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The Use of a Single Derivative in the Configurational Assignment of Ketone Cyanohydrins

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Keywords: Chirality / Configuration determination / Cyanohydrins / Methoxyphenylacetic acid / NMR spectroscopy

The absolute stereochemistry of ketone cyanohydrins can be easily determined by preparing a single MPA derivative. The comparison of two NMR spectra at different temperatures allows the assignment by just paying attention to the evolution of the cyanohydrin chemical shifts. The special case of α-aryl-substituted cyanohydrins is also described.

Introduction

The NMR methods[1] for assigning the absolute configuration of organic compounds based on the preparation of two derivatives of a chiral auxiliary reagent have proved to be suitable procedures for this purpose. Moreover, the use of a single derivative allows to save time, sample, reagents, and to minimize purification steps.[1] Recently, methods for the assignment of difunctional compounds (diols and amino alcohols)[2] were developed, and the use of resin-bound auxiliaries allows to save even more amount of sample and time.[3]

In previous reports, the assignment of the absolute configuration of optically active aldehyde[4] and ketone[5] cyanohydrins were described. In order to determine the absolute configuration of cyanohydrins, the preparation of diastereomeric esters by using both enantiomers of 2-methoxy-2-phenylacetic acid (MPA) as chiral derivatizing agent (CDA) is required.

Here we present a single derivatization procedure for the determination of the absolute configuration of ketone cyanohydrins by using only one MPA [(*R*) or (*S*)] derivative based on the differences of chemical shifts found in the ^{1}H NMR spectra performed at two different temperatures ($\Delta\delta^{T1T2}$).[6]

When energy calculations were carried out on ketone cyanohydrins, different conformational compositions were obtained for dialkyl and alkyl aryl cyanohydrins.[5] Therefore, the results on those two classes of cyanohydrins are presented separately in this communication.

Results and Discussion

Dialkyl-Substituted Cyanohydrins

The relative energies calculated[7] for the conformers of (*R*)- and (*S*)-MPA derivatives of (*S*)-2-hydroxy-2-methylhexanenitrile (**1**, taken as model compound) are shown in Figure 1.

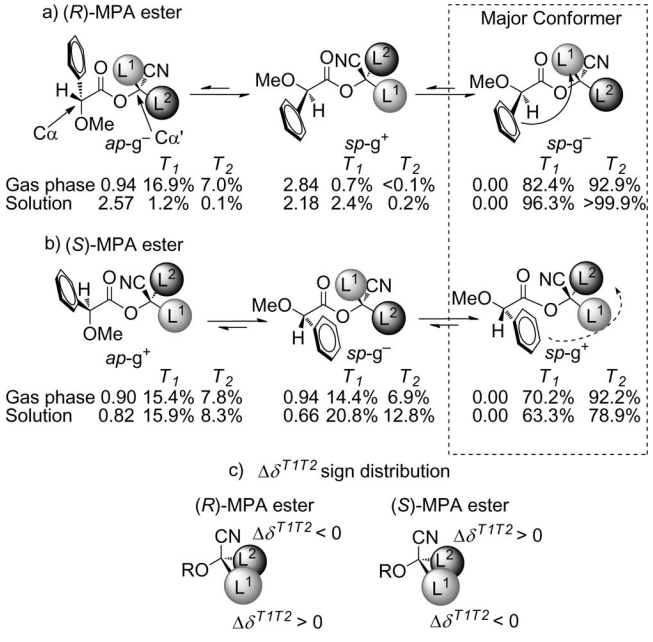

Figure 1. Main conformations for (a) (*R*)-MPA ester and (b) (*S*)-MPA ester of a typical ketone cyanohydrin. Relative energies, both in the gas phase [B3LYP/6-31+G(d); kcal/mol] and in solution [PCM, B3LYP/6-31+G(d); $CHCl_3$; free energies; kcal/mol] are shown for each conformation of the (*R*)- and (*S*)-MPA esters of (*S*)-2-hydroxy-2-methylhexanenitrile (**1**). Expected populations, based on Boltzmann distributions at 298 K (T_1) and at 183 K (T_2), are also shown, as well as the shieldings of the main conformation (curved arrows). (c) Sign distributions for L^1 and L^2 substituents.

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The most populated conformations for (*R*)- and (*S*)-MPA derivatives are *sp*-g^+ and *sp*-g^-, respectively (Figure 1). Main conformations were generated around the Cα-C(O) (MPA moiety) and O-Cα′ (cyanohydrin moiety) bonds. Rotation around the Cα–C(O) bond provided two main conformers, *sp* and *ap*, whereas rotation around O–Cα′ gave rise to another two conformers, g^+ and g^-, in which the dihedral angle formed by atoms C(O)–O–Cα′–CN is ca. +60° and –60° respectively. In the (*R*)-MPA derivative, the L^1 substituent is under the shielding cone of the phenyl group, whereas in the (*S*)-MPA derivative the substituent shielded by the phenyl ring is L^2.[8]

Lowering of the temperature of the NMR probe modifies the relative populations, increasing those of the most stable conformers [*sp*-g^- and *sp*-g^+ for the (*R*)- and (*S*)-MPA derivatives, respectively; Figure 1]. Consequently, in the (*R*)-MPA derivative, the number of molecules with L^1 shielded increases at lower temperatures. The populations of the next conformers in energy terms for the (*R*)-MPA ester – *sp*-g^+ and *ap*-g^-, where none of the substituents L^1 or L^2 are shielded – decrease after lowering of the temperature. Therefore, L^2 signals should show either no significant differences or just a slight deshielding due to the loss of population of higher energy conformations. For its part, the *sp*-g^+ conformation of the (*S*)-MPA derivative increases its population at lower temperatures. Thus, as the L^2 substituent is shielded in this conformation, its NMR signals move to higher field. The next conformers in energy terms for the (*S*)-MPA ester are *sp*-g^- and *ap*-g^+, in which none of the substituents is shielded. For this reason, a weak deshielding of L^1 is expected due to the loss of contribution of the remaining conformations.

Therefore, for a cyanohydrin derivatized with (*R*)-MPA, the chemical shift differences ($\Delta\delta^{T1T2}$)[9] are positive for L^1 and negative for L^2 (Figure 1).[10] Similar reasoning for the (*S*)-MPA derivative leads to positive $\Delta\delta^{T1T2}$ values for L^2 and negative for L^1.

In accordance with this reasoning, the NMR spectra at variable temperatures of the (*R*)-MPA ester derivative of (1*R*,2*S*,5*R*)-1-hydroxy-2-isopropyl-5-methylcyclohexanecarbonitrile (**2**; Figure 2a) show that the signals corresponding to Me (8′,9′), H(2′) and H(7′) (L^1 in the model) are more shielded at lower temperatures, whereas those of Me(10′), H(6′) and H(5′), located at the other side of the stereogenic carbon atom (L^2 in the model) are deshielded (Figure 2a).

For its part, the (*S*)-MPA ester derivative of **2** shows that H(6′) and Me(10′) become shielded at lower temperatures, whereas Me(8′,9′) and H(7′) are deshielded (Figure 2b).

This correlation between the chemical shifts and the absolute configuration holds for the series of dialkyl cyanohydrins of known absolute configuration shown in Figure 3 and can therefore be used as a tool for their configurational assignment.

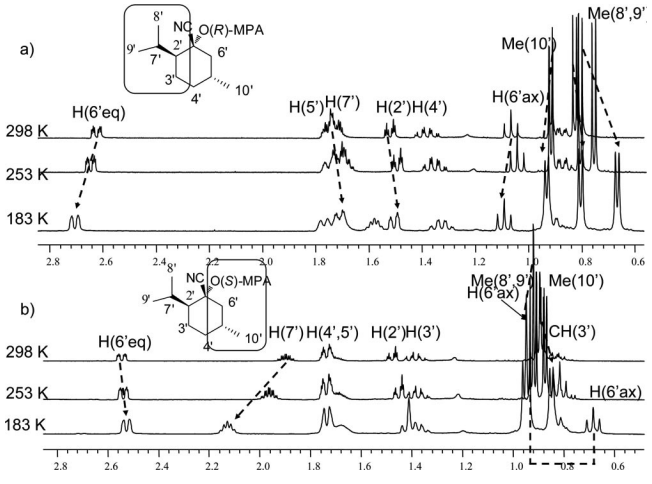


Figure 2. Partial ^{1}H NMR spectra at different temperatures of (a) (*R*)-MPA and (b) (*S*)-MPA esters of (1*R*,2*S*,5*R*)-1-hydroxy-2-isopropyl-5-methylcyclohexanecarbonitrile (**2**) (500 MHz; CS_2/CD_2Cl_2, 4:1).

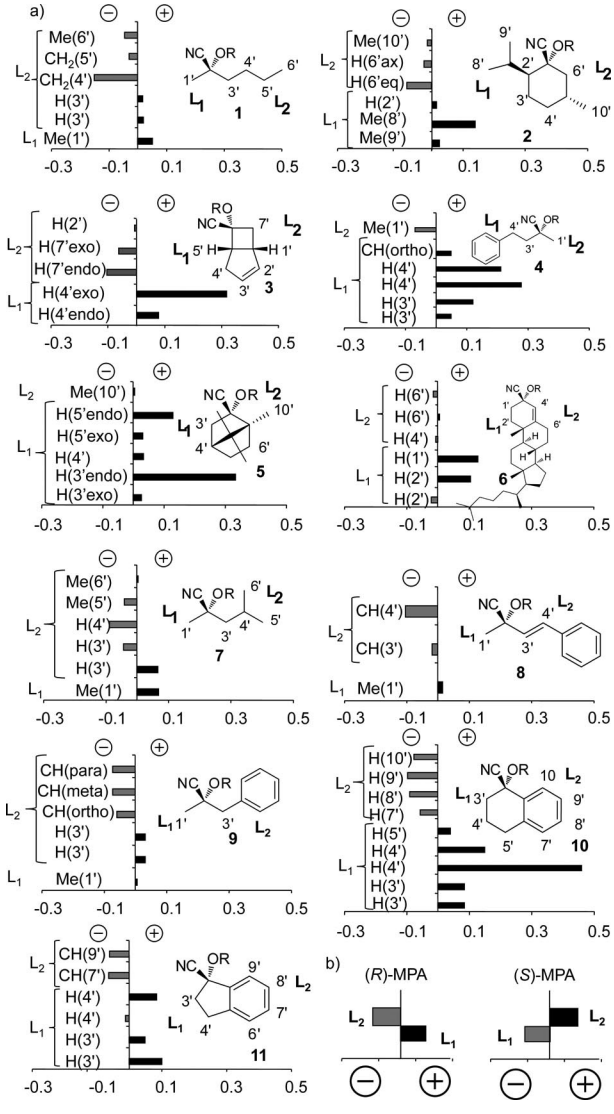


Figure 3. (a) $\Delta\delta^{T1T2}$ signs and values for (*R*)-MPA cyanohydrin derivatives, and (b) sign distributions for L^1 and L^2 substituents (T_1 = 298 K, T_2 = 183 K). $\Delta\delta^{T1T2}$ values for (*S*)-MPA derivatives are included in the Supporting Information (Figure S1).

It should be noted that in the case of acyclic cyanohydrins, one or both of the protons of the methylene group adjacent to the asymmetric carbon atom can show anomalous $\Delta\delta^{T1T2}$ signs. This is originated by the anisotropic effect of the carbonyl group that affects those diastereotopic protons.[11] As shown in Figures 3 and S1, in some cases one proton lies on the shielding zone, while the other is located at the deshielding one [i.e. $CH_2(3')$ in **7**, Figure 3; $CH_2(3')$ in **1**, Figure S1]. In other cases, both protons are affected [i.e. $CH_2(3')$ in **1**, Figure 3; $CH_2(3')$ in **4**, Figure S1].

Alkyl-Aryl-Substituted Cyanohydrins

It is known that alkyl-aryl-substituted cyanohydrins possess a different conformational composition than dialkyl-substituted ones.[5] In order to obtain more information on this phenomenon and to take into account the role of the solvent, we performed DFT calculations (PCM, B3LYP) on (*R*)- and (*S*)-MPA esters of (*S*)-2-hydroxy-2-phenylacetonitrile (**12**). The results show that for these compounds, and when the solvent is considered, the most stable conformer for both the (*R*)- and the (*S*)-MPA derivatives is *sp*-g^+ (Figure 4). Anisotropic effects from the MPA phenyl group are different in both derivatives. In the case of the (*R*)-MPA derivative, neither the Ar nor the L group are shielded by the auxiliary. The second and third more stable conformers are *sp*-g^- (Me group shielded) and *ap*-g^+ (Ar group shielded) respectively (Figure 4a). Consequently, when the temperature drops, the relative populations of the second

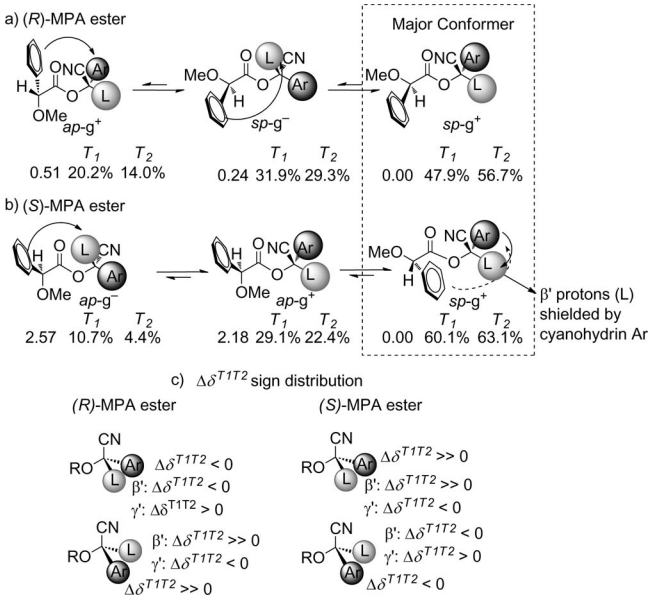


Figure 4. Main conformations for (a) (*R*)-MPA ester and (b) (*S*)-MPA ester of a typical alkyl aryl cyanohydrin. Relative free energies in solution [PCM, B3LYP/6-31+G(d); $CHCl_3$; kcal/mol] are shown for each conformation of the (*R*)- and (*S*)-MPA esters of (*S*)-2-hydroxy-2-phenylacetonitrile (**12**). Expected populations, based on Boltzmann distributions at 298 K (T_1) and at 183 K (T_2), are also shown, as well as the shieldings of the main conformation by curved arrows. (c) Sign distributions for Ar and L substituents.

(*sp*-g^-) and third (*ap*-g^+) conformer decrease, therefore a deshielding is expected for the Me and Ar groups. This is in fact observed in the ^{1}H NMR spectra of the (*R*)-MPA (*S*)-2-hydroxy-2-phenylacetonitrile derivative (**12**; Figure 5a), where all the Ar and L protons show small values and negative $\Delta\delta^{T1T2}$ signs (Figure 6).

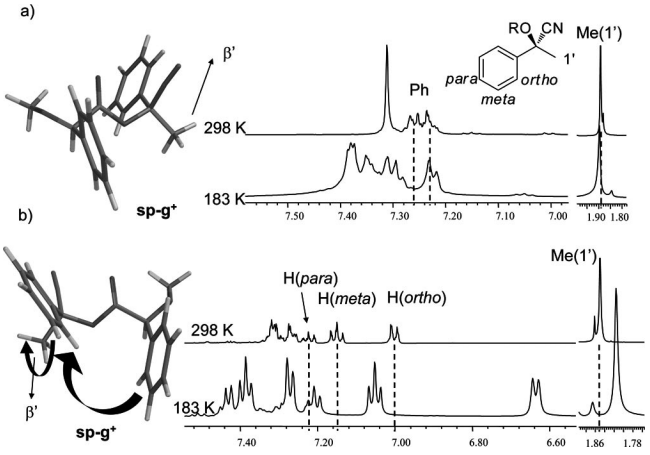


Figure 5. Partial ^{1}H NMR spectra at different temperatures of (a) (*R*)-MPA and (b) (*S*)-MPA esters of (*S*)-2-hydroxy-2-phenylacetonitrile (**12**). The structures of the most stable conformers and their shieldings are also shown (500 MHz; CS_2/CD_2Cl_2, 4:1).

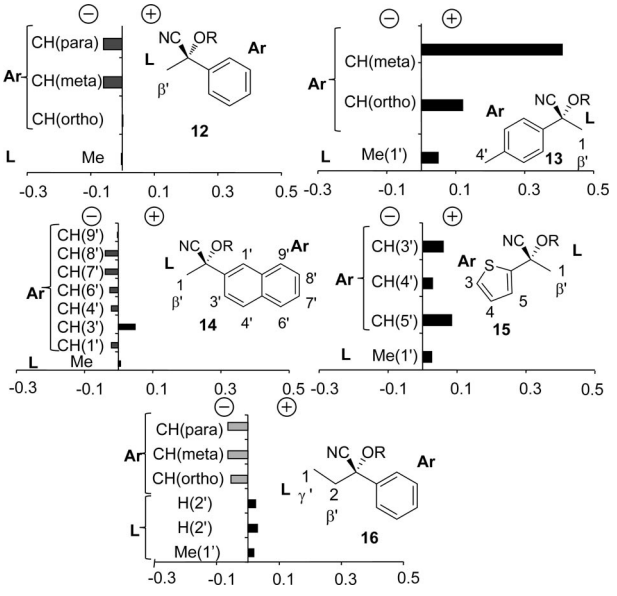


Figure 6. $\Delta\delta^{T1T2}$ signs and values for (*R*)-MPA alkyl aryl cyanohydrin derivatives (T_1 = 298 K, T_2 = 183 K).

For its part, the most stable conformer for the (*S*)-MPA derivative causes the shielding of the cyanohydrin Ar substituent by the MPA moiety (Figure 5b). This disposition enables the cyanohydrin aryl ring to shield protons belonging to the other substituent (Me, β′ protons).[5] Since this conformation increases its population after lowering the temperature, both cyanohydrin aryl and methyl substituents are more shielded at low temperatures (positive $\Delta\delta^{T1T2}$).

This additional effect does not occur on protons at further distance, such as the γ′ protons (**16**; Figure 6), that exhibit negative $\Delta\delta^{T1T2}$ values.

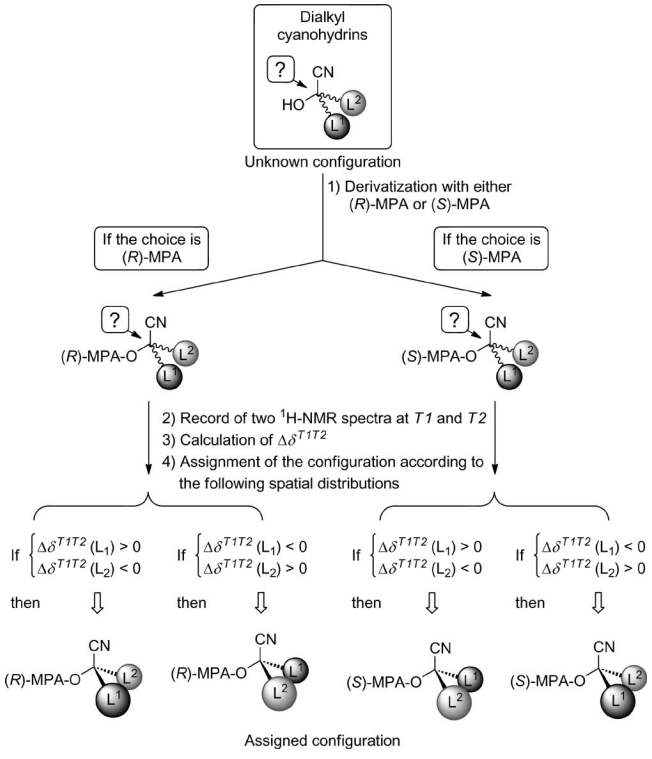
Figure 6 shows the experimental $\Delta\delta^{T1T2}$ values obtained for aryl alkyl cyanohydrins of known absolute configuration. These results allow to establish a correlation between configuration and $\Delta\delta^{T1T2}$ signs. In this way, a cyanohydrin derivatized with (*R*)-MPA presents small and negative $\Delta\delta^{T1T2}$ signs for Ar and β′ protons, and positive $\Delta\delta^{T1T2}$ signs for γ′ protons (Figure 4b). If the cyanohydrin possesses the opposite configuration, Ar and β′ protons show longer and positive $\Delta\delta^{T1T2}$ values, whereas the γ′ protons show negative values (Figure 4b). A cyanohydrin derivatized with (*S*)-MPA gives rise to opposite signs with regard to the (*R*)-MPA derivative.

Especially rigid alkyl aryl cyanohydrins (such as **10** and **11**) present a behavior similar to that of dialkyl cyanohydrins. Their particular geometry, essentially planar, imposes that in those cases some protons belonging to the cyanohydrin aryl group are hidden from the MPA shielding effect and may remain unaffected as it is observed in the (*S*)-MPA derivatives of **10** and **11** (see Figures S1 and S2), providing non diagnostic $\Delta\delta^{T1T2}$ values.

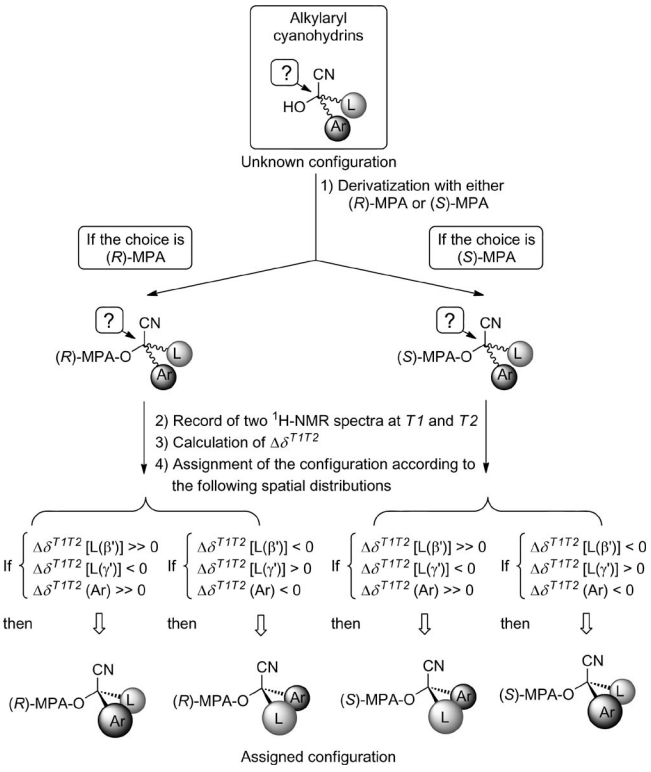
Conclusions

Comparison of the NMR spectra of just one MPA ester [either (*R*) or (*S*)] of a ketone cyanohydrin, taken at different temperatures, allows the assignment of its absolute configuration by examination of the signs of $\Delta\delta^{T1T2}$ obtained for the substituents L^1/L^2.

The methodology here presented is based on both theoretical and experimental data. Summaries of the steps to follow and how to assign the absolute configuration of dialkyl and alkyl aryl cyanohydrins can be found in Schemes 1 and 2, respectively. We have recently demonstrated that these approaches based on ^{1}H NMR spectroscopy can be complemented with ^{13}C NMR spectroscopic data.[12]



Scheme 1. Diagram to deduce the absolute configuration of a chiral dialkyl cyanohydrin from $\Delta\delta^{T1T2}$ experimental signs of either its (*R*)- or its (*S*)-MPA ester.



Scheme 2. Diagram to deduce the absolute configuration of a chiral alkyl aryl cyanohydrin from $\Delta\delta^{T1T2}$ experimental signs of either its (*R*)- or its (*S*)-MPA ester.

Experimental Section

General Esterification Procedure: The MPA esters were prepared by treatment of the compound (1.00 equiv.) with the corresponding (*R*)- or (*S*)-MPA (1.25 equiv.) in the presence of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDC·HCl, 1.25 equiv.) and cat. DMAP (20 mol-%) in dry CH_2Cl_2 and under nitrogen. The reaction mixtures were stirred overnight. Next, the organic layer was sequentially washed with water, HCl (1 M), water, $NaHCO_3$ (satd.) and water. Then, the organic layer was dried (anhydr. Na_2SO_4) and concentrated under reduced pressure to provide the corresponding esters. If needed, further purification was achieved by means of flash column chromatography (silica gel 230–400; elution with hexanes/ethyl acetate, 9:1 to 4:1; ca. 80% yields after purification). MPA racemization was never observed at any extent.

NMR Spectroscopy: Low-temperature ^{1}H NMR spectra were recorded with a 500 MHz (500.13 MHz) spectrometer. The solvent used was a mixture of CD_2Cl_2/CS_2 in a 1:4 ratio. ^{1}H chemical shifts

are internally referenced to the TMS signal (δ = 0.00 ppm). We found that temperatures in the range of 180–240 K are low enough to see the evolution of the signals when compared to spectra recorded at room temp.

Supporting Information (see footnote on the first page of this article): $\Delta\delta^{T1T2}$ values for dialkyl (Figure S1) and alkyl aryl (Figure S3) cyanohydrin (*S*)-MPA derivatives; details concerning theoretical calculations and selected NMR spectroscopic data (spectra) recorded at different temperatures.

Acknowledgments

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[7] Calculations were performed with Gaussian 03: 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, 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, and J. A. Pople, *Gaussian 03*, revision E.01; Gaussian, Inc., Wallingford, CT, **2004**.

[8] L^1 and L^2 correspond to the substituents placed spatially as shown in Figure 1 independently of their size. The steric bulk of these substituents does not determine the main conformational preferences, that are mainly controlled by the position of the CN group as shown by the calculations and the NMR experimental data.

[9] $\Delta\delta^{T1T2} = \delta(T_1) - \delta(T_2)$, where T_1 is the higher temperature (i.e. 298 K) and T_2 is the lower one (i.e. 183 K).

[10] For the (*R*)-MPA ester, the magnitudes of the $\Delta\delta^{T1T2}$ values for L^2 are smaller than for L^1. In the case of the (*S*)-MPA ester, the values for L^1 are smaller than for L^2.

[11] In secondary alcohols, the carbonyl group bisects the methylene group, and consequently both protons are affected in the same way.

[12] I. Louzao, J. M. Seco, E. Quiñoá, R. Riguera, *Chem. Commun.* **2010**, *46*, 7903–7905.

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