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# Reversible microencapsulation of pybox–Ru chiral catalysts: scope and limitations

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**Abstract**—Chiral Pybox–Ru catalysts can be microencapsulated into linear polystyrene as a method to recover and recycle the valuable catalyst. These catalysts allow 60–68% yields to be achieved with enantioselectivities in the range 75–85% ee in the benchmark cyclopropanation reaction between styrene and ethyl diazoacetate. The catalyst is soluble in the reaction solvent and is re-encapsulated at the end of the reaction. The great advantage of this methodology is that the chiral ligand does not need to be modified, but the recycling is highly solvent dependent—in contrast with the catalysts immobilized through covalent bonds.


## 1. Introduction

Immobilization on organic polymers is one of the most widely used strategies to support chiral catalysts and is a way to make them recoverable and reusable—with the associated practical advantages.[1] The chiral catalyst can be linked to the polymeric support either through strong bonds/interactions (e.g., covalent bond or electrostatic interaction) or through weak interactions. Covalent bonding is by far the most common method,[2] but has the drawback of requiring chemical modification of the chiral ligand to introduce additional functionality to form the covalent bond with the support. This requirement makes the preparation of the catalyst more difficult, which is often a serious limitation for the industrial application of the immobilized chiral catalysts,[3] in contrast with the recent applications described for analogous non-chiral systems.[4]

In terms of immobilization through weak interactions, a number of examples have been described for the entrapment of chiral catalysts within polymers, either in cross-linked polymers[5] or in linear polymers to give microcapsules.[6,7] In both cases, the preparation of the catalyst is rather simple and this method does not require any modification of the chiral ligand.

Our group is working in the field of chiral catalyst immobilization, with special emphasis on oxazoline-containing ligands[8] —particularly pyridinebis(oxazoline) ligands (pybox). The immobilization of these systems through covalent bonding to organic polymers was assessed in two ways: polymerization and grafting (Fig. 1). The polymerization method involves functionalization of the chiral pybox with a group that can polymerize with other monomers, such as styrene.[9] In this case the synthetic effort is double because the polymerizable ligand and the polymeric support with a suitable morphology must be considered. In the case of grafting (Fig. 1), well-characterized, commercially available supports can be used, so the synthetic effort for this method is restricted to the modified chiral ligand.[10]

Given the attractiveness of the microencapsulation methodology (Fig. 2) we decided to investigate this area with the same types of catalysts to evaluate the advantages and disadvantages of this system in comparison with the methods involving ligand-support covalent bonding.

## 2. Results and discussion

One important limitation of the microencapsulation method is compatibility with the solvent. Indeed, cyclopropanation

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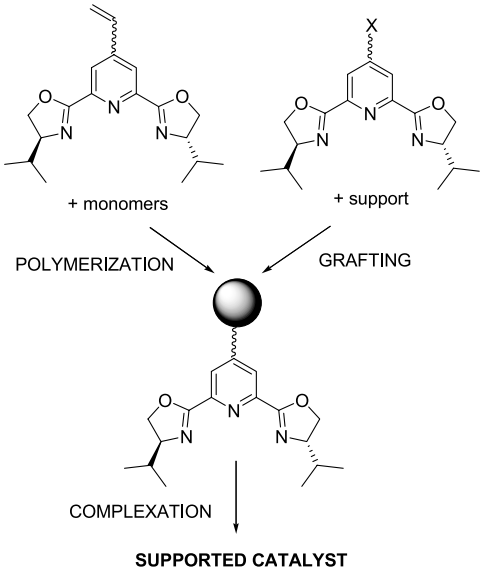



**Figure 1.** Polymerization and grafting methods for pybox immobilization.

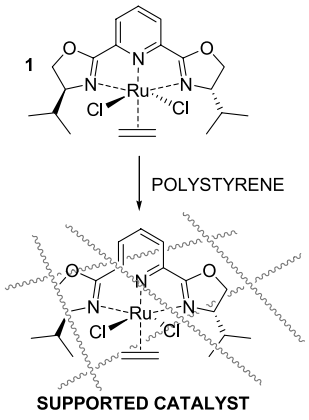



**Figure 2.** Microencapsulation of pybox–Ru chiral catalyst.

reactions with pybox–Ru catalysts are usually carried out in dichloromethane, a solvent in which linear polystyrene is soluble. We therefore envisaged microencapsulation as a reversible method for immobilization. The catalyst and support will be soluble in the reaction medium (homogeneous catalysis) but can be recovered by re-encapsulation at the end of the reaction.[11]

The pybox–Ru complex **1** was prepared from pybox ligand and $[Ru(p\text{-cymene})Cl_2]_2$ in an ethylene atmosphere using the method described by Nishiyama et al.[12] Ethylene plays an important role in the stability and efficiency of the catalyst[7] as it protects the ruthenium centre from other strongly coordinating molecules such as oxygen. A solution of pybox–Ru complex in dichloromethane was added to a solution of the linear polystyrene in warm cyclohexane and the solvents were slowly evaporated. The Ru content was determined by plasma emission spectroscopy and, in the fresh catalysts, was slightly lower than the theoretical value (0.225–0.230 mmol/g vs 0.258 mmol/g). FTIR (Fig. 3) shows the presence of the Ru catalyst in the solid.

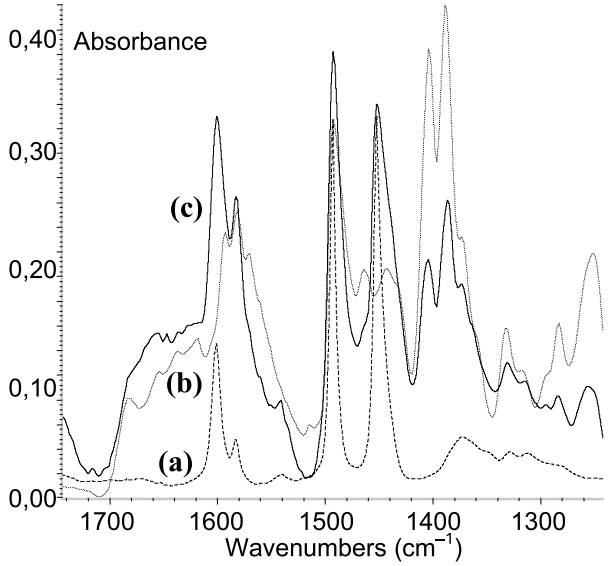
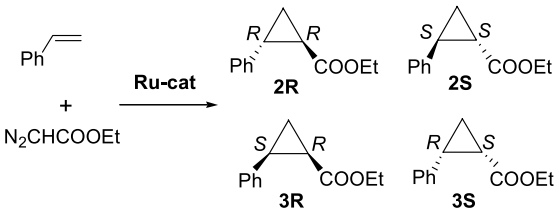



**Figure 3.** FTIR spectra of the polystyrene matrix (a), the Ru–pybox complex (b), and the microencapsulated the Ru–pybox complex (c).

The asymmetric cyclopropanation reactions between styrene and ethyl diazoacetate (Scheme 1) were carried out in dichloromethane, with only one exception (MC3). Under these conditions the encapsulated catalyst was completely soluble in the reaction medium and behaved as a homogeneous catalyst. However, the addition of a solvent such as hexane or cyclohexane led to the formation and hardening of the capsules, which were filtered off, washed and reused. The reaction conditions, results and recycling method are collected in Table 1. One set of experiments in the homogeneous phase (Hom in Table 1) was conducted under the same conditions for the sake of comparison.




**Scheme 1.** Asymmetric cyclopropanation reaction.

Comparison of MC1 and the homogeneous test clearly shows that the use of polystyrene increases the recyclability of the complex, which maintains good yield and enantioselectivity up to the fourth run. However, a small amount of Ru is lost in each recycle, as shown by the colour of the washings. However, the amount leached in each batch is so small that it cannot be accurately analyzed, meaning that it must be less than 5%. The analysis of joint mother liquors after four batch reactions shows an overall loss of Ru of about 15% (0.01 mmol). The worst property of this type of complex is its mechanical weakness—the solid is ground by the magnetic stirrer and is almost completely destroyed after four runs. An interesting aspect is the higher stability of this catalyst in comparison with the homogeneous one. All of the recycling operations were carried out in air without loss of activity or selectivity, in contrast with the grafted catalysts.[10] Despite this finding, all recycling operations in

**Table 1**. Asymmetric cyclopropanation reactions with microencapsulated catalysts

| Experiment | Solvent (mL)[a] | Run | Yield %[b,c] | *trans*/*cis*[b] | %ee *trans*[b] | %ee *cis*[b] | Hexane addition[d] | Evaporation[d] | Washing solvent and temperature[d] |
|---|---|---|---|---|---|---|---|---|---|
| Hom[e] | DCM (5+1) | 1 | 49 | 88/12 | 81 | 52 | 15 mL | Yes | Hex (6×12 mL) rt |
| | | 2 | 50 | 90/10 | 84 | 63 | | | |
| | | 3 | 13 | 87/13 | 74 | 41 | | | |
| MC1 | DCM (5.4+1) | 1 | 46 | 85/15 | 75 | 37 | No | Yes | CHex (6×15 mL) rt |
| | | 2 | 63 | 87/13 | 85 | 45 | | | |
| | | 3 | 63 | 88/12 | 83 | 47 | | | |
| | | 4 | 48 | 88/12 | 84 | 45 | | | |
| MC2 | DCM (10+2) | 1 | 36 | 88/12 | 78 | 43 | 15 mL | Yes | Hex (6×12 mL) −20 °C |
| | | 2 | 37 | 88/12 | 83 | 48 | | | |
| | | 3 | 29 | 87/13 | 75 | 40 | | | |
| | | 4[f] | 11 | 77/23 | 45 | 10 | | | |
| MC3 | CHex (10+2) | 1 | 31 | 94/6 | 85 | 68 | No | Yes | CHex (6×15 mL) rt |
| | | 2 | 12 | 91/9 | 66 | 35 | | | |
| MC4 | DCM (10+2) | 1 | 44 | 88/12 | 84 | 50 | 15 mL | Yes | Hex (6×10 mL) 0 °C |
| | | 2 | 41 | 89/11 | 86 | 61 | | | |
| | | 3 | 25 | 88/12 | 84 | 54 | | | |
| MC5 | DCM (2+0.5) | 1 | 42 | 88/12 | 81 | 50 | 20 mL | No | Hex (5×10 mL) 0 °C |
| | | 2 | 51 | 88/12 | 82 | 43 | | | |
| | | 3 | 32 | 86/14 | 75 | 40 | | | |
| | | 4 | 8 | 76/24 | 23 | 5 | | | |
| MC6 | DCM (2+0.5) | 1 | 62 | 88/12 | 83 | 52 | 20 mL | No | Hex (5×10 mL) −20 °C |
| | | 2 | 68 | 86/14 | 80 | 35 | | | |
| | | 3 | 61 | 87/13 | 73 | 30 | | | |
| | | 4 | 18 | 72/28 | 20 | 2 | | | |
| Grafted[f,g] | DCM | 1 | 38 | 86/14 | 77 | 43 | | | |
| | | 2 | 47 | 88/12 | 83 | 54 | | | |
| | | 3 | 41 | 88/12 | 81 | 50 | | | |
| | | 4 | 36 | 84/16 | 56 | 23 | | | |
| Polym[h] | DCM | 1 | 52 | 88/12 | 85 | 54 | | | |
| | | 2 | 67 | 90/10 | 91 | 67 | | | |
| | | 3 | 70 | 90/10 | 89 | 64 | | | |
| | | 4 | 68 | 90/10 | 87 | 63 | | | |
| | | 5 | 32 | 88/12 | 74 | 63 | | | |

[a] DCM=dichloromethane; Chex=cyclohexane; Hex=hexane. The two different quantities indicate the amount solvent used to dissolve the catalyst and styrene and to dilute ethyl diazoacetate, respectively.
[b] Determined by gas chromatography. **2R** and **3R** are the major products.
[c] In all cases complete disappearance of ethyl diazoacetate is observed, therefore yields reflect chemoselectivity rather that catalyst activity.
[d] Steps in recycling of the catalyst: addition of hexane to the reaction mixture, evaporation of the solvents and washing the solids with solvent at different temperatures. The combined solutions were analyzed to determine the results and the resulting solid was reused under the same conditions.
[e] Homogeneous reaction. Non-encapsulated catalyst.
[f] Run not carried out under inert atmosphere.
[g] 4-Vinylpybox immobilized on Merrifield's resin. Data from Ref. 10.
[h] 4-Vinylpybox polymerized with styrene and divinylbenzene. Data from Ref. 10.

the other experiments were carried out under an inert atmosphere. In recovered catalysts ethylene must be replaced by other molecule, most probably the reacting alkene—styrene in this case—as it has been recently shown in a theoretical study on the mechanism of this reaction.[13]

An increase in the amount of reaction solvent seemed to have a slightly negative effect on the yield, and cyclohexane (MC3) proved more detrimental than dichloromethane. In experiment MC2 hexane was added to the reaction mixture to harden the capsules prior to evaporation and washing. In this way recycling is experimentally easier and more efficient. The fourth run was carried out without an inert atmosphere in order to assess the stability of the system in air. The poor result, both in terms of activity and stability, shows that the enhanced stability is not effective when the catalyst is under reaction conditions, probably because it is homogeneous in nature.

The stability of the catalyst is improved by recovering it at 0 °C instead of −20 °C, probably due to a more efficient extraction of the reaction products and by-products. In fact, complexation of ruthenium by maleate and fumarate may contribute to catalyst deactivation. Another method to increase the mechanical stability is the use of orbital shaking instead of stirring in the experiments from MC4.

In another set of experiments, the amount of dichloromethane was markedly reduced in order to allow the collapse of the capsules without the need for evaporation. This method works effectively but a significant loss of activity and enantioselectivity was observed in the fourth run. In this case the collapse and extraction at lower temperature (MC6) improve the yield with no significant modification of the enantioselectivity, but again the cyclopropane yields noticeably decrease after the third run.

The results and stability of the microencapsulated catalysts were compared with those prepared by grafting 4-mercaptopybox or by polymerization of 4-vinylpybox.[10] In both cases the catalysts covalently linked to the polymeric support show enhanced stability—both chemical

and mechanical. The grafted catalyst leads to slightly lower yields than the microencapsulated one and has comparable enantioselectivity, which begins to drop in the fourth run. In contrast, the polymerized catalyst is as good as the microencapsulated one, with higher enantioselectivity and better recoverability—as shown by the excellent results in the fourth run and the moderate loss of activity and enantioselectivity only in the fifth run. Although polymerization is the best method for the immobilization of the pybox–Ru system, microencapsulation is an interesting alternative to grafting owing to its simplicity and similar performance.

## 3. Conclusions

Microencapsulation allows the reversible immobilization of enantioselective pybox–Ru catalysts. In this way the solid catalyst is solubilized under the reaction conditions and can be re-encapsulated at the end of the reaction. When compared with the grafting and polymerization methods for covalent bonding to the polymeric support, the microencapsulation technique shows some advantages, for example, it is not necessary to modify the chiral ligand and this leads to an easier preparation. On the other hand, microencapsulation leads to less stable catalysts in terms of mechanical attrition and leaching, making recovery and reuse more difficult. In conclusion, microencapsulation is an interesting methodology that should be taken into account when a chiral immobilized catalyst has to be designed for a given application. This approach requires almost no supplementary synthetic effort in comparison with the polymerization or grafting techniques, although for this particular case the grafted catalyst performs better, and it would be interesting to assess this method in immobilization work.

## 4. Experimental

### 4.1. Preparation of microencapsulated catalysts

Ethylene was bubbled for 1 h into a solution of 2,6-[4′-(*S*)-isopropyloxazolin-2′-yl]pyridine (400 mg, 1.33 mmol) and $[RuCl_2(p\text{-cymene})]_2$ (408 mg, 0.67 mmol) in anhydrous dichloromethane (15 mL). After purging with nitrogen, the solution was added to *n*-heptane (HPLC grade, 100 mL) and the resulting solid was collected by filtration and dried under vacuum. Yield of **1** 550 mg (82%).

A suspension of linear polystyrene (MW = 280,000, 246 mg) in anhydrous cyclohexane (20 mL) was heated at 45 °C for 90 min until complete dissolution. A solution of complex **1** (36.7 mg, 0.073 mmol) in anhydrous dichloromethane in (1.5 mL) was added and the resulting solution was stirred at 30 °C for 1 h. The solvent was evaporated at room temperature under reduced pressure and the solid was used without further treatment.

### 4.2. Asymmetric cyclopropanation reactions

A solution of styrene (0.57 mL, 5 mmol) in the corresponding anhydrous solvent (see Table 1) was added to the immobilized catalyst (ca. 0.06 mmol). A solution of ethyl diazoacetate (114 mg, 1 mmol) in the same solvent was slowly added (6 h). The solution was shaken for an additional period of 17 h. The catalyst was collapsed by the addition of hexane or cyclohexane. The exact method is described in Table 1. The solid catalyst was washed with the same solvent and the combined organic solutions were analyzed by gas chromatography. The dried solid catalyst was reused several times under the same conditions.

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