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Remarkable Efficiency Improvement in the Preparation of Insoluble Polymer-Bound (IPB) Enantioselective Catalytic Systems by the Use of Silicone Chemistry

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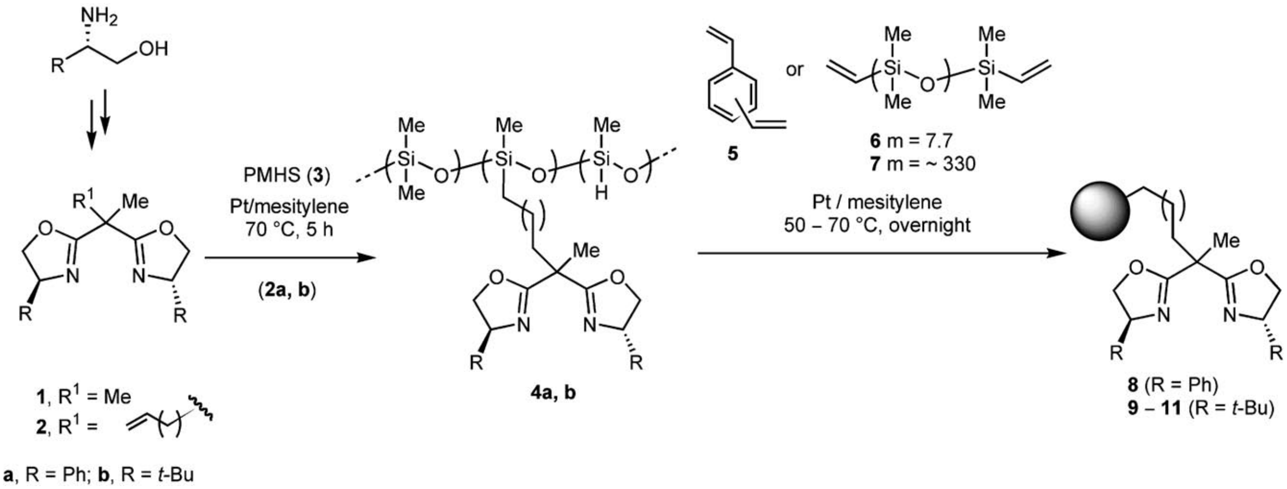
Abstract: The use of platinum-catalyzed hydrosilylation chemistry of silicones greatly simplifies the preparation of bis-oxazoline (box) ligands covalently bound to an insoluble polymeric support. The use of such immobilized chiral ligands in different copper-catalyzed asymmetric transformations (carbonyl-ene, Mukaiyama aldol and olefin cyclopropanation reactions) allows the attainment of high levels of enantioselectivity (91–99% *ee*).

Keywords: asymmetric catalysis; bis-oxazoline; C–C bond formation; silicones; supported catalysts

The development of easily recoverable variants of chiral catalysts has been pursued for over three decades as a means to improve homogeneous enantioselective systems,[1] but the actual exploitation of this concept in a real scenario seems to be still awaiting a convincing proof.[2] Arguably, this is a consequence of the inherent limitations of the approaches disclosed so far, including the additional synthetic efforts for the preparation of recoverable derivatives and the frequent reduction in the catalytic performances with respect to the parent (unmodified) catalyst. In this regard, the covalent binding of a chiral ligand to an insoluble polymer (IPB approach) has been often considered a least attractive option, because of the difficulties in the handling of sensitive (e.g., styrene-type) monomer derivatives or the poor overall yield of the heterogenization procedure.[2] Depending upon the strategy adopted, additional shortcomings are also frequently encountered, such as the adverse effect of the support structure on stereoselectivity and the occurrence of a significant fraction of chiral units buried inside the polymer network, which are virtually unavailable for catalysis.

In an effort to solve these problems, we recently undertook an investigation of cross-linked poly(dimethylsiloxane) (PDMS) as a new support type.[3,4] The underlying idea of this approach was that the robust Pt-catalyzed hydrosilylation technology[5] could significantly improve the covalent heterogenization efficiency, yet still providing insoluble materials with a proper microenvironment for asymmetric transformations. Given the current interest in the development of recoverable bis-oxazolines (box) and the array of techniques explored for this purpose,[6,7] the anchoring of box ligands was chosen as a convenient arena for testing this hypothesis.

With this aim in mind, a route was designed (Scheme 1) which involves the use of a simple modified box, provided with a terminal olefin group. By following the same procedures described for the parent ligands **1a**, **b**,[8] the derivatives **2a**, **b** were therefore easily prepared from the corresponding chiral amino alcohols and subjected to immobilization into an insoluble PDMS matrix by a two-step procedure. Accordingly, **2a** or **2b** was initially reacted under Pt catalysis with linear poly(dimethylsiloxane-*co*-methylhydrosiloxane) (PMHS, **3**), to afford the soluble silicones **4a**, **b**, and then made insoluble by cross-linking with a suitable diene compound (**5**–**7**). This choice allowed the monitoring of the first stage by ^{1}H and ^{13}C NMR, which confirmed the consumption of the olefinic double bond of **2a**, **b** and ruled out any significant isomerization of the alkene moiety or degradation of the box core (Supporting Information). Initial attempts to cross-link **4a**, **b** with divinylbenzene (**5**) in bulk, afforded the materials **8** and **9** as insoluble powders, but the yields were fair at most. In order to improve both the anchoring efficiency and



Scheme 1. Preparation of silicones-type IPB-box materials **8–11**

the handling of the final IPB-box, the preparation of polymeric films was therefore explored.[4,5b] For this purpose, a solution of **4b** was transferred to a Teflon-lined vessel, a diene was added and the resulting mixture was gently cured under air, followed by end-capping of residual Si–H with 1-hexadecene. Under these conditions the use of **5** as the cross-linker resulted in extremely fragile materials, but its replacement with a combination of low and high molecular weight vinyl-terminated PDMS (**6** and **7**) was sufficient for obtaining the IPB-box **10** and **11** as robust films. After removal of any soluble component by continuous extraction, nitrogen elemental analysis of **8–11** allowed us to calculate the ligand loading (L) and the yield of supported chiral units with respect to starting **2a** or **2b** (Y_a, see Table 1). These data confirmed a dramatic improvement in the anchoring efficiency by the film technique with siliconic cross-linkers. In fact, thanks to the nearly quantitative incorporation of **2b** into the insoluble network (Table 1, entries 3 and 4), the overall yield of IPB-box **10** and **11** from the common (*S*)-*tert*-leucinol precursor (77–80%) appears comparable to that of the corresponding soluble ligand **1b** (87%).[8b]

Table 1. Characterization of the IPB-box ligands **8–11**.

Entry	IPB-box	R	L $[\text{mmol g}]^{-1}$[a]	Y_a [%][b]	U $[\text{mmol g}]^{-1}$[c]	A [%][d]
1	**8**	Ph	0.20	35	0.13	65
2	**9**	*t*-Bu	0.35	67	0.14	40
3	**10**	*t*-Bu	0.22	92	0.23	>95
4	**11**	*t*-Bu	0.17	96	0.18	>95

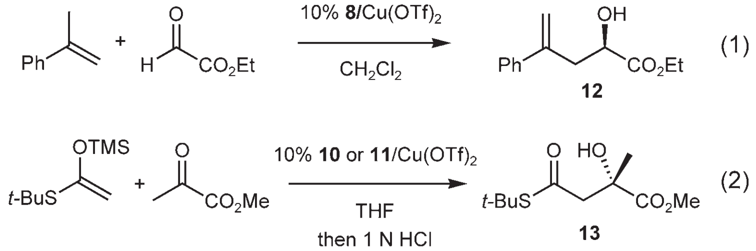
[a] The box loading, determibned by N analysis.
[b] Yield of the anchoring step, based on the amount of **2a** or **2b**.
[c] $Cu(OTf)_2$ uptake from THF.
[d] U/L ratio.

In order to evaluate the accessibility of the anchored chiral units in the materials **8–11**, their Cu(II) ion uptake (U) from a THF solution of $Cu(OTf)_2$ was also determined (Table 1 and Supporting Information). From these data the available box fraction (A) could be calculated, as the U/L ratio, which was found to be strongly dependent upon the support composition and curing procedure. Indeed, while in **8** and **9** only 40–65% of the ligand content proved to be readily involved in the metal complexation, in the case of **10** and **11** the U and L values appeared to match each other, within the experimental accuracy. As a result, a complete accessibility of the chiral sites in the latter materials seems therefore possible, highlighting a significant improvement attained with the support architecture of **10** and **11**.

The performances of **8–11** were initially tested in some of the enantioselective transformations developed by Evans and co-workers,[9] where a [box-Cu-$(OTf)_2$] complex behaves as a chiral Lewis acid. Accordingly, the Ph-substituted material **8** was loaded with $Cu(OTf)_2$ and employed to promote the benchmark addition of α-methylstyrene to ethyl glyoxylate.[9a] In comparison to the use of the soluble ligand **1a** and a previously reported polystyrene IPB-box,[6d] some reduction in activity was evident under these conditions, but we were pleased to find that [**8**·Cu-$(OTf)_2$] smoothly promoted the formation of the ene product **12** (Table 2, entry 1),[10] with an *ee* value slightly exceeding that provided by the soluble catalyst from **1a**.[9a] As already demonstrated for a similar IPB-box system,[6d] the supported complex could be recovered by filtration and directly used in two further runs, without any major loss of catalytic efficiency (Table 2, entries 2 and 3).

Moving to the *t*-Bu-substituted materials, the Mukaiyama aldol reaction was selected as competent Cu(II)-catalyzed processes.[9b] When the addition was

Table 2. Asymmetric ene and Mukaiyama reactions with the IPB-box ligands **8**, **10** or **11**.[a]



Entry	Eq.	Ligand	Cycle	T [°C]	t [h]	Product	Yield [%][b]	*ee* [%][c]
1	(1)	**8**	0	0	22	**12**	83	91 (89)
2	(1)	**8**	1	0	22	**12**	70	91
3	(1)	**8**	2	0	22	**12**	72	91
4	(2)	**10**	0	0	2	**13**	83	94 (94)
5	(2)	**10**	1	0	2	**13**	84	92
6	(2)	**10**	2[d]	0	2	**13**	82	92
7	(2)	**11**	0	0	2	**13**	98	93
8	(2)	**11**	1	-78	22	**13**	91	99 (99)
9	(2)	**11**	2[d]	0	2	**13**	95	93

[a] *Reagents and conditions*: for Eq. (1) α-methylstyrene (0.18 mmol), ethyl glyoxylate (4 equivs.); for Eq. (2) methyl pyruvate (0.25 mmol), 1-(*tert*-butylthio)-1-(trimethylsiloxy)ethene (1.2 equivs.).

[b] Isolated yield. For runs 4–9, GLC yield with methyl 1-naphthoate as internal standard; 82% yield after purification of the pooled crude products

[c] By HPLC. In parentheses *ee* values with **1a** or **1b**.[9a,b]

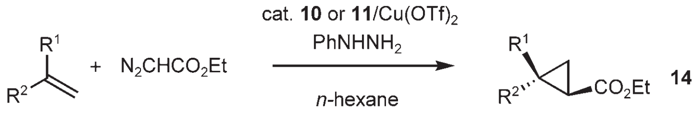
[d] After recharging with $Cu(OTf)_2$ and adding 3 Å MS.

carried out at 0 °C, in the presence of the materials **10** and **11** charged with $Cu(OTf)_2$, the product **13** was isolated in high yield and *ee* values (Table 2, entries 4 and 7), which again appear to match those provided by the soluble counterpart [**1b**·$Cu(OTf)_2$].[9b] Recycling of the supported catalysts proved also readily feasible (Table 2, entries 5, 6, 8, and 9). In this regard, the film shape of **10** and **11** greatly aided the recovery of the material, allowing the separation from the reaction mixture by siphoning instead of filtration. In addition to this practical improvement, another remarkable advantage of the siliconic architecture became evident by running the reaction at low temperature. Indeed, at variance with polystyrene materials which perform poorly under these conditions,[6b] [**11**·Cu-$(OTf)_2$] was effective even at −78 °C, smoothly affording **13** in good yield and with an excellent 99% *ee* (Table 2, entry 8).

For testing the *t*-Bu-substituted ligands **9–11** in a process involving box-Cu(I) species,[9c] olefin cyclopropanation was explored next. With this aim, the supported complex obtained by phenylhydrazine reduction of [**9**·$Cu(OTf)_2$] was initially employed under standard conditions in CH_2Cl_2,[9c] but the *ee* values were disappointing (10–76%). Reasoning that the poor results were related to an ill match between the rigid structure of **9** and the chlorinated reaction medium, further runs were carried out in *n*-hexane with the film-type ligands **10** and **11**. Much to our delight, this proved sufficient to cause a large improvement of the enantioselectivity, eventually leading to the cyclopropanes **14** with *ee* values within 1% of those provided by **1b** under comparable conditions (Table 3, entries 1–3).[11] With this simple modification, the supported catalysts were also found to be effective at low loadings and in the course of several recycle runs (Table 3, entries 1 and 4–8, respectively), outperforming in this case also analogous polystyrene-supported systems.[6c,e,f] More in general, the materials **8** and **10–11** provided the highest *ee* values reported to date for any Evans' type IPB-box ligand (either on organic[6b–f] or inorganic supports),[6g] in the aforementioned reactions. For the sake of comparison it is worth noting that catalyst loadings and *ee* values higher than those attained in this work (0.50–0.90 mmol Cu g^{-1}, 95–99% *ee*) have been recently described by Mayoral and Reiser, in the cyclopropanation of styrene with a structurally related aza-box on a Merrifield resin;[12] this class of ligands, however, appears to have a somewhat different reaction and substrate scope than carbon-based box ligands.[12]

In conclusion, a new strategy has been described for the covalent immobilization of chiral ligands in a cross-linked, insoluble matrix. With respect to established routes to chiral IPB systems, the main advantages of this approach include the need of minimally functionalized chiral precursors and their effective incorporation into a PDMS network made of technical-

Table 3. Asymmetric cyclopropanation of olefins with IPB-box ligands **10** and **11**.[a]



Entry	Product R^1, R^2	Ligand[b]	Cycle	*T* [°C]	*t* [h][c]	Yield [%][d]	*ee* [%][e]
1	Me, Me	**10** (0.2)	0	0	22	90	96
2	Ph, Ph	**10** (1)	1	25	22	96	95
3	H, Ph	**10** (1)	2	25	22	96[f]	95
4	Me, Me	**11** (0.5)	0	0	4	91[g]	97
5	Me, Me	**11** (0.5)	1	0	4	-[g]	95
6	Me, Me	**11** (0.5)	2	0	4	-[g]	96
7	Me, Me	**11** (0.5)	3[h]	0	4	-[g]	91
8	Me, Me	**11** (0.5)	4	0	4	-[g]	91

[a] *Reagents and conditions*: ethyl diazoacetate (1 mmol), olefin (2–7 equivs.), $PhNHNH_2$ (2 equivs. *vs.* Cu).

[b] Amount of supported complex in parentheses [mol%].

[c] Addition time of ethyl diazoacetate.

[d] By GLC with dodecane as internal standard.

[e] By HPLC or GLC; *ee* values with **1b** in parentheses.

[f] *trans*:*cis* = 78:22 (*cis* 90% *ee*).

[g] With 5 mmol of ethyl diazoacetate per run; 75% isolated yield after distillation of the pooled crude product.

[h] Material recharged with $Cu(OTf)_2$ and reduced before use.

grade chemicals. As demonstrated herein for the box case, this may allow an unprecedented simple preparation of the IPB system. Moreover, thanks to the specific properties of the PDMS network a virtually complete access to the supported chiral units and the attainment of an adequate microenvironment for a range of mechanistically different asymmetric transformations seems possible: In fact, besides closely mimicking the corresponding soluble ligands in each case, the optimized materials obtained in this work appear to rank as the most effective Evans' type IPB-box systems reported so far.

The application of the present strategy to other supported enantioselective catalysts is currently underway.

Experimental Section

Detailed procedures for the synthesis of monomers **2a** and **b**, shown in Scheme 1, are given in the Supporting Information. Mesitylene-solvated Pt catalyst (1 mg Pt/mL) was prepared by metal vapor synthesis (MVS) as described before.[13]

Preparation of 10 and 11 by Cross-Linking in Film; Representative Procedure

Under a nitrogen flow, a Schlenk tube was charged with the monomer **2a** or **2b** (0.2–1 mmol; for the exact quantities see the Supporting Information), PMHS **3** (5–6 equivs. SiH) and the Pt/mesitylene solution (molar ratio SiH/Pt = 4200–5000). After heating for 5 h at 70 °C. NMR analysis of a sample diluted with C_6D_6 confirmed the consumption of C=C bonds. The solution was placed under air into a flat PTFE-lined vessel (40 cm^2 bottom area), together with a solution of **6** and **7** in toluene (2 mL). The vessel was covered with a glass plate and heated overnight at 50 °C. The resulting film was swollen with a solution of 1-hexadecene (0.56 mL) in toluene (1 mL) and the solvent was evaporated again, by gently heating for 2 h at 50 °C. The polymer film was moistened with a little *n*-hexane, transferred to a metal-net thimble, and countinuously extracted in a Soxhlet device, for 2–3 days, with dry CH_2Cl_2 and THF; the UV spectra of the final washings were flat in the 240–350 nm region ($A < 0.005$, 1 cm cell). The almost colorless and nearly transparent films **10** and **11** (approx. 0.2–0.4 mm thick) were dried under reduced pressure and characterized by IR, elemental analysis and copper uptake measurements.

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