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One-Step Preparation of *O*-(α-Bromoacyl) Cyanohydrins by Minor Enantiomer Recycling: Synthesis of 4-Amino-2(5*H*)-furanones

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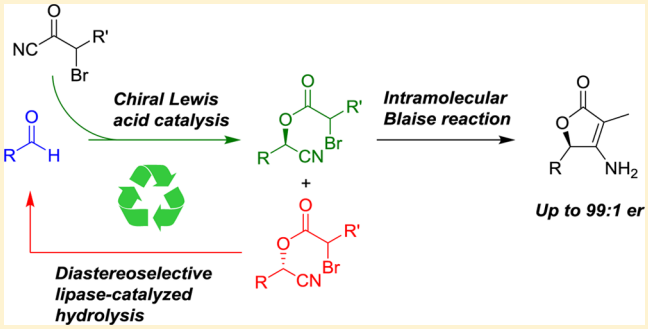
Supporting Information

ABSTRACT: *O*-(α-Bromoacyl) cyanohydrins were prepared in a single step from a range of different aldehydes in combination with α-bromoacyl cyanides. By the use of a cyclic procedure where the two minor diastereoisomers from a chiral Lewis acid-catalyzed reaction undergo *Candida antarctica* lipase B (CALB)-catalyzed hydrolysis followed by dehydrocyanation to regenerate the starting material, the products were obtained in good to high yields and in most cases with excellent diastereoselectivites. The synthetic importance of these compounds was demonstrated by the synthesis of 4-amino-2(5*H*)-furanones, a class of compounds that have shown both biological activity and utility as synthetic intermediates. This transformation was achieved by an intramolecular Blaise reaction, which gave the products in high to excellent yields and enantiomeric ratios.



INTRODUCTION

The 2(5*H*)-furanone structural motif (Figure 1) is found in a wide range of compounds, many of which exhibit interesting

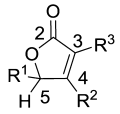


Figure 1. The 2(5*H*)-furanone structural motif.

biological properties.[1] For this reason, extensive efforts have been devoted to syntheses of furanone derivatives.[2] Among these, 4-amino-substituted furanones are of particular interest because of their importance as synthetic intermediates as well as their biological activity. The introduction of an amino group in the furanone part of the natural product squamocin, for example, gave a product with increased cytotoxic activity that was found to inhibit both mitochondrial complexes I and III.[3] Betulin derivatives functionalized with different 4-amino-2(5*H*)-furanones showed in several cases higher cytotoxic activity toward human cancer cell lines than the native compound.[4] 4-Amino-2(5*H*)-furanones have been used as intermediates in the synthesis of (+)-eldanolide[5] as well as in the synthesis of the antibiotic virginiamycin M2.[6] Furthermore, amino-substituted five-membered lactones have been used as starting materials for the synthesis of several β-lactams and β-amino esters.[7]

Diverse methodologies have been developed for the synthesis of aminofuranones. Achiral 3-substituted aminofuranones have been obtained by electrocyclic ring opening of 4-hydroxy-3-aminocyclobutenones,[8] and racemic 5,5-disubstituted derivatives have been formed from 3-hydroxyalkynes via sequential Pd-catalyzed oxidative carbonylation, conjugate addition, and lactonization.[9] Enantioenriched aminofuranones have been prepared by diastereoselective alkylation of lithium enolates of vinylogous urethanes[10] as well as by enantioselective alkyne additions to aldehydes using (*S*)-BINOL for the chiral induction followed by conjugate addition of an amine; this latter method afforded 4-amino-2(5*H*)-furanones with 84−90% ee.[11] A similar procedure was used for the synthesis of enantioenriched tetronic acids [4-hydroxy-2(5*H*)-furanones or tetrahydrofuran-2,4-diones].[12]

Cyanohydrins derived from both aldehydes and ketones have frequently been employed as starting materials for the preparation of aminofuranones. In the presence of a strong base, such as $LiN(SiMe_3)_2$, ester enolates of *O*-acylated racemic[13] or enantioenriched[14] cyanohydrins, the latter obtained via kinetic resolution of the acylated ketone cyanohydrins[14a] or enzyme-catalyzed HCN addition to ketones,[14b] cyclize to give aminofuranones. An alternative procedure consisting of the addition of a Reformatsky reagent to TMS-protected cyanohydrins (the Blaise reaction[15]) followed by deprotection and lactonization was applied to the synthesis of both tetronic acids[16] and 4-aminobutyrolactones.[17] The latter type of products were also shown to be accessible by cyclization of 3-acetamido-4-acetoxyalkanoic acids, which in turn were obtained via a reaction sequence consisting of the initial addition of an allyl-Grignard reagent to the same cyanohydrins.[18] Enantioenriched *O*-(α-bromoacyl) cyanohy-

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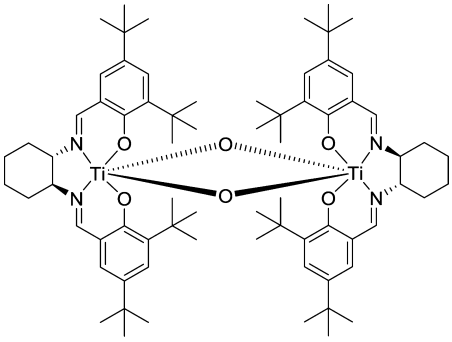
drins have also been used in an intramolecular Blaise reaction to give 4-amino- and 4-hydroxyfuranones.[19] A derivative of the latter type was recently employed as starting material for the preparation of a compound originally assumed to be identical to gobienine A.[20]

We previously developed a convenient one-step method for the synthesis of highly enantioenriched *O*-acylated cyanohydrins from aldehydes and acyl cyanides that employs a dual-activation catalytic system consisting of the chiral titanium salen dimer **1**[21] and a Lewis base (e.g., a tertiary amine) at −40 °C.[22] The enantiomeric ratio was generally in the range 95:5 to 98:2,[22] but lower selectivities were observed for products that undergo racemization in the presence of the base needed for the catalytic reaction.[23] In order to further increase the enantioselectivity and at the same time avoid problems connected to the presence of base, we developed a recycling procedure involving two chiral catalysts. Here, by the use of a second chiral catalyst, the minor enantiomer from the product-forming catalytic reaction undergoes a reversed process to restore the prochiral starting material, thereby establishing a cyclic process. With the combination of the titanium salen dimer **1** and a biocatalyst, highly enantioenriched *O*-acylated cyanohydrins were obtained, in most cases in high yields, from the reaction between aldehydes and acyl cyanides.[24] A thermodynamic driving force maintaining a unidirectional cycle is secured by a constant feed of acyl cyanide and the irreversible formation of carboxylate ions.



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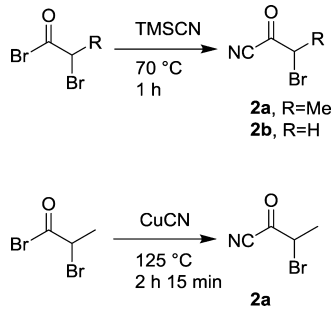
We anticipated that a direct route for the preparation of *O*-(α-bromoacyl) cyanohydrins, avoiding the intermediacy of racemization-prone cyanohydrins, would constitute an attractive initial step toward the preparation of enantioenriched aminofuranones. The use of α-bromoacyl cyanides in the cyanation of aldehydes would give direct access to the products needed for the subsequent Blaise cyclizations.[19]

RESULTS AND DISCUSSION

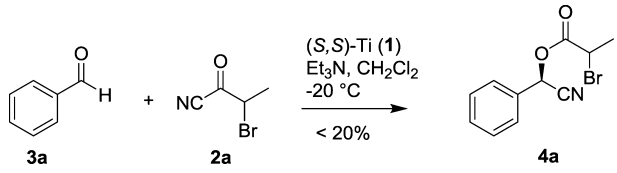
The required α-bromoacyl cyanides **2a** and **2b** (**2a** in racemic form) were synthesized from the appropriate acyl bromides and TMSCN according to a literature procedure.[25] Compound **2a** could also be prepared using the less expensive CuCN as source of cyanide (Scheme 1).

We first attempted our standard acylcyanation conditions[22] for the reaction of benzaldehyde (**3a**) with acyl cyanide **2a** at −20 °C in dichloromethane, employing a catalytic system consisting of titanium salen dimer **1** and triethylamine (Scheme 2). Not surprisingly, because of the high reactivity of acyl bromides with triethylamine,[26] low conversion of the aldehyde and only minor amounts of product were observed. The minor

Scheme 1. Synthesis of Acyl Cyanides 2



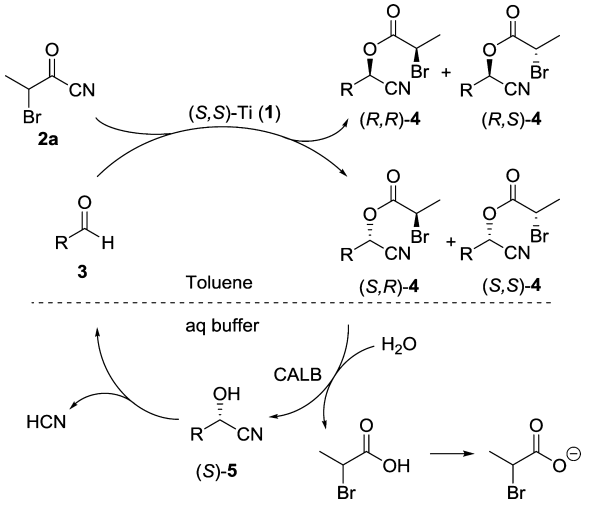
Scheme 2. Attempted Acylcyanation of 3a Using the Dual-Activation Procedure



enantiomer recycling procedure does not require the presence of base and was therefore assumed to be more beneficial.

When a combination of the (*S*,*S*)-Ti catalyst **1** and *Candida antarctica* lipase B (CALB) in a two-phase system consisting of toluene and aqueous buffer was employed, the desired products were indeed obtained (Table 1). Since racemic **2a** was used, four stereoisomers of the product were expected to form. Whereas the stereocenter in the acyl part of the product would

Table 1. Synthesis of *O*-Acylated Cyanohydrins 4 via Minor Enantiomer Recycling



entry	product	R	yield (%)[a]	[(*R*,*S*) + (*R*,*R*)]/[(*S*,*R*) + (*S*,*S*)][b]
1	**4a**	C_6H_5	64	99.4:0.6
2	**4b**	4-ClC_6H_4	78	98.6:1.4
3	**4c**	4-$MeOC_6H_4$	64	~98:2[c]
4	**4d**	4−BrC_6H_4	80	96.1:3.9
5	**4e**	4-MeC_6H_4	68	97.2:2.8
6	**4f**	(*E*)-$CH_3CH{=}CH$	51	97.4:2.6
7	**4g**	*n*-C_4H_9	65	99.0:1.0

[a]Isolated yields. [b]Determined by chiral GC or HPLC. [c]Measured between only two peaks because of poor separation.

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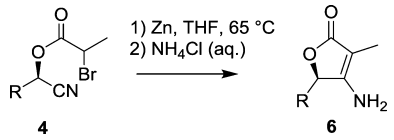
be lost in the subsequent Blaise reaction, the configuration at the C−O stereocenter was crucial. When benzaldehyde (**3a**) was used as a substrate, excellent selectivity for the isomers with the *R* absolute configuration at the C−O stereocenter was observed, and the products (*R*,*R*)- and (*R*,*S*)-**4a** were isolated in good combined yield (entry 1). High yields and selectivities were observed for both electron-rich (entries 3 and 5) and electron-deficient substrates (entries 2 and 4). The product from (*E*)-butenal (**3f**) (containing ca. 5% of the *Z* isomer) was obtained in somewhat lower yield as a result of the presence of the nonacylated cyanohydrin (**5f**) but still with high selectivity (entry 6). The *E*/*Z* ratio of the products was essentially the same as that of the starting material.

In the reaction with pentanal (entry 7), both the yield of product **4g** and the [(*R*,*R*) + (*R*,*S*)] to [(*S*,*R*) + (*S*,*S*)] isomer ratio increased as expected during the initial part of the reaction, whereafter a slight decline in the isomeric ratio was observed. We assumed that this effect was due to enzyme inhibition, leading to a lower rate of hydrolysis of (*S*,*R*)- and (*S*,*S*)-**4g**; the enzyme was indeed shown to exhibit decreased activity toward these minor isomers of **4g** in the presence of **2a**. A gradual decrease in the rate of addition of **2a** served to maintain a balance between the rates of the product-forming forward reaction and the reverse hydrolysis, whereby the decrease in stereoselectivity could be avoided (see the Supporting Information). However, a more convenient synthetic procedure consisted of the addition of acyl cyanide **2a** over 8 h, which gave the products with a diastereomeric ratio of 80:20, followed by kinetic resolution, achieved by continued stirring in the presence of the enzyme. In this way, a 65% yield of **4g** with a diastereomeric ratio of 99:1 could be isolated.

The enantioenriched products **4** obtained from the minor enantiomer recycling were then subjected to an intramolecular Blaise reaction using metallic zinc in THF at 65 °C followed by quenching with NH_4Cl(aq), which afforded 4-amino-2(5*H*)-furanones **6** (Table 2). In most cases, the reaction resulted in high yield and no or little racemization. The small differences between the isomeric ratios of the starting materials and products observed in a few cases (**4d** and **4f**) could be the result of slightly different reactivities of the diastereomeric *O*-acyl cyanohydrins (Table 2, entries 4 and 6).

Table 2. Synthesis of Aminofuranones (*R*)-6 via Intramolecular Blaise Reaction



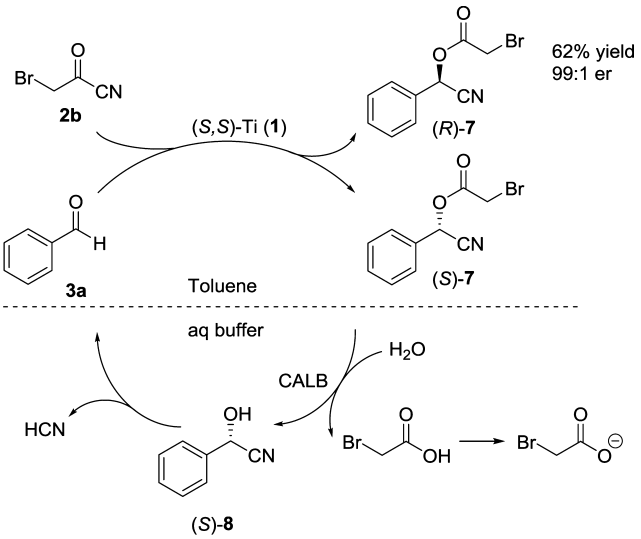
4 **6**

entry	product	R	yield (%)[a]	er[b]
1	**6a**	C_6H_5	86	98.6:1.4
2	**6b**	4-ClC_6H_4	97	98.4:1.6
3	**6c**	4-$MeOC_6H_4$	98	97.9:2.1
4	**6d**	4-BrC_6H_4	73	97.3:2.7
5	**6e**	4-MeC_6H_4	93	97.3:2.7
6	**6f**	(*E*)-CH_3CH=CH	94	95.4:4.6
7	**6g**	*n*-C_4H_9	71	98.8:1.2

[a]Isolated yields. [b]Determined by chiral GC or HPLC.

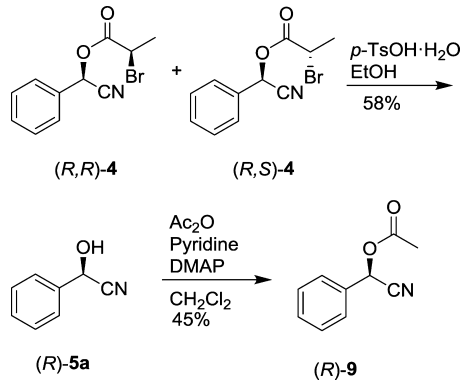
We then proceeded with the synthesis of *O*-(α-bromo)-acetylated cyanohydrin **7**. Because of the poor solubility of **2b** in toluene, this reaction was run in the more polar solvent cyclopentyl methyl ether, which has a boiling point similar to that of toluene. However, as shown by ^{1}H NMR spectroscopy, large amounts of free cyanohydrin (**8**) were present, and as a consequence, low yields of the acylated products were obtained. These problems were solved when **2b** dissolved in cyclopentyl methyl ether was added to the reaction mixture in toluene. Under these conditions, benzaldehyde (**3a**) and acyl cyanide **2b** afforded the desired product (*R*)-**7** with excellent er (99:1) and in good yield (62%) (Scheme 3).

Scheme 3. Synthesis of (*R*)-7 via Minor Enantiomer Recycling



To verify the absolute configuration at the C−O stereocenter of the products, the *O*-acylated product **4a** was cleaved by *p*-TsOH in EtOH to give cyanohydrin **5a** (Scheme 4). This cyanohydrin was then acetylated using acetic anhydride to give the known compound (*R*)-**9**. Comparison of the sign of the optical rotation of (*R*)-**9** with literature data[27] unambiguously confirmed the absolute configuration to be *R*. Products **4b**−**g** and **7** were treated in the same way to give the corresponding acetylated compounds. The HPLC retention order of the products derived from **4b**,[28a] **4c**,[28b] and **4d**[28a] were compared to literature data, which showed the absolute configuration of the C−O stereocenter in all cases to be *R*. To assign the configurations of **4e**,[28c] **4f**,[24c] and **4g**,[28d] the GC or HPLC

Scheme 4. Synthesis of (*R*)-9 for Determination of the Absolute Configuration



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retention times of the acetylated compounds were compared to samples known to have *R* configuration; these samples were obtained by previously described enzyme-catalyzed hydrolysis of the racemic compounds. The GC retention time of the acetylated compound derived from **7** was shown to be the same as that of (*R*)-**9**.

CONCLUSION

O-(α-Bromoacyl) cyanohydrins with high diasteromeric purity were obtained by a one-step recycling procedure consisting of acylcyanation of prochiral aldehydes and regeneration of the starting material from the minor, undesired diastereomers of the product. When the reverse reaction, which is a kinetic resolution, was allowed to continue after addition of acyl cyanide was terminated, the two minor diastereomers were completely consumed. The *O*-(α-bromoacyl) cyanohydrins obtained were transformed into (*R*)-4-amino-2(5*H*)-furanones in high yields; these furanone products can serve as starting materials for the synthesis of a variety of biologically active compounds. High enantiomeric purities of the cyclized products were observed. This is particularly important for synthetic applications where no additional stereogenic centers are present in the target compounds, since cumbersome separation of enantiomers is avoided.

EXPERIMENTAL SECTION

General. Dry dichloromethane and THF were taken from a Glass Contour solvent dispensing system. Oven- or flame-dried glassware was used when necessary. (*S*,*S*)-[(4,6-Bis(^{t}butyl)salen)Ti(μ-O)]$_2$ (**1**) was prepared according to a published procedure.[21] Immobilized (acrylic resin, ≥5000 units/g) *Candida antarctica* lipase B (CALB) and zinc powder (<10 μm) were purchased from Sigma Aldrich a commercial supplier. Benzaldehyde, 4-methoxybenzaldehyde, 4-methylbenzaldehyde, (*E*)-2-butenal, and pentanal were distilled, and 4-chlorobenzaldehyde and 4-bromobenzaldehyde were recrystallized from EtOH/H_2O 3:1 prior to use. ^{1}H and ^{13}C NMR spectra were recorded at 500 and 125 MHz, respectively. The ^{1}H and ^{13}C chemical shifts are reported in parts per million relative to residual $CHCl_3$ or CD_2HOD in $CDCl_3$ and CD_3OD, respectively. GC analyses were conducted with a FID detector and a chiral column (CYCLOSIL B, 30 m × 0.25 mm × 0.25 μm). HPLC analyses were conducted with a UV detector and a chiral column (Daicel Chiralpak IC, 0.46 cm × 25 cm, and Daicel Chiralcel OD-H, 0.46 cm × 25 cm).

2-Bromopropanoyl Cyanide (2a). 2-Bromopropionyl bromide (4.0 mL, 38.2 mmol) was added to a two-neck flask containing CuCN (3.87 g, 43.2 mmol) under nitrogen, and the mixture was stirred at 125 °C for 2 h 15 min. Vacuum distillation (~9 mbar) directly from the reaction flask at 60 °C gave **2a** (2.50 g, 40%) as a pale-yellow liquid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.56 (q, *J* = 6.8 Hz, 1 H), 1.89 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.5, 111.7, 46.4, 18.8.

General Procedure for Minor Enantiomer Recycling. Aldehyde (1 equiv) and (*S*,*S*)-[(salen)Ti(μ-O)]$_2$ (5−10 mol %) (**1**) were dissolved in toluene, and CALB and phosphate buffer were added. The mixture was stirred at room temperature or 40 °C while acyl cyanide **2a** (3 equiv) dissolved in toluene was added to the organic phase over 24−50 h using a syringe pump. When the addition was complete, the phases were separated, and the aqueous phase was extracted with Et_2O. The combined organic phases were dried over $MgSO_4$ and the solvents evaporated. The crude product was purified by flash chromatography.

(*R*)-Cyano(phenyl)methyl 2-Bromopropanoate (4a). The general procedure was followed using benzaldehyde (240 μL, 2.36 mmol), CALB (200 mg), and (*S*,*S*)-[(salen)Ti(μ-O)]$_2$ (144 mg, 0.118 mmol) in toluene (10 mL) and 2 M pH 6 buffer (10 mL) at 40 °C. **2a** (1.15 g, 7.10 mmol) in toluene (2.5 mL total volume) was added over 50 h. Flash chromatography (hexanes/EtOAc 39:1 to 19:1, R_f = 0.24 hexanes/EtOAc 19:1) gave **4a** (406 mg, 64%, [(*RS* + *RR*)/(*SR* + *SS*)] = 99.4:0.6) as a colorless oil. HPLC (Daicel Chiralpak IC, hexanes/2-propanol 99.5:0.5, flow rate = 0.6 mL/min, detection at 220 nm): t_R (minor) 26.0 min, t_R (major) 27.8 min, t_R (minor) 31.1 min, t_R (major) 39.1 min. $[\alpha]_D^{21}$ +7.4 (*c* 1.0, $CHCl_3$). IR: 2965, 2360, 2343, 1760, 1210, 1142, 757, 696 cm^{-1}. Mixture of diastereoisomers: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52−7.57 (m, 2H), 7.45−7.51 (m, 3H), 6.44 and 6.45 (s, 1H), 4.43 and 4.41 (q, *J* = 6.9 Hz, 1H), 1.87 and 1.85 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.6 and 168.5, 131.2 and 131.1, 130.9 and 130.8, 129.51 and 129.48, 128.1 and 127.9, 115.7 and 115.5, 64.3 and 64.2, 38.5 and 38.4, 21.4 and 21.3. HRMS (ESI-Orbitrap) *m*/*z*: [M + H]$^+$ calcd for $C_{11}H_{11}BrNO_2$ 267.9968, found 267.9960.

(*R*)-Cyano(4-chlorophenyl)methyl 2-Bromopropanoate (4b). The general procedure was followed using 4-chlorobenzaldehyde (337 mg, 2.40 mmol), CALB (200 mg), and (*S*,*S*)-[(salen)Ti(μ-O)]$_2$ (146 mg, 0.120 mmol) in toluene (10 mL) and 2 M pH 7 buffer (10 mL) at 40 °C. **2a** (1.17 g, 7.25 mmol) in toluene (2.5 mL total volume) was added over 24 h. Flash chromatography (hexanes/EtOAc 19:1 to 9:1, R_f = 0.24 hexanes/EtOAc 19:1) gave **4b** (567 mg, 78%, [(*RS* + *RR*)/(*SR* + *SS*)] = 98.6:1.4) as a colorless oil. HPLC (Daicel Chiralpak IC and Daicel Chiralcel OD-H in series, hexanes/2-propanol 99:1, flow rate = 0.4 mL/min, detection at 220 nm): t_R (major) 83.8 min, t_R (minor) 114.7 min, t_R (minor) 123.1 min, t_R (major) 134.8 min. $[\alpha]_D^{21}$ −3.0 (*c* 1.0, $CHCl_3$). IR: 2978, 2931, 2360, 2342, 1757, 1494, 1140, 1093, 822 cm^{-1}. Mixture of diastereoisomers: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49 (d, *J* = 8.6 Hz, 2H), 7.44−7.47 (m, 2H), 6.42 and 6.40 (s, 1H), 4.43 and 4.40 (q, *J* = 6.9 Hz, 1H), 1.86 and 1.85 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.5 and 168.3, 137.2 and 137.1, 129.82 and 129.80, 129.7 and 129.6, 129.5 and 129.3, 115.3 and 115.1, 63.6 and 63.5, 38.4 and 38.2, 21.4 and 21.3. HRMS (ESI-Orbitrap) *m*/*z*: [M + Na]$^+$ calcd for $C_{11}H_9BrClNO_2Na$ 323.9397, found 323.9390.

(*R*)-Cyano(4-methoxyphenyl)methyl 2-Bromopropanoate (4c). The general procedure was followed using 4-methoxybenzaldehyde (290 μL, 2.38 mmol), CALB (200 mg), and (*S*,*S*)-[(salen)Ti(μ-O)]$_2$ (290 mg, 0.238 mmol) in toluene (10 mL) and 2 M pH 7 buffer (10 mL) at room temperature. **2a** (1.16 g, 7.15 mmol) in toluene (2.5 mL total volume) was added over 50 h. Flash chromatography (first one separation with hexanes/EtOAc 9:1 then one with 100% dichloromethane as eluent, R_f = 0.23 hexanes/EtOAc 9:1) gave **4c** (452 mg, 64%, [(*RS* + *RR*)/(*SR* + *SS*)] ≈ 98:2) as a pale-yellow oil. HPLC (Daicel Chiralpak IC, hexanes/2-propanol 99.5:0.5, flow rate = 0.6 mL/min, detection at 220 nm): t_R (major and minor overlapped) 42.1 min, t_R (minor) 54.4 min, t_R (major) 59.5 min. $[\alpha]_D^{21}$ −10.9 (*c* 1.0, $CHCl_3$). IR: 2963, 2937, 2840, 2360, 2342, 1752, 1611, 1515, 1255, 1141, 831 cm^{-1}. Mixture of diastereoisomers: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47 (dd, *J* = 1.8, 8.7 Hz, 2H), 6.96 (d, *J* = 8.7 Hz, 2H), 6.39 and 6.38 (s, 1H), 4.40 and 4.38 (q, *J* = 6.9 Hz, 1H), 3.84 (s, 3H), 1.85 and 1.83 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.7 and 168.5, 161.51 and 161.47, 129.9 and 129.7, 123.2 and 123.1, 115.9 and 115.7, 114.80 and 114.79, 64.1 and 64.0, 55.60 and 55.59, 38.6 and 38.5, 21.40 and 21.35. HRMS (ESI-Orbitrap) *m*/*z*: [M + Na]$^+$ calcd for $C_{12}H_{12}BrNO_3Na$ 319.9893, found 319.9887.

(*R*)-Cyano(4-bromophenyl)methyl 2-Bromopropanoate (4d). The general procedure was followed using 4-bromobenzaldehyde (178 mg, 0.963 mmol), (*S*,*S*)-[(salen)Ti(μ-O)]$_2$ (58.4 mg, 0.0480 mmol), and CALB (80 mg) in toluene (4 mL) and 2 M pH 7 buffer (4 mL) at room temperature. **2a** (465 mg, 2.87 mmol) in toluene (1 mL total volume) was added over 50 h. Flash chromatography (hexanes/EtOAc 39:1 to 19:1, R_f = 0.32 hexanes/EtOAc 19:1) gave **4d** (266 mg, 80%, [(*RS* + *RR*)/(*SR* + *SS*)] = 96.1:3.9) as a colorless oil. HPLC (Daicel Chiralpak IC and Daicel Chiralcel OD-H in series, hexanes/2-propanol 98.5:1.5, flow rate = 0.4 mL/min, detection at 220 nm): t_R (major) 75.1 min, t_R (minor) 99.6 min, t_R (minor) 106.1 min, t_R (major) 121.2 min. $[\alpha]_D^{21}$ −5.0 (*c* 0.66, $CHCl_3$). IR: 2961, 2931, 2360, 2343, 1756, 1490, 1140, 1073, 871 cm^{-1}. Mixture of diastereoisomers: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.60−7.63 (m, 2H), 7.41−7.44 (m, 2H), 6.40 and 6.39 (s, 1H), 4.42 and 4.40 (q, *J* = 6.9 Hz, 1H), 1.86 and 1.85 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.5 and 168.3, 132.79 and 132.77, 130.2 and 130.1, 129.6 and 129.5, 125.4 and

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125.3, 115.2 and 115.1, 63.7 and 63.5, 38.4 and 38.1, 21.4 and 21.3. HRMS (ESI-Orbitrap) m/z: $[M + H]^+$ calcd for $C_{11}H_{10}Br_2NO_2$ 347.9052, found 347.9041.

(*R*)-Cyano(4-methylphenyl)methyl 2-Bromopropanoate (4e). The general procedure was followed using 4-methylbenzaldehyde (285 μL, 2.42 mmol), CALB (201 mg), and (*S*,*S*)-[(salen)Ti(μ-O)]$_2$ (147 mg, 0.121 mmol) in toluene (10 mL) and 2 M pH 7 buffer (10 mL) at 40 °C. **2a** (1.18 g, 7.32 mmol) in toluene (2.5 mL total volume) was added over 50 h. Flash chromatography (hexanes/dichloromethane 1:1, R_f = 0.38) gave **4e** (466 mg, 68%, [(*RS* + *RR*)/(*SR* + *SS*)] = 97.2:2.8) as a colorless oil. HPLC (Daicel Chiralpak IC and Daicel Chiralcel OD-H in series, hexanes/2-propanol 99:1, flow rate = 0.4 mL/min, detection at 220 nm): t_R (major) 63.2 min, t_R (minor) 84.8 min, t_R (major) 88.2 min, t_R (minor) 96.0 min. $[\alpha]_D^{21}$ −0.88 (*c* 1.0, $CHCl_3$). IR: 2978, 2928, 2360, 2343, 1755, 1209, 1142, 814 cm^{-1}. Mixture of diastereoisomers: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.43 (d, *J* = 7.0 Hz, 2H), 7.27 (d overlapped with $CHCl_3$, 2H), 6.41 and 6.40 (s, 1H), 4.41 and 4.39 (q, *J* = 6.9 Hz, 1H), 2.40 (s, 3H), 1.84 and 1.86 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.6 and 168.5, 141.2 and 141.1, 130.14 and 130.12, 128.3 and 128.14, 128.09 and 127.9, 115.8 and 115.6, 64.3 and 64.2, 38.6 and 38.5, 21.5, 21.40 and 21.35. HRMS (ESI-Orbitrap) m/z: $[M + Na]^+$ calcd for $C_{12}H_{12}BrNO_2Na$ 303.9944, found 303.9938.

(*R*)-1-Cyano-[(*E*)-1-propenyl]methyl 2-Bromopropanoate (4f). The general procedure was followed using (*E*)-2-butenal (200 μL, 2.41 mmol), CALB (201 mg), and (*S*,*S*)-[(salen)Ti(μ-O)]$_2$ (147 mg, 0.121 mmol) in toluene (10 mL) and 2 M pH 7 buffer (10 mL) at 40 °C. **2a** (1.18 g, 7.32 mmol) in toluene (2.5 mL total volume) was added over 50 h. Flash chromatography (hexanes/EtOAc 9:1, R_f = 0.39) gave **4f** (284 mg, 51%, [(*RS* + *RR*)/(*SR* + *SS*)] = 97.4:2.6) as an orange oil. GC-FID (CYCLOSIL B, flow rate = 1.0 mL/min, 60 °C for 10 min, 5 °C/min to 100 °C, hold 30 min, 0.5 °C/min to 122 °C): t_R (major) 84.0 min, t_R (major) 86.4 min, t_R (minor) 88.1 min, t_R (minor) 89.6 min. $[\alpha]_D^{21}$ −12.5 (*c* = 1.0, $CHCl_3$). IR: 2979, 2948, 2360, 2343, 1752, 1144 cm^{-1}. Mixture of diastereoisomers: ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.23 (dq, *J* = 6.7, 13.5 Hz, 1H), 5.83 (dd, *J* = 6.0, 11.9 Hz, 1H), 5.60 (split dd, *J* = 6.8, 15.3 Hz, 1H), 4.39 and 4.38 (q, *J* = 6.9 Hz, 1H), 1.86 (d, *J* = 7.0 Hz, 3H), 1.83 (dd, *J* = 0.7, 6.7 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.6 and 168.5, 136.9 and 136.8, 120.8 and 120.6, 115.3 and 115.1, 62.9 and 62.8, 38.6 and 38.5, 21.44 and 21.40, 17.9. HRMS (ESI-Orbitrap) m/z: $[M + Na]^+$ calcd for $C_8H_{10}BrNO_2Na$ 253.9787, found 253.9777.

(*R*)-1-Cyanohexyl 2-Bromopropanoate (4g). Pentanal (255 μL, 2.40 mmol) and (*S*,*S*)-[(salen)Ti(μ-O)]$_2$ (146 mg, 0.120 mmol) were dissolved in toluene (10 mL), and CALB (200 mg) and 2 M pH 7 buffer (10 mL) were added. The mixture was stirred at room temperature while **2a** (1.17 g, 7.22 mmol) in toluene (2.5 mL total volume) was added over 8 h using a syringe pump. After the addition was finished, the mixture was allowed to continue stirring. After 17 h another portion of CALB (100 mg) was added, and the stirring was continued for 7 h. The phases were separated, and the aqueous phase was extracted with Et_2O. The combined organic phases were dried over $MgSO_4$ and the solvents evaporated. The crude product was purified by flash chromatography (petroleum ether/EtOAc 19:1, R_f = 0.47) to give **4g** (384 mg, 65%, [(*RS* + *RR*)/(*SR* + *SS*)] = 99.0:1.0) as a pale-yellow oil. GC-FID (CYCLOSIL B, flow rate = 2.0 mL/min, 60 °C for 10 min, 10 °C/min to 100 °C, hold 10 min, 1 °C/min to 150 °C): t_R (major) 56.0 min, t_R (major) 57.2 min, t_R (minor) 58.0 min, t_R (minor) 60.0 min. $[\alpha]_D^{20}$ +48.0 (*c* 1.0, $CHCl_3$). IR: 2960, 2934, 2873, 1755, 1212, 1150 cm^{-1}. Mixture of diastereoisomers: ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.37 and 5.36 (t, *J* = 6.8 Hz, 1H), 4.40 and 4.39 (q, *J* = 6.9 Hz, 1H), 1.94−1.98 (m, 2H), 1.86 and 1.85 (d, *J* = 6.9 Hz, 3H), 1.47−1.55 (m, 2H), 1.40 (sextet, *J* = 7.3 Hz, 2H), 0.94 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.9 and 168.7, 116.5 and 116.3, 62.6 and 62.5, 38.7 and 38.4, 31.99, 26.62 and 26.56, 22.05 and 22.03, 21.5 and 21.3, 13.9. HRMS (ESI-Orbitrap) m/z: $[M + H]^+$ calcd for $C_9H_{15}BrNO_2$ 248.0281, found 248.0272.

General Procedure for the Blaise Cyclization. The Zn powder was activated prior to use by washing with 3 M HCl(aq), distilled water until neutral, acetone, and dry Et_2O. The activated Zn was dried under vacuum at 100 °C and stored under nitrogen.

Activated Zn and THF were added to a vial under nitrogen, and the vial was sealed. The mixture was stirred at 65 °C in an oil bath while **4** dissolved in THF was added dropwise using a syringe. When the reaction was finished, the mixture was cooled to −78 °C, and NH_4Cl(aq, sat.) was added. The mixture was allowed to reach room temperature and was then extracted with EtOAc. The combined organic phases were dried over $MgSO_4$ and the solvents evaporated. The crude product was purified by flash chromatography.

(*R*)-4-Amino-3-methyl-5-phenylfuran-2(5*H*)-one (6a). The general procedure was followed using Zn (146 mg, 2.24 mmol) in THF (0.3 mL) and **4a** (201 mg, 0.750 mmol) in THF (0.15 + 0.1 mL). NH_4Cl(aq, sat.) (0.3 mL) was added after 2 h of reaction. Flash chromatography (hexanes/EtOAc 1:4, R_f = 0.46) gave **6a** (122 mg, 86%, 98.6:1.4 er) as a white solid. Mp = 160−172 °C. GC-FID (CYCLOSIL B, flow rate = 2.0 mL/min, 60 °C for 1 min, 10 °C/min to 100 °C, hold 5 min, 5 °C/min to 200 °C, hold 45 min): t_R (major) 68.3 min, t_R (minor) 73.1 min. $[\alpha]_D^{20}$ −98.5 (*c* 1.3, EtOH). IR: 3444, 3304, 3193, 1716, 1646, 1617 cm^{-1}. ^{1}H NMR (500 MHz, CD_3OD): δ 7.38−7.43 (m, 3H), 7.30−7.32 (m, 2H), 5.64 (s, 1H), 1.72 (s, 3H). ^{13}C NMR (125 MHz, CD_3OD): δ 179.2, 168.4, 137.4, 130.4, 129.9, 128.5, 89.6, 81.1, 6.2. HRMS (ESI-Orbitrap) m/z: $[M + H]^+$ calcd for $C_{11}H_{12}NO_2$ 190.0863, found 190.0854.

(*R*)-4-Amino-5-(4-chlorophenyl)-3-methylfuran-2(5*H*)-one (6b). The general procedure was followed using Zn (132 mg, 2.02 mmol) in THF (0.3 mL) and **4b** (200 mg, 0.662 mmol) in THF (0.15 + 0.15 mL). NH_4Cl(aq, sat.) (0.2 mL) was added after 1.5 h of reaction. Flash chromatography (hexanes/EtOAc 1:2, R_f = 0.43) gave **6b** (144 mg, 97%, 98.4:1.6 er) as a white solid. Mp = 132−140 °C. HPLC (Daicel Chiralcel OD-H, hexanes/2-propanol 85:15, flow rate = 0.6 mL/min, detection at 254 nm): t_R (minor) 24.1 min, t_R (major) 58.8 min. $[\alpha]_D^{22}$ −94.3 (*c* 1.0, EtOH). IR: 3459, 3297, 3198, 1720, 1635, 1610, 1597 cm^{-1}. ^{1}H NMR (500 MHz, CD_3OD): δ 7.40−7.43 (m, 2H), 7.29−7.32 (m, 2H), 5.64 (s, 1H), 1.71 (s, 3H). ^{13}C NMR (125 MHz, CD_3OD): δ 178.9, 168.0, 136.3, 136.2, 130.1, 130.0, 89.8, 80.2, 6.2. HRMS (ESI-Orbitrap) m/z: $[M + H]^+$ calcd for $C_{11}H_{11}ClNO_2$ 224.0473, found 224.0468.

(*R*)-4-Amino-5-(4-methoxyphenyl)-3-methylfuran-2(5*H*)-one (6c). The general procedure was followed using Zn (140 mg, 2.14 mmol) in THF (0.3 mL) and **4c** (206 mg, 0.691 mmol) in THF (0.15 + 0.15 mL). NH_4Cl(aq, sat.) (0.2 mL) was added after 2 h of reaction. Flash chromatography (hexanes/EtOAc 1:4, R_f = 0.41) gave **6c** (149 mg, 98%, 97.9:2.1 er) as a colorless gum. HPLC (Daicel Chiralcel OD-H, hexanes/2-propanol 85:15, flow rate = 0.6 mL/min, detection at 254 nm): t_R (minor) 36.6 min, t_R (major) 74.7 min. $[\alpha]_D^{22}$ −54.0 (*c* 1.1, EtOH). IR: 3344, 3213, 2936, 1723, 1646, 1610, 1515 cm^{-1}. ^{1}H NMR (500 MHz, CD_3OD): δ 7.22−7.24 (m, 2H), 6.94−6.96 (m, 2H), 5.59 (s, 1H), 3.80 (s, 3H), 1.71 (s, 3H). ^{13}C NMR (125 MHz, CD_3OD): δ 179.2, 168.4, 162.0, 130.0, 129.1, 115.3, 89.8, 80.9, 55.8, 6.2. HRMS (ESI-Orbitrap) m/z: $[M + H]^+$ calcd for $C_{12}H_{14}NO_3$ 220.0968, found 220.0963.

(*R*)-4-Amino-5-(4-bromophenyl)-3-methylfuran-2(5*H*)-one (6d). The general procedure was followed using Zn (42.2 mg, 0.645 mmol) in THF (0.1 mL) and **4d** (75.0 mg, 0.215 mmol) in THF (0.1 mL). Additional THF (0.3 mL) was added to facilitate stirring during the reaction. NH_4Cl(aq, sat.) (0.2 mL) was added after 4.5 h of reaction. Flash chromatography (hexanes/EtOAc 1:2, R_f = 0.38) gave **6d** (42.1 mg, 73%, 97.3:2.7 er) as a white solid. Mp = 170−180 °C. HPLC (Daicel Chiralcel OD-H, hexanes/2-propanol 85:15, flow rate = 0.6 mL/min, detection at 254 nm): t_R (minor) 23.5 min, t_R (major) 58.4 min. $[\alpha]_D^{22}$ −88.3 (*c* 0.20, EtOH). IR: 3452, 3293, 3193, 1731, 1720, 1634, 1610, 1591 cm^{-1}. ^{1}H NMR (500 MHz, CD_3OD): δ 7.56 (d, *J* = 8.4 Hz, 2H), 7.24 (d, *J* = 8.4 Hz, 2H), 5.63 (s, 1H), 1.71 (s, 3H). ^{13}C NMR (125 MHz, CD_3OD): δ 178.9, 168.0, 136.7, 133.1, 130.4, 124.2, 89.7, 80.2, 6.24. HRMS (ESI-Orbitrap) m/z: $[M + H]^+$ calcd for $C_{11}H_{11}BrNO_2$ 267.9968, found 267.9966.

(*R*)-4-Amino-3-methyl-5-(4-methylphenyl)furan-2(5*H*)-one (6e). The general procedure was followed using Zn (140 mg, 2.14 mmol) in THF (0.3 mL) and **4e** (201 mg, 0.714 mmol) in THF (0.15

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+ 0.15 mL). NH_4Cl(aq, sat.) (0.3 mL) was added after 2 h of reaction. Flash chromatography (hexanes/EtOAc 1:4, R_f = 0.42) gave **6e** (134 mg, 93%, 97.3:2.7 er) as a colorless gum. HPLC (Daicel Chiralcel OD-H, hexanes/2-propanol 85:15, flow rate = 0.6 mL/min, detection at 254 nm): t_R (minor) 22.4 min, t_R (major) 56.4 min. $[\alpha]_D^{22}$ −74.3 (*c* 1.0, EtOH). IR: 3342, 3212, 2922, 1725, 1652, 1646 cm^{-1}. ^1H NMR (500 MHz, CD_3OD): δ 7.22 (d, *J* = 8.1 Hz, 2H), 7.17−7.20 (m, 2H), 5.60 (s, 1H), 2.35 (s, 3H), 1.71 (s, 3H). ^{13}C NMR (125 MHz, CD_3OD): δ 179.3, 168.5, 140.5, 134.3, 130.5, 128.5, 89.6, 81.0, 21.3, 6.2. HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{12}H_{14}NO_2$ 204.1019, found 204.1012.

(*R*)-4-Amino-3-methyl-5-((*E*)-prop-1-en-1-yl)furan-2(5*H*)-one (6f). The general procedure was followed using Zn (220 mg, 3.36 mmol) in THF (0.3 mL) and **4f** (154 mg, 0.665 mmol) in THF (0.15 + 0.15 mL). NH_4Cl(aq, sat.) (0.2 mL) was added after 2 h of reaction. Flash chromatography (hexanes/EtOAc 1:4, R_f = 0.37) gave **6f** (95.5 mg, 94%, 95.4:4.6 er) as a yellow gum. GC-FID (CYCLOSIL B, flow rate = 1.0 mL/min, 60 °C for 10 min, 10 °C/min to 100 °C, hold 5 min, 3 °C/min to 200 °C, hold 20 min): t_R (major) 63.8 min (*E* + *Z*), t_R (minor) 64.4 min (*Z*) and 65.2 min (*E*). $[\alpha]_D^{22}$ −36.5 (*c* 1.1, EtOH). IR: 3346, 3215, 1724, 1652, 1646 cm^{-1}. ^1H NMR (500 MHz, CD_3OD): δ 6.00 (dq, *J* = 6.6, 13.2 Hz, 1H), 5.34 (ddq, *J* = 1.7, 8.0, 15.2 Hz, 1H), 5.04 (d, *J* = 8.0 Hz, 1H), 1.77 (dd, *J* = 1.6, 6.6 Hz, 3H), 1.62 (s, 3H). ^{13}C NMR (125 MHz, CD_3OD): δ 179.0, 168.3, 134.2, 127.3, 88.9, 80.3, 17.9, 6.2. HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_8H_{12}NO_2$ 154.0863, found 154.0856.

(*R*)-4-Amino-5-butyl-3-methylfuran-2(5*H*)-one (6g). The general procedure was followed using Zn (150 mg, 2.29 mmol) in THF (0.2 mL) and **4g** (190 mg, 0.766 mmol) in THF (0.2 + 0.2 mL). NH_4Cl(aq, sat.) (0.6 mL) was added after 4 h of reaction. Flash chromatography (petroleum ether/EtOAc 1:3, R_f = 0.44) gave **6g** (91.9 mg, 71%, 98.8:1.2 er) as a colorless oil. GC-FID (CYCLOSIL B, flow rate = 2.0 mL/min, 60 °C for 1 min, 10 °C/min to 100 °C, hold 5 min, 5 °C/min to 180 °C, hold 60 min): t_R (major) 57.9 min, t_R (minor) 59.1 min. $[\alpha]_D^{20}$ +26.9 (*c* 1.0, EtOH). IR: 3347, 3217, 2957, 2931, 1716, 1647, 1616 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 4.68 (split d, *J* = 5.1 Hz, 1H), 4.44 (bs, 1H), 4.38 (bs, 0.6 H), 1.82−1.90 (m, 1H), 1.67 (s, 3H), 1.51−1.58 (m, 1H), 1.30−1.45 (m, 4H), 0.90 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 175.6, 163.5, 93.2, 77.5, 32.7, 26.3, 22.6, 14.0, 6.4. HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_9H_{16}NO_2$ 170.1176, found 170.1169.

(*R*)-Cyano(phenyl)methyl 2-Bromoacetate (7). Benzaldehyde (150 μL, 1.48 mmol) and (*S*,*S*)-$[(salen)Ti(\mu\text{-}O)]_2$ (90 mg, 0.074 mmol) were dissolved in toluene (6 mL), and CALB (123 mg) and 1 M pH 8 buffer (6 mL) were added. **2b** (1.10 g, 7.43 mmol) dissolved in cyclopentyl methyl ether (1.58 mL total volume) was added to the organic phase over 50 h at 40 °C. When the addition was finished, the phases were separated, and the organic phase was extracted with Et_2O. The combined organic phases were dried over $MgSO_4$ and the solvents evaporated. The crude product was purified by flash chromatography (hexanes/EtOAc 9:1, R_f = 0.28) to give **7** (233 mg, 62%, 99:1 er) as a pale-yellow oil. GC-FID (CYCLOSIL B, flow rate = 2.0 mL/min, 60 °C for 10 min, 20 °C/min to 100 °C, hold 5 min, 5 °C/min to 160 °C, hold 32 min): t_R (major) 52.4 min, t_R (minor) 58.0 min. $[\alpha]_D^{22}$ −4.1 (*c* 1.0, $CHCl_3$). IR: 3036, 2960, 2360, 2342, 1756, 1255, 1131, 761, 697 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.52−7.56 (m, 2H), 7.46−7.51 (m, 3H), 6.45 (s, 1H), 3.92 (A part of AB, *J* = 12.7 Hz, 1H), 3.90 (B part of AB, *J* = 12.7 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.6, 131.1, 130.9, 129.5, 128.1, 115.5, 64.5, 24.5. HRMS (ESI-Orbitrap) *m*/*z*: $[M + Na]^+$ calcd for $C_{10}H_8BrNO_2Na$ 275.9631, found 275.9619.

(*R*)-2-Hydroxy-2-phenylacetonitrile (5a). Compound **4a** (47.5 mg, 0.177 mmol) was dissolved in EtOH (1.1 mL), and *p*-TsOH·H_2O (41.0 mg, 0.216 mmol) was added; the solution was then stirred at room temperature. After 4 days, the solvent was evaporated. The crude product was purified by flash chromatography (hexanes/EtOAc 9:1, R_f = 0.25) to give **5a** (13.6 mg, 58%) as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$): δ 7.53−7.57 (m, 2H), 7.43−7.49 (m, 3H), 5.56 (d, *J* = 7.0 Hz, 1H), 2.54 (d, *J* = 7.2 Hz, 1H).

(*R*)-Cyano(phenyl)methyl Acetate (9). Compound **5a** (13.6 mg, 0.102 mmol) was dissolved in dichloromethane (0.2 mL). Acetic anhydride (20 μL, 0.21 mmol), pyridine (25 μL, 0.31 mmol), and DMAP (1.3 mg, 0.011 mmol) were added to the solution, which was stirred at room temperature for 30 min. NH_4Cl(aq, sat.) was added, and the aqueous phase was extracted with dichloromethane. The combined organic phases were dried over $MgSO_4$, and the solvent was evaporated. The crude product was purified by flash chromatography (hexanes/EtOAc 9:1, R_f = 0.36) to give **9** (8.0 mg, 45%, 99.4:0.6 er) as a colorless oil. GC-FID (CYCLOSIL B, flow rate = 2.0 mL/min, 60 °C for 10 min, 10 °C/min to 100 °C, hold 5 min, 5 °C/min to 200 °C, hold 1 min): t_R (major) 31.4 min, t_R (minor) 32.9 min. $[\alpha]_D^{20}$ +4.9 (*c* 0.54, $CHCl_3$) [lit.[27] $[\alpha]_D^{20}$ +4.5 (*c* 1.8, $CHCl_3$, >99% ee)]. ^1H NMR (500 MHz, $CDCl_3$): δ 7.50−7.54 (m, 2H), 7.43−7.48 (m, 3H), 6.42 (s, 1H), 2.17 (s, 3H).

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^1H NMR and ^{13}C NMR spectra of all compounds, GC and HPLC chromatograms of enantioenriched compounds, hydrolysis curves for **4g**, and a graph showing product formation and changes in ee over time in the reaction with **4g** with a gradual decrease in the addition rate of **2a**. 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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