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A reusable, insoluble polymer-bound bis(oxazoline) (IPB-box) for highly enantioselective heterogeneous cyclopropanation reactions†

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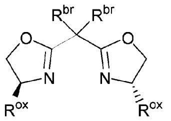
A reusable, insoluble polystyrene-supported bis(oxazoline) was developed, affording e.e.s > 90% in the heterogeneous enantioselective cyclopropanation of styrene and 1,1-disubstituted alkenes with ethyl diazoacetate.

The stereoselective synthesis of cyclopropane derivatives is a topic of major current interest,[1] in view of the strong configuration–bioactivity relationship displayed by several pharmaceutical and agrochemical compounds containing this structural unit. Given the ready availability of the starting materials and the high activity/low cost of copper salts, as far as the preparation of enantioenriched chiral cyclopropanecarboxylic acids is concerned, the Cu(I)-catalysed enantioselective cyclopropanation of olefins with diazoesters is one of the most convenient options. Besides the use of chiral Schiff base–Cu complexes (Sumitomo process for Cilastatin intermediate),[2] work by several groups[1] demonstrated that bis(oxazolines) **1** (box) often represent the ligand of choice in terms of enantiodiscrimination ability. However, the high cost of **1** (especially for R^{ox} = *t*-Bu) severely limits the practical application of this class of auxiliaries in asymmetric synthesis, prompting the search for easily recoverable analogues, either by preparation of modified soluble box[3] and aza-box ligands,[4] or by immobilization onto insoluble supports.[5]



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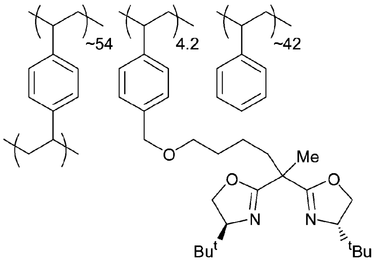

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Focusing on the latter IPB approach, it is worth noting that while satisfactory activity and stereoselectivity values have been achieved for a few miscellaneous transformations,[5] the results in the case of heterogeneous catalytic cyclopropanation appear to lag behind those provided by the best soluble parent ligands **1** (R^{ox} = *t*-Bu, R^{br} = H or Me), that are known to afford 93–99% e.e. in the benchmark reaction of styrene with ethyl diazoacetate.[6] In spite of considerable efforts, most notably by Mayoral's group,[7,8] only recently the use of composite organic/inorganic ion exchange supports led in fact to e.e. values higher than 90%, albeit with low yields and some ligand leaching problems.[9] Regarding the covalent anchoring to insoluble organic materials, best results (e.e. ≤ 79%) were obtained with resins prepared from box monomers bearing two 4-vinylbenzyl groups at the bridging carbon, although these materials suffer from inefficient use of the chiral ligand, with only 4–38% of the chiral units available for Cu complexation.[8] While the reduction of stereoselectivity with respect to the soluble counterparts has been correlated to the loss of C_2 symmetry, excessive cross-linking or to the occurrence of unfavourable site–site interactions,[5] from the practical point of view of e.e. maximization it seemed however possible that the relatively unsuccessful attempts reported to date would result from the failure to replicate the optimal structure of **1** in the materials described so far. For this reason we decided to evaluate the asymmetric cyclopropanation reaction of the supported ligand **2**, whose box units were likely to experience a minimal increase of steric hindrance at the bridging methylene carbon compared to **1** (R^{ox} = *t*-Bu, R^{br} = Me).

The highly (~54%) cross-linked material **2** (ligand loading: 0.31 mmol g^{-1}, from nitrogen elemental analysis) was obtained by AIBN-initiated radical copolymerisation of the corresponding monomers, as described before.[10] In spite of the remarkably compact texture by SEM analysis (Fig. 1) and low surface area in the dry state (< 5 m^2 g^{-1}), **2** appeared to swell in a solution of $Cu(OTf)_2$ in THF. Accordingly, the rapid uptake of 0.18–0.20 mmol g^{-1} of the metal salt took place, demonstrating that about 60% of the supported box units could be readily engaged in the metal complexation.

In order to avoid the use of toxic and unstable $CuOTf\cdot\frac{1}{2}C_6H_6$,[6] the resulting supported complex was directly used as the catalyst precursor. To obtain the catalytically active Cu(I) species, reduction of the metal centre was effected *in situ* before the catalysis runs, by warming $\mathbf{2}\cdot Cu(OTf)_2$ with a slight excess of the diazoester **4**.[6]

The cyclopropanation experiments (Scheme 1) were carried out in CH_2Cl_2 at 0 °C, normally with 2 equiv. of the alkene substrate and adding the diazoester dropwise, to improve the chemoselectivity by minimization of maleate and fumarate byproducts. In view of the modifications introduced to the standard procedure by Evans,[6] homogeneous control runs with the soluble ligand **1** (R^{ox} = *t*-Bu, R^{br} = Me) were initially repeated under the conditions of heterogeneous experiments (Table 1, entries 1, 3 and 5). Because only minor reductions of stereoselectivity were observed with respect to the best literature results,[6] and considering that e.e. values in the

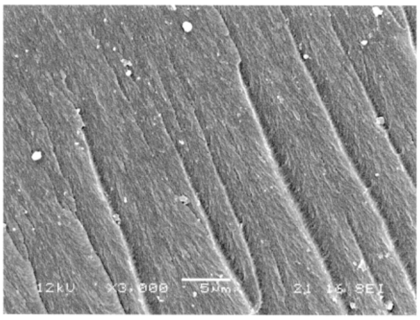
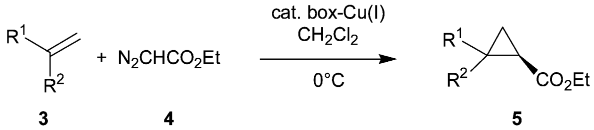


Fig. 1 SEM image of the material **2**.



3 **4** **5**

Scheme 1 Cyclopropanation of alkenes with ethyl diazoacetate **4**.

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† Electronic supplementary information (ESI) available: experimental. See http://www.rsc.org/suppdata/cc/b3/b306483b/

Table 1 boxCu-catalysed homogeneous and heterogeneous enantioselective cyclopropanation of alkenes with ethyl diazoacetate **4**

Run	**3** (R^1,R^2)	Ligand	**4**/box	**4**/Cu	Time/h	Chemosel. (%)[a,b]	**5**		
							Yield (%)[c]	D.r.[b,d]	E.e. (%)[e]
1	Ph,H	**1** (R^{ox} = *t*-Bu, R^{br} = Me)	45	50	3	63	61	71 : 29	94[f,g] (99) 92[g,h] (97)
2	Ph,H	**2**	28	50	3	61	60	67 : 33	93 90
3	Ph,Ph	**1** (R^{ox} = *t*-Bu, R^{br} = Me)	45	50	3	n.d.[m]	97	—	98[i] (>99)
4	Ph,Ph	**2**	28	50	3	n.d.[m]	75	—	91
5	Me,Me	**1** (R^{ox} = *t*-Bu, R^{br} = Me)	455	500	16	97	92	—	97[l] (>99)
6	Me,Me	**2**	566	1000	44	85	53	—	92
7	Me,Me	**2**	283[n]	500	22	88	84[o]	—	92
8	Me,Me	**2**	283[n]	500	22	88	84[o]	—	91
9	Me,Me	**2**	283[n]	500	22	89	84[o]	—	91

[a] Chemoselectivity in the formation of cyclopropane products. [b] By GLC. [c] Isolated yields. [d] *Trans* : *cis* ratio. [e] Absolute configuration of the prevailing enantiomer: *1R*. In parentheses, e.e. values with CuOTf·$\frac{1}{2}C_6H_6$ as the catalyst precursor (from ref. 6). [f] E.e. of *trans* product. [g] By HPLC (Chiralcel OJ, hexane : 2-propanol = 99.5 : 0.5). [h] E.e. of *cis* product. [i] By HPLC (Chiralcel OD–H, hexane : 2-propanol = 99.4 : 0.6). [l] By GLC (Astec G-TA). [m] Not determined. [n] Recycled ligand from the previous run. [o] Overall yield, by distillation of the pooled crude products from runs 7–9.

92–98% range could be nonetheless attained for all the substrates examined, the modified procedure was judged suitable for this exploratory study.

With this information, the heterogeneous catalysis in the benchmark cyclopropanation of styrene was examined first. Using 3.6 mol% of the supported box **2** (2 mol% of catalyst precursor, estimated from Cu uptake), total conversion of the diazoester was observed within 5 min of the addition completion, with formation of the cyclopropane product **5**, as a mixture of *trans* and *cis* diastereomers, in satisfactory overall yield (entry 2). Control experiments demonstrated that no activity was present in the filtrate from **2**·Cu, confirming the truly heterogeneous nature of the catalytic system. Concerning the stereoselectivity, a slight reduction in the diastereomeric ratio was observed with the supported complex, possibly as a result of increased steric hindrance at the box methylene, but this did not translate into a substantial decrease of enantioselectivity, as e.e. values within 1–2% of the homogeneous reference run were obtained in both the *trans* and *cis* manifold.

To assess the possibility of reusing the supported catalyst, at the end of the reaction the polymer material was filtered, washed with CH_2Cl_2, dried and directly used in a further run. Following this procedure 5 recycles could be easily carried out (Fig. 2), achieving in each case complete conversion and almost unchanged chemo- and stereoselectivity values.

The scope of the heterogeneous asymmetric cyclopropanation with **2**·Cu could also be extended to the 1,1-disubstituted olefins 1,1-diphenylethylene (entry 4) and isobutene (entry 6), obtaining for both alkenes e.e. values >90%. In fact, for the latter substrate the reaction was initially run at a diazoester/Cu ratio of 1000, to have a comparison with the results published for the soluble ligand **1** (R^{ox} = *t*-Bu, R^{br} = Me),[6] but under these conditions (7.5 equiv. isobutene *vs.* **4**, 6 h addition time) the reaction proved relatively slow, with largely incomplete conversion (66%) even after 44 h. Speculating that the diazoester accumulation, due to the reduced catalytic activity, would eventually result in catalyst deactivation, further runs with recovered material were carried out at a **4**/Cu ratio of 500 and adding **4** over 16 h with a syringe pump. Indeed, although direct reuse of the **2**·Cu complex was precluded at these low catalyst loadings, probably because of extensive metal leaching, after recharging the recovered ligand with the copper salt and repeating the reduction step, conversion values of 95–99% and e.e.s of 91–92% could be attained in 22 h under these conditions (entries 7–9). Actually, by making use of the concept of ligand economy introduced by Mayoral and co-workers,[7] the data from runs 6–9 correspond to a total TON of 1010 with respect to the supported box, demonstrating that **2**·Cu is significantly more effective than any recoverable box–Cu cyclopropanation catalytic system reported to date,[11] either soluble[4] or insoluble.[5,8]

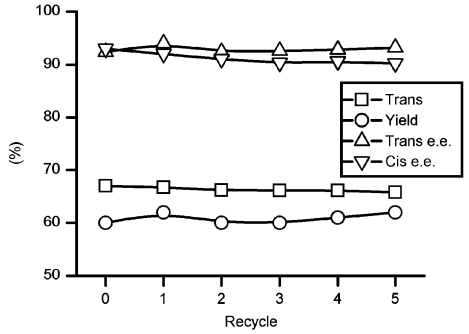

Fig. 2 Recycling of **2**·Cu in the cyclopropanation of styrene.

In conclusion, this preliminary work demonstrates that proper design of the copolymer architecture, with a single, flexible spacer linking the ligand moiety to the inert polystyrene backbone, appears effective in providing the box units in **2** with solution-like behaviour, leading to satisfactory ligand availability and catalytic activity. Even more importantly, in spite of the formal loss of C_2 symmetry of the supported ligand, e.e. values higher than 90% could be obtained for the first time in the heterogeneous cyclopropanation of different alkenes, using a bis(oxazoline) covalently anchored to an insoluble support.

Work is currently underway to optimise the stereoselectivity and to address in greater detail the issue of catalyst recycling.

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