# Alkene epoxidation with a polystyrene immobilised metal salen catalyst in a continuous-flow microfluidic reactor

Cite as: J. Appl. Phys. **105**, 102007 (2009); https://doi.org/10.1063/1.3116084
Submitted: 18 March 2008 . Accepted: 11 September 2008 . Published Online: 19 May 2009

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# Alkene epoxidation with a polystyrene immobilised metal salen catalyst in a continuous-flow microfluidic reactor

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(Received 18 March 2008; accepted 11 September 2008; published online 19 May 2009)

The epoxidation of styrene using a modularly constructed polymer immobilized Mn(III)-salen catalyst has been demonstrated within a continuous-flow glass fabricated microfluidic reactor. © *2009 American Institute of Physics*. [DOI: 10.1063/1.3116084]

## I. INTRODUCTION

In the early 1990s Zhang *et al.*[1] reported the synthesis of a chiral Mn(III)-salen complex and demonstrated its efficiency for enantioselective epoxidation of unfunctionalized olefins. This was of particular importance because previous systems had required functionalization close to the alkene, which was not always possible. The generality of Jacobsen's catalyst has led to wide exploitation within the field of natural product synthesis. Since that time there has been significant development of metallated salen catalysts with a wide range of reactivities.[2] Industrially, the importance of such enantioselective catalysts stems from their ability to produce chiral synthetic intermediates such as epoxides. These are increasingly used in the production of chiral pharmaceuticals and remove the need for tedious enantiomeric separations. However, homogeneous organometallic catalysts do have the disadvantages of being very expensive and notoriously difficult to separate from reaction solutions. An interesting solution to both these problems involves the immobilization of homogeneous organometallic catalysts onto insoluble supports.[3] Such an approach allows the benefits of heterogeneous catalysis to be utilized within homogeneous systems and indeed has been used with metal salen catalytic systems.[4]

The immobilization of homogeneous organic catalysts by attachment to insoluble polymeric supports is the most popular method of heterogenization.[5] Polymer supported metallated salen catalysts can be synthesized by either the formation of a covalent bond between the salen ligand and a commercially purchased resin bead or the copolymerization of salen compounds with accessible vinylic groups with other vinylic monomers. Recently both these methods have been applied to metallated salen catalysts demonstrating reactivity for both the asymmetric epoxidation of alkenes[6–8] and hydrolytic kinetic resolution of epoxides.[9] This immobilization of homogeneous organometallic catalysts is advantageous since it allows a more facile isolation of the catalyst, simplifying product purification and catalyst recycling procedures. Immobilization also creates a potential for the catalyst to be used in continuous-flow processes. Continuous-flow processes are mostly associated with large scale production; however, developments in the recently expanding field of microfluidics suggest the possibility of using continuous-flow microfluidic reactors to improve the efficiency of biphasic catalyst systems.

Recent interest in microfluidic technologies has led to an increase in their use in a wide range of synthetic applications.[10–12] Microfluidic reactors can be defined as miniaturized reaction systems with internal structural dimensions most conveniently measured in microns. The reduced dimensions (with respect to conventional reactors) provide a direct route in improving the speed, efficiency, and control of synthetic processes through enhancements in mass and thermal transport. This control can lead to more efficient and specific production of condition-sensitive products such as nanoparticles[13] or to intrinsically safe reaction conditions.[14] In addition, a key feature of microfluidic systems is a dramatic increase in associated surface area-to-volume ratios which directly results from their decrease in physical size. Specific surfaces of microstructured devices can be as high as 50 000 $m^2\ m^{-3}$ which compares favorably with values for macroscale environments which usually do not exceed 1000 $m^2\ m^{-3}$. Such high surface area-to-volume ratios are not only effective at thermal control but also have been shown to accelerate multiphase reactions.[15–17] Microfluidic devices have also been used to increase the throughput of combinatorial library generation;[18] however, the use of microfluidic systems to screen catalytic systems for activity is an area that has heretofore been neglected.

One of the difficulties in comparing batch processes to continuous-flow processes comes in assessing the relative rate of product formation within the reaction system. The convention most normally used for comparison is the space-time yield, which in its simplest form is the amount of product produced (in percent of the maximum theoretical yield) divided by the reaction time and is commonly expressed in $\%\ s^{-1}$.

This is a direct measurement of the reaction rate rather than the reaction kinetics *per se*, the assumption being normally made that the intrinsic kinetics of bulk reaction hold good on the microscale.

Herein we describe the copolymerization of a styrene

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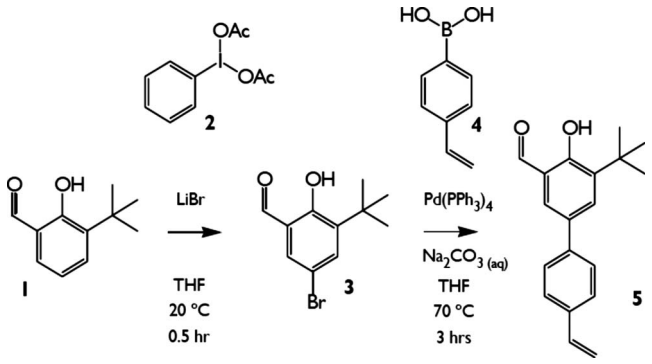


FIG. Scheme1. Synthesis of functionalized comonomer 5.

functionalized salicaldehyde within glass microfluidic channels and a series of surface modification reactions to generate a metal salen catalyst within a microchannel reactor.

The most suitable approach to immobilize the metal salen catalyst on a polymer within a microchannel is to copolymerize a functional monomer within a standard polystyrene polymerization procedure, while incorporating a siloxane monomer unit into the copolymer.[19] This guarantees that the catalyst is immobilized on the polymer via a robust covalent bond. To this end we sought to synthesize the salicylaldehyde functionalized monomer unit 5.

## II. RESULTS AND DISCUSSION

The monomer 5 was synthesized by the coupling of a styrene functionality to a salicaldehyde functionality. These functionalities allow the copolymerization with styrene and a modular construction of a salen ligand. A rapid and mild bromination reaction[20] was applied to the substrate 3-*t*-butyl-2-hydroxybenzaldehyde 1 selectively brominating in the para-position. The styrene functionality was then introduced by coupling the brominated product 3 under Suzuki conditions with 4-vinylboronic acid 4, producing the desired comonomer 5 (see Scheme 1). The synthesis proceeded with a good yield over the two stages of 50%.

The derivatization techniques (Scheme 2) used in the current studies were based on a general strategy previously developed within our laboratories.[19] Adaptation of this approach involved the inclusion of the salicaldehyde functionalized monomer 5 which was insoluble in decamethylpentasiloxane. Consequently, a mixed solvent system

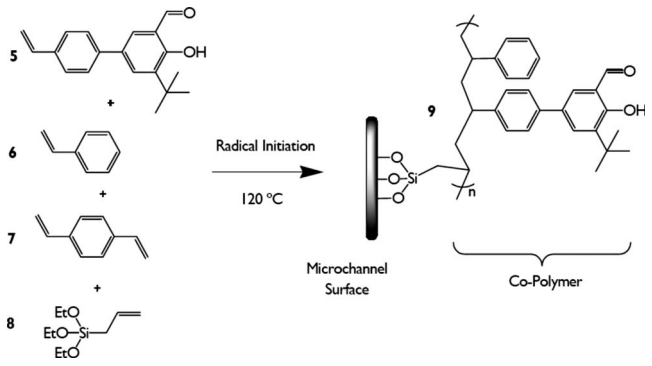


FIG. Scheme2. Derivatization of microfluidic channel surface.

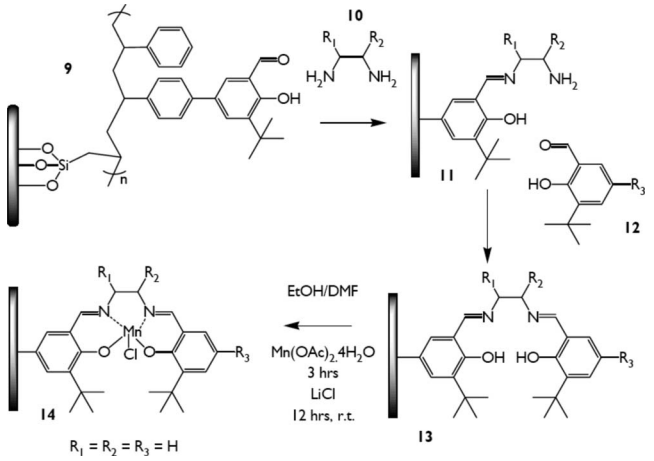


FIG. Scheme3. Modular surface modification generating metal salen catalyst immobilized on polystyrene support within the microchannel reactor.

(decamethylpentasiloxane 4:1 xylene) was found to retain the high boiling point and low polarity essential for an even surface coating.

The amount of functional monomer included within the copolymer mixture was 12 mol %; a level of loading that affords a good density of catalyst on the surface for reactivity while ensuring that the active centers are well dispersed and thus prevent the formation of catalytically inactive bridging oxodimers. The cleaned and dried microfluidic channels were filled with the copolymer and left for 10 min at room temperature. Thermal polymerization *in situ* produced a thin cohesive layer of polymer on the chip wall.

With the salicaldehyde functionality immobilized on the microchannel surface 9, it was then necessary to construct the salen ligand by the sequential condensation of ethylenediamine 10 and 3-*t*-butyl-2-hydroxybenzaldehyde 12. Imine formation reactions were assessed by monitoring a beige to strong yellow color change. The synthesis of the catalytic polymer was assessed using infrared spectroscopy and observing imine bond formation through the disappearance of the salicaldehyde C=O stretch (1651 $cm^{-1}$) and the appearance of the imine C=N stretch (1632 $cm^{-1}$). Subsequently, metallation with manganese acetate and LiCl solutions completed the generation of the polymer immobilized metal salen catalyst 14 (Scheme 3). The reactivity explored in the current studies focuses on demonstrating the activity of a polymer immobilized metal salen epoxidation catalyst within a continuous-flow microreactor, with catalyst 14 having R1, R2, and R3 as protons. However, it is important to realize that the modular ligand construction shown in Scheme 3 has great potential for introducing combinatorial variation in the functionality and stereochemistry of the groups R1, R2, and R3.

Epoxidation reactions were performed using the low temperature epoxidation technique reported by Palucki *et al.* (Scheme 4).[21] Although meta chloroperoxybenzoic acid (mCPBA) gradually epoxidizes styrene, under these conditions the presence of excess methylmorpholine-N-oxide (NMO) completely shuts this mechanism down with no detectable background reaction in the absence of a catalyst. The epoxide is then formed from the alkene via the metal center,

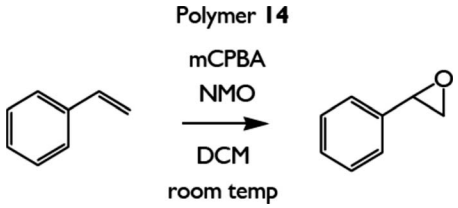


FIG. Scheme4. Epoxidation conditions adapted for immobilized metal salen catalyst from Jacobsen's low temperature epoxidation technique (Ref. 14).

allowing the ligand system to impose its stereochemistry onto the product. To prevent a direct reaction of the alkene with the mCPBA in the microfluidic reactor, a solution of styrene containing an excess of NMO was mixed with the mCPBA solution in a separate microfluidic reactor. This was connected in series with the microfluidic reactor functionalized by the metal salen containing polymer. Control reactions using these solutions and a microfluidic reactor coated with unfunctionalized polystyrene resulted in no epoxidation.

Flowing the reaction solution through a microfluidic reactor coated with a polymer containing the Mn(III)salen catalyst 14 showed epoxide formation with a yield of 36%. With a total reaction volume of 2.1 $\mu$l at a total flow rate of 20 $\mu$l min$^{-1}$, the reactor generates an average residence time of 6.3 s and thus yields a space-time yield of 5.7% s$^{-1}$. This is a significant improvement on laboratory scale reactions using the same polymer immobilized catalyst, which exhibits space-time yields of 0.03% s$^{-1}$. It is likely that the improvement in space-time yield is due largely to the improved contact between reactants and catalytic surface rather than by a modification of the reaction mechanism. The large surface area to volume ratio ensures that every reactant molecule will encounter the catalyst surface at least twice within a normal transit of the reactor.

In conclusion, a polymer immobilized Mn(III)-salen epoxidation catalyst has been modularly constructed within a continuous-flow microfluidic system. Achievable reaction yields were similar to those performed within macroscale environments but in dramatically reduced reaction times. Moreover, the modular construction of the salen ligand within microchannel shows exciting potential for the development of parallel microreactors on a monolithic device containing a library of catalysts with applications toward asymmetric catalyst screening (see Fig. 1).

## III. EXPERIMENTAL

### A. Microfluidic device fabrication

Soda lime glass substrates precoated with a positive photoresist (AZ 1518) and a low reflective chromium layer (Nanofilm, Westlake Village, CA) were exposed with the reactor design using a darkfield acetate/emulsion photomask (JD Photo Tools, Lancashire, UK) and an UV lightbox.[22] The photoresist was developed (Microposit EC 351, Shipley Europe Ltd., Coventry, UK) and channels isotropically etched into the substrate to a depth of 50 $\mu$m using a buffered oxide etching solution (20% 7:1 HF/$NH_4F$). External access holes were mechanically drilled, and the remaining photoresist and chromium layers were removed. Enclosed channels were formed by cleaning the substrate and glass coverplate with concentrated sulfuric acid followed by thermal bonding at 600 °C in a furnace (Heraeus Instruments GmbH, Hanau, Germany). The channel was then cleaned with methanol, heated to 60 °C in a drying oven, and flushed with anhydrous nitrogen.

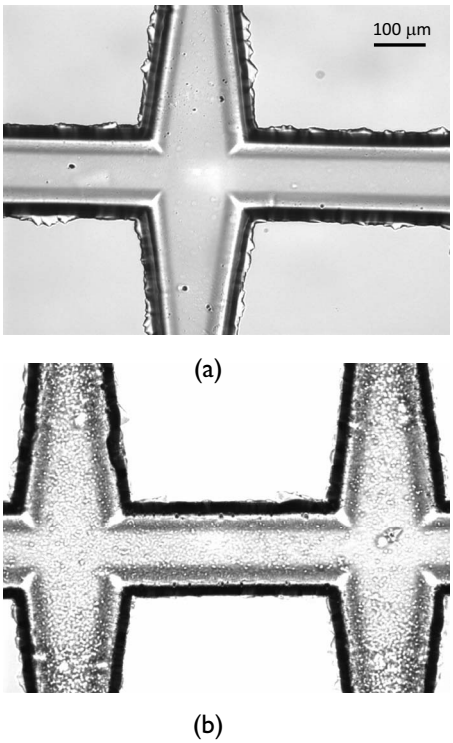


FIG. 1. Photographs of microchannels (a) before and (b) after derivatization.

### B. Monomer synthesis

#### 1. 5-bromo-3-t-butyl-2-hydroxybenzaldehyde (3)

(Diacetoxyiodo)benzene 2 (3.97 g, 12.34 mmol) was added to a solution of 3-*t*-butyl-2-hydroxybenzaldehyde 1 (2.00 g, 11.22 mmol) and lithium bromide (1.07 g, 12.34 mmol) in dry tetrahydrofuran (THF) (20 ml) over a period of 5 min.[20] The suspension was stirred at room temperature for a further 25 min, water (20 ml) was added, and the reaction was extracted with dichloromethane (40 ml). The organic fraction was washed with water (40 ml) and brine (40 ml), dried over $MgSO_4$, and concentrated under reduced pressure. Flash column chromatography (1:19, ethyl acetate:40–60 °C petroleum ether) gave the title compound 3 (2.08 g, 72%) as a yellow crystalline solid; $R_f$=0.40 (1:19, ethyl acetate:40–60 °C petroleum ether); $^1$H NMR (400 MHz; $CDCl_3$) $\delta$ 11.72 (1H, *s*, Ar–OH), 9.81 (1H, *s*, Ar–CO–H), 7.58 (1H, *d*, *J*=2.4 Hz, Ar–H), 7.52 (1H, *d*, *J*=2.4 Hz, Ar–H), 1.41 (9H, *s*, C–$CH_3$); and $^{13}$C NMR (100 MHz; $CDCl_3$) $\delta$ 196.0, 160.2, 141.1, 137.0, 133.6, 121.7, 111.1, 35.1, 29.1; MS ($CI^+$, $CH_4$) *m*/*z* 257 $(M+H)^+$, 259 $(M+H)^+$ (isotopes of bromine-prod mw 256/258).

#### 2. 5-styrene-3-t-butyl-2-hydroxybenzaldehyde (5)

Under nitrogen a solution of 5-bromo-3-*t*-butyl-2-hydroxybenzaldehyde 3 (750 mg, 2.92 mmol), 4-vinyl phe-

nylboronic acid 4 (500 mg, 3.39 mmol), $[Pd(PPh_3)_4]$ (101.6 mg, 0.088 mmol), and $Na_2CO_3$ (2*M*, 3.8 ml, 7.6 mmol) in THF (11.25 ml) was heated under reflux for 3 h.[23] The organic phase was separated and the aqueous layer was extracted twice with diethyl ether (20 ml). The combined organic phases were dried (twice with $MgSO_4$) and concentrated onto silica under reduced pressure. Flash column chromatography (1:19, ethyl acetate:40–60 °C petroleum ether) gave the title compound 5 (565 mg, 69%) as a yellow crystalline solid; $R_f$=0.28 (1:19, ethyl acetate:40–60 °C petroleum ether); $^1$H NMR (400 MHz; $CDCl_3$) $\delta$ 11.80 (1H, *s*, Ar–OH), 9.96 (1H, *s*, Ar–CO–H), 7.77–7.48 (6H, *m*, Ar–H), 6.76 (1H, *dd*, *J*=17.6, 10.9 Hz, Ar–CH=$CH_2$), 5.80 (1H, *d*, *J*=17.6 Hz, Ar–CH=C(H)H, trans coupling), 5.29 (1H, *d*, *J*=10.9 Hz, Ar–CH=C(H)H, cis coupling), 1.51 (1H, *s*, C–$CH_3$); and $^{13}$C NMR (100 MHz; $CDCl_3$) $\delta$ 197.3, 160.7, 139.5, 138.8, 136.6, 136.3, 133.0, 132.0, 129.9, 126.8, 126.7, 120.8, 114.0, 35.1, 29.2; MS ($CI^+$,$NH_3$) *m*/*z* 281 $(M+H)^+$.

### C. Copolymer formation and surface modification

The copolymer solutions were made up as follows: the salicaldehyde functionalized monomer 5 (56 mg, 0.2 eq) was dissolved in a mixture of styrene 6 (111 $\mu$l, 1 eq), divinylbenzene 7 (57 $\mu$l, 0.43 eq), and allyltriethoxysilane 8 (22 $\mu$l, 0.1 eq). Dicyclohexylazo-bis-carbonitrile (24 mg, 0.5 eq) was then dissolved in the mixture. A mixed solvent system of xylene (0.1 ml) followed by decamethylpentasiloxane (0.4 ml) was added. The solution was refrigerated until use and not stored for longer than 4 h. The microfluidic channel was filled with the comonomer solution and left to stand for 10 min at room temperature. Subsequently, the reactor was lowered into an oil bath and heated at 120 °C for 1.5 min before being removed and allowed to cool for 2 min. The channels were then washed with methanol (50 $\mu$l min$^{-1}$ for 10 min) and cyclohexane (50 $\mu$l min$^{-1}$ for 10 min) before being dried under nitrogen.

Hydrodynamic infusion pumps motivated a solution of ethylenediamine 10 (3.0*M* in ethanol) through the microchannel at a rate of 10 $\mu$l min$^{-1}$ over 3 h. After washing, a solution of 3-*t*-butyl-2-hydroxybenzaldehyde 12 (1.2*M* in ethanol) was infused at 2 $\mu$l min$^{-1}$ for a period of 3 h. The chelation of the manganese center was facilitated by a flow of manganese acetate tetrahydrate solution (0.25*M* in dimethylformamide 2:1 ethanol) at 10 $\mu$l min$^{-1}$ for 3 h. The manganese was then oxidized to Mn(III) with a lithium chloride solution (0.5*M* in dimethylformamide 2:1 ethanol) at 2 $\mu$l min$^{-1}$ for 16 h. The microchannel was washed repeatedly with methanol and dichloromethane (to remove excess manganese salts and LiCl) before drying with nitrogen. Between each of these reactions the microchannels were cleaned with 10 min washes of methanol followed by dichloromethane.

### D. Epoxidation reactions

A solution of styrene 6 (21 mg, 1 eq.) in dichloromethane (2.5 ml) containing an excess of NMO (108 mg, 5 eq.) was mixed using a microfluidic mixer with a solution of mCPBA (82.5 mg) in dichloromethane (2.5 ml). The resulting mixture was passed through a microfluidic reactor functionalized by the metal salen containing polymer 14 described above at a volumetric flow rate of 20 $\mu$l min$^{-1}$. The chip effluent was collected over a period of 10 min and analyzed by off-line gas chromatography, showing the presence of styrene oxide (36%, calibrated).

## ACKNOWLEDGMENTS

C.J.C acknowledges GlaxoSmithKline Ltd. for the award of an EPSRC CASE Studentship.

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