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Enantioenriched ω-bromocyanohydrin derivatives. Improved selectivity by combination of two chiral catalysts

Robin Hertzberg, Khalid Widyan [†], Berenice Heid, Christina Moberg [*]

KTH Royal Institute of Technology, School of Chemical Science and Engineering, Department of Chemistry, Organic Chemistry, SE 100 44 Stockholm, Sweden

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ABSTRACT

Highly enantioenriched (*R*)-4-bromo-1-cyanobutyl acetate and (*R*)-5-bromo-1-cyanopentyl acetate were prepared by acetylcyanation of 4-bromobutanal and 5-bromopentanal, respectively, catalyzed by (*S*,*S*)-[(4,6-bis(*t*-butyl)salen)Ti(μ-O)]$_2$ and triethylamine followed by enzymatic hydrolysis of the minor enantiomer. A cyclic procedure employing the same two chiral catalysts provided inferior results due to a slowly reached steady state and, in reactions with the former substrate, to ring-closure of the free cyanohydrin formed as an intermediate in the reaction. Hydrolysis of the acylated cyanohydrins followed by $AgClO_4$-promoted cyclization provided (*R*)-2-cyanotetrahydrofuran and (*R*)-2-cyanotetrahydropyran in essentially enantiopure form.

1. Introduction

Chiral enantioenriched cyanohydrins derived from ω-bromoalkanals serve as versatile starting materials for a variety of nonracemic heterocyclic compounds. Cyclization of the cyanohydrins obtained from 4-bromobutanal and 5-bromopentanal leads directly to 2-cyanotetrahydrofuran and 2-cyanotetrahydropyran.[1] The former compound in enantioenriched form has been used for the preparation of tertahydrofuranyl ketones[2] as well as atropisomeric bipyridine derivatives via cobalt-catalyzed [2+2+2]-cyclotrimerization of the nitrile and a tetraalkyne,[3] and the racemic compound has been transformed to bicyclic ethers.[4] Chiral tetrahydrofurans are also present as structural elements in a variety of natural products and are therefore currently attractive synthetic targets.[5] From the initially obtained cyanohydrins, a variety of piperidine *N*,*N*′-dioxide derivatives[6] and azacycloalkanols have also been prepared via other types of synthetic transformations.[7]

The required enantioenriched cyanohydrins are usually obtained by oxynitrilase catalyzed addition of HCN to the appropriate aldehyde.[8] By employing (*R*)-oxynitrilase from almonds and ketone cyanohydrins as sources of HCN, the desired products were obtained with 91–92% ee[1] Similar enantioselectivity of 90–94% ee was observed in the hydrocyanation of 5-bromopentanal by the use of crude preparations from the leaves of food plants and HCN.[9] By an alternative procedure, 2-cyanotetrahydrofuran with 86.8% ee was prepared from tetrahydrofurfurylamine subsequent to its resolution using tartaric acid.[10]

Since the enantiopurity of the final products is normally limited by the selectivity of the initial process, methods providing the cyanohydrins with higher purity are desirable, in particular for the preparation of biologically active compounds.

The combination of two chiral catalysts can lead to higher enantioselectivity than that observed using a single catalyst. Most commonly consecutive catalytic processes have been performed where an enantioselective reaction is followed by a kinetic resolution, in which the minor enantiomer is transformed to some compound, which easily can be separated from the product (Fig. 1a).[11,12] We have recently described an alternative cyclic procedure where the minor enantiomer is recycled by transformation back to the prochiral starting material by use of a second chiral catalyst (Fig. 1b).[13] In the first type of process, the enantiopurity of the desired product increases steadily over time, at the same time as the yield decreases; enantiopure products can thus be obtained, but yields may be low. The advantage of the cyclic procedure is that higher yields can be obtained. The selectivity does not exceed $E_1 \times E_2$, where E_1 and E_2 are the selectivities of the forward and reverse reactions, respectively, but is higher than that of the individual steps.[14] By using a combination of a chiral Lewis acid catalyst and a biocatalyst, *O*-acetylmandelonitrile, for example, has been obtained with higher enantioselectivity via the cyclic

* Corresponding author. Tel.: +46 8 790 9036; fax: +46 8 791 2333; e-mail address: kimo@kth.se (C. Moberg).
† Present address: Department of chemistry, Tafila Technical University, Tafila-Jordan.

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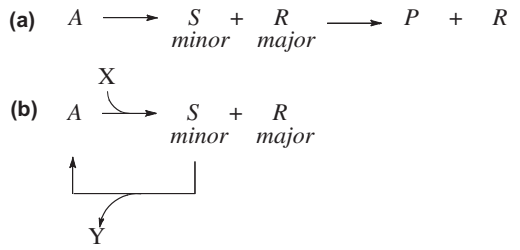


Fig. 1. (a) Enantioselective reaction followed by kinetic resolution; (b) Enantioselective reaction combined with recycling of the minor enantiomer to starting material. A unidirectional cycle is achieved by continuous addition of a reagent X and formation of a compound Y.

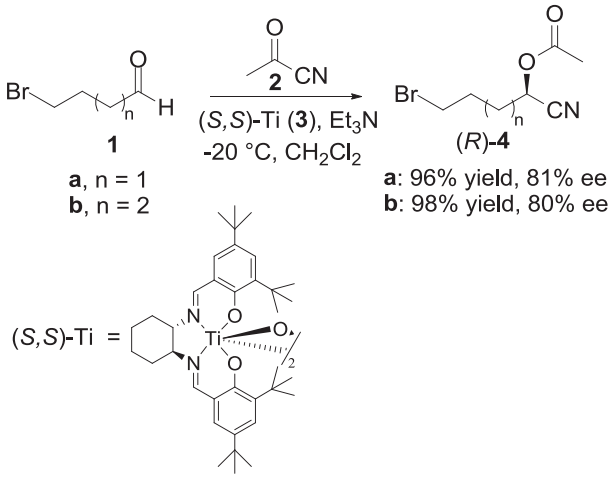
procedure than by any other method, and at the same time in close to quantitative yield.[13a]

Due to the different yield/selectivity profiles of the two processes, either a consecutive or a cyclic process may be the optimal choice in a particular case. This is illustrated here by acetylcyanations of 4-bromobutanal and 5-bromopentanal.

2. Results and discussion

2.1. Sequential reactions

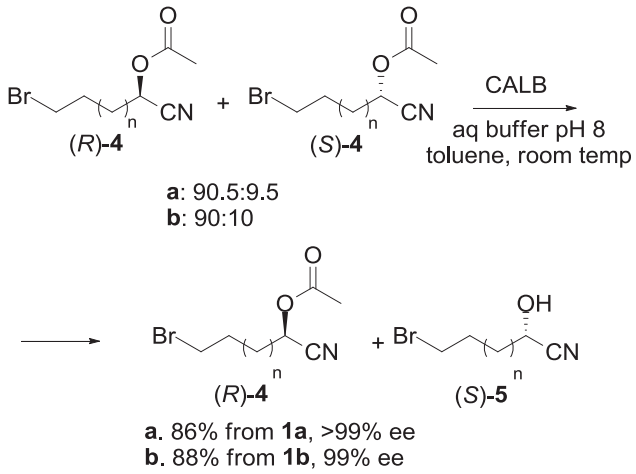
The addition of acyl cyanides to prochiral aldehydes proceeds readily in the presence of a dual Lewis acid/Lewis base catalytic system consisting of a chiral titanium-salen dimer and a tertiary amine to provide high yields of enantioenriched *O*-acylated cyanohydrins.[15] Treatment of 4-bromobutanal[16] (**1a**) and 5-bromopentanal[17] (**1b**) with acetyl cyanide (**2**) in the presence of (*S*,*S*)-[(4,6-bis(*t*-butyl)salen)Ti(μ-O)]$_2$[18] (**3**) and triethylamine at −20 °C in dichloromethane gave, however, unsatisfactory results: 96% of (*R*)-**4a** with 81% ee and 98% of (*R*)-**4b** with 80% ee (Scheme 1). At −40 °C somewhat higher selectivities were observed, but the reactions were slow and the yields were too low to be acceptable.



Scheme 1. Acetylcyanation of 4-bromobutanal and 5-bromopentanal catalyzed by Ti complex **3** and triethylamine.

It is known that *Candida antarctica* lipase B (CALB) hydrolyses a variety of cyanohydrin esters with high selectivity,[19,20] and we therefore decided to treat the products obtained from the acetylcyanations with this enzyme in toluene/aqueous buffer pH 6–8. We were pleased to find that the (*S*)-enantiomers of the present acylated cyanohydrins were hydrolyzed with equally high selectivity at pH 8 (E>100), although with different rates, (*S*)-**4a** undergoing hydrolysis considerably faster than (*S*)-**4b** (see Supplementary data). At lower pH slightly lower selectivites were observed (E=99 for **4a**). Hydrolyses of *rac*-**4a** as well as *rac*-**4b** catalyzed by *Candida Rugosa* lipase (CRL) and *Candida antarctica* lipase A (CALA) were less selective, the former preferentially hydrolyzing the (*R*)-enantiomer.

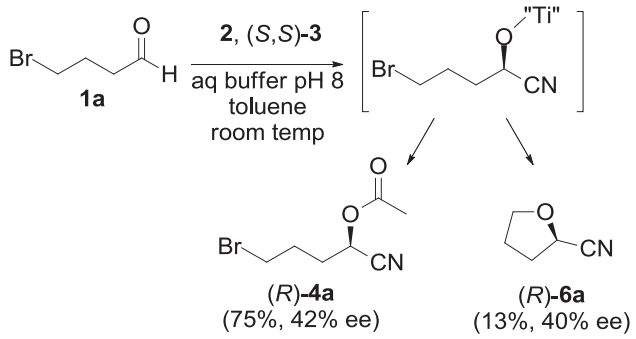
Treatment of enantioenriched **4a** with 81% ee (obtained as described above, whereafter the crude product mixture was filtered through silica using diethyl ether as eluent) with CALB/buffer pH 8 at room temperature resulted after an additional 5 h in 86% (from **1a**) of (*R*)-**4a** with >99% ee (Scheme 2). The same treatment of **4b** with 80% ee resulted after 24 h in (*R*)-**4b** in 88% yield (from **1b**) and 99% ee.



Scheme 2. Enzymatic hydrolysis of enantioenriched **4**.

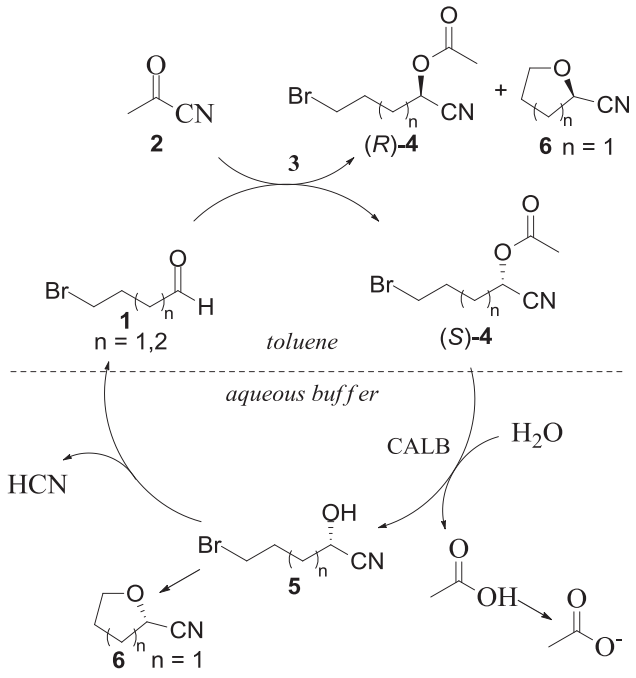
2.2. Minor enantiomer recycling

The results obtained from the sequential processes were compared to those from minor enantiomer recycling employing titanium catalyst **3** for the forward reaction and CALB for selective hydrolysis of the minor (*S*)-enantiomer using a two-phase system consisting of toluene and aqueous buffer. In order to verify whether the acetylcyanation of **1a** and **1b** was compatible with conditions used for the recycling process, the Ti-catalyzed reactions were first run in toluene/aqueous buffer pH 8 at room temperature. Although the presence of base is required for the reactions to work at −20 °C, at higher temperatures the reactions proceed readily in the absence of base. Reaction of **1a** under these conditions afforded (*R*)-**4a** in 75% yield with 42% ee after 24 h. Cyclization to yield **6a** with 40% ee was observed (13% yield by ^{1}H NMR spectroscopy after isolation of the product mixture); this product was not obtained when the reaction was run in dichloromethane in the absence of aqueous phase. It is assumed that the two products are formed via an intermediate titanium(IV) complex (Scheme 3). Under the same conditions (*R*)-**4b** was formed from **1b** in 78% yield and 22% ee, and at 40 °C in the same yield but merely 11% ee.



Scheme 3. Formation of (*R*)-**4a** and (*R*)-**6a** via proposed common intermediate.

For the cyclic process, a two-phase system consisting of **1a**, titanium complex **3**, and CALB in toluene/aqueous buffer was prepared. Acetyl cyanide was added to the organic phase at room temperature over 25 h, resulting in an increase in both yield and ee over time (Scheme 4).



Scheme 4. Minor enantiomer recycling.

In the reaction of **1a**, extensive cyclization to **6a** occurred at pH 8, and yields of the desired product were therefore low (Table 1, entries 1 and 2). As a consequence, fewer cycles were needed to reach steady state, resulting at 40 °C in high ee (entry 2). At lower pH, the yields of acylated cyanohydrin were higher (compare entries 1, 3, and 5), but it took a long time to reach steady state. After complete addition of acetyl cyanide at pH 7 the yield was however still only 57% of a product with 87% ee (entry 3). By allowing the reaction mixture to stir for an additional 13 h after complete addition of acetyl cyanide, enantiomerically pure product was obtained, but in a yield of merely 50% (entry 3). The same reactions at 40 °C resulted after complete addition in higher ee, 99 and 90% at pH 7 and 6, respectively, but in low yields (entries 4 and 6). Cyclized product **6a** was formed in all reactions, and as expected in higher amounts at the higher temperature. At pH 6, **6a** was obtained in 17 and 28% yields from reactions that had been left to stir for 15 h after complete addition of acetyl cyanide at room temperature and 40 °C, respectively (reactions entries 5 and 6); in the latter reaction racemic **6a** was obtained, whereas in the room temperature process, (*S*)-**6a** (i.e., with absolute configuration opposite to that formed in the two-phase forward reaction) with 33% ee was obtained. These results demonstrate that (*R*)-**6a** is formed along with (*R*)-**4a** in the forward reaction, whereas in the reverse process, which comprises the hydrolysis of (*S*)-**4a**, the opposite enantiomer is formed.

Table 1
Minor enantiomer recycling

Entry	Aldehyde	pH	Temp (°C)	Yield (%) of **4**	ee (%) of **4**
1	**1a**	8	rt	46	82
2	**1a**	8	40	26	100
3	**1a**	7	rt	57	87[a]
4	**1a**	7	40	21	99
5	**1a**	6	rt	70	82[b]
6	**1a**	6	40	42	90[c]
7	**1b**	7	rt	84	61
8	**1b**	7	40	78	86[d]

Acetyl cyanide (3 equiv) was added over 24–25 h to the aldehyde in toluene/aq buffer.

[a] Continued stirring for 13 h gave 50% of (*R*)-**4a** with 100% ee.

[b] Continued stirring for 15 h gave 62% of (*R*)-**4a** with 99% ee, 17% **6a** with −33% ee, and 10% **5a**.

[c] Continued stirring for 15 h gave 34% of (*R*)-**4a** with 100% ee, 28% racemic **6a** and 3% of **5a**.

[d] Continued stirring for 15 h gave 67% of (*R*)-**4b** with >99% ee.

When aldehyde **1b** was subjected to the same procedure, (*R*)-**4b** was obtained in higher yield than (*R*)-**4a** under the same conditions (compare entries 7 and 8 with entries 3 and 4), but steady state was not reached within a reasonable time, resulting in low enantioselectivities (entries 7 and 8). By leaving the reaction mixture to stir for an additional 15 h after complete addition of acetyl cyanide, highly enantioenriched product (>99% ee) was obtained, but the yield, 67% (entry 8), was lower than that obtained from the sequential process (88%).

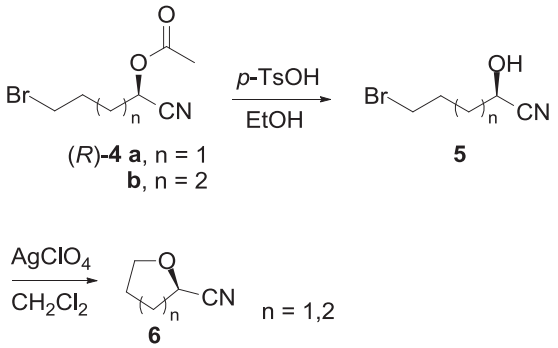
In contrast to the present results, the recycling process[13a,21] has proven to afford superior results than the sequential processes for other aldehydes.[21,22] The major reason for the low yields observed in the cyclic process in the present case are, for **1a**, the tendency of the cyanohydrin to cyclize to **6a**, and for **1b** its comparably slow enzymatic hydrolysis.

2.3. Opposite enantiomer

Reaction of **1a** with acetyl cyanide in the presence of (*R*,*R*)-[(4,6-bis(*t*-butyl)salen)Ti(*μ*-O)]$_2$ and triethylamine at −20 °C afforded (*S*)-**4a** in quantitative yield with 78% ee. Addition of pH 8 buffer and CRL resulted in slow hydrolysis with only a slight preference for the (*R*)-enantiomer. After 125 h, 87% of (*S*)-**4a** with 91% ee was obtained.

2.4. Hydrolysis and cyclization

Since the sequential procedure proved advantageous for the prepraration of (*R*)-**4a** and (*R*)-**4b**, this procedure was used for preparative scale (2.4 mmol) syntheses. After chromatographic purification, 71% of **4a** with >99% ee and 61% of **4b** with 99.6% ee were isolated. The compounds were hydrolyzed (*p*-toluenesulfonic acid, ethanol)[23] to afford the free cyanohydrins in 93 and 84% yields, respectively (Scheme 5). The (*R*)-absolute configurations were confirmed by comparison of the optical rotations with those of the known compounds.[1] Cyclization using $AgClO_4$[1] gave (*R*)-**6a** in 57% yield with 98% ee, whereas tetrahydropyran (*R*)-**6b** was obtained in 41% yield with 99.6% ee.



Scheme 5. Hydrolysis and cyclization of (*R*)-**4**.

3. Conclusion

Good yields of highly enantioenriched (≥99% ee) acetylated cyanohydrins were obtained by sequential dual Lewis acid-Lewis base

catalyzed acetylcyanation of prochiral 4-bromobutanal and 5-bromopentanal using acetyl cyanide and enzyme catalyzed hydrolysis of the minor, undesired enantiomer. Hydrolysis of the acetylated cyanohydrins followed by cyclization to (*R*)-2-cyanotetrahydrofuran and (*R*)-2-cyanotetrahydropyran, respectively, occurred with minor or no loss in ee.

4. Experimental section

4.1. General

CH_2Cl_2 was dried using a Glass Contour solvent dispensing system. Aldehydes **1a**,[16] and **1b**,[17] and (*S*,*S*)-, and (*R*,*R*)-[(4,6-bis(*t*-butyl)salen)Ti(μ-O)]$_2$[18] were prepared following literature procedures. *rac*-**4a** and *rac*-**4b** were prepared in the same way as analogous compounds.[21] Immobilized (acrylic resin, ≥10,000 U/g) *Candida antarctica* lipase B, immobilized (Immobead 150) *Candida antarctica* lipase A, and *Candida rugosa* lipase (CRL) were purchased from Sigma–Aldrich. ^{1}H NMR spectra were recorded at 500 MHz and ^{13}C NMR spectra at 125 MHz. The ^{1}H and ^{13}C chemical shifts are reported relative to $CHCl_3$. Optical rotations were measured with a Rudolph Research Analytical Autopol IV polarimeter, HRMS on a Bruker Daltonik GmbH micrOTOF and IR spectra on a Mettler Toledo ReactIR iC10. Yields and enantiomeric excesses were determined with a GC-FID equipped with a chiral column (CYCLOSIL-B, 30 m×0.25 mm×0.25 μm) using *n*-undecane as internal standard. Samples were taken from the organic phase, filtered through a short silica plug and eluted with Et_2O directly into the GC-vial.

*4.1.1. (R)-4-Bromo-1-cyanobutyl acetate (**4a**).* 4-Bromobutanal (363 mg, 2.40 mmol), (*S*,*S*)-[(salen)Ti(μ-O)]$_2$ (146 mg, 0.120 mmol) and Et_3N (34 μL, 0.24 mmol) were dissolved in dry CH_2Cl_2 (10 mL). The solution was cooled to −20 °C under nitrogen and stirred for 15 min before AcCN (340 μL, 4.80 mmol) was added. After a total of 16 h of stirring at −20 °C, the mixture was filtered through a short pad of silica and eluted with Et_2O. The solvents were evaporated in vacuo, the residue was dissolved in toluene (10 mL), and CALB (200 mg) and 1 M phosphate buffer pH 8 (10 mL) were added. The two-phase mixture was stirred at room temperature. After 5.5 h, the phases were separated, the aqueous phase extracted with Et_2O, the combined organic phases dried over $MgSO_4$, and the solvents evaporated in vacuo. The crude product was purified by flash chromatography (hexanes/EtOAc 9:1, R_f=0.24) to give (*R*)-**4a** (374 mg, 1.70 mmol, 71%, >99% ee) as a pale yellow oil. $[\alpha]_D^{22}$+64.8 (*c* 1.0, $CHCl_3$); IR (film): ν_{max} 2972, 2966, 2901, 2877, 1754, 1442, 1375, 1222, 1041 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ=5.37–5.40 (m, 1H), 3.45–3.48 (m, 2H), 2.16 (s, 3H), 2.06–2.13 (m, 4H); ^{13}C NMR (500 MHz, $CDCl_3$): δ=169.1, 116.6, 60.4, 31.8, 31.1, 27.7, 20.5; HRMS (ESI): (M+Na)$^+$, found 241.9784. $C_7H_{10}BrNNaO_2$ requires 241.9787.

*4.1.2. (R)-4-Bromo-1-cyanobutyl acetate (**4a**) (analytical scale).* 4-Bromobutanal (36.2 mg, 0.240 mmol), (*S*,*S*)-[(salen)Ti(μ-O)]$_2$ (14.6 mg, 0.0120 mmol) and Et_3N (3.4 μL, 0.024 mmol) were dissolved in dry CH_2Cl_2 (1 mL) under nitrogen. The solution was cooled to −78 °C and stirred for 15 min before AcCN (51 μL, 0.72 mmol) was added. The solution was stirred at −20 °C for 44 h, then allowed to reach room temperature, filtered through a short pad of silica and eluted with Et_2O. The solvents were evaporated in vacuo, the residue was dissolved in toluene (1 mL), and CALB (20 mg) and 1 M phosphate buffer pH 8 (1 mL) were added. The two-phase mixture was stirred at room temperature while the reaction was monitored by chiral GC using undecane (10 μL, 0.0473 mmol) as internal standard. After 5 h of stirring, 86% yield of (*R*)-**4a** with>99% ee was observed.

*4.1.3. (R)-5-Bromo-1-cyanopentyl acetate (**4b**).* 5-Bromopentanal (397 mg, 2.40 mmol), (*S*,*S*)-[(salen)Ti(μ-O)]$_2$ (147 mg, 0.121 mmol), and Et_3N (34 μL, 0.24 mmol) were dissolved in dry CH_2Cl_2 (10 mL). The mixture was cooled to −78 °C under nitrogen and stirred for 15 min before AcCN (511 μL, 7.21 mmol) was added. The solution was stirred at −20 °C for 16 h, then allowed to reach room temperature and filtered through a short pad of silica and eluted with Et_2O. The solvents were evaporated in vacuo, the residue was dissolved in toluene (10 mL), and CALB (200 mg) and 1 M phosphate buffer pH 8 (10 mL) were added. The two-phase mixture was stirred at room temperature. After 22.5 h the phases were separated, the aqueous phase extracted with Et_2O, the combined organic phases dried over $MgSO_4$, and the solvents evaporated in vacuo. The crude product was purified by flash chromatography (hexanes/EtOAc 9:1, R_f=0.26) to give (*R*)-**4b** (342 mg, 1.46 mmol, 61%, 99.6% ee) as a pale yellow oil. $[\alpha]_D^{23}$+55.1 (*c* 1.0, $CHCl_3$); IR (film): ν_{max} 2964, 2950, 2877, 1750, 1461, 1459, 1373, 1215, 1050 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ=5.34 (t, *J*=6.6 Hz, 1H), 3.42 (t, *J*=6.6 Hz, 2H), 2.15 (s, 3H), 1.91–1.97 (m, 4H), 1.65–1.71 (m, 2H); ^{13}C NMR (500 MHz, $CDCl_3$): δ=169.2, 116.8, 60.9, 32.7, 31.8, 31.6, 23.4, 20.5; HRMS (ESI): (M+Na)$^+$, found 255.9937. $C_8H_{12}BrNNaO_2$ requires 255.9944.

*4.1.4. (R)-5-Bromo-1-cyanopentyl acetate (**4b**) (analytical scale).* 5-Bromopentanal (40.1 mg, 0.243 mmol), (*S*,*S*)-[(salen)Ti(μ-O)]$_2$ (14.7 mg, 0.0121 mmol), and Et_3N (3.4 μL, 0.024 mmol) were dissolved in dry CH_2Cl_2 (1 mL). The solution was cooled to −20 °C and stirred for 15 min before AcCN (34 μL, 0.45 mmol) was added. Stirring at −20 °C was continued for 43 h. The solution was filtered through a short pad of silica, and eluted with Et_2O. The solvents were evaporated in vacuo, the residue was dissolved in toluene (1 mL), and CALB (20 mg) and 1 M phosphate buffer pH 8 (1 mL) were added. The two-phase mixture was stirred at room temperature while the reaction was monitored by chiral GC using undecane (10 μL, 0.0473 mmol) as internal standard. After 24 h of stirring, 88% yield of (*R*)-**4b** with 99% ee was observed.

*4.1.5. (R)-4-Bromo-1-cyanobutyl alcohol (**5a**).*[1] *p*-TsOH·H_2O (239 mg, 1.26 mmol) was added to compound (*R*)-**4a** (230 mg, 1.05 mmol, >99% ee) in EtOH (5 mL), and the resulting solution was stirred at room temperature. After 44.5 h of stirring the solvent was evaporated in vacuo. The crude product was purified by flash chromatography (hexanes/EtOAc 4:1, R_f=0.20) to give (*R*)-**5a** (174 mg, 0.977 mmol, 93%) as a pale yellow oil. $[\alpha]_D^{22}$+19.6 (*c* 1.0, $CHCl_3$); lit.:[1] +16.1 (*c* 1.0, $CHCl_3$, 92% ee); ^{1}H NMR (500 MHz, $CDCl_3$): δ=4.57 (q, *J*=6.1 Hz, 1H), 3.48 (t, *J*=6.2 Hz, 2H), 2.37 (bs, 1H), 2.08–2.16 (m, 2H), 2.02–2.07 (m, 2H); ^{13}C NMR (500 MHz, $CDCl_3$): δ=119.4, 60.7, 33.8, 32.4, 27.7.

*4.1.6. (R)-5-Bromo-1-cyanopentyl alcohol (**5b**).*[6a] *p*-TsOH·H_2O (309 mg, 1.62 mmol) was added to compound (*R*)-**4b** (315 mg, 1.35 mmol, 99.6% ee) in EtOH (6 mL), and the solution was stirred at room temperature. After 44.5 h of stirring the solvent was evaporated in vacuo. The crude product was purified by flash chromatography (hexanes/EtOAc 4:1, R_f=0.26) to give (*R*)-**5b** (218 mg, 1.14 mmol, 84%) as a colorless oil. $[\alpha]_D^{23}$+14.1 (*c* 1.0, $CHCl_3$); lit.:[1] +10.7 (*c* 1.0, $CHCl_3$, 91% ee); ^{1}H NMR (500 MHz, $CDCl_3$): δ=4.52 (q, *J*=6.4 Hz, 1H), 3.43 (t, *J*=6.6 Hz, 2H), 2.29 (d, *J*=6.1 Hz, 1H), 1.87–1.97 (m, 4H), 1.65–1.73 (m, 2H); ^{13}C NMR (500 MHz, $CDCl_3$): δ=119.6, 61.3, 34.5, 33.0, 32.0, 23.4.

*4.1.7. (R)-Tetrahydrofuran-2-carbonitrile (**6a**).*[24] $AgClO_4$ (175 mg, 0.844 mmol) was added to compound (*R*)-**5a** (136 mg, 0.766 mmol) in dry CH_2Cl_2 (5 mL). The mixture was stirred at room temperature for 1 h. Brine was added, the phases were separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$ and the solvents evaporated in vacuo. The crude product was purified by flash chromatography (petroleum ether/Et_2O 4:1, R_f=0.44) to give (*R*)-**6a** with <5% impurities (42.7 mg, 0.440 mmol, 57%, 98% ee) as a colorless oil.

$[\alpha]_D^{22}$ −34.2 (*c* 1.0, $CHCl_3$); lit.:[1] −26.1 (*c* 0.85, $CHCl_3$, 92% ee); ^{1}H NMR (500 MHz, $CDCl_3$): δ=4.71 (dd, *J*=7.1, 4.6 Hz, 1H), 3.92–4.02 (m, 2H), 2.21–2.31 (m, 2H), 2.09–2.19 (m, 1H), 1.97–2.05 (m, 1H); ^{13}C NMR (500 MHz, $CDCl_3$): δ=119.5, 69.2, 66.4, 31.8, 25.0.

*4.1.8. (R)-Tetrahydro-2H-pyran-2-carbonitrile (**6b**).*[25] $AgClO_4$ (252 mg, 1.22 mmol) was added to compound (*R*)-**5b** (195 mg, 1.02 mmol) in dry CH_2Cl_2 (7 mL). The mixture was stirred at room temperature for 1.75 h. Brine was added, the phases were separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$ and the solvents evaporated in vacuo. The crude product was purified by flash chromatography (petroleum ether/Et_2O 9:1, R_f=0.41) to give (*R*)-**6b** (45.7 mg, 0.411 mmol, 41%, 99.6% ee) as a pale yellow oil. $[\alpha]_D^{22}$ −44.1 (*c* 1.0, $CHCl_3$); lit.:[1] −32.9 (*c* 0.77, $CHCl_3$, 91% ee); ^{1}H NMR (500 MHz, $CDCl_3$): δ=4.63 (t, *J*=4.3 Hz, 1H), 3.89 (m, 1H), 3.77 (dt, *J*=11.8, 4.4 Hz, 1H), 1.81–1.96 (m, 3H), 1.71–1.77 (m, 1H), 1.61–1.66 (m, 2H); ^{13}C NMR (500 MHz, $CDCl_3$): δ=118.0, 66.3, 65.3, 29.4, 25.2, 20.3.

4.2. General procedure for minor enantiomer recycling

Aldehyde (0.24 mmol) and (*S*,*S*)-[(salen)Ti(μ-O)]$_2$ (5 mol %) were dissolved in toluene (1 mL), and buffer (1 mL) and CALB (20 mg) were added. AcCN (3 equiv diluted to 250 μL with toluene) was added to the organic phase with a constant rate over 24–25 h using a syringe pump. The reaction was monitored by chiral GC using undecane (10 μL, 0.0473 mmol) as internal standard.

4.3. General procedure for two-phase reaction without enzyme

Aldehyde (1 equiv) and (*S*,*S*)-[(salen)Ti(μ-O)]$_2$ (5 mol %) were dissolved in toluene (1 mL), and buffer (1 mL) was added. The mixture was stirred at the given temperature while AcCN (3 equiv, diluted to a total volume of 250 μL with toluene) was added over 25 h using a syringe pump. The reaction was monitored by chiral GC using undecane (10 μL, 0.0473 mmol) as internal standard.

4.4. General procedure for the enzymatic hydrolysis

Racemic compound **4a** or **4b** was dissolved in toluene (1 mL). Enzyme (50 wt % compared to the racemic compound) and buffer (1 mL) were added and the mixture was stirred at the given temperature. The reaction was monitored by chiral GC using undecane (10 μL, 0.0473 mmol) as internal standard.

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Supplementary data

Procedure for the preparation of (*S*)-4a. Experimental curves for enzymatic hydrolyses of *rac*-**4a** and *rac*-**4b**, copies of ^{1}H and ^{13}C NMR spectra of compounds **4a**, **4b**, **5a**, **5b**, **6a**, and **6b**, and gas chromatograms of racemic and enantiomerically enriched compounds. Supplementary data related to this article can be found online at doi:10.1016/j.tet.2012.05.090.

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