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A Flexible and Versatile Strategy for the Covalent Immobilization of Chiral Catalysts Based on Pyridinebis(oxazoline) Ligands

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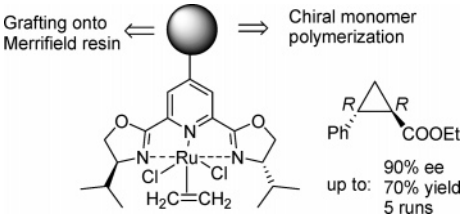
Received March 14, 2005



Flexible and versatile methods have been developed for the immobilization of chiral pyridinebis(oxazoline) ligands by covalent bonding to a solid support, either by grafting or by polymerization. Different spacers can easily be introduced to modulate the support−ligand distance and the electronic properties of the chiral ligand. As an example, 2,6-bis[(*S*)-4-isopropyloxazolin-2-yl]pyridine has been immobilized on polystyrene resins, both on a Merrifield-type resin by grafting and on supports prepared by polymerization of 4-vinyl-substituted ligands. The corresponding Ru complexes have been tested as catalysts in the cyclopropanation reaction between styrene and ethyl diazoacetate. The catalytic activity, the enantioselectivity, and the recyclability are strongly dependent on the catalyst preparation method and the total exclusion of oxygen and moisture in the filtration process. Under such optimized conditions, yields over 60% with up to 90% ee can be obtained in four successive reactions—the best cyclopropanation results described to date for a chiral solid ruthenium catalyst.

Introduction

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 through the formation of covalent bonds between the support and the chiral ligand.[2] Given that this type of immobilization requires significant 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.[3] The related pyridinebis(oxazoline) (pybox) ligands have also shown wide applicability,[4] and they are more suitable than bis(oxazoline) ligands for some metals, such as ruthenium or rhodium. However, the immobilization of such systems has attracted considerably less attention than that of bis(oxazolines). Our group published an initial paper describing the synthesis and polymerization of 4-vinyl-substituted pybox,[5] and the subsequent grafting of these materials onto silica supports[6] was briefly reported. On the other hand, Moberg and co-workers described the immobilization of the same type of ligand

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10.1021/jo0505041 CCC: $30.25
Published on Web 06/15/2005

by grafting on TentaGel[7] or by microcontact printing on silicon chips.[8] The analogous pincer 1,3-bis[(*S*)-4-isopropyloxazolin-2-yl]benzene was immobilized on Wang resin by solid-phase synthesis.[9] In this paper we present a complete overview of our efforts on the immobilization of pybox ligands on polystyrene resins through two complementary approaches, polymerization and grafting, together with the importance of the complex preparation method in the ruthenium-catalyzed cyclopropanation reaction.

Results and Discussion

Immobilization of Chiral Pyridinebis(oxazoline) Ligands by Polymerization. In our preliminary paper,[5] we reported the immobilization of pybox ligands by polymerization. In that case it was necessary to introduce a polymerizable vinyl group, and position 4 of the pyridine ring was chosen to maintain the *C*2 symmetry of the ligand, although it had been previously shown that this is not a prerequisite to obtain good enantioselectivities.[10] The key intermediates in the synthesis of 4-substituted pyridinebis(oxazolines) were the 4-bromo- and 4-chloropybox (**5a** and **5b**) compounds, which were prepared from chelidamic acid (**1**) in four steps (Scheme 1) following the classical route[11] with only minor modifications. The vinyl group was introduced by a Stille coupling between 4-bromopyridinebis(oxazoline) **5a** and tributylvinylstannane to give the 4-vinylpybox **6** in 65% isolated yield. It is worth noting that the analogous 4-chloropybox **5b** did not react under the same conditions. To move the catalyst further from the polymeric backbone, three more functionalized ligands were prepared. The reaction between 4-bromostyrene and Sn_2Bu_6 gave the air-stable tributyl(4-vinylphenyl)stannane, which undergoes a Stille coupling reaction with 4-bromopybox **5a** to give to the corresponding 4-(4-vinylphenyl)pybox **7** (Scheme 1) in 55% isolated yield.

Another strategy was envisaged to introduce a longer spacer between the support and ligand. 4-Halopyridines react readily in S_NAr reactions, and this behavior was found to be useful to introduce phenoxide anions.[6] One possibility was substitution with *p*-bromophenol in a basic medium (Scheme 1), which led to the 4-(*p*-bromophenoxy)pybox intermediate **8**. The aryl bromo group was suitable for Stille coupling with tributylvinylstannane, leading to 4-(*p*-vinylphenoxy)pybox **9**. However, this compound was obtained in a lower isolated yield because its high solubility in hexane made purification difficult. A longer spacer can be introduced by reaction with a hydroquinone derivative, 4-(4-vinylbenzyloxy)-phenol, in a basic medium, leading to the substituted pybox **10** (Scheme 1). In this case the yield is lower than with other phenols due to the occurrence of side reactions involving the hydroquinone derivative.

The polymers were prepared with the functionalized monomer (**m** = **6**, **7**, **9**, or **10**), styrene, and divinylbenzene by block polymerization initiated by AIBN[12] (Scheme 2). On the basis of previous results,[5] toluene was chosen as the solvent and the molar content of pybox was kept constant at 7%. Highly cross-linked polymers (macroreticular-type) were prepared by using 51% divinylbenzene in the polymerization mixture. These materials are denoted P$\mathbf{m}_{51}$, where P stands for polymerized materials, **m** is the pybox monomer, and the subscript is the cross-linking degree (% of divinylbenzene). A gel-type polymer was prepared from pybox monomer **6** by using only 2% divinylbenzene (denoted as P$\mathbf{6}_2$) for the sake of comparison with the Merrifield-grafted ligands. Most of the chiral pybox was incorporated into the polymer, and the final functionalization was in the range of 0.4−0.51 mmol g^{-1} (Table 1).

Immobilization of Chiral Pyridinebis(oxazoline) Ligands by Grafting. The other general strategy to immobilize chiral ligands through covalent bonding involves the use of a preformed support. In the case of polymers, the most widely used supports are probably the Merrifield resins (MRs),[13] which are poly(styrene−divinylbenzene) polymers with a low cross-linking degree. To tether the pybox ligand, it was necessary to introduce

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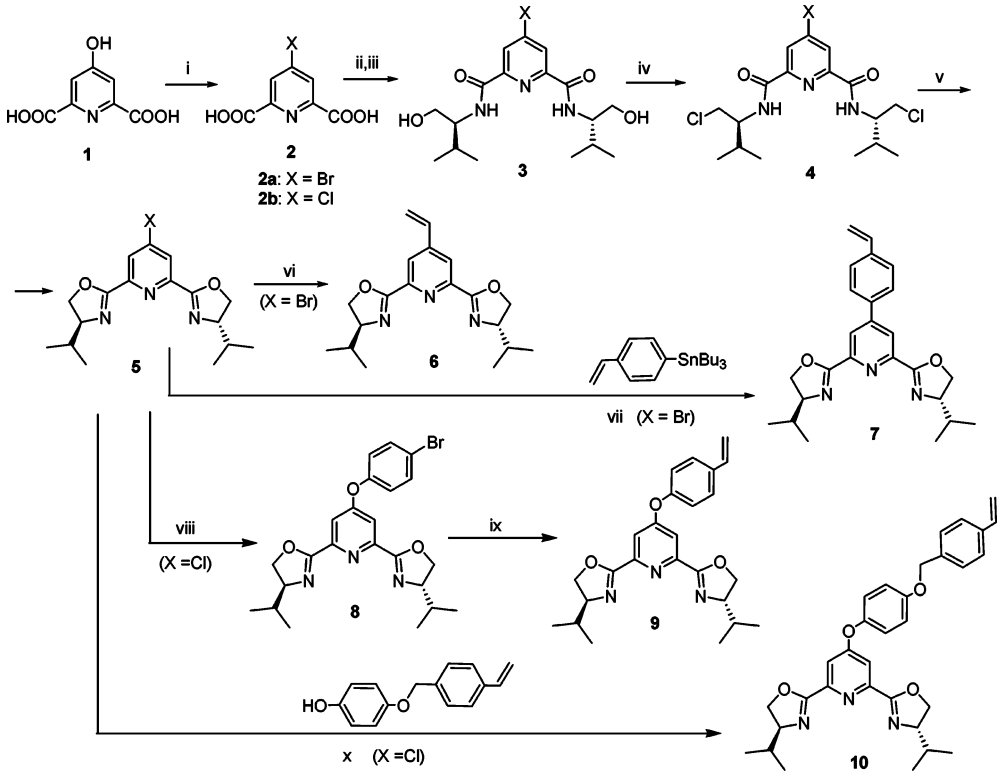
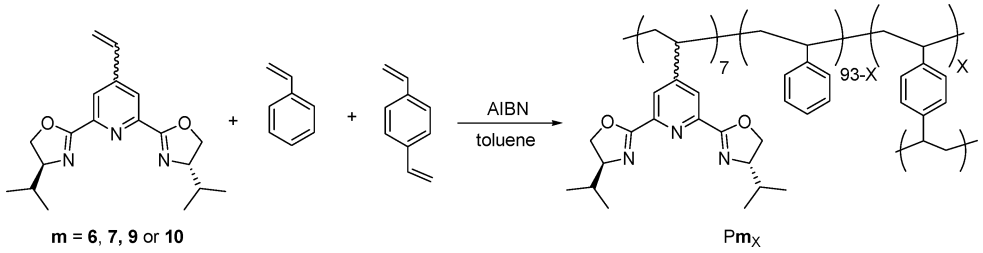
SCHEME 1. Preparation of Vinyl-Functionalized Pybox Ligands[a]



[a] Reagents and conditions: (i) PX_5, chlorobenzene, reflux, 14 h (55% for Br, 65% for Cl); (ii) for X = Br, oxalyl chloride, CH_2Cl_2, rt, 7 h (90%); for X = Cl, $SOCl_2$, chlorobenzene, reflux, 3.5 h (95%); (iii) (*S*)-valinol, NEt_3, CH_2Cl_2, rt, 24 h (75%, X = Br; 80%, X = Cl); (iv) $SOCl_2$, chloroform, reflux, 1.5 h (70%); (v) NaH, THF, 0 °C, 45 min (70%); (vi) tributylvinyltin, $Pd(PPh_3)_2Cl_2$, toluene, 75 °C, 1 h (65%); (vii) $Pd(PPh_3)_2Cl_2$, toluene, reflux, 1.5 h (60%); (viii) *p*-bromophenol, K_2CO_3, DMF, 100 °C, 7 h (75%); (ix) tributylvinyltin, $Pd(PPh_3)_4$, toluene, reflux, 48 h (25%); (x) K_2CO_3, DMF, 100 °C, 17 h (30%).

SCHEME 2. Polymerization of Vinyl-Functionalized Pybox Ligands

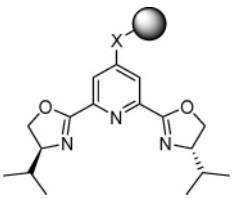


a functional group, and position 4 of the pyridine ring was again chosen for this purpose. The reactivity of the halopyridines in S_NAr reactions proved to be very convenient, and two different precursors were prepared (Scheme 3). First, the 4-chloropybox **5b** was reacted with NaHS to give the 4-mercaptopybox **11** in high isolated yield. The reactivity with phenols was used again, and the reaction with *p*-aminophenol gave the amino-functionalized pybox **12**.

With regard to the grafting process, the benzyl chloride on the Merrifield resin showed low reactivity toward both the amino and the mercapto groups in **12** and **11**, respectively. In an attempt to increase the reactivity, chlorine was replaced by bromine by nucleophilic substitution with NaBr using phase-transfer catalysis (Scheme 4). This method leads to the brominated resin MR−Br, with a substitution degree around 70−80% of the initial chlorine. This solid showed enhanced reactivity with the functionalized pybox ligands in the presence of bases (Scheme 4). The resulting polymers, MR**11** and MR$\mathbf{12}_{am}$, reached a functionalization degree of 0.45−0.50 mmol of ligand g^{-1} (Table 1). In the case of the aminopybox **12** an alternative method was envisaged through imine formation (MR$\mathbf{12}_{im}$), which allowed the introduction of a longer spacer between the pybox and the polymer backbone. For this purpose the Merrifield resin was initially converted into an aldehyde resin (MR−CHO) by reaction with *p*-hydroxybenzaldehyde in a basic medium (Scheme 4). However, the functionalization degree in MR$\mathbf{12}_{im}$ was much lower than in the resin prepared by the alkylation method (MR$\mathbf{12}_{am}$).

Preparation of Ruthenium Catalysts. The first step in the preparation of the catalysts was complexation of the immobilized ligands with the stoichiometric amount of $[Ru(p\text{-cymene})Cl_2]_2$, the procedure used for the in situ preparation of the homogeneous catalysts for cyclopropanation.[14] The analyses of these solids, identified as support−Ru, are gathered in Table 1. In the case of

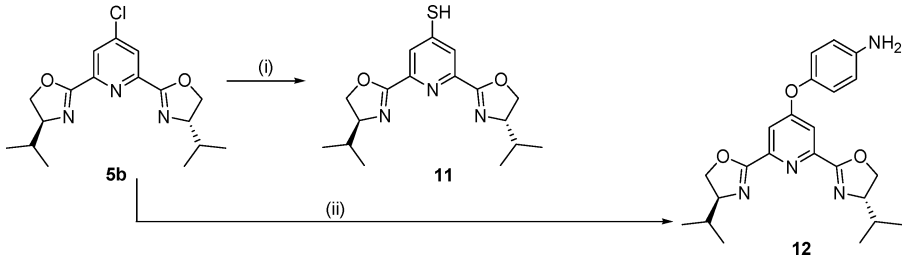
TABLE 1. Solids Obtained by Polymerization (P) of Functionalized Pybox's 6, 7, 9, and 10, or Grafting of Pybox's 11 and 12 onto Merrifield Resin (MR)[a]



polymer	spacer (X)	polymerization mixture (%) pybox	styrene	DVB	concn, mmol/g pybox[b]	Ru[c]
P**6**$_{51}$		7	42	51	0.443	0.274
P**6**$_2$		7	91	2	0.514	0.402
P**7**$_{51}$	$-C_6H_4-$	7	42	51	0.400	0.265
P**9**$_{51}$	$-OC_6H_4-$	7	42	51	0.315	0.214
P**10**$_{51}$	$-OC_6H_4OCH_2C_6H_4-$	7	42	51	0.421	0.342
MR**11**	$-SCH_2C_6H_4-$				0.512	0.436
MR**12**$_{am}$	$-OC_6H_4$-NH$CH_2C_6H_4-$				0.450	0.421
MR**12**$_{im}$	$-OC_6H_4N{=}CHC_6H_4OCH_2C_6H_4-$				0.155	0.094

[a] Polymerization conditions: toluene/monomer mixture = 1.5 (w/w), 80 °C, 24 h. The polymers were crushed and washed with THF in a Soxhlet apparatus. [b] Calculated from nitrogen analysis. [c] Ru content after treatment with the stoichiometric amount of $[RuCl_2(p\text{-cymene})]_2$ in CH_2Cl_2 for 24 h.

SCHEME 3. Synthesis of Functionalized Pybox Ligands for Grafting[a]



[a] Reagents and conditions: (i) NaHS, K_2CO_3, DMF, 75 °C, 6 h (85%); (ii) *p*-aminophenol, K_2CO_3, DMF, 100 °C, 24 h (75%).

polymerized ligands, the spacer length and the cross-linking degree are the factors that control the functionalization degree. In P**6**$_{51}$−Ru, which does not have a spacer but has a high cross-linking degree, only 60% of the pybox ligand is able to complex Ru. The introduction of longer spacers, as in P**7**$_{51}$−Ru, P**9**$_{51}$−Ru and P**10**$_{51}$−Ru, increases the functionalization degree to 65%, 68%, and 80%, respectively. The same high functionalization level can be obtained with a gel-type polymer, as in the case of P**6**$_2$−Ru, without the need for a spacer.

The same level of functionalization—or even higher (>90% in MR**12**$_{am}$−Ru)—can be achieved in the case of Merrifield-immobilized ligands. This result is consistent with the better accessibility of the grafted ligands, which are mostly located in the outer part of the polymer, in comparison to the polymerized ones, a proportion of which are located in the nonaccessible core of the solid.

This type of complex was tested as a catalyst in our preliminary paper.[5] However, the yields obtained with those immobilized complexes were not comparable to those reported in solution.[14] In fact, the results are difficult to compare as they come from different approaches—an in situ preparation of the complex in the case of the homogeneous catalyst and an isolated complex in the case of the immobilized one. Quantum mechanical (DFT) calculations showed that, due to steric hindrance, *p*-cymene cannot easily be accommodated in the coordination sphere of ruthenium once the pybox ligand is coordinated. To simplify the calculations, a nonsubstituted pybox was chosen for the molecular modeling study. The calculated structure of the pybox−$RuCl_2$−ethylene complex was in excellent agreement with the experimental (X-ray) geometry of an analogous pybox−$RuCl_2$−ethylene complex,[14] as shown by overlaying the two structures (Figure 1). On the other hand, the calculated structure of the related pybox−$RuCl_2$−*p*-cymene complex shows that the *p*-cymene ligand is loosely bound to the ruthenium center (Figure 2), and far from classical metal−arene coordination. The calculated binding energy (at the B3LYP/6-31G(d) level) is −25.3 kcal mol^{-1} for the ethylene complex and +1.2 kcal mol^{-1} for the *p*-cymene complex. The positive sign indicates that, in the latter case, the coordination is disfavored. If we consider Gibbs free energies (at 298 K), the relative differences are maintained, but now the coordination of a *p*-cymene molecule is still more disfavored (+15.8 vs −10.3 kcal mol^{-1}), due to the disfavorable entropic term. Obviously, if we consider a chiral pybox, the coordination of the *p*-cymene becomes still more difficult because of the new steric interactions introduced by the substituents in the stereogenic centers.

This loose coordination situation would easily lead to a vacant site that, in the open air, would be occupied by

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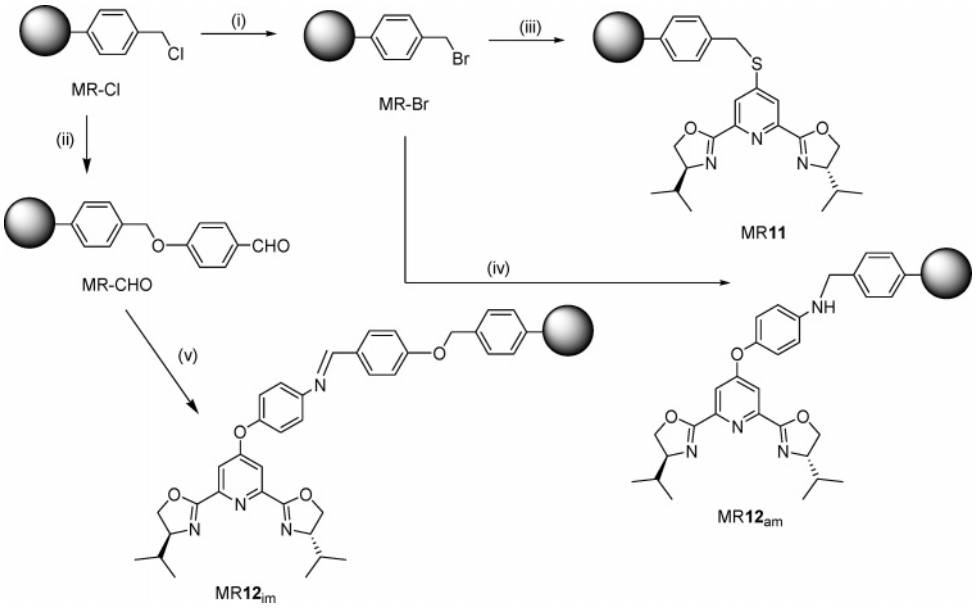
SCHEME 4. Grafting of Functionalized Pybox onto Merrifield Resins (MRs)[a]



[a] Reagents and conditions: (i) NaBr, Et_4NBr, benzene/water, 80 °C, 7 d; (ii) *p*-hydroxybenzaldehyde, KOH, Bu_4NOH, *o*-dichlorobenzene/water, 100 °C, 4 d; (iii) 4-mercaptopybox **11**, NaH, DMF, 100 °C, 72 h; (iv) 4-aminophenoxypybox **12**, K_2CO_3, Bu_4NI, 18C6, DMF, 90 °C, 4 d; (v) 4-aminophenoxypybox **12**, ethanol, reflux, 2 d.

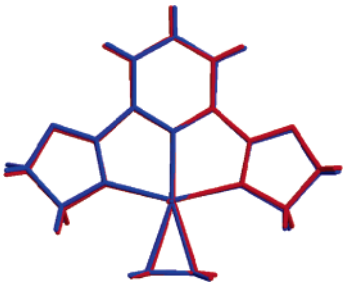


FIGURE 1. Overlay between the calculated (B3LYP/SDD-6-31G*) (red) and the experimental (X-ray) (blue) structures of the nonsubstituted pybox−$RuCl_2$−ethylene complex.

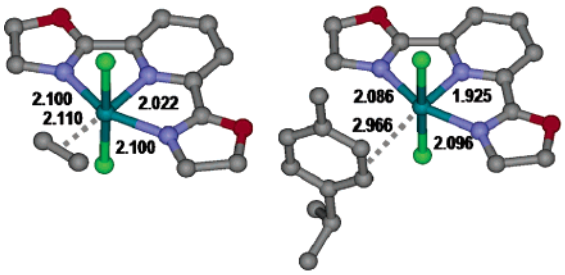


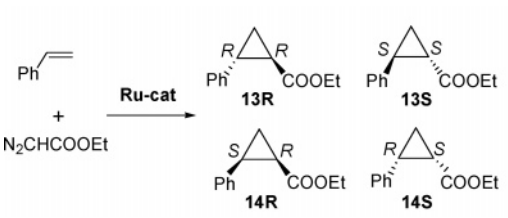
FIGURE 2. Some geometrical parameters of the calculated (B3LYP/SDD-6-31G*) structures of the pybox−$RuCl_2$−ethylene and pybox−$RuCl_2$−*p*-cymene complexes. Hydrogen atoms omitted for clarity.

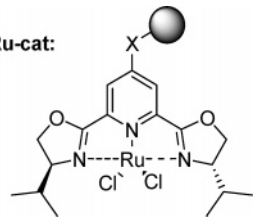
water, oxygen, or another small molecule that would be difficult to replace with the diazoacetate. In view of this finding, we tried to reproduce the preparation of a stable catalytic complex by bubbling ethylene in the solution in which the immobilized complex was being prepared. This process gave the immobilized complexes denoted as support−Ru−// (// represents the coordinated ethylene). These complexes were filtered off and washed, either in the open air or under an inert atmosphere.

Catalytic Results. The Ru complexes were tested in the benchmark asymmetric cyclopropanation reaction between styrene and ethyl diazoacetate, and the most interesting results are gathered in Table 2. Three different sets of conditions were tested with complexes derived from MR**11** polymer to assess their effect. In the first attempt, the complex MR**11**−Ru, prepared directly from the precursor $[Ru(p\text{-cymene})Cl_2]_2$ (entry 2), led to a low yield (24%), good *trans*/*cis* selectivity (84/16), and modest to low enantioselectivities, 61% ee in the *trans* and 30% ee in the *cis* isomers. In an attempt to reproduce the homogeneous conditions, the complex was prepared under an ethylene atmosphere (entry 3), and this change led to a considerable increase in yield (41%) and enantioselectivities, both in the *trans* (75% ee) and in the *cis* isomers (51% ee). However, the results were much worse after recycling (entry 4), with a loss of activity and selectivity. Finally, the catalyst was prepared in the same way, but all the filtration and recycling manipulations were carried out under an inert atmosphere (entry 5). In the first reaction the results were not too different from those obtained with the catalyst filtered in the open air. In contrast, the recycling process was much better (entries 6−8), and an even better yield (47%) was obtained and the selectivities improved (up to 83% ee in the *trans* isomers). These figures were maintained in a second recycling stage but were lower in the third one. The lower selectivities in the first run can be ascribed to the presence of residual non-pybox-complexed ruthenium centers, which are completely removed after the first catalytic run. In fact, the filtrate after the first run was slightly colored and showed some residual catalytic activity when ethyl diazoacetate was added, demonstrating some ruthenium leaching.

In view of these results, the previously described $P\mathbf{6}_{51}$ polymer[5] was used to prepare the corresponding ruthenium complex under the optimized conditions under an

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





entry	catalyst[b]	spacer (X)	run	yield[c] (%)	*trans*/*cis*[c]	ee (%),[d] *trans*	ee (%),[d] *cis*
1	pybox−Ru			34	90/10	88	70
2	MR**11**−Ru	−$SCH_2C_6H_4$−	1	24	84/16	61	30
3	MR**11**−Ru−//	−$SCH_2C_6H_4$−	1	41	87/13	75	51
4			2	10	79/21	46	11
5	MR**11**−Ru−//[e]	−$SCH_2C_6H_4$−	1	38	86/14	77	43
6			2	47	88/12	83	54
7			3	41	88/12	81	50
8			4	36	84/16	56	23
9	MR$\mathbf{12}_{am}$−Ru−//[e]	−$OC_6H_4NHCH_2C_6H_4$−	1	21	81/19	57	19
10			2	25	87/13	75	35
11			3	20	84/16	60	27
12			4	14	77/23	45	14
13	MR$\mathbf{12}_{im}$−Ru−//	−$OC_6H_4N{=}CHC_6H_4OCH_2C_6H_4$−	1	37	86/14	73	45
14			2	15	79/21	28	12
15	P$\mathbf{6}_{51}$−Ru[f]		1	31	85/15	85	41
16			2	28	84/16	84	40
17			3	11	75/25	45	20
18	P$\mathbf{6}_{51}$−Ru−//[e]		1	40	87/13	87	63
19			2	53	88/12	88	70
20			3	50	87/13	87	58
21			4	45	87/13	87	62
22			5	36	85/15	69	49
23			6	17	80/20	52	28
24	P$\mathbf{7}_{51}$−Ru−//[e]	−C_6H_4−	1	26	80/20	63	24
25			2	69	88/12	86	67
26			3	52	88/12	79	58
27			4	54	86/14	75	57
28			5	8	82/18	42	24
29	P$\mathbf{9}_{51}$−Ru−//[e]	−OC_6H_4−	1	12	64/36	12	0
30			2	24	82/18	59	31
31			3	25	85/15	64	27
32			4	21	85/15	64	39
33			5	14	79/21	46	16
34	P$\mathbf{10}_{51}$−Ru−//	−$OC_6H_4OCH_2C_6H_4$−	1	32	86/14	67	33
35			2	27	83/17	54	22
36			3	5	72/28	25	8
37	P$\mathbf{6}_{2}$−Ru−//[e]		1	52	88/12	85	54
38			2	67	90/10	91	67
39			3	70	90/10	89	64
40			4	68	90/10	87	63
41			5	32	88/12	74	63

[a] Reaction conditions: 5 mmol of styrene, 1 mmol of ethyl diazoacetate (slow addition), 3% Ru, CH_2Cl_2, rt. The catalyst was filtered off, washed, and dried before reuse. [b] The catalysts were prepared by treatment of the ligand with $[RuCl_2(p\text{-cymene})]_2$ in CH_2Cl_2. The catalysts marked as Ru−// were prepared by bubbling ethylene for 1 h and stirring under an ethylene atmosphere for 23 h. [c] Determined by GC at total conversion of diazoacetate. [d] Determined by GC with a Cyclodex-B column. **13R** and **14R** are the major products. [e] All the filtrations were carried out under an inert atmosphere. [f] Data from ref 5.

ethylene atmosphere (entry 18). The results obtained in the first run were only slightly better than those obtained for the nonoptimized conditions (entry 15), but the most relevant differences were found after recycling (entries 19−23). The moderate yield, around 50%, together with the high enantioselectivity, 87% ee in the *trans* isomers, was maintained until the fourth run before declining in the fifth one. This set of results confirms the sensitivity of the Ru complex to ambient moisture and/or oxygen.

Another important issue with immobilized catalysts is the accessibility to the catalytic sites. From the Ru analysis, it seems that longer spacers make the access easier, and this factor was studied with Merrifield-immobilized catalysts. In contrast with the initial hypothesis, MR$\mathbf{12}_{am}$ and MR$\mathbf{12}_{im}$ led to catalysts that were less active, less enantioselective, and less stable than MR**11** (entries 9−14). However, in this case the change of spacer is also associated with a modification in the atom directly linked to the pyridine ring, i.e., sulfur in MR**11** and oxygen in both MR**12** systems. A detrimental effect of electron-donating substituents in position 4 of the pyridine ring has been reported.[15] This may be one factor that leads to the lower yield and enantioselectivity,

(15) Park, S.-B.; Murata, K.; Matsumoto, H.; Nishiyama, H. *Tetrahedron: Asymmetry* **1995**, *6*, 2487−2494.

although the presence of new coordinating atoms in the polymer cannot be excluded as an additional factor.

In view of these features, the polymerized ligands that do not include donor atoms directly linked to the pyridine ring would be expected to perform better. To test this hypothesis, we prepared three catalysts from highly cross-linked polymers P**7**$_{51}$, P**9**$_{51}$, and P**10**$_{51}$, with spacers bonded to the pyridine ring through carbon in the case of **7** and oxygen atoms in **9** and **10**. First of all, it is worth noting the poor result obtained with P**7**$_{51}$ in the first run (entry 24). This was due to incomplete removal of the non-pybox-complexed ruthenium, as shown by the extent of Ru leaching after the reaction and the significant activity of the filtrate for nonenantioselective cyclopropanation. The spacer length in P**7**$_{51}$ and P**9**$_{51}$ is markedly different, but catalyst P**7**$_{51}$−Ru−// was much more active and enantioselective (entries 25−28) than P**9**$_{51}$−Ru−// (entries 29−33)—a situation in agreement with the donor character of the spacer in **9**. In fact, the catalytic activity of P**7**$_{51}$−Ru−// is even better than that of MR**11**−Ru−//, which bears a sulfur atom. The P**7**$_{51}$−Ru−// results are better in terms of both yield, around 50%, and enantioselectivity, 86% ee for the *trans*-cyclopropanes in the first run. After recycling, only the enantioselectivity was slightly lower, with the catalytic activity maintained in the second run before showing significant deactivation in the third run. The use of a longer spacer in P**10**$_{51}$ (entries 34−36) does not significantly improve on the results obtained with a shorter spacer in P**9**$_{51}$.

From all these results we considered that the properties necessary to obtain a recoverable highly active and enantioselective catalyst are as follows: improved accessibility, absence of donor atoms directly bonded to the pyridine ring, preparation of the ethylene−ruthenium complex, and manipulations under an inert atmosphere. Thus, monomer **6**, with a C−C bond to the matrix, was used to prepare the polymer P**6**$_2$, which had a low cross-linking degree to ensure accessibility to the catalytic centers. The resulting catalyst was P**6**$_2$−Ru−//, and this gave the best overall results in four consecutive runs (entries 37−41), leading to improved yields in the range of 52−70%, *trans*/*cis* selectivity of 90/10, and enantioselectivity around 85−91% ee for the *trans*-cyclopropanes.

Even in the best case, however, the catalyst is finally deactivated—losing both activity and enantioselectivity. Ruthenium leaching does not account for this deactivation. In fact, only 6% Ru is lost from P**7**$_{51}$−Ru−// after five runs and 13% Ru from P**10**$_{51}$−Ru−// after three runs, whereas the loss in activity is far more pronounced. This deactivation may be caused by poisoning through the adsorption of byproducts (diethyl maleate and fumarate, or their polymerization products), the adsorption of traces of moisture and/or oxygen during recycling, or pore blocking by polymerized byproducts. These possibilities are currently under investigation.

Experimental Section

2,6-Bis[(*S*)-4-isopropyloxazolin-2-yl]-4-(4-vinylphenyl)-pyridine (7). To a stirred solution of hexabutylditin (5.94 mL, 11.17 mmol) in anhydrous toluene (50 mL) were added 4-bromostyrene (1.46 mL, 11.17 mmol) and Pd(PPh$_3$)$_4$ (323 mg, 0.28 mmol) at room temperature. The resulting solution was heated under reflux for 2.5 h. After cooling, the solution was filtered through a Celite pad, and the pad was washed with hexanes. The solvent was evaporated under reduced pressure, and the resulting oil was purified twice by column chromatography (hexanes). Tributyl(4-vinylphenyl)tin (1.50 g, 35%) was obtained as a colorless solid. ^{1}H NMR (CDCl$_3$): δ 7.42−7.27 (m, 4H), 6.68 (dd, 1H, J = 11.0 Hz, J = 17.6 Hz), 5.74 (dd, 1H, J = 0.7 Hz, J = 17.6 Hz), 5.20 (dd, 1H, J = 0.7 Hz, J = 11.0 Hz), 1.64−1.52 (m, 6H), 1.49−1.21 (m, 6H), 1.04−0.99 (m, 6H), 0.87 (t, 9H, J = 7.3 Hz).

To a stirred solution of tributyl(4-vinylphenyl)tin (760 mg, 1.93 mmol) in anhydrous toluene (15 mL) were added 4-bromo-2,6-bis[(*S*)-4-isopropyloxazolin-2-yl]pyridine (**5a**) (668 mg, 1.76 mmol) and Pd(PPh$_3$)$_2$Cl$_2$ (31 mg, 0.04 mmol). The mixture was heated under reflux for 1.5 h. After cooling, the solution was filtered through a Celite pad, and the pad was washed with ethyl acetate. The solvent was evaporated under reduced pressure, and the resulting solid was dissolved in acetonitrile (20 mL). The solution was washed with hexane (5 × 20 mL). The acetonitrile solution was evaporated under reduced pressure, and the yellow solid was purified by flash chromatography on alumina (hexanes/ethyl acetate, 3:1) and subsequent crystallization from hexanes. 2,6-Bis[(*S*)-4-isopropyloxazolin-2-yl]-4-(4-vinylphenyl)pyridine (390 mg, 55%) was obtained as a yellow solid. ^{1}H NMR (CDCl$_3$): δ 8.43 (s, 2H), 7.73 (d, 2H, J = 8.4 Hz), 7.50 (d, 2H, J = 8.4 Hz), 6.75 (dd, 1H, J = 11.0 Hz, J = 17.6 Hz), 5.83 (d, 1H, J = 17.6 Hz), 5.33 (d, 1H, J = 11.0 Hz), 4.54 (dd, 2H, J = 7.7 Hz, J = 9.2 Hz), 4.30−4.10 (m, 4H), 2.16−1.83 (m, 2H), 1.04 (d, 6H, J = 6.6 Hz), 0.96 (d, 6H, J = 6.6 Hz). ^{13}C NMR (CDCl$_3$): δ 162.4, 149.4, 147.5, 139.0, 136.0, 135.9, 129.7, 129.2, 127.5, 127.3, 127.0, 123.6, 123.2, 115.4, 73.0, 71.0, 33.0, 19.3, 18.4. IR (KBr, cm^{-1}): 3093, 2956, 1641, 1603, 1401. Mp: 113 °C. Anal. Calcd for C$_{25}$H$_{29}$N$_3$O$_2$: C, 74.41; H, 7.24; N, 10.41. Found: C, 74.64; H, 7.45; N, 10.22.

4-(4-Bromophenoxy)-2,6-bis[(*S*)-4-isopropyloxazolin-2-yl]pyridine (8). To a suspension of anhydrous K$_2$CO$_3$ (186 mg, 1.35 mmol) in anhydrous DMF (1 mL) was added *p*-bromophenol (233 mg, 1.35 mmol), and the mixture was stirred at room temperature for 30 min. 4-Bromo-2,6-bis[(*S*)-4-isopropyloxazolin-2-yl]pyridine (**5a**) (380 mg, 1 mmol) was then added, and the mixture was heated at 100 °C for 7 h. After cooling, the mixture was poured onto iced water (20 mL), the resulting solid was collected by filtration, dissolved in ethyl acetate (50 mL), and washed with 3% KOH (3 × 40 mL). The organic phase was dried with MgSO$_4$ and evaporated under reduced pressure to give a white solid, which was purified by crystallization from hexanes to give 4-(4-bromophenoxy)-2,6-bis[(*S*)-4-isopropyloxazolin-2-yl]pyridine (354 mg, 75%). ^{1}H NMR (CDCl$_3$): δ 7.71 (s, 2H), 7.53 (d, 2H, J = 8.8 Hz), 6.98 (d, 2H, J = 8.8 Hz), 4.49 (dd, 2H, J = 8.1 Hz, J = 9.5 Hz), 4.23−4.02 (m, 4H), 1.82 (dt, 2H, J = 13.2 Hz, J = 7.0 Hz), 1.01 (d, 6H, J = 6.6 Hz), 0.88 (d, 6H, J = 6.6 Hz).

2,6-Bis[(*S*)-4-isopropyloxazolin-2-yl]-4-(4-vinylphenoxy)-pyridine (9). To a stirred solution of tributylvinyltin (475 mg, 1.50 mmol) in anhydrous toluene (25 mL) were added **8** (354 mg, 0.75 mmol) and Pd(PPh$_3$)$_4$ (130 mg, 0.112 mmol). The resulting solution was heated under reflux for 48 h. After cooling, the solution was filtered through a Celite pad. The solvent was evaporated under reduced pressure to give a dark yellow oil, which was dissolved in acetonitrile (30 mL). The solution was washed with hexane (6 × 10 mL). The acetonitrile solution was evaporated under reduced pressure, and the yellow semisolid was purified by flash chromatography on alumina (hexanes/ethyl acetate, 2:1) to give 2,6-bis[(*S*)-4-isopropyloxazolin-2-yl]-4-(4-vinylphenoxy)pyridine (80 mg, 25%). ^{1}H NMR (CDCl$_3$): δ 7.68 (s, 2H), 7.46 (d, 2H, J = 8.9 Hz), 7.05 (d, 2H, J = 8.9 Hz), 6.72 (dd, 1H, J = 11.0 Hz, J = 17.6 Hz), 5.72 (d, 1H, J = 17.6 Hz), 5.27 (d, 1H, J = 11.0 Hz), 4.49 (t, 2H, J = 8.4 Hz), 4.22−4.02 (m, 4H), 1.91−1.70 (m, 2H), 1.01 (d, 6H, J = 6.5 Hz), 0.90 (d, 6H, J = 6.6 Hz). ^{13}C NMR (CDCl$_3$): 170.0, 164.7, 161.2, 152.6, 148.1, 135.0, 134.5, 127.4, 119.9, 113.3, 72.2, 70.3, 32.2, 18.6, 17.6. IR (KBr, cm^{-1}): 2950, 2873, 1731, 1664, 1581, 1225.

2,6-Bis[(*S*)-4-isopropyloxazolin-2-yl]-4-[4-(4-vinylbenzyloxy)phenoxy]pyridine (10). To a stirred solution of hydroquinone (3.52 g, 32 mmol) in acetone (70 mL) were added 4-vinylbenzyl chloride (1.25 mL, 8 mmol), K_2CO_3 (1.10 g, 8 mmol), and Aliquat 336 (323 mg, 0.8 mmol). The resulting mixture was heated under reflux for 24 h. To the cold solution was added chloroform (25 mL), and the solution was filtered through a silica pad. The filtrate was concentrated under vacuum, and the resulting oil was purified by column chromatography (hexanes/ethyl acetate, 9:1) to give 4-(4-vinylbenzyloxy)phenol (780 mg, 44%) as a solid.

To a stirred suspension of NaH (54 mg, 1.35 mmol) in anhydrous DMF (1 mL) was added 4-(4-vinylbenzyloxy)phenol (305 mg, 1.35 mmol), and the mixture was stirred at room temperature for 10 min. 4-Chloro-2,6-bis[(*S*)-4-isopropyloxazolin-2-yl]pyridine (**5b**) (335 mg, 1 mmol) was added, and the mixture was heated at 100 °C for 2.5 h. After cooling, the mixture was poured onto cold water (25 mL), and the resulting white solid was filtered off. The solid was dissolved in ethyl acetate (25 mL) and washed with water (3 × 25 mL). The filtrate was extracted with ethyl acetate (2 × 25 mL), and the combined organic phases were dried with $MgSO_4$ and evaporated under reduced pressure. The resulting oil was purified by flash chromatography on alumina (hexanes/ethyl acetate, 3:1) to give 2,6-bis[(*S*)-4-isopropyloxazolin-2-yl]-4-[4-(4-vinylbenzyloxy)phenoxy]pyridine (125 mg, 24%) as a solid. ^{1}H NMR ($CDCl_3$): δ 7.69 (s, 2H), 7.45 (d, 2H, J = 8.4 Hz), 7.39 (d, 2H, J = 8.4 Hz), 7.02 (s, 4H), 6.73 (dd, 1H, J = 10.8 Hz, J = 17.5 Hz), 5.77 (d, 1H, J = 17.5 Hz), 5.27 (d, 1H, J = 10.8 Hz), 5.07 (s, 2H), 4.49 (dd, 2H, J = 7.7 Hz, J = 8.9 Hz), 4.24−4.03 (m, 4H), 1.83 (m, 2H), 1.02 (d, 6H, J = 6.7 Hz), 0.90 (d, 6H, J = 6.7 Hz). ^{13}C NMR ($CDCl_3$): 166.2, 162.0, 156.4, 148.7, 147.1, 137.4, 136.3, 136.1, 127.7, 126.4, 121.8, 116.3, 114.2, 113.5, 72.8, 70.9, 70.2, 32.8, 19.1, 18.2. IR (KBr, cm^{-1}): 3088, 2958, 1664, 1641, 1583, 1503, 1210, 984. Mp: 124 °C. Anal. Calcd for $C_{32}H_{35}N_3O_4$: C, 73.12; H, 6.67; N, 7.99. Found: C, 73.26; H, 6.68; N, 7.96.

2,6-Bis[(*S*)-4-isopropyloxazolin-2-yl]-4-mercaptopyridine (11). To a suspension of $NaHS{\cdot}H_2O$ (90%, 332 mg, 4.03 mmol) in anhydrous DMF (1.7 mL) were successively added K_2CO_3 (556 mg, 4.03 mmol) and **5b** (1.0 g, 2.98 mmol). The mixture was heated at 80 °C for 7 h until completion (TLC on alumina, hexanes/ethyl acetate, 1:2). After cooling, the mixture was poured onto iced water (20 mL) and stirred for 10 min. The resulting solid was collected by filtration, dissolved in ethyl acetate (45 mL), and washed with water (3 × 15 mL). The organic phase was dried with $MgSO_4$ and evaporated under reduced pressure to obtain 2,6-bis[(*S*)-4-isopropyloxazolin-2-yl]-4-mercaptopyridine (887 mg, 89%). ^{1}H NMR ($CDCl_3$): δ 8.13 (s, 2H), 4.37 (t, 2H, J = 8.8 Hz), 4.26−4.05 (m, 4H), 1.98−1.75 (m, 3H), 1.01 (d, 6H, J = 6.7 Hz), 0.91 (d, 6H, J = 6.6 Hz). ^{13}C NMR ($CDCl_3$): 161.2, 148.5, 147.1, 121.6, 73.0, 70.9, 32.9, 19.1, 18.2. Mp: 95 °C. IR (cm^{-1}, KBr): 2952, 2870, 1641, 1378, 1118. Anal. Calcd for $C_{17}H_{23}N_3O_2S$: C, 61.23; H, 6.95; N, 12.60. Found: C, 61.47; H, 7.12; N, 12.70.

4-(4-Aminophenoxy)-2,6-bis[(*S*)-4-isopropyloxazolin-2-yl]pyridine (12). To a suspension of anhydrous K_2CO_3 (186 mg, 1.35 mmol) in anhydrous DMF (1 mL) was added *p*-aminophenol (147 mg, 1.35 mmol), and the mixture was stirred at room temperature for 30 min. **5b** (335 mg, 1 mmol) was then added, and the mixture was heated at 100 °C for 17 h. After cooling, the mixture was poured onto iced water (20 mL), and the resulting solid was collected by filtration, dissolved in ethyl acetate (50 mL), and washed with water (3 × 40 mL). The organic phase was dried with $MgSO_4$ and evaporated under reduced pressure to give a black solid, which was purified by column chromatography to give 4-(4-aminophenoxy)-2,6-bis[(*S*)-4-isopropyloxazolin-2-yl]pyridine (285 mg, 70%). ^{1}H NMR ($CDCl_3$): δ 7.66 (s, 2H), 6.88 (d, 2H, J = 7.7 Hz), 6.70 (d, 2H, J = 7.7 Hz), 4.47 (t, 2H, J = 8.8 Hz), 4.21−4.05 (m, 4H), 3.75 (br s, 2H), 1.87−1.77 (m, 2H), 1.00 (d, 6H, J = 6.6 Hz), 0.88 (d, 6H, J = 6.6 Hz). ^{13}C NMR ($CDCl_3$): 166.4, 161.9, 148.4, 144.2, 121.6, 116.2, 113.1, 72.6, 70.8, 32.7, 19.1, 18.2. Mp: 181 °C. IR (KBr): 3405, 3354, 2958, 1645, 1582, 1507, 1213. Anal. Calcd for $C_{23}H_{28}N_4O_3$: C, 67.65; H, 6.86; N, 13.73. Found: C, 67.45; H, 7.10; N, 13.80.

TABLE 3. Composition of the Polymerization Mixtures

	composition (mg)				
polymer	pybox	styrene	DVB	toluene	AIBN
P**6**$_{51}$	50.0	91.4	142.6	436.0	2.9
P**7**$_{51}$	60.2	91.9	141.4	451.8	3.1
P**9**$_{51}$	69.1	97.2	132.3	436.2	2.8
P**10**$_{51}$	69.0	97.0	132.4	436.0	2.8
P**6**$_2$	49.0	219.3	13.5	392.1	3.0

Polymerization Procedure. A solution of the monomers and AIBN in toluene (Table 3) was heated at 80 ± 2 °C in a test tube for 24 h. The resulting solid was washed with THF, dried by suction, and crushed in a mortar. The polymer was washed in a Soxhlet apparatus with THF for 24 h and dried under vacuum at 50 °C overnight. Typical yields were in the range 75−95%.

Grafting Procedures. The starting material was a Merrifield resin (MR−Cl, chloromethylated poly(styrene−divinylbenzene) copolymer, 200−400 mesh) 2% cross-linked with a Cl content of 1.3 mmol g^{-1}.

A. MR−Br. To a solution of NaBr (12.12 g, 117.6 mmol) in water (45 mL) were added tetrabutylammonium bromide (3.15 g, 13.82 mmol), benzene (45 mL), and MR−Cl (1.5 g, 1.95 mmol Cl). The mixture was heated under reflux for 7 d. After cooling, the resin was filtered off and washed with toluene (120 mL), methanol (120 mL), water (120 mL), water/THF (1:3, 120 mL), acetone (120 mL), and diethyl ether (120 mL). The resin was dried under vacuum at 50 °C for 24 h. Anal. Found C, 84.57; H, 6.97; Cl, 1.25; Br, 7.01.

B. MR−CHO. To a solution of KOH (2.53 g, 45.1 mmol) in water (5.5 mL) were successively added 1,2-dichlorobenzene (16.5 mL), *p*-hydroxybenzaldehyde (5.5 g, 45.1 mmol), aqueous tetrabutylammonium hydroxide (40%, 0.1 mL), and MR−Cl (1 g, 1.3 mmol Cl). The suspension was heated at 100 °C for 4 d. After cooling, the resin was filtered off and washed with methanol (120 mL), water (200 mL), water/THF (1:3, 250 mL), and acetone (250 mL). The resin was dried under vacuum at 60 °C for 3 d.

C. MR11. To a suspension of NaH (20 mg, 0.5 mmol) in anhydrous DMF (10 mL) was added **11** (120 mg, 0.36 mmol) at room temperature, and the mixture was stirred for 15 min. MR−Br (200 mg) was then added, and the mixture was heated at 90 °C for 72 h. After cooling, MR**9** was collected by filtration and washed with DMF (50 mL), ethanol (75 mL), water (75 mL), water/THF (1:3, 75 mL), THF (75 mL), dichloromethane (75 mL), and diethyl ether (75 mL). The resin was dried under vacuum at 50 °C for 24 h.

D. MR12$_{am}$. To a suspension of K_2CO_3 (76 mg, 0.55 mmol) in anhydrous DMF (10 mL) were successively added tetrabutylammonium iodide (6 mg, 0.018 mmol), 18C6, **12** (225 mg, 0.55 mmol), and MR−Br (150 mg). The mixture was heated at 85 °C for 4 d. After cooling, **MR12**$_{am}$ was collected by filtration and washed with DMF (50 mL), methanol (75 mL), water (75 mL), water/THF (1:3, 100 mL), dichloromethane (75 mL), and diethyl ether (75 mL). The resin was dried under vacuum at 50 °C for 24 h.

E. MR12$_{im}$. To a suspension of MR−CHO (500 mg) in anhydrous toluene (35 mL) was added **12** (229 mg, 0.56 mmol), and the mixture was heated under reflux in a Dean−Stark apparatus for 72 h. After cooling, MR**12**$_{im}$ was collected by filtration and washed with toluene (100 mL), dichloromethane (75 mL), THF (100 mL), and diethyl ether (100 mL). The resin was dried under vacuum at 50 °C for 24 h. Compound **12** (190 mg) was recovered from the filtrate.

Preparation of the Catalysts. The support−Ru complexes were prepared by adding the corresponding amount of polymer

(0.06 mmol of pybox) to a prefiltered solution of [Ru(*p*-cymene)$Cl_2]_2$ (18.7 mg, 0.03 mmol) in methylene chloride (5 mL). The suspension was stirred at room temperature for 24 h. The solid was filtered off, thoroughly washed with methylene chloride, and dried under vacuum at 50 °C overnight.

The support−Ru−// complexes were prepared in the same way, but ethylene was bubbled through the suspension for 1 h, and the stirring was carried out in an ethylene atmosphere. The filtration was carried out either in the open air or under nitrogen (see Table 2).

Cyclopropanation Reactions. To a suspension of the corresponding supported catalyst (0.03 mmol Ru) in a solution of styrene (0.57 mL, 5.00 mmol) and *n*-decane (ca. 25 mg) in anhydrous degassed methylene chloride (5 mL) was added ethyl diazoacetate (57 mg, 0.50 mmol) in methylene chloride (1 mL) over 6 h using a syringe pump. The reaction was monitored by gas chromatography, and after complete consumption of the diazoacetate, a second portion of this reagent was added in the same way. After the reaction had finished the catalyst was filtered off, washed with methylene chloride, and dried. The recovered catalysts were reused following the same method.

Yields and *trans*/*cis* selectivities were determined with a cross-linked methyl silicone column: 25 m × 0.2 mm × 0.33 μm. Oven temperature program: 70 °C (3 min), 15 °C/min to 200 °C (5 min). Retention times: ethyl diazoacetate, 4.28 min; styrene, 5.03 min; *n*-decane, 6.93 min; diethyl fumarate, 8.73 min; diethyl maleate, 9.04 min; *cis*-cyclopropanes **14**, 11.84 min; *trans*-cyclopropanes **13**, 12.35 min. The asymmetric induction (Figure 2) was determined with a Cyclodex-B column: 30 m × 0.25 mm × 0.25 μm. Oven temperature program: 125 °C isotherm. Retention times: (1*S*,2*R*)-cyclopropane **14S**, 28.3 min; (1*R*,2*S*)-cyclopropane **14R**, 29.1 min; (1*R*,2*R*)-cyclopropane **13R**, 33.9 min; (1*S*,2*S*)-cyclopropane **13S**, 34.3 min.

Theoretical Calculations. Theoretical DFT calculations were carried out using the B3LYP hybrid functional.[16] This functional has already been successfully used in calculations for other ruthenium complexes.[10b,17] A hybrid basis set (denoted as SDD-6-31G*) consisting of the Stuttgart−Dresden effective core potential (ECP)[18] was used for ruthenium and chlorine atoms, and the standard 6-31G(d) basis set was used for the remaining atoms. All the calculations were carried out using the Gaussian 03 program.[19]

Conclusions

The introduction of substituents in position 4 of the pyridine ring is a flexible and versatile strategy for the immobilization of chiral pybox ligands. This strategy allows complete modulation of the final chiral catalyst in different ways, including the structure of the support, the length of the spacer, and the electronic properties of the ligand. In the chosen example, ruthenium catalysts for enantioselective cyclopropanation reactions, the preparation of an efficient heterogeneous catalyst requires careful control of all of these properties. The organic support must be of a gel type and have a low cross-linking degree (2% divinylbenzene) to allow excellent accessibility, as shown by the high functionalization (around 80%) achieved during the complex preparation. It is also very important that there is no electron-donating effect on the pyridine ring, a situation achieved by the formation of a C−C bond between the support and the ligand. 4-Vinylpybox **6** and its polymer P$\mathbf{6}_2$ fulfill all of these requirements. Finally, the complex preparation method is crucial to obtain high catalytic performance and good recyclability. The presence of ethylene during the preparation of the ruthenium complex is an important requisite to prevent rapid deactivation of the catalyst, which can even be completely suppressed when the filtration and all the other manipulations of the complex are carried out under an inert atmosphere. Under such optimized conditions, a highly active (40−65% yield) and enantioselective (87−91% ee) catalyst is obtained, which can be reused at least three times without a reduction in its performance. This represents the best result obtained with an enantioselective heterogeneous ruthenium catalyst.

All of the parameters related to support type and spacer properties could be easily modified in the design of solid catalysts for other enantioselective reactions with different requirements.

Acknowledgment. This work was made possible by the generous financial support of the C.I.C.Y.T. (Project PPQ2002-04012) and the Diputación General de Aragón.

Supporting Information Available: Description of the general experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

JO050504L

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