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# Enantioselective catalysis in water: Mukaiyama-aldol condensation promoted by copper complexes of bisoxazolines supported on poly(ethylene glycol)

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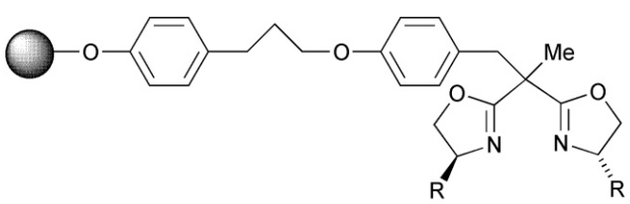
(*S*)-3-Phenyl-2-aminopropanol-derived bisoxazolines supported on a modified poly(ethylene glycol) were shown to be effective Cu(II) ligands for the enantioselective Mukaiyama-aldol condensation of various aldehydes with the trimethylsilyl keteneacetal of methyl isobutyrate carried out in water. Enantiomeric excesses comparable to those obtained with nonsupported ligands in the same solvent were observed. The solubility of the ligand in water, ensured by the presence of the polymeric support, allowed a very convenient catalyst-recycling procedure involving simple removal of the reaction product by extraction in $Et_2O$ and addition of fresh reagents to the catalyst-containing aqueous solution. The chemical and stereochemical efficiency of the catalyst was only marginally eroded over its use in three reaction cycles.

## Introduction

The several advantages offered by the use of water as a solvent in terms of cost, safety, and environmental impact, prompted the development of suitable methods and conditions to carry out some organic reactions in this solvent.[1] However, the number of these processes is drastically reduced when enantioselective catalytic reactions are considered.[2] Solubility reasons are largely responsible for this fact and a variety of expedients have been adopted to circumvent this problem. These mainly include the use of organic cosolvents, surfactants, and hydrophilic auxiliaries.

The presence of an organic cosolvent (typically EtOH or THF as the largely dominant component of mixtures with water) subtracts most of its appeal to operating in what, even if is defined an aqueous medium, really is a very wet organic solvent. The use of surfactants, that in some cases led to very interesting results, suffers from a certain degree of unpredictability, due to modes of action largely depending on the type of reaction.[2] In contrast to this, the method of grafting hydrophilic residues onto water insoluble reactants relies on a simple concept (increased solubility = increased reactivity) and has found extensive applications. For example, in medicinal chemistry chains of poly(ethylene glycols) (PEGs) have been widely employed to increase the bioavailability of certain drugs.[3]

Over the last few years, we have been interested in the immobilization of chiral ligands and catalysts on modified PEGs.[4] Among the supported catalytic systems developed, bisoxazolines **1a** and **1b** (PEG-Box, Chart 1) were found to be efficient and recyclable Cu-ligands for cyclopropanation and ene-type reactions, affording the products in enantiomeric excesses (ee) comparable to those obtained with the nonsupported ligands.[4a,5] The presence of the hydrophilic PEG chain (average $M_r$ 5000 daltons) in these derivatives led us to investigate the use of PEG-Box to perform enantioselective Mukaiyama-aldol condensations in water.[6,7] The solubility of PEG-Box in water could also allow a very simple catalyst recycling, based on extraction of the reaction product in an organic solvent in which the catalyst is not soluble ($Et_2O$, *t*-BuOMe) and addition of fresh substrate and reagent to the catalyst-containing aqueous solution. Here, we wish to report the results of this study.




**1a** R = Ph
**1b** R = *t*Bu
**1c** R = *i*Pr
**1d** R = $PhCH_2$

= $MeO-(CH_2CH_2O)_n-CH_2CH_2-$, n= *ca* 110

**Chart 1** PEG-supported bisoxazolines **1a**–**d**.

## Results and discussion

Inspection of the literature data showed that only two examples of enantioselective catalytic Mukaiyama-aldol reactions in water have been reported. Kobayashi *et al.* described the reaction shown in equation 1 (Scheme 1) that afforded product (*S*)-**2** in 86% yield and 53% ee when carried out in the presence of 3 mol% of Triton®X-100 as a surfactant.[6b] Wang *et al.* reported that in the presence of the gallium (III) complex of a chiral half-crown ether the reaction shown in equation 2 (Scheme 1) proceeded in 41% yield to afford a 90 : 10 *syn* : *anti* mixture of aldol products, the *syn* isomer (*S*,*S*)-**3** having an 84% ee.[6e]

The use of the Cu(II) complexes of PEG-Box **1a**, **1b** in these reactions led to the products in low yield and moderate ee. For example, when the condensation in eq. 2 was carried out with $Cu(SbF_6)_2$/**1a** as the catalyst (20 mol%, water, 0 to 23 °C, 24 h)

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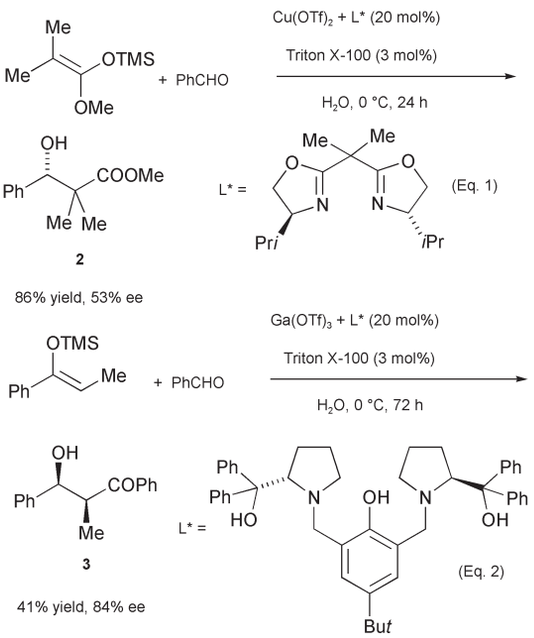


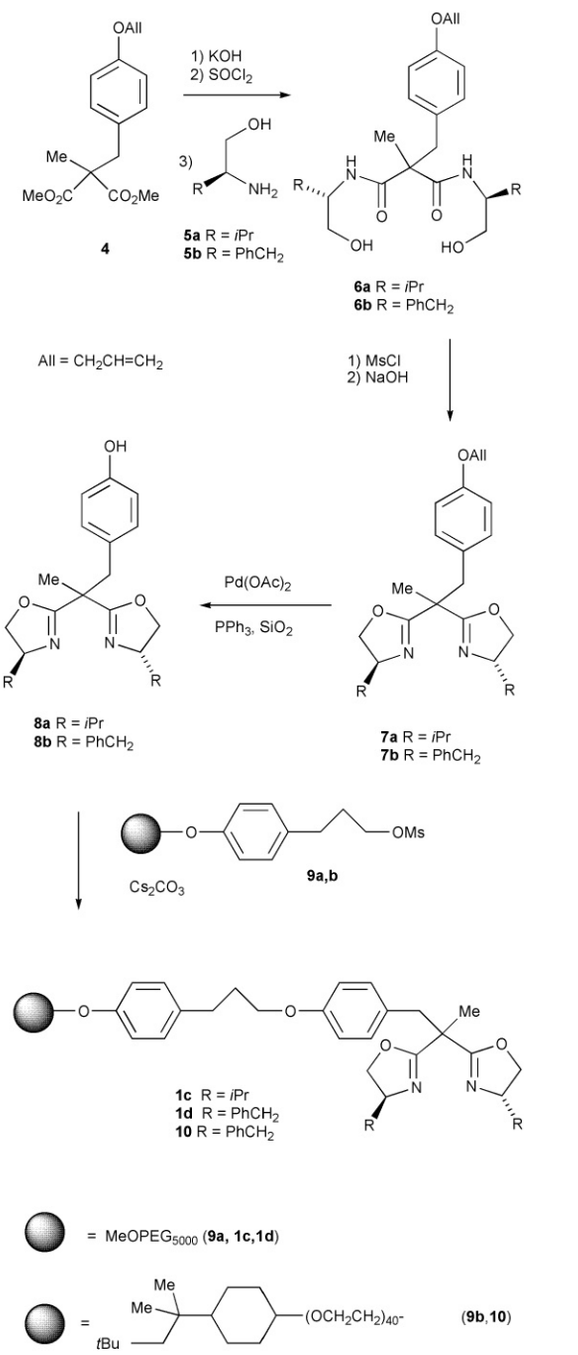

**Scheme 1** Examples of enantioselective catalytic Mukaiyama-aldol reactions carried out in water.

the aldol adduct was isolated in 17% yield as a 75:25 mixture of *syn*:*anti* isomers, compound **3** having 38% ee. Based on the enhanced performances offered by bisoxazolines featuring a benzyl or an *iso*-propyl group at the stereogenic center when the reaction in eq. 1 was carried out in EtOH:water, 9:1,[6b] PEG-Box **1c**, **1d** were prepared following the reaction sequence reported in Scheme 2.

Malonate **4**[4a] was transformed into bisamides **6a**, **6b** by a three step procedure involving ester hydrolysis, acid chloride formation, and reaction with aminoalcohols **5a**, **5b**. The crude products, obtained in 89 and 92% yields, respectively, were used as such owing to the observation that chromatographic purification resulted in some decomposition. Oxazoline-ring closure was performed following the procedure of Denmark *et al.*[8] to give **7a**, **7b** (78% yield for both products). Deallylation[4a] gave the crude phenols **8a**,**b** that were supported on a modified PEG by reaction with the readily available mesylate **9a**[9] in the presence of $Cs_2CO_3$ (DMF, 55 °C, 60 h).[4a] The yields (two steps) for **1c** and **1d** were 78 and 85%, respectively. By the same reaction sequence, bisoxazoline **10** supported on Triton® X-405 (reduced) was prepared in similar yield by reaction of phenol **8b** with *ad hoc* synthesized mesylate **9b**.[10]

Ligands **1c**, **d** were then tested in the synthesis of adduct **2**, that was chosen as the model reaction (20 mol% of ligand, 19 mol% of copper salt, 1.5 mol equiv. of silyl keteneacetal, water, 0 to 23 °C, 24 h). This relatively large amount of catalyst was selected in agreement with that used in similar reactions promoted by polymer-supported bisoxazolines.[5] From the data collected in Table 1 (entries 1–4) it can be seen that the use of the benzyl-substituted PEG-Box **1d** led to the production of (*S*)-**2** in ee (determined by HPLC on a chiral stationary phase) higher than those observed with **1c**, and comparable to or slightly superior than those observed by Kobayashi *et al.* (53%, see above).[6b] However, the reaction occurred in poor yield independently of either the ligand employed, the polymeric support, or the copper counterion. We believe that the poor solubility of the aldehyde substrate in water is likely to be responsible for this result. Triton®-supported ligand **10** performed slightly better than **1d** in terms of stereocontrol but was worse in terms of chemical yield.

The reaction was then extended to other aldehydes to afford the products **11**–**14**, which are presented in Chart 2. As can be seen from the data reported in Table 1, the use of electron-poor aldehydes resulted in improved condensation yields, such as




**Scheme 2** Synthesis of PEG- and Triton®-supported bisoxazolines **1c**, **1d** and **10**.

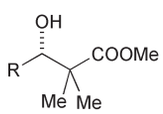
those obtained for adducts **11** (R = 4-$NO_2$Ph, up to 58% yield) and **12** (R = 3-$NO_2$Ph, 55% yield). The yield could be futher increased by using a larger amount of catalyst. For example, with 30 mol% of catalyst **1d**/$Cu(OTf)_2$ adduct **11** was isolated in 83% yield (entry 6). As in the case of the reaction carried out on benzaldehyde, the condensation involving 4-$NO_2$ benzaldehyde proceeded with slightly higher ee in the presence of $Cu(SbF_6)_2$ (entry 7) and Triton®-supported ligand **10** (entries 8 and 9). In contrast to PEG-Box **1d** however, ligand **10** was partially soluble in $Et_2O$, and could be completely separated from the reaction product only by column chromatography.[11] For this reason, the recycling experiments described below were carried out using the catalyst derived from ligand **1d**.

Heteroaromatic aldehydes (R = 2-furyl and 2-thiazolyl) could also be employed in this reaction (entries 11 and 12). The lower ee observed in the case of adduct **14** (R = 2-thiazolyl, ee 31%) was tentatively explained as interference by the heterocyclic nitrogen upon the ligand–copper complexation, resulting in lower stereocontrol. Support of this explanation was found

**Table 1** Enantioselective synthesis of adduct **2** catalyzed by Cu(II) complexes of PEG-box

| Entry | Catalyst | RCHO | Product | Yield (%)[a] | Ee (%)[b] |
|---|---|---|---|---|---|
| 1 | **1c**/$Cu(OTf)_2$ | Ph | **2** | 34 | 40 |
| 2 | **1d**/$Cu(OTf)_2$ | Ph | **2** | 26 | 55 |
| 3 | **1d**/$Cu(SbF_6)_2$ | Ph | **2** | 13 | 62 |
| 4 | **10**/$Cu(OTf)_2$ | Ph | **2** | 12 | 56 |
| 5 | **1d**/$Cu(OTf)_2$ | 4-$NO_2$Ph | **11** | 40 | 50 |
| 6 | **1d**/$Cu(OTf)_2$[c] | 4-$NO_2$Ph | **11** | 83 | 54 |
| 7 | **1d**/$Cu(SbF_6)_2$ | 4-$NO_2$Ph | **11** | 48 | 60 |
| 8 | **10**/$Cu(OTf)_2$ | 4-$NO_2$Ph | **11** | 58 | 58 |
| 9 | **10**/$Cu(SbF_6)_2$ | 4-$NO_2$Ph | **11** | 41 | 63 |
| 10 | **1d**/$Cu(OTf)_2$ | 3-$NO_2$Ph | **12** | 55 | 51 |
| 11 | **1d**/$Cu(OTf)_2$ | 2-Furyl | **13** | 51 | 45 |
| 12 | **1d**/$Cu(OTf)_2$ | 2-Thiazolyl | **14** | 75 | 31 |
| 13 | **1d**/$Cu(OTf)_2$[d] | 4-$NO_2$Ph | **11** | 38 | 45 |
| 14 | **1d**/$Cu(OTf)_2$[e] | 4-$NO_2$Ph | **11** | 38 | 43 |
| 15 | **1d**/$Cu(OTf)_2$[f] | 3-$NO_2$Ph | **12** | 50 | 45 |
| 16 | **1d**/$Cu(OTf)_2$[g] | 3-$NO_2$Ph | **12** | 51 | 38 |

[a] Isolated yields after flash chromatography. [b] As determined by HPLC on a chiral stationary phase (see Experimental section). [c] Reaction carried out in the presence of 0.3 mol equiv. of catalyst. [d] With a catalyst sample recycled from the reaction of entry 5. [e] With a catalyst sample recycled from the reaction of entries 5 and 13. [f] With a catalyst sample recycled from the reactions of entry 5. [g] With a catalyst sample recycled from the reactions of entries 5 and 15.




**11-14**

**11**, R = 4-$NO_2$Ph
**12**, R = 3-$NO_2$Ph
**13**, R = 2-Furyl
**14**, R = 2-Thiazolyl

**Chart 2** Structures of aldol products **11**–**14**.

when the condensation was extended to 2-pyridylcarbaldehyde to afford a racemic product in 77% yield. The existence of a negative stereochemical effect exerted by a chelating substituent on the aldehyde was further demonstrated by the fact that the condensation involving ethyl glyoxalate as the aldehyde afforded the product in 70% yield and only 13% ee.

An interesting opportunity offered by the use of water as reaction solvent for these Cu(II)–PEG-Box catalyzed aldol reactions is represented by the possibility of recycling the catalyst simply by removing the product *via* extraction with a solvent in which the catalyst is not soluble, and adding fresh reagents to the catalyst-containing aqueous phase.[12] This procedure would represent an obvious advantage over the use of Cu–PEG-Box in organic solvent, the recycling of which requires: i) ligand decomplexation with cyanide ions; ii) ligand precipitation with $Et_2O$; and iii) metal replenishment to obtain a species as catalytically active as a freshly prepared catalyst.[4a,13]

To demonstrate the feasibility of this simple recycling procedure, the synthesis of adduct **11** was performed three times under the conditions of entry 5 (entries 5, 13, and 14 in Table 1). In these experiments the product was extracted with diethylether after each cycle and the reagents were added to the aqueous phase containing the catalyst to run the subsequent cycle. We were pleased to find that only a small decrease in chemical yield (from 40%, 1st cycle, to 38%, 2nd and 3rd cycles) and in ee (from 50%, 1st cycle, to 45 and 43%, 2nd and 3rd cycles, respectively) was observed in these experiments, hence allowing one to avoid the tedious procedures often associated with the recovery, reactivation, and recycling of polymer-supported metal-based catalysts.[12] Catalyst recycling could also be performed using the same catalyst in different reactions. Thus, the catalyst employed for the synthesis of adduct **11** (entry 5, Table 1) was successfully recycled twice for the preparation of adduct **12** (entries 15 and 16, Table 1).

## Conclusions

In conclusion, two new PEG-supported enantiomerically pure bisoxazolines have been prepared and employed in combination with Cu(II) salts as catalysts for the Mukaiyama-aldol condensation between the trimethylsilyl keteneacetal of methyl isobutyrate and various aldehydes, carried out in water as the only reaction solvent. Enantiomeric excesses similar to those obtained under the same conditions with nonsupported ligands were observed. The reaction proceeded in higher yields when electron-poor aldehydes were used as the substrates. The high solubility of the ligand in water allowed a very convenient catalyst-recycling procedure involving simple removal of the reaction product by extraction in $Et_2O$ and addition of fresh reagents to the catalyst-containing aqueous solution. The chemical and stereochemical efficiency of the catalyst was only marginally eroded over its use in three reaction cycles. Work is in progress to find new applications of PEG-Box as chiral ligands for catalytic enantioselective reactions in water.

## Experimental

### General

$^1$H NMR spectra were recorded at 300 MHz in chloroform-*d* ($CDCl_3$) unless otherwise stated, and were referenced to tetramethylsilane (TMS) at 0.00 ppm; peak assignments were based on direct and long-range C–H correlations as well as on two-dimensional experiments. $^{13}$C NMR spectra were recorded at 75 MHz and were referenced to 77.0 ppm in $CDCl_3$. Optical rotations were measured at the Na–D line in a 1 dm cell at 22 °C. IR spectra were recorded on thin film or as solutions in DCM. After reactions, PEG-supported product purification involved evaporation of the reaction solvent in a vacuum and addition of the residue dissolved in 2 $cm^3$ of $CH_2Cl_2$ to $Et_2O$ (50 $cm^3$ $g^{-1}$ of polymer), which was stirred and cooled at 0 °C. After 30 min stirring at 0 °C, the obtained suspension was filtered through a sintered glass filter and the solid repeatedly washed on the filter with $Et_2O$ (up to 100 $cm^3$ $g^{-1}$ of polymer, overall).

### Yield and purity determination of PEG-supported compounds

The yield of the PEG-supported compounds were determined by weight with the assumption that $M_r$ is 5000 Da for the PEG fragment. The $M_r$ actually ranged from 4500–5500. The indicated yields were for pure compounds. The purity of these compounds was determined by $^1$H NMR analysis in $CDCl_3$ at 300 MHz with pre-saturation of the methylene signals of the polymer at $\delta$ = 3.63. When recording the NMR spectra, a relaxation time of

6 s and an acquisition time of 4 s were used to ensure complete relaxation and accuracy of the integration. The relaxation delay was selected after $T_1$ measurements. The integration of the signals of the PEG-$OCH_3$ fragment at $\delta$ = 3.36 were used as an internal standard. The estimated integration error was ± 5%. The Triton®-supported compounds were handled similarly, although purity determination was more difficult because Triton®-405 X (reduced) is a mixture of several species.

**(*S*,*S*)-Bis-*N*-1-[1-(1-methylethyl)-2-hydroxyethyl]-2-methyl-2-[4-(1-propenyl-3-oxy) phenylmethyl] 1,3-propandiamide 6a**

To a stirred solution of aminoalcohol **5a** (1.52 g, 14.69 mmol) and triethylamine (5.10 $cm^3$, 36.72 mmol) in dry $CH_2Cl_2$ (25 $cm^3$) stirred under nitrogen and cooled at 0 °C, a solution of the acid dichloride obtained from diester **4**[4a] (2.30 g, 7.64 mmol) in $CH_2Cl_2$ (5 $cm^3$) was added dropwise. The mixture was stirred for 3 h while the reaction temperature was allowed to rise to 23 °C and the reaction was quenched by addition of a saturated aqueous solution of ammonium chloride (30 $cm^3$). The aqueous phase was extracted three times with $CH_2Cl_2$ and the combined organic phases were dried and concentrated under vacuum to give the crude product (2.96 g, 6.80 mmol, 89%). This was shown by $^1$H NMR analysis to be pure enough to be used in subsequent reactions. An analytically pure sample was obtained by flash chromatography, with a 2 : 8 $CH_2Cl_2$ : AcOEt mixture as eluant, as a pale yellow thick oil that solidified on standing in the freezer (the solid melted when warmed-up to room temperature). It had $[\alpha]_D^{22}$ −18.8 (*c* 0.46 in $CH_2Cl_2$). Found: C, 66.5; H, 8.7; N, 6.3; $C_{24}H_{38}N_2O_5$ requires: C, 66.3; H, 8.8; N, 6.5%. IR: $\nu_{max}$/$cm^{-1}$ 3368, 1661. $^1$H NMR: $\delta$ 7.08 (2H, B part of an AB system, *J* = 8.5 Hz, aromatic H *meta* to allyloxy group), 7.01 (1H, d, *J* = 8.8 Hz, NH), 6.79 (2H, A part of an AB system, *J* = 8.5 Hz, aromatic H *ortho* to allyloxy group), 6.63 (1H, d, *J* = 8.6 Hz, NH), 6.07–5.95 (1H, m, C*H*=$CH_2$), 5.39 (1H, d, *J* = 17.2 Hz, C=C*H*H), 5.27 (1H, d, *J* = 10.2 Hz, C=CH*H*), 4.48 (2H, d, *J* = 5.2 Hz, ArOC$H_2$), 3.80–3.45 (8H, m, two C$H_2$O*H* and two C*H*N), 3.35 (1H, B part of an AB system, *J* = 13.3 Hz, C*H*HAr), 2.98 (1 H, part A of an AB system, *J* = 13.3 Hz, CH*H*Ar), 1.85–1.70 (2H, m, two *CH*$Me_2$), 1.29 (3H, s, Me bound to quaternary aliphatic C), 0.94 (3H, d, *J* = 6.9 Hz, one Me of *i*-Pr groups), 0.92 (3H, d, *J* = 6.8 Hz, one Me of *i*-Pr groups), 0.87 (3H, d, *J* = 6.7 Hz, one Me of *i*-Pr groups), 0.78 (3H, d, *J* = 6.8 Hz, one Me of *i*-Pr groups). $^{13}$C NMR: $\delta$ 174.0 (C=O of one amide group), 173.4 (C=O of one amide group), 157.6 (C–allyloxy), 133.2 (*C*H=$CH_2$), 131.0 (2 × C *meta* to allyloxy), 128.6 (C *para* to allyloxy), 117.5 (CH=*C*$H_2$), 114.4 (2 × C *ortho* to allyloxy), 68.7 (ArO$CH_2$), 63.6 (HO$CH_2$ of one aminoalcohol residue), 63.5 (HO$CH_2$ of one aminoalcohol residue), 57.4 (NHCH of one aminoalcohol residue), 57.2 (NHCH of one aminoalcohol residue), 55.0 (quaternary aliphatic C), 43.5 (Ar*C*$H_2$), 29.0 (*C*H$Me_2$ of one aminoalcohol residue), 28.8(*C*H$Me_2$ of one aminoalcohol residue), 19.5 (one Me of *i*-Pr), 18.7 (one Me of *i*-Pr), 18.5 (one Me of *i*-Pr), 18.4 (one Me of *i*-Pr), 18.3 (Me bound to quaternary aliphatic C).

**(*S*,*S*)-Bis-*N*-1-(1-phenylmethyl-2-hydroxyethyl)-2-methyl-2-[4-(1-propenyl-3-oxy) phenylmethyl] 1,3-propandiamide 6b**

To a stirred solution of aminoalcohol **5a** (1.10 g, 7.29 mmol) and triethylamine (2.50 $cm^3$, 18.22 mmol) in dry $CH_2Cl_2$ (20 $cm^3$) stirred under nitrogen and cooled at 0 °C, a solution of the acid dichloride obtained from diester **4**[4a] (1.14 g, 3.79 mmol) in $CH_2Cl_2$ (3 $cm^3$) was added dropwise. The mixture was stirred 3 h while the reaction temperature was allowed to rise to 23 °C and the reaction was quenched by addition of a saturated aqueous solution of ammonium chloride (30 $cm^3$). The aqueous phase was extracted three times with $CH_2Cl_2$ and the combined organic phases were dried and concentrated under vacuum to give the crude product (1.85 g, 3.48 mmol, 92%). This was shown by $^1$H NMR analysis to be pure enough to be used in subsequent reactions. An analytically pure sample was obtained by flash chromatography, with a 2 : 8 $CH_2Cl_2$ : AcOEt mixture as eluant, as a pale yellow thick oil that solidified on standing in the freezer (the solid melted when warmed-up to room temperature). It had $[\alpha]_D^{22}$ −13.1 (*c* 0.4 in $CH_2Cl_2$). Found: C, 72.4; H, 7.2; N, 5.3; $C_{32}H_{38}N_2O_5$ requires: C, 72.4; H, 7.2; N, 5.3%. IR: $\nu_{max}$/$cm^{-1}$ 3340, 1661. $^1$H NMR: $\delta$ 7.31–7.10 (10H, m, aromatic H of two benzyl groups), 6.93 (1H, d, *J* = 8.2 Hz, NH), 6.84 (2H, B part of an AB system, *J* = 8.6 Hz, aromatic H *meta* to allyloxy group), 6.72 (2H, A part of an AB system, *J* = 8.7 Hz, aromatic H *ortho* to allyloxy group), 6.54 (1H, d, *J* = 8.0 Hz, NH), 6.12–5.95 (1H, m, C*H*=$CH_2$), 5.40 (1H, d, *J* = 17.2 Hz, C=C*H*H), 5.28 (1H, d, *J* = 10.2 Hz, C=CH*H*), 4.48 (2H, d, *J* = 5.4 Hz, ArOC$H_2$), 4.25–4.15 (2H, m, two C*H*N), 3.75–3.65 (2H, m, C$H_2$OH), 3.56–3.43 (2H, m, C$H_2$OH), 3.35 (1H, bs, O*H*), 3.20 (1H, bs, O*H*), 3.00–2.70 (6H, m, three C$H_2$Ar), 1.12 (3H, s, Me on quaternary aliphatic C). $^{13}$C NMR: $\delta$ 173.6 (C=O of one amide group), 172.8 (C=O of one amide group), 157.0 (C–allyloxy), 137.5 (aromatic C bound to $CH_2$ in one aminoalcohol residue), 137.1 (aromatic C bound to $CH_2$ in one aminoalcohol residue), 133.2 (*C*H=$CH_2$), 130.9 (2 × C *meta* to allyloxy), 129.1 (2 × C *ortho* to $CH_2$ in the phenyl ring of one aminoalcohol residue), 129.0 (2 × C *ortho* to $CH_2$ in the phenyl ring of one aminoalcohol residue), 128.6 (2 × C *meta* to $CH_2$ in the phenyl ring of one aminoalcohol residue), 128.5 (2 × C *meta* to $CH_2$ in the phenyl ring of one aminoalcohol residue), 128.3 (C *para* to allyloxy), 126.7 (C *para* to $CH_2$ in the phenyl ring of one aminoalcohol residue), 126.6 (C *para* to $CH_2$ in the phenyl ring of one aminoalcohol residue), 117.5 (CH=*C*$H_2$), 114.3 (2 × C *ortho* to allyloxy), 68.7 (O–*C*$H_2$CH=), 64.2 ($CH_2$OH of one aminoalcohol residue), 63.9 ($CH_2$OH of one aminoalcohol residue), 54.6 (quaternary aliphatic C), 53.1 (NHCH of one aminoalcohol residue), 52.8 (NHCH of one aminoalcohol residue), 43.2 ($CH_2$ bound to the quaternary aliphatic carbon) 36.9 ($CH_2$ of benzyl group of one aminoalcohol residue), 36.7 ($CH_2$ of benzyl group of one aminoalcohol residue), 18.2 (Me bound to quaternary aliphatic C).

**Synthesis of Box 7a**

To a stirred solution of bis-amide **6a** (0.30 g, 0.68 mmol) and triethylamine (0.42 $cm^3$, 3.00 mmol) in $CH_2Cl_2$ (5 $cm^3$) kept under nitrogen and cooled at 0 °C, mesyl chloride (0.12 $cm^3$, 1.50 mmol) dissolved in $CH_2Cl_2$ (1 $cm^3$) was added dropwise. The mixture was stirred at RT for 0.5 h. A saturated aqueous solution of ammonium chloride (6 $cm^3$) was then added, and the aqueous phase was extracted three times with $CH_2Cl_2$ (15 $cm^3$). The combined organic phases were dried and concentrated under vacuum to give the crude product. This was added to a 0.5 M solution of NaOH in methanol : water 1 : 1 (4 $cm^3$) and the resulting mixture was stirred at reflux for 3 h. The mixture was then cooled, the organic solvent was evaporated under vacuum, and the aqueous phase was extracted three times with $CH_2Cl_2$ (15 $cm^3$). The combined organic phases were washed with a saturated aqueous solution of NaCl, dried and concentrated under vacuum to give the crude product that was purified by flash chromatography with a 6 : 4 $CH_2Cl_2$ : AcOEt mixture as eluant. The product (0.21 g, 0.53 mmol, 78% yield) was a pale yellow thick oil that solidified on standing in the freezer (the solid melted when warmed-up to room temperature). It had $[\alpha]_D^{22}$ −66.4 (*c* 0.45 in $CH_2Cl_2$). Found: C, 72.0; H, 8.6; N, 7.2; $C_{24}H_{34}N_2O_3$ requires: C, 72.3; H, 8.6; N, 7.0%. IR: $\nu_{max}$/$cm^{-1}$ 1656. $^1$H NMR: $\delta$ 7.09 (2H, B part of an AB system, *J* = 8.7 Hz, aromatic H *meta* to allyloxy group), 6.80 (2H, A part of an AB system, *J* = 8.6 Hz, aromatic H *ortho* to allyloxy group, 6.07–5.95 (1H, m, C*H*=$CH_2$), 5.40 (1H, d, *J* = 17.3 Hz, C=C*H*H), 5.27 (1H, d, *J* = 10.8 Hz, C=CH*H*), 4.51 (2H, d, *J* = 5.3 Hz, ArOC$H_2$), 4.30–4.20 (2H, m, C$H_2$O of oxazoline), 4.12–3.92 (2H, m, C$H_2$O of oxazoline), 3.28 (1H, B part of an AB system, *J* = 13.5 Hz, C*H*HAr), 3.23 (1H, A part of an AB system, *J* = 13.5 Hz, CH*H*Ar), 1.85–1.70 (2H, m, two *CH*$Me_2$),

1.43 (3H, s, Me bound to quaternary aliphatic C), 0.94 (3H, d, $J$ = 6.9 Hz, one Me of *i*-Pr groups), 0.90 (3H, d, $J$ = 7.3 Hz, one Me of *i*-Pr groups), 0.87 (3H, d, $J$ = 7.0 Hz, one Me of *i*-Pr groups), 0.83 (3H, d, $J$ = 6.7 Hz, one Me of *i*-Pr groups). $^{13}$C NMR: $\delta$ 168.0 (C=N of one oxazoline), 167.9 (C=N of one oxazoline), 157.5 (C–allyloxy), 131.8 (2 × C *meta* to allyloxy), 130.8 (*C*H=$CH_2$), 129.4 (C *para* to allyloxy), 117.9 (CH=*C*$H_2$), 114.6 (2 × C *ortho* to allyloxy), 72.4 (CH of one oxazoline), 72.0 (CH of one oxazoline), 70.4 ($CH_2$ of one oxazoline), 70.1($CH_2$ of one oxazoline), 69.2 (Ar*O*$CH_2$), 43.9 (quaternary aliphatic C), 41.7 (Ar$CH_2$), 32.9 (*C*H$Me_2$), 32.6(*C*H$Me_2$), 21.6 (Me on quaternary aliphatic C), 19.2 (one Me of *i*-Pr), 19.0 (one Me of *i*-Pr), 18.2 (one Me of *i*-Pr), 17.8 (one Me of *i*-Pr).

### Synthesis of Box 7b

To a stirred solution of bis-amide **6b** (1.48 g, 2.80 mmol) and triethylamine (1.71 cm$^3$, 12.32 mmol) in $CH_2Cl_2$ (25 cm$^3$) kept under nitrogen and cooled at 0 °C, mesyl chloride (0.48 cm$^3$, 6.16 mmol) dissolved in $CH_2Cl_2$ (5 cm$^3$) was added dropwise. The mixture was stirred at RT for 0.5 h. A saturated aqueous solution of ammonium chloride (30 cm$^3$) was then added and the aqueous phase was extracted three times with $CH_2Cl_2$ (30 cm$^3$). The combined organic phases were dried and concentrated under vacuum to give the crude product. This was added to a 0.5 M solution of NaOH in methanol : water 1 : 1 (17 cm$^3$) and the resulting mixture was stirred at reflux for 3 h. The mixture was then cooled, the organic solvent was evaporated under vacuum, and the aqueous phase was extracted three times with $CH_2Cl_2$ (35 cm$^3$). The combined organic phases were washed with a saturated aqueous solution of NaCl, dried and concentrated under vacuum to give the crude product, that was purified by flash chromatography with a 6 : 4 $CH_2Cl_2$ : AcOEt mixture as eluant. The product (1.08 g, 2.18 mmol, 78% yield) was a pale yellow thick oil that solidified on standing in the freezer (the solid melted on standing at room temperature). It had $[\alpha]_D^{22}$ −30.7 (*c* 0.45 in $CH_2Cl_2$). Found: C, 77.4; H, 6.7; N, 5.8; $C_{32}H_{34}N_2O_3$ requires: C, 77.7; H, 6.9; N, 5.7%. IR: $\nu_{max}$/cm$^{-1}$ 1656. $^1$H NMR: $\delta$ 7.34–7.10 (12H, aromatic H of two benzyl groups and two *meta* H of *Ar*O), 6.85 (2H, A part of an AB system, $J$ = 8.6 Hz, aromatic H *ortho* to allyloxy group), 6.13–5.99 (1H, m, C*H*=$CH_2$), 5.42 (1H, d, $J$ = 17.0 Hz, C=C*H*H), 5.28 (1H, d, $J$ = 11.0 Hz, C=CH*H*), 4.53 (2H, d, $J$ = 5.3 Hz, ArO*C*$H_2$), 4.45–4.35 (2H, m, two C*H*N), 4.23 (2H, dt, $J$ = 8.0, 6.5 Hz, C$H_2$O of oxazoline), 4.02 (2H, dt, $J$ = 8.0, 7.6, C$H_2$O of oxazoline), 3.27 (1H, B part of AB system, $J$ = 13.7 Hz, C*H*HArO), 3.20 (1H, A part of AB system, $J$ = 13.7 Hz, CH*H*ArO), 3.18–3.01 (2H, m, C$H_2$Ar), 2.70–2.46 (2H, m, C$H_2$Ar), 1.43 (3H, s, Me bound to quaternary aliphatic C). $^{13}$C NMR: $\delta$ 168.0 (C=N of one oxazoline), 167.9 (C=N of one oxazoline), 158.0 (C–allyloxy), 137.8 (aromatic C bound to $CH_2$ in one oxazoline), 137.7 (aromatic C bound to $CH_2$ in one oxazoline), 133.3 (*C*H=$CH_2$), 131.4 (2xC *meta* to allyloxy), 129.3 (2 × C *ortho* to $CH_2$ in the phenyl ring of one oxazoline), 129.2 (2 × C *ortho* to $CH_2$ in the phenyl ring of one oxazoline), 128.5 (2 × C *meta* to $CH_2$ in the phenyl ring of one oxazoline), 128.4 (2 × C *meta* to $CH_2$ in the phenyl ring of one oxazoline), 128.0 (C *para* to allyloxy), 126.4 (C *para* to $CH_2$ in the phenyl ring of one oxazoline), 126.3 (C *para* to $CH_2$ in the phenyl ring of one oxazoline), 117.4 (CH=*C*$H_2$), 114.2 (2 × C *ortho* to allyloxy), 72.1 ($CH_2$ in one oxazoline), 71.8 ($CH_2$ in one oxazoline), 68.8 (O–*C*$H_2$CH=), 67.2 (CH in one oxazoline), 67.0 (CH in one oxazoline), 43.3 (quaternary aliphatic C), 41.6 ($CH_2$ of benzyl group of one oxazoline), 41.3 ($CH_2$ of benzyl group of one oxazoline), 41.2 ($CH_2$ bound to quaternary aliphatic carbon), 21.1 (Me bound to quaternary aliphatic C).

### Synthesis of Box 8a

A solution of *O*-allyl protected Box **7a** (0.081 g, 0.20 mmol) in ethanol (3 cm$^3$) containing $Pd(OAc)_2$ (0.005 g, 0.02 mmol) and $PPh_3$ (0.024 g, 0.09 mmol) was refluxed for 60 min. The resulting mixture was cooled at RT and $SiO_2$ (1 g) was added in one portion. After 15 min stirring at RT the mixture was filtered through a Celite cake, the solvent was evaporated under vacuum to give the crude product (0.069 g, 0.19 mmol, 95% yield) as a pale yellow thick oil that was used as such for the subsequent transformation.

### Synthesis of Box 8b

A solution of *O*-allyl protected Box **7b** (0.45 g, 0.90 mmol) in ethanol (14.0 cm$^3$) containing $Pd(OAc)_2$ (0.020 g, 0.09 mmol) and $PPh_3$ (0.105 g, 0.40 mmol) was refluxed for 60 min. The resulting mixture was cooled at RT and $SiO_2$ (2 g) was added in one portion. After 15 min stirring at RT the mixture was filtered through a Celite cake, the solvent was evaporated under vacuum to give the crude product (0.39 g, 0.86 mmol, 95% yield) as a pale yellow thick oil that was used as such for the subsequent transformation.

### Synthesis of PEG-supported Box 1c

To a solution of mesylate **9a**[8] (0.48 g, 0.09 mmol) and Box **8a** (0.047 g, 0.13 mmol) in DMF (4.0 cm$^3$) stirred under nitrogen, $Cs_2CO_3$ (0.14 g, 0.39 mmol) was added. The mixture was warmed up to 55 °C and stirred at that temperature for 60 h. $Cs_2CO_3$ was then removed by filtration of the cooled mixture and the solvent was evaporated under vacuum. The residue was taken up into $CH_2Cl_2$ (1 cm$^3$) and the product was precipitated with $Et_2O$. The product (0.41 g, 0.075 mmol, 82% yield) was isolated by filtration as a pale brown solid. $^1$H NMR: $\delta$ 7.11 (2H, B part of an AB system, $J$ = 8.6 Hz, aromatic H *ortho* to methylene group bound to quaternary aliphatic C), 7.07 (2H, B part of an AB system, $J$ = 8.6 Hz, aromatic H *meta* to MeOPEGO residue), 6.85 (2H, A part of an AB system, $J$ = 8.6 Hz, aromatic H *meta* to methylene group bound to quaternary aliphatic C), 6.77 (2H, A part of an AB system, $J$ = 8.6 Hz, aromatic H *ortho* to MeOPEGO residue), 4.23–3.95 (8H, m, C$H_2$O and C*H*N of Box, and PEGOC$H_2$C$H_2$OPh), 3.90 (2H, t, $J$ = 6.7 Hz, $CH_2CH_2CH_2$OPh), 3.84 (2H, t, $J$ = 6.5 Hz, PEGOC$H_2CH_2$OPh), 3.42 (2H, t, $J$ = 6.7 Hz, MeOC$H_2$C$H_2$O), 3.36 (3H, s, MeOPEG), 3.23 (1H, B part of an AB system, $J$ = 13.5 Hz, one H of methylene group bound to quaternary aliphatic C), 3.19 (1H, A part of an AB system, $J$ = 13.5 Hz, one H of methylene group bound to quaternary aliphatic C), 2.73 (2H, t, $J$ = 6.5 Hz, PEGOPhC$H_2CH_2CH_2$), 2.00–2.10 (2H, m, PEGOPhC$H_2$C$H_2CH_2$), 190–1.65 (2H, m, *CH*$Me_2$), 1.42 (3H, s, Me bound to quaternary aliphatic C), 0.93 (3H, d, $J$ = 6.7 Hz, one Me of *i*-Pr groups), 0.88 (3H, d, $J$ = 7.2 Hz, one Me of *i*-Pr groups), 0.86 (3H, d, $J$ = 7.2 Hz, one Me of *i*-Pr groups), 0.83 (3H, d, $J$ = 6.7 Hz, one Me of *i*-Pr groups).

### Synthesis of PEG-supported Box 1d

To a solution of mesylate **9a** (3.65 g, 0.7 mmol) and Box **8b** (0.512 g, 1.13 mmol) in DMF (12.0 cm$^3$) stirred under nitrogen, $Cs_2CO_3$ (1.10 g, 3.38 mmol) was added. The mixture was warmed up to 55 °C and stirred at that temperature for 60 h. $Cs_2CO_3$ was then removed by filtration of the cooled mixture and the solvent was evaporated under vacuum. The residue was taken up into $CH_2Cl_2$ (4 cm$^3$) and the product was precipitated with $Et_2O$. The product (3.49 g, 0.63 mmol, 89% yield) was isolated by filtration as a pale brown solid. $^1$H NMR: $\delta$ 7.35–7.05 (14H, m, ten hydrogens of benzyl groups and four hydrogens *meta* to oxygen atoms in the other two aromatic rings), 6.87–6.75 (4H, m, four remaining aromatic hydrogens), 4.50–4.40 (2H, m, C*H*N), 4.24–3.99 (6H, PEGC$H_2$OPh and C$H_2$O of oxazolines), 3.95–3.83 (4H, m, PEGOC$H_2CH_2$OPh and $CH_2CH_2CH_2$OPh), 3.42 (2H, t, $J$ = 6.7 Hz, MeOC$H_2$C$H_2$O), 3.36 (3H, s, MeOPEG), 3.25 (1H, B part of an AB system, $J$ = 13.5 Hz, one H of methylene group bound to quaternary aliphatic C), 3.19 (1H,

A part of an AB system, $J$ = 13.5 Hz, one H of methylene group bound to quaternary aliphatic C), 3.15–3.00 (2H, m, two hydrogens of methylenes of oxazoline benzyl group), 2.74 (2H, t, $J$ = 6.8 Hz, PEGOPhC$H_2$CH$_2$CH$_2$), 2.65–2.50 (2H, m, two hydrogens of methylenes of oxazoline benzyl group), 2.00–2.10 (2H, m, PEGOPhCH$_2$C$H_2$CH$_2$), 1.42 (3H, s, Me bound to quaternary aliphatic C).

### Synthesis of mesylate 9b

*Mesylation of Triton® X-405* (*reduced*): To a stirred solution of Triton® X-405 (reduced) (1.01 g, 0.51 mmol) in $CH_2Cl_2$ (8 cm$^3$) kept under nitrogen, mesyl chloride (0.12 cm$^3$, 1.52 mmol) and trioctylamine (0.89 cm$^3$, 2.03 mmol) were added in this order. The mixture was stirred at RT for 24 h, and the volatile materials were removed under vacuum. The resulting residue was dissolved in $CH_2Cl_2$ (1 cm$^3$) and the product was precipitated with diethylether (70 cm$^3$). The solid was filtered, washed on the filter with pentane (10 cm$^3$) and dried under high vacuum, to give 0.780 g of product (75% yield) that was used as such. The $^1$H NMR spectrum (see ref. 10) showed the presence of the $MeSO_2$ group at $\delta$ = 3.10.

**Insertion of the spacer.** To a solution of Triton® X-405 (reduced) mesylate (3.25 g, 1.58 mmol) in dry DMF (11.0 cm$^3$) kept under nitrogen at 55 °C, 3-(4-hydroxyphenyl)propan-1-ol (0.482 g, 3.17 mmol) and $Cs_2CO_3$ (1.03 g, 3.17 mmol) were added. The mixture was stirred at that temperature for 46 h. $Cs_2CO_3$ was then removed by filtration of the cooled mixture and the solvent was evaporated under vacuum. The residue was taken up into $CH_2Cl_2$ (3 cm$^3$) and the product was precipitated with $Et_2O$. The product (2.36 g, 1.11 mmol, 70% yield) was isolated by filtration as a pale brown solid. The $^1$H NMR spectrum showed the presence of the typical resonances of the $C_6H_4CH_2CH_2CH_2OH$ spacer bound to a poly(ethylene glycol) chain.[9]

**Mesylation of the Triton® X-405 (reduced)/spacer adduct.** To a stirred solution of the alcohol (1.30 g, 0.61 mmol) in $CH_2Cl_2$ (9.6 cm$^3$) kept under nitrogen, mesyl chloride (0.14 cm$^3$, 1.84 mmol) and trioctylamine (1.08 cm$^3$, 2.45 mmol) were added in this order. The mixture was stirred at RT for 24 h, and the volatile materials were removed under vacuum. The resulting residue was dissolved in $CH_2Cl_2$ (1.5 cm$^3$) and the product was precipitated with $Et_2O$ (90 cm$^3$). The solid was filtered, washed on the filter with pentane (10 cm$^3$), and dried under high vacuum, to give 1.10 g of product (82% yield) that was used as such for the synthesis of **10**. The $^1$H NMR spectrum showed the presence of the $MeSO_2$ group at $\delta$ = 3.07.[9]

### Synthesis of Triton®-supported Box 10

To a solution of mesylate **9b** (1.10 g, 0.50 mmol) and Box **8b** (0.41 g, 0.90 mmol) in DMF (4.5 cm$^3$) stirred under nitrogen, $Cs_2CO_3$ (0.88 g, 2.71 mmol) was added. The mixture was warmed up to 55 °C and stirred at that temperature for 72 h. $Cs_2CO_3$ was then removed by filtration of the cooled mixture and the solvent was evaporated under vacuum. The residue was taken up into $CH_2Cl_2$ (1.5 cm$^3$) and the product was precipitated with $Et_2O$. The product (0.93 g, 72% yield) was isolated by filtration as a pale brown solid. The $^1$H NMR spectrum showed the presence of the benzyl substituted bisoxazoline residue.

### Aldol condensations (eq. 1)

The synthesis of (*S*)-methyl 2,2-dimethyl-3-hydroxy-3-phenylpropanoate **2** is illustrative of the general procedure: To a stirred solution of PEG-Box **1d** (0.30 g, 0.053 mmol) in dry $CH_2Cl_2$ (2.0 cm$^3$), Cu(OTf)$_2$ (0.019 g, 0.05 mmol) was added and the mixture stirred at 23 °C for 3 h. The solvent was then evaporated under vacuum and the residue was kept under high vacuum for 5 min. The complex thus obtained was dissolved in water (1 cm$^3$), the resulting solution was cooled at 0 °C, and benzaldehyde (0.027 cm$^3$, 0.27 mmol) and the silyl keteneacetal (0.081 cm$^3$, 0.40 mmol) were added in this order. The mixture was stirred for 24 h while the temperature was allowed to rise to 23 °C. The reaction mixture was then extracted with $Et_2O$ (3 × 5 cm$^3$) and the combined organic phases were dried and concentrated under vacuum. The residue was purified by flash chromatography with a hexanes : AcOEt 8 : 2 mixture as eluant to afford the product (*S*)-**2** (0.014 g, 0.07 mmol, 26% yield) as a white solid; mp 70–71 °C (lit.:[14] 71–72 °C); $[\alpha]_D^{22}$ +17.0 (*c* 0.5 in $CHCl_3$) (lit.,[14] $[\alpha]_D^{22}$ +30.6 (*c* 1.05 in $CHCl_3$) for a sample having ee > 99%). The ee was established by HPLC analysis on a Chiralpak AD column, flow rate 0.8 cm$^3$ min$^{-1}$, $\lambda$ = 210 nm; hexane : ethanol 95 : 5; $t_R$ 14.3 min (minor) and 20.4 min (major). The product had $^1$H NMR data identical to those reported.[14]

Cu(SbF$_6$)$_2$ was prepared according to the reported procedure.[15] The reactions performed using the Cu(SbF$_6$)$_2$–PEG-Box complexes were carried out following the same procedure employed in the Cu(OTf)$_2$ catalyzed ones.

Using the procedure described for the synthesis of compound **2**, the following products were obtained. The absolute configurations of these products were tentatively assigned on the basis of a common eluting behavior on the same chiral stationary phase.

### (*S*)-Methyl 2,2-dimethyl-3-hydroxy-3-(4-nitrophenyl)propanoate 11

The product was a pale yellow solid isolated by flash chromatography with a hexanes : AcOEt 8 : 2 mixture as eluant; mp 113–114 °C (lit.,[16] 114.5 °C); $[\alpha]_D^{22}$ +2.0 (*c* 0.62 in $CH_2Cl_2$) for a sample having ee = 50%. The ee was established by HPLC analysis on a Chiralpak AD column, flow rate 0.8 cm$^3$ min$^{-1}$, $\lambda$ = 210 nm; hexane : ethanol 90 : 10; $t_R$ 18.0 min (minor) and 20.5 min (major). The product had $^1$H NMR data identical to those reported.[16]

### (*S*)-Methyl 2,2-dimethyl-3-hydroxy-3-(3-nitrophenyl)propanoate 12

The product was a pale yellow solid isolated by flash chromatography with a hexanes : AcOEt 8 : 2 mixture as eluant; mp 73–75 °C. Found: C, 57.1; H, 5.85; N, 5.5; $C_{12}H_{15}NO_5$ requires: C, 56.9; H, 6.0; N, 5.5%. IR: $\nu_{max}$/cm$^{-1}$ 3450, 1720. $[\alpha]_D^{22}$ +1.8 (*c* 0.25 in $CH_2Cl_2$) for a sample having ee = 51%. The ee was established by HPLC analysis on a Chiralcel AD column, flow rate 0.8 cm$^3$ min$^{-1}$, $\lambda$ = 210 nm; hexane : ethanol 90 : 10; $t_R$ 17.8 min (minor) and 20.5 min (major). $^1$H NMR: $\delta$ 8.16–8.30 (2H, m, aromatic H), 7.51–7.80 (2H, m, aromatic H), 5.06 (1H, s, C*H*OH), 3.75 (3H, s, MeO), 2.10 (bs, 1H, OH), 1.18 (6H, s, two Me's). $^{13}$C NMR: $\delta$ 170.5 (C=O), 149.6 (C–NO$_2$), 137.1 (aromatic *C*–CHOH), 133.9 (C *para* to NO$_2$), 129.51 (C *meta* to NO$_2$), 123.8 (aromatic C between NO$_2$ and alkyl chain), 119.9 (C *ortho* to NO$_2$), 72.0 (OMe), 51.5 (CHOH), 31.9 (quaternary aliphatic C), 19.2 (2 × Me).

### (*R*)-Methyl 2,2-dimethyl-3-hydroxy-3-(2-furyl)propanoate 13

The product was a colorless oil isolated by flash chromatography with a hexanes : AcOEt 8 : 2 mixture as eluant, and had $^1$H NMR data identical to those reported for the racemic compound.[17] A sample of 45% ee had $[\alpha]_D^{22}$ +7.3 (*c* 0.1 in $CH_2Cl_2$). The ee was established by HPLC analysis on a Chiralpak AD column, flow rate 0.8 cm$^3$ min$^{-1}$, $\lambda$ = 210 nm; hexane : ethanol 95 : 5; $t_R$ 15.1 min (minor) and 22.8 min (major).

### (*R*)-Methyl 2,2-dimethyl-3-hydroxy-3-(2-thiazolyl)propanoate 14

The product was a pale yellow solid isolated by flash chromatography with a hexanes : AcOEt 8 : 2 mixture as eluant; mp 63–65 °C. Found: C, 50.3; H, 5.95; N, 6.6; $C_9H_{13}NO_3S$ requires:

C, 50.2; H, 6.1; N, 6.5%. IR: $\nu_{max}$/cm$^{-1}$ 3520, 1710, 1455. A sample of 31% ee had $[a]_D^{22}$ +0.7 (*c* 0.41 in $CH_2Cl_2$). The ee was established by HPLC analysis on a Chiralcel AD column, flow rate 0.8 cm$^3$ min$^{-1}$, $\lambda$ = 210 nm; hexane : ethanol 90 : 10; $t_R$ 12.5 min (minor) and 31.2 min (major). $^1$H NMR: $\delta$ 7.80 (1H, d, *J* = 3.0 Hz, NCH), 7.39 (1H, d, *J* = 3.0 Hz, SCH), 5.10 (1H, s, C*H*OH), 3.72 (3H, s, MeO), 1.15 (6H, s, two Me's). 13C NMR: $\delta$ 171.5 (C=O), 161.5 (C=N), 131.8 (C–N), 127.7(C–S), 69.7 (OMe), 51.1 (CHOH), 29.7 (quaternary aliphatic C), 19.1 (2 × Me).

### Ligand recovery

The ligands were recovered from the aqueous phase after product extraction with $Et_2O$ using the following procedure; to the aqueous solution, water (5 cm$^3$), $CH_2Cl_2$ (10 cm$^3$), and solid KCN (two fold molar excess) were added, and the mixture vigorously stirred at RT for 10 min. The organic phase was separated and the aqueous phase was extracted twice with $CH_2Cl_2$ (2 × 5 cm$^3$). The combined organic phases were dried and concentrated under vacuum to a 1 cm$^3$ volume. The polymer-supported ligand was recovered by precipitation with $Et_2O$ followed by filtration. $^1$H NMR analysis of the recovered material did not show any decomposition. Typical recovery yields ranged from 70 to 85% for the PEG-Box **1c**, **1d** and from 50 to 65% for Triton®-supported **10**, that precipitated less readily than **1c**, **1d** from $Et_2O$.

### Catalyst recycling

This was simply achieved by removal of the reaction product and unreacted starting materials from the aqueous reaction mixture by extraction with $Et_2O$, followed by cooling the aqueous solution at 0 °C and addition of fresh aldehyde and silyl keteacetal.

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