A Sequential Application of Kinetic Resolution and Polymer-Supported Scavenging for the Isolation of Chiral Secondary Alcohols

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Received May 24, 2001

Introduction

The preparation of enantiomerically pure or enantioenriched organic compounds is of great importance.[1] As such, the development of chemical and biochemical catalysts for both enantioselective synthesis and the kinetic resolution of racemates has advanced at an accelerated pace.[2−4] In particular, kinetic resolution is important in asymmetric synthesis since it provides both enantiomers of a compound. Developments in the areas of combinatorial chemistry, catalytic antibodies, site-directed mutagenesis, and directed evolution of biocatalysts have fueled the discovery and optimization of both chemical and biological catalysts.[5,6] As powerful as these technologies have become, the catalyst discovery process still faces a bottleneck centered around the analysis and processing of both catalyst selectivity and activity.[7] In the case of kinetic resolution, the products need to be separated to enable analysis of catalyst activity and selectivity. Therefore, techniques that facilitate the separation of kinetic resolution products without the need for column chromatography are highly desirable.

The preparation of chiral *sec*-alcohols by catalytic processes is a very active area of research because of their importance as building blocks in asymmetric synthesis.[2c] Kinetic resolution can be performed whereby a racemic mixture of *sec*-alcohols is transformed into optically active products (e.g., an ester and remaining alcohol) that can be separated typically by column chromatography. To circumvent the need for time-consuming column chromatography, esterification of *sec*-alcohols with succinic anhydride followed by an acid−base extraction has been reported.[8] This principle has also been extended to the conversion of alcohols to sulfate esters.[9] It should be noted that while these two methods are important, their scope is limited to large-scale reactions. Furthermore, their generality is hampered by the choice of effective acylating agents. A soluble polymer scavenging approach of a racemic trifluoroethyl carbonate through lipase-catalyzed transesterification with poly(ethylene glycol) (PEG) has also been reported.[10] However, this methodology also presents several limitations. First, a unique catalyst accepting PEG is needed. Second, an elaborate synthetic scheme to form each activated carbonate is required for each new acyl donor. More recently, Vedejs has reported a parallel kinetic resolution performed under triphasic conditions.[11] During this process, one of the enantiomers reacts with a polymer-supported reagent enabling separation of the enantiomers by filtration. To complement these existing technologies, we present a method to separate the products from the kinetic resolution of *sec*-alcohols.

Results and Discussion

Our strategy features a simple two-step procedure that combines both kinetic resolution and separation of the products using a solid-phase scavenging or "fishing out" procedure (Scheme 1).[12] The strength of our method is that the kinetic resolution can be performed with either a polymer-supported enzyme or a polymer-supported chemical catalyst.[13,14] Thus, after removal of the catalyst from the kinetically resolved mixture by filtration, the

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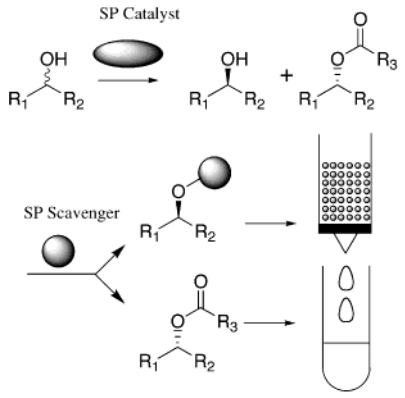
10.1021/jo010529u CCC: $20.00
Published on Web 07/11/2001

Scheme 1. General Strategy for Isolating *sec*-Alcohols



products obtained may be conveniently separated by capture of the remaining alcohol with a suitable scavenging agent. To examine such an approach, a model experiment was performed wherein (*S*)-1-phenylethanol (R_1 = Ph, R_2 = Me, >99% ee) and its corresponding enantiopure (*R*)-acetate (>99% ee) were reacted with a series of resins under standard alcohol loading conditions.[15] Among the functionalized resins examined, polymer-supported benzoyl chloride was found to be the best scavenging resin due to the ease of attachment and subsequent release of the captured (*S*)-**1** alcohol (Scheme 2).[16] Using this resin, all (*S*)-**1** was removed from the reaction mixture within 24 h and the two enantiomers were separated by filtration. The polymer-bound alcohol (*S*)-**1** was released from the resin by hydrolysis in 41% yield and >99% ee. The unbound ester was isolated from the filtrate and hydrolyzed to the corresponding alcohol (*R*)-**1** in 42% yield, >99% ee. Furthermore, no scrambling of the chiral information occurred during the loading of alcohol (*S*)-**1** in the presence of acetate (*R*)-**1a**.

The separation procedure was applied to a series of racemic *sec*-alcohols that were resolved using a polymer-supported lipase[13] (Table 1). Of note, the solid-supported enzyme resolved the *sec*-alcohols and the enantiopreference was in accordance with literature reports (Table 1, entries 1-9).[13,17−19] Both the (*S*)- and (*R*)-enantiomers were isolated in high ee and in greater than 95% purity after the two-step reaction sequence, with yields of ~40% (50% theoretical). This methodology also proved useful with a polymer-supported proline-based chemical catalyst (Table 1, Entry 10), thus showing even greater utility of our method. In this case, the same selectivity value (E = 3) was observed as previously reported.[14] In addition, it was determined (see Experimental Section) that the combination of kinetic resolution with the "fishing out" principle could be used to resolve racemic mixtures of up

(15) The scavenging step was assessed with as follows: (a) Ellman's DHP resin (Novabiochem): Thompson, L. A.; Ellman, J. A. *Tetrahedron Lett.* **1994**, *35*, 9333. (b) Polystyrene diethylsilyl chloride (PS-DES resin, Argonaut Technologies): Hu, Y.; Porco, J. A., Jr.; Labadie, J. W.; Gooding, O. W.; Trost, B. M. *J. Org. Chem.* **1998**, *63*, 4518.

(16) For references on the resin capture or "catch-and-release" principle, see: (a) Keating, T. A.; Armstrong, R. W. *J. Am. Chem. Soc.* **1996**, *118*, 2574. (b) Brown, S. D.; Armstrong, R. W. *J. Am. Chem. Soc.* **1996**, *118*, 6331.

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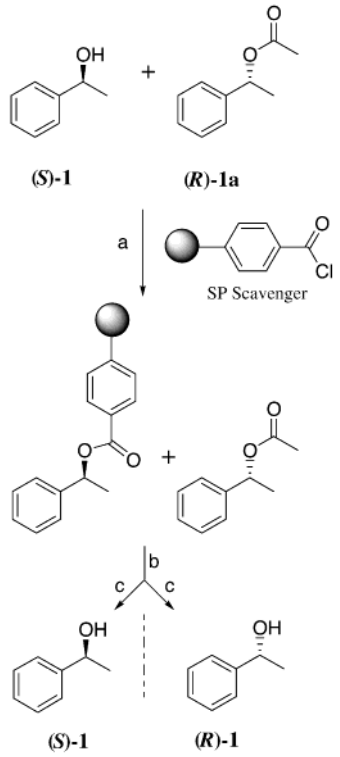
Scheme 2. Separation of the Chiral Alcohol and Ester Using a Solid-Phase Scavenger[a]



[a] Reagents and conditions: (a) Et_3N, catalytic DMAP, CH_2Cl_2; (b) physical separation by filtration; (c) KOH, MeOH.

to 7 mmol (gram-scale of racemic alcohols). Furthermore, the scavenging resin could be recycled by treatment of the polymer-bound carboxylic acid with oxalyl chloride.

Conclusion

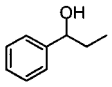
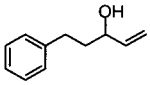
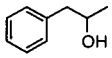
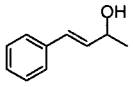
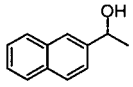
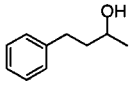
The sequential application of a polymer-supported catalyst and scavenging reagent provides a convenient method for the isolation of chiral *sec*-alcohols. While we have demonstrated this approach with secondary alcohols, we envision that this methodology could be applicable to other nucleophiles, such as secondary amines.[20] Furthermore, because of its simplicity, the entire process could be automated and, thus, utilized in the high-throughput parallel screening of catalysts. Taken in this context, valuable information such as enantiomeric excess, substrate specificity, solvent effects, and temperature dependence for both new and existing catalysts could be quickly amassed.

Experimental Section

General Methods. Reagents were obtained from Sigma-Aldrich Co. (Milwaukee, WI) and were used without purification. Dry solvents (toluene, hexane) were provided in SureSeal bottles and were handled under positive pressure of argon. Other solvents were dried by distillation from sodium benzophenone (THF) or from CaH_2 (CH_2Cl_2). *C. antarctica* lipase B was provided by Novo Nordisk A/S, Denmark. High loading carboxypolystyrene was purchased from Novabiochem Inc. (San Diego, CA). Depending on the scale, polymer-assisted reactions were conducted in either a scintillation vial or a peptide flask (Chemglass Inc., Vineland, NJ) and agitation was provided by

(20) (a) Koeller, K. M.; Wong, C.-H. *Nature* **2001**, *409*, 232. (b) Takayama, S.; Lee, S. T.; Hung, S.-C.; Wong, C.-H. *Chem. Commun.* **1999**, 127.

Table 1. Enantioselectivity of *Candida antarctica* Lipase B and the Polymer-Supported Proline-Based Catalyst Determined after the "Fishing out" Step and Cleavage from the Polymer Support

Entry	Structure	catalyst	f.e.[a]	c (%)[b]	ee_s (%)[c]	ee_p (%)[d]	E[e]
1		CALB	*R*-(+)	50	99	99	> 500
2		CALB	*R*-(-)	45	78	94	75
3		CALB	*R*-(-)	50	94	93	94
4		CALB	*S*-(-)	52	97	88	59
5		CALB	*R*-(-)	50	99	98	> 200
6		CALB	*R*-(+)	49	97	99	> 200
7		CALB	*R*-(+)	51	97	95	> 200
8		CALB	*R*-(+)	51	98	93	114
9		CALB	*R*-(-)	51	97	93	116
10		SP-Proline[f]	*R*-(-)	56	43	34	3[f]

[a] Fast reacting enantiomer. The absolute configuration was based on optical rotation, which were in accordance with those in the literature.[13,14,17] [b] $c = ee_s/(ee_s + ee_p)$.[18,19] [c] Determined by chiral HPLC on a Chiracel OD-H column (hexane/2-propanol mixtures, λ = 254 nm) after cleavage from the resin. [d] Determined on the alcohol corresponding to the acetate formed, by chiral HPLC on a Chiracel OD-H column. [e] $E = \ln[(1 - ee_s)/(1 + ee_s/ee_p)]/\ln[(1 + ee_s)/(1 + ee_s/ee_p)]$.[18,19] [f] See ref 14.

either a 360° LabQuake shaker (Barnstead/Thermolyne) or a 180° wrist-action shaker (MilliGen, Bedford, MA). Optical purities were determined by HPLC using a Chiracel OD-H column (hexane/ 2-propanol mixtures, λ = 254 nm). The structural integrity of the compounds (Table 1, entries 1−10) and their esters was determined by ^{1}H NMR (400 MHz) and compared with the literature.[13,14,17]

Preparation of the Polymer-Bound Benzoyl Chloride. The benzoyl chloride scavenging resin was synthesized according to the procedure of Hodge and co-workers[21] and was used shortly after its preparation.

Enzymatic Kinetic Resolution and Scavenging Procedure in a Parallel Format. The *sec*-alcohols (0.5 mmol) were added to dry vials containing *C. antarctica* lipase B (10 mg) and dry toluene (3 mL) was added. Vinyl acetate (1.5 mmol) was added, and the vials were shaken (200 rpm) at room temperature. After ~50% conversion (estimated by TLC), the lipase was removed by filtration and washed with CH_2Cl_2. The solvent and excess vinyl acetate were removed in vacuo. The conversion and complete removal of the acylating agent were verified by ^{1}H NMR. The mixture was then dissolved in CH_2Cl_2 (2 mL) and added to vials containing polymer-bound benzoyl chloride (2.3 equiv, acid chloride ~1 mmol/g), Et_3N (2 mmol), and catalytic DMAP in CH_2Cl_2 (2 mL). The vials were rotated for 16−24 h at room temperature while the removal of the alcohol from the reaction mixture was monitored by TLC. After complete scavenging, the resin was isolated by filtration and washed with CH_2Cl_2. The filtrate was diluted with excess ether, washed with 1 N HCl, dried ($MgSO_4$), and concentrated in vacuo to give the pure acetate esters. The esters were then cleaved by hydrolysis according to Orrenius et al.,[13] and the ee and purity of the corresponding alcohols were determined by chiral HPLC.[13,14,17] The remaining resin, containing the other enantiomer, was further washed with CH_2Cl_2, THF, and hexane. Thereafter, this resin was added to vials containing THF (2 mL) and a 2.5% (w/v) KOH/methanol solution (2 mL). The release of alcohol was monitored by TLC and was complete within 12 h. The resin was separated by filtration and washed with ether. The ether filtrate was washed with 1 N HCl, and the alcohols were isolated and analyzed as previously described.

Kinetic Resolution with a Chemical Catalyst and Scavenging Procedure. The kinetic resolution by the polymer-supported chemical catalyst was performed according to our previous work,[14] and the scavenging procedure was the same as for the enzyme catalyst (vide supra).

Preparative-Scale Reaction. The racemic mixture of 1-phenylethanol (870 mg; 7.13 mmol) was added to a dry vial containing *C. antarctica* lipase B (200 mg), and then dry CH_2Cl_2 (5 mL) was added. Vinyl acetate (723 μL; 7.8 mmol) was

(21) Hodge, P.; Kemp, J.; Khoshdel, E.; Perry, G. M. *React. Polym.* **1985**, *3*, 299.

added and the vial was shaken (200 rpm) at room temperature. After ~50% conversion (24 h), the lipase was removed by filtration and washed with CH_2Cl_2. The solvent and excess vinyl acetate were removed in vacuo. The conversion and complete removal of the acylating agent were verified by ^1H NMR. The mixture (1.0 g; 3.5 mmol alcohol) was then dissolved in dry CH_2Cl_2 (10 mL) and added to a peptide flask containing swollen polymer-bound benzoyl chloride (7 g; ~1 mmol Cl/g) in 40 mL of dry CH_2Cl_2 with Et_3N (2 mL; 14 mmol) and catalytic DMAP (243 mg; 0.04 M final concentration). The peptide flask was agitated at room temperature until the alcohol was completely removed from the reaction mixture. After complete scavenging (~24 h), the resin was isolated by filtration and washed with CH_2Cl_2 (2 × 20 mL). The filtrate was washed with 1 N HCl, dried (Na_2SO_4), and concentrated in vacuo to give 423 mg of the pure acetate ester. The resin was further washed with THF (4 × 20 mL) and hexane (3 × 30 mL) and then dried under high vacuum. The hydrolysis of both esters was performed as described above to generate, in two distinct vials, 273 mg (32% overall) of (*R*)-1-phenylethanol (96% ee) ((*R*)-**1**) and 292 mg (34% overall) of (*S*)-1-phenylethanol (>99% ee) ((*S*)-**1**).

Acknowledgment. We gratefully acknowledge the financial support of the National Institutes of Health (Grant GM-56154), The Scripps Research Institute, and The Skaggs Institute for Chemical Biology. A.C. is a Skaggs postdoctoral fellow and acknowledges a fellowship from the Wennergren Foundations, Sweden. M.R.T. is a Skaggs postdoctoral fellow and acknowledges a fellowship from the Natural Science and Engineering Research Council of Canada. B.C. is a Skaggs postdoctoral fellow. The provision of enzyme by Novo Nordisk A/S, Denmark is also gratefully acknowledged.

JO010529U