# Supported Ionic-Liquid Films (SILF) as Two-Dimensional Nanoreactors for Enantioselective Reactions: Surface-Mediated Selectivity Modulation (SMSM)

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**Abstract:** Supported ionic-liquid films (SILF) of nanometric thickness containing bis(oxazoline)–copper complexes can be used as recoverable catalysts for enantioselective cyclopropanation reactions. When a thin film of ionic liquid is supported on a clay, the system behaves as a nearly two-dimensional nanoreactor in which the restrictions in rotational mobility and the close proximity to the surface support produce variations in the stereo- and enantioselectivities, leading to a complete reversal of the overall selectivity of the reaction. As an example, the cyclopropanation of styrene changes from a preference for the (1$S$,2$S$)-*trans* isomer in bulk solution to the (1$R$,2$S$)-*cis* isomer in the SILF. This variation is strongly dependent on both the thickness of the film and the nature of the support. Only layered solids with negative charges in the layers (clays) give rise to this type of behaviour, showing that the formation of ion pairs may be a decisive factor. This unexpected effect also shows the existence of differences between bulk and supported ionic liquids.

**Keywords:** asymmetric catalysis · enantioselectivity · ionic liquids · surface effects

## Introduction

Asymmetric heterogeneous catalysis[1] is conceptually very interesting due to the combination of the inherent practical advantages of heterogeneous over homogeneous catalysis and the enantioselectivity required for many products in the fine chemicals or specialities industries, such as pharmaceuticals or agrochemicals. Although the concept of heterogeneous catalysts is usually associated with solid catalysts, biphasic catalysis[2] in two immiscible liquid phases should be also included in the concept, because the catalyst is located in a phase different from that containing the reagents and product, thus making the catalyst easier to recover and reuse. The most studied method to prepare asymmetric heterogeneous catalysts is probably the immobilization of their homogeneous counterparts on solid supports.[3] In this regard, the chiral organic ligand of the catalytic complex offers many possibilities for immobilization through the formation of covalent bonds with the support,[3,4] although in many cases the required synthetic steps can prove to be difficult. Similar difficulties are encountered when modifications of the ligand are required in order to increase the solubility of the complex in the immiscible solvent of the biphasic system. This problem is overcome by the use of ionic liquids as the solvent phase for the catalyst,[5] for which even commercially available ligands and catalysts can be used, as is the case for bis(oxazoline) ligands.[6]

However, the use of ionic liquids has two major drawbacks, namely price and viscosity. The first issue makes it important to reduce the amount of solvent required, whereas the second makes it of interest to seek new methods that enable the easy handling of the ionic liquids. One way to solve these drawbacks would be the immobilization of an ionic-liquid phase on a solid support, a strategy that has already been reported in the literature. In some cases imidazolium salts have been anchored onto solids and the ionic-liquid phase added to these modified supports.[7] However, it has also been shown that it is possible to form films of ionic-liquid phases directly on nonmodified supports, such as silica[8] or diatomaceous earth,[9] and more recently ionic-liquid phases have been occluded during the synthesis of porous solids to give nanoliquids.[10] However, reports concerning applications of supported ionic liquids for asymmet-

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ric catalysis are scarce[11,12] and precedents on the use of lamellar solids as supports do not exist.

In this paper we present our results on the application of supported ionic-liquid films (SILF) for enantioselective cyclopropanation reactions and describe for the first time how this approach can be used to obtain a surface-mediated selectivity modulation (SMSM).

## Results and Discussion

**Preparation and use of SILF**: Laponite (a generous gift from Rockwood Additives Ltd.) was chosen as the support. 5,5′-Isopropylidenebis[(4R)-4-phenyl-4,5-dihydro-1,3-oxazole]
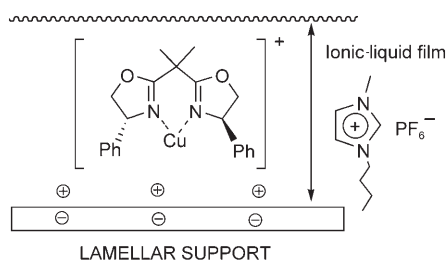


Figure 1. Structure of the catalytic supported ionic-liquid film (SILF).

(Figure 1) was used as the chiral ligand to compare the results obtained with the SILF and those obtained in bulk ionic liquids[6] as well as with the heterogeneous catalysts prepared by cationic exchange on the same support.[13]

The complex was prepared by mixing CuCl, chiral ligand and the ionic liquid—in most cases the commercially available 1-butyl-3-methylimidazolium hexafluorophosphate [bmim][PF$_6$] (Figure 1). The use of chloride as the counterion in cyclopropanation reactions carried out in molecular solvents leads to much worse results due to the influence of the counterion on the geometry of the transition state.[14] However, we have shown that, in ionic liquids, the anion of the solvent plays the role of counterion.[6] Dichloromethane was used to facilitate complex formation and the dispersion of the SILF on the laponite surface. After the addition of the support, the suspension was stirred for 2 h and the chlorinated solvent was removed under vacuum. The resulting solids were free-flowing powders and were used as heterogeneous catalysts in solvent-free cyclopropanation reactions between alkenes and ethyl diazoacetate. The reaction between styrene (**1a**) and ethyl diazoacetate (**2**) was used as a benchmark test (Scheme 1).
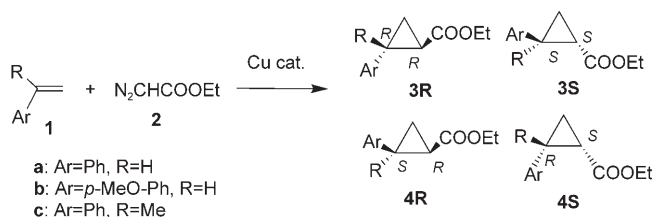


Scheme 1. Cyclopropanation reactions of styrene and related substrates.

Several factors were studied: ionic-liquid/support ratio, catalyst concentration (copper/ionic-liquid ratio), amount of catalyst (diazoacetate/copper ratio), nature of the support and extraction solvent.

**Effect of the amount of ionic liquid**: First of all it was crucial to find the limit to which the SILF can be reduced without significant changes to the results. Different ionic-liquid/support ratios were tested, while the other parameters were kept constant. The results of these experiments are gathered in Table 1. Entries 2–4 also show the effect of catalyst recycling.

When the result in the homogeneous ionic-liquid phase (entry 1) is compared with those obtained with SILF it ap-

Table 1. Effect of film thickness on cyclopropanation reactions between styrene (**1a**) and ethyl diazoacetate (**2**) catalyzed by SILF.[a]

| Entry | [Catalyst] | IL/support | Yield[b] [%] | trans/cis[b] | ee trans[c] [%] | ee cis[c] [%] |
|---|---|---|---|---|---|---|
| 1 | 0.076 | homogeneous | 42 | 67/33 | 54 | 45 |
| 2 | 0.025 | 0.402 | 18 | 60/40 | 43 | 0 |
| | | | 29 | 60/40 | 47 | 2 |
| | | | 38 | 60/40 | 49 | 5 |
| | | | 32 | 60/40 | 53 | 10 |
| 3 | 0.050 | 0.268 | 18 | 58/42 | 43 | −10 |
| | | | 28 | 57/43 | 46 | −7 |
| | | | 28 | 57/43 | 49 | −2 |
| | | | 26 | 58/42 | 51 | 3 |
| | | | 28 | 58/42 | 52 | 7 |
| | | | 31 | 58/42 | 54 | 13 |
| 4 | 0.076 | 0.134 | 12 | 49/51 | 32 | −36 |
| | | | 19 | 50/50 | 40 | −28 |
| | | | 33 | 50/50 | 50 | −17 |
| | | | 32 | 55/45 | 53 | 7 |
| 5 | 0.076 | 0.067 | 3 | 41/59 | 27 | −53 |
| 6[d] | 0.076 | 0.067 | 16 | 37/63 | 28 | −50 |
| 7[e] | 0.076 | 0.067 | 37 | 33/67 | 25 | −56 |

[a] [Catalyst] = mmol Cu mL$^{-1}$ [bmim][PF$_6$]. IL/support = mL g$^{-1}$. Reaction conditions: 1.5 equiv styrene, 1 % catalyst, ethyl diazoacetate slowly added (2 h), room temperature, 24 h. Extraction: hexane (5×3×3×3 mL). [b] Determined by GC. [c] Determined by GC (cyclodex-B column). **3Sa** and **4Sa** are the major enantiomers. Results with a minus sign indicates that **4Ra** is obtained as the major cis enantiomer. [d] Extraction with diethyl ether. [e] 3 % catalyst.

pears that the presence of the support has an influence on the selectivity of the process. A decrease in the amount of ionic-liquid solvent on the surface leads to a decrease in yield and in trans/cis selectivity. Furthermore, both enantioselectivities, that is, for trans and cis isomers, are modified with thinner films. The preference for the enantiomers **3Ra** and **4Ra** is reduced and the enantioselectivity for cis isomers is even reversed, from 45 % ee for **4Ra** to 53 % ee for **4Sa**. This result shows the existence of a surface-mediated selectivity modulation (SMSM) when the mobility of the catalytic complex in the SILF is inhibited by reducing the thickness of the film.

Taking into account the lamellar nature of the laponite support and the measured surface area (370 m$^2$ g$^{-1}$), the thickness of a uniform film can be estimated from the

volume of ionic liquid. This thickness varies from 10.8 Å (entry 2) to 1.8 Å (entry 5), dimensions that seem to be too small to accommodate the complex. This may indicate that only the external surface of the clay tectoids is covered by the ionic-liquid phase, making it difficult to calculate the film thickness. X-ray diffraction patterns of oriented samples were taken from the starting laponite and the support with ionic liquid at different ratios (Figure 2). As can be seen, a
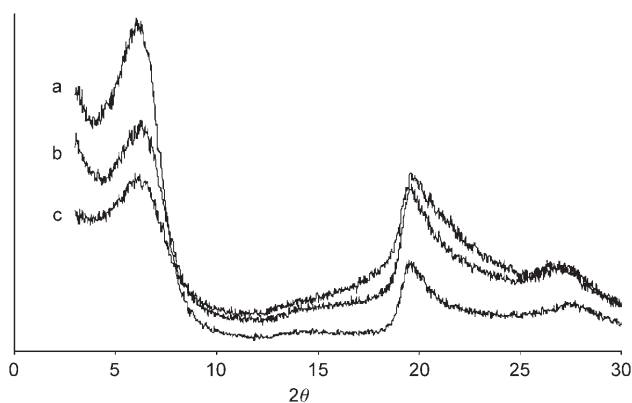


Figure 2. XRD patterns: a) laponite, b) laponite with ionic liquid 0.134 mL g$^{-1}$, c) laponite with ionic liquid 0.402 mL g$^{-1}$.

larger amount of ionic liquid does not produce any increase in the basal spacing of the support but does lead to a decrease in the intensity of the (001) refraction line. From this result we can conclude that a greater level of disorder in the stacking of the clay layers is induced by the ionic liquid and, as a consequence, part of the inaccessible interlamellar surface becomes accessible.

Another interesting aspect of heterogeneous catalysts is the possibility of recovery and reuse. The solids, after extraction with hexane, were reused under the same conditions and the results are shown in Table 1 and Figure 3. A sustained increase in enantioselectivity is observed for *trans* isomers, whereas for the *cis* isomers the enantioselectivity tends to zero or is even reversed, albeit with low values. This behaviour may be due to an increase in the thickness
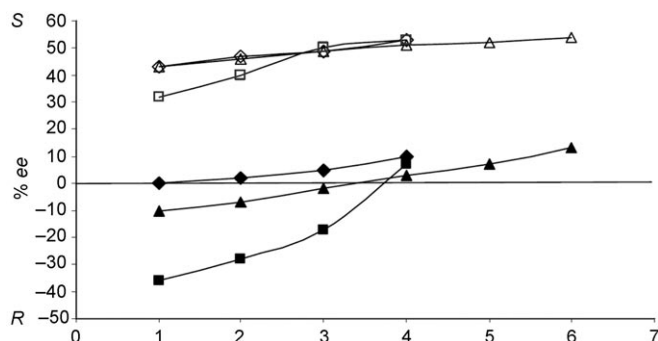


Figure 3. Evolution of enantioselectivity with recovery of SILF with different ionic-liquid/support ratios. Open symbols represent % *ee* for *trans* cyclopropanes and solid symbols % *ee* for *cis* isomers. (◆) 0.402 mL g$^{-1}$, (▲) 0.268 mL g$^{-1}$, (■) 0.134 mL g$^{-1}$.

of the SILF by accumulation of byproducts from the reaction or the presence of residual hexane in the ionic-liquid phase. In fact, the increase in yield observed could also be due to this accumulation, which would allow the extraction of larger amounts of products.

In an attempt to increase the extraction of products, diethyl ether was used as an extraction solvent instead of hexane (entry 6). As expected, the yield obtained under the conditions shown for entry 4 in Table 1 was significantly higher (16% vs. 3% with hexane) and the same selectivities were observed. This extraction method was used in the subsequent catalytic tests.

In spite of these interesting effects on the stereoselectivity, it should be noted that cyclopropanation yields are very low with these thin films, although 37% yield can be obtained when the amount of copper catalyst is increased to a 3% molar ratio without modification of the stereochemical results.

**Effect of the nature of the support and the liquid phase**: We have so far demonstrated the existence a support effect on the selectivities of cyclopropanation reactions when laponite is used as the support for a SILF. In another set of experiments we aimed to study the requirements in terms of the nature of the support to obtain this type of effect. Laponite, as a clay, is a solid with a lamellar structure and with negative charges in the layers. We tried to ascertain whether both properties were necessary for a support effect. Two more clays were tested, bentonite and K10 montmorillonite, together with a tridimensional microporous aluminosilicate (Y zeolite, a nonlamellar solid with negative charges), silica gel (an amorphous uncharged support) and two more lamellar solids—graphite (an uncharged support) and a hydrotalcite (a positively charged solid). The results of these experiments are gathered in Table 2.

Entries 1–5 show the effect of the support with the same IL/support ratio, even below the lowest level used with la-

Table 2. Effect of the nature of the support on cyclopropanation reactions between styrene (**1a**) and ethyl diazoacetate (**2**) catalyzed by SILF.[a]

| Entry | Support | IL/support | Yield[b] [%] | trans/cis[b] | ee trans[c] [%] | ee cis[c] [%] |
|---|---|---|---|---|---|---|
| 1 | bentonite | 0.05 | 76 | 57/43 | 47 | 4 |
| 2 | graphite | 0.05 | 26 | 68/32 | 54 | 45 |
| 3 | hydrotalcite | 0.05 | 48 | 66/34 | 51 | 43 |
| 4 | zeolite Y | 0.05 | 7 | 48/52 | 38 | 20 |
| 5 | silica | 0.05 | 26 | 64/36 | 54 | 38 |
| 6 | bentonite | 0.03 | 36 | 22/78 | 6 | −62 |
| 7 | K10 | 0.03 | 24 | 36/64 | 27 | −42 |
| 8 | K10 | 0.01 | 26 | 23/77 | 5 | −61 |
| 9 | graphite | 0.01 | 19 | 67/33 | 56 | 48 |
| 10 | K10[d] | 0.01 | 28 | 36/64 | 11 | −51 |

[a] [Catalyst] = 0.076 mmol Cu mL$^{-1}$ [bmim][PF$_6$]. IL/support = mL g$^{-1}$. Reaction conditions: 1.5 equiv styrene, 1% catalyst, ethyl diazoacetate slowly added (2 h), room temperature, 24 h. Extraction: diethyl ether (5 × 3 × 3 mL). [b] Determined by GC. [c] Determined by GC (cyclodex-B column). **3Sa** and **4Sa** are the major enantiomers. Results with a minus sign indicates that **4Ra** is obtained as the major *cis* enantiomer. [d] [Oct$_3$NMe][OTf] as ionic liquid.

ponite, just to ensure that the thickness is sufficiently low to observe any effect. It can be seen that graphite, hydrotalcite and silica give rise to the same selectivity results as the homogeneous catalyst, both in *trans/cis* ratio and enantioselectivity. In contrast, zeolite Y and bentonite show a slight effect, with reduced *trans/cis* ratio and enantioselectivity, although the yield is greatly reduced with the zeolitic support. This seems to indicate that the anionic nature of the support is important to obtain any effect, whereas the lamellar structure is only important in combination with this anionic nature. The microporous nature of the zeolite may introduce an additional complication to this interpretation, as the ability of the catalytic complex to enter the micropores is doubtful but the ionic liquid probably fills the void space of the support. As the yield is also very low, the subsequent tests were carried out with bentonite, but K10 montmorillonite was also studied as an example of a delaminated clay.

The support effect can be noticeably increased by reducing the amount of ionic-liquid phase (entry 6), as occurred in the case of laponite. However, with bentonite the selectivity towards the *cis*-cyclopropane **4Ra** is even higher, a consequence of a higher *cis* preference and a higher enantioselectivity (62 % *ee*). In the case of K10 the same effect was observed, but a smaller amount of SILF was necessary to obtain the same selectivity levels (entry 8). As further confirmation of the inability of the uncharged lamellar graphite to produce this effect on selectivity, the same low IL/support was used and identical results in selectivity were obtained.

The nature of the ionic liquid only has a slight influence on the catalytic results (entry 9). This influence is also observed in the bulk ionic-liquid phase[6] and is not due to different surface effects.

The results show how the close proximity of the support surface, controlled by the thickness of the SILF, can be used to modify the stereochemical results of the reaction due to changes in the energies of the different transition states induced by the steric influence of the support. Under these conditions, the minor product in solution becomes the major product in the supported phase. If changes in enantioselectivity for the *cis* products are considered, the influence of the surface modifies the relative energy of the transition states by about 1.4 kcal mol$^{-1}$, a significant effect when compared with the subtle energy differences involved in selectivity.

Although the steric influence of the support is the ultimate reason for this behaviour, the support should fulfil two requirements, namely a negative charge located on a planar surface. The clay-SILF seems to act as an almost two-dimensional nanoreactor in which rotational mobility is strongly hindered so that the reactor wall, that is, the clay surface, is an active component in the process. The necessity for a charged surface may be related to the cationic nature of the catalyst. In fact we had previously observed this influence in reactions carried out in solvents with very low dielectric constants, a situation that induces the formation of strong catalyst–surface ion pairs.[15] It seems that the interaction between catalyst and surface is due to the presence of charges,

which is rather surprising for an ionic liquid, in which strong ion pairs are not expected. This phenomenon has been experimentally demonstrated in this reaction, as complexes prepared with copper triflate and copper chloride display the same results when used in ionic liquids,[6] but not in dichloromethane.[14,16]

**Surface effect in other cyclopropanation reactions**: In an attempt to show the generality of this effect on selectivities, four different alkenes were tested. The results of these experiments are gathered in Table 3. The two cycloalkenes

Table 3. Effect of the surface on cyclopropanation reactions of different alkenes catalyzed by SILF.[a]

| Entry | Alkene | Support | Yield[b] [%] | *trans/ cis*[b] | *ee trans*[c] [%] | *ee cis*[c] [%] |
|---|---|---|---|---|---|---|
| 1 | **5a** | homogeneous | 43 | 96/4 | – | – |
| 2 | **5a** | laponite | 9 | 58/42 | – | – |
| 3 | **5b** | homogeneous | 21 | 80/20 | – | – |
| 4 | **5b** | laponite | 13 | 35/65 | – | – |
| 5 | **1b** | homogeneous | 56 | 68/32 | 66 | 45 |
| 6 | **1b** | laponite | 16 | 40/60 | 28 | −33 |
| 7 | **1c** | homogeneous | 64 | 53/47 | 52 | 47 |
| 8 | **1c** | laponite | 20 | 35/65 | 15 | −37 |

[a] [Catalyst] = 0.076 mmol Cu mL$^{-1}$ [bmim][PF$_6$]. IL/support = 0.01 mL g$^{-1}$. Reaction conditions: 1.5 eq alkene, 1 % catalyst, ethyl diazoacetate slowly added (2 h), room temperature, 24 h. Extraction: diethyl ether (5×3×3×3 mL). [b] Determined by GC. [c] Determined by GC (cyclodex-B column). **3S** and **4S** are the major enantiomers. Results with a minus sign indicates that **4R** is obtained as the major *cis* enantiomer.

were symmetrical and therefore did not give rise to any enantioselectivity (Scheme 2). These compounds were tested to assess the effect on *trans/cis* selectivity of an aliphatic
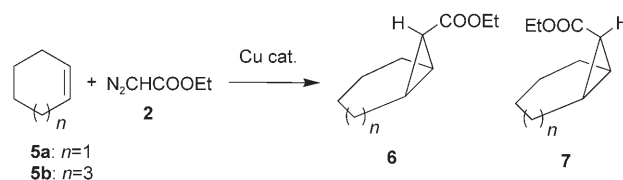


Scheme 2. Cyclopropanation reactions with cycloalkenes.

cyclic chain. As can be seen, the preference is reversed in the SILF with cyclooctene (**5b**) (entry 4), from 80:20 in solution to 35:65 with the SILF, but this is not the case with cyclohexene (**5a**) (entry 2). This result is probably due to the really high *trans* preference in solution, showing that the interaction between the incoming cyclohexene ring and the ester of the diazoacetate moiety in the carbene intermediate is much stronger than in the case of cyclooctene. As the final selectivity is a balance between this interaction and that between the incoming alkene and the catalyst surface, the very high *trans* selectivity in solution (96:4) demonstrates that the steric repulsion is strong in that case and the alkene–surface interaction can only reduce the preference to 58:42.

In the case of an elongated styrene with a methoxy group in the *para* position (**1b**, Scheme 1), a higher interaction with the surface was expected and, consequently, a higher *cis* selectivity. However, this was not the case (entry 6) and this fact may be due to the approach of the alkene not being completely parallel to the surface, a situation that would reduce the influence of the *para* substituent. The enantioselectivities follow the same trend as observed with styrene, with reversal of the induction for the *cis* cyclopropanes. However, in these cases the enantiomeric excesses are lower.

Finally, an additional methyl group was introduced in the alpha position of the styrene (**1c**, Scheme 1) in order to assess the level of the steric effects of both substituents (phenyl and methyl). As expected (entry 8) the *trans*/*cis* selectivity in solution is lower than in the case of styrene and is reversed with the SILF. The enantioselectivities follow the same trend observed with the other styrene derivatives in that it is reduced for the *trans* isomers and reversed for the *cis* cyclopropanes, although the level is only moderate (37 % *ee*, with **4Rc** as the major enantiomer).

This result clearly indicates that the surface effect is strongly dependent on the natures of the substituents on the alkene, as these influence the alkene–surface interaction as well as the ester–alkene interaction already present in solution.

## Conclusion

We have shown that clay–SILFs of suitable thickness can essentially act as nearly bidimensional nanoreactors. The results of the reactions taking place in these new reactors are greatly influenced by the confinement effects, which in turn depend on the ionic nature of the support surface and the thickness of the ionic-liquid film. The modifications, and even reversals, in both *trans*/*cis* and enantioselectivity observed with different alkenes show the generality of these surface effects, which are dependent on the substituents on the alkene. An understanding of the surface–complex–alkene interactions should allow the design of new, more efficient systems that are able to give products that are stereochemically different to those obtained in solution.

## Experimental Section

**Supported ionic-liquid films**: The support was dried under vacuum for 24 h prior to use. The required amount of dried support was mixed with anhydrous dichloromethane (5 mL) and this suspension was added to a mixture of 5,5′-isopropylidenebis[(4R)-4-phenyl-4,5-dihydro-1,3-oxazole],[17] copper chloride and anhydrous ionic liquid (see Tables 1–3 for amounts). After stirring for 2 h, the solvent was evaporated under reduced pressure to give a free flowing powder, which was dried under vacuum overnight.

Two samples without copper and chiral ligand were prepared in the same way. Step-scanned X-ray diffraction patterns of these two oriented samples were collected at room temperature from 3° in 2θ up to 60°, using a D-max Rigaku system with a rotating anode. The diffractometer was op-

erated at 40 kV and 80 mA, and the Cu$_{K\alpha}$ radiation was selected using a graphite monochromator.

**Cyclopropanation reactions**: Styrene was added to the stirred solid catalyst and ethyl diazoacetate was slowly added (2 h) with a syringe pump (see Tables 1–3 for amounts). The solid was stirred for 24 h and the products were extracted with hexane or diethyl ether ($5\times3\times3\times3$ mL). *n*-Decane (100 mg) was added as an internal standard and the results were determined by GC.[18]

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