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Enantioselective Catalysis Using Heterogeneous Bis(oxazoline) Ligands: Which Factors Influence the Enantioselectivity?

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I. Introduction

Chiral bis(oxazoline) (BOX) ligands have been successfully used in the asymmetric catalysis of a variety of reactions for the past decade.[1,2] However, these versatile catalytic systems suffer from one major drawback: a high catalyst-to-substrate ratio is required (generally 1−10 mol %). Their separation and recycling is therefore a prerequisite for their development as useful catalysts. Indeed, since 1997 many attempts to recycle BOX ligands in heterogeneous systems have been reported. The inherent advantage of heterogeneous catalysts over homogeneous ones is their ease of separation and handling.[3−7] Indeed, even though homogeneous catalysts provide more diverse potential applications, heterogeneous nonchiral catalysts are more used in terms of production. This is not yet true for chiral catalysts, and much research is still needed to arrive at a level of recycling of the catalytic systems that would enable the industrial exploitation of heterogeneous chiral catalysts.

This review presents different methods of heterogenization that have been developed for the separation and recycling of bis(oxazoline) ligands. The various methods include immobilization by covalent or noncovalent bonding, on organic or on inorganic supports, and using soluble or insoluble polymers. The review includes all such attempts that have been mentioned in the literature. One recycling process that uses ionic liquids is also reported, as well as some recycling attempts of homogeneous systems.

So far, six reaction types have been performed with heterogeneous BOX ligands: cyclopropanations, ene-reactions, Diels−Alder reactions, allylic substitutions, aziridinations, and Mukaiyama aldol reactions. The review dedicates a chapter to each reaction. The comparison of the various recycling methods for each reaction enables us to draw conclusions concerning the influence of general aspects of heterogenization methods (e.g., the symmetry of the heterogenized ligand, the density of grafting) on the catalytic performance. These conclusions may be relevant to other heterogeneous systems as well.

The symbol → will be used throughout the review to indicate recycling, e.g., “73 → 65” will be taken to mean “73% on the first cycle, and 65% on the second cycle”.

Some of the most commonly used bis(oxazoline) ligands are described in Chart 1. The symbols R_{ox} and R_{brg} will be used throughout the review to indicate the substituents on the oxazoline moieties or on the bridge of the ligand, respectively, as denoted in Chart 1.

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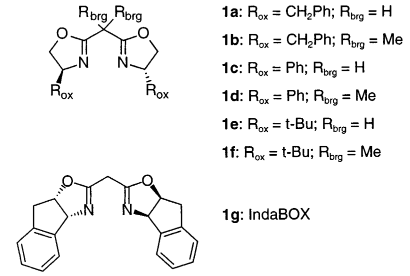
Dalit Rechavi received her B.Sc. from the Tel-Aviv University in 1996. She went on to do her M.Sc. in the same university, under the guidance of Prof. Shlomo Rozen. on the subject of fluorination of organic compounds using BrF_3. After completing her M.Sc. in 1998, she moved to Lyon, France, where she started her Ph.D. in 1999, at the University of Claude Bernard Lyon 1, under the guidance of Prof. Marc Lemaire, on the subject of heterogenization of chiral bis(oxazoline) ligands. Her interests include catalysis in general, and asymmetric catalysis in particular.

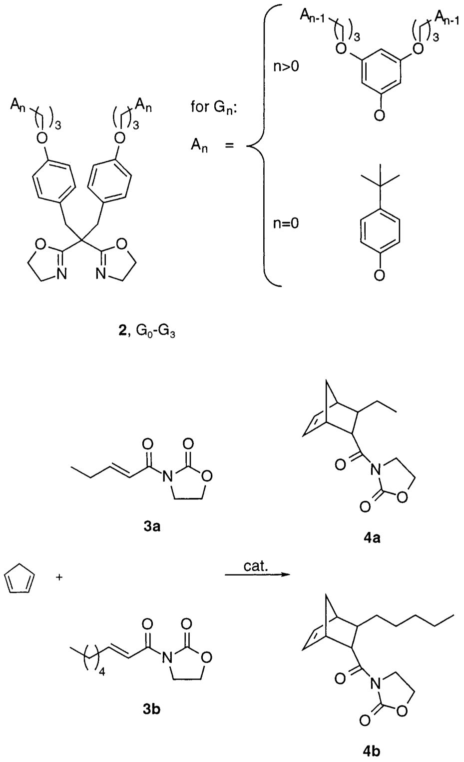
Professor Marc Lemaire was born in 1949 in Paris. He was employed several years in the pharmaceutical industry as a technician, and then he obtained the engineer level (CNAM Paris 1979) and his Ph.D. degree at the Paris VI University (Professor J. P. Guetté; “New chlorinating reagent”). In 1983, he obtained a postdoctoral position in the University of Groningen (The Netherlands; Professor R. M. Kellog; “Thiamacrocycles as ligands for asymmetric catalysis”). He returned to Paris and obtained an assistant position at CNAM, and then he became a professor at the University of Lyon. His group is working in five main areas: (1) heterogeneous catalysis in fine chemistry, (2) asymmetric catalysis, (3) separation science, including new ligands for liquid–liquid extraction, new ionoselective materials, new complexing agents for nanofiltration-complexation systems, (4) organic conductors, including poly(thiophenes) and poly(pyrroles), and (5) deep desulfurization of gasoil.

Chart 1. Some Examples of Bis(oxazoline) Ligands[a]



[a] R_{brg} – substituent on the bridge of the ligand. R_{ox} – substituent on the oxazoline moieties of the ligand.

Scheme 1. Dendrimers 2 (G_1–G_3) as Catalysts for the Diels–Alder Reaction, in an Attempt To Control Substrate Selectivity[a]



[a] The selectivity between **3a** and **3b** was slightly improved by the use of the G_3 dendrimer (see text).

In the context of heterogenization of bis(oxazoline) ligands, it is interesting to examine the dendritic nonchiral bis(oxazolines) **2** (Scheme 1) reported by Chow and Mak in 1997.[8] They proposed the use of bulky dendrimers of increasing size (G_0–G_3) to select between substrates of different size in the Diels–Alder reaction.

Only the G_3 dendrimer gave results that were significantly different from those of the nondendritic ligand in terms of selection between the substrates **3a** and **3b**, but even then the selectivity is only of 1.18 in the ratio of **4a**/**4b** (relative to a selectivity of 1.05 obtained by the nondendritic ligand). On one hand, this result could appear disappointing because of the weak effect on substrate selectivity. On the other hand, the compatibility of the reaction with bulky substituents on the bridge of the ligand is encouraging for the development of heterogeneous catalytic bis(oxazoline) systems.

II. Cyclopropanation

A. Introduction

Cyclopropanation reactions were one of the first intermolecular reactions to be catalyzed in an enantioselective manner, in 1966.[9] The obtained enantioselectivities were rather modest, up to 10%. Since then, much research has been performed to improve the enantioselectivities of the reaction, and several successful catalysts were conceived, e.g., using complexes of Rh with derivatives of carboxylic acids.[10–13]

A major advance was achieved by Pfaltz et al.,[14] who were the first to show that semicorrin–Cu(II)

Scheme 2. The Cyclopropanation Reaction of Styrene with EDA

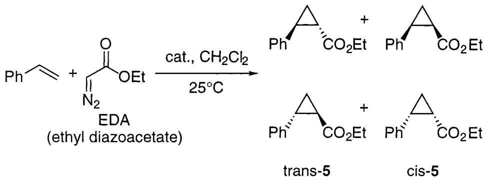
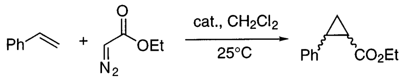


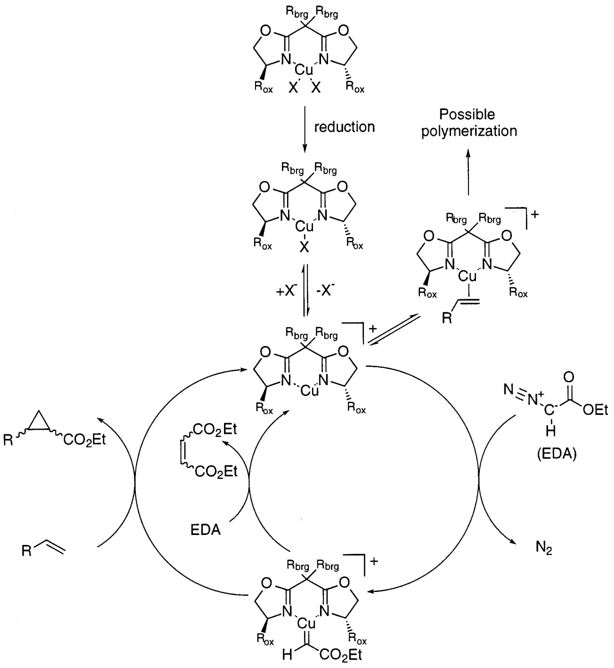
Table 1. Homogeneous Cyclopropanation of Styrene with Ethyl Diazoacetate (EDA)[a]



entry	ligand	R_{ox}	R_{brg}	yield	trans:cis	% ee trans	% ee cis	ref
1	**1a**[a]	CH_2Ph	H	76	71:29	36	15	15
2	**1c**[a]	Ph	H	81	70:30	60	52	15
3	**1e**[a]	t-Bu	H	80	75:25	90	77	15
4	**1e**[b]	t-Bu	H	n.g.[c]	77:23	98	93	16
5	**1f**[b]	t-Bu	Me	77	73:27	99	97	16

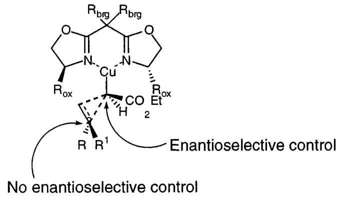
[a] A (ligand)$_2$–Cu complex was prepared using BuLi and $CuCl_2$, and used as 1 mol % (relative to EDA) in dichloroethane, at 25 °C, styrene to EDA ratio = 3:1. Before the addition of EDA, the complex was activated with phenylhydrazine. [b] 1 mol % ligand-Cu(OTf) complex (relative to EDA) in $CHCl_3$, at 25 °C, styrene to EDA ratio = 5:1. [c] n.g. = not given.

Scheme 3. Proposed Cyclopropanation Mechanism[a]



[a] Refs 10, 18–20.

Chart 2. The Proposed Transition State in the Cyclopropanation Reaction—Enantiocontrol Aspects[a]



[a] R_1, R_2 = Ph, H or H, Ph.[14]

complexes are useful catalysts for enantioselective cyclopropanation. Bis(oxazolines) are analogous to semicorrins in both structure and performance, but they are easier to prepare. It was therefore not long before they were likewise tested as catalysts in asymmetric cyclopropanation.[1,15–17] The benchmark reaction between styrene and ethyl diazoacetate (EDA) to give cyclopropane derivatives **5** is represented in Scheme 2. Some of the best results obtained in homogeneous systems using bis(oxazolines) are represented in Table 1. It can be seen from the table that the main difference in enantioselectivity is due to the substituent on the 4-position of the oxazoline moieties (R_{ox}, compare entries 1–3 of Table 1). The method of cyclopropanation employed can also have some influence on the results (Table 1, entries 3 and 4). The substituent on the bridge of the ligand (R_{brg}) has only a small effect on the enantioselectivity (Table 1, entries 4 and 5). This last observation is probably the reason that prompted many groups to use this bridge position to anchor the bis(oxazoline) ligands onto support surfaces.

The active species in the cyclopropanation reaction is the monomeric Cu(I)-ligand complex,[14] whereas the dimer is inactive. The postulated mechanism (Scheme 3) includes a step in which a carbene (ligand)Cu=CHCOOEt complex is formed, with evolution of N_2. This species is then approached by the double-bonded substrate, following which cyclopropanation occurs.[10,18–20] But only the chirality of the CH center which comes from the EDA is well controlled (Chart 2). The prochiral carbon of the double bond substrate is too far from the ligand for it to induce chirality in an efficient manner. Thus, in the case of the reaction in Scheme 2, an *S*,*S*-BOX will induce a 1*S* configuration of the cyclopropane product, for both cis and trans isomers, i.e., the trans/cis selectivity of the system is generally low. The enantioselectivity of the second chiral center can be improved if bulkier diazo esters are used.[16] It is interesting to see that some of the heterogeneous systems influence and even reverse the trans/cis selectivity of the ligands (see sections II.B and II.C).

From 1997 on, heterogeneous bis(oxazolines) have been tested in cyclopropanation reactions. In fact, this is the reaction that has been performed most frequently with heterogeneous bis(oxazolines), and various types of immobilization and recycling methods have been explored.

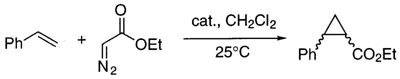
B. Heterogenizations Using Noncovalent Bonding

Heterogenizations using noncovalent interactions, such as ionic or polar ones, are usually easy to perform, since they do not require prior functionalization of the ligand. However, it is not always easy to avoid unwelcome interactions of the support with the catalytic site, as well as some leaching of the ligand and of the metal.

1. Inorganic Solids: Clays

Noncovalent heterogenizations of chiral BOX ligands were reported before covalent ones. The first papers

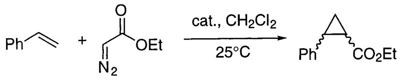
Table 2. Cyclopropanation of Styrene Catalyzed by 1b Ligands (R_{ox} = CH_2Ph; R_{brg} = Me) Immobilized by Ion-Exchange on Laponite[a]



entry	support	X	ion-exchange solvent	Cu (mol %)	catalyst loading[b]	% yield	trans/cis	% ee trans	% ee cis
1	hom.	Cl		10		10	70/30	4	6
2	hom.	OTf		10		58	68/32	59	53
3	Laponite	Cl	MeOH	1.44	0.48	29	58/42	16	16
4	Laponite	OTf	MeOH	1.05 → 0.22	0.35 → 0.073	25 → 32	50/50	24 → 14	19 → 12
5	Laponite	Cl	$EtNO_2$	1.62 → 0.35	0.54 → 0.12	26 → 26	55/45	31 → 30	26 → 26
6	Laponite	OTf	$EtNO_2$	0.63	0.21	33	47/53	15	10

[a] The reactions were carried out at 25 °C, unless indicated otherwise. Styrene to EDA ratio = 1:5. 150 mg of catalyst to 5 mmol of styrene was used in all heterogeneous reactions, regardless of the catalyst loading. [b] Catalyst loading is defined by mmol of Cu/g of polymer.

Table 3. Cyclopropanation of Styrene Catalyzed by 1b Ligands (R_{ox} = CH_2Ph; R_{brg} = Me) Immobilized by Ion-Exchange on Bentonite and on Montmorillonite K10[a]



entry	support	X	ion-exchange solvent	Cu (mol %)	catalyst loading[b]	% yield	trans/cis	%ee trans	%ee cis
1	Bentonite	OTf	MeOH	0.48 → 0.10	0.16 → 0.033	30 → 11	58/42	34 → 18	21 → 17
2	Bentonite	Cl	$EtNO_2$	0.09	0.03	17	55/45	18	18
3	K10	OTf	MeOH	0.33	0.11	11	55/45	18	17
4	K10	Cl	$EtNO_2$	0.06	0.02	6	52/48	30	18

[a] The reactions were carried out at 25 °C, unless indicated otherwise. Styrene to EDA ratio = 1:5. 150 mg of catalyst to 5 mmol of styrene were used in all heterogeneous reactions, regardless of the catalyst loading. [b] Catalyst loading is defined by mmol of Cu/g of polymer.

appeared in 1997. Mayoral et al. heterogenized BOX by cationic exchange with clays and tested these catalysts in the cyclopropanation reaction (Scheme 2).[21−25]

In their first publication on the subject, they reported the use of three inorganic cation-exchange clays. Clays are hydrous aluminum silicate minerals, which may also contain Mg, Al, Fe, Ca, and Na. Clays are structured in layers, mainly tetrahedral silicon dioxide layers which share their oxygen atoms with octahedral aluminum hydroxide layers.[26] The authors used (i) laponite (a synthetic smectite clay silicate, manufactured from salts of Na, Mg, and Li. Laponite has an ordered house of cards structure, made of very thin "cards". It is iron free and has a high swelling ability); (ii) montmorillonite (K10) (a smectite clay, i.e., characterized by a three-layer crystalline structure—one alumina and two silica layers; disordered house of cards structure); and (iii) bentonite (a natural smectite, the sodium form of montmorillonite, with a lamellar structure). For the ion exchange to be successful, it should be performed in a solvent with a high dielectric constant, in which the complex is soluble. The complex ligand·CuX_2 (X = Cl or OTf) was prepared in one solvent (MeOH or $EtNO_2$), and exchanged with a clay in another solvent or in the same one (MeOH or $EtNO_2$ [27]). The cyclopropanation reactions themselves were carried out in CH_2Cl_2, and the complex was activated with ethyl diazoacetate (EDA) to obtain the Cu(I) complex.[28]

Ligand **1b** (R_{ox} = CH_2Ph; R_{brg} = Me) gave best results with Laponite (the only case that recycles well), though enantioselectivities were always low (Table 2, entries 4 and 5). The combinations $Cu(OTf)_2$−MeOH or $CuCl_2$−$EtNO_2$ work best.

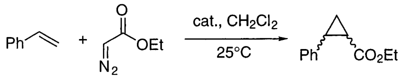
These solvent−anion combinations were the only ones tested with bentonite (Table 3, entries 1 and 2) and montmorillonite K10 (Table 3, entries 3 and 4). Bentonite prepared with $Cu(OTf)_2$−MeOH gave the best enantioselectivities in the first cycle, but these decreased significantly in the second cycle (Table 3, entry 1).

The authors concluded that the solvent in which the complex was prepared does not have a significant influence on the activity and enantioselectivity of the clay.[21] Logically, neither should the exchange solvent or the counteranions used, since the modified materials should not include any of the anions or the exchange solvent. However, probably due to residues of the latter, the combination solvent−anion during the exchange step does have an influence: if the exchange is done using BOX−$CuCl_2$ complex in $EtNO_2$ or using BOX−$Cu(OTf)_2$ in MeOH, the resulting clays differ from those obtained by other solvent−anion combinations by the following aspects: (a) the clays obtained have larger distances between the ligands; (b) they have a higher copper content (mmol of Cu/g of polymer); and (c) they give better enantioselectivities.[28]

Logically, better enantioselectivities should be obtained if the ligands are more separated, since unwanted interactions between ligands can thus be avoided. However, if the ligands are more far apart, it could be expected that the materials have a *lower* copper content, which is exactly the opposite of what is observed. One possible solution to this apparent contradiction is the higher porosity of these materials.

Another complication involves the possible species present—overall four possibilities are conceivable: (1)

Table 4. Cyclopropanation of Styrene Catalyzed by BOX Ligands Immobilized by Ion-Exchange on Inorganic Supports—The Effect of the Ligand Substituent (R_{ox})[a]



entry	support	R_{ox}	Cu (mol %)	catalyst loading[b]	% yield	trans/cis	% ee trans	% ee cis
1	**1d**·$CuCl_2$	Ph	10		18	70/30	3	7
2	**1d**·$(OTf)_2$	Ph	10		33	68/32	60	51
3	**1d**·Laponite[c]	Ph	0.84 → 0.75	0.28 → 0.25	31 → 28	55/45	43 → 41	6 → 13
4	**1f**·$CuCl_2$	*t*-Bu	10		24	70/30	2	7
5	**1f**·$(OTf)_2$	*t*-Bu	10		73	71/29	94	91
6	**1f**·Laponite[d]	*t*-Bu	0.33 → 0.3	0.11 → 0.1	30 → 26	64/36	69 → 43	64 → 37

[a] The reactions were carried out at 25 °C, in CH_2Cl_2. [b] Catalyst loading is defined by mmol of Cu/g of polymer. [c] Ion exchange performed in MeOH, with $Cu(OTf)_2$ as metal precursor. [d] Ion exchange performed in $EtNO_2$, with $CuCl_2$ as metal precursor.

A ligand without copper. This will not contribute to the catalysis at all. (2) A $(BOX)_2$−Cu complex. This will dissociate during the reaction to give species 3. (3) A BOX−Cu complex. This species is the only one that can catalyze the reaction in an enantioselective manner. (4) A Cu-support species. This could catalyze the reaction in a racemic manner, and contribute to the reduction of the enantioselectivity.

The ratio of ligand to copper, as measured by the 2N/Cu ratio, was not constant between the different catalysts described (it was always superior to 1, except in one case, where it was 0.7). Hence, the ratio of the four species described above is probably not the same for all of these materials. This could also explain, in part, the difference in the enantioselectivities observed.

Experiments in the *homogeneous* phase showed that, using $CuCl_2$ as metal precursor, better enantioselectivities were obtained when $EtNO_2$ was used as solvent, rather than CH_2Cl_2.[29] This can also explain the better enantioselectivities obtained when the complex with $CuCl_2$ was prepared in $EtNO_2$, since there is evidence that some of the solvent used for the preparation of the complex stayed in the environment of the complex after its immobilization.[24]

Another important point in the analysis and comparison of the results is the fact that the authors kept constant the *weight* of the clay used rather than the *mol %* of the catalyst relative to the substrate. Thus, in their experiments, the higher the Cu content, the higher the mol %, and this could cause a bias in the results, and explain in part why better enantioselectivities were obtained with those catalysts that had a higher Cu content (see also section II.C).

The authors suggest several possible reasons for the reduction of the enantioselectivity relative to the homogeneous phase. First, if some of the copper is not in a complex with the ligand but only with the surface and with the residual solvent molecules (especially MeOH), it can catalyze the reaction in a nonenantioselective manner.[24] Second, the facility with which the anion can dissociate from the copper complex influences the enantioselectivity, since this dissociation is necessary for the substrate to enter the catalytic cycle (Scheme 3). It is especially important that the anion dissociates more easily than the bis(oxazoline) ligand. The ability of the clays to dissociate from the copper is lower than that of the triflate ions, but higher than that of the chloride ions. Hence, the enantioselectivity the clays give should also be lower than that of the triflate complex, as indeed is the case.[21−25]

The Laponite clay exchanged with **1b**−$CuCl_2$ kept its activity and enantioselectivity upon recycling. However, X-ray diffraction spectra indicated that the structure of the clay was disturbed.[28] The surface area was likewise larger after recuperation. This may be explained if some of the exchange solvent remained in the clay after the exchange, and was washed out in the course of the first reaction cycle.[24]

As mentioned in the introduction to this chapter, the active species in the reaction is in fact Cu(I), and not Cu(II). Complexes of **1a**−Cu(OTf)·C_6H_6 were exchanged with Laponite in $EtNO_2$. The resulting catalysts did give better activities and enantioselectivities (up to 51% ee) than the corresponding clays which were prepared with Cu(II) complexes. However, the enantioselectivity decreased to 33% in the second cycle. The cis−trans selectivity diminished as well. It can be concluded that the Cu(I) catalyst was modified during the recycling process between the two reactions.

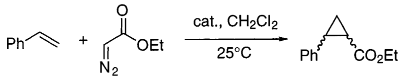
Ligands **1d** (R_{ox} = Ph; R_{brg} = Me) and **1f** (R_{ox} = *t*-Bu; R_{brg} = Me) were also tested (as Cu(II) complexes, on Laponite), and gave better results than those obtained with **1b**. Ligand **1f** gave the best enantioselectivities (Table 4, entry 6). However, these compare very poorly with the enantioselectivities of the homogeneous reaction (Table 4, entry 5). The considerable loss of enantioselectivity upon recycling was attributed to leaching of the ligand. Ligand **1f** leached more than others, probably because of its bulky *t*-Bu substituents, which interfere sterically with the solid surface.

Interestingly, when **1d**−$CuCl_2$ was exchanged with Laponite in $EtNO_2$, the obtained catalyst gave 43% ee for the *trans*-cyclopropane but only 6% for the *cis*-cyclopropane (Table 4, entry 3). In all other cases, the enantioselectivities of the cis and trans cyclopropanes were of the same order of magnitude. This indicates that the heterogeneous matrix has a marked influence on the reaction.

Of all catalysts prepared, only two Laponites maintain their activity and enantioselectivity upon second use: the one prepared from **1b**−$CuCl_2$ in $EtNO_2$ (Table 2, entry 5) and the one obtained from **1d**−$Cu(OTf)_2$ in MeOH (Table 4, entry 3). Further recycling has not been reported.

In a more recent paper,[25] the authors reported an interesting change in both cis/trans selectivity and

Table 5. Solvent Effect on Enantioselectivity and on trans/cis Selectivity in Laponite Exchanged with (*R*,*R*)-1d−Cu(OTf)$_2$ (R$_{ox}$ = Ph; R$_{brg}$ = Me)[a]



entry	support	reaction solvent	trans/cis	% ee trans[b]	% ee cis	% yield
1	hom. (OTf$^-$)	CH_2Cl_2	71:29	54	42(1*S*,2*R*)	33
2	hom. (OTf$^-$)	styrene	69:31	55	42(1*S*,2*R*)	41
3	Laponite	CH_2Cl_2	61:39	49	24(1*S*,2*R*)	28
4	Laponite	styrene	31:69	7	34(1*R*,2*S*)	40
5	Laponite	toluene	40:60	3	21(1*R*,2*S*)	15
6	Laponite	*n*-hexane[c]	31:69	3	33(1*R*,2*S*)	10

[a] Reactions carried out with 1 mol % of catalyst, and EDA to styrene ratio of 1:1, unless styrene is the solvent. [b] Enantiomer (1*S*,2*S*) was the main product. [c] Reaction carried out under reflux.

enantioselectivity due to a solvent effect, which occurred only when Laponite-immobilized BOX was used (and not in the homogeneous reaction). Experiments using (*R*,*R*)-**1d**−Cu(OTf)$_2$ (R$_{ox}$ = Ph; R$_{brg}$ = Me) were reported (Table 5). When CH_2Cl_2 was used as solvent, the Laponite and the homogeneous phase gave the same direction of cis/trans selectivity and enantioselectivity (Table 5, entries 1 and 3). When styrene was used as solvent in the *homogeneous* medium, again the same preferences were observed (Table 5, entry 2). However, when styrene or another nonpolar solvent (toluene, hexane) were used with the Laponite-immobilized (*R*,*R*)-**1d**−Cu(OTf)$_2$, the trans/cis preference was reversed, the enantioselectivity of the trans enantiomer was greatly diminished, and the enantioselectivity of the cis enantiomer was reversed (Table 5, entries 4−6).

The authors explain that this heterogeneous solvent effect is due to the difference in the distance between the complex and the Laponite when different solvents are used. Since the interaction between the complex and the Laponite is electrostatic, a more polar solvent (such as CH_2Cl_2) allows a larger complex−ligand distance than a nonpolar solvent (styrene, toluene, *n*-hexane). When the distance is bigger, the system gives the same preferences as the homogeneous system. When this distance diminishes, the clay has more steric influence, and the conformation of the active Cu(I) trigonal species, as well as that of the transition state when the styrene approaches this species, are influenced so as to give the opposite enantio- and trans/cis selectivities.

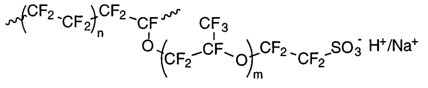
2. Organic Solids

The same laboratory proceeded to noncovalent heterogenizations of the same ligands on organic solids. Several materials with sulfonic acid functional groups were chosen, by analogy to the triflate group of Cu(OTf)$_2$ in the homogeneous phase.

Dowex, a macroporous polystyrene-DVB polymer with sulfonic acid groups, was ion-exchanged with **1d**−Cu(OTf)$_2$ (R$_{ox}$ = Ph; R$_{brg}$ = Me), to give only low enantioselectivities (Table 6, entry 3). Deloxan, a polisiloxane-based polymer, with alkyl sulfonic acid groups, was also tested with the same ligand, with only slightly better results (Table 6, entry 4).

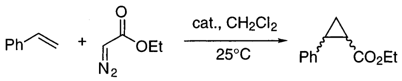
Two solids based on Nafion, a commercially available perfluorosulfonate cation exchange polymer (Chart 3), were also tested. The perfluorosulfonate moieties have a structure that approaches that of the triflate group,[30] and indeed these materials gave better enantioselectivities (Table 6, entries 5 and 6). Two different materials bearing perfluorosulfonated chains were tested: Nafion (an organic polymer) and Nafion-silica (an organic−inorganic nanocomposite, prepared by the authors by dispersing Nafion in silica precursors in a sol−gel technique).[23] The latter has a much larger surface area (4 orders of magnitude), and sulfonate sites are presumably more available, through pores of 10−20 nm, which also improve the accessibility to the catalytic sites. On the other hand, it has a lower cation-exchange capacity.

Chart 3. A Proposed Nafion Structure[30]



The Na-solids were exchanged with **1d**−Cu(OTf)$_2$ (R$_{ox}$ = Ph; R$_{brg}$ = Me) in MeOH (other anion or solvent combinations led to lower Cu content and lower activities and enantioselectivities). The Nafion-silica nanocomposite has a Cu content that is much lower than that of Nafion or Laponite. The Nafion catalyst is more active than the Nafion-silica one (50 vs 40% conversion), but their enantioselectivities are similar (Table 6, entries 5 and 6). The experiments were not carried out under identical conditions, though, and the mol % of catalyst in the Nafion experiment is higher by an order of magnitude, which may account for the difference in activity. Recycling

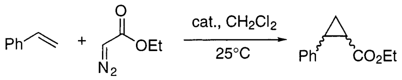
Table 6. Cyclopropanation of Styrene Catalyzed by 1d−Cu(OTf)$_2$ (R$_{ox}$ = Ph; R$_{brg}$ = Me) Immobilized by Ion-Exchange on Organic Supports[a]



entry	support	Cu (mol %)	catalyst loading[b]	% yield	trans/cis	%ee trans	%ee cis
1	**1d**·$CuCl_2$	10		18	70/30	3	7
2	**1d**·Cu(OTf)$_2$	10		33	68/32	60	51
3	Dowex[c]	1.56	0.52	22 → 24	68/32	17 → 2	15 → 2
4	Deloxane	1.29	0.43	25 → 30	64/36	38 → 8	31 → 7
5	Nafion[c]	2.22	0.22	37 → 33	67/33	59 → 58	45 → 47
6	Nafion-Silica	0.30	0.05	27 → 27	66/34	57 → 56	46 → 45

[a] The reactions were carried out at 25 °C, unless indicated otherwise. [b] Catalyst loading is defined as mmol (Cu)/g of polymer. [c] The reaction was performed at 60 °C.

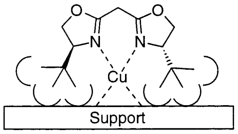
Table 7. Cyclopropanation of Styrene Catalyzed by 1f·$Cu(OTf)_2$ (R_{ox} = *t*-Bu; R_{brg} = Me) Immobilized by Ion-Exchange on Nafion Supports[a]



entry	support	Cu (mol %)	catalyst loading[b]	% yield	trans/cis	% ee trans	% ee cis
1	**1d**·$CuCl_2$	10		24	70/30	2	7
2	**1d**·$Cu(OTf)_2$	10		73	71/29	94	91
3	Nafion	2.77	0.28	26 → 23	63/37	5 → 5	7 → 6
4	Nafion-Silica	0.42	0.07	31 → 31	60/40	23 → 14	19 → 14

[a] The reactions were carried out at 25 °C. [b] Catalyst loading is defined as mmol (Cu)/g polymer.

Chart 4. A Schematic Representation of Steric Interactions between Bulky *t*-Bu Substituents on the BOX Ligand and the Solid Support



the catalyst once gives very similar results, and analyses show no leaching of the catalyst.

When ligands **1b** (R_{ox} = CH_2Ph; R_{brg} = Me) and **1f** (R_{ox} = *t*-Bu; R_{brg} = Me) were tested in the same experiments, significant leaching was observed from the Nafion-silica nanocomposite, accompanied by a lower activity and enantioselectivity after recycling. Ligand **1f** showed particularly low enantioselectivities (Table 7, entries 3 and 4), especially when compared with the results obtained under homogeneous conditions (Table 7, entry 1). This may be explained by the relatively weak coordination between the ligand and the copper due to the steric interactions between the bulky *t*-Bu groups of the ligand and the supporting solid (Chart 4).

An explanation for the loss of enantioselectivity after recycling is given by the loss of the chiral BOX ligand through leaching. Indeed, analyses showed a decrease in the N/Cu ratio, and IR spectra showed that diethyl maleate (a byproduct of the reaction formed through the carbenes present, see Scheme 3) was coordinated with some of the Cu atoms present in the solids, i.e., these byproducts replaced some of the BOX ligands. These nonchiral Cu complexes left were free to catalyze the reaction in a nonenantioselective manner. In addition, leaching of Cu atoms was also observed.

In conclusion, the interaction of the complex with the supporting material around the active site changes the surroundings of the catalytic site, and modifies its behavior. On one hand, it reduces the enantioselectivity of the complex, but on the other hand it can also, under certain circumstances, change the enantiomer obtained and the direction of the cis−trans selectivity. This last attribute, if well controlled, could prove synthetically useful, since the cis−trans selectivity of the cyclopropanation reaction is hard to control. It can be concluded that, in the case of noncovalent immobilization, there are two Achilles' heels on the way to good recycling: the solid-Cu coordination and the Cu−BOX coordination.

C. Covalent Heterogenizations on Insoluble Organic Supports

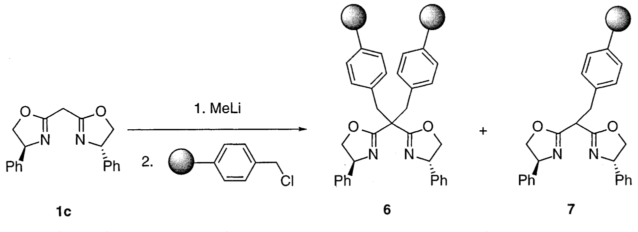
Mayoral et al. used two essentially different methods to support BOX ligands on polystyrene in a covalent manner.[31−33] The first method involves grafting BOX ligands on ready-made Merrifield polymers (Scheme 4). The second is direct polymerization of adequately functionalized bis(oxazoline) ligands (Scheme 5).

When grafting bis(oxazoline) ligands directly onto a commercial Merrifield polymer, the authors claim that they obtained product **6**, in which the ligand is grafted symmetrically. But it is more likely that they obtain a mix of **6** and **7**, in which the ligand is grafted in a nonsymmetrical manner, since the density of the chlorine groups on the Merrifield polymer may not be sufficiently high to favor double grafting of the same ligand (1.04 mmol of Cl/g of polymer[33]).

After grafting, the catalyst loading was of 0.44 mmol of Cu/g of polymer. When tested in the catalysis of the benchmark reaction of styrene with ethyl diazoacetate (0.82 mol % of Cu relative to EDA), the polymer gave 18% yield, with 66/34 trans/cis ratio, 26% ee for the trans isomer, and 21% ee for the cis isomer. The reaction had to be conducted at 60 °C, since at room temperature only very low yields were obtained.

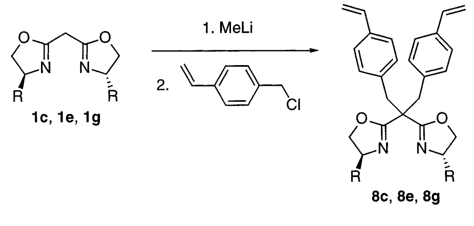
The second method involves introducing p-vinyl benzyl groups on the methylene bridge of **1c** (R_{ox} =

Scheme 4. Grafting of BOX Ligands on a Merrifield Resin[a]



[a] After formation of a complex with $Cu(OTf)_2$ the catalyst loading was of 0.44 mmol of Cu/g of polymer

Scheme 5. Functionalization of Bis(oxazoline) Ligands with Styrene Moieties



Scheme 6. Copolymerization of Ligand 8c with Styrene and Cross-Linking Agents

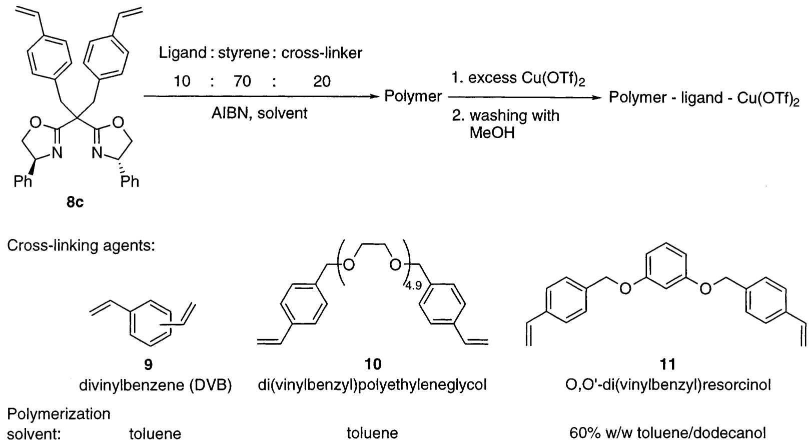
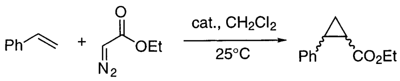


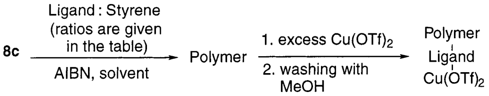
Table 8. Cyclopropanation of Styrene and EDA Using Polymeric Materials Obtained by Copolymerization of Ligand 8c, Styrene, and Cross-linking Agents (Scheme 6)[a]



entry	cross-linker	Cu (mol %)	catalyst loading[b]	% yield[c]	trans/cis	% ee trans	% ee cis
1	hom. **1c**	10		33	68:32	60	51
2	**10**	0.50	0.18	32	67:33	8	8
3	**9**	0.32	0.19	11	71:29	18	18
4	**11**	0.234	0.04	12	58:42	50	46

[a] Ref 34. [b] Catalyst loading = mmol (Cu)/g polymer. [c] Styrene: EDA = 1:1, at 25 °C. The cyclopropanation reaction was conducted in CH_2Cl_2.

Table 9. Cyclopropanation of Styrene and EDA Using Polymeric Materials from Copolymerization of Ligand 8c and Styrene as Catalysts[a]



entry	ligand/styrene	Cu (mol %)	catalyst loading[b]	% yield[c]	trans/cis	% ee trans	% ee cis
1	hom. **1c**	10		33	68:32	60	51
2	7/93[d]	0.45	0.29	22 → 15[e]	64:36	42 → 24	39 → 25
3	10/90[d]	0.54	0.39	28 → 24	60:40	46 → 43	42 → 41
4	20/80[f]	0.33	0.11	20	60:40	46	42
5	80/20[f]	0.48	0.16	26	57:43	56	51
6	50/50[f]	0.27	0.09	18	57:43	57	51

[a] Ref 34. [b] Catalyst loading = mmol (Cu)/g polymer. [c] Styrene: EDA = 1:1, at 25 °C, unless indicated otherwise. [d] Polymerization solvent: toluene. [e] At 60 °C. [f] Polymerization solvent: 60% w/w toluene/dodecanol.

Ph; R_{brg} = H) and **1e** (R_{ox} = *t*-Bu; R_{brg} = H), as well as on that of **1g** (IndaBOX), to obtain **8c**, **8e**, and **8g**, respectively (Scheme 5). These were then polymerized using various methods, with different proportions of ligand/styrene/cross-linking agent (Scheme 5, and Tables 8−13).

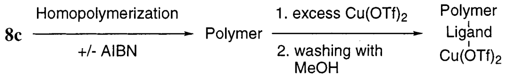
The bifunctionalized bis(oxazoline) **8c** was either (a) copolymerized with styrene and a cross-linking agent such as **9**, **10**, or **11** (Scheme 6, Table 8); (b) copolymerized with styrene in various ratios (Table 9); or (c) homopolymerized either thermally (Table 10, entry 2) or with AIBN (azabisisobutyronitrile) as initiator (Table 10, entries 3 and 4).

To prepare the catalyst itself, whatever the method of immobilization of the ligand, an excess of $Cu(OTf)_2$ was added and the polymer was washed with MeOH, so as to eliminate the excess of the metal on the polymer. Thus, the ligand-to-Cu ratio changes from polymer to polymer (but is always superior to 1). The resulting materials were tested in the cyclopropanation reaction. The results are given in Tables 8−12.

The cross-linked polymers derived from ligand **1c** (R_{ox} = Ph; R_{brg} = H) gave rather poor results (Scheme 6, Table 8). The polymer obtained with cross-linking agent **10** (Scheme 6 and Table 8, entry 2) gave the worst results (8% ee), possibly because the PEG moieties of the polymer served as coordinating sites for some of the metal, which would then catalyze the reaction in a nonenantioselective manner.

The polymer containing the rigid cross-linking agent **9** (Scheme 6 and Table 8, entry 3) gave rather low enantioselectivities as well (18% ee). This is probably due to a diminished access of the substrates to the catalytic sites because of the cross-linked structure.

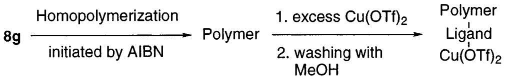
Table 10. Cyclopropanation of Styrene and EDA Using Polymeric Materials from Homopolymerization of Ligand 8c as Catalysts[a]



entry	polymerization solvent	Cu (mol %)	catalyst loading[b]	% yield[c]	trans/cis	% ee trans	% ee cis
1	homogeneous **1c**	10		33	68:32	60	51
2	?[e]	0.30	0.21	45 → 39	47:53	51 → 50	52 → 52
3	toluene/dodecanol[f]	0.20	0.14	40 → 20	53:47	57 → 47	53 → 50
4	toluene	0.014	0.01	28 → 27[d]	66:34	61 → 58	55 → 52

[a] Ref 34. [b] Catalyst loading = mmol (Cu)/g of polymer. [c] Styrene/EDA = 1:1, at 25 °C, unless indicated otherwise. [d] At 60 °C. [e] Thermal polymerization: no AIBN was used. [f] Ratio not given.

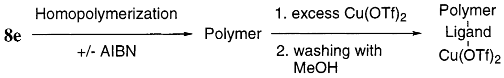
Table 11. Catalysis of Cyclopropanation of Styrene and EDA by Homopolymerized 8g (IndaBOX)[a]



entry	catalyst	Cu (mol %)	catalyst loading[b]	% yield[c]	trans/cis	% ee trans	% ee cis
1	hom. IndaBOX, R_{brg}= CH_2Ph	0.8		49	58:42	83[d]	86[d]
2	**1g** homopolymerized in toluene/ dodecanol (ratio not given)	0.038	0.03	35 → 22	44:56	69 → 69[d]	75 → 75[d]

[a] Refs 31 and 32. [b] Catalyst loading = mmol of Cu/g of polymer. [c] Styrene: EDA = 1:1, at 25 °C. [d] The other enantiomer was obtained (relative to other ligands).

Table 12. Catalysis of the Cyclopropanation Reaction of Styrene with EDA by Homoplymerized Ligand 8e (R_{ox} = *t*-Bu)[a,b]



entry	polymerization solvent	Cu (mol %)	catalyst loading[c]	% yield[d]	trans/cis	% ee trans	% ee cis
1	hom. **1e**	10		72	71:29	94	91
2	?[e]	0.20	0.13	51 → 56	35:65	75 → 74	72 → 70
3	toluene	0.11	0.07	34 → 36	39:61	77 → 77	73 → 73
4	60% w/w toluene/ dodecanol	0.126	0.08	36 → 33	37:63	78 → 75	72 → 72

[a] Refs 31, 33, and 34. [b] AIBN was used as initiator, unless indicated otherwise. [c] Catalyst loading = mmol of Cu/g of polymer. [d] Styrene: EDA = 1:1, at 25 °C. [e] Thermal polymerization: no AIBN was used.

The material obtained with cross-linking agent **11** gave much better enantioselectivities (Scheme 6 and Table 8, entry 4, 46−50% ee). Comparing to cross-linking agent **10**, the oxygen atoms of **11** cannot form a complex with the metal, and this may account for some of the difference in the enantioselectivity obtained. Another reason for the improved performance may be a better porosity, since this polymer was prepared in a mixture of 60% w/w toluene/dodecanol, whereas the other two cross-linked polymers were prepared in toluene. A third possible reason for the better enantioselectivities obtained by this material is the much lower catalyst loading (mmol of Cu/g of polymer), which, as discussed later on, can have a crucial influence on the enantioselectivity obtained.

Ligand **8c** was copolymerized with styrene, without any cross-linking agent, and cyclopropanation experiments were conducted with these materials (Table 9). In general, the enantioselectivities obtained were better than those obtained with the cross-linked materials. Another general trend is that the enantioselectivities of the ligand−styrene copolymers rise when the ligand/styrene ratio goes up (Table 9). A slight exception to the rule is found in entries 5 and 6, where the polymer with 50:50 ligand/styrene ratio (entry 6) gave a slightly better enantioselectivity for the trans isomer than that given by the polymer with an 80:20 ratio (entry 5), but this divergence is within the experimental measuring error of the ee. The enantioselectivity can also be correlated with the catalyst loading: the lower the catalyst loading, the higher the enantioselectivity (again, one exception can be seen: entry 3). The catalysts in entries 2 and 3 were recycled, but only the catalyst in entry 3 kept its enantioselectivity as well as most of its activity in the second catalytic cycle.

Homopolymerization of ligand **8c** was conducted in several solvent combinations (Table 10). The resulting materials gave excellent enantioselectivities, which all approach those of the homogeneous ligand **1c**, and in one case even surpass it slightly (Table 10, entry 4).

The catalyst obtained by thermal homopolymerization (Table 10, entry 2) gave slightly lower enantioselectivities than those obtained by the other two homopolymerized catalysts. It also gave a reverse trans/cis selectivity. This point is interesting, because it shows that the polymeric matrix can have a significant influence on the catalytic results obtained by the polymer. In the case of the cyclopropanation reaction, the cis/trans selectivity is particularly difficult to control, and, if well controlled, this reversal of selectivity could be of synthetic importance.

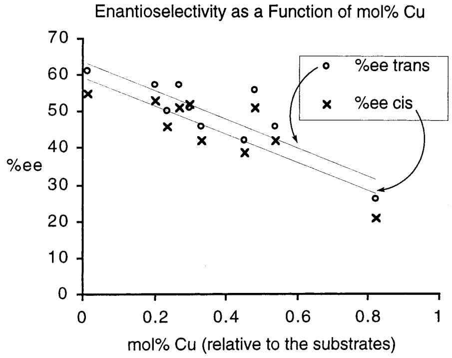


Figure 1. % ee vs mol % Cu (relative to the substrates), according to the data represented in Tables 8−10 and of ligand **1c** grafted onto Merrifield resin (R_{ox} = Ph). The first two points of Table 8 (cross-linked polymers) were omitted from the graph. Correlation: % ee trans: $r = -0.86$; % ee cis: $r = -0.85$ (both are significant).

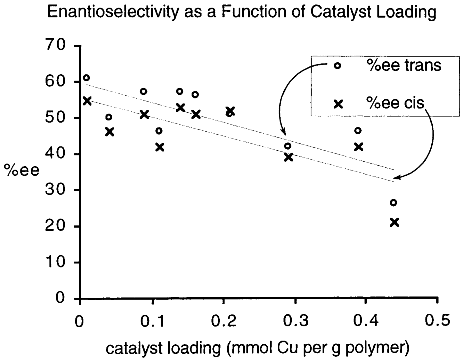


Figure 2. % ee vs catalyst loading (= mmol of Cu/g of polymer), according to the data represented in Tables 8−10, and the results obtained by Merrifield-grafted **1c** (R_{ox} = Ph) (the ratio Cu to ligand is not constant either, but there is always more ligand than Cu[33]). The first two points of Table 8 (cross-linked polymers) were omitted from the graph. Correlation: % ee trans: $r = -0.80$; % ee cis: $r = -0.76$ (both are significant).

The catalyst prepared by homopolymerization in toluene/dodecanol gave better enantioselectivities, but it did not keep its activity and enantioselectivity over the second catalytic cycle (Table 10, entry 3).

The best results were obtained by the homopolymer that was prepared in toluene (Table 10, entry 4). The enantioselectivities obtained by this polymer were even slightly higher than those obtained by the homogeneous **1c**, and they were only slightly reduced in the second cycle. On the other hand, the catalyst loading (mmol of Cu/g of polymer) of this material was very low, and to obtain a reasonable activity the reaction medium had to be heated to 60 °C. This lower activity was probably also because the authors kept constant the *weight* of the polymer and not the mol % of the catalyst relative to the substrates, so that when the catalyst loading was lower, they only used a very small mol % of the catalyst relative to the substrates, and its activity was naturally lower.

As could be observed for Tables 8 and 9, the lower the catalyst loading, the higher the enantioselectivity obtained by the polymerized ligand.

Looking more closely at the results presented in Tables 8−10, it is clear that the mol % of Cu relative to the substrates is not kept constant throughout these experiments. Indeed, it varies between 0.82 and 0.014, i.e., nearly 2 orders of magnitude. In many experimental data concerning homogeneous catalysis, the higher the mol % the better the yield and enantioselectivity. However, a graph (Figure 1) of % ee vs mol % Cu (relative to the substrates) shows exactly the opposite trend: the lower the mol % of the catalyst, the higher the % ee.

This can be explained by looking at the catalyst loading (mmol of Cu/g of polymer) of the polymers in these tables. The catalyst loading is not constant either, but varies between 0.01 and 0.44—again almost 2 orders of magnitude. Drawing a graph of % ee vs catalyst loading (Figure 2), a clear trend is visible: the higher the catalyst loading the lower the % ee.

Such a dependence of enantioselectivity on catalyst loading has already been shown to exist in the study of the reaction of Et_2Zn with ketones and its catalysis by amino-alcohol ligands grafted on polystyrene resins, as presented by Sanders et al.[35] They observed a decrease in the enantioselectivity of the reaction when the loading of the catalyst was increased (and also when the polymer was more cross-linked—another observation that is also true in the case presented here, Table 8, entries 2 and 3). They explained this by unfavorable interactions between two catalytic sites, which formed an inactive dimer, which was also responsible for the chiral amplification observed in these catalytic systems.[36] A similar correlation between catalyst loading and *rate* of catalysis has been observed and quantified for several hydrogenation catalysts.[37,38]

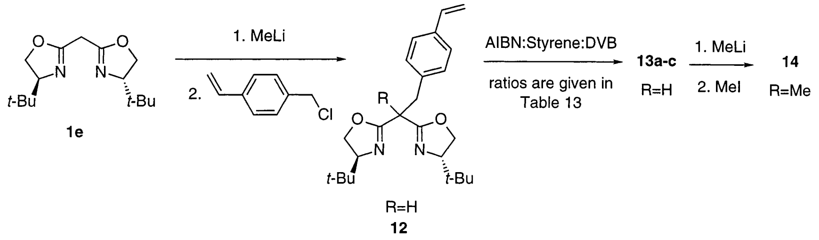
As mentioned in the introduction to cyclopropanation reactions (section II.A), it is the monomeric, and not the dimeric BOX complex that catalyzes the cyclopropanation reaction. Thus, if, on average, the distance between ligands in the polymeric matrix is too small, they will have a tendency to form dimers, and this would clearly reduce the quantity of the active species, and could diminish the enantioselectivity. The reduction in enantioselectivity could also be explained by unfavorable chiral steric interactions between two proximal ligand molecules.

On one hand, cross-linking disturbs the enantioselectivity of the polymeric catalyst. On the other hand, the homopolymer gives the best enantioselectivities. This makes it probable that most of the bis(oxazolines) in the homopolymer do not serve as cross-linking agents, despite the two styrene moieties on the bridge.

IndaBOX **1g** was functionalized with styrene moieties on its bridge to obtain **8g** (Scheme 5). It was then homopolymerized in a toluene/dodecanol mixture, with AIBN as initiator. Its catalytic performance in the cyclopropanation of styrene and EDA is given in Table 11. It gave good enantioselectivities, but not quite as good as those obtained by the homogeneous IndaBOX (Table 11, entries 1 and 2). Once more, homopolymerization led to an inversion of the cis/trans preference, but the difference between the ratios obtained by the homogeneous and the heterogeneous ligands is rather small.

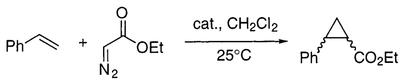
Several immobilizations of ligand **1e** (R_{ox} = *t*-Bu; R_{brg} = H), through its functionalized form **8e** (Scheme

Scheme 7. Preparation and Polymerization of a Monofunctionalized BOX Ligand (1e)[a]



[a] The ratios of polymerization and the catalytic results are given in Table 13.

Table 13. Cyclopropanation Using Polymers 13a–c, 14, Derived from Monofunctionalized Ligand 1e (R_{ox} = *t*-Bu; R_{brg} = H)[a]



entry	**12** /styrene/DVB	Cu (mol %)	catalyst loading[c]	% yield[d]	trans/cis	%ee trans	%ee cis
1	hom. **1e**	10		72	71:29	94	91
2	**13a**: 10/–/90[b]	0.240	0.08	11	58:42	28	33
3	**13b**: 10/70/20[b]	0.210	0.07	21	57:43	29	34
4	**14**: methylated **13b**	0.18	n.g.[e]	16	60:40	23	22
5	**13c**: 10/40/50[b]	0.240	0.08	15	56:44	45	44

[a] Ref 33. [b] Polymerized in a mixture of 60% w/w toluene/dodecanol. [c] Catalyst loading = mmol of Cu/g of polymer. [d] Styrene/EDA = 1:1, at 25 °C. [e] n.g. = not given.

5), have also been reported. Some immobilizations were performed by homopolymerization as presented in Table 12. These gave good enantioselectivities, up to 78% ee (Table 12, entry 4), but still not as high as the 94% ee of the homogeneous ligand under the same conditions (Table 12, entry 1). However, they could be recycled, unlike the noncovalently heterogenized **1f** ligands (R_{ox} = *t*-Bu; R_{brg} = Me, section II.B). The conditions of homopolymerization seem to have only a small effect on the enantioselectivity of the product. It is interesting to notice the reversal of trans/cis selectivity in these immobilized ligands relative to the homogeneous one. This reversal of trans/cis selectivity, which was only slight in the case of one homopolymer of **1c** and of the homopolymer of **1g**, is more significant here, giving up to 65% of the cis enantiomers (Table 12, entry 2), as opposed to only 29% obtained by the homogeneous ligand (Table 12, entry 1).

In an attempt to improve the accessibility of the ligand, another approach to the polymerization of ligand **1e** was tried, through a monofunctionalized ligand monomer (Scheme 7).[33] After the introduction of only one styrene moiety on the bridge of ligand **1e**, to obtain monomer **12**, they polymerized it with different ratios of styrene and DVB (Table 13). The authors tried to obtain in this manner a polymer in which the BOX ligands are necessarily situated on the main chain as a pendant group, rather than at cross-linking points, as is probably the case if the monomeric ligand bears two styrene moieties.

However, as can be seen in Table 13, the resulting polymers **13a**–**c** gave lower enantioselectivities (entries 2, 3, and 5) than those obtained by polymerization of the bifunctional ligand (Table 12). Methylation of the bridge of the ligand in polymer **13b**, to obtain polymer **14** (Scheme 7), gave an even less enantioselective material (Table 13, entry 4). The authors concluded that the conservation of the pseudo-C_2-symmetry in the polymer is important for its enantioselectivity. Going back to the Merrifield-grafted ligand **1c** (Scheme 4)—as mentioned above, it is likely that this ligand was likewise grafted mostly in a nonsymmetrical manner (giving **7** and not **6**), which could explain its exceptionally low enantioselectivity.

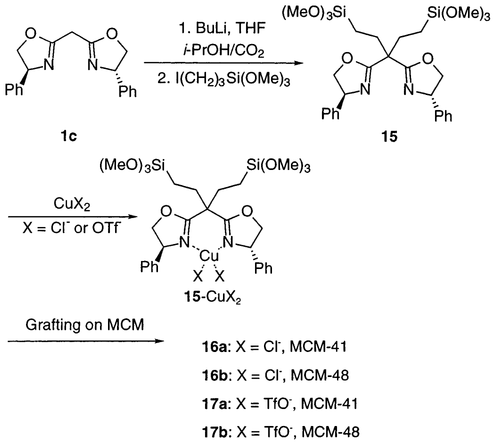
In conclusion, for the cyclopropanation reaction covalent bonding of BOX ligands onto organic materials appears to be much more efficient than noncovalent bonding, in terms of enantio- and cis/trans selectivities. Enantioselectivities using the covalently bonded heterogeneous catalysts equal in some cases the enantioselectivities obtained by the same ligands in homogeneous catalysis.

Several conclusions may be drawn from the results presented in this section: (a) the conservation of the C_2 axis seems to be crucial for the enantioselectivities to remain high. Hence, the grafting onto a Merrifield polymer is of little interest in terms of efficiency and selectivity. (b) Cross-linking of the polymers leads to inferior catalytic performances. (c) On one hand, catalysts obtained by homopolymerization often give better catalytic results than those obtained by copolymerization with styrene. On the other hand, careful analysis of the relationship between copper loading and enantioselectivity shows that the higher the catalyst loading, the lower the enantioselectivity. However, since the ligand-to-copper ratio is not constant, these two observations are not mutually exclusive.

D. Covalent Immobilization on Insoluble Inorganic Supports

Inorganic supports present one major advantage over organic ones: improved mechanical properties. This makes them especially attractive for grafting of catalysts that should be recycled many times.

Scheme 8. Grafting of Bis(oxazoline) 1c on MCMs



In a recent publication, Clarke and Shannon[39] reported an immobilization of **1c** (R_{ox} = Ph; R_{brg} = H) on the surface of the ordered inorganic mesoporous silicate materials MCM-41 and MCM-48.[40-42] These are large-pore silicates with high surface areas, which can be prepared, for example, by calcinations of aluminosilicate gels in the presence of surfactants. MCM-41 has a regular hexagonal array of channels, whereas MCM-48 has a cubic one. The pores, of ca. 30 Å, are large enough to enable the reaction to occur within the cavities.

The authors synthesized the catalysts as shown in Scheme 8, first forming the metal complex **15**$-CuX_2$, and then immobilizing the catalyst on the silicate surface. They aimed at a catalyst loading of ca. 0.2 mmol/g (0.135 mmol was added to 0.65 g of MCM), but found only about 0.04 mmol/g (measured through Cu analysis). This means that the grafting method appears to be of little efficiency, since only ca. 20% of the monomer is found on the grafted material. The results obtained are given in Table 14.

Their results for the homogeneous ligand **1c** (Table 14, entry 2) are slightly lower than those obtained by Mayoral et al. (Table 8, entry 1). The immobilized ligands gave enantioselectivities that approach those of the homogeneous ligand (Table 14, entries 3−6). The heterogeneous catalyst was used in lower substrate-to-catalyst ratios (Cu mol %) than the homogeneous one. Again, the mol % used in the heterogeneous tests is not kept quite constant, but the order of magnitude remains the same (between 0.10 and 0.24 mol %). It is interesting to note that MCM-41 seems to give better results with $CuCl_2$ than with $Cu(OTf)_2$, whereas MCM-48 behaves in the opposite (and more usual) manner. Both MCMs give far better results with $CuCl_2$ than those obtained with the homogeneous **1c**$-CuCl_2$. The authors do not suggest an explanation to this interesting phenomenon.

The results obtained by Clarke and Shannon suit the curve of ee vs catalyst loading obtained with those of Mayoral (Figure 2b), thus providing supporting evidence to the theory proposed above.

Another method for immobilization of BOX ligands onto silica for cyclopropanation was reported.[33] A double bond was first attached to the bridge of the BOX ligand to obtain ligands **18a**, **c**, **e** and **20c**, **e**, **g** (Scheme 9). The silica was functionalized with thiol groups, and the BOX ligands were attached to it by a radical reaction (Scheme 9). This was performed in one of two routes: route A − the BOX ligands were first attached to the silica, and the product was then reacted with $Cu(OTf)_2$ in MeOH to form complexes **19a**, **c** and **21c**, **e**, **g** (Scheme 9). These complexes differ from each other by the length of their spacer. Or else, product **18** was reacted by route B (Scheme 9), forming the complex first and then attaching it to the silica by the same radical reaction, to obtain complexes **19a**, **c**, **e**.

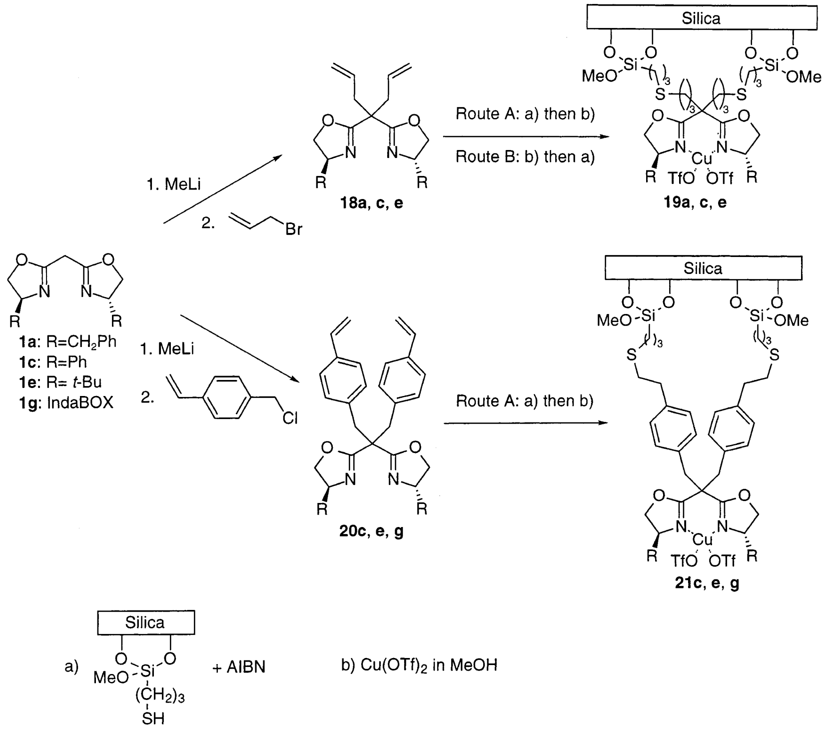
Complexes **19** and **21** were tested in the cyclopropanation reaction of styrene with EDA (Scheme 2). Materials **19** gave very low enantioselectivities (all under 30%), whatever route was used for their synthesis. However, complexes formed by route A gave slightly better enantioselectivities than those formed by route B. Complex **21c**, which has a longer spacer than complex **19c**, gave slightly improved results (33 and 32% ee for the trans and cis isomers, respectively). Complex **21e**, however, did not give better results than complex **19e**, despite its longer spacer. Finally, complex **21g**, an IndaBox derivative, gave better enantioselectivities than any of the others (52% ee for the trans isomer; 65% ee for the cis isomer). Still, it compares poorly with the corresponding homogeneous bridge-substituted ligand **1d** (IndaBOX, R_{brg} = Bz: 83% ee for the trans isomer; 86% ee for the cis isomer).

Once more, the mol % of Cu and the catalyst loading vary quite a lot between reactions, and it is therefore difficult to draw general conclusions from these experiments (the difference between the materials obtained using routes A and B may also be explained on the basis of catalyst loading, for example). Another reason for the low enantioselectivities obtained by **21e** could be the binding of the support at least partly only through one arm, as observed in its Raman spectrum.[33] As seen before in the case of organic solids (section II.C), such nonsymmetrical grafting leads most of the time to lower enantioselectivities than could be expected otherwise. Such unsymmetrical grafting should occur when this grafting method is used, since the BOX ligands are grafted onto functions (thiols) which are attached to the silica surface (see also section IV.F). These

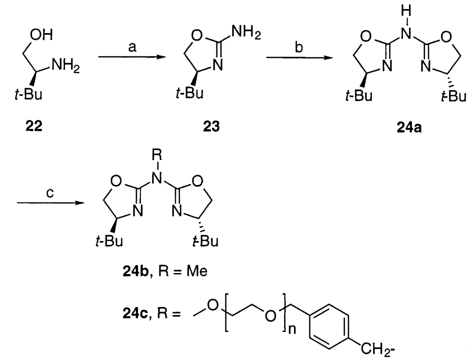
Table 14. Catalytic Tests of MCM-Grafted Bis(oxazolines) in the Cyclopropanation Reaction of Styrene with EDA

entry	catalyst	Cu (mol %)	% yield	trans/cis	% ee cis	% ee trans
1	**1c**$-CuCl_2$ (homo)	1	19.5	67/33	23	21
2	**1c**$-Cu(OTf)_2$ (homo)	1	46.3	67/33	49	58
3	**16a**	0.10	38.7 → 23.7	65/35 → 64/36	48 → 48	54 → 52
4	**17a**	0.24	47.4 → 46.6	66/34 → 64/36	46 → 42	51 → 45
5	**16b**	0.16	36.6 → 27.8	63/37 → 62/38	46 → 44	51 → 46
6	**17b**	0.22	32.3 → 31.0	66/34 → 64/36	50 → 46	54 → 48

Scheme 9. Grafting of Bis(oxazoline) Ligands onto Silica through Previously Introduced Sulfur Functions



Scheme 10. Preparation of PEG-Grafted Aza-Bis(oxazolines)[a]



[a] (a) BrCN, MeOH, O °C (89%). (b) p-TsOH·H_2O (5%), PhCHO, toluene Δ (59%). (c) For **24b**: n-BuLi, MeI, THF (98%); for **24c**: n-BuLi, p-PEG-C_6H_4-CH_2-Br, THF (55%).

functions may not be dense enough to permit both arms on the bridge of all BOX ligands to bind to the silica surface.

Sulfur atoms are known to bind easily to copper. Such binding may lead to unselective catalytic species, which could also contribute to lowering the enantioselectivities obtained by these materials.

E. Covalent Tethering to Soluble Organic Polymers

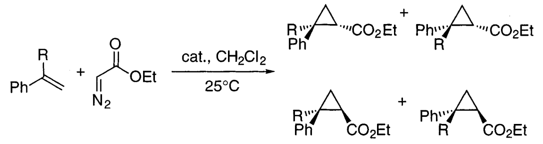
Heterogenization by tethering of ligands to soluble organic polymers combines some of the advantages of a homogeneous reaction (high reaction rate, no problems of accessibility to the catalytic site, and relative ease of characterization of the catalyst), with an ease of recuperation of the catalyst by precipitation with another solvent at the end of the reaction. For example, tethering to PEG (poly(ethylene glycol)) polymers enables a homogeneous reaction in CH_2Cl_2. At the end of the reaction, the PEG-supported ligand is precipitated by the addition of ether. Two such examples are known with BOX ligands.

Glos and Reiser[43] prepared aza-bis(oxazolines) **24a**–**c** (Scheme 10) and demonstrated their utility in cyclopropanation of styrene or of 1,1-diphenylethene with methyl diazoacetate (Table 15). The preparation of these ligands (Scheme 10) is more difficult than that of “normal” BOX ligands, but they can be more easily tethered to the PEG polymer. Amino alcohol **22** was reacted with BrCN to give amino-oxazoline **23**. Self-condensation of **23** in the presence of an acid and an aldehyde gave aza-bis(oxazoline) **24a**, which was reacted with BuLi and a suitable halogenated alkyl to give **24b** and **24c**.

Cozzi et al.[44] reported a similar approach, synthesizing BOX ligands with PEG polymers on the CH_2 bridge (Scheme 11). They chose to synthesize the ligand around a protected alcohol arm, which they then grafted onto PEG. They first protected the phenylic hydroxyl of 4-hydroxymethylphenol **25** with benzyl (Bn), while brominating the benzylic hydroxyl, to obtain **26**. They then reacted it with the lithium enolate of dimethyl methylmalonate, to obtain **27**. The carboxylic esters were transformed into acid chlorides, which were reacted with the appropriate amino alcohol, to obtain the amides, followed by cyclization to obtain bis(oxazolines) **28a** and **28b**, according to a well-known procedure.[45,46] The benzyl was then removed, to obtain **29a** and **29b**, which were reacted with the mesylated PEG to give **30a** and **30b**.

PEG-grafted catalysts **24c** and **30b** (R_{ox} = t-Bu in both cases) were tested in the benchmark reaction of styrene with EDA (Table 15, R = H, entries 4 and 5 respectively). The homogeneous homologues of **24c**, i.e., **24a** and **24b**, were also tested in the reaction, for comparison (Table 15, entries 2 and 3, respectively). The enantioselectivities obtained by **24c** were

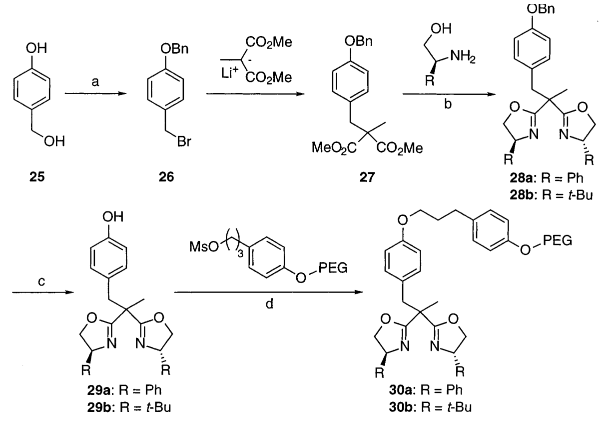
Table 15. PEG-Immobilized Bis(oxazoline) Ligands in the Cyclopropanation Reaction of Styrene and Diphenylethene



		R = H				R = Ph	
entry	ligand	% yield	trans/cis	trans	cis	% yield	% ee
1	**1e** (hom)	77	73/27	99	97	70	99
2	24a	75	67/33	87	80	63	86
3	24b	82	73/27	92	84	41	83
4	24c	69	71/29	91	87	78	90
5	30b	63	70/30	91	n.g.[a]	45	93

[a] n.g. = not given.

Scheme 11. Preparation of PEG-Grafted BOX Ligands[a]



[a] (a) K_2CO_3; BnBr; PBr_3; (b) KOH; $SOCl_2$; the amino alcohol; TsCl; 4-(dimethylamino)pyridine (DMAP); (c) Pd/C, HCO_2NH_4; (d) Cs_2CO_3 or NaH or $Bu_4N^+OH^-$.

similar to those obtained by **24a** and **24b**, but the yield was slightly lower (Table 15, entries 2−4). The enantioselectivity obtained by **30b** was similar to that obtained with **24c**, but the yield was slightly lower.

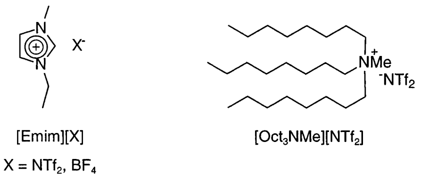
The same catalysts were also tested in the cyclopropanation of 1,1-diphenylethene (Table 15, R = Ph). In this case, the heterogeneous **24c** gave *better* enantioselectivities and better yields compared to its homogeneous homologues (Table 15, entries 7−9). The enantioselectivity obtained by heterogeneous **30b** was even better, but the yield was lower.

F. Recycling of BOX Ligands Using Ionic Liquids

Considering the recent interest in ionic liquids as a means of recycling catalysts, it is not surprising that this technique was tested for BOX ligands.

The ionic liquids [Emim][X] (EMIM = 1-ethyl-3-methylimidazolium) and [Oct_3NMe][NTf_2] (Oct_3NMe = methyltri-*n*-octylammonium) (Chart 5) were tested with ligands **1c** (R_{ox} = Ph; R_{brg} = H) and **1e** (R_{ox} = *t*-Bu; R_{brg} = H).[47] In most cases, the catalyst was prepared with $CuCl_2$ or $Cu(OTf)_2$ in CH_2Cl_2. After evaporation of the solvent, the complex was dissolved in the ionic solvent.

Chart 5. Ionic Liquids Used in Attempts at Recycling Bis(oxazoline) Ligands[a]



[a] Results reported in Table 16.

For ligand **1c** (R_{ox} = Ph; R_{brg} = H) with $CuCl_2$ in [Emim][NTf_2], the results are similar to those obtained with $Cu(OTf)_2$ in CH_2Cl_2 (Table 16, entries 3 vs 1). This indicates that the counterion of the metal in this case is probably the trifluoromethanesulfonimidate (NTf_2^-) of the solvent. This catalyst was also recycled, keeping its activity and enantioselectivity (Table 16, entry 3).

Ligand **1e** (R_{ox} = *t*-Bu; R_{brg} = H) gave better enantioselectivities than ligand **1c** in the nonionic homogeneous phase (compare Table 17 entry 1 vs Table 16 entry 1). In the same manner, ligand **1e** with $Cu(OTf)_2$ in [Emim][NTf_2] gave better results than ligand **1c** with $CuCl_2$ under the same conditions (Table 17 entry 3 vs Table 16 entry 3; the authors did not report an experiment with identical conditions for both ligands). However, in the case of **1e** the enantioselectivities were not as high as those obtained by **1e**·$Cu(OTf)_2$ in CH_2Cl_2 (Table 17, entries 1 vs 3). The activity and enantioselectivity remained essentially constant over three cycles (Table 17, entry 3). When the complex **1e**−$CuCl_2$ was prepared directly in [Emim][NTf_2], the first cycle gave very good enantioselectivities, but these went down considerably in the second cycle (Table 17, entry 4). The authors cannot explain this occurrence.

[Oct_3NMe][NTf_2] gave lower enantioselectivities with both ligands, and its recycling was not attempted (Table 16, entry 4; Table 17, entry 5). [Emim][BF_4] gave no enantioselectivity at all when tried with ligand **1e** (Table 17, entry 6).

The authors did not report experiments with BOX−$Cu(OTf)_2$ prepared directly in [Emim][NTf_2] for comparison with the results obtained with $CuCl_2$, and in the same way maybe complexes with $Cu(NTf_2)_2$ could be tested as well, leaving only one counterion with which the copper could form a complex. More experiments should be performed before it can be determined whether ionic liquids are a suitable medium for the performance of cyclopropanation reactions catalyzed by BOX ligands, and for the recycling of these ligands.

G. Cyclopropanation: Conclusion

In conclusion, for the cyclopropanation reaction covalent heterogenization of BOX ligands seems to be more successful than noncovalent heterogenization in terms of activity, enantioselectivity, and the ability to recycle the catalyst. Nevertheless, in some cases ionic supports appear to have a significant influence on the cis/trans ratio, which could perhaps be synthetically useful if optimized.

Of the covalent immobilization methods tried so far, immobilization on organic solids gave better

Table 16. Recycling of 1c (R_{ox} = Ph; R_{brg} = H) in the Cyclopropanation Reaction Using Ionic Liquids

					% ee	
entry	anion (CuX_2)	solvent	% yield	trans/cis	trans	cis
1	OTf	CH_2Cl_2	33	68/32	60	51
2	Cl	CH_2Cl_2	19	67:33	17	13
3	Cl	[Emim][NTf_2]	34 → 32 → 33	67:33 → 66/34 → 66/34	55 → 53 → 53	47 → 43 → 44
4	Cl	[Oct_3NMe][NTf_2]	18	67/33	49	41

Table 17. Recycling of 1e (R_{ox} = *t*-Bu; R_{brg} = H) in the Cyclopropanation Reaction Using Ionic Liquids

					% ee	
entry	anion (CuX_2)	solvent	% yield	trans/cis	trans	cis
1	OTf	CH_2Cl_2	61	71/29	91	88
2	Cl	CH_2Cl_2	24	70/30	2	7
3	OTf	[Emim][NTf_2]	38 → 38 → 37	64/36 → 64/36 → 65/35	66 → 66 → 64	64 → 64 → 62
4	Cl	[Emim][NTf_2]	50 → 42	62/38 → 60/40	86 → 55	85 → 56
5	OTf	[Oct_3NMe][NTf_2]	18	63/37	23	22
6	OTf	[Emim][BF_4]	3	70/30	0	0

results than those obtained for immobilization on inorganic solids. However, more experiments have been conducted in that direction, and inorganic solids may “catch up” with organic ones as the field develops. Two factors that seem to reduce enantioselectivities in both of these cases are high catalyst loading and a large digression from the pseudo-C_2-symmetry of the ligand. These two attributes should be avoided in the planning of other heterogenization methods of BOX ligands, and perhaps of other ligands as well.

An interesting inversion of the cis/trans preference has been observed in some cases of noncovalent immobilizations as well as in some cases of covalent immobilizations on organic polymers. This effect demonstrates the influence of the matrix on the catalyst, and could prove to be synthetically useful if optimized.

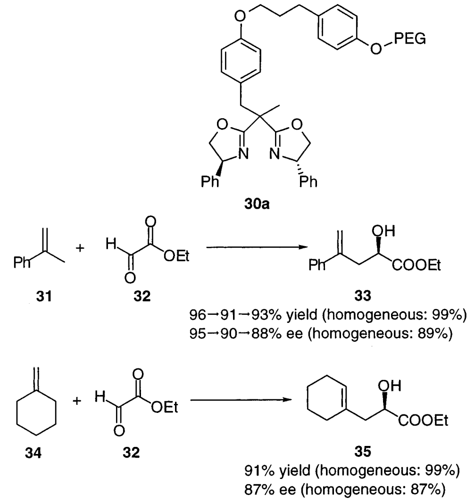
Recycling by means of ionic liquids could prove to be efficient, but much more research is required in this direction before its efficiency can be determined.

Binding of bis(oxazoline) ligands onto soluble PEG polymers gave the best results so far, and these results approach those of the homogeneous ligands.

III. Ene-Reactions

The ene-reaction, a powerful carbon−carbon bond forming reaction, was discovered by Alder in 1943.[48,49] It occurs between an alkene with an allylic hydrogen (the “ene”) and an electron-deficient double bond (the “enophile”). The reaction is concerted, through a six-membered cyclic transition state. The carbonyl ene-reaction (so-called when the enophile is a carbonyl) is limited to highly activated ene-compounds or to highly activated carbonyl compounds, such as glyoxilate **32**, which is therefore one of the most common enophiles used in ene-reactions. The first catalytic enantioselective ene-reaction was promoted by an aluminum complex of a binaphthol derivative.[50] Since then other chiral complexes, notably of binaphthol, BINAP, and bis(oxazoline)[51] ligands, were shown to catalyze the ene-reaction in an enantioselective manner. In most cases, large amounts of the catalyst (5−20 mol %) are needed to achieve good enantioselectivity. This makes the recycling of the catalysts particularly interesting.

Scheme 12. Ene-Reactions Performed with Bis(oxazoline) Ligand 30a



96→91→93% yield (homogeneous: 99%)
95→90→88% ee (homogeneous: 89%)

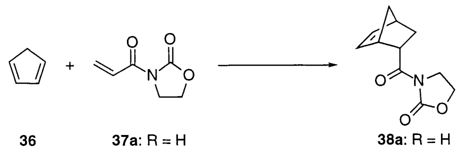
91% yield (homogeneous: 99%)
87% ee (homogeneous: 87%)

Ligand **30a** (a BOX bound onto a soluble PEG polymer, see also section II.E, Scheme 11) was tested in the ene-reaction (Scheme 12).[44]

When **30a** was tested as catalyst of the ene-reactions described in Scheme 12, products **33** and **35** were obtained in yields of 96 and 91% and with 95 and 87% ee, respectively. 10−20 mol % of the catalyst were used, which facilitates the comparison with Evans’ equivalent monomeric catalyst (used in 10 mol %), that gave under similar conditions higher yields (99%) but slightly lower enantioselectivities (89 and 87% ee, respectively).[52]

The reactions were conducted in CH_2Cl_2, in which the polymers are soluble, and the polymer was recovered by precipitation from diethyl ether. Recycling of the ligand required decomplexation of the Cu(II) ions by reaction with aqueous KCN, and only 85% of the ligand could be recovered. Recycling caused only a slight decrease in yield and enantioselectivity of **33**: 96 → 91 → 93% yield and 95 → 90 → 88% ee over three reaction cycles (Scheme 12).

Table 18. Homogeneously Catalyzed Diels−Alder Reactions



entry	ligand (mol %)	metal precursor	T (°C)	time	% yield	endo:exo	% ee endo	ref
1	**1d**[a] (11%)	$Cu(OTf)_2$[d]	−78 −50	1 3	92	95:5	30	58
2	**1f**[b] (11%)	$Cu(OTf)_2$[d]	−78	18	86	98:2	>98	58
3	**1g**[c] (8%)	$Cu(OTf)_2$	−78	8	94	99:1	98	62
4	**1g**[c] (5%)	$Cu(ClO_4)_2 \cdot 6H_2O$	−78	11	80	97:3	92	61
5	**1g**[c] (10%)	$Cu(ClO_4)_2 \cdot 6H_2O$	−78	10	88	>99:1	98	61
6	**1g**[c] (10%)	$Cu(ClO_4)_2 \cdot 6H_2O$	0	1	91	98:2	95	61

[a] **1d**: R_{ox}=Ph; R_{brg}=Me. [b] **1f**: R_{ox}=*t*-Bu; R_{brg}=Me. [c] **1g**: IndaBOX. [d] 10 mol %.

IV. Diels–Alder Reactions

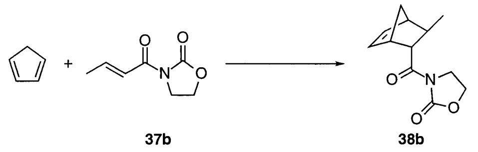
A. Introduction

Diels Alder reactions are important carbon−carbon bond forming reactions, in which up to four new chiral centers can be formed. In the past decade, much progress has been made in the control of the enantioselectivity of these reactions, especially through chiral catalysis. Complexes of BOX ligands have been shown to be efficient catalysts in asymmetric Diels−Alder reactions.[53−55] Much research has been performed and many aspects of the mechanism have been investigated. The substituents on the oxazoline ring (R_{ox}) influence the enantioselectivity, as do, to a lesser extent, the bite angle and the substitution at the bridge of the ligand (R_{brg}).[56,57] A change in the geometry of the complex (tetrahedral, square-planar, or octahedral), induced either by changing the metal[54,55,58] or by adding auxiliary water ligands,[59,60] can switch the preference of the ligand from one enantiomer of the product to the other (when the same enantiomer of the same BOX ligand is used).

Once more, the major drawback of BOX ligands as catalysts for the Diels−Alder reaction is that large amounts of the catalysts are required to achieve good enantioselectivities (around 10 mol % in most cases; compare entries 4 and 5 in Table 18). For this type of reaction to be practically useful, it is therefore necessary to recycle the catalysts.

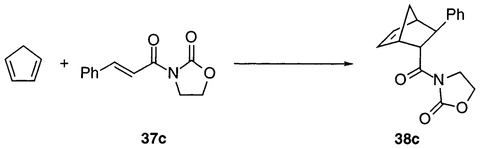
Many metal complexes can be used as catalysts in the Diels−Alder reaction, but Cu complexes were the most commonly used, and often gave the best enantioselectivities.[53,58,61,62] Nearly all the work in the heterogeneous phase was done with Cu complexes, and therefore this introduction will not discuss other metals. Table 18 shows some results obtained in homogeneous catalysis when **37a** was used as dienophile. Reactions involving substrates **37b** and **37c** are represented in Scheme 13 and Scheme 14, respectively.

Scheme 13. Catalysis of the Diels−Alder Reaction of 37b with Cyclopentadiene



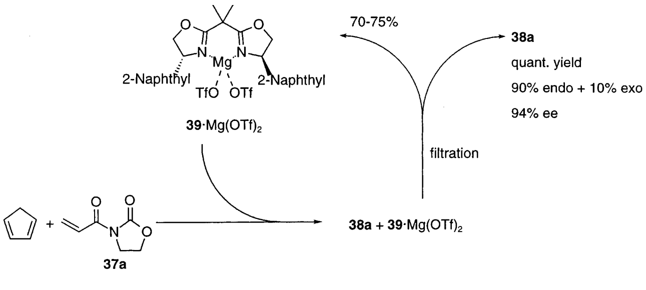
		% yield	endo/exo	%ee endo
1f·$Cu(OTf)_2$ (10 mol%)	-15 °C;30 h;	85	96:4	97[58]
1g·$Cu(OTf)_2$ (40 mol%)	0 °C;26 h;	84	92:8	94[62]
1g·$Cu(ClO_4)_2 \cdot 6H_2O$ (10 mol%)	23 °C; 6 h;	88	94:6	84[61]

Scheme 14. Catalysis of the Diels−Alder Reaction of 37c with Cyclopentadiene



		% yield	endo:exo	%ee endo
1g·$Cu(OTf)_2$ (10 mol%)	23 °C;72 h;	78	80:20	35 (2*R*)[62]
1f·$Cu(OTf)_2$ (8 mol%)[a]	25 °C;24 h;	85	90:10	90 (2*S*)[58]

Scheme 15. Recycling of Bis(oxazoline) 39

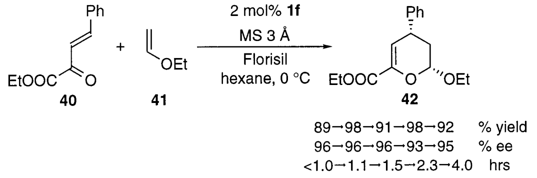


B. Homogeneous Recycling Attempts

Due to the large amounts of catalyst required, attempts to separate and recycle the catalyst were reported even when the reaction was performed in the homogeneous phase, i.e., when the ligand was not modified in any manner, but simply recycled by precipitation from the reaction medium.

Desimoni et al.[63] reported the preparation and use of catalyst **39**·$Mg(OTf)_2$ for the reaction described in Table 18, and obtained 94% ee, a ratio of 90:10 endo/exo, and quantitative yield. The catalyst was only slightly soluble in CH_2Cl_2, and could be recovered in 70−75% yield from the mixture and used as such, keeping activity and enantioselectivity unchanged (Scheme 15). A clear disadvantage of this recycling method is that 25−30% of the catalyst is lost on every cycle.

Scheme 16. Recycling of Complex [1f·Cu(OTf)(H$_2$O)$_2$](OTf) in a Hetero-Diels–Alder Reaction, Using Florisil



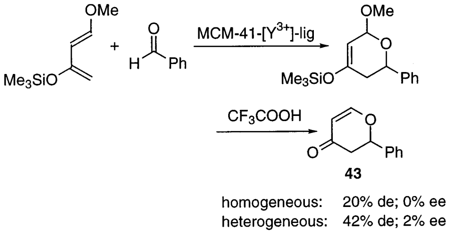
Evans et al.[64] reported a recycling of complex [**1f**·Cu(OTf)(H$_2$O)$_2$](OTf) for the hetero-Diels–Alder reaction in Scheme 16. They performed the reaction in hexanes, in which the ligand is not soluble, in the presence of 3 Å molecular sieves and Florisil (a powdered magnesium-silica gel which serves as an adsorbent). The recycling was performed by decantation of the supernatant by syringe after the disappearance of **40** had been detected by TLC. The remaining solids were then rinsed twice with hexane, more reactants were introduced, and the reaction was repeated. The enantioselectivity of product **42** (93–96% ee) was mostly conserved during five cycles, but the activity (TOF) diminished, requiring longer reaction times (over five reaction cycles, the time needed increased from less than 1 h to 4 h). This reduction in activity could be explained by loss of some of the catalyst. Some loss of the catalyst does not necessarily mean a loss of enantioselectivity (especially if the reaction does not occur without the intervention of the catalyst under these conditions). The authors did not attempt to determine the mol % of the catalyst under which the enantioselectivity diminished. The exact role of the adsorbent was not clear. Recycling was possible in the absence of Florisil, but the activity of the catalysts diminished faster. In the presence of silica, the ee was only of 87%.

C. Heterogenizations Using Noncovalent Bonding

Mayoral et al. have recently reported an attempt to use noncovalently bound BOX systems similar to those presented in section II.B as catalysts in the Diels–Alder reaction.[65] They exchanged **1d**–M complexes (R_{ox} = Ph; R_{brg} = Me; M = Cu, Mg, or Zn) with Laponite and Nafion-silica resins described above (section II.B), and used the resulting catalysts in the benchmark Diels–Alder reaction described in Table 18. However, they obtained only very low enantioselectivities (none above 11%). It seems that the steric requirements of the Diels–Alder reaction render these ion-exchange systems even less enantioselective than they are for the cyclopropanation reaction.

A hetero-Diels–Alder reaction was recently reported.[66] The authors reacted MCM-41 silica with Y[N(SiHMe$_2$)$_2$]$_3$(THF)$_2$, followed by end capping with HN(SiHMe$_2$)$_2$. They then modified the silica with several chiral ligands, among which BOX **1e** (R_{ox} = *t*-Bu; R_{brg} = H). They obtained only very low enantioselectivities of **43** (Scheme 17). This may be due to the chosen metal precursor, seeing that Yttrium is not known to provide good enantioselective catalysts with bis(oxazoline) ligands.

Scheme 17. Immobilization Attempt of Bis(oxazoline) 1e on Silica, in a Noncovalent Manner[a]



[a] Diastereoselectivity increases, but enantioselectivity stays almost null.

D. Covalent Tethering to Soluble Organic Polymers

PEG-grafted Ligand **30b** (R_{ox} = *t*-Bu) presented above (section II.E, Scheme 11) was also tested in the benchmark Diels–Alder reaction presented in Table 18, which proved to be more problematic than the cyclopropanation or ene-reactions (sections II.E and III, respectively). At −78 °C with Cu(OTf)$_2$ as metal precursor, no enantioselectivity was observed, although product **38a** was obtained in 91% yield, with >98% endo-selectivity. When Cu(SbF$_6$)$_2$ was used as the metal precursor, product **38a** was obtained with only 5% ee.

Three possible causes for the low enantioselectivity obtained by **30b** in the Diels–Alder reaction were proposed and tested: (1) the disturbance of the C_2-symmetry; (2) racemic catalysis by the complexes formed between the Cu(II) and the ether oxygens of the PEG chains; (3) the carbonate anions left over from the Cs$_2$CO$_3$ in the last stage of the synthesis of the ligand (section II.E, Scheme 11) could replace the triflate anions as counterions of the Cu(II), and reduce its enantioselectivity.

Possibility (1) was ruled out by the authors after testing a similar ligand, where the PEG moiety was replaced by an allyl, and obtaining 95% ee. It is possible, however, that the allyl moiety does not represent the same steric bulk as the PEG moiety.

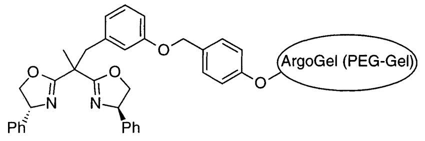
The influence of the complexing properties of the PEG chains was tested by testing ligand **1e** (R_{ox} = *t*-Bu; R_{brg} = H) in the presence of PEG. Again, the enantioselectivity was of 96%, and the authors therefore concluded that this cannot be the cause of the reduced performance of the heterogeneous **30b**.

The influence of the Cs$_2$CO$_3$ on the enantioselectivity was first tested by a more careful elimination of the latter from ligand **30b**. This improved the enantioselectivity to 30%, while the yield was reduced to 70%. When ligand **30b** was prepared using Bu$_4$N$^+$OH$^-$ as base instead of Cs$_2$CO$_3$ (Scheme 11), the ee went up to 45% (83% yield). Hence, the Cs$_2$CO$_3$ was at least in part responsible for the reduced enantioselectivities of **30b** relative to the homogeneous ligand.

The authors cannot explain the rest of the difference between ligand **30b** and its homogeneous homologue, especially in view of the good results they obtained with the same ligands in cyclopropanation and ene-reactions. In our opinion, the reason could be a semi-labile ligand effect: the oxygen atoms of the PEG, when grafted onto the BOX ligand, can ligate more readily to the metal than the free PEG polymers used in the test conducted by the authors. These oxygen atoms thus form a semi-labile ligand, which may change the geometry of some of the complexes, and in any case obstructs its C_2-symmetry and is sterically encumbering. As mentioned in the introduction, the geometry around the metal center of the complex influences the enantioselectivity and can even reverse it. If the geometry of the complex is in an equilibrium between several geometric species, the ee of the product can be much diminished.[59,60]

E. Grafting onto Insoluble Organic Polymers

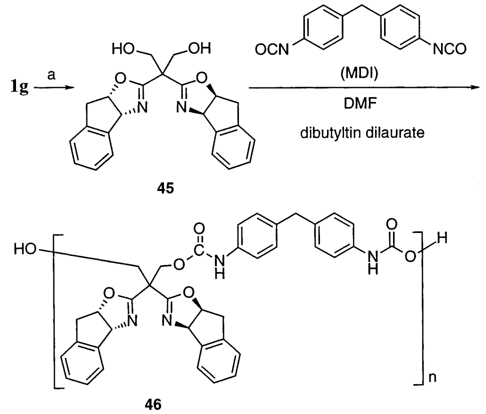
Hallman and Moberg[67] reported recently grafting of BOX **1c** (R_{ox} = Ph; R_{brg} = H) onto ArgoGel, to obtain **44** (which was also used in allylic substitution, Section V). ArgoGel is a graft-copolymer of gel-type polyoxyethylene, with long, flexible poly(ethyleneglycol) linkers. ArgoGel is said to behave like a homogeneous rather than a heterogeneous polymer, due to its good swelling capacity. However, attempts to perform the DA reaction with ligand **44** failed: only traces of the product **38a** were observed and no enantioselectivity was obtained, compared with 85% ee for the equivalent homogeneous ligand **1c** under similar conditions (the catalytic complex was prepared using 10 mol % ZnI_2, 11 mol % ligand, and 20 mol % $AgSbF_6$, in CH_2Cl_2 at room temerature, and the reaction was conducted at −78 °C). When the reaction was conducted at room temperature, a racemic product was obtained if **44** was used as the chiral ligand (it should be noted that the reaction occurs spontaneously, without catalysis, at room temperature). It was concluded that the polymer inhibits the catalytic activity of the metal complex. In our opinion, it is possible that the oxygen in the meta position of BOX **44** coordinates with the metal in the BOX ligand, thus blocking the complexation of the substrate.



44 (0% ee in the DA reaction)

Rechavi and Lemaire have recently reported a polymerization of IndaBOX **1g** as a polyurethane chain polymer.[68] The ligand was first functionalized on the bridge using formaldehyde, to obtain the diol **45**, and then reacted with methylenediphenyl diisocyanate (MDI) to obtain polyurethane **46** (Scheme 18).

Scheme 18. Polymerization of IndaBOX as a Polyurethane Chain Polymer[a]



[a] Paraformaldehyde (2.5 eq.) CH_2Cl_2, dioxane, H_2O, Et_3N, THF (75−85% yield).

Table 19. Recycling of Catalyst 46, Using Cu(OTf)$_2$ as Metal Precursor[a]

entry	cycle	% conversion	% endo	% ee[b]
1	1	100	89	51
2	2	99	90	56
3	3	99	90	56
4	4	99	87	0

[a] Polymer **46**: $Cu(OTf)_2$, in 1:1 ratio, 8 mol % relative to the dienophile **37a**. The reaction was conducted in CH_2Cl_2. Temperature: −78 °C (4 h), then allowed to warm to r.t. overnight. [b] % ee of the endo isomer. The ee was determined by HPLC on Chiralcel-OD column with 95 heptane: 5 2-propanol as the eluent. Absolute configuration: (+)-2*R*.[54,69]

Polymer **46** was tested in the benchmark DA reaction described in Table 18. The results are given in Table 19. The first three reaction cycles gave 51−56% ee, with quantitative yield, and about 90% selection toward the endo enantiomer (entries 1−3 in Table 19). The fourth cycle showed a complete loss of enantioselectivity (entry 4, Table 19). In addition, the mechanical properties of the polyurethane material were of little practical interest. IR spectra also indicated that the composition of the polymer had changed.

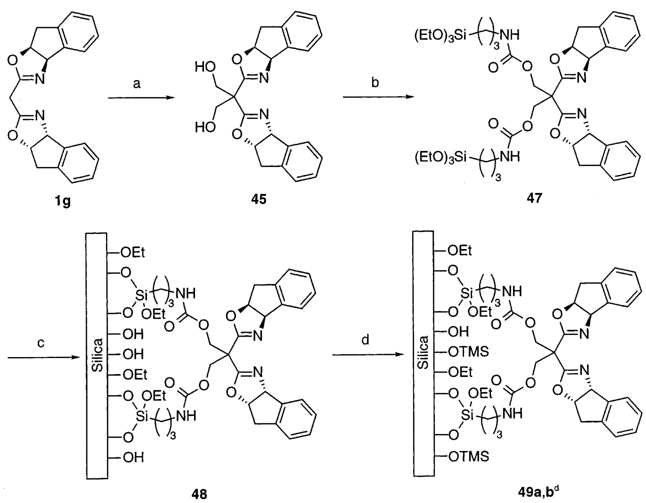
F. Immobilization on Inorganic Solids

Rechavi and Lemaire have also published recently a heterogenization method by grafting onto silica. Catalysts **48** and **49a**,**b** were prepared from IndaBOX **1g** according to the procedure in Scheme 19.

Catalyst **48** was tested in the same Diels−Alder reaction described above. When $Cu(OTf)_2$ was used as the metal precursor, 82% conversion and 87% ee of the endo isomer were obtained at −78 °C after 48 h (Table 20, entry 1). At 0 °C, the conversion went up to 97% after 1 h, but the enantioselectivity went down to 65% ee (Table 20, entry 2). Recycling with this metal precursor, the conversion went down and the enantioselectivity was kept almost constant for three cycles, but lost on the fourth cycle. When $Cu(ClO_4)_2{\cdot}6H_2O$ was used as the catalyst precursor, better enantioselectivities were obtained: 70% ee at 0 °C, and up to 85% ee at −15 °C (Table 20, entry 3). The conversion was likewise higher, and no loss of activity and enantioselectivity occurred over four reaction cycles (Table 20, entry 3). Furthermore, under these conditions, the reaction could be conducted in the open air,[70] as has already been shown by Ghosh for the homogeneous reaction.[61]

It was likely that the free silanol groups of the silica would form complexes with some of the metal precursor, and serve as nonenantioselective catalysts

Scheme 19. Immobilization of IndaBOX on silica[a]



[a] (a) Paraformaldehyde (2.5 eq.) CH_2Cl_2, dioxane, H_2O, Et_3N, THF (75–85% yield). (b) $(EtO)_3Si-(CH_2)_3-NCO$ (3-(Isocyanatopropyl)triethoxysilane), Et_3N, DMF, 48 h, then polystyrene-NH_2 resin, stirring for 1 h, then filtering the PS resin off followed by evaporation of the solvents. (c) Silica (previously activated by HCl), toluene, reflux overnight (75% yield from **47** according to N-content of microanalysis). (d) *N*-trimethylsilylimidazole (TMSIM) **49a**: 1 h; **49b**: 72 h.

in competition with the chiral IndaBOX catalyst. This assumption was tested by conducting two control experiments: homogeneous IndaBOX **1g** was put in two flasks, and nonfunctionalized silica was added to one of the flasks. The enantioselectivity of the reaction in the flask which contained the silica was much lower (67% ee) than that of the reaction in the flask which did not contain any silica (81% ee).[68]

The silanol groups of the silica-grafted **48** were protected with TMS groups, using *N*-trimethylsilylimidazole (TMSIM) to obtain catalysts **49a** and **49b** (1 and 72 h of reaction with TMSIM, respectively; see Scheme 19).[68,70] These catalysts, and especially catalyst **49b**, gave improved enantioselectivities relative to catalyst **48** (Table 21). It is interesting to notice that the difference between the enantioselectivity obtained by **48** (65% ee) and that obtained by **49b** (81% ee) is very similar to the difference observed during the control experiments using homogeneous IndaBOX with and without the presence of silica.[68] Cooling to −78 °C gave 92% ee (Table 21, entry 4), which is similar to the results obtained by Ghosh for the homogeneous ligand (98% ee).

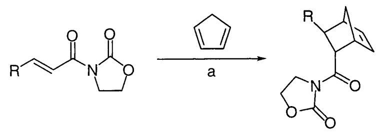
The general nature of the catalyst was tested on other substrates as well. Products **38b** and **38c** were also obtained with good yields (70 and 63%, respectively) and enantioselectivities (70 and 61% ee, respectively, Scheme 20).

Table 21. Influence of Protection of Silanol Groups and of Temperature on Enantioselectivity When $Cu(ClO_4)_2{\cdot}6H_2O$ Is Used as Metal Precursor[a]

entry	catalyst	*T* (°C)	time (h)	% endo	% ee
1	**48**	rt	1	85	65
2	**49a**	rt	1	86	71
3	**49b**	rt	1	86	81
4	**49b**	−78	3	86	92

[a] The conversion is of 99−100% for all reactions.

Scheme 20. Diels-Alder Reaction Catalyzed by Silica-Grafted 48[a]



37b: R = Me
37c: R = Ph

38b: R = Me (70% ee)[b]
38c: R = Ph (61% ee)[c]

[a] 1 (**48**): 1 ($Cu(ClO_4)_2{\cdot}6H_2O$) (10 mol %); CH_2Cl_2, rt. [b]After 3 h: 70% yield (GC), 96% endo, 70% ee (2*R*) (HPLC on Chiralcel OD, 10% 2-propanol in heptane). [c]Reacted for 50 h; isolated on silica column with 0 to 25% EA in pentane. 63% isolated yield; 79% endo, 61% ee (2S), calculated according to α_D in CCl_4 (measured α_D = 109°), by comparison with the literature.[71,72]

More recently, Hyeon, Kim et al.[73] reported the synthesis of a similar type of material. They used MCF (meso cellular foam) silica,[74] which has spherical cells of known size (cell diameter in this case: 8.61 nm), connected by windows of known size (window diameter in this case: 3.5 nm). Their silica had a surface area of 970 m^2/g, and total pore volume of 1.06 cm^3/g. Their catalyst loading was of 0.17−0.24 mmol ligand /g of silica-supported catalyst. They modified this silica with (3-chloropropyl)triethoxysilane, and used the chloride functionalities to graft their bifunctionalized ligand **50c** (Scheme 21). The functionalization of the bridge of the bis(oxazoline) ligand was performed by reacting **1g** with 4-(bromomehtyl)phenyl pivalate, to obtain **50b** and deprotection of the pivalate group by reduction (Scheme 21). Reaction of **50c** with the functionalized silica gave catalyst **51**, and protection of its silanol groups with TMS groups, using hexamethyldisiloxane (HMDSO), gave material **52**. They also prepared an analogous homogeneous ligand **50a** by reacting **1g** with benzyl bromide.

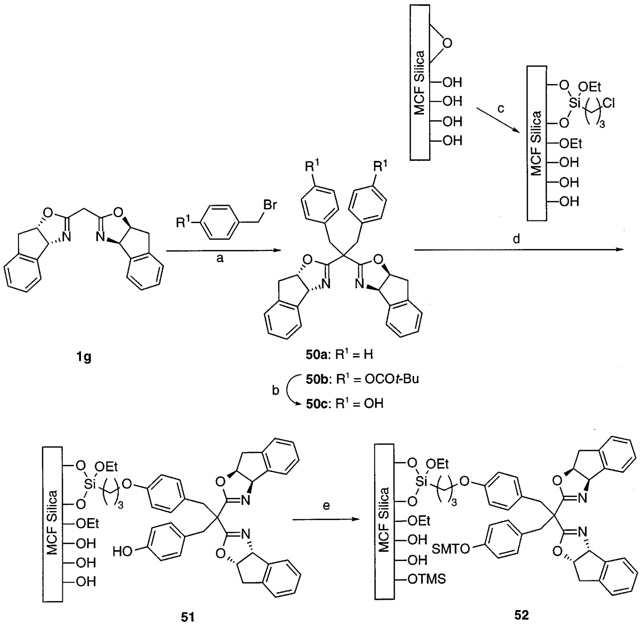
They assumed that only one arm of the bridge of their BOX ligand **50c** was grafted onto the silica surface (compare with the system of Mayoral presented in section II.D). Since they also assumed that the free silanol and OH groups of catalyst **51** can form nonchiral complexes with the copper and thus interfere with the enantioselectivity of the reaction, they protected the OH groups of the grafted catalyst

Table 20. Catalysis of the DA Reaction Described in Table 18 Using Silica-Grafted Catalyst 48

entry	metal	temp (°C) (time (h))	% conversion	% endo	% ee of endo[c]
1	$Cu(OTf)_2$[a]	−78 °C (48 h)	82	96	87
2	$Cu(OTf)_2$[a]	0 °C (1 h)	97 → 53 → 65 → 19	89 → 90 → 88 → 89	65 → 73 → 69 → 26
3	$Cu(ClO_4)_2{\cdot}6H_2O$[b]	0 °C (1 h)	96 → 97[d] → 97[e] → 100	86 → 85[d] → 90[e] → 88	70 → 65[d] → 85[e] → 79

[a] The reaction was conducted under argon, in dry CH_2Cl_2. The catalyst (8 mol %) was separated by centrifuge. The catalyst was dried in a vacuum before reuse. [b] The catalyst (10 mol %) was separated by centrifuge and used directly for the next cycle. [c] The ee was determined by HPLC on Chiralcel-OD column with 95 heptane: 5 2-propanol as the eluent. Absolute configuration: (+)-2R.[54,69] [d] r.t. [e] −15 °C.

Scheme 21. Grafting of IndaBOX on MCF Silica[a]



[a] (a) LiHMDS, THF, −78 °C, 3 h, 77−82% yield. *(*b) LiAlH$_4$, THF, 6 h, quant. (c) Chloropropyltriethoxysilane, toluene, reflux, 12 h. (d) Using **50c**: toluene, reflux, 12 h. (e) HMDSO (hexamethyldisiloxane), reflux, 12 h.

51 with hexamethyldisiloxane (HMDSO) to obtain catalyst **52**. However, when they tested the catalytic activities of catalysts **51** and **52**, they found out that in fact catalyst **51** gave better enantioselectivities, and also a better endo:exo selectivity (Table 22, entries 2−4, vs Table 23). The authors did not propose an explanation to this phenomenon, but it could be due to the high temperature of the reaction they used to protect the silica, which may have damaged it (the silica's structure—porosity as well as surface area—can be reduced.[26,42])

The authors also found that the enantioselectivity depends greatly on the method of preparation of the catalyst. Reacting silica-grafted ligand **52** with 0.6 equiv of Cu(OTf)$_2$ without washing it gave 15% ee (Table 23, entry 1), whereas if it was washed with CH$_2$Cl$_2$ prior to the reaction, 39% ee was obtained (Table 23, entry 2). The enantioselectivity improved upon cooling, up to 75% ee at −78 °C (Table 22, compare entries 6, 7, 9, and 11).

Table 23. MCF-Grafted IndaBOX Ligands 52 as Catalysts in the Diels−Alder Reaction—Testing Reaction Conditions and Recycling[a]

entry	mol % of Cu(OTf)$_2$	*T* (°C)	yield	endo: exo	% ee endo
1	6[a]	0	99	91:9	15
2	6[b]	0	99	89:11	39
3	10[b]	−50	99	90:10	50
4	10[b]	−70	97	92:8	65
5		−70	22	91:9	-
6	10[b]	−78	99	93:7	75
7	20−30[c]	−78	>97[e]	93:7[f]	67 → 75 → 48 → 56[h] → 52

[a] See footnotes of Table 22.

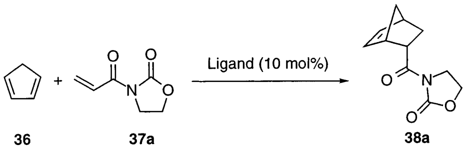
Reacting the substrates at −70 °C in the presence of silica-grafted **52** without any metal for 24 h gave some product (22% yield, Table 23, entry 5), but no enantioselectivity, i.e., the silica alone may serve as a catalyst for the reaction. This may explain the difference in enantioselectivity between the homogeneous ligand (88% ee, Table 22, entry 1) and the best results obtained using silica-grafted **52** (75% ee, Table 23, entry 6). All silica-grafted catalysts gave slightly better endo:exo ratios (up to 94:6, Table 22, entries 2−4) than those obtained with the homogeneous ligand (90:10, Table 22, entry 1).

Some recycling attempts are reported in Table 22 (entries 3 and 4) and in Table 23 (entry 7). The enantioselectivities diminished slightly over 4−5 cycles, but some of the enantioselectivity could be regained if some more Cu(OTf)$_2$ was added. This means that some of the loss of enantioselectivity was due to the leaching of the metal upon recycling. The recycling method is also important, and better results were obtained when the catalyst was washed with a less polar solvent (hexane) between the cycles (Table 22, entry 3 vs entry 4).

Some other products were also prepared using MCF-grafted **52**. The enantioselectivities obtained were only slightly lower than those obtained by the homogeneous ligand (Scheme 22).

Comparing the method of Rechavi and Lemaire with that of Hyeon, Kim et al., it is interesting to observe that the two groups have arrived at similar solutions to the same problem. Both materials give enantioselectivities of the same order of magnitude. The slightly better enantioselectivities of the former

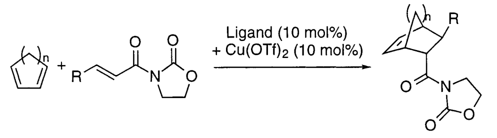
Table 22. MCF-Grafted IndaBOX Ligands 51 as Catalysts in the Diels−Alder Reaction—Testing Reaction Conditions and Recycling



entry	ligand	mol % of Cu(OTf)$_2$	T (°C)	yield	endo:exo	% ee endo
1	**50**[a] (homo.)	10	−78	96	90:10	88
2	**51**[b]	10	−78	99	94:6	78
3	**51**[c]	20−30	−78	>97[e]	94:6[f]	75 → 71 → 69 → 63
4	**51**[d]	20−30	−78	>97[e]	94:6[f]	78 → 72[g] → 73 → 70 → 72[h]

[a] 11 mol % ligand + 10 mol % Cu(OTf)$_2$ were used. [b] Mixing ligand and Cu(OTf)$_2$, then washing with CH$_2$Cl$_2$. [c] Mixing ligand and Cu(OTf)$_2$ in CH$_2$Cl$_2$ for 3 h, followed by filtration and washing with CH$_2$Cl$_2$. The product was dried in a vacuum. Between reaction cycles the catalyst was washed with CH$_2$Cl$_2$ and dried in a vacuum. [d] Mixing ligand and Cu(OTf)$_2$ in CH$_2$Cl$_2$ for 3 h, followed by addition of more CH$_2$Cl$_2$, stirring for 30 min, and then filtration. The product was dried in a vacuum. Between reaction cycles the catalyst was washed with *hexane* and dried in a vacuum. [e] For all cycles. [f] For the first cycle; the ratio then went down, but it was never lower than 92.3:7.7. [g] At −73 °C. [h] Additional Cu(OTf)$_2$ was added before this recycling step.

Scheme 22. Diels−Alder Reactions Catalyzed by MCF-Grafted Bis(oxazoline) 52[a]



		yield[a]	endo: exo[a]	%ee[a]	
36 (n=1)	**37b**: R=Me	99 (95)	80:20 (75:25)	72→72 (85)	**38b**
36 (n=1)	**37d**: R=Et	99 (95)	80:20 (75:25)	65→60 (82)	**38d**
53 (n=2)	**37a**: R=H	53 (95)[b]	>99:1 (>99:1)	53 (61)	**54**

[a] (a) Numbers in brackets represent the results obtained by the homogeneous ligand **50a**; → symbolizes recycling. (b) The homogeneous reaction was run for 3 days, and the heterogeneous one was run for 7 days.

can be explained by the more symmetrical grafting of the ligand, and perhaps also by the milder method used for the protection of the silanol groups. The choice of well-defined mesoporous silica does not seem to improve the catalytic activity and enantioselectivity of the final material.

G. Diels−Alder Reactions: Conclusion

Among the various heterogeneous systems examined for the Diels−Alder reaction, BOX ligands that were covalently immobilized onto silica surfaces gave the best enantioselectivities. Systems that heterogenized the ligands in a noncovalent manner (ion exchange) gave almost no enantioselectivity. The difference between covalent and noncovalent systems is more striking in the case of the Diels−Alder reaction than in that of cyclopropanation reactions, probably because the Diels−Alder reaction is more sterically demanding, and the geometry of the complex plays an important part in the enantiocontrol.

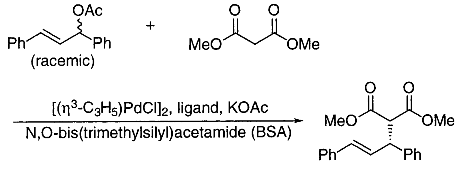
In all cases, competition between catalysis by the BOX complex and catalysis by a complex which involves the support, or indeed by the support itself, should be taken into account. In the case of the silica-grafted ligands, the silanol groups of the silica could interfere. Both groups who attempted this type of heterogenization have therefore tried protecting them. In the case of ligands which were tethered to PEG, whether on soluble or insoluble polymers (ArgoGel), the enantioselectivities were not as high as expected, probably because of complexation of the oxygens of the PEG polymers with the metal.

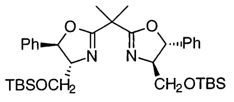
Of the heterogenization methods tested so far, silica-grafted BOX gave the best results. Symmetrical grafting of the BOX ligands influences the enantioselectivity of the reaction, but the effect is not as strong as that found for the cyclopropanation reactions. An interesting conclusion that emerges by the comparison of the two IndaBOX-silica systems reported is that the mesoporous vs amorphous nature of the silica does not seem to influence the enantioselectivity of the catalyst.

V. Allylic Substitution

Pfaltz et al.[17,75] performed allylic substitution reactions using BOX ligands. They studied the reaction of racemic 1,3-diphenyl-2-propenyl acetate with dimethylmalonate, as described in Scheme 23, using several BOX ligands. Ligand **55** gave the best results: 97% yield and 97% ee.

Scheme 23. Allylic Substitution: ArgoGel-Grafted 44 Achieved Excellent Enantioselectivities, with Slightly Lower Yields than Homogeneous 1c



	% yield	% ee
homogeneous **1c**:	67-95	95-96
heterogeneous **44**:	28-70	94-95
 **55**	97	97

Hallman and Moberg[76] used the same ArgoGel-grafted catalytic system **44** (see section IV.E) to effect allylic substitution (Scheme 23). They obtained enantioselectivities of 94−95% and yields of 28−70% with the heterogeneous catalyst **44**, compared to 95−96% ee and 67−95% yield with the homogeneous **1c**. Pd^0 is formed during the reaction, thus preventing the recycling of the polymer. However, removal of the precipitated Pd^0 with KCN in DMSO enabled recycling of the ligand without loss of activity or enantioselectivity (the ligand was recycled 5 times; the yield varied between 29 and 93%, mostly increasing with recycling. The exact results were not given).

It is interesting to note that ArgoGel-grafted **44** was much less successful in the Diels−Alder reaction, as mentioned above (Section IV.E). This proves again the very demanding nature of the Diels−Alder reaction.

VI. Aziridination Reactions

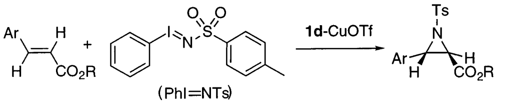
A. Introduction

The aziridination reaction resembles the epoxidation reaction in the form of the reagents and the products, and the interest in aziridines as chiral building blocks equals the interest in epoxides. However, the field of asymmetric aziridination is far less developed than that of asymmetric epoxidation.[77]

Evans and co-workers have shown that CuOTf-BOX or Cu(OTf)$_2$−BOX complexes can be used to catalyze the asymmetric aziridination of olefins by PhI=NTs (*N*-(*p*-tolylsulfonyl)iminophenyliodinane), depicted in Schemes 24 and 25.[78−80] They reacted several different olefins with aromatic substituents. Trans-substituted cinnamate esters gave very good enantioselectivities (Scheme 24). In this case, better enantioselectivities were obtained with ligand **1d** (R_{ox} = Ph; R_{brg} = Me) than with the more sterically demanding **1f** (R_{ox} = *t*-Bu; R_{brg} = Me).

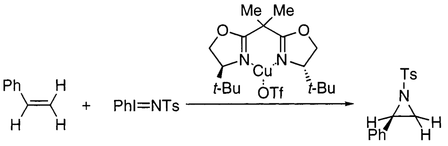
A solvent effect was observed, the direction of which depends on the substrate. For cinnamate esters, better enantioselectivities were obtained with less polar solvents (Scheme 24); for *trans*-*β*-methylstyrene, reaction enantioselectivity improved with

Scheme 24. Aziridination of Cinnamate Derivatives



Ar	R	solvent	%ee	%yield
Ph	Me	MeCN	70	21
Ph	Me	benzene	94	63
Ph	Ph	benzene	97	64

Scheme 25. The Solvent Effect in the Aziridination Reaction of Styrene



56

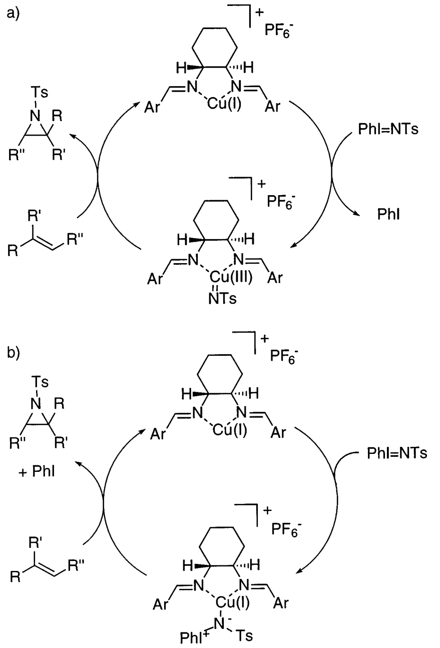
solvent	%ee
MeCN	6
CH_2Cl_2	36
benzene	57
styrene	63

increasing solvent polarity. For styrene, the solvent effect was the same as for the cinnamate esters: better enantioselectivities were obtained in apolar solvents, such as benzene (57% ee) and styrene (63% ee), relative to more polar solvents such as MeCN (6%) and CH_2Cl_2 (36%) (Scheme 25). Alkenes other than styrene were, naturally, not tested using styrene as solvent. For both styrene and trans-β-methylstyrene the more bulky ligand **1f** (R_{ox} = *t*-Bu; R_{brg} = Me) gave best results.

The mechanism of the reaction has not been completely rationalized.[79,80] However, evidence has been found for the presence of a concerted polar mechanism, rather than a radical one.[79] An analogy to the mechanism of cyclopropanation has been proposed and investigated for the reaction of PhI=NTs with various alkenes, in the presence of chiral diimine-Cu complexes.[80] According to Jacobsen et al., the mechanism proceeds in a redox process, through a nitrene–Cu(III) species (Scheme 26a), with dissociation of the PhI before the aziridination occurs. This is supported by the similar enantioselectivities obtained using aziridination agents ArI=NTs with different aryl moieties (16 different catalysts were tried, e.g., Ar = 3,5-$Br_2C_6H_3$, C_6F_5, 1-naphthyl, 2-thiophenyl). However, as described later, Hutchings et al. found that in several cases, a difference in enantioselectivity could occur when a different aziridination agent (PhI=NNs) was used.

Evans et al. suggest yet another possibility, namely, that the active species in the mechanism is a Cu(II) catalyst.[79] They base their hypothesis on competition experiments between three different pairs of olefins. The selectivities between the olefins are very similar whether the metal precursor used was a Cu(I) or a Cu(II) species. They conclude that in both cases the same catalytic complex is formed, and seeing that PhI=NTs is an oxidizing agent, the active catalyst is concluded to be a Cu(II) rather than a Cu(I) species. It should be noted that they conducted these experiments in the absence of chiral ligands, using only $CuClO_4$, CuOTf, or $Cu(OTf)_2$ as catalysts. The mechanism in the presence of a di-imine ligand may not be identical to the mechanism in its absence.

Scheme 26. Proposed Aziridination Mechanism[a]



[a] Ref 80.

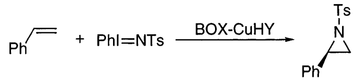
B. Heterogenizations Using Noncovalent Bonding

Hutchings et al. have performed the aziridination reaction with non-covalently bound bis(oxazolines).[81−85] They used zeolite Y as the solid support. Zeolite Y is made of sodium aluminate and sodium silicate with NaOH in a gel process. It has a 3D pore structure, with pore diameter of 7.4 Å, and cavities of diameters of 12 and 24.7 Å. The authors first exchanged zeolite Y with $Cu(OAc)_2$ to obtain CuHY (Cu content 3.2–4% by weight, i.e., 0.50–0.63 mmol/g; ca. 50–60% of available H^+). They then used CuHY as catalyst for the racemic aziridination of styrene (Scheme 25) with PhI=NTs, obtaining good yields of aziridine **56** (measured relative to PhI=NTs). Indeed, the yields were better than those obtained using the homogeneous catalyst when no excess of styrene was used. Many other alkenes were also reacted, with good yields in most cases.

They then modified the CuHY with chiral BOX ligands. This is an original approach: the usual approach involves formation of the chiral complex first, followed by ion exchange with the support (see section II.B).[86,87] This method resembles more the modification of metals with chiral molecules (e.g., cinchona alkaloids[88−90]).

When CuHY was modified with chiral BOX ligands and tested in enantioselective aziridination reactions, either the yield or the enantioselectivity was lower than the ones obtained with the homogeneous catalyst. For example, using ligand **1d** in the aziridination of styrene, a yield of 82% was obtained, with 44% ee (Table 24, entry 1); and when ligand **57**, a py-BOX, was used, the yield was 4%, with 61% ee (Table 24,

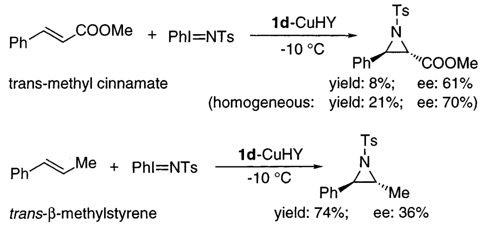
Table 24. Enantioselective Aziridination of Styrene with Bis(oxazoline) Ligands Supported on Zeolite Y[a]



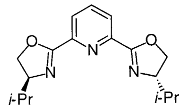
entry	ligand	T (°C)	% yield[b]	% ee[b]
1	**1d**: R_{ox} = Ph; R_{brg} = Me	−10	82	44
2	**1d**: R_{ox} = Ph; R_{brg} = Me	25	87	29
3	**1f**: R_{ox} = t-Bu; R_{brg} = Me	−20	64	0
4	**1f**: R_{ox} = t-Bu; R_{brg} = Me[c]	−20	15 (89)	18 (63)
5	**1c**: R_{ox} = Ph; R_{brg} = H	25	78 (75)	10 (10)
6	**57**	−10	4	61

[a] Reaction conditions: alkene/PhI=NTs = 5/1, solvent: MeCN. [b] Values in parentheses indicate results obtained under the same conditions for the homogeneous reaction. [c] Styrene was used as a solvent.

Scheme 27. Enantioselective Aziridination of Other Substrates with CuHY Modified with a BOX Ligand (1d, R_{ox} = Ph; R_{brg} = Me)



entry 6). A similar trend was observed for other substrates as well (Scheme 27).



57

The authors tested the dependence of the reaction on temperature, solvent, and on the BOX/Cu(II) ratio (Figure 3).[83,91] They found out that using ligand **1d** (R_{ox} = Ph; R_{brg} = Me) best enantioselectivities were obtained at −20 °C, using MeCN as solvent, and a BOX to Cu(II) ratio of 1:2 (yields were measured relative to PhI=NTs). In all experiments, the Cu(II)/PhI=NTs/styrene ratio was kept at 0.1:1:5. The optimum ratio of BOX/Cu(II) = 1:2 means that not all Cu(II) cations were modified at maximum yield, which may account for the loss of enantioselectivity relative to the homogeneous phase. On the other hand, it also means that only relatively small amounts of the expensive chiral modifier were needed to achieve optimal results. The enantioselectivity increased very slightly (35% compared with 34%) when the ratio of BOX/Cu(II) was increased up to 1:1, but the yield dropped significantly (Figure 3b). Further increase in the BOX/Cu(II) ratio did not improve the enantioselectivity, but led to a lower yield as a result of pore clogging. Adding a large excess (up to 1:60) of bis(oxazoline) to the zeolite followed by filtration and washing by MeCN gave the same results as did the preparation of the zeolite directly with a BOX/Cu(II) ratio of 1:2.[81]

Recycling of the catalyst caused a decline in the enantioselectivity, which became more marked from the fourth cycle onward. The activity was gradually lost as well, reaching about 45% yield by the ninth cycle after 35 h vs 87% yield for the first cycle after 1 h.

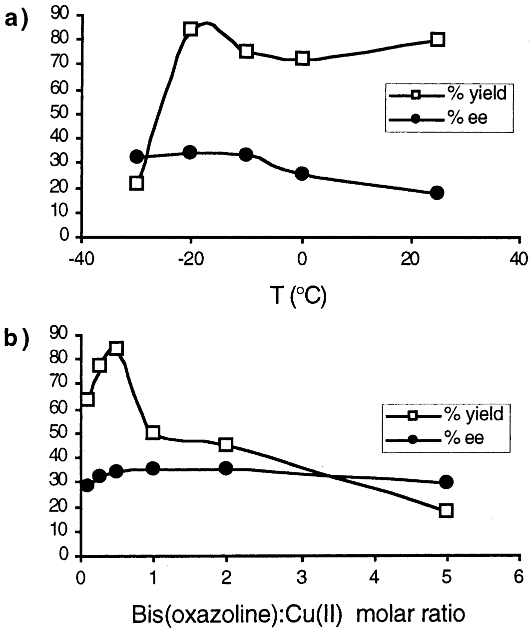


Figure 3. (a) The influence of the temperature on yield and enantioselectivity in the aziridination reaction of styrene with PhI=NTs, when **1d** was used as the chiral modifier of zeolite Y. (b) The influence of the BOX/Cu(II) ratio on yield and enantioselectivity, when **1d** was used as the chiral modifier of zeolite Y. The ratio of Cu(II)/PhI=NTs/styrene was kept at 0.1:1:5 throughout these experiments.

MCM-41 was also tried under similar conditions, and gave up to 87% yield and 37% ee in the aziridination reaction of styrene.[91] Its larger pores permitted the use of more voluminous alkenes and chiral modifiers.

Some structural and mechanistic aspects of the system were also investigated. EPR allows probing of the coordination level and shape around the Cu copmlex. EPR spectra[92] of CuNaY zeolites without BOX provided proof that the Cu is indeed situated in the supercage of the zeolite. With no solvent present, two Cu species were perceptible: pseudo-octahedral and square-pyramidal. This indicates that the Cu is situated in two different sites of the zeolite. When MeCN was added, only the pseudo-octahedral species was observed, meaning that the MeCN molecules completed the coordination sphere of the square pyramidal Cu. The more the MeCN was evaporated, the more square-pyramidal Cu species were observed. Upon addition of BOX in MeCN to the zeolite, two additional species were observed: a different square-pyramidal species, which accounted for 20% of the Cu, and a square planar species, which accounted for another 20% of the Cu present. Both of these species were observed only in the presence of BOX ligands, and they supply strong evidence for the formation of Cu−BOX complexes within the zeolite cavities. Considering that the molar ratio of Cu/BOX of 2:1 was used, this accounts for most of the BOX ligands (80%). If any of the BOX ligands are coordinated so as to form a pseudo-octahedral species, its EPR spectrum may not differ from the original pseudo-octahedral species present in the zeolite. Knowing that the overall Cu concentration is 0.218 mmol/g of catalyst, the ca. 40% of the Cu which is present in complex with BOX ligands means approximately one Cu−BOX complex per supercage.

Addition of either PhI=NTs *or* styrene to the BOX-CuNaY zeolite resulted in partial disappearance of the lowly coordinated Cu(II) species attributed to the BOX−CuNaY complexes (square pyramidal and square planar), indicating that the substrates can form complexes with the Cu−BOX complexes in the zeolite. It also decreased the overall EPR-visible amount of Cu. This indicates the formation of diamagnetic Cu species. Cu(I) and Cu(III) species are diamagnetic, and hence this could supply evidence for the mechanisms suggested by Jacobsen et al. (Scheme 26). However, the authors do not discard the possibility of formation of other diamagnetic species by aggregation or by the formation of EPR-silent Cu(II) species due to fast relaxation processes. Hence, they could not draw a definitive conclusion as to the mechanism of the reaction. They did observe that when *both* PhI=NTs and styrene were added to BOX-CuNaY, the amount of EPR-visible Cu rose almost to the level observed without any substrates, meaning that the EPR-silent species observed upon addition of only one of the substrates disappear when the catalytic cycle operates.

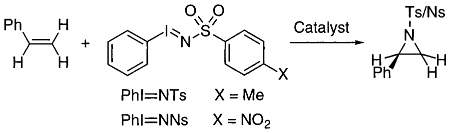
More recently, Hutchings et al. have investigated the effect of the nitrogen donor on the yield and enantioselectivity of the reaction.[93,94] After trying a variety of nitrogen donors, they found out that PhI=NNs (*N*-(*p*-nitrophenylsulfonyl)imino)phenyliodinane) presented several advantages over the conventional PhI=NTs. Most importantly, PhI=NNs achieved good enantioselectivities as well as good yields when the usual 5:1 ratio of styrene to nitrogen donor was used. And at a ratio of 1:1.5, it gave even higher enantioselectivities. In these cases, it also gave higher % ee than those obtained by the equivalent homogeneous system. For PhI=NNs in MeCN, the heterogeneous system modified with **1d** (R_{ox} = Ph; R_{brg} = Me) gave 78% yield with 85% ee (Table 25, entry 1, after 5 h).

Other BOX ligands, such as **1c** (R_{ox} = Ph; R_{brg} = H), **1e** (R_{ox} = t-Bu; R_{brg} = H), and **1f** (R_{ox} = t-Bu; R_{brg} = Me) were also tested, but gave slightly lower enantioselectivities (Table 25). BOX **57** gave much lower enantioselectivities. Interestingly, when **1e** or **1f** was used in the homogeneous phase, the (*S*,*S*)-bis(oxazoline) gave the (*R*)-aziridine (43% ee), whereas in the heterogeneous phase the (*S*)-aziridine was obtained (82% ee). This reversal of induction indicates that in this case the zeolite pores significantly influence the substrate−catalyst interaction.

Other metals (e.g., Zn, Ni, Fe, Mn, Co) have been tested, but yields and enantioselectivities were much lower than those obtained with Cu.[93,95] The main byproduct derived from styrene was benzaldehyde. This was probably due to oxidation by some PhI=O which was formed during the reaction.[95]

In addition, Hutchings et al. tested the poisoning effects of the reaction byproducts PhI and $TsNH_2$ or $NsNH_2$ on the activity of the catalyst, in solution (with Cu(OTf)$_2$ as metal precursor) or on CuHY, with or without bis(oxazolines). They found a complicated relationship, but always the poisoning effect was less significant when the ligand was present than when it was not. The effect was especially interesting in the case of CuHY with PhI=NNs, where the reaction was actually more rapid in the presence of the "poisoning" byproducts than in their absence. In all other cases, the introduction of these byproducts did slow the reaction down. The authors did not report recycling experiments with this system, but they did observe a small leaching (1.0−6.8% of the total Cu^{2+} quantity of the CuHY) of the solution mixture after the solid was filtered off.[94] This Cu^{2+} solution, however, was not active *as is* in further reactions. The authors concluded that this was caused by the poisoning effect the byproducts have on the homogeneous catalyst.

Table 25. Effect of Bis(oxazoline) and of Nitrene Donor (PhI=NTs or PhI=NNs) on the Aziridination of Styrene[a]



		PhI=NTs[f]		PhI=NNs[g]	
entry	BOX	yield	% ee[h]	yield	% ee[h]
1	**1d**[b]	78 (91)	76 *S* (73 *S*)	78 (96)	85 *S* (81 *S*)
2	**1c**[c]	70 (74)	77 *S* (28 *S*)	80 (85)	82 *S* (54 *S*)
3	**1f**[d]	58 (78)	24 *S* (35 *R*)	68 (79)	82 *S* (43 *R*)
4	**1e**[e]	80 (85)	28 *S* (8 *R*)	72 (42)	77 *S* (31 *R*)
5	**57**	55 (70)	5 *S* (11 *S*)	29 (42)	6 *S* (15 *S*)

[a] Styrene: nitrene donor ratio = 1:1.5, 25 °C, CuHY (0.3 g). Figures in parentheses are for the homogeneous catalyst with Cu(OTf)$_2$ as metal precursor (0.015 mmol) under identical conditions. [b] **1d**: R_{ox} = Ph; R_{brg} = Me. [c] **1c**: R_{ox} = Ph; R_{brg} = H. [d] **1f**: R_{ox} = *t*-Bu; R_{brg} = Me. [e] **1e**: R_{ox} = *t*-Bu; R_{brg} = H. [f] Reaction time: 1 h for homogeneous, 3 h for heterogeneous. [g] Reaction time: 1.5 h for homogeneous, 5 h for heterogeneous. [h] Absolute enantioselectivity obtained if the S,S-bis(oxazolines) are used.

Optimization of the reaction conditions, and especially of the molar ratio of styrene to PhI=NNs (Figure 4a) allowed the authors to reach very high enantioselectivities using the heterogeneous system: up to 95% ee was reported, with 76% yield (and 20% yield of benzaldehyde) for a ratio of 1.4 styrene/PhI=NNs, at 25 °C, in MeCN, with **1d** (R_{brg} = Me; R_{ox} = Ph) as chiral modifier of CuHY, and a reaction time of 16 h. This is a better enantioselectivity than they achieved with the homogeneous system under any conditions, making this heterogeneous system particularly interesting, since it is one of the rare cases where the enantioselectivity improves upon heterogenization. As can be seen from Figure 4b, this was not the case when PhI=NTs was used, in which case the homogeneous system seems to be slightly superior to the heterogeneous one.

C. Aziridination: Conclusion

In the case of aziridination reactions, better overall enantioselectivities have been achieved in the heterogeneous than in the homogeneous phase. This is

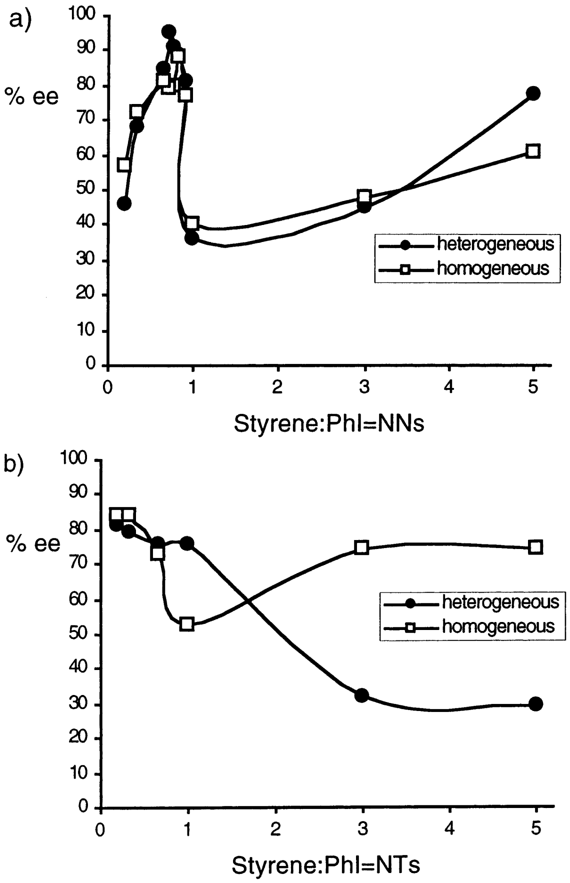


Figure 4. The influence of the ratio of the reagents on the enantioselectivity obtained using **1d** in homogeneous and heterogeneous aziridination reactions. (a) PhI=NNs as nitrene donor. (b) PhI=NTs as nitrene donor.

a rare occurrence in heterogeneous catalysis, and is probably due to favorable steric interactions between the zeolite and the BOX ligands. In some cases, this interaction was strong enough to induce a reversal of the enantioselectivity (relative to that obtained by the same ligand in the homogeneous phase).

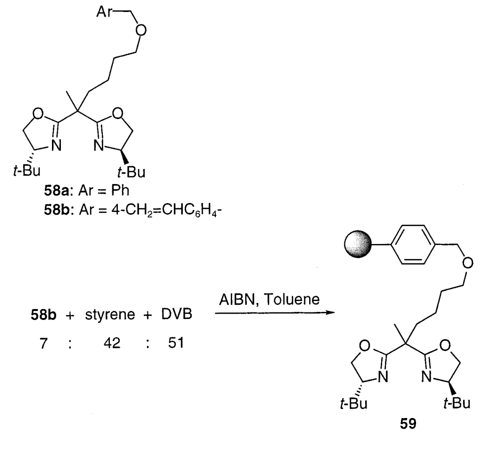
Some leaching of the catalyst was observed, but the leached Cu species did not affect the enantioselectivity of the reaction, apparently because they were poisoned by the byproducts. In one case, an interesting phenomenon was observed, namely, the acceleration of the catalysis in the presence of the byproducts of the reaction. This may be due to poisoning of nonselective sites in the zeolite, and as a result the enantioselectivity of the products was improved.

The original approach used, namely, that of adding the ligand to previously prepared metal–zeolite complexes, may contribute to the success of these catalysts. It may be applicable to other reactions as well. It would be especially interesting to compare the performances of two catalytic systems, prepared using the two different immobilization approaches, in the catalysis of the same reaction.

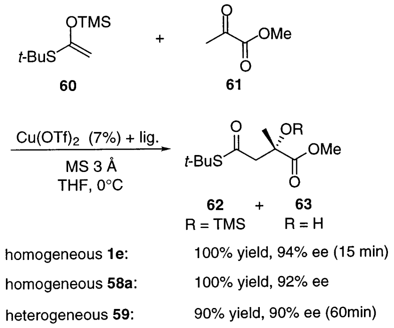
VII. Mukaiyama Aldol Reactions

Very recently, Salvadori et al.[96] have heterogenized BOX **58b** by polymerization with styrene and DVB (ratio: 7:42:51), in the presence of toluene as a porogenic agent, and with AIBN as initiator (Scheme 28). They used the obtained polystyrene polymer **59** (0.31 mmol of ligand/g of polymer) as a catalyst in the Mukaiyama aldol reaction presented in Scheme 29.[97,98]

Scheme 28. Polymerization of Bis(oxazoline) 58b



Scheme 29. The Mukaiyama Aldol Reaction—Comparison of Catalysis by Homogeneous and Heterogeneous Ligands



The catalyst was prepared by mixing polymer **59** with an excess of $Cu(OTf)_2$ in THF. After washing, only 0.18 mmol of metal/g of polymer was found to be present in the polymer (i.e., not all the ligands in the polymer were accessible to the metal).

The catalysis of the Mukaiyama aldol reaction (Scheme 29) was performed in the presence of molecular sieves (MS). Products **62** and **63** were obtained with 90% yield (both products together) and 90% ee after 60 min. These results approach those of the homogeneous ligand **58a** (100% yield and 92% ee), and even those of ligand **1e** (100% yield and 94% ee after 15 min; Scheme 29). The polymer was then recycled by filtering (together with the MS), washing with CH_2Cl_2 and drying in a vacuum. It was then saturated again with $Cu(OTf)_2$ and employed in the same reaction for four more cycles, with no loss of enantioselectivity (88–91% ee), but with loss of activity, which became more marked on the fourth cycle, where only 52% yield was obtained. In addition, more of the deprotected alcohol **63** and less (and eventually none) of the TMS-protected alcohol **62** were obtained. These two phenomena can be explained by the accumulation of moisture in the polymer. Indeed, addition of new MS before the fifth recycling cycle restored the activity of the catalyst and even improved it (96% yield).

The authors noticed that the color of the catalyst after filtration was green, and concluded that at least some of the metal stayed on the catalyst. They therefore conducted runs 6 and 7 of their experiment without adding any $Cu(OTf)_2$ to the catalyst and obtained slightly improved enantioselectivities (93% ee) and 97% yield, but longer reaction times were required (120 min. in the sixth recycling cycle, 240 min in the seventh). This indicates that some of the metal was lost between the reaction cycles.

VIII. Conclusion

Three general methodologies for heterogeneization of BOX ligands have been extensively studied: immobilization using noncovalent interactions, covalent grafting onto organic or inorganic materials, and binding onto soluble polymers, which can be readily precipitated at the end of the reaction.

In most cases, the use of noncovalent ionic interactions proved to be of little practical interest. For the cyclopropanation reaction, for example, the enantioselectivities obtained using this method were much lower than those obtained by the homogeneous ligands (section II.B). The reason for this could be the replacement of the counteranions of the metal by the support. Counteranions are known to influence the activity and enantioselectivity of catalytic complexes in many homogeneous reactions. Recycling of such catalytic materials was also problematic, due to leaching of both the metal and the ligand. Therefore, for such catalytic materials to be successful, it is important to control the design of both the ligand and the material. From this point of view, some recent results are encouraging: good enantioselectivities and an original effect of the inorganic matrix was described with a copper exchanged zeolite for the aziridination reaction (section VI.B). Indeed, this approach used a carefully designed inorganic material modified by chiral BOX ligands. This catalyst gave rise to enantioselectivities which were even better than those obtained in solution in the case of asymmetric aziridination.

The second approach, of grafting the catalyst onto organic or inorganic solids, is more classical in asymmetric heterogeneous catalysis, and was proposed in the early stages of the discovery of practical asymmetric catalysis. Binding of BOX ligands onto organic or inorganic supports was successfully performed in several manners, and allowed the preparation of catalysts which were almost as selective and efficient as their homogeneous homologues. In general, these materials could also be recycled several times without loss of activity or enantioselectivity. Several criteria seem to be required to keep the enantioselectivity high: in most cases it is important to keep a pseudo-C_2 symmetry of the catalyst, i.e., the bridge of the BOX should be functionalized with similar groups. The catalyst loading (mmol of catalyst per gram of polymer) should not be too high, to avoid interactions between the catalytic sites. This is probably true for noncovalent immobilizations as well. And finally, the matrix should preferably not contain groups which are likely to form complexes with the metal (such as ether oxygens, thioethers, silanol groups), since such complexes can either disturb the geometry of the bis(oxazoline) complex and the coordination around it, or form achiral catalytic species which can catalyze the reaction in a racemic manner. If such groups exist in the matrix itself, attempts to protect them should be made. This is especially true in the case of inorganic supports, in which Brønsted and Lewis acids could act as catalysts, and Lewis bases could act as competitive ligands. Interestingly, some reactions are more sensitive to these criteria than others, and some materials can catalyze well one reaction but not another.

The last approach, of tethering the BOX ligands to soluble PEG polymers, is easier to perform, and the catalysts are also easier to characterize. However, the separation of these catalysts from the bulk is based on the difference in the solubilities of the products and the catalysts. This difference could be high, and the separation could therefore be quite good. But it cannot be total, and some loss of the catalyst cannot be avoided. Another disadvantage is the large quantities of solvent required to precipitate the catalyst.

IX. Acknowledgment

D.R. would like to thank Marc Robinson-Rechavi for help with statistical analysis and interpretation of the data.

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