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Comparison of immobilized Box and azaBox–Cu(II) complexes as catalysts for enantioselective Mukaiyama aldol reactions

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Abstract

Enantioselective Mukaiyama aldol reactions of different α-ketoesters was tested with copper complexes of chiral Box and azaBox ligands in both homogeneous and heterogeneous systems. Results in the homogeneous reactions were greatly influenced by the nature of the ketoester, the chiral ligand, and the reaction solvent. In the case of supported catalysts, the use of strongly coordinating azaBox ligands prevented the leaching of metal but reduced the Lewis acidity, and thus the catalytic activity, and did not solve the problem of poisoning by strong coordination of products, byproducts, or solvents. The counter-ion effect also was very significant, and electrostatic immobilization was efficient only with Box ligands (up to 86% ee at room temperature), whereas covalent immobilization allowed the use of azaBox ligands (up to 85% ee at room temperature) in the heterogeneous phase. Recovered deactivated solids could be reused in a reaction with a completely different mechanism that does not require acid centers, such as cyclopropanation.

Keywords: Asymmetric catalysis; Supported catalysis; Bis(oxazoline); Azabis(oxazoline); Mukaiyama aldol reaction; Chiral Lewis acids

1. Introduction

Bis(oxazoline)s (Box) are among the most frequently used families of ligands in the chiral catalysis of enantioselective reactions [1], due to the fact that they can be obtained with a wide variety of structures from readily accessible precursors. Furthermore, these ligands form complexes with a wide variety of metals and metallic cations, and such complexes promote a wide variety of reactions to give high yields and enantioselectivities. This versatility has attracted interest in the immobilization of these ligands [2] in an effort to exploit the advantages of heterogeneous catalysis in terms of catalyst separation and, in some cases, recycling or even use as multipurpose catalysts [3]. However, efficient immobilization of chiral catalysts is not a straightforward task. One of the most frequent problems is leaching of metal or ligand, depending on the immobilization strategy used. When the catalyst is covalently bonded to a solid support through the ligand, metal leaching leads to a reduced number of catalytic centers and, consequently, reduced activity. However, when the catalyst is immobilized by electrostatic interaction of the cation with an anionic support, leaching of chiral ligand leads to the formation of nonenantioselective catalytic centers, and the enantioselectivity decreases [4]. In the homogeneous phase, the latter problem is avoided by using an excess of the chiral ligand, but because this local excess cannot be used in supported phases, immobilization of strong complexes is the best strategy to avoid leaching [5]. This situation is particularly difficult in Lewis acid-catalyzed reactions, in which reagents that are able to form chelate complexes are used to reduce conformational mobility and increase enantioselectivity. In these reactions, the formation of strong complexes of the catalysts with reagents, products, or byproducts favors leaching or poisoning of the catalysts. For these reasons, a large amount of catalyst is frequently used in solution, which in the supported phase implies the use of an overly large amount of solid. An example of this situation is the Mukaiyama aldol reaction, probably one of the most useful reactions for C–C bond formation in an enantioselective manner [6]. Box–copper complexes

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lead to excellent results in the homogeneous phase [7–11]. This method has even been adapted to biphasic conditions, either on a solid support [12] or with water-soluble polymeric ligands [13,14]. But both of these strategies required considerable synthetic effort to modify the chiral ligands. Furthermore, these procedures were not problem-free. The polymerized catalyst required the presence of additional molecular sieves [12], and additional fresh MS and copper salt were necessary after each cycle. The water-soluble catalysts showed poor recyclability [13,14], and the copper salt was leached, leading to recovery of the polymeric ligand alone.

In the present work, we compared the copper complexes of bis(oxazoline) and azabis(oxazoline) [15] (azaBox) ligands (the latter selected due to the formation of stronger complexes [5]) as catalysts in three different Mukaiyama aldol reactions. We also compared the use of electrostatic [16] and covalent immobilization [17].

2. Experimental

2.1. Synthesis of ligands

Ligand **1a** was prepared from (S)-phenylglycinol and dimethylmalononitrile as described previously [18]. Ligands **2a**, **2b**, and **2c** were prepared by methods described by Reiser et al. [15,19–21].

2.2. Immobilization on laponite

Laponite was dried under vacuum at 140 °C for 24 h before use.

2.2.1. Method A (cation exchange)

The chiral ligand (0.11 mmol) and $Cu(OTf)_2$ (40 mg, 0.11 mmol) were dissolved in the minimum amount of anhydrous dichloromethane under an argon atmosphere. The solution was stirred for 15 min and filtered through a PTFE microfilter. The solvent was removed under vacuum, the complex was redissolved in methanol (4 ml), dried laponite (375 mg) was added, and the suspension was stirred for 24 h at room temperature. The solid was filtered off, washed with methanol (10 ml) and dichloromethane (20 ml), and finally dried under vacuum for 24 h.

2.2.2. Method B (adsorption)

The chiral ligand (0.17 mmol) and $Cu(OTf)_2$ (55 mg, 0.151 mmol) were dissolved in anhydrous dichloromethane (5 ml) under an argon atmosphere. The solution was stirred for 30 min and filtered through a PTFE microfilter. This solution was added to dried laponite (1 g) and stirred, and the solvent slowly evaporated under reduced pressure. The solid was dried under vacuum for 24 h.

2.3. Immobilization on Merrifield resin

Synthesis of **7**: Merrifield resin (1 g) was suspended in benzene (30 ml) and treated with a solution of NaBr (4.12 g, 40 mmol) and Bu_4NBr (0.97 g, 3 mmol) in water (30 ml). The mixture was stirred at 60 °C for 5 d. The solid was filtered off and washed with THF to yield the brominated resin.

Azabis(oxazoline) **2** (1.7 mmol) was dissolved in tetrahydrofuran (5 ml), and the solution was cooled to $-78\,^\circ C$. *n*-BuLi (1.17 ml, 1.87 mmol) was added dropwise by syringe and the mixture was allowed to warm up to room temperature. The mixture was stirred for 10 min and was slowly transferred to a suspension of brominated resin (500 mg) in tetrahydrofuran (8 ml). The resulting mixture was heated under reflux for 40 h. The solid was filtered off, washed with tetrahydrofuran, dichloromethane, and methanol, and dried under vacuum at 50 °C overnight to give PS-bound-ligand **7**.

2.3.1. Preparation of **7**–Cu, Method A (complexation)

The PS-bound-ligand **7** (0.1 g) was suspended in a solution of $Cu(OTf)_2$ (36 mg, 0.1 mmol) in methanol (1.7 ml) and shaken for 24 h at room temperature. After this time the solid was filtered off, washed with methanol, and dried under vacuum to yield **7**–Cu.

2.3.2. Preparation of **7**–Cu, Method B (in situ)

α-Ketoester (**3**, 0.5 mmol) and $Cu(OTf)_2$ (14 mg, 0.04 mmol) were dissolved in anhydrous tetrahydrofuran (1 ml) and the solution was added to a suspension of ligand **7** (0.05 mmol of ligand) in anhydrous tetrahydrofuran (2 ml). After 30 min, the Mukaiyama aldol reaction was started by the addition of 1-phenyl-1-(trimethylsilyloxy)ethene (**4**, 0.6 mmol).

2.4. Characterization of immobilized catalysts

Copper analyses were carried out by plasma emission spectroscopy on a Perkin–Elmer Plasma 40 emission spectrometer. Elemental analyses were carried out on a Perkin–Elmer 2400 elemental analyzer. Step-scanned X-ray diffraction patterns of oriented samples were collected at room temperature from 3° in 2θ up to 60°, using a D-Max Rigaku system with a rotating anode. The diffractometer was operated at 40 kV and 80 mA, and the Cu$K\alpha$ radiation was selected using a graphite monochromator. Transmission FTIR spectra of self-supported wafers evacuated ($<10^{-4}$ Torr) at 50 °C were taken with a Nicolet Avatar 360 FTIR spectrophotometer. Surface areas were determined by N_2 adsorption (BET) using a Micromeritics ASAP 2000 apparatus.

2.5. Catalysis

2.5.1. Homogeneous Mukaiyama aldol reactions

A suspension of the corresponding ligand (0.05 mmol) and $Cu(OTf)_2$ (0.05 mmol) in anhydrous dichloromethane (1 ml) was stirred for 15 min under an inert atmosphere. The mixture was filtered through a microfilter and the solvent was evaporated under vacuum. Anhydrous solvent (2 ml), α-ketoester (**3**, 0.5 mmol), and 1-phenyl-1-(trimethylsilyloxy)ethene (**4**, 0.6 mmol) were added by syringe, and the reaction mixture was stirred at room temperature under an inert atmosphere. The consumption of enolsilane was monitored by

GC. The mixture was filtered through a silica pad (2 cm), which was washed with dichloromethane. The resulting solution was concentrated under vacuum, and the mixture was analyzed by HPLC using a Chiralcel OD column, hexane/isopropanol (**3a** 96:4, **3b** and **3c** 97:3), at 1 ml/min. Retention times: **6a** 20.6 min, **5a** 18.9 min; **6b** 8.0 min, **5b** 13.0 min; **6c** 17.1 min, **5c** 18.9 min.

2.5.2. Heterogeneous Mukaiyama aldol reactions

To a solution of α-ketoester (**3**, 0.5 mmol) and 1-phenyl-1-(trimethylsilyloxy)ethene (**4**, 0.6 mmol) in anhydrous solvent (2 ml) was added the solid catalyst (required amount for 0.05 mmol Cu). The resulting suspension was stirred at room temperature under an inert atmosphere. The consumption of enolsilane was monitored by GC. The mixture was filtered, and the filtrate was concentrated under vacuum and analyzed by HPLC. The solid catalyst was washed repeatedly with anhydrous dichloromethane, dried under vacuum, and reused under the same conditions or in a cyclopropanation reaction.

3. Results and discussion

3.1. Homogeneous reactions

Before the immobilization work, it seemed advisable to study the behavior of Box and azaBox ligands in homogeneous Mukaiyama aldol reactions. In addition to the three azaBox ligands (Fig. 1), only the bis(oxazoline)-bearing phenyl substituent (**1a**) was tested in all of the reactions, given the problems encountered in the immobilization of **1c**–Cu complexes [16,22].

The reactions between three different α-ketoesters (**3**) and 1-phenyl-1-(trimethylsilyloxy)ethene (**4**) (Scheme 1) were compared. Three different solvents (tetrahydrofuran, dichloromethane, and hexane) were used to assess the effect reported by Evans et al. [11]. The reactions were conducted at room temperature to facilitate comparison with the heterogeneous cases, thus preventing possible diffusion limitations in the case of solid catalysts. The results obtained with methyl pyruvate (**3a**) are gathered in Table 1. Results in hexane were very similar to those obtained in THF, and they are omitted here for the shake of clarity.

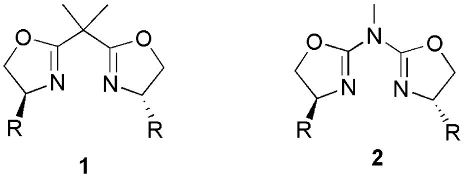
As can be seen, azabis(oxazolines) were efficient ligands for this reaction. As expected, the substituent on the oxazoline ring had a crucial influence on enantioselectivity, with *tert*-butyl (ligand **2c**) giving the best results (up to 91% ee at room temperature), although with an order slightly different than that reported for a related reaction [11], because isopropyl (**2b**) proved better than phenyl (**2a**) (60–69% ee vs 46–59% ee). Similar levels of enantioselection could be obtained with both Box and azaBox ligands (45–64% ee with **1a** and 46–59% ee with **2a**). In agreement with previous results [11], the solvent also had a significant influence on catalytic performance, mainly on enantioselectivity. In general, THF and hexane led to better results than dichloromethane with only one exception, Box ligand **1a**. This general behavior points to a role for solvent polarity in enantioselectivity. The worst results obtained by Evans et al. [11] in hexane were ascribed to the lack of solubility of the complex, but in this case the use of other precursors and higher temperatures could be of help in this regard, allowing the reaction to proceed with similar yields and enantioselectivity. The results obtained with the other two α-ketoesters are given in Tables 2 and 3.

A significant detrimental effect on enantioselectivity has been reported for a closely related reaction [11] after the introduction of a branched chain in position α to the carbonyl group (ketoester **3b**). As shown in Table 2, this is true in most cases. Ligand **2c** led to complexes with very low activity (results not shown), and ligands with phenyl substituents (**1a** and **2a**) suffered a significant drop in enantioselectivity (up to 34%

Table 1
Results obtained in the homogeneous Mukaiyama aldol reactions between methyl pyruvate (**3a**) and 1-phenyl-1-(trimethylsilyloxy)ethene (**4**)[a]

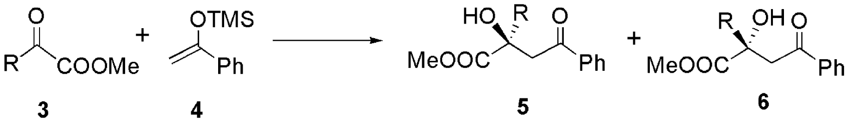
Entry	Ligand	Solvent	t (h)	Yield (%)	ee[b] (%)
1	**1a**	CH_2Cl_2	24	100	64
2		THF	24	76	45
3	**1c**[c]	CH_2Cl_2	24	80	92
4		THF	24	77	99
5	**2a**	CH_2Cl_2	21	80	46
6		THF	18	100	59
7	**2b**	CH_2Cl_2	24	100	60
8		THF	24	100	66
9	**2c**	CH_2Cl_2	24	99	55
10		THF	24	100	91

[a] Reaction conditions: 1 mmol **3**, 1.2 mmol **4**, 10% catalyst, r.t. The catalysts were prepared by treatment of the ligand with $Cu(OTf)_2$ in CH_2Cl_2.
[b] Determined by HPLC with a Chiralcel OD column. **5** is the major product.
[c] Ref. [11], reactions at −78 °C.



a: R = Ph; **b**: R = ^{i}Pr ; **c**: R = ^{t}Bu

Fig. 1. Chiral Box (**1**) and azaBox (**2**) ligands.



a: R= Me; **b**: R= ^{i}Pr; **c**: R= Ph

Scheme 1. Mukaiyama aldol reaction between α-ketoesters (**3**) and 1-phenyl-1-(trimethylsilyloxy)ethene (**4**).

Table 2
Results obtained in the homogeneous Mukaiyama aldol reactions between methyl-3-methyl-2-oxo-butanoate (**3b**) and 1-phenyl-1-(trimethylsilyloxy)ethene (**4**)[a]

Entry	Ligand	Solvent	*t* (h)	Yield (%)	ee[b] (%)
1	**1a**	CH_2Cl_2	24	45	5
2		THF	24	65	27
3	**2a**	CH_2Cl_2	5	100	4
4		THF	18	100	27
5	**2b**	CH_2Cl_2	24	100	46
6		THF	48	20	20

[a] Reaction conditions: 1 mmol **3**, 1.2 mmol **4**, 10% catalyst, r.t. The catalysts were prepared by treatment of the ligand with $Cu(OTf)_2$ in CH_2Cl_2.

[b] Determined by HPLC with a Chiralcel OD column. **5** is tentatively assigned as the major product by mechanistic and chromatographic considerations.

Table 3
Results obtained in the homogeneous Mukaiyama aldol reactions between methyl-2-oxo-2-phenylacetate (**3c**) and 1-phenyl-1-(trimethylsilyloxy)ethene (**4**)[a]

Entry	Ligand	Solvent	*t* (h)	Yield (%)	ee[b] (%)
1	**1a**	CH_2Cl_2	24	100	28
2		THF	24	63	51
3	**2a**	CH_2Cl_2	21	80	41
4		THF	22	100	62
5	**2b**	CH_2Cl_2	36	24	13
6		THF	72	36	38
7	**2c**	THF	48	100	20

[a] Reaction conditions: 1 mmol **3**, 1.2 mmol **4**, 10% catalyst, r.t. The catalysts were prepared by treatment of the ligand with $Cu(OTf)_2$ in CH_2Cl_2.

[b] Determined by HPLC with a Chiralcel OD column. **5** is tentatively assigned as the major product by mechanistic and chromatographic considerations.

ee). The solvent effect followed the general trend, with THF better than dichloromethane and similar to hexane (results not shown).

In view of these results, a phenyl group was introduced in the α-position with respect to the carbonyl group (ketoester **3c**). As shown in Table 3, ligand **2c** again was the most sensitive to the substrate structure. In contrast, the ligand with phenyl groups (**2a**) led to the best results (62–63% ee). With substrate **3c**, the solvent effect was more marked, and hexane was consistently the best solvent (at least as good as THF) for this reaction.

3.2. Heterogeneous reactions

The same catalysts were immobilized onto laponite clay, which has been shown to give better results than other clays in other enantioselective reactions with the same type of catalyst [23]. Laponite is a synthetic and poorly laminated clay with a larger proportion of external exchange sites, which may account for the better accessibility of the catalytic sites. Complexes of chiral ligands with $Cu(OTf)_2$ were immobilized by cation exchange (Method A) using the sodium form of the clay. The complex was dissolved in methanol, a solvent with a sufficiently high dielectric constant to dissolve the outcoming sodium triflate, in this way ensuring a true exchange. Elemental analysis (Table 4) indicated that the amount of exchanged complex depended on the structure of the ligand. Thus the amount of copper was higher for ligands bearing phenyl groups (**1a** and **2a**) compared with aliphatic substituents (**2b** and **2c**). As a consequence of the laponite structure, XRD patterns (Fig. 2) show broad signals, and drawing conclusions from them is difficult. In general, the broad signals indicate partial delamination of the solid, and the increase in the basal spacing indicates that a part of the complex was accommodated within the interlamellar space. The introduction of larger cations led to a reduction in surface area. Infrared spectra showed the presence of the C=N band at 1650–1700 cm^{-1}. The position of this band depended on the ligand; in general, laponites showed two vibrations in this area (Fig. 3). In addition, the presence of the skeletal vibrations (1350–1550 cm^{-1}) is also in agreement with the presence of the complex, with its integrity preserved, after the exchange process.

Table 4
Characterization of the complexes immobilized onto laponite by cation exchange (Method A)

Complex	Cu content (mmol g^{-1})	N:Cu	d_{001} (Å)	Surface area (m^2 g^{-1})
Cu(II)[a]	0.72	–	14.1	290
1a–Cu(II)	0.22	2.30	17.3	225
2a–Cu(II)	0.20	3.30	17.2	232
2b–Cu(II)	0.17	3.35	16.0[b]	219
2c–Cu(II)	0.18	3.15	15.5[b]	214

[a] By exchange with $Cu(OTf)_2$.

[b] Broad signals.

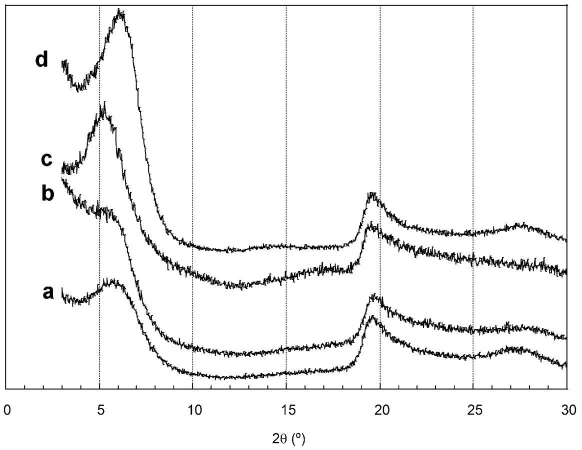


Fig. 2. X-ray diffraction patterns of laponite-supported copper complexes: (a) laponite–**2c**–Cu, (b) laponite–**2b**–Cu, (c) laponite–**1a**–Cu, (d) laponite.

These laponites were tested as catalysts in the Mukaiyama aldol reactions (Scheme 1). The solids containing azaBox ligands were practically inactive, and yields of <5% were obtained in all cases. We considered whether these catalysts were inactive only as Lewis acids or if they demonstrated the same behavior in other reactions as well. In this regard, the clay containing the **2c**–Cu(II) complex was recovered after a Mukaiyama reaction and then reused in the benchmark cyclopropanation reaction between styrene and ethyl diazoacetate (Scheme 2). The mechanism of the cyclopropanation has been described previously [24,25]. The active species was Cu(I), obtained by in situ reduction of Cu(II) by the diazocompound. The

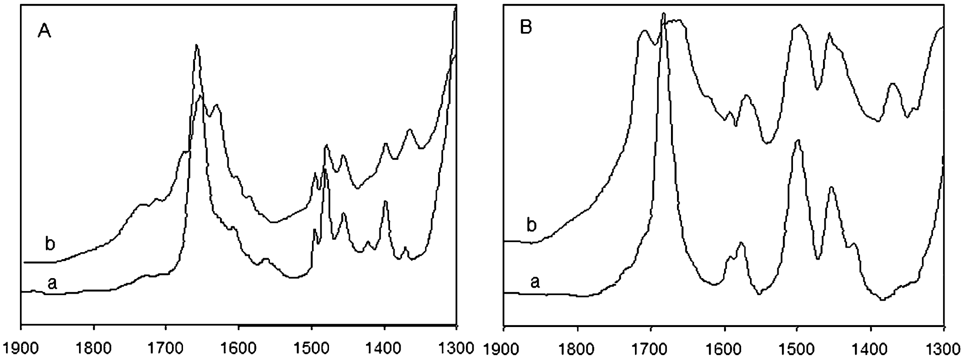
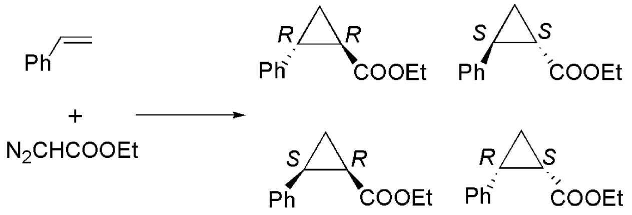


Fig. 3. IR spectra of laponite-supported copper complexes: (A) Box complexes: (a) **1a**–Cu(OTf)$_2$, (b) laponite–**1a**–Cu; (B) azaBox complexes: (a) **2a**–Cu(OTf)$_2$, (b) laponite–**2a**–Cu.



Scheme 2. Cyclopropanation reaction between styrene and ethyl diazoacetate.

limiting step was the formation of a Cu(I)–carbene intermediate that further reacted with the alkene to yield the cyclopropanes. A yield of 82%, with 79% ee for the *trans*-cyclopropanes, was obtained. These results, which are very close to those obtained with the fresh catalyst [5], confirm the accessibility of copper sites, although these were clearly inactive (coordinatively saturated) as Lewis acid sites.

It is well known that Cu(I) is a softer Lewis acid than Cu(II), and thus Cu(I)–oxygen complexes are weaker. Under these conditions, oxygenated compounds may be readily exchanged by the olefin to form the Cu(I)–alkene complex described as the starting point of the catalytic cycle [25]. The oxygenated complexes likely are also catalytically active species, because some of the labile O ligands may be eliminated to form the more stable Box–Cu=CHCOOEt complex.

The laponite containing the **1a**–Cu(II) complex was active in the same reaction (Table 5), demonstrating that the deactivation is reversible depending on the ligand. It was found that, as occurs in solution, the solvent had a crucial influence on the catalytic performance. With methyl pyruvate (**3a**), dichloromethane led to results very similar to those obtained in solution (67% ee vs 64% ee). Moreover, the catalyst could be recovered to give only slightly lower activity and enantioselectivity. The addition of molecular sieves improved both the yield and catalyst recovery without significantly modifying the enantioselectivity (entries 3 and 4).

The role of THF warrants a separate comment. The reaction was slower than in dichloromethane (entry 5), but a significant improvement in enantioselectivity compared with the result in solution was observed (86% ee vs 45% ee). Unfortunately, the catalyst was almost completely deactivated under these conditions. But this deactivation was not permanent; once the catalyst became inactive in THF, it could be reused twice in dichloromethane (entries 7 and 8) with moderate yields and the same enantioselectivity as for the fresh catalyst.

Table 5

Results obtained in Mukaiyama aldol reactions catalyzed by 10% (molar) of **1a**–Cu(II)–laponite prepared by Method A (cation exchange)[a]

Entry	α-Keto-ester	Run	Solvent	t (h)	Yield (%)	ee[b] (%)	Cu[c] (mmol g^{-1})
1	**3a**	1	CH_2Cl_2	48	100	67	
2		2	CH_2Cl_2	48	72	58	0.14
3		1	CH_2Cl_2[d]	24	100	61	
4		2	CH_2Cl_2[d]	24	82	62	0.12
5		1	THF	72	73	86	
6		2	THF	72	8	65	
7		3	CH_2Cl_2	24	43	59	
8		4	CH_2Cl_2	24	46	62	
9		5	CH_2Cl_2	24	4	60	0.11
10	**3b**	1	CH_2Cl_2	144	47	20	0.20
11		1	THF	576	21	9	0.19
12		1	Hexane	288	15	24	0.18
13	**3c**	1	CH_2Cl_2	120	71	14	
14		2	CH_2Cl_2	120	73	16	0.21
15		1	THF	240	0	–	0.21
16		1	Hexane	264	12	59	
17		2	Hexane	264	19	63	0.22

[a] Reaction conditions: 1 mmol **3**, 1.2 mmol **4**, 10% catalyst, r.t.

[b] Determined by HPLC with a Chiralcel OD column.

[c] Analysis of the catalyst after the corresponding runs.

[d] 4 Å molecular sieves were added to the reaction mixture.

The use of other α-ketoesters in solution gave rise to lower yields and ee values (entries 10–16). Catalyst deactivation can be due mainly to two factors: leaching and poisoning. Filtration experiments under reaction conditions indicated that no leaching of active species occurred, and that the reaction took place under truly heterogeneous conditions. As shown by the results given in Table 5, the recovered solids had a lower overall copper content, but during the reaction, the adsorption of organic compounds increased the weight of the solid catalyst; this is considered to be responsible, at least in part, for the decrease in the copper content per unit weight. We can distinguish at least four types of deactivation for Mukaiyama aldol reaction: two ab initio deactivations, either in all of the solvents (immobilized azaBox–Cu) or only in THF (immobilized Box–Cu), and two deactivations for reuse, one partial (only in THF) and other complete (in all of the solvents). Any type of coordina-

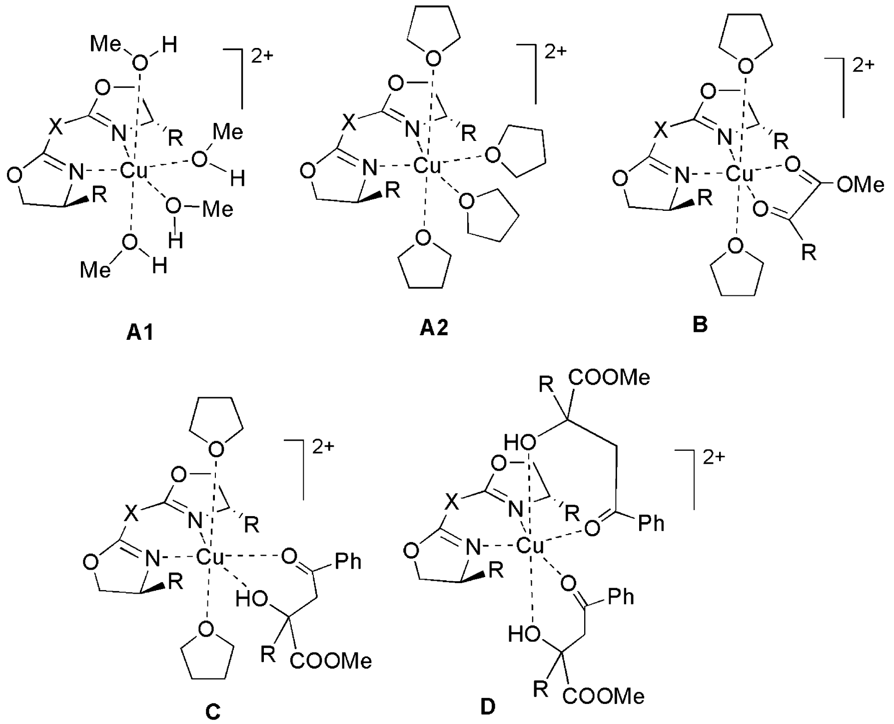


Fig. 4. Possible species of Mukaiyama aldol reaction in THF.

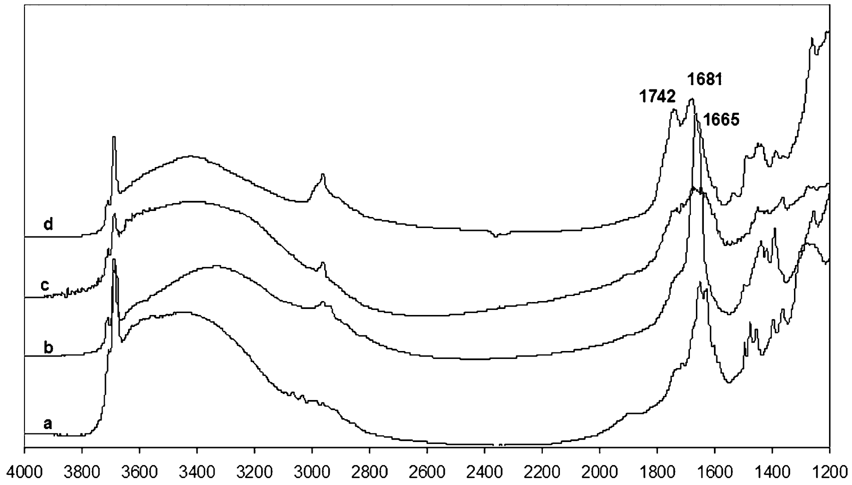


Fig. 5. IR spectra of used laponite-supported **1a**–Cu complexes (Table 5): (a) freshly prepared laponite–**1a**–Cu, (b) catalyst after two runs in CH_2Cl_2 (entry 2), (c) catalyst after two runs in THF (entry 6), (d) catalyst after two runs in hexane (low activity).

tive deactivation must be due to a complete saturation of copper, leading to a quasi-octahedral coordination. The proposed species are depicted in Fig. 4. The intermediate for Mukaiyama aldol reaction in THF might be species B, which would be formed by ligand substitution from species A1 or A2. A1 would be the species formed in the exchange process by solvation with methanol and would be responsible for ab initio deactivation of azaBox–Cu (X = NMe) in all of the solvents. When X = CMe_2, the complex could exchange the methanol molecules in CH_2Cl_2, but in THF it led to species A2, which was inactive due to the left shift of the equilibrium A2 $\rightleftharpoons$ B by the great excess of solvent. Like most of the Lewis acid-catalyzed reactions, Mukaiyama aldol must be product-inhibited. Species with one or two molecules of product coordinated (C and D) would be responsible for the final deactivation. Species C, or analogues, may be active under some conditions (CH_2Cl_2), but the complete deactivation may be due to species of type D.

To gain insight into the nature of adsorbed species, the recovered solids were analyzed by IR spectroscopy; the spectra are shown in Fig. 5. The solid used in CH_2Cl_2 (spectrum b) shows only one band corresponding to the C=N vibration at 1665 cm^{-1}, indicating that only one species is present. The zone between 1300 and 1550 cm^{-1} presents more bands, as does the zone around 3000 cm^{-1}, confirming the probable adsorption of solvent. The solid used in THF (spectrum c) shows a very large band between 1600 and 1800 cm^{-1}, which seems to

Table 6
Results obtained in Mukaiyama aldol reactions catalyzed by 5% (molar) of catalysts immobilized on laponite by Method B (adsorption)[a]

Entry	Ligand	α-Keto-ester	Run	Solvent	*t* (h)	Yield (%)	ee[b] (%)	Cu[c] (mmol g^{-1})
1	**1a**	**3a**	1	CH_2Cl_2	48	35	49	
2			2	CH_2Cl_2	48	9	59	0.09
3			1	THF	240	0	–	0.08
4			1	Hexane	144	38	45	
5			2	Hexane	144	0	–	0.07
6	**2c**	**3a**	1	CH_2Cl_2	24	53	76	
7			2	CH_2Cl_2	24	5	65	0.07
8			1	THF	240	0	–	0.07
9			1	Hexane	144	0	–	0.07
10		**3b**	1	CH_2Cl_2	240	0	–	0.08

[a] Reaction conditions: 1 mmol **3**, 1.2 mmol **4**, 5% catalyst, r.t.
[b] Determined by HPLC with a Chiralcel OD column.
[c] Analysis of the catalyst after the corresponding runs.

indicate adsorption of products. The presence of two carbonyl groups in the molecule (ketone and ester groups) accounts for the bands at around 1740 cm^{-1}. This effect is even more evident in the case of a catalyst used in hexane (spectrum d). This solvent is even worse than THF in the decomplexation of products, and the band at 1742 cm^{-1} is clear.

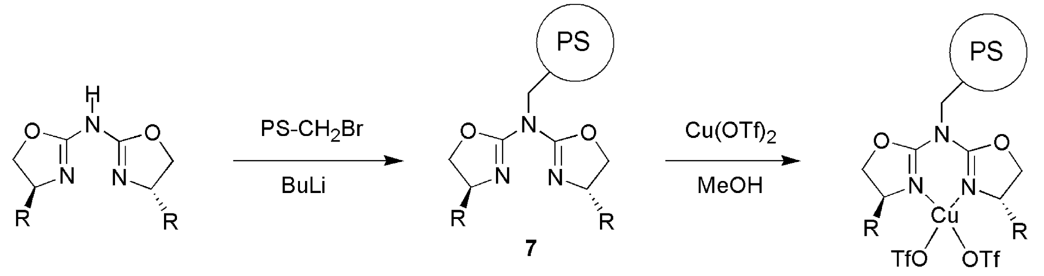
The differences between Box and azaBox may be due to the lower Lewis acidity of copper coordinated to the more donating azaBox [5]. The effect is more important when the triflate anion is replaced by the more basic anionic centers of the clay, reducing the acidity of the copper cations even further. This counterion effect has been observed in other reactions promoted by the same catalysts [26] and it is also related to a solvent effect [27] through the strength of the ion pairing. The lower acidity makes catalytic centers in the clay more sensitive to poisoning by Lewis bases, which may be one reason for the differences between dichloromethane and THF.

In this respect, it is interesting to keep in mind that catalysts were prepared by cation exchange using methanol, a coordinating solvent, which infers that the method used to obtain the catalyst may have affected the catalyst's activity. To investigate this possibility, some catalysts were immobilized onto the same clay using a Method B, in which a solution of the copper complex in dichloromethane was stirred with a suspension of the clay and then the solvent was evaporated under vacuum. This method is in fact an adsorption of the complex on the clay surface. The existence of an interaction (probably of an electrostatic nature) between the support and the complex was confirmed by the lack of solubility in dichloromethane once the complex was immobilized. These solids contained 0.10 mmol Cu g^{-1}, the N:Cu ratios corresponded to the values expected, and the IR spectra exhibited the bands of the ligand, including that corresponding to the C=N vibration. These clays were tested as catalysts in the Mukaiyama aldol reactions (Scheme 1); the results are given in Table 6.

In the case of ligand **1a**, this strategy does not represent any advantage over the conventional cation exchange (entries 1–4). However, with the azaBox ligand **2c**, the catalyst was active in dichloromethane, leading to 76% ee in the reaction of methyl pyruvate (**3a**, entry 6)—an enantioselectivity better than that obtained with the same ligand and solvent in solution (Table 1, entry 9). This result demonstrates the role of methanol in the ab initio deactivation of azaBox–Cu complexes when immobilized by cation exchange. The catalyst became inactive for this reaction after the first batch, but this was not due to catalyst leaching. In fact, the solid recovered from the second reaction was active as a catalyst in the benchmark cyclopropanation (Scheme 2) and led to a yield of 42% and an ee of 82% in the *trans*-cyclopropanes, not far from the values described for the same reaction promoted by the fresh clay prepared by the conventional exchange strategy [5].

It can be concluded that electrostatic interaction with anionic supports is not the best strategy for the immobilization of catalysts for use as Lewis acids in Mukaiyama aldol reactions. Although results can be improved with the correct choice of exchange method and solvent, the greater coordination ability of the solid anion compared with soluble ones such as triflate, reduces the Lewis acidity and makes stronger ligands unsuitable. Problems related to electrostatic immobilization of chiral Lewis acids have been reported for other reactions, such as the Diels–Alder reaction [28].

In view of this disappointing conclusion, and to complete this comparative study, we turned our attention toward the covalent immobilization of azaBox ligands, given that the use of covalently bonded Box in Mukaiyama aldol [12] and other Lewis acid-promoted reactions has been described previously [2]. Furthermore, azaBox–copper complexes bonded to a Merrifield resin have proven to be the best catalysts described to date for enantioselective cyclopropanation reactions [17]. Ligands were covalently bonded to bromomethylated polystyrene divinylbenzene, obtained from a commercial Merrifield resin as described



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a: R= Ph; **b**: R= ^{i}Pr; **c**: R= ^{t}Bu

Scheme 3. Covalent immobilization of azaBox–Cu complexes on polystyrene–divinylbenzene.

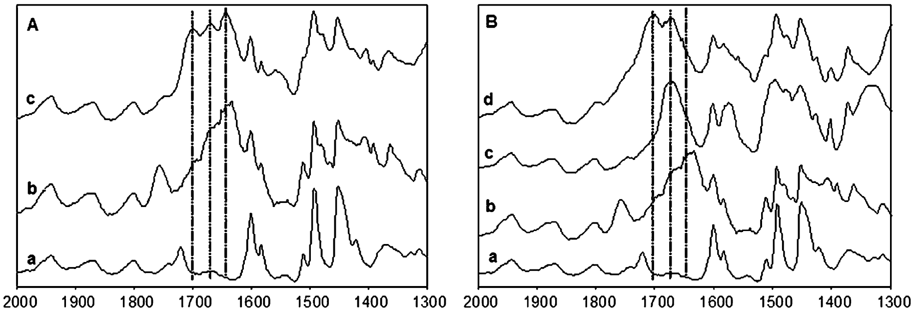

Fig. 6. IR spectra of solids based on Merrifield resins. (A) Complex prepared by Method A (complexation): (a) Merrifield resin, (b) **7c**, (c) **7c**–Cu. (B) Complex prepared by Method B (in situ): (a) Merrifield resin, (b) **7c**, (c) **7c**–Cu, (d) **7c**–Cu used in the Mukaiyama aldol reaction.

previously [17]. From these ligands, catalysts were obtained by treatment with $Cu(OTf)_2$ dissolved in methanol (Method A, Scheme 3), and the complexes were isolated and characterized.

IR spectra of the bonded ligands showed a wide band in the 1600–1680 cm^{-1} range (Fig. 6A, spectrum b), corresponding to the C=N vibration. The skeletal vibrations were partially masked by the bands of the support (spectrum a). On complexation in methanol (Fig. 6A, spectrum c), several bands appeared. The band at 1642 cm^{-1} may be due to noncomplexes ligand, whereas the band at 1672 cm^{-1} is in agreement with complexes azaBox. The band at 1700 cm^{-1} is more difficult to assign. The polymers obtained in this way did not show any catalytic activity in the Mukaiyama aldol reactions, despite their excellent behavior in cyclopropanations [17]. This lack of catalytic activity may again be due to the use of methanol during preparation of the catalyst, leading to inactive grafted species A1 (Fig. 4), and are in agreement with the same lack of activity of laponite-immobilized azaBox–Cu complexes.

The low solubility of copper triflate in less polar solvents precludes their use, unless an additional ligand is added. Method B was then applied to generate the complex under the reaction conditions (in situ method). The required amount of $Cu(OTf)_2$ was dissolved in the solvent selected for the reaction (dichloromethane or THF), along with the corresponding amount of α-ketoester (**3**), which acted as a ligand able to solubilize the copper salt. The polymeric ligand (**7**) was added, and the suspension was left to equilibrate for a certain time to allow the formation of the azaBox–Cu complex, which was used without separation from this medium. Finally, the enolsilane (**4**) was added to start the reaction. Samples of the supported complexes prepared by this method were filtered and washed for analysis and characterization by IR. The copper content was 0.45 $mmol\,g^{-1}$ for **7a**–Cu, 0.48 $mmol\,g^{-1}$ for **7b**–Cu, and 0.54 $mmol\,g^{-1}$ for **7c**–Cu. In this case, complexation with Cu produced only a narrower IR band at 1675 cm^{-1} (Fig. 6B, spectrum c), demonstrating a smaller variety of species.

The catalysis results given in Table 7 show that these were the most active catalysts for Mukaiyama aldol reactions among the immobilized catalysts containing azaBox ligands. They promoted the reaction even in THF (entries 2, 6, and 12) and gave enantioselectivities only slightly lower than those obtained in solution with the same solvents. Catalyst recovery depends on the ligand, so whereas polymers **7a** and **7b** were recovered with the same results (entries 2–7), recovered catalyst coming from **7c** led to a slightly lower yield but with the same enantioselectivity (entries 10–13). Although the copper content was lower in used catalysts than in fresh catalysts, the adsorption of byproducts may have introduced variations in weight, meaning that the analyses are not comparable. Furthermore, filtration experiments demonstrated no leaching of active species. IR spectra of recovered catalyst (Fig. 6B, spectrum d) show a new band at around 1700 cm^{-1} together with the expected band at 1675 cm^{-1} attributed to the C=N vibration. The wavenumbers were not as high as those for laponite-supported catalysts, but the irreversible deactivation of this sample and the presence of this additional band seem to indicate again the strong complexation of copper with some of the reaction products. In fact, the catalyst arising from ligand **7c** was tested after the second reaction (entries 11 and 13) in the aforementioned cyclopropanation (Scheme 2), and in both cases, high yields and enantioselectivities (almost identical to those described for the fresh catalyst [3]) were obtained (98% yield and 95% ee in *trans*-cyclopropanes for the catalyst recovered from entry 11 vs 99% yield and 95% ee in trans cyclopropanes for the catalyst recovered from entry 13). The reduction to the softer

Table 7
Results obtained in Mukaiyama aldol reactions catalyzed by 10% (molar) of polymer-supported azaBox–Cu complexes prepared by Method B (in situ)[a]

Entry	Ligand	α-Keto-ester	Run	Solvent	t (h)	Yield (%)	ee[b] (%)	Cu[c] ($mmol\,g^{-1}$)
1	**7a**	**3a**	1	CH_2Cl_2	24	33	32	0.39
2			1	THF	48	51	39	
3			2	THF	48	51	37	0.43
4	**7b**	**3a**	1	CH_2Cl_2	24	49	51	
5			2	CH_2Cl_2	24	47	55	0.47
6			1	THF	48	67	62	
7			2	THF	48	62	62	0.42
8		**3c**	1	CH_2Cl_2	120	28	21	0.45
9			1	THF	240	3	25	0.33
10	**7c**	**3a**	1	CH_2Cl_2	24	38	71	
11			2	CH_2Cl_2	24	10	71	0.39
12			1	THF	48	44	84	
13			2	THF	48	25	85	0.42
14		**3b**	1	CH_2Cl_2	120	26	30	0.48
15		**3c**	1	CH_2Cl_2	120	16	31	0.48
16			1	THF	240	2	38	0.46

[a] Reaction conditions: 1 mmol **3**, 1.2 mmol **4**, 5% catalyst, r.t.
[b] Determined by HPLC with a Chiralcel OD column.
[c] Analysis of the catalyst after the corresponding runs.

Cu(I) complexes occurred, and the poisoning oxygenated ligands were eliminated to form the Cu(I)–carbene intermediate, as discussed previously for laponite-immobilized catalysts.

These results again demonstrate that deactivation for Lewis acid-catalyzed reactions is specific for this kind of mechanism, but deactivated catalysts can be used in a reaction occurring through a different mechanism and with different steric and electronic requirements. This system would allow prolongation of the useful life of the immobilized catalysts.

4. Conclusion

It can be concluded that covalent bonding is better than electrostatic interaction for immobilizing chiral Lewis acids. Metal leaching can be avoided by using strongly coordinating ligands, but these ligands reduce Lewis acidity and catalytic activity and do not solve the problem of catalyst poisoning due to the coordination to the active center of coordinating solvents, reagents, products, or byproducts. In the case of inorganic solid catalysts, elimination of adsorbed byproducts (or coke) is usually carried out by calcination, a strategy that cannot be used with catalysts containing organic ligands. Instead, recovered solids can be reused in a reaction with a completely different mechanism (i.e., one not requiring acid centers), exemplified in this work by the cyclopropanation of styrene with ethyl diazoacetate. In this way, the utility of the solid catalysts is increased, and they can be considered truly multipurpose catalysts.

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