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Enantioselectivity

Minor Enantiomer Recycling: Application to Enantioselective Syntheses of Beta Blockers

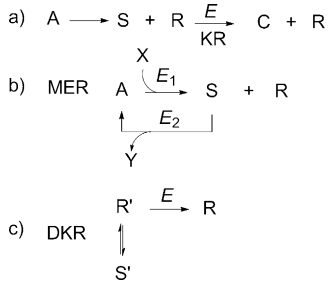
Ye-Qian Wen, Robin Hertzberg, Inanllely Gonzalez, and Christina Moberg*[a]

Abstract: Continuous recycling of the minor product enantiomer obtained from the acetylcyanation of prochiral aldehydes provided access to highly enantiomerically enriched products. Cyanohydrin derivatives, which under normal conditions are obtained with modest or poor enantiomeric ratios, were formed with high enantiomeric purity by using a reinforcing combination of a chiral Lewis acid catalyst and a biocatalyst. The primarily obtained products were transformed into β-adrenergic antagonists (*S*)-propanolol, (*R*)-dichloroisoproterenol, and (*R*)-pronethalol by means of a two-step procedure.

Introduction

Enantioenriched vicinal amino alcohols are conveniently accessible by cyanation of prochiral aldehydes and subsequent reduction of the nitrile function.[1] A variety of chiral catalysts, which comprise metal complexes as well as biocatalysts, are available for the enantioselective cyanide addition, most commonly by using trimethylsilyl cyanide and ethyl or methyl cyanoformate as a source of cyanide ion. We,[2] as well as Sansano and co-workers,[3] found that acyl cyanides are attractive alternatives that provide stable, highly versatile enantioenriched *O*-acylated cyanohydrins in a simple addition process without the accompanying formation of by-products. High enantioselectivities are observed in reactions with a broad range of substrates. In cases in which *O*-acetylated cyanohydrins are obtained with insufficient enantiopurity, subsequent treatment of the primarily obtained product with a suitable biocatalyst capable of selective hydrolysis of the minor enantiomer might lead to a single-product isomer.[4]

Although an enantioselective reaction coupled to a kinetic resolution (KR) might result in an enantiopure product (Scheme 1 a), the gain in selectivity obtained in the second step is necessarily accompanied by a decrease in yield.[5] To circumvent this drawback, we developed a recycling process whereby the minor, undesired, enantiomer is continuously transferred to starting material with the aid of a biocatalyst.[6] A cyclic procedure is maintained by continuous addition of a sacrificial reagent (Scheme 1 b). This minor enantiomer recycling (MER) methodology thus constitutes a combination of an enantioselective forward reaction and a kinetic resolution of the product of the forward reaction. In contrast to a dynamic kinetic resolution (DKR), a reinforcing effect of the two catalysts is achieved, thereby resulting in an enantioselectivity that is higher than that of any of the individual processes. Thus, assuming that E_1 and E_2 are the selectivities for the product-forming and the reverse processes, respectively, the maximum enantiomeric excess (*ee*) is equal to $(E_1E_2-1)/(E_1E_2+1)$, whereas that for a dynamic kinetic resolution (Scheme 1 c) relies on the selectivity of a single catalyst (E) and is equal to $(E-1)/(E+1)$. In both types of processes the enantioselectivities are thus limited, but in the cyclic process an enantiopure product might be obtained if the kinetic resolution is allowed to continue after addition of the sacrificial reagent has ceased.



Scheme 1. a) Enantioselective reaction of a prochiral substrate (A) to yield minor (*S*) and major (*R*) enantiomers followed by kinetic resolution (KR) transforming S to C, where C is a chiral or achiral compound obtained from S, the minor enantiomer, with a selectivity factor *E*. b) Minor enantiomer recycling (MER) using a sacrificial reagent (X). c) Dynamic kinetic resolution (DKR).

We decided to evaluate the process for the synthesis of the β-adrenergic antagonists (*S*)-propanolol (**1 a**),[7] (*R*)-dichloroisoproterenol (**1 b**),[8] and (*R*)-pronethalol (**1 c**) (Figure 1).[7] Several enantioselective methods for the preparation of propanolol, which is active in its *S* form,[9,10] have been reported. In addition to routes based on separation of the enantiomers[11] and use of the chiral pool[12] or readily available enantiopure starting materials,[13] biocatalytic methods have been used for kinetic resolution of either propanolol derivatives or smaller

[a] Dr. Y.-Q. Wen, R. Hertzberg, I. Gonzalez, Prof. C. Moberg
KTH Royal Institute of Technology, Department of Chemistry
Organic Chemistry, 10044 Stockholm (Sweden)
E-mail: kimo@kth.se

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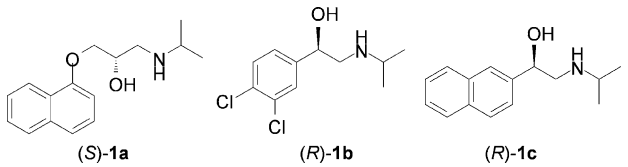
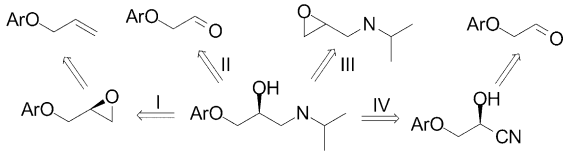


Figure 1. β-Blockers (*S*)-propanolol (**1a**), (*R*)-dichloroisoproterenol (**1b**), and (*R*)-pronethalol (**1c**).

building blocks that serve as precursors to the final compound.[14,15] Although kinetic resolutions might give access to enantiopure products, yields are limited to a maximum of 50% and are often considerably lower owing to insufficient selectivity of the biocatalyst, a circumstance that severely limits the usefulness of these processes. Thus, *Pseudomonas cepacia* lipase (PSL)-catalyzed acetylation of a cyanohydrin precursor of propanolol provided (*S*)-cyanohydrin with 96% *ee* after 56% conversion.[16] A higher yield (71%) was obtained from dynamic kinetic resolution of the azido alcohol precursor, but the *ee* was merely 86%.[17]

A variety of metal-catalyzed synthetic procedures have also been reported. Several routes based on the nucleophilic ring-opening of (2*S*)-3-(1-naphthyloxy)-1,2-epoxypropane, accessible by means of Sharpless epoxidation,[18] dihydroxylation,[19] L-proline-catalyzed α-aminoxylation,[20] and kinetic resolution,[21] have been explored (Scheme 2, route I). A route that comprises



Scheme 2. Retrosynthetic analysis for β-adrenergic antagonists.

a nitroaldol condensation as the key step allowed the product to be isolated in a reasonable overall yield with up to 97% *ee* (Scheme 2, route II).[22] Hydrolytic kinetic resolution of racemic epoxypropylamine[23] (Scheme 2, route III) and nucleophilic attack of 1-naphthol on C_3-symmetric (2*S*,2′*S*,2″*S*)-tris(2,3-epoxypropyl)isocyanurate are additional examples.[24] To our surprise, we have not been able to find any reports on processes that incorporate enantioselective cyanation of prochiral 2-(1-naphthyloxy)propanal (Scheme 2, route IV).

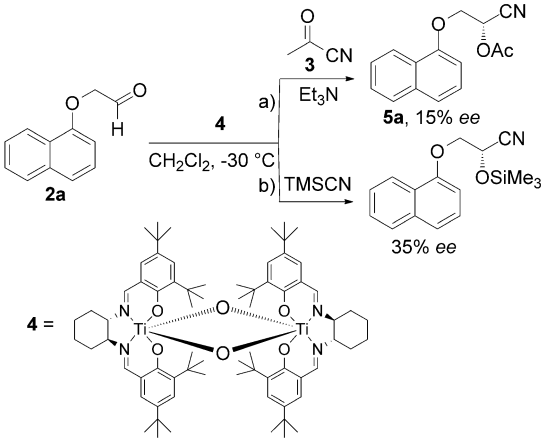
Although cyanation of 2-naphthylaldehyde, employing trimethylsilyl cyanide as well as cyanoformates, results in products with high enantiomeric excess,[25] highly enantioenriched (*R*)-pronethalol (**1c**) has, as far as we are aware, only been prepared by enantioselective reduction of 1-(2-naphthyl)ethanones with a leaving group in the 2-position, followed by substitution with isopropylamine.[26] The same methodology has also been used for the preparation of (*R*)-dichloroisoproterenol (**1b**).[26] A synthetic procedure that involves the cyanation of 3,4-dichlorobenzaldehyde might seem less attractive since the acetylated cyanohydrin from 3,4-dichlorobenzaldehyde has previously been prepared in merely 40% yield and 93% *ee* by enzymatic kinetic resolution of the racemic compound,[27] whereas the corresponding trimethylsilyl (TMS) ether was obtained with 78% *ee* in connection to mechanistic studies.[28]

Our results from an exploration of a route for the synthesis of these β blockers based on acylcyanation of prochiral aldehydes **2a**–**c** by employing the two-catalyst minor enantiomer recycling procedure are reported here.

Results and Discussion

Synthesis of (*S*)-propanolol (1a)

(1-Naphthyloxy)acetaldehyde (**2a**), the aldehyde required for the acetylcyanation, was prepared by means of a previously described procedure, that is, by reaction of 1-naphthol with α-bromoacetaldehyde diethyl acetal followed by hydrolysis.[29] First, conventional methods for the cyanation of **2a** were attempted. The aldehyde was therefore treated with acetyl cyanide (**3**) in the presence of (*S*,*S*)-[{4,6-bis(*tert*-butyl)salen}Ti(μ-O)]$_2$ (**4**) and triethylamine at −30 °C in CH_2Cl_2 (Scheme 3). From

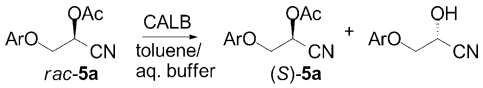


Scheme 3. a) Acetylcyanation and b) silylcyanation of **2a**.

this reaction the desired acylated cyanohydrin **5a** was isolated in 69% yield, although with low enantiomeric purity of 15% *ee*. Treatment of **2a** with trimethylsilyl cyanide in the presence of the same titanium complex[30] also proceeded with low selectivity to give the product with 35% *ee*, as determined after transformation to the *O*-acetylated cyanohydrin.[31] It should also be noted that (*R*)-hydroxynitrilase-catalyzed HCN addition to **2a** has been reported to result in a racemic product.[32] These poor results called for an improved procedure.

Biocatalysts capable of selective hydrolysis of the *R* enantiomer of a racemic mixture of the acetylated cyanohydrin **5a**[33] as well as of acetylation of the racemic cyanohydrin[16] are known. We therefore anticipated that a cyclic process that involves in situ hydrolysis of this undesired enantiomer should lead to higher selectivity than that observed in the reactions shown in Scheme 3, and at the same time to a yield higher than the theoretically maximum 50% obtained by kinetic resolution. By subjecting *rac*-**5a**, which was obtained from alde-

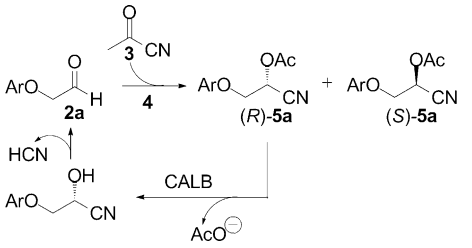
hyde **2a** by reaction with acetyl cyanide in the presence of triethylamine, to different biocatalysts in toluene/aqueous phosphate buffer pH 8, we found that *Candida antarctica* lipase B (CALB) catalyzed the hydrolysis with high preference for the *R* enantiomer (Scheme 4; also see the Supporting Information). In this two-phase system, the product-forming step was found to be unselective, but with the high selectivity observed for the hydrolysis, the cyclic process was expected to lead to preferential formation of the *S* enantiomer.



Scheme 4. Hydrolysis of *rac*-**5** catalyzed by *Candida antarctica* lipase B.

First our standard conditions for minor enantiomer recycling[4d,34]—room temperature, 5 mol% titanium complex **4**, CALB (20 mg), and 25 h addition time of acetyl cyanide (**3**; 3 equiv)—were attempted. This led to unsatisfactory results: 44% yield and 41% *ee* (Table 1, entry 1). The low enantioselectivity suggests that steady state had not been reached. To increase the rate of the catalytic processes, the temperature was increased to 40 °C while other conditions were kept constant. This resulted in both a higher yield and higher *ee* (Table 1, entry 2). That higher *ee* is observed at higher temperature is counterintuitive, but it is characteristic of the process, since the *ee* is steadily increasing as the reaction proceeds. A longer reaction time, with the addition of acetyl cyanide over 50 h, resulted in a further increase in the *ee* (98%; Table 1, entry 3) but in an unacceptable yield of 35%. As expected, a higher amount of enzyme accelerated the hydrolytic reaction and led to an enantiopure product (Table 1, entry 4), but at the same time it led to a further decrease in yield as a result of the reverse process being favored. A successive increase in the amount of titanium complex resulted in gradually improved yields, albeit at some expense to the enantiomeric excess (Table 1, entries 5 and 6).

Table 1. Formation of (*S*)-propanolol precursor (*S*)-**5a** by minor enantiomer recycling.[a]



Entry	T [°C]	t[b] [h]	**4** [mol%]	CALB [mg]	Yield [%][c]	*ee* [%][d]
1	20	25[e]	5	20	44	41
2	40	25[e]	5	20	50	77
3	40	50[f]	5	20	35	98
4	40	50[f]	5	40	11	100
5	40	50[f]	7.5	20	34	95
6	40	50[f]	10	20	61	96

[a] Conditions: 0.24 mmol aldehyde **2a** in 1 mL toluene/1 mL phosphate buffer, pH 8. [b] Time for addition of **3**. [c] Determined by GC by using undecane as internal standard. [d] Determined by chiral GC. [e] Acetyl cyanide was diluted with toluene to a total volume of 250 μL. [f] Acetyl cyanide was diluted with toluene to a total volume of 350 μL.

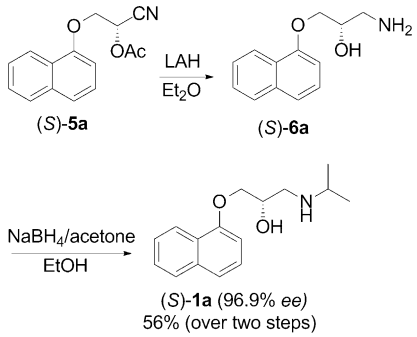
Since the reactions were run in a two-phase system in which the metal-catalyzed reaction occurs in the organic phase and that catalyzed by the enzyme in the aqueous phase, we were concerned that the rate of stirring might influence the results. To test the reproducibility, the reaction was repeated seven times using the conditions described in Table 1, entry 6, but with different stir rates. Yields varied between 55 and 67%, a variation that seemed to be independent of stir rate. However, higher enantiomeric excesses of 96–98% were observed in reactions with fast stirring than in reactions with slow stirring, most probably as a consequence of more efficient phase transfer and therefore more efficient hydrolysis in the former case.

The progress of the reaction was also followed over time. As expected, gradual increases in both yield and *ee* were observed with time. In one case, the *ee* was 96% and the yield 58% at steady state. When the reaction mixture was allowed to stir after terminated addition of acetyl cyanide, the *ee* increased to 99.7%, an increase that was necessarily accompanied by a corresponding decrease in yield.

Although high *ee* was observed, we were concerned about the yields. We suspected that the moderate yields might be due to decomposition of the labile aldehyde. This was indeed found to be the case: treatment of **2a** under the reaction conditions (toluene/**4**/buffer/CALB, 24 h) allowed only approximately 50% of the aldehyde to be recovered.

On the basis of the results from this initial screening, the reaction conditions used in entry 6 of Table 1 were selected for a reaction run on a preparative scale. After purification by column chromatography, the desired compound (*S*)-**5a** was isolated in 59% yield and with 97.6% *ee*.

With the enantioenriched compound (*S*)-**5a** in hand, β-adrenergic antagonist (*S*)-propanolol was successfully synthesized in two steps, which consisted of the reduction of the ester and nitrile functions by using lithium aluminum hydride (LAH) to yield (*S*)-**6a**, followed by reductive amination with acetone and sodium borohydride (Scheme 5).[33] Starting from (*S*)-**5a** with



Scheme 5. Preparation of (*S*)-propanolol (**1a**) from (*S*)-**5a**.

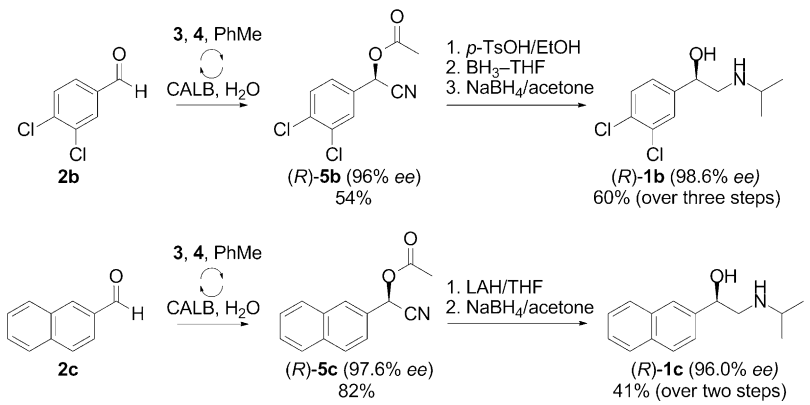
97.6% *ee*, (*S*)-propranolol was obtained in 56% yield (over two steps) and with 96.9% *ee*. Optical rotation showed that the product had *S* absolute configuration.

Synthesis of (*R*)-dichloroisoproterenol (1 b)

We assumed that our minor enantiomer recycling procedure would provide the cyanoacylated product from aldehyde **2 b** with higher enantiopurity than previously observed.[27,28] In an initial experiment, continuous addition of acetyl cyanide to 3,4-dichlorobenzaldehyde (**2 b**), titanium complex **4**, and CALB in toluene/buffer pH 7 over 50 h at 40 °C resulted in a continuous increase in the yield of **5 b**. The enantiomeric excess increased during the first approximately 30 h to 94%, after which time a decrease in enantiomeric purity was observed. We suspected that this decrease could be a result of enzyme inhibition and, as a consequence, to slower enzymatic hydrolysis, in turn leading to an imbalance between the forward and reverse processes. A successive decrease in the rate of addition of acetyl cyanide indeed helped to maintain the high *ee* (see also the Supporting Information). A more convenient procedure for the preparation of **5 b** consisted of the addition of acetyl cyanide over 8 h at 40 °C. Under these conditions, the acetylated cyanohydrin (*R*)-**5 b** was formed with only 70% *ee*. However, the addition of additional CALB gave the product in 54% isolated yield and with 96.0% *ee.* Subsequent LAH reduction and reductive amination according to the procedure used for the preparation of (*S*)-propanolol resulted in considerable erosion of the enantiomeric purity (58% *ee* of (*R*)-**1 b** prepared in this way). In contrast, hydrolysis under acidic conditions (*p*-toluenesulfonic acid) followed by BH_3 reduction and reductive amination using $NaBH_4$/acetone gave the target compound in 60% yield (over three steps) and with 98.6% *ee* (Scheme 6). The absolute configuration was shown to be *R* by comparison of the HPLC elution order to that published.[26b]

Synthesis of (*R*)-pronethalol (1 c)

The same synthetic sequence was applied to 2-naphthylaldehyde (**2 c**), with acetyl cyanide added over 50 h at 40 °C. After the addition was completed, the reaction mixture was left to stir to increase the *ee* of the product. The acylated cyanohydrin **5 c** was then isolated in 82% yield and 97.6% *ee*. This should be compared to lipase-catalyzed dynamic kinetic resolution, which has been reported to give the same acetylated cyanohydrin in 88% yield and with only 85% *ee*.[35] Subsequent LAH reduction and reductive amination gave the target compound (*R*)-**1 c** in 41% yield and with 96.0% *ee*. The absolute configuration was shown to be *R* by comparison of the HPLC elution order to that published.[26b]



Scheme 6. Synthesis of (*R*)-dichloroisoproterenol and (*R*)-pronethalol (**1 c**).

Conclusion

Aldehydes **2 a**–**c** were transformed to acetylated cyanohydrins, which were subsequently used for the preparation of β-adrenergic antagonists (*S*)-propanolol, (*R*)-dichloroisoproterenol, and (*R*)-pronethalol. Although direct cyanation of **2 a** and **2 b** proceeded with low enantioselectivity, a cyclic process that comprised a combination of a Lewis acid catalyst and a biocatalyst provided highly enantioenriched products in good yields. The yields of compounds **5 a** and **5 b** were moderate, but that of **5 a** was considerably higher than the yield obtained by kinetic resolution of the corresponding alcohol. The final products derived from aldehydes **2 a** and **2 c** were obtained without erosion of the *ee* by LAH reduction followed by reductive elimination, whereas an alternative procedure that consisted of acid-catalyzed hydrolysis, BH_3 reduction, and reductive amination was required to obtain (*R*)-dichloroisoproterenol with high enantiomeric excess. The enantioselective synthesis of these pharmaceuticals is another example of the usefulness of the minor enantiomer recycling procedure for the preparation of compounds that are obtained with poor enantioselectivity using conventional methods.

Experimental Section

General

^1H (500 MHz) and ^{13}C (125 MHz) NMR spectra were recorded using a Bruker Avance DMX 500 instrument in $CDCl_3$. Chemical shifts (δ) [ppm] are reported with reference to residual $CHCl_3$ in the solvent. Enantiomeric excess (*ee*) values were determined by gas chromatography using an Agilent Technologies 6850 Chromatograph equipped with a column (30 m × 0.250 mm × 0.25 μm) that contained Cyclosil-B as the stationary phase. HPLC analyses were conducted using a Shimadzu SIL-20A instrument with a UV detector and chiral column (Daicel Chiralpak IC, 0.46 cm × 25 cm, and Daicel Chiralcel ODH, 0.46 cm × 25 cm). Optical rotation was measured using a Perkin–Elmer 341LC instrument. Acetyl cyanide,[36] (*S*,*S*)-[{4,6-bis(*tert*-butyl)salen}Ti(μ-O)]$_2$,[37] and (1-naphthyloxy)acetaldehyde[29] were prepared according to literature procedures. 3,4-Dichlorobenzalde-

hyde and 2-naphthaldehyde were commercial products, which were purified by recrystallization from EtOH/H_2O and EtOH, respectively, before use. All other reagents were commercially available and were used without further purification. Immobilized (acrylic resin, $>5000\ U\,g^{-1}$) *Candida antarctica* lipase B (CALB, expressed in *Aspergillus niger*) was purchased from Sigma Aldrich (product number L4777, EC number 3.1.1.3). Dry solvents were taken from a Glass Contour solvent dispensing system.

General procedure for preparation of racemic acetylated cyanohydrins

Triethylamine (0.1 equiv) was added dropwise to acetyl cyanide (**3**, 1.2 equiv) and the appropriate aldehyde in CH_2Cl_2. The solution was stirred at room temperature overnight before the solvent was removed. The crude product was purified by column chromatography.

General procedure for enzymatic hydrolysis of *O*-acetylated cyanohydrin

Undecane (10 μL) as internal standard was added to the *O*-acetylated cyanohydrin (0.078 mmol) in toluene (1 mL) contained in a vial with 80 mm height and 13 mm diameter equipped with a stir bar. The biocatalyst (10 mg) was then added, followed by aqueous phosphate buffer (1 mL, pH 7 or 8), which was prepared from KH_2PO_4 and NaOH (1 and 2 M for pH 7 and pH 8 buffers, respectively). The reaction was monitored by GC. For this purpose, aliquots were taken from the upper organic phase of the two-phase system; the stirring was maintained at a rate that kept the two phases separated. The samples were filtered through a plug of silica, which was rinsed with diethyl ether, and the solution injected into the GC.

General procedure for the minor enantiomer recycling

Titanium complex **4** (5–10 mol%) and undecane (10 μL) as internal standard were added to the aldehyde (0.24 mmol) in toluene (1 mL) contained in a vial with the dimensions described above and equipped with a stir bar, followed by CALB, then aqueous phosphate buffer solution (1 mL, pH 7 or 8), and the mixture was stirred at the indicated temperature. Acetyl cyanide (51 μL, 0.72 mmol) in toluene was added into the organic phase over the indicated time using a syringe pump. Aliquots of the reaction mixture were taken and analyzed as described above.

(*S*)-1-Cyano-2-(naphthalen-1-yloxy)ethyl acetate ((*S*)-5 a): Preparative scale

(1-Naphthyloxy)acetaldehyde (**2 a**; 223 mg, 1.2 mmol) and titanium complex **4** (146 mg, 0.12 mmol) were dissolved in toluene (5 mL) in a 25 mL round-bottomed flask, and then CALB (100 mg) and phosphate buffer pH 8 (5 mL) were added. The mixture was stirred using a magnetic stir bar at 40 °C while acetyl cyanide (**3**; 255 μL, 3.6 mmol) dissolved in toluene (1.75 mL total volume) was added into the organic phase over 50 h using a syringe pump. After the addition was complete, the two phases were separated, and the aqueous phase was extracted with diethyl ether (2×30 mL). The combined organic phases were washed with brine (1×60 mL) and dried over $MgSO_4$. After the solvent was evaporated, the residue was purified by column chromatography using hexanes/CH_2Cl_2 (1:2) as eluent to give (*S*)-**5 a** as an orange oil (180 mg, 59% yield). The *ee* was determined to be 97.6% by chiral GC analysis (flow 1 mL min^{-1}, 60 °C for 10 min, 10 °C min^{-1} to 100 °C, hold for 5 min, 5 °C min^{-1} to 200 °C, hold for 35 min, 20 °C min^{-1} to 220 °C, hold 5 min): t_R (major) = 63.7 min, t_R (minor) = 64.8 min. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.2 (split d, 1H), 7.82 (split d, 1H), 7.51–7.53 (m, 3H), 7.38 (t, J = 8.0 Hz, 1H), 6.81 (d, J = 7.6 Hz, 1H), 5.91 (t, J = 5.3 Hz, 1H), 4.50 (d, J = 5.3 Hz, 2H), 2.20 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.9, 153.3, 134.6, 127.5, 126.9, 125.9, 125.5, 125.4, 122.0, 121.7, 114.9, 105.3, 66.8, 59.9, 20.4 ppm.

(*S*)-1-(Isopropylamino)-3-(naphthalen-1-yloxy)propan-2-ol ((*S*)-1a)

Compound (*S*)-**5 a** (0.76 g, 3.0 mmol, 97.6% *ee*) in Et_2O (20 mL) was added slowly to a suspension of LAH (0.34 g, 9.0 mmol) in anhydrous Et_2O (30 mL) at 0 °C under an N_2 atmosphere.[38] The mixture was heated at reflux for 5 h before H_2O was added to destroy excess amounts of LAH. The solid was removed by filtration and washed with Et_2O. The combined organic phases were washed with brine and dried over $MgSO_4$. Removal of the solvent under reduced pressure provided a pale white solid (0.53 g; crude yield: 82%[39]), which was dissolved in absolute ethanol (5 mL), then acetone (0.27 mL, 3.68 mmol) was added dropwise, followed by $NaBH_4$ (0.19 g, 4.90 mmol).[11a] The mixture was stirred overnight, then H_2O was added and the pH was adjusted to 8 by the addition of 1 M HCl. After removal of the solvents, a white solid was obtained, which was partly dissolved in ethyl acetate and methanol (9:1, 50 mL). The remaining solid was removed by filtration, then the filtrate was concentrated and purified by column chromatography with dichloromethane/methanol (5:1) as eluent to give (*S*)-**1 a** as a white solid (0.43 g, 68% yield) with 96.9% *ee*.[15b] HPLC conditions: Daicel Chiralcel OD-H column, detection at 254 nm, hexanes/isopropanol/Et_2NH = 90:10:0.1, rate = 0.5 mL min^{-1}, t_R (minor) = 22.7 min, t_R (major) = 46.6 min. $[\alpha]_{20}^{D} = -9.9$ (c = 0.82, EtOH) [Ref. [15b]: $[\alpha]_{20}^{D} = -8.83$ (c = 1, EtOH, 95% *ee*)]; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.26 (split d, 1H), 7.80 (split d, 1H), 7.43–7.50 (m, 3H), 7.35 (t, J = 7.9 Hz, 1H), 6.72 (d, J = 7.6 Hz, 1H), 4.30 (ddt, J = 8.4, 3.5, 5.3 Hz, 1H), 4.20 (A part of ABX, J(A,B) = 9.4 Hz, J(A,X) = 5.3 Hz, 1H), 4.12 (B part of ABX, J(A,B) = 9.4 Hz, J(B,X) = 5.3 Hz, 1H), 3.81 (br s, 2H), 3.07 (A part of ABX, J(A,B) = 12.2 Hz, J(A,X) = 3.5 Hz, 1H), 2.96 (hept, J = 6.2 Hz, 1H), 2.92 (B part of ABX, J(A,B) = 12.2 Hz, J(B,X) = 8.4 Hz, 1H), 1.18 (d, J = 6.2 Hz, 3H), 1.17 ppm (d, J = 6.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 153.8, 134.4, 127.5, 126.5, 125.8, 125.5, 125.3, 121.8, 120.9, 104.9, 69.7, 65.9, 51.6, 48.3, 19.1, 19.0 ppm.

(*R*)-1-Cyano-2-(3,4-dichlorophenyl)methyl acetate ((*R*)-5 b): Preparative scale

3,4-Dichlorobenzaldehyde (**2 c**; 420 mg, 2.4 mmol) and titanium complex **4** (146 mg, 0.12 mmol) were dissolved in toluene (10 mL) in a 50 mL round-bottomed flask, and then CALB (200 mg) and phosphate buffer pH 7 (10 mL) were added. The mixture was stirred using a magnetic stir bar at 40 °C while acetyl cyanide (**3**; 510 μL, 7.2 mmol) dissolved in toluene (1 mL total volume) was added into the organic phase over 8 h using a syringe pump. After the addition was finished, another 200 mg of CALB was added. The mixture was allowed to stir for another 2 h, then the two phases were separated, and the aqueous phase was extracted with diethyl ether (2×60 mL). The combined organic phases were washed with brine (1×100 mL) and dried over $MgSO_4$. After the solvent was evaporated, the residue was purified by column chromatography using hexanes/ethyl acetate (10:1) as eluent to give (*R*)-**5 b** as a yellow oil (314 mg, 54% yield). The *ee* was determined to be 96.0% by chiral GC analysis (flow 1 mL min^{-1}, 60 °C for 10 min, 10 °C min^{-1} to 100 °C, 2 °C min^{-1} to 210 °C): t_R (major) = 56.0 min, t_R

(minor) = 58.1 min. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.62 (d, J = 2.0 Hz, 1H), 7.54 (d, J = 8.3 Hz, 1H), 7.37 (dd, J = 8.3, 2.0 Hz, 1H), 6.36 (s, 1H), 2.19 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.7, 135.0, 133.7, 131.7, 131.3, 129.8, 127.1, 115.4, 61.6, 20.4 ppm.

(*R*)-2-(3,4-Dichlorophenyl)-2-hydroxyacetonitrile

p-TsOH·H_2O (136 mg, 0.71 mmol) was added to a solution of (*R*)-**5b** (173 mg, 0.71 mmol) in ethanol (10 mL). The remaining solution was stirred for 3 days at room temperature before the solvent was removed.[28] The residue was purified by column chromatography with hexanes/EtOAc 5:1 as eluent to give the free cyanohydrin (130 mg, 91% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.65 (d, J = 1.8 Hz, 1H), 7.54 (d, J = 8.3 Hz, 1H), 7.38 (dd, J = 8.3, 1.8 Hz, 1H), 5.54 (d, J = 6.8 Hz, 1H), 2.92 ppm (d, J = 6.8 Hz, 1H).

(*R*)-1-(3,4-Dichlorophenyl)-2-(isopropylamino)ethanol ((*R*)-1b)

BH_3·THF (1.92 mL of 1 M THF solution, 1.92 mmol) was added slowly to a solution of the above cyanohydrin (130 mg, 0.64 mmol) in THF (4 mL) at 0 °C. The remaining solution was heated to reflux for 2 h, then left overnight at room temperature. The reaction was quenched by the addition of methanol (0.5 mL); 15% NaOH was used to adjust the pH to 8. The mixture was diluted with THF, dried over $MgSO_4$ and filtered, and the solvent evaporated under vacuum to provide a white solid (180 mg). The solid was dissolved in EtOH (4 mL) and acetone (125 μL, 1.7 mmol) was added followed by $NaBH_4$ (87 mg, 2.3 mmol) after 0.5 h. The mixture was stirred for 1 h at room temperature before quenching the reaction with 1 M HCl (1 mL). The pH was adjusted to 8 with 15% NaOH. After removal of the solvents, a white solid was obtained, which was partly dissolved in ethyl acetate and methanol (9:1, 50 mL). The remaining solid was removed by filtration, the filtrate was concentrated and purified by column chromatography (EtOAc/MeOH/Et_3N 100:10:1) to provide (*R*)-**1b** as a white solid (105 mg, 66% yield, 98.6% *ee*). HPLC conditions: Chiralpak IC column, detection at 280 nm, hexanes/isopropanol/Et_2NH = 98.4:1.5:0.1, rate = 0.7 mL min^{-1}, t_R (major) = 11.6 min, t_R (minor) = 16.4 min. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.49 (d, J = 1.4 Hz, 1H), 7.41 (d, J = 8.2 Hz, 1H), 7.20 (dd, J = 8.2, 1.4 Hz, 1H), 4.64 (dd, J = 9.0, 3.4 Hz, 1H), 2.96 (A part of ABX, J(A,B) = 12.2 Hz, J(A,B) = 3.6 Hz, 1H), 2.87 (hept, J = 6.2 Hz, 1H), 2.59 (B part of ABX, J(A,B) = 12.2 Hz, J(B,X) = 9.0 Hz, 1H), 2.62 (br s, 2H), 1.12 (d, J = 6.2 Hz, 3H), 1.11 ppm (d, J = 6.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 142.8, 132.5, 131.4, 130.4, 127.8, 125.2, 70.0, 53.8, 49.3, 22.1, 22.0 ppm.

(*R*)-Cyano(naphthalen-2-yl)methyl acetate ((*R*)-5c): Preparative scale

2-Naphthaldehyde (**2c**; 375 mg, 2.40 mmol) and titanium complex **4** (147 mg, 0.121 mmol) were dissolved in toluene (10 mL) in a 50 mL round-bottomed flask, then CALB (200 mg) and phosphate buffer pH 7 (10 mL) were added. The mixture was stirred using a stir bar at 40 °C while acetyl cyanide (**3**; 510 μL, 7.19 mmol) dissolved in toluene (2.5 mL total volume) was added into the organic phase during 50 h. After the addition was completed, the mixture was allowed to stir for another 5 h 40 min. The phases were separated, the aqueous phase was extracted with diethyl ether, the combined organic phases were dried over $MgSO_4$, and the solvents were evaporated. The crude product was purified by column chromatography (petroleum ether/EtOAc 9:1 to 4:1) to give (*R*)-**5c** (442 mg, 82%, 97.6% *ee*) as a yellow oil. GC (flow 1 mL min^{-1}, 60 °C for 10 min, 10 °C min^{-1} to 100 °C, 2 °C min^{-1} to 210 °C): t_R (major) = 65.7 min, t_R (minor) = 66.6 min. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.03 (s, 1H), 7.94 (d, J = 8.6 Hz, 1H), 7.87–7.91 (m, 2H), 7.55–7.60 (m, 3H), 6.59 ppm (s, 1H), 2.19 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.1, 134.0, 133.0, 129.6, 129.1, 128.5, 128.2, 128.0, 127.7, 127.3, 124.4, 116.3, 63.2, 20.7 ppm.

(*R*)-2-(Isopropylamino)-1-(naphthalen-2-yl)ethanol ((*R*)-1c)

Compound (*R*)-**5c** (192 mg, 0.85 mmol, 97.6% *ee*) dissolved in THF (2 mL) was added slowly to a suspension of LAH (100 mg, 2.6 mmol) in THF (3 mL) at 0 °C under an N_2 atmosphere. The mixture was heated to reflux for 2 h and left to stir overnight at room temperature. H_2O (0.7 mL) was added to quench the reaction, then 15% NaOH (0.35 mL) was added. The mixture was diluted with THF, dried over $MgSO_4$, then filtered and evaporated under vacuum to provide a white solid (149 mg). The white solid was dissolved in EtOH (3 mL), and acetone (87 μL, 1.2 mmol) was added followed by $NaBH_4$ (61 mg, 1.6 mmol) after 0.5 h. The mixture was stirred for 1 h at room temperature before the reaction was quenched by the addition of 1 M HCl (1 mL), then the pH was adjusted to 8 with 15% NaOH. After removal of the solvents, a white solid was obtained, which was partly dissolved in ethyl acetate and methanol (9:1, 50 mL). The remaining solid was removed by filtration, then the filtrate was concentrated and purified by column chromatography (EtOAc/MeOH/Et_3N 200:10:1) to provide (*R*)-**1c** as a white solid (80 mg, 41% yield based on (*R*)-**5c**, 96.0% *ee*). HPLC conditions: Chiralpak IC column, detection at 280 nm, hexanes/isopropanol/Et_2NH = 94.9:5:0.1, rate = 0.7 mL min^{-1}, t_R (major) = 14.7 min, t_R (minor) = 23.4 min. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.82–7.87 (m, 4H), 7.45–7.50 (m, 3H), 5.00 (dd, J = 9.1, 3.1 Hz, 1H), 3.10 (A part of ABX, J(A,B) = 12.2 Hz, J(A,X) = 3.4 Hz, 1H), 2.99 (hept, J = 6.1 Hz, 1H), 2.83 (B part of ABX, J(A,B) = 12.2 Hz, J(B,X) = 9.2 Hz, 1H), 2.53 (br s, 2H), 1.19 (d, J = 6.1 Hz, 3H), 1.18 ppm (d, J = 6.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 140.1, 133.3, 133.0, 128.1, 128.0, 127.7, 126.1, 125.8, 124.5, 124.0, 71.9, 54.4, 48.9, 23.1, 22.9 ppm.

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