Angewandte Chemie
Eine Zeitschrift der Gesellschaft Deutscher Chemiker

Supporting Information

for

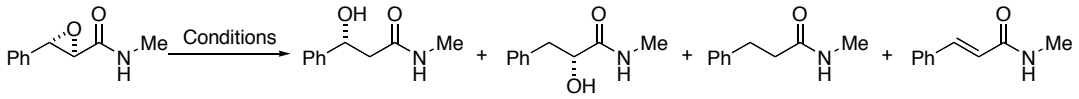
Angew. Chem. Int. Ed. Z52431

69451 Weinheim, Germany

Efficient Synthesis of Chiral α- and β-Hydroxy Amides: Application to Catalytic Asymmetric Synthesis of (*R*)-Fluoxetine

Hiroyuki Kakei, Tetsuhiro Nemoto, Takashi Ohshima, Masakatsu Shibasaki*

SI-1. Preliminary studies on the epoxide opening reaction of 2a (path B).

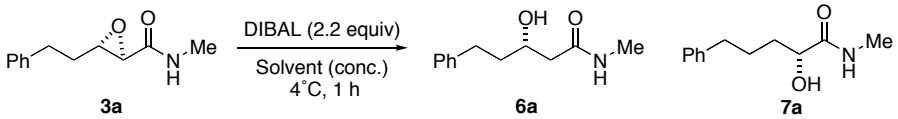


2a **5a** **4a** **18** **19**

Entry	Conditions	*T* [°C]	*t* [h]	Yield [%][a]	Ratio (**5a**:**4a**)[b]	Comments
1	$LiAlH_4$ (1.1 equiv) DME (0.2 M)	4	2.5	90	1:3	
2	DIBAL (2.2 equiv) DME (0.2 M)	4	2.5	72	1:3	
3	Red-Al (1.2 equiv) DME (0.2 M)	4 to RT	2.5	72	2:1	
4	Zn (12 equiv), NH_4Cl EtOH-Et_2O-H_2O	40	8.0	< 5		**19** was major byproduct
5	SmI_2 (3 equiv) MeOH	–78	1.0	< 5		**18** was major byproduct
6	Cp_2TiCl_2 (2 equiv) Zn (5 equiv), THF/MeOH	–78 to RT	3.0	< 5		**19** was major byproduct

[a] Yield of **4a** and **5a**. [b] The ratio was determined by ^{1}H NMR analysis of the crude sample.

SI-2. Concentration effects on epoxide opening reaction of 3a with DIBAL (path C).

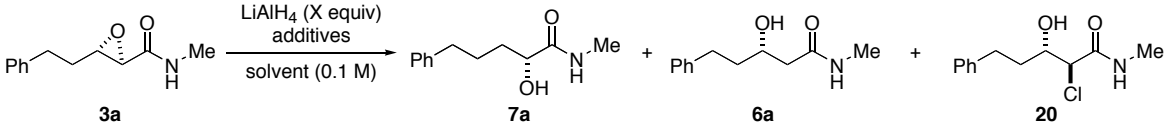


3a **6a** **7a**

Entry	Conc. (M)	Yield [%][a]	Ratio (**6a**:**7a**)[b]
1	0.1	94	22:1
2	0.2	93	11:1
3	0.3	72	9:1

[a] Yield of **6a** and **7a**. [b] The ratio was determined by ^{1}H NMR analysis of the crude sample.

SI-3. Attempts to obtain β-alkyl α-hydroxy amide 7a by reduction of 3a (*path D*).

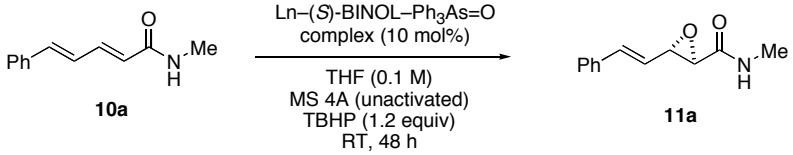


3a **7a** **6a** **20**

Entry	Amount of $LiAlH_4$ (equiv)	*T* [°C]	Additives (1 equiv)	Solvent	*t* [h]	Ratio (**7a**:**6a**)[a]	Comment
1	1.0	–78 to RT		THF	3	1.25:1	
2	1.0	–78 to RT		THF/Toluene (1/7)	5	1:1	
3	2.0	–78 to RT		THF	5	2:1	
4	3.0	–78 to RT		THF	5	2.4:1	
5	5.0	–78 to RT		THF	9	2.7:1	Yield of **7a** and **6a** was 98%.
6	5.0	–78 to 40		THF	12	1.9:1	20% of **3a** was recovered.
7	1.0	–78 to RT	BF_3	THF	4.5	1.6:1	
8	1.0	–78 to RT	$TiCl_4$	THF	6	1:>10	**20** was obtained ca. 50% yield.
9	1.0	–78 to RT	$AlCl_3$	THF	6	1:4.3	**20** was obtained ca. 10% yield.
10	5.0	–78 to RT	BF_3	THF	4.5	1:>10	

[a] The ratio was determined by ^1H NMR analysis of the crude sample.

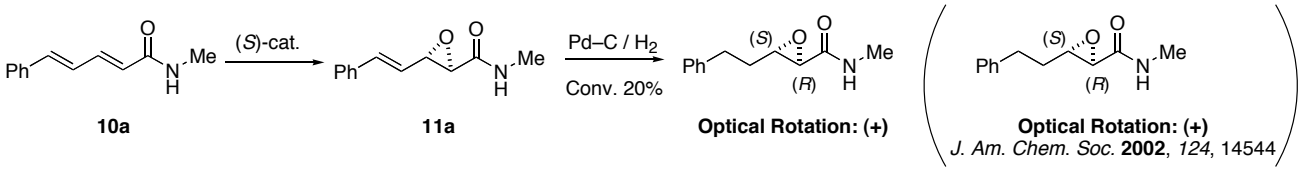
SI-4. Central metal effects on catalytic asymmetric epoxidation of α,β,γ,δ-unsaturated amides.



10a **11a**

Entry	Ln	Yield [%]	Ee [%]
1	Sm	48	97
2	Dy	53	99
3	Gd	61	>99
4	Pr	24	N.D.
5	La	12	N.D.

SI-5. Determination of the absolute configuration of 11a.



10a **11a** **Optical Rotation: (+)**

Optical Rotation: (+)
J. Am. Chem. Soc. **2002**, *124*, 14544

Experimental

General: Infrared (IR) spectra were recorded on a JASCO FT/IR 410 Fourier transform infrared spectrophotometer. NMR spectra were recorded on a JEOL JNM-LA500 spectrometer, operating at 500 MHz for ^{1}H NMR and 125.65 MHz for ^{13}C NMR. Chemical shifts in $CDCl_3$ were reported downfield from TMS (= 0 ppm) for ^{1}H NMR. For ^{13}C NMR, chemical shifts were reported downfield from TMS (= 0 ppm) or in the scale relative to $CHCl_3$ (77.00 ppm for ^{13}C NMR) as an internal reference. Optical rotations were measured on a JASCO P-1010 polarimeter. ESI mass spectra were measured on Waters micromass ZQ. The enantiomeric excess (ee) was determined by HPLC analysis. HPLC was performed on JASCO HPLC systems consisting of the following: pump, 880-PU or PU-980; detector, 875-UV or UV-970, measured at 254 nm; column, CHIRALPAK AS–H, DAICEL CHIRALPAK AD–H, DAICEL CHIRALSEL OD-H; mobile phase, hexane–2-propanol; flow rate, 0.3-1 mL/min. Reactions were carried out in dry solvents under an argon atmosphere, unless otherwise stated. $Ln(O\text{-}i\text{-}Pr)_3$ was purchased from Kojundo Chemical Laboratory Co., LTD., 5-1-28, Chiyoda, Sakado-shi, Saitama 350-0214, Japan (fax: +(81)-492-84-1351). MS 4A (Molecular Sieve UOP 4A, powder) was purchased from Fluka. Other reagents were purified by the usual methods.

Synthesis of the α, β–Epoxy Amides 2a-d, 3a-g.

α, β-Epoxy amides **2a-d and 3a-g** were prepared by catalytic asymmetric epoxidation of the corresponding α,β-unsaturated amides. For details, see: *J. Am. Chem. Soc.* **2002**, *124*, 14544.

Synthesis of the β-aryl β-hydroxy amides 5a-d. General Procedure for the β-selective epoxide opening of β-aryl substituted α,β-epoxy amides using Red-Al and crown ether (path B). To a solution of amide **2a** (53.1 mg, 0.3 mmol) and 15-crown-5 (72 μL, 1.2 equiv) in dry DME (1.5 mL) was added a solution of Red-Al (105 μL, 1.2 equiv, 65% solution in toluene) at –40°C. After stirring for 1 h at the same temperature, the mixture was warmed to room temperature and stirred for 1.5 h. After complete consumption of the starting material, the solution was quenched by the addition of

MeOH (0.5 mL) and diluted with ethyl acetate (10 mL). The organic layer was washed with saturated aqueous NH_4Cl, brine and then dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified by flush column chromatography (SiO_2, hexane/ethyl acetate = 4:1 to hexane/ethyl acetate 4:1 + 5% MeOH) to give the corresponsing β-hydroxy amides **5a** (46.9 mg, 87%, β-OH:α-OH = 18:1) as a white solid. The desired isomer was isolated by preparative thin-layer chromatography. **(3*R*)-3-Phenyl-3-hydroxypropionoic acid methyl amide (5a)**. The enantiomeric excess of **5a** was determined by chiral stationary-phase HPLC analysis (DAICEL CHIRALPAK AS-H, *i*-PrOH/Hexane 1/2, flow rate 1.0 mL/min, t_R 15.9 min (minor) and 19.1 min (major), detection at 254 nm); $[\alpha]_D^{24}$ +26.8 (*c* 0.58, MeOH, 99% ee), lit. $[\alpha]_D^{25}$ +28.3 (*c* 1.25, MeOH, >99% ee). See: *Tetrahedron: Asymmetry* **1998**, *9*, 1637-1640.

(3*R*)-3-(4-Methylphenyl)-3-hydroxypropionoic acid methyl amide (5b). See: *Gazz. Chim. Ital.* **1962,** *92***,** 501-518.

(3*R*)-3-(4-Fluorophenyl)-3-hydroxypropionoic acid methyl amide (5c): white solid; IR (KBr) ν 3304, 1642, 1512, 1231 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.48-2.56 (m, 2H), 2.81 (d, *J* = 5.0 Hz, 3H), 4.32 (d, *J* = 2.8Hz, 1H), 5.08 (br-d, *J* = 8.5 Hz, 1H), 5.74 (br-s, 1H), 7.01-7.05 (m, 2H), 7.31-7.35 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 26.2, 44.5, 70.3, 115.2 (d, *J* = 21.6 Hz) (x 2), 127.3 (d, *J* = 8.1 Hz) (x 2), 138.8, 162.2 (d, *J* = 234.8 Hz), 172.3; ESI-MS *m/z* 220 [M+Na^+]; HR-MS [FAB(+)] calcd for $C_{10}H_{13}FNO_2^+$ [M+H^+]: 198.0930. Found 198.0933; $[\alpha]_D^{22.5}$ +68.1 (*c* 0.71, $CHCl_3$, 99% ee).

(3*R*)-3-Phenyl-3-hydroxypropionic acid benzyl amide (5d). See: *Tetrahedron* **1999**, 55, 5017-5026.

Synthesis of the β-alkyl β-hydroxy amides 6a-g. General Procedure for the β-selective epoxide opening of β-alkyl substituted α,β-epoxy amides using DIBAL (path C). To a solution of amide **3a** (41.0 mg, 0.2 mmol) in dry DME (2.0 mL) was added a solution of DIBAL (220 μL, 2.2 equiv, 1 M

solution in toluene) at 4°C. After stirring for 1 h at the same temperature, the solution was quenched by the addition of MeOH (0.5 mL) and diluted with ethyl acetate (10 mL). The solution was washed with saturated aqueous NH_4Cl, brine and then dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified by flush column chromatography (SiO_2, hexane/ethyl acetate = 4:1 to hexane/ethyl acetate = 4:1 + 5% MeOH) to give the corresponding β-hydroxy amides **6a** (39.1 mg, 94%, β-OH:α-OH = 22:1) as a white solid. The desired isomer was isolated by preparative thin-layer chromatography. ***(3S)-3*-Hydroxy-5-phenylpentanoic acid methyl amide (6a).** The enantiomeric excess of **6a** was determined by chiral stationary-phase HPLC analysis (DAICEL CHIRALPAK OD-H, *i*-PrOH/Hexane 1/4, flow rate 0.3 mL/min, t_R 13.1 min (minor isomer), 15.1 min (major isomer), detection at 254nm); $[\alpha]_D^{23}$ + 6.2 (*c* 0.90, $CHCl_3$, 99% ee). See: *J. Molecular Catalysys B* **2001**, *11*, 893.

(*3S*)-*3*-Hydroxy-5-phenylpentanoic acid benzyl amide (6b): white solid; IR (KBr) ν 3295, 2911, 1640, 1545, 1081, 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.72–1.75 (m, 1H), 1.80-1.87 (m, 1H), 2.33 (dd, *J* = 15.2, 8.6 Hz, 1H), 2.39 (dd, *J* = 15.2, 2.6 Hz, 1H), 2.69 (ddd, *J* = 14.0, 9.3, 7.0 Hz, 1H), 2.81 (ddd *J* = 14.0, 9.5, 5.0 Hz, 1H), 3.77 (m, 1H), 4.02 (s, 1H), 4.26 (d, *J* = 5.8 Hz, 2H), 6.09 (s, 1H), 7.16-7.34 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 31.8, 38.4, 42.4, 43.5 ,67.9 ,125.9, 127.6, 127.8 (x 2), 128.8(x 2), 137.8, 141.8 ,172.1; ESI-MS *m/z* 306 [M+Na^+]; HR-MS [FAB(+)] calcd for $C_{18}H_{22}NO_2^+$ [M+H^+]: 284.1651. Found 284.1649; $[\alpha]_D^{25}$ +7.9 (*c* 0.94, $CHCl_3$, 99% ee).

(3*S*)-Hydroxy-5-phenylpentanoic acid allyl amide (6c): white solid; IR (KBr) ν 3309, 2913, 1641, 1548, 699 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.73-1.76 (m, 1H), 1.80-1.88 (m, 1H), 2.31 (dd, *J* = 15.3, 8.9 Hz, 1H), 2.38 (dd, *J* = 15.3, 2.8 Hz, 1H), 2.68 (ddd, *J* = 13.7, 9.1, 7.0 Hz, 1H), 2.81 (ddd, *J* = 13.7, 9.5, 5.0 Hz, 1H), 3.87 (m, 1H), 4.02 (br-s, 1H), 5.13 (d, *J* = 10.0 Hz, 1H), 5.18 (d, *J* = 17.5 Hz, 1H) 5.80 (ddt, *J* = 17.5, 10.0, 5.5 Hz, 1H), 6.08 (br-s, 1H), 7.16-7.28 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 31.7, 38.5, 41.7, 42.3, 67.9, 116.5, 125.8, 128.4 (x 2), 128.4 (x 2), 133.8, 141.7, 172.2; ESI-MS *m/z* 256 [M+Na^+]; HR-MS [FAB(+)] calcd for $C_{14}H_{20}NO_2^+$ [M+H^+]: 234.1494. Found 234.1499; $[\alpha]_D^{23}$ +6.8 (*c* 1.10, $CHCl_3$,

98% ee).

(3*S*)-3-Hydroxy-5-phenyl-pentanoic acid cyclohexyl amide (6d): white solid; IR (KBr) ν 3322, 2939, 2855, 1637, 1542, 1453 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.08-1.19 (m, 3H), 1.32-1.40 (m, 2H), 1.60-1.72 (m, 4H), 1.80-1.91 (m, 3H), 2.25 (dd, *J* = 15.1, 8.2 Hz, 1H), 2.31 (dd, *J* = 15.1, 2.8 Hz, 1H), 2.69 (ddd, *J* = 13.9, 8.2, 5.3 Hz, 1H), 2.82 (ddd, *J* = 13.9, 9.6, 4.6 Hz 1H), 3.73-3.80 (m, 1H), 4.00 (m, 2H), 5.52 (br-s, 1H), 7.17-7.30 (m 5H); ^{13}C NMR ($CDCl_3$) δ 24.8 (x 2), 25.4, 31.8, 33.1 (x 2), 38.5, 42.4, 48.2, 67.9, 125.8, 128.4 (x 2), 128.5 (x 2), 141.9, 171.4; ESI-MS *m/z* 298 [M+Na^+]; HR-MS [FAB(+)] calcd for $C_{17}H_{26}NO_2^+$ [M+H^+]: 276.1964. Found 276.1956; $[\alpha]_D^{25}$ +5.6 (*c* 0.86, $CHCl_3$, 99% ee).

(3*S*)-3-Hydroxy-5-phenylpentanoic acid *tert*-butyl amide (6e): yellow oil; IR (neat) ν 3317, 2966, 1645, 1550 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35 (s, 9H), 1.66-1.73 (m, 1H), 1.79-1.87 (m, 1H) 2.21 (dd, *J* = 15.3, 8.5 Hz, 1H), 2.26 (dd, *J* = 15.3, 3.1 Hz, 1H), 2.67 (ddd *J* = 12.8, 9.8, 7.0 Hz, 1H), 2.70 (ddd *J* = 12.8, 9.8, 5.2 Hz, 1H), 3.99 (m, 1H), 4.10 (br-s, 1H), 5.52 (br-s, 1H), 7.16-7.29 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 28.7 (x 3), 31.8, 38.4, 42.9, 51.4, 67.9, 125.8, 128.4 (x 2), 128.4 (x 2), 141.9, 171.9; ESI-MS *m/z* 272 [M+Na^+], 250 [M+H^+]; HR-MS [FAB(+)] calcd for $C_{15}H_{24}NO_2^+$ [M+H^+]: 250.1807. Found 250.1809; $[\alpha]_D^{23}$ +5.1 (*c* 1.14, $CHCl_3$, 99% ee).

(3*S*)-3-Hydroxy-7-phenylheptanoic acid methyl amide (6f): white solid; IR (KBr); ν 3333, 2930, 2852, 1646, 1559, 1407 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35-1.68 (m, 6H), 2.23 (dd *J* = 15.2, 9.1 Hz, 1H), 2.32 (dd *J* = 15.2, 2.5 Hz, 1H), 2.60 (t, *J* = 7.6 Hz, 2H), 2.81 (d, *J* = 4.9 Hz, 3H), 3.72 (br-s, 1H), 3.97 (m, 1H), 5.85 (br-s,1H), 7.12-7.31 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 25.1, 26.1, 31.3, 35.8, 36.7, 42.2, 68.5, 125.6, 128.2 (x 2), 128.4 (x 2), 142.5, 173.0; ESI-MS *m/z* 258 [M+Na^+], 236 [M+H^+]; HR-MS [FAB(+)] calcd for $C_{14}H_{22}NO_2^+$ [M+H^+]: 236.1651. Found 236.1647; $[\alpha]_D^{25}$ +18.0 (*c* 0.77, $CHCl_3$, 99% ee).

(3*R*)-3-cyclohexyl-3-hydroxypropionic acid benzyl amide (6g): white solid; IR (KBr) ν 3293, 2914, 2851, 1646, 1561, 1447 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.96-1.05 (m, 2H), 1.09-1.25 (m, 3H), 1.34-1.40 (m, 1H), 1.65-1.67 (m, 2H), 1.74-1.77 (m, 2H), 1.83-1.86 (m, 1H), 2.32 (dd, *J* = 15.1, 9.3 Hz, 1H), 2.39 (dd, *J* = 15.1, 2.5 Hz, 1H), 3.44 (d, *J* = 3.8 Hz, 1H), 3.76-3.79 (m, 1H), 4.45 (d, *J* = 5.5 Hz, 2H), 6.22 (s, 1H), 7.26-7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 26.0, 26.1, 26.4, 28.2, 28.8, 39.7, 43.3, 43.5, 72.8, 127.5, 127.7 (x 2), 128.7 (x 2), 138.0, 172.7; ESI-MS *m/z* 284 [M+Na^+]; HR-MS [FAB(+)] calcd for $C_{16}H_{24}NO_2^+$ [M+H^+]: 262.1807. Found 262.1801; $[\alpha]_D^{23}$ +25.5 (*c* 0.98, $CHCl_3$, 99% ee).

Synthesis of the α,β,γ,δ-unsaturated amides 10a-f. α,β,γ,δ-Unsaturated amides were prepared from the corresponding acid chlorides and amines.

5-Phenylpenta-2,4-dienoic acid methyl amide (10a): white solid; IR (KBr) ν 3255, 3077, 1645, 1608, 1559, 1266, 993, 692 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.92 (d, *J* = 5.1 Hz, 3H), 5.55 (br-s, 1H), 5.95 (d, J = 14.7 Hz, 1H), 6.84-6.89 (m, 2H), 7.26-7.45 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 26.4, 123.9, 126.3, 126.9 (x 2), 128.6, 128.7 (x 2), 136.2, 139.0, 140.6, 166.8; ESI-MS *m/z* 210 [M+Na^+]; Anal. Calcd for $C_{12}H_{13}NO$: C, 76.73; H, 7.07; N, 7.41. Found: C, 76.98; H, 7.00; N, 7.48.

5-Phenylpenta-2,4-dienoic acid benzyl amide (10b). See: *J. Am. Chem. Soc*. **1992**, *114*, 5427-5429.

5-Phenylpenta-2,4-dienoic acid dimethyl amide (10c). See, *J. Org. Chem*. **1978,** *43***,** 1947-1949.

5-Phenylpenta-2,4-dienoic acid cyclohexyl amide (10d): white solid; IR (KBr) ν 3272, 2936, 2852, 1647, 1610, 1553, 1445, 1351, 1255, 999, 756, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.14-1.21 (m, 3H), 1.36-1.43 (m, 2H), 1.62-1.76 (m, 3H), 1.96-2.04 (m, 2H), 3.85-3.91 (m, 1H), 5.54 (d, *J* = 7.7 Hz, 1H), 5.95 (d, *J* = 14.9 Hz, 1H), 6.80-6.87 (m, 2H), 7.26-7.44 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 24.0 (x 2), 24.7, 32.3 (x 2), 47.4, 123.5, 125.5, 126.0 (x 2), 127.7, 127.8 (x 2), 135.5, 138.0, 139.7, 164.1; ESI-MS *m/z* 278

[M+Na$^+$], 256 [M+H$^+$]; Anal. Calcd for $C_{17}H_{21}NO$: C, 79.96; H, 8.29; N, 5.49. Found: C, 79.69; H, 8.37; N, 5.48.

5-Hexa-2,4-dienoic acid benzyl amide (10e). See: *J. Am. Chem. Soc.* **1992**, *114*, 5427-5429.

3-Cyclohex-1-enylacrylic acid benzyl amide (10f): white solid; IR (KBr) ν 3279, 2934, 1646, 1604, 1542, 1341, 1222, 986, 697 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.59-1.70 (m, 4H), 2.10-2.19 (m, 4H), 4.51 (d *J* = 5.8 Hz, 2H), 5.75 (d, *J* = 15.5 Hz, 1H), 5.90 (br-s, 1H), 6.11 (m, 1H), 7.24-7.35 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 22.0, 22.0, 24.2, 26.2, 43.5, 116.8, 127.2, 127.7 (x 2), 128.5 (x 2), 134.5, 137.2, 138.4, 144.4, 166.7; ESI-MS *m/z* 264 [M+Na$^+$], 242 [M+H$^+$]; HR-MS [FAB(+)] calcd for $C_{16}H_{20}NO^+$ [M+H$^+$]: 242.1545. Found 242.1543.

Synthesis of the γ,δ-unsaturated α,β-epoxy amides 11a-f. General procedure for the catalytic asymmetric epoxidation of α,β,γ,δ-unsaturated amides 10a-f using the Gd–BINOL–Ph_3As=O Complex 14. A solution of (*S*)-BINOL (14.3 mg, 0.05 mmol) and triphenylarsine oxide (16.1 mg, 0.05 mmol) in THF (5.0 mL) was added to dried MS 4A [500 mg (1000 mg/mmol of starting material); MS 4A was dried for 3 h at 180˚C under reduced pressure.]. Then Gd(O-*i*-Pr)$_3$ (0.25 mL, 0.05 mmol, 0.2 M solution in THF) was added to the reaction mixture at room temperature. After stirring for 45 min at the same temperature, TBHP (0.10 mL, 0.4 mmol, 4.0 M solution in toluene) was added. After stirring for 10 min, **10a** (62.4 mg, 0.33 mmol) was added directly and the mixture was stirred at room temperature. After stirring for 48 h, the reaction mixture was diluted with ethyl acetate (20 mL) and quenched by the addition of 2% aqueous citric acid (5.0 mL). The water layer was extracted with ethyl acetate (20 mL), the combined organic layers were washed with brine and dried over Na_2SO_4. After concentration in *vacuo*, the residue was purified by flash chromatography (SiO_2 treated with Et_3N, hexane/ethyl acetate = 4/1 to 3/1) to give epoxy amide **11a** (57.7 mg, 85%) as a white yellow solid. **(*2R,3S*)-3-Styryl-oxirane-2-carboxylic acid methyl amide (11a**): IR (KBr) ν 3356, 1662, 1543, 1410, 1277, 964, 700

cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.85 (d, *J* = 4.9 Hz), 3.51 (d, *J* = 1.8 Hz), 3.55 (dd, *J* = 8.0 Hz, 1.8 Hz, 1H), 5.85 (dd, *J* = 15.9, 8.0 Hz, 1H), 6.32 (br-s, 1H), 6.80 (d, *J* = 15.9 Hz, 1H), 7.27-7.34 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 25.6, 57.3, 59.5, 123.9, 126.6 (x 2), 128.6, 128.6(x 2), 135.4, 136.5, 168.3; ESI-MS *m/z* 226 [M+Na^+], 204 [M+H^+]. Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.64; H, 6.53; N, 6.84; The enantiomeric excess of **11a** was determined by chiral stationary-phase HPLC analysis [DAICEL CHIRALPAK AS-H, *i*-PrOH/hexane 1/4, flow rate 1.0 mL/min, t_R 17.4 min ((*2S,3R*)-isomer) and 31.1 min ((*2R,3S*)-isomer), detection at 254 nm]; $[\alpha]_D^{26}$ –55.7 (*c* 0.96, $CHCl_3$, 99% ee)].

(*2R,3S*)-3-Styryloxirane-2-carboxylic acid benzyl amide (11b): yellow solid; IR (KBr) ν 3296, 1655, 1544, 1452, 1260, 970, 747, 691 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.55-3.57 (m, 2H), 4.46 (d, *J* = 6.1 Hz, 2H), 5.87 (dd, *J* =16.0, 7.5 Hz, 1H), 6.46 (br-s, 1H), 6.83 (d, *J* = 16.0 Hz, 1H), 7.23-7.37 (m, 5H); ^{13}C-NMR ($CDCl_3$) δ 42.8, 57.2, 59.4, 123.8, 126.6 (x 2), 127.7 (x 2), 128.5, 128.6 (x 2), 128.7 (x 2), 135.4, 136.5, 137.5, 167.6; ESI-MS *m/z* 302 [M+Na^+]; HR-MS [FAB(+)] calcd for $C_{18}H_{18}NO_2^+$ [M+H^+]: 280.1338. Found 280.1337. The enantiomeric excess was determined by chiral stationary-phase HPLC analysis [DAICEL CHIRALPAK AS-H, *i*PrOH/hexane 1/4, flow rate 1.0 mL/min, t_R 27.5 min (minor) and 61.6 min (major), detection at 254 nm]; $[\alpha]_D^{25}$ –93.2 (*c* 0.43, $CHCl_3$, 98% ee).

(*2R,3S*)-3-Styryloxirane-2-carboxylic acid dimethyl amide (11c): yellow solid; IR (KBr) ν 1652, 1513, 1398, 976, 914, 772, 750, 691 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.98 (s, 3H), 3.13 (s, 3H), 3.67 (d, *J* = 1.4Hz, 1H), 3.72 (dd *J* = 8.1, 1.4 Hz, 1H), 5.94 (dd, *J* = 15.9, 8.1 Hz, 1H), 6.85 (d, *J* = 15.9 Hz, 1H), 7.26-7.38 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 35.5, 36.2, 55.2, 57.8, 124.4, 126.3 (x 2), 128.2, 128.5 (x 2), 135.4, 135.6, 166.4; ESI-MS *m/z* 240 [M+Na^+], 218 [M+H^+]; HR-MS [FAB(+)] calcd for $C_{13}H_{16}NO_2^+$ [M+H^+]: 218.1181 Found 218.1184; The enantiomeric excess was determined by chiral stationary-phase HPLC analysis [DAICEL CHIRALPAK AS-H, *i*-PrOH/hexane 1/4, flow rate 1.0 mL/min, t_R 29.3 min (minor) and 34.6 min (major), detection at 254 nm]; $[\alpha]_D^{24}$ –87.5 (*c* 0.80, $CHCl_3$, 99% ee).

(*2R,3S*)-3-Styryloxirane-2-carboxylic acid cyclohexyl amide (11d): white solid; IR (KBr) ν 3293, 2927, 2854, 1658, 1551, 1450, 1253, 970, 752, 692 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.10-1.41 (m, 5H), 1.55-1.71 (m, 3H), 1.85-1.94 (m, 2H), 3.48 (d, *J* = 1.6 Hz, 1H), 3.52 (dd, *J* = 7.6, 1.6 Hz, 1H), 3.73-3.80 (m, 1H), 5.86 (dd, *J* = 15.9, 7.6 Hz, 1H), 6.83 (d, *J* = 15.9 Hz, 1H), 7.27-7.44 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 24.7 (x 2), 25.3, 32.8, 32.9, 47.6, 57.2, 59.6, 124.0, 126.6 (x 2), 128.5, 128.6(x 2), 135.4, 136.4, 166.7; ESI-MS *m/z* 294 [M+Na^+]; HR-MS [FAB(+)] calcd for $C_{17}H_{22}NO_2^+$ [M+H^+]: 272.1651. Found 272.1645. The enantiomeric excess was determined by chiral stationary-phase HPLC analysis [DAICEL CHIRALPAK AS-H, *i*-PrOH/hexane 1/4, flow rate 1.0 mL/min, t_R 19.7 min (minor) and 44.2 min (major), detection at 254 nm]; $[\alpha]_D^{25}$ +5.70 (*c* 1.02, $CHCl_3$, 99% ee).

(*2R,3S*)-3-Propenyloxirane-2-carboxylic acid benzyl amide (11e): white solid; IR (KBr) ν 3231, 3074, 1655, 1560, 1429, 963, 883, 699 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.76 (dd, *J* = 6.7, 1.7 Hz, 3H), 3.35 (dd, *J* = 8.1, 2.0 Hz, 1H), 3.42 (d, *J* = 2.0Hz, 1H), 4.43 (d, *J* = 5.8 Hz, 2H), 5.18 (m, 1H), (dq, *J* = 15.3, 6.7 Hz, 1H), 7.24-7.35 (m, 5H) ; ^{13}C NMR ($CDCl_3$) δ 17.7, 42.6, 56.7, 59.0, 126.2, 127.4, 127.6 (x 2), 128.5 (x 2), 134.0, 137.5, 167.8; ESI-MS *m/z* 240 [M+Na^+], 218 [M+H^+]; HR-MS [FAB(+)] calcd for $C_{13}H_{16}NO_2^+$ [M+H^+]: 218.1181. Found 218.1178. The enantiomeric excess was determined by chiral stationary-phase HPLC analysis [DAICEL CHIRALPAK AS-H, *i*-PrOH/hexane 1/4, flow rate 1.0 mL/min, t_R 22.5 min (minor) and 42.6 min (major), detection at 254 nm]; $[\alpha]_D^{25}$ –43.3 (*c* 1.29, $CHCl_3$, 99% ee).

(*2R,3S*)-3-Cyclohex-1-enyloxirane-2-carboxylic acid benzyl amide (11f): white solid; IR (KBr) ν 3252, 3075, 1655, 1560, 1421, 1260, 1228, 1031, 884, 778, 748, 716, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.48-1.88 (m ,6H), 2.06 (m, 2H), 3.33 (d, *J* = 2.0 Hz), 3.54 (d, *J* = 2.0 Hz, 1H), 4.38-4.47 (m, 2H), 5.96 (m, 1H), 6.47 (br-s, 1H), 7.17-7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 21.9, 22.1, 22.2, 25.3, 42.8, 54.2, 62.3, 127.7, 127.7 (x 2), 128.8 (x 2), 130.5, 131.6, 137.6, 168.6; ESI-MS *m/z* 280 [M+Na^+], 258 [M+H^+]; HR-MS [FAB(+)] calcd for $C_{16}H_{20}NO_2^+$ [M+H^+]: 258.1494. Found 258.1488. The

enantiomeric excess was determined by chiral stationary-phase HPLC analysis [DAICEL CHIRALPAK AD-H, *i*-PrOH/hexane 1/4, flow rate 1.0 mL/min, t_R 8.3 min (minor) and 20.7 min (major), detection at 254 nm]; $[\alpha]_D^{25}$ +75.6 (*c* 0.59, $CHCl_3$, 99% ee).

Synthesis of the γ,δ-unsaturated α-hydroxy amides 12a-f. General proecdure for the palladium catalyzed regioselective hydrogenolysis of γ,δ-unsaturated α,β-epoxy amides 11a-f with formic acid. A solution of Et_3N (140 μL, 1.0 mmol) and formic acid (196 μL, 2.55 mmol) in THF (1 mL) was added to a solution of $Pd_2(dba)_3$•$CHCl_3$ and Bu_3P (5.4 μL) in THF (0.5 mL) at room temperture. After stirring for 5 min, a solution of γ,δ-unsaturated α,β-epoxy amide **11a** (101.6 mg, 0.5 mmol) in THF (1.5 mL) was added to the mixture and the reaction was stirred for 1 h. The reaction was passed through a short SiO_2 column and the filtrate was concentrated. The residue was purified by flush column chromatography (SiO_2, hexane/ethyl acetate =4:1 to hexane/ethyl acetate = 1:1 + 5% MeOH) to give the corresponding γ,δ-unsaturated α-hydroxy amides **12a** (93.1 mg, 91%) as a white solid. **(*2R*)-2-Hydroxy-5-phenylpent-4-enoic acid methyl amide (12a)**: IR (KBr) ν 3356, 1638, 1543, 1069, 965, 748, 643 cm^{-1}; ^1H NMR ($CDCl_3$); 2.50-2.57 (m, 1H), 2.77-2.83 (m, 4H), 3.48 (br-s, 1H), 4.18-4.21 (m, 1H), 6.15-6.21 (m, 1H), 6.49 (br-d, *J* = 15.9 Hz, 1H), 6.86 (br-s, 1H), 7.20-7.34 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 25.7, 38.4, 71.3, 124.7, 126.1 (x 2), 127.4, 128.5 (x 2), 134.0, 136.8, 173.5; ESI-MS *m/z* 228 [M+Na^+]; HR-MS [FAB(+)] calcd for $C_{12}H_{16}NO_2^+$ [M+H^+]: 206.1181. Found 206.1175; $[\alpha]_D^{26}$ +104 (*c* 0.77, $CHCl_3$, 99% ee).

(*2R*)-2-Hydroxy-5-phenylpent-4-enoic acid benzyl amide (12b): white solid; IR (KBr) ν 3388, 3323, 3031, 1620, 1534, 1065, 967, 742, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.57-2.63 (m, 1H), 2.74 (m, 1H), 3.37 (br-s, 1H), 4.24 (m, 1H), 4.29-4.33 (dd, *J* = 14.8, 5.2 Hz, 1H), 4.47-4.51 (dd, *J* = 14.8, 6.3 Hz, 1H), 6.14-6.20 (m, 1H), 6.47 (d, *J* = 15.1 Hz, 1H), 7.11 (br-s, 1H), 7.21-7.28 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 38.5, 43.1, 71.3, 124.1, 126.2 (x 2), 127.5, 127.7, 127.7 (x 2), 128.6 (x 2), 128.7 (x 2), 134.7, 136.7, 137.9, 172.4; ESI-MS *m/z* 304 [M+Na^+], 282 [M+H^+]; Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N,

4.98. Found: C, 76.58; H, 7.01; N, 5.01. $[\alpha]_D^{25}$ +46.0 (*c* 0.56, $CHCl_3$, 99% ee).

(*2R*)-2-Hydroxy-5-phenylpent-4-enoic acid dimethyl amide (12c): yellow solid; IR (KBr) ν 3417, 2934, 1644, 1497, 1454, 1381, 1092, 750, 701 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.42-2.47 (m, 1H), 2.54- 2.59 (m, 1H), 3.00 (s, 3H), 3.00 (s, 3H), 3.84 (d, *J* = 7.6 Hz), 4.47-4.51 (m, 1H), 6.23-6.29 (m, 1H), 6.46 (d, *J* = 15.9 Hz, 1H), 7.18-7.36 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 35.8, 36.4, 38.6, 67.8, 124.7, 126.1 (x 2),127.2, 128.4 (x 2), 132.8, 137.0, 173.4; ESI-MS *m/z* 242 [M+Na^+], 220 [M+H^+]; HR-MS [FAB(+)] calcd for $C_{13}H_{18}NO_2^+$ [M+H^+]: 220.1338. Found 220.1337; $[\alpha]_D^{24}$ +15.3 (*c* 0.56, $CHCl_3$, 99% ee).

(*2R*)-2-Hydroxy-5-phenylpent-4-enoic acid cyclohexylamide (12d): white solid; IR (KBr) ν 3285, 2936, 2856, 1638, 1548, 1449, 1115, 963, 743, 692 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.12-1.26 (m, 3H), 1.33-1.41 (m, 2H), 1.59-1.71 (m, 3H), 1.88-1.91 (m, 2H), 2.55-2.61 (m, 1H), 2.68 (br-d, *J* = 1.6 Hz, 1H), 2.77-2.81 (m, 1H), 3.78-3.80 (m, 1H), 4.17-18 (br-s, 1H), 6.15-6.25 (m, 1H), 6.44 (br-d, *J* = 7.7 Hz, 1H), 6.82 (br-d, *J* = 15.9 Hz, 1H), 7.22-7.36 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 24.8 (x 2), 25.5, 33.0, 33.1, 38.7, 47.9, 71.1, 124.5, 126.2 (x 2), 127.6, 128.6 (x 2), 134.5, 136.8, 171.6; ESI-MS *m/z* 296 [M+Na^+], 274 [M+H^+]; HR-MS [FAB(+)] calcd for $C_{17}H_{24}NO_2^+$ [M+H^+]: 274.1807. Found 274.1805; $[\alpha]_D^{25}$ +66.2 (*c* 0.61, $CHCl_3$, 99% ee).

(*2R*)-3-cyclohex-1-enyl-2-hydroxypropionic acid benzyl amide (12f): white solid; IR (KBr) ν 3357, 2924, 2833, 1648, 1542, 1437, 1082, 757, 696 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.51-1.70 (m, 5H), 1.84-2.02 (m, 3H), 2.21 (dd, *J* = 13.8, 8.9 Hz, 1H), 2.49 (br-s, 1H), 2.66 (br-d, *J* = 13.8 Hz, 1H), 4.16 (br-d. *J* = 8.9 Hz, 1H), 4.42-4.51 (m, 2H), 5.57 (m, 1H), 7.01 (br-s, 1H), 7.26-7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 22.1, 22.6, 25.3, 27.7, 43.0, 43.5, 69.1, 126.9, 127.5, 127.8 (x 2), 128.7 (x 2), 133.6, 138.0, 173.0; ESI-MS *m/z* 282 [M+Na^+]; HR-MS [FAB(+)] calcd for $C_{16}H_{22}NO_2^+$ [M+H^+]: 260.1651. Found 260.1647; $[\alpha]_D^{26}$ –65.5 (*c* 0.77, $CHCl_3$, 99% ee).

Synthesis of the β-alkyl α-hydroxy amides 7a-f. General proecdure for the reduction of C–C double bonds of γ,δ-unsaturated α-hydroxy amides 12a-f using Pd-C / H_2. To a solution of amide **12a** (41.0 mg, 0.1 mmol) in dry THF/MeOH = 2/1 (1.5 mL) was added Pd–C (5%, 5.4 mg, 0.005 mmol), and the reaction mixture was stirred under hydrogen atmosphere (1 atm) for 1 h. After dilution with ethyl acetate (10 mL), the resulting mixture was filtered through a short pad of celite, washed with brine (5 mL), and dried over Na_2SO_4. After concentration in *vacuo*, the residue was purified by flash chromatography (SiO_2, hexane/ethyl acetate = 4/1 to hexane/ethyl acetate 4/1 + 5% MeOH) to give β-alkyl α-hydroxy amide **7a** (43.4 mg, 97%) as a white solid. **(*2R*)-2-Hydroxy-5-phenylpentanoic acid benzyl amide (7a)**: IR (KBr) ν 3397, 3276, 1645, 1546, 1097, 707 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.61-1.76 (m, 3H), 1.81-1.85 (m, 1H), 2.61-2.64 (m, 1H), 2.79 (d, *J* = 5.0 Hz, 3H), 3.43 (br-s, 1H), 4.07 (m, 1H), 6.66 (br-s, 1H), 7.14-7.28 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 25.8, 26.8, 34.4, 35.6, 72.0, 125.8, 128.3 (x 2), 128.4 (x 2), 142.0, 174.4; ESI-MS *m/z* 230 [M+Na^+], 208 [M+H^+]; HR-MS [FAB(+)] calcd for $C_{12}H_{18}NO_2^+$ [M+H^+]: 208.1338. Found 280.1343; The enantiomeric excess of **7a** was determined by chiral stationary-phase HPLC analysis [DAICEL CHIRALPAK AS-H, *i*-PrOH/hexane 1/4, flow rate 1.0 mL/min, t_R 10.5 min ((*2R*)-isomer) and 28.5 min ((*2S*)-isomer), detection at 254 nm]; $[\alpha]_D^{24}$ +38.7 (*c* 0.69, $CHCl_3$, 99% ee).

(*2R*)-2-Hydroxy-5-phenylpentanoic acid benzyl amide (7b): white solid; IR (KBr) ν 3397, 2924, 1624, 1536, 1096, 742, 697 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.66-1.76 (m, 3H), 1.83-1.90 (m, 1H), 2.62 (t, *J* = 6.9 Hz, 2H), 3.04 (br-s, 1H), 4.13 (m, 1H), 4.41 (d *J* = 5.8 Hz, 2H), 6.86 (br-s, 1H), 7.14-7.32 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 26.7, 34.5, 35.5, 43.1, 72.0, 125.8, 127.5 127.7 (x 2), 128.3 (x 2), 128.4 (x 2), 128.7 (x 2), 137.9, 141.3, 173.6; ESI-MS *m/z* 306 [M+Na^+], 284 [M+H^+]; Anal. Calcd for $C_{18}H_{21}NO_2$: C, 76.29; H, 7.47; N, 4.94. Found: C, 76.28; H, 7.56; N, 5.03. $[\alpha]_D^{25}$ +21.3 (*c* 0.74, $CHCl_3$, 99% ee).

(*2R*)-2-Hydroxy-5-phenylpentanoic acid dimethyl amide (7c): colorless oil**;** IR (neat)

ν 3378, 3028, 1629, 1075, 971, 748, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.44-1.52 (m, 1H), 1.63-1.69 (m, 1H), 1.78-1.84 (m, 2H), 2.60-2.72 (m, 2H), 2.86 (s, 3H), 2.97 (s, 3H), 3.73 (d, *J* = 7.1 Hz, 1H), 4.33-4.36 (m, 1H), 7.17-7.28 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 26.3, 33.8, 35.5, 35.8, 36.2, 67.8, 125.8, 128.3 (x 2), 128.4 (x 2), 141.8, 174.3; ESI-MS *m/z* 244 [M+Na^+], 222 [M+H^+]; HR-MS [FAB(+)] calcd for $C_{13}H_{20}NO_2^+$ [M+H^+]: 222.1494. Found 222.1490; $[\alpha]_D^{23}$ –1.9 (*c* 0.74, $CHCl_3$, 99% ee).

(*2R*)-2-Hydroxy-5-phenylpentanoic acid cyclohexyl amide (7d): white solid; IR (KBr) ν 3390, 3231, 2929, 2853, 1653, 1625, 1536, 1094, 749, 697 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.10-1.25 (m, 3H), 1.33-1.40 (m, 2H), 1.61-1.91 (m, 9H), 2.58 (d, *J* = 5.2 Hz, 1H), 2.62-2.68 (m, 2H), 3.73-3.79 (m, 1H), 4.06-4.10 (m, 1H), 6.22 (br-d, *J* = 7.4 Hz, 1H), 7.16-7.29 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 24.8 (x 2), 25.5, 26.6, 33.1, 33.1, 34.6, 35.6, 47.9, 71.9, 125.8, 128.4 (x 2), 128.4 (x 2), 142.0, 172.4; ESI-MS *m/z* 298 [M+Na^+], 276 [M+H^+]; HR-MS [FAB(+)] calcd for $C_{17}H_{26}NO_2^+$ [M+H^+]: 276.1964. Found 276.1967; $[\alpha]_D^{25}$ +26.4 (*c* 0.87, $CHCl_3$, 99% ee).

(*2R*)-2-Hydroxyhexanoic acid benzyl amide (7e): white solid; IR (KBr) ν 3406, 3298, 2954, 2859, 1627, 1535, 1056, 696 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (t, *J* = 7.2 Hz, 3H), 1.31-1.42 (m, 4H), 1.64-1.68 (m, 1H), 1.85-1.87 (m, 1H), 2.82 (d, *J* = 4.3 Hz, 1H), 4.15 (m, 1H), 4.45 (m, 2H), 6.87 (br-s, 1H), 7.21-7.34 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 13.9, 22.4, 27.1, 34.6, 43.0, 72.1, 127.5, 127.7 (x 2), 128.6 (x 2), 137.9, 174.1; ESI-MS *m/z* 244 [M+Na^+], 222 [M+H^+]; HR-MS [FAB(+)] calcd for $C_{13}H_{20}NO_2^+$ [M+H^+]: 220.1494. Found 220.1491; $[\alpha]_D^{24}$ +20.3 (*c* 1.23, $CHCl_3$, 99% ee).

(*2R*)-3-Cyclohexyl-2-hydroxypropionic acid benzyl amide (7f): white solid; IR (KBr) ν 3347, 2925, 2847. 1647, 1543, 1445, 757, 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (m, 2H), 1.12-1.30 (m, 3H), 1.50-1.83 (m, 8H), 2.42 (d, *J* = 5.2 Hz, 1H), 4.21-4.24 (m, 1H), 4.43-4.51 (m, 2H), 6.76 (br-s, 1H), 7.20-7.36 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 26.0, 26.3, 26.4, 32.2, 33.9, 34.2, 42.6, 43.2, 70.3, 127.5, 127.8

(x 2), 128.7 (x 2), 138.0, 174.2; ESI-MS *m/z* 284 [M+Na^+]; HR-MS [FAB(+)] calcd for $C_{16}H_{24}NO_2^+$ (M+H^+): 262.1807. Found 262.1801;$[\alpha]_D^{24}$ –30.1 (*c* 0.94, $CHCl_3$, 99% ee).

Asymmetric Synthesis of (*R*)-Fluoxetine (17)

Synthesis of the α, β–Epoxy Amides 2a. To a mixture of (*S*)-BINOL (859 mg, 3.0 mmol), triphenylarsine oxide (967 mg, 3.0 mmol) and MS 4A [30 g (1000 mg/mmol of starting material); MS 4A was not dried.] in dry THF (300 mL) was added a solution of Sm(O-*i*-Pr)$_3$ (15.0 mL, 3.0 mmol, 0.1 M solution in THF) at 4˚C. After being stirred for 5 min at the same temperature and additional 45 min at room temperature, TBHP (7.2 mL, 36 mmol, 5 M solution in decane) was slowly added within 5 min. After being stirred for 10 min, α,β-unsaturated amide **15** (4.836 g, 30 mmol) was added in 6 portions every 2 min at 4 ˚C, then the mixture was stirred at room temperature. After complete consumption of the starting material (48 h), the reaction mixture was filtered through a celite pad and diluted with ethyl acetate (500 mL), which was washed with 2% aqueous citric acid (200 mL) followed by 10% aqueous Na_2SO_4 (200 mL). The water layer was extracted with ethyl acetate (200 mL). The combined organic layers were washed with brine (200 mL) and dried over sodium sulphate. After concentration in vacuo, the residue was purified by flash chromatography (SiO_2, hexane/ethyl acetate = 4/1 to 3/1) to give epoxy amide **2a** (4.843 g, 91%, 99% ee) as a white yellow solid. See also: *J. Am. Chem. Soc.* **2002**, *124*, 14544.

Synthesis of the β-Aryl β-Hydroxy Amides 5a. To a solution of amide **2a** (4.62 g, 26.1 mmol) and 15-crown-5 (6.27 mL, 1.2 equiv) in dry DME (130 mL) was slowly added a solution of Red-Al (9.6 mL, 1.2 equiv, 65% solution in toluene) at –40°C over 30 min. After stirring for 1 h at the same temperature, the mixture was gradually warmed to room temperature over 3 h then stirred for 1.5 h at the same temperature. After complete consumption of the starting material, the solution was quenched by the addition of MeOH (20 mL), washed with saturated aqueous NH_4Cl, and filtered through a celite pad. The organic layer was diluted with ethyl acetate (500 mL), washed with brine (twice), and then

dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified by flush column chromatography (SiO_2, hexane/ethyl acetate = 4:1 to hexane/ethyl acetate 4:1 + 5% MeOH) to give the corresponsing β-hydroxy amides **5a** (3.722 g, 80%, β-OH:α-OH = >20:1) as a white solid. 15-crown-5 was recovered in about 87% yield by extraction from aqueous layer with $CHCl_3$ followed by flash chromatography (SiO_2, hexane/ethyl acetate = 4/1 to hexane/ethyl acetate = 1/2 + 5% MeOH).

Conversion of **5a** to **17** was performed by following the reported procedure. See ref. 14e,d.