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Electrostatically immobilised BOX and PYBOX metal catalysts: application to ene reactions

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ABSTRACT

Copper(I), copper(II) and scandium(III) triflate complexes of BOX and PYBOX ligands have been electrostatically immobilised on silica. The performance of the immobilised catalysts, in the two carbonyl-ene reactions studied, compares very well with that of their homogeneous equivalents. The immobilised catalysts were successfully reused a number of times. In the case of a scandium complex, a variation in enantioselectivity of up to 73% was observed on immobilisation compared to its use homogeneously. The reason for this variation in enantioselectivity is explored with the aid of molecular modelling.

Enantioselective catalysis in both research and industry makes extensive use of chiral catalysts derived from chiral ligands and metal salts. Many such catalyst systems offer advantages in terms of activity and selectivity. However, particularly in reactions where large catalyst loadings are required, ligands which are synthesised by multistep sequences from amino acids or expensive metal salts, can make the use of such catalysts impractical on a large scale. Immobilisation and reuse strategies are particularly advantageous in these cases. Immobilisation of catalysts on inorganic materials such as silica or similar materials *via* covalent bonds or by other methods is an active area of research.[1]

We have recently reported an extremely facile method for the immobilisation of copper(I) and copper(II) complexes of bisoxazoline (BOX) and bis(oxazolinyl)pyridine (PYBOX) ligands on silica.[2] These immobilised complexes have been shown to be catalytically active in the Diels–Alder cycloaddition[2a] and the direct addition of terminal alkynes to imines leading to propargylamines.[2] In previous studies, we have also reported on the recyclability of these catalysts.[2]

To expand the range of reactions to which our immobilised catalysts are applied, we studied the carbonyl-ene reaction. In addition, we expanded the scope of the technique by applying it to scandium(III) complexes which, Evans has reported, are active in the homogeneous catalysis of ene type reactions for the synthesis of homopropargylic alcohols.[3] We decided to apply the catalysts to the synthesis of homoallylic alcohols via carbonyl-ene reactions. The carbonyl-ene reaction is a synthetically powerful carbon–carbon bond forming reaction, which forms the useful homoallylic alcohol functional group and can create two stereocentres.[4] Its use has been described in the enantioselective synthesis of many biologically active compounds as well as of many other chiral compounds.[5] A diverse range of catalysts has been described for this reaction.[6] Bisoxazoline- and bis(oxazolinyl)pyridine-based catalysts are used typically in amounts of ~10 mol % and so the ability to reuse the catalyst would present a significant advantage. The complexes of BOX Ligand **1** and PYBOX ligands **2** and **3** (Fig. 1) were used in this study.

The phenyl-substituted copper(II)BOX**1** catalyst was generated in dichloromethane from the ligand and copper(II) triflate, and this solution was added to silica (silica gel 40–63 μm, chromatographic

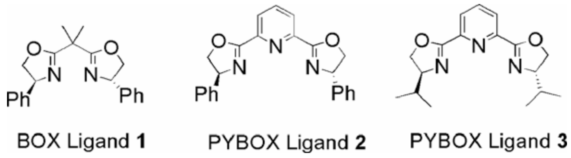

Figure 1.

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grade), which had been dried under vacuum for 2 h at 70 °C. The heterogeneous mixture was stirred until the blue colour disappeared from the solvent and the silica became coloured (~1 min). The organic layer was decanted and the solid was washed with two aliquots of the solvent to be used in the catalytic reaction. Typically, theoretical loadings of 2.8% copper were used in this study. The electrostatically immobilised Cu(II)BOX**1** triflate was tested in the reaction of α-methylstyrene **4** and ethyl glyoxylate **5** by simply mixing the alkene, ethyl glyoxylate and the catalyst suspension under nitrogen. All reactions were carried out at reflux to allow for comparison. After the reaction was complete, the crude reaction mixture was removed from the catalyst by decanting off the liquid and washing the solid with the reaction solvent (2 × 5 ml). The solid catalyst was now ready to be reused and the product was isolated from the solution by removing the solvent under reduced pressure. Cu(I)BOX**1** triflate was also prepared immobilised and tested in a similar manner. The results are shown in Table 1.

The immobilised copper(II) catalyst was as active as its homogeneous counterpart in the first cycle, however, over the course of three uses the conversion dropped from 62% to 42%. In addition, the enantioselectivity obtained was less in the case of the heterogeneous catalyst, 75% ee versus 86% ee for the homogeneous catalyst. The enantioselectivity also fell on reuse. The decrease in conversion and selectivity is likely to be due to a small level of leaching[2b] as well as possible surface contamination of the catalyst.

The copper(I) catalyst was significantly less active on immobilisation, 49% conversion versus 95% conversion. The enantioselectivity achieved by the immobilised copper(I) complex is comparable to that obtained with the homogeneous catalyst 83% ee versus 87% ee, and was largely maintained over three cycles.

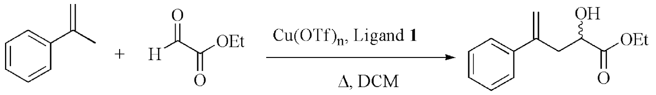
These initial results encouraged us to expand the scope of the study and we decided to investigate the immobilisation of scandium(III)PYBOX catalysts and their activity on immobilisation. The catalysts derived from PYBOX ligands **2** and **3** and scandium(III) triflate were prepared, immobilised and reacted in a similar manner to that described for the copper BOX catalysts. The results are shown in Table 2.

The homogeneous scandium(III)PYBOX**2** complex was an active catalyst for the ene reaction, however, the ee achieved was very poor. When the catalyst was immobilised on silica the activity was maintained but the enantioselectivity remained very poor.

Given our previous experience where phenyl and alkyl BOX catalysts gave very different performances in Diels–Alder reactions on immobilisation[2a] we decided to test the immobilised alkyl PYBOX**3** scandium(III) complex in the ene reaction. Homogeneously, the catalyst gave 100% conversion but only 21% ee. When the catalyst was immobilised electrostatically on silica the activity of the catalysts was largely maintained but there was a large increase in the enantioselectivity. The ee was raised from 21% to 52% when the catalyst was immobilised on chromatographic grade silica. Moreover, the ee remained higher through three cycles than that obtained when the catalyst was used homogeneously. There was some fall off in the catalyst activity across the three cycles which is likely to be due to a small degree of leaching.

Table 1

Immobilised copper BOX**1** catalysis of the canbonyl-ene reaction



4 **5** **6**

Catalyst type[a]	Copper salt	Cycle	Conv[b] (%)	ee[c] (%)
Homogeneous	$Cu(OTf)_2$	N/A	61	86
Heterogeneous	$Cu(OTf)_2$	1st	62	75
Heterogeneous	$Cu(OTf)_2$	2nd	55	78
Heterogeneous	$Cu(OTf)_2$	3rd	42	66
Homogeneous	CuOTf	N/A	95	87
Heterogeneous	CuOTf	1st	49	83
Heterogeneous	CuOTf	2nd	56	83
Heterogeneous	CuOTf	3rd	39	74

[a] Theoretical loading of copper on silica is 2.8% for all heterogeneous catalysis.
[b] With respect to the alkene determined by ^{1}H NMR analysis.
[c] Determined by GC (CYCLODEX B); S-Enantiomer in each case.

Table 2

Immobilised scandium(III)PYBOX catalysis of the carbonyl-ene reaction of α-methylstyrene **4** and ethyl glyoxylate **5**

Catalyst type	Ligand	Cycle	Conv[a] (%)	Ee (%)[b], R/S
Homogeneous	**2**	N/A	79	15, R
Heterogeneous	**2**	1st	87	5, R
Heterogeneous	**2**	2nd	87	5, R
Heterogeneous	**2**	3rd	94	18, R
Homogeneous	**3**	N/A	100	21, S
Heterogeneous	**3**	1st	94	52, S
Heterogeneous	**3**	2nd	87	45, S
Heterogeneous	**3**	3rd	72	33, S

[a] With respect to the alkene determined by ^{1}H NMR analysis.
[b] Determined by GC (CYCLODEX B).

This result was potentially very useful as it represented a way of enhancing the enantioselectivity achieved by a catalyst just by adding silica. We tested the generality of the effect by carrying out another ene reaction using our immobilised catalysts. We reacted methylene cyclohexane **7** with ethyl glyoxylate **5** using a variety of homogeneous and heterogeneous metal complexes as catalysts. The results are shown in Table 3.

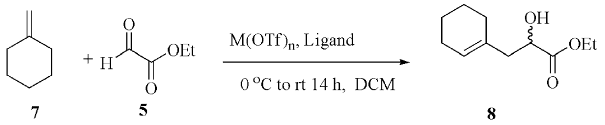
The reactions conducted using copper(I) and copper(II) BOX**1** catalysts gave results largely consistent with those seen with the previous ene reaction. The ees obtained with the homo- and heterogeneous catalysts were broadly similar. The % conversions obtained using the copper(II) catalyst were maintained on immobilisation; however, as with the previous reaction, the copper(I) catalyst activity was severely reduced on immobilisation. When scandium(III) was used with the phenyl-substituted PYBOX**2,** the results were very disappointing. This again is consistent with the previous reaction studied.

The scandium(III) *iso*-propyl-substituted PYBOX**3** again gave very interesting results in the catalysis of this reaction. Used homogeneously, it was very active but not a very enantioselective catalyst, whereas on immobilisation the catalyst activity fell slightly but the product was isolated in 60% ee. Furthermore, the major enantiomer of the product following the homogeneous reaction was R and following the heterogeneous reaction it was S. The enantioselectivity of the reaction swings by 73% on addition of an achiral silica substrate to immobilise the homogeneous catalyst.

We had previously seen how immobilisation of a copper(II)BOX catalyst by this method affected the enantioselectivity achieved in Diels–Alder reactions, which is likely to be due to a change in the geometry about the metal on immobilisation. Jørgensen's[7] work in the area of the effect of additional coordinating ligands or reagents on the geometry of metal BOX systems could be adapted to explain those results. In the case of the scandium PYBOX results reported here, it is more difficult to explain the result.

Evans rationalised the results obtained in the annulation of allenylsilanes on the basis of a model of the scandium(III) PYBOX intermediate which had an octahedral scandium with the PYBOX nitrogens bound in three adjacent equatorial sites.[3a] One apical site was occupied by the one remaining bound triflate and the remaining two sites by the ethyl glyoxylate. He argued that the relative strength of the trans influence of the pyridine of the PYBOX and the triflate determined whether ethyl glyoxylate bound with the aldehyde apically or equatorially.

Table 3
Catalysis of the carbonyl-ene reaction of methylene cyclohexane **7** and ethyl glyoxylate **5**



Metal Source	Ligand	Homo %Conv[a], (%ee)[b]	Hetero run 1%Conv[a], (%ee)[b]	Hetero run 2 %Conv[a], (%ee)[b]
$Cu(OTf)_2$	BOX**1**	98 (82)	96 (79)	69 (72)
CuOTf	BOX**1**	100 (79)	30 (79)	23 (77)
$Sc(OTf)_3$	PYBOX**2**	100 (10)	57 (0)	69 (5)
$Sc(OTf)_3$	PYBOX**3**	100 (13, R)	87 (60, S)	22 (52, S)

[a] With respect to the alkene determined by ^{1}H NMR analysis.
[b] Determined by GC (CYCLODEX B).

One possible explanation for the observed swing in the enantioselectivity achieved when the immobilised catalyst was used may be that coordination of the ethyl glyoxylate to the scandium centre is affected by the interaction of the triflate with the silica solid support. If this interaction altered the relative trans influence of the pyridine and triflate ligand it may alter the binding mode of the aldehyde. We used molecular modelling using the GAUSSIAN-03 program[8] to investigate this possible explanation for our observed results. The structures discussed were optimised using B3LYP density functional calculations (6-31G* basis set).

We first optimised the geometries of the octahedral scandium(III)PYBOX**3** triflate-ethyl glyoxylate complex with the aldehyde apical **A** and equatorial **B** (Fig. 2). **A** and **B** represent likely intermediates in the homogeneously catalysed ene reaction. In **A**, the *re* face of the aldehyde is exposed which would lead to reaction giving the R ene product. In **B**, the *si* face of the aldehyde is exposed which would lead to reaction giving the S ene product. The total energy of complex **A** was marginally lower (4.3 kJ mol^{-1}) indicating that reaction through this complex might be expected to predominate. Interestingly, the optimised structure in both cases had a seven coordinate scandium, two sites being occupied by sulfonate oxygens.

We next modelled the situation when silica was present. Given the limited pre-drying, we applied to our silica the dominant silanol species that is likely to be the gem silanol.[9] A gem silanol might be expected to interact with the available sulfonate oxygens through hydrogen bonding. We modelled how complex **A** or **B** might interact with a bulky gem silanol, which we use to represent the surface of the silica. We positioned the gem silanol within hydrogen bonding distance to the apical triflate sulfonate oxygen.

Interestingly, when the aldehyde is apical the model will not converge and quickly fails, however, when the aldehyde is equatorial the calculation converged. The optimised structure is shown in Figure 3. The gem silanol is positioned directly above the pyridine ring and is within hydrogen bonding distance of the two sulfonate oxygens not coordinated to the scandium.

It appears that, as proposed above, the coordination of the gem silanol to the triflate alters the preferred geometry of coordination of the ethyl glyoxylate from aldehyde apical (no silanol present) to aldehyde equatorial (silanol present). This would expose a different face for reaction and explain the reversal seen in the ene reaction of methylene cyclohexane. It also provides a rationale for why the enantioselectivity of the ene reaction of α-methylstyrene alters as it does when an immobilised catalyst is used. The fact that the homogeneously catalysed scandium(III)PYBOX**3** ene reactions of methylene cyclohexane and α-methylstyrene with ethyl glyoxylate give opposite, albeit poor, selectivities (R vs S) is as yet unexplained.

In conclusion, we have managed to successfully apply immobilised copper- and scandium-based BOX and PYBOX catalysts to the carbonyl-ene reaction. In the cases of copper-based catalysts, the performance on immobilisation largely reflected that in a homogeneous context. The scandium-based catalyst gave variable results on immobilisation. One catalyst, however, on immobilisation gave enantioselectivities that were dramatically different to its homogeneous counterpart. This result is thought to be due to a change in

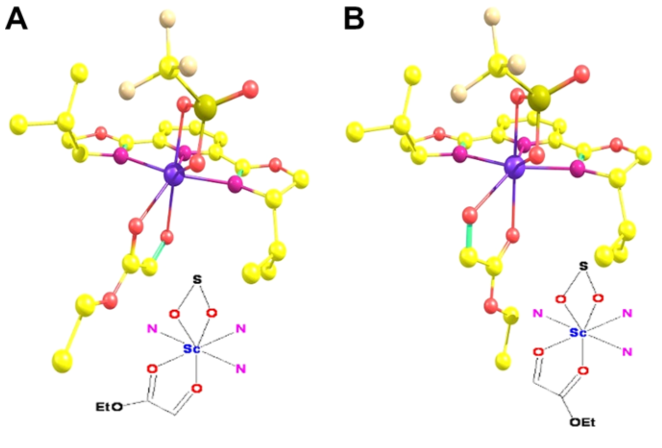


Figure 2. Optimised geometries of possible octahedral scandium(III)PYBOX**3** triflate-ethyl glyoxylate complexes.

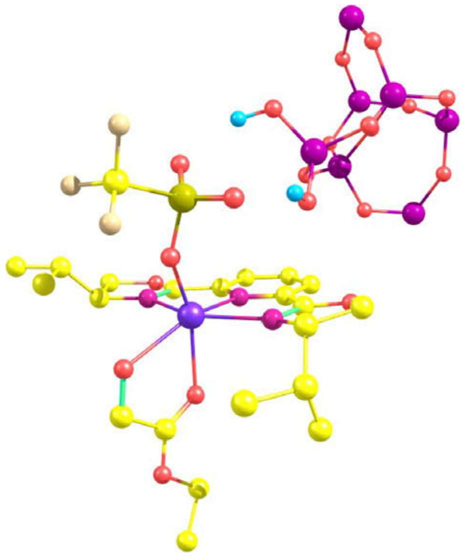


Figure 3. Molecular model of the interaction of a scandium(III)PYBOX**3** triflate-ethyl glyoxylate complex with a gem silanol.

the coordination chemistry during the reaction. We are now undertaking a more substantial modelling study in an attempt to identify catalysts and reactions which may be similarly effected by the presence of a silica support.

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