH), 1605, 1455, 1150(N−O), 1080, 750, 690 cm^{-1}.

^1H NMR (500MHz, $CDCl_3$/TMS): δ = 2.59 (d, 1 H, *J* = 11.9 Hz), 2.64 (q, 1 H, *J* =18.34 Hz), 2.76 (dd, 1 H, *J* = 14.0, 14.0 Hz), 2.89 (dd, 1 H, *J* = 14.0, 14.0 Hz), 3.06 (d, 1 H, *J* = 13.0 Hz), 3.20 (s, 1 H), 3.34 (d, 1 H, *J* = 11.9 Hz), 3.54 (d, 1 H, *J* = 12.0), 4.02 (d, 1 H, *J* = 13.0), 4.09 (d, 1 H, *J* = 12.1 Hz), 4.43 (t, 1 H, *J* = 15.50 Hz), 7.66−6.47 (m, 20 H).

^{13}C NMR (125.76MHz, DEPT, $CDCl_3$): δ = 35.70 (CH_2), 56.92 (CH_2), 57.22 (CH_2), 62.29 (CH), 62.59 (CH_2), 72.88 (CSO_2), 73.68 (CH), 133.61−114.96 (Ph), 137.31 (PhN), 146.68 ($PhSO_2$).

Reductive Desulfurization of (*S*,*S*,*S*)-3a; (1*S*,5*R*,8*S*)-7,8-Dibenzyl-2-phenyl-3-oxa-2,7-diazabicyclo[3,3,0]octane (10a)

A solution of (*S*,*S*,*S*)-**3a** (0.80 mmol) in anhyd THF (10 mL) was slowly added to a slurry of $LiAlH_4$ (3.20 mmol) in THF (10 mL) at 10°C, which was then refluxed for 72 h under N_2 (Scheme 5). To the ice-cold reaction mixture was added dropwise 10% aq KOH solu-

Table 6 Spectroscopic Data of the Cycloadducts **6a−d**

Product	IR (KBr/Neat) ν (cm^{-1})	^1H NMR (500 MHz, $CDCl_3$/TMS) δ, *J* (Hz)	^{13}C NMR (125.76 MHz, $CDCl_3$/TMS) δ	HRMS (FAB), *m*/*z*, (M + 1)	
				calcd	found
(*S*,*S*,*S*)-**6a**[a]	3400, 3075 3025, 2925, 2800, 1600, 1580, 1500, 1450, 1300, 1140, 1080, 740, 680	1.25 (s, 2 H), 2.25 (d, 1 H, *J* = 11.33), 3.32 (d, 1 H, *J* = 11.30), 2.88 (d, 1 H, *J* = 5.60), 3.50 (d, 1 H, *J* = 9.99), 4.06 (d, 1 H, *J* = 10.0), 4.16 (d, 1 H, *J* = 5.40), 4.28 (dd, 1 H, *J* = 7.80, 7.78), 5.55 (s, 1 H), 7.66−7.11 (m, 15 H)	29.36 (CH_2), 36.06 (CH_2), 60.39 (CH_2), 70.12 (CH_2), 70.89 (CH) 77.02 (CH), 81.73 (C−SO_2), 126.48−137.65 (Ph), 146.13 ($PhSO_2$)	435.1742	435.1729
(*S*,*S*,*S*)-**6b**[b]	3425, 3070 3050, 2950, 2925, 2850, 2800, 1580, 1450, 1300, 1020, 820, 740, 680	1.15 (d, 3 H, *J* = 6.05), 2.26 (d, 1 H, *J* = 11.0), 3.43 (d, 1 H, *J* = 11.40), 2.28-2.32 (m, 1 H), 2.86 (d, 1 H, *J* = 13.22), 3.78 (d, 1 H, *J* = 13.10), 3.95 (d, 1 H,*J* = 6.5), 4.05 (d, 1 H, *J* = 9.30), 4.27 (d, 1 H, *J* = 9.0), 5.62 (s, 1 H), 7.72-6.80 (m, 10 H)	17.22 (CH_3), 58.07 (CH_2), 60.32 (CH_2), 65.35 (CH), 76.81 (CH) 77.02 (CH_2), 80.90 (C−SO_2), 136.94−127.17 (Ph), 147.77 ($PhSO_2$)	359.1429	359.1429
(*S*,*S*,*S*)-**6c**[c]	3450, 3075, 3025, 2975, 2925, 2850, 1360, 1300, 1210, 1140, 1080, 1020, 800, 670	0.70 (d, 1 H, *J* = 6.85), 0.85 (d, 3 H, *J* = 5.50), 1.02 (d, 3 H, *J* = 7.05), 1.25 (s, 2 H), 2.30 (dd, 1 H, *J* = 14.65, 14.40), 2.78 (d, 1 H, *J* = 12.92), 3.83 (d, 1 H, *J* = 12.80), 4.07 (d, 1 H, *J* = 9.10), 4.26 (d, 1 H, *J* = 9.30), 4.14 (m, 1 H), 5.29 (s, 1 H), 6.93−7.82 (m, 10 H)	15.37 (CH), 20.16 (CH_3), 26.50 (CH_3), 26.70 (CH_2), 56.70 (CH_2), 60.44 (CH), 69.69 (CH), 76.77 (CH_2) 80.90 (C−SO_2),134.00-125.11 (Ph), 137.06 (PhN),137.78 ($PhCH_2$), 150.22 ($PhSO_2$)	387.1742	387.1737
(*S*,*S*,*S*)-**6d**[d]	3450, 3075 3050, 2975, 2950, 2875, 1590, 1500, 1450, 1380, 1150, 1090, 950, 840, 760, 690	0.88 (d, 3 H, *J* = 6.50), 0.92 (d, 3 H, *J* = 7.65), 0.94 (m, 1 H), 1.28 (d, 2 H, *J* = 13.70), 2.87 (d, 1 H, *J* = 13.35), 3.84 (d, 1 H, *J* = 13.0), 3.42 (d, 2 H, *J* = 7.32) 4.04 (d, 2 H, *J* = 16.51), 4.10 (d, 1 H, *J* = 6.70), 4.23 (d, 1 H, *J* = 14.33), 5.62 (s, 1 H), 7.97−6.99 (m, 10 H)	22.47 (CH_3), 24.35 (CH_3), 24.83 (CH), 29.71 (CH_2), 52.77 (CH_2), 56.80 (CH_2), 60.50 (CH_2), 67.95 (CH), 75.49 (CH), 81.37 (C−SO_2), 137.94−127.12 (Ph), 148.85 ($PhSO_2$)	401.1963	401.1899

[a] Brown amorphous solid, mp 75−76 °C.
[b] Pale yellow syrup.
[c] Yellow syrup.
[d] Brown syrup.

Table 7 Spectroscopic Data of the Cycloadducts **8a–c**

Product[a]	IR (KBr/Neat) ν (cm^{-1})	^{1}H NMR (500 MHz, $CDCl_3$/TMS) δ, *J* (Hz)	^{13}C NMR (125.76 MHz, $CDCl_3$/TMS) δ	HRMS (FAB), *m*/*z*, (M + 1)	
				calcd	found
(*S*,*S*)-**8a**	3075, 2950 2925, 2850, 2800, 1660, 1580, 1500, 1450, 1300, 1140, 1080, 740, 680	1.24 (t, 1 H, *J* = 8.00), 3.10 (d, 2 H, *J* = 12.00), 3.45 (d, 2 H, *J* = 12.00), 3.80 (d, 1 H, *J* = 12.00), 4.11 (d, 1 H, *J* = 8.00), 4.87 (d, 1 H, *J* = 8.00), 7.52–6.81 (m, 15 H)	38.60 (CH_2), 57.10 (CH_2), 58.40 (CH_2), 61.40 (CH), 77.40 (CH_2) 84.90 (C–SO_2), 128.50–137.50 (Ph), 150.50 ($PhSO_2$), 164.90 (C=N)	433.1585	433.1561
(*S*,*S*)-**8b**	3090, 3070 3050, 2950, 2925, 2850, 2800, 1680, 1550, 1300 740, 680	1.14 (d, 3 H, *J* = 6.03), 2.27 (d, 1 H, *J* = 11.24), 2.85 (d, 1 H, *J* = 13.40), 3.41 (d, 1 H, *J* = 11.48), 3.76 (d, 1 H, *J* = 13.19), 3.96 (d, 1 H, *J* = 9.00), 3.98–4.00 (m, 1 H) 4.26 (d, 1 H, *J* = 8.99), 7.76–6.87 (m, 10 H) (C=N)	17.09 (CH_3), 53.43 (CH_2), 56.47 (CH_2), 76.79 (CH), 77.25(CH_2) 80.90 (C-SO_2),137.71–127.10 (Ph),143.89 ($PhSO_2$), 163.08	357.1272	357.1309
(*S*,*S*)-**8c**	3075, 2990 2980, 2950, 2925, 2850, 1660, 1600, 1210, 1140, 1030, 750	1.08 (d, 3 H, *J* = 6.85), 1.17 (d, 3 H, *J* = 6.90), 2.14–2.19 (m, 1 H), 3.20 (d, 1 H, *J* = 12.80), 3.52 (d, 1 H, *J* = 12.85), 3.92–3.96 (m, 1 H), 4.06 (d, 1 H, *J* = 9.90), 4.10 (s, 2 H), 4.72 (d, 1 H, *J* = 10.12), 7.89–7.17 (m, 10 H)	216.19 (CH_3),18.54 (CH_3), 29.25 (CH), 53.99 (CH_2), 58.93 (CH_2), 64.34 (CH),76.34(CH_2),85.09 (C–SO_2), 137.54-127.01 (Ph), 150.32 ($PhSO_2$), 164.53 (C=N)	385.1585	385.1576

[a] All compounds are colored syrups.
[b] 400 MHz NMR spectrum.

tion (0.5 mL) followed by H_2O (0.5 mL). The mixture was then refluxed again for 15 min and the solids that appeared were filtered after cooling. After drying ($MgSO_4$), the solvent was removed and the resultant mass was chromatographed on silica gel (CH_2Cl_2) and the product obtained was recrystallized from isopropyl alcohol to afford the isoxazolidine derivative (*S*,*R*,*S*)-**10a** as white crystals (88%); mp 112–113°C.

HRMS (FAB): *m*/*z* (M + 1) calcd for $C_{25}H_{27}N_2O$: 371.2123, found: 371.2122.

IR(KBr): ν = 3020 (CH, C_6H_5), 2950 (aliphatic CH), 1592 (C=C, C_6H_5),1488 (Ph), 1460 (Ph), 1082 (C–N), 1080, 750, 690 cm^{-1}.

^{1}H NMR (500MHz, $CDCl_3$/TMS): δ = 2.16–2.14 (m, 1 H), 2.93–2.90 (m, 1 H),3.01 (d, 1 H, *J* = 5.65 Hz), 3.23–3.11 (m, 3), 3.28 (dd, 1 H, *J* = 14.6, 14.6 Hz), 3.71 (m, 2 H), 4.05 (m, 1 H), 4.15 (d, 1 H, *J* = 13.0 Hz), 7.43–6.68 (m, 15 H).

^{13}C NMR (125.76MHz, DEPT, $CDCl_3$): δ = 37.45 (CH_2), 46.13 (CH), 57.97 (CH), 58.94 (CH_2), 70.03 (CH), 71.08 (CH_2), 75.61 (CH), 129.92–114.41 (Ph), 138.61 (PhN), 150.73 ($PhSO_2$).

Crystal Data for 3a and 3e
See Tables 8 and 9, respectively.

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Table 8 Summary of Data Collection, Structure solution and Refinement Details for (1*S*,5*S*,8*S*)-(+)-7,8-Dibenzyl-2-phenyl-5-phenylsulfonyl-3-oxa-2,7-diazabicyclo-[3,3,0]octane (**3a**)

Crystal Data		Data Acquisition		Structure Solution and Refinement	
Emperical Formula	$C_{31}H_{30}N_2O_3S$	Diffractometer	Rigaku AFC5S	Structure Solution	Direct Methods
Formula Weight	510.65	Radiation	MoKa (λ = 0.71069Å)	Refinement	Full-matrix
Appearance	white prisms	Temperature	20°C		Least-squares
Crystal Dimension (mm)	0.360 × 0.420 × 0.562	Attenuator	Ni foil (factors: 2.3,5.2,11.7)	Function Minimized	$\sum w(\|Fo\|-\|Fc\|)^2$
Crystal System	orthorhombic	Take-off Angle	6.0°	Least-squares Weights	$4Fo^2/\sigma^2(Fo^2)$
No. Reflections Used for Unit		Detector Aperture	6.0 mm horizontal	p-factor	0.03
Cell Determination (2q) range	25 (33.6−37.4°)		6.0 mm vertical	Anomalous Dispersion	All non-hydrogen
Omega Scan Peak Width		Crystal to Detector Distance	40 cm		atoms
at Half-height	0.14	Scan Type	ω	No. Observations	
Lattice Parameters:	a = 10.114 (4)Å	Scan Rate	16.0°/min (in omega) (2 rescans)	[|>2.00σ(|)]	1868
	B = 25.387 (5)Å	Scan Width	(1.01+0.30 tan q)°	No. Variables	334
	C = 10.055 (4)Å	^{2q}max	55.0°	Reflection/Parameter	
	V = 2582 (2)Å	No. of Reflection Measured	Total: 3380	Ratio	5.59
Space Group	$P2_12_12_1$ (#19)		Unique: 3379 (R_{int}=0.899)	Residuals R:R_w	0.063:0.060
Z value	4	Correlations	Lorentz-polarization	Goodness of Fit	
^{D}calc	1.314 g/cm^3			Indicator	1.59
^{F}000	1080			Max Shift/Error in Final	
$^{\mu}$(MoKa)	1.53 cm^{-1}			Cycle	0.03
				Maximum Peak in	
				Final Diff. Map	0.32e$^-$/Å^3
				Minimum Peak in	

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Table 9 Summary of Data Collection, Structure Solution and Refinement Details for **3e**

Crystal Data		Data Acquisition		Structure Solution and Refinement	
Emperical Formula	$C_{13}H_{16}N_2O_3S$	Diffractometer	Rigaku AFC5S	Structure Solution	Direct Methods
Formula Weight	280.34	Radiation	MoKα (λ = 0.71069Å)	Refinement	Full-matrix
Crystal Color, Habit	yellow, needle	Temperature	23°C		Least-squares
Crystal Dimension (mm)	0.040 × 0.240 × 0.680	Attenuator	Ni foil (factors: 2.3,5.2,11.7)	Function Minimized	$\sum w(\|Fo\|-\|Fc\|)^2$
Crystal System	monoclinic	Take-off Angle	6.0°	Least-squares Weights	$4Fo^2/\sigma^2(Fo^2)$
No. Reflections Used for Unit		Detector Aperture	6.0 mm horizontal	p-factor	0.03
Cell Determination (2q) range	25(36.4−39.8°)		6.0 mm vertical	Anomalous Dispersion	All non-hydrogen
Omega Scan Peak Width		Crystal to Detector Distance	40 cm		atoms
at Half-height	0.14	Scan Type	ω−2q	No. Observations	
Lattice Parameters:	a = 8.250 (9)Å	Scan Rate	16.0°/min (in omega) (2 rescans)	8|>2.00s(|)]	1158
	B = 5.660 (6)Å	Scan Width	(1.311 + 0.30 tan θ)°	No. Variables	171
	C = 13.918(4)Å	^{2q}max	55.0°	Reflection/Parameter	
	V = 647.5 (8)Å^3	No. of Reflection Measured	Total : 1753	Ratio	6.77
Space Group	$P2_1$ (#4)		Unique : 1642 (R_{int} = 0.049)	Residuals R:R_w	0.064 : 0.063
Z value	2	Correlations	Lorentz-polarization	Goodness of Fit	
^{D}calc	1.438g/cm^3			Indicator	1.72
^{F}000	296			Max Shift/Error in Final	
$^{\mu}$(MoKa)	2.44 cm^{-1}			Cycle	0.05
				Maximum Peak in Final Diff. Map	0.52e$^-$/Å^3

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(36) Further details of the crystal structure determination are available on request from Cambridge Crystallographic Data Centre; CCDC-133125 for the compound (*S*,*S*,*S*)-**3a** and CCDC-133126 for (*S*,*R*,*S*)-**3e**.

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