The Role of Binding Constants in the Efficiency of Chiral Catalysts Immobilized by Electrostatic Interactions: The Case of Azabis(oxazoline)–Copper Complexes

José M. Fraile,[a] José I. García,[a] Clara I. Herrerías,[a] José A. Mayoral,*[a] Oliver Reiser,*[b] Antonio Socuéllamos,[a] and Heiko Werner[b]

Abstract: As shown by theoretical calculations, azabis(oxazoline)–copper complexes are considerably more stable than the analogous bis(oxazoline)–copper complexes. This enhanced stability allows them to be efficiently immobilized by means of electrostatic interactions to different anionic supports, such as clays and nafion–silica nanocomposites, without the loss of a ligand, as is observed for bis(oxazolines). As a result, enantioselectivities of around 90% *ee* are obtained in the cyclopropanation reaction between styrene and ethyl diazoacetate. Moreover, the solid catalyst is easily recoverable.

Keywords: cyclopropanation · enantioselectivity · heterogeneous catalysts · immobilized catalysts · N ligands

Introduction

Asymmetric heterogeneous catalysts[1] are very attractive because they have inherently practical advantages over homogeneous catalysts, and because the resultant product enantioselectivities are at the levels required in the pharmaceutical or agrochemical industry. One of the most widely used methods to prepare asymmetric heterogeneous catalysts is to immobilize the homogeneous counterpart on a solid support.[2] Although the attachment of a ligand to a support by covalent bond formation is the most widely used method of immobilization,[2,3] on many occasions the synthetic steps required prove to be difficult. Furthermore, binding the ligand covalently to the support may modify the conformational preferences of the catalytic complex, and thereby lead to changes in enantioselectivity.[4] Alternatively, immobilization can be achieved by electrostatic interaction, although in spite of its simplicity, this method is not often used.[2]

In asymmetric catalysis the binding constant of the complex formed between the chiral ligand and the metal precursor is generally not considered. Nevertheless, a weak complex may lead to the presence of free metal precursor, and consequently, non-enantioselective catalytic centres. In a homogeneous phase this limitation is frequently overcome by adding an excess of chiral ligand. However, in a heterogeneous phase the situation is not so simple because of the phenomenon of site isolation. Consequently, it is very difficult to produce a local excess of chiral ligand on the solid. On the other hand, it is possible to add the chiral ligand to the liquid phase, but this strategy eliminates most of the advantages of immobilization. As a result of this problem it is much easier to find efficient chiral heterogeneous catalysts for ligand-accelerated reactions.[5] Thus, a high binding constant is more important in heterogeneous than in homogeneous asymmetric catalysis, and the best ligand in solution may not be the best one in a heterogeneous phase. Herein we illustrate this reasoning using bis(oxazoline)– and azabis(oxazoline)–copper complexes that have been immobilized by electrostatic interactions onto anionic supports.

In our work on the immobilization of bis(oxazoline)–copper complexes by electrostatic interactions, we have found that clays[6] and nafion-based solids[7] are suitable supports,[8] but their efficiency depends on the nature of the chiral bis(oxazoline) ligand. These divergences come from the different binding constants of the bis(oxazoline)–copper complexes. For example, with 2,2′-isopropylidenebis[(4*S*)-4-

[a] Dr. J. M. Fraile, Dr. J. I. García, Dipl.-Chem. C. I. Herrerías, Prof. Dr. J. A. Mayoral, Dipl.-Chem. A. Socuéllamos
Departamento de Química Orgánica
Instituto de Ciencia de Materiales de Aragón, Facultad de Ciencias
Universidad de Zaragoza-C.S.I.C., 50009 Zaragoza (Spain)
Fax: (+34) 976-762-077
E-mail: mayoral@unizar.es

[b] Prof. Dr. O. Reiser, Dipl.-Chem. H. Werner
Institut für Organische Chemie, Universität Regensburg
Universitätstrasse 31, 93053 Regensburg (Germany)
Fax: (+49) 941-4121
E-mail: Oliver.Reiser@chemie.uni-regensburg.de

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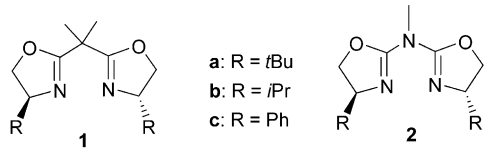
tert-butyl-4,5-dihydro-1,3-oxazole] (**1a**) the corresponding copper complex cannot be efficiently immobilized, and most of the chiral ligand is lost during the cationic-exchange process. Only when an excess of ligand is used in the reaction medium are high enantioselectivities obtained in the cyclopropanation[9] of styrene with ethyl diazoacetate.[10] Unfortunately, the ligand is lost during the washing of the catalyst.



The use of a catalyst in which the metal is more tightly bound to the chiral ligand should overcome this problem. Azabis(oxazolines)[11] **2** that contain an electron-donating amino group in the central bridge were envisioned to be more electron-rich ligands than bis(oxazolines) that have a methylene group as the bridging element of the two oxazoline units.

In the current paper we confirm our hypotheses through theoretical calculations, as well as by experimental data obtained from the electrostatic immobilization of azabis(oxazoline)–copper complexes to different supports and the use of the resultant immobilized catalysts in the asymmetric cyclopropanation reaction between styrene and ethyl diazoacetate.

Results and Discussion

Relative stability of bis(oxazoline)– and azabis(oxazoline)–copper complexes: To confirm the hypothesis that copper(II) ions have a higher affinity for azabis(oxazoline) ligands than bis(oxazoline) ligands, we tried to determine the binding constants for both types of complexes by UV and microcalorimetric measurements. However, several practical problems in the course of our experiments did not allow us to obtain meaningful results. Fortunately, theoretical calculations can give an accurate estimation of relative equilibrium constant values. Initially, the Cu^{II} complexes of bis(oxazolines) were considered as these complexes are used in the exchange process for the preparation of immobilized catalysts, in which ligand loss has been observed. However, two main problems arise with the theoretical calculations of such species. First, the interaction between a doubly charged cation that has a highly localized positive charge and a ligand will be greatly overestimated in a gas-phase calculation, particularly, as in solution this is not as pronounced. The second complication arises from the open-shell character of Cu^{II} complexes that have one unpaired electron, as this may lead to spin contamination and self-consistent field (SCF) convergence problems. In fact, when the Cu^{II} complexes were considered in geometrical optimizations at the UHF/6-31G(d) level, serious problems of convergence, both in the SCF wavefunction and in the geometrical parameters, were encountered.

Therefore, we turned our efforts towards the Cu^{I} complexes, which have only one positive charge, and because of their closed-shell electronic structure, do not contain any unpaired electrons. Although this does not truly reflect the situation present in the exchange process, it should be noted that the Cu^{I} complex is actually the true catalytic species.[12] Moreover, it is also the species that is present when the loss of a chiral ligand occurs by competitive coordination of byproducts. Thus, the higher affinity of the Cu^{I} complex should be reflected in the attainment of higher enantioselectivities when the catalyst is applied in multiple cycles. Moreover, as problems were not observed with the convergence of the theoretical calculations for the Cu^{I} complexes investigated, we will only discuss the results obtained for these.

To estimate the binding affinity of each ligand to copper(I) ions, the following equilibrium was considered [Eq. (1)].

$$\mathbf{1a} + \mathbf{2a}\text{–}Cu^{I} \rightleftharpoons \mathbf{1a}\text{–}Cu^{I} + \mathbf{2a} \quad (1)$$

Initially, full geometrical optimizations of both the **1a**–Cu^{I} and **2a**–Cu^{I} complexes at the Hartree–Fock (HF) level and a 6-31G(d) basis set [HF/6-31G(d)] were carried out. Some geometrical features of the Cu^{I} complexes are shown in Figure 1, and their energies are summarized in Table 1. Although Hartree–Fock theory does not account for correlation energy, the equilibrium considered [Eq. (1)] represents an isodesmic process. Therefore, relative energies calculated at the HF level are expected to be reasonably accurate.[13]

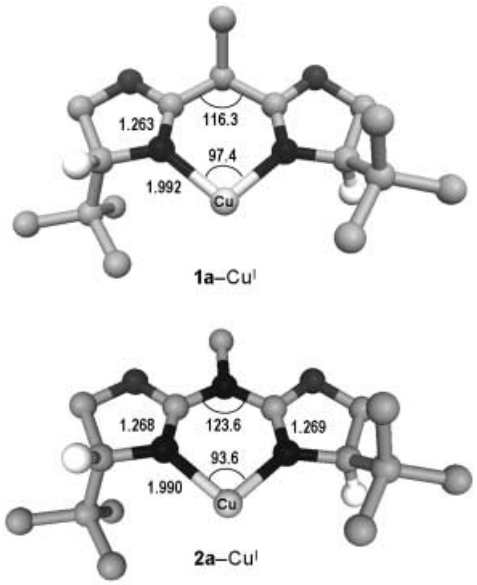


Figure 1. HF/6-31G(d) structures of the **1a**–Cu^{I} and **2a**–Cu^{I} complexes (some hydrogen atoms have been omitted for clarity).

From a geometrical point of view, both complexes are very similar. Thus, the N–Cu distances are almost the same for both compounds (1.99 Å). The azabis(oxazoline) complex is slightly unsymmetrical because of the conformation of the methyl group in the methylamine bridge, while the

Table 1. Results of theoretical calculations for the equilibria between bis(oxazoline) and azabis(oxazoline)–copper(I) complexes in the presence and absence of a Cu coordinated ethylene molecule.

Theoretical level	Energy of the species (Hartrees)				ΔE [kcal mol^{-1}]
	1	**2**–Cu^{I}	**1**–Cu^{I}	**2**	
HF/6-31G(d)	−919.853477	−2535.346509	−2558.380100	−896.811063	+5.5
IPCM/HF/6-31G(d)	−919.857294	−2535.393826	−2558.426551	−896.811500	+6.0
B3LYP/6-31G(d)	−925.827030	−2542.684486	−2565.956341	−902.549634	+3.5
IPCM/B3LYP/6-31G(d)	−925.830096	−2542.730153	−2566.001154	−902.552750	+4.0
	1	**2**–Cu^{I}–C_2H_4	**1**–Cu^{I}–C_2H_4	**2**	
HF/6-31G(d)	−919.853477	−2613.404706	−2636.434460	−896.811063	+7.9
IPCM/HF/6-31G(d)	−919.857294	−2613.450238	−2636.480074	−896.811500	+7.8
B3LYP/6-31G(d)	−925.827030	−2621.323431	−2644.594131	−902.549634	+4.2
IPCM/B3LYP/6-31G(d)	−925.830096	−2621.368062	−2644.638507	−902.552750	+4.3

N−Cu−N angle is somewhat open in the bis(oxazoline) complex. The latter undoubtedly arises because of the smaller C2-C-C2′ angle (116.3°) in comparison to the C2-N-C2′ angle (123.6°), although it should be kept in mind that both chelate complexes are almost completely planar.

The calculated energy variation for this equilibrium is 5.5 kcal mol^{-1}. This suggests that the azabis(oxazoline)–Cu^{I} complex is more stable, and thus, confirms our initial hypothesis. However, calculations carried out in a vacuum may not necessarily represent the behaviour observed in solution. Therefore, polarity solvent effects were taken into account using the isodensity polarizable surface continuum method (IPCM)[14] and the dielectric constant of dichloromethane ($\varepsilon = 8.9$), which was the solvent used in the cyclopropanation reaction. The results (Table 1) show that solvation of analogous species on either side of the equilibrium is very similar. The solvation energy calculated for the bis(oxazoline) **1a** and azabis(oxazoline) **2a** ligands was 2.4 and 2.5 kcal mol^{-1}, respectively. On the other hand, the solvation energy of the corresponding copper complexes was determined to be 29.1 and 29.7 kcal mol^{-1}, respectively, as is expected for charged species. As a consequence, the calculated energy of the equilibrium in solution (6.0 kcal mol^{-1}) was found to be very similar to that determined in a vacuum.

Since Hartree–Fock calculations do not account for electronic correlation energy, a density functional theory (DFT) method was then used on the B3LYP/6-31G(d) basis set both in a vacuum and in dichloromethane.[14] As can be seen (Table 1), the calculated energies of 3.5 and 4.0 kcal mol^{-1} for the equilibria in vacuum and solution, respectively, are slightly lower than those obtained by the HF method. However, the general conclusion from analysis of both methods is the same, namely that the binding constant is not effected greatly by solvation and that it is clearly higher for the azabis(oxazoline)–copper complex than for the analogous bis(oxazoline)–copper complex.

To obtain a deeper insight into the origin of the differential coordination ability of both kinds of ligands, we carried out a natural bond orbital (NBO) analysis on each of the Cu^{I} complexes at the HF/6-31G(d) level. From first analysis, the coordination preference of the azabis(oxazoline) ligand could be ascribed to the electron-donating ability of the bridging nitrogen atom, which would cause the oxazoline nitrogen atoms to have an enhanced electron-donor character. However, to our surprise, the second-order perturbation energy calculations revealed that the interaction between the empty d orbital of the Cu atom and the lone pairs of the oxazoline nitrogen atoms are actually stronger in the bis(oxazoline) **1a** ligand (29.5 kcal mol^{-1} for the **1a**–Cu^{I} complex in comparison to 28.7 kcal mol^{-1} for the **2a**–Cu^{I} complex). Similarly, charge transfer from the ligand to the Cu atom is marginally greater for the bis(oxazoline) ligand (0.040 electron for the **1a**–Cu^{I} complex in comparison to 0.032 electron for the **2a**–Cu^{I} complex), and therefore, indicates that the azabis(oxazoline) ligand does not have a more electron-donating ability.

The electronic effect of the bridging nitrogen atom is noticeable on the atomic charges of the oxazoline nitrogen atoms. Thus, natural population analysis (NPA) shows that the net atomic charges of the oxazoline nitrogen atoms are −0.705 electron for the **1a**–Cu^{I} complex and −0.747 electron for the **2a**–Cu^{I} complex. Figure 2 shows the calculated molecular electrostatic potentials for both complexes, and as can be seen, the negative charge (light gray zone encircled

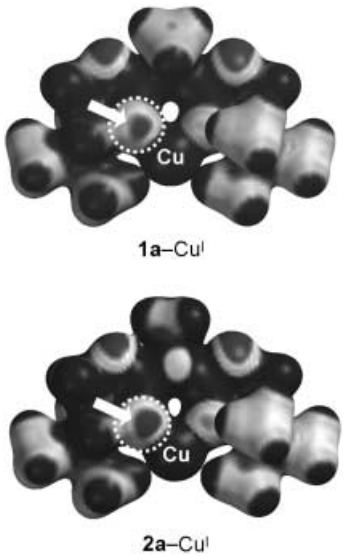


Figure 2. Molecular electrostatic potential maps of the **1a**–Cu^{I} and **2a**–Cu^{I} complexes. Dark gray indicates positive zones, while light gray indicates negative zones. The negative zone around the coordinating nitrogen atom is encircled.

and marked by a white arrow in Figure 2) is more concentrated on the oxazoline nitrogen atoms in the **2a**–Cu^{I} complex. From these results, it can be proposed that the different coordinating ability of ligand **2a** over ligand **1a** possibly arises from an enhanced electrostatic interaction between the Cu cation and the ligand.

To corroborate this explanation, a natural energy decomposition analysis (NEDA)[15] was carried out on both complexes. This analysis evaluates the interaction energy between the Cu^{I} center and the ligand by breaking it up into several terms. Thus, in agreement with previous analyses the charge-transfer term was found to be more important ($-88.4\,kcal\,mol^{-1}$) for ligand **1a** than for ligand **2a** ($-85.1\,kcal\,mol^{-1}$). On the other hand, the reverse is true for the electrostatic term ($-141.2\,kcal\,mol^{-1}$ for the **1a**–Cu^{I} complex in comparison to $-143.5\,kcal\,mol^{-1}$ for the **2a**–Cu^{I} complex). Overall, the interaction energy is higher for the **2a**–Cu^{I} complex than for the **1a**-C-u^{I} complex (-80.2 and $-78.1\,kcal\,mol^{-1}$, respectively). This is in agreement with previous calculations.

A question that concerns the model compounds used for this theoretical study arises. As already mentioned, [16] the Cu^{I} complexes considered are fourteen-electron complexes, and consequently, are probably not the true catalytic intermediates. Therefore, to test the correctness of the conclusions reached, we repeated the calculations using the initial complex in the catalytic cycle, namely the ligand–Cu^{I}–olefin complex. To this end, we considered the following equilibrium [Eq. (2)].

$$\mathbf{1a} + \mathbf{2a}\text{–}Cu^{I}\text{–ethylene} \rightleftharpoons \mathbf{1a}\text{–}Cu^{I}\text{–ethylene} + \mathbf{2a} \quad (2)$$

The same theoretical levels considered in the former study were also used for these compounds. In particular, full geometrical optimizations at the Hartree–Fock level using the 6-31G(d) basis set and single-point energy calculations at the B3LYP/6-31G(d), IPCM/HF/6-31G(d), and IPCM/B3LYP/6-31G(d) theoretical levels were undertaken. Some geometrical features of the Cu^{I} complexes are shown in Figure 3 and their energies are summarized in Table 1.

The same trends observed previously are also reproduced for these complexes. In particular, the equilibrium is shifted to the left, and indicates a preferential coordination of the azabis(oxazoline) **1a** ligand over the corresponding bis(oxazoline) **2a** ligand. Moreover, the energy differences are even greater than those calculated for Equation (1).

The NBO analyses also agreed with the former observations, and NPA revealed that the coordinating nitrogen atoms are more negatively charged in the **2a**–Cu^{I}–ethylene complex (-0.827 electron) than in the **1a**–Cu^{I}–ethylene complex (-0.774 electron). This indicates that the bridging nitrogen atom does have an electron-donating role. In contrast, the Cu atom was found to have an almost identical charge in both complexes (0.982 electron in the **2a**–Cu^{I}–ethylene complex and 0.981 electron in the **1a**–Cu^{I}–ethylene complex). Moreover, the occupancy of the empty Cu orbital implicated in the N→Cu charge transfer is also very similar for both complexes (0.128 electron in the **2a**–Cu^{I}–ethylene complex and 0.126 electron in the **1a**–Cu^{I}–ethylene complex). Finally, the NEDA results showed that the charge-transfer term is more important for the **2a**–Cu^{I}–ethylene complex ($-111.9\,kcal\,mol^{-1}$) than for the **1a**–Cu^{I}–ethylene complex ($-110.3\,kcal\,mol^{-1}$), but that above all, the electrostatic term is much more important for the former ($-148.3\,kcal\,mol^{-1}$) than the latter ($-142.6\,kcal\,mol^{-1}$). Overall, the calculated interaction energy is stronger for the **2a**–Cu^{I}–ethylene complex ($-96.0\,kcal\,mol^{-1}$ in comparison to $-92.5\,kcal\,mol^{-1}$ for the **1a**–Cu^{I}–ethylene complex). This is in agreement with previous calculations.

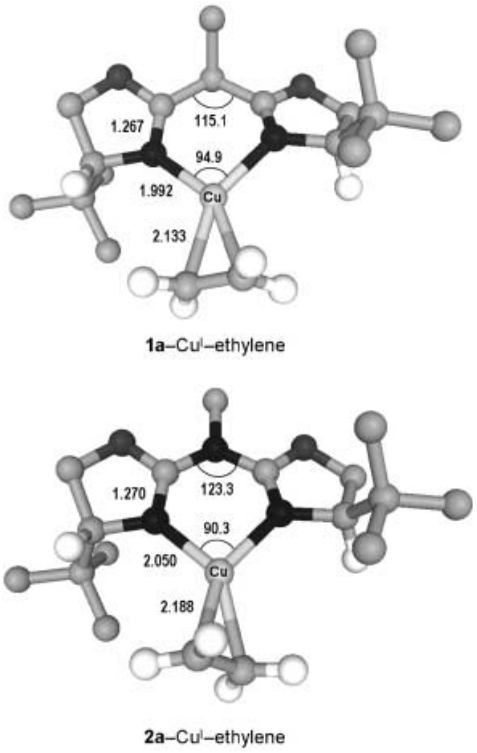


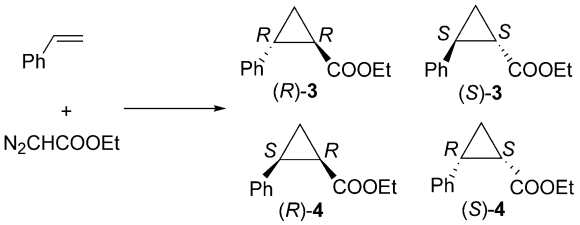
Figure 3. HF/6-31G(d) structures of the **1a**–Cu^{I}–ethylene and **2a**–Cu^{I}–ethylene complexes (some hydrogen atoms have been omitted for clarity).

In summary, azabis(oxazoline)–Cu^{I} complexes are more stable than the analogous bis(oxazoline)–Cu^{I} complexes because of the presence of stronger electrostatic metal–ligand interactions in the former. These in turn result from the electron-donating ability of the bridging nitrogen atom. This fact has important consequences for the electrostatic immobilization of these complexes, since overall the Cu atom keeps most of its positive charge, and hence can establish an efficient interaction with the negatively-charged support.

Control of enantioselectivity by competitive ligand complexation: In principle, the higher metal–ligand affinity the less Lewis acidic the complex, and consequently, the less active the catalyst. On the other hand, a weakly binding ligand might not sufficiently activate a metal for catalysis. To obtain reliable kinetic data for copper(I)-catalyzed diazoacetate cyclopropanations is problematic because the reaction greatly depends upon the slow addition of reagent in order to attain a low concentration of diazoacetate. Therefore, to gain insight into the relative activities of bis(oxazoline) **1**

and azabis(oxazoline) **2** copper complexes, we conducted a series of competition experiments (Table 2) in which copper(I)-catalyzed cyclopropanations in homogeneous solution were carried out in the presence of mixtures of **1a**/**2b** and **1b**/**2a**, respectively. Since the *tert*-butyl-substituted ligands **1a** and **2a** give substantially higher enantioselectivities than their isopropyl-substituted counterparts **1b** and **2b**, analysis of the enantioselectivities obtained with mixtures of **1a**/**2b** and **1b**/**2a** should shed light on the dominant ligand in the catalysis under investigation.

Table 2. Cu^{I}-catalyzed cyclopropanations in the presence of bis(oxazoline) **1** and/or azabis(oxazoline) **2** ligands.[a]



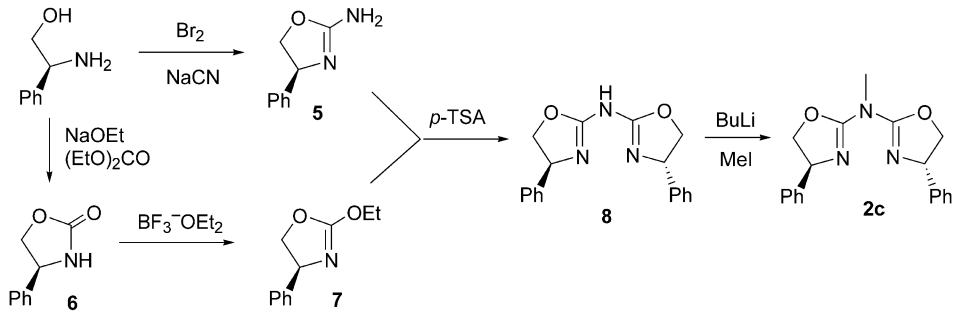
Entry	Ligand **1**	Ligand **2**	(**1** + **2**)/Cu[b]	Yield [%]	**3**:**4**[c]	*ee* of **3**[d] [%]	*ee* of **4**[d] [%]
1[e]	**1a**	–	1.1	77	73:27	99	97
2[e]	**1b**	–	1.1	n.d.	69:31	49	45
3	–	**2a**	2.2	82	73:27	85	75
4	–	**2b**	2.2	85	62:38	56	42
5	**1a**	**2b**	5.0	23	89:11	54	41
6	**1b**	**2a**	2.2	73	62:38	77	67
7	**1a**	**2b**	2.2	76	66:34	61	47

[a] Reaction conditions: diazoester (1 mmol) in CH_2Cl_2 (7 mL), styrene (3 mmol) in CH_2Cl_2 (3 mL), $Cu(OTf)_2$ (0.01 mmol, 1 mol%), room temperature. [b] Equimolar amounts of **1** and **2** were used. [c] Determined by GC using a DB 1301 column. [d] Determined by GC using a CP-Chiralsil DEX CB. [e] Taken from reference [18], five equivalents of styrene were used.

Indeed, reactions performed in the presence of both bis(oxazoline) **1** and azabis(oxazoline) **2** ligands clearly seem to be dominated by the latter. The enantioselectivities obtained (entries 5–7, Table 2) closely resemble the values observed when azabis(oxazoline) **2** ligands are used alone (entries 3 and 4, Table 2). Since formation of the Cu–carbene intermediate, which constitutes the rate-limiting step of the cyclopropanation,[16] is very fast, the reaction is probably not under Curtin–Hammett conditions. As a result, the reaction preferably takes place through the most stable complex rather than being dependent upon the relative activity of the complexes present in equilibrium. In turn, we can conclude that azabis(oxazoline) **2** appears to have a higher binding affinity to copper than bis(oxazoline) **1**.

Exchange of Cu^{II} complexes: The higher stability of azabox–Cu complexes prompted us to immobilize them onto anionic solid supports using the general methodology described in previous papers.[7] Ligands **2a** and **2b** were prepared as previously described,[11] but an alternative method was necessary to prepare ligand **2c** (Scheme 1). (*S*)-2-Amino-4-phenyl-4,5-dihydro-1,3-oxazole (**5**) and (*S*)-2-ethoxy-4-phenyl-4,5-dihydro-1,3-oxazole (**7**), which are readily prepared from (*S*)-phenylglycinol, were condensed in the presence of *p*-toluenesulfonic acid (*p*-TSA) to give **8**. Subsequent methylation of **8** yielded azabis(oxazoline) **2c**, and the copper(II) complexes were then prepared in dichloromethane using equimolecular amounts of $Cu(OTf)_2$ and either chiral ligands **1** or **2**.

Two different types of support were used, namely a synthetic clay (laponite) and a nafion-like material prepared by grafting $(HO)_3Si(CH_2)_3$-$(CF_2)_2O(CF_2)_2SO_3K$ onto silica[17] (Figure 4). Similar nafion–silica hybrid materials have demonstrated to be excellent for immobilization of the **1c**–Cu^{II} complex,[7] but have the disadvantage of low functionalization. The new solid used in the current investigations greatly improved the cationic-exchange capacity and decreased the apparent molecular weight of the immobilized complex, thereby making it much more practical to use. The exchange was carried out in methanol, and the solids were thoroughly washed and then dried under vacuum. The presence of the complexes was confirmed by elemental analysis and IR spectroscopy. For the laponite-based solids the copper content was in the range of 0.1–0.2 mmol g^{-1}, and as shown by the XRD pat-



Scheme 1. Synthesis of *N*,*N*-bis[(4*S*)-4-phenyl-4,5-dihydro-1,3-oxazol-2-yl]methylamine (**2c**).

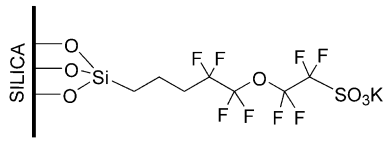
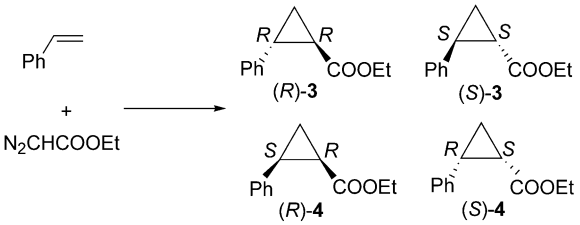


Figure 4. Structure of the nafion–silica support.

tern of oriented samples, expansion was not observed in the basal spacing. These results show that **2**–Cu^{II} complexes are mostly exchanged on the external surface of the clay. Typical copper contents for the nafion–silica solids were in the range 0.25–0.35 mmol g^{-1}.

The prepared solids were then tested in the benchmark cyclopropanation reaction of styrene and ethyl diazoacetate. The reagents were used in equimolecular amounts to allow the results to be compared with those obtained for the analogous solids prepared from bis(oxazoline) **1**. The same amount of catalyst was used each time, but depending on the copper loading of the catalyst, had a range between 0.3 and 1%. The results for both types of ligands are summarized in Table 3. When laponite was used as the support, *tert*-butyl-substituted bis(oxazoline) **1a**, which was found to be the most selective ligand for the asymmetric cyclopropanation of styrene in homogeneous phases,[18] afforded moderate results (up to 69% *ee* compared to 99% *ee* in homogenous solution). On the other hand, the analogous azabis(oxazoline) **2a** performed considerably better. Besides giving rise to higher yields and improved *trans*/*cis* selectivity, the major *trans*-cyclopropane (*R*)-**3** was obtained in 83% *ee*. The difference between the two ligands was even more pronounced when nafion–silica was used as the support. In this case, bis(oxazoline) **1a** gave very poor enantioselectivities ($\leq$18% *ee*) because of ligand loss during the exchange process, whereas azabis(oxazoline) **2a** gave an *ee* (88%) very close to the value described in homogeneous phase (91% *ee*).[11] In agreement with our theoretical calculations, these results clearly demonstrate the higher affinity that copper(I) has for azabis(oxazoline) **2** in comparison to bis(oxazoline) **1**.

Table 3. Results obtained for the Cu^{II}-catalyzed cyclopropanation reactions.[a]



Ligand	Support	Run	Yield [%]	*trans*/*cis*	% ee *trans*	% ee *cis*
1a	Laponite	1	36	64:36	69	64
		2	35	58:42	43	37
2a	Laponite	1	46	71:29	83	76
		2	45	71:29	81	74
1a	Nafion–silica	1	37	60:40	18	16
2a	Nafion–silica	1	30[b]	68:32	88	81
		2	21[b]	66:34	84	77
1b	Laponite	1	31	51:49	5	13
2b	Laponite	1	39	62:38	54	43
		2	26	62:38	53	42
2b	Nafion–silica	1	31	63:37	55	47
		2	24	63:37	55	47
1c	Laponite	1	28	61:39	49	24
2c	Laponite	1	49	64:36	51	38

[a] Reaction conditions: styrene (5 mmol), ethyl diazoacetate (5 mmol, slowly added in two portions), catalyst (150 mg), CH_2Cl_2 (5 mL), room temperature. Yield and selectivities were determined by gas chromatography (methyl silicone and cyclodex-B columns). 3*R* and 4*R* are the major isomers. [b] Heating at 50°C for some minutes was necessary to reduce the Cu^{II} ions to Cu^{I} ions.

Bis(oxazoline) **1a**, which contains *tert*-butyl groups, was not the only compound that displayed problems in the cationic exchange. Ligand **1b**, which contains isopropyl groups, showed the same limitations and afforded very poor enantioselectivities even on a laponite support. In confirmation of the general premise that azabis(oxazoline)–Cu complexes are more stable, the catalysts prepared with ligand **2b** on either laponite or nafion–silica supports gave rise to enantioselectivities that were in good agreement with the results obtained in homogenous solution.

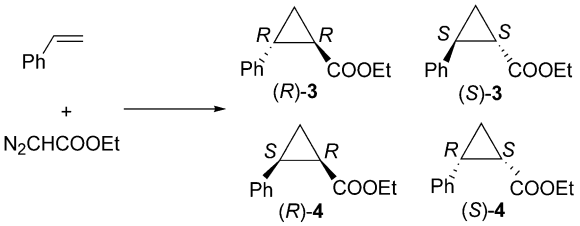
In contrast to the bis(oxazoline) ligands that bear branched alkyl groups, the phenyl-substituted ligand **1c** did not display stability problems either in cationic exchange onto the solid supports or in biphasic systems in which ionic liquids were used.[19] Therefore, the phenyl-substituted azabis(oxazoline) **2c** was prepared and tested for comparative purposes. Once again, azabis(oxazoline) **2c** gave significantly better yields and selectivities than bis(oxazoline) **1c**. As expected, the enantioselectivities for both **1c** and **2c** were very similar, and were close to those obtained in homogeneous phase.

From these results it can be concluded that, in general, higher yields and selectivities are obtained with azabis(oxazoline) catalysts that have been immobilized onto solid supports than with the corresponding bis(oxazoline) catalysts. However, when the copper(II) complex of azabis(oxazoline) **2a** was immobilized onto nafion–silica, the mixture had to be heated at 50°C for some time in order for a reaction to occur. This problem arises because the Cu^{II} ions must firstly be reduced to the Cu^{I} cation as this is actually the active species in the cyclopropanation reaction.[12,16] Once the copper is reduced, the cyclopropanation reaction is fast at room temperature. As a result of these observations, we decided to use copper(I) complexes directly in the exchange process.

Exchange of Cu^{I} complexes: In our initial studies on electrostatic immobilization copper(I) complexes had been tested, but no apparent advantages over the copper(II) species had been observed.[6] Furthermore, copper(I) salts and complexes are less stable in air and are prone to disproportionate; this makes their handling more difficult. However, the difficulties encountered with the in situ reduction of the nafion–silica immobilized **2a**–Cu^{II} complex made the direct immo-

bilization of a copper(I) complex of **2a** desirable. Initially, synthesis of the complex using CuCl as the copper(I) source and the exchange process were conducted under an atmosphere of argon. Surprisingly, although the resultant solid was accidentally exposed to air, excellent results were still obtained and indicated that it was possible to prepare immobilized copper(I) complexes without the use of an inert atmosphere. Thus, CuCl complexes of **2a** were prepared and then exchanged in the same way as the complexes obtained from $Cu(OTf)_2$. The results for the subsequent cyclopropanation reactions using these catalysts are summarized in Table 4.

Table 4. Results obtained for the Cu^I-catalyzed cyclopropanation reactions.[a]



Ligand	Support	Run	Yield [%]	*trans*/*cis*	% *ee trans*	% *ee cis*
2a	Laponite	1	40	69:31	81	58
		2	34	63:37	61	35
2a	Nafion–silica	1	60	66:34	90	83
		2	36	63:37	89	81
		3	35	63:37	40	35
2b	Laponite	1	49	57:43	54	51
		2	35	55:45	54	51
2b	Nafion–silica	1	33	63:37	54	46
		2	25	62:38	53	45

[a] Reaction conditions: styrene (5 mmol), ethyl diazoacetate (5 mmol, slowly added in two portions), catalyst (150 mg), CH_2Cl_2 (5 mL), room temperature. Yield and selectivities were determined by gas chromatography (methyl silicone and cyclodex-B columns). (*R*)-**3** and (*R*)-**4** are the major isomers.

Only minor changes were observed for the catalysts obtained from ligand **2b** and CuCl in comparison to the analogous catalysts obtained from $Cu(OTf)_2$, and which are subsequently reduced during the reaction. Yields were slightly higher for the Cu^I complexes, as was the enantioselectivity obtained for the *cis* isomers. The results obtained for the **2a**–copper(I) complex depended upon the support used. Slightly lower yields and enantioselectivities were obtained when laponite was used, and the catalyst became less efficient upon recovery. However, on a nafion–silica support, the use of Cu^I complexes was completely, if only slightly, advantageous. The reaction takes place at room temperature in 60% yield and 90% *ee* for the *trans* isomer, and only one equivalent of styrene is required. Moreover, the catalyst can be efficiently re-used once after recovery, whereby the same enantioselectivities are obtained. Unfortunately, in a third run a substantial loss of enantioselectivity was detected. We attributed this catalyst deactivation to the formation of byproducts such as diethyl maleate and its polymers, which are formed from the undesired dimerization and oligomerization of diazoacetate. These in turn are able to form copper complexes that act as non-chiral active sites for the cyclopropanation reaction. Consequently, suppression or removal of these byproducts should improve catalyst performance, and protocols to overcome this kind of limitation are currently under development.

Conclusion

The affinity of a metal towards ligands that act as chiral promoters plays a crucial role in the electrostatic immobilization of chiral catalysts. Theoretical calculations indicate that azabis(oxazoline)–copper complexes are significantly more stable than the analogous bis(oxazoline)–copper complexes, and that this is the case because electrostatic metal–ligand interactions make much more important contributions in the former. This hypothesis was corroborated by the efficient electrostatic immobilization of the **2a**–Cu^I complex, and by its successful application in the asymmetric cyclopropanation of styrene in contrast to the results obtained with the analogous bis(oxazoline) catalyst **1a**–Cu^I. The correct choice of support and copper precursor, namely the use of nafion-like supported species on silica and CuCl, leads to results that are comparable to the optimized results obtained in the homogeneous phase (up to 90% *ee*).[11] Although partial loss of enantioselectivity in the third cycle as a result of competitive ligand decomplexation was observed, the results show that efficient heterogeneous catalysts can be prepared by electrostatic immobilization when the binding constant of the chiral complex is high enough so as to make the complex stable against the cationic-exchange process.

Experimental Section

Theoretical calculations: Full geometrical optimizations at the HF/6-31G(d) theoretical level were carried out for the Cu^I complexes of 2,2′-isopropylidenebis[(4*S*)-4-*tert*-butyl-4,5-dihydro-1,3-oxazole] and *N*,*N*-bis[(4*S*)-4-*tert*-butyl-4,5-dihydro-1,3-oxazol-2-yl]methylamine, both in the presence and absence of a Cu coordinated ethylene molecule, as well as for different conformations of the free ligands. On the basis of these geometries, single-point energy calculations through the B3LYP hybrid functional were carried out using the same basis set and a DFT method.[20] Solvation effects through single-point energy calculations were also taken into account, both at the Hartree–Fock and DFT levels, using the IPCM continuum model.[14] These calculations were named IPCM/HF/6-31G(d) and IPCM/B3LYP/6-31G(d). All the calculations were carried out with the Gaussian 98 package.[21]

NBO calculations were carried out on the basis of the HF/6-31G(d) wavefunctions using the NBO 5.0 program[22] as implemented in the NWChem package.[23]

Molecular electrostatic potential plots were generated with the Titan 1.0.5 program[24] by single-point calculations at the HF/LACVP* level using the geometries previously optimized at the HF/6-31G(d) level. The LACVP* basis set uses the standard split-valence double-ζ 6-31G(d) basis set for the light elements, and a Hay–Wadt pseudopotential for Cu.[25]

Synthesis of *N,N*-bis[(4*S*)-4-phenyl-4,5-dihydro-1,3-oxazol-2-yl]methylamine (2c)

(*S*)-2-Amino-4-phenyl-4,5-dihydro-1,3-oxazole (5): Sodium cyanide (5.72 g, 33 mmol) was added in small portions to a solution of bromine (5.27 g, 33 mmol) in methanol (40 mL) at 0 °C. A solution of (*S*)-phenylglycinol (4.11 g, 30 mmol) in methanol (7 mL) was then added and the mixture was stirred for 1 h. After treatment with ammonia (15 mL, 25 % w/w), most of the solvent was evaporated under reduced pressure. The residue was dissolved in NaOH (20 %) and was then extracted with ethyl acetate (4×40 mL). The combined organic phases were dried with $MgSO_4$, the solvent was evaporated under reduced pressure, and the remaining phenylglycinol was removed by kugelrohr distillation (60 °C, 0.01 Torr). Yield: 90 %; ^{1}H NMR ($CDCl_3$): δ = 7.29 (m, 5H), 5.12 (br s, 2H), 5.07 (dd, J = 7.4 and 9.1 Hz, 1H), 4.59 (dd, J = 7.8 and 9.1 Hz, 1H), 4.02 ppm (dd, J = 7.4 and 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ = 162.0, 143.6, 128.5, 127.2, 126.3, 75.1, 67.4 ppm.

(*S*)-4-Phenyl-4,5-dihydro-1,3-oxazol-2-one (6): Sodium (1.53 g, 66.8 mmol) was slowly added to anhydrous ethanol (147 mL), and after it was completely dissolved, a solution of (*S*)-phenylglycinol (10.89 g, 66.74 mmol) in anhydrous ethanol (100 mL) was added followed by diethyl carbonate (8.65 g, 73.3 mmol). The mixture was heated under reflux for 15 h, then it was cooled and concentrated under vacuum. The residue was dissolved in CH_2Cl_2 (196 mL) and the solution was washed with saturated NH_4Cl (98 mL). The aqueous phase was then further extracted with CH_2Cl_2 (2×98 mL), the combined organic phases were dried with Na_2SO_4, and the solvent was evaporated under reduced pressure. The product was purified by crystallization from diethyl ether. Yield: 9.26 g (85 %); ^{1}H NMR ($CDCl_3$): δ = 7.34 (m, 5H), 6.53 (br s, 1H), 4.95 (dd, J = 7.0 and 8.6 Hz, 1H), 4.71 (t, J = 8.6 Hz, 1H), 4.15 ppm (dd, J = 7.0 and 8.6 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ = 160.0, 139.5, 129.1, 128.6, 125.9, 72.4, 56.3 ppm.

(*S*)-2-Ethoxy-4-phenyl-4,5-dihydro-1,3-oxazole (7): A solution of ethyloxonium trifluoroborate (6.05 g, 31.9 mmol) in anhydrous CH_2Cl_2 (50 mL) was added dropwise to a solution of (*S*)-4-phenyl-4,5-dihydro-1,3-oxazol-2-one (4 g, 24.5 mmol) in anhydrous CH_2Cl_2 (50 mL) at 0 °C under an atmosphere of argon. The reaction was stirred at room temperature overnight and then it was slowly poured over a cold, saturated Na_2CO_3 solution (100 mL). The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3×25 mL). The combined organic phases were dried with $MgSO_4$, and the solvent was evaporated under reduced pressure to give the product as a yellow oil. Yield: 97 %; ^{1}H NMR ($CDCl_3$): δ = 7.31 (m, 5H), 5.13 (dd, J = 7.6 and 9.5 Hz, 1H), 4.72 (dd, J = 8.2 and 9.5 Hz, 1H), 4.37 (c, J = 7.1 Hz, 2H), 4.17 (dd, J = 7.6 and 8.2 Hz, 1H), 1.39 ppm (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ = 163.8, 142.8, 128.7, 127.6, 126.4, 75.6, 67.1, 66.9, 14.4 ppm.

***N,N*-Bis[(4*S*)-4-phenyl-4,5-dihydro-1,3-oxazol-2-yl]amine (8)**: A small amount of *p*-toluensulfonic acid was added to a solution of (*S*)-2-amino-4-phenyl-4,5-dihydro-1,3-oxazole (0.972 g, 6.0 mmol) and (*S*)-2-ethoxy-4-phenyl-4,5-dihydro-1,3-oxazole (0.955 g, 5.0 mmol) in anhydrous toluene under an atmosphere of argon, and the mixture was heated at 50 °C for 24 h. The solvent was evaporated under reduced pressure and the crude product was purified by chromatography on silica to yield **8** as an oil. Crystals of **8** were obtained by recrystallization from acetone. Yield: 537 mg (35 %); R_f = 0.17 (ethyl acetete/hexanes 9:1); m.p. 198–201 °C; $[\alpha]_D^{20}$ = +475.8 (c = 1.0 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.25 (m, 10H), 5.13 (dd, J = 7.3 and 9.3 Hz, 2H), 4.72 (dd, J = 8.6 and 9.3 Hz, 2H), 4.18 ppm (dd, J = 7.3 and 8.6 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ = 166.4, 141.3, 128.9, 128.2, 126.4, 73.6, 63.1 ppm; MS (CI, NH_3): m/z: 308.3 $[M+H]^+$; elemental analysis calcd (%) for $C_{18}H_{17}O_2N_3$: C 70.34, H 5.58, N 13.67; found: C 70.36, H 5.49, N 13.63.

***N,N*-Bis[(4*S*)-4-phenyl-4,5-dihydro-1,3-oxazol-2-yl]methylamine (2c)**: *n*BuLi (344 μL, 1.5 N in hexane, 0.52 mmol) was added to a solution of *N,N*-bis[(4*S*)-4-phenyl-4,5-dihydro-1,3-oxazol-2-yl]amine (154 mg, 0.5 mmol) in anhydrous THF (5 mL) at −78 °C under an atmosphere of argon. After 20 min, methyl iodide (156 μL, 2.5 mmol) was added to the resultant red solution, and the reaction mixture was stirred at room temperature for 10 h. The solvent was then evaporated under reduced pressure, the residue was dissolved in CH_2Cl_2 (5 mL), and the organic phase was washed with saturated $NaHCO_3$ solution (5 mL). The aqueous phase was further extracted with CH_2Cl_2 (3×5 mL), the combined organic phase was dried with $MgSO_4$, and the solvent was evaporated under reduced pressure to give *N,N*-bis[(4*S*)-4-phenyl-4,5-dihydro-1,3-oxazol-2-yl]methylamine in quantitative yield. M.p. 60–62 °C; $[\alpha]_D^{20}$ = −61.4 (c = 1.0 in CH_2Cl_2); ^{1}H NMR ($CDCl_3$): δ = 7.39–7.25 (m, 10H), 5.20 (dd, J = 7.5 and 9.3 Hz, 2H), 4.79 (dd, J = 8.4 and 9.3 Hz, 2H), 4.25 (dd, J = 7.5 and 8.4 Hz, 2H), 3.52 ppm (s, 3H); ^{13}C NMR ($CDCl_3$): δ = 158.9, 142.5, 128.6, 127.5, 126.5, 76.3, 67.4, 37.3 ppm; MS (70 eV, EI): m/z (%): 320.8 (100) $[M]^+$; HRMS calcd for $C_{19}H_{19}O_2N_3$: 321.1475; found: 321.1477.

Laponite-immobilized catalysts: Laponite (375 mg) was dried under vacuum for 24 h prior to use. The chiral ligand (0.11 mmol) and the copper precursor ($Cu(OTf)_2$ or CuCl, 0.11 mmol) were dissolved in a minimum amount of anhydrous CH_2Cl_2 under an atmosphere of argon, the resultant solution was stirred for 15 min and was then filtered through a PTFE microfilter. The solvent was evaporated under vacuum, the complex was redissolved in methanol (4 mL), laponite was added, and the suspension was stirred for 24 h at room temperature. The solid was filtered off, washed with methanol (10 mL) and CH_2Cl_2 (20 mL), and was then dried under vacuum for 24 h.

Nafion–silica immobilized catalysts: The sodium form of the support was prepared by passing a 2 M NaCl solution through a column of the acidic form until the pH was neutral. The sodium form was then washed with deionized water and dried under vacuum at 140 °C for 4 h prior to use. The complex (0.19 mmol) was prepared in CH_2Cl_2 as previously described. Nafion–silica (475 mg) was added to a solution of the complex in methanol, and the suspension was stirred for 24 h at room temperature. The resultant solid was filtered, washed, and dried as previously described.

Characterization of the catalysts: Copper analyses were carried out by plasma-emission spectroscopy on a Perkin-Elmer Plasma 40 emission spectrometer. Elemental analyses were carried out on a Perkin-Elmer 2400 elemental analyzer. Step-scanned X-ray diffraction patterns of oriented samples were collected at room temperature from 3° in 2θ up to 60° using a D-max Rigaku system that contains a rotating anode. The diffractometer was operated at 40 kV and 80 mA, and the $Cu_{K\alpha}$ radiation was selected using a graphite monochromator. Transmission FTIR spectra of self-supported wafers evacuated ($< 10^{-4}$ Torr) at 50 °C were taken with a Mattson Genesis Series FTIR.

Cyclopropanation reactions: The solid catalyst (150 mg) was added to a solution of styrene (520 mg, 5 mmol) and *n*-decane (100 mg, internal standard) in anhydrous CH_2Cl_2 (5 mL). A solution of ethyl diazoacetate (290 mg, 2.5 mmol) in anhydrous CH_2Cl_2 (0.5 mL) was then slowly added (2 h) to the reaction mixture with a syringe pump, and the reaction was monitored by GC.[7] After complete conversion of diazoacetate, a second portion was slowly added in the same manner. After the reaction was complete (typically 24 h), the catalyst was filtered off and washed with CH_2Cl_2 (5 mL), and a third portion of diazoacetate was then added to this solution to confirm the loss of catalytic activity. The solid was subsequently washed with CH_2Cl_2, dried under vacuum, and reused under the same conditions.

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