CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.201001608

Tunable Diastereoselection of Biased Rigid Systems by Lewis Acid Induced Conformational Effects: A Rationalization of the Vinylation of Cyclic Nitrones En Route to Polyhydroxylated Pyrrolidines

Ignacio Delso,[a, b] Eduardo Marca,[a] Vanni Mannucci,[a, c] Tomás Tejero,*[a] Andrea Goti,*[c] and Pedro Merino*[a]

Dedicated to Professor José Barluenga on the occasion of his 70th birthday

Abstract: The diastereofacial selection in addition reactions to biased rigid systems can be modulated by the action of Lewis acids. As an example, the stereoselectivity of the nucleophilic addition of vinyl magnesium bromide (VMB) to cyclic nitrones in the presence of diethylaluminum chloride (DEAC) shows a strong dependence on the temperature and the carbon substituent adjacent at the reaction center; it is remarkable that whereas a high selectivity is obtained at higher temperatures, in the presence of DEAC, a trend to invert the stereochemical course of the reaction is observed at lower temperatures, provided the substituent at C3 of the pyrrolidine ring allows delivery of the vinyl moiety. This behavior and difference in selectivity is to be attributed to the high conformational barriers of the intermediate nitrone–DEAC–VMB complex. A clear inversion of the selectivity is observed at −78 °C for the reaction of the nitrone protected as an *O*-methyl derivative. The present study provides a rationalization for the stereocontrolled addition of nucleophiles to rigid systems (cyclic nitrones).

Keywords: heterocycles · nitrones · nucleophilic addition · pyrrolidines · steric hindrance

Introduction

The benefits of diastereofacial selection in addition reactions to sterically biased systems are commonly used in synthesis to form carbon–carbon bonds.[1] Any attempt at directing the facial approach of the reagent is based on perturbing the immediate steric environment of the reaction center, particularly when acyclic compounds with inherent conformational flexibility are used as substrates. In the case of rigid systems with nonequivalent π faces, exploitation of such stereodifferentiation in a controlled manner represents one of the core problems in organic synthesis because, in principle, there is no way of prioritizing the most hindered face owing to lack of conformational flexibility (Scheme 1).

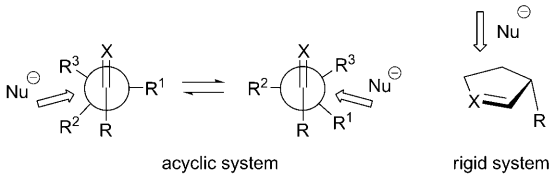
During the course of our research in nucleophilic addition reactions to nitrones, we have been interested in the preparation of a series of polyhydroxylated pyrrolidines. Over the years these compounds have emerged as potent inhibitors of glycosidases from various organisms.[2] Several polyhydroxylated pyrrolidines with interesting pharmacological profiles have been described, including DMDP **1** and its derivatives **2**–**5** (Scheme 2).[3] These compounds attribute their therapeutic properties to their analogy with transition-state spe-

[a] Dr. I. Delso, E. Marca, Dr. V. Mannucci, Prof. T. Tejero, Prof. P. Merino
Laboratorio de Síntesis Asimétrica
Departamento de Química Orgánica
Instituto de Ciencia de Materiales de Aragón
Universidad de Zaragoza, CSIC, Campus San Francisco
50009 Zaragoza, Aragón (Spain)
Fax: (+34) 976-762075
E-mail: pmerino@unizar.es
ttejero@unizar.es

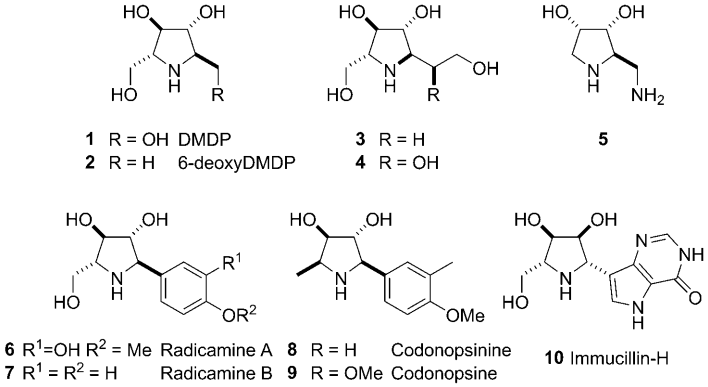
[b] Dr. I. Delso
Servicio de Resonancia Magnética Nuclear
Instituto de Ciencia de Materiales de Aragón
Universidad de Zaragoza, CSIC, Campus San Francisco
50009 Zaragoza, Aragón (Spain)

[c] Dr. V. Mannucci, Prof. A. Goti
Dipartimento di Chimica Ugo Schiff and HeteroBioLab
Università di Firenze, associated with ICCOM-CNR
via della Lastruccia 13, 50019 Sesto Fiorentino, Firenze (Italy)
Fax: (+39) 055-4573531
E-mail: andrea.goti@unifi.it

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201001608.



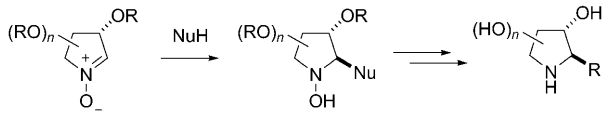
Scheme 1. Facial differentiation in acyclic and rigid systems.



Scheme 2. Biologically active polyhydroxylated pyrrolidines.

cies. In addition to compounds **1**–**5**, polyhydroxylated pyrrolidines that have an aromatic or heteroaromatic ring at C2 also showed interesting biological properties. Examples of these compounds can be found with derivatives possessing a substituted phenyl group such as radicamines A **6** and B **7** or the alkaloids codonopsinine **8** and codonopsine **9**. Some representatives of this latter variation are immucillin-H **10** and their derivatives, which have emerged as compounds with significant antimalarial[4] and antitumoral[5] activities.[6]

To date there have been a number of synthetic approaches to polyhydroxylated pyrrolidines.[1–3] One of the most efficient approaches consists of the addition of a nucleophile, such as an organometallic reagent, to cyclic nitrones readily available from carbohydrate precursors.[7] The resulting hydroxylamine can be further transformed into the target compound in an efficient way (Scheme 3).[8] By using this methodology a number of reports have come from our laboratories concerning the synthesis of various biologically active polyhydroxylated pyrrolidines.[8,9]



Scheme 3. Synthesis of polyhydroxylated pyrrolidines from cyclic nitrones.

A drawback of the methodology outlined in Scheme 3 is that the nucleophilic addition cannot be stereocontrolled, contrary to acyclic nitrones for which the nucleophilic addition can be completely stereocontrolled by the action of either Lewis acids[10] or protecting groups.[11] In the case of cyclic nitrones, the nucleophile attacks in all cases by the less hindered face, affording the corresponding 2,3-*trans* adducts in excellent selectivities. Any attempt of controlling the stereochemical outcome of the addition to cyclic nitrones by using different reagents, conditions, substrates, or additives failed.[12] To circumvent the preferred stereochemical outcome of the reaction and access to 2,3-*cis* derivatives, we developed an oxidation–reduction strategy that allowed the preparation of those compounds in good yields and selectivities.[9] Nevertheless, to exert a direct stereocontrol in the nucleophilic addition to cyclic nitrones that should find general applicability remains still challenging. Therefore, research efforts that provide new methods for the production of 2,3-*cis* polyhydroxylated pyrrolidines would be an important contribution to the field of asymmetric synthesis of glycosidase inhibitors and similar compounds of biological interest.

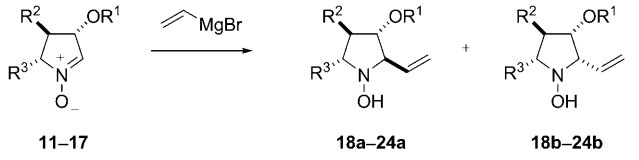
In this context, Trombini and co-workers demonstrated that vinylation of homochiral cyclic nitrones such as **11** constitutes an excellent starting point for the preparation of enantiomerically pure polyhydroxylated pyrrolidines.[13] The addition of vinyl magnesium bromide to nitrone **11** in the absence of any additive took place with excellent 2,3-*trans* selectivity at any temperature. Those authors also studied the addition reaction in the presence of diethyl aluminum chloride (DEAC). Unexpectedly, although a very good selectivity was observed at ambient temperature, a loss of selectivity was detected at low temperature. Because the loss of selectivity was enhanced at lower temperatures, the authors explained such unexpected behavior on the basis of entropy influence. However, Trombini and co-workers only studied the particular case of nitrone **11** and no discussion about the mechanistic insights or the generality of the behavior were given.

Herein, we wish to report a complete study concerning the vinylation of cyclic nitrones[14] as an example of the use of Lewis acids for modulating the stereochemical outcome of additions to biased rigid systems. We offer a general approach to the unexpected behavior observed with nitrone **11** to provide access to 2,3-*cis* pyrrolidines. We also show here that by use of the appropriate protective groups for the hydroxyl group at C3 of cyclic nitrone it is possible to modulate the reaction conditions to obtain predominantly the 2,3-*cis*-adduct. Experimental, spectroscopic, and theoretical studies are discussed.

Results and Discussion

Experimental studies: The starting nitrones **12**–**17** used for this study were prepared from L-malic acid for nitrones **12**–**14**,[15] from L-tartaric acid for nitrone **16**,[16] and from D-arabinose for nitrone **17**.[17] The new nitrone **15** was also prepared from commercially available dimethyl L-malate (see the Supporting Information). The reaction protocol consisted of the addition of 1.1 equiv of vinyl magnesium bromide

(VMB) in diethyl ether to the corresponding nitrone at different temperatures. In the case of the reactions carried out in the presence of 1.0 equiv of diethylaluminum chloride (DEAC), the reaction protocol consisted of in situ precomplexation of the nitrone in diethyl ether for 5 min at the stated temperature, later subjecting the resulting mixture to the addition of 1.1 equiv of VMB (Scheme 4).



11–17 18a–24a 18b–24b

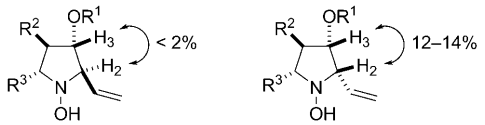
Nitrone	Hydroxylamine	R^1	R^2	R^3
11	**18**	Bn	OBn	H
12	**19**	*t*Bu	H	H
13	**20**	MOM	H	H
14	**21**	Bn	H	H
15	**22**	Me	H	H
16	**23**	*t*Bu	O*t*Bu	H
17	**24**	Bn	OBn	CH_2OBn

Scheme 4. Vinylation of cyclic nitrones (for nitrones **11** and **16** the enantiomeric series are shown).

In the absence of any additive the reaction proceeded with excellent yields and diastereoselectivities (for detailed data see the Supporting Information). In all cases, and whatever the temperature the reaction was conducted at, the 2,3-*trans* adduct was obtained preferentially. For nitrones **12** and **16** that have a *tert*-butoxy group at C3, the chemical yield of the reaction was excellent and ^{1}H NMR analysis (400 MHz) showed that the obtained 2,3-*trans* adducts **19a** and **23a** consisted of single isomers. Lowering the reaction temperature considerably increased the reaction time without significant changes in the diastereofacial selectivity. Only in the case of nitrone **15** a moderate selectivity was observed for all cases (d.r. **15a**:**15b** = 55:45 at 0 °C and d.r. **15a**:**15b** = 67:33 at −78 °C). These results are in agreement with a nucleophilic attack by the less hindered *Re* face, which is described later (see below).

The exposure of nitrones **12**–**16** to DEAC prior to the addition of VMB resulted in the formation of mixtures of two diastereomers depending on the temperature, with the exception of nitrones **12** and **16**, which showed in all cases a complete 2,3-*trans* selectivity. As described by Trombini and co-workers for nitrone **11**, nitrones **13**–**15** and **17** showed a considerable loss of selectivity when the reaction temperature was lowered. Indeed, at −78 °C almost equimolar amounts of both 2,3-*trans* and 2,3-*cis* isomers were obtained from nitrones **13** (d.r. **13a**:**13b** = 52:48) and **17** (d.r. **17a**:**17b** = 55:45), a slight excess of the 2,3-*cis* isomer **21b** was obtained from nitrone **14** (d.r. **14**:**14b** = 31:69), and a complete inversion of the selectivity was observed for nitrone **15** (d.r. **15a**:**15b** = 14:86). Notably, when the same reaction was carried out for the nitrone **14** by exchanging the order of addition of the additive (DEAC) and nucleophile (VMB), the 2,3-*trans* adduct **21a** was formed preferentially with a very good selectivity (d.r. **21**:**21b** = 92:8). Also note that all the reactions performed in the presence of DEAC required a longer time for the reaction to go to completion, clearly indicating that DEAC is far from being a promoter of the reaction, as discussed below. In this respect, we studied the possibility of a transmetalation of the vinylmagnesium bromide to the corresponding diethylvinylaluminum or some related species such as trivinylaluminum. In a separate experiment a solution of vinylmagnesium bromide in THF was treated with diethylaluminum chloride and the resulting mixture was kept at −78 °C for 6 h to induce the formation of vinylaluminum species following a similar reported procedure for the formation of vinylalane reagents.[18] The addition of nitrone **12** to the reaction mixture did not produce any product and the nitrone was recovered.[19] The same result was obtained when nitrone **12** was treated with trivinylaluminum tetrahydrofuranate.[20] In no case was transfer of vinyl or ethyl moieties to the nitrone observed,[21] thus indicating that the reaction takes place through delivery of the vinyl group from the Grignard reagent in agreement with the mechanism previously reported.[22]

The relative configuration of 2,3-*trans* and 2,3-*cis* isomers was unequivocally determined by NMR techniques including nuclear Overhauser effect (NOE) experiments (Scheme 5). For 2,3-*cis* isomers **19b**–**24b** irradiation of H2 had a remarkable NOE with H3 and vice versa. On the other hand, for 2,3-*trans* isomers **19a**–**24a** a negligible NOE was observed between H2 and H3. 2D correlation observed in NOESY experiments confirmed these results.



18a–24a 18b–24b

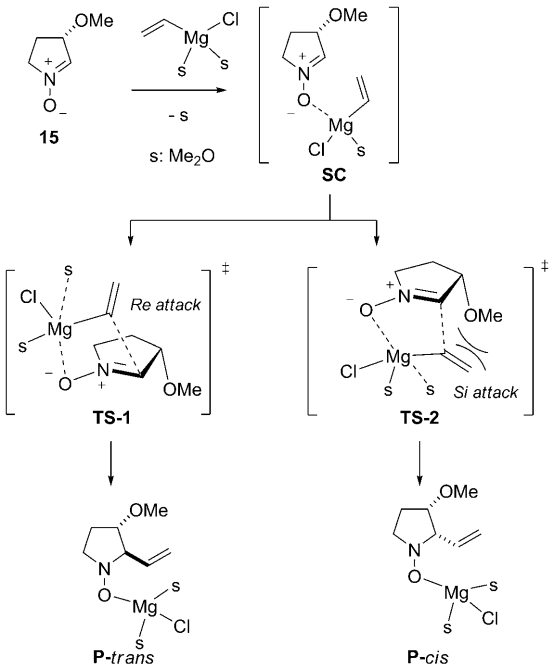
Scheme 5. Observed NOE for 2-vinylpyrrolidines **18**–**24**.

Only in the case of hydroxylamines **22** the *cis* and *trans* isomers could not be separated by chromatographic techniques. In this case, complete identification of the compounds was achieved by selective TOCSY experiments.

Theoretical studies: To estimate the relative energy barriers between the corresponding *Re* and *Si* attacks that lead to 2,3-*trans* and 2,3-*cis* isomers, respectively, we carried out a computational study by using transition-state modeling at the DFT level (B3LYP/6-31G*). To evaluate inclusion of diffuse functions and solvent effects, single-point B3LYP/6-31+G** calculations using Tomasi's PCM model (solvent = THF) were performed on the gas-phase optimized structures.[23] The reaction of a nitrone with a Grignard reagent takes place by firstly forming a complex **SC** without energy barrier. This complex further evolves to the final product by

internal delivery of the vinyl moiety through the corresponding transition states.[22] The studied reaction pathway for nitrone **15** is depicted in Scheme 6. A molecule of solvent (modeled as dimethyl ether) was added when necessary. Two reaction paths corresponding to the attacks by *Re* and *Si* faces of the nitrone have been considered. The energy barriers and reaction coordinate profile are shown in Table 1 and Figure 1, respectively.

The optimized geometries of transition structures **TS-1** and **TS-2** are illustrated in Figure 2. **TS-1** was the lowest energy structure found for the reaction of the *Re* face of the nitrone, whereas **TS-2** was the lowest energy structure found



Scheme 6. Calculated (B3LYP/6-31G* and B3LYP/6-31G*//PCM-B3LYP/6-31+G** (solvent = THF)) reaction pathway for vinylation of nitrone **15**. Vinylmagnesium chloride (VMC) instead of VMB has been considered for calculations. The solvent is modeled by discrete molecules of dimethyl ether.

Table 1. Calculated (B3LYP/6-31G*//PCM-B3LYP/6-31+G**, solvent = THF) free energies (ΔG, hartree) and relative energies ($\Delta\Delta G$, kcal mol^{-1}) of the reagents, complex, transition structures, and products for the nucleophilic addition of vinylmagnesium chloride to **12** and **15** (Scheme 7).

	Nitrone **15** (R = Me)		Nitrone **12** (R = *t*Bu)	
	ΔG	$\Delta\Delta G$	ΔG	$\Delta\Delta G$
nitrone	−400.990070	–	−518.871940	–
VMC	−1048.347774[a]	–	−1048.347774[a]	–
SC	−1294.352047	−2.53[b]	−1412.234320	−2.79[b]
TS-1	−1449.306511	22.19[c]	−1567.187646	22.91[c]
TS-2	−1449.302012	25.02[c]	−1567.179984	27.72[c]
P-*trans*	−1449.370282	−17.82[c]	−1567.253043	−18.13[c]
P-*cis*	−1449.364878	−14.43[c]	−1567.242936	−11.79[c]

[a] Vinylmagnesium chloride; calculated as a complex with two molecules of solvent (Me_2O). [b] Relative to nitrone and VMC complexed with two molecules of solvent. A calculated molecule of Me_2O ($\Delta G = -154.989833$ hartree) has been considered for coherency. [c] Relative to **SC** + Me_2O.

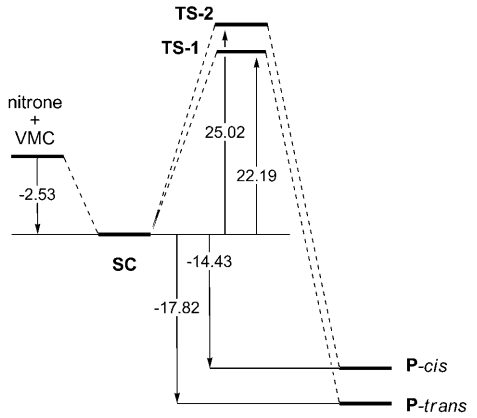


Figure 1. Energy profile for vinylation of nitrone **15** (Scheme 6 and Table 1). Data (B3LYP/6-31G*//PCM-B3LYP/6-31+G**) in kcal mol^{-1}.

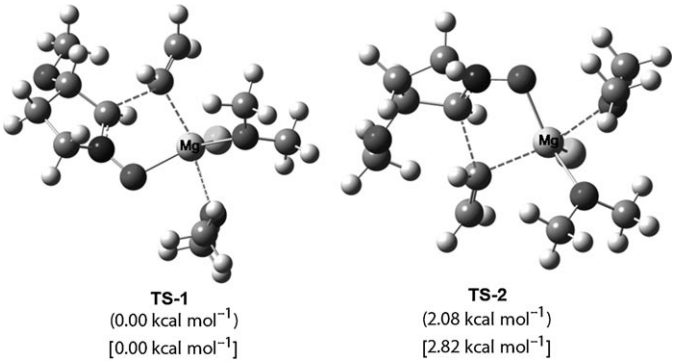
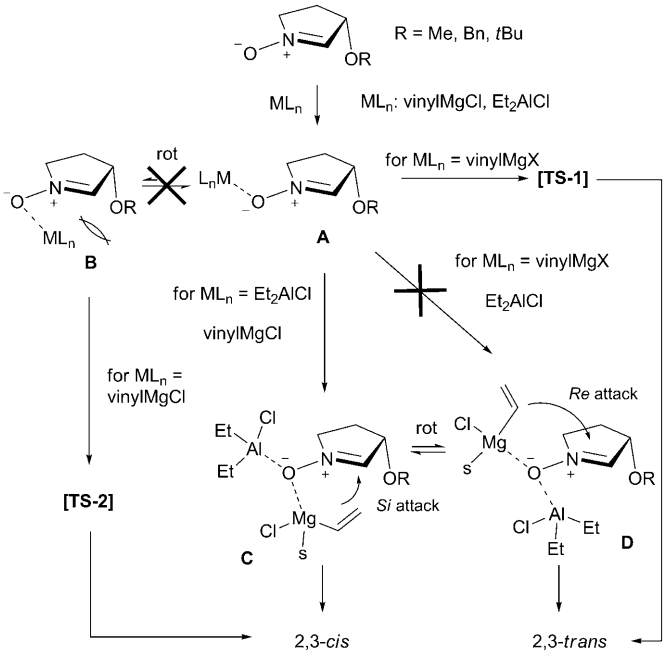


Figure 2. Transition structures for the vinylation of nitrone **15** (optimized at the B3LYP/6-31G* level). Relatives energies are indicated in kcal mol^{-1}. The relative energies corrected by solvation energies in THF solution by using PCM-B3LYP/6-31+G** are given in square brackets.

for *Si*-face attack. This latter TS is disfavored (+2.83 kcal mol^{-1} relative to **TS-1**) due largely to a steric interaction between the alkoxy group adjacent to the nitrone carbon and the incoming vinyl group. Thus, reaction occurs preferentially via **TS-1** in which the vinyl group attacks by the less hindered *Re* face. Replacement of the methyl group in **15** by a *tert*-butyl group (nitrone **12**) increased the energy difference between **TS-1** and **TS-2** up to 4.81 kcal mol^{-1} (Table 1). These results are in agreement with those observed experimentally in the absence of any additive and justify why only single diastereomer is obtained in the vinylation of nitrones **12** and **16** at low temperature, as well as the observation of the minor isomer for the same reaction with nitrones **13**–**15** and **17**.

Our results revealed that the stereochemical course of the reaction is mainly governed by both the substituents at C3 and the presence/absence of DEAC as a precomplexing agent. In this respect, the formation of complexes between cyclic nitrones such as **12**–**17** and DEAC has been previously demonstrated in our group by using NMR spectroscopy.[12a] A closer inspection of the results in the presence of

DEAC also revealed that in addition to the observed longer reaction times with respect to the reaction in the absence of any additive, the bulkier the alkoxy group at C3 is, the longer is the reaction time. The order of steric size of the protective group is as follows: *tert*-butyl ≫ benzyl ≈ MOM > Me. These results suggest that the favorable conformation of the initial complex is fixed according to the size of the protective groups. Thus, after the initial addition of VMB or DEAC the initial complex most probably exists in that conformation in which the metal is oriented to the opposite side of the C3 alkoxy substituent (Scheme 7, **A**), so that it can avoid the steric interference between itself and the alkoxy group (Scheme 7, **B**).



Scheme 7. Transition structures for the vinylation of nitrone **15**.

We assume that the reaction process is as follows: In the case of the addition in the absence of any additive the stereochemical course of the vinyl transfer is governed by the steric hindrance exerted by the C3 substituent as discussed above.

On the other hand, in the case of the addition in the presence of DEAC, a second complex should be formed between nitrone–DEAC complex **A** and the incoming VMC. Because DEAC is preferentially oriented by the less hindered face, VMC only can coordinate by the most hindered one (Scheme 7, **C**). Under this situation both sides of the nitrone are always shielded, one by the C3 substituent and the other by the large diethylaluminum chloride, and as a consequence the reaction in the presence of DEAC is slower. Moreover, the initially formed complex **C** only leads to the 2,3-*cis* isomer in the case of unfavorable steric interactions, which allow, in any extent, the internal delivery of the vinyl group. Otherwise, conformer **C** should convert into conformer **D**, which leads to the 2,3-*trans* isomer. This hypothesis is quite reasonable because the choice of the protective group affects not only the stereoselectivity of the reaction but also the reactivity towards nucleophilic addition.

At this point the effect of the temperature is clear and we can thereby assume that at lower temperatures the rotational conformational barrier between complexes **C** and **D** is comparable to the nucleophilic addition energy barrier. The lower the size of the C3 substituent, the higher the 2,3-*cis* selectivity. For nitrones **12** and **16** the *tert*-butoxy group gives enough steric bias against the nucleophilic addition by the *Si* face thus leading to the slower reaction, which is only produced after formation of **D**. At higher temperatures, the rotational barrier between **C** and **D** is negligible in comparison with reaction energy barriers and the stereoselectivity of the reaction is only governed by the size of the C3 substituent as in the case of the reaction carried out in the absence of any additive. According to this data the initial addition of VMC formed the most favorable conformer **A**, which after further addition of DEAC could lead to **D**. However, further NMR studies (see below) demonstrated that complex **A** with VMC (or VMB) (MLn = vinylMgX) does not coordinate DEAC to form **D** (contrary to complex **A** with DEAC (MLn = Et_2AlCl), which coordinates VMC (or VMB) to form **C**), but directly evolves towards the final product through **TS-1** (Scheme 7). Because the internal delivery of the vinyl moiety is clearly favored in that transition structure, the 2,3-*trans* isomer is obtained preferentially without formation of conformer **C**.

To estimate the conformational barriers between species **C** and **D** (Scheme 7) we also carried out a conformational analysis at a semiempirical level[24] on the rotation of the N–O bond (Figure 3). According to the literature data, which account for the trend of halogen atoms to form bridges between metal atoms such as Mg[25] and Al,[26] we assumed the formation of such complexes and postulated the formation of pentacoordinated aluminum, also in agreement with literature data.[27] For the several possibilities studied, complex **25** resulted the most stable (PM3) and it was used for the above-mentioned conformational study. This study showed the presence of six relevant stationery points, that is, three minima and three maxima (Figure 3). The absolute minimum and one of the relative ones correspond to the orientation of the Mg atom by the most hindered *Si* face, whereas the other relative minimum corresponds to an orientation of the Mg atom by the less hindered *Re* face. The energy barriers between those minima are 27 kcal mol^{-1} and 20 kcal mol^{-1}, which are comparable to those of the nucleophilic addition reaction (18 kcal mol^{-1} for *Re* attack and 20 kcal mol^{-1} for the *Si* attack).[24] These results are also in full agreement with experimental observations because they confirm a preference of the system towards orientation of the Mg atom through the most hindered *Si* face of the nitrone. Of course, delivery of the vinyl moiety by this face can only occur when both the temperature is enough low to slow down conformational equilibrium between **C** and **D** (temperature effect) and the OR group at C3 is enough

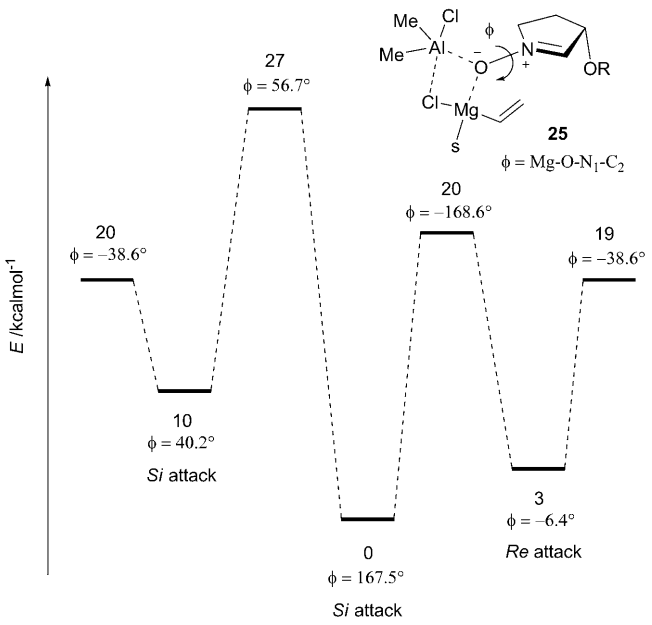


Figure 3. Relevant points from the conformational analysis of the complex **25** formed between nitrone **15**, DEAC, and VMC. Relative energy data are given in kcal mol^{-1}.

small to allow (at least in some extent) the attack of the nucleophile (steric effect).

According to the hypothesis outlined in Scheme 7, any effect additional to temperature, contributing to slow down rotation between **C** and **D** should increase the formation of 2,3-*cis* isomers. To validate our proposal we carried out some reactions in the presence of the bulkier, and commercially available, diisobutyl aluminum chloride (DIAC). The results are given in Table 2.

As expected, whereas at higher temperatures the selectivity was not affected, at −78 °C (Table 2, entries 3, 6, and 9) increased amount of 2,3-*cis* isomers were obtained. This effect can be explained on the basis of a higher rotational barrier between conformers **C** and **D** as a consequence of the increased bulkiness of the aluminum ligands.

Table 2. Nucleophilic additions of VMB to **14**, **15** and **17** in the presence of DIAC.[a]

Entry	Nitrone	T [°C]	t [h][b]	**a**:**b**[c]	Yield [%][d]
1	**14**	0	4	86:14	quant.
2	**14**	−30	12	70:30	92
3	**14**	−78	40	20:80	91
4	**15**	0	4	57:43	96
5	**15**	−30	12	30:70	92
6	**15**	−78	40	12:88	90
7	**17**	0	4	93:7	86
8	**17**	−30	12	65:35	88
9	**17**	−78	40	39:61	80

[a] The reaction was carried out by precomplexing the nitrone with 1.0 equiv of DIAC for 5 min in diethyl ether at which time 1.1 equiv of VMB was added. [b] The reaction was monitored by TLC and NMR spectroscopy. [c] Calculated by NMR analysis of the reaction mixture; **a** and **b** series refer to 2,3-*trans* and 2,3-*cis* isomers, respectively. [d] Isolated yield of the mixture of diastereomers. Quant. = quantitative.

NMR studies: To assess the proposed model for the nucleophilic vinylation of cyclic nitrones in the presence of DEAC we carried out a NMR study of the complex formation.[25] We chose nitrone **13** for the study, which showed variable behavior in the presence and absence of the Lewis acid, and has no aromatic protons that could interfere with the azomethine proton signal. The ^{1}H NMR spectrum of a 0.2 M solution of **13** in [D$_8$]THF at −78 °C (Figure 4, trace a) showed the signal corresponding to the azomethine proton at $\delta =$ 6.99 ppm.

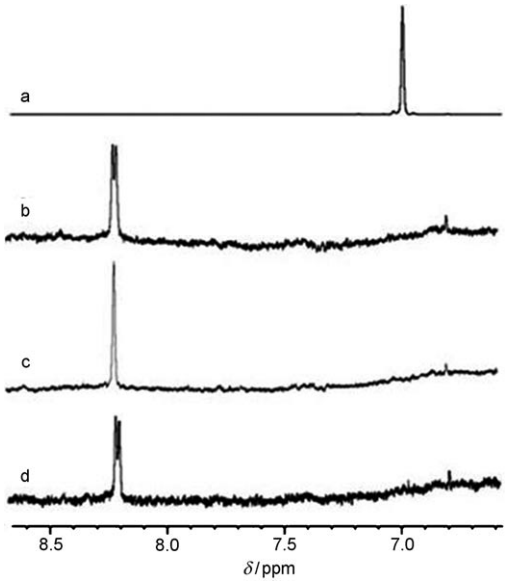


Figure 4. Partial NMR spectra of nitrone **13** complexes with VMB (see text for explanation of traces a–d).

Upon treatment with 1.0 equiv of VMB at −78 °C, a new set of signals rapidly appeared at $\delta = 8.20$ ppm (Figure 4, trace b). This downfield shift for H2 supports the formation of an O−Mg bond between the nitrone oxygen and the metal center. Indeed, the increased complexity of the signal may indicate the presence of different conformers as discussed above. The resulting mixture was then warmed to −50 °C and the signal at $\delta = 8.20$ ppm was significantly simplified (Figure 4, trace c). Cooling again to −78 °C (Figure 4, trace d) returned to the previous situation thus suggesting the possibility of a slow (on an NMR time scale) conformational equilibrium similar to that shown in Scheme 7. Upon prolonged standing of the mixture the intensity of the resonance at $\delta = 8.20$ ppm decreased as a consequence of the progress of the reaction.

In 2003, we reported a NMR study concerning complexation of nitrone **12** with DEAC at −20 °C in CD_2Cl_2.[12a] Under those conditions the signal corresponding to the azomethine proton shifted downfield by 1.1 ppm appearing as a

broad singlet. On the other hand, when a 0.2 M solution of **13** in [D_8]THF was treated with 1.0 equiv of DEAC at −78 °C (Figure 5, trace e) a new set of significantly broadened signals appeared centered at $\delta = 8.0$ ppm. The fluxionality of the nitrone–Al complex could not be "frozen out"

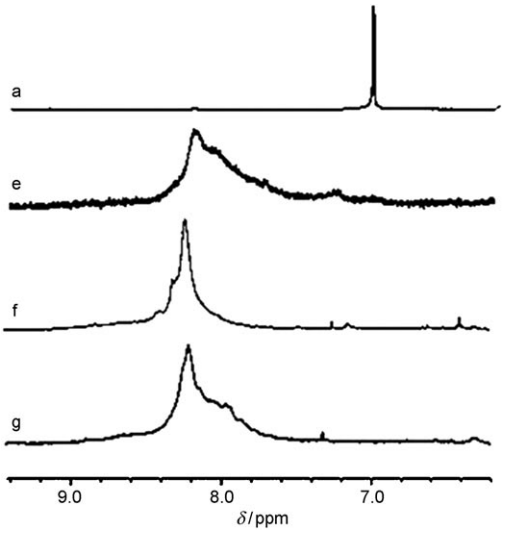


Figure 5. Partial NMR spectra of nitrone **13** complexes with DEAC (see text for explanation of traces a and e–g).

even at −78 °C. At this temperature a lower energy conformational equilibrium is indicated by the broadening of the signal. Warming the mixture to −50 °C (Figure 5, trace f) and further recooling to −78 °C (Figure 5, trace g) confirmed the above picture.

The fluxional behavior of DEAC observed in the spectrum of the nitrone complex appeared to be in agreement with the formation of a tetracoordinate Al complex. Inter- and intramolecular dynamic processes are very likely to be the cause of the observed line broadening, based on the well-known slow dynamics of aluminum complexes involving O–Al bonds.[26] The addition of 1.0 equiv of DEAC to a solution of the nitrone previously treated with VMB had no effect at any temperature thus demonstrating that upon coordination with magnesium the nitrone oxygen is not capable of coordinating aluminum. This result is in full agreement with the experimentally observed selectivity under those conditions (Table 2, entry 13).

We finally examined the influence of the addition of VMB to a solution of nitrone previously treated with 1.0 eqiuv of DEAC. On addition of 1.0 equiv of VMB (Figure 6, trace h) the signals become more complex being centered at $\delta = 8.0$ ppm. These signals collapsed, but did not shift, when the temperature was increased to −50 °C (Figure 6, trace i) and reappear when the mixture was cooled again to −78 °C (Figure 6, trace j).

Also in this case the resonance around $\delta = 8.0$ ppm decreased with time as the reaction progressed. On the whole, these data can be interpreted within the hypothesis that important conformational equilibria take place at low temperature. In [D_8]THF solution the aluminum complexes displayed fluxional behavior, with at least two processes, one with $-50\,^{\circ}C < T_c < 0\,^{\circ}C$, the other slow around −78 °C.

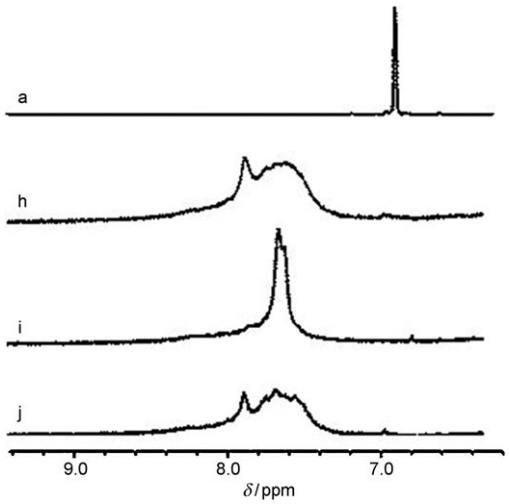


Figure 6. Partial NMR spectra of nitrone **13** complexes with DEAC and VMB (see text for explanation of traces a and h–j).

Conclusion

In summary, we have demonstrated the crucial role exerted in the vinylation of cyclic nitrones by both the precomplexing agent and the size of the substituent at C3 by testing several protected 3-hydroxy pyrrolidine *N*-oxides. Our results confirm those found by Trombini for nitrone **11** and expand the behavior to other nitrones. In the reactions carried out in the presence of DEAC the 2,3-*cis*/*trans* selectivity is determined by the arrangement of both aluminum and magnesium species around the N–O bond as well as by the size of the alkoxy group at C3. Experimental and spectroscopic studies support the hypothesis that the conformational energy barrier between complexes formed with DEAC and VMB is close to the energy barrier corresponding to the nucleophilic addition reaction. Given the conformational fluxionality of the complexes at low temperature, these findings suggest that bulky aluminum complexes of nitrones that have small alkoxy groups at C3 should lead preferentially to 2,3-*cis* adducts in contrast to nitrones that have bulky alkoxy groups at that position, which should lead to the corresponding 2,3-*trans* isomers. This finding has straightforward implications on the possibility of designing hitherto unknown stereocontrolled nucleophilic additions of different nucleophiles to other biased rigid systems. Indeed, we have recently observed a similar behavior for the addition of other Grignard reagents including phenylmagnesium bromide and methylmagnesium bromide thus demonstrating the generality of the observations described herein. Further studies are ongoing with these nucleophiles en route to biologically important compounds and they will be reported in due course.

Experimental Section

General procedure for the addition of vinylmagnesium bromide to nitrones

Without Lewis acid: A solution of nitrone (0.1 mmol) in anhydrous diethyl ether (5 mL) was cooled to the stated temperature (see Table 1) and a solution of vinylmagnesium bromide (0.11 mL of a 1 M solution in THF, 0.11 mmol) was added dropwise. Stirring was maintained for the stated time (see Table 1) and the reaction was quenched by addition of saturated aqueous ammonium chloride (5 mL). The reaction mixture was extracted with diethyl ether (3×10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product, which was analyzed by ^{1}H NMR spectroscopy for determining the diastereoselectivity and purified by radial chromatography (hexane/EtOAc, 4:1).

With diethylaluminum chloride: A solution of nitrone (0.1 mmol) in anhydrous diethyl ether (5 mL) was cooled to the stated temperature (see Table 2) and a solution of diethylaluminum chloride (0.1 mL of a 1 M solution in hexanes, 0.1 mmol) was added dropwise. After stirring for 5 min a solution of vinylmagnesium bromide (0.11 mL of a 1 M solution in THF, 0.11 mmol) was added dropwise. Stirring was maintained for the stated time (see Table 2) and the reaction was quenched by addition of saturated aqueous ammonium chloride (5 mL). The reaction mixture was extracted with diethyl ether (3×10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product, which was analyzed by ^{1}H NMR for determining the diastereoselectivity and purified by radial chromatography (hexane/EtOAc, 4:1).

Spectroscopic data

*(2R,3S)-3-tert-Butoxy-2-vinylpyrrolidin-1-ol (**19a**)*: Oil; $[\alpha]_D^{24}=+13$ ($c=1.00$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=0.93$ (s, 9H; C(CH_3)$_3$), 1.62–1.74 (m, 1H; H_{4a}), 1.99–2.10 (m, 1H; H_{4b}), 2.88 (q, $J=9.9$ Hz, 1H; H_{5a}), 2.98 (t, $J=8$ Hz, 1H; H_2), 3.12 (ddd, $J=9.9$, 8.5, 8.0 Hz, 1H; H_{5b}), 3.62–3.70 (m, 1H; H_3), 5.09 (dd, $J=10.1$, 1.8 Hz, 1H; CH=CHH_{cis}), 5.19 (dd, $J=17.2$, 1.8 Hz, 1H; CH=CHH_{trans}), 5.73 ppm (ddd, $J=17.2$, 11.1, 8.5 Hz, 1H; CH=CH$_2$); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=28.4$ (C(CH_3)$_3$), 31.2 (C_4), 56.2 (C_5), 60.2 (C(CH_3)$_3$), 73.4 (C_2), 77.2 (C_3), 118.7 (CH=CH_2), 136.6 ppm (CH=CH$_2$); elemental analysis calcd (%) for $C_{10}H_{19}NO_2$: C 64.83, H 10.34, N 7.56; found: C 64.92, H 10.51, N 7.38.

*(2R,3S)-3-(Methoxymethoxy)-2-vinylpyrrolidin-1-ol (**20a**)*: Oil; $[\alpha]_D^{24}=+4$ ($c=1.1$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.83$ (dddd, $J=13.6$, 8.7, 3.1, 2.6 Hz, 1H; H_{4a}), 2.06–2.17 (m, 1H; H_{4b}), 3.04 (c, $J=9.8$ Hz, 1H; H_{5a}), 3.25–3.31 (m, 2H; H_2, H_{5b}), 3.34 (s, 3H, OCH$_2$OCH_3), 3.92–3.99 (m, 1H; H_3), 4.61 (d, $J=6.8$ Hz, 1H; OCH_2OCH$_3$), 4.64 (d, $J=6.8$ Hz, 1H; OCH_2OCH$_3$), 5.25 (ddd, $J=10.3$, 1.7, 0.8 Hz, 1H; CH=CHH_{trans}), 5.37 (ddd, $J=17.2$, 1.7, 1.0 Hz, 1H; CH=CHH_{cis}), 5.90 ppm (ddd, $J=17.2$, 10.3, 7.8 Hz, 1H; CH=CH$_2$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=28.5$ (C_4), 55.4 (OCH$_2$OCH_3), 56.0 (C_5), 76.7 (C_2), 78.4 (C_3), 95.5 (OCH_2OCH$_3$), 118.9 (CH=CH_2), 136.7 ppm (CH=CH$_2$); elemental analysis calcd (%) for $C_8H_{15}NO_3$: C 55.47, H 8.73, N 8.09; found: C 55.27, H 8.51, N 8.18.

*(2S,3S)-3-(Methoxymethoxy)-2-vinylpyrrolidin-1-ol (**20b**)*: Oil; $[\alpha]_D^{24}=-55$ ($c=0.15$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.83$ (dddd, $J=13.7$, 9.0, 8.8, 3.0 Hz, 1H; H_{4a}), 2.26 (dddd, $J=13.7$, 9.4, 7.7, 2.9 Hz, 1H; H_{4b}), 2.72 (c, $J=9.5$ Hz, 1H; H_{5a}), 3.17 (dd, $J=8.3$, 6.0 Hz, 1H; H_2), 3.31 (s, 3H; OCH$_2$OCH_3), 3.44 (ddd, $J=9.9$, 8.8, 3.0 Hz, 1H; H_{5b}), 4.20 (ddd, $J=7.7$, 6.0, 3.0 Hz, 1H; H_3), 4.54 (d, $J=6.8$ Hz, 1H; OCH_2OCH$_3$), 4.59 (d, $J=6.8$ Hz, 1H; OCH_2OCH$_3$), 5.29 (ddd, $J=10.3$, 1.9, 0.5 Hz, 1H; CH=CHH_{trans}), 5.33 (ddd, $J=17.4$, 1.9, 0.7 Hz, 1H; CH=CHH_{cis}), 6.02 ppm (ddd, $J=17.4$, 10.3, 8.4 Hz, 1H; CH=CH$_2$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=29.2$ (C_4), 55.4 (OCH$_2$OCH_3), 55.4 (C_5), 75.3 (C_2), 75.3 (C_3), 95.2 (OCH_2OCH$_3$), 119.5 (CH=CH_2), 134.5 ppm (CH=CH$_2$); elemental analysis calcd (%) for $C_8H_{15}NO_3$: C 55.47, H 8.73, N 8.09; found: C 55.63, H 8.49, N 8.25.

*(2R,3S)-3-(Benzyloxy)-2-vinylpyrrolidin-1-ol (**21a**)*: Oil; $[\alpha]_D^{24}=+9$ ($c=0.23$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=1.90$ (tdd, 1H, $J=13.5$, 8.5, 2.9 Hz, 1H; H_{4a}), 2.01–2.15 (m, 1H; H_{4b}), 3.09 (dt, $J=9.9$, 8.5 Hz, 1H; H_{5a}), 3.28 (ddd, $J=10.2$, 7.8, 2.7 Hz, 1H; H_{5b}), 3.41 (dd, $J=6.9$, 6.3 Hz, 1H; H_2), 3.85 (ddd, $J=8.1$, 5.8, 3.3 Hz, 1H; H_3), 4.53 (s, 2H; CH_2Ph), 5.25 (ddd, $J=10.4$, 1.6, 0.9 Hz, 1H; CH=CHH_{cis}), 5.38 (ddd, $J=17.2$, 1.6, 1.1 Hz, 1H; CH=CHH_{trans}), 5.93 (ddd, $J=17.6$, 10.4, 7.4 Hz, 1H; CH=CH$_2$), 7.22–7.39 ppm (m, 5H; Ar); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=28.3$ (C_4), 55.9 (C_5), 76.9 (C_2), 71.4 (CH_2Ph) 80.8 (C_3), 118.8 (CH=CH_2), 127.6 (Ar), 127.7 (Ar), 128.4 (Ar), 136.7 (CH=CH$_2$), 138.0 ppm (Ar); elemental analysis calcd (%) for $C_{13}H_{17}NO_2$: C 71.21, H 7.81, N 6.39; found: C 71.38, H 8.01, N 6.16.

*(2R,3S)-3-(Benzyloxy)-2-vinylpyrrolidin-1-ol (**21b**)*: Oil; $[\alpha]_D^{24}=-21$ ($c=0.85$; $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=1.82$–1.96 (m, 1H; H_{4a}), 2.16–2.29 (m, 1H; H_{4b}), 2.74 (c, $J=9.9$ Hz, 1H; H_{5a}), 3.22 (dd, $J=8.6$, 6.3 Hz, 1H; H_2), 3.44 (ddd, $J=9.9$, 8.8, 3.0 Hz, 1H; H_{5b}), 3.79–3.87 (m, 1H; H_3), 4.47 (d, $J=12.3$ Hz, 1H; CH_2Ph), 4.52 (d, $J=12.3$ Hz, 1H; CH_2Ph), 5.32 (ddd, $J=10.2$, 1.9, 0.6 Hz, 1H; CH=CHH_{trans}), 5.33 (ddd, $J=17.3$, 1.9, 0.6 Hz, 1H; CH=CHH_{cis}), 5.36 (ddd, $J=17.3$, 10.2, 8.6 Hz, 1H; CH=CH$_2$), 7.24–7.37 ppm (m, 5H; Ar); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=29.0$ (C_4), 55.4 (C_5), 71.3 (CH_2Ph), 75.5 (C_2), 78.1 (C_3), 119.6 (CH=CH_2), 127.4 (Ar), 127.7 (Ar), 128.3 (Ar), 134.4 (CH=CH$_2$), 138.3 ppm (Ar); elemental analysis calcd (%) for $C_{13}H_{17}NO_2$: C 71.21, H 7.81, N 6.39; found: C 71.44, H 7.62, N 6.96.

*(2R,3S)-3-Methoxy-2-vinylpyrrolidin-1-ol (**22a**) and (2R,3S)-3-methoxy-2-vinylpyrrolidin-1-ol (**22b**)*: Isomers **22a** and **22b** could not be separated by chromatographic techniques. The corresponding NMR signals for each isomer were identified by carrying out selective TOCSY experiments. **22a**: ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=1.83$ (ddt, 1H, $J=13.6$, 8.4, 2.6 Hz, 1H; H_{4a}), 2.00–2.11 (m, 1H; H_{4b}), 3.03 (c, $J=9.8$ Hz, 1H; H_{5a}), 3.24–3.29 (m, 2H, H_2; H_{5b}), 3.32 (s, 3H; OCH_3), 3.60–3.66 (m, 1H; H_3), 5.24–5.28 (m, 1H; CH=CHH_{cis}), 5.35–5.40 (m, 1H; CH=CHH_{trans}), 5.92 ppm (ddd, $J=17.7$, 10.2, 7.9 Hz, 1H; CH=CH$_2$); 13C NMR (125 MHz, $CDCl_3$): $\delta=27.8$ (C_4), 56.0 (C_5), 57.2 (OCH_3), 76.9 (C_2), 83.1 (C_3), 118.8 (CH=CH_2), 136.7 ppm (CH=CH$_2$). **22b**: ^{1}H RMN (500 MHz, $CDCl_3$): $\delta=1.85$ (dddd, $J=13.4$, 9.3, 8.6, 3.2 Hz, 1H; H_{4a}), 2.23 (dddd, $J=13.7$, 9.0, 7.6, 2.9 Hz,, 1H; H_{4b}), 2.75 (c, $J=9.5$ Hz, 1H; H_{5a}), 3.20 (dd, $J=8.3$, 6.3 Hz, 1H; H_2), 3.29 (s, 3H; OCH_3), 3.44 (ddd, $J=9.7$, 8.5, 2.8 Hz, 1H; H_{5b}), 3.83 (ddd, $J=7.5$, 6.2, 3.5 Hz, 1H; H_3), 5.33 (ddd, $J=10.3$, 1.9, 0.5 Hz, 1H; CH=CHH_{trans}), 5.36 (ddd, $J=17.3$, 1.9, 0.8 Hz, 1H; CH=CHH_{cis}), 6.03 ppm (ddd, $J=17.4$, 10.2, 8.6 Hz, 1H; CH=CH$_2$); ^{13}C RMN (125 MHz, $CDCl_3$): $\delta=28.4$ (C_4), 55.4 (C_5), 57.2 (OCH_3), 75.4 (C_2), 80.5 (C_3), 119.4 (CH=CH_2), 134.3 ppm (CH=CH$_2$).

*(2R,3R,4R)-3,4-Di-tert-butoxy-2-vinylpyrrolidin-1-ol (**23a**)*: White solid; mp: 66–68 °C; $[\alpha]_D^{24}=-82$ ($c=1.02$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=1.08$ (s, 9H; C(CH_3)$_3$), 1.10 (s, 9H; C(CH_3)$_3$), 2.92–3.01 (m, 2H; H_{5a}+H_{5b}), 3.15 (dd, $J=10.7$, 2.6 Hz, 1H; H_2), 3.61 (dd, $J=7.4$, 3.7 Hz, 1H; H_3), 3.84 (pseudo q, $J=3.4$ Hz, 1H; H_4), 5.15 (dd, $J=10.3$, 1.8 Hz, 1H; CH=CHH_{cis}), 5.23 (dd, $J=17.3$, 1.8 Hz, 1H; CH=CHH_{trans}), 5.76 ppm (ddd, $J=17.3$, 10.3, 8.8 Hz, 1H; CH=CH$_2$); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=28.5$ (C(CH_3)$_3$), 29.2 (C(CH_3)$_3$), 63.9 (C_4), 73.7 (C_5), 74.1(C(CH_3)$_3$), 75.6 (C(CH_3)$_3$), 76.5 (C_2), 81.0 (C_3), 119.2 (CH=CH_2), 137.2 ppm (CH=CH$_2$); elemental analysis calcd (%) for $C_{14}H_{27}NO_3$: C 65.33, H, 10.57,N 5.44; found: C 65.48, H 10.32, N 5.63.

*(2R,3R,4R,5R)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-5-vinylpyrrolidin-1-ol (**24a**)*: Oil; $[\alpha]_D^{27}=-198$ ($c=0.48$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=3.56$ (dt, $J=6.4$, 4.7 Hz, 1H; H_2), 3.68 (dd, $J=9.6$, 6.4 Hz, 1H; CH_2OBn), 3.80 (dd, $J=9.7$, 4.9 Hz, 1H; CH_2OBn), 3.84 (dd, $J=8.3$, 5.4 Hz, 1H; H_5), 3.94 (dd $J=5.3$, 3.0 Hz, 1H; H_4), 4.01 (dd, $J=4.1$, 3.2 Hz, 1H; H_3), 4.50 (d, $J=11.9$ Hz, 2H; CH_2Ph), 4.55 (d, $J=6.4$ Hz, 1H; CH_2Ph), 4.57 (d, $J=6.4$ Hz, 1H; CH_2Ph), 4.59 (d, $J=11.4$ Hz, 2H; CH_2Ph), 5.31 (ddd, JJ=10.2, 1.5, 0.6 Hz, 1H; CH=CHH_{trans}), 5.36 (ddd, $J=17.2$, 1.5, 1.0 Hz, 1H; CH=CHH_{cis}), 6.07 (ddd, $J=17.2$, 10.2, 8.3 Hz, 1H; CH=CH$_2$), 7.28–7.39 ppm (m, 15H; Ar); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=67.9$ (CH_2OBn), 69.6 (C_2), 71.7 (CH_2Ph), 71,9 (CH_2Ph), 72.9 (C_5), 73.4 (CH_2Ph), 83.8 (C_3), 86.1 (C_4), 119.3 (CH=CH_2), 127.6 (Ar), 127.7 (Ar), 127.7 (Ar), 127.8 (Ar), 127.9 (Ar), 128.0 (Ar), 128.4 (Ar), 128.4 (Ar), 128.4 (Ar), 135.5 (CH=CH$_2$), 137.9 (Ar), 138.0 (Ar), 138.2 ppm (Ar); elemental analysis calcd (%) for $C_{28}H_{31}NO_4$: C 75.48, H 7.01, N 3.14; found: C 75.26, H 7.18, N 3.06.

*(2R,3R,4R,5R)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-5-vinylpyrrolidin-1-ol (**24b**)*: Oil; $[\alpha]_D^{27}=-340$ ($c=0.48$, $CHCl_3$); ^{1}H NMR (500 MHz,

$CDCl_3$): $\delta = 3.14$ (c, $J = 5.4$ Hz, 1H; H_2), 3.59 (dd, $J = 8.6$, 5.6 Hz, 1H; H_5), 3.71 (dd, $J = 9.8$, 5.6 Hz, 1H; CH_2OBn), 3.75 (dd, $J = 9.8$, 5.3 Hz, 1H; CH_2OBn), 3.83 (dd, $J = 5.3$, 1.0 Hz, 1H; H_3), 3.89 (dd, $J = 5.6$, 0.9 Hz, 1H; H_4), 4.45 (d, $J = 11.9$ Hz, 1H; CH_2Ph), 4.48 (d, $J = 11.9$ Hz, 1H; CH_2Ph), 4.49 (d, $J = 12.1$ Hz, 1H; CH_2Ph), 4.53 (d, $J = 12.1$ Hz, 1H; CH_2Ph), 4.58 (d, $J = 12.0$ Hz, 1H; CH_2Ph), 4.61 (d, $J = 12.0$ Hz, 1H; CH_2Ph), 5.35 (dd, $J = 10.3$, 1.8 Hz, 1H; CH=CHH_{trans}), 5.42 (dd, $J = 17.4$, 1.7 Hz, 1H; CH=CHH_{cis}), 6.16 (ddd, $J = 17.3$, 10.2, 8.6 Hz, 1H; CH=CH_2), 7.25–7.38 ppm (m, 15H; Ar); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta =$ 69.9 (CH_2OBn), 71.5 (CH_2Ph), 72.0 (CH_2Ph), 72.1 (C_2), 73.3 (CH_2Ph), 73.9 (C_5), 82.2 (C_3), 82.5 (C_4), 120.0 (CH=CH_2), 127.7 (Ar), 127.7 (Ar), 127.8 (Ar), 127.9 (Ar), 128.4 (Ar), 128.4 (Ar), 134.3 (CH=CH$_2$), 137.9 (Ar), 137.9 (Ar), 138.2 ppm (Ar); elemental analysis calcd (%) for $C_{28}H_{31}NO_4$: C 75.48, H 7.01, N 3.14; found: C 75.69, H 7.18, N, 3.22.

Acknowledgements

We thank the Spanish Ministry of Science and Education (MEC. Madrid, Spain. Project CTQ2007-67532-C02-01), FEDER Program and the Government of Aragon (Zaragoza, Spain), and MiUR (Italy) for their support of our programs. One of us (E.M.) also thanks the Spanish Ministry of Science and Innovation (MICINN, Madrid, Spain) for a pre-doctoral grant (FPU program).

[1] A. Mengel, O. Reiser, *Chem. Rev.* **1999**, *99*, 1191–1224.
[2] a) *Iminosugars: From Synthesis to Therapeutic Applications* (Eds.: P. Compain, O. R. Martin), Wiley, New York, **2007**; b) *Iminosugars as Glycosidase Inhibitors: Nojirimycin and Beyond* (Ed.: A. Stütz), Wiley-VCH, Weinheim, **1998**.
[3] a) N. Asano, *Glycobiology* **2003**, *13*, 93R–104R; b) N. Asano, R. J. Nash, R. J. Molyneux, G. W. J. Fleet, *Tetrahedron: Asymmetry* **2000**, *11*, 1645–1680; c) Y. Nishimura, *Curr. Top. Med. Chem.* **2003**, *3*, 575–591; d) A. A. Watson, G. W. J. Fleet, N. Asano, R. J. Molyneux, R. J. Nash, *Phytochemistry* **2001**, *56*, 265.
[4] V. L. Schramm, *Nucleosides Nucleotides Nucleic Acids* **2004**, *23*, 1305–1311.
[5] V. L. Schramm, *Biochim. Biophys. Acta Mol. Basis Dis.* **2002**, *1587*, 107–117.
[6] For reviews, see: a) P. Merino, T. Tejero, I. Delso, *Curr. Med. Chem.* **2008**, *15*, 954–967; b) G. Romeo, A. Corsaro, U. Chiacchio. P. Merino *Chem. Rev.* **2010**, *110*, 3337–3370.
[7] a) J. Revuelta, S. Cicchi, A. Goti, A. Brandi, *Synthesis* **2007**, 485–504; b) P. Merino, *Nitrones and Cyclic Analogues in Science of Synthesis, Vol. 27* (Ed.: Padwa), Thieme, New York, **2004**, pp. 511–580.
[8] a) M. Marradi, S. Cicchi, I. Delso, L. Rosi, T. Tejero, P. Merino, A. Goti, *Tetrahedron Lett.* **2005**, *46*, 1287–1290; b) P. Merino, I. Delso, T. Tejero, F. Cardona, A. Goti, *Synlett* **2007**, 2651–2654.
[9] a) I. Delso, T. Tejero, A. Goti, P. Merino, *Tetrahedron* **2010**, *66*, 1220–1227; b) P. Merino, I. Delso, T. Tejero, F. Cardona, M. Marradi, E. Faggi, C. Parmeggiani, A. Goti, *Eur. J. Org. Chem.* **2008**, 2929–2947; c) A. Goti, S. Cicchi, V. Mannucci, F. Cardona, F. Guarna, P. Merino, T. Tejero, *Org. Lett.* **2003**, *5*, 4235–4238.
[10] See, for example: a) A. Dondoni, F. Junquera, F. Merchan, P. Merino, T. Tejero, *Tetrahedron Lett.* **1992**, *33*, 4221; b) A. Dondoni, S. Franco, F. Merchan, P. Merino, T. Tejero, *Synlett* **1993**, 78–80; c) P. Merino, E. Castillo, F. L. Merchan, T. Tejero, *Tetrahedron: Asymmetry* **1997**, *8*, 1725–1729; d) P. Merino, E. M. delAlamo, S. Franco, F. L. Merchan, A. Simon, T. Tejero, *Tetrahedron: Asymmetry* **2000**, *11*, 1543–1554. For an account, see: P. Merino, S. Franco, F. L. Merchan, T. Tejero, *Synlett* **2000**, 442–454.
[11] a) P. Merino, A. Lanaspa, F. L. Merchan, T. Tejero, *Tetrahedron: Asymmetry* **1998**, *9*, 629–646; b) P. Merino, A. Lanaspa, F. L. Merchan, T. Tejero, *Tetrahedron Lett.* **1997**, *38*, 1813–1816.
[12] a) P. Merino, T. Tejero, J. Revuelta, P. Romero, S. Cicchi, V. Mannucci, A. Brandi, A. Goti, *Tetrahedron: Asymmetry* **2003**, *14*, 367–379; b) P. Merino, J. Revuelta, T. Tejero, S. Cicchi, A. Goti, *Eur. J. Org. Chem.* **2004**, 776–782.
[13] a) M. Lombardo, S. Fabbroni, C. Trombini, *J. Org. Chem.* **2001**, *66*, 1264–1268. For a more recent example of vinylation of nitrones directed to the synthesis of (+)-lentiginosine, see: b) F. Cardona, G. Moreno, F. Guarna, P. Vogel, C. Schuetz, P. Merino, A. Goti, *J. Org. Chem.* **2005**, *70*, 6552–6555.
[14] The stereocontrolled vinylation of acyclic (*Z*)-nitrones has also been previously studied in our laboratories, see: a) P. Merino, S. Anoro, S. Franco, J. M. Gascon, V. Martin, J. Revuelta, T. Tejero, V. Tuñon, *Synth. Commun.* **2000**, *30*, 2989–3021; b) P. Merino, S. Anoro, E. Castillo, F. Merchan, T. Tejero, *Tetrahedron: Asymmetry* **1996**, *7*, 1887–1890.
[15] a) S. Cicchi, A. Goti, A. Brandi, *J. Org. Chem.* **1995**, *60*, 4743–4748; b) R. Saladino, V. Neri, F. Cardona, A. Goti, *Adv. Synth. Catal.* **2004**, *346*, 639–647; c) P. Merino, T. Tejero, J. Revuelta, P. Romero, S. Cicchi, V. Mannucci, A. Brandi, A. Goti, *Tetrahedron: Asymmetry* **2003**, *14*, 367–379; d) S.-F. Wu, X. Zheng, Y.-P. Ruan, P.-Q. Huang, *Org. Biomol. Chem.* **2009**, *7*, 2967–2975.
[16] S. Cicchi, I. Hold, A. Brandi, *J. Org. Chem.* **1993**, *58*, 5274–5275.
[17] a) F. Cardona, E. Faggi, F. Liguori, M. Cacciarini, A. Goti, *Tetrahedron Lett.* **2003**, *44*, 2315–2318; b) A. T. Carmona, R. H. Wightman, I. Robina, P. Vogel, *Helv. Chim. Acta* **2003**, *86*, 3066–3073; c) S. Desvergnes, S. Py, Y. Vallee, *J. Org. Chem.* **2005**, *70*, 1459–1462.
[18] H. Schumann, J. Kaufmann, S. Dechert, H.-G. Schmalz, J. Velder, *Tetrahedron Lett.* **2001**, *42*, 5405–5408.
[19] We had already observed a low reactivity for other organoaluminum reagents towards nitrones, see: P. Merino, S. Franco, N. Garces, F. L. Merchan, T. Tejero, *Chem. Commun.* **1998**, 493–494.
[20] B. Bartocha, A. J. Bilbo, D. E. Bublitz, M. Y. Gray, *Z. Naturforsch. B* **1961**, *16*, 357–361.
[21] It has been reported that alkyl transfer is competitive with vinyl transfer when dialkylvinyl aluminum is used as nucleophile, see: A. P. Allwein, J. M. Cox, B. E. Howard, H. W: B. Johnson, J. D. Rainier, *Tetrahedron* **2002**, *58*, 1997–2009.
[22] For the first computational study on Grignard additions to nitrones, see: P. Merino, T. Tejero, *Tetrahedron* **2001**, *57*, 8125–8128.
[23] All critical points were fully optimized by analytical gradient method by using Gaussian 03 Revision E.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, J. A. Pople, Gaussian, Inc., Wallingford CT, **2004**. For further details see the Supporting Information.
[24] Semiempirical conformational calculations were carried out at the PM3 level as implemented in the Gaussian 03 Rev E.01 package of programs (see Ref. [23]). This level is judged sufficient for considering steric and stereoelectronic factors governing the conformational properties of the studied complexes. The conformational analysis was carried out by rotating the N–O bond in one degree steps. A total of 360 conformations were fully optimized. For details see the Supporting Information.
[25] For the structure of Grignard compounds in solution, see: a) G. N. Khairallah, C. Thum, R. A. J. O'Hair, *Organometallics* **2009**, *28*, 5002–5011; b) T. Mori, S. Kato, *J. Phys. Chem. A* **2009**, *113*, 6158–6165.

[26] For an example, see: A. Tarazona, E. Kogin, F. Buda, B. B. Coussens, J. Renkema, S. van Heel, R. J. Meier, *J. Phys. Chem. B* **1997**, *101*, 4370–4378.
[27] Organometallic compounds containing pentacoordinated aluminum have been described and characterized by X-ray crystallography. See for instance Ref. [18]. For a recent reference, see: N. C. Johnstone, E. A. Aazam, P. B. Hitchcock, J. R. Fulton, *J. Organomet. Chem.* **2010**, *695*, 170–176.
[28] Because the conformational barriers have been calculated at a semiempirical level, they should be considered somewhat overestimated with respect to those calculated for the reaction at a DFT level. In any case, the values remain within the same order of magnitude.
[29] The NMR spectra were obtained on Bruker Avance 500 by using a 5 mm BB-^{1}H/^{13}C dual probe. The spectra were recorded as solutions in [D_8]THF by using commercial solutions of VMB and DEAC and at temperatures varying from 0 to −78 °C. NMR spectra were recorded by using standard procedures.
[30] A. Bodor, I. Banyai, L. Zekany, I. Toth, *Coord. Chem. Rev.* **2002**, *228*, 163–173.

Received: June 8, 2010
Published online: August 4, 2010

