Enantiomeric Excesses and Electronic Chirality Measure

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Abstract: We present an approach to measure the amount of chirality in the electronic wave function and apply it to the study of a set of asymmetric aminohydroxylation reactions. The correlation coefficient between the chirality measure and the enantiomeric excesses is larger than 0.9 and suggests that this phenomenological approach can be a valuable tool to investigate and, perhaps in the future, design asymmetric synthesis.

"Chirality" comes from the ancient Greek word that means hand. And yet, if the little finger and the thumb, and the ring finger and the index were the mirror images of each other, a hand would not be chiral. Chirality is therefore removed by introducing a plane of symmetry, and, in the case of a hand, a plane of symmetry perpendicular to its palm.[1] If the introduction of a plane of symmetry, i.e., the process of dechiralization, is made in slow motion, the object goes from more chiral, to less chiral, to nonchiral, and the long-established yes/no, black/white, 0/1 picture used to describe chirality is forsaken.

The chemistry of carbon is an excellent example of the complexity of chirality. Chiral centers exist only in pyramidalized, tetravalent, sp^3-hybridized carbons and never for perfectly planar, sp^2, trivalent carbons (although molecules containing only trivalent atoms such as fullerenes can be chiral[2]). The tetravalent coordination is not sufficient to produce chirality per se and it is usually recognized that it requires the additional condition that no pair of groups attached to a carbon is identical, since they can generate a plane of symmetry. In special circumstances, however, a pair of chemically equivalent groups still produces chirality. Indeed, very recently, we showed that two phenyl groups attached to a larger molecule are locked in a chiral conformation by another part of the system.[3] In that work, the amount of chirality in three molecular fragments was measured quantitatively by an approach developed by Avnir and co-workers,[4a] called continuous chirality measure, CCM, and was compared with the experimental and the quantum chemically calculated signal that expressed chirality in the form of circular dichroic response.

The continuous chirality measure has so far been quite successful and was shown to correlate with a number of energy-related quantities such as, for instance, the binding activities of trypsin/arylammonium inhibitors, D_2-dopamine receptor/dopamine derivative agonists, trypsin/organophosphates inhibitors,

acetylcholinesterase/organophosphate, and butyrylcholinesterase/organophosphates.[4b] In the same spirit, Lipkowitz et al.[5] considered one of the most important aspects of modern synthetic chemistry, namely, asymmetric synthesis and the production of enantiomeric excesses, ee. They investigated reactions with structural variations of the chiral catalysts that are known to yield the same product with different ee. In the first investigation, a parabolic trend (characterized by correlation coefficients $0.84 \leq r \leq 0.98$) was found for asymmetric Diels−Alder reactions of acrylates with cyclopentadiene, with a catalyst containing 2,2′-biaryldiol ligands.[5a] In a second study, a linear trend (characterized by a correlation coefficient $r = 0.99$) was found for asymmetric Diels−Alder reaction between acrylimide with cyclopentadiene with a bisoxazoline-based catalyst.[5b]

The work of Avnir, Lipkowitz, and co-workers proved that a chiraphore exists in molecular or supramolecular systems and that it is the pivotal fragment responsible for stereoinduction. They also concluded that more work is certainly needed to further understand the relationship between chirality content and a molecule's ability to carry out an enantiodifferentiating task.[5b]

Apart from the previously mentioned work on induced circular dichroism,[3] we found that reaction yields, in general, and not only ee can correlate with symmetry measures; for instance, the reaction yields of macrocycle formation at a templating site correlate ($r = 0.97$) with the amount of deviation from perfect symmetry.[6]

To unravel further and exploit the potential of this approach, two steps must be taken:

(a) The success of CCM must be explained, or rationalized, in a wider context, such as by correlating CCM to quantities that directly govern the formation of ee—for instance, the energy of the critical points of the potential energy profile of the reaction pathway—and

(b) situations where the CCM (partly) fails must be documented, and ways to upgrade the model systematically must be found.

(1) In reality, the presence of any rotoreflection axis S_n, $n = 1, 2, 3, ...$, removes chirality.

(2) Fowler, P. W.; Manolopoulos, D. E. *An Atlas of Fullerenes*; Oxford University Press: Oxford, U.K., 1995.

(3) Asakawa, M.; Brancato, G.; Fanti, M.; Leigh, D. A.; Shimizu, T.; Zerbetto, F. *J. Am. Chem. Soc.* **2002**, *124*, 2939−2950.

(4) (a) Zabrodsky, H.; Peleg, S.; Avnir, D. *J. Am. Chem. Soc.* **1992**, *114*, 7843−7851. (b) Keinan, S.; Avnir, D. *J. Am. Chem. Soc.* **1998**, *120*, 6152−6159.

(5) (a) Gao, D.; Schefzick, S.; Lipkowitz, K. B. *J. Am. Chem. Soc.* **1999**, *121*, 1391−1392. (b) Lipkowitz, K. B.; Schefzick, S.; Avnir, D. *J. Am. Chem. Soc.* **2001**, *123*, 6710−6711.

(6) Brancato, G.; Coutrot, F.; Leigh, D. A.; Murphy, A.; Wong, J. K. Y.; Zerbetto, F. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 4967−4971.

Here we address the second point and consider first the geometrical CCM for a series of six reactions of asymmetric aminohydroxylation of different olefins. The results are less successful than what was obtained before[5] and make us shift the focus from the geometrical approach to an electronic chirality measure, ECM (the word continuous is dropped both for simplicity and because once electronic is introduced, a degree of variability must be present in the evaluation of the chirality measure). As in the case of CCM, the approach we propose is not unique. It is based on CCM and further asks the simple question of what happens to the molecular orbitals when chirality is removed from a molecule by the CCM transformation (see details below). We find that ECM correlates well with the enantiomeric excesses, ee. The condition under which this occurs are also discussed.

Computational Background

The geometric continuous chirality measure is calculated as[4]

$$S = \frac{100}{nD^2}\sum_{i=1}^{n}(p_i - \hat{p}_i)^2 \tag{1}$$

where n is the number of would-be symmetry equivalent atoms, p_i are their coordinates, $\hat{p}_i$ are the points of the nearest symmetric, nonchiral, configuration, and D is a normalization factor that makes CCM size-invariant. The nonchiral configuration is here located by numerical optimization, although analytical approaches are, in some cases, possible. Other approaches to the calculation of chirality measures are possible; see ref 7.

An electronic continuous chirality measure was independently proposed by Lipkowitz et al.[8] and by Grimme.[9] In the first approach, the set of points used in the evaluation of CCM no longer corresponds to the atomic positions but to equi-amplitude surface points of the wave function. The second approach considers a generic symmetry operator, $\hat{S}$, present in the molecular structure and calculates its expectation value $\chi = \langle\psi|\hat{S}|\psi\rangle = \pm 1$, where ψ is the electronic wave function. If $\hat{S}$ is not present, $|\chi| \leq 1$ and it is straightforward to take the ECM = $100(1 - |\chi|)$.

Here, we take a related, but partly different approach. Following both eq 1 and Grimme's approach, we define an operator $\hat{S}' = 1 - \hat{Z}$, where $\hat{Z}$ moves the atoms from the p_i to the $\hat{p}_i$ positions. Crucial to calculate the expectation value of $\hat{S}'$ is to define what happens to the wave function when the atomic coordinates p_i are moved to $\hat{p}_i$. Recalculation of the wave function itself with standard methods at $\hat{p}_i$ is probably not in the straightforward spirit of the CCM (and could also pose some very strong practical problems such as that of convergence). Here, we assume that the molecular orbitals are "dragged" from p_i to $\hat{p}_i$, subject only to the condition of remaining orthonormal. This requisite is minimal and is necessary since its removal would result, among the rest, in a change of the number of electrons. To retain orthonormality, one can use the overlap matrixes, O, between the atomic orbitals at the two configurations, p_i and $\hat{p}_i$. For simplicity, they are identified as $O(p_i)$ and $O'(\hat{p}_i)$. Equation 2 shows how to generate the nonchiral orbitals at $\hat{p}_i$

$$\hat{Z}\psi(p_i) = \psi(\hat{p}_i) = O'(\hat{p}_i)^{-\frac{1}{2}}O(p_i)^{\frac{1}{2}}\psi(p_i) \tag{2}$$

$\psi(\hat{p}_i)$ are indeed orthonormal, as one can easily verify by calculating $\langle\psi(\hat{p}_i)O'(\hat{p}_i)\psi(\hat{p}_i)\rangle$.

One of the differences between Grimme's $\hat{S}$ and the present $\hat{S}'$ emerges when the expectation values for their squares is calculated in the presence of chirality. For $\hat{S}^2$, $\langle\psi|\hat{S}^2|\psi\rangle = 1$, while for $\hat{S}'^2$, $\langle\psi|\hat{S}'^2|\psi\rangle$ therefore "extracts" (projects out) the chirality information and once this is obtained, operating again with $\hat{S}'$ cannot "extract" anything else; this is regardless of the number of times it operates. $\hat{S}$, instead, is a "real" symmetry operator operating on a nonsymmetrical wave function. In the present work, the electronic CCM is the expectation value of $\hat{S}'$ multiplied by 100. $\langle\hat{S}'\rangle = 0$ means that the electronic wave function is achiral, $\langle\hat{S}'\rangle = 100$ means that the wave function is annihilated by $\hat{S}'$.

Calculation of ECM is not computationally intensive and is equivalent to a single iteration (not converged) of the method of choice, either self-consistent field (SCF) or density functional theory (DFT). In practice, the whole procedure is done in a few steps:

(1) the molecular geometry is optimized,

(2) the continuous chirality measure of Avnir et al. is calculated and the $\hat{p}_i$ coordinates of eq 1 are stored,

(3) the overlap matrixes between the atomic orbitals at the p_i and the $\hat{p}_i$ geometries are calculated, together with the "mixed" overlap matrix between same orbitals (this is a nonsymmetric matrix whose rows are the orbitals at $\hat{p}_i$ and whose columns are the orbitals at p_i),

(4) the new orbitals at $\hat{p}_i$ are calculated according to eq 2, and

(5) the ECM is calculated as $100(1 - |\chi|)$, where $\chi = \langle\psi(\hat{p}_i)\psi(p_i)\rangle$.

Notice that steps 1 and 2 coincide with Avnir's approach, while steps 3−5 are essentially the detail of the procedure to calculate ECM. Steps 1 and 2 were successful in previous important work that showed the existence between enantiomeric excesses and CCM.[5]

Results and Discussion

In a reaction giving enantiomeric excess, ee, the complexes of each enantiomer (product) with the catalyst form two diasteromeric adducts. The ee is produced by the energy difference of the diasteromeric transition states of the reaction rate-determining step. The use of a chirality measure of the products to rationalize the ee makes some important implicit assumptions:

(1) The reactions is not "complicated", i.e., it takes place in a single cycle, or alternatively, the role of the other cycles is exactly the same and does not unbalances the ee in the reactions that are being compared through the chirality measure. In other words, other intermediates and transition states can occur along the reaction pathway, but they are not at all competitive with that which determines the ee.

(2) The amount of chirality in the products images the properties of the transition state that govern the reaction. In other words, the amount of chirality of the products is similar to that of the transition state, which, in turn, provides a measure of the difference in energy of the diasteromeric transition state.
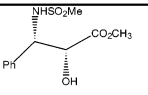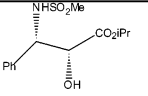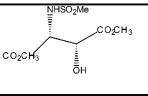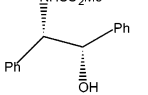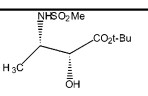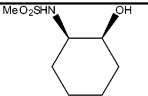
The class of reactions selected for this initial investigation replaces an olefinic double bond with a β-hydroxyamino motif; see Scheme 1.

A practical reason for interest in this reaction is that β-hydroxyamine groups are biologically important. The reaction was discovered by Sharpless and co-workers[10] and successfully optimized to obtain higher enantio- and regioselectivity together with excellent chemoselectivity.[11] To reduce complexity, and in the spirit of the first point raised above, we selected a series of reactions with a small substituent on nitrogen, i.e., a methyl group. Small substituents are known to facilitate the osmium-catalyzed asymmetric aminohydroxylation. The presence of the
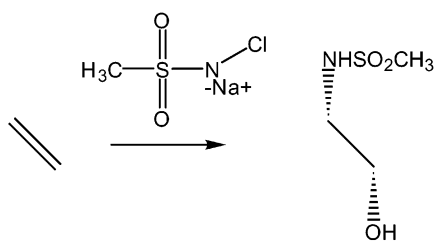
(7) (a) Osipov, M. A.; Pickup, B. T.; Dumnur, D. A. *Mol. Phys.* **1995**, *84*, 1193−1206. (b) Harris, A. B.; Kamien, R. D.; Lubensky, T. C. *Rev. Mod. Phys.* **1999**, *71*, 1745−1757.

(8) Lipkowitz, K. B.; Gao, D.; Katzenelson, O. *J. Am. Chem. Soc.* **1999**, *121*, 5559−5564.

(9) Grimme, S. *Chem. Phys. Lett.* **1998**, *297*, 15−22.

(10) Li, G.; Chang, H.-T.; Sharpless, K. B. *Angew. Chem.*, *Int. Ed. Engl.* **1996**, *108*, 449−452.

(11) (a) Rudolph J.; Sennhenn, P. C., Vlaar, C. P., Sharpless, K. B. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2810−2813. (b) Li, G.; Angert, H. H.; Sharpless, K. B. *Angew. Chem.*, *Int. Ed. Engl.* **1996**, *35*, 2813−2817.

Table 1. Summary of the Calculations of the Electronic, S'_{el} and Geometric, S_g, Continuous Chirality Measures[a]
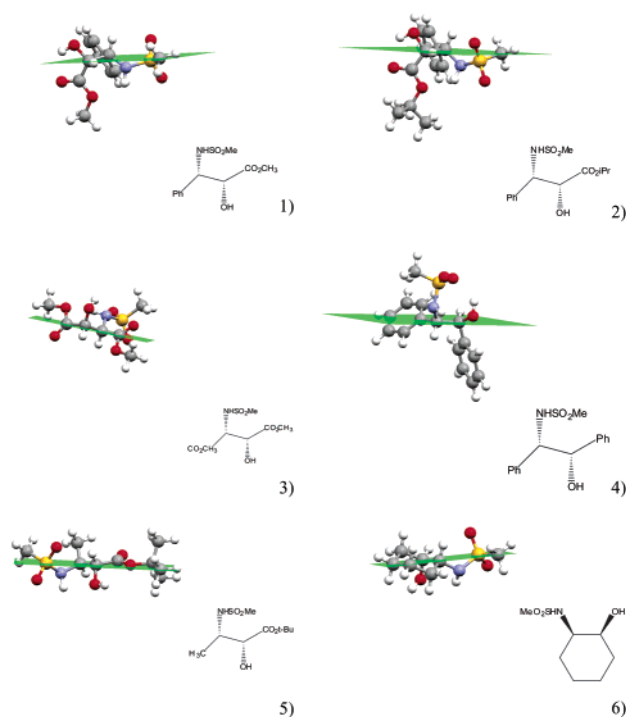
Product	ee	No coupling		Coupling of (C)H-(N)H		Coupling of (C)H-(O)H		Coupling of (C)H-(N)H and (C)H-(O)H		Variation (%)	
		S'_{el}	S_g	S'_{el}	S_g	S'_{el}	S_g	S'_{el}	S_g	S'_{el}	S_g
(NHSO₂Me, CO₂CH₃, Ph, OH)	95	72.98	4.97	73.87	4.59	74.28	5.23	73.91	4.85	1.78	13.94
(NHSO₂Me, CO₂iPr, Ph, OH)	94	74.40	6.30	73.08	6.26	73.43	6.50	73.22	6.46	1.81	3.83
(NHSO₂Me, CO₂CH₃, CO₂CH₃, OH)	95	66.43	3.80	65.52	3.89	66.05	3.74	67.66	3.80	3.27	4.01
(NHSO₂Me, Ph, Ph, OH)	75	55.00	1.71	52.34	1.89	52.38	1.88	52.43	2.06	5.08	20.47
(NHSO₂Me, CO₂t-Bu, H₃C, OH)	80	56.52	1.38	56.45	1.60	58.01	1.35	57.95	1.58	2.76	18.52
(MeO₂SHN, OH cyclohexane)	66	48.32	3.46	50.22	2.95	56.22	3.22	49.97	2.77	16.35	24.91
R		0.96	0.62	0.94	0.70	0.87	0.66	0.96	0.72		

[a] Only the lowest value is the chirality measure; the other values are reported to show the robustness of the procedure. In the last row is shown the correlation coefficient, R, of S vs ee. Also the products and the ee, in percent, are reported (second column).

Scheme 1

CH₃ group in chloramine (shown above the arrow in Scheme 1) is nontrivial for the purposes of the present investigation. Indeed, Sharpless and co-workers reported that it suppresses a deleterious second cycle that competes with the primary one and reduces its enantio- and regioselectivity. For the details of the proposed mechanism, the interested reader is advised to check Scheme 2 of ref 11a and the relevant discussion. Very recently, the same group reported success in the exploitation of the second cycle.[12] The ee reported for six substrates of this reaction investigated here range from 63% to 95%.

The molecular geometries were optimized at several levels of quantum chemical theory, both semiempirical and density functional theory models were used. The B3LYP/6-31G* were so superior in the correlations that only they will be reported. Figure 1 shows the optimized geometries.

(12) Andersson, M. A.; Epple, R.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 472−475.

Figure 1. Optimized geometries and location of the plane that "removes" chirality (see text).
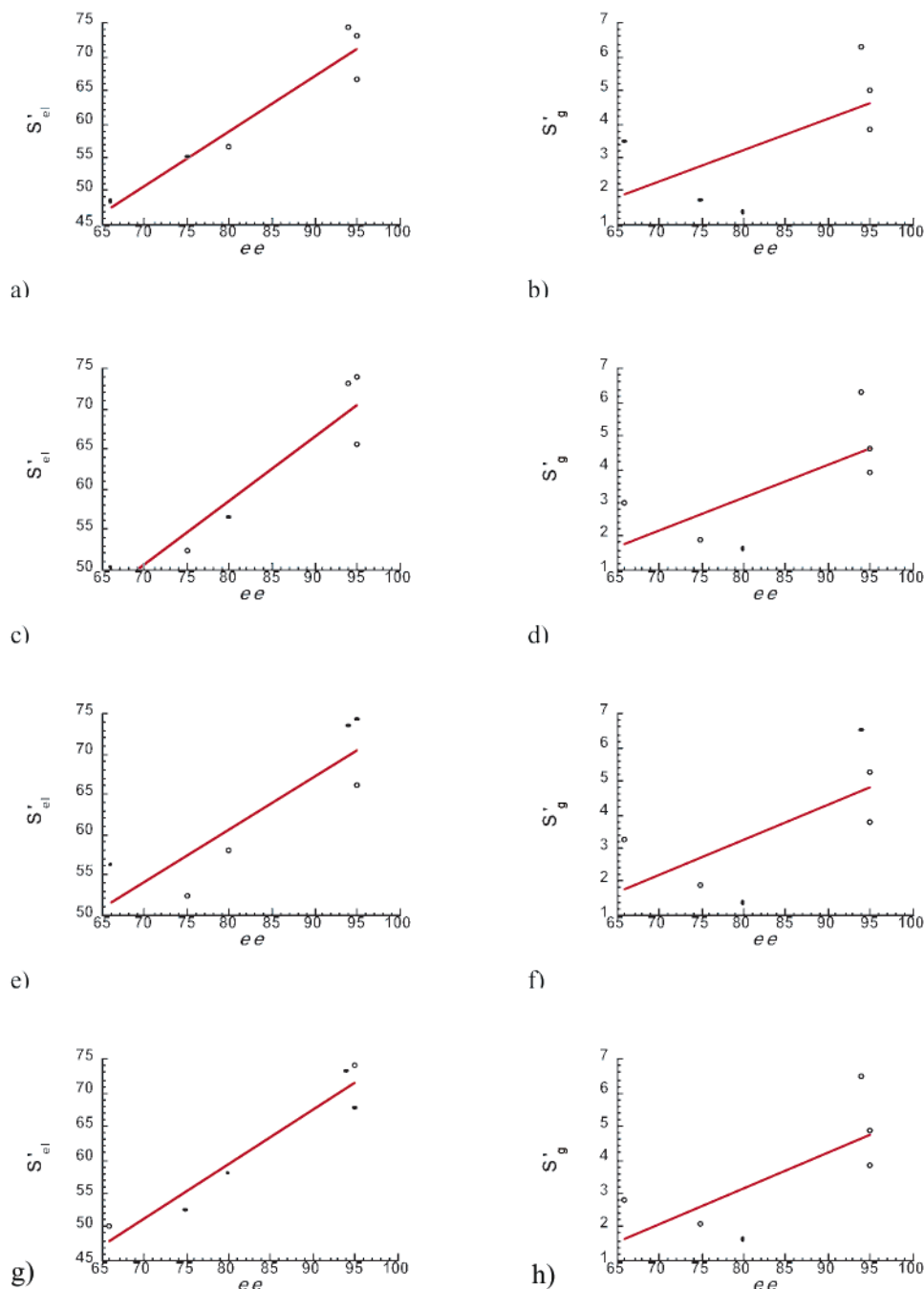
Figure 2. Correlation of S'_{el} vs ee (left) is markedly better than in the case of S_g vs ee (right): (a, b) no coupling (see Table 1); (c, d) coupling (C)H−(N)H; (e, f) coupling (C)H−(O)H; (g, h) coupling (C)H−(N)H and (C)H−(O)H.

They are highly nonplanar. The individual pictures show the "best" plane for each molecule that would remove chirality, if it were a symmetry element of the molecule. Table 1 shows a summary of the results.

The second column reports the experimental ee, while the final row shows the correlation coefficients, R, between the two types of chirality measure, CCM and ECM, and ee. An illustrative example of the correlation between chirality measures and ee is also provided in Figure 2. Visual and data inspection shows that the correlation between ee and ECM (left-hand panels in Figure 2) is satisfactory and markedly better than the correlation between ee and CCM (right-hand panels in Figure 2). On average (see below), ECM obtains correlation coefficients, R, larger than 0.9, while CCM is below 0.7. Notice

that to date there is no proof that a linear correlation has physical foundation: Good fits to other functions are equally good criteria, and increasing or decreasing monotonicity in the correlation is the only correct criterion to adopt. It is, however, evident that in this case ECM is more successful than CCM.

An important issue to address is the robustness of the chirality measure. In a calculation of CCM, the position of the plane of symmetry that removes chirality depends on which atoms are assigned to end, in the nonchiral configuration, in such plane and which are off the plane and therefore have a mirror-image counterpart. The rule adopted in CCM investigation is to take the atom assignment that gives the lowest value. One may, however, ask how much the result differs if other choices are made. The simplest way to remove chirality is to flatten the

whole molecule, i.e., introduce no coupling between the atoms. Alternatively, in the present case, one can couple two pairs of hydrogen atoms that are located at the reaction center. They are the (N)H and its nearby (C)H atoms, and the (O)H and its nearby (C)H atoms. Coupling, or decoupling, these atoms may be critical for the understanding of the chirality content of this reaction. The values and correlations are shown for the CCM and ECM for four different atom couplings in Table 1. Notice that by definition the chirality measure is the smallest possible value of S one can find. In this sense, other nonminimal values calculated with eq 1, or their electronic equivalent, are not real chirality measures. We retain the expression "chirality measure", either electronic or continuous, only to simplify the discussion.

As mentioned above, in all cases, the electronic chirality measures have higher correlation coefficients with the ee than the continuous chirality measure. Indeed, the correlation coefficients go from 0.62 to 0.70 for CCM, while they range from 0.87 to 0.96 for ECM. It appears therefore that, for β-aminohydroxylation, ECM is the more successful approach. Impor-

tantly, both measures are quite robust; that is, they show little change, both when the correlation coefficients are considered and in the values calculated for the individual molecules. The largest variations are up to ~20%, with ECM variations are consistently lower than those reported for CCM.

In conclusion, we have presented and applied a model that evaluates the amount of electronic chirality in a molecular wave function. The procedure applied to the products of a series of asymmetric aminohydroxylation reactions is more successful than the geometric continuous chirality measure on which it is based. We believe that the judicious use of this model, its interplay with CCM, and its systematic application to either the catalysts or the intermediates/transition states or to the products, depending on the nature of the reactions, can provide new, complementary information on the investigation of the reaction pathway and can ultimately suggest possible improvements on the strategy to increase enantiomeric excesses.