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Electronic Supplementary Information (ESI)

Iterative Direct $C_{(sp3)}$ -H Functionalization of Amines: Diastereoselective Divergent Syntheses of α , α' -Disubstituted Alicyclic Amines

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Experimental Section:

General: All reactions involving air- or moisture-sensitive reagents or intermediates were carried out in oven-dried glassware under an argon atmosphere. THF and diethylether (Et₂O) were freshly distilled from Sodium under argon. Commercial grade triethylamine (Et₃N), xylene, benzene and toluene were distilled over CaH₂ and stored under argon. All other solvents and reagents were purified according to standard procedures or were used as received from Aldrich, Acros, Merck and Spectrochem. ¹H, ¹³C NMR spectroscopy: *Varian Mercury plus 400 MHz* and *Bruker 600 MHz* (at 298 K). Chemical shifts, δ (in ppm), are reported relative to TMS (δ (¹H) 0.0 ppm, δ (¹³C) 0.0 ppm) which was used as the inner reference. Otherwise the solvents residual proton resonance and carbon resonance (CHCl₃, δ (¹H) 7.26 ppm, δ (¹³C) 77.23 ppm; CD₃OD, (¹H) 3.31 ppm, δ (¹³C) 49.0 ppm) were used for calibration. Column chromatography: Merck or Fischer Scientific neutral alumina or silica gel 60-120 or under gravity. IR: spectra were recorded on Perkin Elmer Instrument at normal temperature making KBr pellet grinding the sample with KBr (IR Grade). MS (ESI-HRMS): Mass spectra were recorded on Agilent Accurate-Mass Q-TOF LC/MS 6520, and peaks are given in *m/z* (% of basis peak).

X-ray crystallographic data were collected using a Bruker SMART APEX-II CCD diffractometer, equipped with a fine focus 1.75 kW sealed tube Mo-K α radiation (1 = 0.71073 Å) at 296(2) K, with increasing w (width of 0.3° per frame) at a scan speed of 3 s/frame. Structures were solved by direct methods using SHELXS-97 and refined with full matrix least

squares on F^2 using SHELXL–97. Using Olex2¹, structure was solved with the Superflip² structure solution program using Charge Flipping and refined with the olex2.refine³ refinement package using Gauss–Newton minimization. All then non–hydrogen atoms were refined anisotropically.

General procedure for first C-C bond formation (GP 1):

Oxazine (0.32 mmol) was taken in an oven-dried round bottom flask and flashed with argon atmosphere. Suitable Grignard reagent (1M in THF, 0.95 mL) was added dropwise to the oxazine at 0° to -3° C. After completion of the reaction (monitored by TLC), the reaction was quenched with saturated NH₄Cl solution (3 mL) and the mixture was extracted with ethyl acetate (3 X 5 mL). The combined organic layers were dried (over anhydrous Na₂SO₄), concentrated (under vacuum) and the resulting residue was subjected to column chromatography.

1-((2-benzylpyrrolidin-1-yl)(phenyl)methyl)naphthalen-2-ol (4a): According to GP 1: To



the oxazine **2a** (0.25 g, 0.83 mmol), benzylmagnesium chloride (1 M in THF, 2.5 mL, 2.5 mmol) was added dropwise at -3 °C and the mixture was stirred for 1 h under argon atmosphere. The crude product was subjected to neutral alumina column chromatography (EtOAc : hexane, 1 : 80) to afford the desired amino naphthol **4a** as white solid (0.30 g, 92%). FTIR (KBr): $\tilde{\nu} =$

3439, 3058, 2962, 2920, 2832, 1619, 1599, 1518, 1466, 1452, 1405, 1270, 1234, 1104, 1089, 951, 816, 758, 743, 701 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ = 14.13 (s, 1H), 7.83 (d, *J* = 8.6 Hz, 1H), 7.71 – 7.67 (m, 4H), 7.37 – 7.26 (m, 4H), 7.24 – 7.09 (m, 5H), 6.62–6.60 (m, 2H), 5.42 (s, 1H), 3.27 (br. s, 2H), 2.66 – 2.59 (m, 1H), 2.50 – 2.47 (m, 1H), 2.34 – 2.28 (m, 1H), 1.91 – 1.75 (m, 3H), 1.68 – 1.62 (m, 1H). ¹³C NMR (101 MHz, CDCl₃) δ = 155.9, 140.5, 139.4, 132.0, 129.9, 129.8, 129.2, 129.0, 128.9, 128.7, 128.4 (2C), 126.6, 126.2, 122.5, 121.1, 120.2, 116.9, 71.1, 62.8, 55.9, 43.1, 29.9, 23.7. HRMS (ESI) exact mass calculated for C₂₈H₂₈NO⁺ ([M+H]⁺): Cal: 394.2165; Found: 394.2165.

1-(phenyl(2-phenylpyrrolidin-1-yl)methyl)naphthalen-2-ol (4b): According to GP 1: To

the oxazine **2a** (0.40 g, 1.32 mmol), phenylmagnesium bromide (1 M in THF, 3.9 mL, 3.9 mmol) was added dropwise at 0 °C and the mixture was stirred for 30 min under argon atmosphere. The crude product was subjected to OH neutral alumina column chromatography (EtOAc : hexane, 1 : 80) to afford the desired amino naphthol **4b** as white solid (0.45 g, 90%). FTIR (KBr): \tilde{v}

= 3413, 3059, 3026, 2967, 2869, 1620, 1600, 1583, 1519, 1465, 1450, 1415, 1266, 1234, 1079, 951, 810, 758, 694 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ = 14.17 (s, 1H), 7.72 (d, *J* = 7.9 Hz, 1H), 7.67 – 7.63 (m, 2H), 7.34 – 7.29 (m, 3H), 7.21 – 7.14 (m, 2H), 7.04 – 7.03 (m, 3H), 6.93 – 6.91 (m, 3H), 6.78 – 6.77 (m, 2H), 5.28 (s, 1H), 3.96 (br. s, 1H), 3.36 (br. s, 1H), 2.72 – 2.66 (m, 1H), 2.39 – 2.32 (m, 1H), 2.13 – 2.03 (m, 1H), 1.99 – 1.86 (m, 2H). ¹³C NMR (101 MHz, CDCl₃) δ = 155.6, 140.0, 131.8, 129.6, 129.4, 128.9, 128.6, 128.1 (2C), 128.1, 127.7, 126.9, 126.4, 126.3, 122.4, 121.2, 119.9, 117.0, 70.7, 66.5, 55.2, 35.4, 24.1. HRMS (ESI) exact mass calculated for C₂₇H₂₆NO⁺ ([M+H]⁺): Cal: 380.2009; Found: 380.2009.

1-((2-isopropylpyrrolidin-1-yl)(phenyl)methyl)naphthalen-2-ol (4c): According to GP 1:



To the oxazine **2a** (0.15 g, 0.49 mmol), isopropylmagnesium chloride (2 M in THF, 0.74 mL, 1.5 mmol) was added dropwise at -3 °C and the mixture was stirred for 2 h under argon atmosphere. The crude product was subjected to neutral alumina column chromatography (EtOAc : hexane, 1 : 80) to afford an inseparable mixture of diastereomers (95 : 5) of amino naphthol **4c** as

white solid (0.15 g, 89%). Following analytical data are given for major isomer. FTIR (KBr): $\tilde{v} = 3449, 2970, 2839, 1647, 1622, 1470, 1414, 1268, 1259, 1236, 1100, 1015, 949, 813, 741, 699 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) <math>\delta = 14.59$ (s, 1H), 7.77 (d, J = 8.6 Hz, 1H), 7.68 – 7.65 (m, 2H), 7.59 – 7.57 (m, 2H), 7.34 – 7.30 (m, 1H), 7.24 – 7.16 (m, 5H), 5.31 (s, 1H), 3.21 – 3.16 (m, 1H), 2.95 – 2.91 (m, 1H), 2.65 – 2.59 (m, 1H), 1.86 – 1.75 (m, 2H), 1.75 – 1.66 (m, 2H), 1.07 – 1.01 (m, 1H), 0.77 (d, J = 6.7 Hz, 3H), 0.53 (d, J = 6.8 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) $\delta = 156.1, 140.2, 132.0, 129.8, 129.7, 129.0, 128.7, 128.6, 128.2, 126.5, 122.4, 121.1, 120.2 117.3, 71.3, 66.5, 55.8, 30.8, 25.5, 24.3, 20.4, 16.2. HRMS (ESI) exact mass calculated for C₂₄H₂₈NO⁺ ([M+H]⁺): Cal: 346.2165; Found: 346.2161.$

1-((2-allylpyrrolidin-1-yl)(phenyl)methyl)naphthalen-2-ol (4d): Allylmagnesium bromide



was prepared by the reaction of allyl bromide (1.66 mmol) and magnesium (1.72 mmol) in dry THF (1.66 mL). After disappearance of the magnesium, the freshly prepared allylmagnesium bromide solution (1.5 mL) was added dropwise to a powdered oxazine 2a (50 mg, 0.17 mmol) at 0 °C under argon atmosphere. Then the mixture was slowly allowed to reach to room temperature and stirred for 16 h. The crude was subjected to neutral alumina

column chromatography (EtOAc : hexane, 1 : 60) to afford an inseparable mixture of diastereomers (77 : 23) of amino naphthol **4d** as light yellow oil (44 mg, 78%). Following analytical data are given for major isomer. ¹H NMR (400 MHz, CDCl₃) δ = 14.04 (s, 1H), 7.80 (d, *J* = 8.5 Hz, 1H), 7.70 – 7.66 (m, 2H), 7.63 – 7.61 (m, 2H), 7.36 – 7.32 (m, 1H), 7.28 – 7.15 (m, 5H), 5.57 – 5.46 (m, 1H), 5.36 (s, 1H), 4.96 (d, *J* = 10.1 Hz, 1H), 4.82 (d, *J* = 17.2 Hz, 1H), 3.13 (br. s, 2H), 2.64 – 2.57 (m, 1H), 2.05 – 1.97 (m, 1H), 1.85 – 1.68 (m, 5H). HRMS (ESI) exact mass calculated for C₂₄H₂₆NO⁺ ([M+H]⁺): Cal: 344.2009; Found: 344.2001.

1-(phenyl(2-vinylpyrrolidin-1-yl)methyl)naphthalen-2-ol (4e): According to GP 1: To the



oxazine **2a** (0.10 g, 0.33 mmol), vinylmagnesium bromide (1 M in THF, 0.66 mL, 0.66 mmol) was added dropwise at -3 °C and the mixture was stirred for 6 h under argon atmosphere. The crude product was subjected to SiO₂-column chromatography (EtOAc : hexane, 1 : 60 with Et₃N 100 μ L/100 mL) to afford an inseparable mixture of diastereomers (67 : 33) of amino naphthol

4e as light yellow solid (94 mg, 86%). Following analytical data are given for major isomer. ¹H NMR (400 MHz, CDCl₃) δ = 13.91 (s, 1H), 7.81 (d, *J* = 8.6 Hz, 1H), 7.67 – 7.63 (m, 2H), 7.56 – 7.54 (m, 2H), 7.34 – 7.30 (m, 1H), 7.19 – 7.12 (m, 5H), 5.59 (br. 1H), 5.39 (s, 1H), 4.75 – 4.71 (m, 1H), 4.42 (d, *J* = 16.8 Hz, 1H), 3.54 (br. s, 1H), 2.66 – 2.52 (m, 2H), 2.14 – 1.99 (m, 1H), 1.85 – 1.75 (m, 3H). HRMS (ESI) exact mass calculated for C₂₃H₂₄NO⁺ ([M+H]⁺): Cal: 330.1852; Found: 330.1848.

1-((2-benzylpiperidin-1-yl)(phenyl)methyl)naphthalen-2-ol (4f): According to GP 1: To



the oxazine **2b** (95 mg, 0.30 mmol), benzylmagnesium chloride (1 M in THF, 0.90 mL, 0.90 mmol) was added dropwise at -3 °C and the mixture was stirred for 2 h under argon atmosphere. The crude product was subjected to neutral alumina column chromatography (EtOAc : hexane, 1 : 50) to afford the desired amino naphthol **4f**⁴ as white solid (0.11 g, 89%). ¹H NMR (400 MHz, CDCl₃) δ = 14.37 (s, 1H), 8.02 (d, *J* = 7.7 Hz, 1H), 7.69 (d, *J* = 8.1 Hz, 1H), 7.64 (d, *J* = 8.8 Hz, 1H), 7.43 – 7.39 (m, 1H), 7.36 – 7.32 (m,

2H), 7.29 – 7.21 (m, 3H), 7.15 – 7.12 (m, 5H), 6.58 (br. s, 2H), 5.60 (s, 1H), 3.23 - 3.20 (m, 1H), 3.05 - 3.02 (m, 2H), 2.95 - 2.89 (m, 1H), 2.75 (br. s, 1H), 1.83 - 1.70 (m, 3H), 1.59 - 1.46 (m, 3H). ¹³C NMR (101 MHz, CDCl₃) $\delta = 155.9$, 139.6, 139.4, 132.5, 129.5, 129.2, 129.0, 128.8, 128.5, 128.2, 128.0, 126.6, 126.2, 122.5, 121.0, 120.4, 117.0, 68.3, 55.5, 46.0, 27.7, 26.9, 26.0, 18.5. HRMS (ESI) exact mass calculated for C₂₉H₃₀NO⁺ ([M+H]⁺): Cal: 408.2322; Found: 408.2324.

1-(phenyl(2-phenylpiperidin-1-yl)methyl)naphthalen-2-ol (4g): Phenylmagnesium



bromide was prepared by the reaction of bromobenzene (3.20 mmol) and magnesium (3.30 mmol) in dry THF (3.2 mL). After disappearance of the magnesium, the freshly prepared phenylmagnesium bromide solution was cooled and added (1.90 mL) dropwise to a powdered oxazine **2b** (0.20 g, 0.63 mmol) at 0 °C under argon atmosphere. The crude product was subjected to neutral alumina column chromatography (EtOAc : hexane, 1 :

70) to afford the desired amino naphthol **4g** as white solid (0.18 g, 72%) and 2-Phenylpiperidine⁵ (DCM : MeOH, 200 : 1) as brown oil (25 mg, 25%). ¹H NMR (400 MHz, CDCl₃) δ = 14.65 (s, 1H), 7.53 – 7.54 (m, 2H), 7.33 (br. s, 3H), 7.18 – 7.11 (m, 3H), 7.04 – 6.84 (m, 8H), 5.60 (s, 1H), 3.71 (br. s, 1H), 2.94 (br. s, 1H), 1.98 – 1.78 (m, 7H). ¹³C NMR (101 MHz, CDCl₃) δ = 157.1, 141.4, 139.1, 131.4, 130.2, 129.2, 128.8, 128.5, 128.2, 128.1, 127.8, 127.3, 126.5, 125.4, 122.5, 121.9, 120.2, 115.7, 70.5, 68.8, 52.3, 35.4, 26.2, 24.5. HRMS (ESI) exact mass calculated for C₂₈H₂₈NO⁺ ([M+H]⁺): Cal: 394.2165; Found: 394.2164.

2-Phenylpiperidine : ¹H NMR (400 MHz, CDCl₃) δ = 7.37 – 7.29 (m, 4H), 7.26 – 7.22 (m,



1H), 3.60 – 3.57 (m, 1H), 3.21 – 3.18 (m, 1H), 2.84 – 2.76 (m, 1H), 2.03 – 1.94 (m, 1H), 1.90 – 1.88 (m, 1H), 1.81 – 1.78 (m, 1H), 1.67 – 1.65 (m, 1H), 1.57 – 1.49 (m, 2H).

1-((2-allylpiperidin-1-yl)(phenyl)methyl)naphthalen-2-ol (4h): According to GP 1: To the



oxazine **2b** (0.20 g, 0.63 mmol), allylmagnesium bromide (1 M in diethylether, 1.90 mL, 1.90 mmol) was added dropwise at -3 °C and the mixture was stirred for 2 h under argon atmosphere. The crude product was subjected to neutral alumina column chromatography (EtOAc : hexane, 1 : 40) to afford an inseparable mixture of diastereomers of amino naphthol **4h**⁴

as white solid (0.10 g, 45%). HRMS (ESI) exact mass calculated for $C_{25}H_{28}NO^+$ ([M+H]⁺): Cal: 358.2165; Found: 358.2158.

1-((2-benzylazepan-1-yl)(phenyl)methyl)naphthalen-2-ol (4i): According to GP 1: To the



oxazine **2c** (0.10 g, 0.30 mmol), benzylmagnesium chloride (1 M in THF, 0.90 mL, 0.90 mmol) was added dropwise at -3 °C and the mixture was stirred for 3 h under argon atmosphere. The crude product was subjected to neutral alumina column chromatography (EtOAc : hexane, 1 : 50) to afford a diastereomeric mixture of the desired amino naphthol **4i** as white solid (0.12 g, 97%). ¹H NMR (400 MHz, CDCl₃) δ = 14.22 (s, 1H), 8.01 (d, *J* =

8.6 Hz, 1H), 7.81 (br. s, 2H), 7.70 – 7.68 (m, 1H), 7.65 – 7.62 (m, 1H), 7.44 – 7.39 (m, 1H), 7.32 – 7.28 (m, 2H), 7.25 – 7.20 (m, 2H), 7.16 – 7.11 (m, 4H), 6.66 (br. s, 2H), 5.69 (s, 1H), 3.42 - 3.38 (m, 1H), 3.15 - 3.12 (m, 1H), 3.04 - 2.93 (m, 2H), 2.71 - 2.65 (m, 1H), 1.95 - 1.80 (m, 2H), 1.66 - 1.36 (m, 6H). HRMS (ESI) exact mass calculated for $C_{30}H_{32}NO^+$ ([M+H]⁺): Cal: 422.2478; Found: 422.2475.

1-((3-benzylmorpholino)(phenyl)methyl)naphthalen-2-ol (4j): According to GP 1: To the



oxazine **2d** (0.24 g, 0.76 mmol), benzylmagnesium chloride (1 M in THF, 2.3 mL, 2.3 mmol) was added dropwise at -3 °C and the mixture was stirred for 3 h under argon atmosphere. The crude product was subjected to neutral alumina column chromatography (EtOAc : hexane, 1 : 40) to afford the desired amino naphthol **4j** as white solid (0.28 g, 92%). FTIR (KBr): $\tilde{v} =$ 3050, 2956, 2859, 1751, 1621, 1600, 1581, 1497, 1446, 1413, 1266, 1260,

1235, 1117, 1099, 947, 835, 810, 752, 701 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ = 13.55 (s, 1H), 8.04 (d, *J* = 8.5 Hz, 1H), 7.83 (br. s, 2H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.64 (d, *J* = 8.8 Hz, 1H), 7.46 – 7.44 (m, 1H), 7.37 – 7.34 (m, 3H), 7.30 – 7.21 (m, 2H), 7.14 – 7.12 (m, 3H), 6.65 (br. s, 2H), 5.66 (s, 1H), 3.94 – 3.81 (m, 2H), 3.61 – 3.51 (m, 2H), 3.17 – 3.11 (m, 1H), 3.05 – 2.92 (m, 3H), 2.87 – 2.84 (m, 1H). ¹³C NMR (101 MHz, CDCl₃) δ = 155.1, 138.8, 138.6, 132.5, 129.9, 129.4, 129.3, 129.0, 128.6, 128.5, 126.8, 126.4, 122.8, 121.1, 120.2, 116.0, 68.1, 67.9, 67.2, 56.7, 46.4, 26.8. HRMS (ESI) exact mass calculated for $C_{28}H_{28}NO_2^+$ ([M+H]⁺): Cal: 410.2115; Found: 410.2123.

1-(phenyl(3-phenylmorpholino)methyl)naphthalen-2-ol (4k): According to GP 1: To the



oxazine **2d** (0.12 g, 0.38 mmol), phenylmagnesium bromide (1 M in THF, 1.1 mL, 1.1 mmol) was added dropwise at 0 °C and the mixture was stirred for 6 h under argon atmosphere. The crude product was subjected to SiO₂-column chromatography (EtOAc : hexane, 1 : 50 with Et₃N 100 μ L/100 mL) to afford the desired amino naphthol **4k**⁶ as light yellow solid (0.10 g, 68%). ¹H NMR (400 MHz, CDCl₃) δ = 13.50 (s, 1H), 7.74 – 7.71 (m, 2H), 7.49

(d, J = 8.1 Hz, 1H), 7.33 – 7.14 (m, 13H), 5.16 (s, 1H), 4.21 – 4.14 (m, 2H), 4.04 – 3.97 (m, 2H), 3.85 – 3.79 (m, 1H), 2.87 – 2.85 (m, 1H), 2.24 – 2.22 (m, 1H). ¹³C NMR (101 MHz, CDCl₃) $\delta = 156.1$, 138.7, 132.1, 131.2, 130.1, 129.9, 129.1, 129.0, 128.8, 128.2, 128.0, 126.5, 122.8, 121.4, 119.8, 114.9, 71.1, 67.6, 66.8, 59.2, 44.5.

General procedure for Second C-O bond formation (GP 2):

Betti base with mono-functionalized amine **4** (0.18 mmol) was treated with silver oxide (0.22 mmol) in xylene at either room temperature or under heating (60-80 $^{\circ}$ C) condition to obtain the cyclic oxazine.⁷ After completion of the reaction, the reaction mixture passed through small pad of celite and the celite cake was washed with ethyl acetate. The organic layer was concentrated under vaccum and the crude mixture was subjected to column chromatography.

10-benzyl-12-phenyl-8,9,10,12-tetrahydro-7aH-naphtho[1,2-e]pyrrolo[2,1-b][1,3]oxazine



(5a): According to GP 2: Betti base 4a (34 mg, 86 μ mol), Ag₂O (23 mg, 10 μ mol) in *m*-xylene (1 mL) was heated at 60 °C for 12 h. The crude product was subjected to neutral alumina column chromatography (EtOAc : hexane, 1 : 80) to afford an inseparable mixture of diastereomers (89 : 11) of oxazine 5a as a grey solid (25 mg, 78%). Following analytical data are given for major isomer. ¹H NMR (400 MHz, CDCl₃) δ = 7.75 – 7.69

(m, 2H), 7.25 - 7.16 (m, 13H), 7.06 (d, J = 8.9 Hz, 1H), 5.46 (s, 1H), 5.15 - 5.14 (m, 1H), 3.35 - 3.26 (m, 2H), 2.83 - 2.78 (m, 1H), 2.09 - 1.99 (m, 2H), 1.97 - 1.90 (m, 2H). ¹³C NMR (101 MHz, CDCl₃) $\delta = 152.4$, 143.5, 139.4, 132.7, 130.3, 129.4, 128.9, 128.9, 128.7, 128.5, 128.5,

127.3, 126.7, 126.4, 123.1, 122.7, 119.0, 110.5, 97.2, 87.9, 60.7, 54.6, 42.5, 30.2, 27.9. HRMS (ESI) exact mass calculated for C₂₈H₂₆NO⁺ ([M+H]⁺): Cal: 392.2009; Found: 392.2006.

10,12-diphenyl-8,9,10,12-tetrahydro-7a*H*-naphtho[1,2-*e*]pyrrolo[2,1-*b*][1,3]oxazine (5b):



According to GP 2: Betti base **4b** (0.20 g, 0.53 mmol), $Ag_2O(0.15 \text{ g}, 0.63 \text{ mmol})$ in *m*-xylene (2.5 mL) was stirred at room temperature for 8 h. The crude product was subjected to neutral alumina column chromatography (EtOAc : hexane, 1 : 50) to afford an inseparable mixture of regio-isomer

(57:43) of oxazine **5b** as white solid (0.19 g, 93%). HRMS (ESI) exact mass calculated for $C_{27}H_{24}NO^+([M+H]^+)$: Cal: 378.1852; Found: 378.1864.

(7aS,10R,12R)-10-isopropyl-12-phenyl-8,9,10,12-tetrahydro-7aH-naphtho[1,2-e] pyrrolo[2,1-b][1,3]oxazine (5c): According to GP 2: A mixture of Betti base 4c (92 mg, 0.27



mmol) and Ag₂O (74 mg, 0.32 mmol) in *m*-xylene (1 mL) was heated at 60 °C for 12 h. The crude product was subjected to SiO₂-column chromatography (EtOAc : hexane, 1 : 150) to afford oxazine **5c** as a colorless solid (75 mg, 82%). FTIR (KBr): $\tilde{\nu} = 3058$, 2950, 2874, 2817, 1622, 1597, 1509, 1491, 1465, 1386, 1232, 1066, 1012, 892, 814, 751, 698

cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ = 7.91 – 7.70 (m, 3H), 7.50 – 7.43 (m, 2H), 7.31 – 7.28 (m, 5H), 7.13 (d, *J* = 8.8 Hz, 1H), 5.47 (s, 1H), 5.20 (s, 1H), 3.04 (br. s, 1H), 2.24 (br. s, 1H), 2.09 – 1.98 (m, 2H), 1.89 – 1.84 (m, 1H), 1.75 – 1.73 (m, 1H), 1.09 (d, *J* = 4.0 Hz, 3H), 0.93 (d, *J* = 8.0 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) δ = 152.7, 143.8, 132.8, 130.5, 129.1, 129.0, 128.9, 128.5, 127.2, 126.6, 123.0, 122.7, 119.1, 110.7, 88.3, 64.4, 54.3, 30.9, 29.4, 21.6, 20.2, 14.8. HRMS (ESI) exact mass calculated for C₂₄H₂₆NO⁺ ([M+H]⁺): Cal: 344.2009; Found: 344.2011.

11-benzyl-13-phenyl-7a,8,9,10,11,13-hexahydronaphtho[1,2-e]pyrido[2,1-b][1,3]oxazine



(5d): According to GP 2: Betti base 4f (25 mg, 61 µmol) and Ag₂O (17 mg, 66 µmol) in *m*-xylene (1 mL) was refluxed at 140 °C for 18 h. The crude product was subjected to SiO₂-chromatography (EtOAc : hexane, 1 : 40) to afford an inseparable mixture of diastereomers (95 : 5) of oxazine 5d as yellowish solid (17 mg, 69%). Following analytical data are given for major isomer. ¹H NMR (400 MHz, CDCl₃) $\delta = 7.79 - 7.74$ (m, 2H), 7.29 - 7.22 (m, 8H), 7.13 - 7.08 (m, 4H), 7.03 - 7.01 (m, 2H), 5.91 (s, 1H), 4.98 (s, 1H), 3.44 (dd, *J* = 13.2, 4.2 Hz, 1H), 3.10 – 3.05 (m, 1H), 2.72 – 2.66 (m, 1H), 1.97 – 1.92 (m, 1H), 1.81 -1.74 (m, 1H), 1.61 - 1.52 (m, 3H), 1.45 - 1.35 (m, 1H). ¹³C NMR (101 MHz, CDCl₃) $\delta =$

152.9, 143.6, 139.3, 132.9, 129.6, 129.3, 129.2, 128.9, 128.6, 128.4, 128.3, 127.1, 126.7, 126.2, 123.1, 122.6, 118.7, 110.9, 82.4, 55.8, 54.1, 42.2, 31.9, 29.9, 18.5. HRMS (ESI) exact mass calculated for C₂₉H₂₈NO⁺ ([M+H]⁺): Cal: 406.2165; Found: 406.2169.

11,13-diphenyl-7a,8,9,10,11,13-hexahydronaphtho[1,2-e]pyrido[2,1-b][1,3]oxazine (5e



and its regioisomer): According to GP 2: Betti base 4g (34 mg, 86 µmol), Ag₂O (23 mg, 0.10 mmol) in *m*-xylene (1 mL) was heated at 60 °C for 12 h. The crude product was subjected to neutral alumina column chromatography (EtOAc : hexane, 1 : 80) to afford an inseparable mixture of regio-isomer (50

: 50) of oxazine 5e as light yellow solid (25 mg, 74%). HRMS (ESI) exact mass calculated for C₂₈H₂₆NO⁺ ([M+H]⁺): Cal: 392.2009; Found: 392.2009.

11-allyl-13-phenyl-7a,8,9,10,11,13-hexahydronaphtho[1,2-e]pyrido[2,1-b][1,3]oxazine



(5f): According to GP 2: A mixture of Betti base 4h (20 mg, 0.05 mmol) and Ag₂O (15 mg, 0.07 mmol) in *m*-xylene (0.5 mL) was heated at 80 °C for 12 h. The crude product was subjected to SiO₂-column chromatography (EtOAc : hexane, 1:50) to afford an inseparable mixture of diastereomers (78:22) of oxazine 5f as a colorless oil (12 mg, 61%). Following analytical

data are given for major isomer. ¹H NMR (400 MHz, CDCl₃) δ = 7.80 – 7.72 (m, 2H), 7.40 – 7.37 (m, 1H), 7.33 – 7.27 (m, 2H), 7.25 – 7.17 (m, 5H), 7.12 (d, J = 8.9 Hz, 1H), 5.98 – 5.89 (m, 1H), 5.81 (s, 1H), 5.16 – 5.10 (m, 2H), 4.96 (s, 1H), 2.89 – 2.83 (m, 1H), 2.47 – 2.44 (m, 2H), 1.92 – 1.81 (m, 2H), 1.72 – 1.68 (m, 1H), 1.61 – 1.55 (m, 3H). ¹³C NMR (101 MHz, CDCl₃) δ = 152.9, 143.5, 135.3, 132.9, 129.6, 129.2, 128.7, 128.8, 128.3, 127.1, 126.8, 123.1, 122.5, 118.7, 117.2, 111.0, 82.6, 55.4, 52.1, 39.0, 31.5, 29.9, 18.8. HRMS (ESI) exact mass calculated for $C_{25}H_{26}NO^+([M+H]^+)$: Cal: 356.2009; Found: 356.2006.

Oxazine (5g): According to GP 2: A mixture of Betti base 4i (60 mg, 0.14 mmol), Ag₂O (39



mg, 0.17 mmol) in *m*-xylene (1 mL) was heated at 65 °C for 8 h. The crude product was subjected to SiO₂-column chromatography (EtOAc : hexane, 1 : 50) to afford an inseparable mixture of diastereomers (53 : 47) of oxazine **5g** as a colorless oil (40 mg, 67%). Following analytical data are given for major isomer. HRMS (ESI) exact mass calculated for $C_{30}H_{30}NO^+$ ([M+H]⁺): Cal: 420.2322; Found: 420.2310.

General procedure for the disubstituted secondary amines (GP 3):

Suitable Grignard reagent (1 M in THF, 0.51 mmol) was added dropwise to the oxazine **5** (0.17 mmol) at -3 °C (salt-ice bath) under argon atmosphere. Then the bath temperature was allowed slowly to rise to the room temperature and the mixture was stirred for 2-12 h at that temperature. The reaction was then quenched by adding saturated aq. NH₄Cl solution (2 mL). The mixture was extracted (3 X 4 mL) with EtOAc. The combined organic layers were dried over Na₂SO₄ and concentrated in vacuum. Aq. NaOH (6 M, 0.17 mL), THF (0.34 mL) and methanol (0.34 mL) were added successively to the crude product and the mixture was heated at 80 °C for 8-12 h. After the disappearance of the starting material, the reaction mixture was cooled to room temperature and extracted with ethyl acetate (3 X 4 mL). The combined organic layers were dried over Na₂SO₄, concentrated under vacuum and the crude product was subjected to neutral alumina-column chromatography (DCM : MeOH, 500:1) to afford the disubstituted amine.

1-((2,5-dibenzylpyrrolidin-1-yl)(phenyl)methyl)naphthalen-2-ol (11a): According to GP 1: To the oxazine 5a (0.15 g, 0.38 mmol), benzylmagnesium chloride (1 M in THF, 1.22 mL, 1.22 mmol) was added dropwise at -3 °C and the mixture was stirred for 12 h under argon atmosphere. The crude product was subjected to SiO₂-column chromatography (EtOAc : hexane, 1 : 50 with Et₃N 100 μ L/100 mL) to afford an inseparable

hexane, 1 : 50 with Et₃N 100 μ L/100 mL) to afford an inseparable mixture of diastereomers (58 : 42) of amino naphthol **8a** as whitish solid (0.13 g, 66%). The following analytical data are given for

major isomer. HRMS (ESI) exact mass calculated for C₃₅H₃₄NO⁺ ([M+H]⁺): Cal: 484.2635; Found: 484.2638.

cis-2,5-dibenzylpyrrolidine (6a): According to GP 3: To the oxazine 5a (22 mg, 0.06 mmol),



benzylmagnesium chloride (1 M in THF, 0.20 mL, 0.20 mmol) was added dropwise at -3 °C and the mixture was stirred for 12 h under argon atmosphere. After work up, to a suspension of crude in NaOH (6M, 60 µL), THF (0.12 mL) and MeOH (0.12 mL) were added successively and the reaction mixture was heated at 80 °C for 8 h. Neutral alumina column chromatography (DCM)

to afford the analytically pure compound $6a^7$ as brown oil (11 mg, 77%). FTIR (KBr): $\tilde{\nu} =$ 2923, 2852, 1627, 1602, 1495, 1453, 1269, 1220, 1096, 1029, 747, 700 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) $\delta = 7.29 - 7.25$ (m, 5H), 7.20 - 7.16 (m, 5H), 3.22 - 3.19 (m, 2H), 2.81 - 2.69 (m, 4H), 1.80 - 1.75 (m, 2H), 1.49 - 1.42 (m, 2H). ¹³C NMR (101 MHz, CDCl₃) $\delta = 140.1$, 129.2, 128.6, 126.3, 60.5, 42.9, 30.6. HRMS (ESI) exact mass calculated for C₁₈H₂₂N⁺ ([M+H]⁺): Cal: 252.1747; Found: 252.1753.

cis-2-benzyl-5-isopropylpyrrolidine (6b): According to GP 3: To the oxazine 5c (53 mg,



0.15 mmol), benzylmagnesium chloride (1 M in THF, 0.45 mL, 0.45 mmol) was added dropwise at -3 °C and the mixture was stirred for 3 h under argon atmosphere. After work up, to a suspension of the crude in

NaOH (6M, 0.15 mL), THF (0.30 mL) and MeOH (0.30 mL) were added successively and the reaction mixture was heated at 80 °C for 8 h. Neutral alumina column chromatography (DCM) to afford the analytically pure compound **6b** as brown oil (24 mg, 73%). FTIR (KBr): $\tilde{\nu}$ = 3026, 2958, 2871, 1625, 1602, 1495, 1466, 1453, 1384, 1270, 1086, 815, 746, 699 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) $\delta = 7.31 - 7.27$ (m, 2H), 7.23 - 7.18 (m, 3H), 3.26 - 3.20 (m, 1H), 2.86 - 2.81 (m, 1H), 2.74 - 2.69 (m, 1H), 2.66 - 2.60 (m, 1H), 1.84 - 1.75 (m, 2H), 1.57 - 1.48 (m, 1H), 1.46 - 1.37 (m, 2H), 0.93 (d, J = 6.6 Hz, 3H), 0.87 (d, J = 6.6 Hz, 3H). ¹³C NMR (151) MHz, CDCl₃) $\delta = 140.4$, 129.2, 128.6, 126.2, 65.9, 60.8, 42.8, 34.4, 30.9, 29.2, 20.8, 20.0. HRMS (ESI) exact mass calculated for C₁₄H₂₂N⁺ ([M+H]⁺): Cal: 204. 1747; Found: 204.1757.

cis-2-isopropyl-5-phenylpyrrolidine (6c): According to GP 3: To the oxazine 5c (75 mg, 0.22 mmol), phenylmagnesium bromide (1 M in THF, 0.70 mL, 0.70 mmol) was added dropwise at -3 °C and the mixture was stirred for 5 h under argon atmosphere. After work up, to a suspension of the crude in

NaOH (6M, 0.22 mL), THF (0.44 mL) and MeOH (0.44 mL) were added successively and the

reaction mixture was heated at 80 °C for 16 h. Neutral alumina column chromatography (DCM) to afford the analytically pure compound **6c** as brown oil (27 mg, 65%). FTIR (KBr): $\tilde{\nu} = 3059$, 3027, 2957, 2927, 2869, 1626, 1601, 1515, 1493, 1466, 1450, 1069, 1028, 756, 699 cm⁻¹.¹H NMR (600 MHz, CDCl₃) $\delta = 7.35 - 7.30$ (m, 4H), 7.24 - 7.21 (m, 1H), 4.29 - 4.26 (m, 1H), 3.09 - 3.05 (m, 1H), 2.27 - 2.22 (m, 1H), 2.08 - 2.03 (m, 1H), 1.82 - 1.76 (m, 1H), 1.60 - 1.51 (m, 2H), 0.97 (d, J = 6.6 Hz, 3H), 0.92 (d, J = 6.7 Hz, 3H). ¹³C NMR (151 MHz, CDCl₃) $\delta = 146.0$, 128.7, 127.0, 126.6, 65.8, 62.2, 35.6, 34.5, 31.0, 20.7, 19.7. HRMS (ESI) exact mass calculated for C₁₃H₂₀N⁺ ([M+H]⁺): Cal: 190.1590; Found: 190.1594.

cis-2-isopropyl-5-vinylpyrrolidine (6d): According to GP 3: To the oxazine 5c (116 mg, 0.34 mmol), vinylmagnesium bromide (1 M in THF, 1.0 mL, 1.0 mmol) was added dropwise at -3 °C and the mixture was stirred for 6 h under argon atmosphere. After work up, to a suspension of the crude in NaOH (6M, 0.34 mL), THF (0.68 mL) and MeOH (0.68 mL) were added successively and the reaction mixture was heated at 80 °C for 12 h. Then the reaction mixture was extracted with ethyl acetate (3 X 3 mL). Neutral alumina column chromatography (DCM) to afford an mixture of isomer (77 : 23) of the compound **6d** as brown oil (23 mg, 50%). The following analytical data are given for major isomer. FTIR (KBr): $\tilde{\nu} = 2961$, 2923, 1653, 1637, 1454, 1261, 1017, 813 cm⁻¹. ¹H NMR (600 MHz, CDCl₃) $\delta = 6.04 - 5.99$ (m, 1H), 5.29 (d, J = 17.1 Hz, 1H), 5.17 (d, J = 10.2 Hz, 1H), 4.00 (q, J = 14.9, 7.5 Hz, 1H), 3.19 (q, J = 16.0, 8.4 Hz, 1H), 2.08 – 2.02 (m, 2H), 1.85 – 1.82 (m, 1H), 1.64 – 1.57 (m, 2H), 1.06 (d, J = 6.6 Hz, 3H), 0.95 (d, J = 6.7 Hz, 3H). ¹³C NMR (151 MHz, CDCl₃) $\delta = 139.5$, 114.3, 65.7, 61.7, 32.1, 29.6, 22.9, 20.9, 19.6. HRMS (ESI) exact mass calculated for C₉H₁₈N⁺ ([M+H]⁺): Cal: 140.1434; Found: 140.1434.

cis-2-isopropyl-5-phenethylpyrrolidine (6e) : According to GP 3: To the oxazine 5c (60 mg,



0.17 mmol), phenethylmagnesium chloride (1 M in THF, 0.51 mL, 0.51 mmol) was added dropwise at -3 °C and the mixture was stirred for 12 h under argon atmosphere. After work up, to a suspension of

the crude in NaOH (6M, 0.17 mL), THF (0.34 mL) and MeOH (0.34 mL) were added successively and the reaction mixture was heated at 80 °C for 8 h. Neutral alumina column chromatography (DCM) to afford the analytically pure compound **6e** as brown oil (27 mg, 71%). FTIR (KBr): $\tilde{\nu} = 2956$, 2925, 2855, 1654, 1495, 1453, 1414, 1097, 1030, 746, 698 cm⁻¹. ¹H NMR (600 MHz, CDCl₃) $\delta = 7.28 - 7.26$ (m, 2H), 7.19 - 7.16 (m, 3H), 3.14 (p, J = 6.8 Hz, 1H), 2.84 (q, J = 14.7, 7.9 Hz, 1H), 2.69 - 2.60 (m, 2H), 1.99 - 1.94 (m, 2H), 1.92 - 1.88 (m, 2H), 1.83 - 1.79 (m, 1H), 1.70 - 1.64 (m, 1H), 1.50 - 1.45 (m, 1H), 0.92 (d, J = 6.6 Hz,

3H), 0.86 (d, J = 6.7 Hz, 3H). ¹³C NMR (151 MHz, CDCl₃) $\delta = 142.5$, 128.5, 125.9, 64.7, 58.2, 38.9, 34.3, 33.8, 32.9, 30.4, 20.7, 19.6. HRMS (ESI) exact mass calculated for C₁₅H₂₄N⁺ ([M+H]⁺): Cal: 218.1903; Found: 218.1904.

cis-2-allyl-5-phenylpyrrolidine (6f): According to GP 3: To the oxazine 5b (62 mg, 0.16



mmol), allylmagnesium chloride (1 M in THF, 0.49 mL, 0.49 mmol) was added dropwise at -3 °C and the mixture was stirred for 2 h under argon atmosphere. After work up, to a suspension of the crude in NaOH

(6M, 0.16 mL), THF (0.32 mL) and MeOH (0.32 mL) were added successively and the reaction mixture was heated at 80 °C for 8 h. Neutral alumina column chromatography (DCM) to afford the analytically pure compound **6f**⁸ as brown oil (22 mg, 72%). FTIR (KBr): $\tilde{\nu} = 2961, 2924, 2853, 1640, 1623, 1450, 1013, 1027, 912, 756, 699 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) <math>\delta = 7.39 - 7.37$ (m, 2H), 7.33 - 7.30 (m, 2H), 7.25 - 7.21 (m, 1H), 5.93 - 5.83 (m, 1H), 5.14 - 5.03 (m, 2H), 4.14 (t, J = 8.0 Hz, 1H), 3.30 - 3.23 (m, 1H), 2.34 - 2.30 (m, 2H), 2.20 - 2.11 (m, 1H), 2.01 - 1.92 (m, 1H), 1.76 - 1.66 (m, 1H), 1.60 - 1.51 (m, 1H). HRMS (ESI) exact mass calculated for C₁₃H₁₈N⁺ ([M+H]⁺): Cal:188.1434; Found: 188.1439.

(2S,5R)-2-benzyl-5-phenylpyrrolidine (6g): According to GP 3: To the oxazine 5b (68 mg, 0.18 mmol), benzylmagnesium chloride (1 M in THF, 0.54 mL, 0.54 mmol) was added dropwise at -3 °C and the mixture was stirred for 6 h under argon atmosphere. After work up, to a suspension of the crude in NaOH (6M, 0.18 mL), THF (0.36 mL) and MeOH (0.36 mL) were added successively and the reaction mixture was heated at 80 °C for 12 h. Neutral alumina column chromatography (DCM) to afford the analytically pure compound 6g as brown oil (33 mg, 79%). FTIR (KBr): $\tilde{v} = 2961, 2923, 2852, 1652, 1639, 1495, 1453, 1079, 906, 770, 701 cm⁻¹. ¹H NMR (400 MHz,$ $CDCl₃) <math>\delta = 7.27 - 7.25$ (m, 5H), 7.15 - 7.13 (m, 3H), 6.77 - 6.75 (m, 2H), 3.15 - 3.09 (m, 1H), 2.99 - 2.96 (m, 1H), 2.10 - 2.03 (m, 2H), 1.84 - 1.71 (m, 4H). ¹³C NMR (101 MHz, CDCl₃) δ = 137.8 (2C), 130.5, 128.1, 127.9, 126.6, 126.4, 126.4, 68.9, 48.0, 45.0, 37.5, 24.5. HRMS (ESI) exact mass calculated for C₁₇H₂₀N⁺ ([M+H]⁺): Cal: 238.1590; Found: 238.1590.

cis-2,6-dibenzylpiperidine (6h): According to GP 1: To the oxazine 5d (25 mg, 62 μmol), benzylmagnesium chloride (1 M in THF, 0.4 mL, 0.4 mmol) was added dropwise at -3 °C and the mixture was stirred for 12 h under argon atmosphere. The crude product was subjected to neutral

alumina column chromatography (EtOAc : hexane, 1 : 30) to afford **6h**⁹ as brown oil (15 mg,

91%). FTIR (KBr): $\tilde{\nu} = 3029, 2925, 2853, 1494, 1453, 1089, 1056, 1030, 747,702 \text{ cm}^{-1}$. ¹H NMR (400 MHz, CDCl₃) $\delta = 7.23 - 7.20$ (m, 4H), 7.16 - 7.15 (m, 2H), 7.12 - 7.10 (m, 4H), 2.70 - 2.66 (m, 2H), 2.63 - 2.53 (m, 4H), 1.80 - 1.77 (m, 1H), 1.66 - 1.63 (m, 2H), 1.22 - 1.13 (m, 3H). ¹³C NMR (101 MHz, CDCl₃) $\delta = 139.1, 129.3, 128.5, 126.3, 58.6, 43.8, 32.5, 24.8$. HRMS (ESI) exact mass calculated for C₁₉H₂₄N⁺ ([M+H]⁺): Cal: 266.1903; Found: 266.1893.

cis-2,7-dibenzylazepane (6i): According to GP 1: To the oxazine 5g (28 mg, 66 µmol),



benzylmagnesium chloride (1 M in THF, 0.2 mL, 0.2 mmol) was added dropwise at -3 °C and the mixture was stirred for 1 h under argon atmosphere. The crude product was subjected to neutral

alumina column chromatography (EtOAc : hexane, 1 : 30) to afford **6i** as light yellow oil (18 mg, 98%). FTIR (KBr): $\tilde{\nu} = 3064$, 3019, 2915, 2854, 1627, 1602, 1495, 1454, 1261, 1079, 1021, 805,743, 698 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) $\delta = 7.12 - 7.09$ (m, 6H), 6.96 - 6.94 (m, 4H), 2.77 - 2.72 (m, 2H), 2.68 - 2.64 (m, 2H), 2.43 - 2.38 (m, 2H), 1.78 - 1.64 (m, 6H), 1.48 - 1.41 (m, 2H). ¹³C NMR (101 MHz, CDCl₃) $\delta = 139.3$, 128.9, 128.6, 126.3, 60.8, 44.1, 37.4, 25.4. HRMS (ESI) exact mass calculated for C₂₀H₂₆N⁺ ([M+H]⁺): Cal: 280.2060; Found: 280.2058.

1-((2-phenethylpyrrolidin-1-yl)(phenyl)methyl)naphthalen-2-ol (14a): According to GP 1:



To the oxazine **2a** (0.60 g, 1.99 mmol), phenethylmagnesium chloride (1 M in THF, 4.4 mL, 4.40 mmol) was added dropwise at -3 °C and the mixture was stirred for 2 h under argon atmosphere. The crude product was subjected to neutral alumina column chromatography (EtOAc : hexane, 1 : 40) to afford diastereomeric mixture (90 : 10) of amino naphthol **14a** as colorless oil (0.72 g, 89%). Following analytical data are given for major isomer. ¹H NMR (600 MHz, CDCl₃) δ = 14.27 (s, 1H), 7.78 – 7.77 (m, 1H), 7.67 – 7.64 (m, 2H),

7.58 – 7.57 (m, 2H), 7.33 – 7.31 (m, 1H), 7.22 – 7.09 (m, 8H), 6.81 – 6.80 (m, 2H), 5.32 (s, 1H), 3.18 (br. s, 1H), 3.03 (br. s, 1H), 2.59 – 2.55 (m, 1H), 2.39 – 2.35 (m, 1H), 2.21 – 2.18 (m, 1H), 2.07– 2.00 (m, 1H), 1.82 – 1.78 (m, 2H), 1.66 – 1.64 (m, 1H), 1.42 – 1.24 (m, 2H). ¹³C NMR (101 MHz, CDCl₃) δ = 156.0, 141.6, 140.3, 131.9, 129.7 (2C), 129.0, 128.8 (2C), 128.7, 128.3 (2C), 126.5, 125.78, 122.5, 121.1, 120.2, 117.0, 70.6, 60.8, 55.5, 37.5, 32.9, 30.6, 23.6. HRMS (ESI) exact mass calculated for C₂₉H₃₀NO⁺ ([M+H]⁺): Cal: 408.2322; Found: 408.2321.

10-phenethyl-12-phenyl-8,9,10,12-tetrahydro-7aH-naphtho[1,2-e]pyrrolo[2,1-



b][1,3]oxazine (15a): According to GP 2: A mixture of Betti base 14a (75 mg, 0.18 mmol) and Ag₂O (51 mg, 0.22 mmol) in *m*-xylene (1 mL) was heated at 80 °C for 16 h. The crude product was subjected to SiO₂-column chromatography (EtOAc : hexane, 1 : 50) to afford an inseparable mixture of diastereomers (62 : 38) of oxazine 15a as colorless oil (65 mg, 87%). Following analytical data are given for major isomer. HRMS (ESI) exact mass calculated for $C_{29}H_{28}NO^+([M+H]^+)$: Cal: 406.2165; Found: 406.2168.

cis-2,5-diphenethylpyrrolidine (16a): According to GP 1: To the oxazine 15a (47 mg, 0.12



mmol), phenethylmagnesium chloride (1 M in THF, 0.35 mL, 0.35 mmol) was added dropwise at -3 °C and the mixture was stirred for 12 h under argon atmosphere. The

crude product was subjected to neutral alumina column chromatography (DCM : MeOH, 150 : 1) to afford **16a** as brown oil (23 mg, 73%). FTIR (KBr): $\tilde{\nu} = 3450$, 3026, 2924, 2853, 1640, 1626, 1602, 1495, 1454, 1236, 1030, 909, 746, 698 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) $\delta = 7.29 - 7.25$ (m, 4H), 7.19 – 7.17 (m, 6H), 3.01 – 2.98 (m, 2H), 2.69 – 2.64 (m, 4H), 2.07 – 1.98 (m, 2H), 1.92 – 1.84 (m, 4H), 1.82 – 1.72 (m, 2H). ¹³C NMR (101 MHz, CDCl₃) $\delta = 142.3$, 128.5, 126.0, 59.0, 38.3, 33.9, 31.3. HRMS (ESI) exact mass calculated for C₂₀H₂₆N⁺ ([M+H]⁺): Cal: 280.2060; Found: 280.2058.

1-((2-phenethylpiperidin-1-yl)(phenyl)methyl)naphthalen-2-ol (14b): According to GP 1:



To the oxazine **2b** (0.50 g, 1.58 mmol), phenethylmagnesium chlroide (1 M in THF, 4.5 mL, 4.5 mmol) was added dropwise at -3 °C and the mixture was stirred for 1 h under argon atmosphere. The crude product was subjected to neutral alumina column chromatography (EtOAc : hexane, 1 : 70) to afford an inseparable mixture of diastereomers (67 : 33) of amino naphthol **14b** as white solid (0.59 g, 90%). HRMS (ESI) exact mass calculated for $C_{30}H_{32}NO^+$

([M+H]⁺): Cal: 422.2478; Found: 422.2479.

11-phenethyl-13-phenyl-7a,8,9,10,11,13-hexahydronaphtho[1,2-e]pyrido[2,1-



b][1,3]oxazine (15b): According to GP 2: A mixture of Betti base 14b (0.47 g, 1.11 mmol) and Ag₂O (0.35 g, 1.5 mmol) in *m*-xylene (4 mL) was heated at 110 °C for 12 h. The crude product was subjected to neutral alumina column chromatography (EtOAc : hexane, 1 : 50) to afford oxazine 15b as light green oil (0.22 g, 46%). ¹H NMR (400 MHz, CDCl₃) δ = 7.78 – 7.76 (m, 1H), 7.73 (d, *J* = 8.8 Hz, 1H), 7.39 – 7.37 (m, 1H), 7.29 – 7.19 (m, 9H), 7.15 – 7.10 (m, 4H), 5.80 (s, 1H), 4.99 (br. s, 1H), 2.92 – 2.84 (m, 2H), 2.67

-2.52 (m, 1H), 2.09 - 2.02 (m, 1H), 1.93 (m, 3H), 1.87 - 1.82 (m, 1H), 1.65 - 1.55 (m, 3H). 13 C NMR (101 MHz, CDCl₃) $\delta = 152.9$, 143.5, 142.7, 133.0, 129.5, 129.2, 128.9, 128.8, 128.6, 128.4, 128.3, 127.2, 126.9, 126.0, 123.1, 122.5, 118.7, 110.9, 82.5, 55.4, 52.7, 36.7, 31.3 (2C), 30.0, 18.8. HRMS (ESI) exact mass calculated for C₃₀H₃₀NO⁺ ([M+H]⁺): Cal: 420.2322; Found: 420.2322.

cis-2,6-diphenethylpiperidine (16b): According to GP 1: To the oxazine 15b (60 mg, 0.14



mmol), phenethylmagnesium chloride (1 M in THF, 0.72 mL, 0.72 mmol) was added dropwise at -3 °C and the mixture was stirred for 18 h under argon atmosphere. The

crude product was subjected to neutral alumina column chromatography (eluting with DCM) to afford **16b**¹⁰ as brown oil (19 mg, 45%). FTIR (KBr): $\tilde{\nu} = 3442$, 3025, 2924, 2853, 1625, 1602, 1495, 1453, 1030, 747, 698 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) $\delta = 7.29 - 7.25$ (m, 5H), 7.19 - 7.16 (m, 5H), 2.62 (t, *J* = 7.9 Hz, 4H), 2.54 - 2.48 (m, 2H), 1.78 - 1.68 (m, 6H), 1.41 - 1.33 (m, 1H), 1.16 - 1.08 (m, 3H). ¹³C NMR (101 MHz, CDCl₃) $\delta = 142.3$, 128.6, 128.5, 126.0, 56.9, 38.8, 32.6, 32.4, 24.8. HRMS (ESI) exact mass calculated for C₂₁H₂₈N⁺ ([M+H]⁺): Cal: 294.2216; Found: 294.2216.

Amino naphthol (14c): According to GP 1: To the oxazine 2c (0.60 g, 1.82 mmol), phenethylmagnesium chlroide (1 M in THF, 4.0 mL, 4.0 mmol) was added dropwise at -3 °C and the mixture was stirred for 1 h under argon atmosphere. The crude product was subjected to SiO₂-column chromatography (EtOAc : hexane, 1 : 50) to afford an inseparable mixture of diastereomers (62 : 38) of amino naphthol **14c** as brown oil (0.75 g, 95%).

HRMS (ESI) exact mass calculated for $C_{31}H_{34}NO^+$ ([M+H]⁺): Cal: 436.2636; Found: 436.2638.

Oxazine (15c): According to GP 2: A mixture of Betti base 14c (0.26 g, 0.59 mmol) and Ag₂O



(0.17 g, 0.72 mmol) in *m*-xylene (0.5 mL) was heated at 80 °C for 12 h. The crude product was subjected to neutral alumina column chromatography (EtOAc : hexane, 1 : 50) to afford an inseparable mixture of diastereomers (50 : 50) of oxazine **15c** as a colorless oil (0.17 g, 68%). HRMS (ESI) exact mass calculated for $C_{31}H_{32}NO^+$ ([M+H]⁺): Cal: 434.2478; Found: 434.2464.

cis-2,7-diphenethylazepane (16c): According to GP 1: To the oxazine 15c (24 mg, 54 µmol) phenethylmagnesium chloride (1 M in THF, 0.20 mL, 0.20 mmol) was added dropwise at -3 °C and the mixture was stirred for 2 h under argon atmosphere. The crude product was subjected to neutral alumina column chromatography

(eluting with DCM) to afford **16c** as brown oil (15 mg, 90%). FTIR (KBr): $\tilde{\nu} = 3441, 2924, 2853, 1653, 1639, 1495, 1453, 1260, 1078, 1030, 747, 698 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) <math>\delta = 7.30 - 7.25$ (m, 5H), 7.20 - 7.16 (m, 5H), 2.87 - 2.79 (m, 1H), 2.75 - 2.64 (m, 3H), 2.63 - 2.55 (m, 2H), 1.89 - 1.85 (m, 1H), 1.81 - 1.52 (m, 11H). ¹³C NMR (101 MHz, CDCl₃) $\delta = 142.5, 128.6, 126.0, 58.8, 39.9, 37.4, 33.3, 25.5$. HRMS (ESI) exact mass calculated for C₂₂H₃₀N⁺ ([M+H]⁺): Cal: 308.2373; Found: 308.2364.

Crystallographic data

Crystal data and structure refinement for 4b (CCDC 1499395)

Empirical formula	C ₂₇ H ₂₅ N O
Formula weight	379.48
Crystal habit, colour	needle / yellowish
Crystal size, mm ³	0.27 X 0.25 X 0.20 mm
Temperature, T	293(2) K
Wavelength, $\lambda(\text{\AA})$	0.71073

Crystal system	orthorhombic
Space group	'Pna21'
Unit cell dimensions	a = 13.4796(7) Å
	b = 23.9065(12) Å
	c = 6.3744(3) Å
	$\alpha = 90.00^{\circ}, \gamma = 90.00^{\circ}, \beta = 90.00^{\circ}$
Volume, $V(Å^3)$	2054.15(18)
Ζ	4
Calculated density, Mg·m ⁻³	1.227
Absorption coefficient, $\mu(mm^{-1})$	0.074
F(000)	808
θ range for data collection	2.97° to 24.99°
Limiting indices	$-16 \le h \le 7, -28 \le k \le 25, -7 \le l \le 7$
Reflection collected / unique	5614/2523 [R(int) = 0.0215]
Completeness to θ	99.8% ($\theta = 24.99^{\circ}$)
Refinement method	'SHELXL-97 (Sheldrick, 1997)'
Data / restraints / parameters	2523/ 0 /263
Goodness–of–fit on F^2	1.127
Final <i>R</i> indices [<i>I</i> >2sigma(<i>I</i>)]	R1 = 0.0463, wR2 = 0.0771
<i>R</i> indices (all data)	R1 = 0.0592, wR2 = 0.0825
Largest diff. peak and hole	$0.180 \text{ and } -0.162 \text{e} \cdot \text{\AA}^{-3}$

Crystal data and structure refinement for **4k** (CCDC 952461)

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Empirical formula	C ₂₇ H ₂₅ N O ₂
Formula weight	395.48
Crystal habit, colour	needle / yellowish
Crystal size, mm ³	0.32 X 0.30 X 0.26 mm
Temperature, T	293(2) K
Wavelength, $\lambda(\text{\AA})$	0.71073
Crystal system	monoclinic

Space group	'C2/ c'
Unit cell dimensions	a = 26.2548(11)Å
	b = 9.6138(6)Å
	c = 17.4876(7)Å
	$\alpha = 90.00^{\circ}, \gamma = 90.00^{\circ}, \beta = 103.593(4)^{\circ}$
Volume, $V(Å^3)$	4290.4(3)
Ζ	8
Calculated density, Mg·m ⁻³	1.225
Absorption coefficient, $\mu(\text{mm}^{-1})$	0.077
<i>F</i> (000)	1680
θ range for data collection	3.16° to 25.00°
Limiting indices	$-31 \le h \le 29, -11 \le k \le 8, -20 \le l \le 18$
Reflection collected / unique	8463 / 2701 [<i>R</i> (int) = 0.0296]
Refinement method	'SHELXL-97 (Sheldrick, 1997)'
Data / restraints / parameters	2701 / 0 / 272
Goodness–of–fit on F^2	1.079
Final <i>R</i> indices [<i>I</i> >2sigma(<i>I</i>)]	R1 = 0.0530, wR2 = 0.1118
<i>R</i> indices (all data)	R1 = 0.0782, wR2 = 0.1267
Largest diff. peak and hole	0.190 and -0.171e·Å ⁻³

Crystal data and structure refinement for **5c** (CCDC 1506220)

Empirical formula	C ₂₄ H ₂₅ N O
Formula weight	343.45
Crystal habit, colour	needle / yellowish
Crystal size, mm ³	0.32 X 0.24 X 0.12
Temperature, T	293(2) K
Wavelength, $\lambda(\text{\AA})$	0.71073
Crystal system	monoclinic
Space group	'P 21/c'

Unit cell dimensions	a = 9.8047(15)Å
	b = 11.9575(13)Å
	c = 16.3809(17)Å
	$\alpha = 90.00^{\circ}, \gamma = 90.00^{\circ}, \beta = 97.122(8)^{\circ}$
Volume, $V(Å^3)$	1905.7(4)
Ζ	4
Calculated density, $Mg \cdot m^{-3}$	1.197
Absorption coefficient, $\mu(\text{mm}^{-1})$	0.072
<i>F</i> (000)	736
θ range for data collection	2.11° to 25.05°
Limiting indices	$-11 \le h \le 11, -13 \le k \le 14, -19 \le l \le 18$
Reflection collected / unique	13044 / 1750 [R(int) = 0.1741]
Completeness to θ	99.7% ($\theta = 25.05^{\circ}$)
Refinement method	'SHELXL-97 (Sheldrick, 1997)'
Data / restraints / parameters	1750 / 0 / 237
Goodness–of–fit on F^2	1.057
Final <i>R</i> indices [<i>I</i> >2sigma(<i>I</i>)]	R1 = 0.0761, wR2 = 0.1392
<i>R</i> indices (all data)	R1 = 0.1900, wR2 = 0.1791
Largest diff. peak and hole	$0.165 \text{ and } -0.215 e \cdot \text{\AA}^{-3}$

Crystal data and structure refinement for **5d** (CCDC 1507198)

Ad	AT A
Empirical formula	C ₂₉ H ₂₇ N O
Formula weight	405.52
Crystal habit, colour	needle / colorless
Crystal size, mm ³	0.36 X 0.30 X 0.26 mm
Temperature, T	293(2) K
Wavelength, $\lambda(A)$	0.71073

Crystal system	Monoclinic
Space group	'P21/c'
Unit cell dimensions	a = 7.9410(4) Å
	b = 32.3062(15) Å
	c = 17.2176(8) Å
	$\alpha = 90.00^{\circ}, \gamma = 90.00^{\circ}, \beta = 95.624(5)^{\circ}$
Volume, $V(Å^3)$	4395.8(4)
Ζ	8
Calculated density, Mg·m ⁻³	1.225
Absorption coefficient, $\mu(\text{mm}^{-1})$	0.073
<i>F</i> (000)	1728.0
θ range for data collection	2.87° to 25.00°
Limiting indices	$-9 \le h \le 5, -38 \le k \le 38, -20 \le l \le 19$
Reflection collected / unique	17711/4906 [R(int) = 0.0543]
Completeness to θ	99.8% ($\theta = 25.00^{\circ}$)
Refinement method	'SHELXL-97 (Sheldrick, 1997)'
Data / restraints / parameters	4906/ 0 /559
Goodness–of–fit on F^2	1.042
Final <i>R</i> indices [<i>I</i> >2sigma(<i>I</i>)]	R1 = 0.0617, wR2 = 0.1393
<i>R</i> indices (all data)	R1 = 0.1007, wR2 = 0.1658
Largest diff. peak and hole	$0.196 \text{ and } -0.183 \text{e} \cdot \text{\AA}^{-3}$

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