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Catalytic enantioselective conjugate addition of dialkylzinc reagents to *N*-substituted-2,3-dehydro-4-piperidones

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General Methods. All reactions were performed in oven or flame dried glassware under inert atmosphere of N_2 or argon and conjugate additions were carried out using standard Schlenk techniques. Toluene, THF and ether were distilled from sodium, hexane and CH_2Cl_2 from CaH_2. Dialkylzinc reagents: Me_2Zn (2M in toluene), Et_2Zn (1M in hexane) and $i Pr_2Zn$ (1M in toluene) were purchased from Aldrich, Bu_2Zn (1M in heptane) was purchased from Fluka. Thin-layer chromatography (TLC) was performed on Merck silica gel 60 TLC-plates F254 and visualized using UV or phosphomolybdic acid. Flash chromatography was carried out on silica gel (Aldrich, 230 – 400 mesh). ^{1}H NMR spectra were recorded at 300 or 400 MHz with $CDCl_3$ as solvent, ^{13}C NMR were obtained at 50, 75 or 100 MHz in $CDCl_3$ (Varian spectrometers). Chemical shifts were determined relative to the residual solvent peaks ($CHCl_3$, δ = 7.26 ppm for hydrogen atoms, δ = 77.0 for carbon atoms). Optical rotations were recorded on Schmidt+Haench Polartronic MH8 instrument at 589 nm. Gas chromatography was performed on Hewlett-Packard HP 6890 Series GC System with flame ionization detector on chiral columns and HPLC on Shimadzu LC-10AD VP instrument equipped with 6 parallel normal phase chiral columns, using a diode array detector. Mass spectra were recorded on an AEI-MS-902 mass spectrometer. Absolute configurations were assigned on the basis of the facial selectivity observed with the same catalysts with enones.[1]

General procedure A for preparation of substrates 1a,b,d,e

4-Methoxypyridine (1.0 mL, 10 mmol) was dissolved in *i*PrOH (20 mL) and cooled to -20°C. $K(iPrO)_3BH$ [2](20 mL, 20 mmol, 1M in THF) was added followed by the appropriate chloroformate (11 mmol) in Et_2O (3 mL) over 10 min. The reaction mixture was stirred at -20°C for 1h and then it was poured into 1M aq. HCl (30 mL) and stirred for 10 min at r.t. The resulting solution was diluted with Et_2O, the phases separated and the aqueous phase extracted with Et_2O. Combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography or by crystallization.

1-Methoxycarbonyl-2,3-dehydro-4-piperidone (1a)[3]

Following general procedure A pure **1a** was obtained in 49% yield as a colorless oil.
^{1}H NMR (400MHz; $CDCl_3$) δ 7.78 (m, 1H), 5.29 (d, *J*=8.0 Hz, 1H), 3.98 (t, *J*=7.4 Hz, 2H), 3.82 (s, 3H), 2.51 (t, *J*=7.4 Hz, 2H).

1-Ethoxycarbonyl-2,3-dehydro-4-piperidone (1b)[4]

Following general procedure A pure **1b** was obtained in 65% yield as a colorless oil.
^{1}H NMR (400MHz; $CDCl_3$) δ 7.82 (m, 1H), 5.31 (d, *J*=8.0 Hz, 1H), 4.27 (q, *J*=7.1 Hz, 2H), 4.00 (t, *J*=7.4 Hz, 2H), 2.53 (t, *J*=7.2 Hz, 2H), 1.32 (t, *J*=7.2 Hz, 3H).

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[1] B. L. Feringa, M. Pineschi, L. A. Arnold, R. Imbos, A. H. M. de Vries, *Angew. Chem. Int. Ed.* 1997, **36**, 2620.
[2] H. C. Brown, B. Nazer and J. A. Sikorski, *Organometallics*, 1983, **2**, 634.
[3] S. Raucher and J. E. Macdonald, *Synth. Commun*., 1980, **10**, 325.
[4] D. L. Comins, G. Chung and M. A. Foley, *Heterocycles*, 1994, **37**, 1121.

1-*t*-Butoxycarbonyl-2,3-dehydro-4-piperidone (1c)
4-Methoxypyridine (0.50 mL, 5.0 mmol) was dissolved in *i*PrOH (10 mL) and cooled to -15°C (ice-methanol). $K(iPrO)_3BH$ (10 mL, 10 mmol, 1M in THF) was added to this solution followed by Boc_2O (1.20 g, 5.5 mmol) in Et_2O (3 mL). The resulting mixture was stirred for 1 h at -15°C and then 10% aq. citric acid (20 mL) was added and stirring continued for 10 min at r.t. The solution was diluted with Et_2O, phases were separated and the aqueous phase extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography (heptane/AcOEt=2:1) to give 409 mg (41%) of **1c** as a white solid.
M.p. 53-54°C.
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, *J*=5.9 Hz, 1H), 5.29 (d, *J*=8.1 Hz, 1H), 3.96 (t, *J*=7.1 Hz, 2H), 2.53 (t, J=7.1 Hz, 2H), 1.53 (s, 9H).
^{13}C NMR (50 MHz, $CDCl_3$) δ 193.6, 144.0, 106.72, 83.5, 42.3, 41.2, 35.7, 28.0.
Elem. anal. calcd. for $C_{10}H_{15}NO_3$ C 60.90, H 7.67, N 7.10; found C 60.90, H 7.72, N 7.13.
HRMS calc. for $C_{10}H_{15}NO_3$ 197.1052, found 197.1058.

1-Phenoxycarbonyl-2,3-dehydro-4-piperidone (1d)[3]
The crude product obtained by general procedure A was purified by flash chromatography (pentane/AcOEt=2:1) followed by crystallization from CH_2Cl_2/hexane to give pure **1d** in 50% yield as a white solid.
^{1}H NMR (400MHz; $CDCl_3$) δ 7.92 (d, *J*=8.1 Hz, 1H), 7.37 (t, *J*=7.8 Hz, 2H), 7.23 (t, *J*=7.5 Hz, 1H), 7.12 (d, *J*=8.7 Hz, 2H), 5.41 (d, *J*=7.8 Hz, 1H), 4.13 (m, 2H), 2.61 (t, *J*=7.3 Hz, 2H).

1-Benzyloxycarbonyl-2,3-dehydro-4-piperidone (1e)[5]
The crude product obtained by general procedure A was purified by crystallization from AcOEt/hexane to give pure **1e** in 63% yield as a white solid.
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (m, 1H), 7.39 (m, 5H), 5.36 (m, 1H), 5.26 (s, 2H), 4.05 (t, *J*=7.2 Hz, 2H), 2.56 (t, *J*=7.2 Hz, 2H).

1-(Toluene-4-sulfonyl)-4-piperidone (2)[6]
4-Piperidone hydrochloride hydrate (1.54 g, 10 mmol) and K_2CO_3 (4.84 g, 35 mmol) were suspended in CH_3CN (30 mL) and the mixture cooled in an ice-bath. An acetonitrile (20 mL) solution of *p*-TsCl (2.10 g, 11 mmol) was added at once and the reaction mixture was stirred for 18h, allowing the temperature to reach r.t. The solution was acidified with 1M aq. HCl until all white solid dissolved and extracted with AcOEt (3x). The combined organic extracts were washed with $NaHCO_3$ and brine, then dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography (heptane/AcOEt=2:1) to give 2.01 g of **2** (79%) as a white solid.
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, *J*=8.1 Hz, 2H), 7.34 (d, *J*=7.3 Hz, 2H), 3.39 (t, *J*=5.9 Hz, 4H), 2.53 (t, *J*=5.9 Hz, 4H), 2.44 (s, 3H).

1-(Toluene-4-sulfonyl)- 2,3-dehydro-4-piperidone (3)
IBX (2.46 g, 8.8 mmol) and NMO (1.03 g, 8.8 mmol) were dissolved in DMSO (8 mL) at r.t. To this solution piperidone **2** (1.01 g, 4.0 mmol) in DMSO (12 mL) was added at once and the resulting clear solution was stirred for 72 h at r.t. in a flask covered with aluminium foil. The reaction mixture was poured into sat. $NaHCO_3$ solution and extracted with Et_2O (3x). The combined organic extracts were extracted with sat. $NaHCO_3$ solution, H_2O and brine, then dried ($MgSO_4$) and concentrated. The resulting crude product was purified by flash chromatography (heptane/AcOEt=3:1) to yield 0.77 g (77%) of **3** as a white solid.
M.p. 108-111°C.
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (m, 3H), 7.33 (d, *J*=7.7 Hz, 2H), 5.32 (d, *J*=8.1 Hz, 1H), 3.67 (t, *J*=7.0 Hz, 2H), 2.47 (t, *J*=7.0 Hz, 2H), 2.41 (s, 3H).
^{13}C NMR (50 MHz, $CDCl_3$) δ 177.5, 145.4, 143.5, 130.3, 127.3, 108.2, 43.9, 35.4, 21.6, 18.4.

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[5] R. Shintani, N. Tokunaga, H. Doi and T. Hayashi, *J. Am. Chem. Soc*. 2004, **126**, 6240.
[6] K. H. Yoo, H. S. Choi, D. C. Kim, K. J. Kim, Y. S. Song and C. Jin, *Arch. Pharm*. 2003, **336**, 208.

Elem. anal. calcd. for $C_{12}H_{13}NO_3S$ C 57.35, H 5.21, N 5.57, S 12.76; found C 57.80, H 5.43, N 5.38, S 13.07.
HRMS calc. for $C_{12}H_{13}NO_3S$ 251.0616, found 251.0628.

General procedure B for the copper-phosphoramidite conjugate addition of dialkylzinc reagents to *N*-protected-2,3-dehydro-4-piperidones

$Cu(OTf)_2$ (9 mg, 0.025 mmol) and ligand (0.050 mmol) were dissolved in anhydrous toluene (1 mL) and stirred for 40 min at r.t. To this solution was added a solution of substrate (0.50 mmol) in toluene (2 mL) and the mixture cooled to -25°C. A solution of a R_2Zn (1.50 mmol) was added dropwise and the reaction mixture was stirred at specified temperature, then quenched with sat. aq. NH_4Cl and extracted with Et_2O (3x). Combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography.

(*R*)-1-Methoxycarbonyl-2-ethyl-4-piperidone (4a)
The crude product obtained by general procedure B was purified by flash chromatography (pentane/AcOEt=4:1+1% Et_3N) to give pure **4a** in 20% yield as a colorless oil.
^{1}H NMR (400MHz; $CDCl_3$) δ 4.49 (m, 1H), 4.32 (m, 1H), 3.71 (s, 3H), 3.15 (dt, *J*=13.0, 3.6 Hz, 1H), 2.59 (dd, *J*=14.4, 6.8 Hz, 1H), 2.48-2.39 (m, 1H), 2.28 (d, *J*=14.8 Hz, 2H), 1.54-1.41 (m, 2H), 0.83 (t, *J*=7.4 Hz, 3H).
^{13}C NMR (50MHz; $CDCl_3$) δ 207.8, 156.1, 53.6, 52.9, 45.1, 40.5, 38.2, 25.3, 10.0.
HRMS calc. for $C_9H_{15}NO_3$ 185.1052, found 185.1059.
GC on Chiraldex G-TA column, 30m × 0.25mm, He-flow: 1mL/min, oven temp.:100°C, init. time: 15min, rate: 10°C/min, final temp. 150°C, t_R 23.9 (minor), t_R 24.3 (major).
[α] = –16.8 (c=0.58, $CHCl_3$), 88% ee.

(*R*)-1-Methoxycarbonyl-2-isopropyl-4-piperidone (4b)
The crude product obtained by general procedure B was purified by flash chromatography (pentane/AcOEt=4:1+1% Et_3N) to give pure **4b** in 79% yield as a colorless oil.
^{1}H NMR (400MHz; $CDCl_3$) δ 4.51-3.92 (m, 2H), 3.74 (s, 3H), 3.13 (t, *J*=11.4 Hz, 1H), 2.58-2.39 (m, 3H), 2.30 (d, *J*=13.2 Hz, 1H), 1.79-1.66 (m, 1H), 0.96 (d, *J*=6.8Hz, 3H), 0.86 (d, *J*=6.4, 3H).
^{13}C NMR (50MHz; $CDCl_3$) δ 207.9, 156.2, 58.7, 52.9, 43.2, 40.6, 38.8, 29.2, 19.5, 18.7.
It was not possible to obtain exact mass because compound fragmented during HRMS measurement. CI MS calc. for $C_{10}H_{18}NO_3$ (MH^+) 200, found 200.
GC on Chiraldex G-TA column, 30m × 0.25mm, He-flow: 1mL/min, oven temp.:100°C, init. time: 15min, rate: 10°C/min, final temp. 150°C, t_R 23.5 (minor), t_R 23.9 (major).
[α] = +13.6 (c=0.69, $CHCl_3$), 94% ee.

(*R*)-1-Ethoxycarbonyl-2-ethyl-4-piperidone (4c)
The crude product obtained by general procedure B was purified by flash chromatography (pentane/AcOEt=4:1+1% Et_3N) to give pure **4c** in 35% yield as a colorless oil.
^{1}H NMR (400MHz; $CDCl_3$) δ 4.51 (m, 1H), 4.33 (m, 1H), 4.18-4.11 (m, 2H), 3.14 (dt, *J*=12.8, 3.4 Hz, 1H), 2.60 (dd, *J*=14.8, 7.0 Hz, 1H), 2.48-2.39 (m, 1H), 2.28 (dd, *J*=14.4, 1.4 Hz, 2H), 1.54-1.40 (m, 2H), 1.25 (t, *J*=7.2 Hz, 3H), 0.83 (t, *J*=7.6 Hz, 3H).
^{13}C NMR (100MHz; $CDCl_3$) δ 207.9, 155.6, 61.7, 53.5, 45.2, 40.5, 38.1, 25.3, 14.5, 10.0.
HRMS calc. for $C_{10}H_{17}NO_3$ 199.1208, found 199.1204
GC on Chiraldex G-TA column, 30m × 0.25mm, He-flow: 1mL/min, oven temp.:100°C, init. time: 15min, rate: 10°C/min, final temp. 150°C, t_R 23.7 (minor), t_R 24.0 (major).
[α] = –9.3 (c=0.72, $CHCl_3$), 92% ee.

(*R*)-1-Ethoxycarbonyl-2-isopropyl-4-piperidone (4d)

The crude product obtained by general procedure B was purified by flash chromatography (pentane/AcOEt=4:1+1% Et_3N) to give pure **4c** in 80% yield as a colorless oil.

^{1}H NMR (400MHz; $CDCl_3$) δ 4.43 (m, 1H), 4.20-4.16 (m, 3H), 3.12 (t, *J*=6.6 Hz, 1H), 2.54-2.43 (m, 3H), 2.35 (dd, *J*=14.8, 2.0 Hz, 1H), 1.76-1.67 (m, 1H), 1.28 (t, *J*=7.2 Hz, 3H), 0.96 (d, *J*=6.8 Hz, 3H), 0.86 (d, *J*=6.4 Hz, 3H).

^{13}C NMR (50MHz; $CDCl_3$) δ 208.0, 155.7, 61.7, 58.5, 43.2, 40.6, 38.7, 29.2, 19.5, 18.7, 14.6.

HRMS calc. for $C_{11}H_{19}NO_3$ 213.1365, found 213.1376.

GC on Chiraldex G-TA column, 30m × 0.25mm, He-flow: 1mL/min, oven temp.:100°C, init. time: 15min, rate: 10°C/min, final temp. 150°C, t_R 26.3 (minor), t_R 26.5 (major).

[α] = –14.6 (c=0.68, $CHCl_3$), ee=94%.

(*R*)-1-Ethoxycarbonyl-2-butyl-4-piperidone (4e)

The crude product obtained by general procedure B was purified by flash chromatography (pentane/AcOEt=4:1+1% Et_3N) to give pure **4e** in 16% yield as a colorless oil.

^{1}H NMR (400MHz; $CDCl_3$) δ 4.60 (m, 1H), 4.35 (m, 1H), 4.20-4.10 (m, 2H), 3.16 (dt, *J*=12.1, 3.6 Hz, 1H), 2.61 (dd, *J*=16, 6.6 Hz, 1H), 2.49-2.41 (m, 1H), 2.31-2.25 (m, 2H), 1.54-1.42 (m, 1H), 1.41-1.35 (m, 1H), 1.34-1.14 (m, 4H), 1.26 (t, *J*=7.0 Hz, 3H), 0.85 (t, *J*=7.0 Hz, 3H).

^{13}C NMR (50MHz; $CDCl_3$) δ 207.9, 155.6, 61.7, 52.1, 45.5, 40.6, 38.3, 31.9, 27.7, 22.2, 14.6, 13.9.

HRMS calc. for $C_{12}H_{21}NO_3$ 227.1521, found 227.1528

GC on Chiraldex G-TA column, 30m × 0.25mm, He-flow: 1mL/min, oven temp.:100°C, init. time: 15min, rate: 10°C/min, final temp. 150°C, t_R 29.4 (minor), t_R 29.8 (major).

[α] = +19.6 (c=0.73, $CHCl_3$), 74% ee.

(*R*)-1-*t*-Butoxycarbonyl-2-ethyl-4-piperidone (4f)

The crude product obtained by general procedure B was purified by flash chromatography (pentane/AcOEt=4:1+1% Et_3N) to give pure **4f** in 58% yield as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.48 (m, 1H), 4.21 (m, 1H), 3.14 (m, 1H), 2.64 (dd, *J*=14.3, 6.6 Hz, 1H), 2.47 (m, 1H), 2.30 (m, 2H), 1.49-1.25 (m, 3H), 1.49 (s, 9H), 0.87 (t, *J*=7.3 Hz, 3H).

^{13}C NMR (50 MHz, $CDCl_3$) δ 208.3, 154.0, 80.2, 53.4, 45.3, 40.6, 38.1, 28.4, 25.5, 10.2.

HRMS calc. for $C_{12}H_{21}NO_3$ 227.1521, found 227.1337.

HPLC on Chiralpack AS column, (heptane/isopropanol=95:5, flow = 1.0 mL/min): t_R 5.3 (major), t_R 6.4 (minor).

[α] = –4.8 (c=0.40, $CHCl_3$), 91% ee.

(*R*)-1-Phenoxycarbonyl-2-ethyl-4-piperidone (4g)

The crude product obtained by general procedure B was purified by flash chromatography (pentane/AcOEt=4:1+1% Et_3N) to give pure **4g** in 87% yield as a colorless oil.

^{1}H NMR (300MHz; $CDCl_3$) δ 7.33 (t, *J*=7.9 Hz, 2H), 7.17 (t, *J*=7.2 Hz, 1H), 7.07 (d, *J*=8.1 Hz, 2H), 4.63 (m, 1H), 4.48-4.42 (m, 1H), 3.30 (m, 1H), 2.75-2.68 (m, 1H), 2.61-2.49 (m, 1H), 2.38-2.33 (br d, 2H, *J*=15 Hz), 1.61-1.50 (m, 2H), 0.92 (m, 3H).

^{13}C NMR (50MHz; $CDCl_3$) δ 207.1, 151.2, 129.3, 125.5, 121.6, 54.2, 45.1, 40.5, 38.8, 29.7, 25.5, 25.3, 10.2.

HRMS calc. for $C_{14}H_{17}NO_3$ 247.1208, found 247.1120

HPLC on Chiralpak AS column, (heptane/isopropanol=95:5, flow = 1.0 mL/min): t_R 15.8 (major), t_R 19.8 (minor).

[α] = –2.8 (c=0.70, $CHCl_3$), 97% ee.

(*R*)-1-Phenoxycarbonyl-2-isopropyl-4-piperidone (4h)

The crude product obtained by general procedure B was purified by flash chromatography (pentane/AcOEt=4:1+1% Et_3N) to give pure **4h** in 84% yield as a colorless oil.

^{1}H NMR (400MHz; $CDCl_3$) δ 7.33 (t, *J*=7.6 Hz, 2H), 7.17 (t, *J*=7.6 Hz, 1H), 7.07 (d, *J*=8.0 Hz, 2H), 4.53-4.48 (m, 1H), 4.29 (m, 1H), 3.23 (m, 1H), 2.60-2.51 (m, 3H), 2.34 (d, *J*=14.8 Hz, 1H), 1.77 (m, 1H), 0.97 (d, *J*=6.4 Hz, 3H), 0.81 (d, *J*=6.4 Hz, 3H).

^{13}C NMR (50MHz; $CDCl_3$) δ 207.4, 154.1, 151.2, 129.3, 125.5, 121.6, 59.2, 43.2, 40.5, 39.3, 29.4, 19.5, 18.8.
HRMS calc. for $C_{15}H_{19}NO_3$ 261.1365, found 261.1362.
HPLC on Chiralpak AS column, (heptane/isopropanol=95:5, flow = 1.0 mL/min): t_R 10.7 (major), t_R 18.0 (minor).
[α] = +5.5 (c=0.55, $CHCl_3$), 97% ee.

(*R*)-1-Phenoxycarbonyl-2-butyl-4-piperidone (4i)
The crude product obtained by general procedure B was purified by flash chromatography (pentane/AcOEt=4:1+1% Et_3N) to give pure **4i** in 22% yield as a colorless oil.
^{1}H NMR (400MHz; $CDCl_3$) δ 7.34 (t, *J*=7.4 Hz, 2H), 7.18 (t, *J*=7.4 Hz, 1H), 7.07 (d, *J*=7.6 Hz, 2H), 4.72 (m, 1H), 4.45 (q, *J*= 6.9 Hz, 1H), 3.34-3.26 (m, 1H), 2.73-2.70 (m, 1H), 2.60-2.51 (m, 1H), 2.39-2.32 (m, 2H), 1.60 (m, 1H), 1.48-1.44 (m, 1H), 1.31-1.24 (m, 4H), 0.86 (t, *J*=6.8 Hz, 3H).
^{13}C NMR (50MHz; $CDCl_3$) δ 207.3, 153.9, 151.1, 129.3, 125.5, 121.5, 52.7, 45.5, 40.5, 38.8, 32.0, 30.9, 27.7, 22.2, 13.9
HRMS calc. for $C_{16}H_{21}NO_3$ 275.1521, found 275.1534
HPLC on Chiralpak AS column, (heptane/isopropanol=95:5, flow = 1.0 mL/min): t_R 23.5 (minor), t_R 27.5 (major).
[α] = –1.2 (c=0.52, $CHCl_3$), 82% ee.

(*R*)-1-Benzyloxycarbonyl-2-methyl-4-piperidone (4j)
The crude product obtained by general procedure B was purified by flash chromatography (heptane/AcOEt=4:1) to give pure **4j** in 44% yield as a colorless oil.
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (m, 5H), 5.18 (s, 2H), 4.80 (m, 1H), 4.31 (m, 1H), 3.40 (m, 1H), 2.70 (dd, *J*=6.6, 14.6 Hz, 1H), 2.50-2.25 (m, 3H), 1.21 (d, *J*=7.0 Hz, 3H).
^{13}C NMR (50 MHz, $CDCl_3$) δ 207.7, 155.0, 136.4, 128.6, 128.2, 128.0, 67.5, 48.2, 46.5, 40.5, 38.6, 18.9.
HRMS calc. for $C_{14}H_{17}NO_3$ 247.1208, found 247. 1220.
HPLC on Chiralpack AS column (heptane/isopropanol=95:5, flow = 1.0 mL/min): t_R 12.1 (major), t_R 15.5 (minor).
[α] = –6.5 (c=0.37, $CHCl_3$), 96% ee.

(*R*)-1-Benzyloxycarbonyl-2-ethyl-4-piperidone (4k)
The crude product obtained by general procedure B was purified by flash chromatography (heptane/AcOEt=4:1) to give pure **4k** in 70% yield as a colorless oil.
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (m, 5H), 5.18 (s, 2H), 4.58 (m, 1H), 4.41 (m, 1H), 3.22 (m, 1H), 2.65 (dd, *J*=14.6, 6.6 Hz, 1H), 2.47 (m, 1H), 2.33 (m, 2H), 1.61-1.46 (m, 2H), 0.87 (t, *J*=7.3 Hz, 3H).
^{13}C NMR (50 MHz, $CDCl_3$) δ 207.6, 155.5, 136.4, 128.6, 128.2, 127.9, 67.6, 53.8, 45.2, 40.6, 38.4, 25.4, 10.1.
HRMS calc. for $C_{15}H_{19}NO_3$ 261. 1365, found 261.1369.
HPLC on Chiralpack AS column (heptane/isopropanol=95:5, flow = 1.0 mL/min): t_R 11.1 (major), t_R 14.8 (minor).
[α] = –2.3 (c=0.53, $CHCl_3$), 94% ee.

(*R*)-1-Benzyloxycarbonyl-2-(2-propyl)-4-piperidone (4l)
The crude product obtained by general procedure B was purified by flash chromatography (heptane/AcOEt=4:1) to give pure **4l** in 68% yield as a colorless oil.
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (m, 5H), 5.19 (s, 2H), 4.43 (m, 1H), 4.26 (m, 1H), 3.16 (m, 1H), 2.56 (m, 3H), 2.32 (m, 1H), 1.74 (m, 1H), 0.97 (d, *J*=5.9 Hz, 3H), 0.87 (d, *J*=6.2 Hz, 3H).
^{13}C NMR (50 MHz, $CDCl_3$) δ 207.8, 155.5, 136.4, 128.5, 128.2, 127.9, 67.6, 58.7, 43.2, 40.6, 38.9, 29.3, 19.5, 18.8.
HRMS calc. for $C_{16}H_{21}NO_3$ 275.1521, found 275.1530.
HPLC on Chiralpack AS column (heptane/isopropanol=95:5, flow = 1.0 mL/min): t_R 9.7 (major), t_R 13.3 (minor).
[α] = –7.1 (c=0.56, $CHCl_3$), 95% ee.

(*R*)-1-Benzyloxycarbonyl-2-butyl-4-piperidone (4m)

The crude product obtained by general procedure B was purified by flash chromatography (heptane/AcOEt=4:1) to give pure **4m** in 12% yield as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.22 (m, 5H), 5.18 (AB, *J*=3.7 Hz, 2H), 4.68 (m, 1H), 4.39 (m, 1H), 3.22 (m, 1H), 2.64 (dd, J=14.7, 6.6 Hz, 1H), 2.45 (m, 1H), 2.31 (m, 2H), 1.56-1.36 (m, 2H), 1.26 (m, 4H), 0.85 (t, *J*=6.8 Hz, 3H).

^{13}C NMR (50 MHz, $CDCl_3$) δ 207.7, 136.4, 128.5, 128.4, 128.2, 128.0, 67.6, 52.3, 45.6, 40.6, 38.4, 32.0, 27.8, 22.2, 13.9.

HRMS calc. for $C_{17}H_{23}NO_3$ 289.1678, found 289.1679.

HPLC on Chiralpack AS column (heptane/isopropanol=95:5, flow = 1.0 mL/min): t_R 9.0 (major), t_R 10.4 (minor).

[α] = +1.6 (c=0.32, $CHCl_3$), 59% ee.

(*R*)-1-(Toluene-4-sulfonyl)-2-ethyl-4-piperidone (4n)

The crude product obtained by general procedure B was purified by flash chromatography (heptane/AcOEt=4:1) to give pure **4n** in 50% yield as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, *J*=7.7 Hz, 2H), 7.33 (d, *J*=7.3 Hz, 2H), 4.30 (q, *J*=7.0 Hz, 1H), 4.15 (dd, *J*=14.3, 7.0 Hz, 1H), 3.26 (m, 1H), 2.57-2.34 (m, 2H), 2.44 (s, 3H), 2.23 (m, 2H), 1.44 (m, 2H), 0.83 (t, J=7.3 Hz, 3H).

^{13}C NMR (50 MHz, $CDCl_3$) δ 206.5, 143.8, 137.6, 129.9, 127.0, 56.1, 45.1, 40.3, 39.9, 25.4, 21.5, 10.5.

HRMS calc. for $C_{14}H_{19}NO_3S$ 281.1085, found 281.1075.

HPLC on Chiralcel OD column (heptane/isopropanol=90:10, flow = 1.0 mL/min): t_R 10.3 (minor), t_R 11.3 (major).

[α] = +7.3 (c=0.41, $CHCl_3$), 81% ee.

(2*R*,3*R*)-1-Benzyloxycarbonyl-2-ethyl-3-(2-propenyl)-4-piperidone (5)

$Cu(OTf)_2$ (9 mg, 0.025 mmol) and **L1** (27 mg, 0.050 mmol) were dissolved in anhydrous toluene (1 mL) and stirred 40 min at r.t. The substrate **1e** (116 mg, 0.50 mmol) in toluene (2 mL) was added and the resulting solution was cooled to 0°C. Et_2Zn (1M in hexanes, 1.50 mL, 1.50 mmol) was added and the reaction mixture was stirred for 18h at 0°C. Subsequently a solution of $Pd(PPh_3)_4$ (46 mg, 0.040 mmol) and allyl acetate (0.11 mL, 100 mg, 1.0 mmol) in toluene (2 mL), was added and the mixture was stirred for 24 h allowing the temperature to rise gradually to r.t. Reaction was treated with sat. aqueous NH_4Cl solution and extracted with Et_2O (3x). Combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography (heptane/AcOEt=4:1) to give 76 mg (50%) of **5** as a slightly yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (m, 5H), 5.65 (m, 1H), 5.19 (s, 2H), 5.05-4.94 (m, 2H), 4.48-4.34 (m, 2H), 3.14 (m, 1H), 2.55 (m, 1H), 2.30-2.20 (m, 4H), 1.57-1.47 (m, 3H), 0.85 (m, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 210.0, 134.2, 128.5, 128.2, 128.0, 117.8, 67.6, 57.1, 55.2, 38.2, 37.6, 35.3, 25.0, 10.1.

HRMS calc. for $C_{18}H_{23}NO_3$ 301.1678, found 301.1670.

HPLC on Chiralpack AS column (heptane/isopropanol=95:5, flow = 1.0 mL/min): t_R 7.0 (minor), t_R 8.0 (major).

[α] = –50.8 (c=0.89, $CHCl_3$), 84% ee.