DOI: 10.1002/adsc.200606121

Multipurpose box- and azabox-Based Immobilized Chiral Catalysts

José M. Fraile,[a] Ignacio Pérez,[a] José A. Mayoral,[a,*] and Oliver Reiser[b]

[a] Departamento de Química Orgánica, Instituto de Ciencia de Materiales de Aragón and Instituto Universitario de Catálisis Homogénea, Facultad de Ciencias, Universidad de Zaragoza – C.S.I.C., 50009 Zaragoza, Spain
Fax: (+34)-976-762-077; e-mail: mayoral@unizar.es
[b] Institut für Organische Chemie, Universität Regensburg, Universitätsstr. 31, 93053 Regensburg, Germany

Received: March 21, 2006; Accepted: June 13, 2006

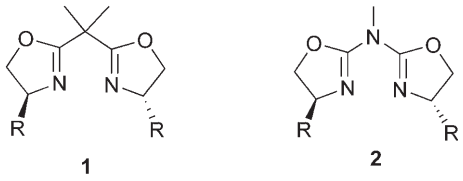
Abstract: Azabis(oxazolines) can be used as chiral ligands in the copper-catalyzed enantioselective Mukaiyama aldol reaction. When supported on solids, azabis(oxazoline)-copper complexes are more easily deactivated than their analogous bis(oxazoline)-copper complexes, and are not compatible with the use of coordinating solvents in the method of preparation. The performance of the immobilized catalysts (up to 86% *ee*) depends on the support and the reaction solvent, with some positive effect on enantioselectivity due to surface effects. The deactivation is not irreversible and the deactivated catalysts show excellent performance in the cyclopropanation reaction, providing added value to the supported multipurpose catalysts.

Keywords: asymmetric catalysis; azabis(oxazolines); cyclopropanation; Mukaiyama aldol; supported catalysts

Introduction

The use of heterogeneous catalysts in enantioselective reactions is an area of increasing interest,[1] which is mainly due to the practical advantage of easy separation of catalyst and products by simple filtration. This significant advantage makes slight reductions in activity or enantioselectivity acceptable. However, this advantage is frequently not sufficient to justify the use of immobilized catalysts when their preparation requires considerable synthetic effort. Although recovery and reuse have been shown to increase the effective TON of the immobilized catalysts, the search for other "added value" for these systems seems to be necessary to increase the acceptance and applicability of immobilized chiral catalysts. Among these 'added value' aspects we can consider three as particularly important aims; (i) a synthetic effort similar to that required to prepare homogeneous catalysts, (ii) improved results in comparison with the homogeneous phase and (iii) the preparation of multipurpose catalysts. The latter two factors are ambitious goals and will require a deep understanding of the immobilized systems.

Regarding the preparation of multipurpose catalysts, bis(oxazoline) ligands (box, **1**; Figure 1) appear to be suitable candidates given that their metal complexes are efficient catalysts for a wide variety of enantioselective reactions.[2] In view of this interest, several authors have attempted the immobilization of chiral box-metal complexes by different strategies.[3]



a: R = Ph; **b**: R = *t*-Bu; **c**: R = *i*-Pr

Figure 1. Chiral box (**1**) and azabox (**2**) ligands.

The formation of covalent bonds between the support and the chiral ligand is the most common immobilization strategy,[4] and this has been applied to bis(oxazolines) using different methods. The polymerization of box substituted with two[5,6] or only one[7,8] vinylbenzyl group has been described. This general strategy has very recently been applied to inorganic supports.[9] Both organic polymers[10] and silicas[11] have been used to anchor bis(oxazolines), although the functionalization of the box is not straightforward.

A simpler strategy involves immobilization through electrostatic interactions. Although less widely used than the covalent strategy,[12] this methodology was the first system employed to immobilize box-copper complexes.[13] Indeed, this approach proved to be useless for Lewis acid-promoted enantioselective reactions.[14]

Azabis(oxazolines) (azabox, **2**) are structural analogues of bis(oxazolines) and have shown excellent behavior as chiral ligands in different asymmetric reactions in the homogeneous phase.[15] The presence of a nitrogen atom instead of a carbon in the central bridge leads to higher stability, improving the efficiency in different immobilized systems,[16] and is advantageous as far as grafting on Merrifield resins is concerned. This method was used to prepare the best heterogeneous catalyst for enantioselective cyclopropanation reactions.[17] This system was the best not only due to the highest selectivity but also to the almost complete chemoselectivity.

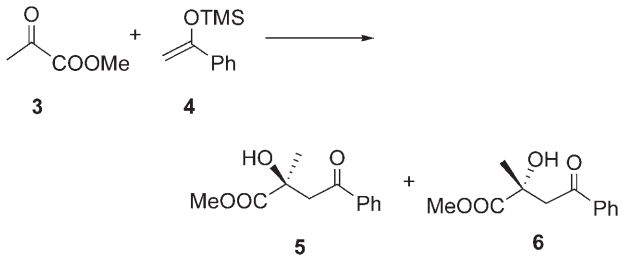
The next objective is to extend these easier methodologies to other enantioselective reactions. The Mukaiyama aldol reaction is probably one of the most useful reactions for C–C bond formation in an enantioselective manner.[18] Bis(oxazoline)-copper complexes lead to excellent results in the homogeneous phase.[19,20] This method has even been adapted to biphasic conditions, either on a solid support[7] or with water-soluble polymeric ligands.[21] However, both of these strategies require considerable synthetic effort to modify the chiral ligands. Furthermore, these procedures were not problem-free. The polymerized catalyst needed the presence of additional molecular sieves[7] and, moreover, additional fresh MS and copper salt were necessary after each cycle. The water-soluble catalysts showed poor recyclability[11] and the copper salt was leached, leading to recovery of the polymeric ligand alone. In this paper we present our efforts to use easily immobilized chiral bis(oxazoline)- and azabis(oxazoline)-copper complexes in enantioselective Mukaiyama aldol reactions.

Results and Discussion

Homogeneous Mukaiyama Aldol Reactions with Azabis(oxazoline)-Cu(OTf)$_2$ Catalysts

Previous to the immobilization work, it seemed advisable to study the behavior of azabis(oxazoline) ligands in homogeneous Mukaiyama aldol reactions. In addition to the three azabis(oxazoline) ligands (Figure 1), only the bis(oxazoline) bearing phenyl substituents (**1a**) was tested for the sake of comparison, given the problems encountered in the immobilization of **1b**-Cu complexes.[13]

The reaction between methyl pyruvate (**3**) and 1-phenyl-1-(trimethylsilyloxy)ethene (**4**) (Scheme 1) was chosen as the test reaction. Three different solvents (tetrahydrofuran, dichloromethane and hexane) were used in order to assess the effect reported by Evans et al.[20] and the surface effect observed in the case of cyclopropanation with catalysts immobilized by electrostatic interactions on Laponite.[22] 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.



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

The results obtained in these reactions are gathered in Table 1. The catalytic activity is not noticeably modified by the chiral ligand and high conversions are obtained after a 24 h period. As far as enantioselectivities are concerned, bis(oxazoline) **1a** led to moderate results (41–64% *ee*), in agreement with the results reported for the trimethylsilylketene acetal of *tert*-butyl thioacetate,[20] although in our case the reaction was carried out at room temperature. It is noteworthy that in this case the use of dichloromethane is more efficient than THF or hexane, a situation in contrast with Evans' results on using ligand **1b**.

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

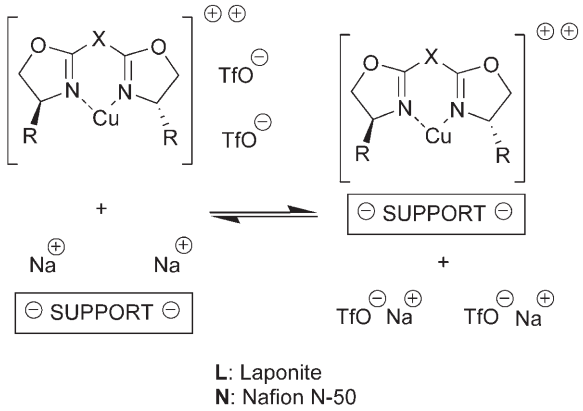
Entry	Ligand	Solvent	t [h]	Yield [%]	% *ee*[b]
1	**1a**	THF	24	76	45
2		CH_2Cl_2	24	100	64
3		Hexane	24	100	41
4	**2a**	THF	18	100	59
5		CH_2Cl_2	21	80	46
6		Hexane	24	72	49
7	**2b**	THF	24	100	91
8		CH_2Cl_2	24	100	55
9		Hexane	24	100	86
10	**2c**	THF	24	100	66
11		CH_2Cl_2	24	99	60
12		Hexane	48	100	69

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

The analogous azabis(oxazoline) **2a** gave a slightly less active catalyst, with enantioselectivities in the same range (46–59% *ee*). In this case, however, THF is the most efficient solvent. The results are slightly better when an isopropyl group is present in the aza-

bis(oxazoline) ligand (**2c**) and 69% *ee* is obtained in hexane, clearly better than the 23% *ee* reported for the silylketene acetal.[20] As expected, the best azabis(oxazoline) ligand is that bearing *tert*-butyl groups (**2b**). THF is again the best solvent (91% *ee*), with the use of hexane leading to only slightly lower enantioselectivity. In this case dichloromethane is clearly less efficient and only 55% *ee* was obtained. If we compare these results with those obtained with silylketene acetal,[20] it can seen that the solvent effect is highly dependent on the silylenol ether used. It is important to note the excellent results obtained with this azabox ligand, which was used in this reaction for the first time.



Scheme 2. Immobilization by electrostatic interactions.

Heterogeneous Catalysts: Preparation, Characterization, and Catalytic Tests

Given the excellent results obtained in the cyclopropanation reactions, we initially prepared the heterogeneous catalysts following the methods reported in previous papers. These methods for electrostatic and covalent immobilization are denoted by the letter A.

The copper complexes of ligands **1a**, **2a**, **2b** and **2c** were prepared with $Cu(OTf)_2$ in dichloromethane, and this solution was filtered to remove any non-complexed $Cu(OTf)_2$ particles. The complexes were dissolved in methanol to carry out the cationic exchange (Scheme 2) onto Laponite (**L**) and Nafion N50 (**N**) according to the standard method used previously for cyclopropanation catalysts.[13,15] In each case the mixture was stirred for 24 h at room temperature and the exchanged solids were filtered off, washed with dichloromethane and dried under vacuum.

These solids were characterized by copper analysis, X-ray diffraction (Laponite-based catalysts) and IR spectroscopy. Laponite-based catalysts contain amounts of copper in the range 0.13–0.23 mmol/g (**L1a** 0.23, **L2a** 0.15, **L2b** 0.18, **L2c** 0.17), which is consistent with our previous results. The reduced intensity of the (001) diffraction line in the X-ray diffraction patterns indicates partial delamination of the layered structure of the clay. This line is slightly shifted to smaller angles, representing partial intercalation of the complexes between the clay layers. This intercalation is more marked in **L1a**, with basal spacing of 17.2 Å (*cf.* 13.8 Å in Cu-Laponite without a chiral ligand), than in the other solids (basal spacing around 15.4 Å). This result is also in agreement with the higher copper content in **L1a**. Nafion-based catalysts show a much higher copper loading, ranging between 0.66 mmol/g in **N1a** and 0.91 mmol/g in **N2c**.

The IR spectra of the supported complexes are shown in Figure 2. The most prominent band is that of the C=N group, which appears in the copper complex at about 1650–1690 cm^{-1}. The Laponite-immobilized complexes generally present a double band in that zone. The band at 1657 cm^{-1} in Cu-**1a** appears in **L1a** as two bands at 1653 and 1631 cm^{-1}. The same band in Cu-**2a** appears at 1682 cm^{-1}, whereas two bands at 1707 and 1668 cm^{-1} are present in the spectrum of **L2a**. The presence of different sites on the solids may account for these differences. Characteris-

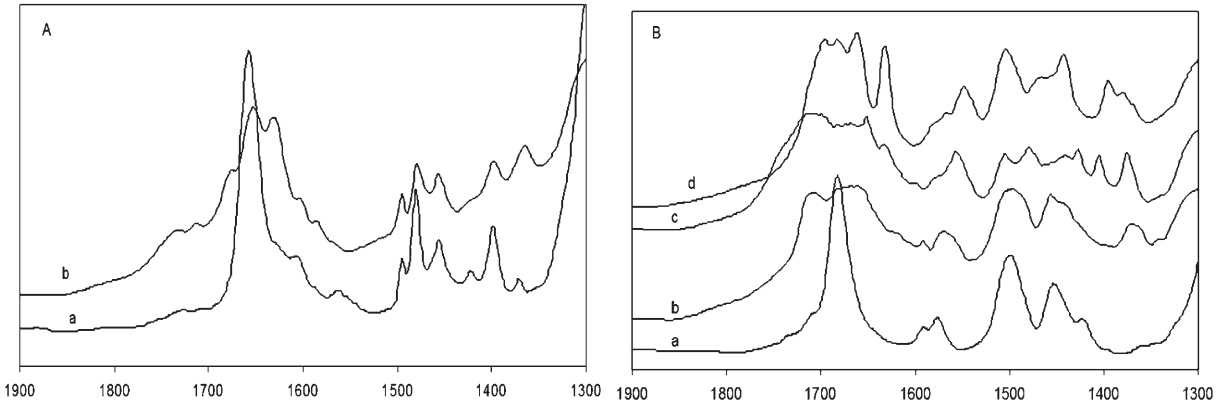
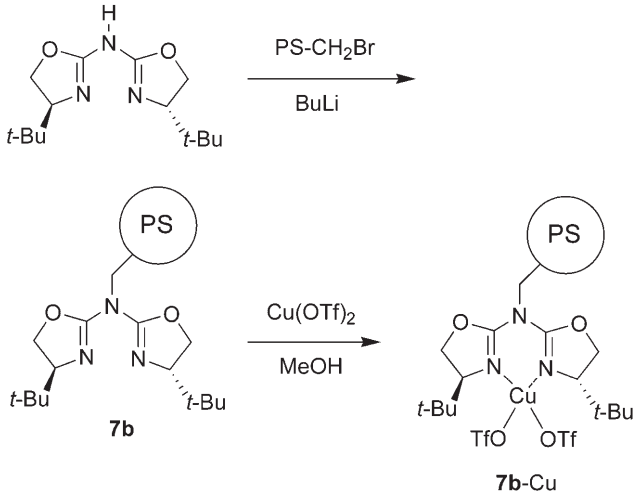


Figure 2. IR spectra of laponite supported copper complexes: A) box complexes: a) **1a**-$Cu(OTf)_2$, b) **L1a**; B) azabox complexes: a) **2a**-$Cu(OTf)_2$, b) **L2a**, c) **L2b** d) **L2c**.

tic bands in the 1600–1350 cm^{-1} region are present in the solids (Figure 2), demonstrating the integrity of the copper complexes.

Covalent immobilization onto a commercially available Merrifield resin was carried out as described elsewhere.[17] Conversion of the chloromethyl to the more reactive bromomethyl group was readily achieved by treatment with $NaBr/NBu_4Br$. Subsequent coupling of the brominated resin with deprotonated azabis(oxazoline) in THF under reflux (Scheme 3) proceeded cleanly to give **7b**. Complexation with $Cu(OTf)_2$ was carried out in methanol, and the solid catalyst was thoroughly washed with the same solvent and dried under vacuum.



Scheme 3. Covalent immobilization on polystyrene-divinylbenzene resin (Merrifield's resin).

The copper content of this resin is high and is in the range 0.75–0.90 mmol/g depending on the batch of resin. The presence of the azabox ligand in **7b** was also confirmed by IR.

Solid catalysts prepared by method A were tested in the Mukaiyama aldol reaction between methyl pyruvate (**3**) and 1-phenyl-1-(trimethylsilyloxy)ethene (**4**) (Scheme 1). The results are gathered in Table 2.

The first conclusion that can be drawn is that the heterogeneous catalysts are noticeably less active than the analogous homogeneous ones. In spite of this, **L1a** (entries 1–5) gives rise to high yields in THF (73%) and dichloromethane (quantitative), although it has a poor activity in hexane. The use of Laponite as the solid support improves significantly the enantioselectivity of the process. Remarkably, the reaction in THF displays 86% *ee*, which is much higher than the value (45% *ee*) obtained in solution, and a similar result is observed on using hexane, 79% *ee vs.* 41% *ee* in solution. In contrast, the enantioselectivity in dichloromethane does not change perceptibly. It is difficult to explain this behavior in the Laponite-immobilized catalysts but it could be due to a surface effect, as shown in the case of cyclopropanation.[22] However, this effect was observed in solvents with low dielectric constants, because of the increase in the ion-pair interaction between support and complex. The effect observed in THF seems to indicate the superimposition of the unexplained solvent effect in solution with the surface effect of the solid catalyst. In this case immobilization gave rise to a better enantioselectivity, which constitutes added value over simple separation, especially given the ease of preparation of the solid catalyst.

Table 2. Results obtained in the Mukaiyama aldol reactions between methyl pyruvate (**3**) and 1-phenyl-1-(trimethylsilyloxy)ethene (**4**) promoted by solids prepared by method A.[a]

Entry	Catalyst	Solvent	Run	*t* [h]	Yield [%]	% *ee*[b]
1	**L1a**	THF	1	72	73	86
2			2	72	8	65
3		CH_2Cl_2	1	48	100	67
4			2	48	72	58
5		hexane	1	168	27	79
6	**L2a**	any	1	24	<5	n.d.
7	**L2b**	any	1	24	<5	n.d.
8	**L2c**	any	1	24	<5	n.d.
9	**N1a**	THF	1	312	31	35
10			2	600	9	18
11		CH_2Cl_2	1	96	100	44
12			2	120	74	43
13		Hexane	1	144	5	30
14	**7b**-Cu	any	1	>144	<5	n.d.
15[c]		CH_2Cl_2	1	24	96	97, 92

[a] *Reaction conditions:* 1 mmol **3**, 1.2 mmol **4**, 10% catalyst, room temperature.
[b] Determined by HPLC with a Chiralcel OD column; **5** is the major product.
[c] Results of the cyclopropanation reaction between styrene and ethyl diazoacetate (Scheme 4). Enantioselectivities are for *trans* and *cis* isomers respectively (*trans*/*cis* = 70:30).

With regard to recoverability, the catalyst used in THF was almost completely deactivated after the first run (entry 2), whereas the catalyst used in dichloromethane maintained a significant part of its activity (entry 4) although it gave slightly lower enantioselectivity. The analysis of the used catalysts (0.18 mmol/g) showed a partial loss of copper. From the mechanism of the copper catalyzed Mukaiyama aldol reaction[18] an intermediate copper aldolate is formed, and in the case of catalysts prepared by cationic exchange, a silylated Laponite must be generated instead of the trimethylsilyl triflate in solution. One possible source of leaching might be the formation of a copper bis(aldolate), that would remain in solution if the solid were less efficient than triflate in the silylation step.

However, this loss of around 20% of the initial copper does not account for a complete deactivation (entry 2), that may be due to strong complexation of copper with products or by-products.

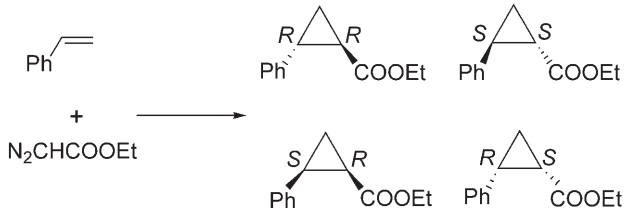
When the azabis(oxazoline)-based catalysts were tested (entries 6–8), the results were highly disappointing. Reactions did not take place irrespective of the solvent used and it appeared as if the freshly prepared catalysts were deactivated in some way.

In view of these results, Nafion N-50 was only used with bis(oxazoline) **1a** (entries 9–13). **N1a** is even less active than **L1a**, in spite of the similar natures of Nafion and triflate. The best solvent in this case was dichloromethane, with total conversion and 44% *ee*. As can be seen, the use of a non-layered support precludes any surface effect, and the enantioselectivities are slightly lower than those obtained in solution: 35% vs. 45% *ee* in THF, 44% vs. 64% *ee* in dichloromethane. This improved behavior of **N1a** in dichloromethane is complemented by better recoverability (entry 12), a situation in agreement with the behavior of **L1a**.

As can be seen, the results with catalysts immobilized by electrostatic interactions are highly dependent on several interrelated factors: support, solvent and chiral ligand.

The polymeric ligand **7b** was used in the same reaction (entry 14) but, as with the exchanged catalysts, it did not show any significant catalytic activity.

These results in Mukaiyama aldol reaction contrasted with the high performance of the same batches of solids in the cyclopropanation reaction between styrene and ethyl diazoacetate (Scheme 4),[16] for example, in the case of **7b** (entry 15). This difference in behavior may arise from the different mechanisms and active species' in the two processes. The presence of methanol as a solvent in the immobilization of azabox-copper complexes may poison the catalysts if methyl pyruvate were not able to displace methanol molecules from the coordination sphere of copper.



Scheme 4. Cyclopropanation reaction between styrene and ethyl diazoacetate.

Heterogeneous Catalysts Prepared in the Absence of Methanol (Method B)

In view of this hypothesis, we developed alternative methods (denoted by the letter B) to prepare both types of immobilized catalyst in the absence of coordinating solvents.

The **2b**-$Cu(OTf)_2$ complex was dissolved in dichloromethane and the Laponite support was suspended in the same solution. After evaporation of the solvent, the complex was immobilized on the Laponite surface. The nature of the complex-support interaction was confirmed by the lack of solubility of the immobilized complex in dichloromethane, and the non-detectable leaching after one cyclopropanation reaction. This solid was used in the Mukaiyama aldol reaction under the same conditions as the solids prepared by method A.

In the case of the Merrifield-based catalyst, $Cu(OTf)_2$ was dissolved in dichloromethane or THF in the presence of the required amount of methyl pyruvate for the catalytic reaction. The polymeric ligand **7b** was suspended in that solution and, after a certain equilibration time, the enol silane (**4**) was added to the mixture.

The catalysis results are gathered in Table 3. As can be seen, both catalysts **L2b** and **7b**-Cu prepared by method B are active in the Mukaiyama aldol reaction – in contrast with the same catalysts prepared by method A. This result demonstrates the role of methanol as a poison for copper-based Lewis acid catalysts. However, it should be noted that the activity of the new catalysts is also limited. The exchanged complex **L2b** is only active in dichloromethane (entry 2), with a moderate yield and a good enantioselectivity (76% *ee*) obtained. This latter value is better than that obtained with the homogeneous catalyst in the same solvent (55% *ee*, see Table 1). The polymeric catalyst **7b**-Cu was only tested in THF (entry 5) and dichloromethane (entry 8) due to the low solubility of the pyruvate-$Cu(OTf)_2$ complex in hexane. In both solvents the results were similar, with slightly better enantioselectivity in THF (84% *ee*), as occurs in solution. The recycled catalysts are less active but the original enantioselectivity is maintained in the subsequent reaction.

These results represent the first use of a chiral catalyst immobilized by ion-pairing in an enantioselective reaction promoted by Lewis acids. This study increases the scope of this approach and shows that the surface effect improves the enantioselectivity from that obtained in solution. The results are strongly dependent on the Lewis acid character of the catalytic centers. Therefore, the stronger complexation of azabox ligands (**2**), which is advantageous from the point of view of catalyst stability,[16] reduces the catalytic activity as a Lewis acid.

Problems in catalyst recovery are common in Lewis acid-promoted reactions given that catalytic centers can be easily poisoned by product, solvent, or ambient water molecules, as clearly shown by the role of methanol in this case. In this respect the multipurpose character of the catalyst may be an additional advant-

Table 3. Results obtained in Mukaiyama aldol reactions between methyl pyruvate (**3**) and 1-phenyl-1-(trimethylsilyloxy)-ethene (**4**) promoted by solids prepared by method B.[a]

Entry	Catalyst	Solvent	Run	Reaction	t [h]	Yield [%]	*Trans*/*cis*	% *ee*[b]
1	**L2b**	THF	1	Mukaiyama	240	<5	-	n.d.
2		CH_2Cl_2	1	Mukaiyama	24	53	-	76
3			2	cyclopropanation[c]	24	48	70:30	82, 76[d]
4		hexane	1	Mukaiyama	144	<5	-	n.d.
5	**7b**-Cu	THF	1	Mukaiyama	48	44	-	84
6			2	Mukaiyama	48	25	-	85
7			3	cyclopropanation[c]	24	99	71:29	97, 92[d]
8		CH_2Cl_2	1	Mukaiyama	24	38	-	71
9			2	Mukaiyama	24	10	-	71
10			3	cyclopropanation[c]	24	98	70:30	95, 91[d]

[a] Reaction conditions: 1 mmol **3**, 1.2 mmol **4**, 10% catalyst, room temperature.
[b] Mukaiyama: determined by HPLC with a Chiralcel OD column; **5** is the major product. Cyclopropanation: determined by GC with a Cyclodex-B column, (1*R*,2*R*) and (1*R*,2*S*) are the major products.
[c] Cyclopropanation reactions were always carried out in dichloromethane, irrespective of the solvent used in the previous Mukaiyama reaction.
[d] Enantioselectivities for the *trans* and the *cis* isomers, respectively.

age, as it can be reused in a different reaction, thus providing added value to the easily obtained solid catalyst. In order to investigate this hypothesis, we tested the used catalysts from entries 2, 6 and 9 (Table 3) in cyclopropanation reactions between styrene and ethyl diazoacetate (Scheme 4). Surprisingly, these solids were at least as active as the fresh catalyst reported elsewhere.[16,17] **7b**-Cu (entries 7 and 10) led to very high yields of cyclopropanes without excess styrene and more than 90% *ee* for both the *trans* and *cis* isomers. The results with **L2b** were more modest but are comparable to those obtained with the fresh catalyst, i.e., 48% yield and 82% *ee* for the *trans* isomers.

Given the differences in behavior of **7b**-Cu catalysts prepared by methods A and B, IR spectra of the different resins were recorded (Figure 3).

As can be seen, the supported ligand **7b** shows a broad signal of C=N stretching (spectrum b), with a maximum at 1640 cm^{-1}. Upon complexation by method B, the band is shifted to 1670 cm^{-1} (spectrum c), and the Mukaiyama reaction leads to a deactivated solid (spectrum d) that presents a new band near 1700 cm^{-1}. This band may be ascribed to the carbonyl groups of the coordinated product, although it is difficult to explain why this molecule of product cannot be replaced by a new silylenol ether molecule in the second run. The difference with **7b**-Cu prepared by method A is clear from the IR spectrum (spectrum e). In this solid it seems that part of the azabox moieties are non-complexed, whereas an important band at 1700 cm^{-1}, analogous to that observed in the deactivated catalyst, is also present. The origin of this band is not clear, but a similar band has been observed in other cases in which partial hydrolysis of the ligand occurred.[13d]

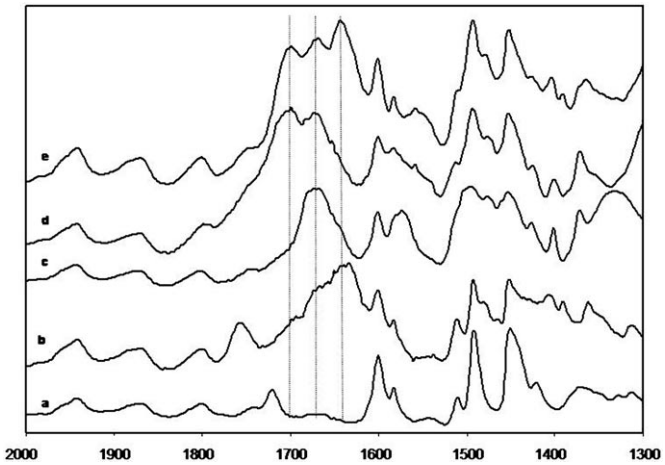


Figure 3. IR spectra of solids based on Merrifield resins: a) Merrifield resin, b) **7b**, c) **7b**-Cu prepared by method B, d) **7b**-Cu prepared by method B and used in Mukaiyama aldol reaction, e) **7b**-Cu prepared by method A.

These results demonstrate that deactivation of a copper complex is highly dependent on the test reaction, and catalysts that are inactive for Lewis acid-promoted reactions are highly active and selective for cyclopropanations. The reversible character of this deactivation and methods to reactivate the catalysts are currently under investigation.

Conclusions

Azabis(oxazolines) show similar performance to bis(oxazolines) as chiral ligands in homogeneous copper-catalyzed enantioselective Mukaiyama aldol

reactions. In spite of this similar behavior in solution, when supported on solids the azabis(oxazoline)-copper complexes are more easily deactivated than their analogous bis(oxazoline)-copper complexes, probably as a consequence of their higher stability. Azabis(oxazolines) are not compatible with the use of coordinating solvents in the immobilization method, and a new method has been developed that allows high enantioselectivity to be obtained with moderate yields. The performance of the immobilized catalysts (up to 86% *ee*) depends on the nature of the support, the immobilization method, and the reaction solvent. There is also some positive effect on enantioselectivity due to surface effects. The deactivation observed in the Mukaiyama aldol reaction is not irreversible, and the deactivated catalysts show excellent performance in a cyclopropanation reaction, a factor that provides added value to these supported multipurpose catalysts.

Experimental Section

General Remarks

Box ligand **1a** was prepared from phenylglycinol and dimethylmalononitrile by a modified procedure.[23] Azabox ligands (**2a**, **2b** and **2c**) were prepared by methods described elsewhere.[15]

Preparation of Immobilized Catalysts by Exchange Procedures

Laponite and Nafion NR-50 (sodium form) were dried under vacuum at 140 °C for 24 h prior to use.

Method A: 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. The Nafion-based catalyst was prepared in the same way from box (0.22 mmol), $Cu(OTf)_2$ (0.2 mmol) and Nafion NR-50 (200 mg).

Method B: 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 the solvent was slowly evaporated under reduced pressure. The solid was dried under vacuum for 24 h.

Synthesis of 7b

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.

Aza-bis(oxazoline) **2b** (0.41 g, 1.7 mmol) was dissolved in tetrahydrofuran (5 mL) and the solution was cooled to −78 °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 **7b**.

Preparation of 7b-Cu

Method A: The PS-bound-ligand **7b** (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 **7b-Cu**.

Method B: Methyl pyruvate (**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 PS-bound-ligand **7b** (0.05 mmol of ligand) in anhydrous tetrahydrofuran (2 mL). After 30 min the Mukaiyama aldol reaction was started by addition of 1-phenyl-1-(trimethylsilyloxy)ethane (0.6 mmol).

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 CuKα radiation was selected using a graphite monochromator. Transmission FT-IR spectra of self-supported wafers evacuated ($<10^{-4}$ torr) at 50 °C were taken with a Nicolet Avatar 360 FTIR spectrophotometer.

Representative Procedure for 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), methyl pyruvate (**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 analyzed by HPLC; Chiralcel OD column, hexane/ethyl acetate (97:3), 1 mL min^{-1}. The absolute configurations of **5** and **6** were assigned by comparison with the results reported by Evans et al.[20]

Representative Procedure for Heterogeneous Mukaiyama Aldol Reactions

To a solution of methyl pyruvate (**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 repeatedly washed with anhydrous dichloromethane, dried under vacuum and reused under the same conditions or in a cyclopropanation reaction.

Representative Procedure for Heterogeneous Cyclopropanation Reactions

To a solution of styrene (2.5 mmol) and *n*-decane (internal standard, 50 mg) in anhydrous dichloromethane (2.5 mL) was added the solid catalyst (required amount for 0.05 mmol Cu). Ethyl diazoacetate (2.5 mmol) was slowly added (4 h) with a syringe pump, and the resulting suspension was stirred at room temperature under an inert atmosphere for 24 h. The mixture was filtered and the filtrate was analyzed by GC.[16,17]

Acknowledgements

This work was supported by the C.I.C.Y.T. (project CTQ2005–08016), the DGA, and the Fonds der Chemischen Industrie. I. P. is indebted to the MEC for a grant.

References

[1] *Chiral Catalysts Immobilization and Recycling*; (Eds.: D. E. De Vos, I. F. J. Vankelecom, P. A. Jacobs), Wiley-VCH, Weinheim, **2000**.
[2] H. A. McManus, P. J. Guiry, *Chem. Rev.* **2004**, *104*, 4151.
[3] a) D. Rechavi, M. Lemaire, *Chem. Rev.* **2002**, *102*, 3467; b) O. Reiser, *Chimica Oggi* **2002**, *20*, 73; c) C. Jönsson, K. Hallman, H. Andersson, G. Stemme, M. Malkoch, E. Malmström, A. Hult, C. Moberg, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1857.
[4] a) N. E. Leadbeater, M. Marco, *Chem. Rev.* **2002**, *102*, 3217; b) C. A. McNamara, M. J. Dixon, M. Bradley, *Chem. Rev.* **2002**, *102*, 3275; c) Q.-H. Fan, Y.-M. Li, A. S. C. Chan, *Chem. Rev.* **2002**, *102*, 3385; d) C. E. Song, S.-G. Lee, *Chem. Rev.* **2002**, *102*, 3495.
[5] a) M. I. Burguete, J. M. Fraile, J. I. García, E. García-Verdugo, S. V. Luis, J. A. Mayoral, *Org. Lett.* **2000**, *2*, 3905; b) E. Díez-Barra, J. M. Fraile, J. I. García, E. García-Verdugo, C. I. Herrerías, S. V. Luis, J. A. Mayoral, P. Sánchez-Verdú, J. Tolosa, *Tetrahedron: Asymmetry* **2003**, *14*, 773.
[6] M. I. Burguete, J. M. Fraile, J. I. García, E. García-Verdugo, C. I. Herrerías, S. V. Luis, J. A. Mayoral, *J. Org. Chem.* **2001**, *66*, 8893.
[7] S. Orlandi, A. Mandoli, D. Pini, P. Salvadori, *Angew. Chem. Int. Ed.* **2001**, *40*, 2519.
[8] a) A. Mandoli, S. Orlandi, D. Pini, P. Salvadori, *Chem. Commun.* **2003**, 2466; b) A. Mandoli, S. Orlandi, D. Pini, P. Salvadori, *Tetrahedron: Asymmetry* **2004**, *15*, 3233.
[9] J. M. Fraile, J. I. García, C. I. Herrerías, J. A. Mayoral, *Chem. Commun.* **2005**, 4669.
[10] a) K. Hallman, C. Moberg, *Tetrahedron: Asymmetry* **2001**, *12*, 1475; b) J. G. Knight, P. E. Belcher, *Tetrahedron: Asymmetry* **2005**, *16*, 1415.
[11] Some examples: a) D. Rechavi, M. Lemaire, *Org. Lett.* **2001**, *3*, 2493; b) R. J. Clarke, I. J. Shannon, *Chem. Commun.* **2001**, 1936; c) J. K. Park, S.-W. Kim, T. Hyeon, B. M. Kim, *Tetrahedron: Asymmetry* **2001**, *12*, 2931; d) A. Corma, H. García, A. Moussaif, M. J. Sabater, R. Zniber, A. Redouane, *Chem. Commun.* **2002**, 1058; e) T. M. Lancaster, S. S. Lee, J. Y. Ying, *Chem. Commun.* **2005**, 3577; f) D. Rechavi, B. Albela, L. Bonneviot, M. Lemaire, *Tetrahedron* **2005**, *61*, 6976.
[12] Examples of electrostatic immobilization: a) M. Mazzei, W. Marconi, M. Riocci, *J. Mol. Catal.* **1980**, *9*, 381; b) R. Selke, H. Häupke, H. W. Krause, *J. Mol. Catal.* **1989**, *56*, 315; c) H. Brunner, E. Bielmeier, J. Wiehl, *J. Organomet. Chem.* **1990**, *384*, 223; d) I. Toth, B. E. Hanson, M. E. Davis, *J. Organomet. Chem.* **1990**, *397*, 109; e) S. Shimazu, K. Ro, P. Sento, N. Ichikuni, T. Uematsu, *J. Mol. Catal. A* **1996**, *107*, 297; f) T. Sento, S. Shimazu, N. Ichikuni, T. Uematsu, *J. Mol. Catal. A* **1999**, *137*, 263; g) R. Margalef-Català, C. Claver, P. Salagre, E. Fernández, *Tetrahedron: Asymmetry* **2000**, *11*, 1469; h) H. H. Wagner, H. Hausmann, W. F. Hölderich, *J. Catal.* **2001**, *203*, 150; i) C. Simons, U. Hanefeld, I. W. C. E. Arends, A. J. Minnaard, T. Maschmeyer, R. A. Sheldon, *Chem. Commun.* **2004**, 2830.
[13] a) J. M. Fraile, J. I. García, J. A. Mayoral, T. Tarnai, *Tetrahedron: Asymmetry* **1997**, *8*, 2089; b) J. M. Fraile, J. I. García, J. A. Mayoral, T. Tarnai, *Tetrahedron: Asymmetry* **1998**, *9*, 3997; c) J. M. Fraile, J. I. García, J. A. Mayoral, T. Tarnai, M. A. Harmer, *J. Catal.* **1999**, *186*, 214; d) J. M. Fraile, J. I. García, C. I. Herrerías, J. A. Mayoral, M. A. Harmer, *J. Catal.* **2004**, *221*, 532.
[14] J. M. Fraile, J. I. García, M. A. Harmer, C. I. Herrerías, J. A. Mayoral, *J. Mol. Catal. A* **2001**, *165*, 211.
[15] a) M. Glos, O. Reiser, *Org. Lett.* **2000**, *2*, 2045; b) H. Werner, R. Vicha, A. Gissibl, O. Reiser, *J. Org. Chem.*

2003, *68*, 10166; c) C. Geiger, P. Kreitmeier, O. Reiser, *Adv. Synth. Catal.* **2005**, *347*, 249; d) A. Gissibl, M. G. Finn, O. Reiser, *Org. Lett.* **2005**, *7*, 2325.

[16] a) J. M. Fraile, J. I. García, C. I. Herrerías, J. A. Mayoral, O. Reiser, A. Socuéllamos, H. Werner, *Chem. Eur. J.* **2004**, *10*, 2997; b) J. M. Fraile, J. I. García, C. I. Herrerías, J. A. Mayoral, O. Reiser, M. Vaultier, *Tetrahedron Lett.* **2004**, *45*, 6765; c) J. M. Fraile, J. I. García, M. A. Harmer, C. I. Herrerías, J. A. Mayoral, O. Reiser, H. Werner, *J. Mater. Chem.* **2002**, *12*, 3290.

[17] H. Werner, C. I. Herrerías, M. Glos, A. Gissibl, J. M. Fraile, I. Pérez, J. A. Mayoral, O. Reiser, *Adv. Synth. Catal.* **2006**, *348*, 125.

[18] E. Carreira, in: *Comprehensive Asymmetric Catalysis*, (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer-Verlag, Berlin, Heidelberg, **1999**; Ch. 29.1, pp. 998–1065.

[19] a) D. A. Evans, J. A. Murry, M. C. Kozlowski, *J. Am. Chem. Soc.* **1996**, *118*, 5814; b) D. A. Evans, M. C. Kozlowski, C. S. Burgey, D. W. C. MacMillan, *J. Am. Chem. Soc.* **1997**, *119*, 7893; c) D. A. Evans, D. W. C. MacMillan, K. R. Campos, *J. Am. Chem. Soc.* **1997**, *119*, 10859; d) D. A. Evans, M. C. Kozlowski, J. A. Murry, C. S. Burgey, K. R. Campos, B. N. Connel, R. J. Staples, *J. Am. Chem. Soc.* **1999**, *121*, 669.

[20] D. A. Evans, C. S. Burgey, M. C. Kozlowski, S. W. Tregay, *J. Am. Chem. Soc.* **1999**, *121*, 686.

[21] a) B.-Y. Yang, X.-M. Chen, G.-J. Deng, Y.-L. Zhang, Q.-H. Fan, *Tetrahedron Lett.* **2003**, *44*, 3535; b) M. Benaglia, M. Cinquini, F. Cozzi, G. Celentano, *Org. Biomol. Chem.* **2004**, *2*, 3401.

[22] A. I. Fernández, J. M. Fraile, J. I. García, C. I. Herrerías, J. A. Mayoral, L. Salvatella, *Catal. Commun.* **2001**, *2*, 165.

[23] A. Cornejo, J. M. Fraile, J. I. García, M. J. Gil, V. Martínez-Merino, J. A. Mayoral, E. Pires, I. Villalba, *Synlett* **2005**, 2321.

