ORGANIC
LETTERS

2003
Vol. 5, No. 20
3663−3665

Polymer-Supported Pyridine–Bis(oxazoline). Application to Ytterbium-Catalyzed Silylcyanation of Benzaldehyde

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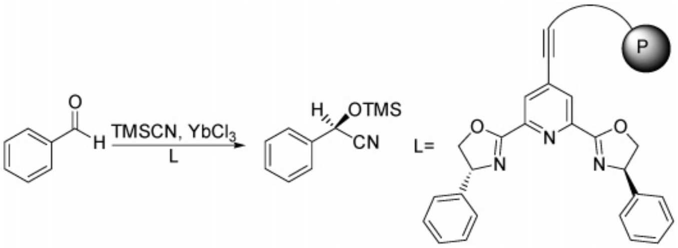
Received July 18, 2003

ABSTRACT



Terminal acetylenes containing hydroxy and carboxylic acid groups were subjected to Sonogashira coupling with 4-bromo-2,6-bis[(*R*)-4-phenyloxazolin-2-yl]pyridine and the resulting pybox derivatives were immobilized on Tentagel resins. Ytterbium(III) chloride complexes of the polymeric ligands catalyzed the addition of trimethylsilyl cyanide to benzaldehyde with 80–81% ee. The ligands were reused more than 30 times without any loss in selectivity or activity, and the metal complexes could be recovered and reused at least four times, although with slightly decreasing activity.

Asymmetric catalysis constitutes a powerful method for the preparation of chiral compounds in enantiomerically pure form.[1] The chiral ligands responsible for the transfer of chirality to the substrates undergoing reaction often require multistep synthetic procedures for their preparation. The possibility of recovering and reusing the ligands is therefore desirable and increases the usefulness of the catalytic methods.[2] This is the reason in recent years considerable attention has been devoted to the development of procedures to attach chiral ligands and catalysts to solid supports, consisting of organic polymers[3] or inorganic materials.[4]

It is particularly valuable to have access to methods allowing the immobilization of ligands with a wide range of catalytic applications. Bisoxazoline, box,[5] and pyridine-2,6-bisoxazoline, pybox,[6] derivatives are examples of ligands which are employed in a variety of metal-catalyzed processes yielding highly enantioenriched products.

While several methods for the preparation of supported box ligands have been reported,[7] only a few examples of the immobilization of pybox derivatives exist.[8] Thus, a chiral pybox with a vinyl group at the 4-position of the pyridine ring, introduced via Stille coupling, was copolymerized with styrene and divinylbenzene.[9] Ruthenium complexes of the

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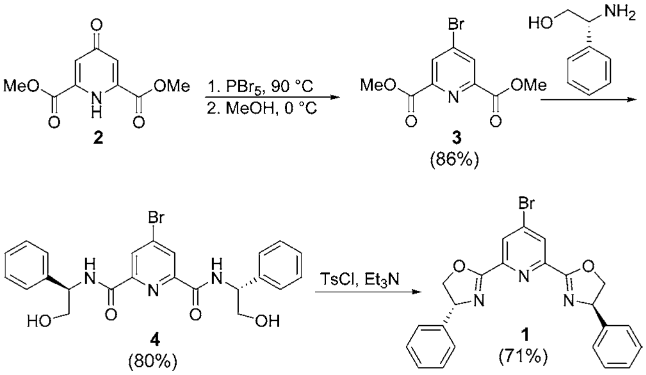
10.1021/ol0353363 CCC: $25.00

resulting insoluble polymer were used in enantioselective cyclopropanations, with results somewhat inferior to those obtained with use of the monomeric analogue. We have previously attached 4-(3-hydroxyethyloxy)-2,6-bis[(*R*)-phenyloxazolin-2-yl]pyridine to silica surfaces via formation of ester bonds.[10] The 4-substituted pybox was prepared by nucleophilic substitution of 4-chloro-2,6-bis[(*R*)-4-phenyloxazolin-2-yl]pyridine with ethylene glycol in the presence of base. Under the basic conditions used for the reaction, some degradation of the oxazoline rings occurred, resulting in variable yields of the product. We therefore desired a more reliable process for the functionalization of the 4-position of the pyridine ring with a substituent containing a suitable functional group for subsequent attachment to a solid support.

Suzuki methodology was recently employed for the coupling of a 4-chlorosubstituted pybox precursor to the 4-position of pyridine.[11] The desired product was obtained in high yield, provided that the palladium-catalyzed coupling was performed prior to ring closure to the final oxazoline compound. Our preliminary experiments aiming at the introduction of aliphatic substituents via palladium-catalyzed coupling with ω-functionalized alkylboronates were unsuccessful, however. We therefore decided to attempt Sonogashira coupling,[12] a Pd−Cu-catalyzed process that tolerates a wide range of functional groups.[13] We were pleased to find that hydroxyalkynyl as well as carboxyalkynyl substituents were conveniently introduced and that immobilization to suitably functionalized cross-linked polymers could be achieved via ester bond formation.

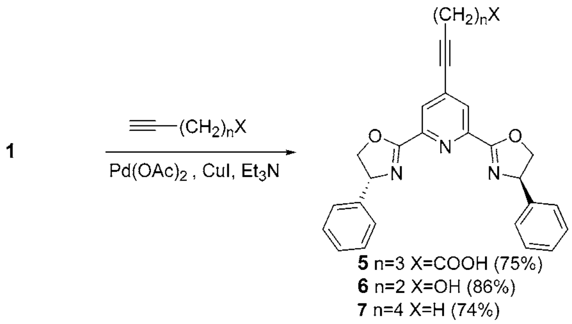
The synthesis of the 4-bromo-substituted phenyl-pybox ligand **1**, selected as a suitable derivative for further functionalization, started from chelidamic acid (**2**), which was transformed to 4-bromopyridine-2,6-dicarboxylic acid dimethyl ester (**3**), in analogy to the procedure described for the corresponding diethyl ester[14] (Scheme 1).[15] Reaction with (*R*)-phenylglycinol generated diamide **4**, which was transformed into **1** in two steps.

Scheme 1. Synthesis of 4-Bromo-Substituted Phenyl-Pybox



To evaluate the efficiency of the Sonogashira coupling two different 1-alkynes with different terminal functional groups, 5-hexynoic acid and 3-butyne-1-ol, were connected to the pyridine ring. The function of the alkyl chain, consisting of three and two carbon atoms, respectively, is to serve as a spacer between the ligand and the polymer. To study whether an acetylene substituent in the 4-position of the pyridine ring has an effect on the outcome of the homogeneous catalytic reaction, ligand **7** was also prepared. The Sonogashira couplings were accomplished in 2 h at 55 °C by using 3.4% Pd(OAc)$_2$ and 1% CuI (Scheme 2). After workup and purification, the desired compounds **5**, **6**, and **7** were obtained in high yields (75, 86%, and 74%, respectively).

Scheme 2. Sonogashira Coupling



The functionalized pybox derivatives **5** and **6** were linked via ester bond formation to resins containing carboxylic acid and hydroxy groups, respectively. Thus, reaction of ligand **5** with TentaGel MB-OH resin and ligand **6** with TentaGel HL-COOH resin in the presence of DCC and DMAP in dichloromethane for 48 h at room temperature gave the desired solid-supported ligands **8** and **9** in high yields (74% and 84%, respectively, according to elemental analyses, Scheme 3).

The polymer-bound pybox ligands were evaluated in asymmetric metal-catalyzed silylcyanations of benzaldehyde to form nonracemic cyanohydrins, which are important chiral building blocks in organic synthesis.[16] The first reported use of pybox in metal-catalyzed addition of trimethylsilyl cyanide (TMSCN) to aldehydes was with isopropyl-pybox and AlCl$_3$.[17] This catalyst provided high yields of products but only modest enantioselectivity in reactions with benzaldehyde. More efficient catalysts, consisting of pybox−lan-

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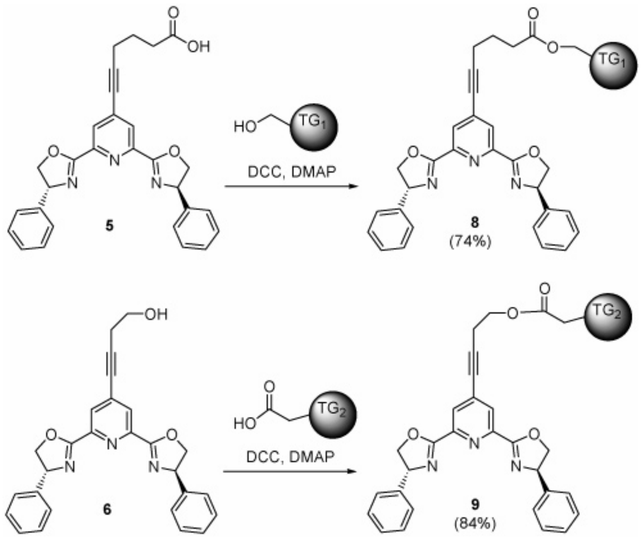
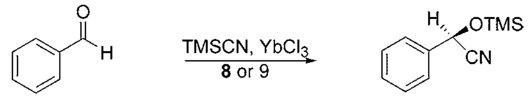
Scheme 3. Preparation of Solid-Supported Ligands **8** and **9**



thanide complexes, were reported later.[18] The highest ee reported for lanthanide-catalyzed addition of TMSCN to benzaldehyde was achieved with a catalyst prepared from phenyl-pybox and ytterbium trichloride.

The solid-supported pybox derivatives **8** and **9** were assessed in the catalytic silylcyanation of benzaldehyde (Scheme 4), using 10% $YbCl_3$ and 20% ligand. The reactions afforded the cyanohydrin with 88−89% conversion within 30 min, which is about the same as that observed for the reaction with the corresponding homogeneous ligand.[18] Somewhat lower enantioselectivity was observed, however. For the homogeneous ligand an enantiomeric excess of 89% was reported,[18] although in our hands, the published procedure resulted in only 84% ee, as compared to 81% and 80% ee for **8** and **9**, respectively.[19] With a lower ligand-to-metal ratio, 1.5:1, a lower ee (72%) was observed, in analogy to the situation with homogeneous catalyst. The slightly lower ee observed in reaction with the polymeric ligands was not due to the presence of the acetylene function, as ligand **7** afforded the product with the same enantioselectivity as the parent phenyl-pybox ligand (84% ee, 92% conversion).

Scheme 4. Asymmetric Ytterbium Catalyzed Silylcyanation of Benzaldehyde



The polymeric ligands could easily be recovered by filtration, washing, and drying after the catalytic reaction and reused over 30 times without any change in the reaction outcome. There was no significant difference in the performance of the two polymer-supported ligands.

Since it would be desirable to be able to recover not only the chiral ligand but also the ligand with the coordinated metal ion, we examined the possibility of recycling the ytterbium−pybox complex. For this purpose, the catalytic reactions were performed in vessels containing a filter, enabling convenient filtering and washing procedures. The results of the recovery of the metal−ligand complexes are summarized in Table 1. After each reaction, the solvent was removed from the reaction vessel and new solutions of reactants were added. No additional ytterbium trichloride was added after the initial loading. The metal complex could be recovered at least four times without any change in ee and only a slight reduction in activity, the later probably being due to decreasing metal loading.

Table 1. Recycling of the Polmeric Ytterbium Complex[a]

run[a]	reaction time [h]	conversion [%][b]		ee [%][b]	
		ligand **8**	ligand **9**	ligand **8**	ligand **9**
1	0.5	89	88	81	80
2	0.5	84	89	80	81
3	0.5	75	82	81	81
4	0.5	66	72	81	81

[a] All reactions were carried out in acetonitrile at room temperature with 1.2 equiv of TMSCN, 20 mol % of polymer-bound ligand, and 10 mol % of $YbCl_3$. [b] Determined by GC analysis, using a chiral column (Supelco Gamma-DEX-120).

In summary, we have developed an efficient procedure for the immobilization of chiral pybox derivatives, which allows for variation of the length and nature of the spacer connecting the ligand and the solid support as well as the functional group used for the attachment to the solid support. The polymeric ligands exhibit as high reactivity as their homogeneous analogues, yielding products with only marginally lower enantioselectivity.

Acknowledgment. This work was supported by the Swedish Foundation for Strategic Research (the Nanochemistry Program).

Supporting Information Available: Experimental procedures for the preparation of **7**, **8**, and **9**, characterization data, and description of catalytic studies. This material is available free of charge via the Internet at http://pubs.acs.org.

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[19] A referee suggested that complexation of ytterbium to the polyether chain of the polymeric backbone might result in a nonselective catalyst. However, a mixture of unfunctionalized TentaGel HL-COOH and $YbCl_3$ afforded merely 2% of the racemic product after 30 min.