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NOREPHEDRINE DERIVED OXAZOLIDINES AS CHIRAL ACYLATING AGENTS: AN NMR STUDY OF THE INTERMEDIATE CATIONS.

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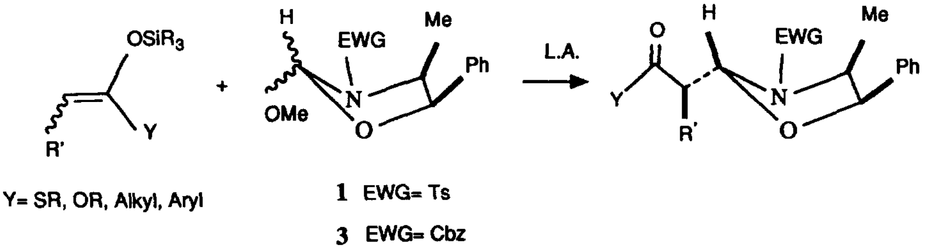
Abstract: *NMR studies proved that cationic species are intermediates in the acid catalyzed reaction of norephedrine-derived oxazolidines with nucleophiles. Information was gathered on the electronic structure of the cations and its dependence on ring substitution.*

Introduction.

Norephedrine derived 2-methoxy oxazolidines **1** and **3** have been shown to react in very stereoselective fashion with various stereogenic nucleophiles, such enamines, silylenolethers, and silylketeneacetals in the presence of Lewis acids.[1] The addition usually occurs with > 95% diastereomeric preference. Upon hydrolysis of the oxazolidine ring, the product of a formal enantioselective formylation can be isolated in good yields (Scheme 1). The same synthetic scheme has also been applied to the 2-methyl substituted anologues and enantioselective acetylation of enolsilanes achieved.[2]

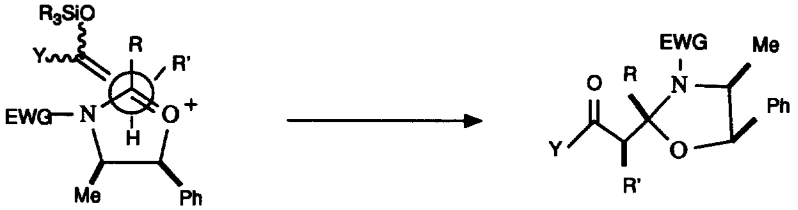
Scheme 1



The level of the observed selectivity often depends on the nature of the oxazolidine N-protecting group, better results being usually achieved with the N-carbobenzyloxy compound **3** than with the N-Tosyl one **1**.[1b]

The model we have proposed to rationalize the stereochemical outcome of enolsilane additions is depicted in Scheme 2.

Scheme 2



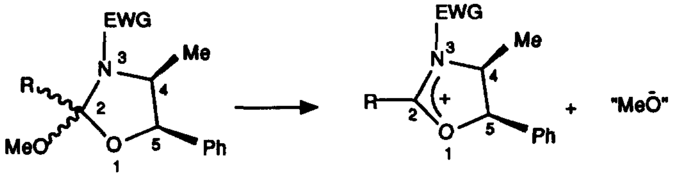
The transition structure involves an intermediate oxazolinium ion, mainly localized on the oxygen atom. The nucleophile approaches the cation from its less hindered α side and with its smallest substituent (H) occupying the most crowded position. An extended conformation of the reacting π systems is also assumed, in keeping with related models.[3a]

The formation of an ionic species upon action of a Lewis acid on 2-methoxy oxazolidines is a reasonable assumption,[3b] but it needs to be supported by some experimental data. Furthermore, knowledge of the nature of such intermediates is crucial for a better understanding of the origin of the observed selectivity and its modulation by the ring substituents. Information on the stability of the presumed cationic species would also be of help in optimizing the reaction conditions and extending the method to different oxazolidine substrates. We therefore undertook an NMR study of the interaction of oxazolidines **1**- **5** (Figure 1) with different Lewis acids and of the nature of the resulting cationic compounds **6-10** (Figure 1).

Materials and Methods

Oxazolidines **1-5** were synthesized as described elsewhere.[1,2] The NMR spectra were recorded with a Bruker AC-300 instrument (^{1}H-300 MHz, ^{13}C-75 MHz) using a 5mm ^{1}H/^{13}C dual probe, in $CDCl_3$ or CD_2Cl_2 at temperatures varying from -78°C to 25°C. For every temperature change the probe was conditioned for ca. 30 min. Lewis acids were added as a concentrated solution in $CDCl_3$ ($TiCl_4$) or neat ($BF_3.OEt_2$), by aliquots, *via* a gas-tight syringe to the NMR tube. All solutions were handled under nitrogen (from liquid N_2) and all the solvents were dried before use with 4A molecular sieves. Typically, for ^{1}H spectra the data were acquired into 8192 data points with a pulse width of 6.7 s (90°). The spectral width, was 4000 Hz leading to an acquisition time of 1.0 s. No relaxation delay was included. Typically for ^{13}C spectra, the data were acquired into 16384 data points using the standard Bruker microprogram JMODXH optimized for all different multiplicities, with a spectral width of 17500 Hz and an acquisition time of 0.46 s. Two-dimensional ^{1}H-^{13}C correlation spectra were measured using the standard Bruker microprogram XHCORR optimized for the one bond coupling constant. A typical observation data size of 1024 points with a spectral width of 12800 Hz was used with a total relaxation delay of 2 s. The spectral width in the proton dimension was 3000 Hz, with the experiment consisting of 128 increments of 128 transients each with zero filling to 1024 points. Chemical shifts of quaternary carbons were confirmed by ^1H-^{13}C COLOC[6] experiments optimised for coupling constants of 3 and 5 Hz and a relaxation delay of 4 s.

Figure 1



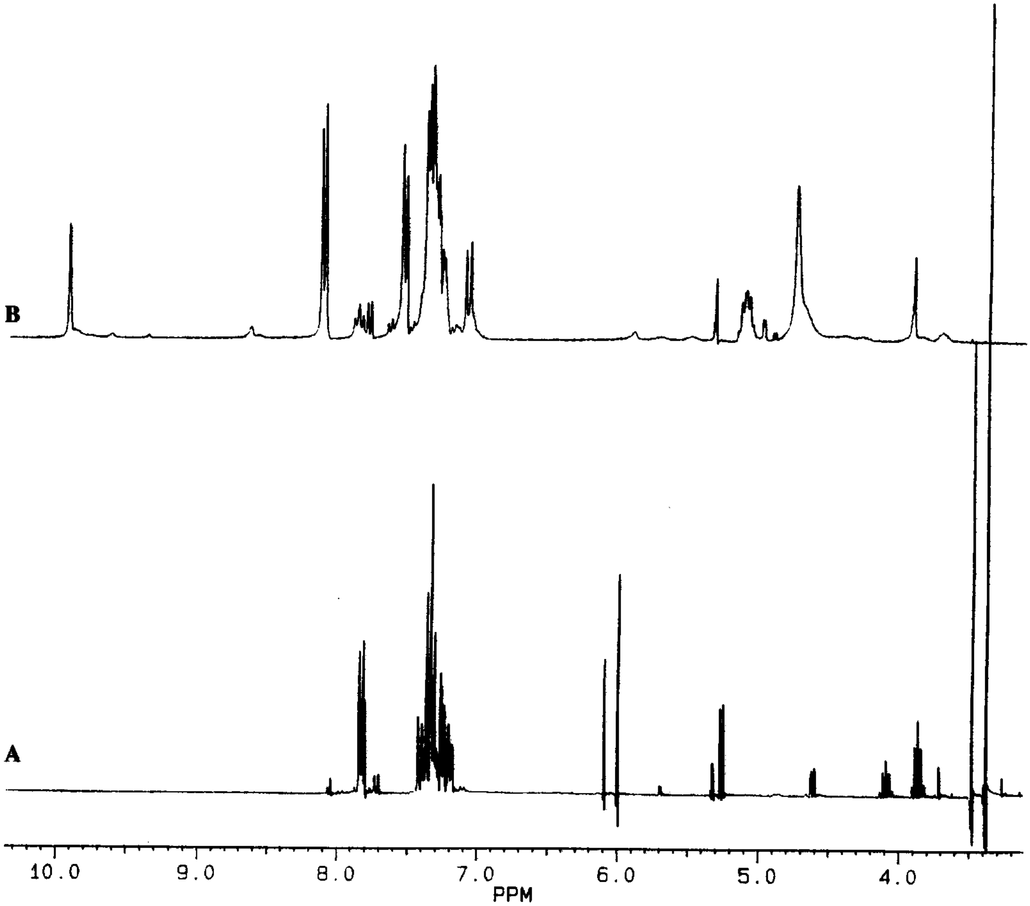
1	R = H	EWG = Ts	6
2	R = Me	EWG = Ts	7
3	R = H	EWG = Cbz	8
4	R = Me	EWG = Cbz	9
5	R = Ph	EWG = Cbz	10

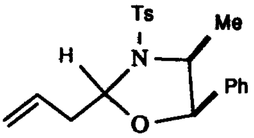
Results and Discussion

As previously reported,[1] the condensation of N-Tosylnorephedrine with trimethylorthoformate gives rise to **1** as a 1:1 mixture of C-2 epimers. These compounds can be separated by flash chromatography and their C-2 stereochemistry established by n.O.e. Rapid equilibration of the two epimers occurs in $CHCl_3$ or CH_2Cl_2 solution, probably catalyzed by traces of acids in these solvents. Shown in Figure 2 is the reaction of oxazolidine **1** with $TiCl_4$ at -20°C, as monitored by ^1H-NMR. The bottom trace A shows the starting material **1**. The signal for H-2, H-4 and H-5 appear respectively as singlet, doublet of quartet, and doublet at 6.1, 4.1 and 4.6 ppm for *cis*-**1** and at 6.0, 3.9 and 5.2 ppm for *trans*-**1**. The *cis* and *trans* -OMe signal resonate at 3.4 and 3.3 ppm respectively. Upon addition of 0.4 eq. of $TiCl_4$ one observes the appearence of a new set of signals, all shifted downfield with respect to the starting material. The *cis* / *trans* ratio also appeares to be modified, with the *cis* epimer diminishing faster than the *trans*. Disappearence of the signals due to **1** is complete after addition of 1 eq. of $TiCl_4$ (trace B). A new compound is formed, which shows a singlet at 9.8 ppm, a doublet at 6.9 ppm and a doublet of quartet at 5.0 ppm coupled to the doublet. The same spectrum as the one reported in trace B of Figure 2 is also obtained by treatment of a 1:1 mixture of **1** with 2 eq. of $BF_3.Et_2O$ at -78°C.[7] Quenching of these solutions with water gives rise to quantitative formation of O-formyl-N-tosyl-ephedrine, whereas addition of allyltrimethylsilane yields the expected 2-allyl oxazolidine **11**.

FIGURE 2

^{1}H-NMR spectra of **1** (trace **A**) and **1** + 1 eq of $TiCl_4$(trace **B**).





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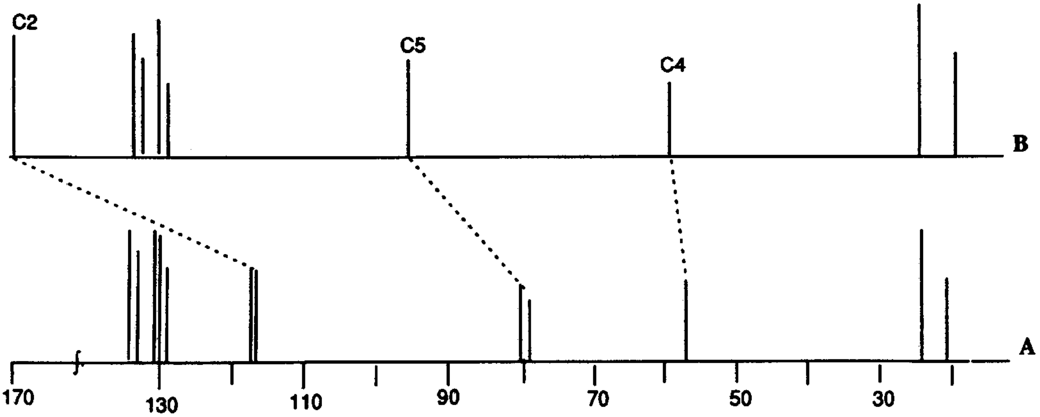
In Figure 3 the reaction of **1** with $TiCl_4$ at -20°C is monitored by ^{13}C-NMR. The signals due to C-2, C-4 and C-5 shift downfield upon addition of 1 eq. of $TiCl_4$ and again, from a 1:1 diastereomeric mixture, a single set of signals is obtained. A 2-D heteronuclear correlation experiment (HETCOR[8]) established a connection between the ^{13}C signal at 170 ppm and the ^{1}H singlet at 9.4 ppm. An INEPT experiment also showed that the $J_{C2\text{-}H2}$, which has a value of 190 Hz in the starting material **1**, changes to 273 Hz in the reaction product, indicating a change from sp^3 to sp^2 hybridization.[9] All these observations are consistent with the formation of the cationic species **6**

Figure 3. ^{13}C-NMR spectra of **1** (trace A) and **1** + 1eq of $TiCl_4$ (trace B).



The same experiments were performed on oxazolidines **2-5**, and again formation of a new set of signals due to a single C-2 epimer and consistent with the cationic structures **7-10** was observed. Selected ^{1}H and ^{13}C chemical shifts of the oxazolidines **1-5** and the corresponding ions **6-10** are reported in Table 1 and Table 2.

Table 1. ^{1}H-NMR of **1-10** in CD_2Cl_2 at -20°C[a]

	1[b]	**6**[c]	**2**[b]	**7**[c]	**3**[b]	**8**[c]	**4**[b]	**9**[c]	**5**[b]	**10**[e]
EWG,R	Ts,H		Ts,Me		Cbz,H		Cbz,Me		Cbz,Ph	
H-2	6.0-6.1	9.8			5.9-5.7	9.8			1.23	
$\Delta\delta_{H2}$	3.7[d]				4.0[d]					
H-4	3.9-4.1	5.0	3.9-4.1	5.0	3.9-4.1	4.7	4.3	5..2	4.0	4.4
$\Delta\delta_{H4}$	1.0[d]		1.0[d]		0.7[d]		0.9		0.4	
H-5	4.6-5.2	6.9	5.1	6.6	5.3	7.1	5.4	6.6	4.8-5.3	5.7
$\Delta\delta_{H5}$	2..0[d]		1.5		1.8		1.2		0.6[d]	
Me-2			2.0-2.1	3.0			1.8-1.9	2.9		
$\Delta\delta_{Me}$			1.0				1.1			

a) Data are reported in ppm on the δ scale. b) 1:1 diastereomeric mixture. c) As obtained upon addition of 1 eq. of $TiCl_4$ to a 5M solution of the parent 2-methoxy oxazolidine. d) Average value. e) Obtained by addition of 1 eq. of $BF_3.OEt_2$ to **5**.

The spectra of the N-carbobenzyloxy compounds **3-5** and **8-10** are more complex than those of the N-tosyl analogues, due to hindered rotation around the N-carbobenzyloxy bond. So, for instance, the ^{13}C-NMR spectrum of **3** appears as a mixture of four isomers at -20°C. However, after the Lewis acid addition, a single set of ^{13}C signals is observed (Figure 4).

Figure 4. ^{13}C-NMR spectra of **3** (trace A) and **3** + 1eq of $TiCl_4$ (trace **B**).

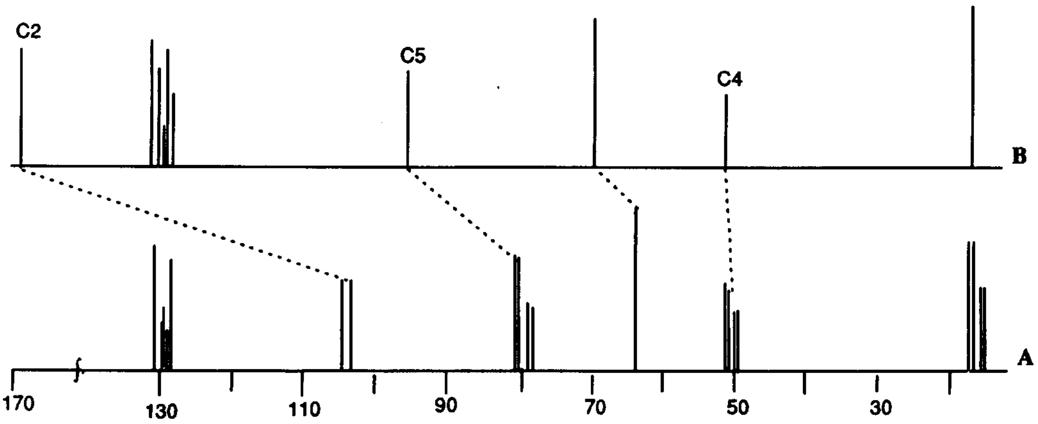


Table 2. ^{13}C-NMR of **1-10** in CD_2Cl_2 at -20°C[a,b]

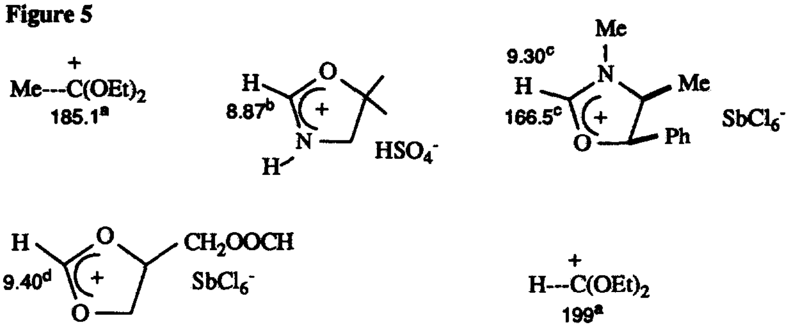
	1[f]	**6**[d]	**2**[f]	**7**[d]	**3**[c]	**8**[d]	**4**[e]	**9**[d]	**5**	**10**[h]
EWG,R	Ts,H		Ts,Me		Cbz,H		Cbz,Me		Cbz,Ph	
C-2	106 107	170	113	183	104.3 104.7 105.0 105.5	171	109 111		115	168
$\Delta\delta_{C-2}$[g]	64		69		67		75		53	
C-4	56	60	58 59	63	52.2 52.6 53.6 53.8	56	56 58	60	52 68	60
$\Delta\delta_{C-4}$[g]	4		4		3		4		0	
C-5	78 80	96	78 79	91	78.2 78.9 80.3 80.8	96	78 79	91	77 90	95
$\Delta\delta_{C-5}$[g]	18		12		18		13		12	

a) Data are reported in ppm on the δ scale. b) The same spectra were observed at -78℃. c) As a mixture of four isomers (see text). d) As obtained upon addition of 1 eq of $TiCl_4$ to a 5 M solution of the parent 2-methoxy oxazolidine. e) The product is a mixture of four isomers but only two sets of signals are distinguishable (see text). f) As a mixture of two isomers. g) Average value. h) Obtained by addinng 2 eq of $BF_3.OEt_2$ to **5**.

For the 2-Me compounds **7** and **9**, the signal due to the C-2 carbon was identified in a COLOC experiment by means of its coupling to the protons of Me-2. In the case of cation **10** the signal due to C-2 was distinguished from the carbobenzyloxy carbonyl carbon, because the latter showed in a COLOC experiment coupling to the benzylic methylene protons.

Cationic species analogous to the ones under present consideration have been described in the literature.[10] Selected examples are shown in Figure 5. The reported chemical shifts for the carbon formally bearing the positive charge and for the hydrogen attached to it are in keeping with those observed in the case of compounds **6-10** (Table 1 and 2).

Figure 5



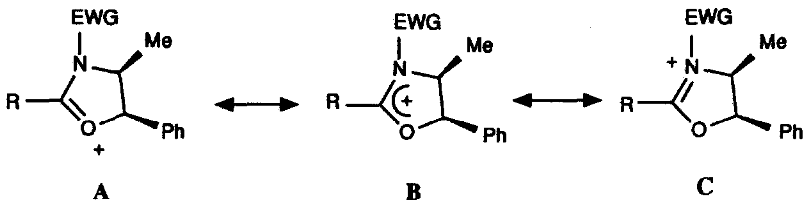
a. CD_3NO_2 solution.from ref. 10a. b. 96% H_2SO_4 solution, from ref. 10b.
c. Acetone-d_6 solution, from ref.10b. d.CD_3CN solution, from ref.10e.

Treatment of oxazolidines **1-4** with $BF_3.OEt_2$ also gives rise to the cationic species **6-9**. However, in this case 2-2.5 eq. of the Lewis acid are needed in order to obtain quantitative formation of the cations at -78°C. Use of $BF_3.OEt_2$ leads to increased stability of the ion solutions compared to those formed with $TiCl_4$. For instance, a CH_2Cl_2 solution of **6** is stable for days at -20°C in the presence of $BF_3.OEt_2$, compared to a few hours in the presence of $TiCl_4$. Above such temperature extensive decomposition is observed.

2-Methyl substitution appears to lend thermal stability to the cations so that a solution of **9** generated with 2.5 eq. of BF_3OEt_2 can be stored for days at room temperature with no appreciable changes in the ^{1}H-NMR spectrum. This increased thermal stability corresponds to a reduced reactivity of **4** compared to **3**.[7]

A more detailed analysis of the spectra of **6-10** allows one to draw some interesting conclusions on the nature of these compounds. The strong downfield shift of C-2 upon treatment of **1 -5** with the Lewis acid is consistent with the formation of a positive charge on this atom. Such a charge will be delocalized on the adjacent heteroatom through n → p interactions, so that the real structure of the cation will be better described as a mixing of the canonical structures A and C. (Figure 6)

Figure 6



This is manifested in the spectra of **6** - **10** by the downfield shifts of the signals for C-4 ($\Delta\delta C_4$ in Table 2) and C-5 ($\Delta\delta C_5$ in Table 2) compared to the parent 2-methoxy oxazolidines. In terms of canonical structures, the relative magnitude of $\Delta\delta C_4$ and $\Delta\delta C_5$ are an indication of the contribution of structures A and C to the description of the species. From the values reported in Table 2 one observes that C-5 always undergoes the largest deshelding upon formation of the cation ($\Delta\delta C_5 > \Delta\delta C_4$). This indicates a stronger participation of the oxygen lone pairs to the stabilization of the positive charge, and therefore support our transition structure model (see Scheme 2).

The contribution to cation stabilization from the nitrogen lone pair is modulated by the different substituents. (Table 3)

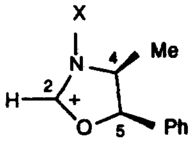


Table 3 . Chemical shifts dependence on the N-substituent (X)

	X	C_2	C_4	C_5	$\Delta\delta H_4$	$\Delta\delta H_5$
8 [a]	Cbz	171	56	96	0.7	1.8
6 [a]	Ts	170	60	96	1.0	2.0
12 [b]	Me	166	62	91	2.3	1.8

a. Spectra in CD_2Cl_2. b. Spectrum in acetone-d_6. From ref.10b

On going from **8** (X=Cbz) to **6** (X=Ts) to **12** (X=Me) the C-2 chemical shifts move from 171 to 170 to 166 ppm, indicating a diminishing positive charge on this atom. Meanwhile the signal due to C-4 moves downfield by 6 ppm (from 56 ppm in **8** to 62 ppm in **12**) and correspondingly, the C-5 signal moves upfield by 5 ppm (from 96 ppm in **8** to 91 ppm in **12**). At the same time the downfield shift of the signal due to H_4 ($\Delta\delta H_4$, Table 3) increases along the series from 0.7 to 2.3 ppm. All these observations are consistent with an increasing delocalization of the charge on the nitrogen atom. Such an effect well accounts for the dramatic difference in reaction rates and stereoselectivities between the N-cbz and the N-Ts-protected oxazolidines.

Also of some interest are the effects on the cation structure arising from C-2 substitution. The data collected in Table 4 show that charge delocalization on the heteroatoms diminishes on going from **8** (R=H) to **9** (R=Me) and to **10** (R=Ph).

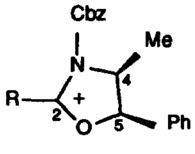


Table 4. Chemical shifts dependence on C-2 substituent (R):

	R	C_2	$\Delta\delta C_5$	$\Delta\delta H_5$	$\Delta\delta H_4$	$\Delta\delta C_4$
8	H	171	18	1.8	0.7	3
9	Me	185	13	1.2	0.9	4
10	Ph	168	12	0.6	0.4	0

These data are in line with the expected stabilization of the cations by C-2 substitution, which reduces the electron withdrawal from the ring. This trend, however, is not reflected in the C-2 chemical shifts. In particular, the signal for C-2 in **9** appears at lower fields than the corresponding signal in **8**. Such a result should not be interpreted as an indication of increased charge localization (and therefore increased reactivity) of carbocationic species,[10b] since this argument applies only when π-electron density is taken into account. On the other hand, inductive effects, such as those due to a methyl group, do not correlate with chemical shifts.[12]

In conclusion, we have now proven that the cationic species **6-10** we have invoked as reactive intermediates in our stereoselective acid catalyzed acylation protocol do indeed exist, and are formed by action of Lewis acids ($TiCl_4$ or $BF_3.OEt_2$) on the norephedrine-derived oxazolidines **1-5**. Cations **6-10** have been fully characterized by their ^1H- and ^{13}C-NMR spectra, which have yielded interesting information on the relative stability and reactivity of these species.

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References

1. a) Bernardi, A.; Cardani, S.; Carugo, O.; Colombo, L.; Scolastico, C.; Villa, R. *Tetrahedron Letters* **1990**,2779. b) Palazzi, C.; Poli, G.; Scolastico, C.; Villa, R. *Tetrahedron Letters,* **1990**,4223. c) Bernardi, A.; Piarulli, U.; Poli, G.; Scolastico, C.; Villa, R. *Bull.Chem.Soc.Fr.* **1990**,*127*,751. d) For related work in the area, see: Conde-Frieboes, K.; Hoppe, D. *SynLett*,**1990**,99.
2. Bernardi, A.; Cavicchioli, M.; Poli, G.; Scolastico, C.; Sidjimov, A. *Tetrahedron* **1991**, *37*, 7925.
3. a) Murata, S.; Suzuki, M.; Noyori, R. *Tetrahedron* **1988**, *44*, 4259.
   b) Addition of 2-methoxy oxazolidines **1-3** to allyltin reagents also displays good selectivity in most of the cases we have analyzed so far (see ref. 2 and 4). However, the stereochemical outcome of these reactions appears to vary dramatically and in unpredictable fashion with seemingly small structural changes in the substrates. Such behavior has been observed in other allylstannane nucleophilic additions, and has been ascribed to the presence of different reaction pathways, inherently close in energy. For a discussion of this issue, see ref.5.
4. Pasquarello,S.;Poli,G.;Potenza,D.; Scolastico,C. *Tetrahedron Asymmetry 1*,**1990**,429.
5. Fleming, I. *Chemtracts-Organic chemistry* **1991**, *4*, 21.
6. Kessler, H.; Griesinger, C.; Zarbock, J.; Loosli, H.R. *J.Mag.Res.* **1984**, *57*, 331.
7. Only minor differences in chemical shifts were observed between the cation solutions generated with $TiCl_4$ and those generated with BF_3.
8. Bax, A. *J.Mag.Res.* **1983**, *53*, 517.
9. Wehrli-Wirthl in "Interpretation of ^{13}C NMR Spectra" Heyden p. 42
10. a) Pindur, U.; Muller, J.; Flo,C.; Witzel, H. *Chem.Soc.Rev.*,**1987**,*16*,75. b) Bigalke, J. Inaugural Dissertation. Philipps-Univerität Marburg/Lahn 1988. We thank Prof. Boche for sending us a copy of this thesis . c)Hart, H., Tomalia, D.A. *Tetrahedron Letters*,**1966**, 3383; *ibid*, 3389. d) Tomalia, D.A.; Paige, J.N. *J.Org.Chem.*,**1973**, *38*, 422. e) Pittman Jr, C.N.; McManus, S.P.; Larsen, J.W. *Chem.Rev.*,**1972**, 376 and references therein. f) Von der Bruggen, U.; Lammers, R.; Mayr, H. *J.Org.Chem.* **1988**, *53*, 2920.
11. BF_3OEt_2 mediated tributylcrotyltin addition to **3** was complete in 1 h. at -78°C, whereas addition to **4** required 18 h. at 0°C. See ref. 2.
12. Bradamante, S.; Pagani, G. *J.Org.Chem.* **1984**, 2863.