# Silica-Bound 3-{2-[Poly(ethylene Glycol)]ethyl}-Substituted 1-Methyl-1*H*-imidazol-3-ium Bromide: A Recoverable Phase-Transfer Catalyst for Smooth and Regioselective Conversion of Oxiranes to *β*-Hydroxynitriles in Water

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A series of *β*-hydroxynitriles were efficiently synthesized from the regioselective ring opening of oxiranes by cyanide anion in the presence of silica-bound 3-{2-[poly(ethylene glycol)]ethyl}-substituted 1-methyl-1*H*-imidazol-3-ium bromide ($SiO_2$–PEG–ImBr) as a novel recoverable phase-transfer catalyst in $H_2O$ (*Scheme 1* and *Table 2*). The workup procedure was straightforward, and the catalyst could be reused over four times with almost no loss of catalytic activity and selectivity.

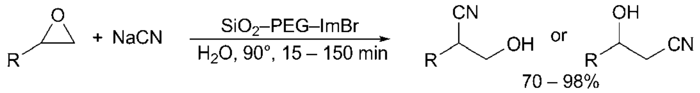
**Introduction.** – Problems associated with the phase separation of an inorganic reagent and an organic substrate can be overcome by the use of phase-transfer catalysts in both homogeneous and heterogeneous forms [1]. One of the major problems associated with the use of soluble catalysts lies in the recovery of the catalyst from the reaction medium. Immobilization of the catalyst on an insoluble surface such as a polymeric matrix, silica gel, *etc.*, can provide a simple solution to this problem [2]. During the last decades, much interest has been focused on the applications of functionalized polymers as phase-transfer catalysts [3] because they provide great ease in separation of the catalyst and isolation of the product.

Recently, poly(ethylene glycols) (PEGs) and their derivatives were used extensively as inexpensive phase-transfer catalysts in a variety of organic reactions [4]. The suitability of these compounds lies in their low cost, availability on an industrial scale, lack of toxicity, high degree of stability in reaction systems, and the fact that they attach easily to insoluble solid substrates.

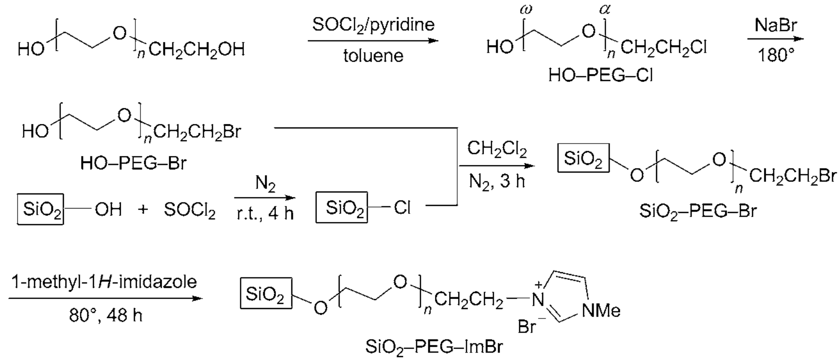
Owing to the widespread interest in *β*-hydroxynitriles, and in conjunction with ongoing work in our laboratory on the synthesis of new phase-transfer catalysts [5][6], we would like to describe the preparation of a new hybrid organic/inorganic silica ($SiO_2$) *i.e.*, a silica-bound poly(ethylene glycol) derivative combined with 1-methyl-1*H*-imidazol-3-ium bromide (ImBr), and its application as a recoverable phase-transfer catalyst in the regioselective ring opening of oxiranes by cyanide anions in $H_2O$ (*Scheme 1*).

**Results and Discussion.** – A general synthetic route for the preparation of the silica-bound phase transfer catalyst $SiO_2$–PEG–ImBr is presented in *Scheme 2*. This organic–inorganic hybrid catalyst contains three different units linked together, and

Scheme 1. *Synthesis of β-Hydroxynitriles from Oxiranes in the Presence of Phase-Transfer Catalyst.* For substrate and product structures, see *Table 2.*




Scheme 2. *Representative Preparation of Silica-Bound 3-{2-[Poly(ethylene glycol)ethyl]-1-methyl-1*H*-imidazol-3-ium Bromide* ($SiO_2$–PEG–ImBr)




we assumed that each unit plays a specific role in the ring opening of oxiranes by cyanide anions. To establish the role of each unit of $SiO_2$–PEG–ImBr, the ring opening of styrene oxide (=2-phenyloxirane; 1 mmol) by NaCN (2 mmol) in the presence of the catalyst (0.2 g) was investigated in $H_2O$ at 90°. Although $SiO_2$–PEG–ImBr acted very efficiently and produced the corresponding *β*-hydroxynitrile, *i.e.*, 3-hydroxy-2-phenylpropanenitrile, within 30 min in 95% yield, all attempts to produce the *β*-hydroxynitrile in the presence of 1-methyl-1*H*-imidazole alone, of silica-bound poly(ethylene glycol), or of poly(ethylene glycol) itself were not successful. In these cases, the reaction did not go to completion after 3 h, and the product was contaminated by the corresponding diol.

It seems that poly(ethylene glycol) units in $SiO_2$–PEG–ImBr encapsulate alkali metal cations, much like crown ethers, and these complexes cause the cyanide anion to be activated. The 1-methyl-1*H*-imidazol-3-ium units introduce ionic-liquid property to the catalyst. In addition, silanol OH-groups at the $SiO_2$ surface, probably, facilitate the ring opening of the oxirane by H-bonding (*Fig. 1*).

Solvent effects on the ring opening of styrene oxide by cyanide anion was also investigated. The reaction was carried out in different solvents such as $Et_2O$, $CHCl_3$, $CH_2Cl_2$, AcOEt, $H_2O$, and MeCN, established that MeCN could also be used as a solvent (*Table 1*). However, because of its toxicity, cost, and possible environmental problems, $H_2O$ was preferred as the most suitable solvent.

To explore the general validity of the protocol, we turned our attention towards the ring opening by cyanide anion in $H_2O$ at 90° of different types of oxiranes carrying activating and deactivating groups (*Table 2*): In these reactions, the product was cleanly, easily, and efficiently obtained as a single isomer, the structure of which was

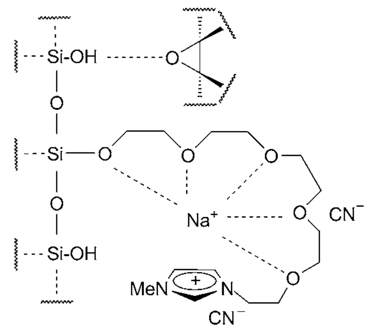



Figure. *Model for the catalytic activity of silica-bound catalyst*

Table 1. *Effect of Solvent on the Reaction of Styrene Oxide with NaCN* (2 mmol) *in the Presence of $SiO_2$–PEG–ImBr*

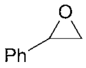
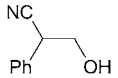
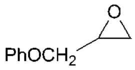
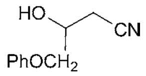
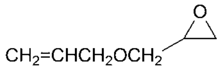
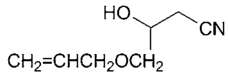
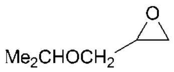
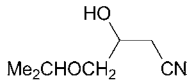
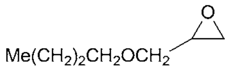
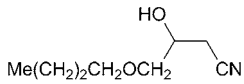
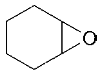
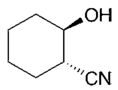
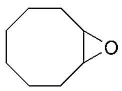
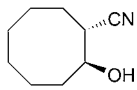
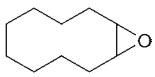
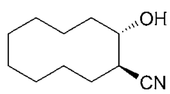
| Solvent | Time [min] | Temperature | Result |
|---|---|---|---|
| $Et_2O$ | 60 | reflux | not completed |
| $CHCl_3$ | 60 | reflux | not completed |
| $CH_2Cl_2$ | 60 | reflux | not completed |
| AcOEt | 60 | reflux | not completed |
| $H_2O$ | 30 | 90° | completed |
| MeCN | 20 | reflux | completed |

confirmed by $^1$H-NMR spectroscopy. The regioselectivity of the ring opening of oxiranes is dependent on the mechanism of the reaction and particularly on steric and electronic factors. The reaction of styrene oxide with cyanide anions in the presence of $SiO_2$–PEG–ImBr gave 3-hydroxy-2-phenylpropanenitrile as sole product. Oxiranes carrying electron-withdrawing groups reacted under similar reaction conditions, but their corresponding cyanohydrins were produced with reversed regioselectivity indicating nucleophilic attack at the less-substituted C-atom of the oxirane. In the case of aliphatic oxiranes, steric factors predominated over electronic factors, thereby facilitating the attack at the less-hindered C-atom of the oxirane ring. Furthermore, oxiranes derived from cycloalkenes, such as 7-oxabicyclo[4.1.0]heptane, reacted smoothly in $S_N2$ fashion to afford the corresponding cyanohydrine; the configuration of the ring-opening products was *trans* according to the coupling constants of the ring H-atoms in $^1$H-NMR spectrum.

It is worthy to note that the phase-transfer catalyst could be reused several times without loss of activity. The catalyst was recovered by filtering and washing with $H_2O$ and MeOH, and was reused efficiently at least four times in the conversion of styrene oxide to the corresponding $\beta$-hydroxynitrile. No loss of its activity was observed, and 3-hydroxy-2-phenylpropanenitrile was produced in 95, 93, 92, and 94% yield, respectively.

In conclusion, a simple and high-yielding synthesis of a new phase-transfer catalyst bound to $SiO_2$ was developed. This catalyst displayed a remarkable efficiency in ring opening of oxiranes with cyanide ion in $H_2O$ at 90°. Simplicity of the reactions, high

Table 2. *Ring Opening of Epoxides with NaCN* (2 mmol) *in $H_2O$ at 90°*

| Substrate | Product[a]) | Time [min] | Yield [%] |
|---|---|---|---|
|  |  | 30 | 95 |
|  |  | 25 | 98 |
|  |  | 30 | 90 |
|  |  | 15 | 85 |
|  |  | 150 | 97 |
|  |  | 45 | 97 |
|  |  | 135 | 70[b])[c]) |
|  |  | 120 | 75[c]) |

[a]) Products were identified by comparison of their physical and spectral data with those of authentic samples. [b]) 3 mmol NaCN was used. [c]) Purified by GC.

product yields, relatively short reaction times, easy workup, and ease of the preparation and recyclability of the catalyst are the most important advantages of this environmentally friendly protocol and makes it useful procedure in addition to the available methods.

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**Experimental Part**

*Generals.* Chemicals were purchased from *Fluka*, *Merck*, and *Aldrich*. Poly(ethylene glycol) *600* was heated at 80° under vacuum for 30 min before use to remove traces of moisture. Yields refer to isolated crude products. TLC: $SiO_2$ *Polygram-SIL-G/UV$_{254}$* plates. NMR Spectra: *Bruker-Advance-DPX-400* spectrometer; in $CDCl_3$.

*Poly(ethylene glycol) Monochloride* (*=α-(2-Chloroethyl)-ω-hydroxypoly(oxyethane-1,2-diyl)*; HO–PEG–Cl) [7]. To a soln. of poly(ethylene glycol) *600* (30 g, 0.1 mol OH) and pyridine (7.9 g, 0.1 mol) in toluene (500 ml), thionyl chloride (8 g, 0.07 mol) was slowly added with stirring within

30 min. The mixture was then refluxed for *ca.* 6 h. After cooling and filtering off the pyridine hydrochloride salt, the solvent was evaporated. The residue was dissolved in $CH_2Cl_2$ and treated with activated alumina. The process was repeated twice. The $CH_2Cl_2$ soln. was filtered and concentrated: HO–PEG–Cl (28 g, 90%).

*Poly(ethylene glycol) Monobromide* (*=α-(Bromoethyl)-ω-hydroxypoly(oxethane-1,2-diyl)*; HO–PEG–Br) [7]. A mixture of HO–PEG–Cl (28 g, 45 mmol) and sodium bromide (15.5 g, 150 mmol) was heated in an oil bath at 120° overnight. After cooling, $CH_2Cl_2$ (20 ml) was added, the soln. filtered, and the solvent evaporated: HO–PEG–Br (26 g, 87%).

*Silica Chloride* (*=Chloropolyhydroxypolysiloxyne*) [8]. To the dried activated $SiO_2$ (20 g) was added dropwise freshly distilled $SOCl_2$ (45 ml) under $N_2$ at r.t. Evolution of copious amounts of HCl and $SO_2$ occurred instantaneously. After stirring for another 4 h, the excess unreacted thionyl chloride was distilled off and the resulting grayish silica chloride was flame dried, stored in an air-tight container, and used as such for the reactions.

*Silica-Bound Poly(ethylene glycol) Monobromide (=α-(Bromoethyl-ω-[(polyhydroxypolysiloxanyl]oxy)poly(oxyethane-1,2-diyl);* $SiO_2$–PEG–Br). To a well-stirred mixture of silica chloride (11 g) and dry $CH_2Cl_2$ (40 ml) was added dropwise HO–PEG–Br (5 g) under $N_2$ at r.t. HCl was instantaneously evoluted. After stirring for another 3 h, the obtained $SiO_2$–PEG–Br was removed by filtration, and the product was washed several times by acetone (3 × 20 ml) and dried.

*Silica-Bound 3-{2-[Poly(ethylene glycol)]ethyl}-Substituted 1-Methyl-1*H*-imidazol-3-ium Bromide (=α-[2-(1-Methyl-1*H*-imidazol-3-ium-3-yl)ethyl]-ω-[(polyhydroxypolysiloxanyl)oxy]poly(oxyethane-1,2-diyl) Bromide (1:1);* $SiO_2$–PEG–ImBr). A mixture of $SiO_2$–PEG–Br (14 g) and 1-methyl-1*H*-imidazole (8.2 g, 0.1 mol) was heated with stirring at 80° in an oil bath for 48 h. The inorganic–organic graft copolymer $SiO_2$–PEG–ImBr was washed with $Et_2O$ (20 ml) and then with MeCN (20 ml) and dried.

*β-Hydroxynitriles: General Procedure.* A mixture of $SiO_2$–PEG–ImBr (0.2 g), oxirane (1 mmol), sodium cyanide (2 mmol, 0.98 g) and $H_2O$ (5 ml) was stirred at 90° (TLC (hexane/AcOEt 5:1) monitoring). After completion of the reaction, the catalyst was recovered for reuse by filtration, and the product was extracted with $Et_2O$ (3 × 10 ml). The extract was dried ($CaCl_2$) and concentrated: *β*-hydroxynitrile (70–98%).

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