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Chiral copper(II) bisoxazoline covalently anchored to silica and mesoporous MCM-41 as a heterogeneous catalyst for the enantioselective Friedel–Crafts hydroxyalkylation

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Two solid catalysts in which a chiral copper(II) bisoxazoline has been covalently anchored on silica and MCM-41 have been prepared; the solids are enantioselective catalysts (up to 92% ee) for the Friedel–Crafts hydroxyalkylation of 1,3-dimethoxybenzene with 3,3,3-trifluoropyruvate.

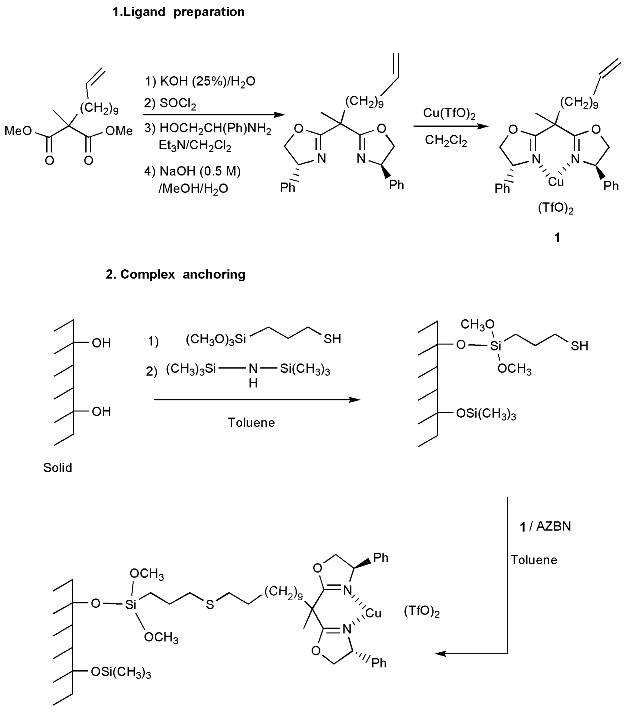
Compared with soluble catalysts the use of solids is advantageous because of their easy separation from the reaction mixture, opening the possibility of their reuse and the design of continuous flow processes.

One general way to transform a homogeneous catalytic reaction into a heterogeneous process involves anchoring the active catalytic site on a solid having a large surface area. While this general methodology has been successfully applied to non-enantioselective reactions, examples describing enantioselective solid catalysts performing in the same way as their homogeneous analogues are quite rare and have been reported only relatively recently.[1–4] Inorganic solids, particularly those having a structured surface, being more robust than organic polymers, have a considerably larger area and, therefore, larger activity should in principle be achievable with these solids. Anchoring the active catalytic center on a large surface area solid would help to overcome the activity decrease generally found in going from homogeneous to heterogeneous catalysis due to inefficient interfacial mass transfer between the liquid phase and the solid. However, in spite of the promising opportunities the fact is that anchoring an enantioselective catalyst on a solid oxide dramatically decreases the enantiomeric excess (ee) compared with those obtained in solution. Immobilization of bisoxazolines has been a very active area of research. These ligands have been immobilized on soluble polymers,[5] silica,[6,7] mesoporous silica,[8] MCM-41 and MCM-48.[9] These ligands have also been immobilized by electrostatic interactions in clays,[10] or zeolites.[11,12] Ee values as high as 95% have been reported for the aziridation of olefins.

Herein we report that anchoring chiral copper(II) bisoxazoline on amorphous or mesoporous silicates produces solid catalysts displaying a high enantioselectivity for the Friedel–Crafts hydroxyalkylation of 1,3-dimethoxybenzene with methyl 3,3,3-trifluoropyruvate. The ee values are even higher than those obtained for the unsupported complex or reported for related phenyl or *tert*-butyl bisoxazoline complexes in solution.[13–15]

The preparation of solid catalysts was accomplished by anchoring a pre-formed, well-characterized copper(II) bisoxazoline complex (**1**) to 3-mercaptopropyl silanized solids using azoisobutyronitrile (AIBN) as radical generator (Scheme 1). Complex **1** was obtained from the corresponding ligand and copper triflate in CH_2Cl_2. The ligand was in turn synthesized reacting dimethyl 2-methyl-2-(ω-undecenyl)malonate with (*R*)-2-amino-2-phenylethanol.[16–18] As a support, high surface silica and mesoporous MCM-41 were used (Table 1). After modification with mercaptopropyl groups in which anchoring is going to occur, the solid was subjected to exhaustive silylation with hexamethyldisilazane to reduce the presence of free OH on the solid surface as indicated in Scheme 1. This strategy based on the anchoring pre-formed complex **1** minimizes the presence of adventitious uncomplexed copper ions on the surface of the solid that could act as non-enantioselective catalytic sites.

The number of 3-mercaptopropyl groups limits the density of complex **1** on the solid surface and it was maintained deliberately low to avoid undesirable complex–complex interactions and association that could decrease enantioselectivity (Table 1). On the other hand the length of the spacer tethering the bisoxazoline complex to the solid surface was selected to be sufficiently long to minimize spatial restrictions on the



Scheme 1

Table 1 Analytical and textural data of the heterogeneous catalyst prepared in this work

Catalyst	Surface area/m^2 g^{-1}	Mercapto groups/mmol g^{-1}	Trimethylsilyl groups/mmol g^{-1}	Complex **1**/mmol g^{-1}
1∝SiO_2	200	0.041	0.028	0.08
1∝MCM-41 (38 Å)	810	0.070	0.072	0.013

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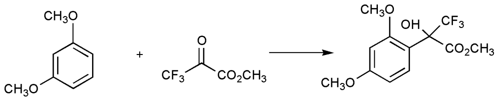
Table 2 Results of the enantioselective Friedel–Crafts alkylation of 1,3-dimethoxybenzene with 3,3,3-trifluoropyruvate[a]



Catalyst		Conversion (%)	Mass balance (%)	Selectivity towards hydroxyalkylation (%)	Ee (%)
1∝SiO$_2$	fresh	72	>95	90	92
1∝MCM-41	fresh	77	>95	98	82
	reuse	73	>95	94	84
1 in homogeneous phase		44	96	94	72

[a] All reactions were performed at room temperature in acetonitrile by using 10% of heterogeneous catalyst, 0.5 mmol of 1,3-dimethoxybenzene and 0.6 mmol of methyl 3,3,3-trifluoropyruvate.The ee% was determined by HPLC (chiralcel OD column).

substrate–complex interaction, which could reduce the ee values.

The success of the covalent anchoring was assessed by analytical and spectroscopic characterization of the resulting solids. The presence of complex **1** was proved by UV–Vis and IR spectroscopies. Combustion chemical analysis (C, N, S and Cu) before and after anchoring the complex gives information not only on the complex density on the solid surface, but also the analytical data indicates the percentage of available mercapto groups being reacted with the terminal C=C side chain of the bisoxazoline in the presence of azobisisobutyronitrile (AZBN) as radical initiator. In addition, the aromatic region of the IR spectrum of MCM-41 containing anchored complex **1** shows the characteristic band at 1645 cm^{-1} and coincides with that of the unsupported complex **1**. This indicates that the anchoring procedure has left the complex unaltered.

The solids were used as enantioselective catalysts for the hydroxyalkylation of 1,3-dimethoxybenzene with methyl 3,3,3-trifluoropyruvate in acetonitrile at room temperature. The results achieved are summarized in Table 2. As it can be seen there high conversions with excellent mass balances are obtained in the presence of the solid catalysts. The same enantiomer was always obtained in excess. As far as we know, these are the highest ee values ever reported for a Friedel–Crafts enantioselective reaction using a metallic complex anchored on a silica surface.

Importantly the ee values achieved are as high as those reported in solution for the same kind of catalyst.[16] It has been recently reported that in diethyl ether solution the di-*tert*-butyl derivative of Cu(II) bisoxazoline catalyzes this Friedel–Crafts alkylation with 56% yield and 86% of ee in the reaction product.[16] Furthermore, although the diphenyl bisoxazoline was not tested for the reaction shown in Table 2, this same study has shown that in general the ee values using the diphenyl derivative are significantly lower than those obtained with *tert*-butyl substituted derivative. This is in spite of the fact that the larger availability of phenylglycinol compared to the *tert*-butyl analogue makes more interesting the use of the diphenyl derivative as in complex **1**. In our hands the ee values for the hydroxyalkylation of 1,3-dimethoxybenzene using unsupported complex **1** in the homogeneous phase was lower than that achieved for the solid-anchored complex (see Table 2).

The lower ee values achieved using MCM-41 as support compared with silica can be interpreted as reflecting the negative influence of the free OH groups. According to IR data of the OH region, silanization of MCM-41 still leaves a residual population of *ca.* 30% of the original groups, while the number of OH groups in silanized silica is comparatively negligible.

To demonstrate that the Friedel–Crafts alkylation is completely heterogeneous and that there is no leaching of the copper ions or metal complex into the solution, a control was carried out. In this control the catalyst was filtered out at 20% conversion and the reaction mixture allowed to react in the absence of solid. This experiment shows that the conversion and the ee are due to the catalyst anchored on the solids, since the reaction completely stopped after removal of the solid by filtration. Analysis of the solution indicates that the Cu^{2+} content is below the detection limit.

After washing with CH$_2$Cl$_2$, the heterogeneous catalyst was recycled for a second reaction. A moderate decrease in the conversion at 48 h reaction time was observed although the ee values remain very high (Table 2). The fact that the ee values of the reused catalyst are still very high points to the fact that deactivation is probably not caused by degradation of the ligand chirality.

In summary, we have shown that anchoring copper bisoxazoline through a long linker on a silanized silica surface is a valid strategy to prepare a high enantioselective heterogeneous catalyst that can be reused without any decrease in its asymmetric induction ability. Our catalyst is different to others in which a chiral complex is simply deposited on the solid surface, for which extensive leaching to the solution occurs.

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