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Obtaining Enriched Compounds via a Tandem Enantioselective Reaction and Kinetic Resolution Polishing Sequence

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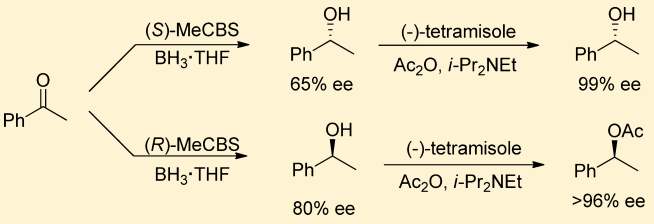
Supporting Information

ABSTRACT: Herein we describe a tandem method of coupling an enantioselective reaction with a nonenzymatic kinetic resolution to prepare highly enantioenriched compounds. The procedure employs a moderately selective enantioselective reaction on a ketone or aldehyde to form an enriched alcohol followed by a kinetic resolution of the alcohol to generate ee's of >99% in yields greater than what is possible with a kinetic resolution. This method highlights an avenue to quickly acquire highly enriched compounds without developing and optimizing a new methodology.

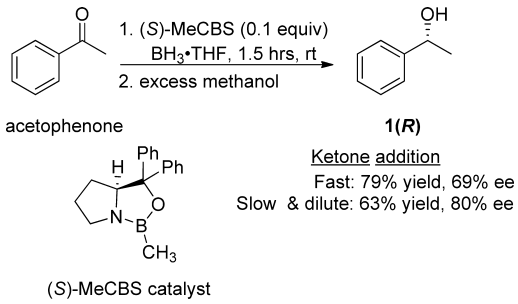


Producing enantiomerically pure compounds is of great importance to both academia and industry. Of the methods available, enantioselective reactions and kinetic resolutions are two common means of achieving enantiomerically enriched compounds. While there are numerous enantioselective reactions and kinetic resolutions[1] that can generate highly enantioenriched compounds (enantiomeric excess (ee) >95%, selectivity factor[2] (s) >25 respectively), there are also many procedures that only achieve moderate selectivities (50−80% ee, s = 10−15). Traditionally, kinetic resolutions and enantioselective reactions are done independently of each other. We will show how moderately selective enantioselective reactions and kinetic resolutions can be carried out consecutively in one-pot to quickly produce high ee's (>95% ee) with yields over 50%. By "polishing" or enhancing the ee of substrates that generate low ee in their enantioselective reactions, enantiomerically pure compounds can be produced quickly without the need to fully optimize reaction conditions.

This project arose from the problem of substrate variability in methodology. Employing a known enantioselective reaction on a new substrate generally results in less than satisfactory results on the first effort. The methodology can be optimized, but this costs valuable time and money, and the optimized procedure may still not generate high ee for the desired substrate. Instead of perfecting the methodology, a known enantioselective reaction can be coupled with a known kinetic resolution that targets either the major or minor enantiomer to achieve high ee's of either the starting material or the product. While this sequential process has been highlighted with enzymatic kinetic resolutions[3,4] to the best of our knowledge, it has not been shown with a less selective nonenzymatic resolution in a one-pot procedure.

In order to demonstrate the utility of this process, a prochiral ketone was reduced by the Corey−Bakshi−Shibata catalyst (S)-MeCBS to produce an enantioenriched alcohol with moderate ee.[5] While (S)-MeCBS can reduce ketones to their corresponding alcohols in ee's greater than 99%, the reaction is sensitive to slight changes in the reaction conditions.[6] This is demonstrated from our results in Scheme 1 where

Scheme 1. Ketone Reduction



acetophenone is reduced to the enantioenriched (R)-phenylethanol (**1**(***R***)) by the (S)-MeCBS catalyst. As expected, the neat addition of the ketone gave lower ee's (69%) than the dilute, slow addition (80%). The unpredictability of this reaction from substrate to substrate and from changes in reaction conditions makes it a good candidate for ee polishing by a kinetic resolution.

Typically, kinetic resolutions are carried out on racemates, not enantiomerically enriched compounds. By performing a kinetic resolution on an enantiomerically enriched substance instead of a racemic mixture, less conversion is required to achieve high ee in the starting material. We chose to explore this concept by utilizing a modified kinetic resolution developed by Birman,[7] which employs the enantioselective

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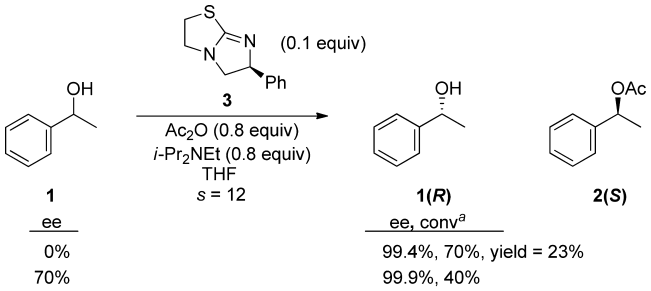
acyl transfer catalyst (−)-tetramisole (**3**), as the second step in our sequential process. When acetic anhydride is employed at room temperature, the selectivity factor for the kinetic resolution of phenylethanol is a moderate s = 12 (Scheme 2).[8] When the kinetic resolution was performed on

Scheme 2. Kinetic Resolution



enantioenriched **1** (70% ee (*R*)), targeting the minor *S* enantiomer for derivatization, only 40% conversion was required to increase the ee of the alcohol **1**(*R*) to >99% (*R*). When starting with racemic starting material, a conversion of 70% was required to obtain the same level of enriched **1**(*R*) (23% yield). By performing the kinetic resolution on an enantioenriched alcohol, the maximum amount of **1**(*R*) that can be recovered increases from 30% to 60%, culminating in an alcohol that is high in ee and has good yields.

The extent of conversion needed to increase the ee of an enriched substrate by kinetic resolution to 99% ee can be calculated from the equation derived by Horeau[9] (eq 1) via substituting in the selectivity factor (s), the starting enantiomeric ratio (er) ($S_{maj}{}^0$, $S_{min}{}^0$), and the desired er (S_{maj}, S_{min}). Table 1 shows the calculated minimum conversion

Table 1. Theoretical Conversions Required To Increase ee of Starting Material to 99% for s = 12

$$C = 1 - \left[\left(\frac{S_{min}}{S_{min}{}^0}\right)\left(\frac{S_{maj}{}^0}{S_{maj}}\right)^s\right]^{1/(s-1)} \quad (1)$$

entry	starting ee of **1**	calcd % conv[a] of **2**	max theor yield (%) of **1**
1	0	69	31
2	50	49	51
3	60	44	56
4	70	38	62
5	80	32	68
6	90	23	77

[a]Conversions to product **2** calculated from eq 1.

needed to obtain 99% enriched starting material when different initial ee's are employed; starting materials with greater initial ee require less conversion to obtain highly enriched material.[10] In theory, performing a kinetic resolution on a starting material with a moderate ee of 50% could result in a 20% higher yield of enriched material versus performing the same resolution on a racemate (Table 1, entries 1 and 2).

Next, the enantioselective reduction and kinetic resolution were employed in a sequential process with the goal of obtaining a one-pot tandem process. The challenge with performing these reactions in one-pot is that the product of the enantioselective reduction is a boronate salt that will not undergo acylation (Table 2, entry 1). Since the addition of methanol is a common workup strategy for the CBS enantioselective reduction,[6] methanol was added as a coupling reagent to free the alcohol **1**(*R*) for the kinetic resolution. Theoretically, only 3 equiv of methanol should be required to cleave off the boron and free the alcohol for the acylation. However, under those conditions the ee of **1**(*R*) only increased slightly and the ester product **2** was produced in minimal yield (Table 2, entry 2). In order to achieve full boron cleavage an excess of methanol is required.[11] This frees the alcohol so it can be acylated and the ee of **1**(*R*) can be polished from 64% up to 97% (**1**(*R*)′) (Table 2, entry 3). Upon scale up (Table 1, entry 4), (*R*)-phenylethanol (**1**(*R*)′) was recovered with an ee of 99% in 55% yield. The sequential reaction yielded more than double the amount of product recovered from the kinetic resolution of the racemic alcohol (Scheme 2, 23% yield), and the ee was greater than that obtained from the enantioselective reduction of the ketone.

This same sequential one-pot process was used to obtain the opposite enantiomer in high ee as the ester product **2**(*S*)**a**,**b** by employing the (*R*)-MeCBS catalyst instead of its *S* enantiomer and keeping the kinetic resolution procedure the same. Now enriched product is obtained instead of the enriched starting material. The (*R*)-MeCBS reduction produced the (*S*)-phenylethanol (**1**(*S*)) in excess, which was then enantioselectively acylated with acetic anhydride in the kinetic resolution by **3** to produce the highly enantioenriched ester product **2**(*S*)**a**, which was recovered in 52% yield with an ee of 96% (Table 3, entry 1). In an effort to improve the ee, the anhydride was changed to propionic anhydride and the reaction was run in chloroform (Birman's original conditions that gave a selectivity factor of 31).[7] These conditions resulted in an ester (**2**(*S*)**b**) with a 56% isolated yield and 99% ee (Table 3, entry 2).

We expanded this one-pot polishing sequence to another system by pairing the CBS reduction to the newly developed silylation based kinetic resolution of cyclic alcohols (Table 4).[13] The (*R*)-MeCBS catalyst was used to reduce the prochiral ketones α-tetralone and thiochromanone to give the alcohols **4a**,**b** in moderate ee (85% for both alcohols, Table 4). After freeing the alcohol with excess methanol, the kinetic resolution was used to silylate the minor enantiomer of **4a**,**b**, providing **4a**,**b**′ enriched with ee's >95% and yields of 68 and 81%. The amount of silyl chloride added (n in Table 4) was determined using eq 1 to calculate the theoretical conversion needed to obtain >95% ee. Because of differences in the selectivity factors for the silylation-based kinetic resolutions of **4a** and **4b** (s = 11 and s = 23, respectively), we were able to obtain **4b**′ in slightly higher yield without compromising the ee. If the same kinetic resolution of **4b** was done on racemic starting material, the highest yield possible of **4**′ would be 43% to obtain the compound with the same ee.

While the one-pot polishing sequence was successful for the previous reactions, when applied to a polishing sequence involving an enantioselective IPC allylation,[14] the procedure could not be performed in one pot. Instead, the polishing procedure only worked if the product of the allylation was purified by column chromatography before being subjected to the kinetic resolution. Benzaldehyde was reacted with the (+)-IPC allylating reagent to give product **6** with a moderate ee of 71%.[15] After purification, the major enantiomer of **6** was targeted in an acylation-based kinetic resolution (s = 54) using

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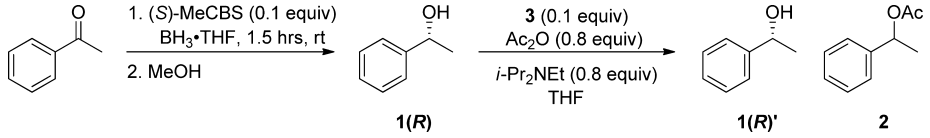
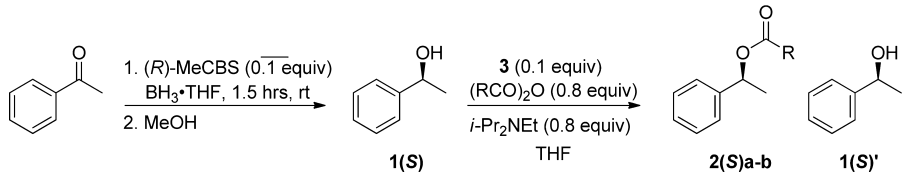
Table 2. One-Pot Process Linking the Enantioselective Reduction to the Kinetic Resolution



entry	MeOH (equiv)	ee of **1**(*R*) (%)	ee **1**(*R*)′ (%)	conv[b] of **1**(*R*) to **2** (%)	yield of **1**(*R*)′ (%)
1[a]	0	66	66	0	
2[a]	3	65	73	7	
3[a,c]	excess	64	97	31	
4[c,d]	excess	65	99	nd	55

[a]Reaction was run on a 0.5 mmol scale. [b]Conversion based on NMR. [c]Reaction mixture was concentrated by rotary evaporator to remove the excess methanol and THF was added prior to the kinetic resolution. [d]Reaction was run on a 2.0 mmol scale.

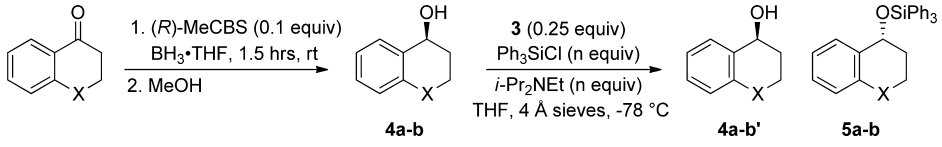
Table 3. One-Pot Sequential Process Where the Kinetic Resolution Acylates the Major Enantiomer



entry[c]	R	ee **1**(*S*) (%)	ee **1**(*S*)′ (%)	ee **2**(*S*) (%)	conv **2**(*S*)[a] (%)	yield **2**(*S*) (%)
1	**a** = Me	80	43	96	55	52
2[b]	**b** = Et	82	48	99	59	56

[a]See ref 12. [b]The reaction was run at 0 °C in chloroform. [c]Reactions were concentrated by rotary evaporator to remove excess methanol, and solvent was added prior to the kinetic resolution.

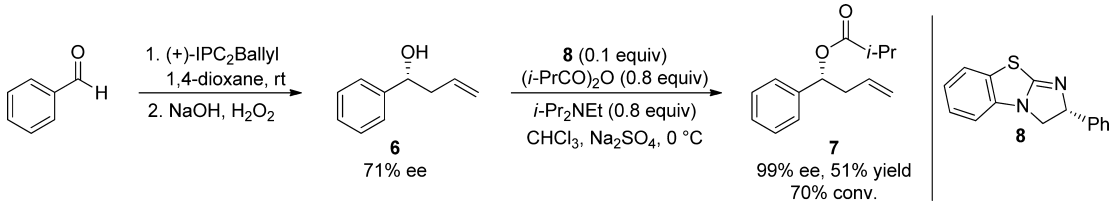
Table 4. One-Pot Sequential Process Where the Kinetic Resolution Silylates the Minor Enantiomer



entry[a]	X	conv of **5** (%)[b]	*n*	ee of **4** (%)	ee of **4**′ (%)	ee of **5** (%)	yield of **4**′ (%)
1	**a** = CH_2	16	0.3	85	96	39	68
2	**b** = S	13	0.2	85	95	19	81

[a]Reactions were concentrated by rotary evaporator to remove excess methanol, and THF was added prior to the kinetic resolution. [b]Theoretical conversion based on eq 1.

Scheme 3. Asymmetric Allylation followed by Acylation-Based Kinetic Resolution



the catalyst benzotetramisole (**8**) to give the ester **7** in high ee (99%) and moderate yield (51%) (Scheme 3).

In conclusion, we have shown how enantioselective reactions and kinetic resolutions with moderate selectivities can be utilized sequentially in one-pot to produce enantiomerically pure materials with high ee (>95%) and good yields (>50%), which gives comparable results to the enzymatic processes in the literature.[3,4] By combining the two reactions, the inherent disadvantages of kinetic resolutions (less than 50% maximum yield) and enantioselective reactions (substrate variability, moderate ee's) can be overcome. The ability to recover both enantiomers as either the starting material or product in high ee and yield is advantageous and overcomes the problem of limited commercial availability of catalyst enantiomers (such as **3**). This methodology allows researchers to quickly obtain highly enriched materials for new substrates while giving them the option of obtaining either the starting material or the product in high ee with good yields.

■ EXPERIMENTAL SECTION

General Methods. All reagents used were obtained from commercial sources and were used as received. Reactions were carried out under a nitrogen atmosphere unless otherwise stated. Dry tetrahydrofuran (THF) was obtained by degassing and then passing

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through an activated alumina column. Flash column chromatography was performed on silica gel (32−63 μm). The chemical shifts are reported as δ values (ppm) relative to the residual chloroform peak. Reactions were monitored by thin-layer chromatography (TLC), carried out on aluminum-backed silica gel 60 F_{254} sheets and visualized by UV light and either a potassium permanganate stain or a phosphomolybdic acid stain. The conversions and selectivities for the kinetic resolution experiments were determined from the enantiomer excess (ee) of the product and recovered starting material using known methods.[1a] Racemic ester product standards were synthesized from reacting the alcohol with the corresponding anhydride and catalytic amounts of *N*,*N*-dimethylaminopyridine. The product's NMR spectra were consistent with known literature values.

Reduction of Acetophenone to Phenylethanol. *Fast Addition.* A small stir bar was added to an oven-dried 2 dram vial which was flushed with nitrogen several times and then capped. To the reaction vessel BH_3·THF (2 mL of 1.0 M, 2.0 mmol) was carefully added via syringe under nitrogen, followed by the addition of (*S*)-MeCBS (200 μL of 1 M in toluene, 0.2 mmol). Acetophenone was added neat (235 μL, 2.0 mmol) and the reaction was stirred for 90 min at room temperature. The reaction was quenched with 1 mL of methanol (evolution of H_2 gas), stirred for at least 30 min, and then concentrated in vacuo. Aqueous HCl (2 mL of 1 M) and 2 mL of ether were then added. The solution was extracted with ether (4 × 2 mL), and the organic layers were combined and then washed with 1 M HCl (2 × 2 mL), water (2 mL), and finally brine (2 mL). The organic layer was then dried over Na_2SO_4, the solid filtered off, and the solution concentrated in vacuo to give 0.178 g of pure phenylethanol as a thick colorless oil (79% yield). The product was analyzed by HPLC on a Chiralcel OD-H column using 96% hexanes and 4% 2-propanol solvent system at 1 mL/min, 210 and 254 nm detection to give the following retention times: 10.29 min (*R*) and 12.84 min (*S*), 69.2% ee (*R*).[5]

Slow Addition. The reaction was carried out as described previously, but the acetophenone was added as a solution (2.0 mmol acetophenone in 0.7 mL THF) dropwise over 68 min (0.141 g, 63% yield, 80% ee (*R*)).

*1-Phenylethanol (**1(R)**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40−7.24 (m, 5H), 4.91 (q, *J* = 3.9 Hz, 1H), 1.82 (s, 1H), 1.50 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 146.0, 128.7, 127.7, 125.6, 70.6, 25.3.

Typical Procedure for the Acylation-Based Kinetic Resolution of Phenylethanol. A stock catalyst solution was made by dissolving (−)-tetramisole (0.102 g, 0.50 mmol) and *i*-Pr_2NEt base (685 μL, 4 mmol) in THF in a 5.00 mL volumetric flask. A stir bar was added to an oven-dried 10-mL round-bottom flask which was then flushed with nitrogen several times and capped. The stock catalyst solution (2000 μL, 0.2 mmol of (−)-tetramisole, 1.6 mmol of *i*-Pr_2NEt), phenylethanol (240 μL, 2.0 mmol), and acetic anhydride (152 μL, 1.6 mmol) were added to the reaction vessel, and the solution was stirred for 24 h at room temperature. The reaction was quenched with 1.0 mL of methanol, stirred for 30 min, concentrated in vacuo, and then purified by flash chromatography (silica gel, 10 cm tall, 3 cm wide) using a hexane and ethyl acetate solvent system (200 mL of 9:1 followed by 200 mL of 1:1) to yield 0.057 g of phenylethanol (23% yield, 99.4% ee (*R*)) and 0.196 g of the ester product **2a** (61% yield, 42.7% ee (*S*)). The product was analyzed by HPLC on a Chiralpak IC column using 96% hexanes and 4% 2-propanol solvent system at 1 mL/min, 210 and 254 nm detection to give the following retention times: 5.46 min (*R*) and 6.07 min (*S*), 42.7% ee (*R*).[5,7]

*1-Phenylethyl Acetate (**2(S)a**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37−7.28 (m, 5H), 5.89 (q, *J* = 6.6 Hz, 1H), 2.08 (s, 3H), 1.55 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.3, 141.7, 128.4, 127.9, 126.1, 72.3, 22.2, 21.4.

Sequential Reduction and Kinetic Resolution. *Target Minor Enantiomer (Table 2, Entry 4).* A stir bar was added to an oven-dried 25 mL round-bottom flask which was then flushed with argon several times and capped. To the reaction vessel was carefully added BH_3·THF (2 mL of 1.0 M, 2.0 mmol) via syringe under nitrogen, followed by the addition of (*S*)-MeCBS (200 μL of 1 M in toluene, 0.2 mmol). Acetophenone was added neat (235 μL, 2.0 mmol), and the reaction was stirred for 90 min at room temperature. The reaction was quenched with 1 mL of methanol (evolution of H_2 gas) and stirred for at least 30 min, and the solvent was removed in vacuo. The reaction vessel was then flushed with argon several times and capped. A stock catalyst solution was made by dissolving (−)-tetramisole (0.104 g, 0.50 mmol) and *i*-Pr_2NEt base (640 μL, 3.7 mmol) in THF in a 5.00 mL volumetric flask. The stock catalyst solution (2000 μL, 0.20 mmol of (−)-tetramisole, 1.6 mmol of *i*-Pr_2NEt) was added to the reaction vessel followed by acetic anhydride (152 μL, 1.6 mmol). After 13 h, the reaction was quenched with 1 mL of methanol and allowed to stir for 10 min, concentrated in vacuo, and then purified by column chromatography (silica gel, 10 cm tall, 3 cm wide) using a hexane and ethylacetate solvent system (250 mL of 9:1 followed by 200 mL of 1:1) to yield 0.133 g of phenylethanol (55% yield, 98.6% ee (*R*)) and 0.102 g of the ester product **2a** (31% yield, 4.90% ee (*S*)).

*Target Major Enantiomer. (Table 3, Entry 1, 1-Phenylethyl Acetate (**2a**)).* Reaction was carried out as described above except (*R*)-MeCBS catalyst was used in the reduction.

*Target Major Enantiomer. (Table 3, Entry 2, 1-Phenylethyl Propionate (**2b**)).* Reaction was carried out as described above except (*R*)-MeCBS catalyst was used in the reduction, and propionic anhydride was used (193 μL, 1.5 mmol) in the kinetic resolution which was carried out at 0 °C in dry chloroform. Purification on silica column yielded 0.064 g of phenylethanol (26% yield, 47.5% ee (*S*)) and 0.200 g of the ester product **2b** (56% yield, 99.0% ee (*S*)). The ester product **2b** was analyzed by HPLC on a Chiralpak IC column using 96% hexanes and 4% 2-propanol solvent system at 1 mL/min, 210 and 254 nm detection to give the following retention times: 4.63 min (*R*) and 4.96 min (*S*), 69.2% ee (*R*).[5,7]

*1-Phenylethyl Propionate (**2b**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37−7.7.29 (m, 5H), 5.91 (q, *J* = 6.6 Hz, 1H), 2.36 (q, *J* = 6.1 Hz, 2H), 1.54 (d, *J* = 6.9 Hz, 3H), 1.15 (t, *J* = 7.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.7, 141.9, 128.5, 127.8, 126.0, 72.1, 27.9, 22.3, 9.1.

Sequential Reduction and Silylation Kinetic Resolution. *Table 4, Entry 2.* A small stir bar was added to an oven-dried 1 dram vial which was then flushed with nitrogen several times and then capped. To the reaction vessel was carefully added BH_3·THF (0.5 mL of 1.0 M, 0.5 mmol) via syringe under nitrogen, followed by the addition of (*R*)-MeCBS (50 μL of 1 M in toluene, 0.1 mmol). The α-tetralone was added neat (67 μL, 0.5 mmol), and the reaction was stirred overnight at room temperature. The reaction was quenched with 0.5 mL of methanol (evolution of H_2 gas) and stirred for at least 30 min, and the solvent was removed in vacuo. To the reaction vessel was then added a small stir bar, 4 Å sieves, (−)-tetramisole (0.026 g, 0.125 mmol), and *i*-Pr_2NEt (26 μL, 0.15 mmol). The reaction vessel was then flushed with nitrogen several times and capped, and 2.5 mL of dry THF was added. A stock Ph_3SiCl solution was made by dissolving triphenylchlorosilane (0.454 g, 1.49 mmol) in THF in a 5.00 mL volumetric flask. The reaction vessel was placed in a −78 °C 2-propanol bath and allowed to equilibrate for at least 15 min. The stock Ph_3SiCl solution (500 μL, 0.15 mmol Ph_3SiCl) was added to the reaction and allowed to stir overnight. After 20 h, the reaction was quenched with 0.5 mL of methanol and allowed to stir for 10 min while warming to room temperature. The crude mixture was then concentrated in vacuo, washed with saturated NH_4Cl, and extracted with CH_2Cl_2 (4 × 1 mL). The organic layers were dried with Na_2SO_4, the solid was filtered off, and the solution was concentrated in vacuo and then purified by column chromatography (silica gel, 12 cm tall, 3 cm wide) using a hexane and dichloromethane solvent system (120 mL of 30% hexane in DCM, followed by 50 mL of DCM, then 120 mL of

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1% methanol in DCM) to yield 0.050 g of tetralol (68% yield, 95.7 ee (*S*)) and 0.033 g of the silyl ether product **5a** (16% yield, 27.1% ee (*S*)). The alcohol was analyzed by HPLC on a Chiralcel OD-H column with 4% isopropanol in hexanes at 0.5 mL/min, 210 and 254 nm detection to give the following retention times: 20.5 min (*S*) and 22.9 min (*R*).[13] The silyl ether was deprotected by adding 1−2 mL of tetrabutylammonium fluoride in THF which was then stirred at room temperature overnight. To the crude mixture was added 1−2 mL of saturated NH_4Cl and the deprotected alcohol was extracted with CH_2Cl_2 (4 × 1 mL), concentrated, and then purified on a silica column using CH_2Cl_2 followed by 1% methanol in CH_2Cl_2. The deprotected alcohol was then analyzed by HPLC using the same procedure as described above. Table 4, entry 2: Reaction was carried out and purified as described above except thiochromanone was used (0.084 g, 0.5 mmol). The alcohol was analyzed by HPLC on a Chiralcel OD-H column with 4% isopropanol in hexanes at 1.0 mL/min, 210 and 254 nm detection to give the following retention times: 19.6 min (*S*) and 25.2 min (*R*).[13]

Kinetic Resolution Procedure for 4a. To an oven-dried 1 dram vial was added a small stir bar, 4 Å sieves, (−)-tetramisole (0.026 g, 0.125 mmol), the alcohol **4a** (0.076 g, 0.5 mmol), and *i*-Pr_2NEt (44 μL, 0.25 mmol). The reaction vessel was then flushed with nitrogen several times and capped, and 2.25 mL of dry THF was added. A stock Ph_3SiCl solution was made by dissolving triphenylchlorosilane (0.453 g, 1.49 mmol) in THF in a 5.00 mL volumetric flask. The reaction vessel was placed in a −78 °C 2-propanol bath and allowed to equilibrate for at least 15 min. The stock Ph_3SiCl solution (850 μL, 0.25 mmol Ph_3SiCl) was added to the reaction and allowed to stir overnight. After 20 h, the reaction was quenched with 0.5 mL of methanol and allowed to stir for 10 min while warming to room temperature. The crude mixture was then concentrated in vacuo, washed with saturated NH_4Cl, and extracted with CH_2Cl_2 (4 × 1 mL). The organic layers were dried with Na_2SO_4, the solid was filtered off, and the solution was concentrated in vacuo and then purified by column chromatography (silica gel, 12 cm tall, 3 cm wide) using a hexane and dichloromethane solvent system (120 mL of 30% hexane in DCM, followed by 50 mL of DCM, then 120 mL of 1% methanol in DCM) to yield 0.046 g of **4a** (62% yield, 50.6% ee) and 0.081 g of the silyl ether product **5a** (49.5% yield, 73.0% ee).

Kinetic Resolution Procedure for 4b. The reaction was carried out as described above except alcohol **4b** was used instead of **4a**. The HPLC conditions were the same as described previously.

Tetralol (4a). ^1H NMR (400 MHz, $CDCl_3$): δ 7.44−7.42 (m, 1H), 7.22−7.20 (m, 2H), 7.12−7.10 (m, 1H), 4.77 (t, *J* = 4.6 Hz, 1H), 2.86−2.71 (m, 2H), 2.18−1.76 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.9, 137.2, 129.1, 128.8, 127.6, 126.2, 76.8, 68.1, 32.3, 29.3, 18.9.

Product (5a). ^1H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, *J* = 6.0 Hz, 6H), 7.47−7.37 (m, 9H), 7.28 (d, *J* = 6.8, 1H), 7.17−7.07 (m, 3H), 4.986 (t, *J* = 5.6 Hz, 1H), 2.85 (m, 1H), 2.73−2.65 (m 1H), 2.11−2.04 (m, 1H), 1.95−1.84 (m, 2H), 1.73−1.70 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.1, 137.2, 135.7, 135.0, 130.1, 128.9, 128.8, 128.0, 127.2, 125.8, 70.4, 32.7, 29.2, 19.3.

Thiochromanol (4b). ^1H NMR (400 MHz, $CDCl_3$): δ 7.32 (d, *J* = 7.6 Hz, 1H), 7.19−7.12 (m, 2H), 7.09−7.05, (m, 1H), 4.81 (dd, *J* = 4.8, 2.8 Hz, 1H), 3.33 (dt, *J* = 12, 3.2, Hz, 1H), 2.89−2.84 (m, 1H), 2.39−2.32 (m, 1H), 2.1−2.01 (m, 1H), 1.78 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 134.7, 133.4, 130.5, 128.6, 126.9, 124.4, 66.7, 30.1, 21.6.

Product (5b). ^1H NMR (400 MHz, $CDCl_3$): δ 7.63−7.56 (m, 6H), 7.48−7.35 (m, 9H), 7.12−7.10 (m, 2H), 6.96 (d, *J* = 7.6 Hz, 1H), 6.91−6.87 (m, 1H), 4.93 (dd, *J* = 5.4, 2.6 Hz, 1H), 3.50 (dt, *J* = 11.6, 3.2, 1H), 2.85−2.79 (m, 1H), 2.25−2.18 (m, 1H), 1.97−1.89 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.5, 135.7, 135.3, 134.5, 130.2, 129.7, 128.0, 127.8, 126.6, 123.8, 68.5, 30.8, 22.0.

Sequential Allylation and Acylation Kinetic Resolution. A stir bar was added to an oven-dried 1 dram vial which was then flushed with nitrogen several times and capped. To the reaction vessel (+)-$IPC_2Ballyl$ (0.5 mL of 1.0 M in dioxane, 0.5 mmol) was carefully added via syringe under nitrogen. Freshly distilled benzaldehyde was added neat (50 μL, 0.5 mmol), and the reaction was stirred for 3 h at room temperature. To the reaction were added 0.25 mL of 3 M NaOH and 0.25 mL of 30% H_2O_2, and the mixture was allowed to stir overnight. Water was added to the reaction mixture, the mixture was extracted with ether (3 × 1 mL), the organic layers were combined and dried with Na_2SO_4, the solid was filtered off, and the solution was concentrated in vacuo and then purified by column chromatography (silica gel, 12 cm tall, 3 cm wide) using a hexane and ether solvent system (400 mL of 9:1 hexane/ether, followed by 300 mL of 4:1 hexane/ether) to yield 0.085 g of **6** with impurity (70.9 ee (*R*)). The allylation product **6** was then added to an oven-dried 1 dram vial with a small stir bar, Na_2SO_4 (0.200 g), and (+)-benzotetramisole (0.012 g, 0.05 mmol) which was then flushed with nitrogen several times and capped. To the reaction vessel were added *i*-Pr_2NEt (60 μL, 0.35 mmol) and 4 mL of dry $CHCl_3$. The reaction was placed in a 0 °C 2-propanol bath and allowed to equilibrate for at least 15 min. The isobutyric anhydride (60 μL, 0.35 mmol) was added, and the reaction was stirred for 24 h. More isobutyric anhydride was added to increase conversion (6 μL, 0.4 mmol), and the reaction mixture was allowed to stir overnight. The reaction was quenched with 0.5 mL of methanol, concentrated in vacuo, and then purified by column chromatography (silica gel, 13 cm tall × 3 cm wide) using a hexane and ether solvent system (400 mL of 9:1 hexane/ether, followed by 300 mL of 4:1 hexane/ether) to yield 0.036 g of **6(*R*)′** (45.2% recovered, 5.6% ee (*R*)) and 0.056 g of **7** (51.4% yield, 98.7% ee (*R*)). The alcohol **6(*R*)′** was analyzed by HPLC on a Chiralcel OD-H column with 4% 2-propanol in hexanes at 0.5 mL/min, 210 and 254 nm detection to give the following retention times: 21.6 min (*R*) and 25.6 min (*S*). The ester **7** was analyzed by HPLC on a Chiralcel OD-H column with 1% isopropanol in hexanes at 0.5 mL/min, 210 and 254 nm detection to give the following retention times: 21.2 min (*R*) and 26.3 min (*S*).

Kinetic Resolution Procedure for 6. A stock catalyst solution was made by dissolving (+)-benzotetramisole (0.025 g, 0.099 mmol) and *i*-Pr_2NEt (240 μL, 1.39 mmol) in dry $CHCl_3$ in a 10 mL volumetric flask. To an oven-dried 1 dram vial was added a small stir bar, the racemic alcohol **6** (0.074 g, 0.5 mmol), and Na_2SO_4 (0.200 g), which was then flushed with nitrogen several times and capped. To the reaction vessel was added 2 mL of the catalyst stock solution (0.25 mmol *i*-Pr_2NEt, 0.02 mmol (+)-benzotetramisole). The reaction was placed in a 0 °C isopropanol bath and allowed to equilibrate for at least 15 min. The isobutyric anhydride (42 μL, 0.25 mmol) was added and the reaction was stirred for 24 h. The reaction was quenched with 0.5 mL of methanol, concentrated in vacuo, and then purified by column chromatography (silica gel, 10 cm tall × 2 cm wide) using a hexane and ethyl acetate solvent system (100 mL of 9:1 hexane/ethyl acetate followed by 50 mL of 3:2) to yield 0.039 g of **6′** (51% recovered, 71.0% ee) and 0.036 g of **7** (33% yield, 98.7% ee).[14,16]

(*R*)-Phenyl-3-buten-1-ol (6). ^1H NMR (400 MHz, $CDCl_3$): δ 7.30−7.26 (m, 4H), 7.23−7.19 (m, 1H), 5.79−5.69 (m, 1H), 5.12−5.05 (m, 2H), 4.67 (dd, *J* = 7.6, 5.2 Hz), 2.47−2.40 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.8, 134.4, 128.4, 127.5, 125.8, 118.4, 73.3, 43.8.

(*R*)-1-Phenylbut-3-en-1-yl isobutyrate (7). ^1H NMR (400 MHz, $CDCl_3$): δ 7.35−7.26 (m, 5H), 5.81 (dd, *J* = 8.0, 5.6 Hz, 1H), 5.76−5.66 (m, 1H), 5.10−5.03 (m, 2H), 2.68−2.52 (m, 3H), 1.17 (q, *J* = 6.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.2, 140.4, 133.4, 128.4, 127.8, 126.4, 118.0, 74.62, 41.0, 34.1, 19.0, 18.9. Optical rotation $[\alpha]^{25}_D$ = +54.2 (*c* = 1.10, $CHCl_3$). HRMS (ESI) (M+): calcd for $C_{14}H_{18}O_2^+$ 218.1307, obsd 218.1305. IR (neat, cm^{-1}): 2974, 1734, 1456, 1387, 1189, 1152, 1068, 917, 758, 698.

■ ASSOCIATED CONTENT

Supporting Information

Chiral HPLC traces, copies of NMR spectra for new compounds, and duplicate run data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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