Polystyrene-Supported Triphenylsilyl Chloride for the Silylation-Based Kinetic Resolution of Secondary Alcohols

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A silyl chloride derivatized styrene polymer was employed in the silylation-based kinetic resolution of secondary alcohols for chromatography-free separation of alcohol enantiomers. Synthetically useful selectivity factors were obtained; furthermore, the polymer was recycled for use in a subsequent kinetic resolution, and it maintained its selectivity and integrity.

The formation or isolation of enantiopure compounds is an important endeavor that is accomplished through a variety of methods, including resolutions.^[1] In particular, kinetic resolutions^[2] play an important role in the chemical and pharmaceutical industries, because enantiomerically pure compounds can always be obtained by controlling the conversion of a reaction. Kinetic resolution is the separation of enantiomers by performing an asymmetric reaction preferentially on one enantiomer over the other enantiomer (Scheme 1 a) on the basis of a difference in reaction rates. A common strategy is to derivatize one



Scheme 1. The difference between a classical kinetic resolution (a) and a kinetic resolution that employs a polymer (b–d).

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of the enantiomers with a protecting group; for example, the esterification^[3] and silylation^[4] of an alcohol. One drawback to some kinetic resolutions is the ultimate separation process of the derivatized enantiomer from the unreacted starting material, which is usually done through column chromatography. Herein, we report a polymer-supported silyl chloride that can be employed in the silvlation-based kinetic resolution of alcohols. One alcohol enantiomer reacts selectively with the polymeric silyl chloride to form a silyl ether derivatized polymer, which is precipitated from the reaction. The silvlated polymer product is then separated by filtration, which allows chromatography-free isolation of the unreacted starting material. Synthetically useful selectivities^[5] were obtained with a number of substrates, and the polymer was recovered, chlorinated, and reused without degradation or loss in selectivity of the kinetic resolution.

Even though kinetic resolutions are valuable processes, one major hurdle preventing broader utilization at the industrial scale is the need for chromatography to separate the products from the unreacted starting materials. Solid-supported catalysis has been around for many decades, but the majority of examples involve a catalyst or a reagent such as an oxidant or reductant attached to a solid support.^[6] For kinetic resolution, it would be beneficial to bind one enantiomer to a solid support, so that it can be easily removed from the solution through filtration versus needing to employ column chromatography. There have been a few examples involving the use of solid supports in kinetic resolutions, which can be categorized as the following: the polymerization of one enantiomer from a racemic mixture to form an enantioenriched polymer (Scheme 1 b),^[7] the removal of one enantiomer from a polymer derivatized with a racemic substrate (Scheme 1 c),^[8] and the selective attachment of one enantiomer to a polymer (Scheme 1 d).^[9] All of these methods allow the precipitation and easy removal of the polymer-bound enantiomer from the unreacted enantiomer after completion of the reaction. Whereas polymerization of one enantiomer from a racemic mixture (Scheme 1 b) has been accomplished successfully with smallmolecule catalysts, the other scenarios (Scheme 1 c, d) have had limited success with non-enzymatic catalysts. To the best of our knowledge, the work described herein is one of the few successful examples of the selective attachment of one enantiomer to a polymer through small-molecule catalyzed kinetic resolution.

Asymmetric silylation^[4] is a valuable alternative to other kinetic resolution methods, and work in this area has included the kinetic resolution of alcohols, the regiodivergent resolution



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of alcohols, and the desymmetrization of *meso*-diols.^[10] Our own work in this area has focused on the silylation-based kinetic resolution of cyclic secondary alcohols,^[11] α -hydroxy lactams, and α -hydroxy lactones with selectivity factors (*s*) up to 100 (Scheme 2).^[12] These reactions are performed with the use



Scheme 2. Silylation-based kinetic resolution developed by the Wiskur group.

of chiral isothiourea catalysts such as tetramisole (1) and benzotetramisole (2),^[13] and triphenylsilyl chloride is used as the silyl source to resolve the alcohols, with the phenyl groups on the silicon proving to be important in obtaining selectivity.^[11] In one of our previous studies, substitution of triphenylsilyl chloride with sterically large alkyl groups in the *para* position actually enhanced selectivity;^[14] therefore, we hypothesized that our methodology would retain selectivity if a polymeric version of triphenylsilyl chloride was employed. Our experimental design would include a relatively low molecular weight polystyrene silyl chloride, so that it would be homogeneous during the reaction. Upon completion of the reaction, the polymer-derivatized product would be precipitated from solution by the addition of methanol for chromatography-free separation of the two enantiomers (Scheme 3).



Scheme 3. Polystyrene-supported silyl chloride for facile product separation.

A polystyrene-supported triphenylsilyl chloride was synthesized in three different lengths to test the effect of polymer molecular weight on selectivity in the silylation-based kinetic resolution. The synthesis of the polymer started with lithiumhalogen exchange of commercially available *para*-bromostyrene (**3**), which was treated with diphenylchlorosilane to gener-



Scheme 4. Synthesis of polymer-supported silyl chloride.

ate silane monomer **4** (Scheme 4).^[15] Three different molecular weight polymers (see compound **6**) were generated through nitroxide-mediated radical polymerization with universal initiator **5**.^[16] The number-average molecular weights (M_n) of silane polymers **6** were calculated from the crude reaction conversions (¹H NMR spectroscopy) and ranged from 4000 to 7500 g mol⁻¹ (Table 1) depending on the amount of initiator



employed. This equated to 13 to 25 repeating units of monomer **4**, respectively. These relatively low molecular weights were designed to facilitate solubility of the polymers in the reaction mixture. The dispersity (D) of the polymers was approximately 1.2–1.3 for all three polymers. Other methods of polymerization generated much higher dispersities, presumably owing to the poor reactivity of the bulky monomer. Finally, these polymers were chlorinated through radical chlorination with sulfuryl chloride^[17] to generate **7**.

The kinetic resolution of (\pm) -**8** was performed with the three different molecular weight silvl chloride polymers (i.e., compound **7**; n = 13, 20, and 25) by using standard reaction condi-



tions developed for our previous work on kinetic resolutions with triphenylsilyl chloride and catalyst 1 (Table 1, entries 1-3). These polymers were soluble at $-78\,^\circ\text{C}$ in THF at the reaction concentration, which fulfilled our requirement for a homogeneous silyl chloride source. Upon reaction completion, the polymer product, enantioenriched silyl ether 9, was isolated by removal of the reaction solvent, followed by precipitation with methanol. The solid polymer products were then isolated by either centrifugation or filtration. Ultimately, the polymer length had little effect on the selectivity of the kinetic resolution, and selectivity factors ranging between 6 to 9 for the three polymers were observed. The higher molecular weight polymer ($M_n = 7580 \text{ g mol}^{-1}$, n = 25) was ultimately chosen for further studies, owing to the increased efficiency of polymer precipitation over the shorter polymers. Ultimately, the selectivity of the polymer-supported reactions decreased relative to that of the unsupported silvl chloride (Ph₃SiCl; Table 1, entry 4). This is presumably due to the different polar environments of the silyl chloride in the polymer versus in solution.[19] The microenvironment of the polymer would provide a less polar environment for the silylation reaction, similar to employing nonpolar solvents, which has been shown to dramatically affect both the conversion and the selectivity of the kinetic resolution.^[11] The slower diffusion of the larger polymer silyl chloride versus Ph₃SiCl could additionally affect the conversion, such that additional equivalents of silyl chloride would be needed if the polymer were employed so that a conversion similar to that obtained with the use of Ph_3SiCI could be achieved (0.8 vs. 0.6 equiv., respectively).

Substrates that were successfully employed in previous silylation-based kinetic resolutions were resolved by utilizing silyl chloride polymer **7**. Two cyclic secondary alcohols (Table 2, entries 1 and 2) and two α -hydroxy lactones (Table 2, entries 3 and 4) were resolved by employing **1** and **2** as the catalysts, respectively. Overall, the substrates resulted in synthetically useful selectivities, ranging from 8 to 16. Although these selectivities are lower than those obtained with triphenylsilyl chloride (Table 2, last column),^[11,12] as discussed above, the results show that efficient resolution is possible with this polymerbound reagent. To the best of our knowledge, this is the most efficient polymer-supported kinetic resolution with the use of a small-molecule catalyst.

Additionally, the need for chromatography was eliminated by use of the silyl chloride polymer. After performing an acid wash to remove the catalyst and amine base, the enantiomers were effectively separated by dissolving the mixture in methanol and filtering off the insoluble polymer-bound silyl ether product. The recovered, unreacted alcohol in the filtrate was generally pure enough to use in further syntheses, if desired. The other enantiomer was cleanly obtained after the silyl ether polymer was treated with tetrabutylammonium fluoride and removal of the silane polymer by precipitation. Even though multiple cycles of precipitation were needed to effectively recover the relatively short polymer (n=25), on large scale this could be more advantageous than methodology employing Ph₃SiCl, which requires two columns to isolate both enantiomers.



[a] Reactions were run at a concentration of 0.2 M (entries 1 and 2) and 0.4 M (entries 3 and 4) with respect to the alcohol for 48 h. [b] See ref. [18]. [c] Employed **7** (1 equiv.) and *i*Pr₂NEt for 94 h. [d] Data was taken from ref. [14] (entry 1), ref. [11] (entry 2, *i*Pr₂NCHEt₂ instead of *i*Pr₂NEt), and ref. [12] (entries 3 and 4); Ph₃SiCl was employed as the silyl source. See references for full experimental details.

To show the recyclability of silyl chloride polymer 7, it was employed in a preparative-scale run with the intention of recovering the polymer, and it was then used in a second kinetic resolution (Scheme 5). The reaction was run under standard reaction conditions by using (\pm) -8 (0.6 g) and 7 (1 g). The selectivity factor for the first run was 6.5, which is only a minor reduction relative to the selectivity of previous smaller scale runs. The polymer product was isolated, and the derivatized alcohol was desilylated by reduction with lithium aluminum hy-



Scheme 5. Recycling of silyl chloride polymer in a subsequent kinetic resolution. [a] See ref. [18]. [b] Kinetic resolutions were run at a concentration of $0.15 \,\text{m}$ with respect to the alcohol.



dride at room temperature to obtain the silane and the alcohol. Lithium aluminum hydride was employed over tetrabutylammonium fluoride for removal of the alcohol to generate the silane polymer instead of the fluorinated silane. The silane was again chlorinated and subjected to a second kinetic resolution, which resulted in a selectivity factor that was comparable to that of the first run (s = 8.6). The dispersity of the recovered silanes (after each kinetic resolution) was identical to that of original silane **6**, which shows that the polymer does not degrade during the kinetic resolution or reduction (see the Supporting Information). This highlights the ability of the polymer to be recycled without degradation while maintaining the selectivity of the reaction, which is an important aspect towards reducing waste and cost.

In conclusion, polystyrene-supported triphenylsilyl chloride was employed in a silylation-based kinetic resolution for the facile separation of alcohol enantiomers. Whereas this technique has been applied to enzyme-catalyzed kinetic resolutions, to the best of our knowledge this is one of the first selective small-molecule-catalyzed versions. Cyclic secondary alcohols and α -hydroxy lactones were resolved with selectivity factors ranging from 8 to 16, which shows the viability of this approach. The enantiomers were separated by simple filtration of the derivatized polymers, and the polymers were recycled by reducing the silyl ether and re-chlorinating the silicon without loss of selectivity or polymer degradation. Future work will be focused on optimization of the polymer support for the silyl chloride to improve polymer recovery and selectivities.

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