# Optically Active Trifluoromethylcarbinols as Chiral Solvating Agents for Asymmetric Transformations at a Ring-Nitrogen Atom. Synthesis of Optically Active *N*-Chloroaziridines and Stereochemical Aspects of Chiral Solvent-Aziridine Solute Complexes

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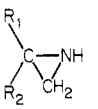
Chlorination at a ring nitrogen of an aziridine substrate, when carried out with *tert*-butyl hypochlorite or *N*-chlorosuccinimide in the presence of chiral trifluoromethylcarbinols, affords optically active *N*-chloroaziridines. Synthesis of chiral *N*-chloroaziridines of known absolute configuration and optical purity shows that the stereochemical features of the chlorination depend on the structure of the aziridine substrate, as well as on the achiral reagent and on the chiral solvating agent (CSA). NMR nonequivalence studies in CSAs are reported in order to get insight into the preferred conformational behavior of trifluoro alcohol–basic aziridine solvates.

Despite considerable interest in the stereochemistry of *N*-chloroaziridines linked to their pyramidal stability at the ring-nitrogen atom, there is no general experimental method for the synthesis of these derivatives in optically active form. More particularly, syntheses of partially optically enriched *N*-chloroaziridines, whose molecular asymmetry is due solely to a trivalent nonbridgehead nitrogen atom, have been reported only for 1-chloro-2,2-diphenylaziridine (**2a**)[1] and 1-chloro-2,2-dimethylaziridine (**2b**) derivatives.[2]

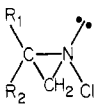
Our prior work has shown that chlorination of aziridine substrates can afford optically active *N*-chloroaziridines if carried out with an achiral reagent in the presence of a chiral type **3** fluoro alcohol.[3] We now report more stereochemical details of this reaction, obtained in the synthesis of chiral *N*-chloroaziridines of established absolute configuration and optical purity.

**Asymmetric Chlorinations.** Chlorination of 2,2-diphenylaziridine (**1a**), 2,2-dimethylaziridine (**1b**), and 2-phenylaziridine (**1c**) has been performed with *tert*-butyl



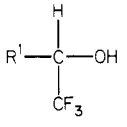
**1**

**1a**, $R_1 = R_2 = C_6H_5$
**b**, $R_1 = R_2 = CH_3$
**c**, $R_1 = C_6H_5$; $R_2 = H$



**2**

**2a**, $R_1 = R_2 = C_6H_5$
**b**, $R_1 = R_2 = CH_3$
**c**, $R_1 = C_6H_5$; $R_2 = H$
**d**, $R_1 = H$; $R_2 = C_6H_5$



(*R*)-(+)-**3a**, $R^1$ = cyclohexyl
(*S*)-(+)-**3b**, $R^1$ = phenyl
(*R*)-(−)-**3c**, $R^1$ = 1-naphthyl
(*S*)-(+)-**3d**, $R^1$ = 9-anthryl
(*R*)-(−)-**3d**, $R^1$ = 9-anthryl

hypochlorite (TBHC) or *N*-chlorosuccinimide (NCS) at −60 °C and in $CH_2Cl_2$ solution containing a 2 molar excess of (*R*)-(+)-2,2,2-trifluoro-1-cyclohexylethanol (**3a**), (*S*)-(+)-2,2,2-trifluoro-1-phenylethanol (**3b**), (*R*)-(−)-2,2,2-trifluoro-1-(1-naphthyl)ethanol (**3c**), or (*S*)-(+)- and (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol (**3d**) as a chiral solvating agent (CSA).

Chlorination of racemic $Ph_2$-**1a** and $Me_2$-**1b** derivatives, which are composed of enantiomeric molecules rapidly equilibrating by pyramidal inversion at the asymmetric nitrogen atom,[4] was effected with an equimolecular amount of TBHC or NCS. This reaction gave the corresponding 1-chloro-2,2-diphenylaziridine (**2a**) and 1-chloro-2,2-dimethylaziridine (**2b**) in 80–90% yields and in optically active form. Chlorination of 2-phenylaziridine (**1c**), which is a 2.3:1 mixture of racemic *E*/*Z* diastereomers[5] pyramidally unstable at the nitrogen site and stable at the chiral 2-ring carbon, was carried out under conditions of kinetic resolution, i.e., with an insufficient amount (0.5 molar equiv) of the achiral reagent. In this case we obtained optically active (*E*)- (**2c**) and (*Z*)-1-chloro-2-phenylaziridine (**2d**) diastereomers, as well as optically active unreacted aziridine substrate **1c**. Separation of **2c**, **2d**, and **1c** from each other and separation of all *N*-chloro derivatives **2** from traces of optically active solvent were accomplished by column chromatography on silica gel with *n*-hexane–ethyl ether (9:1) as the eluant or by distillation at low temperature and pressure. All reactions take place rapidly and without formation of trifluoromethyl ketones or intermediate hypochlorites of the trifluoro alcohols, as indicated by TLC and IR spectra.

**Stereochemical Assignments to *N*-Chloroaziridines 2.** The absolute configurations and the optical yields (percent enantiomeric excess) reported in Tables I and II for *N*-chloro derivatives **2** have been established as follows. The (*R*)-(−) and (*S*)-(+) configurations of 1-chloro-2,2-diphenylaziridine (**2a**) were determined by *X*-ray analysis, as recently reported.[6] The *R* configuration has been assigned to partially enriched (−)-1-chloro-2,2-dimethylaziridine (**2b**) on the basis of its CD behavior.[2] The optical purities of **2a** and **2b** were determined by using a chiral shift reagent. Accuracy is within ±2%. The *E* and *Z* configurations of the **2c** and **2d** diastereomeric forms of 1-chloro-2-phenylaziridine, respectively, have been estab-

(1) Annunziata, R.; Fornasier, R.; Montanari, F. *J. Chem. Soc., Chem. Commun.* **1972**, 1133.
(2) Kostyanovsky, R. G.; Kadorkina, G. K. *Izv. Akad. Nauk. SSSR, Ser. Khim.* **1977**, 1686.
(3) Forni, A.; Moretti, I.; Prosyanik, A. V.; Torre, G. *J. Chem. Soc., Chem. Commun.* **1981**, 588.
(4) (a) Lehn, J. M.; Wagner, J. *Chem. Commun.* **1968**, 148. (b) Martino, R.; Lopez, A.; Lattes, A. *Org. Magn. Reson.* **1976**, *8*, 332.
(5) Lopez, A.; Gauthier, M. M.; Martino, R.; Lattes, A. *Org. Magn. Reson.* **1979**, *12*, 418.
(6) Brückner, S.; Forni, A.; Moretti, I.; Torre, G. *J. Chem. Soc., Chem. Commun.* **1982**, 1218.

0022-3263/83/1948-2640$01.50/0 

Table I. Asymmetric Chlorination of Aziridines 1 with TBHC in the Presence of Chiral Trifluoromethylcarbinols 3[a]

| | | N-chloroaziridine | | | | | |
|---|---|---|---|---|---|---|---|
| entry | alcohol | no. | $R_1$ | $R_2$ | $[\alpha]^{20}_D$,[b] deg | % ee[c] | abs config[d] |
| 1 | (R)-(+)-3a | 2a | $C_6H_5$ | $C_6H_5$ | +22.5 | 6.7 | S |
| 2 | (S)-(+)-3b | | | | −4.6 | 1.4 | R |
| 3 | (R)-(−)-3c | | | | +23.1[e] | 6.9 | S |
| 4 | (S)-(+)-3d | | | | −95.6[f] | 28.7 | R |
| 5 | (R)-(+)-3a | 2b | $CH_3$ | $CH_3$ | +3.0[g] | 2.7 | R |
| 6 | (S)-(+)-3b | | | | +3.8[g] | 3.5 | R |
| 7 | (R)-(−)-3c | | | | −1.7[g] | 1.5 | S |
| 8 | (S)-(+)-3d | | | | −12.7[g,h] | 11.3 | S |
| 9 | (R)-(−)-3d | | | | +13.8[g] | 12.3 | R |
| 10 | (R)-(−)-3c | (E)-2c[i] | $C_6H_5$ | H | +17.4[j] | 4.5 | 1S,2S |
| 11 | (S)-(+)-3d | | | | −50.7[k] | 13.2 | 1R,2R |
| 12 | (R)-(−)-3d | | | | +48.7[l] | 12.7 | 1S,2S |
| 13 | (R)-(−)-3c | (Z)-2d[i] | H | $C_6H_5$ | +6.2[j] | 6.7 | 1S,2R |
| 14 | (S)-(+)-3d | | | | +4.2[k] | 4.5 | 1S,2R |
| 15 | (R)-(−)-3d | | | | −3.1[l] | 3.3 | 1R,2S |

[a] Reactions at −60 °C and in $CH_2Cl_2$ solution. [b] Data for chloroform solution (c in the range 2-15 M); values corrected for optically pure carbinols. [c] ±2%; enantiomeric excess estimated by integration of the NMR peak areas of enantiotopic groups which appear anisochronous when the spectrum of partially optically active N-chloroaziridines 2 is registered in $CDCl_3$ and at increasing concentrations of d-Eu(hfc)$_3$ chiral shift reagent. [d] The absolute configurations of N-chloroaziridines 2a,c,d have been determined as described in the text; the absolute configuration of 2b is reported in ref 7. [e] $[\alpha]^{20}_D$ +22.2° (c 8, acetone). [f] Chlorination carried out at 25 °C afforded 2a which shows $[\alpha]^{20}_D$ +5.7° (c 3.9, $CHCl_3$). [g] Optical activity in $CH_2Cl_2$ solution. [h] $[\alpha]^{25}_D$ −21.4° (c 1.0, n-hexane). [i] Chlorination carried out with 0.5 molar equiv of TBHC; the 2c and 2d N-chloroaziridines were obtained as 2.3:1 mixture of E/Z diastereoisomers. [j] The 2-phenylaziridine (1c) recovered from this reaction shows $[\alpha]_D$ 0.0° (c 4.5, $CHCl_3$). [k] The 2-phenylaziridine (1c) recovered from this reaction shows $[\alpha]^{20}_D$ + 6.4° (c 5, $CHCl_3$). [l] From reaction in Scheme I.

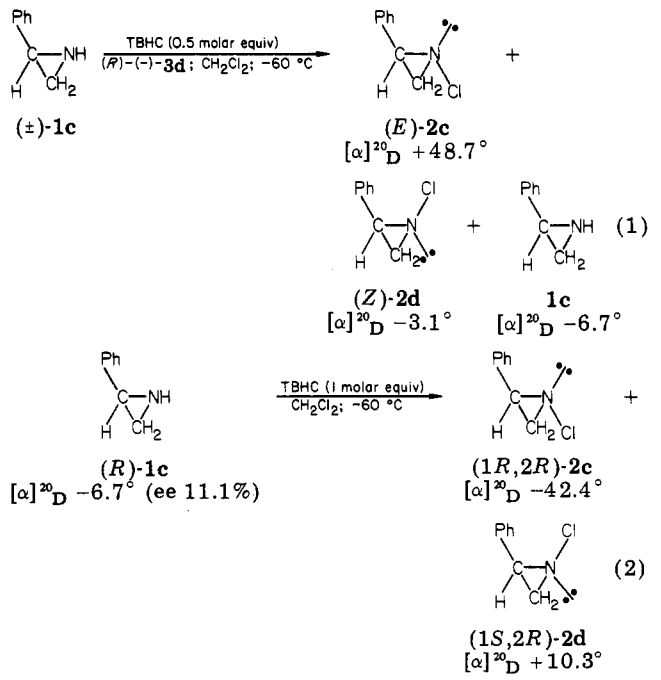
Table II. Asymmetric Chlorination of Aziridines 1 with NCS in the Presence of Chiral Trifluoromethylcarbinols 3[a]

| | | N-chloroaziridine | | | | | |
|---|---|---|---|---|---|---|---|
| entry | alcohol | no. | $R_1$ | $R_2$ | $[\alpha]^{20}_D$,[b] deg | % ee[c] | abs config[d] |
| 1 | (R)-(−)-3c | 2a | $C_6H_5$ | $C_6H_5$ | −15.3 | 4.5 | R |
| 2 | (S)-(+)-3d | | | | −10.1 | 3.0 | R |
| 3 | (R)-(−)-3d | | | | +11.7 | 3.5 | S |
| 4 | (S)-(+)-3d | 2b | $CH_3$ | $CH_3$ | 0.0 | | |
| 5 | (R)-(−)-3c | (E)-2c[e] | $C_6H_5$ | H | −11.4[f] | 3.0 | 1R,2R |
| 6 | (S)-(+)-3d | | | | +15.5[g] | 4.1 | 1S,2S |
| 7 | (R)-(−)-3c | (Z)-2d[e] | H | $C_6H_5$ | −2.0[f] | 2.2 | 1R,2S |
| 8 | (S)-(+)-3d | | | | +7.5[g] | 8.1 | 1S,2R |

[a-d] As in Table I. [e] Obtained as 19:1 mixture of E/Z diastereoisomers by chlorination of 2-phenylaziridine (1c) with 0.5 molar equiv of NCS. [f] The 2-phenylaziridine (1c) recovered from the reaction mixture shows $[\alpha]^{20}_D$ +0.33° (c 10.4, $CHCl_3$). [g] The 2-phenylaziridine (1c) recovered from the reaction mixture shows $[\alpha]^{20}_D$ −0.71° (c 7.0, $CHCl_3$).

lished by NMR and epimerization studies.[7] The absolute configuration and the optical purity of these two isomers were determined by means of reactions 1 and 2 of Scheme I. In particular, chlorination of racemic **1c** with 0.5 molar equiv of TBHC in the presence of (*R*)-(−)-**3d** gave the (+)-**2c** and (−)-**2d** diastereomers and unreacted (−)-**1c** aziridine of known optical purity (11.1%) and *R* configuration at the chiral carbon[8] (reaction 1 of Scheme I). Complete chlorination of (*R*)-(−)-**1c** with TBHC as summarized in reaction 2 provided (−)-**2c** and (+)-**2d** *N*-chloroaziridines with the same optical purity and *R* configuration at carbon as the starting aziridine, and with *R* and *S* configurations at nitrogen, respectively. The percent enantiomeric excess (% ee) of these two isomers has been checked also by use of a chiral shift reagent. Agreement was within ±1% ee.

Scheme I




(7) The *E*/*Z* yield ratio of *N*-chloroaziridines **2c** and **2d** appears to be strongly dependent on the chlorinating agent and on the reaction medium. Until now, only the synthesis and the properties of the major (*E*)-**2c** component have been reported. For examples, see: (a) Kostyanovsky, R. G.; Fomichev, A. A.; Novikov, V. M. *Zh. Strukt. Khim.* **1971**, *12*, 722. (b) Paulsen, H.; Greve, W. *Chem. Ber.* **1970**, *103*, 486. Studies on this reaction and on the properties of both **2c** and **2d** isomers are in progress in our laboratory, and the results will be published elsewhere.

(8) Fujita, S.; Imamura, K.; Nosaki, H. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 1975.

## Results and Discussion

The results obtained with TBHC are reported in Table I. The results obtained with NCS are summarized in Table II. All these data indicate that the stereochemical features of the chlorination are dependent on the structure and nature of the aziridine substrate, of the achiral reagent, and of the CSA. Chlorination of the 2-phenylaziridine (**1c**) with TBHC affords **2c** and **2d** in a 2.3:1 *E*/*Z* yield ratio. On the contrary, chlorination of **1c** with NCS is strongly in favor of the *trans*-**2c** isomer (19:1 *E*/*Z* ratio).[7] Furthermore, under the same reaction conditions, the % ee of the reactions carried out with TBHC (Table I) is generally higher than the % ee observed with NCS (Table II).

The optical yields obtained with the cyclohexyl (**3a**), phenyl (**3b**), and 1-naphthyl (**3c**) CSAs are not particularly high (max 7% ee). Better results can be obtained by chlorinations carried out with TBHC in the presence of the 9-anthryl (**3d**) solvent. For istance, 28.7% ee has been observed for the diphenyl derivative **2a**, and 12–13% optical yields have been obtained for the dimethyl-substituted (**2b**) and the 2-phenyl-substituted (**2c**) aziridines (Table I, entries 4, 9, and 11).

The optical activities of **2a** and **2b** reported in Tables I and II compare very favorably with the activities reported for the same two compounds in ref 1 and 2, respectively. Taking into account that the best conditions so far tried may well be improved upon, we may conclude that present type of asymmetric chlorination at the ring-nitrogen atom of aziridines represents a very favorable route to optically active *N*-chloroaziridines.[9]

**Absolute Stereochemistry of the Chlorination.** The structural and chemical properties of the interacting species and of the CSA play also an important role in the control of the absolute stereochemistry of the reaction. Chlorination with TBHC shows correlation between the configuration at nitrogen of **2** and the configuration of the CSA only in the cases of *N*-chloroaziridines **2a** and **2c** (Table I, entries 1–4 and 10–12). It is noteworthy that these two compounds both contain a phenyl group syn to the nitrogen lone pair of electrons. Configurational correlation is no longer observed in correspondence of the dimethyl derivative **2b** and of the (*Z*)-**2d** aziridine having the phenyl ring anti to the lone pair of the ring nitrogen.

The absolute stereochemistry of the chlorination is even more complex when NCS is used as a achiral chlorinating agent. Similarity between the stereochemical behavior of the structurally related **2a** and **2c** derivatives is not observed in this case. (*R*)-(−)-**2a** is obtained independently of whether (*R*)-**3c** or (*S*)-**3d** is used as the CSA (Table II, entries 1 and 2). Moreover, correlation between the configuration of the chiral solvent and the configuration of the optically active *N*-chloro derivatives is observed only in the cases of the 2-phenyl diastereomers (*E*)-**2c** and (*Z*)-**2d**.

**NMR in CSA.** NMR spectra of partially enriched (*R*)-(−)-2-phenylaziridine (**1c**) and of optically active *N*-chloroaziridines **2** have been recorded in the presence of (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol (**3d**). The results obtained are summarized in Table III. Chemical shift doubling is observed in correspondence of the resonances of the methylene $H_1$ and $H_2$ protons of all the compounds examined, as well as of the methyl groups of

Table III. NMR Data for Enantiomerically Enriched 2-Phenylaziridine (1c) and *N*-Chloroaziridines 2

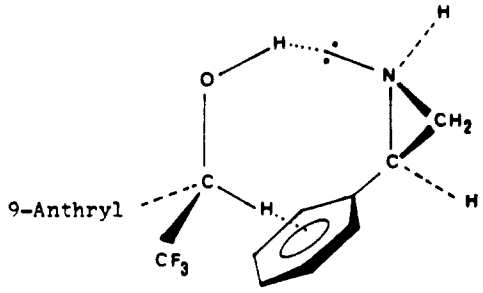


| entry | compd | $R_1$ | $R_2$ | X | $[\alpha]^{20}_D$, [e] deg | % ee | abs config | chemical shift in $CDCl_3$ [a] $R_1$ | $R_2$ | $H_1$ | $H_2$ | nonequivalence, [b] Hz [c]/sense [d] $R_1$ | $R_2$ | $H_1$ | $H_2$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | **1c** | $C_6H_5$ | H | H | −6.7 [f] | 11.1 | *R* | 7.29 m | 3.02 q | 1.81 d | 2.21 d | | 32.7/H | 9.1/L | 2.1/L |
| 2 | **2a** | $C_6H_5$ | $C_6H_5$ | Cl | −255.0 [g] | 76.3 | *R* | 7.18 $s^1$ | 7.35 $s^1$ | 2.82 $d^2$ | 3.07 $d^2$ | | | 1.0/H | 1.3/H |
| 3 | **2b** | $CH_3$ | $CH_3$ | Cl | −12.7 [h] | 11.3 | *S* | 1.21 $s^3$ | 1.52 $s^3$ | 1.94 $d^4$ | 2.21 $d^4$ | 18.2/L | 7.4/L | 19.2/H | 27.6/H |
| 4 | **2c** | $C_6H_5$ | H | Cl | −42.4 [f] | 11.1 | 1*R*,2*R* | 7.26 m | 3.37 q | 2.55 q | 2.69 q | | 1.4/H | 6.1/H | 6.6/H |
| 5 | **2d** | H | $C_6H_5$ | Cl | +10.3 [f] | 11.1 | 1*S*,2*R* | 3.44 q | 7.42 m | 2.77 q | 2.66 q | 17.2/H | | 11.5/L | *i* |

[a] Chemical shifts are reported downfield from tetramethylsilane on the δ scale. Assignments bearing the same numerical superscript may be interchanged. [b] Nonequivalence was caused by adding a 2-fold excess of (*R*)-(−)-**3d** trifluoro alcohol to a dilute $CDCl_3$ solution of the compound. [c] At 200 MHz and 20 °C. [d] H refers to a high-field sense and L to a low-field sense relative to the enantiotopic groups of samples of **1c** and **2** having the reported absolute configurations. [e] In $CHCl_3$ solution. [f] Compound obtained from reactions in Scheme I. [g] Obtained by fractional crystallization from ethyl ether–petroleum ether of **2a** which shows $[\alpha]^{20}_D$ −95.6°. [h] Obtained by chlorination of 2,2-dimethylaziridine (**1b**) with TBHC in the presence of (*S*)-(+)-**3d** (see Table I). [i] Not determined, owing to overlap of resonances of the enantiomeric molecule.

(9) The effectiveness of optically active trifluoro alcohols as CSAs for asymmetric reactions and/or kinetic resolutions has been already documented by other asymmetric inductions at the nitrogen atom, involving basic prochiral imines and achiral *m*-chloroperoxybenzoic acid. Bucciarelli, M.; Forni, A.; Moretti, I.; Torre, G. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2152.

Chart I

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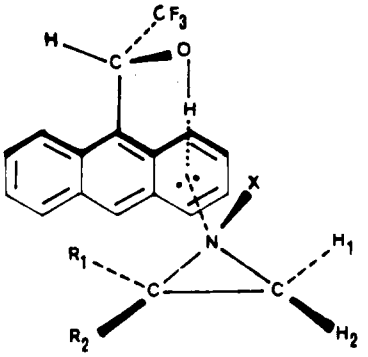
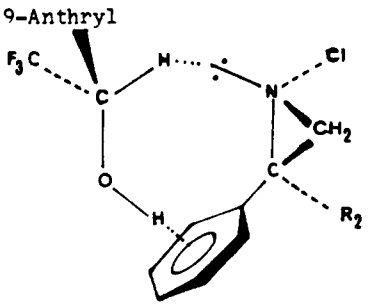



5a, X = H; $R_1$ = H; $R_2$ = $C_6H_6$
b, X = Cl; $R_1$ = H ($C_6H_5$); $R_2$ = $C_6H_5$ (H)




6, $R_2$ = H ($C_6H_5$)

**2b** (entry 3) and of the methine proton of **1c**, **2c**, and **2d** (entries 1, 4, and 5). The magnitudes of nonequivalence are quite high and allow determination of nonequivalence sense and of enantiomeric purity.

The use of the trifluoro alcohol CSA–NMR technique as a means for determining enantiomeric purity and for assigning absolute configuration from the observed senses of nonequivalence of partially enriched enantiomers has been recently reviewed.[10] Experience shows that in many cases two different types of solvation models can be advanced to rationalize the nonequivalence behavior of a variety of chiral solutes. The first of these models applies to enantiomers having two appropriately located basic sites.[10] The second model has been recently proposed for monobasic solutes also having carbinyl hydrogens.[10]

**Solvation Models.** The *E* and *Z* diastereomers of 2-phenylaziridine (**1c**) meet the requirements of the two general models. The conformational features of the (*E*)-**1c**–**3d** and (*Z*)-**1c**–**3d** solvates are depicted in **4** and **5**, respectively (Chart I). With these models it is assumed that primary bonding interaction occurs between the nitrogen lone pair of electrons of the aziridine ring and the hydroxy group of the carbinol, whereas differences between the two conformations result from two different types of secondary attractive forces. In model **4** secondary bonding arises from the basic phenyl group syn to the nitrogen lone pair of (*E*)-**1c** and the carbinyl hydrogen of **3d**. In model **5** conformational control is from hydrogen bonding by the (*Z*)-**1c** solute carbinyl ring proton ($R_1$ = H) to the anthryl group of **3d**. In this last case, preferential rotameric disposition of the 9-anthryl carbinol moiety, dictated by peri interactions, is also assumed.[11] In model **4**, as well as in model **5**, the carbinyl hydrogen is the more shielded, and the methylene $CH_1H_2$ protons are the less shielded substituents. Therefore, both conformations correctly predict the senses of nonequivalence observed (Table III, entry 1) and can be considered as potential contributors to the NMR dissimilarities induced by the (*R*)-**3d** CSA to the rapidly equilibrating *E*–*Z* mixture of (*R*)-(–)-**1c**. Quite probably, solvates of this type also play an important role in the asymmetric syntheses of *N*-chloroaziridines **2**. Nevertheless, how this occurs is unclear at present. More systematic study of this problem is now in progress.

Rationalization of the NMR nonequivalence behavior of *N*-chloroaziridines **2** by means of dibasic and monobasic solute models is less obvious. For instance, dibasic models correctly accommodate the high-field sense of nonequivalence of $CH_1H_2$ protons of the structurally related (*R*)-**2a** and (*E*)-(*1R,2R*)-**2c** derivatives only if one assumes that chlorine substituent changes the relative basicities of the nitrogen and phenyl sites, so that the primary bond occurs at phenyl and the secondary interaction is at nitrogen, as depicted in solvate **6**. Moreover, this same model does not account for the resonance behavior of the methine hydrogen of (*E*)-**2c**, which shows the same nonequivalence sense as $CH_1H_2$ protons (Table III, entry 4). Monobasic solute model **5** works very nicely for the (*Z*)-**2d** *N*-chloroaziridine. It also can be applied to rationalize the nonequivalence of the methylene hydrogens of **2a** and (*E*)-**2c** but, like model **6**, fails for the methine proton of (*E*)-**2c**. Finally, nonequivalences of the methyl groups and of the methylene hydrogens of the dimethyl derivative (*S*)-**2b**, even if quite well separated and of clear low-field and high-field sense, respectively (entry 3), cannot be accounted for either by dibasic solute models **4** and **6** or by monobasic one **5**. A possible origin of the NMR behavior of *N*-chloroaziridines **2** may stem from chemical shift perturbation by the electron-withdrawing chlorine atom. On the other hand, differences in steric and electronic interactions between the substituents of the carbinol solvent and of the rigid aziridine ring would also play an important role in the control of solvate conformations responsible of the observed resonances of **2**.

## Experimental Section

All melting points and boiling points are uncorrected. NMR spectra were recorded in $CDCl_3$ on a Varian XL-200 instrument at 20–25 °C. Tetramethylsilane was the internal standard, and chemical shifts are reported as $\delta$ values. NMR determinations of enantiomeric purity were performed in $CDCl_3$ by using increasing concentrations of the chiral shift reagent tris[3-[(heptafluoropropyl)hydroxymethylene]-*d*-camphorato]europium(III). Relative peak area measurements were determined by integration. Mass spectra were obtained on a Varian MAT-112 instrument.

**Chlorinating Agents.** NCS was obtained commercially and used as such. TBHC was prepared according to a published procedure.[12]

**Chiral Trifluoromethylcarbinols 3.** (*R*)-(+)-2,2,2-Trifluoro-1-cyclohexylethanol (**3a**) and (*R*)-(–)-2,2,2-trifluoro-1-(1-naphthyl)ethanol (**3c**) were obtained by reduction of the corresponding ketones by actively fermenting yeast.[13] (*S*)-(+)-2,2,2-Trifluoro-1-phenylethanol (**3b**) was obtained by fractional crystallization of the esters of the racemate with (–)-ω-camphanic acid.[14] (*S*)-(+)- and (*R*)-(–)-2,2,2-trifluoro-1-(9-anthryl)ethanol

(10) Pirkle, W. H.; Hoover, D. J. *Top. Stereochem.* **1982**, *13*, 263.
(11) Pirkle, W. H.; Simmons, K. A. *J. Org. Chem.* **1981**, *46*, 3239.
(12) Mintz, M. J.; Walling, C. "Organic Syntheses"; Wiley: New York, 1973; Collect. Vol. V, pp 184–187.
(13) Bucciarelli, M.; Forni, A.; Moretti, I. Torre, G. *J. Chem. Soc., Chem. Commun.* **1978**, 457.

(3d) were purchased from Ega-Chemie and used without additional purificarion.

**Aziridines.** Diphenyl-2,2-aziridine (1a),[15] dimethyl-2,2-aziridine (1b),[16] and phenyl-2-aziridine (1c)[17] were prepared as described in the literature.

**General Procedure for Asymmetric Chlorination of Aziridines 1 to *N*-Chloroaziridines 2.** A mixture of the aziridine 1 (1 mmol) and the chiral alcohol (2 mmol) was diluted with $CH_2Cl_2$ (2.5 mL) and treated at -60 °C with a solution of freshly prepared TBHC (1 mmol) or with NCS (1 mmol) in $CH_2Cl_2$ (2 mL). Chlorination of aziridine 1c was carried out with 0.5 mmol of TBHC or NCS reagent. The reaction mixture was kept for 3 h at -60 °C, and the $CH_2Cl_2$ solvent was then evaporated in vacuo. Optically active *N*-chloroaziridines 2 were recovered (80-90% yield) free from traces of the optically active solvent (NMR, TLC and GLC analysis) by rapid distillation at low temperature and pressure (for aziridine 2b) or by column chromatography on silica gel with *n*-hexane-ether (9:1) as the eluant [for aziridines 2a, (*E*)-2c, and (*Z*)-2d]. *N*-Chloroaziridines (2) obtained in this way release 1 molar equiv of iodine from an acetic acid solution of potassium iodide. NMR properties of these compounds are reported in Table III. In all cases, chiral trifluoromethylcarbinols (3) have been recovered quantitatively and without loss of optical activity.

**1-Chloro-2,2-diphenylaziridine (2a).** This compound is a relatively stable crystalline solid. Noteworthy is the fact that fractional crystallization of partially optically active 2a, as can be obtained by chlorination of 1a with TBHC in the presence of the cyclohexyl-substituted 3a, 1-naphthyl-substituted 3c, or 9-anthryl-substituted 3d carbinols (Table I), affords the highly optically pure derivative. For istance, crystallization of 2a having $[\alpha]_D$ -95.6° (*c* 3.1 $CHCl_3$) from ethyl ether-petroleum ether (bp 40-60 °C) solution gave a sample which shows the following: mp 26-30 °C; $[\alpha]_D$ -283.7° (*c* 2.8 $CHCl_3$).

**1-Chloro-2,2-dimethylaziridine (2b).** This compound has been recovered as clear colorless liquid by distillation of the reaction mixtures at low temperature (-5 °C) and pressure (15 mm).

**1-Chloro-2-phenylaziridines (*E*)-2c and (*Z*)-2d.** Clean separation of the (*E*)-2c major component, of the slow moving (*Z*)-2d diastereoisomer, and of unreacted partially optically active 1c aziridine could be achieved by column chromatography, and the compounds have not been subjected to additional purification. Diastereoisomeric 1-chloro-2-phenylaziridines 2c and 2d are clear colorless liquids which show the following mass spectra data (40 eV): *m/e* 155 ($M^+$, $^{37}Cl$), 153 ($M^+$, $^{35}Cl$), 118, 103, 91, 77, 65, 51. NMR spectra and epimerization studies agree upon the *E* and *Z* configurational assignment for the 2c and 2d *N*-chloroaziridines, respectively.[7]

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**Registry No.** 1a, 25564-63-0; 1b, 2658-24-4; (±)-1c, 55297-79-5; (*R*)-(-)-1c, 18142-08-0; (*S*)-(+)-2a, 39830-44-9; (*R*)-(-)-2a, 79258-01-8; (*R*)-(+)-2b, 28112-60-9; (*S*)-(-)-2b, 83664-41-9; (1*S*,2*S*)-(+)-2c, 86014-25-7; (1*R*,2*R*)-(-)-2c, 86014-26-8; (1*S*,2*R*)-(+)-2d, 86014-27-9; (1*R*,2*S*)-(-)-2d, 86014-28-0; (*R*)-(+)-3a, 68128-21-2; (*S*)-(+)-3b, 340-06-7; (*R*)-(-)-3c, 22038-90-0; (*S*)-(+)-3d, 60646-30-2; (*R*)-(-)-3d, 53531-34-3; TBHC, 507-40-4; NCS, 128-09-6.

(14) Jurczak, J.; Konowal, A.; Krawczyk, Z. *Synthesis* **1977**, 258.
(15) Hassner, A.; Galle, J. E. *J. Am. Chem. Soc.* **1970**, *92*, 3733.
(16) Campbell, K. N.; Sommers, A. H.; Campbell, B. K. "Organic Syntheses"; Wiley: New York, 1956; Collect. Vol. III, pp 148-150.
(17) Brois, S. J. *J. Org. Chem.* **1962**, *27*, 3532.

# Difunctionalized Trans-2,5-Disubstituted Pyrrolidine (Azethoxyl) Nitroxide Spin-Labels

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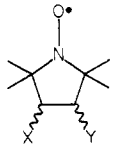
The synthesis of two short-chain trans-2,5-difunctionalized azethoxyl nitroxide spin-labels, dinitrile 12 and dicarboxylic acid 14, is described. The trans stereochemistry of 12 and 14 was established by conversion of 12 to a diastereomeric mixture of *N*-hydroxy esters 13, which was analyzed by NMR spectroscopy.

Functionalized, stable nitroxide free radicals[1] enjoy wide application as spin-labels for the study of biological and other macromolecular assemblies by electron spin resonance (ESR) spectroscopy.[2] Most of the available spin-labels bear only one functional group, although recently, several 3,4-difunctionalized 2,2,5,5-tetramethylpyrrolidinyl-1-oxy nitroxides 1 have been described.[3,4]



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Difunctional nitroxides are important as potential cross-linking agents because they have the possibility of attachment to a macromolecule at two sites. The motion of such a nitroxide would consequently be largely confined to that of the macromolecule, an advantage in applications involving the relatively new saturation transfer electron paramagnetic resonance (STEPR) methodology for studying molecular motion in the correlation time range $10^{-7} < \tau < 10^{-3}$ s.[5]

Azethoxyl nitroxides 2, originally introduced by us[6,7] as minimum steric perturbation spin-labels for lipid systems,

(1) (a) For reviews see: Keana, J. F. W. *Chem. Rev.* **1978**, *78*, 37-64. (b) Keana, J. F. W. In "Spin Labeling: Theory and Applications"; Berliner, L. J., Ed.; Academic Press: New York, 1979.
(2) Berliner, L. J., Ed. "Spin Labeling: Theory and Applications"; Academic Press: New York; 1976, Vol. I; 1979, Vol. II.
(3) For leading references see: Keana, J. F. W.; Hideg, K.; Birrell, G. B.; Hankovszky, H. O.; Ferguson, G.; Parvez, M. *Can. J. Chem.* **1982**, *60*, 1439-1447.
(4) Hankovszky, H. O.; Hideg, K.; Lex, L.; Kulcsár, G.; Halász, H. A. *Can. J. Chem.* **1982**, *60*, 1432-1438.
(5) Hyde, J. S.; Dalton, L. R. In "Spin Labeling: Theory and Applications"; Berliner, L. J., Ed.; Academic Press: New York, 1979; Cherry, R. J. *Biochim. Biophys. Acta* **1979**, *559*, 289-327.
(6) Lee, T. D.; Keana, J. F. W. *J. Org. Chem.* **1978**, *43*, 4226-4231.
(7) Lee, T. D.; Birrell, G. B.; Bjorkman, P. J.; Keana, J. F. W. *Biochim. Biophys. Acta* **1979**, *550* 369-383.

0022-3263/83/1948-2644$01.50/0 