Molecular Modeling

Asymmetric versus C_2-Symmetric Ligands: Origin of the Enantioselectivity in Ruthenium–Pybox-Catalyzed Cyclopropanation Reactions**

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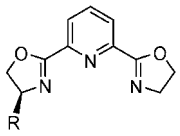
In memory of Juan Carlos del Amo

Enantioselective homogeneous catalysis is one of the most efficient ways of introducing chirality in a controlled manner in organic synthesis.[1] Although there are some exceptions,[2] C_2-symmetric ligands are usually preferred over asymmetric (C_1) ligands for enantioselective catalytic applications. Those ligands with C_1 symmetry that are successful for catalytic applications are generally both electronically and sterically asymmetric, such as salicylaldimines[2a] and phosphinooxazolines.[2b] Of course, there are evident advantages in using C_2-symmetric ligands. For example, fewer reaction channels are possible for the reaction, thus simplifying the induction of enantioselectivity. Furthermore, the synthesis of the ligands is often simpler.

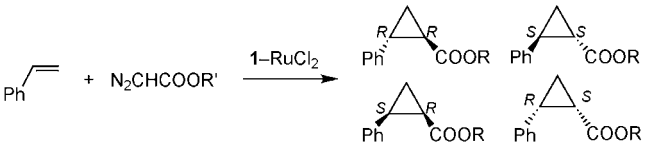
Oxazoline-based ligands, such as bis(oxazoline), azabis(oxazoline), and pyridinebis(oxazoline) (pybox) ligands, have attracted much attention because they have been used successfully in many different enantioselective organic reactions.[3] In the vast majority of cases, these ligands have C_2 symmetry.

In general, in cases in which the use of C_2-symmetric ligands leads to good enantioselectivities, the use of sterically asymmetric (but electronically symmetric, in the sense of a close similarity of the coordinating groups) analogues results in a dramatic worsening of the results. We recently found this behavior in the case of an asymmetric azabis(oxazoline) ligand used in the copper-catalyzed cyclopropanation of styrene with methyl diazoacetate.[4] However, there is at least one case in which the use of sterically asymmetric ligands results in enantioselectivities comparable to those obtained with the corresponding C_2-symmetric analogues, namely, the so-called "single-chiral" pybox ligands, described by Nishiyama et al. (Scheme 1).[5] When these ligands are used in the ruthenium-catalyzed cyclopropanation of styrene with alkyl diazoacetates (Scheme 2), very good enantioselectivities are observed for the *trans* cyclopropanes (up to 94% *ee*).[5] This result was explained by assuming that the carbene intermediate with the ester group *anti* to the bulky substituent of the ligand is the major intermediate, so that the carbene addition takes place mainly from the *Re* face (Figure 1).



1a: R = *i*Pr
1b: R = *t*Bu

Scheme 1. Structures of the asymmetric pyridinebis(oxazoline) (pybox) ligands of Nishiyama et al.



Scheme 2. A typical cyclopropanation reaction with styrene.

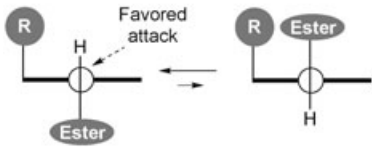


Figure 1. Schematic explanation given in the work of Nishiyama et al. for the good enantioselectivity observed with the asymmetric pybox ligands.

This is too simple an explanation, because the system is under Curtin–Hammett conditions at room temperature, as demonstrated by NMR spectroscopic experiments,[5] and hence the selectivity will only depend on the relative energies of the corresponding transition states (TSs) that result from the different ruthenium–carbene intermediates. The ester group can adopt, in principle, two different conformations with regard to the R substituent of the pybox ligand, so that four different carbene intermediates are possible. If only the *trans* addition to styrene from the *Re* and *Si* faces of the carbene is considered, eight different TSs are possible for this reaction, four of which lead to one cyclopropane enantiomer and the other four to the opposite enantiomer (Figure 2). The final enantioselectivity in the *trans*-cyclopropane products will then be determined by the relative energies of these TSs.

It is not evident at all, from an inspection of Figure 2, why high enantioselectivity should be expected for this system. In a first approach, if a mechanism for asymmetric induction similar to that described for copper–bis(oxazoline) complexes is assumed,[6] the steric interaction between the ester group and the R substituent of the chiral ligand should be responsible for the enantiodifferentiation. In the case of an

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Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

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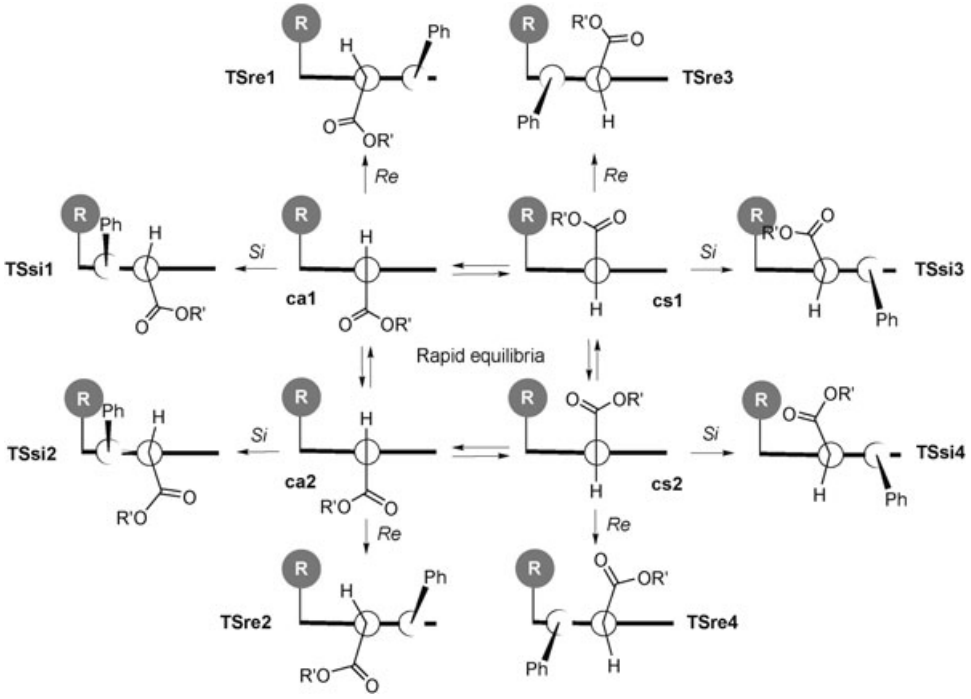

Figure 2. Schematic representation of the possible carbene intermediates and transition-state structures that lead to the *trans* cyclopropanes in the reaction of styrene with alkyl diazoacetates catalyzed by an asymmetric ruthenium–pybox complex.

asymmetric ligand, **TSsi1** and **TSsi2** would lack this interaction, so their energies should not differ very much from those, for example, of **TSre1** and **TSre2**, and there would be essentially no enantiodifferentiation. This situation is precisely that observed experimentally for asymmetric copper–azabis(oxazoline) complexes.[4] However, in the case of the asymmetric ruthenium–pybox complex this reasoning does not correspond with the experimental results, so it is clear that the enantiodifferentation mechanism must be different. Importantly, in the case of the copper–bis(oxazoline) catalysts, the approaching direction of the alkene to the carbon atom of the carbene avoids any steric interaction with the chiral ligand, since it takes place with the double bond in the plane of the complex and the phenyl group on the outside, far away from the R substituent of the chiral ligand, as would be the case for **TSsi1** and **TSsi2** if the same model were applicable.

We undertook the calculation of the critical points represented in Figure 2, with R = isopropyl (ligand **1a**), R′ = methyl (methyl diazoacetate as the diazo compound), and styrene as the alkene, with the aim of finding an explanation for the unexpectedly high enantioselectivity observed with these kinds of asymmetric ligands. All the calculations were carried out at the B3LYP/LANL2DZ level (see computational details in the Experimental Section), which has been proven to provide a good representation of the structures and energies of these systems.[7,8]

First, we calculated the energies of the four possible ruthenium–carbene intermediates shown in Figure 2. The relative energies of these intermediates are gathered in Table 1. Contrary to the assumption of Nishiyama et al., the four carbene intermediates have a very similar energy, and in fact the most stable structure, **cs1**, corresponds to a situation in which the R substituent and the ester group are in a *syn* arrangement. Questions can be raised concerning the accuracy of the B3LYP functional to describe steric interactions. Although it is known that this functional performs well in the calculation of conformer energy differences and conformational energy barriers of small molecules,[9] we decided to test this point further by carrying out some single-point energy calculations by using a two-layer ONIOM QM/MM scheme.[10] To this end, the isopropyl group of the pybox ligand was represented by the UFF force field[11] in the low layer, with the rest of the structure being calculated at the

Table 1: Calculated relative energies of the carbene intermediates and transition-state structures that lead to the *trans* cyclopropanes.

Structure	$\Delta\Delta E_{DFT}$ [kcal mol^{-1}][a]	$\Delta\Delta E_{ON}$ [kcal mol^{-1}][b]
ca1	0.4	0.0
ca2	0.5	0.6
cs1	0.0	0.2
cs2	0.4	1.4
TSre1	0.3	0.0
TSre2	1.1	0.6
TSre3	0.0	0.0
TSre4	0.3	0.5
TSsi1	3.2	3.4
TSsi2	2.7	2.8
TSsi3	0.9	1.0
TSsi4	1.3	3.7

[a] B3LYP/LANL2DZ level. [b] Single-point energy ONIOM B3LYP/LANL2DZ:UFF calculations; the isopropyl group is treated only at the MM level.

B3LYP/LANL2DZ level in the high layer. In this way, any interaction between the isopropyl group and the ester group is never calculated at the DFT level, so that we have an independent estimation of the importance of this steric interaction. The results shown in Table 1 corroborate the theory that the origin of the enantioselectivity cannot be that a single carbene is favored energetically. As with the full DFT calculations, carbenes **cs1** and **ca1** have almost the same energy, although at this level the *anti* carbene is slightly favored.

Next, we calculated the eight possible transition-state structures that can result from the *Re* and *Si* approaches of styrene to the carbene carbon atom. The calculated relative energies of these TSs are also gathered in Table 1. There are three TSre states that are lower in energy than any of the TSsi states. The lowest energy TSsi state, **TSsi3**, is approximately 1 kcal mol^{-1} higher in energy than the lowest energy TSre state, **TSre3**. By considering a Boltzmann distribution of products based on the relative transition-state energies, the calculated *ee* value is approximately 74%, which is close to the experimental value of 71% *ee* described for the same system.[5] Of course, we do not claim that the theoretical level used is able to describe the relative energies to such a high accuracy, and the excellent numerical agreement is probably only coincidental, but it points to the origin of the behavior observed, as discussed below.

Independent estimations of the importance of steric effects were obtained by using the ONIOM QM/MM scheme. The phenyl group of styrene, the isopropyl group of the pybox ligand, and the methyl group of the ester were treated at the MM level. The corresponding results are gathered in Table 1, and they show essentially few differences with regard to the full DFT calculations. The stability of the TSre states relative to that of the TSsi states is somewhat enhanced and leads to a calculated value of 84% *ee*.

These results suggest that the origin of the enantioselectivity does not lie in one transition state being favored significantly over the others, but rather in the existence of more reaction channels that lead to *Re* than to *Si* products. The only TSsi states that contribute significantly to the reaction are **TSsi3** and **TSsi4**, and both are approximately 1 kcal mol^{-1} higher in energy than the corresponding **TSre3** and **TSre4** states. This energy difference can be explained by the steric interaction between the R and ester groups in the TSsi states. However, **TSsi1** and **TSsi2** represent the true critical points for explaining the high enantioselectivity observed experimentally.

A careful examination of the calculated geometries of the TSs (Figure 3) reveals some systematic differences with respect to the TSs from the copper–bis(oxazoline) complexes, with the most significant being the approaching direction of the alkene molecule. In the case of the ruthenium complexes, this approaching direction is out of the plane of the complex, with dihedral angles for the center of the double bond–$C_{carbene}$–Ru–$N_{oxazoline}$ of approximately 24–36° for the TSre states and approximately 30–73° for the TSsi states. This circumstance may result in close contacts between the alkene and the isopropyl group of the pybox ligand in some TSs, as discussed below.

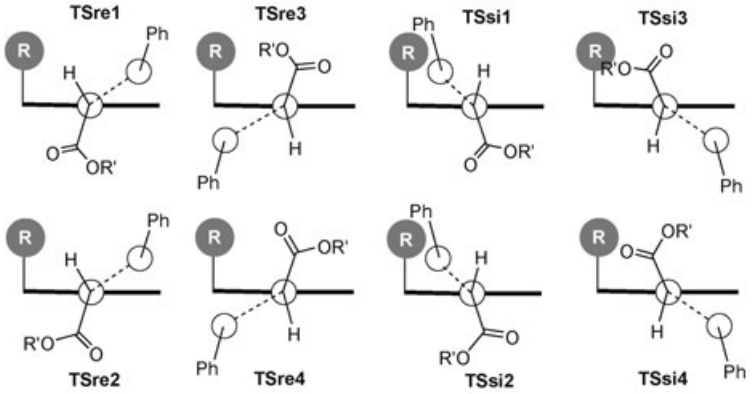

Figure 3. Calculated direction of approach of the styrene molecule to the pybox–ruthenium–carbene complex for the eight possible transition states.

TSsi1 and **TSsi2** are the only TSs for which the approach of the styrene molecule takes place in the same quadrant of the complex plane as that occupied by the isopropyl group. This direction of approach is a consequence of the general stereoelectronic requirements of the TS, as the pyramidalization of the carbene carbon atom results in dihedral angles for the center of the double bond–$C_{carbene}$–Ru–C_{ester} of approximately 120–130° in all cases (Figure 3). This fact leads to some geometrical differences in **TSsi1** and **TSsi2** with regard to the six other TSs (Figure 4). In the case of **TSsi1**, to avoid the steric interaction between the isopropyl group and one of

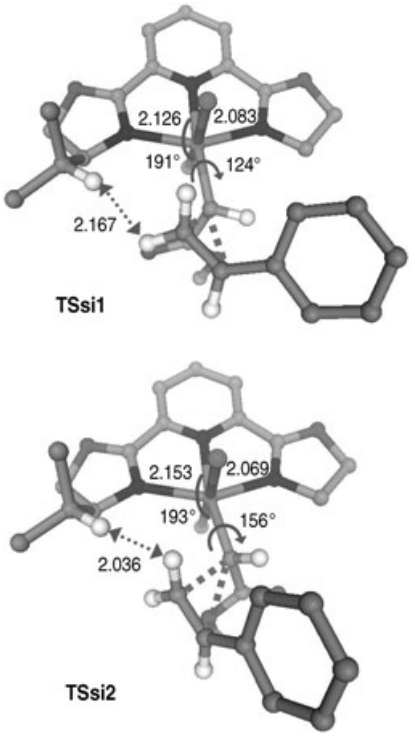

Figure 4. Some selected geometrical features of **TSsi1** and **TSsi2**. Most of the hydrogen atoms have been omitted for clarity.

the hydrogen atoms of styrene, the carbene moiety is much more twisted relative to the complex plane (dihedral angle of 72.5° instead of the typical values of around 30° found in most of the other TSs). The $N_{pyridine}$–Ru–$C_{carbene}$ angle also deviates more from a straight line in **TSsi1** and **TSsi2** relative to the other TSs. In the case of **TSsi2**, this results in a more deformed complex, with one $N_{oxazoline}$–Ru distance significantly longer than the other. In spite of this deformation, there is a close contact between the isopropyl group and one of the hydrogen atoms of styrene.

It can therefore be concluded that the steric interaction between the incoming styrene and the isopropyl group of the chiral ligand is the origin of the high relative instability of **TSsi1** and **TSsi2**. On the other hand, the TSre states lack any steric interaction, either between the ester and the R group or between the styrene and the R group, which explains their closer relative energies.

As a corollary, it can be concluded that when the steric interaction between the ester group and the R group of the chiral ligand (an intramolecular interaction) dominates, as is the case for copper–bis(oxazoline) and copper–azabis(oxazoline) catalysts, the C_2 symmetry is mandatory to obtain good enantioselectivities. On the other hand, when the steric interaction between the R group and the incoming alkene (an intermolecular interaction) becomes dominant, as in the case described herein, a C_1 ligand can be enough to provide similar levels of enantioselectivity as a consequence of the subtle geometrical changes in the TS imposed by changes in the metal and the ligand, which modify the steric requirements of the reactions remarkably.

These conclusions contrast with the previously proposed explanation that both **TSsi1** and **TSsi2** present an *anti* arrangement of the R and ester groups, thereby suggesting that "chemically intuitive" stereochemical models may fail to explain the behavior of complex systems, such as enantioselective catalysts. These results also suggest that the establishment of a priori analogies to explain the behavior of different catalytic systems, even for the same reaction by the same mechanism, can give rise to misleading conclusions.

Experimental Section

All the theoretical calculations were carried out with the Gaussian 03 program.[12] The structures of the carbenes and TSs were optimized by using the B3LYP functional[13] and the LANL2DZ basis set, which consists of the valence double-zeta D95V basis set for first-row atoms[14] and the Los Alamos effective core potential[15] for Cl and Ru. In selected cases, the nature of the stationary points found was tested by the presence of the correct number of negative eigenvalues of the Hessian matrix by means of frequency calculations. Single-point energy calculations were carried out by following the ONIOM QM/MM scheme,[10] as implemented in Gaussian 03.

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