Surface-enhanced stereoselectivity in Mukaiyama aldol reactions catalyzed by clay-supported bis(oxazoline)–copper complexes†

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Surface effects on a laponite-exchanged bis(oxazoline)–copper complex modify the stereochemical course of the Mukaiyama aldol reaction between 2-(trimethylsilyloxy)furan and α-ketoesters, leading up to 90% ee (dr 86 : 14) becoming the best overall result obtained for this reaction and significantly improving the homogeneous process.

Immobilization of chiral metal complexes is the most used strategy to obtain heterogeneous catalysts for enantioselective processes.[1,2] In spite of the inherent practical advantages of heterogeneous over homogeneous catalysts, the important synthetic effort required for the immobilization through covalent bonding to the support of most chiral catalysts, together with the loss of activity and/or selectivity upon immobilization, make any industrial application difficult.[3]

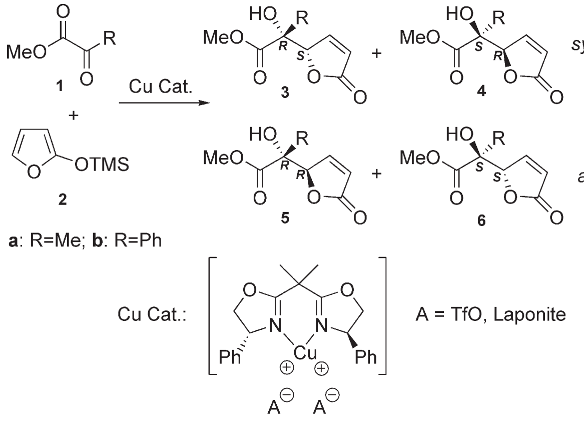
Cationic exchange represents an interesting alternative to covalent immobilization, given that the same homogeneous complex can be used for immobilization without any modification, whereas a strong electrostatic interaction holds the complex firmly attached to the support, in contrast with other non-covalent immobilization methods.[4] In addition to this advantage, we described some years ago an important effect of the support surface on the stereochemical course of cyclopropanation reactions when clays were used as supports for bis(oxazoline)–copper complexes.[5,6] This result was very promising, as it opened the way to new developments, given that products with different stereochemistry from that obtained in solution can be obtained under the influence of a bidimensional clay surface.

Far from being a single case, the surface effect was confirmed by the use of non-symmetrical pyridineoxazoline[7] and quinolineoxazoline[8] ligands, and also by an alternative immobilization method, namely clay-supported ionic liquid films.[9] The restriction of this effect to cyclopropanation reactions was discarded by the improvement in enantioselectivity observed in the C–H carbene insertion reaction catalyzed by the same type of immobilized complexes.[10] However both reactions take place through the same Cu(I)–carbene intermediate, therefore it was important to analyze whether the advantageous surface influence can be extended to reactions with a completely different mechanism.

In this paper we present the first example of a clay surface effect on a reaction that does not take place through a Cu(I)–carbene intermediate, but it is catalyzed by Cu(II) complexes acting as Lewis acids, namely the Mukaiyama aldol reaction. Other authors have reported effects of immobilization on the stereoselectivity of Diels–Alder,[11] epoxidation,[12] or Friedel–Crafts[13] reactions, using either amorphous or crystalline silicas as supports. However, the participation of the surface is not unequivocally demonstrated, as other effects such as anion change, different reaction mechanism, or site isolation might be the origin of the enantioselectivity enhancement.

In previous works, the reactions of 1-phenyl-1-trimethylsilyloxyethene with α-ketoesters[14,15] catalyzed by supported bis(oxazoline)–copper complexes (BoxCu) showed interesting results, but no significant effects on the enantioselectivity. In this paper, we compare the same kind of catalysts in the Mukaiyama aldol reaction using a cyclic enol silyl ether, 2-(trimethylsilyloxy)furan, and two different α-ketoesters (Scheme 1), showing how the structure of both substrate and reagent produce an important effect on both diastereo- and enantioselectivity, allowing us to obtain for the first time the *anti* stereoisomer with high optical purity.

Only the bis(oxazoline) ligand bearing phenyl groups was tested because of the problems found in the immobilization of the complex with the ligand bearing *tert*-butyl groups, due to the



Scheme 1

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Table 1 Results obtained in the Mukaiyama aldol reactions between 2-(trimethylsilyloxy)furan (**2**) and α-ketoesters (**1**)[a]

Subst.	Catalyst	t/d	Yield[b] (%)	*anti* : *syn*[b]	*anti* ee[b,c] (%)	*syn* ee[b] (%)
1a	BoxCu(OTf)$_2$	0.02	74	89/11	20	4
	BoxCuLaponite	2	100	65/35	63	7
1b	BoxCu(OTf)$_2$	1	100	38/62	16	7
	BoxCuLaponite	10	74	86/14	90	9
	recovered	5	86	82/18	82	−10

[a] Reaction conditions: 1 mmol of **1**, 1.2 mmol of **2**, 10% catalyst, CH_2Cl_2 solvent, rt. [b] Determined by HPLC using Chiralcel AD-H (**1a**) or Chiralcel OD-H (**1b**) columns. [c] **5** is the major product.

low formation constant.[6,16] Laponite has shown to give better results than other clays in enantioselective reactions promoted by the same type of bis(oxazoline)–copper complexes.[17] Chiral complexes were immobilized by cation exchange using the sodium form of the clay and methanol as solvent.[16] Characterization by copper analysis (0.23 mmol g^{-1}), elemental analysis, and IR spectroscopy confirmed the presence of the complete complex. The exchanged complex is mainly placed on the external surface of the clay tectoids, with a small part of intercalation between the clay sheets, as shown by X-ray diffraction.

Both homogeneous and heterogeneous catalysts were tested in the Mukaiyama aldol reactions between 2-(trimethylsilyloxy)furan (**2**) and methyl pyruvate (**1a**) or methyl 2-oxo-2-phenylacetate (**1b**) (Scheme 1) at room temperature in dichloromethane. The relative *anti* or *syn* configuration, and the absolute configurations of the *anti* enantiomers in the case of methyl pyruvate (**5a** and **6a**) were assigned according to the data reported in the literature.[18] To the best of our knowledge, the reaction with **1b** had not been previously described in the literature and it was necessary to characterize the products in order to determine the relative and absolute configuration of the compounds. First of all, the racemic mixture of one of the two possible diastereomers was separated and the obtained single crystal was analyzed by X-ray diffraction.‡ The X-ray crystal structure showed the presence of the two *syn* enantiomers (Fig. 1) and this result allowed the identification of the peaks in the HPLC chromatogram. At this point, it was not possible to assign the absolute configuration because the mixtures obtained had not a high enough enantiomeric richness to separate both enantiomers by fractioned crystallization.

From the catalytic results (Table 1) it can be seen that the homogeneous chiral catalyst BoxCu(OTf)$_2$ was not efficient for these reactions, and very low enantioselectivity for both *anti* and *syn* stereoisomers was obtained with any of the ketoesters. The difference in stereoselectivity depending on the substituent in α-position to the ketone is remarkable. Much better stereoselectivity with *anti* preference was obtained in the case of methyl pyruvate (**1a**) whereas substrate **1b** led to a slight *syn* preference. Results changed dramatically with the heterogeneous chiral catalyst BoxCuLaponite. First of all immobilization led to a drop in catalytic activity, and consequently much longer reaction times were needed to reach high conversions. This low activity precluded any attempt of selectivity improvement by lowering the reaction temperature. The most noticeable changes were observed in the stereoselectivity. In the case of methyl pyruvate (**1a**) the high *anti* selectivity in the homogeneous phase was reduced with the solid catalyst. The slight *syn* preference obtained with methyl 2-oxo-2-phenylacetate (**1b**) in solution was reversed to a remarkable *anti* preference (86 : 14) when the solid catalyst was used. Undoubtedly the most interesting results are related to the improvement of enantioselectivity with solid catalysts from the low values obtained in solution (up to 20% ee). Much better enantioselectivity was obtained for methyl pyruvate (63% ee), and the presence of a phenyl group in **1b** allowed obtaining of 90% ee. It is also remarkable that this heterogeneous catalyst was recoverable once with similar performance regarding selectivity but with significantly improved catalytic activity.

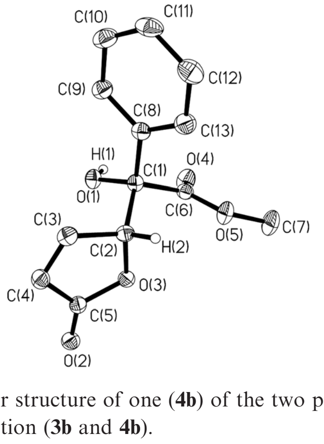

Fig. 1 Molecular structure of one (**4b**) of the two products with *syn* relative configuration (**3b** and **4b**).

The good diastereoselectivity (86 : 14) together with the high enantioselectivity obtained for the major *anti* enantiomer (90% ee) in the reaction catalyzed by BoxCuLaponite allowed us to take up again the problem of determination of the absolute configuration. These values correspond to 82 mol% of the major *anti* enantiomer with respect to the other three stereoisomers. The reaction was scaled up (2.5 mmol of 2-oxo-2-phenylacetate) to obtain a quantity of the major stereoisomer (86% ee) enough to carry out the purification and crystallization. Then, the molecular structure was determined by X-ray diffraction using copper radiation (Fig. 2).‡ In this way, it was found that the major enantiomer had the (R,R) absolute configuration.

It is difficult to give an explanation for the results obtained in the reactions promoted by the laponite-based catalyst. In previous works we demonstrated how the lamellar structure of clays is responsible for changes in stereoselectivity.[6,9] This is due to a change in the symmetry of the complex when placed in the vicinity of the clay surface, shown by the important rise of enantioselectivity when C_1 symmetric chiral ligands were

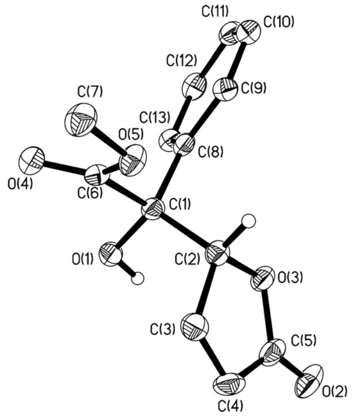

Fig. 2 X-Ray structure of the major *anti* enantiomer with (*R*,*R*) configuration (**5b**).

used.[7,8,10] According to the model proposed by Evans *et al.*[18] an almost square planar Box-Cu-ketoester would be the intermediate for the Mukaiyama aldol reaction. The presence of the surface on one side of the intermediate complex would eliminate the C_2-symmetry of the complex, leading to two non-equivalent species (Fig. 3). The tile angle imposed by the bulkiness of the phenyl substituents of the chiral ligand would provoke a distinct steric interaction with the surface depending on the orientation of the coordinated α-ketoester. The different size of the R group may control the preferred orientation of the intermediate, with either R or methoxy groups far from the surface. Thus, steric (and perhaps electronic) interactions of the incoming 2-(trimethylsilyloxy)-furan with the clay surface would be added to those with substrate and chiral ligand already existing in solution, giving as a result a very complicated pattern of possible diastereomeric transition states.

In conclusion these results demonstrate that immobilization of chiral catalysts is not necessarily detrimental for enantioselectivity. On the contrary, in this case the enhanced stereo- and enantioselectivities have made possible the separation, identification, and determination of the absolute configuration of a new compound obtained from a Mukaiyama aldol reaction. Further studies regarding the origin of this effect and the possibilities to extend its applications are currently under development.

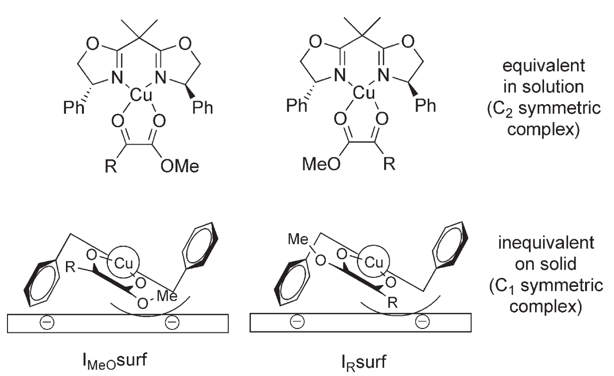

Fig. 3 Possible intermediate complexes on laponite surface.

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Notes and references

‡ Crystal data for (**3b** + **4b**): $C_{13}H_{12}O_5$, M = 248.23, monoclinic, $P2(1)/c$, a = 11.5169(15), b = 7.9585(11), c = 13.1517(17) Å, β = 94.033(2)°, V = 1202.5(3) Å^3, Z = 4, D_c = 1.371 g cm^{-3}, μ (Mo-Kα) = 1.06 cm^{-1}. Crystal dimensions 0.164 × 0.163 × 0.161 mm, 7457 reflections measured, 2602 unique (R_{int} = 0.0222); number of data/restrains/parameters 2602/0/211; final GoF 1.046, R = 0.0425 (2295 reflns, $I > 2\sigma(I)$), $wR2$ = 0.1075 for all data. CCDC 684313. Crystal data for **5b**: $C_{13}H_{12}O_5$, M = 248.23, monoclinic, $P2(1)$, a = 7.5836(15), b = 5.7612(12), c = 13.331(3) Å, β = 102.73(3)°, V = 568.1(2) Å^3, Z = 2, D_c = 1.451 g cm^{-3}, μ(Cu-Kα) = 9.49 cm^{-1}. Crystal dimensions 0.124 × 0.120 × 0.074 mm, 5624 reflections measured, 2199 unique (R_{int} = 0.0214); number of data/restrains/parameters 2199/1/211; final GoF 1.127, R = 0.0316 (2088 reflns, $I > 2\sigma(I)$), $wR2$ = 0.0841 for all data. CDC 684314.

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