Incorporation of Zr(IV) Lewis Acids in Microfluidic Devices for Enantiomeric Separation

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Abstract

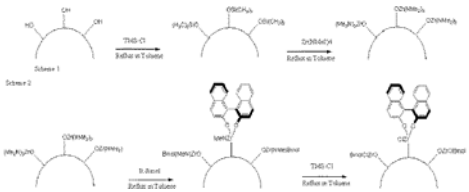
We have found homogeneous Zr (IV) complexes to be active Lewis acid catalysts for the silylcyanation of aldehydes. If the complex is chiral, stereoselectivity may result. Incorporating these support catalysts in a microfluidics device (MD) fabricated from poly(dimethylsiloxane) (PDMS), allows for the separation of minute quantities of enantiomeric material. Herein, we describe a multi-step grafting approach (Scheme 1) utilized to attach Zr metal to the surface of silica gel beginning with a $Zr(N(CH_3)_2)_4$ precursor. Subsequently, R-Bi-2-naphthol was grafted onto the metal silica complex to render it chiral. These compounds were characterized by ^{13}C solid state NMR and FT-IR. These supported chiral complexes catalyze the silylcyanation of benzaldehyde without a change in activity after three runs suggesting minimal leeching. The catalysts were then packed into a MD for the silylcyanation of benzaldehyde.

Introduction

Asymmetric or chiral synthesis introduces one or more new and desired elements of chirality to a molecule. Because the different enantiomers or diastereomers of a molecule often have very different biological activity in an organism, selective chiral synthesis is critical for the pharmaceutical industry. MDs offer the potential for highly efficient, simultaneous analysis of a large number of biologically important molecules including diastereoisomers. Unlike conventional analytical techniques such as HPLC, MDs require small volumes of sample, are inexpensive to fabricate, are portable, provide fast sampling times, and can incorporate multiple laboratory steps (synthesis, separation, and analysis) in a single device. Zr (IV) complexes immobilized on silica gel behave as Lewis acid catalysts for the silylcyanation of aldehydes and, if the complex is chiral, stereoselectivity can result. Incorporating these chiral support catalysts within the channel of a MD allows for both the synthesis and separation of minute quantities of diastereomeric material.

Synthesis and Characterization

A multi-step grafting approach (Schemes 1 and 2) was utilized to functionalize 45 μm diameter silica gel. The MDs consist of PDMS chips prepared by soft lithography. The chosen pattern consisted of a cross-T type channel 50-100 μm wide with a height of 50-60 μm. ^{13}C and FT-IR spectrometry were utilized to monitor the functionalization of the silica gel (Fig. 1 and 2)



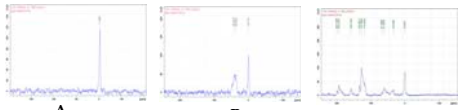


Figure 1. ^{13}C Solid State NMR of modified silica gel (A) TMS modified. (B) $Zr(NMe_2)_4$ modified. (C) R-binol modified.

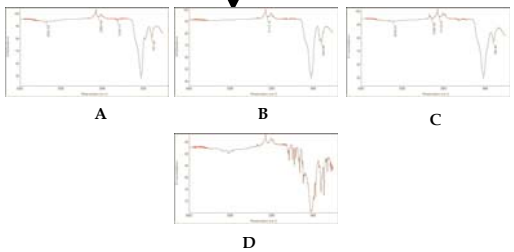


Figure 2. FT–IR of silica gel. (A) Dried Silica gel. (B) TMS modified. (C) $Zr(NMe_2)_4$ modified. (D) R-binol modified

Preparation of PDMS Chip

A 10:1 ratio mixture of PDMS oligomer and cross-linking agent (Sylgard 184) was prepared (Fig. 3). The Si wafer was then cured at 80 °C for 45 or 70 min overnight. After the PDMS replica was peeled off from the mold, holes (2mm diameter) were punched through the PDMS chi to introduce sample. The PDMS was then plasma sealed to a glass substrate. Silica gel was introduced into the chip (Fig. 4) as a slurry in heptane/isopropanol.

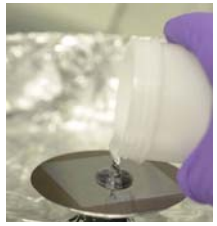


Figure 3. PDMS being poured onto the mold to form chip.

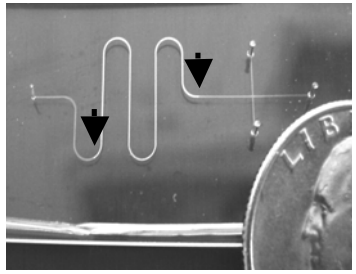


Figure 4. Sample PDMS chip packed with C18 beads compared to a U.S. quarter. Channel length within arrows shows packing of beads.

Results

Previous work utilizing Zr(IV) and Ta(IV) Lewis acid complexes as catalysts have shown that the silylcyanation of benzaldehyde (Fig. 5) is complete In one hour. Initial loading of the similar silica bound catalysts was hampered by the size of the silica gel. Additionally, this reaction occurs in a mixture of dichloromethane/toluene so care must be taken not to prolong the solvent interaction with PDMS otherwise swelling occurs.

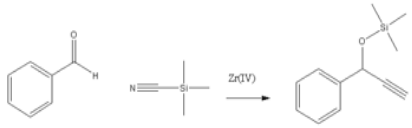


Figure 5. Silylcyanation of benzaldehyde.

Future Work

Further work is focused on utilizing smaller sized silica gel, incorporating PDMS modified surfaces to handle more robust solvent systems, and the use of nitro containing benzaldehyde compounds for possible colorimetric silylcyanation reactions.

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