Electronic Supplementary Information

for

Unprecedented copper-catalyzed asymmetric conjugate addition of organometallic reagents to a,b-unsaturated lactams.

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General Methods. All reactions were conducted in flame dried glassware with magnetic stirring under an atmosphere of argon. Toluene and THF were distilled from sodium/benzophenone ketyl and stored under argon. Analytical TLC were performed on Alugram SIL G/UV254 silica gel sheets (Macherey-Nagel) with detection by 0.5% phosphomolybdic acid solution in 95% EtOH. Silica gel 60 (Macherey-Nagel 230-400 mesh) was used for flash chromatography. Solvents for extraction and chromatography were HPLC grade.

^{1}H NMR spectra were recorded on a Bruker AC-200 spectrometer. Chemical shifts are reported in ppm downfield from tetramethylsilane with the solvent resonance as the internal standard (deuterochloroform: δ **7.26**). ^{13}C NMR spectra were recorded on a Bruker AC-200 (50 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm downfield from tetramethylsilane with the solvent resonance as the internal standard (deuterochloroform: δ **77.7**). Analytical high performance liquid chromatography (HPLC) was performed on a Waters 600E equipped with a Varian Prostar 325 detector using Daicel Chiralcel OD-H or OB-H columns with a 0.5 mL solvent flow and detection at 254 nm.

Mass spectra ESIMS were measured on a Finnigan LC-Q Deca Termoquest spectrometer, equipped with a software Xcalibur.

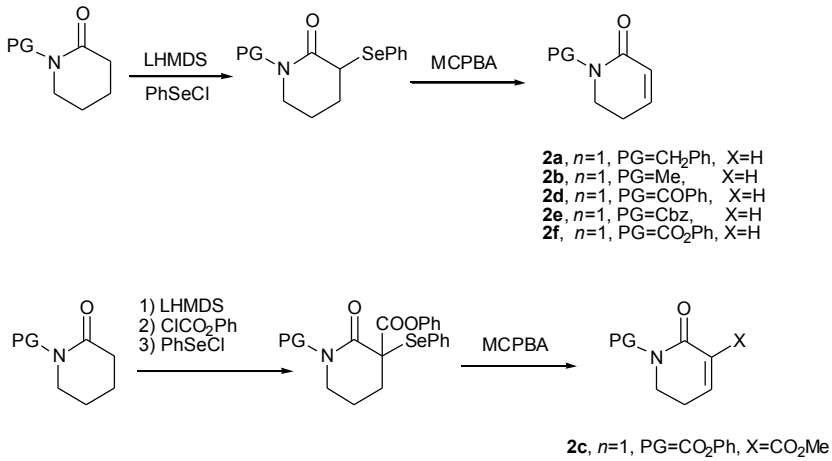
Elemental analyses were performed in our analytical laboratory with a Carlo Erba DP200 instrumentation and agreed with the theoretical values to within +/-0.4%.

High resolution mass spectra (HRMS) were recorded on a AEI MS-902.

Absolute configurations were assigned on the basis of the facial selectivity observed with the same chiral catalysts with enones.[1]

Synthesis of 5,6-dihydro-2(1*H*)-pyridones 2a-f used as substrates.

New compounds **2a-f** were prepared from the corresponding protected δ-valerolactams following established procedures (Scheme 1).[2a]



Scheme 1

***N*-Benzyl-5,6-dihydro-2(1*H*)-pyridone (2a).**

Colorless liquid.

^{1}H NMR ($CDCl_3$) δ 7.19-7.26 (m, 5H), 6.42-6.48 (m, 1H), 5.86-5.91 (d, 1H, *J*=9.8 Hz), 4.52 (s, 2H), 3.19 (t, 2H, *J*=7.1 Hz), 2.16-2.21 (m, 2H).

^{13}C NMR ($CDCl_3$) δ 164.8, 137.8, 128.9, 128.3, 127.7, 125.6, 49.9, 44.9, 24.5.

HRMS calc. for $C_{12}H_{13}ON$ 187.100, found 187.100.

***N*-Methyl-5,6-dihydro-2(1*H*)-pyridone (2b).**

Colorless liquid.

^{1}H NMR ($CDCl_3$) δ 6.42 (m, 1H), 5.84 (m, 1H), 3.34 (dt, 2H, *J*=6.0, 1.0 Hz), 2.90 (d, 3H, *J*=1.7 Hz), 2.33 (m, 2H).

^{13}C NMR ($CDCl_3$) δ 165.5, 139.7, 125.8, 48.0, 35.0, 24.5.

HRMS calc. for C_6H_9ON 111.068, found 111.068.

***N*-Phenoxycarbonyl-3-carbomethoxy-5,6-dihydro-2(1*H*)-pyridone (2c)**.

Solid. M.p. 86-88°C (recrystallized from hexanes containing 20% of AcOEt).

^{1}H NMR ($CDCl_3$) δ 7.11-7.60 (m, 6H), 3.98 (t, 2H, *J*=6.4 Hz), 3.79 (s, 3H), 1.99-2.52 (m, 2H).

^{13}C NMR ($CDCl_3$) δ 164.7, 160.3, 153.3, 151.3, 151.0, 130.5, 129.9, 126.7, 121.9, 53.0, 44.3, 25.3.

Anal. Calcd. for $C_{14}H_{13}NO_5$: C, 61.09; H, 4.76; N, 5.09. Found: C 60.90, H, 4.70, N, 5.28.

***N*-Benzoyl-5,6-dihydro-2(1*H*)-pyridone (2d).**

Solid. M.p. 83-85°C.

^{1}H NMR ($CDCl_3$) δ 7.37-7.59 (m, 5H), 6.92-7.02 (dt, 1H, *J* = 9.7, 4.3 Hz), 5.99 (dt, 1H, *J*= 9.7, 1.8 Hz) 3.99 (t, 2H, *J*= 6.6 Hz), 2.04-2.53 (m, 2H).

^{13}C NMR ($CDCl_3$) δ 173.8, 165.5, 145.4, 136.1, 131.6, 128.2, 128.0, 125.3, 43.3, 24.9.

Anal. Calcd. for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51; N, 6.96. Found: C 71.71, H, 5.48, N, 6.97.

***N*-Benzyloxycarbonyl-5,6-dihydro-2(1*H*)-pyridone (2e).**

Light yellow liquid.

^{1}H NMR ($CDCl_3$) δ 7.21-7.37 (m, 5H), 6.64-6.71 (dt, 1H, *J*= 9.7, 4.8 Hz), 5.85 (d, 1H, *J*= 9.7 Hz), 5.19 (s, 2H), 3.80 (t, 2H, *J*= 6.4 Hz), 2.23-2.34 (m, 2H).

^{13}C NMR ($CDCl_3$) δ 163.5, 154.1, 144.6, 135.8, 128.8, 128.8, 128.1, 125.9, 68.6, 44.1, 24.8.

HRMS calc. for $C_{13}H_{13}ON_3$ 231.090, found 231.090.

***N*-Phenoxycarbonyl -5,6-dihydro-2(1*H*)-pyridone (2f).**

Solid. M.p. 107°C.

^{1}H NMR ($CDCl_3$) δ 7.04-7.16 (m, 5H), 6.81-6.90 (m, 1 H), 5.99-6.05 (m, 1H), 4.02 (t, 2H, *J*=6.4 Hz), 2.43-2.52 (m, 2H).

^{13}C NMR δ 163.8, 153.4, 151.3, 145.4, 129.9, 126.6, 126.3, 122.1, 44.7, 25.2.

Anal. Calcd. for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.45. Found: C 66.14, H, 5.02, N, 6.34.

***N*-Boc-dihydropyrrol-2-one (3)** was prepared in accordance with a previously reported procedure.[3]

General Procedure for the copper-phosphoramidite asymmetric conjugate alkylation of* a,b*-unsaturated lactams with organometallic reagents:

A solution of $Cu(OTf)_2$ (2.5 mg, 0.0069 mmol) and (*R,S,S*)-**1** (7.5 mg, 0.00138 mmol) in anhydrous toluene (1 ml) was stirred at room temperature for 40 min. The colorless solution was initially cooled to -78°C and subsequently additioned with a solution of the lactam (0.46 mmol) in the minimal amount of toluene (or CH_2Cl_2 for **2f**) and of R_2Zn (0.69 mmol) or R_3Al (0.92 mmol). The reaction was followed by TLC analysis, quenched with saturated aqueous NH_4Cl and extracted several times with Et_2O.

Reactions with dialkylzinc reagents (R_2Zn).

***N*-Benzyl-4-ethyl-2-piperidinone (4).**[4]

With lactam **2a** useful conversions can only be obtained by the use of THF as the reaction solvent. A solution of $Cu(OTf)_2$ (2.7 mg, 0.0075 mmol) and (*R,S,S*)-**1** (8.0 mg, 0.0015 mmol) in anhydrous THF (0.8 ml) was stirred at room temperature for 40 min. The colorless solution was cooled to 0°C and subsequently additioned with a solution of the lactam **2a** (93.5 mg, 0.50 mmol) in THF (0.5 mL) and 1.14 mL of Et_2Zn (1.25 mmol, 2.5 equiv). After 12 at r.t., usual workup afforded a crude mixture (114 mg) which was purified by flash chromatography (hexanes containing 40% AcOEt as the eluant) to give pure **4** (47 mg, 43% yield), as a liquid.

^{1}H NMR ($CDCl_3$) δ 7.24-7.27 (m, 5H), 4.68 (AB q, 1H, *J*=14.6 Hz), 4.48 (d, 1H, *J*=14.6 Hz), 3.17-3.19 (m, 2H), 2.50-2.57 (m, 2H), 1.35-2.12 (m, 5H), 0.90 (t, 3H, *J*=7.2 Hz).

^{13}C NMR ($CDCl_3$) δ 169.4, 137.9, 129.1, 128.6, 127.9, 50.5, 47.0, 39.2, 35.3, 29.3, 28.9, 11.7.

HRMS calc. for $C_{14}H_{19}NO$ 217.147, found 217.147.

***trans*-*N*-Phenoxycarbonyl-2-carbomethoxy-4-ethyl-2-piperidinone (5).** Following the general procedure, a solution of lactam **2c** (137.5 mg, 0.5 mmol) in CH_2Cl_2 (0.4 mL), was added to a solution of $Cu(OTf)_2$ (2.7 mg, 0.0075 mmol) and ligand (*R,S,S*)-**1** (8.1 mg, 0.015 mmol) in 0.8 mL of toluene. The obtained solution was cooled to –

78°C and Et_2Zn (0.75 mmol, 0.680 mL of a 1.1 M solution in toluene) was added. After 1h at −78°C the usual workup afforded a crude reaction mixture (132 mg) constituted by a ca. 9/1 mixture of *cis* and *trans* isomer of **5** which was not further purified.

Spectral data for *trans*-**5**: ^{1}H NMR ($CDCl_3$) δ 7.10-7.53 (m, 5H), 4.06 (dt, 1H, *J*=13.0, 4.9 Hz), 3.75-3.94 (m, 1H), 3.86 (s, 3H), 3.40 (d, 1H, *J*=9.8 Hz), 1.88-2.46 (m, 2H), 1.30-1.78 (m, 3H), 1.03 (t, 3H, *J*=7.4 Hz).

^{13}C NMR ($CDCl_3$) δ 170.5, 168.2, 153.3, 151.1, 130.0, 126.7, 121.9, 58.5, 53.2, 46.1, 38.0, 27.7, 26.9, 11.1.

A very similar reactivity can be obtained by the use of the same reaction condition without the use of phosphoramidite chiral ligand **1**.

Enantiomer separation was obtained by chiral HPLC (Daicel OB-H) eluting with hexanes/isopropanol 85/15. Retention times: 32.6 min and 38.4 min.

(4*R*)-*N*-Benzoyl-4-ethyl-2-piperidinone (6).

Following the general procedure, a solution of lactam **2d** (100 mg, 0.5 mmol) in toluene (0.5 mL), was added to a solution of $Cu(OTf)_2$ (2.7 mg, 0.0075 mmol) and ligand (*R,S,S*)-**1** (8.1 mg, 0.015 mmol) in 1.0 mL of toluene. The obtained solution was cooled to −78°C and Et_2Zn (0.75 mmol, 0.68 mL of a 1.1 M solution in toluene) was added. After 4h at 0°C (83% conversion) the usual workup afforded a crude reaction mixture (110 mg) which was subjected to flash chromatography (hexanes/AcOEt= 7/3, R_f=0.40) to give 58 mg of pure **6** (50% yield), as a white solid. M.p. 53-55°C. $[\alpha]_D^{20}$=+9.8 (c=1.0, MeOH).

^{1}H NMR ($CDCl_3$) δ 7.18-7.68 (m, 5H), 3.92-4.03 (m, 1H), 3.57-3.71 (m, 1H), 2.51-2.67 (m, 1H), 1.35-2.31 (m, 6H), 0.95 (t, 3H, *J*= 7.23 Hz).

^{13}C NMR δ 175.2, 174.0, 136.7, 132.1, 128.7, 128.5, 45.9, 41.5, 35.8, 29.2, 11.7.

Anal. Calcd. for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C 72.57, H, 7.31, N, 5.78.

Enantiomeric excess (26%) was determined by chiral HPLC (OD-H) (hexanes/isopropanol:9/1): t_R 27.9 (minor), t_R 25.8 (major).

(4*R*)-*N*-Benzyloxycarbonyl-4-ethyl-2-piperidinone (7).

Following the general procedure, a solution of lactam **2d** (100 mg, 0.46 mmol) in toluene (0.5 mL), was added to a solution of $Cu(OTf)_2$ (2.5 mg, 0.0069 mmol) and ligand (*R,S,S*)-**1** (7.5 mg, 0.0138 mmol) in 1.0 mL of toluene. The obtained solution was cooled to –78°C and Et_2Zn (0.69 mmol, 0.626 mL of a 1.1 M solution in toluene) was added. After 2h at 0° C (complete conversion) the usual workup afforded a crude reaction mixture which was subjected to flash chromatography (hexanes/AcOEt= 1/1) to give 80 mg of pure **7** (70% yield), as a light yellow liquid.

$[\alpha]_D^{20}$=+16.2 (c=1.5, MeOH).

^{1}H NMR ($CDCl_3$) δ 7.19-7.34 (m, 5H, aromatici), 5.22 (s, 2H), 3.76-3.87 (dt, 1H, *J*=12.8 Hz, 4.5 Hz), 3.41-3.55 (dt, 1H, *J*= 10 Hz, 4.4 Hz), 2.53-2.64 (dd, 1H, *J*= 16.8 Hz, 3.8 Hz), 2.06 (dd, 1H, *J*= 16.8 Hz, 10.5 Hz), 1.58-1.96 (m, 3H), 0.85 (t, 3H, *J*= 7.32).

^{13}C NMR ($CDCl_3$) δ 171.62, 154.7, 136.12, 129.17, 128.86, 128.65, 107.59, 69.02, 46.35, 41.67, 34.69, 29.14, 11.61.

Anal. Calcd. for $C_{15}H_{19}NO_3$: C, 68,94; H, 7,33; N, 5,36. Found: C, 68.88, H, 7.14, N, 5. 40.

Enantiomeric excess (75%) was determined by chiral HPLC (OD-H) (hexanes/isopropanol:97/3): t_R 39.5 (major), t_R 42.5 (minor).

(4*R*)-*N*-Phenoxycarbonyl-4-ethyl-2-piperidinone (8a).

Following the general procedure, lactam **2f** (100 mg, 0.46 mmol), previously dissolved in 0.3 ml of CH_2Cl_2, was added to a solution of $Cu(OTf)_2$ (2.5 mg, 0.0069 mmol) and ligand (*R,S,S*)-**1** (7.5 mg, 0.0138 mmol) in 1.0 mL of toluene. The obtained solution was cooled to –78°C and Et_2Zn (0.69 mmol, 0.626 mL of a 1.1 M solution in toluene) was added. After 2h at –50°C (complete conversion) the usual workup afforded a crude reaction mixture (110 mg) which was subjected to flash chromatography (hexanes/AcOEt= 1/1, R_f=0.52) to give 74 mg of pure **8a** (65% yield), as a solid. $[\alpha]_D^{20}$=+2.7 (c=0.5, MeOH).

^{1}H NMR ($CDCl_3$) δ 7.00-7.35 (m, 5H), 3.93 (dt, 1H, *J*= 13.0, 4.6 Hz), 3.60 (ddd, 1H, *J*= 13.0, 10.8, 4.4 Hz), 2.65 (ddd, 1H, *J*= 16.8, 5.3, 1.9 Hz), 2.15 (dd, 1H, *J*= 16.8, 10.5 Hz), 1.2-1.85 (m, 5H), 0.87 (t, 3H, *J*= 7.2 Hz).

^{13}CNMR ($CDCl_3$) δ 171.8, 153.5, 151.3, 129.9, 126.6, 122.1, 46.7, 41.7, 34.8, 29.1, 11.6.

Anal. Calcd. for $C_{14}H_{17}NO_3$: C, 68,00; H, 6,93; N, 5,66. Found: C, 68.09, H, 6.88, N, 5. 70.

Enantiomeric excess (95.3%) was determined by chiral HPLC (OB-H) (heptane/isopropanol:9/1): t_R 58.8 (minor), t_R 60.3 (major).

(4*R*)-*N*-Phenoxycarbonyl-4-butyl-2-piperidinone (8b).

Following the general procedure, lactam **2f** (54.75 mg, 0.25 mmol), previously dissolved in 0.2 ml of CH_2Cl_2, was added to a solution of $Cu(OTf)_2$ (1.3 mg, 0.0039 mmol) and ligand (*R,S,S*)-**1** (4.0 mg, 0.0075 mmol) in 0.5 mL of toluene. The obtained solution was cooled to –78°C and Bu_2Zn (0.375 mmol, 0.375 ml of a solution 1 M in heptane) was added. After 4 h at 0°C the usual work-up afforded a crude reaction mixture (65.8 mg) which was subjected to flash chromatography (hexanes/AcOEt=1/1, R_f=0.52) to give 34 mg of pure **8c** (52% yield), as a white solid. M.p. 88-91°C.

^{1}H NMR ($CDCl_3$)δ 7.05-7.39 (m, 5H), 3.95 (dt, 1H, *J*= 12.8, 4.7 Hz), 3.60 (ddd, 1H, *J*= 12.8, 10.8, 4.2 Hz), 2.66 (ddd, 1H, *J*= 16.9, 5.2, 1.8 Hz), 2.16 (dd, 1H, *J*= 16.9, 10.4 Hz), 1.19-2.05 (m, 9H), 0.78-0.93 (m, 3H).

^{13}C NMR ($CDCl_3$) δ 172.0, 153.7, 151.4, 130.1, 126.8, 122.2, 46.9, 42.3, 36.2, 33.3, 29.7, 29.4, 23.4, 14.7.

Anal. Calcd. for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.49, H, 7.34, N. 5. 23.

Enantioselectivity (>90%, not complete baseline separation) was determined on a separate experiment after quenching of the zinc enolate with CH_3CHO and subsequent oxidation (vide infra for the procedure) to give (3*R*, 4*R*)-*N*-phenoxycarbonyl-3-acetyl-4-butyl-2-piperidinone. HPLC (OB-H) (hexanes/isopropanol:85/15): t_R 39.5 (minor), t_R 42.7 (major).

***N-t*-Butyloxycarbonyl-3-ethyl-2-pyrrolidinone (9).**

Following the general procedure, a solution of lactam **3** (100 mg, 0.55 mmol) in toluene (0.5 mL), was added to a solution of $Cu(OTf)_2$ (2.9 mg, 0.00825 mmol) and ligand (*R,S,S*)-**1** (8.9 mg, 0.0165 mmol) in 1.0 mL of toluene. The obtained solution

was cooled to −78°C and Et_2Zn (0.825 mmol, 0.75 mL of a 1.1 M solution in toluene) was added. After 4h at 0°C (ca. 90% conversion) the usual workup afforded a crude reaction mixture which was subjected to flash chromatography (hexanes/AcOEt= 8/2) to give 18 mg of pure **9** (15% yield). R_f 0.33 (hexanes/AcOEt=6:4).

^{1}H NMR ($CDCl_3$)δ 3.82 (dd, 1H, *J*=10.6, 7.3 Hz), 3.29 (dd, 1H, *J*=10.6, 7.3 Hz), 2.52-2.70 (m, 1H), 2.10-2.25 (m, 2H), 1.38-1.55 (m, 2H), 1.51 (s, 9H), 0.92 (t, 3H, *J*=7.3 Hz).

Enantioselectivity (35% ee) was determined after conversion into the corresponding ***N*-benzyl-3-ethyl-pyrrolidinone 9a** (vide infra).

Reaction with trialkylaluminum reagents (R_3Al).

Following the general procedure, lactam **2f** (50 mg, 0.23 mmol), previously dissolved in 0.2 ml of CH_2Cl_2, was added to a solution of $Cu(OTf)_2$ (1.26 mg, 0.0035 mmol) and (*R,S,S*)-**1** (3.726 mg, 0.0069 mmol) in 0.5 ml of toluene. The obtained solution was cooled to –78°C and Et_3Al (0.46 mmol, 0.51 ml of a 0.9 M solution in toluene) was added. After 1.5h at –50°C the usual workup and chromatography afforded 50 mg of pure **8a** (88% yield). Enantiomeric excess (28%) was determined by chiral HPLC (OB-H) (hexanes/isopropanol=88/12): t_R 67.5 (minor), t_R 74.6 (major).

(4*R*)-*N*-Phenoxycarbonyl-4-methyl-2-piperidinone (8c).

Following the general procedure, lactam **2f** (50.0 mg, 0.23 mmol), previously dissolved in 0.2 ml of CH_2Cl_2 dry, was added to a solution of $Cu(OTf)_2$ (1.26 mg, 0.0035 mmol) and (*R,S,S*)-**1** (3.726 mg, 0.0069 mmol) in 0.5 ml of toluene. The obtained solution was cooled to –78°C and Me_3Al (0.46 mmol, 0.23 ml of a 2.0 M solution in toluene) was added. After 2 h at -50°C usual workup and chromatography afforded 42 mg of pure **8c** (78% yield), as a white solid. M.p. 86-89°C. $[\alpha]_D^{20}$=+1.7 (c=0.5, MeOH).

^{1}H NMR ($CDCl_3$)δ 7.10-7.42 (m, 5H), 3.99 (dt, 1H, *J*= 12.8, 4.4 Hz), 3.65 (ddd, 1H, *J*= 12.9, 11.1, 4.3 Hz), 2.68 (ddd, 1H, *J*= 16.1, 4.2, 2.0 Hz), 2.12-2.36 (m, 1H), 1.93-2.10 (m, 2H), 1.44-1.65 (m, 1H), 1.05 (d, 3H, *J*= 6.1 Hz).

^{13}C NMR ($CDCl_3$) δ 151.9, 153.6, 151.4, 130.1, 126.7, 122.1, 46.9, 43.8, 31.5, 28.5, 21.8.

Enantiomeric excess (66.7%) was determined by chiral HPLC (OB-H) (hexane/isopropanol:85/15): t_R 57.3 (minor), t_R 60.1 (major).

Anal. Calcd. for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.61, H, 6.11, N. 5. 73.

***N*-Benzyl-3-ethyl-pyrrolidinone (9a)**.[5]

Following the general procedure, a solution of lactam **3** (100 mg, 0.55 mmol) in toluene (0.5 mL), was added to a solution of $Cu(OTf)_2$ (2.9 mg, 0.00825 mmol) and ligand (*R,S,S*)-**1** (8.9 mg, 0.0165 mmol) in 1.0 mL of toluene. The obtained solution was cooled to –78°C and Et_3Al (0.46 mmol, 0.23 ml of a 2.0 M solution in toluene)

was added. After 2 h at 0°C (ca. 95% conversion) usual workup afforded a crude reaction mixture (80 mg) which was treated with a 3N solution of HCl in AcOEt (4 mL). After 40 min $NaHCO_3$ was added until gas evolution was detected. The reaction was filtered washing with AcOEt and dried over $MgSO_4$. Evaporation gave a crude oil (42.6 mg) which was suspended in toluene (3.0 mL) containing 16 mg of H_2O and mixed with benzyl chloride (0.030 mL), K_2CO_3 (104 mg) and tetrabutylammonium bromide (7.9 mg) and warmed at 80°C for 18h under vigorous stirring.[6] Filtration, evaporation and subsequent flash chromatography (hexanes/AcOEt= 6:4) gave 28 mg of pure **9a**.[5]

^{1}H NMR ($CDCl_3$)δ 7.14-7.30 (m, 5H), 4.36 (AB q, 2H), 3.23-3.28 (m, 1H), 2.82-2.88 (m, 1H), 2.53-2.70 (m, 1H), 2.09-2.30 (m, 2H), 1.31-1.39 (m, 2H), 0.80 (t, 3H, *J*=7.4 Hz). ^{13}C NMR ($CDCl_3$) δ 175.1, 137.1, 129.3, 128.7, 128.1, 52.8, 47.1, 38.0, 33.9, 28.2, 12.3.

Enantiomeric excess (3%) was determined by chiral HPLC (OB-H) (hexanes/isopropanol:95/5): t_R 22.5 (minor), t_R 21.6 (major).

Enantioselective tandem conjugate addition aldol reaction.

(3*R*, 4*R*, 1'*S*) and (3*R*, 4*R*, 1'*R*) *N*-Phenoxycarbonyl-3-1'-hydroxyethyl-4-ethyl-2-piperidinone (10).

A solution of $Cu(OTf)_2$ (5.43 mg, 0.015 mmol) and (*R,S,S*)-**1** (16.2 mg, 0.03 mmol) in anhydrous toluene (1 ml) was stirred at room temperature for 40 min. The colorless solution was initially cooled to -78°C and subsequently additioned with a solution of the lactam **2f** (217 mg, 1.0 mmol) in CH_2Cl_2 (0.3 mL) and Et_2Zn (1.36 mL, 1.5 mmol). After 2 h at –50°C, freshly distilled acetaldehyde (0.3 mL, 10 mmol) in toluene (0.5 mL) was dropwise added. After 2h at –50°C the reaction was treated with a NH_4Cl saturated aqueous (3 mL) solution and extracted with Et_2O. After evaporation of the dried ($MgSO_4$) organic solvent a crude reaction mixture was obtained (293 mg) which was subjected to flash chromatography (hexanes/AcOEt =6:4 as the eluant) to give 186 mg (64%) of **10a,b**, as ca. 60/40 mixture of diastereoisomers. ^{1}H NMR ($CDCl_3$)δ 7.21-7.53 (m, 5H), 4.19 (ddd, 1H, *J*=10.2, 6.5, 3.9 Hz), 4.08-4.12 (m, 1H), 3.75 (ddd, 1H, *J*=13.2, 10.2, 3.9 Hz), 2.66 (dd, 1H, *J*=8.3, 3.4 Hz), 2.12-2.26 (m, 1H), 1.62-1.88 (m, 2H), 1.55 (d, 3H, *J*=5.4 Hz), 1.44 (d, 3H, *J*=6.3Hz), 1.32-1.49 (m, 2H), 1.08 (t, 3H, *J*=7.3 Hz). ^{13}C NMR ($CDCl_3$) δ 171.9,

170.4, 151.6, 151.2, 130.1, 130.0, 126.9, 126.0, 122.2, 74.5, 68.8, 61.1, 56.6, 49.9, 46.2, 40.3, 38.2, 36.6, 32.8, 27.6, 25.8, 21.9, 21.3, 20.0, 11.5. ESIMS (neg.): *m/z* 308 [M- H + H_2O].

The enantioselectivity of compounds **10a,b** was determined on the corresponding **(3*R*, 4*R*)-*N*-phenoxycarbonyl-3-acetyl-4-ethyl-2-piperidinone (12).** To a mixture of **10a,b** (0.130 g, 0.446 mmol) in CH_2Cl_2 (5.0 mL) was added molecular sieves (4 Å, 0.31 g) and PCC (0.194 g, 0.90 mmol) at 0˚C. After 1h stirring at rt the reaction mixture was diluted with diethyl ether, filtered over Celite and evaporated to dryness. Purification by flash chromatography (50% ethyl acetate, 50% hexanes) provided **12** (0.066 g), as a solid. M.p. 40-43°C.

^{1}H NMR (MeOD)δ 7.13-7.48 (m, 5H), 4.03 (dt, 1H, *J*=12.8, 4.86 Hz), 3.76 (ddd, 1H, *J*=12.8, 10.1, 4.2 Hz), 3.57 (d, 1H, *J*=9.2 Hz), 2.18 (s, 3H), 1.23-2.27 (m, 5H), 0.96 (t, 3H, *J*=7.3 Hz).

^{13}C NMR (MeOD) δ 206.5, 171.1, 161.4, 153.5, 130.5, 127.2, 122.6, 65.1, 46.8, 37.4, 28.0, 27.2, 11.0.

The enantiomeric excess (94% *ee*) was determined by chiral HPLC (OB-H) (hexanes/isopropanol:85/15): t_R 54.2 (minor), t_R 59.6 (major).

Enantioselective tandem conjugate addition-allylation reaction. (3*R*, 4*R*)-*N*-Phenoxycarbonyl-3-(2-propenil)-4-ethyl-2-piperidinone (11).

A solution of $Cu(OTf)_2$ (1.9 mg, 0.00525 mmol) and (*R,S,S*)-**1** (5.67 mg, 0.00105 mmol) in anhydrous toluene (0.5 mL) was stirred at room temperature for 40 min. The colorless solution was initially cooled to -78°C and subsequently additioned with a solution of the lactam **2f** (75 mg, 0.35 mmol) in CH_2Cl_2 (0.2 mL) and Et_2Zn (1.36 mL, 1.5 mmol). After 2 h at –78°C, a Pd-allyl complex, obtained by mixing $Pd(Ph_3)_4$ (15 mg, 0.0133 mmol) and allyl acetate (0.046 mL, 0.42 mmol) in toluene (1.0 mL), was added via cannula. After 18h at 0°C the reaction was treated with a NH_4Cl saturated aqueous (3 mL) solution and extracted with Et_2O. After evaporation of the organic solution (washed quickly with NaOH 2.5% in order to eliminate PhOH formed during the reaction and afterward washed with brine) and dried ($MgSO_4$), a crude reaction mixture was obtained (70 mg), which was subjected to flash

chromatography (hexanes/AcOEt =8:2 as the eluant, R_f=0.35) to give 35 mg (35%) of **11**, as a semisolid.

^{1}H NMR ($CDCl_3$)δ 7.09-7.21 (m, 5H), 5.65-5.82 (m, 1H), 5.01-5.10 (m, 2H), 3.81-3.93 (m, 1H), 3.57-3.67 (m, 1H), 2.61-2.68 (m, 1H), 2.42-2.58 (m, 2H), 1.80-1.88 (m, 1H), 1.65-1.77 (m, 2H), 1.17-1.28 (m, 2H), 0.88 (t, 3H, *J*=7.3 Hz).

^{13}C NMR ($CDCl_3$) δ 174.9, 156.3, 153.8, 135.5, 130.1, 126.8, 122.2, 118.4, 61.3, 50.5, 45.8, 37.6, 35.4, 26.9, 11.5.

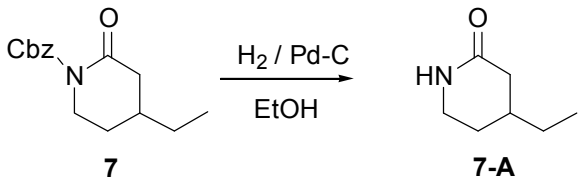
ESIMS (pos.): *m/z* 310 [M+Na^+].

The same reaction can be carried out with a Pd-allyl complex obtained by mixing $Pd[(Ph)_3]_4$ and allyl bromide. In this case compound **11** was obtained with a slighty lower yield (25% yield).

Enantiomeric excess (89%) was determined by chiral HPLC (OB-H) (hexanes/isopropanol:80/20): t_R 50.2 (minor), t_R 40.4 (major).

Removal of the *N*-substituents.

Deprotection of CBz-protecting group of compound 7 (Scheme 2).



7 **7-A**

Scheme 2

Pd/C (10 mg) was addes to a solution of compound **7** (35.0 mg, 0.134 mmol) in anhydrous EtOH (3 mL). After two vacuum/H_2 cycles, the reaction mixture was placed under a ballon atmophere of H_2 and allowed to stir for 18h. The mixture was filtered through Celite and the solvent was removed in vacuo to give 17.0 mg (99% crude yield) of a crude semisolid consisting of **4-ethyl-2-piperidinone** (**7-A**).[7]
^{1}H NMR ($CDCl_3$)δ 6.60-6.94 (m, 1H, NH), 3.16-3.45 (m, 2H), 2.47 (dd, 1H, *J*=13.6, 3.9 Hz), 1.79-2.05 (m, 2H), 1.57-1.78 (m, 1H), 1.20-1.49 (m, 3H), 0.91 (t, 3H, *J*=7.3 Hz). ^{13}C NMR ($CDCl_3$) δ 173.1, 42.0, 38.4, 34.9, 29.1, 28.5, 11.8.

All attempted removal in acidic or basic conditions of other protecting groups present in compounds **6** and **8a-c** resulted in extensive ring opening of the lactam.

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