Homogeneous and Supported Copper Complexes of Cyclic and Open-Chain Polynitrogenated Ligands as Catalysts of Cyclopropanation Reactions

F. Adrián,[a] M. I. Burguete,[a] J. M. Fraile,[b] J. I. García,[b] J. García,[b] E. García-España,[c] S. V. Luis,*[a] J. A. Mayoral,*[b] A. J. Royo,[a,b] and M. C. Sánchez[b]

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Cu^I and Cu^{II} complexes of cyclic and open-chain polyaza compounds have been tested as catalysts in the benchmark cyclopropanation reaction of styrene with ethyl diazoacetate. In general, only small amounts of copper are needed to promote the reaction. The catalytic activity depends on the structure of the ligand, e.g. amine–amides are more efficient than polyamines, and on the oxidation state of copper, Cu^{II} being more active than Cu^I. Given that Cu^I is the active species, these changes of behavior must be related to the stabilities of the complexes. The nature of the counterion also has a noticeable influence on the catalytic activity, the role of which is discussed. XAS measurements suggest the formation of oligomeric species. Some of the chiral ligands lead to small enantiomeric excesses. Open-chain ligands can easily be supported on organic polymers and their complexes can be used as catalysts. Furthermore, cyclic and acyclic complexes can be supported on clays by cation exchange and the solids obtained tend to promote the reaction with a decrease in the *trans*/*cis* ratio.

Introduction

The search for new ligands suitable for incorporation into homogeneous and heterogeneous catalysts for organic reactions is a field of considerable interest. As far as possible, such ligands should be easy to prepare and they should be amenable to facile chemical modification so as to obtain chiral derivatives from simple, accessible starting materials. On the other hand, their incorporation into a heterogeneous support has to be easily accomplished with minimum structural modification. In this regard, polynitrogenated compounds fulfil such requirements. These ligands can selectively bind metal cations and can distinguish between oxidation states.[1] They can be obtained as open-chain or macrocyclic compounds, and also in chiral forms by the incorporation of chiral diamines, amines, or amino acid derivatives. Furthermore, the chiral auxiliaries can be incorporated at different sites in the molecules leading to ligands with different symmetries. In particular, they can easily be obtained with C_2 symmetry.[2] They can also be supported on organic or inorganic materials, which opens up the possibility of using their complexes as solid catalysts in the fine chemicals industry.[3] The chiral compounds would, of course, open the way to chiral heterogeneous catalysts.[4] Given the presence of nitrogen atoms related by the symmetry elements of the molecule, they can be grafted onto a flexible support without losing their symmetry.[5] It is important to note that in a significant number of examples of heterogeneous chiral catalysts, the symmetry of the chiral ligand is lost when it is grafted onto the support, which may be one of the reasons for the lower efficiency of these catalysts in inducing asymmetry.[4]

Porphyrin complexes have been described as catalysts in several reactions,[6] including cyclopropanations.[7] Complexes of other cyclic polynitrogenated systems have also been used.[8] Since open-chain polynitrogenated compounds have not been used in this context, we felt that it would be interesting to compare several of these ligands (cyclic and open-chain, non-chiral and chiral, amines and amides, unsupported and supported) in a benchmark reaction. In this paper, we present the results obtained using copper complexes of these polyaza derivatives (Figure 1) as catalysts of the cyclopropanation reaction between styrene and ethyl diazoacetate. The effect of the oxidation state of the copper and the nature of the counterion are also analyzed.

Results and Discussion

Polyamines as Ligands

We first tested a cyclic ligand, 14,15,17,18-tetramethyl-2,5,8,11-tetraaza[12]paracyclophane (**L$_1$**, Figure 1) since ligands of this type have been show to stabilize Cu^I with respect to its disproportionation into Cu^{II} and Cu^0.[10] We prepared its Cu^I complex in situ and used it as a catalyst in the cyclopropanation reaction of styrene (**1**) with ethyl diazoacetate (**2**) (Scheme 1). The results obtained are presented in Table 1.

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[a] Departamento de Química Inorgánica y Orgánica,
E.S.T.C.E, Universitat Jaume I,
P. O. Box 224, E-12080 Castellón, Spain
Fax: (internat.) + 34-964/728214
E-mail: luiss@qio.uji.es
[b] Facultad de Ciencias,
Instituto de Ciencia de Materiales de Aragón,
Universidad de Zaragoza - C.S.I.C.,
E-50009 Zaragoza, Spain
E-mail: mayoral@posta.unizar.es
[c] Departamento de Química Inorgánica,
Universidad de Valencia,
E-46100 Burjassot (Valencia), Spain
E-mail: Enrique.Garcia-Es@uv.es

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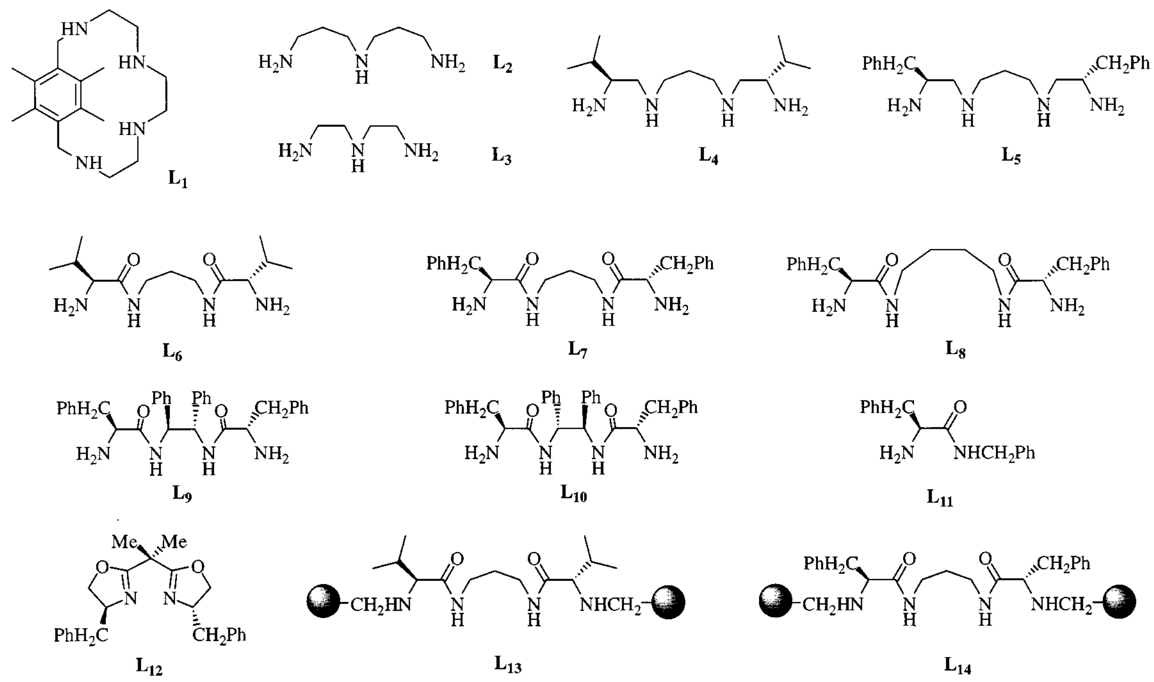
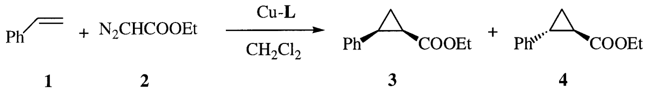


Figure 1. Ligands used in this work



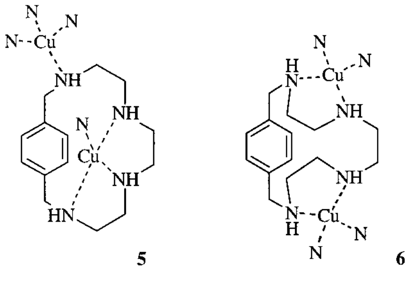
Scheme 1

Table 1. Results obtained from the reaction of styrene (**1**) with ethyl diazoacetate (**2**) promoted by CuOTf−$\mathbf{L_1}$ complexes in CH_2Cl_2 at 25 °C[a]

Entry	Cu/$\mathbf{L_1}$	Cu/styrene (%)	*t* (h)[b]	% yield[c]	**4**:**3**[c]
1	–	0.1	1.5	26	2.6
2			2.0	30	2.6
3	1:1.1	0.1	2.2	–	–
4			2.5	4	–
5			6.0	30	2.3
6	1:0.75	0.1	1.2	–	–
7			1.3	4	–
8			4.0	28	2.2
9	1:0.5	0.1	1.0	–	–
10			1.1	4	–
11			3.5	31	2.3
12	1:0.25	0.1	0.75	11	2.3
13			3.0	32	2.4
14	1:1.1	1	1.45	38	2.3

[a] Reactions carried out under argon atmosphere using a twofold excess of **1**. − [b] **2** was slowly added over a period of 45 min.; the time is given from the beginning of the addition. − [c] Determined by gas chromatography.

Copper(I) compounds are known to be very active catalysts in the cyclopropanation of alkenes with diazo compounds.[9] However, addition of the ligand in an almost equimolecular ratio results in the appearance of a period of induction. After this period, the color of the solution changes to yellow and the reaction ultimately yields a final result comparable to that obtained with CuOTf. This period of induction is reduced when the ligand/copper molar ratio is decreased. The addition of an excess of the ligand is of little consequence. Such an induction period is only observed when the complex is used in a ratio of 0.001:1 with respect to the styrene and is no longer seen when it is used in a ratio of 0.01:1 (see entry 14, Table 1). This result indicates the formation of a stable complex of the ligand with Cu^I,[10] which reduces the rate of formation of the reactive copper−carbene intermediate. The most rational explanation for this behavior is the formation of aggregates of the Cu^I-L_1 complexes, in which the copper cation is much less accessible for the interaction with the reagents to give the active metal−carbene species. The formation of aggregates has recently been reported to hamper the hydrolytic catalytic activity of some copper−polyamine complexes.[14] A key feature of tetraaza[*n*]paracyclophanes is that a maximum of three of the four nitrogen atoms can be simultaneously coordinated to a metal cation. This leaves a non-coordinated benzylic nitrogen atom, which can interact with another metal cation (see structure **5**, Figure 2), thereby favoring the formation of complex aggregates. This is particularly the case when the solvent is changed from water to a less polar medium such as CH_2Cl_2. The formation of species such as **5** has been observed in the solid state and has also been inferred from the results of NMR spectroscopic studies.[11][12] As a matter of fact, it has been shown that, in water, tetraaza[12]paracyclophanes such as $\mathbf{L_1}$ can form dinuclear copper(II) complexes (see **6**, Figure 2) which, at least in the solid state, are polymerically associated.[13] The involvement of complexes of the general structure **6** accounts for the fact that even at low $\mathbf{L_1}$/Cu ratios (≈0.5) (entry 9, Table 1) the induction period persists. Only below this ratio is some free copper available and hence the induction period drastically decreases (entry 12, Table 1).



5 6

Figure 2. Binuclear structural patterns found for tetraaza[*n*]paracyclophanes

In order to improve the yields, we added a fresh aliquot of ethyl diazoacetate (**2**) (0.5 mol for each mol of remaining styrene) (Table 2). Surprisingly, the period of induction was no longer observed after the second addition. This kinetic behavior is characteristic of product-accelerated reactions, in which a side product, formed via a non-catalytic pathway, is the species involved. In this context, we have to consider that decomposition of ethyl diazoacetate gives rise to the formation of coordinating species, namely ethyl fumarate and maleate. These by-products are produced in large excess with respect to $\mathbf{L_1}$ and, once formed, should favor disruption of aggregates through coordination to the metal cation. Displacement of these kinetically labile ligands from the coordination sphere of the metal by the carbene-forming species thus becomes easier and so the induction period is much decreased or is not seen at all. To check this hypothesis, we stirred a solution of CuOTf and $\mathbf{L_1}$ for 3 h in CH_2Cl_2 with 50 equiv. of ethyl acetate (the same ratio of ethyl diazoacetate used in the reactions) prior to addition of the ethyl diazoacetate. Following this treatment, the period of induction was not seen (entry 5, Table 2).

Table 2. Effect of a second addition of ethyl diazoacetate (**2**) and the addition of ethyl acetate

Entry	Cu/L$_1$	Cu/styrene (%)	*t* (h)	% yield	**4**:**3**
1	1:1.1	0.1	24.0[a]	30	2.3
2			24.5	35	2.3
3			26.0	54	2.3
4			31.0	57	2.3
5	1:1.1	0.1[b]	0.75	4	–
6			2.0	20	2.3
7			16.0	28	2.4

[a] After this time, an additional amount of **2** was added over a period of 45 min. – [b] The Cu–L$_1$ complex was stirred with ethyl acetate prior to use.

In order to study the influence of ligand topology on the catalyst activity, we tested several open-chain tri- and tetraamines ($\mathbf{L_2}$–$\mathbf{L_5}$). The results obtained (Table 3) show that the effect of these ligands is to increase the period of induction compared to that observed using $\mathbf{L_1}$ under the same conditions. Furthermore, this period is longer with triamines, and in particular with L$_3$ (entries 5–6, Table 3). Again, the formation of aggregates has to be considered. Clearly, this phenomenon has to be more important for those ligands ($\mathbf{L_2}$ and $\mathbf{L_3}$) providing a smaller number of nitrogen donor atoms. The presence of bulky C-substituents ($\mathbf{L_4}$ and $\mathbf{L_5}$) should also be reflected in a decreased tendency for aggregation.

Although the design of efficient chiral auxiliaries was not the main aim of this work, the enantiomeric excesses achieved in the reactions using the chiral ligands $\mathbf{L_4}$ and $\mathbf{L_5}$ were examined. In neither case was any asymmetric induction observed.

Table 3. Results obtained in the reactions promoted by CuOTf–linear polyamine ($\mathbf{L_2}$–$\mathbf{L_5}$) = 1:1.1 complexes, using 0.1% catalyst with respect to styrene in CH_2Cl_2 at 25 °C

Entry	Ligand	*t* (h)	% yield	**4**:**3**	% *ee* (**3**)[a]	% *ee* (**4**)[a]
1	$\mathbf{L_2}$	24	–	–	–	–
2		27	23	2.1	–	–
3		96	26	2.2	–	–
4	$\mathbf{L_3}$	96[b]	–	–	–	–
5		98	–	–	–	–
6		117	29	2.2	–	–
7	$\mathbf{L_4}$	4	–	–	–	–
8		8	27	2.5	0	0
9		23	33	2.5	0	0
10	$\mathbf{L_5}$	5	–	–	–	–
11		8	11	2.3	0	0
12		23	36	2.3	0	0

[a] Determined by gas chromatography using a chiral stationary phase. – [b] After this time, the reaction mixture was heated under reflux.

Amides as Ligands

A further structural change was considered by using the diamides $\mathbf{L_6}$–$\mathbf{L_{10}}$. The results obtained with $\mathbf{L_6}$ and $\mathbf{L_7}$, when compared to those with $\mathbf{L_4}$ and $\mathbf{L_5}$ (entries 2 and 6, Table 4 *vs.* entries 8 and 11, Table 3), show that the presence of carbonyl groups leads to a decrease in the induction period and, in the case of the (*S*)-phenylalanine derivative ($\mathbf{L_7}$), to a decrease in the *trans*/*cis* ratio and a measurable enantioselectivity. These data suggest that, for $\mathbf{L_6}$ and $\mathbf{L_7}$, the changes in geometry and donor characteristics associated with the presence of the amide functionalities lead to an increased rate of copper–carbene intermediate formation.

Table 4. Results obtained in the reactions promoted by CuOTf–linear amide–amine ($\mathbf{L_6}$–$\mathbf{L_{10}}$) = 1:1.1 complexes, using 0.1% catalyst with respect to styrene in CH_2Cl_2 at 25 °C

Entry	Ligand	*t* (h)	% yield	**4**:**3**	% *ee* (**3**)[a]	% *ee* (**4**)[a]
1	$\mathbf{L_6}$	3.0	–	–	–	–
2		4.0	16	2.1	0	0
3		6.5	31	2.2	0	0
4		24.0	29	2.1	0	0
5	$\mathbf{L_7}$	2.5	–	–	–	–
6		3.5	11	1.8	12	8
7		6.5	29	1.8	12	8
8		24.0	33	1.8	12	8
9	$\mathbf{L_8}$	1.0	–	–	–	–
10		2.0	25	1.8	11	7
11		3.0	29	1.8	11	7
12	$\mathbf{L_9}$	0.75	13	1.8	0	0
13		1.25	30	1.8	0	0
14	$\mathbf{L_{10}}$	24.0	–	–	–	–
15		48.0	24	2.2	0	0

[a] In cases with asymmetric induction, (1*R*)-cycloadducts are preferably obtained.

In comparison to $\mathbf{L_6}$ and $\mathbf{L_7}$, the period of induction is clearly reduced with $\mathbf{L_8}$, which has a longer bridge, but the *trans/cis* ratio and enantioselectivity remain unchanged. Two diastereomeric ligands ($\mathbf{L_9}$ and $\mathbf{L_{10}}$) were also tested and showed very different behaviors. Whereas the reaction is very fast with $\mathbf{L_9}$, use of $\mathbf{L_{10}}$ leads to an extremely long period of induction. Clearly, the *cis,trans,cis*-arrangement of the substituents in complexed $\mathbf{L_9}$ disfavors aggregation, while the opposite is true for the all-*trans* diastereomer formed from $\mathbf{L_{10}}$, for which the access for the formation of the carbene−copper species should again be restricted. The introduction of chirality in the central bridge is always detrimental for the enantioselectivity.

The Effect of the Oxidation State of Copper: The Use of $Cu^{I}L$ vs. $Cu^{II}L$ Complexes

It is known that Cu^{I} is the active species in these reactions and that Cu^{II} is reduced to Cu^{I} in the presence of diazoacetate.[9] Thus, Cu^{II} complexes can also be used as catalysts. In view of this, we tested the cyclic ligand ($\mathbf{L_1}$), two open-chain polyamines ($\mathbf{L_3}$ and $\mathbf{L_5}$), and an amide-containing ligand ($\mathbf{L_7}$) in the same reaction using $Cu(OTf)_2$. The results obtained (entry 1, Table 5) show that the induction period with $\mathbf{L_1}$ decreases and that it is very short even on halving the amount of catalyst (entries 3−4, Table 5). The induction period is no longer seen with $\mathbf{L_5}$ and $\mathbf{L_7}$, but persists with $\mathbf{L_3}$. Therefore, other than in the case of $\mathbf{L_3}$, the metal center in the Cu^{II} complexes is much more accessible to the additional exogenous ligands. Once Cu^{II} is reduced to Cu^{I}, i.e. in the presence of diazoacetate, the strongly active yellow complex is immediately formed.

Table 5. Results obtained in the reactions promoted by $Cu(OTf)_2-L$ = 1:1.1 complexes in CH_2Cl_2 at 25 °C

Entry	Ligand	Cu/**1** (%)	*t* (h)	% yield	**4**:**3**	% *ee* (**3**)[a]	% *ee* (**4**)[a]
1	$\mathbf{L_1}$	0.1	1.0	21	2.0	–	–
2			1.75	33	2.1	–	–
3	$\mathbf{L_1}$	0.05	1.3	6	2.4	–	–
4			2.5	15	2.3	–	–
5			24.0	25	2.1	–	–
6	$\mathbf{L_3}$	0.1	26.0	–	–	–	–
7			29.5	23	2.1	–	–
8	$\mathbf{L_5}$	0.1	1.0	16	2.1	–	–
9			2.5	26	2.1	–	–
10	$\mathbf{L_7}$	0.1	0.75	18	1.8	10	6
11			2.5	29	1.8	10	6
12	$\mathbf{L_{11}}$	0.1	0.75	19	1.7	10	6
13			1.5	33	1.7	10	6

[a] In cases with asymmetric induction, (1*R*)-cycloadducts are preferably obtained.

In the reactions promoted by $\mathbf{L_7}-Cu^{I}$ and Cu^{II} complexes, the *trans/cis* ratios and enantioselectivities are the same, and so it would seem reasonable to assume that the reactive intermediate is the same $\mathbf{L_7}-Cu^{I}$ carbene complex.

It can be concluded that the only difference between Cu^{I} and Cu^{II} is the decrease in the induction period, whereas the selectivities and the relative catalytic activities of the different complexes are the same.

Structural XAS/EXAFS Studies

In order to gain further insight into the structural characteristics of these complexes, we studied the structures of the species derived from three representative ligands, $\mathbf{L_1}$, $\mathbf{L_5}$ and $\mathbf{L_7}$, and $CuCl_2$ by X-ray absorption spectroscopy (XAS). The use of $CuCl_2$ instead of $Cu(OTf)_2$ leads to complexes with lower catalytic activity (Table 6) and this has been attributed to the presence of the chloride counterion.[15] However, we decided to use $CuCl_2$ in order to be able to distinguish between the anion (Cl) and the coordinating groups in the ligand (N, O).

Table 6. Results obtained in the reactions promoted by $CuCl_2-L$ = 1:1.1 complexes in CH_2Cl_2 using 0.1% catalyst with respect to styrene

Entry	Ligand	*t* (h)	% yield	**4**:**3**	% *ee* (**3**)[a]	% *ee* (**4**)[a]
1	$\mathbf{L_1}$	24[a]	–	–	–	–
2		24[b]	24	2.5	–	–
3	$\mathbf{L_3}$	24[a]	–	–	–	–
4		7[b]	29	2.4	–	–
5	$\mathbf{L_5}$	24[a]	–	–	–	–
6		7[b]	28	2.4	0	0
7	$\mathbf{L_7}$	24[a]	–	–	–	–
8		7[b]	31	2.2	0	0

[a] Reaction at room temperature. − [b] Reaction under reflux conditions after the initial period at room temperature.

The experimental EXAFS signal was extracted from the raw spectra according to standard methods.[16] The threshold energy E_0, defining the zero wavevector, was taken at the inflection point of the absorption edge. Figure 3 shows the Fourier transform (FT) of the Cu-*K* edge $k\,\chi(k)$ spectra of the three complexes. The FT was calculated using a Gaussian window in the range 2.2−12.5 Å^{-1}. EXAFS spectra of the three samples are very similar and show little resolution of structure, indicating structural disorder. The moduli of the FTs of the $\mathbf{L_1}$ and $\mathbf{L_5}$ complexes show two main peaks, while that of the $\mathbf{L_7}$ complex shows an additional peak in the region of 3−4 Å.

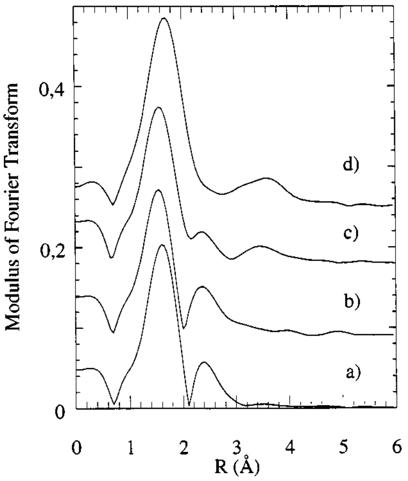


Figure 3. Fourier transforms of the EXAFS spectra: (a) $\mathbf{L_1}-CuCl_2$ complex; (b) $\mathbf{L_5}-CuCl_2$ complex; (c) $\mathbf{L_7}-CuCl_2$ complex; (d) $\mathbf{L_{12}}-CuCl_2$ complex

Table 7. Results obtained from analyses of the EXAFS spectra of $\mathbf{L_1}$, $\mathbf{L_5}$, $\mathbf{L_7}$ and $\mathbf{L_{12}}$−$CuCl_2$ complexes

		Cu−N (O)			Cu−C			Cu−Cl	
Ligand	*n*°	*R* (Å)	$\Delta\sigma^2$ 10^3Å^2	*n*°	*R* (Å)	$\Delta\sigma^2$ 10^3Å^2	*n*°	*R* (Å)	$\Delta\sigma^2$ 10^3Å^2
$\mathbf{L_1}$	5.4±0.3	2.03±0.01	4.97±0.003	3.4±0.7	2.93±0.03	5.21±0.005	–	–	–
$\mathbf{L_5}$	5.2±0.3	2.01±0.01	6.75±0.003	4.2±0.8	2.93±0.03	5.17±0.006	–	–	–
$\mathbf{L_7}$[a]	6.2±0.4	2.02±0.02	8.0±0.003	3.3±0.4	2.87±0.03	11.7±0.005	2.1±0.5	3.85±0.04	12.9±0.006
$\mathbf{L_7}$[b]	3.1±0.4	2.09±0.02	7.0±0.003	3.3±0.4	2.87±0.03	11.7±0.005	2.1±0.5	3.85±0.04	12.9±0.006
	2.6±0.4	1.98±0.02	6.3±0.003						
$\mathbf{L_{12}}$	2.0±0.6	1.97±0.02	3.2±0.004				2.0±0.4	2.21±0.01	2.7±0.003

[a] Considering Cu−N contributions only. − [b] Considering Cu−N and Cu−O contributions.

The first-shell contribution was extracted by Fourier filtering of the FT spectra in the range 0.8−2.2 Å, and the corresponding structural parameters were obtained by least-squares fitting of the filtered *k*-weighted spectrum to the EXAFS formula:[16]

$$(k) = \Sigma\ (\rho/k)\ (N_i/R_i^2)\ A_i(k)\ \sin[2kR_i+\phi_i(k)]$$

The amplitudes $A_i(k)$ and phase shifts $\phi_i(k)$ used in the best fit were generated from the FEFF3.11 code.[16e] The best-fit parameters obtained for the different complexes are reported in Table 7. The data for the $\mathbf{L_1}$ and $\mathbf{L_5}$ complexes were found to be very similar and showed the copper to be surrounded by five nitrogen or/and oxygen atoms at an average distance of 2.02 Å. For the second shell, the best fit was obtained solely with carbon atoms at 2.93 Å. We did not observe Cu−Cl contributions in these complexes. On the other hand, the high DW values obtained for both the first and second shells, together with the large error margins associated with the fit of structural parameters of the second shell indicate a high degree of structural disorder in these compounds. The absence of a Cu−Cl contribution in these complexes may be accounted for in terms of the significant structural disorder, the presence of different Cu−Cl and Cu−C distances in the second shell, or a very long Cu−Cl distance with a large vibrational DW factor. The presence of a large number of donor atoms in close proximity to the metal supports the formation of aggregate species with more than one ligand being involved in the complexation of the copper.

The best-fit results for the $\mathbf{L_7}$ complex reveal a slightly different structure. Cu−O and Cu−N cannot be clearly distinguished by EXAFS, hence we considered both possibilities in the theoretical fit of the experimental spectra. If we consider only Cu−N contributions, we obtain 6 nitrogen atoms at a distance of 2.02 Å. A similar fit is obtained considering Cu−N and Cu−O contributions at two different distances. An important difference between $\mathbf{L_7}$ and $\mathbf{L_1}$ and $\mathbf{L_5}$ is the observation of two distant chlorine atoms in the complex of the former. The presence of these chlorine atoms suggests less structural disorder and a higher accessibility of the copper in this complex. These structural changes, which may be due to the planarity imposed by the amide system, the presence of oxygen atoms, or both these factors, must also be responsible for the changes in the *trans*/*cis* ratio and the enantioselectivity.

After background subtraction from the raw spectra, the XANES spectra were normalized taking unity to indicate atomic absorption. The XANES spectra of the complexes of $\mathbf{L_1}$ and $\mathbf{L_5}$ with $CuCl_2$ were found to be almost superimposable, which was not the case with the $\mathbf{L_7}$−$CuCl_2$ complex. This fact is in good agreement with the differences observed by EXAFS.

The formation of copper−$\mathbf{L_7}$ oligomeric species might suggest that each amine−amide moiety of the ligand participates in the complexation of different copper atoms. This suggestion led us to examine the behavior of the simplest ligand L_{11}. Unfortunately, the corresponding XAS spectrum could not be obtained. However, the close similarity of their catalytic behavior (Table 5) lends support to this hypothesis.

The results obtained from the EXAFS measurements show the absence of chlorine atoms in close proximity to the copper ions, which would seem to be at variance with the influence of this counterion on the catalytic activity. Thus, we investigated whether the same structural behavior is observed with other ligands, such as bis(oxazolines), where the same influence of the counterion has been described.[15] To this end, we studied the EXAFS spectrum of the L_{12}−$CuCl_2$ complex. The EXAFS and the FT of the Cu-*K* edge $k\ \chi(k)$ spectrum is shown in Figure 3 and the best-fit parameters are given in Table 7. As can be seen, the spectra show clear differences and chlorine is observed at a distance of 2.21 Å from the copper, justifying its strong influence on the catalytic activity.

Comparison of this result with those obtained for the polynitrogenated compounds shows that the use of the latest ligands leads to oligomeric complexes with considerable disorder in the environment of the copper, and with chlorine at greater distances. In spite of these differences, the counterion has the same influence on the catalytic activity. It may be speculated that, in accordance with the period of induction, the oligomeric species are fragmented to yield the reactive copper−carbene intermediate, and that the reactivity of this intermediate depends on the nature of the counterion. Unfortunately, it has not been feasible to design an EXAFS experiment to check this hypothesis.

Supported Complexes as Catalysts

As a final avenue of investigation, we tested the behavior of some of these ligands supported in various ways. The formation of aggregates should be disfavored when using such immobilized ligands. This, along with the changes in the micro-environments of the ions, could lead to significant changes in reactivity. Open-chain systems can be grafted onto polystyrene−divinylbenzene through the primary amine functionalities and ligands $\mathbf{L}_{13}$ and $\mathbf{L}_{14}$ were obtained in this way.[5] In accordance with our expectations, the reactions took place without an induction period. The results obtained (Table 8) show that the stereochemical course of the reaction is influenced by the presence of the support. A decrease in the *ee*, relative to that achieved with the same ligand in solution, was observed. Similar changes in the stereochemical course of reactions upon immobilization of a chiral auxiliary have repeatedly been observed.[3]

Table 8. Results obtained in the reactions promoted by Cu^{II} using polymeric ligands ($\mathbf{L}_{13}$−$\mathbf{L}_{14}$) in CH_2Cl_2 at 25 °C

Entry	Ligand	Cu/**1** (%)	*t* (h)	% yield	**4**:**3**	% *ee* (**3**)	% *ee* (**4**)
1	$\mathbf{L}_{13}$[a]	0.1	1.5	12	2.0	–	–
2			2.0	19	2.0	–	–
3			24.0	28	1.8	0	0
4	$\mathbf{L}_{14}$[a]	0.1	1.0	17	1.6	–	–
5			23.0	31	1.6	4	3

[a] $\mathbf{L}_{12}$ contains 0.30 mmol ligand g^{-1} and $\mathbf{L}_{13}$ 0.46 mmol ligand g^{-1}.

Given that the complexes used as catalysts are cationic, they can also be supported using of a different strategy, i.e. they can be electrostatically entrapped using anionic solids. To test this approach, we used a synthetic laponite with a high swelling ability. Cation exchange was carried out in methanol using the $CuCl_2$ complexes of a cyclic ($\mathbf{L}_1$) and an open-chain ($\mathbf{L}_3$) ligand. Table 9 shows the results of analyses of the clays. In both cases, 0.1 mmol Cu g^{-1} are introduced, the Li:Cu stoichiometry is 1:1, and the presence of the complex produces a decrease in the surface area. With $\mathbf{L}_1$, the basal spacing increases, indicating that the complex is accommodated into the interlamellar space, at least in part. With $\mathbf{L}_3$, no change in basal spacing is observed, which may either be due to the smaller size of the complex or to a disposition of this complex on the external surface of the clay. In view of the result obtained with $\mathbf{L}_1$, the first explanation seems more plausible.

Table 9. Analysis of the laponites exchanged with the complexes of $CuCl_2$ with $\mathbf{L}_1$ and $\mathbf{L}_3$

Entry	Ligand	Cu (mmol g^{-1})	N/Cu	d_{001} (•)	*S* (m^2 g^{-1})
1	–	–	–	16	289
2	$\mathbf{L}_1$	0.1	3.9	19	245
3	$\mathbf{L}_3$	0.1	3.8	16	239

Table 10 shows the results obtained with these clay-supported catalysts. As can be seen in Table 6, the use of chloride in place of triflate significantly reduces the catalytic activity in solution and it is necessary to carry out the reaction under reflux. This can only be related to the effect of the more coordinating chloride counterion. In the case of $\mathbf{L}_3$, the catalytic activity of the supported catalyst is similar to that seen for the homogeneous complex, while for $\mathbf{L}_1$ it is even superior. However, a simple comparison cannot be made because in the supported catalyst the counterion is changed from chloride to the clay surface, and the nature of the counterion has a decisive influence on the catalytic activity. The *trans*/*cis* ratio decreases, hence the proportion of the less stable product increases. This has previously been observed with clay catalysts and has been explained in terms of the isolation of the catalytic sites and the dimensionality of the clay, which should also be related to the higher catalytic activity.[17]

Table 10. Results obtained in the reactions promoted by $CuCl_2$−$\mathbf{L}_1$ and $\mathbf{L}_3$ (1:1.1) complexes exchanged in laponite, in CH_2Cl_2 using a Cu/**1** ratio of 0.001

Entry	Ligand	*t* (h)	% yield	**4**:**3**
1	$\mathbf{L}_1$	24[a]	–	–
2		7[b]	20	1.1
3		24[b]	30	1.1
4	$\mathbf{L}_3$	24[a]	–	–
5		7[b]	27	1.1
6		24[b]	29	1.1

[a] Reaction at room temperature. − [b] Reaction under reflux conditions after initial period at room temperature.

Conclusions

The results presented here open the way for the design of novel polynitrogenated ligands for use in copper-catalyzed processes and for understanding the different factors affecting the activity of such species. The copper(I) and copper(II) complexes of some cyclic and non-cyclic polyamines, as well as of some diamides, have been assayed in the benchmark cyclopropanation reaction of styrene with ethyl diazoacetate. First and foremost, all the complexes examined showed an appreciable catalytic activity, even at very low catalyst concentrations. All data suggest that formation of the carbene−copper complex is the rate-limiting step. For polyamines, aggregation hinders the formation of the active carbene−copper complexes and as a result induction periods are observed in non-coordinating solvents (CH_2Cl_2). The addition or the *in situ* generation of kinetically labile coordinating species such as EtOAc or ethyl fumarate (formed by decomposition of the diazoacetate) disrupts aggregation and allows the facile formation of the active complexes. Aggregation is more significant with polyamines having a smaller number of nitrogen donor atoms and with less bulky ligands, and is much reduced with amides.

The induction periods are more important for Cu^{I} than for Cu^{II} complexes, according to the different coordination geometries. This seems to be associated with the formation of more accessible Cu^{II} sites that readily interact with the carbene-forming species and are reduced to Cu^{I} complexes, which are the active catalytic species. No other differences (e.g. in terms of selectivity) are associated with the use of Cu^{I} or Cu^{II} and, accordingly, the use of the more stable Cu^{II} compounds is clearly favored.

Polyamine or amide ligands of this type can easily be supported by anchoring on functionalized polymers or by cation exchange in clays. The resulting supported Cu^{II} complexes show higher activities than their homogeneous analogues. This can be rationalized in terms of the pseudodilution effects operative in the solid materials, which will disfavor the aggregation processes.

Finally, small enantioselectivities have been observed on using some of the chiral ligands. However, more work is needed in this regard if novel chiral ligands able to improve the observed enantioselectivities are to be developed

Experimental Section

Preparation of the Ligands: **L$_2$** and **L$_3$** are commercial compounds. **L$_1$**,[12] **L$_4$−L$_7$**[18] and **L$_{13}$−L$_{14}$**[5] were prepared as described previously. **L$_8$**, **L$_9$** and **L$_{10}$** were obtained by reaction of the *N*-hydroxysuccinimide esters of the *N*-Cbz protected amino acids with the corresponding diamines, followed by deprotection of the *N*-Cbz groups.

General Procedure for the Preparation of *N*-Hydroxysuccinimide Esters of Amino Acids: The appropriate *N*-Cbz-protected amino acid (3.34 mmol) and *N*-hydroxysuccinimide (3.34 mmol) were suspended in anhydrous DME at 0°C. Once a clear solution had been obtained, DCC (3.67 mmol) was added and the resulting solution was stirred at 0−5°C for 20 h. The dicyclohexylurea formed was filtered off and the filtrate was concentrated to dryness. The crude product was recrystallized from propan-2-ol to furnish the pure product. *N*-Hydroxysuccinimide ester of *N*-Cbz-L-phenylalanine: yield 87%; m.p. 137−140°C. − ^{1}H NMR: δ = 2.80 (br. s, 4 H), 3.13−3.41 (m, 1 H), 5.09 (s, 4 H), 7.29−7.4 (m, 10 H). − ^{13}C NMR: δ = 25.4, 37.8, 52.9, 67.2, 127.3, 128.0, 128.2, 128.5, 128.7, 129.5, 134.3, 167.5, 168.7. − $[\alpha]_D^{25}$ = −11.1 (*c* = 2, dioxane). − $C_{21}H_{20}N_2O_6$: calcd. C 63.6, H 5.1, N 7.1; found C 63.5, H 5.5, N 7.4.

General Procedure for the Preparation of *N*,*N*′-Bis(*N*-Cbz-aminoacyl)diamines: The *N*-hydroxysuccinimide ester of the appropriate amino acid (7.44 mmol) was dissolved in anhydrous DME cooled in an ice bath, and the diamine (3.72 mmol) was added dropwise. The reaction mixture was stirred at room temp. for 18 h. The white solid formed was filtered off and washed with water and cold methanol.

Deprotection of *N*-Cbz Groups: The *N*,*N*′-bis(*N*-Cbz-aminoacyl)-1,3-diaminopropanes were added to HBr/AcOH (33%) and the respective mixtures were stirred at room temp. until CO_2 evolution ceased. At this point, diethyl ether was added to the clear solution, which led to the deposition of a white precipitate. This was filtered off and dried to afford the pure product.

L$_8$: M.p. 140−143°C. − $[\alpha]_D^{20}$ = −89.42 (*c* = 1, CHCl$_3$). − ^{1}H NMR: δ = 1.5 (m, 4 H), 2.7 (dd, J_1 = 9.2, J_2 = 14 Hz, 2 H), 3.25 (m, 6 H), 3.6 (dd, J_1 = 3.8, J_2 = 9.2 Hz, 2 H), 7.3 (m, 10 H). − ^{13}C NMR: δ = 27.0, 38.7, 41.1, 56.5, 126.8, 128.7, 129.4, 138.0, 174.3. − $C_{22}H_{30}N_4O_2$: calcd. C 69.1, H 7.9, N 14.6; found C 69.3, H 8.3, N 15.0.

L$_9$: M.p. 137−141°C. − $[\alpha]_D^{20}$ = −17.16 (*c* = 1, CHCl$_3$). − ^{1}H NMR: δ = 1.31 (d, *J* = 6.5 Hz, 4 H), 2.6 (dd, J_1 = 9.5, J_2 = 13.5 Hz, 2 H), 3.32 (dd, J_1 = 3.8, J_2 = 13.5 Hz, 2 H), 3.55 (m, 2 H), 5.28 (m, 2 H), 7.2 (m, 20 H), 8.2 (m, 2 H). − ^{13}C NMR: δ = 40.7, 56.5, 59.0, 126.8, 127.6, 127.7, 128.5, 128.7, 129.3, 137.8, 138.6, 174.7. − $C_{32}H_{34}N_4O_2$•1/2 H_2O: calcd. C 74.5, H 6.8, N 10.9; found C 74.4, H 6.9, N 10.5.

L$_{10}$: M.p. 213−217°C. − $[\alpha]_D^{20}$ = −80.02 (*c* = 1, CHCl$_3$). − ^{1}H NMR: δ = 1.3 (m, 4 H), 2.6 (dd, J_1 = 10, J_2 = 14 Hz, 2 H), 3.18 (dd, J_1 = 4.5, J_2 = 14 Hz, 2 H), 3.58 (m, 2 H), 5.3 (m, 2 H), 7.2 (m, 20 H), 8.26 (m, 2 H). − ^{13}C NMR: δ = 41.5, 56.8, 56.9, 58.7, 126.9, 127.6, 127.7, 128.5, 128.7, 128.8, 129.3, 138.0, 138.4, 174.7. − $C_{32}H_{34}N_4O_2$•H_2O: calcd. C 73.3, H 6.9, N 10.7; found C 73.4, H 7.0, N 10.8.

L$_{11}$: M.p. 67−71°C. − $[\alpha]_D^{20}$ = −69.1 (*c* = 1, CHCl$_3$). − ^{1}H NMR: δ = 1.56 (br. s, 2 H), 2.78 (dd, J_1 = 9.8, J_2 = 13.8 Hz, 1 H), 3.27 (dd, J_1 = 4.5, J_2 = 13.8 Hz, 1 H), 3.62 (dd, J_1 = 4.6, J_2 = 9.4 Hz, 1 H), 4.43 (d, *J* = 6.5 Hz, 2 H), 7.25 (m, 10 H), 8.19 (t, *J* = 6.3 Hz, 2 H). − ^{13}C NMR: δ = 41.1, 43.2, 56.5, 126.8, 127.4, 127.7, 128.3, 129.4, 138.0, 173.4. − $C_{16}H_{18}N_2O$: calcd. C 75.6, H 7.1, N 11.0; found C 75.5, H 7.1, N 11.3.

Preparation of the Cationic Complexes Supported on Clays: A solution of the complex was first prepared by stirring CuCl2•2H2O (1 mmol) and the appropriate ligand (**L$_1$** or **L$_3$**, 1 mmol) in methanol (50 mL) for 45 min. To this green solution, laponite (10 g) was added and the mixture was shaken for 22 h. After this time, the blue clay was separated by filtration and washed with methanol. The residue obtained by evaporation of the solvent from the colorless solution was found to contain NaCl.

The copper content was analyzed by plasma emission spectroscopy using a Perkin−Elmer Plasma 40 emission spectrometer. Carbon and nitrogen analyses were carried out using a Perkin−Elmer 2400 elemental analyzer. Step-scanned X-ray diffraction patterns of oriented samples were collected at room temperature from 3° in 2& thetas; up to 60° using a D-max Rigaku system with a rotating anode. The diffractometer was operated at 40 kV and 80 mA and Cu-K_α radiation was selected using a graphite monochromator. Surface areas were calculated from BET nitrogen isotherms determined at 77 K.

Cyclopropanation Reactions with Homogeneous Catalysts: Under argon, a mixture of the requisite amount of the ligand (Tables 1−5) and CuOTf•1/2C_6H_6 or Cu(OTf)$_2$ (0.1 mmol) in dry CH_2Cl_2 (60 mL) was stirred at room temperature for 30 min. Then, a solution of styrene (100 mmol) and *n*-decane (2 g) in dry CH_2Cl_2 (50 mL) was added and the resulting solution was stirred for 10 min. After this time, ethyl diazoacetate (50 mmol) was slowly added by means of a syringe pump over a period of 45 min. The reactions were monitored by gas chromatography using *n*-decane as an internal standard; FID from Hewlett-Packard 5890 II; cross-linked methyl silicone column 25 m × 0.2 mm × 0.33 µm; helium as carrier gas, 20 psi; injector temperature 230°C; detector temperature 250°C; over temperature program: 70°C (3 min)−15°C/min−200°C (5 min); retention times: ethyl diazoacetate (**2**) 4.28 min, styrene (**1**) 5.03 min, *n*-decane 6.93 min, diethyl fumarate 8.73 min, diethyl maleate 9.04 min, *cis*-cyclopropanes (**3**) 11.84 min, *trans*-cyclopropanes (**4**) 12.35 min.

Asymmetric induction in the reactions using chiral ligands was also assessed by gas chromatography; cyclodex-B column 30 m × 0.25 mm × 0.25 µm; oven temperature program: 125°C isothermal; retention times: (1*S*,2*R*)-cyclopropane 28.9 min, (1*R*,2*S*)-cyclopropane 29.8 min, (1*R*,2*R*)-cyclopropane 34.3 min, (1*S*,2*S*)-cyclopropane 34.9 min. The peaks were assigned to the corresponding enantiomers by comparison with previous results.

In general, the onset of the reactions is signified by a color change from green to yellow. In one case (entry 4, Table 3), the reaction did not take place at room temperature and had to be carried out under reflux. In another case (entry 2, Table 2), after the consumption of the ethyl diazoacetate an additional amount of this reagent was added in the same manner. In another reaction (entry 5, Table 2), the **L$_1$**−CuOTf complex was stirred with ethyl acetate (5 mmol) for 3 h prior to addition of the reagents.

Cyclopropanation Reactions with Polymeric Catalysts: The appropriate amount of polymer (0.37 g of **L$_{12}$** or 0.24 g of **L$_{13}$**) was stirred under argon in a solution of $Cu(OTf)_2$ (1 mmol) in CH_2Cl_2 for 24 h. After this time, the solution was decanted off and the remaining solid was washed with CH_2Cl_2. To a suspension of the catalyst in dry CH_2Cl_2 (60 mL), the internal standard and the reagents were added and the reaction was monitored as described above.

Cyclopropanation Reactions with Clay-Supported Catalysts: To a suspension of the clay (1 g) in dry CH_2Cl_2 (60 mL), the reagents and the internal standard were added and the reaction was monitored as described above.

EXAFS and XANES Experiments: X-ray absorption experiments at the Cu-*K* edge were carried out at the synchroton radiation source, Daresbury, U.K. A double-crystal Si(111) monochromator was used. The storage ring operated at 2 GeV with an average beam current of 150 mA. The experiments were performed at room temperature in the transmission mode, and the signal was collected by means of ion chambers. For the XAS measurements, solid samples of the $\mathbf{L_1}$, $\mathbf{L_5}$, $\mathbf{L_7}$ and $\mathbf{L_{12}}-CuCl_2$ complexes were pressed into thin pellets. The thickness of the samples was optimized in order to obtain the best signal-to-noise ratio.

Samples were prepared using the ligand and $CuCl_2$ in an equimolar ratio; the amounts of the two components were adjusted in order to obtain 100 mg of complex. To a solution of the ligand in CH_2Cl_2 (5 mL), the requisite amount of CuCl2•2H2O was added. The resulting suspension was stirred at room temperature for 5 h, which led to the gradual disappearance of the solid $CuCl_2$. After this time, the solution was filtered through a plug of cotton wool and the solvent was evaporated from the filtrate under reduced pressure. The solid complexes were dried in vacuo for 24 h at 50°C. All complexes showed the expected IR bands and gave appropriate elemental analyses.

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