Formation of Chiral *N*-Oxides from 2-Azabicyclo[3.3.0]octanes

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Enantiopure 2-azabicyclo[3.3.0]octanes **1a–d** and *ent*-**1e** were oxidized with *m*CPBA to provide either diastereomeric pairs of *N*-oxides (**2a/3a** and **2b/3b**) or diastereomerically pure compounds (**2c**,**d** and *ent*-**2e**). The structure of compounds **2a** and *ent*-**2e** was confirmed by an X-ray study. The factors that affect the oxidation process are discussed.

Introduction

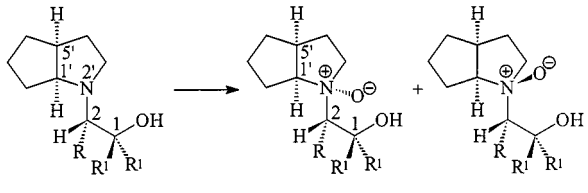
The formation of amine *N*-oxides by oxidation of tertiary amines with reagents such as hydrogen peroxide, peracids or organyl hydroperoxides in the presence of metal catalysts is an interesting possibility to manipulate the amine function.[1] The N-inversion typical for amines is of course lost after conversion to *N*-oxides. In this way from ring-substituted *N*-alkylazacycloalkanes diastereomeric *syn*- and *anti*-*N*-oxides may be formed that are individual species and for this reason do not convert into one other. The oxidation of cyclic tertiary amines has been studied in particular with respect to this feature.[1a,2–4] Thus, Shvo et al. demonstrated that oxidation of substituted piperidines frequently proceeds diastereoselectively.[2a,2b] In connection with studies on the reverse Cope reaction Ciganek et al. found that oxidation of 1,2-dimethylpyrrolidine with hydrogen peroxide afforded a mixture of the (*Z*) and (*E*) form of the corresponding amine *N*-oxide in the ratio of 4:1, whereas the (*Z*)/(*E*) ratio was only 3:2 in the oxidation of 1,2-dimethylpiperidine.[3] O′Neil et al. described in a series of papers the oxidation of *N*-alkylated derivatives of the α-amino acid (*S*)-proline with *meta*-chloroperbenzoic acid (*m*CPBA) at −78°C.[4] The most striking feature of their studies is that a single diastereomer is formed in the oxidation of *N*-benzylproline derivatives bearing a functional group (XH, X = COO, CONR or O) in the side chain, that is capable of hydrogen bonding. Thus, in *N*-benzylproline or the corresponding amides and alcohols, the oxidation is controlled by the hydrogen-bonding group to give exclusively the (*Z*)-amine *N*-oxides by *syn* addition. Consequently, the diastereoselectivity of the oxidation is thought to be due to intermolecular hydrogen bonding between the functional group and the peracid. In the amine *N*-oxides intramolecular hydrogen bonding between such functional groups and the oxygen atom of the NO group could be detected by various methods, particularly by crystal-structure determination.[4]

In fact, if a hydrogen-bond donor is missing as in the *N*-benzylproline esters the high degree of stereoselectivity is lost. However, the diastereoselectivity increases with increasing size of the ester group, as is exemplified by the (*Z*)/(*E*) ratio, which changes from 2:1 to 4:1 and finally 9:1 for *N*-benzyl-(*S*)-proline methyl ester, ethyl ester and *tert*-butyl ester, respectively.[4b] Hence, the conclusion must be drawn that in these cases oxidation proceeds preferentially from the sterically more hindered face of the molecule.

Only recently we had prepared a series of enantiopure *N*-substituted β-hydroxyalkyl-2-azabicyclo[3.3.0]octanes.[5] Oxidation of these compounds should make amine *N*-oxides accessible, which possibly are also capable of intramolecular hydrogen bonding. Thus, we decided to study their oxidation.

Results and Discussion

The enantiopure *N*-hydroxyalkyl-substituted 2-azabicyclo[3.3.0]octanes **1a–d** and *ent*-**1e**[5] were oxidized with *m*CPBA at 0°C in dichloromethane. In fact, oxidation of compounds **1c–d** and *ent*-**1e** proceeded with complete stereoselectivity providing the enantiopure amine *N*-oxides **2c**,**d** and *ent*-**2e**, respectively, as a single diastereomer. In contrast, oxidation of compounds **1a**,**b** afforded a mixture of the diastereomers **2a/3a** and **2b/3b**. The (*Z*)/(*E*) ratio for the pair **2b/3b** was approximately 1:2 in favor of **3b**, whereas for **2a/3a** a 1:1 ratio resulted. When the oxidation of **1a** was performed at −78°C a slight excess of the (*E*) isomer **3a** (ratio 2:3) was formed. Attempts to separate the diastereomeric pairs by chromatography failed. However, from



1 **2** **3**

	a	b	c	d	e
R	Me	Ph-CH_2	Me	Ph-CH_2	Ph
R^1	H	H	Ph	Ph	Ph

Scheme 1. Formation of bicyclic *N*-oxides by oxidation with *m*CPBA

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the mixture of **2a/3a** a crystal suitable for X-ray analysis could be selected.

With the exception of **2d** the amine *N*-oxides are stable under normal conditions. Thus, **2b/3b** remained unchanged after more than 8 months, whereas a considerable amount of **2d** was decomposed after a few days even in the solid state. In solution, however, decomposition of a small amount of **2b/3b** could be observed after a few days. Usually amine *N*-oxides are strongly hygroscopic;[1] however, in the case of compounds **2** and **3** this is true only for the diastereomeric pair **2a/3a**.

Whereas the ^{1}H-NMR spectra, in particular those of the diastereomeric mixtures, are rather complex,[6] the ^{13}C-NMR spectra are more conclusive. The most characteristic signals of **2c**,**d** and *ent*-**2e** appear at δ = 38.0−39.0 (C-5′), 85.8−86.9 (C-1′) and 79.0−81.0 (C-1). In the two sets of signals of the diastereomeric pairs **2a/3a** and **2b/3b** the signal of the C-5′ atom allows an unambigious assignment of the most other signals to either **2** or **3**. The minor compounds from oxidation of **1a** (reaction at −78°C) and **b** show the signal of C-5′ at δ = 39.6 and 39.8, respectively. Thus, structures **2a** and **b** are assigned to these compounds. The corresponding signal of the major compounds to which structures **3a** and **b** are ascribed appears at δ = 43.8 and 43.6, respectively.

An X-ray study[7] of compound *ent*-**2e** disclosed that the oxygen atom O-2′ of the amine oxide group is in *syn* position to 1′-H at the *exo* face of the bicyclic framework. Furthermore, there exists an intramolecular hydrogen bond between this O atom and the H atom of the OH group (distance OH···O = 1.50 Å) (Figure 1). The agreement of the ^{13}C-NMR data of compounds **2c** and **2d** with those of *ent*-**2e** confirms the structure of the former.

An X-ray study revealed that the O-2′ atom of the amine oxide group is also in *syn* position to the 1′-H atom at the *exo* face of the bicyclic framework in the crystal selected from the mixture of the diastereomers **2a/3a**, establishing structure **2a** for this component[7] (Figure 2).

Whereas bond lengths and bond angles are very similar in the bicyclic framework of compounds *ent*-**2e** and **2a**, a fundamental difference exists concerning hydrogen bonding in the crystalline state. In contrast to *ent*-**2e** with its intramolecular hydrogen bond, the hygroscopic compound **2a** exhibits only intermolecular hydrogen bonds. Such hydrogen bonds exist between the O-2′ atom of the amine oxide group and the H atom of the OH group of another molecule (d = 1.64 Å), as well as between the H atoms of the crystal water and the O-2′ atom (d = 1.87 Å) on one hand or the O-1 atom of the OH group (d = 1.93 Å) on the other hand. Presumably, the different behavior of these two amine oxides may be due to an effect similar to the *gem*-dialkyl effect[8] by which the phenyl substituents of *ent*-**2e** may give rise to the intramolecular hydrogen bonding.

Usually, oxidation of ring-substituted cyclic tertiary amines takes place from the sterically more hindered face to give the more stable of the two diastereomers in excess.[2,3,4b] This points to a product-like transition state. Obviously, on the reaction path to the more stable diastereomer of the *N*-oxides a less extensive steric interaction arises. Thus, for instance in the simple case of the 1,2-di-

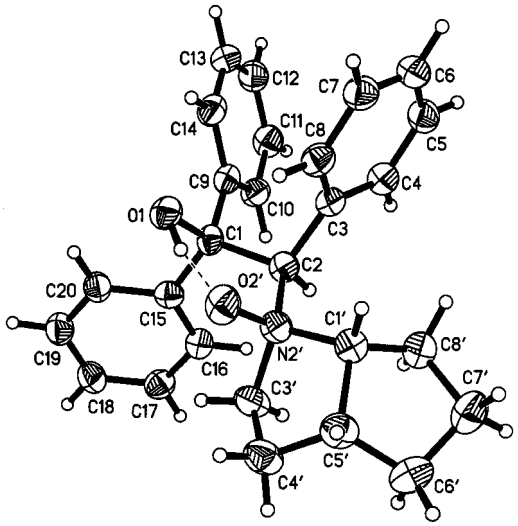

Figure 1. Molecular plot of (2*R*,1′*R*,2′*R*,5′*R*)-(+)-2-(2′-azabicyclo[3.3.0]oct-2′-yl)-1,1,2-triphenylethanol *N*-oxide (*ent*-**2e**); selected bond lengths [Å]: C1′−N2′ 1.531 (4), C1′−C5′ 1.557 (4), C1′−C8′ 1.525 (4), N2′−C2 1.545 (3), N2′−O2′ 1.398 (3), N2′−C3′ 1.508 (4), C3′−C4′ 1.526 (4), C4′−C5′1.524 (4), C5′−C6′ 1.540 (5), C6′−C7′ 1.516 (5), C7′−C8′ 1.520 (4) O1−H1 1.01 (4); selected bond angles[°]: N2′−C1′−C5′ 104.2 (2), O2′−N2′−C3′ 107.2 (2), N2′−C3′−C4′ 102.2 (2), O2′−N2′−C1′ 107.3 (2), O2′−N2′−C2 110.8 (2), C3′−N2′−C1′ 102.9 (2), C4′−C5′−C6′ 115.0 (3), C4′−C5′−C1′ 105.8 (2), C5′−C4′−C3′ 104.5 (2), C6′−C5′−C1′ 104.2 (3), C6′−C7′−C8′ 102.4 (3), C7′−C6′−C5′ 105.3 (3), C7′−C8′−C1′ 102.7 (3), C8′−C1′−N2′ 116.7 (2), C8′−C1′−C5′ 106.1 (3)

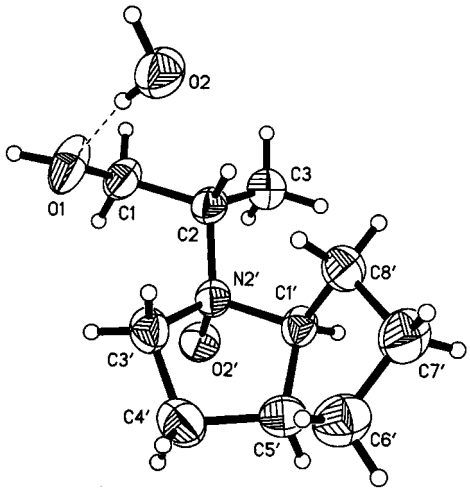

Figure 2. Molecular plot of (2*S*,1′*S*,2′*S*,5′*S*)-2-(2′-azabicyclo[3.3.0]oct-2′-yl)propanol *N*-oxide (**2a**); selected bond lengths [Å]: C1′−N2′ 1.520 (3), C1′−C5′ 1.535 (3), C1′−C8′ 1.526 (3), N2′−C2 1.519 (3), N2′−O2′ 1.3944 (19), N2′−C3′ 1.506 (3), C3′−C4′ 1.519 (4), C4′−C5′ 1.535 (4), C5′−C6′ 1.533 (3), C6′−C7′ 1.519 (4), C7′−C8′ 1.514 (3), O1−H11 0.96 (4); selected bond angles[°]: N2′−C1′−C5′ 104.78 (18), C2−N2′−C3′ 115.12 (14), N2′−C3′−C4′ 103.31 (17), O2′−N2′−C1′ 106.99 (13), O2′−N2′−C2 109.84 (15), C3′−N2′−C1′ 102.65 (16), C4′−C5′−C1′ 105.71 (19), C5′−C4′−C3′ 105.08 (19), C6′−C5′−C1′ 105.20 (19), C6′−C5′−C4′ 115.4 (2), C7′−C6′−C5′ 105.7 (2), C7′−C8′−C1′ 102.11 (19), C8′−C1′−N2′ 116.08 (16), C8′−C1′−C5′ 105.72 (18), C8′−C7′−C6′ 103.5 (2)

methylpyrrolidine *N*-oxides the destabilizing interaction between the O atom and the methyl group of the (*Z*) form should be weaker than the interaction between the two methyl groups of the (*E*) form.[9] Consequently, the formation of the (*Z*) form is preferred. The same argument holds to explain the preferred formation of diastereomers **3a** or **b** by attack from the more hindered *endo* face, on comparison of the interaction of the cyclopentane fragment of the bicyclic framework with the O atom on the one hand and the 1-hydroxyisopropyl group on the other hand. However, in the case of oxidation of **1a** the effect is relatively small and **3a** is formed in excess only at −78°C.

The high diastereoselectivity found by O′Neil et al.[4] for the oxidation of proline derivatives must be due, at least partly, to stabilization of the product by intramolecular hydrogen bonding. However, hydrogen bonding cannot be the only reason for the high diastereoselectivity in the oxidation of **1c**,**d** and *ent*-**1e**, because in both of the potential products **2** and **3** hydrogen bonding between the OH group and the *N*-oxide group should be possible. However, in compounds **1** an additional stereogenic center exists at the hydroxyalkyl side chain (C-2). Whereas this stereogenic center does not play an important role in the oxidation of **1a** and **b** (R^1 = H), it becomes crucial if the hydroxymethyl group of **1a**,**b** is replaced by the larger diphenyl hydroxymethyl group in **1c**,**d** and *ent*-**1e** (R^1 = Ph). Thus, the steric effects of this asymmetric center in cooperation with the increased tendency to intramolecular hydrogen bonding favor oxidation of **1c**,**d** and *ent*-**1e** at the less hindered *exo* face of the bicyclic framework.

Conclusion

The stereochemical course of the oxidation of enantiopure *N*-hydroxyalkyl-substituted 2-azabicyclo[3.3.0]octanes is determined by opposite effects due to asymmetric induction by the stereogenic centers of the bicyclic framework (C-1′ and C-5′) and of the *N*-hydroxyalkyl side chain (C-2). In the reaction of **1a** and **b** the effect of C-1′ and C-5′ predominates providing a slight excess of the diastereomers **3a** and **b**, respectively, which are formed by oxidation at the more hindered *endo* face. In contrast, oxidation of **1c**,**d** and *ent*-**1e** proceeds with complete diastereoselectivity affording exclusively enantiopure compounds **2c**,**d** and *ent*-**2e**, respectively. This reaction is controlled by the effect of the stereogenic center at the side chain (C-2) coupled with intramolecular hydrogen bonding giving rise to oxidation at the less hindered *exo* face.

Experimental Section

General Remarks: Elemental analyses were performed by the division Routine-Analytik, Fachbereich Chemie, University of Marburg. Spectra were recorded with following instruments: NMR: Bruker AMX 500 (500 MHz, for ^{1}H) and Bruker AC 300 (300 MHz and 75 MHz, for ^{1}H and ^{13}C, respectively) using the residues of ^{1}H (δ = 7.24) or of ^{13}C (δ = 77.0) of the solvent $CDCl_3$ and the residues of ^{1}H (δ = 3.35 and 4.78) or of ^{13}C (δ = 49.3) of the solvent [D_4]methanol as internal standard. As far as not stated otherwise ^{1}H-NMR spectra were recorded at 300 MHz with $CDCl_3$ as solvent. − MS: Varian CH7 (EI). − IR: IFS 88-FT-IR. − Optical rotations: Polarimeter Perkin−Elmer 241; at 589 nm.

X-ray Crystallographic Studies

Crystal Data for 2a: $C_{10}H_{21}NO_3$, M_r = 203.28, F(000) = 224, monoclinic, a = 8.882(3) Å, b = 8.045(1) Å, c = 8.915(2) Å, β = 116.865(18)°, V = 568.3(2) Å^3, space group $P2_1$, Z = 2, D_x = 1.188 g/cm^3, μ(Cu-K_α) = 7.03 cm^{-1}. The experimental data were collected at 293(2) K with a Nonius CAD4 diffractometer using graphite-monochromated Cu-K_α radiation (λ = 1.54178 Å). An absorption correction was not applied. The structure was solved by direct methods and difference fourier synthesis.[10] Full-matrix refinement on F^2 values led to the final R values wR_2 = 0.0937 (all data) and the conventional R = 0.0365 [$I > 2\sigma(I)$].

Crystal Data for *ent*-2e: $C_{27}H_{29}NO_2$, M_r = 399.51, F(000) = 856, orthorhombic, a = 5.984(1) Å, b = 15.996(1) Å, c = 21.462 (2) Å, V = 2054.5(3) Å^3, space group $P2_12_12_1$, Z = 4, D_x = 1.292 g/cm^3, μ(Cu-K_α) = 6.28 cm^{-1}. The experimental data were collected at 213(2) K with a Nonius CAD4 diffractometer using graphite-monochromated Cu-K_α radiation (λ = 1.54178 Å). Absorption correction: Empirical (PLATON/DIFABS). The structure was solved by direct methods and difference fourier synthesis.[10] Full-matrix refinement on F^2 values led to the final R values wR_2 = 0.1337 (all data) and the conventional R = 0.0470 [$I > 2\sigma(I)$].

General Oxidation Procedure with *m*CPBA: A solution of *m*CPBA (90% purity, 2.0 mmol) and K_2CO_3 (3.0 mmol, 1.5 equiv.) in CH_2Cl_2 (15 ml) was added dropwise to a solution of the 2-azabicyclo[3.3.0]octane **1** (2.0 mmol) in CH_2Cl_2 (10 ml) at 0°C. The mixture was stirred for 3 h at 0°C and additional 15 h at room temp. Then the solution was separated from the precipitate and the solvent removed by distillation.

(2*S*,1′*S*,2′*S*/*R*,5′*S*)-2-(2′-Azabicyclo[3.3.0]oct-2′-yl)propanol *N*-Oxide (2a/3a): Chromatographic purification (ethanol, R_f = 0.04) gave 0.28 g of **2a/3a** (76%), as highly hygroscopic colorless needles, mixture of two diastereomers. − IR (KBr): ṽ = 3242 (br.) cm^{-1}. − ^{1}H NMR: δ = 1.34−1.78 (m, 7 H), 1.46 (d, ^3J = 6.7 Hz, 3 H, CH_3), 1.57 (d, ^3J = 6.5 Hz, 3 H, CH_3), 1.86−2.10 (m, 4 H), 2.55−2.84 (m, 3 H), 3.01−3.23 (m, 6 H), 3.44−3.58 (m, 2 H), 3.60−3.74 (m, 4 H), 3.82−3.93 (m, 2 H), 4.08 (dd, ^3J = 2.1 Hz, ^2J = 12.3 Hz, 1 H, 1-H), 4.23 (dd, ^3J = 2.0 Hz, ^2J = 12.3 Hz, 1 H, 1-H). − ^{13}C NMR, the signals of the minor diastereomer **2a** are given in brackets: δ = 13.4 [12.8] (CH_3), 27.1, 27.6, 28.6, 32.4 [25.0, 29.4, 30.0, 33.3] (C-4′, C-6′, C-7′ and C-8′), 43.7 [39.7] (C-5′), 64.9, 67.7, 68.7 [63.6, 64.5, 64.6] (C-1, C-2 and C-3′), 82.2 [83.8] (C-1′). − MS (EI); *m*/*z* (%): 138 (100) [$C_9H_{16}N^+$], 154 (40) [$C_9H_{16}NO^+$], 185 (7) [M^+]. − $C_{16}H_{19}NO_2$ (185.3): calcd. C 64.82, H 10.33, N 7.56; found C 64.53, H 9.98, N 7.64.

(2*S*,1′*S*,2′*S*/*R*,5′*S*)-2-(2′-Azabicyclo[3.3.0]oct-2′-yl)-3-phenylpropanol *N*-Oxide (2b/3b): Recrystallization from ethyl acetate/petroleum ether (4:1) gave 0.40 g of **2b/3b** (77%), white solid, mixture of two diastereomers. − IR (KBr): ṽ = 3440 (br.) cm^{-1}. − ^{1}H NMR (500 MHz): Signals of the major diastereomer **3b**: δ = 1.57−1.68 (m, 5 H), 2.00−2.10 (m, 2 H), 2.70−2.85 (m, 2 H) (4′-H, 4′-H′, 5′-H, 6′-H, 6′-H′, 7′-H, 7′-H′, 8′-H, 8′-H′), 3.13 (m, ^3J = 10.1 Hz, ^3J = 3.9 Hz, ^3J = 2.9 Hz, ^3J = 1.4 Hz, 1 H, 2-H), 3.21 (dd, ^2J = 13.5 Hz, ^3J = 3.9 Hz, 1 H, 3-H), 3.25 (ddd, ^2J = 12.1 Hz, ^3J = 10.1 Hz, ^3J = 7.0 Hz, 1 H, 3′-H), 3.51 (dd, ^2J = 13.5 Hz, ^3J = 10.1 Hz, 1 H, 3-H′), 3.57 (dd, ^2J = 12.7 Hz, ^3J = 2.9 Hz, 1 H, 1-H), 3.76 (ddd, ^2J = 12.1 Hz, ^3J = 9.6 Hz, ^3J = 5.4

Hz, 1 H, 3′-H′), 3.99 (m, ^3J = 10.2 Hz, ^3J = 7.2 Hz, ^3J = 2.8 Hz, 1 H, 1′-H), 4.03 (dt, ^2J = 12.7 Hz, ^3J = 1.4 Hz, 1 H, 1-H′), 7.20−7.31 (m, 5 H, aromatic H); signals of the minor diastereomer **2b**: δ = 1.48 (m, 1 H), 1.55−1.68 (m, 2 H), 1.79 (m, 1 H), 1.95−2.10 (m, 2 H), 2.19 (m, 1 H), 2.70−2.85 (m, 1 H), 3.11−3.28 (m, 4 H), 3.66 (m, ^2J = 12.9 Hz, ^3J = 2.3 Hz, 1 H, 1-H), 3.74−3.84 (m, 2 H), 4.08 (m, ^2J = 12.9 Hz, 1 H, 1-H′), 4.18 (q, ^3J = 7.9 Hz, 1 H, 1′-H), 7.20−7.31 (m, 5 H, aromatic H). − ^{13}C NMR, the signals of the minor diastereomer **2b** are given in brackets: δ = 26.9, 28.2, 28.8, 32.2, 32.6 [25.2, 29.7, 29.7, 31.8, 33.3] (C-4′, C-6′, C-7′, C-8′and C-3), 45.6 [39.8] (C-5′), 60.6 [69.9] (C-1), 69.2 [64.0] (C-3′), 75.2 [70.2] (C-2), 83.1 [83.8] (C-1′), 126.8 [126.9], 128.7 [128.7], 129.4 [129.6], 137.5 [137.1] (aromatic C). − MS (EI); *m/z* (%): 92 (81) [$C_7H_8^+$], 98 (100) [$C_7H_{14}^+$], 105 (46) [$C_7H_5O^+$]. − $C_{16}H_{23}NO_2$ (261.4): calcd. C 73.52, H 8.87, N 5.36; found C 73.55, H 8.74, N 5.39.

(2*S*,1′*S*,2′*S*,5′*S*)-(+)-2-(2′-Azabicyclo[3.3.0]oct-2′-yl)-1,1-diphenylpropanol *N*-Oxide (2c): Recrystallization from ethyl acetate/petroleum ether (1:2) gave 0.20 g of **2c** (30%), beige solid, m.p. 209−212°C. − $[\alpha]_D^{20}$ = +4.4 (c = 1.2, ethanol). − IR (KBr): $\tilde{\nu}$ = 3440 (br.), 2471 (br.) cm^{-1}. − ^{1}H NMR: δ = 1.25 (m, ^2J = 10.8 Hz, ^3J = 6.7 Hz, ^3J = 7.6 Hz, ^3J < 1 Hz, 1 H, 4′-H), 1.34 (m, 1 H, 6′-H), 1.52 (d, ^3J = 6.4 Hz, 3 H, 3-H), 1.52−1.62 (m, 2 H, 7′-H and 8′-H), 1.72 (m, 1 H, 7′-H′), 1.91 (m, 1 H, 6′-H′), 2.08 (m, 1 H, 8′-H′), 2.54 (m, ^2J = 10.8 Hz, ^3J = 11.5 Hz, ^3J = 12.3 Hz, ^3J = 7.9 Hz, 1 H, 4′-H′), 2.63 (m, ^2J = 10.1, ^3J = 6.7 Hz, ^3J = 11.5 Hz, 1 H, 3′-H), 2.69 (m, ^2J = 10.1 Hz, ^3J = 7.6 Hz, ^3J = 12.3 Hz, 1 H, 3′-H′), 2.92 (m, ^3J = 7.9 Hz, ^3J < 1 Hz, ^3J = 7.9 Hz, ^3J = 5.4 Hz, ^3J = 7.9 Hz, 1 H, 5′-H), 4.08 (q, ^3J = 7.7 Hz, 1 H, 1′-H), 4.30 (q, ^3J = 6.4 Hz, 1 H, 2-H), 7.10−7.80 (m, 10 H, aromatic H). − ^{13}C NMR: δ = 13.5 (q, C-3), 24.9 (t, C-7′), 29.7 (t, C-8′), 30.9 (t, C-4′), 33.2 (t, C-6′), 38.0 (d, C-5′), 65.8 (t, C-3′), 68.2 (d, C-2), 79.9 (s, C-1), 86.3 (d, C-1′), 124.9−128.3, 148.1, 148.8 (aromatic C). − MS (EI); *m/z* (%): 105 (50) [$C_7H_5O^+$], 138 (100) [$C_9H_{16}N^+$]. − $C_{22}H_{27}NO_2$ (337.5): calcd. C 78.29, H 8.06, N 4.15; found C 78.47, H 8.32, N 4.04.

(2*S*,1′*S*,2′*S*,5′*S*)-(−)-2-(2′-Azabicyclo[3.3.0]oct-2′-yl)-1,1,3-triphenylpropanol *N*-Oxide (2d): Chromatographic purification [ethyl acetate/petroleum ether (4:1), R_f = 0.11] gave 0.79 g of **2d** (95%), white solid, m.p. 129°C, decomposes after some time. − $[\alpha]_D^{20}$ = −29.9 (c = 0.7, ethanol). − IR (KBr): $\tilde{\nu}$ = 3442 (br.), 2249 (br.) cm^{-1}. − ^{1}H NMR: δ = 0.65−0.82 (m, 2 H), 1.00−1.60 (m, 5 H) (4′-H, 6′-H, 6′-H′, 7′-H, 7′-H′, 8′-H, 8′-H′), 2.43 (m, 1 H, 4′-H′), 2.59 (m, 1 H, 3′-H), 2.79 (m, 1 H, 3′-H′), 2.87 (m, 1 H, 5′-H), 3.11 (dd, ^3J = 2.9 Hz, ^2J = 17.0 Hz, 1 H, 3-H), 3.86 (dd, ^3J = 6.1 Hz, ^2J = 17.0 Hz, 1 H, 3-H′), 3.96 (m, 1 H, 1′-H), 4.63 (dd, ^3J = 6.1 Hz, ^3J = 2.9 Hz, 1 H, 2-H), 6.93−7.26 (m, 15 H, aromatic H), 7.77 (br. s, 1 H, OH). − ^{13}C NMR: δ = 24.3 (t, C-7′), 28.9 (t, C-6′ or C-8′), 30.3 (t, C-4′), 32.6 (t, C-8′ or C-6′), 33.2 (t, C-3), 39.0 (d, C-5′), 66.8 (t, C-3′), 73.6 (d, C-2), 80.9 (s, C-1), 85.8 (d, C-1′), 125.6−128.6, 140.2, 147.4, 149.1 (aromatic C). − MS (EI); *m/z* (%): 105 (100) [$C_7H_5O^+$]. − $C_{28}H_{31}NO_2$ (413.6): calcd. C 81.31, H 7.55, N 3.39; found C 81.47, H 7.46, N 3.30.

(2*R*,1′*R*,2′*R*,5′*R*)-(+)-2-(2′-Azabicyclo[3.3.0]oct-2′-yl)-1,1,2-triphenylethanol *N*-Oxide (*ent*-2e): Recrystallization from ethyl acetate/petroleum ether (4:1) gave 0.40 g of *ent*-**2e** (45%), colorless needles, m.p. 145−148°C. − $[\alpha]_D^{23}$ = +161.3 (*c* = 0.2, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 3445 (br.), 2178 (br.) cm^{-1}. − ^{1}H NMR (500 MHz) ($CDCl_3$ with 15% [D$_4$]methanol): δ = 1.19 (m, ^2J = 12.8 Hz, ^3J = 7.4 Hz, 1 H, 4′-H), 1.25−1.32 (m, 2 H), 1.48−1.60 (m, 4 H) (6′-H, 6′-H′, 7′-H, 7′-H′, 8′-H, 8′-H′), 2.38 (m, ^2J = 12.8 Hz, ^3J = 10.5 Hz, ^3J = 8.4 Hz, ^3J = 11.0 Hz, 1 H, 4′-H′), 2.68 (m, 1 H, 5′-H), 2.78 (m, ^2J = 11.2 Hz, ^3J = 8.4 Hz, 1 H, 3′-H), 2.82 (m, ^2J = 11.2 Hz, ^3J = 10.5 Hz, ^3J = 7.4 Hz, 1 H, 3′-H′), 3.42 (q, ^3J = 7.0 Hz, 1 H, 1′-H), 4.05 (br. s, 1 H, OH), 5.08 (s, 1 H, 2-H), 6.72−7.30 (m, 13 H, aromatic H), 7.85 (d, *J* = 7.6 Hz, 1 H, aromatic H), 8.38 (d, *J* = 8.1 Hz, 1 H, aromatic H). − ^{13}C NMR ($CDCl_3$ with 15% [D$_4$]methanol): δ = 24.0 (t, C-7′), 29.4 (t, C-6′ or C-8′), 30.4 (t, C-4′), 32.3 (t, C-8′ or C-6′), 38.3 (d, C-5′), 66.8 (t, C-3′), 75.9 (d, C-2), 81.0 (s, C-1), 86.9 (d, C-1′), 125.6−133.3, 145.3, 147.6 (aromatic C). − MS (EI); *m/z* (%): 77 (78) [$C_6H_5^+$], 105 (100) [$C_7H_5O^+$], 182 (40) [$C_{13}H_{10}O^+$]. − $C_{27}H_{29}NO_2$ (399.5): calcd. C 81.18, H 7.32, N 3.51; found C 81.06, H 7.24, N 3.44.

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[6] In the ^{1}H-NMR spectrum of the mixture of diastereomers **2b**/**3b** only a few of the signals are sufficiently separated to be unambiguously assigned. The most informative of them is the signal for 1′-H at the bridgehead atom C-1′. For **2b**, in which this proton is *syn*-orientated to the amine oxide O-2′ atom, the signal appears at δ = 4.18, whereas in the spectrum of **3b** with *anti* orientation of 1′-H and O-2′ it is observed at δ = 3.99.
[7] Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambidge Crystallographic Data Centre as supplementary publication no. CCDC-112045 and -112046. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: int. code + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].
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[9] At the starting point of the reaction the *syn* and the *anti* form of 1,2-dimethylpyrrolidine interconvert by N-inversion establishing a dynamic equilibrium. Both of them exist, presumably, in two different conformations with the unpaired electron pair either in a quasi-axial or a quasi-equatorial position. These conformers may interconvert by a ring-inversion process. Thus, oxygen transfer to the N atom may occur either to the quasi-axial or to the quasi-equatorial position of either the *syn* ot the *anti* form. In contrast to N-inversion such a ring inversion is of course also possible in the corresponding pyrrolidine *N*-oxides.
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