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Journal of Catalysis 221 (2004) 532–540
JOURNAL OF CATALYSIS
www.elsevier.com/locate/jcat

Bis(oxazoline)–copper complexes supported by electrostatic interactions: scope and limitations

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Received 2 July 2003; revised 8 September 2003; accepted 10 September 2003

Abstract

Bis(oxazoline)–copper complexes have been supported by cation exchange in laponite and nafion-like solids. The results obtained with these catalysts in cyclopropanation reactions depend on the nature of both the chiral ligand and the support. On using the complex of 2,2′-isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline] with Cu(II), direct exchange in methanol leads to low enantioselectivities in nafion-type solids. Some improvement in enantioselectivity can be obtained by using the less coordinating nitroethane as the exchange solvent or by exchanging the support prior to use with a more soluble tetraalkylammonium cation. Another strategy consists of the exchange of copper(II) and subsequent treatment with the chiral bis(oxazoline) ligand. This system leads to slower reactions and similar enantioselectivities to those obtained by direct exchange. The best enantioselectivity obtained in the reaction between styrene and ethyl diazoacetate is around 70% ee. The recovery of the catalysts leads to a partial loss of enantioselectivity. The stability of the bis(oxazoline)–copper complex is the crucial factor for this behavior. The selectivity can be improved with the bulkier (1*R*, 2*S*, 5*R*)-menthyl diazoacetate, up to 83% ee, although the reactivity in this case is much lower.

Keywords: Immobilized chiral catalysts; Enantioselective cyclopropanation

1. Introduction

Enantioselective synthesis promoted by chiral catalysts is a topic of significant importance in chemical research [1]. Within this field, the development of heterogeneous catalysts that are able to promote enantioselective organic reactions is an area of growing interest due to the inherent advantages of heterogeneous as opposed to homogeneous catalysts [2].

One of the main strategies for preparing chiral heterogeneous catalysts is the immobilization of chiral metal complexes [3]. The formation of a covalent bond between the solid support and the chiral ligand is the most frequently used method for immobilization. However, this approach requires chemical modification of the chiral ligand, a change that has unpredictable consequences on the enantioselectivity even if the modification is carried out in a position far away from the catalytic center [4]. In complexes that are cationic in nature it is possible to immobilize them by ion pairing with an anionic solid, a simple strategy that does not require any further modification of the chiral ligand. Thus, chiral cationic Rh–diphosphine complexes have been immobilized on clays [5], anionic resins [6], or Al-MCM-41 [7], and the resulting solids have been used as catalysts in hydrogenation reactions. Mn–salen oxidation catalysts have also been immobilized on inorganic supports [8]. Problems arising during the immobilization process by cationic exchange have not been reported in any of the examples described.

Bis(oxazoline)–copper complexes have been immobilized by covalent bond formation between the chiral bis(oxazoline) and a support [9]. Organic polymers, both soluble [10] and insoluble [11,12], as well as silicas, both amorphous [12,13] and mesoporous crystalline [14], have been used as supports. However, these methods require considerable synthetic effort—a situation that contrasts with the simplicity of the cationic exchange method. In previous papers we have described the electrostatic immobilization of

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0021-9517/$ – see front matter
doi:10.1016/j.jcat.2003.09.017

bis(oxazoline)–copper complexes on different anionic supports and their use as catalysts in cyclopropanation [15–17] and Diels–Alder [18] reactions. A similar strategy was followed to immobilize bis(oxazoline)–copper complexes on USY [19], and these catalysts were used to promote the aziridination of alkenes.

In contrast with Rh–diphosphine and Mn–salen complexes, the immobilization of bis(oxazoline)–copper complexes by electrostatic interactions presents a number of problems related to the nature of both the chiral ligand and the support. Whereas the complex of 2,2′-isopropylidenebis[(4*S*)-4-phenyl-2-oxazoline] (**1b**) with copper(II) can be efficiently immobilized irrespective of the solid support, this is not the case with 2,2′-isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline] (**1a**) (Scheme 1). Analysis of the solids and/or the mother liquor of the exchange process indicates a partial exchange of free copper [17], a process that is responsible for the low enantioselectivities. This point was confirmed by the addition of excess of chiral bis(oxazoline) to the reaction medium [20] in order to shift the equilibrium to the complexed form. In this case, it was possible to reproduce the high enantioselectivity obtained in the homogeneous phase [21,22].

In this paper we present a study into the different strategies to improve the incorporation of the cationic 2,2′-isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline]–copper(II) complex onto different supports and attempt to identify the origin of the problems encountered in the cationic exchange process.

2. Experimental

2,2′-Isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline] (**1a**) was purchased from Aldrich. Laponite was obtained from Laporte Adsorbents. SAC-13 was prepared and exchanged following previously described methods [16,23]. SiO_2–CF_2SO_3H was prepared from $(HO)_3Si(CH_2)_3(CF_2)_2O(CF_2)_2SO_3K$ as described in the literature [24].

2.1. Preparation and characterization of the catalysts

2.1.1. Preparation of SiO_2–CF_2SO_3Na and SiO_2–$CF_2SO_3NBu_4$

Prior to exchange with the chiral catalyst, SiO_2–CF_2SO_3H was transformed into its sodium form by passing 2 M aqueous NaCl through a column of the solid until neutral pH was obtained. The solid was then washed with deionized water and dried under vacuum at 150 °C overnight. A portion of this sodium form was transformed into the tetrabutylammonium form by treatment of the SiO_2–CF_2SO_3Na (2 g) with a solution of tetrabutylammonium iodide (369 mg, 1 mmol) in methanol (10 mL). The suspension was stirred at room temperature for 24 h, the solid was filtered off, thoroughly washed with methanol, and dried in air. The exchange process was repeated once under the same conditions and finally the solid was dried under vacuum at 50 °C overnight.

2.1.2. Preparation of SiO_2–CF_2SO_3Cu catalysts by direct exchange in methanol

To a solution of the bis(oxazoline) (0.55 mmol) in methanol (5.5 mL) was added $Cu(OTf)_2$ (0.55 mmol). The dried (140 °C, vacuum overnight) SiO_2–CF_2SO_3Na or SiO_2–$CF_2SO_3NBu_4$ (1 g) was slowly added to the above blue solution and the suspension was stirred at room temperature for 24 h. The solid was filtered off, thoroughly washed with methanol and dichloromethane, and dried in air before use.

2.1.3. Preparation of nafion-like catalysts by direct exchange in nitroethane

The method was the same as for the exchange in methanol. The complex was prepared directly in nitroethane and the sodium form of the nafion-type support was added to the solution. The amounts of the different components per gram of support were 0.2 mmol complex in 4 ml of solvent for SAC-13 and 0.55 mmol complex in 5.5 mL of solvent for SiO_2–CF_2SO_3Na.

2.1.4. Preparation of catalysts by the two-step method

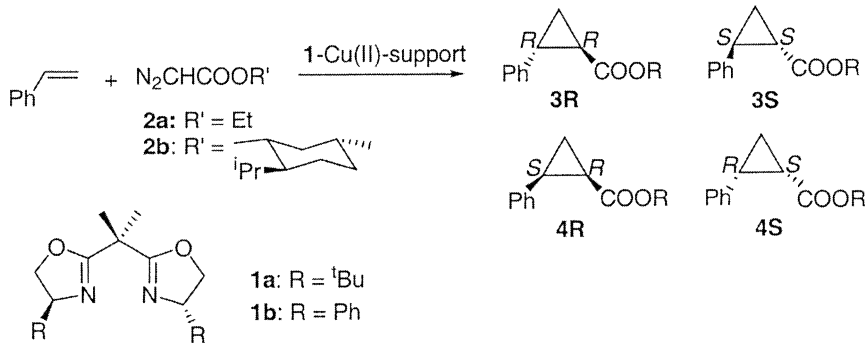
To a solution of $Cu(OTf)_2$ (0.1 mmol) in methanol (3 mL) was added the sodium form of the support (1 g of laponite or SAC-13). The suspension was stirred at room temperature for 24 h. The solid was filtered off, thoroughly washed with methanol, and dried under vacuum. The resulting solid was added to a solution of 2,2′-isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline] (**1a**) (0.15 mmol) in nitroethane (5 mL) and the suspension was stirred at room temperature for 24 h. The solid was filtered off, thoroughly washed with nitroethane and then with dichloromethane, and dried under vacuum. The treatment with the bis(oxazoline) was repeated once more.

2.1.5. Characterization of the catalysts

Copper analyses were carried out by plasma emission spectroscopy on a Perkin-Elmer Plasma 40 emission spectrometer. Nitrogen and sulfur analyses were carried out on a Perkin-Elmer 2400 elemental analyzer. Transmission FTIR spectra of self-supported wafers evacuated ($< 10^{-4}$ Torr) at 50 °C were recorded with a Mattson Genesis Series FTIR spectrophotometer.

2.2. Cyclopropanation reactions

To a suspension of the corresponding supported catalyst (300 mg of nafion-like catalyst or 150 mg of laponite catalyst) in a solution of styrene (5 mmol) and *n*-decane (100 mg) in dichloromethane (5 mL) was added ethyl diazoacetate (**2a**) (2.5 mmol) in the same solvent (0.5 mL), under an argon atmosphere, for 2 h using a syringe pump.



Scheme 1.

The reaction was monitored by gas chromatography, and after consumption of the diazoacetate, a second portion of this reagent was added in the same way. After the reaction the catalyst was filtered off, washed with the same solvent, and dried. The absence of copper in solution was verified by the lack of activity after addition of a supplementary portion of diazoacetate. The recovered catalysts were reused following the same method.

The results of the reactions were determined by gas chromatography: FID from Hewlett-Packard 5890II; cross-linked methyl silicone column, 25 m × 0.2 mm × 0.33 μm; helium as carrier gas, 20 p.s.i.; injector temperature, 230 °C; detector temperature, 250 °C; oven temperature program, 70 °C (3 min), 15 °C min^{-1} to 200 °C (5 min); retention times, ethyl diazoacetate (**2a**) 4.28 min, styrene 5.03 min, *n*-decane (internal standard) 6.93 min, diethyl fumarate 8.73 min, diethyl maleate 9.04 min, *cis*-cyclopropanes (**4**) 11.84 min, *trans*-cyclopropanes (**3**) 12.35 min.

The asymmetric inductions of the reactions were also determined by gas chromatography: FID from Hewlett-Packard 5890II, Cyclodex B column, 30 m × 0.25 mm × 0.25 μm; helium as carrier gas, 20 p.s.i.; injector temperature, 230 °C; detector temperature, 250 °C; oven temperature program, 125 °C isotherm; retention times, (1*S*, 2*R*)-cyclopropane (**4*S***) 28.9 min, (1*R*, 2*S*)-cyclopropane (**4*R***) 29.8 min, (1*R*, 2*R*)-cyclopropane (**3*R***) 34.3 min, (1*S*, 2*S*)-cyclopropane (**3*S***) 34.9 min.

In the reaction with (1*R*, 2*S*, 5*R*)-menthyl diazoacetate (**2b**) the same conditions were used. In some cases (see Table 2) a 5-fold excess of styrene was used under the same conditions. The reaction was monitored by gas chromatography with a cross-linked methyl silicone column, 25 m × 0.2 mm × 0.33 μm); helium as carrier gas, 20 p.s.i.; injector temperature, 230 °C; detector temperature, 250 °C; oven temperature program, 100 °C (0 min), 4 °C min^{-1} to 200 °C (30 min); retention times, styrene 2.18 min, *n*-decane (internal standard) 2.83 min, (1*R*, 2*S*, 5*R*)-menthyl diazoacetate (**2b**) 13.23 min, (1*S*, 2*R*)-cyclopropane (**4*S***) 30.33 min, (1*R*, 2*S*)-cyclopropane (**4*R***) 30.59 min, (1*R*, 2*R*)-cyclopropane (**3*R***) 32.30 min, (1*S*, 2*S*)-cyclopropane (**3*S***) 32.97 min.

3. Results and discussion

3.1. Direct exchange of chiral complexes

In previous work [15–17] it was shown that SAC-13 was the best support for the electrostatic immobilization of the complex formed between 2,2′-isopropylidenebis[(4*S*)-4-phenyl-2-oxazoline] (**1b**) and copper(II), as demonstrated by the cyclopropanation reaction between styrene and ethyl diazoacetate (**2a**) (Scheme 1). SAC-13 [23] is a nafion-silica nanocomposite, produced using an in situ sol-gel technique in which soluble silica precursors are mixed with a nanometer-sized colloidal dispersion of nafion in a polar solvent. The nafion is dispersed at the nanometer level within the silica, with a nafion content of about 13% w/w. In this way the surface area of nafion can be increased up to 180 $m^2 g^{-1}$. The efficient behavior of SAC-13, both in terms of selectivity and recoverability, was ascribed to the similar nature of the exchanged sites to the triflate anion, which is one of the best anions for catalysts for cyclopropanation reactions [21,22]. The exchange process of the chiral complex was carried out in methanol [16]. This solvent was chosen because of the high solubility of the complex and sodium triflate, which is obtained as a by-product of the exchange process.

However, this good behavior was not observed with 2,2′-isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline] (**1a**). Low enantioselectivities were obtained even with the freshly prepared catalyst (Table 1, entry 2), despite being the best ligand for the homogeneous cyclopropanation reaction [21] (Table 1, entry 1). Nitrogen analysis demonstrated the incorporation of free copper on the solid [17]. The higher activity of noncomplexed copper, that leads to the instantaneous conversion of ethyl diazoacetate during the slow addition (Table 1, entries 14–16), accounts for these results, but an explanation for the presence of noncomplexed copper is not straightforward. Given that the complex **1b**–Cu(II) does not show similar behavior, the role of the chiral bis(oxazoline) ligand is clear and the difference is probably due to a lower binding constant in the case of **1a**–Cu(II). This lower stability makes decomplexation during the exchange process easier.

Table 1
Results obtained from the reaction of styrene with ethyl diazoacetate promoted by catalysts prepared by direct exchange of 2,2′-isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline]–copper(II) complex[a]

Entry	Support	Exchange solvent	Cu content (mmol g^{-1})	Cu[b] (%)	Run	*t* (h)	Yield[c] (%)	**3**/**4**[c]	**3**[d] (% ee)	**4**[d] (% ee)
1	–[e]	–	–	10	1	24	72	71/29	94	91
2	SAC-13 (Na)	MeOH	0.07	0.42	1	24	23	60/40	23	19
3					2	24	31	61/39	14	14
4	SiO_2–CF_2SO_3Na	MeOH	0.27	1.6	1	24	37	60/40	18	16
5					2	24	31	61/39	9	11
6	SAC-13 (Na)	$EtNO_2$	0.10	0.60	1	24	41	65/35	53	47
7					2	24	27	65/35	8	9
8	SiO_2–CF_2SO_3Na	$EtNO_2$	0.55	3.3	1	24	27	64/36	28 → 4[f]	20 → 5[f]
9	SiO_2–$CF_2SO_3NBu_4$	$EtNO_2$	0.39	2.3	1	24	28	60/40	53	47
10					2	96	35	60/40	41 → 33[f]	41 → 34[f]
11		$EtNO_2$[g]	0.48	2.9	1	24	49	64/36	69	67
12	Laponite	$EtNO_2$	0.11	0.33	1	24	30	64/36	69	64
13					2	24	26	58/42	43	37
14	Laponite (no box)[h]	H_2O	0.72	2.2	1	2	20	58/42	–	–
15	SAC-13 (no box)[i]	MeOH	0.01	0.06	1	2	35	70/30	–	–
16	– (no box)[j]	–	–	1.5	1	2	46	70/30	–	–

[a] Reactions carried out in dichloromethane at room temperature with styrene/diazoacetate = 1.
[b] Cu/diazoacetate ratio in the cyclopropanation reaction.
[c] Determined by GC.
[d] Determined by GC using a Cyclodex-B column. Major enantiomers: **3*R*** and **4*R***.
[e] Homogeneous reaction with bis(oxazoline)–$Cu(OTf)_2$.
[f] The enantioselectivity drops along the reaction. Initial and final values are indicated.
[g] Solvent stirred with K_2CO_3 in order to eliminate acid traces.
[h] Catalyst prepared by exchange with $CuCl_2$ without bis(oxazoline).
[i] Catalyst prepared by exchange with $Cu(OTf)_2$ without bis(oxazoline).
[j] Homogeneous reaction with $Cu(OTf)_2$ without bis(oxazoline).

However, the better results obtained with laponite [16] also highlight the role of the anionic support. In this case, some kind of steric interaction between the support and the chiral ligand can be proposed. In the case of laponite, the negative charge would presumably be delocalized along the clay sheets, leading to a weaker ion pair. In contrast, the negative charge will be more concentrated in the case of SAC-13, giving rise to a strong electrostatic interaction. Although the nafion chains are entrapped within the silica matrix, some of them may be close to the silica surface and thus may increase the surface–bis(oxazoline) steric interaction. Another drawback of SAC-13 is the very low cation exchange capacity (CEC), typically 0.15 meq g^{-1}, which limits the functionalization of the chiral-immobilized catalyst.

In an attempt to overcome these limitations, another kind of support was tested. SiO_2–CF_2SO_3H was prepared by grafting a sulfonic acid group with a partially fluorinated chain [≡Si–$(CH_2)_3$–$(CF_2)_2$–O–$(CF_2)_2SO_3H$] onto a silica support (Figure 1) [24]. In this way the CEC is higher, about 0.50 meq g^{-1}, and the distance between the exchange center and the silica surface is fixed. The **1a**–Cu(II) complex immobilized on this new support was tested in the same cyclopropanation reaction and the results (Table 1, entries 4 and 5) are compared with those previously described.

The copper content of the new SiO_2–CF_2SO_3Cu catalyst is higher than that of SAC-13, as expected given the higher

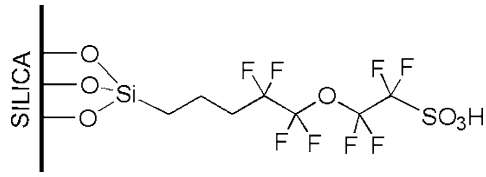
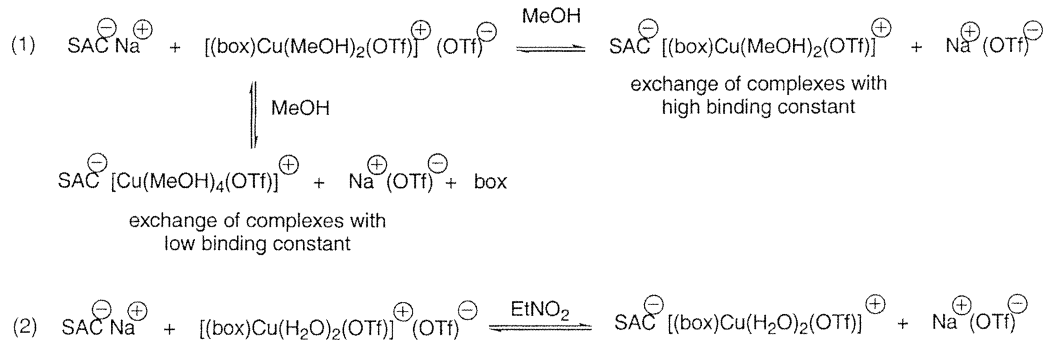


Fig. 1. Structure of the SiO_2–CF_2SO_3H support.

level of functionalization. As far as the cyclopropanation results are concerned, the enantioselectivities were even lower than those obtained with the SAC-13 catalyst and, of course, much worse than in the homogeneous phase.

Several characterization methods were applied to elucidate whether part of the copper had been exchanged free of ligand in the support. In general, analysis of the nafion-containing solids is not accurate enough to determine the nitrogen content; thus, the analysis was carried out with the residue obtained after cation exchange and the loading in the solid was calculated by difference. The nitrogen analysis shows that in the SiO_2–CF_2SO_3Cu catalyst the ligand content is only 0.11 mmol g^{-1}, leaving 0.16 mmol Cu g^{-1} free of bis(oxazoline) ligand. Again the higher activity of the noncomplexed copper present in the solid accounts for the very low enantioselectivity obtained with this catalyst.

Another interesting feature of the analysis is the indication that a proportion of the triflate anions remains in the solid after exchange. In fact, the sulfur analysis is consis-



Scheme 2.

tent with the introduction of one triflate per copper, showing that only one positive charge of each copper ion is compensated by the support. The problem could arise from the need for the reduction of copper(II) to copper(I) to generate the active species of the catalyst. In that situation this species needs only one compensating anion, which could be chosen between the sulfonic acid group of the solid and the triflate. The analysis of the solids after reaction fits well with the initial content, within the experimental error, and the analysis of the solution shows that only 0.09% of the initial amount of copper is leached from the solid. As additional evidence, in all the cases the solution obtained by filtration at the end of the reaction was monitored after addition of a new portion of diazoacetate, with no significant improvement of yield ($< 1\%$). A similar result was obtained after filtration in the early stage of the reaction (only 15% diazoacetate added). When the rest of diazoacetate was added, only 0.8% yield was obtained after 24 h with 0% ee. When the high activity of the homogeneous copper species is taken into account, these results demonstrate that the cyclopropanation reaction takes place in the heterogeneous phase, with no significant contribution of a homogeneous reaction.

Thus, the distance between the exchange center and the silica surface does not seem to be an important factor, unless a chain of 8 atoms was not sufficiently long to reduce the ligand–silica interaction. The reason for the loss of chiral bis(oxazoline) ligand in the exchange process apparently lies in an intrinsic property of the **1a**–Cu(II) complex, probably the binding constant.

3.2. Use of nitroethane in the immobilization process

In order to consider the whole exchange process, it is necessary to have an idea of the complex structure. Evans et al. demonstrated by X-ray diffraction the presence of two molecules of water as a solvate in the structure of bis(oxazoline)–Cu(II) complexes [25]. This water is introduced by manipulation of the complexes in the open air. When the exchange is carried out in methanol, it is almost certain that at least two molecules of methanol are present as solvates of the complexes. In the case of a highly stable complex, such as **1b**–Cu(II), the entire complex takes part in the exchange, leading to the structure on the right in (Eq. (1) in Scheme 2). If the complex is not so stable, as in the case of **1a**–Cu(II), and especially if a steric interaction exists with the surface of the support, then substitution of the bulky chiral bis(oxazoline) ligand by two new methanol molecules would be more favorable. This structure would be more easily exchanged, giving rise to the structure at the bottom of Eq. (1) (Scheme 2). Taking into account this hypothesis, a solvent that is less coordinating than methanol would be more suitable for the exchange process.

Nitroethane was chosen because of its relatively high dielectric constant ($\varepsilon_r = 35$), which is necessary to dissolve the sodium triflate produced in the exchange process (Eq. (2) in Scheme 2). The effect of the exchange solvent has already been described for laponite [15], a synthetic iron-free clay with a lamellar structure, high swelling ability, and a rather high surface area (225 $m^2\,g^{-1}$). In that case, the use of nitroethane was shown to be positive when copper chloride was used instead of triflate. The enantioselectivities obtained with the immobilized complex **1a**–Cu(II) were only moderate and the catalyst was not fully recoverable as it showed partial loss of enantioselectivity.

The results obtained upon using nitroethane in the direct exchange are gathered in Table 1. In the case of SAC-13 (entry 6), the use of nitroethane shows a clear positive effect on the enantioselectivity, which reaches around 50% ee. It is difficult to give an explanation based on the amount of copper exchanged in its free form. In fact, the nitrogen analysis of the residue is not reliable, perhaps due to the presence of a certain amount of remaining nitroethane that cannot be completely removed under vacuum. The effect of nitroethane is less positive with SiO_2–CF_2SO_3Na (entry 8). In this case the full exchange of the support represents a higher concentration of sodium triflate in the final solution (0.1 vs 0.025 M in the case of SAC-13). If the solubility of this species is not high enough, perhaps the equilibrium position is shifted to a situation in which part of the bis(oxazoline) ligand is coordinating the outcoming species. In fact, the higher copper content reached with this method seems to indicate the easier loss of ligand under these exchange conditions. One possible way to overcome this problem is the prior exchange of SiO_2–CF_2SO_3H with a cation that is more soluble in the organic solvent. With this aim in mind, tetrabutylammonium was exchanged in SiO_2–CF_2SO_3H in methanol and the solid

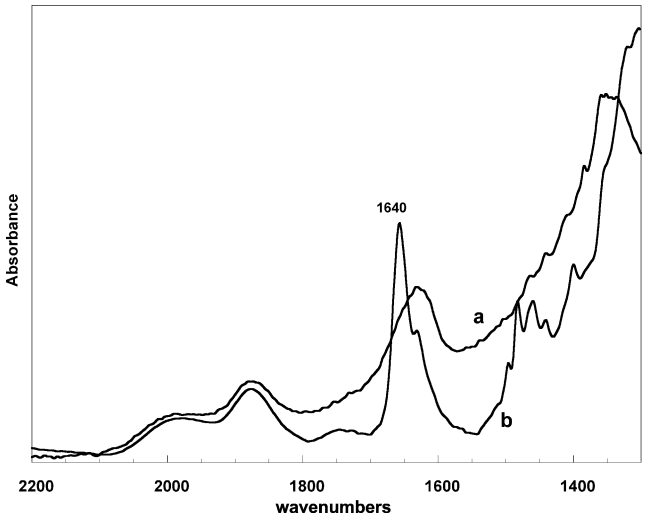


Fig. 2. IR spectra of the SiO_2–CF_2SO_3Na catalysts prepared by direct exchange in methanol with: (a) **1a**–$Cu(OTf)_2$ and (b) **1b**–$Cu(OTf)_2$.

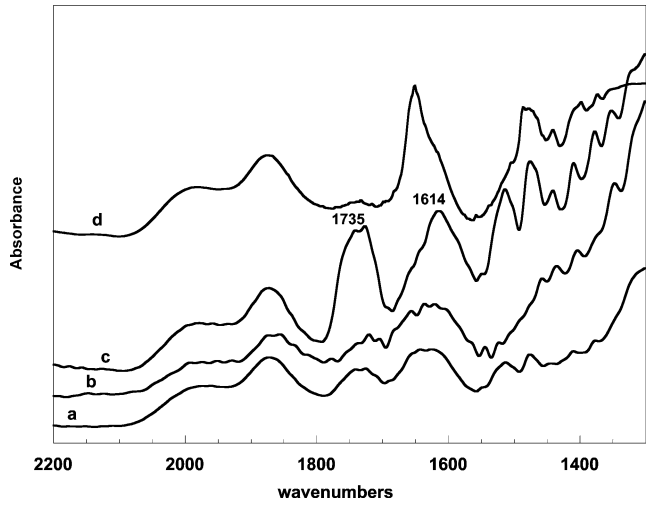


Fig. 3. IR spectra of the catalysts prepared by direct exchange of **1a**–$Cu(OTf)_2$ in nitroethane: (a) SAC-13, (b) SiO_2–CF_2SO_3Na, (c) SiO_2–$CF_2SO_3NBu_4$, and (d) SiO_2–$CF_2SO_3NBu_4$ with nitroethane neutralized with K_2CO_3.

was filtered off, washed, and dried. The solid was then exchanged with complex **1a**–Cu(II) in nitroethane. This new solid showed the same enantioselectivities (entry 9) as the SAC-13 analogs, i.e., around 50% ee. Although the solid could be more efficiently recycled, this fact must be due to the higher amount of copper used in the case of SiO_2–CF_2SO_3Cu given its higher functionalization. It is therefore expected that greater quantities of by-products would be necessary to shift the complexation equilibrium to the deactivated position. In any case, none of the nafion-like solids reaches the moderately good results of laponite.

3.3. IR study of the immobilized catalysts

The different immobilized catalysts prepared by the different methods were studied by IR spectroscopy in order to compare the ligand content. This study was performed because the nitrogen analysis did not give reliable results in the case of catalysts prepared in nitroethane.

The spectra of solids prepared by exchange of SiO_2–CF_2SO_3Na in methanol are shown in Fig. 2. In the spectrum of the exchanged **1b**–Cu(II) complex, the bands of the bis(oxazoline) are clearly present—an intense band corresponding to the C=N double bond at 1640 cm^{-1} and several bands in the range 1500–1450 cm^{-1}. The presence of the bis(oxazoline) ligand is less clear in the case of **1a** because of the lower intensity of the band in the zone of 1640 cm^{-1} and the difficulty in identifying the bands between 1500 and 1450 cm^{-1}. The IR spectra confirm the enantioselectivities and analysis data concerning the presence of bis(oxazoline) ligands in the solid catalysts.

Surprisingly, the spectra of solids prepared in nitroethane by direct exchange (Fig. 3) showed more bands than expected with the exception of laponite-based catalysts. The most striking band appears in the region around 1735 cm^{-1}, a typical zone for carbonyl groups. As none of the molecules introduced in the exchange process contain carbonyl groups, it seems that these groups must be formed during the process. The presence of a significant band at 1614 cm^{-1} indicates that some proportion of the oxazoline rings remain intact on the solids, thus accounting for the moderate enantioselectivity obtained with several of the solids prepared in nitroethane. The zone between 1550 and 1350 cm^{-1} is also more complicated than expected and this is due to the presence of several different species. The IR spectrum of **1a**–Cu(II) exchanged on SiO_2–$CF_2SO_3NBu_4$ (Fig. 3c) shows a higher bis(oxazoline) ligand content than that prepared from SiO_2–CF_2SO_3Na (Fig. 3b). This observation explains the higher enantioselectivity obtained with the former system.

With regard to the species bearing a carbonyl group, it seems possible that the bis(oxazoline) ligands are hydrolyzed, at least partially, by traces of moisture in combination with residual acidity. First of all, nitroethane was tested as source of acid traces by stirring **1a** and **1a**–$Cu(OTf)_2$ complex in nitroethane overnight at room temperature. An intense carbonyl band at 1736 cm^{-1} was apparent in the IR spectrum of the complex, whereas only a weak band at 1712 cm^{-1} was present in the spectrum of the free ligand, demonstrating that the bis(oxazoline) is more prone to hydrolysis when complexed. In order to eliminate those acid traces, nitroethane was stirred with K_2CO_3 overnight and the experiments were repeated with the filtered solvent. No carbonyl bands were present in that case, so this neutralized nitroethane was used in the exchange process. When **1a**–Cu(II) is exchanged on SiO_2–$CF_2SO_3NBu_4$ with the treated nitroethane, the carbonyl band noticeably decreases (Fig. 3d). This solid was tested in the cyclopropanation reaction (Table 1, entry 11) and improved activity and enantioselectivities (up to 69% ee) were obtained, in agreement with the higher stability of the bis(oxazoline) ligand. However, the enantioselectivity was still far from the result in homogeneous phase.

Table 2
Results obtained from the reaction of styrene with diazoacetates promoted by catalysts prepared by the stepwise method[a]

Entry	Diazoacetate	Support	Cu content (mmol g^{-1})	Cu[b] (%)	Run	t (h)	Yield[c] (%)	**3**/**4**[c]	**3**[d] (% ee)	**4**[d] (% ee)
1	**2a**	–[e]	–	10	1	24	72	71/29	94	91
2		SAC-13 (Na)	0.01[f]	0.06	1	96	5[g]	60/40	26→ 17[h]	27→ 19[h]
3		Laponite	0.06[f]	0.18	1	48	23	66/34	69	69
4					2	144	20	61/39	66→ 52[h]	64→ 46[h]
5					1[i]	24	39	64/36	67	65
6					2[i]	24	36	60/40	56	53
7					1[j]	48	24	67/33	74	71
8	**2b**	–[e]	–	10	1	48	20	79/21	77	90
9		Laponite	0.06[f]	0.18	1	144	26	78/22	79	83

[a] Reactions carried out in dichloromethane at room temperature with styrene/diazoacetate = 1.
[b] Cu/diazoacetate ratio in the cyclopropanation reaction.
[c] Determined by GC.
[d] Determined by GC using a Cyclodex-B column. Major enantiomers: **3*R*** and **4*R***.
[e] Homogeneous reaction with bis(oxazoline)–$Cu(OTf)_2$.
[f] Analysis prior to treatment with chiral ligand.
[g] At 50 °C.
[h] The enantioselectivity drops along the reaction. Initial and final values are indicated.
[i] Using 5 eq of styrene.
[j] Reaction in the absence of *n*-decane. Only final result was determined.

The above results show that, although the presence of residual acidity in the solvent is more important, the acidity of the support also plays a role in the degradation of the chiral bis(oxazoline) ligand. Following this hypothesis, laponite would be a less acidic support than nafion-silica in its sodium form. The partial degradation of the bis(oxazoline) was not observed in the solids prepared in methanol, probably because of the higher basicity of this solvent compared to nitroethane, a factor that allows neutralization of the residual acidity of the support.

Two possible acid sites are residual nonexchanged sulfonic acid groups (in acidic form) or silanol groups in the silica portion of the support. Several attempts were made to remove these sources of acidity. SiO_2–CF_2SO_3Na was treated with hexamethyldisilazane in order to eliminate at least some proportion of the surface silanol groups. One other sample with SiO_2–CF_2SO_3Na was prepared by treatment of SiO_2–CF_2SO_3H with NaOH instead of NaCl. This compound was prepared in an attempt to neutralize all of the acidic sites. None of these treatments, however, led to an improvement in the results.

3.4. Stepwise exchange method

In addition to the direct exchange of the complex, another strategy exists for the preparation of this type of immobilized complex—namely the exchange of copper and the subsequent treatment of the solid with the ligand to form the complex. In order to prevent the exchange of free copper in sites that are inaccessible for the bulkier bis(oxazoline)–copper complex, the amount of copper in the exchange solution was kept low with regard to the loading of complex obtained by direct exchange. The first exchange was carried out with $Cu(OTf)_2$ in methanol. As expected, the loading of copper was much lower than in the case of direct exchange. In the case of SAC-13 the treatment with bis(oxazoline) **1a** in nitroethane led to worse results (Table 2) than those obtained by direct exchange in nitroethane. There is no apparent reason for this behavior, but the lack of accurate nitrogen analysis makes of it impossible to offer a hypothesis.

In the case of laponite, the results with the as-prepared catalyst were similar to those obtained by the direct exchange, but in this case the stability seemed to be better. The use of an excess of styrene is a well-known method to increase the yield of cyclopropanes through the improvement in the selectivity of diazoacetate. This strategy would also serve to decrease the amount of by-products with the associated positive influence on the stability of the recycled catalyst. With laponite–Cu–**1a** this change in reaction conditions led to better yields and similar enantioselectivities. However, the recovery of the catalyst was not improved in this case. The use of excess styrene also has the effect of reducing the dielectric constant of the reaction medium, and this has a negative effect on enantioselectivity by bringing the catalytic complex closer to the clay surface and distorting the accessibility of the copper-carbene intermediate [15d]. In fact, the small amount of decane used as an internal standard also has a small detrimental effect, given that the reaction without decane leads to slightly better enantioselectivities (74 and 71% ee for *trans* and *cis* isomers, respectively).

Another possibility for reducing the amount of by-products is the use of a less reactive diazoacetate with a lower tendency to decomposition. For example, the use of $(1R, 2S, 5R)-$menthyl diazoacetate (**2b**), which also has the advantage of a bulkier ester group, leads to higher *trans*/*cis* and enantioselectivities [26]. In fact, in accordance with the expected results, the selectivities are higher, up to 83% ee., but the reaction is very slow and a reaction time

of 144 h is necessary for complete conversion of the diazoacetate. Given this low reactivity the catalyst was not recovered.

4. Conclusion

The possibility of preparing chiral heterogeneous catalysts by cationic exchange mainly depends on the stability of the complex. Highly stable complexes such as **1b**–Cu(II) can be exchanged on all types of supports and lead to efficient catalysts. In the case of catalysts that are not so stable, such as **1a**–Cu(II), an equilibrium between complexed and free metal is established, which can be shifted toward one or other form by altering several parameters, namely the support, the exchange solvent, and the cation leaving the support. Of the supports studied in this and preceding papers, laponite clay seems to be the most suitable for this kind of unstable complex. Nafion-like solids lead to a significant loss of chiral ligand during the exchange process, irrespective of the nature of the support (nanocomposite of grafted fluorinated chains). A less coordinating solvent, such as nitroethane, has a positive effect on the incorporation of the chiral bis(oxazoline) but at the same time it allows some side reactions, probably hydrolysis, leading to partial destruction of the ligand. Increasing the solubility of the leaving salt in the organic medium also improves the incorporation of ligand, but in no case were the results obtained with the nafion-like solids near the level of enantioselection obtained with laponite clay (up to 74% ee. with ethyl diazoacetate and up to 83% de with the menthyl derivative).

Acknowledgments

This work was made possible by the generous financial support of the C.I.C.Y.T. (Project PPQ2002-04012). One of us (C.I.H.) acknowledges the Spanish Ministry of Science and Technology for a grant.

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