Poly(ethylene glycol)-Supported Bisoxazolines as Ligands for Catalytic Enantioselective Synthesis

Rita Annunziata, Maurizio Benaglia, Mauro Cinquini, Franco Cozzi,* and Manuela Pitillo

Centro CNR and Dipartimento di Chimica Organica e Industriale, Universita' degli Studi di Milano, Via Golgi 19−20133 Milano, Italy

franco.cozzi@unimi.it

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Two chiral bisoxazolines (box) supported on a modified poly(ethylene glycol) (PEG) have been prepared by a reaction sequence that involved formation of the properly functionalized box and their attachment to the polymer matrix by means of a spacer and a linker. The solubility properties of PEG allowed use of the supported box as ligands in some catalytic asymmetric transformations carried out under homogeneous conditions and to recover the ligands as if bound to an insoluble support. When the supported box were employed in combination with Cu(II) salts in the Diels−Alder cycloaddition between cyclopentadiene and *N*-acryloyloxazolidinone, low levels of enantioselectivity were observed (up to 45% ee). Much better results were obtained in the cyclopropanation of styrenes carried out in the presence of CuOTf (up to 93% ee) and in the ene-reaction between α-methylstyrene or methylenecyclohexane and ethylglyoxalate (up to 95% ee). One of the ligands, readily recovered by precipitation and filtration, was recycled two times in the ene-reaction with marginal loss in the catalytic activity and very limited erosion of the enantioselectivity.

Introduction

The immobilization of chiral ligands and catalysts on polymer supports is a current subject of intense research activity. This effort aims to improve the efficiency of asymmetric catalysis[1] by allowing simple ligand or catalyst recovery and recycle.

While the use of insoluble polymeric supports has been widespread,[2] immobilization on soluble polymers has received much less attention.[3] This is surprising since soluble polymers, allowing the reaction to be carried out under homogeneous conditions, secure higher enantioselectivity and more catalytic cycles than insoluble supports, as recently demonstrated by Janda and Reger.[3e,4] Moreover, a judicious choice of the soluble polymer can provide an ideal support, that combines the advantages of running a reaction under homogeneous conditions with those of recovering and recycling a heterogeneous catalyst.

Modified poly(ethylene glycol)s (PEGs) of M_w > 2000 Da recently emerged as readily functionalized, inexpensive polymers that, conveniently, are soluble in some solvents and insoluble in a few other solvents.[5] Recently, the monomethyl ether of PEG $_{5000}$ (MeOPEG) has successfully being used for supporting chiral *ligands* to be transformed in catalysts for the asymmetric dihydroxylation [3a,b] and epoxidation reactions.[3e] MeOPEG has also been employed by us for the immobilization of achiral[6] and chiral[7] *catalysts*. In both cases the obtained species showed catalytic activity and stereocontrol ability very similar to (and in some instances even superior than) those displayed by the nonsupported catalysts.

As a part of these studies, here we report the immobilization on MeOPEG of two chiral ligands belonging to the extremely useful bisoxazoline (box) family,[8] and the use of these soluble polymer-supported ligands in some enantioselective transformations.[9]

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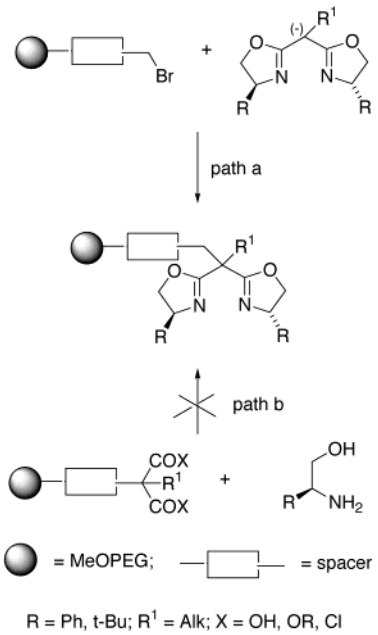
Scheme 1. Different Approaches to the Synthesis of MeOPEG-Supported Bisoxazolines



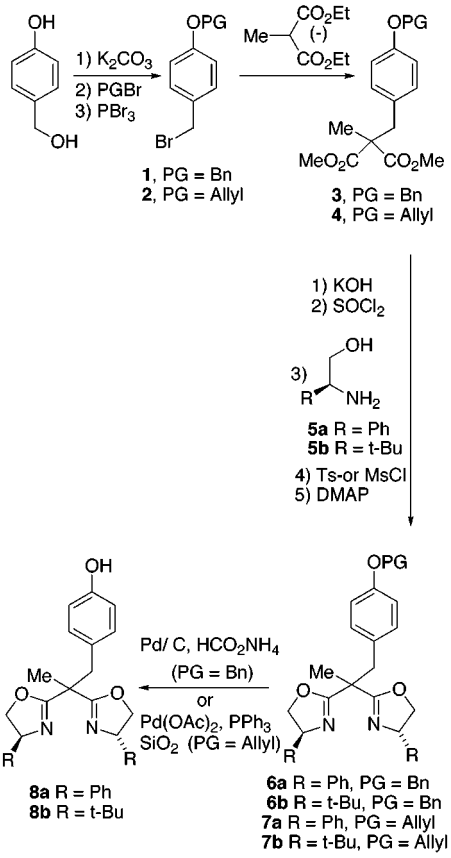
R = Ph, t-Bu; R^1 = Alk; X = OH, OR, Cl

Results and Discussion

Two different strategies can in principle be followed to prepare MeOPEG-supported box: reaction of a preformed, metalated box with a MeOPEG activated toward nucleophilic substitution (Scheme 1, path a); or construction of the box moiety on a MeOPEG carrying a malonate-type substitution (Scheme 1, path b). Path b had the advantages of a polymer-supported stepwise synthesis (easy product isolation and purification) and in principle seemed more appealing. However, preliminary experiments showed MeOPEG malonic acid derivatives to be poorly reactive. Therefore, path a was pursued.

The synthesis of the box ligands was designed, taking into account (i) the necessity of introducing a spacer to separate the MeOPEG core from the ligand; (ii) a mild and efficient reaction to attach the box/spacer array to the polymer; and (iii) the need for disubstitution at the box bridging atom, a feature known to enhance the stereoselectivity of box-promoted reactions.[8] On the basis of our previous experience in the field of PEG-supported synthesis of small organic molecules,[6,10] the reaction sequence outlined in Scheme 2 was performed.

Scheme 2. Synthesis of Box 8a and 8b



O-Benzyl and -allyl protected 4-alkoxybenzyl bromides **1** and **2** were easily obtained from the commercially available 4-hydroxymethylphenol by phenoxide ion alkylation and reaction with PBr_3 (80 and 82% overall yield for **1** and **2**, respectively). These bromides were used to alkylate the lithium enolate of dimethyl methylmalonate to afford esters **3** (R = benzyl, 86%) and **4** (R = allyl, 94% yield). These were then transformed by standard procedures into the corresponding dichlorides that were obtained as crude products in ≥ 95% yield.

Conversion to box was accomplished by a stepwise procedure[11] involving amide formation with commercially available (*S*)-amino alcohols **5a** (R = Ph) and **5b** (R = t-Bu), followed by alcohol activation as tosylate (R = Ph) or mesylate (R = t-Bu), and oxazoline ring closure promoted by DMAP. The overall yields from esters **3** and **4** were 47% for **6a**, 45% for **6b**, 40% for **7a**, and 72% for **7b**.

Finally, deprotection of the phenol oxygen was studied. After some attempts, it was found out that microwave-promoted transfer hydrogenation[12] gave **8a** and **8b** in 66 and 32% yield, respectively. These products were obtained in higher yield (67 and 82%, respectively) by deallylation of **7a**,**b**, that was best accomplished by a modification of a literature procedure[13] involving the use of $Pd(OAc)_2$ and PPh_3 in EtOH in the presence of SiO_2.

(4) For recent studies on the effect of polymer matrixes on the reactivity of supported organic molecules, see: (a) Li, W.; Yan, B. *J. Org. Chem.* **1998**, *63*, 4092−4097. (b) Gerritz, S. W.; Trump, R. P.; Zuercher, W. J. *J. Am. Chem. Soc.* **2000**, *122*, 6357−6363.

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(9) During the completion of this work, two syntheses of polymer-supported bisoxazolines have been reported. In the first case (ref 3f) the new ligands aza-bisoxazolines were synthesized, attached to MeOPEG, and tested in the asymmetric cyclopropanation of styrene. In the second case (ref 2q) different insoluble polymers containing bisoxazoline units have been prepared and used in the same reaction. The results obtained with these supported ligands are discussed in the text.

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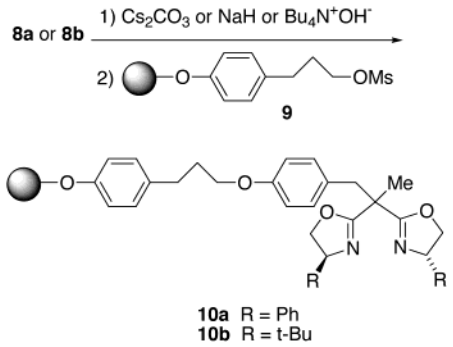
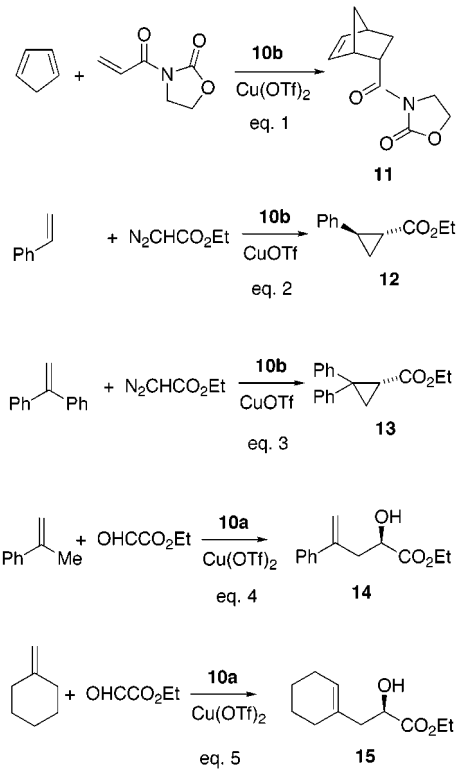
(13) Guibe', F. *Tetrahedron* **1998**, *54*, 2967−3042, and references therein.

Scheme 3. Synthesis of MeOPEG-Supported Box Ligands 10a and 10b



Scheme 4. Enantioselective Reactions Catalyzed by Metal Complexes of Box Ligands 10a and 10b



Mesylate **9** (easily prepared in >98% yield from MeOPEG)[10c] was selected for immobilization of box **8a**,**b** (Scheme 3). The reaction was performed in DMF using different bases to generate the phenoxide ion. Supported box **10a** and **10b** were obtained in 90 and 92% yield using Cs_2CO_3, 60 and 57% yield using NaH, and 83 and 87% yield using $Bu_4N^+HO^-$ (see the Experimental Section for isolation, purification, and yield and purity determination of PEG-supported compounds).

The supported ligands **10a**,**b** were then tested in the representative enantioselective transformations reported in Scheme 4 (eqs 1−5). The results were collected in Table 1.

The Diels Alder cycloaddition between cyclopentadiene (10 mol equiv) and *N*-acryloyloxazolidinone (1.0 mol equiv) was carried out in CH_2Cl_2 in the presence of 15 mol % each of ligand **10b** and $Cu(OTf)_2$ (−78 °C for 3 h and then from −78 °C to RT, total reaction time 15 h).[14] The reaction occurred to afford adduct **11** in good yield, excellent *endo* stereoselectivity, but with no enantioselectivity. Also the use of $Cu(SbF_6)_2$ [14] was unsuccessful,

Table 1. Enantioselective Reactions Catalyzed by Ligands 10a,b

eq	catalyst (mol %)	product	isolated yield %	diast. ratio[a]	ee %[b]
1	**10b**/$Cu(OTf)_2$ (15)	**11**	91	>98:2	0
1	**10b**/$Cu(SbF_6)_2$ (15)	**11**	98	>98:2	5
1	**10b**/$Cu(OTf)_2$ (15)[c]	**11**	70	>98:2	30
1	**10b**/$Cu(OTf)_2$ (15)[d]	**11**	83	>98:2	45
2	**10b**/CuOTf (10)	**12**	45	70:30	87
2	**10b**/CuOTf (10)	**12**	63	77:23	91
3	**10b**/CuOTf (10)	**13**	45	−	93
4	**10a**/$Cu(OTf)_2$ (10)	**14**	96	−	95
5	**10a**/$Cu(OTf)_2$ (10)	**15**	91	−	87
4	**10a**/$Cu(OTf)_2$ (10)[e]	**14**	91	−	90
4	**10a**/$Cu(OTf)_2$ (10)[f]	**14**	93	−	88

[a] For product **11**: *endo:exo* ratio; for product **12**: *trans:cis* ratio. These ratios were determined by ^{1}H NMR on the crude reaction products. [b] As determined by ^{1}H NMR/chiral shift reagent technique (for **11**), by optical rotation measurement (on pure samples of **12** and **13** obtained by flash chromatography), or by the Mosher ester method (for **14** and **15**); in the case of compound **12** the ee determined by optical rotation was confirmed by chiral HPLC. [c] With a sample of ligand prepared by reaction of the Cs salt of **8b** with **9** and thoroughly washed with water. [d] With a sample of ligand prepared by reaction of the Bu_4N^+ salt of **8b** with **9**. [e] With a sample of ligand employed in eq 4 and recovered and recycled for the 2nd run. [f] With a sample of ligand employed for two runs in eq 4 and recovered and recycled for the 3rd run.

as that of other Lewis acids ($Mg(OTf)_2$,[15] MgI_2/I_2 [16]) in combination with ligand **10a**.

Many factors can be responsible for the observed poor enantioselectivity. For instance, the supported ligands **10a**,**b** lack the C_2 symmetry common to the most effective box ligands for the Diels Alder reaction.[8] However, we could show that the complex formed by nonsupported box **7b** and $Cu(OTf)_2$ catalyzed the reaction of eq 1 leading to **11** in 88% yield, complete *endo* selectivity, and 95% enantiomeric excess (ee).[17]

PEG itself was also considered as a potential disturbing factor for a metal-promoted reaction such as that of eq 1, on the basis of the possible interference exerted by the PEG oxygens with the box/copper (II) coordination process. However, this phenomenon was also ruled out when the synthesis of **11** performed in the presence of the commercially available *gem*-dimethyl-substituted box derived from (*S*)-*tert*-leucinol (**8b** with two methyls at the bridging carbon atom), $Cu(OTf)_2$, and the bismethyl ether of PEG_{2000} gave the product in 90% yield and 96% ee.

Another explanation for the poor enantiocontrol exerted by ligand **10b** in eq 1 was envisaged in the possible contamination by (^{1}H NMR undetectable) minor amounts of Cs_2CO_3 that could coprecipitate during ligand isolation. Cs_2CO_3 could provide a carbonate counterion for copper(II) other than the triflate and/or Cs ions that can possibly act as catalysts per se. In both cases a poorly enantioselective catalyst can be at work.[18] Partial support to this hypothesis was found when the Diels−Alder cycloaddi-

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(15) Carbone, P.; Desimoni, G.; Faita, G.; Filippone, S.; Righetti, P. *Tetrahedron* **1998**, *54*, 6099−6110.

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(18) For a discussion on the importance of Cu(II) counterions in determining the stereoselectivity of the box/Cu(II)-catalyzed Diels Alder reaction, see ref 14.

tion was run with a sample of **10b** prepared by reaction of the Cs salt of **8b** with **9**, that was thoroughly washed with water and reprecipitated. In this case the adduct **11** was obtained in 70% yield and 30% ee. Further improvement of the enantioselectivity was observed using a sample of ligand obtained by reacting PEG **9** with the phenoxide ion of box **8b** prepared with $Bu_4N^+HO^-$ as base. This reaction releases $Bu_4N^+MsO^-$, a species that being soluble in diethyl ether can readily be eliminated during the purification of **10b**, affording a "counterion free" ligand. The use of this ligand in eq 1 led to the formation of adduct **11** in 83% yield and 45% ee.[19]

The low degree of enantioselectivity observed in the Diels Alder cycloadditions remained unexplained and was even more surprising in the light of the much better results obtained in other asymmetric catalytic transformations promoted by the supported box ligands.

The cyclopropanation of styrene (5 mol equiv) carried out with ethyl diazoacetate (1 mol equiv, addition time 1.5 h) in the presence of 10 mol % each of ligand **10b** and CuOTf in CH_2Cl_2 (20 h, RT; Scheme 4, eq 2) gave a 70:30 mixture of the *trans*:*cis* cyclopropane adducts in 45% yield.The major *trans* isomer **12** had an 87% ee. An increase of the time of addition of ethyl diazoacetate from 1.5 to 5.0 h and the reaction time from 20 to 40 h led to **12** in 63% yield and 91% ee (*trans*:*cis* = 77:23). When the reaction was carried out on 1,1-diphenylethylene (eq 3) under the same conditions, adduct **13** was obtained in 45% yield and 93% ee.[20]

These results were inferior to those observed by Evans [21a] while studying the same reactions carried out with the *gem*-dimethyl-substituted box related to **10b** (1 mol % of catalyst). In this case, compound **12** was obtained in 99% ee (77% yield for the *trans*:*cis* 73:27 mixture), and compound **13** in 70% yield and 99% ee. Another relevant comparison can be made between our results and those obtained by Reiser with a similarly substituted, MeOPEG-supported aza-bisoxazoline (2.2 mol % of catalyst).[3f] In this case, cyclopropyl esters **12** and **13** were obtained in 69 and 78% yield, and 91 and 90% ee, respectively. Finally, it is worth mentioning that our PEG-supported ligand perfomed better than those obtained by Mayoral with *insoluble* polymers containing various bisoxazoline ligands (up to 79% ee for compound **12**).[2q]

From these comparisons it can be concluded that the catalytic activity of the **10b**/CuOTf complex is inferior to both that of Evans's nonsupported catalyst and (at a lesser extent) of Reiser's supported aza-bisoxazoline/CuOTf complex. In terms of enantioselectivity, however, the two MeOPEG-supported catalysts behaved very similarly, with a slight preference for our ligand. Once again, however, immobilization of chiral ligands on soluble polymeric supports led to an enantioselective catalytic system more efficient than its heterogeneous counterpart, as elsewhere shown by Janda.[3c]

The good levels of stereocontrol observed in the cyclopropanation reactions were maintained by the ene-reaction described in eqs 4 and 5 (Scheme 4). The addition of α-methylstyrene and methylenecyclohexane (1 mol equiv) to ethyl glyoxylate (50% solution in toluene, 10 mol equiv) carried out from 0 °C to RT for 18 h in CH_2Cl_2 in the presence of 10 mol % each of ligand **10a** and $Cu(OTf)_2$ afforded adducts **14** and **15** in 96 and 91% yield, and 95 and 87% ee, respectively (ee determined by the Mosher ester method).[22] Using the unsupported catalytic system at identical concentration, Evans[23] isolated adducts **14** and **15** in higher yields (99% for both compounds) and in 89 and 87% ee, respectively.

The recovery and recycle of the supported ligands was then studied in the case of eq 4. The high enantioselectivity of this reaction was considered a probing test to show erosion of the ligand efficiency upon recycle. When a sample of catalyst employed in the synthesis of compound **14** was recovered by precipitation and filtration, the isolated material showed a poorly resolved ^{1}H NMR spectrum, possibly because it contained an undetermined amount of Cu(II) ions.[24] Decomplexation of the pale green CH_2Cl_2 solution of this species with a 0.3 M aqueous solution of KCN gave back ligand **10a** in 85% isolated yield.[25] This recovered ligand was employed in the reaction of eq 4, leading to compound **14** in slightly lower yield (91 vs 96%) and ee (90 vs 95%). A second recycle afforded **14** in 93% yield and 88% ee.

Conclusions

In conclusion, a modified poly(ethylene glycol) has been used for the immobilization of ad hoc synthesized, enantiomerically pure bis-oxazolines, that have been suitably functionalized for anchoring to the polymer. The supported ligands were employed in combination with Cu(II) and Cu(I) salts in some representative homogeneous catalytic asymmetric reactions. The results depended on the reaction type. Poor enantioselectivity was observed in the Diels−Alder cycloaddition between *N*-acryloyloxazolidinone and cyclopentadiene (up to 45% ee). Better stereocontrol was observed in the cyclopropanations of styrene and 1,1-diphenylethylene with ethyl diazoacetate (up to 93% ee), and in the ene-reactions between ethyl-glyoxalate and α-methylstyrene or methylenecyclohexane (up to 95% ee). In the last two reactions, ee comparable to those observed with structurally related, nonsupported ligands were observed. Experimentally simple recovery and recycling of one of the ligand was shown to be possible with marginal erosion of the catalytic activity and very limited loss in the enantioselectivity. As a

(19) It is worth mentioning that insertion of a longer spacer between the box ligand and the PEG core (by two or three iterations of the −O−Ph$(CH_2)_3$−O unit) did not lead to an improvement of the ee of adduct **11**.

(20) Remarkably, in the cyclopropanation reaction high ee were obtained independently of the method of preparation of the ligand.

(21) (a) Evans, D. A.; Woerpel, K. A.; Hinman, M. N.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726−728. See also: (b) Lowenthal, R. E.; Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1990**, *31*, 6005−6009.

(22) The ee of both alcohols **14** and **15** were determined by ^{1}H NMR analysis of the corresponding Mosher's esters obtained by reaction with the (*R*)-enantiomer of the Mosher's acid chloride. The esters gave signals identical to those reported by Evans (see the Supporting Information of ref 23). For the esters of compound **14** the diagnostic signals were those of the vinyl protons that resonated at δ 5.40 and 5.22 for the major (*R*,*R*)-isomer and at δ 5.23 and 5.02 for the minor (*S*,*R*)-isomer. Since the peaks of the minor isomer were barely detectable, their identity was unambiguously established by preparing the enantiomer of the (*S*,*R*)-isomer reacting **14** with the (*S*) acid chloride. The diagnostic peaks for the esters derived from alcohol **15** were the broad singlets of the vinyl proton at δ 5.52 for the major (*R*,*R*)-isomer and at δ 5.22 for the minor (*S*,*R*)-isomer, and the singlets of the methoxy protons at δ 3.56 for the major isomer and at δ 3.64 for the minor isomer.

(23) Evans, D. A.; Tregay, S. W.; Burgey, C. S.; Paras, N. A.; Vojkovsky *J. Am. Chem. Soc.* **2000**, *122*, 7936−7943.

(24) Further support to this hypothesis was found when a sample of the recovered material was shown to catalyze the reaction of eq 4, leading to compound **14** in 45% isolated yield and 83% ee.

(25) An excess of KCN was used to ensure complete Cu(II) removal from the ligand.

whole, these results confirm that chiral ligands immobilized on a soluble polymeric matrix can partecipate in enantioselective, catalytic transformations at least as efficiently as their counterparts supported on insoluble polymers.

Experimental Section

General. ^{1}H NMR spectra were recorded at 300 MHz and were referenced to tetramethylsilane (TMS) at 0.00 ppm. ^{13}C NMR spectra were recorded at 75 MHz and were referenced to 77.0 ppm in chloroform-*d* ($CDCl_3$). 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 solution in CH_2Cl_2.

All the PEG samples were melted at 80 °C in a vacuum for 30 min before use to remove traces of moisture. After reaction, PEG-supported product purification involved evaporation of the reaction solvent in vacuum and addition of the residue dissolved in a few milliliters of CH_2Cl_2 to diethyl ether (50 mL g^{-1} of polymer), which was stirred and cooled at 0 °C. After 20−30 min stirring at 0 °C, the obtained suspension was filtered through a sintered glass filter and the solid repeatedly washed on the filter with diethyl ether (up to 100 mL g^{-1} of polymer, overall).

Yield and Purity Detertmination of PEG-Supported Compounds. The yield of the PEG-supported compounds were determined by weight with the assumption that M_w is 5000 Da for the PEG fragment. The M_w actually ranged from 4500 to 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 presaturation of the methylene signals of the polymer at $\delta = 3.63$. In 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 CH_2OCH_3 fragment at $\delta = 3.30$ and 3.36 were used as internal standard. The estimated integration error was ± 5%.

Synthesis of Box 8a,b. These compounds were prepared by a multistep synthesis starting from the known benzyl bromides **1**[26] and **2**.[27]

Synthesis of the Bis-Alkylated Malonates 3 and 4. To a stirred solution of LDA (10.7 mmol) in dry THF (30 mL) cooled at 0 °C under nitrogen was added dimethyl methyl malonate (1.3 mL, 9.75 mmol) in THF, 10 mL) dropwise. After 1 h stirring at 0 °C, the benzyl bromide (9.75 mmol) in THF (10 mL) was added dropwise, and the reaction mixture was stirred for 1 h at 0 °C and then 15 h at RT. The rection was quenched by the addition of a saturated aqueous solution of NaCl (20 mL), and the resulting mixture was extracted three times with 20 mL of Et_2O. The combined organic phases were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography with a 9:1 hexanes:EtOAc mixture as eluant.

Dimethyl 2-Methyl-2-(4-phenylmethoxy)phenylmethyl-1,3-propandioate 3. Yield 86%. White solid, mp 70−71 °C. IR: 1735, 1510, 1245 cm^{-1}. ^{1}H NMR: δ 7.50−7.35 (m, 5H), 7.08 (B part of an AB system, $J = 8.5$ Hz, 2H), 6.90 (A part of an AB system, $J = 8.5$ Hz, 2H), 5.00 (s, 2H), 3.75 (s, 6H), 3.15 (s, 2H), 1.33 (s, 3H). Anal. Calcd for $C_{20}H_{22}O_5$: C, 70.16; H, 6.48. Found: C, 70.02; H, 6.61.

Dimethyl 2-Methyl-2-[4-(1-propenyl-3-oxy)phenylmethyl]-1,3-propandioate 4. Yield 94%. Colorless liquid. IR: 1735, 1510, 1245 cm^{-1}. ^{1}H NMR: δ 7.03 (B part of an AB system, $J = 8.6$ Hz, 2H), 6.83 (A part of an AB system, $J = 8.6$ Hz, 2H), 6.00 (m, 1H), 5.41 (dq, $J = 17.2$, 1.5 Hz, 1H), 5.28 (dq, $J = 10.2$, 1.4 Hz, 1H), 4.51 (m, 2H), 3.73 (s, 6H), 3.18 (s, 2H), 1.36 (s, 3H). Anal. Calcd for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 65.62; H, 6.79.

Ester Hydrolysis. This was performed by treating a 0.1 M solution of the esters **3** and **4** (8.0 mmol) in a 3:1 EtOH: water mixture (80 mL) with solid KOH (1.46 g, 25.6 mmol) at reflux for 48 h. The crude acids were obtained in quantitative yield by acidification with 1 N aqueous HCl, followed by extraction with CH_2Cl_2, anidrification, and evaporation of the solvent under vacuum. The benzyl-protected acid had mp 165 °C; the allyl protected acid had mp 126−128 °C.

Synthesis of the Acid Chlorides. This was performed by treating a solution of the acids (3.34 mmol) in dry toluene (25 mL) with a 10-fold excess of freshly distilled thionyl chloride (2.45 mL, 33.4 mmol) at reflux for 4 h. The solvent was then evaporated under vacuum and the oily residue thoroughly dried under high vacuum. The crude dark yellow products were used as such.

Synthesis of the Amides. To a stirred solution of amino alcohols **5a**,**b** (8.35 mmol) and triethylamine (1.86 mL, 13.4 mmol) in dry CH_2Cl_2 (20 mL) stirred under nitrogen was added a solution of the acid chloride (3.34 mmol) in CH_2Cl_2 (10 mL) dropwise. The mixture was stirred at RT for 15 h, and the reaction was quenched by addition of a saturated aqueous solution of ammonium chloride. 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 products. These were purified by flash chromatography with a 9:1 CH_2Cl_2:MeOH mixture as eluant.

(*S*,*S*)-Bis-*N*-1-(1-phenyl-2-hydroxyethyl) 2-methyl-2-(4-phenylmethoxy)-phenyl methyl 1,3-propandiamide (from 5a). Yield 82%. Thick yellow oil. $[\alpha]^{22}_D$ +32.1 (*c* 1.1 in $CHCl_3$). IR: 3349, 1672, 1510, 1265 cm^{-1}. ^{1}H NMR: δ 7.33−7.04 (m, 15H), 6.88 (B part of an AB system, $J = 8.5$ Hz, 2H), 6.69 (A part of an AB system, $J = 8.5$ Hz, 2H), 6.00 (bs, 2H), 5.02 (m, 2H), 4.92 (s, 2H), 4.10 (bs, 2H), 3.80 (B part of an AB system, $J = 12.0$, 4.1 Hz, 2H), 3.73 (A part of an AB system, $J = 6.8$, 4.1 Hz, 2H), 3.18 (B part of an AB system, $J = 13.5$ Hz, 1H), 3.02 (A part of an AB system, $J = 13.5$ Hz, 1 H), 1.32 (s, 3H). ^{13}C NMR: δ 174.0, 157.8, 143.0, 138.6, 131.1, 129.8, 128.8, 128.3, 127.9, 127.8, 127.4, 126.6, 114.5, 69.9, 66.2, 56.0, 55.0, 43.9, 18.7. Anal. Calcd for $C_{34}H_{36}N_2O_5$: C,73.89; H, 6.56; N, 5.07. Found: C, 73.72; H, 6.69; N, 4.93.

(*S*,*S*)-Bis-*N*-2-(1-hydroxy-3,3-dimethylbutyl) 2-methyl-2-(4-phenylmethoxy)-phenylmethyl 1,3-propandiamide (from 5b). Yield 90%. Thick yellow oil. $[\alpha]^{22}_D$ −5.9 (*c* 0.2 in $CHCl_3$). IR: 3358, 1672, 1510, 1266 cm^{-1}. ^{1}H NMR: δ 7.46−7.33 (m, 5H), 7.13 (B part of an AB system, $J = 8.2$ Hz, 2H), 6.93 (d, $J = 9.0$ Hz, 1H), 6.87 (A part of an AB system, $J = 8.2$ Hz, 2H), 6.67 (d, $J = 9.0$ Hz, 1H), 5.04 (s, 2H), 3.93−3.73 (m, 4H), 3.50−3.37 (m, 2H), 3.05 (bs, 1H), 2.95 (A part of an AB system, $J = 13.4$ Hz, 1H), 2.65 (bs, 1H), 1.35 (s, 3H), 0.95 (s, 9H), 0.87 (s, 9H). ^{13}C NMR: δ 174.0, 173.0, 157.5, 137.0, 131.2, 128.9, 128.5, 127.9, 127.4, 114.6, 70.0, 63.0, 62.4, 60.1, 59.6, 55.0, 43.6, 33.5, 33.1, 26.8, 18.2. Anal. Calcd for $C_{30}H_{44}N_2O_5$: C, 70.28; H, 8.65; N, 5.46. Found: C, 70.51; H, 8.77; N, 5.39.

(*S*,*S*)-Bis-*N*-1-(1-phenyl-2-hydroxyethyl) 2-methyl-2-[4-(1-propenyl-3-oxy) phenylmethyl] 1,3-propandiamide (from 5a). Yield 70%. Pale yellow solid, mp 58−60 °C. $[\alpha]^{22}_D$ +32.1 (*c* 0.6 in $CHCl_3$). IR: 3332, 1642, 1511 cm^{-1}. ^{1}H NMR: δ 7.33−7.25 (m, 8H), 7.17 (m, 2H), 6.97 (B part of an AB system, $J = 8.5$ Hz, 2H), 6.72 (A part of an AB system, $J = 8.5$ Hz, 2H), 6.00 (m, 1H), 5.43 (dq, $J = 17.2$, 1.8 Hz, 1H), 5.30 (dq, $J = 10.2$, 1.4 Hz, 1H), 5.12 (m, 2H), 4.49 (d, $J = 5.0$ Hz, 2H), 3.93−3.77 (m, 4H), 3.28 (B part of an AB system, $J = 13.5$ Hz, 1H), 3.13 (part A of an AB system, $J = 13.5$ Hz, 1 H), 1.39 (s, 3H). ^{13}C NMR: δ 173.5, 172.8, 157.6, 138.6, 138.5, 133.3, 131.1, 128.8, 128.7, 128.3, 127.8, 127.7, 126.7, 126.6, 117.6, 114.4, 68.7, 66.1, 66.0, 55.9, 55.8, 43.8, 18.6. Anal. Calcd for $C_{30}H_{34}N_2O_5$: C, 71.69; H, 6.82; N, 5.57. Found: C, 71.53; H, 6.66; N, 5.48.

(*S*,*S*)-Bis-*N*-2-(1-hydroxy-3,3-dimethylbutyl) 2-methyl-2-[4-(1-propenyl-3-oxy) phenylmethyl] 1,3-propandiamide (from 5b). Yield 90%. White solid, mp 46−48 °C. $[\alpha]^{22}_D$ −5.1 (*c* 0.5 in $CHCl_3$). IR: 3358, 1662, 1510, 1265 cm^{-1}. ^{1}H NMR: δ 7.11 (B part of an AB system, $J = 8.5$ Hz, 2H), 7.00

(26) Cho, H. F.. Mak, C. C. *J. Org. Chem.* **1997**, *62*, 5116−5127. In this paper compound **1** was synthesized en route to an achiral dendritic box ligand.

(27) Nakayama, T.; Nomura, M.; Haga, K.; Ueda, M. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 2979−2984.

(d, J = 7.0 Hz, 1H), 6.80 (A part of an AB system, J = 8.5 Hz, 2H), 6.61 (d, J = 7.0 Hz, 1H), 6.05−5.95 (m, 1H), 5.43 (dq, J = 17.2, 1.5 Hz, 1H), 5.30 (dq, J = 10.2, 1.4 Hz, 1H), 4.49 (dt, J = 5.2, 1.5 Hz, 2H), 3.93−3.77 (m, 4H), 3.48 (B part of an AB system, J = 13.5 Hz, 1H), 3.48−3.40 (m, 2H), 2.95 (part A of an AB system, J = 13.5 Hz, 1 H), 1.33 (s, 3H), 0.95 (s, 9H), 0.86 (s, 9H). ^{13}C NMR: δ 174.4, 173.4, 157.55, 133.2, 131.2, 128.7, 117.5, 114.4, 68.7, 62.5, 62.2, 59.9, 59.6, 55.3, 43.5, 33.4, 33.1, 26.8, 26.7, 18.1. Anal. Calcd for $C_{26}H_{42}N_2O_5$: C, 67.50; H, 9.15; N, 6.06. Found: C, 67.73; H, 9.34; N, 6.22.

Synthesis of Box 6a and 7a. To a stirred solution of bisamide (1 mmol), triethylamine (0.61 mL, 4.4 mmol), and DMAP (12 mg, 0.1 mmol) in CH_2Cl_2 (15 mL) kept under nitrogen was added tosyl chloride (380 mg, 2 mmol) dissolved in CH_2Cl_2 (5 mL) dropwise. The mixture was stirred at RT for 24 h. A saturated aqueous solution of ammonium chloride was then added, and the aqueous phase was extracted three times with CH_2Cl_2 (15 mL). The combined organic phases were washed with a saturated aqueous solution of sodium bicarbonate, dried, and concentrated under vacuum to give the crude product that was purified by flash chromatography with a 8:2 CH_2Cl_2:AcOEt mixture as eluant.

Box 6a. Yield 57%. Thick yellow oil. $[\alpha]^{22}_D$ −72.7 (c 0.8 in $CHCl_3$). IR: 1656, 1512, 1216 cm^{-1}. ^{1}H NMR: δ 7.38−7.19 (m, 13H), 7.09 (B part of an AB system, J = 8.7 Hz, 2H), 7.02 (d, J = 7.5 Hz, 2H), 6.80 (A part of an AB system, J = 8.7 Hz, 2H), 5.18 (t, J = 8.2, 1H), 5.15 (dd, J = 8.2, 7.7 Hz, 1H), 4.98 (s, 2H), 4.60 (dd, J = 10.0, 8.2 Hz, 2H), 4.15−4.05 (m, 2H), 3.32 (s, 2H), 1.56 (s, 3H). ^{13}C NMR: δ 169.7, 169.6, 158.3, 143.0, 142.5, 137.5, 132.0, 129.0, 128.9, 128.3, 127.9, 127.1, 114.9, 75.7, 70.4, 70.0, 66.2, 44.3, 22.0. Anal. Calcd for $C_{34}H_{32}N_2O_3$: C, 79.04; H, 6.24; N, 5.42. Found: C, 78.88; H, 6.38; N, 5.28.

Box 7a. Yield 57%. Thick yellow oil. $[\alpha]^{22}_D$ −62.6 (c 0.4 in $CHCl_3$). IR: 1656, 1511, 1216 cm^{-1}. ^{1}H NMR: δ 7.35−7.25 (m, 8H), 7.15 (B part of an AB system, J = 8.5 Hz, 2H), 7.08 (d, J = 7.5 Hz, 2H), 6.85 (A part of an AB system, J = 8.5 Hz, 2H), 6.11−6.04 (m, 1H), 5.43 (dq, J = 17.2, 1.0 Hz, 1H), 5.30 (dq, J = 10.2, 1.0 Hz, 1H), 5.28−5.18 (m, 2H), 4.71 (t, J = 8.5 Hz, 2H), 4.54 (dd, J = 5.0, 1.4 Hz, 2H), 4.20 (t, J = 8.0 Hz, 1H), 4.13 (t, J = 8.3 Hz, 1H), 3.40 (s, 2H), 1.63 (s, 3H). ^{13}C NMR: δ 169.3, 157.7, 142.3, 142.1, 131.5, 130.6, 128.7, 128.6, 128.5, 127.6, 127.5, 126.7, 117.6, 114.4, 75.3, 75.2, 69.5, 68.8, 43.8, 41.3, 21.6. Anal. Calcd for $C_{30}H_{30}N_2O_3$: C, 77.23; H, 6.48; N, 6.00. Found: C, 77.54; H, 6.61; N, 5.87.

Synthesis of Box 6b and 7b. To a stirred solution of bisamide (1 mmol) and triethylamine (0.61 mL, 4.4 mmol) in CH_2Cl_2 (15 mL) kept under nitrogen at 0 °C was added mesyl chloride (0.193 mL, 2.5 mmol) dissolved in CH_2Cl_2 (5 mL) dropwise. The mixture was stirred at 0 °C for 20 min and at RT for 2 h. A saturated aqueous solution of ammonium chloride was then added, and the aqueous phase was extracted three times with CH_2Cl_2 (15 mL). The combined organic phases were washed with a saturated aqueous solution of sodium chloride, dried, and concentrated under vacuum to give the crude product. A solution of this crude mesylate, triethylamine (0.61 mL, 4.4 mmol), and DMAP (12 mg, 0.1 mmol) in CH_2Cl_2 (20 mL) was stirred at 30 °C under nitrogen for 48 h. A saturated aqueous solution of ammonium chloride was then added, and the aqueous phase was extracted three times with CH_2Cl_2 (15 mL). The combined organic phases were washed with a saturated aqueous solution of sodium bicarbonate, dried, and concentrated under vacuum to give the crude product that was purified by flash chromatography with a 9:1 CH_2Cl_2:AcOEt mixture as eluant.

Box 6b. Yield 50%. Thick yellow oil. $[\alpha]^{22}_D$ −47.4 (c 0.54 in $CHCl_3$). IR: 1661, 1512, 1240 cm^{-1}. ^{1}H NMR: δ 7.46−7.33 (m, 5H), 7.12 (B part of an AB system, J = 8.0 Hz, 2H), 6.87 (A part of an AB system, J = 8.0 Hz, 2H), 5.04 (s, 2H), 4.23−4.11 (m, 3H), 4.05 (t, J = 7.5 Hz, 1H), 3.89 (dd, J = 9.0, 7.1 Hz, 1H), 3.83 (dd, J = 7.0, 10.0 Hz, 1H), 3.33 (B part of an AB system, J = 13.5 Hz, 1H), 3.17 (A part of an AB system, J = 13.5 Hz, 1H), 1.44 (s, 3H), 0.89 (s, 9H), 0.86 (s, 9H). ^{13}C NMR: δ 167.7, 167.2, 157.6, 137.2, 131.5, 129.2, 128.5, 127.9, 127.5, 114.3, 75.6, 75.4, 70.0, 68.7, 43.5, 41.2, 34.0, 33.8, 25.8, 25.7, 21.1. Anal. Calcd for $C_{30}H_{40}N_2O_3$: C, 75.60; H, 8.46; N, 5.88. Found: C, 75.51; H, 8.67; N, 5.77.

Box 7b. Yield 80%. Thick yellow oil. $[\alpha]^{22}_D$ −75.5 (c 1.3 in $CHCl_3$). IR: 1656, 1513, 1217 cm^{-1}. ^{1}H NMR: δ 7.10 (B part of an AB system, J = 8.5 Hz, 2H), 6.80 (A part of an AB system, J = 8.5 Hz, 2H), 6.10−6.02 (m, 1H), 5.39 (dq, J = 17.2, 1.5 Hz, 1H), 5.28 (dq, J = 10.2, 1.4 Hz, 1H), 4.50 (dt, J = 5.2, 1.5 Hz, 2H), 4.20 (B part of an AB system, J = 10.0, 4.0 Hz, 1H), 4.16 (B part of an AB system, J = 9.0, 4.0 Hz, 1H), 4.12 (dd, J = 7.0, 8.0 Hz, 1H), 4.05 (t, J = 8.0 Hz, 1H), 3.88 (A part of an AB system, J = 10.0, 8.0 Hz, 1H), 3.81 (A part of an AB system, J = 10.0, 7.0 Hz, 1H), 3.33 (B part of an AB system, J = 13.6 Hz, 1H), 3.16 (A part of an AB system, J = 13.6 Hz, 1 H), 1.43 (s, 3H), 0.88 (s, 9H), 0.85 (s, 9H). ^{13}C NMR: δ 167.7, 167.3, 157.4, 133.5, 131.5, 129.1, 117.5, 114.2, 75.6, 75.4, 68.8, 68.7, 43.5, 41.2, 33.9, 33.8, 25.8, 25.7, 21.1. Anal. Calcd for $C_{26}H_{38}N_2O_3$: C, 73.20; H, 8.98; N, 6.57. Found: C, 73.41; H, 8.77; N, 6.84.

Deprotection of Box 6a,b and 7a,b to Box 8a,b. Debenzylation. This was accomplished following the described procedure.[12] In a typical experiment to a solution of *O*-benzyl-protected box **6a** and **6b** (0.15 mmol) in ethylene glycol (10 mL) were added 10% Pd/C (50 mg) and ammonium formate (63 mg, 1 mmol) in this order. The resulting mixture was heated at 150 °C in a microwave oven for 6 min. After cooling, the mixture was filtered through a Celite cake, and the filtrate was diluted with water (10 mL) and extracted three times with CH_2Cl_2 (15 mL). The combined organic phases were dried and concentrated under vacuum. The residue was purified by flash chromatography with a 7:3 CH_2Cl_2:AcOEt mixture as eluant to give the product.

Box 8a. Yield 66%. White solid, mp 89−91 °C. $[\alpha]^{22}_D$ −90.4 (c 0.56 in $CHCl_3$). IR: 3583, 1652, 1515, 1266 cm^{-1}. ^{1}H NMR: δ 7.38−7.25 (m, 9H), 7.10 (t, J = 7.5 Hz, 4H), 6.67 (d, J = 7.5 Hz, 2H), 5.27 (dd, J = 10.0, 8.0, 1H), 5.21 (dd, J = 10.0, 7.5 Hz, 1H), 4.72 (m, 2H), 4.22 (t, J = 8.2 Hz, 1H), 4.14 (t, J = 8.0 Hz, 1H), 3.38 (s, 2H), 1.64 (s, 3H). ^{13}C NMR: δ 169.0, 155.6, 142.0, 131.0, 131.55, 128.6, 127.5, 126.65, 115.1, 75.2, 69.4, 44.0, 41.3, 21.5. Anal. Calcd for $C_{27}H_{26}N_2O_3$: C, 76.03; H, 6.14; N, 6.57. Found: C, 75.91; H, 6.06; N, 6.73.

Box 8b. Yield 32%. White solid, mp 171−173 °C. $[\alpha]^{22}_D$ −120.7 (c 0.17 in $CHCl_3$). IR: 3583, 1653, 1516, 1266 cm^{-1}. ^{1}H NMR: δ 6.97 (B part of an AB system, J = 8.5 Hz, 2H), 6.62 (A part of an AB system, J = 8.5 Hz, 2H), 6.33 (bs, 1H), 4.30−4.15 (m, 3H), 4.06 (t, J = 8.5 Hz, 1H), 3.88 (dd, J = 10.0, 8.5 Hz, 2H), 3.35 (B part of an AB system, J = 14.0 Hz, 1H), 3.13 (A part of an AB system, J = 14.0 Hz, 1H), 1.42 (s, 3H), 0.89 (s, 9H), 0.85 (s, 9H). ^{13}C NMR: δ 168.5, 168.2, 155.3, 131.1, 127.3, 115.0, 75.45, 74.9, 68.9, 68.7, 43.8, 40.9, 34.1, 33.85, 25.7, 25.6, 20.7. Anal. Calcd for $C_{23}H_{34}N_2O_3$: C, 71.47; H, 8.87; N, 7.25. Found: C, 71.20; H, 9.04; N, 7.45.

Deallylation. This was accomplished by modification of a described procedure.[13] In a typical experiment a solution of *O*-allyl protected box **7a** and **7b** (1 mmol) in ethanol (15 mL) containing $Pd(OAc)_2$ (22.4 mg, 0.1 mmol) and PPh_3 (115 mg, 0.44 mmol) was refluxed for 90 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, and the residue was purified by flash chromatography with a 7:3 CH_2Cl_2: AcOEt mixture as eluant to give **8a** in 67% yield and **8b** in 82% yield.

Synthesis of PEG-Supported Box 10a,b. To a solution of mesylate **9**[10c] (2.34 g, 0.45 mmol) and box **8a** or **8b** (0.50 mmol) in DMF (10 mL) stirred under nitrogen was added tetrabutylammonium hydroxide (0.4 mL of a 40 wt % solution in water, 0.607 mmol). The mixture was warmed to 60 °C and stirred at that temperature for 48 h. The solvent was then evaporated under vacuum, and the residue was taken up into CH_2Cl_2 (20 mL). This solution was washed with water, dried over sodium sulfate, filtered, concentrated under vacuum, and precipitated with diethyl ether (see above). The product was isolated by filtration.

PEG-Supported Box 10a. Yield 83%. ^{1}H NMR: δ 7.20−7.00 (m, 14H), 6.88−6.82 (m, 4H), 5.31−5.17 (m, 2H), 4.71 (t,

J = 9.0 Hz, 1H), 4.20 (t, J = 9.0 Hz, 1H), 4.12 (t, J = 6.5 Hz, 2H), 3.94 (t, J = 6.5 Hz, 1H), 3.92−3.81 (m, 3H), 3.41 (t, J = 7.0 Hz, 2 H), 3.38 (s, 3H), 2.75 (t, J = 7.0 Hz, 2H), 2.12−2.04 (m, 2H), 1.63 (s, 3H).

PEG-Supported Box 10b. Yield 87%. ^{1}H NMR: δ 7.11 (B part of an AB system, J = 8.8 Hz, 2H), 7.08 (B part of an AB system, J = 8.8 Hz, 2H), 6.85 (A part of an AB system, J = 8.8 Hz, 2H), 6.75 (A part of an AB system, J = 8.8 Hz, 2H), 4.20−4.12 (m, 3H), 4.05 (t, J = 7.5 Hz, 1H), 3.99−3.93 (m, 4 H), 3.41 (t, J = 7.0 Hz, 2 H), 3.38 (s, 3H), 3.33 (B part of an AB system, J = 13.5 Hz, 1H), 3.15 (A part of an AB system, J = 13.5 Hz, 1H), 2.74 (t, J = 7.0 Hz, 2H), 2.03 (m, 2H), 1.42 (s, 3H), 0.88 (s, 9H), 0.85 (s, 9H).

Stereoselective Syntheses Promoted by PEG-Supported Ligands 10a,b

Diels−Alder Cycloaddition. A solution was prepared by dissolving under nitrogen **10b** (200 mg, 0.036 mmol) and Cu(OTf)$_2$ (11.6 mg, 0.032 mmol) in dry CH_2Cl_2 (2 mL). To the resulting bright green solution, finely grounded 3 Å molecular sieves (200 mg) were added. The mixture was stirred under nitrogen for 4 h at RT and then was cooled at −78 °C, whereupon *N*-acryloyl oxazolidinone (51 mg, 0.36 mmol) and cyclopentadiene (0.3 mL, 3.6 mmol) were added in this sequence. The reaction mixture was then allowed to warm to RT, stirred for 15 h, and then filtered through a Celite cake. The filtrate was concentrated under vacuum and the residue dissolved in CH_2Cl_2 (2 mL) was slowly added to diethyl ether. The precipitate was removed by filtration, and the filtrate was concentrated under vacuum to give the crude product that was purified by flash chromatography with a 1:1 CH_2Cl_2:AcOEt mixture as eluant. Yields and ee of adduct **11** were reported in Table 1.

Cyclopropanation. A solution was prepared by stirring, at RT for 1 h under nitrogen, **10b** (200 mg, 0.036 mmol) and commercially available CuOTf·0.5 PhH (8 mg, 0.032 mmol) in dry CH_2Cl_2 (2 mL). To the resulting bright green solution was added freshly distilled styrene (0.200 mL, 1.8 mmol). Ethyl diazoacetate (0.038 mL, 0.36 mmol) dissolved in CH_2Cl_2 (1 mL) was added over a period of 5 h by a syringe pump, and the reaction was stirred for 40 h at RT. The mixture was then concentrated under vacuum, and the residue, dissolved in CH_2Cl_2 (2 mL), was slowly added to diethyl ether. The precipitate was removed by filtration, and the filtrate was concentrated under vacuum to give the crude product that was purified by flash chromatography with a 97:3 hexanes:diethyl ether mixture as eluant. Yields and ee of adduct **12** were reported in Table 1. Compound **13** was similarly obtained from 1,1-diphenylethylene.

Ene-Reaction. A solution was prepared by dissolving under nitrogen **10a** (250 mg, 0.045 mmol) and Cu(OTf)$_2$ (15.9 mg, 0.044 mmol) in dry CH_2Cl_2 (4 mL). The resulting dark green solution was stirred at RT for 4 h and then cooled to 0 °C, whereupon α-methylstyrene (0.029 mL, 0.225 mmol) and ethyl glyoxylate (0.446 mL of a 50% solution in toluene, 2.25 mmol) were added in this order. The resulting mixture was stirred overnight while the temperature was allowed to slowly increase from 0 °C to RT. The mixture was then concentrated under vacuum, and the residue, dissolved in CH_2Cl_2 (2 mL), was slowly added to diethyl ether. The precipitate was removed by filtration, and the filtrate was concentrated under vacuum to give the crude product that was purified by flash chromatography with a 7:3 hexanes:diethyl ether mixture as eluant. Yields and ee of adduct **14** were reported in Table 1. Compound **15** was similarly obtained from methylenecyclohexane.

Ligand Recovery. The precipitated PEG-supported catalyst was dissolved in CH_2Cl_2 (3 mL g^{-1} of polymer) and trteated dropwise with a 0.3 M solution of KCN in water until the organic phase turned permanently from pale green to colorless. The mixture, diluted with CH_2Cl_2, was dried, filtered, and concentrated under vacuum to give a solid residue that was used as such. Purification of this material was possible by the usual procedure to afford a ligand identical by NMR to a sample freshly prepared.

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