Insoluble polystyrene-bound bis(oxazoline): batch and continuous-flow heterogeneous enantioselective glyoxylate–ene reaction

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Abstract—The use of a new, insoluble polymer-bound bis(oxazoline) ligand (IPB–box) for the copper-catalyzed heterogeneous enantioselective glyoxylate–ene reaction is described. Good activity and ee values in the range 85–95% have been obtained during five to seven recycles, either in batch mode or under flow conditions, demonstrating also the recovery and reuse of the whole catalytically active copper complex.
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1. Introduction

As the number of successful applications of metal-bis(oxazoline) complexes (box–M) is continuously growing,[1] members of the box class of ligands **1** appear to have been accepted as 'privileged chiral catalyst' precursors, that is, the restricted set of auxiliaries that are able to provide high enantioselectivity values over a wide range of different and mechanistically unrelated reactions.[2]

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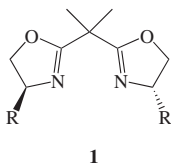
However, the cost of several box derivatives, together with the relatively high catalyst loading required by most asymmetric transformations (0.1–20 mol%), often hamper the application of these ligands for medium and large-scale preparative purposes, unless the effective recovery and reuse of the catalytic system (or its chiral portion) can be guaranteed. While this has been achieved directly in a few instances, exploiting the peculiar solubility profile of the original box–M complex,[3] or by using ionic liquids,[4] the inherent limitations in this approach has prompted the search for modified systems, with improved separation and recovery properties.[5] With this aim, alternative strategies were explored, including the ion-exchange of the complex or the covalent immobilization of the ligand onto organic or inorganic insoluble materials and tethering to soluble organic polymers or fluorous tails.[6] Eventually, these efforts by several research groups were rewarded with the development of systems with both satisfactory activity, high enantioselectivity (ee's >90%), and promising recycling effectiveness, especially in the case of the Mukaiyama, Diels–Alder, Friedel–Crafts, and aziridination reactions and the actively pursued olefin cyclopropanation.[6d,7] On the contrary, the box–Cu catalyzed asymmetric carbonyl–ene reaction received much less attention, despite the mild homogeneous protocol developed by Evans et al. (Scheme 1)[8] seems well suited for the regio- and stereocontrolled preparation of functionalized chiral building-blocks of pharmaceutical interest.[9,10]
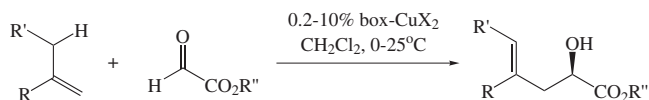
Scheme 1.

In fact, while most of the work on recoverable catalysts for the above mentioned reaction, focused on the

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BINOL–Ti system developed by Mikami (BINOL = 1,1′-bi(2-naphthol)),[10] by using either polymer-supported BINOL's or coordination polymer catalysts,[11–13] as far as box ligands are concerned we are aware of only three reports.

In a study devoted to poly(ethylene glycol)-supported bis(oxazolines) (PEG–box), the group of Cinquini and Cozzi employed 2-Cu(OTf)$_2$ for the catalysis of the reaction between ethyl glyoxylate and α-methylstyrene or methylenecyclohexane, achieving good results in terms of isolated yields and enantioselectivity values (95% and 87% ee, respectively).[14] Although in the case of the former alkene substrate the ee was remarkably high, recycling of the system proved somewhat troublesome, because the precipitation of the copper complex with Et$_2$O and the direct reuse of the recovered material afforded the ene product with substantially reduced yield and ee. Copper decomplexation with an excess of aqueous KCN gave back the free ligand 2, but the subsequent use of the material, after the addition of Cu(OTf)$_2$, led to a progressive reduction of enantioselectivity. Perfluoroalkyl-substituted box ligands (F–box) 3a-d for the glyoxylate–ene reaction of α-methylstyrene have also been reported.[15] Possibly due to excessive steric hindrance at the methylene bridge and specific perfluorinated ponytail effects,[15] the 3-Cu complexes led however to moderate ee values (7–74%). After copper decomplexation, the ligands could be obtained intact, affording almost unchanged ee value in recycling runs.

Even if these investigations clearly demonstrated the viability of recovering and reusing box ligands in the ene reaction, from a practical point of view some drawbacks are apparent. The strategy of altering the solubility profile of the catalyst, by modification with a polymeric or fluorous tail, appeared in fact to disturb the chemistry involved in the construction of the oxazoline moieties,[14] forcing their introduction after the set-up of the precious chiral box core via two additional steps.[14,15] Moreover, although the relative cost of the box ligands and of Cu(OTf)$_2$ make the recovery of the latter a less important issue, practical and environmental advantages would be gained by being able to recycle the whole system. Indeed, considering that the initial box–

Cu(II) species is likely to remain unchanged during the catalytic cycle,[16] its separation and direct reuse could be pursued, in principle.

While this manuscript was in preparation, Hutchings et al. reported a different approach, making use of a copper exchanged zeolite Y (Cu–HY) modified by soluble box ligands, as a heterogeneous catalyst for the ene reaction.[17] By employing different electrophiles (ethyl glyoxylate, methyl pyruvate or imines), the reaction of unfunctionalized olefins afforded the corresponding carbonyl–ene or imino–ene products with 23–91% yield and 72–94% ee. However, as far as the cheapest ligand 1 (R = Ph) is concerned, satisfactory catalytic activity and stereoselectivity could not be attained simultaneously in the reaction of carbonyl compounds. While methylene cyclopentane and hexane led to excellent ee values (93–94%), but required a reaction time of 100 h to afford the products in acceptable yields (65–71%), α-methylstyrene appeared in fact to react faster, but in this case just 77–82% ee was observed. For the latter substrate only by switching to much more expensive tert-leucine derived ligands, an improvement in the catalytic performances could be achieved (87–91% yield and 85–93% ee in 12 h). Recycling of the heterogeneous catalytic system was studied, starting with 5 mol% of 1 (R = Ph) as the Cu–HY modifier. With this experimental set-up, the insoluble catalyst (recovered by filtration, washing, and drying) could be used in four successive runs between α-methylstyrene and either ethyl glyoxylate or methyl pyruvate, affording the ene products with good yields and enantioselectivity (80–82% ee for glyoxylate and 83–89% ee for pyruvate). Interestingly, a very limited metal leaching was found for this system (1% of the initial zeolite copper content), demonstrating that the copper ions are quite firmly retained by the zeolite network, but no attempt to assess the loss of the chiral ligand was reported, in spite of the occurrence of this phenomenon with similar ion-exchanged materials.[18]

In the ongoing search of recoverable catalytic systems for the enantioselective C–C bond formation,[19] we report herein a third approach to the heterogeneous catalysis of the ene reaction, based on the use of an insoluble polymer-bound bis(oxazoline) ligand (IPB–box).
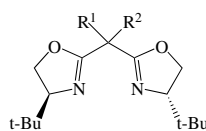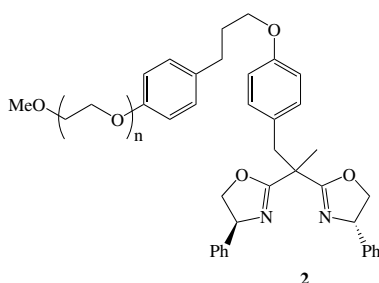
3a R^1 = Me, R^2 = R′f
3b R^1 = R^2 = R′f
3c R^1 = Me, R^2 = R″f
3d R^1 = R^2 = R″f
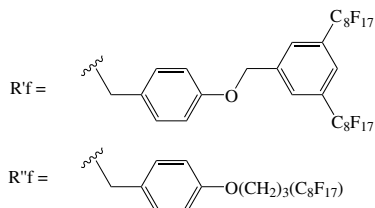
2. Results and discussion

According to the work of Evans et al.[8] the 4-phenyl substituted box **1** (R = Ph) is a suitable ligand for the reaction under study. Even if [box–Cu]$^{2+}$·2SbF$_6^-$ from **1** (R = *t*-Bu) appears to be a generally superior catalyst in terms of activity and ee's, the former ligand is cheaper and allows the direct use of the complex with Cu(OTf)$_2$, avoiding the dechlorination step required to prepare the cationic species. Because this protocol appeared simpler to be implemented in the solid phase, the preparation of a polymer-supported analogue of **1** (R = Ph) was therefore decided. For this purpose the synthetic route already developed for the *tert*-butyl substituted box was followed (Scheme 2).[7a,d]

Starting from readily available compounds, the modified malonic acid **8a** (containing a styrene unit linked through a spacer group) was prepared and converted into the box monomer **11a** (74% yield over two steps) by a modification of the procedure described for the parent ligand **1** (R = Ph, 76% over two steps).[20] Indeed, in spite of the presence of a sensitive unsaturated group, all the derivatives involved in the sequence proved remarkably stable, allowing the direct use of the crude reaction product in the case of the intermediates **8**–**10a**, or the chromatographic purification of the final monomer **11a**. In order to have a soluble model of the box unit embedded in the polymeric network, the ligand **11b** was also prepared by a similar sequence. The radical copolymerization of **11a** (7 mol%) was next carried out at 80 °C in toluene solution, using styrene (43 mol%) as the diluting monomer, *p*-divinylbenzene (DVB, 50 mol%) as the cross-linker and AIBN as the initiator. Under these conditions gelation was observed within 40 min, eventually leading to an opaque mass that was crushed and continuously extracted with dry THF and CH$_2$Cl$_2$, until disappearance of UV absorbing species in the washings. The IPB–box **12** (87% yield) was characterized by elemental analysis, IR, scanning electron microscopy (SEM), and determination of the surface area. From the nitrogen content a ligand loading of 0.22 mmol/g was estimated, suggesting the approximate comonomer composition in the Scheme 2,[21] that corresponds to about 40% incorporation of the initial feed of **11a** in the final material **12**. The IR spectrum of **12** showed the typical box C=N stretching at 1653 cm^{-1},[22] while the lack of any prominent absorption at 1630 cm^{-1} confirmed a substantial consumption of the DVB residual double bond, qualitatively verified also by CP-MAS ^{13}C NMR.[23] Based on the data by Millar et al.[24] the feed composition adopted in the polymerization (50 mol% DVB, achiral monomers volume fraction $F_m \approx 0.6$, toluene as the porogen solvent) should lie within the macroreticular domain in the pseudo-phase diagram for polystyrene materials. Accordingly, a macroporous texture for **12** was expected, that however was not confirmed by the value of the surface area in the dry state (<5 m^2/g) and was barely visible in the SEM micrographs (Fig. 1). Although this may be related to the presence of the box comonomer **12** (that modifies the solubility/polymerization behavior respect to simple polystyrene systems) or to the sample history,[21a,25] when the copolymer **12** was suspended in a solution of an excess of Cu(OTf)$_2$ in THF, swelling and the prompt (<2 min) development of a strong blue-green coloration of the polymeric material was observed. As already noted with supported *tert*-butyl substituted ligands,[7a,d] it was hence clear that some of the box units within **12** were readily available for copper complexation, in spite of the apparently compact texture and high cross-linking degree of the material.
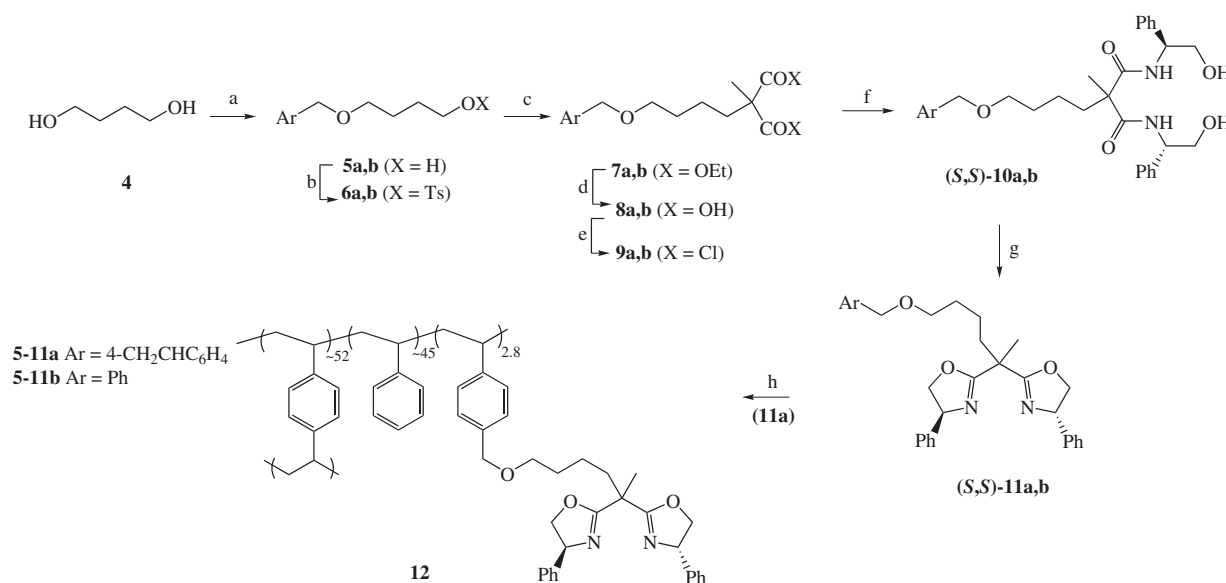
Scheme 2. Reagents and conditions: (a) NaH, DMF then 4-CH$_2$CHC$_6$H$_4$CH$_2$Cl, 0 °C → rt, 3 h (**5a**, 65%) or NaH, THF then C$_6$H$_5$CH$_2$Br, reflux, 18 h (**5b**, 68%). (b) TsCl, Et$_3$N, cat DMAP, CH$_2$Cl$_2$, 0 °C, 3 h (**6a** 79%, **6b** 72%). (c) Diethyl methylmalonate, NaH, THF, reflux, 24 h (**7a** 65%, **7b** 70%). (d) 18 M KOH, reflux, 14 h (**8a** 86%, **8b** 80%). (e) (COCl)$_2$, cat DMF, CH$_2$Cl$_2$, 0 °C → rt, 18 h (≈quant.). (f) (S)-PhCH(NH$_2$)CH$_2$OH, Et$_3$N, CH$_2$Cl$_2$, 0 °C → rt, 1–3 h. (g) TsCl, Et$_3$N, cat DMAP, CH$_2$Cl$_2$, 0 °C → rt, 24 h (**11a** 74%, **11b** 70% over two steps). (h) Styrene, DVB, AIBN, toluene, 80 °C, 18 h.
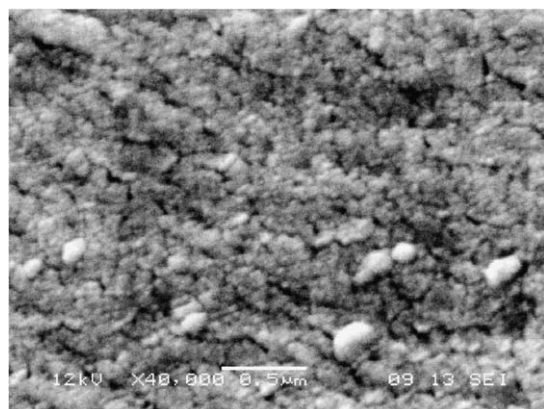
Figure 1. SEM image of fractured material **12**.

By spectrophotometric quantification of the residual copper ions in solution, a metal uptake of 0.18 mmol/g was estimated for **12**, demonstrating that more than 80% of the ligand units embedded in the polymeric network could be actually accessed by the reagents in solution. After washing with dry CH_2Cl_2, the supported complex **12**·Cu(OTf)$_2$ was therefore tested in the ene addition of 1,1-disubstituted alkenes **13a–d** and 1-methylcyclohexene **13e** to ethyl glyoxylate **14**. For comparative purposes, runs with the model ligand **11b** were also carried out. Under conditions that, apart from the use of the modified or heterogeneous catalytic system, were otherwise identical to those reported for the parent ligand **1** (R = Ph),[8] the results summarized in the Table 1 were obtained.

Table 1. Enantioselective homogeneous and heterogeneous glyoxylate–ene reaction

Run	Substrate **13**	Product **15**	Ligand (mol%)	T (°C)	t (h)	Conv. (%)[a]	Yield (%)[b]	Ee (%) (Config.)[c,d]
1	**13a**	**15a**	**1** (R = Ph) (10)	0	6	—	99[e]	89 (R)[e]
2			**11b** (10)	0	6	>95	98	87 (R)
3			**12** (10)	0	6	90	96	90 (R)
4	**13b**	**15b**	**1** (R = Ph) (2)	25	12	—	88[e]	92 (R)[e]
5			*ent*-**1** (R = Ph) (10)	25	12	86	75	91 (S)
6			**11b** (10)	25	12	78	71	91 (R)
7			**12** (10)[f]	25	24	87	65	91 (R)
8	**13c**	**15c**	**1** (R = Ph) (10)	25	12	—	85[e]	91 (R)[e]
9			**11b** (10)	25	12	94	72	84 (R)
10			**12** (10)[f]	25	24	90	70	85 (R)
11	**13d**	**15d**	**1** (R = Ph) (10)	0	12	—	99	87 (R)[e]
12			**11b** (10)	0	24	>95	99	88 (R)
13			**12** (10)	0	36	90	83	88 (R)
14			**12** (2)[f,g]	0	48	80	71	87 (R)
15	**13e**	**15e**	**1** (R = Ph) (10)	25	18	—	86	92 (1′R,2R)[e]
16			*ent*-**1** (R = Ph) (10)	25	18	95	89	91 (1′S,2S)[h]
17			*ent*-**1** (R = Ph) (10)	0	24	84	83	94 (1′S,2S)[h]
18			**11b** (10)	0	24	89	86	95 (1′R,2R)[h]
19			**12** (10)[f]	0	24	83	70	95 (1′R,2R)[h]

[a] Determined by GC, after calibration of the detector response.
[b] Isolated yield, after column chromatography.
[c] **15a–c**: by HPLC with Daicel chiral stationary phase columns; **13d–e**: by GC with Cyclodex-B column (see Ref. 8).
[d] Absolute configuration of the prevailing enantiomer, determined by comparison of the sign of $[\alpha]_D$ and chromatographic retention times with those of authentic samples (Ref. 8).
[e] Data taken from Ref. 8.
[f] Recovered polymeric ligand recharged with Cu(OTf)$_2$ (see text).
[g] MS 3A added.
[h] Diastereomer ratio (1′R*,2R*):(1′R*,2S*) = 97:3:96:4, by GC and ^{1}H NMR (Section 4).

As expected from previous findings with the PEG–box **2**,[14] the introduction of the spacer arm onto the box core did not seem to disturb to any great extent the effectiveness of the ligand architecture. Similar reaction rates and ee values within 3% of those reported for **1** (R = Ph) were in fact obtained with the soluble model **11b** for the less sterically hindered alkenes α-methylstyrene **13a**, 3-benzyloxy-2-methylpropene **13b**, methylenecyclohexane **13d**, and 1-methylcyclohexene **13e** (entries 1 vs 2, 4 vs 5, 11 vs 12, and 15 vs 17, respectively). Only in the case of the demanding olefin **13c**, bearing a bulky *tert*-butyl-diphenylsilyloxy group, was a larger reduction of enantioselectivity observed (entry 8 vs 9). From these comparisons in the homogeneous phase, it was concluded that the anchoring of the box fragment through a single linear spacer group connected to the methylene bridge, should afford a ligand with almost unchanged asymmetric induction ability respect to **1** (R = Ph), for all but the most encumbered substrates. More interestingly, when the supported catalytic system from the IPB–box **12** was employed in the benchmark reaction of α-methylstyrene **13a**, the smooth formation of the corresponding ene product **15a**, also with high enantioselectivity (entry 3) was observed. In order to compare more precisely the activity of the heterogeneous catalyst with those of the soluble ones, the reaction progress at intermediate times was monitored by GC. Remarkably, although only traces of the starting olefin were present after 6 h when using the homogeneous complexes, 90% conversion was also achieved with **12·Cu(OTf)₂** in the same timeframe (entries 1, 2, and 3), demonstrating a substantial catalytic activity by the supported system. In fact, when the anchored catalyst was filtered off after 12 h, the chromatographic purification of the crude mixture (to remove the glyoxylate excess) afforded the ene product **15a** in high isolated yield and with 90% ee, values that are essentially identical to those reported with the parent box **1** (R = Ph) under the same conditions (entry 1).[8]

Because control experiments ruled out any significant contribution to catalysis in solution, thereby demonstrating its true heterogeneous nature, the issue of catalyst recycling was examined next. Indeed, in view of the attained activity and enantioselectivity levels, it was likely that during the reaction a substantial fraction of the copper ions remained coordinated to the supported ligand, but at this stage it was not possible to exclude the occurrence of metal leaching, or other modifications of the catalyst structure, that could prevent its effective reuse. To address this point, the polymeric catalyst particles, retained by the glass frit after filtration of the reaction mixture, were therefore washed with dry CH₂Cl₂ under inert atmosphere (Section 4) and suspended again in the same solvent. Following the addition of more α-methylstyrene **13a** and ethyl glyoxylate **14**, the data summarized in the Figure 2 were obtained in the course of four successive recycles by this procedure. From these results it is evident that although some decrease in reaction rate took place (as witnessed by the progressive reduction of the olefin conversion at the intermediate time of 6 h), the recovered material appeared to retain much of its initial catalytic activity.
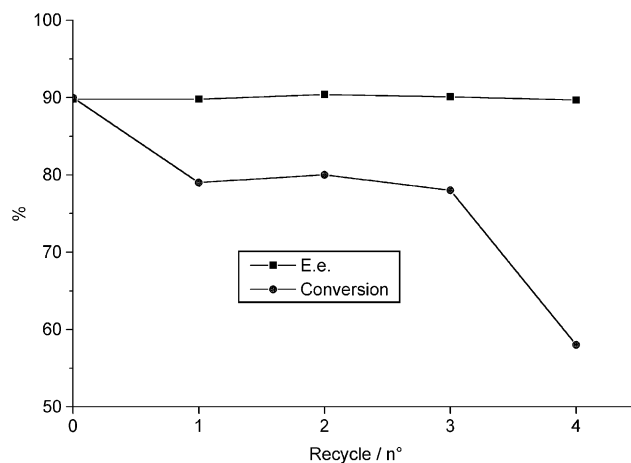

Figure 2. Conversion after 6 h and final ee values for the recycles of **12·Cu(OTf)₂**, in the ene reaction of α-methylstyrene **13a** and ethyl glyoxylate **14**.

In fact complete consumption of the substrate and >95% isolated yield could be obtained even in the last recycle, just by increase of the reaction time to 18 h. Moreover, constant ee values (89.9 ± 0.4%) were achieved in these runs, as expected for a reaction with negligible background (uncatalyzed) rate, under the hypothesis of some metal leaching but a substantial preservation of the ligand integrity.

Having demonstrated the effective recovery of the supported box, the polymeric ligand was subsequently tested in the addition to ethyl glyoxylate **14** of trisubstituted **13e** and functionalized or unfunctionalized 1,1-disubstituted alkenes **13b–d**. To be able to compare reaction rates with those of the soluble counterparts, these additional recycles were carried out after recharging the recovered material with the initial amount of Cu(OTf)₂, filtering, and washing to remove uncomplexed copper species. For the less reactive olefins **13b–e** a reduction in rate respect to **13a** was observed under these conditions (entries 7, 10, 13, 14, and 19), with a more evident difference in catalytic activity between the homogeneous and heterogeneous systems. Nonetheless, even by lowering the catalyst loading to 2 mol% (entry 14), acceptable conversion values and isolated yields were attained within 24–48 h, eventually leading to the corresponding ene products in 85–95% ee. In this respect, it is worth noting that, besides sharing the same topicity, the asymmetric induction degree of the IPB–box **12** is not only identical or slightly superior to that of its soluble model **11b** for all the substrates examined but, in the case of the smaller alkenes **13a,b,d**, also strictly comparable to that reported for the parent ligand **1** (R = Ph). Interestingly, with 1-methylcyclohexene **13e** a slight improvement of enantio- and especially diastereoselectivity was observed by the use of either the supported ligand **12** or its soluble model **11b** [entries 18 and 19: (1′R*,2R*):(1′R*,2S*) = 97:3, 95% ee of (1′R,2R)], respect to the data reported for the ligand **1** (R = Ph) [(1′R*,2R*):(1′R*,2S*) = 89:11, 92% ee].[8] To clarify if the observed differences arose from the modification of the ligand structure, two additional runs with the commercial (R,R) ligand *ent*-**1** (R = Ph)

were carried out, both at 0 or 25 °C (entries 16 and 17). As no major variation of the diastereomeric ratio was recorded in comparison with the use of **11b** and **12**, it seems however that some subtle differences in the reaction conditions, more than the introduction of the spacer group in the modified ligands, are responsible for the changes in the stereoselectivity, confirming once again the stereochemical equivalence of the supported box **12** with the parent compound **1** (R = Ph).[†]

As a final topic, the possibility of exploiting the supported catalytic system for the development of a continuous-flow process was briefly examined. In fact, even if all the recycling runs described in this work could be carried out without problems during the filtration stage, stirring promoted break-down of the polymeric particles to fines can be a serious issue in practical applications, prompting sometimes the investigation of columns packed with heterogenized catalytic systems, as fixed-bed reactors.[26] Because of the small flow rates required by these experiments, a modified HPLC system was chosen as the reactor/reagent delivery assembly.[27] With this aim, a standard 25 cm × 4.6 mm id stainless steel column was packed with the polymeric box **12**, connected to the HPLC system and charged with the copper salt by slowly pumping through the ligand bed an excess of $Cu(OTf)_2$ in dry THF, followed by washing with THF and CH_2Cl_2. Determination of the copper content in the eluate indicated that 0.19 mmol of $Cu(OTf)_2$ per gram of **12** had be retained by the column, in substantial agreement with the metal uptake found under batch conditions (vide supra). After cooling at 0 °C, feeding of a solution of **13a** (0.32 M) and glyoxylate **14** (2.6 equiv) in CH_2Cl_2 was begun.[‡] In view of the relatively low rate of the reaction under study, for the purpose of increasing the contact time between the reagents and the catalyst, the pump control device was recalibrated to provide reduced solution flow (0.015–0.025 mL min^{-1}). Under these conditions, the olefin **13a** and toluene (the solvent in commercial grade **14**) were detected in the column efflux after 5 h, while glyoxylate **4** and the product **15a** required nearly one additional hour to reach the reactor outlet, probably because of strong retention by the supported box–Cu sites. When a stationary process was eventually achieved, GC analysis of the eluate indicated a molar ratio **15a**:**13a** = 83:17, hence confirming an acceptable conversion of the substrates with the adopted experimental arrangement. Although the complete consumption of the starting olefin could be presumably attained by fur-

ther reduction of the flow rate or by adopting product recirculation, the current operation scheme was maintained in order to assure a reasonable throughput and to address the issue of recycling the complex **12**·$Cu(OTf)_2$. Five successive batches of solution of **13a** and **14** were thus fed, with intermediate washing of the column with dry CH_2Cl_2 to prevent extensive clogging by small amounts of polymeric byproducts. By this procedure, overall 23 mmol of **13a** could be effectively converted during 80 h with essentially unchanged enantioselectivity between the successive runs (Fig. 3), eventually leading to **15a** in 78% yield and 88% ee. In fact, in addition of providing constant stereoselectivity values, sustained catalytic activity was also observed in these continuous-flow experiments, with the fraction of **15a** approximately constant (79–84 mol%) under steady conditions. Taking into account the operating parameters, these data translate into a volume productivity of 15 g L^{-1} h^{-1} and a total turnover number (TTN, overall molar amount of isolated product per mol of initial catalyst component) of 44 and 51 versus the supported box ligand and copper salt, respectively.
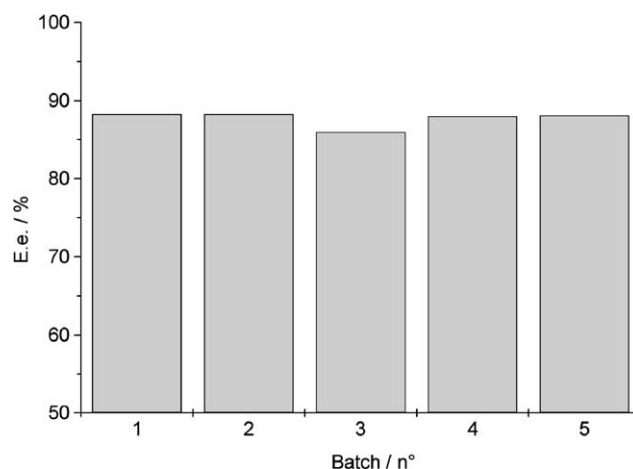
Figure 3. Enantioselectivity values in the continuous-flow ene reaction of α-methylstyrene **13a** and ethyl glyoxylate **14**.

In discussing the findings of this work, it seems appropriate to make a comparison with previous results from the literature, especially for the soluble PEG–box **2** and the box-modified Cu–HY material.[14,17] Regarding the preparation of the modified box, the stability and smooth reactivity of the intermediates **5–10a** allowed the synthesis of the monomer **11a** via a simple modification of the route for the parent ligand. By pushing all the additional steps, required to introduce the styrene and spacers groups, before the set-up of the bis-oxazoline core, no significant synthetic overhead was placed at this stage on the use of the starting chiral material (S)-phenylglycinol, respect to **1** (R = Ph). However, because of both the limited incorporation of **11a** into the material **12** and the incomplete availability of the immobilized box units, the overall efficiency, as the fraction of the starting aminoalcohol converted into accessible supported ligand, results slightly inferior for the IPB–box **12** than for the PEG–box **2**. From this point of view,

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[†] It must be noted that because of a typographical mistake in Ref. 8b (Prof. D. A. Evans, personal communication), for the purified ≈97:3 diastereomer mixtures obtained in runs 16, 17, 18 and 19, the correlation between the sign of the optical rotatory power and the absolute configuration of the prevailing stereoisomer is opposite to that previously reported. In particular, the (1′S,2S)-enriched product **15e** results laevorotatory (Section 4).

[‡] Control experiments revealed that the solution of the reagents **13a** and **14** is remarkably stable, only leading to less than 1% of conversion into the product **15a**, after 96 h at rt. Moreover, pumping in the HPLC system did not change the solution composition, as verified for a sample taken just before the column inlet.

although the lack of direct kinetic data does not allow an easy estimation of the fraction of chirally modified zeolite sites that are actually involved in the catalysis, the possibility of using the commercial box **1** (R = Ph) arguably makes the chiral modification of Cu–HY zeolite the most efficient approach available at present, for the preparation of a supported enantioselective catalytic system for the ene reaction. Moving to the recycling of the box ligands, it is worth noting that while the insoluble material **12** could be recovered in virtually quantitative yield by filtration or in the flow system, only 85% of PEG–box **2** was obtained back by the reported solvent precipitation technique. With a 15% loss of **2** per cycle, it may be estimated that the efficiency of the IPB–box approach of this work is competitive with the soluble polymer strategy already at the first reuse of the material, becoming more and more convenient as the number of recycles increase. In view of the demonstrated possibility of employing the material in four successive runs, with no large difference in isolated yields and enantioselectivity,[17] a limited leaching of the box modifier is expected in the case of the Cu–HY zeolite catalyst. In any case, using the published data TTN values of ≈30 and 66 can be calculated for the soluble ligand **2** and the box modifier in the Cu–HY system, respectively, to be compared with the result achieved with the IPB–box **12**, in batch (Table 1, TTN = 51–54) or continuous-flow (TTN = 44) operation modes. In general, it may be therefore concluded that all the approaches reported hitherto permit a productivity improvement over the benchmark conditions for α-methylstyrene (Table 1, entry 1, TTN ≈ 10), but also that the advantages over the most favorable results, occasionally reported for the soluble box–Cu(OTf)$_2$ catalytic system (e.g., TTN ≈ 50, Table 1, entry 4)[8a] are marginal if any.

Besides allowing the complete recovery of the precious chiral ligand, the possibility of separating **12** from the reaction mixture by physical means also led to a minimal disturbance of the supported copper complex, whose recovery and reuse as an active catalyst could indeed be demonstrated. In this respect, the relatively extended lifetime of **12**·Cu(OTf)$_2$ appears superior than expected on the basis of previous results with IPB–box ligands,[7a,d,18] suggesting that neither a dramatic metal leaching occurs (in spite of the large **14**/Cu ratio in the reaction mixture), nor the catalytic activity is seriously suppressed by the presence of adventitious water, even when the handling is carried out without sophisticated (e.g., inert atmosphere box)[8] techniques. Taken together these observations point therefore to a quite strong binding of the copper salt to the supported box ligand and a high activity of the supported box–Cu(OTf)$_2$ units, apparently concurring to the relatively extended durability of the catalytic material. Interestingly, this conclusion is common to both the use of a metal salt complexed to an insoluble box ligand [i.e., **12**·Cu(OTf)$_2$] and the case of the copper-containing insoluble material modified by a soluble box compound (i.e., **1**/Cu–HY);[17] by comparison with previous findings,[7a,d,18] it seems however rather specific for the carbonyl–ene reaction, probably as a consequence of favorable matching be-

tween ligand and substrates structures, metal oxidation state and catalyst loading/activity profile.

From the point of view of catalytic performances, the use of fresh PEG–box **2** in the ene reaction of **13a** and **13d** (87–95% ee) appears comparable or slightly superior to **12**, even if the soluble ligand suffered from a drop in the ee values on recycling. As noted in the introduction, the Cu–HY zeolite modified by **1** (R = Ph) led to variable ee values,[17] whose dependence on the olefin structure does not match the trend reported for the analogous homogeneous catalytic system. In fact, while an intriguing beneficial effect was observed for methylenecycloalkanes (7–17% ee improvement),[17] in the case of acyclic alkenes the ee values dropped 7–19% below those reported for the soluble catalytic system from **1** (R = Ph),[8] suggesting that a particular combination of chiral ligand and zeolite structure may not be optimally suited for the reaction of structurally different olefin substrates. The restraints imposed by the spatial confinement within the zeolite pores appear also to limit reagents diffusion, with substantially reduced reaction rates in the case of the phenyl-substituted chiral modifier. On the contrary, the IPB–box **12** affords sustained catalytic activity and ee values that are easily predictable on the basis of the stereoselectivity of the parent ligand **1** (R = Ph) or, more consistently, of the soluble model **11b**. Indeed, although some mass diffusion limitation still occurs respect to the soluble box–Cu complexes, the strict correspondence of the ee values between the IPB–box **12** and its model **11b** clearly indicate that no unfavorable (stereoselectivity determining) interaction with the highly cross-linked polymeric chains is taking place. In this regard, the lower ee value in the heterogeneous ene reaction of the sterically demanding olefin **13c** (observed also with the model ligand **11b**) is probably caused by the increased hindrance of the substituted box bridging carbon rather than any heterogenization related effect; accordingly it is likely to be common to every immobilization strategy based on the covalent linking through the methylene position.[§] In conclusion it seems that the design of **12**, based on the use of a flexible linker connecting the box units to a highly cross-linked polystyrene backbone, is sufficient to avoid any interference by the surrounding macromolecular network at the catalytic sites, yet providing a mechanically robust material. This allowed **12** to be recycled easily with remarkably constant enantioselectivity levels, slightly superior in batch runs (90% ee) than under continuous operation mode (86–88% ee).

Finally, the supported system **12**·Cu(OTf)$_2$ appears to afford yield and ee values that are comparable with those provided by some of the BINOL–Ti polymeric systems reported in the literature, either assembled catalysts from non-cross-linked chiral copolymers

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[§] Albeit barely significant, the generally slightly better enantioselectivity of the supported catalytic system **12**·Cu(OTf)$_2$, with respect to the soluble ones, could be linked to a higher box/Cu ratio or the effective removal of uncomplexed achiral copper species from the heterogeneous catalytic system.

(81–88% ee over four recycles)[11a] or metal-bridged polymers (88–92% ee over four recycles).[12a] In fact, other macromolecular systems from this class of catalysts proved exceptionally stereoselective in the ene reaction (up to 98% ee), at the expenses however of extended reaction times (30–120 h) and the need of considerable preparative efforts.[11b,12b]

3. Conclusion

As already shown for other asymmetric transformations,[7] the present work confirms that IPB–box ligands stand as effective and easily recoverable catalyst precursors also in the case of the glyoxylate–ene reaction. By embedding a few key elements in the design of **12**, that is, an inert, highly cross-linked polystyrene matrix and a single attachment point for the box units, through a flexible spacer group, the enantioselectivity of the parent ligand **1** (R = Ph) may be transferred from the homogeneous to the heterogeneous phase, without much sacrifice in terms of catalytic activity. Thanks to the satisfactory mechanical properties of **12**, the separation from the reaction mixture was achieved by what is probably the simplest conceivable technique (filtration), and in turn this allowed the anticipated reuse of the catalytically active copper complex. As noted above, given the relative cost of the chiral inductor and of the copper salt, the recovery of the chiral ligand appears to be the major economic issue here; nonetheless the ability of directly reusing the supported catalytic system, without the need of hazardous regeneration steps, undoubtedly constitutes a remarkable environmental and practical benefit, naturally stemming from the adopted immobilization strategy. In the end, not only could **12** be reused up to seven times in batch runs and five times in a flow system, without noting any degradation of the enantioselectivity, but also most of the recycles were carried out without the need of any additional Cu(OTf)$_2$.

Studies are currently underway to improve the overall heterogenization effectiveness and to evaluate to a longer extent the possibility of recycling this class of chiral ligands.

4. Experimental

4.1. General

All reactions involving sensitive compounds were carried out under dry nitrogen, in flame-dried glassware with magnetic stirring. Before use, the solvents were refluxed over the appropriate drying agent and distilled under nitrogen or reduced pressure: THF from potassium; toluene from sodium; n-hexane from Na–K alloy; Et$_3$N, DMF, and CH$_2$Cl$_2$ from calcium hydride. DVB (Aldrich 95%), styrene, and α-methylstyrene **13a** were distilled under reduced pressure and stored at −20 °C. Ethyl glyoxylate **14** was obtained from the commercial solution (50%, Fluka) as described in Ref. 8 and contained 30 mol% of toluene (by ^{1}H NMR and GC). The other reagents were generally used as received. The

box **1** (R = Ph) and Cu(OTf)$_2$ (Aldrich) were stored in a desiccator over silica-gel. Compounds **5b** and **13b–c** were prepared from the corresponding diol or alcohol.[28] Malonyl dichloride **9a** was prepared as described previously.[7d] For the homogeneous catalysis experiments, product purification and ee determination, the procedure A and conditions in Ref. 8 were followed. TLC analysis were carried out with Merk 60 F_{254} plates (0.2 mm) and chromatography purifications with Macherey–Nagel flash grade silica-gel (230–400 mesh). Melting points (uncorrected) were measured with a Reichert hot stage apparatus. Optical rotation were measured as solutions in 1 dm cells at the sodium D line, using a Jasco DIP360 polarimeter. UV–vis spectra were recorded on a Perkin–Elmer Lambda-9 UV–vis–NIR spectrophotometer. IR spectra were recorded neat or as KBr disks, using a Perkin–Elmer 1600 Series FT-IR; the wavenumber of the principal peaks are reported in cm^{-1}. ^{1}H and ^{13}C NMR spectra were recorded as CDCl$_3$ solutions, on a Varian Gemini 200 or a Varian XL 300, and are reported in ppm relative to TMS (^{1}H) or to the solvent (^{13}C, CDCl$_3$ at 77.0 ppm). Ion-spray mass spectra (IS-ms) were recorded as methanol solutions on a Perkin–Elmer-Sciex Api III spectrometer. For the GC analysis a BP-1 column (25 m) on a Perkin–Elmer 8420 or a Cyclodex-B (30 m) on a Perkin–Elmer Autosystem XL gas chromatograph were used, with nitrogen as the carrier gas; the response factors of the flame ionization detector for relevant compounds were calibrated against standard solutions. HPLC analyses were carried out on a Jasco PU-980 chromatograph, equipped with an UV-975 detector. The continuous ene experiments were carried out using a Jasco Twincle pump, whose analog pressure sensor had been trimmed to provide a reduced flow rate. Nitrogen absorption isotherms for the material **12** were determined with a Sorptomatic 1900 instrument, at the Instituto CNR per la Chimica del Terreno (Pisa). Further determinations were obtained from facilities of the University of Pisa. Elemental analysis were performed by the microanalytical laboratory of the Dipartimento di Farmacia. SEM images were determined at the Dipartimento di Ingegneria Chimica, using a JEOL 5600 LV instrument.

4.2. Preparation of the monomer and soluble model box ligands

4.2.1. *p*-Toluenesulfonate 6b.
A 100 mL two-necked flask, equipped with a dropping funnel, was charged with 39 mmol of the alcohol **5b**, 10 mL of dry CH$_2$Cl$_2$, 79 mmol of Et$_3$N, and 3.9 mmol of 4-dimethylaminopyridine (DMAP). After cooling in an ice bath, a solution of 47 mmol of *p*-toluenesulfonyl chloride (TsCl) in 25 mL of CH$_2$Cl$_2$ was added dropwise and the mixture was stirred at the same temperature, monitoring the disappearance of the starting alcohol by GC. The resulting suspension was washed with water (3 × 20 mL) and the aqueous phases were back-extracted with CH$_2$Cl$_2$ (3 × 10 mL). After drying over Na$_2$SO$_4$, the combined organic phases were concentrated under reduced pressure and the residue was purified by flash chromatography, obtaining the product as a colorless liquid in 72% yield.

Compound **6b**: TLC R_f = 0.61 (Pet. ether:Et$_2$O = 3:1). ^{1}H NMR δ: 1.5–1.8 (m, 4H), 2.43 (s, 3H), 3.41 (t, J = 6 Hz, 2H), 4.05 (t, J = 6 Hz, 2H), 4.44 (s, 2H), 7.2–7.4 (m, 7H), 7.80 (d, J = 8 Hz, 2H). ^{13}C NMR (CDCl$_3$) δ: 21.4, 25.5, 25.7, 69.0, 70.3, 72.6, 127.3, 127.6, 128.1, 129.6, 132.9, 138.2, 144.5.

4.2.2. Diethyl malonate 7b. A 100 mL two-necked flask, equipped with a dropping funnel and a reflux condenser, was charged with 50% NaH in mineral oil ($\approx$24 mmol) and, after washing with dry hexane (2 × 5 mL), the hydride was suspended in dry THF (18 mL). While cooling in an ice bath, diethyl methylmalonate (19.6 mmol), was added dropwise to the rapidly stirred mixture. When the gas evolution had ceased (30 min), the resulting suspension was allowed to warm to room temperature and a solution of the tosylate **6b** (21.5 mmol) in THF (10 mL) was added dropwise. The mixture was heated and kept under reflux until disappearance (GC) of the starting malonic ester (24 h). After cooling in an ice bath, the resulting suspension was cautiously treated with saturated NH$_4$Cl solution (40 mL) and most of the organic solvent removed with a rotary evaporator. The resulting mixture was extracted with Et$_2$O (3 × 30 mL) and the combined organic phases were washed with water until neutral and dried over Na$_2$SO$_4$. The solvent was removed under reduced pressure and the residue was purified by distillation, obtaining **7b** as a colorless liquid in 70% yield.

Compound **7b**: Bp 123 °C (5 × 10^{-3} mmHg). ^{1}H NMR δ: 1.21 (t, J = 8 Hz, 3H), 1.2–1.4 (m, 2H), 1.40 (s, 3H), 1.5–1.9 (m, 4H), 3.84 (t, J = 6 Hz, 2H), 4.54 (q, J = 8 Hz, 4H), 4.87 (s, 2H), 7.2–7.4 (m, 5H). ^{13}C NMR δ: 13.9, 19.7, 20.9, 29.9, 35.2, 53.6, 61.0, 69.9, 72.8, 127.4, 127.5, 128.3, 138.5, 172.3.

4.2.3. Malonic acid 8b. A 25 mL two-necked flask, equipped with a reflux condenser, was charged with the ester **7b** (11 mmol) and 4 mL of 18 M KOH solution (CAUTION). The biphasic mixture was heated under reflux, until disappearance of the upper organic layer (2–3 h), cooled to room temperature, diluted with water (20 mL), and extracted with Et$_2$O (2 × 5 mL). After placing in an ice bath, to the rapidly stirred aqueous solution 37% HCl was cautiously added, adjusting the pH below 2. The resulting white suspension was extracted with AcOEt (3 × 20 mL), washing the combined organic phases with water (3 × 10 mL). Removal of the solvent under reduced pressure afforded the malonic acid **8b** as a white solid in 80% yield. NMR analysis confirmed that the product was pure enough to be used in the following step without further purification.

Compound **8b**: Mp 110–111 °C. IS-ms (m/z) -279 (M$-$H$^+$)$^-$. IR (KBr): 2954, 2872, 1748, 1706, 1462, 1413, 1371, 1297, 1215, 1198, 1162, 1122, 1093, 1070, 978, 946, 909, 870, 768, 748, 732, 699, 663. ^{1}H NMR δ: 1.2–1.7 (m, 7H), 1.8–2.0 (m, 2H), 3.45 (t, J = 8 Hz, 2H), 4.50 (s, 2H), 7.2–7.4 (m, 5H), 9.70 (br s, 2H). ^{13}C NMR δ: 19.9, 21.1, 29.6, 35.4, 53.7, 69.7, 72.8, 127.6, 127.8, 128.3, 138.0, 177.6.

4.2.4. Malonyl dichloride 9b. A two-necked 50 mL flask, equipped with a dropping funnel, was charged with the acid **8b** (4.8 mmol), dry CH$_2$Cl$_2$ (8 mL), and DMF (50 μL). After cooling in an ice bath, oxalyl chloride (14 mmol) was added dropwise over 1.5 h and the mixture was allowed to warm at room temperature and stirred overnight. The volatiles were removed under reduced pressure (20 mmHg), affording the acid chloride **9b** as dark yellow oils, pure enough for the use in the following step.

Compound **9b**: ^{1}H NMR δ: 1.3–1.7 (m, 7H), 2.0–2.1 (m, 2H), 3.48 (t, J = 7 Hz, 2H), 4.49 (s, 2H), 7.2–7.5 (m, 5H). ^{13}C NMR δ: 20.3, 20.7, 29.5, 35.3, 69.3, 73.0, 127.5, 127.6, 128.3, 138.2, 171.4.

4.2.5. Bis(hydroxyamides) (*S*,*S*)-10a and (*S*,*S*)-10b. General procedure. A 50 mL two-necked flask, equipped with a dropping funnel, was charged with (*S*)-phenylglycinol (8 mmol, 2 equiv), dry CH$_2$Cl$_2$ (8.5 mL), and Et$_3$N (20 mmol, 5 equiv). While cooling at 0 °C, a solution of the crude acid chloride **9a** or **9b** (4 mmol) in CH$_2$Cl$_2$ (3.5 mL) was added dropwise over 0.5 h to the rapidly stirred solution. After 1 h the resulting suspension was diluted with CH$_2$Cl$_2$ (20 mL) and washed sequentially with HCl 1 N (25 mL), satd NaHCO$_3$ solution (20 mL), and brine (20 mL), back-extracting each time the aqueous layer with CH$_2$Cl$_2$ (10 mL). The combined organic phases were dried over Na$_2$SO$_4$ and the removal of the solvent under reduced pressure (35 °C, 20 mmHg) afforded the amides **10a** and **10b** as off-white solids, which could be directly used in the following step. For characterization purposes, samples of the products were purified by flash chromatography (**10a**, 80% yield) or crystallization from AcOEt (**10b**, 50% yield).

(*S*,*S*)-**10a**: Mp 127–128 °C. $[\alpha]_D^{25}$ = +40.0 (c 1.0, MeOH). IS-ms (m/z) 545 (M + H)$^+$. IR (KBr): 3321, 2930, 2862, 1638, 1543, 1456, 1361, 1284, 1258, 1107, 1062, 1026, 823, 755, 700, 642, 529. ^{1}H NMR δ: 1.2–1.4 (m, 2H), 1.46 (s, 3H), 1.5–1.6 (m, 2H), 1.8–1.9 (m, 2H), 3.38 (t, J = 6 Hz, 2H), 3.7–3.9 (m, 4H), 4.43 (s, 2H), 5.0–5.1 (m, 2H), 5.22 (d, J = 10 Hz, 1H), 5.72 (d, J = 16 Hz, 1H), 6.70 (dd, J_1 = 10 Hz, J_2 = 16 Hz, 1H), 7.1–7.5 (m, 17H). ^{13}C NMR δ: 19.4, 21.4, 29.7, 38.1, 53.8, 55.70, 55.76, 65.9, 69.8, 72.4, 113.7, 126.5, 127.7, 127.8, 128.7, 136.5, 138.7, 173.3, 173.8.

(*S*,*S*)-**10b**: Mp 149–150 °C. $[\alpha]_D^{25}$ = +52.7 (c 1.0, MeOH). IS-ms (m/z) 519 (M + H)$^+$, 536 (M + NH$_4$)$^+$, 541 (M + Na)$^+$. IR (KBr): 3311, 2922, 2856, 1733, 1639, 1544, 1494, 1450, 1361, 1283, 1255, 1100, 1072, 1028, 800, 756, 733, 694, 644, 527. ^{1}H NMR δ: 1.2–1.3 (m, 2H), 1.46 (s, 3H), 1.5–1.6 (m, 2H), 1.9–2.0 (m, 2H), 3.17 (br s, 2H), 3.38 (t, J = 6 Hz, 2H), 3.7–3.9 (m, 4H), 4.43 (s, 2H), 5.0–5.1 (m, 2H), 7.2–7.3 (m, 17H). ^{13}C NMR δ: 19.3, 21.3, 29.7, 38.1, 53.7, 55.6, 55.7, 65.8, 69.9, 72.8, 126.5, 127.5, 127.6, 128.3, 128.7, 138.7, 173.2, 173.7.

4.2.6. Bis(oxazolines) (*S*,*S*)-11a and (*S*,*S*)-11b. General procedure. A 50 mL two-necked flask, equipped with a dropping funnel, was charged with the bis(amide) **10a** or **10b** (3.9 mmol) and dry CH$_2$Cl$_2$ (15 mL), followed by

DMAP (0.38 mmol), and Et$_3$N (22 mmol). In the case of the styrene derivative **10a**, few crystals of hydroquinone were also added as polymerization inhibitor. A solution of TsCl (7.7 mmol) in CH$_2$Cl$_2$ (4.5 mL) was added drop-wise at room temperature and the resulting solution was stirred for 24 h, whereupon a white suspension was obtained. The mixture was diluted with CH$_2$Cl$_2$ (30 mL) and washed sequentially with satd NH$_4$Cl (30 mL) and 10% NaHCO$_3$ solution (20 mL), back-extracting each time the aqueous layer with CH$_2$Cl$_2$ (10 mL). The combined organic extracts were dried over Na$_2$SO$_4$ and the volatiles were removed under vacuum (35 °C, 20 mmHg) to give a thick oil that was purified by flash chromatography (AcOEt/MeOH = 99:1 as eluent).

(*S,S*)-**11a** (74% yield over two steps): TLC R_f = 0.60 (AcOEt/MeOH = 99:1). $[\alpha]_D^{25}$ = −84.8 (*c* 2.6, MeOH). IS-MS (*m/z*) 509 (M + H)$^+$, 531 (M + Na)$^+$. IR (KBr): 2938, 2864, 1653, 1512, 1493, 1454, 1357, 1268, 1239, 1106, 1047, 980, 909, 825, 732, 700, 646. ^{1}H NMR δ: 1.4–1.5 (m, 2H), 1.6–1.7 (m, 5H), 1.9–2.0 (m, 2H), 3.49 (t, *J* = 6 Hz, 2H), 4.0–4.1 (m, 2H), 4.47 (s, 2H), 4.6–4.7 (m, 2H), 5.2–5.3 (m, 3H), 5.71 (dd, J_1 = 1.2 Hz, J_2 = 16 Hz, 1H), 6.69 (dd, J_1 = 10 Hz, J_2 = 16 Hz, 1H), 7.2–7.3 (m, 14H). ^{13}C NMR δ: 20.9, 21.3, 29.7, 36.1, 42.4, 69.2, 69.3, 69.9, 72.2, 74.9, 75.0, 113.3, 125.9, 126.2, 127.2, 127.5, 128.4, 136.3, 142.1, 142.2, 169.4, 169.5.

(*S,S*)-**11b** (70% yield over two steps): TLC R_f = 0.70 (AcOEt/MeOH = 99:1). $[\alpha]_D^{25}$ = −98.3 (*c* 1.4, CH$_2$Cl$_2$). IS-ms (*m/z*) 483 (M + H)$^+$, 501 (M + NH$_4$)$^+$, 505 (M + Na)$^+$. IR (KBr): 2935, 2852, 1648, 1488, 1452, 1353, 1265, 1229, 1172, 1104, 1027, 975, 913, 731, 695. ^{1}H NMR δ: 1.4–1.6 (m, 2H), 1.6–1.8 (m, 5H), 2.0 (m, 2H), 3.49 (t, *J* = 6 Hz, 2H), 4.08–4.18 (m, 2H), 4.49 (s, 2H), 4.59–4.70 (m, 2H), 5.17–5.28 (m, 2H), 7.2–7.3 (m, 15H). ^{13}C NMR δ: 21.1, 21.5, 29.9, 36.3, 42.6, 69.5, 69.6, 70.0, 72.8, 75.2, 75.3, 126.4, 127.5, 127.5, 128.3, 128.6, 142.3, 142.4, 169.6, 169.7.

4.3. Preparation and characterization of the polymeric ligand 12

4.3.1. Copolymerization.
A polymerization vial was charged with a solution of the monomer **11a** (0.960 g, 1.89 mmol) in dry toluene (2.2 mL, ~40% v/v respect to the total monomers amount) and degassed by three freeze–thaw cycles. Divinylbenzene (1.9 mL, 13.5 mmol) and styrene (1.3 mL, 11.6 mmol) were added, followed by AIBN (40 mg, 1% wt/wt respect to the monomers). The vial was sealed and immersed in an oil bath heated at 80 °C, observing gelation in about 40 min. After 18 h, the volatiles were removed under vacuum (0.1 mmHg) and the opaque glassy polymer was crushed and continuously extracted under nitrogen in a Soxhlet device with THF and then CH$_2$Cl$_2$, containing little CaH$_2$ as dehydrating agent. The UV spectra of the final washings were virtually flat in the 240–350 nm region (A < 0.005, 1 cm cell), where the monomer **11a** absorbs (ε = 1800 M^{-1} cm^{-1} at 285 nm). After drying under vacuum, 3.40 g (87% yield) of the polymeric material **12** were obtained as a white powder.

Compound **12**: IR (KBr): 3022, 2911, 2855, 1939, 1872, 1800, 1739, 1653, 1600, 1489, 1447, 1350, 1261, 1100, 1022, 978, 894, 789, 755, 694. Elemental analysis 90.20% C, 8.28% H, 0.61% N.

4.3.2. Copper uptake determination.
(a) *Calibration curve*: 0.5–1.0 mL aliquots of a stock solution of Cu(OTf)$_2$ in dry THF (C_0 = 0.0200 M) were filtered through a 0.2 μm Teflon membrane in 5 mL volumetric flasks, followed by 1 mL THF rinse. The solvent was gently evaporated with a nitrogen flow and then under vacuum (0.01 mmHg) and the residue was taken up and diluted to volume with 3 M NH$_3$. The UV–vis spectra in the 400–800 nm region of the bright blue tetraaminocopper(II) solutions were recorded in a 2 cm quartz cell. Using the peak absorbance at 624 nm to build the calibration curve, a straight line ($R^2 \geqslant 0.995$) was obtained.

(b) *Uptake determination*: In a dry 25 mL Schlenk tube, a weighed amount P of **12** (≈100 mg) was suspended in 5.0 mL of the stock Cu(OTf)$_2$ solution in THF and stirred under nitrogen for 3 h. Then stirring was stopped and the resulting blue-green material was allowed to settle. By taking a 1.0 mL aliquot of the clear colorless surnatant, that was treated as described at (a) above, the residual copper concentration in solution (C) could be determined from the observed absorbance at 624 nm and the calibration curve. The metal uptake U for the polymeric ligand **12** was calculated as $U = (C_0 − C) \times 5/P$, from which a value of 0.18 mmol/g resulted.

4.4. Heterogeneous enantioselective ene reactions

4.4.1. Batch runs. General procedure.
All the handling was carried out under nitrogen, in a purpose designed 10 mL Schlenk tube, provided with a magnetic stirring bar and a side glass frit ending with a stopcock. The polymeric ligand **12** (208 mg, 0.045 mmol of supported box) was suspended in a solution of dry Cu(OTf)$_2$ (12.6 mg, 0.035 mmol) in THF (1 mL) and kept stirring for 1 h. After that, the Schlenk tube was turned horizontal and the solution removed by filtration through the frit, washing the polymeric catalyst with dry CH$_2$Cl$_2$ (2 × 1 mL) and briefly drying under vacuum. The green material retained by the frit was returned to the bottom of the tube, suspended in CH$_2$Cl$_2$ (1 mL), and the olefin **13a–e** (0.35 mmol) and the glyoxylate **14** (200 μL, 1.5 mmol) were added, cooling if appropriate (Table 1). After 12–48 h, GC analysis of the surnatant generally revealed ≥90% substrate conversion. The reaction mixture was therefore removed through the frit, followed by CH$_2$Cl$_2$ washing (3 × 1 mL). Chromatographic purification of the combined filtrates afforded the ene products **15a–e** in 65–96% yield. After briefly drying under vacuum, the recovered catalyst could be reused directly or after repeating the copper complexation step with Cu(OTf)$_2$ in THF.

The identity of the purified products **15a–d** was checked by NMR and GC–MS with results in agreement with

published data. The configuration of the prevailing enantiomer was established by comparison of chiral HPLC or GC elution order and the sign of $[\alpha]_D$, with those reported in Ref. 8. In the case of **15e** an inseparable ≈97:3 mixture of the (1′R*,2R*) and (1′R*,2S*) diastereomers (contaminated by minor amounts of regioisomeric compounds) was obtained, as determined by GC–MS and 600 MHz ^{1}H NMR. Based on the data from Ref. 8b, further GC analyses with a Cyclodex-B column allowed to evaluate the stereoisomeric composition as follows: for the product **15e** from the run with *ent*-**1** (R = Ph) at 25 °C (Table 1, entry 16), (1′S,2S): (1′R,2R):(1′R*,2S*) = 92.0:4.3:3.7 (t_r = 90.7, 92.4, and 96.7, respectively);¶ the mixture had $[\alpha]_D^{25} = -18.1$ (*c* 0.74, CHCl$_3$). At 0 °C with the same ligand (Table 1, entry 17), (1′S,2S):(1′R,2R):(1′R*,2S*) = 93.4:2.8: 3.8; the mixture had $[\alpha]_D^{25} = -23.2$ (*c* 0.79, CHCl$_3$). For the products obtained using (S,S)-**11b** or (S,S)-**12** (Table 1, entries 18 and 19), (1′S,2S): (1′R,2R): (1′R*,2S*) = 2.2:95.3:2.6; the mixture had $[\alpha]_D^{25} = +22.1$ (*c* 0.89, CHCl$_3$).

4.4.2. Continuous-flow ene reaction of 13a and 14. A 25 cm × 46 mm id stainless steel column was packed with the ligand **12** (2.37 g, 0.52 mmol of supported box) and connected to the HPLC system. After flushing with dry THF (25 mL), a solution of Cu(OTf)$_2$ (0.314 g, 0.86 mmol) in the same solvent was slowly pumped in the column, stopping the flow for 1.5 h to load the polymeric box with the copper salt. The catalytic bed was washed with THF (5 mL) and CH$_2$Cl$_2$ (3 × 10 mL), resulting in an uptake of 0.19 mmol of salt per gram of **12**, as evaluated by measuring the copper content in the combined eluates by the method described above. The column was then placed in an ice bath and the slow pumping of a solution of **13a** (0.67 g, 5.7 mmol) and **14** (2.20 g, 15.2 mmol) in CH$_2$Cl$_2$ (15 mL) was begun. From the weight of solution eluted in a given time, an actual flow of 0.015–0.025 mL min^{-1} was observed in the course of these experiments. After flushing with CH$_2$Cl$_2$ (5 mL), four further batches of reagents were passed through the catalytic bed. Purification of the combined eluates afforded **15a** in 78% yield and 88% ee.

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