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A Chemoenzymatic Dynamic Kinetic Resolution Approach to Enantiomerically Pure (*R*)- and (*S*)-Duloxetine

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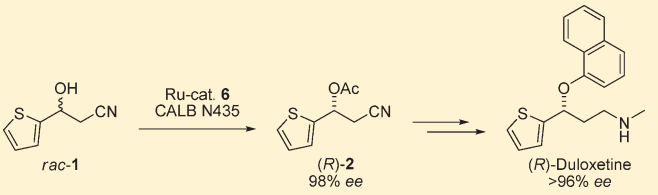
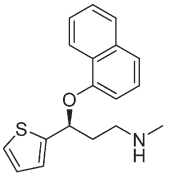
Supporting Information

ABSTRACT: The synthesis of (*R*)-duloxetine is described. Dynamic kinetic resolution of β-hydroxynitrile *rac*-**1** using *Candida antarctica* lipase B (CALB, N435) and ruthenium catalyst **6** afforded β-cyano acetate (*R*)-**2** in high yield and in excellent enantioselectivity (98% ee). The subsequent synthetic steps were straightforward and (*R*)-duloxetine was isolated in 37% overall yield over 6 steps. The synthetic route also constitute a formal total synthesis of (*S*)-duloxetine.

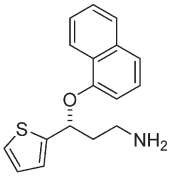


INTRODUCTION

Duloxetine is an antidepressant drug targeting the presynaptic cell. It is a dual inhibitor preventing the reuptake of serotonin as well as norepinephrine. In addition to being an important pharmaceutical in the short term treatment of major depressive disorders, it can be used to treat urinary incontinence and obsessive compulsive disorder. Duloxetine is sold in its (*S*)-form as a hydrochloride salt under the name Cymbalta.[1]



(*S*)-Duloxetine



(*R*)-Norduloxetine

In 1992 the U.S. Food and Drug Administration and the European Committee for Proprietary Medicinal Products determined that each enantiomer of a potential drug has to be characterized for their individual physiological action.[2] This demand calls for simple and straightforward preparation of both enantiomers with high degree of purity, which can be a challenge. For duloxetine the (*S*)-enantiomer has been found to be twice as potent as the (*R*)-enantiomer, whereas for norduloxetine the (*R*)-enantiomer was found more potent than the (*S*)-enantiomer as reuptake inhibitor of the human serotonin transporter.[1c] Different methods have been reported for the enantioselective synthesis of duloxetine where asymmetric reduction[3] and kinetic resolution[4] are most commonly employed.

Dynamic kinetic resolution is the concept of combining a kinetic resolution (KR) with *in situ* racemization and is a growing research area of great importance (Scheme 1).[5] In a KR, a chiral catalyst, for example, an enzyme, transforms one enantiomer of a racemate much faster than the other enantiomer. By combining this with a continuous racemization of the substrate, a theoretical yield of 100% of the enantiopure product can be obtained. In a chemoenzymatic DKR an enzyme is employed as catalyst for the resolution while, e.g., a transition metal catalyst is employed for the racemization. Our group has successfully applied the concept of DKR to several substrate classes such as secondary alcohols,[6] amines,[7] diols,[8] amino alcohols,[9] and β-hydroxynitriles.[10]

Herein we report on the enantioselective synthesis of duloxetine via a DKR. The strength of the synthetic route described lies in utilizing DKR in the enantiodetermining step where we take advantage of the high selectivity of enzyme catalysis while circumventing the limitation of a normal kinetic resolution by converting the slow-reacting enantiomer to the fast reacting one.

RESULTS AND DISCUSSION

Synthetic routes toward duloxetine utilizing β-hydroxynitrile as a chiral intermediate are not as well explored as those with γ-chloro ketones, and only a few syntheses are reported.[3d,4d] β-Hydroxynitriles are versatile intermediates since they give access to both β-hydroxy acids and γ-amino alcohols through simple transformations.[10] We envisioned starting from a readily available and inexpensive starting material such as 2-thiophene carboxaldehyde. Subjecting the β-hydroxynitrile to DKR would give the enantiomerically pure β-cyano acetate. The latter compound could easily be reduced to give the γ-hydroxyamine, which subsequently could be protected with ethyl chloroformate. Reduction of the carbamate followed by a nucleophilic aromatic substitution to introduce the naphthyl would give (*R*)-duloxetine (Scheme 3). As described in the literature (*S*)-duloxetine is also available by subjecting Boc-protected (*R*)-**4** to a Mitsunobu reaction.[4d]

By starting from 2-thiophene carboxaldehyde the β-hydroxynitrile was obtained in 91% yield through a condensation reaction with acetonitrile. The following transformation to acquire the enantiomerically enriched β-cynao acetate requires a successful DKR. To find suitable conditions the KR and racemization was studied

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Scheme 1. Schematic Picture of Dynamic Kinetic Resolution

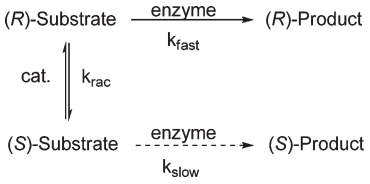
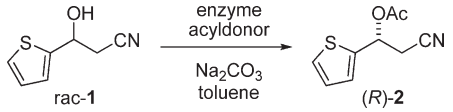


Table 1. Investigating the Selectivity of Different Enzymes in Kinetic Resolution of β-Hydroxynitrile 1[13]



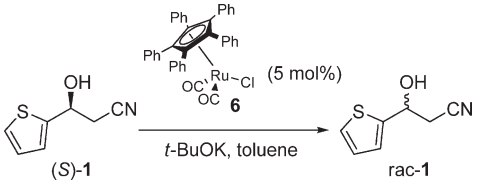
entry	enzyme	T (°C)	t (h)	conv (1)[a] (%)	% ee (1)[b]	% ee (2)[b]	E[c]
1	PS-IM	rt	3	35	52	97	110 (*R*)
2	PS-C	rt	3	44	76	96	112 (*R*)
3	PS-D	rt	2	33	54	98	170 (*R*)
4	PS-D	80	2	38	51	82	16 (*R*)
5	CALB N435	rt	6	6	6	>99	>200 (*R*)
6	CALB N435	50	4	21	25	>99	>200 (*R*)
7	CALB N435	70	2	23	27	98	128 (*R*)
8	CALB N435	80	4	35	56	96	86 (*R*)
9[d]	CALB-W104A[e]	50	24	14	14	81	10 (*S*)
10[d]	subtilisin[f]	38	4	41	5	8	1.2 (*S*)
11[d]	subtilisin[f]	50	5	23	6	18	1.5 (*S*)

[a] Measured by ^{1}H NMR. [b] Measured by chiral HPLC. [c] Calculated values. [d] The (*S*) form of the acetate was obtained. [e] A mutated form of CALB proven to be (*S*)-selective.[14] [f] 1:4:4 subtilisin:Brij:octyl-β-D-glucopyranoside.

separately before being combined in a DKR. In non-aqueous media (e.g., toluene), lipases catalyze transesterification of a wide range of substrates such as carboxylic acids, alcohols, amines, or esters. The reaction usually proceeds with high regio- and/or enantioselectivity, and as a result, lipases have attracted considerable attention. In agreement with Kazlauskas' rule,[11] lipases display (*R*)-selectivity in transesterification reactions, whereas serine porteases (e.g., *Subtilisin Carlsberg*) display (*S*)-selectivity. The selectivity of different enzymes was initially determined (Table 1). From our previous work it was known that enzymatic resolution of β-hydroxynitriles with *Candida antarctica* lipase B (CALB) works very well.[10] In the literature, however, *Burkholderia cepacia* lipase (previously *Pseudomonas cepacia* lipase) is most commonly used in the KR of *rac*-**1**.[4d,12] The enantioselectivity (*E* value) of the kinetic resolution was measured in toluene using isopropenyl acetate or trifluoroethyl butyrate as acyl donor. Both (*R*)- and (*S*)-selective enzymes were investigated for their selectivity.

Burkholderia cepacia lipase (PS-IM, PS-C, PS-D) and CALB show high selectivity at room temperature (entries 1−3, 5) with PS-D giving an *E* value of 170 (entry 3), whereas CALB gave an *E* value >200 (entry 5). However the activity of CALB at room temperature was extremely low with only 6% conversion after 6 h. At higher temperature the selectivity of PS-D dropped considerably (entry 4), while CALB still showed excellent to good selectivity but more importantly higher activity (entries 6−8). The (*S*)-selective enzymes employed (entries 9−11) showed very low selectivity.

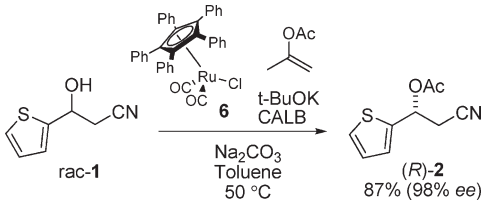
Table 2. Racemization of (*S*)-β-Hydroxynitrile at Room Temperature, 50, 70, and 80 °C[13]



entry	T (°C)	t (min)	ee[a] (%)
1	rt	120	57
2	50	20	0
3	70	5	0
4	80	5	0

[a] Measured by chiral HPLC.

Scheme 2. DKR of 1



The racemization of β-hydroxynitrile was investigated at room temperature, 50, 70, and 80 °C employing ruthenium complex **6**. From the results it was clear that an elevated temperature was necessary for the racemization to be sufficiently efficient in a DKR (Table 2). The ee of the (*S*)-β-hydroxynitrile only decreases to 57% within 2 h at room temperature (entry 1). At higher temperature the rate of racemization was sufficient (entries 2−4) and at ≥70 °C (*S*)-β-hydroxynitrile was fully racemized within 5 min (entries 3, 4).

From these individual studies it seemed that the optimal conditions for a successful DKR would be to run the reaction at a temperature above 70 °C employing CALB for the resolution. However, when the DKR was run at 70 °C, the ee of the acetate decreased with time and as much as 20% elimination product was observed. Running a control experiment where the enzyme was excluded showed that a background reaction of chemical acylation was taking place, which lowers the ee of the acetate. It was also found that water increased the amount of elimination product. In the presence of water, the acyl donor and the acetate (*R*)-**2** can be hydrolyzed forming acetic acid. If the heterogeneous Na_2CO_3 does not neutralize the acid immediately, these slightly acidic conditions will promote protonation of the product, which in turn initiates elimination. By careful optimization it was found that by increasing the amount of enzyme as well as the acyl donor (isopropenyl acetate) and running the reaction at 50 °C the elimination was kept to a minimum (Scheme 2). Under these reaction conditions the DKR reached 93% conversion within 25 h and only 2% elimination product was observed. Cyanoacetate (*R*)-**2** was isolated in 87% yield in 98% ee.

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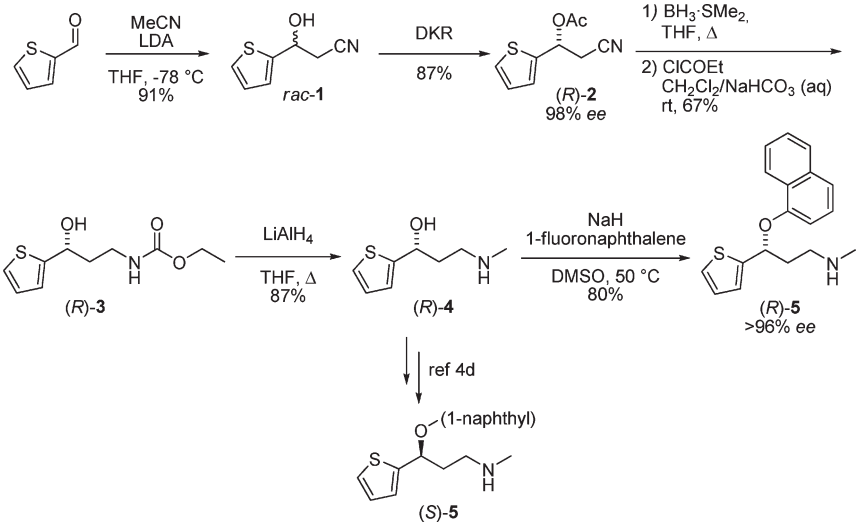
Scheme 3. Synthesis of Duloxetine



By reducing the nitrile and subsequently protecting it as a carbamate, the hydroxyl amide (*R*)-**3** was formed. Different conditions were tried for this two-step transformation, and it was found that subjecting the nitrile to 3.8 equiv of $BH_3 \cdot SMe_2$ and subsequently quenching with MeOH, followed by immediate treatment of the crude product with ethyl chloroformate in $CH_2Cl_2/NaHCO_3$ (aq), gave the desired product ((*R*)-**3**) in 67% yield over two steps. This was followed by a $LiAlH_4$ reduction, which afforded the amino alcohol (*R*)-**4** in 87% yield. The final step in the synthesis toward (*R*)-duloxetine was a nucleophilic aromatic substitution. Deprotonation of the amino alcohol (*R*)-**4** and subsequent substitution with 1-fluoronaphthalene yielded (*R*)-**5** in 80% yield (Scheme 3). The optical purity was maintained at a high level throughout the synthesis (>96% ee).[15] Prolonged reaction time and increased temperature during the nucleophilic aromatic substitution decreased the enantiomeric excess of the final product. This scheme also provides a formal total synthesis of (*S*)-**5**, since the transformation of (*R*)-**4** to (*S*)-**5** has previously been described.[4d]

CONCLUSION

We have reported a direct and efficient synthetic route for (*R*)-duloxetine as well as a formal total synthesis of (*S*)-duloxetine. By employing DKR in the enantiodetermining step the β-cyano acetate, (*R*)-**2**, was obtained in high yield and excellent enantioselectivity (98% ee). Further elaboration, via the γ-amino alcohol (*R*)-**4**, afforded (*R*)-duloxetine ((*R*)-**5**). The target molecule (*R*)-**5** was obtained in 37% overall yield from thiophene carboxaldehyde over six steps in high enantiomeric excess (>96%).[15]

EXPERIMENTAL SECTION

General. KR, DKR, and racemization reactions were carried out under dry argon atmosphere using standard Schlenk technique. The racemic 3-hydroxy-3-(thiophen-2-yl)propanenitrile (*rac*-**1**) was dried over molecular sieves (4 Å) before using it in DKR. Isopropenyl acetate was dried over $CaCl_2$ and distilled before use. Dry THF and toluene were obtained from a VAC solvent purifier. Acetonitrile was dried through distillation over CaH. All other chemicals and solvents were used as purchased. The enantiomeric excess of the compounds was determined by chiral HPLC using racemic compounds as references. Racemic acetate (*rac*-**2**) was obtained from the racemic alcohol (*rac*-**1**) by standard acylation. Silica column chromatography was performed with chromatographic silica (0.035−0.070 mm) for separation and purification applications.

HPLC samples were run on HPLC with a photodiode array detector. ^1H and ^{13}C NMR were recorded at 400 and 100 MHz, respectively. Optical rotation was measured with a polarimeter equipped with a Na lamp. HR-MS was recorded on an ESI MS. Ruthenium complex **6** ($\eta^5C_5Ph_5$)Ru(CO)$_2$Cl was synthesized according to a literature procedure.[6a] CALB (Novozym 435), PS-IM, PS-C, and PS-D are commercially available. CALB-W104A was obtained according to ref 14c. The subtilisin used was prepared according to ref 16.

3-Hydroxy-3-(thiophen-2-yl)propanenitrile (*rac*-1). To a solution of diisopropylamine (1.5 mL, 11 mmol) in 10 mL of dry THF under an argon atmosphere at −78 °C was added dropwise *n*-BuLi (2.5 M in hexanes, 4 mL, 10 mmol). After 0.5 h acetonitrile (0.5 mL, 10 mmol) in 5 mL of dry THF was added dropwise. The mixture was stirred for an additional 0.5 h at −78 °C before 2-thiophenecarboxaldehyde (0.94 mL, 10 mmol) dissolved in 5 mL of dry THF was added. After 18 h of stirring, the reaction was quenched by addition of 30 mL of saturated aqueous NH_4Cl solution. The water phase was extracted with Et_2O (3 × 30 mL), and the combined organic phases were dried over $MgSO_4$, filtered, and evaporated. The crude product was purified by flash chromatography (SiO_2, pentane/EtOAc 4:1) yielding **1** (1.4 g, 9.1 mmol, 91%) as a yellow oil. Spectral data were in accordance with those reported in the literature.[12] ^1H NMR (400 MHz, $CDCl_3$): δ 7.33 (dd, J = 5.1 Hz, 1.2 Hz, 1H), 7.10 (dt, J = 3.6 Hz, 1.1 Hz, 1H), 7.01 (dd, J = 5.1 Hz, 3.6 Hz, 1H), 5.31 (app t, J = 6.2 Hz, 1H), 2.89 (dd, J = 6.3 Hz, 1.8 Hz, 2H), 2.48 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.4, 127.1, 125.7, 124.7, 116.9, 66.2, 28.2. HPLC: Chiralpak OJ column, *i*-hexane/*i*-PrOH, 85:15 for 80 min, 0.5 mL·min^{-1}, 25 °C, UV at 230 nm, t_{R1} = 40 min (*S*)-**1**, t_{R2} =44 min (*R*)-**1**.

General Procedure for KR of *rac*-1. The corresponding enzyme (see Table 3 for the appropriate amount) and Na_2CO_3 (53 mg, 0.5 mmol) were added to a vial. The *rac*-3-hydroxy-3-(thiophen-2-yl)propanenitrile (*rac*-**1**) (77 mg, 0.5 mmol) dissolved in dry toluene (1 mL) was added to the vial, and the mixture was stirred. After a few minutes isopropenyl acetate (see Table 3 for the appropriate amount) was added to the reaction mixture. Samples for HPLC analysis were collected with a

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Table 3. Kinetic Resolution of *rac*-1

entry	enzyme	enzyme (mg/mmol)	OAc[a] (equiv)	T (°C)	t (h)	conv (**1**)[b] (%)	% ee (**1**)[c]	% ee (**2**)[c]	E[d]
1	PS-IM	50	2	rt	3	35	52	97	110 (*R*)
2	PS-C	50	2	rt	3	44	76	96	112 (*R*)
3	PS-D	50	2	rt	2	33	54	98	170 (*R*)
4	PS-D	50	2	80	2	38	51	82	16 (*R*)
5	CALB N435	50	2	rt	6	6	6	>99	>200 (*R*)
6	CALB N435	50	2	50	4	21	25	>99	>200 (*R*)
7	CALB N435	100	2	50	4	33	47	98	158 (*R*)
8	CALB N435	100	3	50	4	32	44	98	152 (*R*)
9	CALB N435	50	2	70	2	23	27	98	128 (*R*)
10	CALB N435	50	2	80	4	35	56	96	86 (*R*)
11	CALB-W104A[e]	100	3	50	24	14	14	81	10 (*S*)
12	subtilisin[f]	100	3[g]	38	4	41	5	8	1.2 (*S*)
13	subtilisin[f]	100	3[g]	50	5	23	6	18	1.5 (*S*)

[a] OAc = isopropenyl acetate. [b] Measured by ^{1}H NMR. [c] Measured by chiral HPLC. [d] Calculated values. The selectivity displayed by the enzyme is given in parentheses. [e] A mutated form of CALB proven to be (*S*)-selective.[14,f] 1:4:4 subtilisin:Brij:octyl-β-D-glucopyranoside. [g] Trifluoroethyl buturate was used as acyl donor.

syringe after 0.5, 2, 3, 4, 5, 6, and 24 h. HPLC: Chiralpak OJ column, *i*-hexane/*i*-PrOH, 85:15 for 80 min, 0.5 mL·min-1, 25 °C, UV at 230 nm, t_{R1} = 40 min (*S*)-**1**, t_{R2} = 44 min (*R*)-**1**, t_{R3} = 57 min (*S*)-**2**, t_{R4} = 62 min (*R*)-**2**.

General Procedure for Racemization of (*S*)-1. Ruthenium complex **6**, ($\eta^5C_5Ph_5$)Ru(CO)$_2$Cl (9.5 mg, 0.015 mmol), and Na_2CO_3 (32 mg, 0.3 mmol) were added to a Schlenk tube. Dry toluene (0.3 mL) was added, and the resulting yellow solution was stirred. A THF solution of *t*-BuOK (30 μL, 0.5 M in dry THF, 0.015 mmol) was added to the reaction mixture. The reaction turned orange. After approximately 6 min of stirring (*R*)-3-hydroxy-3-(thiophen-2-yl)propanenitrile ((*R*)-**1**) (46 mg, 0.3 mmol), dissolved in dry toluene (0.3 mL), was added to the reaction mixture, and the reaction was heated to the appropriate temperature. Samples for HPLC analysis were collected with a syringe after 5, 15, 30, 60, and 120 min. HPLC: Chiralpak OJ column, *i*-hexane/*i*-PrOH, 85:15 for 80 min, 0.5 mL·min^{-1}, 25 °C, UV at 230 nm, t_{R1} = 40 min (*S*)-**1**, t_{R2} = 44 min (*R*)-**1**.

2-Cyano-1-(thiophen-2-yl)ethyl Acetate ((*R*)-2). Ruthenium complex **6** ($\eta^5C_5Ph_5$)Ru(CO)$_2$Cl (16 mg, 0.025 mmol), CALB (50 mg, 100 mg/mmol substrate), and Na_2CO_3 (53 mg, 0.5 mmol) were added to a Schlenk tube. Dry toluene (0.5 mL) was added, and the resulting yellow solution was stirred. A THF solution of *t*-BuOK (50 μL, 0.5 M in dry THF, 0.025 mmol) was added to the reaction mixture. The reaction turned orange. After approximately 6 min of stirring, *rac*-**1** (77 mg, 0.5 mmol) dissolved in dry toluene (0.5 mL) was added to the reaction mixture. After an additional 4 min, isopropenyl acetate (165 μL, 1.5 mmol) was added. The reaction was heated to 50 °C. After 25 h the reaction mixture was filtered and concentrated. Purification by column chromatography (SiO_2; pentane/Et_2O 4:1) afforded 85 mg (0.435 mmol, 87%) of (*R*)-**2** in 98% ee. Spectral data were in accordance with those reported in the literature.[12] ^{1}H NMR (400 MHz $CDCl_3$): δ 7.33 (dd, *J* = 5.1 Hz, 1.2 Hz, 1H), 7.16 (dt, *J* = 3.6 Hz, 1.1 Hz 1H), 7.00 (dd, *J* = 5.1 Hz, 3.6 Hz, 1H), 6.26 (app t, *J* = 6.3 Hz, 1H), 2.99 (dd, *J* = 6.3 Hz, 1.8 Hz, 2H), 2.12 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4, 139.3, 127.0, 126.5, 126.4, 115.7, 66.2, 25.6, 20.8. $[\alpha]^{20}_D$ = +94 (*c* 1.16, MeOH), $[\alpha]^{20}_D$ = +96 (*c* 0.93, $CHCl_3$); lit.[12] $[\alpha]^{20}_D$ = +94 (*c* 1, $CHCl_3$, 95% ee (*R*)-enantiomer). HPLC: Chiralpak OJ column, *i*-hexane/*i*-PrOH, 85:15 for 80 min, 0.5 mL·min^{-1}, 25 °C, UV at 230 nm, t_{R1} = 57 min (*S*)-**2**, t_{R2} = 62 min (*R*)-**2**.

(*R*)-3-Amino-1-(thiophen-2-yl)propan-1-ol. BH_3·Me_2S (1 mL, 2.0 mmol, 2 M in THF) was added to a two-necked round bottomed flask and heated to 80 °C for 30 min. Acetate (*R*)-**2** (87 mg, 0.45 mmol) was dissolved in 2 mL of dry THF and was then added dropwise to the mixture under gas formation. After 2 h the reaction was quenched by slow addition of 4 mL of MeOH at 0 °C followed by addition of 2 mL of H_2O. After filtration the organic solvent was evaporated, and the crude product obtained was used in the next step without further purification. If purification is desirable it can be done with flash chromatography (EtOAc/MeOH/NH_4OH 9:1:0.2) yielding the pure amino alcohol as a clear oily solution. ^{1}H NMR (400 MHz D_2O): δ 7.34−7.32 (m, 1H), 7.00−6.96 (m, 2H), 5.04−5.00 (m, 1H), 3.02−2.88 (m, 2H), 2.12−2.06 (m, 2H).

(*R*)-Ethyl 3-Hydroxy-3-(thiophen-2-yl)propylcarbamate ((*R*)-3). To a solution of crude (*R*)-3-amino-1-(thiophen-2-yl)propan-1-ol (originated from 0.45 mmol (*R*)-**2**) in CH_2Cl_2 (4 mL) was added 4 mL of saturated aqueous $NaHCO_3$ solution. Ethyl chloroformate (0.10 mL, 0.1 mmol) was added dropwise to the two phase mixture. After 1 h of stirring the product was extracted with CH_2Cl_2 (3 × 5 mL), dried over $MgSO_4$, filtered and concentrated. Purification by flash chromatography (SiO_2, pentane/EtOAc 3:1) yielded (*R*)-**3** as a colorless oil (69 mg, 0.3 mmol, 67% over two steps, 98% ee). Spectral data were in accordance with those reported in the literature.[3c] ^{1}H NMR (400 MHz $CDCl_3$): δ 7.24 (dd, *J* = 4.5 Hz, 1.8 Hz, 1H), 6.96−6.93 (m, 2H), 5. 09 (br s, 1H), 5.01−4.98 (m, 1H), 4.13 (q, *J* = 7.2 Hz, 2H), 3.54−3.46 (m, 1H), 3.29−3.21 (m, 1H), 2.02−1.96 (m, 2H), 1.23 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.5, 148.1, 126.7, 124.5, 123.4, 67.7, 61.1, 39.5, 37.8, 14.6. HPLC: Chiralpak OD-H column, *i*-hexane/*i*-PrOH, 97:3 for 120 min, 1.0 mL·min^{-1}, 30 °C, UV at 230 nm, t_{R1} = 85 min (*R*)-**3**, t_{R2} = 97 min (*S*)-**3**.

3-(Methylamino)-1-(thiophen-2-yl)propan-1-ol ((*R*)-4). A flame-dried two-necked round bottomed flask was charged with $LiAlH_4$ (330 mg, 8.7 mmol) and (*R*)-**3** (570 mg, 3.3 mmol) dissolved in 35 mL of dry THF was added. The suspension was heated to reflux and stirred for 14 h. 500 μL of ethylenediamine, 600 μL of aq. NaOH (10 w%), and 600 μL of H_2O was added subsequently with 10 min intervals. The gray mixture was filtered through a thin pad of Celite and washed with 50 mL of THF. The organic solvent was stripped off at reduced pressure. The aqueous phase was diluted and extracted with Et_2O (3 × 30 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, gradient eluent from 100% CH_2Cl_2 to 90:15:2 CH_2Cl_2/MeOH/NH_4OH) yielding (*R*)-**4** (491 mg, 2.87 mmol, 87%) as a clear oil that crystallized upon standing. Spectral data were in accordance with those reported in the literature.[3c,17] ^{1}H NMR (400 MHz $CDCl_3$) δ 7.21 (dd, *J* = 5.12 Hz, 1.33 Hz, 1H), 6.98−6.96 (m, 1H), 6.92 (dt, *J* = 3.5 Hz, 1.1 Hz, 1H), 5.20 (dd, *J* = 8.4 Hz, 3.3 Hz, 1H), 2.97 (ddd, *J* = 12.3 Hz, 5.9 Hz,

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3.4 Hz,1H), 2.87 (ddd, J = 12.3 Hz, 9.6 Hz, 3.4 Hz, 1H), 2.44 (s, 3H), 2.03−1.94 (m, 1H), 1.94−1.84 (m, 1H). ^{13}C NMR (100 MHz $CDCl_3$): δ 149.5, 126.6, 123.8, 122.6, 71.0, 49.6, 37.1, 35.8.

(*R*)-*N*-Methyl-3-(naphthalen-1-yloxy)-3-(thiophen-2-yl)-propan-1-amine ((*R*)-5). To a solution of (*R*)-**4** (45 mg, 0.26 mmol) dissolved in 1.7 mL of dry DMSO was added NaH (60% in mineral oil, 16 mg, 0.39 mmol)). The white suspension formed was stirred at ambient temperature for 30 min followed by an increase of reaction temperature to 50 °C and addition of 1-fluoronaphthalene (44 μL, 0.34 mmol). A red suspension was initially generated, which turned green after a few minutes of stirring. After 1 h the mixture was cooled to room temperature, and 4 mL of aq NaOH (1 M) was added in order to quench the reaction. The product was extracted with EtOAc (3 × 10 mL), and the combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The remaining DMSO was removed by Kugelrohr distillation (0.6 mmHg, 45 °C). Purification by flash chromatography (SiO_2, CH_2Cl_2/MeOH/NH_4OH 19:1:0.1) afforded (*R*)-**5** (61 mg, 0.21 mmol, 80%) as a colorless oil in >96% ee (determined by chiral HPLC). Spectral data were in accordance with those reported in the literature.[3c] ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37−8.33 (m, 1H), 7.80−7.77 (m, 1H), 7.51−7.46 (m, 1H), 7.42 (d, J = 8.2 Hz, 1H), 7.29−7.25 (m, 1H), 7.21 (dd, J = 5.0 Hz, 1.0 Hz, 1H), 7.06 (d, J = 3.3 Hz, 1H), 6.94 (dd, J = 4.9 Hz, 3.5 Hz, 1H), 6.86 (d, J = 7.7 Hz, 1H), 5.79 (dd, J = 7.6 Hz, 5.2 Hz, 1H), 2.87−2.81 (m, 2H), 2.51−2.40 (m, 1H), 2.44 (s, 3H), 2.28−2.16 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.3, 145.2, 134.6, 127.5, 126.6, 126.3, 126.2, 125.7, 125.3, 124.7, 124.6, 122.1, 120.6, 107.0, 74.7, 48.2, 38.8, 36.4. $[\alpha]^{21}_D$ = −114.3 (*c* 1, MeOH); lit.[3d] $[\alpha]^{20}_D$ = +110.5 (*c* 1.1, MeOH, 95% ee (*S*)-enantiomer). HPLC: Chiralpak OJ column, *i*-hexane/EtOH/diethylamine, 90:10:0.1 for 40 min, 1.0 mL·min^{-1}, 25 °C, UV at 229 nm, t_{R1} = 19 min (*S*)-**5**, t_{R2} = 24 min (*R*)-**5**

■ ASSOCIATED CONTENT

Supporting Information. ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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