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The Resolution of Terminal 1,2-diols via Silyl Transfer

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Abstract

Through kinetic analysis and optimization we report an improved resolution of terminal 1,2-diols via asymmetric silyl transfer. Because the reaction is a regiodivergent resolution the monoprotected product could be isolated in excess of 95:5 er and 40% yield. The described method offers a means of chemically differentiating a terminal 1,2-diol with concomitant resolution of the enantiomers.

Terminal 1,2-diols have been shown to be practical building blocks in the synthesis of biologically relevant compounds.^{1,2} Based on the synthetic value of these compounds, several metal-catalyzed methods have been explored for their asymmetric synthesis including: hydrolytic kinetic resolution of epoxides,³⁻⁵ as well as, diboration/oxidation⁶⁻⁸ and dihydroxylation^{2,9} of terminal olefins. An alternative approach to the synthesis of enantiopure terminal 1,2-diols is through kinetic resolution via electrophile transfer.¹⁰⁻¹² The robust nature and chemical orthogonality of silyl protecting groups¹³⁻¹⁵ has made asymmetric silyl transfer particularly synthetically valuable in the resolution of alcohols. Early work by Ishikawa demonstrated that chiral guanidine catalysts successfully promote the resolution of indanol *via* silyl transfer.¹⁶ Subsequently, both metal¹⁷⁻²⁰ and non-metal catalysts,²¹⁻²⁷ have been found to effectively promote enantio- and stereoselective silyl transfer to alcohols.

Recently, Hoveyda and Snapper disclosed the kinetic resolution of 1,2-diols via silylation with an organic catalyst.²² The same groups²³ and our group²⁶ reported a highly effective regiodivergent resolution of 1,2-diols. In a regiodivergent resolution of a racemic mixture (RRM),²⁸⁻³¹ the enantiomers of the starting material are preferentially converted into constitutionally isomeric products. The advantage of the regiodivergent RRM over a traditional kinetic resolution is that it is generally easier to obtain the products of the transformation in both high yield and enantioselectivity. The net effect is that in a single step the regiodivergent resolution resolves the enantiomers and generates a synthetically more valuable product. For example, using catalysts **4a** and **4b** we demonstrated that the regiodivergent resolution of terminal 1,2-diols is an efficient means of accessing enantiopure products with the silyl-protected secondary hydroxyl (Scheme 1). In this transformation we

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Supporting Information Available. ¹H and ¹³C NMR spectra for the products. This information is available free of charge via the Internet at <http://pubs.acs.org/>.

resolve the enantiomers and simultaneously chemically differentiate the primary and secondary hydroxyls.

A unique feature of catalysts **4a** and **4b** are their ability to reversibly and covalently bond with organic molecules, which is in part responsible for the protection of the inherently less reactive secondary hydroxyl (Scheme 1). Organic catalysts and metal-binding ligands that use reversible covalent bonding have seen a resurgence over the past decade as a means of controlling selectivity in a range of reactions.³²⁻⁴⁰ The majority of this effort has focused on using reversible covalent bonding to control site and regioselectivity, whereas less progress has been made in the area of enantioselective catalysis.⁴¹⁻⁴⁴ In this article, we reevaluate the reaction conditions of our original divergent resolution in order to provide a practical method for obtaining enantioenriched terminal 1,2-diols in which the primary hydroxyl is silylated.

In our initial publication on the regiodivergent RRM, we found using 15% of **4b** that the secondary protected product **3a** formed in 40% yield and 99:1 er, while the primary protected product **2a** formed in a more modest 91:9 er (Scheme 1). In an effort to improve the catalyst performance, we monitored the conversion and selectivity of the reaction at a reduced catalyst loading (10% **4b**, Figure 1). To our surprise, the enantioselectivity for both **2a** and **3a** increase with time under these sub-optimal conditions; moreover, the rate of reaction appears to accelerate over time (Figure 1). A potential explanation for the increasing enantioselectivity is that at low conversion the catalyzed reaction could be limited by the rate of the exchange between catalyst **4b** and **1a**, which allows for unselective background silylation to be competitive. As the reaction progresses, the concentration of silyl chloride decreases slowing the silylation step; moreover, acid is generated in the reaction, which catalyzes the exchange reaction. To test this hypothesis, we monitored the reaction while adding the silyl chloride at a rate such that conversion and silyl chloride addition were matched thus limiting the amount of excess electrophile in solution (Figure 2). In addition we found that performing the reaction at room temperature provided the optimal results. Under these conditions, the formation of **2a** proceeds in 97:3 er at low conversion (10 minutes) with a small decrease in er (94.5:5.5) after 110 min. The conversion to **3a** still shows a small increase in enantioselectivity at the beginning of the reaction, but the effect is considerably smaller and the final product is formed in high enantioselectivity (96:4 er). Based on the time course, the formation of **3a** clearly accelerates as the reaction progresses. In Figure 2 we have drawn a simplified version of the kinetics model; notably we have only shown the pathways for the major products formed ((*R*)-**2a** and (*S*)-**3a**). Furthermore, we have not included the equilibria for product bound to catalyst even though these equilibria are present. The rapid formation of (*R*)-**2a** is consistent with the primary alcohol being the inherently more reactive alcohol and the substrate being stereochemically matched to the catalyst. The accelerated formation of **3a** as the reaction progresses can be rationalized by considering that the majority of **3a** is the *S* enantiomer (er = 96:4). Therefore any catalyst bound to (*R*)-**1a**, either through the primary or secondary alcohol, is lowering the concentration of catalyst bound to (*S*)-**1a**, effectively inhibiting the formation of (*S*)-**3a**. The formation of (*R*)-**3a** is likely slow, because of a mismatched relationship between the catalyst and (*R*)-**1a**. Therefore, as (*R*)-**1a** is converted to (*R*)-**2a** (where the primary hydroxyl is silylated), this increases the concentration of catalyst bound to (*S*)-**1a** thereby accelerating the rate of formation of (*S*)-**3a**.

Analysis of the time course suggests that to obtain the optimal yield and enantioselectivity of **2a** approximately 0.7 equiv of TESC1 is required. With this in mind, we examined the substrate scope of the regiodivergent resolution with the aim of obtaining **2a** in high yield and enantioselectivity. To improve the operational practicality, we employed a portion wise addition of the silyl chloride rather than a syringe pump addition. Under these conditions, **2a**

was formed in 46% yield and 96.5:3.5 er (Table 1, entry 1), matching the time course data. As a note of comparison, a traditional kinetic resolution catalyst would need to operate with a selectivity factor (*s*) of 67 to obtain similar yield and enantioselectivity of **2a**.

Under these modified conditions, the substrate scope was examined, and in general, the primary protected products (**2**) are isolated in synthetically practical levels of enantioselectivity (>95:5 er) and yields 40% (Table 1). In these cases, groups both small (R=*n*-Bu, Table 1, entry 2) and large (R= *t*-Bu, Table 1, entry 4) provide the desired products in high yield and enantioselectivity. For Table 1 the majority of substrates undergo a regiodivergent resolution; however, the conditions are run such that only a minimal amount of **3** is formed during the reaction. One substrate that did not undergo a regiodivergent resolution was substrate **1d** (R= *t*-Bu); in this case the product with the secondary hydroxyl protected (**3d**) was never observed even with excess silyl chloride. Even though a regiodivergent kinetic resolution does not occur with **1d**, a traditional kinetic resolution provides **2d** in 43% yield and 95.5:4.5 er (*s* = 44, Table 1, entry 4). The substrates with the lowest enantioselectivities and yields were **2e** and **2i**, which have the smallest R substituents (R= Me and vinyl, Table 1, entries 5 and 9). A benzyl protected glycerol derivative also functions in the reaction yielding the differentially protected triol in 40% yield and 95:5 er (Table 1, entry 7). Under the reaction conditions, halogen-containing substrates, both Cl and Br, provide the highest stereoselectivities of the silylated products while maintaining excellent yields (Table 1, entries 11 and 12). As further evidence of the practicality of the reaction, we performed a larger scale reaction. Using 10 mmol of **1l** (R= CH₂Cl) the resolution produced **2l** in 45% yield and 97:3 er (eq 1), consistent with the smaller scale reaction.

(1)

Having explored the substrate scope of the resolution to form the primary protected products, we next investigated the range of silyl groups that could be transferred enantioselectively. By employing more bulky silylating agents, it was discovered that the product with the secondary hydroxyl protected (**3**) does not form in appreciable quantities. Consequently, reactions with the larger silylating agents undergo traditional kinetic resolutions rather than the regiodivergent RRM. Using TBSCl in the resolution of 1,2-hexanediol provides (*R*)-**2** in 45% yield and 89:11 er (*s* = 15). Increasing the steric bulk of the silylating reagent to TIPSCl provides a significant increase in *s*-factor to 45 allowing the product to be isolated in 40% yield and 96:4 er, comparable to the results with TESCl (eq 2).

TBSCl: yield= 45%, er= 89:11, *s*= 15

TIPSCl: yield= 40%, er= 96:4, *s*= 45

(2)

We have demonstrated that a catalyst that uses reversible covalent bonding is effective at the resolution of 1,2-diols. By monitoring the reaction kinetics we were able to improve the yield and selectivity of the reaction while also gaining insight into the mechanism of the reaction. We believe the above method will be a practical means of accessing enantiopure terminal 1,2-diols in which the hydroxyls have been chemically differentiated.

Experimental Section

General Considerations

Unless otherwise noted, all reagents were obtained from commercial suppliers and used without further purification. Lithium reagents were titrated against 2-pentanol using 1,10-phenanthroline as the indicator. All experiments were performed in oven or flame dried glassware under an atmosphere of nitrogen or argon using standard syringe and cannula techniques, except where otherwise noted. All reactions were run with dry, degassed solvents dispensed from a glass contour solvent purification system. *tert*-amyl alcohol and *tert*-butanol were distilled over CaH₂ and stored over 3 Å molecular sieves in a dry box under a nitrogen atmosphere. Deuterated solvents were stored over 3 Å molecular sieves. C₆D₆ was degassed by three successive freeze-pump-thaw cycles and stored over 3 Å molecular sieves in a dry box under a nitrogen atmosphere. Column chromatography was performed using an automatic purification system pre-packed columns. All NMR chemical shifts are reported in ppm relative to residual solvent for ¹H and ¹³C NMR. Coupling constants are reported in Hz. All IR spectra values are reported in cm⁻¹. High resolution mass spectra (HRMS) were taken using a TOF analyzer.

The following compounds were made according to literature procedure: 1-benzyloxy-2,3-propanediol⁴⁵, 4-methylpentane-1,2-diol²⁶, 1-cyclohexylethane-1,2-diol²⁶, 3-phenylpropane-1,2-diol²⁶, **4a**,²⁵**4b**²⁶.

Reaction Time Course at 0 °C with a single addition of TESC (Figure 1)

In a dry box, a solution of diol **1a** (24 mg, 0.20 mmol), catalyst **4b** (6.2 mg, 0.02 mmol, 10 mol %), and *N,N*-diisopropylethylamine hydrochloride (2.0 mg, 1.2×10⁻² mmol, 6 mol %) in anhydrous *tert*-butanol (3 mL) was prepared in an oven-dried glass reaction vial. A solution of 1,3,5-trimethoxybenzene as internal standard (50 μL, 2.0×10⁻² mmol, 10 mol %, 0.40 M in CDCl₃,) was added. The reaction was brought out of the dry box, and was stirred at 4 °C for 15 minutes. *N,N*-diisopropylethylamine (49 μL, 0.28 mmol, 1.4 equiv) was added, followed by addition of chlorotriethylsilane (44 μL, 0.26 mmol, 1.2 equiv). The reaction was stirred at room temperature for 1 hour. Aliquots (0.5 mL) were taken at every 10 min. Methanol (5 μL) was added to quench the aliquot. The solvent was removed under reduced pressure, Chiral GLC analysis of the crude mixture afforded the yield and selectivity. Chiral GLC Analysis (Beta Dex 120 (30 m × 0.15 mm × 0.25 mm film thickness), 90 °C for 135

min, 20 °C/min to 160 °C, 160 °C for 20min, 20 °C/min to 180 °C, 180°C for 20 min, 15 psi, $t_{(S)\text{-}2a}$ = 96.2 min, $t_{(R)\text{-}2a}$ = 97.4 min, $t_{(S)\text{-}3a}$ = 104.2 min, $t_{(R)\text{-}3a}$ = 110.9 min, t_{standard} = 143.7 min), Response Factors ((*S*)-**2a**: 0.59, (*R*)-**2a**: 0.59, (*S*)-**3a**: 0.66, (*R*)-**3a**: 0.66, standard: 1.0).

Reaction Time Course at room temperature with a syringe pump addition of TESCl (Figure 2)

In a dry box, a solution of diol **1a** (240 mg, 2.0 mmol), catalyst **4b** (61 mg, 0.20 mmol, 10 mol %), and *N,N*-diisopropylethylamine hydrochloride (20 mg, 0.12 mmol, 6 mol %) in anhydrous *tert*-butanol (30 mL) was prepared in an oven-dried glass reaction vial. The solution brought out of the dry box, and a solution of 1,3,5-trimethoxybenzene as internal standard (0.50 mL, 0.20 mmol, 10 mol %, 0.40 M in CDCl₃) was added. The reaction was stirred at room temperature for 15 minutes. *N,N*-diisopropylethylamine (490 µL, 2.8 mmol, 1.4 equiv) was added, followed by addition of chlorotriethylsilane (440 µL, 2.6 mmol, 1.2 equiv) in 2 mL THF via syringe pump over 1.5 hours. The reaction was stirred at room temperature for 2 hour. Aliquots (0.5 mL) were taken every at 10 min. Methanol (5 µL) was added to quench the aliquot. The solvent was removed under reduced pressure, Chiral GLC analysis of the crude mixture afforded the yield and selectivity.

General Procedure for Kinetic Resolution of Terminal 1,2-Diols

In a dry box, a solution of diol substrate (1.0 mmol), catalyst **4b** (31 mg, 0.10 mmol, 10 mol %), and *N,N*-diisopropylethylamine hydrochloride (10 mg, 6.0×10^{-2} mmol, 6 mol %) in anhydrous *tert*-butanol (15 mL) was prepared in an oven-dried glass reaction vial. The reaction was brought out of the dry box, and was stirred at room temperature for 15 minutes. *N,N*-diisopropylethylamine (120 µL, 0.70 mmol, 0.70 equiv) was added, followed by addition of chlorotriethylsilane (100 µL, 0.60 mmol, 0.60 equiv) in 4 portions every 15 minutes (dropwise addition was performed for each portion added). The reaction was stirred at room temperature for 1 hour (starting from the first addition of chlorotriethylsilane). Methanol (150 µL) was added to quench the reaction. The solvent was removed under reduced pressure, and flash column chromatography (hexanes:EtOAc = 60:1) afforded pure product. Chiral GLC or HPLC analysis of the product afforded the selectivity.

(R)-4-methyl-1-((triethylsilyl)oxy)pentan-2-ol (2a, Table 1, entry 1)—The general procedure was followed using 10 mol % catalyst **4b**, 0.80 equiv *N,N*-diisopropylethylamine, and 0.70 equiv chlorotriethylsilane to yield product as colorless oil (Run 1: 108 mg, 46%, er = 96.5:3.5, Run 2: 46%, er = 96:4). Chiral GLC Analysis (Beta Dex 120 (30 m × 0.15 mm × 0.25 mm film thickness), 95 °C for 90 min, 20 °C/min to 180 °C, 180°C for 20 min, 15 psi, t_{rminor} = 74.4 min, t_{rmajor} = 74.8 min). ¹H NMR (CDCl₃, 500 MHz) δ 3.71 (ddd, 1H, *J* = 16.4, 7.8, 3.2), 3.58 (dd, 1H, *J* = 9.8, 3.2), 3.33 (dd, 1H, *J* = 9.8, 7.8), 2.40 (d, 1H, *J* = 3.2), 1.74–1.82 (m, 1H), 1.36 (ddd, 1H, *J* = 14.2, 8.8, 5.9), 1.11 (ddd, 1H, *J* = 13.5, 8.5, 4.2), 0.95 (t, 9H, *J* = 7.8), 0.92 (d, 3H, *J* = 6.6), 0.90 (d, 3H, *J* = 6.6), 0.60 (q, 6H, *J* = 7.8); ¹³C NMR (CDCl₃, 125 MHz) δ 70.3, 67.6, 42.0, 24.8, 23.6, 22.4, 6.9, 4.6; IR: 2954, 2912, 2876, 1096, 1049, 1004, 789, 726 cm⁻¹; HRMS (ESI+) calcd. for C₁₂H₂₈O₂NaSi: [M+Na]⁺: 255.1751, found: 255.1763. [α]_D²⁰ = -1.9 (*c* = 1.0, CH₂Cl₂, *l* = 50 mm).

(R)-1-((triethylsilyl)oxy)hexan-2-ol (2b, Table 1, entry 2)—The general procedure was followed using 10 mol % catalyst **4a**, 0.70 equiv *N,N*-diisopropylethylamine, and 0.60 equiv chlorotriethylsilane to yield product as colorless oil (Run 1: 101 mg, 43%, er = 96:4, Run 2: 44%, er = 95.5:4.5). Chiral GLC Analysis (Beta Dex 120 (30 m × 0.15 mm × 0.25 mm film thickness), 95 °C for 120 min, 20 °C/min to 180 °C, 180°C for 20 min, 15 psi, t_{rminor} = 102.5 min, t_{rmajor} = 103.4 min). ¹H NMR (CDCl₃, 500 MHz) δ 3.59–3.64 (m, 2H), 3.36 (dt, 1H, *J* = 2.0, 8.8), 2.44 (d, 1H, *J* = 3.2), 1.22–1.45 (m, 6H), 0.94 (t, 9H, *J* = 7.8),

0.89 (t, 3H, $J = 7.1$), 0.60 (q, 6H, $J = 7.8$); ^{13}C NMR (CDCl_3 , 125 MHz) δ 72.1, 67.2, 32.7, 28.0, 23.0, 14.2, 6.9, 4.6; IR: 2955 cm^{-1} ; HRMS (ESI+) calcd. for $\text{C}_{12}\text{H}_{28}\text{O}_2\text{NaSi}$: $[\text{M} + \text{Na}]^+$: 255.1751, found: 255.1745. $[\alpha]_{\text{D}}^{20} = -3.2$ ($c = 1.0$, CH_2Cl_2 , $l = 50$ mm).

(R)-1-cyclohexyl-2-((triethylsilyl)oxy)ethanol (2c, Table 1, entry 3)—The general procedure was followed using 10 mol % catalyst **4b**, 0.70 equiv *N,N*-diisopropylethylamine, and 0.60 equiv chlorotriethylsilane to yield product as colorless oil (Run 1: 123 mg, 48%, er = 95:5, Run 2: 46%, er = 96.5:3.5). Chiral GC Analysis (Gamma Dex 120 (30 m $\times$ 0.25 mm $\times$ 0.25 μm film thickness), 115 $^\circ\text{C}$ for 180 min, 20 $^\circ\text{C}/\text{min}$ to 180 $^\circ\text{C}$, 180 $^\circ\text{C}$ for 20 min, 15 psi, $t_{\text{r major}} = 172.2$ min, $t_{\text{r minor}} = 169.5$ min). ^1H NMR (CDCl_3 , 500 MHz) δ 0.59 (q, 6H, $J = 7.8$), 0.94 (t, 9H, $J = 7.8$), 0.98–1.06 (m, 2H), 1.10–1.25 (m, 3H), 1.33–1.40 (m, 1H), 1.57–1.65 (m, 2H), 1.69–1.75 (m, 2H), 1.87–1.91 (m, 1H), 2.48 (d, 1H, $J = 2.9$), 3.34–3.38 (m, 1H), 3.44 (dd, 1H, $J = 9.8$, 8.3), 3.67 (dd, 1H, $J = 9.8$, 3.2); ^{13}C NMR (CDCl_3 , 125 MHz) δ 4.6, 6.9, 26.3, 26.4, 26.7, 29.0, 29.1, 40.7, 65.2, 76.0; IR: 2921, 2875, 2852, 1450, 1112, 1079, 1004, 817, 726 cm^{-1} ; HRMS (ESI+) calcd. for $\text{C}_{14}\text{H}_{30}\text{O}_2\text{NaSi}$: $[\text{M} + \text{Na}]^+$: 281.1907, found: 281.1915. $[\alpha]_{\text{D}}^{20} = -7.4$ ($c = 1.0$, CH_2Cl_2 , $l = 50$ mm).

(R)-3,3-dimethyl-1-((triethylsilyl)oxy)butan-2-ol (2d, Table 1, entry 4)—The general procedure was followed using 15 mol % catalyst **4b**, 0.70 equiv *N,N*-diisopropylethylamine, 0.60 equiv chlorotriethylsilane, and *t*-Amyl-OH as solvent. Reaction was run at 4 $^\circ\text{C}$ for 2 hours to yield product as colorless oil (Run 1: 104 mg, 45%, er = 96:4, Run 2: 42%, er = 95.5:4.5). Chiral GLC Analysis (Gamma Dex 120 (30 m $\times$ 0.15 mm $\times$ 0.25 mm film thickness), 95 $^\circ\text{C}$ for 120 min, 20 $^\circ\text{C}/\text{min}$ to 180 $^\circ\text{C}$, 180 $^\circ\text{C}$ for 20 min, 15 psi, $t_{\text{r minor}} = 43.7$ min, $t_{\text{r major}} = 45.0$ min). ^1H NMR (CDCl_3 , 500 MHz) δ 3.69 (dd, 1H, $J = 9.8$, 3.2), 3.43 (t, 1H, $J = 9.3$), 3.30 (ddd, 1H, $J = 9.0$, 3.2, 2.0), 2.65 (d, 1H, $J = 2.2$), 0.95 (t, 9H, $J = 8.1$), 0.90 (s, 9H), 0.60 (q, 6H, $J = 8.1$); ^{13}C NMR (CDCl_3 , 125 MHz) δ 78.9, 63.5, 33.4, 26.2, 6.9, 4.6; IR: 2954, 2912, 2877, 1460, 1108, 1067, 1003, 817, 726 cm^{-1} ; HRMS (ESI+) calcd. for $\text{C}_{12}\text{H}_{29}\text{O}_2\text{Si}$: $[\text{M} + \text{H}]^+$: 233.1937, found: 233.1940. $[\alpha]_{\text{D}}^{20} = -21.2$ ($c = 1.0$, CH_2Cl_2 , $l = 50$ mm).

(R)-1-((triethylsilyl)oxy)propan-2-ol (2e, Table 1, entry 5)—The general procedure was followed using 15 mol % catalyst **4b**, 0.90 equiv *N,N*-diisopropylethylamine, and 0.80 equiv chlorotriethylsilane to yield product as colorless oil (Run 1: 72 mg, 36%, er = 94.5:5.5, Run 2: 38%, er = 93.5:6.5). Chiral GLC Analysis (Beta Dex 120 (30 m $\times$ 0.15 mm $\times$ 0.25 mm film thickness), 80 $^\circ\text{C}$ for 45 min, 20 $^\circ\text{C}/\text{min}$ to 180 $^\circ\text{C}$, 180 $^\circ\text{C}$ for 20 min, 15 psi, $t_{\text{r minor}} = 35.4$ min, $t_{\text{r major}} = 36.5$ min). ^1H NMR (CDCl_3 , 500 MHz) δ 3.77–3.84 (m, 1H), 3.57 (dd, 1H, $J = 9.8$, 3.4), 3.32 (dd, 1H, $J = 9.8$, 7.8), 2.48 (d, 1H, 3.0), 1.10 (d, 3H, $J = 6.4$), 0.94 (t, 9H, $J = 7.8$), 0.60 (q, 6H, $J = 7.8$); ^{13}C NMR (CDCl_3 , 125 MHz) δ 68.4, 68.2, 18.4, 6.9, 4.6; IR: 2955, 2911, 2877, 1459, 1239, 1087, 1006, 801, 724 cm^{-1} ; HRMS (ESI+) calcd. for $\text{C}_9\text{H}_{22}\text{O}_2\text{NaSi}$: $[\text{M} + \text{Na}]^+$: 213.1281, found: 213.1271. $[\alpha]_{\text{D}}^{20} = -11.2$ ($c = 1.0$, CH_2Cl_2 , $l = 50$ mm).

(R)-1-phenyl-3-((triethylsilyl)oxy)propan-2-ol (2f, Table 1, entry 6)—The general procedure was followed using 10 mol % catalyst **4b**, 0.80 equiv *N,N*-diisopropylethylamine, and 0.70 equiv chlorotriethylsilane to yield product as a colorless oil (Run 1: 107 mg, 41%, er = 96:4, Run 2: 40%, er = 96:4). Chiral HPLC Analysis (OD-H, hexanes/*i*PrOH = 98/2, 1.0 mL/min, 220 nm, $t_{\text{r major}} = 5.51$ min and $t_{\text{r minor}} = 6.12$ min). ^1H NMR (CDCl_3 , 500 MHz) δ 7.27–7.30 (m, 2H), 7.18–7.22 (m, 3H), 3.85–3.90 (m, 1H), 3.60 (dd, 1H, $J = 10.0$, 3.7), 3.46 (dd, 1H, $J = 9.8$, 6.8), 2.78 (dd, 1H, $J = 13.7$, 7.1), 2.74 (dd, 1H, $J = 13.7$, 6.4), 2.42 (d, 1H, $J = 3.9$), 0.94 (t, 9H, $J = 7.8$), 0.59 (q, 6H, $J = 7.8$); ^{13}C NMR (CDCl_3 , 125 MHz) δ 138.5, 129.5, 128.6, 126.5, 73.0, 66.2, 39.8, 6.9, 4.6; IR: 2953, 2911, 2876, 1239, 1111, 1031, 792,

727, 698 cm^{-1} ; HRMS (ESI+) calcd. for $\text{C}_{15}\text{H}_{26}\text{O}_2\text{NaSi}$: $[\text{M}+\text{Na}]^+$: 289.1594, found: 289.1600. $[\alpha]_{\text{D}}^{20} = +3.2$ ($c = 1.0$, CH_2Cl_2 , $l = 50$ mm).

(R)-1-(benzyloxy)-3-((triethylsilyl)oxy)propan-2-ol (2g, Table 1, entry 7)—The general procedure was followed using 15 mol % catalyst **4a**, 0.70 equiv *N,N*-diisopropylethylamine, and 0.60 equiv chlorotriethylsilane to yield product as colorless oil (Run 1: 122 mg, 41%, $er = 95:5$, Run 2: 40%, $er = 95:5$). Chiral HPLC Analysis (OD-H, hexanes/*i*PrOH = 95/5, 1.0 mL/min, 220 nm, $t_{\text{rminor}} = 7.12$ min and $t_{\text{rmajor}} = 8.19$ min). ^1H NMR (CDCl_3 , 500 MHz) δ 7.26–7.35 (m, 5H), 4.54 (s, 2H), 3.82–3.87 (m, 1H), 3.66 (dd, 1H, $J = 10.0$, 4.9), 3.62 (dd, 1H, $J = 10.0$, 5.9), 3.53 (dd, 1H, $J = 9.5$, 4.9), 3.49 (dd, 1H, $J = 9.5$, 5.9), 2.48 (d, 1H, $J = 4.9$), 0.94 (t, 9H, $J = 7.8$), 0.59 (q, 6H, $J = 7.8$); ^{13}C NMR (CDCl_3 , 125 MHz) δ 138.4, 128.6, 128.0, 127.9, 73.7, 71.3, 71.0, 64.0, 6.9, 4.6; IR: 2953, 2910, 2875, 1089, 1004, 804, 728, 696 cm^{-1} ; HRMS (ESI+) calcd. for $\text{C}_{16}\text{H}_{28}\text{O}_3\text{NaSi}$: $[\text{M}+\text{Na}]^+$: 319.1700, found: 319.1697. $[\alpha]_{\text{D}}^{20} = -1.1$ ($c = 1.0$, CH_2Cl_2 , $l = 50$ mm).

(R)-1-phenoxy-3-((triethylsilyl)oxy)propan-2-ol (2h, Table 1, entry 8)—The general procedure was followed using 15 mol % catalyst **4a**, 0.80 equiv *N,N*-diisopropylethylamine, and 0.70 equiv chlorotriethylsilane. The reaction was stirred for 2 hours to yield product as colorless oil (Run 1: 98 mg, 35%, $er = 95:5$, Run 2: 37%, $er = 94:6$). Chiral HPLC Analysis (OD-H, hexanes/*i*PrOH = 90/10, 1.0 mL/min, 220 nm, $t_{\text{rminor}} = 5.11$ min and $t_{\text{rmajor}} = 10.66$ min). ^1H NMR (CDCl_3 , 500 MHz) δ 7.25–7.28 (m, 2H), 6.92–6.96 (m, 1H), 6.89–6.91 (m, 2H), 3.99–4.05 (m, 3H), 3.78 (dd, 1H, $J = 10.3$, 4.6), 3.74 (dd, 1H, $J = 10.3$, 5.1), 2.55 (d, 1H, $J = 5.1$), 0.94 (t, 9H, $J = 7.8$), 0.61 (q, 6H, $J = 7.8$); ^{13}C NMR (CDCl_3 , 125 MHz) δ 158.9, 129.7, 121.2, 114.8, 70.5, 68.7, 63.7, 6.9, 4.6; IR: 2953, 2876, 1599, 1495, 1458, 1242, 1079, 1043, 1005, 802, 745, 727, 689 cm^{-1} ; HRMS (ESI+) calcd. for $\text{C}_{15}\text{H}_{26}\text{O}_3\text{NaSi}$: $[\text{M}+\text{Na}]^+$: 305.1543, found: 305.1552. $[\alpha]_{\text{D}}^{20} = +1.2$ ($c = 1.0$, CH_2Cl_2 , $l = 50$ mm).

(R)-1-((triethylsilyl)oxy)but-3-en-2-ol (2i, Table 1, entry 9)—The general procedure was followed using 15 mol % catalyst **4b**, 0.80 equiv *N,N*-diisopropylethylamine, and 0.70 equiv chlorotriethylsilane to yield product as colorless oil (Run 1: 84 mg, 42%, $er = 89:11$, Run 2: 40%, $er = 89:11$). Chiral GLC Analysis (Beta Dex 120 (30 m $\times$ 0.15 mm $\times$ 0.25 mm film thickness), 90 $^\circ\text{C}$ for 50 min, 20 $^\circ\text{C}/\text{min}$ to 180 $^\circ\text{C}$, 180 $^\circ\text{C}$ for 20 min, 15 psi, $t_{\text{rminor}} = 42.9$ min, $t_{\text{rmajor}} = 44.6$ min). ^1H NMR (CDCl_3 , 500 MHz) δ 5.80 (ddd, 1H, $J = 17.1$, 10.5, 5.6), 5.33 (dt, 1H, $J = 17.4$, 1.5), 5.17 (dt, 1H, 10.5, 1.5), 4.13–4.18 (m, 1H), 3.64 (dd, 1H, $J = 10.0$, 3.7), 3.42 (dd, 1H, $J = 10.0$, 7.8), 2.57 (d, 1H, 3.4), 0.95 (t, 9H, $J = 7.8$), 0.60 (q, 6H, $J = 7.8$); ^{13}C NMR (CDCl_3 , 125 MHz) δ 136.8, 116.7, 73.3, 66.9, 6.9, 4.6; IR: 2955, 2912, 2877, 1238, 1102, 1004, 923, 795, 725 cm^{-1} ; HRMS (ESI+) calcd. for $\text{C}_{10}\text{H}_{22}\text{O}_2\text{NaSi}$: $[\text{M}+\text{Na}]^+$: 225.1281, found: 225.1285. $[\alpha]_{\text{D}}^{20} = +0.3$ ($c = 1.0$, CH_2Cl_2 , $l = 50$ mm).

(R)-1-phenyl-2-((triethylsilyl)oxy)ethanol (2j, Table 1, entry 10)—The general procedure was followed using 15 mol % catalyst **4b**, 0.60 equiv *N,N*-diisopropylethylamine, 0.50 equiv chlorotriethylsilane, and *t*-Amyl-OH as solvent to yield product as colorless oil (Run 1: 96 mg, 38%, $er = 96:4$, Run 2: 39%, $er = 95:5$). Chiral HPLC Analysis (OD-H, hexanes/*i*PrOH = 95/5, 1.0 mL/min, 220 nm, $t_{\text{rminor}} = 4.84$ min and $t_{\text{rmajor}} = 5.56$ min). ^1H NMR (CDCl_3 , 500 MHz) δ 7.31–7.37 (m, 4H), 7.25–7.28 (m, 1H), 4.74 (dt, 1H, $J = 8.3$, 3.2), 3.75 (dd, 1H, $J = 10.3$, 3.7), 3.52 (dd, 1H, $J = 10.0$, 9.0), 2.97 (d, 1H, $J = 2.2$), 0.95 (t, 9H, $J = 8.1$), 0.61 (q, 6H, $J = 8.1$); ^{13}C NMR (CDCl_3 , 125 MHz) δ 104.5, 128.5, 128.0, 126.4, 74.6, 68.8, 6.9, 4.6; IR: 2954, 2911, 2876, 1454, 1103, 1062, 1004, 727, 698, 532 cm^{-1} ; HRMS (ESI+) calcd. for $\text{C}_{14}\text{H}_{23}\text{OSi}$: $[\text{M}-\text{OH}]^+$: 235.1518, found: 235.1523. $[\alpha]_{\text{D}}^{20} = -26.2$ ($c = 1.0$, CH_2Cl_2 , $l = 50$ mm).

(S)-1-bromo-3-((triethylsilyl)oxy)propan-2-ol (2k, Table 1, entry 11)—The general procedure was followed using 10 mol % catalyst **4b**, 0.80 equiv *N,N*-diisopropylethylamine, and 0.70 equiv chlorotriethylsilane, to yield product as colorless oil (Run 1: 110 mg, 41%, er = 97.5:2.5, Run 2: 40%, er = 97.5:2.5). Chiral GLC Analysis (Gamma Dex 120 (30 m × 0.15 mm × 0.25 mm film thickness), 110 °C for 160 min, 20 °C/min to 180 °C, 180 °C for 20 min, 15 psi, $t_{\text{rminor}} = 73.6$ min, $t_{\text{rmajor}} = 74.8$ min). ^1H NMR (CDCl_3 , 500 MHz) δ 3.83 (ddd, 1H, $J = 16.4, 6.1, 4.9$), 3.72 (dd, 1H, $J = 10.0, 4.6$), 3.68 (dd, 1H, $J = 10.0, 4.9$), 3.41–3.49 (m, 2H), 2.56 (d, 1H, $J = 6.4$), 0.93–0.96 (m, 9H), 0.61 (q, 6H, $J = 7.8$); ^{13}C NMR (CDCl_3 , 125 MHz) δ 71.3, 64.0, 34.7, 6.9, 4.5; IR: 2955, 2876, 1459, 1240, 1108, 1006, 799, 727, 671 cm^{-1} ; HRMS (ESI+) calcd. for $\text{C}_9\text{H}_{22}\text{BrO}_2\text{Si}$: $[\text{M}+\text{H}]^+$: 269.0572, found: 269.0576. $[\alpha]_{\text{D}}^{20} = -1.0$ ($c = 1.0$, CH_2Cl_2 , $l = 50$ mm).

(S)-1-chloro-3-((triethylsilyl)oxy)propan-2-ol (2l, Table 1, entry 12)—The general procedure was followed using 10 mol % catalyst **4b**, 0.80 equiv *N,N*-diisopropylethylamine, and 0.70 equiv chlorotriethylsilane, to yield product as colorless oil (Run 1: 94 mg, 42%, er = 97.5:2.5, Run 2: 40%, er = 97.5:2.5). Chiral GLC Analysis (Gamma Dex 120 (30 m × 0.15 mm × 0.25 mm film thickness), 110 °C for 50 min, 20 °C/min to 180 °C, 180 °C for 20 min, 15 psi, $t_{\text{rminor}} = 44.3$ min, $t_{\text{rmajor}} = 45.0$ min). ^1H NMR (CDCl_3 , 500 MHz) δ 3.80–3.86 (m, 1H), 3.66–3.72 (m, 2H), 3.54–3.61 (m, 2H), 2.54 (d, 1H, $J = 6.4$), 0.93–0.96 (m, 9H), 0.61 (q, 6H, $J = 8.1$); ^{13}C NMR (CDCl_3 , 125 MHz) δ 71.6, 63.3, 45.6, 6.9, 4.5; IR: 3425, 2955, 2877, 1459, 1240, 1111, 1006, 804, 740 cm^{-1} ; HRMS (ESI+) calcd. for $\text{C}_9\text{H}_{22}\text{ClO}_2\text{Si}$: $[\text{M}+\text{H}]^+$: 225.1070, found: 225.1078. $[\alpha]_{\text{D}}^{20} = -2.5$ ($c = 1.1$, CH_2Cl_2 , $l = 50$ mm).

Large Scale Experiment (equation 1)

In a dry box, a solution of 3-chloropropane-1,2-diol (1.1 g, 10 mmol), catalyst **4b** (310 mg, 1.0 mmol, 10 mol %), and *N,N*-diisopropylethylamine hydrochloride (99 mg, 0.60 mmol, 6 mol %) in anhydrous *tert*-butanol (150 mL) was prepared in an oven-dried 250 mL round-bottom flask. The reaction was brought out of the dry box, and was stirred at room temperature for 45 minutes. *N,N*-diisopropylethylamine (1.4 mL, 8.0 mmol) was added, followed by addition of chlorotriethylsilane (1.2 mL, 7.0 mmol) in 4 portions every 15 minutes (dropwise addition was performed for each portion added). The reaction was stirred at room temperature for 1 hour (starting from the first addition of chlorotriethylsilane). Methanol (1.5 mL) was added to quench the reaction. The solvent was removed under reduced pressure, and flash column chromatography (hexanes:EtOAc = 60:1) afforded pure product as colorless oil (940 mg, 45%, er = 97:3).

Kinetic Resolution Using *tert*-Butyldimethylsilyl Chloride (equation 2)

In a dry box, a solution of hexane-1,2-diol (120 mg, 1.0 mmol), catalyst **4a** (42 mg, 0.15 mmol, 15 mol %), and *N,N*-diisopropylethylamine hydrochloride (10 mg, 0.060 mmol, 6 mol %) in anhydrous *tert*-butanol (15 mL) was prepared in an oven-dried glass reaction vial. The reaction was brought out of the dry box, and was stirred at room temperature for 45 minutes. *N,N*-diisopropylethylamine (140 μL , 0.80 mmol) was added, followed by addition of *tert*-butyldimethylsilyl chloride (110 mg, 0.70 mmol). The reaction was stirred at 4 °C for 24 hours. Methanol (150 μL) was added to quench the reaction. The solvent was removed under reduced pressure, and flash column chromatography (hexanes:EtOAc = 60:1) afforded pure product as colorless oil (Run 1: 106 mg, 46%, er = 89:11, Run 2: 101 mg, 43%, er = 89:11). Chiral GLC Analysis (Beta Dex 120 (30 m × 0.15 mm × 0.25 mm film thickness), 95 °C for 80 min, 20 °C/min to 180 °C, 180 °C for 20 min, 15 psi, $t_{\text{rminor}} = 56.9$ min, $t_{\text{rmajor}} = 57.8$ min).

(R)-1-((*tert*-butyldimethylsilyl)oxy)hexan-2-ol (2ba)— ^1H NMR (CDCl_3 , 500 MHz) δ 3.59–3.63 (m, 2H), 3.37 (dd, 1H, $J = 10.5, 8.3$), 2.38 (d, 1H, $J = 3.4$), 1.24–1.43 (m, 6H),

0.86-0.90 (m, 12H), 0.05 (s, 6H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 72.1, 67.5, 32.7, 28.0, 26.1, 23.0, 18.5, 14.2, -5.1, -5.2; IR: 2955, 2929, 2858, 1463, 1254, 1098, 835, 775 cm^{-1} ; HRMS (ESI+) calcd. for $\text{C}_{12}\text{H}_{29}\text{O}_2\text{Si}$: $[\text{M}+\text{H}]^+$: 233.1937, found: 233.1938. $[\alpha]_{\text{D}}^{20} = -4.6$ ($c = 1.0$, CH_2Cl_2 , $l = 50$ mm).

Kinetic Resolution Using Triisopropylsilyl Chloride (equation 2)

In a dry box, a solution of hexane-1,2-diol (120 mg, 1.0 mmol), catalyst **4a** (42 mg, 0.15 mmol, 15 mol %), and *N,N*-diisopropylethylamine hydrochloride (10 mg, 0.060 mmol, 6 mol %) in anhydrous *tert*-butanol (15 mL) was prepared in an oven-dried glass reaction vial. The reaction was brought out of the dry box, and was stirred at room temperature for 45 minutes. *N,N*-diisopropylethylamine (140 μL , 0.80 mmol) was added, followed by addition of triisopropylsilyl chloride (150 μL , 0.70 mmol). The reaction was stirred at 4 $^\circ\text{C}$ for 48 hours. Methanol (150 μL) was added to quench the reaction. The solvent was removed under reduced pressure, Flash column chromatography (hexanes:EtOAc = 60:1) afforded pure product as colorless oil (Run 1: 115 mg, 42%, er = 95:5, Run 2: 105 mg, 38%, er = 97:3). Chiral GLC Analysis (Gamma Dex 120 (30 m $\times$ 0.15 mm $\times$ 0.25 mm film thickness), 110 $^\circ\text{C}$ for 150 min, 20 $^\circ\text{C}/\text{min}$ to 180 $^\circ\text{C}$, 180 $^\circ\text{C}$ for 20 min, 15 psi, $t_{\text{rminor}} = 137.4$ min, $t_{\text{rmajor}} = 140.7$ min).

(R)-1-((triisopropylsilyl)oxy)hexan-2-ol (2bb)— ^1H NMR (CDCl_3 , 500 MHz) δ 3.64 (dd, 1H, $J = 9.5, 3.2$), 3.56-3.61 (m, 1H), 3.40 (dd, 1H, $J = 9.5, 7.6$), 2.47 (d, 1H, 3.2), 1.25-1.39 (m, 6H), 0.95-1.07 (m, 21H), 0.84 (m, 3H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 72.2, 67.8, 32.7, 28.0, 23.0, 18.2, 14.2, 12.1; IR: 2940, 2865, 1463, 1103, 882, 797, 681, 660 cm^{-1} ; HRMS (ESI+) calcd. for $\text{C}_{15}\text{H}_{35}\text{O}_2\text{Si}$: $[\text{M}+\text{H}]^+$: 275.2406, found: 275.2415. $[\alpha]_{\text{D}}^{20} = -4.2$ ($c = 1.0$, CH_2Cl_2 , $l = 50$ mm).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Reaction time course at 0 °C with a single addition of TESCI

Figure 2. Reaction time course at room temperature with a syringe pump addition of TESCl

Scheme 1. Regiodivergent kinetic resolution of terminal 1,2-diol

Scheme 2. Kinetic model for formation of (S)-3a

Table 1
Kinetic Resolution of 1,2-diols

entry	R	catalyst	yield 2 (%) ^g	er 2 (%)
1 ^a	-CH ₂ CH(CH ₃) ₂ (a)	10% 4b	46	96.5:3.5
2 ^b	-(CH ₂) ₃ CH ₃ (b)	10% 4a	44	96:4
3	-Cy (c)	10% 4b	47	96:4
4 ^c	- <i>t</i> -Bu (d)	15% 4b	43	95.5:4.5
5 ^d	-CH ₃ (e)	15% 4b	37	94:6
6 ^a	-CH ₂ Ph (f)	10% 4b	41	96:4
7 ^b	-CH ₂ OBn (g)	15% 4a	40	95:5
8 ^e	-CH ₂ OPh (h)	15% 4a	36	94.5:5.5
9 ^a	-CH=CH ₂ (i)	15% 4b	41	89:11
10 ^f	-Ph (j)	15% 4b	39	95.5:4.5
11 ^a	-CH ₂ Br (k)	10% 4b	40	97.5:2.5
12 ^a	-CH ₂ Cl (l)	10% 4b	41	97.5:2.5

^a 0.70 equiv TESCl and 0.80 equiv DIPEA were used.

^b 0.60 equiv TESCl and 0.70 equiv DIPEA were used.

^c 0.60 equiv TESCl and 0.70 equiv DIPEA were used, *t*-Amyl-OH was used as solvent, reaction was run at 4 °C for 2 h.

^d 0.80 equiv TESCl and 0.90 equiv DIPEA were used.

^e 0.70 equiv TESCl and 0.80 equiv DIPEA were used, reaction time was 2 h.

^f 0.50 equiv TESCl and 0.60 equiv DIPEA were used, *t*-Amyl-OH was used as solvent.

^g isolated yields.