Electrostatic immobilization of bis(oxazoline)-copper complexes on mesoporous crystalline materials: cation exchange vs incipient wetness methods

Robert A. Feldman, José M. Fraile*

Instituto de Síntesis Química y Catálisis Homogénea (ISQCH), Facultad de Ciencias, C.S.I.C. - Universidad de Zaragoza, E-50009 Zaragoza, Spain. E-mail: jmfraile@unizar.es

Abstract

Chiral copper complexes with bis(oxazoline) and azabis(oxazoline) ligands have been immobilized by non-covalent interactions on mesoporous materials. The presence of negative charges achieved by the isomorphous substitution of silicon by aluminum is required to retain the complexes on the support. Cation-exchange was found to be not as efficient as observed with layered clays, and produce catalysts which lose their chiral ligand and give low enantioselectivity. A method employing incipient wetness produces more stable catalysts, whose activity varies to some extent according to the structure of the mesoporous material on which it is supported, and the nature of the chiral ligand.

Keywords: asymmetric catalysis; immobilized catalysts; mesoporous materials; bis(oxazolines); copper;

1. Introduction

Enantioselective catalysts immobilized on solid supports [1-3] have the practical advantages of heterogeneous catalysts, regarding easy recovery and reuse. However, the additional cost of the preparation, together with the unpredictable effects of immobilization, hinders their application on an industrial scale. Non-covalent immobilization methods [4] using already existing unmodified ligands and complexes, significantly reduce the synthetic cost and effort of immobilization. Among the different methods utilizing non-covalent support-catalyst interactions, electrostatic immobilization is very useful and practical to immobilize charged complexes, as our group has demonstrated in the case of copper (II) complexes with different types of chiral ligands, such as bis(oxazolines) [5], azabis(oxazolines) [6], quinolineoxazolines [7], and pyridine-azaioxazolines [8]. The most successful support has been laponite, which is a synthetic clay with the intrinsic advantages of having small particles, and reliably consistent composition. Importantly, the electrostatic immobilization on this support leads to important effects on diastereo- and enantioselectivities of cyclopropanation [5,9] and other reactions [10-13], which have not been detected with other types of support. The lamellar nature of the clays, that provides a flat surface of contact for the complex, has been proposed to be the origin of this effect.

Confinement effects have also been described for mesoporous materials with different complexes immobilized through both covalent bonds and non-covalent interactions [14]. In such cases, the effects have been explained by the support causing restrictions on the conformational freedom of the complex, and controlling or limiting the number of attack trajectories of the reaction substrates [15]. In spite of the usefulness of bis(oxazoline)-copper complexes in homogeneous catalysis [16], the number of examples of their immobilization on mesoporous materials is limited. Many works concern the covalent immobilization of complexes on mesocellular foam silicas [17-21] or other supports such as MCM41 and MCM48 [22], hierarchically-ordered mesocellular mesoporous silica [23], SBA15 and HMS [24,25]. On the contrary, the examples of non-covalent immobilization are more scarce, but include hydrogen bonding of ion-tagged box-ligands on SBA15 [26] and electrostatic interactions with Al-MCM41 and Al-SBA15 [27] or Al-TUD1 [28]. In this paper we present our

preliminary results of the electrostatic immobilization of bis(oxazoline)- and azabis(oxazoline)-copper complexes (Figure 1), on Al-MCM41 and Al-HMS as supports.

Figure 1. Ligands used in this work.

2. Experimental

Al-MCM41 was prepared from sodium aluminate and fumed silica in a basic medium with cetyl trimethyl ammonium as the template [29]. In one case (Al-MCM41 with Si/Al = 10), 1,3,5-trimethylbenzene was also added to the gel to expand the pore size [30]. Al-HMS was prepared from tetraethoxy silane and aluminium isopropoxide with hexadecylamine in alcoholic solvent [31].

2.1 Immobilization of the catalysts

The complex was prepared by dissolving the ligand (0.15 mmol) in dichloromethane (1 mL) and adding it to copper (II) triflate (40 mg, 0.1 mmol) suspended in dichloromethane (2 mL). After stirring for 20 min, the solution was microfiltered to ensure the removal of uncomplexed copper (II).

2.1.1 Immobilization by cation-exchange of the complex.

After the preparation of the complex the solvent was evaporated under a flow of argon to yield a green solid. The complex was redissolved in the exchange solvent (methanol, acetonitrile or nitromethane, 5 mL) and the pre-calcined support (1 g) was added to this solution. The suspension was gently stirred for 24 h at room temperature, and the solid was filtered, and then dried under vacuum for 12 h prior to use.

2.1.2 Immobilization by cation-exchange of copper and modification with chiral ligand.

In a typical experiment, copper (II) triflate (110 mg, 0.3 mmol) was dissolved in acetonitrile (5 mL), calcined Al-MCM41(15) (1 g) was added to the solution, and the suspension was stirred for 24 h at room temperature. The solid was filtered, washed with methanol in a Soxhlet extractor for 24 h and then dried under vacuum for 12 h. This solid can be used as catalyst for non-enantioselective reactions or modified with chiral ligand. In order to be modified by chiral ligand, the supported copper(II) (1 g) was added to a solution of the ligand (0.45 mmol) in dichloromethane (5 mL), and the suspension was stirred for 24 h at room temperature. The solid was filtered and then dried under vacuum for 12 h prior to use.

2.1.3 Immobilization by incipient wetness of the complex.

After the preparation of the complex the solvent was evaporated under a flow of argon to yield a green solid. The complex was redissolved in the required amount of methanol (0.6 mL for Al-MCM41(10) and 0.3 mL for Al-MCM41(15)), the calcined support (0.5 g) was added and the flask was shaken to ensure the even distribution of the solution. The solid was dried under vacuum for 12 h prior to use.

2.2 Characterization methods

Powder X-ray diffraction (XRD) data were obtained on a CGR Theta-60 diffractometer with an Inel drive, using monochromated Cu K α radiation. The adsorption-desorption isotherms of nitrogen at 77 K were measured using either a Micromeritics ASAP 2000 or an ASAP 2020 instrument. Each sample was outgassed at 250°C after being calcined until a stable static vacuum of 3×10^{-3} torr was reached. The aluminium analysis was determined using Energy-dispersive X-ray spectroscopy (EDX) on the calcined solid. Particle morphology was observed using a Hitachi S-4500 I scanning electron microscope (SEM). The order in the silica network was examined by transmission electron microscopy (TEM) images obtained using a Philips CM 20 apparatus operating at 100 keV.

2.3 Catalytic tests

2.3.1 Homogeneous cyclopropanation.

At room temperature, ethyl diazoacetate (2.5 mmol, 285 mg) dissolved in dichloromethane (0.5 mL) was added over the course of 2 h with a syringe pump to a solution containing the copper catalyst (0.025 mmol), *n*-decane (100 mg) and styrene (2 mL for reactions in excess of alkene or 2.5 mmol, 260 mg, in 2 mL dichloromethane for stoichiometric reactions). After the addition, the reaction was left to stir for 30 min and then analysed by CG [5-9].

2.3.2 Heterogeneous cyclopropanation.

The supported catalyst (50 mg) was suspended in either styrene or dichloromethane (2 mL) with *n*-decane (100 mg) and ethyl diazoacetate (2.5 mmol, 285 mg) dissolved in dichloromethane (0.5 mL) was added over the course of 2 h with a syringe pump. After the addition, the reaction was left to stir for 30 min and then analysed by CG. The catalyst was filtered, rinsed with dichloromethane (5 mL) and then added directly to the next reaction.

3. Results and discussion

The mesoporous supports were prepared by well-established methods [29-31] and the textural properties and composition (Table 1) were in agreement with the expected values. The absence of extraframework octahedral Al in Al-MCM41 was confirmed by ²⁷Al MAS NMR, but a small amount was detected in Al-HMS, probably because the preparation protocol requires that washing is not done after the filtration of the as-synthesized material. In the case of Al-MCM41(10) the expansion in the pore size has the effect of severely disrupting the symmetry of the support, such that hexagonal symmetry features of the MCM41 structure, are not clearly observed by small angle XRD.

Table 1. Composition and textural properties of the mesoporous supports.

Support	Si/Al	Surface area (m ² /g)	Pore volume (ml/g)	Pore diameter (Å)
Al-MCM41(10)	10	628	1.2	92
Al-MCM41(15)	15	860	0.6	36
MCM41	∞	967	0.7	36
Al-HMS-(25)	25	1029	0.9	33

3.1 Immobilization by cation-exchange of the pre-formed complex

The simplest method of electrostatic immobilization is the direct cation exchange of the pre-formed complex on the support (Scheme 1). This method has been commonly used in the case of immobilization on laponite clay [5-13]. The bis(oxazoline)-copper(II) triflate complex is stirred with the support in a solvent with a high dielectric constant, able to dissolve the sodium triflate generated in the exchange process, which should then subsequently eliminated by filtration. The amount of copper complex used in the exchange process was selected to be 0.3 mmol/g, far below the theoretical exchange capacity, and was chosen in an attempt to prevent immobilization by other kinds of interactions, and to prevent pore blocking with excess copper complex. The green solids were tested in the benchmark cyclopropanation reaction of styrene with ethyl diazoacetate (Scheme 2).

Scheme 1. Processes of immobilization by cation-exchange.

Scheme 2. Cyclopropanation of styrene with ethyl diazoacetate.

In the beginning, an attempt was made to support the boxPh-Cu complex on Al-MCM41(15), since this is a complex has been commonly supported on laponite. The yield produced by the supported complex (Table 2) was much lower than that of the homogeneous complex, and the enantioselectivity was significantly lower. If this result were caused by a confinement effect, as happened in the case of laponite [5,9], a significant variation in *cis/trans* diastereoselectivity would be expected. Since this is not the case, a more obvious cause for the reduction in enantioselectivity would be there being an almost complete decomplexation of the chiral ligand from the copper during the cation-exchange process, which results from a low stability of the complex. The low yield could potentially result from a partial pore blocking of the support.

The triflate counter-ion has been described as acting as a linker through hydrogen bonding to the support for bis(oxazoline)-metal complexes on the silica surface [32-35]. To be sure that the aluminium sites in Al-MCM41 were playing some role in supporting the complex, the complex was deposited on a purely siliceous MCM41 solid with similar textural properties to Al-MCM41(15) (Table 1). The green solid that was obtained following the implementation of the cation-exchange conditions lost its color in an instant when it was rinsed with a small amount of methanol and the material left over was not active in the cyclopropanation reaction. This is in contrast to when the complexes are supported on Al-MCM41 using the same conditions, but washed with much larger volumes of methanol. Using Al-MCM41, the solids always retain their green colour after washing and are active for at least one reaction. Thus, in this way one can infer that the aluminum sites play a decisive role in the immobilization of our Cu complexes.

Table 2. Results of the cyclopropanation of styrene with ethyl diazoacetate catalyzed by solids prepared by cation-exchange of the pre-formed box-Cu complexes.

Ligand	Support	Reaction cond. ^a	Run	Yield (%)	TON ^b	<i>cis</i> / <i>trans</i>	% ee	
							<i>cis</i>	<i>trans</i>
boxPh	none	Homog.	-	63	63	30:70	51	72
	Al-MCM41(15)	Stoich.	1	10	17	34:66	16	18
	Al-MCM41(10)	Stoich.	1	24	40	39:61	32	50
			2	23	38(78)	43:57	32	44
			3	23	38(116)	46:54	28	37
aza ⁱ Pr	none	Homog.	-	49	49	30:70	70	83
	Al-MCM41(10)	Stoich.	1	44	73	37:63	42	65
			2	34	57(130)	36:64	44	64
			3	43	72(202)	36:64	44	63
			4	11	-	39:61	0	0
		Styrene	1	44	73	47:53	46	52
			2	7	12(85)	48:52	38	33
			3	1	-	45:55	n.d.	n.d.

^aHomog.: reaction in homogeneous phase with the LCu(OTf)₂ complex. Stoich.: heterogeneous reaction with stoichiometric amounts of styrene and ethyl diazoacetate. Styrene: heterogeneous reaction with a large excess of styrene. ^bTON= mmol of cyclopropanes per mmol of Cu. In parenthesis the cumulative TON in all the runs with similar enantioselectivities.

Logically, the loss of chiral ligand during the exchange process may be a consequence of the steric interactions of the bulky complex with the material walls, within the mesopores. When Al-MCM41(10) was used as support the results were significantly better than those obtained with Al-MCM41(15) (Table 2). The yield was improved over the result obtained on Al-MCM41(15), the diastereoselectivity was very similar, albeit with a slightly higher amount of *cis* isomer being formed. The enantioselectivity was also better such that a 50% ee was obtained in the *trans* cyclopropanes vs 18% ee with the same complex supported in the smaller pores of Al-MCM41(15). This result could imply that there is a very important role of the pore size in determining the catalytic performance of our catalysts. The higher enantioselectivity in the larger pore would show that the complex is more stable, and one would also expect there to be lower diffusion limitations on the complex and reaction substrates than there would be in

smaller pores. Nonetheless, in spite of these improved results, upon recycling, the enantioselectivity steadily decreases following each run. This loss of enantioselection would be explained by the chiral ligand progressively being separated from the copper centres due to a lack of stability, or being displaced by the by-products of the cyclopropanation reaction [36].

Taking into account this hypothesis, we decided to attempt the immobilization of an azabox-Cu complex, since azabox complexes are more stable than the analogous box-Cu [6]. Using the support with the largest pore size, Al-MCM41(10), with the hope to having the least steric problems, as expected, azaⁱPr-Cu(II) immobilized on Al-MCM41(10) produced better results (Table 2). Yield and *cis/trans* diastereoselectivity were very similar to those obtained in solution, but the enantioselectivity was lower than in homogeneous phase; with a 65% ee in the *trans* isomers with the supported catalyst in comparison with 83% ee in solution. In contrast to the result obtained with boxPh, this catalytic performance was stable during 3 consecutive cycles, leading to a cumulative TON of 200, but with an almost complete deactivation by the fourth cycle. Thus, in this example, a more stable complex gives better initial activity following cation-exchange and better performance when re-used, but the life time of the catalyst is still limited.

In the case of laponite-supported catalysts, the changes in selectivities of the supported complexes were enhanced by the use of solvents with low dielectric constant [9], which favour the close proximity of the support-catalyst ion pair. A reaction was therefore performed with a large excess of styrene using azaⁱPr-Cu(II) immobilized on Al-MCM41(10) (Table 2). Comparing the result obtained with Al-MCM41(10) and laponite, the parallel exists that excess styrene produces a slight increase in the amount of *cis*-diastereoisomer formed, but with Al-MCM41(10), it also produces a slightly lower enantioselectivity in the *trans* products. There is no doubt that in terms of enantioselection, using excess styrene with the complexes supported on laponite, gives a more profound effect than what is seen with MCM41. Furthermore, with Al-MCM41(10), the use of the larger amount of styrene does not improve the yield (representative for chemoselectivity of the process with respect to side reactions of diazoacetate). On the contrary, the use of excess styrene produced a rapid deactivation,

resulting in an almost complete deactivation by the second cycle. Following the reactions in excess styrene, one can see unmistakably that the support becomes coated with hydrophobic polymeric products that can also be seen by thermal gravimetric analysis, and this would point to side reactions of styrene, such as oligomerization, as being the cause for this faster deactivation.

The choice of solvent is important for cation exchange of complexes [37], as there is a competitive equilibrium that takes place between the box ligand and solvent coordination on the copper(II) centres, and if the balance of this equilibrium is disfavoured, it results in there being a larger number of non-chiral copper sites complexed with solvent molecules. For the reason of its larger pore size, Al-MCM41(10) was used as support to immobilize boxPh-Cu(II) by direct exchange, using different solvents and the results obtained in the cyclopropanation reaction using these catalysts are presented in Figure 2.

Figure 2. Effect of exchange solvent on the cyclopropanation yield (continuous lines) and enantioselectivity of the *trans* isomers (dashed lines): methanol (■), acetonitrile (◆), nitromethane (▲). Grey lines represent the values in the homogeneous reaction.

When acetonitrile or nitromethane were used instead of methanol, a higher initial enantioselectivity in the *trans*-diastereoisomer is observed, even higher than the result obtained by the homogenous phase catalyst in the case of acetonitrile. Being that the dielectric constants of the three solvents are quite similar, any differences that result from solvent effects could be attributed to the lower coordinating ability of acetonitrile and nitromethane, that can be represented by their donor number values (DN [38]: acetonitrile = 14.1, nitromethane = 2.7, methanol = 30). If the exchange solvent is less prone to substitute itself for the position of the chiral ligand, then the overall enantioselectivity of the catalyst should be higher, at least at the outset.

However, once again, the intrinsic lack of stability of the complex leads to a progressive loss of chiral ligand by substitution with reaction products and/or by-products. The extent of the drop does not change with respect to the exchange solvent, and this is shown by the steady decline in the enantioselection that occurs for all of the catalysts. One would favour the hypothesis of loss of ligand over deactivation of the copper(II) centres because while the enantioselection falls, the yield remains relatively stable. Moreover, when ethyl diazoacetate was added to the solutions that are obtained after the separation of the catalyst by filtration, all of the solutions were catalytically active and this would indicate the leaching of active copper species.

3.2 Complexation of copper-exchanged mesoporous support with chiral ligand

Given the problems to prepare selective and stable catalysts by direct exchange of pre-formed complexes, another strategy that consists of two steps was formulated (Scheme 1), that involves the exchange of copper(II) on the support, and the subsequent formation of the complex by the addition of ligand using a non-coordinating solvent of low dielectric constant, such as dichloromethane. In this way the diffusion of the chiral ligand through the pores would be improved by the higher conformational freedom of the non-bound chiral ligand compared to the full complex. Once the copper centers are installed, complex formation could potentially be optimized by using an excess of ligand with respect to copper. For the first step, calcined Al-MCM41 was added to a solution of the copper(II) triflate in methanol, containing a quantity of copper corresponding to a final content of 3.8wt% Cu. One half of the copper that was added to

the cation exchange suspension was detected on the support, thus giving a loading of 1.9wt%. Simple washing with small amounts of MeOH did not affect the copper loading but on the other hand, Soxhlet extraction with methanol for 12 h reduced the copper content to 1.3wt%. After Soxhlet extraction, it is reasonable to suppose that weakly or only partially bound copper had been removed.

Copper(II) triflate was supported on both the Al-MCM41(10) and Al-MCM41(15) solids in this way and then tested in the cyclopropanation of styrene with ethyl diazoacetate, without the use of chiral ligand, in order to independently examine the effect of the ligand and support (Table 3). The result was that in each case, a higher level of *cis*-diastereoisomers was produced than the homogenous phase analogues. One could attribute this effect to the elimination of weakly supported copper(II) following the soxhlet extraction phase, and the slightly raised level of the *cis*-diastereomers being due to a support interaction such as described with laponite [9]. The copper supported on Al-MCM41(10) produced the highest level of *cis*-diastereomers and one could speculate that the origin of this effect could be the larger diameter of the support. The larger the pore diameter would geometrically produce an internal surface that would be relatively flat, and so in this way, the surface more closely approximates the surface of laponite.

Table 3. Results of the cyclopropanation of styrene with ethyl diazoacetate catalyzed by Cu(II)-exchanged Al-MCM41.

Support	Reaction cond. ^a	Yield (%)	TON ^b	<i>cis/trans</i>
none ^b	Styrene	47	47	30:70
Al-MCM41(15)	Stoich.	32	78	44:56
	Styrene	43	105	47:53
Al-MCM41(10)	Stoich.	32	78	39:61
	Styrene	49	120	53:47

^aStoich.: reaction with stoichiometric amounts of styrene and ethyl diazoacetate. Styrene: reaction with a large excess of styrene. ^bReaction catalyzed by Cu(OTf)₂. ^cTON= mmol of cyclopropanes per mmol of Cu.

After one reaction, the copper content of the solid drops from 1.3 to 0.8 wt%. The fact that this occurs after Soxhlet extraction, and that there is no other species present that would be expected to exchange with the copper(II) sites, would suggest that at least some of the copper(II) is only partially exchanged onto the support. Considering that the first step of the cyclopropanation reaction is a Cu(II) to Cu(I) reduction, the initial presence of $[\text{Al-MCM41}]^-\text{[CuOTf]}^+$ species would produce either $[\text{Al-MCM41}]^-\text{Cu}^+$, that would remain on the solid, or CuOTf, that would have a higher chance of being leached into the solution.

In spite of anticipating leaching, the formation of the chiral complex was implemented by treating this Cu(II) supported on Al-MCM41(10) with 1.5 molar equivalents (with respect to the amount of copper) of boxPh in dichloromethane at room temperature. In the beginning the complex formation step was done over the course of 12 h to favour the diffusion of the ligand inside the pores, and the partial success of this effort was demonstrated by the cyclopropanation results (Method A, Table 4) that show a moderate initial activity and enantioselectivity (40% ee in the *trans* isomers). A significant drop that occurs when the catalyst is re-used was due in part to copper leaching, demonstrated by the activity of the filtrate, but also to the loss of ligand, demonstrated by the drop in enantioselectivity. The effect of the diffusion of the ligand was studied by treatment for a much shorter time of 5 min (Method B, Table 4). This catalyst was less active in terms of its yield. Should the result of the shorter dispersion time be that the ligand is densely distributed around outer periphery of the pores, this would inevitably block some copper sites from reacting, and would thus reduce the yield of the reaction. On the other hand, this catalyst gave slightly higher enantioselectivity and was more stable upon recycling.

These results show that direct cation exchange on the mesoporous Al-MCM41, either of the pre-formed box-Cu complex or simply $\text{Cu}(\text{OTf})_2$, is not as simple as it was with a layered clay such as laponite. Thus, the immobilization by this method is not as straightforward, and a new methodology based on incipient wetness was designed.

Table 4. Results of the cyclopropanation of styrene with ethyl diazoacetate^a catalyzed by Cu(II)-exchanged Al-MCM41(10) modified with boxPh-Cu.

Method ^b	Run	Yield (%)	TON ^c	<i>cis/trans</i>	% ee	
					<i>cis</i>	<i>trans</i>
	Homog. ^d	63	63	30:70	51	72
A	1	46	112	40:60	31	40
	2	12	29(141)	37:63	17	17
B	1	24	59	39:61	32	50
	2	23	56(115)	43:57	32	44
	3	23	56(171)	46:54	28	37
	4	14	34(205)	44:56	26	34

^aReactions carried out in dichloromethane with the stoichiometric amount of styrene. ^bMethod A: treatment with ligand (1/10 w/w with respect to solid) in dichloromethane for 12 h at rt, filtration and drying under vacuum. Method B: treatment with the same amount of ligand for only 5 min, evaporation of solvent and immediate use in the reaction. ^cTON= mmol of cyclopropanes per mmol of Cu. In parenthesis the cumulative TON in all the runs with similar enantioselectivities. ^dReaction carried out with boxPh-Cu(OTf)₂ in solution.

3.3 Immobilization by incipient wetness of the pre-formed complex

The deposition of the complex by incipient wetness refers to the process of addition of a solution of the complex to the dry support, using a volume that is equal to or less than its internal volume, and in this way, the complex enters the solid by capillary action.

3.3.1 Immobilization of boxPh-Cu

BoxPh-Cu(OTf)₂ was dissolved in the required amount of MeOH and added to pre-calcined Al-MCM41(15). Adsorption by incipient wetness was completed by removal of the solvent under reduced pressure. As a copper loading of 0.3 mmol/g (1.9wt%) after cation-exchange resulted in leaching, a smaller amount of copper was added for incipient wetness in an attempt to address this problem, and this level was 0.2 mmol/g

(1.5wt%). Whereas the intention of cation-exchange is to separate the triflate counter-ion from the copper sites, ion-pairing is more likely to occur in incipient wetness, with triflate anions remaining on the solid (Figure 3).

Figure 3. Proposed ion-pairing interaction after incipient wetness immobilization.

This catalyst was tested in the cyclopropanation between ethyl diazoacetate and a stoichiometric quantity of styrene (Table 5). When compared with the solid prepared by cation exchange on the same support (Table 2) it can be seen that incipient wetness produces a much more active and enantioselective catalyst, although always with values below those obtained with the homogeneous catalyst.

Table 5. Results of the cyclopropanation of styrene (stoichiometric amount) with ethyl diazoacetate catalyzed by boxPh-Cu(OTf)₂ immobilized by incipient wetness.

Support	Run	Yield (%)	TON ^b	<i>cis/trans</i>	% ee	
					<i>cis</i>	<i>trans</i>
none	-	63	63	30:70	51	72
Al-MCM41(15)	1	37	93	38:62	27	42
	2	32	80(173)	38:62	24	38
	3	30	75(248)	37:63	37	52
	4	22	55(303)	43:57	32	44
	5 ^a	45	112(415)	33:67	45	49
Al-HMS(25)	1	37	93	36:64	30	55
	2	11	28(121)	43:57	25	34
	3	38	95(216)	36:64	32	43
	4	29	73	50:50	12	5
	5	17	43	44:56	16	24

^aBefore the reaction, the supported catalyst was recovered, dried, and washed in a Soxhlet with dichloromethane for 12 h. ^bTON= mmol of cyclopropanes per mmol of Cu. In parenthesis the cumulative TON in all the runs with similar enantioselectivities.

The catalyst shows a remarkable degree of stability along four consecutive runs, with a cumulative TON of 300. Considering that the drop in yield of the fourth may be due to pore blocking, the catalyst was washed in a Soxhlet extractor for 12 h with dichloromethane. This treatment gave an improvement in the yield, reaching a cumulative TON higher than 400, even the enantioselectivity rose, and this shows how by-products can deactivate the catalyst. The lower enantioselectivity in comparison with the homogeneous result is likely to be due to a confinement effect within the pores which modifies the steric environment of the catalytic center, however, one cannot discount the possibility of there being a partial loss or degradation of the ligand during the impregnation process. Both of these scenarios would favour the formation of a mixture of chiral and non-chiral centers. It would be highly desirable to determine the proportion of chirally and non-chirally modified centres however, this would not be achieved as simply as determining the elemental composition of the catalyst since the free ligand is also present on the support.

In order to examine how the structure of the support could affect the activity, Al-HMS(25) was used to immobilize the same complex under the same conditions. The performance of this catalyst (Table 5) was quite erratic, with results of yield and selectivities that were much less stable than those obtained with Al-MCM41. In addition to differences in the morphology and textural properties of this support, one must consider that the Al-HMS support was prepared using $\text{Al}(\text{O}^i\text{Pr})_3$ as the aluminium precursor, whereas the Al-MCM41 materials were made with sodium aluminate. This means that following the removal of the template by calcination, the aluminium sites of Al-HMS(25) are present in their protic form, whereas the Al-MCM41 aluminium sites are stabilized by sodium. We speculate that the protic form could be potentially deleterious to the stability of the bis(oxazoline) ligand.

Nonetheless, the merits of incipient wetness are that it is quicker to implement than cation-exchange in a suspension, uses less solvent and the copper complex is more efficiently introduced into the mesoporous support. Moreover this approach produces

more active and stable catalysts. In view of all those advantages, this procedure was tested with the most efficient ligand in solution.

3.3.2 Immobilization of *aza*^tBu-Cu

Given the steric volume of the *tert*-butyl substituents, *aza*^tBu-Cu(OTf)₂ was deposited inside Al-MCM41(10) by incipient wetness following the same procedure as with boxPh. On the first occasion when the catalyst was used in a cyclopropanation reaction, unlike on all previous occasions, during the addition of ethyl diazoacetate, the reaction did not begin immediately. One hour after all of the ethyl diazoacetate had been added, the reaction suddenly began and continued for a little while in an uncontrollable manner. At this point, GC analysis showed that a significant amount of diazoacetate remained unreacted, a very low amount of cyclopropane products had been formed, but most importantly, the enantioselection of this catalyst was very similar to the homogenous phase catalyst result (Table 6).

Table 6. Results of the cyclopropanation of styrene with ethyl diazoacetate catalyzed by *aza*^tBu-Cu(OTf)₂ immobilized on Al-MCM41(10) by incipient wetness.

Reaction conditions ^a	Temp. (°C)	Run	Yield (%)	TON ^b	<i>cis/trans</i>	% ee	
						<i>cis</i>	<i>trans</i>
Homog.	25	-	44	44	24:76	87	93
Stoich.	25	1	3	8	24:76	82	91
Styrene	90	1	56	140	24:76	69	85
		2	39	98	31:69	15	15
		3	21	53	35:65	10	2

^aStoich.: reaction with stoichiometric amounts of styrene and ethyl diazoacetate. Styrene: reaction with a large excess of styrene. ^bTON= mmol of cyclopropanes per mmol of Cu.

The Cu(I) is the active species [39] in the cyclopropanation reaction and since we are using a precursor of Cu(II), this Cu(II) needs to be reduced to Cu(I) [40,41] before the catalytic cycle can proceed. In general, the ethyl diazoacetate carries out the reduction. In another example of electrostatic immobilization of *aza*^tBu-Cu(II), for example on

naftion-silica, it was necessary to heat the catalyst at 50°C in the presence of ethyl diazoacetate for a few minutes in order to promote the reduction to Cu(I) [6]. Here, the same method was not adequate and so a series of experiments was performed in which ethyl diazoacetate was added to a heated suspension of $\text{aza}^t\text{Bu-Cu(OTf)}_2$ immobilized on Al-MCM41(10) in styrene. Below 50°C the reaction does not take place, in the range of 50-80°C reaction occurs slowly but is not completely under control. The optimal temperature was found to be 90°C, as higher temperatures produced a syrupy mixture due to styrene polymerization. Using a temperature of 90°C produces an immediate reaction when the addition of ethyl diazoacetate is initiated, and this reaction stops the moment that the addition of ethyl diazoacetate is halted. The need for this high temperature demonstrates the high stability of this aza-Cu(II) complex against reduction, as already observed in previous work [6]. The activity and selectivities were very good in the first reaction (Table 6), however, the enantioselectivity is virtually lost following the first recycle. The rapid loss of activity would imply that although the complex is very stable, it is still prone to substitution with by-products and the gradual decrease in yield is probably indicative of poisoning with styrene oligomers due to the high temperature.

4. Conclusions

Cation exchange was found to be unsuitable as a method for the electrostatic immobilization of bis(oxazoline)-copper complexes on mesoporous materials due to a combination of factors, such as the rather poor stability of the complex, leading to non-chiral active sites, and the steric constraints for diffusion of the rather bulky complex inside the pores. The use of azabis(oxazoline) ligands, whose copper complexes have higher formation constants, solids with larger pores, and less coordinating exchange solvents, minimizes these problems, but the recyclability of the catalysts in the cyclopropanation reactions is furthermore limited by the ligand replacement with reaction by-products.

Deposition of the complex by incipient wetness overcomes some of the problems of the restricted diffusion in the pores and the resulting catalyst is more active and more stable against deactivation. The aza^tBu copper complex deposited on Al-MCM41 in this way is of such a stability that in order to achieve the necessary reduction of Cu(II) to Cu(I), a

high reaction temperature is needed and this leads to a fast deactivation due to styrene polymerization.

Acknowledgement

This research was made possible by the financial support from the Spanish Ministerio de Economía y Competitividad (Project CTQ2011-28124) and the European Commission (NANO-HOST program no. PITN-GA-2008-215193). Dr. Anne Galarneau (Institute Charles Gerhardt, CNRS Montpellier) is gratefully acknowledged for providing the samples of MCM41.

References

- [1] D. E. De Vos, I. F. J. Vankelecom, P. A. Jacobs (Eds.), *Chiral Catalysts Immobilization and Recycling*, Wiley-VCH, Weinheim, 2000.
- [2] P. Barbaro, F. Liguori (Eds.), *Heterogenized Homogeneous Catalysts for Fine Chemicals Production*, Springer, Dordrecht, 2010.
- [3] M. Heitbaum, F. Glorius, I. Escher, *Angew. Chem. Int. Ed.* 45 (2006) 4732–4762.
- [4] J. M. Fraile, J. I. García, J. A. Mayoral, *Chem. Rev.* 109 (2009) 360–417.
- [5] J. I. García, B. López-Sánchez, J. A. Mayoral, E. Pires, I. Villalba, *J. Catal.* 258 (2008) 378–385.
- [6] J. M. Fraile, J. I. García, C. I. Herrerías, J. A. Mayoral, O. Reiser, A. Socuélamos, H. Werner, *Chem. Eur. J.* 10 (2004) 2997–3005.
- [7] J. M. Fraile, J. I. García, G. Jiménez-Osés, J. A. Mayoral, M. Roldán, *Organometallics* 27 (2008) 2246–2251.
- [8] J. I. García, G. Jiménez-Osés, B. López-Sánchez, J. A. Mayoral, A. Vélez, *Dalton Trans.* 39 (2010) 2098–2107.
- [9] A. I. Fernández, J. M. Fraile, J. I. García, C. I. Herrerías, J. A. Mayoral, L. Salvatella, *Catal. Commun.* 2 (2001) 165–170.
- [10] J. M. Fraile, J. I. García, J. A. Mayoral, M. Roldán, *Org. Lett.* 9 (2007) 731–733.
- [11] J. M. Fraile, P. López-Ram-de-Viu, J. A. Mayoral, M. Roldán, J. Santafé-Valero, *Org. Biomol. Chem.* 9 (2011) 6075–6081.

- [12] M. J. Fabra, J. M. Fraile, C. I. Herrerías, F. J. Lahoz, J. A. Mayoral, I. Pérez, *Chem. Commun.* (2008) 5402–5404.
- [13] J. M. Fraile, N. García, C. I. Herrerías, *ACS Catal.* 3 (2013) 2710–2718.
- [14] J. M. Fraile, J. I. García, C. I. Herrerías, J. A. Mayoral, E. Pires, *Chem. Soc. Rev.* 38 (2009) 695–706.
- [15] J. M. Thomas, R. Raja, *Acc. Chem. Res.* 41 (2008) 708–720.
- [16] G. Desimoni, G. Faita, K. A. Jorgensen, *Chem. Rev.* 111 (2011) PR284–PR437.
- [17] J. K. Park, S.-W. Kim, T. Hyeonb, B. M. Kim, *Tetrahedron: Asymmetry* 12 (2001) 2931–2935.
- [18] T. M. Lancaster, S. S. Lee, J. Y. Ying, *Chem. Commun.* (2005) 3577–3579.
- [19] S. S. Lee, S. Hadinoto, J. Y. Ying, *Adv. Synth. Catal.* 348 (2006) 1248–1254.
- [20] S. S. Lee, J. Y. Ying, *J. Mol. Catal. A* 256 (2006) 219–224.
- [21] J. Lim, S. N. Riduan, S. S. Lee, J. Y. Ying, *Adv. Synth. Catal.* 350 (2008) 1295–1308.
- [22] R. J. Clarke, I. J. Shannon, *Chem. Commun.* (2001) 1936–1937.
- [23] J.-M. Lee, J. Kim, Y. Shin, C.-E. Yeom, J. E. Lee, T. Hyeon, B. M. Kim, *Tetrahedron: Asymmetry* 21 (2010) 285–291.
- [24] A. R. Silva, H. Albuquerque, S. Borges, R. Siegel, L. Mafra, A. P. Carvalho, J. Pires, *Microporous Mesoporous Mater.* 158 (2012) 26–38.
- [25] A. R. Silva, L. Carneiro, A. P. Carvalho, J. Pires, *Catal. Sci. Technol.* 3 (2013) 2415–2424.
- [26] Z.-H. Li, Z.-M. Zhou, X.-Y. Hao, J. Zhang, X. Dong, Y.-Q. Liu, *Chirality* 24 (2012) 1092–1095.
- [27] Y. Wan, P. McMorn, F. E. Hancock, G. J. Hutchings, *Catal. Lett.* 91 (2003) 145–148.
- [28] S. Telalović, U. Hanefeld, *Appl. Catal. A* 372 (2010) 217–223.
- [29] J. M. Kim, J. H. Kwak, S. Jun, R. Ryoo, *J. Phys. Chem.* 99 (1995) 16742–16747.
- [30] A. Galarneau, M. Cangiotti, F. di Renzo, F. Sartori, M. F. Ottaviani, *J. Phys. Chem. B* 110 (2006) 20202–20210.
- [31] T. R. Pauly, Y. Liu, T. J. Pinnavaia, S. J. L. Billinge, T. P. Rieker, *J. Am. Chem. Soc.* 121 (1999) 8835–8842.
- [32] P. O’Leary, N. P. Krosveld, K. P. De Jong, G. van Koten, R. J. M. Klein Gebbink, *Tetrahedron Lett.* 45 (2004) 3177–3180.

- [33] H. Wang, X. Liu, H. Xia, P. Liu, J. Gao, P. Ying, J. Xiao, C. Li, *Tetrahedron* 62 (2006) 1025–1032.
- [34] C. McDonagh, P. O’Leary, *Tetrahedron Lett.* 50 (2009) 979–982.
- [35] E. P. Carreiro, N. M. M. Moura, A. J. Burke, *Eur. J. Org. Chem.* (2012) 518–528.
- [36] J. M. Fraile, J. I. García, J. A. Mayoral, T. Tarnai, M. A. Harmer, *J. Catal.* 186 (1999) 214–221.
- [37] J. M. Fraile, J. I. García, C. I. Herrerías, J. A. Mayoral, M. A. Harmer, *J. Catal.* 221 (2004) 532–540.
- [38] Y. Marcus, *J. Solut. Chem.* 13 (1984) 599–624.
- [39] J. M. Fraile, J. I. García, V. Martínez-Merino, J. A. Mayoral, L. Salvatella, *J. Am. Chem. Soc.* 123 (2001) 7616–7625.
- [40] R. G. Salomon, J. K. Kochi, *J. Am. Chem. Soc.* 95 (1973) 3300–3310.
- [41] R. L. Safiullin, V. A. Dokichev, L. R. Yakupova, R. M. Sultanova, S. L. Khursan, R. N. Zaripov, Yu. V. Tomilov, *Kinet. Catal.* 49 (2008) 43–51.