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An efficient procedure for the resolution of α-cyano-α-fluoro-*p*-tolylacetic acid (CFTA) via the diastereomeric *N*-carbobenzyloxy-*cis*-1-amino-2-indanol esters

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Abstract—Development of a new, efficient resolution method of α-cyano-α-fluoro-*p*-tolylacetic acid (CFTA) **2a** has been successfully achieved, which has been troublesome to obtain by conventional methods, in spite of its outstanding ability as an NMR chiral derivatizing agent. Fractional recrystallization of a mixture of the diastereomeric CFTA esters prepared from racemic CFTA chloride and (1*R*,2*S*)-*N*-carbobenzyloxy-*cis*-1-amino-2-indanol (−)-**B** afforded the less-soluble diastereomer, which was hydrolyzed to give (*S*)-**2a**. It has also been demonstrated that optically active *N*-acetyl-*cis*-1-amino-2-indanol is effective for the chromatographic resolution of α-arylacetic acids including ibuprofen and naproxen.

1. Introduction

One of the most convenient and reliable methods for the determination of enantiomeric excess (% ee) and absolute configuration of chiral molecules is NMR spectroscopic analysis of the diastereomers obtained by condensation with chiral derivatizing agent (CDA) such as α-methoxy-α-trifluoromethylphenylacetic acid (MTPA).[1] Among various CDAs developed to date for this purpose, α-cyano-α-fluorophenylacetic acid (CFPA) **1a**[2] and α-cyano-α-fluoro-*p*-tolylacetic acid (CFTA) **2a**[3] have been found to be particularly effective from the viewpoint of both reactivity and NMR resolution ability. Thus, owing to the strong electron-withdrawing character of both fluorine and cyano groups on the α-carbon of the acetate structure, the corresponding acid chlorides of these acids are highly reactive such as to allow condensation with even sterically hindered alcohols and amines. For example, it has been shown that CFPA chloride (CFPA-Cl) **1b** can react with pinacolyl alcohol 500 times faster than MTPA chloride.[2b] Such high reactivity would eliminate or minimize any kinetic resolution that may occur during derivatization, which is desirable for obtaining accurate % ee values. Additionally, ^{19}F chemical shift differences ($\Delta\delta_F$) between a diastereomeric pair of CFPA or CFTA esters and amides are 5–50 times greater than those of MTPA derivatives. Values for % ee can be determined, even for alcohols that have the stereogenic center located seven bonds from the functionality.[2a]

The CFTA method using **2a** has also been applied for assigning the absolute configurations of secondary alcohols[4] and primary amines.[5] ^1H chemical shift differences ($\Delta\delta_H$) between the diastereomeric pairs of CFTA derivatives were greater than those for MTPA derivatives. Moreover, the signs of $\Delta\delta_H$ were consistently correlated with the absolute configurations of the substrates. It has been demonstrated that the ^{19}F chemical shift nonequivalence between the two CFTA diastereomers are useful in assigning the absolute configuration for α-amino esters.[6] Similarly, the use of ^{19}F chemical shift nonequivalence is highly promising for assignment of the absolute configurations of secondary alcohols.[3a]

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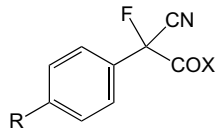
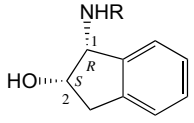


CFPA **1a**: R = H, X = OH
CFPA-Cl **1b**: R = H, X = Cl
CFTA **2a**: R = CH_3, X = OH
CFTA-Cl **2b**: R = CH_3, X = Cl



R = Ac: (-)-**A**
R = Cbz: (-)-**B**; (1*S*,2*R*): (+)-**B**

Despite the advantages of **1a** and **2a** over existing CDAs, including MTPA, utilization of **1a** and **2a** has been limited, primarily due to the rather involved synthetic steps in obtaining the optically active agents. The enantiomers of CFTA have been obtained by enzymatic resolution using *Candida rugosa* lipase pretreated with 2-propanol.[3b] Although this method is effective in affording enantiomerically pure (*R*)-CFTA on a gram scale, the (*S*)-isomer is obtained in rather low yields. Furthermore, the pretreatment procedure of enzyme is generally unfamiliar to organic chemists, and therefore, development of a simple, effective method for enantiomeric separation of CFTA is highly desirable for those chemists currently engaged in recent asymmetric and natural product synthesis. Since CFTA itself decomposes slowly at room temperature, the resolution of CFTA must be carried out as its stable chiral derivative. For a laboratory-scale production of both enantiomers of CFTA, we anticipated that the chromatographic separation of the CFTA diastereomers, by monitoring the extent of purity, would be more practicable than the fractional recrystallization of the diastereomeric amine salts.

2. Results and discussion

2.1. Resolution of CFTA

Since CFTA is somewhat unstable, the chiral auxiliary used must be removed under mild conditions. Therefore, although diastereomeric amides generally afford better separation[7] than diastereomeric esters, ester derivatives, which can be hydrolyzed easier than amide derivatives, were prepared. Unfortunately, due to the relatively low polarity, separation was not detected for the diastereomeric CFTA esters of 1-phenylethanol, *trans*-2-phenylcyclohexanol, menthol, and 8-phenylmenthol, as determined by silica gel HPTLC plates. Subsequently, to increase polarity, *N*-acyl-*cis*-1-amino-2-indanols[8] were examined as chiral auxiliaries, in which the polarity can be adjusted by selecting a proper *N*-acyl group to vary the overall chromatographic behavior. It was also expected that *cis*-amide groups adjacent to the CFTA ester groups would provide an additional site of interaction with the stationary phase resulting in greater difference of chromatographic behavior between the diastereomeric esters.

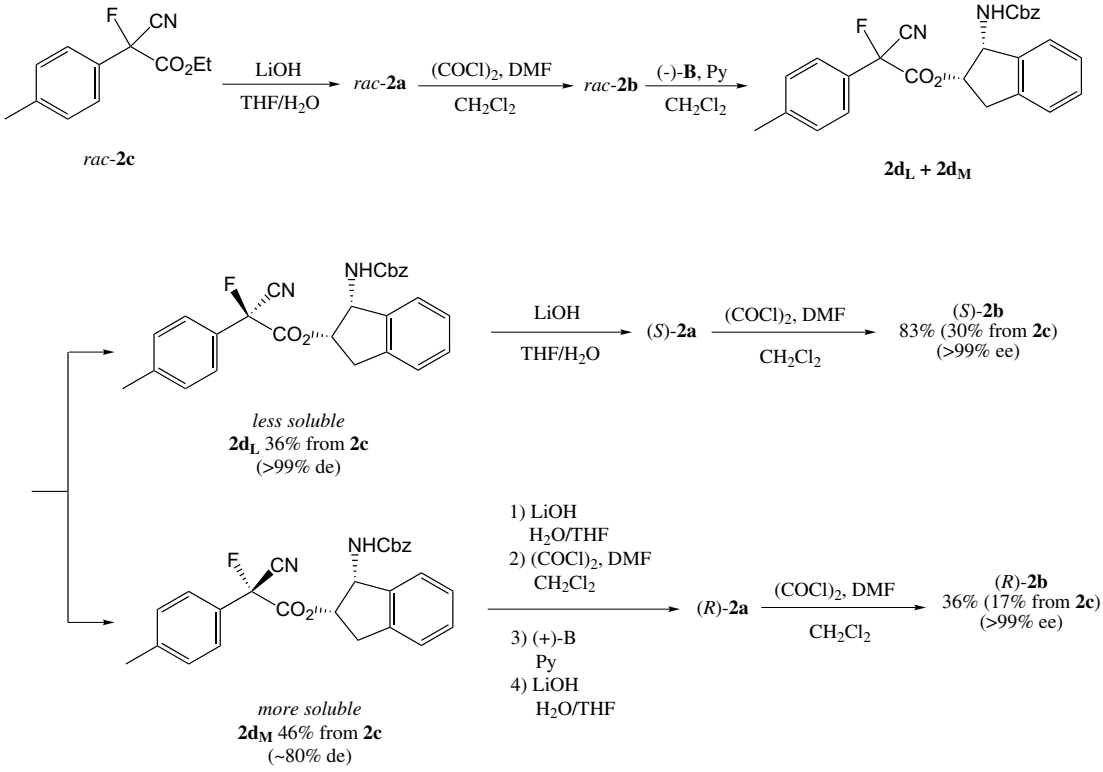
As a chiral auxiliary, (−)-*N*-acetyl-(1*R*,2*S*)-*cis*-1-amino-2-indanol (−)-**A** was initially examined. Reaction of (−)-**A** with an equimolar of racemic CFTA chloride *rac*-**2b**, prepared from *rac*-CFTA ethyl ester **2c**, proceeded smoothly to give the diastereomeric esters in quantitative yield. However, contrary to our expectation, separation of the diastereomers was not observed by HPTLC using various solvent systems. The diastereomers were instead separated by fractional recrystallizations from hexane/$CHCl_3$; five repeated recrystallizations afforded the less-soluble isomer in a diastereomerically pure form.

Following similar methods as described above for the acetyl derivative, (−)-*N*-Cbz-(1*R*,2*S*)-*cis*-1-amino-2-indanol (−)-**B** was used to prepare the diastereomeric esters of CFTA in 83% yield. The separation of the resulting diastereomers was relatively simpler (Scheme 1); only two recrystallizations were required to afford less-soluble isomer $\mathbf{2d_L}$ as a diastereomerically pure form. The mother liquor was subsequently concentrated and subjected to repeated recrystallizations. The combined yield of diastereomerically pure $\mathbf{2d_L}$ was 36% (based on the starting ester **2c**). Attempted hydrolysis of the ester $\mathbf{2d_L}$ with LiOH successfully produced the acid (*S*)-**2a** in almost quantitative yield, accompanied by 80% recovery of the resolving agents, (−)-**B** and its deprotected compound (+)-(1*R*,2*S*)-*cis*-1-amino-2-indanol. The rather unstable acid (*S*)-**2a** thus obtained was converted to the acid chloride (*S*)-**2b** in a usual way to give in 83% yield after distillation.

The more-soluble ester $\mathbf{2d_M}$ was obtained from the combined filtrates in 46% yield with de of 80%. The ester $\mathbf{2d_M}$ was hydrolyzed and successively converted to the acid chloride, and then was transformed to the ester of (+)-**B**. Similarly to (*S*)-**2b**, diastereomerically pure (*R*)-CFTA ester of (+)-**B** was obtained by crystallization, followed by the conversion to enantiopure (*R*)-**2b**. The yields of enantiopure (*S*)- and (*R*)-**2b** were 30% and 17% (based on *rac*-**2c**), respectively. By this procedure several grams of optically active **2b** can be easily prepared.

2.2. Crystal structures of $\mathbf{2d_L}$ and $\mathbf{2d_M}$

To gain insight into the different crystallization behaviors of $\mathbf{2d_L}$ and $\mathbf{2d_M}$, X-ray single-crystal analyses were carried out on these diastereomers. Results showed that both compounds crystallize in an acentric space group, and that the solid-state structures of both compounds exhibit an infinite N–H···O hydrogen bonding between the Cbz groups along the shortest crystal axis, as shown in Figure 1. Comparatively, the shorter N···O distance of $\mathbf{2d_L}$ (2.793 Å) indicates stronger hydrogen bonding than that of $\mathbf{2d_M}$ (2.969 Å). The longer N···O distance of the latter is attributable to the steric repulsion between cyano and *p*-tolyl groups that prevents compact packing. Furthermore, weak π/π stacking between Ph/Ph in the Cbz groups (mean interplanar distance = 3.410 Å, the shortest C···C distance = 3.584 Å) was observed for $\mathbf{2d_L}$. However, such π/π stacking was



Scheme 1. Resolution of *rac*-CFTA **2a**.

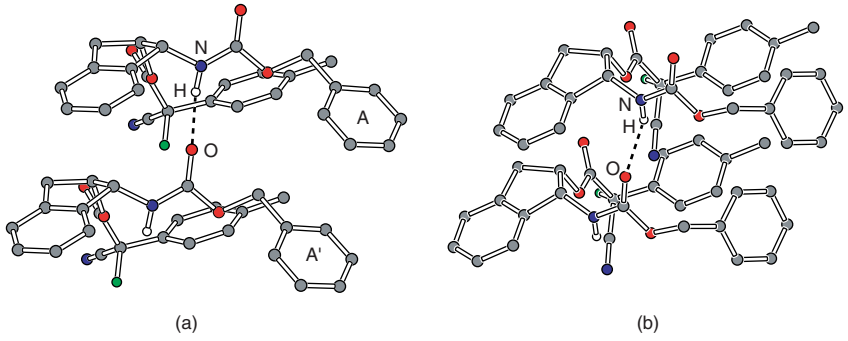
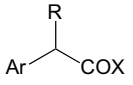


Figure 1. Parts of NH---O=C hydrogen bonding chains in the crystal. Hydrogen atoms, except for NH, are omitted for clarity. (a) Compound $\mathbf{2d_L}$, molecules are stacked along *b*-axis (4.904 Å), O---N: 2.793 Å, NH---O: 1.92 Å, N–H: 0.88 Å, N–H---O: 172.0°; (b) compound $\mathbf{2d_M}$, molecules are stacked along *a*-axis (5.100 Å), O---N: 2.969 Å, NH---O: 2.20 Å, N–H: 0.84 Å, N–H---O: 152.2°. Weak π/π stacking is observed between Ph/Ph (A---A′) of the Cbz groups for the compound $\mathbf{2d_L}$, centroid---centroid distance: 4.904 Å, mean interplanar distance: 3.410 Å.

not observed for $\mathbf{2d_M}$. These differences in the crystal structures explain the ease of crystallization for $\mathbf{2d_L}$ in comparison to $\mathbf{2d_M}$.



3-7

3: R = Me, Ar = Ph
4: R = Me, Ar = 4-^{t}BuC$_6$H$_4$
5: R = Me, Ar = 6-MeOC$_{10}$H$_6$
6: R = Et, Ar = Ph
7: R = OMe, Ar = Ph

a: X = OH
b: X = Cl
c: X = 2-(1-aminoindanyl)

2.3. Chromatographic resolution of α-arylacetic acids

N-Acyl-1-amino-2-indanols **A** and **B** have been shown to be effective for the separation of CFTA enantiomers. To investigate the range of applications, **A** and **B** were applied for the resolution of various α-arylacetic acids **3a**–**7a**, including well-known pharmaceutical compounds, ibuprofen **4a** and naproxen **5a**.[9]

Although **B** was more effective than **A** for the resolution of CFTA, it appeared that **B** was not sufficiently reactive toward α-arylacetyl chlorides and, therefore, was not suitable for the resolution of these acids. For example, attempted esterification of (−)-**B** with *rac*-2-phenylpropanoyl chloride **3b** in dichloromethane was sluggish

and afforded a mixture of diastereomeric esters **3c** in low yields. On the other hand, reaction between *N*-Ac derivative (−)-**A** and a small excess of acid chloride **3b** at room temperature for 24 h afforded the diastereomeric esters of **3c** in 81% yield (Scheme 2). Similarly, reactions of acid chlorides **4b**–**7b** with (−)-**A** gave the corresponding esters **4c**–**7c** in comparable yields (see Scheme 2).

In contrast to the diastereomeric CFTA esters of (−)-**B**, these diastereomers showed well-resolved chromatographic separation, as expected. The separation of diastereomers on a silica gel TLC plate is shown in Figure 2. Preparative separation of the diastereomers of **3c** was performed by silica gel flash column chromatography. The yields of the first-eluted $\mathbf{3c_{1st}}$ and the second-eluted $\mathbf{3c_{2nd}}$ in 43% and 35% yields (based on **A**), respectively. Separation of diastereomeric esters of **4c**–**7c** was carried out in a similar fashion.

In order to avoid possible racemization of the acid, which possesses an active hydrogen, hydrolysis of the purified ester was carried out under acidic conditions. For example, hydrolysis of ester $\mathbf{4c_{1st}}$ was complete within 1 h at 100 °C using 6 M HBr/AcOH to afford acid (*S*)-**4a** in 94% yield with 97% ee, as determined by HPLC. Similarly, the other esters were hydrolyzed to give the corresponding acids in good yields with slight racemization. Upon recrystallization, acids (*S*)-**4a**, (*R*)-**4a**, (*S*)-**5a**, (*R*)-**5a**, (*S*)-**7a**, and (*R*)-**7a** were obtained with over 99% ee. Acids (*S*)-**3a**, (*R*)-**3a**, (*S*)-**6a**, and (*R*)-**6a** were converted into their sodium salts, and then recrystallized to afford salts that were nearly enantiopure. Overall yields of the acids and salts (based on the acid chlorides) on 0.2 mmol-scale experiments are summarized in Table 1.

The same procedure was applied for the resolution of **4a** in gram scale. Using 1.54 g (6.84 mmol) of racemic **4b** and 1.0 g (5.26 mmol) of (−)-**A**, 350–370 mg of each enantiomer of **4a** was obtained in 32–34% yield. In this resolution, 76% of (−)-**A** was recovered.

In summary, a practical method for the resolution of α-cyano-α-fluoro-*p*-tolylacetic acid (CFTA) **2a** using *N*-Cbz-*cis*-1-amino-2-indanol **B** was developed. This method will allow wider usage of CFTA as a versatile CDA. It was also demonstrated that *N*-Ac-*cis*-1-amino-2-indanol **A** can be an effective agent for the chromatographic resolution of a series of α-arylacetic acids.

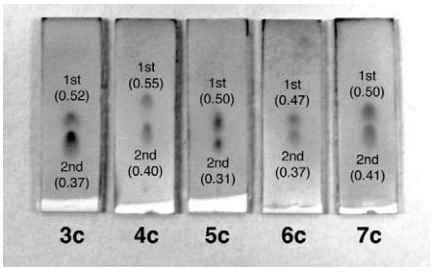


Figure 2. Diastereomer separation of **3c**–**7c** using silica gel TLC (hexane/$CHCl_3$/AcOEt = 3:3:1 for **3c**–**5c**, 2:2:1 for **6c**, **7c**). The values for R_f of the compounds are shown in parentheses.

Table 1. Yields of enantiomerically pure α-arylacetic acids[a]

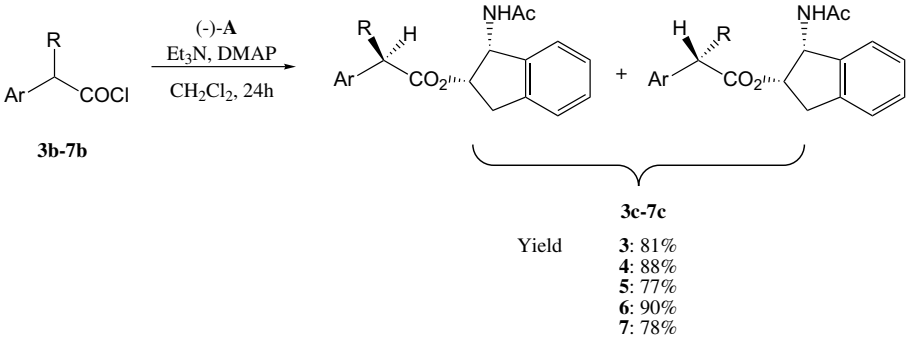
Acid	Yield (%)	Acid	Yield (%)
(*S*)-**3a**	30[b] (36[b])	(*R*)-**3a**	20[b] (24[b])
(*S*)-**4a**	35 (42)	(*R*)-**4a**	32 (38)
(*S*)-**5a**	29 (35)	(*R*)-**5a**	23 (27)
(*S*)-**6a**	29[b] (35[b])	(*R*)-**6a**	27[b] (32[b])
(*S*)-**7a**	31 (37)	(*R*)-**7a**	25 (30)

[a] Based on acid chloride; the values in parentheses: based on **A**.
[b] Yields of sodium salt.

3. Experimental

3.1. General

Optically active *cis*-1-amino-2-indanols were purchased from Aldrich. Dichloromethane was distilled from CaH_2 under argon atmosphere. Purification by flash chromatography was performed on Merck 9385 silica gel. Thin layer chromatography was performed on Merck 5715 glass plates. NMR spectra were recorded on a JEOL GSX-400 spectrometer (400 MHz for ^1H, 100 Hz for ^{13}C, and 376 MHz for ^{19}F) in $CDCl_3$ at room temperature. Chemical shifts are expressed in ppm values from TMS, $CDCl_3$, and $CFCl_3$ as internal standard for ^1H, ^{13}C, ^{19}F NMR, respectively. Optical rotations were determined on a Perkin–Elmer 241 polarimeter. IR



Scheme 2. Preparation of diastereomeric (−)-**A** esters of α-arylacetic acids.

spectra were recorded on a Shimadzu FTIR-8100M. MS was taken on a JEOL JMS-GCMATE. HRMS was determined on a JEOL JMS-AX505HAD. Melting points were determined on a Yanaco MP-S3. The enantiomeric purity of α-arylacetic acids was determined by HPLC using Daicel Chiralcel OD or AD-H column ($0.46^{\varnothing} \times 250^{l}$ mm); with hexane/2-propanol containing trifluoroacetic acid as an eluent.

3.2. Preparation of *N*-acyl-*cis*-1-amino-2-indanols

N-Acyl-*cis*-1-amino-2-indanols were prepared according to the method described in the literature.[10]

3.2.1. *N*-Acetyl-(1*R*,2*S*)-*cis*-1-amino-2-indanol (−)-A. Mp 182–183 °C (hexane/AcOEt); $[\alpha]_D^{22} = -39.0$ (*c* 1.0, EtOH) {lit.[11] $[\alpha]_D^{20} = +38.3$ (*c* 0.84, EtOH for the enantiomer)}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.11 (3H, s), 2.94 (1H, dd, $J = 16.4$, 2.4 Hz), 3.17 (1H, dd, $J = 16.4$, 5.2 Hz), 4.62 (1H, td, $J = 4.4$, 2.4 Hz), 5.37 (1H, dd, $J = 6.0$, 5.2 Hz), 6.22 (1H, br d, $J = 6.0$ Hz), 7.21–7.27 (4H, m). Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 68.83; H, 6.81; N, 7.16.

3.2.2. *N*-Carbobenzyloxy-(1*R*,2*S*)-*cis*-1-amino-2-indanol (−)-B. Mp 129–130 °C ; $[\alpha]_D^{24} = -11.2$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.89 (1H, dd, $J = 16.6$, 1.7 Hz), 3.09 (1H, dd, $J = 16.6$, 4.9 Hz), 4.55 (1H, br s), 5.10–5.19 (3H, m), 5.48 (1H, br s), 7.18–7.39 (9H, m).

3.2.3. *N*-Carbobenzyloxy-(1*S*,2*R*)-*cis*-1-amino-2-indanol (+)-B. Mp 129–130 °C (hexane/$CHCl_3$); $[\alpha]_D^{25} = +11.3$ (*c* 0.39, $CHCl_3$).

3.3. Resolution of *rac*-CFTA *rac*-2a via diastereomeric ester formation with enantiopure *N*-Cbz-*cis*-1-amino-2-indanol and preparation of enantiopure CFTA-Cl 2b

Racemic CFTA ethyl ester *rac*-**2c** (3.49 g, 15.8 mmol) was dissolved in 53 mL of THF/H_2O (1:1). To this solution was added 1 M lithium hydroxide aqueous solution (15.8 mL, 15.8 mmol) and the mixture was stirred at room temperature for 15 min. After evaporation of THF under reduced pressure, unreacted ester **2c** was removed by ether extraction. The aqueous layer was acidified (pH ~ 1) with 10% aqueous HCl at 0 °C. The solution was saturated with NaCl and extracted with AcOEt. The organic layer was washed with brine and dried over $MgSO_4$. After removal of the solvent, the residual water was removed as azeotrope with benzene to give crude racemic CFTA *rac*-**2a** as a colorless oil. It was subsequently dissolved in dried CH_2Cl_2 (132 mL) containing a catalytic amount of DMF (0.17 mL, 2.2 mmol) under an argon atmosphere. To the solution was added oxalyl chloride (2.8 mL, 31.6 mmol) at 0 °C and the mixture was stirred at room temperature for 3 h. After removal of the solvent, benzene was added to the residue and insoluble precipitate was filtered off. The filtrate was concentrated to give crude racemic CFTA-Cl *rac*-**2b** as yellow oil (3.12 g, 93%).

Crude *rac*-**2b** was dissolved in 60 mL of dried CH_2Cl_2 under an argon atmosphere. To the solution were added pyridine (2.39 mL, 29.5 mmol) and *N*-Cbz-(1*R*,2*S*)-1-amino-2-indanol (−)-**B** (4.18 g, 14.8 mmol) at 0 °C and the mixture was stirred at room temperature for 15 h. Solvent was evaporated and the residue was dissolved in AcOEt. The solution was washed with water and brine. The organic layer was dried over $MgSO_4$ and evaporated. Flash column chromatography (eluent: $CHCl_3$/AcOEt = 10:1) gave the mixture of $\mathbf{2d_L}$ and $\mathbf{2d_M}$ as a pale yellow solid. The solid was suspended in 250 mL of hexane and the mixture was heated (80 °C, bath temp). At the temperature, $CHCl_3$ was added until the solid disappeared. The solution was stood at room temperature overnight. Precipitate was filtered off and recrystallized again to give 1.42 g of less-soluble isomer $\mathbf{2d_L}$ as very thin fiber-like crystals in >99% de. The mother liquor was concentrated and recrystallization was repeated. The final yield of $\mathbf{2d_L}$ based on *rac*-**2c** was 36% (2.58 g, >99% de as checked by ^{19}F NMR).

$\mathbf{2d_L}$: Mp 149–150 °C (hexane/$CHCl_3$); $[\alpha]_D^{24} = +92.4$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32 (3H, s), 2.87 (1H, dd, $J =$ 17.4, 1.7 Hz), 3.18 (1H, dd, $J = 17.4$, 5.1 Hz), 5.05 (1H, br d, $J =$ 9.3 Hz), 5.16 (1H, d, $J = 18.6$ Hz), 5.49 (1H, dd, $J = 9.3$, 5.1 Hz), 5.73 (1H, m), 7.11–7.14 (3H, m), 7.26–7.28 (3H, m), 7.32–7.39 (7H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.22, 36.52, 57.80, 67.26, 79.34, 86.97 (d, $J = 198.4$ Hz), 114.02 (d, $J = 33.5$ Hz), 123.86, 124.97, 125.19 (d, $J = 6.1$ Hz), 127.67, 128.11, 128.15 (d, $J = 22.9$ Hz), 128.18, 128.53, 128.73, 129.87, 136.15, 138.25, 139.07, 141.60 (d, $J = 3.0$ Hz), 156.14, 162.35 (d, $J = 30.5$ Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −147.11; IR (KBr) 3600–3200 (br), 3308, 3050–2850, 2250 (vw), 1754, 1698, 1538, 1293, 1254, 1057 cm^{-1}; MS (EI, 70 eV) *m*/*z* 458 (M^+), 366, 341, 311, 302, 289, 265. Anal. Calcd for $C_{27}H_{23}FN_2O_4$: C, 70.73; H, 5.06; N, 6.11. Found: C, 70.81; H, 5.28; N, 6.24.

Diastereomerically pure $\mathbf{2d_L}$ (1.20 g, 2.62 mmol) was hydrolyzed with 5.2 mL of 1 M lithium hydroxide aqueous solution in 20 mL of THF/H_2O (1:1) at room temperature. After evaporation of THF under reduced pressure, the mixture was extracted with Et_2O. From the aqueous layer, (*S*)-**2a** was obtained and then converted to (*S*)-**2b** in the similar manner to the *rac*-**2b**. Distillation of the crude product gave 0.46 g of enantiopure (*S*)-**2b** (2.18 mmol, 83%). The Et_2O layer was evaporated and the residue was chromatographed (SiO_2 15 g, hexane/AcOEt = 1 to AcOEt). The resolving agent **B** was recovered in 65% yield (0.48 g, 1.70 mmol) accompanied by 59 mg of (1*R*,2*S*)-*cis*-1-amino-2-indanol (0.39 mmol, 15%).

(*S*)-**2b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.43 (3H, br s), 7.34 (2H, br d, $J = 7.8$ Hz), 7.54 (2H, br d, $J = 7.8$ Hz); IR (neat) 1794 cm^{-1}.

The combined mother liquor was concentrated and crystallized from hexane/$CHCl_3$ to give $\mathbf{2d_M}$ in 46% yield

(~80% de). In the same manner as described for **2d$_L$**, **2d$_M$** (~80% de) was converted to the acid chloride, which was allowed to react with *N*-Cbz-(1*S*,2*R*)-*cis*-1-amino-2-indanol (+)-**B**. The resulting (*R*)-CFTA ester of (+)-**B** was purified by recrystallization and was converted to the acid chloride (*R*)-**2b** (0.56 g, 2.65 mmol) in the same way described for (*S*)-**2b**.

(*S*)- and (*R*)-**2b** were identified as (*S*)-1-phenylethylamides prepared from (*S*)-1-phenylethylamine and (*S*)- and (*R*)-**2b**. Spectral data of the amides were identical to an authentic (*S*)-1-phenylethylamides prepared using (*S*)- and (*R*)-**2b** obtained by enzymatic resolution.[3a] Enantiomeric excesses (*S*)- and (*R*)-**2b** were determined to be more than 99% as checked by ^{19}F NMR spectra of the corresponding amides.

3.3.1. (*S*)-2-Cyano-2-fluoro-*N*-[(*S*)-1-phenylethyl]-2-*p*-tolylacetamide.[3a] (*S*)-**2b** (25 μL, 0.156 mmol) was reacted with (*S*)-1-phenylethylamine (21 μL, 0.156 mmol) in CH_2Cl_2 (1 mL) in the presence of pyridine (25 μL, 0.31 mmol) to give 41.8 mg (90%) of the amide. Mp 69–72 °C; $[\alpha]_D^{27} = -88.9$ (*c* 1.22, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.61 (3H, d, J = 7.1 Hz), 2.36 (3H, d, J = 1.9 Hz), 5.16 (1H, qd, J = 7.1, 6.9 Hz), 6.68 (1H, br s), 7.22 (2H, br d, J = 8.3 Hz), 7.26 (2H, m), 7.31 (1H, m), 7.33 (2H, m), 7.39 (2H, br d, J = 8.3 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −140.96; IR (KBr) 3330, 2252, 1680 cm^{-1}. MS (EI, 70 eV) 297 (M^++1), 296 (M^+). Anal. Calcd for $C_{18}H_{17}FN_2O$: C, 72.95; H, 5.78; N, 9.45. Found: C, 72.87; H, 5.52; N, 9.48.

3.3.2. (*R*)-2-Cyano-2-fluoro-*N*-[(*S*)-1-phenylethyl]-2-*p*-tolylacetamide. [3a] (*R*)-**2b** (25 μL, 0.156 mmol) were reacted with (*S*)-1-phenylethylamine (21 μL, 0.156 mmol) in the presence of pyridine (25 μL, 0.31 mmol) in CH_2Cl_2 (1 mL) to give 43.2 mg (93%) of the amide. Mp 125–131 °C; $[\alpha]_D^{26} = -89.6$ (*c* 1.64, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.53 (3H, d, J = 7.1 Hz), 2.40 (3H, d, J = 1.5 Hz), 5.14 (1H, qd, J = 7.1, 6.8 Hz), 6.68 (1H, br s), 7.28 (2H, br d, J = 7.6 Hz), 7.33 (1H, m), 7.35 (2H, m), 7.36 (2H, m), 7.50 (2H, br d, J = 7.5 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −142.25; IR (KBr) 3328, 2252, 1676 cm^{-1}; MS (EI, 70 eV) 297 (M^++1), 296 (M^+). Anal. Calcd for $C_{18}H_{17}FN_2O$: C, 72.95; H, 5.78; N, 9.45. Found: C, 72.97; H, 5.89; N, 9.31.

3.4. X-ray crystallography

Single crystals of **2d$_L$** were prepared by recrystallization of **2d$_L$** with >99% de from hexane/$CHCl_3$. Single crystals of **2d$_M$** formed together with crystals of **2d$_L$** in recrystallization of **2d$_L$** with ~90% de from the same solvent system.

Crystal data for **2d$_L$**: $[C_{27}H_{23}N_2O_4F]\cdot CHCl_3$, M = 577.87, monoclinic, $P2_1$ (no 4), a = 14.395(6), b = 4.904(2), c = 19.085(8) Å, β = 97.329(9)°, V = 1336.3 Å^3, Z = 2, Dc = 1.436 g/cm^{-3}, μ(MoKα) = 3.87 mm^{-1}, T = 173 K, colorless needles (0.35 × 0.08 × 0.05 mm), 18,479 measured, 5724 unique, R_1 = 0.068, wR_2 = 0.162 for all reflections (SHELX97 refinement), solvent $CHCl_3$ is located in disorder, and does not appear in clear shape, but molecular structure of **2d$_L$** was well refined.

Crystal data for **2d$_M$**: $C_{27}H_{23}N_2O_4F$, triclinic, P_1 (no 1), M = 458.79, a = 5.1000(5), b = 10.180(2), c = 11.760(3) Å, α = 73.29, β = 72.270(6), γ = 79.44(1)°, V = 551.5 Å^3, Z = 1, Dc = 1.380 g/cm^{-3}, μ(MoKα) = 0.99 mm^{-1}, T = 150 K, colorless prism (0.20 × 0.15 × 0.10 mm), 5740 measured, 2403 unique, R_1 = 0.034, wR_2 = 0.093 for all reflections (SHELX97 refinement).

Crystallographic data (excluding structure factors) for the structures of **2d$_L$** and **2d$_M$** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 223739 for **2d$_L$** and CCDC 223740 for **2d$_M$**. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44-(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

3.5. Resolution of racemic 2-arylacetic acids 3a–7a through chromatographic separation of their diastereomeric esters of (−)-A 3c–7c

Typical example: Separation of the diastereomers of **3c**: To the suspension of (−)-**A** (38.0 mg, 0.20 mmol) in 5 mL of CH_2Cl_2 were added triethylamine (56 μL, 0.24 mmol), racemic 2-phenylpropionyl chloride **3b** (36 μL, 0.24 mmol), and catalytic amount of 4-(*N*,*N*-dimethylamino)pyridine (3.0 mg, 0.024 mmol). After stirring at room temperature for 24 h, the solvent was removed under reduced pressure. Column chromatography of the residue (SiO_2 5 g, hexane/$CHCl_3$/AcOEt = 4:4:1) gave 28.9 mg (0.086 mmol, 43%) of **3c$_{1st}$** and 23.9 mg (0.070 mmol, 35%) of **3c$_{2nd}$**. Other diastereomeric esters of **4c**–**7c** were obtained in the similar way.

3c$_{1st}$: Mp 194 °C (hexane/$CHCl_3$); $[\alpha]_D^{24} = +40.4$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46 (3H, d, J = 6.8 Hz), 1.56 (3H, s), 3.01 (1H, d, J = 17.6 Hz), 3.21 (1H, J = 17.6, 4.8 Hz), 3.63 (1H, q, J = 6.8 Hz), 5.16 (1H, br d, J = 8.0 Hz), 5.54 (1H, td, J = 4.8, 0.8 Hz), 5.58 (1H, dd, J = 8.0, 4.8 Hz), 7.21–7.34 (9H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.70, 22.77, 37.61, 45.29, 55.52, 75.94, 123.60, 124.92, 127.14, 127.35 (br), 128.09, 128.94, 139.14, 140.78, 140.92, 169.96, 173.27; IR (KBr) 3600–3300 (br), 3291, 3200–2800, 1722, 1653, 1549, 1202, 1174, 752, 727, 696 cm^{-1}; MS (EI, 70 eV) m/z 323 (M^+), 263, 190, 173. Anal. Calcd for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33. Found: C, 74.02; H, 6.66; N, 4.29.

3c$_{2nd}$: Mp 171 °C (hexane/$CHCl_3$); $[\alpha]_D^{25} = +68.6$ (*c* 0.33, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.48 (3H, d, J = 7.2 Hz), 1.82 (3H, s), 2.86 (1H, dd, J = 16.4, 1.2 Hz), 3.18 (1H, dd, J = 16.4, 5.2 Hz), 3.70 (1H, q, J = 7.2 Hz),

5.41 (1H, br d, $J = 9.2$ Hz), 5.57 (1H, td, $J = 5.2$, 2.0 Hz), 5.63 (1H, dd, $J = 9.2$, 5.2 Hz), 7.16–7.30 (9H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.83, 22.83, 37.14, 45.73, 75.56, 123.58, 124.78, 127.05, 127.20, 127.24, 127.33, 128.11, 128.53, 139.19, 139.78, 140.31, 169.93, 173.27; IR (KBr) 3700–3200 (br), 3299, 3200–2800, 1716, 1653, 1553, 1219, 1207, 1192, 754, 733, 700 cm^{-1}; MS (EI, 70 eV) m/z 323 (M^+), 321, 274, 241, 206. Anal. Calcd for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33. Found: C, 74.52; H, 6.73; N, 4.26.

4c$_{1st}$: Mp 207 °C (hexane/$CHCl_3$); $[\alpha]_D^{25} = +17.2$ (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (6H, d, $J = 4.0$ Hz), 1.46 (3H, d, $J = 6.8$ Hz), 1.58 (3H, s), 1.78–1.86 (1H, m), 2.43 (2H, d, $J =$ 7.2 Hz), 2.85 (1H, d, $J = 17.2$ Hz), 3.16 (1H, dd, $J = 17.2$, 4.8 Hz), 3.66 (1H, q, $J = 7.2$ Hz), 5.50–5.65 (3H, m), 7.02–7.27 (8H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.68, 22.31, 22.36, 22.72, 30.10, 37.67, 44.87, 44.91, 55.61, 75.88, 123.58, 124.92, 127.05, 127.14, 128.08, 129.63, 138.05, 139.20, 140.81, 140.86, 169.94, 173.49; IR (KBr) 3600–3200 (br), 3318, 3200–2800, 1728, 1651, 1541, 1200, 1175, 779, 762, 764 cm^{-1}; MS (EI, 70 eV) m/z 379 (M^+), 318, 205, 187, 173. Anal. Calcd for $C_{24}H_{29}NO_3$: C, 75.96; H, 7.70; N, 3.69. Found: C, 75.82; H, 7.89; N, 3.63.

4c$_{2nd}$: Mp 127 °C (hexane/$CHCl_3$); $[\alpha]_D^{25} = +52.6$ (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (6H, d, $J = 4.0$ Hz), 1.44 (3H, d, $J = 7.2$ Hz), 1.58 (3H, s), 1.78–1.86 (1H, m), 2.43 (2H, d, $J =$ 7.2 Hz), 3.00 (1H, d, $J = 17.6$ Hz), 3.20 (1H, dd, $J = 17.6$, 4.8 Hz), 3.60 (1H, q, $J = 7.2$ Hz), 5.25 (1H, br d, $J = 8.4$ Hz), 5.50–5.63 (2H, m), 7.02–7.27 (8H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.64, 21.89, 22.16, 29.63, 36.67, 44.41, 44.68, 55.08, 74.98, 123.22, 124.25, 126.50, 126.64, 127.52, 128.78, 136.82, 138.90, 139.98, 140.04, 169.94, 173.27; IR (KBr) 3600–3200 (br), 3314, 3200–2800, 1734, 1655, 1541, 1198, 1159, 750, 741, 729 cm^{-1}. Anal. Calcd for $C_{24}H_{29}NO_3$: C, 75.96; H, 7.70; N, 3.69. Found: C, 75.92; H, 7.85; N, 3.72.

5c$_{1st}$: Mp 230 °C (hexane/$CHCl_3$); $[\alpha]_D^{24} = -14.2$ (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11 (3H, s), 1.54 (3H, d, $J = 7.1$ Hz), 3.03 (1H, d, $J = 17.2$ Hz), 3.21 (1H, dd, $J = 16.9$, 4.2 Hz), 3.76 (1H, q, $J = 7.1$ Hz), 3.92 (3H, s), 5.05 (1H, br d, $J = 8.8$ Hz), 5.52–5.58 (2H, m), 7.09 (2H, m), 7.15 (1H, dd, $J = 9.1$, 2.7 Hz), 7.15–7.28 (3H, m), 7.29 (1H, dd, $J = 8.3$, 1.7 Hz), 7.59 (1H, d, $J =$ 1.8 Hz), 7.64 (1H, d, $J = 9.0$ Hz), 7.68 (1H, d, $J = 8.8$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.64, 22.11, 37.69, 45.20, 55.29, 55.55, 75.94, 105.48, 119.40, 123.60, 124.92, 125.76, 125.89, 127.12, 127.44, 128.08, 128.88, 129.13, 133.72, 135.88, 139.16, 140.83, 157.89, 169.91, 173.42; IR (KBr) 3700–3200 (br), 3319, 3100–2900, 1724, 1651, 1545, 1192, 1032, 855, 735 cm^{-1}; MS (EI, 70 eV) m/z 403 (M^+), 229, 211, 184, 172; HRMS calcd for $C_{25}H_{25}NO_4$: 403.1784; found: 403.1762. Anal. Calcd for $C_{25}H_{25}NO_4$: C, 74.42; H, 6.25; N, 3.47. Found: C, 74.42; H, 6.25; N, 3.51.

5c$_{2nd}$: Mp 203 °C (hexane/$CHCl_3$); $[\alpha]_D^{24} = +65.6$ (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.56 (3H, d, $J = 6.8$ Hz), 1.56 (1H, d, $J = 7.1$ Hz), 2.84 (1H, dd, $J = 17.1$, 1.6 Hz), 3.17 (1H, dd, $J =$ 16.9, 4.8 Hz), 3.83 (1H, q, $J = 7.1$ Hz), 5.33 (1H, br d, $J = 9.6$ Hz), 5.57 (1H, dd, $J = 5.1$, 1.5 Hz), 5.61 (1H, dd, $J = 9.1$, 5.1 Hz), 7.09 (1H, d, $J = 2.5$ Hz), 7.12–7.19 (3H, m), 7.21–7.27 (2H, m), 7.29 (1H, dd, $J = 8.6$, 1.9 Hz), 7.57 (1H, d, $J = 1.5$ Hz), 7.61 (1H, d, $J = 9.1$ Hz), 7.64 (1H, d, $J = 8.6$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.85, 22.61, 37.20, 45.78, 55.23, 55.49, 75.68, 105.43, 119.14, 123.62, 124.86, 125.89, 125.97, 127.06, 127.11, 128.14, 128.72, 129.14, 133.66, 134.82, 139.23, 140.40, 157.74, 169.90, 173.42; IR (KBr) 3700–3200 (br), 3302, 1717, 1653, 1549, 1196, 1181, 1030, 812, 758, 731 cm^{-1}; MS (EI, 70 eV) m/z 403 (M^+), 342, 229, 211; HRMS calcd for $C_{25}H_{25}NO_4$: 403.1784; found: 403.1766.

6c$_{1st}$: Mp 81–82 °C (hexane/$CHCl_3$); $[\alpha]_D^{20} = +48.7$ (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85 (3H, t, $J = 7.3$ Hz), 1.55 (3H, s), 1.77 (1H, ddq, $J = 13.7$, 7.6, 7.3 Hz), 2.08 (1H, ddq, $J = 13.7$, 7.6, 7.3 Hz), 2.98 (1H, br d, $J = 17.1$ Hz), 3.22 (1H, br dd, $J =$ 17.1, 4.9 Hz) 3.36 (1H, t, $J = 7.6$ Hz), 5.20 (1H, br d, $J = 7.4$ Hz), 7.16 (1H, br d, $J = 7.6$ Hz), 7.18–7.34 (9H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.82, 22.68, 37.69, 55.05, 55.49, 75.65, 123.58, 124.88, 127.11, 127.36, 127.72, 128.06, 128.86, 139.17, 139.39, 140.75, 169.90, 172.79; IR (KBr) 3600–3200 (br), 3332, 3200–2800, 1725, 1655, 1534, 1199, 1173, 750, 727, 694 cm^{-1}; MS (EI, 70 eV) m/z 337 (M^+), 294, 277, 249, 190, 173. Anal. Calcd for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15. Found: C, 74.66; H, 7.12; N, 4.05.

6c$_{2nd}$: Mp 124–126 °C (hexane/AcOEt); $[\alpha]_D^{20} = +51.3$ (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (3H, t, $J = 7.3$ Hz), 1.78 (3H, s), 1.79 (1H, m), 2.02 (1H, ddq, $J = 13.9$, 7.6, 7.3 Hz), 2.86 (1H, br d, $J = 16.6$ Hz), 3.17 (1H, dd, $J = 17.1$, 4.9 Hz), 3.44 (1H, t, $J =$ 7.9 Hz), 5.46 (1H, br d, $J = 8.3$ Hz), 5.60 (1H, dt, $J = 5.1$, 1.2 Hz), 5.62 (1H, m), 7.16–7.30 (10H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.05, 22.94, 37.34, 53.94, 55.55, 75.64, 123.58, 124.90, 127.14, 127.37, 127.92, 128.17, 128.64, 138.60, 139.28, 140.49, 169.89, 172.67; IR (KBr) 3600–3100 (br), 3312, 3100–2800, 1732, 1655, 1541, 1196, 1163, 738, 694 cm^{-1}; MS (EI, 70 eV) m/z 337 (M^+), 294, 277, 249, 190, 173. Anal. Calcd for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15. Found: C, 74.83; H, 6.87; N, 4.19.

7c$_{1st}$: Mp 192–194 °C (hexane/AcOEt); $[\alpha]_D^{20} = +77.0$ (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.58 (3H, s), 3.03 (1H, br d, $J =$ 17.5 Hz), 3.22 (1H, dd, $J = 17.5$, 4.9 Hz), 3.38 (3H, s), 4.69 (1H, s), 5.10 (1H, br d, $J = 8.5$ Hz), 5.61 (1H, m), 5.64 (1H, m), 7.14 (1H, br d, $J = 7.4$ Hz), 7.26 (4H, m), 7.35 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.72, 37.53, 55.61, 57.21, 76.68, 81.95, 123.44, 124.94, 127.14, 127.21, 128.15, 128.96, 128.98, 136.62, 138.98, 140.45, 169.40, 169.91; IR (KBr) 3600–3200 (br), 3318, 3200–2800, 1740, 1651, 1549, 1194, 1117, 997, 988, 750, 725, 698 cm^{-1}; MS (EI, 70 eV) m/z 339 (M^+), 279, 236, 204, 173. Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.62; H, 6.31; N, 4.11.

7c$_{2nd}$: Mp 167 °C (hexane/$CHCl_3$); $[\alpha]_D^{21} = +21.2$ (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.84 (3H, s),

2.85 (1H, br d, $J = 17.4$ Hz), 3.19 (1H, br dd, $J = 17.4$, 5.1 Hz), 3.36 (3H, s), 5.58–5.69 (3H, m), 7.17 (1H, ddd, $J = 5.1$, 3.9, 0.9 Hz), 7.20–7.28 (4H, m), 7.30–7.37 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.76, 37.06, 55.48, 57.25, 76.30, 82.69, 123.55, 124.84, 126.69, 127.14, 128.18, 128.59, 128.71, 135.95, 139.04, 140.12, 169.81, 170.09; IR (KBr) 3700–3100 (br), 3285, 3200–2800, 1748, 1651, 1541, 1204, 1172 1107, 1040, 1020, 752, 735, 696 cm^{-1}; MS (EI, 70 eV) m/z 239 (M^+), 279, 236, 204, 173. Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.65; H, 6.34; N, 4.09.

3.6. Hydrolysis of the esters of *N*-Ac-*cis*-1-amino-2-indanol 3c–7c

Typical example: Ester of ibuprofen **4c$_{1st}$** (35.3 mg, 0.090 mmol) was dissolved in 1.9 mL of acetic acid. To this solution, 0.95 mL of hydrobromic acid (47% aqueous solution) was added and the mixture was heated at 100 °C for an hour. After cooling with an ice bath, brine was added and the mixture was extracted with $CHCl_3$. The organic layer was washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure to give a pale yellow oil, which was purified by silica gel column chromatography to give (*S*)-**4a** in 94% yield (18.1 mg, 0.88 mmol) with 97% ee. Repeated recrystallization from MeOH/H_2O furnished 16.8 mg of enantiopure (*S*)-**4a** (0.081 mmol, 90%).

3.6.1. (*S*)-(+)-Ibuprofen (*S*)-4a (hydrolysis product of 4c$_{1st}$) . Mp 49–50 °C (lit.[12] 50–52 °C); $[\alpha]_D^{23} = +55.0$ (c 2.0, EtOH) {lit.[12] $[\alpha]_D^{20} = +59$ (c 2.0, EtOH)}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (6H, d, $J = 6.6$ Hz), 1.50 (3H, d, $J = 7.1$ Hz), 1.84 (1H, sept, $J = 6.7$ Hz), 2.44 (2H, d, $J = 7.1$ Hz), 3.71 (1H, q, $J =$ 7.1 Hz), 7.10 (2H, dt, $J = 8.1$, 1.9 Hz), 7.21 (dt, $J = 8.1$, 2.0 Hz). Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.61; H, 8.79.

Hydrolyses of other esters were conducted in the same manner.

3.6.2. (*R*)-(−)-Ibuprofen (*R*)-4a (hydrolysis product of 4c$_{2nd}$). Mp 50.0–50.8 °C; $[\alpha]_D^{23} = -55.0$ (c 2.0, EtOH). Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.43; H, 8.76.

3.6.3. (*S*)-α-Phenylpropionic acid (*S*)-3a (hydrolysis product of 3c$_{1st}$). ^{1}H NMR (400 MHz, D_2O) δ 1.52 (3H, d, $J = 6.8$ Hz), 3.74 (1H, q, $J = 6.8$ Hz), 7.27 (1H, m), 7.30–7.36 (4H, m); sodium salt: gradually decomposed over 250 °C; $[\alpha]_D^{24} = +0.3$ (c 1.0, H_2O); ^{1}H NMR (400 MHz, D_2O) δ 1.41 (3H, d, $J = 7.1$ Hz), 3.65 (1H, q, $J = 7.1$ Hz), 7.30 (1H, tt, $J = 6.9$, 1.8 Hz), 7.34–7.42 (4H, m). Anal. Calcd for $C_9H_9O_2Na{\cdot}0.2H_2O$: C, 61.50; H, 5.39. Found: C, 61.59; H, 5.32. Anal. Calcd for benzylthiouronium salt of (*S*)-**3a** ($C_{17}H_{20}N_2O_2S$): C, 64.53; H, 6.37; N, 8.85; S, 10.11. Found: C, 64.23; H, 6.55; N, 8.80; S, 10.19.

3.6.4. (*R*)-α-Phenylpropionic acid (*R*)-3a (hydrolysis product of 3d$_{2nd}$). Sodium salt: gradually decomposed at 250 °C; $[\alpha]_D^{24} = -0.3$ (c 1.0, H_2O). Anal. Calcd for $C_9H_9O_2Na{\cdot}0.2H_2O$: C, 61.50; H, 5.39. Found: C, 61.64; H, 5.31. Anal. Calcd for benzylthiouronium salt of (*R*)-**3a** ($C_{17}H_{20}N_2O_2S$): C, 64.53; H, 6.37; N, 8.85; S, 10.11. Found: C, 64.27; H, 6.57; N, 8.85; S, 10.13.

3.6.5. (*S*)-(+)-Naproxen (*S*)-5a (hydrolysis product of 5c$_{1st}$). Mp 151–152 °C ($CHCl_3$/hexane) (lit.[13] 152–154); $[\alpha]_D^{21} = +65.3$ (c 1.0, $CHCl_3$) [lit.[13] +66 (c 1.0, $CHCl_3$)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.59 (3H, d, $J = 7.1$ Hz), 3.88 (1H, q, $J = 7.1$ Hz), 3.91 (3H, s), 7.11 (1H, br d, $J = 2.5$ Hz), 7.13 (1H, dd, $J = 8.8$, 2.5 Hz), 7.41 (1H, dd, $J = 8.6$, 1.7 Hz), 7.68 (1H, br s), 7.70 (1H, br dd, $J = 8.8$, 2.2 Hz). Anal. Calcd for $C_{14}H_{14}O_3$: C, 73.03; H, 6.13. Found: C, 72.76; H, 6.24.

3.6.6. (*R*)-(+)-Naproxen (*R*)-5a (hydrolysis product of 5c$_{2nd}$). Mp 150–151 °C ($CHCl_3$/hexane); $[\alpha]_D^{21} = -65.4$ (c 1.0, $CHCl_3$). Anal. Calcd for $C_{14}H_{14}O_3$: C, 73.03; H, 6.13. Found: C, 72.76; H, 6.24.

3.6.7. (*S*)-α-Phenylbutyric acid (*S*)-6a (hydrolysis product of 6c$_{1st}$). ^{1}H NMR (400 MHz, D_2O) δ 0.90 (3H, t, $J = 7.4$ Hz), 1.82 (1H, dqd, $J = 15.0$, 7.4, 7.0 Hz), 2.09 (1H, ddq, $J = 15.0$, 8.6, 7.4 Hz), 3.45 (1H, t, $J = 7.0$ Hz), 7.28 (1H, m), 7.30–7.36 (4H, m); sodium salt: gradually decomposed at 240 °C; $[\alpha]_D^{24} = +0.5$ (c 1.0, H_2O); ^{1}H NMR (400 MHz, D_2O) δ 0.90 (3H, t, $J = 7.4$ Hz), 1.74 (1H, dqd, $J = 15.0$, 7.4, 7.0 Hz), 1.97 (1H, ddq, $J = 15.0$, 8.6, 7.4 Hz), 3.40 (1H, dd, $J = 8.6$, 7.0 Hz), 7.31 (1H, m), 7.36–7.42 (4H, m). Anal. Calcd for $C_{10}H_{11}O_2Na{\cdot}0.3H_2O$: C, 62.69; H, 6.10. Found: C, 62.51; H, 6.22. Anal. Calcd for benzylthiouronium salt of (*S*)-**6a** ($C_{18}H_{22}N_2O_2S$): C, 65.42; H, 6.71; N, 8.48; S, 9.70. Found: C, 65.12; H, 6.77; N, 8.48; S, 9.88.

3.6.8. (*R*)-α-Phenylbutyric acid (*R*)-6a (hydrolysis product of 6c$_{2nd}$). Sodium salt: gradually decomposed at 230 °C; $[\alpha]_D^{24} = -0.4$ (c 1.0, H_2O). Anal. Calcd for $C_9H_9O_2Na{\cdot}0.3H_2O$: C, 62.69; H, 6.10. Found: C, 62.67; H, 6.23. Anal. Calcd for benzylthiouronium salt of (*R*)-**6a** ($C_{18}H_{22}N_2O_2S$): C, 65.42; H, 6.71; N, 8.48; S, 9.70. Found: C, 65.12; H, 6.71; N, 8.48; S, 9.82.

3.6.9. (*S*)-α-Methoxyphenylacetic acid (*S*)-7a (hydrolysis product of 7c$_{1st}$). Mp 64–66 °C (H_2O/MeOH) (lit.[14] 65–67 °C); $[\alpha]_D^{23} = +143.8$ (c 1.0, EtOH) [lit.[14] +143.4 (c 1, EtOH)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.44 (3H, s), 4.79 (1H, s), 7.35–7.45 (5H, m). Anal. Calcd for $C_9H_9O_3$: C, 65.05; H, 6.07. Found: C, 65.04; H, 6.16.

3.6.10. (*R*)-α-Methoxyphenylacetic acid (*R*)-7a (hydrolysis product of 7c$_{2nd}$). Mp 64–65 °C (H_2O/MeOH); $[\alpha]_D^{23} = -144.2$ (c 1.0, EtOH). Anal. Calcd for $C_9H_9O_3$: C, 65.05; H, 6.07. Found: C, 65.08; H, 6.06.

3.6.11. Enantiomer separation of 4a in preparative scale. A mixture of 1.00 g (5.26 mmol) of (−)-**A** and 1.45 mL (6.84 mmol) of triethylamine in CH_2Cl_2 (100 mL) was cooled to 0 °C. Then racemic 2-(4-isobutylphenyl)propanoyl chloride (1.54 g, 6.84 mmol) and 64 mg (0.52 mmol) of 4-(*N*,*N*-dimethylamino)pyridine were added. After stirring at room temperature for 24 h, brine was added and the mixture was extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$ and the solvent was evaporated. Crude material was subjected to flash column chromatography (SiO_2 70 g, i.d. of column: 30 mm, eluent: hexane/$CHCl_3$/AcOEt = 5:5:1) to give **4c$_{1st}$** (0.88 g, 2.31 mmol) and **4c$_{2nd}$** (1.04 g, 2.51 mmol) in 44% and 48% yield, respectively. The aqueous layer was acidified with 2 M HCl and then saturated with NaCl. The solution was extracted with $CHCl_3$ and the organic layer was washed with brine and dried over $MgSO_4$. The solvent was removed and the residue was purified by silica gel short column to recover **4a** (ibuprofen) in 64 mg (0.31 mmol).

A mixture of the ester **3c$_{1st}$**, 20 mL of aqueous 47% HBr and 40 mL of AcOH was heated at 100 °C for 1 h. After cooling to room temperature, 30 mL of brine was added and the mixture was extracted with $CHCl_3$. The organic layer was washed with brine then dried over $MgSO_4$. After removal of the solvent, hexane was added to the residue and insoluble precipitate of **A** was filtered off. The filtrate was concentrated and chromatographed (eluent: hexane/CH_2Cl_2/AcOEt = 5:5:1). Removal of the solvent afforded crude ibuprofen as crystals, which was recrystallized from H_2O/MeOH. To the aqueous layer, 2 M NaOH was added until pH of the layer slightly exceeded 11. The solution was repeatedly extracted with $CHCl_3$ until the spot of **A** was disappeared on TLC. The combined organic layer was dried over $MgSO_4$ and the solvent was removed to give crude **A**. Hydrolysis of the ester **4c$_{2nd}$** was conducted in the same way as described above to give (*R*)-**4a** and **A**. The yields of (*S*)- and (*R*)-**4a** based on **A** were 32% (350 mg, 2.18 mmol) and 34% (372 mg, 2.32 mmol), respectively. All **A** recovered from hydrolysis of **4c$_{1st}$** and **4c$_{2nd}$** was combined and recrystallized from hexane/$CHCl_3$. The recovery of (−)-**A** was 76% (758 mg, 3.99 mmol).

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