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Surface confinement effects in enantioselective catalysis: Design of new heterogeneous chiral catalysts based on C_1-symmetric bisoxazolines and their application in cyclopropanation reactions

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Dedicated to Professor Vicente Gotor on the occasion of his 60th birthday

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ABSTRACT

Surface confinement effects are extremely important in determining the stereochemical course of cyclopropanation reactions catalyzed by C_2-symmetric bisoxazoline–copper complexes immobilized on laponite. In the case of the PhBox ligand, complete reversal of *trans*/*cis*-diastereoselectivity is observed, as well as a reversal in the absolute configuration of the major *cis*-cyclopropane. Furthermore, the enantioselectivity obtained with the immobilized catalyst is better than that obtained in the homogeneous phase, indicating that support effects can be beneficial to the stereoselectivity of the reaction. The design of C_1-symmetric bisoxazoline ligands specifically for heterogeneous catalysis allows improvement of the *cis*-selectivity of the benchmark cyclopropanation reaction up to 91% *cis*-cyclopropanes. This finding is in agreement with a closer complex surface approach. Experiments carried out with reagents with a greater steric demand highlight the existence of reaction channels in which the ester group points toward the support surface, a factor that was disregarded in the former stereoinduction model.

1. Introduction

Asymmetric heterogeneous catalysis [1,2] is conceptually very interesting due to the combination of the inherent practical advantages of heterogeneous catalysis over homogeneous catalysis and the increasing requirement for high enantiomeric purity in many products in the fine chemicals or specialties industries, such as pharmaceuticals and agrochemicals. However, immobilization of chiral catalysts requires additional synthetic effort, and often the results are worse than those achieved in solution. In those cases, reuse of the catalyst is not sufficient to justify the use of these systems, and it is important to find added value to help convince the synthetic community of the advantages of such catalysts. In this regard, we have recently shown that a supported azabis(oxazoline)–copper catalyst can be efficiently used as a multitask catalyst [3].

In general, it is thought that immobilized catalysts should be designed to minimize the possible interactions between the catalytic sites and the support, to avoid unpredictable effects of the latter on the stereochemistry of the reaction. But this interaction can be used to improve and even modify the stereochemical results. In this way, the solid catalyst can lead to products that are difficult to obtain in solution, and thus its use is clearly justified.

One of the most commonly used strategies for preparing chiral heterogeneous catalysts is immobilization of the most efficient homogeneous ones onto a support. In most cases, this immobilization is carried out through covalent bonding of the chiral ligand to the support [4]. In this approach, chemical modification of the ligand is required, resulting in more synthetic steps. When the chiral homogeneous catalyst is a charged metal complex (and it remains charged throughout the entire catalytic cycle), immobilization through electrostatic interactions [5,6] also is possible. Such is the case for bis(oxazoline)–copper (Box–Cu) complexes, which are useful catalysts for cyclopropanation reactions [7]. These complexes are cationic in nature, and they can be supported on a variety of anionic supports.

Our group has experience in the immobilization of Box–Cu complexes by covalent bonding to a solid support [8,9]. When these catalysts are used to promote the benchmark cyclopropanation reaction between styrene and ethyl diazoacetate, they lead to *trans*/*cis*-selectivities that are comparable to those obtained in solution, with enantioselectivities slightly worse or of the same order. The cationic complexes also can be immobilized by electrostatic interactions with anionic supports, and the situation is the same when these are used in dichloromethane, with stere-

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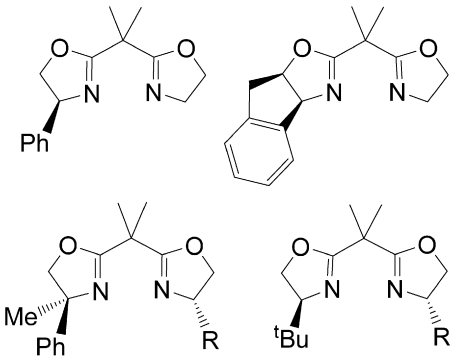


Fig. 1. Some structures of Box ligands lacking C_2-symmetry.

oselectivities similar or worse than those in the homogeneous phase [10,11].

However, surface-mediated selectivity has been observed in this reaction either by changing the reaction solvent [12] or by using supported ionic liquid films [13]. The decrease in either the dielectric permittivity of the solvent or the thickness of the ionic liquid film induces the approach of the Box–Cu complex to the clay sheet in the immobilized catalyst, leading to a reversal of the diastereoselectivity (*cis*-cyclopropanes are the major products) and also to a reversal of the absolute configuration of the major *cis*-cyclopropane. These surface effects also have been reported for the same cyclopropanation reaction when immobilized pyridinoxazoline–copper (Pyox–Cu) complexes were used as catalysts [14], as well as for Diels–Alder reactions catalyzed by Box–Cu complexes immobilized on silica [15,16]. In fact, given the fact that chirality is easier to achieve in two dimensions than in three dimensions [17,18], heterogeneous catalysis should take advantage of surface confinement effects more often if such effects were sought out, instead of trying to avoid them.

In the case of cyclopropanation reactions, previous results have demonstrated the crucial influence of the clay surface on the stereochemical course of the reaction. In these cases, ligand C_2-symmetry disappears through the effect of the surface. These results demonstrate the need to design tailored Box ligands for heterogeneous catalysis to enhance the surface effect and to promote the preferential formation of *cis*-cyclopropanes, some of which have interesting applications [19–21] and are difficult to obtain in other ways [19,22–27]. Following this idea, we recently reported the synthesis of a new family of chiral Box ligands that lack C_2-symmetry and have different steric surroundings (Fig. 1) [28]. Other authors also have recently reported the synthesis of C_1-symmetric Box ligands, but with a different purpose [29]. Experimental studies carried out in the homogeneous phase, together with theoretical calculations, show that C_2-symmetry is not a prerequisite to obtaining good enantioselectivity [30,31] and that enantioselection comes from the different favored reaction channels, as a function of the different steric interactions between the ester group and the Box substituents.

One aim of the present work was to prove that specially designed ligands can lead to results in the heterogeneous phase that are rarely achieved in homogeneous conditions. Another aim was to try to rationalize the role of the clay surface in the stereochemical course of cyclopropanation reactions, catalyzed by immobilized Box–Cu complexes, by comparing the results obtained using C_2- and C_1-symmetric Box ligands. The general structures of all the bisoxazoline ligands used in this work are shown in Fig. 2.

2. Experimental

2.1. Synthesis of Box ligands

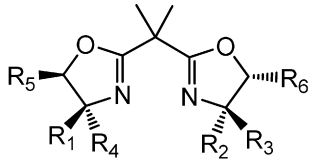
Bis(oxazoline) ligands were synthesized as described previously [28,32]. The novel Box (5*R*, 5′*R*)-2,2′-(propane-2,2-diyl)bis(5-phenyl-4,5-dihydrooxazole) (**1gs**) was prepared from 2,2-dimethylmalononitrile and (*R*)-2-amino-1-phenylethanol to yield 83% of the target compound in a reaction time of 72 h. The crude product was purified by recrystallization from diethyl ether (Et_2O) to afford **1gs** as a white solid. $[\alpha]_D = -153.22$ ($c = 1$, CH_2Cl_2). ^{1}H NMR: 7.24–7.18 (m, 10 H), 5.45 (dd, $J = 10.26$, 8.27 Hz, 2H), 4.24 (dd, $J = 14.39$, 10.26 Hz, 2H), 3.74 (dd, $J = 14.39$, *8.27 Hz, 2H), 1.60 (s, 6H). ^{13}C NMR: 169.24, 140.84, 128.69, 128.18, 125.89, 81.63, 62.85, 38.92, 24.49. Elemental analysis. Experimental: C, 74.97; H, 6.70; N, 8.28; O, 10.05. Calculated: C, 75.42; H, 6.63; N, 8.38; O, 9.57.

2.2. Immobilization of Box–Cu(OTf)$_2$ complexes on laponite

Laponite was dried at 140 °C overnight before the immobilization process. The Box–Cu complexes were prepared by dissolving the copper salt ($CuOTf_2$, 0.18 mmol) and the ligand (0.20 mmol) in anhydrous dichloromethane (1.5 ml). The mixture was stirred for 15 min, and the insoluble materials were removed by microfiltration. The solvent was evaporated under reduced pressure, and the complex was redissolved in methanol (13 ml). Laponite (0.5 g) was then added to the solution. The suspension was stirred at room temperature for 24 h, after which the solid was filtered off and thoroughly washed with methanol and dichloromethane. The catalyst was dried for 24 h under vacuum at room temperature before use.

2.3. Catalyst characterization

Copper analyses were carried out by plasma emission spectroscopy on a Perkin–Elmer Plasma 40 emission spectrometer. Transmission FTIR spectra of self-supported wafers evacuated ($<10^{-4}$ Torr) at 120 °C were recorded with a Mattson Genesis



R_1=Ph, R_2=R_3=R_4=R_5=R_6=H:	**1a**	R1=R_2=Ph, R_3=R_4=R_5=R_6=H:	**1as**
R_1=^{t}Bu, R_2=R_3=R_4=R_5=R_6=H:	**1b**	R_1=R_2=^{t}Bu, R_3=R_4=R_5=R_6=H:	**1bs**
R_1, R_5=Indanyl, R_2=R_3=R_4=R_6=H:	**1c**	R_1,R_5=R_2, R_6=Indanyl, R_3=R_4=H:	**1cs**
R_1=Ph, R_2=R_3=R_5=R_6=H, R_4=Me:	**1f**	R_1=R_2=Me, R_3=R_4=R_5=R_6=H:	**1ds**
R_1=^{t}Bu, R_2=Me, R_3=R_4=R_5=R_6=H:	**1h**	R_1=R_2=^{i}Pr, R_3=R_4=R_5=R_6=H:	**1es**
R_1=^{t}Bu, R_2=CH_2Ph, R_3=R_4=R_5=R_6=H:	**1i**	R_1=R_2=Ph, R_3=R_4=Me, R_5=R_6=H:	**1fs**
R_1=^{t}Bu, R_2=Ph, R_3=R_4=R_5=R_6=H:	**1j**	R_1=R_2=R_3=R_4=H, R_5=R_6=Ph:	**1gs**

Fig. 2. General structure of all the Box ligands used in this work.

Series FTIR spectrophotometer. Step-scanned X-ray diffraction patterns of oriented samples were collected at room temperature from 3° in 2θ up to 60°, using a D-Max Rigaku system with a rotating anode. Surface areas were determined by N_2 adsorption (BET) using a Micromeritics ASAP 200 apparatus.

2.4. Cyclopropanation reaction of styrene (**2**) and ethyl diazoacetate (**3**)

Ethyl diazoacetate (two additions of 2.5 mmol) was slowly added with a syringe pump to a solution of styrene (5 mmol) and *n*-decane (100 mg) in the corresponding solvent (5 ml of dichloromethane or styrene itself) containing the copper catalyst (0.05 mmol of Box–Cu complex or 150 mg of exchanged laponite) at room temperature. After total consumption of the diazoacetate was achieved, the solid catalyst was filtered off, washed with dichloromethane, and air-dried. The reaction was monitored by gas chromatography. FID from Hewlett–Packard 5890-II, cross-linked methyl silicone column: 25 m × 0.2 mm × 0.33 μm; helium as carrier gas. 20 psi; injector temperature: 230 °C; detector temperature: 250 °C; oven program: 70 °C (3 min), 15 °C min^{-1} to 200 °C (5 min); retention times: ethyl diazoacetate 3.2 min, styrene 3.82 min, *n*-decane 5.47 min, diethyl maleate 7.84 min, diethyl fumarate 8.02 min, *cis*-cyclopropanes 10.91 min, *trans*-cyclopropanes 11.41 min. The asymmetric inductions of the reactions also were determined by gas chromatography with a Cyclodex-β column. Oven temperature program: 125 °C isotherm; retention times: (1*S*, 2*R*)-cyclopropane 28.9 min, (1*R*, 2*S*)-cyclopropane 29.8 min, (1*R*, 2*R*)-cyclopropane 34.3 min, (1*S*, 2*S*)-cyclopropane 34.9 min.

2.5. Cyclopropanation reaction of 4-vinylbiphenyl (**6**) and ethyl diazoacetate (**3**)

Each reaction was carried out in the same way as the cyclopropanation reaction between ethyl diazoacetate and styrene, but using dichloromethane and toluene as solvents. The reaction was monitored by gas chromatography; FID from Hewlett–Packard 5890-II, cross-linked methyl silicone column: 25 m × 0.2 mm × 0.33 μm; helium as carrier gas. 20 psi; injector temperature: 230 °C; detector temperature: 250 °C. Oven program 100 °C (2 min), 20 °C min^{-1}, 220 °C (10 min); retention times, ethyl diazoacetate 2.33 min, 4-vinylbiphenyl 8.57 min, diethyl fumarate 4.59 min, diethyl maleate 4.73 min, *cis*-cyclopropanes 14.90 min, *trans*-cyclopropanes 16.87 min. Asymmetric inductions were determined by HPLC chromatography using a Daicel Chiralpack IA column 0.36 cm × 25 cm, flow rate: 0.8 ml min^{-1}, hexane/ethyl acetate/chloroform 97/1/2; detected on a UV/VIS spectrometer at retention times (1*S*, 2*R*)-cyclopropane 19.95 min, (1*R*, 2*S*)-cyclopropane 22.2 min, (1*R*, 2*R*)-cyclopropane 30.75 min, (1*S*, 2*S*)-cyclopropane 36.64 min.

2.6. Cyclopropanation reaction of styrene (**2**) and tert-butyl diazoacetate (**9**)

tert-Butyl diazoacetate (one addition of 2 mmol) was slowly added with a syringe pump to a solution of styrene (2 mmol) and *n*-decane in the corresponding solvent (5 ml of dichoromethane or styrene) containing the copper catalyst (0.02 mmol of Cu–Box complex or 100 mg of exchanged laponite) at room temperature. The reaction was monitored by gas chromatography; FID from Hewlett–Packard 5890II, using the same conditions as for the ethyl diazoacetate reaction. Retention times: *tert*-butyl diazoacetate 2.3 min, styrene 3.8 min, *n*-decane 5.5 min, di-*tert*-butyl fumarate 9.5 min, di-*tert*-butyl maleate 9.9 min, *cis*-cyclopropanes 11.4 min, *trans*-cyclopropanes 11.8 min. The asymmetric inductions were determined by transesterification of the reaction mixture with ethanol, catalyzed by *p*-toluenesulfonic acid, to obtain the ethyl esters and then by gas chromatography using the same conditions as for the enantioselectivity determination in the reactions with ethyl diazoacetate.

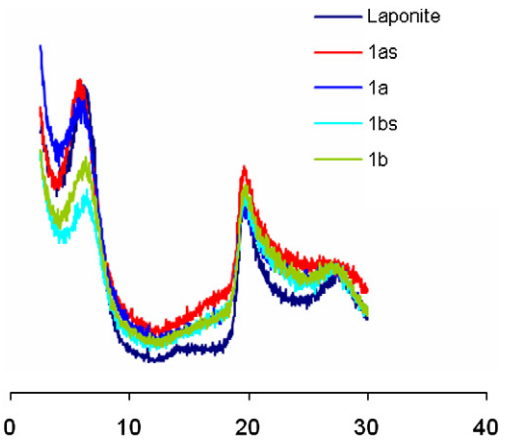


Fig. 3. XRD patterns of exchanged Cu(II) complexes on laponites: (a) lap–Cu**1a**, (b) lap–Cu**1as**, (c) laponite (**black line**), (d) lap–Cu**1b**, (e) lap–Cu**1bs**.

Table 1
Copper analyses of the supported Box–Cu(II) complexes

Ligand	Cu (mmol g^{-1})	Ligand	Cu (mmol g^{-1})
1as	0.28	**1b**	0.25
		Recov.	0.22
1bs	0.29	**1c**	0.22
		Recov.	0.15
1ds	0.23	**1f**	0.30
		Recov.	0.27
1es	0.21	**1h**	0.30
	0.18	Recov.	0.29
1fs	0.34	**1i**	0.25
Recov.	0.26	Recov.	0.20
1a	0.25	**1j**	0.21
Recov.	0.21	Recov.	0.15

3. Results and discussion

3.1. Characterization of Box–Cu complexes supported on laponite

Heterogeneous catalysts were characterized by different techniques to study the structure of the support after ion exchange and also to provide evidence for the desired exchange of Cu–ligand complex onto the clay. The broadening of the (100) X-ray diffraction line (Fig. 3) and its lower intensity after cationic exchange of the voluminous bisoxazoline–copper complexes indicate partial loss of the lamellar structure (long-range order) of the synthetic laponite. BET isotherms of the exchanged solids showed a decrease in surface area from values of around 300 $m^2 g^{-1}$ for laponite to 200–225 $m^2 g^{-1}$ in exchanged solids.

The copper analysis results (Table 1) show that the amount of exchanged complex was similar in all cases, regardless of the ligand used. The analysis results on the solids recovered after the reactions demonstrate the absence of copper leaching, as would be expected for an ion-exchange support.

IR spectroscopy was used to confirm the presence of the complex exchanged onto the laponite and its structural integrity. Fig. 4 shows the IR spectra of the supported Box **1a**- and **2b**–copper complexes, along with the spectrum of the same complex in solution. Peaks at 1650 cm^{-1} for the exchanged **1a**–Cu complex and 1660 cm^{-1} for the **1b**–Cu complex, corresponding to the C=N double bond of the oxazoline ring, demonstrate the presence of the ligand in the solid, thus indicating exchange of the entire complex into the clay.

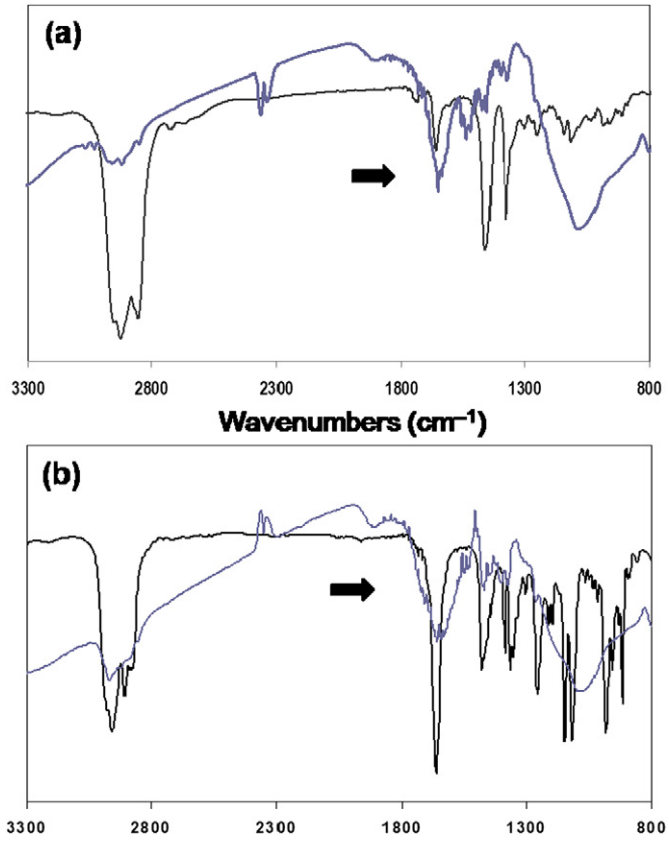
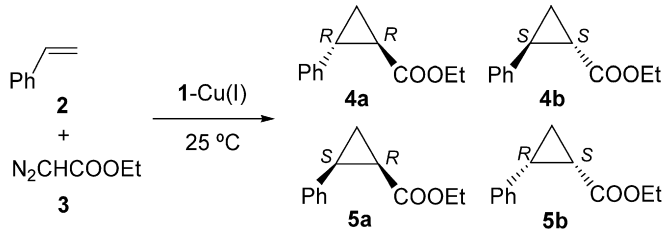


Fig. 4. Comparison of the IR absorption spectra of the **1a**–Cu(II) (a) and **1b**–Cu(II) (b) complexes exchanged onto laponite (gray line) and in solution (dark line).



Scheme 1. Cyclopropanation reaction between styrene (**2**) and ethyl diazoacetate (**3**).

3.2. Asymmetric cyclopropanation catalyzed by C_2-symmetric Box–Cu complexes

The reaction between styrene (**2**) and ethyl diazoacetate (**3**) was used as the benchmark reaction to study the effect of the surface on stereoselectivity (Scheme 1). The reaction was catalyzed by several Box–Cu complexes, either in the homogeneous phase (as trifluoromethylsulfonate salts) using CH_2Cl_2 as the reaction medium or immobilized onto laponite using a medium with a low dielectric constant to favor the approach of the complex to the laponite and maximize the surface effect. Styrene was chosen as the reaction medium for heterogeneous catalysts.

The catalytic studies started with several C_2-symmetric Box–Cu complexes (**1**–Cu). Substituents were chosen to tune the proximity of the complex to the surface. Table 2 gives the results of the benchmark cyclopropanation reaction catalyzed by these supported complexes, long with results from homogeneous-phase reactions for comparison.

The first interesting observation concerns *trans*/*cis*-diastereoselectivity. As described previously, using a low dielectric constant solvent in the heterogeneously catalyzed reaction (in this case, styrene itself) resulted in reversal of the *trans*/*cis*-selectivity with regard to homogeneous-phase reactions. A diastereoselectivity of up to 80% in *cis*-cyclopropanes was obtained with the C_2-symmetric ligands. This finding is interesting, because relatively few catalytic methods have demonstrated this preference, and most of those that have are based on the use of rather special ligands [19,22–27]. Furthermore, *cis*-cyclopropane structures are interesting for some types of biological activity, including drugs [19–21].

Table 2
Results of the cyclopropanation reaction of styrene with ethyl diazoacetate catalyzed by chiral **1**9-CuOTf complexes

Entry	Ligand	Homogeneous (CH_2Cl_2 as solvent)				Heterogeneous (styrene as solvent)			
		Yield	**4**/**5**	%ee (**4**)[a]	%ee (**5**)[b]	Yield	**4**/**5**	%ee (**4**)	%ee (**5**)
1	**1as**[c]	33	68/32	60	51	40	30/70[a]	7	−34[d]
2	**1as**[e]	–	–	–	–	30	20/80	4	−72
3	**1bs**	72	71/29	94	91	54	42/58	16	2
4	**1cs**	52	60/40	85	81	49	47/53	8	−10
5	**1ds**	50	70/30	66	62	53	17/83	18	−23
6	**1es**	53	70/30	72	63	88	22/78	19	−62
7	**1es**[f]	–	–	–	–	66	31/69	29	−20
8	**1fs**	72	60/40	−12	−31	66	38/62	4	−2
9	**1gs**	32	77/23	12	8	42	29/71	32	−33

[a] **4a** was the major product.
[b] **5a** was the major product.
[c] Previous results [12].
[d] Negative sign indicates that 1*S*-cyclopropanes (**4b**, **5b**) are the major enantiomers.
[e] Freshly prepared catalyst.
[f] Recovered catalyst.

Concerning enantioselectivity, the absolute configuration of the major *cis*-cyclopropanes was reversed with ligands **1as**, **1cs**, **1ds**, **1es**, and **1gs** compared with the homogeneous-phase results. Major effects were observed for ligands bearing phenyl, methyl, and *iso*-propyl groups, with a moderate enantioselectivity in *cis*-cyclopropanes obtained with the latter group. Surprisingly, the ligand bearing *tert*-butyl groups (**1bs**) was not as efficient, probably due to the relative weakness of the **1bs**–Cu complex, resulting in ligand leaching [10,33–35].

The enantioselectivity values obtained with ligand **1as** warrant particular attention. A previous study [12] found much lower enantioselectivity values for this ligand (up to 34% ee in *cis*-cyclopropanes; entry 1) than those obtained in the present investigation (entry 2). Replication of the catalyst immobilization experiments and catalytic reactions demonstrated that the freshly prepared catalyst led to an enantioselectivity of up to 72% in *cis*-cyclopropanes (with **5b** being the major product). In contrast, when the immobilized catalyst was stored for a prolonged time before use, the enantioselectivity in *cis*-cyclopropanes markedly decreased, likely due to degradation of the Box ligand on the laponite.

It is important to note that the enantioselectivity in *cis*-cyclopropanes obtained with ligand **1as** in the immobilized Cu complex was greater than that obtained in the homogeneous phase with the same catalyst in either *trans*- or *cis*-cyclopropanes. This finding nicely illustrates that the support can act as a beneficial factor in enantioselective catalysis, in contrast to the generally accepted wisdom.

Ligand **1fs** was found to be a special case (entry 8). Studies in the homogeneous phase [30,36] and theoretical studies [36] have demonstrated that the methyl group is more stereodirecting than the phenyl group in Box ligands, and for this reason, **4b** and **5b** are the major products obtained in the homogeneous phase. The presence of two substituents on the same carbon atom makes the approach of the complex to the laponite surface more difficult (and

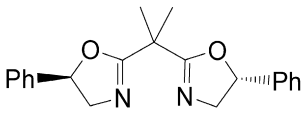


Fig. 5. Structure of ligand **1gs**.

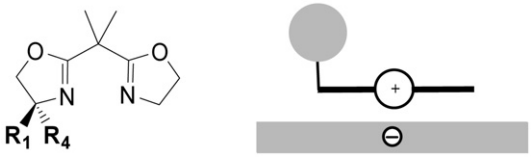


Fig. 6. Structure of C_1-symmetric ligands.

Table 3
Selectivity results in the cyclopropanation reaction using Box **(1a–f)**–Cu(I) complexes[a]

Ligand	Homogeneous (CH_2Cl_2 as solvent)				Heterogeneous (CH_2Cl_2 as solvent)				Heterogeneous (styrene as solvent)			
	4/**5**	%ee		F/M[d]	4/5	%ee		F/M[d]	**4**/**5**	%ee		F/M[d]
		(**4**)[b]	(**5**)[c]			(**4**)	(**5**)[e]			(**4**)	(**5**)	
1a	71/29	20	8	62/38	28/72	15	−32	40/60	9/91	15	−41	10/90
1b	68/32	29	8	53/47	53/47	15	−10	61/39	15/85	13	−48	19/81
1c	69/31	33	25	51/49					16/84	30	−32	15/85
1f	69/31	−8	−24	50/50					20/80	10	−25	

[a] Yields reached in each case are about 40% in homogeneous phase and using CH_2Cl_2 as solvent and 60% with styrene.
[b] **4a** was the major product.
[c] **5a** was the major product.
[d] F/M represents diethyl fumarate/diethyl maleate ratio.
[e] Negative sign indicates that 1*S*-cyclopropanes (**4b**, **5b**) are the major enantiomers.

probably also in a different orientation), so only a slight stereoselectivity reversal trend could be seen in the heterogeneous phase.

The effect of the position of the substituent on the oxazoline ring also was evaluated through the results obtained with ligand **1gs** (Fig. 5). In cases where the phenyl groups were located in the 5-position, far from the metal in the complex, poor enantioselectivity was expected for this ligand in the homogeneous phase, and this indeed was the case. But the same trend for *cis*-preference and reversal of absolute configuration in the major *cis*-cyclopropane was observed in the heterogeneous phase, pointing to a joint ligand–support effect on the stereoselectivity of the reaction.

In summary, our findings demonstrate surface confinement effects for catalysts derived from several C_2-symmetric ligands. The best results were obtained using ligand **1as**, which also was recoverable.

3.3. Asymmetric cyclopropanation catalyzed by C_1-symmetric Box–Cu complexes

Results with C_2-symmetric ligands **1** led us to consider how to make the clay surface act not only as a simple support for metal complexes, but also as a regulator for chiral reaction space. The easiest way to achieve this seemed to be to make the surface play the role of a bulky substituent. Consequently, we designed a new family of ligands that lack C_2-symmetry (**1a**–**1f**) and have substituents on only one of the oxazoline rings (Fig. 6). We hypothesized that the use of immobilized (**1a**–**1f**)–Cu complexes in a low-dielectric medium, such as styrene, would enhance the surface confinement effect.

Table 3 presents our results with (**1a**–**1f**)–Cu complexes in the benchmark cyclopropanation reaction in the homogeneous and heterogeneous phases in CH_2Cl_2 and styrene. In this case, even

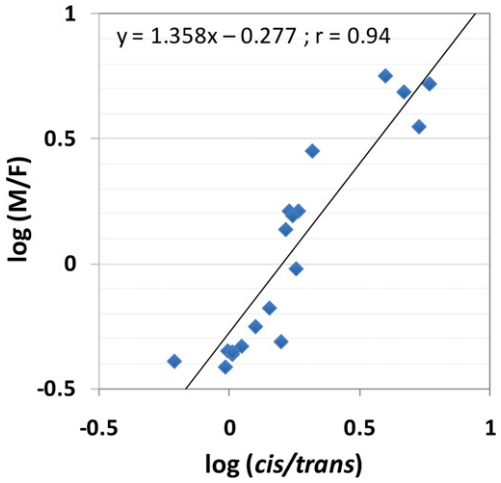


Fig. 7. Relationship between the *trans*/*cis*-selectivity in cyclopropanes and the maleate/fumarate ratio. A logarithmic scale has been chosen for the sake of LFER, but the correlation between raw data is also good ($r = 0.94$).

when CH_2Cl_2 was used as the solvent with the immobilized catalysts, the surface effect was clear. A reversal of *trans*/*cis*-selectivity was observed in all cases. As such, we managed to design new ligands that become situated closer to the surface, which improved the *cis*-selectivity obtained with C_2-symmetric ligands by up to 91%.

In parallel to the study of *trans*/*cis*-selectivity, we investigated the levels of diethyl maleate and diethyl fumarate formed as byproducts in the cyclopropanation reaction. The fumarate/maleate ratios (F/M) are given in Table 3. Curiously, a similar trend was seen, with diethyl fumarate the major side product when *trans*-cyclopropanes were the major products and diethyl maleate the major side product when *cis*-cyclopropanes were the major products. Indeed, comparing the stereoselectivity for C_1- and C_2-symmetric ligands in homogeneous and heterogeneous reactions demonstrates a fairly good linear relationship (Fig. 7). Based on these findings, we can conclude that the steric influence of the surface on the key Box–Cu–carbene intermediate (common to the cyclopropanation and dimerization reactions) is the main cause of the stereoselectivity changes observed.

Close examination of the enantioselectivity results led us to conclude that C_1-symmetric ligands were not appropriate for homogeneous-phase catalysis, as would be expected. The absence of bulky groups in one of the oxazoline rings led to poor enantioselectivity.

In the heterogeneous phase, the major product was the *cis*-cyclopropane **5b** (1*S*, 2*R*), as found when using C_2-symmetric ligands. This finding makes it quite difficult to propose a standard model to explain enantioselection in heterogeneous catalyzed cyclopropanation reactions using box C_2 and C_1 ligands.

Having demonstrated the surface effect with C_2- and C_1-symmetric box ligands, we decided to carry out further experimental work that involved changing the steric requirements of both the chiral ligand and the reagents. In an effort to confirm that the reversal of selectivity was due to the approach to the laponite surface, we designed a series of C_1-symmetric Box ligands bearing a *tert*-butyl group in one of the oxazoline rings and a variable volume substituent in the other ring (ligands **1h**–**1j** in Fig. 3).

The copper complexes were tested in the homogeneous phase and immobilized onto laponite and tested using styrene as the reaction medium. The results, shown in Fig. 8, demonstrate how an increase in the volume of the substituent resulted in an increase in enantioselectivity in homogeneous-phase reactions, whereas a decrease in the substituent volume resulted in an increase in *cis*-selectivity and enantioselectivity in *cis*-cyclopropanes

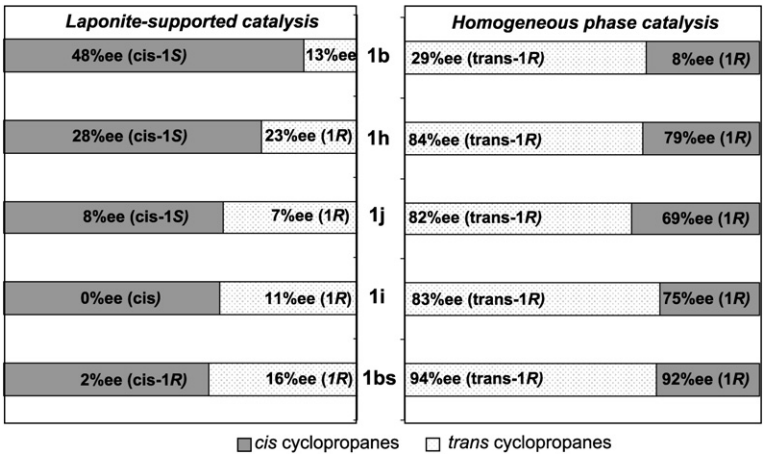
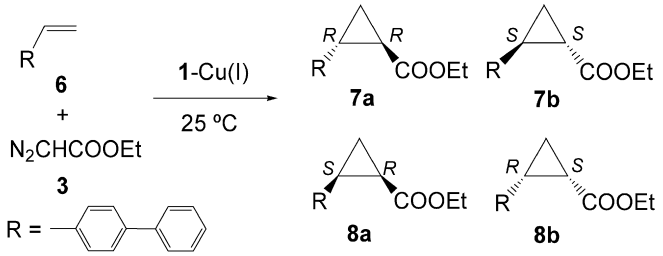


Fig. 8. *Trans*/*cis*-selectivities and enantioselectivities obtained in the cyclopropanation reaction of styrene and ethyl diazoacetate in homogeneous and heterogeneous phase using (**1b**, **1bs**, **1h**–**1j**)–Cu complexes.



Scheme 2. Cyclopropanation reaction between ethyl diazoacetate (**3**) and *p*-phenylstyrene (**6**).

in heterogeneous-phase reactions. The best results were obtained when R_2 = Me and H. These findings indicate that the substituent volume was directly related to the approach of the complex to the laponite surface and thus also to the stereochemical course of the reaction.

3.4. Cyclopropanation reactions with other reagents

Another way in which to influence the steric relationship of the catalytic complex and the laponite surface is to use reactants with bulkier groups. Thus, we attempted to increase the size of the alkene substituent or the ester group. Cyclopropanation reactions were carried out using *p*-phenylstyrene (4-vinylbiphenyl) (**6**) instead of styrene (**2**) as the alkene (Scheme 2), along with ethyl diazoacetate (**3**). Ligands **1a**, **1as**, **1b**, and **1bs** were chosen as representative for this study.

Reactions were carried out in the homogeneous phase using CH_2Cl_2 as the solvent. In the heterogeneous phase, toluene was selected as a reaction medium with a low dielectric constant, because *p*-phenylstyrene is a solid. It is worth noting that in previous studies, using styrene or toluene as a reaction medium led to the same stereoselectivities [12].

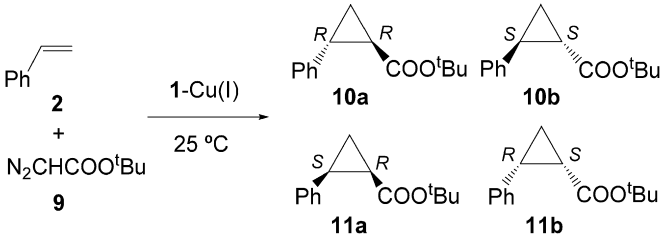
Surprisingly, the results obtained in these reactions (Table 4) are very similar to those previously obtained with styrene. A *cis*-preference was still observed in the heterogeneous phase, albeit no better than those obtained with styrene, even when the alkene bears a bulkier group that, in principle, makes *trans*-approach more difficult. Analogously, a reversal of enantioselectivity in *cis*-cyclopropanes in the heterogeneous reactions was observed, but without an improvement in the enantioselectivity.

Cyclopropanation reactions also were carried out using *tert*-butyl diazoacetate (**9**) as the carbene precursor (Scheme 3). The reactions of styrene with this diazo ester were catalyzed by Cu complexes of Box **1a**, **1as**, **1b**, and **1bs**. The solvent was CH_2Cl_2 in the

Table 4
Selectivity results in cyclopropanation reaction between *p*-phenylstyrene and ethyl diazoacetate using Box ligands **1a**, **1as**, **1b** and **1bs**

Ligand	Homogeneous (CH_2Cl_2 as solvent)			Heterogeneous (styrene as solvent)		
	7/**8**	%ee (**7**)[a]	%ee (**8**)[b]	**7**/**8**	%ee (**7**)[c]	%ee (**8**)
1as	69/31	63	52	28/71	52	−56
1bs	71/29	92	87	31/61	−8	−14
1a	68/32	19	8	11/89	15	−38
1b	66/34	27	8	18/82	19	−38

[a] **7a** was the major product.
[b] **8a** was the major product.
[c] Negative sign indicates that 1*S*-cyclopropanes (**7b**, **8b**) are the major enantiomers.



Scheme 3. Cyclopropanation reaction between *tert*-butyl diazoacetate (**9**) and styrene (**2**).

homogeneous-phase reactions and styrene in the heterogeneous-phase reactions with the immobilized complexes. The results of these experiments are gathered in Table 5.

As can be seen, the presence of a bulky unit in the ester group favored the formation of *trans*-cyclopropanes in the homogeneous phase, with greater *trans*-selectivities than those observed with ethyl diazoacetate. But the surface confinement effect in the case of immobilized catalysts was still able to reverse the *trans*/*cis*-diastereoselectivity, leading to a clear *cis*-preference. Again, the result obtained with ligand **1bs** was less reliable, because of the poorer stability of the Box–Cu complex [10,33–35].

The enantioselectivity values indicate that the presence of the bulky *tert*-butyl group prevented reversal of the absolute configuration of the major *cis*-cyclopropane when C_1-symmetric Box **1a** and **1b** were used as chiral ligands in the heterogeneous reactions.

Closer inspection of the enantioselectivities described in this work leads us to conclude that the proposed enantioselection model presented in previous reports on heterogeneously catalyzed cyclopropanation reactions [37] (Fig. 9a), in which principal re-

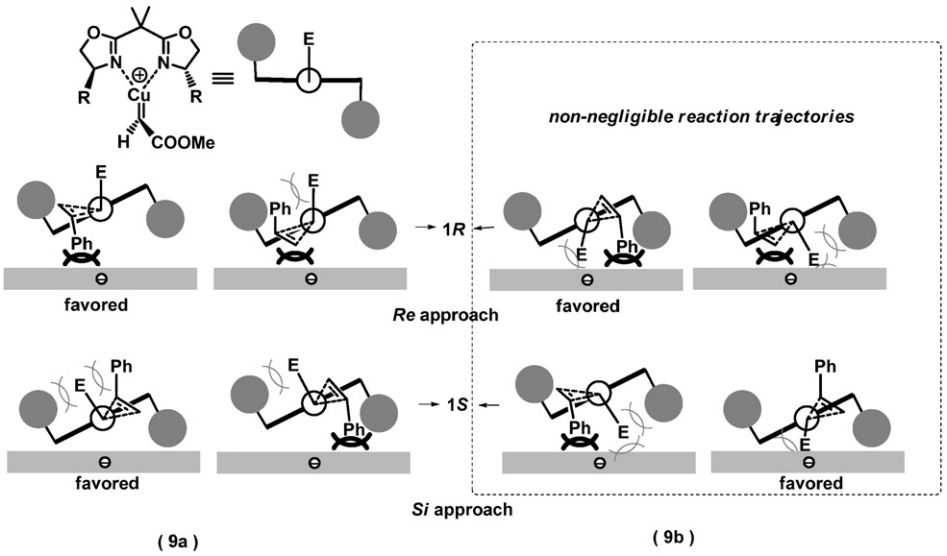


Fig. 9. Model previously proposed to explain enantioselection in asymmetric heterogeneously catalyzed cyclopropanation reactions (**9a**). Nonnegligible reaction trajectories with the ester group pointing toward the laponite surface (**9b**).

Table 5
Selectivity results in the Cu-catalyzed cyclopropanation reactions between styrene (**2**) and *tert*-butyl diazoacetate (**9**) using Box ligands **1a**, **1as**, **1b** and **1bs**

Ligand	Homogeneous (CH_2Cl_2 as solvent)			Heterogeneous (styrene as solvent)		
	10/**11**	%ee (**10**)[a]	%ee (**11**)[b]	**10**/**11**	%ee (**10**)	%ee (**11**)[c]
1as	85/15	70	59	23/77	40	−59
1bs	80/20	91	84	41/59	22	−11
1a	83/17	25	26	17/83	45	31
1b	80/20	26	25	32/68	3	8

[a] **10a** was the major product.
[b] **11a** was the major product.
[c] Negative sign indicates that 1*S*-cyclopropane **11b** is the major enantiomer.

action channels involve transition states with the ester group located far from the surface, is too simplistic and cannot explain either the reversal of enantioselectivities or the low values observed. When using such a model, one would not expect a reversal of enantioselectivity in *cis*-cyclopropanes when the reaction is catalyzed by C_1-symmetric Box in styrene; reversal indicates that pathways with the ester group pointing toward the surface are possible (Fig. 9b). Increases in the volume of the ester group (i.e., reaction with *tert*-butyl diazoacetate) disfavor the reaction channels, as indicated by the nonreversal of enantioselectivity. These results show that the steric repulsion of the clay surface may have been overemphasized and can be partially overcome by other attracting interactions (such as coulombic and dispersion forces).

Unfortunately, experimentally verifying these mechanistic proposals is not possible. Only indirect evidence, such as that presented in this work, and molecular modeling studies are able to shed light on these interesting but extremely complicated catalytic systems. Efforts in this direction are currently underway in our group.

4. Conclusion

Surface confinement effects can be very important in determining the stereochemical course of cyclopropanation reactions catalyzed by C_2-symmetric Box–Cu complexes. Complete reversal of *trans*/*cis*-diastereoselectivity was systematically observed, and even a reversal in the absolute configuration of the major *cis*-cyclopropane occurred. In some cases, such as the PhBox ligand (**1as**), the enantioselectivity obtained in the immobilized catalyst exceeded that obtained in the homogeneous phase. This indicates that support effects can be beneficial to the stereoselectivity of the reaction and allows one to obtain stereoisomers that are difficult to synthesize with homogeneous catalytic systems. Furthermore, alternating homogeneous and heterogeneous catalysis (or even changes in the dielectric permittivity of the reaction medium in the heterogeneous systems) can lead to different major stereoisomers of the cyclopropane products.

The design of C_1-symmetric Box ligands specifically for heterogeneous catalysis allowed improvement of the *cis*-selectivity of the benchmark cyclopropanation reaction up to 91% *cis*-cyclopropanes. This is consistent with a closer complex-surface approach, a situation corroborated by the less marked influence of the solvent on the stereochemical course of the reaction. On the other hand, the enantioselectivity in the major *cis*-cyclopropane did not improve with regard to the best C_2-symmetric ligand, and a reversal of the absolute configuration of the major product remained, a finding that is difficult to explain using the formerly proposed stereoinduction model.

Experiments carried out with reagents with greater steric demand highlight the existence of reaction channels in which the ester group points toward the support surface, a factor that had been disregarded in the former model. This factor makes it more difficult than expected to design chiral ligands to exploit surface confinement effects and suggests that more experimental and theoretical work is necessary to understand these otherwise interesting and synthetically useful effects.

Acknowledgments

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