Surface Confinement Effects on Enantioselective Cyclopropanation. Reactions with Supported Chiral 8-Oxazolinylquinoline−Copper Complexes

José M. Fraile,* José I. García, Gonzalo Jiménez-Osés, José A. Mayoral,* and Marta Roldán

Departamento de Química Orgánica, Instituto de Ciencia de Materiales de Aragón and Instituto Universitario de Catálisis Homogénea, Facultad de Ciencias, Universidad de Zaragoza−CSIC, E-50009 Zaragoza, Spain

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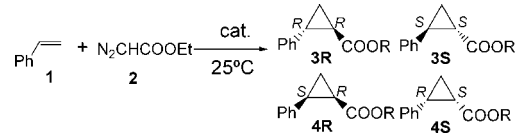
Chiral quinolinoxazoline ligands, a class of C_1-symmetric chiral ligands, are tested in the enantioselective supported catalysis of a cyclopropanation reaction, trying to improve surface confinement effects of the clay support on the reaction stereoselectivity. In the case of *trans/cis* diastereoselectivity, these surface effects lead to a complete reversal of selectivity, with *cis* selectivity values superior to those previously found using C_2-symmetryic bisoxazoline ligands. On the other hand, the enantioselectivities do not display important variations in the supported catalysts. A theoretical (DFT) mechanistic study is carried out to explain the origin of the enantioselectivity in homogeneous phase at a molecular level.

Introduction

The use of biphasic catalysts in enantioselective reactions is an area of increasing interest,[1] which is mainly due to the practical advantage of an easy separation of catalyst and products by simple filtration in the case of catalysts immobilized onto a solid phase. One of the dogmas in the field of chiral catalysts immobilization is that the interaction between the catalytic complex and the support may reduce stereoselectivities, and hence the placement of the catalytic complex far away from the surface is highly desirable in order to get a homogeneous-like environment around the catalytic site. Excellent catalysts in solution are then modified to be immobilized, and the main objective in such cases is, at most, to reproduce the homogeneous selectivities.[2]

Confinement effects on regio- and stereoselectivity have been described in reactions carried out inside the pore system of zeolites.[3] The restricted disposition of the substrates inside the zeolite micropores has been invoked as the origin for those effects. Very recently, increases in enantioselectivities with Mn(salen)-supported catalysts have been ascribed to not completely understood support effects.[4] Those effects have been reported as restrictions in the rotation of a radical intermediate, although the origin of this restriction remains unclear owing to the open structure of the used supports. Support effects have also been invoked to explain stereoselectivity changes in the Diels−Alder reaction of cyclopentadiene with oxazolidine crotonate, catalyzed by bis(oxazoline)-Cu(OTf)$_2$ complexes immobilized onto silica.[5]

Scheme 1. Cyclopropanation Reaction between Styrene and Ethyl Diazoacetate



On the other hand, we described the first unequivocally demonstrated surface effect on an enantioselective reaction. In that case the cyclopropanation between styrene and ethyl diazoacetate (Scheme 1), catalyzed by the C_2-symmetric bis(oxazoline)-bearing phenyl groups (PhBox), suffered a complete reversal of selectivities due to the use of a lamellar solid, namely, laponite, a synthetic clay, as the support.[6] The use of a nonpolar solvent led to a *cis* preference, in contrast to the *trans* preference in solution, and the asymmetric induction for the major *cis* isomers was completely reversed. As a consequence the isomer *cis*-(1*S*,2*R*)-(**4S**) was preferably obtained instead of the major *trans*-(1*R*,2*R*)-(**3R**) in solution. The fact that a nearly planar surface is needed was inferred from the lack of effect with other types of solid, either amorphous or crystalline. An extensive study on the importance of the nature of the support has been recently reported, confirming the need of having a lamellar anionic support, as is the case of clays, to observe surface effects. Neither crystalline nor amorphous anionic supports (such as zeolites or cation-exchange resins), nor lamellar nonanionic supports (such as graphite or hydrotalcite), display this behavior.[7]

A simple model was proposed to explain those results, taking into account the strong ion-pair interaction between the key

* Corresponding authors. (J.A.M.) Phone and Fax: +34 976762077. E-mail: mayoral@unizar.es.

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copper−carbene intermediate[8] and the solid surface, as well as the steric constraints of the catalytic complex. From that model we proposed the synthesis of chiral ligands without C_2 symmetry as a method to enhance the surface−complex proximity and hence the support−complex interaction, allowing the surface to effectively shield one face of the complex. Several 2-oxazolinylpyridine ligands were prepared and tested as chiral ligands for immobilized copper complexes.[9] The surface effect was again demonstrated with a clear *cis* preference, but enantioselectivities were not good, probably due to the formation of five-membered chelates.[10]

In this paper we report the preparation of chiral 8-oxazolinylquinoline ligands (henceforth Quinox), their immobilized copper complexes, and the surface effect in the benchmark enantioselective cyclopropanation reaction of styrene with ethyl diazoacetate (Scheme 1), together with a molecular modeling study to explain the results obtained.

Experimental Section

The Quinox ligands were synthesized by the method described by Wu et al.[11]

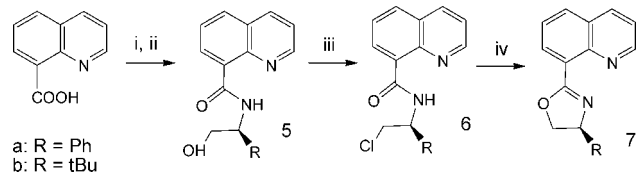
Preparation of Immobilized Catalysts. The complex for cationic exchange was prepared by mixing $Cu(OTf)_2$ (65.1 mg, 0.18 mmol) with a solution of 8-(oxazole-2-yl)quinoline (0.20 mmol) in dichloromethane (2 mL). After stirring for 30 min under inert atmosphere, the solution was filtered through a syringe PTFE microfilter, and the solvent was evaporated under reduced pressure. The residue was redissolved in anhydrous methanol (3 mL), and dried laponite (500 mg) was added to this solution. The suspension was stirred at room temperature for 24 h, and the solid was filtered and washed with anhydrous methanol (7 mL) and dichloromethane (10 mL). The resulting freshly exchanged catalyst was dried under vacuum overnight.

The catalysts were characterized by elemental analysis, copper analysis, step-scanned X-ray diffraction patterns of oriented samples, and transmission FT-IR spectroscopy of self-supported wafers evacuated ($<10^{-4}$ Torr) at 50 °C (tables with the N and Cu elemental analyses, figures with the X-ray diffraction patterns, and FT-IR spectra of solution and supported catalysts are available in the Supporting Information).

Catalytic Tests. Homogeneous Phase. The complex was prepared by mixing $Cu(OTf)_2$ (65.1 mg, 0.18 mmol) with a solution of 8-(oxazole-2-yl)quinoline (0.20 mmol) in dichloromethane (2 mL). After stirring for 30 min under inert atmosphere, the solution was filtered through a syringe PTFE microfilter and added to a solution of styrene (520 mg, 5.0 mmol) and *n*-decane (100 mg, internal standard) in anhydrous dichloromethane (3 mL). Ethyl diazoacetate (580 mg, 5 mmol) in dichloromethane (1.6 mL) was slowly added over 4 h with a syringe pump. The reaction was monitored by gas chromatography with DB-1 and cyclodex-B columns.

Heterogeneous Phase. Ethyl diazoacetate (580 mg, 5 mmol) was slowly added with a syringe pump over 4 h to a suspension of laponite catalyst (150 mg) in styrene (5 mL or 520 mg in 3 mL of methylene chloride) containing *n*-decane (internal standard, 100 mg) at room temperature. The reaction was monitored by gas chromatography with DB-1 and cyclodex-B columns. After total consumption of the diazoacetate the solid catalyst was filtered off. Additional ethyl diazoacetate (285 mg, 2.5 mmol) was slowly added to the filtrate, and the absence of reaction was tested by GC. The solid was washed with dichloromethane, dried under vacuum, and reused under the same conditions.

Scheme 2. Synthesis of Chiral 8-(Oxazolin-2-yl)quinolines[a]



[a] (i) $SOCl_2$, toluene, reflux, 22 h; (ii) (*S*)-phenylglycinol or (*S*)-*tert*-leucinol, NEt_3, CH_2Cl_2, rt, 24 h; (iii) $SOCl_2$, CH_2Cl_2, reflux, 1 h; (iv) NaOH, MeOH, reflux, 24 h.

Theoretical Calculations. Quantum chemical calculations were carried out by means of the B3LYP hybrid functional[12] because of the satisfactory performance of this technique in the chemistry of transition metals[13] particularly in the systems studied here.[8,14] Full geometrical optimizations using the 6-31G(d) basis set were carried out with the Gaussian 03 package.[15] Real system modeling was carried out using the ONIOM QM/MM scheme,[16] as implemented in Gaussian 03. The UFF force field was used in the MM part of the calculations.[17] This methodology has proven to give good results, even of predictive quality, in similar systems.[14b] Analytical frequencies were calculated at the same level used in the geometry optimization, and the nature of the stationary points was determined in each case according to the right number of negative eigenvalues of the Hessian matrix. Hard data on electronic energies, enthalpies, and Gibbs free energies of the different conformations of all structures considered are available as Supporting Information.

Results and Discussion

The Quinox ligands were synthesized (Scheme 2) by the method described by Wu et al.,[11] with some minor modifications. The corresponding carboxamide (**5**) of each amino alcohol was obtained from the acyl chloride, prepared by treatment of

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Table 1. Results of the Cyclopropanation between Styrene and Ethyl Diazoacetate Catalyzed by 8-(Oxazolin-2-yl)quinoline−Copper and 2-(Oxazoline-2-yl)pyridine−Copper Complexes in Homogeneous Phase and Supported on Laponite

entry	catalyst	solvent	yield (%)	*trans*/*cis*	% ee *trans*	% ee *cis*
1	**7a**-Cu(OTf)$_2$	CH_2Cl_2	58	71:29	24	25
2	**7a**-Cu(Laponite)	CH_2Cl_2	45	27:73	34	33
3	**7a**-Cu(Laponite)	styrene	67	14:86	39	30
4	**7b**-Cu(OTf)$_2$	CH_2Cl_2	65	68:32	48	28
5	**7b**-Cu(Laponite)	CH_2Cl_2	59	54:46	34	30
6	**7b**-Cu(Laponite)	styrene	59	23:77	24	33
7[a]	**8a**-Cu(OTf)$_2$	CH_2Cl_2	65	67:33	5	17
8[a]	**8a**-Cu(Laponite)	styrene	68	31:69	65	24

[a] Results from ref 7.

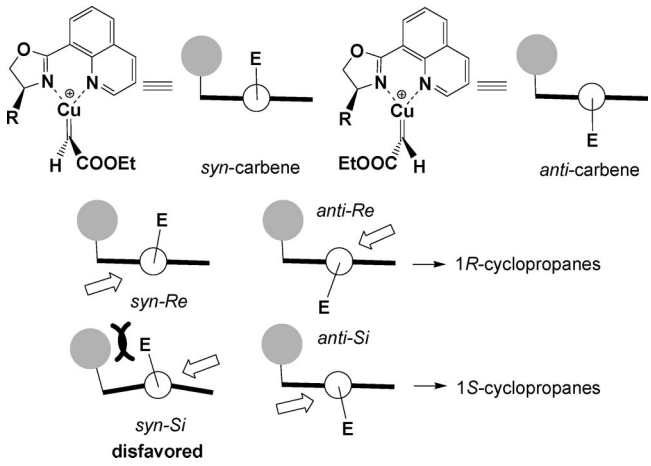


Figure 1. Possible mechanism to explain the low, but significant enantioselectivities observed with C_1-symmetric ligands: only one of four main possible reaction channels is disfavored.

quinoline-8-carboxylic acid with thionyl chloride. The substitution of the hydroxyl by a chlorine group (**6**) was carried out also with thionyl chloride, and the oxazoline ring was obtained by cyclization with NaOH.

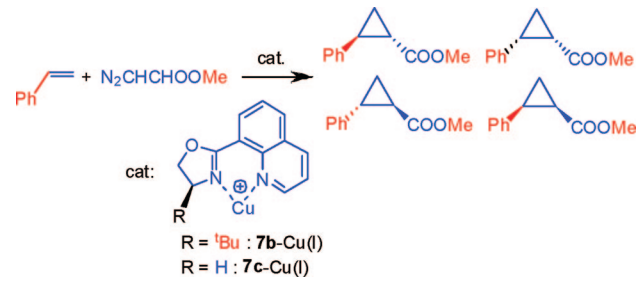
Although these chiral ligands had previously been used in homogeneous cyclopropanation,[11] our standard conditions are rather different. For example, instead of Cu(OTf)·1/2C_6H_6 we use the more stable and easier to handle Cu(OTf)$_2$, which is reduced *in situ* by ethyl diazoacetate. Because of these differences, the chiral ligands were used in homogeneous reactions (Table 1) for the sake of comparison with the heterogeneous catalysts.

The results of the homogeneous-phase reactions (entries 1 and 4) are in good agreement with those reported in the literature[11] and show a low but significant enantioselectivity, mainly in the case of ligand **7b** (48% ee). On the contrary, the analogous 2-(oxazoline-2-yl)pyridine (henceforth Pyox) ligands (**8**) exhibit lower enantioselectivities (entry 7), as expected for this type of C_1-symmetric ligands, leading to five-membered chelate complexes with many possible transition states without apparent steric hindrance.

At first sight, it may be surprising that a chiral ligand bearing only one stereocenter was able to induce a significant enantioselectivity. However, it is easy to see that enantioselectivities up to ca. 30% ee can be easily explained invoking one disfavored reaction channel from four possible. Figure 1 illustrates this point, by showing the four main reaction channels possible for a C_1-symmetric ligand.

However, this may be a too simplistic explanation, given that the ester group has two possible conformers (doubling the number of possible reaction channels), and the energy of the transition states "allowed" will not be exactly the same.

Scheme 3. Model Reaction and Catalysts Used in the Theoretical Study, Together with the QM/MM Partition Scheme Employed (red color: MM part; blue color: QM part)



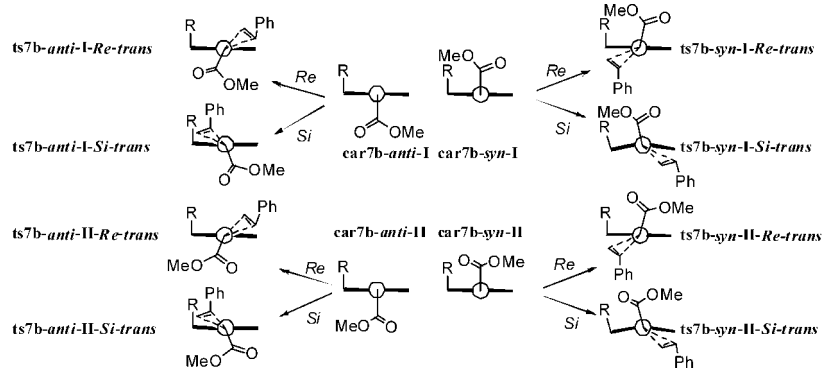
Furthermore the 48% ee obtained with the *tert*-butyl-substituted Quinox ligand (**7b**) seems to be too high to be accounted for by this simple model. In order to gain more insight in the mechanisms of stereodifferentiation with this C_1-symmetric Quinox ligand, we carried out a molecular modeling study, based on QM/MM calculations.

To this end, the enantioselectivity-determining step of the prototypical cyclopropanation reaction of styrene with methyl diazoacetate, catalyzed by Quinox−Cu(I) complexes (Scheme 3), was calculated using the ONIOM(B3LYP/6-31G(d):UFF) QM/MM scheme. In closely related bisoxazoline−copper catalysts, QM/MM schemes have shown to be able to model the stereoselectivities of the benchmark cyclopropanation reaction, even predicting the stereodirecting ability of a completely new ligand.[14b] The QM/MM partition scheme used in the calculations is shown in Scheme 3.

With this model, there are eight possible TSs for each *trans* and *cis* diastereomeric reaction channels, by considering *syn* and *anti* carbene dispositions, *trans* and *cis* relative disposition of the phenyl and carbene moieties, *re* and *si* approach trajectories of styrene, and the two possible conformations of the ester group (I and II). Scheme 4 illustrates these possible reaction trajectories for the *trans* approach of styrene, and Figure 2 shows some selected examples of calculated TS structures. The relative energies of these TSs are gathered in Table 2, together with the calculated diastereo- and enantioselectivities.

The first observation made from energy values in Table 2 is that conformations labeled as II are always less favored than the corresponding I; that is, lowest energy conformations are always associated with a far position of the carbonyl group with regard to the incoming alkene (Scheme 4). Assuming a Boltzmann distribution based on the TS energy differences, the calculated *trans*/*cis* diastereoselectivity is 76:24, in good agreement with the experimental values obtained in homogeneous phase with these ligands (Table 1). Regarding the enantioselectivity, it can be seen that the calculated % ee's are in good qualitative agreement with the experimental values observed for *trans*- (66 vs 48% ee) and *cis*-cyclopropanes (21 vs 28 %

Scheme 4. Eight Possible Reaction Trajectories for the *trans*-Approach of Styrene to the Different Conformers of the Carbene in their *syn*- and *anti*-Forms (*re* approaches lead to 1*R*-cyclopropanes, and *si* approaches to 1*S*-cyclopropanes)



ee). In particular, the model correctly predicts the unexpected higher enantioselectivity in *trans*-cyclopropanes. An analysis of the origin on the enantioselectivity reveals that the *re* reaction channels are always lower in energy than their corresponding *si* counterparts, which is in agreement with the 1*R*, absolute configuration of the major *trans*- and *cis*-cyclopropanes experimentally observed. A more detailed analysis of the relative energies of the TS reveals that the *syn*-I-*re* reaction trajectory leads to the lowest energy TS in both the *trans* and *cis* reaction channels. This preference of *syn*-I over the corresponding *anti*-I TS in the *re* reaction channels contrasts with the foreseeable steric repulsion between the ester and *tert*-butyl groups when they occupy relative *syn* positions. However, QM/MM calculations carried out on the carbene intermediate structures (see Supporting Information for details) indicate that *syn*-carbenes are indeed lower in energy than their *anti* counterparts by ca. 1.5 kcal mol^{-1}. The reversal stability is found in full-QM (B3LYP/6-31G(d)) calculations, indicating that attractive van der Waals forces (taken into account by the MM force field, but not by the pure DFT calculations) may be important to ascertain the steric interactions responsible for the selectivity observed.[14b] In the *si* reaction channels, however, the close proximity of the ester and the *tert*-butyl groups results in a deformation of the chelate geometry, already observed with C_2-symmetric ligands, which leads to higher relative energies for the *syn* disposition, so that *anti-Si* TS are more stable in these cases. Finally, *re* reaction channels are always favored over their respective *si* counterparts, both in *syn* and *anti* carbene dispositions, which is somewhat surprising in the case of the latter, given the lack of steric interaction. In this case, a possible origin of this behavior is a steric repulsion between the ester carbonyl oxygen and the quinoline hydrogen atom in 2-position, showing that steric interactions different from those originated at the stereogenic centers of the chiral ligand may also operate in determining the final enantioselectivity of the catalyst.

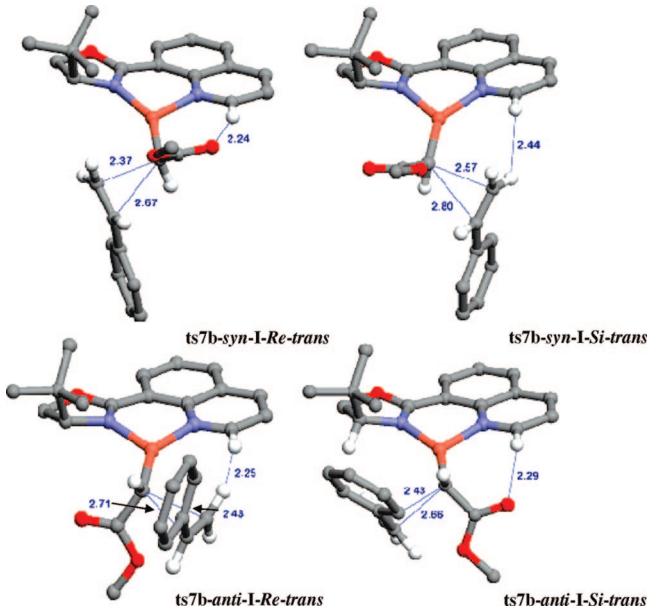


Figure 2. Some selected geometrical parameters of the lowest energy TS for ligand **7b** in the *trans* reaction channels. Most of the hydrogen atoms are omitted for clarity.

Table 2. Calculated [ONIOM(B3LYP/6-31G(d):UFF)] Relative Energies[a] [kcal mol^{-1}], *trans*/*cis* Diastereoselectivities, and Enantioselectivities of the Carbene Addition Step of the Cyclopropanation Reaction of Styrene with Methyl Diazoacetate, Catalyzed by the 7b−Cu(I) and 7c−Cu(I) Complexes

entry	TS	$\Delta\Delta G^{\ddagger}$ (kcal mol^{-1})	% mol	cumulative% mol	cyclopropane configuration
1	**ts7b-*anti*-I-*re*-*trans***	0.94	11.3	70.8	1*R*,2*R*
2	**ts7b-*anti*-II-*re*-*trans***	1.93	2.1		
3	**ts7b-*syn*-I-*re*-*trans***	**0.00**	55.0		
4	**ts7b-*syn*-II-*re*-*trans***	1.88	2.3		
5	**ts7b-*anti*-I-*re*-*cis***	1.66	3.4	22.6	1*R*,2*S*
6	**ts7b-*anti*-II-*re*-*cis***	3.09	0.3		
7	**ts7b-*syn*-I-*re*-*cis***	0.64	18.7		
8	**ts7b-*syn*-II-*re*-*cis***	3.29	0.2		
9	**ts7b-*anti*-I-*si*-*trans***	1.76	2.8	5.1	1*S*,2*S*
10	**ts7b-*anti*-II-*si*-*trans***	3.56	0.1		
11	**ts7b-*syn*-I-*si*-*trans***	2.00	1.9		
12	**ts7b-*syn*-*si*-II-*trans***	3.13	0.3		
13	**ts7b-*anti*-I-*si*-*cis***	2.49	0.8	1.5	1*S*,2*R*
14	**ts7b-*anti*-II-*si*-*cis***	4.06	0.1		
15	**ts7b-*syn*-I-*si*-*cis***	2.93	0.4		
16	**ts7b-*syn*-*si*-II-*cis***	3.36	0.2		

[a] Gibbs free energies calculated at 298.15 K.

The support can also produce important steric effects and change the stereochemical reaction course.[6,9] To test this possibility, the copper complexes of ligands **7a** and **7b** were prepared and immobilized on laponite. Laponite is an entirely synthetic clay, with lamellar structure, whose main features are its cation-exchange ability, due to isomorphic substitutions in the unit cell (typically 50 mmol of negative charges per 100 g of clay, or 0.7 charges per unit cell), and nanosized disk-shaped particles, with a planar surface. More details on this material are given in the Supporting Information, as well as crystallographic images illustrating the short-range planarity of the support surface. Copper and nitrogen analyses, together with the IR spectra, confirmed that the complexes remained intact after immobilization. XRD patterns showed that the ordered stacked structure of laponite was partially lost after immobilization, giving rise to a house of cards structure and favoring in

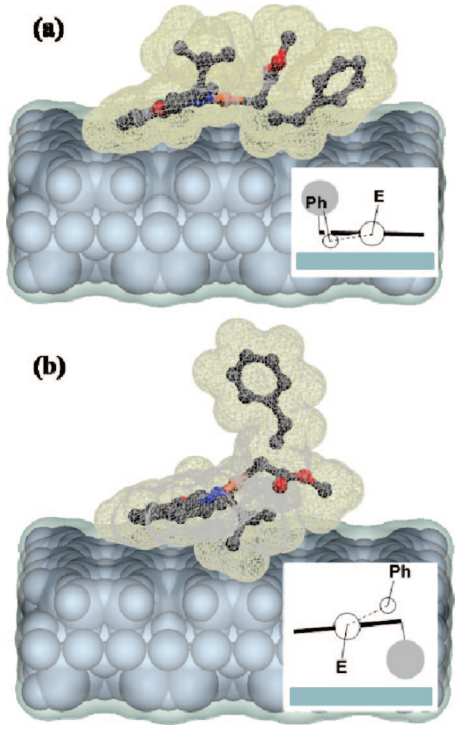


Figure 3. Two ideal (not calculated) catalyst−support dispositions for the lowest energy *cis* (a) and *trans* (b) TS of the cyclopropanation reaction of styrene with methyl diazoacetate.

this way the behavior of the support as a true surface. These solids were tested as catalysts in the same benchmark reactions. Table 1 gathers the most relevant results of these reactions.

As can be seen, the complete reversal of *trans/cis* diastereoselectivity demonstrates that there are important support effects in these catalytic systems. Thus, the ca. 70:30 *trans* preference in homogeneous phase becomes ca. 15:85 *cis* preference for ligand **7a** and ca. 25:75 *cis* preference for ligand **7b**. This is an interesting result from a synthetic point of view, since there are few catalytic systems described able to lead preferently to *cis*-cyclopropanes.[18] Furthermore, some *cis*-cyclopropanes have interesting biological activities as insecticides and drugs.[19]

Asymmetry of ligand structure favors this *cis* preference, as indicated by the solvent effect. Thus, with PhBox, a C_2-symmetric ligand, diastereoselectivity reversal was observed only when the reactions were carried out in solvents of low polarity (perfluoroheptane, hexane, or styrene itself), whereas in CH_2Cl_2, the *trans/cis* selectivity obtained in heterogeneous reactions was similar to those observed in homogeneous phase. On the contrary, with the Quinox ligands, even the heterogeneous reactions in CH_2Cl_2 display a *cis* preference, which points to a closer complex−support disposition that enhances the steric support effect. Figure 3 displays two idealized catalyst−support dispositions for the lowest energy TS (just for illustration, not coming from molecular modeling), where it can be realized that the *cis* TS is better accommodated to the support surface.

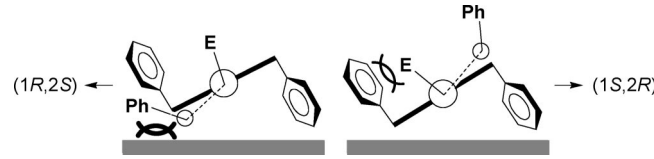


Figure 4. Surface model to account for the major *cis*-cyclopropane obtained in the heterogeneous cyclopropanation reactions catalyzed by the PhBox−Cu(I) complex.

Unfortunately, this support effect does not have a strong effect on the enantioselectivities obtained with the Quinox ligands. Thus, with **7a**, a slight enantioselectivity improvement in *trans*- and *cis*-cyclopropanes with regard to the homogeneous reaction is obtained. On the contrary, with **7b**, a slight decrease in enantioselectivity of *trans*-cyclopropanes is observed, whereas *cis*-cyclopropanes are obtained with the same enantioselectivity. These results strongly contrast with those observed for the pyridineoxazoline **8a** ligand. In that case, a significant improvement in the enantioselectivity of *trans*-cyclopropanes by support effect was observed (Table 1).[9]

Another remarkable observation concerns the absolute configuration of the major *cis*-cyclopropanes. It has been reported[6] that with the supported C_2-symmetric PhBox ligand there is an inversion of this configuration with regard to homogeneous phase results. However, it can be seen that with the C_1-symmetric ligands **7** and **8** the absolute configuration of the major cyclopropane enantiomers does not change. All these experimental observations can be used to propose an explanation to the support the effects observed.

In the case of the C_2-symmetric ligands, a model has been proposed to account for the reversal in diastereoselectivity and absolute configuration of the major *cis*-cyclopropane (Figure 4).[9]

In this model, the TS leading to the least steric interactions between the support and the incoming styrene becomes the most stable in heterogeneous catalysis, leading to the major observed product. In the case of C_1-symmetric ligands, the number of possible reaction channels doubles. Thus, considering the *syn*−*anti* ester disposition, the two conformations of the ester group, the position of the support (either far or near the ester group) and the *re*−*si* approaches of styrene, there are at least 16 reaction channels leading to *trans*-cyclopropanes and 16 leading to *cis*-cyclopropanes. The theoretical calculations have shown that ester conformations labeled as II lead always to TSs higher in energy, which does not contribute significantly to the reaction. Even disregarding these conformations, we have eight possible reaction channels for each diastereomeric pair of cyclopropanes. Figure 5 outlines these reaction channels.

As can be seen in this figure, in most of the *trans*-TSs the Cu center must be placed far from the surface, in order to accommodate the incoming styrene, the substituent of the ligand, or the ester group. In low-polarity solvents, tight ion pairs are favored, so these TSs will be disfavored with regard to those *cis*-TSs in which the complex can be placed closer to the support, such as **1c** and **5c**. This may explain the high *cis* selectivity observed for these supported catalysts.

Concerning the enantioselectivity, in both *trans*- and *cis*-cyclopropanes, it can be speculated that for all main approaches there are reaction channels allowed (i.e., not too far in relative energy), for instance, in the case of *trans*-TSs, **2t**, **3t**, and **7t**, and in the case of *cis*-cyclopropanes **1c**, **4c**, **5c**, and **8c**. This circumstance would explain the low enantioselectivities obtained

(18) Co-salen: Niimi, T.; Uchida, T.; Irie, R.; Katsuki, T. *Tetrahedron Lett.* **2000**, *41*, 3647. Cu: Uchida, T.; Irie, R.; Katsuki, T. *Tetrahedron* **2000**, *56*, 3501. Cu: Diaz-Requejo, M. M.; Belderrain, T. R.; Trofimenko, S.; Pérez, P. J. *J. Am. Chem. Soc.* **2001**, *123*, 3167. Ru: Bachmann, S.; Furler, M.; Mezzetti, A. *Organometallics* **2001**, *20*, 2102. Bonaccorsi, C.; Mezzetti, A. *Organometallics* **2005**, *24*, 4953–4960. Rh: Ref 19.

(19) See for instance: (a) Hu, W.; Simmons, D. J.; Doyle, M. P. *Org. Lett.* **2002**, *4*, 901–904. (b) Kazuta, Y.; Hirano, K.; Natsume, K.; Yamada, S.; Kimura, R.; Matsumoto, S.-i.; Furuichi, K.; Matsuda, A.; Shuto, S. *J. Med. Chem.* **2003**, *46*, 1980–1988. (c) Brana, M. F.; Guisado, C.; Alguacil, L. F.; Garrido, E.; Perez-García, C.; Ruiz-Gayo, M. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3561–3563.

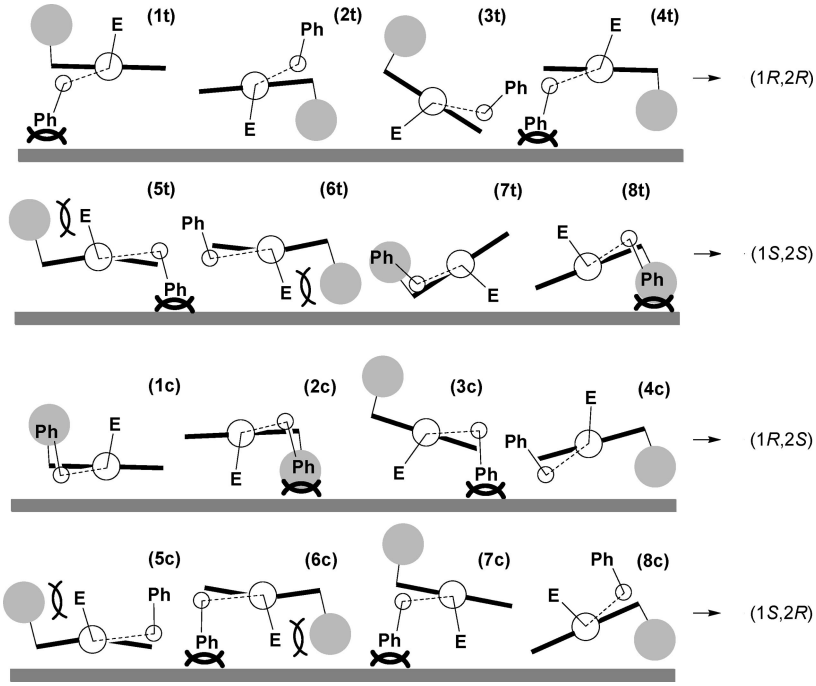


Figure 5. Possible dispositions of the TS with regard to the support in the heterogeneous cyclopropanation reactions catalyzed by the **7**−Cu(I) complexes.

with the supported catalysts and probably also the lack of inversion of the absolute configuration of the major *cis*-cyclopropane, given that, unlike the case of the C_2-symmetric PhBox ligand (Figure 3), the *re* approach of the alkene is not clearly disfavored.

Conclusions

Chiral quinolinoxazoline ligands, a class of C_1-symmetric chiral ligands with a single stereogenic center, have been tested in the enantioselective supported catalysis of the cyclopropanation reaction of styrene with ethyl diazoacetate, with the aim to improve surface confinement effects of the clay support on the reaction stereoselectivity, due to the foreseeable better adaptation of the chiral complex to the surface. In the case of *trans/cis* diastereoselectivity, these surface effects lead to a complete reversal of selectivity, with excellent *cis* selectivity values (up to 86%), superior to those previously found using C_2-symmetric bisoxazoline ligands. This result may be of synthetic interest, given that *cis*-cyclopropanes are usually difficult to obtain selectively. On the other hand, the enantioselectivities do not display important variations upon supporting catalysts, which points to multiple dispositions of the complex reaction intermediates with regard to the support surface. More work is therefore necessary to improve the ligand design to take advantage of surface confinement effects in the enantioselective catalysis of this reaction.

A theoretical mechanistic study is carried out to explain the origin of the enantioselectivity in homogeneous phase at a molecular level. The theoretical study allows to conclude that steric interactions different from those originated at the stereogenic centers of the chiral ligand might also be important in determining the final enantioselectivity of the catalyst. This knowledge can help in the design of more efficient chiral ligands, lacking C_2 symmetry.

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Supporting Information Available: Tables of electronic energies, as well as enthalpies, entropies, and Gibbs free energies (the last three data series at 25 °C) for the different conformations of the structures considered in this work. Calculated geometries of the structures discussed in this paper. Details about the characterization of the heterogeneous catalysts and the structure of the support. This material is available via the Internet at http://pubs.acs.org.

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