Catalysis Today 140 (2009) 51–57

Contents lists available at ScienceDirect

Catalysis Today

journal homepage: www.elsevier.com/locate/cattod

# Some factors affecting the catalytic efficiency in the enantioselective cyclopropanation of olefins by the use of insoluble polystyrene-bound bisoxazoline-copper(I) complex

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ARTICLE INFO

*Article history:*
Available online 5 September 2008

*Keywords:*
Asymmetric catalysis
Supported catalysts
Cyclopropanation

ABSTRACT

A new insoluble polymer-bound bisoxazoline (IPB-box) was prepared by grafting a suitable chiral ligand derivative onto a commercial Merrifield resin. The material obtained by this route was employed in the asymmetric copper-catalyzed olefin cyclopropanation, obtaining good activity and enantioselectivity values (54–84% yield, 71–93% ee) for a range of substrates. In addition, some key factors required for the development of effective IPB-box systems are discussed, including the local ligand symmetry and the influence of immobilization technique and catalyst loading.



## 1. Introduction

The preparation of supported systems has been a recurrent theme in the field of catalysis, since its dawn. In addition to classical hydrogenation systems, this led recently to the development and commercial availability of several encapsulated transition metal systems (*e.g.* EnCat® Pd, Pt and Os), which allow a better purification of the crude product by the separation and recovery of precious or toxic species. While such an approach to reduce metallic contaminants is gaining increasing momentum, especially in high throughput work [1], the simultaneous recovery of added organic ligands cannot be always guaranteed by this strategy. Given the high cost (and molecular weight) of most of the chiral ligands in the current practice, this can turn to be a serious issue when enantioselective catalytic systems for chiral fine chemicals preparation are concerned.

To solve this problem, several strategies have been explored [2,3], amongst which the covalent binding of the chiral fragment to an insoluble support (insoluble polymer-bound approach, IPB) [4] has shown both advantages and limitations. Therefore, the clarification of the key aspects required for satisfactory catalytic performances of IPB asymmetric systems and the development of effective heterogeneization procedures seems to be a continuing challenge.

In this respect, the case of bisoxazoline (box) ligands in benchmark copper-catalyzed olefin cyclopropanation reactions appears largely paradigmatic of the need to clearly define the basic design elements for a successful immobilized catalyst [5–7]. In fact, after the pioneering work of Mayoral and co-workers with polystyrene-anchored IPB-box ligands [8], several groups, including our one [9], added to this topic using either organic [10–16] or inorganic supports [10,11,17–21]. Related studies involved the heterogeneization of aza-box ligands [22,23].

From this body of work several conclusions and guiding principles in the design of IPB-box systems could be drawn, some of which were summarized by Rechavi and Lemaire in a *Chem. Rev.* paper [5]. However, in view or the advancements in the field, three of these concepts appear to lack a general validity and deserve some comments:

### 1.1. $C_2$ vs. not-$C_2$ heterogeneization

The preservation of the $C_2$-symmetry of the original soluble ligands **1** ($R^{br}$ = H or Me) upon anchoring to an insoluble support through the central methylene bridge (Fig. 1) has been regarded as a desirable feature in different immobilization approaches [8,10,11,16]. Moreover, the failure in achieving this goal has been sometimes related to the reduced performances of some IPB-box systems, leading to the conclusion that the conservation of the $C_2$ axis was thought to be crucial for the enantioselectivities to remain high [5].

Nonetheless, the materials obtained immobilizing **1** according to this "$C_2$-conservative" concept could not provide ee values

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doi:10.1016/j.cattod.2008.07.007

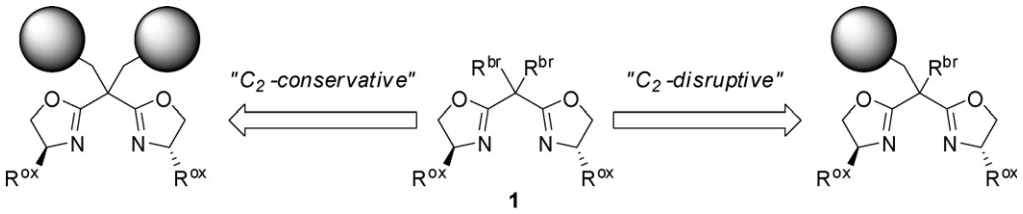



**Fig. 1.** "$C_2$-conservative" *vs.* "$C_2$-disruptive" strategies in the heterogeneization of box ligands.

higher than 78% in the benchmark cyclopropanation of styrene [11]. On the contrary, early results by Cozzi and co-workers with soluble polymer-bound ligands [24], and our work with IPB systems [9], clearly demonstrated that boxs with two identical $R^{br}$ groups (*i.e.* $C_2$-symmetric) are not generally required for the attainment of >90% ee values in the cyclopropanation of different olefin substrates. In this regard it is worth noting that this conclusion has been recently discussed in some detail by Knight and Ying's groups [15,21], and proved also true for other Cu-catalyzed asymmetric transformations with IPB-box ligands [25–27].

### 1.2. Copolymerization vs. grafting

In consideration of the low ee values observed with box ligands anchored on a Merrifield resin or silica gel [11,12], it was suggested that in the present case grafting is of little interest in terms of efficiency and selectivity. Sometimes this conclusion was also discussed in connection with the problem noted above, reasoning that any attempt to anchor a box derivative (even a $C_2$-symmetric one) to a preformed support cannot guarantee the attainment of $C_2$-symmetric supported units [5]. Since then, the idea of the potential advantages in the preparation IPB-box systems by copolymerization of functional monomers, as opposed to grafting, has been echoed in other papers [14,16]. Nevertheless, the suitability of the latter approach has been recently demonstrated by Ying and co-workers [21] and by Mayoral, Reiser and co-workers [22] albeit only in the specific cases of box ligands onto siliceous supports and related aza-box systems, respectively.

### 1.3. Effect of catalyst loading

Through regression analysis of the results reported by Mayoral and co-workers, a significant inverse linear relationship between enantioselectivity and catalyst (copper) loading was demonstrated by Rechavi and Lemaire [5]. In particular, a rather large drop (~30%) in the ee values was noted on increasing the metal content of the supported system from 0.01 to 0.44 mmol $g^{-1}$ in polystyrene IPB-box ligands ($R^{ox}$ = Ph), and a similar trend was deemed to occur also for siliceous materials. Accordingly, the preparation of lightly functionalized IPB-box materials was recommended, in order to obtain optimal catalytic performances in the asymmetric cyclopropanation.

As a possible explanation of the observed relationship, the occurrence of unwanted site–site interactions (dimer formation) was suggested [5]. Although it was later argued that available data cannot rule out alternative explanations [16], it is clear that, should this relationship be general, then the preparation of IPB-box-Cu catalysts would be hampered by the unpractically low loadings that seem required to attain best ee values.

Given the continuing interest in the development of recovery methods for box ligands, as well as the conceptual importance of the points noted above for the whole field of IPB enantioselective systems, we report herein our observations on the influence of the material architecture in the Cu-catalyzed enantioselective olefin cyclopropanation with polystyrene-anchored box ligands. In particular a grafting route to a new IPB-box (**G1**) is described and the catalytic results compared and contrasted with previous findings in the literature, including the use of material (**P1**) previously prepared in our group by a copolymerization approach [9].

## 2. Experimental

### 2.1. General

All reactions involving sensitive compounds and the catalysis runs were carried out under dry nitrogen, in flame-dried glassware with magnetic stirring. Before use, the solvents were refluxed over the proper drying agent and distilled under nitrogen or at reduced pressure [28]. Styrene was distilled under reduced pressure and stored at −20 °C. The other reagents were used without further purification. The Merrifield resin (2% C.L., 2.9 mmol Cl $g^{-1}$) was purchased from Aldrich.

TLC analysis was carried out with Merk 60 $F_{254}$ plates (0.2 mm) and chromatography purifications with Macherey-Nagel flash grade silica gel (230–400 mesh). Optical rotation was measured as solutions in 1 dm cells at the sodium D line, using a Jasco DIP360 polarimeter. UV–vis spectra were recorded on a PerkinElmer Lambda-9 UV–vis–NIR spectrophotometer. IR spectra were recorded neat or as KBr discs, using a PerkinElmer 1600 Series FT-IR; the wavenumber of the principal peaks are reported in $cm^{-1}$. $^1H$ 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 ($^1H$) 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 PerkinElmer-Sciex Api III spectrometer. GLC and HPLC analyses were carried out with a PerkinElmer Autosystem XL and a Jasco PU-980 chromatograph (with UV-975 detector), respectively.

### 2.2. Preparation of soluble model compounds

The box ligands (*S,S*)-**2** and **3** (Fig. 2) were prepared by the method of Evans et al. [29] starting from the corresponding substituted malonic acid and (*S*)-*tert*-leucine.

#### 2.2.1. Compound (S,S)-2

Obtained as a light yellow oil, in 40% overall yield from *tert*-leucine. $[\alpha]_D^{25} = -97.5$ (c 2.44, $CHCl_3$). $^1H$ NMR (300 MHz): $\delta$ = 0.84–0.94 (m, 21H), 1.20–1.37 (m, 4H), 1.48 (s, 3H), 1.75–2.08 (m, 2H), 3.79–3.91 (m, 2H), 3.98–4.22 (m, 4H). $^{13}C$ NMR

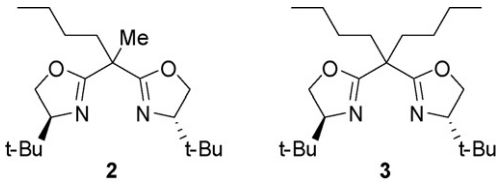



**Fig. 2.** Box soluble model compounds.

(75 MHz): $\delta$ = 14.1, 21.5, 23.1, 25.8, 25.9, 26.7, 33.9, 34.0, 36.2, 42.4, 68.7, 68.8, 75.4, 75.6, 168.1, 168.3. ESI-MS: $m/z$ = 337 $[M+H]^+$, 359 $[M+Na]^+$.

*2.2.2. Compound (S,S)-3*

Obtained as a light yellow oil, in 60% overall yield from *tert*-leucine. $[\alpha]_D^{25} = -83.0$ (c 1.25, $CH_2Cl_2$). $^1H$ NMR (300 MHz): $\delta$ = 0.80–1.00 (m, 24H), 1.09–1.44 (m, 8H), 1.76–2.20 (m, 4H), 3.85 (dd, $J_1$ = 10.2 Hz, $J_2$ = 7.1 Hz, 2H), 3.94–4.20 (m, 4H). $^{13}C$ NMR (75 MHz): $\delta$ = 14.1, 23.0, 25.9, 26.3, 32.5, 33.9, 46.0, 68.4, 75.5, 167.4. ESI-MS: $m/z$ = 379 $[M+H]^+$.

*2.3. Preparation of IPB-box ligands*

The IPB-box copolymer **P1** was obtained by the *route a*, as described before [9]. The preparation of the Merrifield resin-grafted ligand **G1** was carried out according to the *route b* summarized in Scheme 1.

*2.3.1. Preparation of (S,S)-5*

A 100 mL two necked flask, fitted with a dropping funnel, stirring bar, and silicone septum was charged with a solution of [9-BBN] in THF (0.5 M, 17 mL, 8.5 mmol, 4.8 eq.). After placing in an ice bath, the solution of (*S*,*S*)-**4** (770 mg, 1.78 mmol, 1 eq.) [30] in dry THF (16 mL) was slowly cannulated into the flask. The cooling bath was removed and the mixture stirred overnight at room temperature. Then, the borane product was oxidized by the dropwise addition of NaOH 4 M/30% $H_2O_2$ = 2/1, followed by vigorous stirring until the gas evolution ceased. After addition of EtOH (16 mL) the mixture was concentrated under reduced pressure, extracted with $Et_2O$, and washed with water (2 × 10 mL). The ethereal layer was dried ($Na_2SO_4$) and evaporated under reduced pressure. The residue was purified by flash chromatography ($CH_2Cl_2$/AcOEt = 7/3 as the eluant), affording 750 mg (93%) of (*S*,*S*)-**5** as a clear oil. $R_f$ ($SiO_2$, $CH_2Cl_2$/AcOEt 7/3): 0.26. $[\alpha]_D^{25} = -55.9$ (c 2.07, $CHCl_3$). $^1H$ NMR (200 MHz): $\delta$ = 0.84 (s, 18H), 1.15-1.40 (m, 17H), 1.44 (s, 3H), 1.46–1.60 (m, 2H), 1.65–2.30 (m, 2H), 3.59 (t, $J$ = 6.6 Hz, 2H), 3.76–3.86 (m, 2H), 3.96–4.14 (m, 4H). $^{13}C$ NMR (75 MHz): $\delta$ = 21.3, 24.2, 25.7, 25.8, 29.38, 29.43, 29.45, 29.52, 29.8, 32.7, 33.7, 33.9, 36.4, 42.4, 62.7, 68.6, 68.7, 75.3, 75.5, 168.1, 168.3. ESI-MS: $m/z$ = 451 $[M+H]^+$, 469 $[M+NH_4]^+$.

*2.3.2. Preparation of G1 by grafting onto the Merrifield resin*

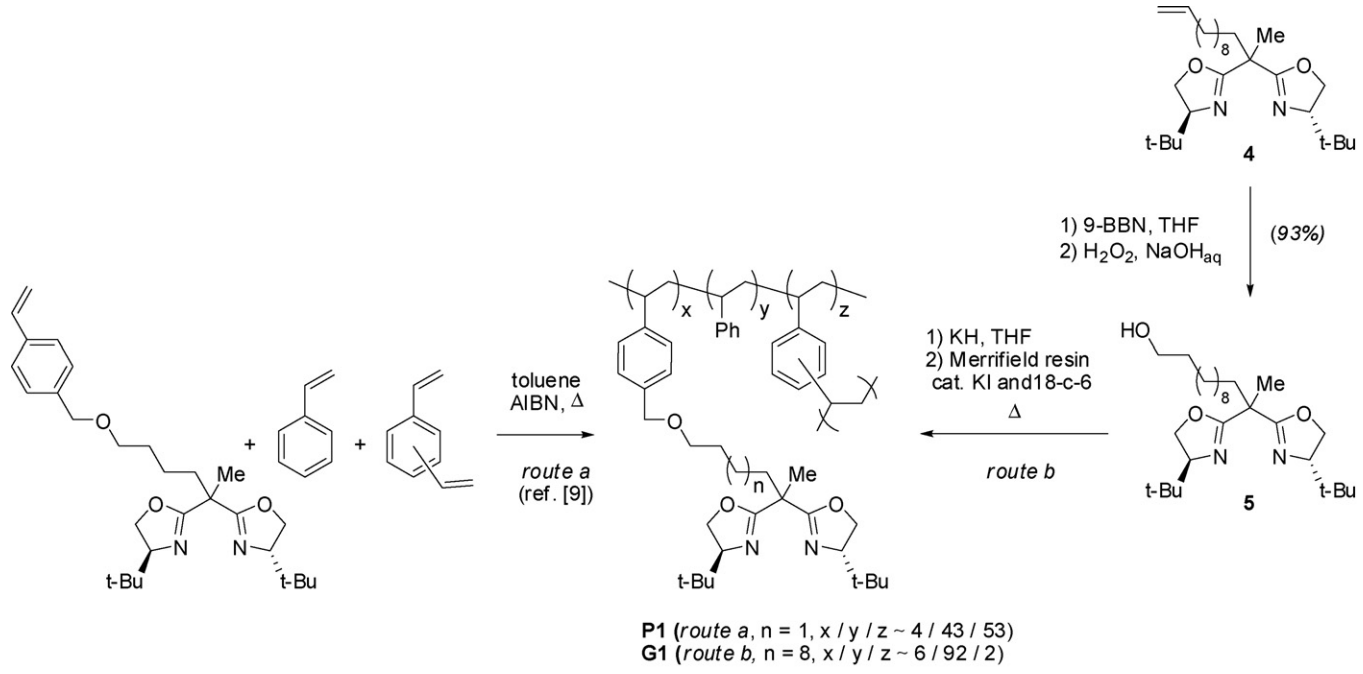
A 100 mL three-necked flask, fitted with a dropping funnel, reflux condenser, stirring bar, and silicone septum was charged with 30% KH in mineral oil (221 mg, 1.7 eq.) and dry THF (10 mL). The flask was transferred into an ice bath and (*S*,*S*)-**5** (451 mg, 1 mmol, 1 eq.) in dry THF (10 mL) was added to the rapidly stirred mixture, followed by further stirring for 1 h at r.t. The Merrifield resin (435 mg, 1.26 eq. Cl), KI (28.5 mg, 0.17 eq.), 18-c-6 (28.5 mg, 0.10 eq.), and dry THF (15 mL) were added next and the suspension was refluxed for 48 h. After cooling, excess KH was quenched by the dropwise addition of MeOH (5 mL) and the mixture was stirred for 1 h. The resin was recovered by filtration, washed on the frit with $H_2O$, DMF, MeOH, acetone, THF, and $CH_2Cl_2$ and continuously extracted with dry THF for 24 h. After drying in vacuo, **G1** was obtained as a free-flowing clear powder (540 mg). The material was characterized as described below.

*2.4. Characterization*

The supported ligand **G1** was subjected to FT-IR (as KBr disc, Fig. 3a) and to elemental analysis. From the nitrogen content (1.41%), the loading of supported box units was estimated to be 0.50 mmol $g^{-1}$.

Moreover, in order to evaluate the metal uptake, **G1** (100 mg) was suspended in an excess of $Cu(OTf)_2$ 0.50 M in dry THF (5 mL, 2.5 mmol) and stirred for 3 h at r.t. The residual copper in solution was then determined spectrophotometrically, as detailed before [25], and the metal absorbed by the resin ($U$ = 0.53 mmol Cu $g^{-1}$) was calculated by difference.

The suspension was filtered, under inert atmosphere, through a frit and the recovered light blue resin was washed with dry $CH_2Cl_2$ (2 × 1 mL) and dried under reduced pressure, before recording the IR spectrum of the supported box-Cu(II) complex (as KBr disc, Fig. 3b).




**Scheme 1.** Preparation and structures of the IPB-box ligands **P1** and **G1** (AIBN = 2,2′-azobisisobutyronitrile; 9-BBN = 9-borabicyclo[3.3.1]nonane; 18-c-6 = 18-crown-6 ether).

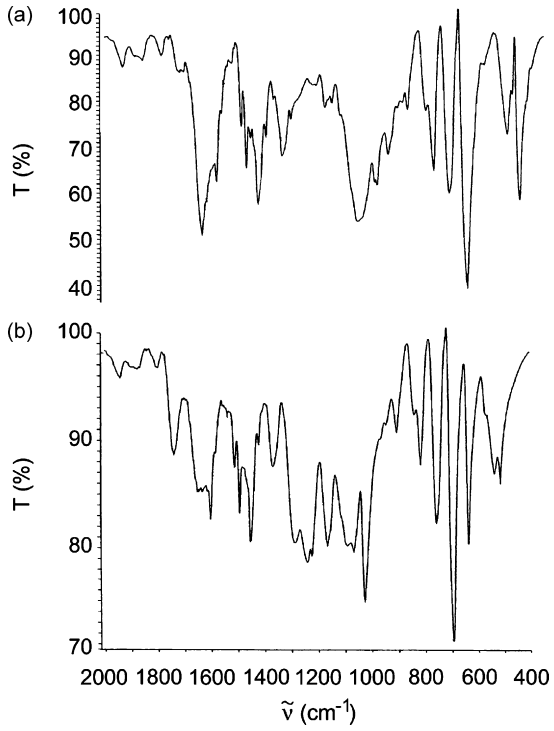



**Fig. 3.** FT-IR spectra (400–2000 cm$^{-1}$ region) of (a) the IPB-box **G1** and (b) the material charged with $Cu(OTf)_2$.

### 2.5. Catalytic tests

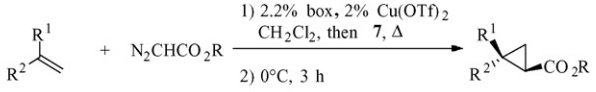
Homogeneous catalysis runs with the model ligands **2** and **3** (see Table 1) were carried out in $CH_2Cl_2$ at 0 °C, as described [9]. Diazoacetate conversion, chemoselectivity and, when applicable, the *trans*/*cis* diastereomeric ratio (dr) were evaluated by GLC with a DB-1 column (detector response calibrated against standard solutions). The enantiomeric excess of the products were determined by HPLC or GLC with chiral stationary phases [9].

#### 2.5.1. Heterogeneous catalysis runs: general procedure

A Schlenk tube provided with a frit, a stirring bar, and a dropping funnel was charged with $Cu(OTf)_2$ (7.2 mg, 0.02 mmol). After drying by briefly heating under reduced pressure (0.05 mbar) with a small flame, the copper salt was dissolved with dry THF (1 mL). The supported ligand **P1** or **G1** (0.022 mmol based on nitrogen content) was added and the suspension was stirred for 3 h at r.t. The solution was removed by filtration under inert atmosphere, the light blue resin was rinsed with dry $CH_2Cl_2$ ($2 \times 1$ mL) and finally suspended in the same solvent (1 mL). One drop of a solution of the diazoacetate (1 mmol) in $CH_2Cl_2$ (3 mL) was added and the mixture was briefly heated to reflux, observing the rapid turning of the resin to a reddish brown color. The Schlenk tube was placed in an ice bath and the olefin (2 mmol) was added, followed by the dropwise addition of the remaining of the diazoacetate solution, over 2.5 h. After 30 min the solution was filtered through the frit and the recovered resin was washed with dry $CH_2Cl_2$ ($3 \times 1$ mL), to be directly reused in further catalysis runs. The combined filtrates were assayed by GLC or HPLC as described for the homogeneous runs, above.

For the cyclopropanation of *iso*-butene (**6b**), the olefin (70–100 mmol) was condensed into the vessel and the solution of the diazoacetate (10 mmol) was slowly added over 16 h with a syringe pump.

**Table 1**
Homogeneous and heterogeneous enantioselective cyclopropanation of olefins (**6**) with diazoacetates (**7**), by the use of soluble (**1**–**3**) and polystyrene-bound box ligands (**P1** and **G1**)




**6a** $R^1$ = H, $R^2$ = Ph
**6b** $R^1 = R^2$ = Me
**6c** $R^1 = R^2$ = Ph

**7a** R = Et
**7b** R = *t*-Bu

**8**

| Entry | Olefin | Diazo | Box | Cycle | Chemoselectivity % (yield %)[a] | dr[b] | ee%[c] |
|---|---|---|---|---|---|---|---|
| 1 | **6a** | **7a** | **1** ($R^{ox}$ = *t*-Bu, $R^{br}$ = Me) | – | 63 (61) | 71/29 | 94/92 |
| 2 | **6a** | **7a** | **2** | – | 69 | 69/31 | 93/91 |
| 3 | **6a** | **7a** | **3** | – | 68 | 66/34 | 85/83 |
| 4 | **6a** | **7a** | **P1** | 1 | 61 (60) | 67/33 | 93/90 |
| 5 | **6a** | **7a** | **P1** | 2 | (72) | 67/33 | 94/90 |
| 6 | **6a** | **7a** | **P1** | 3 | (60) | 66/34 | 93/91 |
| 7 | **6a** | **7a** | **G1** | 1 | 67 | 67/33 | 92/90 |
| 8 | **6a** | **7a** | **G1** | 2 | 54 | 67/33 | 92/90 |
| 9 | **6a** | **7a** | **G1** | 3 | 67 | 67/33 | 93/90 |
| 10 | **6a** | **7b** | **P1** | 1 | (65) | 75/25 | 83/71[d] |
| 11 | **6a** | **7b** | **G1** | 1 | (66) | 78/22 | 85/83[d] |
| 12 | **6b** | **7a** | **P1**[e] | 2 | 88 (84) | – | 91 |
| 13 | **6b** | **7a** | **G1**[e] | 2 | 85 (75) | – | 91 |
| 14 | **6c** | **7a** | **P1** | 1 | (75) | – | 91 |
| 15 | **6c** | **7a** | **G1** | 1 | (70) | – | 89 |

[a] Chemoselectivity in the transformation of **7** into **8** *vs.* fumarate and maleate byproducts, by GLC. In parentheses, isolated yield after chromatographic purification or distillation.
[b] *Trans*/*cis* diastereomeric ratio, by GLC.
[c] Enantiomeric excess by HPLC or GLC [9]. For the products obtained as a mixture of diastereomers, the values are reported as ee *trans*-**8**/ee *cis*-**8**. In each case the prevailing enantiomer had (1R) configuration [31].
[d] The diastereomers were separated by column chromatography and the ee of *cis*-**8** was determined by GLC (Astec G-TA); the ee of the *trans* product was evaluated by HPLC (Chiralcel OJ), after reduction with $LiAlH_4$ to the corresponding alcohol [32].
[e] With 0.2 mol% supported catalyst and slow addition of the diazoacetate solution over 16 h.

The results of the homogeneous and heterogeneous catalytic runs are summarized in Table 1, together with those previously reported with the **P1** IPB-box material and the literature ligand **1** ($R^{ox}$ = *t*-Bu, $R^{br}$ = Me) under the same conditions [9].

## 3. Results and discussion

As noted in Section 1, one of the most basic issues in the development of IPB-box systems is the choice of the anchoring strategy. In particular, the immobilization through the central methylene bridge of **1** leaves two options (Fig. 1), *i.e.* the linking of the chiral units to the insoluble support by the use of two identical tethers ("$C_2$-conservative" strategy) as opposed to the decision to effect the anchoring by a single linking group ("$C_2$-disruptive" strategy).

In spite of the general advantages associated with the use of $C_2$ chiral ligands, including the bisoxazoline ones [33], in the present case the selection of the former strategy appears, however, far from obvious. This is especially true when one considers that a very effective soluble ligand **1** ($R^{ox}$ = *t*-Bu, $R^{br}$ = Me) is already known from the work of Evans and co-workers [29]. In principle, the development of efficient IPB-box materials should then be possible, provided the transfer from the homogeneous to the heterogeneous phase can take place without dramatically modifying the original ligand structure. In this respect it is worth noting that the catalytic performances will be eventually influenced by

the actual three-dimensional box geometry, including the nature and steric hindrance caused by bridge substituents, and not by symmetry itself. Accordingly, the "$C_2$-conservative" strategy is expected to lead to a larger departure from the optimal structure **1** ($R^{ox}$ = *t*-Bu, $R^{br}$ = Me) than a "$C_2$-disruptive" one, with the latter representing the minimal box modification required to effect the anchoring through the bridge carbon atom.

Nonetheless it must be emphasized that, besides the similarity with the original ligand, there is no particular reason to believe that any of the two alternative strategies will provide a more effective modified ligand than the other one. Therefore, before moving to the IPB stage, the importance of this hypothesis was initially checked by studying proper model compounds, as discussed in the next paragraph.

### 3.1. Influence of "local" symmetry and structure of supported box units

Although ring-substituted benzyl groups have been often employed as bridge substituents in the covalent immobilization of box derivatives, for the same reasons noted above the choice of linear, flexible linkers seems nonetheless advantageous as a mean to reduce to a minimum the structural perturbation required to effect the anchoring. With this idea in mind, straight alkyl chains were selected as tethering groups and the ligands **2** and **3** were synthesized as soluble models of box units anchored through a "$C_2$-disruptive" and "$C_2$-conservative" strategy, respectively.

The use of these new ligands in the benchmark cyclopropanation of styrene revealed a significant influence of the bridge substituents on the enantioselectivity of the homogeneous reaction (Table 1). Indeed, while the not $C_2$-symmetric box **2** (entry 2) proved nearly as effective as the literature ligand **1** ($R^{ox}$ = *t*-Bu, $R^{br}$ = Me) under the same conditions (entry 1), a substantial drop in the ee of the cyclopropane products was observed with the more symmetric box **3** (entry 3). In this regard it should be noted that **2** resulted also more effective than previously reported soluble ligands, characterized by the presence of one or two benzyl substituents on the carbon bridge, *i.e.* the bisbenzyl-substituted box **1** ($R^{ox}$ = *t*-Bu, $R^{br}$ = Bn), studied by Mayoral and co-workers [8] and the PEG-tethered ligand **1** ($R^{ox}$ = *t*-Bu, $R^{br}$ = Me and 4-MeOPEG-$C_6H_4CH_2$), reported by Cozzi and co-workers [24] Interestingly, while these box's afforded variable enantioselectivity levels in the benchmark styrene cyclopropanation (*trans*/*cis* = 32/68, *trans* = 70% ee, *cis* = 79% ee and *trans*/*cis* ~70/30, *trans* = 87–91% ee, respectively), in this case also the not $C_2$-symmetric ligand appears to provide higher ee values then the $C_2$-symmetric one. Therefore, by comparison of the results discussed so far the stereochemical efficiency of box ligands with different $R^{br}$ groups may be ranked in the order: $(ArCH_2)_2$ - < $R_2$ < Me,$ArCH_2$ < Me,R ~ $Me_2$ (R and Ar are a linear alkyl and an aromatic group, respectively), which obviously matches the variations in the steric hindrance at the bridge position but not those in the ligand symmetry [15].

### 3.2. Preparation of polystyrene-grafted box ligands

As far as the supported box units in an IPB material may be provided with a solution-like behavior (*i.e.* major heterogeneization effects do not come into play), the findings of the previous paragraph point to the choice of the "$C_2$-disruptive" strategy, by the use of a single linear alkyl linker, as a very effective way to preserve the high efficiency of **1** ($R^{ox}$ = *t*-Bu, $R^{br}$ = Me). As anticipated, this hypothesis could be proved, already, in the case of the material **P1**, prepared by copolymerization of the corresponding functional monomer [9]. Indeed, as summarized in Table 1 (entries 4–6) the results obtained with **P1** not only appear completely consistent with those provided by the model compound **2** of this work, but are also the highest reported to date for an Evan's type IPB-box on polystyrene support [8,10–16]. Clearly, as these findings demonstrate that the preservation of $C_2$-symmetry is not a mandatory requirement for the preparation of highly enantioselective IPB-box systems, this leads to the second general point noted in Section 1, *i.e.* the failure in achieving $C_2$-symmetric units as a possible explanation of the poor results obtained to date in the grafting of box ligands onto polystyrene resins [5,16]. Although the validity of this argument looks difficult to assess for the literature materials (also because the lack of tests with suitable model compounds), in the context of the present work it was not expected to constitute a major problem, anyway. In particular, as long as the attainment of supported units closely related to **2** can be guaranteed, the results discussed above suggest that the immobilization technique should have a minor impact on catalytic performances.

To test this hypothesis, a new approach to IPB-box ligands was explored (Scheme 1, *route b*). Accordingly, the unsaturated box ligand **4** was subjected to hydroboration–oxidation to afford the corresponding alcohol derivative **5**, which was grafted to a commercial Merrifield resin under Williamson conditions. The progress of the latter step was monitored by IR (Fig. 3a), observing the disappearance of the C–Cl stretching at 1265 $cm^{-1}$ [34], and the growth of a new band at 1655 $cm^{-1}$, characteristic of the box C=N stretching [35]. After continuous extraction with dry THF, to remove any soluble component, and drying, the elemental analysis of the material **G1** confirmed the anchoring of the box ligand. In particular, the nitrogen content of **G1** allowed to estimate a box loading of 0.50 mmol $g^{-1}$, which represents a nearly two-fold increase with respect to the previously reported copolymer **P1** (0.31 mmol $g^{-1}$) [9].

In order to characterize the complexation capacity of **G1** *vs.* copper ions, the uptake *U* of $Cu(OTf)_2$ from a THF solution was determined. The result (*U* = 0.53 mmol $g^{-1}$) not only appears to match the ligand loading of **G1**, within the experimental uncertainty, but is also significantly higher than the value found for the material **P1** (*U* = 0.18–0.20 mmol $g^{-1}$) [9]. The grafting approach to IPB-box systems appears therefore somewhat advantageous over the previously investigated copolymerization strategy, both in terms of the better use of the expensive chiral derivative (due to the complete ligand accessibility) [13] and also in view of the higher absolute metal loading.

After washing and drying of the light blue resin recovered from uptake experiments, the supported precatalyst **G1**-$Cu(OTf)_2$ was also characterized by IR (Fig. 3b). By comparison with the spectrum of the ligand **G1**, several new bands were observed some of which (1287, 1240, 1165, and 1027 $cm^{-1}$) may be assigned to the triflate counterions [36].

### 3.3. Heterogeneous enantioselective cyclopropanation of olefins

In order to make an easier comparison, catalytic tests with the new polystyrene-supported box **G1** (see Table 1) were carried out by the procedure described before for **P1** [9]. Thus, the **G1**-Cu(II) precatalyst was obtained by stirring the IPB-box with a THF solution of $Cu(OTf)_2$, followed by washing with dry THF to remove any unbound metal salt and rinsing with the reaction solvent ($CH_2Cl_2$). The reduction of the supported Cu(II) complex to the catalytically active Cu(I) form was accomplished by adding a small amount of the diazoester **7** to the suspension of **G1**-$Cu(OTf)_2$ in $CH_2Cl_2$ and briefly heating to reflux [31]. Analogously to what is observed in the homogeneous reaction, gas evolution and the fast turning of resin's color from light blue to reddish-brown was observed under these conditions.

The cyclopropanation runs were carried out at 0 °C, with styrene (**6a**), *iso*-butene (**6b**) or 1,1-diphenylethylene (**6c**) and ethyl (**7a**) or *tert*-butyldiazoacetate (**7c**). The diazoester **7** to Cu ratio (S/C) was kept at 50 in the reaction of **6a** and **6c**, while in the cyclopropanation of **6b** it was raised to 200. In order to reduce the formation of fumarate and maleate byproducts, **7** was slowly added to the catalyst suspended in the olefin solution, either dropwise over 2.5 h (**6a** and **6c**) or with a syringe pump over 16 h (**6b**).

As summarized in Table 1, the supported system obtained from **G1** proved active for all the substrates examined, leading to the complete conversion of **7a** or **7b** in the indicated time. Fair to good chemoselectivity in the formation of the cyclopropane products **8** (or isolated yields) were also obtained, although with some variations from run to run, probably due to the scarce reproducibility of the diazoester addition. From this point of view, results were definitively better in the cyclopropanation of *iso*-butene (**6b**, entry 13), where the use of a larger excess of the olefin substrate (7–10 eq. *vs.* **7a**) [31] and a longer addition time could even compensate for the much reduced catalyst loading (S/C = 200).

Turning the attention to the stereoselectivity in the benchmark styrene cyclopropanation, the supported catalyst obtained from **G1** appears to match within 2% ee the results provided not only by the model compound **2** (entries 7–9 *vs.* entry 2), but also by the literature ligand **1** ($R^{ox}$ = *t*-Bu, $R^{br}$ = Me, entry 1). In addition, the grafted ligand **G1** proved also essentially equivalent to the copolymer **P1** for all the olefin/diazoacetate pairs examined in this study. This close similarity includes significant enantioselectivity levels (89–93% ee) in all the cyclopropanation reactions involving ethyl diazoacetate (**7a**), some drop in ee with the more hindered diazoester **7b** (entry 10 *vs.* entry 11), and the possibility to recover and effectively re-use the supported IPB-box-Cu(I) catalyst (entries 7–9 *vs.* entries 4–6).

In view of the strong impact of material architecture and immobilization technique on the catalytic performances of many polystyrene IPB-box systems reported in the literature (see Section 1), the substantial equivalence **G1** and **P1** looks remarkable and deserves some comments.

First of all, it should be clear that, for the problem at hand, no significant difference between grafting and copolymerization was observed. As anticipated, this is most likely a consequence of the success in (a) achieving "locally similar" anchored chiral units in **G1** and **P1** (*i.e.* structures analogous to **2**) and (b) removing any major support influence, thanks to the presence of the linking group. Regarding the latter factor, it is interesting to note that in **G1** and **P1** the chiral box fragments are separated from the polymeric matrix by a spacer of 4 and 11 carbon atoms, respectively. Given the equivalent catalytic performances of **G1** and **P1**, it seems therefore that, in the case under study, a 4 atom linear tether can be sufficient to get rid of unfavorable interactions with the support.

Recalling the analysis by Rechavi and Lemaire [5], discussed in Section 1, the second noteworthy result of this work is the lack of an important influence of the catalyst (copper) loading on the ee of cyclopropane products. Indeed, despite the rather different metal uptake of the materials of this study (0.53 and 0.18 mmol Cu $g^{-1}$, respectively), the supported system prepared from **G1** afforded enantioselectivity levels within 1–2% of those provided by **P1**, for all the substrates examined. Therefore, the unfavorable loading effect evidenced with early polystyrene IPB-box ligands, does not seem to be the rule for this class of supported catalysts and, in fact, it appears negligible for the IPB-box architecture and metal content range span by **P1** and **G1**. Given the relatively high Cu loading in **G1**, also in comparison with the polystyrene materials discussed in Section 1, the practical consequence of these findings is the demonstration that effective asymmetric IPB-box systems can be prepared without the need to limit the metal content in the low end range. In this regard, it should be noted that a similar conclusion may also be drawn when the most effective IPB systems reported to date for the reaction under study (*i.e.* the box ligand onto a siliceous support, by Ying et al. [21] and the Merrifield resin-grafted aza-box ligand developed by Mayoral, Reiser and co-workers [22]) are considered.

## 4. Conclusions

In summary, a new approach has been explored for the covalent immobilization of a chiral bisoxazoline onto an insoluble polystyrene support, based on the grafting of a ligand derivative onto a commercial Merrifield resin. The IPB-box material obtained by this route (**G1**) was employed in the copper-catalyzed enantioselective cyclopropanation of olefins, obtaining good results in terms of activity (60–84% yield) and enantioselectivity (71–93% ee).

Moreover, the comparison of the catalytic performances of **G1** with those of a related IPB-box **P1** obtained by copolymerization, as well by suitable model compounds, allowed to elucidate some key elements in the design of this class of supported ligands. At variance with the guiding principles of early studies in the field, it is worth noting that these elements may be reduced to the idea of preserving to the maximum possible extent the structure of the original soluble ligand **1** ($R^{ox}$ = *t*-Bu, $R^{br}$ = Me), upon immobilization. As a matter of facts, this could be achieved for both **G1** and **P1**, by anchoring the box units through a single linear alkyl spacer. In spite of the formal loss of the original ligand $C_2$-symmetry, and regardless of other details like the anchoring technique and metal loading, this proved indeed sufficient for the development of the most enantioselective Evan's type IPB-box ligands on organic supports reported to date for the cyclopropanation reaction [37].

Studies are currently underway for a more detailed characterization of the immobilized catalytic systems discussed in this work.

## Note added in proof

After the submission of this manuscript, a few papers have appeared dealing with IPB-box ligands in olefin cyclopropanation. These papers are referenced now in Ref [37].

## Acknowledgements

Work financed by M.I.U.R. and Università di Pisa (Project PRIN 2005 "Sintesi e stereocontrollo di molecole organiche per lo sviluppo di metodologie innovative di interesse applicativo").

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