Electronic Supplementary Information

for

Unprecedented copper-catalyzed asymmetric conjugate addition of organometallic reagents to $\alpha,\beta$-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: $\delta$ 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: $\delta$ 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(1H)-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](image)

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

Colorless liquid.

¹H NMR (CDCl₃) 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).

¹³C NMR (CDCl₃) δ 164.8, 137.8, 128.9, 128.3, 127.7, 125.6, 49.9, 44.9, 24.5.

HRMS calc. for C₁₂H₁₃ON 187.100, found 187.100.

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

Colorless liquid.

¹H NMR (CDCl₃) 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$_3$) $\delta$ 165.5, 139.7, 125.8, 48.0, 35.0, 24.5.

HRMS calc. for C$_6$H$_9$ON 111.068, found 111.068.

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

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

$^1$H NMR (CDCl$_3$) $\delta$ 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$_3$) $\delta$ 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(1H)-pyridone (2d).


$^1$H NMR (CDCl$_3$) $\delta$ 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$_3$) $\delta$ 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(1H)-pyridone (2e).

Light yellow liquid.

$^1$H NMR (CDCl$_3$) $\delta$ 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$_3$) $\delta$ 163.5, 154.1, 144.6, 135.8, 128.8, 128.8, 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(1H)-pyridone (2f).

Solid. M.p. 107°C.

$^1$H NMR (CDCl$_3$) $\delta$ 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 $\delta$ 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 α,β-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$_2$Cl$_2$ for 2f) and of R$_2$Zn (0.69 mmol) or R$_3$Al (0.92 mmol). The reaction was followed by TLC analysis, quenched with saturated aqueous NH$_4$Cl and extracted several times with Et$_2$O.

**Reactions with dialkylzinc reagents (R$_2$Zn).**

*N*-Benzyl-4-ethyl-2-piperidinone (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$_2$Zn (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-Phenoxy carbonyl-2-carbomethoxy-4-ethyl-2-piperidinone (5).** Following the general procedure, a solution of lactam 2c (137.5 mg, 0.5 mmol) in CH$_2$Cl$_2$ (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$_2$Zn (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.

(4R)-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$_2$Zn (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/acetone= 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).
(4R)-N-Benzylxocarbonyl-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\(_2\)Zn (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\(_3\)) \(\delta\) 7.19-7.34 (m, 5H, aromatic), 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\(_3\)) \(\delta\) 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).

(4R)-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\(_2\)Cl\(_2\), 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\(_2\)Zn (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\(_3\)) \(\delta\) 7.00-7.35 (m, 5H), 3.93 (dt, 1H, \(J= 13.0\) Hz, 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).
CNMR (CDCl$_3$) $\delta$ 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).

(4R)-N-Phenoxy carbonyl-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$_2$Cl$_2$, 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$_2$Zn (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$_3$)$\delta$ 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$_3$) $\delta$ 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.


Enantioselectivity (>90%, not complete baseline separation) was determined on a separate experiment after quenching of the zinc enolate with CH$_3$CHO and subsequent oxidation (vide infra for the procedure) to give (3R, 4R)-N-phenoxy carbonyl-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 Et₂Zn (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).

1H NMR (CDCl₃) 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 ($R_3\text{Al}$).

Following the general procedure, lactam 2f (50 mg, 0.23 mmol), previously dissolved in 0.2 ml of $\text{CH}_2\text{Cl}_2$, 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 $\text{Et}_3\text{Al}$ (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-Phenoxy carbonyl-4-methyl-2-piperidinone (8c).

Following the general procedure, lactam 2f (50.0 mg, 0.23 mmol), previously dissolved in 0.2 ml of $\text{CH}_2\text{Cl}_2$ 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 $\text{Me}_3\text{Al}$ (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).

$^1\text{H}$ NMR (CDCl$_3$)$\delta$ 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).

$^{13}\text{C}$ NMR (CDCl$_3$) $\delta$ 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 $\text{Et}_3\text{Al}$ (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$_2$O and mixed with benzyl chloride (0.030 mL), K$_2$CO$_3$ (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.**

(3R, 4R, 1’S) and (3R, 4R, 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$_2$Cl$_2$ (0.3 mL) and Et$_2$Zn (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$_4$Cl saturated aqueous (3 mL) solution and extracted with Et$_2$O. 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,
The enantioselectivity of compounds 10a,b was determined on the corresponding (3R, 4R)-N-phenoxy carbonyl-3-acetyl-4-ethyl-2-piperidinone (12). To a mixture of 10a,b (0.130 g, 0.446 mmol) in CH$_2$Cl$_2$ (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) $\delta$ 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) $\delta$ 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. (3R, 4R)-N-Phenoxy carbonyl-3-(2-propenyl)-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$_2$Cl$_2$ (0.2 mL) and Et$_2$Zn (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$_4$Cl saturated aqueous (3 mL) solution and extracted with Et$_2$O. 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 \textbf{11}, as a semisolid.

$^1$H NMR (CDCl$_3$) $\delta$ 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$_3$) $\delta$ 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 \textbf{11} was obtained with a slightly 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).

\[
\begin{array}{c}
\text{Cbz} \\
\text{N} \\
\text{O} \\
\text{H}_2 / \text{Pd-C} \\
\text{EtOH} \\
\end{array} \xrightarrow{\text{7}} \begin{array}{c}
\text{HN} \\
\text{O} \\
\end{array} \xrightarrow{\text{7-A}}
\]

Scheme 2

Pd/C (10 mg) was added to a solution of compound 7 (35.0 mg, 0.134 mmol) in anhydrous EtOH (3 mL). After two vacuum/H₂ cycles, the reaction mixture was placed under a balloon atmosphere of H₂ 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

¹H NMR (CDCl₃) 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). ¹³C NMR (CDCl₃) 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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