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The First Immobilization of Pyridine-bis(oxazoline) Chiral Ligands

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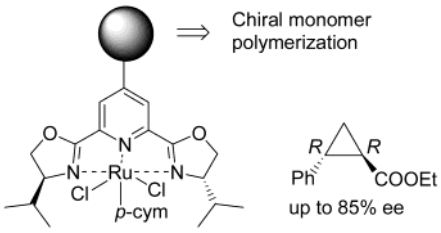
ABSTRACT



A chiral pyridine-bis(oxazoline) ligand, functionalized with a vinyl group in the pyridine ring, can be polymerized with styrene and divinylbenzene to obtain supported chiral ligands. As proof of the usefulness of this supported ligands, the corresponding ruthenium complexes are catalysts for the cyclopropanation reaction of styrene with ethyl diazoacetate with up to 85% ee.

The development of new chiral heterogeneous catalysts to promote enantioselective reactions is a field of growing interest as a result of the applications of heterogeneous catalysts in the industrial preparation of fine chemicals and specialities.[1] The most widely used strategy to prepare chiral heterogeneous catalysts is the immobilization of chiral complexes onto insoluble supports. Given that the immobilization process requires synthetic effort, it is of interest to design general strategies that allow the immobilization of chiral ligands with wide applicability. In this regard, the immobilization of chiral catalysts based on bis(oxazoline) ligands has received a great deal of attention in recent years and has led to the development of efficient chiral heterogeneous catalysts for several reactions. Cationic bis(oxazoline) complexes have been immobilized onto inorganic, organic, and hybrid anionic supports.[2]

Bis(oxazoline) ligands have been covalently bonded to insoluble organic[3] and inorganic materials,[4] as well as soluble polymers.[5] The closely related azabis(oxazoline) ligands have been immobilized by grafting onto a soluble organic polymer.[6] Finally, the recovery of bis(oxazoline)−copper catalysts used in ionic liquids has also been described.[7] From the same family of ligands, C_2-symmetric pyridine-bis(oxazoline) (pybox) compounds have shown their utility as tridentate ligands in many asymmetric organic reactions.[8] However, the immobilization of this type of chiral ligand has not been described to date. In this communication, we describe the first strategy to immobilize pybox by formation of a covalent bond between the pyridine ring and the insoluble support.

The objective of the work described here was the introduction of a vinyl group into the pybox ligand, with

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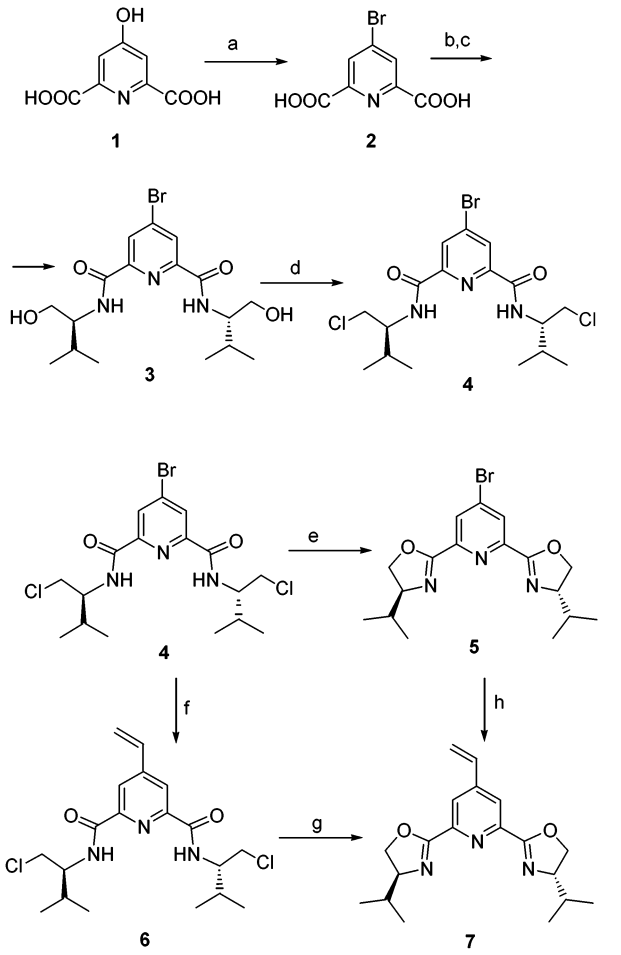
the aim of preparing polymers using the chiral ligand as a co-monomer. The similarity in the reactivities of 4-vinylpyridine and styrene, and the fact that 4-position in the pyridine ring of pybox is free, prompted us to try the introduction of a vinyl group in that position by means of a Stille coupling reaction. It was therefore necessary to first prepare the corresponding 4-bromopybox. The synthetic pathway, adapted from that described in the literature,[9] is represented in Scheme 1. Bromination of chelidamic acid (**1**) with $POBr_3$ led to 4-bromopyridine-2,6-dicarboxylic acid (**2**). This acid was used in the synthesis of diamide **3** with (*S*)-valinol. The 4-bromopybox **5** was obtained in two steps by substitution of the hydroxyl groups by chloride groups and subsequent cyclization with sodium hydride. The desired 4-vinylpybox **7** could be prepared either by direct reaction of **5** with tributylvinyltin in the presence of a palladium catalysts or by reaction of intermediate **4** and cyclization of the resulting vinyldiamide **6**. Vinylpybox **7** was used in different block copolymerizations with styrene and divinylbenzene using a porogen and AIBN as a radical initiator, according to the general protocol described by Fréchet for the preparation of monolithic resins.[10] Three different polymers (**P1**−**P3**) were obtained from vinylpybox **7** by changing the degree of cross-linking and the porogen (Table 1). In all cases, the pybox ligand was incorporated into the polymer with high yield (75−95%), as shown by the elemental analysis data. The polymers were also characterized by IR spectroscopy, with the spectra showing in all cases the typical bands corresponding to the pybox ligand (1640 and 1599 cm^{-1}). These polymers were transformed into immobilized ruthenium catalysts by treatment with $[RuCl_2(p\text{-cymene})]_2$. According to metal analyses, about 50−60% of the chiral pybox was functionalized with Ru, which seems to indicate that a significant proportion of the ligand is situated in inaccessible sites within the polymer. This situation is particularly evident in the case of **P3**, in which Ru functionalization is even lower. Another polymeric catalyst (**P4**) was obtained by

Scheme 1[a]



[a] Reagents and conditions: (a) $POBr_3$, chlorobenzene, reflux, 14 h (55%); (b) oxalyl chloride, CH_2Cl_2, rt, 7 h (90%); (c) (*S*)-valinol, NEt_3, CH_2Cl_2, rt, 24 h (75%); (d) $SOCl_2$, chloroform, reflux, 1.5 h (70%); (e) NaH, THF, 0 °C, 45 min (70%); (f) tributylvinyltin, $Pd(PPh_3)_2Cl_2$, toluene, 60 °C, 6 h (55%); (g) NaH, THF, 45 °C, 1.5 h (65%); (h) tributylvinyltin, $Pd(PPh_3)_2Cl_2$, toluene, 75 °C, 1 h (65%).

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Table 1. Polymers Used in This Work[a]

	polymerization mixture (%)				mmol/g	
polymer	pybox (**7**)	styrene	DVB	porogen	pybox[b]	Ru[c]
P1	7	42	51	toluene	0.443	0.274
P2	7	63	30	tol/dodec[d]	0.426	0.258
P3	7	42	51	tol/dodec[d]	0.405	0.143
P4	7[e]	42	51	toluene		0.247

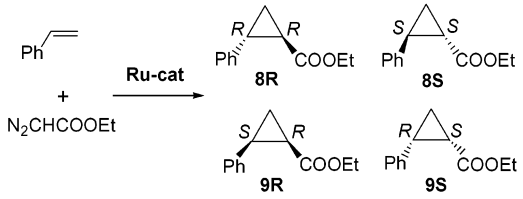
[a] Polymerization conditions: porogen/monomers mixture = 1.5 (w/w), 80 °C, 24 h. Polymers were crushed and washed with THF in a Soxhlet. [b] Calculated from nitrogen analysis. [c] Ru content after treatment with a stoichiometric amount of $[RuCl_2(p\text{-cymene})]_2$ in CH_2Cl_2 for 24 h. [d] Mixture of toluene/1-dodecanol = 1/5 (w/w). [e] Polymerization with the complex prepared with pybox (**7**) and $[RuCl_2(p\text{-cymene})]_2$ in CH_2Cl_2.

polymerization of the complex **7**−Ru, which was formed in solution prior to polymerization. In this case, the elemental analysis was not accurate due to the presence of Ru.

Excellent results have been reported for homogeneous phase cyclopropanation reactions with analogous pybox−Ru catalysts.[11] Thus, the benchmark reaction between styrene and ethyl diazoacetate was used as a test of the catalyst properties. However, in the homogeneous phase, the reported results were obtained using the pybox ligand in either 2 or 4 molar excess over Ru. It is quite difficult to obtain a local excess of chiral ligand on a heterogeneous catalyst, so the polymers were compared with the homogeneous catalysts prepared with equimolecular amounts of pybox and Ru. The results are gathered in Table 2. In all cases, the heterogeneous catalyst was filtered off and an additional quantity of ethyl diazoacetate was added to the solution to confirm the heterogeneous character of the catalyst.[12]

As can be seen, the use of dodecanol in the porogenic mixture seems to be detrimental to the trans/cis selectivity and enantioselectivity (**P1** vs **P3**), probably due to the reduced accessibility of the sites, as evidenced by the lower Ru functionalization. In fact, high trans/cis selectivity and enantiomeric excess (85% ee trans) were obtained with the polymer prepared in toluene, and these results are only slightly lower than those obtained with the homogeneous ligands. In contrast, the enantioselectivity for the cis isomer is reduced to 41% ee, demonstrating an effect of the immobilization on this particular selectivity. It is difficult to offer an explanation for this effect, although it is clear that the support has a different influence on the energy of the four diastereomeric transition states. The detrimental effect of dodecanol is not particularly important when a lower degree of cross-linking is used (**P2**). This seems to confirm that the observed effects are related to lower accessibility

Table 2. Results Obtained in the Cyclopropanation Reaction[a]



catalyst[b]	run	% yield[c]	trans/cis[c]	% ee trans	% ee cis[d]
P1−Ru	1	31	85/15	85	41
	2	28	84/16	84	40
	3	11	75/25	45	20
P2−Ru	1	32	78/22	76	41
	2	35	85/15	75	42
	3	28	75/25	44	18
P3−Ru	1	26	77/23	54	18
	2	39	72/28	30	13
P4	1	17	81/19	80	29
	2	9	78/22	84	30
5−Ru	1	45	87/13	92	71
10−Ru[e]	1	34	90/10	88	70

[a] Reaction conditions: 5 mmol of styrene, 1 mmol of ethyl diazoacetate (slow addition), 3% Ru, CH_2Cl_2, rt. Catalyst was filtered, washed, and dried before reuse. [b] Catalysts were prepared by treatment of the ligand with $[RuCl_2(p\text{-cymene})]_2$ in CH_2Cl_2. [c] Determined by GC at total conversion of diazoacetate. [d] Determined by GC with a cyclodex-B column. Compounds **8R** and **9R** were the major products. [e] Result with the pybox without substitution at the 4-position.

of the reactive sites. Thus, the polymer morphology, which is controlled by cross-linking and the nature of the porogen, determines the performance of the immobilized catalyst, a situation that has been described in other cases.[13] The best catalysts were reused twice, with similar efficiencies observed in the first recycle but a marked decrease in both selectivities and activity in the case of **P1**. The coordination of byproducts may be responsible for this deactivation, with a partial decoordination of Ru from the chiral ligand, which can act as a bidentate ligand with a corresponding decrease in enantioselectivity. Finally, the polymer prepared by polymerization of the complex **7**−Ru is clearly less active than the other catalysts, although a high enantioselectivity in the trans isomers is observed. In this case, the possible inclusion of the complex in nonaccessible sites would lead to a lower activity due to the lower effective amount of catalyst in the reaction mixture. This low activity may also be due to the complexation of Ru by AIBN, which would also explain the need for an excess of AIBN to promote the polymerization of the **7**−Ru complex (see Supporting Information).

In conclusion, we have developed a simple and efficient methodology for the immobilization of chiral pybox systems. This new route opens the way for the preparation of a range

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of different supported pybox-based catalysts for a wide variety of enantioselective reactions

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Supporting Information Available: Experimental details for the synthesis of compounds **2**−**7** and polymerization and cyclopropanation reactions. This material is available free of charge via the Internet at http://pubs.acs.org.

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