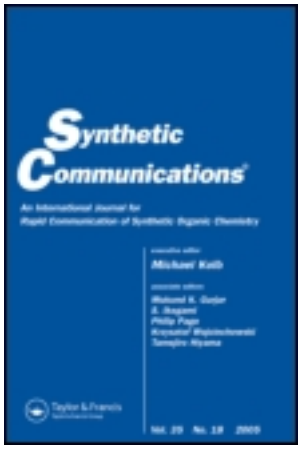

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PEG-Supported Recyclable Catalyst for Enantioselective Ethylations

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PEG-SUPPORTED RECYCLABLE CATALYST FOR ENANTIOSELECTIVE ETHYLATIONS

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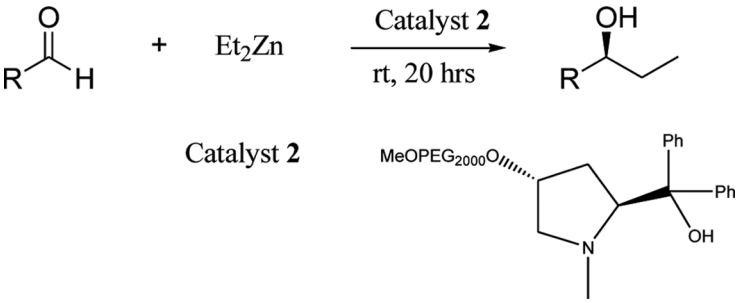
GRAPHICAL ABSTRACT



Abstract *A β-amino alcohol derived from 4-hydroxyproline was bound to polyethylene glycol (PEG) and used in the enantioselective ethylation of aryl aldehydes with diethyl zinc. Isolated yields of the corresponding alcohols ranged from 53 to 93% with* ee*'s of 91–97%. Full recovery of the catalyst was accomplished by addition of diethyl ether. The polymer-bound catalyst could be recycled without loss of activity.*

Keywords Enantioselective ethylation; PEG; polymer support; soluble polymer-supported catalyst

INTRODUCTION

The enantioselective alkylations of aldehydes and ketones with chiral catalysts are convenient for the preparation of secondary and tertiary chiral alcohols, respectively, which are of interest in natural products and pharmaceuticals. The catalysts were developed by structural modifications and tested on simple aryl aldehyde substrates for optimization. Since the pioneering work of Oguni and Omi,[1] numerous chiral ligands have been developed with varying success.[2] Among these, the amino alcohols are among the best catalysts, allowing the preparation of chiral alcohols in good yields and enantiomeric excesses.[3] In a number of instances Ti(IV) is used for cocatalysis [4] in less reactive carbonyl substrates. The use of solid polymer-supported

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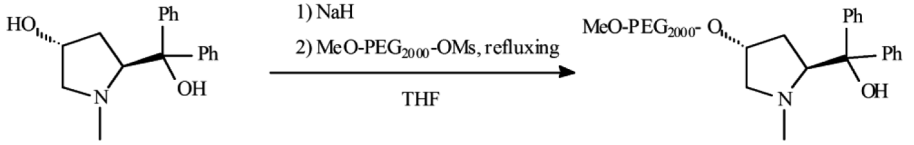
catalysts has gained increasing popularity for their ease of separation, recyclability, and their adaptability to flow process operations. However, heterogenous reactions are, in principle, inherently inefficient. Many of the conventional polystyrene-based supports suffer from limiting mechanical properties and poor thermo-oxidative stabilities. Solid-phase supports have been used to immobilize pyrrolidinyl methanol derivatives for catalysis in the enantioselective alkylation of aldehydes with moderate success.[5,6] The use of soluble polymer supports such as polyethylene glycol (PEG) has provided an alternative to some of the limiting aspects of solid-phase chemistry in that homogenous reaction conditions are restored and the polymer support can be readily separated by precipitation with the dilution of an "antisolvent."[7] Our interest in liquid polymer-support chemistry [8,9] caused us to initiate the current study of their application in immobilizing chiral ligands of the pyrrolidinyl methanol variety and their use in enantioselective ethylations. One such independent report appeared recently in which a pyrollidinyl methanol (**1**) is attached to both an insoluble polystyrene resin as well as soluble PEG, the latter via a succinyl ester linkage. Although the heterogenous reaction showed excellent recyclability, the enantioselective efficiency was moderate for the diethyl zinc ethylation of aryl aldehydes (34–71% *ee*). The PEG-supported ligand, while showing better enantioselectivity (42–90% *ee*) than the insoluble counterpart, suffers from the diminishing efficiency even after one recovery cycle (yield 94→17%, *ee* 90→78%).[10] The reduced efficiency is attributed to the labile nature of the succinate diester linker under the reaction conditions.

RESULTS AND DISCUSSION

We report here the attachment of amino alcohol **1**[10] to $MeOPEG_{2000}$ via an ether linkage to give the PEG ($MeOPEG_{2000}$)–supported ligand **2**, which was chosen for its suitable solubility properties and suitability as an NMR marker (MeO terminus) for assessing the loading levels of the coupling reaction.



1 **2**

The stability of the ether linkage in **2** under the reaction conditions should retain the efficacy of this catalyst on recycling in contrast to a previously reported analog, which was attached by a succinate ester linker.[10]

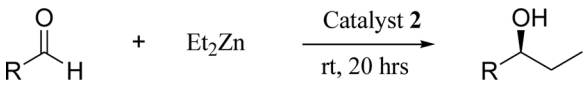
(*3R,5S*)-5-(Hydroxydiphenylmethyl)-1-methylpyrrolidin-3-ol (**1**)[10] was directly attached to $MeOPEG_{2000}OH$ via its methanesulfonate ester to give **2** in 97% yield. The preparation of $MeOPEG_{2000}OMs$ has been previously reported by our group.[9] To optimize conditions for the catalytic enantioselective ethylation of benzaldehyde with diethyl zinc, a solvent study using hexane, benzene, and toluene solutions of **2** with substrate was carried out. Slightly better recovered yields of 1-phenyl-1propanol (**3a**) and enantioselectivity was observed for benzene solutions (Table 1). All reactions were run at room temperature for 20 h in an argon atmosphere. The isolated yields

Table 1. Yields and enantioselectivity of arylaldehyde catalytic ethylations with **2**

Entry	Aldehyde (R)	Recycling times	Solvent	Isolated yield (%)[a]	$[\alpha]_D^{23}$ deg (solvent)	*ee* (%)[b]	*ee* (%)[c]
1	C_6H_5	0	Hexane	53	−31.83 ($CHCl_3$)	69.9	
2	C_6H_5	0	Toluene	69	−38.50 ($CHCl_3$)	84.6	
3	C_6H_5	0	Benzene	70	−38 ($CHCl_3$)	85.1	91.4
4	C_6H_5	0	Benzene	72	−38 ($CHCl_3$)	85.1	
5	C_6H_5	0	Benzene	76	−38 ($CHCl_3$)	84.8	
6	C_6H_5	1	Benzene	79	−36 ($CHCl_3$)	80.0	
7	C_6H_5	1	Benzene	76	−37 ($CHCl_3$)	82.3	
8	C_6H_5	2	Benzene	57	−37 ($CHCl_3$)	83.5	
9	C_6H_5	2	Benzene	69	−38 ($CHCl_3$)	83.8	
10	4-ClC_6H_5	0	Benzene	89	−28 (Benzene)	120	95.8
11	2-Naphth	0	Benzene	93	−34 (Benzene)	86.0	96.6
12	(*E*)-PhCH=CH	0	Benzene	84	−11 ($CHCl_3$)	131	94.9
13	4-$MeOC_6H_5$	0	Benzene	89	−35 (Benzene)	105	96.5
14	4-MeC_6H_5	0	Benzene	73	−37 (Benzene)	92.3	96.8

[a]Isolated.
[b]Based on reported specific rotations.[11,12].
[c]Based on chiral column (Chiralcel 5 micron ChiralPAK) separation and integrations.

and enantiomeric excess were reproducible for independent experiments (Table 1, entries 3–5). Recovery of the catalyst (typically 80%) and enantioselectivity efficiency was very good (Table 1, entries 6–9) after two recycles of the supported ligand. The catalyst is readily recovered by concentration of the solution and addition of ether as the antisolvent. This is in sharp contrast to the observations for the succinate-appended ligand **1**, where a substantial reduction in recovery and loss of enantioselectivity were observed even after one reuse.[10]



The PEG-attached ligand **2** was also shown to exhibit excellent properties for the enantiomeric zinc ethylation of other aryl aldehydes (Table 1, entries 10–14) with recovery yields ranging from 73–93% and *ee*'s from 95 to 97%. Enantioselectivity determinations based on optical activity measurements and comparisons with literature values are prone to errors (entries 10, 12, and 13). Determination of *ee*'s using high-performance liquid chromatographic (HPLC) analyses on a chiral column remains a more reliable method.

The use of soluble polymer-supported reagents and catalysts offers certain advantages over their insoluble counterparts in bestowing homogenous conditions for maximizing reaction efficiency. This was seen in the reported enantioselectivities for the diethyl zinc alkylations of aryl aldehydes catalyzed by **2** when compared with the polystyrene-based analogs.[10] Attachment of ligand **1** to PEG through an ether linkage imparts greater hydrolytic stability as compared to a diester function, allowing for the recovery of the catalyst with retention of its efficiency.

EXPERIMENTAL

All reactions were done in dried glassware. All solvents used for the reactions were dried and distilled. Melting points were obtained with a Fisher-Johns melting-point apparatus and are uncorrected. Ultraviolet (UV) spectra were determined in MeOH solutions using an Ultraspec 4300 pro UV spectrometer. Infrared (IR) spectra were recorded on a Pye Unicam SP3-200 spectrometer as thin KBr pellets and are reported in cm^{-1}. Mass spectra were recorded on a QStar Elite spectrometer. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker ARX 400-MHz superconducting NMR spectrometer. Data for ^1H NMR are referenced relative to residual $CDCl_3$ proton signals at δ 7.27 ppm and to dimethylsulfoxide (DMSO-d^6) δ at 2.50 ppm. Data for ^{13}C NMR are referenced relative to $CDCl_3$ at δ 77.16 ppm and to DMSO-d^6δ at 39.52 ppm. Data for ^1H are reported as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, h = heptet, m = multiplet) and integration. Analytical thin-layer chromatography (TLC) was performed on silica-gel 60 Alugram sheets and silica gel (40–63 μm) was used for column chromatography. Preparative TLC was conducted using predried glass plates coated with silica gel (0–20 μm). All reagents employed were purchased from commercial sources and used without further purification.

Optical rotations were obtained on a Perkin-Elmer 241 polarimeter using 1-dm cells. Solutions containing 20–30 mg of analyte in 1.2 mL of $CHCl_3$ were prepared for the measurements..

HPLC analyses were carried out on a Waters 2695 HPLC with a Waters 2996 PDA detector. Approximately 4 mg of the purified sample was dissolved in a 1:1 (v/v) mixture of HPLC-grade hexanes and 2-propanol and further diluted to a concentration of ~2 mg/mL using HPLC-grade hexanes. Samples (injection volume = 1 μL) were run with an isocratic mixture of 99.5:0.5 (v/v) of HPLC-grade hexanes and 2-propanol at 15 °C through a Chiralcel ChiralPAK IA column (5 micron, 250 mm × 4.6 mm) using a Waters 2695 HPLC system. Flow rates of individual runs were reported on the spectra. Enantiomeric excess was determined by integrating UV response of two peaks originating from the enantiomers of interest at a suitable wavelength using a Waters 2996 detector (PDA). Purity of individual samples was also verified with an isocratic run using 65:35 (v/v) mixture of HPLC-grade acetonitrile and water at 1 mL/min flow rate through a Phenomenex Luna C18(2) HPLC column (5 microns, 250 mm × 4.6 mm).

Preparation of Polymer-Supported Catalyst: MeO-PEG-OMs

Mesyl chloride (4 mL, 51.7 mmol) was added dropwise to a stirred solution of MeO-PEG-OH (20 g, 10 mmol, Mw = 2000) and tripentylamine (8.25 mL, 28.4 mmol) in CH_2Cl_2 (100 mL). After stirring for 16 h at room temperature, most of the solvent was removed under reduced pressure. Ether (1 L) was added to the residue and cooled to 0 °C with stirring, which was continued for 1 h. The precipitated white solids were collected by filtering and then redissolved in 20 mL of CH_2Cl_2. The solution was cooled to 0 °C and mixed with ether. After stirring for 1 h, the monomesylated product (20.1 g, 97%) was collected as a white solid by filtering and drying in air. ^1H NMR (400 MHz, $CDCl_3$-d, δ): 4.37 (m, 2H), 3.80–3.40 (m, 177H), 3.34 (s, 3H), 3.06 (s, 3H).

Preparation of 2

MeO-PEG-OMs (13.76 g, 6.62 mmol) was added to a stirred mixture of (*3R,5S*)-5-(hydroxydiphenylmethyl)-1-methylpyrrolidin-3-ol (**1**) (2 g, 7.5 mmol), which had been synthesized following a reported procedure[10] and treated with sodium hydride (0.384 g, 15 mmol) in dry THF (120 mL) for 30 min under reflux in argon. The resulting mixture was stirred under reflux overnight, followed by evaporation of solvents under reduced pressure. The residue was dissolved in 30 mL of water and extracted with CH_2Cl_2 (3×150 mL). The organic phases were combined and dried over Na_2SO_4. Most of the solvents were removed by evaporation under reduced pressure. The remaining (ca. 30 mL) was mixed with 1 L of ether and stirred for 1 h at 0 °C. The precipitated solids were filtered off and washed with ether and hexane. The catalyst (14 g, 93%) was collected as a white solid after drying in air. ^{1}H NMR (400 MHz, $CDCl_3$-d, δ): 7.53–7.08 (m, 10H), 4.02–3.87 (m, 2H), 3.87–3.30 (m, 261H), 3.19–3.11 (m, 1H), 2.50–2.41 (m, 3H), 1.95–1.74 (m, 2H).

Enantioselective Ethylation of Aryl Aldehydes: General Procedure

Diethylzinc (1.0 M solution in hexane, 2.4 mL) was added to a solution of catalyst **2** (2.0 g, 7.7 mol%) in anhydrous benzene (10 mL) under argon at 0 °C, and stirred for 20 min. Aldehyde (1.5 mmol) was added, and the mixture was stirred at room temperature for 20 h. The reaction was quenched by pipetting four drops of 2 M HCl. Most of the solvents were removed under reduced pressure, the mixture was cooled to 0 °C, and Et_2O (50 mL) was added. The precipitated catalyst was recovered by filtration and air and vacuum dried for subsequent use (recovery of 1.5 to 1.9 g). Evaporation of the filtrate gave the crude product, which was purified on a silica-gel column to afford the pure *sec*-alcohol.

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