Stereochemistry of the Oxidation of Imines Derived from Substituted Cyclohexanones: Axial vs Equatorial Attack and Evidence for Delivery by an Adjacent Hydroxyl Group

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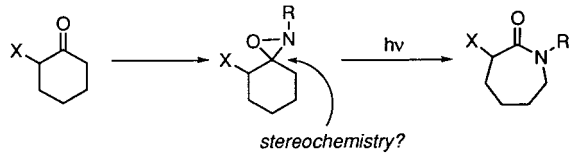
A set of conformationally biased imines derived from substituted cyclohexanones and benzylamine or diphenylmethylamine, respectively, were oxidized to the corresponding oxaziridines. The structures of the oxaziridines were determined via NMR comparison of two series of differently *N*-substituted oxaziridines. Thus, those compounds having an axially disposed nitrogen substituent displayed an upfield-shifted axial proton in a 1,3-relationship to the oxaziridine nitrogen in the *N*-diphenylmethyl series relative to the *N*-benzyl compounds. Analysis of the products obtained from these reactions suggests that (1) adjacent hydroxyl groups favor syn oxidant addition and (2) imines containing adjacent methoxy groups preferentially undergo attack anti to the resident alkoxy substituent.

Two of the most useful unifying concepts in organic stereochemistry are the effect of conformation on the reactions of cyclic structures[1] and the delivery of reagents through prior coordination with a nearby functional group.[2] Both of these concepts pervade the field of chemical synthesis; in particular, the latter idea has been a mainstay of oxidation chemistry since the early observations of Henbest on the oxidation of allylic alcohols.[3]

Oxaziridines are established intermediates in synthetically useful ring-expansion processes[4] and are even better known as oxidizing reagents. In particular, chiral sulfonylozaziridines often afford high levels of enantioselectivity in reactions with various double bonds or sulfides.[5] The single most common method for oxaziridine synthesis is the oxidation of an imine with a peracid such as *m*-chloroperoxybenzoic acid (*m*-CPBA). These imines are typically derived from cyclohexanone derivatives. In such cases, equatorial attack of the oxidant is generally favored, leading to oxaziridines bearing an axial nitrogen substituent. However, relatively little is known about the effect of adjacent substitution on the course of such reactions, which are especially useful as they constitute the first step in the only general route for nitrogen insertion anti to the more substituted carbon (Scheme 1).[6−8]

In this paper, we examine the effect of polar substituents on the stereochemistry of oxaziridine formation.

Scheme 1



Such effects have been extensively investigated in terms of addition to α-substituted ketones[9] but have been much less recognized in the context of imine oxidation reactions. In so doing, we present evidence that polar substituents can lead to axial addition of an oxidizing agent in favorable circumstances. In addition, the first documented case of substrate-directed delivery in the case of an imine oxidation reaction will be presented.

Results and Discussion

Background and Research Plan. The observation of equatorial attack by *m*-CPBA onto 4-substituted cyclohexylimines was first made by Oliveros, Rivière, and Lattes.[10] Although this course of reaction has proved general in our experience, there have been examples that suggest other reaction courses might be possible. Consider the case presented in Scheme 2, in which the isomer shown was the only oxaziridine isolated.[7] It is reasonable to suppose that the reaction proceeds by equatorial

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(1) Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; John Wiley & Sons: New York, 1994.
(2) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307−1370.
(3) Henbest, S. W.; Wilson, R. A. L. *J. Chem. Soc.* **1957**, 1968−1965.
(4) Aubé, J. *Chem. Soc. Rev.* **1997**, *26*, 269−277.
(5) (a) Davis, F. A.; Sheppard, A. C. *Tetrahedron* **1989**, *45*, 5703−5742. (b) Davis, F. A.; Chen, B.-C. *Chem. Rev.* **1992**, *92*, 919−934.
(6) (a) Lattes, A.; Oliveros, E.; Rivière, M.; Belzecki, C.; Mostowicz, D.; Abramskj, W.; Piccinni-Leopardi, C.; Germain, G.; Van Meerssche, M. *J. Am. Chem. Soc.* **1982**, *104*, 3929−3934. (b) Aubé, J.; Wang, Y.; Hammond, M.; Tanol, M.; Takusagawa, F.; Vander Velde, D. *J. Am. Chem. Soc.* **1990**, *112*, 4879−4891.
(7) For examples of the oxidation of imines containing adjacent alkyl groups, see: (a) Oliveros, E.; Rivière, M.; Lattes, A. *Org. Magn. Reson.* **1976**, *8*, 601−606. (b) Oliveros, E.; Rivière, M.; Lattes, A. *Nouv. J. Chim.* **1979**, *3*, 739−753. (c) Oliveros, E.; Rivière, M.; Lattes, A. *J. Heterocycl. Chem.* **1980**, *17*, 107−112. (d) Aubé, J.; Hammond, M.; Gherardini, E.; Takusagawa, F. *J. Org. Chem.* **1991**, *56*, 499−508; correction *J. Org. Chem.* **1991**, *56*, 4086.
(8) For examples of the oxidation of imines containing adjacent heteroatom-containing groups, see: (a) Felluga, F.; Nitti, P.; Pitacco, G.; Valentin, E. *J. Chem. Res., Synop.* **1992**, 86−87. (b) Czarnocki, Z. *J. Chem. Res., Synop.* **1992**, 334−335. (c) Wolfe, M. S.; Dutta, D.; Aubé, J. *J. Org. Chem.* **1997**, *62*, 654−663.
(9) Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, *99*, 1191−1224.
(10) Oliveros, E.; Rivière, M.; Lattes, A. *Org. Magn. Reson.* **1976**, *8*, 601−606.

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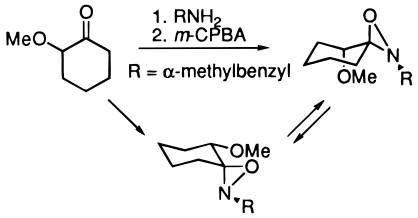
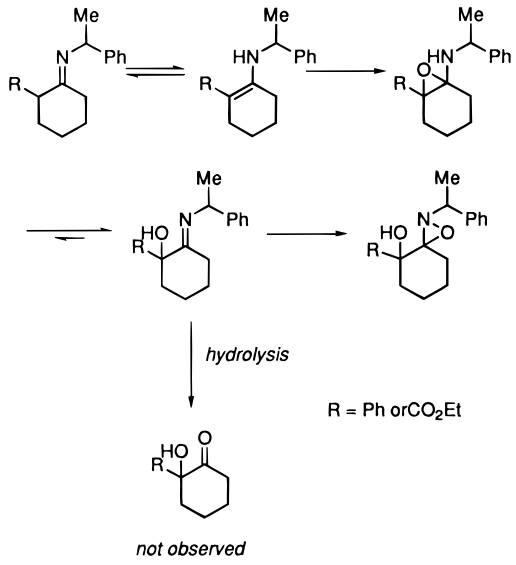
Scheme 2



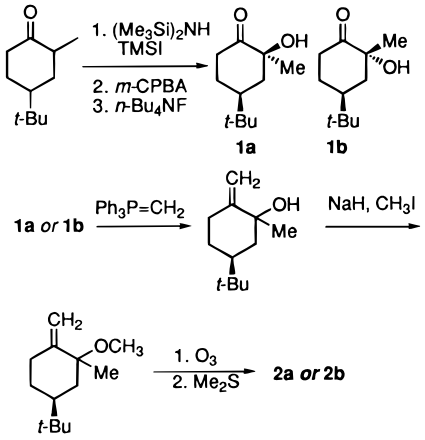
Scheme 3



addition of oxygen onto a conformation of imine bearing the methoxy group in an axial position, followed by equilibrium to the more stable oxaziridine containing an equatorial nitrogen group.[10] A possible electronic contribution to the stereoselectivity was suggested by the fact that although a series of α-substituted cyclic imines all afforded the major stereoisomer as shown in Scheme 2, there was a marked dependence of product ratio on the nature of the resident substituent (Me, 1.2:1; Ph, 3.3:1, OMe, >10:1; only the last example is shown in Scheme 2). In light of Cornforth and Felkin-Ahn considerations that suggest that nucleophilic addition to carbonyls occurs anti to such polar groups, the possibility of a hitherto unobserved axial addition had to be considered as well. However, the conformational mobility of the product in this case did not permit us to distinguish between these possibilities. In another study, cyclic imines containing a 2-NHBoc substituent also appeared to prefer attack of the oxidant anti to the polar substituent, but these results were complicated by issues of double diastereoselectivity thus prohibiting firm mechanistic conclusions.[8]

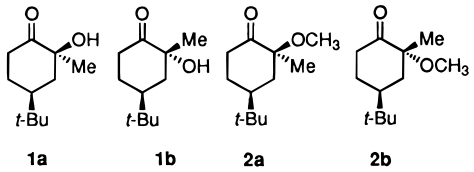
An additional observation bearing on the possibility of hydroxyl group delivery is presented in Scheme 3.[7] In this interesting double oxidation reaction, the enamine form stabilized by an adjacent carboalkoxy or phenyl group undergoes initial oxidation and then opens to reveal a new imine moiety. With less electrophilic oxidizing agents, such as monoperoxyphthalate, the amount of simple imine oxidation product observed relative to the hydroxylated ketone is diminished. The relevant observation is that *in no case was any of the ketone resulting from enamine oxidation without subsequent oxaziridination observed*. Indeed, the results seem to indicate that

Scheme 4



the α-hydroxylated imine preferentially soaks up oxidizing agent in the presence of its less hindered, nonhydroxylated precursor. This can be taken as circumstantial evidence for rate acceleration present in the α-hydroxylated imine, which is one hallmark of delivery of oxidizing agent.

To examine these effects systematically, a series of ketones **1a**,**b** and **2a**,**b** were synthesized and the oxidation stereochemistry of their derived imines examined. We expected that each imine would exist predominantly as a single chairlike conformation anchored by the 4-*tert*-butyl substituent. The 2-methyl group was considered necessary (1) to prevent enamine-mediated epimerization of the derived imines and (2) to keep adjacent ketone and hydroxyl groups from scrambling through a common enol. Similar approaches have been used successfully in studying steric and electronic effects in reactions of alkenes[11] and ketones.[12]



Preparation of Ketones 1 and 2. The requisite ketones were prepared as shown in Scheme 4. Thus, 4-*tert*-butyl-2-methylcyclohexanone[13] was treated with hexamethyldisilazane and trimethylsilyl iodide in pentane to form the thermodynamically equilibrated enol ether, which was then oxidized with *m*-CPBA.[14] The resulting epoxide was reacted with *n*-tetrabutylammonium fluoride to generate α-hydroxycyclohexanones **1a**,**b**, which were readily separated by flash column chromatography. The overall yield of each ketone was about 27%.

The assignments of stereochemical structures for isomers **1a**,**b** were based on proton NMR analysis. Because of deshielding by the axial hydroxyl group in isomer **1b**, the axial C-6 proton was shifted downfield to 2.82 ppm,

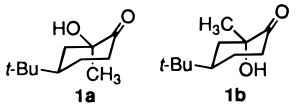
(11) (a) Vedejs, E.; Dent, W. H., III. *J. Am. Chem. Soc.* **1989**, *111*, 6861−6862. (b) Vedejs, E.; Dent, W. H., III.; Kendall, J. T.; Oliver, P. A. *J. Am. Chem. Soc.* **1996**, *118*, 3556−3567.

(12) Paquette, L. A.; Stepanian, M.; Mallavadhani, U. V.; Cutarelli, T. D.; Lowinger, T. B.; Klemeyer, H. J. *J. Org. Chem.* **1996**, *61*, 7492−7507.

(13) Stork, G.; Darling, S. D. *J. Am. Chem. Soc.* **1964**, *86*, 1761−1768.

(14) Miller, R. D.; McKean, D. R. *Synthesis* **1979**, 730−731.

Table 1. ^{1}H NMR Comparison of Ketones 1a and 1b



1a **1b**

	axial C-4 proton		axial C-6 proton	
isomer	δ (ppm)	J_{vic} (Hz)	δ (ppm)	J_{vic} (Hz)
1a	1.60	tt, 12.6, 2.8	2.54	td, 1.40, 6.0
1b	1.79	tt, 12.6, 3.5	2.82	td, 13.8, 6.4

as was the axial C-4 proton to 1.79 ppm (Table 1). The axial C-6 and C-4 protons were assigned according to their coupling patterns. These assignments were confirmed by an X-ray crystallographic study of ketone **1b**.

Attempts to directly methylate these hydroxyl groups were unsuccessful, so ketones **1a**,**b** were separately subjected to Wittig reaction followed by methylation and ozonolysis. In this way, ketones **2a** and **2b** were obtained in 34% and 37% overall yield, respectively. The stereostructures of isomers **2a**,**b** were deduced from those of ketones **1a**,**b**.

Synthesis of Oxaziridines and Structure Determination. The next stage of the project was to prepare imines from ketones **1** and **2** and determine the face selectivities of their oxidation reactions (Table 2). Benzylamine **3** and diphenylmethylamine **4** were chosen as amine components for the initial condensation reaction. The usual method for oxaziridine synthesis was used: the crude imine solutions were added dropwise to a suspension of *m*-CPBA kept at −78 °C. The reactions were complete within a few minutes and quenched by the addition of sodium bisulfite to the mixture at low temperatures. The yields of the reactions were generally middling compared to previously reported examples. However, none of these examples were subjected to extensive optimization, inasmuch as some erosion of efficiency was expected in light of the highly hindered substrates. The product ratios were deduced from the crude ^{1}H NMR spectra of the reactions, but most of the oxaziridines were separable and their structures analyzed as pure materials.

Whereas the relative stereochemistry of the methyl, hydroxyl, and methoxy groups in the oxaziridines could be inferred from their precursor ketones, the relationship between the more highly substituted C-4 carbon and the nitrogen alkyl group was much more difficult to assess. All of the oxaziridines were presumed to have a trans relationship between the (nonepimerizable[4]) nitrogen substituent and the more highly substituted C-position on the basis of literature precedence (C-4, see Tables 2 and 3).[6−8] In addition, this was confirmed in several cases by nuclear Overhauser effect (NOE) studies. Thus, irradiation of the benzylic protons in **5a**, **7eq**, and **11eq** + **11ax** (studied as an inseparable mixture) resulted in enhancement of the signal corresponding to one of the C-8 protons (Table 3). These signals were assigned to the equatorial C-8 proton as a result of coupling with its geminal axial proton (one large coupling) and its adjacent C-7 protons (two small couplings).

Initially, we prepared only the *N*-benzyl series of oxaziridines (Table 2, odd-numbered entries) in the hope that we would be able to assign the stereostructures through NOE or X-ray techniques. Although these efforts did not succeed, previous work in this laboratory has shown that the axial or equatorial disposition of an oxaziridine nitrogen can be determined from the chemical shift of a proton having a 1,3-diaxial/syn relationship to the nitrogen substituent (Figure 1).[15] We therefore prepared the four analogues containing *N*-(diphenyl)-methyl substituents (Table 2, even-numbered entries), with the expectation that the axial C-7 proton in such oxaziridines with an axial nitrogen substituent would appear at unusually high field in the ^{1}H NMR spectrum.

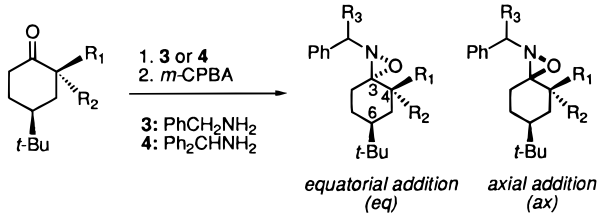
Comparison of the ratios of *N*-benzyl vs *N*-diphenylmethyl oxaziridines obtained from a given ketone indicates that the stereochemical course is similar in each series. Comparison of spectral data then allowed the assignment of stereoisomers for each set of products. Thus, three compounds exhibited a strong upfield shift of the C-7 proton in the *N*-diphenylmethyl series when compared to the *N*-benzyl compounds, indicating that the nitrogen group of the oxaziridine in these compounds occupies an axial position. The assignments of the upfield proton as the axial C-7 proton were based on coupling pattern analysis. For example, the upfield proton in oxaziridine **6eq** showed a clear quartet of doublets that resulted from three large couplings (two vicinal and one geminal) and one small coupling, consistent with only the axial C-7 proton. Accordingly, **6eq**, **8eq**, and **10eq** were assigned as arising from equatorial attack by the peracid oxidant. In contrast, both *N*-diphenylmethyl oxaziridines that did not show an upfield C-7 axial proton displayed upfield shifts of the methoxy protons on the C-4 (quaternary) stereocenter (see **6ax** and **12ax** in Table 4). This can be ascribed to shielding by one of the phenyl groups attached to equatorial nitrogen as illustrated in the minimized (MM2) conformer depicted in Figure 2 and is absent in the products containing an axial (trans-disposed) nitrogen.

Discussion of Stereoselectivity. Three considerations could factor into the selectivity of these imine oxidation reactions: (1) equatorial vs axial attack, of which the former is usually favored in the absence of additional effects,[10] (2) the syn-directing effect of the hydroxy group through hydrogen bonding, or (3) attack anti to an electron-withdrawing substituent. As in previous studies using 2-substituted-4-cyclohexanone derivatives,[11,12] it is assumed that the central ring persists in a well-behaved chair conformation throughout the reaction coordinate. This supposition is supported by NMR measurements, which are consistent with such a conformation for both starting ketones and oxaziridine products. As noted in the Introduction, neither oxidant delivery nor polar directing effects have been previously demonstrated in imine oxidation reactions.

The mechanism of the oxaziridine formation is generally considered a nucleophilic, Baeyer−Villiger type of process rather than concerted oxygen transfer (Figure 3). Much circumstantial evidence supports the former: (1) the reaction being stereoselective but nonstereospecific inasmuch as imine geometry is not reflected in the product oxaziridines;[16−18] (2) the preferential oxidation of imines in the presence of olefins at low temperatures,[19,20] which is more consistent with the electron-poor

(15) Usuki, Y.; Wang, Y.; Aubé, J. *J. Org. Chem.* **1995**, *60*, 8028−8035.
(16) Boyd, D. R.; Neill, D. C.; Watson, C. G.; Jennings, W. B. *J. Chem. Soc., Perkin Trans. 2* **1975**, 1813−1818.
(17) Belzecki, C.; Mostowicz, C. *J. Org. Chem.* **1975**, *40*, 3878−3880.
(18) Aubé, J.; Wang, Y.; Hammond, M.; Tanol, M.; Takusagawa, F.; Vander Velde, D. *J. Am. Chem. Soc.* **1990**, *112*, 4879−4891.

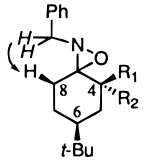
Table 2. Face Selectivity of Imine Oxidation Reactions



entry	ketone	amine	R_1	R_2	R_3	product(s)	eq:ax ratio[a]	yield (%)
1	**1a**	**3**	OH	Me	H	**5a** + **5b**	50:50	63
2	**1a**	**4**	OH	Me	Ph	**6eq** + **6ax**	39:61	83
3	**1b**	**3**	Me	OH	H	**7eq**[b]	>95:5	67
4	**1b**	**4**	Me	OH	Ph	**8eq**	>95:5	63
5	**2a**	**3**	OMe	Me	H	**9eq**[b]	>95:5	70
6	**2a**	**4**	OMe	Me	Ph	**10eq**	>95:5	40
7	**2b**	**3**	Me	OMe	H	**11eq** + **11ax**[b,c]	17:83	64
8	**2b**	**4**	Me	OMe	Ph	**12ax**	<5:95	49

[a] Determined by ^{1}H NMR examination of the crude reaction mixture. [b] Structures assigned in analogy to the experiment summarized in the succeeding entry. [c] Stereoisomers not separable by column chromatography.

Table 3. NOE Results from Selected Oxaziridines



				eq C-8 proton[a]	
entry	oxaziridine	R_1	R_2	δ (ppm)	coupling data
1	**5a**	OH	Me	1.95	dt (15, 3 Hz)
2	**7eq**	Me	OH	1.80	dt (16, 3 Hz)
3	**11eq** + **11ax**	Me	OMe	1.84	dt (15, 5 Hz)

[a] Revealed through irradiation of the *N*-benzylic protons and assigned from coupling and chemical shift data.

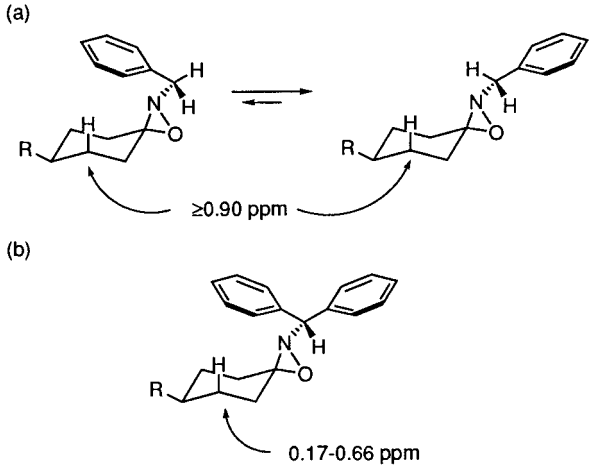


Figure 1. Comparison of chemical shifts in (a) *N*-benzyl and (b) *N*-diphenylmethyl oxaziridines derived from 4-substituted ketones (R = Me, *t*-Bu, Ph).[15]

imine acting as an electrophile rather than a nucleophile; (3) the formation of oxaziridine in lieu of the isomeric nitrone, which might reasonably be expected to predominate via nucleophilic attack of the imine lone pair on an electrophilic oxidizing agent (although some exceptions are known in special cases[21]); and (4) solvent effects.[16,22]

A theoretical study also concluded that the two-step mechanism was more reasonable.[23] A detailed analysis of the kinetics of the oxidation reaction also supported the two-stage mechanism and additionally indicated that the initial addition step to the imine (or the protonated form) is generally rate-limiting.[22]

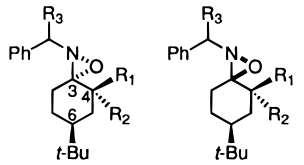
In this scenario, the equatorial/axial selectivity of oxidant delivery is established in the first step of the mechanism, with configuration of the stereogenic nitrogen resulting from the minimization of nonbonded interactions in the second. Since the initial step is rate-limiting, the oxaziridine ratios reflect the equatorial/axial ratios of this first step. The intrinsic kinetic selectivity for imine oxidations in similar systems is for equatorial addition of oxidant, resulting in an oxaziridine bearing an axial nitrogen substituent (Figure 4a). In conformationally mobile systems, these products typically undergo a ring flip to place the oxaziridine nitrogen in the more stable equatorial position. In simple systems, the ratios of equatorial/axial oxidation are generally quite high (>10:1).[18] Inspection of the results herein indicate that the preference for equatorial addition selectivity has been substantially undermined in half of the examples shown in Table 2.

Accordingly, it appears that the hydrogen-bond-donating hydroxyl group is able to direct oxaziridination in much the same manner as is well-known for epoxidation reactions (Figure 4b). Although this syn-directing effect is not strong enough to completely bias addition into the axial direction for substrates containing an equatorially disposed hydroxyl group, it has become competitive with the sterically preferred addition from the equatorial direction (Table 2, entries 1 and 2). As expected, when the 2-hydroxyl group is itself in an axial orientation, high equatorial addition selectivity is once again observed (Table 2, entries 3 and 4).

When the alcohol is converted into an ether substituent, the C-2 substituent exerts the opposite directing effect (Figure 4c). In this case, however, the anti-directing

(19) Aubé, J.; Peng, X.; Wang, Y.; Takusagawa, F. *J. Am. Chem. Soc.* **1992**, *114*, 5466−5467.
(20) Aubé, J.; Ghosh, S.; Tanol, M. *J. Am. Chem. Soc.* **1994**, *116*, 9009−9018.
(21) Boyd, D. R.; Coulter, P. B.; McGuckin, M. R.; Sharma, N. D.; Jennings, W. B.; Wilson, V. E. *J. Chem. Soc., Perkin Trans. 1* **1990**, 301−306.
(22) (a) Ogata, Y.; Sawaki, Y. *J. Am. Chem. Soc.* **1973**, *95*, 4687−4692. (b) Ogata, Y.; Sawaki, Y. *J. Am. Chem. Soc.* **1973**, *95*, 4692−4698.
(23) Azman, A.; Koller, J.; Plesnicar, B. *J. Am. Chem. Soc.* **1979**, *101*, 1107−1109.

Table 4. Selected ^{1}H NMR Data of Oxaziridines



		N-benzyl series (R_3 = H)			*N*-diphenylmethyl series (R_3 = Ph)		
R_1	R_2	oxaziridine	δ, ax H-7 proton	δ, R_2 substituent	oxaziridine	δ, ax H-7 proton	δ, R_2 substituent
OH	Me	**5a**[a]	≥0.70	1.27	**6eq**	0.08	1.23
OH	Me	**5b**[a]	≥0.70	1.17	**6ax**	≥0.70	0.96
Me	OH	**7eq**	≥0.70	1.12	**8eq**	0.18	1.24
OMe	Me	**9eq**	≥0.70	1.25	**10eq**	0.21	1.25
Me	OMe	**11eq**[b]	≥0.70	3.06	**12eq**	nd[c]	
Me	OMe	**11ax**[b]	≥0.70	3.08	**12ax**	≥0.70	2.63

[a] Stereostructure not assigned. [b] Stereoisomers not separable by column chromatography. [c] Not detected.

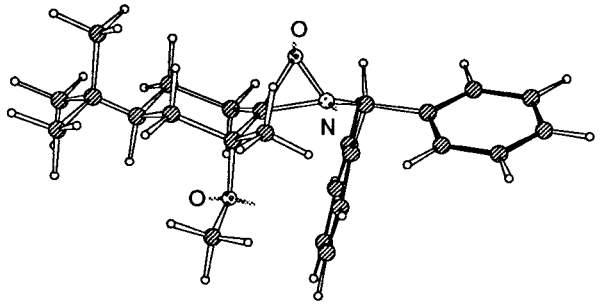


Figure 2. Proposed conformation of oxaziridine **12ax**. In this depiction, the *N*-diphenylmethyl substituent extends in back of the plane of the oxaziridine ring.

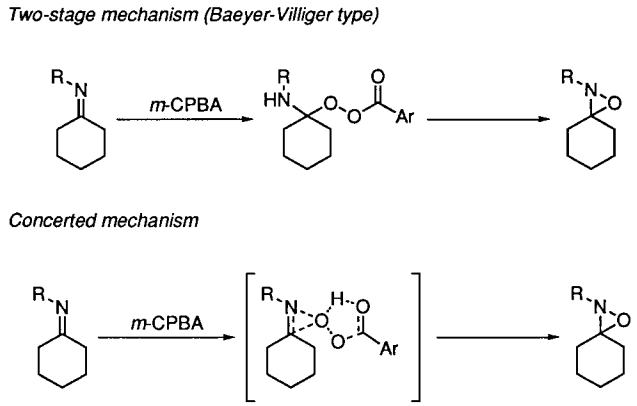


Figure 3. Possible mechanisms for imine oxidation reactions.

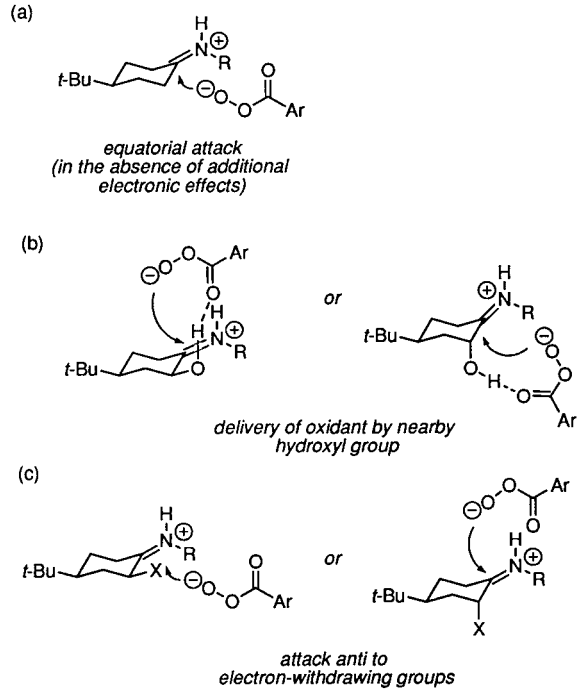


Figure 4. Proposed transitions structures for oxaziridination reactions. Although an initial proton transfer prior to attack by the peracid is shown (and has been previously proposed, as noted in the text), this step is not required by the data.

effect is able to surmount the substrate's natural preference for equatorial attack to the extent of ≥5:1 in favor of axial addition for imines containing a C-2 methoxy group in the axial position (Table 2, entries 7 and 8). Again, attack anti to a C-2 methoxy group in an equatorial position results in equatorial addition because both directing effects are additive.

Summary. Evidence for two previously unobserved modes of attack of nucleophilic addition of an oxidant to imines has been obtained in a conformationally fixed cyclic system. The stereochemical determinations were carried out using NMR techniques previously developed in these labs. 2-Hydroxylated imines undergo competitive delivery of the oxidant to afford products unusually enriched in the syn adduct. Although the results are related to those obtained in Henbest-styled alkene epoxidations, the peracid acts as the nucleophile in these cases rather than as an electrophile. Finally, these effects are potent enough to surmount the normal tendency of imine oxidation reactions to occur via equatorial attack. These results should prove useful in the design of asymmetric oxaziridine syntheses, of which no efficient cases are currently known.[24]

Experimental Section

General methods have been published.[7d]

4-(1,1-Dimethylethyl)-2-hydroxy-2-methylcyclohexanone (1). 2-Methyl-4-*tert*-butylcyclohexanone (7.50 g, 47.5 mmol)[13] was dissolved in pentane (250 mL) and cooled to 0 °C under argon. Hexamethyldisilazane (12.0 mL, 57.1 mmol) was

(24) Davis, F. A.; Jenkins, R. H., Jr. In *Asymmetric Synthesis*; Morrison, J. D., Scott, J. W., Eds.; Academic Press: Orlando, 1984; Vol. 4, pp 313−353.

added slowly, followed by iodotrimethylsilane (6.40 mL, 47.5 mmol). The reaction mixture was stirred at 0 °C for 10 min and then kept at room temperature for 2 h. It was washed with saturated $NaHCO_3$ and dried with $MgSO_4$. The organic solution was concentrated and added to a solution of *m*-CPBA (9.90 g, 57.1 mmol) in dichloromethane (150 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 10 min and then at room temperature for 30 min before it was quenched with 10% aqueous $Na_2S_2O_3$. It was extracted with dichloromethane, washed with saturated $NaHCO_3$, and dried with $MgSO_4$. After the organic solvent was removed, the oily residue was added to 100 mL of 1.0 N *n*-tetrabutylammonium fluoride in hexane and stirred overnight. Standard aqueous workup and separation by column chromatography (5% ethyl acetate/hexane) afforded two known[11] isomers, respectively. Isomer **1a [(2*S**,4*S**)-1]** (R_f = 0.40, 15% ethyl acetate/hexane): 2.30 g, 28%; isomer **1b [(2*R**,4*S**)-1]** (R_f = 0.33, 15% ethyl acetate/hexane): 2.42 g, 29%. **1a**: crystallization in diethyl ether at −20 to −24 °C afforded isomer **1a** as colorless crystals, mp 51−52 °C: IR ($CDCl_3$) 3493, 2962, 1711 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.85 (s, 9H), 1.36 (s, 3H), 1.38−1.46 (m, 2H), 1.56 (tt, J = 12.5, 2.8 Hz, 1H, C_4 axial H), 2.06−2.19 (m, 2H), 2.42 (m, 1H), 2.50 (td, J = 14.2, 6.1 Hz, 1H), 3.91 (br s, 1H, −OH); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 25.8, 27.6, 28.8, 32.3, 36.9, 43.2, 44.7, 76.0, 214.7; HRMS calcd for $C_{12}H_{22}O_2$ 198.1620, found 198.1607; MS *m/e* 185 (M^+ + 1), 167 (100), 141. Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.70; H, 10.94. Found: C, 71.34; H, 10.80. **1b**: colorless crystals, mp 80−81 °C; IR ($CDCl_3$) 3493, 2962, 2872, 1711 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.86 (s, 9H), 1.27 (s, 3H), 1.36−1.50 (m, 2H), 1.78 (tt, J = 12.6, 3.4 Hz, 1H, C_4 axial H), 1.96−2.09 (m, 2H), 2.31 (dq, J = 14.0, 3.2 Hz, 1H), 2.74−2.85 (m, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 24.9, 27.2, 27.3, 31.8, 36.6, 41.4, 41.6, 74.9, 213.9; MS *m/e* 185 (M^+ + 1), 167, 141 (100). Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.70; H, 10.94. Found: C, 71.68; H, 10.71.

(1*S,5*S**)-5-(1,1-Dimethylethyl)-1-methyl-2-methylenecyclohexanol.** Methyltriphenyl phosphonium bromide (9.66 g, 26.5 mmol) and potassium *tert*-butoxide (3.02 g, 25.6 mmol) in THF (30 mL) were allowed to reflux for 30 min. Ketone **1a** (1.57 g, 9.0 mmol) was added, and the reaction mixture was allowed to reflux for 10 min. Standard aqueous workup and purification by column chromatography (5% ethyl acetate/hexane) gave the title product (1.47 g, 95%): IR ($CDCl_3$) 3595, 2953, 1646 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.85 (s, 9H), 0.95−1.34 (m, 3H), 1.32 (s, 3H), 1.64−1.71 (br s, 1H), 1.78−1.91 (m, 2H), 2.05−2.17 (m, 1H), 2.32−2.41 (m, 1H), 4.69 (d, J = 1.7 Hz, 1H), 4.96 (d, J = 1.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 26.8, 27.3, 28.6, 32.0, 33.2, 43.9, 45.8, 73.9, 104.2, 155.4; MS *m/e* 182 (M^+), 165 (100, M^+ − OH), 109. This compound was used without further purification.

(1*R,5*S**)-5-(1,1-Dimethylethyl)-1-methyl-2-methylenecyclohexanol** was prepared as described for the preceding compound (1.60 g, 90%): ^1H NMR ($CDCl_3$, 300 MHz) δ 0.85 (s, 9H), 0.95−1.15 (m, 2H), 1.47 (s, 3H), 1.63 (tt, J = 12.4, 3.2 Hz, 1H, C_5 axial H), 1.81−1.91 (m, 2H), 2.21 (dt, J = 13.3, 3.1 Hz, 1H), 2.45 (m, 1H), 4.74 (s, 1H), 4.84 (s, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 27.3, 27.9, 28.6, 31.8, 32.3, 41.6, 42.5, 71.4, 106.6, 153.2; MS *m/e* 182 (M^+), 165 (100, M^+ − OH), 149, 125, 109, 95. This compound was used without further purification.

(1*S,5*S**)-5-(1,1-Dimethylethyl)-1-methoxy-1-methyl-2-methylene- cyclohexane.** (1*S**,5*S**)-5-(1,1-Dimethylethyl)-1-methyl-2-methylenecyclohexanol (0.810 g, 4.5 mmol) was added to 60% NaH (0.23 g, 5.9 mmol) in THF (15 mL), and the reaction mixture was allowed to reflux for 1 h. The reaction mixture was cooled to room temperature, iodomethane (1.14 g, 8.00 mmol) added, and the reaction mixture was stirred at room temperature for 3 h. It was worked up by addition of hexane (10 mL) and filtration through a pad of Celite. The filtrate was concentrated and purified by column chromatography (4% ethyl acetate/hexane) to afford the title product as an oil (0.610 g, 75%): IR ($CDCl_3$) 2952, 1368 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.84 (s, 9H), 0.89−1.19 (m, 2H), 1.28 (s, 3H), 1.75 (m, 2H), 2.12 (m, 1H), 2.34 (m, 1H), 3.28 (s, 3H), 4.72 (s, 1H), 4.89 (s, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 13.8, 22.4, 24.4, 27.3, 28.3, 31.4, 32.7, 33.2, 37.5, 45.2, 49.3, 77.9, 106.0, 151.0; MS *m/e* 197 (M^+ + 1), 165 (100), 149, 109, 95. This compound was used without further purification.

(1*R,5*S**)-5-(1,1-Dimethylethyl)-1-methoxy-1-methyl-2-methylene-cyclohexane** was prepared from (1*S**,5*S**)-5-(1,1-dimethylethyl)-1-methyl-2-methylenecyclohexanol as described for the preceding compound (oil, 0.540 g, 84%): IR ($CDCl_3$) 2948, 1366 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.84 (s, 9H), 0.85−1.21 (m, 2H), 1.25 (s, 3H), 1.65 (m, 1H), 1.83 (m, 1H), 1.91 (m, 1H), 2.15 (m, 1H), 3.04 (s, 3H), 4.80 (s 1H), 4.91 (s, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 21.4, 27.3, 28.6, 31.8, 32.6, 41.6, 41.7, 49.2, 76.0, 109.6, 150.8; MS *m/e* 197 (M^+ + 1), 165 (100), 109. This compound was used without further purification.

(2*S,4*S**)-4-(1,1-Dimethylethyl)-2-methoxy-2-methylcyclohexanone (2a).** (1*S**,5*S**)-5-(1,1-Dimethylethyl)-1-methoxy-1-methyl-2-methylenecyclohexane (0.340 g, 1.7 mmol) was dissolved in 15 mL of a mixture of methanol and dichloromethane (2:1) at −78 °C. Ozone was passed through the solution until the deep blue color persisted. The reaction was quenched by addition of dimethyl sulfide (2 mL). Concentration and purification by column chromatography (5% ethyl acetate/hexane) of the reaction mixture afforded the title compound as a colorless oil (0.341 g, 99%): IR ($CDCl_3$) 2957, 1718 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.89 (s, 9H), 1.40 (s, 3H), 1.36−1.48 (m, 1H), 1.58 (tt, J = 12.0, 2.9 Hz, 1H, C_4 axial H), 1.70 (t, J = 12.3 Hz, 1H), 1.91−2.05 (m, 2H), 2.32−2.49 (m, 2H), 3.33 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 22.4, 27.4, 27.5, 32.2, 38.7, 38.8, 44.3, 51.2, 81.1, 212.5; MS *m/e* 199 (M^+ + 1), 167 (100), 149; HRMS calcd for $C_{12}H_{22}O_2$ (M + H) 198.1620, found 198.1607.

(2*R,4*S**)-4-(1,1-Dimethylethyl)-2-methoxy-2-methylcyclohexanone (2b).** (1*R**,5*S**)-5-(1,1-Dimethylethyl)-1-methoxy-1-methyl-2-methylenecyclohexane (0.210 g, 1.1 mmol) was reacted as described for the preceding compound to afford a colorless oil (0.189 g, 89%): IR ($CDCl_3$) 2934, 1715 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.83 (s, 9H), 1.13 (s, 3H), 1.15−1.39 (m, 2H), 1.89 (tt, J = 12.4, 3.3 Hz, 1H, C_4 axial H), 1.96−2.23 (m, 3H), 2.65−2.76 (m, 2H), 3.08 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 17.8, 27.3, 28.6, 31.7, 37.9, 40.8, 41.8, 50.7, 79.9, 213.8; MS *m/e* 199 (M^+ + 1, 100), 167, 141, 84; HRMS calcd for $C_{12}H_{22}O_2$ (M + H) 198.1620, found 198.1626.

General Procedure for Oxaziridine Synthesis. A solution of ketone (1.0 equiv) and amine (1.2−1.5 equiv) in toluene was allowed to reflux for 5−7 h in a round-bottom flask that was equipped with a condenser connected via a Dean−Stark trap. The solution was then cooled to room temperature and added dropwise to a suspension of *m*-CPBA (1.2 equiv) in CH_2Cl_2 kept at −78 °C (dry ice/acetone bath). The oxidation reaction was usually completed within 20 min (TLC analysis) and quenched with saturated $Na_2S_2O_4$ at low temperature. The reaction mixture was poured into a separation funnel and partitioned between saturated $Na_2S_2O_4$ and diethyl ether. The organic layer was washed with saturated $NaHCO_3$ and brine and dried with Na_2SO_4. Products were isolated by concentration followed by column chromatography (1:9 ethyl acetate/hexane).

[2*S,3*S**,4*S**,6*S**]-6-(1,1-Dimethylethyl)-4-hydroxy-4-methyl-2-(phenylmethyl)-1-oxa-2-azaspiro[2.5]octane and [2*R**,3*R**,4*S**,6*S**]-6-(1,1-Dimethylethyl)-4-hydroxy-4-methyl-2-(phenylmethyl)-1-oxa-2-azaspiro[2.5]octane (5a and 5b).** According to the general procedure, ketone **1a** (0.423 g, 2.4 mmol) afforded two oxaziridines in a combined 63% yield isomers (1:1 ratio determined by ^1H NMR of the crude mixture). The isomer with high R_f value is designated as **5a**, and the low R_f value isomer is assigned as **5b**. **5a**: R_f = 0.48, 10% ethyl acetate/hexane, colorless oil; IR ($CDCl_3$) 3477, 2960 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.76 (s, 9H), 0.81−0.95 (m, 2H), 1.11 (t, J = 12.8 Hz, 1H), 1.27 (s, 3H), 1.75−1.80 (m, 1H), 1.89−1.99 (m, 2H), 2.12 (td, J = 14.2, 4.4 Hz, 1H), 3.25 (s, 1H), 4.03 (AB q, J = 14.2 Hz, $\Delta\nu$ = 42.9 Hz, 2H), 7.21−7.42 (m, 5H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 21.7, 24.0, 25.1, 27.2, 31.9, 41.8, 44.3, 56.9, 69.8, 87.2, 127.9, 128.6, 128.8, 136.1; MS *m/e* 290 (M^+), 246, 168, 106 (100); HRMS calcd for $C_{18}H_{28}NO_2$ (M + H) 290.2120, found 290.2126. **5b**: R_f = 0.35, 10%

ethyl acetate/hexane, colorless oil; IR ($CDCl_3$) 3533, 2959 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.87 (s, 9H), 1.18 (s, 3H), 1.25−1.41 (m, 3H), 1.81−2.05 (m, 4H), 2.56 (s, 1H), 4.03 (AB q, J = 13.7 Hz, $\Delta\nu$ = 64.3 Hz, 2H), 7.29−7.42 (m, 5H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 23.8, 24.7, 25.1, 27.2, 32.0, 39.1, 44.1, 56.8, 69.6, 87.1, 127.9, 128.7, 128.9, 135.9; MS. *m/e* 290 (M^+), 246, 168, 106 (100); HRMS calcd for $C_{18}H_{28}NO_2$ (M + H) 290.2120, found 290.2128.

[2*R,3*R**,4*S**,6*S**]-6-(1,1-Dimethylethyl)-4-hydroxy-4-methyl-2-(diphenylmethyl)-1-oxa-2-azaspiro[2.5]-octane (6ax) and [2*S**,3*S**,4*S**,6*S**]-6-(1,1-Dimethylethyl)-4-hydroxy-4-methyl-2-(diphenylmethyl)-1-oxa-2-azaspiro[2.5]octane (6eq).** According to the general procedure, ketone **1a** (0.190 g, 1.1 mmol) afforded the title compound as an oil (0.330 g, 83%, 61:39 as determined by ^1H NMR of the crude mixture). **Mixture**: IR ($CDCl_3$) 3521, 2959, 2889 cm^{-1}; MS *m/e* 366 (M^+ + 1, 100), 182, 167; HRMS calcd for $C_{24}H_{31}NO_2$ 365.2355, found 365.2343. **6ax**: ^1H NMR ($CDCl_3$, 400 MHz) δ 0.79 (s, 9H), 0.96 (s, 3H), 1.13−1.36 (m, 3H), 1.71−2.11 (m, 4H), 2.69 (s, 1H), 4.81 (s, 1H), 7.21−7.49 (m, 10H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 22.0, 23.0, 24.6, 27.3, 32.0, 39.2, 44.0, 69.0, 69.7, 87.7, 127.0, 127.6, 128.2, 128.6, 138.7, 141.2. **6eq**: ^1H NMR ($CDCl_3$, 400 MHz) δ 0.13 (qd, J = 13.2, 3.6 Hz, 1H, axial C-7 proton), 0.53 (s, 9H), 1.23 (s, 3H), 3.49 (s, 1H), 4.69 (s, 1H), 7.21−7.49 (m, 10H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 24.2, 27.1, 31.8, 41.2, 43.8, 69.6, 69.9, 87.7, 127.1, 127.3, 128.0, 128.3, 128.9, 139.1, 141.3.

[2*S,3*S**,4*R**,6*S**]-6-(1,1-Dimethylethyl)-4-hydroxy-4-methyl-2-(phenylmethyl)-1-oxa-2-azaspiro[2.5]octane (7eq).** According to the general procedure, ketone **1b** (0.533 g, 3.1 mmol) afforded a single isomer (^1H NMR of crude reaction mixture) as colorless solid (0.593 g, 67%): mp 86−87 °C (CH_3CN); IR ($CDCl_3$) 2941, 1480 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.79 (s, 9H), 0.88 (m, 2H), 1.12 (s, 3H), 1.15 (t (partially obscured), J = 13.4 Hz, 1H, C_5 axial H), 1.62 (tt, J = 12.5, 3.4 Hz, 1H, C_6 axial H), 1.53 (br d, 1H), 1.78−1.88 (m, 2H), 2.54 (td, J = 13.8, 4.4 Hz, 1H), 4.04 (AB q, J = 14.4 Hz, $\Delta\nu$ = 62.4 Hz, 2H), 7.31−7.42 (m, 5H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 22.7, 23.6, 24.9, 27.2, 31.7, 39.3, 41.3, 57.3, 73.5, 87.0, 127.7, 128.4, 128.7, 136.9. Anal. Calcd for $C_{18}H_{27}NO_2$: C, 74.70; H, 9.40; N, 4.84. Found: C, 74.82; H, 9.49; N, 4.99.

[2*S,3*S**,4*R**,6*S**]-6-(1,1-Dimethylethyl)-4-hydroxy-4-methyl-2-(diphenylmethyl)-1-oxa-2-azaspiro[2.5]-octane (8eq).** According to the general procedure, ketone **1b** afforded the title compound as an oil (0.230 g, 63%, a single isomer, as determined by ^1H NMR of the crude reaction mixture): IR ($CDCl_3$) 3589, 2957 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.18 (qd, J = 14.0, 3.6 Hz, 1H, axial C-7 proton), 0.63 (s, 9H), 1.02 (t, J = 13.3 Hz, 1H), 1.24 (s, 3H), 1.43−1.58 (m, 2H), 1.75 (br s, 1H), 1.80−1.93 (m, 2H), 2.52 (td, J = 14.3, 4.3 Hz, 1H), 4.71 (s, 1H), 7.21−7.59 (m, 10H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 23.1, 24.1, 24.5, 27.2, 31.6, 38.9, 40.8, 69.9, 87.3, 127.1, 127.1, 127.6, 127.7, 128.4, 128.8, 140.1, 142.3; MS *m/e* 365 (M^+), 182, 167 (100), 84; HRMS calcd for $C_{24}H_{31}NO_2$ 365.2355, found 365.2343.

[2*S,3*S**,4*S**,6*S**]-6-(1,1-Dimethylethyl)-4-methoxy-4-methyl-2-(phenylmethyl)-1-oxa-2-azaspiro[2.5]octane (9eq).** According to the general procedure, ketone **2a** (0.188 g, 1.0 mmol) afforded a single isomer (^1H NMR of the crude reaction mixture) as colorless oil (0.212 g, 70%): IR ($CDCl_3$) 2954, 1463 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.77 (s, 9H), 0.96 (m, 1H), 1.26 (s, 3H), 1.22−1.37(m, 3H), 1.72 (br d, 1H), 1.82 (d, J = 11.9 Hz, 1H), 1.92−1.98 (m, 2H), 3.25 (s, 3H), 3.99 (AB q, J = 14.3 Hz, $\Delta\nu$ = 12.8 Hz, 2H), 7.25−7.47 (m, 5H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 18.6, 24.5, 25.1, 27.2, 27.4, 32.1, 37.6, 43.6, 51.2, 57.4, 74.6, 88.6, 127.5, 128.6, 128.6, 137.1; MS *m/e* 304 (M^+ + 1, 100), 288; HRMS calcd for $C_{19}H_{29}NO_2$ + Na (M) 326.2096, found 326.2091.

[2*S,3*S**,4*S**,6*S**]-6-(1,1-Dimethylethyl)-4-methoxy-4-methyl-2-(diphenylmethyl)-1-oxa-2-azaspiro[2.5]-octane (10eq).** According to the general procedure, ketone **2a** afforded the title compound as a solid (0.88 g, 40%, a single isomer as determined by ^1H NMR of the crude reaction mixture): mp 116−118 °C, IR ($CDCl_3$) 2957, 1494 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.21 (m, 1H, axial C-7 proton), 0.58 (s, 9H), 1.16−1.21 (m, 2H), 1.26 (s, 3H), 1.39 (m, 1H), 1.64 (m, 1H), 1.92−1.98 (m, 2H), 3.36 (s, 3H), 4.62 (s, 1H), 7.12−7.55 (m, 10H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 19.0, 24.2, 25.4, 27.2, 32.0, 37.9, 43.3, 51.8, 70.2, 74.4, 89.6, 127.1, 127.2, 127.7, 128.4, 128.8, 140.2, 142.5; MS *m/e* 379 (M^+), 349, 322, 167 (100); HRMS calcd for $C_{25}H_{33}NO_2$ 379.2511, found 379.2506.

[2*R,3*R**,4*R**,6*S**]-6-(1,1-Dimethylethyl)-4-methoxy-4-methyl-2-(phenylmethyl)-1-oxa-2-azaspiro[2.5]octane (11ax) and [2*S**,3*S**,4*R**,6*S**]-6-(1,1-Dimethylethyl)-4-methoxy-4-methyl-2-(phenylmethyl)-1-oxa-2-azaspiro-[2.5]octane (11eq).** According to the general procedure, ketone **2b** (0.312 g, 1.7 mmol) afforded the title products (0.321 g, 64%) as an 83:17 mixture of isomers (^1H NMR of the crude reaction mixture). **Mixture**: IR ($CDCl_3$) 2953, 1462 cm^{-1}; MS *m/e* 304 (M^+ + 1, 100), 272, 246, 197; HRMS calcd for $C_{19}H_{29}NO_2$ (M + H) 304.2277, found 304.2277. **11ax**: ^1H NMR ($CDCl_3$, 400 MHz) δ 0.89 (s, 9H), 1.03 (s, 3H), 1.21 (m, 1H), 1.34 (qd, J = 13.4, 3.7 Hz, 1H, C_7 axial H), 1.59 (tt, J = 12.5, 3.3 Hz, 1H), 1.87 (tt, J = 13.9, 3.1 Hz, 1H), 1.98 (dt, J = 12.8, 3.2 Hz, 1H), 2.27 (td, J = 13.4, 4.3 Hz, 1H), 3.06 (s, 3H), 4.00 (AB q, J = 14.5 Hz, $\Delta\nu$ = 10.7 Hz, 2H), 7.25−7.47 (m, 5H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 16.8, 23.7, 25.2, 27.3, 31.8, 37.5, 40.9, 49.4, 56.8, 77.5, 85.1, 127.7, 128.7, 128.9, 136.9. **11eq**: ^1H NMR ($CDCl_3$, 300 MHz, diagnostic peaks only) δ 0.77 (s, 9H), 1.06 (s, 3H), 3.21 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.4 MHz, diagnostic peaks only) δ 17.9, 23.1, 28.7, 86.5.

[2*R,3R*,4R*,6S*]-6-(1,1-Dimethylethyl)-4-methoxy-4-methyl-2-(diphenylmethyl)-1-oxa-2-azaspiro[2.5]-octane (12ax).** According to the general procedure, ketone **2b** afforded the title product (0.198 g, 49%) as an oil (a single isomer by ^1H NMR of crude reaction mixture): IR ($CDCl_3$) 2954, 1462 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.78 (s, 9H), 1.05 (s, 3H) CH_3), 1.15 (t, J = 13.2, 1H), 1.25 (qd, J = 12.9, 4.0 Hz, 1H), 1.48 (tt, J = 12.5, 3.2 Hz,), 1.75 (dt, J = 14.0, 3.0 Hz, 1H), 1.82−1.95 (m, 2H), 2.08 (td, J = 13.0, 4.3 Hz,), 2.63 (s, 3H), 4.79 (s, 1H), 7.25−7.57 (m, 10H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 16.9, 24.2, 25.5, 27.4, 31.9, 38.1, 40.8, 49.2, 69.0, 76.6, 86.6, 127.0, 127.2, 127.9, 128.3, 128.4, 128.7, 139.0, 142.4; MS *m/e* 279 (M^+), 322, 167 (100); HRMS calcd for $C_{25}H_{33}NO_2$ 379.2511, found 379.2511.

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Supporting Information Available: ^1H and ^{13}C NMR for compounds **1a**, **1b**, **2a**, **2b**, **5a**, **5b**, **6eq** + **6ax**, **7eq**, **8eq**, **9eq**, **10eq**, **11eq** + **11ax**, and **12ax**. This material is available free of charge via the Internet at http://pubs.acs.org.

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