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Soluble polyisobutylene-supported reusable catalysts for olefin cyclopropanation

David E. Bergbreiter* and Jianhua Tian

Department of Chemistry, Texas A&M University, PO Box 30012, College Station, TX 77842-3012, USA

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Abstract—Polyisobutylene oligomers (PIB) have been used as soluble supports for the immobilization of cyclopropanation catalysts. In addition to simple carboxylate ligands, chiral bisoxazolines have been successfully attached to these heptane-soluble polymers. Their use and recovery has been investigated using cyclopropanation of styrene as an example. An achiral PIB-bound Rh(II) catalyst showed good activity and could be easily recycled nine times using a liquid–liquid biphasic separation technique. PIB-supported bisoxazoline ligands for Cu(I) catalysts were also prepared. These chiral catalysts showed good catalytic activity and stereoselectivity. A chiral ligand prepared from phenylglycine provided the most effective stereocontrol and gave the trans- and cis-cyclopropanation products in 94% ee and 68% ee, respectively. All three PIB-bound chiral bisoxazoline-Cu(I) catalysts prepared could be reused five to six times.

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1. Introduction

The use of polymers as supports to facilitate the recovery and recycling of both transition metal catalysts and ligands for transition metal catalysts continues to be a current topic of great interest. During the past several decades, most of the research in this area has been focused on the immobilization of ligands and catalysts on insoluble polymeric supports.[1] Soluble supports, however, can be used too.[2,3] A solid/liquid separation like that typically effected with a cross-linked polymer can be carried out with soluble polymers using either solvent precipitation or the upper critical solution temperature for specific polymers. However, the higher temperatures, limited solvent choices or the need for excess solvent in a precipitation have hindered the widespread use of such strategies. For example, while most recent work on polymer-bound cyclopropanation catalysts has focused on using insoluble polymer supports,[4–6] we earlier described polyethylene (PE)-bound cyclopropanation catalysts that separate as solids on simple cooling.[7] These supports are effective but require elevated temperature—a problem when chiral ligands were appended to the polymer for asymmetric catalysis.[8] An alternative approach developed by our group in the last few years that has parallels in the strategy used in fluorous biphasic catalysis is to use phase selectively soluble hydrocarbon-soluble polymers as supports. Such polymers can be used as homogeneous catalysts in a single phase with the substrate and then separated using either thermomorphic or latent liquid–liquid biphasic approaches.[9,10] Either approach can be a convenient and efficient way to effect the separation of a soluble polymer-supported homogeneous catalyst from a product if the polymer selectively dissolves in a phase different than that of the product. Such separations are most practical if the polymer can be isolated as a hydrocarbon (e.g., heptane) solution, where the polymer has a phase selective solubility of 200:1, or more because most organic products of interest are more soluble in polar phases.[11] Here, we describe an example of this sort of approach and its application with a low temperature, heptane-soluble polyisobutylene oligomer (PIB), that can be used to support achiral or chiral transition metal cyclopropanation catalysts.

2. Results and discussion

The dimer of rhodium(II) acetate is an established catalyst for cyclopropanation of alkenes by diazoalkanes. In

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Keywords: Cyclopropanation; Bisoxazoline; Polyisobutylene; Polymer supports.

* Corresponding author. Tel.: +1 979 845 3437; fax: +1 979 845 4719; e-mail: bergbreiter@tamu.edu

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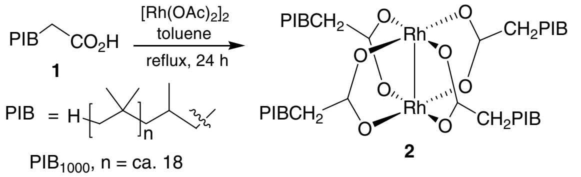
a previous study, a polyethylene (PE) supported rhodium carboxylate dimer was prepared and successfully used in catalytic alkene cyclopropanation reactions.[7] This PE-bound rhodium catalyst was successfully reused 10 times in cyclopropanation of 2,5-dimethyl-2,4-butadiene. Analysis of the product phase showed that less than 1% of the charged metal leached into product phase. However, because polyethylene and polyethylene oligomers are insoluble in all organic solvents at room temperature, the reaction had to be conducted in toluene under reflux. This proved to be a limitation when a similar PE support was used in asymmetric catalysis.[8] Since our earlier work has shown that polyisobutylene (PIB) derivatives are soluble in a wide range of organic solvents, even at −78 °C,[11] we have prepared a carboxylated PIB support and used it to prepare a rhodium carboxylate, that was in turn used as a catalyst for cyclopropanation reactions.

The carboxylated PIB support PIB-CH_2CO_2H **1** was prepared according to a reported procedure.[12] Subsequent ligand exchange with $[(CH_3CO_2)_2Rh]_2$ in refluxing toluene yielded the PIB-supported Rh(II) carboxylate **2** as a blue-green viscous oil with a metal loading of 0.36 mmol of Rh/g as determined by ICP-MS of a digested sample (Scheme 1).

The PIB-bound Rh catalyst **2** prepared as shown above was first compared to the soluble $[(PE\text{-}CO_2)_2Rh]_2$ catalysts we described earlier, as a recyclable catalyst for olefin cyclopropanation. As shown in Table 1, cyclopropanations using 1 mol % **2** as catalyst at 25 °C in heptane are comparable to those using the $[(PE\text{-}CO_2)_2Rh]_2$ catalyst at 110 °C. The catalyst **2** was successfully reused through 9 cycles without an obvious decrease in activity. In all cases the reactions were carried out as a single phase in heptane. The catalyst separation/recycling process was carried out in one of the two ways. Specifically, the products were extracted from a heptane solution of the catalyst after the reaction was complete using either acetonitrile or ethyleneglycol diacetate (EGDA). While either solvent was effective, acetonitrile was generally preferred because the cyclopropanation product could be more easily isolated using this lower boiling point solvent. Analysis of the polar phase for rhodium showed that about 2% (1.8% and 2.3%, respectively) of the charged rhodium had leached into the EGDA and acetonitrile phases, respectively, in each cycle. The higher leaching in the case of acetonitrile might reflect the better coordination ability of acetonitrile to the metal ion. Indeed, there was evidence for complexation between acetonitrile and the rhodium of the PIB-bound rhodium carboxylate dimer, since once acetonitrile was added to a solution of **2** in the heptane, the color of the solution changed from green to pink immediately. However, while there is acetonitrile present in the heptane solution of recycled catalyst, this acetonitrile had no discernable negative influence on the catalysis observed in the reactions listed in Table 1.



Scheme 1. Synthesis of a PIB-supported Rh(II) carboxylate dimer.

We also looked at 1-octene as a substrate with the catalyst **2**. As expected, 1-octene was a suitable substrate for this reaction. When the reaction was carried out in heptane under the same condition as that used for styrene except addition of EGDA, an overall 68% yield was obtained after 4 cycles. However, the yields with 1-octene after biphasic separations were lower. Together these experiments show that catalyst **2** is comparably active to the prior polyethylene-bound Rh(II)cyclopropanation catalysts with the important distinction that the catalysis can be carried out at 25 °C.

Table 1. PE and PIB_{1000} supported rhodium carboxylate catalyzed cyclopropanation reactions

Catalysts	Substrate	Work up	Temperature	Cycle	Yield (%)	Trans/cis (average)[e]
$[(PE\text{-}CO_2)_2Rh]_2$	2,5-Dimethyl-2,4-hexadiene	Cooling and filtration	110 °C in toluene	1	54	71/29
				10	59	
	Styrene	Cooling and filtration	110 °C in toluene		96	64/36
$[(PIB\text{-}CH_2CO_2)_2Rh]_2$[a]	Styrene	Liquid–liquid extraction with EGDA[b]	25 °C in heptane	1	44	59/41
				2	66	
				3–9	76[d]	
		Liquid–liquid extraction with acetonitrile[c]	25 °C in heptane	1	53	59/41
				2	75	
				3–9	77[d]	

[a] In a typical cyclopropanation reaction, 1 mol % PIB-bound catalyst was used and the reaction was carried out in heptane or cyclohexane with 5- to 10-fold excess of substrate at room temperature. The solution of ethyl diazoacetate in the same non-polar solvent was added to the reaction mixture via a syringe pump over 5–8 h period. After each cycle, the non-polar phase was extracted with ethyleneglycol diacetate (EGDA) or acetonitrile to separate the cyclopropanation product from the PIB-bound catalyst. After that, a portion of the non-polar solvent was evaporated and the substrate was added for the next cycle. The EGDA phase was analyzed by GC using an internal standard to determine the yield.

[b] This reaction used 0.5 mmol of ethyl diazoacetate.

[c] This reaction used 1 mmol of ethyl diazoacetate.

[d] Average yield over seven cycles. In the case of using EGDA, for example, the yields for the 3rd and 9th cycles are 79% and 75%, respectively.

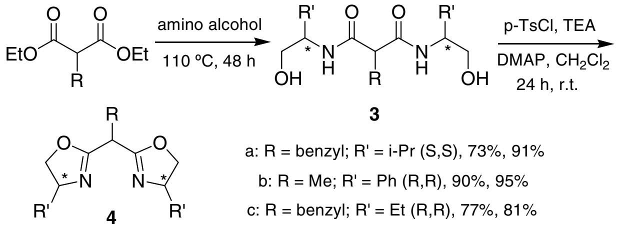
[e] Determined by GC.

Over recent years, chiral bisoxazoline ligands have been recognized as a broadly useful class of chiral ligands and they have been used in a large number of asymmetric transformations.[13] Usually the catalysis is conducted at room temperature or below, with 1–10 mol % of bisoxazoline-ligated transition metal catalyst. Given the cost of the chiral bisoxazoline ligands, the accepted desirability of recovering transition metal catalysts, and the utility of the PIB-bound catalysts at room temperature, we extended our work with **2** to include the synthesis of chiral bisoxazoline-ligated catalysts.

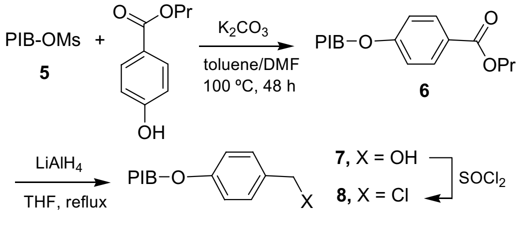
Bisoxazolines **4a–c** were synthesized as shown in Scheme 2. The dihydroxy malonodiamides **3a–c** were readily prepared from diethyl methyl-, or benzylmalonate and corresponding chiral amino alcohols in good to excellent yields. The cyclization was accomplished by a one pot literature method involving activation of the terminal hydroxyl groups with *p*-toluenesulfonyl chloride, followed by a DMAP promoted ring closure.[14]

The PIB-mesylate **5** was prepared as a racemic compound. To eliminate the possible interference from the racemic center of PIB on the catalysis, we added a linker between the polymer chain and bisoxazolines **4**. The synthesis of the PIB derivative is shown in Scheme 3. PIB-mesylate **5** was converted to the PIB-bound *n*-propyl benzoate **6** by an S_N2 substitution. The ester group on **6** was then reduced by $LiAlH_4$. The resulting alcohol **7** was treated with $SOCl_2$ to afford the desired PIB-benzylchloride **8**.

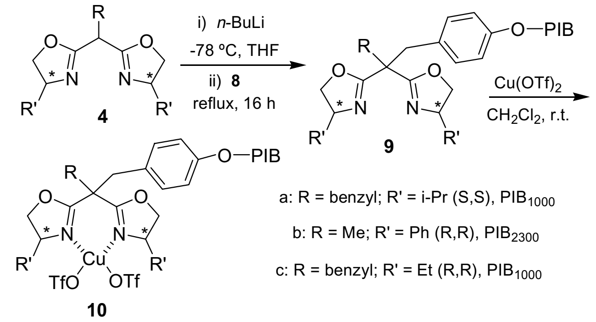
With PIB-benzylchloride **8** and bisoxazoline **4** in hand, PIB supported ligands **9a–c** were prepared by alkylation of **4a–c** with **8** (Scheme 4). All of these reactions of PIB had the attractive feature, that they could be analyzed by solution state ^{1}H NMR spectroscopy which verified that the conversion of **8** to **9** was quantitative. Figure 1 shows a portion of the ^{1}H NMR spectrum of **9**, illustrating that the solution state resolution is attainable in analyses of terminally-functionalized PIB oligomers. These syntheses were facilitated by the heptane solubility of the PIB derivatives which reduced purification to a simple heptane extraction step. Reaction of **9** with $Cu(OTf)_2$ in dichloromethane at room temperature led to the complexes **10a–c** with metal loadings of 0.50, 0.21 and 0.44 mmol of Cu/g, respectively. The resulting copper complexes were studied as asymmetric catalysts for the cyclopropanation of styrene with ethyl diazoacetate. The results of these cyclopropanation reactions are collected in Table 2.



Scheme 2. Synthesis of bisoxazoline ligands.



Scheme 3. Synthesis of benzylchloride-terminated PIB oligomer.



Scheme 4. Preparation of PIB-supported bisoxazoline ligands and catalysts.

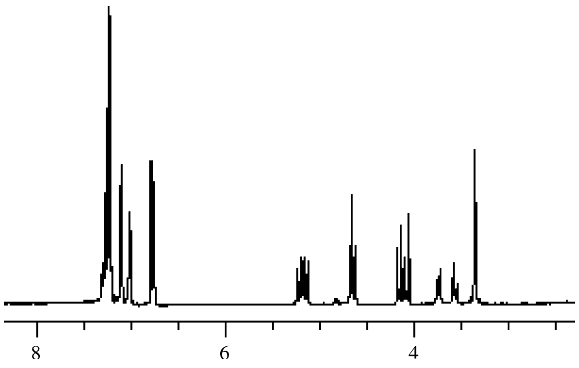


Figure 1. ^{1}H NMR spectrum of PIB-supported bisoxazoline ligand **9b**.

Table 2. PIB-supported bisoxazoline-Cu(I) complex catalysed cyclopropanation of styrene

Catalysts[a]	Cycle	Yield[b] (%)	Trans/cis[b]	Trans ee%[c]	Cis ee%[c]
10a	1	68	69/31	37	70
	2–5	58			
10b	1–6	48	81/19	92	68
10c	1–6	54	66/34	68	40

[a] The procedure for cyclopropanation reactions using catalysts **10** is same as that used in Table 1 except that the active copper(I)species was generated in situ by reducing copper(II) with phenylhydrazine (5% in DCNM, v/v) After each cycle, EGDA was used to extract cyclopropanation products from the heptane phase. Reaction of **10a** and **10c** used ca.1.9 mol % catalyst. Reactions with **10b** used 1 mol %. The yield and stereoselectivity values are reported as average values over several cycles instead of as individual values for each cycle. In the case of using **10b**, for example, the yields for the 1st and 6th cycle were 32% and 56%.

[b] Determined by GC.

[c] Determined by GC using a chiral cyclodextrin-β-CD column.

All three PIB-supported bisoxazoline ligands showed moderate catalytic activity and modest to very good stereoselectivity. Of these catalysts, **10b** demonstrated a higher diastereoselectivity (trans/cis 81/19) and good enantioselectivity in both cis- and trans-cyclopropanation (68% ee, and 92% ee, respectively). Cyclopropanation of styrene with ethyl diazoacetate using catalyst **10a** afforded the cis- product in 70% ee while a similar reaction with catalyst **10c** yielded the trans-product in 68% ee. These results are encouraging as they suggest that the soluble PIB support and its use in heptane-rich solution is compatible with an asymmetric catalytic reaction at room temperature.

Both catalysts **10b** and **10c** could be reused up to six times without a decrease in the enantio- and diastereoselectivity. The PIB_{2300}-supported copper catalyst showed slightly lower catalytic activity compared to the PIB_{1000} version. In the case of using **10c**, 33%, 16% and 5% of metal leaching was observed in the EGDA phases for the 1st, 2nd and 5th cycles, respectively, by ICP-MS analysis. We believe this reflects mass transfer of a portion of the PIB-bound copper catalyst **10c** to the polar phase because the polar part of these ligands is relatively large in comparison to the size of the non-polar PIB group. This makes the catalysts less phase selectively soluble. The decrease in leaching through several cycles is presumed to reflect a greater loss of less phase selectively soluble lower molecular weight fractions of the polydisperse PIB-bound catalyst in the initial biphasic separations. The loss of PIB-bound copper species into the polar phase is thus both greater than that seen for **2** and decreases as the number of cycles increases.

We also analyzed EGDA phases in another recycling experiment using the higher molecular weight PIB-bound catalyst **10b**. This catalyst too was reusable through multiple cycles. Metal leaching for the 1st, 2nd, 3rd, 4th and 6th cycles was 13%, 7%, 6% 7% and 7% of the charged catalyst, respectively. These leaching rates are larger than we wished. Nonetheless, they show that the recyclability of PIB_{2300} supported Cu(I) catalysts is better than that seen for PIB_{1000} supported catalysts, a result which we ascribe to the larger non-polar PIB chain in **10b**.

Separate experiments examined the phase selective solubility of **10b** in a heptane/EGDA biphasic extraction in the absence of a catalytic reaction to confirm that the observed leaching reflects the inherent phase selective solubility of these oligomeric PIB-bound bisoxazoline catalysts in liquid/liquid biphasic separations. EGDA was added to a heptane solution of **10b** and the concentration of **10b** in both the heptane and EGDA phases was analyzed by UV–visible spectroscopy using the absorbance of **10b** at 720 nm. Assuming that the extinction coefficient of **10b** in the heptane and EGDA phases is the same, we estimate the phase selective solubility of **10b** in the first two cycles in this experiment where the condition that no reaction occurs is ca. 14% and 7%, respectively. These UV–visible spectroscopy results match our ICP-MS results and support the notion that the lower phase selectivity of the PIB-bound catalyst is the origin of the catalyst leaching problem. This suggests that a higher molecular weight PIB will afford a more recyclable catalyst.

3. Conclusions

In summary, both PIB-bound rhodium carboxylate and bisoxazoline-copper triflate complexes have been synthesized and used in the olefin cyclopropanation reactions. Catalyst reusability was demonstrated in both heptane/EGDA and heptane/acetonitrile solvent systems. Oligomeric PIB-carboxylate ligands can be used to prepare rhodium(II) cyclopropanation catalysts that work at room temperature and that can be recycled and reused in both heptane/EGDA and heptane/acetonitrile solvent systems with liquid/liquid catalyst recovery and separation. Up to 9 cycles with ca. 2% metal leaching were seen in a typical cyclopropanation. PIB-supported bisoxazoline-Cu(I) complexes were prepared and were shown to have moderate to good activity and enantioselectivity at room temperature. Catalyst **10b** was the most effective of these catalysts yielding 68% ee and 92% ee for the cis- and trans-cyclopropanation product, respectively. However, catalyst leaching for PIB-bound copper catalysts is more problematic due to the higher mass percent loading of polar groups in these oligomeric catalysts. Recyclability can be improved by increasing the length of PIB chain but metal leaching is still a problem with PIB groups having a degree of polymerization of 40–50.

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